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Evaluation of a spray-dried dispersion (SDD) formulation of MGCD265, a receptor tyrosine kinase (RTK) inhibitor, in a phase 1 study of patients (pts) with advanced solid tumors.

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Abstract Text:

Background: MGCD265 is an ATP-competitive inhibitor of MET and Axl RTKs and has demonstrated anti-tumor activity in xenograft cancer models of MET or Axl dysregulation and in Phase 1 clinical trial pts selected for these alterations. **Methods:** Study objectives were to evaluate the maximum tolerated dose/recommended phase 2 dose (MTD/RP2D), safety, PK, PD, and clinical activity of MGCD265. Eligible pts received MGCD265 on Cycle 1 Day 1 and initiated continuous dosing on Cycle 1 Day 3 in 21-day cycles. PK/PD were evaluated after single and repeated dose administration. **Results:** 18 pts received MGCD265 – 12 in softgel capsules and 6 in SDD tablets. With softgel capsules the MTD was established at 1050 mg BID; treatment-related AEs (> 20% all grades) included diarrhea, nausea, vomiting, fatigue, AST increase, ALT increase and lipase increase. With 500 mg SDD, exposures partially overlapped those observed with 1050 mg softgel capsules. 1 of 6 SDD pts experienced a dose-limiting toxicity (DLT) of Gr 3 transaminase increase without clinical symptoms. Treatment-related AEs reported in > 20% of pts included Gr 1-2 diarrhea and Gr 2 fatigue, with fewer patients treated for diarrhea. Dose escalation of SDD is ongoing at 1000 mg BID. The rates of absorption and elimination of the two formulations were comparable with a median t_{max} of 8 hrs and an average $t_{1/2}$ of 40 ± 17 hrs for SDD versus 35 ± 12 hrs for softgel capsules. The extent of absorption was 1.8 times greater with SDD tablets. The observed $C_{ave,ss}$ and $AUC_{0\text{-}12,ss}$ were 480 ng/mL and 5757 ng•h/mL with 500 mg BID of SDD tablets and 561 ng/mL and 6731 ng•h/mL with 1050 mg BID of softgel capsules, respectively. **Conclusions:** The SDD tablet formulation of MGCD265 shows similar PK characteristics as the softgel capsule formulation but with greater bioavailability, thus reducing the pill burden, and a more favorable safety profile to date. Expansion cohorts of softgel capsules demonstrating antitumor activity in pts with NSCLC with genetic alterations for *MET* and *AXL* are ongoing and may include evaluation of the SDD formulation as emerging data confirm similar or greater exposure and a better safety profile.