# Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer

For screen – contains redacted information

**Technology appraisal committee D [03 October 2024]**

**Chair:** Megan John

**Lead team:** Paul Caulfield, Sofia Dias, Craig Cook

**External assessment group:** University of Bristol Technology Assessment Group

**Technical team:** George Millington, Albany Chandler, Ian Watson

**Company:** AstraZeneca

# Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer

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

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# Background on EFGR- positive non-small-cell lung cancer

## Epidemiology

- In 2022, 36,886 new lung cancer cases in England of which 80-85% are NSCLC
- Around 15% of advanced NSCLC cases have EFGR mutations
- Median age of diagnosis 60 years old, more common in females and non-smokers

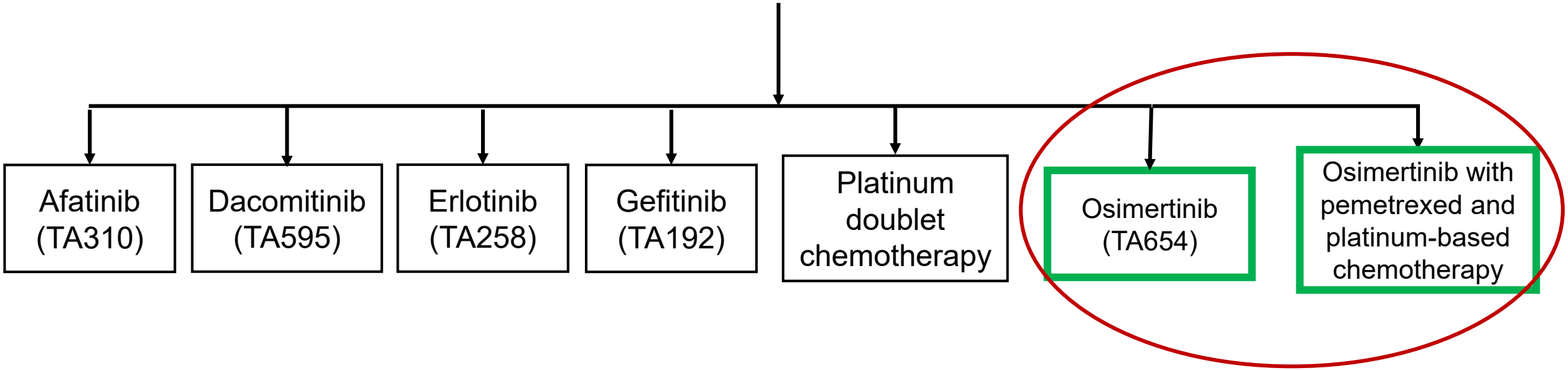
## Symptoms

- Symptoms are non-specific and may be disregarded leading to advanced cancer diagnosis

## Prognosis

- In 2022, 66% of NSCLC diagnoses were in advanced stages (3/4)
- Estimated 5-year survival for advanced stages was 7.7% from 2016-2020
- Advanced lung cancer frequently metastasise to the central nervous system (brain metastasis)

# Treatment pathway for previously untreated locally advanced or metastatic EGFR-positive NSCLC




**Company**

Osimertinib monotherapy is the current standard of care for patients in England who are receiving first-line treatment for locally advanced or metastatic NSCLC. Osimertinib monotherapy is given to 86% of EGFRm patients.

**EAG**

The EAG has no concerns regarding the choice of comparator.

# Clinical perspectives

## Submission from British Thoracic Oncology Group

- Main aim of treatment is to prolong survival and maintain or improve quality of life
- An improvement of 3 or more months to OS or PFS is clinically significant
- The accepted standard of care first line treatment is osimertinib
- Osimertinib plus chemo is expected to improve survival but will also increase toxicity, although this should be manageable with extra resource and consideration of side effects
- Treatment would be discontinued on loss of clinical benefit or unmanageable toxicities

# Patient perspectives

**Submissions from Roy Castle Lung Cancer Foundation and a carer**

- EGFR mutation patients tend to be diagnosed later, as they do not fit the ‘typical’ lung cancer patient profile
- Targeted therapies, such as osimertinib, have been a major step forward in the treatment of lung cancer, and a great source of hope for patients. However, disease progression is likely to occur eventually
- Progression free survival appears to be longer when osimertinib is in combination with pemetrexed and platinum-based chemotherapy
- Osimertinib side effects can be debilitating, adding chemotherapy will likely decrease the quality of life of people receiving treatment
- Osimertinib is an oral therapy, so can be acquired from pharmacies. Adding chemotherapy will require IV treatment and more time spent at hospitals

# Equality considerations

No equalities issues were raised by any stakeholders during the appraisal process

- Will osimertinib with pemetrexed and platinum-based chemotherapy only be suitable for fitter people?
- Does the committee consider that there are any relevant equality issues that it should consider in its decision making and, if so, how?

# Key issues

| Key issues | ICER impact |
|---|---|
| Subgroups according to central nervous system (CNS) metastases | Large |
| Extrapolation of overall survival | Moderate |
| Extrapolation of time to treatment discontinuation | Large |
| Progression free health state utility | Moderate |
| Measurement of resource use | Moderate |
| Assumptions on subsequent treatments at second line (2L) | Large |

| Other issues (smaller impact on ICER) |
|---|
| Average starting age in the model |
| Distribution of platinum chemotherapy |
| Relative dose intensity (RDI) of chemotherapy |
| Progressed disease health state utility |
| Unit costs |

# Osimertinib (Tagrisso, AstraZeneca)

Technology details

| | |
|---|---|
| **Marketing authorisation** | • Osimertinib is indicated in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.<br>• Marketing authorisation was granted in September 2024 |
| **Mechanism of action** | • Highly selective and irreversible inhibition of activating sensitising EGFR mutation (EGFRm+) and activating resistance mutation T790M |
| **Administration** | • 80mg oral dose once daily |
| **Price** | • List price of £5,770 per 30 tablets (40 mg or 80 mg)<br>• Average cost of a course of treatment at list price is £104,705.51<br>• Osimertinib has a commercial arrangement |



Abbreviations: EGFR, epidermal growth factor receptor; MHRA: Medicines and Healthcare products Regulatory Agency; NSCLC: non-small cell lung cancer; PAS: patient access scheme

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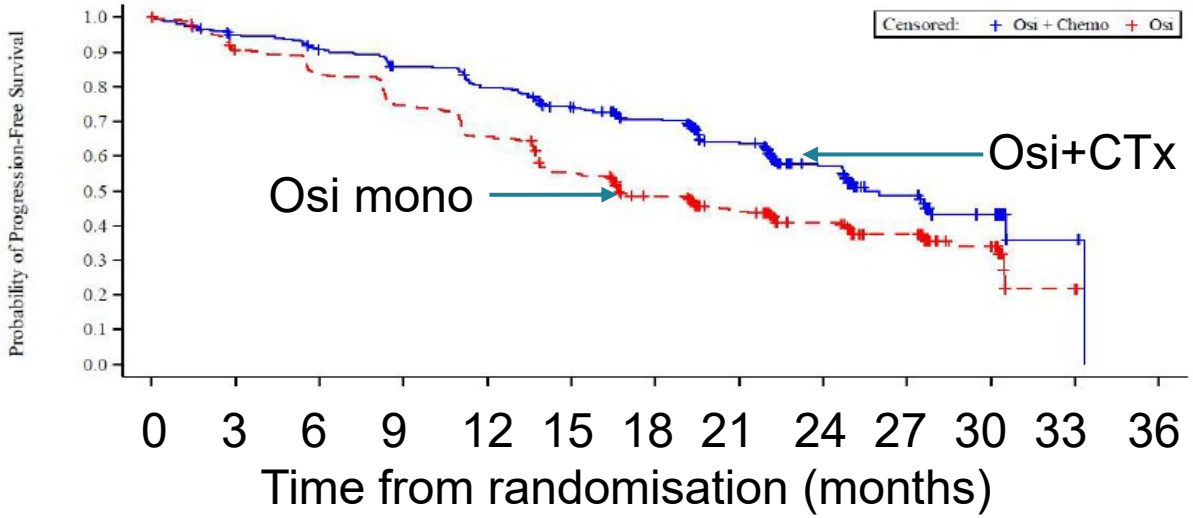
# Key clinical trial results – FLAURA2

For more info
see appendix

## Osimertinib+chemo (n=279) improves PFS and OS compared to osimertinib mono (n=278)

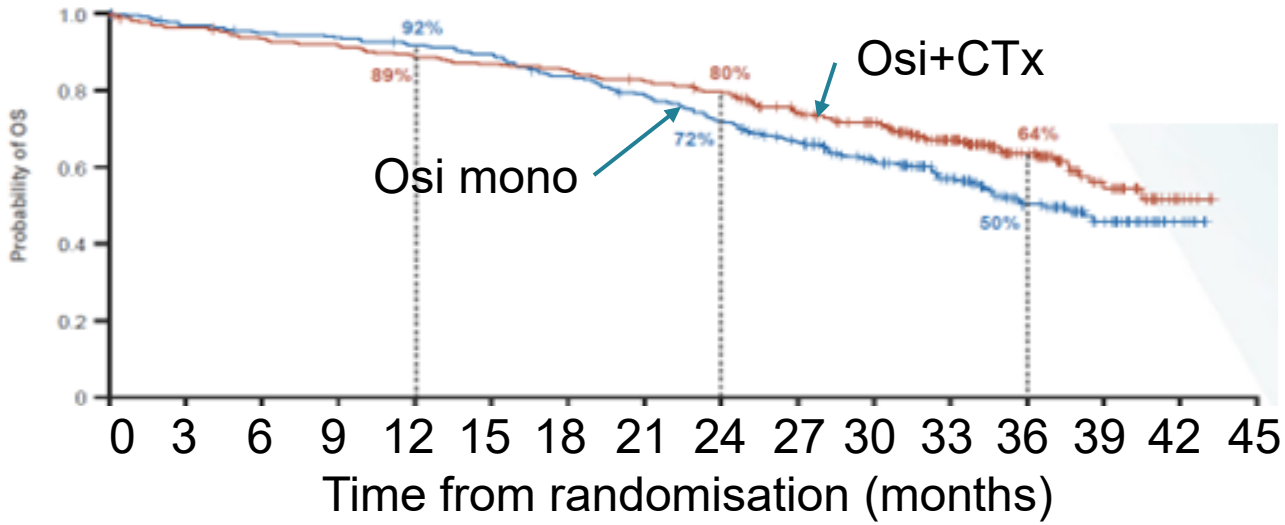
### Osimertinib+chemo vs osimertinib mono – PFS randomised period - FAS




| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CTx | 279 | 254 | 241 | 225 | 207 | 187 | 165 | 133 | 84 | 42 | 21 | 3 | 0 |
| Mono | 278 | 246 | 227 | 203 | 178 | 148 | 119 | 94 | 67 | 48 | 21 | 1 | 0 |

| | |
|---|---|
| HR (95% CI; p-value) | 0.62 (0.49, 0.79) p<0.0001 |

### Osimertinib+chemo vs osimertinib mono – OS January 2024 DCO




| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CTx | 279 | 267 | 258 | 253 | 245 | 240 | 236 | 226 | 218 | 190 | 169 | 121 | 71 | 31 | 5 | 0 |
| Mono | 278 | 267 | 260 | 257 | 251 | 244 | 228 | 213 | 195 | 170 | 142 | 102 | 64 | 34 | 7 | 0 |

| | |
|---|---|
| HR (95% CI) | 0.75 (0.57, 0.97) |

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Abbreviations: CI, confidence interval; CTx, chemotherapy; DCO, data cut off; FAS, full analysis set; HR, hazard ratio; OS, overall survival; PFS, progression free survival

# Key issues: Subgroups according to CNS metastases

Subgroup results

Osimertinib plus chemotherapy appears more cost-effective in people with CNS metastases

## Background

- No subgroups identified in the NICE scope or company submission

## Company

- Data indicates osi+chemo offers clinically meaningful CNS benefit vs osimertinib alone
- CNS metastases may disrupt blood-brain barrier, facilitating penetration of chemotherapy
- Subgroup results consistent with ITT - ITT remains decision making population of interest

## EAG comments

- FLAURA2 indicates that osimertinib plus chemotherapy may have a greater benefit for both PFS and OS in people with baseline CNS metastases - no statistically significant differences between subgroups, although analyses lacked statistical power
- EAG clinical advisors said they would like to use osi+chemo in this subgroup
- With company's base-case settings, CNS metastases subgroup more cost effective

## Tech team comments

- CNS metastases subgroups considered appropriate in another NSCLC TA (TA909)

Are people with CNS metastases before treatment a clinically distinct and identifiable subgroup?

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# Key issue: Extrapolation of overall survival

Company prefer 2-knot normal model for both treatments, EAG prefer odds and 1-knot for osi mono

## Background

- Company analysed OS from January 2024 DCO, OS data violated PH assumption, requiring separate models for each arm – EAG agree. From visual inspection, company determined standard parametric models not suitable
- Final OS DCO will be conducted when data are approximately 60% mature

## Company

- 2-knot normal model for osi mono aligns closest with long-term OS estimates of clinicians
- 2-knot normal model for osi+chemo provided best fit, gave conservative long-term OS

## EAG comments

- Trial data (FLAURA) for osi mono suggests around 38% OS at 4 years, likely lower in FLAURA2 due to higher proportion of people with CNS metastases
- 1-knot odds spline model for osi mono fits trial data, also aligns with company clinical experts: OS 35% at 4 years, 25% at 5 years, 5% at 10 years
- 2-knot odds spline model for osi+chemo shows OS curves converging but still slightly separated at 10 years - aligns with company prediction of when both arms stop 1L treatment



Abbreviations: 1L, first line; CNS, central nervous system; DCO, data cut-off; OS, overall survival; PH, proportional hazards; TTD, time to treatment discontinuation

# Key issue: Extrapolation of overall survival

For graphical version – see appendix

**Osimertinib monotherapy** – observed data and company and EAG preferred models

| | Mean | Med | 1 year | 2 years | 3 years | 5 years | 10 year | 15 years |
|---|---|---|---|---|---|---|---|---|
| Observed | - | 36.5 months | 92.0% | 72.1% | 50.3% | - | - | - |
| Pred. (2 knot normal - company) | 46.2 months | 36.5 months | 89.8% | 72.5% | 52.2% | 24.8% | 4.4% | 1.1% |
| Pred. (1 knot odds - EAG) | 49.7 months | 36.5 months | 89.8% | 72.4% | 52.2% | 25.9% | 6.8% | 2.8% |

**Osimertinib plus chemo** - observed data and company and EAG preferred models

| | Mean | Med | 1 year | 2 years | 3 years | 5 years | 10 year | 15 years |
|---|---|---|---|---|---|---|---|---|
| Observed | - | - | 88.8% | 79.7% | 63.7% | - | - | - |
| Pred. (2 knot normal - company) | 53.3 months | 43.4 months | 88.7% | 78.9% | 61.8% | 32.6% | 6.8% | 1.8% |
| Pred. (2 knot odds - EAG) | 54.8 months | 42.4 months | 88.7% | 78.9% | 61.9% | 32.0% | 7.8% | 3.0% |

Which models provide the most plausible long-term OS estimates?

Abbreviations: Med, median; OS, overall survival; pred, predicted

# Key Issue: Extrapolation of time to treatment discontinuation

EAG and company disagree on TTD extrapolation for osi mono arm: company use gamma, EAG Gompertz

**Company**

- Based on AIC and BIC rankings, loglogistic was most suitable TTD extrapolation in the osimertinib monotherapy arm
- Loglogistic predicts decreasing hazard ratio, so may overpredict treatment duration
- Gamma distribution had 2nd best AIC/BIC, did not appear to overpredict treatment duration

**EAG comments**

- Nearly all the osimertinib monotherapy TTD extrapolations are implausible because they gave estimates substantially above the PFS curve
  - PFS curve reasonable and TTD is a bigger driver of ICER than PFS in model so appropriate to consider changes to TTD curve
- Gompertz didn't give best AIC or BIC, but the model fit statistics are adequate, the visual fit appears to be good, and extrapolations are plausible compared with the curve used for PFS
- EAG therefore uses the Gompertz for osimertinib monotherapy TTD in its base-case

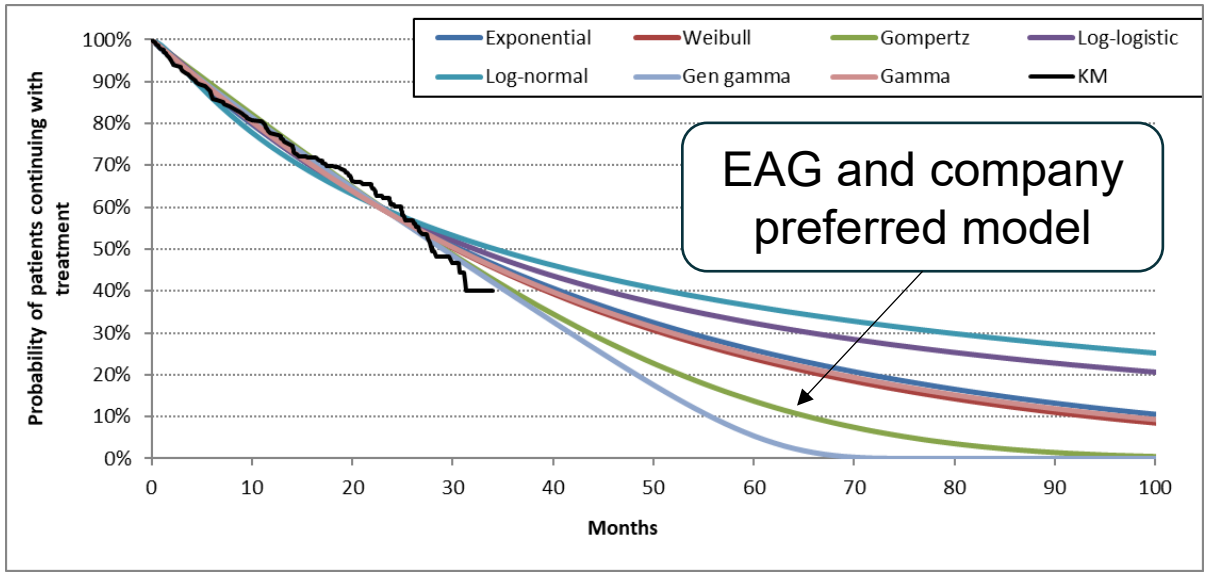


Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; TTD, time to treatment discontinuation

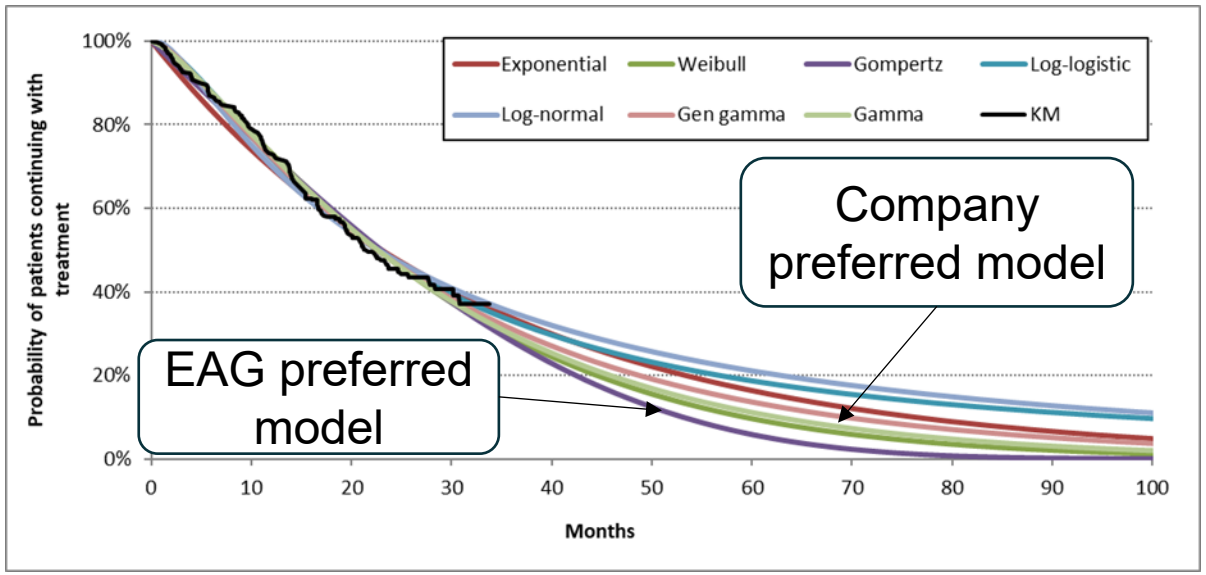
For TTD curves alongside PFS curve – see appendix

# Key Issue: Extrapolation of time to treatment discontinuation

EAG and company disagree on TTD extrapolation for osi mono arm: company use gamma, EAG Gompertz




FLAURA2 TTD Kaplan-Meier and extrapolations for osimertinib plus chemotherapy




FLAURA2 TTD Kaplan-Meier and extrapolations for osimertinib monotherapy

Is the Gompertz or the gamma extrapolation more plausible for osimertinib monotherapy TTD?

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

# Key Issue: Progression free health state utility

EAG concerned that PFS utility is too high

For more info see appendix

**Company**

- Utilities for PFS state from FLAURA2 EQ-5D-5L responses mapped using Hernandez-Alava
- Missing EQ-5D-5L responses are adjusted for using a MMRM model
- Disutility applied to osi+chemo arm at model start to account for AEs due to chemotherapy use
- Disutility values and adverse event durations were obtained from TA654 submission

**Other considerations**

- Patient expert noted AEs of osimertinib can be debilitating, adding chemo may worsen QoL

**Table** Company and EAG base case PFS utility and utility decrement from chemo use in each arm

| | Company base case | EAG base case |
|---|---|---|
| **Base PFS utility** | [redacted] | 0.794 |
| **Chemo decrement** | [redacted] | [redacted] |
| **Length of decrement** | First model cycle (30 days) | Entire PFS health state (osi+chemo only) |

Abbreviations: AEs, adverse events; MMRM, mixed models for repeated measures; PFS, progression free survival; QoL, quality of life

# Key Issue: Progression free health state utility

EAG concerned that PFS utility is too high

For more info
see appendix

**EAG comments**

- PFS values lack face validity compared with general population (0.799 for age 55 to 64) and NSCLC population in literature. Possible reasons for overestimate:
  - Missing utility data may overvalue PFS utility - MMRM not adequate to address bias as more missing data for osi+chemo group, specifically in period on chemo when QoL expected to be lower due to adverse events
  - Mapping model may derive higher than expected utilities
- AE disutility from chemo use too small and would last longer than first model cycle
- EAG's alternative approach:
  - use TA654 PFS utility (0.794)
  - apply utility decrement to mean duration of PFS in osi+chemo arm, calculated from the difference in improvement in utility from baseline to mean progression-free period between arms ([redacted])

What utility value should be used for the progression free health state?
How should the effect of chemo on quality of life be captured in the model?

# Key Issue: Measurement of resource use

Company and EAG differ in updates to resource use source

For discussion of unit costs see appendix

**Background**

- Company incorporated resource use from Brown et al. (2013), updated based on advice from their clinical experts

**Company**

- Brown et al. has been used as the resource use source in many previous NSCLC TAs
- Clinical feedback was sought to ensure inputs were reflective of current UK clinical practice

**EAG comments**

- Brown et al. resource estimations are a decade old - fewer treatment options were available
- Sought own clinical advice to update Brown et al. resource use estimations



Abbreviations: NSCLC, non-small-cell lung cancer; TA, technology appraisal

# Key Issue: Measurement of resource use

For discussion of unit costs see appendix

Company and EAG differ in updates to resource use source

| | Progression-free health state* | | Progressed disease health state* | |
|---|---|---|---|---|
| Resource type | Company base-case | EAG base-case | Company base-case | EAG base-case |
| Outpatient visits | 9.61 | 12.175 | 7.91 | 9.5 |
| MRI scans | 2.00 | 2 (or 4 for those with CNS metastases) | 2.00 | 2 (or 4 for those with CNS metastases) |
| CT scans (chest) | 0.62 | 2 | 0.24 | 2 |
| CT scans (other) | 0.36 | 2 | 0.42 | 2 |
| ECG | 1.04 | 2 | 0.88 | 0 |
| Clinical nurse specialist | 12 hours contact time | 12 hours contact time | 12 hours contact time | 12 hours contact time |
| A&E visits | 0 | 0 | 3.96 consultations | 2 |

*Resource use per person, per year

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What are the most appropriate resource use data?

# Key Issue: Assumptions on subsequent treatments at second line (2L)

EAG disagrees with proportions of subsequent treatments used in each treatment arm

## Background

- In company's model, proportions of patients that receive each subsequent treatment was estimated from FLAURA2 trial data (although no ABCP use in trial) and expert opinion

## Company

- Clinical experts advised 10–20% of patients receiving 2L treatment could receive ABCP
- Assumption of no ABCP use does not accurately reflect NHS practice

## EAG comments

- Proportion receiving subsequent anticancer treatments after discontinuing 1L treatment in FLAURA2 was higher ([redacted]) for osi mono compared with osi+chemo ([redacted])
- Clinical advice suggested small proportion (<10%) would receive ABCP after 1L treatment – conducted scenario with ABCP use at 10%
- Clinical advice suggested that only difference in how people are treated at 2L, is that pemetrexed would not be used at later lines following osi+chemo at 1L
- EAG base case changes subsequent treatments proportions, including no ABCP in either arm – subsequent treatments in model only affects costs

Abbreviations: 1L, first line; 2L, second line; ABCP, Atezolizumab + bevacizumab + carboplatin + paclitaxel

# Key Issue: Assumptions on subsequent treatments at second line (2L)

Company base case for distribution of subsequent treatments at 2L in patients who received them

| From ↓To → | PDC | Pemetrexed | Docetaxel | ABCP |
|---|---|---|---|---|
| Osimertinib + chemotherapy | [redacted] | [redacted] | [redacted] | [redacted] |
| Osimertinib | [redacted] | [redacted] | [redacted] | [redacted] |

EAG base case for distribution of subsequent treatments at 2L in patients who received them

| From ↓To → | PDC | Pemetrexed | Docetaxel | ABCP |
|---|---|---|---|---|
| Osimertinib + chemotherapy | [redacted] | [redacted] | [redacted] | [redacted] |
| Osimertinib | [redacted] | [redacted] | [redacted] | [redacted] |

EAG scenario for distribution of subsequent treatments at 2L in patients who received them

| From ↓To → | PDC | Pemetrexed | Docetaxel | ABCP |
|---|---|---|---|---|
| Osimertinib + chemotherapy | [redacted] | [redacted] | [redacted] | [redacted] |
| Osimertinib | [redacted] | [redacted] | [redacted] | [redacted] |

What is the most appropriate distribution of subsequent treatment?

Abbreviations: 2L, second line; ABCP, Atezolizumab + bevacizumab + carboplatin + paclitaxel; PDC, Platinum Doublet Chemotherapy

# Summary of company and EAG base case assumptions

| Assumption | Company base case | EAG base case |
|---|---|---|
| PFS utility value | [redacted] | 0.794 and [redacted] disutility in the PFS health state for osi+chemo |
| OS extrapolations | 2-knot spline normal models for both treatments | 1-knot odds spline for osi mono<br>2-knot odds spline for osi+chemo |
| TTD extrapolations* | Gompertz model for osi+chemo<br>Gamma model for osi mono | Gompertz model for both treatments |
| Resource use | See slide 21 | See slide 21 |
| Subsequent treatments at 2L | See slide 23 | See slide 23 |
| **Assumptions with minimal impact on ICER** | | |
| Starting age (see appendix) | 61 years | 65.6 years |
| Platinum chemo distribution | 50% carboplatin, 50% cisplatin | 100% carboplatin |
| Relative dose intensity (RDI) of chemotherapy | 100% | 96.4% |
| PD utility value (see appendix) | 0.64 | 0.678 |
| Unit costs | See appendix slide 40 | See appendix slide 40 |

*pemetrexed modelled separately - both company and EAG base cases use exponential distribution for pemetrexed TTD extrapolation

# Cost-effectiveness results

- All ICERs are reported in PART 2 slides because they include confidential discounts
- When confidential discounts are included, the company base case is in the range normally considered a cost-effective use of NHS resources
- The EAG base case is significantly above the range normally considered a cost-effective use of NHS resources

ICER: Incremental cost effectiveness ratio

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# Managed access

Criteria for a managed access recommendation

**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**.

**Managed access team comments**

- No managed access proposal submitted

What further data cuts from FLAURA2 are expected?

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# Key issues

| Issue | ICER impact | Slide |
|---|---|---|
| Subgroups according to central nervous system (CNS) metastases | Large  | Slide 12 |
| Extrapolation of overall survival | Moderate  | Slide 14 |
| Extrapolation of time to treatment discontinuation | Large  | Slide 16 |
| Progression free health state utility | Moderate  | Slide 18 |
| Measurement of resource use | Moderate  | Slide 20 |
| Assumptions on subsequent treatments at second line (2L) | Large  | Slide 22 |

# Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer

# Supplementary appendix

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# Decision problem

Population, intervention, comparators and outcomes from the scope

| | Final scope | Company | Rationale if different from the final NICE scope |
|---|---|---|---|
| **Population** | Adults with untreated advanced EGFR mutation-positive NSCLC | [redacted] | In line with the population of the pivotal FLAURA2 trial, and consistent with the anticipated licensed indication |
| **Intervention** | Osimertinib with pemetrexed and platinum-based chemotherapy | As per NICE scope | N/A |
| **Comparators** | Established clinical management without osimertinib with pemetrexed and platinum-based chemotherapy including: Osimertinib, Dacomitinib, Afatinib, Erlotinib, Gefitinib | Osimertinib | Osimertinib monotherapy represents the current SoC for patients in England who are receiving first-line treatment for locally advanced/metastatic NSCLC and is used in 86% of EGFRm patients |
| **Outcomes** | The outcome measures to be considered include: OS, PFS response rates, DoR, TTD, AEs, HRQoL | As per NICE scope | N/A |

# Key clinical trial

Return to main slide

## Further data cut from FLAURA2 expected

Clinical trial designs and outcomes

| | FLAURA2 (NCT04035486) |
|---|---|
| **Design** | Phase 3, international, open-label, randomised study |
| **Population** | Patients with EGFRm (exon 19 deletion or L858R mutation) advanced NSCLC who had not previously received treatment for advanced disease |
| **Intervention** | Osimertinib + pemetrexed and cisplatin/carboplatin |
| **Comparator(s)** | Osimertinib |
| **Median duration of follow-up*** | Osi+chemo PFS: 19.5 months; Osi mono PFS:16.5 months |
| **Primary outcome** | PFS based on investigator's assessment |
| **Key secondary outcomes** | OS, response rates, duration of response, TTD adverse effects of treatment, HRQoL |
| **Locations** | Multinational (151 sites in 21 countries [5 UK sites]) |
| **Used in model?** | Yes |

A final analysis of OS will be conducted when the data are approximately 60% mature

Return to main slide

# FLAURA2 baseline characteristics and subgroup results

Baseline characteristics for intervention and comparator

| Characteristic | Osi+chemo (n=279) | Osi mono (n=278) |
|---|---|---|
| Age (median, years) | 61.0 | 61.5 |
| Female | 62.0% | 60.8% |
| Metastatic at study entry | 95.0% | 97.5% |
| CNS metastases at study entry | 41.6% | 39.6% |

PFS results according to CNS metastases at baseline

| CNS metastases at baseline | Treatment group | N | Number (%) of patients with progression | Hazard ratio | 95% CI |
|---|---|---|---|---|---|
| Yes | Osi + chemo | 116 | 52 (44.8) | 0.47 | (0.33, 0.66) |
| | Osi mono | 110 | 79 (71.8) | | |
| No | Osi + chemo | 163 | 68 (41.7) | 0.75 | (0.55, 1.03) |
| | Osi mono | 168 | 87 (51.8) | | |

Return to issues

# Other issue: Generalisability of the FLAURA2 trial

EAG concerned with the generalisability of the FLAURA2 trial results to NHS practice

## Background

- FLAURA2 included 23 people from the UK with a total study population of 557
- The average age of study participants was 61 years

## Company

- Advisors in the UK advisory board agreed the FLAURA2 patient population was representative of the EGFRm NSCLC population in the UK
- Subsequent treatments observed in FLAURA2 were reweighted by clinical experts to reflect NHS practice

## EAG comments

- Identified three issues relating to the external validity of the FLAURA2 study:
  - FLAURA2 participants were younger (average age 61) and more likely to be diagnosed at stage 4A compared to published UK survey data (Molife et al. 2023)
  - 2- and 3L therapies in FLAURA2 and whether these treatments are routinely available on NHS
  - Proportion of FLAURA2 participants with CNS metastases at baseline not representative of NHS practice
- Recommends changing starting age in model to 65.6 years to align with Molife et al. (2023)
- Further changes to address other generalisability issues discussed in other key issues

Are the results of FLAURA2 generalisable to NHS practice?
What should the starting age in the model be?

# Adverse events

| AE category | Number (%) of patients | |
|---|---|---|
| | Osi + chemo (N=276) | Osimertinib (N=275) |
| **Any AE of CTCAE Grade ≥3** | 176 (63.8) | 75 (27.3) |
| Causally related to treatment | 146 (52.9) | 29 (10.5) |
| Causally related to osimertinib | 81 (29.3) | 29 (10.5) |
| Causally related to chemotherapy | 138 (50.0) | NA |
| Causally related to carboplatin/cisplatin | 104 (37.7) | NA |
| Causally related to pemetrexed | 130 (47.1) | NA |
| **Any SAE (including events with outcome of death)** | 104 (37.7) | 53 (19.3) |
| Causally related to treatment | 52 (18.8) | 15 (5.5) |
| Causally related to osimertinib | 36 (13.0) | 15 (5.5) |
| Causally related to chemotherapy | 48 (17.4) | NA |
| Causally related to carboplatin/cisplatin | 36 (13.0) | NA |
| Causally related to pemetrexed | 46 (16.7) | NA |
| **Any AE leading to discontinuation of any study drug** | 132 (47.8) | 17 (6.2) |
| Leading to osimertinib discontinuation | 30 (10.9) | 17 (6.2) |
| Leading to chemotherapy discontinuation | 125 (45.3) | NA |
| Causally related to carboplatin/cisplatin | 46 (16.7) | NA |
| Causally related to pemetrexed | 119 (43.1) | NA |

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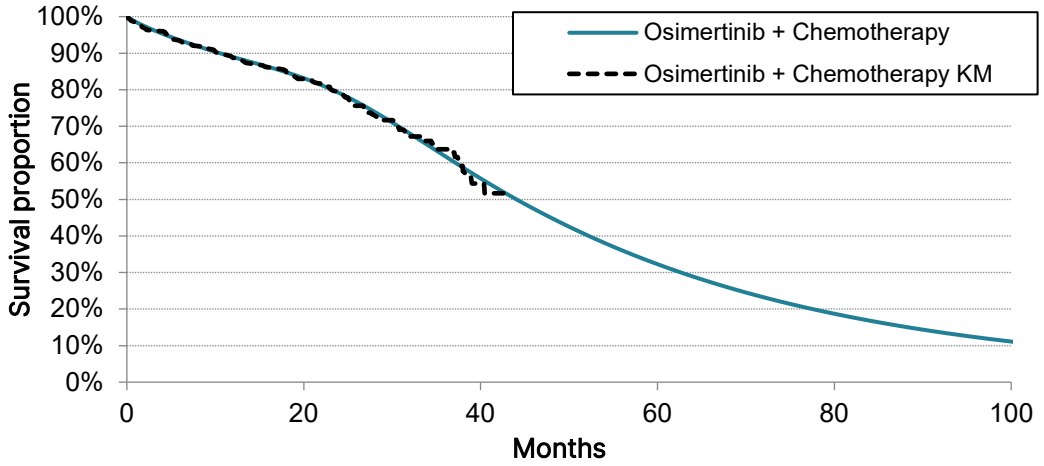
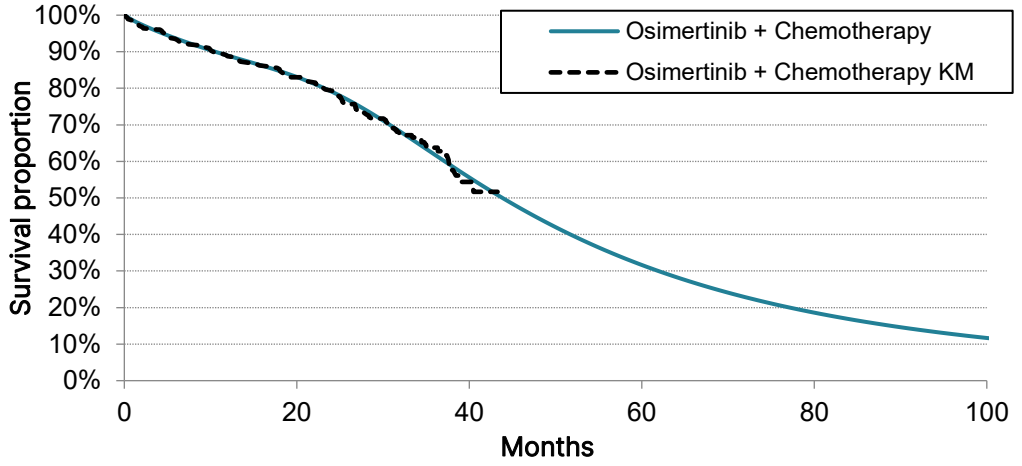
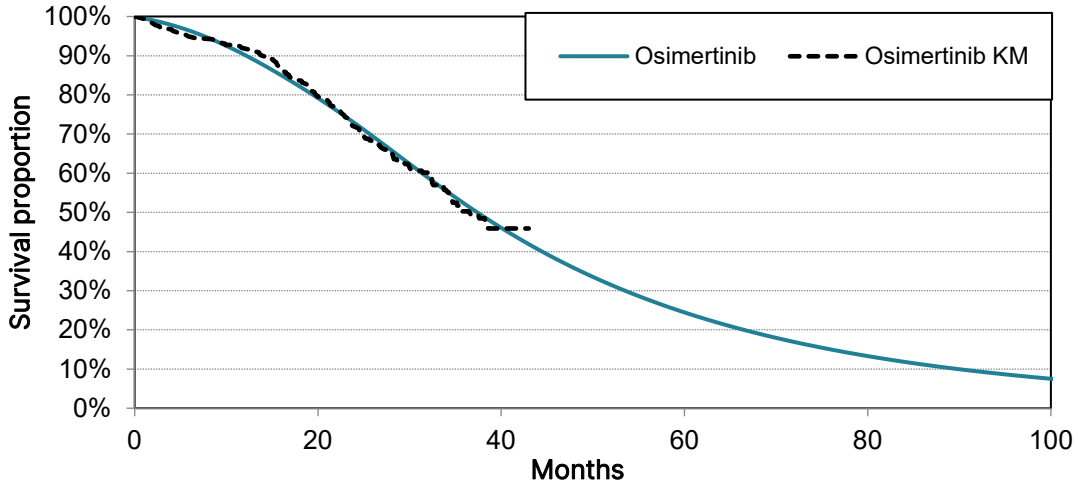
# Key issue: Extrapolation of overall survival appendix



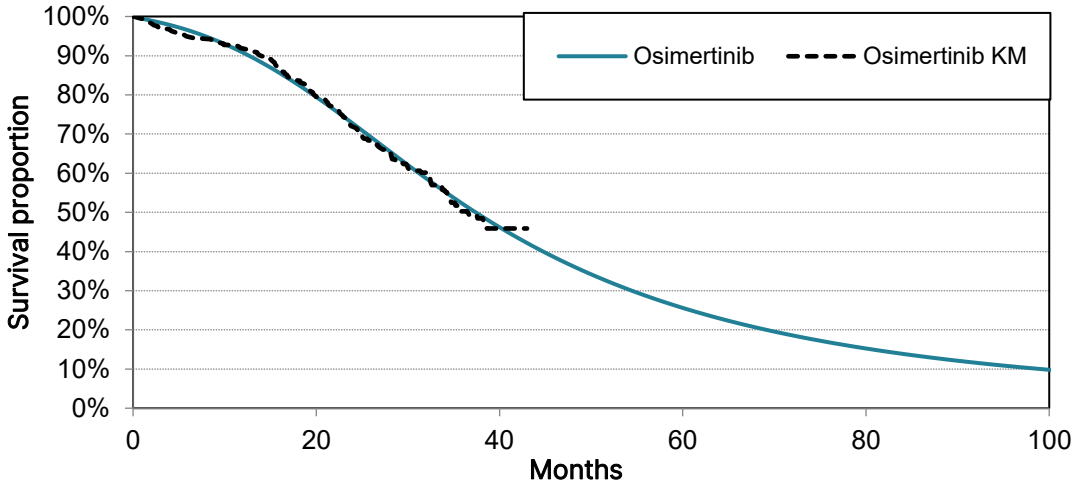

2-knot normal model (company preference)




2-knot odds model (EAG preference)




2-knot normal model (company preference)




1-knot odds model (EAG preference)

NICE

Which models are the most suitable for extrapolating OS?

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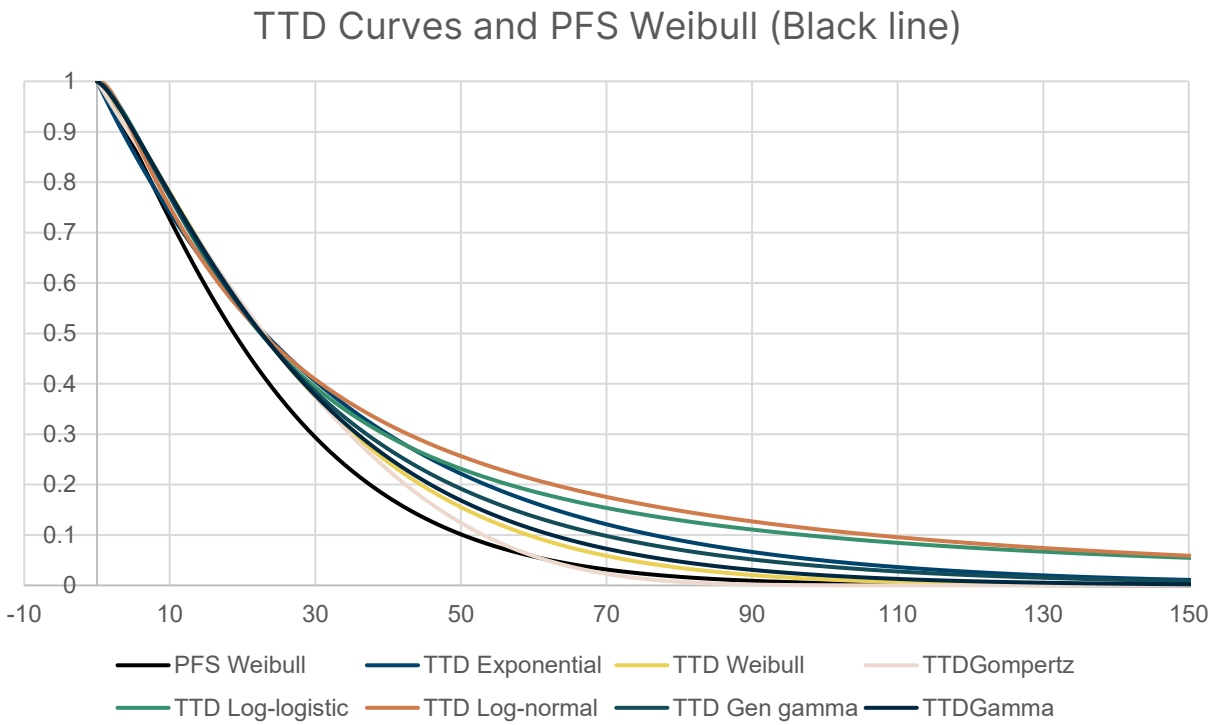
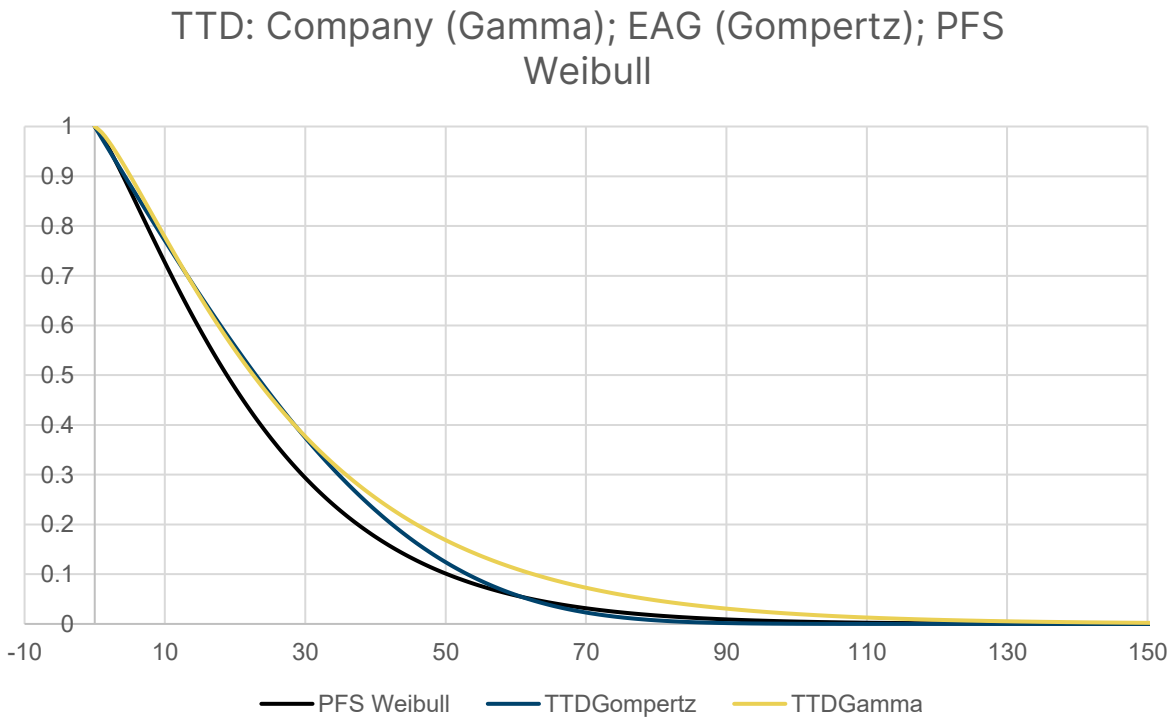
# Key Issue: Extrapolation of time to treatment discontinuation

EAG and company disagree on TTD extrapolation for osi mono arm: company use gamma, EAG Gompertz




Company and EAG preferred PFS curve with all extrapolations of TTD




Company and EAG preferred PFS curve with company preferred TTD extrapolation (gamma) and EAG preferred TTD extrapolation (Gompertz)

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

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# Key Issue: Progression free health state utility

| Health state (source) | Utility value | |
|---|---|---|
| | Osi+chemo | Osi mono |
| Baseline (FLAURA2) | [redacted] | [redacted] |
| Progression-free (FLAURA2) | [redacted] | [redacted] |
| Difference baseline to mean progression-free (FLAURA2) | [redacted] | [redacted] |
| Progression-free (TA654) | 0.794 | |

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# Other Issue: Progressed disease health state utilities

EAG concerned that PD utility is too low

**Company**

- Utility for the PD state sourced from Labbe et al. 2017 - a Canadian longitudinal cohort study of NSCLC, including 183 people with EFGR mutations - very similar to those used and accepted by EAGs in two previous NSCLC TAs

**EAG comments**

- Company's PD utility value results in a decrement of [redacted], which is more than differences between these health states reported for other TAs in the same population
- The EAG's preference is for using TA654 utility values of 0.794 for PFS and 0.678 for PD



What is the most appropriate utility value for the PD health state?

# Other Issue: Unit costs in the model

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Company and EAG differ in cost source

**Background**

- Company base-case uses NHS payment scheme 2023/25 tariffs and PSSRU 2022

**EAG comments**

- EAG considers NHS reference costs better portray the true opportunity cost of resource use on the NHS

**Tech team comments**

- NHS reference costs typically used, manual states “costs relevant to the UK healthcare system should be used” – both sources relevant to UK healthcare

| Resource type | Company base-case (NHS payment scheme 2023/25 and PSSRU 2022) | EAG base-case (NHS reference costs) |
|---|---|---|
| Outpatient visits | £141 | £164 |
| MRI scans | £150 | £240 |
| CT scans (chest) | £91 | £119 |
| CT scans (other) | £93 | £182 |
| ECG | £135 | £301 |
| Clinical nurse specialist | £52 | £119 |
| A&E visits | £275 | £158 |