Lead team presentation Dabrafenib in combination with trametinib for adjuvant treatment of resected BRAF V600 positive malignant melanoma

1st Appraisal Committee meeting

Background and Clinical Effectiveness

Committee A

Lead team: Adrian Griffin, Justin Daniels and Pam Rees

ERG: Warwick Evidence

NICE technical team: Sana Khan, Zoe Charles

19 July 2018

Key issues - clinical effectiveness

- What are the committee's conclusions on COMBI-AD?
  - quality, risk of bias and generalisability?
- The active treatment was for 12 months, what conclusions can be drawn about relapse free survival and the effect on overall survival given the immaturity of the data?
- A key uncertainty is whether treatment with dabrafenib and trametinib mainly postpones disease recurrence or permanently cures the disease. Remaining disease-free and the avoidance of metastatic disease drive the QALY gains. What is the committee's view on this?
- The American Joint Committee on Cancer (AJCC) 8th edition has redefined stage III groupings and included an additional stage IIID subgroup. Does the committee consider this will affect the generalisability of COMBI-AD to clinical practice in England in the future?

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Disease 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)
- It occurs more commonly in fair-skinned people and there is strong evidence that ultra violet exposure is causal. People with an above-average mole count, sun-sensitive skin, or a strong family history of melanoma are at increased risk
- In 2016, melanoma was the fifth most common cancer in the UK, with over 13,000 cancer registrations. 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 historically 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 40-65% 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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Current management

- Standard treatment of stage III melanoma, usually possible for 90% of patients, is resection including removal of the primary tumour and associated lymph nodes
- Following complete resection, people are still at a high risk of disease recurrence, with 5- and 10-year relapse free survival (RFS) rates of 57% and 36%[1]
- In the EU, interferon-α-2b is the only licensed therapy for the adjuvant treatment of stage III melanoma in people who are disease-free after surgery but at high risk of systemic recurrence
  - however, interferon-α-2b is not used in clinical practice in the UK because of uncertainty in the reported overall survival (OS) benefit and associated adverse events
- Standard of care for patients with resected stage III melanoma in the UK is routine surveillance which includes regular clinical review and imaging surveillance

[1] Leiter U, Buettner PG, Eigentler TK, et al. Hazard rates for recurrent and secondary cutaneous melanoma: an analysis of 33,384 patients in the German Central Malignant Melanoma Registry. J Am Acad Dermatol 2012;66:37-45.

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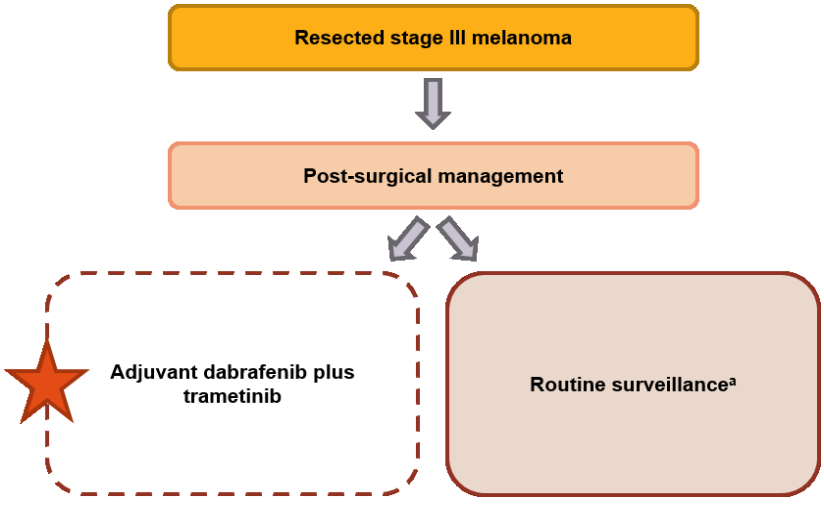
Details of the technologies

	Dabrafenib (Tafinlar; Novartis)	Trametinib (Mekinist; Novartis)
Anticipated MA	[redacted]	
Mechanism of action	Selective inhibitor of BRAF V600 kinase activity and blocks the activity of mutant protein 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,150 mg (two 75 mg capsules) twice daily	2 mg (one tablet) once daily
Duration of treatment	12 months or less if there is disease recurrence or unacceptable toxicity	12 months or less if there is disease recurrence or unacceptable toxicity
Cost	List price for 28 capsules of dabrafenib 75 mg: £1,400	List price for 30 tablets of trametinib 2 mg: £4,800
	Patient access schemes agreed for each technology involving a single confidential discount applied to the list price of dabrafenib and trametinib	
Avg cost of course of treatment	Based on average number of packs in COMBI-AD: List price: £[redacted] PAS price: £[redacted]	
Other licensed indications	Licensed as monotherapies or in combination for treatment of adults with unresectable or metastatic melanoma with a BRAF V600 mutation. Recommended in NICE TA 396 (combination) and TA321 (Dabrafenib)	

Treatment Pathway in the UK



Adapted from NICE NG14 and expert clinician feedback

[a] No adjuvant systemic therapies included in NG14

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Decision problem

	NICE scope	Company submission
Population	People with completely resected, stage III melanoma with BRAF V600 positive mutations	Adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection
Intervention	Dabrafenib plus trametinib	Dabrafenib plus trametinib
Comparator	Routine surveillance	Routine surveillance
Outcomes	Overall survival Relapse-free survival Distant metastases free survival Adverse effects of treatment Health-related quality of life	Relapse-free survival Overall survival Distant metastases free survival Freedom from relapse Adverse effects of treatment Health-related quality of life

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Clinical expert comments

- Aim of the new treatment is to reduce the risk of people diagnosed with primary melanoma developing metastatic disease, thereby improving overall survival
- No adjuvant treatment currently available. Standard of care is observation with additional scanning for patients at high risk of developing metastases – there is a major unmet need
- Adjuvant treatment with dabrafenib and trametinib will require additional resource use in the form of more staff, outpatient visits and investigations with subsequent effects on additional appointments, blood tests and imaging
- Treatments are generally well tolerated and side effects are manageable with quality of life maintained
- A clinically significant treatment response would be a reduction in the risk of relapse or death by more than 10%
- Expectation that significant numbers of patients will be cured with adjuvant treatment

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Company's clinical evidence: COMBI-AD

Design	Randomised, double-blind, placebo-controlled, phase III
Population (n= 870)	Adults with completely resected, histologically confirmed, BRAF V600E/K mutation-positive, high risk (defined as stage IIIA [lymph node metastasis >1 mm], IIIB or IIIC) cutaneous melanoma; patients with initial resectable lymph node recurrence after a diagnosis of stage I or II melanoma were also eligible
Intervention	Dabrafenib 150 mg twice daily plus trametinib 2 mg once daily for 12 months **(n=438)**
Comparator	Two matched placebos for 12 months **(n=432)**
Location	169 international study sites in 26 countries from Europe (including 13 sites in the UK), North and South America, Asia and Oceania. This included 86 patients from the UK: [redacted]
Primary endpoint	Relapse free survival (RFS) - investigator assessed
Key secondary endpoints	• Overall survival (OS) • Distant metastasis free survival (DMFS), • Freedom from relapse (FFR) • Safety
Duration of study and follow-up	Treatment period 12 months. Discontinuation could occur earlier due to disease recurrence, death, unacceptable toxicity or withdrawal of consent. Median follow-up time was [redacted] in the dabrafenib plus trametinib arm and [redacted] in the placebo arm at data cut-off for the primary analysis (30th June 2017)

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Baseline characteristics in COMBI-AD

Characteristic	Dabrafenib plus trametinib (N=438)	Placebo(N=432)
Demographics		
Age, median years (range)	50 (18–89)	51 (20–85)
Sex, n (%)		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Disease characteristics		
BRAF mutation status, n (%)		
V600E	397 (91)	395 (91)
V600K	41 (9)	37 (9)
Disease stage, n (%)		
IIIA	83 (19)	71 (16)
IIIB	169 (39)	187 (43)
IIIC	181 (41)	166 (38)
III unspecified	5 (1)	8 (2)
Prior therapy		
Sentinel lymphadenectomy, n (%)	[redacted]	[redacted]
Lymph node dissection, n	[redacted]	[redacted]
Median number of lymph node removed	[redacted]	[redacted]
Median time from initial diagnosis (months)	[redacted]	[redacted]

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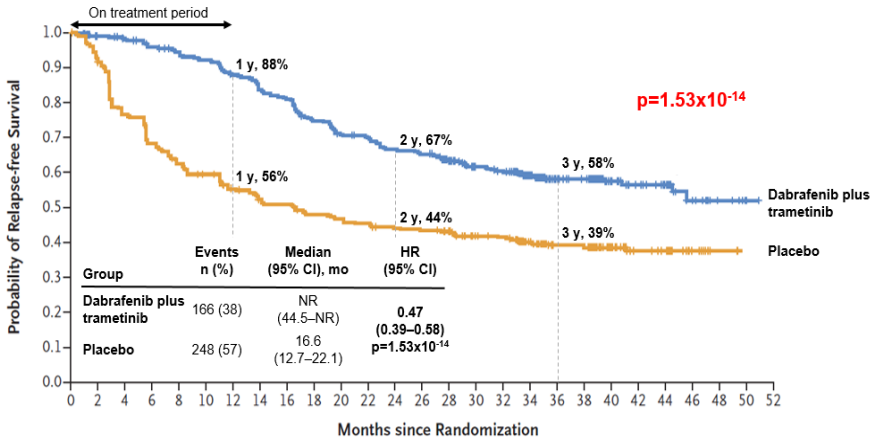
Primary efficacy results: investigator assessed RFS (ITT population)

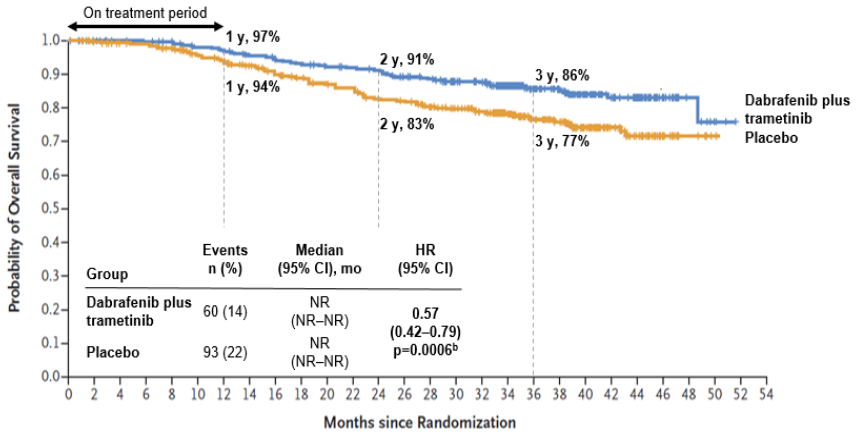


No. at Risk

Dabrafenib plus trametinib	438	413	405	392	382	373	355	336	325	299	282	276	263	257	233	202	194	147	116	110	66	52	42	19	7	2	0
Placebo	432	387	322	280	263	243	219	203	198	185	178	175	168	166	158	141	138	106	87	86	50	33	30	9	3	0	0

Abbreviations: CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat; NR: not reached; RFS: relapse-free survival. 11

Secondary efficacy results: OS (ITT population)

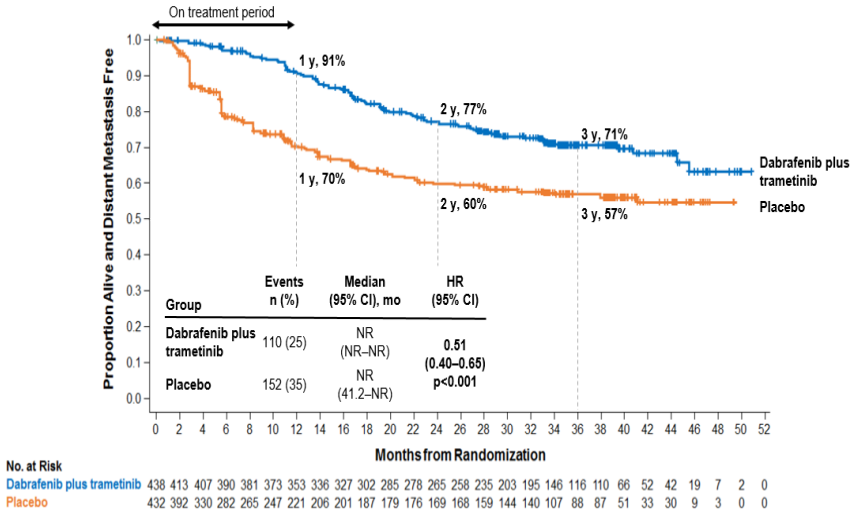


No. at Risk

Dabrafenib plus trametinib	438	426	416	414	408	401	395	387	381	376	370	366	362	352	328	301	291	233	180	164	105	82	67	28	12	5	0	0
Placebo	432	425	415	410	401	386	378	362	346	337	328	323	308	303	284	269	252	202	164	152	94	64	51	17	7	1	0	0

[b] Prespecified significant boundary p=0.000019.
Abbreviations: CI: confidence interval; ITT: intention-to-treat; NR: not reached; OS: overall survival. 12

Secondary efficacy results: distant metastasis-free survival (ITT population)



Abbreviations: CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat.

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Exploratory efficacy results: patient reported HRQoL (EQ-5D-3L)

[redacted]

- [redacted]
- When assessed using mixed-model repeated measures analyses, there was [redacted]
- NOTE: COMBI-AD was not powered to detect differences in HRQoL

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Dose modification and discontinuation rates in COMBI-AD

- Dose interruptions were more frequent in the treatment arm ([redacted]) compared to placebo ([redacted])
  - most common reason was [redacted] in the treatment arm ([redacted]), and [redacted] in the placebo arm ([redacted])
- Dose reductions were [redacted] in the treatment arm([redacted]) compared to placebo ([redacted]).
  - most common reasons in both arms were [redacted]
- Permanent discontinuation of a trial drug due to AEs occurred in 114 patients (26%) in the treatment arm compared with 12 (3%) in placebo arm
  - company notes that rate of treatment discontinuation was higher than observed for metastatic disease

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Adverse events

- Safety population included patients who received at least one dose of randomised treatment (435 people in treatment arm; 432 people on placebo)
- At least one AE was reported in 97% of patients in the treatment arm and 88% of patients in placebo arm, with serious adverse events (SAEs) occurring in 36% and 10% of the treatment and placebo arms respectively
- Most frequently reported AEs in the treatment arm were pyrexia (63% of patients), fatigue (47%), and nausea (40%). With placebo, these were fatigue (28%), headache (24%), and nausea (20%)
- AEs related to study treatment (grade 1 or 2 in severity) occurred in [redacted] of people in the treatment arm and [redacted] in the placebo arm:
  - [redacted]
- [redacted]

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ERG's comments on clinical evidence

- COMBI-AD was well conducted, quality is reasonable, and baseline demographic characteristics of patients are comparable to patients in the UK, however:
  - potential bias from imbalance between study arms in numbers and timing of patients ending follow-up before study cut-off may influence outcomes, especially those involving time to event analysis
  - higher rate in placebo arm of deaths from non-melanoma or unknown causes may be suggestive of poorer health at baseline or differences in post recurrence treatments
  - some outcomes were investigator-assessed when they could have been assigned to an Independent Review Committee masked to treatment assignments
  - imaging to detect recurrence was only performed every 3 months during the first 24 months and every 6 months thereafter. Accuracy of RFS may be limited due to this
- Data is immature for both RFS and OS:
  - a major uncertainty is whether dabrafenib and trametinib delays disease recurrence, so that recurrence incidence in the intervention arm eventually catches up with that in the control arm, or whether treatment leads to a proportion of patients being "cured"
  - pattern of recurrence is not well served by the composite outcome (RFS) used in most adjuvant trials

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ERG comments on adverse events

- Concern that, in [redacted] patients in the placebo arm who had serious side effects, these were related to study treatment
  - remaining patients in the placebo arm were assumed to have experienced a SAE due to underlying disease morbidities
  - therefore, difficult to decipher whether AEs in the intervention arm were also due to progression of the underlying disease/patient comorbidities, or the treatment itself
- Concern that side effects which may potentially be responsible for malabsorption of drugs, such as diarrhoea, reported in 115 patients in the treatment arm, may preclude compliance and efficacy of treatment
- Costs for some AEs may be underestimated as they are difficult to predict in a non-trial setting (costs discussed further under cost effectiveness)

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