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NICE National Institute for Health and Care Excellence

Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer

Lead team presentation

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Background: HER2-positive early breast cancer (EBC)

- 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 elsewhere.
- Human epidermal growth factor receptor 2 (HER2) is a receptor for a growth factor which occurs naturally in the body. In some people the breast cancer cells in their body are HER2-positive.
- In 2016 in England, around 45,960 people were diagnosed with breast cancer. Approximately 15-25% of people have HER2-positive tumours.
- People with detectable invasive tumour after neoadjuvant therapy have residual invasive disease (RID).
- The company estimated that of 3,113 people treated neoadjuvantly in England:
  - 809 (26%) have node-negative disease and 227 (28%) have RID
  - 2,304 (74%) have node-positive disease and 783 (34%) have RID

Early breast cancer (EBC): HER2-positive

Chemotherapy and endocrine therapy (NG101)

Biological therapy:
- Pertuzumab + trastuzumab + chemotherapy (TA424)
- trastuzumab + chemotherapy

Endocrine therapy: 5 years tamoxifen/ aromatase inhibitors (NG101)

Optional treatments dependant on tumour stage:

Bisphosphonate therapy (ES15)

Chemotherapy (NG101)

Radiotherapy (NG101)

Node negative (N-)

Node positive (N+)

Trastuzumab for N- & N+ (NG101)

NEW: Trastuzumab emtansine (ID1516) for N- & N+ with residual invasive disease (RID)

Pertuzumab + trastuzumab + chemotherapy (TA569) for N+ only

Neratinib (ID981) for HR+ & <1 year after adjuvant trastuzumab: only if trastuzumab is the only prior HER2 adjuvant treatment & with RID if neoadjuvant chemotherapy

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Trastuzumab emtansine

Marketing authorisation	Indicated for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have **residual invasive disease**, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy.
Administration	• intravenous infusion at 3.6 mg/kg of body weight every 3 weeks (21 days) • patients should be treated for a total of 14 cycles unless there is disease recurrence or unmanageable toxicity.

- People who have **residual disease** after neoadjuvant therapy are considered at **higher risk** than those who had a pathological complete response (no residual disease at surgery) after neoadjuvant therapy.

Key clinical effectiveness issues

- **Issue 1 - Treatment pathway**

For whom would trastuzumab emtansine be suitable as adjuvant therapy? Would it be mainly those with node-negative disease who are currently not eligible for the HER2 pertuzumab + trastuzumab combination recommended by NICE?

- **Issue 2 - Indirect comparison of trastuzumab emtansine and pertuzumab plus trastuzumab**

How comparable are the populations in the KATHERINE (trastuzumab emtansine) and APHINITY studies (pertuzumab + trastuzumab) for comparing node-positive disease outcomes?

Are the results suitable for decision making?

Could analyses using ITT population from the trials be used to support the committee's decision?

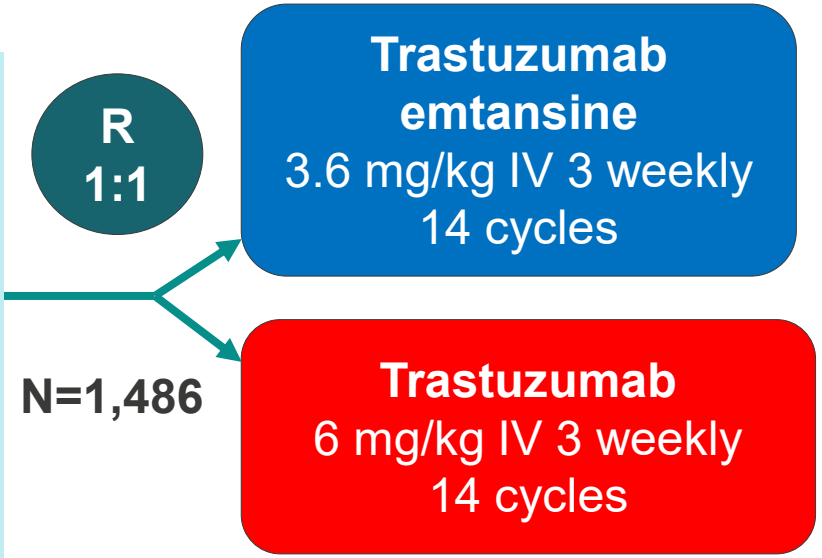
  - Trastuzumab emtansine versus trastuzumab (node-negative population)
  - Trastuzumab emtansine versus pertuzumab + trastuzumab (node-positive population)

Patient and carer perspectives

- Trastuzumab emtansine provides significant improvements in three-year invasive disease-free survival in patients who have residual disease after neoadjuvant chemotherapy, an outcome welcomed by those with breast cancer.
- Trastuzumab emtansine should be available to all eligible patients on the NHS who are fit enough to receive it - when there is residual disease after surgery for HER2 positive breast cancer - and who have previously received neoadjuvant treatment.
- There are several significant side effects with trastuzumab emtansine, which can have very negative impacts on a patient's quality of life and may cause them to discontinue treatment.
- Mandatory monitoring of cardiac toxicity and side-effects is essential to ensure that patients receive the most suitable care.
- Patients who have residual disease following neoadjuvant therapy have a poorer prognosis, and adjuvant trastuzumab emtansine could offer a valuable new treatment option for this group of patients - one which is sorely needed.

KEY trial: KATHERINE: (all post HER2 neoadjuvant therapy *and* residual disease at surgery)

- Centrally confirmed HER2-status
- Received neoadjuvant therapy:
  - Minimum of 6 cycles of chemotherapy
  - Minimum of 9 cycles of trastuzumab
    - Second HER2-targeted agent allowed
- Pathologic residual invasive tumour in breast or axillary lymph nodes (RID)
- ECOG ≤ 1
- Randomisation within 12 weeks of surgery
- **Primary outcome: IDFS = invasive disease free survival**



- If trastuzumab emtansine stopped due to AEs switch to trastuzumab permitted

FOLLOW-UP 10 YEARS

Stratification factors:

- Clinical presentation: inoperable (cT4 or cN2-3) vs operable (cT1-3NO-1)
- Hormone receptor status
- Preoperative therapy: trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: positive vs negative/not done

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KATHERINE: baseline characteristics

		ITT		Node-positive (46%)		Node-negative (54%)	
		T (n=743)	TE (n= 743)	T (n=346)	TE (n= 343)	T (n=397)	TE (n= 400)
HR-positive		540 (72.7%)	534 (71.9%)	244 (70.5%)	241 (70.3%)	296 (74.6%)	293 (73.3%)
Tumour stage T4	At diagnosis	88 (11.8%)	102 (13.7%)	56 (16.2%)	61 (17.8%)	32 (8%)	41 (10.3)
	At surgery	10 (1.3%)	12 (1.6%)	9 (2.6%)	10 (2.9%)	1 (0.3%)	2 (0.5%)
Neo-adjuvant	T	596 (80.2%)	600 (80.8%)	277 (80.1%)	277 (80.8%)	319 (80.4%)	323 (80.8%)
	P+T	139 (18.7%)	133 (17.9%)	67 (19.4%)	64 (18.7%)	72 (18.1%)	69 (17.3%)

Key: P+T , pertuzumab + trastuzumab; T, trastuzumab; TE , trastuzumab emtansine.

- Only approximately 1/5 of patients had neoadjuvant P+T in KATHERINE
- TA424 recommends neoadjuvant P+T for HER2-positive early breast cancer.

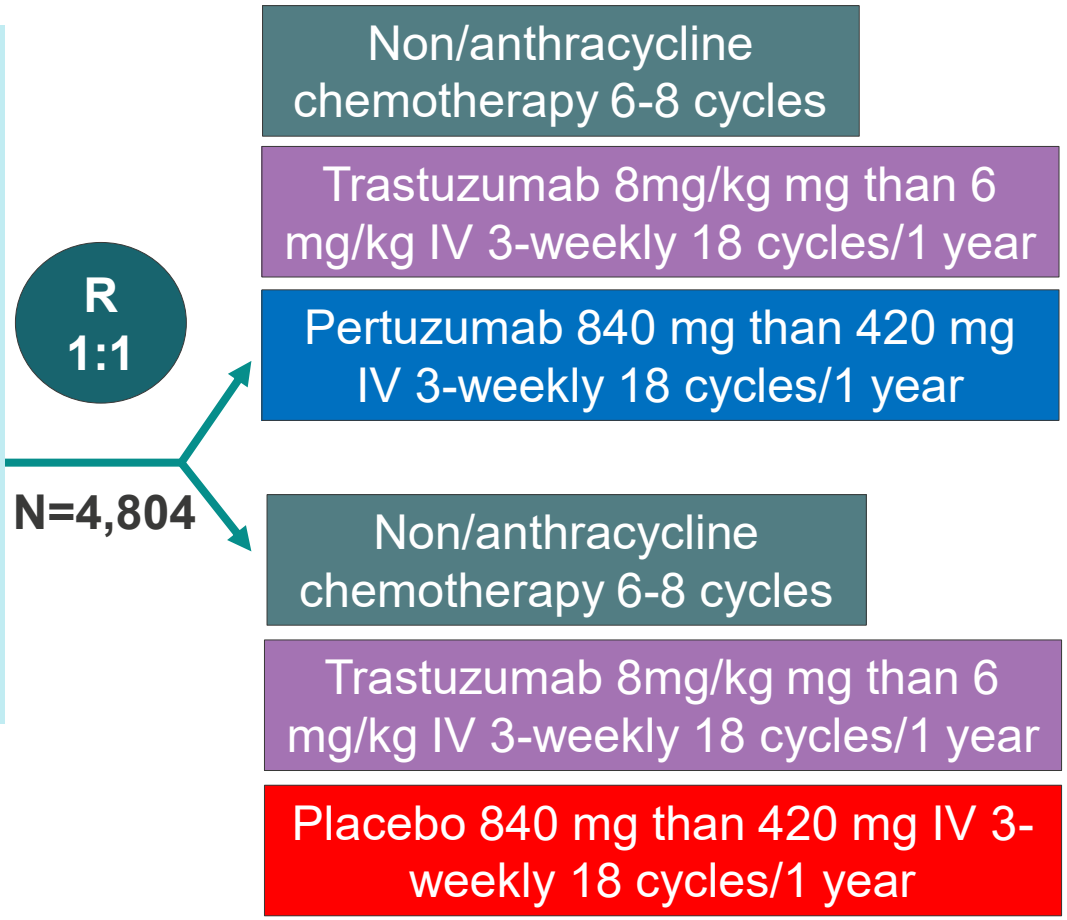
KATHERINE: results

			IDFS		OS	
			Events, % (n)	HR (95%CI)	Events, % (n)	HR (95%CI)
ITT population	All	T (n=743)	22.2 (165)	**0.50 (0.39 to 0.64)**	7.5 (56)	0.70 (0.47 to 1.05)
		TE (n= 743)	12.2 (91)		7.5 (56)	
	Prior neoadjuvant T only	T (n=596)	23.7 (141)	**0.49 (0.37 to 0.65)**	NR	NR
		TE (n=600)	13 (78)		NR	
	Prior neoadjuvant P+T	T (n=139)	17.3 (24)	0.50 (0.25 to 1.00)	NR	NR
		TE (n=133)	9 (12)		NR	
Node-positive population		T (n=346)	NR	**0.52 (0.38 to 0.71)**	NR	NR
		TE (n= 343)	NR		NR	
Node-negative population		T (n=397)	15.6 (62)	**0.44 (0.28 to 0.68)**	4.0 (16)	0.79 (0.38 to 1.63)
		TE (n= 400)	7.3 (29)		3.3 (13)	

Key: P+T, pertuzumab + trastuzumab; T, trastuzumab; TE, trastuzumab emtansine.

APHINITY trial: adjuvant pertuzumab plus trastuzumab but *no prior neoadjuvant*

- Non-metastatic operable primary invasive HER2-positive carcinoma of the breast that is histologically confirmed, and adequately excised (T4 excluded)
- **Prior use of anti-HER2 therapy for any reason not allowed**
- Node positive disease or node-negative disease with a tumour >1 cm
- After 3,655 pts enrolled only node-positive were recruited (protocol change)
- ECOG ≤ 1
- **Primary outcome: IDFS**



Stratification factors:

- nodal status
- adjuvant chemotherapy regimen
- hormone receptor status
- geographic region
- protocol version

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KATHERINE and APHINITY: baseline for node-positive populations

(pertuzumab only recommended for node positive)

	KATHERINE Node-positive		APHINITY Node-positive	
	T (n=346)	TE (n= 343)	P+T (n=1,503)	PBO+T (n= 1,503)
Median age (range)	49 (27–78)	49 (25–79)	51 (21-86)	51 (19-85)
HR-positive	244 (70.5%)	241 (70.3%)	947 (63.0%)	965 (64.2%)
Neoadjuvant HER2	**100%**	**100%**	**0%**	**0%**
Neoadjuvant trastuzumab alone	**278 (80.3%)**	**277 (80.8%)**	**0%**	**0%**
Prior anthracycline	**253 (73.1%)**	**261 (76.1%)**	**0%**	**0%**
Adjuvant anthracycline	NR	NR	1216 (80.9%)	1219 (81.2%)
Asian	**31 (9.0%)**	**33 (9.6)**	**390 (26.0%)**	**393 (26.2%)**
Black or African American	14 (4.0%)	10 (2.9)	21 (1.4%)	24 (1.6%)
White	241 (69.7%)	248 (72.3)	1045 (69.7%)	1041 (69.4%)
Other	30 (8.7%)	33 (9.6)	44 (2.9%)	43 (2.9%)

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KATHERINE versus APHINITY

- Patients in the KATHERINE study were pre-treated with neoadjuvant trastuzumab (second HER2-targeted treatment was allowed) + chemotherapy whereas patients in the APHINITY trial were treatment-naïve
- Patients included in the KATHERINE study were only those who did not achieve a pathological complete response (no residual disease at surgery) following neoadjuvant treatment, and therefore had residual invasive disease in the breast and/or axillary lymph nodes.
- Approximately 18% of people In KATHERINE had pertuzumab plus trastuzumab as their neoadjuvant therapy.
- APHINITY excluded patients with prior use of anti-HER2 therapy for any reason.
- APHINITY also evaluated 18 cycles of adjuvant treatment compared to 14 cycles in KATHERINE.

Issue 1: Treatment pathway

TR questions:

- Is there any reason to prefer trastuzumab emtansine over pertuzumab plus trastuzumab in node-positive disease?
- In clinical practice, do patients with node-positive disease only receive pertuzumab plus trastuzumab or are there some people with node-positive disease who would receive trastuzumab monotherapy?

Breast Cancer Now

- Some node-positive patients may prefer side effect profile of trastuzumab emtansine compared to that of P+T.

Company

- Suggests that trastuzumab emtansine, due to different mechanism of action, is preferred in the event of the suboptimal outcome of RID after neoadjuvant therapy including P+T. This preference is driven by the RID, not the nodal status.
- The majority of patients with node-positive disease receive P+T. This is because P+T is deemed more effective than trastuzumab monotherapy.

For whom would trastuzumab emtansine be suitable as adjuvant therapy? Would it be mainly those with node-negative disease who are currently not eligible for the HER2 pertuzumab/trastuzumab combination recommended by NICE?

Issue 2: Indirect comparison

Background

- The company conducted an indirect comparison using KATHERINE (pre-treated patients) and APHINITY (treatment naïve patients) trials to compare trastuzumab emtansine with pertuzumab + trastuzumab (P+T).
- The results are associated with a high degree of uncertainty.

Company post TE

- During technical engagement teleconference, clinical experts considered trastuzumab emtansine more efficacious than P+T in people with RID following neoadjuvant therapy.
- They considered the indirect comparison results a conservative estimate of trastuzumab emtansine efficacy due to the study population differences
- Therefore the company did not consider that cost-comparison would be suitable.
- Company updated indirect comparison results with longer follow-up data from APHINITY.
- The updated analyses are used in the company's updated base-case.
- No other relevant new evidence was identified.

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How comparable are KATHERINE and APHINITY studies?

Issue 2: Indirect comparison IDF results

- Post technical engagement (TE), results were updated with a longer follow-up data from APHINITY.
- Updated results suggest a smaller benefit of trastuzumab emtansine compared with P+T than the pre-TE results.

Population	KATHERIE HR (95% CI)	APHINITY HR (95% CI)		Indirect comparison HR (95% CI)	
		Pre TE 4 yrs follow-up	Post TE 6 yrs follow-up	Pre TE 4 yrs follow-up	Post TE 6 yrs follow-up
Node-positive populations	0.52 (0.38–0.71)	0.77 (0.62–0.96)	0.72 (0.59-0.87)	**0.675 (0.461–0.989)**	0.722 (0.50-1.04)
ITT populations	0.50 (0.39–0.64)	0.81 (0.67–1.00)	0.76 (0.64-0.91)	**0.617 (0.449–0.849)**	**0.658 (0.49-0.89)**
APHINITY node positive & KATHERINE ITT	0.50 (0.39–0.64)	0.77 (0.62–0.96)	0.72 (0.59-0.87)	**0.649 (0.467–0.904)**	**0.694 (0.51-0.95)**

Given the differences between the KATHERINE and APHINITY trials, how reliable are the results for decision making?

Key clinical effectiveness issues

- **Issue 1 - Treatment pathway**

For whom would trastuzumab emtansine be suitable as adjuvant therapy? Would it be mainly those with node-negative disease who are currently not eligible for the HER2 pertuzumab + trastuzumab combination recommended by NICE?

- **Issue 2 - Indirect comparison of trastuzumab emtansine and pertuzumab plus trastuzumab**

How comparable are the populations in the KATHERINE (trastuzumab emtansine) and APHINITY studies (pertuzumab + trastuzumab) for comparing node-positive disease outcomes?

Are the results suitable for decision making?

Could analyses using ITT population from the trials be used to support the committee's decision?

  - Trastuzumab emtansine versus trastuzumab (node-negative population)
  - Trastuzumab emtansine versus pertuzumab + trastuzumab (node-positive population)

Key cost-effectiveness issues

- **Issue 4 - Trastuzumab emtansine treatment effect waning**

What evidence exists about the long term benefit of HER2 directed therapy in the adjuvant setting and how long it persists?

Is the ERG's assumption, that trastuzumab emtansine treatment effect waning starts at year 3 and stops at year 8 clinically plausible?

- **Issue 5 - Utilities**

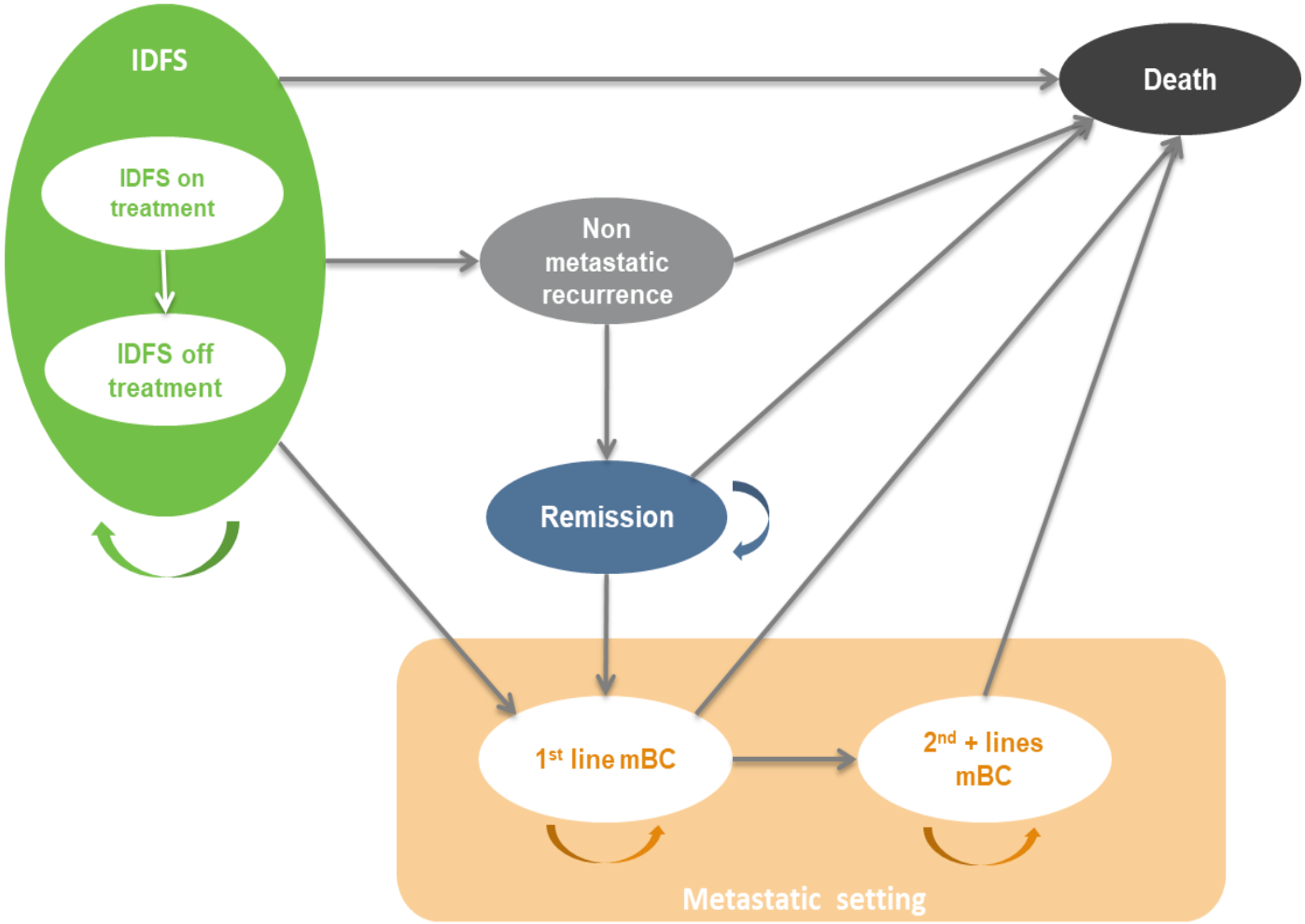
The company accepted ERG's changes and adopted ERG's approach in its updated base case post technical engagement.

Lloyd et al. 2006 utility values have been used in previous appraisals for the metastatic state. However Lidgren et al. 2007 values were used in TA612.

Does the committee agree with the use of Lidgren et al. utilities for metastatic states?

Company's model: Markov model

- Model is similar to previous models in this disease area (TA107, TA424 and TA569).
- Results provided for three populations: intention to treat (ITT), node-positive, and node-negative disease.
- Time horizon: 52 years.
- Cycle length of one month with half-cycle correction.



Key: Markov model with 9 states: IDFS: on treatment and off treatment; non-metastatic recurrence; remission: early or late (before or after 18 months respectively); first line for metastatic disease (mBC); subsequent lines for mBC; and death.

Issue 4: Trastuzumab emtansine treatment effect

Background

- Company assumed that treatment waning starts at year 7 & stops at year 10
- ERG assumed that treatment effect waning starts at year 3 & stops at year 8
- TA569 assumed that treatment effect waning starts at year 4 & stops at year 7

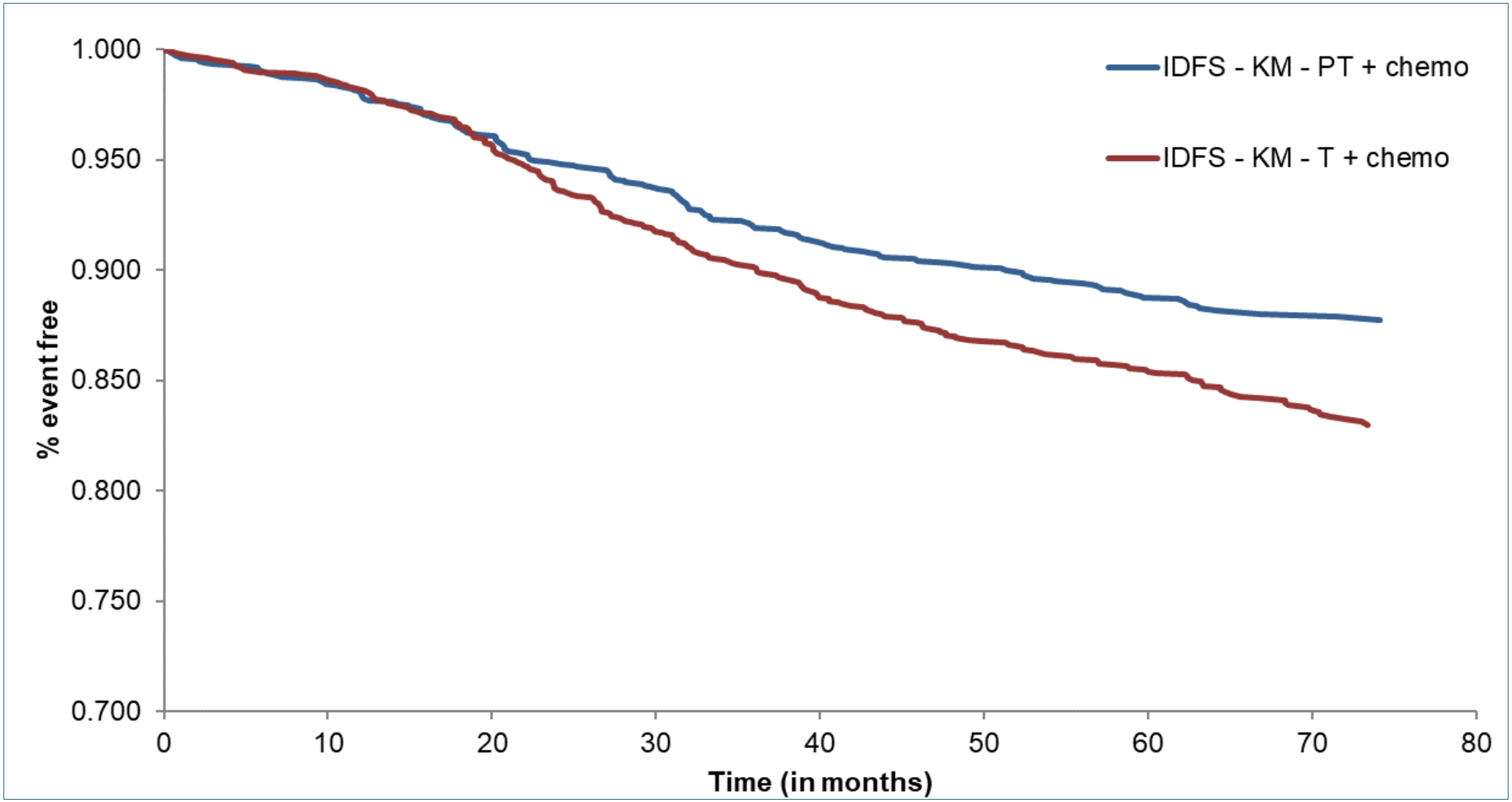
Company post TE

- ERG's assumptions are uncertain and likely underestimate treatment effect
  - annualised hazard ratios are uncertain due to limited patients at risk (due to censoring) and event numbers.
- TA569 was based on primary analysis of IDFS in APHINITY with ~4 years of follow-up. The median duration of follow-up is now ~6 years in the node-positive population.
  - At median follow-up, treatment effect is still increasing. To assume that treatment effect has begun to wane from year 4 is overly conservative and clinically implausible.
- Scenario analyses: even assuming that the treatment effect ceases at the end of the KATHERINE follow-up period (~48 months) – which is an implausibly conservative scenario - the ICER <£20,000 / QALY gained.
- Although the company does not agree with the ERG, for pragmatic purposes, the ERG's approach was adopted in the company's new base case.

Issue 4: Trastuzumab emtansine treatment effect cont.

APHINITY node-positive population: KM IDFS curves – capped at median follow-up

- separation in curves at 73.5 months, suggests that pertuzumab treatment effect is still increasing at median follow-up



Issue 4: Trastuzumab emtansine treatment effect cont.

ERG

- Acknowledges the uncertainty and limitations of the duration of the treatment effect assumptions. However, it still considers that KATHERINE data (annualised hazard ratios) is the best available source to inform the model.
- Agrees with company that updated APHINITY data suggests that assumptions in TA569 underestimated treatment effect of pertuzumab. However, this does not imply that the same will occur with trastuzumab emtansine.
- Further KATHERINE data will provide more reliable estimate of trastuzumab emtansine treatment effect.

Is the ERG's assumption, that trastuzumab emtansine treatment effect waning starts at year 3 and stops at year 8 clinically plausible?

Issue 5: Utilities

Background

- Company used utility values from KATHERINE trial for IDFS. No significant difference was found between the EQ-5D results of the two arms, therefore utilities were pooled, assuming that patients receiving the different treatments have equal utility.
- EQ-5D was not collected in patients who had progressed in KATHERINE. Lloyd et al. utilities were used by the company for first and subsequent line metastatic recurrences, because this source has been used in previous appraisals.
- As the company has chosen to omit disutilities for adverse events, the ERG considers it inappropriate to pool utilities across treatment groups as this fails to capture any differences between groups – effectively assuming that the incremental impact of AEs between the two groups is zero. The ERG therefore prefers utilities per treatment for IDFS.
- The ERG explained, that Lloyd et al. does not reflect the NICE reference case. In comparison, Lidgren et al., measured EQ-5D-3L in breast cancer patients and not the general population. The ERG therefore prefers Lidgren et al. to Lloyds et al. study.

Post technical engagement

- The company accepted ERG's changes and adopted ERG's approach in its updated base case post technical engagement.

Issue 5: Utilities continued

Heath state	Company pre TE Utility	ERG and company post TE Utility
IDFS – On treatment	KATHERINE, pooled: Trastuzumab emtansine & trastuzumab = 0.775	KATHERINE, per treatment: Trastuzumab emtansine = 0.774 Trastuzumab = 0.776
IDFS – Off treatment	KATHERINE, pooled: Trastuzumab emtansine & trastuzumab = 0.788	KATHERINE, per treatment: Trastuzumab emtansine = 0.784 Trastuzumab = 0.791
Non metastatic occurrence	= IDFS on treatment	= IDFS on treatment
Remission	= IDFS off treatment	= IDFS off treatment
Metastatic recurrence 1st line	Lloyd et al.: 0.765	Lidgren et al.: 0.685
Metastatic recurrence 2nd line	Lloyd et al.: 0.508	Lidgren et al.: 0.685

- Lloyd et al. 2006 has been used in previous appraisals. However, Lidgren et al. 2007 has been used in the recent appraisal of neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab TA612 (November 2019).

Does the committee agree with the use of Lidgren et al. utilities for metastatic states in this appraisal?

Issues agreed at technical engagement

Issue	Stakeholder response and agreement between ERG and company post technical engagement
Issue 3 - IDFS extrapolation	ERG considers the company's original approach overestimated IDFS for trastuzumab during the observed period of KATHERINE. The ERG suggested using the KM data plus extrapolation is more appropriate. The company adopted ERG's approach post TE.
Issue 6 – Drug costs and modelling assumptions	Company's assumptions in their original submission followed those in TA569 and were validated during TE and so are suitable for decision making. No changes to model needed post TE.
Issue 7 – model using the ITT population	The updated model is suitable for decision making.
Issue 8 - model using the node-positive population	The updated model is suitable for decision making.

Cost effectiveness results

Company's key assumption post technical engagement:

- ERG's approach to IDFS modelling (Issue 3)
- ERG's approach to treatment effect (Issue 4)
- Arm specific utilities and Lidgren et al. utilities (Issue 5)
- Making the same assumption about trastuzumab use in the early recurrence as TA569 (Issue 6)
- Results updated with population specific data (recurrence rates, baseline characteristics, time on treatment) as relevant
- Indirect comparison results updated with further follow-up from APHINITY
- Analyses based on ITT population from KATHERINE were used for a comparison vs P+T by using indirect comparison results with APHINITY & KATHERINE node-positive populations. Analyses based on the ITT population are considered supportive of updated results provided for the node-negative and node-positive populations (Issue 7 & 8)

Cost effectiveness results: vs trastuzumab

Pre TE	Inc. cost	Inc. QALY	ICER vs trastuzumab
Company: node-negative population	[redacted]	[redacted]	£2,634
TR ICER: node-negative population	[redacted]	[redacted]	£9,339
Company: ITT population	[redacted]	[redacted]	£1,247
TR ICER: ITT population	NR	NR	£7,648

Post TE: node negative population	Inc. cost	Inc. QALY	ICER vs trastuzumab
Company's base case post TE	[redacted]	[redacted]	£8,829
ERG: agrees with the company's revised base-case for node negative population			

Post TE: ITT population results	Inc. cost	Inc. QALY	ICER vs trastuzumab
Company	IDFS modelling : KM + exponential curve		
Company's base case post TE	[redacted]	[redacted]	£5,985
ERG	IDFS modelling: KM + generalised gamma curve		
ERG's preferred ICER	[redacted]	[redacted]	£7,213

- Results include commercial arrangements for trastuzumab emtansine, pertuzumab & trastuzumab, and assumed discount for trastuzumab biosimilars of 70%.

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Note: results with all commercial arrangements will be presented in Part 2

Cost effectiveness results: vs P+T

Pre TE: node-positive population	Inc. cost	Inc. QALY	ICER vs P+T
Company's base case before TE	XXXX	XXXX	£303
TR ICER: TR ICER is not available, the technical team requested updated analyses.			

Post TE: node-positive population	Inc. cost	Inc. QALY	ICER vs P+T
Company's base case post TE	XXXX	XXXX	£4,955
ERG: agrees with the company's revised base-case for node-positive population			

Post TE: ITT population results	Inc. cost	Inc. QALY	ICER vs P+T
Indirect results using APHINITY & KATHERINE node-positive populations were used:			
Company	IDFS modelling : KM + exponential curve		
Company's base case post TE	XXXX	XXXX	£8,203
ERG	IDFS modelling: KM + generalised gamma curve		
ERG's preferred ICER	XXXX	XXXX	£6,388

- Results include commercial arrangements for trastuzumab emtansine, pertuzumab & trastuzumab, and assumed discount for trastuzumab biosimilars of 70%.

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ERG's scenario analyses: HRs trastuzumab emtansine vs pertuzumab + trastuzumab

Scenario	Trastuzumab emtansine vs P+T HR	ICER Node-positive population		ICER ITT population	
		vs P+T	Δ	vs P+T	Δ
Company's base case: ITC with N+ KATHERINE & N+ APHINITY	**0.722**	**£4,955**	**£0**	**£8,203**	**£0**
ITC with ITT KATHERINE & N+ APHINITY	**0.694**	**£2,468**	-£2,487	**£5,598**	-£2,605
ITC with ITT KATHERINE & ITT APHINITY	**0.658**	**£69**	-£4,886	**£2,913**	-£5,290
HR ~ ICER 20K	**0.800**	**£19,248**	+£14,293	**£20,456**	+£12,253
HR ~ ICER 30K	**0.830**	**£33,166**	+£28,213	**£29,241**	+£21,048

Key: N+, node-positive population; ITC, indirect treatment comparison; ITT intention to treat population; P+T, pertuzumab + trastuzumab.

Additional areas of uncertainty

Issue	Why issue is important	Impact on ICER
Systematic reviews	The ERG identified a number of issues with cost-effectiveness and cost and resource searches.	Unknown
Treatment switching	From the 71 patients who switched to trastuzumab from trastuzumab emtansine, a total of 63 patients (88.7%) completed the 14 cycles of trastuzumab emtansine and trastuzumab.	Minor, but unknown.
Dose reductions	Dose reductions were permitted in KATHERINE trial but were not included in the model	Minor, the approach is considered to be conservative.
Adjuvant chemotherapy	Chemotherapy would have been received in neoadjuvant setting, therefore no chemotherapy was included in the model as part of adjuvant pertuzumab + trastuzumab treatment	Likely a minor decrease in cost-effectiveness estimates.

Key cost-effectiveness issues

- **Issue 4 - Trastuzumab emtansine treatment effect waning**

What evidence exists about the long term benefit of HER2 directed therapy in the adjuvant setting and how long it persists?

Is the ERG's assumption, that trastuzumab emtansine treatment effect waning starts at year 3 and stops at year 8 clinically plausible?

- **Issue 5 - Utilities**

The company accepted ERG's changes and adopted ERG's approach in its updated base case post technical engagement.

Lloyd et al. 2006 utility values have been used in previous appraisals for the metastatic state. However Lidgren et al. 2007 values were used in TA612.

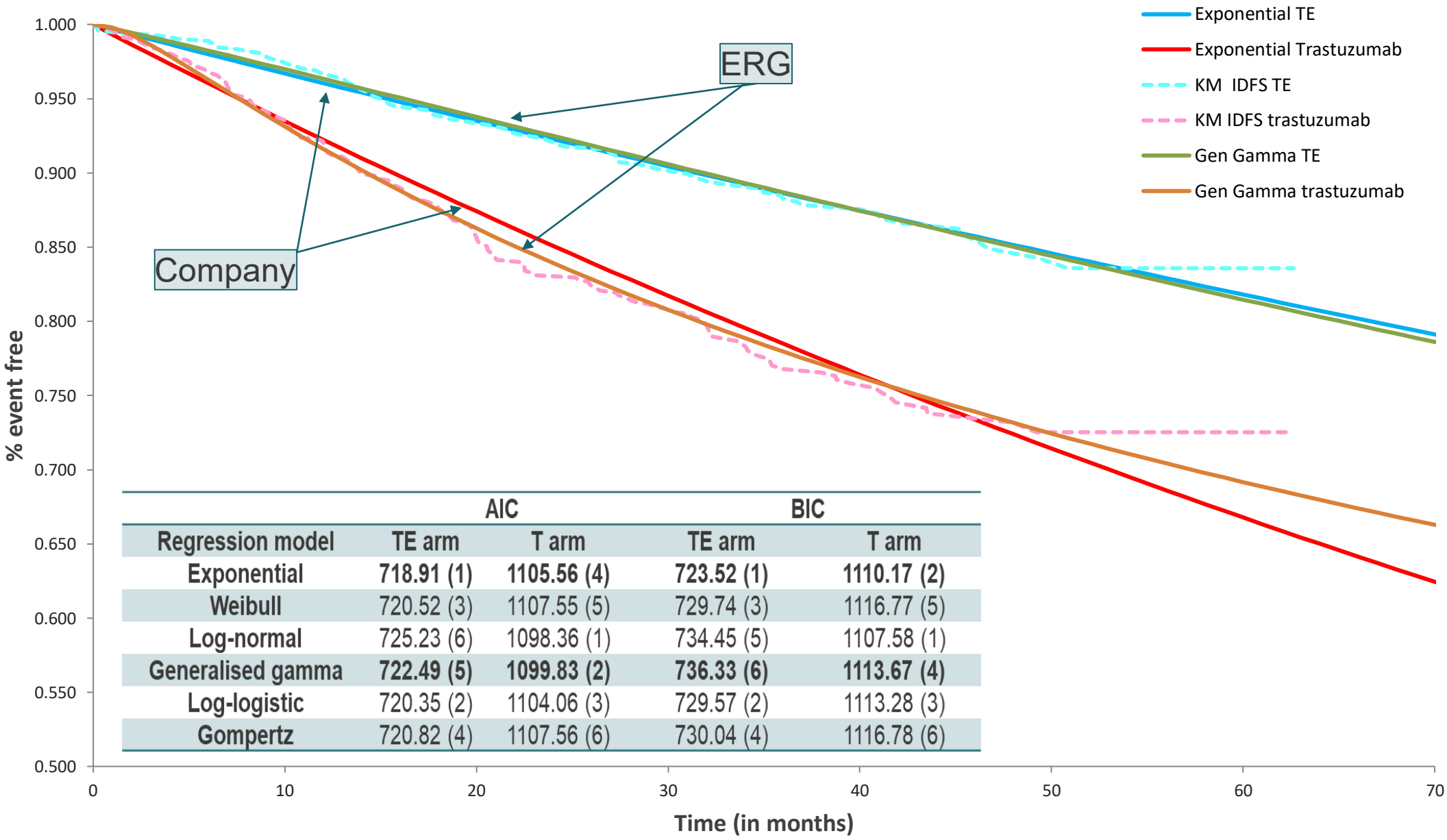
Does the committee agree with the use of Lidgren et al. utilities for metastatic states?

Back up slides

Issue 4: Treatment effect scenarios

Treatment effect	ICER Node-negative population		ICER Node-positive population	
	vs trastuzumab (/QALY gained)	Δ from base case	vs P+T (/QALY gained)	Δ from base case
Company's revised base case:				
• Begins waning at 3 years ceases at 8 years	**£8,829**	£0	**£4,955**	£0
Scenario				
• Stops at 4 years	**£14,654**	+£5,825	**£13,071**	+£8,116
• Begins waning at 4 years ceases at 7 years	**£9,115**	+£286	**£4,454**	-£501
• Begins waning at 5 years ceases at 8 years	**£6,534**	-£2,295	**£1,889**	-£3,066
• Begins waning at 6 years ceases at 9 years	**£4,942**	-£3,887	**£389**	-£4,566
• Begins waning at 7 years ceases at 10 years	**£3,988**	-£4,841	**TE dominant**	N/A

IDFS extrapolation ITT population



	AIC		BIC	
Regression model	TE arm	T arm	TE arm	T arm
Exponential	**718.91 (1)**	**1105.56 (4)**	**723.52 (1)**	**1110.17 (2)**
Weibull	720.52 (3)	1107.55 (5)	729.74 (3)	1116.77 (5)
Log-normal	725.23 (6)	1098.36 (1)	734.45 (5)	1107.58 (1)
Generalised gamma	**722.49 (5)**	**1099.83 (2)**	**736.33 (6)**	**1113.67 (4)**
Log-logistic	720.35 (2)	1104.06 (3)	729.57 (2)	1113.28 (3)
Gompertz	720.82 (4)	1107.56 (6)	730.04 (4)	1116.78 (6)