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.

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.
4- US FDA - CDER “Application number 206192Orig1s000. Medical review(s)” 8 December 2015: 235 pages.