Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (review of TA761) [ID5120]

Redacted – for screen

Technology appraisal committee D [04 September 2024]

Chair: Megan John

External assessment group: SCHARR

Technical team: Sally Lewis, Michelle Green, Ross Dent

Company: AstraZeneca

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- ✓ **Recap**
- ❑ Response to consultation

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DG recommendation – June 2024

Osimertinib is not recommended, within its marketing authorisation, for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (review of TA761)

Reasons the committee made this decision:

- Uncertain whether osimertinib is a cure or delays cancer coming back (DG 3.13, 3.14, 3.15)
- Uncertainty in when and how many people are retreated with osimertinib (DG 3.10)
- Because of this uncertainty, the most likely cost-effectiveness estimates are above the range that NICE normally considers an acceptable use of NHS resources (DG 3.20)

Consultation responses received from:

- Astra Zeneca (company) – **new analyses and base case provided**

Patient and clinical organisations:

- EGFR+ UK

- **Web comments** (n=1)

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Abbreviations: DG, draft guidance; EGFR, epidermal growth factor receptor

Committee preferred assumptions and requested analyses

Preferred assumptions	Company updated base case
Using the EAG's corrections for model and costing errors (including having EGFR testing costs)	**Partly** - EGFR tests are excluded. Corrections included
No warm-up period prior to cure	**No** - warm-up period included (4 years for osimertinib and 1 year for active monitoring)
Cure-point of 5 years for active monitoring	**Yes**
Cure-point of 5 years plus time on treatment (1 minus time to treatment discontinuation function) for osimertinib	**No** – 8 years
Retreatment allowed from 3 years after starting osimertinib	**No** – 3.5 years
70% of people in the osimertinib group who develop distant metastases will have osimertinib in the first-line setting	**No** – 60% retreated
Starting age of 70 years in the economic model	**No** – 63 years

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Abbreviations: EAG, external assessment group; EGFR, epidermal growth factor receptor

See section 3.21 in the draft guidance

Osimertinib (Tagrisso, AstraZeneca)

Marketing authorisation	• Osimertinib is licensed as 'adjuvant treatment following complete tumour resection in adults with stage IB to IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations'
Mechanism of action	• Osimertinib is a CNS-active TKI. Osimertinib targets EGFR exon 19 deletions or exon 21 substitution mutations of the EGFR-TK and kills cancer cells which express these mutations. Osimertinib has minimal activity against wild-type EGFR
Administration	• Orally at a dose of 80mg once daily. • TA761 rec has a stopping rule of 3 years, as per ADAURA trial design. Summary of product characteristics states *'patients in the adjuvant setting should receive treatment until disease recurrence or unacceptable toxicity. Treatment duration for more than 3 years was not studied'*
Price	• The list price for osimertinib is £5,770 for a 30 pack of 80mg • There is a confidential patient access scheme (no change since ACM1)

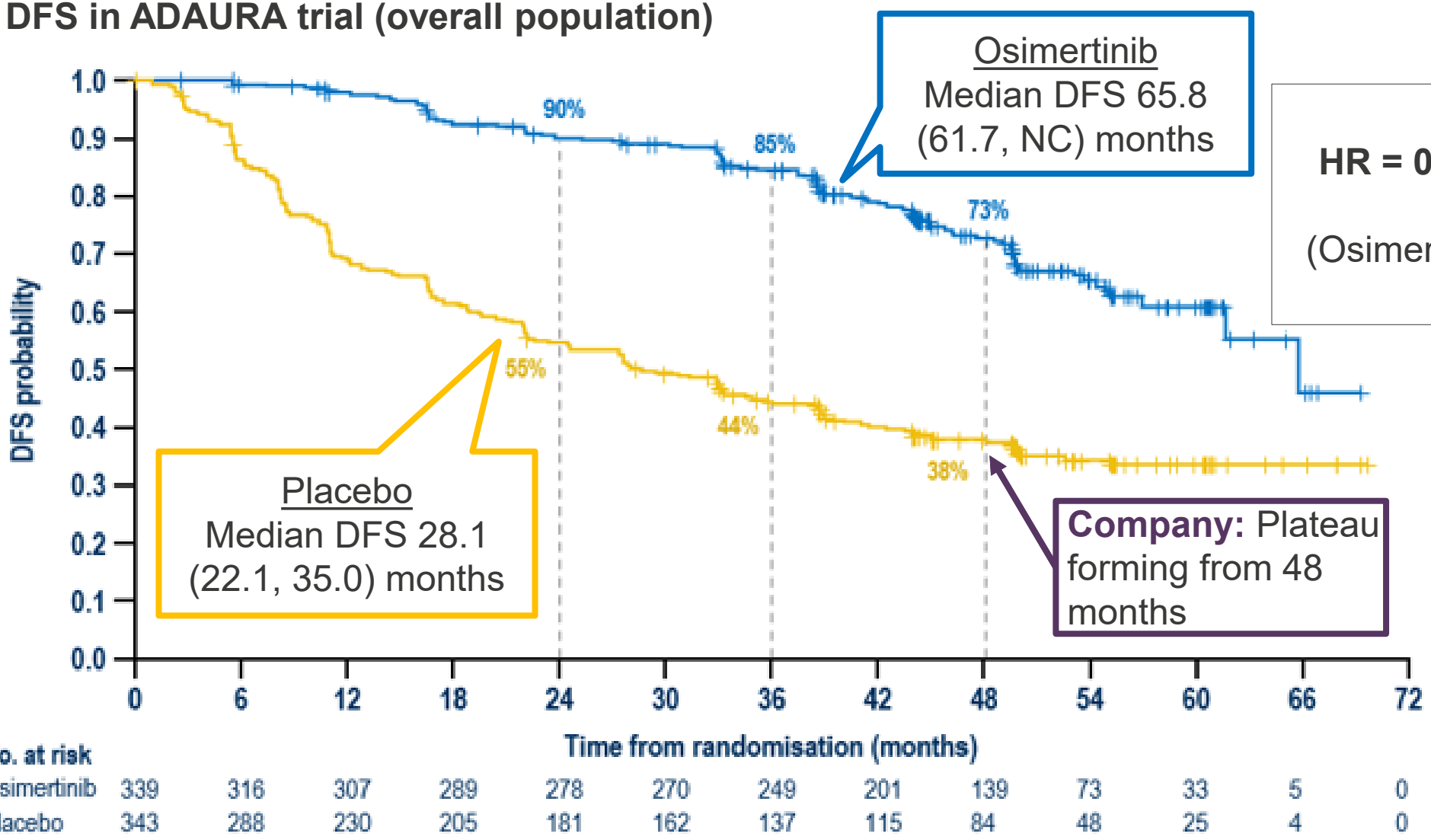
Osimertinib also has a marketing authorisation:

- 'as first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations'
- 'as treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC'

Abbreviations: ACM, appraisal committee meeting; EGFR, epidermal growth factor receptor; NSCLC, Non-small-cell lung cancer; TKI, tyrosine kinase inhibitor

Kaplan-Meier plot of DFS in key trial - ADAURA

DFS in ADAURA trial (overall population)

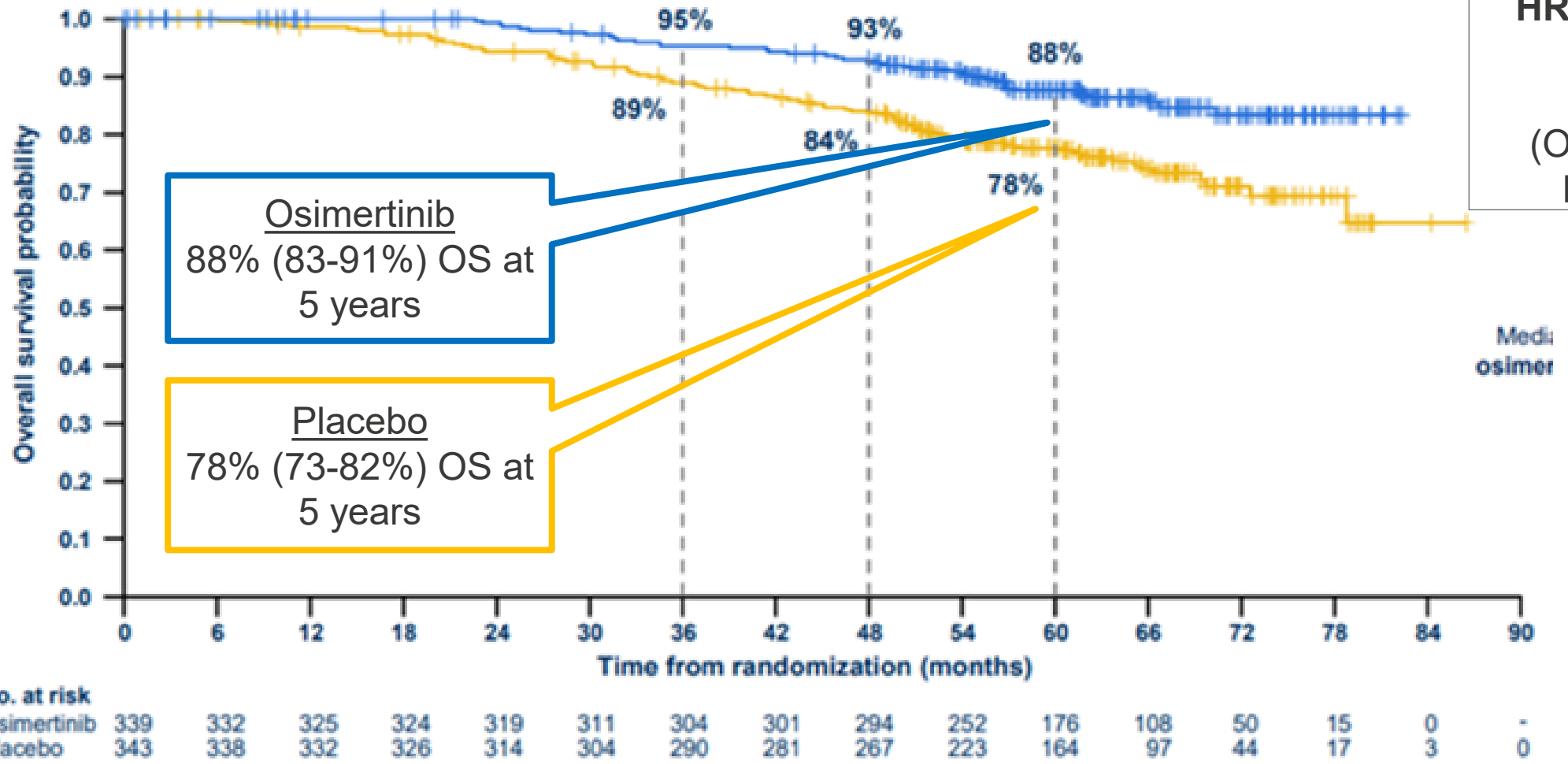


No. at risk													
Osimertinib	339	316	307	289	278	270	249	201	139	73	33	5	0
Placebo	343	288	230	205	181	162	137	115	84	48	25	4	0

CI - confidence interval; DFS, disease-free survival; NC, not calculable; NR, not reached. Tick marks indicate censored data.

Kaplan-Meier plot of OS in key trial - ADAURA

OS in ADAURA trial (overall population)



Osimertinib
88% (83-91%) OS at 5 years

Placebo
78% (73-82%) OS at 5 years

HR = 0.49 (95% CI: 0.34, 0.70)
Maturity 18%
(Osimertinib 12%, Placebo 24%)

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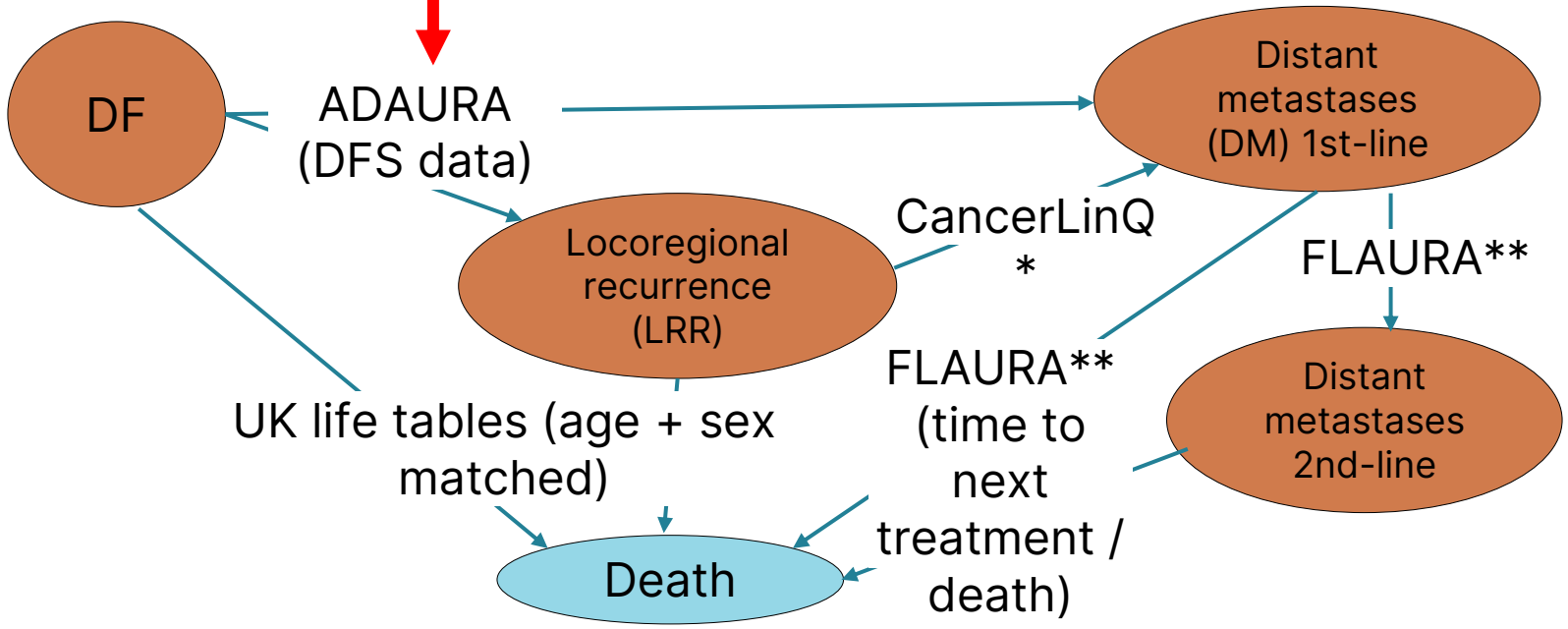
Abbreviations: HR, hazard ratio; OS, overall survival

Model structure

Model structure: 5-state semi-Markov model with 37-year time horizon

Cure assumption: Reduces predicted probability of leaving disease-free (DF) state (relapsing). “Cure proportion” in company base case is 0% at end of year 4 and increases roughly linearly to 95% by final cure point (end of year 5 for monitoring or year 8 for osimertinib). Period from end of year 4 to final cure point is "warm-up period."



Key assumptions:

- Cure assumption
- In DF state, no excess risk of mortality (fully cured if no relapse)
- Adjuvant osimertinib reduces risk of relapse and less chance of having osimertinib for metastatic disease which reduces costs.
- Re-treatment with first-line osimertinib is assumed after 4 years in the adjuvant osimertinib group (1 year after max. 3 years on adjuvant osimertinib treatment)

*real-world evidence source for US cancer patients
** Osimertinib trial in metastatic setting (transitions constrained by UK life tables); DM1-DM2 also used TKI vs chemo comparison in Holleman NMA to inform effects of chemo; DM2-death also informed by ABCP arm of IMPower150 study
Abbreviations: DM, distant metastases; DF, disease-free

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- ❑ Recap
- ✓ **Response to consultation**

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Outstanding issues

Issue and committee position in DG	ICER impact	Company analyses
Modelling of cure: • no warm-up period prior to cure • cure-point of 5 years for active monitoring • cure-point of 5 years plus time on treatment (1 minus time to treatment discontinuation function) for osimertinib	Large	Company maintains previous base case and includes scenarios with no warm-up
Starting age in model: • Consider age of 70 years based on SACT data	Large	Company uses starting age of 63 years (from ADAURA)
Uncertainty in retreatment: • retreatment allowed from 3 years after starting osimertinib • 70% of people in the osimertinib group who develop distant metastases will have osimertinib in the first-line setting	Small	Company – updated model to include retreatment from 3.5 years and retreatment rate of 60%
EAG corrections and EGFR testing costs: • Should be included where there are additional costs (stage 1b disease)	Small	Company's new model includes EAG corrections

EAG presents committee position with scenarios for a starting age of 63 and 70 years

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Abbreviations: DG, draft guidance; EAG, external assessment centre; EGFR, epidermal growth factor receptor; SACT, systemic anti-cancer therapy

Consultation responses (1/2)

Consultation comments received from:

- AstraZeneca (manufacturer of osimertinib)
- EGFR+ UK (patient group)
- One web comment from the Society of Cardiothoracic Surgeons UK & Ireland

AstraZeneca

- Suggested that committee's preferred assumptions on long term outcomes are overly conservative and inconsistent with evidence and expert opinion
- Noted that a statistically significant DFS and OS benefit has already been demonstrated for osimertinib in the ADAURA study and it is expected to result in a DFS plateau for osimertinib
- Provided:
  - Updated model incorporating scenarios of some of the committee's preferred assumptions
  - Justification where the committee's preferred assumptions were not incorporated in the model and additional evidence on age of diagnosis
- Reported inaccuracies in the DG relating to:
  - Inclusion of warm-up period in EAG base case
  - Committee preferred assumption for cure point in TA761
  - Number of clinical experts supporting inclusion of a warm-up period
  - Drop in risk in DFS curves for previous (2nd generation) TKIs not considered relevant as osimertinib is a 3rd generation TKI

Abbreviations: DG, draft guidance; DFS, disease free survival; EAG, external assessment group; OS, overall survival; TKI, Tyrosine kinase inhibitors

Consultation responses (2/2)

EGFR+ UK

- A 10% increase in 5-year survival rates is both clinically and personally meaningful, as is the very significant increase seen in the DFS data
- 2024 survey of EGFR+ members (n=233) found median age to be 60-64 years
- Urges committee to work with company to establish more accurate modelling
- Costs associated with supporting patients with clinically significant anxiety and/or depression should be included. Vital to consider the qualitative impact on people's quality of life
- Many people with stage 1 disease receive testing as part of their standard care – 11% of members diagnosed with stage 1 disease

Society of Cardiothoracic Surgeons UK & Ireland

- Adjuvant osimertinib is the only option for patients with EGFR positive disease after surgery
- Results from ADAURA trial are impressive. Scenarios extrapolated far beyond median follow up were punitive with uncertainties openly acknowledged by the NICE committee

Abbreviations: DFS, disease free survival; EGFR, epidermal growth factor receptor

Key issue: Cure assumption (1/2)

Large

Committee conclusions at first meeting

- No explicit warm-up period prior to cure
- Cure-point: 5 years for active monitoring & 5 years plus time on treatment (1 minus time to treatment discontinuation function) for osimertinib

Company

- Osimertinib shown to be highly effective in ADUARA, uncertainty in long term outcomes would never have been resolved by SACT data collected in CDF
- 5 clinicians agreed that cure should be included; 2/5 said this should be at 5 years for both arms
- Company base case is conservative – state 11% increase in maximum proportion of patients cured with osimertinib. Figure provided to show the absolute proportion of patients cured over time
- Warm-up period is pragmatic and has been used in a previous appraisals (TA876, TA761* and TA632*)
- Provided scenarios without warm up period, with cure for active monitoring at 5 years and cure for osimertinib at 5 to 8 years
  - Cure timepoint of 5 or 6 years reduces ICER versus company base case
  - Cure timepoint of 7 or 8 years increases ICER versus company base case
- Argue company base case or scenario with no warm-up period and cure from 5 years are the only scenarios to accurately capture cure from 5 years for patients who complete 3-years of adjuvant osimertinib, and cure from 5 years is reasonable based on clinical expert feedback

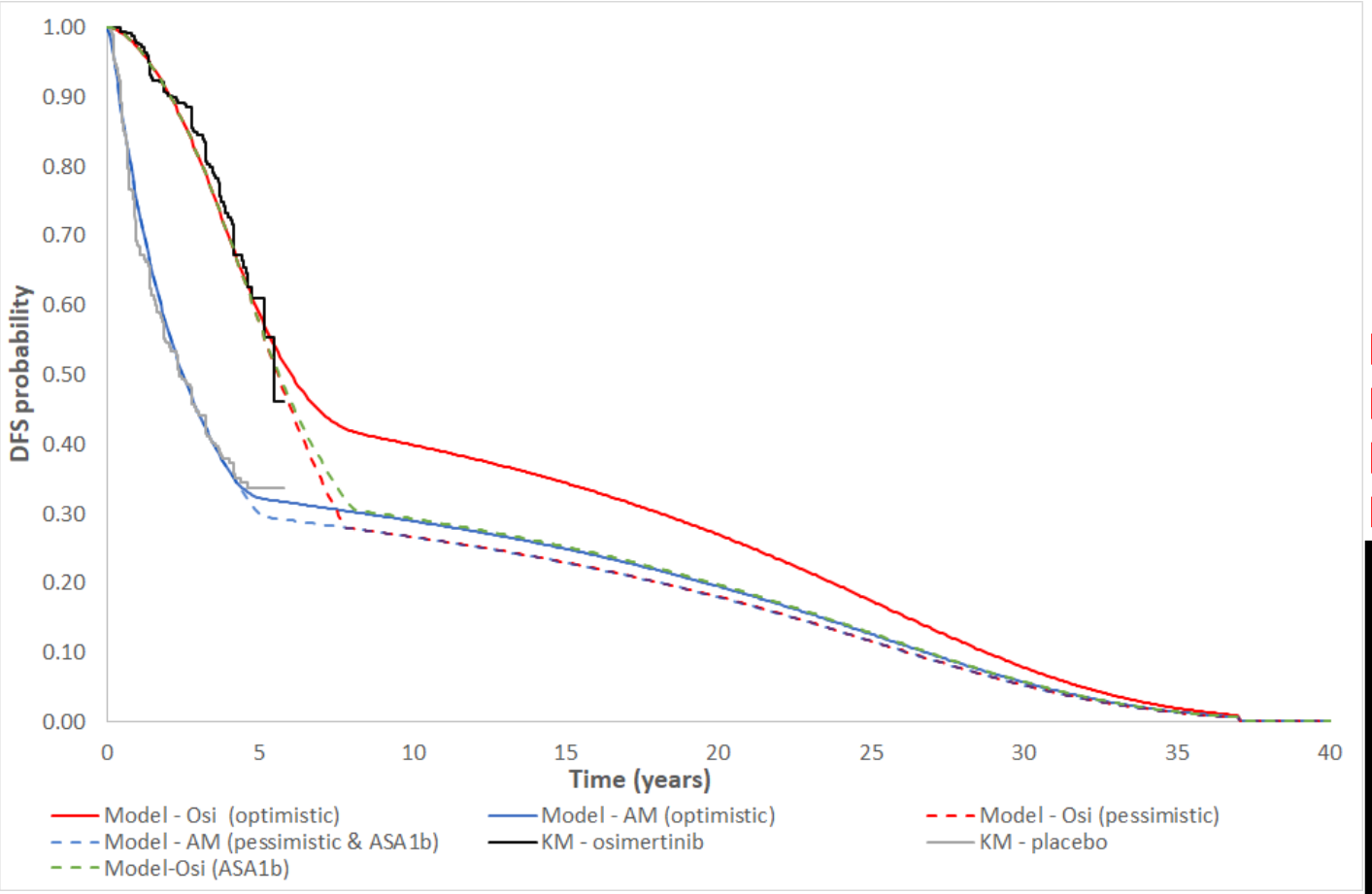
Cure assumptions in TA876 and TA632 were uncertain and not key drivers of ICERs and cure modelling in TA761 led to highly uncertain ICERs (see slide on previous appraisals.)

Abbreviations: CDF, cancer drugs fund; ICER, incremental cost-effectiveness ratio; SACT, systemic anti-cancer therapy. *Raised in clarification response

Key issue: Cure assumption (2/2) - EAG Response

Large

Model predicted DFS



EAG optimistic bound/company – substantial and sustained gap between osimertinib (solid red line) and active monitoring (solid blue line)

Committee preference – markedly smaller gap in DFS between the groups over time (dashed green line versus dashed blue line)

EAG pessimistic bound – DFS functions meet with no subsequent gap (dashed red line versus dashed blue line)

EAG comments

- Company's new analyses of absolute cured proportions in model - mathematically incorrect
- Warm-up period in previous appraisals - applied to both treatment arms, not key driver, uncertain
- Committee's preference applies the same initial cure time point (starting at 5 years) in both arms
- No strong basis for selecting any specific cure assumption within EAG's optimistic and pessimistic range

Have committee conclusions relating to cure assumptions changed based on the consultation response?

Abbreviations: AM, active monitoring; ASA1b, additional scenario analysis 1b; DFS, disease free survival; EAG, external assessment group; KM, Kaplan Meier

Large

Key issue: Starting age in model

Committee conclusions at first meeting

- Economic model should consider a starting age of 70 years from SACT data (instead of 63 years from ADAURA), which would also reduce the time horizon of the model by 7 years (to 30 years)

Company

- SACT data is from a small sample size (n=143) and inconsistent with ADAURA which is used for other key parameters (e.g., DFS data, treatment duration and utilities)
- Clinicians - baseline characteristics of the ADAURA trial broadly representative of clinical practice
- 2024 survey of EGFR+ members (n=233) found median age to be 60-64 years

EAG comments

- EGFR+ UK survey doesn't reflect target population for this appraisal (72% stage 4 disease at diagnosis)
- SACT should reflect age of target population for adjuvant osimertinib, but population is small (n=143)
- Use of SACT introduces inconsistency in model:
  - time-to-event data from ADAURA with mean age of 63 years
  - distant relapse outcomes data from FLAURA with mean age of 64 years
- TA876 (nivolumab for neoadjuvant NSCLC) used trial to inform starting age (64 years)

Should the model starting age be 63 years (ADUARA) or 70 years (SACT)?

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Abbreviations: DFS, disease-free survival; EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer; SACT, systematic anti-cancer therapy

Small

Key issue: Retreatment with osimertinib

Committee conclusions at first meeting

- Retreatment allowed from 3 years after starting osimertinib
- Likely that much more than 50% of people would have osimertinib as a retreatment in the metastatic setting and 70% would be a more reasonable estimate.

Company

- Retreatment immediately after completing 3-years of adjuvant osimertinib treatment is clinically implausible:
  - Delay needed for scan, diagnosis of advanced disease and starting retreatment
  - Model updated to include 6-month (rather than 12-month) treatment break - conservative
- 70% retreatment rate not supported by evidence – value uncertain due to data maturity. Model updated to assume 60% retreatment rate (rather than 50%) but value uncertain

EAG comments

- Retreatment at 3.5 year is reasonable but clinicians may wish to retreat sooner if patients discontinued prior to completing 3 years of treatment
  - Company clinician interviews: [redacted]
  - True proportion retreated remains unknown; but clinical advice suggests it may be higher than 60%

Have committee conclusions relating to retreatment changed based on the consultation response?

Small

Key issue: EGFR testing costs

Committee conclusions at first meeting

- EGFR testing costs should be included where there are additional costs (e.g. for people with stage 1b disease)

Company

- Test costs should not be included. EGFR mutation testing conducted routinely as per NG151 and NHSE national genomic test directory
- Clinician interviews in 2023 confirmed EGFR testing for early-stage NSCLC is part of routine practice and is conducted on biopsied tissue prior to surgery where possible

EAG comments

- Agrees that most patients will undergo EGFR testing via next-generation sequencing but some of the costs of EGFR testing are attributable to adjuvant osimertinib
- Costs should be considered at least in sensitivity analyses
- EAG presented a scenario analysis including EGFR testing costs for Stage 1b patients who receive adjuvant osimertinib

Is including EGFR testing costs for all patients appropriate?

Abbreviations: EGFR, epidermal growth factor receptor; NG, NICE guideline; NSCLC, non-small-cell lung cancer; TKI, tyrosine kinase inhibitors

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

comparator PAS discounts

- Subsequent treatments osimertinib, afatinib and atezolizumab have PAS discounts
- Subsequent treatments pemetrexed and bevacizumab are subject to confidential commercial arrangements
- Acceptable ICER around or below £20,000 per QALY gained (see section 3.20 of draft guidance)
- Company and EAG ICERs are above this threshold

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Thank you.

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Supplementary appendix

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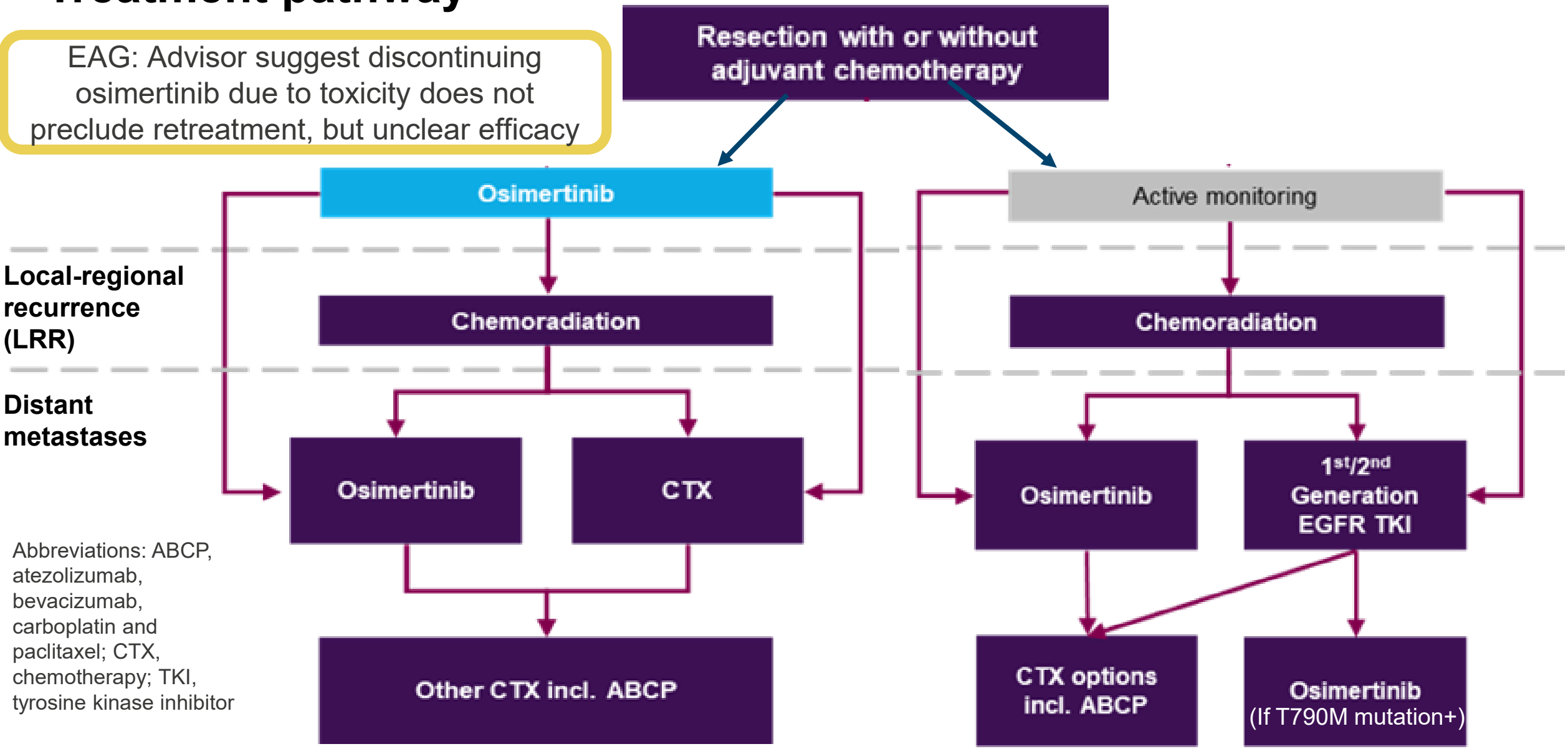
Treatment pathway

EAG: Advisor suggest discontinuing osimertinib due to toxicity does not preclude retreatment, but unclear efficacy



Abbreviations: ABCP, atezolizumab, bevacizumab, carboplatin and paclitaxel; CTX, chemotherapy; TKI, tyrosine kinase inhibitor

EAG: Advisor suggests ~1/3 with metastatic relapse following 1st line treatment for distant metastases decline active treatment (have palliative or best supportive care | People with LRR may also receive surgery

Key trial ADAURA results

	Key outcomes	Osimertinib	Placebo
Overall population (stage IB-IIIA)	Number in study, n	339	343
	Median DFS (months)	65.8 (not reached in original submission)	28.1 (27.5 in original submission)
	DFS (%)	48 months: 73% [redacted]	48 months: 38% [redacted]
	Median OS (months)	Not reached	Not reached
	OS (%)	48 months: 93% 60 months: 88%	48 months: 84% 60 months: 78%
	CNS recurrence (%)	5.9%	11.1%
	Grade 3+ adverse event related to treatment	11%	2%
	Discontinued due to adverse event	12.1%	3.2%
	Discontinued due to progression	9.7%	50.1%

Company claims plateau forms from 48 months for DFS in placebo

Median OS still not reached

For further information, see slide on trial structure and subgroup results in appendix

Abbreviations: DFS, disease-free survival; OS, overall survival

Cure modelling in previous appraisals

TA876 – Nivolumab neoadjuvant NSCLC

- **Company:** Base case included a cure assumption between 5 to 7 years where 95% were assumed cured by year 7. Applied to every treatment in model.
- **EAG:** Little supporting empirical evidence for cure assumption with a small effect on the ICER.
- **Committee:** Cure assumption was uncertain.

TA761 – Osimertinib adjuvant EGFR+ NSCLC*

- **Company:** 5-year functional cure point for both arms in initial base case. No warm-up period. Considered cure at 6 years for osimertinib post technical engagement.
- **EAG:** Presented optimistic (aligned with company) and pessimistic scenarios.
- **Committee:** Significant uncertainty around cure assumptions and impact on the range of plausible ICERs. Considered both EAG scenarios.

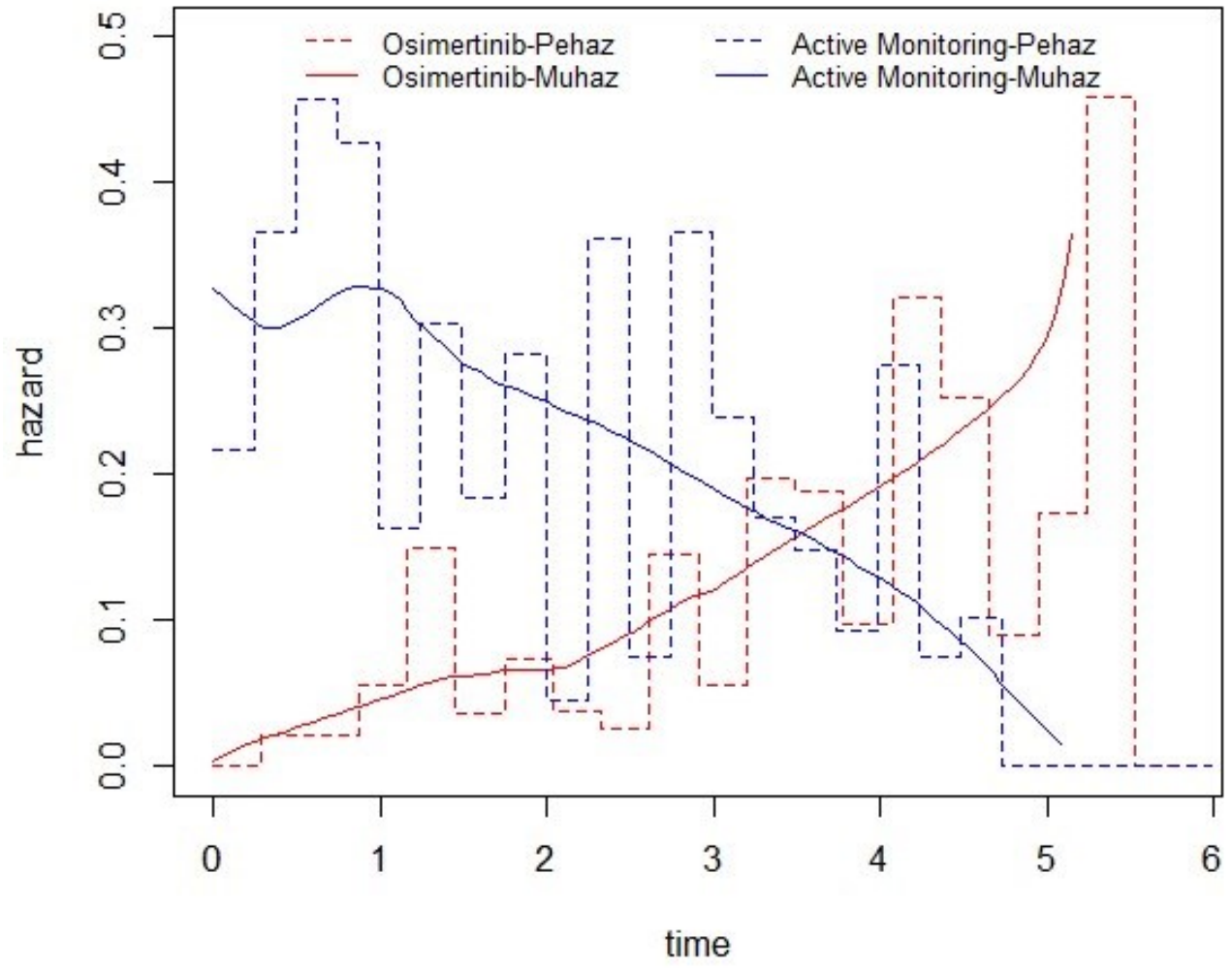
TA632 – Trastuzumab emtansine adjuvant HER2+ breast cancer

- **Company:** Cure assumption from 36 months to 120 months where proportion of cured increases linearly from 0% to 95%. Applied to both arms.
- **EAG:** Accepted companies' analysis as no alternative evidence to support a better-informed choice of parameters and the impact on ICER was minor.
- **Committee**: not discussed as impact on ICER minimal

Abbreviations: ICER, incremental cost-effectiveness ratio; NSCLC, non-small-cell lung cancer.

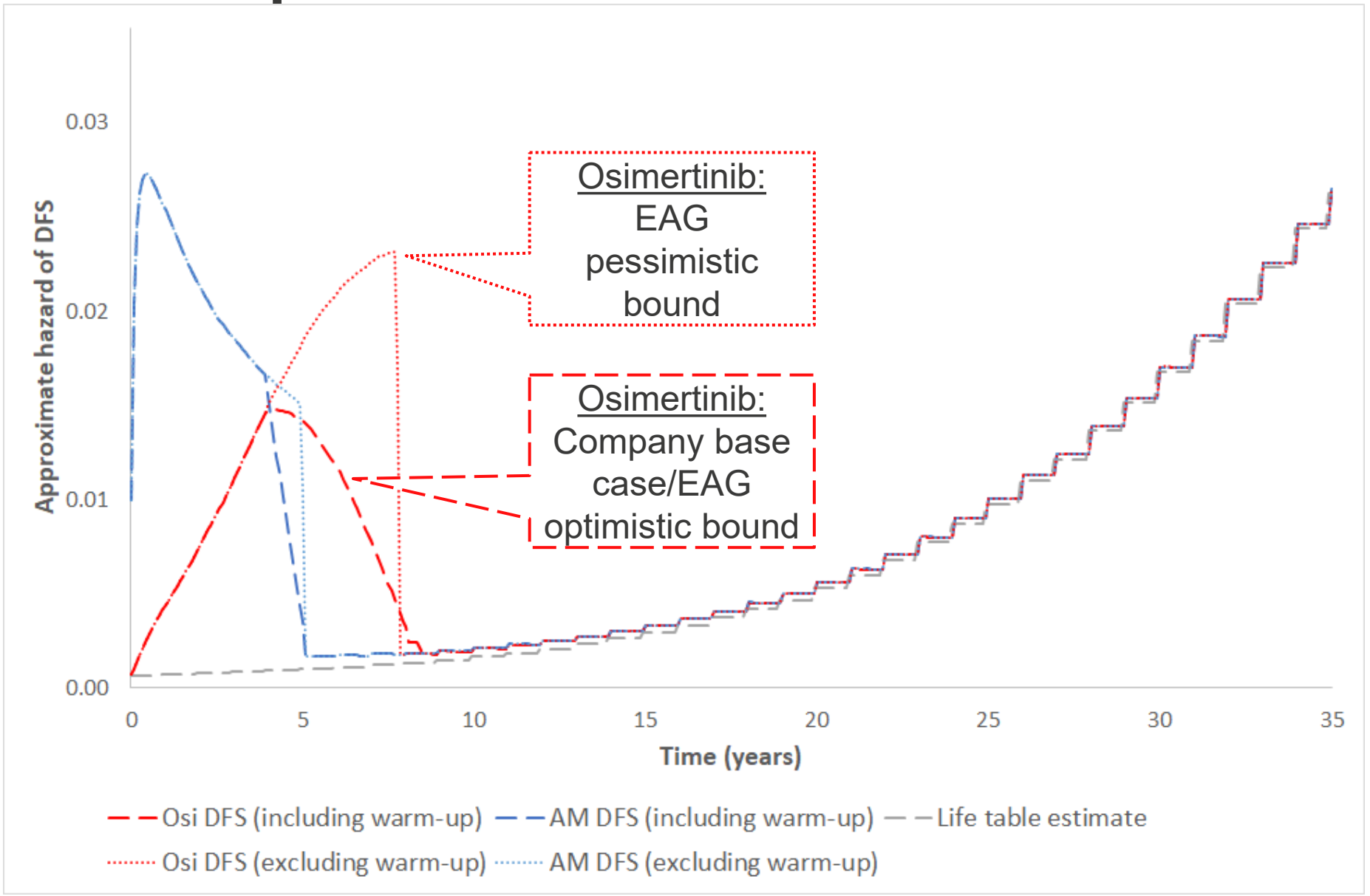
*original appraisal prior to entry to CDF

Smoothed hazard plot for DFS in ADUARA



NICE Abbreviations: DFS, disease free survival
Pehaz and Muhaz: packages within R

Modelled hazard plot for DFS



Abbreviations: AM, active monitoring; DFS, disease free survival