NICE National Institute for Health and Care Excellence

PART 1 – Public observer handouts

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection

Chair's presentation

Chair: Lindsay Smith

ERG: ScHARR

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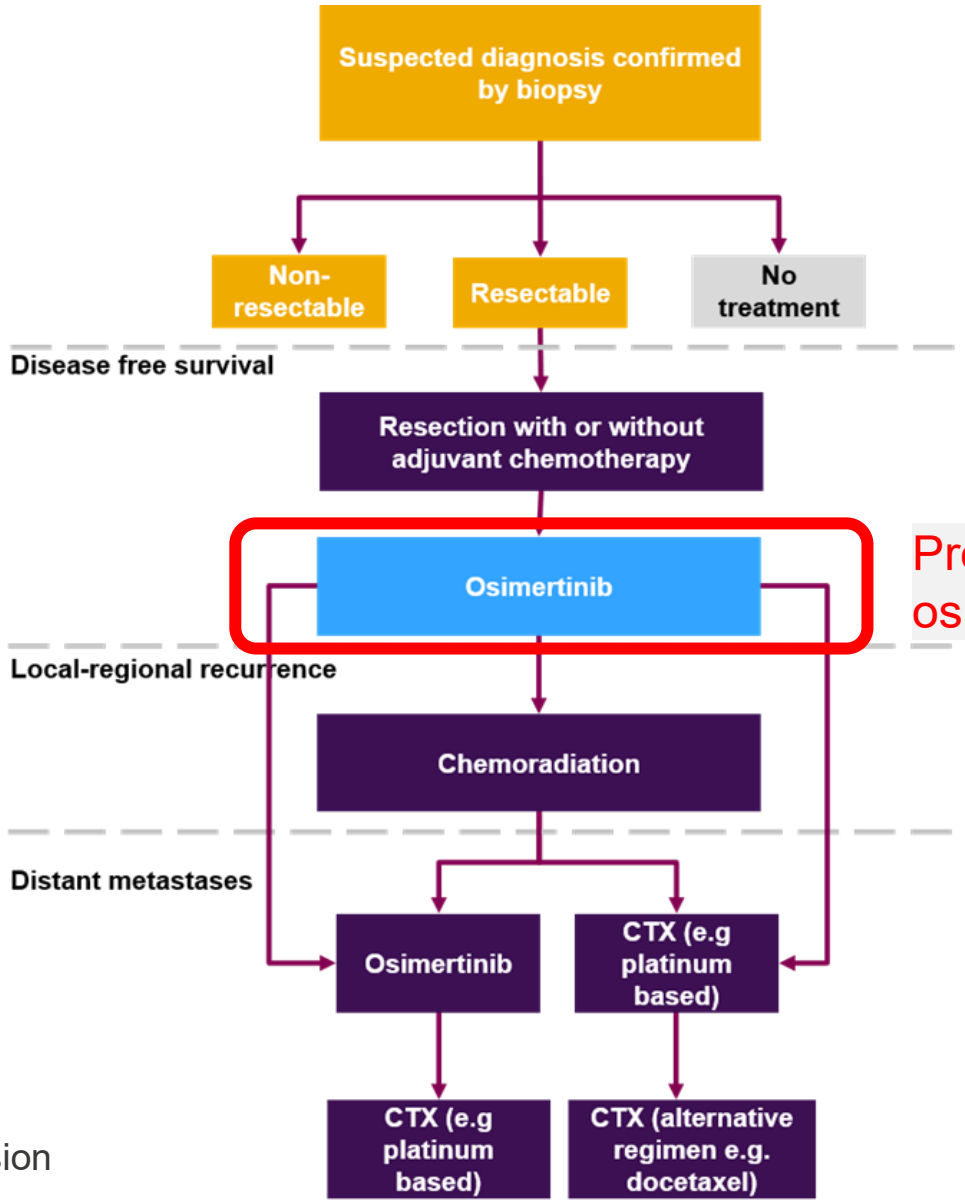
Company: AstraZeneca

ACM2 date: 16th September 2021

Positioning in treatment pathway



Proposed positioning of osimertinib as adjuvant treatment

Source: Company submission
Part B, Figure 4

Abbreviations: CTX, chemotherapy; EGFRm, epidermal growth factor receptor mutation; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer.

Osimertinib (Tagrisso, AstraZeneca)

Marketing authorisation	Osimertinib as adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.
Mechanism of action	Selective, small molecule tyrosine kinase inhibitor that targets the sensitising (exon 19 deletions and exon 21 L858R point mutations) and T790M mutant forms of the EGFR-TK, while having minimal activity against wild-type EGFR
Administration	• Orally at a dose of 80mg once daily. • Model includes a stopping rule for osimertinib at 3 years based on the design of the ADAURA trial. • SmPC states that *'patients in the adjuvant setting should receive treatment until disease recurrence or unacceptable toxicity. Treatment duration for more than 3 years was not studied'*
Cost (list price)	The list price for 30 tablets is £5,770. At list price, the total cost is approximately £210,000 per patient (36 months treatment duration). Commercial access arrangements are in place for osimertinib (as a downstream treatment) [redacted]

Background

Clinical trial: ADAURA	Phase III, randomised, double-blind, multicentre study
Comparators	Active monitoring (placebo in ADAURA trial)
Population and subgroups	• **Overall:** Adults with fully resected, stage IB-IIIA EGFRm-positive NSCLC • **Subgroups**: Stage IB and stage II-IIIA EGFRm-positive NSCLC
Key results for the overall population (interim results: data cut-off 17 January 2020)	• [redacted] • DFS: HR 0.20 (99.12% CI 0.14, 0.30; p<0.001) • CNS: HR: 0.18 (95% CI: 0.10, 0.33; p<0.0001) ADAURA study was unblinded 2 years early due to overwhelming efficacy. OS results have [redacted] maturity
Model	State transition (semi-Markov) approach.

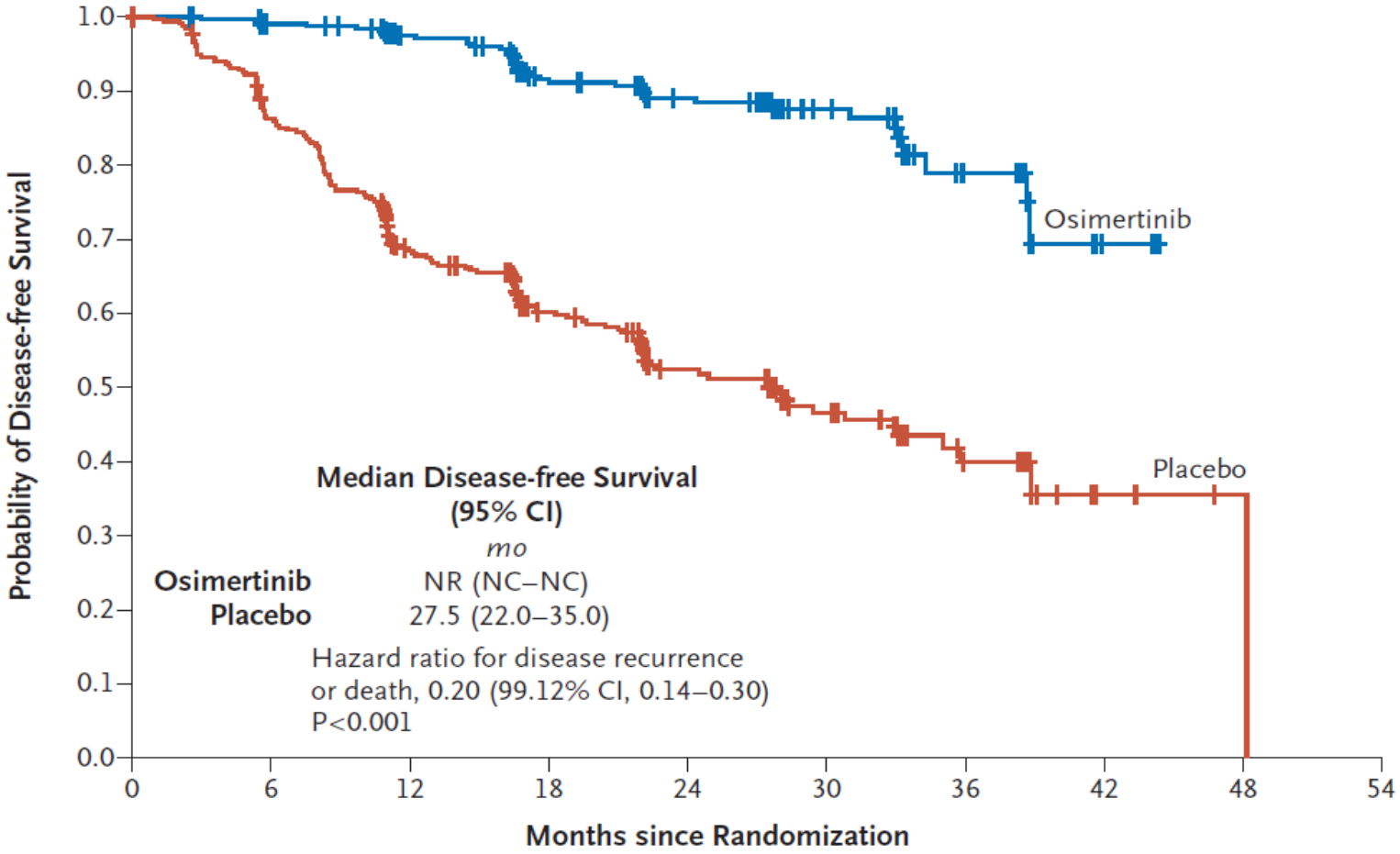
Key trial results

	Key outcomes*	Osimertinib	Placebo
	Number in study (n)	339	343
Overall population (stage IB-IIIA)	Median DFS (months)	Not reached	27.5
	DFS benefit	HR: 0.20; 99.12% CI: 0.14, 0.30; p<0.001	
	Proportion of patients alive and disease free at 24 months (%)	89.1 (95% CI: 84.5, 92.4)	52.4 (95% CI: 46.4, 58.1)
	Median OS (months)	[redacted]	[redacted]
	CNS recurrence	4 patients (1.2%)	33 patients (9.6%)

*Interim results: data cut-off 17January 2020

**[redacted]

Kaplan-Meier plot of DFS in ADAURA - Overall population



No. at Risk										
Osimertinib	339	313	272	208	138	74	27	5	0	
Placebo	343	287	207	148	88	53	20	3	1	0

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

Original source: Wu Y-L, Tsuboi M, He J, et al. Osimertinib in resected EGFR-mutated non–small-cell lung cancer. N Engl J Med 2020;383:1711-23. DOI: 10.1056/NEJMoa2027071

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Source: Company submission Part B, Figure 7

Kaplan-Meier plot of OS in ADAURA - Overall population

OS - overall survival.
Source: ADAURA CSR.

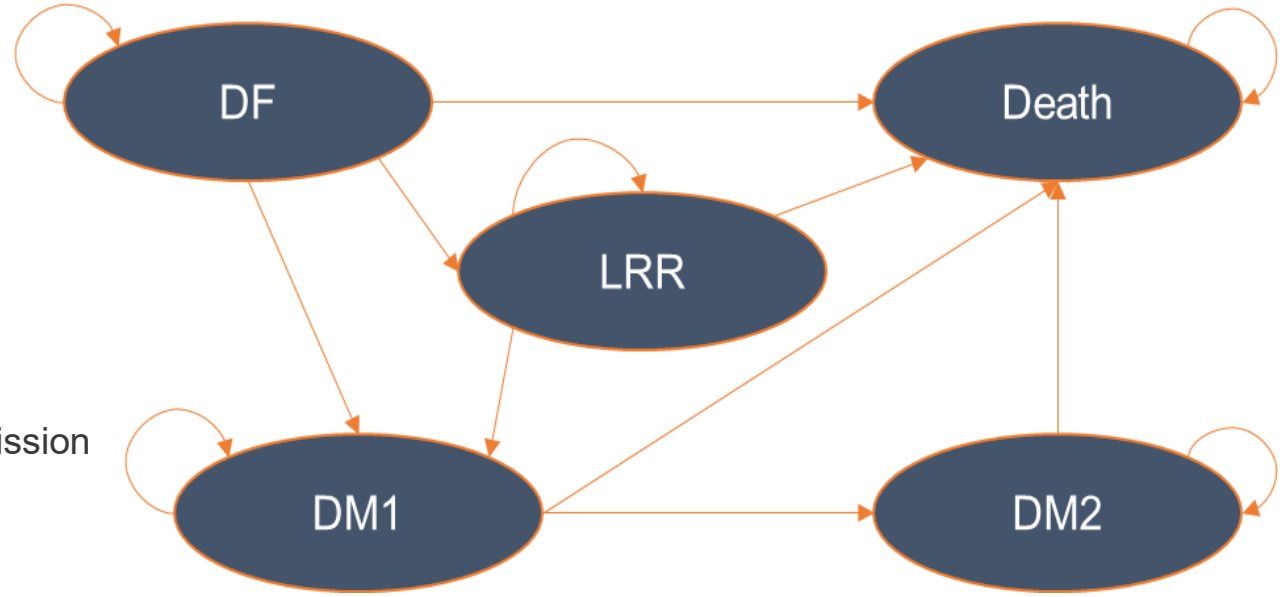
Source: Company submission Part B, Figure 10

Observed and model-predicted OS, based on ADAURA & company model (re-drawn by ERG using company's updated model)

OS - overall survival.

NICE Source: ERG Post-FAC Report, Figure 21

Model structure:



Source: Company submission
Part B, Figure 13

Structure	Semi-Markov model with 5 health states: • 'Disease-free (DF)', • 'Locoregional recurrence (LRR)', • '1st line treatment for distant metastatic NSCLC (DM1)', • '2nd line treatment for distant metastatic NSCLC (DM2)', • and 'Death'

ACD preliminary recommendation

- The committee recognised that osimertinib is promising, but was not persuaded that there is sufficient evidence of clinical and cost effectiveness to recommend it for routine commissioning in this indication.
- The committee saw that osimertinib may be suitable for use in the Cancer Drugs Fund.
- Therefore, the company is invited to submit a proposal for including osimertinib in the Cancer Drugs Fund.

Recap: ACD considerations

Issue	Committee's considerations
Uncertain if a benefit in DFS will translate to a benefit in OS (ACD 3.5)	• Very few patients reached 3-years of treatment with osimertinib • Data on recurrence after stopping treatment not presented • → uncertain to what extent a benefit in disease-free survival translates into a benefit in overall survival.
Uncertainty around cure assumption (ACD 3.6-3.9)	• Max. follow-up in ADAURA was 4 years and very few patients reached 3-years of treatment with osimertinib • → ERG pessimistic analysis (5-year cure in active monitoring arm, 8 years for osimertinib [3 yrs tx + 5 yrs]) plausible.
Downstream treatment pathways (ACD 3.10)	• Not appropriate to assume 100% of people in active monitoring arm have osimertinib as 1st treatment for metastatic disease • → appropriate to base analyses on the latest prescribing data.
Retreatment with osimertinib (ACD 3.3)	• Assumption 50% of people who develop distant metastases would be retreated with osimertinib as 1L therapy is arbitrary.
Cancer Drugs Fund (ACD 3.14)	• Uncertainty could be resolved with further data collection in the Cancer Drugs Fund

Key issues after consultation

Issue	Impact	Slides
Issue 1: Uncertain whether a benefit in DFS will translate to a benefit in OS		14
Issue 2: Uncertainty around how osimertinib's mode of action and clinical benefit differs from previous first and second generation EFGR tyrosine kinase inhibitors (TKIs)		15
Issue 3: Uncertainty about the company's OS predictions- Modelling survival		16-19
Issue 4: Uncertainty about the Company's cure assumptions and timing of cure		20
Issue 5: Uncertainty about later treatments with or without adjuvant osimertinib (including retreatment with osimertinib)		21
Issue 6: Innovation status		22
Issue 7: Appropriateness of the Cancer Drugs Fund		23-24

 Model driver

 Unknown impact

 Small/Moderate impact

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ACD consultation responses

- AstraZeneca (company)
- Clinical expert, thoracic surgeon
- Clinical expert, consultant medical oncologist

ACD consultation comments – Issue 1

Uncertainty about the extent a benefit in DFS translates into a benefit in OS

Company comments

- DFS benefit demonstrated in ADAURA is likely to be maintained.
- Extending the disease-free period ➔ long-term benefits compared to existing active monitoring, even in the absence of long-term OS.
- Longer disease-free period ➔ delay and avoid costs of progression to advanced disease.
- Clinical rationale and UK expert opinion suggests DFS benefit will translate into OS.
- If DFS benefit significantly reduced over time, osimertinib remains cost-effective ➔ tipping point analysis conducted.

ERG critique

- Agree that there is value in extending DFS in patients with resected EGFRm NSCLC.
- Agree that the reasons provided as to why adjuvant osimertinib is expected to result in a significant OS benefit are all plausible. However, due to the immaturity of OS data from ADAURA, the magnitude of any OS benefit is very uncertain.
- Unclear how tipping point scenario has been implemented → unable to validate

Clinical expert comments

- Clear significant clinical benefit has been outlined ➔ seems that there is overreliance on OS
- DFS, alongside the very important CNS DFS, are in themselves the clinically meaningful and patient-centric endpoints

ACD consultation comments – Issue 2

Uncertainty around how osimertinib's mode of action and clinical benefit differs from previous first and second generation EFGR tyrosine kinase inhibitors (TKIs)

ACD: committee was concerned that the experience with earlier generation TKIs such as erlotinib suggested that disease often recurred after stopping treatment.
However, a clinical expert cautioned against placing too much weight on this because erlotinib does not have the same brain penetration as osimertinib.

Company comments

- Comparison to earlier EGFR-TKI data in the adjuvant setting is not appropriate.
- Osimertinib is a third generation, differentiated EGFR-TKI designed to provide targeted, irreversible inhibition of both EGFRm and EGFR T790M, with demonstrated CNS penetration.
- Osimertinib is the first EGFR-TKI to provide a significant DFS benefit vs placebo, across stages IB-IIIA EGFRm NSCLC.

ERG critique

- The company's submission highlights that previous trials of EGFR-TKIs erlotinib and gefitinib as adjuvant therapies have demonstrated initially promising DFS rates, but few long-term benefits.
- Given limited OS data, it is reasonable to consider this aspect of benefit to be highly uncertain.

Clinical expert comments

- Not the same technology as previous generation TKIs in similar population ➔ unfair comparison

ACD consultation comments – Issue 3

Alternative plausible modelling assumptions for the transition from the disease free to distant metastatic NSCLC health states using a log-normal distribution in: i) both arms of the model, ii) In the treatment arm of the model only

Company comments

- Disagree that choice of extrapolations driven by the cure assumption rather than goodness of fit.
- Disagree that the survival predictions may be optimistic. Extrapolation of DFS from ADAURA are based on a period that appears to correspond with an increased risk of recurrence rate.
- ASA4a is clinically implausible as it produces a pattern of disease recurrence that directly contradicts the efficacy seen in ADAURA. For DF to DM1: curves cross at around 22 years.
- ASA4b is clinically implausible as it assumes that patients progress faster following treatment with osimertinib than receiving placebo. For DF to DM1: curves cross at around 11 years.

Clinical expert comments

- Extrapolations are somewhat arbitrary and need reassessing when longer term data is available
- ERG modelling appears clinically implausible ➔ those on osimertinib do worse in long term

ACD consultation comments – Issue 3

Alternative plausible modelling assumptions for the transition from the disease free to distant metastatic NSCLC health states using a log-normal distribution in: i) both arms of the model, ii) In the treatment arm of the model only

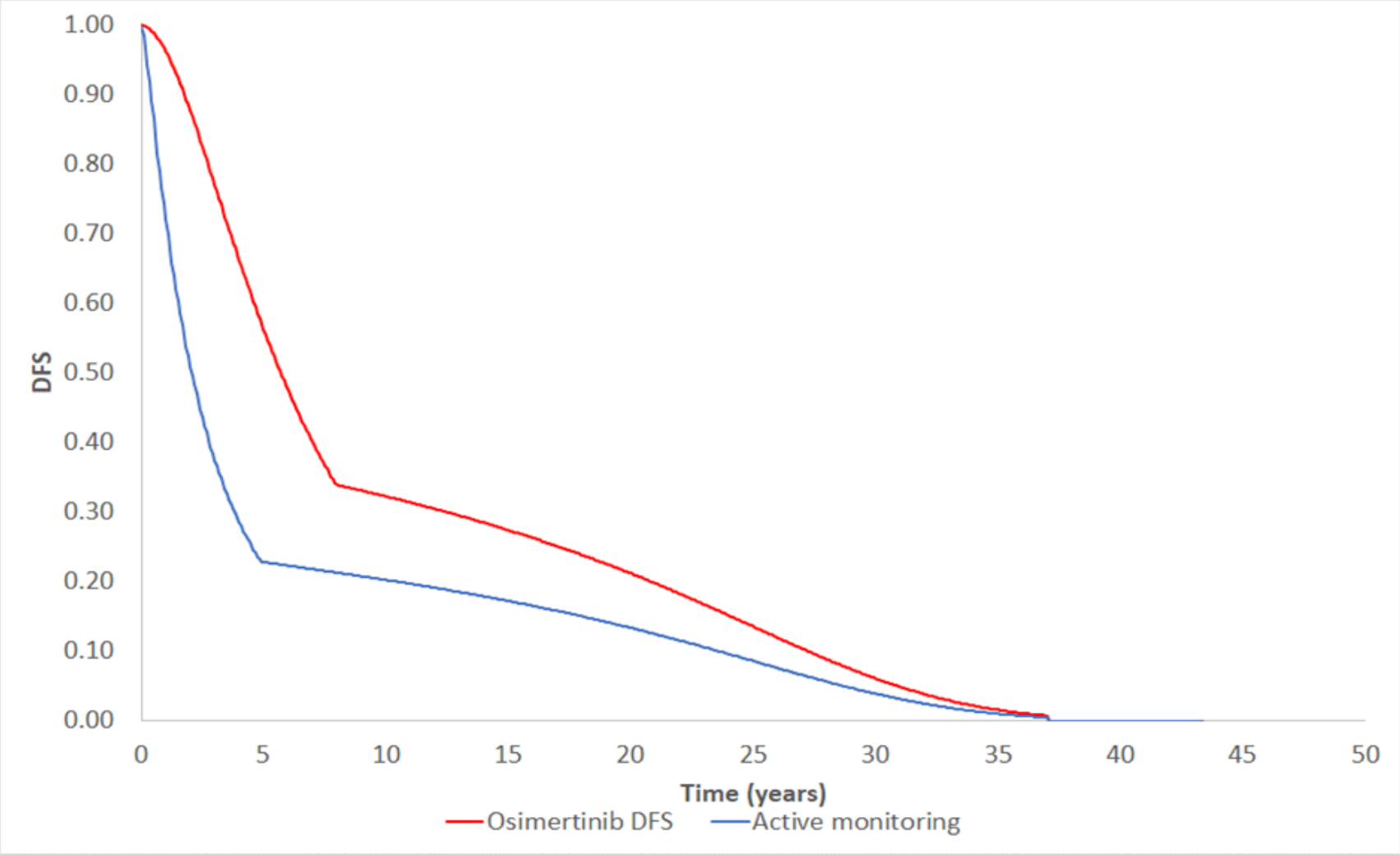
ERG critique

- Company parametric survival models reflect the trend in the underlying hazard of relapse over time in the trial
  - the structural cure assumption results in low relapse probabilities beyond the cure timepoint, irrespective of which parametric survival model is selected.
- When the cure assumption is included in ASA4a and ASA4b, the DFS curves don't cross – see figures in next slides
- Reasonable to consider relaxing the requirement for using the same model in both groups because the intervention group has an active treatment, while the comparator group does not

From original ERG report

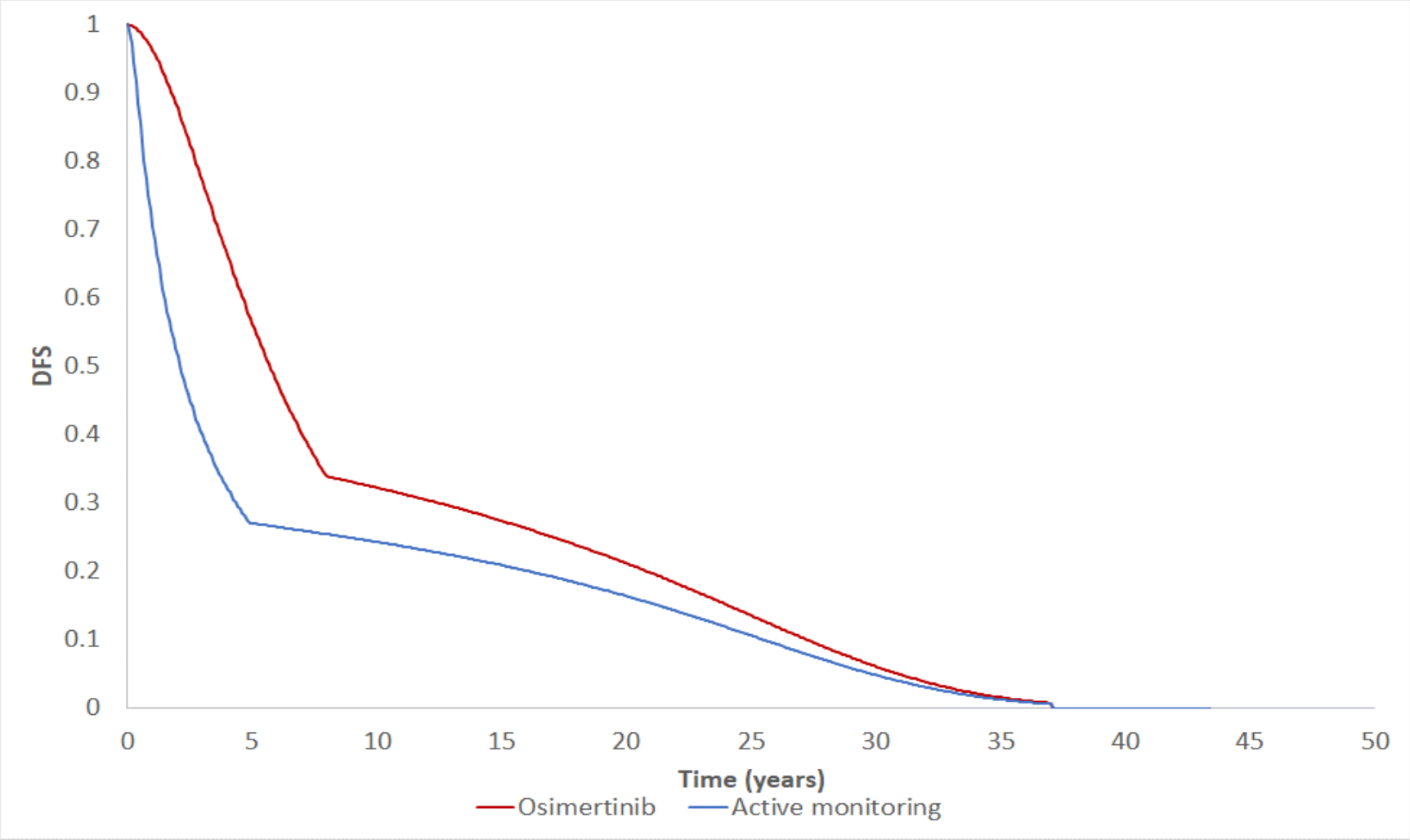
- Generalised gamma used in company base case had lowest AIC/BIC for placebo arm but log-normal had best statistical fit to osimertinib arm
- Because of the cure assumption, it is appropriate to give more weight to the statistical fit
  - extrapolations beyond the 5-year timepoint have a limited impact on the model predictions, as the cure assumption largely overrides the probabilities predicted by models

Issue 3: DFS plot for ERG ASA4a (pessimistic)



ASA4a uses a log-normal distribution for transition probability 2 in both groups.
This graph reflects the 8-year cure timepoint for osimertinib and the 5-year cure timepoint for the active monitoring group.

Issue 3: DFS plot for ERG ASA4b (pessimistic)



ASA4b uses a log-normal distribution for transition probability 2 in the osimertinib group and keeps the generalised gamma distribution in the active monitoring group.
This graph reflects the 8-year cure timepoint for osimertinib and the 5-year cure timepoint for the active monitoring group.

ACD consultation comments – Issue 4

Cure point at 8 years for the osimertinib group and 5 years for the active monitoring group

Company comments

- A significant proportion of patients achieve a functional “cure” with current standard of care.
- 5-year functional cure in both arms is supported by clinical evidence and expert opinion.
- ERG pessimistic scenario (cure at 8 yrs for osimertinib vs 5 yrs for placebo) is overly pessimistic
  - clinical experts agreed that timing of cure assumption should be consistent across arms
- If the structural cure assumption is removed, osimertinib remains cost-effective.

ERG critique

- Would prefer formal statistical modelling of cure (e.g. using a mixture-cure model) ➔ accepts that the limited OS data from ADAURA may preclude such an analysis.
- Clinical advisers suggested that osimertinib may delay disease relapse rather than prevent it.
- Does not consider the analysis of removing the structural cure assumption to be meaningful ➔ applies parametric survival models which do not allow for the potential of cure, where cure is expected for some patients.

Clinical expert comments

- Patients in both arms should be subjected to the same cure or progression assumptions.
- The emphasis on cure underestimates the significant clinical impact of delaying progression.
- A most conservative scenario that delays progression only in this disease with very high metastatic propensity still would result in substantial clinical efficacy.
- “Cure" assumptions seems arbitrary ➔ varies with a) how hard you look for recurrence and b) time frame.

ACD consultation comments – Issue 5

Uncertainty about later treatments (including retreatment with osimertinib)

Company comments

Without adjuvant osimertinib:

- Clinical experts agreed they would prescribe osimertinib to all newly diagnosed with metastatic disease. Focusing on only newly diagnosed patients → market share between 80% and 100%.
- Company did 2 exploratory analyses that assume 80% and 90% of patients in the active monitoring arm have treatment with osimertinib in DM1. Remainder have other TKIs.

Retreatment:

- Not possible to predict proportion of patients prescribed osimertinib for metastatic NSCLC following successful adjuvant treatment (50% assumed to be a conservative approach).
- Sensitivity analysis explore different % of osimertinib retreatment (40%, 60%)
- 100% that recur while on treatment with adjuv osimertinib, would have pemetrexed and cisplatin.
- For patients that progress in the metastatic setting, a proportion of patients would receive ABCP.
- Re-treatment with other EGFR-TKIs would not be considered ➔ less potent and less efficacious

ERG critique

- ERG pref. analyses assume 100% osi. → analyses with updated prescribing data would be useful
- The ERG's preferred analyses assume no retreatment with osimertinib.
- The proportion of patients who would be retreated with osimertinib is unknown → there are no studies of osimertinib in patients with metastatic disease who previously had adjuv osimertinib.
- Agree that use of ABCP in metastatic setting is low.

Clinical expert comments

- Decision to exclude treatment based on receipt of adjuvant osimertinib seems overly restrictive

ACD consultation comments – Issue 6

Innovation status

Company comments

- Disagrees that all additional benefits associated with osimertinib have been captured in the economic analysis ➔ cost-effectiveness analyses undertaken are high conservative.
- Other benefits include:
  - reduction in the fear of cancer due to improved DFS
  - the transformed patient journey
  - reduced monitoring costs and resources
  - improvements in health-related quality of life from reduced CNS recurrence
  - impact on family members and carers; patient's social life, mental health, ability to work and emotional wellbeing.

ERG critique

- Analysis is in line with the NICE reference case ➔ not appropriate to include indirect costs.
- No evidence presented to quantify the impact on carers.
- Model includes general population utility values for patients in the disease free health state. Already included additional costs associated with the treatment of CNS metastasis.
- Does not believe that any relevant aspects of the value of osimertinib have obviously been omitted.

ACD consultation comments – Issue 7

Appropriateness of the Cancer Drugs Fund

Company comments

- Should be recommended for routine commissioning ➔ cost-effective at the PAS price.
- All clinically plausible scenarios are below the NICE willingness to pay threshold.
- Committee-proposed scenarios (ASA4a/b) were not openly discussed and are considered clinically implausible by clinical experts.
- Further data collection in the Cancer Drugs Fund would not reduce uncertainty in a reasonable time frame ➔ DFS benefit will not change significantly.
- Project Orbis stated "it is unlikely that any remaining information gained from these analyses will change the assessment of effectiveness of osimertinib as adjuvant treatment for early stage EGFRm NSCLC which is based on a robust clinically meaningful and statistically significant improvement in DFS without a detriment in OS".

ERG critique

- Data from ADAURA would reduce uncertainty, particularly around DFS and stopping at 3 years.

Clinical expert comments

- Osimertinib should be recommended based on existing evidence that is sufficiently strong.
- Trial was stopped early because the data is overwhelmingly in favour of osimertinib ➔ recommendation suggests that trials should continue accruing death and recurrence in the non-treatment arm in order to satisfy a higher level of certainty for the purposes of commissioning.
- Although there is uncertainty regarding extent of OS prolongation, it seems unlikely that DFS outcomes will change significantly with further follow up.

Cancer Drugs Fund

Committee decision-making criteria:

ADAURA trial is currently ongoing. Next data cut [redacted] with study completion expected [redacted]

Proceed down if answer to each question is yes

Starting point: drug not recommended for routine use due to **clinical uncertainty**

1. Is the model structurally robust for decision making? (omitting the clinical uncertainty)

2. Does the drug have plausible potential to be cost-effective at the offered price, taking into account end of life criteria?

3. Could further data collection reduce uncertainty?

4. Will ongoing studies provide useful data?

and

5. Is CDF data collection via SACT relevant and feasible?

Consider recommending entry into CDF (invite company to submit CDF proposal)

Define the nature and level of clinical uncertainty. Indicate the research question, analyses required, and number of patients in NHS in England needed to collect data.

Key issues after consultation

Issue at ACM2	Questions for committee
Issue 1: DFS benefit translating to OS benefit	Is a statistically significant disease free survival (DFS) benefit likely to translate into a significant overall survival (OS) benefit?
Issue 2: Osimertinib vs. previous EFGR TKIs	Does osimertinib's mode of action and clinical benefit differ from previous first and second generation EFGR tyrosine kinase inhibitors (TKIs)?
Issue 3: Modelling distributions	Are the modelling assumptions for the transition from the disease free to distant metastatic NSCLC health states using a log-normal distribution plausible?
Issue 4: Cure point	What should be the timing of the cure assumption under current practice (active monitoring) and adjuvant osimertinib? Is the cure point at 8 years for the osimertinib group and 5 years for the active monitoring group reasonable?
Issue 5: Later treatments	Are the later treatments with or without adjuvant osimertinib (including retreatment with osimertinib) included in the economic analysis plausible?
Issue 6: Innovation status	Have all relevant aspects of the value of osimertinib been included in the economic analyses?
Issue 7: Cancer Drugs Fund	Should osimertinib be considered for the CDF?

Analyses that will be considered by the committee

- Different cure assumptions:
  - ERG: optimistic (5yrs both groups), pessimistic (8yrs osimertinib)
  - Company: 8yrs both groups, no cure
- Proportion of osimertinib use for metastatic disease in comparator
  - Company and ERG base case, 100%
  - ERG ASA3 – [redacted] based on prescribing data
  - Company scenarios, 80% and 90%
- Osimertinib retreatment
  - ERG base case = 0%
  - Company base case = 50% and scenarios with 40% and 60%
- Transition from disease free to distant metastases health states
  - Scenarios using a log-normal distribution in: i) both arms of the model, ii) treatment arm of the model only

Cost-effectiveness results

All cost-effectiveness results are reported in private PART 2 slides because they include confidential PAS discounts for other treatments