NICE National Institute for Health and Care Excellence

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

Chair's presentation

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ERG: Warwick Evidence
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Company: Pierre Fabre
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Recap: Decision problem

Marketing authorisation

Adults with metastatic colorectal cancer + BRAF V600E mutation and prior systemic therapy

- Must confirm BRAF V600E mutation with a validated test

Population

- Company position 2nd/ 3rd line
- License and NICE scope 2nd line use and later

Intervention

Encorafenib and cetuximab
Encorafenib route of administration/dose: oral capsules 300 mg (4*75 mg) daily
Encorafenib price: List price - £1,400 per pack of 42 x 75 mg capsules, £622.22 per pack of 28 x 50 mg capsules

Comparators

NICE scope - 4:

1. Folinic acid+fluorouracil + irinotecan (FOLFIRI)
2. Trifluridine-tipiracil*
3. Irinotecan
4. Best supportive care

Company - 2:

1. FOLFIRI
2. Trifluridine-tipiracil*

Clinical trial

BEACON CRC: Global multicentre, randomised, open-label, active controlled phase 3 study. Encorafenib + cetuximab vs 'investigator's choice' of chemotherapy [(FOLFIRI or irinotecan) + cetuximab]

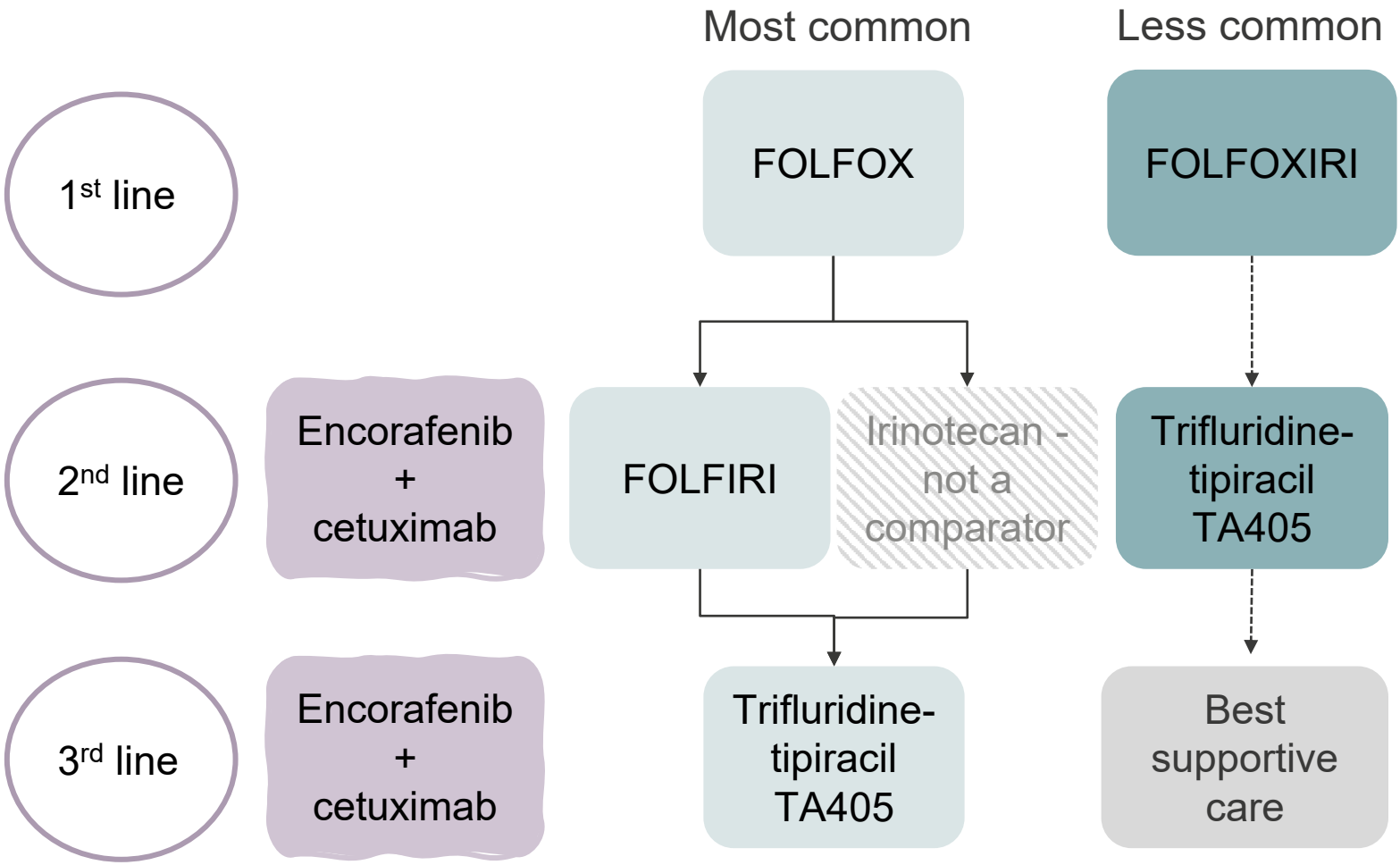
*after fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies or where not tolerated or unsuitable

Encorafenib + cetuximab: place in the treatment pathway

License allows encorafenib + cetuximab 2nd line and later

2nd line comparators: FOLFIRI; trifluridine-tipiracil. Committee dismissed irinotecan

3rd line comparators: trifluridine-tipiracil; best supportive care



FOLFOX = folinic acid, fluorouracil (5-FU) and oxaliplatin
FOLFORXIRI = folinic acid, 5-FU, irinotecan and oxaliplatin
FOLFIRI = folinic acid, 5-FU and irinotecan

Draft recommendations 1st committee meeting

- Encorafenib + cetuximab is not recommended
- Encorafenib + cetuximab meets NICE's criteria for being a life-extending treatment at the end of life
- Cost-effectiveness estimates are higher than what is normally considered a cost-effective use of NHS resources
- Collecting further data is unlikely to address the clinical uncertainty
- Current estimates for encorafenib + cetuximab did not have plausible potential to be cost effective
- Therefore, not recommended for the Cancer Drugs Fund

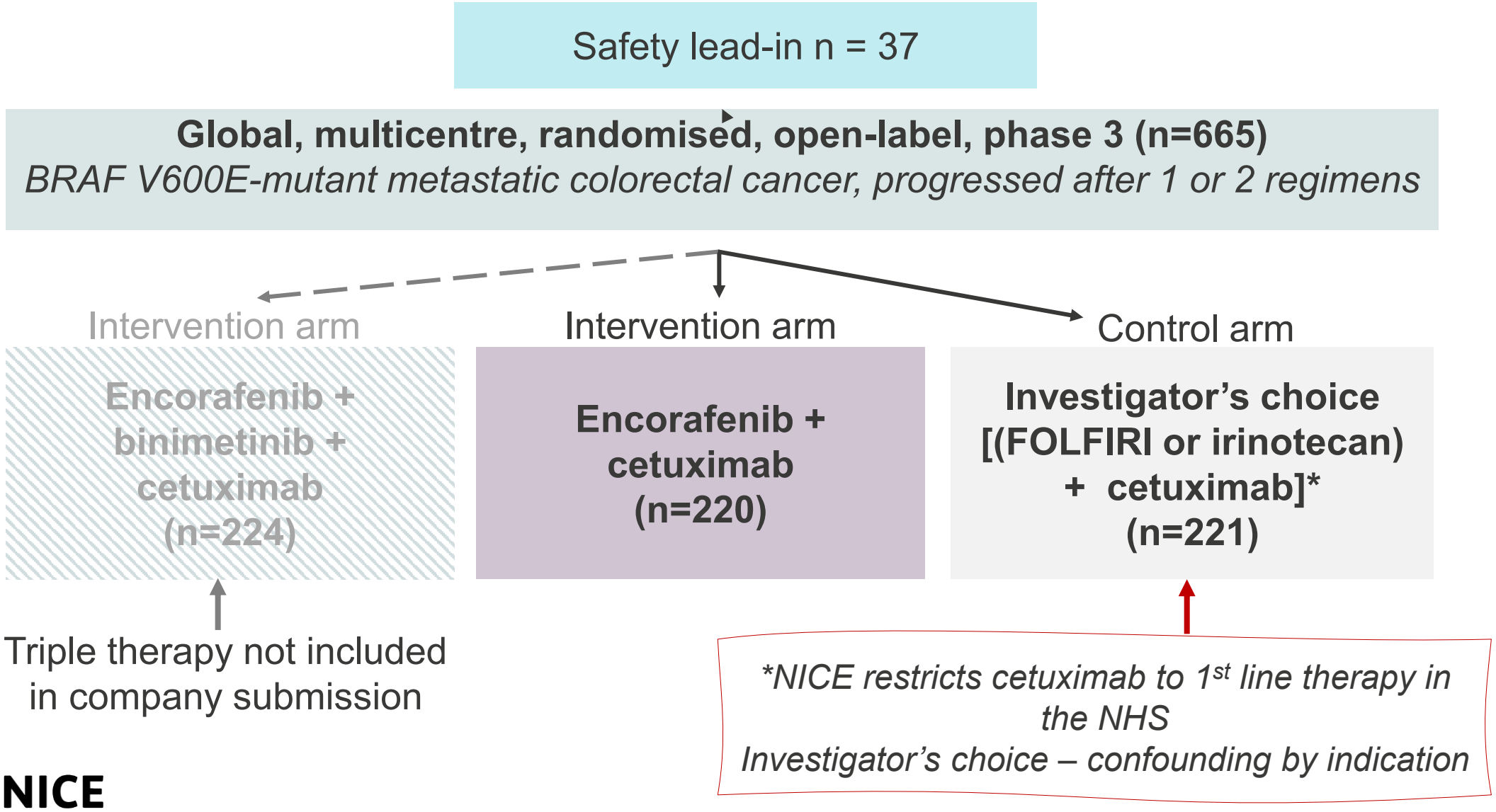
RECAP: clinical evidence

License allows use of encorafenib + cetuximab in 2nd line and later

Main trial has blended comparator not used in NHS practice

BEACON CRC trial

Comparator does not reflect decision problem or UK clinical practice
1º endpoint – Overall survival and overall response rate for triple therapy vs. control
2º endpoints include overall survival, progression free survival for 'doublet' vs control



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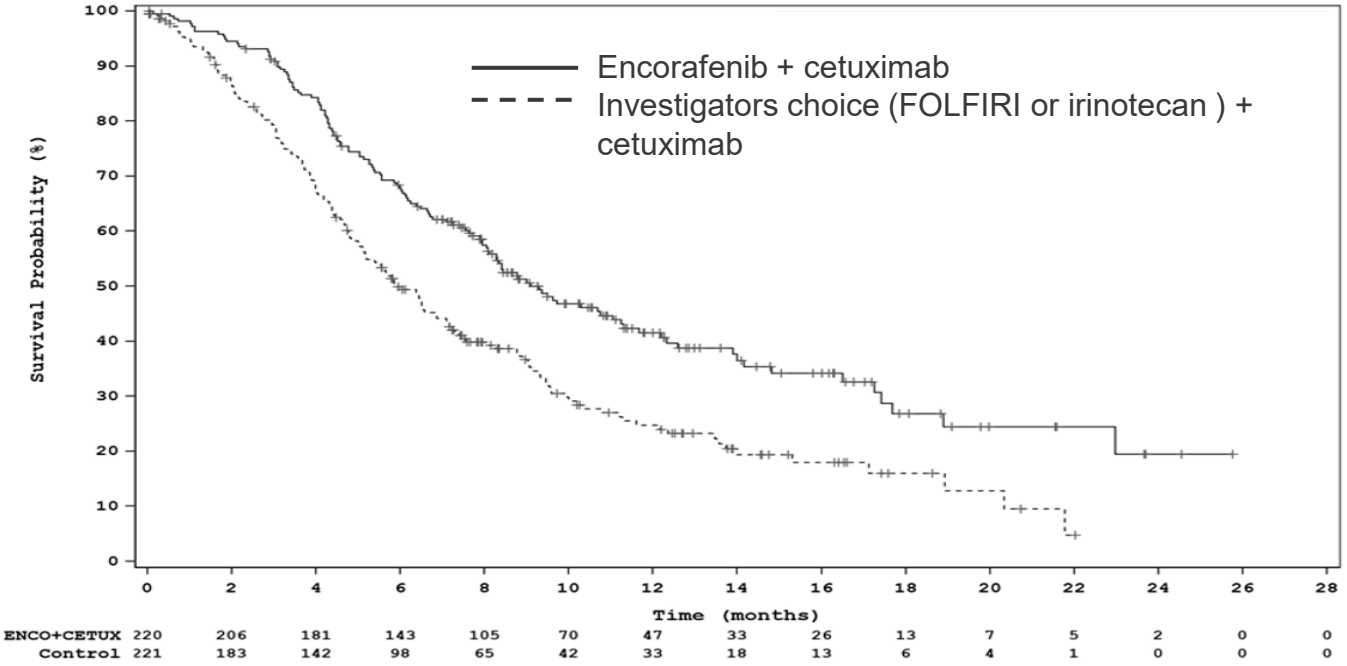
BEACON results August 2019 final data cut encorafenib + cetuximab overall survival

Longer survival for encorafenib + cetuximab vs investigators' choice + cetuximab

Subsequent treatments in BEACON CRC do not reflect NHS clinical

Kaplan Meier (KM) data for overall survival



Outcome	Encorafenib + cetuximab	(FOLFIRI or irinotecan) + cetuximab	Hazard ratio
Overall survival, median no. months (95% CI)	9.3 (8.1-11.3)	5.9 (5.1-7.1)	HR=0.61 (0.48-0.77), p<0.0001
Progression free survival, median months (95% CI)	4.3 (4.1-5.5)	1.5 (1.5-1.9)	HR=0.44 (0.35-0.55), p<0.0001

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Comparing to FOLFIRI

FOLFIRI as comparator summary of sources

2 trials

2 methods: Direct with wrong control group; indirect treatment comparison requires assumptions

Encorafenib + cetuximab

BEACON CRC

- People with previously treated BRAF V600E-mutant positive metastatic colorectal cancer
- **Intervention** arm

Vs

BEACON CRC

- **Comparator** arm [(FOLFIRI or irinotecan) + cetuximab]
- used as proxy for FOLFIRI efficacy

OR

Vs

Indirect treatment comparison

- Peeters 2015 phase III trial 2nd line
  - FOLFIRI + panitumumab vs. FOLFIRI
  - subgroup with BRAF V600E-mutations
- Not possible to form connected network with BEACON CRC without assuming:
  - FOLFIRI = irinotecan
  - Cetuximab = panitumumab
- Cetuximab (panitinumab) adds benefit?

Comparing to trifluridine-tipiracil

Summary of sources vs trifluridine-tipiracil

Indirect comparison to treatment arm of RECOURSE trial adjusted for BRAF status
3 sources to adjust survival for BRAF-mutant vs BRAF wild-type populations

Encorafenib + cetuximab

BEACON CRC

- People with previously treated BRAF V600E-mutant positive metastatic colorectal cancer
- ≤2 prior therapies

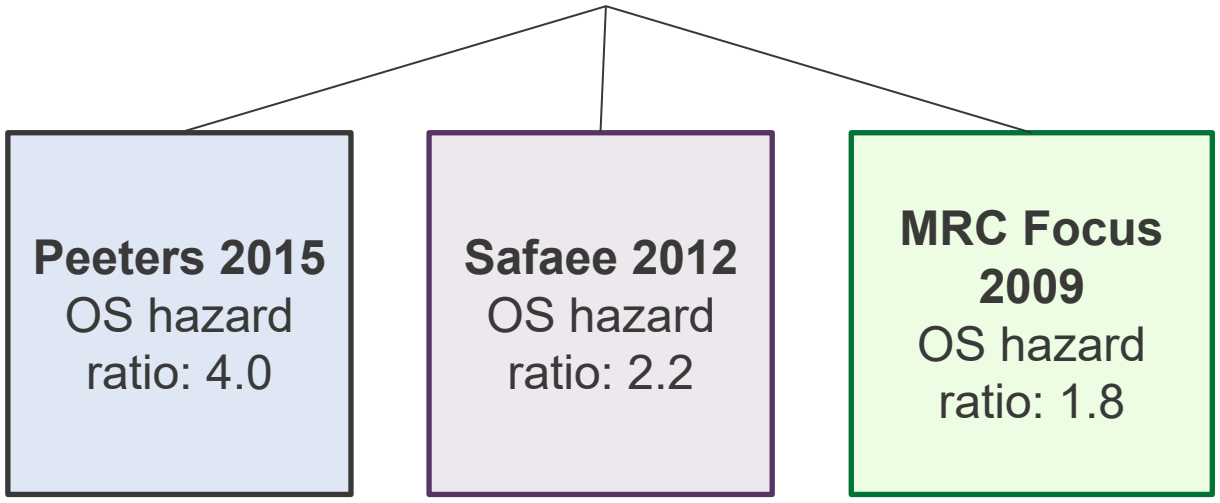
Vs

Trifluridine-tipiracil

RECOURSE

- RCT phase 3
- Trifluridine-tipiracil vs best supportive care
- BRAF status unknown
- >60% had ≥4 prior therapies
- Intervention group used for naïve comparison

Survival adjusted for difference in mortality for BRAF-mutant vs BRAF wild-type populations



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Comparing to best supportive care

Comparison with best supportive care

Company

- Best supportive care (BSC) would generally be confined to later lines of therapy, when all active treatments have been exhausted

ERG

- Best supportive care is not an appropriate comparator
- It is reserved for when other treatment regimens have failed later in the treatment pathway

Clinical experts

- No active treatment options after trifluridine-tipiracil
- Encorafenib + cetuximab could be used when no other active treatment options are available
- However at this point in the pathway people may not be well enough to have active treatment

Committee's conclusions and company response

Issue	Committee preference	Provided by company for 2nd committee meeting? (✔ / X)
Comparing to FOLFIRI		
Company did not prove equivalent effectiveness for FOLFIRI and irinotecan	Analyses from the control arm of BEACON CRC split by treatment: • a log-rank test to assess difference overall and progression-free survival between FOLFIRI and irinotecan • adjust for potential confounders	Partially – did not assess progression free survival • ? Provided stratified log-rank test for overall survival • ✔ Multivariate Cox analysis for overall survival, adjusted results for potential confounders
Progression free survival vs FOLFIRI	Company to model progression-free survival using Kaplan-Meier data from BEACON CRC	✔
Further exploration needed to model overall survival for FOLFIRI	A range of piecewise extrapolations for overall survival of encorafenib + cetuximab and of FOLFIRI	✔
	Present analyses using: • BEACON CRC and • Indirect treatment comparison to adjust for the presence of cetuximab in control arm of BEACON CRC	✔

Committee's conclusions and company response

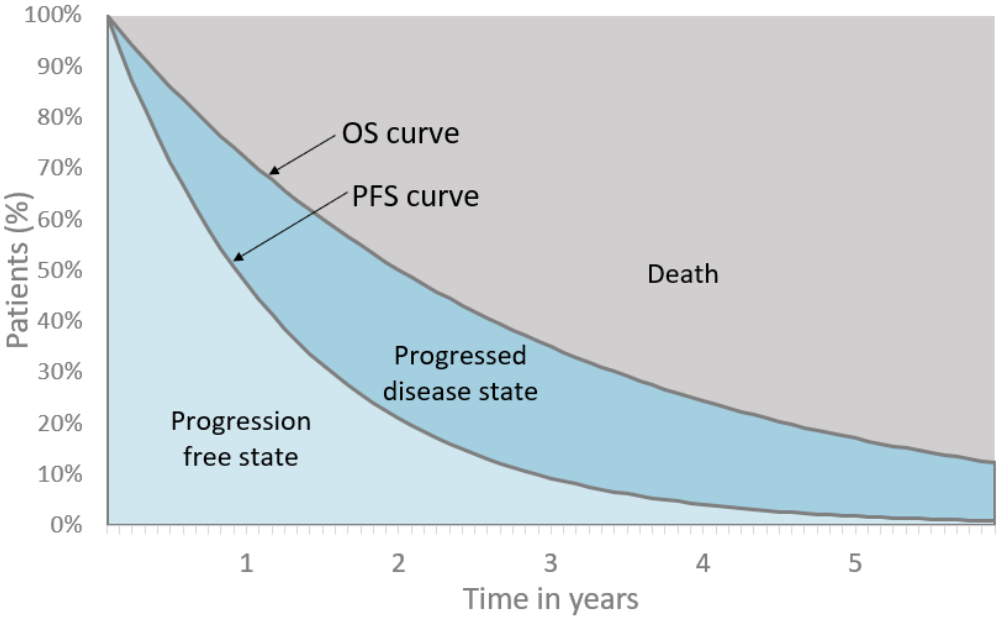
Issue	Committee preference	Provided by company for 2nd committee meeting? (✔/ X)
Comparing to trifluridine-tipiracil		
Modelling encorafenib plus cetuximab vs trifluridine–tipiracil	Adjust RECOURSE survival curves to account for differences other than BRAF in population in RECOURSE vs BEACON CRC	**?** – Partially Adjusted for BRAF vs wildtype survival outcomes, but not for other confounders e.g. number of previous treatments
Comparing to best supportive care		
Company did not include best supportive care as 3rd line comparator	Include best supportive care	✔ –'Best supportive care is not relevant comparator'

RECAP: cost effectiveness evidence

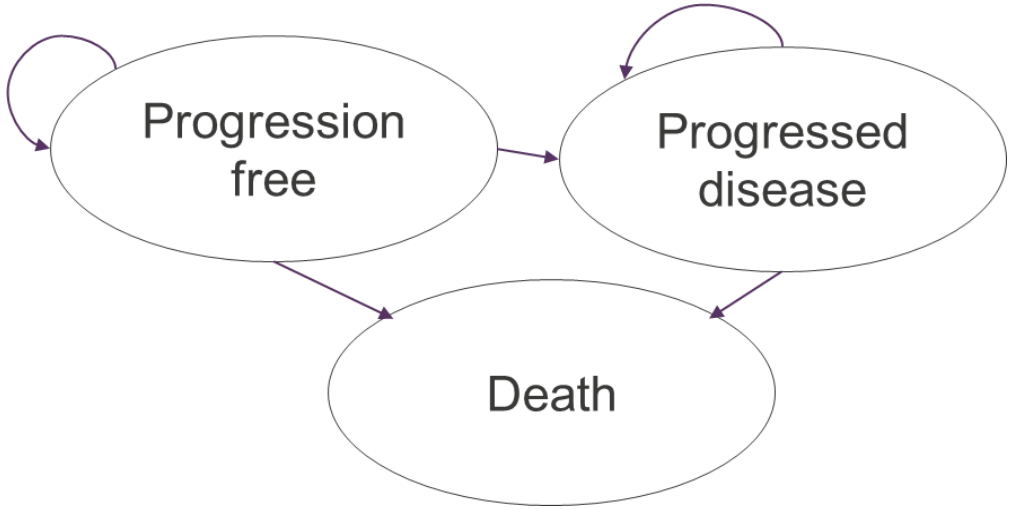
Model is appropriate for decision making

Committee had not seen estimates reflecting its preferred modelling

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

Recap of committee modelling preferences

Treatment	Data and modelling preference
Encorafenib + cetuximab	BEACON data extrapolated using May 2020 data
FOLFIRI	BEACON May 2020 control arm & applying ITC HR to BEACON May 2020 data
Trifluridine-tipiracil	RECOUSE data adjusted for histology and confounders

REDACTED

Committee's conclusions, company response

Issue	Committee preference or decision	Provided by company for 2nd committee meeting? ✔ / X
Unplanned May 2020 data cut provided from BEACON CRC to update survival outcomes	Prefer latest data cut from BEACON CRC, May 2020	✔
No adjustment for subsequent treatments used in trial but not used in NHS	Adjust for subsequent treatments	***X*** – not relevant and unable to do • Scenario accounting for **costs but not benefit** of subsequent treatment in BEACON CRC
Progression free survival used as proxy for time to treatment discontinuation	Use time to treatment discontinuation	✔ - Provided only for encorafenib + cetuximab vs FOLFIRI when using data from BEACON CRC
No drug wastage	Apply 10% drug wastage for oral treatments	✔ – Scenario
End of life criteria	Met	N/A
Innovative?	Yes	N/A

ACD consultation responses

- Consultees:
  - Pierre Fabre, manufacturer of encorafenib
  - Royal College of Physicians

- Commentators:
  - Merck Serono, manufacturer of cetuximab

- Web comments:
  - 109 public web comments

Professional perspective

Royal College of Physicians

Unmet need and rarity of the BRAF V600E mutation

- Lack of effective treatment options and no other targeted therapy
- Only 200 to 300 patients per year in the UK

Uncertain effect of comparator treatments

- Cetuximab likely to have survival benefit compared to FOLFIRI or irinotecan alone
- Should use encorafenib + cetuximab early in treatment pathway
  - WOSCAN data showed < 50% of patients fit for 2nd line treatment and none fit for 3rd line treatment
- Trifluridine-tipiracil predominantly useful in patients with ‘slow burn’ disease
- Trifluridine-tipiracil worse than FOLFIRI
- Extremely unlikely that patient with BRAF mutation would respond to trifluridine-tipiracil

COVID-19 considerations

- Encorafenib + cetuximab well tolerated and has fewer adverse effects
- No need for Peripherally Inserted Central Catheter (PICC) line

Commentator comments

Merck Serono – makes cetuximab

- ‘Step change in treatment’
- ‘Committee remit to consider proper use of financial resources is supported as population size is limited, identifiable through testing’
- ‘Clinical experts have confirmed that patient response is frequently quick and quantifiable, further limiting the possibility of extensive prescribing without benefit’

Web comments (n=109)

- **Generalisability of the BEACON CRC trial to NHS clinical practice**
  - "Trials were based upon 60 year old patients, and discriminate against younger people with a better prognosis."
- **Analyses do not fully capture quality of life benefit**
  - "I feel that some of the data analysis and qualitative and quantitative methods miss capturing real life stories and evidence"
  - "Quality and quantity of life have not been given enough weight."
- **Company does not capture cost savings from other treatments**
  - "I would urge that you consider the cost of chemotherapy, hospital admittance, other therapies for patients as well"
- **Complete evidence base not explored**
  - "I don't think the most recent data sets have been taken into account"
  - "A separate study has shown that 75.9% of patients received some benefits to these drugs as compared 31.2% with the usual drugs"
- **COVID-19 benefit**
  - "Cost of keeping the patient alive, not in chemotherapy and perhaps not being constantly admitted to hospital, taking up chemo spaces of those whose chemotherapy is shown to work must be of some benefit."

COVID-19 update

Interim treatment change options during the COVID-19 pandemic, endorsed by NHS England

- For treatments that are ‘less immunosuppressive’ **or** ‘can be administered at home..’ **or** ‘less resource intensive’ **and** ‘is feasible’ **and** ‘there is likely to be adequate capacity …to deliver the treatment’
- Option to give encorafenib and cetuximab for BRAF positive metastatic disease instead of chemotherapy to reduce risk of immunosuppression
- ‘The interim treatment options will remain in place for the remainder of financial year 2020/21 to support patient access during the COVID-19 pandemic.’
- ‘These interim treatment changes do not constitute NICE guidance’
- All patients who start on an ‘interim treatment during the COVID-19 pandemic should be allowed to continue the treatment’
- NICE technology appraisals will supersede any changes

Source: https://www.nice.org.uk/guidance/ng161/resources/interim-treatment-change-options-during-the-covid19-pandemic-endorsed-by-nhs-england-pdf-8715724381

Key issues

1. Most appropriate model for extrapolating survival for encorafenib + cetuximab
2. How to best compare encorafenib + cetuximab to each comparator?

FOLFIRI

   a. Does cetuximab when used with FOLFIRI or irinotecan provide additional benefit over chemotherapy alone for people with BRAF V600E mutations?
   b. Is FOLFIRI clinically equivalent to irinotecan?
   c. Most appropriate model for extrapolating survival for FOLFIRI

Trifluridine-tipiracil

   d. Which hazard ratio is most appropriate to adjust RECOURSE survival curves to account for poorer outcomes in BRAF population?

3. Has the company adequately controlled for subsequent treatments?
4. Equalities

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

Modelling **encorafenib + cetuximab** beyond trial

Piecewise approach is preferred for modelling overall survival – further exploration needed

Kaplan–Meier data should be used to model progression-free survival

◉ What is the most appropriate model for extrapolating overall survival for encorafenib + cetuximab beyond the trial period?

Modelling overall survival encorafenib + cetuximab (1)

Piecewise log-logistic curve projects similar survival to real world evidence

Committee discussion: Further exploration of piecewise approaches using BEACON May 2020 data cut. A variety of curve extrapolations are needed.

Company:

- Piecewise approach used to model overall survival for encorafenib + cetuximab
- Log-logistic provided best fit based on AIC/BIC statistics
- Not validated by expert opinion but long-term projections plausible
- Projections are similar to real world evidence for patients in Scandinavia with BRAF-mutant mCRC treated with first-line chemotherapy (Nunes 2020)

Encorafenib + cetuximab overall survival estimates (%)	Time, years						
	1	1.5	2	2.5	3	4	5
BEACON May 2020 KM	[redacted]	[redacted]	[redacted]	[redacted]†	NA	NA	NA
Company piecewise log-logistic (May 2020)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nunes 2020 ‡	-	-	20	-	12	5	-

† 2.5 year estimate is subject to some uncertainty due to low numbers of patients at risk

‡ estimates by visual inspection of survival curve from patients with BRAF-mutant mCRC treated with first-line chemotherapy.
Abbreviations: KM, Kaplan-Meier, NA, not applicable

Modelling overall survival encorafenib + cetuximab

Comparison of parametric models fitted to BEACON encorafenib + cetuximab overall survival Kaplan-Meier curves (May 2020)

Model	% alive			
	1 year	3 years	5 years	10 years
Exponential	xxx	xxx	xxx	xxx
G. gamma	xxx	xxx	xxx	xxx
Gompertz	xxx	xxx	xxx	xxx
Log-logistic	xxx	xxx	xxx	xxx
Log-normal	xxx	xxx	xxx	xxx
Weibull	xxx	xxx	xxx	xxx

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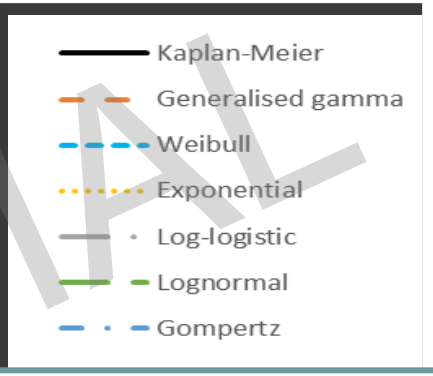


ERG:

- Low numbers at risk towards the tail of the KM curve
- Difficult to distinguish between the parametrised curves by visual inspection
- 10 year survival proportions are non-negligible for many of the curves

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

2nd line treatment options

Encorafenib + cetuximab vs **FOLFIRI**

Main trial has blended comparator not used in NHS practice

Not possible to form connected network without assuming:

FOLFIRI = irinotecan ?

Cetuximab = panitumumab ✔

◉ *What is the best estimate for comparing encorafenib + cetuximab vs FOLFIRI*

Decision summary vs FOLFIRI

- Benefit of cetuximab when used with FOLFIRI or irinotecan for people with BRAF V600E mutations uncertain

BEACON CRC

- Control includes FOLFIRI + cetuximab, not used in NHS 2nd line

Does cetuximab when used with FOLFIRI or irinotecan provide additional benefit over chemotherapy alone?

Cetuximab added to chemotherapy benefits BRAF + patients mutation 1st line

Committee discussion:
- Benefit of cetuximab when used with FOLFIRI or irinotecan unknown

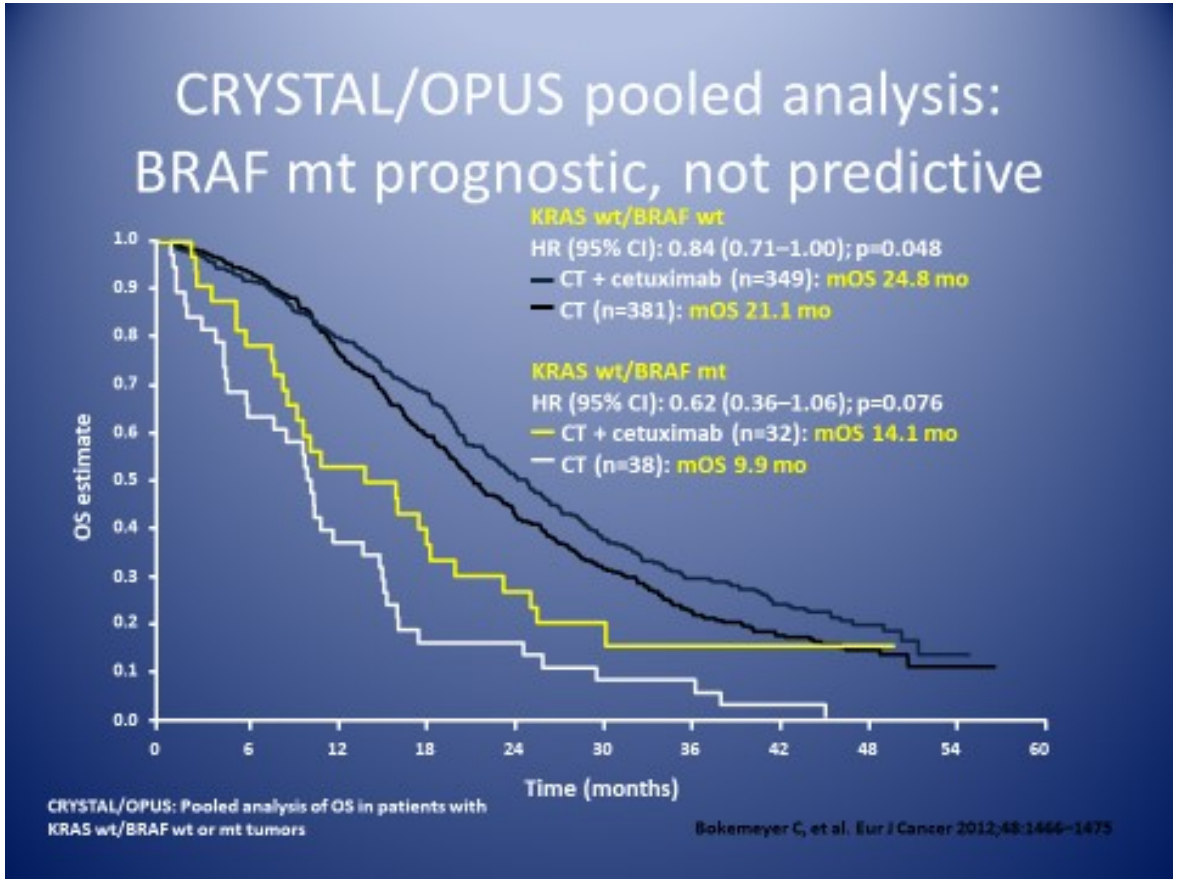
Bockemeyer 2012 pooled individual patient level data cetuximab + chemo vs. chemo.

Overall survival (hazard ratio 0.81; p=0.006)

Royal College of Physicians

Cetuximab is not standard of care in UK 2nd line

- 'Data from CRYSTAL estimate that cetuximab would add about 6 weeks to survival vs FOLFIRI or irinotecan alone'



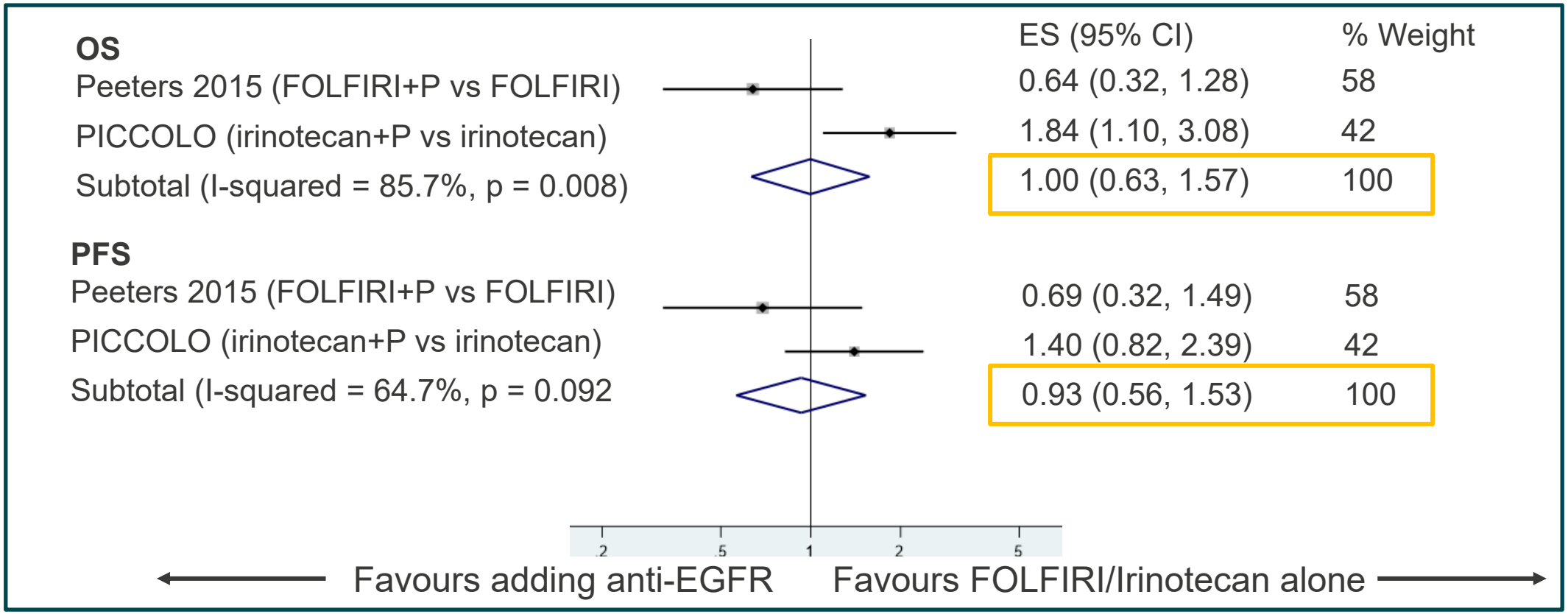
◉ *Does cetuximab when used with FOLFIRI or irinotecan provide additional benefit for people with BRAF V600E mutations? Is this likely to differ for 2nd line? How is this likely to affect modelling?*

Benefit of cetuximab in BEACON CRC trial

Effect size of cetuximab may differ if added to FOLFIRI or irinotecan

ERG:

- PICCOLO trial – irinotecan + panitinumab vs irinotecan
- PICCOLO: shows potentially harmful effect of panitumumab when used with irinotecan
- Mixed effect model combines relevant estimates from Peeters 2015 and PICCOLO trials
- Effects of cetuximab + FOLFIRI and cetuximab + irinotecan might cancel each other out so BEACON CRC a suitable estimate for FOLFIRI / Irinotecan



◉ *What are the implications, if any, when translating the evidence based to the decision problem?*

Decision summary vs FOLFIRI

- 2 main sources of efficacy estimates for encorafenib + cetuximab vs FOLFIRI

BEACON CRC

- Control includes FOLFIRI + cetuximab, not used in NHS 2nd line

Indirect treatment comparison

- Not possible to form connected network without assuming
  - Cetuximab contributes benefit **?**
  - FOLFIRI = irinotecan **?**
  - Cetuximab = panitumumab ✔

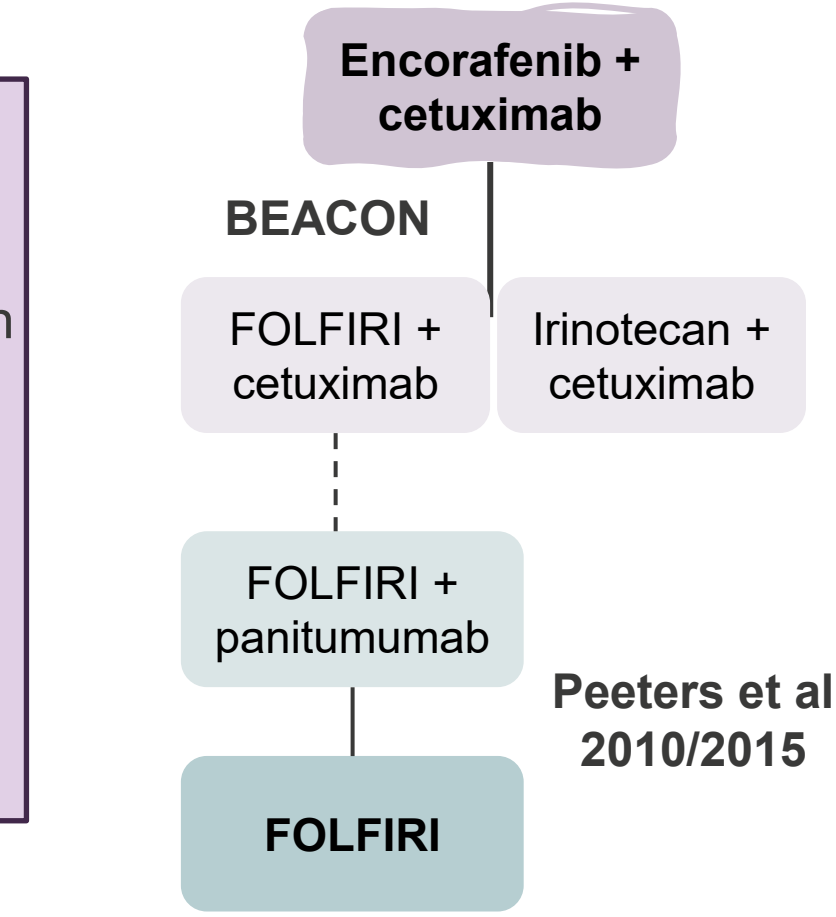
Encorafenib + cetuximab vs FOLFIRI: Company's indirect treatment comparison

No common comparator – not possible to connect network

- No common comparators between BEACON CRC and Peeters et al 2015

Committee discussion:
Company assumes equal effectiveness of:

1. **? FOLFIRI = irinotecan**
   - Unclear whether FOLFIRI and irinotecan are equally effective
   - Allocation to irinotecan + cetuximab OR FOLFIRI + cetuximab not randomised - affects clinical outcomes
2. ✔ **Cetuximab = panitumumab**
   - Cetuiximab and panitumumab are equally effective



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Clinical equivalence of FOLFIRI and irinotecan

No statistical difference in OS between treatments in comparator arm

Committee discussion:

Test assumption 'FOLFIRI = irinotecan' using analyses from control arm of BEACON CRC:

- adjustment for potential confounders
- a log-rank test to assess the overall and progression-free survival.

Company:

- BEACON trial designed assuming equivalence of comparator treatment
- Trial not powered to test differences between encorafenib + cetuximab (n=220) and each of comparators clinician could include (irinotecan+ cetuximab n=92, or FOLFIRI + cetuximab n=129)
- No significant difference between 2 curves for each comparator overall survival (HR 1.1; 95% CI [redacted]; stratified log rank one-sided [redacted]) data cut May 2020
- Multivariate Cox analysis adjusted for potential confounders → no significant difference in overall survival (HR [redacted]; Irinotecan/cetux vs. FOLFIRI/cetux 95% CI [redacted]) data cut May 2020

ERG

- New analyses appear comprehensive, although residual confounding remains possible
- Analysis under-powered so cannot rule out important differences
- Company did not compare PFS curves between the two subgroups
- Log-rank test (Aug 2019 data cut) estimated a p-value of [redacted]

Clinical equivalence of FOLFIRI and irinotecan

Uncertainty in the evidence around tolerability and effectiveness of FOLFIRI and irinotecan

Commentator: Merck Serono

- Irinotecan = FOLFIRI supported by two randomized controlled trials which showed irinotecan and FOLFIRI without cetuximab did not differ statistically in overall and progression free survival for second-line treatment of metastatic colorectal cancer (Clarke 2011, Graeven 2007)
  - Clarke et al 2011: randomised phase II study DaVINCI, patients with advanced colorectal cancer receiving either FOLFIRI (n=44) or irinotecan (n=45)
  - Graeven et al 2007: randomised phase II study, second line therapy in patients with metastatic colorectal cancer receiving FOLFIRI or irinotecan

Consultee: Royal College of Physicians

- It is widely accepted that patients tolerate FOLFIRI significantly better than single agent irinotecan.

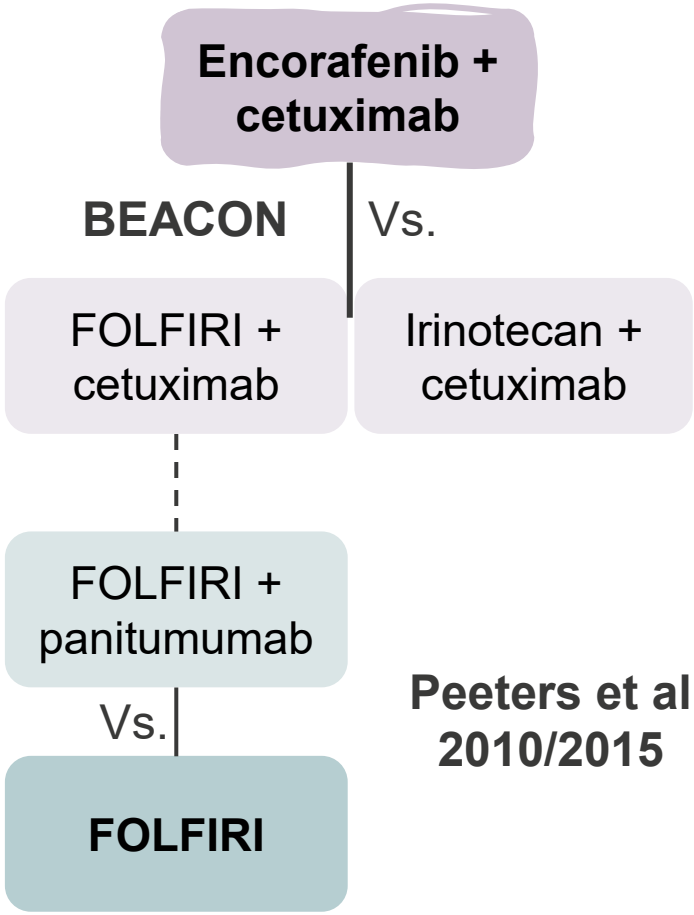
◉ *Is it reasonable to assume equivalence of FOLFIRI and irinotecan?*

Decision summary vs FOLFIRI

Decision Problem

Encorafenib + cetuximab Vs. **FOLFIRI**

Evidence



◉ *What is the best estimate for comparing encorafenib + cetuximab vs FOLFIRI*

RECAP: 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

		ACM1: Base case		Committee preference
		Company	ERG	
Overall survival	**Data source**	BEACON trial May 2020 data cut, HR from indirect comparison applied for comparator arm	BEACON trial to answer decision problem Aug 2019	Consider both
	Extrapolation	Jointly fitted log-logistic to May 2020 data cut	Piecewise exponential to Aug 2019 data cut	Piecewise exponential to May 2020 data cut
Progression free survival		Jointly fitted log-logistic May 2020	Raw Kaplan-Meier curves using Aug 19	Raw Kaplan-Meier curves using May 2020 data
Time to treatment discontinuation		Assumed equal to progression free survival		Use time to treatment discontinuation

Decision summary vs FOLFIRI

- 2 main sources of efficacy estimates for encorafenib + cetuximab vs FOLFIRI

BEACON CRC

Indirect treatment comparison

Modelling overall survival FOLFIRI: indirect treatment comparison

Committee discussion:
Consider modelling using both BEACON control arm and ITC
Experts suggest that survival with FOLFIRI is less than 10% at 3 years and 5% at 5 years

Company:
- Using the control arm from BEACON would overestimate the survival estimates for FOLFIRI alone
- Selected log-logistic curve to align with encorafenib + cetuximab extrapolation

FOLFIRI overall survival estimates using BEACON control arm

Model	% alive		
	1yr	3 yrs	5 yrs
Exponential	XXX	XX	XX
G. gamma	XXX	XX	XX
Gompertz	XXX	XX	XX
Log-logistic	XXX	XX	XX
Log-normal	XXX	XX	XX
Weibull	XXX	XX	XX

FOLFIRI overall survival estimates using: Hazard ratio from ITC applied to BEACON CRC

Model	% alive		
	1yr	3 yrs	5 yrs
Exponential	XXX	XX	XX
G. gamma	XXX	XX	XX
Gompertz	XXX	XX	XX
Log-logistic	XXX	XX	XX
Log-normal	XXX	XX	XX
Weibull	XXX	XX	XX

◉ *Is log-logistic curve appropriate?*

Benefit of cetuximab when modelling FOLFIRI

Exploring the duration of cetuximab effect impacts survival in ITC model

ERG:

- Interaction between the duration of the cetuximab effect and the choice of curve
- ERG explored duration of the cetuximab effect
- Applying cetuximab effect for a lifetime results in FOLFIRI OS curve at 3 years and at 5 years below the 10% and 5% prediction expected for standard of care
- May be appropriate to restrict the duration of the assumed cetuximab effect for BRAF patients

Undiscounted OS months by curves and duration of cetuximab effect with FOLFIRI

	Duration of cetuximab effect when added to FOLFIRI					
	Life	2 year	1 year	6 month	3 month	None
Gompertz	XXX	XXX	XXX	XXX	XXX	XXX
Log-normal	XXX	XXX	XXX	XXX	XXX	XXX
Log-logistic	XXX	XXX	XXX	XXX	XXX	XXX
Gen. gamma	XXX	XXX	XXX	XXX	XXX	XXX
Weibull	XXX	XXX	XXX	XXX	XXX	XXX
Exponential	XXX	XXX	XXX	XXX	XXX	XXX

ITC

BEACON CRC

◉ *Should duration of cetuximab effect be adjusted for in the model?*

Decision summary vs FOLFIRI

Committee discussion:
- Experts suggest that survival with FOLFIRI is less than 10% at 3 years and 5% at 5 years

BEACON CRC | **Adjusted duration of cetuximab effect** | **Indirect treatment comparison**

Source and model		% alive 1yr	3 yrs	5 yrs
BEACON CRC control	Piecewise Loglogistic	XXX	XXX	XXX
	Piecewise Weibull	XXX	XXX	XXX
BEACON CRC adjusted duration of cetuximab (Piecewise Loglogistic)	3 months	XXX	XXX	XXX
	6 months	XXX	XXX	XXX
	1 year	XXX	XXX	XXX
	2 years	XXX	XXX	XXX
Indirect treatment comparison	Piecewise Loglogistic	XXX	XXX	XXX
	Piecewise Weibull	XXX	XXX	XXX

◉ *Which approach is best to extrapolate overall survival for FOLFIRI?*

2nd / 3rd line treatment options

Encorafenib + cetuximab
vs
trifluridine-tipiracil

No direct trial data

◉ *What is the best estimate for comparing encorafenib + cetuximab vs trifluridine-tipiracil?*

Summary of sources vs trifluridine-tipiracil

Indirect comparison to treatment arm of RECOURSE trial adjusted for BRAF status
3 sources to adjust survival for BRAF-mutant vs BRAF wild-type populations

Encorafenib + cetuximab

BEACON CRC

- People with previously treated BRAF V600E-mutant positive metastatic colorectal cancer
- ≤2 prior therapies

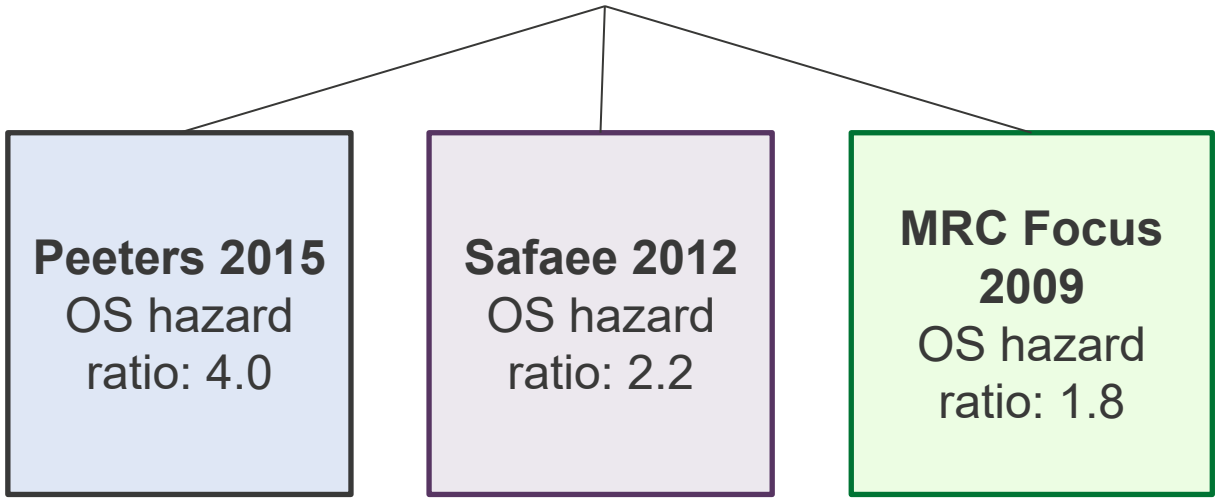
Vs

Trifluridine-tipiracil

RECOURSE

- RCT phase 3
- Trifluridine-tipiracil vs best supportive care
- BRAF status unknown
- >60% had ≥4 prior therapies
- Intervention group used naïve comparison

Overall survival adjusted for difference in mortality for BRAF-mutant vs BRAF wild-type populations



NICE

Naïve comparison vs trifluridine-tipiracil

Hazard ratios reflecting poor survival mutation vs. wild-type vary widely

Committee discussion:
- Not clear which hazard ratio provided an appropriate adjustment

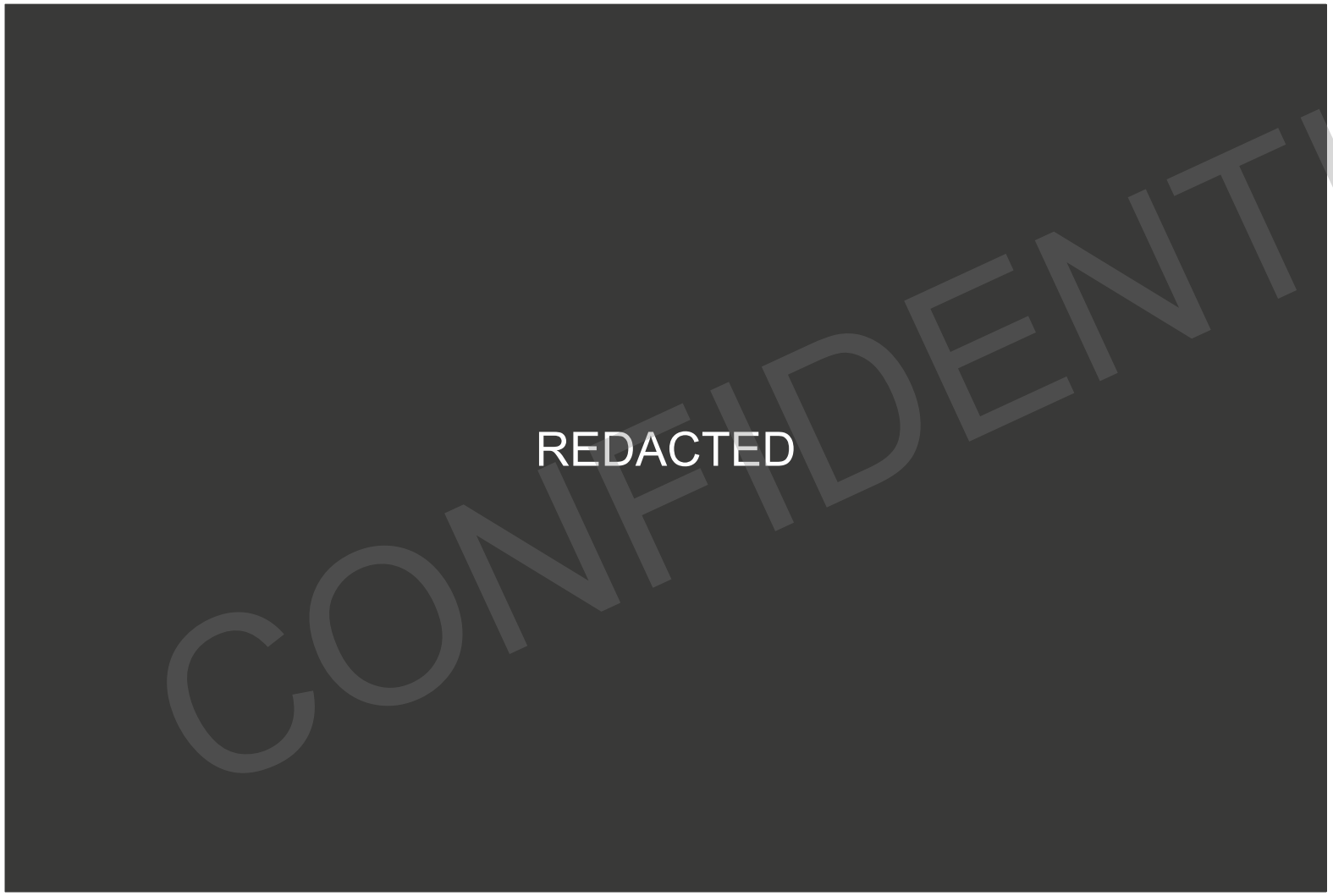
Company:
- Original base case: Peeters 2015
- Updated base case: Safaee 2012 because it was derived from multiple studies identified by systematic review

ERG:
- Substantial variation in hazard ratios
- Safaee meta-analysis high level of statistical heterogeneity (I^2 >70%)
- ERG adjusts using UK-based MRC FOCUS trial (Richman 2009)
- Presents scenario with no adjustment

Source	Peeters et al 2015	Safaee Ardekani 2012	MRC FOCUS, Richman 2009	Unity (RECOURSE)
Treatment	FOLFIRI + panitumumab vs FOLFIRI	Meta-analysis - 26 trials	FU, FU/ irinotecan, FU/oxilaplatin	Trifluridine-tipiracil vs BSC
Hazard ratio OS	4.0	2.2	1.8	1.0
Hazard ratio PFS	3.6	Same as OS	1.1	1.0

Decision summary vs trifluridine-tipiracil

Hazard ratios for adjusting for differences in population vary widely



Unity
OS hazard ratio: 1.00

MRC Focus 2009
OS hazard ratio: 1.82

Safaee 2012
OS hazard ratio: 2.24

Peeters 2015
OS hazard ratio: 4.00

◉ Which HR is most appropriate to adjust survival outcomes for difference in mortality for BRAF-mutant vs BRAF wild-type populations?

Modelling overall survival Trifluridine- tipiracil

Trifluridine-tipiracil modelled by adjusting RECOUSE for difference in survival for BRAF-mutant vs BRAF wild-type

Company: AIC/BIC statistics for BEACON (encorafenib/cetuximab) and RECOURSE (trifluridine-tipiracil) OS show log-logistic is the best fitting model based on the lowest mean AIC and BIC

	AIC			BIC		
Model	Encorafenib/ cetuximab	RECOURSE	Mean	Encorafenib / cetuximab	RECOURSE	Mean
Exponential	1020	2438	1729	1024	2443	1733
Generalised gamma	1014	2360	1687	1024	2373	1699
Gompertz	1012	2409	1710	1019	2417	1718
Log-logistic	1012	2354	1683	1019	2362	1690
Log-normal	1015	2371	1693	1022	2380	1701
Weibull	1016	2370	1693	1023	2378	1701

ERG comments:

- Adjustment causes large shift in survival from RECOURSE trial
- HRs derived from different populations than population in RECOUSE trial
- Trial might have included both BRAF V600E mutant and wild type meaning potential for double counting

◉ *Which extrapolation is appropriate?*

3rd /4th line treatment options

Encorafenib + cetuximab
vs
best supportive care

Not included in company original submission

Comparison vs best supportive care

BSC is a comparator but people may not be fit enough at this point in the treatment pathway to have encorafenib + cetuximab

Committee discussion: best supportive care is a relevant comparator for encorafenib plus cetuximab after 2 previous lines of treatment

Company: "encorafenib/cetuximab would be used predominantly ahead of FOLFIRI as a second-line therapy or, ahead of trifluridine-tipiracil as a third-line therapy, and on this basis we feel that best supportive care is not an appropriate comparator."

Web comment: Given this short Overall Survival from initial presentation it is likely that many with BRAF V600E mutations patients do not survive long enough to receive 3rd line chemotherapy and that available 2nd line standard chemotherapy is of limited benefit. Therefore this small cohort of patients are a niche group that are in need novel targeted treatment in the 2nd line setting.

◉ *Is best supportive care a relevant comparator?*

Modelling overall survival: best supportive care (1)

Company: No connected network with BEACON CRC
Similar approach taken to comparing with trifluridine-tipiracil, 3 suitable studies identified

	Karapetis 2014		Kim 2018		Peeters 2013	
Line of therapy	≥2		≥2		3	
Intervention	BSC + cetuximab	BSC	BSC + panitumumab	BSC	BSC + panitumumab	BSC
N	4	6	9	11	9	6
Median OS (months)	1.77	2.97	4.1	3.0	NR	NR
HR (95% CI)	0.84 (0.2, 3.58); p=0.81		0.39 (0.1, 1.51); p=0.1597		-	
Median PFS (months)	NR	NR	1.5	1.3	NR	NR
HR (95% CI)	0.76 (0.19, 3.08); p=0.69		0.28 (0.07, 1.08); p=0.0502		0.34 (0.09, 1.24); p=0.1035	

Small number treated with BSC
PFS curve not reported

Survival curves not reported

Kim 2018: company selected as most appropriate source

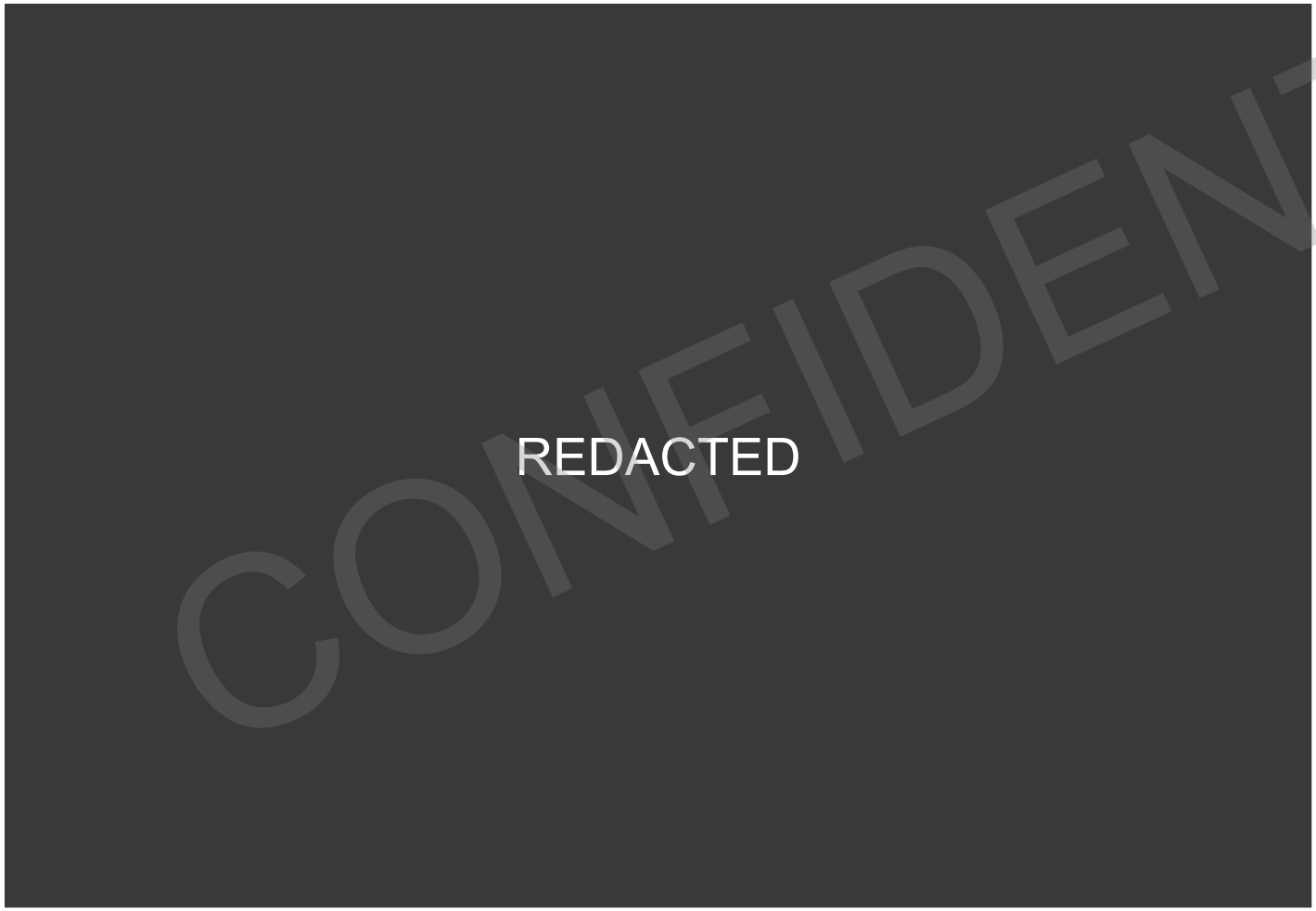
- Reported survival curves for overall population
- Includes hazard ratio for wild type disease versus BRAF-mutant disease (HR overall survival 0.33; 95% CI 0.17, 0.66)

◉ *What is the most appropriate source for modelling survival for best supportive care?*

Modelling overall survival: encorafenib vs best supportive care

Company:

- Survival curves and adjustment for BRAF-mutation hazard ratio (3.03) from Kim 2018
- Log-logistic curve selected for consistency with other comparisons



ERG:

- Kim 2018 reasonable data source
- Adjustment for BRAF-mutation higher than used by company in comparison with trifluridine-tipiracil
- Log-logistic is the worst fit but consistent with DSU recommendation

Subsequent treatments in BEACON CRC

Subsequent treatments in BEACON CRC

Subsequent treatments unlikely to impact survival

Committee discussion:

- Some subsequent treatments in BEACON CRC are not available in the NHS
- Prefer analyses adjusting overall survival and costs for subsequent trial treatments

Company adjusts for cost but not impact on survival

- Similar proportion of people in both arms received subsequent treatments
- Immunotherapy use was low in both arms and lower in encorafenib arm
  - Encorafenib XXX, control XXX
- "It is therefore extremely unlikely that these agents would have had any influence on the survival estimates generated within the trial"
- "Analyses have not been possible (nor deemed relevant…), to adjust survival estimates for subsequent treatments not available in the NHS."

ERG:

- Large number of different regimens listed
- Major bias in favour of encorafenib + cetuximab due to subsequent treatments unlikely

Subsequent treatments in BEACON CRC (2)

Subsequent systemic anti-cancer therapy by drug category received by more than 1% of patients in BEACON CRC

Category	Encorafenib/ cetuximab (N=220), n (%)	Control (N=221), n (%)
Any regimen	XXX	XXX
irinotecan combination + VEGFi	XXX	XXX
chemotherapy	XXX	XXX
irinotecan combination	XXX	XXX
kinase inhibitor	XXX	XXX
oxaliplatin combination	XXX	XXX
irinotecan + oxaliplatin combination + VEGFi	XXX	XXX
irinotecan	XXX	XXX
immunotherapy	XXX	XXX
irinotecan combination + EGFRi	XXX	XXX
oxaliplatin combination + VEGFi	XXX	XXX
other	XXX	XXX
irinotecan + EGFRi	XXX	XXX
chemotherapy + VEGFi	XXX	XXX
BRAFi + MEKi + EGFRi	XXX	XXX
BRAFi + EGFRi	XXX	XXX
BRAFi + EGFRi + irinotecan	XXX	XXX

◉ *Are subsequent treatments received in BEACON CRC likely to have an impact on overall survival?*

Subsequent treatment scenario in company model

- Company provides subsequent treatment scenario analyses adjusted for cost but not impact on survival
- Subsequent treatment usage used in scenario:

Subsequent therapy	Encorafenib/ cetuximab	Control (used for FOLFIRI)	Average (used for trifluridine-tipiracil)
Aflibercept	XXX	XXX	XXX
Bevacizumab	XXX	XXX	XXX
Cetuximab	XXX	XXX	XXX
Dabrafenib	XXX	XXX	XXX
Fluorouracil	XXX	XXX	XXX
Folinic acid	XXX	XXX	XXX
Irinotecan	XXX	XXX	XXX
Oxaliplatin	XXX	XXX	XXX
Panitumumab	XXX	XXX	XXX
Regorafenib	XXX	XXX	XXX
Trametinib	XXX	XXX	XXX
Trifluridine-tipiracil	XXX	XXX	XXX
Vemurafenib	XXX	XXX	XXX

Time to treatment discontinuation

Assumptions required to model TTD for all comparisons not directly using BREACON CRC data

Treatment	Company base case	ERG
Encorafenib + cetuximab	Time to treatment discontinuation	Time to treatment discontinuation
FOLFIRI BEACON CRC control arm	Time to treatment discontinuation using log-logistic curve	Time to treatment discontinuation
FOLFIRI Indirect treatment comparison	Progression free survival used as proxy	Applies the same HR to the BEACON control arm TTD curve
Trifluridine-tipiracil		Increases discounted treatment costs by the same proportion as the encorafenib discounted treatment costs are increased by applying the TTD curve rather than the PFS curve
Best supportive care		

ERG: TTD=PFS will generally bias the analysis in favour of Encorafenib + cetuximab

◉ *Are assumptions for modelling TTD appropriate?*

Drug wastage and relative dose intensity

Company:

- Company does not include wastage when estimating costs
- Scenario analysis assumed that 10% of patients would waste some tablets in a pack by rounding up to the nearest whole pack

ERG comments:

- Company retain the mean encorafenib relative dose intensity (RDI) of XX for 90% of patients and assumes an encorafenib RDI of 100% for 10% of patients.
- Increases base case by 1%
- ERG present scenario analyses increasing the encorafenib costs by 10% to account for wastage

◉ *Which approach, if either, best reflect wastage?*

Company's updated base case (1)

	Company original base case assumptions	Company updated base case assumptions Address committee preference (✔ / X)	
vs FOLFIRI *Source: BEACON CRC, May 2020 and Peeters 2015*			
Overall survival	Fully parametric curve fitted to BEACON CRC with ITC HR applied for comparator arm	✔	Piecewise, Kaplan-Meier to 2.8 months then parametric with ITC HR applied for comparator arm
Progression free survival	Fully parametric curve fitted to BEACON CRC	✔	Kaplan-Meier data to end of trial
Vs trifluridine-tipiracil *Source: RECOURSE*			
Overall and progression free survival	BEACON and RESOURCE data, fully parametric	✔	Fully parametric
Adjustment for histology and other confounders	BRAF-mutant adjustment HR applied	?	BRAF-mutant vs WT adjustment HR applied No additional adjustments made
Vs best supportive care *Source: Kim 2018*			
Overall survival Progression free survival	New analyses provided in response to ACD	✔	Fully parametric fitted curves with BRAF-mutant adjustment HR applied although company deem the comparison inappropriate

Company's updated base case (2)

	Company original base case assumptions	Company updated base case assumptions	
		Address committee preference (✔ / X)	
Time to treatment discontinuation	Progression free survival used to model time to treatment discontinuation	?	• Time to treatment discontinuation is used in analyses using BEACON control arm as proxy for FOLFIRI • All other analyses use progression free survival Committee discussion: Time to treatment discontinuation should be applied in the model
Drug wastage	No wastage	X	No wastage in primary analyses • Scenario – no intravenous wastage, 10% of patients waste some tablets in a pack by rounding up to the nearest whole pack **Committee discussion:** It is appropriate to assume 10% drug wastage for oral treatments **ERG:** Increases the encorafenib costs by 10% to account for wastage
Subsequent treatments	Only trifluridine-tipiracil and best supportive care	X	Only trifluridine-tipiracil and best supportive care • BEACON trial-based subsequent treatments modelled in scenario analyses.

Equalities

15 web comments state draft guidance discriminates against the young:

- "The BEACON trial recruits patients where the average age is 60-62 and this therefore denies younger people e.g. in their 30s a chance of life saving drugs."
- "Discriminates against younger people with a better prognosis."
- "Young people are an increasing group within this patient group. They are not being given life-extending options. It feels ageist to deny them a chance of a better quality of life."
- "Younger people are less likely to be able to pay for this treatment privately"

Baseline characteristics of BEACON CRC trial

		Enco with cetuximab N=220	Control N=221
Age (years)	Mean (SD)	XXXXX	XXXXX
	Median	61	60
	Min, max	30, 91	27, 91

◉ *Does this reflect an equalities issue?*

Innovation

- Encorafenib plus cetuximab represents a step change in treatment for people with BRAF V600E mutation-positive colorectal cancer
- High unmet need for an effective treatment as no other BRAF V600E targeted treatments available for this population
- The committee noted that because the treatment is not a chemotherapy, it is transformative for people's quality of life

Web comments:

- "[encorafenib with cetuximab] is the first major breakthrough for this patient group"

◉ *Any additional innovation considerations?*

Key issues

1. Most appropriate model for extrapolating survival for encorafenib + cetuximab
2. How to best compare encorafenib + cetuximab to each comparator?

FOLFIRI

   a. Does cetuximab when used with FOLFIRI or irinotecan provide additional benefit over chemotherapy alone for people with BRAF V600E mutations?

   b. Is FOLFIRI clinically equivalent to irinotecan?

   c. Most appropriate model for extrapolating survival for FOLFIRI

Trifluridine-tipiracil

   d. Which hazard ratio is most appropriate to adjust RECOURSE survival curves to account for poorer outcomes in BRAF population?

3. Has the company adequately controlled for subsequent treatments?
4. Equalities