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
Clinical 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 - clinical effectiveness

- How generalisable are the COLUMBUS results?
  - Is COLUMBUS population representative of those who would receive a targeted therapy for a BRAF V600 mutation-positive melanoma in the NHS?
  - In the COLUMBUS trial only 6% of patients had prior immunotherapy. Does this reflect current practice in the NHS or are targeted therapies usually given after immunotherapy in the metastatic setting?
- What is committee's view on the indirect clinical evidence provided by the company?
  - Are the network meta-analyses comparing encorafenib + binimetinib with dabrafenib + trametinib robust?
  - Is there a clinically meaningful difference in the clinical effectiveness of encorafenib + binimetinib and dabrafenib + trametinib?
- Does the committee consider that encorafenib+binimetinib has a more favourable safety profile than dabrafenib + trametinib?

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Background

- Melanoma is a cancer of the skin that in its advanced stages can spread or metastasise to nearby lymph nodes (stage III) or to other parts of the body (stage IV)
- In 2016, melanoma was the fifth most common cancer in the UK. In England, 6% of melanomas were diagnosed at stage III and 2% at stage IV
- Around half of people with stage III melanoma will experience a distant (metastatic) recurrence, for which the prognosis is extremely poor (5-year overall survival [OS] rates range from 5% to 20%)
- A mutated form of the BRAF gene (BRAF V600) is found in about 50% of melanomas. The mutated gene means that the cells produce too much BRAF protein, leading to uncontrolled cell division and growth of the tumour. A diagnostic test is used to detect the BRAF mutation
- Melanoma disproportionately affects a younger population than other cancers, with a significant impact on patients, carers and wider society

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Details of the technologies

	Encorafenib (Braftovi; Pierre Fabre)	Binimetinib (Mektovi; Pierre Fabre)
Marketing authorisation	Encorafenib in combination with binimetinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation	
Mechanism of action	Selective RAF kinase activity inhibitor that suppresses RAF/MEK/ERK pathway in tumour cells expressing mutant BRAF kinase causing the cancer cells to stop growing and die	Inhibitor of MEK1 and MEK2 kinases and blocks the action of the abnormal BRAF protein, with the aim of slowing growth and spread of the cancer
Administration & dosage	Oral, 450 mg (six 75 mg capsules) once daily	45 mg (three 15 mg tablets) twice daily 12 hours apart
Cost	List price for 42 capsules of encorafenib 75 mg: £1,400 (7 day treatment) List price for 28 capsules of encorafenib 50 mg: £622.22 (3.11 day treatment)	List price for 84 tablets of trametinib 15 mg: £2,240 (14 days treatment)
	Patient access schemes agreed for each technology involving a single confidential discount applied to the list price of encorafenib and binimetinib	
Average cost of course of treatment	Based on median dose exposure from COLUMBUS (11.8 months): List price: £129,210 PAS price: £[redacted]	

Treatment pathway in the UK

Immunotherapies recommended by NICE (irrespective of BRAF V600 mutation)	Targeted therapies recommended by NICE (people with BRAF V600 mutation
1. nivolumab in combination with ipilimumab (TA400) 2. nivolumab monotherapy (TA384) 3. pembrolizumab monotherapy (TA366, TA357), and 4. ipilimumab monotherapy (TA319, TA268)	**BRAF inhibitor (BRAFi) monotherapies**: 1. vemurafenib (TA269) 2. dabrafenib (TA321) **BRAFi/MEK inhibitor (MEKi) combination:** 3. dabrafenib and trametinib (TA396)*

NICE clinical guideline 14 and European guidelines from the European Society for Medical Oncology do not state preference for either targeted BRAFi/ MEKi or immunotherapy for first line treatment of BRAF V600 mutation-positive metastatic melanoma:

- ERG clinical expert opinion suggests that first-line treatment in the NHS is with immunotherapy (pembrolizumab, nivolumab or nivolumab with ipilimumab) followed by combination dabrafenib and trametenib (Dab + Tram) on disease progression
- Only subgroup of people with highly symptomatic, rapidly progressing disease are offered Dab + Tram as first-line. Vemurafenib or dabrafenib monotherapy may be used to treat patients with contra-indications to Dab + Tram

Decision problem

	NICE scope	Company submission
Population	Adults with unresectable or metastatic BRAF V600 mutation-positive melanoma	As per scope
Intervention	Encorafenib plus binimetinib	Encorafenib plus binimetinib
Comparator	Dabrafenib with trametinib	Dabrafenib with trametinib
Outcomes	Progression free survival Overall survival Response rate Adverse effects of treatment Health-related quality of life	As per scope
Subgroups	Where the evidence allows, the following subgroups will be considered: • people with previously untreated disease • people with previously treated disease that progressed on or after first line immunotherapy	Subgroups based on prior treatment experience in the metastatic setting not considered in company's economic evaluation due to small patient numbers (6% of people in COLUMBUS trial received prior therapy with immunotherapy in the metastatic setting)

Clinical expert comments

- Aim of treatment is to reduce burden of metastatic disease, minimise symptoms, and extend life while maintaining quality of life (QoL)
- Median survival with immunotherapy and BRAF targeted therapies is at best 3 years.
- Encorafenib + binimetinib is at least as efficacious as the current standard of Dab+Tram
- Encorafenib + binimetinib offers a better side effects profile than current treatments:
  - Current treatments are associated with chronic drug-related toxicity that require treatment interrupting, dose modifications and hospitalisations leading to significantly reduced QoL
  - vemurafenib monotherapy is clinically inferior to combination BRAF/MEK inhibitors and associated with higher skin-related side effects
  - encorafenib+binimetinib would not alter the current pathway of care. Instead, an additional BRAF targeted therapy option would be available for people who are intolerant of other drugs currently approved in this setting
- Both immunotherapy and BRAF targeted therapy are offered as first line treatment to people with advanced BRAF positive melanoma. There is no evidence to support the order of access of these treatments:
  - all patients with BRAF mutation should be offered access to BRAF directed therapy at some stage in their treatment pathway
- Encorafenib+binimetinib offers benefits to the NHS and to patients in requiring less safety monitoring, fewer treatment-related hospitalisations and not requiring refrigeration

[redacted]

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Patient perspective (Melanoma UK)

- Stress of living with melanoma can be seen physically, mentally and emotionally in both patients and carers
- Patients with BRAF-mutant melanoma still face significant challenges managing their disease and there remains a substantial need for well-tolerated treatments that delay disease progression and improve overall survival
- Key concerns for patients include uncertainty about their future, outcomes if melanoma were to spread or return and the lack of adequate/limited treatment options available
- Most patients do not know the significance of QALY, they are too busy fighting for their life

[redacted]

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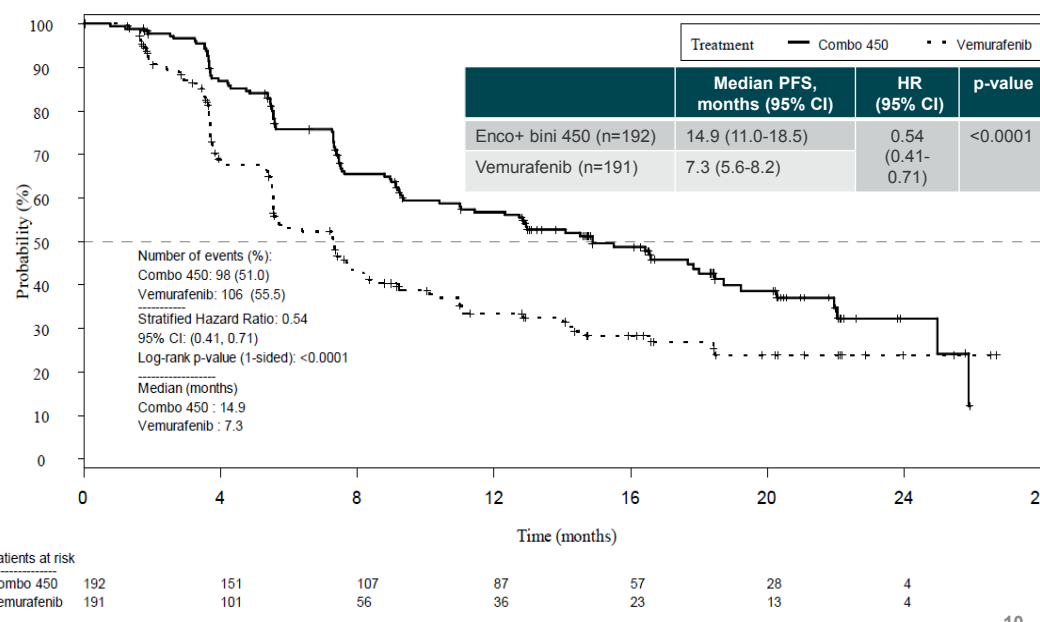
Company's clinical evidence: COLUMBUS

Design	**2 part, open-label RCT (only part 1 of the trial relevant to appraisal)**
Population (Part 1 relevant to decision problem only) (n= 577)	Adults with histologically confirmed locally advanced unresectable or metastatic BRAF V600E/V600K-mutant melanoma (cutaneous or unknown primary, stage IIIB, IIIC or IV). Treatment naïve or progressed on or after previous immunotherapy (6%) 72% ECOG P0 28% ECOG PS 1
Intervention	Enco+Bini 450 arm: encorafenib 450 mg QD plus binimetinib 45 mg BID (n=192)
Comparator	Vemurafenib arm: vemurafenib 960 mg BID monotherapy (n=191) Enco 300 arm: encorafenib 300 mg QD monotherapy (n=194)
Location	162 international study sites in 28 countries from Europe (including 8 sites in the UK), North America and selected other countries. 14 patients from the UK were included in the analysis of the trial
Primary outcome	Progression free survival (PFS) for Enco+Bini 450 vs vemurafenib
Other outcomes	• Overall survival (OS) • Overall response rate (ORR) • Duration of response (DOR) • Disease control rate (DCR) • Time to objective response (TTR) • Patient reported outcomes • Adverse events
Duration of study and follow-up	Median follow-up time was 32.3 months (range 31.7-34.9) in the encorafenib plus binimetinib arm and 22.2 months (range 11.1-32.3) in the vemurafenib arm at data cut-off of 7th November 2017)

Primary efficacy outcome: blinded independent review (BIRC) PFS FAS population, data cut-off 19 May 2016



Abbreviations: FAS- full analysis set

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PFS by BIRC and local investigator review for Enco+Bini 450 compared to vemurafenib

	Enco+Bini 450 N=192	Vemurafenib N=191
BIRC, FAS, Part 1, data-cut off 19 May 2016		
Patients with events (% of total)	98 (51.0)	106 (55.5)
HR (95% CI), stratified one-sided log-rank p-value	0.54 (0.41 to 0.71); p<0.0001	
BIRC, FAS, Part 1, data-cut off 7 November 2017		
Patients with events (% of total)	[redacted]	[redacted]
HR (95% CI), stratified one-sided log-rank p-value	0.51 (0.39 to 0.67); p<0.0001	
Investigator review, FAS, Part 1, data-cut off 19 May 2016		
Patients with events (% of total)	102 (53.1)	121 (63.4)
HR (95% CI), stratified one-sided log-rank p-value	0.49 (0.37 to 0.64);p<0.0001	
Investigator review, FAS, Part 1, data-cut off 7 November 2017		
Patients with events (% of total)	[redacted]	[redacted]
HR (95% CI), stratified one-sided log-rank p-value	[redacted]	

[redacted]

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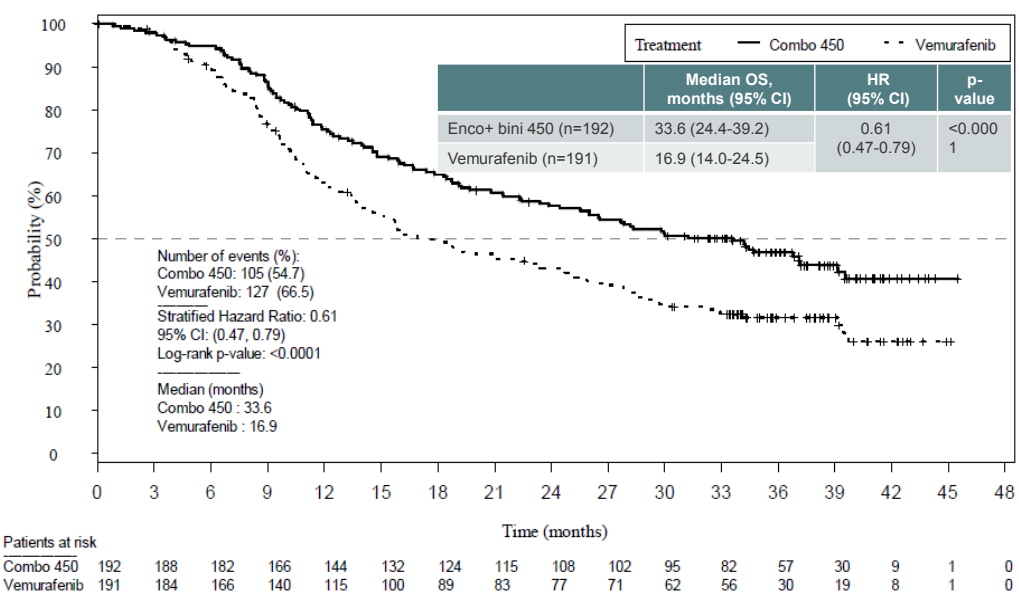
Secondary efficacy outcome: Interim OS FAS population, data cut-off 7th November 2017



Abbreviations: FAS- full analysis set

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Adverse events (data cut off 9th November 2016)

- People in the Enco+Bini 450 arm had longer time on treatment compared with other 2 arms of trial but frequency of AEs was similar in all groups of patients
- The most common any grade AEs in Enco+Bini 450 arm were nausea [redacted], diarrhoea [redacted], vomiting , fatigue [redacted], arthralgia [redacted] increased creatine phosphokinase [redacted], headache [redacted], constipation [redacted], and asthenia [redacted]
- The most common all grade SAEs were pyrexia [redacted], abdominal pain [redacted], acute kidney injury [redacted] and anaemia [redacted] in the Enco+Bini 450 arm and general physical health deterioration [redacted] in the vemurafenib arm

- Adverse events profile is for comparison with vemurafenib and not relevant comparator (Dab +Tram)

[redacted]

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ERG critique: overview of clinical evidence

- COLUMBUS is a good quality, well conducted trial that included blinded independent review of PFS outcomes and collection of HRQoL data
- Patients recruited to the trial largely representative of patients with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma in the NHS.
  - However, very few people in COLUMBUS had brain metastases and none had a poor PS (i.e., PS ≥2)
- Although outcomes of COLUMBUS favour the use of Enco+Bini 450 and show that it has a favourable safety profile, the trial does not provide direct evidence for the clinical effectiveness of Enco+Bini 450 versus Dab+Tram
- Only descriptive OS data from COLUMBUS provided due to the limitations imposed by the hierarchical approach to statistical testing used to analyse the COLUMBUS trial data

[redacted]

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Indirect clinical evidence: mixed treatment comparisons via network meta-analyses

- No direct evidence comparing Enco+Bini 450 with dabrafenib in combination with trametenib (Dab+Tram), so the company carried out network meta-analyses (NMAs) to indirectly estimate relative treatment efficacy (PFS and OS), HRQoL and incidence of grade 3/4 AEs
- Response rates were not included in NMA's & incidence of AEs other than grade 3/4 also not considered (RCTs were not powered to detect differences in specific AEs)
- 7 RCTs (COLUMBUS, COMBI-v, COMBI-d, BRF113220 Part C, coBRIM, BREAK-3 and BRIM-3) investigating BRAFi therapies reported clinical efficacy and safety data. 5 RCT's also reported HRQoL data
- Company NMA results based on fixed-effects models. This was considered appropriate in preference to random-effects models due to sparseness of networks of evidence (consisting mainly of a single RCT per pairwise comparison)
- Investigator assessed (rather than BIRC) PFS included in the NMA'S as BIRC data not available for all trials

[redacted]

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NMA results

NMA results for PFS	HR (95% CrI)	
	Enco+Bini 450 vs Dab+Tram	Dab+Tram vs Enco+Bini 450
Base-case	0.77 (0.57,1.04)	1.30 (0.96,1.77)
NMA results for OS	**HR (95% CrI)**	
	Enco+Bini 450 vs Dab +Tram	**Dab+Tram vs Enco+Bini 450**
Base-case	0.89 (0.65,1.23)	1.12 (0.81,1.53)
NMA results for EQ-5D utility score	**Dt (95% CrI)**	
	Enco+Bini 450 vs Dab+Tram	**Dab+Tram vs Enco+Bini 450**
EQ-5D utility score, pre-progression	-0.02 (-0.05, 0.01)	0.02 (-0.01, 0.05)
EQ-5D utility score, DCFB at Week 32	-0.04 (-0.10, 0.02)	0.04 (-0.02, 0.10)
EQ-5D utility score, DCFB at disease progression	-0.04 (-0.12, -0.04)	0.04 (-0.04, 0.12)
NMA results for any grade ≥3 AEs	**OR (95% CrI)**	
	Enco+Bini 450 vs Dab+Tram	**Dab+Tram vs Enco+Bini 450**
	1.18 (0.70, 1.98)	0.85 (0.51, 1.43)

- NMAs comparing Enco+Bini 450 with Dab+Tram showed no statistically significant difference for investigator-assessed PFS, OS, AEs and HRQoL. For all base case and sensitivity analyses, credible intervals (CrIs) were wide and crossed 1

[redacted]

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Company assessment of NMA limitations

- Some of included trials permitted crossover of patients, possibly leading to underestimate of benefits
  - Crossover-adjusted estimates of OS HR using the rank-preserving structural failure time model considered in a sensitivity analysis showed similar results to base-case estimates
- The majority of trials were open-label (potential source of bias for subjective endpoints, such as PFS and patient-reported outcomes such as HRQoL)
  - PFS results from COMBI-v (open-label) and COMBI-d (double-blinded), which both assessed Dab+Tram, demonstrated similar absolute median PFS results (11.4 months vs. 11 months) suggesting that the impact of blinding on PFS may be minimal
- Assessment of effect modification found small study design and population variations within RCTs included in the NMAs. Variation was largely driven by studies of BRAFi treatments not directly relevant to this appraisal:
  - Sensitivity analyses of PFS evaluating the impact of using post-hoc data from COLUMBUS adjusting for stratification factors and other baseline variables produced similar results to base-case analysis

[redacted]

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ERG critique: NMAs

- The patient population in COLUMBUS is similar to the patient populations in the COMBI-v and COMBI-d RCTs (sources used by the company for clinical effectiveness evidence for treatment with Dab+Tram).
- The PFS outcome results from the vemurafenib arms of the COLUMBUS trial and the COMBI-v trial are comparable.
- However results from the NMAs should be viewed with caution due to numerous methodological limitations. These include:
  - sparsity of evidence in the networks (particularly HRQoL network),
  - variability in lengths of trial follow-up (2 years to 6 years),
  - differences between trials in median follow-up for OS (11 months to 33.3 months),
  - inclusion of dacarbazine within the networks,
  - NMA of PFS by local investigator review (rather than BIRC) was only feasible.
  - 5 of the 7 trials included within the NMAs were open-label; therefore investigator assessment of PFS in open-label trials may be subject to bias.
- Clinical expert opinion however highlights that the clinical effectiveness outcomes for patients who are treated with Enco+Bini 450 and Dab+Tram are likely to be similar

[redacted]

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Key issues - clinical effectiveness

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[redacted]

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