About Tafinlar® (dabrafenib) and Mekinist™ (trametinib) Combination Therapy and Metastatic Melanoma

What is Metastatic Melanoma?
Melanoma is the most serious type of skin cancer and develops when unrepaired DNA damage to skin cells triggers genetic changes that cause them to form malignant tumors. If melanoma metastasizes, or spreads to other parts of the body, it becomes difficult to treat and can be fatal.

There are about 200,000 new cases of melanoma diagnosed worldwide each year. While the average age of a newly diagnosed melanoma patient is 61, it is the most common cancer in young adults, ages 25-29. In some parts of the world, especially Western countries, melanoma is becoming more common every year. Due to their relative lack of skin pigmentation, Caucasian populations have a much higher risk of getting melanoma than dark-skinned populations. However, excessive exposure to intense sunlight can damage any skin type.

Melanoma is the most common cancer killer of young women, more common than breast cancer in ages 29 – 34. About one in two patients worldwide with metastatic melanoma is expected to survive for a year after diagnosis of metastatic disease, with approximately 46,000 annual melanoma-related deaths worldwide.

What Role Do Genes Play in Melanoma?
Melanoma is a complex genetic disease, and multiple genetic alterations have been reported to play a role in the disease’s progression. In metastatic melanoma, approximately half of all patients have a mutation known as BRAF. Of those, more than 70 percent have a BRAF V600E mutation and approximately 20 percent have a BRAF V600K mutation.

Genetic tests should be performed on patients with melanoma to determine whether their tumor demonstrates a gene mutation. Results can play a key role in prognosis and determining which treatment is the most appropriate therapy for the genetic makeup of the tumor. New targeted therapies are changing the treatment landscape for patients with metastatic melanoma.

About Tafinlar (dabrafenib) and Mekinist (trametinib) Combination Therapy in Metastatic Melanoma
- Tafinlar (dabrafenib) and Mekinist (trametinib) are the first oral targeted therapies approved in the United States as a combination treatment in adult patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test. They are not currently approved for this indication anywhere else in the world.
- Tafinlar and Mekinist are also indicated in more than 35 countries worldwide as single agents to treat patients with unresectable or metastatic melanoma.
- Tafinlar, targeting BRAF, and Mekinist, targeting MEK, target two different tyrosine kinases in the RAS/RAF/MEK/ERK pathway. Cancer cells that do not respond to BRAF inhibitors use alternate pathways to grow and divide, which can be targeted by Mekinist. When used with Tafinlar, the combination has been shown to slow tumor growth more effectively compared with either drug alone.
Clinical Evidence Supporting Tafinlar and Mekinist in Metastatic Melanoma
A multicenter, open-label, randomized Phase II study of 162 patients with BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma demonstrated the following results11,12:

<table>
<thead>
<tr>
<th>Efficacy outcome measure based on investigator assessment</th>
<th>Tafinlar (150mg) + Mekinist (2mg)</th>
<th>Tafinlar (150mg)</th>
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<tr>
<td><strong>Overall Response Rate</strong> The percentage of patients who achieve a partial response or better after starting treatment.</td>
<td>76% (95% CI, 62, 87)</td>
<td>54% (95% CI, 40, 67)</td>
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<td><strong>Median Duration of Response</strong> The median length of time tumor reduction lasted before disease progression.</td>
<td>10.5 months (95% CI, 7, 15)</td>
<td>5.6 months (95% CI, 5, 7)</td>
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Safety Profile of Tafinlar and Mekinist Combination Therapy

The most common adverse reactions (≥20%) for Tafinlar in combination with Mekinist are pyrexia, chills, fatigue, rash, nausea, vomiting, diarrhea, abdominal pain, peripheral edema, cough, headache, arthralgia, night sweats, decreased appetite, constipation, and myalgia11,12.

Tafinlar and Mekinist Important Safety Information

New Primary Malignancies (cutaneous and non-cutaneous)
When Tafinlar was used in combination with Mekinist at the recommended dose, the incidence of basal cell carcinoma was increased. The incidence of basal cell carcinoma was 9% (5/55) in patients receiving the combination compared to 2% (1/53) in patients receiving Tafinlar as a single agent. Tafinlar results in an increased incidence of cutaneous squamous cell carcinoma (cuSCC), keratoacanthoma and melanoma. Cutaneous squamous cell carcinoma, including keratoacanthoma, occurred in 7% of patients receiving the combination and 19% of patients receiving Tafinlar as a single agent.

Tumour Promotion in Wild-Type BRAF Melanoma
In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in wild-type BRAF cells that are exposed to BRAF inhibitors.2

Haemorrhage
Treatment with the combination resulted in an increased incidence and severity of haemorrhagic events: 16% (9/55) of patients treated with the combination compared with 2% (1/53) of patients.
treated with Tafinlar as a single agent. Intracranial haemorrhage was fatal in two (4%) patients receiving the combination.

**Venous Thromboembolic Events**
Treatment with the combination resulted in an increased incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE): 7% (4/55) of patients treated with the combination compared with none of the 53 patients treated with Tafinlar as a single agent. Pulmonary embolism was fatal in one (2%) patient receiving the combination.

**Cardiomyopathy**
When Mekinist was used in combination with Tafinlar at the recommended dose, cardiomyopathy (defined as cardiac failure, left ventricular dysfunction, or decreased left ventricular ejection fraction [LVEF]) occurred in 9% (5/55) of patients treated with the combination and in none of patients treated with Tafinlar as a single agent.

**Ocular Toxicities**
Retinal Vein Occlusion (RVO): across clinical trials of Mekinist the incidence of RVO was 0.2% (4/1,749). RVO may lead to macular oedema, decreased visual function, neovascularisation, and glaucoma.

Retinal Pigment Epithelial Detachment (RPED): in the randomised Phase II part of the Phase I/II open-label study 2% (1/55) of patients receiving Mekinist in combination with Tafinlar developed RPED.

Uveitis and Iritis: across clinical trials of the combination, uveitis occurred in 1% (2/202) of patients.

**Interstitial lung disease (ILD)**
In clinical trials of Mekinist (N = 329) as a single agent, ILD or pneumonitis occurred in 2% of patients.

**Serious Febrile Drug Reactions**
Serious febrile reactions and fever of any severity accompanied by hypotension, rigors or chills, dehydration or renal failure, can occur when Mekinist is used in combination with Tafinlar. The incidence and severity of pyrexia are increased when Mekinist is given with Tafinlar compared with Tafinlar alone.

The incidence of fever (serious and non-serious) was 71% (39/55) in patients treated with the combination and 26% (14/53) in patients treated with Tafinlar as a single agent. Febrile reactions of any severity, accompanied by hypotension, rigors or chills, occurred in 25% (14/55) of patients treated with the combination compared with 2% (1/53) of patients treated with Tafinlar as a single agent.

**Serious Skin Toxicity**
The incidence of any skin toxicity, the most common of which were rash, dermatitis acniform rash, palmar-plantar erythrodysesthesia syndrome or erythema, was similar for patients receiving the combination (65% [36/55]) compared with patients receiving Tafinlar as a single agent (68%
Across all clinical trials of the combination (N = 202), severe skin toxicity requiring hospitalisation occurred in 2.5% (5/202) of patients.

**Hyperglycaemia**
Hyperglycaemia can occur when Mekinist is used in combination with Tafinlar. The incidence of Grade 3 hyperglycaemia based on laboratory values was 5% (3/55) in patients treated with the combination compared with 2% (1/53) in patients treated with Tafinlar as a single agent.

**Glucose-6-Phosphate Dehydrogenase Deficiency**
Tafinlar, which contains a sulfonamide moiety, confers a potential risk of haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

**Embryofetal Toxicity**
Tafinlar and Mekinist both can cause foetal harm when administered to a pregnant woman. Tafinlar can also render hormonal contraceptives ineffective.

**Drug Interactions**

**Effects of Other Drugs on Dabrafenib**
Drugs that Inhibit or Induce Drug-Metabolising Enzymes: dabrafenib is primarily metabolised by CYP2C8 and CYP3A4. Strong inhibitors or inducers of CYP3A4 or CYP2C8 may increase or decrease, respectively, concentrations of dabrafenib.

Drugs that Affect Gastric pH: Drugs that alter the pH of the upper GI tract (e.g., proton pump inhibitors, H2-receptor antagonists, antacids) may alter the solubility of dabrafenib and reduce its bioavailability.

**Effects of Dabrafenib on Other Drugs**
Dabrafenib induces CYP3A4 and CYP2C9. Dabrafenib decreased systemic exposures of midazolam (a CYP3A4 substrate), S-warfarin (a CYP2C9 substrate) and R-warfarin (a CYP3A4/CYP1A2 substrate). Coadministration of dabrafenib with other substrates of these enzymes, including dexamethasone, or hormonal contraceptives, can result in decreased concentrations and loss of efficacy.

**Combination of trametinib with dabrafenib**
Co-administration of trametinib 2mg once daily and dabrafenib 150mg twice daily resulted in no clinically relevant pharmacokinetic drug interactions.

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