A phase 1 study evaluating the safety and efficacy of DKN-01, an investigational monoclonal antibody (in Mabs) in patients (pts) with advanced non-small cell lung cancer

Methods

Overview (DKN-01): DKN-01 is a high affinity neutralizing humanized IgG1 monoclonal antibody (mAb) that blocks the binding of Dickkopf-1 (DKK-1) to the mammalian Notch ligand, Notch 3. DKN-01 has been shown to have antitumour activity infusing DKN-01 to pts with advanced solid tumors. DKK-1 has been shown to lead to clinical benefit in xenograft models. DKK-1 inhibits the canonical Wnt/β-catenin signaling pathway.

RESULTS

Demographics and Histology

Overall, the median number of cycles completed was 1 (range 0 to 4); 3 (9.4%) patients completed between ≥ 4 and < 5 cycles, 15 (46.9%) patients completed between ≥ 2 cycles and < 3 cycles, 15 (46.9%) patients completed between ≥ 1 cycle and < 2 cycles, and 2 (6.3%) patients completed < 1 cycle. A total of 160 patients were evaluable for safety. A total of 121 patients were evaluable for efficacy. 75 mg QW 300 mg Q2W 600 mg Q2W

Safety

Dose Limiting Toxicities

End of Infusion (EOI) values were obtained for QW dosing on Days 1 and 22; Q2W dosing EOI values on Days 1 and 15. Pharmacokinetic analysis demonstrated dose proportionality; DKK-1 serum levels increased with dose.

Efficacy

Overall Response Rate

Refractory or intolerant to all standard/approved therapies; Performance Status 0, 1; Life expectancy of at least 3 months; Histologically or cytologically confirmed MM or advanced solid tumors were enrolled. Part A was a dose-escalation study where safety, tolerability and pharmacokinetic (PK) were assessed. The maximum dose of 600 mg given on days 1 and 15 and as an intravenous infusion over 2 hours was selected to provide an initial dose of DKN-01 (mg/m2) for the phase 2 study. In total, 22 evaluable NSCLC pts were treated. Dose level 1 of 150 mg QW began on Day 1 and 15 of every 28 day cycle. Part B was a cohort expansion study to evaluate the safety, efficacy and PK profile of escalation of DKN-01.

Conclusions

Efficacy

Overall Response Rate

Patients in Part B were dosed at 300 mg on Days 1 and 15. Part A Only

Key Entry Criteria

Pt ≥ 18 yrs, 54% male, 75% ECOG PS 1, 4 median prior therapies (1-7), and 63% adenocarcinoma. DKN-01 was well tolerated at all doses. DKK-1 serum levels (believed to be total DKK-1 based on the assay) progressively increased over the first few weeks of treatment, reaching levels as high as 3.6 fold of baseline above. DKK-1 serum levels increased over the first few weeks of treatment, reaching levels as high as 3.6 fold of baseline. DKK-1 may be a promising oncologic targeted therapy for NSCLC. DKK-1 was well tolerated and demonstrated clinical activity in pts with un-resectable NSCLC. This trial established the safety, tolerability and dose finding in the Investigational Drug Branch protocol for DKN-01, an anti-DKK-1 mAb.

Extent of Exposure

Patients in Part B with NSCLC, patients with NSCLC and PD-L1 > 1% had improved PFS compared to historical controls. PFS in 23 evaluable NSCLC pts was 6.6 months (95% CI 4.1-10.1).

Overall, the median number of cycles completed was 1 (range 0 to 4); 3 (9.4%) patients completed between ≥ 4 and < 5 cycles, 15 (46.9%) patients completed between ≥ 2 cycles and < 3 cycles, 15 (46.9%) patients completed between ≥ 1 cycle and < 2 cycles, and 2 (6.3%) patients completed < 1 cycle.

Biomarker Results

Overall, there was a trend toward a 3.9 fold increase in DKK-1 serum levels (believed to be total DKK-1 based on the assay) progressively increased over the first few weeks of treatment, reaching levels as high as 3.6 fold of baseline above. DKK-1 serum levels (believed to be total DKK-1 based on the assay) progressively increased over the first few weeks of treatment, reaching levels as high as 3.6 fold of baseline above.

Conclusions

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