# #3377: NAI, an IL-15 Superagonist, a New Class of Lymphocyte Stimulating Agent (LSA) Prolongs OS in NSCLC by Reversing Lymphopenia

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## INTRODUCTION

- **Prior to the approval of Nogapendekin alfa inbakicept (NAI),** an IL-15 receptor superagonist which stimulates lymphocytes important in immunogenic cell death (natural killer cells, CD4+ CD8+ T cells and memory T cells)[1,2], **no treatment existed to address lymphopenia** as measured by the absolute lymphocyte count (ALC) in the CBC differential.
- **Severe lymphopenia (ALC<1,000 cells/μL) significantly lowers overall survival in NSCLC**, is well recognized as a **poor prognostic factor as part of the LIPI (Lung Immune Prognostic Index)** and is associated with the adverse treatment effects of chemotherapy, immunotherapy, and radiation.[3,4]
- While absolute neutrophil count (ANC) is widely used to identify neutropenic fever risk, **ALC has been largely ignored by clinicians since no therapy existed to treat lymphopenia.**
- The Phase II QUILT-3.055 (NCT03228667) trial enrolled participants with advanced NSCLC who had acquired resistance to checkpoint inhibitor immunotherapy (CPI) who were then treated with the same CPI+NAI to **test the hypothesis that NAI, a lymphocyte stimulating agent (LSA), prolongs OS** by reversing lymphopenia and maintaining median ALC≥1,200 cells/μL.

## METHODS

- The change in ALC (absolute cell count and percentage change from baseline) with NAI and CPI during study and its relationship to median OS was the primary endpoint for LSA.
- Median baseline ALC in the full cohort was 1,200 cells/μL which was used to stratify the analysis. Statistical differences between OS among participants who failed to reverse lymphopenia (ALC<1,200 cells/μL) during treatment vs. those who had a baseline ALC≥1200 cells/μL and maintained a group mean ALC≥1,500 cells/μL while on treatment were compared.
- The proportion of participants with lymphopenia reversal (baseline ALC<1,200 cells/μL and at least one on-treatment ALC≥1,200 cells/μL) was also assessed.

## CONCLUSION

- For the first time, ALC is an **actionable accessible biomarker** to recognize and treat therapy-induced lymphopenia to prolong OS in participants with CPI refractory NSCLC.
- Lymphopenia is addressed with the availability of NAI, a new class of LSA. With NAI, most participants (80%) exceeded and/or maintained an ALC of 1,200 cells/μL which **was associated with prolonged mOS** compared to participants who failed to achieve ALC>1,200 cells/μL (mOS 15.8 months vs. 11.5 months, [p=0.0057])
- Furthermore, **over half of participants with NSCLC (60%)** treated with NAI **experienced lymphopenia reversal** during treatment.

## REFERENCES

1. NAI Package Insert, FDA April 2024 – Section 12.1 Mechanism of Action.
2. Rubinstein, et al. Clinical Trial J Immunol. 2022 Mar 15;208(6):1362-1370
3. Grossman, et al. J Natl Compr Canc Netw. 2015 Oct;13(10):1225
4. Zhang Y, et al. Front Oncol. 2023 Dec 1;13:1287555

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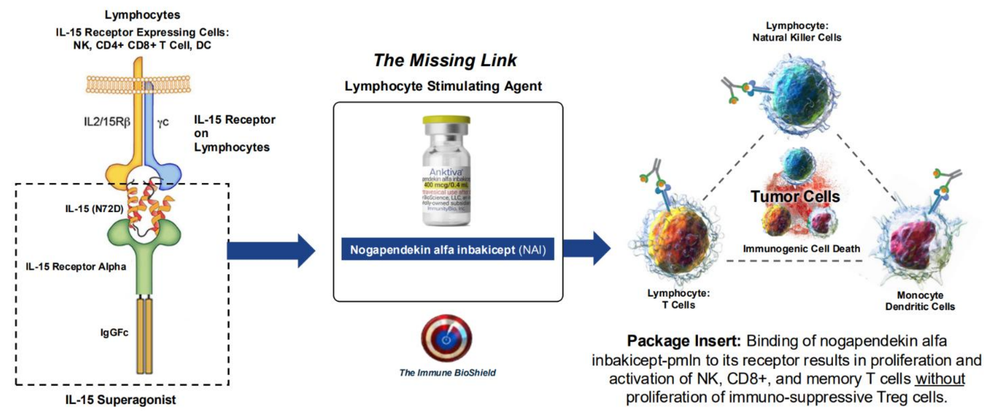
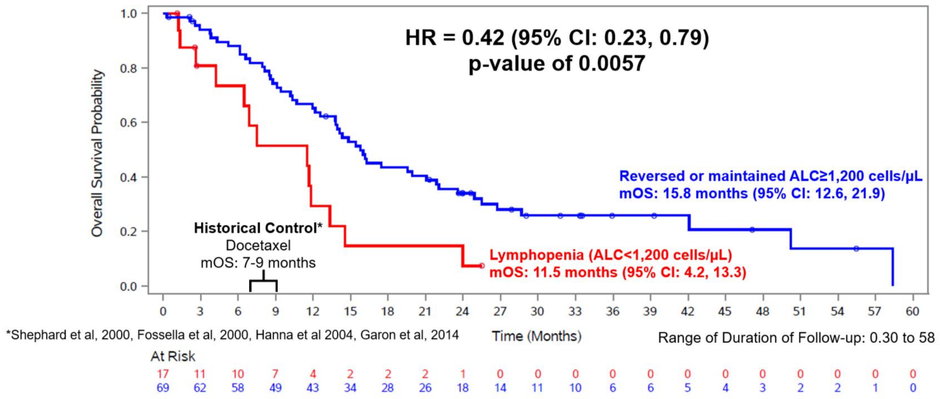
## RESULTS

**Figure 1:** Nogapendekin alfa inbakicept (NAI) Structure & MOA: First-in-class Lymphocyte Stimulating Agent (LSA)[1]



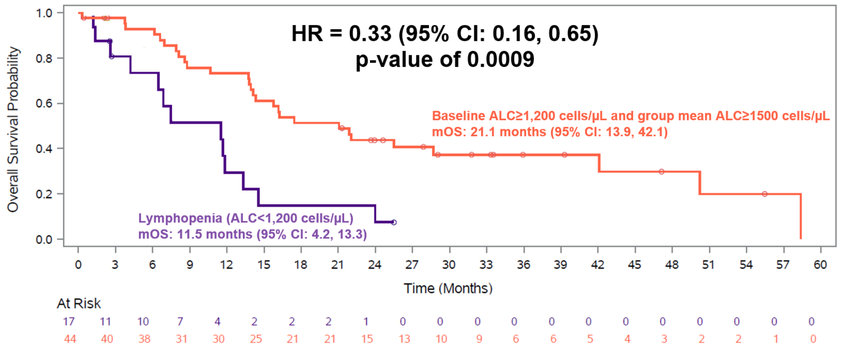

- Median OS (mOS) for participants with NSCLC (2nd line [51%] and 3rd line+ [49%]) was 14.3 months (95% CI 11.7, 17.4) with 23 of 86 participants alive at data cutoff (Dec 2024).
- Notably, **60% of participants (25/42) treated with NAI reversed their lymphopenia** during at least one on-treatment timepoint.

**Figure 2:** Overall Survival by ALC among 2L & 3L+ Line NSCLC Patients with Acquired Resistance to CPI




- With NAI, 69/86 (80%) exceeded an ALC of 1,200 cells/μL with a median OS of 15.8 months (12.6, 21.9) compared to participants who failed to achieve ALC>1,200 cells/μLwith median OS 11.5 months (4.2, 13.3) [Figure 2].

**Figure 3:** Overall Survival among 2L & 3L+ Line NSCLC Patients with Acquired Resistance to CPI who had a baseline ALC≥1,200 cells/μL and maintained a group mean ALC≥1500 cells/μL during treatment




- Participants with a baseline ALC≥1,200 cells/μL and a group mean ALC≥1500 cells/μL at each on-treatment time point (N=44) had **greater prolonged OS** (21.1 months, 95% CI: 13.9. 42.1) [Figure 3].