Ceritinib

(Zykadia), approved by the FDA in April 2014 for treatment of NSCLC.

Ceritinib is a next generation ALK inhibitor (ALKi), approved by the European Medicines Agency in 2015. In the first-in-human, phase I study, ceritinib demonstrated rapid and durable responses in ALK patients previously treated with a different ALKi and in those who were ALKi-naive. As ceritinib is starting to be used routinely for the treatment of patients with ALK+ NSCLC, experience is growing with regard to ideal therapy management.

Das et al. tested two novel drugs: INC280 (Capmatinib: a highly selective c-Met receptor tyrosine kinase-RTK inhibitor) and LDK378 (Ceritinib: a highly selective anaplastic lymphoma kinase-ALK inhibitor), aiming to overcome TMZ resistance in MGMT-unmethylated Glioblastoma cells in in vitro cell culture models. Treatments were examined using MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay, caspase-3 assay and western blot analysis. Results obtained from our experiments demonstrated that preconditioning with INC280 and LDK378 drugs exhibit increased MMR protein expression, specifically MMR protein MLH1 (MutL Homolog 1) and MSH6 (MutS Homolog 6) and sensitized TMZ in MGMT-unmethylated Glioblastoma cells via suppression of ALK and c-Met expression. INC280 and LDK378 plus TMZ also induced apoptosis by modulating downstream signaling of PI3K/AKT/STAT3. Taken together, this data indicates that co-inhibition of ALK and c-MET can enhance growth inhibitory effects in MGMT-unmethylated cells and enhance TMZ sensitivity in-vitro, suggesting c-Met inhibitors combined with ALK-targeting provide a therapeutic benefit in MGMT-unmethylated Glioblastoma patients [1)]

In a review Califano et al. provide a brief background to the development of ceritinib. The optimal treatment management and adverse events associated with ceritinib in clinical trials and in clinical practice are then discussed in detail, and where applicable, an expert consensus on specific recommendations are made. In clinical trials, the most common adverse events related to ceritinib are nausea, vomiting, and diarrhea. However, the majority of these are mild and, in the opinion of the authors, can be effectively managed with dose modifications. Based on clinical data, ceritinib has demonstrated efficacy as a first-line therapy and in patients who have relapsed on crizotinib, including those with brain metastases at baseline. Unfortunately, at some point, all patients experience progressive disease, with the central nervous system being a common site of metastases. Recommendations are made for continuing treatment beyond disease progression as long as a clinical benefit to patients is observed.

Here, they review management of ceritinib treatment and adverse events and make recommendations on optimal management of patients [2)].

Compared with crizotinib and the second-generation ALK/ROS1 inhibitors ceritinib and alectinib, PF-06463922 showed significantly improved inhibitory activity against ROS1 kinase. A crystal structure of the PF-06463922-ROS1 kinase complex revealed favorable interactions contributing to the high-affinity binding. In vivo, PF-06463922 showed marked antitumor activity in tumor models expressing FIG-ROS1, CD74-ROS1, and the CD74-ROS1(G2032R) mutation. Furthermore, PF-06463922

demonstrated antitumor activity in a genetically engineered mouse model of FIG-ROS1 glioblastoma. Taken together, our results indicate that PF-06463922 has potential for treating ROS1 fusion-positive cancers, including those requiring agents with CNS-penetrating properties, as well as for overcoming crizotinib resistance driven by ROS1 mutation [3].

1)
Das A, Alshareef M, Porto GBF, Infinger LK, Vandergrift WA 3rd, Lindhorst SM, Varma AK, Patel SJ, Cachia D. Preconditioning with INC280 and LDK378 drugs sensitizes MGMT-unmethylated glioblastoma to temozolomide: Pre-clinical assessment. J Neurol Sci. 2020 Nov 15;418:117102. doi: 10.1016/j.jns.2020.117102. Epub 2020 Aug 21. PMID: 32866816.
2)
Califano R, Greystoke A, Lal R, Thompson J, Popat S. Management of ceritinib therapy and adverse events in patients with ALK-rearranged non-small cell lung cancer. Lung Cancer. 2017 Sep;111:51-58. doi: 10.1016/j.lungcan.2017.06.004. Epub 2017 Jun 9. Review. PubMed PMID: 28838397.
3)
Zou HY, Li Q, Engstrom LD, West M, Appleman V, Wong KA, McTigue M, Deng YL, Liu W, Brooun A, Timofeevski S, McDonnell SR, Jiang P, Falk MD, Lappin PB, Affolter T, Nichols T, Hu W, Lam J, Johnson TW, Smeal T, Charest A, Fantin VR. PF-06463922 is a potent and selective next-generation ROS1/ALK inhibitor capable of blocking crizotinib-resistant ROS1 mutations. Proc Natl Acad Sci U S A. 2015 Mar 17;112(11):3493-8. doi: 10.1073/pnas.1420785112. Epub 2015 Mar 2. PubMed PMID: 25733882; PubMed Central PMCID: PMC4371934.

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