

A Phase 1, first-in-human study of TAK-280, a B7-H3 × CD3ε COBRA T-cell engager, in adult patients with unresectable, locally advanced, or metastatic solid tumors

Gary Richardson, Beckie Hopper, Ganessan Kichenadasse, Bernard Doger, David Starks, Elizabeth Ahern, Meena Subramanyam, Xin Ma, Advaitaa Haripershad, Luisa Maseira, Benjamin Garmezzy, Ashlee Hearnden, Leah Cushing, Jon Moran

Background

B7-H3 (CD276) is overexpressed in a wide array of solid tumours and it is commonly associated with advanced disease stages, poor prognosis, and enhanced tumor progression. TAK-280 is a COnditional Bispecific Redirected Activation (COBRA) TCE designed to bind to both B7-H3 and CD3ε following conditional activation in the TME. Preclinical data for the closely-related COBRA molecule, TAK-186, have provided a strong rationale for advancing TAK-280 into clinical evaluation.

Methods

Eligibility criteria Adult patients with histologically or pathologically proven, unresectable, locally advanced or metastatic solid tumors that, based on literature reports, are considered to express B7-H3. Patients were either ineligible for or intolerant of standard therapies, had no approved therapy with demonstrated benefit available, or exhausted all available standard therapies. ECOG PS ≤1’ Measurable disease per RECIST v1.1 except for patients with mCRPC with bone metastases only

Primary endpoints: incidence of DLTs and other toxicities according to NCI CTCAE v5.0 and ASTCT CRS consensus grading

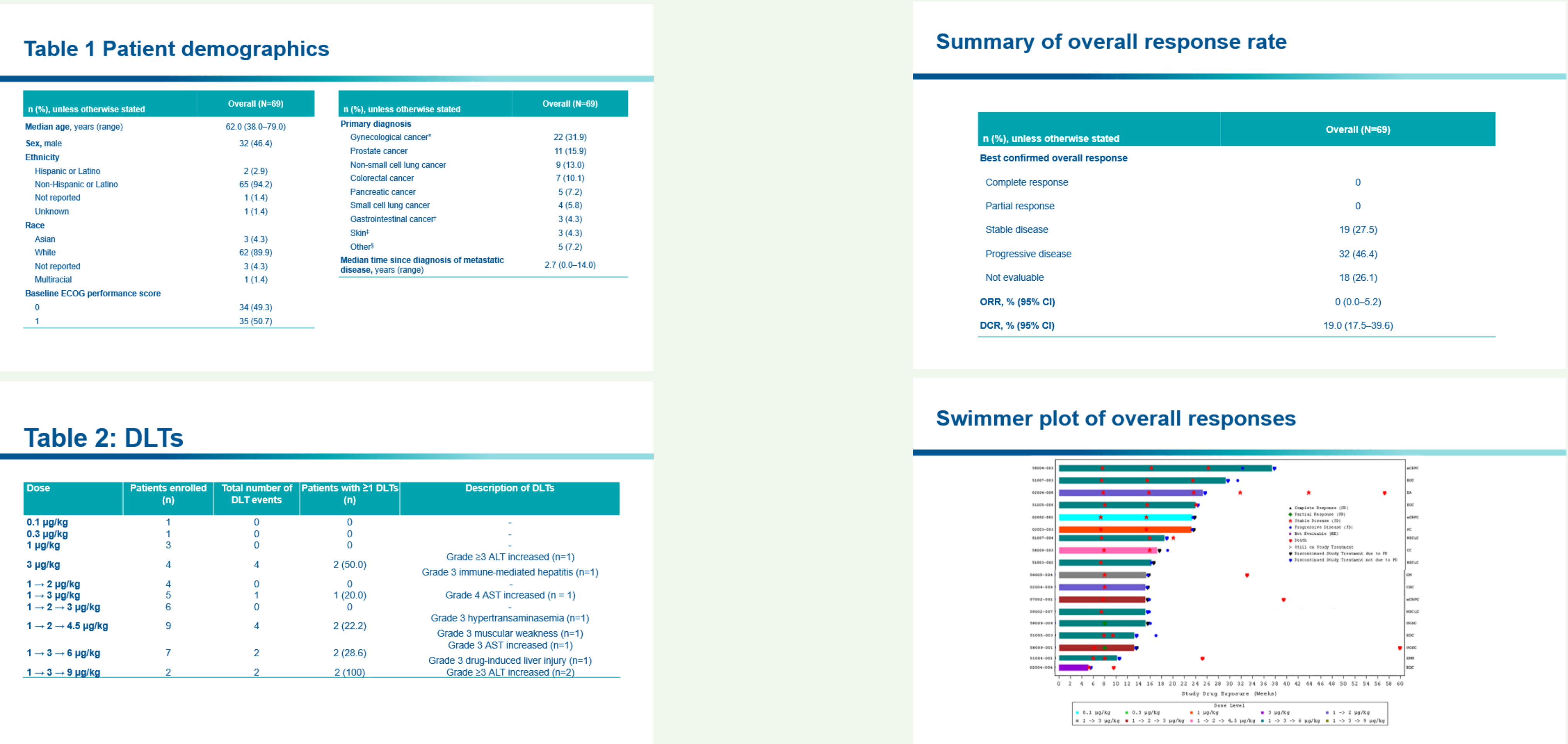
Secondary endpoints: PK, efficacy, and immunogenicity data

Dose escalation: Single-patient cohort at 0.1 and 0.3 µg/kg. Cohort size was converted to ≥3 patients for all subsequent predefined dose levels of 1, 3, 6, 12, 18, and 27 µg/kg. Dose-escalation and de-escalation decisions were guided by BOIN design

LiD Strategy: initiated at first occurrence of grade ≥2 CRS. LiD levels were defined in the dose-escalation phase and used as the initial does in each subsequent cohort, followed by the cohort-assigned dose for each.

Results

69 patients were recruited. 32 were male. Most common cancers were gynaecological (32%), prostate cancer (16%), NSCLC (13%), colorectal cancer5 (10%) and pancreatic cancer (7%). Thirteen DLTs were reported in 9 (21.4%) patients. CRS was the most common TEAE and was reported in 41 (59.4%) patients. Most CRS events were low grade (grade 1–2, n=39), with grade 3 CRS occurring in 2 patients. CRS events were lower with TAK-280 compared to TAK-186 where CRS was reported in 77.9% of patients, with grade ≥3 CRS occurring in 10 patients. Response rates included 19 patients with stable disease and 32 with progressive disease. 18 patients were not evaluable.



Conclusion

TAK-280 was a well-tolerated agent during the dose escalation study. There were no responses, although a significant number of patients had stable disease.