Application of MET Pharmacodynamic Assays to Compare Effectiveness of Five MET Inhibitors to Engage Target in Tumor Tissue

Several MET inhibitors that block aberrant HGF-MET signaling in different cancers are currently under clinical investigation. We utilized validated MET pharmacodynamic (PD) assays to compare complete dose-magnitude-inhibition and reversibility of MET suppression by small molecule MET inhibitors. We selected five MET inhibitors that were available to NCI. These agents broadly represent three MET inhibitors that were available to NCI. These agents broadly represent three classes of MET inhibitors: (A) selective MET kinase inhibitors (e.g., ARQ197, EMD1214063, and ARQ614); (B) selective MET receptor tyrosine kinase (RTK) inhibitors (e.g., XL184, XL880, and EMD1214063); and (C) nonselective MET kinase inhibitors (e.g., ARQ197, ARQ614, and ARQ924). The MET signaling pathway in cancer: 1) allosteric inhibition of MET by XL184; 2) tumor regression with minimal toxicity. For EMD1214063 and XL880, compounds, the PD modulation was directly related 90% or greater MET inhibition. These studies could also suggest that MET pathway suppression thresholds to achieve similar effects and differences in the extent and duration of MET inhibition varied considerably among MET inhibitors. Following general similarities and differences in the extent and duration of MET inhibition was observed with EMD1214063 and XL880. The MTD was set at 44 mg/kg for ARQ197, 22 mg/kg for EMD1214063, and 40 mg/kg for XL880. These studies could also suggest that MET pathway suppression thresholds to achieve similar effects and differences in the extent and duration of MET inhibition varied considerably among MET inhibitors. Following general similarities and differences in the extent and duration of MET inhibition was observed with EMD1214063 and XL880. The MTD was set at 44 mg/kg for ARQ197, 22 mg/kg for EMD1214063, and 40 mg/kg for XL880. These studies could also suggest that MET pathway suppression thresholds to achieve similar effects and differences in the extent and duration of MET inhibition varied considerably among MET inhibitors. Following general similarities and differences in the extent and duration of MET inhibition was observed with EMD1214063 and XL880. The MTD was set at 44 mg/kg for ARQ197, 22 mg/kg for EMD1214063, and 40 mg/kg for XL880.