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Phase I/II study of gedatolisib in combination with darolutamide in metastatic castration-resistant prostate cancer (mCRPC)

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Background

Preclinical studies demonstrated interaction between the androgen receptor (AR) and phosphoinositide 3-kinase (PI3K)-protein kinase B (AKT)-mechanistic target of rapamycin (mTOR) pathways through reciprocal negative feedback, whereby inhibition of one pathway cross activates the other. Furthermore, elevated androgen levels upregulate the PI3K-AKT-mTOR (PAM) pathway, with oncogenic activation associated with resistance to androgen deprivation therapy, disease progression, and poor outcomes in prostate cancer. These data suggest that combining a PAM inhibitor with an AR pathway inhibitor (ARPi) may induce a synergistic antitumor effect in mCRPC patients, including those whose disease progressed on prior ARPi treatment. Preliminary clinical data further support this hypothesis (Sweeney CCR 2022). Gedatolisib, a potent pan-PI3K, mTORC1/2 inhibitor that comprehensively blockades the PAM pathway, is being studied in combination with the ARPi, darolutamide, in an ongoing phase 1/2 clinical trial.

Methods

In the phase 1 portion of the trial, 2 doses of gedatolisib were administered intravenously (IV) on an intermittent schedule (Days 1, 8, 15 of each 28-day cycle) at 120 mg (Arm 1; N=19) and 180 mg (Arm 2; N=19), along with darolutamide 600 mg daily. Study objectives include safety, recommended phase 2 dose (RP2D), pharmacokinetics, landmark progression free survival at 6, 9, and 12 months, overall response rate, and overall survival.

Results

To date, gedatolisib 120 mg or 180 mg treatments in combination with darolutamide have demonstrated manageable safety profiles, with no dose-limiting toxicities or Grade 4/5 treatment-related adverse events. Additional safety and preliminary efficacy data will be presented.

Conclusions

Following promising safety results from Arms 1 and 2, the study was recently amended to include intermittent dosing Arms 3 (gedatolisib 240 mg) and 4 (300 mg), along with an optional weekly dosing Arm 5 (dose TBD). Two dose levels from Arms 1–5 may then be evaluated on both intermittent and weekly schedules in the randomized phase 1b stage to formally define the RP2D and optimal dosing strategy, with further clarification achieved in the phase 2 expansion.

Clinical trial identification

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