Slides for public observers-contain no ACIC

NICE National Institute for Health and Care Excellence

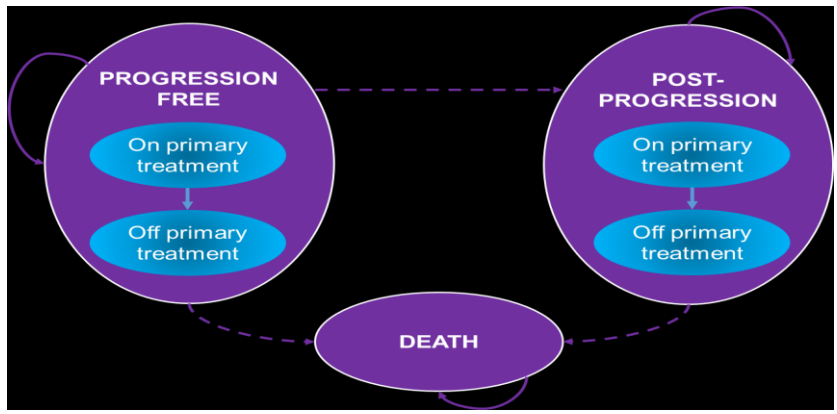
Encorafenib in combination with binimetinib for advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma Lead Team presentation

1st appraisal committee meeting
Cost effectiveness
Committee A
Lead team: Mohit Sharma and Ellen Rule
ERG: Liverpool Reviews and Implementation Group (LRiG)
NICE technical team: Sana Khan, Joanna Richardson
Company: Pierre Fabre
15 November 2018

Key issues - cost effectiveness

- What is the committee's view of the company's model?
- What is the committee's view of the company's data and assumptions?
- Is the committee minded to consider that encorafenib plus binimetinib and dabrafenib plus trametinib are similar?
  - If so is the ERG's suggestion of a cost minimisation approach reasonable?

Company 3 state partitioned survival model comparing Enco+Bini 450 with Dab+Tram



Factor	Chosen values
Time horizon	30 years (lifetime assumed)
Perspective	NHS and PSS
Discount rate	3.5% per year
Cycle length	One month (half cycle correction included)

[redacted]

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Clinical inputs to company model

Efficacy and clinical data inputs used in the model derived from COLUMBUS:

- Patient baseline characteristics
- OS rates from the observed trial period for the Enco+Bini 450 arm
- Probability of PFS during the observed trial period for Enco+Bini 450 arm
- Time on treatment from post-hoc analysis of COLUMBUS for the Enco+Bini 450 arm
- Health related quality of life
- Adverse events

Efficacy and clinical data inputs for the Dab+Tram arm:

- Company NMAs

Clinical data from other sources:

- Extrapolation of OS using survival observations from American Joint Committee on Cancer (AJCC) registry data (then validated by clinical expert opinion)
- General population mortality rates derived from National Life-Tables for England and Wales

[redacted]

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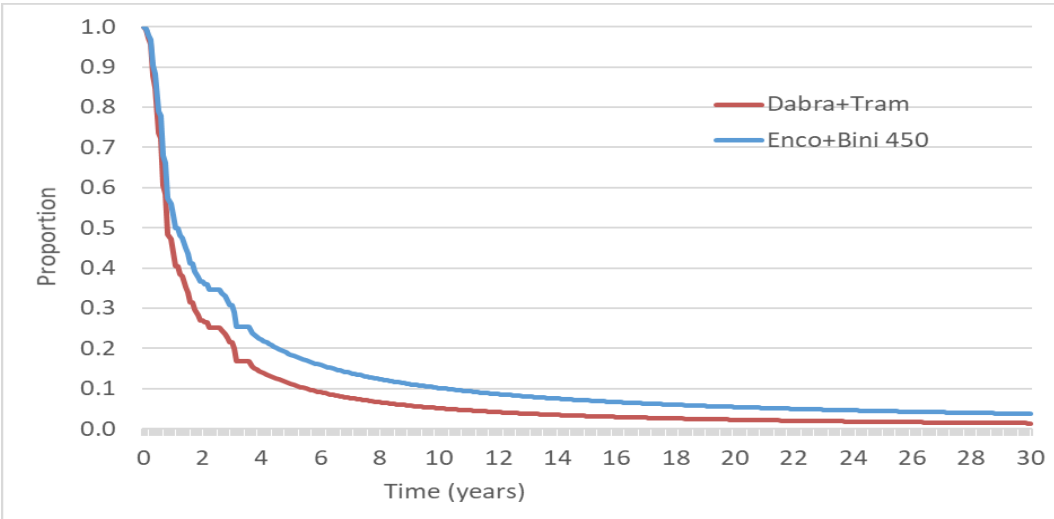
Company model: PFS

Enco+Bini 450: COLUMBUS K-M PFS data by local review until 43 months + gamma parametric extrapolation

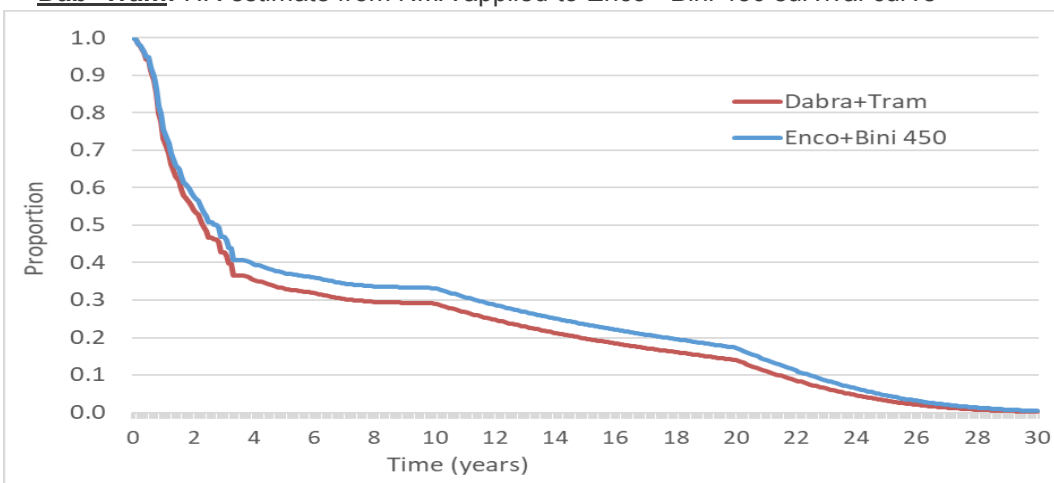
Dab+Tram: HR estimate from NMA applied to Enco+Bini 450 survival curve



Company model: OS

Enco+Bini 450: COLUMBUS K-M OS data till 44 months + adjusted OS K-M curves from AJCC data from 44 months to year 10 + constant hazard extrapolation of OS K-M curves from AJCC during year 10-20 + general population mortality uplifted by increased risk of death in melanoma patients

Dab+Tram: HR estimate from NMA applied to Enco+ Bini 450 survival curve



Company model: health state utilities

- EQ-5D-5L data collected during COLUMBUS. Utility values derived by mapping EQ-5D-5L responses onto the EQ-5D-3L UK valuation set
  - Regression-based method used to control for ECOG PS, AJCC cancer stage, healthcare provider visits, progression status (pre-progression, at disease progression and post-progression) and treatment status (on or off any antineoplastic treatment)
- Company NMA compared utility score for patients treated with Enco+Bini 450 versus those treated with Dab+Tram at pre-progression, at 32 weeks post-treatment and at disease progression.
- NMA results showed that that mean utility score for patients treated with Dab+Tram was higher than the mean utility score for Enco+Bini 450 at the three time-points of interest, but the differences were not statistically significant.

Health state	Utility value, mean (SD)		Source
	Enco+Bini 450	Dab+Tram	
Progression-free	0.778 (0.015)	0.800 (0.015)	NMA
Post-progression	0.675 (0.030)	0.675 (0.030)	NMA

[redacted]

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Company model: adverse events

- AEs are applied in the model as one-off costs and not associated with any particular health state. QoL decrements due to AEs are taken into account within utility values estimated for COLUMBUS patients; therefore no additional AE disutilities are included in the model
- The model incorporates AEs likely to have a notable impact on costs (Grade 3/4 with incidence of at least 5% in either the Enco+Bini 450 arm of COLUMBUS, or the Dabra+Tram arms of COMBI-v and COMBI-d)
  - weighted average of incidence rates from COMBI-v and COMBI-d using data from the latest available data cut-offs used for Dab+Tram, arm

Grade 3/4 AEs	Enco+Bini 450	Dabra+Tram
	COLUMBUS Nov 2016 cut-off	COMBI-d/ COMBI-v weighted average
Hypertension	[redacted]	11.8%
Pyrexia	[redacted]	5.4%
Blood CK increased	[redacted]	0.0%
GGT increased	[redacted]	3.4%
ALT increased	[redacted]	2.5%

Abbreviations: ALT: alanine aminotransferase, CK: creatine phosphokinase, GGT: gamma-glutamyl transferase

[redacted]

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ERG critique: adverse events

- As there is no statistically significant difference in incidence of Grade ≥3 AEs, and the impact of the cost of treating AEs on model cost effectiveness results is negligible, the AE costs associated with Enco+Bini 450 and Dab+Tram can be assumed to be equal
- Use of a simple pooled analysis to compare AE rates from the COMBI-d and COMBI-v trials with AE rates from the COLUMBUS trial does not generate robust results as this approach fails to take account of differences between trials in patient baseline characteristics, recorded AEs, AE definitions and methods for reporting AEs

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ERG critique: values in model

- Values for PFS, OS, utility values in different heath states and AE rates were derived from COLUMBUS. COLUMBUS is a well-conducted trial and trial data has been correctly included in the company model
- In the absence of direct evidence comparing the clinical effectiveness of Enco+Bini 450 versus Dab+Tram, NMAs were carried out by the company which showed no statistically significant difference between Enco+Bini 450 versus Dab+Tram for investigator-assessed PFS, OS, AEs and HRQoL
- Therefore, it is inappropriate to model any difference in efficacy or utility as the results of the NMAs indicate that there are no statistically significant differences in these outcomes

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Company model: costs and resource use

Drug costs for primary treatment:

- Estimate of quantity of Enco+Bini 450 or Dab+Tram used per patient per month derived from COLUMBUS
- Proportion of patients receiving Enco+Bini 450 and Dab+Tram obtained from company base case projection of TTD in the model
- Relative dose intensity multipliers included to account for patients receiving less than full dose
- One-off treatment initiation cost of £415.89 applied for the cost of hospital visits and examinations that are carried out before BRAFI+MEKi therapies are prescribed

Administration costs:

- £15.22 administration cost per model cycle included based on assumption that it takes a pharmacist 12 minutes to dispense Enco+Bini 450 or Dab+Tram

AE costs:

- Total cost per AE calculated using the weighted average cost of inpatient and outpatient costs. Outpatient appointments and inpatient stays considered to be the proportions of people with Grade 3 and Grade 4 AEs in COLUMBUS respectively

Resource use by health state:

- One-off terminal care cost of £7,608 applied to people who transit to the death health state
- Resource use in the post progression health state was divided into routine management during antineoplastic treatment, disease management at progression and the routine management part of BSC with corresponding costs (see table 24 in the ERG report)

[redacted]

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Company model: subsequent therapy cost

- Single, weighted subsequent therapy cost included in the model.
  - Cost is applied to all patients who discontinue either Enco+Bini 450 or Dab+Tram. Applying a one-off subsequent therapy cost unlikely to have a large impact on ICER per QALY gained since the mean treatment duration with subsequent therapy is short
  - Approach is consistent with TA369 that evaluated the cost effectiveness Dab+Tram for advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma
- One-off subsequent therapy cost was calculated as the sum of the weighted total cost for each subsequent therapy
  - Subsequent therapy cost weighted by multiplying the per-cycle cost (drug cost and administration cost) for each therapy by mean treatment duration for therapy
  - For both arms of the model, the total cost for each subsequent therapy was weighted by the proportion of patients in the Enco+Bini 450 arm of COLUMBUS that received that particular therapy

[redacted]

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Company model: base case results (PAS price Enco+ Bini 450, list price Dab+Tram)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc costs	Inc LYG	Inc QALYs	ICER (£/ QALY)
Enco+Bini 450	[redacted]	5.884	4.223	[redacted]	0.613	0.453	Dominant
Dab+Tram	353,603	5.271	3.770				

Deterministic sensitivity analyses showed that the company model is most sensitive to variation in the base case TTD hazard ratio

Probabilistic sensitivity analyses showed that the company model probabilistic results (incremental cost of [redacted] and incremental QALY gain of +0.431) are similar to the model deterministic results.

[redacted]

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Company model: scenario analysis

Most analyses are robust to changes to most model parameters excluding applying a [redacted] discount to the list price of Dab+Tram and assuming equal effectiveness between Enco+Bini 450 and Dab+Tram in terms of OS, PFS, PF utility and AE rates

Scenario	Incremental		ICER
	Costs	QALYs	
Base case	[redacted]	0.453	Dominant
Equal effectiveness for Dab+Tram and Enco+Bini 450 (OS, PFS, PF utility, AE rates)	[redacted]	0.000	Less costly, equal effectiveness
PF utilities equal for Dab+Tram and Enco+Bini 450	[redacted]	0.501	Dominant
HR for TTD for Dab+Tram vs Enco+Bini 450 = 0.9	[redacted]	0.453	Dominant
HR for TTD for Dab+Tram vs Enco+Bini 450 = 1.1	[redacted]	0.455	Dominant
Constant hazard approach for extrapolation of both TTD/ PFS	[redacted]	0.418	Dominant
TTD any reason (not censored)	[redacted]	0.453	Dominant
HR adjustment for AJCC =1	[redacted]	0.366	Dominant
OS crossover adjustment applied	[redacted]	0.422	Dominant
RDIs all set to 1	[redacted]	0.453	Dominant
Remove utility decrement for age	[redacted]	0.461	Dominant
Subsequent treatment option 2	[redacted]	0.453	Dominant
Subsequent treatment option 3	[redacted]	0.453	Dominant
Vial wastage excluded	[redacted]	0.453	Dominant
Exclude terminal care cost	[redacted]	0.453	Dominant
Both grade 3 and 4 AEs hospitalised	[redacted]	0.453	Dominant
List price for both Enco+Bini 450 and Dab+Tram	[redacted]	0.453	Dominant
PAS price for Enco+Bini 450 and [redacted] discount applied to Dab+Tram	[redacted]	0.453	[redacted]
Discount rates 0% for both costs and outcomes	[redacted]	0.664	Dominant
Discount rates 6% for both costs and outcomes	[redacted]	0.358	Dominant

ERG's preferred assumptions and changes to the model

- As OS, PFS, utility values and AEs can all be assumed to be equal for patients treated with Enco+Bini 450 and those treated with Dab+Tram, the only difference between the two treatment combinations that affects model results is treatment-related costs
  - In the company model, treatment-related costs are a function of time on treatment, administration costs, RDI multipliers and drug costs
  - company has assumed that the RDI multiplier associated with treatment with Enco+Bini 450 (Enco 0.91, Bini 0.88) is lower than with Dab+Tram. This analysis is not robust and multipliers should be the same for both treatments
- Time on treatment estimates for patients receiving Enco+Bini 450 and Dab+Tram are also likely to be the same as well as the administration costs of the two treatment combinations (given that they have the same mode of delivery)
- ERG's preferred scenario assumes there is no difference in efficacy (PFS or OS), utility values or AEs between treatments and the RDI multipliers for Enco+Bini 450 and Dab+Tram are both set to 1

[redacted]

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ERG adjustments to company base case (PAS price Enco+Bini, list price Dab+Tram)

Scenario/ERG amendment	Enco+Bini 450		Dab+Tram		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A. Company's base case (RDI values corrected)	[redacted]	4.22	£353,603	3.77	[redacted]	0.45	Dominant
B. ERG preferred scenario (cost-minimisation analysis)	[redacted]	4.22	£373,318	4.22	[redacted]	0.00	-
B1. ERG preferred scenario with RDI multipliers for Enco+Bini 450 and Dab+Tram as in company base case	[redacted]	4.22	£356,094	4.22	[redacted]	0.00	-

- At list prices for both, the ERG's preferred scenario results in estimated costs and QALYs being identical for Enco+Bini and Dab+Tram.
  Using PAS prices only for Enco+Bini, this leads to a cost saving of [redacted] per person compared with Dab+Tram

[redacted]

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