![NICE National Institute for Health and Care Excellence]

Slides for public – redacted

Trifluridine–tipiracil for treating metastatic gastric or gastro-oesophageal junction cancer after 2 or more therapies [ID1507]

Lead team presentation

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Company: Servier Laboratories

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Gastric or gastro-oesophageal junction cancer

- Stomach cancer is a malignant tumour arising from cells in the stomach

  - 95% gastric or gastro-oesophageal junction adenocarcinoma

  - Gastro-oesophageal junction cancer treatment follows ESMO gastric cancer guideline

  - *"Gastric cancer"* used from now on to capture both types

- Initial symptoms are vague and similar to other stomach conditions, but for advanced stages may include lack of appetite and weight loss, fluid in the abdomen and blood in the stool

- No standard therapy for previously treated advanced or metastatic disease. The ESMO guideline recommends:

  - for untreated disease (first line): chemotherapy (such as doublet or triplet platinum or fluoropyrimidine combinations)

  - after 1 or more treatments (second- and subsequent-lines): taxane (docetaxel, paclitaxel) or irinotecan (ramucirumab is not recommended in TA378)

  - trifluridine–tipiracil recommended as 3L treatment in people with PS 0-1 (Nov 2019 update)

- In practice, paclitaxel is generally used after 1 treatment. Irinotecan is more likely to be used after 2 treatments, though BSC often used here.

Trifluridine-tipiracil hydrochloride (Lonsurf, Servier Laboratories)

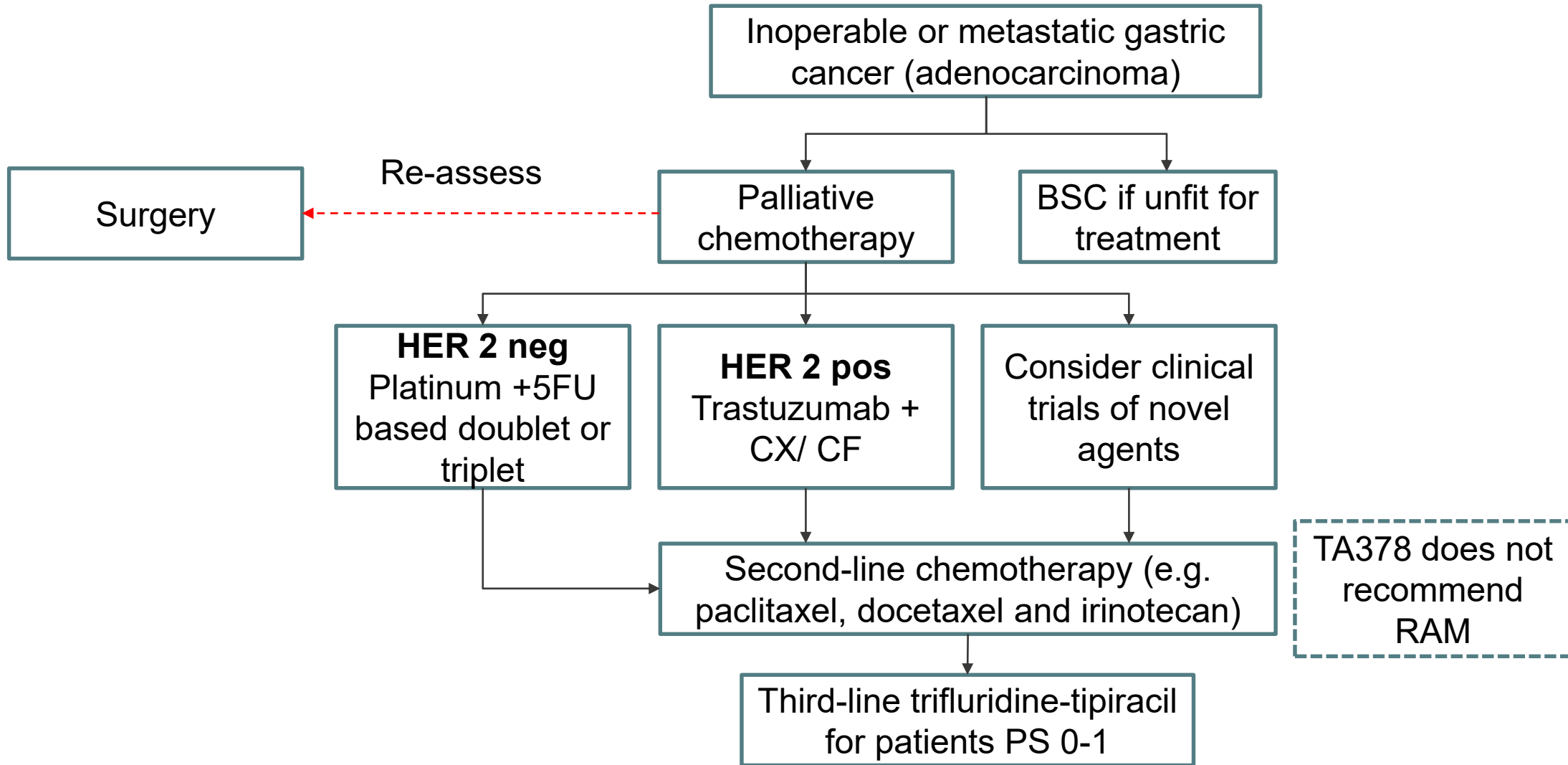|	
Marketing authorisation (received Sept 2019)	**License extension**: Trifluridine-tipiracil is indicated as monotherapy for the treatment of adult patients with metastatic gastric cancer including adenocarcinoma of the gastro-oesophageal junction, who have been previously treated with at least two prior systemic treatment regimens for advanced disease.
Mechanism of action	Antineoplastic thymidine-based nucleoside analogue, trifluridine, and the thymidine phosphorylase (TPase) inhibitor, tipiracil hydrochloride
Administration	The recommended starting dose of trifluridine-tipiracil in adults is 35 mg/m^2/dose administered orally twice daily on days 1 to 5 and days 8 to 12 of each 28-day cycle as long as benefit is observed or until unacceptable toxicity occurs. The dosage is calculated according to body surface area (BSA). The dosage must not exceed 80 mg/dose.
Price	List price: 20 x 15 mg tablets: £500; 60 x 15 mg tablets: £1,500; 20 x 20 mg tablets: £666.67; 60 x 20 mg tablets: £2,000. Average cost per 28-day cycle: £2,017. Commercial arrangement (simple discount patient access scheme [PAS]) approved during TA405.
Other guidance	ESMO (Nov 2019) recommended as 3L treatment in people with PS 0-1.

Treatment pathway based on ESMO guideline

Inoperable or metastatic gastric cancer (adenocarcinoma)

Surgery ← Re-assess --- Palliative chemotherapy

BSC if unfit for treatment

HER 2 neg
Platinum +5FU based doublet or triplet

HER 2 pos
Trastuzumab + CX/ CF

Consider clinical trials of novel agents

Second-line chemotherapy (e.g. paclitaxel, docetaxel and irinotecan)

TA378 does not recommend RAM

Third-line trifluridine-tipiracil for patients PS 0-1

Source: based on ESMO guideline (updated Nov 2019)
Note: untreated disease (first-line), after 1 treatment (second-line), after 2 treatments (third-line)

Abbreviations: BSC, Best supportive care; CF: cisplatin and 5-fluorouracil; CX: cisplatin and capecitabine; HER2, Human epidermal growth factor receptor 2 negative/positive; RAM, ramucirumab

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Background

Comparator	**Company**: Best supportive care (BSC) **Tech team**: Accept company approach but small proportion may have third-line chemotherapy in addition to BSC → unknown cost-effectiveness estimate
Subgroups	**Company base case**: No prior ramucirumab (in line with NHS practice) **Tech team**: ERG scenario that uses full intention-to-treat population is likely to be the most appropriate. The EU subgroup is not a pre-specified subgroup analysis therefore it is still important to consider the cost effectiveness of TFT in the full ITT population.
Clinical trial	TAGS, randomised controlled trial comparing trifluridine–tipiracil + BSC vs placebo + BSC in 507 patients with metastatic gastric cancer
Key results	Statistically significant improvement in overall survival & PFS

	Full ITT population	No prior ramucirumab
OS	HR 0.69 (0.56 to 0.85)	HR 0.66 (0.51 to 0.86)
PFS	HR 0.57 (0.47 to 0.70)	HR 0.58 (0.46 to 0.75)

ICER	**Company**: £45,164 per QALY gained (after clarification) **Tech team**: Between £52,655 and £58,651 per QALY gained but the upper limit of this could be higher because the cost-effectiveness estimates are not known for some plausible scenarios

Patient and carer perspectives

- No patient expert submission for this appraisal

- GO cancer progresses rapidly with a substantial impact on patients' quality of life (QoL).

- Patients want a plan that respects their life goals and treatment preferences:

  – probable life expectancy and realistic QoL v. the time it takes to benefit from a treatment.

- TFT is self-managed and minimises disruption:

  – remain at home

  – once a month hospital visit

  – continue with best supportive care.

"This cancer's a weight I can never put down. The less strength I have, the heavier it is to carry even when others help me."

"Come celebrate with me that every day this disease and its offspring have tried to kill me and have failed."

Outstanding issues after technical engagement

No issues were resolved during technical engagement

- **Issue 1:** Comparator

- **Issue 2a:** Generalisability of TAGS (prior RAM & geographical region)

- **Issue 2b:** Generalisability of TAGS (prior therapies & ECOG)

- **Issue 3:** Extrapolation of overall survival

- **Issue 4:** End of life

- **Issue 5:** Utility values

Issue 1: Comparator - *Summary*

Company	ERG/Technical team
• Only a very small proportion would have third-line chemotherapy in clinical practice → this is supported by clinical experts • Lack of evidence to support the use of third-line chemotherapy & this is usually restricted to trials • Only present cost-effectiveness estimates for TFT vs. BSC in line with TAGS trial	• ERG's clinical advice supports the company's view that there are no established treatments after 2 prior treatments • Tech team accepts BSC is the main comparator – a small proportion may have third-line chemotherapy alongside BSC but the cost effectiveness of this is unknown.

Clinical expert advice

• Both experts agree only a small proportion (<15% estimated by 1 expert) would have third-line chemotherapy

• If it is used, 1 clinical expert suggests treatment is in line with the ESMO Guideline for gastric cancer which recommends irinotecan or a taxane (docetaxel, paclitaxel). However, because paclitaxel is generally used in second line, irinotecan is the most commonly-used 3rd line treatment.

•   **Is BSC alone the most appropriate comparator for 3rd line treatment?**   8

Issues 2a & 2b: Generalisability issues

Prior RAM

Company base case uses **no prior RAM** subgroup (67% of trial population) as more relevant to NHS:

- TA378 does not recommend RAM in NHS
- Less heavily pre-treated (≥3 treatments: ▉ vs. ▉ in prior RAM subgroup)
- Lower proportion from Japan (▉ vs. ▉ in prior RAM subgroup)

Tech team: May not be appropriate to exclude 33% of trial data from patients who had prior RAM & company's preferred subgroup still includes relatively high proportion of people from Japan

Pre-specified subgroup analysis of no prior RAM shows treatment effect is consistent with main analysis and there is similar median survival

	Full ITT population		No prior RAM	
	TFT	**BSC**	**TFT**	**BSC**
Median OS	5.7 (4.8 to 6.2)	3.6 (3.1 to 4.1)	6.0 (5.1 to 6.9)	3.3 (2.8 to 3.9)
OS HR	0.69 (0.56 to 0.85)		0.66 (0.51 to 0.85)	

▉

Issues 2a & 2b: Generalisability issues

Geographical region

- Company base case includes patients from all regions (consistent with previous TAs)
- European subgroup without prior RAM is a posthoc analysis

Tech team: Clinical advice is mixed but the EU subgroup may be appropriate and should be considered

- Patients from Japan had longer median OS compared with rest of the world
    - Japan: TFT 6.3 months, BSC 5.9
    - Rest of world: TFT 5.4, BSC 3.3
- Company submission suggests there may be biological difference in gastric cancer between East Asian and non-Asian populations
- ERG suggest could be biological and/or treatment pathway differences between Japan and EU

No of prior therapies & ECOG score

- Company → would expect fewer number of prior therapies in NHS compared with TAGS trial therefore survival outcomes may be underestimated
- TAGS included ECOG 0-1 but this is generalisable to the expected NHS population

Tech team: ECOG and no. of prior therapies may differ from clinical practice in the NHS but unlikely to affect relative treatment effect

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Issues 2a & 2b: Generalisability issues - *Baseline characteristics*

Characteristic	Full ITT population		No prior RAM		EU (no prior RAM)	
	TFT (n=337)	Placebo (n=170)	TFT (n=223)	Placebo (n=115)	TFT (n=█)	Placebo (n=█)
Median age <65	183 (54%)	96 (56%)	■	■	■	■
Male	252 (75%)	117 (69%)	■	■	■	■
HER Positive	67 (20%)	27 (16%)	■	■	■	■
Measurable disease	306 (91%)	150 (88%)	■	■	■	■
ECOG 1	214 (64%)	102 (60%)	■	■	■	■
1-2 metastatic sites	155 (46%)	72 (42%)	■	■	■	■
≥3 metastatic sites	182 (54%)	98 (58%)	■	■	■	■
2 prior treatment	126 (37%)	64 (38%)	■	■	■	■
3 prior treatment	134 (40%)	60 (35%)	■	■	■	■
≥4 prior treatment	77 (23%)	46 (27%)	■	■	■	■
Prior RAM	114 (34%)	55 (32%)	■	■	■	■
Region: USA	21 (6%)	5 (3%)	■	■	■	■
Region: Europe	270 (80%)	138 (81%)	■	■	■	■
Region: Japan	46 (14%)	27 (16%)	■	■	■	■

Abbreviations: NA; not applicable

Issues 2a & 2b: Generalisability issues - *Summary*

Clinical expert advice

1) **Prior RAM** → Mixed response from clinicians but generally experts, ERG, tech team & company agree there is no evidence that prior RAM affects OS or treatment effect

2) **Region** → Clinical experts advised that recruitment from Japan was capped at 15%, described as low, and is unlikely to impact on trial results. Both clinical experts agreed the full TAGS population was likely to be generalisable to the NHS in England

3) **No. of prior therapies** → Both experts agreed that the proportion of people having 3 prior treatments would be much lower in England (approximately < 5%).

Technical report

- These are generalisability issues and tech team prefers using the full intention-to-treat population to estimate overall survival and the relative effectiveness of trifluridine-tipiracil.

- The use of RAM and number of prior treatments in the TAGS trial may differ from clinical practice in the NHS in England but this is unlikely to impact clinical outcomes.

- The EU subgroup is not a prespecified subgroup, therefore it is still important to consider the cost effectiveness of TFT in the full ITT population
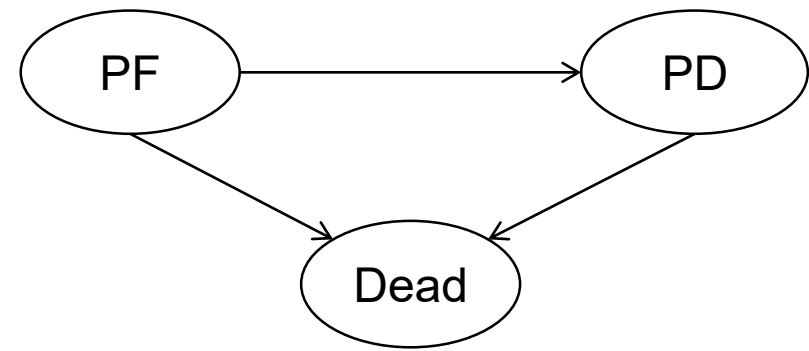
Issues 2a & 2b: Generalisability issues
## *Questions for committee*

- The TAGS trial population was 15% from Japan, 5% from USA and 80% from Europe.
  - What data should be used to model OS & treatment efficacy?
    - All regions or Europe only?

- Ramucirumab (RAM) is not used in NHS. The company suggests the 'no prior RAM' subgroup is more reflective of NHS patients because it is less heavily pre-treated & only ▮ are from Japan.
  - What data should be used to model OS & treatment efficacy:
    - Full ITT population or no prior ramucirumab subgroup?

- Is the trial population in TAGS generalisable, in terms of ECOG status and prior number of therapies, to the population expected to receive trifluridine–tipiracil in the NHS in England?

Issue 3: OS extrapolation - *Company base case*

Issue	Company
Population	Base case models survival using: 1) TAGS subgroup without previous RAM 2) All regions (Japan, EU & USA)

Extrapolation	• OS modelled using **accelerated failure time model with log-normal extrapolation** & included a dependent variable to capture the effect of treatment
	    – it had lowest AIC/BIC
	    – OS data (no prior RAM) suggests treatment effect is constant over time
	    – in line with clinical expectation of long-term survival

Company base case (no prior RAM, dependent model with lognormal curve)
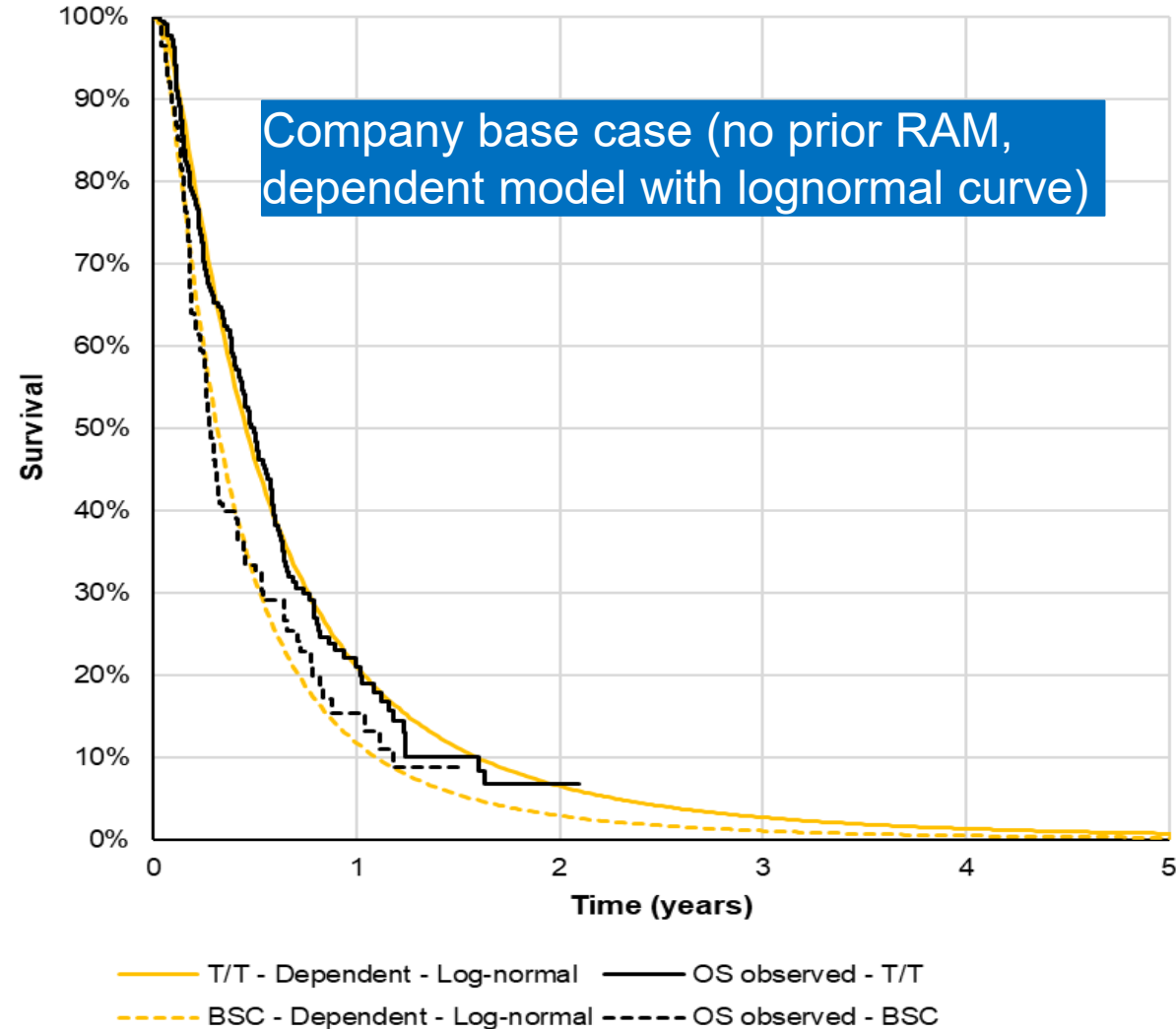
Issue 3: OS extrapolation – *ERG comments*

ERG comments

- ERG prefers independent models because statistical fit of dependent & independent models are similar (< 3-point difference in AIC/BIC)
- Avoids assumption about constant treatment effect over time (curves almost converge at 8 & 15 months)
- ERG exploratory analysis request by technical team: use observed, mature TAGS data to model OS and apply parametric curves only to extrapolate beyond the data
- ERG prefers using a parametric model for the entire modelling horizon because:
  - time-point when the parametric curve should replace the Kaplan Meier (KM) data is arbitrary decision
  - curve was fitted to full duration of KM data (rather than end portion)

Tech team preferred:	
Tech team preferred: 1. Population: full ITT 2. Extrapolation: independent lognormal or loglogistic curves for entire model duration	• In the full ITT population, independent lognormal or log-logistic curves for the entire duration of the model is most consistent with clinical expert advice for BSC • Cost-effectiveness estimates are higher when using parametric curves only to extrapolate **beyond** data

What is the most clinically plausible extrapolation method for overall survival?   15

Issue 4: End of life - *Background*

Issue	Company	Tech team
Short life expectancy (normally <24 months)	Company states this criterion is met because most people with metastatic gastric cancer on 3rd line treatment have survival < 4 months (e.g. median OS is 3.6 in Shitara et al & median OS is 4.1 months in Kang et al)	life expectancy without TFT is <24 months
Extension to life (normally at least 3 months)	Company states this criterion is met because: • the company model predicts a median OS gain for TFT of 2.1 months in ITT population & 2.7 months in population without prior RAM (82% extension in median survival) • should be considered in relation to poor prognosis of this population • OS extension for TFT is superior to that in TA476 (extension to life criterion accepted but was < 3 mths for metastatic pancreatic cancer)	• Less straightforward • Company model estimates mean life extension of 2.7 months for group without prior RAM • Tech team preferred: 2.1 months from ITT all regions population model

Clinical expert advice

• Both experts agree that a survival benefit of around 2 months would be considered clinically meaningful for this population, particularly if it can be achieved with a good quality of life

Issue 4: End of life - *Summary*

Scenario	OS (months) with standard care	OS (months) with intervention	OS gain (months, %) with intervention
TAGS trial (no prior RAM subgroup)	Median: 3.3	Median: 6.0	2.7 (82%)
TAGS trial (ITT population)	Median: 3.6	Median: 5.7	2.1 (58%)
The company's base case model (no prior RAM subgroup)	Mean: 6.2	Mean: 8.9	2.7 (44%)
The company's model (ITT population)	Mean: 6.2	Mean: 8.5	2.3 (37%)
Tech team's preferred model (ITT & all regions)	Mean: 6.3	Mean: 8.3	2.1 (33%)
EU subgroup & no prior RAM (from model)	Mean: 6.5	Mean 8.1	1.7 (26%)

- NICE methods guide for extension to life criterion:
  - "There is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, **normally of a mean value of at least an additional 3 months**, compared with current NHS treatment"
  - "Committees will need to be satisfied that estimates are sufficiently robust and the assumptions used are plausible, objective and robust"
- **Company**: TA476 had mean OS gain of 2.4 months (28%) in model, and data considered robust and relative to poor prognosis for metastatic pancreatic cancer.

Is an extension to life of less than 3 months clinically meaningful for this population?

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Issue 5: Utility values - *Background*

Company

- EORTC QLQ-C30 collected in TAGS

- Mapped to EQ-5D-3L using algorithm from Greek study (n=48) but this did not include any people with metastatic gastric cancer

- Includes the key domains expected to be affected by gastric cancer

- Impact on family and carers not captured

Prog-free: 0.764   **Progressed:** 0.652

- TA378 utilities based on mean values from single points in time

- Did not account for correlation between utility scores for the same patient.

Prefers TAGS values mapped to EQ-5D

TA378 (ramucirumab)

- EQ-5D-based values available from TA378

- 1 previous treatment

- TA378 committee preferred the ERG's analysis:
  - pre-prog data from multiple time points
  - multiple time points not available for post-progression utility values

- Resulting utility values similar to previous TA208 for trastuzumab (0.729 & 0.577)

Prog-free: 0.737   **Progressed:** 0.587

Technical team

- Company's utility values may be plausible

- Post-progression values considerably higher than previous TAs

- Lower values may also be plausible

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Issue 5: Utility values – *Alternative data sources*

- At clarification, ERG requested scenario analyses using alternative mapping algorithms from a recent review (Versteegh et al. 2012, Longworth et al. 2014).
- Company did not use these, but did report utility values using an alternative mapping (Marriot 2017)

Data source	Population	PF	PD	Diff	Company base case	
					ICER	QALY gain
Company base case	**Gastric cancer (uses mapping from non-metastatic gastric cancer population)**	**0.764**	**0.652**	**0.11**	**£45,164**	**0.153**
TA378*	Metastatic or non-resectable locally advanced gastric cancer after 1 previous therapy	0.737	0.587	0.15	£47,857	0.144
TA208†	Previously untreated inoperable locally advanced or recurrent and/or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction	0.729	0.577	0.15	£48,473¥	0.142¥
Company scenario: Marriot (2017)	Previously untreated metastatic colorectal cancer	0.789	0.720	0.07	NR	NR

Note: the company submission also included a scenario analysis using utility values from TA378. ICERs reported in this table for data sources: Company base case and TA378 are from ERG report
¥ ICER calculated by technical team using the ERG model.

Issue 5: Utility values - *Summary*

Technical report

- The company's utility values may be reasonable, but the company's post-progression values are considerably higher than those used in other published technology appraisals in the same disease area.

- Therefore, lower utility values may also be clinically plausible for this population, and sensitivity of cost-effectiveness estimates to alternative values should be considered.

- What utility values should be used?
  - Mapped EQ-5D-3L values from TAGS using an algorithm from a small study that did not include people with metastatic disease
  - Trial-based EQ-5D values from TA378, a previous appraisal in a similar disease area but with only 1 previous treatment

- Are there any benefits not currently captured in the model?

Additional areas of uncertainty

From table 8 in technical report → these are areas of uncertainty that cannot be resolved. Committee should be aware of these when making its recommendations.

Issue	Why issue is important	Impact on ICER
Trial population	The inclusion criteria of the TAGS trial were more restrictive compared with the full marketing authorisation for trifluridine-tipiracil because the trial only included people: • with ECOG performance score 0 or 1 • who have had at least 2 prior regimens that must have included a fluoropyrimidine, platinum, and either a taxane and/or irinotecan-containing regimen	Unknown
Potential clinical subgroups	Subgroup analyses from TAGS suggest there may be clinically relevant subgroups based on prior irinotecan, prior taxane, site of cancer (gastric or gastro-oesophageal junction) & HER-2 status	Unknown

ERG scenarios

- ERG reports 8 alternative scenarios varying 3 main parameters:
  - Population to model OS (full ITT population or no prior RAM subgroup)
  - Population to model treatment efficacy (full ITT population or no prior RAM subgroup)
  - Geographical region (all regions, EU subgroup only)

Company base case = scenario 1

Tech team preferred = scenarios 2 and 6

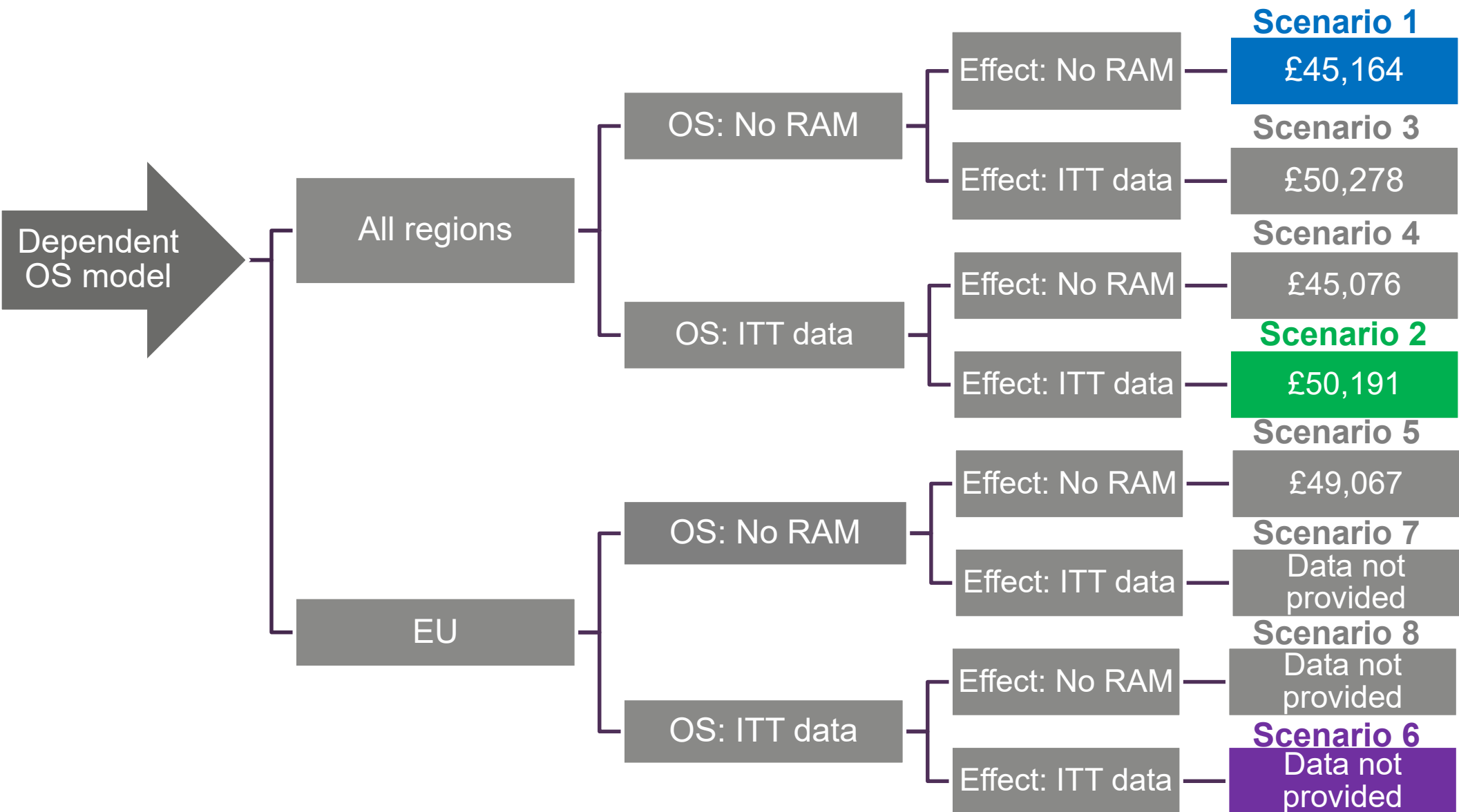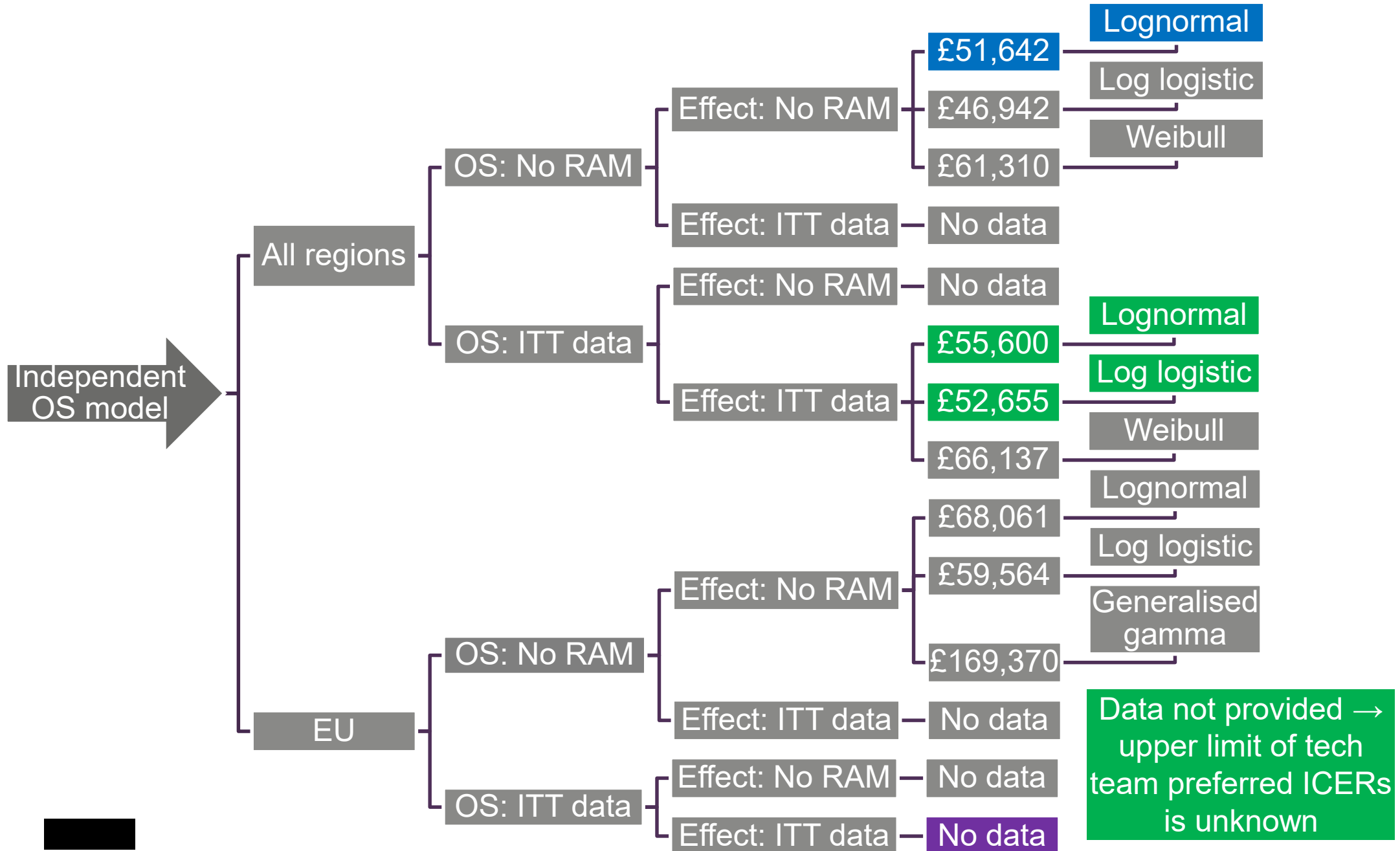| Overall survival data	Relative effectiveness of trifluridine–tipiracil†	
	No prior RAM subgroup	Full ITT population
No prior RAM subgroup	**Scenario 1: all regions included** Scenario 5: EU subgroup	Scenario 3: all regions included Scenario 7: EU subgroup*
Full ITT population	Scenario 4: all regions included Scenario 8: EU subgroup*	**Scenario 2: all regions included** **Scenario 6: EU subgroup***
*The ERG was not able to calculate ICERS for scenarios 6, 7 and 8 because the data were not available † the hazard ratio (or acceleration factor) comparing trifluridine–tipiracil + BSC vs. placebo + BSC for overall survival (see issue 3)		

ERG tentative = scenario 6

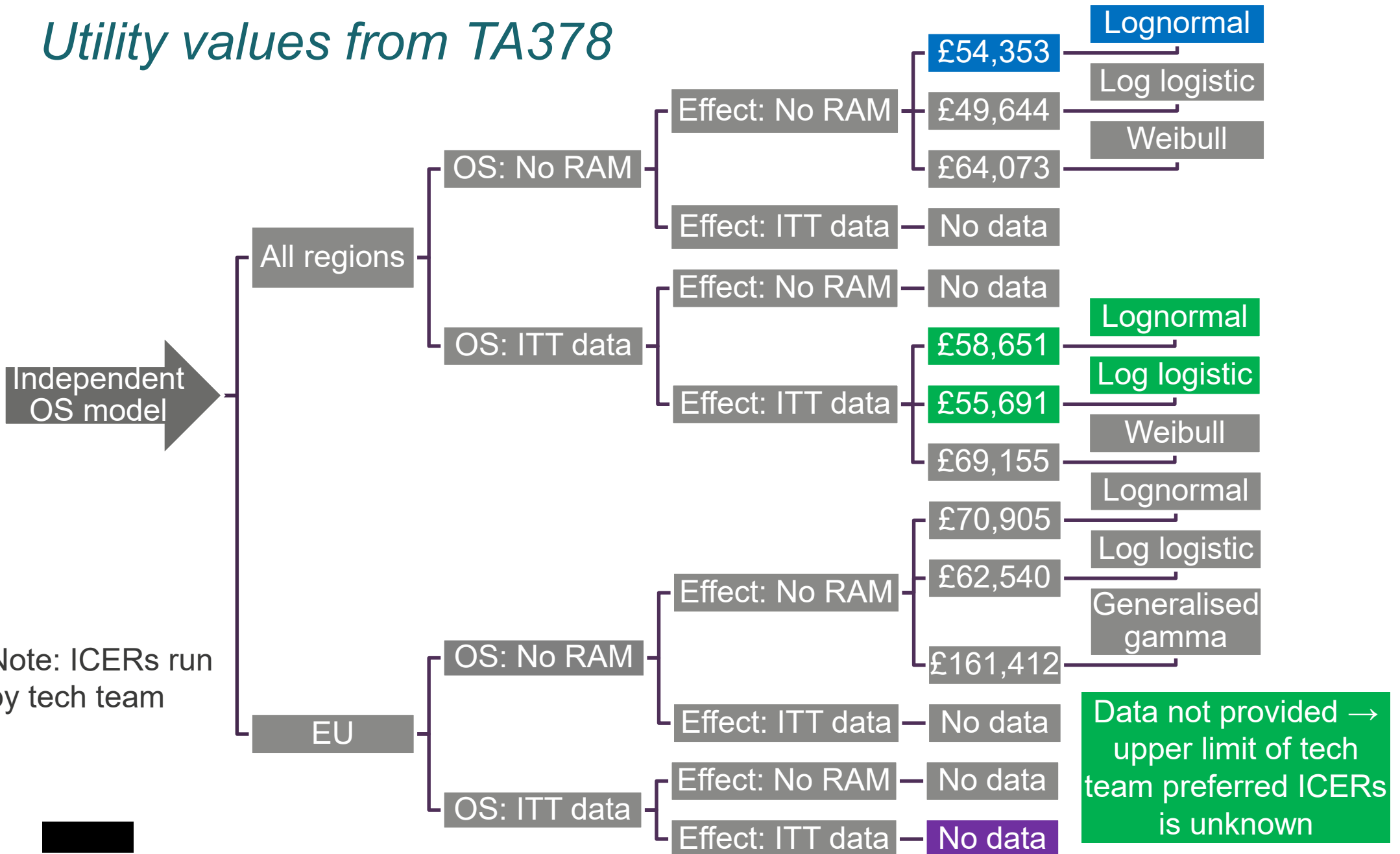# Company ICERs with PAS (after tech engagement)
Dependent lognormal model for OS

Tech team ICERs with PAS – *Independent model for OS*

Independent OS model

- All regions
  - OS: No RAM
    - Effect: No RAM
      - £51,642 — Lognormal
      - £46,942 — Log logistic
      - £61,310 — Weibull
    - Effect: ITT data — No data
  - OS: ITT data
    - Effect: No RAM — No data
    - Effect: ITT data
      - £55,600 — Lognormal
      - £52,655 — Log logistic
      - £66,137 — Weibull
- EU
  - OS: No RAM
    - Effect: No RAM
      - £68,061 — Lognormal
      - £59,564 — Log logistic
      - £169,370 — Generalised gamma
    - Effect: ITT data — No data
  - OS: ITT data
    - Effect: No RAM — No data
    - Effect: ITT data — No data

Data not provided → upper limit of tech team preferred ICERs is unknown

Tech team ICERs with PAS – *Independent model for OS*
Utility values from TA378

Independent OS model

- All regions
  - OS: No RAM
    - Effect: No RAM
      - £54,353 — Lognormal
      - £49,644 — Log logistic
      - £64,073 — Weibull
    - Effect: ITT data — No data
  - OS: ITT data
    - Effect: No RAM — No data
    - Effect: ITT data
      - £58,651 — Lognormal
      - £55,691 — Log logistic
      - £69,155 — Weibull
- EU
  - OS: No RAM
    - Effect: No RAM
      - £70,905 — Lognormal
      - £62,540 — Log logistic
      - £161,412 — Generalised gamma
    - Effect: ITT data — No data
  - OS: ITT data
    - Effect: No RAM — No data
    - Effect: ITT data — No data

Data not provided → upper limit of tech team preferred ICERs is unknown

Note: ICERs run by tech team

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Exploratory scenario for OS

- Tech team requested ERG to produce ICERs using mature TAGS data to model OS and apply parametric curves only to extrapolate beyond the data (issue 3)

- In exploratory analyses, ERG consider 12 month cut point more appropriate due to small patient numbers at later time points:

  - 12 months in ITT: 31 in the TFT arm and 10 in BSC

  - 18 months in ITT: 7 in the TFT arm and 0 in BSC

- ERG & tech team preference unchanged (using a parametric model for the entire modelling horizon) because:

  - time-point when the parametric curve should replace the Kaplan Meier (KM) data is arbitrary decision

  - the extrapolated portion use the same hazards derived from the parametric curves as before, which were fitted to the whole dataset rather than the last portion of the KM data

Exploratory scenario – *OS data from KM for 12 months*

Note: ICERs from ERG
revised addendum
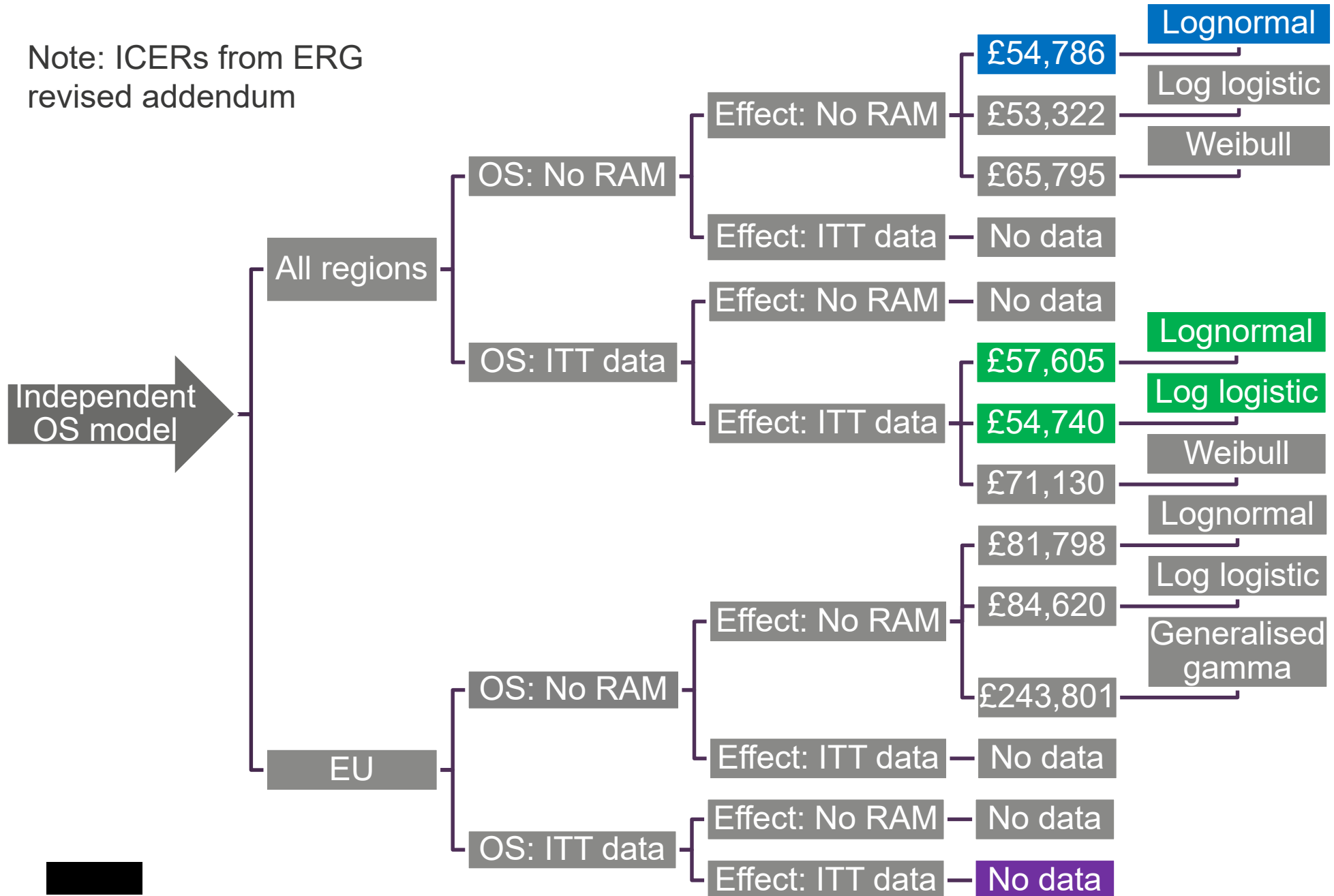
CE plane scatterplot for company base case
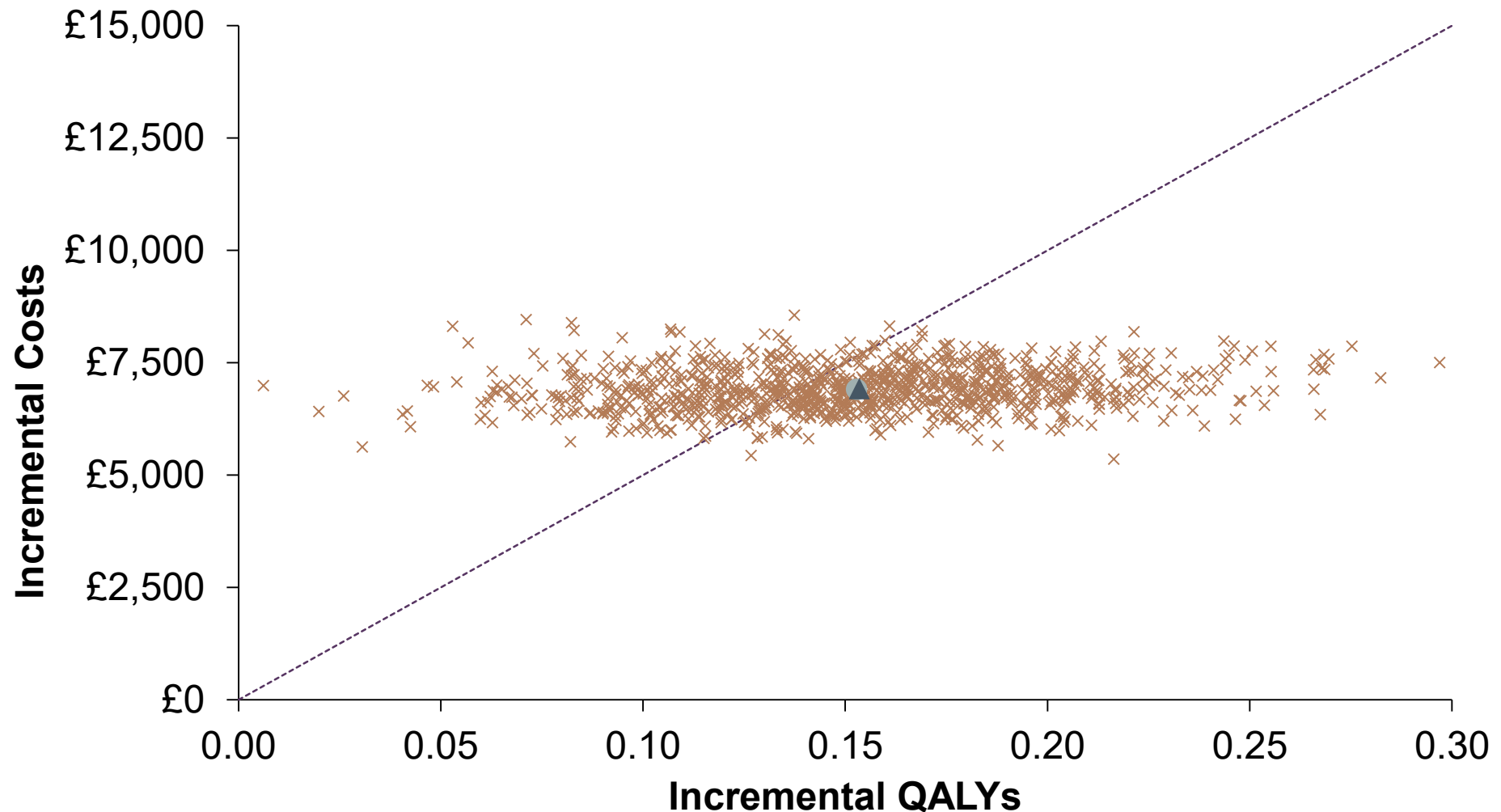
Innovation and Equality

Technical report

- The company considers trifluridine/tipiracil to be innovative.
    - The technical team considers that all relevant benefits associated with trifluridine/tipiracil are adequately captured in the model.
- The company submission does not identify any specific equalities considerations

📈 **Model driver**

Key issues *(1)*

Issue 1: Comparator

- Is BSC alone the most appropriate comparator for 3rd line treatment?

Issue 2a: Generalisability of TAGS (geographical region & prior RAM) 📈

- TAGS trial included 15% from Japan, 5% from USA and 80% from Europe.
  - What data should be used to model OS & treatment efficacy?
    - **All regions** or **Europe only**?
- Ramucirumab (RAM) is not used in the NHS. Company suggests the 'no prior RAM' subgroup is more reflective of NHS: less heavily pre-treated & only ■ from Japan.
  - What data should be used to model OS & treatment efficacy?
    - **Full ITT** population or **no prior RAM** subgroup?

Issue 2b: Generalisability of TAGS (no. of prior therapies & ECOG)

- TAGS trial included people with ECOG score 0–1 and around 63% had ≥3 prior therapies
  - Is this generalisable to the people expected to receive trifluridine–tipiracil in the NHS?

Key issues *(2)*

Issue 3: Survival extrapolation

- What is the most clinically plausible extrapolation method for overall survival?

  – Independent or dependent models

  – Lognormal, Log-logistic or Weibull model

  – Use the full curve or use observed data and extrapolate tail only

Issue 4: End-of-life

- Is an extension to life of less than 3 months clinically meaningful for this population?

Issue 5: Utility values

- What utility values should be used?

  – EORTC QLQ-C30 values from TAGS, mapped to EQ-5D-3L using a study that did not include people with metastatic disease

  – EQ-5D-3L values from TA378, a previous appraisal in gastric cancer but with only 1 previous treatment

- Are there any benefits not currently captured in the model?