c-Met inhibitor

c-MET inhibitors are a group of drugs that could help NSCLC patients with MET alterations, especially exon 14 skipping mutation, present in 2–3% of lung cancers.

see Capmatinib.

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)]

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.