# Tarlatamab for previously treated advanced small-cell lung cancer ID6364

For public –no CON information

**Technology appraisal committee A [8th October 2024]**

**Chair:** Radha Todd

**Lead team:** Mohammed Farat, Min Ven Teo, Richard Ballerand

**External assessment group:** Southampton

**Technical team:** Emma Douch, Mary Hughes, Emily Crowe

**Company:** Amgen

# Tarlatamab for previously treated advanced small-cell lung cancer  ID6364

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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

*Rapidly progressive cancer with poor prognosis; around 7% of all lung cancer cases*

Small-cell lung cancer (SCLC) is a type of lung cancer that spreads quickly

**Causes:** various, including exposure to tobacco smoke or environmental agents (asbestos, radon)

**Epidemiology:** In 2022 there were 2,501 SCLC diagnoses (7% of total lung cancer diagnoses) in England*

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

- ES-SCLC has spread beyond a single radiotherapy field (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

**Symptoms and prognosis:** weight loss, malaise, bone pain, breathlessness and haemoptysis (coughing up blood)

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



*Sources: Royal College of Surgeons of England (2022), National Lung Cancer Audit 2024: Data and statistics (for 2022).

# Tarlatamab (Imdyllta, Amgen)

*Novel immunotherapy for SCLC with use as a 3rd or later treatment*

| | Details of the technology |
|---|---|
| **Market authorisation** | Marketing 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 |
| **Mechanism of action** | Bispecific T-cell engager (BiTE): simultaneously binds to delta-like ligand 3 (DLL3) on tumour cells and CD3 complex on T-cells, triggering T-cell activation and breakdown of the tumour cell |
| **Administration** | Given as IV infusion:<br>• Day 1: 1 mg<br>• 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<br>• List price for 12 months of treatment: £248,982*<br>• A patient access scheme has been agreed |

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*Source: company's budget impact analysis. IV, intravenous; mg, milligram; SCLC, small cell lung cancer

Link to supplementary slides: AEs of special interest

# Patient and clinical perspectives

*Submissions from Roy Castle Lung Cancer Foundation and clinical experts*

Rapidly progressive cancer and patients are very symptomatic

Unmet need → no approved 3rd line treatments:

- Treatment for ES-SCLC non-curative: aim to shrink / stabilise tumour, delay progression, improve QoL and reduce symptoms
- High relapse rate and poor outcomes after initial treatment, especially once current options exhausted (few months survival only)
- Even modest extensions in life important for patients and families

Tarlatamab is a step change in treatment:

- Side effects of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome needs managing and monitoring (including hospitalisation for initial treatments)

*"A diagnosis of extensive SCLC is devastating."*

*"…an aggressive disease, with very few advances in treatment over decades."*

*[Survival rates with tarlatamab] hitherto not seen in this disease setting*



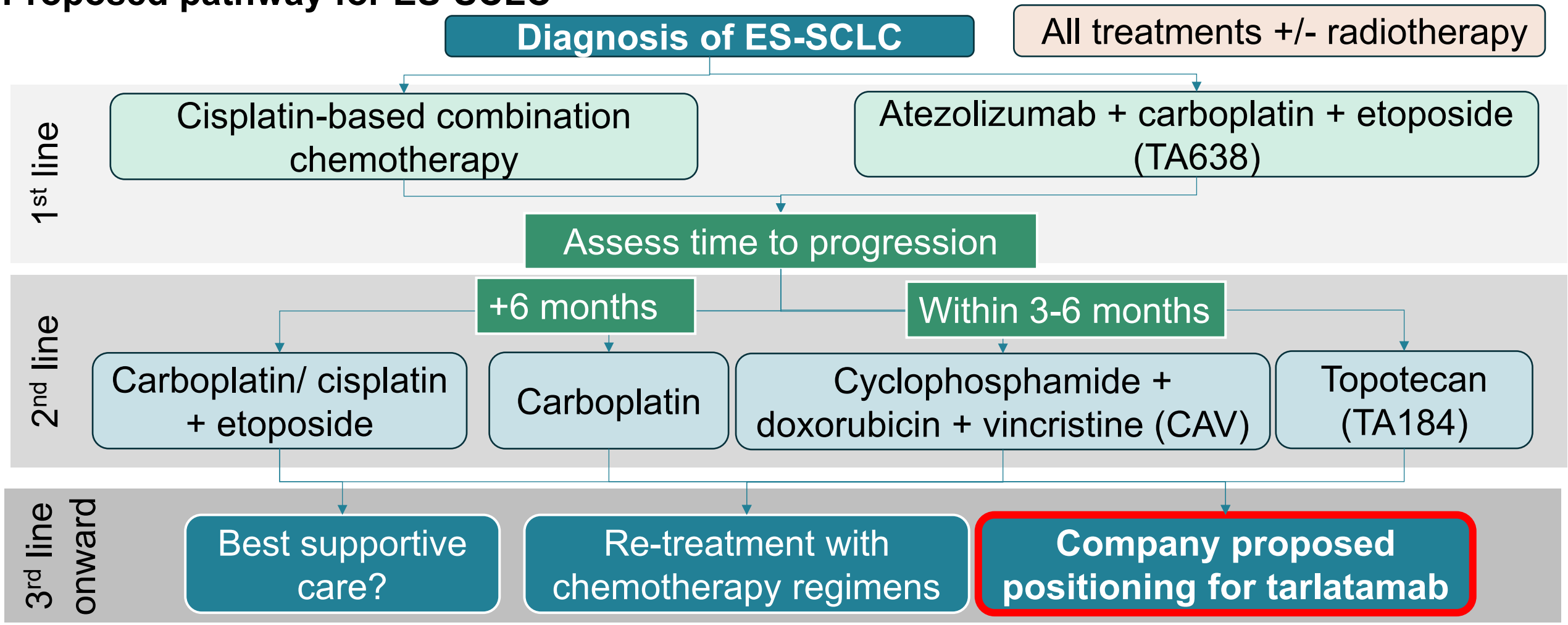
ES-SCLC, extensive-stage small cell lung cancer; QoL, quality of life

# Treatment pathway



*Company focusses on ES-SCLC. No licenced treatments for 3rd line: 2nd line treatments offered*

## Proposed pathway for ES-SCLC




Who receives best supportive care in clinical practice? Would these people have tarlatamab? Is the proposed positioning for tarlatamab appropriate?

# Key issues: Population and comparators (1)

*Company DP includes different population and comparators than NICE scope*

**Background:** Company's decision problem narrower than scope as company:

- limits population to people with ECOG performance status 0 or 1
- excludes best supportive care (BSC) as a comparator

**Company:** Different populations on systemic therapy (ECOG 0-1) & BSC (ECOG 2+)
Tarlatamab only used in people with ECOG 0 or 1, reflective of clinical evidence

**EAG comments:** EAG's clinical experts agree with proposed pathway:
No established treatment at 3rd line +:

- Most people not fit enough for systemic treatments → have BSC (symptom management)
- Agree eligible population = ECOG 0 or 1:
  - ❖ Must be fit enough for tarlatamab associated toxicity & hospitalisation for AE monitoring
  - ❖ Of the few patients with ECOG 0-1, most choose retreatment with 2nd line systemic therapies (usually CAV or topotecan) not BSC (1 EAG expert: <20% receive BSC).
- Company DP and clinical evidence narrower than SmPC → does not limit by ECOG status

AE, adverse event; BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; DP, decision problem; SmPC, summary of product characteristics;

Link to supplementary slides: Decision problem

# Key issues: Population and comparators (2)

*Clinical experts: small population have systemic treatment at 3L, tarlatamab not used in people with poor performance status*

**Clinical experts:** few patients alive or well enough for 3rd line treatment:

- Only ~2% SCLC population have 3rd line and <1% have 4th line treatment → choice based on performance status, previous duration of response, patient preferences
- If fit enough for systemic treatment (3L+) usually enrol in clinical trials
- People with poor performance status would not have tarlatamab
- Safety in ECOG 3-4 cannot be determined as lack of clinical evidence

**Technical team considerations:** Pivotal trial for atezolizumab + carboplatin + etoposide limited to ECOG 0-1.

- Technology not recommended in ECOG 2+. Clinical experts → lower effectiveness of immunotherapies in people with higher treatment burden

- Would people with an ECOG status of 3 or 4 have tarlatamab in clinical practice? If yes, is the DeLLphi-301 trial data generalisable to this population?
- Should BSC be included as a comparator?



BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; DP, decision problem; SmPC, summary of product characteristics;

# Key issues

| Issue | ICER impact |
|---|---|
| **Comparator:** Is BSC a comparator for tarlatamab? Would people who currently have BSC have tarlatamab if it was a treatment option? | Unknown |
| **Population:** Would people with ECOG performance status 2+ have tarlatamab in clinical practice? | Unknown |
| **Uncertainty in the MAIC:**<br>• Have the appropriate covariates been adjusted for in the analyses?<br>• What is the extent of the uncertainty in the indirect comparison? | Large |
| **Overall survival and progression free survival extrapolations:** Should the same parametric curves be fitted to the data for tarlatamab and SoC? If so, is it appropriate to use the best fitting to tarlatamab or SoC? | Large |
| **Health state utilities:** Should utilities derived from the tarlatamab trial or NSCLC literature be used? | Large |

BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group (ECOG); ICER, incremental cost effectiveness ratio; ITC, indirect treatment comparison; MAIC, matching adjusted indirect comparison; NSCLC, non-small cell lung cancer; SoC, standard of care

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# 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

# Key clinical trial results – DeLLphi-301 trial

*Trial reports median PFS of ~5 months and OS of ~14 months with tarlatamab*

Results presented in BICR Full Analysis Set (people who had ≥1 dose tarlatamab and ≥ 1 measurable baseline lesions, N=99). Median follow up time [redacted] months for PFS, 10.6 months for OS.

| Outcome | Result – interim analyses June 2023 |
|---|---|
| Objective response rate | 40.4% (97.5% CI 29.4 to 52.2) |
| Median PFS | 4.9 months (95% CI 2.9 to 6.7) |
| Median overall survival | 14.3 months (95% CI 10.8 to not reached) |
| Number of OS events | 35 (35.4%) |

**EAG comments:**

- Potential unblinding of PFS assessment by BICR in DeLLphi-301 because [redacted]
- [redacted] people continued tarlatamab after disease progression, which is not permitted in SmPC.

Link to supplementary slides: DeLLphi-301 OS & PFS curves, results censoring for post-progression tarlatamab use, adverse events of special interest

BICR; Blinded independent central review; CI, confidence interval; N, number; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response evaluation criteria in solid tumours; TTD, time to discontinuation, SmPC summary of product characteristics

# Company's indirect treatment comparison

Link to supplementary slides: MAIC methodology, UK CAS data sources

*Unanchored MAIC using basket of SoC treatments.*

**Background:** no direct evidence tarlatamab vs comparators → company use unanchored MAIC vs basket of comparators: CAV (38%), topotecan (42%), carboplatin + etoposide (20%)

| Treatment | Data source | N before matching | ESS after matching |
|---|---|---|---|
| Tarlatamab | DeLLphi-301, 10mg dose (Part 1 or 2) | 97 | [redacted] |
| SoC (basket weighted by use in UK CAS) | Aggregate data from UK CAS (combined registry of adults in England treated in NHS) 3rd line, diagnosed 2013-2020, ECOG 0 or 1 | 540 | 540 |

- **Outcomes**: OS and PFS → PFS not reported in UK CAS so TTD used as proxy
  - ❖ People in DeLLphi-301 who had tarlatamab post-progression at point of progression censored. EAG agreed appropriate.
- **Adjusts for**: sex, ECOG (0 vs 1), brain & liver metastases, chemotherapy-free interval, age and stage at diagnosis, time from diagnosis to line of therapy
  - ❖ Age & sex not found prognostic but included in published population adjustment in SCLC

CAV, cyclophosphamide, doxorubicin and vincristine; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; MAIC, matching adjusted indirect treatment comparison; N, number; OS, overall survival; PFS, progression-free survival; SoC, standard of care; TTD, time to discontinuation

Link to supplementary slides: MAIC scenarios

# Company's ITC: Results

*Results favour tarlatamab vs. SoC (HR <1). Censoring for post-progression tarlatamab use reduces median overall survival estimate*

**MAIC results, tarlatamab vs SoC; OS & TTD censored for post-progression tarlatamab use**

| | OS | PFS (uses TTD for SoC) |
|---|---|---|
| HR (95% CI) | 0.367 (0.202, 0.667) | 0.184 (0.100, 0.340) |

**Median OS, PFS and OS of tarlatamab and standard of care**

| Outcomes (months) | Tarlatamab | | | SoC |
|---|---|---|---|---|
| | Before weighting | After weighting +/- censoring for post-progression tarlatamab | | |
| | | Without censoring | With censoring | |
| OS | 14.3 | [redacted] | [redacted] | [redacted] |
| PFS | [redacted] | [redacted] | [redacted] | [redacted] |
| TTD | [redacted] | [redacted] | [redacted] | [redacted] |

MAIC, matching adjusted indirect treatment comparison; CI, confidence interval; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; SoC, standard of care; TTD, time to discontinuation

Link to supplementary slides: MAIC scenarios

# Key issue: Uncertainty in the ITC

*EAG concerns: unanchored ITC, small ESS, varying PDL-1 inhibitor use between trials*

**Company:** UK CAS study current and representative of NHS patients and treatments

- Scenarios vary adjusted covariates & SoC data sets

**EAG comments:** MAIC (& covariates) correctly chosen & implemented but results uncertain:

1. Indirect evidence with no anchor: systematic error likely from unadjusted covariates
2. Small ESS in company base case for tarlatamab (N=[redacted])
3. Differences in prior PD-L1 inhibitor treatment: 73% DeLLphi-301 vs. [redacted]% UK CAS:
   - ❖ Most have PD-L1 inhibitor at 1st line: effect unknown as covariate use not adjusted

- UK CAS cohort data generalisable to NHS but excludes people diagnosed between [redacted] and 2013. Impact unclear but potential selection bias?
- Reasonable to use TTD as proxy for PFS → experts state MAIC median SoC PFS reflects NHS clinical practice

**Clinical experts:** response to tarlatamab not expected to vary with prior PDL-1 use → drugs have different MoAs

ESS, effective sample size; BICR; Blinded independent central review; MAIC, matching indirect treatment comparison; MoA, mechanism of action; N, number; PFS, progression free survival; SoC, standard of care

# Company's ITC scenarios

*Scenarios vary adjusted covariates and source for SoC data*

Link to supplementary slides: full ITC scenario results



**MAIC scenarios presented by company**

| Analysis | Rationale for scenario |
|---|---|
| Removing following covariates: | |
| - chemotherapy-free interval | 30% DeLLphi-301 missing outcome |
| - ES-SCLC at diagnosis | Proxy for preferred outcome, stage at treatment initiation |
| - Sex and age at diagnosis | EAG requested: Unclear if prognostic from expert elicitation and meta-analysis |
| Including only 'very important' covariates | EAG requested → increases ESS |
| [redacted] | Base case assumptions varying data sources for SoC treatment effect |
| [redacted] | |
| [redacted] | |
| TTD for tarlatamab | EAG requested but not presented: company states weights equal regardless of outcome |

- Is the MAIC robust for decision making?
- Have all appropriate covariates been adjusted for? Is prior PDL-1 inhibitor use prognostic?

ESS, effective sample size; MAIC, matching adjusted indirect comparison; N, number; SoC, standard of care

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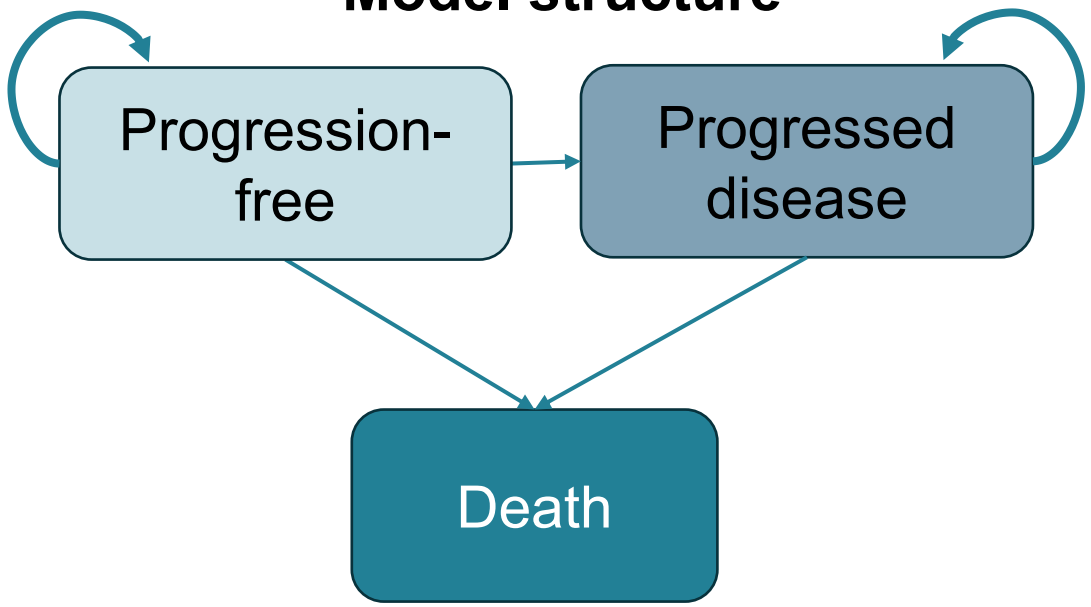
# Company's model overview

*Partitioned survival model with 3 health states, 10-year time horizon*

**Model structure**




1 week cycle length + half cycle correction

**EAG comments:** No issues with the model structure and aligns with other TAs for SCLC.

- Comparator -basket of SoC: 38% CAV, 20% platinum + etoposide chemo, 42% topotecan
- OS, PFS (TTD for SoC) TTD data from the MAIC, with extrapolation
- HRQoL data from DeLLphi-301 for pre- and post- progression health states. Same for both arms
- Cost and disutility of Grade 3+ adverse events included & grade 1-2 CRS and ICANs for tarlatamab

AE, adverse event; CRS, cytokine release syndrome; HRQoL, health related quality of life; ICANS, immune effector cell-associated neurotoxicity syndrome; ICER, incremental cost effectiveness ratio; OS, overall survival; QALY, quality adjusted life years; SCLC, small cell lung cancer; TA, technology appraisal

Link to supplementary slides: hazard plots

# Key Issue: Overall survival modelling

*Company selects OS curve based on fit to tarlatamab data; EAG based on fit to SoC*

**Background**

- OS data from DeLLphi-301 trial (tarlatamab) and UK CAS study (SoC)
- Company says proportional hazards do not hold → fits curves to arms separately
- Company uses exponential for OS in both arms based on fit to tarlatamab KM data

**Company:** NICE DSU TSD 14 advises applying same distribution to each arm. Exponential best fits tarlatamab data and produces higher OS estimates than KM data: conservative

**EAG comments**

- Agree proportional hazards assumption not supported.
- UK-CAS data more mature and from larger population than MAIC adjusted DeLLphi-301 data (n=540 vs [redacted])

***Base case***: gamma curve → best fitting to SoC data (visual and statistically) and good fit to tarlatamab data

- Weibull curve also plausible

KM, Kaplan–Meier; n, number; OS, overall survival; SoC, standard of care; DSU, Decision Support Unit; TSD Technical Support Document

# Key Issue: Survival models (2)

Link to supplementary slides: full OS function extrapolations



## OS parametric survival function extrapolations

[redacted]

**Gamma**: EAG preferred → best fit to SoC data

**Exponential**: company preferred → best fit to tarlatamab data

## % SoC arm alive over time with varying parametric curves

| Curve | % alive at year: | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Exponential | [redacted] | [redacted] | [redacted] |
| Gamma | [redacted] | [redacted] | [redacted] |
| Weibull (scenario) | [redacted] | [redacted] | [redacted] |

Tarlatamab, exponential
Tarlatamab, gamma
Tarlatamab, KM
SoC, exponential
SoC, gamma
SoC, KM

KM, Kaplan–Meier; OS, overall survival; SoC, standard of care; SmPC, summary of product characteristics

People having tarlatamab post-progression censored at time of progression in line with SmPC

Should the choice of distribution be informed by data from tarlatamab or SoC?
Which parametric curve best reflects expected survival outcomes for 3rd line SCLC patients?

# Key Issue: Survival models, PFS

*Company prefer log-normal; EAG exponential*

**Exponential**: EAG preferred → avoids different distributions per arm as exponential used for SoC TTD (proxy for PFS)

[redacted]

**PFS parametric survival function extrapolations**

**Log-normal**: company preferred based on best fit to tarlatamab K-M data

Should the same parametric curves be fitted to the data for tarlatamab and SoC? If so, which distribution should be applied? The best fitting to tarlatamab or SoC?

Link to supplementary slides: DeLLphi-301 & Chouaid et al. patient characteristics

# Key issue: Health state utilities

*Company model health state utilities using trial data; EAG use NSCLC estimates*

**Background:** No treatment specific utilities → EQ-5D-5L from DeLLphi-301 mapped to 3L (age and sex adjusted)

**Company:** DeLLphi-301 best represents relevant population and use aligns with NICE methods

**Alternative sources for utility values**

| Health states | Base case | |
|---|---|---|
| | Company: trial data | EAG: Chouaid et al. |
| Baseline | [redacted] | - |
| Progression-free | [redacted] | 0.62 |
| Post-progression | [redacted] | 0.47 |

**EAG:** company's utilities may be overestimated:

- Based on full DeLLphi-301 (N=97) not MAIC population (N=[redacted] → latter better matches SoC population.
- Higher than utilities for 3rd line NSCLC patients (Chouaid et al., N=263)

***Base case:*** utilities from Chouaid et al. (NSCLC) as proxy for SCLC as: a) no well conducted SCLC studies to inform utilities; b) 2/3 EAG's clinical experts suggest QoL for NSCLC similar (may be slightly better) than SCLC

N, number; NSCLC, non-small-cell lung cancer; QoL, quality of life; SCLC, small-cell lung cancer; SoC, standard of care

**Clinical experts:** symptoms similar but SCLC may progress quicker (QoL deteriorates faster) than NSCLC → quicker rate of end organ failure

- Are utility values from NSCLC generalisable to SCLC?
- Which estimates (if any) best reflect QoL for 3rd line SCLC?

QALY, quality-adjusted life year; SoC, standard of care

# QALY weightings for severity

*Both company and EAG agree a 1.7 QALY weight applies*

**Severity modifier calculations and components**

QALYs people without the condition (A)

QALYs people with the condition (B)

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 using the company and EAG base cases**

| Base case | QALYs without condition (trial population characteristics) | Proportional QALY shortfall | Weight |
|---|---|---|---|
| Company (revised) | 12.03 | Over 0.95 | **X 1.7** |
| EAG | 12.03 | Over 0.95 | **X 1.7** |

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

# Summary of company and EAG base case assumptions

*EAG prefer different extrapolations for PFS and OS, HRQoL sources and AE costs*

**Assumptions in company and EAG base case**

| Assumption | Company base case | EAG base case |
|---|---|---|
| OS | Exponential both arms | Gamma both arms |
| PFS | Log-normal tarlatamab<br>Exponential SoC (N.B. TTD used as proxy) | Exponential both arms (to align with curve used for SoC TTD) |
| HRQoL | DeLLphi-301 | NSCLC utilities from Chouaid et al. |
| AE costs | Company calculated values - if multiple HRG codes tended to use highest | EAG recalculated values using weighted average of HRG codes. Updated cost: febrile neutropenia = non sepsis infection |

**EAG corrections to company model:**

- Corrected frequency of CRS / ICANS adverse events
- 4 x 1mg topotecan capsules for cost and capsule size, given 5x not 1x per cycle
- Increased the frequency of blood tests

CRS, cytokine release syndrome; AE, adverse event; HRQoL, health related quality of life; ICANS, immune effector cell-associated neurotoxicity syndrome; NSCLC, non-small-cell lung cancer; SOC, standard of care; TTD, time to discontinuation

# Company base case results

## Company deterministic base case results

| | Total costs (£) | Total QALYs | Inc. costs (£) | Inc. QALYs with severity modifier (£/QALY) | ICER with severity modifier (£/QALY) | ICER without severity modifier (£/QALY) |
|---|---|---|---|---|---|---|
| SoC | [redacted] | [redacted] | - | - | | |
| Tarlatamab | [redacted] | [redacted] | [redacted] | [redacted] | £33,785 | £57,434 |

## Company probabilistic base case results

| SoC | Total costs (£) | Total QALYs | Inc. costs (£) | Inc. QALYs with severity modifier (£/QALY) | ICER with severity modifier (£/QALY) |
|---|---|---|---|---|---|
| SoC | [redacted] | [redacted] | - | - | - |
| Tarlatamab | [redacted] | [redacted] | [redacted] | [redacted] | £34,507 |

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ICER, incremental cost-effectiveness ratio; Inc., incremental; QALYs, quality-adjusted life years.

# EAG exploratory base case results

## EAG cumulative deterministic base case results

| Preferred assumption | Inc. costs | Inc. weighted QALYs | Cumulative weighted ICER £/QALY | Impact |
|---|---|---|---|---|
| EAG corrected company base-case model | [redacted] | [redacted] | £34,958 | - |
| + OS: gamma for both arms | [redacted] | [redacted] | £40,442 | +£5,484 |
| + PFS: exponential for both arms | [redacted] | [redacted] | £42,045 | +£1,603 |
| + HRQoL: use Chouaid et al. | [redacted] | [redacted] | £55,097 | +£13,052 |
| + EAG calculated AE costs: ***EAG base case*** | [redacted] | [redacted] | £58,847 | +£3,750 |

## EAG probabilistic base case results

| Technologies | Inc. costs (£) | Inc. weighted QALYs | Weighted ICER vs. baseline (£/QALY) |
|---|---|---|---|
| Standard of care | - | - | |
| Tarlatamab | [redacted] | [redacted] | £56,825 |

All results include PAS for tarlatamab. QALYs and ICER with 1.7 severity modifier applied.

AE, adverse event; ICER, incremental cost-effectiveness ratio; Inc., incremental; OS, overall survival; QALYs, quality-adjusted life years.

# EAG deterministic scenario analysis

Link to supplementary slides for further company and extrapolation scenarios

*Varying approach to extrapolation & adjusted covariates in MAIC have large effect on ICER*

| Theme | Scenario | Weighted ICER (£/QALY) | Δ from base case |
|---|---|---|---|
| **EAG base case** | | **£58,847** | **-** |
| Varying extrapolation | Exponential for OS | £51,592 | -£7,255 |
| | Weibull for OS | £60,640 | +£1,793 |
| | Post-progression tarlatamab not censored (OS & TTD) | £69,309 | +£10,462 |
| MAIC covariates | No matching for age and sex at diagnosis (because may not be prognostic) | £45,730 | -£13,117 |
| | Only 3 main prognostic factors considered 'very important' by company clinical experts (ECOG PS, disease stage, response to previous treatment) | £39,720 | -£19,127 |
| Utilities | Treatment-specific utility values in PFS state | £53,056 | -£5,791 |
| | QoL values from Nafees et al. (NSCLC) | £56,412 | -£2,435 |

All results include PAS for tarlatamab. QALYs and ICER with 1.7 severity modifier applied.

AE, adverse event; ICER, incremental cost-effectiveness ratio; Inc., incremental; MAIC, Matching Adjusted Indirect Comparison; OS, overall survival; QALYs, quality-adjusted life years.

# Company deterministic scenario analysis

*Varying adjusted covariates in MAIC only scenario to lower ICER under 30K*

| Scenario | Incremental costs | Incremental QALYs | Weighted ICER (£/QALY) | Change in ICER |
|---|---|---|---|---|
| Scenarios applied to company base case before clarification: | | | **£33,774** | |
| No matching for age and sex at diagnosis (because may not be prognostic) | [redacted] | [redacted] | £23,290 | -£10,484 |
| Only 3 main prognostic factors considered 'very important' by company clinical experts (ECOG PS, disease stage, response to previous treatment) | [redacted] | [redacted] | £21,328 | -£12,446 |

All results include PAS for tarlatamab. QALYs and ICER with 1.7 severity modifier applied.

AE, adverse event; ICER, incremental cost-effectiveness ratio; Inc., incremental; MAIC, Matching Adjusted Indirect Comparison; OS, overall survival; QALYs, quality-adjusted life years.

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# Equality considerations

No equalities issues were raised during the course of this appraisal

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- ✓ **Summary**

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# Key issues

| Issue | ICER impact |
|---|---|
| **Comparator:** Is BSC a comparator for tarlatamab? Would people who currently have BSC have tarlatamab if it was a treatment option? | Unknown |
| **Population:** Would people with ECOG performance status 2+ have tarlatamab in clinical practice? | Unknown |
| **Uncertainty in the MAIC:**<br>• Have the appropriate covariates been adjusted for in the analyses?<br>• What is the extent of the uncertainty in the indirect comparison? | Large |
| **Overall survival and progression free survival extrapolations:** Should the same parametric curves be fitted to the data for tarlatamab and SoC? If so, is it appropriate to use the best fitting to tarlatamab or SoC? | Large |
| **Health state utilities:** Should utilities derived from the tarlatamab trial or NSCLC literature be used? | Large |

BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group (ECOG); ICER, incremental cost effectiveness ratio; ITC, indirect treatment comparison; MAIC, matching adjusted indirect comparison; NSCLC, non-small cell lung cancer; SoC, standard of care

# Tarlatamab for previously treated advanced small-cell lung cancer ID6364

# Supplementary appendix

NICE National Institute for Health and Care Excellence

# Decision problem

Link to main slides: Population and comparators

**Population, intervention, comparators and outcomes from the scope**

| | Final scope | Company | EAG comments |
|---|---|---|---|
| **Population** | Adults with advanced SCLC with disease progression on or after prior therapy | Adults with advanced SCLC after platinum-based chemotherapy and ≥1 other treatment | Narrower than scope and draft SmPC indication: 3rd line+. |
| **Intervention** | Tarlatamab | Tarlatamab 10 mg Q2W | In line with scope |
| **Comparators** | Established clinical management without tarlatamab, which may include:<br>• Chemotherapy, including anthracycline-containing or platinum-based regimen.<br>• Oral topotecan (when re-treatment with 1L regimen not considered appropriate & cyclophosphamide, doxorubicin + vincristine contraindicated)<br>• Best supportive care | No dedicated 3L options<br>Basket of comparators including:<br>• Topotecan<br>• Cyclophosphamide + doxorubicin + vincristine<br>• Carboplatin + etoposide | Basket of comparators appropriate but further clinical expert opinion needed about whether or not best supportive care is also a relevant comparator. |
| **Outcomes** | Overall survival, progression-free survival, response rates, adverse effects of treatment, health-related quality of life. | As per scope | In line with scope |

NICE

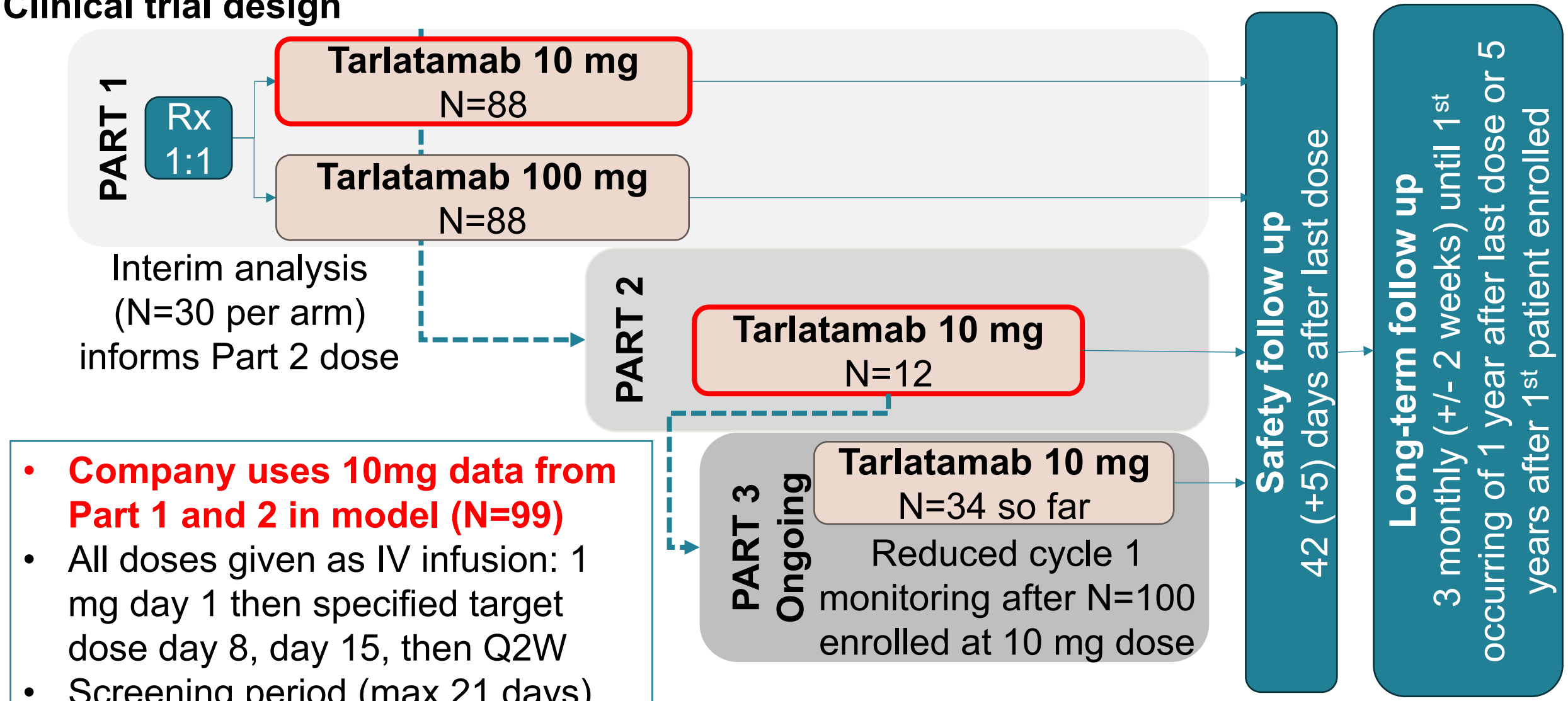
Q2W, 2 weekly; SCLC, small cell lung cancer; SmPC, summary of product characteristics

# 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



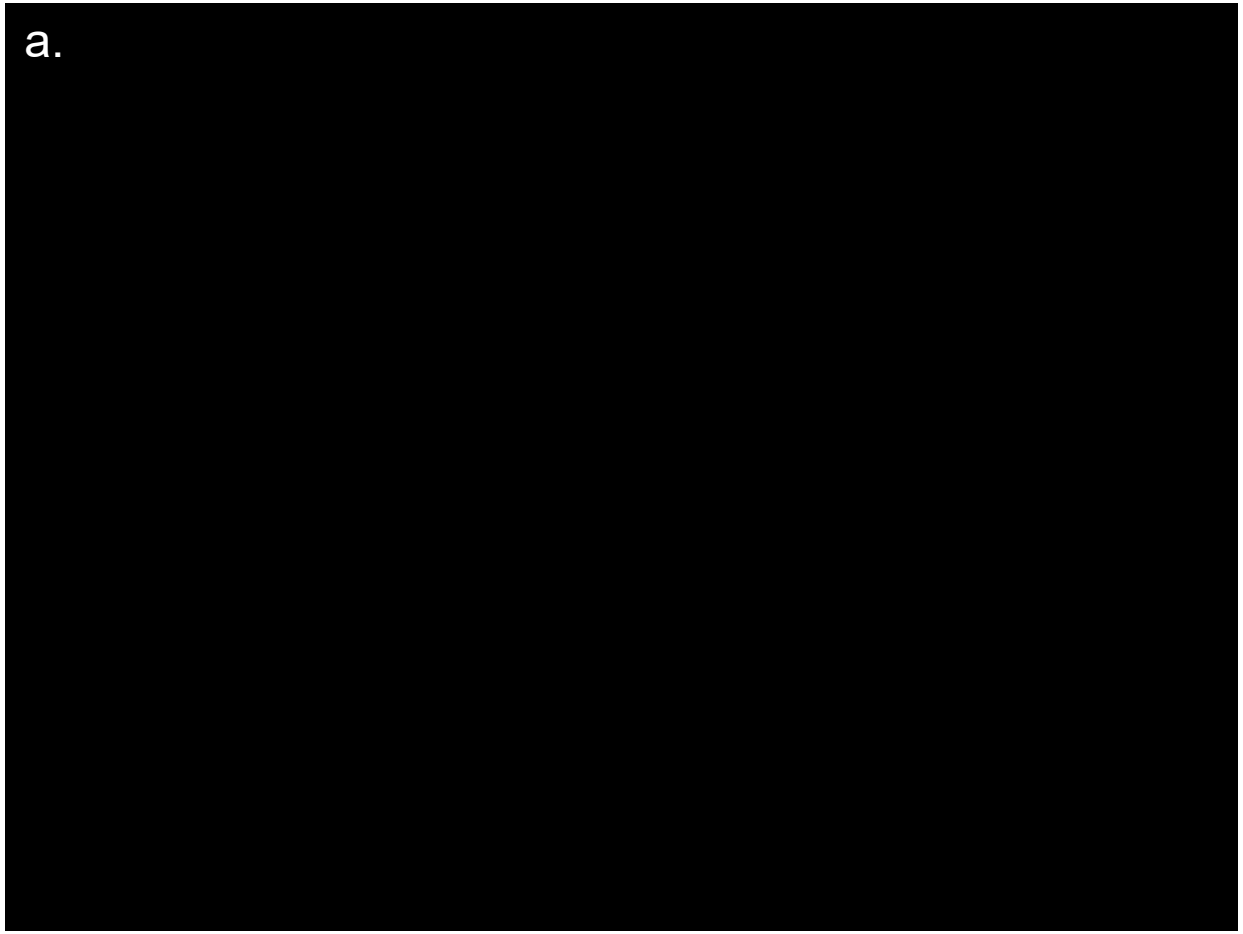

- **Company uses 10mg data from Part 1 and 2 in model (N=99)**
- All doses given as IV infusion: 1 mg day 1 then specified target dose day 8, day 15, then Q2W
- Screening period (max 21 days) for all study stages

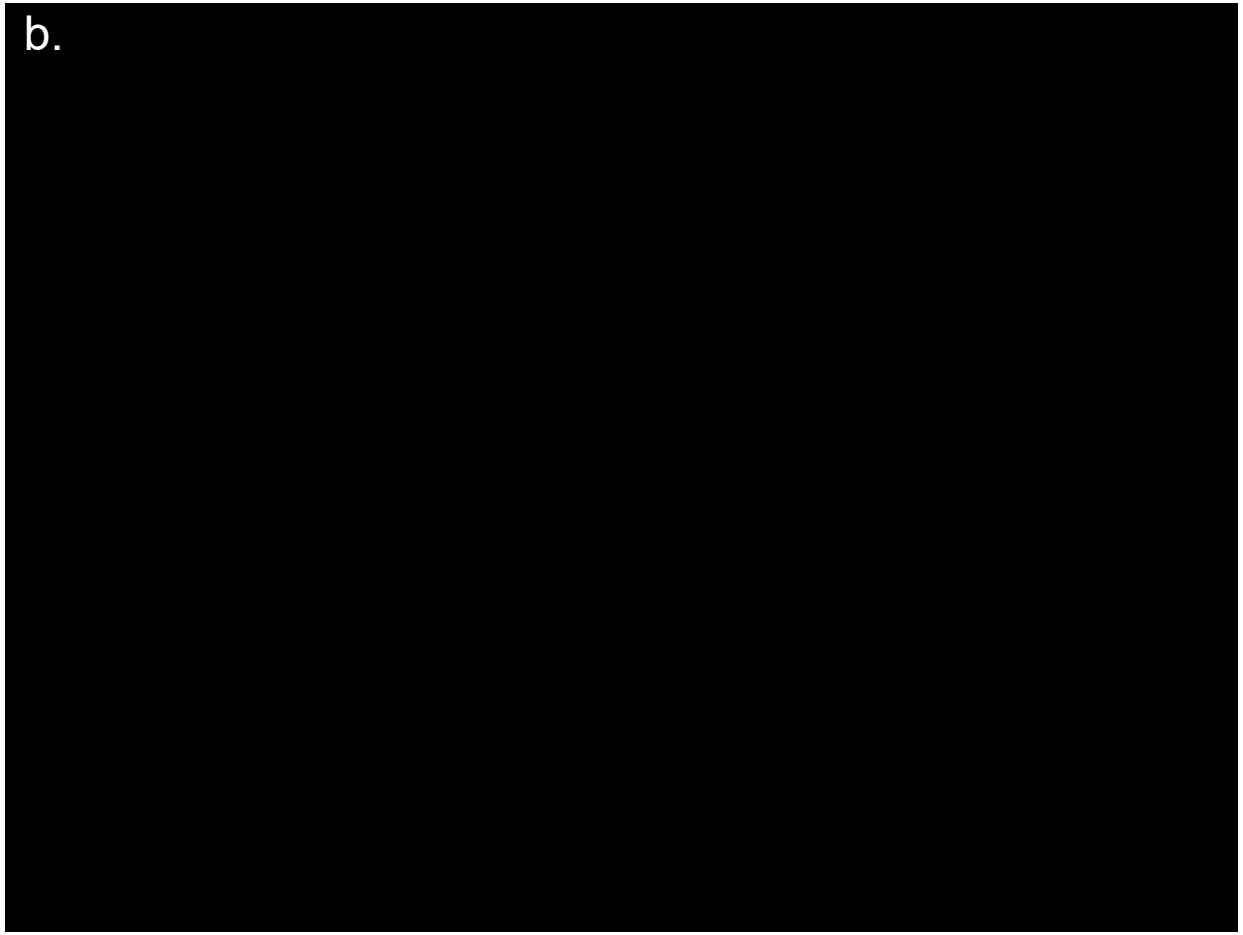
IV, intravenous; mg, milligram; N, number; Q2W, 2 weekly; Rx, randomisation

# DeLLphi-301 trial, Kaplan-Meier plots for PFS and OS

*Trial reports median PFS of ~5 months and OS of ~14 months with tarlatamab*

## DeLLphi-301 Kaplan-Meier plot: a) PFS and b) OS




Results presented in BICR Full Analysis Set (people who had ≥1 dose tarlatamab and ≥ 1 measurable baseline lesions (assessed by BICR using RECIST 1.1 criteria) in part 1 or 2, N=99),10mg group. OS results censor people treated beyond progression.

BICR; Blinded independent central review; CI, confidence interval; N, number; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response evaluation criteria in solid tumours; TTD, time to discontinuation

# DeLLphi-301: Adverse events of special interest

Tarlatamab associated with increased rates of:

- Cytokine release syndrome (CRS): acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction.
- Immune effector cell associated neurotoxicity syndrome (ICANs): pathological process involving CNS.
  - ❖ Neurological symptoms including headache, pain, short-term memory loss, altered mental status, impaired speech (dysarthria and/or aphasia), impaired cognitive skills, motor weakness, movement disorders (tremor, myoclonus and/or facial automatisms), seizures, encephalopathy and cerebral oedema

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

| Event of Interest, n (%) | All | Grade 2 | Grade 3 |
|---|---|---|---|
| Cytokine release syndrome | 49 (49.5) | [redacted] | 0 (0.0) |
| ICANs and associated neurological events | 7 (7.1) | [redacted] | [redacted] |
| Neurological events | [redacted] | [redacted] | [redacted] |
| Neutropenia | [redacted] | [redacted] | 6 (6.1) |

- Treatment related AEs reported in 89% patients. 31% of people had an AE leading to dose interruption and/or reduction of tarlatamab
- 7 treatment emergent AEs led to discontinuation of tarlatamab



AE, adverse event; CNS, central nervous system; mg, milligram; N, number.

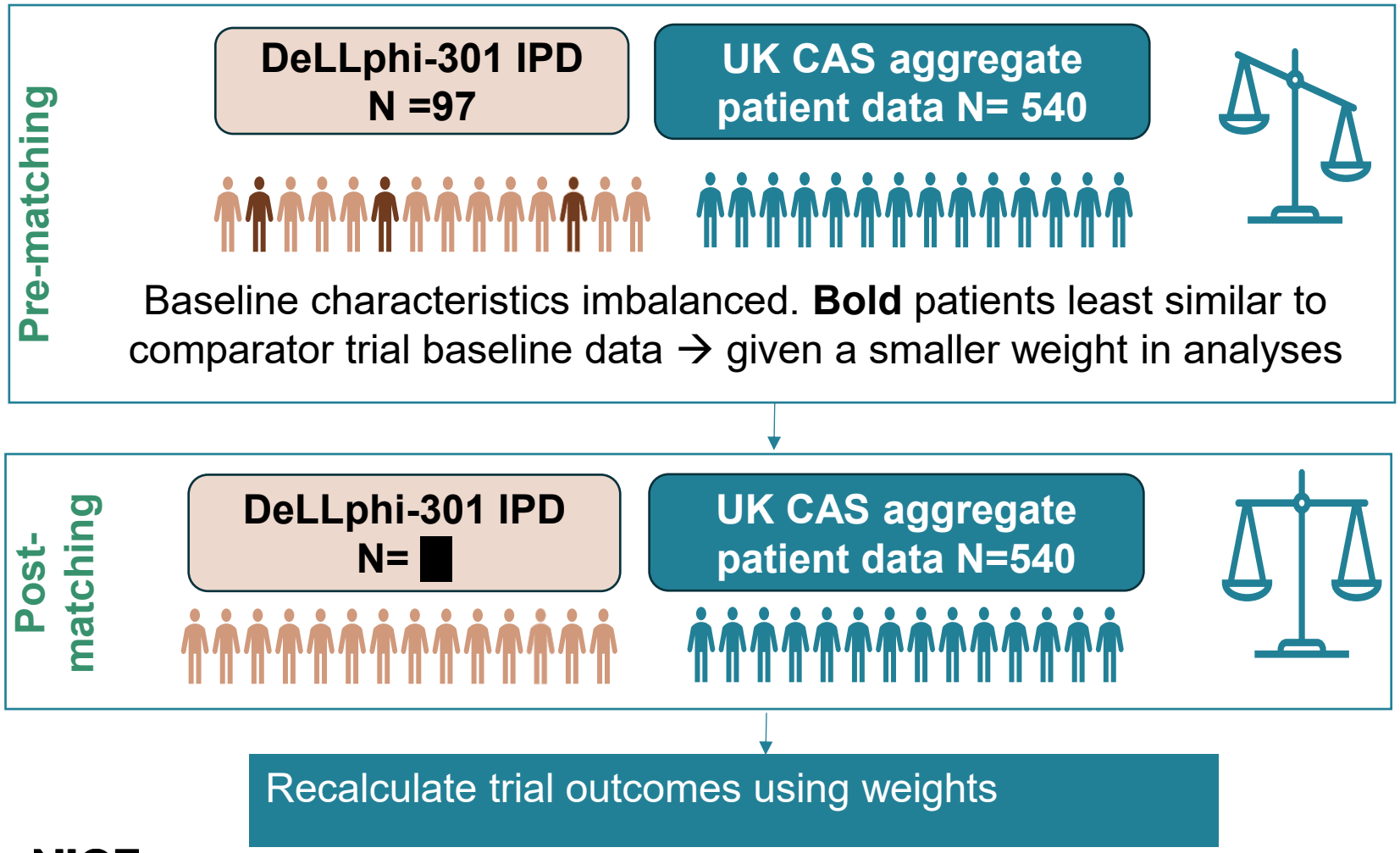
Link to main slides: DeLLphi-301 trial results

Link to main slides: Company's ITC

# Company's ITC methodology

*MAIC associated with uncertainty because only uses IPD data from intervention study*

**Methodology of the MAIC**




- No IPD data for UK-CAS study
- Company weight DeLLphi-301 baseline characteristics to balance covariates across trials
- People treated post progression censored from OS analysis and TTD
- **High uncertainty,** especially if covariate overlap poor (small ESS) and not all prognostic factors included
- MAIC assumes population in comparator study more representative of target patient population than intervention's trial's population

ESS, effective sample size; IPD, individual patient data; MAIC, matching adjusted indirect treatment comparison; N, number; OS, overall survival; TTD time to discontinuation

Link to main slides: Company's ITC

# UK CAS study: data sources and availability

*MAIC uses aggregate data from multiple national databases*

**Data sources used in the UK CAS study**

| Source | Data used | Data availability |
|---|---|---|
| Cancer Outcomes and Services Dataset (COSD) | • Diagnoses<br>• Demographics and clinical characteristics at diagnosis | 1st July 2011 to 31st December 2020 |
| Systemic Anti-Cancer Therapy (SACT) database | • Post-diagnosis treatment use and clinical outcomes | July 2011 to 31st May 2022 |
| Hospital Episodes Statistics (HES) | | July 2011 to May 2022 |
| Radiotherapy treatment data (RTDS) | | July 2011 to May 2022 |
| National Death registry (held by ONS) | • Mortality | July 2011 to 31st May 2022 |

MAIC, matching adjusted indirect treatment comparison; ITC, indirect treatment comparison; ONS, Office for National Statistics

# Comparison of DeLLphi-301 and CAS Control Cohorts

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

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;

Link to main slides: Company's ITC results



# Company's ITC scenarios

*Results favour tarlatamab vs comparators in all analyses (HR less than 1)*

**MAIC base case results and scenarios. ESS shown for tarlatamab (ESS SoC = 540).**

| Analysis | Rationale for scenario | ESS | OS | PFS |
|---|---|---|---|---|
| | | | HR (95% CI) | HR (95% CI) |
| **MAIC: company and EAG base case** | | [redacted] | **0.367 (0.202, 0.667)** | **0.184 (0.100, 0.340)** |
| Scenarios removing following covariates: | | | | |
| - chemotherapy-free interval | 30% DeLLphi-301 missing outcome | [redacted] | [redacted] | [redacted] |
| - ES-SCLC at diagnosis | Proxy for preferred outcome, stage at treatment initiation | [redacted] | [redacted] | [redacted] |
| - Sex and age at diagnosis | Unclear if prognostic from expert elicitation and meta-analysis | [redacted] | [redacted] | [redacted] |
| Including only 'very important' covariates | EAG requested → increases ESS | [redacted] | [redacted] | [redacted] |
| [redacted] | Base case assumptions varying data sources for SoC treatment effect | [redacted] | [redacted] | [redacted] |
| [redacted] | | [redacted] | [redacted] | [redacted] |
| TTD for tarlatamab | Not presented: company states weights equal regardless of outcome | | | |

CI, confidence interval; ES-SCLC, extensive stage small-cell lung cancer; ESS, effective sample size; HR, hazard ratio; MAIC, matching adjusted indirect comparison; N, number; OS, overall survival; PFS, progression free survival; SoC, standard of care

# Key Issue: Survival models

Link to main slides: Key issue: survival models (1)



*Proportional hazards do not hold for OS and PFS. Company fitted independent treatment*

**PFS (treated until progression)**

[redacted]

**OS (treated until progression)**

[redacted]

IV, intravenous; mg, milligram; OS, overall survival; PFS, progression free survival; SoC, standard of care

# Key Issue: Survival models, OS

*Company prefer exponential; EAG prefer gamma*

Link to main slides: Key issue: survival models (2)

## Full OS parametric survival function extrapolations

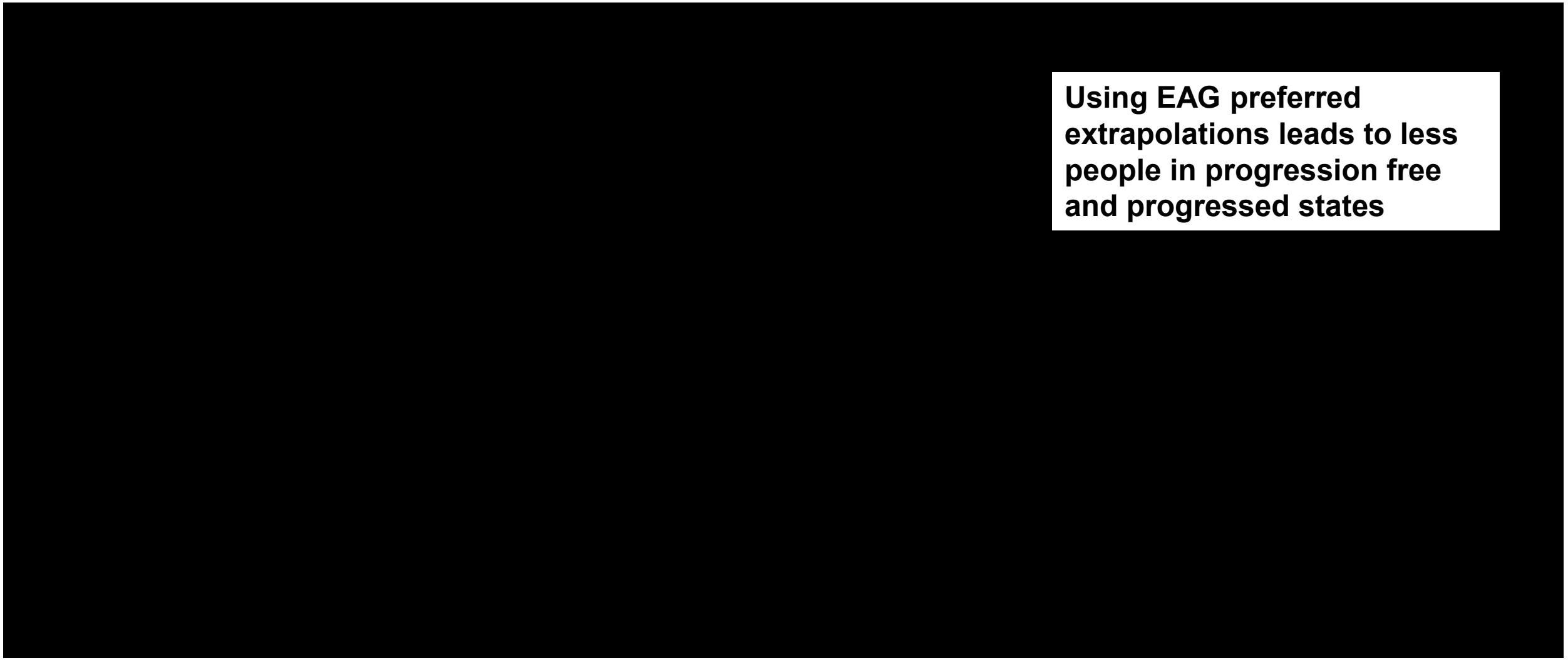
- Company preferred exponential → best fit to tarlatamab K-M data
- EAG preferred gamma → best fit to SoC data



K-M, Kaplan–Meier; OS, overall survival; SoC, standard of care

# Model outputs: health state occupancy

*More time in progression free and progressed health state with tarlatamab vs SoC*




PFS, progression free survival; PD, progressed disease; SoC, standard of care

# DeLLphi-301 and Chouaid et al baseline characteristics

| | DeLLphi-301 (N=99) | Chouaid et al. n = 263 |
|---|---|---|
| Male n (%) | 71 (71.7%) | 161 (61.2%) |
| Smoking history, n (%) | | |
| Never-smoker | 8 (8.1%) | 41 (15.6%) |
| Current/ever-smoker | 91 (91.9%) | 219 (83.3%) |
| Clinical stage at first diagnosis, n (%) | | |
| Ia–IIIa | N/R | 30 (11.4%) |
| IIIb | N/R | 44 (16.7%) |
| IV | N/R | 156 (59.3%) |
| Metastatic | 97 (98.0%) | |
| Clinical stage at time of survey, n (%) | | |
| IIIb | 5 (5.1%) | 47 (17.9%) |
| IV | 87 (87.9%) | 216 (82.1%) |
| Mean Charlson Comorbidity Index (SD) | N/R | 6.45 (0.9) |
| ECOG status at baseline , n (%) | | N/R |
| 0 | 26 (26.3%) | N/R |
| 1 | 73 (73.7%) | N/R |
| Line of treatment, n (%) | | |
| First- | 2 (2.0%) | 145 (55.1%) |
| Second- | 65 (65.7%) | 65 (24.7%) |
| Third/fourth- | 32 (32.3%) | 47 (17.9%) |
| BSC | N/R | 6 (2.3%) |

ECOG, Eastern Cooperative Oncology Group; n, number; SD, standard deviation

# Other issues identified by the EAG

Link to main slides: Assumptions in EAG and company base case



*EAG amends issues with costs and resource use in its base case*

| EAG comment | EAG base case (b.c) or scenario (s.) |
|---|---|
| Company uses log-normal for tarlatamab PFS and exponential for SoC TTD (proxy for PFS). | **B.c.** Exponential: best fit for SoC data. Varying curves per arm inappropriate |
| Company mostly chose highest cost code for AEs where several available. Inconsistent cost code choice febrile neutropenia & non-sepsis infection | **B.c.** Weighted average of all relevant cost codes. Costs febrile neutropenia = non-sepsis infection |
| Company: 16 x 0.25mg topotecan capsules but mean dose 4.094mg (2.3mg/$m^2$ x average BSA 1.78$m^2$). | **B.c.** 4 x 1mg topotecan capsules for cost and capsule size |
| Topotecan administration frequency incorrect | **B.c.** topotecan 5x not 1x per cycle |
| EAG's clinical experts: blood test frequency high | **B.c.** 0.29 not 0.13 per week |
| Von Pawel et al., 1999 reports 0% for several AEs with CAV → implausible? | **S.** CAV AE rates = average of topotecan & platinum chemo |
| No additional costs for PD when no subsequent treatment. Clinical experts: patients still monitored | **S.** 0.1 hospital visits, 0.25 GP visits & 0.5 community nurse visits/week |

AE, adverse event; BSA, body surface area; CAV, cyclophosphamide, doxorubicin and vincristine; m, meter; mg, milligram; PFS, progression free survival; SoC, standard of care; TTD, time to discontinuation

# Deterministic scenario analysis varying OS extrapolation

*Choice of curve has large impact on ICER*

| Scenario | Applied to company base case | | Applied to EAG base case | |
|---|---|---|---|---|
| | Weighted ICER (£/QALY) | Change from base case | Weighted ICER (£/QALY) | Change from base case |
| **Base case** | **£33,785** | **-** | **£58,847** | **-** |
| Exponential | - | - | £51,592 | -£7,255 |
| Gamma | £39,074 | +£5,289 | - | - |
| Weibull | £40,449 | +£6,664 | £60,640 | +£1,793 |
| Lognormal | £21,665 | -£12,120 | £33,767 | -£25,080 |
| Log-logistic | £23,778 | -£10,007 | £36,959 | -£21,888 |
| Gompertz | £45,030 | +£11,245 | £66,338 | +£7,491 |
| Generalised gamma | £16,664 | -£17,121 | £26,162 | -£32,685 |

All results include PAS for tarlatamab. QALYs and ICER with 1.7 severity modifier applied.

ICER, incremental cost-effectiveness ratio; Inc., incremental; PAS, patient access scheme; OS, overall survival; QALYs, quality-adjusted life years. Link to main slides EAG deterministic scenarios

# Company deterministic scenario analysis

*Varying adjusted covariates in MAIC only scenario to lower ICER under 30K*

| Scenario | Incremental costs | Incremental QALYs | Weighted ICER (£/QALY) | Change in ICER |
|---|---|---|---|---|
| **Company revised base case** | [redacted] | [redacted] | **£33,785** | |
| Time horizon 5 years | [redacted] | [redacted] | £35,280 | +£1,495 |
| Time horizon 15 years | [redacted] | [redacted] | £33,743 | -£42 |
| Treatment-specific utility values used the PFS state | [redacted] | [redacted] | £33,011 | -£774 |
| All SOC patients received topotecan | [redacted] | [redacted] | £32,300 | -£1,485 |
| All SOC received CAV | [redacted] | [redacted] | £34,983 | +£1,198 |
| All SOC patients received platinum-based chemotherapy | [redacted] | [redacted] | £34,631 | £846 |
| No post-infusion hospitalisation costs for tarlatamab | [redacted] | [redacted] | £32,935 | -£850 |
| Do not adjust tarlatamab OS & TTD for post-progression use | [redacted] | [redacted] | £43,548 | +£9,763 |
| Scenarios applied to company base case before clarification: | | | **£33,774** | |
| MAICs omitting age + sex at diagnosis | [redacted] | [redacted] | £23,290 | -£10,484 |
| MAICs using only include 3 main prognostic factors | [redacted] | [redacted] | £21,328 | -£12,446 |

All results include PAS for tarlatamab. QALYs and ICER with 1.7 severity modifier applied.



ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; QALYs, quality-adjusted life years.

# Managed access

**Company has not made a managed access proposal for this topic**

Criteria for a managed access recommendation

**Reminder: The committee can make a recommendation with managed access if:**

- 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**.