Tarlatamab for previously treated advanced small-cell lung cancer ID6364

Part 1 - for public
No CON information

Technology appraisal committee A [3rd June 2025]

Chair: Radha Todd

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Company: Amgen

Tarlatamab for previously treated advanced small-cell lung cancer ID6364

- ✓ **Recap**
- ❑ Summary of consultation comments
- ❑ Key issues

NICE National Institute for Health and Care Excellence

Background on extensive-stage small-cell lung cancer (ES-SCLC)

Rapidly progressive cancer; around 7% of all lung cancer cases

- ES-SCLC is an aggressive cancer with poor prognosis: median survival ~9 months from starting treatment.

Epidemiology: In 2022 there were 2,501 SCLC diagnoses in England*.

Diagnosis and classification: Defined as limited or extensive stage (LS- or ES-)SCLC:

- ES-SCLC has spread widely through initial lung, to other lung or nearby lymph nodes or other parts of body.
- Around 60% to 80% of SCLC diagnoses are ES-SCLC

Eligible population:

- Estimated that around 22% of people with SCLC receive third-line treatment.†±
- Applying estimated proportions to 2,501 SCLC diagnoses gives an estimated number of patients eligible for treatment of 330-440

*Sources: Royal College of Surgeons of England (2022), National Lung Cancer Audit 2024: Data and statistics (for 2022). ±Simos et al 2014 † Steffens et al 2019

Tarlatamab (Imdyllta, Amgen)

Use as a 3rd or later line treatment

	Details of the technology
Market authorisation	• Treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) with disease progression on or after at least two prior lines of therapy including platinum-based chemotherapy. • Marketing authorisation granted 31 December 2024
Administration	IV infusion on: • Day 1: 1 mg • Days 8, 15, then 2 weekly until disease progression or unacceptable toxicity: 10mg
Price	• List price: per 1 mg vial: £955, per 10 mg vial: £9,550 • A patient access scheme has been agreed

IV, intravenous; mg, milligram; SCLC, small cell lung cancer

Preliminary decision

- Tarlatamab is not recommended, within its marketing authorisation, for treating extensive-stage small-cell lung cancer in adults whose cancer has progressed after 2 or more lines of treatment, including platinum-based chemotherapy.

Why the committee made this decision:

- The results of the indirect treatment comparison were uncertain
- All cost-effectiveness estimates were above the range that NICE considers an acceptable use of NHS resources

Committee considerations from ACM 1 [1]

Issue (section)	Committee conclusion	Committee request(s)	Updated?
Comparator (4.2)	• Re-treatment with chemotherapy (standard of care is carboplatin/ cisplatin + etoposide, CAV, topotecan or carboplatin). • BSC not a comparator	-	Retained in company base case
Clinical effectiveness (4.3)	• Tarlatamab could be clinically effective, but uncertain because data immature and DeLLphi-301 was a single arm trial	Updated results from most recent DeLLphi-301 data cut	Yes – updated data cut
Indirect treatment comparison (4.5)	• Tarlatamab vs basket of SoC from UK CAS study using matching adjusted indirect comparison (MAIC) • MAIC uncertain because it was unanchored and because of small ESS after matching	Suggested scenarios: • MAIC adjusting for variance • Exploration of alternative methods of population adjustment, e.g. STC or ML-NMR	Yes – alternative ITC
Adverse events and need for monitoring (4.6)	• Serious side effects with tarlatamab (CRS and ICANS -need staff training and capacity to monitor and manage)	Further information from updated data cut on adverse events and risk management	Yes – updated safety data

Abbreviations: ACM, Appraisal Committee Meeting; BSC, best supportive care; CAS, Cancer Analysis Service; CAV, cyclophosphamide, doxorubicin, vincristine; CRS cytokine release syndrome, ICANS immune effector cell associated neurotoxicity; ITC, indirect treatment comparison; MAIC, matching adjusted indirect comparison; ML-NMR, multi-level network meta-regression; STC, simulated treatment comparison

Committee considerations from ACM 1 [2]

Issue (section)	Committee conclusion	Committee request(s)	Updated?
OS and PFS curves (4.8)	• If PH do not hold, different extrapolation curves may be applied to each arm • If fitting the same curve to each arm, choice of curve should be informed by arm with most mature data.	• Review best-fitting curves to updated DeLLphi-301 data cut, separate curves if reflects underlying hazards • Exponential should not be used in both arms if PH not met	Yes – best-fitting curves reassessed
Modelling PFS for SoC (4.9)	• No PFS data in UK CAS study so company used TTD as proxy for PFS for SoC arm • TTD might not be suitable surrogate for PFS in SoC arm: people may stop treatment before progression because of toxicity	Scenarios: • Adjusting TTD for SoC by ratio between PFS and TTD in DeLLphi-301, • Using ratio between PFS and TTD from literature	Yes – scenario provided

Abbreviations: ACM, Appraisal Committee Meeting; CAS, Cancer Analysis Service; EAG, external assessment group; OS, overall survival; PFS, progression-free survival; PH, proportional hazards; SoC, standard of care; TTD, time to treatment discontinuation;

Committee considerations from ACM 1 [3]

Issue (section)	Committee conclusion	Committee request(s)	Updated?
Utilities (4.10)	Company's utilities from DeLLphi-301 may overestimate but preferred over EAG's approach (using NSCLC utilities)	Scenario using utilities from the DeLLphi 301 subgroup in the MAIC	Yes – scenario provided
Severity (4.12)	1.7 x modifier appropriate	Reassess for updated base case	Yes- remains 1.7
ICER threshold (4.13)	High uncertainty, but will be determined following requested data and analyses		-

Abbreviations: ACM, Appraisal Committee Meeting; ICER, incremental cost-effectiveness ratio;; MAIC, matching adjusted indirect comparison; NSCLC, non-small cell lung cancer

Tarlatamab for previously treated advanced small-cell lung cancer ID6364

- ❑ Recap to background and key issues
- ✓ **Summary of consultation comments**
- ❑ Key issues

NICE National Institute for Health and Care Excellence

Roy Castle Lung Cancer Foundation

Disappointed with decision not to recommend tarlatamab

- **High unmet need:** Woefully poor outcomes from standard treatment for this group of patients and no approved therapies after 2L
- **Tarlatamab is a novel and innovative treatment,** and is shown to beneficial in the management of patients with previously treated advanced SCLC
- **Found acceptability for tarlatamab from people with SCLC** via online survey. Of 10 responses received:
    - 3 patients willing to spend up to 5 days in hospital to monitor side effects
    - 6 want to know more before making a decision
    - 1 patient would not accept a treatment requiring additional days in hospital
- Urge the committee to reconsider their decision

This is a group of patients who do not have time to wait

Abbreviations: 2L, second line; SCLC, small cell lung cancer

Company's response to consultation

Company provided:

1. Updated data cuts of DeLLphi-301 trial with more recent efficacy and safety data
2. Information on risk management plan for tarlatamab
3. Updated MAIC using October 2023 data cut and a scenario with variance adjustment
4. An alternative ITC which uses a different data source for SoC (US Flatiron dataset)
5. A revised base case which applies committee's preference from ACM1 for approach to adverse event costs and new parametric curves applied to extrapolate PFS and OS
6. Scenarios for alternative approaches to modelling PFS for SoC, health state utility values, and using the Flatiron ITC analysis

Abbreviations: ACM, appraisal committee meeting; ITC, indirect treatment comparison; MAIC, matching adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; SoC, standard of care

Tarlatamab for previously treated advanced small-cell lung cancer ID6364

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Summary of key issues

Key issue	ICER impact†
1. Updated DeLLphi-301 data cuts	Small
2. Indirect treatment comparison (ITC)	Unknown*
3. Choice of survival extrapolations	Small
4. Modelling PFS for SoC	Small
5. Health state utilities	Small
Severity: company and EAG agree 1.7x modifier appropriate	-
• What is committee's preferred ICER threshold?	-

*Presented scenarios have a small impact on the ICER but high uncertainty associated with the ITC
†All alternative presented scenarios have <£3,000 per QALY gained impact on company base case ICER

Abbreviations: ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; MAIC, matching adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; RMP, risk management plan; SoC, standard of care; TTD, time to treatment discontinuation

Updated DeLLphi-301 data cuts (efficacy)

Link to OS KM plots

Data from October 2023 data cut are consistent with the June 2023 data cut

Median follow-up data (months) available from DeLLphi-301 data cuts

DCO	ORR	DOR	PFS	OS
June 2023	[redacted]	[redacted]	[redacted]	10.6
October 2023	[redacted]	[redacted]	[redacted]	[redacted]
January 2024	16.6	15.1	16.4	NA
May 2024	NA	NA	NA	20.7

Used in original submission

Used in updated base case

Key efficacy data

DCO	Median PFS months (95% CI)	Median OS months (95% CI)
June 2023	4.9 (2.9, 6.7)	14.3 (10.8, NE)
October 2023	[redacted]	[redacted]
January 2024	4.3 (3.0, 5.6)	NA
May 2024	NA	15.2 (10.8, NE)

Company:

- October 2023 data cut used in updated base case for consistency in outcomes (not all outcomes collected in 2024 data cuts)
- Slight difference in estimated median PFS attributable to censored events in June 2023 data cut becoming progression events in October 2023 data cut

EAG:

- LTFU data consistent with results from June 2023 DCO

Does the October 2023 data cut reduce uncertainty in the PFS and OS data?

Abbreviations: CI, confidence interval; DCO, data cut-off; DOR, duration of response; EAG, external assessment group; LTFU, long term follow up; NA, not available; NE, not estimable; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival;

Updated DeLLphi-301 data cuts (safety)

Data from the October 2023 data cut included in updated base case

Recap (**see DG section 4.6**)

- The CDF lead noted that a later data cut from DeLLphi-301 suggested that CRS occurs in the first few weeks of treatment and resolves reasonably quickly. This data cut was not available at time of submission.
- Committee concluded that healthcare staff training and capacity planning will be required to monitor and manage side effects of tarlatamab.

Company:

- Provided later data cuts: Median time to resolution of grade ≥2 CRS was [redacted] days and of grade ≥2 ICANS was [redacted] days (Oct 23). Median time to resolution of any grade ICANS was 33 days (Jan 24)
- Reduction in number and rates of unresolved grade ≥2 ICANS at October 2023 DCO vs June 2023 DCO
- Risk management plan (RMP) for dealing with serious side effects in place.
- Training will reactively be offered to healthcare staff on monitoring and management of side effects

EAG:

- No new safety concerns from October 2023 DCO.
- Slight increase in rate of CRS at one of 2024 DCOs and at least one grade 3 CRS in 2024 DCOs.

Do the data suggest that CRS (and ICANS) events resolve relatively quickly?
Does the RMP reduce committee's concern about capacity and training required to deal with side effects?

Abbreviations: CDF, Cancer Drugs Fund; CI, confidence interval; CRS, cytokine release syndrome; DCO, data cut-off; EAG, external assessment group; ICANS, immune effector cell-associated neurotoxicity syndrome; LTFU, long term follow up; MSL, Medical Science Liaison; NR, not reported; RMP, risk management plan

Key issue 2: Indirect treatment comparison (ITC)

Link to overview of Flatiron ITC

Recap (**see DG section 4.8**)

- Company's ITC compared the effectiveness of tarlatamab with chemotherapy. Clinical effectiveness data for SoC came from UK CAS study, which used registry data from adults who had treatment for SCLC in NHS in England.
- Company did unanchored MAIC because IPD not available in UK CAS study and no comparator arm in DeLLphi-301.
- EAG concerned that ESS was small after matching, indicating little overlap in baseline characteristics.
- Committee agreed that prognostic factors included in analysis were appropriate but results highly uncertain.
- Committee requested:
  a. Analysis that includes variances in covariate adjustment
  b. Exploration of alternative population adjustment methods.

Company provided the following analyses at consultation:

1. Updated MAIC using October 2023 DeLLphi-301 data cut
2. Scenario for updated MAIC that includes variances in covariate adjustment
3. Alternative ITC for consideration:
   - Patient-level ITC using propensity score weighting (PSW) approach with data for SoC from US Flatiron Health Research Database.
   - Included patients at ~280 US community oncology practices and several academic centres diagnosed with SCLC who received 1L platinum-based regimen and at least 2 additional lines of therapy

Abbreviations: 1L, first line; CAS, Cancer Analysis Service; EAG, external assessment group; ESS, effective sample size; IPD, individual patient-level data; ITC, indirect treatment comparison; MAIC, matching adjusted indirect comparison; SCLC, small cell lung cancer; SoC, standard of care; US, United States

Critique of Flatiron ITC provided by company in DG response

Company

- Flatiron ITC addresses key limitations to UK CAS MAIC, including small ESS and TTD used as proxy for PFS → Utilises patient-level data adjustment to achieve cohort balance while maintaining reasonable ESS for assessing treatment effects and includes PFS data for SoC. Presents as supportive data, uses UK CAS MAIC in base case

EAG: Flatiron ITC leads to further uncertainty about the relative treatment effect of tarlatamab vs. SoC

- Unclear which DeLLphi-301 data cut was used in Flatiron ITC
- No information on therapies patients received in US-based Flatiron external control arm → uncertainty about extent to which external control arm reflects standard care at 3L in the NHS
- Prognostic factors included in Flatiron ITC differ to those included in company's base case MAIC
  - Smoking status is a covariate in the Flatiron ITC but was omitted from base case MAIC
  - Presence of liver metastases included as a covariate in base case MAIC but not in Flatiron ITC → Clinical experts advised EAG that liver metastases considered important prognostic factor.
- Company did not provide information about distribution of weights for PSW → uncertainty about no. of patients removed from analysis and whether analysis is driven by small no. of patients with high weights
- Differing censoring rules could bias the results in favour of tarlatamab: [redacted]

[redacted]

[redacted]

Abbreviations: 3L, third line; CAS, Cancer Analysis Service; EAG, external assessment group; ESS, effective sample size; ITC, indirect treatment comparison; MAIC, matching adjusted indirect comparison; PFS, progression-free survival; PSW, propensity score weighting; SoC, standard of care; TTD, time to treatment discontinuation

Link to Updated MAIC KM plots

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Unknown ICER impact

Key issue 2: ITC results

- All ITC results showed improved OS and PFS with tarlatamab compared with standard care.
- The HRs in the updated MAIC (using the October 2023 data cut) were similar to the HRs in the original MAIC.
- EAG note consistency of MAIC results but reiterate its concerns about the small ESS in original and updated MAIC analyses meaning results could be unstable.
- For OS and PFS, the magnitude of effect was weaker in the Flatiron ITC than the original or updated MAICs.

Analysis	ESS	OS HR (95% CI)	PFS HR (95% CI)
Original CS MAIC (using June 2023 data cut)	[redacted]	0.367 (0.202, 0.667)	0.184 (0.100, 0.340)
Updated MAIC (using October 2023 data cut)	[redacted]	[redacted]	[redacted]
Updated MAIC with variance adjustment	[redacted]	[redacted]	[redacted]
Flatiron ITC	N/A	[redacted]	[redacted]
Flatiron ITC including adjustment for post-progression tarlatamab use	N/A	[redacted] (NR, NR)	N/A

- Do the additional analyses support the company's estimated relative effectiveness of tarlatamab compared with standard care?
- Is the Flatiron ITC informative for decision making?
- What is committee's preferred ITC analysis?

Abbreviations: CI, confidence interval; CS, company submission; ESS, effective sample size; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; KM, Kaplan-Meier; MAIC, matching adjusted indirect comparison; N/A, not applicable; NR, not reached; OS, overall survival; PFS, progression-free survival

Key issue 3: Choice of survival extrapolations

Small ICER impact

Recap (**see DG section 4.8**)

- Committee: different extrapolation curves may be applied to each arm if PH assumption does not hold.
- If the same curve is fitted to each arm, choice of curve should be informed by the treatment arm with the most mature data.

	Company choice of curve in DG response	EAG choice of curve in DG response
Tarlatamab OS	Exponential	Gamma
Tarlatamab PFS	Log-normal	Log-normal
Tarlatamab TTD	Exponential	Gen. gamma
SoC OS	Gamma	Gamma
SoC TTD (proxy for PFS)	Gen. gamma	Gen. gamma

Company

- PH assumption violated so extrapolations selected separately for each arm based on best statistical fit.

EAG

- For OS, EAG prefers to use the same curves for both treatment arms. Gamma is good fit for both arms.
- For tarlatamab TTD, exponential curve does not provide good visual fit and is the worst fit by AIC. Gen. gamma provides better fit.

What is committee's preferred approach to the extrapolations for OS, PFS and TTD?

Abbreviations: AIC, Akaike Information Criterion; DG, draft guidance; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; SoC, standard of care; TTD, time to treatment discontinuation

Key issue 4: Modelling PFS for SoC

Small ICER impact

Recap (**see DG section 4.9**)

- Committee considered that using TTD data to estimate PFS for SoC was uncertain.
- Committee requested further analyses that explore different approaches to modelling PFS in SoC arm, e.g.
  a) Adjusting TTD for SoC by the ratio between PFS and TTD for tarlatamab reported in DeLLphi-301
  b) Using the ratio between PFS and TTD obtained from a systematic review of the literature

Company

- Maintained TTD as proxy for PFS for SoC in base case but provided scenario where ratio per cycle between PFS and TTD was calculated from tarlatamab extrapolation and applied to SoC TTD curve to estimate PFS
- Considers applying TTD/PFS ratio for tarlatamab to SoC unsuitable because:
  i. Survival outcomes for SoC are poor so any differences between TTD and PFS likely to be small
  ii. Tarlatamab has novel mechanism of action so not clinically valid to assume that difference between TTD and PFS observed in DeLLphi-301 is applicable to SoC
  iii. AE profiles differ between tarlatamab and chemotherapy, potentially resulting in different relationships between TTD and PFS

EAG

- Agrees with company approach of assuming PFS to be equal to TTD for SoC
- Satisfied that scenario requested by committee has minimal impact on ICER

Is committee satisfied with the company approach of using TTD as proxy for PFS for SoC?

Abbreviations: AE, adverse event; DG, draft guidance; PFS, progression-free survival; ICER, incremental cost-effectiveness ratio; MoA, mechanism of action; SoC, standard of care; TTD, time to treatment discontinuation

Key issue 5: Health state utility values

Small ICER impact

Recap (**see DG section 4.9**)

- Committee preferred to use utility estimates from DeLLphi-301 for decision making and requested to see utility values derived for the MAIC-adjusted population because may better reflect people having SoC

Health state	Unadjusted	MAIC-adjusted
	Mean (SE)	Mean (SE)
Pre-progression	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]

Company

- Pre-progression utilities are unchanged in the MAIC-adjusted population, post progression utilities are higher
- Maintained unadjusted utilities in base case.
- Consider the MAIC-adjusted utilities to be less robust and less valid compared to the unadjusted utility values.
- Increase in post-progression utility for MAIC-adjusted value may be attributable to drop in ESS after weighting of DeLLphi-301 cohort and higher amount of missing data.

EAG

- Considers the MAIC-adjusted utility values more appropriate and have included these in the EAG base case.
- Using MAIC-adjusted values results in slight decrease in ICER, so company approach is conservative.

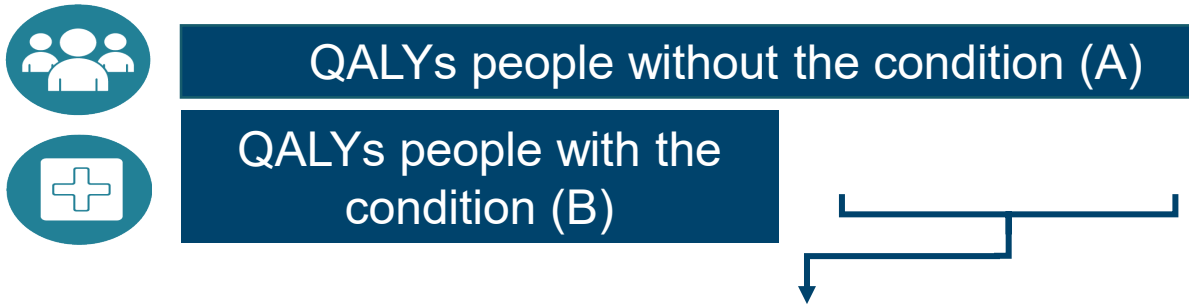
Does the committee prefer to use the unadjusted or MAIC-adjusted utility values from DeLLphi-301?

Abbreviations: EAG, external assessment group; ESS, effective sample size; ICER, incremental cost-effectiveness ratio; MAIC, matching adjusted indirect comparison; SE, standard error; SoC, standard of care

QALY weightings for severity

Both company and EAG agree a 1.7 QALY weight applies unless Flatiron ITC preferred

Severity modifier calculations and components



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

QALY weightings based on whichever of shortfall implies greater severity.

Absolute and proportional shortfall: no change to base case estimates since ACM 1

Scenario	Absolute QALY shortfall	Proportional QALY shortfall	Weight
Company base case	12.03	Over 0.95	**X 1.7**
EAG base case	12.03	Over 0.95	**X 1.7**
Using Flatiron ITC	NA	<0.95	**X 1.2**

Does committee agree it is appropriate to apply a 1.7x QALY weighting for severity?

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Abbreviations: ITC, indirect treatment comparison; NA, not available; QALY, quality-adjusted life year; SoC, standard of care

Summary of company and EAG base case assumptions

EAG prefer different extrapolations for Tarlatamab OS and TTD, and different utility values

Assumption	Committee preference at ACM1	Company base case at ACM2	EAG base case at ACM2
ITC	Requested updated data cut and further analyses	MAIC using October 2023 data cut and UK CAS study	MAIC using October 2023 data cut and UK CAS study
OS, PFS and TTD extrapolations	Acceptable to fit curves independently if PH not held. If same curves used, choose curve based on arm with most mature data	**OS:** Tarlatamab, Exponential; SoC: Gamma **PFS:** Tarlatamab, log-normal **TTD:** Tarlatamab, exponential; SoC, gen. gamma (proxy for PFS)	**OS:** Gamma both arms **PFS:** Tarlatamab, Log-normal **TTD:** Tarlatamab, Gen. Gamma; SoC, gen. Gamma (proxy for PFS)
Utilities	Utilities from DeLLphi-301	Unadjusted from DeLLphi-301	MAIC-adjusted from DeLLphi-301
Adverse event costs	Weighted average for all severities of AE levels	Weighted average for all severities of AE levels	Weighted average for all severities of AE levels
Severity	1.7x QALY weight but needs reassessing	1.7x QALY weight	1.7x QALY weight
Base case ICER	-	Deterministic: £28,449 per QALY gained	Deterministic: £31,437 per QALY gained

NICE

Abbreviations: ACM, appraisal committee meeting; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; MAIC, matching adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; SoC, standard of care; TTD, time to treatment discontinuation

Managed access

- **Company has not made a managed access proposal for this topic**
- **Committee cannot make a managed access recommendation until the company has submitted a proposal and this has been reviewed by NICE.**

Criteria for a managed access recommendation:

- The technology cannot be recommended for use because the evidence is too uncertain
- The technology has the **plausible potential** to be cost effective at the **currently agreed price**
- New evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- Data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

Summary of key issues and questions for committee

Key issue	ICER impact
1. Updated DeLLphi-301 data cuts: • Does the October 2023 data cut reduce uncertainty in the OS and PFS data? • Does the data suggest that CRS (and ICANS) events resolve relatively quickly? • Does the company's RMP reduce committee's concern about capacity and training required to deal with serious side effects of treatment?	Small
2. Indirect treatment comparison (ITC): • Do the additional analyses support the company's estimated relative effectiveness of tarlatamab compared with standard care? • Is the Flatiron ITC informative for decision making? • What is committee's preferred ITC analysis?	Unknown
3. Choice of survival extrapolations: • What is committee's preferred approach to the extrapolations for OS, PFS and TTD?	Small
4. Modelling PFS for SoC: • Is committee satisfied with the company approach of using TTD as proxy for PFS for SoC?	Small
5. Health state utilities: • Does committee prefer to use the unadjusted or MAIC-adjusted utility values from DeLLphi-301?	Small
Severity: Company and EAG agree that 1.7x severity modifier is appropriate	-
• What is committee's preferred ICER threshold?	-

Abbreviations: ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; MAIC, matching adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; RMP, risk management plan; SoC, standard of care; TTD, time to treatment discontinuation

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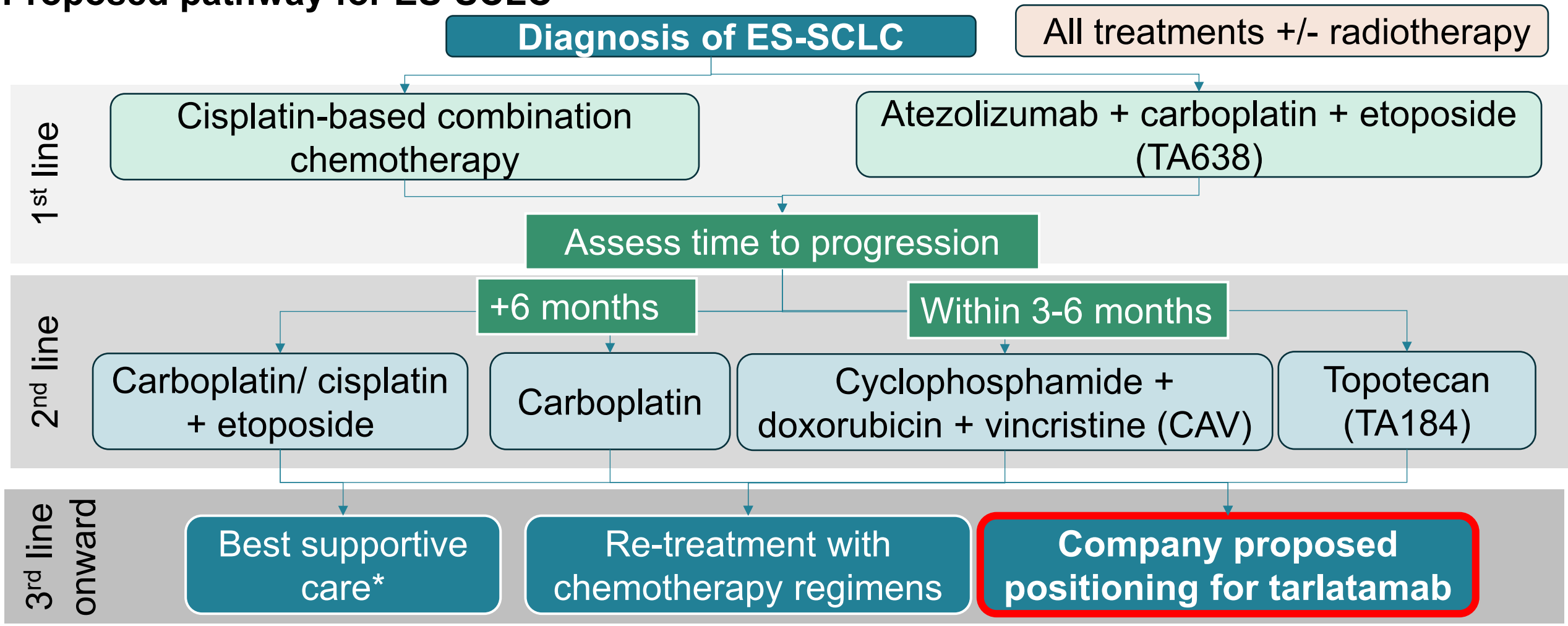
Supplementary appendix

NICE National Institute for Health and Care Excellence

Treatment pathway

Chemotherapy regimens used at 2L deemed relevant comparator at ACM1

Proposed pathway for ES-SCLC



*Committee concluded at ACM1 that best supportive care is not a relevant comparator for tarlatamab

Key clinical trial

Pivotal trial: 3-part single arm study – data from 10 mg dose (3 enrolment groups) in model

	DeLLphi-301 (N=134 at licensed dose, N=99 from 2 enrolment groups informing model)
Design	Uncontrolled, open-label, phase 2 study
Population	Relapsed or refractory SCLC with disease progression or recurrence following 1 platinum-based regimen and at least 1 other line, ECOG 0-1
Intervention	1mg day 1 followed by 10 mg on days 8,15 and every 2 weeks thereafter (n.b. trial also assessed 100mg dose but only 10mg dose licensed)
Duration of treatment	Until disease progression (RECIST 1.1 criteria) or unacceptable toxicity. (n.b. some people continued post-progression if perceived benefit).
1º outcome	ORR (including CR and PR), TEAEs, PK
Key 2º outcomes	DOR, PFS, OS, HRQoL, DC, DoDC, anti-tarlatamab antibody formation
Locations	56 centres worldwide, 2 UK centres
Used in model?	Yes, from a matched population to UK cohort receiving standard care

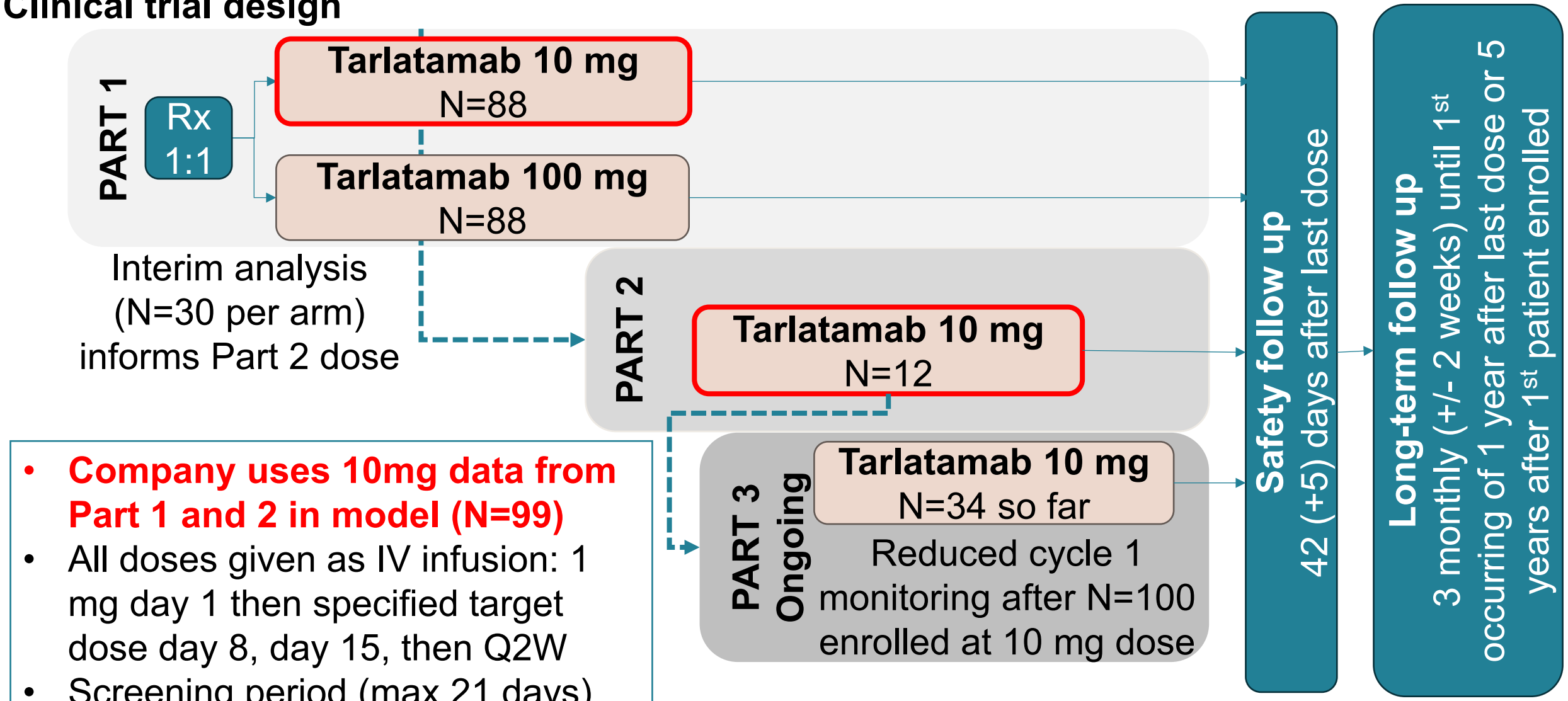
CR, complete response; DC, disease control; DoDC, duration of disease control; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; IV, intravenous; N, number; OR, objective response rate; OS, overall survival; PR, partial response; SCLC, small-cell lung cancer; TEAE, treatment-emergent adverse event

DeLLphi-301 trial design

Link to main slides: DeLLphi-301 clinical trial

3-part trial including dose finding and dose expansion phases. 10 mg dose licenced.

Clinical trial design



- **Company uses 10mg data from Part 1 and 2 in model (N=99)**
- All doses given as IV infusion: 1 mg day 1 then specified target dose day 8, day 15, then Q2W
- Screening period (max 21 days) for all study stages

IV, intravenous; mg, milligram; N, number; Q2W, 2 weekly; Rx, randomisation

Link to Key Issue

DeLLphi-301 KM plot for overall survival (June 2023, October 2023 and May 2024 DCOs)

Abbreviations: DCO, data cut off; KM, Kaplan-Meier

Link to Key Issue

Overview of Flatiron ITC provided by company in DG response

Patient-level ITC using US-based RWE and propensity score weighting (PSW) approach

Treatment	Data source	n
Tarlatamab	DeLLphi-301, 10mg dose (Part 1 or 2)	97

SoC	• Flatiron Health Research Database: longitudinal EHR database comprising IPD from ~280 community oncology practices and several academic cancer centres in the US
	• Patients included in dataset were:
	  • diagnosed with SCLC from 1/1/2013
	  • received 2L treatment between 1/1/2018 and 30/4/2021
	  • had failed 1L platinum-based regimen and received at least two additional lines of therapy
		184

- **Outcomes**: OS, TTD, TTNTD, PFS, ORR, OS adjusted for post-progression use of tarlatamab, and TTD adjusted for post-progression use of tarlatamab
- **Adjusts the Flatiron external control arm for**: age, sex, ECOG performance status (0 vs 1), TNM disease stage chemotherapy-free interval after 1L therapy, number of lines of therapy at index, presence of brain metastases, smoking status, time from SCLC diagnoses to index
- **Standardised mortality ratio (SMR) weighting** used to reweight patients so that distributions of baseline characteristics of patients treated with comparator therapies matched that of patients treated with tarlatamab

NICE

Abbreviations: 1L, first line; 2L, second line; DG, draft guidance; ECOG, Eastern Cooperative Oncology Group; IPD, individual patient-level data; ITC indirect treatment comparison; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; RWE, real world evidence; SCLC, small cell lung cancer; SoC, standard of care; TNM, tumour, node metastasis; TTD, time to treatment discontinuation; TTND, time to next treatment or death

Link to Key Issue

Updated KM curves tarlatamab vs SoC (without MAIC variance adjustment)

OS

PFS

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

Link to Key Issue

Updated KM curves tarlatamab vs SoC (with MAIC variance adjustment)

OS

PFS

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

Comparison of DeLLphi-301 and CAS Control Cohorts

	DeLLphi-301 (N=97)	CAS Control Cohort (N=540)
PFS (months) median (95% CI)		-
OS (months) median (95% CI)		
Extensive stage at diagnosis (stage 4)		
ECOG PS 0 at LOT initiation		
ECOG PS 1 at LOT initiation		
Presence of brain metastases at LOT initiation		
Presence of liver metastases at LOT initiation		
Prior therapies		
Platinum resistant (CFI <90 days), n (%)		
Platinum sensitive (CFI ≥180 days), n (%)		
Exposure to prior PD-L1 inhibitor, n (%)		
Age at diagnosis (years), mean (SD)		
Gender (female), n (%)		
Asian		
White		
Mean time from diagnosis to index LOT (3L), days (SD)		
Comorbidities (at index for DeLLphi-301 vs. at diagnosis for UK-CAS)		
Hypertension		
Chronic obstructive pulmonary disease (COPD)		
Diabetes mellitus (DM)		

3L, third line; ECOG PS, Eastern Cooperative Oncology Group performance status; CFI, chemotherapy-free interval; LOT, line of treatment; n, number; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression free survival; SD, standard deviation;

Equality considerations

No equalities issues were raised during the course of this appraisal