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Background

Immune checkpoint inhibitors (CPIs) are approved as monotherapy and in combination with chemotherapy in advanced or metastatic NSCLC (mNSCLC). Most patients with mNSCLC will experience progression with limited treatment options beyond cytotoxic chemotherapy, highlighting an important unmet need for those without actionable biomarkers.

Mechanisms of resistance to CPIs include T cell exhaustion and loss of MHC molecules on the tumor, reducing antigen expression and immune recognition. Here we present a potential mechanism to overcome CPI resistance with a novel immunotherapy regimen leveraging damage-associated molecular patterns (DAMPs) to increase tumor antigen expression and activate killer T cells to reignite tumor killing (FIGURE 2).

The rationale for ResQ201A-NSCLC (NCT06745908) is based on the Phase 2 QUILT-3.055 trial (NCT03228667), wherein the addition of NAI as a lymphocyte stimulating agent to CPI at first mNSCLC progression demonstrated prolonged median OS (mOS) of 14.3 months overall and 21.1 months when ALC $\geq 1,200$ cells/ μ L was maintained.²

Randomized clinical trials (PRAGMATICA-LUNG, TROPION-Lung01) have demonstrated that docetaxel, the standard of care in the 2L+ NSCLC setting, results in a mOS of approximately 9.3-11.8 months.^{3,4}

Study Schema

ResQ201A-NSCLC: Global, Randomized, Open-Label Phase 3 Trial – Actively Enrolling

Adult mNSCLC patients with acquired resistance* to CPI plus platinum-based chemotherapy

N = up to 462

STRATIFIED BY:

- Geographical Region (Americas vs. Asia PAC vs. Other)
- Histology (Squamous or Non-squamous NSCLC)
- AGA vs. No AGA (Actionable Genomic Alterations)

Randomization 2:1

Experimental Arm B (3-week cycles)

N = up to 308

Induction (Cycles 1 & 2)

- NAI/N-803 (SC 1.2 mg)
- Prior failed CPI (per CPI label in region)
- Docetaxel (IV 75 mg/m²)

Maintenance (Cycles ≥ 3)

- NAI/N-803 (SC 1.2 mg)
- Prior failed CPI (per CPI label in region)

Control Arm B (3-week cycles)

N = up to 154

- Docetaxel (IV 75 mg/m²)

Treatment until disease progression, unacceptable toxicity, withdrawal of consent, or if the investigator feels it is no longer in their best interest to continue treatment.

*Defined as disease progression immediately following an initial response (CR or PR of any duration) or SD (~ 6 months' duration [± 2 weeks])

FIGURE 1. *Nogapendekin Alfa Inbakicept (NAI) Structure & MOA*

Nogapendekin alpha inbakicept (NAI/N-803) is an IL-15 receptor agonist that induces proliferation and activation of natural killer (NK) cells, CD8+ T cells, and memory T cells without activating regulatory T cells, enhancing both the innate and adaptive immune systems to maximize immunogenic cell death.¹

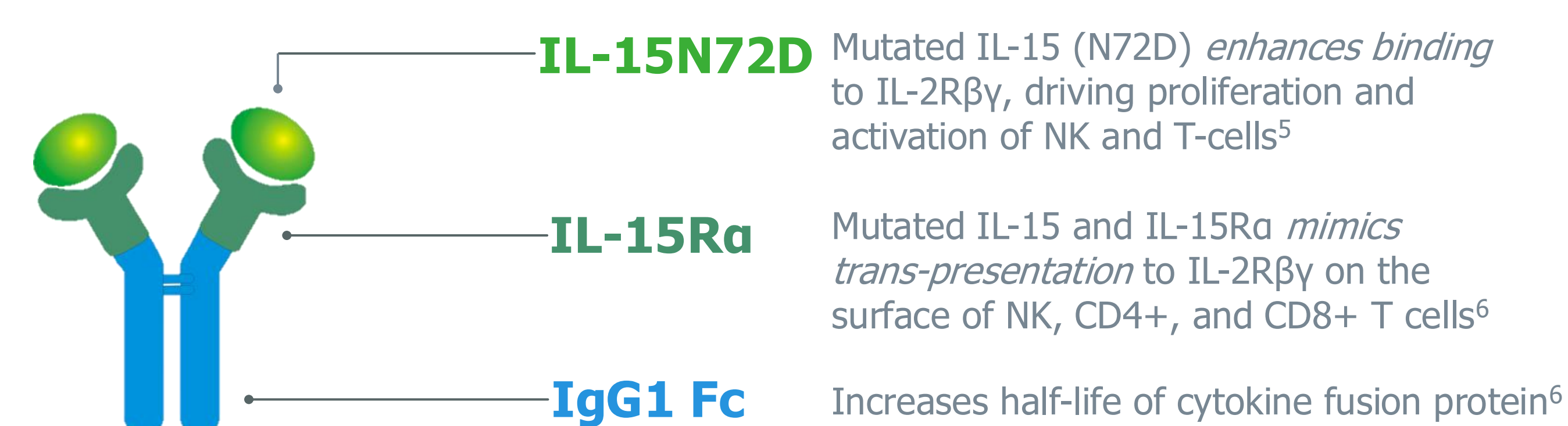
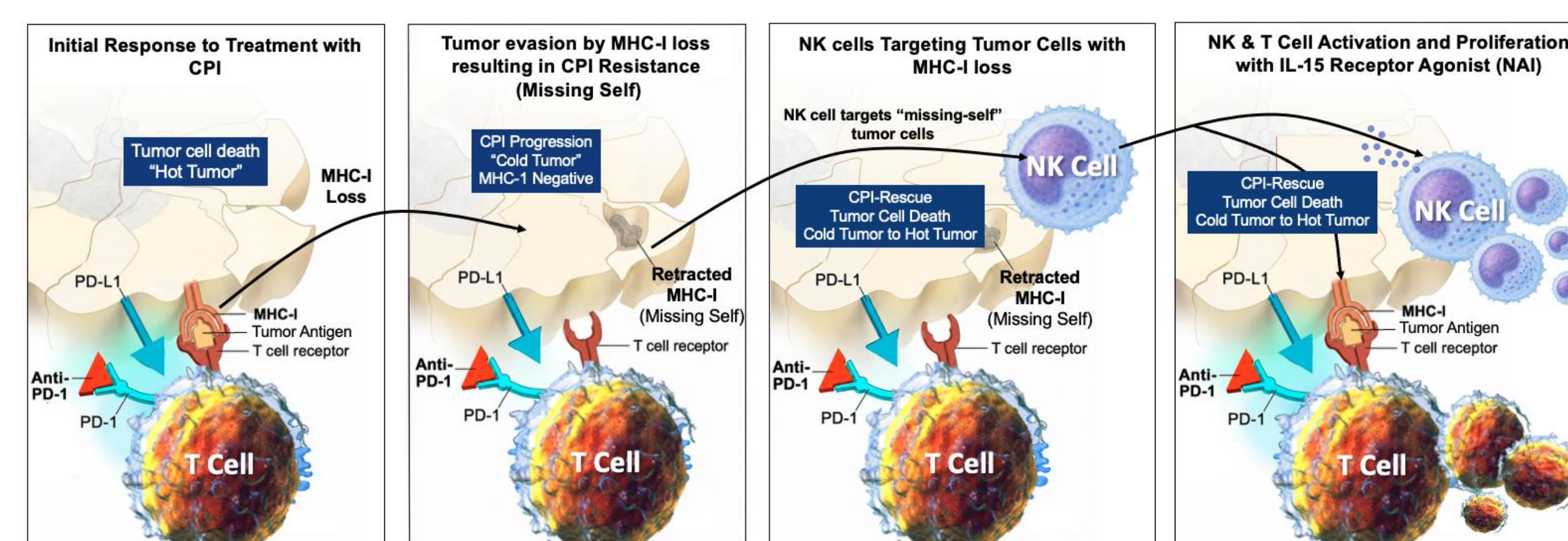


FIGURE 2. *Acquired CPI Resistance & ResQ201A-NSCLC Rationale*



Modified from: <https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/checkpoint-inhibitors>

Study Endpoints

Primary Endpoint:

- Overall Survival by KM (defined as time from randomization to death resulting from any cause).

Secondary Endpoints:

- Change in ALC values over time.
- Immune disease control rate (iDCR) per iRECIST; progression-free survival (iPFS), overall response rate (iORR), and duration of response (iDOR).
- AEs and SAEs (NCI CTCAE v6.0).

Exploratory Endpoints:

- Disease-specific survival (DSS), defined as time from randomization to death resulting from NSCLC & PFS, DOR, DCR, ORR per RECIST v1.1
- Maintenance of immune competence during treatment via ALC measurements.
- Assess whole slide images and tumor molecular profiles and correlate with participant outcomes.
- Longitudinal blood collection for ctDNA analyses.



RESOURCES

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