A Phase 2 Clinical Trial of Nemvaleukin Alfa (ALKS 4230) Combined With Pembrolizumab in Patients With Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC): the ION-01 Trial

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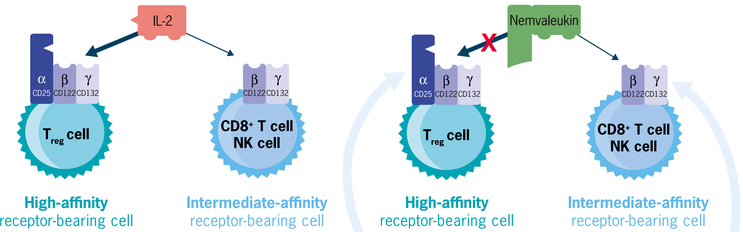
BACKGROUND

Nemvaleukin Alfa (Nemvaleukin, ALKS 4230) Is a Novel, Engineered Cytokine

- Stable, covalent fusion of circularly permuted interleukin-2 (IL-2) and the α subunit of the IL-2 receptor (IL-2Rα).
  - Inherently active, does not require any metabolic or proteolytic conversion, and does not degrade into native IL-2.
- Selectively binds the intermediate-affinity IL-2R complex to preferentially activate CD8+ T cells and natural killer (NK) cells with minimal expansion of regulatory T cells (T_{regs}) (Figure 1).
- Designed to leverage antitumor effects of the IL-2 pathway while mitigating potential toxicity that would limit use (Figure 1).

FIGURE 1: Cell Activation by IL-2 and Nemvaleukin



- IL-2 more potently activates the high-affinity IL-2R, preferentially expressed on immunosuppressive T_{regs} and upregulated on vascular endothelial cells.
- Preferential activation of high-affinity IL-2R-expressing cells by IL-2 leads to expansion of T_{regs}, which may counteract antitumor activity, and is associated with a high incidence of acute toxicities, including capillary leak syndrome.
- Nemvaleukin is sterically occluded from binding to the high-affinity IL-2R.[1]
- Nemvaleukin is designed to selectively bind to the intermediate-affinity IL-2R for preferential activation and expansion of tumor-killing CD8+ T cells and NK cells, with minimal activation of T_{regs}, as well as to mitigate the toxicities associated with the preferential binding of IL-2 to high-affinity IL-2R.[1]

Clinical and Preclinical Studies Support the Potential for the Broad Use of Nemvaleukin

- Both intravenous (IV) and subcutaneous (SC) administrations of nemvaleukin demonstrated dose-dependent, selective expansion of CD8+ T and NK cells, with minimal expansion of T_{regs}.[2,3]
- Monotherapy antitumor activity was confirmed in checkpoint inhibitor (CPI)-experienced patients with melanoma and renal cell carcinoma who have had disease progression.[4]
- Durable and deepening responses were achieved in combination with pembrolizumab in both CPI-approved and -unapproved tumor types.[4,5]
- Antitumor activity in combination with multiple agents was observed in preclinical studies.

METHODS

ION-01 (NCT04144517) is a multicenter nonrandomized, open-label phase 2 study of nemvaleukin in combination with the anti-PD-1 antibody pembrolizumab in patients with advanced or recurrent HNSCC without complete remission on prior anti-PD-(L)1 therapy

Primary Objective
To estimate response to nemvaleukin and in combination with pembrolizumab in patients with HNSCC who did not achieve complete response to prior anti-PD-(L)1 therapy.

Secondary Objectives
- To evaluate of duration of response, progression-free survival, time to progression, and overall survival, and
- To evaluate of safety and tolerability.

Exploratory Objectives
- To evaluate whether assessment of pretreatment or on-treatment biopsies can identify patients who are more likely to respond to nemvaleukin or can predict response or failure to the addition of nemvaleukin.

Patient Population
Adults aged ≥ 18 years with histologically or cytopathologically confirmed diagnosis of metastatic/recurrent HNSCC (RECIST v1.1).
- ECOG performance status of 0-2.
- Adequate organ function.
- Anti-PD-(L)1 as most recent systemic therapy without complete response.

Group 1
- Patients on prior anti-PD-(L)1 therapy with ≥ 12 weeks of stable disease or ≥ 8 weeks with partial response without further tumor regression

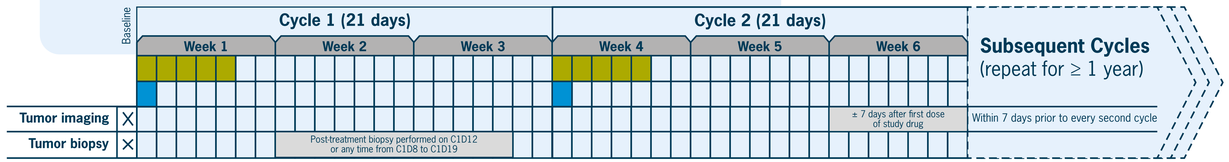
Group 2
- Patients with progressive disease after ≥ 8 weeks on anti-PD-(L)1 therapy.

As of April 26, 2021, 14 patients have been enrolled into Group 2
- The study is no longer recruiting.
- Group 1 was closed due to lack of enrollment.

Efficacy Assessments
For the primary endpoint, antitumor activity will be measured by radiological assessment compared to screening. Response rates will be determined per RECIST v1.1 criteria.

Dosing Regimen

IV nemvaleukin (3 µg/kg) on days 1-5 + **IV pembrolizumab (200 mg) on day 1**



As of April 16, 2021, 14 patients have received up to 8 cycles of combination therapy with nemvaleukin and pembrolizumab
- The combination treatment regimen is generally well tolerated and adverse events are consistent with those observed in other ARTISTRY studies with IV dosing.[2,4]

C1D8, cycle 1 day 8; C1D12, cycle 1 day 12; C1D19, cycle 1 day 19; ECOG, Eastern Cooperative Oncology Group; PD-1, programmed cell death-1; PD-(L)1, programmed death (ligand) 1; RECIST, Response Evaluation Criteria In Solid Tumors.

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Acknowledgments and Disclosures

The authors would like to thank all the patients who are participating in this trial and their families and caregivers. Many thanks to all the investigators and site personnel for their participation in this study. The trial is sponsored by Alkermes, Inc. Medical writing and editorial support was provided by Parexel and funded by Alkermes, Inc.

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