Antibody targeting of WNT signaling modulator dickkopf1 (DKK1) enhances innate anti-tumor immunity and complements anti-PD-1 and paclitaxel therapy

Introduction

- DKK1 expression in cancer tissue has been associated with poor prognosis in multiple cancers, including esophageal, gastric, prostate, and CNS cancers, where augmented DKK1 may be linked to invasiveness and tumor growth.
- DKK1 has a critical role in mediating an immunosuppressive tumor microenvironment, including the suppressive effects of MDSCs and downregulating NK and T-cells on tumor cells.
- DKN-01 is a high affinity antibody for DKK1, a secreted modulator of Wnt signaling.
- DKN-01 has additive activity with an anti-PD-1 antibody in syngeneic tumor models.
- DKN-01 has demonstrated activity as a monotherapy and in combination with paclitaxel in heavily pretreated patients with esophageal cancer.
- DKN-01 in combination with pembrolizumab demonstrates promising clinical activity in subjects with heavily pretreated, anti-PD-1/PD-L1 naive GEJ/Gastric adenocarcinoma in subgroups less likely to respond to pembrolizumab monotherapy (e.g., MSS, PD-L1 negative).
- DKN-01 in combination with pembrolizumab may have additive clinical benefit through the targeting of both innate and adaptive immunity.

Clinical Results

- DKN-01 in combination with pembrolizumab has shown promising clinical activity in subjects with heavily pretreated, anti-PD-1/PD-L1 naive GEJ/Gastric adenocarcinoma.
- DKN-01 in combination with pembrolizumab demonstrates clinical activity in patients with esophageal cancer, where augmented DKK1 may be linked to invasive tumor growth.
- DKK1 expression in cancer tissue has been associated with poor prognosis in multiple cancers, including esophageal, gastric, prostate, and CNS cancers.

Non-Clinical Results

- DKN-01 Activity Is NK Cell Dependent But Not T/B Cell Dependent

Conclusions

- DKN-01 has innate immune modulatory activity and works effectively in combination with checkpoint inhibitors and/or chemotherapy.
- DKN-01 in combination with paclitaxel demonstrates promising clinical activity including overall survival (61.1 weeks), response rates (46.7%), and progression free survival (19.6 weeks) as a second line therapy in a heterogeneous population of patients with esophageal cancer.
- Importantly, there appears to be clinical benefit in patients with esophageal squamous cell carcinoma (ORR: 33.3%, PFS: 13.7 weeks and OS: 31.0 weeks) regardless of number of prior therapies; additional development in this population of significant unmet medical need is warranted.

References

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