Cobimetinib (GDC-0973, XL518)

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Contents

1 Structure and Mechanism of Action 178

2 Preclinical Data 179

3 Clinical Data 181

4 Toxicity 182

5 Drug Interactions 183

6 Biomarkers 183

7 Summary and Perspectives 183

References 184

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Abstract

The mitogen-activated protein kinase cascade (MAPK/ERK pathway) is a signaling pathway activated as a cellular response to various stimuli and for regulating the proliferation and survival of several types of eukaryotic cells, among others a wide variety of tumor cells. Mutations of the proteins involved in this pathway have been discovered in several tumor entities, indicating their inhibition as a potential therapeutic target. BRAF inhibitors have been in the clinical use since 2011. Several MEK inhibitors have been studied for metastatic cancer treatment in the recent past. After trametinib, cobimetinib is another potent, selective oral MEK1/2 inhibitor that was approved by European Medicine Agency (EMA) and Food and Drug Administration (FDA) in 2015 for treatment of malignant melanoma in a combination with the BRAF inhibitor vemurafenib.

Keywords

Cobimetinib · MAPK/ERK pathway · MEK inhibitors · BRAF/MEK inhibition · Combination therapy

1 Structure and Mechanism of Action

Cobimetinib is an orally bioavailable small-molecule inhibitor of mitogen-activated protein kinase kinase 1 (MAP2K1 or MEK1). This kinase is a part of the MAPK/ERK signaling pathway (also known as the Ras–Raf–MEK–ERK pathway) that affects cell cycle, proliferation, differentiation, and secretion as a response to diverse stimuli (e.g., growth factors, cytokines, and proto-oncogene) (Boulton et al. 1990; Cobb et al. 1991; Robbins et al. 1992; Moodie et al. 1993). Since the discovery of BRAF mutation in 66% of melanomas and approximately 15% of other tumors (Davies et al. 2002), which results in a constitutive activation of this pathway, its inhibition on different levels has been studied. The MAPK/ERK pathway is depicted in Fig. 1.

Similar to trametinib, cobimetinib (GDC-0973, XL518) is a carboxamide-based allosteric MEK inhibitor, which binds to and selectively inhibits MEK1 and MEK2. The inhibition results in decreased ERK1/2 phosphorylation. Cobimetinib maintains its inhibitory effect even when MEK is already phosphorylated. The half-maximal inhibitory concentration was established 4.2 nmol/L for MEK1. Cobimetinib is a very selective MEK inhibitor, its sensitivity is more than 100-fold higher for MEK compared to over 100 other serine–threonine and tyrosine kinases. The predisposition to sensitivity to cobimetinib in the in vitro studies was a mutation in RAF or RAS gene. Nevertheless, not all RAF- or RAS-mutated cell lines were sensitive to cobimetinib, in contrast to some wild-type cells. This indicates that the sensitivity to cobimetinib is multifactorial (Hoeflich et al. 2012). The efficacy of MEK inhibitors in BRAF-mutated versus BRAF wild-type and KRAS-mutated tumors depends on the form of interaction with MEK. Some MEK

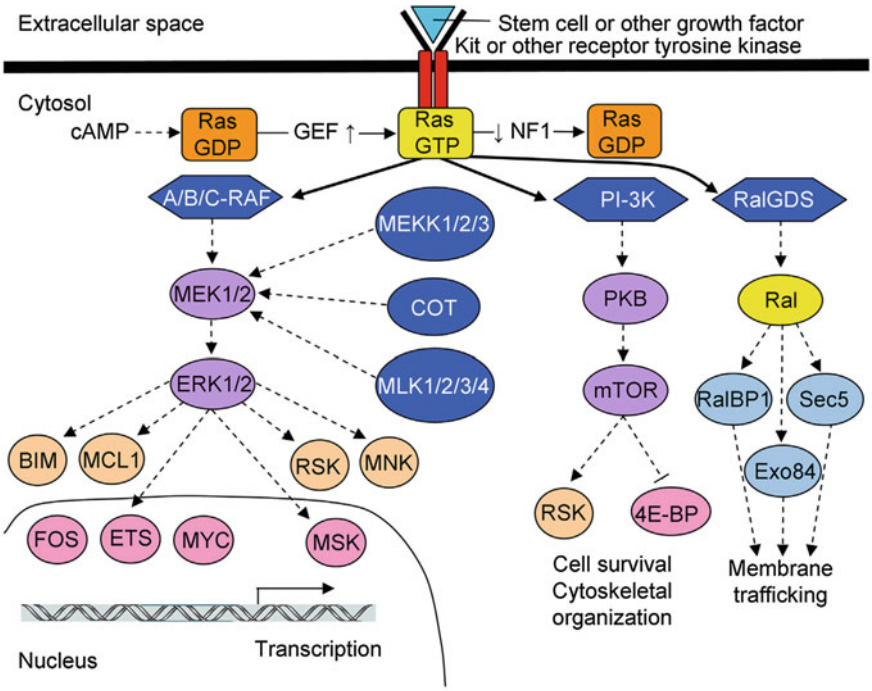

Fig. 1 Signaling pathways downstream RAS activation, including RAS/RAF/MEK/ERK signaling pathway. Modified after Roskoski (2017)

inhibitors form a strong hydrogen-bond interaction with S212 part of the kinase and, therefore, prevent its phosphorylation by wild-type RAF. Cobimetinib, on the other hand, has a stronger binding capacity to phosphorylated MEK and, therefore, shows a higher efficacy in the BRAF-mutated tumors (Hatzivassiliou et al. 2013). The drug elimination of cobimetinib is mostly intestinal (Han et al. 2015; Takahashi et al. 2015), in the liver it is metabolized via CYP3A and UGT2B7 (Musib et al. 2013). An impaired renal function does not have an effect on its elimination (Han et al. 2015).

The structure and chemical characteristics of cobimetinib are shown in Fig. 2.

2 Preclinical Data

In the first preclinical studies, cobimetinib showed a strong inhibition of cellular viability in several tumor cell lines, particularly those harboring a mutation in the RAS or RAF gene. Altogether 80% of the cells lines carrying BRAF mutation (V600E or non-V600E) and 54% carrying NRAS or KRAS mutation were sensitive to cobimetinib. Nevertheless, 35% of wild-type cells responded as well

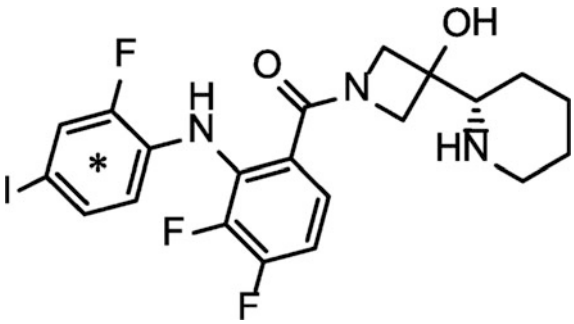

Fig. 2 The structure and chemical characteristics of cobimetinib. Mol. mass: 531.318 g/mol. Molecular formula: $C_{21}H_{21}F_3IN_3O_2$, chemical name: 3,4-difluoro-2-(2-fluoro-4-iodoanilino) phenyl]-[3-hydroxy-3-[(2*S*)-piperidin-2-yl]azetidin-1-yl]methanone

(Hoeflich et al. 2012). The single-agent efficacy and pharmacodynamics of cobimetinib were tested in xenograft models of acute myeloid leukemia, melanoma, non-small cell lung cancer, pancreatic, colorectal, ovarian, and breast cancer. Cobimetinib was administered in three different doses per oral gavage during 21 days after the subcutaneous tumor inoculation. The tumor size was measured on consecutive days. A response was observed under different doses (1–10 mg/kg body weight) in different tumor types. The highest efficacy was observed in the BRAF V600E-mutated melanoma model. Apart from this mutation, no other mutations strictly correlated with the response. The mechanism of action was inhibition of ERK phosphorylation (Hoeflich et al. 2012). In a combination therapy with a PI3K inhibitor GDC-0941, induction of pro-apoptotic proteins Bim and cleaved PARP caused apoptosis in the examined cell lines and a potent inhibition of tumor growth in xenograft models (Hoeflich et al. 2012). Exposure to the combination of these two inhibitors led to increased phosphorylation of proteins involved in DNA damage response (Kirkpatrick et al. 2013). The combination of cobimetinib with GDC-0941 and gemcitabine led to a remarkable tumor growth inhibition compared to gemcitabine alone treatment in a KRAS-driven genetic mouse model for pancreatic cancer (Junttila et al. 2015). In a pharmacokinetics–pharmacodynamics study of cobimetinib, immunodeficient mice were inoculated subcutaneously with a BRAF V600 mutated A375 melanoma cell line or a BRAF V600E mutated, PTEN deficient WM-266-4 melanoma cells (Wong et al. 2012). When the tumors reached the size of 100–120 mm^3 (day 11 or 13), they were randomized into eight groups treated with either vehicle or different doses of cobimetinib. Mice were sacrificed at different timepoints and the tumor tissue was analyzed for ERK inhibition and the inhibitor concentrations in the tumor and plasma. The BRAF V600 mutated melanomas were very sensitive to MEK inhibition. The WM-266-4 xenografts responded only moderately to cobimetinib, yet the slower response allowed for a more sufficient tumor mass for further analysis. The concentrations of the inhibitor were higher in tumor tissue than the plasma and were detectable in tumor for a longer period of time. The in vivo IC50 values were between 0.52 and

3.89 mmol/L and the response rate increased with a higher concentration of cobimetinib in the tumor (Wong et al. 2012).

3 Clinical Data

Mutations in BRAF gene occur in approximately 15% of all tumors (Davies et al. 2002). RAS mutations are variable throughout the tumor spectrum and the type of Ras protein (K-Ras, N-Ras and H-Ras), overall about 30% of all tumors carry a mutation in one of the RAS genes (Forbes et al. 2011). Therefore, the inhibitors of the Ras/Raf/MEK/ERK pathway have been subject of preclinical and clinical studies in the last 15 years. The first FDA and EMA approved BRAF inhibitors were vemurafenib (McArthur et al. 2014) and dabrafenib (Hauschild et al. 2012) for metastatic malignant melanoma. The BRAF inhibitors proved to be very potent, nevertheless, virtually all treated patients developed resistance throughout the course of treatment. A significant part of the resistance mechanisms was MEK-dependent, therefore a need of combination therapy emerged. So far two combination treatments showed superiority over the single-agent treatment with a BRAF inhibitor. One of them combines the BRAF inhibitor dabrafenib with a MEK inhibitor trametinib (Robert et al. 2015; Long et al. 2015). The other combination treatment included cobimetinib with a BRAF inhibitor vemurafenib (Ribas et al. 2014; Larkin et al. 2014; Ascierto et al. 2016). In a phase Ib trial, 129 patients who displayed a tumor progress under vemurafenib (66 patients), or never received any BRAF-targeted treatment (63 patients) were treated with vemurafenib and cobimetinib. The endpoint of the trial was safety and efficacy. The maximum tolerated doses was established to 960 mg vemurafenib twice daily and 60 mg of cobimetinib once a day for 21 days of a 28-day treatment period. The most common adverse events (AE) included diarrhoea (64%), non-acneiform rash (60%), increased liver enzymes (50%), fatigue (48%), nausea (45%), and photosensitivity (40%) with most of them being mild to moderate. Response rates reached 15% in patients with a progressive disease under vemurafenib and 87% in patients never treated with a BRAF inhibitor, with median progression-free survival 13.7 months. A complete response was achieved by 10% of the patients (Ribas et al. 2014). In a multicentric, randomized, double blind phase III trial co-BRIM, 495 previously untreated patients with stage III or IV BRAF-mutant melanoma were randomized to receive either vemurafenib and cobimetinib combination treatment, or vemurafenib with a placebo (Ascierto et al. 2016). The response rate, overall survival and progression-free survival data showed a clear advantage of the combination treatment, with response rate 70% versus 50%, overall survival 22.3 versus 17.4 months (HR 0.70, 95% CI 0.55–0.90; $p = 0.005$) and progression-free survival 11.0 versus 8.8 months (HR 0.58, 95% CI 0.46–0.72, $p < 0.0001$) in favor of the combined vemurafenib and cobimetinib treatment. The combination treatment showed slightly higher levels of toxicity, where serious adverse events occurred in 37% of the patients, compared to 28% of the patients in the vemurafenib arm.

However, the incidence of secondary dermatological malignities typical for vemurafenib treatment was lower in the combination arm. The occurrence of cutaneous squamous cell carcinoma, keratoacanthoma, or Bowen's disease was only 6% in the combination arm compared with 20% in the vemurafenib arm. This can be explained by blocking the paradoxical ERK activation, following BRAF inhibition, by adding a Mek inhibitor (Ascierto et al. 2016).

Currently, combinations of cobimetinib with other targeted therapies are being studied in clinical trials. Cobimetinib with duligotuzumab, an inhibitor of both epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 3 (HER3) were tested in various KRAS-mutated solid tumors in a phase Ib study (Lieu et al. 2017). However, the trial was associated with limited efficacy and high toxicity accompanying the use of the drug combination. Ongoing or terminated, yet unpublished trials include combinations of cobimetinib with Akt inhibitors, different PI3K inhibitors, bevacizumab, and checkpoint inhibitors, such as atezolizumab, in different types of solid tumors. The vemurafenib/cobimetinib combination is being tested for melanoma brain metastases and in the neoadjuvant setting. In the malignant hematology, the trials testing the combination of cobimetinib with venetoclax and ±atezolizumab in relapsed multiple myeloma and cobimetinib with venetoclax or idasanutlin for elderly patients with acute myeloid leukemia are currently recruiting. For more detailed information, visit https://clinicaltrials.gov.

4 Toxicity

A maximum tolerated dose for cobimetinib 60 mg for 21 days of a 28-day cycle was estimated in a dose escalation study together with vemurafenib (Ribas et al. 2014). The data from the dose escalation study with cobimetinib alone were not published (NCT00467779). The treatment-related adverse events were evaluated from the phase III trial of cobimetinib in combination with vemurafenib versus vemurafenib and placebo (co-BRIM) in a detailed safety analysis report (Dréno et al. 2017). The most frequent AE for both drugs included rash, photosensitivity, diarrhoea, serous retinopathy, increase in blood creatine kinase and alanine aminotransferase, fatigue, nausea and vomiting, alopecia, hyperkeratosis, and a decrease in left-ventricular ejection fraction. More frequent adverse events in the combination arm in comparison to patients treated only with vemurafenib were the increase of creatine kinase (+32.4%) and aspartate aminotransferase (+11.7%), diarrhoea (+27.4%), serous retinopathy (+23.4%), nausea (+16.5%), vomiting (+11.4%), and photosensitivity (+10%), grade 3 and 4 being the increase in liver enzymes and diarrhoea. The most common serious adverse events for both arms were pyrexia and dehydration (both 2% of the total number of patients). In most cases, dose reduction and supportive therapy was a sufficient AE management. The therapy had to be discontinued in less than 20% of patients.

5 Drug Interactions

Cobimetinib is mostly eliminated intestinally (Han et al. 2015; Takahashi et al. 2015). In the liver, the drug was metabolized via CYP3A and UGT2B7 in healthy volunteers (Musib et al. 2013). However, another study showed that CYP3A is responsible for ca. 78% of the total clearance of cobimetinib (Budha et al. 2016) and moderate (erythromycin and diltiazem) and strong (itraconazole) inhibitors of this enzyme lead to three- to seven-fold increase in cobimetinib exposure (area under the plasma-time curve, AUC). Similarly, CYP3A inducers, such as efavirenz and rifampicin lead to decrease in cobimetinib exposure.

6 Biomarkers

The mutated BRAF is a strong predictor of sensitivity to MEK inhibition and only patients with BRAF mutation were included in the clinical trial of vemurafenib and cobimetinib. Biomarker analysis of the phase 1b trial of vemurafenib and cobimetinib could show that the pERK inhibition was reflected by the decrease in the proliferation marker Ki67. S6 inhibition was much more variable across the groups (Yan et al. 2014). In the analysis of the co-BRIM trial, patients receiving vemurafenib with a high Ki67 expression had a shorter overall survival. On the contrary, the response of the patients receiving the combination therapy was not dependent on Ki67 expression. The levels of pERK and S6 did not have any association with the overall survival (Ascierto et al. 2016). In the further analysis, mutations in RAS, PTEN and RTK did not have an effect on the progression-free survival. Interestingly, the loss of PTEN was a negative biomarker in the progression-free survival of the patients receiving only vemurafenib, however, it did not have any effect on the PFS in the combination group (unpublished data, presented at ASCO 2015).

7 Summary and Perspectives

Based on the latest preclinical studies and clinical trials, the use of cobimetinib has proven beneficial in the combination therapy, especially in the combination with the BRAF inhibitor vemurafenib in the treatment of stage III and IV BRAF-mutated malignant melanoma. The adverse effects of this combination were slightly higher than in the monotherapy with vemurafenib, yet manageable with supportive therapy and dose adjustment. Therefore, the targeted therapy in combination is a serious candidate for the first line treatment in metastatic melanoma. The current discussion in the scientific community is about the superiority of this treatment as the first line option for BRAF-mutated melanoma in comparison to the checkpoint inhibition in different subgroups of patients. The clinical trials studying the combination of

BRAF + MEK inhibitor with checkpoint inhibitors are underway, the main concern is the toxicity of such combination. The combination of vemurafenib and cobimetinib is currently tested in the treatment of brain metastases. Based on the preclinical data, cobimetinib may be effective with other drugs, such PI3K inhibitors in various solid tumors.

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