Single Technology Appraisal

Tarlatamab for previously treated advanced small-cell lung cancer [ID6364]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Tarlatamab for previously treated advanced small-cell lung cancer [ID6364]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Amgen UK:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Roy Castle Lung Cancer Foundation

4. **Expert statements**
   a. Yvonne Summers, Consultant Medical Oncologist - clinical expert nominated by British Thoracic Oncology Group
   b. Fiona Blackhall, Professor of Thoracic Oncology – clinical expert nominated by Amgen

5. **External Assessment Report** prepared by Southampton Health Technology Assessments Centre (SHTAC),

6. **External Assessment Report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Tarlatamab for previously treated advanced small-cell lung cancer

[ID6364]

Document B

Company evidence submission

October 2024

File name	Version	Contains confidential information	Date
ID6364_Tarlatamab in SCLC_Document B [Redacted]	V1.2	Yes	2nd October 2024

Contents

Tables and figures

Abbreviations

Abbreviation	Definition
1L	first line
2L	second line
3L	third line
AE	adverse event
AMQ	Amgen medDRA query
AS	absolute shortfall
BICR	blinded independent central review
BiTE	bispecific t-cell engager
BNF	British National Formulary
BOI	burden of illness
BSA	body surface area
BSC	best supportive care
CADTH	Canada's Drug And Health Technology Agency
CAS	Cancer Analysis Service
CAV	cyclophosphamide, doxorubicin and vincristine
CC	complication and comorbidity
CD3	cluster of differentiation 3
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CFI	chemotherapy free interval
CI	confidence interval
CMU	commercial medicines unit
COVID-19	coronavirus disease 2019

CR	complete response
CRS	cytokine release syndrome
CSR	clinical study report
DARE	database of abstracts of reviews of effects
DC	disease control
DCO	data cut-off
DLL3	delta-like ligand 3
DoDC	duration of disease control
DOR	duration of response
DSA	deterministic sensitivity analysis
DSU	decision support unit
EAG	external assessment group
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
eMIT	electronic market information tool
EORTC	European Organization for Research and Treatment of Cancer
ERG	evidence review group
ES	extensive-stage
ESS	effective sample size
FDA	Food and Drug Administration
GP	general practitioner
HCRU	healthcare resource utilisation
HLE	half-life extended
HR	hazard ratio
HRG	healthcare resource group
HRQoL	health-related quality of life
HTA	health technology assessment
IASLC	international association for the study of lung cancer
ICANS	immune effector cell associated neurotoxicity syndrome
ICD-10	international classification of diseases version 10
ICER	incremental cost-effectiveness ra
IP	investigational product
IPD	patient-level data
ITC	indirect treatment comparison
ITT	intent-to-treat
IV	intravenous
IVSS	IV solution stabiliser
KM	Kaplan-Meier
PD-L1	programmed death ligand 1
LCI	lower confidence interval
LOT	lines of therapy

LS	limited-stage
LYG	life years gained
M	metastasis
MAIC	matching-adjusted indirect comparison
mets	metastases
mg	milligram
MHC	major histocompatibility complex
MHRA	the medicines and healthcare products regulatory agency
min	minimum
MRI	magnetic resonance imaging
MRU	medical resource use
N	node
NA	not applicable
NE	not estimable
NHS	national health service
NICE	national institute for health and care excellence
NR	not reported
NSCLC	non-small cell lung cancer
ONS	office for national statistics
ORR	objective response rate
OS	overall survival
PAS	patient access scheme
PBAC	pharmaceutical benefits advisory committee
PD	progressed disease
PF	progression free
PFS	progression-free survival
PICOS	population interventions, comparators, outcomes, and study design
PK	pharmacokinetics
PP	post progression
PR	partial response
PRISMA	preferred reporting items for systematic reviews and meta-analyses
PRO	patient-reported outcomes
PS	proportional shortfall
PSA	probabilistic sensitivity analysis
PSM	partitioned survival model
PSS	personal social services
PSSRU	personal social services research unit
PSW	propensity score weighting
Q2W	once every other week
QALE	quality-adjusted life expectancy
QALY	quality-adjusted life year
QLQ-C30	quality of life questionnaire core 30

QLQ-LC13	quality of life questionnaire lung cancer module
RDI	relative dose intensity
RECIST	response evaluation criteria in solid tumours
RPA	recursive partitioning analysis
RTOG	radiation therapy oncology group
RWE	real-world evidence
SACT	systemic anti-cancer therapy
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
scFc	single chain fragment crystallizable
SCLC	small-cell lung cancer
SD	standard deviation
SE	standard error
SLR	systematic literature review
SMD	standardised mean difference
SmPC	summary of product characteristics
SOC	standard of care
STA	single technology appraisal
TA	technology appraisal
TEAE	treatment-emergent adverse event
TLR	targeted literature review
TNM	tumour, node, metastasis
TSD	technical support document
TTD	time-to-treatment discontinuation
UCI	upper confidence interval
UK	united kingdom
US	united states
VALSG	veterans' administration lung study group
WHO	world health organisation
WTP	willingness-to-pay
mL	milliliter

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 *Decision problem*

The decision problem addressed in this submission, compared to that defined in the final scope issued by NICE, is summarised in Table 1. As outlined below, tarlatamab is anticipated to receive a marketing authorisation for the treatment of adult patients with advanced small-cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy at a dose of 10 mg every two weeks (Q2W).[1] This submission is [redacted]. This is in line with the NICE final scope (see Table 1) and the clinical evidence base available for this treatment (see Section B.2.6).

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adult patients with advanced SCLC with disease progression on or after prior therapy	Adult patients with advanced SCLC after platinum-based chemotherapy and at least one other treatment	The population addressed in this submission is narrower than the NICE scope, requiring patients to have advanced disease after platinum-based chemotherapy and at least one other treatment. This narrower population reflects the clinical evidence available for tarlatamab in this indication.
Intervention	Tarlatamab	Tarlatamab 10 mg Q2W	N/A – in line with NICE scope
Comparator(s)	Established clinical management without tarlatamab, which may include: • Chemotherapy, including anthracycline-containing or platinum-based regimen • Oral topotecan (when re-treatment with the first-line regimen is not considered appropriate and the combination of cyclophosphamide, doxorubicin and vincristine is contraindicated) • Best supportive care	Third-line treatment standard of care (SOC) has been modelled as a single comparator, comprising the following treatments: • Topotecan • Cyclophosphamide + doxorubicin + vincristine • Carboplatin + etoposide	Patients with advanced SCLC following two or more prior treatments do not have dedicated treatment options. Patients consequently face extremely poor outcomes, with expected survival of only a few months, regardless of treatment received. The proposed treatment regimens, modelled as a single basket comparator, are considered an appropriate reflection of treatments typically prescribed at this stage of disease, given the similarly poor outcomes associated with each treatment. In line with discussion with the NICE technical team and external assessment group (EAG), pairwise analyses against each individual comparator (topotecan, CAV and platinum-based chemotherapy) have also been conducted as scenario analyses.
Outcomes	The outcome measures to be considered include: • overall survival (OS) • progression-free survival (PFS)	• Response rates • PFS • OS • TEAEs	N/A – in line with NICE scope[2]

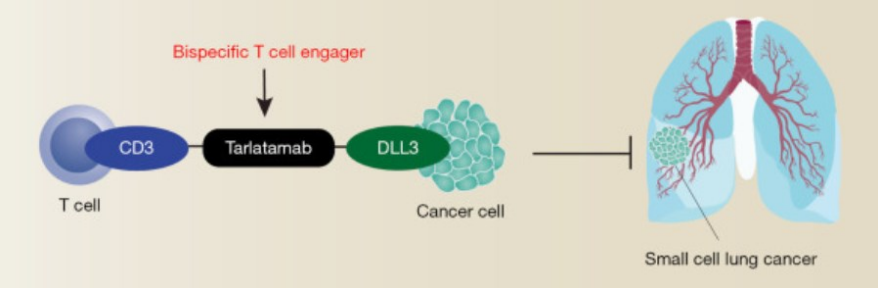
	• response rates • adverse effects of treatment • health-related quality of life (HRQoL)	• HRQoL	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	The economic analysis is expected to be in line with that described in the NICE decision problem	N/A – in line with NICE scope[2]

Abbreviations: EAG: external assessment group; HRQoL: health-related quality of life; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OS: overall survival; PFS: progression-free survival; PR: partial response; Q2W: once every other week; SCLC: small-cell lung cancer; SOC: standard of care; TEAE: treatment-emergent adverse event.

B.1.2 *Description of the technology being evaluated*

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements associated with tarlatamab are presented in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	Tarlatamab ([redacted]®)
Mechanism of action	Tarlatamab is a first-in-class half-life extended bispecific T-cell engager, comprising an antibody construct with two binding domains: one recognising delta-like ligand 3 (DLL3) and the other recognising T cells. Simultaneously binding to DLL3 and the CD3 complex on T cells triggers T-cell activation, which in turn leads to T cell-mediated tumour lysis.[3] This mechanism is shown in Figure 1. **Figure 1: Mechanism of action of tarlatamab**  **Source:** Tang and Kang (2023)[4]
Marketing authorisation/CE mark status	Tarlatamab is anticipated to receive a marketing authorisation in [redacted], for the treatment of adult patients with advanced small cell lung cancer with disease progression on or after platinum-based chemotherapy.[1] The Medicines and Healthcare products Regulatory Agency (MHRA) will review new information on this medicinal product at least every year.[1]
Indications and any restriction(s) as described in the SmPC	Tarlatamab is indicated for the treatment of adult patients with advanced small cell lung cancer with disease progression on or after platinum-based chemotherapy. This submission is [redacted]. Tarlatamab is contraindicated in patients with hypersensitivity to the active substance or any of these excipients:[1] Powder: • L-glutamic acid • Sucrose • Polysorbate 80 • Sodium hydroxide IV Solution stabiliser (IVSS): • Citric acid monohydrate (E330) • Lysine hydrochloride • Polysorbate 80 • Sodium hydroxide (for pH adjustment) • Water for injections

Method of administration and dosage	Tarlatamab dosing schedule starts with 1 mg on Day 1 followed by 10 mg on Days 8, 15, and every 2 weeks thereafter. Treatment with tarlatamab is given until disease progression or unacceptable toxicity. Tarlatamab is administered as an intravenous (IV) infusion.
Additional tests or investigations	N/A
List price and average cost of a course of treatment	List price for tarlatamab 1 mg: [redacted] List price for tarlatamab 10 mg: [redacted]
Patient access scheme (if applicable)	A confidential simple patient access scheme (PAS) will apply to tarlatamab in this indication. The with-PAS price for tarlatamab is [redacted] and [redacted] per 1 mg and 10 mg vial, respectively, equating to a discount to the list price of [redacted]

Abbreviations: DLL3: delta-like ligand 3; NA: not applicable; PAS: patient access scheme; Q2W: once every two weeks; SmPC: summary of product characteristics.
Source: Tarlatamab Summary of Product Characteristics (Amgen data on file).[1]

B.1.3 *Health condition and position of the technology in the treatment pathway*

Summary of relapsed/refractory small cell lung cancer

- Lung cancer is a complex disease originating in the trachea, bronchus or lung tissue and is composed of diverse histological and molecular types, with patients typically initially presenting with dyspnoea and a persistent cough.[5, 6, 7]
- SCLC is a rare and aggressive disease which is associated with rapid growth, a high likelihood of metastasis, poor prognosis and neuroendocrine differentiation.[5, 8]
- SCLC is a highly metastatic disease, with close to 70% of patients already having metastatic disease at the time of diagnosis, where macro-metastases often exceeding 2mm in diameter are commonly found in the lymph nodes, brain, liver and bones.[9]
- SCLC is classified into limited-stage (LS) and extensive-stage (ES) disease, but the tumour, node, metastasis (TNM) pathological staging system has been introduced more recently, giving individual stages to the primary tumour, the regional lymph nodes and metastasis.[10] This system is therefore useful in refining appropriate therapeutic options for patients.[10]
- Patients with SCLC generally have a poor prognosis; patients in England have a 5-year survival rate of only 10%.[11] In particular, patients with relapsed/refractory SCLC who have previously received two or more prior therapies are likely to have ES disease and have a high likelihood of developing brain metastases.[12]
    - Brain metastases are associated with a very low 2-year survival rate of 8%, alongside a high burden or neurological symptoms such as headaches, vomiting, cognitive decline and seizures.[12]

Current treatment pathway and unmet need

- For patients diagnosed with SCLC, treatment options are typically based around cisplatin-based combination chemotherapy, with or without radiotherapy.[13] Patients with ES disease may alternatively receive atezolizumab in combination with carboplatin and etoposide.[14]
- Patients who progress to second line treatment can receive either planinum- or cyclophosphamide-based chemotherapy, or topotecan[13]
- For patients in the indication of interest in this submission, whose disease progresses following two or more treatments, treatment options are currently limited to re-treatment with previous second line therapies, as no dedicated treatments available for these patients.[13]
- The poor prognosis faced by patients whose disease progresses following more than two lines

of treatment, combined with the lack of remaining treatment options at this stage in the current treatment pathway, means there is a significant unmet need for novel treatment options for patients at this stage of their disease.

Tarlatamab and its proposed positioning within the treatment pathway

- Tarlatamab is a first-in-class half-life extended bispecific T-cell engager immunotherapy, which simultaneously binds to DLL3 and the CD3 complex on T cells, triggering T-cell activation which in turn leads to T cell-medicated tumour lysis.[3] Tarlatamab is anticipated to be licensed for the treatment of patients with SCLC whose disease has progressed on or after platinum-based chemotherapy, representing the first approved treatment at this stage of disease
- Within UK clinical practice, tarlatamab is positioned for use as a treatment for patients whose disease has progressed following two prior treatments, in line with the NICE final scope and the trial evidence base for tarlatamab.
- The introduction of tarlatamab to the current NICE treatment pathway would fulfil a significant unmet need for an effective and well-tolerated treatment option in this patient population, reducing the need for re-treatment.

B.1.3.1 Health condition

Disease overview

Lung cancer is a complex disease originating in the trachea, bronchus or lung tissue and is composed of diverse histological and molecular types, with patients typically initially presenting with dyspnoea and a persistent cough.[5, 6, 7] Lung cancer is divided into two main subtypes based upon the microscopic appearance of the tumour cells: SCLC and non-small cell lung cancer (NSCLC).[15] Histological and molecular distinction of these subtypes is clinically important given their progression and treatment differ.[6] SCLC is a rare and aggressive disease which is associated with rapid growth, a high likelihood of metastasis, poor prognosis and neuroendocrine differentiation.[3, 8] The rare nature of the disease is evidenced by the European Medicines Agency's (EMA) orphan designation for tarlatamab.[16]

Lung cancer is termed "primary" when tumours first originate in lung tissue, usually in the cells lining the bronchi and other parts of the lung (e.g., bronchioles or alveoli). If the cancer spreads to other parts of the body, it is termed "secondary", or "metastatic".[5] SCLC is a highly metastatic disease, with close to 70% of patients already having metastatic disease at the time of diagnosis, where macro-metastases often exceeding 2mm in diameter are commonly found in the lymph nodes, brain, liver and bones.[9]

Clinical staging

SCLC is often classified using the Veterans' Administration Lung Study Group (VALSG) two-stage classification scheme, which has been routinely used for clinical staging of SCLC since the late 1950s.[10] The system classifies SCLC into limited-stage (LS) and extensive-stage (ES) SCLC, with this distinction informing NICE treatment guidelines in lung cancer (NG122).[10] In 1989, the International Association for the Study of Lung Cancer (IASLC) proposed a modification of the VALSG system in which the LS classification is expanded to include contralateral mediastinal or supraclavicular lymph node metastases and ipsilateral pleural effusions independent of cytology.[10]

LS-SCLC is defined as disease that is confined to one side of the chest, with any spread being localised to nearby lymph nodes only.[10] In LS-SCLC, the primary tumour and any nearby lymph nodes can be simultaneously targeted by radiotherapy. In contrast, ES disease is defined as

disease where the primary tumour has spread beyond the primary lung to other organs, distant lymph nodes, or tissues.[10] In the case of ES disease, the cancer has spread beyond a single area means that all affected areas cannot be treated simultaneously with radiotherapy.[17]

Beyond the LS and ES classification, recently published data on resected SCLC have suggested that tumour, node, metastasis (TNM) pathological staging correlates with the survival of resected patients.[18] This staging system gives individual stages to the primary tumour, the regional lymph nodes and metastasis and is therefore useful in refining appropriate therapeutic options for patients:[10]

- Primary tumour (T): The size of the primary cancer and how far it has spread into nearby tissue, rated as 1 to 4 to denote ascending size order
- Regional lymph nodes (N): Involvement of the lymph nodes, rated as 0 to 3 to denote no lymph node metastasis (0) to metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s) (3)
- Distant metastasis (M): Spread of the cancer to another part of the body, rated as 0 (denoting no distant metastasis) or 1 (denoting distant metastasis)

Epidemiology

Lung cancer is the second most common cancer in England, accounting for approximately 12% of all new cancer cases, with 40,168 people newly diagnosed with lung cancer in England in 2019.[19] Lung cancer is also the leading cause of cancer-related death in England, with an age-standardised mortality rate for women and men of 43.4 and 61.5, respectively per 100,000 in 2019.[20] As such, lung cancer represents a key clinical and public health challenge.[15, 21] SCLC accounts for approximately 15–20% of cases of lung cancer.[5]

In the past decade, age-standardised incidence rates for lung cancer increased by 1% overall, with a 15% increase in females and 11% decrease in males. Cancer Research UK has reported 48,549 new cases of lung cancer between 2016 and 2018 in the UK, equating to more than 130 new cases daily, with projections suggesting as many as 66,200 new cases every year in the UK by 2038−2040.[22] Incidence rates are highest in the UK in people aged 85 to 89, with 44% of all new lung cancer cases in the UK being diagnosed in people aged 75 and over.[22]

Prognosis

Lung cancer continues to be the leading cause of UK cancer deaths, accounting for 21% of all deaths from cancer.[23] Patients with SCLC generally have a poor prognosis, with SCLC in England being associated with a five-year survival rate of only 10%, which is worse than SCLC patients in other European countries.[11] Prognosis deteriorates as clinical stage progresses, with one-year survival rates for SCLC reported in the UK in 2018 as 83% for all patients with Stage 1 disease versus 17% for Stage 4 disease.[23] Aside from disease stage, other factors which predict poor survival outcomes in patients with SCLC include ES disease, performance status (PS), weight loss, and markers associated with excessive bulk of disease.[24] Importantly, survival worsens with each line of treatment,[25] meaning very few patients survive to receive a third line of treatment, highlighting the considerable unmet need in this population.

Improvement in the survival rates in SCLC patients is slow: data from a US cancer centre show the five-year overall survival rate of patients only increased from 8.3% to 11.0% from 1986−1999

to 2000−2008, and a South Korean registry study reported five-year survival rates of SCLC in 2023 remain low at 16% and 4% for LS disease and ES disease, respectively.[26]

In addition, patients with SCLC commonly experience brain metastases which represent the most common and severe complication of SCLC, and are associated with a low quality of life and a particularly poor prognosis.[12, 27, 28] Approximately 10−20% of SCLC patients present with brain metastases at the time of diagnosis, and a further 40−80% of patients will subsequently develop brain metastases after diagnosis.[8, 28, 29]

Current treatment in SCLC is largely based on cytotoxic chemotherapy (see Section B.1.3.3). Response rates to chemotherapy in patients with SCLC disease are initially high at around 70% to 90%, and median OS is approximately 25 to 30 months.[8, 30] However, up to 80% of patients with LS SCLC and nearly all patients with ES SCLC relapse in time, usually within the first year after treatment.[8, 31-33] Very few patients survive to third-line, at which point survival is dismal, with OS typically less than six months.[34, 35]

B.1.3.2 Disease burden

Symptom burden

Typically, patients with SCLC present with initial symptoms including difficulty breathing (dyspnoea) and a persistent cough, and common co-morbidities include pulmonary disease, hypertension, cardiac disease and diabetes.[7] The disease can also cause neurological problems, recurrent nerve pain, fatigue and anorexia. Patient health is further compromised by the effects of toxicities during chemotherapy treatment for SCLC such as nausea and vomiting, diarrhoea, alopecia, sore mouth, myelosuppression, and peripheral neuropathy.[36]

As previously mentioned, the likelihood of developing brain metastases is also particularly high in SCLC patients, with 40−80% of patients developing brain metastases after diagnosis.[8, 28] The development of brain metastases is associated with a high burden or neurological symptoms including headaches, nausea, vomiting, focal motor deficits, cognitive decline, delirium and seizures.[12]

HRQoL burden

SCLC represents a significant humanistic burden on patients. Disease symptoms caused by SCLC, and the various therapies aiming to cure or manage them, impact the emotional and physical functioning of patients.[37] However, there is limited availability of data on the health-related quality of life (HRQoL) impact of SCLC, especially when compared to NSCLC.[3]

Whilst data are limited, evidence suggests that patients with SCLC experience reduced HRQoL when compared with general population HRQoL. A 2017 systematic literature review conducted by Bennet *et al.* assessed global HRQoL in patients with SCLC, finding that EORTC QLQ-C30 scores were lower across normative global health status and physical functioning, as compared with scores reported by the general population.[37] Additionally, the review identified a study comparing groups of different types of lung cancer patients in which newly diagnosed treatment-naïve SCLC patients experienced higher levels of depression than NSCLC patients, which is likely linked to the poorer prognosis of SCLC at diagnosis.[37]

Overall, the literature pointed towards a trend for global/overall HRQoL to remain stable over time whilst patients were on treatment, irrespective treatment type; indeed, four studies reported

stable or increased physical functioning over time whilst on treatment regardless of treatment type.[37] Treatments for SCLC may improve these outcomes, with two studies reporting a potential therapeutic benefit in terms of physical functioning.[37]

Economic burden

In addition to the humanistic burden of lung cancer, its financial costs are substantial, estimated to be £307 million in England in 2010 through direct (medical) costs to the NHS and indirect costs (loss of productivity) to society.[38] Direct cost drivers for the economic burden of SCLC include drug acquisition costs, administration costs, healthcare resource use costs (e.g. GP or outpatient visits), monitoring costs, palliative care costs and costs associated with adverse events of treatment.[39]

B.1.3.3 Clinical pathway of care

Current treatment pathway

The treatment of SCLC in the UK has been assessed by NICE through both published guidelines (NG122) and previous technology appraisals (TA184 and TA638).[13, 14] This current treatment pathway for SCLC is described below in Figure 2. Unlike in the treatment of NSCLC, there are few actionable gene mutations contributing to the pathogenesis of SCLC.[40] In alignment with this, current clinical practice is principally reliant on treatment with non-targeted anti-proliferative chemotherapeutic regimens that may be associated with harmful adverse effects which negatively impact patient quality of life.[37]

First-line treatment

For patients diagnosed with LS-SCLC, treatment options are typically based around cisplatin-based combination chemotherapy with alternative platinum agents offered in some cases depending on renal function, PS or significant comorbidity. If patients with LS-SCLC present with a PS of 0 or 1 (as measured on the World Health Organisation [WHO] score), they may be considered for radiotherapy.[13] Underlining the clinical relevance of brain metastases in these patients, prophylactic cranial irradiation may also be offered to patients with LS-SCLC.[13]

For patients who present with, or who progress to, ES-SCLC, available treatments include platinum-based combination chemotherapy, radiotherapy and prophylactic cranial irradiation dependent on patient response to treatment and resulting toxicity.[13] In addition, atezolizumab combination therapy has recently been recommended as a first-line treatment for patients with ES disease, and clinical expert opinion is that it has largely become the preferred treatment option at this stage of treatment.[13, 41] Despite this recent development in the initial treatment of SCLC, median OS remains only one year.[42]

Second-line treatment

NICE guidance indicates that people whose disease has not responded to first-line treatment and has subsequently relapsed are unlikely to benefit from further treatment with existing chemotherapeutic regimens available. Despite this, due to a lack of alternative treatments, relapsed SCLC is treated with an anthracycline-containing chemotherapy regimen or re-treatment with a platinum-based regimen.[13]

Patients who progress to second line treatment typically receive chemotherapy in the form of carboplatin/cisplatin in combination with etoposide, carboplatin as a monotherapy, or

cyclophosphamide, doxorubicin and vincristine (CAV) combination therapy with or without concurrent treatment with radiotherapy.[13]

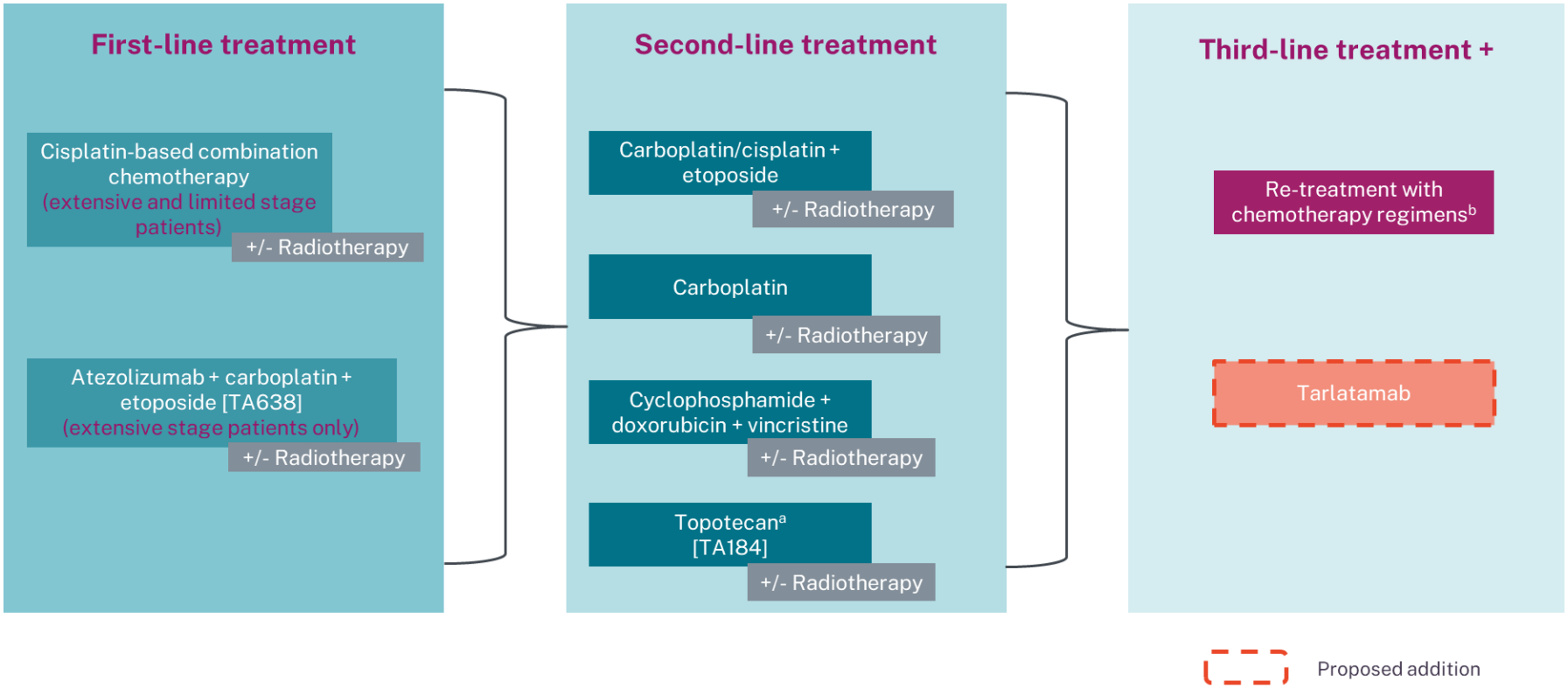
Another treatment option for patients in the second line is topotecan, which is recommended by NICE for use in the UK patients for whom re-treatment with first-line therapies is not considered appropriate, or for whom CAV is contraindicated.[43]

Third-line treatment

No treatments are currently recommended by NICE or approved by the Medicines and Healthcare products Regulatory Agency (MHRA) for treatment of SCLC following two prior lines of treatments (i.e., in the third-line and beyond). For patients whose disease progresses to this point, current third line treatments options are limited to re-treatment with previous second line therapies, even if this means re-treatment with the same or a similar treatment option.[13] These treatments are associated with extremely poor outcomes, with no dedicated treatments available for these patients.

Therefore, the introduction of tarlatamab as a treatment option following two previous lines of therapy would fulfil a significant unmet need for a well-tolerated treatment option able to extend survival and improve quality of life in this underserved patient population. If recommended for use, tarlatamab would become the first treatment specifically approved for treatment of third-line SCLC, with a novel mechanism of action based on bispecific T-cell engagement designed to target delta-like ligand 3 (DLL3), which is highly expressed in SCLC.[44] Tarlatamab would provide a dedicated third-line treatment option, ultimately leading to improved outcomes in these patients.

Figure 2: NICE treatment pathway for SCLC[b]



[a]Topotecan recommended in cases where treatment with platinum-based chemotherapy is not recommended and treatment with CAV is contraindicated.
[b]Patients are offered re-treatment with platinum-based regimens to a maximum of 6 cycles.
Abbreviations: CAV: Cyclophosphamide, doxorubicin and vincristine; SCLC: small-cell lung cancer.
Source: NICE Lung Cancer Diagnosis and Management (2023).[13]

Unmet need

With a five-year survival of 5% to 10%, SCLC has one of the poorest prognoses of any lung cancer subtype.[25, 45] Despite the recent addition of atezolizumab in combination with chemotherapy as first-line treatment option, rates of relapse remain high, and rates of subsequent response to second-line treatment are low.[42, 46] Cytotoxic chemotherapy still represents the mainstay of treatment in SCLC, but is associated with serious side effects, negatively impacting patient HRQoL.[36]

Patients whose disease progresses following a second treatment face extremely limited options, with no treatments approved or specifically recommended at this stage of treatment. Furthermore, response to treatment becomes increasingly unlikely; NICE guidelines specifically recommend clinicians to advise patients that limited evidence exists for the benefit of second-line chemotherapy following initial treatment.[13]

As such, patients with advanced SCLC following two or more prior treatments, who represent the indication of interest in this submission, face an extremely poor prognosis and a lack of effective treatment options in current clinical practice. Therefore, there remains a significant unmet need for a new, effective treatment option able to extend life and improve patient symptoms and HRQoL at this stage of disease.

Tarlatamab

Tarlatamab is a first-in-class half-life extended bispecific T-cell engager immunotherapy, which simultaneously binds to DLL3 and the CD3 complex on T cells, triggering T-cell activation which in turn leads to T cell-medicated tumour lysis.[3] DLL3 is an inhibitory notch ligand that is expressed on the surface of up to 85% of SCLC cells but is minimally expressed in normal tissues, making it a compelling therapeutic target for SCLC.[3] Tarlatamab has promoted tumour regression in pre-clinical models of SCLC and is the first DLL3-targeted immune therapy to be evaluated in SCLC.[3]

As there are no dedicated treatment options specifically for third-line treatment of SCLC, patients would otherwise receive re-treatment with previous-line chemotherapies.[13] In an analysis of real-world evidence using the CAS dataset, three main treatment regimens were highlighted that patients receive at third-line or after: cyclophosphamide combination therapy, carboplatin in combination with etoposide, and topotecan.[47] Re-treatment with previous therapies upon disease progression in SCLC is associated with a high likelihood of treatment resistance, due to the large degree of heterogeneity existing in SCLC tumours.[8] NG122 notes that there is very limited evidence that chemotherapy used past the first line would be of benefit to patients whose disease has progressed.[13] This highlights the need for the development of more effective therapies in this setting.

Therefore, the introduction of tarlatamab to the current NICE treatment pathway would fulfil a significant unmet need for an effective and well-tolerated treatment option in this patient population. Tarlatamab would provide a dedicated third-line treatment option with a novel mechanism of action, ultimately leading to improved outcomes in these patients.

B.1.4 *Equality considerations*

It is not expected that this appraisal will exclude any people protected by equality legislation, nor is it expected to lead to a recommendation that would have a different impact on people

protected by equality legislation than on the wider population. Similarly, it is not expected that this appraisal will lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

B.2 Clinical effectiveness

Clinical efficacy and safety evidence for tarlatamab in patients with small-cell lung cancer (SCLC) whose disease has progressed following two prior treatments

- A systematic literature review (SLR) was carried out in order to identify all clinical evidence relevant to the proposed indication, which identified only one viable source of safety and efficacy data for tarlatamab. The DeLLphi-301 trial is an ongoing, Phase II, open-label study in patients with relapsed/refractory (r/r) SCLC after two or more lines of treatment which forms the clinical evidence base for tarlatamab in patients with SCLC whose disease has progressed following two prior treatments
- The DeLLphi-301 trial is aligned with the decision problem specified in the NICE scope and the anticipated marketing authorisation of tarlatamab, and the trial includes a population of patients reflective of patients in UK clinical practice with SCLC whose disease has progressed following two prior treatments

Efficacy outcomes

- In the population of patients receiving the (anticipated) licensed dose of tarlatamab (10 mg target dose; N=99), tarlatamab drove clinically meaningful, deep and durable responses, with an overall response rate (ORR, primary endpoint) of 40.4% (97.5% CI: 29.4%, 52.2%), with 1 patient (1.0%) achieving a confirmed complete response (CR) and 39 patients (39.4%) achieving a confirmed partial response (PR)[48]
- Additionally, median time to response in patients in the 10 mg target dose group was 1.4 months (range: 1.1 to 2.8) and the median duration of response (DOR) was not reached (95% CI: 5.9, NE months)[48]
    - At the time of the June 2023 DCO, 55.0% of responders (22/40) in the 10 mg target dose group were still having ongoing responses (on treatment without disease progression or death), including [redacted] patients ([redacted]%) whose responses reached at least 6 months[48, 49]
- In the 10 mg target dose group, median progression-free survival (PFS) and overall survival (OS) were 4.9 months (95% CI: 2.9, 6.7) and 14.3 months (95% CI: 10.8, NE), respectively[48]

Indirect treatment comparison (ITC)

- A *de novo* ITC analysis compared tarlatamab in DeLLphi-301 to treatments currently received in UK clinical practice reported in the Cancer Analysis Service (CAS) real-world evidence (RWE) study conducted by Amgen. The UK CAS RWE study is considered to be highly generalisable to the population of patients anticipated to receive tarlatamab in the UK
- In the base case ITC approach, a matching-adjusted indirect comparison (MAIC) matching process was performed on the individual patient data (IPD) from DeLLphi-301 and the pseudo-IPD from the CAS Control Cohort.
- Treatment with tarlatamab provided a statistically significantly longer OS compared to currently available treatment options (HR 0.367 [95% CI: 0.202, 0.667]; P=0.001). In the same MAIC analysis, tarlatamab was associated with significantly longer PFS (HR 0.184 [95% CI: 0.100, 0.340]; P<0.0001). Results were consistent in two scenario analyses, as well as the unadjusted naïve analyses.

Patient-reported outcomes

- In the DeLLphi-301 trial, 10 mg tarlatamab treatment resulted in an improvement in QLQ-LC13 scores from baseline, with least squares mean (LSM) changes from baseline up to cycle 12 of [redacted] (95% CI: [redacted], [redacted]) for cough, [redacted] (95% CI: [redacted], [redacted]) for chest pain, and [redacted] (95% CI: [redacted], [redacted]) for dyspnoea composite score[49]
- LSM changes from baseline for the QLQ-C30 subscales of global health status indicated an increasing trend toward improvement. At cycle 12, LSM changes from baseline were [redacted] (95% CI: [redacted], [redacted]) in the 10 mg target dose group[49]

Safety outcomes

- Safety outcomes were assessed in Phase I and Phase II of DeLLphi-301 and overall tarlatamab was well-tolerated, with low rates of treatment discontinuation due to adverse events (AEs)
- In the 10 mg target dose group, 7 patients (7.1%) had AEs leading to discontinuation of tarlatamab. Grade ≥ 3 AEs were reported for 57 patients (57.6%) and were considered treatment related for 29.3% of patients[48]
- Of note, of the three patients (3.0%) that had fatal AEs; none of the deaths were considered by the investigator to be related to tarlatamab[48]

Conclusions

- Overall, tarlatamab represents a highly effective treatment option able to induce durable response in patients, and extend survival outcomes, whilst being associated with a manageable safety profile
- Tarlatamab addresses the high unmet need for an effective and well-tolerated treatment option faced by patients with SCLC whose disease has progressed following two prior treatments, representing a step-change in the treatment landscape at this late stage of disease, for which no treatments are currently approved

B.2.1 *Identification and selection of relevant studies*

A *de novo* systematic literature review (SLR) was conducted in April 2022 to identify relevant clinical evidence on the clinical efficacy and safety outcomes in patients with small-cell lung cancer (SCLC) whose disease has progressed following two prior treatments. The SLR was subsequently updated in December 2023 to ensure recently published evidence was included.

For the original searches conducted in April 2022, 9,988 records were identified, of which 3,491 were removed as duplicate records between bibliographic databases. 6,497 records were screened at the title and abstract level, of which 5,837 were excluded. The remaining 660 records were retrieved for full-text review, of which 30 records met the final inclusion criteria. For the updated searches run in December 2023, 1,573 records were returned, of which 514 records were removed as duplicate records between bibliographic databases and overlap with the original SLR. 1,059 records were screened at the title and abstract level, of which 968 were excluded. The remaining 91 records were retrieved for full-text review, of which 8 records met the final inclusion criteria. Two additional records were identified through hand-searches.

Across both searches, 40 publications were included, reporting on 21 unique studies in 3L+ SCLC. Full details of the SLR, including the search strategy, study selection process and detailed results are presented in Appendix D.

B.2.2 *List of relevant clinical effectiveness evidence*

As described above, the SLR identified 21 unique studies in 3L+ SCLC. Of these studies, only one (DeLLphi-301) provides evidence for the clinical efficacy and safety of tarlatamab in the patient population of interest for this appraisal (patients with SCLC whose disease had advanced following two or more lines of treatment).

DeLLphi-301

To date, the main body of evidence for tarlatamab to address the decision problem is derived from the DeLLphi-301 trial, which was used to support the application for marketing authorisation for tarlatamab in the indication of relevance to this submission. DeLLphi-301 is an ongoing, Phase II, open-label, single arm, registrational trial investigating the safety and efficacy of tarlatamab in patients with relapsed or refractory (r/r) SCLC after two or more lines of treatment. An overview of DeLLphi-301 is presented in Table 3 below. The methodology and results are presented in Section B.2.3 onwards.

The efficacy information presented in this submission focuses on the BICR analysis set (see Section B.2.4), which has been derived from the DeLLphi-301 CSR.[49] Results from the DeLLphi-301 trial have been published in the publication in the New England Journal of Medicine by Ahn *et al.* (2023).[48] The publication provides details of the trial design and presents the key efficacy results in the ITT population, which differs from the analysis presented in this submission, as it included one patient who did not receive 10 mg tarlatamab in Part 1 of the trial.

Table 3: Clinical effectiveness evidence

Study	**DeLLphi-301 (NCT03319940)**		
Study design	Ongoing Phase II, open-label, single-arm trial		
Population	Patients with r/r SCLC who have progressed or recurred following one platinum-based regimen and at least one other line of therapy		
Intervention(s)	**Part 1:** Tarlatamab 10 mg or 100 mg (1:1, N=176) **Part 2 (dose expansion phase):** Tarlatamab 10 mg (selected target dose following interim analysis on N=30/arm; N=12) **Part 3 (modified safety protocol)[a]:** Tarlatamab at selected target dose of 10 mg (N=34)		
Comparator(s)	N/A. DeLLphi-301 is a single arm trial. See Section B.2.9 for further details on comparative efficacy results.		
Indicate if study supports application for marketing authorisation	Yes	**Indicate if study used in the economic model**	Yes
Rationale if study not used in model	N/A		
Reported outcomes specified in the decision problem	• ORR (CR and PR) • DOR • PFS • OS • TEAEs • HRQoL		

Study	DeLLphi-301 (NCT03319940)
All other reported outcomes	• Serum concentrations of tarlatamab • DC • DoDC • Incidence of anti-tarlatamab antibody formation

[a] Not presented in this submission and does not inform the economic model.
Abbreviations: CR: complete response; DC: disease control; DoDC: duration of disease control; DOR: duration of response; HCRU: healthcare resource use; HRQoL: health-related quality of life; OR: objective response rate; OS: overall survival; PR: partial response; SCLC: small cell lung cancer; TEAE: treatment-emergent adverse event.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO).[49]

B.2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

B.2.3.1 Trial design

The clinical evidence base for tarlatamab as a treatment for patients with SCLC whose disease has progressed following two prior treatments is based on the pivotal DeLLphi-301 trial. DeLLphi-301 is an ongoing Phase II, open-label, registrational study in patients with r/r SCLC who have progressed or recurred following one platinum-based regimen and at least one other line of therapy. The study consisted of three parts:[48]

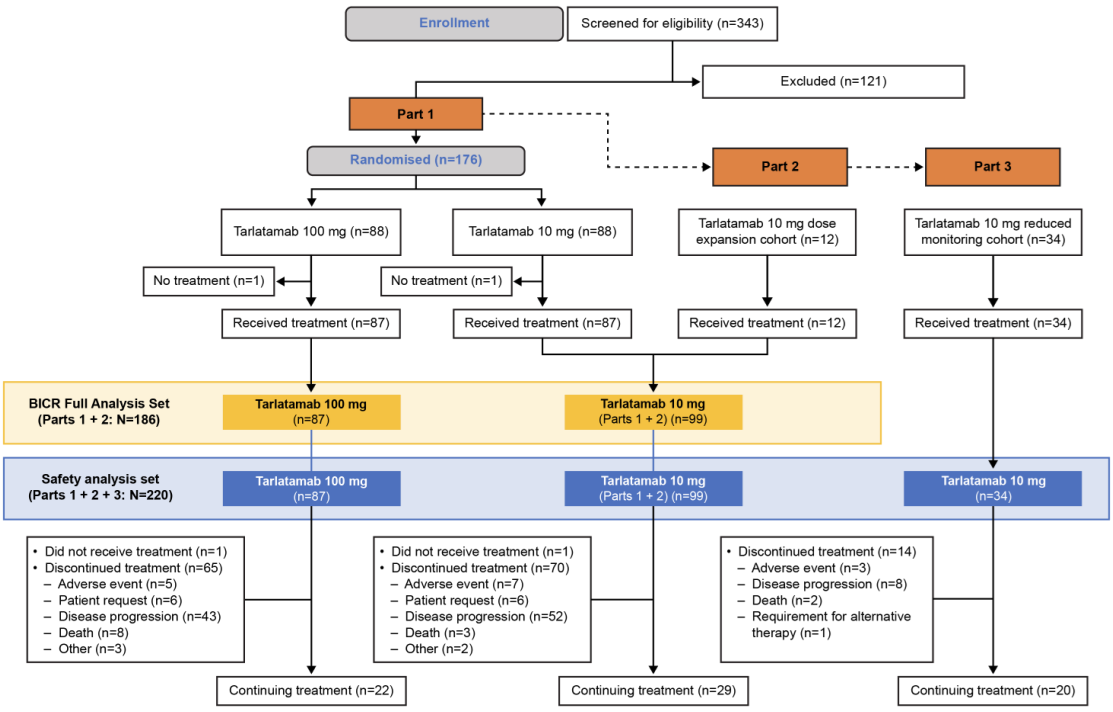
- **Part 1 (dose escalation phase)** evaluated 2 dose levels of tarlatamab in which approximately 180 eligible patients were planned to be enrolled and randomised 1:1 to treatment with a target dose of either 10 mg or 100 mg tarlatamab. To mitigate the risk of cytokine release syndrome (CRS), all patients received 1 mg of tarlatamab for the first dose (Cycle 1, Day 1) and then received step-up doses of 10 mg or 100 mg according to their assigned group. To select a target dose for expansion, an interim analysis was performed after 30 patients in each arm in Part 1 had opportunity to confirm an objective response after the first post-treatment scan, or up to 13 weeks of follow-up, whichever occurred first. In the event, 176 patients were recruited in Part 1, evenly randomised to 10 mg and 100 mg tarlatamab
- **Part 2 (dose expansion phase)** involved patients receiving tarlatamab at the selected target dose based on an interim analysis of Part 1 and enrolled until approximately 100 patients (from Part 1 and Part 2 combined) had been enrolled at the selected target dose level. 12 patients were enrolled in Part 2 of the trial, meaning that 100 patients received the selected target dose of 10 mg tarlatamab in Parts 1 and 2 of the trial
- **Part 3 (modified safety protocol)** was initiated after completing enrolment of Part 1 and Part 2, to enrol up to approximately 30 additional patients at the selected dose, with modified cycle 1 monitoring criteria. Hospitalisation for safety monitoring (potential CRS and/or neurological events) was required for 48 hours following the first two tarlatamab infusions in Parts 1 and 2 of the study; this was reduced to 24 hours in Part 3. 34 patients were enrolled in Part 3 of the trial

Patients were treated until progression regardless of the dose to which they were randomised. Following documented radiographic progression, patients had the option to remain on tarlatamab, if they continued to have clinical benefit in the investigator's judgement and had no significant or unacceptable toxicities. Upon permanent discontinuation from the study treatment

for any reason, a safety follow-up visit was performed approximately 42 (+5) days after the last dose of tarlatamab, even if subsequent anti-cancer therapy had been initiated within that period. After the safety follow-up visit, patients entered long-term follow-up to assess survival and/or the initiation of subsequent cancer therapy. Long-term follow-up was to be conducted every three months (+/- two weeks) for one year after the last dose of tarlatamab or five years from the first patient enrolled, whichever occurred first.[49]

The study design of the DeLLphi-301 trial is presented in Figure 3 below.

Figure 3: Study design of DeLLphi-301



Abbreviations: IV: intravenous; Q2W: every other week.
Source: Adapted from Ahn *et al.* (2023).[48]

B.2.3.2 Trial methodology

A summary of the methodology and trial design of DeLLphi-301 is presented in Table 4 below.

Table 4: Summary of DeLLphi-301 trial methodology

Trial name	DeLLphi-301
Location	The study was conducted at 56 centres in Austria, Belgium, Denmark, France, Germany, Greece, Italy, Japan, Netherlands, Poland, Portugal, South Korea, Spain, Switzerland, Taiwan, United Kingdom (two study centres), and the United States.
Trial design	Ongoing Phase II, open-label, registrational study in patients with recurrent SCLC who had progressed or recurred following 1 platinum-based regimen and at least 1 other line of therapy
Eligibility criteria for patients	**Key inclusion criteria:** • Patient had provided informed consent/assent prior to initiation of any study specific activities/procedures. • Male and female patients ≥ 18 years of age (or legal adult age within country) at the time of signing the informed consent • Histologically or cytologically confirmed r/r SCLC • Patients who progressed or recurred following 1 platinum-based regimen and at least 1 other prior line of therapy. • Patients willing to provide archived tumour tissue samples or willing to undergo pre-treatment tumour biopsy. • ECOG performance status of 0 or 1 • Minimum life expectancy of 12 weeks. • Measurable lesions as defined per RECIST 1.1 within 21 days prior to the first dose of tarlatamab. • Patients with treated brain metastases were eligible provided they meet defined criteria. **Key exclusion criteria:** Disease related: • Untreated or symptomatic brain metastases and leptomeningeal disease • Had evidence of interstitial lung disease or active, non-infectious pneumonitis • Patients who experienced recurrent pneumonitis (grade 2 or higher) or severe, life-threatening immune-mediated adverse events or infusion-related reactions including those that lead to permanent discontinuation while on treatment with immune-oncology agents • Unresolved toxicity from prior anti-tumour therapy, defined as per protocol Other medical conditions: • History of other malignancy within the past 2 years, with exceptions • Myocardial infarction and/or symptomatic congestive heart failure (New York Heart Association > class II) within 12 months of first dose of tarlatamab

	• History of arterial thrombosis (e.g., stroke or transient ischemic attack) within 12 months of first dose of tarlatamab • History of hypophysitis or pituitary dysfunction • Exclusion of hepatitis infection based on the results and/or criteria per protocol • Major surgery within 28 days of first dose of tarlatamab • History or evidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Patient is eligible if no acute symptoms of coronavirus disease 2019 (COVID-19) within 14 days prior to first dose of tarlatamab (counted from day of positive test for asymptomatic patients) Other exclusions: • Female patients of childbearing potential unwilling to use protocol specified method of contraception during treatment and for an additional 72 days after the last dose of tarlatamab • Female patients who were breastfeeding or who plan to breastfeed while on study through 72 days after the last dose of tarlatamab • Female patients planning to become pregnant while on study through 72 days after the last dose of tarlatamab. • Female patients of childbearing potential with a positive pregnancy test assessed at screening and/or day 1 by a highly sensitive urine or serum pregnancy test • Patient likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures • History or evidence of any other clinically significant disorder, condition or disease determined by the investigator or Amgen physician A full list of study eligibility criteria is provided in Appendix M.
Method of study drug administration	Tarlatamab 1 mg step dose was given on Cycle 1 Day 1. The full dose of tarlatamab was randomised between 10 mg or 100 mg, and was given on day 8 and 15 of Cycle 1, and every 2 weeks (Q2W) thereafter. Administration of tarlatamab was an IV infusion for 60 minutes. An 8 mg dose of dexamethasone was administered IV before tarlatamab was given on Days 1 and 8 of Cycle 1, and prophylactic hydration (1 litre of normal saline) was administered IV after each dose in Cycle 1.
Permitted and disallowed concomitant medication	Throughout the study, investigators were permitted to prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care, except for: • Other investigational agents • Concurrent experimental or approved anti-tumour therapies other than study drugs • Radiation therapy (with the exception of for symptom control) • Immunosuppressive agents Concomitant therapies were recorded from informed consent through to the end of the study.
Primary outcome	The primary outcomes were:

	• OR (including CR and PR) • Incidence of TEAEs • Serum concentrations of tarlatamab
Secondary and exploratory outcomes	The key secondary outcomes were: • DOR • DC • DoDC • PFS • OS • TEAEs • Serum concentrations of tarlatamab • Incidence of anti-tarlatamab antibody formation
Pre-planned subgroups	Pre-planned subgroup analyses were carried out for the following patient characteristics: • Age (<65 vs ≥65) • Region (North America vs Europe vs Asia vs Rest of World) • Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple, Other) • DLL3 cut points: <75% vs ≥75% and <25% vs ≥25% at moderate (2+) and strong (3+) staining intensities • Number of prior lines of anti-cancer therapy (2 vs ≥3) • Prior PD-1 or PD-L1 inhibitor therapy (Yes vs No) • Sum of diameters of target lesions at baseline (<median vs ≥median) • Platinum sensitivity (<90 days, ≥90 and <180 days, and ≥180 days) • Brain metastasis at baseline (Yes vs No) • Liver metastasis at baseline (Yes vs No)
Duration of study and follow-up	The study is ongoing, with the first patient enrolled on the 1st December 2021. At the latest DCO (27th June 2023), the median duration of follow-up was 10.6 months for OS.

Abbreviations: CR: complete response; DC: disease control; DCO: data cut-off; DLL3: delta-like ligand 3; DoDC: duration of disease control; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; HRQoL: health-related quality of life; OR: objective response; OS: overall survival; PFS: progression-free survival; PD-L1: programmed death-ligand 1; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumours; r/r: relapsed/refractory; SCLC: small-cell lung cancer; TEAE: treatment-emergent adverse event.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO).;[49] Ahn *et al.* (2023).[48]

Definition of outcomes

Table 5 below details the definitions used for each efficacy outcome reported in the DeLLphi-301 trial, and the statistical tests used in the analysis of each outcome.

Table 5: Efficacy endpoint definitions and statistical tests in DeLLphi-301

Endpoint	Definition	Statistical Test
Primary		
ORR	Proportion of patients with best overall response of CR or PR per RECIST v1.1. Patients without a post-baseline tumor assessment were considered non-responders.	Summarised with Clopper-Pearson exact 97.5% CI
Secondary		
DC	Best overall response of CR, PR, or SD per RECIST v1.1	Summarised with Clopper-Pearson exact 95% CI
PFS	Time from first dose of tarlatamab to the earlier of PD per RECIST v1.1 or death due to any cause • Patients without an event (PD or death) who have not started new anti-cancer therapy were censored on the date of the last visit; otherwise, the date of the first dose of tarlatamab • Patients starting new anti-cancer therapy prior to PD or death were censored on the date of the last visit prior to the new treatment; otherwise, the date of the first dose of tarlatamab • Patients with an event (PD or death) > 14 weeks after the last visit were censored on the date of the last visit prior to PD or death; otherwise, the date of the first dose of tarlatamab	Estimated using Kaplan-Meier method with 95% CI calculated using the Brookmeyer and Crowley method PFS rate at 6 and 12 months reported with 95% CI using the Greenwood formula
DOR[a]	Time from first evidence of CR or PR per RECIST v1.1 to disease progression or death due to any cause, whichever occurs first	
DoDC[a]	Time from first dose of tarlatamab to disease progression or death due to any cause, whichever occurs first. DoDC will be calculated only for patients with a best overall response of CR, PR, or SD	
OS	Time from first dose of tarlatamab to death due to any cause. Patients still alive were censored at the date last known to be alive or the analysis data cut-off date, whichever was earlier	

[a] Patients were censored following the censoring strategy described for PFS
Abbreviations: CI: confidence interval; CR: complete response; DC: disease control; DoDC: duration of disease control; DOR: duration of response; ORR: objective response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumours; SD: stable disease.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO)[49]

B.2.3.3 Trial enrolment

The target enrolment for the interim analysis was met on 15th June 2022.[49] Overall, 222 patients were randomised (Part 1) or enrolled (Parts 2 and 3), and 220 patients received at least 1 dose of tarlatamab, including 99 patients in the 10 mg target dose group across Parts 1 and 2, 87

patients in the 100 mg target dose group in Part 1, and 34 patients in the Part 3 modified safety monitoring 10 mg target dose group.[48]

Following target enrolment, interim analyses were conducted and submitted to the Food and Drug Administration (FDA) on 5th October 2022, following which the 10 mg target dose was selected for further enrolment in the dose expansion Part 2 of the study, and enrolment for the non-selected 100 mg dose stopped. Part 3 was initiated after completion of enrolment for Part 1 and Part 2, with modified cycle 1 monitoring criteria, to evaluate safety of reduced inpatient monitoring. Hospitalisation for safety monitoring was required for 48 hours following the first 2 tarlatamab infusions in Parts 1 and 2 of the study, which was reduced to 24 hours in Part 3.

Target dose

The target dose group of relevance to this submission is the 10 mg target group, denoted as '1-> 10 mg' throughout the submission, as this is the dose of tarlatamab that is anticipated to be licensed in the UK.[1] Therefore, the evidence in this submission will solely focus on patients who received the 10 mg target dose across Parts 1 and 2. Due to the immaturity of the data from the Part 3 modified safety monitoring 10 mg target dose group, and the small patient numbers (N=34), this subgroup will not be considered in this submission.[48, 49] Results for the 100 mg Parts 1 and 2 study population, and for the 10 mg Part 3 study population are available in the DeLLphi-301 clinical study report (CSR) included in the reference pack provided alongside this submission.[49]

B.2.3.4 Baseline characteristics

A summary of patient demographics, along with other baseline characteristics, is provided in Table 6 below for the patients in the 10 mg target dose group (N=99).

The majority of patients were white (57.6%) and male (71.7%). The median age was 64.0 (35 to 82) years.[48] Clinical experts confirmed that the baseline demographics were generalisable to UK clinical practice.

Table 6: Baseline demographics of patients in the DeLLphi-301 trial (10 mg dose; Parts 1 and 2)

Demographic characteristic	1->10 mg (N=99)
Sex, n (%)	
Male	71 (71.7)
Female	28 (28.3)
Race, n (%)	
American Indian or Alaska Native	0 (0.0)
Asian	41 (41.4)
Black or African American	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)
White	57 (57.6)
Ethnicity, n (%)	
Hispanic or Latino	1 (1.0)

Not Hispanic or Latino	56 (56.6)
Multiple	0 (0.0)
Other	1 (1.0)
Age (years)	
n	99
Mean	[redacted]
SD	[redacted]
Median	64.0
Q1, Q3	[redacted]
Min, Max	35, 82
Age group, n (%)	
18 - 64 years	[redacted]
65 - 74 years	[redacted]
75 - 84 years	[redacted]
≥ 85 years	[redacted]
Region, n (%)	
North America	3 (3.0)
Europe	55 (55.6)
Asia	41 (41.4)
Rest of the world	0 (0.0)

1 -> 10 mg = 1 mg step dose to 10 mg target dose
Abbreviations: SCLC: small-cell lung cancer; SD: standard deviation.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[49] Ahn *et al*. 2023.[48]

Key baseline disease characteristics are presented in Table 7. Patients in the 10 mg target dose group had a median of 2 prior lines of therapy (LOT), including prior PD-1 or PD-L1 (72.2%) and prior radiotherapy ([redacted]%).[48, 49] Two patients were protocol violators and had not received two prior LOTs. Most patients had metastatic disease (98.0%) with no brain metastases (77.8%) or liver metastases (61.6%), and an Eastern Cooperative Oncology Group (ECOG) score of 1 (73.7%).[48] Additionally, [redacted]% of patients had Stage IV disease, representing a population of patients with a particularly high disease burden due to the level of disease progression.

Table 7: Baseline disease characteristics of patients in the DeLLphi-301 trial (10 mg dose; Parts 1 and 2)

Disease characteristic	1->10 mg (N=99)
ECOG status at baseline[a], n (%)	
0	26 (26.3)
1	73 (73.7)
Smoking history, n (%)	
Never	8 (8.1)
Current	18 (18.2)
Former	73 (73.7)
Prior lines of therapy, n (%)	
1	2 (2.0)
2	65 (65.7)

3	18 (18.2)
>3	14 (14.1)
Number of prior lines of therapy	
n	[redacted]
Mean	[redacted]
SD	[redacted]
Median	2.0
Q1, Q3	[redacted]
Min, Max	1, 6
Prior PD-1 or PD-L1, n (%)	
Yes	72 (72.7)
No	27 (27.3)
Prior radiotherapy for current malignancy, n (%)	
Yes	[redacted]
No	[redacted]
Prior surgery for current malignancy, n (%)	
Yes	[redacted]
No	[redacted]
Disease stage at screening, n (%)	
Stage 0	[redacted]
Stage I	[redacted]
Stage II	[redacted]
Stage III	[redacted]
Stage IV	[redacted]
Unknown/Missing	[redacted]
Metastatic at baseline, n (%)	
Yes	97 (98.0)
No	2 (2.0)
Platinum sensitivity, n (%)	
< 90 days	27 (27.3)
≥ 90 and < 180 days	22 (22.2)
≥ 180 days	20 (20.2)
Unknown	30 (30.3)
Brain metastases at baseline, n (%)	
Yes	22 (22.2)
No	77 (77.8)
Liver metastases at baseline, n (%)	
Yes	38 (38.4)
No	61 (61.6)

1 -> 10 mg = 1 mg step dose to 10 mg target dose

[a] 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.

[B] Platinum sensitivity is calculated as end of first line platinum therapy to date of first progression.
Abbreviations: ECOG: Eastern Cooperative Oncology Group; SCLC: small-cell lung cancer.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[49] Ahn *et al*. 2023.[48]

B.2.4 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

Analysis sets

A summary of the analysis set in DeLLphi-301 is provided in Table 8 below. Primary analysis was based on the disease response assessment by blinded independent central review (BICR) per RECIST 1.1 criteria.

Table 8: Analysis sets in DeLLphi-301

Analysis Set	Definition
Presented in the submission	
BICR Full Analysis Set **(primary analysis set)**	All patients who were randomised (Part 1) or enrolled (Part 2), received at least 1 dose of tarlatamab, and had 1 or more measurable lesions at baseline as assessed by BICR using RECIST 1.1 criteria.
Safety Analysis Set	All patients who received at least 1 dose of tarlatamab. Analysis of all safety endpoints, unless noted otherwise, were conducted on the Safety Analysis Set.
Available in the CSR	
Investigator Full Analysis Set	All patients who were randomised (Part 1) or enrolled (Part 2), received at least 1 dose of tarlatamab, and had 1 or more measurable lesions at baseline as assessed by investigator using RECIST 1.1 criteria.
Interim Efficacy Analysis Set	All patients in the Safety Analysis Set who were followed at least up to 12 weeks starting from day 1. Patients who stopped disease assessments prior to 12 weeks were included in this analysis set if the data cut-off was at least 12 weeks after their first dose date.
BICR Interim RECIST Analysis Set[a]	All Part 3 patients in the Safety Analysis Set who had an opportunity to be followed for at least 7 weeks starting from day 1, and had 1 or more measurable lesions at baseline as assessed by investigator using RECIST 1.1 criteria. Patients who stopped disease assessments prior to 7 weeks were included in this analysis set if the data cut-off was at least 7 weeks after their first dose date.
PK Analysis Set	All patients who received at least 1 dose of the tarlatamab and had at least 1 PK sample collected. These patients were evaluated for PK analysis unless the number of data points required for analysis was not enough, significant protocol deviations affected the data, or key dosing or sampling information was missing. For all study parts, the PK Analysis Set was used to conduct the analysis of PK data, unless otherwise specified
ITT Analysis Set	All patients who were randomised (Part 1) and enrolled (Part 2) according to assigned treatment dose levels during randomisation and enrolment of the study. Analyses of PRO endpoints were conducted on the ITT Analysis Set for Part 1 and Part 2. Part 3 of the study was not considered for the PRO analysis.

[a] For primary analysis, all efficacy analyses for Part 3 were based on interim RECIST analysis sets.
Abbreviations: BICR: blinded independent central review; ITT: intent-to-treat; PK: pharmacokinetics; PRO: patient-reported outcomes; RECIST: Response Evaluation Criteria In Solid Tumours.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO)[49]

Statistical analysis methods

Statistical analysis methods for the primary analysis of DeLLphi-301 are presented in Table 9.

Table 9: Statistical methods for the analysis of DeLLphi-301

Hypothesis testing, sample size, power calculation	Approximately 100 subjects (includes ~90 patients from Part 1 and ~10 patients from Part 2) were planned to be enrolled at the selected target dose. To adjust for multiplicity with an interim analysis to select a dose, a 97.5% two-sided confidence interval (CI) were used. With 100 subjects, the lower boundary of the 97.5% two-sided CIs for ORR above 15% was considered clinically meaningful based on the results of open-label studies of pembrolizumab (Chung *et al.,* 2020)[50] and nivolumab (Ready *et al.,* 2019)[51] in 3L+ SCLC (ORR of 19% and 12%, respectively). An observed ORR of more than 24% is expected for the lower boundary of the 97.5% two-sided CI to exceed 15%.
Statistical analysis	For time-to-event variables, the Kaplan-Meier (KM) estimates and corresponding two-sided 95% CIs were provided. The confidence level of 97.5% for ORR was used; for subgroup analysis, 95% CIs for objective response rate. CIs for proportions were estimated using an exact proposed by Clopper-Pearson method. KM methods were used to estimate the median and percentiles for time to event endpoints with CI calculated using the Brookmeyer and Crowley method. KM methods were used to estimate landmarks for time to event endpoints (eg, 1-year overall survival), with the Greenwood formula used to estimate the standard error used in CI calculation.
Data management, patient withdrawals	The imputation for missing or incomplete data was performed, if required.

Abbreviations: CI: confidence interval; KM: Kaplan-Meier; ORR: objective response rate; SCLC: small cell lung cancer.
Source: Amgen Data on File. DeLLphi-301 SAP (28th June 2023)[52]

B.2.5 *Critical appraisal of the relevant clinical effectiveness evidence*

A summary of the quality assessment of the DeLLphi-301 trial is presented in Table 10. DeLLphi-301 was assessed for risk of bias using the modified Downs and Blacks checklist for non-randomised trials.[53] This modified checklist contained 27 questions, covering the concepts of study reporting, external validity, bias, confounding, and power. Overall, the study scored as 'good' with a total score of 20/28, meaning the trial was associated with a low risk of bias.[54] The results from the quality assessment are presented in Table 10.

Table 10: Quality assessment of the DeLLphi-301 trial (Down and Black's checklist)

Outcomes	Score	Definition
Reporting		
Is the hypothesis /aim/ objective of the study clearly described?	1	Yes
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	1	Yes
Are the characteristics of the patients included in the study clearly described?	1	Yes
Are the interventions of interest clearly described?	1	Yes
Are the distributions of principal confounders in each group of patients to be compared clearly described?	0	Unable to determine
Are the main findings of the study clearly described?	1	Yes
Does the study provide estimates of the random variability in the data for the main outcomes?	1	Yes
Have all important adverse events that may be a consequence of the intervention been reported?	1	Yes
Have the characteristics of patients lost to follow-up been described?	1	Yes
Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	1	Yes
External Validity		
Were the patients 1asked to participate in the study representative of the entire population from which they were recruited?	1	Yes
Were those patients who were prepared to participate representative of the entire population from which they were recruited?	1	Yes
Were the staff, places, and facilities where the patients were treated, representative of the treatment most patients receive?	1	Yes
Internal Validity - bias		
Was an attempt made to blind study patients to the intervention they have received?	0	No
Was an attempt made to blind those measuring the main outcomes of the intervention?	0	No
If any of the results of the study were based on "data dredging", was this made clear?	1	Yes
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	1	Yes
Were the statistical tests used to assess the main outcomes appropriate?	1	Yes
Was compliance with the intervention/s reliable?	1	Yes

Were the main outcome measures used accurate (valid and reliable)?	1	Yes
Internal validity – confounding factors		
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	0	Unable to determine
Were study patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	0	Unable to determine
Were study patients randomised to intervention groups?	1	Yes
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was finished?	0	No
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	0	Unable to determine
Were losses of patients to follow-up taken into account?	1	Yes
Power		
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	1	Yes
Final score	**20**	

B.2.6 *Clinical effectiveness results of the relevant studies*

Summary of the clinical effectiveness of tarlatamab

- The efficacy and tolerability of tarlatamab for the treatment of patients whose disease has progressed following two prior treatments was assessed in the DeLLphi-301 trial: an ongoing, Phase II, open-label study
  - The primary endpoint of DeLLphi-301 was ORR, as assessed by BICR, with tarlatamab providing a high ORR in patients in the 10 mg target dose group of 40.4% (97.5% CI, 29.4, 52.2)
  - In the 10 mg target dose group, 1 patient (1.0%) achieved a confirmed CR and 39 patients (39.4%) achieved a confirmed PR.[48]
- Additionally, median time to response in patients in the 10 mg target dose group was 1.4 months (range: 1.1 to 2.8) and the median DOR was not reached (95% CI: 5.9, NE months)[48]
  - At the time of the June 2023 DCO, 22 of 40 responders (55.0%) in the 10 mg target dose group were still having ongoing responses (on treatment without disease progression or death), including [redacted] patients ([redacted]%) whose responses reached at least 6 months and were still ongoing[48, 49]
- At the time of the June 2023 DCO, median duration of disease control (DoDC) by BICR assessment was 6.9 months (95% CI: 5.4, 9.7)[48]
- In the 10 mg target dose group, median PFS and OS were 4.9 months (95% CI: 3.0, 6.7) and 14.3 months (95% CI: 10.8, NE), respectively[48]
- Tarlatamab was associated with improvements in patients-reported outcomes (PROs), with

clinically meaningful improvements shown in EORTC QLQ-LC13 and QLQ-C30 scores from baseline
    - Least squares mean (LSM) changes from baseline for QLQ-LC13 in patients in the 10 mg target dose group up to cycle 12 were [redacted] (95% CI: [redacted]) for cough and [redacted] (95% CI: [redacted]) for chest pain
    - At cycle 12, LSM changes from baseline in QLQ-C30 scores were [redacted] (95% CI: [redacted]) in the 10 mg target dose group
- Overall, tarlatamab is associated with a clinically meaningful ORR, disease control, DOR, median OS and PFS in patients with r/r SCLC in DeLLphi-301, corresponding to clinically meaningful improvements in health-related quality of life (HRQoL) and prolonged survival
- Taken together, these results show tarlatamab to be a highly effective treatment for patients with advanced SCLC having experienced disease progression after two prior lines of treatments, and is supported by a favourable risk-benefit profile

B.2.6.1 Primary endpoint (objective response) for Part 1 and Part 2

Objective response rate (ORR) was defined as a best overall response of either complete response (CR) or partial response (PR) per RECIST 1.1 criteria. Of the 99 patients in the BICR Full Analysis Set for Part 1 and Part 2 receiving the 10 mg target dose, 1 patient (1.0%) had a confirmed CR and 39 patients (39.4%) had a confirmed PR.[48] The ORR for these patients was 40.4% (97.5% confidence interval [CI]: 29.4%, 52.2%).[48] An overview of objective response for patients in the 10 mg target dose group is presented in Table 11 below.

Table 11: Objective response as assessed by BICR (BICR Full Analysis Set for Part 1 and Part 2; 10 mg dose)

	1->10 mg (N=99)
Best overall response[a], n (%)	
Confirmed complete response	1 (1.0)
Confirmed partial response	39 (39.4)
Stable disease	30 (30.3)
Progressive disease	19 (19.2)
Not evaluable	2 (2.0)
No post-baseline scan	8 (8.1)
Objective response rate	
n (%)	40 (40.4)
97.5% CI[b]	(29.4, 52.2)
Disease control rate	
n (%)	70 (70.7)
95% CI[b]	(60.7, 79.4)
Any tumour shrinkage, n (%)	
Yes[c]	[redacted]
At least 30% tumour shrinkage[d]	[redacted]
No	[redacted]
Missing	[redacted]

1->10 mg = 1 mg step dose to 10 mg target dose

[a] Assessment of disease response was determined based on RECIST 1.1 guidelines. [B] Exact confidence interval was calculated using the Clopper Pearson method.[c] Includes patients who had any tumour shrinkage in the target lesions at post-baseline assessment. [D] Includes patients who had at least 30% tumour shrinkage in the target lesions at post-baseline assessment.
Abbreviations: BICR: blinded independent central review; RECIST: Response Evaluation Criteria In Solid Tumours.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[49] Ahn *et al.* 2023.[48]

B.2.6.2 Secondary endpoints

Duration of response

Duration of response (DOR) among confirmed responders in the 10 mg target dose group is presented in Table 12, with a Kaplan-Meier (KM) plot of duration of response presented in Figure 2.

Duration of response was defined as the time from first evidence of CR or PR to disease progression or death due to any cause, whichever occurred first. In the 10 mg target dose group, the median time to response was 1.4 months (range: 1.1 to 2.8) and the median DOR was not reached (95% CI: 5.9, NE months).[48] The median follow-up time of response was [redacted] months.[49] Of the 40 responders in the 10 mg target dose group, 23 patients (57.5%) and 10 patients (25.0%) had a DOR of at least 6 and 9 months, respectively.[48] As of the latest DCO (27th June 2023), 22 of 40 responders (55.0%) in the 10 mg target dose group were still having ongoing responses (on treatment without disease progression or death), including [redacted] patients ([redacted]%) whose responses reached at least 6 months.[48, 49]

Table 12: Duration of response among confirmed responders as assessed by BICR (BICR Full Analysis Set for Part 1 and Part 2; 10 mg dose)

Duration of response	1->10 mg (N=99)
Number of confirmed responders	40
Patient status	
Events, n (%)	[redacted]
Death	[redacted]
Disease progression	[redacted]
Censored, n (%)	[redacted]
On study without disease progression or death	[redacted]
No evaluable post-baseline disease assessment	[redacted]
Missed 2 or more consecutive assessments	[redacted]
Started new anti-cancer therapy	[redacted]
Withdrawal of consent from study	[redacted]
Decision by sponsor	[redacted]
Lost to follow-up	[redacted]
Completed study without disease progression or death	[redacted]
Duration of response (KM) (months)[a]	
25th percentile (95% CI)	4.4 (2.8, 7.1)
Median (95% CI)	NE (5.9, NE)
75th percentile (95% CI)	NE (NE, NE)

Min, Max (+ for censored)	[redacted]
Follow-up time for DOR (KM) (months)[a]	
25th percentile (95% CI)	[redacted]
Median (95% CI)	[redacted]
75th percentile (95% CI)	[redacted]
Min, Max (+ for censored)	[redacted]
Time to objective response (months)	
Number of patients with objective response	40
Mean (SD)	[redacted]
Median	[redacted]
Q1, Q3	[redacted]
Min, Max	[redacted]
Kaplan-Meier estimate (%) (95% CI)[b]	
At 3 months	[redacted]
At 6 months	66.5 [redacted]
At 9 months	[redacted]
At 12 months	[redacted]
Observed duration of response, n (%)	
≥3 months of observed DOR	35 (87.5)
On study without disease progression or death	[redacted]
≥ 6 months of observed DOR	23 (57.5)
On study without disease progression or death	[redacted]
≥ 9 months of observed DOR	10 (25.0)
On study without disease progression or death	[redacted]
≥12 months of observed DOR	[redacted]
On study without disease progression or death	[redacted]

1->10 mg = 1 mg step dose to 10 mg target dose
[A] Median and percentiles were estimated using Kaplan-Meier method and their 95% CI were estimated using log-log transformation of KM survival estimate by Brookmeyer and Crowley (1982) method. [B] 95% CIs were estimated using Kalbfleisch and Prentice (1980) method.
Abbreviations: BICR: blinded independent central review; DOR: duration of response; KM: Kaplan-Meier; min: minimum; NE: not estimable; RECIST: Response Evaluation Criteria In Solid Tumours.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[49] Ahn *et al.* 2023.[48]

Figure 4: KM plot for duration of response as assessed by BICR (BICR Full Analysis Set for Part 1 and Part 2)

1->10 mg = 1 mg step dose to 10 mg target dose
Abbreviations: BICR: blinded independent central review; KM: Kaplan-Meier.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO)[49]

Disease control

The disease control rate was defined as the proportion of patients with a best overall response of CR, PR, or stable disease. Duration of disease control (DoDC) was defined as time from first dose of tarlatamab to disease progression or death due to any cause, whichever occurred first. Duration of disease control results as assessed by BICR are provided in Table 13. A KM plot for disease control in patients with r/r SCLC in DeLLphi-301 is presented in Figure 5.

In the 10 mg target dose group, the median DoDC by BICR was 6.9 months (95% CI: 5.4, 9.7). The Kaplan-Meier estimate of duration of disease control at 6 months was [redacted]% (95% CI: [redacted]%, [redacted]%).[48, 49]

Table 13: Duration of disease control as assessed by BICR (BICR full analysis set for Part 1 and 2; 10 mg dose)

	1->10 mg (N=99)
Number of patients with a best overall response of CR, PR or stable disease	70
Patient status	
Event, n (%)	[redacted]
Death	[redacted]
Disease progression	[redacted]
Censored, n (%)	[redacted]
On study without disease progression or death	[redacted]
No evaluable post-baseline disease assessment	[redacted]
Missed 2 or more consecutive assessments	[redacted]
Started new anti-cancer therapy	[redacted]
Withdrawal of consent from study	[redacted]
Decision by sponsor	[redacted]
Lost to follow-up	[redacted]
Completed study without disease progression or death	[redacted]
Duration of disease control (KM) (Months)[a]	
25th percentile (95% CI)	[redacted]
Median (95% CI)	6.9 (5.4, 9.7)
75th percentile (95% CI)	[redacted]
Min, max (+ for censored)	[redacted]
Follow-up time for DoDC (KM) (months)[a]	
25th percentile (95% CI)	[redacted]
Median (95% CI)	[redacted]
75th percentile (95% CI)	[redacted]
Min, max (+ for censored)	[redacted]
Kaplan-Meier estimate (%) (95% CI)[b]	
At 3 months	[redacted]
At 4 months	[redacted]
At 6 months	[redacted]

At 9 months	[redacted]
At 12 months	[redacted]

1->10 mg = 1 mg step dose to 10 mg target dose. [a] Median and percentiles were estimated using Kaplan-Meier method and their 95% CI were estimated using log-log transformation of KM survival estimate by Brookmeyer and Crowley (1982) method. [b] 95% CIs were estimated using Kalbfleisch and Prentice (1980) method.
Abbreviations: BICR: blinded independent central review; CR: complete response; DoDC: duration of disease control; KM: Kaplan-Meier; min: minimum; NE: not estimable; PR: partial response; RECIST: Response Evaluation Criteria In Solid Tumours.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[49] Ahn *et al.* 2023.[48]

Figure 5: KM plot for duration of disease control as assessed by BICR (BICR Full Analysis Set for Part 1 and Part 2)

1->10 mg = 1 mg step dose to 10 mg target dose
Abbreviations: BICR: blinded independent central review; KM: Kaplan-Meier.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO)[49]

Progression-free survival

Progression-free survival (PFS) was defined in DeLLphi-301 as the interval from the date of first dose of tarlatamab to the event of disease progression per RECIST 1.1 or death due to any cause. PFS results, as assessed by BICR, for patients receiving the 10 mg target dose are presented in Table 14, with a KM plot of results presented in Figure 6. In the 10 mg target dose group, median PFS by BICR was 4.9 months (95% CI: 2.9, 6.7), with a median follow-up time of [redacted] months.[48, 49] The percentage of patients with event of disease progression or death was 56.6% and 8.1%, respectively. The Kaplan-Meier estimates for PFS at 6 and 12 months were 40.8% and [redacted]%, respectively.[49]

Table 14: Progression-free survival as assessed by BICR (BICR Full Analysis set for Part 1 and 2; 10 mg dose)

	1->10 mg (N=99)
Number of patients who received at least 1 dose of tarlatamab	99
Patient status	
Events, n (%)	64 (64.6)
Death	8 (8.1)
Disease progression	56 (56.6)
Censored, n (%)	35 (35.4)
On study without disease progression or death	25 (25.3)
No evaluable post-baseline disease assessment	2 (2.0)
Missed 2 or more consecutive assessments	3 (3.0)
Started new anti-cancer therapy	2 (2.0)
Withdrawal of consent from study	3 (3.0)
Decision by sponsor	0 (0.0)
Lost to follow-up	0 (0.0)
Completed study without disease progression or death	0 (0.0)
Progression-free survival (KM) (months)[a]	
25th percentile (95% CI)	2.4 (1.4, 2.8)
Median (95% CI)	4.9 (2.9, 6.7)
75th percentile (95% CI)	NE (7.1, NE)
Min, Max (+ for censored)	0.0+, 13.7+
Follow-up time of progression-free survival (KM) (months)[a]	
25th percentile (95% CI)	[redacted]
Median (95% CI)	[redacted]
75th percentile (95% CI)	[redacted]
Min, Max (+ for censored)	[redacted]
Kaplan-Meier estimate (%) (95% CI)[b]	
At 3 months	58.8 (48.1, 68.1)
At 6 months	40.8 (30.6, 50.7)
At 9 months	28.5 (19.2, 38.6)
At 12 months	[redacted]

1->10 mg = 1 mg step dose to 10 mg target dose. [a] Median and quantiles were estimated using Kaplan-Meier method and 95% CI of median were estimated using log-log transformation of KM survival estimate by Brookmeyer and Crowley (1982) method. [B] 95% Cis were estimated using Kalbfleisch and Prentice (1980) method.
Abbreviations: BICR: blinded independent central review; KM: Kaplan-Meier; min: minimum; NE: not estimable; RECIST: response evaluation criteria in solid tumours.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[49] Ahn *et al*. 2023.[48]

Figure 6: KM plot for progression-free survival as assessed by BICR (BICR Full Analysis Set for Part 1 and Part 2)

1->10 mg = 1 mg step dose to 10 mg target dose
Abbreviations: BICR: blinded independent central review; PFS: progression-free survival; RECIST: Response Evaluation Criteria in Solid Tumours.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO)[49]

Overall survival

Overall survival (OS) was defined as the interval from the date of first dose of tarlatamab to the event of death due to any cause. In the 10 mg target dose group, median OS was 14.3 months (95% CI: 10.8, NE), with a median follow-up time of 10.6 months.[48] The Kaplan-Meier estimates for OS at 6 and 12 months were 73.4% and [redacted]%, respectively.[48, 49]

An overview of overall survival results for patients in the 10 mg dose group is presented in Table 15, and a KM plot of overall survival is presented in Figure 7.

Table 15: Analysis of overall survival (Safety Analysis Set)

	1->10 mg (N=99)
Number of patients who received at least 1 dose of tarlatamab	99
Patient status	
Events, n (%)	35 (35.4)
Death	35 (35.4)
Censored, n (%)	64 (64.6)
Alive at last follow-up	57 (57.6)
Withdrawal of consent from study	6 (6.1)
Decision by sponsor	0 (0.0)
Lost to follow-up	1 (1.0)
Completed study without death	0 (0.0)
Overall survival (KM) (months)[a]	
25th percentile (95% CI)	5.7 (4.7, 10.5)
Median (95% CI)	14.3 (10.8, NE)
75th percentile (95% CI)	NE (NE, NE)
Min, Max (+ for censored)	0.3+, 15.2+
Follow-up time (months)[a]	
25th percentile (95% CI)	[redacted]
Median (95% CI)	10.6 (9.2, 11.5)
75th percentile (95% CI)	[redacted]
Min, Max (+ for censored)	[redacted]
Kaplan-Meier estimate (%) (95% CI)[b]	
At 3 months	88.7 (80.5, 93.6)
At 6 months	73.4 (63.2, 81.2)
At 9 months	68.0 (57.1, 76.6)
At 12 months	[redacted]

1->10 mg = 1 mg step dose to 10 mg target dose. [a] Median and quantiles were estimated using Kaplan-Meier method and 95% CI of median were estimated using log-log transformation of KM survival estimate by Brookmeyer and Crowley (1982) method. [B] 95% Cis were estimated using Kalbfleisch and Prentice (1980) method.
Abbreviations: KM: Kaplan-Meier; min: minimum; NE: not estimable.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[49] Ahn *et al*. 2023.[48]

Figure 7: KM plot for overall survival (Safety Analysis Set)

1->10 mg = 1 mg step dose to 10 mg target dose
Abbreviations: NE: not estimable; OS: overall survival.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO)[49]

B.2.6.3 Exploratory endpoints

Analyses of patient-reported outcomes (PROs) for exploratory endpoints in DeLLphi-301 were conducted for Part 1 and Part 2. Patients were scored on multiple scales including: European Organization for Research and Treatment Of Cancer (EORTC) quality of life questionnaire lung cancer module (QLQ-LC13), subscales global health status/quality of life (QoL) and physical functioning from EORTC quality of life questionnaire core 30 (QLQ-C30).

The completion rate of all baseline PRO questionnaires was at least [redacted]% in the 10 mg target dose group. Mean baseline EORTC QLQ-LC13 scores for cough, chest pain and dyspnoea composite score were [redacted], [redacted], and [redacted], respectively, in the 10 mg target dose group.[49]

Mean baseline scores for global health status/QoL and physical function were [redacted] and [redacted], respectively, in the 10 mg target dose group and were below those for the normative sample of patients with SCLC ([redacted]). Least squares mean (LSM) changes from baseline for QLQ-LC13 up to cycle 12 were [redacted] (95% CI: [redacted], [redacted]) for cough, [redacted] (95% CI: [redacted], [redacted]) for chest pain, and [redacted] (95% CI: [redacted], [redacted]) for dyspnoea composite score in the 10 mg target dose group.[49]

LSM changes from baseline for the QLQ-C30 subscales of global health status indicated an increasing trend toward improvement. At cycle 12, LSM changes from baseline were [redacted] (95% CI: [redacted], [redacted]) in the 10 mg target dose group.[49]

B.2.7 *Subgroup analysis*

Subgroup analyses were conducted to explore the consistency of the treatment effect across subgroups as assessed by an investigator. Response was seen across all subgroups for patients with and without prior treatment with PD-1 or PD-L1 and for patients whose disease progressed <90 days, ≥90 to <180 days, and ≥180 days or had an unknown response after platinum therapy. Results from analyses across all relevant subgroups were generally consistent with BICR assessment.[49] A forest plot of the subgroup analysis of objective response rate as assessed by BICR for Part 1 and 2 are presented in Figure 8 below.

Figure 8: Forest plot of subgroup analysis of objective response rate as assessed by BICR (BICR Full Analysis Set for Part 1 and Part 2)

1->10 mg = 1 mg step dose to 10 mg target dose
Abbreviations: BICR: blinded independent central review; DLL3: delta-like ligand 3; NE: not estimable; ORR: objective response rate; PD-1: programmed cell death 1; PD-L1: programmed death ligand 1; RECIST: response evaluation criteria in solid tumours.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO)[49]

B.2.8 *Meta-analysis*

As DeLLphi-301 is the only trial for tarlatamab in patients with advanced SCLC with disease progression on or after platinum-based chemotherapy, no meta-analysis was possible.

B.2.9 *Indirect and mixed treatment comparisons*

Summary of indirect and mixed treatment comparisons

Methods

- DeLLphi-301 is a single-arm trial, meaning indirect treatment comparisons (ITCs) were required to inform the relative efficacy estimates for tarlatamab versus the relevant comparators for this submission
- Additionally, due to no common trial arms being available to conduct anchored ITCs or network meta-analyses, an unanchored matching-adjusted indirect comparison (MAIC) method was used to estimate the comparative efficacy of tarlatamab and the relevant comparators
- A UK RWE CAS study using Systemic Anti-Cancer Therapy (SACT) data was selected as the most reliable source of an external control to use as the base case. This included a population of patients with advanced SCLC receiving third line treatment and was therefore considered generalisable to those who would be expected to receive tarlatamab in UK clinical practice
- As individual patient data (IPD) were not available for the CAS Control Cohort, Kaplan-Meier OS curves were digitised, and pseudo-patient level data were created, and the matching process was performed on the IPD from DeLLphi-301 and the pseudo-IPD from the CAS Control Cohort to adjust for the imbalanced covariates and generate statistical weights
- Since no PFS data were available from the SACT datasets used in the UK RWE study, time-to-treatment discontinuation (TTD) data were used as a proxy for PFS.

Results

- In the base case OS analysis, when adjusting for clinically relevant covariates, tarlatamab was associated with a statistically significant [redacted]% lower mortality risk vs currently available treatment options with a hazard ratio (HR) of 0.367 (95% CI: 0.202, 0.667; P=0.001).
- Similarly in the analysis of PFS, tarlatamab was associated with statistically significant [redacted]% lower risk of disease progression or death vs available treatment options with an HR of 0.184 (95% CI: 0.100, 0.340; P<0.0001) following adjustment
- Two scenario analyses were conducted to explore the impact of covariate selection on OS and PFS outcomes in the MAIC. In both scenarios, similarly significant reduced mortality and progression risks for patients who received tarlatamab compared with those who received available treatment options was observed

Conclusions

- Overall, the results of the UK CAS RWE study underlined the extremely poor survival outcomes currently experienced by patients receiving third-line treatment in UK practice. The MAIC analyses demonstrated that treatment with tarlatamab results in a significantly increased OS compared with currently available treatments
- The results of the analyses performed (base case and scenarios) show a similar magnitude of incremental benefit regardless of the prognostic covariates used, thus indicating that the comparative efficacy results derived from the analysis are robust for decision-making

As discussed in Section B.2.1, an SLR was conducted was conducted in April 2022 and a subsequent update conducted in December 2023, to identify all relevant clinical evidence on the efficacy and safety of tarlatamab and potential comparators for the treatment of tarlatamab in patients with advanced SCLC with disease progression on or after platinum-based

chemotherapy. DeLLphi-301 is a single-arm trial and no head-to-head trials with available data comparing tarlatamab to the relevant comparators were identified in the clinical SLR.

Therefore, an indirect treatment comparison (ITC) was conducted to inform the comparative efficacy estimates for tarlatamab versus the relevant comparators for this appraisal. The following section provides an overview of the ITC methodology and results. Further methodological detail is provided in Appendix D.

B.2.9.1 Analysis methods

Since there are no direct comparative data for tarlatamab and no common trial arms with which to conduct anchored ITCs or network meta-analyses, unanchored methods for estimating the comparative efficacy of tarlatamab and the relevant comparator were needed. Matching-adjusted indirect comparison (MAIC) is a form of propensity score weighting (PSW) that is applicable where individual patient-level data (IPD) are available in one population while aggregate data are available in another. Individuals in the IPD population were weighted by the inverse of their propensity score to balance the covariate distribution with that of the target aggregate population. A novel approach to estimating the propensity score was taken since IPD was only available in one of the two populations.

B.2.9.2 Identification of covariates for MAIC analysis

An unanchored MAIC assumes that differences between absolute outcomes that would be observed in each study are explained by imbalances in observed prognostic variables and treatment effect modifiers. As such, MAICs requires the matching of prognostic patient characteristics to generate robust comparative treatment effect estimates. In order to identify these prognostic variables, a rigorous selection process was used to identify prognostic variables, as outlined below.

During the SLR, the scientific literature was reviewed, and a study was identified that reported the findings of a targeted literature review (TLR) conducted to identify relevant prognostic factors that could potentially be adjusted for in a MAIC for nivolumab versus historical control data in patients with SCLC in 3L.[55] The TLR identified 39 studies reporting prognostic factors for OS. Most studies were based in Europe, and seven studies were conducted in the US. Based on this TLR, a starting list of 35 candidate prognostic covariates was compiled.

These 35 candidate prognostic covariates were subsequently included in a survey of clinical experts.[56] During validation of the identified prognostic variables by UK clinical experts, three variables were considered ‘very important’ by at least two of three clinicians. These were ECOG PS, disease stage, and response to previous treatment (platinum sensitivity).[56]

In addition to this, univariate and multivariate Cox regressions were performed on the IPD from DeLLPhi-301 to screen the candidate prognostic factors for statistical significance. A p-value of ≤0.05 was used as the threshold. The analyses indicated two covariates to be significant predictors of OS: ECOG PS and presence of brain metastases, both of which were confirmed by clinical opinion to be important.

Lastly, a meta-regression analysis was performed to explore the potential relationship between population characteristics and study outcomes from SLRs of 2L and 3L+ clinical studies in patients with r/r SCLC utilising all reported evidence on specified variables independent of

timepoint of measurement. The meta-regression performed using extracted data identified five variables found to be statistically significant for at least one outcome (OS, PFS or ORR) at using an alpha value of 0.05. Factors identified as possibly predictive of outcomes included sex, treatment class, ECOG PS, line of therapy, and extensive stage (ES) disease, with age showing no evidence of impact by the crude measure used (i.e., median/mean).[57]

The base case analysis included a combination of variables deemed to be most clinically relevant (per clinical opinion) and those that were statistically significant in the meta-regression: age at diagnosis, sex, smoking, ECOG, presence of brain metastases, presence of liver metastases, chemotherapy free interval (CFI), extensive stage disease, and time from diagnosis to line of therapy (Table 16). Although age and sex were not consistently considered to be prognostic or predictive of outcomes by clinicians, the decision to adjust for them was made based on their inclusion in prior population-adjustment analyses in SCLC.[55]

Two scenario analyses relating to the included prognostic factors were performed (Table 16). Due to a missing CFI in 30% of patients in the DeLLphi-301 trial leading to the assumption that all patients with missing values had a CFI ≥ 180 days, it was considered that the inclusion of CFI in the MAIC may introduce a source of bias. Similarly, advice from clinicians was that the presence of extensive stage disease at initiation of treatment is considered a prognostic factor, but staging at diagnosis was used in the base case MAIC analysis due to lack of availability of data the RWE dataset relating to staging at initiation of 3L treatment. Therefore, scenarios that excluded CFI or excluded the presence of extensive stage disease were explored as sensitivity analyses to assess impact on the results. Full results of these two scenarios for OS and PFS are presented in Appendix D.1.7.

Table 16: Prognostic factors adjusted for in the MAIC

Prognostic variable	Base case[a]	Scenario 1	Scenario 2
Age at diagnosis (prior to first-line treatment)	✔	✔	✔
Sex (male vs female)	✔	✔	✔
ECOG PS (0 vs 1)[b]	✔	✔	✔
Brain metastases[b]	✔	✔	✔
Liver metastases[b]	✔	✔	✔
Chemotherapy-free interval (≥ 180 days)[c]	✔		✔
Chemotherapy-free interval (≥ 90 and < 180 days)[d]	✔		✔
Extensive-stage disease at diagnosis[d]	✔	✔	
Time from diagnosis to line of therapy	✔	✔	✔

[a] Deemed most clinically relevant (per clinician survey) and statistically significant in the meta-regression. Although age and sex were not consistently considered to be prognostic or predictive of outcomes by clinicians, the decision to adjust for them was made based on their inclusion in prior publications reporting MAIC analyses of SCLC patient data.
[b] At initiation of index line of treatment.
[c] At completion of first-line treatment.
[d] Only TNM stage was reported in the DeLLphi-301 trial; stage IV was assumed to be extensive-stage.
Abbreviations: CAS: Cancer Analysis System; ECOG PS: Eastern Cooperative Oncology Group performance status; IPD: individual patient-level data; MAIC: matching-adjusted indirect treatment comparison; OS: overall survival; SCLC: small cell lung cancer; US: United States.

B.2.9.3 Compatibility of DeLLphi-301 and RWE dataset in MAIC analyses

In the absence of head-to-head trials between tarlatamab and relevant comparators, real-world evidence (RWE) from the observational study conducted by Amgen using the Cancer Analysis System (CAS) dataset was used to inform the external control arm for estimating the treatment effect of tarlatamab monotherapy in DeLLphi-301 relative to available treatment options. The CAS dataset captured data on patients in England with SCLC who received systemic anti-cancer treatments (1L+) between 1st January 2013 and 31st May 2021; the MAIC analysis focused on patients receiving 3L treatment, in order to reflect the anticipated place of tarlatamab in the treatment pathway. As the CAS study uses an England-based cohort, it is expected to be generalisable to UK clinical practice, as confirmed by UK clinical experts.[41]

The CAS Control cohort used in the MAIC is a subgroup of a broader retrospective analysis that captured 17,100 eligible patients with SCLC who received at least one systemic anti-cancer therapy. For the purposes of this analysis, the CAS Control cohort refers only to the CAS subgroup in 3L, in alignment with the intended positioning of tarlatamab and the clinical evidence base from DeLLphi-301. Rationale for the choice of the UK CAS RWE study as the source of comparative efficacy evidence in the MAIC analysis are presented in Table 17.

Table 17: Rationale for selection of CAS as the external control for the MAIC analysis

Cancer Analysis Registry (CAS)
• Use of treatments (topotecan, CAV, and platinum plus etoposide) that are generally representative of treatments across different geographies and in line with published RWE studies in the US, Europe and Asia • Reported baseline demographic and clinical characteristics that included important prognostic covariates; baseline characteristics were generally similar between the DeLLphi-301 study and CAS with respect to mean age, ECOG score, disease stage, proportion of patients who had brain and liver metastases, and previous LOTs • ECOG scores were reported by LOT in CAS • Differences in Dellphi-301 vs CAS datasets included a lower proportion of female patients (27% vs [redacted]%), and a different distribution of patients who were platinum resistant (27% vs [redacted]%) or platinum sensitive (CFI ≥ 180 days) (51% vs [redacted]%), respectively.[48, 49] • No patients had received prior PD-L1 inhibitor treatment in CAS • Provides a population that has previously had platinum-based chemotherapy • Provided most effective sample size (n=540) to maximize information from the DeLLphi-301 study (97 patients), with narrower confidence intervals that increase the robustness of the MAIC HRs

Abbreviations: 3L: third line; CAV: cyclophosphamide/doxorubicin/vincristine; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; LOT: line(s) of treatment; MAIC: matching adjusted indirect comparison; PD-L1: programmed cell death ligand 1; RWE: real-world evidence; US: United States.

Estimation of progression-free survival

PFS is not always captured in real-world datasets and was not available in the CAS Control cohort. Time-to treatment discontinuation (TTD) was therefore used as a proxy for PFS. The results of the TTD analysis of the CAS control cohort are presented in Section B.2.9.6 below. Whilst the use of TTD as a proxy in the absence of PFS data in real-world settings is an established method, it is associated with the important assumption that patients discontinue solely due to disease progression. In practice, patients may discontinue for a variety of reasons, and may also continue treatment despite disease progression, if treating clinicians deem there to be clinical benefit to continuing treatment.

Censoring of patients treated beyond progression

In the DeLLphi-301 trial, some patients received treatment with tarlatamab beyond disease progression. Treatment beyond progression is not considered standard practice in the UK, as reflected by the lack of treatment past progression in the CAS RWE study and is therefore not expected to occur with tarlatamab in UK practice. This discrepancy between observed trial results and available RWE data and clinical practice was addressed in the synthesis of comparative evidence by censoring patients from the DeLLphi-301 trial who received treatment beyond the point of disease progression from the MAIC. Patients in the DeLLphi-301 trial who received treatment past progression were censored at the point of progression in the MAIC analyses of survival endpoints (OS, PFS). This approach ensures that comparative efficacy results are most reflective of anticipated clinical practice.

A further analysis is currently underway which will utilise a two-stage approach (similar to crossover adjustment) to estimate the counterfactual OS for tarlatamab patients who received treatment beyond progression, i.e. the survival outcomes for these patients if they did not receive treatment beyond progression.

B.2.9.4 Comparison of DeLLphi-301 and CAS control cohorts

Both the DeLLphi-301 and CAS Control cohorts included patients aged ≥18 years with LS or ES SCLC in 3L therapy and beyond who had ECOG PS ≤ 1 and had received prior platinum-based chemotherapy. The CAS study represents a cohort of patients receiving 3L+ treatment in real-world NHS practice, and is therefore expected to provide outcomes generalisable to the population of interest to this submission.

Baseline characteristics were generally similar between patients in DeLLphi-301 and the CAS Control cohort with respect to mean age, distribution of patients with ECOG PS of 0 or 1, number of patients diagnosed with limited-stage SCLC, proportion of patients who had brain metastases and liver metastases, and number of prior lines of therapy. Differences between the DeLLphi-301 and CAS Control datasets included a lower proportion of female patients (27% vs [redacted]%, respectively), a higher proportion of patients who had received prior PD-L1 treatment (72% vs [redacted]%, respectively), and a different distribution of patients who were platinum resistant (27% vs [redacted]%, respectively) or platinum sensitive (chemotherapy-free interval [CFI] ≥ 180 days) (51% vs [redacted]%, respectively).

A comparison of the DeLLphi-301 and CAS Control cohorts is presented in Table 18. Overall, in the context of no available comparator trial data for patients with r/r SCLC in the 3L+ setting, an ITC using DeLLphi-301 and CAS as data sources is feasible and appropriate. This approach to

estimating comparative efficacy between tarlatamab and standard of care (SOC) was validated during a 2023 UK advisory board meeting.[41]

Table 18: Comparison of DeLLphi-301 and CAS Control Cohorts

	DeLLphi-301 (N=97)	CAS Control Cohort (N=540)
Study design	Phase 2, single-arm, open-label, registrational study	Retrospective observational research study
Population	Patients with r/r SCLC who have progressed or recurred following 1 platinum-based regimen and at least 1 other line of therapy	Patients with SCLC (ICD-10 codes C34 and morphology codes 8041/3, 8042/3, 8043/3, 8044/3, 8045/3) with an incident diagnosis during the diagnostic inclusion period
Treatments in 3L	Tarlatamab 10 mg	Topotecan (40%) CAV (35%) Platinum + etoposide (20%)
PFS (months) median (95% CI)	4.9 (2.9, 6.7)	-
OS (months) median (95% CI)[c]	14.3 (10.8, NE)	[redacted]
Disease stage at diagnosis, n (%)[a]		
Stage 0	[redacted]	–
Stage I	[redacted]	–
Stage II	[redacted]	–
Stage III	[redacted]	–
Stage IV	[redacted]	–
Unknown/missing	[redacted]	–
Limited stage at diagnosis	–	[redacted]
Extensive stage at diagnosis	–	[redacted]
ECOG PS 0 at LOT initiation	25 (25.8%)	[redacted]
ECOG PS 1 at LOT initiation	74.2%	[redacted]
Presence of brain metastases at LOT initiation	22 (22.7%)	[redacted]
Presence of liver metastases at LOT initiation	37 (38.1%)	[redacted]
Prior therapies		
Mean number of prior LOTs[b]	[redacted]	[redacted]
Platinum resistant (CFI <90 days), n (%)	27 (27.3)	[redacted]
Platinum sensitive (CFI 90 to <180 days), n (%)	22 (22.2)	[redacted]
Platinum sensitive (CFI ≥180 days), n (%)	49 (50.5%)	[redacted]
Exposure to prior PD-L1 inhibitor, n (%)	72 (72.7)	[redacted]
Demographic characteristics		

	DeLLphi-301 (N=97)	CAS Control Cohort (N=540)
Age at diagnosis (years), mean (SD)	[redacted]	[redacted]
Gender (female), n (%)	26.8%	[redacted]
Time from diagnosis to index LOT (3L), days		
Mean (SD)	[redacted]	[redacted]

[a] Disease stage is presented based on the TNM staging system at diagnosis for patients in the DeLLphi-301 cohort; disease stage at initiation of therapy (0% at Stage 0 and 1; 1% [n = 1] at Stage 2; 5% [n = 5] at Stage 3; and 89% [n = 87] at Stage 4) were not used in the MAIC. Limited or extensive disease stage at diagnosis is reported for the CAS Control cohort.
[b] Two patients in DeLLPhi-301 cohort were protocol violators and had not received 3 LOTs
[c] OS is presented for patients in the ITT analysis group in the DeLLphi-301 study and 3L+ for the CAS Control study
Abbreviations: CAV: cyclophosphamide, doxorubicin and vincristine; CFI: chemotherapy-free interval; ECOG: Eastern Cooperative Oncology Group; ES: extensive stage; ITT: intention-to-treat; LOT: line of treatment; LS: limited stage; NE: not estimable; NR: not reported; PD-L1: programmed death ligand 1; PFS: progression-free survival; OS: overall survival; r/r: relapsed/refractory; SCLC: small cell lung cancer; TNM: tumour, node, metastasis.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[49] Ahn *et al*. 2023.[48]

B.2.9.5 Matching and adjusting individual patient-level data (IPD)

As patient-level data were not readily available for the CAS Control cohort, Kaplan-Meier OS curves were digitised and pseudo-patient level data were created using the algorithm of Guyot *et al*.[58] An unanchored MAIC was conducted as detailed below, using the method described by Signorovitch *et al*.[59]

As highlighted in Table 7 above, two of the 99 patients in the analysis set from the DeLLphi-301 trial violated the per protocol inclusion criteria (they had only received 1 prior line of treatment).[48] These patients were deemed not to accurately reflect treatment efficacy of tarlatamab in the population of interest, and were therefore removed from the MAIC analysis. The MAIC matching process was performed on the IPD from the remaining 97 patients in the DeLLphi-301 and pseudo-IPD from the CAS Control cohort to adjust for the imbalanced covariates and generate statistical weights. These statistical weights were then used to adjust the IPD for OS outcomes in DeLLphi-301 for their over- or under-representation relative to that observed in RWE datasets. Subsequently, the weighted DeLLphi-301 IPD (each patient was assigned a weight derived from MAIC) was combined with pseudo-IPD (each patient was assigned a weight of 1) and an HR was estimated from a weighted Cox proportional hazards model with treatment as a covariate; robust standard errors were also generated.

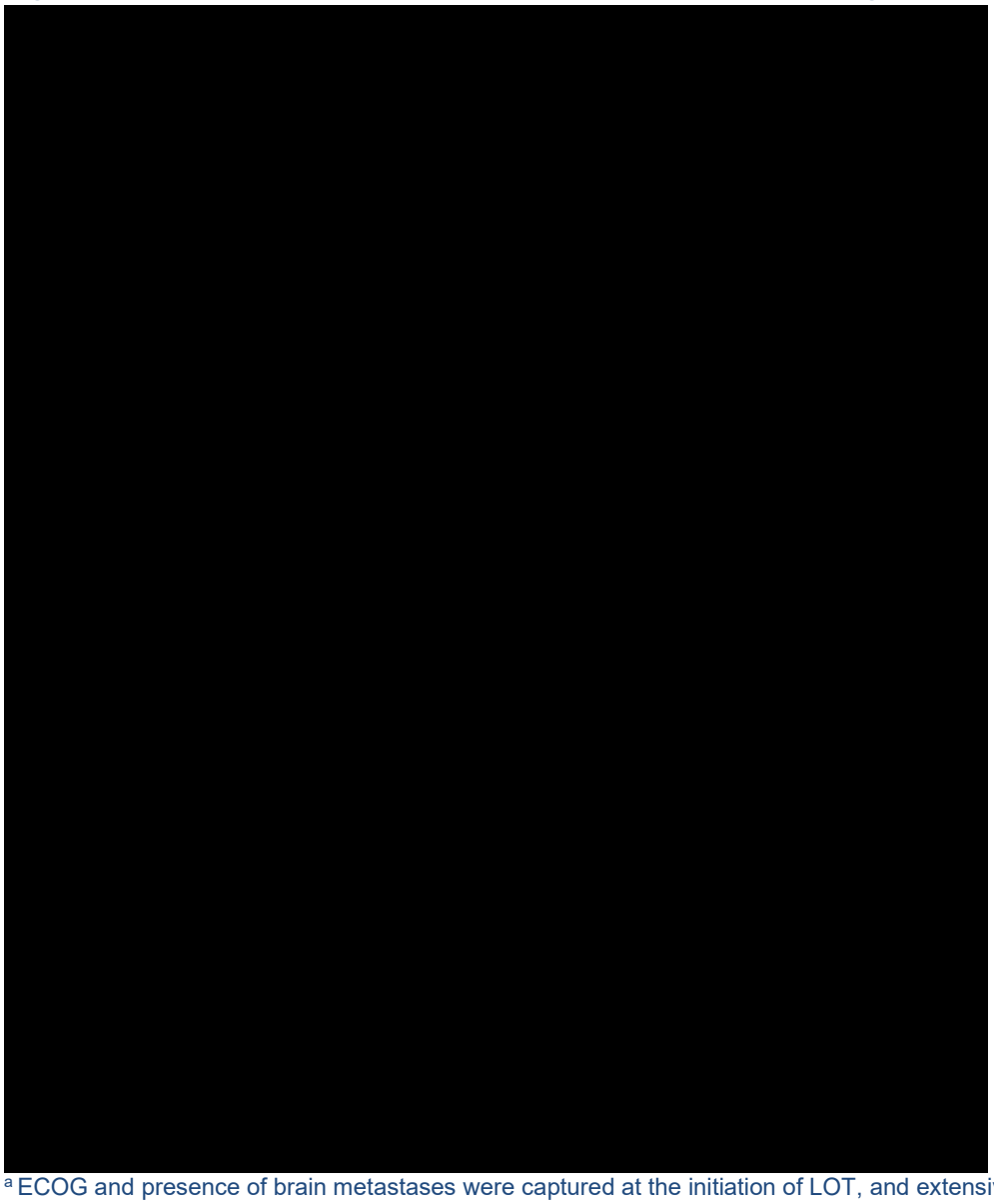
B.2.9.6 Results

Matching

A comparison of the pre- and post-matching for covariates included in the base case analysis is presented in Figure 9 below. Post-matching, covariates were well balanced, with perfect matching for the nine covariates included in the base case MAIC analysis.

The distribution of the weights is presented in Figure 10. The rescaled weights ranged from [redacted] to [redacted], with the median being skewed toward [redacted]. Application of these weights to the dataset caused the effective sample size (ESS) to decrease from 97 to [redacted].

Figure 9: Standardised mean difference before and after matching[a]



[a] ECOG and presence of brain metastases were captured at the initiation of LOT, and extensive disease stage in CAS and TNM staging in DeLLphi-301 were captured at diagnosis. Age was captured at diagnosis in the CAS dataset but at LOT initiation in DeLLphi-301.
Abbreviations: ECOG: Eastern Cooperative Oncology Group; LCI: lower confidence interval; mets: metastases; SMD: standardised mean difference; UCI: upper confidence interval.

Figure 10: Weight distribution after matching

Overall survival

A summary of the estimated treatment effect for OS for the unadjusted and the MAIC-adjusted analyses is presented in Table 19. These clinical outcomes included HR point estimates and 95% CIs derived using the weighted Cox models fitted to the MAIC-adjusted survival data for tarlatamab and available treatment options. Plots for unadjusted (unweighted) and MAIC-adjusted (weighted) Kaplan-Meier data for OS are shown in Figure 11.

OS was significantly longer with tarlatamab vs available treatment options in both the unadjusted comparison and after matching. Before matching, tarlatamab was associated with a significant [redacted]% lower mortality risk vs available treatment options with an HR of 0.278 (95% CI: 0.194, 0.399; P<0.001). Matching based on prognostic covariates resulted in a relative efficacy of tarlatamab vs available treatment options to a [redacted]% lower mortality risk (HR 0.367; 95% CI 0.202, 0.667; P=0.001). MAIC adjustments had little impact on median OS with tarlatamab: median OS was 14.3 months (95% CI: 10.8, NE) in the naïve comparison and [redacted] months (95% CI: [redacted]) in the MAIC-adjusted analysis, respectively.[48]

Table 19: Adjusted and unadjusted MAIC results for tarlatamab versus available treatment options (OS)

	ESS	HR (95% CI)	SE	p-value
Unadjusted		0.278 (0.194, 0.399)	[redacted]	<0.0001
MAIC-adjusted	[redacted]	0.367 (0.202, 0.667)	[redacted]	0.001

Abbreviations: CI: confidence interval; ESS: effective sample size; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; OS: overall survival; SE: standard error.

Figure 11: KM of the weighted and unweighted tarlatamab curve vs available treatment options (OS)

Abbreviations: KM: Kaplan-Meier; OS: overall survival.

Median OS in the UK CAS RWE study was just [redacted] months, underlining the extremely poor survival outcomes currently experienced by patients receiving third-line treatment for advanced SCLC. This extremely short survival highlights the severity of the disease, with patients experiencing a large loss of QALYs compared to general population (see Section B.3.6).

Progression-free survival

PFS is not always captured in real-world datasets and was not available in the CAS Control cohort. Time to treatment discontinuation (TTD) was therefore used as a proxy for PFS estimates for SOC in the MAIC. Whilst this approach is associated with some uncertainty, it is not expected to be associated with substantial bias, given that current practice is to treat patients until disease progression.

Results of the base case PFS MAIC analysis are presented in Table 20, with Kaplan-Meier curves for PFS are shown in Figure 12 below. These similarly indicate better PFS in the tarlatamab group relative to the comparator therapy group, both before and after adjustment for baseline differences. Median PFS in the tarlatamab group was [redacted] months (95% CI: [redacted], [redacted]) before weighting and [redacted] months (95% CI: [redacted]) after weighting. In comparison, median PFS (proxied by time to treatment discontinuation or death) in the comparator CAS cohort was [redacted] months (95% CI: [redacted], [redacted]).

Table 20: Adjusted and unadjusted MAIC results for tarlatamab versus available treatment options (PFS, base case)

	ESS	HR (95% CI)	SE	p-value
Unadjusted		0.206 (0.150, 0.282)	[redacted]	<0.0001
MAIC-adjusted	[redacted]	0.184 (0.100, 0.340)	[redacted]	<0.0001

Abbreviations: CI: confidence interval; ESS: effective sample size; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; PFS: progression-free survival; SE: standard error.

Figure 12: Kaplan-Meier curves of PFS for tarlatamab vs. comparator therapies (CAS) groups

Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival.

Scenario analyses

Two scenario analyses were conducted to explore the impact of covariate selection on OS and PFS outcomes in the MAIC, including:

- **Scenario 1:** The included covariates were all of the covariates included in the base case analysis except for minus chemotherapy-free interval (CFI; >90 days, <180 days and ≥180 days)
- **Scenario 2:** The included covariates were all of the covariates included in the base case analysis, except for presence of ES disease at diagnosis

Due to a missing CFI in 30% of patients in the DeLLphi-301 trial leading to the assumption that all patients with missing values had a CFI ≥ 180 days, it was considered that the inclusion of CFI in the MAIC may introduce a source of bias, the direction of which is unknown, and this was therefore tested in Scenario 1. Similarly, advice from clinicians was that the presence of ES disease at initiation of treatment is considered a prognostic factor, but staging at diagnosis was

used in the MAIC analysis due to lack of availability of data in the RWE dataset relating to staging at initiation of 3L treatment. The impact of this heterogeneity in definitions was tested in Scenario 2, by excluding presence of ES disease as covariate. Results of these scenario analyses, presented in detail in Appendix D.1.7, were consistent with the base case analysis, indicating the analysis to be robust to changes in covariate selection.

B.2.9.7 Uncertainties in the indirect and mixed treatment comparisons

While unanchored MAICs remove or reduce observed cross-study differences, the inability to account for all treatment effect modifiers and prognostic factors may result in residual confounding. Although a rigorous process was followed to ensure that all relevant prognostic factors were identified, in line with NICE's Decision Support Unit (DSU) Technical Support document 18 (TSD 18),[60] potential confounders could not be included in the MAIC due to a lack of availability in the CAS Control dataset or high level of missingness in the DeLLphi-301 trial.

In addition, IPD from the CAS Control dataset were not available; therefore, KM curves from the study report were used to re-create pseudo-IPD. While every effort was taken to ensure the pseudo-IPD closely matched the reported KM from the study, there are known limitations of the KM curve extraction method.[58] A key limitation is that the reported curves from the CAS Control dataset will have pooled data across different covariates that might be prognostic of survival. Given the inability to derive separate KM curves for different subgroups or to model joint effects of covariates, the risk of aggregation bias on the results could not be completely excluded from the analysis.

The presence of patients who were treated with tarlatamab past the point of progression in the DeLLphi-301 trial represents a further limitation of the analysis set, given that treatment with tarlatamab past progression is not anticipated to be common clinical practice, as its anticipated license specifies treatment to progression only. Treatment past progression with currently available third line treatments for SCLC is not common practice either. This means that the treatment benefit associated with tarlatamab may have been overestimated in the DeLLphi-301 trial as compared to expected clinical practice.

This was addressed in the MAIC analysis by application of censoring: patients who received treatment past progression in the trial were censored at the point of progression. This addresses the potential overestimation of tarlatamab treatment benefit and is therefore considered to represent a more accurate reflection of the relative treatment effect of tarlatamab. An exploratory analysis is being undertaken to adjust observed outcomes for treatment past progression which occurred during the trial, using methods similar to crossover adjustment, to avoid the limitation of the use of informative censoring in the analysis. However, whilst the currently-presented analysis in which patients are censored based on treatment past progression is associated with limitations, it is the analysis currently available that most accurately represents the expected comparative efficacy of tarlatamab and can be considered robust. This approach, coupled with baseline patient characteristics in the DeLLphi-301 trial being broadly generalisable to patients currently receiving third-line treatment in the UK, ensures that comparative efficacy results are most reflective of anticipated clinical practice.

ECOG and presence of brain metastases were captured at the initiation of LOT, and extensive disease stage in CAS and tumour, node, metastasis (TNM) staging in DeLLphi-301 were defined at diagnosis. Age was defined at diagnosis in the CAS dataset but at LOT initiation in DeLLphi-

301. While these covariates were adjusted for in the MAIC, the different points at which these covariates were captured in the datasets represents a limitation.

Masking rules that were applied to the CAS Control dataset to preserve patient anonymity may have impacted the precision of the estimates of outcomes from this study and, consequently, the resulting comparative effectiveness estimates from the MAIC. For example, masking of categorical outputs included suppression of patient numbers ≤9, rounding of all numbers above ten to the nearest ten, rounding of percentages to the nearest 5%, and replacement of minimum and maximum with 5th and 95th percentile.

Despite these inherent limitations, both scenario analyses undertaken to explore the impact of the prognostic factors that were available for inclusion resulted in consistent HRs, demonstrating the presented analyses to be robust to uncertainty relating to covariate selection.

B.2.9.8 Conclusions of the indirect and mixed treatment comparisons

In the base case (the matched analysis considering all relevant covariate selection), OS was significantly longer with tarlatamab than with available treatment options (HR 0.367 [95% CI: 0.202, 0.667]; P=0.001). Matching based on prognostic covariates essentially maintained the reduced mortality risk for patients who received tarlatamab compared with patients who received available treatment options; before matching, tarlatamab was still associated with a significant [redacted]% lower mortality vs available treatment options (HR: 0.278; 95% CI: 0.194, 0.399; P<0.001).

The base case analysis represents the most relevant analysis, as it included all potentially relevant covariates, identified through a TLR, clinician feedback, and meta-regression and multivariate analyses.[41] However, in order to consider the impact of varying the prognostic factors included, two scenario analyses were performed: CFI was removed from the adjustment in one scenario as 30% of patients in the DeLLphi-301 had missing data (scenario 1), and ES disease was not adjusted (Scenario 2), as only TNM staging was reported in the DeLLphi-301 trial, which necessitated assuming that stage IV represented ES disease in the base case analysis. In these two scenario analyses, the reduced mortality risk for patients who received tarlatamab compared with those who received available treatment options was maintained (Scenario 1: HR [redacted] [95% CI: [redacted], [redacted]], P<0.0001; Scenario 2: HR [redacted] [95% CI: [redacted], [redacted]], P<0.001).

The results of these analyses (base case, Scenario 1, and Scenario 2) show a similar magnitude of incremental benefit regardless of the prognostic covariates used, thus suggesting that the efficacy benefit of tarlatamab is consistent and there is low variability in the distribution of covariates across studies. This is further supported by the statistically significant difference in mortality before matching, and the HRs and CIs being in close alignment across the base case and scenario analyses. Together, these results indicate that the selection of prognostic factors for inclusion in the analysis is not considerably impactful on the overall results, and that tarlatamab provides an important clinical benefit over currently available 3L+ treatment options in England.

B.2.10 *Adverse reactions*

Safety analyses were conducted using the Safety Analysis Set (N=220), which included patients receiving 10 mg or 100 mg tarlatamab in Parts 1 and 2 of the trial, and 10 mg tarlatamab in the modified safety Part 3 of the trial.[48, 49] However, as discussed in Section B.2.3.3, due to

tarlatamab being anticipated to be licensed at the 10 mg dose only in the UK, along with the small patient number in the Part 3 modified safety monitoring dose group, only the 10 mg target dose group from the Safety Analysis Set in Part 1 and 2 is considered in this section (N=99).[48] Adverse events (AEs) were defined as treatment-emergent if their onset occurred after the administration of the first dose of tarlatamab and up to and including 47 days after the last dose of tarlatamab or the end of study date, whichever was earlier.[49]

B.2.10.1 Summary of the safety of tarlatamab

A summary of treatment-emergent adverse events (TEAEs) for tarlatamab in patients in the 10 mg target dose group in DeLLphi-301 is presented in Table 21. In the 10 mg target dose group across Part 1 and Part 2, 96 patients (97.0%) had at least 1 adverse event. Grade ≥3 adverse events were reported for 57 patients (57.6%), and were considered treatment-related for 29.3% of patients.[48]

Serious adverse events (SAEs) were reported for 58 patients (58.6%) in the 10 mg target dose group, with SAEs considered by the investigator to be related to tarlatamab reported for 37.4% of all patients.[48] AEs that led to discontinuation of investigational product were reported for 7 patients (7.1%).[48] Fatal AEs were reported for 3 patients (3.0%), none of which were considered by the investigator to be related to tarlatamab.[48]

Table 21: Summary of incidence of treatment-emergent adverse events (Safety Analysis Set; 10 mg Parts 1 and 2)

Treatment-emergent adverse events, n (%)	1->10 mg (N=99)
All treatment-emergent adverse events	96 (97.0)
Grade ≥2	86 (86.9)
Grade ≥3	57 (57.6)
Grade ≥4	16 (16.2)
Serious adverse events	58 (58.6)
Leading to dose interruption and/or reduction of tarlatamab	31 (31.3)
Leading to discontinuation of tarlatamab	7 (7.1)
Serious	[redacted]
Nonserious	[redacted]
Fatal adverse events	[redacted]

1 -> 10 mg = 1 mg step dose to 10 mg target dose
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[49] Ahn *et al.* (2023).[48]

B.2.10.2 Extent of exposure

As of the data cut-off date 27th June 2023, at least 1 dose of tarlatamab was administered to all patients (N=99) in the 10 mg target dose group across Part 1 and Part 2.[48] An overview of exposure to tarlatamab in the 10 mg target dose group is provided in Table 22 below.

In the 10 mg target dose group (Part 1 and Part 2), patients were treated with tarlatamab for a median of [redacted] weeks (range: [redacted] to [redacted]), with [redacted]% and [redacted]% of patients receiving ≥6 and ≥9 months of treatment, respectively. The median relative dose intensity was [redacted]%.[49]

Table 22: Exposure to tarlatamab (Safety Analysis Set; 10 mg Parts 1 and 2)

	1->10 mg (N=99)
Patients ending IP with reasons related to COVID-19, n (%)	[redacted]
Number of patients who missed at least 1 dose of tarlatamab related to COVID-19, n (%)	[redacted]
Number of doses per patient	
n	[redacted]
Mean	[redacted]
SD	[redacted]
Median	[redacted]
Q1, Q3	[redacted]
Min, Max	[redacted]
Cumulative dose (mg)	
n	[redacted]
Mean	[redacted]
SD	[redacted]
Median	[redacted]
Q1, Q3	[redacted]
Min, Max	[redacted]
Relative dose intensity (%)[a]	
n	[redacted]
Mean	[redacted]
SD	[redacted]
Median	[redacted]
Q1, Q3	[redacted]
Min, Max	[redacted]
Treatment duration (weeks)	
n	[redacted]
Mean	[redacted]
SD	[redacted]
Median	[redacted]
Q1, Q3	[redacted]
Min, Max	[redacted]
Treatment duration (months), n (%)	
≥3	[redacted]
≥6	[redacted]
≥9	[redacted]
≥12	[redacted]

1 -> 10 mg = 1 mg step dose to 10 mg target dose. [a] Relative dose intensity (%) = (Actual cumulative dose / Planned cumulative dose) x 100.
Abbreviations: IP: investigational product; min: minimum.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[49] Ahn *et al.* (2023).[48]

B.2.10.3 Most frequent treatment-emergent adverse events

An overview of TEAEs in DeLLphi-301 is presented in Table 23 below. The most frequently reported (≥20% of patients) adverse events by preferred term in Part 1 and Part 2 (10 mg target dose) were cytokine release syndrome (CRS) (49.5%), pyrexia (38.4%), constipation (28.3%), anaemia (26.3%), decreased appetite (25.3%), dysgeusia (24.2%), fatigue (21.2%) and asthenia (20.2%).[49]

Table 23: Incidence of treatment-emergent adverse events occurring in >10% of patients (Safety Analysis Set; 10 mg Parts 1 and 2)

Preferred Term, n (%)	1->10 mg (N=99)
Number of patients with treatment-emergent adverse events	96 (97.0)
Cytokine release syndrome	49 (49.5)
Decreased appetite	25 (25.3)
Pyrexia	38 (38.4)
Constipation	28 (28.3)
Anaemia	26 (26.3)
Asthenia	20 (20.2)
Dysgeusia	24 (24.2)
Fatigue	21 (21.2)
Hyponatraemia	15 (15.2)
Nausea	14 (14.1)
COVID-19	13 (13.1)
Dyspnoea	14 (14.1)
Alanine aminotransferase increased	11 (11.1)
Cough	13 (13.1)
Weight decreased	10 (10.1)
Hypokalaemia	10 (10.1)
Blood creatinine increased	10 (10.1)

1 -> 10 mg = 1 mg step dose to 10 mg target dose
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[49] Ahn *et al.* (2023).[48]

B.2.10.4 Treatment-related treatment-emergent adverse events

Treatment-related adverse events were reported for 89 patients (89.9%) in the 10 mg target dose group in Part 1 and Part 2. An overview of treatment-related TEAEs is provided in Table 24 below.[48]

The most frequently reported (≥20% of patients) treatment-related TEAEs by preferred term in Part 1 and Part 2 (10 mg target dose group) were CRS (49.5%), pyrexia (34.3%), decreased appetite (21.2%) and dysgeusia (20.2%).[49]

Table 24: Treatment-related treatment-emergent adverse events by preferred term for >5% of patients overall (Safety Analysis Set; 10 mg Parts 1 and 2)

Preferred Term, n (%)	1->10 mg (N=99)
Number of patients reporting treatment-related treatment-emergent adverse events	89 (89.9)
Cytokine release syndrome	49 (49.5)
Pyrexia	34 (34.3)
Decreased appetite	21 (21.2)
Dysgeusia	20 (20.2)
Asthenia	14 (14.1)
Fatigue	14 (14.1)
Anaemia	16 (16.2)
Constipation	12 (12.1)
Pruritus	7 (7.1)
Nausea	8 (8.1)
Alanine aminotransferase increased	9 (9.1)
Aspartate aminotransferase increased	7 (7.1)
Lymphopenia	[redacted]
Neutropenia	[redacted]
Taste disorder	8 (8.1)
Vomiting	5 (5.1)
Lymphocyte count decreased	[redacted]
Neutrophil count decreased	[redacted]
White blood cell count decreased	[redacted]
Blood creatinine increased	5 (5.1)

1 -> 10 mg = 1 mg step dose to 10 mg target dose
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[49] Ahn *et al.* (2023).[48]

B.2.10.5 Serious adverse events

The frequencies of SAEs (grade ≥3) in patients in DeLLphi-301 are presented in Table 25. Grade ≥3 adverse events were reported for 57 patients (57.6%) in the 10 mg target dose group in Part 1 and Part 2.[48] The most frequently reported (≥5% of patients) grade ≥3 adverse events by preferred term in this target dose group were anaemia ([redacted]%), lymphocyte count decreased ([redacted]%), lymphopenia ([redacted]%), fatigue ([redacted]%) and hyponatremia ([redacted]%).[49]

Table 25: Treatment-emergent grade 3 or higher adverse events for >2% of patients overall (Safety Analysis Set; 10 mg Parts 1 and 2)

System Organ Class Preferred Term, n (%)	1->10 mg (N=99)
Number of patients with grade ≥3 treatment-emergent adverse events	**57 (57.6)**
Blood and lymphatic system disorders	[redacted]
Anaemia	[redacted]
Lymphopenia	[redacted]

Neutropenia	[redacted]
General disorders and administration site conditions	[redacted]
Fatigue	[redacted]
Asthenia	[redacted]
Immune system disorders	[redacted]
Cytokine release syndrome	[redacted]
Infections and infestations	[redacted]
Pneumonia	[redacted]
Investigations	[redacted]
Lymphocyte count decreased	[redacted]
Neutrophil count decreased	[redacted]
Metabolism and nutrition disorders	[redacted]
Hyponatraemia	[redacted]

1 ->10 mg = 1 mg step dose to 10 mg target dose
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[49] Ahn *et al.* (2023).[48]

B.2.10.6 Deaths

Patient incidence of fatal treatment-emergent adverse events by system organ class and preferred term in DeLLphi-301 for the 10 mg target dose group is presented in Table 26. Fatal adverse events were reported for 3 patients (3.0%) in the 10 mg target dose group in Part 1 and Part 2.[48] [redacted] fatal adverse events by preferred term were reported for more than 1 patient in the 10 mg target dose group in Part 1 and Part 2.[49]

Table 26: Patient incidence of fatal treatment-emergent adverse events by system organ class and preferred term (Safety Analysis Set; 10 mg Parts 1 and 2)

System Organ Class Preferred Term, n (%)	1->10 mg (N=99)
Number of patients with fatal treatment-emergent adverse events	**3 (3.0)**
Cardiac disorders	[redacted]
Cardio-respiratory arrest	[redacted]
Cardiac arrest	[redacted]
Hepatobiliary disorders	[redacted]
Hepatic failure	[redacted]
Infections and infestations	[redacted]
COVID-19	[redacted]
Coronavirus infection	[redacted]
Pneumonia	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]
Aspiration	[redacted]
Dyspnoea	[redacted]
Pulmonary embolism	[redacted]
Respiratory acidosis	[redacted]
Respiratory failure	[redacted]

1 -> 10 mg = 1 mg step dose to 10 mg target dose
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[49] Ahn *et al.* (2023).[48]

B.2.10.7 Adverse events of special interest

Patient incidences for AEs of interest are summarised for the 10 mg target dose group in Table 27 below. The incidences of cytokine release syndrome (CRS), immune effector cell associated neurotoxicity syndrome (ICANS) with neurological events, neurological events, and neutropenia were summarised according to the search strategy categories using Amgen MedDRA Queries (AMQs). Preferred terms consistent with CRS events of interest were identified using AMQ (broad and narrow) search criteria; ICANS and associated neurological events were based on select preferred terms with AMQ broad search; neurological events were identified using nervous system disorders SOC and psychiatric disorders SOC; and neutropenia events of interest were identified using AMQ (broad and narrow) search criteria.[49]

The most common AEs of special interest were CRS (49.5%) and neurological events ([redacted]%). Neutropenia was seen in [redacted]% of patients and ICANS were reported in 7.1% of patients in the 10 mg target dose group.[48, 49]

Table 27: Summary of patient incidence of treatment-emergent adverse events of interest (Safety Analysis Set; 10 mg Parts 1 and 2)

Event of Interest, n (%)	1->10 mg (N=99)
Cytokine release syndrome (AMQ narrow search)	
All treatment-emergent adverse events	**49 (49.5)**
Grade ≥2	[redacted]
Grade ≥3	**0 (0.0)**
Immune effector cell associated neurotoxicity syndrome and associated neurological events (AMQ broad search)	
All treatment-emergent adverse events	**7 (7.1)**
Grade ≥2	[redacted]
Grade ≥3	[redacted]
Neurological events (nervous system disorders [SOC] + psychiatric disorders [SOC])	
All treatment-emergent adverse events	[redacted]
Grade ≥2	[redacted]
Grade ≥3	[redacted]
Neutropenia (AMQ narrow search)	
All treatment-emergent adverse events	[redacted]
Grade ≥2	[redacted]
Grade ≥3	6 (6.1)

1 ->10 mg = 1 mg step dose to 10 mg target dose
Abbreviations: AMQ: Amgen MedDRA query; SOC: system organ class
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[49] Ahn *et al.* (2023).[48]

B.2.11 *Ongoing studies*

DeLLphi-301 is the only ongoing study of tarlatamab in patients of relevance to this submission: those with advanced SCLC with disease progression on or after two or more prior lines of therapy. The only other ongoing study of tarlatamab is the DeLLphi-304 study, in which recruited patients have received one previous line of chemotherapy and tarlatamab is used second-line. This indication is not relevant to this submission.

B.2.12 *Interpretation of clinical effectiveness and safety evidence*

Principal findings from DeLLphi-301

The pivotal evidence for tarlatamab in this submission is provided by the DeLLphi-301 trial, an ongoing, Phase II, open-label study in patients with r/r SCLC following one platinum-based regimen and at least one other line of therapy.[49]

Tarlatamab provided an ORR in patients in the 10 mg target dose group of DeLLphi-301 of 40.4% (97.5% CI: 29.4, 52.2).[48] Among responders, median DOR in the 10 mg target dose group was 1.4 (range: 1.1 to 2.8) months and the median DOR was not reached (95% CI: 5.9, NE) months. In the 10 mg target dose group, median PFS by BICR was 4.9 months (95% CI: 3.0, 6.7) and median OS was 14.3 months (95% CI: 10.8, NE).[48] Overall, tarlatamab is associated with a clinically meaningful ORR, disease control, DOR, median OS and PFS in patients with r/r SCLC in DeLLphi-301, corresponding to clinically meaningful improvements in HRQoL and prolonged survival.[49]

Generalisability of DeLLphi-301 to clinical practice in England

Results from DeLLphi-301 can be considered generalisable to a patient population with SCLC in the 3L+ setting in UK clinical practice. Similar to the population of patients expected to receive tarlatamab in real-world, the majority of the patients were male and White or Asian, smoked or had a history of smoking, had a median age of 64 years, and had PRO scores that were aligned with normative values in patients with SCLC.[48] In addition, as patients had ECOG PS ≤1, received prior platinum-based chemotherapy and PD-L1 therapy, and had treated and stable brain metastases, the DeLLphi-301 study cohort represents a 3L+ SCLC population who has received SOC and can receive active systemic therapy.

As the populations in DeLLphi-301 and the real-world studies were generally equivalent as discussed further below, the improved outcomes with tarlatamab versus available treatments may be due to its novel mechanism of action. Downregulation of MHC class I is a mechanism of immune escape for some agents, including PD-L1 inhibitors,[61] whereas tarlatamab targets DLL3 and does not rely on the presentation of MHC class I antigen.[48] This mechanism of action may make tarlatamab particularly relevant in the treatment of SCLC.

Strengths and limitations of the clinical evidence base

Due to single-arm nature of DeLLphi-301, no direct comparative evidence is available. However, to determine the relative treatment effect of tarlatamab versus current treatment options, a MAIC versus the most comprehensive and generalisable real-world cohort available was developed, with appropriate adjustment for potential differences in patient selection. This real-world cohort used to inform the comparator arm of the MAIC was a UK-based RWE study (CAS) of SCLC patients receiving tarlatamab in UK clinical practice who had received at least one systemic anti-

cancer therapy, and it included a subgroup of patients who had received at least two prior therapies. Consequently, this subgroup in the CAS study is in full alignment with the target population for tarlatamab in this submission, and thus these patients are expected to be generalisable to patients eligible to receive tarlatamab in typical UK clinical practice.

Results from the MAIC provide compelling evidence that tarlatamab is more effective than relevant current treatment options. Whilst it is not possible to remove all possible residual confounding associated with such analyses, sensitivity analysis of the MAIC confirmed the strong treatment effect of tarlatamab. These highly encouraging comparative efficacy results can therefore be expected to be applicable to routine clinical practice in the UK, should tarlatamab reimbursed for routine commissioning. Alongside this, results from the DeLLphi-301 trial demonstrate that tarlatamab is well tolerated, and results in an increase in HRQoL over time, therefore fulfilling the high unmet need in patients with advanced SCLC.

Overall summary

Compelling evidence of tarlatamab treatment benefit for patients with advanced SCLC was demonstrated in the DeLLphi-301 study with an unprecedented level of response and DOR leading to a life extension for patients never seen before in this disease.[49] A MAIC demonstrated a significant OS benefit of tarlatamab over available treatment options. In addition, tarlatamab treatment resulted not only in extension of life, but in improvement in symptomatic control and overall HRQoL with limited toxicity in the DeLLphi-301 trial, an extremely valuable outcome to patients at this stage of their disease.

Tarlatamab was well tolerated, with an acceptable and manageable safety profile. Based on the mechanism of action of tarlatamab as a T-cell immunotherapy, CRS and ICANS were considered AEs of interest. These events are predictable, occurred during the first cycle, and were managed with conventional supportive care. Grade 3 or higher CRS was rare, occurring in only one patient, and there were no Grade 3 or above ICANS events. Rates of discontinuation and more serious interventions were infrequent. Therefore, enabling access to tarlatamab is expected to lead to a significant improvement in the lives of patients and a transformational change in the management of patients with SCLC having experienced disease progression following two or more prior treatments.

B.3 Cost effectiveness

B.3.1 *Published cost-effectiveness studies*

B.3.1.1 Published economic analyses

A targeted literature review (TLR) was conducted to identify economic models pertaining to interventions used for relapsed SCLC to identify previously-used model structures, methods and outcomes used in relapsed 3L+ SCLC. The literature review followed methodological and reporting requirements specified by the PRISMA statement.[62, 63]

Comprehensive search strategies were developed using terms encompassing the population interventions, comparators, outcomes, and study design (PICOS) criteria described in Table 28.

Table 29Searches were conducted using the Embase and MEDLINE databases via the Ovid platform. The searches were performed on April 19, 2023.

The bibliographies of relevant systematic reviews identified through the database searches were cross-referenced against both the results of the database searches and the final inclusion list to ensure no relevant studies were missed. Publications identified through this process were eligible for inclusion if they met all PICOS criteria.

All records were screened by one reviewer and validated by an independent reviewer at both the title/abstract and full-text levels, with conflicts resolved by a third, independent reviewer. The study selection process followed the pre-defined PICOS criteria. Reasons for exclusion were recorded for both screening phases.

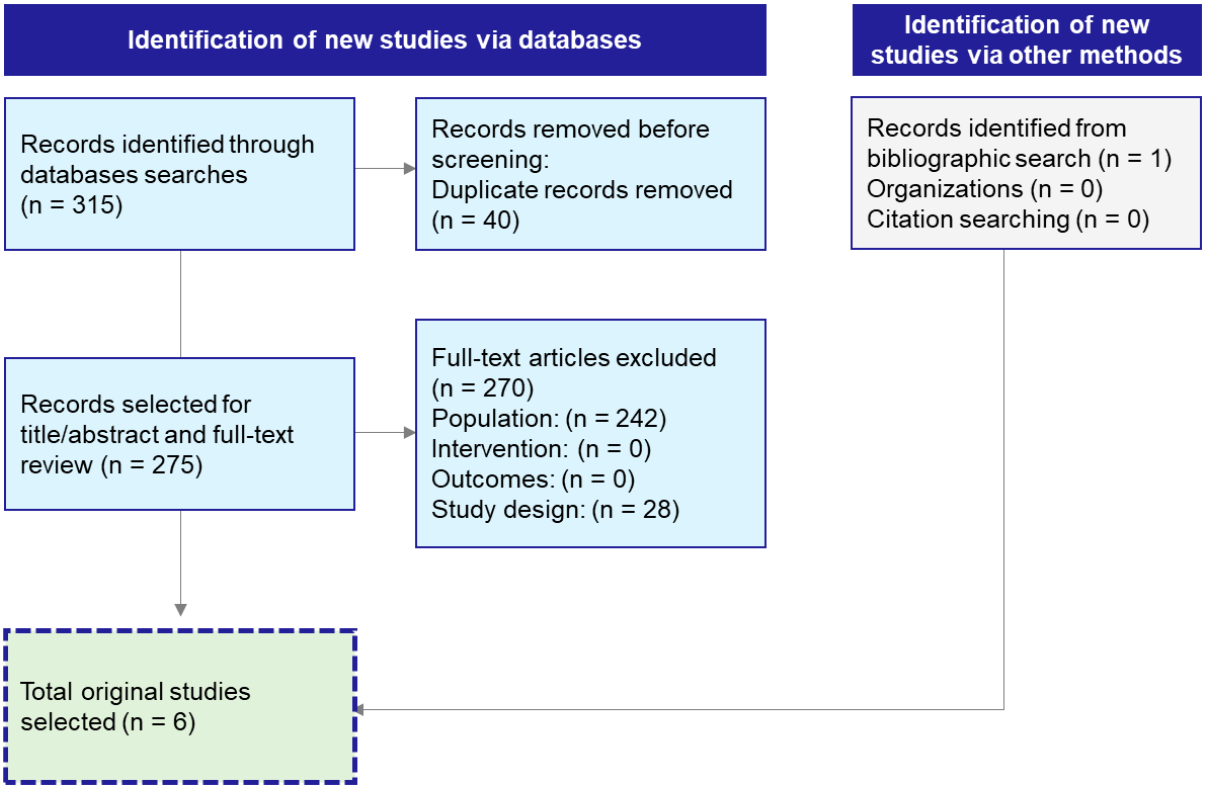
Table 28: Inclusion and exclusion criteria for the economic evaluation TLR

	Inclusion criteria	Exclusion criteria
Population	Patients with relapsed SCLC	• Non-human • Patients without relapsed SCLC
Interventions and comparator(s)	No restriction	N/A
Outcomes	• Model summary (including perspective, time horizon, cycle length, and discounting) • Model type (Markov, decision tree, partitioned survival, microsimulation) • Model structure • Sensitivity analysis (deterministic, probabilistic, scenario analysis) • Model results (QALY, ICER)	Studies not including at least one of the outcomes of interest
Study design	• Cost-consequence • Cost-minimisation • Cost-effectiveness • Cost-utility • Budget impact	• Non-human studies or pre-clinical studies • Non-interventional studies
Other restrictions	Less than 10 years prior to search	More than 10 years prior to search

Abbreviations: N/A; not applicable.

The database searches returned 315 records, 275 of which were selected for title/abstract and full-text review, leading to the inclusion of five publications based on the review's full eligibility criteria. A further publication was identified via the bibliographic search, for a total of six identified original studies identified. The PRISMA diagram for the literature review is shown in Figure 13.

Figure 13: PRISMA diagram of published cost-effectiveness studies



Six economic models were identified by the TLR;[64-70] three originated from China,[65-67] two were from the US,[64, 68] and one was from the UK.[69, 70] All studies reported an incremental cost per QALY.

Two model types were used across the studies; state-transition (Markov) models (n=3)[65-67] and PSMs (n=3).[64, 68-70] All models used the same health states; progression free (PF), progressed disease (PD) and death. Where studies derived health state utility values from previously published studies, the PF state varied from 0.673 to 0.804 and PD from 0.321 to 0.473. Two studies used mean EQ-5D utility values from the CheckMate 032 trial (PF, 0.791; PD, 0.786). Two of the three models that included topotecan as a comparator reported on patients receiving 2L treatment.[66, 69, 70] Two models used a lifetime time horizon (20 years).[64, 68] Two used a 5-year time horizon[65, 70] and one used a 4-year time horizon;[67] one model did not report this information.[66] An overview of the characteristics of studies identified by the TLR is presented in Table 29.

Table 29: Summary list of published cost-effectiveness studies

Study	Country	Population	Model Type	Perspective	Health States	Time Horizon	Cycle Length	Sensitivity analyses	Utility source	Comparators
Roth et al, 2020[64]	US	3L+ advanced (stage IIIB/IV) relapsed SCLC	PSM	US payer	PF, PD, and death	Lifetime (20 years)	14 days	PSA and scenario analysis	Trial	Immunotherapy (nivolumab) vs standard cytotoxic therapy (usual care and topotecan)
Gong et al, 2021[65]	China	3L+ relapsed SCLC	Markov	Chinese society	PF, PD, and death	5 years	One month	One-way and PSA	Published studies	Anlotinib vs placebo
Zhou et al, 2018[66]	China	2L sensitive relapsed SCLC	Markov	Chinese cost-effectiveness	PF, PD, and death	Not reported	One month	One-way and PSA	Published studies	Cisplatin, etoposide, and irinotecan vs topotecan alone
Fei et al, 2023[67]	China	3L relapsed SCLC	Markov	Chinese healthcare system	PF, PD, and death	4 years	3 weeks	Scenario analysis and PSA	Published studies	Anlotinib vs pembrolizumab and nivolumab
Smare et al, 2021[68]	US	3L relapsed SCLC	PSM	US payer	PF, PD, and death	Lifetime (20 years)	One week	DSA and PSA	Trial	Nivolumab monotherapy vs topotecan or other 3L treatments[a]
Hartwell et al, 2011[69] and Loveman et al, 2010[70] [	UK	2L sensitive relapsed SCLC	PSM	NHS and PSS	Relapsed SCLC, PD death	5 years	3 weeks	DSA and PSA	Published studies	Topotecan plus BSC vs BSC alone

[a] Paclitaxel, gemcitabine, irinotecan, docetaxel, carboplatin + etoposide, carboplatin + paclitaxel, carboplatin + irinotecan, cyclophosphamide + doxorubicin + vincristine, etoposide + paclitaxel + topotecan

Abbreviations: 2L: second line; 3L: third line; BSC: best supportive care; DSA: deterministic sensitivity analysis; IV: intravenous; NHS: National Health Service; PD: progressive disease; PF: progression free; PSA: probabilistic sensitivity analysis; PSM: partitioned survival model; PSS: Personal Social Services; QALY: quality-adjusted life year; SCLC: small-cell lung cancer; UK: United Kingdom; US: United States

B.3.1.2 HTA search

A review was conducted to identify submissions for previously untreated ES-SCLC and relapsed/refractory SCLC to several HTA agencies, including NICE, CADTH, and PBAC as well as submissions to the Institute for Clinical and Economic Review (an independent nonprofit organization based in Boston, MA, US). There were a limited number of submissions for relapsed SCLC; therefore, 1L SCLC therapies were included in this assessment.

The review identified two NICE submissions, one 1L SCLC and one relapsed SCLC. There were three CADTH submissions, of which two were 1L SCLC and one was relapsed SCLC. Three submissions to PBAC were identified, and similarly as to CADTH, two were in 1L SCLC and one was for relapsed/refractory SCLC. No SCLC submissions to the Institute for Clinical and Economic Review were identified.

A 3-health state partitioned survival model (PSM) was the most used (n = 5) model structure in SCLC, meaning that efficacy was modelled using PFS and OS. Limited information were available on utility values as they were either redacted or not reported in most submissions. However, the topotecan NICE submission (TA184) assumed a baseline utility of 0.7 and used a three-month-stepwise decrement to derive utility over time instead of modelling utility per health state. Most of the 1L therapies (atezolizumab, topotecan, durvalumab and lurbinectedin) were compared against platinum-based chemotherapies (e.g., cisplatin and carboplatin) and required indirect treatment comparisons to compare against available treatment options. Reporting on indirect treatment comparisons was limited and was usually performed as a naïve comparison. The key criticism across the HTA agencies was uncertainty on OS. The outcomes of HTA appraisals are summarised in Table 30 - Table 32.

Table 30: Overview of published NICE STAs in SCLC

Drug	Population*	Published Year	Model Type	Comparators	Time Horizon	Perspective	Cycle Length
Atezolizumab (TA638)[14]	Previously untreated ES-SCLC	2020	PSM	Chemotherapy (carboplatin-etoposide)	Lifetime (20 years)	UK NHS and PSS	1 week
Topotecan (TA184)[43]	Relapsed SCLC	2009	Survival model	Best-supportive care	Lifetime (5 years)	UK NHS and PSS	21 days

*Adult population. Notes: Platinum-based anticancer drugs include cisplatin, carboplatin, oxaliplatin, nedaplatin, and lobaplatin.[71] TA662 (durvalumab in previously untreated ES-SCLC) was withdrawn (durvalumab, TA662),[71] whereas TA184 (topotecan in relapsed SCLC) only has summary data.[43]
Abbreviations: ES: extensive stage; NHS: National Health Service; PSM: partitioned survival model; PSS: Personal Social Services; SCLC: small-cell lung cancer; TA: technology appraisal; UK: United Kingdom.

Table 31: Overview of published CADTH HTAs in SCLC

Drug	Population*	Recommendation	Published Year	Time Horizon	Model Type	Comparators	Cycle Length
Atezolizumab (resubmission)[72]	Previously untreated ES-SCLC†	Reimburse with clinical criteria and/or conditions	2021	1 year	Cost minimization model	Durvalumab + platinum-based	3 weeks‡

Drug	Population*	Recommendation	Published Year	Time Horizon	Model Type	Comparators	Cycle Length
						chemotherapy + etoposide	
Lurbinectedin[73]	SCLC with 1 prior chemotherapy-containing line of therapy	Do not reimburse	2022	Lifetime (25 years)	PSM	IV topotecan Carboplatin + etoposide A mixture of post-platinum systemic therapies	3 weeks‡
Durvalumab[74]	Previously untreated ES-SCLC	Reimburse with clinical criteria and/or conditions	2020	Lifetime (10 years)	PSM	Etoposide with either carboplatin or cisplatin	1 week

*Adult population. † Chemotherapy-naïve for their ES disease. ‡Not explicitly mentioned, assumption based upon dosing schedule. **Abbreviations**: ES, extensive stage; IV, intravenous; PSM, partitioned survival model; SCLC, small-cell lung cancer

Table 32: Overview of published PBAC HTAs in SCLC

Drug	Population*	Recommendation	Published Year	Time Horizon	Model Type	Comparators	Cycle Length
Durvalumab[75]	Previously untreated ES-SCLC	Recommended	2020	NA	Cost-minimization model	Atezolizumab + etoposide	NA
Atezolizumab + carboplatin or carboplatin + etoposide[76]	Previously untreated ES-SCLC	Rejected	2019	5 years	3-state PSM	Platinum-based chemotherapy (CE + placebo)	1 week
Topotecan[77]	Relapsed or refractory SCLC	Rejected	2010	4.98 years (71 cycles)	Stepped analysis	BSC	21 days

*The population was not specified whether it was specific to adults or not.
Abbreviations: BSC, best supportive care; ES, extensive stage; NA, not applicable; PSM, partitioned survival model; SCLC, small-cell lung cancer

B.3.1.3 Implications for health economic model

The findings from the TLR and the search of relevant HTA submissions demonstrated that a 3-health-state PSM with a 3-week cycle length was the most frequently used. Given the data maturity of DeLLphi-301, the life expectancy of patients with 3L+ SCLC, and the lack of head-to-head clinical trial or real-world data for tarlatamab, the OS and PFS of tarlatamab and its

comparators were informed by DeLLphi-301 and SACT respectively. Given that no external data could be leveraged to inform the post-progression health state of a state-transition (Markov) model, and that no post-progression data were available for comparators (only OS and TTD as a proxy for PFS), a PSM was deemed to be the most appropriate choice to address the decision problem.

Treatment guidelines and treatment patterns identified in the SACT study informed the choice of comparators used in the model. These included:

- Platinum-based chemotherapy
- Topotecan
- Cyclophosphamide + doxorubicin + vincristine (CAV)

B.3.2 *Economic analysis*

Given that none of the cost-effectiveness analyses (CEAs) identified in the economic SLR included tarlatamab as a comparator, it was necessary to generate a *de novo* economic model for the purposes of this submission. The objective of the economic model was to assess the cost-effectiveness of tarlatamab for the treatment of patients with advanced SCLC after two or more lines of therapy versus the comparators specified in the company decision problem outlined in Table 1 in Section B.1.1.

The clinical data used to support the base case analysis are from two main sources, including:

- DeLLphi-301 (described in Section B.2.2): a single-arm, Phase II study of tarlatamab in patients with SCLC with at least one prior line of therapy, although data included in this submission are for patients with at least two prior lines of therapy only
- A MAIC (described in Section B.2.9) which compared outcomes for tarlatamab patients from DeLLphi-301 with those of patients receiving SoC from a real-world UK dataset (NHS SACT)

B.3.2.1 Patient population

[redacted], the modelled patient population represented adult patients with r/r SCLC after two or more prior lines of treatment. The model population was consistent with the population enrolled in derived from the pivotal clinical trial - DeLLphi-301 (NCT05060016) (see Section B.2.3).This is consistent with the NICE scope and decision problem (see Table 1, Section B.1.1) and the population of patients included in the DeLLphi-301 study. This is restricted from the anticipated UK marketing authorisation for tarlatamab, which is expected to include patients with advanced SCLC who have received one or more prior lines of therapy. The reason for this restriction is described in Section B.1.1.

The characteristics of patients in the base case cohort reflected those of the patients who were randomised to the 10 mg Q2W dose of tarlatamab in the DeLLphi-301 study (Part 1 and Part 2 patients), adjusted by the weighting applied by the MAIC. Only patients who received two or more prior lines of therapy were included (n=97, down from n=99 in the ITT population).

B.3.2.2 Model structure

Justification of model structure

A partitioned survival model (PSM) with a lifetime time horizon was developed to determine the cost-effectiveness of tarlatamab versus SoC, as defined in the decision problem for patients with advanced SCLC who have received two prior lines of therapy (Section B.1.1). PSMs are a well-established method of modelling solid tumours. The PSM approach has several advantages over alternative approaches, including:

- OS and PFS data from the DeLLphi-301 study and the MAIC can be used directly in the model
- Parametric survival models allow for flexibility in the time-varying hazard functions to be modelled, unlike a state-transition model which would require a semi-Markov structure (multiple transition matrices) to allow for changing probabilities over time

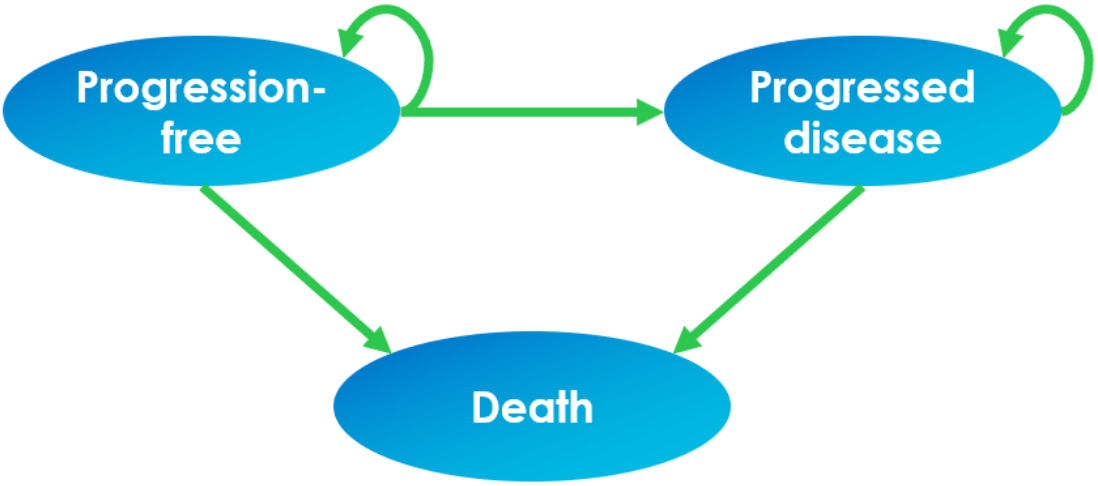
Model structure description

The model structure was similar to those used in prior NICE STAs for solid tumours. The model incorporated three mutually-exclusive health states:

- Progression-free survival
- Progressed disease
- Death

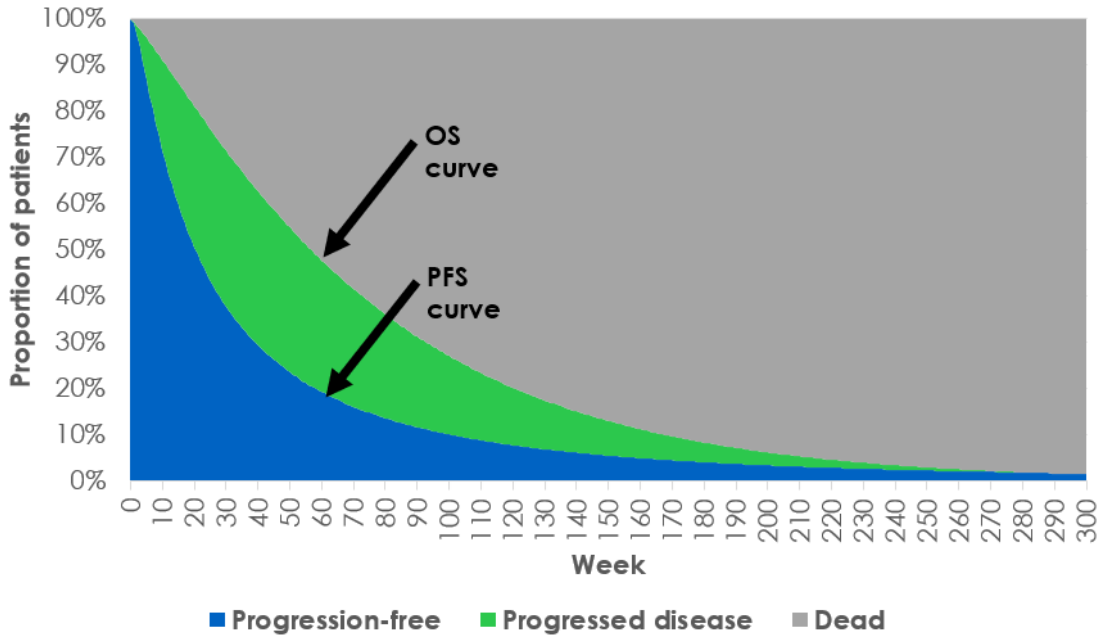
A diagram of the model structure is presented below in Figure 14. Patients started in the "progression free" health state, and were able to either remain in that state, or were able to transition from the "progression-free" health state to the "progressed disease" or "death" health states. Patients in the "progressed disease" health state were able to remain as "progressed" or transition to the "death" health state.

Figure 14: Model structure diagram



Health state occupancy was determined by the relationship between the OS curves and PFS curves modelled for each comparator as shown in Figure 15. The PFS curve was used to directly estimate the proportion of patients in the progression-free health state. The proportion of patients who were dead at any given timepoint was calculated by using the inverse probability of the OS curve at that timepoint, i.e. if 90% of patients were alive at a given timepoint, 10% were dead. The progressed disease health state occupancy was derived as the proportion of patients who were neither progression-free nor dead. Costs, life-years (LYs) and quality-adjusted life years (QALYs) were estimated according to the proportion of patients in the progression-free and progressed disease health states over time. The model was developed in Microsoft Excel®.

Figure 15: Health state occupancy and relationship with OS and PFS curves



Abbreviations: OS: overall survival; PFS: progression-free survival.

Time horizon and cycle length

The base case time horizon was 10 years. This was selected as it was deemed long enough to capture all important differences in costs or outcomes between the intervention and comparators as per the NICE health technology evaluation manual.[78] After 10 years, under base case assumptions, [redacted]% of the patients in the tarlatamab arm were predicted to be dead. Therefore, a 10-year time horizon was determined to correspond to a lifetime projection.

Model perspective and discounting

The economic analysis uses an NHS and Personal Social Services (PSS) public payer perspective, with the societal perspective not being considered. Caregiver disutility was also not modelled. Both costs and outcomes were discounted at 3.5%. These approaches are in line with guidance published in the NICE health technology evaluation manual.[78]

Outcomes

The economic analysis estimated both disaggregated and total costs and clinical outcomes for tarlatamab and available treatment options. Outcomes included: costs for drug acquisition, drug administration, subsequent treatment, monitoring, management of AEs, and terminal care. The health outcomes included LYs and QALYs. Incremental costs and clinical outcomes were then used to determine the cost-effectiveness of tarlatamab compared with available treatment options via calculation of an ICER. The model results are reported for both discounted and undiscounted scenarios.

Features of the economic analysis

A search of previous NICE TAs was performed via the NICE website to identify previous economic evaluations in SCLC. Two previous NICE STAs in SCLC were identified – one in first-

line SCLC (TA638) and another in relapsed SCLC (TA184).[14, 43] A comparison of the features of the economic analysis in the previous appraisals identified and this appraisal are outlined in Table 33 below.

Table 33: Features of the economic analysis

Factor	Previous appraisals		Current appraisal	
	TA184[14]	TA638[14]	Chosen values	Justification
Year published	2009	2020	N/A	N/A
Population	Relapsed SCLC patients considered unsuitable for further chemotherapy	Previously untreated ES-SCLC	Patients with SCLC who have had two prior lines of therapy	Representative of population in DeLLphi-301 trial
Intervention	Topotecan	Atezolizumab with carboplatin and etoposide	Tarlatamab	N/A
Comparator(s)	Best supportive care	Carboplatin with etoposide	Topotecan, CAV, platinum-based chemotherapy	Based on real-world treatment patterns identified in SACT database
Model structure	PSM	PSM	PSM	Trial outcomes and hazard function
Time horizon	Lifetime (5 years)	Lifetime (20 years)	Lifetime	Necessary to capture all costs and benefits
Treatment waning effect?	None considered	None considered	None considered	No evidence of treatment waning in DeLLphi-301
Source of utilities	O'Brien et al, 2006[79]	IMpower133 study (data on file)	DeLLphi-301 trial	Highest-quality data source available
Source of costs	BNF; NHS Schedule of Reference Costs; Southampton University Hospitals Trust	CMU eMIT; BNF; NHS Schedule of Reference Costs	CMU eMIT; BNF; NHS Schedule of Reference Costs	As per NICE reference case

Abbreviations: BNF: British National Formulary; CAV: cyclophosphamide, doxorubicin and vincristine; CMU: Commercial Medicines Unit; CSR: Clinical Study Report; eMIT: electronic Market Information Tool; ERG: Evidence Review Group; ES: extensive-stage; PSM: partitioned survival model; SACT: systemic anti-cancer therapy; SCLC: small-cell lung cancer.

B.3.2.3 Intervention technology and comparators

Intervention included in the model

The intervention in the analysis was tarlatamab, as per the Company decision problem (described in Section B.1.1). Tarlatamab is a novel half-life extended (HLE) bispecific T-cell engager (BiTE®) molecule designed to direct T effector cells toward DLL3-expressing cells, with a tandem single chain fragment crystallizable (scFc) moiety for extended half-life. The

pharmacological effect of tarlatamab is mediated by specific redirection of previously primed cytotoxic cluster of differentiation (CD)3-positive T lymphocytes to kill DLL3-expressing cells. The dose of tarlatamab used in the model was consistent with the draft Summary of Product Characteristics; tarlatamab was administered as a 60-minute IV infusion with a step-up dose of 1 mg on Cycle 1 Day 1, followed by a 10 mg target dose on Day 1, Day 8 and Day 15, and every two weeks (Q2W) thereafter (i.e. in Cycle 2, 10 mg of tarlatamab was administered on Day 1 and Day 15) in a 28-day treatment cycle.[1] The model assumed that hospitalisation was required for 24 hours post-infusion on Cycle 1 Day 1, and Cycle 1 Day 8, in line with the anticipated marketing authorisation for tarlatamab. Continued treatment with tarlatamab after radiologic disease progression is permitted in the DeLLPhi-301 trial if the investigator judged that it could provide clinical benefits to the patient. The base-case CEA model assumed no continued use of tarlatamab post-progression.

Comparators included in the model

The model included a basket of treatments as a comparator. These treatments were identified in the UK CAS historical control study. The basket of treatments was comprised of the following:

- Cyclophosphamide, doxorubicin and vincristine (CAV) (38%)
- Platinum + etoposide chemotherapy (17%)
- Topotecan (37%)
- Other (9%)

The treatments categorised as “other” were not modelled independently due to the low uptake of the individual therapies and the fact that they were not included in the final NICE scope. The proportion of treatments identified as “other” were therefore re-allocated to CAV, platinum + etoposide chemotherapy, and topotecan. The final weights used for the basket of treatments were as follows:

- CAV (38%)
- Platinum + etoposide chemotherapy (20%)
- Topotecan (42%)

The selection of the treatment regimens, in addition to the proportion of patients receiving them, was based on the most frequently observed treatments administered to patients in the UK as identified in the CAS historical control study. Table 34 provides an overview of the dosing and administration schedule of the selected comparators.

Table 34: Overview of dosing and administration schedule of comparators

Administration/dosage	CAV	Platinum + etoposide chemotherapy	Topotecan
Administration route	IV	IV	Oral
Dosage	Cyclophosphamide: 1000mg/m^2 Doxorubicin: 45 mg/m^2 Vincristine: 2mg	Carboplatin: 5mg/mL per minute Etoposide: 100mg/m^2	2.3mg/m^2 per day

Administration/dosage	CAV	Platinum + etoposide chemotherapy	Topotecan
Administration schedule	Patients were given CAV on day 1 of 21-day cycles until disease progression or unacceptable toxicity	Patients were given carboplatin on day 1 and etoposide on day 1–3 of 21-day cycles until disease progression or unacceptable toxicity	Patients were given topotecan for 5 consecutive days every 21 days until disease progression or unacceptable toxicity

Abbreviations: CAV: cyclophosphamide, doxorubicin and vincristine; IV: intravenous.

B.3.2.4 Summary of model features

For quick reference, a summary of the model features is presented below in Table 35.

Table 35: Summary of model features

Factor	Base-case features	Justification
Perspective	NICE NHS and PSS	As per the NICE reference case[78]
Time horizon	10 years	After 10 years, under base-case assumptions, over 99% of patients in the tarlatamab arm are projected to be dead. A 10-year time horizon therefore corresponds to a lifetime projection, as per the NICE reference case[78]
Cycle length	One week	Considered short enough to capture changes in health and captures the dosing schedules
Half-cycle correction	Included	In line with previous NICE appraisals of lung cancer treated with cancer immunotherapy treatments and included here to mitigate potential bias
Discount rate	3.5% annually for costs and outcomes	As per the NICE reference case[78]
Source of clinical inputs	• Tarlatamab: OS, PFS and time to TTD based on the target population from the DeLLphi-301 trial • SOC: OS, PFS and TTD based on target population in the UK CAS historical control study or assumptions	
Source of utility inputs	• EQ-5D utilities collected from the target population in the DeLLphi-301 trial • Literature values used for AE-related disutilities and age- and sex-related utility adjustment	

Factor	Base-case features	Justification
Source of cost inputs	• BNF • Electronic market information tool (eMIT) • NHS England Payment Scheme • NHS Reference Costs • PSSRU • Literature	
Model outputs	• Total costs (including cost breakdown), QALYs, LYs • Incremental costs, QALYs, LYs • Incremental costs per QALY gained • Incremental costs per LY gained	

Abbreviations: AE: adverse event; BNF: British National Formulary; eMIT: electronic market information tool; LY: life year; OS: overall survival; PFS: progression-free survival; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; QALY: quality-adjusted life year; SOC: standard of care; TTD: time to treatment discontinuation.

B.3.3 *Clinical parameters and variables*

Efficacy inputs included OS and PFS by treatment. The OS, PFS, and TTD inputs for tarlatamab were based on the DeLLphi-301 trial (NCT05060016).[48]

DeLLphi-301 is a phase 2, open-label, registrational study in patients with recurrent SCLC who have progressed or recurred following 1 platinum-based regimen (with or without checkpoint inhibitor) and at least 1 other line of therapy. The DeLLphi-301 trial was conducted in 3 parts. Part 1 evaluated 2-dose levels of tarlatamab in which eligible patients were randomized 1:1 to a target dose of 10 mg or 100 mg tarlatamab. Part 2 was a dose-expansion phase at the selected target dose (10 mg) based on an interim analysis of part 1. After the target dose was selected based on Part 1 findings, enrolment continued only at the selected dose until approximately 100 patients were enrolled at that dose level. Part 3 was initiated after completing enrolment of part 1 and part 2, to enroll up to approximately 30 additional patients at the selected dose.

Overall, 222 subjects were randomized (part 1) or enrolled (parts 2 and 3) and 220 subjects received at least 1 dose of tarlatamab. Among them, 99 subjects received the 10 mg target dose across parts 1 and 2, including 97 subjects received at least 2 prior lines of therapy and 2 subjects received only 1 prior line of therapy. Because the label of tarlatamab will be in 3L+ SCLC with a dose of 10 mg, only the 97 patients who received at least 2 lines of prior therapy and 10 mg tarlatamab during part 1 and part 2 of the trial were included in the current analysis.

Given DeLLphi-301 is a single-arm study, two systematic literature reviews (SLRs), one focused on clinical studies and another focused on burden of illness (BOI) in the 3L SCLC setting, respectively, were conducted to identify potential data sources for SOC.[80, 81]In total, 17 publications reporting 14 unique studies were identified from the clinical SLR, but none assessed the comparator in the 3L SCLC setting.[81] 46 studies identified from the BOI SLR were also explored. These studies were deemed unsuitable as inputs for SOC due to various limitations, including small sample size, limited geographic coverage (multiple studies are in Asia only), not fully relevant patient population, unavailability of important prognostic covariates, and

unavailability of OS and PFS Kaplan-Meier (KM) curves.[80] As such, a de-novo retrospective observational study was conducted using data from the UK CAS dataset to inform the efficacy of SOC as a 3L treatment in SCLC. Adults with SCLC diagnosed between July 1, 2011 and December 31, 2020 who have received a 3L treatment after two prior lines of therapy including one platinum-based regimen were selected. In addition, patients were required to have an ECOG value of 0 or 1 at 3L initiation to match with the inclusion criteria of the DeLLPhi-301 trial. The selected cohort from CAS was referred to as the UK CAS historical control 3L cohort thereafter in this report. Even though DeLLPhi-301 trial has 14% of patients receiving tarlatamab as fourth and above line treatment, to be conservative against tarlatamab, only patients received 3L treatment were selected from the UK CAS to form the historical control cohort.

To further account for different baseline characteristics between patients enrolled in DeLLphi-301 and patients included the UK CAS study, an indirect treatment comparison (ITC) was performed to compare tarlatamab versus SOC. Because individual patient data (IPD) from the CAS dataset are not available for ITC analysis due to data usage agreement, a MAIC based on propensity score weighting was used in to compare tarlatamab with SOC as detailed in section B.2.9. One limitation associated with the UK CAS dataset is that it does not capture disease progression based on scans and therefore does not report PFS data. As such, time to treatment discontinuation or death was used to proxy PFS in the current analysis.

Finally, given the limited treatment options after 3L in SCLC, patients in DeLLPhi-301 were allowed to stay on tarlatamab upon radiologic disease progression if the investigator judged that it could provide clinical benefits. The intended labelling for tarlatamab will recommend discontinuation upon disease progression. Among these 97 patients, at the time of this analysis, [redacted] received at least one dose of tarlatamab after disease progression (data cut-off: June 2023). To remove the impact of post-progression tarlatamab treatment, patients who received tarlatamab post-progression were censored at the time of progression for both OS and TTD analysis as described in Section B.3.3.1. Censoring OS at time of progression assumes these patients had the same survival as those who were not censored. This is conservative because those who received tarlatamab post-progression are the ones who would benefit from post-progression tarlatamab treatment. As such, the current approach likely underestimated the clinical benefits associated with tarlatamab observed in the trial.

During the MAIC analysis, propensity score weighting was applied to the DeLLPhi-301 trial data to balance the baseline characteristics of the trial population with those of the UK CAS historical control 3L cohort. As a result, weighed PFS, OS and TTD curve from the MAIC analysis were used for tarlatamab in the CEA model to ensure a fair comparison with the UK CAS historical control 3L cohort. A comparison of these measures before MAIC weighting and after MAIC weighting are summarised below (Table 36). The KM curves of OS and PFS for tarlatamab and SOC before MAIC weighting without post-progression tarlatamab use are presented in Figure 16 and Figure 17 respectively. The KM curves of OS and PFS for both arms after MAIC weighting with post-progression tarlatamab use are presented in Figure 18.

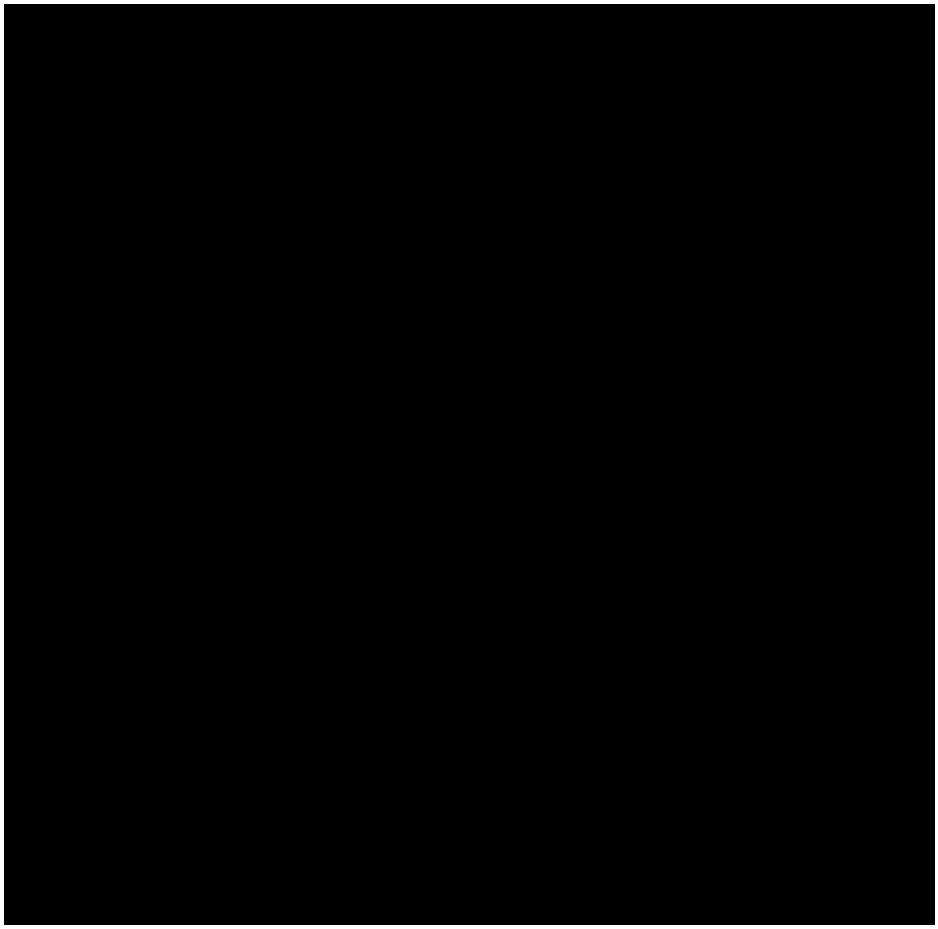
Table 36: Median OS, PFS and OS of tarlatamab and SOC

Outcomes (months)	Tarlatamab			SOC
	Before weighting	After weighting (without adjustment)	After weighting (with adjustment)	
OS	14.3	[redacted]	[redacted]	[redacted]

PFS	[redacted]	[redacted]	[redacted]	[redacted]
TTD	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS, overall survival; PFS, progression-free survival; SOC, standard of care; TTD, time to treatment discontinuation

Figure 16: KM curves of OS and PFS for tarlatamab before MAIC weighting without adjustment for post-progression tarlatamab use

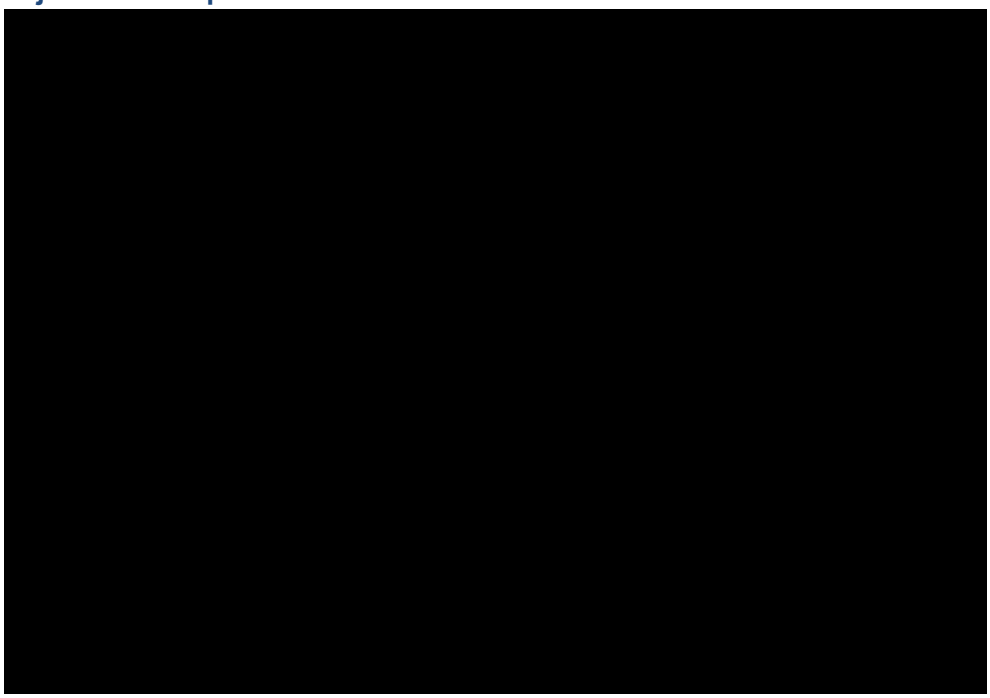


Abbreviations: KM: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; OS: overall survival; PFS: progression-free survival.

Figure 17: KM curves of OS and PFS for SOC before MAIC weighting without adjustment for post-progression tarlatamab use

Abbreviations: CAS: Cancer Analysis System; KM: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; OS: overall survival; PFS: progression-free survival; SOC: standard of care.

Figure 18: KM curves of OS and PFS for tarlatamab and SOC after MAIC weighting with adjustment for post-tarlatamab use



Abbreviations: KM: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; OS: overall survival; PFS: progression-free survival; SOC: standard of care.

The methodology for modelling comparative efficacy is described in more detail in Section B.2.9. The key patient characteristics before and after MAIC weighting, and the design of the data source considered for tarlatamab and SOC, are summarised in Table 37.

Table 37: Clinical data sources for base case analysis

Comparator arm	Source	Patient population	Main patient characteristics	Sample size
Tarlatamab	DeLLphi-301 (data cutoff: June 2023)	Adult patients with r/r SCLC who received at least 2 lines of prior therapy and received 10 mg tarlatamab in DeLLphi-301	Before matching Mean age: [redacted] Female: 26.8% ECOG PS 0 at initiation of treatment: 25.8% ECOG PS 1 at initiation of treatment: 74.2% Presence of brain metastasis: 22.7% Presence of liver metastasis: 38.1% Platinum resistant (CFI <90 days) after 1L: 27.3% Platinum sensitive (CFI between 90-180 days) after 1L: 22.2% Platinum sensitive (CFI ≥180 days) after 1L: 50.5% Disease stage as extensive at initial diagnosis: [redacted] Time from diagnosis to start of line of treatment: [redacted] days After matching	97

Comparator arm	Source	Patient population	Main patient characteristics	Sample size
			Mean age: [redacted] Female: [redacted] ECOG PS 0 at initiation of treatment: [redacted] ECOG PS 1 at initiation of treatment: [redacted] Presence of brain metastasis: [redacted] Presence of liver metastasis: [redacted] Platinum resistant (CFI <90 days) after 1L: [redacted] Platinum sensitive (CFI between 90-180 days) after 1L: [redacted] Platinum sensitive (CFI ≥180 days) after 1L: [redacted] Disease stage as extensive at initial diagnosis: [redacted] Time from diagnosis to start of line of treatment: [redacted] days	
SOC	UK CAS historical control 3L cohort (July 2011-May 2022)	Adult patients with r/r SCLC who received a 3L systemic anti-cancer treatment	Mean age: [redacted] Female: [redacted] ECOG PS 0 at initiation of treatment: [redacted] ECOG PS 1 at initiation of treatment: [redacted] Presence of brain metastasis: [redacted] Presence of liver metastasis: [redacted] Platinum resistant (CFI <90 days) after 1L: [redacted] Platinum sensitive (CFI between 90-180 days) after 1L: [redacted] Platinum sensitive (CFI ≥180 days) after 1L: [redacted] Disease stage as extensive at initial diagnosis: [redacted] Time from diagnosis to start of line of treatment: [redacted] days	540

Abbreviations: 3L, third line; CAS, Cancer Analysis System; CFI, chemotherapy-free interval; ECOG PS: Eastern Cooperative Oncology Group performance status; r/r, relapsed/refractory; SCLC, small-cell lung cancer; SOC, standard of care; UK, United Kingdom

B.3.3.1 Adjustment for post-progression treatment for OS, PFS and TTD

Given the limited treatment options after 3L in SCLC, patients in DeLLPhi-301 were allowed to stay on tarlatamab upon radiologic disease progression if the investigator judged that it could provide clinical benefits. The intended labelling for tarlatamab will recommend discontinuation upon disease progression. Among the 97 patients from the trial, at the time of this analysis, [redacted] continued tarlatamab treatment with at least one dose after (BICR) disease progression (data cut-off: June 2023). To adjust for the impact of this, patients who received tarlatamab post-progression were censored at the time of progression for OS, and TTD was capped at progression (Table 38). Censoring OS at time of progression assumes these patients had the

same survival as those who were not censored. This is conservative because those who received tarlatamab post-progression are those who are fit enough to tolerate further treatment. As such, the current approach likely underestimated the clinical benefits associated with tarlatamab observed in the trial.

Table 38: Event / censoring rules applied to adjust for post-progression tarlatamab use

Scenario in DeLLphi-301	Change in variables to adjust for post-progression use
No event for PFS and no event for TTD	No change
No event for PFS but event for TTD	No change
Event for PFS and event for TTD (N=[redacted])	If PFS time greater than/equal to TTD time, no change (N=[redacted]). If PFS time smaller than TTD time then (N=[redacted]): OS censored at PFS time, TTD time set equal to PFS time and TTD censoring variable is set to event
Event for PFS but no event for TTD (N=[redacted])	OS censored at PFS time, TTD time set equal to PFS time and TTD censoring variable is set to event

Abbreviations: OS, overall survival; PFS, progression-free survival; TTD, time-to-treatment discontinuation

B.3.3.2 Overall survival

Tarlatamab OS for the base-case model was estimated based on the weighted OS from the MAIC analysis comparing tarlatamab 10mg (N=97; data cutoff: June 2023) with the UK CAS historical control 3L cohort. OS of tarlatamab was defined as time from tarlatamab initiation to death due to any cause. OS of SOC was evaluated from the time of 3L treatment initiation to death due to any cause; it was estimated based on aggregated OS data from 540 patients included in the UK CAS historical control 3L cohort.[82]

To help inform the most feasible extrapolation approach, an assessment of whether the proportional hazards assumption was met was performed for tarlatamab OS after MAIC weighting without adjustment for post-progression tarlatamab use and SOC OS. This assessment is summarised in the document entitled “Survival analyses” in the reference pack provided alongside this submission. Based on the assessment, the proportional hazard assumption was violated and therefore standard parametric models (Exponential, Weibull, Log-Logistic, Lognormal, Gompertz, Generalized Gamma, and Gamma) were used to fit the OS curves for tarlatamab and SOC separately in the base-case.

Tarlatamab

The overlay of the MAIC weighted KM curve with adjustment for post-progression tarlatamab use and the predicted curves based on different parametric functions and the associated goodness-of-fit (i.e., Akaike information criterion [AIC], Bayesian information criterion [BIC]) are presented in Figure 19 and Table 39. The extrapolated 1-year and 2-year OS outcomes based on each parametric function are summarised in Table 40.

Figure 19: Standard parametric models of tarlatamab OS

Abbreviations: KM: Kaplan-Meier; OS: overall survival.

Table 39: Goodness-of-fit and model parameters for standard parametric models of tarlatamab OS

Parametric function (parameter name)	AIC	BIC	Parameter 1	Parameter 2	Parameter 3
Exponential (parameter 1 = shape)	78.0	80.6	[redacted]	-	-
Weibull (parameter 1 = shape, parameter 2 = scale)	79.8	85.0	[redacted]	[redacted]	-
Log-logistic (parameter 1 = shape, parameter 2 = scale)	79.8	84.9	[redacted]	[redacted]	-
Lognormal (parameter 1 = meanlog, parameter 2 = sdlog)	79.4	84.5	[redacted]	[redacted]	-
Gompertz (parameter 1 = shape, parameter 2 = scale)	79.9	85.1	[redacted]	[redacted]	-
Generalised Gamma (parameter 1 = mu, parameter 2 = sigma, parameter 3 = Q)	81.3	89.0	[redacted]	[redacted]	[redacted]
Gamma (parameter 1 = mu, parameter 2 = sigma)	79.8	84.9	[redacted]	[redacted]	-

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Table 40: Extrapolated 1-year and 2-year tarlatamab OS

Parametric function	1-year OS	2-year OS
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]

Parametric function	1-year OS	2-year OS
Gamma	[redacted]	[redacted]
Observed	47.0%	Not reached

Abbreviations: OS: overall survival.

SOC

The overlay of the KM curve and the predicted curves based on different parametric functions and the associated goodness-of-fit (i.e., AIC, BIC) for SOC are presented in Figure 20 and Table 41. The extrapolated 1-year and 2-year OS based on each parametric function is summarised in Table 42. Following NICE DSU 14, the same base-case distribution, i.e., exponential, was selected for SOC as for tarlatamab and was bolded in the tables.[83] The exponential distribution predicted a higher OS at year 1 and 2, compared to other options, indicating that the current base-case model was conservative against tarlatamab. OS outcomes of SOC based on alternative parametric functions were assessed in scenario analyses.

Figure 20: Standard parametric models of SOC OS

Table 41: Goodness-of-fit and model parameters for standard parametric models of SOC OS

Parametric function	AIC	BIC	Parameter 1	Parameter 2	Parameter 3
Exponential (parameter 1 = shape)	**2932.4**	**2936.7**	[redacted]	-	-
Weibull (parameter 1 = shape, parameter 2 = scale)	2839.1	2847.7	[redacted]	[redacted]	-
Log-logistic (parameter 1 = shape, parameter 2 = scale)	2832.0	2840.5	[redacted]	[redacted]	-
Lognormal (parameter 1 = meanlog, parameter 2 = sdlog)	2854.3	2862.9	[redacted]	[redacted]	-
Gompertz (parameter 1 = shape, parameter 2 = scale)	2895.4	2903.9	[redacted]	[redacted]	-

Parametric function	AIC	BIC	Parameter 1	Parameter 2	Parameter 3
Generalised Gamma (parameter 1 = mu, parameter 2 = sigma, parameter 3 = Q)	2825.7	2838.5	[redacted]	[redacted]	[redacted]
Gamma (parameter 1 = mu, parameter 2 = sigma)	2825.6	2834.2	[redacted]	[redacted]	-

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Table 42: Extrapolated 1-year and 2-year SOC OS

Parametric function	1-year OS	2-year OS
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Observed	[redacted]	[redacted]

Abbreviations: OS, overall survival.

B.3.3.3 Progression-free survival

Tarlatamab PFS for the base-case model was estimated based on the weighted PFS from the MAIC analysis comparing tarlatamab 10mg (N=97; data cutoff: June 2023) with the UK CAS historical control 3L cohort. PFS of tarlatamab was defined as the time from tarlatamab initiation to the first documented date of radiographic progression per RECIST v1.1 or death, whichever occurred first.

Similar to OS, to help inform the most feasible extrapolation approach, an assessment of whether the proportional hazards assumption was met was performed for tarlatamab PFS after MAIC weighting and SOC TTD (as a proxy for SOC PFS). This assessment is summarised in the document labelled “Survival analyses” in the reference pack provided alongside this submission. Based on the assessment, the proportional hazard assumption was violated and therefore standard parametric models (Exponential, Weibull, Log-Logistic, Lognormal, Gompertz, Generalized Gamma, and Gamma) were used to fit the PFS curves for tarlatamab and SOC separately in the base-case.

Tarlatamab

The overlay of the weighted KM curve from MAIC and the predicted curves based on different parametric functions and the associated goodness-of-fit (i.e., AIC, BIC) are presented in Figure 21 and Table 43. The extrapolated 1-year and 2-year PFS based on each parametric function is summarised in Table 44. The log-normal distribution was selected as the base-case parametric function based on AIC and visual inspection and is highlighted in bold in the below tables.

Figure 21: Standard parametric models of tarlatamab PFS

Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival.

Table 43: Goodness-of-fit and model parameters for standard parametric models of tarlatamab PFS

Parametric function	AIC	BIC	Parameter 1	Parameter 2	Parameter 3
Exponential (parameter 1 = shape)	99.7	102.2	[redacted]	-	-
Weibull (parameter 1 = shape, parameter 2 = scale)	101.7	106.8	[redacted]	[redacted]	-
Log-logistic (parameter 1 = shape, parameter 2 = scale)	100.3	105.4	[redacted]	[redacted]	-
Lognormal (parameter 1 = meanlog, parameter 2 = sdlog)	**99.3**	**104.5**	[redacted]	[redacted]	-
Gompertz (parameter 1 = shape, parameter 2 = scale)	101.0	106.2	[redacted]	[redacted]	-
Generalised Gamma (parameter 1 = mu, parameter 2 = sigma, parameter 3 = Q)	100.2	107.9	[redacted]	[redacted]	[redacted]
Gamma (parameter 1 = mu, parameter 2 = sigma)	101.7	106.8	[redacted]	[redacted]	-

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Table 44: Extrapolated 1-year and 2-year tarlatamab PFS

Parametric function	1-year PFS	2-year PFS
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]

Parametric function	1-year PFS	2-year PFS
Lognormal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Observed	33%	Not reached

Abbreviations: PFS, progression-free survival

SOC

Because PFS data are not available from the UK CAS database, the PFS for SOC was assumed to be the same as TTD; please refer to section B.3.3.4 for details on SOC TTD extrapolations.

B.3.3.4 Time to treatment discontinuation

Tarlatamab TTD for the base-case model was estimated based on the MAIC weighted TTD with adjustment for post-progression tarlatamab use. Specifically, TTD was defined as the time from tarlatamab initiation to treatment discontinuation. For patients without post-progression tarlatamab treatment, those who did not discontinue tarlatamab were censored at the time of data-cut. For patients with post-progression tarlatamab treatment, they were censored at the time of progression, regardless of treatment discontinuation status. For SOC, TTD was defined as time from 3L treatment initiation to death or the discontinuation of 3L treatment, whichever earlier. Patients who did not discontinue 3L treatment were censored at the earliest among the occurrence of loss to follow-up, the last time known to be alive, or end of data availability. TTD for SOC was estimated based on aggregated data from 540 patients in the UK CAS historical control 3L cohort.[82]

Standard parametric models (Exponential, Weibull, Log-Logistic, Lognormal, Gompertz, Generalized Gamma, and Gamma) were used to fit the TTD curves for tarlatamab and SOC separately in the base-case.

Tarlatamab

The overlay of the MAIC weighted KM curve of TTD with adjustment for post-progression tarlatamab use and the predicted curves based on different parametric functions and the associated goodness-of-fit (i.e., AIC, BIC) are presented in Figure 22 and Table 45.

The exponential distribution was selected as the base-case parametric function for tarlatamab TTD because the projected proportions of patients staying on tarlatamab treatment by 1-year and 2-year after treatment initiation (i.e., 18.7% and 3.5%) were the most clinically plausible. Comparable TTD data were reported by in the phase 1, dose-escalation DeLLPhi-300 study evaluating tarlatamab monotherapy and in combination with anti-PD-1 therapy in patients who had progressed or recurred after at least 1 previous platinum-based regimen. Specifically, among patients who received 10mg tarlatamab monotherapy, 18.5% stayed on treatment for 1 year.[84]

Figure 22: Standard parametric models of tarlatamab TTD

Abbreviations: KM: Kaplan-Meier; TTD: time-to-treatment discontinuation.

Table 45: Goodness-of-fit for standard parametric models of tarlatamab TTD

Parametric function	AIC	BIC	Parameter 1	Parameter 2	Parameter 3
Exponential (parameter 1 = shape)	**111.6**	**114.1**	[redacted]	-	-
Weibull (parameter 1 = shape, parameter 2 = scale)	108.9	114.0	[redacted]	[redacted]	-
Log-logistic (parameter 1 = shape, parameter 2 = scale)	108.9	114.1	[redacted]	[redacted]	-
Lognormal (parameter 1 = meanlog, parameter 2 = sdlog)	110.0	115.1	[redacted]	[redacted]	-
Gompertz (parameter 1 = shape, parameter 2 = scale)	109.4	114.5	[redacted]	[redacted]	-
Generalised Gamma (parameter 1 = mu, parameter 2 = sigma, parameter 3 = Q)	110.8	118.5	[redacted]	[redacted]	[redacted]
Gamma (parameter 1 = mu, parameter 2 = sigma)	109.1	114.2	[redacted]	[redacted]	-

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Table 46: Extrapolated 1-year and 2-year tarlatamab TTD

Parametric function	1-year TTD	2-year TTD
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Observed	27.5%	Not reached

Abbreviations: TTD, time to treatment discontinuation.

SOC

The overlay of the KM curve and the predicted curves based on different parametric functions and the associated goodness-of-fit (i.e., AIC, BIC) are presented in Figure 23 and Table 47. The extrapolated 1-year and 2-year TTD based on each parametric function was summarised in Table 48. Following NICE DSU 14, the same base-case distribution, i.e., exponential, was selected for standard of care as for tarlatamab and was bolded in the tables.[83]

Figure 23: Standard parametric models of SOC TTD

Abbreviations: KM: Kaplan-Meier; SOC: standard of care; TTD: time-to-treatment discontinuation.

Table 47: Goodness-of-fit for standard parametric models of SOC TTD

Parametric function	AIC	BIC	Parameter 1	Parameter 2	Parameter 3
Exponential (parameter 1 = shape)	**1666.3**	**1670.6**	[redacted]	-	-

Parametric function	AIC	BIC	Parameter 1	Parameter 2	Parameter 3
Weibull (parameter 1 = shape, parameter 2 = scale)	1665.6	1674.2	[redacted]	[redacted]	-
Log-logistic (parameter 1 = shape, parameter 2 = scale)	1840.7	1849.3	[redacted]	[redacted]	-
Lognormal (parameter 1 = meanlog, parameter 2 = sdlog)	1869.4	1878.0	[redacted]	[redacted]	-
Gompertz (parameter 1 = shape, parameter 2 = scale)	1641.6	1650.2	[redacted]	[redacted]	-
Generalised Gamma (parameter 1 = mu, parameter 2 = sigma, parameter 3 = Q)	1613.3	1626.2	[redacted]	[redacted]	[redacted]
Gamma (parameter 1 = mu, parameter 2 = sigma)	1668.0	1676.6	[redacted]	[redacted]	-

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; SOC: standard of care; TTD: time-to-treatment discontinuation.

Table 48: Extrapolated 1-year and 2-year SOC TTD

Parametric function	1-year TTD	2-year TTD
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Observed	[redacted]	[redacted]

Abbreviations: SOC: standard of care; TTD: time-to-treatment discontinuation.

B.3.3.5 Summary of overall survival, progression-free survival, and time to treatment discontinuation extrapolation

OS for tarlatamab was projected with an exponential model fitted to MAIC weighted DeLLPhi-301 OS data with adjustment for post-progression tarlatamab use and OS for SOC was projected with an exponential model fitted to the UK CAS 3L historical control data. PFS for tarlatamab was projected with a lognormal model fitted to MAIC weighted DeLLPhi-301 data and PFS for SOC

was proxied by TTD because PFS information is not available from the UK CAS data. The base-case extrapolations of OS and PFS for both tarlatamab and SOC are presented in Figure 24.

Figure 24: Base case PFS and OS extrapolations for tarlatamab and SOC

Abbreviations: KM: Kaplan-Meier; OS: overall survival; PFS: progression-free survival; SOC: standard of care.

TTD for tarlatamab was estimated with an exponential model fitted to MAIC weighted DeLLPhi-301 TTD data with adjustment for post-progression tarlatamab use and OS for SOC was projected with an exponential model fitted to the TTD data from the CAS 3L historical control cohort. The base-case extrapolations of TTD for both tarlatamab and SOC are presented in Figure 25.

The model parameters and variance-covariance data for the OS, PFS and TTD used in the base case analysis are presented in the document labelled “Survival analyses” in the reference pack provided alongside this submission.

Figure 25: Base-case TTD extrapolations for tarlatamab and SOC

Abbreviations: KM: Kaplan-Meier; SOC: standard of care; TTD: time-to-treatment discontinuation.

B.3.4 *Measurement and valuation of health effects*

B.3.4.1 Health-related quality-of-life data from clinical trials

The base-case utilities for progression-free and post-progression states were independent of treatment, which means the same utility assumed for tarlatamab and SOC arm when they were in the same health states. Disutilities due to AEs were separately considered. The utilities for health states were estimated based on the patient-level EuroQol-5 dimension-5 level Instrument (EQ-5D-5L)[85] data collected in the DeLLphi-301 trial (data cutoff: June 27, 2023).[86] All available EQ-5D-5L measures for tarlatamab 10mg in the 3L+ setting from the DeLLphi-301 trial were used in the utility analysis. Based on the individual patient's health states at the time of EQ-5D-5L evaluation, the observed EQ-5D-5L scores were classified into the following categories, which corresponded to health states considered in the model:

- **EQ-5D measures before treatment:** Any EQ-5D assessment before the treatment initiation date.
- **EQ-5D measures for the PF health state:** Any EQ-5D assessment corresponding to patients in the progression-free state were used. This included all data collected from treatment initiation up to the date of the first documented progression, death due to any cause, or censoring date based on PFS definition per DeLLphi-301 trial protocol.
- **EQ-5D measures for the PD health state:** Any EQ-5D assessment corresponding to patients in the post-progression state were used. This included all data collected on or after the first documented progression event.

The EQ-5D-5L measures were mapped to EQ-5D-3L utility scores using the preference-weights for the UK.[87] This analysis did not impute values for missing evaluations. The utility scores were measured repeatedly over time (Day 1, 8, and 22 of Cycle 1, Day 1 and 15 of Cycle 2, and thereafter every 6 weeks until week 48), which resulted in correlation of observations across different time points for the same patient.[86] To account for the repeated and longitudinal nature of the data, a mixed-effects model was developed to estimate the health state utility values at a population level.

In the mixed effects model, utility was estimated considering both the between-patient variation and the within patient variation (before treatment vs. progression-free vs. post-progression). That is, random intercept and random slope were both included in the regression. Utility estimated by the mixed effects model was used in the base-case analysis.

The death state was assumed to have 0 utility. No other covariates were included in the models because the purpose of the analysis was to generate utility values for the CEA model, i.e., averaged values that were reflective of the DeLLphi-301 trial population. The model-based utility estimates by health states from DeLLphi-301 trial based on UK tariffs are presented in Table 49.

Table 49: Model estimates on EQ-5D-3L utility scores in the DeLLphi-301 trial

Health states	N patients	N assessments	Mixed effects model	
			Mean	SE
Before treatment	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]	[redacted]

The same patient could have multiple health states at different visits. The statistics presented here reflect the number of patients with at least one assessment with the specified health state.
Abbreviations: SE: standard error.

B.3.4.2 Mapping and age- and sex-adjustment

As described in section B.3.4.1, EQ-5D-3L analyses, UK-specific preference weights were obtained using the EQ-5D-5L to EQ-5D-3L mapping algorithm by Hernandez-Alava.[87] An age and sex-related utility adjustment was also applied to health state utilities over the modelled time horizon to reflect decreases in health-related quality of life seen in the UK general population.[88]

B.3.4.3 Adverse reactions

Disutilities associated with grade 3+ AEs occurring in >3% of patients in any treatment arm were included. In addition, disutilities for grade 1/2 CRS and grade 1/2 ICANS were included given these are AEs specific to tarlatamab due to its mechanism of action. There was no grade 3/4 CRS or ICANS observed in the DeLLPhi-301 trial. Overall disutility due to AEs was applied to each treatment arm in the first cycle of the model, estimated based on disutility per AE event and AE rate. AE rates were based on the DeLLphi-301 trial for tarlatamab.[86] For SOC, AE rates associated with each treatment regimen (i.e. platinum-based chemotherapy, CAV, and topotecan) were separately sourced from the literature (Table 50).[14] AE disutility associated with SOC was estimated as the weighted average of AE disutility associated with each regimen. The weight associated with each regimen was informed by the UK CAS study as described in section B.3.2.3. The grade 3+ AE disutility values were based on literature and assumptions and were assumed to last for 28 days. For grade 1/2 CRS and ICANS, due to lack of data, the disutility

values were assumed to be maximum disutility (-0.22) among grade 3+ AEs; the duration of CRS and ICANS was assumed to be 4 days.

Table 50: AE rate inputs

AEs	AE rates				Reference
	Tarlatamab	Topotecan	Platinum-based chemotherapy	CAV	
Grade 3+ AEs					AE rates of tarlatamab: DeLLphi-301 trial (data cutoff: June 27, 2023);[49] Ahn *et al.* (2023)[48] AE rates of topotecan: O'Brien et al., 2006[79] AE rates of carboplatin + etoposide chemotherapy: NICE TA638[14] AE rates of CAV: von Pawel et al., 1999[89]
Anaemia	[redacted]	25.00%	12.24%	19.23%	
Diarrhea	[redacted]	6.00%	0.51%	0.00%	
Fatigue	1.01%	4.00%	0.51%	8.65%	
Febrile neutropenia	1.01%	3.00%	6.12%	0.00%	
Leukopenia	[redacted]	0.00%	4.08%	78.85%	
Lymphocyte count decreased	[redacted]	0.00%	0.00%	0.00%	
Lymphopenia	[redacted]	0.00%	0.00%	0.00%	
Nausea	[redacted]	0.00%	0.51%	5.77%	
Neutropenia	1.01%	61.00%	24.49%	82.69%	
Neutrophil count decreased	[redacted]	0.00%	16.84%	0.00%	
Non-sepsis infection	[redacted]	14.08%	0.00%	0.00%	
Thrombocytopenia	[redacted]	38.00%	7.65%	14.42%	
Grade 1-2 CRS and ICANS (no grade 3+ CRS or ICANS events were observed)					
CRS	[redacted]	-	-	-	
ICANS	[redacted]	-	-	-	

Abbreviations: AE: adverse event; CAV: cyclophosphamide: doxorubicin and vincristine; CRS: cytokine-release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome.

B.3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis

A summary table of all quality-of-life inputs used in the economic analysis is presented below in Table 51.

Table 51: Utility and disutility inputs

Variable	Value	Reference
Health state utilities		
Progression-free	[redacted]	DeLLphi-301 trial[49]
Post-progression	[redacted]	
Disutility per grade 3+ AE		
Anaemia	−0.02	Sullivan *et al*. 2011[90]
Diarrhoea	−0.05	Nafees *et al*. 2008[91]

Fatigue	−0.07	
Febrile neutropenia	−0.09	
Leukopenia	−0.04	Sullivan *et al*. 2011[90]
Lymphocyte count decreased	−0.01	
Lymphopenia	−0.07	
Nausea	−0.05	Nafees *et al*. 2008[91]
Neutropenia	−0.07	Sullivan *et al*. 2011[90]
Neutrophil count decreased	−0.07	
Non-sepsis infection	−0.22	Stein *et al*. 2018[92]
Thrombocytopenia	−0.07	Sullivan *et al*. 2011[90]
Disutility per grade 1/2 CRS / ICANS		
CRS	-0.22	Assumed the same as the maximum disutility among grade 3+ AEs
ICANS	-0.22	
Duration of AE		
Grade 3+ AEs	28 days	Assumption
Grade 1/2 CRS / ICANS	4 days	
Utility adjustment by age and sex		
Adjustment factor relative to the baseline age of 64 years (pooling adjustment by proportion female and male)	Range from 0.770 (age of 100 years) to 0.995 (age of 65 years)	Hernández Alava et al., 2022[87]

Abbreviations: AE: adverse event; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

B.3.5 *Cost and healthcare resource use identification, measurement and valuation*

Costs for the following categories were included in the model: (1) drug and administration, (2) monitoring, (3) AEs, (4) subsequent treatment, and (5) end of life. When necessary, all costs were inflated to 2023 values using the UK Health Consumer Price Index. As of the development of this dossier, the NHS cost inflation index for 2023 had not yet been published; therefore, it was assumed that the inflation rate in 2023 was the same as in 2022.

B.3.5.1 Intervention and comparators' costs and resource use

A summary of drug cost inputs used in the economic analysis is presented in Table 52. For tarlatamab, the anticipated PAS price of [redacted] per 10 mg vial and [redacted] per 1 mg vial was used. Pre-treatment with dexamethasone was included in the model and its price was obtained from the UK drugs and pharmaceutical eMIT.[93] The dosing schedule of tarlatamab and dexamethasone was sourced from study protocol of the DeLLphi-301 trial and the RDI was obtained from the DeLLphi-301 trial (data cutoff: June 27, 2023).[86]

For SOC, separate drug cost inputs were collected for each regimen. The drug cost estimates of each available treatment were then applied with the weights to derive the drug costs of the comparator arm. Dosing schedules for included treatment regimens were based on respective NICE submission or literature. The unit price of oral topotecan was obtained from the British

National Formulary (BNF) database and the unit prices of the other chemotherapies were obtained from eMIT.[93, 94] RDIs of each treatment regimen were based on respective trial publications or assumptions. In the base-case analysis, drug wastage was considered for both the IV and oral drugs.

The proportion of patients on treatment in each model cycle was based on the TTD inputs of tarlatamab and SOC as described in Section B.3.3.4.

Table 52: Drug costs used in the economic analysis

Treatment	Admin Route	Dosing Schedule	Price	RDI	Reference for Dosing Schedule, Price & RDI
Tarlatamab					
Dexamethasone (pre-treatment)	IV	8 mg, on day 1 and 8 of cycle 1 only	£5 / 6.60-mg vial	86%	DeLLphi-301 trial;[95] eMIT;[93] Assume the same as tarlatamab
Tarlatamab	IV	1 mg on cycle 1 day 1, followed by a 10 mg target dose on cycle 1, day 8 and day 15, and Q2W thereafter (i.e., cycle 2 day 1 &15 dosing) in a 28-day cycle; treatment continues until confirmed radiographic progression or disease progression	[redacted]/ 1-mg vial [redacted]/ 10-mg vial	86%	DeLLphi-301 trial[95]
Topotecan					
Topotecan	Oral	2.30 mg/m^2/d, 5 consecutive days every 21 days; until they and their clinicians consider it appropriate to stop	£8 / 0.25-mg capsule	98%	Topotecan NICE submission;[43] BNF;[94] O'Brien et al., 2006[79]
Carboplatin + etoposide chemotherapy					
Carboplatin	IV	5 mg/mL/min, on days 1 of each 21-day cycle; until disease progression or unacceptable toxicity	£15 / 450-mg vial	93%	Mansfield et al., 2020;[96] eMIT;[93] Horn et al., 2018[42]]
Etoposide	IV	100 mg/m^2, on days 1, 2, and 3 of each 21-day cycle; until disease progression or unacceptable toxicity	£11 / 500-mg vial	90%	
CAV					
Cyclophosphamide	IV	1,000 mg/m^2, on day 1 of 21-day cycles; Until disease progression or unacceptable toxicity	£13 / 1000-mg vial	100%	Aix et al. 2023;[97] eMIT;[93] Assume 100%
Doxorubicin	IV	45 mg/m^2, on day 1 of 21-day cycles; Until disease progression or unacceptable toxicity	£17 / 200-mg vial	100%	

Treatment	Admin Route	Dosing Schedule	Price	RDI	Reference for Dosing Schedule, Price & RDI
Vincristine	IV	2 mg, on day 1 of 21-day cycles; Until disease progression or unacceptable toxicity	£7 / 2-mg vial	100%	

Abbreviations: IV: intravenous; BNF: British National Formulary; CAV: cyclophosphamide: doxorubicin and vincristine; eMIT: electronic market information tool; NICE: National Institute for Health and Care Excellence; Q2W: once every 2 weeks; RDI: relative dose intensity.

Administration, monitoring and test costs

A summary of drug administration cost inputs and treatment-related hospitalisation cost inputs is presented in Table 53. The administration cost of oral chemotherapy (i.e., topotecan in the present CEA) and IV chemotherapies (i.e., carboplatin + etoposide chemotherapy and CAV in the present CEA) was based on the NHS England Payment Scheme 23/24 prices.[98] The administration cost of dexamethasone and tarlatamab was assumed to be the same as that of simple IV chemotherapy.

In addition, patients treated with tarlatamab are subject to inpatient monitoring requirements as per study protocol of the DeLLphi-301 trial. Specifically, patients were assumed to be hospitalized for 24 hours post-tarlatamab infusion for day 1 and day 8 of cycle 1. In the following treatment cycles, hospitalization was not required for patients unless they experienced any grade CRS or neurological events.

Table 53: Drug administration cost inputs and treatment-related hospitalisation cost inputs

Model Input	Unit Cost	Reference
Drug administration costs		
Oral chemotherapy	£27.4	NHS England Payment Scheme 23/24 prices: Unbundled chemotherapy delivery SB11Z- Deliver exclusively oral chemotherapy[98]]
IV chemotherapy (first attendance)	£172.0	NHS England Payment Scheme 23/24 prices: Unbundled chemotherapy delivery SB12Z- Deliver simple Parenteral Chemotherapy at first attendance[98]]
IV chemotherapy (first administration of cisplatin etoposide)	£515.0	NHS England Payment Scheme 23/24 prices: Unbundled chemotherapy delivery SB14Z- Deliver Complex Chemotherapy, including Prolonged infusional Treatment, at First Attendance[98]
IV chemotherapy (subsequent attendance)	£343.0	NHS England Payment Scheme 23/24 prices: Unbundled chemotherapy delivery SB15Z- Deliver subsequent elements of a chemotherapy cycle[98]
Hospitalisation costs for tarlatamab at treatment initiation		
Required hospitalization for 24 hours	£488.0	NHS England Payment Scheme 23/24 prices: Healthcare resource group (HRG) WH16A observation or counselling with CC score1+[98]

Abbreviations: HRG: Healthcare resource group; IV: Intravenous; NHS: National Health Service.

B.3.5.2 Health-state unit costs and resource use

Medical resource use (MRU) and monitoring costs were informed by the NICE submission of atezolizumab in SCLC patients (TA638), and the same frequency until progression was assumed.[14] It was assumed that patients who received tarlatamab or SOC incurred MRU and monitoring costs, and that the costs were identical for both arms. Unit costs for MRU and monitoring were obtained from the NHS England Payment Scheme 23/24 prices, PSSRU 2022 or the NHS Schedule of Reference Costs 2021/22; where costs were historical (i.e, not for 2023/2024), costs were inflated to 2023 values.[98-100] Health state costs and frequencies are presented in Table 54.

Table 54: MRU use per patient per unit

Cost input	Unit cost	Reference for unit cost	Frequency / week	Reference for frequency / week
Outpatient visit	£141	NHS England Payment Scheme 23/24 prices: WF01A follow up outpatient attendance single professional, Consultant Led, Service code 800, Clinical Oncology[98]	0.29	NICE submission for atezolizumab in SCLC (TA638)[14]
GP visit - surgery	£42	PSSRU 2022: cost per patient contact lasting 9.22 minutes, including direct care staff costs with qualification costs[100]	0.06	
GP visit - home	£90	PSSRU 2022: 20 minutes of patient contact[100]	0.05	
Cancer nurse visit	£56	Following NICE TA638, assuming to be 66.7% of community nurse cost[100]	0.07	
Community nurse visit	£85	PSSRU 2022: cost per hour Band 8a inc qualifications[100]	0.04	

Abbreviations: GP: general practitioner; PSSRU, Personal and Social Services Research Unit.

Monitoring and test cost inputs are outlined in Table 55. Similar to the MRU costs, monitoring and testing costs were only assumed for the PF health state and no costs were considered in the PD health state.

Table 55: Monitoring and test costs per patient per unit

Test	Unit cost	Reference for unit cost	Frequency / week	Reference for frequency
Electrocardiogram	£134	NHS England Payment Scheme 23/24 prices: EY51Z – Electrocardiogram Monitoring or Stress Testing[98]	0.01	NICE submission for atezolizumab in SCLC (TA638)[14]

Test	Unit cost	Reference for unit cost	Frequency / week	Reference for frequency
Chest X-ray	£29	NHS England Payment Scheme 23/24 prices: Direct access plain film X-ray[98]	0.11	
CT scan unit cost	£99	NHS England Payment Scheme 23/24 prices: RD24Z – Computerised Tomography Scan of two areas, with contrast[98]	0.09	
Brain MRI unit cost	£209	NHS England Payment Scheme 23/24 prices: RD05Z -Magnetic Resonance Imaging Scan of Two or Three Areas, with Contrast[98]	0.01	
Blood test unit cost	£3	NHS Cost collection 2021/22: DAPS05 – haematology[98]	0.13	

Abbreviations: CT: computed tomography; MRI: magnetic resonance imaging.

B.3.5.3 Adverse reaction unit costs and resource use

In the base case analysis, costs associated with grade 1/2 CRS and ICANS and grade 3+ AEs other than CRS and ICANS occurring in greater than 3% of patients in any treatment arm were included. For tarlatamab, AEs were based on the DeLLphi-301 clinical study report; AE rates for the available treatment options arm were based on previous submissions and published studies. For AEs other than CRS and ICANS, the unit cost per event was obtained from NHS England Payment Scheme 2023/24 prices.[98] The unit costs of AEs per treatment are summarised in Table 56, and Table 57 lists the proportion of patients who experienced AEs. The rate per cycle was calculated based on the trial duration and the proportion of patients with AEs. Where multiple potential HRG codes could apply, the costliest HRG code was used, with the exception of for febrile neutropenia and leukopenia, where the same codes could have applied; in this case, the most costly code was used for febrile neutropenia (SA08G) whilst the less-costly HRG code was used for leukopenia (SA08H). Management costs per case of CRS consisted of one dose of tocilizumab based on the BNF and one hospitalization based on the NHS Reference Costs.[94, 98] The unit cost for ICANS management was obtained from NHS Reference Costs.[99] All cost inputs were inflated to the cost year 2023.

Table 56: AE costs used in the model

AE	HRG code	Unit cost	Description	Source
Anaemia	SA01G	£6,124	Non-elective admitted care: Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 8+	NHS England Payment Scheme 2023/24 prices workbook[98]
Diarrhoea	FD10E	£7,609	Non-elective admitted care: Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, with CC Score 9+	

AE	HRG code	Unit cost	Description	Source
Fatigue	SA01G	£6,124	Non-elective admitted care: Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 8+	
Febrile neutropenia	SA08G	£4,810	Non-elective admitted care: Other Haematological or Splenic Disorders, with CC Score 6+	
Leukopenia	SA08H	£2,196	Non-elective admitted care-: Other Haematological or Splenic Disorders, with CC Score 3-5	
Lung infection	800	£303	Clinical Oncology Service	
Lymphocyte count decreased	SA08H	£2,196	Non-elective admitted care-: Other Haematological or Splenic Disorders, with CC Score 3-5	
Lymphopenia	800	£313	Clinical Oncology Service	
Nausea	SA08H	£2,196	Non-elective admitted care-: Other Haematological or Splenic Disorders, with CC Score 3-5	
Neutropenia	800	£303	Clinical Oncology Service	
Neutrophil count decreased	WH07C	£5,358	Non-elective admitted care: Infections or Other Complications of Procedures, with Single Intervention, with CC Score 2+	
Non-sepsis infection	SA12G	£5,764	Non-elective admitted care: Thrombocytopenia with CC Score 8+	
Thrombocytopenia	SA01G	£1,255	Non-elective admitted care: Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 8+	

Abbreviations: AE: adverse event; CC: complication and comorbidity; HRG: healthcare resource group; NHS: National Health Service.

Table 57: CRS / ICANs costs used in the model

Parameter	Value	Description
Grade 1/2 CRS		
Proportion used tocilizumab among CRS	10%	CSR of DeLLphi-301 trial data (data cutoff: June 27, 2023)[86]
Cost of tocilizumab per dose	£922	BNF 2023 - A single dose of 8 mg/kg was assumed[94]
Proportion hospitalized among CRS	53%	CSR of DeLLphi-301 trial data (data cutoff: June 27, 2023)[86]
Cost of hospitalisation per day	£2,186	NHS Reference Costs 2021/22 - Weighted average of XC01Z-XC07Z[99]
Grade 1/2 ICANS		
Cost per ICANS management	£523	NHS Reference Costs 2021/22 - Weighted average of AA22C-AA22G (daycase)[99]

Abbreviations: CRS: cytokine release syndrome; HRG: healthcare resource group; ICANS: immune effector cell-associated neurotoxicity syndrome; NHS: National Health Service.

B.3.5.4 Subsequent treatment costs

After disease progression, a proportion of patients was assumed to receive subsequent active treatments, while the rest of patients was assumed to receive no active treatment. For tarlatamab, the proportion of patients receiving subsequent active treatments and the distribution of active treatments were sourced from the DeLLphi-301 trial; for SOC, these inputs were obtained from the UK CAS natural history study. An overview of the subsequent treatment distributions used in the model is given in Table 58; the same costs were used as described in section B.3.5.1.

Table 58: Subsequent treatment distribution by treatment arm

Subsequent treatment	Subsequent treatment duration (weeks)[b]	Proportion post-tarlatamab	Proportion post-SOC	Source
Topotecan	[redacted]	[redacted]	[redacted]	Treatment duration and treatment distribution post-SOC: UK CAS natural history study Treatment distribution post-tarlatamab: DeLLphi-301 trial
Clinical trials[a]	[redacted]	[redacted]	[redacted]	
Platinum-based regimen	[redacted]	[redacted]	[redacted]	
CAV	[redacted]	[redacted]	[redacted]	
No treatment	[redacted]	[redacted]	[redacted]	

[a] These represent novel treatment still under assessment or not approved in the UK for 3L+ SCLC. Their associated subsequent treatment costs were therefore not considered and 0 treatment duration was assumed
[b] For topotecan, CAV and carboplatin + etoposide, a treatment duration of 6 weeks was assumed as observed for patients receiving fourth-line treatment in the CAS historical control dataset.
Abbreviations: CAV: cyclophosphamide + doxorubicin + vincristine.

B.3.5.5 End-of-life costs

The costs applied on death are shown below in Table 59. The cost is applied when a patient transitions to the death state. The cost was inflated to the 2023 cost year.

Table 59: Palliative care costs for lung cancer

Event	Cost[101]	Cost year	Inflated unit cost
End-of-life	£7,467	2014	£8,408

B.3.6 *Severity*

The expected quality-adjusted life expectancy (QALE) for the general population was calculated in line with the methods provided by Schneider et al. (2022).[102] The total life expectancy for the modelled population was calculated using population mortality data from the Office for National Statistics (ONS) for 2017–2019. The total life expectancy was quality-adjusted using UK population norm values for EQ-5D as reported by Hernández Alava et al. (2022) through the NICE DSU.

The total QALYs for the current UK population of patients with advanced SCLC following two or more lines of treatment was based on the CAS RWE study. The proportional QALY shortfall compared to the population receiving treatment with SOC was above the threshold of 95%, therefore, a severity modifier of x1.7 applied to incremental QALYs should be considered for base case results for this comparison.

Table 60: Summary features of QALY shortfall analysis

Factor	Value	Reference to section in submission
Percentage female	[redacted]	Section B.3.2.1
Starting age (years)	[redacted]	

Abbreviations: QALY: quality-adjusted life year.

Table 61: QALY shortfall analysis results

Treatment	Expected total QALEs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute shortfall (AS)	Proportional shortfall (PS)	Severity modifier versus comparator
SOC	12.03	0.41	11.62	96.59%	1.7x

Abbreviations: AS: absolute shortfall; PS: proportional shortfall; QALE: quality-adjusted life expectancy; QALY: quality-adjusted life year; SOC: standard of care.

B.3.7 *Summary of base case analysis inputs and assumptions*

B.3.7.1 Summary of base case analysis inputs

Table 62: Summary of base case analysis inputs

Variable	Value	Measurement of uncertainty and distribution: SE (distribution)	Reference to section in submission
Patient characteristics			
Age	[redacted]	[redacted]	Section B.3.3
Proportion female	[redacted]	[redacted]	
Mean BSA (m^2)	1.78	0.36 (Normal, assumption)	
Mean weight (kg)	[redacted]	[redacted]	
OS inputs			
Tarlatamab OS distribution	Exponential	Implemented via variance-covariance matrix	Economic model: "ITC inputs" worksheet
SOC OS distribution	Exponential	Implemented via variance-covariance matrix	Economic model: "ITC inputs" worksheet
PFS inputs			
Tarlatamab PFS distribution	Lognormal	Implemented via variance-covariance matrix	Economic model: "ITC inputs" worksheet
SOC PFS distribution	As per TTD	N/A	N/A
TTD inputs			

Variable	Value	Measurement of uncertainty and distribution: SE (distribution)	Reference to section in submission
Tarlatamab TTD distribution	Exponential	Implemented via variance-covariance matrix	Economic model: "ITC inputs" worksheet
SOC TTD distribution	Exponential	Implemented via variance-covariance matrix	Economic model: "ITC inputs" worksheet
Cost inputs			
Oral chemotherapy administration cost	£27.40	£5.48 (Gamma, assumption)	Section B.3.5.1
Unit cost of required hospitalisation for 24 hours post-infusion	£488.00	£97.60 (Gamma, assumption)	Section B.3.5.1
IV chemotherapy (first attendance) admin cost	£172.00	£34.40 (Gamma, assumption)	Section B.3.5.1
IV chemotherapy (First administration of cisplatin etoposide) admin cost	£515.00	£103.00 (Gamma, assumption)	Section B.3.5.1
IV chemotherapy(subsequent attendance) admin cost	£343.00	£68.60 (Gamma, assumption)	Section B.3.5.1
Topotecan weight (%)	42%	Dirichlet	Section B.3.5.1
Platinum-based regimen weight (%)	20%		
CAV weight (%)	38%		
Tarlatamab unit cost (1 mg)	[redacted]	[redacted]	Section B.3.5.1
Tarlatamab unit cost (10 mg)	[redacted]	[redacted]	Section B.3.5.1
Topotecan cost per admin	£127.50	Not varied	Section B.3.5.1
Carboplatin cost per admin	£29.38	Not varied	Section B.3.5.1
Etoposide cost per admin	£10.69	Not varied	Section B.3.5.1
Cyclophosphamide cost per admin	£25.92	Not varied	Section B.3.5.1
Doxorubicin cost per admin	£17.18	Not varied	Section B.3.5.1
Vincristine cost per admin	£6.78	Not varied	Section B.3.5.1
Dexamethasone cost per admin	£9.68	Not varied	Section B.3.5.1
Tarlatamab Post-Progression cost - Platinum-based regimen	£48.11	£9.62 (Gamma, assumption)	Economic model: "Costs worksheet" (result of calculation and not described in submission); Section B.3.5.4

Variable	Value	Measurement of uncertainty and distribution: SE (distribution)	Reference to section in submission
Tarlatamab Post-Progression cost - CAV	£6.57	£1.31 (Gamma, assumption)	Economic model: "Costs worksheet" (result of calculation and not described in submission); Section B.3.5.4
Tarlatamab Post-Progression cost - No treatment	£0.00	£0.00 (Gamma, assumption)	Economic model: "Costs worksheet" (result of calculation and not described in submission); Section B.3.5.4
Standard of Care - Post-Progression cost - Topotecan	£62.33	£12.47 (Gamma, assumption)	Economic model: "Costs worksheet" (result of calculation and not described in submission); Section B.3.5.4
Standard of Care - Post-Progression cost - Platinum-based regimen	£44.38	£8.88 (Gamma, assumption)	Economic model: "Costs worksheet" (result of calculation and not described in submission); Section B.3.5.4
Standard of Care - Post-Progression cost - CAV	£36.84	£7.37 (Gamma, assumption)	Economic model: "Costs worksheet" (result of calculation and not described in submission); Section B.3.5.4
Standard of Care - Post-Progression cost - No treatment	£0.00	£0.00 (Gamma, assumption)	Economic model: "Costs worksheet" (result of calculation and not described in submission); Section B.3.5.4
MRU frequency - Outpatient visit	0.29	0.06 (Normal, assumption)	Section B.3.5.2
MRU frequency - GP visit - surgery	0.06	0.01 (Normal, assumption)	Section B.3.5.2
MRU frequency - GP visit - home	0.05	0.01 (Normal, assumption)	Section B.3.5.2
MRU frequency - Cancer nurse visit	0.07	0.01 (Normal, assumption)	Section B.3.5.2
MRU frequency - Community nurse visit	0.04	0.01 (Normal, assumption)	Section B.3.5.2
Monitoring frequency - ECG	0.01	0.00 (Normal, assumption)	Section B.3.5.2

Variable	Value	Measurement of uncertainty and distribution: SE (distribution)	Reference to section in submission
Monitoring frequency - Chest X-ray	0.11	0.02 (Normal, assumption)	Section B.3.5.2
Monitoring frequency - CT scan frequency	0.09	0.02 (Normal, assumption)	Section B.3.5.2
Monitoring frequency - Brain MRI	0.01	0.00 (Normal, assumption)	Section B.3.5.2
Monitoring frequency - Blood test frequency	0.13	0.03 (Normal, assumption)	Section B.3.5.2
Outpatient visit unit cost	£141.00	£28.20 (Gamma, assumption)	Section B.3.5.2
GP visit - surgery unit cost	£41.80	£8.36 (Gamma, assumption)	Section B.3.5.2
GP visit - home unit cost	£90.06	£18.01 (Gamma, assumption)	Section B.3.5.2
Cancer nurse visit unit cost	£56.44	£11.29 (Gamma, assumption)	Section B.3.5.2
Community nurse visit unit cost	£84.62	£16.92 (Gamma, assumption)	Section B.3.5.2
ECG unit cost	£134.00	£26.80 (Gamma, assumption)	Section B.3.5.2
Chest X-ray unit cost	£29.00	£5.80 (Gamma, assumption)	Section B.3.5.2
CT scan unit cost	£99.00	£19.80 (Gamma, assumption)	Section B.3.5.2
Brain MRI unit cost	£209.00	£41.80 (Gamma, assumption)	Section B.3.5.2
Blood test unit cost	£3.02	£0.60 (Gamma, assumption)	Section B.3.5.2
End of life cost	£8,407.69	£1,681.54 (Gamma, assumption)	Section B.3.5.5
Adverse event rates			
Patients with AEs (tarlatamab) - Anaemia	4.04%	2.00% (Beta)	Section B.3.4.3
Patients with AEs (tarlatamab) - Diarrhea	0.00%	0.00% (Beta)	Section B.3.4.3
Patients with AEs (tarlatamab) - Fatigue	1.01%	1.02% (Beta)	Section B.3.4.3
Patients with AEs (tarlatamab) - Febrile neutropenia	1.01%	1.02% (Beta)	Section B.3.4.3
Patients with AEs (tarlatamab) - Leukopenia	0.00%	0.00% (Beta)	Section B.3.4.3
Patients with AEs (tarlatamab) - Lymphocyte count decreased	6.06%	2.42% (Beta)	Section B.3.4.3

Variable	Value	Measurement of uncertainty and distribution: SE (distribution)	Reference to section in submission
Patients with AEs (tarlatamab) - Lymphopenia	7.07%	2.60% (Beta)	Section B.3.4.3
Patients with AEs (tarlatamab) - Nausea	0.00%	0.00% (Beta)	Section B.3.4.3
Patients with AEs (tarlatamab) - Neutropenia	1.01%	1.02% (Beta)	Section B.3.4.3
Patients with AEs (tarlatamab) - Neutrophil count decreased	1.01%	1.02% (Beta)	Section B.3.4.3
Patients with AEs (tarlatamab) - Non-sepsis infection	2.02%	1.43% (Beta)	Section B.3.4.3
Patients with AEs (tarlatamab) - Thrombocytopenia	0.00%	0.00% (Beta)	Section B.3.4.3
Patients with AEs (tarlatamab) - CRS	51.52%	5.07% (Beta)	Section B.3.4.3
Patients with AEs (tarlatamab) - ICAN	5.05%	2.22% (Beta)	Section B.3.4.3
Patients with AEs (topotecan) - Anaemia	25.00%	Not varied	Section B.3.4.3
Patients with AEs (topotecan) - Diarrhea	6.00%	Not varied	Section B.3.4.3
Patients with AEs (topotecan) - Fatigue	4.00%	Not varied	Section B.3.4.3
Patients with AEs (topotecan) - Febrile neutropenia	3.00%	Not varied	Section B.3.4.3
Patients with AEs (topotecan) - Leukopenia	0.00%	Not varied	Section B.3.4.3
Patients with AEs (topotecan) - Lymphocyte count decreased	0.00%	Not varied	Section B.3.4.3
Patients with AEs (topotecan) - Lymphopenia	0.00%	Not varied	Section B.3.4.3
Patients with AEs (topotecan) - Nausea	0.00%	Not varied	Section B.3.4.3
Patients with AEs (topotecan) - Neutropenia	61.00%	Not varied	Section B.3.4.3
Patients with AEs (topotecan) - Neutrophil count decreased	0.00%	Not varied	Section B.3.4.3
Patients with AEs (topotecan) - Non-sepsis infection	14.08%	Not varied	Section B.3.4.3

Variable	Value	Measurement of uncertainty and distribution: SE (distribution)	Reference to section in submission
Patients with AEs (topotecan) - Thrombocytopenia	38.00%	Not varied	Section B.3.4.3
Patients with AEs (platinum-based regimen) - Anaemia	12.24%	2.35% (Beta)	Section B.3.4.3
Patients with AEs (platinum-based regimen) - Diarrhea	0.51%	0.51% (Beta)	Section B.3.4.3
Patients with AEs (platinum-based regimen) - Fatigue	0.51%	0.51% (Beta)	Section B.3.4.3
Patients with AEs (platinum-based regimen) - Febrile neutropenia	6.12%	1.72% (Beta)	Section B.3.4.3
Patients with AEs (platinum-based regimen) - Leukopenia	4.08%	1.42% (Beta)	Section B.3.4.3
Patients with AEs (platinum-based regimen) - Lymphocyte count decreased	0.00%	0.00% (Beta)	Section B.3.4.3
Patients with AEs (platinum-based regimen) - Lymphopenia	0.00%	0.00% (Beta)	Section B.3.4.3
Patients with AEs (platinum-based regimen) - Nausea	0.51%	0.51% (Beta)	Section B.3.4.3
Patients with AEs (platinum-based regimen) - Neutropenia	24.49%	3.09% (Beta)	Section B.3.4.3
Patients with AEs (platinum-based regimen) - Neutrophil count decreased	16.84%	2.69% (Beta)	Section B.3.4.3
Patients with AEs (platinum-based regimen) - Non-sepsis infection	1.02%	0.72% (Beta)	Section B.3.4.3
Patients with AEs (platinum-based regimen) - Thrombocytopenia	7.65%	1.91% (Beta)	Section B.3.4.3
Patients with AEs (CAV) - Anaemia	19.23%	3.90% (Beta)	Section B.3.4.3
Patients with AEs (CAV) - Diarrhea	0.00%	0.00% (Beta)	Section B.3.4.3
Patients with AEs (CAV) - Fatigue	8.65%	2.78% (Beta)	Section B.3.4.3

Variable	Value	Measurement of uncertainty and distribution: SE (distribution)	Reference to section in submission
Patients with AEs (CAV) - Febrile neutropenia	0.00%	0.00% (Beta)	Section B.3.4.3
Patients with AEs (CAV) - Leukopenia	78.85%	4.04% (Beta)	Section B.3.4.3
Patients with AEs (CAV) - Lymphocyte count decreased	0.00%	0.00% (Beta)	Section B.3.4.3
Patients with AEs (CAV) - Lymphopenia	0.00%	0.00% (Beta)	Section B.3.4.3
Patients with AEs (CAV) - Nausea	5.77%	2.31% (Beta)	Section B.3.4.3
Patients with AEs (CAV) - Neutropenia	82.69%	3.75% (Beta)	Section B.3.4.3
Patients with AEs (CAV) - Neutrophil count decreased	0.00%	0.00% (Beta)	Section B.3.4.3
Patients with AEs (CAV) - Non-sepsis infection	0.00%	0.00% (Beta)	Section B.3.4.3
Patients with AEs (CAV) - Thrombocytopenia	14.42%	3.48% (Beta)	Section B.3.4.3
Adverse event unit cost - Anaemia	£6,124.00	£1,224.80 (Gamma, assumption)	Section B.3.5.3
Adverse event unit cost - Diarrhea	£7,609.00	£1,521.80 (Gamma, assumption)	Section B.3.5.3
Adverse event unit cost - Fatigue	£6,124.00	£1,224.80 (Gamma, assumption)	Section B.3.5.3
Adverse event unit cost - Febrile neutropenia	£4,810.00	£962.00 (Gamma, assumption)	Section B.3.5.3
Adverse event unit cost - Leukopenia	£2,196.00	£439.20 (Gamma, assumption)	Section B.3.5.3
Adverse event unit cost - Lymphocyte count decreased	£303.00	£60.60 (Gamma, assumption)	Section B.3.5.3
Adverse event unit cost - Lymphopenia	£2,196.00	£439.20 (Gamma, assumption)	Section B.3.5.3
Adverse event unit cost - Nausea	£312.64	£62.53 (Gamma, assumption)	Section B.3.5.3
Adverse event unit cost - Neutropenia	£2,196.00	£439.20 (Gamma, assumption)	Section B.3.5.3
Adverse event unit cost - Neutrophil count decreased	£303.00	£60.60 (Gamma, assumption)	Section B.3.5.3
Adverse event unit cost - Non-sepsis infection	£5,358.00	£1,071.60 (Gamma, assumption)	Section B.3.5.3
Adverse event unit cost - Thrombocytopenia	£5,764.00	£1,152.80 (Gamma, assumption)	Section B.3.5.3

Variable	Value	Measurement of uncertainty and distribution: SE (distribution)	Reference to section in submission
Quality-of-life inputs			
Utility tarlatamab - progression free	0.79	0.020 (Beta)	Section B.3.4.1
Utility tarlatamab - post progression	0.68	0.020 (Beta)	Section B.3.4.1
Utility SoC - progression free	0.79	0.020 (Beta)	Section B.3.4.1
Utility SoC - post progression	0.68	0.020 (Beta)	Section B.3.4.1
Adverse event duration (days) - Anaemia	28.00	5.60 (Gamma, assumption)	Section B.3.4.4
Adverse event duration (days) - Diarrhoea	28.00	5.60 (Gamma, assumption)	Section B.3.4.4
Adverse event duration (days) - Fatigue	28.00	5.60 (Gamma, assumption)	Section B.3.4.4
Adverse event duration - Febrile neutropenia	28.00	5.60 (Gamma, assumption)	Section B.3.4.4
Adverse event duration - Leukopenia	28.00	5.60 (Gamma, assumption)	Section B.3.4.4
Adverse event duration - Lymphocyte count decreased	28.00	5.60 (Gamma, assumption)	Section B.3.4.4
Adverse event duration - Lymphopenia	28.00	5.60 (Gamma, assumption)	Section B.3.4.4
Adverse event duration - Nausea	28.00	5.60 (Gamma, assumption)	Section B.3.4.4
Adverse event duration - Neutropenia	28.00	5.60 (Gamma, assumption)	Section B.3.4.4
Adverse event duration - Neutrophil count decreased	28.00	5.60 (Gamma, assumption)	Section B.3.4.4
Adverse event duration - Non-sepsis infection	28.00	5.60 (Gamma, assumption)	Section B.3.4.4
Adverse event duration - Thrombocytopenia	28.00	5.60 (Gamma, assumption)	Section B.3.4.4
Adverse event duration - CRS	28.00	5.60 (Gamma, assumption)	Section B.3.4.4
Adverse event duration - ICAN	28.00	5.60 (Gamma, assumption)	Section B.3.4.4
Adverse event QALY loss - Anaemia	0.02	0.00 (Beta, assumption)	Section B.3.4.4
Adverse event QALY loss - Diarrhea	0.05	0.01 (Beta, assumption)	Section B.3.4.4
Adverse event QALY loss - Fatigue	0.07	0.01 (Beta, assumption)	Section B.3.4.4

Variable	Value	Measurement of uncertainty and distribution: SE (distribution)	Reference to section in submission
Adverse event QALY loss - Febrile neutropenia	0.09	0.02 (Beta, assumption)	Section B.3.4.4
Adverse event QALY loss - Leukopenia	0.04	0.01 (Beta, assumption)	Section B.3.4.4
Adverse event QALY loss - Lymphocyte count decreased	0.01	0.00 (Beta, assumption)	Section B.3.4.4
Adverse event QALY loss - Lymphopenia	0.07	0.01 (Beta, assumption)	Section B.3.4.4
Adverse event QALY loss - Nausea	0.05	0.01 (Beta, assumption)	Section B.3.4.4
Adverse event QALY loss - Neutropenia	0.09	0.02 (Beta, assumption)	Section B.3.4.4
Adverse event QALY loss - Neutrophil count decreased	0.07	0.01 (Beta, assumption)	Section B.3.4.4
Adverse event QALY loss - Non-sepsis infection	0.22	0.04 (Beta, assumption)	Section B.3.4.4
Adverse event QALY loss - Thrombocytopenia	0.07	0.01 (Beta, assumption)	Section B.3.4.4
Adverse event QALY loss - CRS	0.22	0.04 (Beta, assumption)	Section B.3.4.4
Adverse event QALY loss - ICAN	0.22	0.04 (Beta, assumption)	Section B.3.4.4
Relative Dose intensity - Tarlatamab	0.86	0.02 (Beta)	Section B.2.10.2; B.3.5.1
Relative Dose intensity - Topotecan	0.98	0.20 (Beta, assumption)	Section B.3.5.1
Relative Dose intensity - Carboplatin	0.93	0.19 (Beta, assumption)	Section B.3.5.1
Relative Dose intensity - Etoposide	0.90	0.18 (Beta, assumption)	Section B.3.5.1
Relative Dose intensity - Cyclophosphamide	1.00	0.20 (Beta, assumption)	Section B.3.5.1
Relative Dose intensity - Doxorubicin	1.00	0.20 (Beta, assumption)	Section B.3.5.1
Relative Dose intensity - Vincristine	1.00	0.20 (Beta, assumption)	Section B.3.5.1
Relative Dose intensity - Dexamethasone	0.86	0.17 (Beta, assumption)	Section B.3.5.1

Abbreviations: CI: confidence interval.

B.3.7.2 Assumptions

The key assumptions used in the model are described below in Table 63.

Table 63: Summary of key assumptions used in the economic analysis

Parameter	Assumptions
Efficacy	• PFS and OS inputs for tarlatamab in the CEA model were adjusted PFS and OS informed by a MAIC comparing tarlatamab vs. the UK CAS historical control 3L data; PFS and OS inputs for SOC were informed by the UK CAS historical control 3L data • There are no PFS data in the UK CAS data. Therefore, time to treatment discontinuation (TTD) was used as a proxy for PFS of SOC • For PFS, in the base-case model, parametric function with log-normal distribution was used for tarlatamab based on best AIC fit • For OS, parametric function with exponential distribution was used for tarlatamab based on best AIC fit in the base-case; following NICE Decision Support Unit (DSU) 14, the same distribution was used to extrapolate OS for SOC[83]
Health states and utilities by health states	• At the start of each cycle, patients were redistributed among the 3 health states (PF, PP and death), with death being the absorbing state • Utilities of health states, in the absence of AEs, were assumed to be dependent only on health state and independent on treatment arm. In addition, age- and sex-adjusted utilities were considered
Disutility	• Treatment disutilities included the disutilities of grade 1/2 cytokine release syndrome (CRS), grade 1/2 immune effector cell-associated neurotoxicity syndrome (ICANS), and grade 3+ AEs other than CRS and ICANS. There are no grade 3+ CRS or ICANS observed in the DeLLPhi-301 trial. • Disutilities of CRS and ICANs were applied for patients with CRS or ICANS respectively for a duration of 4 days. Disutilities due to grade 3+ AEs other than CRS and ICANS were applied for a duration of 28 days. Both durations were based on assumptions • The sum of disutilities across AE was applied to each treatment arm in the first cycle of the model
Treatment costs	• Based on the DeLLphi-301 trial protocol,[86] it was assumed all patients received tarlatamab were hospitalized for 24 hours post-tarlatamab infusion at dose 1 and 2, and therefore incurred hospitalization costs at treatment initiation • The base-case assumed tarlatamab was used until disease progression, consistent with the anticipated product label of tarlatamab. The TTD of tarlatamab was informed by MAIC weighted TTD data from the DeLLphi-301 trial and the TTD of SOC was informed by the UK CAS historical control 3L data • For both intravenous (IV) and orally administered drugs, drug wastage was considered in the base-case analysis
Subsequent treatment	• Subsequent treatments were included in the model to reflect the natural treatment course patients experienced; efficacy of subsequent treatment was not explicitly modelled but was reflected in the OS of initial treatments. Costs of subsequent treatments were included for the proportion of patients who received them.
AE costs and medical costs	• Costs for grade 1/2 CRS and ICANS and grade 3+ AEs other than CRS and ICANs were included in the model. Only AEs occurring in more than 3% of patients in any of the treatment arms were included. AE costs were added as one-time costs in the model for both treatment arms. • In addition to treatment and AE costs, the model considered additional medical costs including MRU and monitoring costs and terminal care costs.

Parameter	Assumptions
	• MRU and monitoring costs were assumed to only incur when patients were on treatment and the frequency were independent of treatment arms. • All patients incurred one-time terminal care costs before death.

Abbreviations: 3L: third line; AE: adverse event; AIC: Akaike information criteria; CAS: Cancer Analysis System; CEA: cost-effectiveness analysis; CRS: cytokine-release syndrome; DSU: Decision Support Unit; ICANS: immune effector cell-associated neurotoxicity syndrome; IV: intravenous; MAIC: matching-adjusted indirect comparison; MRU: medical resource use; NICE: National Institute of Health and Care Excellence; OS: overall survival; PF: progression free; PFS: progression-free survival; PP: post progression; SOC: standard of care; TTD: time to treatment discontinuation; UK: United Kingdom.

B.3.8 *Base case results*

The probabilistic and deterministic base case results are presented below in Table 64 and Table 65 respectively.

B.3.8.1 Base case incremental cost-effectiveness analysis results

Table 64: Base case results (probabilistic)

Technologies	Total costs (£) [95% CI]	Total LYG [95% CI]	Total QALYs [95% CI]	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Standard of care	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Tarlatamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,506.58	£34,506.58

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 65: Base case results (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Standard of care	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Tarlatamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,011.93	£35,011.93

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

B.3.9 *Exploring uncertainty*

B.3.9.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to estimate the probability for tarlatamab to be cost-effective compared to SOC, based on different WTP thresholds. A Monte-Carlo simulation with 5,000 iterations was conducted to ensure convergence of model results as shown in Figure 26. In each iteration, the model inputs were randomly drawn from the specified distributions, as summarised in Section B.3.7.1.

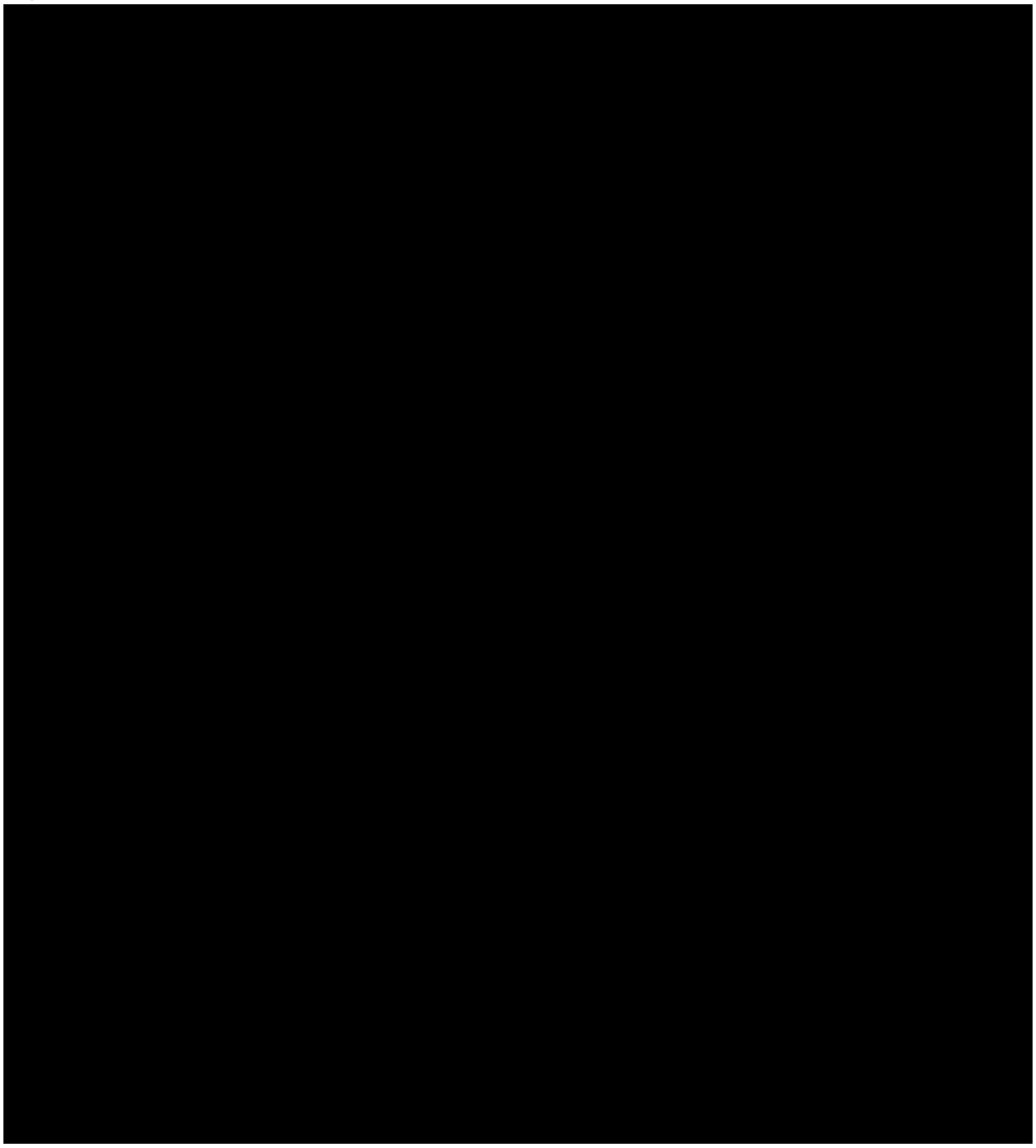
Whenever available, the SE of the selected distribution was obtained directly from the same data source that informed the mean value. In the absence of data on the variability around health state cost values, the SE for each cost parameter was assumed to be equal to 20% of the mean value.

The cost-effectiveness plane for the base case analysis is presented below in Figure 27. 99.9% of PSA iterations were in the Northeastern quadrant of the cost-effectiveness plane, indicating that tarlatamab is both more costly and more effective than SOC.

The cost-effectiveness acceptability curve (CEAC) is presented in Figure 28. Assuming a willingness-to-pay threshold of £30,000 and a disease severity modifier of 1.7, tarlatamab has a 36.4% probability of being cost-effective versus SOC.

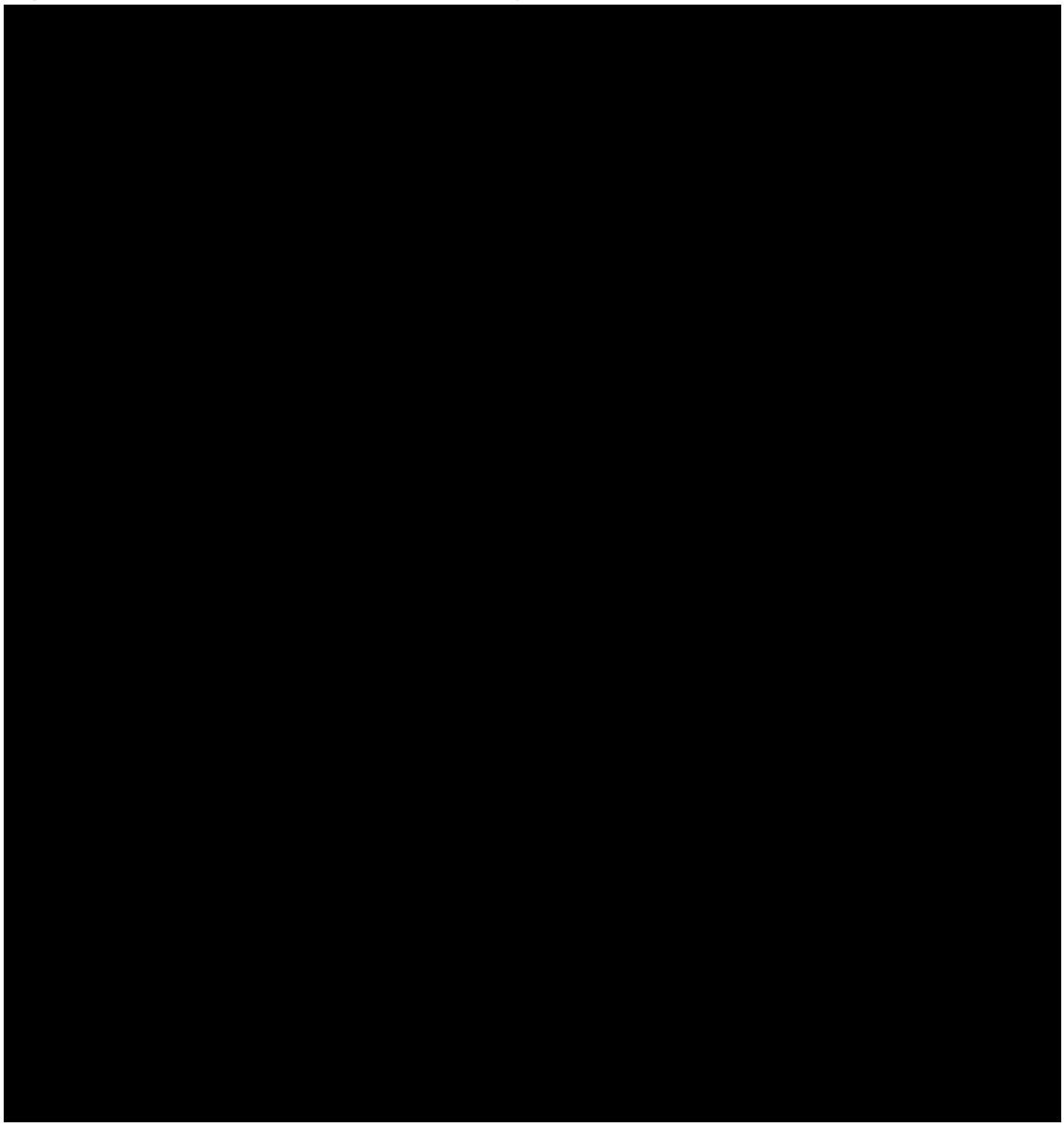
Figure 26: ICER convergence

Figure 27: Incremental cost-effectiveness plane - tarlatamab versus SOC



Abbreviations: SOC: standard of care; QALYs: quality-adjusted life years.

Figure 28: Cost-effectiveness acceptability curve for tarlatamab versus SOC



Abbreviations: CAS: Cancer Analysis System; QALY: quality-adjusted life year; WTP: willingness-to-pay.

B.3.9.2 Deterministic sensitivity analysis

The results of the deterministic sensitivity analysis are presented in a tornado diagram (Figure 29) and tabulated in Table 66. Model parameters were varied by +/- 20% of the deterministic point estimate for each parameter. The top 10 most influential variables are plotted; the utility value for tarlatamab patients who are progression-free, the RDI for tarlatamab, and the unit cost for tarlatamab are the three most influential variables on the model results.

Figure 29: Tornado diagram - tarlatamab versus SOC

Abbreviations: ICER: incremental cost-effectiveness ratio; IV: intravenous; SOC: standard of care; QALY: quality-adjusted life year.

Table 66: Tabulated DSA results

Rank	Parameter	Point estimate	Low parameter value	High parameter value	ICER low value	ICER high value	Difference between low and high
1	Utility tarlatamab - progression free	[redacted]	[redacted]	[redacted]	£76,556	£48,686	£27,869
2	Relative Dose intensity - Tarlatamab	0.86	0.68	1.03	£47,158	£71,882	£24,724
3	Tarlatamab unit cost (10 mg)	[redacted]	[redacted]	[redacted]	£47,234	£71,807	£24,573
4	Utility tarlatamab - post progression	[redacted]	[redacted]	[redacted]	£66,250	£54,032	£12,218
5	Utility SoC - post progression	[redacted]	[redacted]	[redacted]	£54,794	£65,139	£10,345
6	Utility SoC - progression free	[redacted]	[redacted]	[redacted]	£57,249	£61,979	£4,730

Rank	Parameter	Point estimate	Low parameter value	High parameter value	ICER low value	ICER high value	Difference between low and high
7	IV chemotherapy (first attendance) admin cost	172.00	137.60	206.40	£58,659	£60,381	£1,722
8	Adverse event unit cost - Neutropenia	£2,196.00	£1,756.80	£2,635.20	£59,921	£59,120	£801
9	Adverse event unit cost - Thrombocytopenia	£5,764.00	£4,611.20	£6,916.80	£59,917	£59,124	£792
10	IV chemotherapy (First administration of cisplatin etoposide) admin cost	£515.00	£412.00	£618.00	£59,849	£59,191	£658

Abbreviations: DSA: deterministic sensitivity analysis; ICER: incremental cost-effectiveness ratio; IV: intravenous; SOC: standard of care; QALY: quality-adjusted life year.

B.3.9.3 Scenario analysis

A series of scenarios were considered for the cost-utility analysis. A list of the scenarios and the rationale for their inclusion is presented in Table 67.

Table 67: List of scenarios

Scenario number	Scenario	Rationale
1	Set costs and discount rates to 1.5%	To demonstrate the stability of the ICER under a range of discounting scenarios
2	Set costs and discount rates to 5%	
3	Time horizon 5 years	A conservative analysis wherein longer-term benefits of tarlatamab are truncated and all benefits are captured within 5 years of treatment initiation
4	Time horizon 15 years	To demonstrate the stability of the ICER when a longer time horizon than the base case is utilised
5	OS distribution selection: Weibull	To show the impact of fitting different parametric distributions to the OS data for tarlatamab and SOC, as other distributions may be plausible.
6	OS distribution selection: lognormal	
7	OS distribution selection: log-logistic	
8	OS distribution selection: Gompertz	
9	OS distribution selection: generalised gamma	
10	OS distribution selection: gamma	
11	Treatment-specific health state utility values used in the PFS state	To allow for utility values to differentiate based on treatment and health state rather than health state alone; may reflect impact of less-severe adverse events (grades 1 and 2) which are captured by using treatment arm-specific utilities

Scenario number	Scenario	Rationale
12	SOC composition: all patients received topotecan	Scenarios to investigate pairwise comparisons against the individual treatments comprising SOC; same efficacy data used for all analyses
13	SOC composition: all patients received CAV	
14	SOC composition: all patients received platinum-based chemotherapy	
15	Do not consider post-infusion hospitalisation costs for tarlatamab	Scenario which may be reflective of future practice in the NHS when monitoring may not be required to be as extensive as in the anticipated marketing authorisation
16	Do not consider impacts of CRS and ICANS	Scenario which excludes CRS and ICANS events costs and disutilities which may be reflective of clinicians becoming more experienced in treating these AEs
17	Do not adjust tarlatamab OS and TTD for post-progression tarlatamab use	Conservative scenario where TTD is modelled as per DeLLphi-301, i.e., treatment is permitted beyond disease progression
18	Do not consider vial wastage	Scenario where vial sharing may be possible in some treatment centres

Abbreviations: CAV, cyclophosphamide, doxorubicin and vincristine; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ICER, incremental cost-effectiveness ratio; OS, overall survival; SOC, standard of care.

B.3.9.4 Summary of sensitivity analyses results

The results of the scenario analyses are presented below in Table 68. All scenarios were conducted probabilistically using 5,000 samples as for the base case.

Table 68: Scenario analysis results

Scenario number	ICER	Tarlatamab			SOC			Incremental		
		Costs	QALYs	LYs	Costs	QALYs	LYs	Costs	QALYs	LYs
1	£33,501	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	£35,302	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	£37,228	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	£34,545	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	£38,531	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	£22,881	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	£24,405	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	£24,599	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	£13,810	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	£39,268	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario number	ICER	Tarlatamab			SOC			Incremental		
		Costs	QALYs	LYs	Costs	QALYs	LYs	Costs	QALYs	LYs
11	£33,721	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	£34,808	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	£35,250	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	£34,402	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	£33,635	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	£34,065	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	£44,433	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	£34,644	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life year; SOC: standard of care; QALY: quality-adjusted life year.

B.3.10 *Subgroup analysis*

The analysis does not consider any subgroups of the previously-treated SCLC population. No subgroups of the anticipated licenced indication are deemed to be appropriate for this evidence submission.

B.3.11 *Benefits not captured in the QALY calculation*

All benefits are captured in the QALY calculations.

B.3.12 *Validation*

B.3.12.1 Validation of cost-effectiveness analysis

The current model used efficacy data from the DeLLphi-301 trial for tarlatamab and the UK CAS study data for SOC to simulate the disease course of the target population over a lifetime horizon. Because data from both sources had limited follow-up, but the impact of the treatments on the disease have effect on the scale of the lifetime of patients, it necessitates the use of a modelling approach to evaluate the long-term value of the treatments.

Survival extrapolation was essential to quantify the survival benefit beyond the trial period and a robust and comprehensive approach was followed during the survival extrapolation to ensure the methods were statistically sound, but also clinically plausible. The validity of the model prediction was first assessed by comparing modelled efficacy outcomes against the original sources that informed the efficacy inputs (Figure 30, Figure 31).

Figure 30: Tarlatamab OS: comparison between predicted vs. observed

Abbreviations: OS: overall survival.

Figure 31: SOC OS: comparison between predicted vs. observed

Abbreviations: OS: overall survival.

Overall, the predicted curves fitted the observed data well (Table 69). The predicted median OS was close to the observed median OS. Particularly, the curves for both arms validated well during the first 16 months after treatment initiation where the observed data from the DeLLphi-301 trial are available. For example, the observed OS by month 6 for tarlatamab and SOC was 73% and 46%, while the predicted OS was 72% and 43%, respectively. In addition, for SOC, the predicted OS underestimated the observed OS for the first 7 months but remained to be higher than the observed OS afterwards, suggesting the base case analysis may have overestimated the OS of SOC and therefore is conservative against tarlatamab.

Table 69: Observed and predicted OS

Treatment arm	Time points	Observed	Predicted	Difference (predicted-observed)[a]
Tarlatamab	Median	[redacted]	[redacted]	
	1 month	[redacted]	[redacted]	2%
	6 months	[redacted]	[redacted]	-1%
	12 months	[redacted]	[redacted]	5%
	24 months	Not reached	[redacted]	Not available
SOC	Median	[redacted]	[redacted]	
	1 month	[redacted]	[redacted]	-10%
	6 months	[redacted]	[redacted]	-3%
	12 months	[redacted]	[redacted]	5%
	24 months	[redacted]	[redacted]	2%

[a] For tarlatamab, the observed OS was based on MAIC-weighted data after adjusting for post-progression tarlatamab use.

Abbreviations: OS, overall survival; SOC, standard of care. Interpretation and conclusions of economic evidence

B.3.13 *Interpretation and conclusions of economic evidence*

SCLC is a rare and aggressive disease associated with extremely poor survival outcomes and severely reduced HRQoL for patients. Current treatment options offer limited survival benefits, and survival worsens with each subsequent line of treatment. For the few patients who reach third-line treatment, options are limited to re-treatment with previously failed therapies, with very poor OS outcomes.

The DeLLphi-301 trial demonstrated tarlatamab to be associated with high response rates, which were durable and led to survival benefits well above those seen with current treatments: a UK RWE study conducted by Amgen showed current third-line treatments to be associated with OS of less than [redacted] months, compared to OS of 14.3 months in the DeLLphi-30 trial.

In order to robustly compare these different outcomes, a MAIC analysis was carried out to ensure patient characteristics and outcomes from the DeLLphi-301 were most reflective of those expected in current UK practice. The analysis compared tarlatamab against comparators which were found to be used in routine clinical practice in 3L SCLC via analysis of the SACT database of outcomes and treatment patterns in England. As there is no single defined SOC in third-line SCLC, a “basket of comparators” approach was taken, reflective of current UK clinical practice as described in Section B.1.3.3. The results of the MAIC confirmed the compelling reduction in both risk of death and disease progression, showing OS and PFS HRs of 0.367 and 0.184, respectively. A *de novo* economic evaluation has attempted to estimate the cost-effectiveness of tarlatamab for adult patients with previously treated advanced SCLC in line with its anticipated marketing authorisation, and in line with the population defined in the NICE final scope and company decision problem. Efficacy estimates in the model were informed by MAICs to estimate comparative efficacy in terms of OS and PFS (using TTD as a proxy for PFS in the comparator arm). This evidence synthesis approach used the most robust statistical methods available and used the most UK-relevant data possible.

In terms of the survival curves selected for OS, PFS and TTD, curve selections were made by a combination of visual inspection, feedback from clinical experts, and validation against the DeLLphi-300 first-in-human study. The curve selections were conservative, as there were other plausible distributions which could have fit to the observed data well and would have predicted higher OS, PFS and TTD.

The base case analysis adjusted for tarlatamab patients who received treatment beyond progression by censoring these patients at the point of disease progression from the OS and PFS analyses. This adjustment was made in order to reflect the expected use of tarlatamab in NHS practice, in line with its anticipated license. All costs were taken from the most relevant cost sources, including eMIT, the NHS Schedule of Reference Costs, and NHS Cost Collections. Where these costs were not available, they were sourced from the literature and previous NICE TAs.

A NICE positive recommendation for tarlatamab would ensure patients have access to the first immunotherapy specifically approved in third-line SCLC and enabling severely ill patients to significantly extend and improve their lives.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Tarlatamab for previously treated advanced small-cell lung cancer

[ID6364]

Summary of Information for Patients (SIP)

May 2024

File name	Version	Contains confidential information	Date
ID6364_Tarlatamab in SCLC_SIP_24May24 [NoCON]	V1.1	No	24th May 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

Please note: Cross-references to figures, tables, other sections with the document or to other documents are highlighted in **orange**. Further explanations for the words and phrases highlighted in **black bold text** are provided in the glossary (**Section 4b**).

1a) Name of the medicine (generic and brand name):

Generic name: Tarlatamab

Brand name: IMDYLLTRA®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

This medicine is under consideration for the treatment of adult patients with advanced small-cell lung cancer (SCLC) after 2 or more treatments. As defined in **Section 2a**) The condition – clinical presentation and impact below, patients are said to have advanced disease when the primary cancer tumour has spread to other parts of the body.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The Medicines and Healthcare products Regulatory Agency (MHRA) is reviewing whether tarlatamab should be approved and granted **marketing authorisation** as a

treatment for adult patients with advanced SCLC with **disease progression** on or after platinum-based chemotherapy. It is anticipated that tarlatamab will be granted authorisation for use under a 'conditional approval' scheme, meaning that further evidence on the medicine will be required in order to gain full marketing approval. The marketing authorisation for tarlatamab is pending the outcome of this assessment, and more information on this can be found in **Document B** in **Section B.1.2**.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Amgen have not engaged with any patient advocacy groups for SCLC.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

The condition that tarlatamab plans to treat is small-cell lung cancer (SCLC)

What is SCLC?

Lung cancer is a complex disease originating in the trachea, bronchus or lung tissue and is divided into two subtypes based on the relative size of the cancer cells under a microscope: small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).[1, 2] As the name suggests, cancerous cells in SCLC appear smaller and rounder when studied under a microscope, as compared with cells in NSCLC. SCLC is associated with rapid tumour growth and there is a high likelihood that secondary cancer growths (separate from the primary site) will develop; this is called **metastasis**.[3]

SCLC can be divided further, into **limited-stage** or **extensive-stage** disease. In limited-stage disease, the cancer is confined to one side of the chest, with any spread being limited to nearby lymph nodes only (small glands that filter fluid containing white blood cells to help fight infection). In contrast, in extensive-stage disease, the primary cancer tumour has spread to other parts of the body to other organs, lymph nodes or tissues.[4] Additionally, patients with extensive-stage disease often develop brain metastases (spread of cancer cells to the brain), which can cause neurological symptoms such as headaches, vomiting, cognitive decline and seizures.[5] Clinical distinctions between extensive-stage and advanced SCLC exist, however these terms may sometimes be used interchangeably. The term “advanced SCLC” is used in this submission to describe the disease tarlatamab is intended to treat.

How common is SCLC?

In England, lung cancer is the second most common cancer, accounting for approximately 12% of all new cancer cases, and is most common in people aged 85 to 89 years old.[6, 7] In 2019, 40,168 people were diagnosed with lung cancer in England and it is estimated that there will be as many as 66,200 new cases every year in the UK by 2038−2040.[8] SCLC accounts for approximately 15–20% of cases of lung cancer.[1]

What is the impact of SCLC (disease burden)?

Life expectancy

The impact of SCLC is different for each patient, depending on several factors such as age, other conditions the patient may have and other disease-specific factors such as disease stage, aggressiveness and response to therapy. Overall, **prognosis** remains poor: on average, only 5−10% of patients with SCLC are expected to survive for five years following diagnosis.[9, 10] In particular, there is a lack of effective treatment options in the UK for patients with advanced SCLC who have received two or more prior treatments, and this is reflected in the even poorer prognosis, where clinical studies have reported average life expectancy to be between 1.1 to 7.0 months in these patients.[11]

Symptoms of SCLC and their physical impact

Patients with SCLC often experience shortness of breath, a persistent cough and other symptoms associated with co-existing health conditions such as high blood pressure (hypertension), cardiac disease and diabetes.[12] Metastases, which often occur in the brain, are also associated with worsening symptoms such as neurological problems, nerve pain, fatigue and anorexia, further increasing the burden for patients. The health of patients with SCLC may also be impacted negatively by the **side effects** of chemotherapy, which can cause vomiting, diarrhoea, hair loss (alopecia), sore mouth, a decrease in the ability of the bone marrow to produce blood cells (myelosuppression), and damage to nerves in the peripheral nervous system (peripheral neuropathy).[13]

Impact on quality of life

In addition to the physical symptoms associated with the disease, SCLC also significantly impacts the mental and emotional health of patients. In medicine, the physical and mental wellbeing of patients are referred to as their health-related quality of life (**HRQoL**). The HRQoL of patients is typically measured through patient questionnaires, and the scores of patients with a disease are compared to those of the general population (without the disease) to assess the disease impact on wellbeing. In general, a higher HRQoL is beneficial and reflects a better **quality of life** in terms of physical and mental wellbeing, and vice versa.

Whilst there are limited data for SCLC specifically, evidence suggests that patients with SCLC experience poor HRQoL due to highly bothersome symptoms that impact them physically, emotionally and socially.[14] In particular, patients often experience difficulties in doing everyday activities and participating in hobbies due to fatigue and difficulty breathing.[14] The impact of SCLC on HRQoL is further discussed in Section 2d) Patient-based evidence (PBE) about living with the condition.

Impact on carers

Studies of carers of patients with SCLC have reported the significant financial, social and emotional burden associated with caring for a patient with the disease. In particular, carers reported a reduced ability to participate in their own social lives and emphasised the negative emotional impact this brings.[14] Additionally, caregivers for patients with SCLC may experience financial burden disproportionately relative to caregivers of patients with other diseases, due to the intensity of care that they provide.[15] For example, carers of patients with SCLC may also accompany patients to attend medical appointments which can disrupt their employment, leading to missed workdays, increasing the financial impact felt by carers. The impact of SCLC on carers is further discussed in Section 2d) Patient-based evidence (PBE) about living with the condition.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How is SCLC diagnosed?

If SCLC is suspected due to symptoms such as a cough, chest pain, fatigue and shortness of breath, doctors will use various tests to diagnose the disease, including:[16]

- Performing a bronchoscopy (inserting a flexible tube through the nose or mouth and down the windpipe) in order to take a biopsy (a small sample of body tissue) of the suspicious lung mass, which is then tested to confirm the disease diagnosis
- Performing imaging tests to identify tumours in the lungs or other parts of the body
- Using a fine needle and syringe to withdraw the suspected tumour mass from locations that cannot be reached by a bronchoscopy, whilst the needle is being viewed on a computer scan by a doctor (a transthoracic needle aspiration)

In order to accurately treat patients with SCLC, assessing the stage of the disease is also required. Imaging is used to determine whether the disease is confined to the lungs and one side of the chest (limited stage disease) or has spread to other parts of the body (extensive stage disease).[16]

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What are the current treatment options for SCLC?

The treatment guidelines for SCLC in the UK are available from the National Institute of Health and Care Excellence (NICE) (NG122).[2] Whilst treatments exist for patients with SCLC, some patients will experience disease that continues to grow despite receiving two previous treatments (termed “disease progression”). Treatment options for these patients with progressive disease are extremely limited, with no dedicated treatment options available.

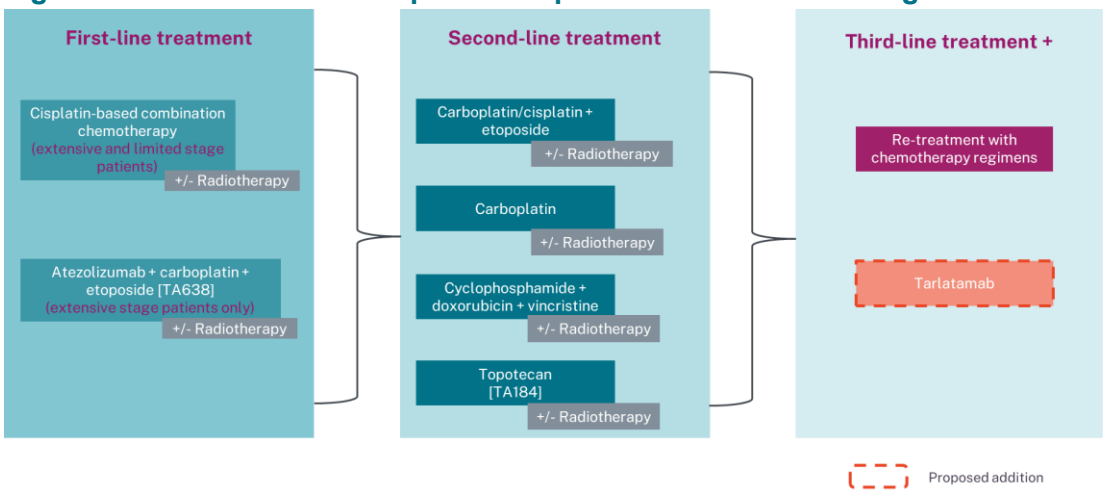
Current treatment pathway

Figure 1 outlines the current treatment options for patients with SCLC in England. Treatments for patients who have not yet received any treatment for SCLC (first-line therapy [1L]) usually involve different types of chemotherapy, dependent on kidney function and other co-existing illnesses.[17]

For patients whose disease progresses following first-line treatment and therefore need to receive a second-line (2L) treatment, guidelines indicate that further chemotherapy using the existing regimens is unlikely to be beneficial. Therefore, these patients typically receive a new treatment out of the options outlined in Figure 1.[17] Patients may additionally receive **radiotherapy** alongside 1L and 2L treatments, often to prevent the cancer spreading to the brain.[17]

Patients with SCLC whose disease has progressed following two lines of therapy currently face a lack of third-line (3L) treatment options: patients are limited to being re-treated with therapy types they have already received. These treatments did not prevent disease progression at the first use, and after receiving a treatment, patients can often become **refractory** (resistant) to the treatment. Therefore, receiving a previously-used treatment is not usually effective. These patients are subsequently left with no dedicated treatment options in the current treatment pathway, as outlined in Figure 1.[17]

Figure 1: Current treatment options for patients with SCLC in England



Source: National Institute of Health and Care Excellence (2023).[17]
Abbreviations: SCLC: small-cell lung cancer.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

SCLC from the patient perspective

Impact on HRQoL

Patients with SCLC experience reduced HRQoL when compared to the general population in England, with one study in 2017 finding that global health status (a measure of quality of life where patients are scored from zero [very poor] to 100 [very good]) and physical functioning scores were lower in patients with SCLC compared to the general population.[18] This low HRQoL is likely attributable to the high symptom burden of the disease and the negative impact on the emotional and physical functioning of patients. Findings from a systematic literature review (SLR) of clinical trials and **real-world evidence (RWE)** reported that physical functioning and activities of daily living were the domains most affected by SCLC and the impact on HRQoL was greater with more advanced disease. In addition, approximately 80% of patients with extensive-stage disease experience disrupted sleep.[14] Therefore, patients whose disease progresses following two or more treatments will experience a particularly poor HRQoL.[18]

Caregiver burden

Similar to the burden that SCLC places on patients, caregivers are impacted by the negative effects of the disease on physical aspects (e.g. activities of daily living), social interactions, and mental health (e.g. psychological distress). In a 2021 survey carried out by Lung Cancer Europe, the burden involved in caregiving for a patient with lung cancer was shown to create psychological distress for the families.[19] In the survey of 285 caregivers for patients with lung cancer, around 79% spent a lot of time thinking about the disease and around 66% felt like their life was dominated by the disease.[19]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

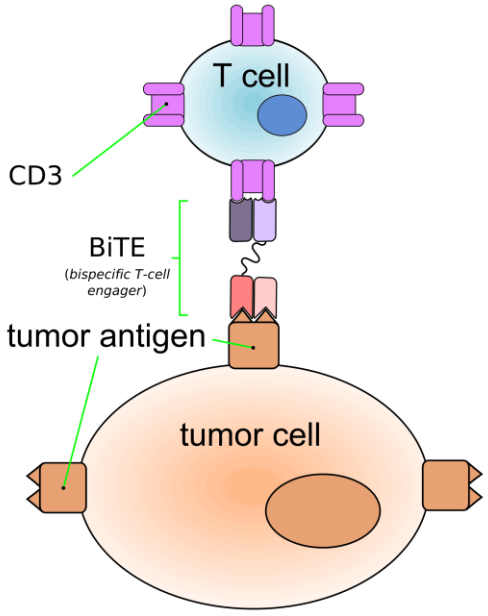
What is tarlatamab and how does it work?

Tarlatamab is a type of immunotherapy, which are therapies that enable the **immune system** to recognise and kill cancer cells. Tarlatamab is a bi-specific T-cell engager antibody (a type of **protein** which has been designed to recognise and attach to two specific targets in the body at the same time). These two different proteins are:

- Delta-like ligand 3 (DLL3), which is found on cancerous SCLC cells (but is not very highly expressed in normal tissues, making it cancer-cell specific)
- Cluster of differentiation 3 (CD3), which is found on specific cells in the body's immune system called T cells

By recognising and attaching to these two cells at the same time, tarlatamab forces the cancerous SCLC cells and the T cells from the body's immune system into close proximity, so that the T cell can kill the cancer cells. A diagram showing how tarlatamab works is provided in Figure 2 below.

Figure 2. How tarlatamab works



Source: National Cancer Institute (2017)[20]
Abbreviations: BITE: bi-specific T cell engager; CD3: cluster of differentiation 3.

How is tarlatamab different from existing treatment options for SCLC?

As mentioned in Section 2c) Current treatment options:, there are currently no treatment options dedicated specifically for patients with SCLC whose disease has progressed to a more advanced stage after two or more treatments. Patients will therefore receive re-treatment with drug classes they have already been exposed to, which is associated with

poor outcomes for patients.[17] As such, patients with advanced SCLC have particularly poor treatment outcomes, resulting in an increased frequency of symptoms experienced, poor HRQoL and a short life expectancy.[11]

The way in which tarlatamab works (its "mechanism of action") is entirely new and unique as compared with all other existing treatments; it is a first-in-class treatment. Tarlatamab has also been shown to achieve high response rates, extending overall life expectancy in patients with advanced SCLC (see **Section 3e**) Efficacy for further efficacy results).[21] Tarlatamab therefore represents a novel treatment option that is able to extend life and improve symptoms and HRQoL for patients at this stage of disease, who would otherwise have limited effective treatment options.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Tarlatamab is not intended to be used in combination with any other treatments in this patient population.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

How is tarlatamab taken?

Tarlatamab is delivered as an injection by trained medical personnel directly into a vein, known as an intravenous injection.[22]

How much medicine do patients take and when?

Patients will receive an initial dose of 1 mg, which is then increased to 10 mg, according to the following dosage regime:[22]

- 1 mg on Day 1
- 10 mg on Day 8
- 10 mg on Day 15 and every 2 weeks thereafter

Patients continue to receive doses of 10 mg every two weeks until their disease

progresses, or they experience unacceptable toxicity. Patients are monitored during the first infusion on Day 1 and for at least 16 hours afterwards. On Day 1 and Day 8, patients are recommended to stay within 1 hour of a healthcare setting for 24 hours after each infusion of tarlatamab is complete, such that any side effects experienced can be managed appropriately.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Studies of tarlatamab in SCLC

The DeLLphi-301 trial (NCT03319940) collected data on how well tarlatamab worked (**efficacy**) and how well **tolerated** it was (safety) in patients with **relapsed** or refractory SCLC whose disease has progressed or recurred following one platinum-based regimen and at least one other line of therapy.[23] Therefore, this trial provides the main evidence base for tarlatamab in the population that will use it in clinical practice in the UK. The trial was initiated on the 1st December 2021 and is expected to be completed in February 2025.[23]

The DeLLphi-301 trial is an international, **Phase II**, open-label, single-arm trial. This means that all patients in the trial are receiving tarlatamab and that all patients know they are receiving tarlatamab. In total, 100 patients were enrolled to receive tarlatamab at the dose specified in Section 3c. These patients were enrolled in initial parts of the trial that aimed to establish the optimal dose of tarlatamab to be administered (labelled Parts 1 and 2). One patient discontinued prior to receiving tarlatamab and therefore 99 patients were included in the analysis of efficacy and safety reported below. Data collected in the DeLLphi-301 trial have been reported in the publication by Ahn *et al.* (2023).[21]

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Trial results

In the DeLLphi-301 trial, the efficacy of tarlatamab was measured by the following

outcomes listed below.[21] More efficacy results can be found in **Document B**, **Section 2.6**.

Objective response rate

Objective response rate is the proportion of patients whose disease has shown a partial response or a complete response to treatment, as measured by the diameter of target lesions. A partial response means that the diameters of target lesions have decreased by at least 30% since the start of a patient's treatment. A complete response means that all target lesions have disappeared and any pathological lymph nodes have had a reduction in short axis to <10 mm.[24] In the DeLLphi-301 trial, a high objective response rate was observed in patients receiving tarlatamab, with 40% of patients achieving a partial or complete response in their disease to treatment.[21]

Duration of response

Duration of response was measured in the DeLLphi-301 trial as the time between a patient achieving a partial response or complete response in their disease and the progression of disease or death. Duration of response is therefore an important readout of how effective the treatment is, as it assesses how long the treatment response lasts for. In the DeLLphi-301 trial, at the time of the last published data, 57.5% and 25.0% of patients had a duration of response of their disease to treatment of at least 6 and 9 months, respectively.[21]

Progression-free survival

Progression-free survival was measured in the DeLLphi-301 trial as the time between patients receiving their first dose of tarlatamab and having signs that their disease has progressed, or death. Progression-free survival is a particularly important outcome for patients, as progressed disease is associated with worse outcomes overall, including significant reductions in HRQoL. Additionally, progression-free survival is closely related to overall survival, as when disease progression occurs, risk of death increases substantially. In the DeLLphi-301 trial, patients reported a median progression-free survival of 4.9 months, meaning on average, patients received treatment for 4.9 months before showing signs that their disease had progressed.[21]

Overall survival

Overall survival (OS) is the time from the first dose of treatment to the time of death due to any cause. Patients in the DeLLphi-301 trial had a median overall survival of 14.3 months, where estimates of survival at 9 months were 68%.[21] In comparison, patients receiving the currently available treatments in the UK face an estimated overall survival of just 1.1 to 7.0 months.[11]

Indirect treatment comparison

When there are no trial data directly comparing two drugs, an indirect treatment comparison (ITC) is typically performed. This is a form of statistical analysis where the results of two (or more) different studies which evaluated the effects of two (or more) different drugs are compared, to estimate the comparative efficacy of the drugs versus

each other. The analysis was done for patients tarlatamab versus receiving the current standard of care, comparing the outcomes of the DeLLphi-301 trial (tarlatamab) to the outcomes in the UK RWE Cancer Analysis System (CAS) study (standard of care).

The CAS is a national cancer registry linked to national mortality and other healthcare databases in England. In this submission, Amgen initiated a registry study using the CAS database, hereafter called the UK RWE CAS study, capturing data on patients with SCLC who received systemic anti-cancer treatments between January 2013 and May 2021. A subset of these patients was receiving third-line treatment and beyond, aligning with the population of patients who would receive tarlatamab. The data from these patients in the UK RWE CAS study and from the DeLLphi-301 study were then used to estimate the effectiveness of tarlatamab as compared with current UK standard of care.

Statistical methods were used to adjust for any differences in patient characteristics in the DeLLphi-301 trial and the UK RWE CAS study which might impact patient outcomes. This was performed to ensure that the comparison of outcomes between tarlatamab and the current standard of care remained as fair as possible, ensuring that differences in outcomes were due to the treatment received and not due to other factors. Further details on the indirect treatment comparison are provided in **Document B, Section B.2.9.**

Outcomes that were investigated in the indirect treatment comparison included:

- OS: referring to the length of time people live for after receiving treatment
- Time to treatment discontinuation (TTD): referring to the length of time a patient receives treatment for before stopping treatment for any reason (discontinuing treatment)

Overall, the results of the ITC demonstrated **statistically significant** (very likely to have happened due to a real treatment effect and not by chance) increases in both OS and TTD with treatment with tarlatamab compared to the current standard of care.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Quality of life impact of tarlatamab

During the DeLLphi-301 trial, patients were asked to answer questions about their quality of life, using various questionnaires called EQ-5D-5L, QLQ-C30 and QLQ-LC13. The results from these questionnaires showed that treatment with tarlatamab resulted in:[21]

- A trend towards improvement from baseline in the severity of symptoms including dyspnoea (shortness of breath), chest pain and pain
- Improvements from baseline in symptoms associated with chemotherapy such as nausea/vomiting and diarrhoea

Results from the assessment of quality of life of patients in the DeLLphi-301 trial are reported in detail in **Document B, Section B.2.6.3**.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

What are the side-effects?

Every medicine has its own side effects and the same medicine can produce different reactions in different people.

In the DeLLphi-301 study, tarlatamab was generally well tolerated. The most common side effects of treatment experienced by patients receiving tarlatamab were:[21]

- Cytokine release syndrome (CRS; occurring in just under half of patients). CRS is an inflammatory immune response, and symptoms can include high fever and chills. Although CRS can be life-threatening, all instances in the trial were of low severity, meaning minimal medical intervention was required
- Pyrexia (a high temperature; occurring in 34% of patients)
- Decreased appetite (occurring in 21% of patients)
- Dysgeusia (an unpleasant taste sensation in the mouth, occurring in 20% of patients)

The proportion of patients who stopped their treatment (or “discontinued”) because of side effects during DeLLphi-301 was only 7%. Of note, three patients died as a result of adverse events experienced during the trial, however none of these were deemed to be

related to tarlatamab by the treating clinician.[21]

Managing side-effects

In the DeLLphi-301 trial, patients were monitored during each infusion and for at least 16 hours after the first infusion. On Day 1 and Day 8, patients were also recommended to stay within one hour of an appropriate healthcare setting for 24 hours after each infusion of tarlatamab to ensure prompt and effective management of any side effects. Often side effects can be managed by supportive care, dose adjustments or permanent dose discontinuation. Details on the management of side effects can be found in the draft **Summary of Product Characteristics** of tarlatamab.[22]

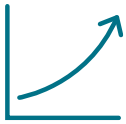
3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

There are currently no dedicated treatment options available for patients with advanced SCLC whose disease has progressed following two or more treatments. Patients will typically be treated with drug classes they have already been exposed to, resulting in low disease response rates to the treatment. This leads to patients experiencing a high symptom burden, poor HRQoL and poor clinical outcomes, with a notably short life expectancy. This highlights the crucial need for a dedicated, effective treatment option for this group of patients. The key benefits of tarlatamab to patients with advanced SCLC include:

Novel mechanism of action: Tarlatamab is a first-in-class treatment with a distinct target of DLL3 found on cancerous SCLC cells and CD3 found on T-cells of the immune system, removing the need to re-use a treatment of the same drug class a patient has already received.



Longer life expectancy: Treatment with tarlatamab results in deep and sustained response rates for patients with SCLC. This means that tarlatamab extends overall life expectancy for patients with SCLC who have received two or more prior treatments, compared to those receiving the current standard of care, who have a short estimated life expectancy of 1.1 to 7.0 months.[11]

Well tolerated safety profile: Tarlatamab has a tolerable safety profile, with the majority of patients able to continue receiving treatment benefit for a prolonged duration. It is anticipated that any side effects will be manageable using dose reductions or supportive care.

Improved patient and carer HRQoL: Tarlatamab delivers meaningful clinical benefits to patients with SCLC by providing an effective treatment option and reducing the impact of symptoms experienced. SCLC and the chemotherapy-based treatments currently used to treat it not only impact the quality of life of patients but also that of their caregivers. As mentioned in **Section 2d**) Patient-based evidence (PBE) about living with the condition, caregivers often experience increased emotional burden and distress associated with caring for someone with SCLC. By improving patient quality of life and reducing the burden of care, the benefits of treatment with tarlatamab experienced by patients would hence reduce the impact felt by caregivers also.[19]

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Efficacy

Similar to all existing SCLC treatments, tarlatamab may not work for everyone and therefore some patients may not respond to treatment. However, the results from the DeLLphi-301 trial showed that 40% of patients experienced a disease response to treatment with tarlatamab, and overall, treatment with tarlatamab resulted in substantially improved progression-free survival and OS when compared with the current standard of care, as mentioned in the results from the ITC performed in **Section** Error! Reference source not found..

Side effects

Treatment with tarlatamab can result in potentially life-threatening side effects, such as CRS, in a small proportion of patients. However, all cases of CRS in the DeLLphi-301 trial were of low-grade severity and in clinical practice patients would be carefully monitored after each treatment for signs and symptoms of CRS to ensure they receive the necessary care should symptoms arise. Furthermore, tarlatamab is required to be given in a

healthcare setting under the supervision of healthcare professionals who are experienced in the treatment of SCLC. These healthcare facilities are required to be equipped with appropriate medical equipment to manage severe reactions, such as CRS.

Administration

Tarlatamab should be taken for as long as the patient continues to receive benefit (i.e. no signs of disease progression). Hence, patients would make fortnightly visits to a healthcare setting to receive their maintenance dose of tarlatamab from a trained healthcare professional.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

In order to assess whether a new medicine provides 'good value for money' compared to existing medicines, healthcare administrators look at the costs of the new medicine and how the health of patients is likely to improve if they take it. The pharmaceutical company that develops the medicines provides this information to healthcare administrators using a **health economic model**. The pharmaceutical company uses this health economic model to perform an analysis, which compares the costs and benefits of the new treatment (tarlatamab) with the existing treatment options that are shown in **Figure 1** above in a theoretical modelled cohort of patients.

How the model reflects advanced SCLC

The economic model was designed to reflect the key features of SCLC and clinical practice in the UK. To do this, a model structure called a **partitioned survival model** was chosen, as this is used commonly to model treatments for advanced SCLC. The model was used to predict future survival of the theoretical modelled cohort of patients with SCLC following two unsuccessful prior treatments and compares tarlatamab with current treatment, which is a basket of 3L treatment options that are collectively termed "standard

of care" (SOC).

Modelling how much tarlatamab improves overall survival and progression-free survival

The results of the DeLLphi-301 trial were used to inform the economic model, as they represent the best available data assessing the efficacy and safety of tarlatamab in a population of patients representative of those with advanced SCLC who would be expected to receive tarlatamab in the UK if tarlatamab were recommended as a new treatment option. The main results from the DeLLphi-301 trial that were used in the model were overall survival (how long patients lived for) and progression-free survival (how long patients lived without experiencing a worsening of their disease). These were the main results used in the model because they were considered relevant to what would be considered a successful outcome when treating advanced SCLC in clinical practice, i.e. a treatment's ability to prevent a disease progressing and killing patients.

The results of the DeLLphi-301 trial only cover the study follow-up duration of 10.6 months, but the economic model need to simulate the theoretical patient cohort for the rest of their lifetime which is a longer period of time than the length of the trial. Therefore, the longer-term impact of tarlatamab was evaluated by **extrapolating** trial data, using statistical methods and clinical feedback to select plausible estimates of what proportion of patients would be expected to be progression-free and alive over a 10-year time period.

Modelling how much tarlatamab improves quality of life

The quality-of-life (QoL) data that informed the model were derived from responses to QoL questionnaires from patients in the DeLLphi-301 trial. QoL measurements were converted to **health utility inputs** to inform the economic model. The DeLLphi-301 trial represents the best source of QoL data to inform the model given it represents the same set of patients informing the efficacy and safety of tarlatamab.

Modelling how the costs of treatment differ with the new treatment

Various cost categories are included in the model for the different advanced SCLC treatments. These costs include:

- The cost of the medicine itself and how much it costs to administer it, as well as any other medicines patients may receive subsequently
- The cost of starting treatment, the cost of monitoring the patients during treatment, and general costs associated with monitoring the disease
- The cost of treating side effects that happen during treatment, and end-of-life costs associated with caring for patients in their last months prior to death

These costs are considered for the new drug (tarlatamab) and for the old treatment option (SOC). Comparing these costs shows how the cost of treating patients would change if tarlatamab were recommended for use.

Uncertainty

There are various assumptions that were made in the model. Information on these

assumptions can be found in **Document B, Section 3.6.2.**

Variations of other inputs in the model were also tested and the results of these tests are explained in **Document B, Section 3.8.**

Cost effectiveness results

In the model, tarlatamab treatment was associated with higher costs, but also higher benefits (or '**quality-adjusted life years'** [**QALYs**]) than SOC. This resulted in an **incremental cost-effectiveness ratio (ICER)** of £35,012 per QALY gained when compared to SOC. It should be noted that these results are based on company-preferred assumptions and do not account for any confidential discounts available for treatments forming part of SOC.

Benefits of tarlatamab not captured in the economic analysis

A **decision modifier** for cancer drugs called the "end-of-life criteria" was previously used to assess the benefits of treatments for diseases associated with short life expectancy. If the "end-of-life" criteria were met (people with the disease were expected to live less than 24 months *and* the new treatment was anticipated to extend their life by more than three months), then the NHS would consider treatments with higher costs per health benefit gained could be within the threshold considered cost-effective. This may have been up to £50,000 per QALY gained. However, a new decision modifier was introduced from 2022 onwards for all types of illnesses. This is called the **severity modifier** and has replaced the end-of-life criteria which are no longer used. The following text explains the impact of the severity modifier on the economic analysis for tarlatamab.

Disease severity can be measured as the future health that would be lost by people with advanced SCLC, compared with someone who does not have the condition. Benefits measured in terms of QALYs are valued more highly for severe diseases. If patients are expected to lose 85–95% of QALYs compared to someone without the disease of the same age, then the disease is considered severe, and the QALYs expected to be gained from the new treatment are multiplied by 1.2 (i.e. the NHS is willing to pay more for these additional QALYs). If a patient with the condition is expected to lose more than 95% of remaining QALYs, then this increases to multiplying by 1.7. Using the health economic model, the company has calculated that a patient with advanced SCLC following two prior treatments would be expected to lose more than 95% of expected QALYs, meaning the QALYs are multiplied by 1.7 in the analysis. When this severity modifier is applied, tarlatamab was associated with an ICER of £35,012 per QALY gained when compared with SOC. These results are based on company-preferred assumptions and do not account for any confidential discounts available for treatments forming part of SOC.

When considered in the context of a very advanced stage of disease with limited treatment options and extremely poor prognosis, tarlatamab offers this patient population an innovative, dedicated treatment option able to improve survival compared with existing treatment options. The results of the economic analysis show that for the proposed group of patients to receive tarlatamab, it offers the best value for money to the NHS when compared with currently available treatments.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Tarlatamab is an innovative treatment which would represent an important advancement in the treatment of advanced SCLC

As mentioned in **Section** Error! Reference source not found., there is a lack of new, dedicated treatment options available for patients with SCLC whose disease has progressed following two or more treatments, resulting in poor HRQoL and short life expectancy.[11] Patients will often be re-treated with drug classes they have already been exposed to, resulting in poor clinical outcomes.[17] The impact of these poor outcomes in SCLC, resulting from the disease not responding to treatment, is felt by both patients and caregivers on their mental and emotional wellbeing and quality of life. Importantly, re-treatment with previously received drug classes also results in poor survival outcomes for patients with SCLC. Therefore, there is a critical unmet need for a new and effective therapy for this patient population.

Tarlatamab offers a treatment option that is first of its drug class, for patients who otherwise have no dedicated treatment option at this line of therapy in the UK. As tarlatamab has a novel mechanism of action, it avoids the need to re-use treatments from existing drug classes patients will have been exposed to earlier in the treatment pathway, and results in improvements in patient HRQoL, progression-free survival and overall life expectancy.[21]

A recommendation of tarlatamab for use in patients with advanced SCLC would therefore address the critical unmet need for a new and effective treatment option which results in improved and sustained treatment responses, leading to improvements in both HRQoL and longer overall life expectancy.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

No potential equality issues are anticipated for the use of tarlatamab in adult patients with advanced SCLC with disease progression following two or more treatments.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Further information on SCLC:

- Macmillan Cancer Support website: Small cell lung cancer (SCLC) | Macmillan Cancer Support
- Cancer Research UK: Treatment options for small cell lung cancer (SCLC) | Lung cancer | Cancer Research UK

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

This glossary explains terms highlighted in **black bold text** in this summary of information for patients. At times, an explanation for a term might mean you need to read other terms to understand the original terms.

Advanced stage cancer	Cancer that has progressed beyond its initial stage and has spread from its site of origin to other parts of the body. This stage of cancer is often characterised by the presence of metastases, where cancer cells have migrated through the bloodstream or lymphatic system to form tumours in distant organs or tissues. Advanced cancer is typically more difficult to treat than early-stage cancer and may require a combination of therapies. In the context of SCLC, this is sometimes referred to as **extensive-stage** cancer.
Clinical trial/clinical study	A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis or treatment of a disease.
Decision modifier	This refers to factors which have not been directly included in the calculation of improvement in quality of life, but are important factors that would influence the decision-making to recommend treatments.
Disease progression	The worsening of the disease, evaluated by the size of a tumour increasing over time.
Efficacy	The ability of a drug to produce the desired beneficial effect on your disease or illness in a **clinical trial.**
Extensive stage cancer	Where the primary cancer tumour has spread beyond the lung to other parts of the body, such as other organs, lymph nodes or tissues. This is sometimes referred to as **advanced stage cancer** in the context of SCLC**.**
Extrapolation	The process of estimating values beyond the range of known data. In the health economic model, this means making

	predictions about patient survival times beyond the observed trial period based on the available data.
Health economic model	A theoretical model used to predict the costs and health benefits associated with new drug over time .
Health-related quality of life	A term used in medicine to describe the physical and mental wellbeing of patients.
Health utility inputs	A measure of the preference or value that an individual or society gives a particular health state. This is generally a number between 0 (representing death) and 1 (representing perfect health).
Incremental cost-effectiveness ratio (ICER)	The difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest.
Immune system	A complex network of cells, tissues, organs and the substances they make that helps the body fight infections and other diseases.
Limited stage cancer	Cancer that is confined to one side of the chest, with any spread being limited to nearby lymph nodes only.
Marketing authorisation	The legal approval by a **regulatory body** that allows a medicine to be given to patients in a particular country.
Medicines and Healthcare products Regulatory Agency (MRHA)	The **regulatory body** that evaluates, approves and supervises medicines throughout the United Kingdom.
Partitioned survival model	A type of economic model commonly used to map the life of cancer patients. The model predicts the probability of patients

	staying in pre-specified states of health over a specific time period.
Phase II clinical trial	This type of **clinical trial** that tests the safety and how well a new treatment works in patients with the disease.
Prognosis	The prediction of the future course of a disease.
Protein	These are structures inside all cells of our body that are important for many activities including growth and repair.
Quality-adjusted life year (QALY)	A measure of the state of health of a person, where the length of life is adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale, where 0 represents death and 1 represents perfect health). It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance.
Quality of life	The overall enjoyment of life. Many **clinical trials** assess the effects of cancer and its treatment on the quality of life of patients. These studies measure aspects of a patient's sense of well-being and their ability to carry out activities of daily living.
Radiotherapy	A type of cancer therapy that uses radiations to kill cancer cells.
Real-world evidence	Evidence that has come from routine clinical practice and not a **clinical trial**.

Refractory	Cancer that does not respond to treatment. The cancer may be resistant at the beginning of treatment or it may become resistant during treatment.
Regulatory bodies	These are legal bodies that review the quality, safety and **efficacy** of medicines and medical technologies.
Relapse/relapsed	The return of a disease or the signs and symptoms of a disease after a period of improvement.
Severity modifier	A method used to place an increased value in the improvement in quality of life, measured by QALYs, in people with severe diseases. In more severe diseases, these QALY measurements would be further multiplied by a value of either 1.2 or 1.7.
Side effect (also called adverse event)	An unexpected medical problem that arises during treatment. Side effects may be mild, moderate or severe.
Statistically significant results	Results that are likely to represent a real treatment effect rather than having occurred by chance.
Summary of Product Characteristics	The regulatory legal paperwork describing a drug, outlining important information such as the drug form, properties, dosing schedule and safety information.
Tolerated	The ability of a patient to put up with the **side effects** of treatment.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Tarlatamab for previously treated advanced small-cell lung cancer [ID6364]

Clarification questions

October 2024

File name	Version	Contains confidential information	Date
ID6364 tarlatamab clarification questions to PM for company [Redacted]	0.2	Yes	02/10/2024

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Decision problem

A1. Priority question: Please clarify why the company's decision problem does not include best supportive care as a comparator, as specified in the NICE scope (CS Table 1).

Best supportive care was not included as a comparator as the Company believes that patients who are candidates for best supportive care (i.e. palliative, non-systemic therapy) belong to a different patient population than those who are candidates for systemic anti-cancer therapy. Patients who are candidates for palliative care have worse Eastern Cooperative Oncology Group (ECOG) performance status (PS) than patients who are not. The inclusion criteria for DeLLphi-301 limited enrolment to patients with an ECOG PS of 0 or 1 (amongst other inclusion criteria). This was supported by input from clinicians who confirmed that the only appropriate comparators for tarlatamab were carboplatin + etoposide, cyclophosphamide + doxorubicin + vincristine (CAV), and topotecan.

A2. Priority question: CS Table 1 ('The decision problem') states that the comparators included in the single basket comparator [i.e. topotecan, cyclophosphamide + doxorubicin + vincristine (CAV), and carboplatin + etoposide] have "similarly poor outcomes". Please provide evidence to support this statement of similar efficacy.

Results from a 1999 randomised, multicentre study of topotecan and CAV in patients with SCLC who had relapsed at least 60 days after completion of first-line therapy, show similar overall response rate (ORR), time to progression, and overall survival (OS) between patients receiving topotecan and those receiving CAV; p>0.05 for all three outcomes (Table 1).[1]

Table 1: ORR, median time to progression and median OS for topotecan and CAV reported in von Pawel *et al.* (1999)

	Topotecan (N=107)	CAV (N=104)	p-value
ORR, n (%)	26 (24.3)	19 (18.3)	0.285
Median time to progression, weeks (range)	13.3 (0.4, 55.1)	12.3 (0.1, 75.3)	0.552
Median OS, weeks (range)	25.0 (0.4, 90.7)	24.7 (1.3, 101.3)	0.795

Abbrevitions: CAV: cyclophosphamide + doxorubicin + vincristine; ORR: overall response rate; OS: overall survival.
Source: von Powel *et al.* (1999).[1]

Additionally, results from a 2018 open-label, randomised, Phase III study of carboplatin + etoposide and topotecan in patients with histologically or cytologically confirmed advanced stage IV or locally relapsed SCLC, provide evidence for efficacy outcomes in second-line (2L) sensitive SCLC. This study reported no significant difference in median OS for the carboplatin + etoposide group (7.5 months; 95% CI: 5.4, 9.5) versus the topotecan group (7.4 months; 95% CI: 6.0, 8.7; p=0.94), as shown in Table 2.[2]

Table 2: ORR, median PFS and median OS for topotecan and CAV reported in Baize *et al.* (2020)

	Topotecan (N=81)	CAV (N=81)	p-value
ORR, n (%)	19.0 (25.0)	39.0 (49.0)	0.0024
Median PFS, months (90% CI)	2.7 (2.3, 3.2)	4·7 (3.9, 5.5)	0·0041
Median OS, months (95% CI)	7.5 (5.4, 9.5)	7.4 (6.0, 8.7)	0.94

Abbrevitions: CAV: cyclophosphamide + doxorubicin + vincristine; ORR: overall response rate; OS: overall survival.
Source: Baize *et al.* (2020).[2]

The Company is currently generating descriptive analyses comparing OS and baseline characteristics between the CAV, topotecan, and carboplatin + etoposide components of the SOC arm included in the main submission. Results for these analyses are not yet available, but will be shared with the EAG as soon as they are completed.

Systematic literature review

A3. Please provide the full citations for the following references excluded from the systematic literature review: 1) ‘A Phase 2 Study of Tarlatamab in Patients With

Small Cell Lung Cancer (SCLC)', and 2) 'Study Comparing Tarlatamab With Standard of Care Chemotherapy in Relapsed Small Cell Lung Cancer'.

Both citations are trial registry records retrieved via the 'EBM Reviews - Cochrane Central Register of Controlled Trials' database:

- A Phase 2 Study of Tarlatamab in Patients With Small Cell Lung Cancer (SCLC) (Number 671) is from the Japan Registry of Clinical Trials – https://jrct.niph.go.jp/pages/en-detail/18625/jRCT/3
- Study Comparing Tarlatamab With Standard of Care Chemotherapy in Relapsed Small Cell Lung Cancer (Number 679) is a clinicaltrials.gov record – https://www.clinicaltrials.gov/study/NCT05740566

A4. Appendix D.1.2 Table 9. Please confirm that a population threshold of 80% with the 3L indication was applied to 2L+ studies where outcomes were not stratified by line of treatment.

The systematic literature review (SLR) indeed applied the criteria to include 2L+ studies for which ≥80% are third line (3L)+ patients where line-specific outcomes were not reported. However, none of the 2L+ studies identified met this criterion. All studies of 2L+ cohort where outcomes were not stratified by line of therapy (LOT) were therefore excluded due to ineligible population.

DeLLphi-301 trial

A5. Please clarify how many participants were recruited and randomised in the DeLLphi-301 study from the two United Kingdom study centres.

Five patients were recruited and randomised from the two UK centres; four at one centre, and one at another.

A6. CS Figure 3. Please state whether the 'No treatment (n=1)' patients are included again nearer the bottom of the figure 'Did not receive treatment (n=1)' i.e. those not undergoing treatment with tarlatamab are logged twice in the figure.

Amgen confirm that the same patient is captured in the 'No treatment (n=1)' and the 'Did not receive treatment (n=1)' figures for both the 10 mg and 100 mg dose groups in Figure 3 of the Company submission. Only one patient it total from the 10 mg dose group, and one patient from the 100 mg dose group did not receive treatment with tarlatamab.[3]

A7. Please provide a critical appraisal of the DeLLphi-301 trial using the criteria for non-randomised and non-controlled studies set out in section 2.5 of the NICE 'Single technology appraisal and highly specialised technologies evaluation: User guide for

company evidence submission template. Process and methods' guide. We have a provided a blank table to fill in below.

DeLLphi-301 trial	Answer (yes/no/not clear/N/A)	Supporting information for answer
Was the cohort recruited in an acceptable way?	Yes	The cohort was recruited based on strict inclusion criteria, including confirmed SCLC, previous treatments, and measurable lesions, ensuring a representative sample of the target population.
Was the exposure accurately measured to minimise bias?	Yes	The administration of tarlatamab was consistent across the study with specific dosages (10 mg and 100 mg) and schedules, and adherence was monitored closely. Adherence challenges were noted with 6 patients in the 10 mg group and 14 patients in the 100 mg group dying before the post-baseline scan.
Was the outcome accurately measured to minimise bias?	Yes	Outcomes were measured using objective criteria (RECIST 1.1) and assessed by blinded independent central review. Objective response rates were 40% (97.5% CI: 29-52) for the 10 mg group and 32% (97.5% CI: 21-44) for the 100 mg group.
Have the authors identified all important confounding factors?	Yes	The study design and statistical analysis accounted for several potential confounders, including prior treatments and patient baseline characteristics.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Confounders were considered in the study design and analyses, as seen in the stratification of patients and adjustment in the statistical models.
Was the follow-up of patients complete?	Yes	Follow-up was thorough, with scheduled imaging assessments and safety follow-ups detailed in the study protocol.
How precise (for example, in terms of confidence interval and p values) are the results?	NA	Results of all primary and secondary efficacy analyses were reported with appropriate confidence interval margins.

A8. Please confirm how disease progression was assessed by the blinded independent central review (BICR) body. Have we understood correctly from the trial protocol [redacted]

[redacted]

A9. CS Tables 13, 14 and 15: What time point are the listed patient statuses for?

The outcomes reported in Tables 13, 14 and 15 of the Company Submission correspond to the latest data cut for the DeLLphi-301 trial, 27th June 2023. Patients were assessed for treatment response and disease progression every six weeks (± one week) until Week 48 (or more frequently if clinically necessary by treating physicians), and every 12 weeks thereafter (± one week).

A10. CS Figures 4 to 7: Please clarify what the shaded areas either side of the solid line represent.

The shaded areas either side of the solid lines in Figures 4−7 of the Company submission represent the 95% confidence intervals (CIs).

A11. Please provide data on time to treatment discontinuation (TTD) in a similar format to that provided in CS section B.2.6.2 for progression-free survival (PFS). Please provide results with and without adjustment for post-progression tarlatamab use.

Data on TTD among 99 patients who received at least 1 dose of tarlatamab in the 10mg group of DeLLphi-301 is summarised in Table 2 below.

The 'Unadjusted' column summarises the TTD data observed in DeLLphi-301, including use of tarlatamab after progression as assessed by independent assessors (i.e., blinded independent central review [BICR]). In this analysis, patients still receiving tarlatamab at the data cutoff (DCO) of the primary analysis (PA; June 27, 2023) were censored, with their censoring time being the time of their last tarlatamab exposure before DCO. Patients who had discontinued tarlatamab by the PA DCO were treated as events, with their event time being the time of their last tarlatamab exposure.

The 'Adjusted' column summarises the TTD that would have been observed had there been no post-progression (as assessed by BICR) use of tarlatamab. In this analysis, patients with post-progression use of tarlatamab were instead treated as having discontinued at time of progression, with their event/censoring status and times updated accordingly. Event/censoring status and times for patients without post-progression use of tarlatamab were unchanged from the unadjusted analysis.

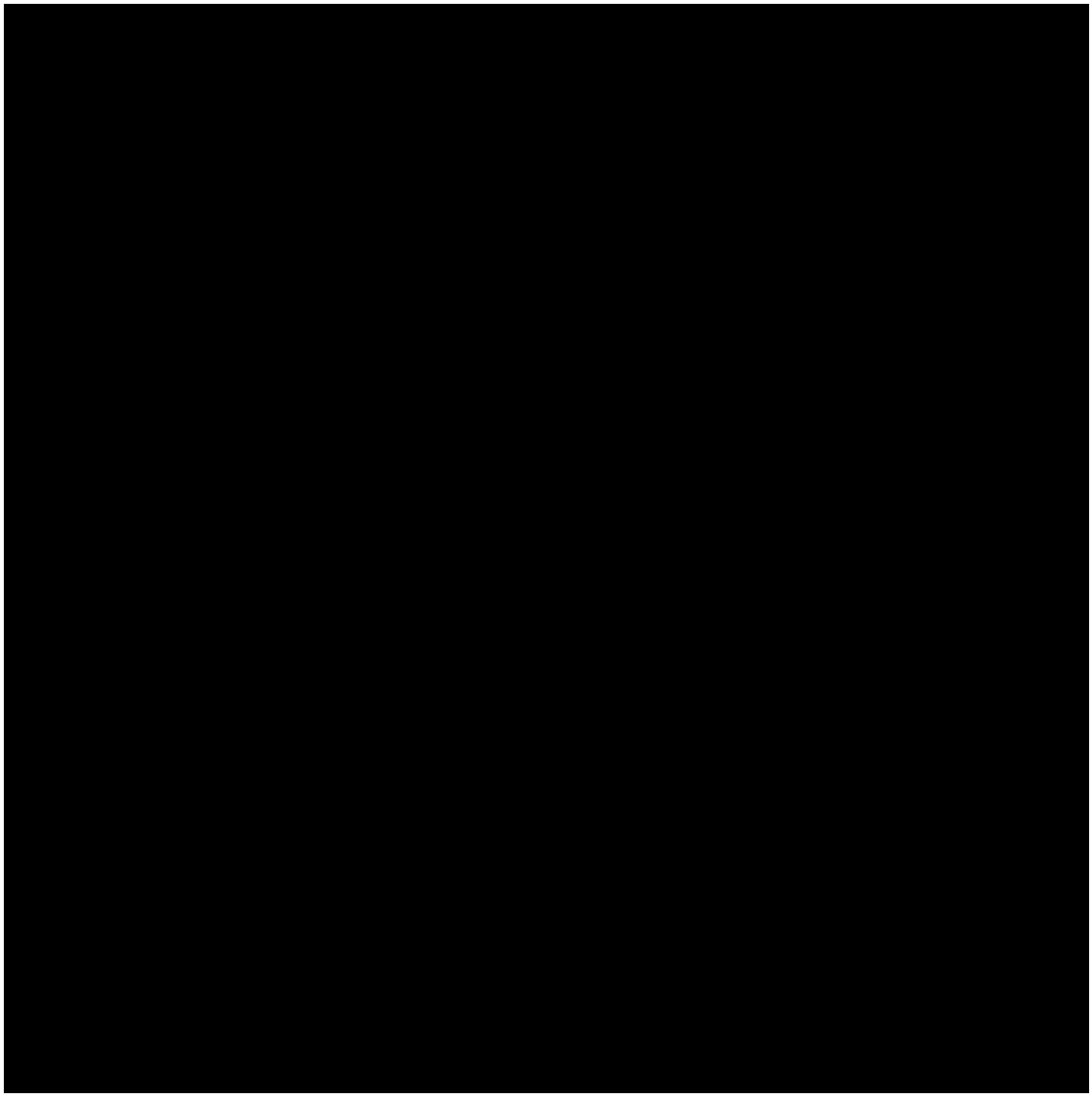
Kaplan-Meier (KM) plots for adjusted and unadjusted TTD for tarlatamab are presented in Figure 1 and Figure 2, respectively, with combined results presented in Figure 3.

Table 3: Time to treatment discontinuation

Patient status	1->10 mg (N=99)[a]	
	Unadjusted	Adjusted
Event (discontinuation), n (%)	[redacted]	[redacted]
Censored (still on treatment), n (%)	[redacted]	[redacted]
Time to treatment discontinuation (KM) (months)[b]		
25% percentile (95% CI)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
75% percentile (95% CI)	[redacted]	[redacted]
Min, Max (+ for censored)	[redacted]	[redacted]
Follow-up time (months)[b]		
25% percentile (95% CI)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
75% percentile (95% CI)	[redacted]	[redacted]
Min, Max (+ for censored)	[redacted]	[redacted]
Kaplan-Meier estimates (%) (95% CI)[c]		
At 3 months	[redacted]	[redacted]
At 6 months	[redacted]	[redacted]
At 9 months	[redacted]	[redacted]
At 12 months	[redacted]	[redacted]

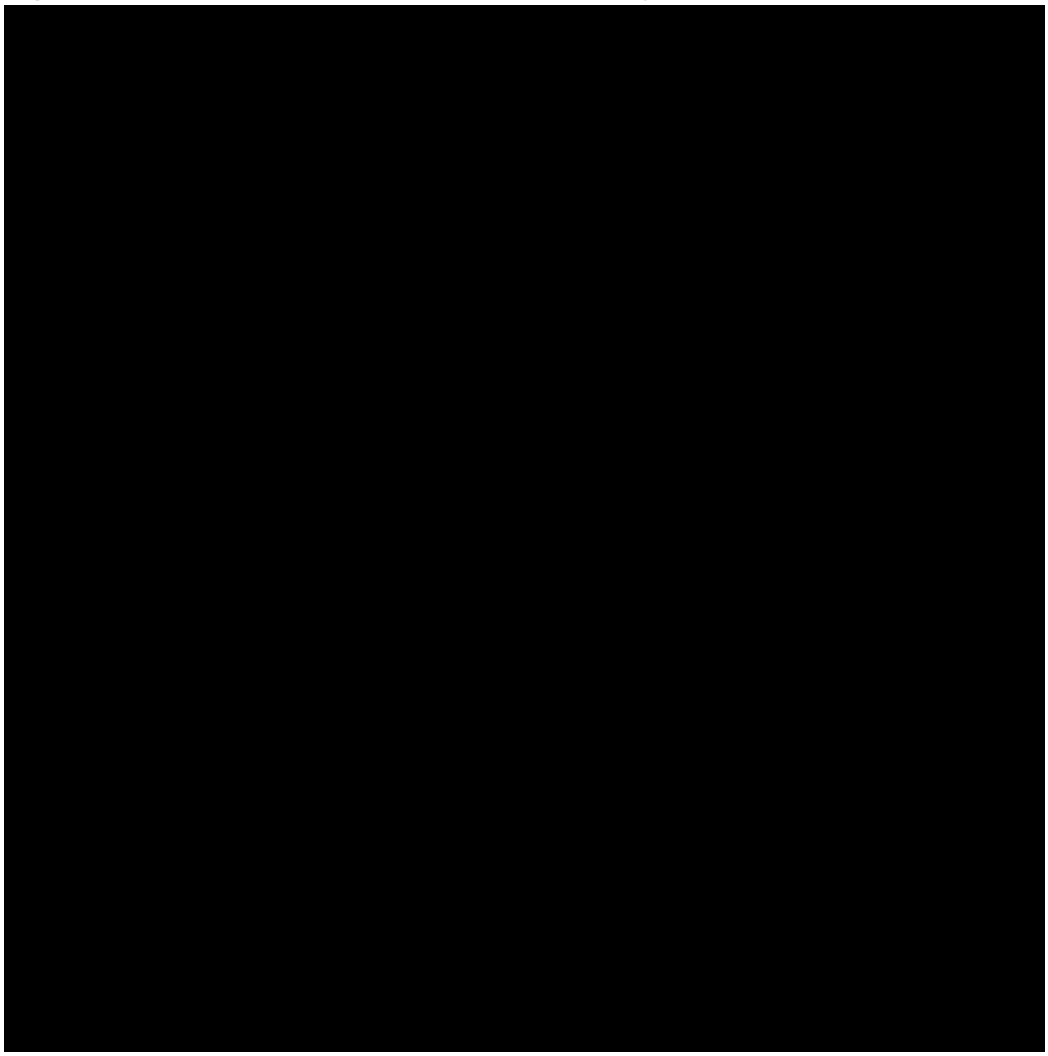
1->10 mg = 1 mg step dose to 10 mg target dose.
[a] This analysis included 99 patients who received at least 1 dose of tarlatamab in the 10mg group of DeLLphi-301. [b] Median and quantiles were estimated using Kaplan-Meier method and 95% CI of median were estimated using log-log transformation of KM survival estimate by Brookmeyer and Crowley (1982) method. [c] 95% CIs were estimated using Kalbfleisch and Prentice (1980) method.
Abbreviations: KM: Kaplan-Meier; min: minimum; max: maximum; NE: not estimable.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO).[4]

Figure 1: KM plot for time to discontinuation (unadjusted)



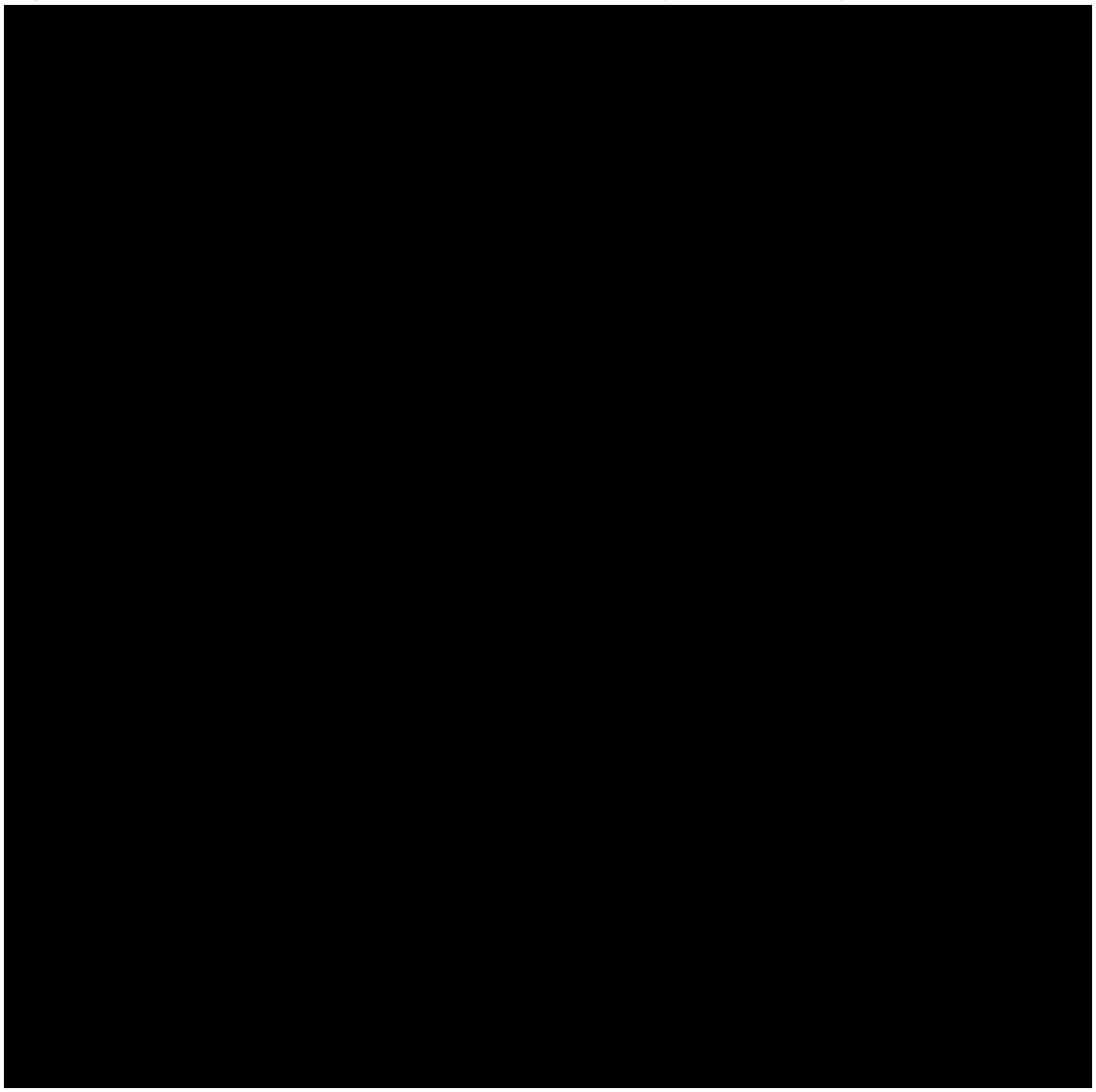
Abbreviations: KM: Kaplan-Meier.

Figure 2: KM plot for time to discontinuation (adjusted)



Abbreviations: KM: Kaplan-Meier.

Figure 3: KM plot for time to discontinuation (unadjusted and adjusted)



Abbreviations: KM: Kaplan-Meier; TTD time to treatment discontinuation.

A12. Please describe the patient-reported outcomes (PROs) that were measured as exploratory endpoints in DeLLphi-301 because these do not appear in either CS Table 4 or CS Table 5. From the results presented these appear to have included the European Organization for Research and Treatment Of Cancer (EORTC) quality of life questionnaire lung cancer module (QLQ-LC13), subscales global health status/quality of life (QoL), physical functioning from EORTC quality of life questionnaire core 30 (QLQ-C30) and the EQ-5D-5L [redacted]. If other measures were used for which results have not been included please note these too.

PROs were evaluated as exploratory endpoints and measured in Parts 1 and 2 of DeLLphi-301. Patient reported symptoms, functioning, and QOL were measured using European Organization for Research and Treatment of Cancer (EORTC) 30-item Quality of Life Questionnaire (QLQ-C30)[5], the 13-item lung cancer module (QLQ-LC13), and the EQ-5D-5L questionnaire (including visual analogue scale [VAS] scores). Burden for important symptoms of SCLC, i.e., cough, chest

pain, and dyspnea, was also measured by Patient Global Impression of Severity/Change (PGI-S and PGI-C).

Patient reported adverse events were measured using selected questions concerning arm or leg swelling, heart palpitations, headache, anxiety, shivering or shaking chills, rash, and problems with concentration from the Patient Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Overall symptom burden was measured by the GP5 question of the Functional Assessment of Cancer Therapy – General Form (FACT-G).[6]

A13. Please provide a summary of the [redacted] as measured by the EQ-5D-5L (exploratory outcome). The CSR for DeLLphi-301 that has been provided in the reference pack indicates [redacted] and CSR section 10.4 states the [redacted] but that section is not present in the CSR supplied to us.

A summary of EQ-5D-5L VAS scores over time is presented in Table 14-4.4.701 in the DeLLphi-301 Clinical Study Report (CSR). In the 10 mg group, mean visual analogue scale (VAS) score at baseline was [redacted] (0 as worst and 100 as best health imaginable) indicating generally moderate to good health from patients' perspective, which is in concordance with the DeLLphi-301 population with baseline ECOG PS at 0 or 1. During treatment (up to cycle 15), VAS scores only varied slightly, with observed mean changes from baseline ranging from [redacted] to [redacted]. The mixed model repeated measure (MMRM) analysis of EQ-5D-5L VAS Score showed a trend toward improvement with the estimated least square mean changes from baseline in cycle 12 of [redacted] (95% CI: [redacted], [redacted]) (Table 14-4.2.806 in the CSR).

CSR section 16.1.13.8 can be found in the reference pack.

A14. Priority question: Please provide a summary of the adverse event data for the 34 participants who were enrolled in Part 3 of the study. In the context of the Part 1 and 2 10mg participant group of only 99 participants, safety data for another 34 participants would be a valuable addition.

A summary of treatment-emergent adverse events (TEAEs) for tarlatamab in patients in the Part 3 modified safety monitoring 10 mg target dose group in DeLLphi-301 is presented in Table 2. All 34 patients had at least 1 adverse event, and grade ≥3 adverse events were reported for 22 patients (64.7%). Adverse events were considered treatment-related for 85.3% of patients.[3]

Serious adverse events (SAEs) were reported for 14 patients (41.2%) in the Part 3 modified safety monitoring 10 mg target dose group, with SAEs considered by the investigator to be related to tarlatamab reported for 20.6% of all patients.[3] AEs that led to discontinuation of investigational product were reported for 3 patients (8.8%).[3] Fatal AEs were reported for [redacted] patients ([redacted]%), of which [redacted] ([redacted]%) was considered by the investigator to be related to tarlatamab.[4]

Table 4: Summary of incidence of treatment-emergent adverse events (modified safety monitoring dose group; Part 3)

Treatment-emergent adverse events, n (%)	1->10 mg Modified Safety Monitoring (N=34)
All treatment-emergent adverse events	34 (100.0)
Grade ≥2	33 (97.1)
Grade ≥3	22 (64.7)
Grade ≥4	7 (20.6)
Serious adverse events	14 (41.2)
Leading to dose interruption and/or reduction of tarlatamab	5 (14.7)
Leading to discontinuation of tarlatamab	3 (8.8)
Serious	[redacted]
Nonserious	[redacted]
Fatal adverse events	[redacted]
Treatment-related treatment-emergent adverse events	29 (85.3)
Grade ≥2	23 (67.6)
Grade ≥3	5 (14.7)
Grade ≥4	2 (5.9)
Serious adverse events	7 (20.6)
Leading to dose interruption and/or reduction of tarlatamab	3 (8.8)
Leading to discontinuation of tarlatamab	0 (0.0)
Fatal adverse events	[redacted]

1 -> 10 mg = 1 mg step dose to 10 mg target dose.
Source: Ahn *et al.* (2023);[3] Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO).[4]

Statistical analysis of the DeLLphi-301 trial

A15. Please clarify the reasons for missing PRO data across the measures used in the 10mg target dose group (CS section B.2.6.3).

In DeLLphi-301, PROs were collected at on-treatment visits at Cycle 1 (days 1, 8, 22), Cycle 2 (days 1, 15) then every 6 weeks until Week 48. Thereafter, they were collected every 12 weeks until end of study treatment. Baseline PRO data were available for [redacted] ([redacted]) patients for QLQ-LC13 and EQ-5D (VAS) and [redacted] ([redacted]) patients for QLQ-C30 in the 10mg target dose group. Compliance rates (percentage of patients who completed at least one item in the subscale of the questionnaire among those expected to have an assessment) remained very high and [redacted] for all cycles up to Cycle 12 Day 1. Completion rates (the percentage of patients who completed at least 1 item in the subscale of the questionnaire among all randomised/enrolled patients) decreased to [redacted] by Cycle 6, which was expected given that patients stopped PRO assessments due to disease progression or death. Detailed compliance and completion rates for the QLQ-C30, QLQ-LC13 and EQ-5D-5L (VAS) instruments till Cycle 15 (Day 1) are provided in Table 3. Other than disease progression or death, specific reasons for missing PRO data were not collected in DeLLphi-301.

Table 5: Completion and Compliance Rates in QLQ-C30, QLQ-LC13 and EQ-5D-5L Scales Over Time

Visit	QLQ-C30		QLQ-LC13		EQ-5D (VAS)	
	Completion n/N1 (%)	Compliance n/N2 (%)	Completion n/N1 (%)	Compliance n/N2 (%)	Completion n/N1 (%)	Compliance n/N2 (%)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 1 Day 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 1 Day 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2 Day 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4 Day 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7 Day 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 10 Day 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 12 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 15 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Completion rate (at visit x) = (Number of patients who completed at least 1 item in the subscale of the questionnaire at visit x/ N1) * 100%.
Compliance rate (at visit x) = (Number of patients who completed at least 1 item in the subscale of the questionnaire at visit x/ N2) * 100%.
Completion and compliance rates are calculated for all visits with PRO collection according to schedule of assessment per protocol
Abbreviations: N1: Number of all randomized or enrolled patients; N2: Number of eligible patients who are expected to complete the PRO assessment per protocol at visit x, ie, still on study and still alive, excluding the patients who are missing by design, such as death, study discontinuation, etc; n: Number of patients with observed data; PRO: patient-reported outcome; QLQ-C30: quality of life questionnaire 30-item core module; QoL: quality of life; EQ-5D-5: EuroQol-5 dimension-5 level; VAS: visual analog scale.

A16. CS Table 9: What data were missing or incomplete and had to be imputed? Please describe the imputation methods used.

No imputation was performed for efficacy endpoints (including PRO endpoints). In case of missing or incomplete information on dates of adverse event and concomitant medication use, imputation was carried out as described in Appendix A of the statistical analysis plan (SAP) of DeLLphi-301 (28th June 2023).

A17. CS section B.2.6 Clinical effectiveness results: Were any sensitivity analyses undertaken e.g. analyses omitting the two protocol violators who had not received two prior lines of therapy, analyses under alternative definitions for disease progression date, alternative censoring rules, alternative imputation methods for missing data or alternative data cut-off points? If so, please provide results.

Sensitivity analyses were conducted using alternative censoring rule for duration of response (DOR), duration of disease control (DoDC) and PFS by considering events that occurred after consecutive assessments or new anti-cancer therapies. Results are presented in Tables tuk14-04-003-002, tuk14-04-005-004 and tuk14-04-004-002 provided separately in the reference pack.

Results using alternative censoring rules are very similar to the primary analysis with median DOR of [redacted] ([redacted], [redacted]) (vs [redacted] [[redacted], [redacted]], DODC of 6.9 ([redacted], [redacted]) (vs [redacted] [[redacted], [redacted]] and PFS of [redacted] ([redacted], [redacted]) (vs [redacted] [[redacted], [redacted]].

Post-hoc analyses were carried out to describe the OS and PFS of a cohort omitting the two protocol violators who had not received two prior lines of therapy. Efficacy data from this 3L+ cohort (n=97) were used in subsequent indirect treatment comparisons and cost-effectiveness analyses as described in section B.2.9 of the company submission.

A18. CS Table 9: Was a formal method used to determine sample size? If so, please provide a description and citation for the method used.

Detailed sample size rationale is provided in the SAP of DeLLphi-301 (28th June 2023), Section 3.2. A lower boundary of the 97.5% two-sided CI for ORR above 15% was considered clinically meaningful based on the results of open-label studies of pembrolizumab (Chung *et al*, 2020) and nivolumab (Ready *et al*, 2019) in 3L+ SCLC (ORR of 19% and 12%, respectively). Based on the clinically meaningful threshold as supported by the literature, a sample size of 100 patients at the selected target dose would satisfy this criteria with a probability of the expected lower boundary of 97.5% two-sided CI for an observed ORR higher than 15% (Table 4).

For Parts 1 and 2 of the study, a sample size of 100 patients at the selected target dose was estimated to provide a 63% probability of observing at least 1 adverse event, with a true 1% incidence rate and 99% probability of observing at least 1 adverse event with a true 5% incidence rate. For Part 3 of the study, a sample size of 30 patients at the selected target dose was providing a 26% probability of observing at least one adverse event with a true 1% incidence rate and 79% probability of observing at least one adverse event with a true 5% incidence rate.

Table 6: Probability of expected lower boundary of 97.5% two-sided CI

True ORR	Probability
0.20	19%
0.24	54%
0.26	71%
0.28	84%
0.30	92%

Abbreviations: CI: confidence interval; ORR: overall response rate.

A19. CS Table 9: Was the objective response rate outcome the only outcome that was assessed at the interim analysis?

A non-binding futility and safety interim analysis occurred in Part 1 when 30 patients per dose level had the opportunity to confirm an objective response after the first post-treatment scan or up to 13 weeks of follow-up, whichever occurred first. The futility analysis was based on confirmed overall response (OR) per investigator assessment.

In parallel to the futility analysis, a dose-selection committee independent to Amgen evaluated the totality of the safety and efficacy data assessed at the interim analysis and selected the 10 mg bi-weekly (Q2W) regimen using a step-dose of 1 mg as the target dose to be further evaluated in Part 2 of the study.

A20. CS Table 9: Was the adjustment for multiplicity based on a formal method? If so, please provide a description and citation for the method used.

Adjustment for multiplicity between the pre-planned interim and primary analysis for ORR was based on the Bonferroni method using a 97.5% two-sided CI for ORR.[7] The choice of method was approved by the US FDA.

A21. CS Table 9. Please explain why a multiplicity adjustment was not used for the subgroup analyses of objective response rate? (Table 9 states “for subgroup analysis, 95% CIs for objective response rate”).

Multiplicity adjustment was unnecessary as no statistical inference was pre-specified for subgroup analyses of ORR.

Matching-adjusted indirect comparison (MAIC)

A22. Priority question: Please clarify why CS Appendix Table 15 shows that the time period of SACT data used for the UK CAS RWE study was “01/01/2013 to 31/12/2020” yet CS Appendix D.1.4 states that data “between 1st January 2013 and 31st May 2021” were used, [redacted]

The maximum study follow-up period of the CAS real-world evidence (RWE) study was defined as the start of data (01/01/2013) to the end of data (31/05/2022), i.e., the latest dataset available

from CAS at the time of the analysis. The reference of 31st May **2021** in Appendix D.1.4 of the Company submission is a typographical error and should be corrected to 31st May **2022**.

The CAS study defined 01/01/2013 – 31/12/2020 as the diagnosis identification period, i.e., any patients meeting the diagnostic criteria during this period were included in the study. The end of the diagnosis identification period was set to be 1.5 years earlier than the end of data to capture patients with sufficient follow-up data.

A23. Priority question: Please clarify why the UK CAS study used data on patients up to 31st May 2021 (CS Appendix D.1.4). Were more recent data also available, and, if so, why were these not additionally used?

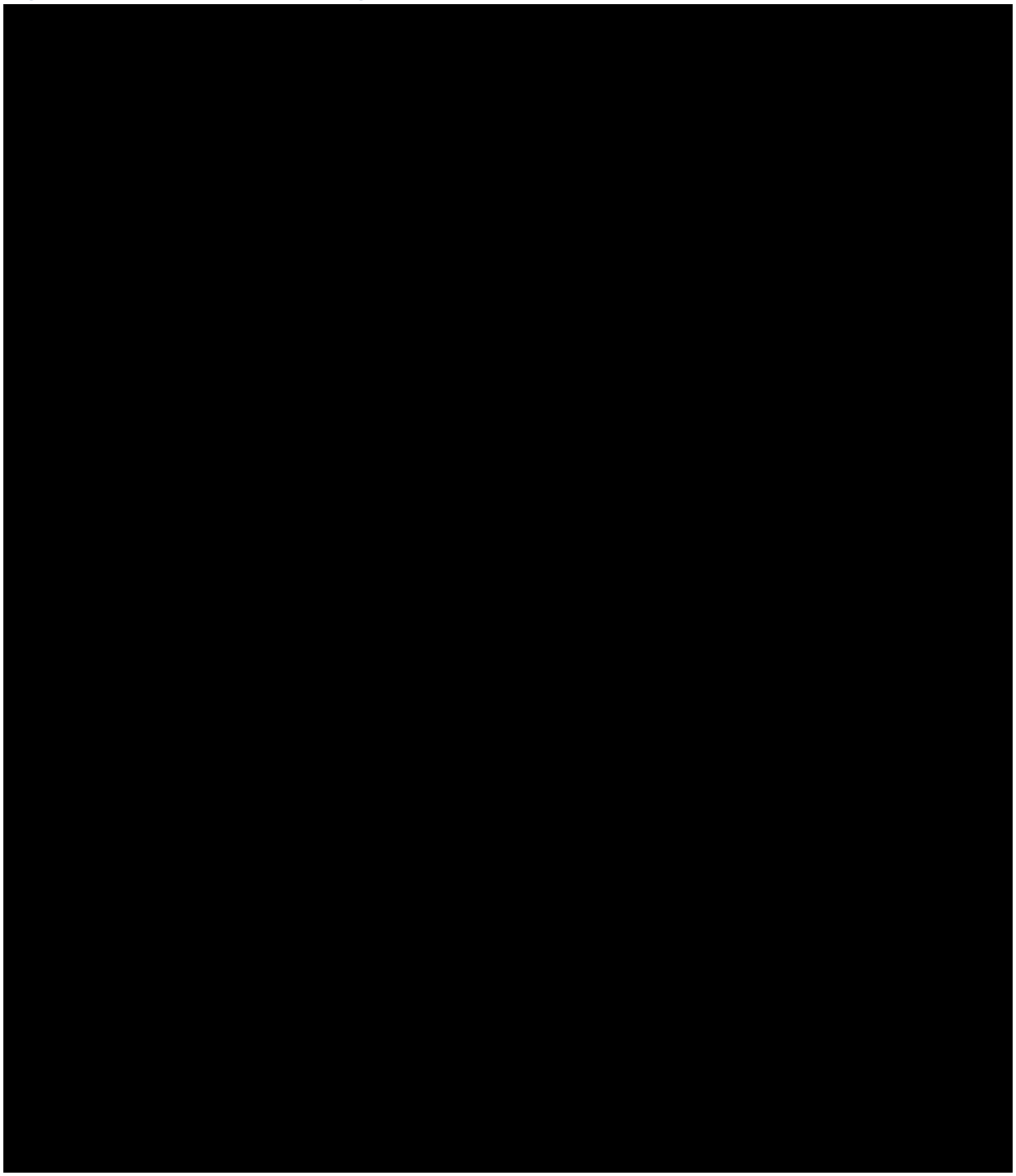
The latest available data at the time of the analysis were up to 31st May 2022 and were used in the analysis.

A24. Priority question: Please provide a flowchart showing and/or describe how the final sample of N = 540 was selected from the raw SACT dataset for the UK CAS RWE study. Were the 540 selected patients all the third-line therapy+ patients available in the SACT dataset?

A flowchart describing how the final sample of N=540 used in the MAIC for tarlatamab was selected from the overall SCLC population in the UK CAS RWE is described in Figure 4 below.

The study identified [redacted] adults diagnosed with SCLC between 2013 and 2020; of these [redacted] did not receive any systematic anti-cancer therapy (SACT) within 30 days prior to, on, or at any time after diagnosis and were therefore excluded. Approximately [redacted] of the remaining cohort were excluded due to having another primary malignancy diagnosis, while a further [redacted] were excluded due to missing tumour, node and metastasis (TNM) staging information. Only small numbers of patients (<1%) were excluded due to the other exclusion criteria. The final cohort included [redacted] SACT-treated patients with SCLC diagnosed between 2013 and 2020. Of the overall cohort ([redacted] patients) receiving at least one LOT, [redacted] received a second LOT, and only [redacted] ([redacted] patients) received a third LOT. Additional key important inclusion criteria consistent with those in the DeLLphi-301 trial (i.e., ECOG PS ≤ 1, and receipt of prior platinum-based chemotherapy) were applied to patients receiving a third LOT to derive the historical control cohort used in the MAIC. After exclusion of approximately [redacted] patients with a missing ECOG performance status, and approximately [redacted] patients with ECOG PS >1, 540 patients were included in the final MAIC cohort.

Figure 4. Attrition table selecting 3L SCLC for the MAIC cohort



Abbreviations: ECOG: Eastern Cooperative Oncology Group; ICD: International Classification of Diseases; MAIC: matching-adjusted indirect comparison; SACT: systemic anti-cancer therapy, SCLC; small-cell lung cancer; TNM: tumour, node and metastasis; LOT: line of treatment.

A25. Please provide a list of and the PDFs of the systematic literature reviews of 2L and 3L+ clinical studies that were used in the meta-regression referred to in CS section B.2.9.2, paragraph five.

Two SLRs conducted by Amgen were used in the meta-regression:

- Systematic literature review on the clinical efficacy and safety of clinical trial data in third-line and beyond relapsed/refractory small cell lung cancer (report date: 15th December 2022)

- Systematic literature review on the clinical efficacy and safety of clinical trial data in second-line relapsed/refractory small cell lung cancer (report date: 30th December 2022)

Reports of these SLRs can be found in the reference pack.

A26. Did the company perform a risk of bias assessment of the targeted literature review (CS reference 55) used as the basis for the identification of prognostic factors (CS section B.2.9.2)? If so, please provide the results.

The literature review used to identify probable prognostic factors was obtained from the supplementary material (Appendix B) of a published comparative analysis (Keeping *et al.* 2020).[8]

Keeping *et al.* did not disclose whether a quantitative bias assessment of studies identified through the targeted literature review was carried out nor reported the assessment findings (if performed). Amgen did not perform an additional assessment on top of the publication.

A27. CS section B.2.9.2 states that response to previous treatment (platinum sensitivity) was identified as a 'very important' prognostic factor from the clinician survey. Are we correct in our understanding that this variable is considered to be captured by the 'Chemotherapy-free interval (≥ 180 days)' and 'Chemotherapy-free interval (≥ 90 and < 180 days)' factors listed in CS Table 16?

Amgen can confirm that this is correct. Patients who have chemotherapy-free intervals ≥ 180 days and ≥ 90 and < 180 days between the end of first line (1L) treatment and progression to 2L treatment are considered to be platinum-sensitive and those with a chemotherapy-free interval between the end of 1L treatment and progression to 2L treatment <90 days are considered to be platinum refractory/resistant.

A28. Footnote 'b' to CS Table 16: Please define what is meant by the "index line of treatment".

In Table 16 of the Company submission, index LOT refers to the line of therapy that patients initiated on the index date, i.e., day 0 for patients to be included into the cohort study and being followed-up for survival outcomes and duration on therapy. In particular, the index dates of all 540 patients included in the CAS cohort for MAIC were defined as the date they initiated their 3L treatment (see Figure 4). In DeLLphi-301 65 patients (65.7%) entered the trial and received tarlatamab as their 3L treatment, while 32 patients (32.3%) received tarlatamab as their fourth or later lines of treatment. Two patients received tarlatamab as their 2L treatment and were therefore excluded from the CAS cohort for MAIC as described in Table 16 of the Company submission.

A29. Priority question: Please clarify why CS section B.2.9.2 states that smoking was included in the MAIC base case as a prognostic factor yet it is not listed in CS Table 16 as among the prognostic factors adjusted for in the MAIC. Was smoking adjusted for in the base case? If not, please conduct and provide results of sensitivity analyses of OS and PFS when this prognostic

factor is included along with all the others used in the base case analyses as specified in CS Table 16. Please also conduct a cost-effectiveness scenario using these data.

Following discussions with the EAG, it has been agreed that a response to this question is not required.

A30. CS Table 18 provides a comparison of the characteristics of the DeLLphi-301 and CAS Control Cohorts and the participants included in each of these cohorts, but does not include smoking status. Please provide this information for the participants in both these cohorts.

Following discussions with the EAG, it has been agreed that a response to this question is not required.

A31. Please confirm that the comparison of the characteristics of the DeLLphi-301 and CAS Control Cohorts provided in CS Table 18 is comprehensive and that there are no missing baseline characteristics. If there are missing characteristics, please provide the relevant information for each of the cohorts.

Please see Table 5 below where additional variables available in CAS are now reported with the corresponding values from DeLLphi-301. All the statistics for DeLLphi-301 in this table below are based on N=97 patients i.e. those receiving tarlatamab 10 mg as third line or later. Of note, age at index in Table 18 of the original CS was mislabelled as age at diagnosis, which is now fixed in the extended table here.

Table 7: Comparison of DeLLphi-301 and CAS Control Cohorts

	DeLLphi-301 (N=97)	CAS Control Cohort (N=540)
Disease stage at diagnosis, n (%)		
Stage 0	[redacted]	-
Stage I	[redacted]	-
Stage II	[redacted]	-
Stage III	[redacted]	-
Stage IV	[redacted]	-
Unknown/missing	[redacted]	-
Limited stage at diagnosis[a]	[redacted]	[redacted]
Extensive stage at diagnosis[a]	[redacted]	[redacted]
ECOG PS 0 at index[b]	25 (25.8)	[redacted]
ECOG PS 1 at index	72 (74.2)	[redacted]
Presence of brain metastasis (at index in DeLLphi-301 vs. prior to 1L initiation in CAS)	22 (22.7)	[redacted]
Unknown/missing	0 (0)	[redacted]
Presence of liver metastasis (at index in DeLLphi-301 vs. prior to 1L initiation in CAS)	37 (38.1)	[redacted]

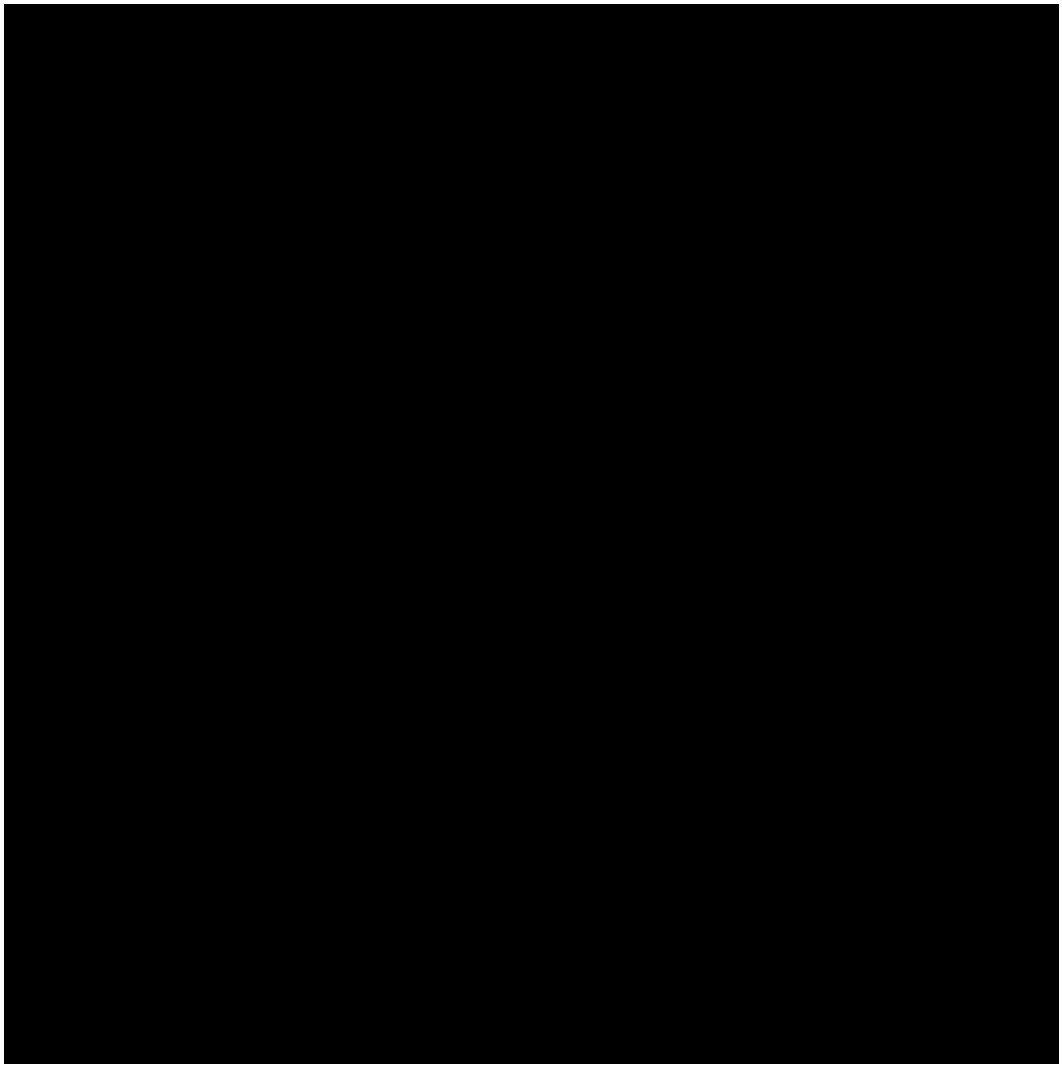
Unknown/missing	0 (0)	[redacted]
Demographic characteristics		
Age at index (years), mean (SD)	[redacted]	[redacted]
Age at diagnosis (years), mean (SD)	[redacted]	[redacted]
Gender, n (%)		
Female	26 (26.8)	[redacted]
Male	71 (73.2)	[redacted]
Unknown/missing	0 (0)	[redacted]
Ethnicity at diagnosis		
Asian	41 (42.3)	[redacted]
White	55 (56.7)	[redacted]
Other	1 (1.0)	-
Unknown/missing	0 (0)	-
Time from diagnosis to index, days		
Mean (SD)	[redacted]	[redacted]
Platinum resistant status		
Platinum resistant (CFI <90 days), n (%)	26 (26.8)	[redacted]
Platinum resistant (CFI 90 to <180 days), n (%)	22 (22.7)	[redacted]
Platinum resistant (CFI ≥180 days), n (%)	20 (20.6)	[redacted]
Missing[c]	29 (29.9)	[redacted]
Prior therapies		
Mean number of prior LOTs	[redacted]	[redacted]
Exposure to prior PD-L1 inhibitor, n (%)	71 (73.2)	[redacted]
Year of SCLC diagnosis		
2013	[redacted]	[redacted]
2014	[redacted]	[redacted]
2015	[redacted]	[redacted]
2016	[redacted]	[redacted]
2017	[redacted]	[redacted]
2018	[redacted]	[redacted]
2019	[redacted]	[redacted]
2020	[redacted]	[redacted]
2021	[redacted]	[redacted]
2022	[redacted]	[redacted]
Unknown/missing	[redacted]	[redacted]
Comorbidities (at index for DeLLphi-301 vs. at diagnosis for CAS)[d]		
Hypertension	[redacted]	[redacted]
Ischemic heart disease	[redacted]	[redacted]
Cerebrovascular disease	[redacted]	[redacted]
Chronic obstructive pulmonary disease (COPD)	[redacted]	[redacted]
Diabetes mellitus (DM)	[redacted]	[redacted]

[a] In DeLLphi-301, only TNM stage was reported. For SCLC stage categorization, patients with stage I-III were classified as having limited disease, and stage IV and unknown stage were classified as extensive disease.
[b] In DeLLphi-301, index date is date of initiation of tarlatamab in 3L or later. In CAS, index date is date of 3L initiation of available treatment options.
[c] In DeLLphi-301, 20 patients had observed CFI ≥ 180 days. 29 patients with missing CFI values were assumed to have CFI ≥ 180 days for the MAIC analyses.
[d] In DeLLphi-301, comorbidities were reported at index, which is, a mean of 590.5 days away from diagnosis date. In CAS control cohort, comorbidities were reported at diagnosis.
Abbreviations: CFI: chemotherapy-free interval; COPD: Chronic obstructive pulmonary disease; DM: Diabetes mellitus; ECOG: Eastern Cooperative Oncology Group; LOT: line of therapy; SD: standard deviation.

A32. Whilst the distributions of weights are provided for the base case (CS Figure 10), these are not reported for the MAIC scenario analyses. Please provide these.

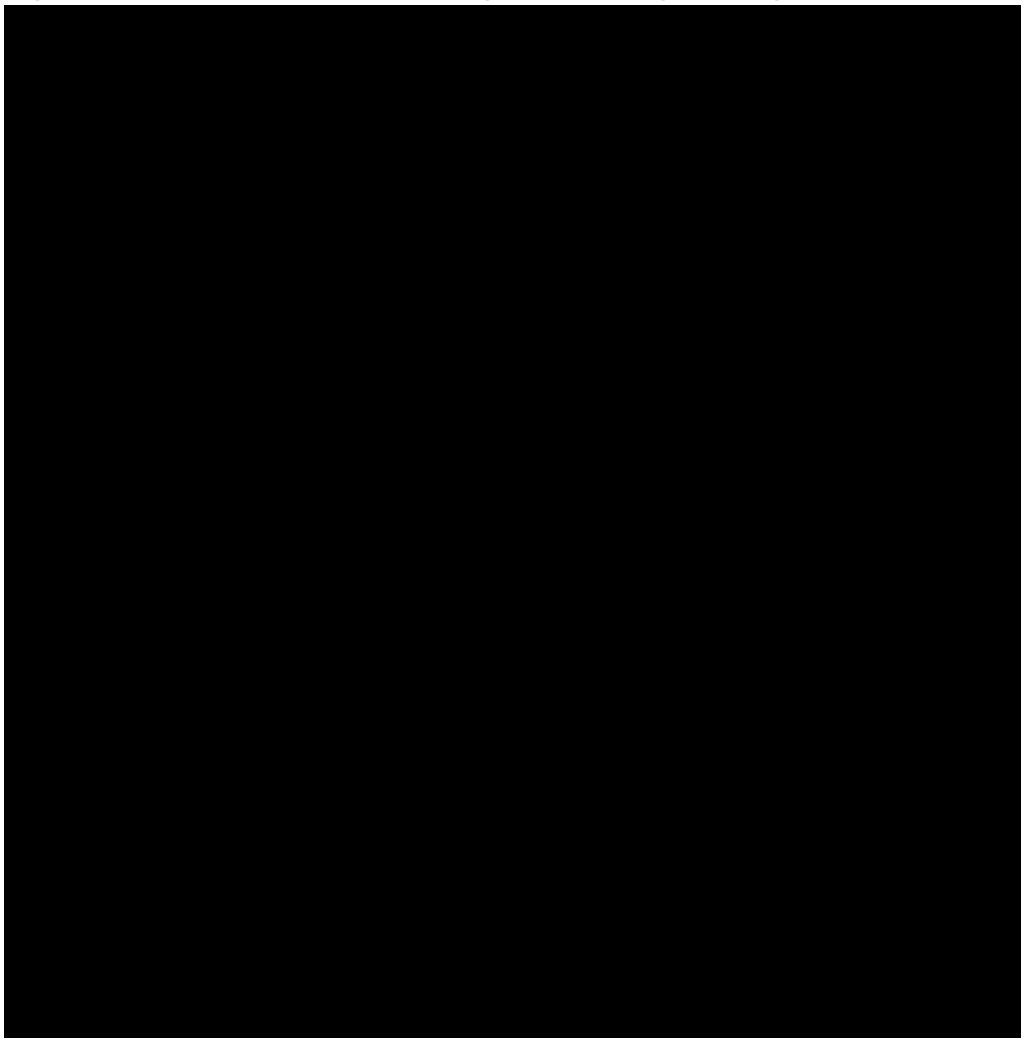
Distribution of weights for scenario analysis 1 and 2 are provided in Figure 5 and Figure 6 below, respectively.

Figure 5: MAIC scenario 1 (excluding chemo-free interval)



Abbreviations: MAIC: matching-adjusted indirect treatment comparison.

Figure 6: MAIC scenario 2 (excluding disease stage at diagnosis)



Abbreviations: MAIC: matching-adjusted indirect treatment comparison.

A33. CS section B.2.9.6: In addition to the SMDs (standardised mean differences), please report the raw data pre- and post-match.

Table 6 shows baseline characteristics of the tarlatamab (before and after matching) and the CAS control groups included in the base case MAIC. Before matching, patients in the tarlatamab group were less likely to be female, more likely to have brain or liver metastases prior to index, and more likely to have shorter CFI. Smaller between-group differences existed for ECOG PS, disease stage at diagnosis, and time from diagnosis to index treatment initiation. All imbalances in baseline characteristics were eliminated after matching.

Table 8: Baseline characteristics for tarlatamab and available treatment options (CAS) groups

Prognostic variables	Tarlatamab (before matching) N=97	Tarlatamab (after matching; base case)	Available treatment options (CAS) N=540
Age at index (years) - mean (SD)	[redacted]	[redacted]	[redacted]
Sex (female %)	26.8%	[redacted]	[redacted]
ECOG PS 0 at index	25.8%	[redacted]	[redacted]
ECOG PS 1 at index	74.2%	[redacted]	[redacted]
Presence of brain metastases[a]	22.7%	[redacted]	[redacted]
Presence of liver metastases[a]	38.1%	[redacted]	[redacted]
Platinum resistant (CFI <90 days) after 1L treatment	27.3%	[redacted]	[redacted]
Platinum sensitive (CFI 90 to <180 days) after 1L treatment	22.2%	[redacted]	[redacted]
Platinum sensitive (CFI ≥180 days) after 1L treatment[b]	50.5%	[redacted]	[redacted]
Disease stage – ES at initial diagnosis	[redacted]	[redacted]	[redacted]
Time from diagnosis to index (days) – mean (SD)	[redacted]	[redacted]	[redacted]

[a] Presence of brain and liver metastases were assessed at index in DeLLphi-301 but prior to 1L initiation in CAS.
[b] In DeLLphi-301, some patients had missing data for disease stage at diagnosis and CFI. For disease stage, it was assumed that all patients with missing data had extensive-stage disease. For CFI, it was assumed that all patients with missing data had a CFI longer than 180 days.
To preserve patient anonymity, masking rules were applied to outputs from CAS study. All numbers above 10 were rounded to the nearest 10, percentages were presented rounded to the nearest 5%, and minimum and maximum were replaced with 5th and 95th percentiles.
Abbreviations; 1L: first line; CFI: chemotherapy-free interval; ECOG: Eastern Cooperative Oncology Group; ES: extensive stage; PS: performance score; SD: standard deviation.

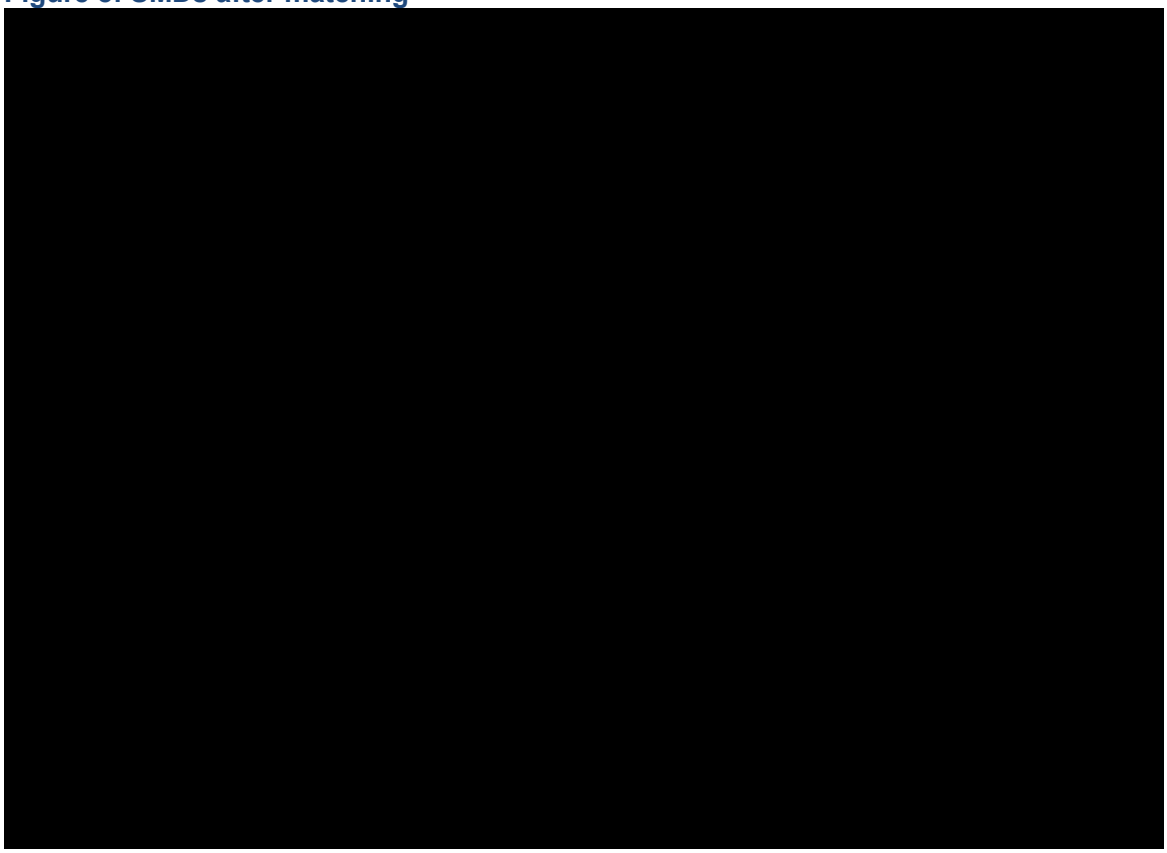
A34. CS Figure 9 shows standardised mean differences before and after matching. Please also report results for any unmatched variables after matching of the selected prognostic factors.

The standardised mean differences (SMDs) before and after matching, including both matched and unmatched variables, are presented in Figure 7 and Figure 8 below, respectively.

Figure 7: SMDs before matching

Abbreviations: COPD: Chronic obstructive pulmonary disease; DM: diabetes mellitus; ECOG: Eastern Cooperative Oncology Group; LOT: line of therapy; SMD: standardised mean difference.

Figure 8: SMDs after matching



Abbreviations: COPD: Chronic obstructive pulmonary disease; DM: diabetes mellitus; ECOG: Eastern Cooperative Oncology Group; LOT: line of therapy; SMD: standardised mean difference.

A35. Please report the median OS and PFS for the tarlatamab group before and after weighting, and for the comparator CAS cohort, for the scenario analyses reported in CS Appendix D.1.7.

A summary of the base case and scenario MAIC analyses included as part of the Company submission is presented in Table 7. In the base case, tarlatamab was associated with significantly better OS than available treatment options from the CAS study in both unadjusted and adjusted analyses (adjusted HR for OS [95% CI]: 0.37 [0.20, 0.67]). The median OS in the tarlatamab group was 14.3 months (95% CI: 10.8, not estimable [NE]) after weighting (base case). In comparison, median OS in the comparator CAS group was 5.6 months (95% CI: 5.2, 6.1). Results were similar across sensitivity analyses adjusting for different sets of prognostic factors. The results similarly indicated better PFS in the tarlatamab group relative to the CAS control group both before and after adjustment for baseline differences across all scenarios.

Table 9: Summary of median OS, PFS and HRs for tarlatamab vs available treatment options (unadjusted and MAIC adjusted)

	OS			PFS		
	HR (95% CI)	Median OS		HR (95% CI)	Median PFS	
		DeLLphi-301	CAS		DeLLphi-301	CAS
Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Base case	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Scenario 1	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Scenario 2	[redacted]	[redacted]	-	[redacted]	[redacted]	-

Progression-free survival in CAS and Oncology Outcomes studies was proxied by TTD. HR < 1 favours tarlatamab, HR > 1 favours comparator therapies.
CAS study adjustment factors: Base case: Age at index, sex, ECOG PS at index, brain metastases (at index for tarlatamab vs. at 1L for comparator), liver metastases (at index for tarlatamab vs. at 1L for comparator), disease stage at diagnosis, CFI, time from diagnosis to index. Scenario 1: Base case, excluding CFI. Scenario 2: Base case, excluding disease stage at diagnosis.
Abbreviations: 1L: first-line; CAS: Cancer Analysis System; CI: confidence interval; CFI: chemotherapy-free interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation or death.

A36. Why was a simulated treatment comparison not considered as an alternative to conducting a MAIC?

In the absence of relative efficacy estimates based on head-to-head data, MAIC and simulated treatment comparison (STC) are both discussed in the NICE Decision Support Unit Technical Support Document 18 ('Methods for Population-Adjusted Indirect Comparisons in Submissions to NICE'). For the current study, an unanchored MAIC approach to estimate the relative efficacy between tarlatamab versus current treatment options was used for multiple reasons.

Firstly, STCs rely on relative homogeneity of populations between trials for which outcomes are simulated. As shown in Table 6 above and the distribution of weights presented in the Company submission, the two populations in the DeLLphi-301 and RWE studies were heterogeneous, with differences in identified prognostic variables and effect modifiers. The simulated outcomes generated from these heterogeneous populations would likely have failed to adequately adjust for differences in prognostic variables and effect modifiers. In contrast, the weighting applied to selected variables in the MAIC analysis led to perfect matching across both study populations (see Table 6), ensuring adjusted outcomes reflected the UK RWE patient population most reflective of patient population of interest in this submission.

Secondly, STCs are often more restricted than MAICs as STCs are done via parametric prediction model that requires various criteria being satisfied or specified, including proportional hazards or accelerated failure times, interactions between covariates or time-dependency of cofactors. In contrast, an MAIC model minimises the risk of violated assumptions or incorrect model specification and brings the benefit of not imposing a fixed distribution on the resulting outcome. Additionally, unanchored MAICs have been previously used to compare different treatment options for relapsed SCLC.[9, 10]

Finally, no guidance or literature had proven one methodology being superior to the other, and that both methods may reach similar findings in situations where there is sufficient overlap in

prognostic factors and treatment effect modifiers between the study populations, such as in the current MAIC analysis.

Given the practical advantages of the MAIC approach and that unanchored MAICs have been commonly applied in oncology including SCLC, an unanchored MAIC approach to estimate the relative efficacy between tarlatamab and current treatment options was deemed sufficient and appropriate.

A37. Please conduct and provide results of sensitivity analyses of OS and PFS omitting sex and age at diagnosis as prognostic factors from the analyses (i.e. an analysis including all the base case covariates except for these two). Please report differences in these variables pre- and post-match. Please also conduct a cost-effectiveness scenario using these data.

MAIC weights, SMDs and baseline characteristics before and after weighting are shown in Figure 9 and Figure 10 below, and in Table 6 above. Omitting sex and age increases the effective sample size (ESS) from 27 (base case) to 44.

Similar to the base case MAIC analysis, the results of this scenario indicate significantly better OS and PFS in the tarlatamab group relative to the available treatment options group, with an OS HR of 0.35 (0.21, 0.57) [base case MAIC: 0.37 (0.20, 0.67)] and a PFS HR of 0.22 (0.15, 0.33) [base case MAIC: 0.18 (0.10, 0.34)]. KM plots for OS and PFS are shown in Figure 11 and Figure 12.

Updated base case cost-effectiveness results based on the base case MAIC are presented in Table 9 below. Results of the cost-effectiveness scenario analysis omitting sex and age at diagnosis as prognostic factors are presented in Table 10 below.

Figure 9: Weight distribution after matching

Figure 10: Standardised mean difference - before and after matching

Abbreviations: ECOG: Eastern Cooperative Oncology Group; LCI: lower confidence interval; LOT: line of therapy; SMD: standardised mean difference; UCI: upper confidence interval.

Table 10: Adjusted and unadjusted MAIC results tarlatamab vs available treatment options

	ESS	HR (95% CI)	Robust SE	p-value	Median (months) Tarlatamab	Median (months)- available treatment options
OS						
Unadjusted	-	0.278 (0.194, 0.399)	[redacted]	<0.0001	[redacted]	[redacted]
MAIC-adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
PFS						
Unadjusted	-	0.206 (0.150, 0.282)	[redacted]	<0.0001	[redacted]	[redacted]
MAIC-adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: CI: confidence interval; ESS: effective sample size; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; OS: overall survival; SE: standard error.

Figure 11: KM curves of weighted and unweighted OS for tarlatamab vs. available treatment options

Abbreviations: KM: Kaplan-Meier; OS: overall survival.

Figure 12: KM curves of weighted and unweighted PFS for tarlatamab vs. available treatment options

Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival.

Table 11: Updated base case results (using base case MAIC)

Treatment	Costs	LYs	QALYs	Incr. costs	Incr. LYs	Incr. QALYs	ICER
SOC	[redacted]	[redacted]	[redacted]				
Tarlatamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,774.22

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life year; MAIC: matching-adjusted indirect treatment comparison; QALY: quality-adjusted life year; SoC: standard of care.

Table 12: Updated base case results (using MAICs which omit age + sex at diagnosis)

Treatment	Costs	LYs	QALYs	Incr. costs	Incr. LYs	Incr. QALYs	ICER
SOC	[redacted]	[redacted]	[redacted]				
Tarlatamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,289.74

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life year; MAIC: matching-adjusted indirect treatment comparison; QALY: quality-adjusted life year; SoC: standard of care.

A38. Priority question: Please conduct and provide the results of sensitivity analyses of OS and PFS, including the effect on the effective sample size (ESS), that include only the three prognostic factors considered to be 'very important' by the company's clinical experts (i.e. ECOG PS, disease stage, and response to previous treatment). Please also conduct a cost-effectiveness scenario using these data.

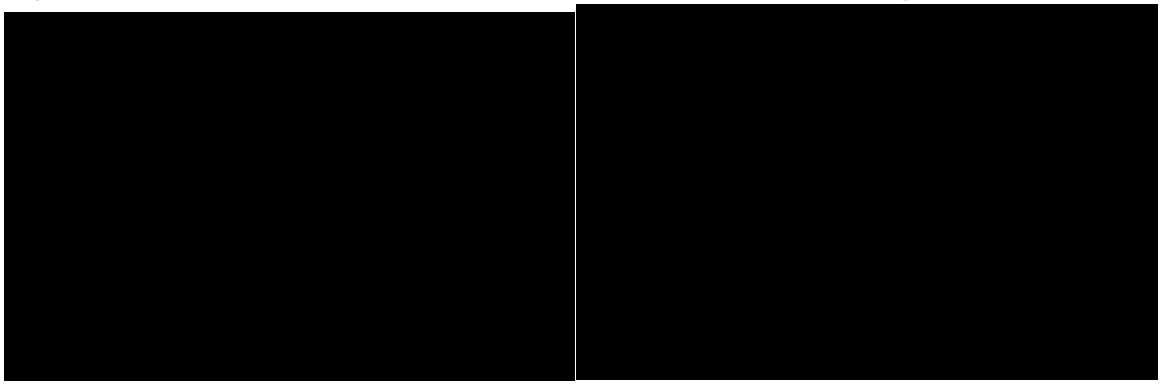
MAIC weights, standardized mean differences and baseline characteristics before and after weighting are shown in Figure 13, Figure 14 and below. Omitting sex and age increases the ESS from 27 (base case) to 73.

Similar to the base case MAIC analysis, the results of this scenario indicate significantly better OS and PFS in the tarlatamab group relative to the available treatment options group with an OS HR of [redacted] ([redacted]) [base case MAIC: [redacted] ([redacted])] and a PFS HR of [redacted] ([redacted]) [base case MAIC: [redacted] ([redacted])]. KM plots for OS and PFS are shown in Figure 15 and Figure 16.

Updated base case cost-effectiveness results based on the base case MAIC are presented in Table 13 below. Results of the cost-effectiveness scenario analysis using MAICs which only include the three main prognostic factors are presented in Table 14 below.

Figure 13: Weight distribution after matching

Figure 14: Standardised mean difference - before and after matching



Abbreviations: ECOG: Eastern Cooperative Oncology Group; LCI: lower confidence interval; SMD: standardised mean difference; UCI: upper confidence interval.

Table 13: Baseline characteristics before and after matching

Prognostic variables	DeLLphi-301 (n = 97)	CAS study (n = 540)	DeLLphi-301 after matching

ECOG PS 0 at initiation of treatment	25.8%	[redacted]	[redacted]
ECOG PS 1 at initiation of treatment	74.2%	[redacted]	[redacted]
Platinum resistant (CFI <90 days) after 1L treatment	27.3%	[redacted]	[redacted]
Platinum sensitive (CFI 90 to <180 days) after 1L treatment	22.2%	[redacted]	[redacted]
Platinum sensitive (CFI ≥180 days) after 1L treatment	50.5%	[redacted]	[redacted]
Disease stage – ES at initial diagnosis	[redacted]	[redacted]	[redacted]

Abbreviations: 1L: first line; CFI: chemotherapy-free interval; ECOG: Eastern Cooperative Oncology Group; ES: extensive stage; PS: performance status.

Table 14: Adjusted and unadjusted MAIC results tarlatamab vs available treatment options (OS)

	ESS	HR (95% CI)	Robust SE	p-value	Median OS (months) Tarlatamab	Median OS (months)- available treatment options
OS						
Unadjusted	-	0.278 (0.194, 0.399)	[redacted]	<0.0001	[redacted]	[redacted]
MAIC-adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
PFS						
Unadjusted	-	0.206 (0.150, 0.282)	[redacted]	<0.0001	[redacted]	[redacted]
MAIC-adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: CI: confidence interval; ESS: effective sample size; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; OS: overall survival; SE: standard error.

Figure 15: KM curves of weighted and unweighted OS for tarlatamab vs. available treatment options

Abbreviations: KM: Kaplan-Meier; OS: overall survival.

Figure 16: KM curves of weighted and unweighted PFS for tarlatamab vs. available treatment options

Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival.

Table 15: Updated base case results (using base case MAIC)

Treatment	Costs	LYs	QALYs	Incr. costs	Incr. LYs	Incr. QALYs	ICER
SOC	[redacted]	[redacted]	[redacted]				

Tarlatamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,774.22

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life year; MAIC: matching-adjusted indirect treatment comparison; QALY: quality-adjusted life year; SoC: standard of care.

Table 16: Updated base case results (using MAICs which only include 3 main prognostic factors)

Treatment	Costs	LYs	QALYs	Incr. costs	Incr. LYs	Incr. QALYs	ICER
SOC	[redacted]	[redacted]	[redacted]				
Tarlatamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,328.38

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life year; MAIC: matching-adjusted indirect treatment comparison; QALY: quality-adjusted life year; SoC: standard of care.

A39. Priority question: Please conduct a MAIC sensitivity analysis using TTD from the DeLLphi-301 trial (instead of PFS) versus TTD from the UK CAS RWE study and provide the results of this analysis. Please also conduct a cost-effectiveness scenario using these data.

This analysis can be performed using data which are already present in the economic model. The MAIC weights are the same regardless of the outcome (TTD or PFS) which is used. To generate the results for this analysis, an option to set PFS equal to TTD for the tarlatamab arm has been included in the "EAG options" worksheet in the updated economic model. The results of the analysis compared to the updated base case are presented below. Please note that this analysis utilises the same censoring approach as per the base case analysis, that is, that patients who received treatment beyond progression were censored from OS and TTD.

Base case cost-effectiveness results using PFS as per the original base case, and updated base case results using TTD as a proxy for PFS for the tarlatamab arm are presented in Table 15 and Table 16, respectively. Please note that these results are deterministic.

Table 17: Updated base case results (using PFS as per original base case)

Treatment	Costs	LYs	QALYs	Incr. costs	Incr. LYs	Incr. QALYs	ICER
SOC	[redacted]	[redacted]	[redacted]				
Tarlatamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,774.22

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life year; PFS: progression-free survival; QALY: quality-adjusted life year; SoC: standard of care.

Table 18: Updated base case results (using TTD as a proxy for PFS for the tarlatamab arm)

Treatment	Costs	LYs	QALYs	Incr. costs	Incr. LYs	Incr. QALYs	ICER
SOC	[redacted]	[redacted]	[redacted]				
Tarlatamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,168.20

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life year; PFS: progression-free survival; QALY: quality-adjusted life year; SoC: standard of care.

Section B: Clarification on cost-effectiveness data

B1. There is a discrepancy between the adverse event costs in the economic model and in CS Table 56. The costs for anaemia, diarrhoea, fatigue, febrile neutropenia, and leukopenia match, but the costs of the remaining adverse events in the model do not correspond with the costs reported in the CS. Please indicate which costs are correct and please update the economic model accordingly.

The costs presented in the economic model are correct, with the exception of the cost for Nausea, which was £313. This is a typographical error, and has been updated to the correct value of £303. The model has been updated accordingly and is provided alongside these question responses.

B2. Please explain why only adverse events costs related to CC (complication and comorbidity) score of 8+ are used for some of the adverse events, rather than a weighted cost across all CC levels.

To prevent underestimation of AE costs, the highest complication and comorbidity (CC) scores were used as these corresponded to the highest costs for each AE. This was done to reflect the severity of the AEs modelled (grade 3 and 4), which the Company assumes have higher costs associated with them than less-severe (grade <3) adverse events.

B3. The EAG have identified a cost for oral chemotherapy of £137 from the NHS Payment Scheme; CS Table 53 reports a cost of £27.40. Please indicate the correct cost to be used in the economic model and update the model accordingly.

This change has been made in the updated version of the Company model.

B4. CS Table 51 reports a disutility of -0.07 for neutropenia, whilst the corresponding disutility in the economic model is -0.09. Please indicate which disutility is correct and update the economic model accordingly.

This is a typographical error in Table 51 of the Company submission. The correct value is −0.09, as used in the model.

B5. The EAG are unable to locate the health state utilities stated to be sourced from the DeLLphi-301 trial in CS Table 51. Please identify where these figures can be found in the provided reference.

The utility analyses were not included in the CSR and were a *de novo* analysis. This has been included as data on file accompanying this response.

B6. The EAG are unable to replicate the ICER for Scenario 8 in CS Table 68. The table reports an ICER of £24,599 per QALY, while the company's economic model presents an ICER of £46,706 per QALY. Please advise which result is correct.

This is a typographical error in the original submission. Amgen can confirm that an ICER of £46,706 for this scenario is correct.

B7. Priority question: Page 109 of the CS states that there are no resource use costs or monitoring and testing costs for patients in the progressed disease (PD) health state. However, a proportion of patients in the PD health state are on subsequent treatment as outlined in CS Table 58, which would incur additional resource and monitoring costs. Please justify this approach.

Whilst most patients (80.8% in the tarlatamab arm, and 85% in the SoC arm) did not receive subsequent therapy, and so would not incur medical resource use costs and monitoring costs, the Company acknowledges that patients who receive subsequent therapy would incur these costs. The economic model has been updated with medical resource use and monitoring costs for patients who receive subsequent therapy. This change has been made to the model and the Company proposes it should be considered as the new base case. The impact of this change is shown in Table 17 and Table 18 below.

Table 19: Updated base case (without MRU/ monitoring costs for patients who received subsequent therapy)

Treatment	Costs	LYs	QALYs	Incr. costs	Incr. LYs	Incr. QALYs	ICER
SOC	[redacted]	[redacted]	[redacted]				
Tarlatamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,774.22

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life year; MRU: monitoring resource use; QALY: quality-adjusted life year; SoC: standard of care.

Table 20: Updated base case (with MRU/ monitoring costs included for patients who received subsequent therapy)

Treatment	Costs	LYs	QALYs	Incr. costs	Incr. LYs	Incr. QALYs	ICER
SOC	[redacted]	[redacted]	[redacted]				
Tarlatamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,784.71

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life year; MRU: monitoring resource use; QALY: quality-adjusted life year; SoC: standard of care.

B8. The CS states on page 75 that the cost effectiveness literature review searches were conducted on April 19, 2023. Please inform us of any additional cost effectiveness studies that have been published since that date.

Amgen is not aware of any cost-effectiveness study for relapsed/refractory SCLC published since April 19, 2023.

B9. CS Table 52 reports a cost of [redacted]/1mg vial for tarlatamab, whereas the economic model report a cost of [redacted]/1mg vial. Please indicate the correct treatment cost.

The correct, confidential, treatment cost is [redacted]/1 mg vial. These values were not correctly marked as confidential in Document B and should be redacted. The Company has provided an updated version of Document B with these values marked as confidential.

B10. The EAG are unable to locate the 86% relative dose intensity for tarlatamab in the DeLLphi-301 trial reference as reported in CS Table 52. Please identify where in the reference this RDI is reported and explain the reasons for treatment interruption.

The relative dose intensity data is presented in Table 14-5.1.1. in the full CSR which has been shared alongside this response. This CSR document contains all the end-of-text tables which were omitted from the version of the CSR which was previously shared alongside our submission. The reasons for treatment interruption are also presented in Table 14-5.1.2 of the full CSR.

B11. CS section B.3.2.3 – Comparators included in the model: Please describe how the proportion of treatments identified as "other" was re-allocated to CAV, platinum + etoposide chemotherapy and topotecan. Why did the proportion of patients assumed to be receiving CAV remain 38% after this process?

There are typographical errors in the original distribution of treatments presented in the original submission. The correct versions are used in the model, and are as follows:

- Topotecan: 39%
- CAV: 35%
- Platinum-based chemotherapy: 19%
- Other: 7%

B12. We note that the eMIT prices in the company submission do not align with the prices on eMIT accessed in May 2024. Please review the discrepancies below and update the model and cost effectiveness results where necessary.

Drug/ dose/ unit	Price in submission appendix K (per vial)	Price in EMIT accessed May 2024 (per vial)
Carboplatin 450 mg vial	£14.69	£48.09
Etoposide 500mg vial	£10.69	£13.40
Cyclophosphamide 1g vial	£12.96	£13.14
Doxorubicin 200mg vial	£17.18	£15.98
Vincristine 2mg vial	£6.78	£6.64

Dexamethasone 6.60mg vial	£4.84	£0.375

The model has been updated with the latest eMIT prices as identified by the EAG.

Section C: Textual clarification and additional points

Textual clarifications

C1. The 'Population' row of CS Table 18 states that the CAS Control Cohort included patients "with an incident diagnosis during the diagnostic inclusion period" – please clarify what "incident diagnosis" means.

Amgen can confirm that "incident diagnosis" refers to the first confirmed diagnosis of SCLC, designated by the ICD-10 and morphology codes specified in Table 18 of the Company submission.

C2. CS Table 18: Please provide the missing n value for the 'Gender (female)' row of this table.

The missing n value for the 'Gender (female)' row is presented in Table 19.

Table 21: Comparison of DeLLphi-301 and CAS Control Cohorts

	DeLLphi-301 (N=97)	CAS Control Cohort (N=540)
Demographic characteristics		
Age at diagnosis (years), mean (SD)	[redacted]	[redacted]
Gender (female), n (%)	26 (26.8)	[redacted]

Abbreviations: SD: standard deviation.
Source: Amgen Data on File. DeLLphi-301 CSR (27th June 2023 DCO);[4] Ahn *et al.* (2023).[3]

C3. CS Appendix Table 16 ('Assessment of UK CAS RWE study data quality') appears to be an incomplete table. Please provide a completed version of this table.

Table 16 in the CS appendices was included in error. The SACT database is managed by NHS Digital and is widely used in CDF submissions as part of Commercial Access Agreements, therefore the Company did not feel it was appropriate or necessary to assess the quality of SACT as a data source.

Confidentiality marking

C4. The zipped folder of references that the company provided has '[CON]' in the filename but the folder within, 'Final Reference Pack' does not and many of the references within are publicly available and therefore are not confidential. Some references begin with 'Amgen Data on File'. Should the information in all of these

data on file references be treated as confidential? Are there any other references that should be treated as confidential?

All references labelled ‘Amgen Data on File’ should please be treated as confidential. No other references should be treated as confidential.

References

C5. Copies of reports of the UK CAS natural history study (referred to in CS Table 58 as the source of the subsequent treatment distributions data for the standard of care arm) and the UK CAS RWE study do not appear to have been provided with the CS. Please supply these.

Please note that the ‘UK CAS natural history study’ and ‘UK CAS RWE study’ references are both referring to the same UK CAS RWE study data file, provided as an excel document in the reference pack titled ‘Amgen Data on File (CAS RWE Study Results)’.

References

1. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol 1999;17:658-67.
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3. Ahn MJ, Cho BC, Felip E, et al. Tarlatamab for Patients with Previously Treated Small-Cell Lung Cancer. N Engl J Med 2023.
4. Amgen Data on File. DeLLphi-301 Clinical Study Report (June 2023 DCO).
5. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. JNCI: Journal of the National Cancer Institute 1993;85:365-376.
6. Griffiths P, Peipert JD, Leith A, et al. Validity of a single-item indicator of treatment side effect bother in a diverse sample of cancer patients. Supportive Care in Cancer 2022;30:3613-3623.
7. Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. Bmj 1995;310:170.
8. Keeping et al. Comparative effectiveness of nivolumab versus standard of care for third-line patients with small-cell lung cancer. J Comp Eff Res 2020 Dec;9(18):1275-1284. doi: 10.2217/cer-2020-0134. Epub 2020 Nov 3.
9. Hanvesakul R, Rengarajan B, Naveh N, et al. Indirect treatment comparison of lurbinectedin versus other second-line treatments for small-cell lung cancer. Journal of Comparative Effectiveness Research 2023;12:e220098.
10. Smare C, Dave K, Juarez-Garcia A, et al. Cost-effectiveness of nivolumab monotherapy in the third-line treatment of small cell lung cancer. Journal of Medical Economics 2021;24:1124-1133.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Tarlatamab for previously treated advanced small-cell lung cancer [ID6364]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Roy Castle Lung Cancer Foundation
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, work in lung cancer patient care (information, support and advocacy activity) and raise awareness of the disease and issues associated with it. Our funding base is a broad mixture including community, retail, corporate, legacies and charitable trusts. Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 15%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of small cell lung cancer.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in	**RCLCF has received the following funding :** - Amgen (£30,000 for 1 year funding of Global Lung Cancer Coalition (GLCC) project; £15,000 grant for Information Services; £165 Advisory Meeting Honorarium) - BMS (£30,000 for 1 year funding of GLCC project; £1100 for Advisory board Honorarium) - Lilly (£30,000 for 1 year funding of GLCC project) - Boehringer Ingelheim (£30,000 for 1 year funding of GLCC project; £1040 Advisory board Honorarium) - Novartis (£30,000 for 1 year funding of GLCC project); £3656.50 for 4 Advisory Boards and Quarterly Consultations) - Sanofi (£30,000 for1 year funding of GLCC project) - Pfizer (£30,000 for 1 year funding of GLCC project)

the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	- Novocure (£30,000 for 1 year funding of GLCC project) - Roche (£30,000 for 1 year funding of GLCC project; £525 Speaker Fee, Lung Cancer Conference) - Regeneron (£30,000 for 1 year funding of GLCC project) - Merck (£30,000 for 1 year funding of GLCC project - AstraZeneca (£30,000 for 1 year funding of GLCC project; £19,500 for GLCC Project Translation; £300 for Advisory Board Honorarium) - Daiichi Sankyo (£30,000 for 1 year funding of GLCC project; £131.50 for Advisory Board Honorarium) - Takeda (£30,000 for 1 year funding of GLCC project; £260 Speaker Fee) - Janssen (£24,000 grant funding for Ask The Nurse Service)
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	no
5. How did you gather information about the experiences of patients and carers to include in your submission?	The Foundation has contact with patients/carers through its UK wide network of Lung Cancer Patient Support Groups, Patient Information Days, patient/carer panel, online forums, Keep in Touch' service and its nurse-led Lung Cancer Information Helpline.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The National Lung Cancer Audit 2024 (for patients diagnosed in 2022), reported around 10% of lung cancer being of small cell pathological sub type. SCLC is widely accepted to be around 10 to 15% of lung cancer cases. A diagnosis of extensive SCLC is devastating. Small cell is a particularly aggressive type of cancer, patients often being very symptomatic at presentation. This is a rapidly progressive disease and as such, patients should be assessed quickly and systemic anticancer treatment started quickly. SCLC is very responsive to initial chemotherapy/immunotherapy. However, despite the sometimes dramatic response, many patients relapse and die within six months of diagnosis. The overall 5 year survival for SCLC (limited and extensive stage disease) is only about 5%. Thus, this group of lung cancer patients have a particularly poor outlook. with an obvious impact on family and carers. Symptoms such as breathlessness, cough and weight loss are difficult to treat, without active anti-cancer therapy. Furthermore, these are symptoms which can be distressing for loved ones to observe.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Outcomes of current treatment remain poor in SCLC. There have been relative few developments in the treatment of this type of lung cancer in decades. As such, there is a huge need for therapies with better outcomes than currently available.
8. Is there an unmet need for patients with this condition?	Massive unmet need

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The results of the Phase 2 DeLLphi-301 study, published in the NEJM showed encouraging findings. In the trial, tumours shank in 40% of people given 10mg of Tarlatamab every 2 weeks and in about 32% of people receiving a 100mg dose. (We understand that in people treated with current therapies for SCLC which has relapsed, the response rate is around 15%). Furthermore, in more than half of all patients whose tumours shrank with Tarlatamab (59%), the treatment kept the cancer at bay for at least 6 months – and in many, it did so for 9 months or longer. Though relatively modest, the potential for extensions in life, is of paramount importance to this patient population and their families. New therapy options provide much needed hope in this patient group.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The side effects of the treatment. The most common being cytokine release syndrome, a potentially life threatening reaction in which inflammation spreads through the body. This necessitates patients being in hospital and monitored, for their initial treatments. We understand that in the study, most cases of CRS were managed with supportive care (such as IV fluids and drugs to control fever and inflammation). Other common side effects included decreased appetite and fever. However, the study reported that, only 3% discontinued Tarlatamab because of treatment related side effects.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• SCLC is an aggressive disease, with very few advances in treatment over decades. • The outcome from current standard treatment, for this patient group, is woefully poor. There is massive unmet need. • Tarlatamab is a new type of immunotherapy drug known as a bispecific T-cell engager, or BiTE, • Tarlatamab is shown to be of benefit in the management of patients with previously treated advanced SCLC.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

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Please select YES if you would like to receive information about other NICE topics - YES or NO

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Tarlatamab for previously treated advanced small-cell lung cancer [ID6364]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **30 August 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating small-cell lung cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Yvonne Summers
2. Name of organisation	The Christie
3. Job title or position	Consultant Medical Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with small-cell lung cancer? ☒ A specialist in the clinical evidence base for small-cell lung cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	nil
8. What is the main aim of treatment for small-cell lung cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To improve disease related symptoms To shrink cancer To delay progression

	To improve overall survival To improve or maintain quality of life
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Partial response is defined by recist as a 30% reduction in target lesion diameters, but more minor responses and prolonged disease stability are clinically significant, particularly in a disease where time to progression (despite initial response) can be very short lived
10. In your view, is there an unmet need for patients and healthcare professionals in small-cell lung cancer?	Yes, current second line therapies have modest efficacy with limited progression free survival (PFS) time. In SCLC disease progression is often accompanied by disabling symptoms and mortality within few months.
11. How is small-cell lung cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	SCLC is treated according to NICE guidance and TA's. Pathways are standard following initial treatment, but there is some variation in the rates of concurrent versus sequential chemo-radiation across England in the first line. Patients with limited stage disease are treated with combination chemotherapy and radiotherapy (concurrent preferably, or sequential). Surgery is only carried out in a very small number of patients with T1N0 disease as the disease is rapidly progressive and requires systemic therapy with chemotherapy as soon as possible. Patients with extensive stage disease are treated with chemotherapy +/- atezolizumab according to performances status (TA638). Following progression, after initial treatment, patients may be rechallenged with carboplatin and etoposide depending on the initial response and time to progression (denoting platinum sensitivity), or receive 2nd line cyclophosphamide, adriamycin and vincristine (CAV) or Topotecan (TA184). The technology would replace CAV or Topotecan.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	The technology would be similar to the current treatments in that: • It would be delivered in secondary care • Tarlatamab is an intravenous treatment (as is CAV) and would be delivered via chemotherapy/SACT delivery units

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)
• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)
	• There are similar radiology requirements
	There are some differences in that:
	• Topotecan is an oral treatment, Tarlatamab is iv
	• The treatment schedule is different:
	  ○ CAV is 3 weekly iv
	  ○ Tarlatamab is 1mg iv day 1, 10mg iv day 8 and 15, then 10mg iv every 2 weeks
	• Tarlatamab has a risk of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) which needs to be monitored and managed
	No special equipment is required.

13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes. Overall response rate (ORR) with CAV and Topotecan is about 20% (from numerous trials), and progression free survival (PFS) about 3-4 months, and overall survival (OS) about 6-7 months, with significant grade 3/4 myelosuppression. Tarlatamab doubles ORR (40%), the duration of response is 9.7 months and the median OS has not yet been reached (at the time of publication one quarter of patients were still alive more 14 months – further follow up will give more information on OS). Patient reported outcome shows improved chest pain and breathlessness
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients need to be of good performance status (PS 0-1)
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?	There are more visits to the chemotherapy suite for treatment and the risk of CRS and ICANS needs to be discussed and monitored.

(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	PROMS were collected in DeLLphi 301 which demonstrated improved chest pain and breathlessness. Global QoL assessment was used. Many patients receive CAV rather than topotecan (and there has been a shortage of oral topotecan necessitating iv use of late) and so many patients do not currently receive oral therapy.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes, it is a step change. The tail on the survival curve is impressive and hitherto not seen in this disease setting.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There is less myelosuppression and infection risk, but patients and healthcare professionals need to be educated about the risk of CRS and ICANS.
20. Do the clinical trials on the technology reflect current UK clinical practice?	Patients are of better performance status in clinical trials than standard populations. Importantly patients with brain metastases were included in the trial.

• If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	In a disease where outcomes are so poor, OS remains the most important outcome, but ORR provides valuable information about efficacy and patients often have symptomatic improvement with response to therapy. The improved duration of response gives insight into the different mechanism of action of Tarlatamab compared to chemotherapy and provides hope that further follow up will demonstrate the expected significant improvements in median OS (currently not reached, which in itself is significant). DeLLphi-301 demonstrated that Tarlatamab doubles ORR (40%), the duration of response is 9.7 months and the median OS has not yet been reached (at the time of publication one quarter of patients were still alive more 14 months – further follow up will give more information on OS). No further safety concerns have come to light.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance 662?	no
23. How do data on real-world experience compare with the trial data?	Nil available
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	no

belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	
25. What factors influence treatment decisions after 2 previous treatments for small cell lung cancer? Specifically: • What proportion of people offered third line systemic treatment chose to have best supportive care instead? • What are the reasons people may have best supportive care rather than third line systemic treatment options currently available in clinical practice? Would people who currently have best supportive care have tarlatamab if it was a treatment option?	Patients performance status and previous duration of response are the key drivers of whether or not a patient will be offered and accept a further therapy. Shared decision making, in the context of modest benefit, limited duration of response and accompanied toxicity of treatment means that many patients do not have a second or third line of treatment. Less than 10% of patients will have a third line treatment. Patients who were poor performance status would not have tarlatamab (and very many patients are poor PS at 3rd line). A small number of patients where a treatment would have been offered, but the patient declined through personal choice, may accept Tarlatamab because of improved outcomes compared to current standard therapies. Poor PS patients are not suitable for Tarlatamab.

• Would clinicians tarlatamab be a suitable treatment option for people with an ECOG performance status of 3 or 4?	
26. In your experience, would you expect people with and without prior programmed cell death ligand 1 (PD-L1) inhibitor treatment to respond to third line treatment differently? If so, how?	I do not have sufficient experience to confidently comment.
27. How comparable is the quality of life expected to be for people with advanced small-cell and advanced non-small-cell lung cancer who are having third line treatment, and whose cancer progresses after 3rd line treatment?	Symptoms may be similar, but symptoms are often more rapidly progressive with SCLC.

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

SCLC currently has very poor treatment options beyond first line therapy

Tarlatamab doubles ORR (40%) compared to current standard therapies

Duration of response is 9.7 months

Overall Survival is improved compared to existing treatment and median OS in the trial has not yet been reached (at the time of publication one quarter of patients were still alive more 14 months).

Patient reported outcome shows improved chest pain and breathlessness

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Single Technology Appraisal

Tarlatamab for previously treated advanced small-cell lung cancer [ID6364]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **30 August 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Treating small-cell lung cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor Fiona Blackhall
2. Name of organisation	The Christie NHS Foundation Trust and Manchester University
3. Job title or position	Honorary Consultant, Professor of Thoracic Oncology
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with small-cell lung cancer? ☒ A specialist in the clinical evidence base for small-cell lung cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil to disclose
8. What is the main aim of treatment for small-cell lung cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aim of treatment for small cell lung cancer is to either cure the cancer or control the growth and spread of the cancer to prolong life expectancy and quality of life. The aim depends on the initial stage of the cancer at presentation and is based on current evidence of effectiveness of available treatments. The

	majority of patients present with advanced, metastatic stage for which there is not currently a curative intent treatment and for which the treatment aim is palliative.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A clinically significant treatment response in a patient with small cell lung cancer is a stabilisation of the tumour or tumours or any shrinkage of the tumour(s).
10. In your view, is there an unmet need for patients and healthcare professionals in small-cell lung cancer?	There is a high unmet need for patients and healthcare professionals in small cell lung cancer. Fewer than 10% of patients will survive beyond 5 years. Effective treatments for small cell lung cancer have lagged behind those for non-small cell lung cancer.
11. How is small-cell lung cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Small cell lung cancer is treated according to national and international guidelines. The pathway of care is well defined. **National Guidelines** : Topotecan for the treatment of relapsed small-cell lung cancer (2009). NICE technology appraisal 184. Atezolizumab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer (2020). NICE technology appraisal 638. Lung cancer: diagnosis and management (2019) NICE guideline NG122. Updated 2023 **International Guidelines** : Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up A.-M.C. Dingemans et al. Ann Oncol 2021 The technology being evaluated would provide an additional therapeutic option to the current pathway of care.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology will be provided in the clinical setting of secondary or tertiary care in treatment facilities with specialism in cancer care.

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	This class of technology is currently in use for other types of cancer. Training and experience is in place in specialist cancer sites to provide this technology. No additional facilities or equipment is required for this technology.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	I would expect the technology to increase length of life and health related quality of life more than current care, considering results from previous 2nd line and 3rd line clinical trials. Tarlatamab, in the 3rd line setting resulted in an objective response rate of 40% with a median duration of response of 9.7 months. I would expect this to be of clinically meaningful benefit to patients given that response rates to second-line chemotherapy are lower ranging from 15-30% depending on response and duration since first line treatment. *(Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up A.-M.C. Dingemans et al. Ann Oncol 2021)*
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology would be applicable for any patient with small cell lung cancer and with the eligibility criteria for the DeLLphi-301 [NCT05060016], an open-label, multicenter, multi-cohort study . Patients with symptomatic brain metastases, interstitial lung disease or non-infectious pneumonitis, and active immunodeficiency were excluded from the clinical trial of tarlatamab DeLLphi-301 [NCT05060016], an open-label, multicenter, multi-cohort study. There is therefore no evidence base for patients with these factors to receive this technology.

15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	The technology is associated with some side effects including cytokine release syndrome (CRS). This side effect requires patients to be monitored in hospital following infusion of tarlatamab and depending on its severity further treatment is required to manage the CRS symptoms. Monitoring includes checking blood pressure, heart rate and oxygen levels. The experience from clinical trials of the technology suggests that the risk of CRS decreases after the initial 1-2 treatment cycles.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional biopsy or testing is required to start treatment with the technology. The technology is discontinued if there is lack of clinical benefit or unacceptable toxicity.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Yes
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Currently there is no approved 3rd line treatment for patients with advanced small cell lung cancer. Small cell lung cancer is rapidly progressive, one of the fastest growing cancers, such that survival is very short – discussed with patients as a few months at best and often only a few weeks – once available treatment options are exhausted. This technology would be a step-change in the clinical management of small cell lung cancer and address the high unmet need for treatment to improve duration and quality of life. The response rate ~ 40% and the duration of response for a cancer that is frequently chemoresistant after initial first line treatment signals a clinically meaningful step change in the management and a technology engineered to overcome drug resistance that has proved a barrier to drug development for several decades.

19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The clinical trials on the technology have been conducted in multiple countries including in the UK and in countries with similar treatment practice as in the UK. The trials reflect current UK clinical practice. The most important outcomes for small cell lung cancer are response rate, duration of response, survival, side effect profile and patient reported quality of life. These were measured in the trials of this technology. These outcome measures predict for long term outcomes, noting that survival rates for small cell cancer are very poor with median overall survival rates of just over one year with currently available first line treatment. Adverse events were captured in the trials to date with to my knowledge no other side effects that have subsequently come to light.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance 662?	No
23. How do data on real-world experience compare with the trial data?	To my knowledge there is no real-world experience for tarlatamab. There is experience of testing other experimental agents in the 3rd and later line setting and in a similar patient population selected and eligible for a clinical trial. For example in the TRINITY trial conducted in a similar patient population response rates achieved ranged from 12.4 -14.3% and median overall survival of 5.6 months. (*reference Morgensztern D Clinical Cancer Research 2019*)
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this	There are no potential equality issues to be taken into account relating to specific protected characteristics and equality legislation. Small cell lung cancer

treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	risk is not influenced by protected characteristics and indeed can affect people with any of the characteristics considered by equality legislation.
25. What factors influence treatment decisions after 2 previous treatments for small cell lung cancer? Specifically: • What proportion of people offered third line systemic treatment chose to have best supportive care instead?	The main factor that influences treatment decision after 2 previous treatments for small cell lung cancer is lack of evidence for a 3rd line treatment. For 3rd line treatment enrolment into a clinical trial is preferred. Factors that influence enrolment into a clinical trial are patient fitness including organ function ie liver function, renal and respiratory function, a patient's preference based on

• What are the reasons people may have best supportive care rather than third line systemic treatment options currently available in clinical practice? Would people who currently have best supportive care have tarlatamab if it was a treatment option? • Would clinicians tarlatamab be a suitable treatment option for people with an ECOG performance status of 3 or 4?	tolerance of previous treatments, response and duration of response to previous treatments, quality of life and goals of care. The proportion of patients who receive third line treatment is very low. In a real-world evidence study of a total of 5832 patients with extensive/ advanced stage small cell lung cancer treated between 2018 and 2021 in Italy (31.7%, 1850/5832), Germany (26.0%, 1518/5832), the UK (19.7%, 1149/5832), Spain (13.2%, 771/5832) and France (9.3%, 544/5832) the majority of patients (84.0%, 4898/5832) were receiving first line treatment at the time of data collection, 13.8% (804/5832) were receiving 2L treatment, **1.7% (98/5832) were receiving 3L treatment and 0.6% (32/5832) were receiving fourth-line treatment.** (*Reference A cross-sectional analysis of treatment patterns in small-cell lung cancer in five European countries Noemi Reguart et al. Future Oncology 2023*) In current UK practice the proportion of patients fit to receive 2nd line treatment, or who wish to receive further treatment after progression on first line therapy falls to ~ 20% with even fewer eligible for consideration of third line treatment. This is due to decline in fitness from prior treatment, from increasing cancer burden often involving multiple organs, including a high prevalence of brain metastases, and rapid evolution of biological resistance of cancer cells to further chemotherapy after 1st and 2nd line treatment. This means that few patients either survive or remain fit for a 3rd line of therapy. Those patients fit to be offered tarlatamab will make an informed choice based on the benefits and risks, their experience with prior treatment, the effect the cancer and treatment has on their quality of life and their personal goals of care. A proportion of patients will have experienced a benefit from prior treatment, will remain fit and will opt for further active treatment with tarlatamab in attempt to optimise quality and duration of life for as long as possible in the knowledge that best supportive care will become inevitable due to the nature of small cell cancer.

	Experience in recruiting to the clinical trials of tarlatamab in the UK identified a relatively small number of patients nationally who continue to be fit for treatment beyond standard 2nd line options. Tarlatamab has not been tested in patients with an ECOG performance status of 3 or 4. On this basis the safety of tarlatamab and suitability cannot be determined.
26. In your experience, would you expect people with and without prior programmed cell death ligand 1 (PD-L1) inhibitor treatment to respond to third line treatment differently? If so, how?	No. The mechanism of action of tarlatamab differs to a PDL1 inhibitor.
27. How comparable is the quality of life expected to be for people with advanced small-cell and advanced non-small-cell lung cancer who are having third line treatment, and whose cancer progresses after 3rd line treatment?	The course of progression for patients with small cell lung cancer is generally faster than for patients with non-small cell lung cancer. The doubling time for small cell lung cancer is 30 days compared to 3 months for NSCLC; quality of life for a patient with small cell lung cancer would generally deteriorate faster due to rate of end organ failure compared to a patient with non-small cell lung cancer.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Small cell lung cancer is a lethal disease with a severe impact on quantity and quality of life and very poor survival rates.

Tarlatamab provides a meaningful chance of symptom relief and longer life for patients who have exhausted all standard treatments.

Thank you for your time.

Your privacy

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External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Tarlatamab for previously treated advanced small-cell lung cancer

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Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
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Declared competing interests of the authors and advisors

The authors, and Dr Young and Dr Dorey report none. Dr Cave reports that Amgen funded her to access the American Society of Clinical Oncology conference online in 2020. Dr Cave also reports that she expressed an interest in being a Principal Investigator for a study of tarlatamab but did not become an investigator following this.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Karen Pickett critically appraised the clinical effectiveness systematic review, the company's matching adjusted indirect comparison (MAIC), drafted the report, project managed the review and is the project guarantor; Asyl Hawa critically appraised the health economic systematic review and the economic evaluation, and drafted the report; Keith Cooper critically appraised the health economic systematic review and the economic evaluation, and drafted the report; Jo Picot critically appraised the clinical effectiveness systematic review and the company's MAIC, and drafted the report; David Alexander Scott critically appraised the company's MAIC, and drafted the report.

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LIST OF ABBREVIATIONS

AE	Adverse event
AIC	Akaike information criterion
BIC	Bayesian Information criterion
BICR	Blinded independent central review
BNF	British National Formulary
CAS	Cancer Analysis System
CAV	Cyclophosphamide, doxorubicin and vincristine
CI	Confidence interval
CIC	Commercial in confidence
CQ	Clarification question
CR	Complete response
CRS	Cytokine release syndrome
CS	Company submission
CSR	Clinical study report
CT	Computed tomography
DC	Disease control
DoDC	Duration of disease control
DOR	Duration of response
DSU	Decision Support Unit
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group
eMIT	Electronic market information tool
EORTC	European Organization for Research and Treatment of Cancer

EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
ESS	Effective sample size
GP	General practitioner
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
ICANS	Immune effector cell associated neurotoxicity syndrome
ICER	Incremental cost-effectiveness ratio
IV	Intravenous
KM	Kaplan-Meier
LSM	Least squares mean
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
MRI	Magnetic resonance imaging
MRU	Medical resource use
N	Number
N/A	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PFS	Progression-free survival
PICOD	Patient, intervention, comparator, outcome, design
PR	Partial response
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit

Q2W	Once every other week (i.e. once every 2 weeks)
QALY	Quality-adjusted life year
QLQ-C30	Quality of life questionnaire core 30
QLQ-LC13	Quality of life questionnaire lung cancer module
QoL	Quality of life
r/r	Relapsed or refractory
RCT	Randomised controlled trial
RECIST	Response evaluation criteria in solid tumours
RR	Relative risk/risk ratio
SCLC	Small-cell lung cancer
SD	Standard deviation
SE	Standard error
SmPC	Summary of product characteristics
SOC	Standard of care
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TNM	Tumour, node, metastases
TSD	Technical Support Document
TTD	Time to treatment discontinuation
UK	United Kingdom
US	United States
VAS	Visual analogue scale

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, health technology, evidence and information on the issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1 Summary of key issues

ID	Summary of issue	Report sections
1	Uncertainty associated with the unanchored MAIC overall survival (OS) and progression-free survival (PFS) estimates	3.2.1, 3.2.2, 3.3.2, 3.4, 3.6, 5.2.2 and 6.3.1
2	Parametric curve used for modelling OS	4.2.6.1
3	Quality of life estimates used in the economic model	4.2.8.2
4	Exclusion of best supportive care as a comparator	2.3
5	Company submission (CS) evidence focuses on patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1	2.2.3, 2.3, 3.2.1, 3.3 and 4.2.3

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are the parametric distribution used for OS and the source of the quality-of-life values.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Following their response to the clarification questions, the company updated their economic model. The company's revised base case deterministic cost-effectiveness results are shown in Table 2 with a confidential patient access scheme (PAS) discount applied for tarlatamab.

The ICER is £33,785 per QALY for tarlatamab versus standard of care (SOC), with a QALY gain of [redacted] and an additional cost of [redacted]. The results include a severity multiplier of 1.7 applied to the incremental QALYs.

Table 2 Company revised base case results with PAS for tarlatamab

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tarlatamab	[redacted]	[redacted]	[redacted]	[redacted]	£33,785

Source: Table 20 of company's clarification response, includes severity response
SOC, standard of care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

1.3 The decision problem: summary of the EAG's key issues

The EAG have not identified any key issues in relation to the company's decision problem.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Uncertainty associated with the unanchored MAIC OS and PFS estimates

Report section	3.2.1, 3.2.2, 3.3.2, 3.4, 3.5, 3.6, 5.2.2 and 6.3.1
Description of issue and why the EAG has identified it as important	No head-to-head randomised controlled trials (RCTs) of tarlatamab versus the company's selected standard of care comparators, carboplatin and etoposide chemotherapy (carboplatin + etoposide), cyclophosphamide in combination with doxorubicin and vincristine (CAV) and topotecan were identified in the company's decision problem population of patients receiving a third-line or later therapy (third-line therapy+). Therefore, an unanchored MAIC was conducted to compare the clinical efficacy of tarlatamab against a single basket standard of care comparator, incorporating these three treatments, in terms of OS and PFS. Data for tarlatamab came from a single-arm study (DeLLphi-301), and data for standard of care was derived from a UK real-world evidence study (the UK Cancer Analysis System [CAS] study). We consider the OS and PFS estimates from the unanchored MAIC base case uncertain, because: • Indirect comparative evidence is inferior to direct comparative data. Residual systematic error due to unobserved prognostic variables and effect modifiers cannot be entirely eliminated in an unanchored MAIC.[1] • An interim data-cut of the DeLLphi-301 trial, based on 97 participants, informed the data inputs for tarlatamab in the MAIC.

	• There was an uncertainty about the accuracy of the assessment of PFS in the DeLLphi-301 trial due to potential for unblinding of the Blinded Independent Central Review group. • There were differences between the participants in the DeLLphi-301 trial and UK CAS studies in the proportions who had received prior programmed cell death ligand 1 (PD-L1) inhibitor treatment. This was not included as a covariate in the MAIC analyses. It is unknown if this difference might affect the MAIC results. • The effective sample size was greatly reduced to just [redacted] participants, making the MAIC estimates potentially unreliable. This issue is important as the OS and PFS estimates from the MAIC were used in the company's economic model.
What alternative approach has the EAG suggested?	The EAG believe the unanchored MAIC was carried out appropriately and that there was no alternative analysis approach the company could have undertaken given the lack of head-to-head evidence. The EAG's clinical experts thought that the list of prognostic factors included in the MAIC base case was generally reasonable. The EAG asked the company to carry out two MAIC scenario analyses varying the prognostic factors to explore the impact on the results. These resulted in [redacted] effective sample sizes and [redacted] results for tarlatamab for PFS and [redacted] results for tarlatamab for OS than the base case analyses. The changes in the OS and PFS values were [redacted] but resulted in around a £10,000 to £12,000 reduction in the ICER compared to that obtained when using the MAIC base case results in the company's revised economic model base case. It would be useful to know why the CS and clarification response A22 state patients were included in the UK CAS study if they met diagnostic criteria between 1st January 2013 and 31st December 2020, while a confidential report of the MAIC states [redacted].[2] The EAG suspects this is an error, but an explanation would help further assess if there is a risk of selection bias.
What is the expected effect on the cost-effectiveness estimates?	Unknown. OS particularly drives the cost-effectiveness results, so any uncertainty in the precision of the OS estimate may alter the ICERs.
What additional evidence or analyses might help to resolve this key issue?	An explanation for the inconsistency in dates reported in the CS and the MAIC report regarding the diagnostic period in which participants were eligible for the UK CAS study. Provision of an unanchored MAIC analysis using more mature OS data from the DeLLphi-301 trial (if available) and a cost-effectiveness scenario analysis using the result of this may also help to address the concern above about the immaturity of the data.

	The other limitations identified by the EAG likely cannot be addressed within this appraisal, given the nature of the available evidence.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Parametric curve used for modelling overall survival

Report section	4.2.6.1
Description of issue and why the EAG has identified it as important	The company model uses the exponential distribution for OS for the tarlatamab and SOC arm. The company fits the best fitting curve to the tarlatamab arm and then uses the same curve for the SOC arm.
What alternative approach has the EAG suggested?	The EAG prefers to use the gamma distribution for OS for the tarlatamab and SOC arms, based on the best fitting curve to the SOC arm. The EAG prefers to fit curves for OS to the SOC arm, rather than to the tarlatamab arm, as the SOC arm data are more mature and it has a larger sample size (n=540) for SOC vs (n=[redacted]) for tarlatamab arm.
What is the expected effect on the cost-effectiveness estimates?	Using the gamma distribution instead of the exponential distribution for both arms increases the ICER for the revised company base case from £33,785 to £39,074 per QALY.
What additional evidence or analyses might help to resolve this key issue?	Longer follow-up for the tarlatamab arm would improve the certainty of curve fitting for this arm.

Quality of life estimates used in the economic model

Report section	4.2.8.2
Description of issue and why the EAG has identified it as important	The company use the quality-of-life values from the DeLLphi-301 study for the progression-free and post-progression model health states, regardless of the treatment.
What alternative approach has the EAG suggested?	The EAG notes that the quality-of-life values are higher than would be expected and come from the full DeLLphi-301 dataset (n=97). We would have preferred to explore using quality-of-life values from the population used in the MAIC (n=[redacted]) which would better match the SOC population but whether these would also be higher than expected is unknown. We have used a study by Chouaid et al for the quality-of-life values in the EAG base case, although the population is third-line treatment for patients with non-small cell lung cancer (NSCLC), rather than small-cell lung cancer (SCLC).
What is the expected effect on the cost-effectiveness estimates?	Using the quality-of-life values from Chouaid et al. increases the ICER for the revised company base case from £33,785 to £43,521 per QALY.

What additional evidence or analyses might help to resolve this key issue?	Further clinical advice on whether quality-of-life data from a population of patients with NSCLC are generalisable to patients with SCLC.

1.6 Other key issues: summary of the EAG's view

Exclusion of best supportive care as a comparator

Report section	2.3
Description of issue and why the EAG has identified it as important	Best supportive care was included as a comparator in the NICE scope, but not in the company's decision problem. The company argue that patients who are candidates for best supportive care are a different population to those who are suitable for systemic therapy and will have worse ECOG performance status.
What alternative approach has the EAG suggested?	Clinical expert advice to the EAG is that the third-line therapy+ patients with SCLC who are likely to be treated with tarlatamab in clinical practice will be those who have an ECOG performance status of 0 or 1 and these patients currently tend to opt for systemic treatment. They considered the proportion of patients eligible for third-line treatment+ with an ECOG performance status of 0 or 1 who receive best supportive care to be low (one expert more specifically estimated <20%). One of the EAG's three clinical experts felt it was reasonable to not include best supportive care as a comparator, with the other two not commenting on this. The EAG suggests that obtaining further expert opinion about the relevance of this comparator would be beneficial, given that it was specified in the NICE scope.
What is the expected effect on the cost-effectiveness estimates?	The cost-effectiveness of tarlatamab versus best supportive care is currently unknown.
What additional evidence or analyses might help to resolve this key issue?	Further clinical expert opinion about whether or not best supportive care is a relevant comparator for tarlatamab.

CS evidence focuses on patients with an ECOG performance status of 0 or 1

Report section	2.2.3, 2.3, 3.2.1, 3.3 and 4.2.3
Description of issue and why the EAG has identified it as important	The clinical and cost effectiveness of tarlatamab versus standard of care is examined in the CS specifically among a population of patients with an ECOG performance status of 0 or 1 at third-line therapy+. The only identified trial of tarlatamab treatment at third-line therapy+ (DeLLphi-301) was conducted in this group of patients. This is a narrower population than that specified in the NICE scope and the company decision problem, [redacted]. The wording in the draft Summary of Product Characteristics (SmPC)

	[redacted] but the evidence from the trial may not be generalisable to patients with an ECOG performance status other than 0 and 1.
What alternative approach has the EAG suggested?	None. Clinical expert advice to the EAG is that only patients with an ECOG performance status of 0 or 1 at this stage will be suitable for tarlatamab. Therefore, we regard the company's focus on this population to be appropriate.
What is the expected effect on the cost-effectiveness estimates?	The company's model restricts the patient population to those with an ECOG performance status of 0 and 1, so the ICERs are only valid for this population. The cost-effectiveness for a wider group of patients, including those with a worse performance status has not been modelled.
What additional evidence or analyses might help to resolve this key issue?	Further discussion about the population of patients expected to be suitable for tarlatamab treatment in clinical practice.

1.7 Summary of EAG's preferred assumptions and resulting ICER

Based on the EAG's critique of the company's model (discussed in section 4), we have identified the following key aspects of the company base case with which we disagree. Our preferred model assumptions are the following:

- Overall survival: use gamma distribution for the tarlatamab and standard of care arms, instead of exponential distribution (section 4.2.6.1)
- Progression-free survival: use exponential distribution for tarlatamab arm, instead of lognormal for the tarlatamab arm (section 4.2.6.3)
- Health-related quality of life (HRQoL): use Chouaid et al. instead of DeLLphi-301 study (section 4.2.8.2),
- Adverse event costs: EAG recalculated values (section 4.2.9.3.2).

Table 2 shows the cumulative cost-effectiveness results of applying the EAG preferred model assumptions to the company's revised base case including the PAS discount for tarlatamab. Incorporating all the EAG assumptions, the ICER for tarlatamab vs BSC increases to £58,847 per QALY (including a severity multiplier of 1.7).

Table 3 EAG's preferred model assumptions: cumulative impact (deterministic) with PAS for tarlatamab

Preferred assumption	Treatment	Total costs	Total QALYs	Cumulative ICER £/QALY
	SOC	[redacted]	[redacted]	

Preferred assumption	Treatment	Total costs	Total QALYs	Cumulative ICER £/QALY
EAG corrected company revised base case	Tarlatamab	[redacted]	[redacted]	£34,958
+ OS: gamma for both arms	SOC	[redacted]	[redacted]	
	Tarlatamab	[redacted]	[redacted]	£40,442
+ PFS: exponential for both arms	SOC	[redacted]	[redacted]	
	Tarlatamab	[redacted]	[redacted]	£42,045
+ HRQoL: use Chouaid et al. (PFS 0.62; PD 0.47)	SOC	[redacted]	[redacted]	
	Tarlatamab	[redacted]	[redacted]	£55,097
+ Adverse event costs: EAG recalculated.	SOC	[redacted]	[redacted]	
	Tarlatamab	[redacted]	[redacted]	£58,847
EAG base case	SOC	[redacted]	[redacted]	
	Tarlatamab	[redacted]	[redacted]	£58,847

EAG evidence assessment group; OS overall survival; PFS progression-free survival; HRQoL health-related quality of life; PD progressed disease.
Severity multiplier of 1.7 applied to QALYs.

The change that has the most significant impact on the cost-effectiveness results is using the gamma distribution for OS and using a different source for the HRQoL. Further details of the exploratory and sensitivity analyses done by the EAG are provided in section 6.3.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to the National Institute of Health and Care Excellence (NICE) from Amgen on the clinical effectiveness and cost effectiveness of tarlatamab for treating previously treated advanced small-cell lung cancer (SCLC). It identifies the strengths and weakness of the CS. Clinical experts were consulted to advise the external assessment group (EAG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the EAG via NICE on 5th June 2024. A response from the company via NICE was received by the EAG on 20th June 2024 and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

The company provides background information on lung cancer, and SCLC in particular, in CS section B.1.3.1 which provides an overview of lung cancer and describes clinical staging, epidemiology and prognosis of SCLC. CS section B.1.3.2 describes the symptom, health-related quality-of-life (HRQoL) and economic burdens of SCLC.

2.2.1 Background information on SCLC

SCLC is the rarer of the two main subtypes of lung cancer, the other main subtype being non-SCLC. Evidence indicates that the proportion of lung cases in England that are SCLC has been falling for at least two decades and in 2022 about 7% were SCLC.[3 4] People typically present with symptoms such as dyspnoea and a persistent cough and about two thirds of people with SCLC will already have metastatic disease (i.e. disease that has already spread to other parts of the body) when they are diagnosed.[5,6]

SCLC is classified as either limited stage or extensive stage disease. Our clinical experts advised us that people with limited stage SCLC will be treated with curative intent. Limited stage SCLC is where disease can be encompassed within a single radiotherapy field. These people receive multi-modality treatment usually involving combination chemotherapy and radiotherapy, although surgery is sometimes used. People with disease that cannot be encompassed within a radical radiotherapy field (which includes all those with metastatic SCLC) are considered to have extensive stage disease. One of our experts stated that 80% of patients with SCLC will present with extensive stage disease. If people with extensive stage disease have limited lymph node involvement, they may still be treated aggressively with curative intent, but more usually people are treated with palliative intent with

chemotherapy ± immunotherapy ± radiotherapy. People whose disease has relapsed after treatment for limited stage disease are usually considered to have extensive stage disease and one of our clinical experts advised are rarely salvageable with radical radiotherapy.

The focus of this NICE appraisal is previously treated advanced small-cell lung cancer. Our clinical experts advised us that advanced small-cell lung cancer corresponds to extensive-stage disease.

As the company state, lung cancer is the second most common cancer in England with approximately 40,000 new cases in England each year,[7] although we note that lung cancer diagnoses fell during the COVID-19 pandemic[8] and data for 2022 shows there were 36,886 lung cancer diagnoses in England.[4] The CS states that SCLC accounts for approximately 15-20% of lung cancer cases (CS section B.1.3.1) however, as noted above, the proportion of lung cases in England that are SCLC has been falling.[3] In 2022 there were 2,501 SCLC diagnoses among the total 36,886 lung cancer diagnoses in England which equates to 7%, in Wales the proportion was 9% among 2,211 lung cancer diagnoses.[4] The median age at SCLC diagnosis in England in 2019/2020 was 80 years whereas in Wales it was 70 years.[9]

SCLC is an aggressive disease which, coupled with the high likelihood of metastasis, means that it typically has a poor prognosis, particularly when extensive disease is present. A recent retrospective chart review of patients in France, Italy and the UK[10] found that among 231 first-line treated patients with limited SCLC median overall survival (OS) was 17.3 months whereas among the 308 first-line treated patients with extensive SCLC median OS was just 8.8 months. In patients with relapsed/refractory SCLC initiating second line treatment (n=225) median OS dropped to 6.6 months. Our clinical experts agreed that prognosis is poor. Some patients are not well enough to receive a second-line therapy whilst others choose not to receive one. There is no established third-line treatment and the proportion of patients who remain fit for third-line treatment is small.

In CS section B.1.3.2 the company summarise the symptom burden of SCLC initially due to the effects of the disease itself and then the additional symptom burden of chemotherapy. Brain metastases, which have been found to be present in more than 10% of patients at diagnosis,[10,11] also develop after diagnosis in another 40-50% of SCLC patients.[12] Brain metastases are associated with a high burden of neurological symptoms which have been summarised by the company.

In discussing the HRQoL burden of SCLC, the company highlight the limited data available for this type of lung cancer. Evidence from a systematic review found that HRQoL is lower

for patients with SCLC than the general population and tends to remain stable when patients are receiving treatment.[13] The company also highlight the substantial financial burden of lung cancer which was estimated to be £307 million in England in 2010 to the National Health Service (NHS) and wider economy.[14]

2.2.2 Background information on tarlatamab

Tarlatamab (brand name [redacted]®) is a type of targeted immunotherapy known as a bispecific T-cell engager (BiTE).[15] Each of tarlatamab's two arms has a binding domain, one that binds to tumour cells, and one that binds to T-cells. When tarlatamab simultaneously binds to tumour cells and T-cells, the T-cell is activated which leads to breakdown of the tumour cell membrane and then disintegration of the tumour cell.[15,16] The company describe tarlatamab in CS section B.1.2, CS Table 2 and show its mechanism of action in CS Figure 1.

The company anticipate that tarlatamab will receive a [redacted] marketing authorisation[17] in [redacted]. The company have provided the draft Summary of Product Characteristics (SmPC) as part of their submission to NICE which states that tarlatamab is indicated for "[redacted]".

2.2.3 Tarlatamab is administered as

[redacted]

2.2.4 The position of tarlatamab in the treatment pathway

The company describes the clinical pathway of care for SCLC in CS section B.1.3.3, drawing on NICE NG122[18] and NICE Technology Appraisals (TAs) 184[19] and 638[20] to outline the treatment options available for patients at first-, second- and third-line or beyond (the latter is referred to as 'third-line therapy+' throughout this report). All three of the EAG's clinical experts agreed with the company's depiction of the treatment pathway, as shown in CS Figure 2, but it was noted that best supportive care – which the company did not include – is also an option.

We understand from our clinical experts that:

- At first-line therapy, as is indicated by the company in CS section B.1.3.3, most patients will receive a programmed cell death ligand 1 (PD-L1) inhibitor (atezolizumab) with carboplatin and etoposide, with or without radiotherapy, unless there is a major contraindication. CS Figure 2 shows that, as per NICE TA638,[20] this option is recommended for patients with extensive-stage disease only. The CS figure shows that cisplatin-based combination chemotherapy, with or without radiotherapy, is also available for patients with extensive- or limited-stage disease.

- The choice of second-line treatment for SCLC depends on the interval between first-line therapy and relapse. If patients have a chemotherapy-free interval of six or more

months, they are considered to still be platinum-sensitive and the generally preferred treatment option is to re-challenge with platinum-based chemotherapy (e.g. carboplatin/cisplatin plus etoposide chemotherapy (hereafter referred to as 'carboplatin + etoposide') or carboplatin alone). If patients have disease progression after three to six months, they are considered platinum-chemotherapy refractory and so topotecan (a topoisomerase 1 inhibitor chemotherapy) or cyclophosphamide in combination with doxorubicin and vincristine (CAV) might be considered. The use of topotecan may vary between individual centres. CS Figure 2 shows that these treatments can be used either alone or alongside radiotherapy.

- As stated in CS section B.1.3.3 and section 2.2.1, there are currently no established third-line therapy+ options available for SCLC. Our clinical experts also noted that the proportion of patients who remain fit enough for third-line treatment is small and therefore patients rarely receive third-line therapy. Most patients at this stage will have had re-treatment with platinum-based chemotherapy at second-line. The majority of patients go onto best supportive care at third-line after a trial of two chemotherapy regimens. However, if a patient's Eastern Cooperative Oncology Group (ECOG) performance status score remains within the range of 0 or 1 (indicating no or mild restriction in performing daily activities and self-care[21]) and systemic treatments are available, patients will likely accept these.

- Given the lack of established treatments at third-line therapy+, the systemic therapies that are currently available at this stage are those that are used at second-line: carboplatin + etoposide, CAV, and topotecan. We understand from our clinical experts that patients may be re-treated with a therapy they have had before, and most patients will receive either CAV or topotecan. The EAG's experts indicated that carboplatin only and cisplatin + etoposide (both with or without radiotherapy) – which are second-line therapy options shown in CS Figure 2 – are rarely used at the third-line stage. Two of the EAG's experts noted that there have been topotecan product supply issues affecting the NHS recently, but they indicated that this was a temporary problem.

Best supportive care is aimed at managing patients' symptoms and is considered palliative care, with patients discharged back to their general practitioner (GP) or community palliative care team. Best supportive care has a number of components, which may differ depending on needs of the patient, including nursing and physical care, provision of equipment (such as

a hospital bed at home), nutritional support, help with activities of daily living, and medical interventions such as oxygen, analgesia, and sometimes dexamethasone and palliative radiotherapy.

The company is positioning tarlatamab as a third-line therapy+ option in the SCLC clinical pathway (CS Figure 2). All three of the EAG's experts agreed with the company's proposed positioning. One expert commented that this was because the available clinical effectiveness evidence is in relation to tarlatamab used as a third-line therapy+, but that, in their opinion, it would also be desirable for tarlatamab to be available as a second-line treatment. This expert anticipated that if tarlatamab is approved, then it may change clinical practice as clinicians may try to move patients to third-line therapy more quickly, which could potentially increase the number of patients who might receive third-line treatment. The EAG's experts also indicated that it is expected that patients will need to be fit to receive tarlatamab, so it is anticipated that the patients who will be treated with tarlatamab in clinical practice will have an ECOG performance status of 0 or 1. This is due to its potential toxicity and the need for hospital admission to monitor for adverse events. (As outlined in section 2.2.2, the draft SmPC [redacted];[22] a cost for a hospitalisation period of 24 hours at tarlatamab treatment initiation is included in the company's economic model (CS Table 53).) Our experts said that in practice, most patients at the third-line therapy stage have performance statuses of 2 to 4, so only a small, select group of patients will be suitable for tarlatamab.

EAG comment on background information and treatment pathway

The company provides accurate background information and an accurate depiction of the treatment pathway for SCLC in the CS, but they do not include best supportive care, which is also an option for patients. The company's proposed positioning of tarlatamab as a third-line therapy+ is appropriate. The EAG's clinical experts noted that only patients with an ECOG performance status of 0 or 1 at this stage will be suitable for tarlatamab.

2.3 Critique of the company's definition of the decision problem

Table 4 summarises the company's decision problem in relation to the final scope issued by NICE and includes the EAG's comments. In their decision problem, the company focus on a third-line therapy+ population of patients with advanced SCLC rather than the second-line therapy+ population specified in the NICE scope. This is appropriate, as it reflects the patient

population the EAG's clinical experts expect to be treated with tarlatamab in clinical practice (please see Table 4 below and section 2.2.3 above).

In their decision problem, the company have selected the comparators of topotecan, CAV and carboplatin + etoposide and conceptualised these as a "*single basket*" standard of care (SOC) comparator. The company's selection of these comparators reflects those specified in the NICE scope and those used in clinical practice (confirmed by our experts; please see Table 4). We also consider that the single standard of care comparator approach is appropriate; please see Table 4 for our reasons. Best supportive care was also specified as a comparator in the NICE scope, but the company have excluded this from their decision problem without explanation. We asked the company for their reason in clarification question A1. The company responded that patients who are candidates for best supportive care are a different patient population to those who are suitable for systemic therapy and will have worse ECOG performance status. Our clinical experts informed us that best supportive care is a relevant comparator for a third-line therapy+ population. However, as is outlined in section 2.2.3, our experts expect that the third-line therapy+ patients who will likely be treated with tarlatamab in clinical practice will be those who have an ECOG performance status of 0 or 1. Our experts indicated that these fitter patients tend to currently opt for systemic treatment and the remaining proportion who receive best supportive care is low (one expert estimated less than 20%). In one of the EAG's expert's opinion, it is reasonable to not include best supportive care as a comparator, but the other two experts made no comment. Another expert made the point that the proportion of patients who will be treated with best supportive care will depend on the other treatment options available.

Table 4 Summary of the decision problem

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Population	Adults with advanced small-cell lung cancer with disease progression on or after prior therapy	Adult patients with advanced SCLC after platinum-based chemotherapy and at least one other treatment	The population addressed in this submission is narrower than the NICE scope, requiring patients to have advanced disease after platinum-based chemotherapy and at least one other treatment. This narrower population reflects the clinical evidence available for tarlatamab in	The company focus on a third-line therapy+ population which is a subgroup of the NICE scope population [redacted]. All the EAG's clinical experts agreed with this proposed positioning of tarlatamab and agreed that the prior therapies that this group would have received reflect clinical practice.

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
			this indication.	
Intervention	Tarlatamab	Tarlatamab 10 mg Q2W	N/A – in line with NICE scope	The intervention matches the NICE scope and reflects [redacted].[17] See section 2.2.2 of this report for details of the specific draft SmPC-recommended dosing regimen for tarlatamab.
Comparators	Established clinical management without tarlatamab, which may include: • Chemotherapy, including anthracycline-containing or platinum-based regimen. • Oral topotecan (when re-treatment with the first-line regimen is not considered appropriate and the combination of cyclophosphamide, doxorubicin and vincristine is contraindicated)	Third-line treatment standard of care (SOC) has been modelled as a single comparator, comprising the following treatments: • Topotecan • Cyclophosphamide + doxorubicin + vincristine • Carboplatin + etoposide	Patients with advanced SCLC following two or more prior treatments do not have dedicated treatment options. Patients consequently face extremely poor outcomes, with expected survival of only a few months, regardless of treatment	The EAG's clinical experts agreed that the company's selected comparators are an appropriate reflection of the treatments patients with advanced SCLC who have already received platinum-based chemotherapy and at least one other treatment typically receive at third-line therapy+ in clinical practice. As detailed above, clinical expert advice to the EAG is that the proportion of patients with an ECOG performance status score of 0 or 1 who receive best supportive care (another comparator specified in the NICE scope) in practice is low, with one expert stating they believed it was reasonable for it not to have been included as a comparator in the CS. In clarification question A2 we asked the company to provide evidence for their statement that their three selected comparators have similar efficacy. The company provided information in response, which we have summarised in Appendix 1. Some differences were identified in the efficacy of the treatments. However, we do not perceive that to be a reason not to include the treatments in a single basket comparator as long as the treatment distributions reflect the extent to which they are used in clinical practice.

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	• Best supportive care		received. The proposed treatment regimens, modelled as a single basket comparator, are considered an appropriate reflection of treatments typically prescribed at this stage of disease, given the similarly poor outcomes associated with each treatment. In line with discussion with the NICE technical	All three of the EAG's clinical experts considered that it was reasonable to treat the three comparators as a single basket standard of care comparator. One expert commented that it is likely there would be no meaningful data available to compare tarlatamab to the comparators individually. All of the EAG's experts agreed that topotecan, CAV and carboplatin + etoposide have similarly poor treatment outcomes. Overall, the single basket standard of care comparator approach appears reasonable.

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
			team and external assessment group (EAG), pairwise analyses against each individual comparator (topotecan, CAV and platinum-based chemotherapy) have also been conducted as scenario analyses.	
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment	• Response rates • PFS • OS • TEAEs • HRQoL	N/A – in line with NICE scope	The outcomes selected by the company match the NICE scope. Due to data availability, the company have used time-to treatment discontinuation as a proxy for PFS for the standard of care comparator (CS section B.2.9.3). Please see section 3.3.4 for a discussion about this.

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	• health-related quality of life.			
Economic analysis	The reference case states the following requirements for cost-effectiveness analyses: costs assessed as cost per quality-adjusted life year (QALY), adequate time horizon, NHS and Personal Social Services perspective, commercial arrangements and managed access taken into account and availability and cost of biosimilar and generic products taken into account. (NICE scope wording abridged by EAG here for brevity.)	The economic analysis is expected to be in line with that described in the NICE decision problem	N/A – in line with NICE scope	The company's economic analysis matches NICE's reference case requirements. CS Table 2 includes details of a simple patient access scheme (PAS) discount for tarlatamab. The anticipated PAS price was used in the company's economic analysis (CS section B.3.5.1). The company used a multiplier for disease severity of 1.7 in their base case.
Subgroups	None specified	N/A	N/A	In practice the CS focuses on a sub-population of advanced SCLC patients who are receiving third-line therapy+. The CS

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
				also presents subgroup analyses from the tarlatamab trial (the DeLLphi-301 trial) by various patient characteristics in CS section B.2.7.
Special considerations including issues related to equity or equality	None specified	N/A	N/A	The company have not identified any issues related to equity or equality. Two of the EAG's experts were not aware of any equity or equality issues potentially related to this appraisal. The other expert noted if the DeLLphi-301 trial protocol of admitting patients to hospital for monitoring of adverse events post-treatment after the first two infusions (see section 3.2.1.1) is adopted in clinical practice, this could create a resource issue and difficulties for patients who want to receive treatment outside major cancer centres. (The draft SmPC recommendations regarding monitoring are outlined in sections 2.2.2 and 2.2.3.)

Source: Partly reproduced from CS Table 1.
CAV, cyclophosphamide, doxorubicin and vincristine; CS, company submission; EAG, External Assessment Group; HRQoL, health-related quality of life; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; Q2W, once every other week; QALY, quality-adjusted life year; SCLC, small-cell lung cancer; SmPC, summary of product characteristics; TEAEs, treatment-emergent adverse events

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company conducted a systematic literature review to identify studies on the clinical efficacy (or effectiveness) and safety of treatments for patients with SCLC who have previously received two or more treatments and who have experienced disease progression on or after any prior therapy (CS section B.2.1 and CS Appendix D, section D.1). The searches for the systematic review (original search and an update search) covered a period from 2012 to 19th December 2023. As only approximately five months had elapsed since 19th December 2023 upon receiving the CS on 16th May 2024, we considered the searches to be sufficiently up to date. The search terms were appropriate, but we note that the company did not include terms for randomised controlled trials (RCTs) in their search strategies, despite this study design being listed in the eligibility criteria for the review (CS Appendix D, section D.1.2, Table 9). However, we do not believe that any relevant evidence has been omitted as a result. The EAG have not re-run the company's searches using a term for RCTs, but non-systematic searches we have conducted in the clinicaltrials.gov and PubMed databases have not identified any relevant RCTs of tarlatamab in the company's decision problem population. Our detailed assessment of the company's systematic review methods can be found in Appendix 1.

3.2 Critique of studies of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

The company's systematic literature review identified one study of tarlatamab relevant to their decision problem population. This was the ongoing DeLLphi-301 phase 2 trial[23] (CS section B.2.2).

The trial has been reported in a journal article, which the company supplied as part of their CS.[23] The company also provided the trial clinical study report (CSR).[24]

3.2.1.1 Study characteristics

The DeLLphi-301 trial is an open-label, registrational trial of tarlatamab examining the efficacy and safety of tarlatamab in people with relapsed or refractory SCLC after two or more previous lines of therapy. It does not compare tarlatamab to any other treatments. The trial was funded by the company (Amgen).[23] The CS states that the trial supported the marketing authorisation application for tarlatamab (CS section B.2.2).

The characteristics of the DeLLphi-301 trial are shown in Table 5. It consisted of three parts:

- In Part 1, participants were randomised to tarlatamab 10 mg every two weeks (Q2W) or 100 mg Q2W. During Part 1, an interim analysis determined which of the two initially examined tarlatamab doses would be the focus for Part 2 of the study.
- Part 2 was the dose expansion phase of the trial. From the interim analysis, the 10 mg Q2W dose was selected for Part 2 and additional participants were recruited to receive this dose only.
- In Part 3, a modified safety protocol was implemented for newly recruited participants with safety monitoring for potential Cytokine Release Syndrome (CRS) and/or neurological events changed from 48 hours (as it had been in Parts 1 and 2) to 24 hours.

The selected dose of 10 mg Q2W and the tarlatamab treatment regimen used in the DeLLphi-301 trial [redacted]. All our clinical experts confirmed that the permitted and disallowed medications and treatments in the DeLLphi-301 trial, as shown in Table 5, are reflective of how third-line therapy+ patients eligible for tarlatamab (if it is approved) would be treated in clinical practice.

All three of the EAG's clinical experts considered that the key inclusion criteria of the trial reflect the patients with SCLC who are expected to receive tarlatamab in clinical practice. However:

- One expert noted that the key inclusion criteria required participants to have measurable lesions within a 21-day period before taking their first dose of tarlatamab, and one expert noted that in practice, clinicians would not look at measurable lesions and patients would be treated regardless.
- The same expert also noted that the trial required re-biopsy, while in practice relapsed disease is not usually re-biopsied.
- Regarding the requirement for patients to have had one platinum-based regimen and at least one other prior line of therapy, another expert noted that 'one other prior line of therapy' would include re-treatment with chemotherapy.

One expert was also satisfied that the DeLLphi-301 trial key exclusion criteria were also representative of the patients expected to receive tarlatamab in clinical practice. The other two experts did not comment on this.

Our clinical experts noted that the DeLLphi-301 trial inclusion criteria represent a highly selected, small group of third-line therapy+ patients who will be fit enough and suitable to receive tarlatamab (i.e. people with an ECOG performance status of 0 or 1). Our experts said that in practice, most patients who reach third-line treatment will be more poorly and thus will not be suitable for tarlatamab.

In the trial, participants were treated until disease progression (CS section B.2.3.1). After this, participants could stay on tarlatamab if the investigator judged that they were receiving benefit and there were no unacceptable or significant co-morbidities. [redacted] Two of the EAG's three clinical experts do not expect that tarlatamab will be used post-progression in clinical practice, while one expected that it would be if it was clinically appropriate because this was how it was used in the trial and evidence suggests that tarlatamab is well-tolerated. Additionally, one expert commented that there can be doubt sometimes in practice about whether true progression is being observed and if there is some uncertainty about this, continuing treatment until the next assessment may be appropriate.

Interim results for the DeLLphi-301 trial are presented in the CS from a data-cut dated 27th June 2023. Of the participants eligible for the trial, 176 were randomised in Part 1 to either tarlatamab 100 mg (n = 88) or 10 mg (n = 88) (CS Figure 3), with one participant in each of these arms not receiving the allocated treatment. Another 12 participants received tarlatamab 10 mg in Part 2. Thus, 99 participants received tarlatamab in both Parts 1 and 2 of the trial. This population is referred to in the CS as the "*10 mg target group*" (CS section B.2.3.2) and is the focus of the evidence presented in the submission. In Part 3, 34 participants have so far received the 10 mg target dose, but due to immaturity of data, the company have not included either efficacy or safety results for these patients in the CS. However, results are available in the trial CSR[24] provided with the CS. In terms of presenting the clinical efficacy results in the CS, the EAG regards this as reasonable. However, in the context of the Part 1 and 2 10 mg participant group of only 99 participants, we believe that safety data for another 34 participants would be valuable and thus asked the company to provide a summary of the adverse event data for the Part 3 participants in clarification question A14 and the company accordingly provided these results.

The following outcomes from the DeLLphi-301 trial inform the company's economic analysis: OS, progression-free survival (PFS), time to treatment discontinuation (TTD), HRQoL (as measured by the European Quality of Life Working Group Health Status Measure 5

Dimensions, 5 levels [EQ-5D-5L]) and adverse event rates (specifically grade 1-2 CRS and immune effector cell-associated neurotoxicity syndrome (ICANS), and grade 3+ adverse events) (CS sections B.3.3 and B.3.4).

Table 5 DeLLphi-301 study design and characteristics

Study characteristics	Details
Population	Patients with relapsed or refractory SCLC whose disease has progressed or recurred following one platinum-based regimen and at least one other line of therapy.
Intervention(s) and number of participants randomised or enrolled at each stage of the trial	• Part 1 (dose escalation phase): Tarlatamab 10 mg or 100 mg (participants randomised 1:1; N = 176). Participants received 1 mg of tarlatamab for the first dose (Cycle 1, day 1), and then step-up doses of 10 mg or 100 mg depending on their treatment arm. • Part 2 (dose expansion phase): Tarlatamab 10 mg (selected target dose following interim analysis on N=30/arm; N enrolled = 12) • Part 3 (modified safety protocol): Tarlatamab at selected target dose of 10 mg (N enrolled = 34). Safety monitoring reduced from 48 to 24 hours (please see row below).
Method of administration of tarlatamab and safety monitoring	Tarlatamab 1 mg was given on Cycle 1 Day 1. The full dose of either 10 mg or 100 mg was given on day 8 and 15 of Cycle 1, and Q2W after this. Administration was via an IV infusion for 60 minutes. An 8 mg dose of dexamethasone was administered IV before tarlatamab was given on Days 1 and 8 of Cycle 1, and prophylactic hydration (1 litre of normal saline) was administered IV after each dose in Cycle 1. Hospitalisation for safety monitoring was needed for 48 hours after the first two infusions of tarlatamab in Parts 1 and 2. This was reduced to 24 hours in Part 3.
Comparator	No comparator.
Key inclusion criteria	• Patient had provided informed consent/assent prior to initiation of any study specific activities/procedures. • Male and female patients ≥ 18 years of age (or legal adult age within country) at the time of signing the informed consent. • Histologically or cytologically confirmed r/r SCLC • Patients who progressed or recurred following 1 platinum-based regimen and at least 1 other prior line of therapy. • Patients willing to provide archived tumour tissue samples or willing to undergo pre-treatment tumour biopsy. • ECOG performance status of 0 or 1 • Minimum life expectancy of 12 weeks. • Measurable lesions as defined per RECIST 1.1 within 21 days prior to the first dose of tarlatamab. • Patients with treated brain metastases were eligible provided they met defined criteria.
Permitted and disallowed concomitant medications and treatments	Investigators were permitted to prescribe any concomitant medications or treatments deemed necessary for adequate supportive care, except for: • Other investigational agents

Study characteristics	Details
	• Concurrent experimental or approved anti-tumour therapies other than study drugs • Radiation therapy (with the exception of for symptom control) • Immunosuppressive agents
Study centres and locations	The study was conducted at 56 centres in Austria, Belgium, Denmark, France, Germany, Greece, Italy, Japan, Netherlands, Poland, Portugal, South Korea, Spain, Switzerland, Taiwan, United Kingdom (two study centres), and the United States. The company confirmed in clarification question response A5 that 5 patients were recruited from the two UK centres (1 at one centre, and 4 at the other).
Study start date and expected completion date	• The first patient was enrolled on 1st December 2021. • The estimated study completion date is 31st October 2025.
Follow-up	• Upon permanent discontinuation of tarlatamab, participants had a safety follow-up visit at around 42 (+5) days after their last tarlatamab dose. • After the safety follow-up visit, patients entered long-term follow-up, conducted every three months (+/- two weeks) for a year following the last dose of tarlatamab or five years following the first participant being enrolled (whichever occurred first), to measure OS and/or the initiation of subsequent cancer therapies. • At the interim data cut of 27th June 2023, the median duration of follow-up was 10.6 months for OS.
Primary outcomes	• OR (including CR and PR) • Incidence of TEAEs • Serum concentrations of tarlatamab
Other outcomes	DOR, PFS, OS, HRQoL, DC, DoDC, incidence of anti-tarlatamab antibody formation.

Source: Partly reproduced from CS Tables 3 and 4, CS section B.2.3 and clarification response A5. Estimated study completion date sourced from the clinicaltrials.gov DeLLphi-301 trial record.[25]
CR, complete response; DC, disease control; DoDC, duration of disease control; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; IV, intravenous; N, number; OR, objective response rate; OS, overall survival; PR, partial response; RECIST, response evaluation criteria in solid tumours; r/r, relapsed or refractory; SCLC, small-cell lung cancer; TEAE, treatment-emergent adverse event.

3.2.1.2 Patients' baseline characteristics

The company provide the baseline demographic and disease characteristics of the 99 participants in the DeLLphi-301 trial who received tarlatamab in both Parts 1 and 2 of the trial in CS section B.2.3.4. CS Table 6 shows the baseline demographic characteristics. Our clinical experts considered the characteristics presented to be representative of the patients seen in clinical practice, but two of the three experts noted that there was a higher proportion of Asian participants in the trial (41.4%) than observed in practice. The other expert noted that the proportion of patients who are Asian in practice will depend on geographical area.

The experts did not expect that race or ethnicity would impact on treatment response. The mean age of the trial participants was [redacted] years (standard deviation [SD] [redacted]). Two of the experts commented that the age of the participants in the trial is in keeping with the expectation that patients will only be suitable for tarlatamab if they have a performance status of 0 or 1.

CS Table 7 shows the baseline disease characteristics of the 99 DeLLphi-301 trial participants who received the 10mg target dose of tarlatamab in both Parts 1 and 2 of the trial. Overall, our experts thought these looked reasonable. Most of the patients had had two or more prior lines of therapy (n=97/99, 98.0%; percentage calculated by EAG), with the majority having two prior lines (65.7%). Of the 99 participants, 72.7% had received a prior programmed cell death protein 1 (PD-1) or PD-L1 inhibitor treatment, which is in line with clinical expert advice to the EAG that the majority of fit patients will have previously received atezolizumab (a PD-L1 inhibitor therapy). Other than the reporting of the proportion of patients who had received a prior PD-1 or PD-L1 inhibitor therapy, the EAG note that details of the specific therapies participants had previously received are not provided in Document B of the CS, so it is not possible to determine to what extent they reflect clinical practice. Two participants were protocol violators because they had not received two previous lines of therapy.

The proportions of patients who had an ECOG performance status of 0 or 1 at baseline were 26.3% and 73.7%, respectively (CS Table 7). One of our experts felt that this distribution reflected the patients seen in clinical practice (i.e. that the majority of third-line therapy+ patients who will be suitable for tarlatamab will have a performance status of 1). Another noted it was similar to the performance status distributions presented from a real-world study of UK patients with a performance status of either 0 or 1 used in the company's indirect comparison (see section 3.3). However, the remaining expert stated that they would not expect around a quarter of patients to have a score of 0 at third-line therapy. It is unclear if this expert's comment was in relation all third-line patients or just those with an ECOG performance status of 0 or 1.

Two of our experts thought the proportion of participants who had never smoked (8.1%; CS Table 7) was higher than is seen in practice. One commented that it would be expected that most or all SCLC patients would be current or former smokers. The other estimated that typically less than 5% of SCLC patients in practice have never smoked. Clinical expert advice to the EAG is that people who have never smoked are likely to be fitter and have

better outcomes, but all our experts felt the high proportion who had never smoked in the DeLLphi-301 trial was unlikely to affect the results.

3.2.1.3 Ongoing studies

As stated above, the DeLLphi-301 trial is ongoing and is estimated to complete in October 2025 (see Table 5). In the CS, the company states there is an ongoing trial of tarlatamab in a second-line therapy population, called the DeLLphi-304 trial (CS section B.2.11). We note, this is the phase 3 NCT05740566 trial that is comparing tarlatamab with standard of care in participants with relapsed SCLC after receiving platinum-based chemotherapy at first-line treatment.[26] The trial started on 31st May 2023 and is estimated to complete on 1st August 2027.[26] The company state that the indication is not relevant to the present submission. We agree that it is not relevant to the company's decision problem population, but it is relevant to the population specified in the NICE scope. It is unclear when interim results might become available from this trial.

EAG comment on included studies

The participants included in the DeLLphi-301 trial are generally representative of third-line patients seen in clinical practice and those expected to be treated with tarlatamab (i.e. patients with an ECOG performance status of 0 or 1). Limitations of the trial are: 1) it does not compare tarlatamab to any relevant comparators, and 2) only interim data are currently available.

3.2.2 Risk of bias assessment

The company did not state which source(s) of evidence they used to complete their assessment of the risk of bias (e.g. CS, CSR &/or journal publication by Ahn et al. 2023[23]). We have used the CS and journal publication by Ahn et al. 2023 supplemented with information from the trial CSR and protocol where necessary and we focus on the risk of bias for the 10mg target dose group treated as a single-arm study (i.e. participants in the 10mg target dose group in Part 1 and those from Part 2 of the study).

The company used the modified Downs and Black checklist for non-randomised trials[27] and state that the study scored as 'good', going on to say that this means the trial was associated with a low risk of bias. We find that that whilst the source paper cited by the company (Hooper et al.[27]) does ascribe 'quality levels' to score ranges we found no evidence in the paper to describe how they mapped the score ranges to the quality terms used (i.e. excellent, good, fair and poor). Additionally, the term 'bias' does not appear in the modified Downs and Black checklist so it is not clear what evidence the company has used to

determine that a 'good' quality level on this checklist aligns with a low risk of bias. In our view, a single-arm study is inherently likely to be at a high risk of bias because there is no comparator/control group to mitigate confounding.

The EAG's additional concerns about using the Downs and Black checklist are that the questions are equally weighted (scoring either 0 or 1) and then the scores are summed to give the overall 'quality' score. There is the potential for a study to achieve a relatively good score even if it is at a high risk of bias. Some of the questions asked by the checklist assume that there is a comparator arm (e.g. "Are the distributions of principal confounders in each group of patients to be compared clearly described?") which is not the case for the company's DeLLphi-301 study 10mg target dose group in Part 1 and 2 of the trial.

To compare the company's assessment and with our own we have completed the Downs and Black Checklist which can be seen in full in Appendix 3. As noted above, we are assessing the quality of the 10mg tarlatamab target dose as a 'single arm' of the DeLLphi-301 study (i.e. the participants receiving the target dose in both Parts 1 and 2 of the trial). This is important because for questions such as "Have all important adverse events that may be a consequence of the intervention been reported?" we agree that this is the case for the DeLLphi-301 10mg target dose group, but note that, in our view, adverse events have not been fully reported in the CS (e.g. data were not reported for the participants in Part 3 receiving the 10mg dose, but were provided in response to clarification question A14). Our assessment using the Downs and Black checklist differed from that of the company for five of the 26 questions and for one question we judged unclear (this was scored as zero). We do not agree with summing scores but for ease of comparison our assessment would be scored 15 (quality level 'fair') whereas the company assessment scored 20 (quality level 'good').

We asked the company to provide a critical appraisal of the DeLLphi-301 trial using the criteria for non-randomised and non-controlled studies as set out in section 2.5 of the NICE company evidence submission template guidance.[28] Process and methods' guide' (clarification question A7). The company's critical appraisal using these criteria is shown in Table 6 with our judgements using these criteria and comments added. Our judgements differ from those of the company regarding whether the outcome was accurately measured to minimise bias and whether the follow-up of patients was complete. In the latter case, this may be down to differences in how we have interpreted in the question. The company have focused on the thoroughness of follow-up procedures whereas we believe the question is

asking about the length of follow-up (sufficient to capture the outcomes of interest) and completeness of follow-up (i.e. have all patients completed the study).

Table 6 Critical appraisal of the Dellphi-301 trial using NICE's criteria for non-randomised and non-controlled studies.

Question	Company answer	Supporting information for answer	EAG answer and comments
Was the cohort recruited in an acceptable way?	Yes	The cohort was recruited based on strict inclusion criteria, including confirmed SCLC, previous treatments, and measurable lesions, ensuring a representative sample of the target population.	**Yes**, study enrolment criteria ensure the patients represent the relevant population, although only five patients were recruited from the UK.
Was the exposure accurately measured to minimise bias?	Yes	The administration of tarlatamab was consistent across the study with specific dosages (10 mg and 100 mg) and schedules, and adherence was monitored closely. Adherence challenges were noted with 6 patients in the 10 mg group and 14 patients in the 100 mg group dying before the post-baseline scan.	**Yes**. CS section B.2.10.2 provides reporting on exposure at the data cut-off date (27th June 2023).
Was the outcome accurately measured to minimise bias?	Yes	Outcomes were measured using objective criteria (RECIST 1.1) and assessed by blinded independent central review. Objective	**Uncertain**. Objective criteria assessed by BICR, however we have concerns that blinding could have been compromised if the BICR body [redacted]

Question	Company answer	Supporting information for answer	EAG answer and comments
		response rates were 40% (97.5% CI: 29-52) for the 10 mg group and 32% (97.5% CI: 21-44) for the 100 mg group.	[redacted]. In their response to clarification question A8, the company did not address this point.
Have the authors identified all important confounding factors?	Yes	The study design and statistical analysis accounted for several potential confounders, including prior treatments and patient baseline characteristics.	**Yes**. The CSR lists a number of covariates that were included, where appropriate, in subgroup and multivariate analyses. Covariates included platinum sensitivity, and brain and liver metastases at baseline.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Confounders were considered in the study design and analyses, as seen in the stratification of patients and adjustment in the statistical models.	**Yes**. The CSR states that [redacted].
Was the follow-up of patients complete?	Yes	Follow-up was thorough, with scheduled imaging assessments and safety follow-ups detailed in the study protocol.	**No**. Study is ongoing and of the 99 patients who received tarlatamab in the 10mg target group (Part 1 and Part 2 of the study) 29 (29.3%) were still continuing treatment at the interim analysis.
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	Results of all primary and secondary efficacy analyses were reported with appropriate confidence interval margins.	Confidence intervals are reported where appropriate but, because the study is still ongoing, some values are not estimable yet.

Source: Based on the table in company clarification response A7 supplemented with EAG answers and comments.

BICR, blinded independent central review; CS, company submission; CSR, clinical study report; EAG, External Assessment Group; MAIC, matching-adjusted indirect comparison; N/A, not applicable; RECIST, response evaluation criteria in solid tumours.

EAG comment on risk of bias assessment

Overall, we find the company's DeLLphi-301 trial to be a well conducted single-arm study which is subject to the risk of bias that is associated with this study design. We have particular concerns about the potential for blinding of the independent central review body to have been undermined if it was [redacted]. The study is ongoing so final results are not yet available.

3.2.3 Outcomes assessment

The CS lists the outcomes measures included in the DeLLphi-301 trial in CS Table 4 (three primary and eight 'key' secondary).The EAG notes that two of the three listed primary outcomes in CS Table 4 also appear in the list of key secondary outcomes in Table 4 (treatment emergent adverse events and serum concentrations of tarlatamab). CS Table 5 provides outcome definitions for a single primary outcome, objective response rate, and five secondary endpoints. The outcomes presented in CS Table 4 and CS Table 5 include all those listed in the NICE scope and company decision problem except for HRQoL. We note however that CS section B.2.6.3 presents results for patient reported outcomes obtained using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire lung cancer module (QLQ-LC13), subscale global health status/quality of life (QoL) and the physical functioning scale of the EORTC quality of life questionnaire core 30 (QLQ-C30). These HRQoL outcomes are described as 'exploratory endpoints' and in response to clarification question A12 the company confirmed that the EQ-5D-5L questionnaire (including visual analogue scale [VAS] scores) was also used and symptom burden (i.e. cough, chest pain and dyspnoea) was measured by the Patient Global Impression of Severity/Change (PGI-S and PGI-C). As stated in section 3.2.1, the data cut-off date for the outcomes presented in the CS was 27th June 2023 (median length of treatment was [redacted] weeks (range [redacted] to [redacted] weeks).

The outcomes that inform the economic model are:

- OS
- PFS

- TTD (note this outcome was not reported in CS section B.2.6 so we requested the results in clarification question A11)
- EQ-5D utilities (as no EQ-5D results were reported in CS section B.2.6 we requested a summary of the VAS scores in clarification question A13)
- Adverse events (Grade 3+ events and Grade 1-2 CRS and ICANS).

3.2.3.1 Efficacy outcome(s)

In this section we focus on the primary outcome of objective response and the efficacy outcomes that inform the economic model: OS, PFS and TTD. The CS does not state the frequency of outcome assessments but the trial publication[23] states that imaging assessments were scheduled every six weeks for the first year and every 12 weeks thereafter.

CS Table 5 states that the primary outcome of objective response rate was defined as the proportion of patients with best overall response of complete response or partial response assessed using the RECIST (Response Evaluation Criteria in Solid Tumours) criteria version 1.1. The primary analysis, which is presented in the CS, is based on the assessment by blinded independent central review (BICR). We asked the company to confirm how disease progression was assessed by the BICR body (clarification question A8) and the company responded that [redacted]. It is not clear from the company's answer whether some images were sent to the BICR body from unscheduled visits when no progression was detected nor whether the BICR body was aware that at least some, if not all, of the images sent from unscheduled visits [redacted]. Our concern is that if the BICR body knew that images from unscheduled visits [redacted] that this could lead to unblinding of the BICR body as noted in our risk of bias assessment in section 3.2.2. The CS presents results from the BICR Full Analysis Set (CS Table 8) which includes all patients from Part 1 or Part 2 of the trial who received at least one dose of tarlatamab and who had one or more measurable lesions at baseline that could be assessed by BICR using the RECIST 1.1 criteria.

OS was calculated as "*the time from the first dose of tarlatamab to death due to any cause. Any patients known to be alive were censored either at the date last known to be alive or at the analysis data cut-off date, whichever was earlier*".

PFS was calculated as the time from the first dose of tarlatamab to the earliest event of progressive disease assessed by RECISTS 1.1 or death due to any cause. Three groups of patients were censored in the PFS analysis (these are described in CS Table 5) and the EAG does not have any concerns about them.

TTD was not included as an outcome in the clinical effectiveness results section of the CS (CS B.2.6) but we asked the company to provide these data (clarification question A11). We requested the TTD results (with and without adjustment for post-progression tarlatamab use) because TTD from the real-world UK Cancer Analysis System (CAS) Registry dataset was used as a proxy for PFS estimates for the standard of care in the matching-adjusted indirect comparison (MAIC) (see section 3.3 of this report for our critique of the MAIC). In the unadjusted TTD analyses (which include the use of tarlatamab after progression) participants still in receipt of tarlatamab at the data cut-off were censored and their censoring time was the time of their last tarlatamab exposure before the data cut-off. Discontinuation of tarlatamab by participants prior to the data cut-off was counted as an event and the event time was the time of the participants last tarlatamab exposure. For the adjusted TTD analyses (which aim to provide an estimate of the TTD that would have been observed if there had been no post-progression use of tarlatamab) those participants who had continued to receive tarlatamab after progression had their event times altered so that their TTD was set to the time of progression (i.e. they were treated as having discontinued tarlatamab at the time of progression). Participants who did not have post-progression use of tarlatamab were treated in the same way as in the unadjusted analysis.

3.2.3.2 HRQoL outcomes

HRQoL outcomes are not described in CS section B.2.3 which summarises the methodology of the relevant clinical effectiveness evidence (although the abbreviation HRQoL is listed at the foot of CS Table 4 the term HRQoL does not appear in that table). However, some results are presented for patient-reported outcomes in CS section B.2.6.3 'Exploratory endpoints'. We asked the company to describe these endpoints (clarification question A12). In response to clarification question A12 the company stated that the following measures were used:

- The EORTC 30-item Quality of Life Questionnaire (QLQ-C30),[29]
- The 13-item lung cancer module (QLQ-LC13)
- The EQ-5D-5L questionnaire (including VAS scores)
- The Patient Global Impression of Severity/Change (PGI-S and PGI-C)

- The GP5 question of the Functional Assessment of Cancer Therapy – General Form (FACT-G).[30]

The company did not provide details of the score ranges or direction of scoring for the above measures.

3.2.3.3 Safety outcomes

The Safety Analysis Set was defined as all participants who received at least one dose of tarlatamab (CS Table 8). However, the company explain in CS section B.2.10 that adverse events are only reported in the CS for the subgroup of participants from the Safety Analysis Set who received the [redacted] 10 mg dose of tarlatamab in either Part 1 or part 2 of the trial. Participants who received 10 mg of tarlatamab in Part 3 of the trial were not included. The company provided the data for the Part 3 participants in response to Clarification question A14. In response to clarification question A12 the company state that patient reported adverse events were measured using selected questions from the Patient reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).

Adverse events were defined as treatment-emergent when they occurred after the first dose of tarlatamab was administered and up to and including 47 days after the last dose of tarlatamab was administered, or the end of study date (whichever was earlier). The study publication[23] states that:

- adverse events were graded using the CTCAE version 5.0, which incorporates some elements of the Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 terminology.
- CRS events and ICANS events were identified on the basis of a narrow search and a broad search respectively for preferred terms in the MedDRA version 26.0.
- the severity of CRS events and ICANS events were graded according to the American Society for Transplantation and Cellular Therapy 2019 consensus guidelines.

A safety follow-up visit occurred approximately 42 (+5) days after the last dose of tarlatamab (CS section B.2.3.1) even if participants were receiving a subsequent anti-cancer therapy.

EAG comment on outcomes assessment

We consider that the outcome measures reported for the DeLLphi-301 trial are appropriate. The company include those listed in the NICE scope and the company decision problem. We have no concerns about the outcome definitions, but we note that

the company did not provide details of the score ranges or direction of scoring for the exploratory HRQoL measures used in the DeLLphi-301 trial.

3.2.4 Statistical methods of the included studies

The EAG's critique of the statistical methods used in the DeLLphi-301 trial is presented in Table 7.

Table 7 EAG critique of the statistical methods of the DeLLphi-301 trial

DeLLphi-301
Analysis populations
Brief description CS Table 8 defines the DeLLphi-301 analysis populations, two of which are presented in the CS: the BICR Full Analysis Set (primary analysis set) and the Safety Analysis Set. BICR Full Analysis Set defined as all patients who were randomised (Part 1) or enrolled (Part 2), who received at least one dose of tarlatamab, and had one or more measurable lesions at baseline as assessed by BICR using the RECIST 1.1 criteria. Safety Analysis Set defined as all patients who received at least one dose of tarlatamab.
EAG comment: The BICR Full Analysis Set does not contain any patients from Part 3 of the trial. Additionally, although CS Table 8 states that this population is presented in the CS, in terms of results, the CS only presents results for those participants who received the 10mg tarlatamab dose, because this is the [redacted] dose. CS Figure 3 shows that 99 of a possible 100 participants due to receive 10mg tarlatamab were included in the CS BICR Full Analysis Set results because one participant did not receive any treatment. The CS also presents data for the Safety Analysis Set only for those patients who received the [redacted] dose of 10mg tarlatamab in Parts 1 and 2 of the trial. The EAG views it as acceptable to have limited reporting to those participants who received the [redacted] dose of tarlatamab. However, we note that 34 participants enrolled in Part 3 of the trial received the 10mg dose, yet safety results were not presented for these participants in the CS. We believe that the safety results from these participants would be valuable, so we therefore requested these results in clarification question A14 and the company provided them in response.
Sample size calculations
Brief description

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It was not clear to the EAG if a formal method had been used to determine sample size. In response to clarification question A18 the company explain the rationale for their chosen sample size, expanding on the information provided in CS Table 9. The company planned to enrol approximately 100 participants in total at the selected target dose for Part 1 and Part 2 of the trial. Initially patients would be enrolled and randomised in Part 1 to one of two doses (tarlatamab 100mg or 10mg, approximately 90 participants expected to be enrolled at each dose). An interim analysis took place to select a target dose for expansion after 30 patients had been recruited to each of the Part 1 doses, with recruitment continuing to Part 1 as the interim analysis took place. When the target dose had been selected the final approximately 10 participants were enrolled to Part 2 at the selected dose. The results from two open-label studies, one of pembrolizumab[31] and one of nivolumab,[32] which reported objective response rates (ORRs) of 19% and 12% respectively for patients with SCLC who had received two or more previous lines of therapy (i.e. the current therapy was third line or later) informed the company's determination of the appropriate sample size. For Parts 1 and 2 of the study, which are the focus of the CS, a sample size of 100 participants receiving the 10mg target tarlatamab dose was estimated to provide a 63% probability of observing at least one adverse event with a true 1% incidence rate, and a 99% probability of observing at least one adverse event with a true 5% incidence rate. For Part 3 of the study a sample size of 30 receiving the 10mg target tarlatamab dose was estimated to provide a 26% probability of observing at least one adverse event with a true 1% incidence rate, and a 79% probability of observing at least one adverse event with a true 5% incidence rate.
EAG comment: The sample size of 100 participants in total at the selected target dose for Part 1 and Part 2 of the trial appears to have been calculated appropriately and 99 participants are included in the BICR full analysis set for Parts 1 and 2 at the 10mg target dose.
Methods to account for multiplicity
Brief description To adjust for multiplicity a 97.5% two-sided confidence interval was used for the ORR whereas for other outcomes at 95% two-sided confidence interval was used. In response to clarification question A20 the company stated their adjustment for multiplicity was based on the Bonferroni method.
EAG comment: The company had an appropriate procedure in place to reduce the risk of statistically significant effects being detected by chance.

DeLLphi-301
Analysis of outcomes
Brief description Time to event variables (duration of response, duration of disease control, PFS, OS, and TTD, the latter provided in response to clarification question A11): reported as Kaplan-Meier estimates of the median time to event and percentiles with associated two-sided confidence intervals [97.5% confidence intervals (CIs) for ORR and 95% CIs for other outcomes and the subgroup analyses of ORR]. Confidence intervals for Kaplan-Meier estimates of median time to event were calculated using the Brookmeyer and Crowley method. Landmarks for time to event endpoints (e.g. 1-year OS): estimated using Kaplan-Meier methods. The Greenwood formula was used to estimate the standard error subsequently used in the calculation of the confidence interval. Proportions: Confidence intervals were estimated using the Clopper-Pearson method[33] Censoring rules: Provided in CS Table 5 for PFS and OS and in the response to clarification question A11 for TTD.
EAG comment: Appropriate analysis methods have been used for the primary outcome and the time to event outcomes, including those that inform the economic model. However, we note that CS section B.3.3.1 states that [redacted] participants continued tarlatamab post-disease progression in total in the study; whereas, CS section B.3.3 states that this figure was [redacted] participants. Patients continuing tarlatamab post-progression do not appear to have been censored from the analyses of the participants receiving the 10mg target dose in Parts 1 and 2 of the study, the results of which are presented in CS section B.2.6. Given this, some of the results, depending on the outcome, may not fully reflect those that might occur in clinical practice if tarlatamab is approved, because, as is stated in section 3.2.1.1, [redacted].
Handling of missing data
Brief description Table 9 states that imputation for missing or incomplete data was performed if required. However, in response to clarification question A16 the company states that no imputation was performed for efficacy endpoints or PRO endpoints. If dates were missing or incomplete for adverse events and concomitant medication use, imputation was carried out as per the statistical analysis plan. In response to clarification question A15 the company state that reasons for missing PRO data (other than disease progression or death) were not collected in DeLLphi-301 and they provide details of the completion (for all randomised participants) and compliance (for participants still in the study who would

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be expected to be able to complete the PRO instrument at that visit) rates for the QLQ-C30, QLQ-LC13 and EQ-5D-5L scales at study visits from baseline to Cycle 15 Day 1.
EAG comment: For the efficacy and PRO endpoints no imputation for missing data was used. For the primary outcome, as patients without a post-baseline tumour assessment (n=[redacted], CS Table 11) were considered non-responders (CS Table 5), this would lead to a conservative estimate of treatment effect.
Sensitivity & post-hoc analyses
Brief description Few sensitivity analyses were described in the CS so we sought clarification (clarification question A17). In response to clarification question A17 the company confirmed that sensitivity analyses were conducted using an alternative censoring rule for DOR, DoDC and PFS and they provide the results of these analyses which are similar to the primary analysis.
EAG comment: Appropriate sensitivity analyses have been conducted to test the use of an alternative censoring rule.

Source: Table compiled by the EAG
BICR, blinded independent central review; CI, confidence interval; CS, company submission; DOR, duration of response; DoDC, duration of disease control; EAG, external assessment group; MAIC, matching-adjusted indirect comparison; OR, objective response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumours; SCLC, small-cell lung cancer; TTD, time to treatment discontinuation.

EAG comment on study statistical methods

The statistical methods used in the DeLLphi-301 study appear to be appropriate and the EAG has no concerns, but it should be noted that the trial results presented in CS section B.2.6 include the participants who received tarlatamab post-progression. We note a lack of clarity in the CS about the number of participants who received tarlatamab post-progression.

3.2.5 Efficacy results of the intervention studies

In this section we report on the primary outcome of the DeLLphi-301 trial (objective response), the outcomes that inform the economic model (OS, PFS and TTD), HRQoL outcomes, subgroup analyses for the primary outcome and safety outcomes. The CS additionally provides data for the secondary outcomes of duration of response and disease control (CS section B.2.6.2) which we do not include here.

3.2.5.1 Objective response (Primary outcome)

The objective response rate (best overall response of either complete response or partial response) for the 99 participants assigned to the 10mg dose of tarlatamab in either Part 1 or Part 2 of the DeLLphi-301 study was 40.4% (97.5% confidence interval [CI] 29.4% to 52.2%). Only one (1.0%) participant had a confirmed complete response and 39 (39.4%) had a confirmed partial response. Response outcomes do not contribute data to the economic model. CS Table 11 provides a summary of objective response.

3.2.5.2 OS

Median OS for the 99 participants who received at least one dose of tarlatamab after assignment to the 10mg dose in either Part 1 or Part 2 of the DeLLphi-301 trial was 14.3 months (95% CI: 10.8 months to not estimable) with a median follow-up time of 10.6 months (Table 8 and Figure 1). Thirty-five participants (35.4%) had experienced an event at the time of analysis, and, of the remaining 64 participants who were censored, 57 were alive at the last follow-up and continuing in the study, six had withdrawn consent from the study and one had been lost to follow-up.

Table 8 Analysis of OS (safety analysis set)

	Participants, N
Number of patients who received at least 1 dose (1-10mg[a]) of tarlatamab	99
Patient status	Participants, N (%)
Events	35 (35.4)
- Death	35 (35.4)
Censored	64 (64.6)
- Alive at last follow-up	57 (57.6)
- Withdrawal of consent from study	6 (6.1)
- Decision by sponsor	0 (0.0)
- Lost to follow-up	1 (1.0)
- Completed study without death	0 (0.0)
OS (KM) (months)[b]	
25th percentile (95% CI)	5.7 (4.7, 10.5)
Median (95% CI)	14.3 (10.8, NE)
75th percentile (95% CI)	NE (NE, NE)
Min, Max (+ for censored)	0.3+, 15.2+
Follow-up time of OS (KM) (months)[b]	
25th percentile (95% CI)	[redacted]
Median (95% CI)	10.6 (9.2, 11.5)
75th percentile (95% CI)	[redacted]
Min, Max (+ for censored)	[redacted]

	Participants, N
Kaplan-Meier estimate (%) (95% CI)[c]	
At 3 months	88.7 (80.5, 93.6)
At 6 months	73.4 (63.2, 81.2)
At 9 months	68.0 (57.1, 76.6)
At 12 months	[redacted]

Source: Reproduced from CS Table 15 with the addition of footnote 'a' by the EAG and minor formatting alterations.
BICR, blinded independent central review; CI, confidence interval; EAG, External Assessment Group; KM, Kaplan-Meier; Max, maximum; Min, minimum; N, number; OS, overall survival.
[a] Participants enrolled in Part 1 of the study and randomised to receive 10mg tarlatamab and participants due to receive the selected 10mg dose in Part 2 of the study, received 1mg of tarlatamab for the first dose (Cycle 1, Day 1) before receiving step-up doses of 10mg tarlatamab. This was to mitigate the risk of cytokine release syndrome.
[b] Median and quantiles were estimated using Kaplan-Meier method and 95% CI of median were estimated using log-log transformation of KM survival estimate by Brookmeyer and Crowley (1982) method[34]
[c] 95% Cis were estimated using Kalbfleisch and Prentice (1980) method[35]

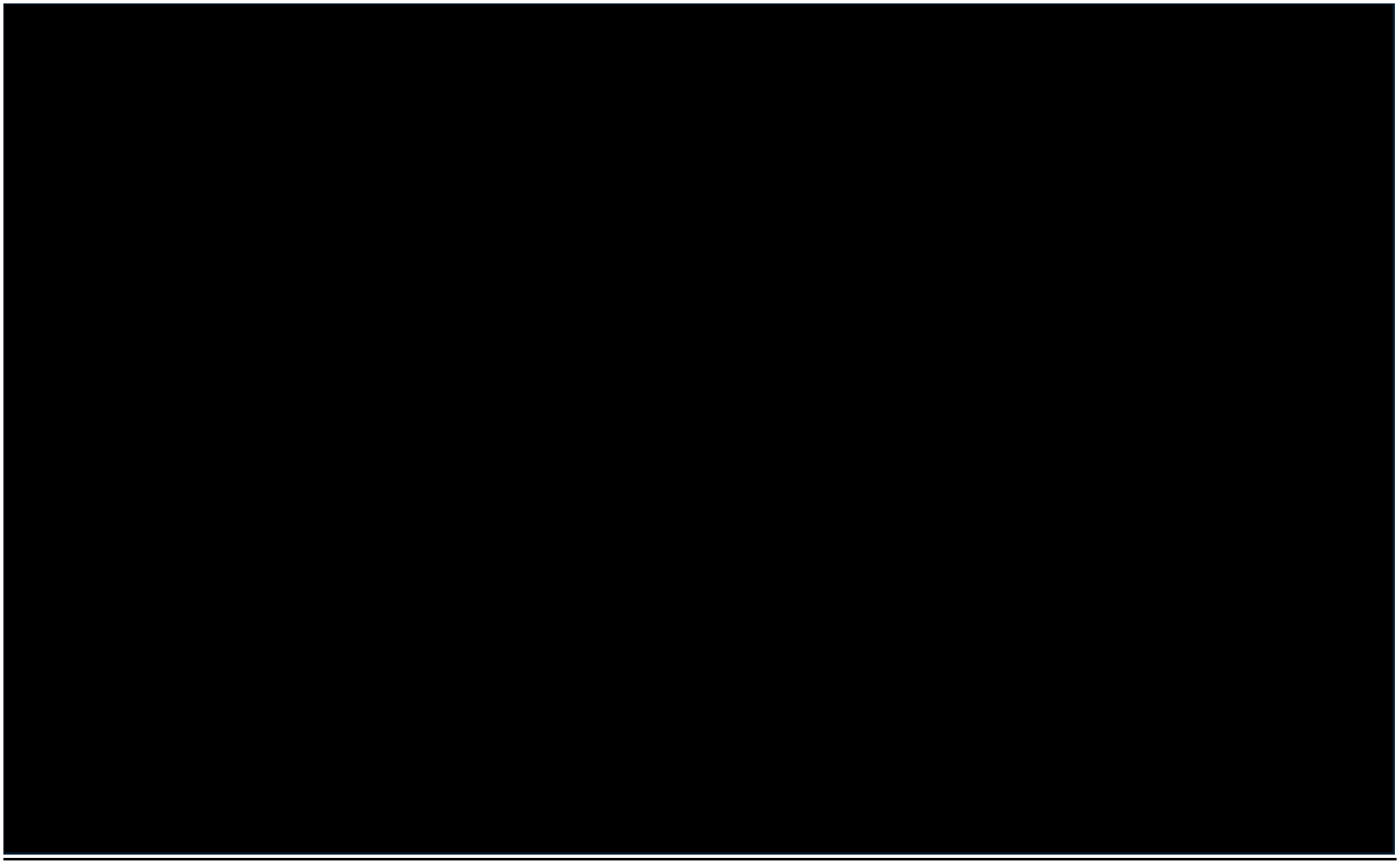

Figure 1 KM plot for overall survival (Safety analysis set)

Source: Reproduction of CS Figure 7
KM, Kaplan-Meier

3.2.5.3 PFS

Median PFS for the 99 participants who received at least one dose of tarlatamab after assignment to the 10mg dose in either Part 1 or Part 2 of the DeLLphi-301 as assessed by BICR was 4.9 months (95% CI: 2.9 to 6.7 months) with a median follow-up time of [redacted] months (Table 9 and Figure 2). There were eight (8.1%) deaths, 56 (56.6%) participants with disease progression and the remaining 35 (35.4) participants were censored, primarily because they remained in the study without disease progression or death (25 participants).

Table 9 PFS as assessed by BICR (BICR Full Analysis set for Part 1 and 2; 10 mg dose)

	Participants, N
Number of patients who received at least 1 dose (1-10mg[a]) of tarlatamab	99
Patient status	Participants, N (%)
Events	64 (64.6)
- Death	8 (8.1)
- Disease progression	56 (56.6)
Censored	35 (35.4)
- On study without disease progression or death	25 (25.3)
- No evaluable post-baseline disease assessment	2 (2.0)
- Missed 2 or more consecutive assessments	3 (3.0)
- Started new anti-cancer therapy	2 (2.0)
- Withdrawal of consent from study	3 (3.0)
- Decision by sponsor	0 (0.0)
- Lost to follow-up	0 (0.0)
- Completed study without disease progression or death	0 (0.0)
PFS (KM) (months)[b]	
25th percentile (95% CI)	2.4 (1.4, 2.8)
Median (95% CI)	4.9 (2.9, 6.7)
75th percentile (95% CI)	NE (7.1, NE)
Min, Max (+ for censored)	0.0+, 13.7+
Follow-up time of PFS (KM) (months)[b]	
25th percentile (95% CI)	[redacted]
Median (95% CI)	[redacted]
75th percentile (95% CI)	[redacted]
Min, Max (+ for censored)	[redacted]
Kaplan-Meier estimate (%) (95% CI)[c]	
At 3 months	58.8 (48.1, 68.1)
At 6 months	40.8 (30.6, 50.7)
At 9 months	28.5 (19.2, 38.6)

	Participants, N
At 12 months	[redacted]

Source: Reproduced from CS Table 14 with the addition of footnote 'a' by the EAG and minor formatting alterations.
BICR, blinded independent central review; CI, confidence interval; EAG, External Assessment Group; KM, Kaplan-Meier; Max, maximum; Min, minimum; N, number; PFS, progression-free survival.
[a] Participants enrolled in Part 1 of the study and randomised to receive 10mg tarlatamab and participants due to receive the selected 10mg dose in Part 2 of the study, received 1mg of tarlatamab for the first dose (Cycle 1, Day 1) before receiving step-up doses of 10mg tarlatamab. This was to mitigate the risk of cytokine release syndrome.
[b] Median and quantiles were estimated using Kaplan-Meier method and 95% CI of median were estimated using log-log transformation of KM survival estimate by Brookmeyer and Crowley (1982) method[34]
[c] 95% Cis were estimated using Kalbfleisch and Prentice (1980) method[35]

Figure 2 KM plot for PFS as assessed by BICR (BICR Full Analysis Set for Part 1 and Part 2)

Source: Reproduction of CS Figure 6
BICR, blinded independent central review; KM, Kaplan-Meier; PFS, progression-free survival.

3.2.5.4 TTD

In response to clarification question A11 the company provided data on TTD for the 99 participants who received at least one dose of tarlatamab in the 10mg target dose group. Results are provided including data for participants who continued to receive tarlatamab after BICR assessed progression (the unadjusted results) whose data were censored at the time of their last tarlatamab exposure before the data cut-off. Adjusted results are also provided in which the patients who continued to receive tarlatamab after progression were instead treated as if they had discontinued tarlatamab at the time of progression. Median TTD in the unadjusted analysis was [redacted] months and in the adjusted analysis was [redacted] months (Table 10). The Kaplan-Meier plot showing the unadjusted and adjusted curves together is provided in Figure 3 (figures showing the unadjusted and adjusted Kaplan-Meier plots in separate figures are available in clarification response A11 Figure 1 and Figure 2).

Table 10 TTD

	Participants, N	
Number of patients who received at least 1 dose (1-10mg[a]) of tarlatamab	99	
Patient status	Participants, N (%)	
	Unadjusted	Adjusted
Event (discontinuation), n (%)	[redacted]	[redacted]
Censored (still on treatment), n (%)	[redacted]	[redacted]
TTD (KM) (months)[b]		
25th percentile (95% CI)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]
Min, Max (+ for censored)	[redacted]	[redacted]
Follow-up time (months)b		
25th percentile (95% CI)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]
Min, Max (+ for censored)	[redacted]	[redacted]
Kaplan-Meier estimate (%) (95% CI)c		
At 3 months	[redacted]	[redacted]
At 6 months	[redacted]	[redacted]
At 9 months	[redacted]	[redacted]
At 12 months	[redacted]	[redacted]

Source: Reproduced from company response to clarification question A11 with minor formatting alterations by the EAG.
CI, confidence interval; EAG, External Assessment Group; KM, Kaplan-Meier; Max, maximum; Min, minimum; N, number; TTD, time to treatment discontinuation

[a] Participants enrolled in Part 1 of the study and randomised to receive 10mg tarlatamab and participants due to receive the selected 10mg dose in Part 2 of the study, received 1mg of tarlatamab for the first dose (Cycle 1, Day 1) before receiving step-up doses of 10mg tarlatamab. This was to mitigate the risk of cytokine release syndrome.
[b] Median and quantiles were estimated using Kaplan-Meier method and 95% CI of median were estimated using log-log transformation of KM survival estimate by Brookmeyer and Crowley (1982) method[34]
[c] 95% Cis were estimated using Kalbfleisch and Prentice (1980) method[35]

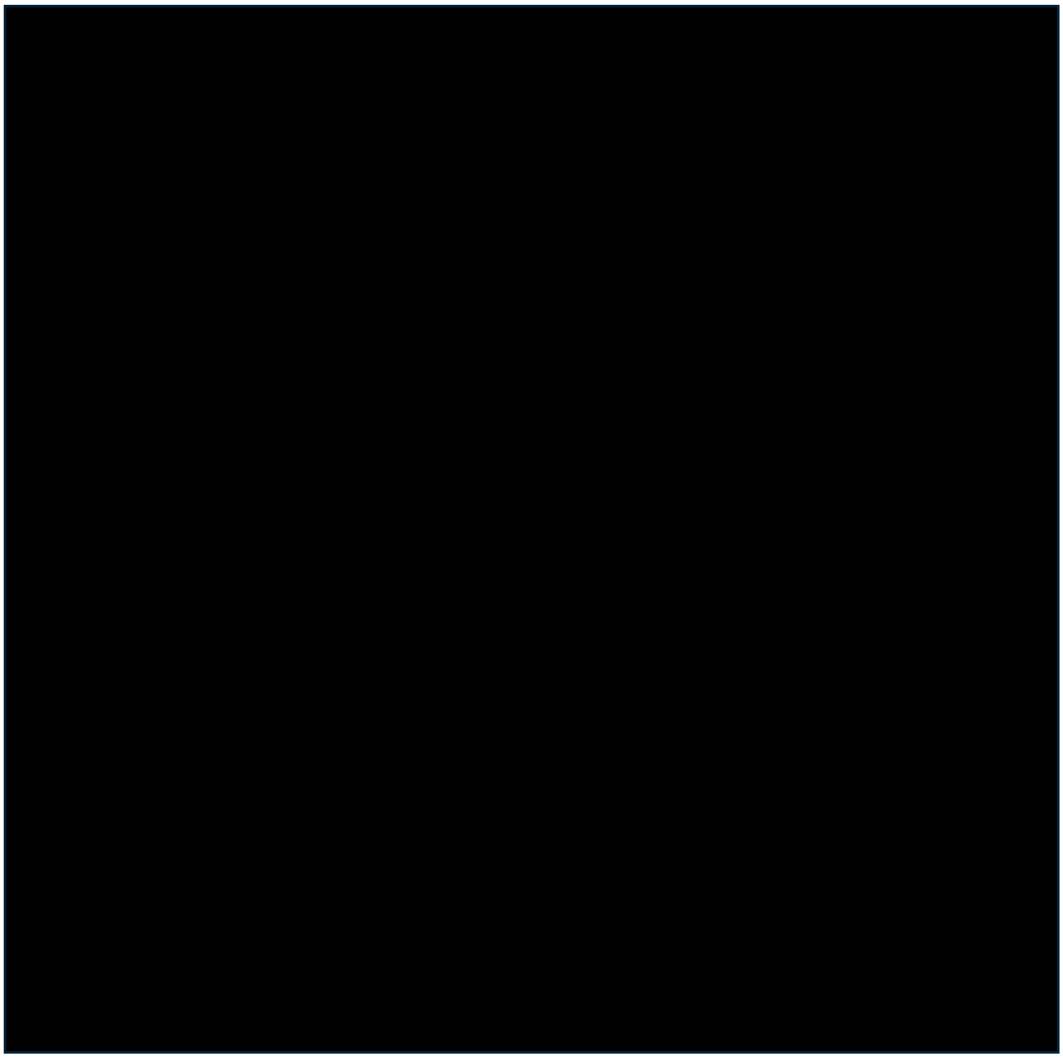

Figure 3 KM plot for time to discontinuation (unadjusted and adjusted)

Source: Reproduced from company response to clarification question A11, Figure 3.
CI, confidence interval; TTD, time to treatment discontinuation

3.2.5.5 HRQoL outcomes

CS section B.2.6.3 presents results of patient-reported outcomes which were exploratory outcomes in DeLLphi-301 and in response to clarification question A13 the company provided a summary of the VAS scores. These results are summarised in Table 11.

The company state in clarification response A13 that, reflecting the trial entry criteria that patients should have an ECOG performance status of 0 or 1, patients had generally moderate to good health at baseline by the EQ-5D-5L visual analogue scale (where 0 is the worst and 100 is the best health imaginable). The global health status/QoL and physical function baseline scores from the EORTC QLQ-C30 were below those for the normative sample of patients with SCLC (i.e. they were worse).

EORTC QLQ-LC13 least squares mean (LSM) score changes from baseline for cough, chest pain and the dyspnoea composite [redacted] indicating a [redacted] in these symptoms up to cycle 12. The EORTC-QLQ-C30 global health status/QoL LSM score [redacted] the baseline value indicating [redacted] QoL at cycle 12. The MMRM analysis of the EQ-5D-5L VAS scores showed that this [redacted] with respect to baseline in cycle 12 and during treatment the change from baseline ranged from [redacted] to [redacted].

Health state utility values in the economic model were based upon EQ-5D-5L data collected in the DeLLphi-301 trial which is discussed further in section 4.2.8.2 of this report.

Table 11 Patient reported outcomes results in DeLLphi-301

	Mean baseline score	LSM change from baseline
EORTC QLQ-LC13[a]		Up to cycle 12
- cough	[redacted]	[redacted] (95% CI: [redacted])
- chest pain	[redacted]	[redacted] (95% CI: [redacted])
- dyspnoea composite	[redacted]	[redacted] (95% CI: [redacted])
EORTC QLQ-C30[b]		At cycle 12
Global health status/QoL	[redacted][c]	[redacted] (95% CI: [redacted])
Physical function	[redacted][c]	Not reported
EQ-5D-5L		MMRM analysis LSM change from baseline in cycle 12
EQ-5D-5L VAS[d]	[redacted]	[redacted][e] (95% CI: [redacted])
		During treatment (up to cycle 15) Mean change from baseline
EQ-5D-5L VAS[d]	[redacted]	Range [redacted] to [redacted]

Source: EAG table based on information presented in CS section B.2.6.3 and the company response to clarification question A13.
EORTC, European Organization for Research and Treatment of Cancer; LSM, least squares mean; QLQ-C30, quality of life questionnaire core 30; QLQ-LC13, quality of life questionnaire lung cancer module
[a] Score range 0-100. A high score represents a high level of symptoms.[36]
[b] Score range 0-100. A high score for global health status/QoL represents high QoL. A high score for physical function represents a high level of physical functioning.[29,37]
[c] These baseline scores were below those for the normative sample of patients with SCLC ([redacted])
[d] Score range 0-100, where 100 is the best possible health state.

[e] In the response to clarification question A13 this is given as [redacted] which appears to be an error. The value in CSR Table 14-4.2.806 is [redacted].

3.2.5.6 Subgroup analyses

CS Table 4 lists the 10 patient characteristics for which pre-planned subgroup analyses were conducted. Subgroup analysis results are presented in CS section B.2.7 and CS Figure 8. An objective response was seen across [redacted] subgroups (with the exception of the [redacted] which included [redacted] and [redacted] patients, respectively).

3.2.5.7 Safety outcomes

The CS presents safety outcomes for the 99 participants in the Safety analysis set who were in the 10mg target dose group because tarlatamab is [redacted] (CS section B.2.10). Participants who were enrolled in Part 3 of the study (n=34) were not included in CS section B.2.10 so the EAG asked the company to provide a summary of the adverse event data for these patients in clarification question A14.

Adverse events with an onset that occurred after the first dose of tarlatamab was administered and up to and including 47 days after the last dose of tarlatamab or the end of study date (whichever was earlier) were defined as treatment-emergent. The CS summarises the incidence of treatment-emergent adverse events (TEAEs) in section B.2.10.1 and CS Table 21. Greater detail on TEAEs is then provided in CS sections B.2.10.3 (most frequent TEAEs), B.2.10.4 (treatment-related TEAEs), B.2.10.5 (serious TEAEs), B.2.10.6 (fatal TEAEs) and B.2.10.7 (adverse events of special interest).

3.2.5.7.1 Summary of TEAEs for participants in Part 1 and Part 2 10mg target dose group in the DeLLphi-301 study

In the tarlatamab 10mg target dose group for Part 1 and Part 2 of the study 97% of the 99 participants had at least one adverse event. Over half the participants (57.6%) experienced a TEAE of Grade ≥3 (Table 12) and TEAEs were considered treatment-related for 29.3% of participants. For serious adverse events, which were reported for 58.6% of the 10mg target dose participants, 37.4% were considered treatment-related. Seven participants (7.1%) discontinued tarlatamab because of an adverse event and there were three fatal adverse events.[23] None of the fatal adverse events were considered to be related to tarlatamab.

Table 12 Summary of incidence of treatment-emergent adverse events (Safety Analysis Set; 10 mg Parts 1 and 2)

Treatment emergent adverse events, n (%)	Tarlatamab 10mg target dose (N=99)
All treatment-emergent adverse events	96 (97.0)
- Grade ≥2	86 (86.9)
- Grade ≥3	57 (57.6)
- Grade ≥4	16 (16.2)
- Serious adverse events	58 (58.6)
Leading to dose interruption and/or reduction of tarlatamab	31 (31.3)
- Leading to discontinuation of tarlatamab	7 (7.1)
- Serious	[redacted]
- Nonserious	[redacted]
- Fatal adverse events	3 (3.0)

Source: Reproduction of CS Table 21 with some minor editing by the EAG.
N or n, number

3.2.5.7.2 Most frequent treatment-emergent adverse events

CS Table 23 presents the incidence of TEAEs that occurred in more than 10% of patients. The most frequent event, experienced by almost half of the participants (n=49, 49.5%) was CRS and pyrexia (fever) occurred in over a third of participants (n=38, 38.4%). Constipation (28.3%), anaemia (26.3%), decreased appetite (25.3%), dysgeusia (24.2%), fatigue (21.2%) and asthenia (20.2%) were the next most frequently experienced events, affecting 20% or more of the participants. The remaining nine TEAEs listed in CS Table 23 were experienced by between 10% and 15% of participants.

3.2.5.7.3 Treatment-related treatment-emergent adverse events

Treatment-related TEAEs that occurred in more than 5% of participants overall are summarised in CS Table 24. The eight most common treatment-related TEAEs are the same as the eight most common TEAEs (CS Table 23). We have combined elements of CS Table 23 and CS Table 24 to provide an overview of the eight most common TEAEs and show what proportion of these events were considered to be treatment-related (Table 13). All of the CRS TEAEs were considered to be treatment related and 89.5% of the pyrexia TEAEs. Decreased appetite and dysgeusia (altered taste) were also commonly considered treatment related. Of the top eight TEAEs, constipation was the event that was considered to be treatment related in the smallest proportion of participants (42.9%).

Table 13 Overview of the eight most common TEAEs and the proportion of these that were considered treatment-related

Preferred Term, n (%)	Tarlatamab 10mg target dose (N=99)		
	Patients with TEAEs N (%)	Patients with treatment-related TEAEs N (%)	Proportion of TEAEs considered treatment-related
Overall	96 (97.0)	89 (89.9)	92.7%
The eight most common TEAEs			
Cytokine release syndrome	49 (49.5)	49 (49.5)	100%
Pyrexia	38 (38.4)	34 (34.3)	89.5%
Constipation	28 (28.3)	12 (12.1)	42.9%
Anaemia	26 (26.3)	16 (16.2)	61.5%
Decreased appetite	25 (25.3)	21 (21.2)	84.0%
Dysgeusia	24 (24.2)	20 (20.2)	83.3%
Fatigue	21 (21.2)	14 (14.1)	66.7%
Asthenia	20 (20.2)	14 (14.1)	70.0%

Source: Table compiled by EAG by combining elements of CS Table 23 and CS Table 24 with the proportion of TEAEs considered treatment-related calculated by the EAG.
TEAE, treatment-emergent adverse event

3.2.5.7.4 Serious adverse events

Serious adverse events (TEAEs of Grade 3 or higher) were reported for 57 participants in the tarlatamab 10mg target dose group in Part 1 and Part 2 of the DeLLphi-301 study. These are summarised in CS Table 25. The Grade ≥3 adverse events by preferred term that were the most frequently reported in the tarlatamab 10mg target dose group were anaemia ([redacted] %), lymphocyte count decreased ([redacted]%), lymphopenia ([redacted]%), fatigue ([redacted]%) and hyponatremia ([redacted]%). There were [redacted] serious adverse events among those with CRS.

3.2.5.7.5 Fatal treatment-emergent adverse events.

Three fatal adverse events occurred in the tarlatamab 10mg target dose group in Part 1 and Part 2 of the DeLLphi-301 study (CS Table 26). None of the fatal adverse events were considered by the investigator to be related to tarlatamab treatment (CS section B.2.10.1).

3.2.5.7.6 Adverse events of special interest

CS Table 27 reports data for four adverse events of special interest:

- CRS
- ICANS and associated neurological events

- Neurological events and psychiatric disorders
- Neutropenia

Neurological events ([redacted]%) and CRS (49.5%) were the most common adverse events of special interest among participants in the 10mg target dose group in Part 1 and Part 2 of the DeLLphi-301 study. There were [redacted]%) Grade ≥3 neurological events and no Grade ≥3 CRS events. For neutropenia, which was seen in [redacted]% of participants there were 6 (6.1%) Grade ≥3 events and ICANS was reported in 7 (7.1%) of participants with [redacted] Grade ≥3 ICANS events.

3.2.5.7.7 Adverse events for participants in Part 3 (10mg target dose) of the DeLLphi-301 study

In response to clarification question A14 the company provided a summary of TEAEs for the 34 participants in Part 3 of the DeLLphi-301 study and we have reproduced the company's table below as Table 14. The proportion of participants experiencing a TEAE in Part 3 of the study (100%) was similar to that of participants in Part 1 and Part 2 of the study (97%). The distribution of Grade ≥2, Grade ≥3 and Grade ≥4 events was also similar. The proportion of serious adverse events (41.2%) was a little lower than in Part 1 and Part 2 of the study (58.6%). A lower proportion of participants had an event leading to dose interruption and/or reduction of tarlatamab (14.7% versus 31.3% in Part 1 and Part 2 of the study). Most TEAEs were considered treatment-related (85.3%) which is similar to Part 1 and Part 2 of the study (89.9%). There were [redacted] fatal TEAEs, [redacted] of which was considered treatment related. The majority of other treatment-related TEAEs were Grade ≥2 (67.6%).

Table 14 Summary of incidence of TEAEs (modified safety monitoring dose group; Part 3)

Treatment-emergent adverse events, n (%)	Tarlatamab 10mg target dose (N=34)
All treatment-emergent adverse events	34 (100.0)
Grade ≥2	33 (97.1)
Grade ≥3	22 (64.7)
Grade ≥4	7 (20.6)
Serious adverse events	14 (41.2)
Leading to dose interruption and/or reduction of tarlatamab	5 (14.7)
Leading to discontinuation of tarlatamab	3 (8.8)
Serious	[redacted]
Nonserious	[redacted]
Fatal adverse events	[redacted]

Treatment-emergent adverse events, n (%)	Tarlatamab 10mg target dose (N=34)
Treatment-related treatment-emergent adverse events	29 (85.3)
Grade ≥2	23 (67.6)
Grade ≥3	5 (14.7)
Grade ≥4	2 (5.9)
Serious adverse events	7 (20.6)
Leading to dose interruption and/or reduction of tarlatamab	3 (8.8)
Leading to discontinuation of tarlatamab	0 (0.0)
Fatal adverse events	[redacted]

Source: Reproduction of Company's response to clarification question A14, Table 4 with minor amendment to heading of column 2.
N or n, number

3.2.6 Pairwise meta-analysis of intervention studies

The company state that meta-analysis was not conducted as DeLLphi-301 is the only trial of tarlatamab that they identified in decision problem indication (CS section B.2.8).

3.3 Critique of studies included in the indirect comparison and/or multiple treatment comparison

3.3.1 Rationale for ITC

The company carried out an ITC because the DeLLphi-301 trial was a single-arm study and the company's systematic literature review did not identify any relevant head-to-head trials of tarlatamab for which data were available (CS section B.2.9). As discussed in section 3.1, the company did not include search terms for randomised controlled trials in their search strategies, and therefore RCTs would not necessarily have been retrieved. Despite this limitation, the EAG do not expect there to be any RCTs available of the use of tarlatamab as a third-line therapy+ (see section 3.1). We agree it is appropriate that the company has conducted an ITC to compare the efficacy of tarlatamab to that of standard of care.

The company used unanchored MAIC methodology to compare the clinical efficacy of tarlatamab, in terms of OS and PFS, versus the single basket standard of care comparator defined in the company decision problem, which consisted of CAV, topotecan and carboplatin + etoposide (see section 2.3). The OS and PFS estimates from the unanchored MAIC informed the company's economic model (CS section B.3.3). An unanchored MAIC approach is suitable when only single-arm trials are available or there is a disconnected network, as in the present case.[1] The company describe the unanchored MAIC methodology

used in CS section B.2.9 and CS Appendix D, sections D.1.4 to D.1.9. The company additionally supplied a data-on-file, confidential report of the MAIC with the CS.[2]

3.3.2 Identification, selection and feasibility assessment of studies for ITC

The DeLLphi-301 trial, identified from the company's systematic literature review, provided individual patient data for the MAIC for tarlatamab. As described in section 3.2.1.1, [redacted]

Of these, two patients had not received two prior lines of therapy and one did not receive tarlatamab, which resulted in an available sample of 97 participants for the ITC of patients who had received the target 10 mg dose in both study parts (CS section B.2.9.5). The trial is described in more detail in section 3.2.1.

[redacted] was conducted to [redacted] for the standard of care comparators, as the company's original systematic literature review did not identify any studies of these comparators in a third-line setting (section 2.4) [redacted] In the EAG's opinion, the methodology used to [redacted] lacks transparency. [redacted] a retrospective, UK real-world evidence study the company had conducted – the UK CAS study – was selected to be the external control arm for the unanchored MAIC (CS Appendix D, section D.1.4). The confidential report of the MAIC[2] describes this as [redacted] (pages 7, 14-15, and 17).

The company selected the UK CAS study as the external control for the MAIC because they argue it is the most up-to-date source of evidence and it is expected to be representative of the patients seen and treatments used in UK clinical practice (CS Appendix D, section D.1.4). The supplied MAIC report shows that unanchored MAICs were [redacted] for the standard of care comparator [redacted] We note that these were [redacted] and thus are less likely to be representative of UK practice.

[redacted]

[redacted]In the UK CAS study, [redacted][2] The databases used and the data that were sourced from them are shown in Table 15. [redacted][2] The CS states that patient-level data were *"not readily available"* (CS section B.2.9.5).

Table 15 Data sources used in the UK CAS study

Source	Data used	Data availability
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]	[redacted]	[redacted]

Source: EAG created table, using information sourced from the company's Data on File MAIC report.[2]
[a] In their response to clarification question A22, the company stated that the diagnosis identification period of the UK CAS study was 1st January 2013 to 31st December 2020.
[b] CS Appendix Table 15 states that the time period of data used from the SACT was 1st January 2013 to 31st December 2020. CS Appendix D.1.4 states that data *"between 1st January 2013 and 31st May 2021"* were used. The company clarified in their response to clarification question A22 that the whole UK CAS study period was 1st January 2013 to 31st May 2022. The company stated the reference to May 2021 was an error and that this should read "*2022*". The company stated in clarification response A23 that 31st May 2022 was the latest date of data availability in the UK CAS study at the time of the analysis.

Participants from the CAS database were included in the UK CAS dataset for this study if they had:

[redacted]Table 15 [redacted]

In total, [redacted] patients in England were included in the UK CAS study (CS Table 18). Outcomes were available for participants up to [redacted]

Table 15 [redacted]

A MAIC approach to an ITC essentially adjusts the intervention's treatment effect (in this case tarlatamab), using selected covariates, to reflect the effect that would be observed in the population of patients receiving the intervention who have the characteristics of the patients included in the comparator study (in this case, of standard of care).[1] Therefore a

fundamental assumption of a MAIC is that the population included in the comparator study is more representative of the target patient population who will be treated with the intervention in clinical practice than the intervention's trial's population.[1] A NICE Decision Support Unit (DSU) Technical Support Document (TSD18) suggests that, when conducting a MAIC, the target population for a decision is likely to be appropriately reflected through the use of a UK registry or cohort study.[1] The UK CAS study included adult patients in England treated within the NHS who had had two previous lines of therapy and who had an ECOG performance status of 0 or 1 at initiation of third-line therapy, as per the population of patients expected to be treated with tarlatamab in clinical practice (see section 2.2.3). One of the EAG's experts commented that the characteristics of the patients included in the UK CAS study and the treatments used were a reasonable representation of the patients treated and treatments used in clinical practice. The other two experts did not comment on this. Overall, in our opinion, the UK CAS study provides an appropriate comparator to which to adjust the DeLLphi-301 trial clinical efficacy estimates in an unanchored MAIC as it is likely to be a representative UK study (with the exception of prior PD-L1 inhibitor treatment; please see bullet point three below and section 3.3.3.3).

We do, though, note the following uncertainties about the use of the UK CAS study, the first of which was, as detailed below, addressed through the company's response to one of our clarification questions:

- From the information available in the CS and the MAIC report,[2] it was unclear how the [redacted] patients identified for inclusion in the UK CAS study were selected from the patients available in the [redacted].[2] The company did not provide a flowchart or a description of the number of patients available and numbers excluded from the final sample due to not meeting the study inclusion criteria or other reasons, such as data availability. Thus, there was a lack of transparency about how patients were selected for inclusion in the final sample. The EAG asked the company to provide a flowchart and/or to describe how the final sample was selected in clarification question A24. The company responded with both a flowchart and a description. Based on this information, the selection process appears reasonable. We note that as part of the process, the company applied inclusion criteria to ensure the selected sample aligned with DeLLphi-301 trial sample in terms of having previously received platinum-based chemotherapy (clarification response A24).
- Clarification response A22 states that the diagnosis identification period was 1st January 2013 to 31st December 2020, whereby any patients meeting diagnostic criteria during this time were included in the UK CAS study, while it is reported in the

MAIC report [redacted] were included in the study. There is a lack of clarity about whether the start date of the diagnostic period and therefore the study was [redacted] or 2013. This may be due to an error in reporting but if it is not and the start date was 2013 then this raises [redacted] of the patients included in the UK CAS study had had exposure to a prior PD-L1 inhibitor. The reason for this is unclear, but it might be because the dataset included patients who had been [redacted] and NICE guidance (TA638) on atezolizumab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer was not published until the 1st July 2020.[38] Clinical expert advice to the EAG is that most patients in practice receive atezolizumab with carboplatin and etoposide as a first-line therapy. In this respect, the UK CAS study cohort does not represent the patients treated in clinical practice. Based on our experts' advice, we understand that it is unknown if this would affect outcomes from the MAIC. Furthermore, the company have not provided subgroup analyses of survival in the CS for the DeLLphi-301 study by prior PD-1 or PD-L1 inhibitor therapy (the only subgroup analyses by prior PD-1 or PD-L1 inhibitor therapy (Yes/No) presented in the CS are of the objective response rate (ORR) outcome; CS section B.2.7).

3.3.3 Clinical heterogeneity assessment

A key assumption of an unanchored MAIC is that all treatment effect modifiers and prognostic factors that are imbalanced between the included studies have been accounted for in the analysis.[1] As is noted in DSU TSD18, this assumption is considered nearly impossible to meet, which means that there will likely be residual bias present in a treatment effect estimate from an unanchored MAIC.[1] When conducting a MAIC, efforts should be undertaken to include relevant prognostic factors, selected *a priori* using clinical expert opinion or from undertaking a thorough review of the topic area, and to match these patient characteristics across the studies of the treatments being compared in the analyses.[1]

3.3.3.1 Company's approach to identifying prognostic factors

Prior to conducting the CS MAIC, the following steps were undertaken to identify prognostic factors that could potentially be adjusted for in the analyses:

- A **targeted literature review** was identified from the systematic literature review that included 39 studies that reported factors prognostic of OS. We asked the company in clarification question A26 if they performed a risk of bias assessment of the review. The EAG found the company's response ambiguous, with the company stating that they did not conduct an additional assessment to that which may or may not have been carried out in the publication. From the targeted literature review, 35 potential prognostic factors were identified. The 35 factors were validated in a **survey of [redacted] clinical experts** and the experts considered the following to be 'very important': ECOG performance status, disease stage, and response to previous treatment (as captured by platinum sensitivity).
- **Analyses were undertaken of the DeLLphi-301 trial data** and this process identified ECOG performance status and brain metastases as significant predictors of OS, which clinical experts confirmed to be important.
- A **meta-regression** was carried out of two systematic literature reviews of second-line and third-line therapy+ studies, respectively,[40] in patients with relapsed or refractory SCLC to identify statistically significant factors that moderated OS, PFS and ORR outcomes. The company provided the references for these systematic literature reviews in response to clarification question A25. The following factors were identified as *"possibly"* (CS section B.2.9.2) predictive: sex, class of treatment, ECOG performance status, treatment line, and extensive stage disease. It was noted that age was not found to be a prognostic factor.

Using a combination of expert opinion about the important prognostic factors and the factors that were found to be statistically significant in the meta-regression, the following were selected for use in the MAIC base case as covariates (CS section B.2.9.2):

- Age at diagnosis
- Sex
- Smoking
- ECOG performance status (0 vs 1) (at initiation of third-line+ treatment, as clarified in the company's response to clarification question A28)
- Presence of brain metastases
- Presence of liver metastases
- Chemotherapy-free interval (≥ 180 days) (this captures response to previous treatment. Patients with this interval between the end of first- and second-line treatment are considered to be platinum-sensitive; clarification response A27)

- Chemotherapy-free interval (≥ 90 and < 180 days) (this captures response to previous treatment. Patients with this interval between the end of first- and second-line treatment are considered to be platinum-sensitive. Those with a chemotherapy-free interval of <90 days are considered to be refractory or resistant to platinum; clarification response A27)
- Extensive-stage disease at diagnosis (as there was a lack of real-world data to obtain stage at initiation of third-line treatment)
- Time from diagnosis to line of therapy

The company notes that age and sex were not universally agreed by the clinicians they consulted to be prognostic factors, but they were included as covariates in the MAIC analyses as they had previously been included in other population-adjusted analyses in SCLC.

We note that smoking is stated in CS section B.2.9.2 to have been selected as a prognostic factor for inclusion in the base case, but it was not actually used as a covariate in the end (CS Table 16). We asked the company the reason for this in clarification question A29. In the company's written response, they stated that following discussions with the EAG it was agreed that an answer was not required (clarification response A29). The company provided their reason during the clarification questions meeting with NICE and the EAG noted it was due to data availability. We therefore agree with the company's approach of not including smoking as a covariate, particularly as one of our experts did not believe that it was a prognostic factor.

3.3.3.2 EAG's critique of the company's approach to selecting prognostic factors

In the EAG's opinion, broad work was undertaken to identify potential prognostic factors on which to match patients in the MAIC. Both clinical expert opinion and reviews of the topic area were used, thus reflecting both the recommended approaches in DSU TSD18.[1] A minor criticism is that there is a lack of transparency about how the targeted literature review and the [redacted] systematic literature reviews used for the meta-regression were selected, leading to some uncertainty about whether or not these were the most relevant data sources available. A further minor criticism is that the clinical expert survey was limited to [redacted] respondents. This is probably sufficient for eliciting opinion, but a larger sample would have been ideal.

All three of our clinical experts considered that the company's selected list of prognostic factors was reasonable. One noted, though, that sex and, as stated above, smoking are not convincing factors (the latter because most patients will have smoked). As is also noted

above, smoking was not included in the company's unanchored MAIC base case. Our experts all agreed that previous response to treatment (i.e. platinum resistance or sensitivity as measured by chemotherapy-free interval) is one of the most important prognostic factors. The other factors considered to be most important by at least one of our three experts were: time since diagnosis, ECOG performance status and maintaining performance status, burden of disease, presence of brain/liver metastases, and progression-free interval.

Two of the three clinical experts we consulted pointed out that prognostic scoring systems are available for SCLC (e.g. the Manchester Scoring Index) and it was noted that paraneoplastic syndromes (e.g. low sodium, neuropathy), which affect a small number of patients, can have a negative prognostic effect. This was not a prognostic factor identified for inclusion in the company's analyses, however, as noted by one of our experts, if this information is not prospectively recorded, then it will not be accessible for use in analyses.

An uncertainty about the company's selected prognostic factors is that age and sex were included in their analyses as covariates, yet there was not a consensus between the clinicians they consulted that these were prognostic and the meta-regression did not find age (when measured as the median or the mean) to be a prognostic factor either. We therefore asked the company to carry out a MAIC sensitivity analysis excluding these covariates to explore the impact of this on the results (clarification question A37), which the company provided in response along with a cost-effectiveness scenario analysis incorporating these results, as we requested (clarification response A37).

To explore the impact of the covariate selection further on the results of the unanchored MAIC analyses, we also asked the company to provide sensitivity analyses of OS and PFS in which only the prognostic factors considered to be 'very important' by the company's clinical experts were controlled for (i.e. ECOG performance status, disease stage and response to previous treatment) (clarification question A38). We also requested the company provided a cost-effectiveness scenario analysis using the results. The company provided the requested analyses (clarification response A38) and the results are presented in section 3.5.

3.3.3.3 Heterogeneity between the DeLLphi-301 trial participants and the CAS Control Cohort patients

We note there were baseline characteristic differences between the DeLLpi-301 trial participants and the CAS Control Cohort on the following prognostic factors controlled for in the analyses: presence of brain or liver metastases (the company state in CS section B.2.9.4 that these characteristics were generally similar, but the EAG disagree), platinum-sensitivity

(chemotherapy-free interval of ≥180 days), extensive disease at 'diagnosis' (measured by a proxy of the presence of extensive disease at initiation of third-line therapy+) and gender (CS Table 18). Clinical expert advice to the EAG is that the difference between the studies in the presence of extensive disease would favour tarlatamab, while the difference between the studies in the presence of liver metastasis would favour standard of care. A clinical expert commented that it is unclear whether the gender differences are important. Additionally, there was a substantial difference in the proportions of participants who had previously received a PD-L1 inhibitor (DeLLphi-301: 72.7%; CAS Control Cohort: [redacted]) but this was not a covariate included in the MAIC analyses. It is unknown what impact this difference might have on the results (please see discussion in section 3.3.2). As noted in section 3.3.2, clinical expert advice to the EAG is that most patients in practice receive atezolizumab with carboplatin and etoposide as a first-line therapy.

It is unclear if there were any other baseline differences between the patients in the study that could potentially affect the outcomes, as baseline characteristics were reported for only a limited number of variables in CS Table 18 that were not selected prognostic factors. We therefore asked the company to confirm if the list of characteristics the DeLLphi-301 and CAS Control Participants were compared on in CS Table 18 was comprehensive and that there were no missing characteristics (clarification question A31). In response to this, the company provided a comparison on some additional characteristics (clarification response A31). This showed that the two samples differed in terms of the proportions of participants who were Asian or White. As discussed in section 3.2.1.2, our experts do not expect that race or ethnicity would impact on treatment response. There were differences in the presence of the following comorbidities too: hypertension (DeLLphi-301: 45.4%, CAS Control Cohort: [redacted]), chronic obstructive pulmonary disease (10.3% versus [redacted]) and diabetes mellitus (20.6% versus [redacted]). Our clinical experts were of the opinion that these differences would likely not impact or have limited impact on the OS and PFS outcomes.

3.3.4 Similarity of treatment effects

As outlined in section 3.3.1, the company included unanchored MAICs of OS and PFS in the CS. Table 16 shows how these outcomes were defined in DeLLphi-301 and UK CAS study. The OS outcome definitions are comparable. In terms of PFS, real-world evidence data was not available for this outcome from the UK CAS study and thus TTD was used as a proxy for PFS for the standard of care comparator. We note that in the literature, in non-small-cell lung cancer (i.e. a different indication to this appraisal), TTD and PFS have been found to have a high but not perfect correlation (r = 0.87).[41] In the absence of PFS data, the EAG consider using TTD as a proxy is acceptable, but it may potentially disadvantage standard of care as

TTD may be shorter than PFS, because patients may discontinue treatment for reasons other than disease progression, such as unacceptable toxicity or to switch to a new therapy prior to progression. To address this uncertainty, we asked our clinical experts how well the median PFS found in the company's MAIC analyses for standard of care, which was [redacted] months (95% CI: [redacted], [redacted]) (see section 3.5), reflects that expected in clinical practice. All three felt it was a reasonable reflection, which provides some confidence that TTD may adequately represent PFS in the present analyses. We also asked the company to provide an unanchored MAIC sensitivity analysis using TTD from DeLLphi-301, instead of PFS, versus TTD from the UK CAS study and a cost-effectiveness scenario analysis using the result (clarification question A39). In response, the company provided information on how the analysis can be performed in the economic model, using the option of TTD instead of PFS for tarlatamab, and provided the result of the requested cost-effectiveness scenario analysis (clarification response A39). This indicated that when TTD was used for tarlatamab, comparable cost-effectiveness results were obtained to the company's updated base case (based on deterministic analyses).

Table 16 Definitions of OS and PFS outcomes in the DeLLphi-301 and UK CAS studies

Outcome	Tarlatamab (DeLLphi-301)	Standard of care (UK CAS study)
OS	Time from index treatment initiation to death from any cause.	
PFS	Time from third-line+ treatment initiation to progression or death (whichever happened first). Assessed by BICR using the RECIST v 1.1 criteria.	TTD used as a proxy for PFS, as PFS not available. TTD was defined as time from the start of third-line therapy to the end of that treatment or death (whichever happened first).

Source: CS Appendix D, section D.1.5
BICR, blinded independent central review; CAS, Cancer Analysis System; OS, overall survival; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumours; TTD, time to treatment discontinuation.

3.3.5 Risk of bias assessment for studies included in the ITC

The company critically appraised the DeLLphi-301 trial using the Downs and Black checklist[42] (CS Appendix D, section D.1.9). Please see section 3.2.2 for a discussion of the results of this and the EAG's critical appraisal of the study. The company did not, however, carry out a risk of bias assessment of the UK CAS study. We therefore carried out an assessment using the criteria recommended by NICE for critically appraising non-randomised and non-controlled studies.[28] Our full appraisal of the study is available in Appendix 4. As this shows, in our opinion, there is an unclear risk of selection bias because

it is unclear whether the start of the diagnosis identification period of the study for patient inclusion was in [redacted] or 2013 due to inconsistency in reporting of these dates. Additionally, the CAS Control Cohort is not fully representative of the patients treated in practice, as [redacted] had received a prior PD-L1 inhibitor and the impact of this on the results is unknown (see section 3.3.2). We also have concerns about potential detection bias due to TTD being used as a proxy for PFS, which could potentially lead to an underestimation of PFS for standard of care. However, as discussed in section 3.3.4, our experts were satisfied that the median PFS found in the MAIC for standard of care was reflective of that seen in clinical practice, so this may not be an issue.

EAG comment on the studies included in the ITC

The company's selection of the UK CAS study to represent the standard of care comparator in the unanchored MAIC is appropriate, as it is a large UK study that is likely generally representative of the characteristics of the patients treated in clinical practice and the treatments they receive at third-line therapy+, except in terms of receipt of a prior PD-L1 inhibitor. The potential impact the latter could have on the results of the MAIC is unknown.

There is an unclear risk of selection bias in how participants were selected for inclusion in the UK CAS study, as the dates during which patients meeting the diagnostic criteria for eligibility are inconsistently reported. The EAG suspects this is likely due to an error in reporting. Additionally, arguably, a more recent data cut of the UK CAS study than 31st May 2022 could have been used, but the company indicate that this was the end of data availability at the time of the analyses (there is no indication that the analyses were specifically carried out for the NICE submission).

Our experts confirmed that the company's selection of covariates to use in their unanchored MAIC base case analyses was generally reasonable. The use of TTD as a proxy for PFS for standard of care also appears reasonable in the absence of PFS data.

3.4 Critique of the indirect treatment comparison

As described in sections 3.3.1 and 3.3.4, the company conducted unanchored MAICs comparing tarlatamab to standard of care on the outcomes of OS and PFS (using TTD as a

proxy for PFS for standard of care). The single-arm trial design of the DeLLphi-301 study necessitated an ITC.

3.4.1 Data inputs to the ITC

As noted in section 3.3.2, the company used the DeLLphi-301 trial to represent tarlatamab in the unanchored MAIC and the UK CAS study as the external control arm to represent standard of care. Individual patient data were used from 97 participants in the DeLLphi-301 trial, but CS section B.2.9.5 highlights that that because individual patient data were not *"readily"* (CS section B.2.9.5) available for the CAS Control cohort, pseudo-patient level data were created using a published method[43] and used for the selected [redacted] patients. This is a limitation, as the DeLLphi-301 trial participants were matched to the aggregate values from the CAS control cohort rather than the variance, which creates some uncertainty around the reliability of the data.

As noted in section 3.2.1.1, participants in DeLLphi-301 could receive tarlatamab past disease progression, [redacted].[17] CS section B.2.9.3 states that in the unanchored MAIC analyses, participants from DeLLphi-301 who received tarlatamab after progression were censored when disease progression occurred in the OS analyses. The EAG agrees that this is appropriate. CS section B.2.9.3 also states that these participants were censored from the PFS analyses, but information in CS section B.3.3.1 and clarification response A39 suggest that they were not (there may be an error in reporting in CS section B.2.9.3). The EAG believes it would be appropriate to not censor these participants from the PFS analyses and to include their PFS data points. Participants receiving tarlatamab post-progression were also censored from the EAG-requested sensitivity analysis provided in response to clarification question A39, in which TTD from DeLLphi-301 was used instead of PFS and compared with TTD from the UK CAS study (clarification response A39). The censoring rules are not clearly outlined in the clarification response. It is unclear if the same approach, as set out in CS Table 38 for TTD and in clarification response A11 for the censored TTD analyses from the DeLLphi-301 trial, was used. If it was, then we agree that the company's approach is appropriate. We note that there is a lack of clarity in the CS about how many participants received tarlatamab post-progression (see Table 7 in section 3.2.4).

3.4.2 Statistical methods for the ITC

The individual patient data from DeLLphi-301 and the pseudo-individual patient data from the CAS Control cohort were used in the unanchored MAIC matching process to adjust

imbalances in the covariates and to derive statistical weights (CS section B.2.9.5). A form of propensity score weighting was used to create the weights (CS Appendix D.1.6). The weights were used to adjust the DeLLphi-301 trial outcomes so that the tarlatamab patient population aligned to that of the CAS Control cohort (CS section B.2.9.5). Hazard ratios were generated from weighted Cox proportional hazards models, with treatment used as a covariate. Standard errors were also generated and effective sample sizes provided. The effective sample size is the number of non-weighted participants that would be needed to obtain the same estimate as in the weighted sample (CS Appendix D.1.6). When the effective sample size is considerably reduced compared to the original sample size, estimates may be unreliable.[1] The company provided the results of the matching process showing the standardised mean differences on each of the prognostic factors before and after matching (CS section B.2.9.6 Figure 9). However, they did not report the raw data pre- and post-match, and so we requested these in clarification question A33, which the company provided in response (clarification response A33). We also asked for the standardised mean difference results before and after matching for any unmatched baseline characteristic variables, which the company also provided (clarification response A34).

The company carried out two MAIC scenario analyses in which they removed selected prognostic factors and reported results of these in the CS:

- Scenario 1: chemotherapy-free interval data were missing for 30% of participants in the DeLLphi-301 trial and an assumption had been accordingly used in the base case that these participants had a chemotherapy-free interval of ≥ 180 days (CS section B.2.9.2). To explore whether this was a potential source of bias, the company excluded chemotherapy-free intervals as prognostic factors from the MAIC.
- Scenario 2: Stage of disease at diagnosis had to be used as a covariate in the base case in the absence of the preferred prognostic factor of presence of extensive disease at initiation of treatment. Therefore, this factor was excluded in a scenario analysis.

As detailed above, the EAG also requested three sensitivity analyses in clarification questions A37, A38 and A39, to explore the robustness of the results to the removal of selected covariates and to explore the impact of using TTD from DeLLphi-301 instead of PFS in the comparison against TTD for standard of care:

- EAG clarification question A37 requested sensitivity analysis: analyses of OS and PFS omitting sex and age as prognostic factors (requested for the reasons outlined in section3.3.3).

- EAG clarification question A38 requested sensitivity analysis: analyses of OS and PFS that only include the three prognostic factors considered to be 'very important' by the company's clinical experts (i.e. ECOG performance status, disease stage, and response to previous treatment). This analysis was requested as the company's MAIC base case effective sample size was markedly reduced and we wished to explore the robustness of the results when fewer prognostic factors were included in the analyses.
- EAG clarification question A39 requested sensitivity analysis: an analysis using TTD from DeLLphi-301, instead of PFS, versus TTD from the UK CAS study (requested to explore the impact on the results when a more comparable outcome from the DeLLphi-301 trial was used to that from the UK CAS study to examine the potential robustness of using TTD as a proxy for PFS for standard of care). The company did not clearly state the prognostic factors used in this analysis but stated that the MAIC weights are the same for the TTD and PFS outcomes, which suggests the company used the base case matching factors.

We also asked the company to provide cost-effectiveness scenario analyses using the results of each of these sensitivity analyses. We summarise the prognostic factors included in the company's unanchored MAIC base case, two scenario analyses and the EAG's two requested sensitivity analyses in which we requested alterations to the included covariates in Table 17.

Table 17 Prognostic factors adjusted for in the unanchored MAIC

Prognostic variable	Company base case ESS = [redacted]	Company scenario 1 ESS = [redacted]	Company scenario 2 ESS = [redacted]	EAG clarification A37 ESS = [redacted]	EAG clarification A38 ESS = [redacted]
Age at diagnosis (prior to first-line treatment)	✓	✓	✓		
Sex (male vs female)	✓	✓	✓		
ECOG PS (0 vs 1) [a]	✓	✓	✓	✓	✓
Brain metastases [a]	✓	✓	✓	✓	
Liver metastases [a]	✓	✓	✓	✓	

Chemotherapy-free interval (≥ 180 days) [b]	✓		✓	✓	✓
Chemotherapy-free interval (≥ 90 and < 180 days) [b]	✓		✓	✓	✓
Extensive-stage disease at diagnosis [c]	✓	✓		✓	✓
Time from diagnosis to line of therapy	✓	✓	✓	✓	

Source: Partly reproduced from CS Table 16, with additional information sourced from clarification questions A37 and A38
CS, Company Submission; EAG, External Assessment Group; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; PS, performance status; TNM, tumour, node, metastases.
[a] At initiation of index line of treatment.
[b] At completion of first-line treatment.
[c] Only TNM stage was reported in the DeLLphi-301 trial; stage IV was assumed to be extensive-stage.

The company provided the results of the requested EAG sensitivity analyses and cost-effectiveness scenarios in their clarification responses A37 and A38. In response to clarification question A39, the company provided information on how the analysis can be performed in the economic model, using the option for TTD instead of PFS for tarlatamab, and provided just the result of a requested cost-effectiveness scenario analysis (clarification response A39) rather than the MAIC results for TTD from the DeLLphi-301 trial versus TTD from the UK CAS study.

We note that the company did not provide the distribution of weights for the company's unanchored MAIC scenario analyses 1 and 2, so we requested these in clarification question A32, which the company accordingly provided (clarification response A32). The company also did not provide the median OS and PFS for either the tarlatamab or standard of care group before and after weighting for the two company scenario analyses, so we requested these results in clarification question A35, and the company responded with the requested information (clarification response A35).

The EAG considers that the unanchored MAIC methodology has been appropriately chosen, with appropriate prognostic factors and treatment effect modifiers adjusted for in the base case analyses. As stated in section 3.3.3.2, the EAG's clinical experts confirmed that the

selection of prognostic factors and treatment effect modifiers was reasonable. The MAIC methodology appears to have been correctly implemented, although no individual patient data was available to the EAG to confirm this. The matching process was successful, and the prognostic variables appeared to be well-balanced post-match. The distribution of weights also appears reasonable, but there was a high reduction in the base case effective sample size ([redacted]), which resulted in an effective sample size of just [redacted] patients. The company's two scenario analyses provided similar OS and PFS results to the base case results (see section 3.5). The EAG's two requested sensitivity analyses, requesting the removal of selected covariates from the analyses, resulted in smaller reductions in the effective sample size ([redacted] and [redacted], respectively). A limitation of these analyses, however, is that stronger assumptions were made about what factors were prognostic and there were differences between the samples in brain and liver metastases (which would not have been controlled for in the sensitivity analysis conducted in response to clarification question A38) and gender between the two studies (see section 3.3.3.3) and we do not know what the differences post-match for these unmatched variables were. Both the EAG requested sensitivity analyses produced results that were [redacted] to tarlatamab for PFS or [redacted] to tarlatamab for OS than the base case (see section 3.5).

3.4.3 Summary of EAG critique of the ITC

The unanchored MAIC methodology has been appropriately chosen and implemented. We are satisfied with the use of the MAIC base case OS and PFS results in the cost-effectiveness analyses. However, a limitation of the base case analyses of OS and PFS is that they resulted in an effective sample size of just [redacted] participants. When the effective sample size is greatly reduced, MAIC estimates may become unreliable.[1] In addition, a limitation of an unanchored MAIC approach is that systematic error is likely to still be present due to the likelihood that there are unaccounted for covariates in such analyses.[1]

3.5 Results from the indirect comparison

3.5.1 OS

OS with tarlatamab treatment was significantly longer in comparison to the available treatment options, represented by the UK CAS patients treated with systemic anti-cancer therapies, in both the unadjusted and MAIC-adjusted comparisons (Table 18). In the unadjusted analysis there was a [redacted]% lower mortality risk with tarlatamab and in the MAIC-adjusted analysis the mortality risk with tarlatamab was [redacted]% lower. Figure 4 (which is a reproduction of CS Figure 11) shows the Kaplan-Meier plots for both the unadjusted (unweighted) and MAIC-adjusted (weighted) OS data. As stated in section 3.2.5.2 median

OS with tarlatamab (unadjusted) was 14.3 months (95% CI: 10.8, NE). In the MAIC-adjusted analysis it was [redacted] months (95% CI: [redacted]), as reported in CS section B.2.9.6. We note, however, that median OS after MAIC weighting and with censoring of patients who received at least one dose of tarlatamab post-progression is reported to be [redacted] months in CS Table 36. In comparison, median OS in the UK CAS study was [redacted] months. Based on the information presented in CS Table 36, the EAG suggests that in CS section B.2.9.6 the company has reported the median OS for tarlatamab after weighting in the MAIC, but without censoring for patients who received tarlatamab post-progression.

Table 18 OS for tarlatamab versus available treatment options (unadjusted and MAIC adjusted results)

	ESS	HR (95% CI)	SE	p-value
Unadjusted		0.278 (0.194, 0.399)	[redacted]	<0.0001
MAIC-adjusted	[redacted]	0.367 (0.202, 0.667)	[redacted]	0.001

Source: Table reproduced from CS Table 19
CI, confidence interval; ESS, effective sample size; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival; SE, standard error.

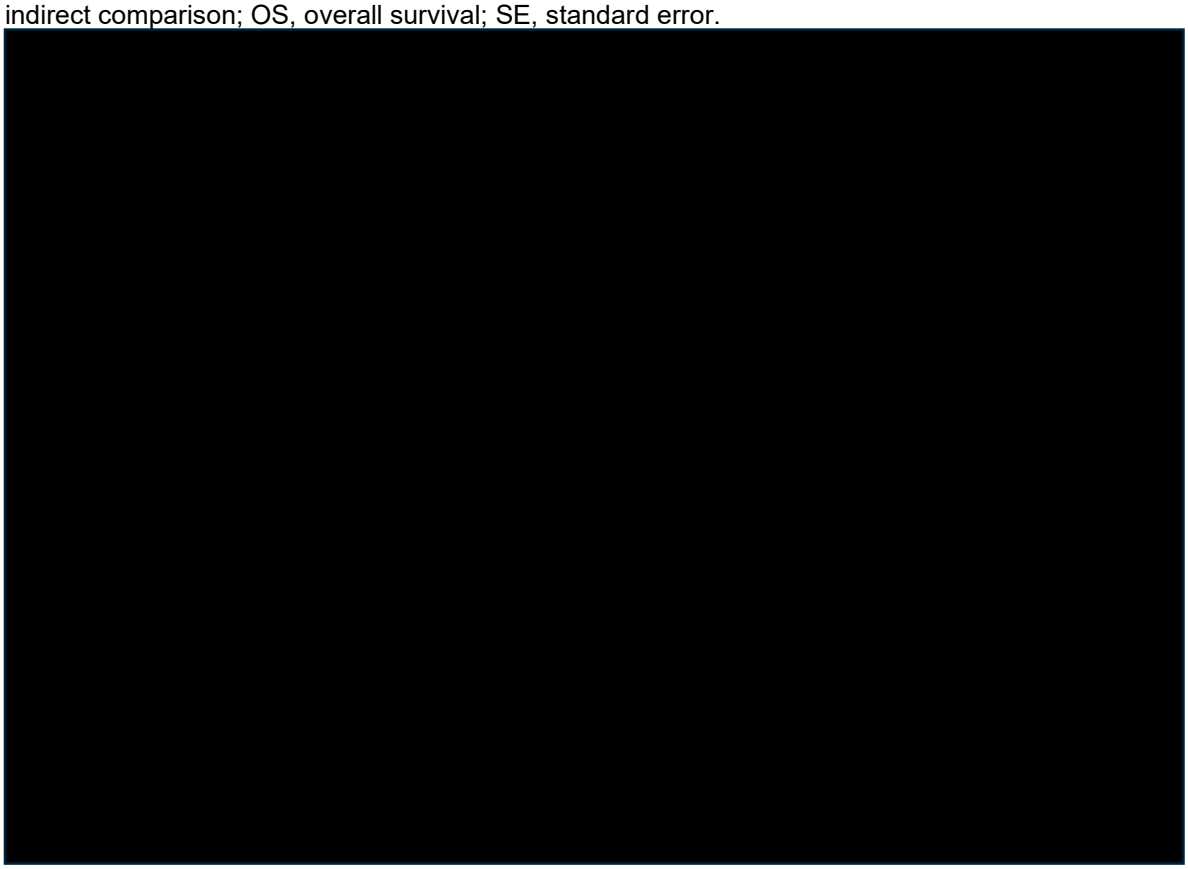

Figure 4 Kaplan-Meier plot of OS for tarlatamab (unadjusted and MAIC adjusted) versus available treatment options

Source: Reproduction of CS Figure 11
MAIC, matching-adjusted indirect comparison; OS, overall survival

3.5.1.1 ITC scenario analyses for OS

The company's two scenarios and the EAG requested scenarios have been discussed in section 3.4.2 and shown in Table 17. The company scenario results were reported in CS Appendix D.1.7 and the results for two of the EAG requested scenarios were provided in response to clarification questions A37 and A38. As can be observed from the hazard ratios reported in Table 19, under company scenario 1 the MAIC-adjusted hazard ratio [redacted] in comparison to the base case MAIC-adjusted hazard ratio thus [redacted] the relative efficacy of tarlatamab from [redacted]% in the base case to [redacted]%. Under company scenario two the MAIC-adjusted hazard ratio was [redacted] the base case MAIC-adjusted value. The results from both company scenario analyses still demonstrate significantly improved survival with tarlatamab in comparison to the available treatment options. For the two scenario analyses that the EAG requested, both led to [redacted] in the MAIC-adjusted hazard ratio in comparison to the base case (i.e. there was [redacted] in the relative efficacy of tarlatamab).

Table 19 OS for tarlatamab versus available treatment options in the company and EAG scenarios compared to the base case (MAIC adjusted results)

		ESS	HR (95% CI)	SE	p-value
Company base case[a]	Unadjusted	-	0.278 (0.194, 0.399)	[redacted]	<0.0001
	MAIC-adjusted	[redacted]	0.367 (0.202, 0.667)	[redacted]	0.001
Company scenario 1[b]	MAIC-adjusted	[redacted]	[redacted]	[redacted]	<0.001
Company scenario 2[c]	MAIC-adjusted	[redacted]	[redacted]	[redacted]	<0.001
EAG scenario clarification A37[d]	MAIC-adjusted	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario clarification A38[e]	MAIC-adjusted	[redacted]	[redacted]	[redacted]	[redacted]

Source: EAG compiled table combining CS Table 19, CS Appendix D.1.7 Table 11 and Table 12, Clarification response to A37 Table 10 and Clarification response to A38 Table 14.
CI, confidence interval; EAG, External Assessment Group; ESS, effective sample size; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival; SE, standard error.
[a] The prognostic factors adjusted for in the Company base case unanchored MAIC were: Age at diagnosis (prior to first-line treatment); Sex (male vs female); ECOG performance status (0 vs 1) at initiation of index line of treatment; Brain metastases at initiation of index line of treatment; Liver metastases at initiation of index line of treatment; Chemotherapy-free interval (≥ 180 days) at completion of first-line treatment; Chemotherapy-free interval (≥ 90 and < 180 days) at completion of first-line treatment; Extensive-stage disease at diagnosis (Only TNM stage was reported in the DeLLphi-301 trial; stage IV was assumed to be extensive-stage); Time from diagnosis to line of therapy
[b] Chemotherapy-free interval (≥ 180 days) and Chemotherapy-free interval (≥ 90 and < 180 days) were not adjusted for in this scenario.
[c] Extensive-stage disease at diagnosis was not adjusted for in this scenario.

[d] Age at diagnosis (prior to first-line treatment) and sex (male vs female) were not adjusted for in this scenario
[e] Four prognostic factors were adjusted for in this scenario: ECOG performance status (0 vs 1) at initiation of index line of treatment; Chemotherapy-free interval (≥ 180 days) at completion of first-line treatment; Chemotherapy-free interval (≥ 90 and < 180 days) at completion of first-line treatment; Extensive-stage disease at diagnosis

3.5.2 PFS

PFS was not available in the CAS Control cohort so TTD was used as a proxy for PFS.

PFS with tarlatamab treatment was significantly better than in the comparator therapy group in both the unadjusted and MAIC-adjusted comparisons (Table 20). In the unadjusted analysis the risk of progression with tarlatamab was [redacted]% lower than the available treatment options, in the MAIC-adjusted analysis it was [redacted]% lower. Figure 5 shows the Kaplan-Meier plots for the unadjusted (unweighted) and MAIC-adjusted (weighted) PFS data. Median PFS with tarlatamab (unadjusted) was [redacted] months (95% CI: [redacted]) and in the MAIC-adjusted analysis it was [redacted] months (95% CI: [redacted]). In the comparator CAS cohort median PFS (for which TTD or death was used as a proxy) was [redacted] months (95% CI: [redacted]).

Table 20 PFS for tarlatamab versus available treatment options (unadjusted and MAIC adjusted results)

	ESS	HR (95% CI)	SE	p-value
Unadjusted		0.206 (0.150, 0.282)	[redacted]	<0.0001
MAIC-adjusted	[redacted]	0.184 (0.100, 0.340)	[redacted]	<0.0001

Source: Reproduction of CS Table 20
CI, confidence interval; ESS, effective sample size; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; SE, standard error.

Figure 5 Kaplan-Meier plot of PFS for tarlatamab (unadjusted and MAIC adjusted) versus available treatment options

Source: Reproduction of CS Figure 12
MAIC, matching-adjusted indirect comparison; PFS, progression-free survival.

3.5.2.1 ITC scenario analyses for PFS

Table 21 shows the MAIC-adjusted results for the two company scenarios and the two EAG requested scenarios in comparison to the company MAIC base case for PFS of tarlatamab compared with available treatment options. Across all four scenarios the MAIC-adjusted hazard ratio for PFS was [redacted] giving relative efficacies for tarlatamab that lay between [redacted]% and [redacted]% in comparison to the company base case MAIC-adjusted value of [redacted]%. The results from both company scenario analyses [redacted] indicate significantly improved PFS with tarlatamab in comparison to the available treatment options.

Table 21 PFS for tarlatamab versus available treatment options in the company and EAG scenarios compared to the base case (MAIC adjusted results)

		ESS	HR (95% CI)	SE	p-value
Company base case[a]	Unadjusted		0.206 (0.150, 0.282)	[redacted]	<0.0001
	MAIC-adjusted	[redacted]	0.184 (0.100, 0.340)	[redacted]	<0.0001
Company scenario 1[b]	MAIC-adjusted	[redacted]	[redacted]	[redacted]	<0.001

		ESS	HR (95% CI)	SE	p-value
Company scenario 2[c]	MAIC-adjusted	[redacted]	[redacted]	[redacted]	<0.001
EAG scenario clarification A37[d]	MAIC-adjusted	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario clarification A38[e]	MAIC-adjusted	[redacted]	[redacted]	[redacted]	[redacted]

Source: EAG compiled table combining CS Table 20, CS Appendix D.1.7 Table 13 and Table 14, Clarification response to A37 Table 10 and Clarification response to A38 Table 14.
CI, confidence interval; EAG, External Assessment Group; ESS, effective sample size; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; SE, standard error.
[a] The prognostic factors adjusted for in the Company base case unanchored MAIC were: Age at diagnosis (prior to first-line treatment); Sex (male vs female); ECOG performance status (0 vs 1) at initiation of index line of treatment; Brain metastases at initiation of index line of treatment; Liver metastases at initiation of index line of treatment; Chemotherapy-free interval (≥ 180 days) at completion of first-line treatment; Chemotherapy-free interval (≥ 90 and < 180 days) at completion of first-line treatment; Extensive-stage disease at diagnosis (Only TNM stage was reported in the DeLLphi-301 trial; stage IV was assumed to be extensive-stage); Time from diagnosis to line of therapy
[b] Chemotherapy-free interval (≥ 180 days) and Chemotherapy-free interval (≥ 90 and < 180 days) were not adjusted for in this scenario.
[c] Extensive-stage disease at diagnosis was not adjusted for in this scenario.
[d] Age at diagnosis (prior to first-line treatment) and sex (male vs female) were not adjusted for in this scenario.
[e] Four prognostic factors were adjusted for in this scenario: ECOG performance status (0 vs 1) at initiation of index line of treatment; Chemotherapy-free interval (≥ 180 days) at completion of first-line treatment; Chemotherapy-free interval (≥ 90 and < 180 days) at completion of first-line treatment; Extensive-stage disease at diagnosis.

3.5.3 TTD

The EAG asked the company to conduct a MAIC sensitivity analysis using TTD from the DeLLphi-301 trial (instead of PFS) versus TTD from the UK CAS study, to provide the results of this analysis and then to conduct a cost-effectiveness scenario using these data (clarification question A39). In response, the company stated that the MAIC weights are the same regardless of whether the outcome is TTD or PFS. The company provided the requested cost-effectiveness scenario analysis, and we summarise the results in section 5.2.2.

3.6 Conclusions on the clinical effectiveness evidence

The company's decision problem adequately reflects the NICE scope but focuses on a narrower population. The NICE scope specified a population of patients with advanced SCLC who had had disease progression on or after prior therapy, while the company has focused on patients who have advanced SCLC and who have received platinum-based chemotherapy and at least one other treatment, reflecting the company's proposed

positioning of tarlatamab as a third-line therapy+. The EAG's clinical experts agreed with the company's proposed positioning of tarlatamab and their decision problem population. Our experts confirmed that the company's selected comparators, carboplatin + etoposide, CAV and topotecan, reflect those used in clinical practice at third-line therapy+. The EAG agree with the use of these as a single basket standard of care comparator. The company have not included best supportive care as a comparator, even though this was specified in the NICE scope. One of the EAG's three clinical experts felt it was reasonable to not include best supportive care as a comparator, with the other two not commenting on this. Obtaining further clinical expert opinion about this during the appraisal may be beneficial.

The company identified and included one single-arm trial of tarlatamab in the CS – the DeLLphi-301 trial. The included participants are generally representative of the patients seen in clinical practice and those expected to be treated with tarlatamab (i.e. third-line therapy+ patients with an ECOG performance status of 0 or 1). In an unanchored MAIC analysis, the company compared tarlatamab, using data from DeLLphi-301, to standard of care using a generally representative UK real-world evidence study – the UK CAS study – as the source of data for standard of care. The EAG was satisfied with the selection of these studies as the data sources. The EAG were also satisfied with the covariates selected for inclusion in the analysis.

The unanchored MAIC base case, adjusted-analyses resulted in an OS hazard ratio of 0.367 (95% CIs: 0.202, 0.667), favouring tarlatamab. This represented a [redacted] lower mortality risk for patients treated with tarlatamab versus standard of care. Median OS for tarlatamab in the adjusted-analyses was [redacted] months (95% CIs: [redacted]). Median OS for standard of care was [redacted] months (95% CIs not reported). Additionally, the MAIC base case adjusted-analyses resulted in a PFS hazard ratio of 0.184 (95% CIs: 0.100, 0.340), favouring tarlatamab. Median PFS for tarlatamab in the adjusted-analyses was [redacted] months (95% CIs: [redacted]). Median PFS for standard of care population, using TTD as a proxy for PFS, was [redacted] months (95% CIs: [redacted]). However, in the base case analyses the effective sample size was reduced to [redacted] participants. The OS and PFS estimates from the MAIC were used in the company's economic model. Neurological events and CRS were the most common adverse events of special interest experienced by the participants receiving the 10mg target dose of tarlatamab in Parts 1 and 2 of the DeLLphi-301 trial (experienced by [redacted]% and 49.5% of these 99 participants, respectively).

The EAG have identified the following concerns and uncertainties associated with the OS and PFS estimates (both of which inform the economic model) in the CS:

- No RCT, head-to-head trials of tarlatamab versus the standard of care comparators, carboplatin + etoposide, CAV and topotecan, were identified, so comparative efficacy data are only available from an indirect treatment comparison (i.e. the unanchored MAIC), which is inferior to direct comparative data. Residual systematic error is likely in an unanchored MAIC due to unobserved prognostic variables and effect modifiers.[1]
- Interim data from the tarlatamab DeLLphi-301 trial informed the OS and PFS estimates presented in the CS both from the trial and from the unanchored MAIC. For OS, 57.6% of participants were still alive at the time of analysis and for PFS 25.3% remained on the study without disease progression or death. The results could potentially change when the trial is complete or updated analyses are undertaken.
- There was potential for blinding of the DeLLphi-301 trial independent central review body who assessed disease progression to have been undermined if they were [redacted] which might affect the accuracy of the assessment of the PFS outcome.
- The UK CAS study participants were not representative of the patients currently seen in practice in terms of prior PD-L1 inhibitor treatment. The potential impact of this on the CS MAIC analyses is unknown.
- The unanchored MAIC base case effective sample size was just [redacted] participants, reduced from 97 participants. A greatly reduced effective sample size may make MAIC estimates unreliable.[1]

An additional likely minor point is that there is an unclear risk of selection bias in the patient selection for the UK CAS study due to inconsistency in the reporting of the dates of the diagnosis identification period (the EAG suspects this is an error).

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company conducted a targeted literature search for economic models for interventions used for relapsed SCLC. The inclusion and exclusion criteria are shown in CS Table 28. The searches were conducted in Medline and Embase on April 19 2023 and the search strategy is outlined in CS Appendix G. Six studies were identified and are shown in CS Table 29. One study was from the UK comparing topotecan vs best supportive care and is the Evidence Assessment Group report and economic model for the NICE appraisal of topotecan (TA184).[44] None of the other studies were for tarlatamab.

A search was also undertaken for submissions for SCLC to Health Technology Assessment (HTA) agencies, including NICE, Canada's Drug and Health Technology Agency (CADTH), Pharmaceutical Benefit Advisory Committee (PBAC) and the Institute for Clinical and Economic Review. For relapsed SCLC, one submission was identified for NICE (TA184) for topotecan,[44] one for CADTH (lurbinectedin)[45] and one for PBAC (topotecan).[46] Details of the studies are shown in CS Tables 30-32.

EAG comment

We consider the cost-effectiveness search strategy and review to be reasonable, however the searches are a year out of date so it is unclear if any studies have been missed. The company responded to clarification question B8 that they were not aware of any further studies published in the last year.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

The EAG assessment of the company's economic analysis in relation to the NICE reference case is shown in Table 22.

Table 22 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes (patient only) Carer outcomes are not included.

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on costs	NHS and PSS	Yes, NHS and PSS costs.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes, effectively lifetime (10 years from initial age of [redacted] in base case).
Synthesis of evidence on health effects	Based on systematic review	Yes.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes, EQ-5D data used.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes, from DeLLphi-301 trial.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes. Utilities mapped from EQ-5D-5L to UK 3L values using the Hernández-Alava algorithm.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes.

Source: Table produced by EAG
EAG, External Assessment Group; EQ-5D, European Quality of Life Working Group Health Status Measure 5 Dimensions; NHS, National Health Service; PSS, personal social services; QALY, quality-adjusted life year.

4.2.2 Model structure

4.2.2.1 Overview of the model structure

The company's model structure is described in CS section B.3.2.2. A partitioned survival model was developed in Microsoft Excel with a time horizon of 10 years and a cycle length of one week. The model structure comprises three health states: progression-free, progressed disease, and death. The structure is illustrated in CS Figure 14 (reproduced in Figure 6 below).

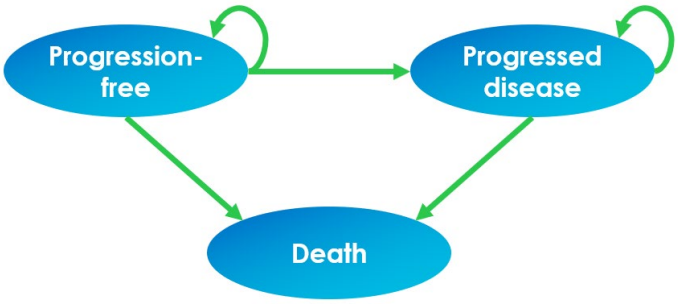

Figure 6 Company economic model structure

Source: Reproduced from CS Figure 14

Patients enter the model in the progression-free health state and are able to transition to the progressed disease or death health states. Patients in the progressed disease health state are only able to remain in the progressed disease state or transition to the death state. The proportion of patients in the progression-free health state is estimated directly from the PFS curves modelled for each comparator, whilst the proportion of patients in the death state at a given time point is calculated using the inverse probability of the OS curve at that time point. The proportion of patients in neither the progression-free nor death health states make up the progressed disease health state. A proportion of patients in the progressed disease state are provided with subsequent treatment; see section 4.2.9.3.3. Costs and QALYs were estimated using the proportion of patients in each of the health states over time. The model ensures that there is consistency between PFS, TTD and OS, such that PFS and TTD remain below OS.

EAG comment on model structure

The company clearly justify their use for a partitioned-survival model using OS and PFS data from the DeLLphi-301 study with parametric survival curves. The EAG

notes that partitioned-survival models were used in previous appraisals for SCLC (TA184 for Topotecan[44] and TA638 for atezolizumab with carboplatin and etoposide[20]). The EAG have no concerns with the model structure used.

4.2.3 Population

The modelled population is described in CS section B.3.2.1. It comprises adult patients with resistant or relapsed SCLC after two or more prior lines of treatment, at least one of which is a platinum-based chemotherapy. The baseline mean age of patients in the model is [redacted] years, and [redacted] of the patients are female; these figures are obtained from the CAS historical control study. The population reflects those patients who are fit enough for treatment with an ECOG performance status of 0 or 1. See section 3.2.1.2 for the EAG's critique of the representativeness of the patient characteristics from the DeLLphi-301 trial of the patients treated in clinical practice.

EAG comment on model population

The population modelled differs from the original NICE scope, as it comprises people who have received two prior treatments, one of which must have been a platinum-based chemotherapy. The EAG consider the focus on this population to be acceptable as it appears to match the clinical evidence provided, and experts we consulted were also in agreement with the population chosen.

4.2.4 Interventions and comparators

The economic model compares the incremental cost-effectiveness of tarlatamab to a basket of treatments as a comparator. Tarlatamab is administered as a 60-minute intravenous (IV) infusion with a step-up dose of 1mg on Cycle 1 Day 1, followed by a 10mg dose on Cycle 1, Day 8, and Day 15, and every two weeks thereafter (Q2W) in a 28-day treatment cycle. Hospitalisation is required for 24 hours post-infusion on Cycle 1 Day 1 and Cycle 1 Day 8. The EAG notes that this differs to the draft SmPC recommendation, which states that [redacted]. In the model, it is assumed that patients stop tarlatamab treatment once their disease has progressed.

The comparator treatment is a basket of treatments comprising the following:

- Cyclophosphamide, doxorubicin and vincristine (CAV) (38%)
- Platinum and etoposide chemotherapy (20%)

- Topotecan (42%)

These treatments and proportions are based upon those in the CAS historical control study (see section 3.3.2 of this report for more information on the CAS study). Seven percent of patients in the CAS study had treatments different from those above and so this proportion was re-allocated among the three treatments (clarification response question B11). CS Table 34 reports the dosing and administration schedule of the treatments in the comparator arm.

EAG comment on intervention and comparators

Clinical experts consulted for this appraisal by the EAG agree that the basket of treatments suggested by the company is an appropriate comparator. The percentage split of treatments is in line with that seen in UK clinical practice, as agreed by our clinical experts. Two of the three experts were also in agreement that tarlatamab administration would cease following disease progression, [redacted]; see section 3.2.1.1 for further information.[17] The EAG do not suggest any changes to the economic base case regarding the intervention or comparators. However, as is stated in section 3.6, obtaining further clinical expert opinion about the relevance of best supportive care as a comparator for tarlatamab may be beneficial (we raise this as an 'other key issue' in section 1.6).

4.2.5 Perspective, time horizon and discounting

The model follows the NHS reference case with respect to the perspective for costing (NHS and Personal Social Services), the time horizon (10 years, effectively lifetime) and discounting (3.5% for costs and health effects).

4.2.6 Treatment effectiveness and extrapolation

The economic model uses parametric curves fit to the observed data for OS, PFS and TTD. The observed survival data are from the DeLLphi-301 trial for tarlatamab and the UK CAS study for standard of care. More details about these studies are given in section 3.

In order to compare tarlatamab with standard of care (SOC), the company conducts a MAIC analysis by applying propensity score weighting to the DeLLphi-301 trial data to balance characteristics of the trial population with those from the UK CAS study. The EAG's description and critique of the MAIC is given in sections 3.3 and 3.4. The Kaplan-Meier curves of the OS and PFS for tarlatamab and standard of care before MAIC weighting are shown in CS Figures 16 and 17 respectively.

In the DeLLPhi-301 trial, [redacted] of 97 patients were allowed to continue treatment with tarlatamab beyond radiologic disease progression. However, the intended marketing authorisation for tarlatamab is for treatment to stop at disease progression. To adjust for this, patients who received tarlatamab post-progression were censored at the time of progression for OS and TTD. The median OS and PFS for tarlatamab before and after adjustment and standard of care are shown in Table 23 (CS Table 36). The Kaplan-Meier curves of OS and PFS for tarlatamab and standard of care after MAIC weighting with adjustment for post-tarlatamab use are shown in CS Figure 18. Clinical advice to the EAG confirmed that the survival estimates for the standard of care arm were reasonable for third-line SCLC patients.

Table 23 Median OS, PFS and OS of tarlatamab and standard of care

Outcomes (months)	Tarlatamab			SOC
	Before weighting	After weighting (without adjustment)	After weighting (with adjustment)	
OS	[redacted]	[redacted]	[redacted]	[redacted]
PFS	[redacted]	[redacted]	[redacted]	[redacted]
TTD	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS Table 36
OS, overall survival; PFS, progression-free survival; SOC, standard of care; TTD, time to treatment discontinuation

The survival data described in the following sections for tarlatamab refers to the data after MAIC weighting and adjustment for post-progression tarlatamab treatment.

4.2.6.1 Overall survival

The company assess whether the proportional hazard assumption holds for OS. Based on the assessment, the proportional hazard assumption did not hold and therefore standard parametric curves were fit to the OS curves for tarlatamab and standard of care separately. The EAG agrees with the company's judgement that the proportional hazard assumption is not supported.

The fitted parametric curves (exponential, Weibull, log-logistic, lognormal, Gompertz, generalised gamma and gamma) compared to the tarlatamab OS trial data are shown in CS Figure 19. The goodness of fit was calculated for Akaike information criterion (AIC) and Bayesian Information criterion (BIC) and are shown in CS Table 39. The extrapolated 1- and

2-year OS outcomes for each of the parametric functions are shown in CS Table 40. Based on the AIC/BIC data, the exponential curve is chosen (lowest AIC/BIC values).

The fitted parametric curves compared to the standard of care OS data are shown in CS Figure 20. The goodness of fit using AIC/BIC was calculated and are shown in CS Table 41. The extrapolated 1- and 2-year OS outcomes for each of the parametric functions are shown in CS Table 42. The CS states that the exponential is chosen for the standard of care arm as the same distribution should be chosen for both arms (NICE DSU 14 guidance [47]). The CS states that the exponential produces higher OS estimates at 1 and 2 years than the observed data and is therefore conservative against tarlatamab. The company chooses the exponential distribution for its base case and provides scenarios for the alternative distributions in CS table 68.

The EAG notes that the company fits the parametric curve to the tarlatamab Kaplan-Meier data and then uses the same curve for standard of care. The EAG prefers to fit the parametric curve to the standard of care data and then use the same curve for the tarlatamab data because the standard of care data are mature and the population is much larger for the standard of care arm (n=540) than the tarlatamab arm (n=[redacted]. Based on visual fit and AIC/BIC statistical fit to the standard of care Kaplan-Meier data, the EAG considers the most appropriate model is the gamma and this model also provides a good fit for the tarlatamab arm. An alternative would be the Weibull distribution. The EAG uses the gamma distribution in our base case in section 6 and the Weibull in a scenario analysis (Table 38). The company and EAG's preferred curves for OS compared to the observed data are shown Figure 7.

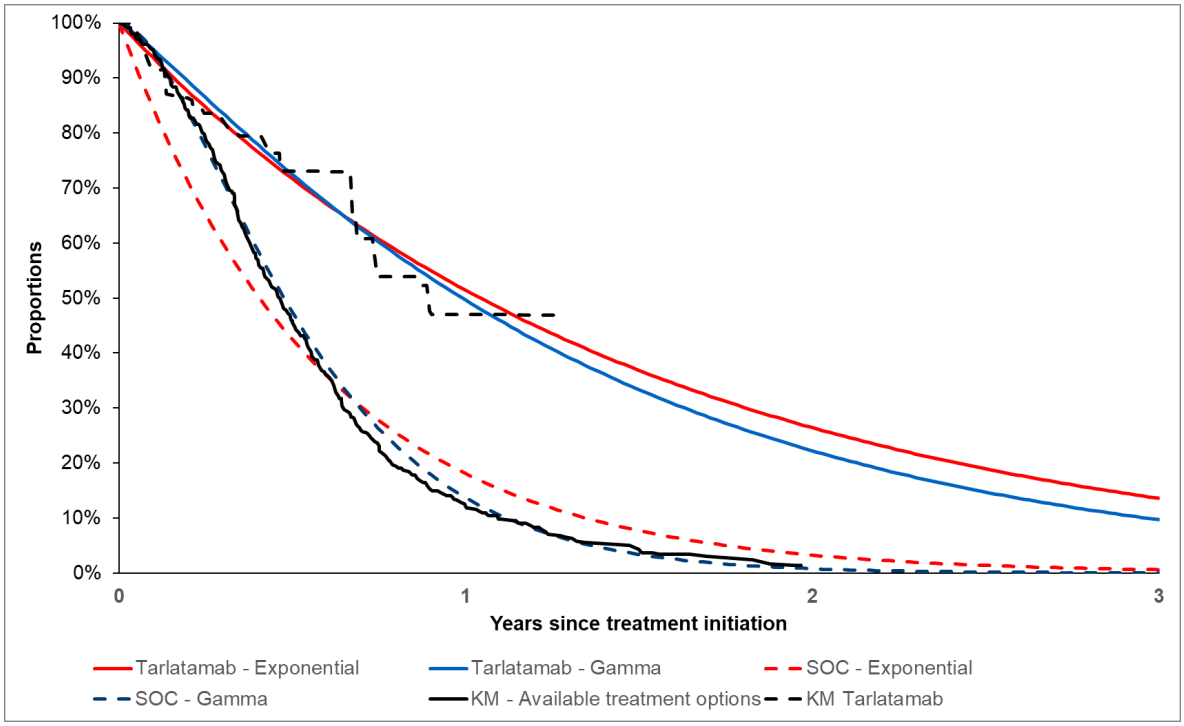

Figure 7 Selected parametric curves versus observed data for tarlatamab and standard of care for OS

Source: EAG created figure

4.2.6.2 Time to treatment discontinuation

The fitted parametric curves (exponential, Weibull, log-logistic, lognormal, Gompertz, generalised gamma and gamma) compared to the tarlatamab TTD trial data are shown in CS Figure 22. The goodness of fit was calculated for AIC and BIC and are shown in CS Table 45. The extrapolated 1 and 2 year TTD outcomes for each of the parametric functions are shown in CS Table 46. The exponential curve is chosen by the company based on this being the most clinically plausible.

The fitted parametric curves compared to the standard of care TTD data are shown in CS Figure 23. The goodness of fit using AIC/BIC was calculated and are shown in CS Table 47. The extrapolated 1 and 2 year TTD outcomes for each of the parametric functions are shown in CS Table 48. The CS states that the exponential is chosen as the same distribution should be chosen for both arms (NICE DSU 14 guidance [47]). The company chooses the exponential distribution for its base case.

The EAG notes that for the tarlatamab arm, all fitted curves for TTD cross the OS or PFS curves except for the exponential. Therefore, we prefer to also use the exponential curve in

our base case. The company and EAG's preferred curves for TTD compared to the observed data are shown in Figure 8.

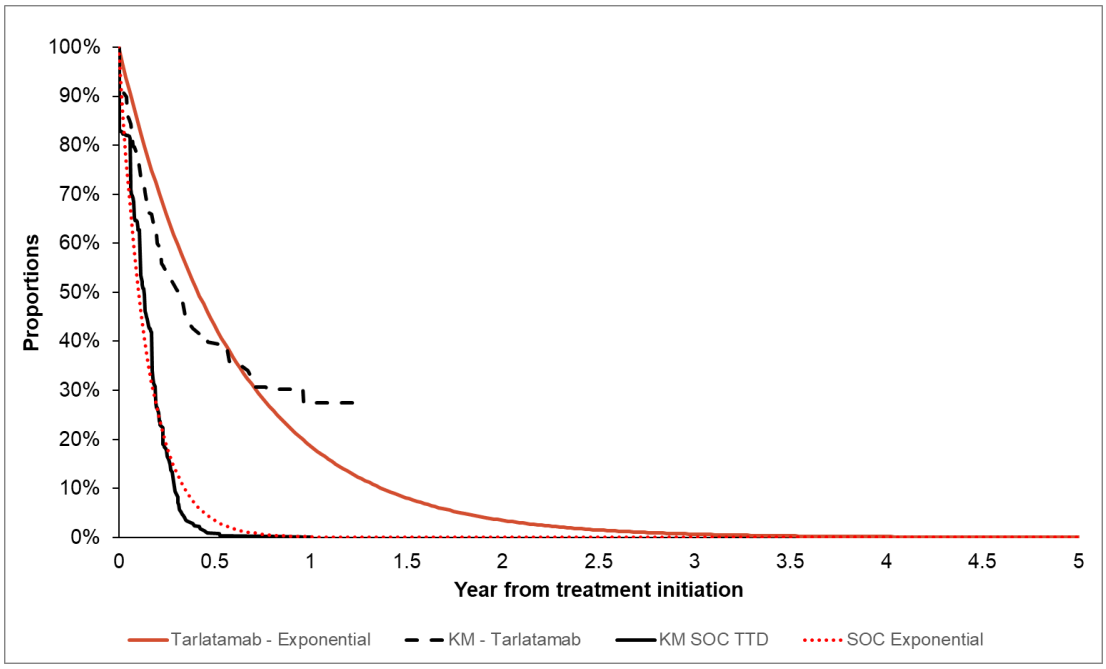

Figure 8 Selected parametric curves versus observed data for tarlatamab and standard of care for TTD

Source: EAG created figure

4.2.6.3 Progression-free survival

PFS was not available from the UK CAS study for the standard of care arm, and therefore the PFS is assumed to be the same as TTD. The company assessed whether the proportional hazard assumption holds for PFS. Based on the assessment, the proportional hazard assumption did not hold and therefore standard parametric curves were fit to the PFS curves for tarlatamab and standard of care separately. The EAG agrees with the company's judgement that the PH assumption is not supported.

The fitted parametric curves compared to the tarlatamab PFS trial data are shown in CS Figure 21. The goodness of fit was calculated for AIC and BIC and are shown in CS Table 43. The extrapolated 1- and 2-year PFS outcomes for each of the parametric functions are shown in CS Table 44. Based on the AIC/BIC data, the log-normal was chosen (lowest AIC/BIC values).

For the standard of care arm, as the PFS is assumed to be the same as the TTD, the exponential distribution is used.

We note that the distributions used for PFS are different between arms, and this is contrary to the advice provided in NICE DSU 14.[47] We therefore prefer to use the exponential distribution for both treatment arms.

EAG comment on treatment effectiveness and extrapolation

For OS, the company uses the exponential curve fitted to the observed data for both tarlatamab and standard of care. The EAG considers the gamma curve provides a better fit to the standard of care arm and prefers to use this curve for both treatments. We agree with the company's choice for modelling TTD. For PFS, the company uses the log-normal for the tarlatamab arm. For consistency between arms, we prefer to use the exponential curve for both the tarlatamab and standard of care arms.

4.2.7 Adverse events

Adverse events with grade ≥ 3 are included in the economic model for both arms. The frequency of serious adverse events is reported in CS Table 50 and included events such as anaemia, diarrhoea and febrile neutropenia. In addition, grade 1/2 CRS and grade 1/2 ICANS are included as these are specific to tarlatamab and its mode of action. [redacted] of patients had a CRS and [redacted] had an ICANS. Disutilities and costs were applied for each adverse event, reported below in sections 4.2.8.2 and 4.2.9. The duration of the adverse event is assumed to be 28 days for the serious adverse events and four days for grade 1/2 CRS and ICANS events.

We note that the adverse events for CAV were 0% for several AEs (e.g. diarrhoea, febrile neutropenia, lymphopenia, non-sepsis infection). Clinical advice to the EAG suggest that some of these AEs may have been underestimated, such as febrile neutropenia and diarrhoea. We conducted a scenario assuming the frequency of AEs for diarrhoea and febrile neutropenia was the average of that for topotecan and platinum-based chemotherapy (Table 38).

4.2.8 Health-related quality of life

4.2.8.1 Systematic literature review for utilities

The company conducted a systematic literature review of existing HRQoL studies, detailing the search and findings in CS Appendix H. The original search was conducted on 9th May

2022, with an updated search on 19th December 2023. The inclusion criteria are shown in CS Appendix H Table 37, with the main element being patients with small-cell lung cancer with disease progression on or after two lines of therapy. Two studies were identified and reported in CS Appendix H Table 38, however no references were provided for these texts and the EAG were unable to locate them. The EAG looked for further studies and found informative non-small-cell lung cancer papers. Clinical experts consulted on this appraisal agreed that non-small-cell lung cancer was a suitable proxy for small-cell lung cancer for HRQoL. A study performed by Chouaid et al.[48] comprised 263 patients in 25 hospitals internationally, with the EQ-5D questionnaire used to capture HRQoL, and a publication by Nafees et al. 2008[49] elicited UK utility values from 100 participants using a standard gamble approach.

4.2.8.2 Health state utility values used in the economic model

Health state utility values in the economic model were based upon EQ-5D-5L data collected in the DeLLphi-301 trial. These EQ-5D-5L utilities were mapped to European Quality of Life Working Group Health Status Measure 5 Dimension, 3 level (EQ-5D-3L) utility scores using the mapping algorithm by Hernandez-Alava,[50] and an age and sex-related utility adjustment was also applied to the health state utilities using general population utility values. The company developed a mixed-effects model to account for the repeated and longitudinal data collected in the DeLLphi-301 trial. The same utilities are assumed for both tarlatamab and standard of care arms in each health state; the death state is assumed to have a utility of zero. Table 24 below reports the health state utilities implemented in the model. The utilities implemented in the company model are derived from the entire DeLLphi-301 population, rather than the MAIC population (n=[redacted]); the utilities appear to be more favourable given the status of the patient population receiving third-line treatment compared with similar populations with NSCLC. Therefore, the EAG have used non-small-cell lung cancer as a proxy and have used utilities from Chouaid et al.[48] in the EAG base case. A scenario analysis using utilities from Nafees et al. 2008[49] is also performed in section 6.3.1.

Table 24 Model estimates on EQ-5D-3L utility scores in the DeLLphi-301 trial

Health states	N patients	N assessments	Mixed effects model		EAG base case (Chouaid et al. [48])
			Mean	SE	
Before treatment	[redacted]	[redacted]	[redacted]	[redacted]	-
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]	0.62

Health states	N patients	N assessments	Mixed effects model		EAG base case (Chouaid et al. [48])
			Mean	SE	
Post-progression	[redacted]	[redacted]	[redacted]	[redacted]	0.47

Source: Reproduced from CS Table 49
EQ-5D-3L, European Quality of Life Working Group Health Status Measure 5 Dimensions, 3 levels; SE, standard error.

4.2.8.2.1 Adverse event disutilities

The company's economic model includes disutilities for grade 3+ for adverse events occurring in greater than 3% of patients in either treatment arm. These disutilities, based on the literature and assumptions, were assumed to last 28 days, and are reported in CS Table 51. The model also included disutilities for grade 1 and 2 CRS and ICANS, which were assumed to be equivalent to the maximum disutility of the adverse events and last 4 days. The EAG notes that the disutility for neutropenia from Sullivan et al[51] is reported incorrectly in CS Table 51; the correct disutility is -0.09. Table 25 below presents the utilities and disutilities used in the company model.

Table 25 Adverse event disutilities used in the revised company model

Adverse event disutilities	Value	Reference
Anaemia	-0.02	Sullivan et al. 2011[51]
Diarrhoea	-0.05	Nafees et al. 2008[49]
Fatigue	-0.07	
Febrile neutropenia	-0.09	
Leukopenia	-0.04	Sullivan et al. 2011[51]
Lymphocyte count decreased	-0.01	
Lymphopenia	-0.07	
Nausea	-0.05	Nafees et al. 2008[49]
Neutropenia	-0.09	Sullivan et al. 2011[51]
Neutrophil count decreased	-0.07	
Non-sepsis infection	-0.22	Stein et al. 2018[52]
Thrombocytopenia	-0.07	Sullivan et al. 2011[51]
CRS and ICANS disutilities		
CRS	-0.22	Assumed the same as maximum adverse event disutility
ICANS	-0.22	

Source: Reproduced from CS Table 51

CRS, cytokine release syndrome; ICANS, immune effector cell associated neurotoxicity syndrome.

EAG comment on HRQoL

Published literature for patient populations with NSCLC suggests that the baseline utility for patients in the progression free and progressed disease health states should be lower than those reported by the company. The company have used the entire DeLLphi-301 population (n=97) to inform baseline utilities, rather than the population used in the MAIC (n=[redacted]) which would better match the standard of care population. The EAG were unable to find well conducted studies for health state utilities for SCLC, and have therefore opted to use non-small-cell lung cancer as a proxy to inform baseline health state utilities in the EAG base case, which was deemed suitable by clinical experts consulted on this appraisal.

4.2.9 Resources and costs

4.2.9.1 Drug acquisition

CS Table 52 reports the dosing schedule and costs of drugs used in the model. The cost for tarlatamab used in the model is [redacted] per 10mg vial and [redacted] per 1mg vial. These prices are using the current Patient Access Scheme (PAS) discount. The DeLLphi-301 study informed the dosing schedule of tarlatamab, and the model incorporates pre-treatment with dexamethasone on day 1 and day 8 of the 1st cycle only. For standard of care, costs were obtained from the British National Formulary (BNF) and the drugs and pharmaceutical electronic market information tool (eMIT).[53,54] The EAG notes that the costs reported in the company submission for dexamethasone, carboplatin, etoposide, cyclophosphamide, doxorubicin and vincristine, all obtained from eMIT, were incorrect. Following clarification question B12, the company updated the economic model with the current prices. Table 26 below reports the prices used in the revised company model.

The company selected a cost of £7.50 per 0.25mg capsule of topotecan from the BNF. However, as the dose is 2.3mg/m^2 and the average body surface area of patients is 1.78m^2, the average dose would be 4.094mg. Therefore, it is more suitable to use 4 x 1mg capsules, rather than 16 x 0.25mg. The EAG have included this change in cost and capsule size as an EAG correction in section 5.3.3.

Table 26 Drug costs and dosing schedule used in the revised company model

Treatment	Admin Route	Dosing	Price	Reference
Tarlatamab				
Dexamethasone	IV	8mg on days 1 and 8 of cycle 1	£0.38 /6.60mg vial	DeLLphi-301 trial[24], eMIT[54]
Tarlatamab	IV	1mg on cycle 1 day 1, 10mg target dose on cycle 1 day 8 and day 15, Q2W thereafter in a 28-day cycle	[redacted]/10mg vial, [redacted]/1mg vial	DeLLphi-301 trial[24]
Topotecan				
Topotecan	Oral	2.30mg/m^2/d, 5 consecutive days every 21 days	£7.50/0.25mg capsule £36 /1 mg capsule	TA184[44], BNF[53]
Carboplatin + etoposide chemotherapy				
Carboplatin	IV	5mg/mL/min, on day 1 of each 21-day cycle	£48.09/450mg vial	Mansfield et al. 2020[55], eMIT[54]
Etoposide	IV	100mg/m^2, on days 1, 2, and 3 of each 21-day cycle	£13.40/500mg vial	
CAV				
Cyclophosphamide	IV	1000mg/m^2, on day 1 of 21-day cycle	£13.14/1000mg vial	Aix et al. 2023[56], eMIT[54]
Doxorubicin	IV	45mg/m^2, on day 1 of 21-day cycle	£15.98/200mg vial	

Treatment	Admin Route	Dosing	Price	Reference
Vincristine	IV	2mg, on day 1 of 21-day cycle	£6.64/2mg vial	

Source: Reproduced from CS Table 52
BNF, British National Formulary; IV, intravenous; CAV, cyclophosphamide, doxorubicin and vincristine; eMIT, electronic market information tool; min, minute; Q2W, once every 2 weeks.

4.2.9.2 Drug administration

The CS reports the drug administration costs for oral chemotherapy (topotecan) and intravenous chemotherapy (carboplatin + etoposide and CAV) in CS Table 53. Costs were obtained from the NHS England Payment Scheme 23/24.[57] The company assumed that the administration cost of dexamethasone and tarlatamab were equivalent to the cost of a simple IV chemotherapy. In the DeLLphi-301 trial, patients on tarlatamab were hospitalised for 24 hours following the tarlatamab infusion on days 1 and 8 of cycle 1. This incurred an additional cost of £488 which was included as an administration cost in the model. The EAG notes that the cost for oral chemotherapy provided in the CS was incorrect; the reported cost was £27.40, whilst the correct cost is £137. The company rectified the model in response to clarification question B3. Topotecan oral medication is provided to patients to take at home. The EAG notes that the topotecan administration in the model is incorrect, as it is applied five times per cycle rather than once. The EAG have made this change in the model as an EAG correction; see section 5.3.3. Table 27 reports the administration costs included in the company base case model.

Table 27 Drug administration costs used in the revised company model

Administration	Unit cost	Reference
Oral chemotherapy	£137	NHS England Payment Scheme 23/24 prices: Unbundled chemotherapy delivery SB11Z- Deliver exclusively oral chemotherapy[57]
IV chemotherapy (first attendance)	£172	NHS England Payment Scheme 23/24 prices: Unbundled chemotherapy delivery SB12Z- Deliver simple Parenteral Chemotherapy at first attendance[57]
IV chemotherapy (first administration of cisplatin etoposide	£515	NHS England Payment Scheme 23/24 prices: Unbundled chemotherapy delivery SB14Z- Deliver Complex Chemotherapy, including Prolonged infusional Treatment, at First Attendance[57]

Administration	Unit cost	Reference
IV chemotherapy (subsequent attendance)	£343	NHS England Payment Scheme 23/24 prices: Unbundled chemotherapy delivery SB15Z- Deliver subsequent elements of a chemotherapy cycle[57]
Required hospitalisation for 24 hours post-tarlatamab	£488	NHS England Payment Scheme 23/24 prices: Healthcare resource group (HRG) WH16A observation or counselling with CC score1+[57]

Source: Reproduced from CS Table 53 with oral chemotherapy cost corrected by the company
IV, intravenous.

4.2.9.3 Resource use

4.2.9.3.1 Medical resource use and monitoring costs

The medical resource use (MRU) and monitoring frequency and costs for patients receiving tarlatamab or standard of care was taken from the NICE submission for atezolizumab (TA638).[20] The costs and frequencies were assumed to be the same for both treatment arms and are applied until progression. CS Table 54 reports the MRU costs and frequencies, whilst CS Table 55 presents the monitoring and test costs and frequencies. Unit costs were acquired from the NHS England Payment Scheme 23/24,[57] PSSRU 2022,[58] and the NHS Schedule of Reference Costs 2011/22.[59] All frequencies were obtained from the NICE submission for atezolizumab (TA638).[20] Costs were inflated to 2023 values where required.[58] The CS originally applied MRU and monitoring costs to patients in the progression-free health state only. However, a proportion of patients in the progressed disease health state are on subsequent treatment (CS Table 58) and would incur additional resource use and monitoring costs. The EAG raised this issue in clarification question B7, and the company updated the economic model to incorporate MRU and monitoring costs for those patients in the progressed disease health state. Table 28 below presents the MRU and monitoring costs and frequencies used in the company's base case model.

The EAG notes that there are no additional costs for patients in the progressed disease state who are not on subsequent treatment. Clinical experts agree that these patients would still receive basic monitoring and therefore incur health care costs. However, the EAG consider that excluding these costs are not likely to have a significant impact on the model results. Further some of these costs may be included in the terminal care costs. Clinical advice to the EAG suggested that patients not on treatment would receive 0.1 hospital visits /week, 0.25 GP visits / week and 0.5 community nurse visits / week. We have used these values in a scenario in section 6.3.1.

Clinical experts consulted by the EAG suggest that the frequency of blood tests should be higher than those used by the company (0.13/week). As a result, the EAG have amended the frequency as an EAG correction to match that of outpatient visits, at 0.29 blood tests per week; see section 6.3.

Table 28 Medical resource use and monitoring used in the revised company model

Resource	Unit cost	Frequency/week	
Outpatient visit	£141	0.29	NICE submission for atezolizumab (TA638)[20]
GP visit – surgery	£42	0.06	
GP visit – home	£90	0.05	
Cancer nurse visit	£56	0.07	
Community nurse visit	£85	0.04	
Electrocardiogram	£134	0.01	
Chest X-ray	£29	0.11	
CT scan unit cost	£99	0.09	
Brain MRI unit cost	£209	0.01	
Blood test unit cost	£3	0.13	

Source: Reproduced from CS Table 54 and CS Table 55
GP, general practitioner; CT, computed tomography; MRI, magnetic resonance imaging

4.2.9.3.2 Adverse event costs

The company economic model includes costs for grade 3+ adverse events occurring in greater than 3% of patients in either treatment arm, as well as those for grades 1 or 2 CRS and ICANS. Unit costs per adverse event were acquired from NHS England Payment Scheme 23/24,[57] and costs for CRS and ICANS were obtained from the DeLLphi-301 trial,[24] the BNF,[53] and the NHS Reference Costs 2021/22,[59] inflated to 2023 prices.[58] For almost all adverse events where multiple potential HRG codes could apply, the company selected the most expensive HRG code. However, as the same set of HRG codes applied for febrile neutropenia and leukopenia, the company chose the most expensive cost for the former (SA08G) and the least expensive for the latter (SA08H). The cost per cycle was calculated based on the trial duration and the proportion of patients with adverse events.

The management cost per case of CRS comprised one dose of tocilizumab for 10% of patients and hospitalisation for 53% of patients (see CS Table 57). The EAG noted that the costs provided in CS Table 56 for adverse events are incorrect; the company acknowledged that the costs in the CS are incorrect, but that the costs in the company model are correct

with the exception of nausea, following clarification question B1. The EAG preferred choice of adverse event costs is to use a weighted average across all severity of complication levels available. We also consider the choice of HRG code for febrile neutropenia chosen by company to be unsuitable; instead, we have matched the cost for febrile neutropenia to non-sepsis infection. The EAG base case costs for adverse events are presented in Table 29 below.

Table 29 Adverse event costs used in the EAG base case model

Parameter	HRG code	EAG costs	Description	Reference
Anaemia	SA01G-SA01K	£2,055	Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, CC score 0-8+	NHS Reference Costs 2021/22[59], NHS Cost Inflation Index[58]
Diarrhoea	FD01E-FD01H	£3,689	Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, CC score 0-9+	
Fatigue	SA01G-SA01K	£2,055	Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, CC score 0-8+	
Febrile neutropenia	WH07C-WH07D	£5,071	Infections or Other Complications of Procedures, with Single Intervention, CC score 0-2+	
Leukopenia	SA08G-SA08J	£1,392	Other Haematological or Splenic Disorders, CC score 0-6+	
Lymphocyte count decreased	800	£303	Clinical Oncology Service	
Lymphopenia	SA08G-SA08J	£1,392	Other Haematological or Splenic Disorders, CC score 0-6+	
Nausea	800	£303	Clinical Oncology Service	

Parameter	HRG code	EAG costs	Description	Reference
Neutropenia	SA08G-SA08J	£1,392	Other Haematological or Splenic Disorders, CC score 0-6+	
Neutrophil count decreased	800	£303	Clinical Oncology Service	
Non-sepsis infection	WH07C-WH07D	£5,071	Infections or Other Complications of Procedures, with Single Intervention, CC score 0-2+	
Thrombocytopenia	SA12G-SA12K	£1013	Thrombocytopenia, CC score 0-8+	

Source: Partly reproduced from CS Table 56 and company economic model
CRS, cytokine release syndrome; EAG, External Assessment Group; HRG, Healthcare Resource Group; ICANS, immune effector cell-associated neurotoxicity syndrome; NHS, National Health Service

4.2.9.3.3 Subsequent treatment costs

A proportion of patients in the progressed disease health state were assumed to receive subsequent treatments and the remainder received no further treatment. The proportion of patients and the distribution of treatments were sourced from the DeLLphi-301 trial and the UK CAS natural history study for tarlatamab and standard of care, respectively. CS Table 58 presents the subsequent treatment distributions implemented in the company's economic model; this has been reproduced in Table 30 below. Clinical advice to the EAG confirmed that most patients would have no further treatment and that the subsequent treatment distribution for those patients who do receive further treatment was reasonable. Patients not on subsequent treatment may also incur monitoring costs in the progressed disease state, which have not been explicitly modelled by the company. However, these costs may be included in end-of-life costs; therefore, the EAG have included this as a scenario in section 6.3.1.

Table 30 Subsequent treatment distribution in the revised company model

Treatment	Duration (weeks)	Proportion post-tarlatamab	Proportion post-standard of care	Source
Topotecan	[redacted]	[redacted]	[redacted]	

Treatment	Duration (weeks)	Proportion post-tarlatamab	Proportion post-standard of care	Source
Clinical trials	[redacted]	[redacted]	[redacted]	UK CAS natural history study[60], DeLLphi-301 trial[24]
Platinum-based regimen	[redacted]	[redacted]	[redacted]	
CAV	[redacted]	[redacted]	[redacted]	
No treatment	[redacted]	[redacted]	[redacted]	

Source: Reproduced from CS Table 58
CAV, cyclophosphamide, doxorubicin and vincristine; SOC, standard of care

4.2.9.3.4 End of life costs

The company implemented an end-of-life cost of £8,408, applied when a patient transitions to the death state.[61]

EAG comment on resources and costs

The EAG has made changes to the economic model for dosing and administration frequency of topotecan.

For adverse events, the company selected costs corresponding to the highest CC score from the NHS England Payment scheme. The EAG prefer to have a weighted average approach across all CC scores; this has been implemented in the EAG base case model.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company's base case results are shown in CS Table 64 with an incremental cost-effectiveness ratio (ICER) of £35,012 per QALY for tarlatamab versus standard of care for patients with previously treated advanced SCLC. This and all other cost effectiveness results in this report are conducted with a confidential PAS price discount for tarlatamab of [redacted]. The results are also shown with a severity multiplier of 1.7 which is applied to the incremental QALYs (see section 7). In response to the EAG's clarification questions, the company corrected the following input parameters in a revised base case:

- Adverse event costs of nausea of £303 instead of £313 (clarification question B1),
- Administration cost for oral chemotherapy of £137 instead of £27.40 (clarification question B3),
- Medical resource use and monitoring costs for patients receiving subsequent therapy (clarification question B7),
- Comparator drug costs taken from eMIT (clarification question B12), see table below.
- The EAG notes that the company also reduced the frequency of CRS / ICANS adverse events to zero in the model. We have corrected this is in the model, see section 5.3.3.

Table 31 Corrected comparator drug costs from eMIT

Drug/ dose/ unit	Price in submission appendix K (per vial)	Price in EMIT accessed May 2024 (per vial)
Carboplatin 450 mg vial	£14.69	£48.09
Etoposide 500mg vial	£10.69	£13.40
Cyclophosphamide 1g vial	£12.96	£13.14
Doxorubicin 200mg vial	£17.18	£15.98
Vincristine 2mg vial	£6.78	£6.64
Dexamethasone 6.60mg vial	£4.84	£0.375

Source: Clarification question B12

The revised base case results are shown in Table 32. The ICER for tarlatamab vs standard of care is £33,785 per QALY.

Table 32 Company revised base case after clarification response

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER with severity modifier (£/QALY)	ICER without severity modifier (£/QALY)
Standard of care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Tarlatamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,785	£57,434

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year

5.2 Company's sensitivity analyses

5.2.1 Deterministic sensitivity analyses

The CS reports deterministic sensitivity analyses in section B.3.9.2 using the company's original model. Parameters were varied by +/- 20% of the deterministic point estimate for each parameter. The top 10 most influential variables were then plotted in a tornado diagram (CS Figure 29). The three most influential parameters were the utility value for tarlatamab patients who are progression-free, the relative dose intensity for tarlatamab and the unit cost for tarlatamab. The EAG notes that the results are shown without the severity multiplier and the results vary between £47,158 and £76,556 per QALY. Most parameters have been included in the deterministic sensitivity analyses. Adverse event frequency for patients on topotecan, adverse event duration and proportions on standard of care treatments were not included.

5.2.2 Scenario analysis

The list of the company's 18 scenarios and the rationale for including them are shown in CS Table 67. These include scenarios for the following:

- Discount rate,
- Time horizon,
- OS distribution,
- Utility,
- standard of care composition,
- Post-infusion costs,
- Impacts of CRS and ICANS,
- Post-progression tarlatamab use
- Vial wastage.

The results of the scenario analyses are shown in CS Table 68 using the company's original model. All scenarios were conducted probabilistically using 5000 iterations. The scenario ICERs ranged from £13,810 (OS distribution selection: generalised gamma) to £44,433 per QALY (No adjustment for post-progression tarlatamab use). The EAG has conducted these scenarios using the company's revised model and the results are shown in Table 36.

The company also conducted scenario analyses using their revised model following clarification questions A37-39. These scenarios are omitting sex and age at diagnosis from the MAIC (A37), including only the three prognostic factors considered to be the most important by the clinicians consulted by the company (A38) and using TTD instead of PFS from the DeLLphi-301 trial (A39). The cost effectiveness of tarlatamab versus standard of

care reduced to £23,290 for clarification question A37, £21,328 for clarification question A38, £33,168 per QALY for clarification question A39 respectively.

5.2.3 Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA) with input parameters and distributions detailed in CS Table 62. The PSA was run for 5000 iterations. The standard errors for the parameters were taken, where possible, from the parameters' data source or else the standard error of the parameter was assumed to equal 20% of the mean value. Most parameters have been included in the PSA and the EAG considers that the distributions used are reasonable. Adverse event frequency for patients on topotecan, comparator unit costs were not included. The cost-effectiveness plane and cost-effectiveness acceptability curve using the company original model are shown in CS Figure 27 and Figure 28 respectively. The probabilistic results, shown in Table 33 below (CS Table 64), were in line with the deterministic results. Tarlatamab was associated with 36.4% probability of being cost-effective versus standard of care assuming a willingness-to-pay of £30,000 and including the severity modifier of 1.7.

Table 33 Base case results (probabilistic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Standard of care	[redacted]	[redacted]	[redacted]	[redacted]	-
Tarlatamab	[redacted]	[redacted]	[redacted]	[redacted]	£34,507

Source: EAG created table
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year..
Results include 1.7 severity multiplier applied to QALYs.

5.3 Model validation and face validity check

5.3.1 Company validation

The CS does not give any details of the technical checks conducted by the company to ensure the accuracy of the model.

The company discussed validation of the model by considering the survival extrapolation of the model compared to the observed data for tarlatamab and standard of care in CS section 3.12.1. The comparisons between the fitted curves against the observed data are shown in

CS Figure 30 and 31. The CS states that the predicted curves fitted the observed data well. The EAG provides a detailed critique of the fitted survival curves in section 4.2.6 above.

5.3.2 EAG validation

We conducted a range of checks on the company's model using an EAG checklist:

- Input checks: comparison of all parameter values in the model against the values stated in the CS and cited sources.
- Output checks: replication of results reported in the CS using the company model.
- 'White box' checks: manual checking of formulae which includes reviewing the calculations across each cycle and working backwards to trace links to input parameters and forwards to the results.
- 'Black box' checks: working through a list of tests to assess whether changes to key model inputs or assumptions have the expected effects on the model results.

5.3.3 Corrections to the company model

The EAG corrected the costs for topotecan and the administration costs for topotecan, as described in section 4.2.9.1. In addition, we increased the frequency of blood tests so this would be the same as the frequency of outpatient visits. The EAG notes that the company also reduced the frequency of CRS / ICANS adverse events to zero in the revised company model. We have corrected this is in the model.

The corrected model results are shown in Table 34. The corrected revised company model gives an ICER of £34,958 per QALY for tarlatamab vs standard of care.

Table 34 EAG corrections to the company revised base case model

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER with severity modifier (£/QALY)	ICER without severity modifier (£/QALY)
Standard of care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Tarlatamab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,958	£59,429

Source: EAG created table
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

5.3.4 EAG summary of key issues and additional analyses

A full summary of EAG observations on key aspects of the company's economic model is presented in Table 35.

Table 35 EAG observations of the key aspects of the company's economic model

Parameter	Company base case	EAG comment	EAG base case
Model structure			
Model structure	Partitioned survival model with states for PFS, PD and OS	We agree	No change
Population	Section 4.2.3	We agree	No change
Comparators	Standard of care (section 4.2.4)	We agree	No change
Perspective	NHS and PSS	We agree	No change
Time horizon	Lifetime	We agree	No change
Discounting	3.5% for costs and outcomes	We agree	No change
Survival curves			
OS	Exponential distribution for tarlatamab and SOC arms	We consider gamma distribution provides better fit to SOC (section 4.2.6.1)	Gamma distribution for tarlatamab and SOC arms
PFS	Lognormal distribution for the tarlatamab arm and exponential distribution for the SOC arm	We consider the same distribution should be used for both arms (section 4.2.6.3)	Exponential arm for both treatment arms.
TTD	Exponential distribution for tarlatamab and SOC arms	We agree	No change
Adverse events			
Frequency of adverse events	CS Table 50	We agree	No change
Utilities			
Patient utilities	Section 4.2.8.2	We consider the utility values not to be generalisability to patients receiving third line treatment.	We use the utility values from Chouaid et al. in patients with NSCL.

Parameter	Company base case	EAG comment	EAG base case
AEs disutilities	Section 4.2.8.2	We agree	No change
Severity modifier	Severity modifier of 1.7 used	We agree	No change
Resource use and costs			
Drug acquisition and administration	Section 4.2.9	We agree	No change
Healthcare resource use	Section 4.2.9.3	We agree	No change
Adverse event costs	Section 4.2.9	The adverse event costs were chosen for the most severe complication level.	We use adverse events costs calculated using the weighted average of complication severity.

Source: EAG created table
AE, adverse events; EAG, External Assessment Group; NHS, National Health Service; NICE, The National Institute for Health and Care Excellence; PSS, Personal Social Services; SOC, standard of care.

6 EAG'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

The EAG repeated the company scenario analyses using the revised version of the model submitted with their clarification response. The results are shown in Table 36. The results are most sensitive to changes in the distributions fitted to the OS curves which vary between £21,665 (lognormal) and £45,030 per QALY (Gompertz).

Table 36 Company scenarios with revised version of the company model, including PAS for tarlatamab

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company revised base case	[redacted]	[redacted]	£33,785
Set costs and discount rates to 1.5%	[redacted]	[redacted]	£33,078
Set costs and discount rates to 5%	[redacted]	[redacted]	£34,303
Time horizon 5 years	[redacted]	[redacted]	£35,280
Time horizon 15 years	[redacted]	[redacted]	£33,743
OS distribution selection: Weibull	[redacted]	[redacted]	£40,449
OS distribution selection: lognormal	[redacted]	[redacted]	£21,665
OS distribution selection: log-logistic	[redacted]	[redacted]	£23,778
OS distribution selection: Gompertz	[redacted]	[redacted]	£45,030
OS distribution selection: generalised gamma	[redacted]	[redacted]	£16,664
OS distribution selection: gamma	[redacted]	[redacted]	£39,074
Treatment-specific health state utility values used in the PFS state	[redacted]	[redacted]	£33,011
SOC composition: all patients received topotecan	[redacted]	[redacted]	£32,300
SOC composition: all patients received CAV	[redacted]	[redacted]	£34,983
SOC composition: all patients received platinum-based chemotherapy	[redacted]	[redacted]	£34,631
Do not consider post-infusion hospitalisation costs for tarlatamab	[redacted]	[redacted]	£32,935

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
Do not consider impacts of CRS and ICANS	[redacted]	[redacted]	£33,785
Do not adjust tarlatamab OS and TTD for post-progression tarlatamab use	[redacted]	[redacted]	£43,548
Do not consider vial wastage	[redacted]	[redacted]	£33,849

Source: From company model; includes severity multiplier of 1.7.
CAV, cyclophosphamide, doxorubicin and vincristine; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ICER, incremental cost-effectiveness ratio; OS, overall survival; SOC, standard of care.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

6.3 EAG's preferred assumptions

Based on the EAG critique of the company's model discussed in Table 35, we have identified several key aspects of the company base case with which we disagree. Our preferred model assumptions are the following:

- Overall survival: use gamma distribution for tarlatamab and standard of care arms, instead of exponential distribution (section 4.2.6.1)
- Progression-free survival: use exponential distribution for tarlatamab arm, instead of lognormal for the tarlatamab arm (section 4.2.6.3)
- Health-related quality of life: use Chouaid et al. instead of DeLLphi-301 study (section 4.2.8.2),
- Adverse event costs: EAG recalculated values (section 4.2.9.3.2).

The EAG base case results are shown in Table 37 using the EAG's preferred assumptions. When using these assumptions, the ICER increases to £58,847 per QALY for tarlatamab vs standard of care. The model results are most sensitive to using the gamma distribution for OS and changing the source of the HRQoL values.

Table 37 EAG's preferred model assumptions: cumulative impact (deterministic) with PAS for tarlatamab

Preferred assumption	Treatment	Total costs	Total QALYs	Cumulative ICER £/QALY
EAG corrected company base-case model	SOC	[redacted]	[redacted]	
	Tarlatamab	[redacted]	[redacted]	£34,958
+ OS: gamma for both arms	SOC	[redacted]	[redacted]	
	Tarlatamab	[redacted]	[redacted]	£40,442
+ PFS: exponential for both arms	SOC	[redacted]	[redacted]	
	Tarlatamab	[redacted]	[redacted]	£42,045
+ HRQoL: use Chouaid et al. (PFS 0.62; PD 0.47)	SOC	[redacted]	[redacted]	
	Tarlatamab	[redacted]	[redacted]	£55,097
+ Adverse event costs: EAG recalculated.	SOC	[redacted]	[redacted]	
	Tarlatamab	[redacted]	[redacted]	£58,847
EAG base case	SOC	[redacted]	[redacted]	
	Tarlatamab	[redacted]	[redacted]	£58,847

Source: EAG created table
EAG, evidence assessment group; OS, overall survival; PFS, progression-free survival; HRQoL, health-related quality of life; PD, progressed disease.
Severity multiplier of 1.7 applied to incremental QALYs.

6.3.1 EAG scenario analyses

We performed a range of scenario analyses with the EAG base case to analyse the impact of changing some model assumptions on the final cost-effectiveness results. Table 38 below summarises the results of the scenario analyses on the EAG base case. The following scenarios were conducted:

- Selection of the company's scenario analyses (CS Table 68)
- Alternative QoL values from Nafees et al. (PFS 0.653, PD 0.473)
- Clarification questions A37 (MAIC omitting age and sex) and A38 (MAIC with 3 main prognostic factors).
- Alternative values for AEs for CAV for diarrhoea and febrile neutropenia
- Health care resource costs for patients with progressed disease not on treatment (0.1 hospital visits /week, 0.25 GP home visits / week and 0.5 community nurse visits / week).

The ICERs for the scenarios varied between £26,162 (OS distribution selection: generalised gamma) and £69,309 per QALY (Do not adjust tarlatamab OS and TTD for post-progression tarlatamab use).

Table 38 EAG's scenario analyses with PAS for tarlatamab

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
EAG base case	[redacted]	[redacted]	£58,847
Company scenarios (CS 67-68)			
Set costs and discount rates to 1.5%	[redacted]	[redacted]	£57,898
Set costs and discount rates to 5%	[redacted]	[redacted]	£59,545
Time horizon 5 years	[redacted]	[redacted]	£59,764
Time horizon 15 years	[redacted]	[redacted]	£58,837
OS distribution selection: Weibull	[redacted]	[redacted]	£60,640
OS distribution selection: lognormal	[redacted]	[redacted]	£33,767
OS distribution selection: log-logistic	[redacted]	[redacted]	£36,959
OS distribution selection: Gompertz	[redacted]	[redacted]	£66,338
OS distribution selection: generalised gamma	[redacted]	[redacted]	£26,162
OS distribution selection: exponential	[redacted]	[redacted]	£51,592
Treatment-specific health state utility values used in the PFS state	[redacted]	[redacted]	£53,056
SOC composition: all patients received topotecan	[redacted]	[redacted]	£54,654
SOC composition: all patients received CAV	[redacted]	[redacted]	£56,036
SOC composition: all patients received platinum-based chemotherapy	[redacted]	[redacted]	£53,171
Do not consider post-infusion hospitalisation costs for tarlatamab	[redacted]	[redacted]	£53,635
Do not consider impacts of CRS and ICANS	[redacted]	[redacted]	£53,857
Do not adjust tarlatamab OS and TTD for post-progression tarlatamab use	[redacted]	[redacted]	£69,309
Do not consider vial wastage	[redacted]	[redacted]	£54,944
Additional EAG scenarios			
QoL values from DeLLphi-301 study	[redacted]	[redacted]	£44,907
QoL values from Nafees et al. (PFS 0.653, PD 0.473)	[redacted]	[redacted]	£56,412

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
CQ A37 MAIC omit age and sex at diagnosis	[redacted]	[redacted]	£45,730
CQ A38 MAIC only include 3 main prognostic factors	[redacted]	[redacted]	£39,720
AEs for CAV, diarrhoea 3.26%, febrile neutropenia 4.56%	[redacted]	[redacted]	£58,639
Health care resource costs for patients with progressed disease not on treatment.	[redacted]	[redacted]	£59,979

Source: From company model; includes severity multiplier of 1.7.
CAV, cyclophosphamide, doxorubicin and vincristine; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ICER, incremental cost-effectiveness ratio; OS, overall survival; SOC, standard of care; CQ clarification question; MAIC matching-adjusted indirect comparison.

6.3.2 Probabilistic sensitivity analysis

The EAG conducted a PSA for the EAG base case analysis with 5000 simulations. The results are shown in Table 39. The ICER is £56,825 per QALY for tarlatamab vs standard of care. Tarlatamab has a 0.6% probability of being cost-effective at a willingness threshold of £30,000 per QALY.

Table 39 Probabilistic results for the EAG base case results (probabilistic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Standard of care	[redacted]	[redacted]	[redacted]	[redacted]	
Tarlatamab	[redacted]	[redacted]	[redacted]	[redacted]	£56,825

Source: EAG created table
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Results include 1.7 severity multiplier applied to QALYs.

6.4 Conclusions on the cost effectiveness evidence

The company developed a model to estimate the cost-effectiveness of tarlatamab compared to standard of care for patients with previously treated SCLC. The EAG considers the structure of the model to be reasonable, appropriate and consistent with previous cost-effectiveness models for lung cancer. The company made some minor changes to the model in response to clarification questions. The company's revised base case shows an ICER of

£33,785 per QALY for tarlatamab versus standard of care, including a PAS discount for tarlatamab of [redacted] and including a severity multiplier of 1.7.

The EAG made corrections for the cost and administration of topotecan and the frequency of blood tests.

The EAG disagrees with several of the assumptions in the company's model. Our preferred assumptions include:

- Overall survival: use the gamma distribution for the tarlatamab and standard of care arms, instead of the exponential distribution,
- Progression-free survival: use the exponential distribution for the tarlatamab arm, instead of the lognormal distribution,
- Health-related quality of life: use Chouaid et al. instead of DeLLphi-301 study,
- Adverse event costs: EAG recalculated values.

Incorporating the EAG preferred assumptions, the ICER increase to £58,847 per QALY for tarlatamab vs standard of care. The model results are most sensitive to using the gamma distribution for OS and changing the source of the HRQoL values.

7 SEVERITY

The company calculated the QALY shortfall for tarlatamab by using the online tool published by Schneider et al.[62] The company used the sex distribution ([redacted]) and starting age ([redacted]) from the tarlatamab population after MAIC matching (CS Table 62). The QALYs for patients with third-line SCLC are taken from the standard of care arm. Clinical advice to the EAG confirmed that the OS estimates for the standard of care arm are consistent with those in UK clinical practice. The proportional QALY shortfall for tarlatamab is more than 95% (see Table 40 below). We also calculated the absolute and proportional QALY shortfall using the EAG base case (Table 37) and obtained similar results to the company's revised base case (Table 40) so we agree that there is a case for applying a multiplier for disease severity of 1.7 which the company used in the base case analysis.

Table 40 QALY shortfall analysis

	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportionate QALY shortfall
Company's revised base case	12.03	[redacted]	[redacted]	[redacted]
EAG base case	12.03	[redacted]	[redacted]	[redacted]

Source: Schneider et al. 2021[63]
QALY, quality adjusted life-year.

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9 APPENDICES

Appendix 1

In clarification question A2 we asked the company to provide evidence for their statement that their three selected comparators have similar efficacy. The company provided results from two selected studies in response. One study showed no statistically significant differences between topotecan and CAV on ORR, median time to progression and median OS in patients with SCLC who had relapsed after a minimum of 60 days following the end of first-line therapy. The other study showed statistically significant differences between topotecan and CAV on ORR and median PFS, but not OS, among patients with advanced stage IV or locally relapsed SCLC. Additional analyses of UK data used for standard of care that the company submitted in response to clarification question A3 show that TTD and OS are similar for topotecan and CAV, but both outcomes are better for patients treated with platinum. Drawing on a point the company makes in a covering letter to these additional analyses, this may be due to these participants still being platinum-sensitive, but it is possible that the results may also reflect differences in the efficacy of the treatments.

Appendix 2

Table 41 EAG appraisal of systematic review methods

Systematic review components and processes	EAG response	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	The aim of the systematic review was "*to identify relevant clinical evidence on the clinical efficacy and safety outcomes in patients with SCLC whose disease has progressed following two prior treatments*" (CS section B.2.1). CS Appendix D.1.2 Table 9 describes the eligibility criteria in PICOD format.
Were appropriate sources of literature searched?	Yes	Good coverage of sources including MEDLINE, Embase, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, conference abstracts. Did not search clinical trial registries for ongoing studies.
What time period did the searches span and was this appropriate?	The initial search was from 2012 to 19th April 2022. An update search spanned the period from 1st January 2022 to 19th December 2023. This is an appropriate time span.	Conferences were included in the Embase search from 2018 and handsearching of major oncology and lung cancer conferences was from 2022 onwards.
Were appropriate search terms used and combined correctly?	No	Search strategies provided in CS Appendix D.1.1 Tables 1 to 8. Relevant subject headings and relevant free text terms were used in the searches. Terms for RCTs were not included in the search strategies. A reason for this is not given in the CS. However, we do not believe any relevant evidence has been missed.
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and	Yes, specified inclusion and exclusion criteria were appropriate and relevant to the decision problem.	Eligibility criteria provided in CS Appendix D.1.2 Table 9. For study design, this included RCTs but, as noted in the row above, no search

Systematic review components and processes	EAG response	EAG comments
relevant to the decision problem?		terms for RCTs were included in the search strategies.
Were study selection criteria applied by two or more reviewers independently?	Yes	CS Appendix D.1.2 states two independent reviewers screened both titles and abstracts and then screened the retrieved full papers in a double-blind manner.
Was data extraction performed by two or more reviewers independently?	No	Data extraction was carried out by one reviewer. A second reviewer verified all extracted data.
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes	CS Appendix D.1.2 states the Cochrane risk of bias tool (RoB2) [64] was used to assess each RCT, but as stated previously, RCTs were not searched for, and none are included in the CS. Single-arm trials were assessed using the Downs and Black tool.[42]
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	No	Study quality assessment was carried out by one reviewer. A second reviewer validated the assessment.
Is sufficient detail on the individual studies presented?	Yes	Evidence summarised in CS sections B.2.3 to B.2.7 and B.2.10. The evidence used in the indirect comparison is summarised in CS Appendix D.1.4 to D.1.5 and CS section B.2.9.4.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Yes	The EAG is generally satisfied with the methods the company used to carry out an unanchored MAIC of tarlatamab versus standard of care. Please see sections 3.3 and 3.4.

Source: EAG table.
CS, company submission; EAG, external assessment group; MAIC, matching-adjusted indirect comparison; PICOD, patient, intervention, comparator, outcome, design; RCT, randomised controlled trial

Appendix 3

Table 42 Assessment of Methodological Quality of the DeLLphi-301 study (modified Downs and Black checklist[27]

Outcomes	Company (CS Table 10)		EAG
	Score	Definition	Comments
Reporting			
Is the hypothesis /aim/ objective of the study clearly described?	1	Yes	**Agree**: CS section B.2.2 states the trial is investigation the safety and efficacy of tarlatamab in patients with relapsed or refractory SCLC after two or more lines of treatment.
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	1	Yes	**Agree**: Outcomes are listed in CS Tables 3 and 4 and are defined in CS Table 5
Are the characteristics of the patients included in the study clearly described?	1	Yes	**Agree**: CS Table 6 reports baseline demographics of trial participants in receipt of 10mg tarlatamab dose. CS Table 7 reports the disease characteristics for this group.
Are the interventions of interest clearly described?	1	Yes	**Agree**: Clearly described in CS section B.2.3.3 (Target dose) with additional details elsewhere in the CS.
Are the distributions of principal confounders in each group of patients to be compared clearly described?	0	Unable to determine	**Agree:** No groups compared as this is a single-arm study.
Are the main findings of the study clearly described?	1	Yes	**Agree**: Results relevant to the appraisal (Full analysis set (BICR) and Safety analysis set) presented in CS section B.2.6 with results for other analysis sets available in the CSR. Sufficient information is provided (e.g. numerators and denominators reported, numbers at risk reported).
Does the study provide estimates of the random variability in the data for the	1	Yes	**Agree**: Confidence intervals, 25th and 75th percentiles, minimum and maximum values, quartile values reported.

Outcomes	Company (CS Table 10)		EAG
	Score	Definition	Comments
main outcomes?			
Have all important adverse events that may be a consequence of the intervention been reported?	1	Yes	**Agree**: Adverse events are reported from the DeLLphi-301 study for the 10mg target dose participants in Parts 1 and 2 of the trial. However, we note that reporting of adverse events in the CS is incomplete because data for the 34 participants enrolled in Part 3 of the study were not included. The company provided these data in response to clarification question A14.
Have the characteristics of patients lost to follow-up been described?	1	Yes	**Agree.** The flow of participants through the trial is shown in CS Figure 3, which includes reasons for discontinuing treatment (which were disease progression and death). The CS also reports [redacted] participants were lost to follow-up in the duration of response and duration of disease control analyses. No participants were lost to follow-up in the PFS analyses. [redacted] participant was lost to follow-up in the OS analysis.
Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	1	Yes	**Disagree**: Single-arm trial so no comparative statistics for the main outcomes for which a p-value would be reported.
External validity			
Were the patients asked to participate in the study representative of the entire population from which they were recruited?	1	Yes	**Agree:** Supplementary table S1 to the published paper Ahn et al. 2023[23] lists the reasons why 124 patients failed entry screening for the DeLLphi-301 trial. There were not many patients in this list (n=21) that our clinical experts would expect to potentially treat in clinical practice (i.e. those excluded due to lack of consent, perceived inability to complete study activities, with another condition that might pose a risk to safety or study activities or with no tumour tissue sample provided). One expert commented that the majority of exclusions were likely to be those whose disease was progressing quickly i.e. poor performance status, deteriorating organ function and untreated or symptomatic brain metastases. Therefore it seems likely that the participants were representative of the entire population from which they were recruited.

Outcomes	Company (CS Table 10)		EAG
	Score	Definition	Comments
Were those patients who were prepared to participate representative of the entire population from which they were recruited?	1	Yes	**Disagree:** No data presented for patients who met the inclusion criteria but who declined to participate in the trial. Ahn et al. 2023[23] supplementary table S1 shows 8 patients did not provide consent prior to initiation of study activities.
Were the staff, places, and facilities where the patients were treated, representative of the treatment most patients receive?	1	Yes	**Disagree**: CS Table 4 shows the study took place across 56 centres in 17 countries. Two centres were in the United Kingdom which recruited five participants in total (clarification response A5). CS Table 6 shows 41.4% of participants were from Asia and 3% from North America where health care systems (staff, places and facilities) may be different from those in Europe and the UK specifically.
Internal validity - bias			
Was an attempt made to blind study patients to the intervention they have received?	0	No	**Agree:** Single-arm study with no blinding.
Was an attempt made to blind those measuring the main outcomes of the intervention?	0	No	**Unclear**: Although this was a single-arm study with no blinding, the primary analysis was based on the disease response assessment by BICR. However, we have concerns that blinding could have been compromised if the BICR body [redacted]. In their response to clarification question A8, the company did not address this point.
If any of the results of the study were based on "data dredging", was this made clear?	1	Yes	**Agree:** CS Table 4 lists the pre-planned subgroups and this matches the subgroups presented in CS Figure 8.
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in	1	Yes	**Agree:** different lengths of follow-up adjusted for by survival analysis.

Outcomes	Company (CS Table 10)		EAG
	Score	Definition	Comments
case-control studies, is the time period between the intervention and outcome the same for cases and controls?			
Were the statistical tests used to assess the main outcomes appropriate?	1	Yes	**Agree:** As this was a single-arm study there was very limited statistical analysis. The statistical analysis appears appropriate.
Was compliance with the intervention/s reliable?	1	Yes	**Agree**: CS B.2.10.2 reports extent of exposure which shows the mean relative dose intensity was [redacted]% and the median relative dose intensity was [redacted]%.
Were the main outcome measures used accurate (valid and reliable)?	1	Yes	**Agree**: Outcome measures are clearly described and well-known measures.
Internal validity – confounding factors			
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	0	Unable to determine	**Agree:** single-arm trial.
Were study patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over	0	Unable to determine	**Agree:** single-arm trial.

Outcomes	Company (CS Table 10)		EAG
	Score	Definition	Comments
the same period of time?			
Were study patients randomised to intervention groups?	1	Yes	**Disagree:** although there was randomisation to two tarlatamab doses, only one of those doses is relevant and there is no comparator for that study arm.
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was finished?	0	No	**Agree:** single-arm trial.
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	0	Unable to determine	**Agree:** single-arm trial.
Were losses of patients to follow-up taken into account?	1	Yes	**Disagree**: In response to clarification question A16 the company state that no imputation was performed for efficacy endpoints. However, the extent and type of missing data is unclear as the company did not answer this part of the question. Imputation did occur when dates of adverse events or concomitant medication use were missing or incomplete. As stated above, there were no or minimal loss to follow-up on the outcomes of duration of response, duration of disease control, PFS and OS.
Power			
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	1	Yes	**Agree**: Sample size rationale provided in the Statistical Analysis plan with additional detail given in response to clarification question A18.
Final score	20		

Source: CS Table 10 supplemented with EAG comments.

BICR, blinded independent central review; CS company submission; CSR, clinical study report; OS, overall survival; PFS, progression-free survival; SCLC, small-cell lung cancer; TTD, time to treatment discontinuation.

Appendix 4

The EAG's risk of bias assessment of the UK CAS study that formed the external control arm of the MAIC is shown in Table 43.

Table 43 EAG risk of bias assessment of the UK CAS study

Criterion	EAG assessment of UK CAS study (Yes / No / Unclear)
Was the cohort recruited in an acceptable way?	**Unclear.** The company provided information in response to clarification question A24 about how the CAS Control Cohort patients were selected for the MAIC from the wider UK CAS study database. In the EAG's opinion the selection process is transparent and reasonable. As outlined in section 3.3.2 of this report, it is unclear whether the start of the diagnosis identification period of the study for patient inclusion was in [redacted] or 2013 due to inconsistency in reporting of these dates. This may be an error, but if it is not and the start date of the study was 2013 then it raises the possibility that not all patients with data available have been included in the cohort as data appear to have been available from [redacted] [2] Additionally, the CAS Control Cohort is not fully representative of the patients treated in practice, as [redacted] had received a prior PD-L1 inhibitor and the impact of this on the results is unknown (see section 3.3.2).
Was the exposure accurately measured to minimise bias?	**Yes**. CS Table 18 provides information about the proportions of patients in the CAS Control Cohort who were treated with topotecan, CAV and platinum + etoposide. It is unclear though which platinum treatment participants received. One of the EAG's experts commented that the distribution of the standard of care treatments was a reasonable representation of those used in clinical practice.
Was the outcome accurately measured to minimise bias?	**No**. TTD was used as a proxy for PFS due to data availability. There is a risk that this could under-estimate PFS in the standard of care comparator, as patients may discontinue treatment for reasons other than disease progression. The EAG considers the approach to estimating OS, however,

Criterion	EAG assessment of UK CAS study (Yes / No / Unclear)
	acceptable and we do not have concerns about bias in relation to this outcome.
Have the authors identified all important confounding factors?	**Yes**. Confounding factors were not controlled for in the UK CAS study. However, prognostic factors were identified and controlled for in the MAIC analyses. Our experts considered the company's selection of prognostic factors reasonable.
Have the authors taken account of the confounding factors in the design and/or analysis?	**Yes**. As stated above, prognostic factors were identified and controlled for in the company's MAIC.
Was the follow-up of patients complete?	**Yes**. The company allowed a period of at least 1.5 years for follow-up (clarification response A22), which appears sufficient for measuring the OS and PFS (using TTD as a proxy for PFS) outcomes in a SCLC population.
How precise (for example, in terms of confidence interval and p values) are the results?	The confidence intervals for median OS from the UK CAS study are not provided in the CS but were available from the MAIC report[2] and are narrow. Narrow confidence intervals are also reported for median PFS (using TTD as a proxy).

Source: EAG created table, using NICE-recommended criteria for the quality assessment of non-randomised and non-controlled studies.[28]
CAS, Cancer Analysis System; CAV, cyclophosphamide, doxorubicin and vincristine; EAG, External Assessment Group; MAIC, matching-adjusted indirect comparison; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; SCLC, small-cell lung cancer; TTD, time-to-treatment discontinuation.

Single Technology Appraisal

Tarlatamab for previously treated advanced small-cell lung cancer [ID6364]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 30 July 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Uncertainty in survival estimates

Description of problem	Description of proposed amendment	Justification for amendment
Page 12, Issue 1, Section 1.4 of the report states: "We consider the OS and PFS estimates from the unanchored MAIC base case uncertain"	Please consider amending this statement: "We consider the OS and PFS estimates **for tarlatamab** from the unanchored MAIC base case uncertain"	In the context of the EAG's key issue 1, the sources of uncertainty in survival estimates appear to relate to tarlatamab only. It would therefore be appropriate to clearly indicate that the EAG only considers the tarlatamab survival estimates to be uncertain.

Issue 2 Discussion of PD-L1 subgroup analysis of the DeLLphi-301 trial and inclusion as a covariate in the MAIC analysis

Description of problem	Description of proposed amendment	Justification for amendment
Page 13, Issue 1, Section 1.4 of the report states: "• There were differences between the participants in the DeLLphi-301 trial and UK CAS studies in the proportions who had received prior programmed cell death ligand 1 (PD-L1) inhibitor treatment. This was not included as a covariate in the MAIC analyses."	Please consider adding relevant information regarding PD-L1 subgroup analyses to these statements: "• There were differences between the participants in the DeLLphi-301 trial and UK CAS studies in the proportions who had received prior programmed cell death ligand 1 (PD-L1) inhibitor treatment. This was not included as a covariate in the MAIC analyses. **Subgroup analysis of the DeLLphi-301 trial showed the same treatment effect for tarlatamab in patients who had**	When discussing adjustment for prior PD-L1 treatment in the MAIC, important context is provided by the subgroup analysis of the DeLLphi-301 which showed this had no impact on tarlatamab treatment effect. Exclusion of this context is misleading and therefore represents a factual inaccuracy by omission, so the company request that the EAG add this context where relevant in its report.

	received prior PD-L1 inhibitor treatments as those who had not."	
Page 63, Section 3.3.2 of the report states: "Furthermore, the company have not provided subgroup analyses of survival in the CS for the DeLLphi-301 study by prior PD-1 or PD-L1 inhibitor therapy (the only subgroup analyses by prior PD-1 or PD-L1 inhibitor therapy (Yes/No) presented in the CS are of the objective response rate (ORR) outcome; CS section B.2.7)."	Please consider summarising the results of the subgroup analysis by prior PD-L1 treatment presented for objective response rate: "Furthermore, the company have not provided subgroup analyses of survival in the CS for the DeLLphi-301 study by prior PD-1 or PD-L1 inhibitor therapy (the only subgroup analyses by prior PD-1 or PD-L1 inhibitor therapy (Yes/No) presented in the CS are of the objective response rate (ORR) outcome ; CS section B.2.7).**The subgroup analysis for ORR showed no difference in treatment effect for tarlatamab in patients who received prior PD-L1 treatment and those who had not.**"	The EAG highlight the lack of pre-planned subgroup analyses of survival outcomes by prior PD-L1 treatment but exclude to mention the result of the subgroup analysis of ORR which showed no impact on tarlatamab treatment effect. Given the anticipated correlation between OR and survival outcomes, discussion of the results of this subgroup analysis are warranted in this context.
Page 67, Section 3.3.3 of the report states: "Additionally, there was a substantial difference in the proportions of participants who had previously received a PD-L1 inhibitor (DeLLphi-301: 72.7%; CAS Control Cohort: [redacted]) but this was not a covariate included in the MAIC analyses. It is unknown what impact this difference might have	Please consider discussing the potential limitations of including prior PD-L1 treatment as a covariate, and the company's reasoning for not doing so: "Additionally, there was a substantial difference in the proportions of participants who had previously received a PD-L1 inhibitor (DeLLphi-301: 72.7%; CAS Control Cohort: [redacted]) but this was not a covariate included in the MAIC analyses, **as clinical expert feedback received by the company did not indicate this to be an important variable to adjust for in the MAIC, and**	The company outlined its reasoning for inclusion or exclusion of variables in the MAIC, which should be clearly reported in the EAG's report. Furthermore, potential limitations of adjusting for prior PD-L1 treatment as a covariate in the MAIC should be made clear, notably the loss of sample size.

on the results (please see discussion in section 3.3.2)."	**was not identified as such in meta-regression analyses or SLRs of important prognostic factors in SCLC.** It is unknown what impact this difference might have on the results (please see discussion in section 3.3.2). **Results from a subgroup analysis of the DeLLphi-301 trial show no difference overall response rate in patients with and without prior PD-L1 treatment. Given the differences in the proportion of patients with prior PD-L1 treatment in the RWE CAS study, adjustment would have led to very limited effective sample sizes."**	

Issue 3 Description of MAIC results

Description of problem	Description of proposed amendment	Justification for amendment
Page 13, Issue 1, Section 1.4 of the report states: "• The effective sample size was greatly reduced to just [redacted] participants, making the MAIC estimates potentially unstable." Page 71, Section 3.4.2 of the report states: "As is outlined in the CS, when the effective sample size is	Please consider removing this description of the MAIC results as "unstable", or using alternative wording: "• The effective sample size was greatly reduced to just [redacted] participants, making the MAIC estimates potentially **unreliable**." "~~As is outlined in the CS, w~~When the effective sample size is considerably reduced compared to the original sample size, estimates may be **unreliable**."	Results of the MAIC show consistent results across a number of different scenario analyses, conducted by both the company and EAG, with similar effective sample sizes. It is therefore inappropriate to describe the results of the MAIC as unstable, given the consistency of the results. The company suggests that "unreliable" may be more appropriate, as used by the EAG

considerably reduced compared to the original sample size, estimates may be unstable.”		further down in its report. Despite this, the company maintain that the scenario analyses all showing statistically significant improvements in survival associated with tarlatamab show the MAIC results to be robust, despite the reduction in effective sample sizes. If retaining the description of the results as “unstable”, please could the EAG expand on this description in its report, as this is currently unclear.

Issue 4 EAG alternative source of utility values and description of DeLLphi-301 HRQoL data

Description of problem	Description of proposed amendment	Justification for amendment
Page 14, Issue 3, Section 1.5 of the report states: “The EAG notes that the quality-of-life values are higher than would be expected, due to the company using the full DeLLphi-301 dataset (n=97), rather than the population used in the MAIC (n=[redacted]) which would better match the SOC population.”	The company suggest removing this sentence.	The statement assumes that adjusting the HRQoL values reported in the DeLLphi-301 trial would lower the utility value. The variables adjusted for in the MAIC were chosen based on their predicted impact on survival, as indicated by meta-regression analyses and clinical expert feedback. Their impact on HRQoL was not assessed, and so the impact is unknown.

Page 92, Section 4.2.8 of the EAG report states: "The utilities implemented in the company model are derived from the entire DeLLphi-301 population, rather than the MAIC population (n=[redacted]); the utilities appear to be more favourable given the status of the patient population receiving third-line treatment compared with similar populations with NSCLC."	The company suggest removing this sentence.	The DeLLphi-301 trial provides the most representative data available for the relevant patient population of interest: patients with advanced SCLC with two prior lines of treatment. It cannot be assumed that the HRQoL of patients in the DeLLphi-301 trial is comparable to a population with NSCLC, as these are clinically distinct diseases. The company considers the EAG's use of utility values derived from an NSCLC population inappropriate. The NICE guidance manual only recommends sourcing HRQoL values from the literature if these are not available from relevant clinical trials.

Issue 5 Best supportive care as a comparator

Description of problem	Description of proposed amendment	Justification for amendment
The EAG has noted the exclusion of best supportive care as a key issue in its report.	Please consider removing this as a key issue.	Clinical expert feedback to both the company and the EAG agreed with the choice of comparators for the population of interest, i.e. patients fit

		enough and willing to receive further systemic third-line therapy. The EAG itself notes that if third-line systemic treatments are available, patients fit enough to receive these "will likely accept these" (EAG report, Page 12, Section 2.2.3). The EAG also notes throughout its report that it did not receive clinical feedback that best supportive care should be included as a comparator, with one expert agreeing with its exclusion, and two others not commenting. Furthermore, whilst the EAG raises the exclusion of best supportive care as a key issue in the context of the decision problem, the EAG state that they "do not suggest any changes to the economic base case regarding the intervention or comparators" (EAG report, Page 76, Section 4.2.4). As the economic model reflects the decision problem, raising the exclusion of best supportive care as a comparator whilst agreeing with the modelled comparators appears to be a contradictory position.

		Therefore, the Company suggest that the EAG remove the exclusion of best supportive care as a key issue in its report.

Issue 6 Clarification of the percentage of patients with ECOG score 0

Description of problem	Description of proposed amendment	Justification for amendment
Page 34, Section 3.2.1 of the report states: "However, the remaining expert stated that they would not expect around a quarter of patients to have a score of 0 at third-line therapy."	Please clarify if the clinical expert was talking about *all* third-line patients, or third-line patients with ECOG score 0-1.	The proportion of patients being referred to here is reflective of the RWE study, which only included third-line patients with ECOG 0-1. The company is unclear whether this proportion is then referred to in the context of third-line patients with ECOG score 0-1, or all third line patients.

Issue 7 Clarification of subgroup analyses

Description of problem	Description of proposed amendment	Justification for amendment
Page 45, Section 3.2.5 of the report states: "A response was seen across [redacted] subgroups (with the exception of the [redacted] which included	Please consider clarifying the outcome specified in the subgroup analysis: "A**n objective** response was seen across [redacted] subgroups (with the exception of the [redacted] which included [redacted] and [redacted] patients, respectively)."	The subgroup analysis of the DeLLphi-301 trial assessed objective response rate specifically, which should be made clear in the EAG's report.

[redacted] and [redacted] patients, respectively)."		

Issue 8 Data and confidentiality highlighting amendments

Description of problem	Description of proposed amendment	Justification for amendment
On Page 102 (Section 6.3.1) of EAG report, the upper limit of the range of ICERs calculated in EAG scenario analysis is stated to be £66,338 per QALY (OS distribution selection: Gompertz). As per Table 38 (Page 103, Section 6.3.1), the upper limit is £69,309.	This sentence should be amended to reflect the upper ICER range.	The presented value is incorrect.
Table 42 on Page 125 (Appendix 3) of the EAG report applies confidentiality highlighting to the number of patients lost to follow-up for the PFS analyses.	Confidentiality mark-up can be removed from the number of patients lost to follow-up for the PFS analyses. Confidentiality highlighting should be retained for the number of patients lost to follow-up for the duration of response and duration of disease control analyses.	Confidentiality highlighting is not required for the number of patients lost to follow-up for the PFS analyses as these data are published.
Page 12 (Section 1.2) of the EAG report presents the incremental costs and QALYs of the company revised base case without confidentiality highlighting.	Apply confidentiality highlighting to all incremental costs and QALYs throughout the report. Here, the marking should be revised as follows:	All incremental costs and QALYs must be redacted to prevent calculation of the confidential tarlatamab PAS price.

	"The ICER is £33,785 per QALY for tarlatamab versus standard of care (SOC), with a QALY gain of [redacted] and an additional cost of £[redacted]. The results include a severity multiplier of 1.7 applied to the incremental QALYs."	
Page 85 (Section 4.2.3) of the report presents the value for the proportion of female patients without confidentiality highlighting.	Apply confidentiality highlighting to this value ([redacted]).	This value is unpublished and confidential, as per Table 7 of the Clarification Questions Response Document and Table 62 in the submitted Document B.

Issue 9 Typographical and formatting errors

Description of problem	Description of proposed amendment	Justification for amendment
Broken cross-references appearing as "Section 0" are present throughout the document.	Please amend these references to refer to the correct Section in the report.	Minor typographical error.
Page 20, Section 2.2.2 of the report contains a minor typographical error: "When tarlatamab simultaneously binds to tumour cells and T-cells, the T-cell is activated which leads to breakdown of the tumour cell membrane and then disintegration of the tumour cell**)**."	Please remove the redundant parenthesis.	Minor typographical error.

Page 23, Section 2.2.3 of the report contains a minor typographical error: “a cost for a hospitalisation period of 24 hours at tarlatamab treatment initiation is included in the company’s economic model (CS Table 53).**)**”	Please remove the redundant parenthesis.	Minor typographical error.
Table 33 on Page 105 (Section 5.2.3) of EAG report presents column headers of ‘Total costs (£) [95% CI]’ and ‘Total QALYs [95% CI]’. However, total values only are presented; CI values are not currently reported.	The column heading should be updated to remove mention of 95% CIs.	Minor typographical error.