PEMDA-HN, an Open-Label, Phase II, Randomized Controlled Study of Danvatirsen Plus Pembrolizumab Compared to Pembrolizumab Alone in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (RM HNSCC)

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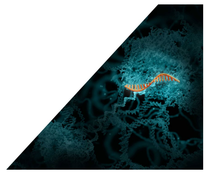

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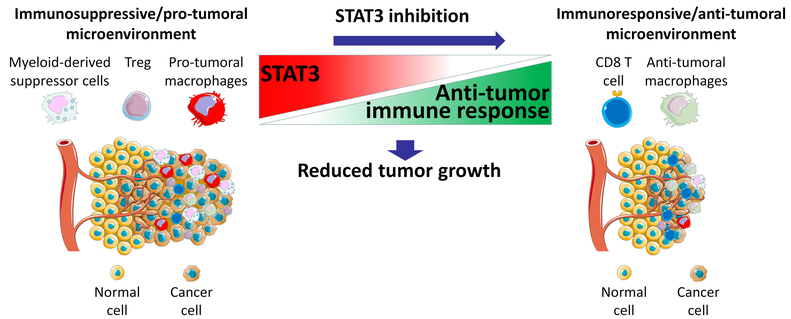
BACKGROUND

- Head and neck cancer is the sixth most common cancer worldwide, with the predominant histology being head and neck squamous cell carcinoma (HNSCC). Despite aggressive, combined modality treatment, a significant proportion of patients will develop recurrent or metastatic (RM) disease that is no longer amenable to curative therapy.
- Signal transducer and activator of transcription 3 (STAT3) plays a critical role in promotion of an immune-suppressive tumor microenvironment and survival of tumor cells[1].
- Danvatirsen (DANVA) is a 16-nucleotide, generation 2.5 antisense oligonucleotide (ASO) licensed from Ionis Pharmaceuticals and designed to down-regulate the expression of human STAT3.

Figure 1: Proposed mechanism for STAT3 inhibition within the tumor

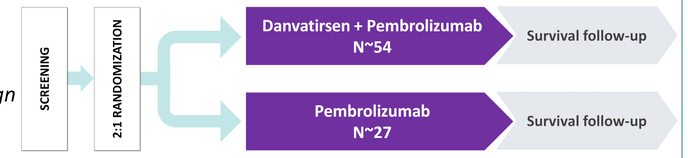


- STAT3 ASOs potentiate the activity of immune checkpoint inhibitors in preclinical cancer model[2].
- Over 500 patients with solid tumors or hematologic malignancies have been exposed to DANVA monotherapy or in combination. A tolerable safety profile has been demonstrated for DANVA and toxicities are manageable.
- The SCORES Study in RM HNSCC patients naïve to programmed cell death (ligand)1 (PD-(L)1) therapy demonstrated that DANVA in combination with the PD-L1 inhibitory antibody durvalumab improved the objective response rate (ORR) seen with durvalumab alone in previous studies (22.6% [12.3-36.2]) in second-line patients [3]. Several patients had complete responses (CR, 9.4%). The response rate was higher in patients with a PD-L1 tumor proportion score (TPS) ≥20 based on a retrospective analysis.
- The current randomized, Phase 2 will evaluate the efficacy and safety of DANVA in combination with pembrolizumab, an approved anti-PD-1 monotherapy for first-line RM HNSCC, compared with pembrolizumab alone as first-line treatment of patients with RM HNSCC and a combined positive score (CPS) ≥20. The primary objective of the study is to improve the ORR of the combination arm to approximately 43%. Patients with a CPS ≥20 were selected for study because they have the greatest opportunity to respond based on SCORES.

STUDY DESIGN

- Multicenter, open-label, randomized phase 2 study based on a Bayesian Optimal design
- Approximately 81 first line RM HNSCC patients with a CPS ≥20
- Patients will be randomized in a 2:1 ratio to receive until disease progression:
  - DANVA (Week1: 3 mg/kg intravenously [IV] Day1, 3, and 5; Week ≥2: 3 mg/kg IV weekly) and pembrolizumab (200 mg IV every 3 weeks)
  - Or pembrolizumab alone (200 mg IV every 3 weeks)

Figure 2: Study design



- Safety will be assessed on a continuous basis
- Patients in both treatment arms will have radiologic tumor assessments every 6 weeks

STUDY OBJECTIVES

Primary Objective

- To determine the ORR by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) as determined by the Investigator for the combination of DANVA and pembrolizumab compared with pembrolizumab alone

Secondary Objectives

- To characterize the safety and tolerability of the combination of DANVA and pembrolizumab
- To evaluate additional efficacy parameters for the combination of DANVA and pembrolizumab compared with pembrolizumab alone (e.g. CR, DoR, PFS, OS)
- To characterize the pharmacokinetics (PK) of DANVA
- To determine the immunogenicity of DANVA

Exploratory Objectives

- To determine the pharmacodynamic activity of DANVA in pre- and on-treatment tumor and blood specimens
- To determine the relationship between clinical activity and human papillomavirus (HPV) and other biomarkers in pre- and on-treatment specimens

PATIENT POPULATION

Key Inclusion Criteria

- Recurrent/metastatic histologically or cytologically proven squamous cell carcinoma of the head and neck that is considered incurable by local therapy. Eligible primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx
- Presence of measurable tumor per RECIST v1.1 criteria
- Detectable PD-L1 expression in tumor, defined as CPS ≥20 determined by a Food and Drug Administration-approved test.
- ECOG Performance status of 0 or 1
- Estimated life expectancy of at least 3 months

Key Exclusion Criteria

- Prior therapy for metastatic HNSCC
- Primary tumor of the nasopharynx
- Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2
- Known autoimmune disease that has required systemic treatment (i.e., use of disease modifying agents, corticosteroids, or immunosuppressive drugs) in the past year
- Prior allogeneic tissue/solid organ transplant
- History of (non-infectious) pneumonitis that required steroids or current pneumonitis

STUDY STATUS

- Enrolment is ongoing in US sites and will be opening in additional countries.
- Clinical trial identification: NCT05814666

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