NICE Final Appraisal Determination recommends Tafinlar® (dabrafenib) + Mekinist® (trametinib) for adult patients with advanced melanoma in England

- Patients have been unable to access the combination since its launch in September 2015 due to the closure of the Cancer Drugs Fund to new medicines last year
- The NICE decision to proceed straight to Final Appraisal Determination (FAD) is expected to lead to significantly faster access for patients in need of this important new treatment option
- Dabrafenib + trametinib is the first oral combination treatment for patients with advanced melanoma, the most serious form of skin cancer

Frimley, 29 April, 2016 - The National Institute for Health and Care Excellence (NICE) has today issued a positive Final Appraisal Determination recommending the routine NHS use of Tafinlar® (dabrafenib) + Mekinist® (trametinib), the first targeted oral combination therapy to be licensed for for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

Metastatic melanoma is the most serious and life-threatening type of skin cancer, with only 20% of patients living beyond five years of diagnosis. There are more than 13,000 cases of melanoma a year in the UK, around 37 new cases a day. Within a decade, melanoma is predicted to be the fourth most common cancer for men and women in the UK.

Like many cancers, abnormal gene changes (mutations) can lead to the development of melanoma. Approximately half of all melanoma cases have what is known as a BRAF mutation, which leads to uncontrolled growth of the skin cells and the development of tumours. The combination of dabrafenib + trametinib targets two different proteins that are involved in the development of these tumours to block their activity and slow growth of the tumours. Using both medicines as a combination has been shown to be more effective than a BRAF inhibitor on its own.

"Understanding what drives melanoma at a genetic level has transformed the way we treat this devastating cancer. The positive recommendation is important news for patients who have been waiting to obtain access to this new treatment option. This combination has been shown to be more effective than monotherapy in extending the time before the cancer progresses and for the first time we are seeing median overall survival of more than two years alongside an acceptable safety profile," said Dr Paul Nathan, Consultant Medical Oncologist, Mount Vernon Cancer Centre, Middlesex.

"Evidence presented to the NICE committee demonstrated the major impact of advanced melanoma on both the quality and length of life for patients. The conclusion of the committee reflects the views of clinicians and patients that the availability of a new combination treatment that slows disease progression and improves quality of life is very important to patients and their families", he added.

"At Novartis, we are delighted with this decision, particularly the unusual step of NICE proceeding straight to Final Appraisal Determination, which should mean significantly faster access for patients", said Barbara McLaughlan, Head of External Affairs, Novartis Oncology UK and Ireland. "We have worked hard to provide NICE with the evidence and
an agreed discount through patient access schemes in the hope that this decision could be reached as soon as possible for patients. This positive guidance reinforces the views and submissions from the clinical and patient community that strongly supported the need for this combination treatment as a new option for people living with this devastating cancer."

- Ends -

Notes to editors

The MAPK pathway and the dabrafenib + trametinib combination
The Mitogen-Activated Protein Kinase (MAPK) pathway regulates the normal growth and death of cells, including skin cells. When signaling in the MAPK pathway is disrupted, it can be responsible for uncontrolled cell growth that leads to cancer.

In about half of all melanomas, MAPK signaling is altered by a mutation in the BRAF gene. These changes cause the gene to make an altered BRAF protein that signals the melanoma cells to grow and divide quickly.6

Dabrafenib and trametinib work to block abnormal signalling, targeting two specific points in the pathway, potentially stopping or slowing tumour cell growth.9-12

Dabrafenib binds to, and inhibits the activity of the altered BRAF protein, and can be used alone to treat metastatic melanoma. However, the disease eventually becomes resistant to BRAF inhibition, activating another point on the MAPK pathway - the MEK protein kinase. This continues to promote the growth of tumour cells.

Trametinib binds to, and inhibits the activity of, the MEK protein kinase.9-12

Therefore, dual targeted treatment with dabrafenib + trametinib may delay resistance by providing more complete inhibition of the MAPK pathway.7,8

Clinical data
The EU license for the combination of dabrafenib + trametinib is based on results from the Phase III COMBI-v7,13 and COMBI-d8 studies.

COMBI-v
COMBI-v was a two-arm, open-label, Phase III study comparing the combination of dabrafenib + trametinib with vemurafenib monotherapy in patients with BRAF V600E/K mutation-positive unresectable or metastatic melanoma. The primary endpoint of this study was overall survival (OS).

Updated results from the study demonstrated that the combination of dabrafenib + trametinib achieved:

- a statistically significant OS benefit compared to vemurafenib monotherapy (median for the combination 25.6 months vs 18.0 months; HR 0.66 [95% CI, 0.53-0.81], p<0.001)13
- a statistically significant reduction of 39% in the risk of death among patients receiving combination therapy13
- a progression free survival (PFS) of 12.6 months vs. PFS of 7.3 months for vemurafenib monotherapy; HR 0.61 [95% CR 0.51-0.73], p<0.001
- an Overall Response Rate (ORR) of 65.6% vs 52.8% for vemurafenib monotherapy14
- a median duration of response (DoR) of 13.8 months compared to a DoR of 8.5 months for vemurafenib monotherapy13
The most frequent adverse events in the Tafinlar + Mekinist combination arm (>=30%) were pyrexia (fever), nausea, diarrhoea, and chills.\(^\text{13}\)

Adverse events occurring more frequently in the combination arm compared with the vemurafenib monotherapy arm included pyrexia, 53% (n=184) vs 21% (n=73), respectively, and bleeding events, 18% (n=62) vs 7% (n=25), respectively.\(^\text{13}\)

For the combination group compared to the vemurafenib group, there was a lower incidence of rash, 22% (n=76) vs 43% (n=149); photosensitivity reaction, 4% (n=13) vs 22% (n=78); hand-foot syndrome, 4% (n=14) vs 25% (n=87); skin papillomas, 2% (n=6) vs 23% (n=80); squamous-cell carcinomas and keratoacanthomas, 1% (n=5) vs 18% (n=63); and hyperkeratosis, 4% (n=15) vs 25% (n=86).\(^\text{13}\)

**COMBI-d**

COMBI-d was a pivotal Phase III, randomised, double-blinded study comparing the combination of dabrafenib + trametinib to dabrafenib monotherapy and placebo in patients with unresectable (Stage IIIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma. The study randomised 423 patients and the primary endpoint of this study was investigator-assessed progression-free survival (PFS). Secondary endpoints included overall survival (OS), overall response rate (ORR), duration of response (DoR), and safety. There was no crossover between treatment arms.

Updated results from the COMBI-d study showed that the combination of dabrafenib + trametinib achieved:

- a statistically significant OS benefit compared to dabrafenib monotherapy (median of 25.1 months vs 18.7 months; HR 0.71 [95% CI, 0.55-0.92], p=0.011). In those who received the combination, OS was 74% at 1 year and 51% at 2 years versus 68% and 42% for those who received monotherapy only, respectively.\(^\text{8}\)
- The analysis for the combination also showed median PFS of 11.0 months, ORR of 69%, and median DoR of 12.9 months.\(^\text{8}\)

The most common adverse events (>=20%) in the combination arm were pyrexia (fever), fatigue, nausea, headache, chills, diarrhoea, rash, arthralgia (joint pain), hypertension, vomiting, cough, and peripheral oedema.\(^\text{8}\)

Increased incidence (57% vs 33%) and severity (grade 3, 7% (n=15) vs 2% (n=4)) of pyrexia (fever) occurred with combination treatment as compared to monotherapy.\(^\text{8}\)

There was a lower incidence of cutaneous squamous cell carcinoma (cuSCC) including keratoacanthoma with the combination arm (3% (n=6)) compared to the monotherapy arm (10% (n=22)).\(^\text{8}\)

**Quality of life**

Dabrafenib + trametinib is the first combination therapy to report significantly improved overall Quality of Life (QoL) over BRAF inhibitor monotherapy.\(^\text{1}\)

QoL was assessed using three recognised QoL measures that are used in thousands of studies worldwide to assess the quality of life of patients in clinical studies.

**NICE process**

By publishing a Final Appraisal Determination (FAD), NICE has made its final recommendations on how dabrafenib + trametinib should be used in the NHS. If there are no successful appeals, the final recommendations will be issued as NICE guidance.
**Reporting of side effects**
This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) for how to report side effects.

**About Novartis**
Novartis provides innovative healthcare solutions that address the evolving needs of patients and societies. Headquartered in Basel, Switzerland, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, eye care and cost-saving generic pharmaceuticals. Novartis is the only global company with leading positions in these areas. In 2015, the Group achieved net sales of USD 49.4 billion, while R&D throughout the Group amounted to approximately USD 8.9 billion (USD 8.7 billion excluding impairment and amortization charges). Novartis Group companies employ approximately 119,000 full-time-equivalent associates. Novartis products are available in more than 180 countries around the world. For more information, please visit [http://www.novartis.com](http://www.novartis.com).

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**References**

1. Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma. Final appraisal determination. NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. Available at: [https://www.nice.org.uk/guidance/ind/19365](https://www.nice.org.uk/guidance/ind/19365).

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