Vemurafenib

Vemurafenib (INN, marketed as **Zelboraf**) is a B-Raf enzyme inhibitor developed by Plexxikon (now part of Daiichi-Sankyo) and Genentech for the treatment of late-stage melanoma.[1] The name "vemurafenib" comes from **V**600**E** **mu**tated B**RAF** **inhib**ition.

1 Approvals

Vemurafenib received FDA approval for the treatment of late-stage melanoma on August 17, 2011,[2] making it the first drug designed using fragment-based lead discovery to gain regulatory approval.[3]

Vemurafenib later received Health Canada approval on February 15, 2012.[4]

On February 20, 2012, the European Commission approved vemurafenib as a monotherapy for the treatment of adult patients with BRAF V600E mutation positive unresectable or metastatic melanoma, the most aggressive form of skin cancer.[5]

2 Mechanism of action

Vemurafenib causes programmed cell death in melanoma cell lines.[6] Vemurafenib interrupts the B-Raf/MEK step on the B-Raf/MEK/ERK pathway – if the B-Raf has the common V600E mutation.

Vemurafenib only works in melanoma patients whose cancer has a V600E BRAF mutation (that is, at amino acid position number 600 on the B-Raf protein, the normal valine is replaced by glutamic acid).[7] About 60% of melanomas have this mutation. It also has efficacy against the rarer BRAF V600K mutation. Melanoma cells without these mutations are not inhibited by vemurafenib; the drug paradoxically stimulates normal BRAF and may promote tumor growth in such cases.[8][9]

2.1 Resistance

Three mechanisms of resistance to vemurafenib (covering 40% of cases) have been discovered:

- Cancer cells begin to overexpress cell surface protein PDGFRB, creating an alternative survival pathway.
- A second oncogene called NRAS mutates, reactivating the normal BRAF survival pathway.[10]
- Stromal cell secretion of hepatocyte growth factor (HGF).[11][12]

3 Clinical trials

In a phase I clinical study, vemurafenib (then known as PLX4032) was able to reduce numbers of cancer cells in over half of a group of 16 patients with advanced melanoma. The treated group had a median increased survival time of 6 months over the control group.[13][14][15][16]

A second phase I study, in patients with a V600E mutation in B-Raf, ~80% showed partial to complete regression. The regression lasted from 2 to 18 months.[17]

In early 2010 a Phase I trial[18] for solid tumors (including colorectal cancer), and a phase II study (for metastatic melanoma) were ongoing.[19]

A phase III trial (vs dacarbazine) in patients with previously untreated metastatic melanoma showed an improved rates of overall and progression-free survival.[20]

In June 2011, positive results were reported from the phase III BRIM3 BRAF-mutation melanoma study.[21] The BRIM3 trial reported good updated results in 2012.[22]

Further trials are planned including a trial of vemurafenib co-administered with GDC-0973 (cobimetinib), a MEK-inhibitor.[21] After good results in 2014 the combination was submitted to the EC and FDA for marketing approval.[23]

In January 2015 trial results compared vemurafenib with the combination of dabrafenib and trametinib for metastatic melanoma.[24]

3.1 Side effects

At the maximum tolerated dose (MTD) of 960 mg twice a day 31% of patients get skin lesions that may need surgical removal.[1] The BRIM-2 trial investigated 132 patients; the most common adverse events were arthralgia in 58% of patients, skin rash in 52%, and photosensitivity in 52%. In order to better manage side effects some form of dose modification was necessary in 45% of patients. The median daily dose was 1750 mg, 91% of the MTD.[25]

A trial combining vemurafenib and ipilimumab was

stopped in April 2013 because of signs of liver toxicity.[26]

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