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Abstract 1473

AMPLIFY-7P Phase 1a: Lymph node-targeted amphiphile therapeutic cancer vaccine in patients with high relapse risk KRAS mutated pancreatic ductal adenocarcinoma and colorectal cancer

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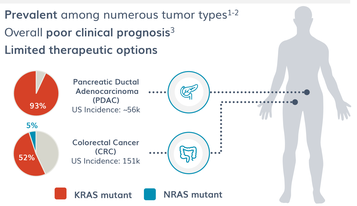
ClinicalTrials.gov Identifier: NCT05726864

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**



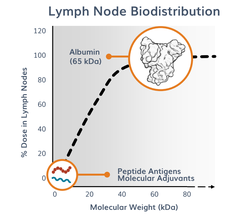
2 Mutant KRAS is a Promising Tumor Antigen

- **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]
- **Demonstrated Clinical MOA**: ELI-002 2P induced mKRAS-specific T cells correlated with a reduced risk of relapse or death by 86%[9]
- **Multi-targeting potential**: recognition of clonal and subclonal mKRAS variants to prevent escape[10]

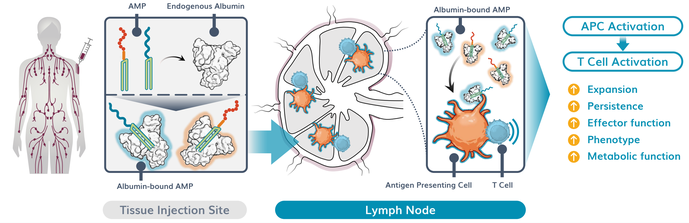
The AMP-Platform: Enhanced Lymph Node Delivery

- **Smart trafficking to the lymph nodes** after subcutaneous dosing demonstrates immune responses with increased magnitude, function, and durability[11-12]
- **Designed to take 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

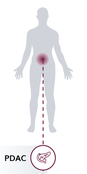


Mechanism of Action



AMPLIFY 7P: Trial Design

Phase 1 Schema



Prior Therapy

Locoregional Therapy:
- Surgery
- Chemotherapy
- +/- Radiation

Screening Period

- mKRAS+ G12(D, R, V, C, S, A) or G13D
- No Evidence of Disease Imaging Negative
- Minimal Residual Disease+ ctDNA+ or serum biomarker+ (Required for Phase 1 only)

Prime Immunization | No Dosing Period | Booster Immunization | Follow-up Period

ctDNA / serum biomarkers

Imaging assessment for relapse

Immunogenicity

Evaluation of escalating dose of Amph-Peptides 7P (1.4 mg and 4.9 mg) and fixed Amph-CpG adjuvant dose (10.0 mg)

Dose Level	Ascending Dose Amph-Peptides 7P	Fixed Dose Amph-CpG-7909
1	1.4 mg	10.0 mg
2	4.9 mg	10.0 mg

Patients Safety

Baseline Characteristics: 13 Pancreatic (PDAC), 1 Colorectal (CRC) were evaluated for safety

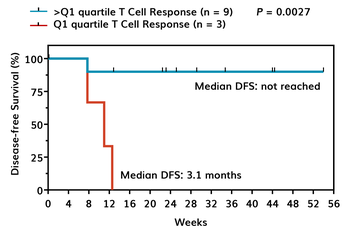
Safety: No treatment-related SAEs, no dose-limiting toxicities, no discontinuation of study drug due to AE, no CRS or T cell related side effects. Infrequent observation of injection site reaction, common vaccine associated AEs (fatigue, malaise), all grade 1-3[13]

AMPLIFY 7P: Immunogenicity Methods

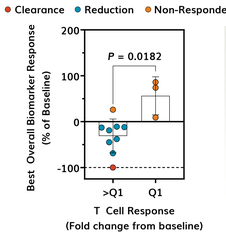
- **Immunogenicity of ELI-002 7P** was assessed using longitudinally collected peripheral blood from 12 evaluable patients to assess specificity, polyfunctionality, and antigen breadth. Phenotype of mKRAS-specific T cells was assessed in 6 evaluable patients.
- PBMCs from each patient were individually 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), cytokines (IFNγ, TNFα, IL2), cytolysis (GrB, Perforin), activation (CD137, CD154), and proliferation (Ki67).

mKRAS T Cell Responses Correlate with Increased Disease-free Survival

Strength of T Cell Response ➤ Longer Disease-free survival

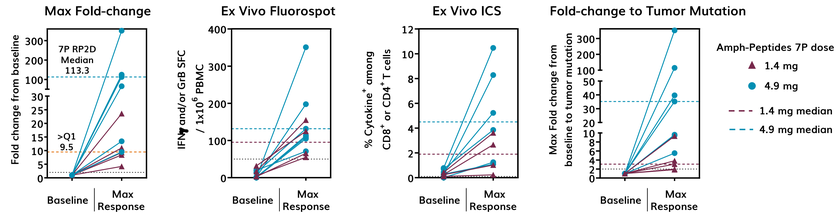


Best Overall Tumor Biomarker Response



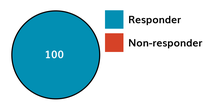
- Strength of ELI-002 7P induced mKRAS-specific T cell response significantly correlated to longer DFS (median DFS not reached)
- 89% of patients with T cell fold-change above the first quartile (>9.5) had biomarker reduction or clearance observed while 100% of patients with lower (<9.5) T cell fold-change are biomarker non-responders

Expansion, Specificity and Durability of T cells Targeting mKRAS

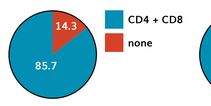


4.9 mg Amph-Peptides 7P dose (RP2D)

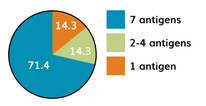
Ex Vivo mKRAS T Cell Response



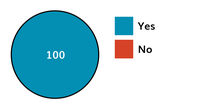
CD4 / CD8 T Cell Response



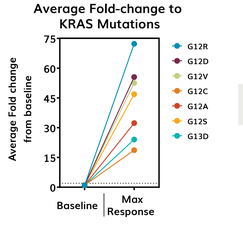
mKRAS Specificity



Response to Tumor mutation



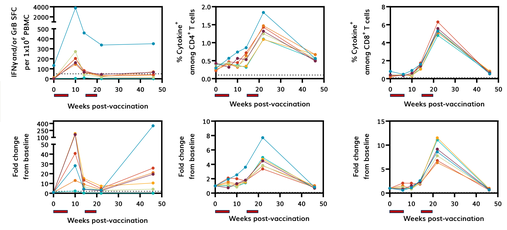
Average Fold-change to KRAS Mutations



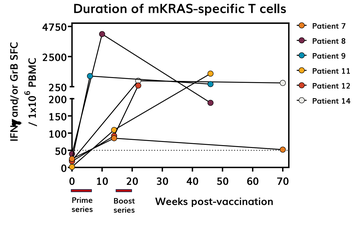
SFC / % Frequency

Patient 8

Fold change



Duration of mKRAS-specific T cells



- 100% (12/12) of patients induce an ex vivo mKRAS-specific T cell response based on Fluorospot and ICS
- >12x Improved median T cell fold-change in RP2D dose group (113.3 vs 9.3 FC)
- At the RP2D 4.9 mg Amph-Peptides 7P dose:
  - 85.7% of patients (6/7) induce both CD4 and CD8 T cell responses
  - 71.4% have T cell responses to all 7 targeted mKRAS antigens
  - 100% of patients (7/7) induce a positive T cell response to their tumor mutation
  - A robust positive response was detected to all KRAS mutations, with the highest responses induced to the 3 most common variants:
    - G12R, G12D, and G12V
  - 100% of patients (5/5) maintained elevated positive T cell responses relative to baseline levels after the booster doses

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Acknowledgements

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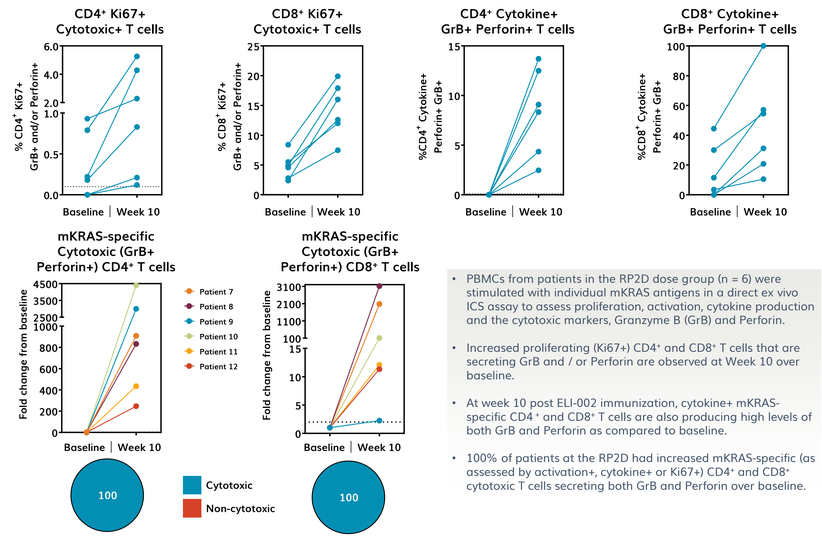
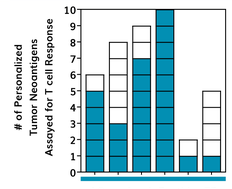
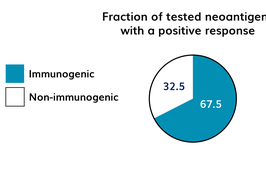
ELI-002 7P Vaccination Amplifies Cytotoxic mKRAS-specific CD4$^+$ and CD8$^+$ T cells



- PBMCs from patients in the RP2D dose group (n = 6) were stimulated with individual mKRAS antigens in a direct ex vivo ICS assay to assess proliferation, activation, cytokine production and the cytotoxic markers, Granzyme B (GrB) and Perforin.
- Increased proliferating (Ki67+) CD4$^+$ and CD8$^+$ T cells that are secreting GrB and / or Perforin are observed at Week 10 over baseline.
- At week 10 post ELI-002 immunization, cytokine+ mKRAS-specific CD4$^+$ and CD8$^+$ T cells are also producing high levels of both GrB and Perforin as compared to baseline.
- 100% of patients at the RP2D had increased mKRAS-specific (as assessed by activation+, cytokine+ or Ki67+) CD4$^+$ and CD8$^+$ cytotoxic T cells secreting both GrB and Perforin over baseline.

ELI-002 7P Vaccination Induces Antigen Spreading to Personalized, Non-immunizing Tumor Neoantigens





Fraction of tested neoantigens with a positive response

- Non-immunizing antigens from each patient's personal tumor mutanome were selected from whole exome sequencing and peptides were used to stimulate PBMCs directly ex vivo for assessment by Fluorospot and ICS.
- ELI-002 7P induces increased T cell responses targeting non-immunizing, personalized tumor neoantigens in 6/6 (100%) patients treated at the 4.9 mg RP2D dose level.
- 67.5% of the tested non-immunizing tumor neoantigens induced a positive T cell response.

Randomized, Controlled Phase 2 Study Ongoing for Adjuvant Treatment of PDAC

Randomized Phase 2

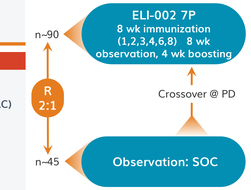
Monotherapy (no chemo, CPI combo)

- ✓ mKRAS: Expanded Antigen Coverage: G12D / V / R / C / A / S / G13D

Phase 2: Key Criteria

- ✓ Includes: mKRAS G12D / V / R / C / A / S / G13D
- ✓ Up front resectable Stage I, II or III disease (PDAC)
- ✓ Complete R0/R1 resection
- ✓ Radiographic NED status within 6 months following completion of locoregional treatment
- ✓ MRD agnostic (biomarker +/- included)

Schema



Endpoints

- Primary Endpoint: Disease-Free Survival
- Overall Survival
- Tumor Biomarker Response (in the biomarker subset)
- Safety
- iRECIST Overall Response Rate (in the crossover subset)
- Immunogenicity

TAKE HOME MESSAGES

Lymph node-targeted mKRAS specific cancer vaccine ELI-002 7P:

- ➢ **Strength of mKRAS-specific T cell response correlated to longer DFS:** Patients above 25th percentile T cell response (median not yet reached) versus below 25th percentile (3.1 months); *P = 0.0027*
- ➢ Direct *ex vivo* mKRAS-specific T cell responses observed in 100% of patients, with 12x higher immune responses in the RP2D dose group relative to 1.4 mg dose level
- ➢ Robust ex vivo T cell responses induced to all 7 targeted KRAS mutants, with highest response to the 3 most common variants: G12R, G12D, and G12V
- ➢ 100% (5/5) of patients had durable T cell responses up to 1.5 years from initial ELI-002 vaccination
- ➢ Induced mKRAS-specific CD4$^+$ and CD8$^+$ T cells were cytotoxic, secreting both GrB and Perforin
- ➢ Antigen spreading is induced by ELI-002 7P vaccination in 100% of RP2D-treated patients, with responses to 67.5% of tested non-immunizing neoantigens
- ➢ Data suggests ELI-002 7P is well-tolerated, with no dose limiting toxicity or CRS observed
- ✓ **Randomized Phase 2 Ongoing: ELI-002 7P (NCT05726864) in PDAC: targeting G12D R V C A S, G13D**