Capmatinib

Patients with non-Small-cell lung cancer (NSCLC) initially responding to tyrosine kinase inhibitors (TKIs) eventually develop resistance due to accumulating Epidermal growth factor receptor mutations and additional lesser investigated mechanisms such as the participation of the tumor microenvironment (TME).

Zhu et al. examined the potential for c-MET inhibitor capmatinib for the treatment of osimertinib-resistant NSCLCs and normalizing the TME.

They first established that HCC827 and H1975 cells showed increased resistance against osimertinib when co-cultured with CAFs isolated from osimertinib-resistant patients. Additionally, they showed that CAFs promoted epithelial-mesenchymal transition (EMT) and self-renewal ability in both HCC827 and H1975 cells. We subsequently found that both CAF-cultured HCC827 and H1975 showed a significantly higher expression of MET, Akt, Snail and IL-1β, which were associated with survival and inflammatory responses. These cells in turn, promoted the generation of CAFs from normal lung fibroblasts. Subsequently, we observed that the treatment of capmatinib resulted in the re-sensitization of CAF-co-cultured H1975 and HCC827 to osimertinib, in association with reduced EMT and self-renewal ability. MET-silencing experiment using siRNA supported the observations made with capmatinib while with a greater magnitude. MET-silenced cell exhibited a severely hindered expression of inflammatory markers, IL-1β and NF-κB; EMT markers, Snail and Vimentin, while increased E-cadherin. Finally, we demonstrated that the combination of capmatinib and osimertinib led to an increased tumor inhibition and significantly lower number of CAFs within the patient derived xenograft (PDX) model.

Taken together, the findings suggested that an increased MET/Akt/Snail signaling was induced between the NSCLC cells and their TME (CAFs), resulting in osimertinib resistance. Suppression of this pathway by capmatinib may bypass the EGFR activating mutation and overcomes osimertinib resistance by targeting both tumor cells and CAFs [1].

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 [2]

1)

Zhu K, Lv Z, Xiong J, Zheng H, Zhang S, Jin H, Yu L, Li Z, Zhang J, Li C, Liang P. MET inhibitor, capmatinib overcomes osimertinib resistance via suppression of MET/Akt/snail signaling in non-Small-cell lung cancer and decreased generation of cancer-associated fibroblasts. Aging (Albany NY). 2021

Feb 17;13. doi: 10.18632/aging.202547. Epub ahead of print. PMID: 33621951.
2)

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.