see also p. 285 and 289

Translated from ***Rev Prescrire*** **September 2016; 36 (395): 655-656**

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.

Selected references from Prescrire's literature search.

In response to our request for information, Roche provided us with administrative documents, published articles and packaging items.

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.
2- Prescrire Rédaction "tramétinib-Mekinist°. 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 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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