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

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Technology appraisal committee D [06 June 2024]

Chair: Megan John

Lead team: Paul Caulfield, Martin Bradley, Sofia Dias

External assessment group: SCHARR

Technical team: Tom Jarratt, Christian Griffiths, Ross Dent

Company: AstraZeneca

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

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

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Background on EGFR mutation-positive non-small-cell lung cancer (NSCLC)

Causes

- Lung cancer is the proliferation of cancerous cells in the lungs and is commonly linked to smoking

Epidemiology

- Lung cancer is 3rd most common cancer (~ 40,000 new cases each year) and leading cause of cancer mortality
- NSCLC accounts for ~ 80-85% of lung cancers
- EGFR mutations found in 8%-16% of early-stage (IB-IIIA) NSCLC and are more common in younger people, Asian populations, females and never smokers

Diagnosis and classification

- NSCLC is staged 0-4, most people with early-stage NSCLC can undergo surgical resection with curative intent

Prognosis

- Estimated risk of 5-year recurrence increases with stage: 45% Stage IB, 62% Stage II, 76% Stage III
- Post-surgery relapses are typically rapidly occurring (18-24 months after surgery) distant recurrences
- People with EGFR mutations have twice the risk of brain metastases, higher likelihood of distant recurrences
- No available curative options for people who develop distant metastases following resection and limited survival data (though people with brain metastases have <18 months survival following metastatic diagnosis)

Patient perspectives

Disease and current treatments are debilitating

- Lower stage NSCLC can be asymptomatic for years → wide-ranging often later arise (cough, chest pain, dyspnoea, weight loss, fatigue, bone pain)
- Learning that surgery is a potentially curable option is often a relief
- Doing nothing after surgery can lead to significant anxiety and panic but physical and psychological impact of chemotherapy often huge
    - Side effects can be brutal

> ‘when you have surgery you think it is all fixed but it isn’t. The combination of osimertinib and regular scans makes me more optimistic and that it is the best it can be. My quality of life is pretty good and osimertinib has given me a lot of hope.’

Fear of recurrence is a major source of anxiety

- Recurrent disease has devastating effects on patients and loved ones, and is a significant cause of anxiety
- Close monitoring reduces recurrence fears, but frequency of scans differs depending on stage, this plus concerns around stopping osimertinib can be considerable source of anxiety
- Brain metastases common in EGFR+ lung cancer
    - Osimertinib is only tyrosine-kinase inhibitor (TKI) that offer protection
- Brain metastases are a particular fear for people not taking osimertinib and can have devastating effects (including meaning the person must stop driving which can impact their ability to get to appointments)

Abbreviations: NSCLC, Non-small-cell lung cancer

Clinical perspectives

Highly targeted technology represents step change in management of EGFR+ disease

- No other treatment options after chemotherapy to prevent or delay recurrence
- Audits show variation in resection rates and access to adjuvant treatment between multidisciplinary teams in UK: Rates lower than in Europe

Osimertinib is effective and tolerable

- Osimertinib extends disease-free survival (DFS) and overall survival (OS)
  - Allow people to experience good quality of life and disease-free for longer (and potentially cured)
  - Administered in specialist clinic → requires monitoring and more appointments
- Side effects favourable compared with chemo, rarely leads to discontinuation as improve with dose reduction
- When osimertinib has been used in more advanced cancer settings, benefit and toxicity has been similar to that seen in clinical trials
- After stopping at 3 years, there is likely to be a rebound in recurrence → need to consider longer prescribing periods for example in advanced disease

Abbreviations: NSCLC, Non-small-cell lung cancer

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 tyrosine kinase inhibitor (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. • TA 761 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

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'

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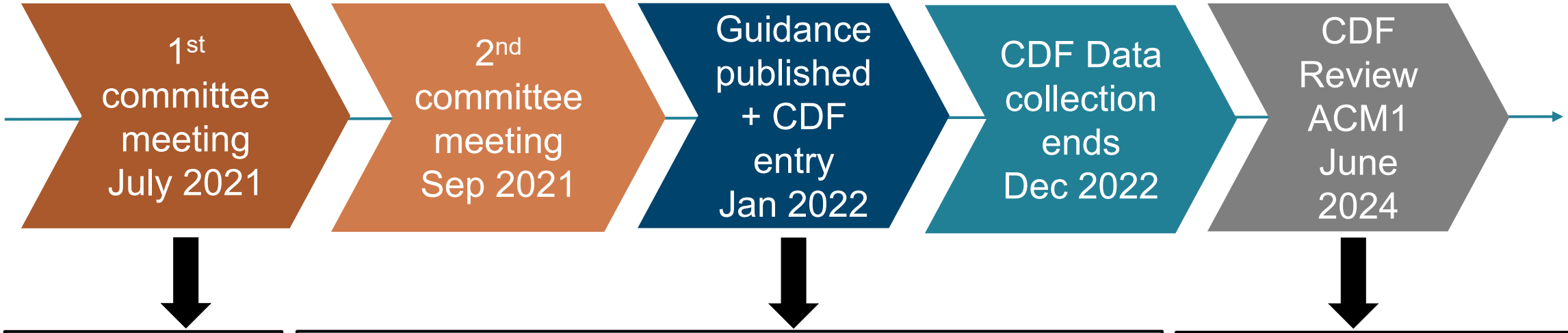
Abbreviations: NSCLC, Non-small-cell lung cancer

Summary of original appraisal (TA761) and CDF Review



- Low level of OS data maturity

TA761: Recommended for use in CDF as adjuvant treatment after complete tumour resection in adults with stage 1b-3a NSCLC whose tumours have EGFR exon 19 deletions or exon 21 substitution mutations (3-year stopping rule).

Key areas of uncertainty:

- If extent of DFS benefit extends to OS
- Cure proportion and timepoint
- Impact of 3 year stopping rule
- % retreated

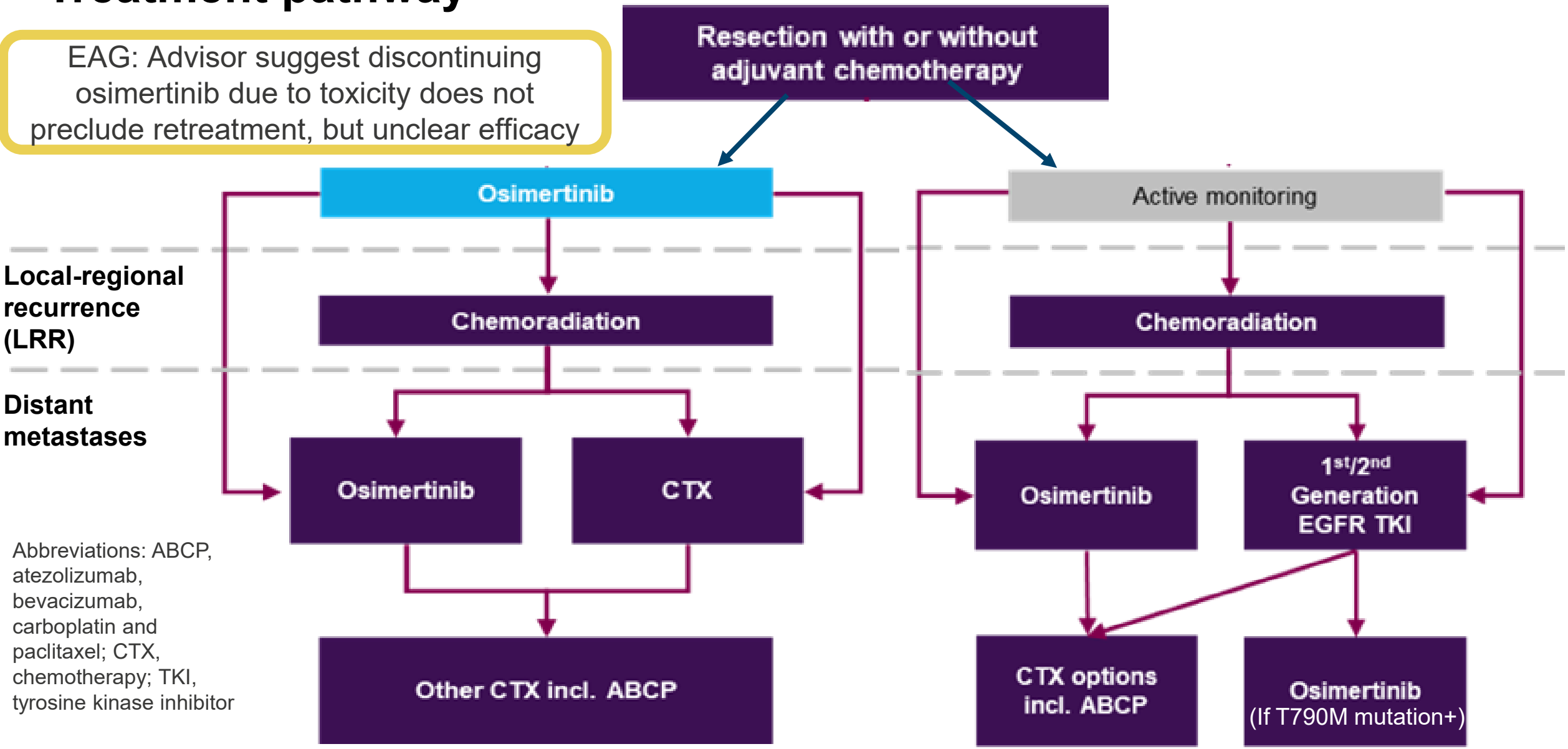
Review of TA761

- Previous submission used data cut-off (DCO) of Jan 2020
- New submission DCO April 2022 for DFS and Jan 2023 for OS
- 18% OS maturity
- New data from Systemic Anti-Cancer Therapy (SACT) dataset

Abbreviations: ACM1, first appraisal committee meeting; CDF, cancer drugs fund; DFS, disease-free survival; OS, overall survival

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

Issues

Key issues

Issue	ICER impact
Uncertainty around re-treatment	Small-moderate
Company modelling of cure includes warm-up period (risk of recurrence/event gradually decreases from 4 years to a final cure point) • Should warm-up period be applied? • Concerns that modelled benefit deviates from observed data, uncertainty around final cure point	Large

Other issues

- Subgroups not in economic evaluation (see slide on subgroup clinical results)
- Capping of DFS and LRR utility values (see slide on other issues)
- Exclusion of certain costs from model (such as DFS costs, wastage, EGFR testing)

Abbreviations: DFS, disease-free survival; LRR, locoregional recurrence

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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

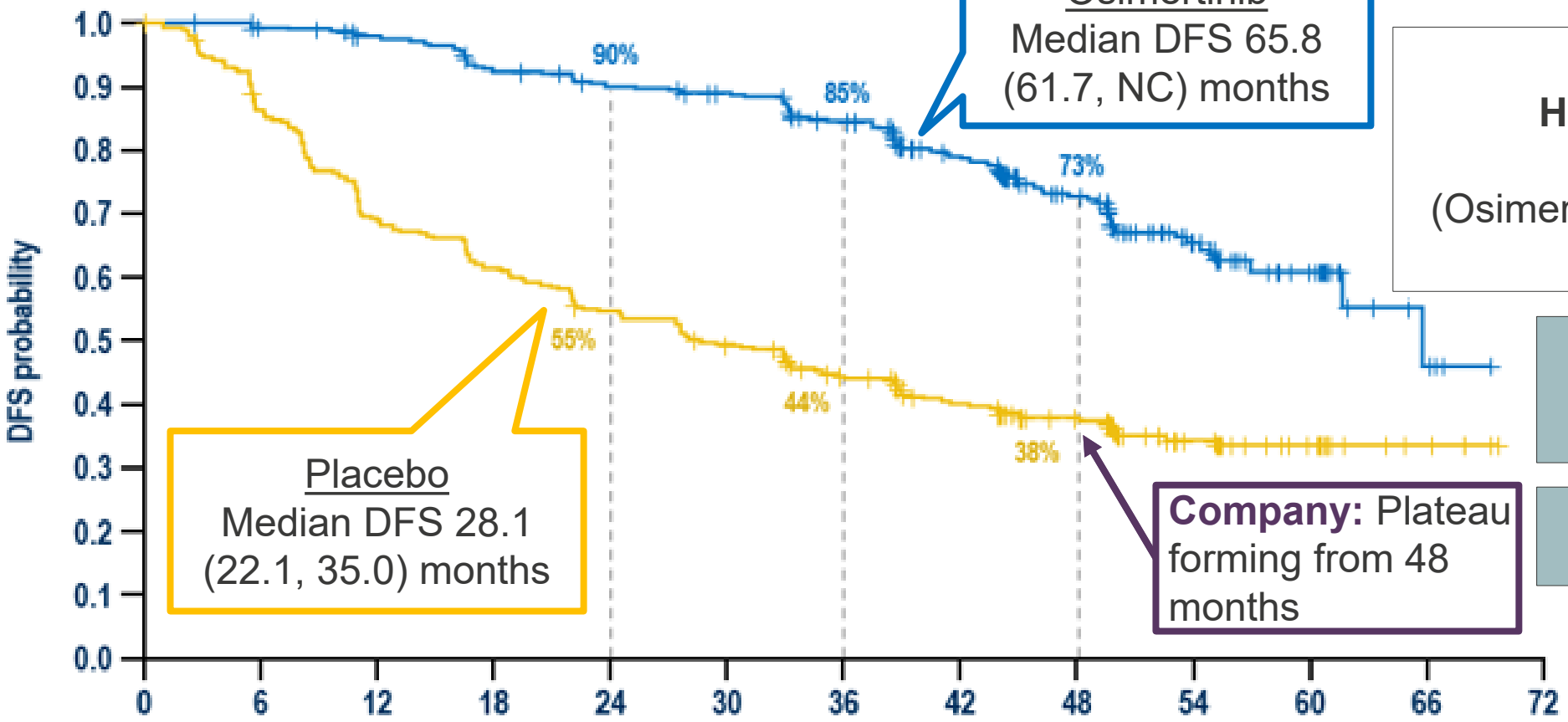
Median OS still not reached

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

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

Kaplan-Meier plot of DFS in ADAURA - Overall population

DFS in ADAURA trial (overall population)



Osimertinib
Median DFS 65.8
(61.7, NC) months

Placebo
Median DFS 28.1
(22.1, 35.0) months

HR 0.27 (0.21, 0.34)
Maturity 45%
(Osimertinib 28%, Placebo 62%)

II-IIIA subgroup: HR 0.23
(0.18, 0.30)

IB subgroup: HR
0.41 (0.23, 0.69)

Company: Plateau forming from 48 months

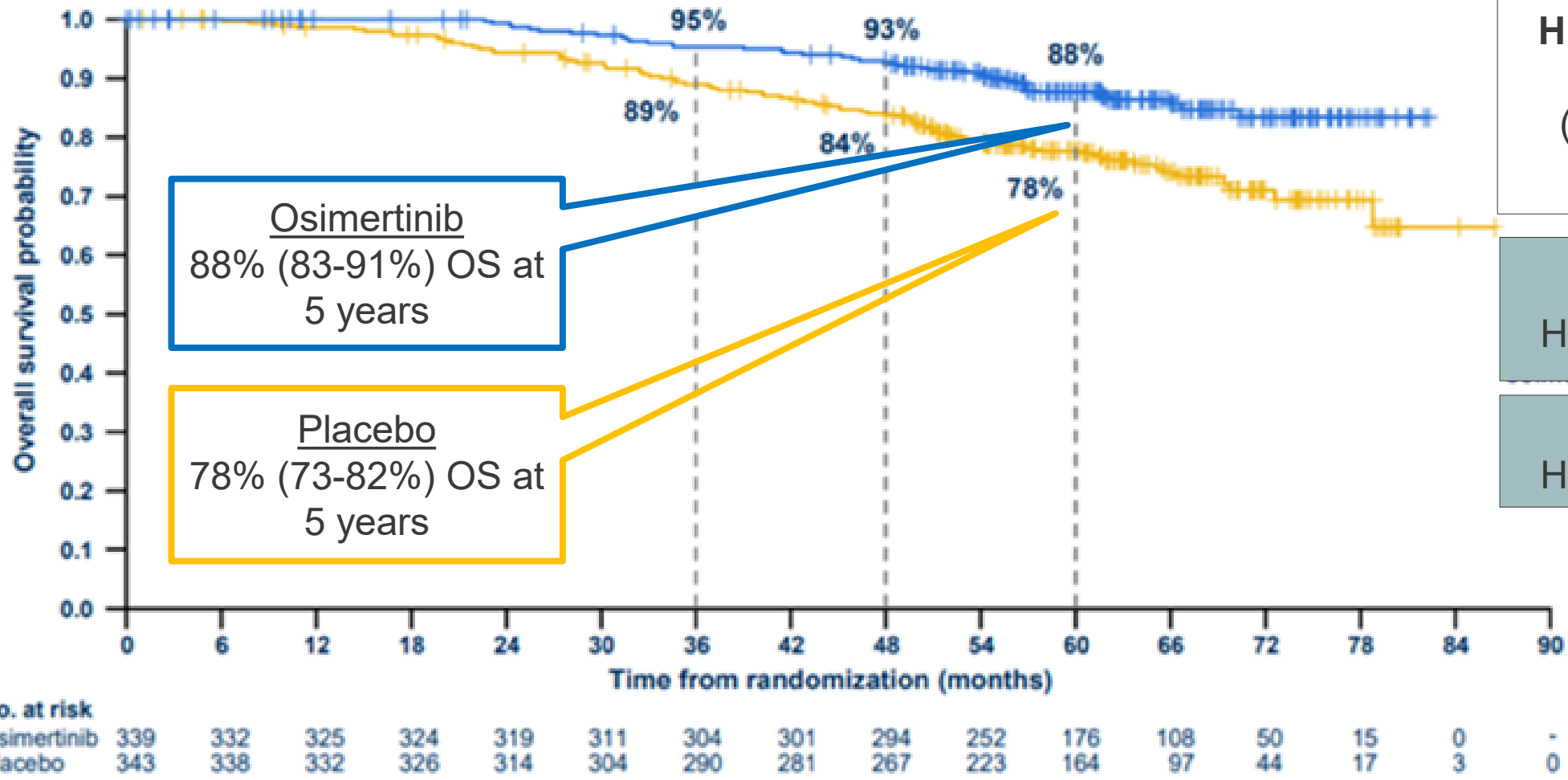
No. at risk													
Osimertinib	339	316	307	289	278	270	249	201	139	73	33	5	0
Placebo	343	288	230	205	181	162	137	115	84	48	25	4	0

Subgroups not in economic analysis. Is treatment effect sufficiently similar to overall population?

Abbreviations: DFS, disease-free survival; HR, hazard ratio

Kaplan-Meier plot of OS in ADAURA - Overall population

OS in ADAURA trial (overall population)



HR 0.49 (0.34, 0.70)
Maturity 18%
(Osimertinib 12%, Placebo 24%)

II-IIIA subgroup:
HR 0.49 (0.33, 0.73)

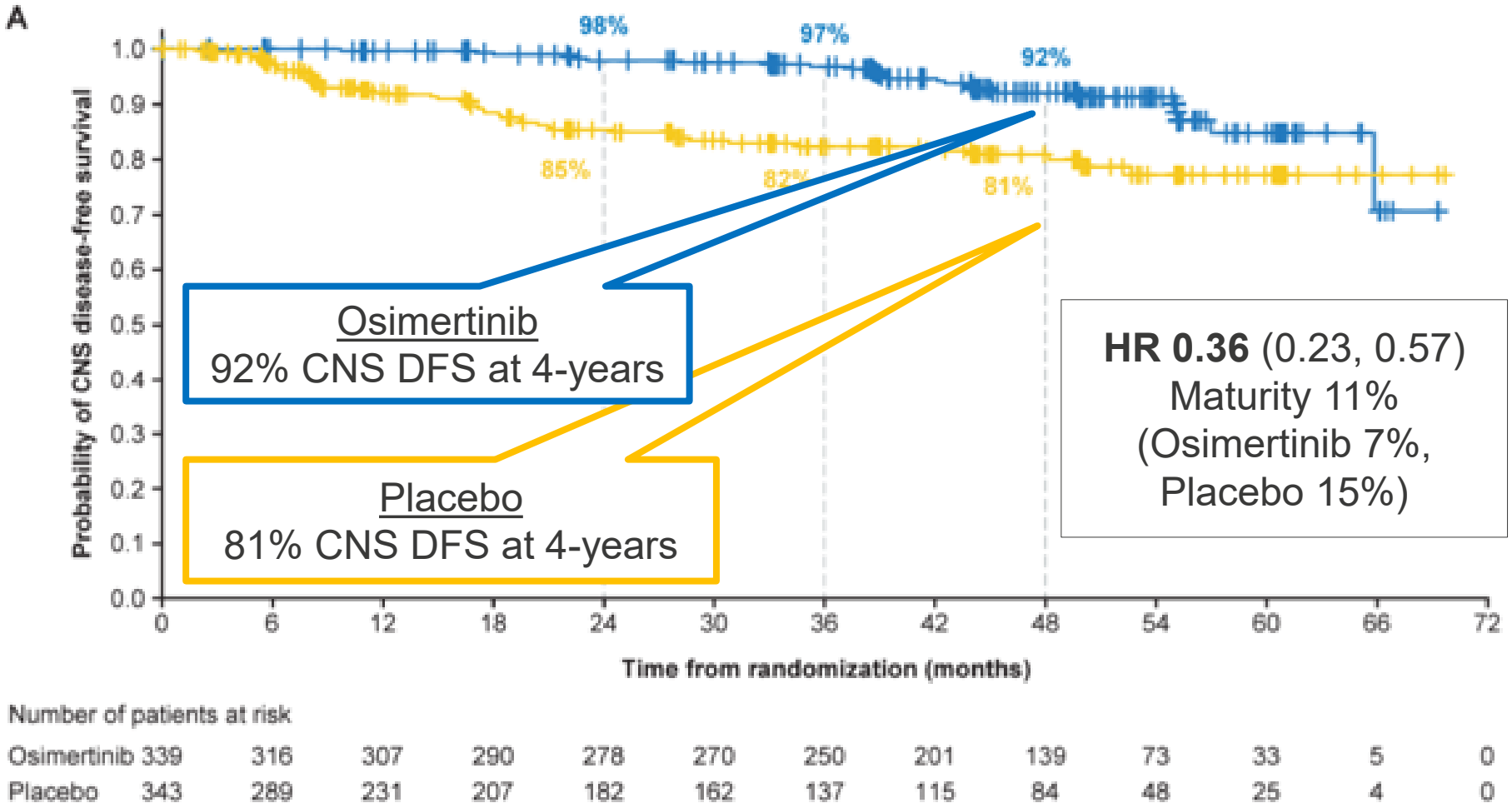
IB subgroup:
HR 0.44 (0.17, 1.02)

Subgroups not in economic analysis. Is treatment effect sufficiently similar to overall population?

Abbreviations: HR, hazard ratio, OS, overall survival

Kaplan-Meier plot of CNS metastases in ADAURA - Overall population

CNS DFS in ADAURA trial (overall population)



Osimertinib
92% CNS DFS at 4-years

Placebo
81% CNS DFS at 4-years

HR 0.36 (0.23, 0.57)
Maturity 11%
(Osimertinib 7%,
Placebo 15%)

II-IIIA subgroup:
HR 0.24 (0.14, 0.42)

IB subgroup:
Not reported

Subgroups not in economic analysis

Abbreviations: HR, hazard ratio, OS, overall survival

SACT dataset for managed access period

- Collected data on 143 people receiving osimertinib between November 2021 and December 2022

Patient characteristics in SACT compared with ADAURA

	SACT dataset (N=143)	ADAURA osimertinib arm (N=339)
Setting (N)	UK	212 sites in 24 countries
Females, N (%)	110 (77%)	230 (68%)
Age ≥50 years, N (%)	135 (94%)	Median = 64, range 30–86
Stage IB disease, N (%)	41 (29%)	102 (30%)
Stage II-IIIA disease, N (%)	91 (63%)	220 (65%)
Exon 19 deletion, N (%)	77 (54%)	185 (55%)
Exon 21 substitution mutation	65 (45%)	153 (45%)
Prior chemotherapy %	39 (27%)	202 (60%)
Median treatment duration	14.7 months	35.8 months
On treatment %	6 months: 81%, 12 months: 75%	6 months: 98%, 12 months: 96%
Data-maturity at DCO*	6.2% (DCO April 2023)	12% (18% overall population)
Median OS	Not reached	Not reached
OS	6 months: 96%, 12 months: 92%	36 months: 95%; 60 months: 88%

Abbreviations: DFS, disease-free survival; OS, overall survival; SACT, systemic anti-cancer therapy

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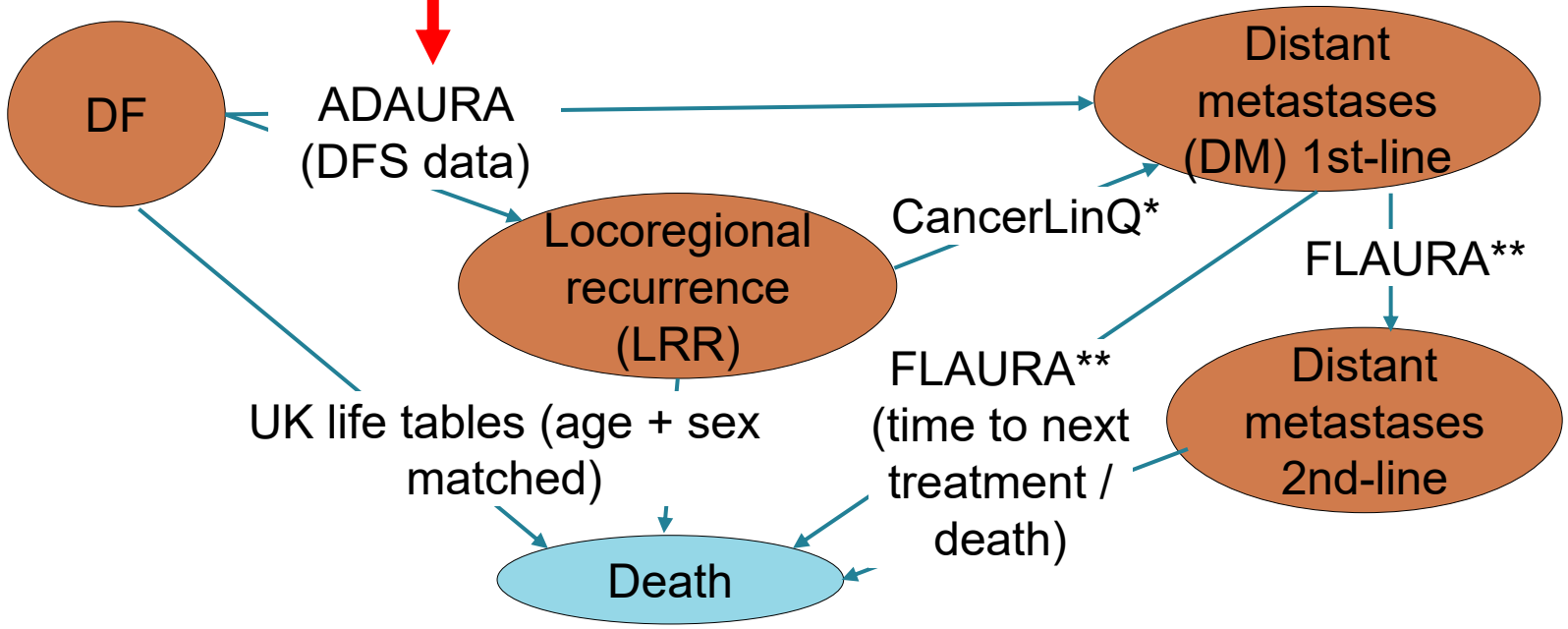
Model structure

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” 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 referred to as the "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

Key issue: Re-treatment with osimertinib

Background

- TA761 assumed 50% of people who have distant relapse >5 years after initiating osimertinib would be re-treated
- Committee concerned that 50% figure was arbitrary and that some people would be re-treated <5 years
- Current model has same assumption but lowers timepoint from which re-treatment is possible to 4 years
- Current model assumes 83% in monitoring arm receive osimertinib in first-line treatment for metastatic disease
- Data on re-treatment not collected in SACT

Company

- SACT was unlikely to provide reasonable data on re-treatment in given timeframe
- 41% of those who had subsequent treatment in osimertinib arm (ADAURA) received osimertinib (Tsuboi, 2023)

EAG comments

- No new evidence to address uncertainty → sensitivity analyses around timepoint but not proportion
- Unclear if those who received osimertinib as first post-study therapy had previously progressed on osimertinib
- Clinical advice suggests vast majority (>50%) retreated in metastatic setting after 4 years, may be offered sooner if discontinued before completing 3 years. → likely >83% would receive osimertinib in monitoring group
- Assumption has greater impact on ICER now due to later final cure timepoint
- Assumed no loss in efficacy → advice to EAG: This is reasonable but so is earlier resistance / reduced efficacy

From what timepoint would re-treatment be offered? What proportion would be re-treated? Would there be a drop in efficacy?

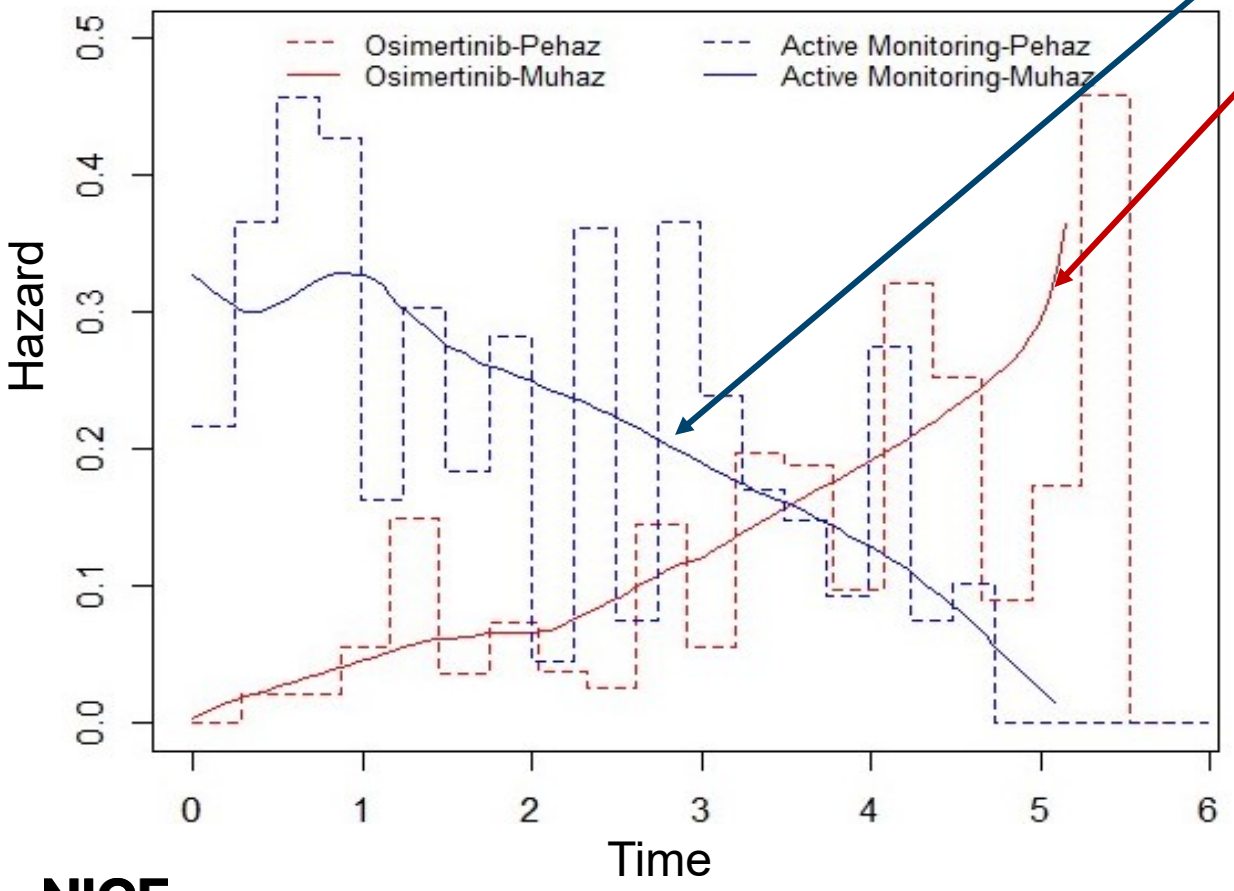
Abbreviations: ICER, incremental cost-effectiveness ratio; SACT, systemic anti-cancer therapy;

Observed versus modelled data

Background

- Distributions selected for each transition probability (TP) → TP1+2 choices informed by observed ADAURA data
- EAG: distributions are not good match to data, more flexible model forms would better reflect observed hazards

Smoothed and empirical hazards for DFS in ADAURA



Placebo: Risk of relapse or death decreases over time

Osimertinib: Observed hazards increase over time, modelled hazards decrease after year 4, very low by year 8 due to cure assumptions

EAG

- TP1 (DF to LRR) osimertinib observed hazards show two turning points, company model only allows one
- TP2 (DF to DM) no good fit for monitoring group. Weibull and Gompertz better fit to empirical hazard plot for osimeritinb
  - **Company:** EAG choices give sharply increasing hazards overtime, overly influenced by curve tail (which is uncertain due to high censoring)

Scenario analyses using different distributions for TP1 and 2

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Abbreviations: DF, disease-free; DM, distant metastases; LRR, locoregional recurrence; TP, transition probability

Key issue: Long-term outcomes (cure)

Background

- Current model assumes that after a **final cure point** (5 years in monitoring group, 8 years in osimertinib group), risk of loco-regional or distant relapse is 5% of predicted probabilities → small proportion will still relapse
- **Warm-up phase**: risk of relapse decreases approx. linearly from end of year 4 until **final cure point**

EAG:

- **Warm-up** not included in TA761, has big impact on ICER
- **Warm-up** was included in TA632 (early-stage breast cancer) but minimal impact on ICER as same cure assumptions in both arms
- Unconventional approach to modelling cure → usually have subgroups (cured/non-cured) who have different relapse risks
- EAG used individual patient data to create mixture-cure models (MCMs): Fewer could be fitted to osimertinib arm suggesting insufficient DFS data for cure.
- ADAURA DFS follow-up ~6 years [redacted]
- One clinical advisor suggests 8 years cure-point reasonable, second unsure if gap in DFS and OS would be maintained

Scenario analyses: Osimertinib cure point 7 years / 1-TTD + 5 years

Estimate cure fractions in EAG's MCMs

Model	Osimertinib	Monitoring
Exponential	0% (0, 100)	**26% (18, 35)**
Weibull	0% (0, 100)	**32% (26, 39)**
Gompertz	**41% (11, 80)**	**31% (24, 40)**
Log-normal	0% (0, 100)	**23% (14, 36)**
Log-logistic	0% (0, 100)	**24% (16, 34)**
Gamma	0% (0, 100)	**32% (26, 38)**
Gen. gamma	**24% (0, 100)**	1% (0, 100)

Company: Curable potential of resection is well established | Placebo DFS curve in ADAURA begins to plateau ~48 months | Osimertinib plateau expected but interpretation >48 months limited by censoring, low number at risk.

- Warm-up period more plausible than sudden drop, was accepted in TA632

NICE **When (if at all) should cure be applied for each group? Should there be a warm-up period?**

Abbreviations: DFS, disease-free survival; ICER, incremental cost-effectiveness ratio; OS, overall survival; TTD, time to treatment discontinuation

Company base case and EAG scenarios

No.	Scenario (applied to company base case)	ICER (£/QALY) versus active monitoring
1	**Company base case**	
2	Correction of modelling errors	
3	Use of Hernandez Alava *et al.* to cap DFS/LRR utility values and for age-adjustment	
4	All patients incur DFS costs until the final cure timepoint	
5	Include wasted costs for osimertinib and early-TKIs	
6	No warm-up period for applying cure	
7	**EAG optimistic scenario analysis (2-5 combined)**	
8	**EAG pessimistic scenario analysis (2-6 combined)**	

Results do not include confidential commercial discounts for comparators

Abbreviations: DFS, disease-free survival; LRR, locoregional recurrence; TKI, tyrosine kinase inhibitors

EAG base-case: Optimistic vs. pessimistic impact on DFS

Effect of preferred scenarios on DFS modelling

[redacted]

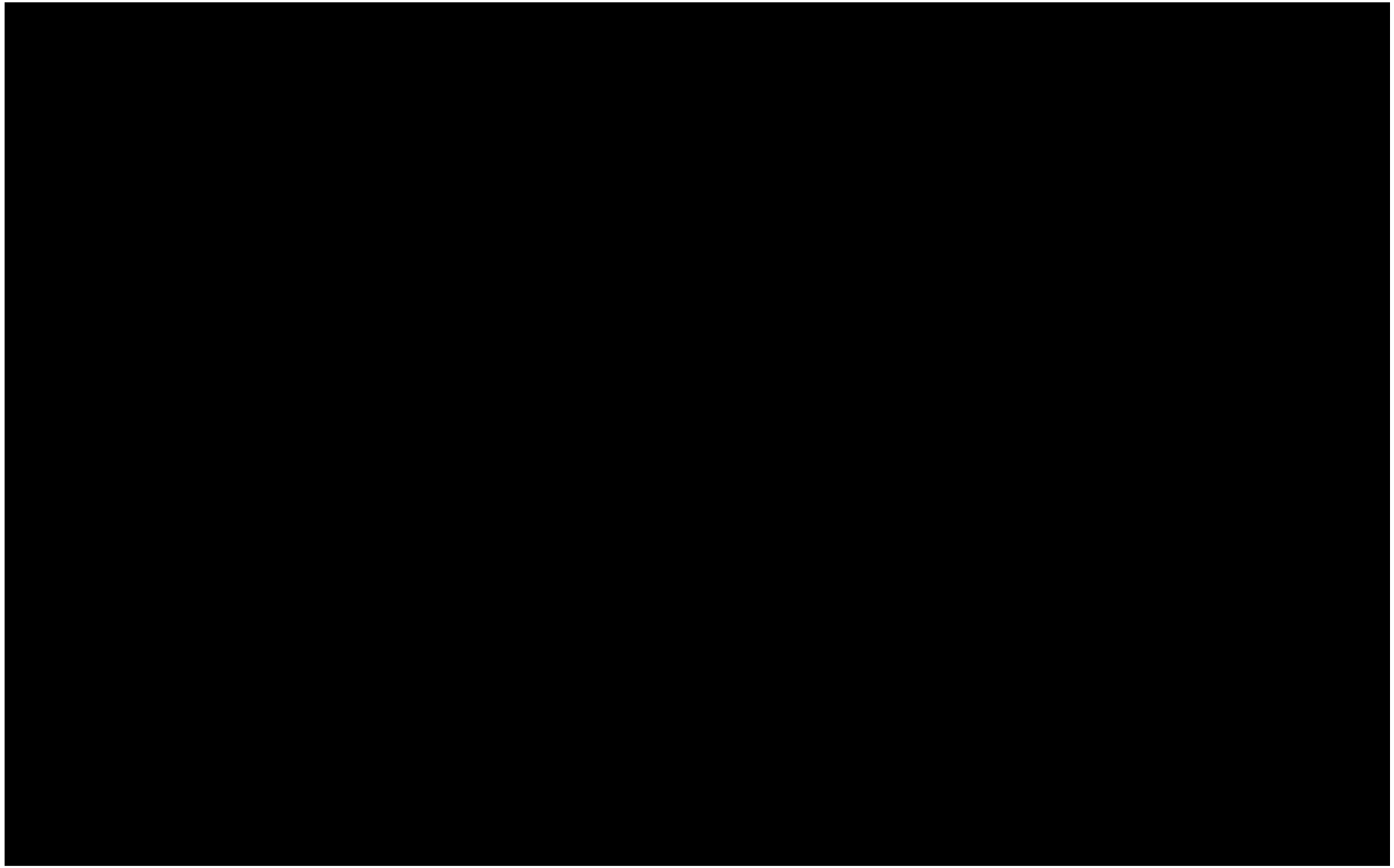
EAG: Advisors thought that both optimistic and pessimistic were plausible

See slide on optimistic vs. pessimistic (non-confidential) for a non-confidential version of this graph (no scenario for TTD-informed cure-point)

Abbreviations: AM, active monitoring; DFS, disease-free survival; OS, overall survival, Osi, Osimertinib; TTD, time to treatment discontinuation

EAG base-case: Optimistic vs. pessimistic impact on OS

Effect of preferred scenarios on OS modelling



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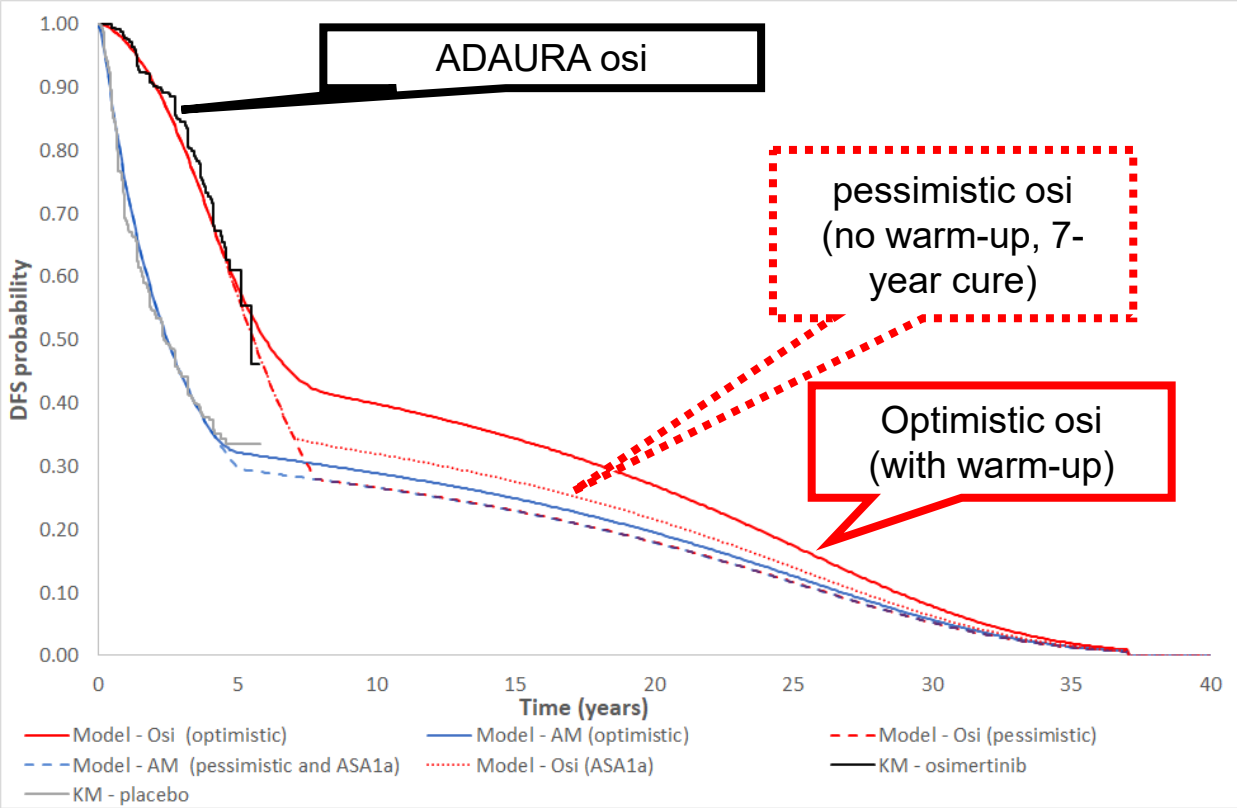
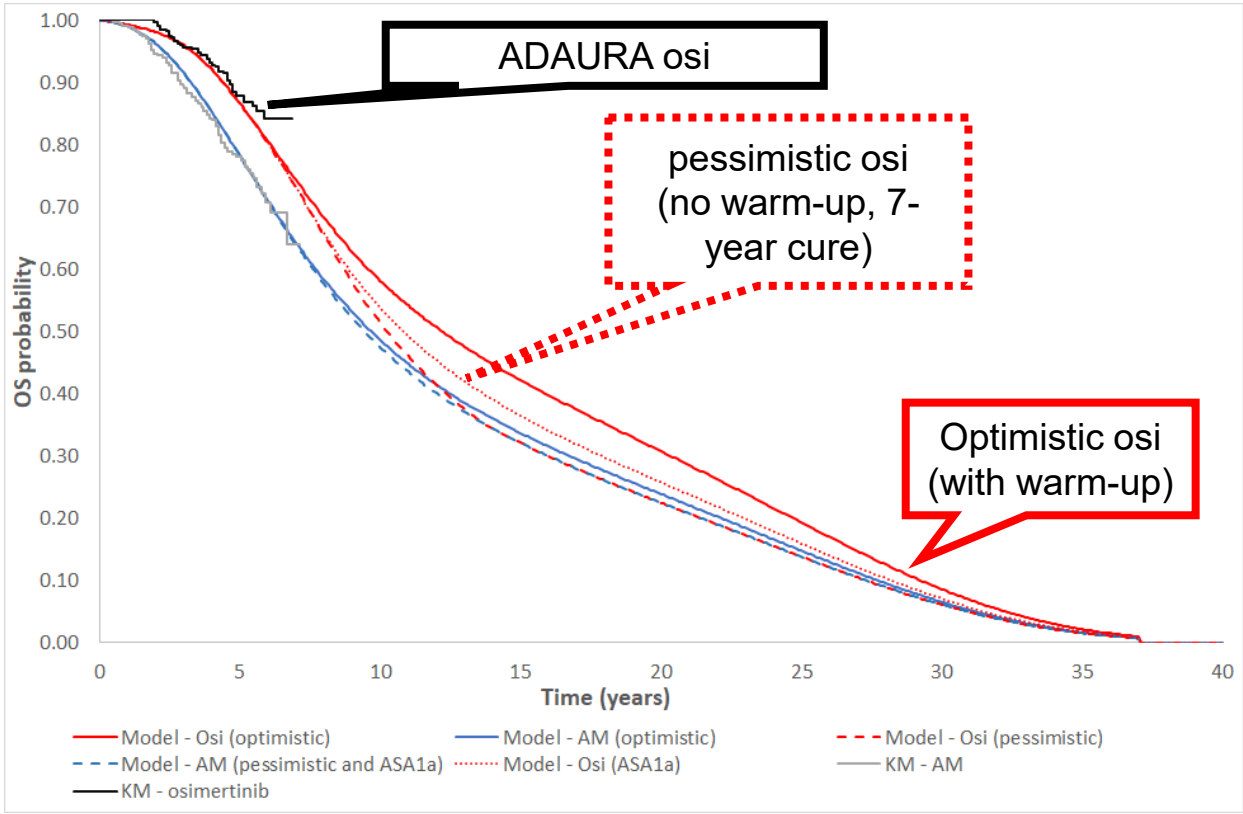
EAG base-case: Optimistic vs. pessimistic

Effect of preferred scenarios on DFS modelling



Effect of preferred scenarios on OS modelling



EAG: Advisors thought that both optimistic and pessimistic were plausible

 Abbreviations: AM, active monitoring; DFS, disease-free survival; OS, overall survival, Osi, Osimertinib; TTD, time to treatment discontinuation

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

Other issues

EGFR testing costs not included in current company base-case (included in TA761)

- Company: EGFR testing now routine for early-stage NSCLC via next generation sequencing panel testing.
- EAG: some costs of EGFR testing are attributable to adjuvant Osimertinib, these should be included.
- EAGs clinical advisors: Prior to adjuvant osimertinib, EGFR testing not conducted for people without metastatic NSCLC, some centres may test for EGFR only. For some people EGFR testing would still be needed even if no osimertinib (such as neoadjuvant nivolumab)

Modelling errors

- DF and LRR health utilities are equivalent, slightly higher than age/sex-matched general population (implausible)
- Corrected errors in downstream portions of model

Equality considerations and severity

No issues identified

- Company submission does not make a case for severity weighting and states that no equality issues were identified relevant to access of osimertinib
- EAG advises no severity modifier should be applied (weight of 1.0 should be applied)
- No equality issues raised during scoping

Are there any equality issues relevant to the potential recommendations?

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Issues

Key issues

Issue	ICER impact
Uncertainty around re-treatment	Small-moderate
Company modelling of cure includes warm-up period (risk of recurrence/event gradually decreases from 4 years to a final cure point) • Should warm-up period be applied? • Concerns that modelled benefit deviates from observed data, uncertainty around final cure point	Large

Other issues

- Subgroups not in economic evaluation (see slide on subgroup clinical results)
- Capping of DFS and LRR utility values (see slide on other issues)
- Exclusion of certain costs from model (such as DFS costs, wastage, EGFR testing)

Abbreviations: DFS, disease-free survival; LRR, locoregional recurrence

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Thank you.

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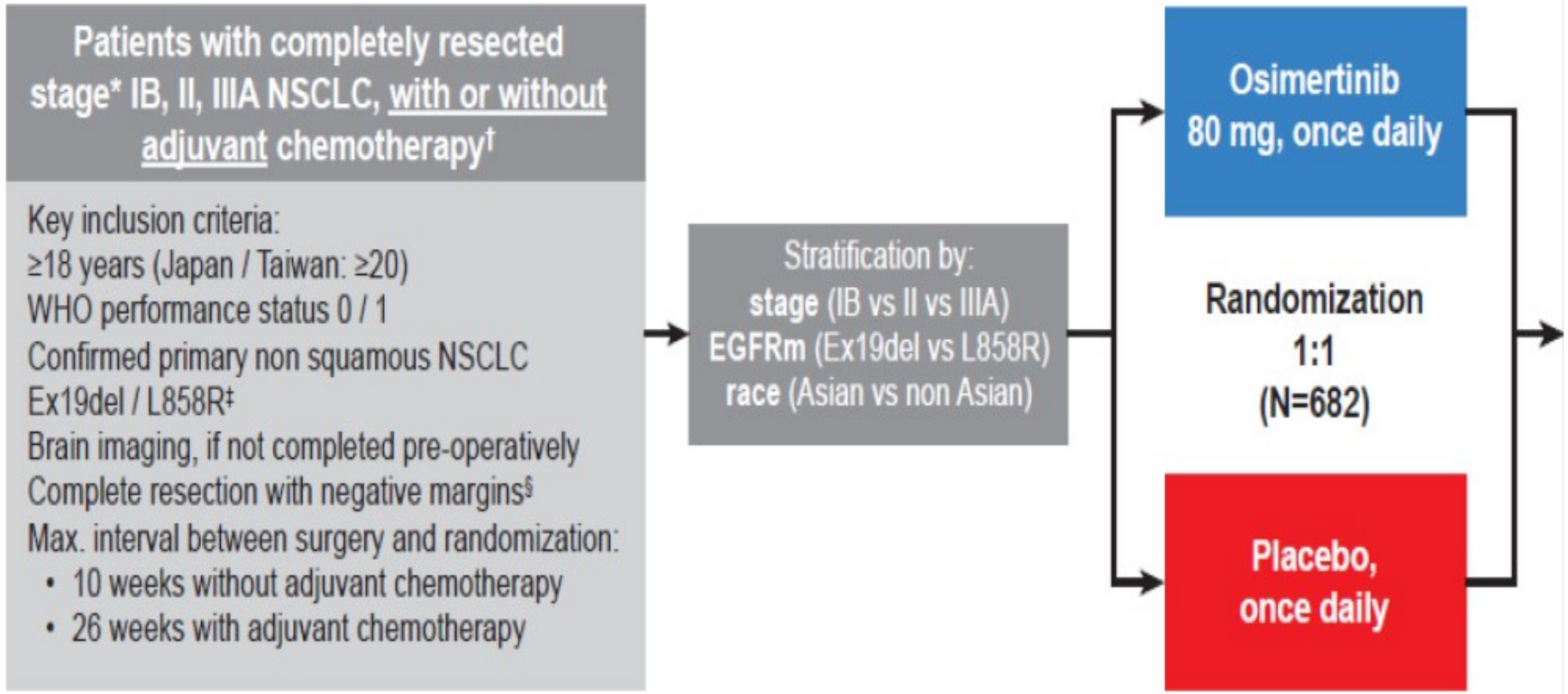
Back-up slides

Decision problem table

	Final NICE scope	Company submission	Rationale
Population	Stage IB to IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, after complete tumour resection (with or without adjuvant chemotherapy)	As per scope	N/A
Intervention	Osimertinib	As per scope	N/A
Comparator(s)	• Platinum-based chemotherapy • Established clinical management without osimertinib (active monitoring)	Active monitoring	ADAURA evaluated osimertinib as add-on to surgery (with or without chemotherapy) → not intended to displace adjuvant chemotherapy
Outcomes	• OS, DFS, TTD • Sites and rates of recurrence • Adverse effects of treatment • HRQoL	As per scope	N/A
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • stage IB versus II-IIIA	Subgroups in ADAURA but not in cost-effectiveness analysis.	Subgroups not powered to detect significant effects. Consistent treatment effect observed

Abbreviations: DFS, disease-free survival; NSCLC, non-small-cell lung cancer; OS, overall survival; TTD, time to treatment discontinuation

Key clinical trial: ADAURA



- Follow-up: weeks 12, 24 → every 24 weeks to 5 years → annually
- (If recur: follow-up every 24 weeks to 5 years → annually)
- Data-cuts used in submission: April 2022 for DFS, Jan 2023 for OS (median follow-up 60.4 months for Osimertinib, 59.4 months for placebo)
- 3 years treatment(or until recurrence or discontinuation criteria met)

EAG: TARGET study currently recruiting in stage II-IIIB EGFRm NSCLC, completion expected 2029

Abbreviations: AJCC, American Joint Committee on Cancer; CT, computed tomography; DFS, disease-free survival; EGFRm, EGFR mutation positive; Ex19del, exon 19 deletion; NSCLC, non-small cell lung cancer; OS, overall survival; WHO, World Health Organization.

Key trial ADAURA subgroup results

	Key outcomes	Osimertinib	Placebo
Subgroup (stage IB)	Number in study, n	106	106
	DFS (%)	48 months: 80% 60 months: 78%	48 months: 59% 60 months: 53%
	Median OS (months)	Not reached	Not reached
	OS (%)	60 months: 94%	60 months: 88%
	Number in study, n	233	237
Subgroup (stage II–IIIA)	Median DFS (months)	65.8 (not reached in original submission)	21.9 (19.6 in original submission)
	DFS (%)	48 months: 70% [redacted]	48 months: 29% [redacted]
	Median OS (months)	Not reached	Not reached
	OS (%)	60 months: 85%	60 months: 73%
	CNS recurrence (%)	7.7%	13.5%

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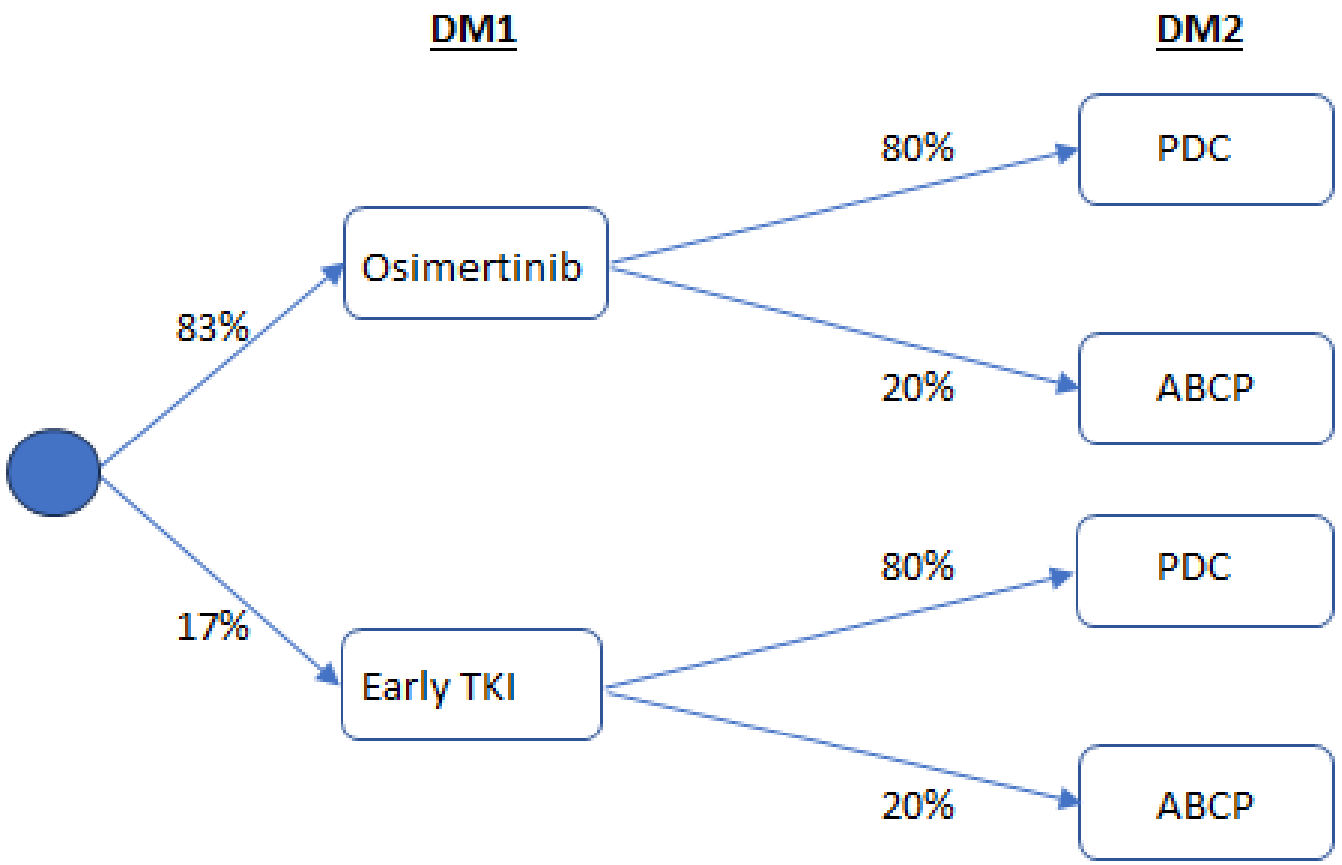
Abbreviations: CNS, central nervous system; DFS, disease-free survival; OS, overall survival

Treatment pathway for distant metastases in active monitoring group

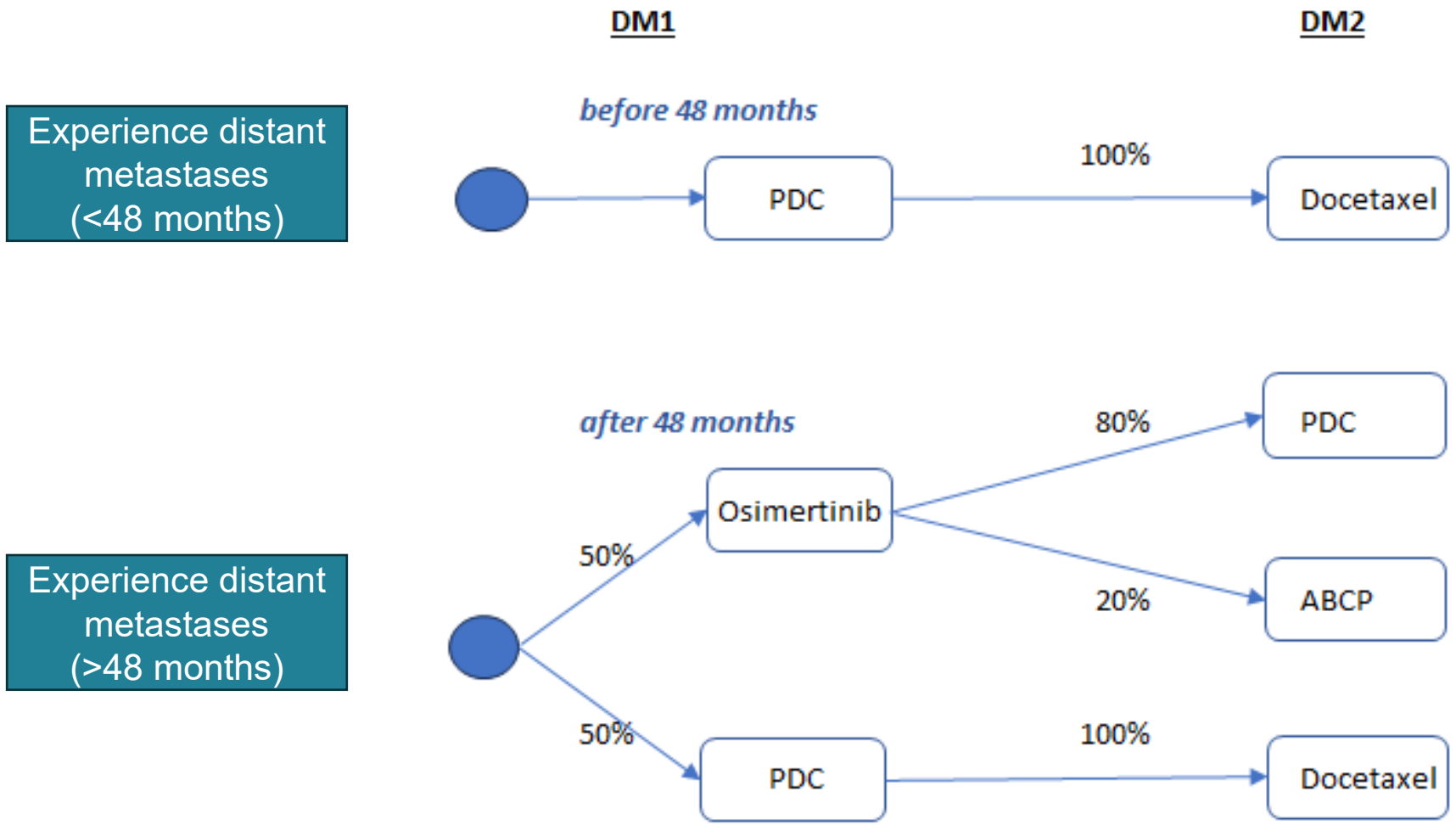
Treatment pathway for people assigned to active monitoring



Abbreviations: ABCP, atezolizumab plus bevacizumab plus carboplatin plus paclitaxel; DM1, distant metastases (first-line); PDC, pemetrexed plus cisplatin ; TKI, tyrosine kinase inhibitor

Treatment pathway for distant metastases in osimertinib group

Treatment pathway for people assigned to active monitoring



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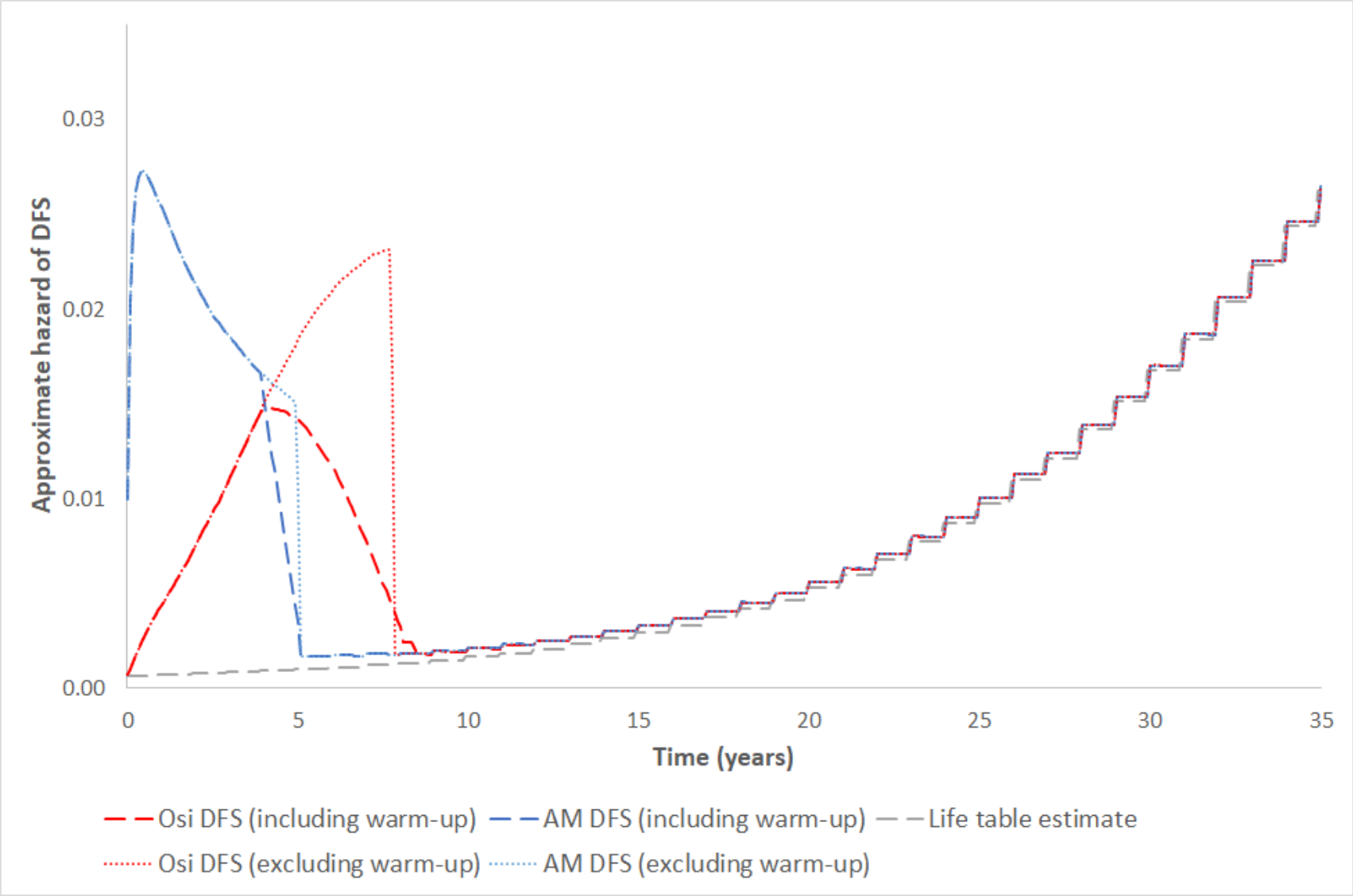
Company model-predicted DFS hazards over time

Company's model-predicted DFS hazards



EAG: Osimertinib hazards increase over time whereas monitoring decrease

Abbreviations: DFS, disease-free survival; MCM, mixture-cure model