A Phase 2 Study of Evorpacept (ALX148) in Combination with Pembrolizumab in Patients with Advanced Head and Neck Squamous Cell Carcinoma (HNSCC); ASPEN-03

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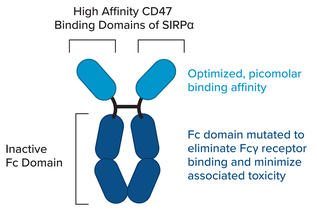
Background

- The innate and adaptive immune responses play key roles in anticancer immunity.
- CD47 is a marker of self that interacts with SIRPα on myeloid immune cells, inhibiting their function. CD47 is upregulated by tumors to evade immune responses and its expression is associated with poor prognosis.
- Evorpacept is a high affinity CD47-blocking fusion protein with an inactive Fc region (**Figure 1**) designed to enhance standard anticancer therapeutics without exacerbating their toxicities.
- The combination of evorpacept + pembrolizumab has shown preliminary activity and acceptable tolerability in patients with previously untreated and ≥2nd line advanced HNSCC in the Phase 1 ASPEN-01 study[1].
- The **ASPEN-03** study will assess the efficacy and safety of evorpacept in combination with pembrolizumab in previously untreated patients with metastatic or unresectable, recurrent PD-L1 positive HNSCC.

Figure 1. Evorpacept Selectively and Potently Binds CD47 to Block Interaction with SIRPα

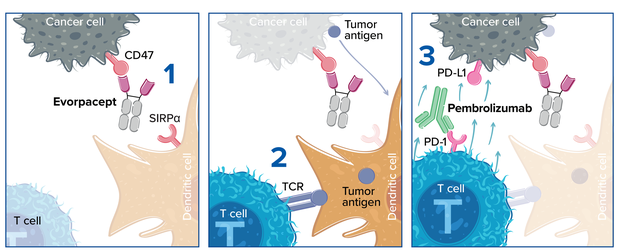


- Fc domain enables antibody-like PK.
- Molecular weight half the size of typical antibody.

Evorpacept and Pembrolizumab Have Complementary Mechanisms of Action

- Pembrolizumab inhibits PD-1/PD-L1 signaling, which is a T cell immune checkpoint, and pembrolizumab has demonstrated anti-tumor efficacy through activation of tumor-infiltrating lymphocytes.
- Pembrolizumab as a single agent is a standard treatment option for patients with previously untreated recurrent or metastatic (R/M) HNSCC with PD-L1-positive (combined positive score [CPS] ≥1) tumors[2].
- The combination of evorpacept with pembrolizumab has the potential to augment both adaptive and innate anti-tumor immune responses (**Figure 2**).

Figure 2. The Combination of Evorpacept and Pembrolizumab Can Bridge the Innate and Adaptive Immune Responses



1 Evorpacept binds to CD47 expressed by cancer cells to block the CD47-SIRPα myeloid checkpoint leading to activation of dendritic cells and enhanced phagocytosis

2 Activated dendritic cells cross-present tumor antigens to cytotoxic T cells

3 Pembrolizumab binds to PD-1, relieving PD-1/PD-L1-mediated inhibition of activated T cells leading to enhanced T cell cytotoxic activity against cancer cells

Acknowledgments

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This trial is being conducted in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.
Contact email: info@alxoncology.com
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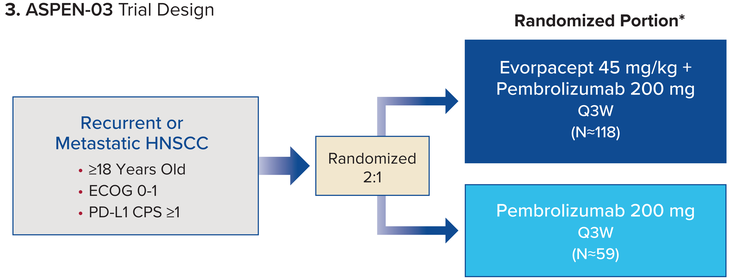
Study Methods

- **ASPEN-03** (**Figure 3**) is an ongoing, non-comparative, open-label, randomized Phase 2 global study of evorpacept + pembrolizumab or pembrolizumab alone in patients with metastatic or unresectable recurrent, PD-L1-positive (CPS≥1) HNSCC who have not yet been treated for their advanced disease.
- **ASPEN-03** will randomize approximately 177 patients to receive evorpacept + pembrolizumab or pembrolizumab alone using a 2:1 allocation after an initial safety lead-in.
- Geography, CPS, HPV (p16) status, tobacco habits and ECOG will be used as minimization factors across both arms.
- Patients in the evorpacept + pembrolizumab treatment arm will receive evorpacept 45 mg/kg IV Q3W.
- All patients will receive pembrolizumab 200 mg IV Q3W (for a maximum of 35 cycles).

Figure 3. ASPEN-03 Trial Design



*The study includes a safety lead-in for Evorpacept+ Pembrolizumab (N≥6) prior to initiation of randomized portion.

Eligibility Criteria

Key Inclusion Criteria

- Patients with PD-L1 positive metastatic/unresectable, recurrent HNSCC who have not received prior systemic therapy for their advanced disease.
  - Prior systemic therapy for treatment of locoregionally advanced disease is permitted if it was completed more than 6 months prior to enrollment.
- Measurable disease (RECIST v1.1).
- Adequate renal, liver and bone marrow function.
- Age ≥18 years.
- ECOG performance status ≤1.

Key Exclusion Criteria

- HNSCC amenable to local therapy.
- Progressive disease within 6 months of completion of systemic therapy for the treatment of locoregionally advanced HNSCC.
- Nasopharyngeal carcinoma (NPC).
- Prior treatment with any anti-CD47 or anti-SIRPα agent.
- Prior treatment with an anti-PD-1 or anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T cell receptor (e.g., CTLA-4, CD137, OX40).

Study Endpoints

Co-Primary Endpoints

- 12-month overall survival rate
- Objective response rate

Key Secondary Endpoints

- Duration of response
- Progression-free survival
- Overall survival
- Safety

Exploratory endpoints will characterize pharmacodynamic properties.

Sample Size Determination

- Statistical assumptions for the sample size determination:
  - 1-sided α = 2.5% and 80% power for 12-month OS rate.
  - Rule out 12-month OS rate of 51%[3], assuming a 12-month OS rate of 63.7% for the Evorpacept + Pembrolizumab arm.
- Testing strategy: Fixed sequence procedure will be used for the testing of co-primary endpoints.

References

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