Lymphopenia Rescue (Cancer BioShield™) Results in Significantly Prolonged Overall Survival Following IL-15 Superagonist NAI and PD-L1 t-haNK Chemo-Immunotherapy in 3rd to 6th Line Metastatic Pancreatic Cancer Patients

Tara Seery[1,2], Chaitali Nangia[1], Heidi McKean[3], Phillip Reid[4], Katayoun Moini[1], Paul Bhar[5], Hui Zhang[5], Patricia Spilman[5], Lennie Sender[5], Sandeep B. Reddy[5], Patrick Soon-Shiong[5]

[1]Chan Soon-Shiong Institute for Medicine, El Segundo, CA; [2] Hoag Memorial Presbyterian Hospital, Newport Beach, CA; [3]Avera Cancer Institute, Sioux Falls, SD; [4]Astera Cancer Care, East Brunswick, NJ.; [5]ImmunityBio, Inc., Culver City, CA.

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Background: The Cancer BioShield™

Lymphopenia, characterized as low Absolute Lymphocyte Count (ALC), defined as less than <1,000 lymphocyte cells/μL in blood. Low levels of lymphocyte subsets of NK cells and T cells contribute to poor prognosis and early mortality in patients with cancer. [2] Lymphopenia and treatment induced lymphopenia (from chemotherapy, radiation, and immunotherapy) has been poorly recognized since no treatment existed to date until the development of NAI, an IL-15 superagonist and the ex-vivo infusion of CAR-NK (PD-L1 t-haNK). Currently, no treatment for lymphopenia exists. [5]

For the first time, the in-vivo protection of lymphocytes (via subcutaneous injection of NAI) and the ex-vivo protection of the collapse of the immune system (via infusion of PD-L1 t-haNK), presents a paradigm change in the treatment of cancer.

We postulate that the fundamental root cause of early death in patients with cancer across all tumor types is the collapse of the immune (lymphocyte) system and that cancer is a symptom. Survival is closely associated with lymphopenia and ALC, with patients who develop lymphopenia due to the cancer itself, or as a consequence of standard-of-care radiation (SBRT) or chemotherapy, having shorter survival than those with ALC in the normal range [1].

Neutropenia, as well as a high **neutrophil to lymphocyte ratio (NLR)** similarly impacts treatment outcomes. Current methods for neutrophil stimulation, such as GCSF, can result in expansion of immunosuppressive neutrophils (N2) as myeloid-derived suppressor cells (MDSCs). Together with chemotherapy induced lymphopenia and GM-CSF induced MDSCs, a high NLR ratio is predictive of early mortality across multiple tumor types. The collapse of the immune system (lymphocytes) key to immunogenic cell death, combined with enhanced immuno-evasion by suppressive neutrophils counts for early mortality in patients with cancer. [3]

Lymphopenia (ALC <1,000), high NLR ratio and high CA19-9 levels are associated with poor prognosis in pancreatic cancer [1]. The IL-15 superagonist and Lymphocyte-Stimulating Agent (LSA) nogapendekin alfa inbakicept (NAI; N-803) rescues lymphocytes [2] by proliferating and activating natural killer (NK) and CD8+ and memory T cells [7] and prolongs overall survival in patients with advanced pancreatic cancer who have failed all standards of care.

Programmed death-ligand 1 (PD-L1) targeting high-affinity NK (PD-L1 t-haNK) are engineered to express high-affinity CD16 and PD-L1 specific chimeric antigen receptor (CAR-NK). These ex-vivo lymphocytes, when given in combination with NAI (in-vivo stimulation of lymphocytes), target immunosuppressive MDSCs to augment tumor response and patient outcomes. By overcoming immune evasion and rescuing the treatment induced collapsed immune system, prolonged overall survival can be achieved

METHODS: QUILT-88 (NCT04390399) was a phase 2 open-label multicenter study wherein cohort C patients with locally advanced or mPC who had progressed after 2nd to 6th line therapy received SBRT, low-dose chemotherapy, NAI, and PD-L1 t-haNK cells [4].Median Overall Survival (mOS), CA19-9 (a indicator of tumor burden) ALC & NLR levels were assessed. Associations between these parameters were determined, specifically between mOS for those with ALC < vs. ≥ the on-treatment median (580 cells/μL); for those with CA19-9 < or ≥ the baseline median (3,852 U/mL); and for those who overcame severe lymphopenia. In addition, mOS by the neutrophil-to-lymphocyte (NLR) ratio was analyzed to examine the effect of overcoming high immunosuppressive neutrophils and overcoming lymphopenia.

FINDINGS:

- **Significant prolonged survival is associated with lymphopenic rescue (ALC). (Fig. 1)**
- **Significant prolonged survival is associated with the reduction of Neutrophil-to-Lymphocyte Ratio (NLR) and tumor burden (CA19-9). (Fig. 2).**
- **Further prolonged survival is associated with level of lymphocytes (ALC) rescue achieving ALC ≥ 1,000, independent of CA19-9 tumor burden (Fig. 3).**
- **Further prolonged survival is associated with level of lymphocytes (ALC) and CA19-9 tumor burden (Fig 4).**
- **The first treatment approved as a Lymphocyte Stimulating Agent (NK, CD4+ CD8+ T cells and Memory T Cells) in patients with immunocompromised BCG unresponsive bladder cancer with prolonged disease-free survival.**

Findings

Figure 1: ALC LEVELS - Significant Prolongation of Overall Survival in 3rd to 6th line Metastatic Pancreatic Cancer Patients with Reconstitution of Lymphocytes by In-Vivo & Ex-Vivo Lymphocyte Stimulating Agents Independent of Tumor Burden and by ALC Levels

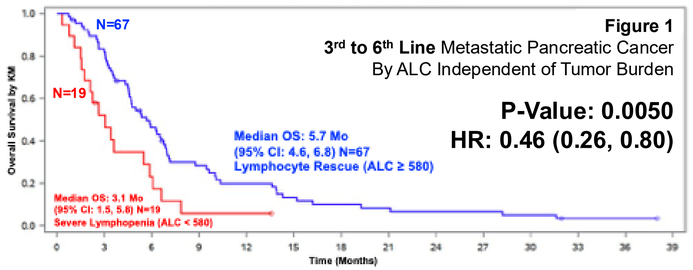


Figure 2: NLR & TUMOR BURDEN - Significant Prolongation of Overall Survival in 3rd to 6th line Metastatic Pancreatic Cancer Patients with Reconstitution of Lymphocytes by In-Vivo & Ex-Vivo Lymphocyte Stimulating Agents with Lower Tumor Burden and Lower NLR Ratio

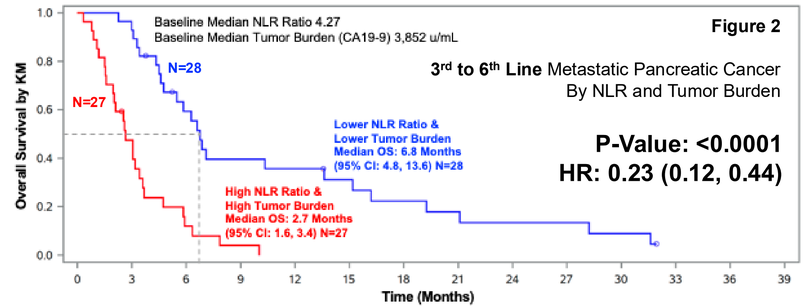
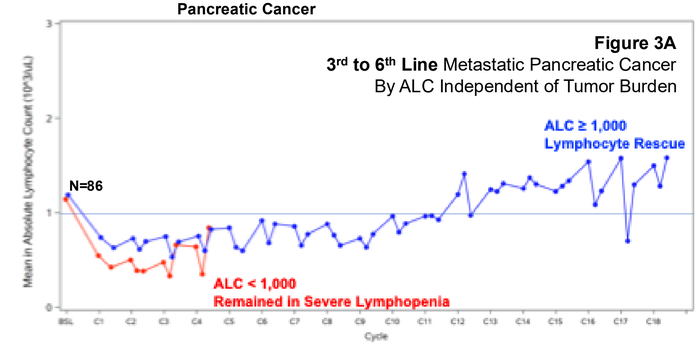


Figure 3A & 3B: EFFECT OF ALC LEVELS (≥1,000) ON OVERALL SURVIVAL: Subjects with Prolonged Survival Achieve an ALC ≥ 1,000 with Lymphocyte Rescue. The Long-Tail in the KM of 7.9 Months (95% CI: 6.8, 10.3) is Seen with Subjects Who Achieve an ALC ≥ 1,000 and Maintain Treatment Beyond Cycle 5 Independent of Tumor Burden in 3rd to 6th Line Metastatic Pancreatic Cancer



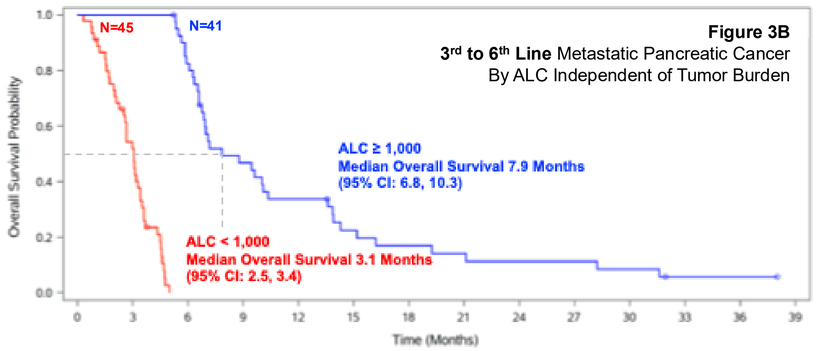
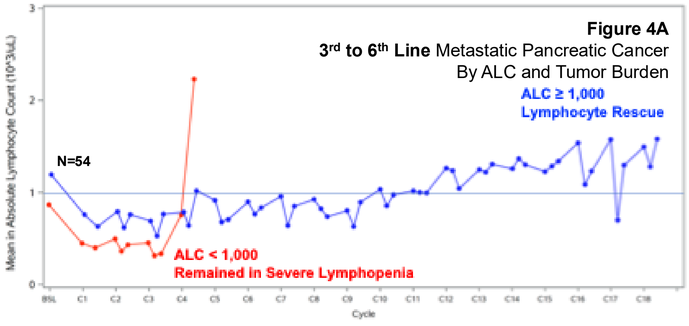
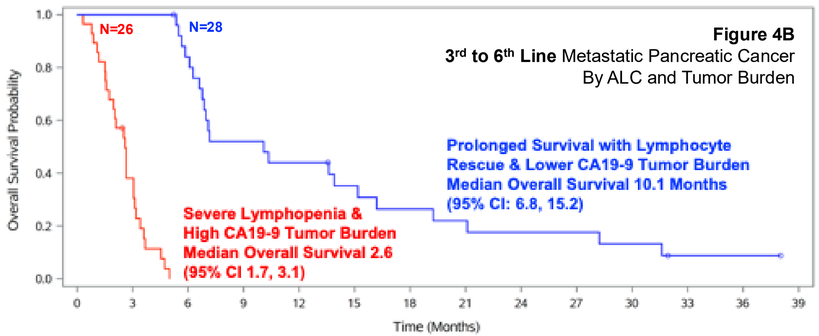


Figure 4A & 4B: EFFECT OF TUMOR BURDEN AND ALC LEVELS ON OVERALL SURVIVAL: Subjects with Lower Tumor Burden and Lymphocyte Rescue (ALC ≥ 1,000) Demonstrate a Prolonged Survival of 10.1 Months (95% CI: 6.8, 15.2) Compared to Subjects with Higher Tumor Burden (CA19-9 Median ≥ 3,852 u/mL) and in Severe Lymphopenia (ALC < 1,000)





Conclusions

- NAI, the first therapy approved as a Lymphocyte-Stimulating Agent (LSA) in bladder cancer, by proliferating NK and CD8+ T cells, improves ALC and reduces NLR [5].
- First-in-Class Lymphocyte Stimulating Agent (LSA) to treat lymphopenia
- In-vivo LSA and Ex-vivo CAR-NK rescues a collapsed immune system
- Reversal of lymphopenia with higher ALC and lower NLR associated with significant prolonging of overall survival in patients with pancreatic cancer
- Achieving ALC ≥ 1,000 further prolongs survival suggesting the benefit of increasing ALC
- PD-L1 t-haNK (CAR-NK) overcomes immunosuppressive MDSCs and plays a role by providing an exogenous (ex-vivo) source of active NK cells [6].

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REFERENCES
1. Am J Clin Oncol. 2015; 38(3):259
2. J Immunol. 2022;;208(6):1362
3. Protein Cell. 2016; 7(2):130-140
4. J Clin Oncol. 2022; 40(16_suppl)
5. Drugs 2024;84(7):867
6. J Immunother Cancer.;8(1):e000450
7. NAI Package Insert, FDA April 2024 – Section 12.1 Mechanism of Action