

Selumetinib

Selumetinib (AZD6244) is a drug that was discovered by Array BioPharma and was licensed to AstraZeneca. It is being investigated for the treatment of various types of cancer, such as non-small cell lung cancer (NSCLC).

1 Mechanism of action

The gene *BRAF* is part of the MAPK/ERK pathway, a chain of proteins in cells that communicates input from growth factors. Activating mutations in the *BRAF* gene, primarily V600E (meaning that the amino acid valine in position 600 is replaced by glutamic acid), are associated with lower survival rates in patients with papillary thyroid cancer. Another type of mutation that leads to undue activation of this pathway occurs in the gene *KRAS* and is found in NSCLC. A possibility of reducing the activity of the MAPK/ERK pathway is to block the enzyme MAPK kinase (MEK), immediately downstream of *BRAF*, with the drug selumetinib. More specifically, selumetinib blocks the subtypes MEK1 and MEK2 of this enzyme.^[1]

2 Possible uses

In addition to thyroid cancer, *BRAF*-activating mutations are prevalent in melanoma (up to 59%), colorectal cancer (5–22%), serous ovarian cancer (up to 30%), and several other tumor types.^[2]

Selumetinib has also been shown to inhibit growth of GNAQ mutated uveal melanoma cell lines.^[3] Furthermore, preliminary results suggest that selumetinib treatment of uveal melanoma patients can result in tumor shrinkage as the consequence of sustained inhibition of ERK phosphorylation.^[4]

KRAS mutations appear in 20 to 30% of NSCLC cases and about 40% of colorectal cancer.^[1]

A Phase II clinical trial about selumetinib in NSCLC has been completed in September 2011;^[5] one about cancers with BRAF mutations is ongoing as of June 2012.^[6]

In July 2015 selumetinib failed a Phase III trial testing whether the drug significantly prolonged the survival of patients in a study on melanoma that has spread to the eye. In the 152-patient trial, a combination of selumetinib and dacarbazine failed to improve progression-free survival compared with just the old drug alone.^{[7][8]}

As of March 2016 there are other phase 3 trials registered for thyroid cancer,^[9] and KRAS Positive NSCLC.^[10]

3 References

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- [2] Davies, H.; Bignell, G. R.; Cox, C.; Stephens, P.; Edkins, S.; Clegg, S.; Teague, J.; Woffendin, H.; Garnett, M. J.; Bottomley, W.; Davis, N.; Dicks, E.; Ewing, R.; Floyd, Y.; Gray, K.; Hall, S.; Hawes, R.; Hughes, J.; Kosmidou, V.; Menzies, A.; Mould, C.; Parker, A.; Stevens, C.; Watt, S.; Hooper, S.; Wilson, R.; Jayatilake, H.; Gusteron, B. A.; Cooper, C.; Shipley, J. (2002). "Mutations of the BRAF gene in human cancer". *Nature*. **417** (6892): 949–954. doi:10.1038/nature00766. PMID 12068308.
- [3] "Identification of unique MEK-dependent genes in GNAQ mutant uveal melanoma involved in cell growth, tumor cell invasion, and MEK resistance". *Clinical Cancer Research*. Jul 1, 2012. doi:10.1158/1078-0432.CCR-11-3086.
- [4] "Pharmacodynamic activity of selumetinib to predict radiographic response in advanced uveal melanoma". 2012.
- [5] Clinical trial number *NCT00890825* for "Comparison of AZD6244 in Combination With Docetaxel Versus Docetaxel Alone in KRAS Mutation Positive Non Small Cell Lung Cancer (NSCLC) Patients" at ClinicalTrials.gov
- [6] Clinical trial number *NCT00888134* for "AZD6244 in Cancers With BRAF Mutations" at ClinicalTrials.gov
- [7] "AstraZeneca - AstraZeneca provides update on selumetinib in uveal melanoma". *astrazeneca.com*.
- [8] "AstraZeneca's once-lauded drug flunks a Phase III eye cancer trial". *FierceBiotech*.
- [9] Study Comparing Complete Remission After Treatment With Selumetinib/Placebo in Patient With Differentiated Thyroid Cancer (ASTRA)
- [10] Assess Efficacy & Safety of Selumetinib in Combination With Docetaxel in Patients Receiving 2nd Line Treatment for v-Ki-ras2 Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS) Positive NSCLC (SELECT-1)

4 Further reading

- Ho, Alan L.; Grewal, Ravinder K.; Leboeuf, Rebecca; Sherman, Eric J.; Pfister, David G.; Deandreis, Desiree; Pentlow, Keith S.; Zanzonico, Pat B.; et al. (2013). “Selumetinib-Enhanced Radioiodine Uptake in Advanced Thyroid Cancer”. *New England Journal of Medicine*. **368** (7): 623–32. doi:10.1056/NEJMoa1209288. PMC 3615415. PMID 23406027.

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