NICE National Institute for Health and Care Excellence

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Nivolumab in combination with chemotherapy for untreated advanced gastric, gastro-oesophageal junction cancer or oesophageal adenocarcinoma

2nd Committee Meeting

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ERG: Liverpool Reviews & Implementation Group
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Company: Bristol-Myers Squibb
ACM2: 15th February 2022

Recap: disease background

- **Gastric adenocarcinoma:** originates in the cells of the stomach
- **Gastro-oesophageal junction adenocarcinoma:** the centre of the tumour is less than 5cm above or below where the oesophagus meets the stomach.
- **Oesophageal adenocarcinoma:** originates from cells lining the oesophagus.
  - Can be collectively referred to as **gastroesophageal adenocarcinoma**.

Note: 95% of cancers of the stomach are adenocarcinomas. Adenocarcinoma arises in the glandular tissue. In oesophageal or gastro-oesophageal junction cancer, adenocarcinoma is mostly found in the lower oesophagus and accounts for ~2/3 of UK cases.

Diagnosis is often at an advanced stage. The 5-year survival for people with gastroesophageal adenocarcinoma between 2013 and 2017 was between 17-22%.

- In the UK between 40-50% of all new cases of gastroesophageal adenocarcinoma are diagnosed in people aged 75 years and over.

Nivolumab with chemotherapy

- At 1st committee meeting (Aug 2021) the regulatory CHMP decision was pending.
- Marketing authorisation granted for a narrower population than trial population + final scope issued by NICE → people with HER2 negative cancer with a PD-L1 combined positive score ≥ 5.

Mechanism	Fully human, monoclonal immunoglobulin antibody (IgG4) that acts as a checkpoint inhibitor of PD-1.
Marketing authorisation October 2021	Nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of advanced or metastatic HER2- negative gastric, gastro-oesophageal junction or oesophageal adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 5.
Administration	Nivolumab + fluoropyrimidine- and platinum-based chemotherapy intravenously over 30 minutes: 1. 360 mg nivolumab + chemotherapy every 3 weeks or 2. 240 mg nivolumab + chemotherapy every 2 weeks. ➢ Nivolumab is given first, followed by chemotherapy. ➢ Treatment until disease progression or unacceptable toxicity. ➢ Maximum treatment duration for nivolumab is 24 months.
Price	Confidential patient access scheme for nivolumab is in place. Updated since 1st committee meeting.

CHMP: Committee for Medicinal Products for Human use

Advanced HER2- negative gastric, gastro-oesophageal junction (GOJ) or oesophageal adenocarcinoma

1st line

NG 83 Palliative chemotherapy oesophago-gastric cancer :

- **Doublet chemotherapy**: fluorouracil or capecitabine + cisplatin or oxaliplatin
  - fluorouracil + oxaliplatin: (FOLFOX = fluorouracil + folinic acid + oxaliplatin)
  - XELOX = capecitabine + oxaliplatin
  - cisplatin + fluorouracil
  - cisplatin + capecitabine
- **Triplet chemotherapy**
  - doublet treatment with epirubicin and best supportive care

TA191 Gastric cancer:

- Capecitabine + platinum-based regimen

Proposed ID1465: Nivolumab + chemotherapy (FOLFOX or XELOX) for HER2- negative **gastric**, **GOJ and oesophageal adenocarcinoma PD-L1 CPS ≥ 5**

Pembrolizumab with platinum and fluoropyrimidine-based chemotherapy for **HER2-negative GOJ (adenocarcinoma) and oesophageal (squamous cell or adenocarcinoma) PD-L1 CPS >10 cancer** TA737 guidance published October 2021 (not a comparator in this appraisal)

2nd line

Palliative chemotherapy and best supportive care (NG83)

Pivotal trial: CheckMate 649

Trial design	Phase 3 trial, open-label, randomised, multi-centre trial: • 175 centres across 29 countries - 38 patients from 5 UK centres
Population	Untreated and inoperable, advanced or metastatic (regardless of PD-L1 status): – gastric ([redacted]), – gastro-oesophageal junction ([redacted]), – or oesophageal adenocarcinoma ([redacted]) • ≥18 years; ECOG performance status 0 or 1; patients with known HER2-positive status and with untreated CNS metastases were excluded. • Mean age [redacted] years (PD-L1 ≥5 = [redacted] years)
Intervention	Nivolumab + chemotherapy (n=789): XELOX ([redacted]) or FOLFOX ([redacted]). • (PD-L1 ≥5 = 468: XELOX ([redacted]) or FOLFOX ([redacted]))
Comparator	Chemotherapy (n=792): XELOX ([redacted]) or FOLFOX ([redacted]). • (PD-L1 ≥5 = 465: XELOX ([redacted]) or FOLFOX ([redacted]))
Primary Outcomes	PFS by BICR and OS in PD-L1 CPS ≥5 participants.

Abbreviations: CNS = central nervous system, XELOX = capecitabine+oxaliplatin, FOLFOX = fluorouracil+folinic acid+oxaliplatin, OS = overall survival, PFS = progression-free survival, BICR = blinded independent central review, PD-L1 = programmed death ligand 1, CPS = combined positive score, HER2 = human epidermal growth factor receptor 2

Clinical effectiveness results: ACM1

- July 20 data-cut + [redacted] data presented after technical engagement
- Trial data mature ~ 70% events had occurred for both progression free survival (PFS) and overall survival (OS)
- Nivolumab + chemotherapy improved PFS and OS compared with chemotherapy

[redacted] results

Progression free survival	Nivolumab + Chemotherapy	Chemotherapy
All randomised patients with PD-L1 CPS ≥5 (n = 955)		
Median Months (95% CI)	[redacted]	[redacted]
HR (CI)	[redacted]	
Overall survival	**Nivolumab + Chemotherapy**	**Chemotherapy**
All randomised patients with PD-L1 CPS≥5 (n = 955)		
Median Months (95% CI)	[redacted]	[redacted]
HR (CI)	[redacted]	

NICE

ACM, appraisal committee meeting; PFS, progression free survival; OS, overall survival

Generalisability of trial data: age

- Trial mean age was [redacted] years and most patients ([redacted]) were aged under 65 years

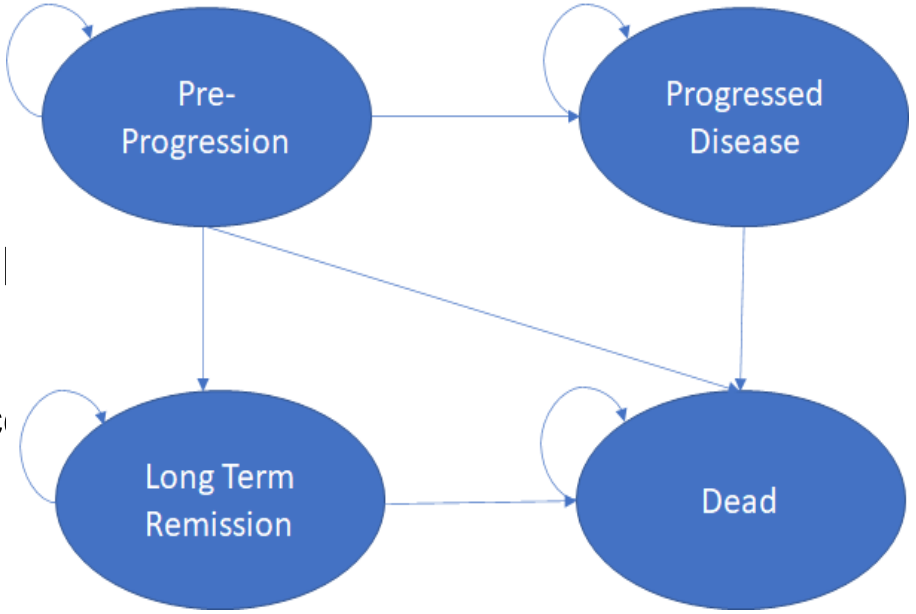
ERG:

- Age is lower in CheckMate 649 than average age reported by:
  - ERG's clinical advisor (70 to 75 years).
  - Cancer Research UK (published 2018, mean 64.15 years).
  - The Royal Marsden Hospital Trust data (published 2018, median 66 years).
- After technical engagement company used mean age of 64.15 in its modelling

Conclusions at 1st meeting

- Clinical experts: average age of trial population is expected to be lower than average age of NHS population with condition. No evidence that treatment would be less effective in older people (ACD 3.5)
- Patient experts noted increasing numbers of younger people being diagnosed (ACD 3.1)
- Committee agreed Checkmate 649 data generalisable to UK population and appropriate to use average age for modelled cohort based on Cancer research UK rather than trial data (ACD 3.9)

Model summary: ACM1



- Cohort-based semi-Markov with 4-states:
- Long-term remission state for people whose cancer
  months:
  - people in this state assumed to have same chanc
    population.
  - model does not allow for possibility of relapsing
- Model differs from the 3-state partitioned survival model frequently used in NICE oncology technology appraisals (e.g. TA208, TA483, TA484).

Data cut	July 2020
Baseline age	64.15 years based on UK data (Cancer Research UK)
Results presented	• Whole trial population • PD-L1 CPS ≥5 subgroup
Sensitivity analyses	Around whole trial population results only
Comparators	XELOX or FOLFOX
Overall survival (OS)	Trial OS not directly modelled. Instead, chance of dying derived from PFS data. **Modelled OS was higher than observed OS data from CheckMate 649**
PD-L1 testing	Costs not included

End of Life (EoL)

Criterion	Company evidence	ERG
The treatment is indicated for patients with a short life expectancy *(normally less than 24 months)*	• CheckMate 649 chemotherapy arm median OS = [redacted] months (ITT) and [redacted] months (PD-L1 CPS >5). • Royal Marsden Hospital data median OS 11.5 months.	Agree
Evidence to indicate that the treatment offers an extension to life *(normally at least an additional 3 months compared with current NHS treatment)*	CheckMate 649 OS median gain ([redacted] data) • PD-L1 CPS >5: [redacted] months. Model predicted OS gain (discounted LY) in PD-L1 CPS >5: • Company: [redacted] years ([redacted] months). • ERG = [redacted] years ([redacted] months).	Met for PD-L1 CPS ≥5 subgroup.

Clinical expert:

- Agree with ERG: OS gain >3 months expected in PD-L1 CPS ≥5 subgroup.

Note: EoL criteria was accepted based on assessment of the [redacted] data cut

Abbreviations: OS = overall survival

Committee conclusions: issues raised at ACM1

✓ Issue resolved

✗ Issue not resolvable in company model: model not suitable for decision making

ACM1 Issue		Committee conclusions	ACD Section
Comparators: XELOX and FOLFOX the relevant comparators?	✓	Key comparator is XELOX.	3.3
Generalisability: is the trial/model population younger/fitter?	✓	The CheckMate 649 trial is generalisable to NHS practice.	3.5
End of Life: are the criteria met?	✓	Met in PD-L1 CPS ≥5 population.	3.13
PD-L1 testing: costs are not included in company model.	✓	PD-L1 CPS testing should be included.	3.10
Long-term remission: People in this state have same life expectancy as the general population and can't relapse - are 'cured'. Is this plausible?	✗	• People may have long-term remission, but no data to support cure. • Some people's cancer will relapse • Life expectancy expected lower after having advanced cancer + chemotherapy	3.6, 3.8, 3.12
Overall survival: mature trial OS data was not directly used in the model and modelled OS did not match observed OS over trial period	✗	The model lacks face validity and is not appropriate for decision making as OS not directly used and modelled.	3.7, 3.12

The Committee requested a new model following ACM1

The new model should:

- be a 3-state partitioned survival model that directly utilises OS data from CheckMate 649.
  - Mixture cure modelling approaches may be acceptable if adequately justified and the impact of any assumptions is explored with sensitivity analyses
- be populated with the most recent data cut off from CheckMate 649.
- use data to reflect the marketing authorisation population PD-L1 with CPS ≥5.
- include costs of PD-L1 CPS testing.
- compare nivolumab + XELOX with XELOX.
- include probabilistic, scenario and deterministic sensitivity analyses

ACD consultation responses

Responses received from:

- Experts: 1 clinical expert
- Company: Bristol-Myers Squibb
  - New partitioned survival model using latest data cut for the population included in the marketing authorisation
  - Re-ran original model using latest data cut for the population included in the marketing authorisation
    - Presented narrative review of data suggesting proportion of people have long term remission.
    - No additional data presented to support modelling assumptions for people in long-term remission health state in original model.

ACD response: clinical expert

Generalisability of CheckMate 649:

- Younger patients are being diagnosed more now than ever before.
- Setting the mean age of 64.15 years does not show the true age, younger patients although potentially fitter are more often diagnosed at a later stage and an effective treatment is lacking.

Long-term remission:

- 30 months is too short a time for many patients to be considered cured.
- 36 – 48 months is seen within patient support groups as more appropriate but is based on lived experiences not clinical data.
- Agree that being cured of cancer is different to being cured with same risk of dying of the general population.
- The effect of treatment alone puts them in a different group than the general population.

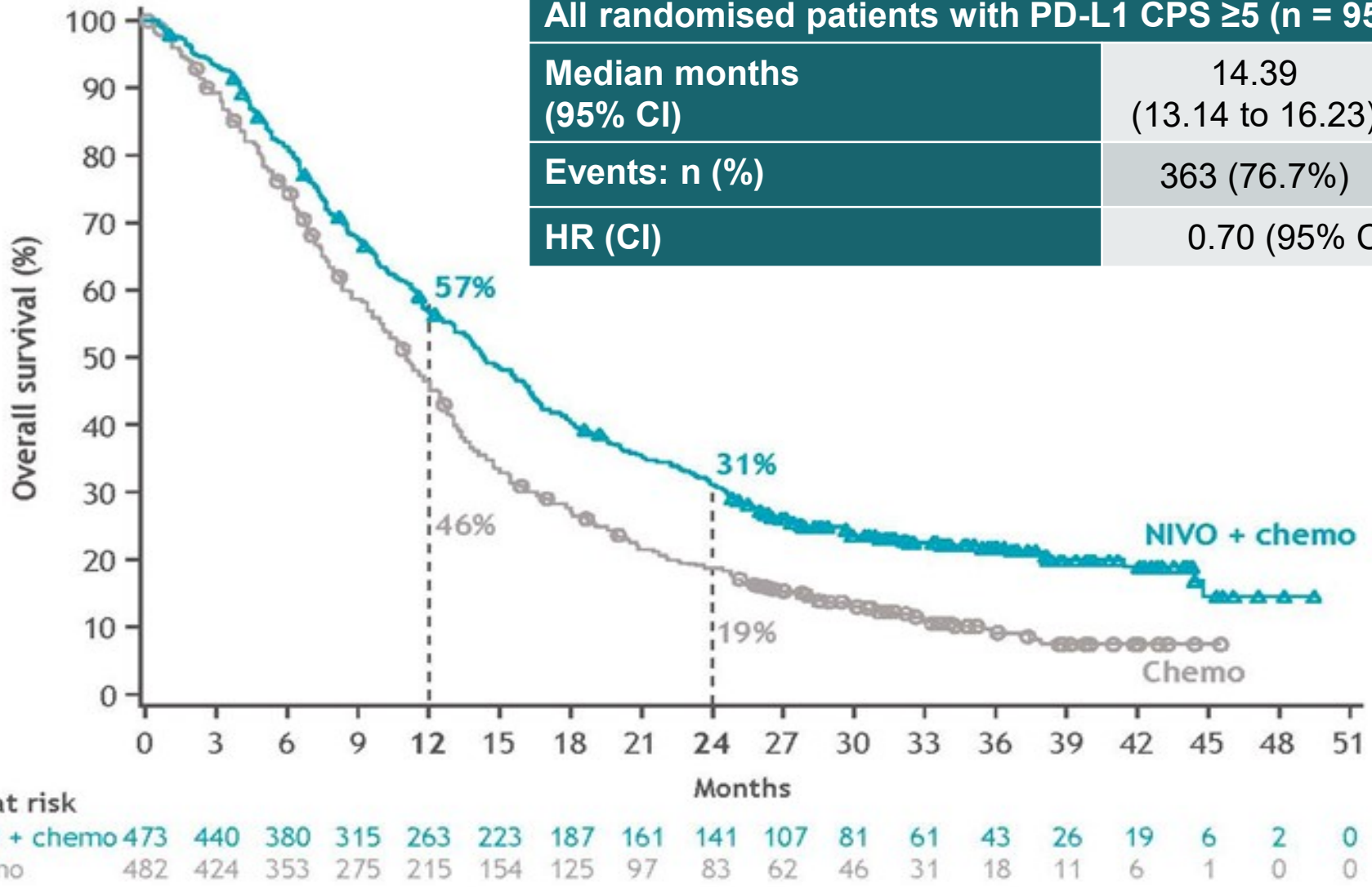
Model suitability:

- Agreed that the model is not suitable and a new model is appropriate and needed.

CheckMate 649: updated overall survival results

Note: data taken from [redacted] database lock. Used in the updated model.

	Nivolumab + Chemotherapy	Chemotherapy
All randomised patients with PD-L1 CPS ≥5 (n = 955)		
Median months (95% CI)	14.39 (13.14 to 16.23)	11.10 (10.05 to 12.25)
Events: n (%)	363 (76.7%)	416 (86.3%)
HR (CI)	0.70 (95% CI: 0.61 to 0.81)	

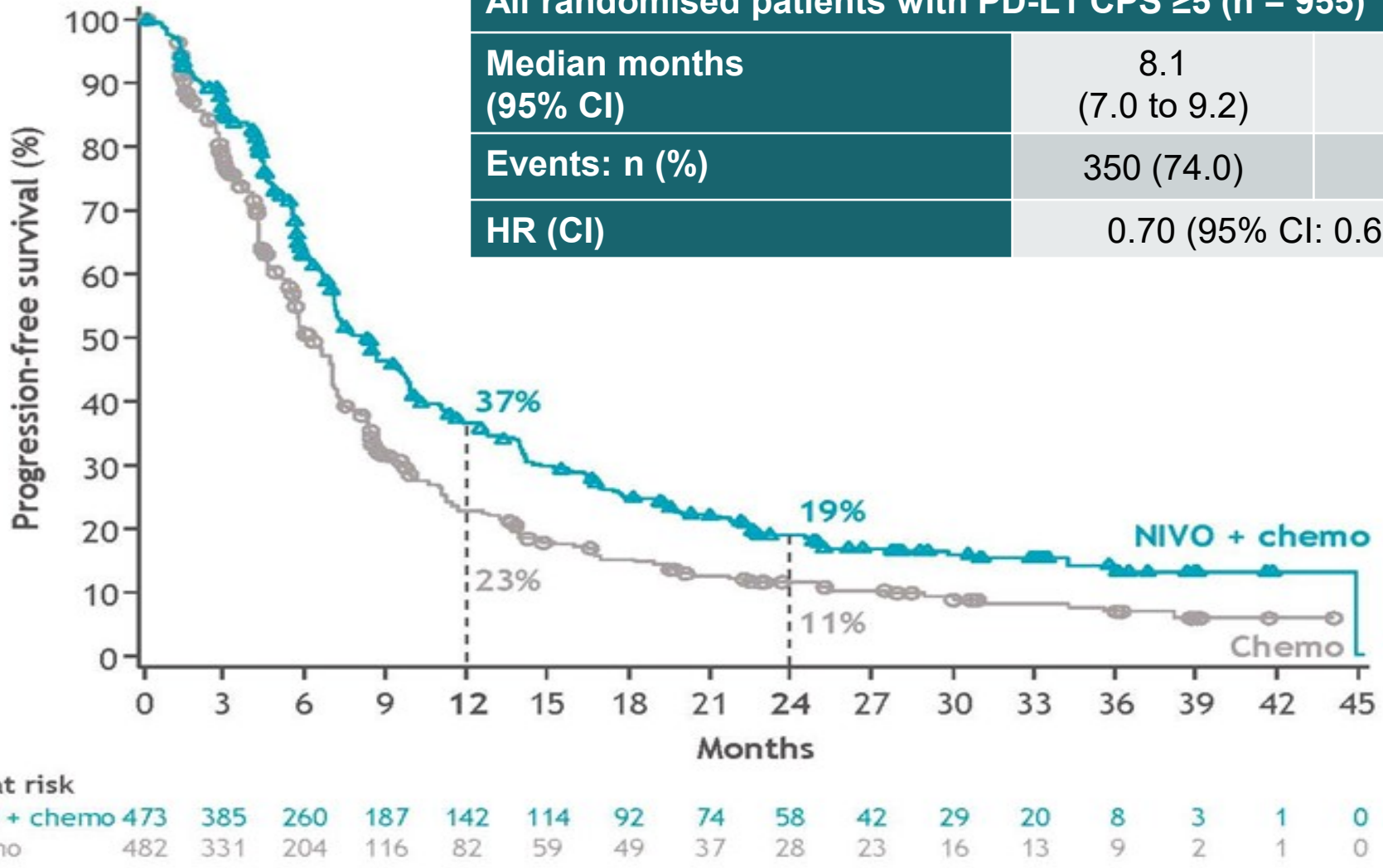


Are further data cuts expected? How many people are still being followed?

CheckMate 649: updated PFS results

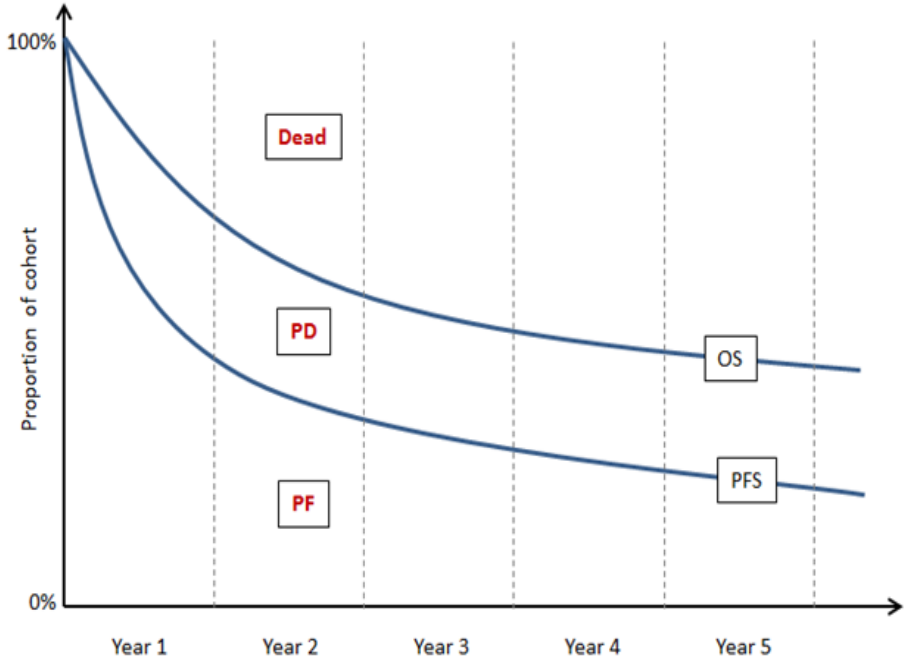
Note: data taken from [redacted] database lock. Used in the updated model.

	Nivolumab + Chemotherapy	Chemotherapy
All randomised patients with PD-L1 CPS ≥5 (n = 955)		
Median months (95% CI)	8.1 (7.0 to 9.2)	6.1 (5.6 to 6.9)
Events: n (%)	350 (74.0)	370 (76.8)
HR (CI)	0.70 (95% CI: 0.60 to 0.81)	



Model summary

- Post ACD updated model: 3-state partitioned survival model.
  - Aligns with models used frequently in NICE oncology technology appraisals (e.g. TA208, TA483, TA484).
- Company also presented original semi-Markov with 4-states including long-term remission state- did not update assumptions for this state.



Model type	New partitioned survival model
Data cut for PFS, OS, Utility values	Updated with later data cut [redacted] (minimum follow up 24 months)
Population	Adults with previously untreated advanced or metastatic, HER2-negative, gastric or gastro-oesophageal junction or oesophageal adenocarcinoma PD-L1 with CPS ≥5 . Model baseline age 64.15 years based on Cancer Research UK mean age.
Comparators	XELOX
Modelling of PFS and OS	Used Kaplan Meier data from trial with semi-parametric extrapolation
PD-L1 testing	Costs included £82.08 per test
Nivolumab costs	Updated with new patient access scheme price

Modelling approach: progression free survival

Company:

- Semi-parametric approach: Kaplan-Meier estimates were directly used for the first 6.44 months and then parametric extrapolation
- 6.44 month cut-off point was chosen to reflect the fact that high frequency assessments, which could influence the timing of PFS measurements, had ceased
- Log-normal distribution used for extrapolation for both Nivolumab + XELOX and XELOX modelled treatment arms

ERG:

- Agreed with semi-parametric approach taken and use of log-normal distribution in company base case noting that there was no clinical evidence other than CheckMate 649 to choose between alternative parametric distributions

Modelling approach: overall survival

Company:

- Semi-parametric approach: used Kaplan-Meier data from CheckMate 649 to 6.44 months then extrapolated using Gompertz distribution based on statistical fit (lowest AIC/BIC scores) in both modelled treatment arms
- Modelling included new approach to try to add excess mortality of people with condition to mortality of general population

ERG:

Approach of adding excess mortality to general population mortality

- Innovative and potentially good approach but the company implemented inappropriately
  - company adds all cause mortality from trial to all cause mortality of general population which could double count some deaths.

Plausibility of modelled overall survival compared with general population

- Most distributions have falling or constant mortality hazard (chance of dying over time) whereas in the general population the mortality hazard increases as people age.
- This means distributions will at some point have mortality hazards lower than hazards in general population. This is implausible.

ERG's alternative modelling approach: overall survival

- ERG corrected company's modelled overall survival (Gompertz):
  - Modelled OS directly follows OS curves from trial (i.e. uses standard all-cause mortality data rather than trying to estimate excess mortality with condition)
  - Set mortality hazard so it will never be lower than that in general population. At point mortality hazard becomes same as general population modelled to follow general population hazards thereafter
  - ERG considers correction still may not be accurate because committee agreed at 1st meeting there will be excess mortality even if in remission because of having had advanced cancer and cytotoxic chemotherapy
- ERG preferred choice of distribution for extrapolation: generalised gamma
  - Both Gompertz and generalised gamma have good statistical fit to trial data
  - Differ in when the mortality hazard in modelled treatment arm curves meet that of general population (generalised gamma later than Gompertz).
  - ERG consider later time at which generalised gamma mortality hazard meets that of general population key reason generalised gamma more plausible option.

Distribution	Time mortality hazard meets		% alive when mortality hazard meet	
	Nivo + XELOX	XELOX	Nivo + XELOX	XELOX
Gompertz	10.3 years	12.9 years	9.1%	1.3%
Generalised gamma	23.9 years	26.1 years	0.3%	<0.0%

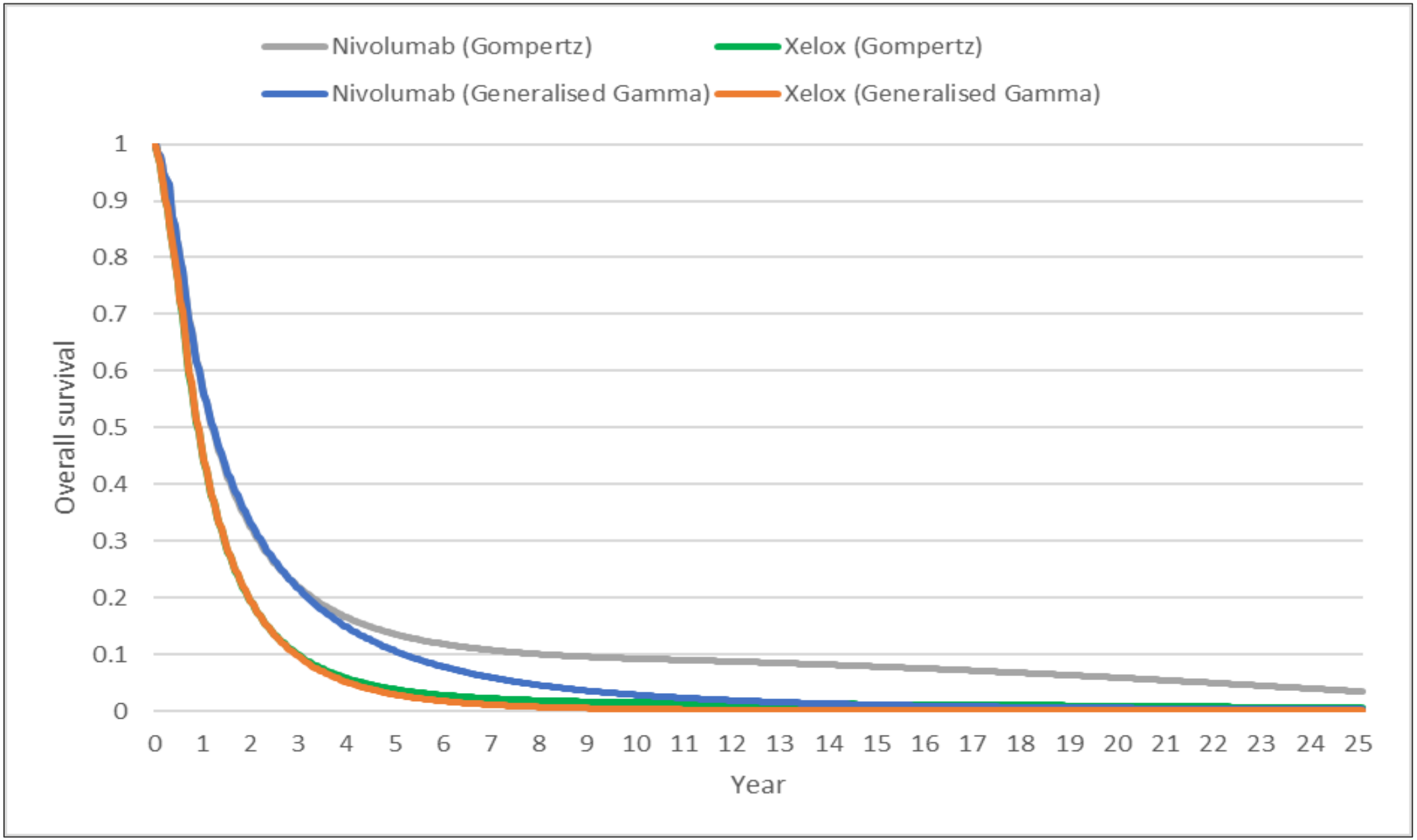
Modelled overall survival: predicted % alive

Comparison of using Gompertz vs. generalised gamma

- Both give conservative estimates of % alive in XELOX arm at 5 years vs. Royal Marsden data
- Predicted % alive becomes markedly different after 5 years
- Generalised gamma predicts fewer people alive in both treatment arms than Gompertz
- Difference in % alive between treatment arms smaller if generalised gamma used.

Distribution	5-year	10-year	20-year
Nivolumab+XELOX % alive			
Company base case (Gompertz)	[redacted]		
ERG correction to company Gompertz	13.6%	9.2%	5.9%
ERG generalised gamma	10.6%	2.8%	0.5%
XELOX % alive			
Company base case (Gompertz)	[redacted]		
ERG correction to company Gompertz	3.8%	1.5%	0.9%
ERG generalised gamma	2.9%	0.3%	0.2%
Royal Marsden	4.0%	-	-
Difference between treatment arms in % alive			
Company base case (Gompertz)	[redacted]		
ERG correction to company	9.8%	7.7%	5.0%
ERG generalised gamma	7.7%	2.5%	0.3%

Modelled overall survival: predicted % alive



NICE

Figure produced by ERG at request of NICE

Treatment effect waning

Company:

- There is a 2-year stopping rule in CheckMate 649 and in summary of product characteristics for nivolumab

ERG:

- Considers that a scenario should be explored whereby any treatment effect from NIVO+XELOX compared to XELOX is not maintained for life.
- In line with previous nivolumab submissions, the ERG produced a scenario whereby the mortality hazard for those treated with NIVO+XELOX is equal to that of those treated with XELOX at 5 years (i.e., 3 years after treatment with nivolumab has stopped for all patients).
- Notes the scenario is not evidence-based and does not form part of the ERG preferred base case. The results are presented with the ERG cost-effectiveness results.

Effect of treatment waning on ERG corrected Gompertz in Nivo+XELOX arm

Distribution	Time mortality hazard meets	% alive when mortality hazard meets	% alive at 5 years	% alive at 10 years	% alive at 20 years
Gompertz	10.3 years	9.1%	13.6%	9.2%	5.9%
Gompertz + waning	12.9 years	4.5%	13.4%	5.3%	3.1%
Generalised Gamma	23.9 years	0.3%	10.6%	2.8%	0.5%

Cost-effectiveness estimates

Scenario/ERG amendment	Incremental		ICER
	Costs	QALYs	£/QALY gained
Company base case	[redacted]	[redacted]	£45,383
Company base case (probabilistic)	[redacted]	[redacted]	£47,873
ERG corrected company base case (includes removal of incorrect excess mortality calculation and sets mortality hazard to never fall below that of general population)	[redacted]	[redacted]	£41,738
ERG corrected company base case + with treatment effect waning	[redacted]	[redacted]	£49,840
ERG exploratory base case ERG corrected company base case + generalised gamma distribution for OS	[redacted]	[redacted]	£58,816
ERG corrected company base case + generalised gamma distribution for OS + treatment effect waning	[redacted]	[redacted]	£70,681

Key issues

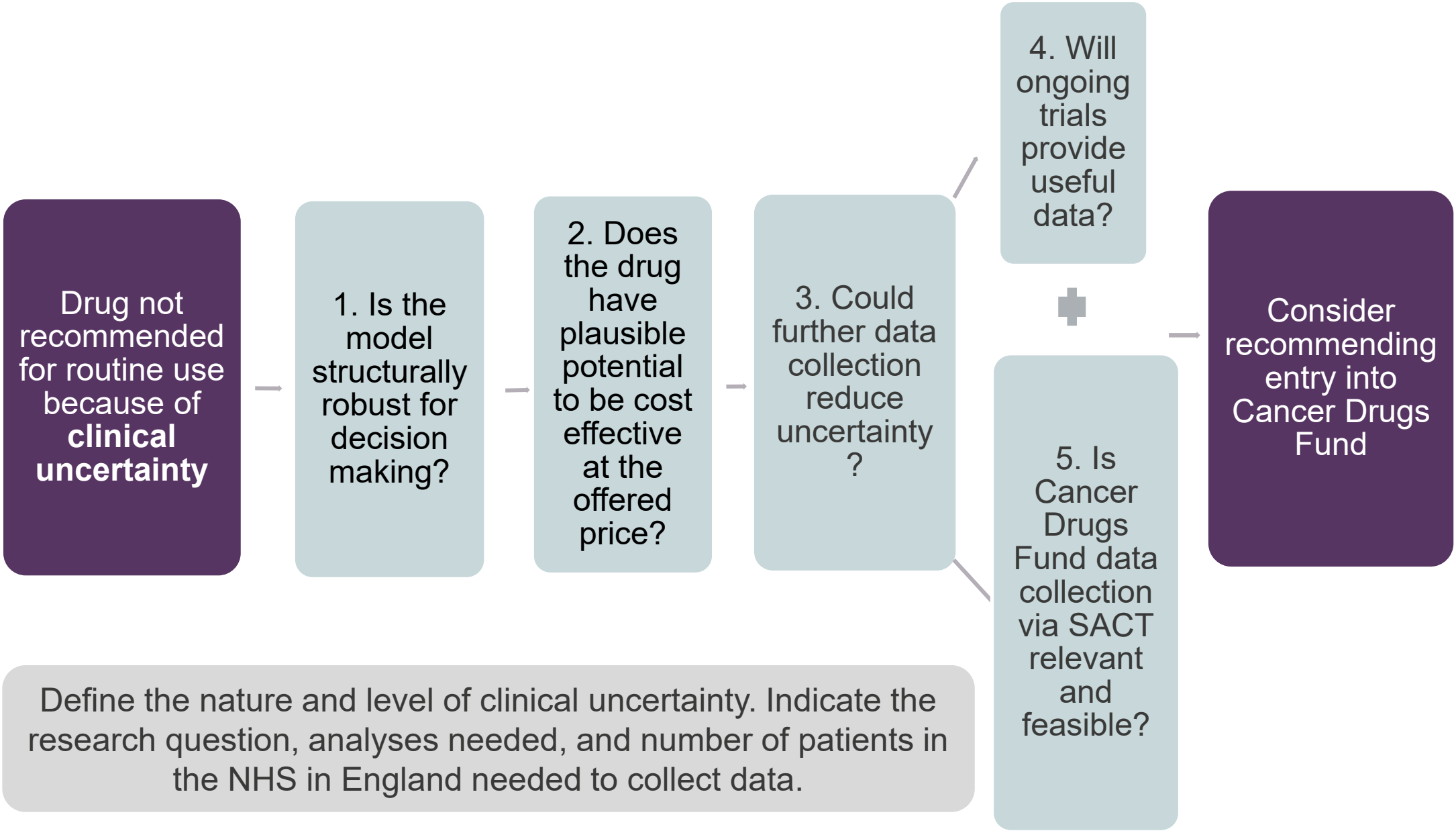
Which approach for extrapolating overall survival gives the most plausible modelled outcomes – Gompertz (the company) or generalised gamma (ERG)?

What are committee's views on:

- When the modelled mortality hazard becomes the same for people with the condition as the general population with both approaches?
- The long term (5 years +) predictions of the proportions of people who will be alive?
- The expected difference in the proportion of people who will be alive between treatment arms in the long term?

Are there data that will be, or could be collected to resolve uncertainty around long-term overall survival?

Cancer Drugs Fund



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