Presented at the AACR Annual Meeting, 5-10 April 2024, San Diego, CA, USA, and online

Abstract CT107

Durable immunogenicity of ELI-002 2P in AMPLIFY-201: Lymph node targeted mKRAS-specific amphiphile vaccine in pancreatic and colorectal cancer

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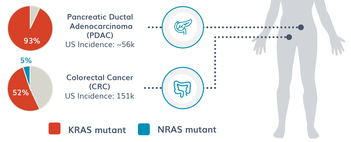
Why Target mutated KRAS with Therapeutic Vaccination?

1 Mutant KRAS Drives 25% of Solid Human Cancers

- **Prevalent** among numerous tumor types[1-2]
- Overall **poor clinical prognosis**[3]
- **Limited therapeutic options**



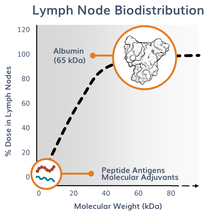
2 Mutant KRAS is a Promising Tumor Antigen

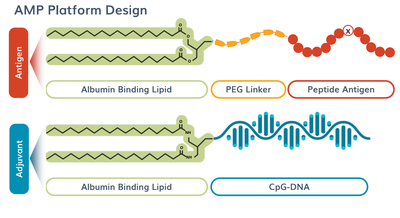
- **Truncal**: mutations occur early, expressed uniformly in all tumor cells
- **Driver**: mKRAS signaling is required for tumor growth and survival
- **Highly prevalent**: involved in ~25% of solid tumors[1-2]
- **Public neoantigen**: not centrally tolerized, cognate TCRs present in naïve repertoire[4-5]
- **Promiscuous HLA presentation**: potential off-the-shelf use in diverse patient population[6-8]
- **Proven Clinical MOA**: mKRAS-specific T cells known to mediate anti-tumor efficacy[4-5]
- **Multi-targeting potential**: recognition of clonal and subclonal mKRAS variants to prevent escape[9]

The AMP-Platform: Enhanced Lymph Node Delivery

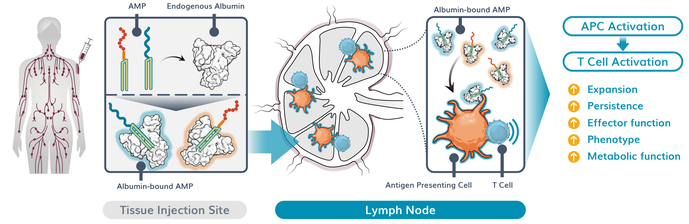
- **Smart trafficking to the lymph nodes** after subcutaneous dosing generates immune responses with increased magnitude, function, and durability[10-11]
- **Takes advantage of potent lymph node immune mechanisms**, including activation of innate and adaptive immune cells, antigen-spreading, and improved tumor T cell trafficking / infiltration

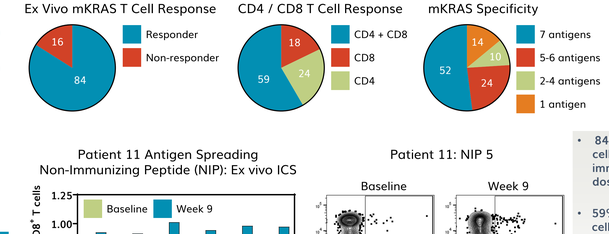
Vaccine Design



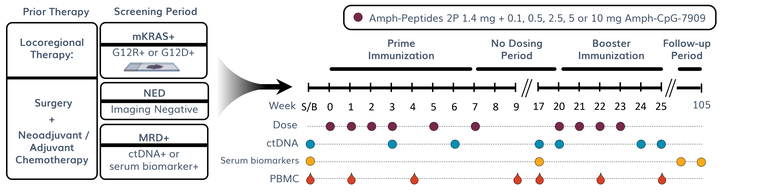


Mechanism of Action





AMPLIFY 201: Trial Design[12]



Patients

Safety

Baseline Characteristics: 20 Pancreatic (PDAC), 5 Colorectal (CRC) were evaluated for safety as of data cutoff: Sept. 6th, 2023[12]

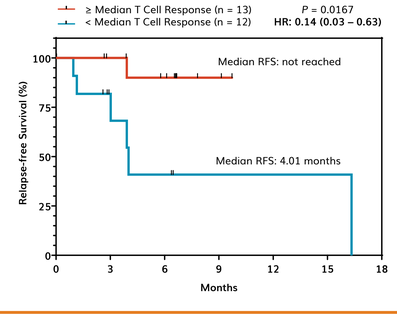
Safety: No TEAEs ≥ Grade 3, no Dose Limiting Toxicities, no Cytokine Release Syndrome observed across all dose levels; 44% had Grade 1-2 TEAEs: e.g. injection site reaction, fatigue, headache, nausea[12]

AMPLIFY 201: Immunogenicity Methods

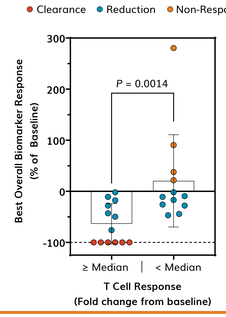
- **Immunogenicity of ELI-002 2P** was assessed using longitudinally collected peripheral blood from 23 evaluable patients to assess specificity, polyfunctionality, and antigen breadth. Phenotype of mKRAS-specific T cells was assessed in 19 evaluable patients.
- PBMCs from each patient were individually stimulated with overlapping peptides for each of the seven mKRAS antigens (G12R, G12D, G12V, G12C, G12A, G12S and G13D) for evaluation of mKRAS-specific T cell responses using **direct *ex vivo*** assays.
- **T cell responses** and **polyfunctionality** were determined by a direct *ex vivo* IFNγ/Granzyme B (GrB) Fluorospot, where a positive immune response was defined as >2-fold over baseline and at least 50 SFC per million PBMCs.
- **Polyfunctionality** and **phenotype** of patient T cells were further characterized using an *ex vivo* intracellular cytokine staining (ICS) assay, where responder populations were defined as >2-fold over baseline and a frequency of at least 0.1% Cytokine⁺. The ICS assay included markers for CD3, CD4, CD8, Memory (CCR7, CD45RA, CD45RO), cytokines (IFNγ, TNFα, IL2), cytolysis (GrB, Perforin, CD107a), activation markers (CD69, CD137, CD154), and proliferation (Ki67).

mKRAS T Cell Responses Correlate with Reduction in Risk of Relapse or Death[12]

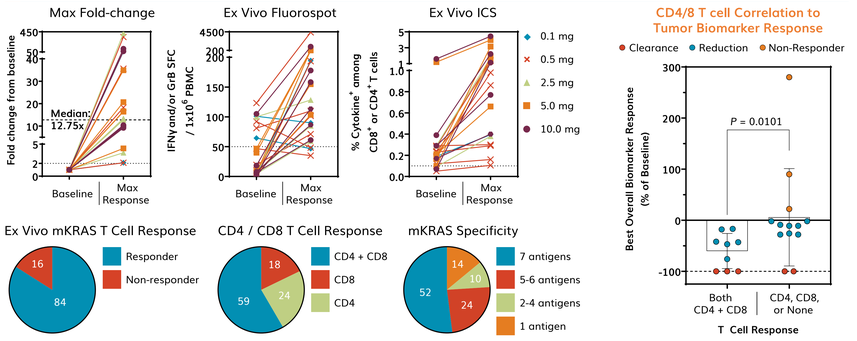
Strength of T Cell Response ➤ 86% Reduced Risk of Relapse or Death

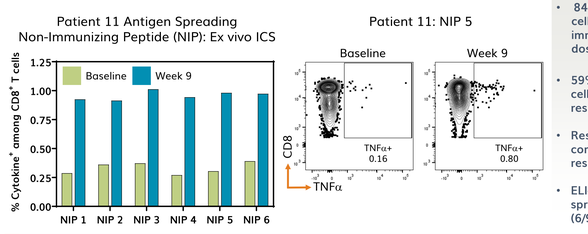


Best Overall Tumor Biomarker Response



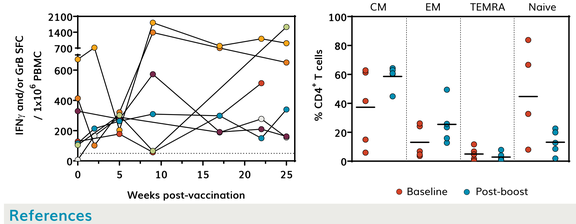
Expansion of T cells Targeting mKRAS and Antigen Spreading





- 84% of patients generated mKRAS-specific T cell responses following ELI-002 2P immunization; 100% responders at the highest dose levels (5.0 and 10.0 mg)
- 59% of patients induced both CD4⁺ and CD8⁺ T cell responses, 76% of patients induced responses to ≥5 mKRAS antigens
- Response to both CD4⁺ and CD8⁺ T cells correlated with overall tumor biomarker response
- ELI-002 2P vaccination induces antigen spreading to non-immunizing antigens in 66.7% (6/9) of patients

Durable mKRAS-Specific Immunogenicity after ELI-002 2P Booster Vaccinations



- 86% (6/7) of patients maintained elevated T cell response relative to baseline levels or increased response after boost
- Post-boost mKRAS-specific CD4⁺ T cells had increased central and effector memory cells and decreased naïve T cells compared to baseline

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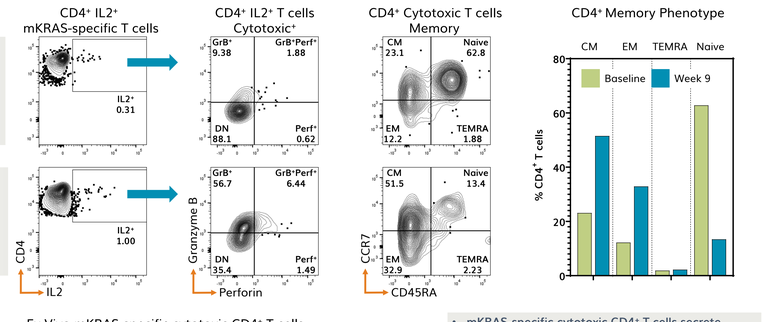
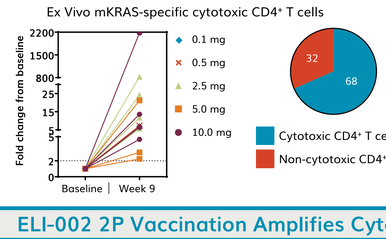
Acknowledgements

- We are grateful to the patients who participated in the study, their families, and the investigators and staff at the participating institutions.

ELI-002 2P Vaccination Amplifies Cytotoxic mKRAS-specific CD4⁺ T cells

➤ 68% of patients (13/19) have cytotoxic mKRAS-specific CD4⁺ T cells

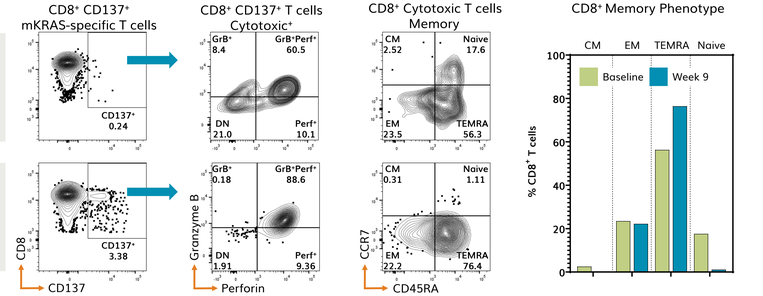


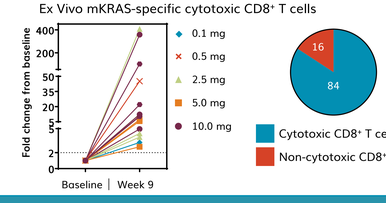


- mKRAS-specific cytotoxic CD4⁺ T cells secrete Granzyme B and Perforin
- Cytotoxic CD4⁺ T cells are predominantly central and effector memory post vaccination shifting from naïve T cells at baseline
- Of the 68% of patients who had mKRAS-specific CD4⁺ cytotoxic T cells, the median fold change was 7.4, ranging from 2.23 to 2183, with 66.7% (4/6) cytotoxic responders at the RP2D
- CD4⁺ regulatory T cells are not observed in any patients (0/19)

ELI-002 2P Vaccination Amplifies Cytotoxic mKRAS-specific CD8⁺ T cells

➤ 84% of patients (16/19) have cytotoxic mKRAS-specific CD8+ T cells





- Cytotoxic CD8⁺ T cells secrete high levels of both Granzyme B and Perforin
- After vaccination, cytotoxic CD8⁺ T cells are predominantly TEMRA memory which are known for lower proliferative capacity but increased cytotoxic function
- Of the 84% of patients who had mKRAS-specific CD8⁺ cytotoxic T cells, the median fold change was 10.4, ranging from 2.73 to 407, with 66.7% (4/6) cytotoxic responders at the RP2D

TAKE HOME MESSAGES

T Cell Response MOA Correlated to:

- **86% Reduced Risk of Relapse or Death**
- **Tumor Biomarker Response**

- Direct *ex vivo* mKRAS-specific T cell responses observed in 84% of patients
- 86% (6/7) of patients had durable T cell responses with memory T cells increased from baseline
- Ex vivo T cell responses to non-immunizing antigens are induced by ELI-002 2P vaccination
- mKRAS-specific CD4⁺ T cells were cytotoxic, predominantly central and effector memory phenotype
- No increases in CD4⁺ regulatory T cells were observed after vaccination with ELI-002 2P
- 84% (16/19) of patients have cytotoxic mKRAS-specific CD8⁺ T cells, primarily TEMRA phenotype

✓ **Randomized Phase 2 Ongoing: ELI-002 7P (NCT05726864) in PDAC: targeting G12D R V C A S, G13D**