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Phase Ib/II study of durvalumab plus guadecitabine in advanced clear cell renal cell cancer (ccRCC)

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Background

Checkpoint inhibitor (CPI) immunotherapy directed at PD1/PDL1 either as monotherapy or in combination with anti-VEGF agents has shown clinical efficacy in advanced ccRCC. However, the benefit is limited to a small group of patients and hence there is an unmet need to improve the clinical outcomes. The chemokines CXCL9 and CXCL10 in the tumor micro-environment are chemo-attractants for activated NK and Th1 cells and are critical for anti-tumor immunity. Hypermethylation induced silencing of CXCL9/10 signaling is an important tumor immune evasion mechanism. Preclinical studies with the combination of hypomethylating agent and CPIs led to higher levels of CXCL 9/10, reversal of immune evasion, and potent tumor regression. We hypothesized that the combination of guadecitabine plus durvalumab would increase T lymphocyte infiltration & result in antitumor activity.

Methods

This is a single arm, multi-site, phase 1b/2 trial through the Big Ten Cancer Research Consortium of guadecitabine (G) plus durvalumab (D) in 28-day cycles in pts with advanced ccRCC. Phase Ib dose de-escalation portion evaluated the safety of combination at two dose levels of D (level 0: 60 mg/m^2 and level -1: 45 mg/m^2). The primary endpoints are safety and objective response rate (ORR, CR+PR) by RECIST 1.1.

Results

As of April 2020, six patients were enrolled in the phase Ib portion of the study. Dose limiting toxicity of neutropenia was seen with D at 60 mg/m^2. The dose level -1 of G at 45 mg/m^2 subcutaneously for 5 days starting day 1 of a 28-day cycle plus D 1500 mg IV on day 8 was deemed safe for phase II evaluation. The ORR in phase Ib was 33.3% (95% CI, 9.7% - 70%). The median PFS and OS were not reached; The 1-yr PFS was 83.3% (95% CI: 58.3%). The incidence of treatment related adverse events (TRAE) of any grade with G was 24.4%, D was 20.1%, and either G or D was 35.4%. The most common grade 3 AE was neutropenia. The other Gr3 AEs noted in one patient each were abdominal pain, diarrhea, dyspnea and pneumonitis. No treatment related deaths were seen. One patient discontinued the study due to pneumonitis.

Conclusions

The combination of guadecitabine plus durvalumab in advanced ccRCC is safe with promising antitumor activity in phase Ib participants. The phase 2 portion of the study is ongoing.

Legal entity responsible for the study

BIG TEN Cancer Research Consortium.

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Disclosure

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