T cell responses and clinical outcomes in pancreatic and colorectal cancer patients with Minimal Residual Disease in AMPLIFY-201, a Phase 1 trial of a first-in-class Amphiphile lymph node targeted mutant KRAS vaccine

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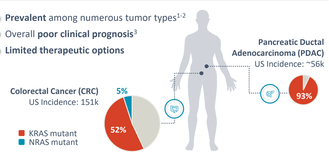
Why Target mutated KRAS with Therapeutic Vaccination?

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[7-8]
- **Promiscuous HLA presentation**: potential off-the-shelf use in diverse patient population[4-6]
- **Proven Clinical MOA**: mKRAS-specific T cells known to mediate anti-tumor efficacy[7-8]
- **Multi-targeting potential**: recognition of clonal and subclonal mKRAS variants to prevent escape[9]

HYPOTHESIS: mKRAS Vaccination will Prevent Tumor Recurrence in High Relapse-Risk Patients Following Standard Therapy

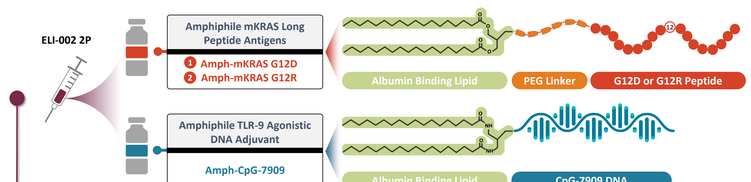
1 Technological Innovation: Amphiphile Lymph Node Targeting Platform[10-11]

- **Smart trafficking to the lymph nodes** after subcutaneous dosing generates immune responses with increased magnitude, function, and durability
- **Takes advantage of potent lymph node immune mechanisms**, including activation of innate and adaptive cells, antigen-spreading, and improved tumor T cell trafficking / infiltration
- Mutant KRAS peptides provide a **validated antigen** for application of the Amphiphile platform
- Lymph node delivery of potent adjuvants **prevents systemic exposure to improve safety**

2 Clinical Innovation: Treatment in High Relapse-Risk Adjuvant Setting

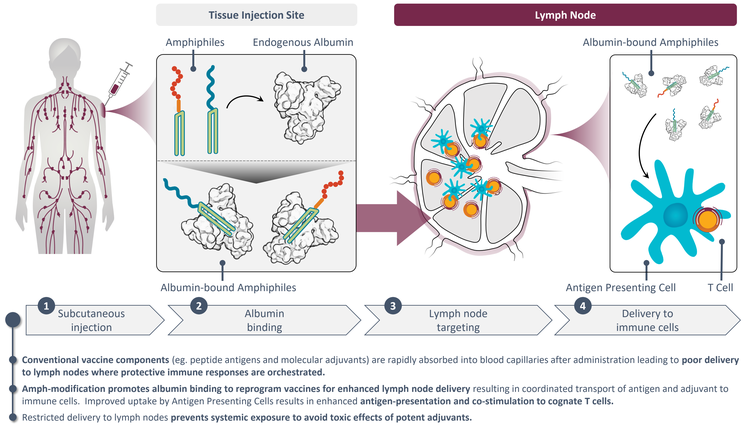
- Targeting surgically debulked tumors **enables T cells to address minimal residual disease to potentially eliminate** remaining tumor cells and protect against recurrence
- Activating the immune system **before loss of HLA expression** in the tumor microenvironment in a chemotherapy-free window of opportunity
- Other oncology vaccines have typically been used in later lines of therapy for advanced disease, **after onset of tumor immune resistance**
- In the adjuvant setting, **tumor biomarkers (ctDNA, serum tumor antigen) are early predictors of disease control or recurrence**

Designing a Therapeutic Vaccine Targeting mKRAS: ELI-002 2P



- Inclusion of **18-mer G12D and G12R mKRAS peptides** allows for delivery of **diverse HLA I and II –restricted epitopes** for presentation on varied patient HLA molecules
- **Amphiphile (Amph)-modification of peptides** promotes binding to endogenous albumin at the injection site to promote collection in lymphatic vessels for **lymph node delivery**, and prevents peptide uptake into local capillaries avoiding delivery to irrelevant or tolerogenic sites
- **Amph-CpG-7909 provides** potent immune activation via TLR-9 stimulation of lymph node-resident professional antigen presenting dendritic and other key immune cells

The Amphiphile Platform: Targeting the Lymph Nodes[10-11]



- **Conventional vaccine components** (eg. peptide antigens and molecular adjuvants) are rapidly absorbed into blood capillaries after administration leading to **poor delivery to lymph nodes where protective immune responses are orchestrated.**
- **Amph-modification promotes albumin binding to reprogram vaccines for enhanced lymph node delivery** resulting in coordinated transport of antigen and adjuvant to immune cells. Improved uptake by Antigen Presenting Cells results in enhanced **antigen-presentation and co-stimulation to cognate T cells.**
- Restricted delivery to lymph nodes **prevents systemic exposure to avoid toxic effects of potent adjuvants.**

Patients[12] Safety

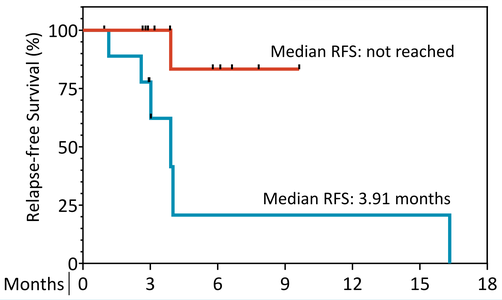
Baseline Characteristics: 20 Pancreatic (PDAC), 5 Colorectal (CRC) were evaluated for safety as of data cutoff: April 25, 2023

Safety: no related TEAEs ≥ Grade 3, no Dose Limiting Toxicities, no Cytokine Release Syndrome across all dose levels; 44% (11/25) had related Grade 1-2 TEAEs: e.g. injection site reaction, fatigue, headache, nausea

mKRAS T Cell Responses Correlate with Reduction in Risk of Relapse and Death[a]

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

≥ Median T Cell Response (n = 12) | *P* = 0.0134
< Median T Cell Response (n = 10) | HR: 0.138 (0.031-0.610)

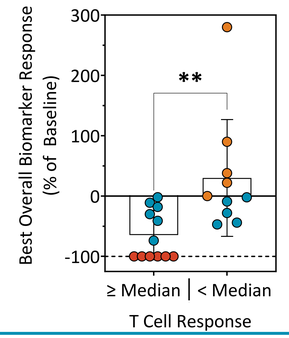


[a] 18 PDAC, 4 CRC evaluable at data cutoff April 25, 2023; RFS supervised by median T cell response fold-change over baseline (13x); median follow-up 7.6 months

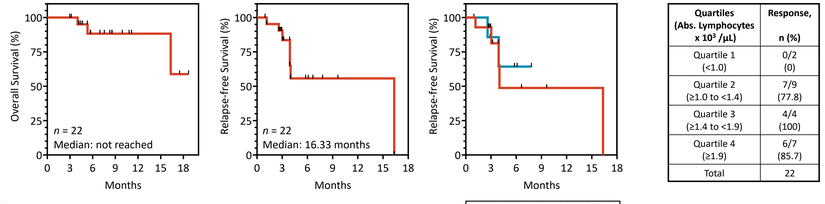
Strength of T Cell Response ➤ Tumor Biomarker Response

Best Overall Tumor Biomarker Response
- Clearance
- Reduction
- Non-Responder

P = 0.0017



Clinical Outcomes are not Correlated to Stage or Baseline Immune Status



RFS: Absolute Lymphocyte Count

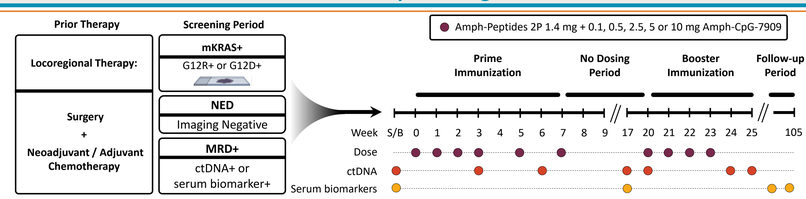
Quartiles (Abs. Lymphocytes x 10^3 /µL)	Response, n (%)
Quartile 1 (<1.0)	0/2 (0)
Quartile 2 (≥1.0 to <1.4)	7/9 (77.8)
Quartile 3 (≥1.4 to <1.9)	4/4 (100)
Quartile 4 (≥1.9)	6/7 (85.7)
Total	22

Tumor stage at diagnosis was **not correlated to Risk of Relapse and Death**

Baseline **Absolute Lymphocyte Count showed a trend to RFS,** suggesting extent of recovery from prior lymphodepleting chemotherapy may support more favorable clinical responses to ELI-002 2P

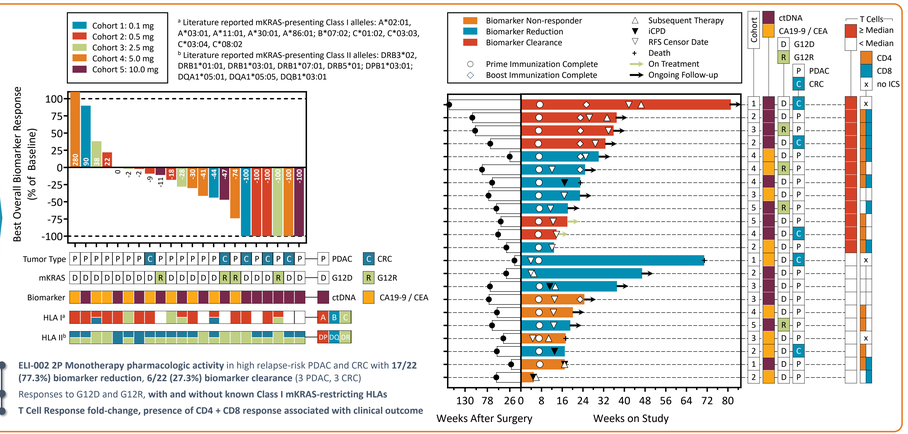
AMPLIFY 201: Prevention of Relapse in High-risk PDAC and CRC

Schema



Tumor Biomarker Response and Relapse ➤ T cell Response Strength and Quality

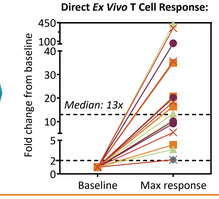
Tumor ctDNA / Serum Tumor Antigen



- **ELI-002 2P Monotherapy pharmacologic activity** in high relapse-risk PDAC and CRC with **17/22 (77.3%) biomarker reduction**, **6/22 (27.3%) biomarker clearance** (3 PDAC, 3 CRC)
- Responses to G12D and G12R, **with and without known Class I mKRAS-restricting HLAs**
- **T Cell Response fold-change, presence of CD4 + CD8 response associated with clinical outcome**

Expansion of mKRAS-specific Immune Responses by ELI-002 2P Immunization

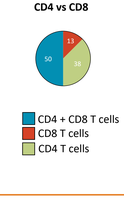
All Patients



Response per Dose Level

Amph-CpG Dose Level	*ex vivo* T cell response (n, %)	Average fold-change
0.1 mg	2/3 (67%)	30
0.5 mg	5/6 (83%)	82
2.5 mg	4/5 (80%)	113
5.0 mg	5/5 (100%)	19
10.0 mg	4/4 (100%)	26
Total	20/23 (87%)	56

CD4 vs CD8



ELI-002 2P-induced T Cell Responses

- **87% of Patients** generated expanded mKRAS-specific T cell responses following ELI-002 2P Immunization, with **100% Responders at the highest dose levels**
- **CD4 and CD8 T cell responses were observed**, with 50% generating mixed CD4 + CD8 responses
- mKRAS-specific **T cells were polyfunctional** (IFNγ, TNFα, IL-2) with **central and effector memory phenotype**

TAKE HOME MESSAGES

T Cell Response MOA Correlated to:
- ➤ **86% Reduced Risk of Relapse and Death**
- ➤ **Tumor Biomarker Response**

Lymph node-targeted Therapeutic mKRAS-specific Cancer Vaccine ELI-002 2P:
- ➤ Safe and Well-tolerated, no Dose Limiting Toxicity, no CRS
- ➤ High Proportion with Tumor Biomarker Reduction (77%) & Clearance (27%)

✓ **Phase 1, randomized Phase 2 Study of ELI-002 7P (NCT05726864) in PDAC patients: targeting G12D, R, V, C, A, S, G13D**

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- For author disclosures please refer to the abstract.

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