NICE National Institute for Health and Care Excellence

Encorafenib in dual or triple therapy for previously treated BRAF V600E mutation-positive metastatic colorectal cancer

Lead team presentation

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Chair: Amanda Adler
ERG: Warwick Evidence
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Company: Pierre Fabre

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Key issues

1. Treatment pathway:
   - What is the appropriate position in the treatment pathway?
     - 2nd and/or 3rd line?
   - What are the relevant comparators at 2nd line?
2. In absence of a direct comparison, are the results valid from the:
   - indirect treatment comparison?
   - naïve comparison?
3. What are the most appropriate models for extrapolating:
   - Overall survival (OS)
   - Progression-free survival (PFS)
4. How should time to treatment discontinuation (TTD) be modelled?
5. Are the costs included appropriately?
6. Does encorafenib + cetuximab meet NICE's end of life criteria?

BRAF V600E mutation-positive metastatic colorectal cancer

- Metastatic colorectal cancer: malignant tumour of the large intestine (colon and rectum), that has spread beyond the large intestine and nearby lymph nodes.
- 10% of people with colorectal cancer have tumours with the BRAF V600E mutation
- Metastatic colorectal cancer with BRAF mutation, associated with poorer prognosis and greater risk of disease recurrence than ‘wild-type’ (‘normal’ non-mutated)
- NICE clinical guideline 151 recommends testing for BRAF V600E mutations in all people with metastatic colorectal cancer suitable for systemic anti-cancer treatment
- Aim of treatment for metastatic colorectal cancer is to prolong survival and improve quality of life
- Currently no treatments available specifically for tumours with BRAF V600E mutations

Encorafenib (BRAFTOVI, Pierre Fabre)

Marketing authorisation	Adult patients with metastatic colorectal cancer with BRAF V600E mutation, who have had prior systemic therapy
Mechanism of action	**Encorafenib**: blocks MAPK# cell signalling pathway in BRAF V600E mutation-positive tumours **In combination with cetuximab**: prevents activation of feedback loop (EGRF) that BRAF inhibition alone would activate
Additional tests	Must confirm BRAF V600E mutation with a validated test
Administration and dose	**Encorafenib**: oral. 300 mg (four 75 mg capsules) once daily. Continue until patient no longer benefits or until development of unacceptable toxicity **Cetuximab**: intravenous. Initial dose 400 mg/m^2 body surface area, all subsequent doses 250 mg/m^2 weekly*
Cost	**Encorafenib**: List price - £1,400 per pack of 42 x 75 mg capsules, £622.22 per pack of 28 x 50 mg capsules **Cetuximab:** List price - £890.50 per 500 mg/100 mL† Commercial arrangements in place for encorafenib and cetuximab, making them available to the NHS with a discount. Cetuximab made by Merck.

MAPK = mitogen-activated protein kinase

†National Cancer Drugs Fund list*: recommends cetuximab is given once every 2 weeks at a dose of 500mg/m^2

Professional organisation perspective

Submission from Royal College of Physicians

- BRAF mutant colorectal cancer is a very rare sub-type of colorectal cancer.
- Very little shift in median survival for BRAF mutant cancer, despite advances in RAS wild type ('normal' non-mutated) colorectal cancer.
- FOLFIRI or alternatively trifluridine-tipiracil are currently used in clinical practice for BRAF mutant colorectal cancer.
- Encorafenib + cetuximab would be used in 2nd or 3rd line.
- No significant difference in adverse events expected compared with current treatments.
- Encorafenib + cetuximab represents a 'step-change' in treatment. It is the only treatment to date that demonstrates both a clinically meaningful and statistically significant difference in terms of overall survival in this patient population in a phase 3 trial.

Patient and carer perspectives

Unmet need

- Little movement in the drugs used for many years; survival has hardly improved in the last 5 years
- Mental and physical challenges from poor prognosis

Novel treatment options required

- Current treatment is harsh, 21 cycles and 2 years later I still have neuropathic damage

Encorafenib + cetuximab

- Treatment* gave me life, and response was quick
- Suggest using sooner rather than last line
- Adverse effects are manageable with education, but more knowledge on best ways to manage them must be obtained whilst in use.
  - "Change of Bowel Habits, Eye changes, Skin rashes and Tiredness are for me the key side effects."

 **Patient expert received triplet therapy which is not included in company submission*

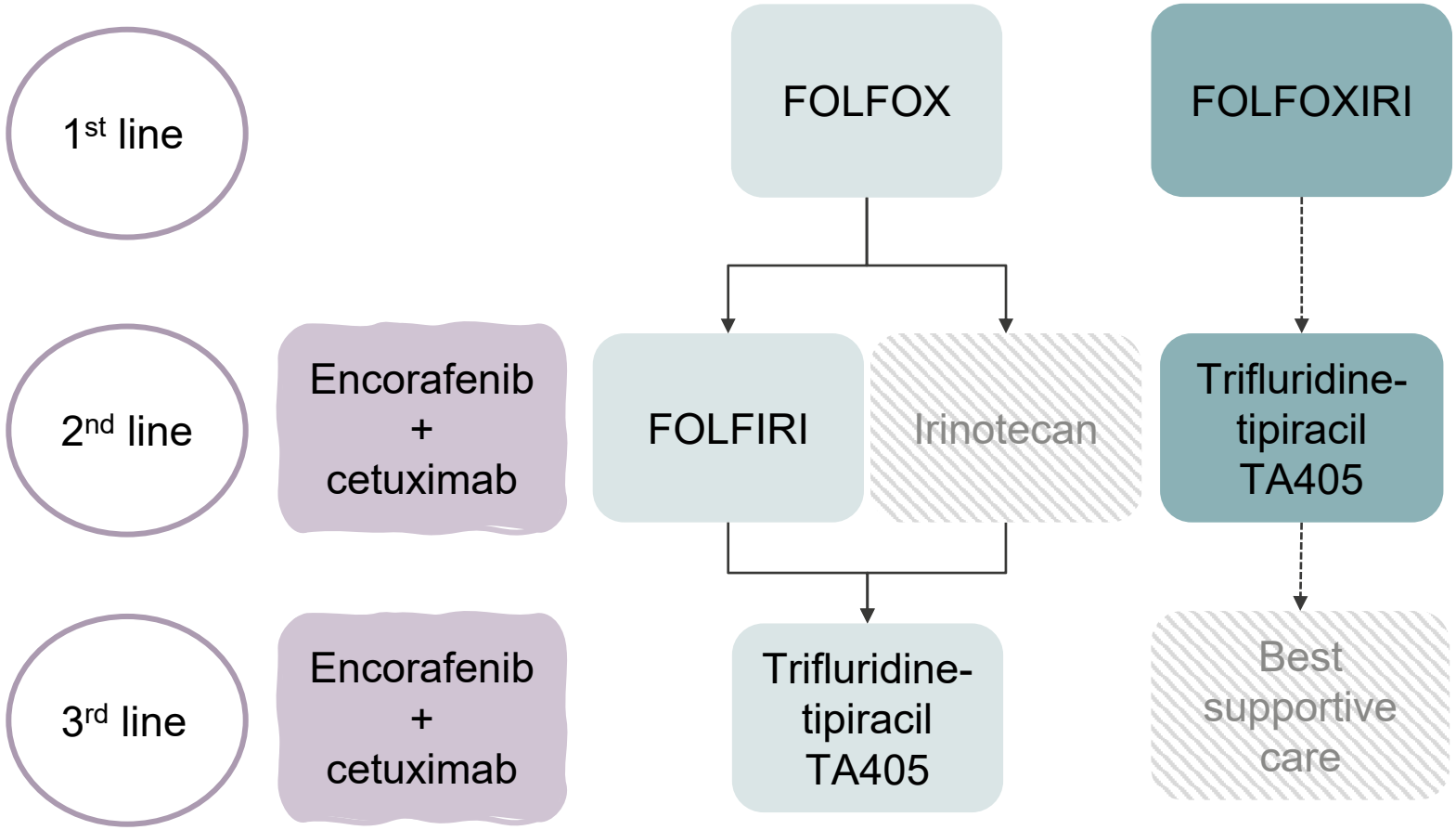
The decision problem

	Final scope issued by NICE	Company submission deviations
Population	People with previously treated BRAF V600E mutation-positive metastatic colorectal cancer	As in scope: company present evidence for people who received 1 or 2 prior therapies
Intervention	1. Encorafenib + cetuximab 2. Encorafenib + cetuximab and binimetinib	**Company:** Marketing authorisation for encorafenib + cetuximab Triple therapy not relevant
Comparators	1. Folinic acid plus fluorouracil plus irinotecan (FOLFIRI) 2. Trifluridine-tipiracil* 3. Irinotecan 4. Best supportive care	**Company exclude irinotecan** because low use in practice based on clinical expert opinion and market survey **Company exclude best supportive care** because encorafenib + cetuximab would be used earlier in the treatment pathway, when active treatment options are still available

*after treatment with fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies or where these are not tolerated or unsuitable

Encorafenib + cetuximab: place in the treatment pathway

Marketing authorisation: Adult patients with metastatic colorectal cancer with BRAF V600E mutation, who have had prior systemic therapy



Bowel cancer UK: encorafenib + cetuximab would be used 2nd line most frequently.

3rd line appropriate in patients who have progressed to 3rd line chemotherapy and have a performance status of 0-1

◉ *What is the committee's view on the positioning in the treatment pathway - are both 2nd and 3rd line positionings acceptable?*
What are the potential comparators at each line?

Encorafenib + cetuximab: appropriate comparators – 2nd line

FOLFIRI assumed to be a comparator

Irinotecan

Company: Systemic Anti-Cancer Therapy (SACT) data show 1.8% receive irinotecan 2nd line

Bowel Cancer UK: Irinotecan an established 2nd line treatment, but used less than FOLFIRI

Clinical experts submission to NICE: Single agent irinotecan associated with many toxicities and FOLFIRI now preferred 2nd line therapy

Trifluridine-tipiracil

TA405: In clinical practice, trifluridine–tipiracil offered at 3rd line when there are no further treatment options

Clinical experts submission to NICE: UK pathway follows 1st line FOLFOXIRI -> 2nd line trifluridine-tiparacil or 1st line FOLFOX/CAPOX ->2nd line FOLFIRI ->3rd line trifluridine-tiparacil

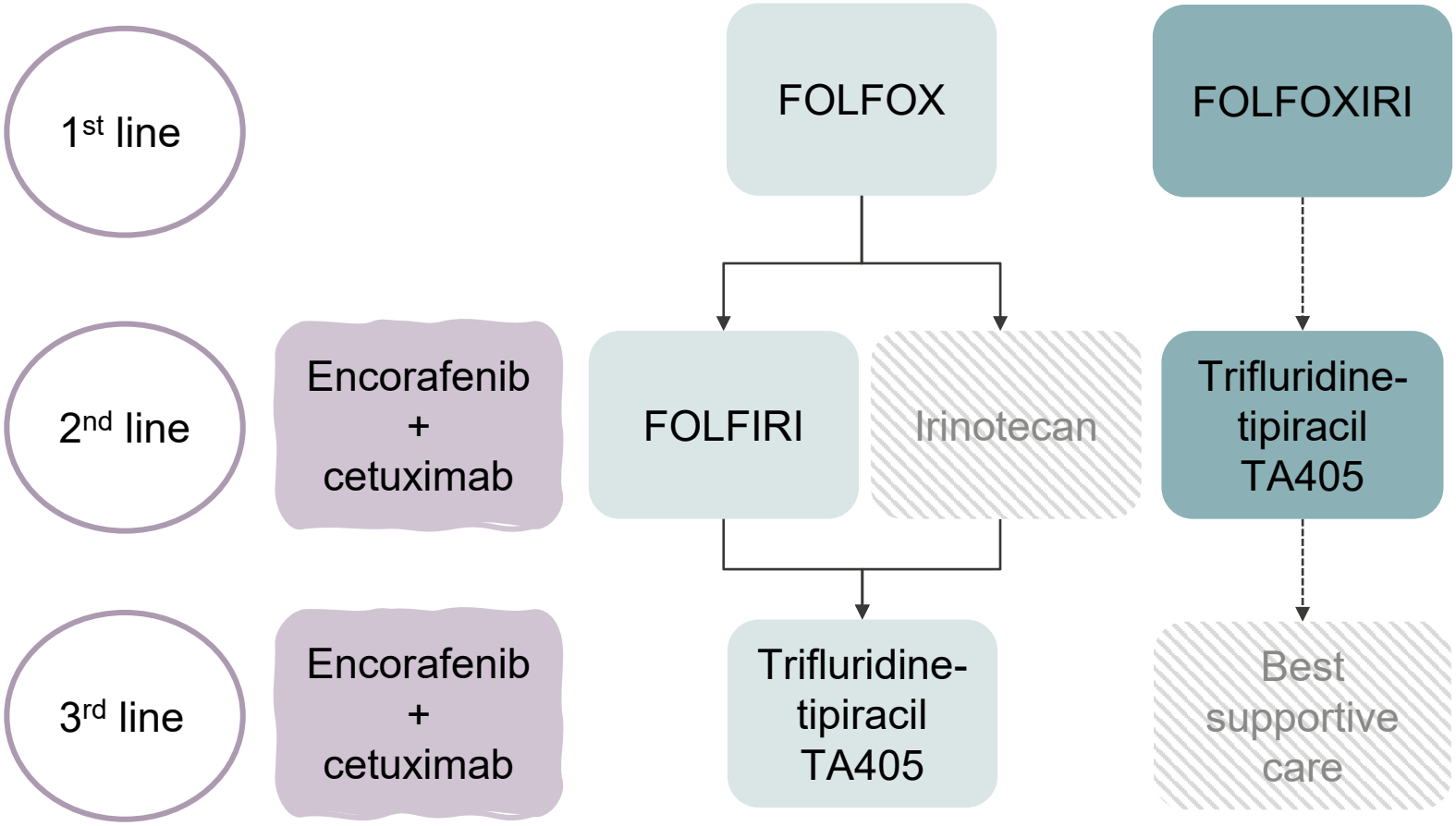
Company: trifluridine–tipiracil used either at 2nd-line if all options are given in one regimen or at 3rd-line if given sequentially (e.g. FOLFOX 1st-line and FOLFIRI at 2nd-line).

ERG: FOLFOXIRI 1st line (2nd line trifluridine-tipiracil) currently applies to a minority of patients, potential to increase if encorafenib + cetuximab approved at 2nd line against trifluridine–tipiracil

- *Does everyone agree that single agent irinotecan is an inappropriate comparator?*
- *Is trifluridine-tipiracil an appropriate comparator after 1 prior therapy?*

Appropriate comparators at 3rd line

Company disregards best supportive care



◉ *What are the comparators at 3rd line?*

Clinical effectiveness

No head to head trials for encorafenib + cetuximab with relevant comparators

Encorafenib + cetuximab
vs
FOLFIRI

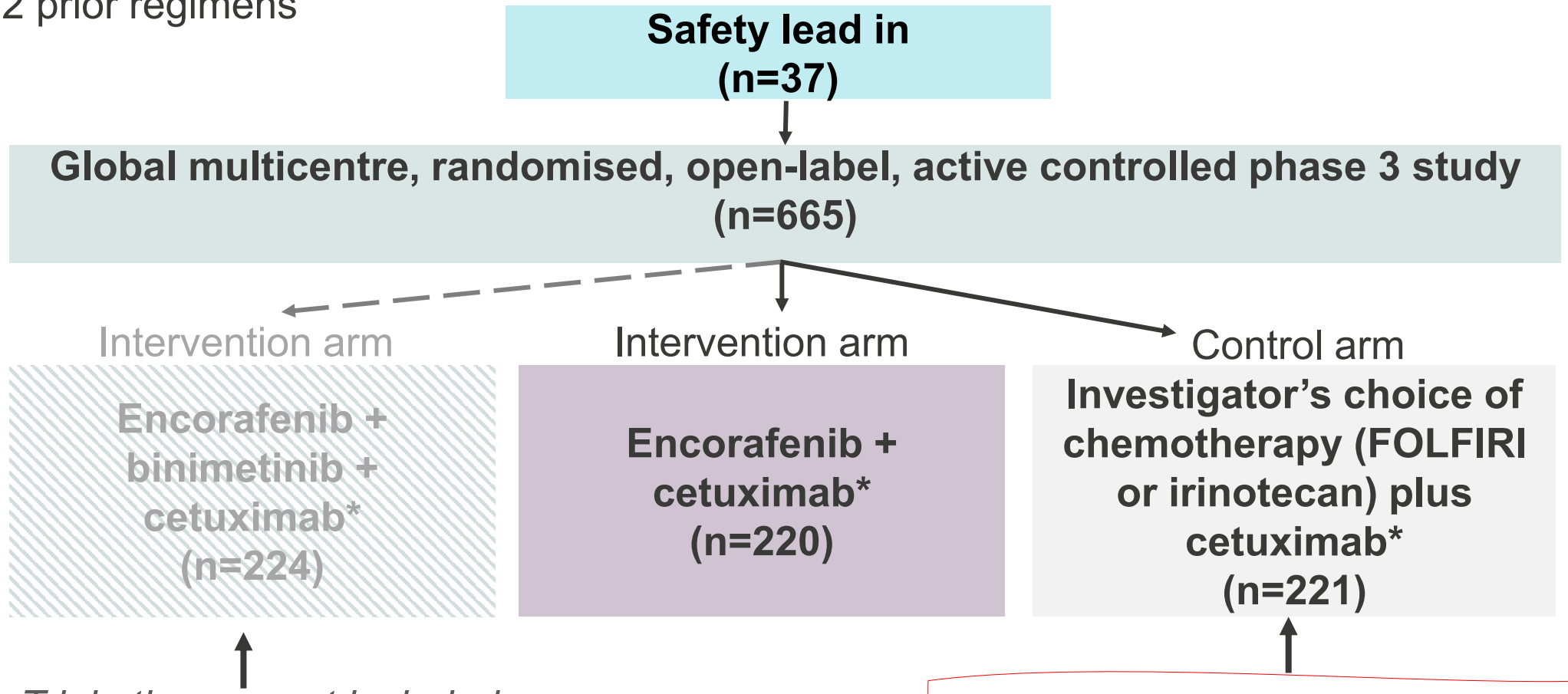
Main trial has blended comparator not used in NHS practice

Indirect treatment comparison has no common link

Encorafenib + cetuximab vs FOLFIRI: BEACON CRC trial

Comparator in key trial does not reflect UK clinical practice

Population: BRAF V600E-mutant metastatic colorectal cancer, progressed after 1 or 2 prior regimens



Triple therapy not included in company submission

**NICE guidance restricts the use of cetuximab to first-line therapy in England – trial does not represent clinical practice*

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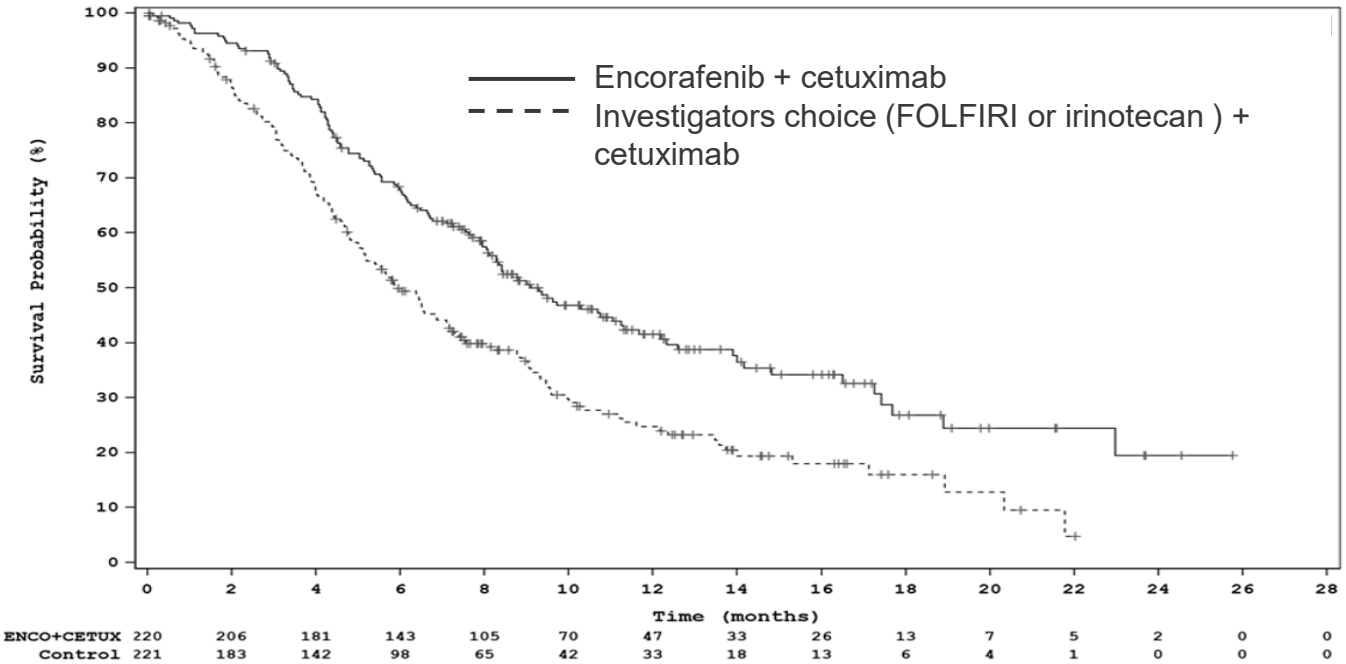
Encorafenib + cetuximab vs FOLFIRI: BEACON CRC results

Trial doesn't address decision problem. Longer survival for encorafenib + cetuximab vs investigators' choice (FOLFIRI or irinotecan) + cetuximab

Kaplan Meier (KM) data from BEACON CRC for overall survival



Outcome	Encorafenib + cetuximab	(FOLFIRI or irinotecan) + cetuximab	Difference between the study groups
OS, median no. months (95% CI)	9.30 (8.05-11.30)	5.88 (5.09-7.10)	HR=0.61 (0.48-0.77), p<0.0001
PFS, median no. months (95% CI)	4.27 (4.07-5.45)	1.54 (1.48-1.91)	HR=0.44 (0.35-0.55), p<0.0001
ORR, % (95% CI)	19.5 (14.5- 25.4)	1.8 (0.5-4.6)	p<0.0001

◉ *Does Committee consider encorafenib + cetuximab more effective than **FOLFIRI + cetuximab?***

Encorafenib + cetuximab vs FOLFIRI: additional clinical trial evidence. Indirect treatment comparison

No head to head trials for encorafenib + cetuximab with relevant comparators

Company identified 1 randomised controlled trial (Peeters et al. 2010/2015) for indirect treatment comparison (ITC) of encorafenib + cetuximab vs FOLFIRI

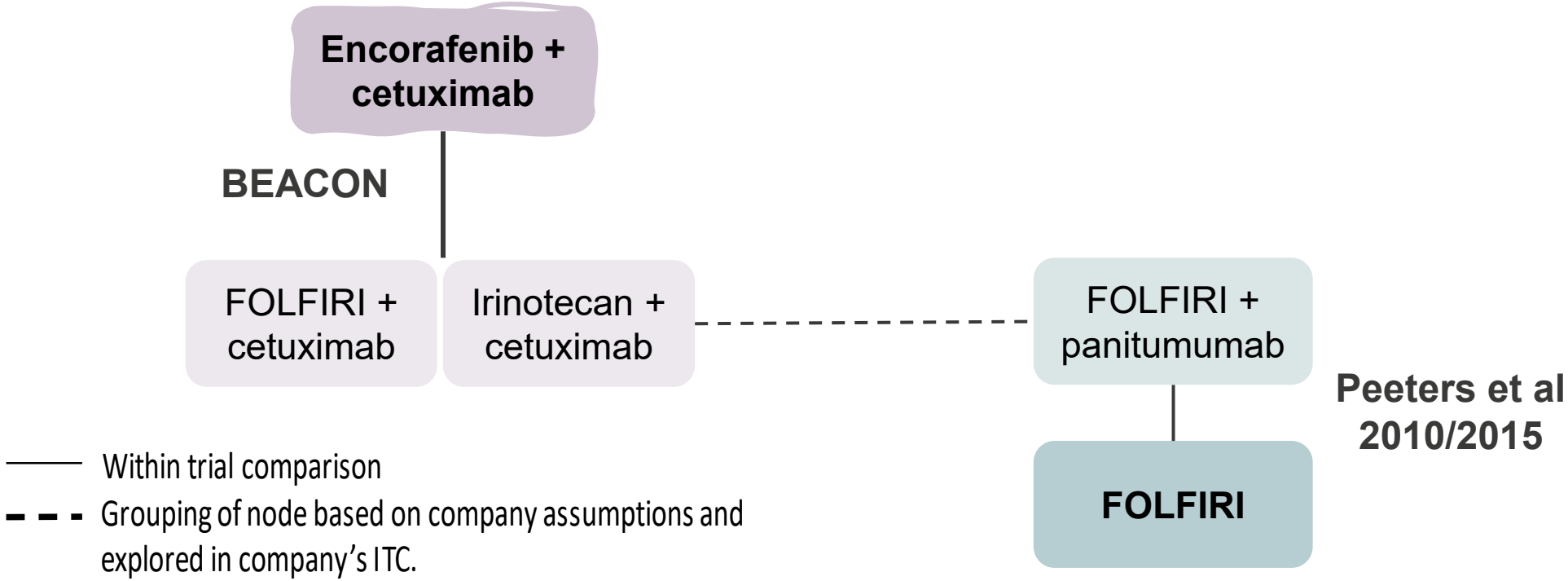
Study title	**BEACON CRC**	**Peeters et al. 2010/2015**
Study design	RCT phase 3	RCT phase 3
Population	BRAF V600E-mutant metastatic colorectal cancer ≤2 prior therapies	Metastatic colorectal cancer, 1 prior chemotherapy **Subpopulation BRAF-mutant**
Intervention(s)	Encorafenib + cetuximab	FOLFIRI + panitumumab
Comparator(s)	Investigators choice (FOLFIRI or Irinotecan) + cetuximab	FOLFIRI
1◦ outcomes	Outcomes for triple arm therapy	Progression-free survival and overall survival
2◦ endpoints	Overall survival, overall response rate, progression free survival	Overall response rate

Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf; FOLFIRI, folinic acid plus 5-fluorouracil plus irinotecan. RCT Randomised controlled trial

Encorafenib + cetuximab vs FOLFIRI: Company's indirect treatment comparison

No common comparator – not possible to connect network

- No common comparators between BEACON CRC and Peeters et al
- So, company assumes equivalence between comparators
  1. FOLFIRI and irinotecan equally effective
  2. Cetuximab and panitumumab equally effective



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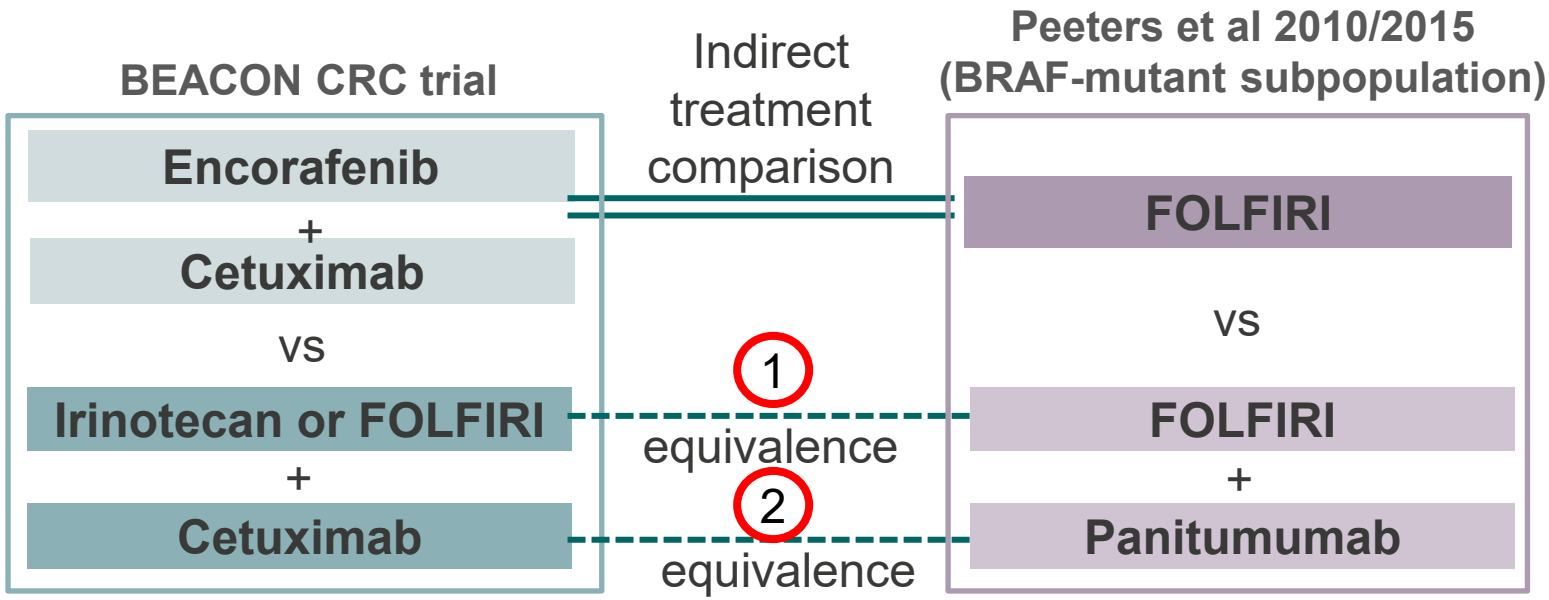
Encorafenib + cetuximab vs FOLFIRI: Company's Indirect treatment comparison – another visual

Company assumes equivalence between comparators in trials for ITC



1. **FOLFIRI and irinotecan have equivalent clinical effectiveness**
   - Assumption from 2 clinical trials (not BRAF mutant population)
2. **Cetuximab and panitumumab have equivalent clinical effectiveness**
   - Equivalence assumed based on class effect, both EGRF inhibitors
   - Supported by NICE clinical experts and committee opinion NICE TA439

Encorafenib + cetuximab vs FOLFIRI:
2 assumptions of the indirect treatment comparison

1. Company assumes FOLFIRI and irinotecan equally effective

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Source ERG critique of company technical engagement response p6, figure 3

ERG: treatments in control arm not randomised
company data suggest big differences between FOLFIRI + cetuximab vs irinotecan + cetuximab

Company: Overall and progression free survival curves split between control arm treatments are broadly aligned

Clinical experts: limited data but efficacy of FOLFIRI and irinotecan equal for wildtype and BRAF-mutant populations

◉ *What's the committee's views on the assumption of equivalence for FOLFIRI and irinotecan? If equivalent, why aren't they used equally in NHS?*

Encorafenib + cetuximab vs FOLFIRI:
2 assumptions of the indirect treatment comparison

2. Cetuximab and panitumumab equally effective

- Company assumes class effect applies as both are EGFR inhibitors
- Company's clinical experts support this
- Committee conclusion in NICE TA439 cetuximab and panitumumab for previously untreated metastatic colorectal cancer, 'cetuximab and panitumumab were likely to have similar effectiveness in treating RAS wild-type metastatic colorectal cancer'

◉ *What's the committee's views on the assumption of equivalence for cetuximab and panitumumab?*

Encorafenib + cetuximab vs FOLFIRI: benefit of cetuximab without encorafenib

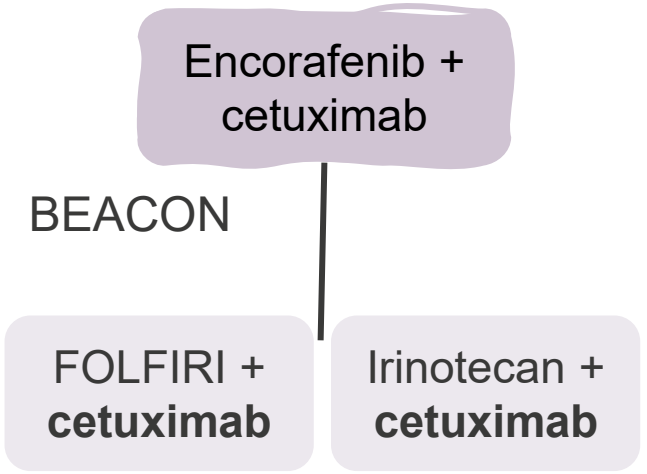
Limited evidence on clinical effectiveness of cetuximab without encorafenib for BRAF V600E

Company

- Need to remove benefit of cetuximab in control arm to estimate relative efficacy of encorafenib + cetuximab vs FOLFIRI.
- Point estimates from 2 published meta-analyses (Pietrantonio 2015; Rowland 2015) favour EGFR inhibitors for progression-free survival and overall survival vs chemotherapy or best supportive care alone
  - but small sample size, wide confidence intervals, not statistically significant

Clinical experts:

- Cetuximab is an effective treatment for BRAF V600E but less than the wild type.



ERG:
Prefer use of data direct from BEACON CRC to estimate efficacy of encorafenib + cetuximab vs FOLFIRI

◉ *Is cetuximab in combination with FOLFIRI or irinotecan, likely to provide additional clinical benefit for people with BRAF V600E mutations?*

Encorafenib + cetuximab vs FOLFIRI results indirect treatment comparison

BEACON CRC and ITC shows encorafenib + cetuximab improves overall survival and progression free survival compared with FOLFIRI

ERG use OS and PFS directly

Study	Overall survival (hazard ratio)	Progression free survival (hazard ratio)	
BEACON CRC trial	Encorafenib + cetuximab vs. (FOLFIRI or irinotecan) plus cetuximab		
	0.61 (0.48, 0.77)	0.44 (0.35, 0.55)	Direct comparison
Peeters et al. 2010/2015	FOLFIRI + panitumumab vs. FOLFIRI		
	0.64 (0.32, 1.28)	0.69 (0.32, 1.49)	Direct comparison
	Encorafenib + cetuximab vs. FOLFIRI		
BEACON CRC trial Peeters et al. 2010/2015	0.39 (0.19, 0.81)	0.30 (0.14, 0.68)	Indirect comparison

Company applies hazard ratio

◉ *What is the committee's view on the source of efficacy data for encorafenib + cetuximab vs FOLFIRI?*

◉ *Are results direct from BEACON CRC or from the ITC more appropriate?*

Encorafenib + cetuximab
vs
trifluridine-tipiracil

No direct trial data

Encorafenib + cetuximab vs trifluridine-tipiracil - additional trial evidence

Indirect treatment comparison not possible - no data for BRAF-mutant cancer

- Company naïvely compared encorafenib + cetuximab using data from BEACON with data on trifluridine-tipiracil from RECOURSE
- RECOURSE not done in BRAF mutant

Title	**BEACON CRC**	**RECOURSE (Mayer 2015)**
Design	RCT phase 3	RCT phase 3
Population	BRAF V600E-mutant metastatic colorectal cancer ≤2 prior therapies	Metastatic colorectal cancer refractory or intolerant to standard therapies >60% had ≥4 prior therapies
Intervention(s)	Encorafenib + cetuximab	Trifluridine-tipiracil
Comparator(s)	Investigators choice (FOLFIRI or Irinotecan) + cetuximab	Best supportive care
1◦ outcomes	Triple arm therapy outcomes only	Overall survival
2◦ endpoints	Overall survival, overall response rate, progression free survival	Performance status, progression free survival

Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf; FOLFIRI, folinic acid plus 5-fluorouracil plus irinotecan. RCT randomised controlled trial

Encorafenib + cetuximab vs trifluridine-tipiracil: company's naïve comparison

Populations differ between 2 sources: BRAF mutant vs BRAF wild-type

Survival from RECOURSE trial and BEACON trial

Study	Treatment	Overall survival	Progression Free Survival
RECOURSE	**Trifluridine-tipiracil**	**7.1 (6.5, 7.8)**	**2.0 (1.9, 2.1)**
	Placebo	5.3 (4.6, 6.0)	1.7 (1.7, 1.8)
BEACON	**Encorafenib + cetuximab**	**9.3 (8.1, 11.3)**	**4.3 (4.1, 5.5)**
	FOLFIRI / Irinotecan + cetuximab	5.9 (5.1, 7.1)	1.5 (1.5, 1.9)

Company: adjusts for difference in survival for BRAF-mutant vs BRAF wild-type populations using hazard ratios from the Peeters 2010/15 trial

- acknowledge the uncertainty of approach, but highlight paucity of data available

Outcome	BRAF V600E versus BRAF wild-type hazard ratio
Overall survival	4.0 (2.8, 5.6)
Progression free survival	3.6 (2.5, 5.0)

◉ Do the population differs in ways other than histology? Is this approach valid?

Encorafenib + cetuximab vs trifluridine-tipiracil:

Difference in survival BRAF V600E mutant vs wild type

Company presented a meta-analysis (Safaee Ardekani et al. 2012) with an alternative estimate to adjust for difference in survival between BRAF and wild-type . Scenario uses HR= 2.24

	Wildtype vs BRAF V600E adjustment for trifluridine tipiracil				
Source	Peeters et al 2015	Safaee Ardekani 2012	MRC FOCUS (ERG alternative from meta analysis)	BEACON	
Treatment	FOLFIRI + panitumumab vs FOLFIRI	Meta-analysis - 26 trials	FU, FU/ irinotecan, FU/oxilaplatin	(FOLFIRI or irinotecan) + cetuximab	Encorafenib + cetuximab
OS proportions	HR=4.00	HR=2.24	HR=1.82		
3 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Used in Company model

Key: FU, Fluorouracil

Source: ERG critique of company TE response table 1 p5

Encorafenib + cetuximab vs trifluridine-tipiracil:

ERG's questions validity of naïve comparison

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Source: ERG critique of company technical engagement response p3, figure 1

ERG

- RECOURSE not restricted to BRAF mutation
- Survival considerably worse than encorafenib + cetuximab
- RECOURSE survival curve similar to BEACON trial BRAF V600E mutant control arm
- Raises concerns around naïve comparison and application of BRAF V600E hazard ratio

Encorafenib + cetuximab vs trifluridine-tipiracil: effect of prior treatment regimes on overall survival

RECOURSE trial data shows longer OS with increased prior treatments
ERG does not use these data

RECOURSE overall survival (OS) Kaplan-Meier curves by number of prior regimens

Source: Company technical engagement response p71, figure 6

Company: shows trifluridine-tipiracil more effective with later lines of therapy

May be explained by presence of good prognostic characteristics

Prior regimens	HR for OS (95% CI)
2	1.05 (0.68-1.63)
3	0.74 (0.51-1.08)
4+	0.59 (0.47-0.73)

ERG Prefer BEACON control arm as proxy for trifluridine tipiracil: Generalisability of the RECOURSE trial to the BEACON population is limited.Substantial differences in treatment history. Confounding variables may differ between prior treatment subgroups

◉ *What is the committee's view on the RECOUSE data as the source for the naïve comparison?*

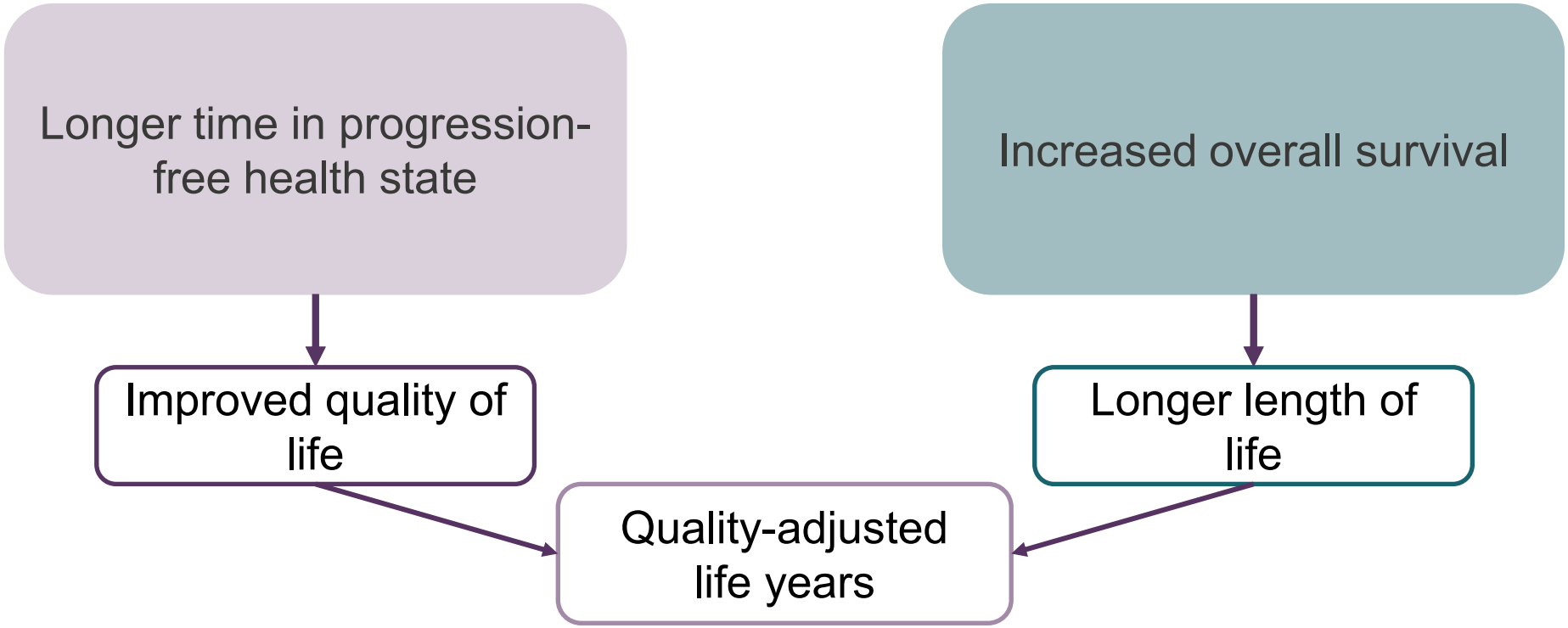
Encorafenib + cetuximab: summary of clinical effectiveness evidence

Comparator	Company		ERG	
	Data used	**Rationale**	**Data used**	**Rationale**
FOLFIRI	BEACON control arm with an indirect treatment comparison with assumptions because of no link	BEACON includes cetuximab in comparator arm but not used in practice; ITC adjusts for this	BEACON control arm	Uncertain assumptions needed to form network. Benefit of cetuximab low in BRAF V600E population.
Trifluridine-tipiracil	Naïve comparison with RECOURSE trial HR applied from Peeters et al for BRAF V600E mutant vs wild type	Best approach with available evidence. RECOURSE trial needs adjusting because population different to BEACON	BEACON control arm	Generalisability of the RECOURSE trial to the BEACON population is limited. Poor outcomes from RESOURCE trial likely biases in favour of encorafenib + cetuximab

◉ *Which reflect comparisons that generate valid results?*

Cost effectiveness

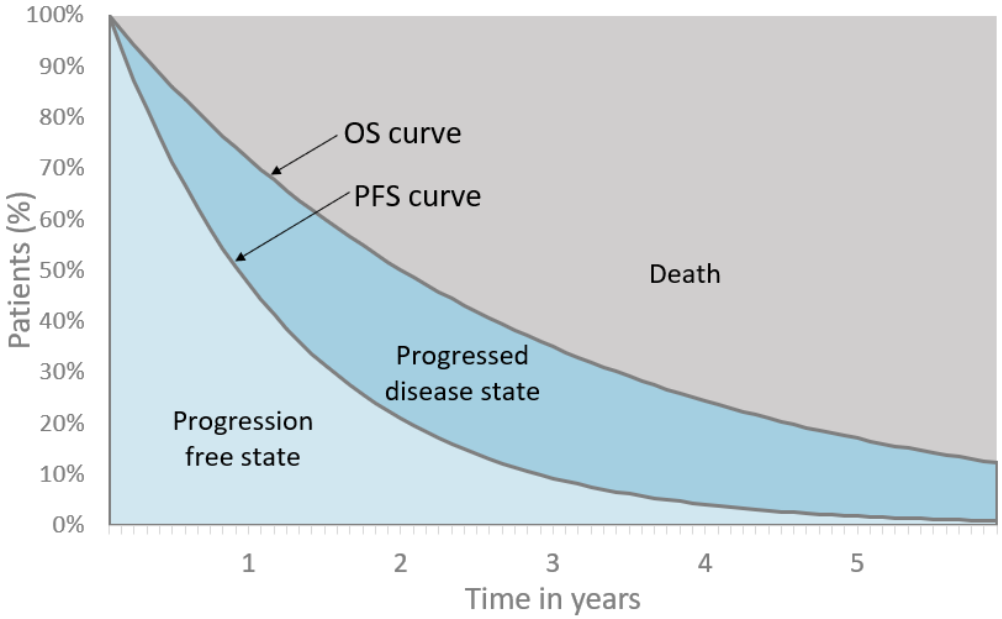
Overview: how quality-adjusted life years accrue



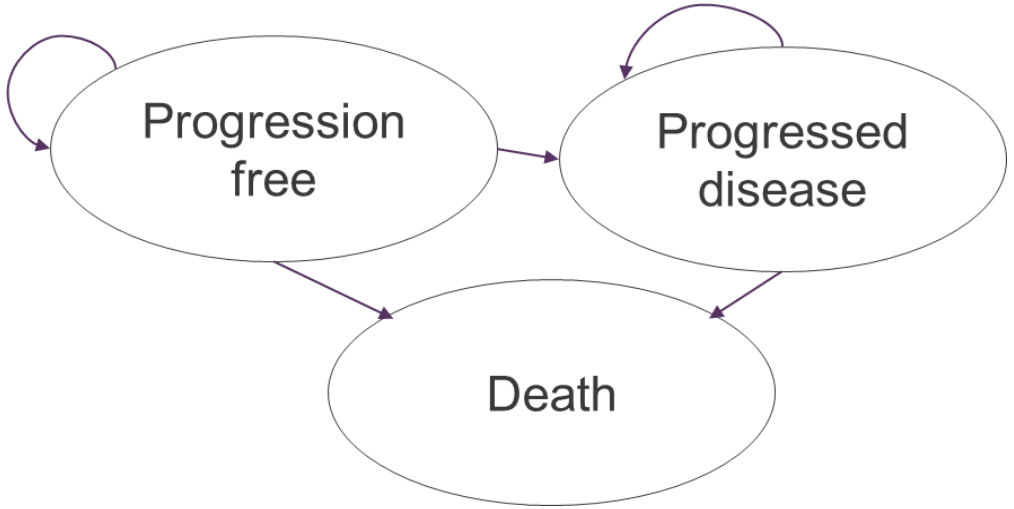
Utility values used in company model in response to technical engagement

	Mean utility		
Treatment	**Encorafenib + cetuximab**	**FOLFIRI**	**Trifluridine- tipiracil**
Source	BEACON CRC	BEACON CRC	BEACON CRC average of encorafenib with cetuximab and FOLFIRI with cetuximab
Progression-free	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]

Company's model structure



Partitioned survival model, 3 health states



- Monthly cycle
- 10 year time horizon

Company's key assumptions

- Time on treatment = progression free survival
- Post progression survival costs same for all comparators
- Adverse events affect only costs; BEACON EQ-5D measures quality of life
- Vial sharing for intravenous therapy with no wastage.
- Patients do not change treatment in 'progression free' health state
- At progression:
  - 1 month of treatment with trifluridine-tipiracil
  - No further treatment after trifluridine-tipiracil

◉ *Are these assumptions reasonable?*

Summary: extrapolating overall survival, progression free survival, and time to treatment discontinuation vs FOLFIRI

Key driver of cost effectiveness: extrapolating overall survival + data source for comparators

		Base case		ERG sensitivity analysis
		Company	**ERG**	
Overall survival	**Data source**	BEACON trial May 2020 data cut, HR from ITC applied for comparator arm	BEACON trial Aug 2019	None
	Extrapolation	Jointly fitted log-logistic to May 2020 data cut	Piecewise exponential to Aug 2019 data cut	Alternative extrapolations, piecewise from 3 months
Progression free survival		Jointly fitted log-logistic May 2020	Raw Kaplan-Meier curves using Aug 19	Piecewise from 2 months using Aug 19 data cut
Time to treatment discontinuation		Assumed equal to progression free survival		None

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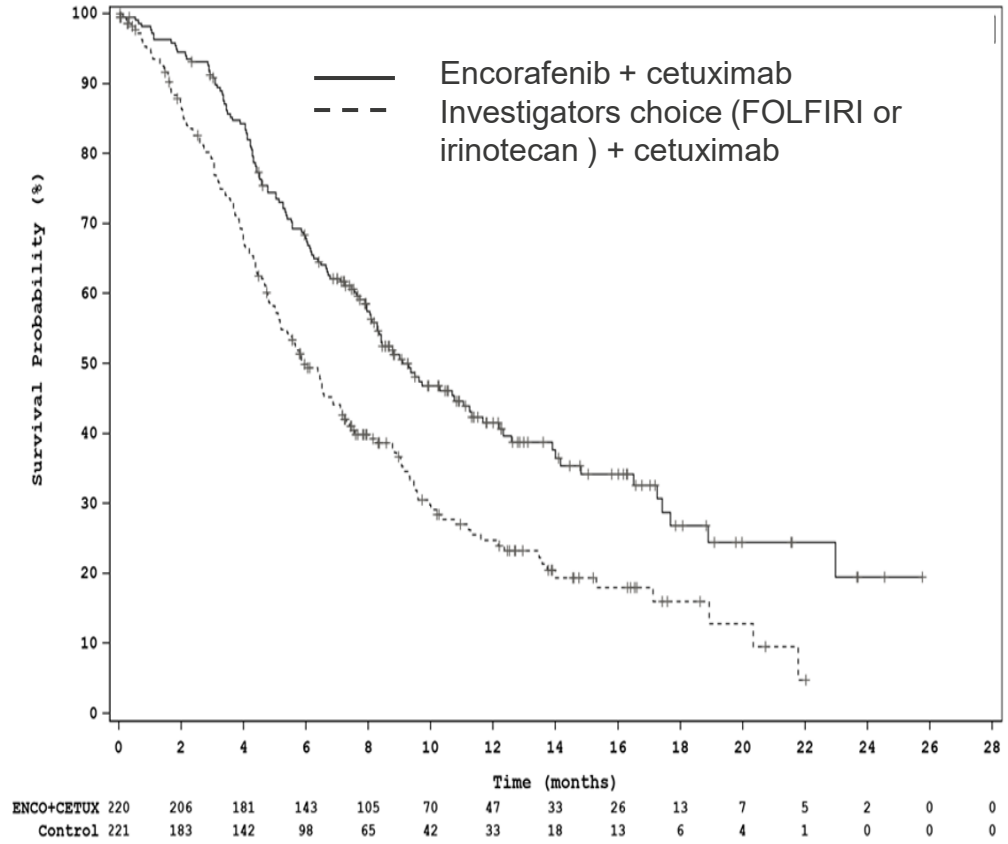
Overall survival: encorafenib + cetuximab: BEACON CRC

Unplanned data cut from company in response to technical engagement

Data set has been fully validated by the company

BEACON overall survival for encorafenib + cetuximab vs control (August 2019)



BEACON overall survival for encorafenib + cetuximab vs control (May 2020)

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Source: company response to technical engagement p13, 15, figure 2 & 3

◉ *Does committee consider it appropriate to use the unplanned data cut?*

Company's extrapolation of overall survival: parametric models fitted to encorafenib + cetuximab BEACON data

Selected log-logistic model from goodness of fit, visual comparison and clinical expert input

BEACON May 2020 data cut overall survival

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Source: company response to technical engagement p19, figure 6

ERG's extrapolation of overall survival: parametric models fitted to encorafenib + cetuximab BEACON data

All parametric curves fitted poorly to trial data – piecewise approach preferred
ERG estimates much shorter than company's

ERG (August 2019 data cut):

- All the curves fitted poorly to trial data
- Cumulative hazard → change of trajectory of hazard rate at 2.8 months
- KM data applied before 2.8 months
- Models after 2.8 months
- Chose exponential model on AIC, BIC, plausibility

Overall survival predictions encorafenib + cetuximab		% alive at:		
		3 yrs	5 yrs	10 yrs
ERG (Aug 19 data cut) beyond 2.8 months	**Exponential**	xxx	xxx	xxx
	Weibull	xxx	xxx	xxx
	Log-normal	xxx	xxx	xxx
	Log-logistic	xxx	xxx	xxx
	Gompertz	xxx	xxx	xxx
	G. gamma	xxx	xxx	xxx
Company (updated May 2020)	Log-logistic	xxx	xxx	xxx
	Piecewise log-logistic	xxx	xxx	xxx

Cumulative hazard plot of encorafenib OS data from BEACON CRC trial

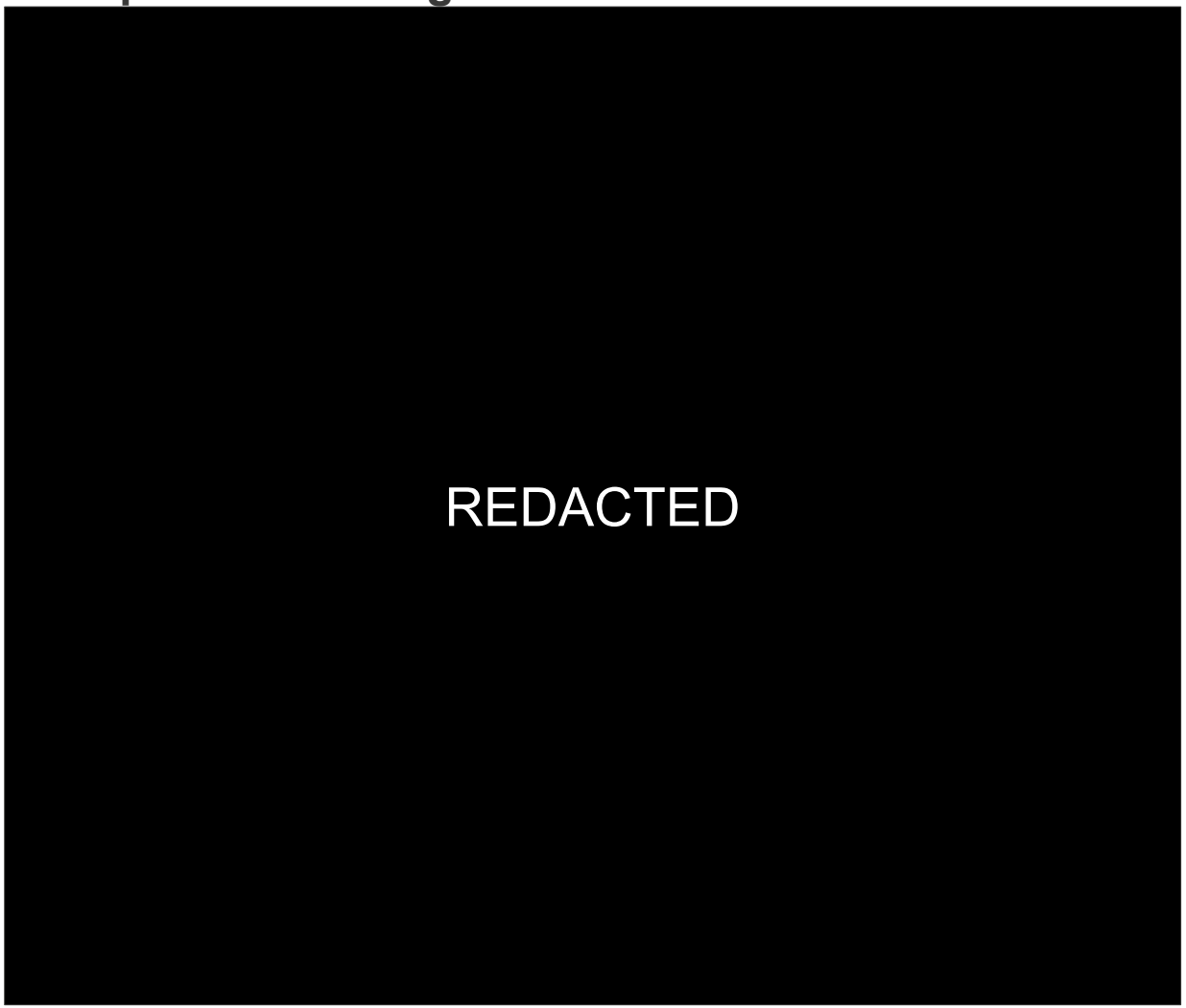
REDACTED

Source: ERG report p81, figure 18

Company's response to technical engagement: extrapolation of overall survival encorafenib + cetuximab

ERG's piecewise extrapolation appears pessimistic when compared to the observed data

Extrapolation of August 2020 data cut



Source: company response to technical engagement p16, figure 4

Company:
BEACON CRC 2020 dataset suggests ERG's preferred piecewise/exponential curve pessimistic; it estimates 14.7% alive at 2 years and 5.2% alive at 3 years.

ERG – response:

- Little difference between curves by goodness of fit AIC criteria
- Limited information provided for scenarios analyses
- Scenarios using piecewise curves similar to ERG original approach not adequately explored
- Need to explore other suitable curves

◉ *Which approach is best to extrapolate overall survival for encorafenib + cetuximab?*

Note: title of graph amended post committee, factual inaccuracy identified by company during meeting. Date in title changed from May 2020 to August 2019

Company's extrapolation of overall survival & progression free survival: FOLFIRI

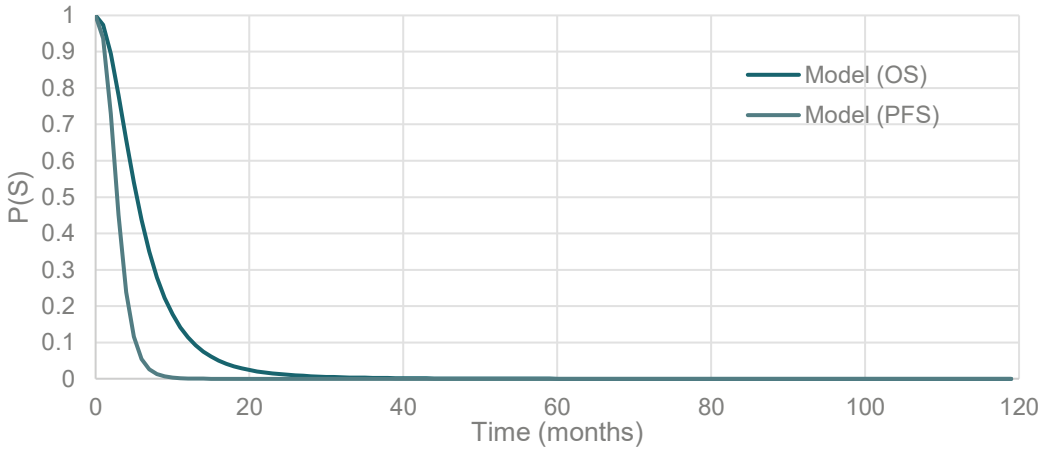
Applies hazard ratio from ITC to encorafenib + cetuximab curves to model FOLFIRI

Company base case: To model FOLFIRI - Hazard ratio from ITC applied to encorafenib + cetuximab curves – log logistic

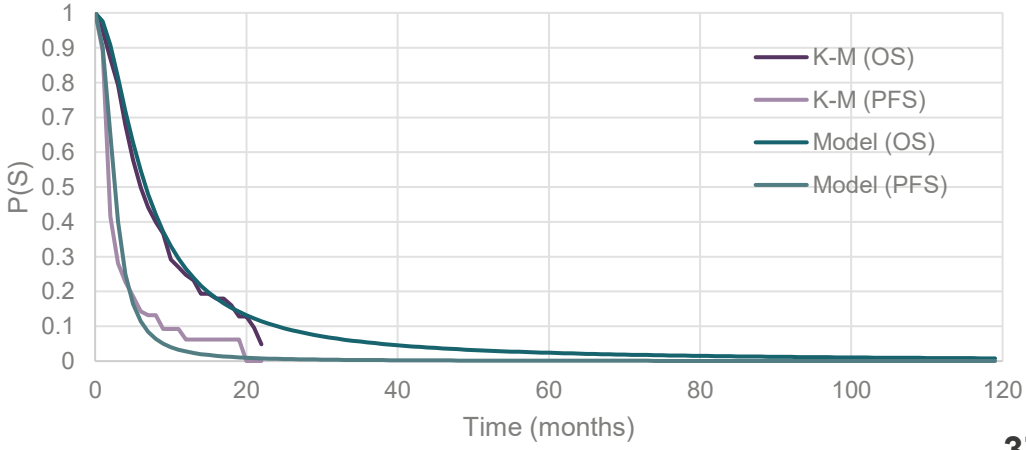
Company scenario analysis: clinical experts note limited benefit of cetuximab with FOLFIRI

Scenario provided where OS and PFS of FOLFIRI estimated using BEACON **control** arm. Company chose log-logistic curve based on AIC/BIC, visual inspection and clinical expert opinion

Model fits for Base-case FOLFIRI (generated from HRs applied to encorafenib + cetuximab from ITC)



Model fits for scenario FOLFIRI (generated from beacon CRC control data)



Source: company submission p109, figures 11 & 12

NICE

Note: slide adjusted after committee meeting, factual inaccuracy identified by company. 'Clinical expert opinion' added to second box.

ERG's extrapolation of overall survival: FOLFIRI

Company's approach varies from considerably from observed BEACON control arm data

ERG: Company's base case approach (applying HR from ITC) results in estimates that vary considerably from BEACON CRC control arm

Given concerns around ITC, ERG modelled FOLFIRI by fitting curves to control arm of BEACON CRC trial:

- All curves fitted poorly to trial data
- Both arms of the BEACON CRC trial modelled simultaneously using 2.8 months as time 0

◉ *Which approach is most appropriate for extrapolating overall survival for FOLFIRI?*

- *Application of ITC hazard ratio*
- *Beacon control data – loglogistic extrapolation*
- *Piecewise approach – exponential curve using 2.8 months as time 0*

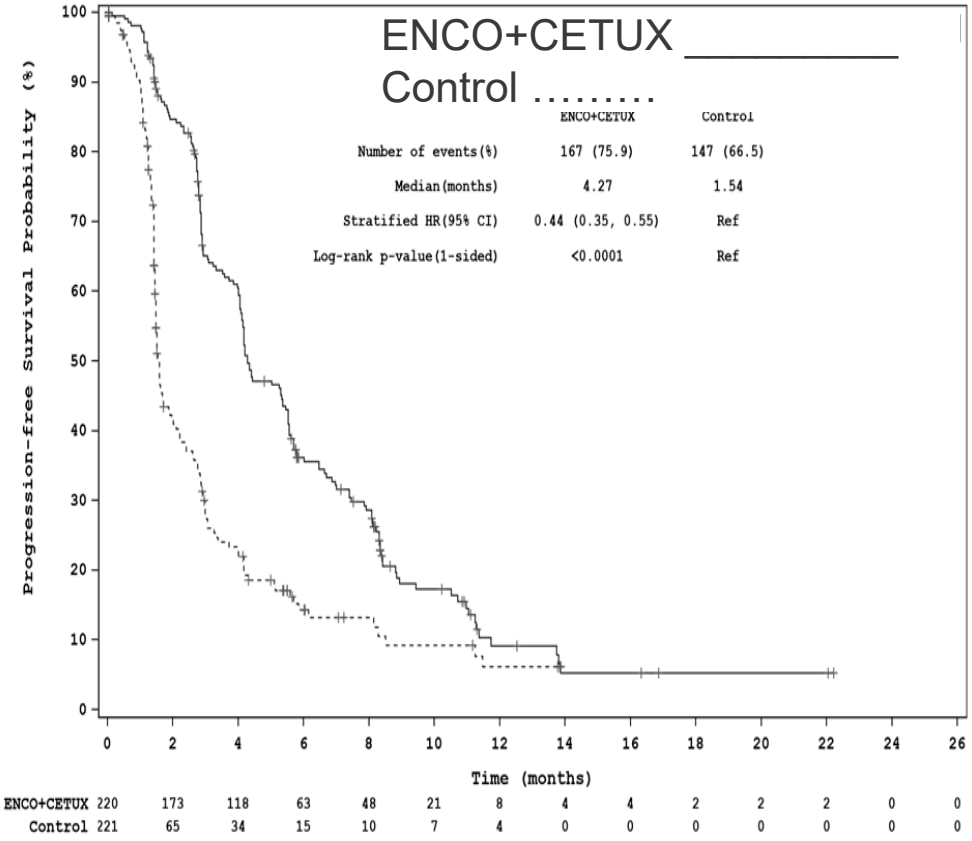
Company modelling of overall survival and BEACON CRC trial control arm (Aug 2019)

Source ERG report p79, figure 17

Overall survival predictions FOLFIRI		% alive at:		
		3 yrs	**5 yrs**	**10 yrs**
ERG (Aug 19 data, model fitted beyond 2.8m, no HR applied)	**Exponential**	xxx	xxx	xxx
	Weibull	xxx	xxx	xxx
	Log-normal	xxx	xxx	xxx
	Log-logistic	xxx	xxx	xxx
	Gompertz	xxx	xxx	xxx
	G. gamma	xxx	xxx	xxx
Company (May 2020)	Loglogisitc & HR from ITC	xxx	xxx	xxx
	Loglogisitc BEACON data	xxx	xxx	xxx

BEACON results progression free survival 2 data cuts

Encorafenib + cetuximab vs control August 2019



Source: company submission document B p53, figure 4

Company: Jointly-fitted loglogistic chosen on statistical and visual fit for both August 2019 and May 2020 data cuts

Encorafenib + cetuximab vs control May 2020

REDACTED

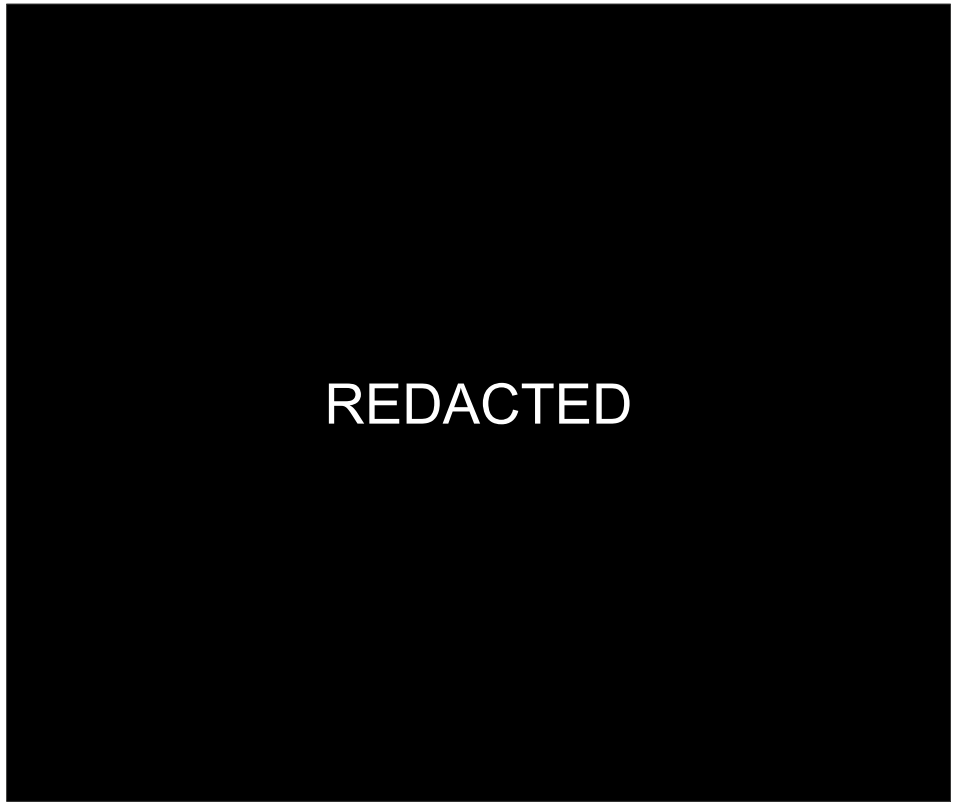
Source: Company response to technical engagement p15, figure 3

Model	AIC	BIC
Exponential	1195.84	1199.23
Weibull	1193.20	1199.99
Gompertz	1197.83	1204.62
Lognormal	1182.59	1189.38
Generalised gamma	1183.48	1193.67
Log-logisitc	1178.12	1184.91

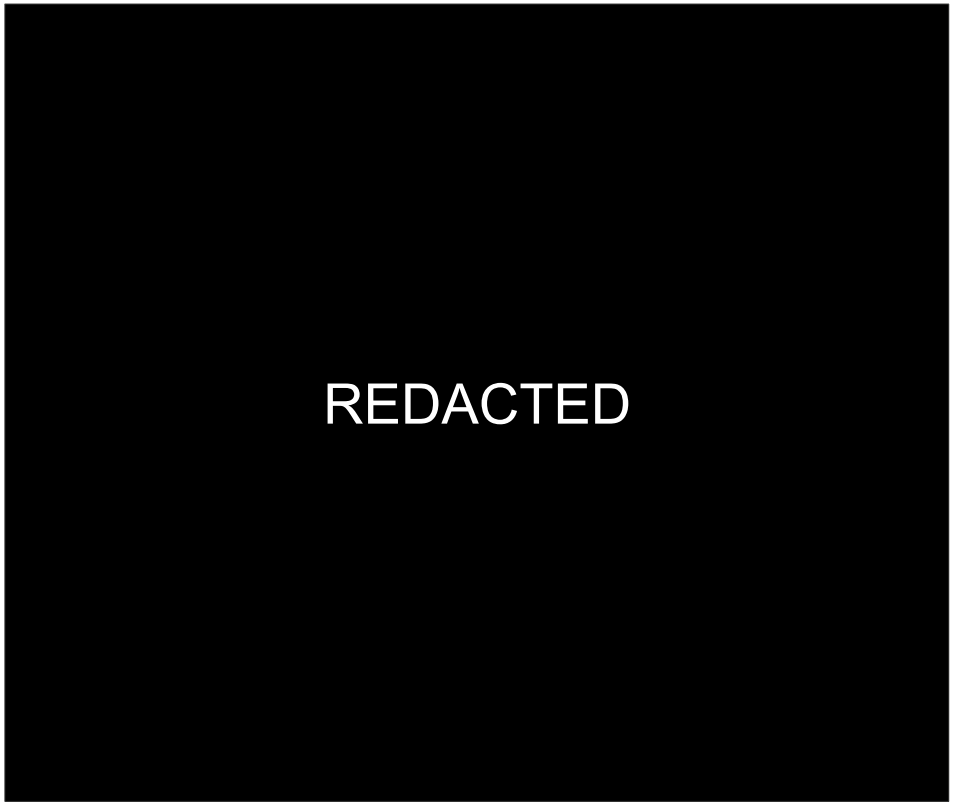
ERG extrapolating progression free survival, BEACON control arm

ERG models raw KM data because none of curves offered a good fit to observed data

Parametric survival curves fitted to PFS Aug 19 data for control arm of BEACON



Cumulative hazard of parametric survival curves fitted to PFS data for control arm of BEACON



Source: ERG report p85, figure 20 and 21

◉ *Is it appropriate to apply raw KM data to the model or use company extrapolations?*

Summary: extrapolating overall survival, progression free survival vs trifluridine-tipiracil

Key driver of cost effectiveness: extrapolating overall survival + data source for comparators

		Base case for trifluridine-tipiracil	
		Company	**ERG**
Overall survival	**Data source**	RECOURSE adjusted using HR from Peeters et al 2015	BEACON trial August 2019 control arm
	Extrapolation	Log-logistic	Piecewise exponential to August 2019 data cut
Progression free survival		Log-logistic extrapolation of RECOURSE data adjusted using HR from Peeters et al 2015	Raw Kaplan-Meier curves

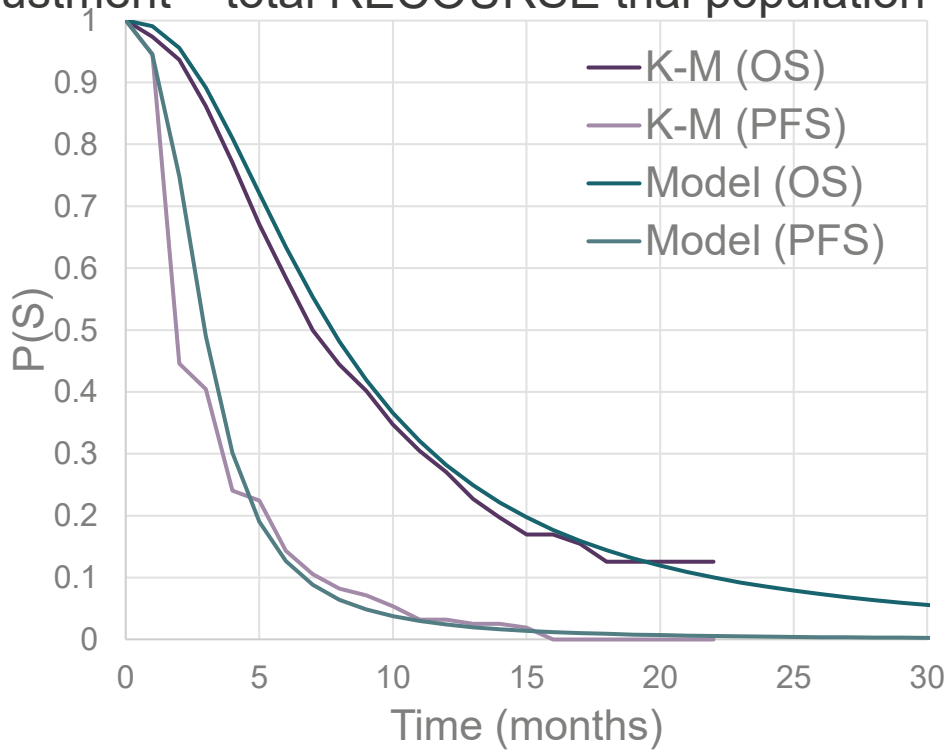
Company's extrapolating survival : trifluridine-tipiracil

Reconstructs individual patient level data from RECOURSE publication

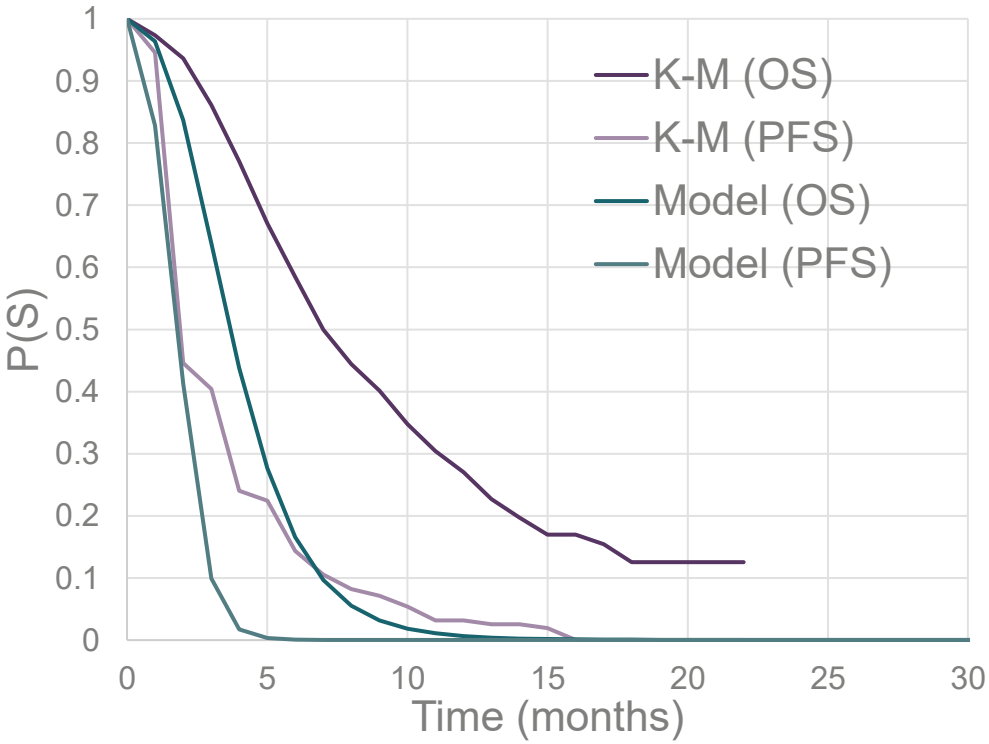
Company: Uses Guyot method then fits parametric models fitted to reconstructed data. Then applies HR applied from Peeters et al. for OS and PFS to adjust for outcomes in BRAF+ population

Outcome	BRAF V600E versus BRAF wild-type hazard ratio rounded
Overall survival	4.0 (2.8, 5.6)
Progression free survival	3.6 (2.5, 5.0)

OS and PFS curves without BRAF V600E adjustment – total RECOURSE trial population



OS and PFS curves with BRAF V600E adjustment



Source: company submission document B p119, figure 14 and 15

Encorafenib + cetuximab vs trifluridine-tipiracil: ERG's critique of the naïve comparison (repeated)

Source: ERG critique of company technical engagement response p3, figure 1

Company's time to treatment discontinuation encorafenib + cetuximab

Company assumes equal to progression free survival

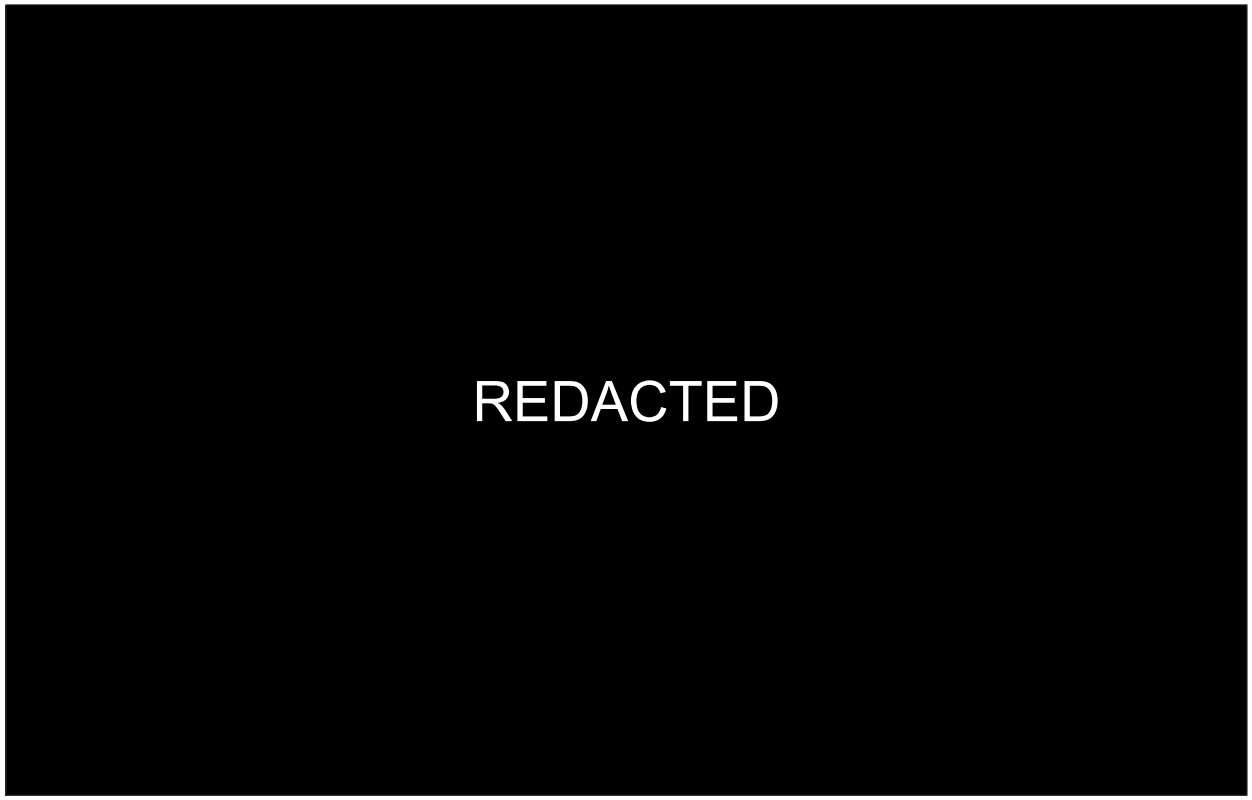
Company
- Provides scenario using TTD curve

ERG: Company scenario using TTD is counterintuitive, suggests that TTD curve results in lower costs than PFS curve, but KM data shows TTD generally lies above PFS

Possibly because Weibull used for TTD and log-logistic used for PFS

Source ERG report p74, figure 15

Progression free survival and time to treatment discontinuation KM curves: encorafenib + cetuximab August 2019 data cut



◉ *What is the best way to model time to treatment discontinuation?*

Drug wastage and relative dose intensities

Company assumes no waste; ERG assume waste

Drug wastage

Company base case assumes vial sharing where possible, based on clinical input
Company provides scenario that assumes vial wastage occurs in 10% patients

ERG considers company base case wastage assumption inappropriate

Relative dose intensities (RDI) - ratio of 'delivered' to the 'planned' dose intensity

Company: base case uses mean RDI and provides scenarios using median RDI. Mean is a better reflection of clinical practice

ERG: data for RDI from BEACON CRC is skewed, median RDI is higher than the mean, this could be because 'some patients faring poorly in the early period of the trial' mean RDI may underestimate cetuximab use

◉ *What is committees view on drug wastage and relative dose intensities?*

End of Life

	Company	ERG
Does encorafenib + cetuximab extend life by 3 months or more compared with current practice?	• BEACON CRC: median overall survival of 3.4 months for encorafenib + cetuximab vs control chemotherapy • Control arm included cetuximab which is expected to have additional benefit vs standard care in UK	• BEACON CRC: risk of bias unclear or high in several domains, magnitude of improvement is uncertain
Under standard care is the life expectancy of adults with previously treated BRAF-V600E mutation positive metastatic colorectal cancer less than 24 months?	• BEACON CRC: median OS with FOLFIRI or irinotecan + cetuximab = 5.9 months	Literature suggests median survival for previously treated patients with BRAF V600E mutation shorter than 12 months ERG agrees patient population meets this criterion

Technical team opinion:

- Results of BEACON CRC suggest that encorafenib + cetuximab increases survival by at least 3 months compared with comparator arm of the trial.
- Both the company's and the ERG's models estimate a survival gain of over 3 months, however the results are uncertain.

◉ *What are committee's views on whether end of life criteria are met?*

Issues resolved after technical engagement

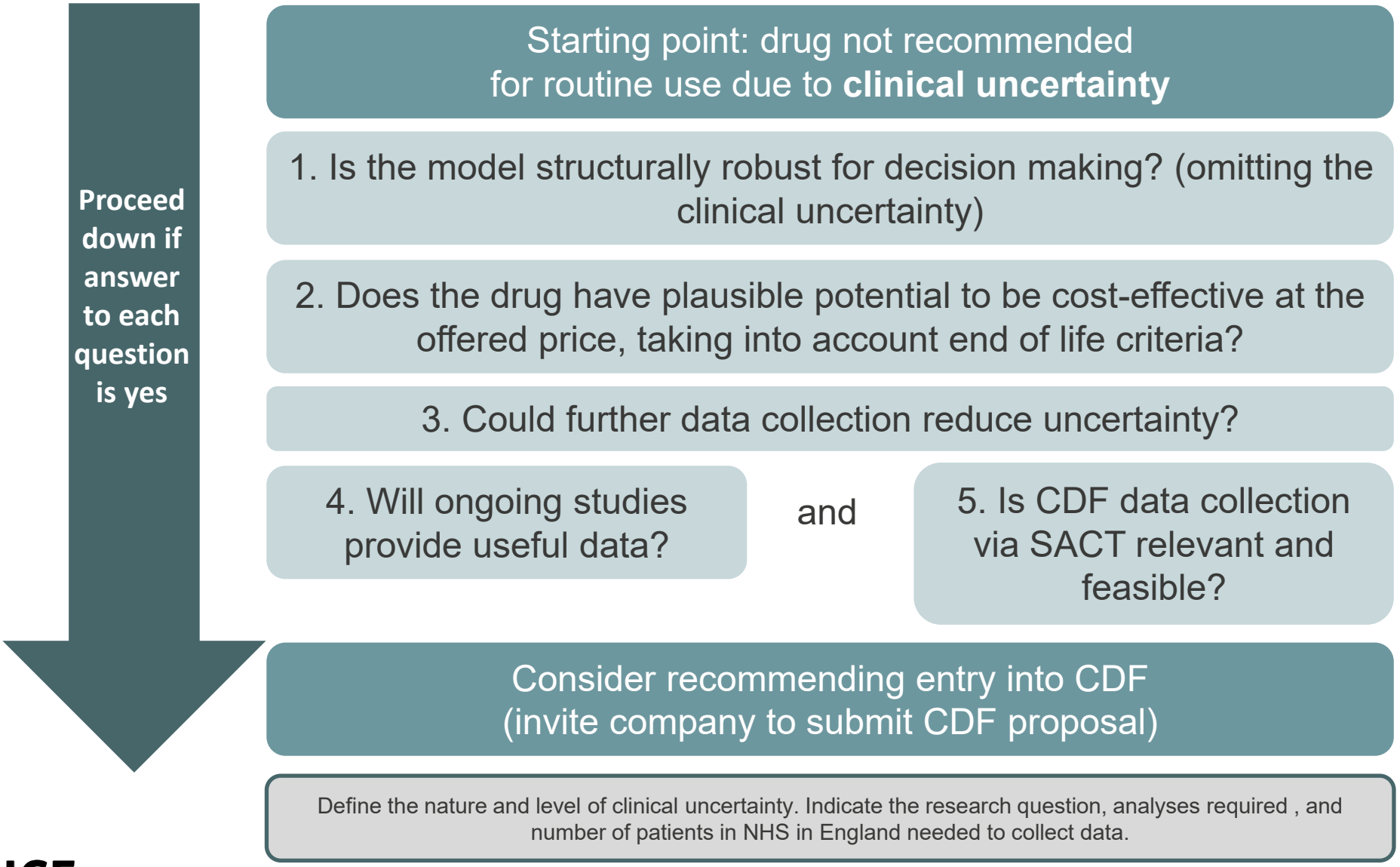
Summary	Stakeholder responses	Technical team consideration
Health utilities:	Company amended so utility value for progression free health state	Results more likely to reflect clinical practice
Costs:	Company amended to cost drugs at start of cycle - as recommended by ERG	Amendments more accurately reflect costs

All ICERs are reported in PART 2 slides because they include confidential PAS discounts for comparators and intervention

Key issues

1. Treatment pathway:
   - What is the appropriate position in the treatment pathway?
     - 2nd and/or 3rd line?
   - What are the relevant comparators at 2nd line?
2. In absence of a direct comparison, are the results valid from the:
   - indirect treatment comparison?
   - naïve comparison?
3. What are the most appropriate models for extrapolating:
   - Overall survival (OS)
   - Progression-free survival (PFS)
4. How should time to treatment discontinuation (TTD) be modelled?
5. Are the costs included appropriately?
6. Does encorafenib + cetuximab meet NICE's end of life criteria?

Committee decision making: CDF recommendation criteria



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