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Cobimetinib (Cotellic°) and metastatic melanoma

BRAF V600 mutation: a second MEK kinase inhibitor

Cobimetinib (Cotellic°, Roche) is another MEK kinase inhibitor. It is solely authorised in the European Union for use in combination with *vemurafenib*, both drugs being marketed by Roche (1,2).

First-line use: longer survival, as with trametinib. Clinical evaluation of cobimetinib is based on only one comparative, randomised, double-blind, placebo-controlled trial of cobimetinib + vemurafenib versus placebo + vemurafenib (3-4). It included 495 patients with BRAF V600-positive melanoma, which was either metastatic (93% of patients) or locally advanced and inoperable (7%). The patients had not previously received treatment for this stage of the disease. This trial was ongoing in mid-2016 (3).

After a median follow-up of 18.5 months, the estimated median survival time was 22.3 months in the *cobimetinib* + *vemurafenib* group and 17.4 months in the placebo + *vemurafenib* group, a statistically significant difference. An inherently unreliable indirect comparison suggests that this survival advantage is no better than that reported elsewhere with the *trametinib* + *dabrafenib* combination (2).

The cobimetinib + vemurafenib combination was also assessed in a dose-finding study with 129 patients. A tumour response was observed in 26% of 27 patients in whom vemurafenib had failed and who received the authorised dose of cobimetinib plus vemurafenib (3,4).

Adverse effects: similar to those of trametinib. *Trametinib*, a drug belonging to the same class as *cobimetinib*, can cause damage to nearly every organ system, with potentially life-threatening consequences that include heart failure, deep vein thrombosis, haemorrhaging, retinal disorders, pneumopathy, diarrhoea, neutropenia, and elevated liver enzymes and creatine phosphokinase activity (2).

The main clinical trial showed that the adverse effect profile of *cobimetinib* was similar to that of *trametinib*, including

gastrointestinal disorders, ocular disorders, liver enzyme elevation, hypersensitivity reactions, and a reduced left ventricular ejection fraction, but not venous thrombosis. Some of these adverse reactions were severe (3,4).



High risk of drug interactions. *Cobimetinib* is mainly metabolised by cytochrome P450 isoenzymes

CYP 3A4 and CYP 3A5, and by glucuronidation. It is also a P-glycoprotein substrate *in vitro*. This creates a risk of multiple pharmacokinetic interactions (3). *Trametinib* is also a P-glycoprotein substrate but is not metabolised by cytochrome P450 isoenzymes or by glucuronidation (2).



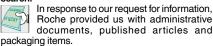
Do not use during pregnancy. *Cobimetinib* is teratogenic in rats and should be avoided in pregnant

women, as there are no relevant human data (3).

In practice, in mid-2016, there seems to be no noteworthy clinical difference between the harm-benefit balance of the *cobimetinib* + *vemurafenib* combination and the *trametinib* + *dabrafenib* combination. However, the *trametinib* + dabrafenib combination is better-evaluated and carries a lower risk of drug interactions.

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Selected references from Prescrire's literature search.



- 1- Prescrire Editorial Staff "Vemurafenib with longer follow-up. Metastatic melanoma: a few extra months of life, but many adverse effects" *Prescrire Int* 2015: 24 (159): 89-90
- Prescrire Int 2015; **24** (159): 89-90. **2-** Prescrire Rédaction "tramétinib-Mekinisto". Mélanomes métastasés ou non opérables avec mutation BRAF V600: quelques mois de vie en plus" *Rev Prescrire* 2016; **36** (393): 490-491.
- **3-** EMA CHMP "Public assessment report for Cotellic. EMEA/H/C/003960/0000" 24 September 2015: 139 pages. **4-** US FDA CDER "Application number
- **4-** US FDA CDER "Application number 206192Orig1s000. Medical review(s)" 8 December 2015: 235 pages.

cobimetinib tablets

COTELLIC°

• 20 mg of cobimetinib

antitumoural drug; MEK kinase inhibitor

Indication: "in combination with vemurafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation".

[EU centralised procedure]

NOTHING NEW



Clinical evaluation of cobimetinib in patients with metastatic or inoperable melanoma positive for the BRAF V600

mutation confirms that frontline treatment with a MEK kinase inhibitor plus a BRAF inhibitor prolongs survival by a few months, at a cost of many potentially serious adverse effects. The adverse effect profile of cobimetinib is similar to that of trametinib. Its higher potential for drug interactions makes cobimetinib more difficult to use than trametinib.

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