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NICE National Institute for Health and Care Excellence

Neratinib for treating early hormone receptor-positive, HER2-positive breast cancer after adjuvant trastuzumab [ID981]

1st Appraisal Committee meeting

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Company: Pierre Fabre

ACM1: 16th July 2019

Background: Early hormone receptor-positive, HER2-positive breast cancer

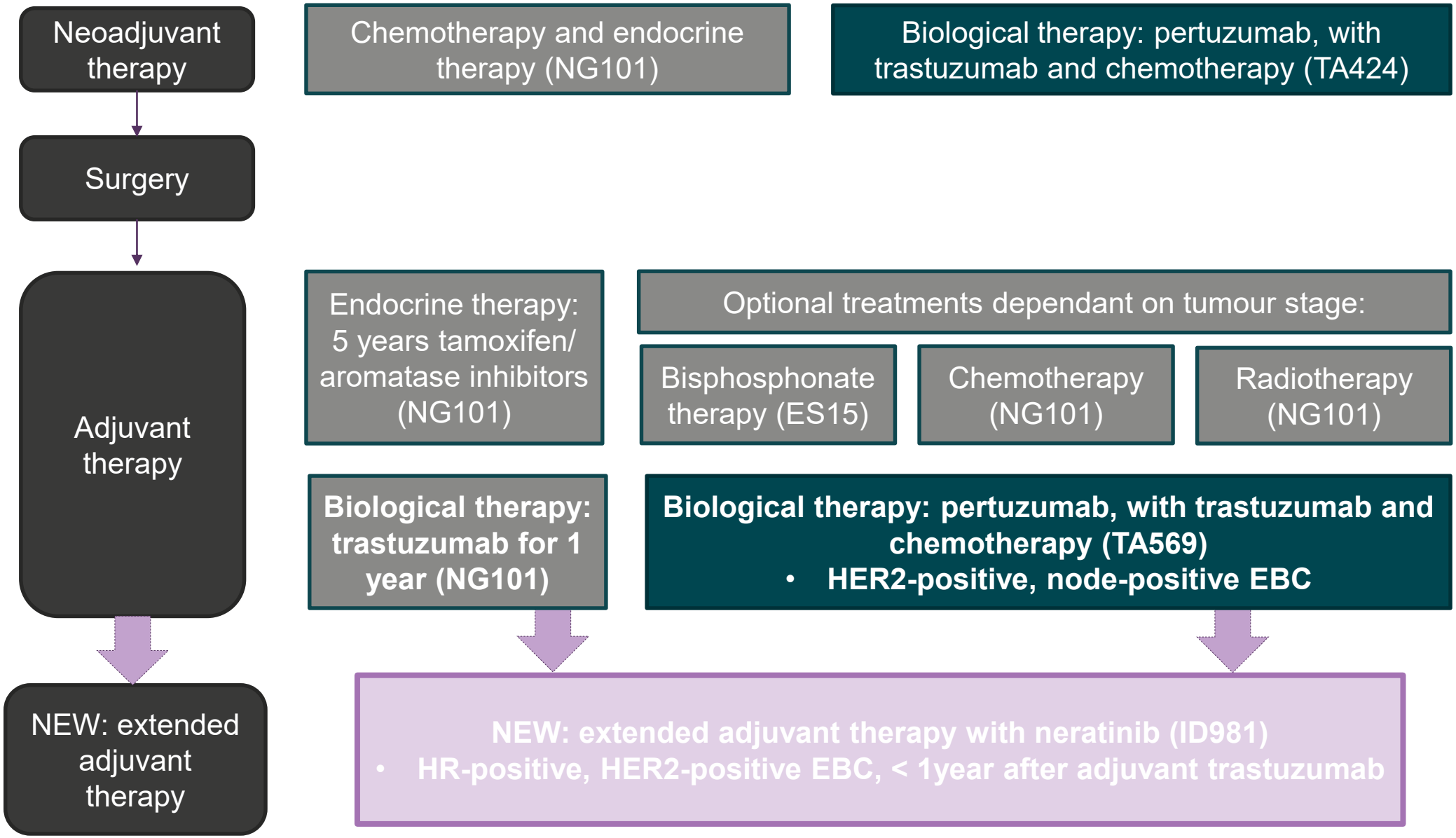
- Breast cancer is the most common cancer in the UK among women.
- Is described as ‘early’ if it is restricted to the breast, or the breast and nearby lymph nodes, and has not spread to other parts of the body
- Hormone receptor-positive (HR-positive) breast cancer cells co-express oestrogen or/and progesterone (it is rare to express only progesterone).
- Human epidermal growth factor receptor 2 (HER2) is a receptor for a growth factor which occurs naturally in the body. Breast cancer cells with higher than normal level of HER2 receptors are HER2-positive.
- In 2016 in England, around 45,960 people were diagnosed with breast cancer. It is estimated that approximately 15-25% of women with breast cancer will have HER2-positive tumours. Approximately two thirds have hormone receptor-positive breast cancer.

Neratinib (Nerlynx, Pierre Fabre)

- Tyrosine kinase inhibitor that blocks signal transduction through epidermal growth factor receptors (ErbB1/HER1, ErbB2/HER2 & ErbB4).

Marketing authorisation (August 2018)	Neratinib is indicated for the extended adjuvant treatment of adults with early-stage HR+, HER2-overexpressed/amplified breast cancer and who are less than 1 year from the completion of prior adjuvant trastuzumab-based therapy.
Administration	Neratinib is administered orally. The recommended dose is 240 mg neratinib, administered as 6 × 40 mg tablets taken once daily and continually for 1 year.

Treatment Pathway: HR+ HER2+ EBC



Patient Issues

Breast Cancer Now and Breast Cancer Care and UK Breast Cancer Group

- Initial diagnosis of breast cancer can be devastating
- Fear of recurrence, metastasis and incurable disease
- Around a quarter of women with HER2 positive experience recurrence
- Neratinib provides improvements in iDFS and a recurrence
- Oral treatment that can be taken at home
- Neratinib involves extended treatment time, monitoring & associated hospital appointments, plus the likelihood of experiencing side effects
- Patients differ in their attitudes to/ experience of risk, side effects, drawbacks & benefits.

Key issues

- Given the addition of pertuzumab in the treatment pathway, which patients would receive neratinib in clinical practice?
- Is the ERG's or the company's approach to iDFS modelling more appropriate?
- Is the general population mortality assumption in the model appropriate for decision making?
- Is the ERG's or the company's approach to duration and type of treatment effect more appropriate?
- Taking into account the additional areas of uncertainty, how confident is the committee in the resulting ICERs?

[redacted]

Clinical evidence: ExteNET and CONTROL

Study	ExteNET	CONTROL
Study design	Phase 3 multicentre, randomised, double-blind, placebo-controlled trial, stratified by HR, nodal status, and trastuzumab regimen.	Phase 2 open-label safety and tolerability study.
Population	Patients with HER2+ breast cancer who completed 1 year of trastuzumab within 2 years. • **Label population:** HR+ completing prior trastuzumab ≤ 1 year from randomisation (reflects MA)	Patients with HER2+ breast cancer who completed trastuzumab adjuvant therapy, or experienced side effects resulting in early discontinuation, with last trastuzumab > 2 weeks and < 2 years before enrolment.
Intervention and comparator	**Intervention:** • Neratinib (ITT: n = 1,420) • **Label population: (n = 670)** **Comparator:** • Placebo (ITT: n = 1,420; • **Label population: (n = 664)**	Neratinib cohorts: **loperamide prophylaxis (n = 137);** loperamide + budesonide (n = 64); loperamide + colestipol (n = 120); colestipol + loperamide as needed (recruiting); cycle 1 dose escalation + loperamide as needed (recruiting); cycle 2 dose escalation+ loperamide as needed (recruiting).
Model use	Clinical effectiveness from the label population (n = 1,334).	Rates of adverse events from the neratinib + loperamide prophylaxis cohort (n = 137).

Baseline characteristics

Characteristic n (%)	ExteNET label population		CONTROL
	Neratinib (n = 670)	Placebo (n = 664)	Loperamide cohort (n=137)
Age, years (median [range])	51 (25-83)	51 (23-78)	53 (30-86)
Prior (neo)adjuvant therapy			
Trastuzumab	670 (100.0)	664 (100.0)	136 (99.3)
Taxanes	167 (24.9)	159 (23.9)	131 (95.6)
Anthracycline	67 (10.0)	58 (8.7)	36 (26.3)
Pertuzumab	0 (0)	0 (0)	55 (40.1)
Tumour stage at diagnosis, %			
T1	191 (28.5)	218 (32.5)	209 (31.5)
T2	366 (54.7)	270 (40.3)	250 (37.7)
≥ T3	103 (15.4)	61 (9.1)	65 (9.8)
Unknown	-	121 (18.1)	140 (21.1)
Nodal status			
Negative nodal status	130 (19.4)	125 (18.8)	NR
1-3 positive nodes	339 (50.6)	334 (50.3)	NR
≥ 4 positive nodes	201 (30.0)	205 (30.9)	NR

ExteNET label population: results

- Estimated 5-year event free rates:

	Neratinib (n=670)	Placebo (n=664)	Effect estimate
Invasive disease-free survival (iDFS)	90.8%	85.7%	HR 0.58 (95% CI 0.41 to 0.82)
Disease-free survival including ductal carcinoma in situ (DFS-DCIS)	90.6%	84.8%	HR 0.55 (95% CI 0.39 to 0.77)
Time to distant recurrence (TTDR)	92.6%	88.2%	HR 0.58 (95% CI 0.39 to 0.85)
Distant disease-free survival (DDFS)	92.4%	87.7%	HR 0.57 (95% CI 0.39 to 0.83)

- **OS:** 121 deaths reported across both treatment groups combined
  - final ITT analysis: estimated to be in [redacted] when 248 events have been reported, and final label population analysis in [redacted] as more events will be needed and these are likely to happen later.

[redacted]

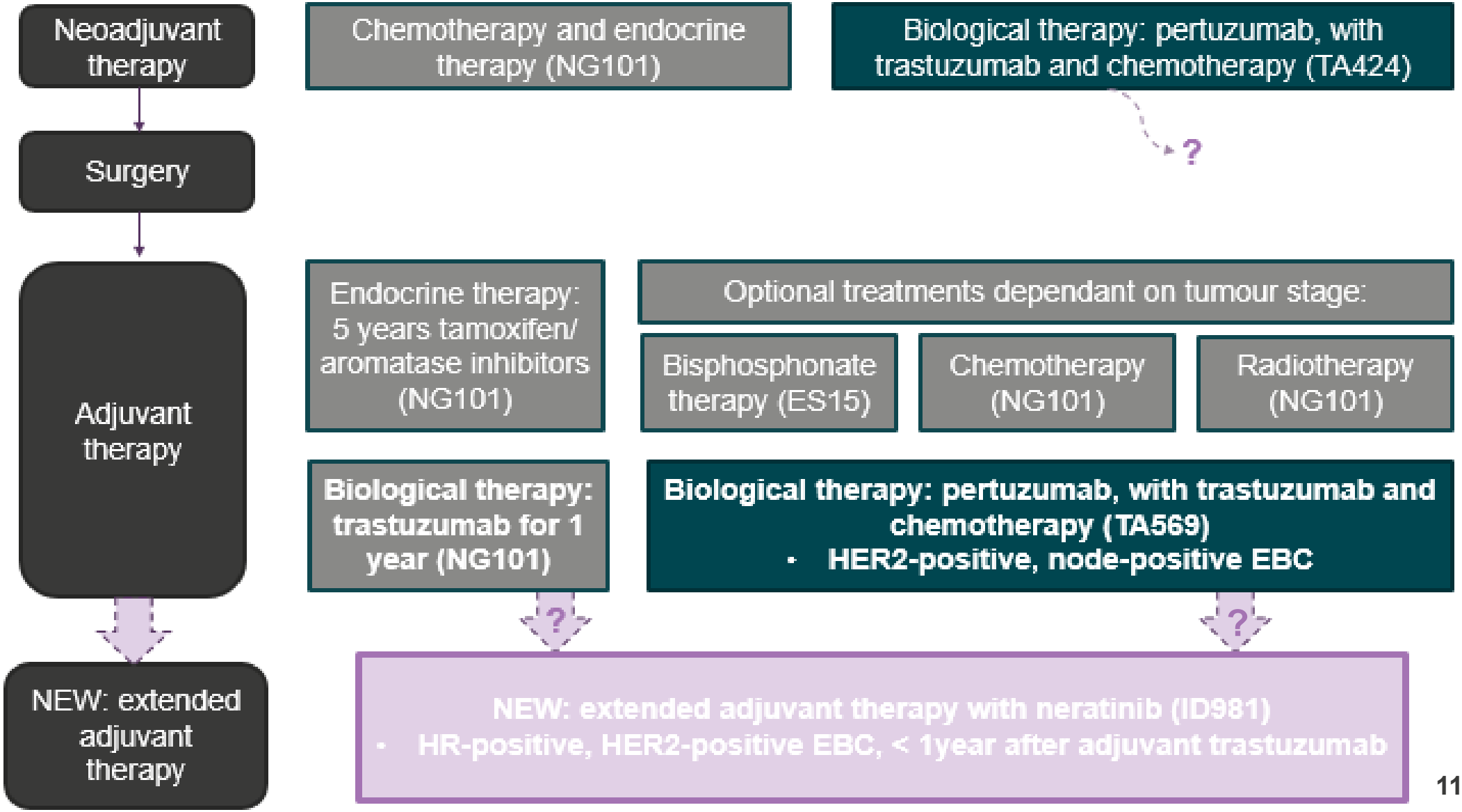
Adverse events (AEs): in ≥ 10% label safety population of ExteNET

Adverse event n (%)	ExteNET				CONTROL	
	Neratinib (n=662)		Placebo (n=657)		Loperamide (n=137)	
	Grade 1-2	Grade 3	Grade 1-2	Grade 3	Grade 1-2	Grade 3
Diarrhoea	365 (55.1)	261 (39.4)	213 (32.4)	7 (1.1)	[redacted]	[redacted]
Nausea	280 (42.3)	9 (1.4)	135 (20.5)	2 (0.3)	[redacted]	[redacted]
Fatigue	177 (26.7)	13 (2.0)	129 (19.6)	2 (0.3)	[redacted]	[redacted]
Vomiting	150 (22.7)	24 (3.6)	41 (6.2)	2 (0.3)	[redacted]	[redacted]
Abdominal pain	145 (21.9)	11 (1.7)	58 (8.8)	1 (0.2)	[redacted]	[redacted]
Headache	119 (18.0)	6 (0.9)	125 (19.0)	1 (0.2)	[redacted]	[redacted]
Upper abdominal pain	90 (13.6)	6 (0.9)	35 (5.3)	3 (0.5)	[redacted]	[redacted]
Rash	90 (13.6)	3 (0.5)	40 (6.1)	0	[redacted]	[redacted]
Decreased appetite	79 (11.9)	1 (0.2)	13 (2.0)	0	[redacted]	[redacted]
Muscle spasms	81 (12.2)	0	21 (3.2)	1 (0.2)	[redacted]	[redacted]

[redacted]

Key issue 1: Treatment pathway has changed

- **HR-positive, HER2-positive early breast cancer**



Issue 1: Treatment pathway has changed

Background

- TA424: neoadjuvant pertuzumab. March 2019 TA569: adjuvant pertuzumab for HER2-positive, lymph node-positive EBC.
- ExteNET: HER1/HER2 therapy other than trastuzumab not permitted.
- No applicable clinical data on which to base recommendation for neratinib after pertuzumab.

Breast Cancer Care & Breast Cancer Now

- Pertuzumab recommended for node-positive disease only
- Decision on treatment based on relative risks and benefits in relation to patient's individual circumstances & preferences

Company

- Mechanisms of action are different, neratinib would show benefit regardless of prior pertuzumab.
- Naive comparison indicates a higher iDFS rate for neratinib vs. pertuzumab.
- Oral treatment may be preferable, but other factors would also be taken into account.

Clinical expert

- Following prior pertuzumab, neratinib could be potentially considered in a limited patient group with high risk disease.
- If neratinib was recommended, clinicians could choose not to use adjuvant therapy with pertuzumab in people with node-positive disease.

Technical team: For lymph node-positive disease, decision on the best treatment option, would be based on patient's individual circumstances and preferences, however there is no evidence comparing extended adjuvant therapy with neratinib with pertuzumab-based adjuvant therapy.

[redacted]

⊙ *Given the addition of pertuzumab in the treatment pathway, which patients would receive neratinib in clinical practice?*

Model

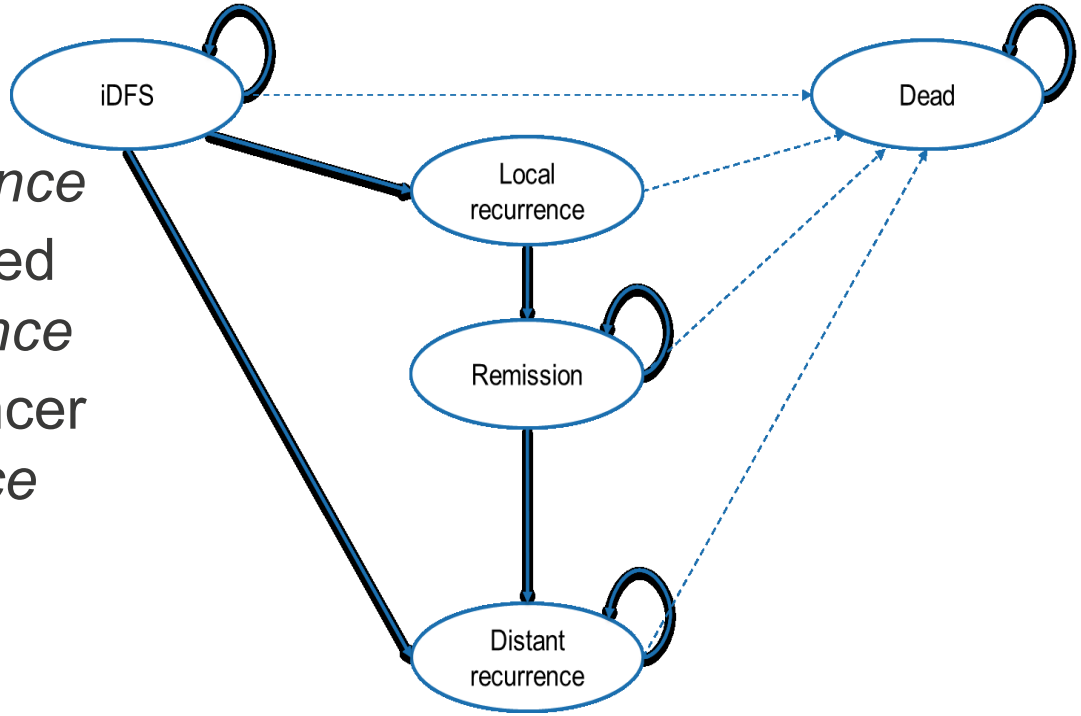
- Markov model with 5 states
- Life time horizon (55 years) with mean age of 51.2 years at baseline

Inputs:

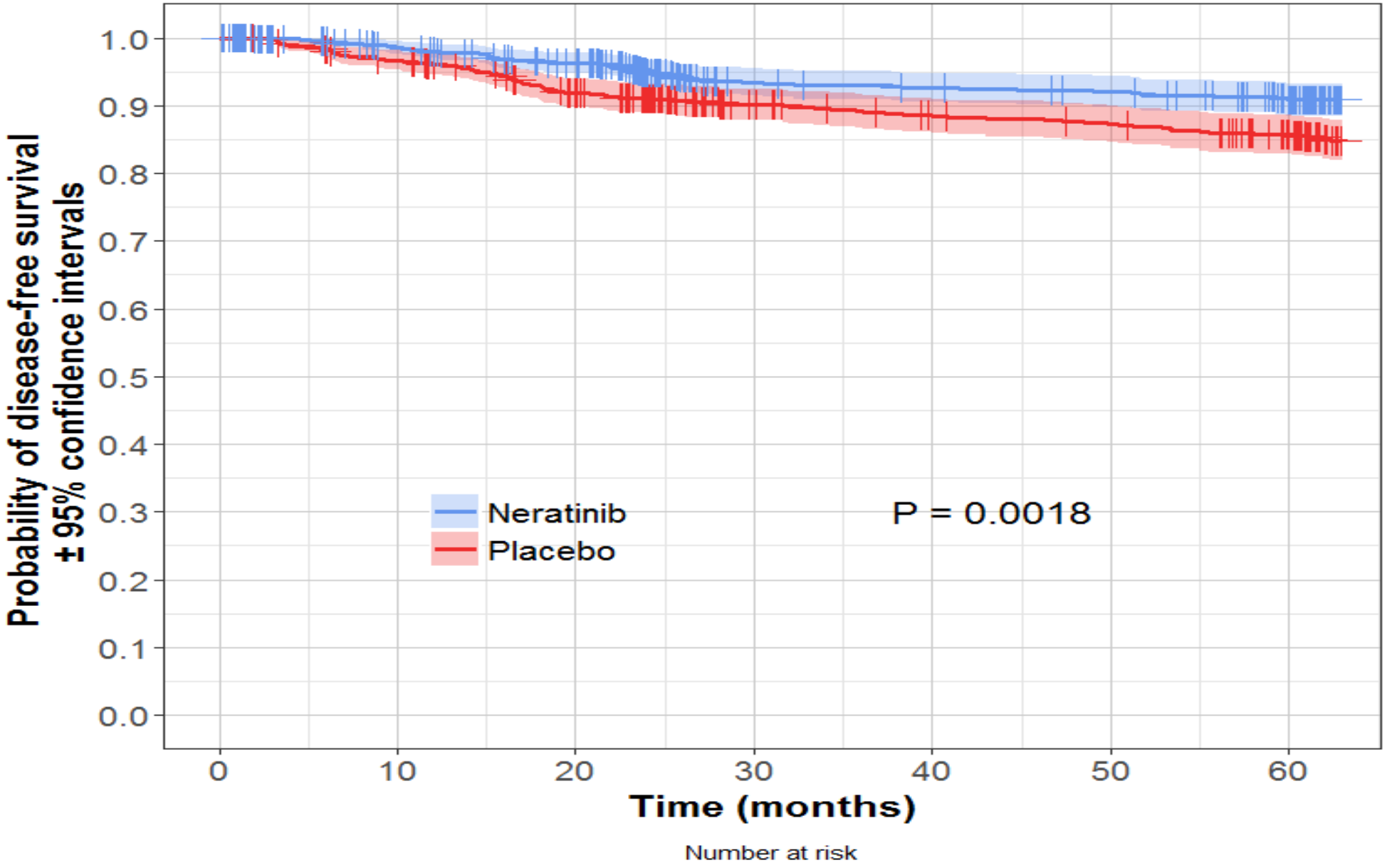
- iDFS, post-distant recurrence mortality, AEs, iDFS utility, treatment duration and dose from ExteNET
- diarrhoea AEs with prophylaxis from CONTROL
- transition probabilities: *remission* to *distant recurrence* from TA569, transition to *local* and *distance recurrence* from ExteNET

Assumptions:

- patients stay 1 year in *local recurrence*
- general population mortality assumed for all states except *distant recurrence*
- all patients who die from breast cancer first move through *distant recurrence*



Issue 3: iDFS modelling - KM data



Number at risk

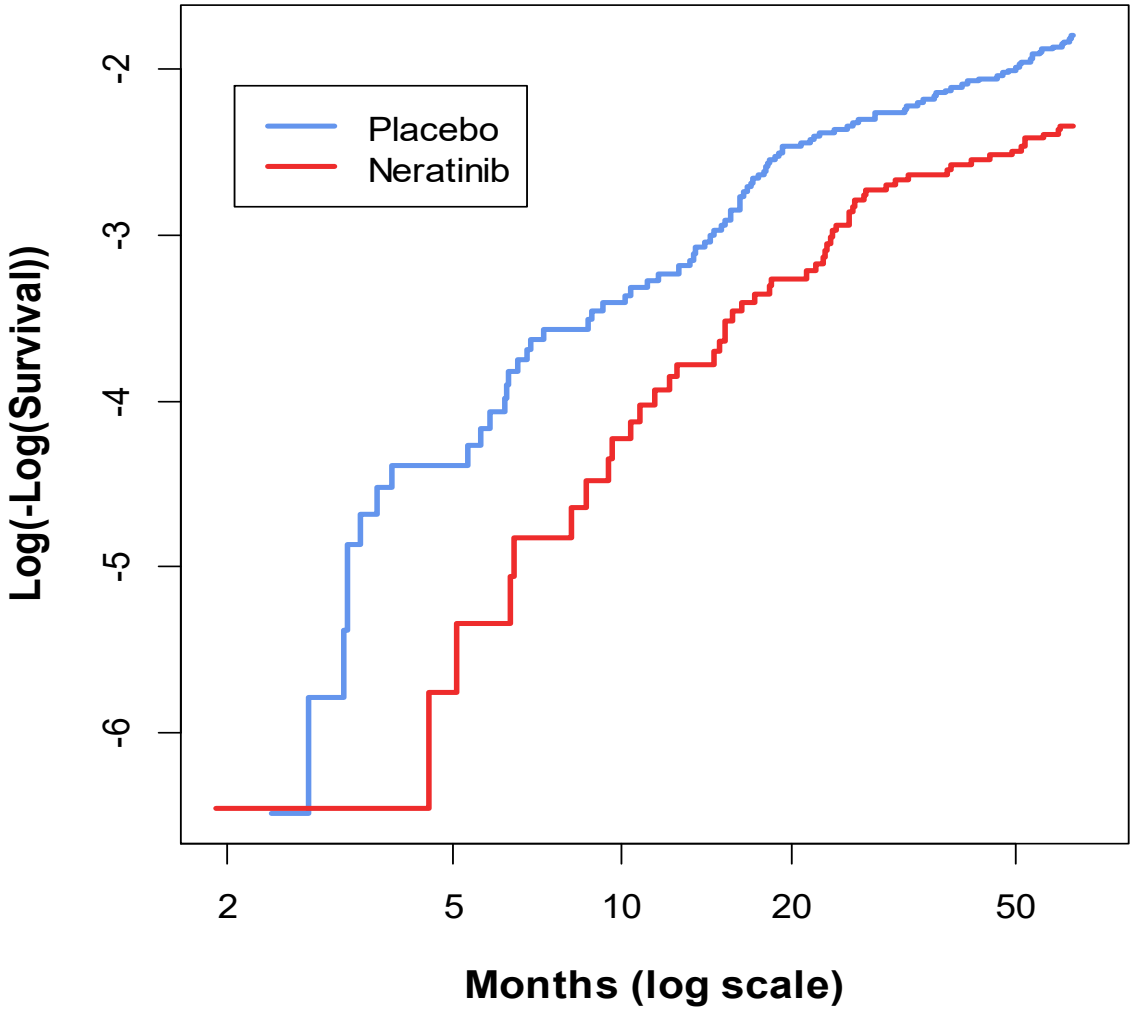
Placebo	664	621	567	481	464	456	433
Neratinib	670	606	570	469	462	456	428

Issue 3: iDFS proportional hazards

Company concluded that proportional hazards assumption was met.

- **Therneau-Grambsch test** for non-proportional hazards: non-significant (p=0.575)

- **Log-(log) survival plot**: lines parallel



Log-(log) survival plot

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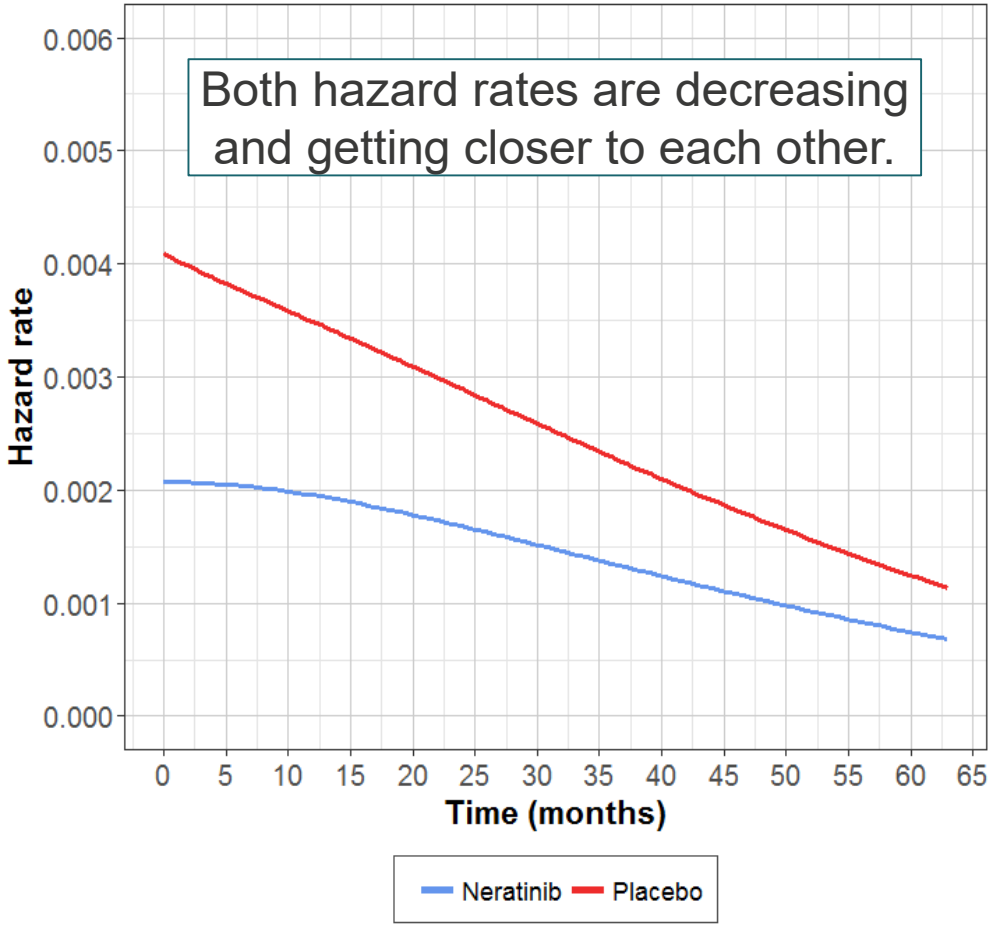
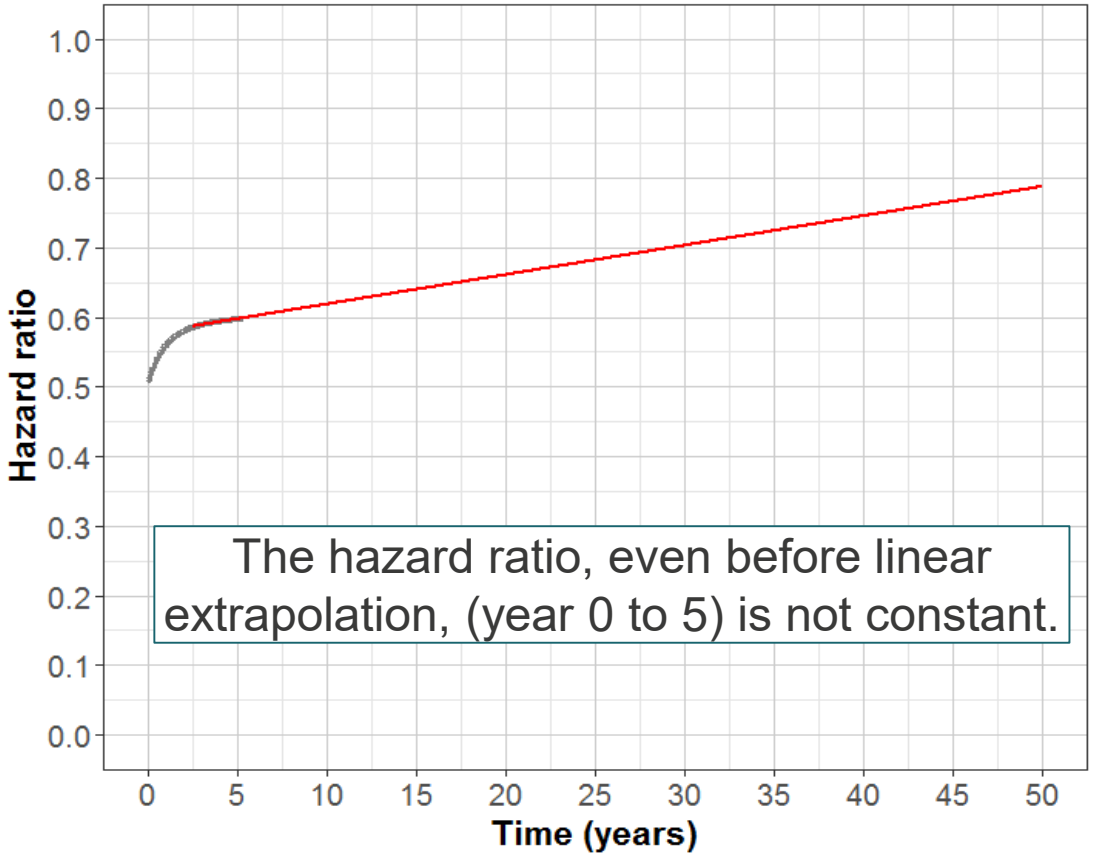
Issue 3: iDFS proportional hazards cont.

ERG questioned proportional hazards assumption.

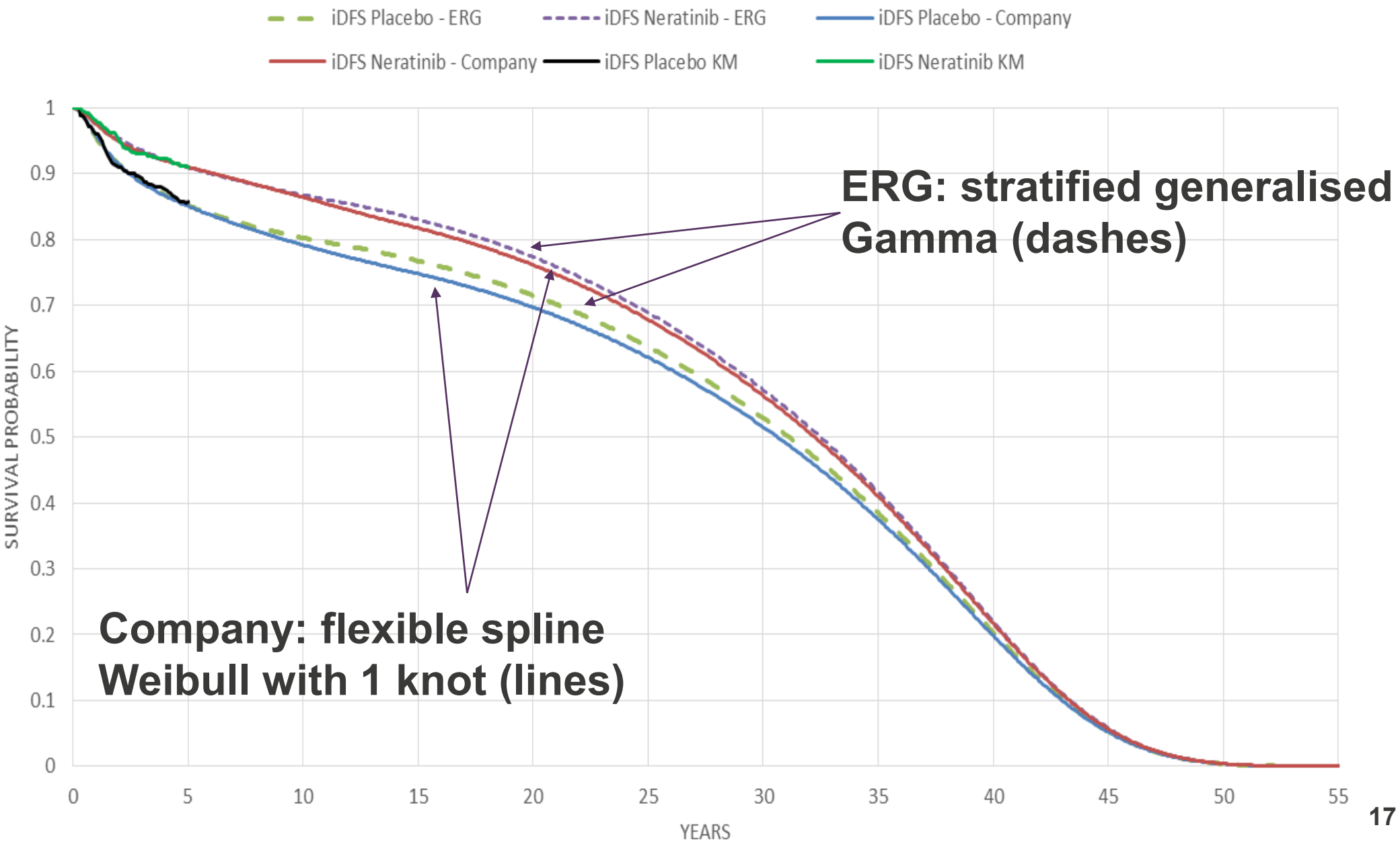




[redacted] Smoothed hazard rates

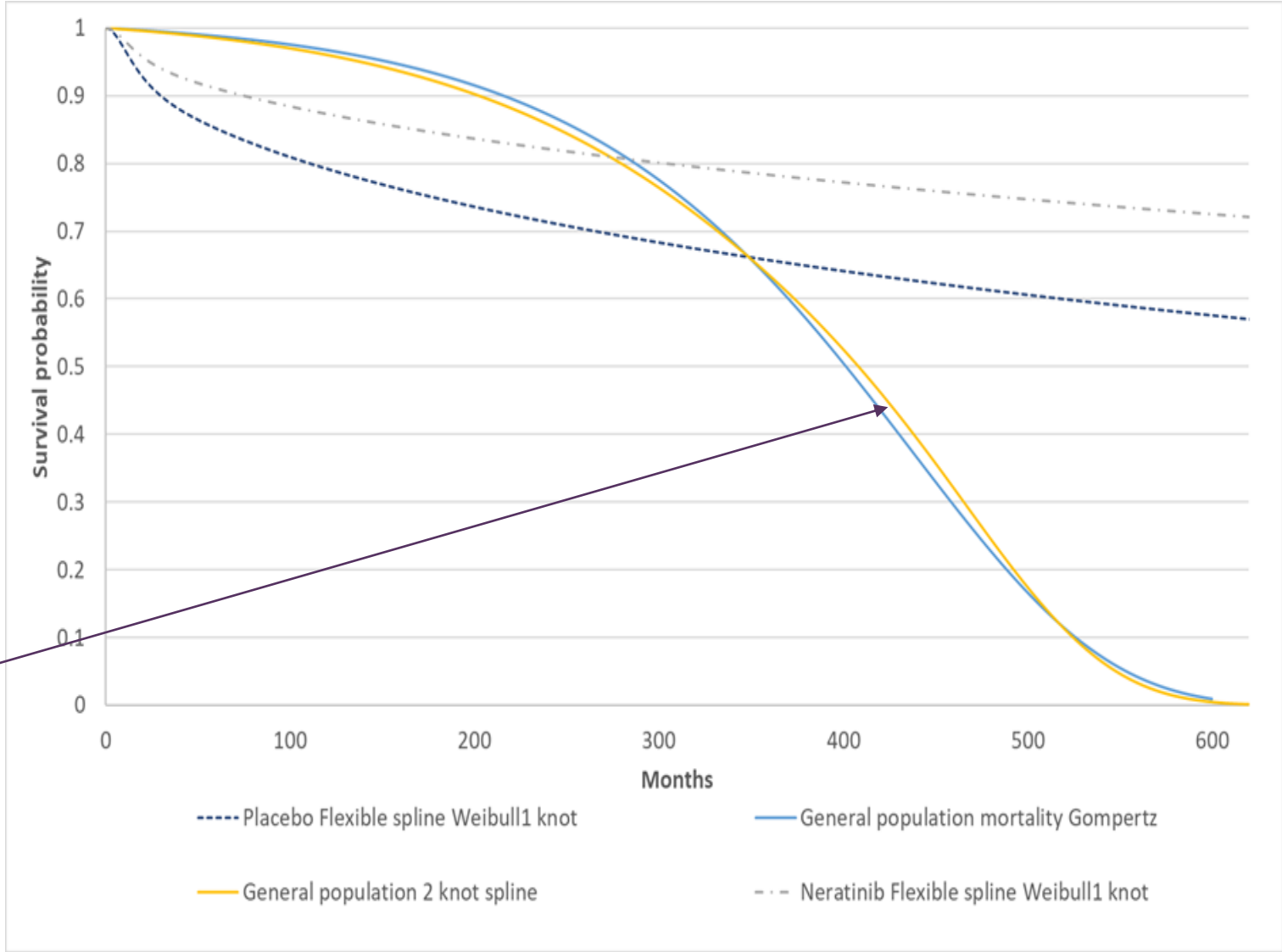
Hazard ratio

Issue 3: iDFS modelling



Issue 3: general population mortality modelling

- General population survival data needed due to immaturity of data, causing implausible extrapolations of long-term survival curves
- **Company**: flexible-spline Weibull with two knots (yellow) chosen to model general population mortality.
- **ERG:** flexible-spline Weibull with two knots (yellow) is appropriate; is applied in its preferred base-case [redacted]



Issue 3: iDFS modelling summary

Background

Company: assumed PH and used flexible spline Weibull with 1 knot

ERG: Did not assume PH and used stratified generalised Gamma

Model: death due to breast cancer is only possible from distant recurrence health state and mortality risk for all other health states (iDFS, local recurrence & remission) is based on general population mortality.

Company:

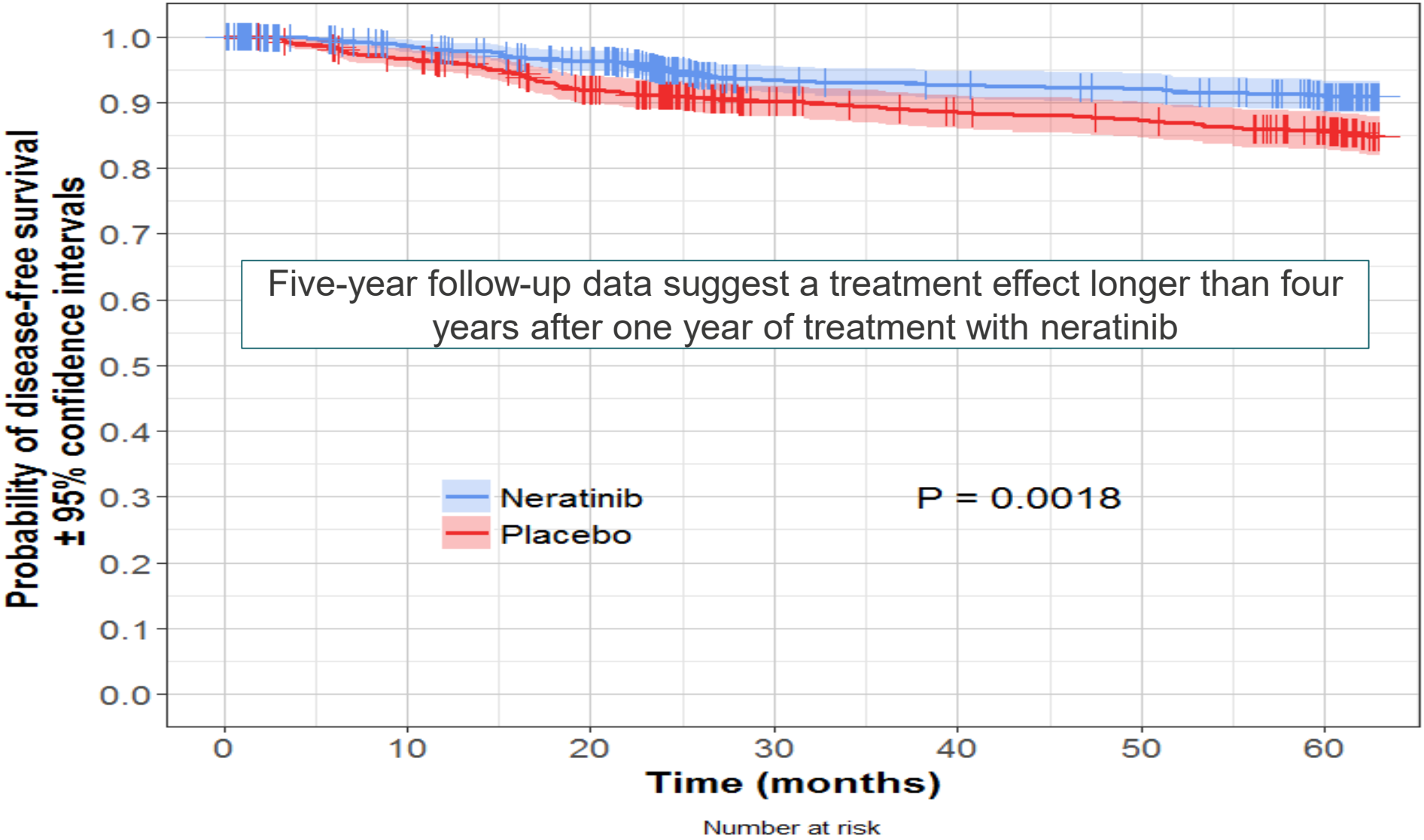
- no clear evidence of PH assumption violation
- considers ERG's curve to be a conservative approach representing the high end of the most plausible ICERs.
- assumption around general population mortality in the model is appropriate:
  - ExteNET: all death from breast cancer after distant recurrence.
  - ExteNET: non-cancer mortality was lower–not higher–than the UK general population
  - same approach was used in TA569

Technical team:

- Stratified models more appropriate and ERG's approach is suitable for decision making
- Was persuaded that the use of general population mortality in model is appropriate
- However, notes that the OS estimates based on iDFS modelling are uncertain.

⊙ *Is the ERG's or the company's approach to iDFS modelling more appropriate?*
⊙ *Is the general population mortality assumption in the model appropriate for decision making?*

Issue 4: Duration and type of treatment effect – iDFS KM data label population

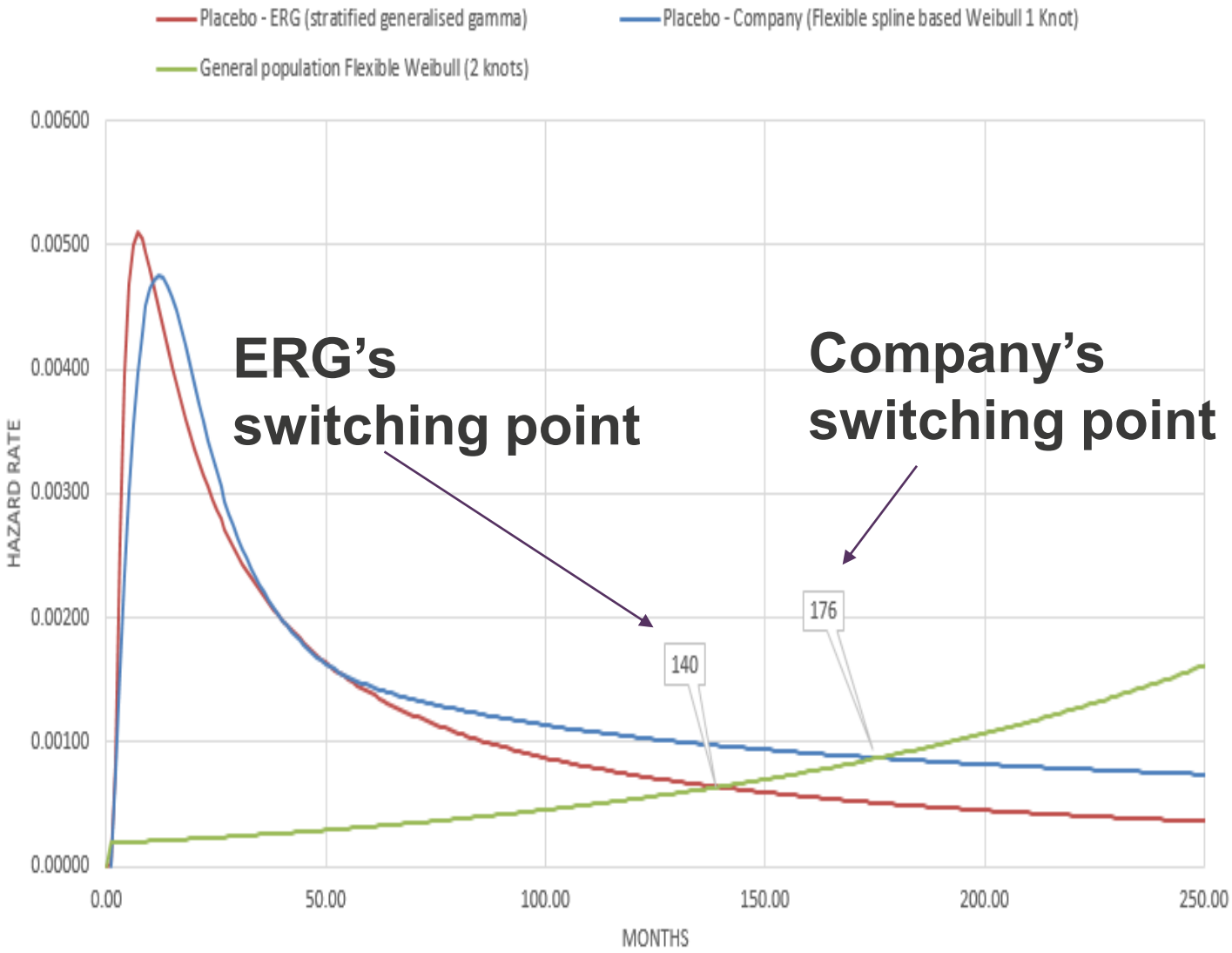


Issue 4: Duration and type of treatment effect – general population mortality

Background
"Switching point" determines the maximum duration of treatment effect and depends on extrapolation of iDFS and general population mortality.

Company: Assumed continued treatment effect until month 129 (neratinib crosses general population), followed with taper period until month 176 (where placebo and general population mortality hazards are the same).

ERG: Taper period starts at the end of ExteNET 5-year follow-up (month 62.98) until month 140.



Placebo iDFS and general population mortality hazard rates

Issue 4: Duration and type of treatment effect continued

Company

- Accepts ERG's assumption of a tapering of treatment effect for neratinib of 6.4 years, starting after the ExteNET trial, but consider this to be a conservative assumption:
- HER2-positive and ER-positive tumours tend to experience recurrence later than ER-negative tumours: longer treatment effect would be expected for neratinib vs pertuzumab
- Neratinib and pertuzumab have different modes of action; thus, their treatment effect patterns would not necessarily be the same
- Neratinib's blocks multiple ErbB receptors and inhibits bidirectional crosstalk between HER2 and ERs that contributes to drug resistance to both HER2-directed agents and endocrine therapy, something that has not been shown with trastuzumab-based regimens and is likely to increase the treatment effect of neratinib.

Clinical expert:

- ERG's approach to treatment effect tapering is plausible.

Technical team: The ERG's assumption of a tapering of treatment effect for neratinib of 6.4 years, starting after the ExteNET trial is appropriate for decision making.

⊙ *Is ERG's or company's approach to duration & type of treatment effect more appropriate?*

[redacted]

Cost-effectiveness results - including PAS

Alteration	Notes	PAS ICER
Company post TE base-case	**What is new: age-adjusted utilities**	[redacted]
1. Lidgren et al. 2007 utility for distant recurrence state instead of Lloyd et al. 2006	Issue 6 – Utilities used in the model	[redacted]
2. Stratified generalised gamma to model iDFS instead of flexible-spline Weibull with 1 knot	Issue 3 – Invasive disease-free survival modelling	[redacted]
3. Declining treatment effect at 140 months (11.67 years) instead of 166.8 months (13.9 years).	Issue 4 – Duration and type of treatment effect	[redacted]
Cumulative assumptions 1-3: ERG's post TE base case	**What is new: ExteNET dose ([redacted])**	[redacted]

[redacted]

Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Updated base case?
2	iDFS definition used in ExteNET did not include second primary invasive cancer (non-breast cancer) and ductal carcinoma in situ.	The definition was standard at the time and is suitable for OS extrapolation.	In absence of OS data, iDFS is suitable for decision making. However, as surrogate outcome is used, the estimated OS is uncertain.	Company **NA** ERG **NA**
5	Company: mean neratinib's treatment duration of [redacted] months & dose of [redacted] from ExteNET. ERG: Dose should be higher if diarrhoea prophylaxis was used: [redacted] is its preferred dose. TEAE leading to neratinib discontinuation similar in CONTROL and ExteNET: treatment duration based on ExteNET.	To avoid additional uncertainty, ERG removed the assumption of increased dose intensity from ERG's post TE base-case	Neratinib dose and duration based on ExteNET are appropriate for decision making. However, there is uncertainty around the impact of anti-diarrhoeal prophylaxis on neratinib dose and treatment duration.	Company ✓ ERG ✓

[redacted]

Issues resolved after technical engagement continued

	Summary	Stakeholder responses	Technical team consideration	Updated base case?
6	Company base-case: utilities not age-adjusted. *Disease-free state* (0.837) based on ExteNET (also used for *remission*). Lloyd et al. 2006 used for *distant recurrence;* Lindgren at al. 2007 for *local recurrence.* ERG: added age-adjustment and considered Lindgren at al. 2007 more suitable for *local recurrence*.	Company adopted age-adjusted utilities in post TE base-case and considers Lindgren at al. 2007 to be suitable for *local recurrence*.	Age-adjusted utilities, ExteNET value for disease-free state, and Lindgren et al. 2007 for *distant recurrence are* suitable for decision making. However, concerns about value for *disease-free state* due to a large number of missing data remain; it was estimated with large numbers of missing data.	Company ✓ ERG ✓

Additional areas of uncertainty

Issue	Why issue is important	Impact on ICER
ExteNET and label population	Submission is based on label population (n=1,334) , a subgroup of ExteNET trial (n=2,840). Subgroups results should be interpreted with caution. ExteNET was not designed to have statistical power to detect differences between treatments within subgroups.	Unknown.
ExteNET generalisibility	Only 80 patients at 13 sites in the UK were recruited overall, and only 41 (19 in the neratinib arm and 22 in the placebo arm) of these were in the label population (n=1,334). In addition, differences in iDFS by geographical region were reported.	Unknown.
ExteNET and immature overall survival (OS)	OS data for the intention to treat (ITT) and the label population by treatment arm are not available.	Unknown.

Additional areas of uncertainty continued

Issue	Why issue is important	Impact on ICER
Adverse events (AEs): diarrhoea AEs with prophylaxis	Diarrhoea AEs with prophylaxis were taken from CONTROL trial. This population does not match the ExteNET label population in terms of length of time from trastuzumab or hormone receptor status.	Unknown.
Subsequent treatments following recurrence	In the company base-case, the cost of distant recurrence was assumed to be £175,390. This value was taken from TA569 appraisal. Treatments and treatment shares identified through expert elicitation differed somewhat from those obtained from TA569. However, the values from expert elicitation were not explored in scenario analyses.	When cost was increased to £200,000, the ERG's preferred ICER was reduced by [redacted] per QALY gained. When cost was decreased to £150,000, the ICER was increased by [redacted] per QALY gained.

[redacted]

Additional areas of uncertainty continued

Issue	Why issue is important	Impact on ICER
Transition probability from remission to distant recurrence	The probability of transition from the remission health state to the distant recurrence health state was fixed and equal to 0.757% as in TA569.	Halving the transition probability, increased the ERG's preferred ICER by [redacted] per QALY gained. When the transition probability was doubled the ICER decreased by [redacted] per QALY gained.

[redacted]

Key issues

- Given the addition of pertuzumab in the treatment pathway, which patients would receive neratinib in clinical practice?
- Is the ERG's or the company's approach to iDFS modelling more appropriate?
- Is the general population mortality assumption in the model appropriate for decision making?
- Is the ERG's or the company's approach to duration and type of treatment effect more appropriate?
- Taking into account the additional areas of uncertainty, how confident is the committee in the resulting ICERs?

[redacted]