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PANCREATIC CANCER
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AACR American Association for Cancer Research®

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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Presented by Eileen M. O'Reilly M.D[9].

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AMPLIFY-201: Background

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Mutant KRAS Drives 25% of Solid Human Cancers (Pancreas >90%, Colon ~50%)

Mutant KRAS Neoantigens are Promising Immunotherapy Targets:

- HLA C*08:02 restricted G12D KRAS T cells -> PR in pancreatic[1] and colorectal cancers
- Adoptive therapy is limited to selected HLAs / mutations, manufacturing cost / complexity, potential CRS

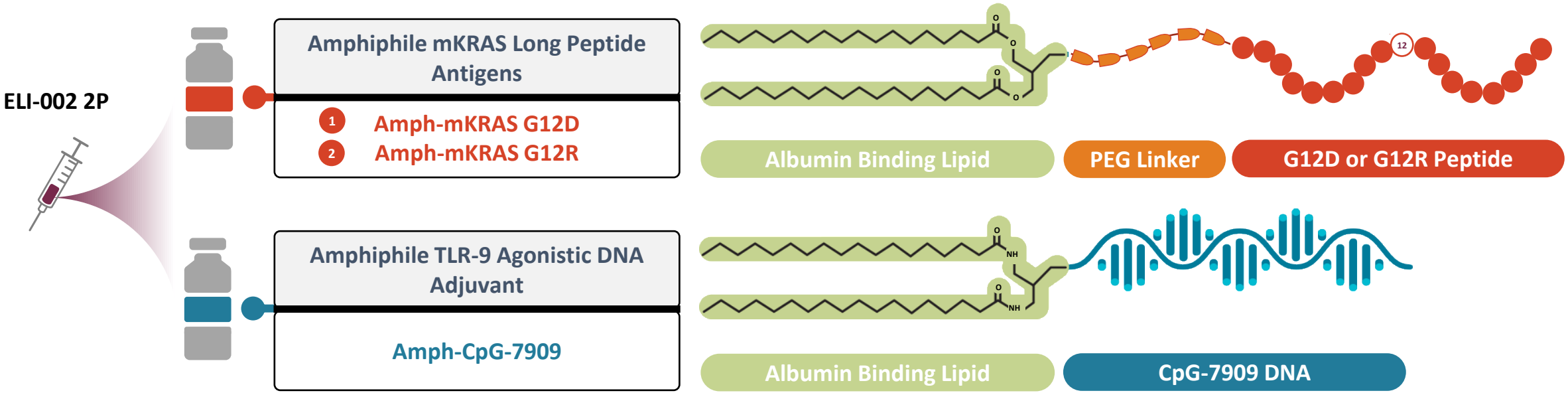
ELI-002: A 3-component, mKRAS G12D / R and TLR-9 Adjuvant, Lymph Node Targeting, Amphiphile Cancer Vaccine

Amphiphile Lymph Node Targeting:

- Increased Immunogenicity and Safety vs Soluble Vaccines
- Long-term Eradication of Murine Solid Tumors
- Enhanced T cell Expansion, Tumor Infiltration, and Functional Quality

Leidner et al., 2022 **NEJM;** Tran et al., 2016 **NEJM;** Liu et al., 2014 **Nature;** Moynihan et al., 2016 **Nature Medicine;** Ma et al., 2019 **Science**

ELI-002 2P Vaccine Components



ELI-002 2P Mechanism:

Targeting Lymph Nodes to Increase Immune Response

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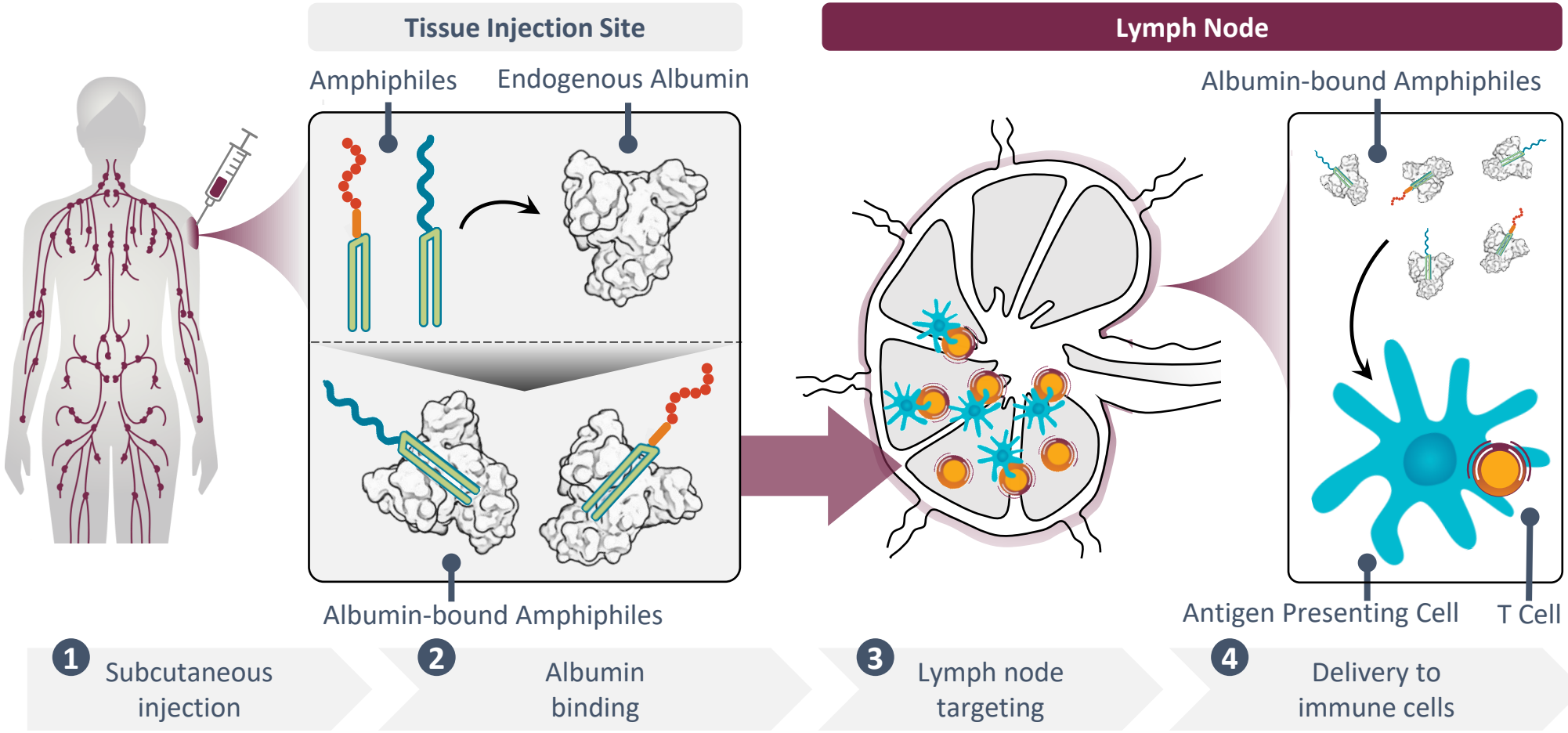
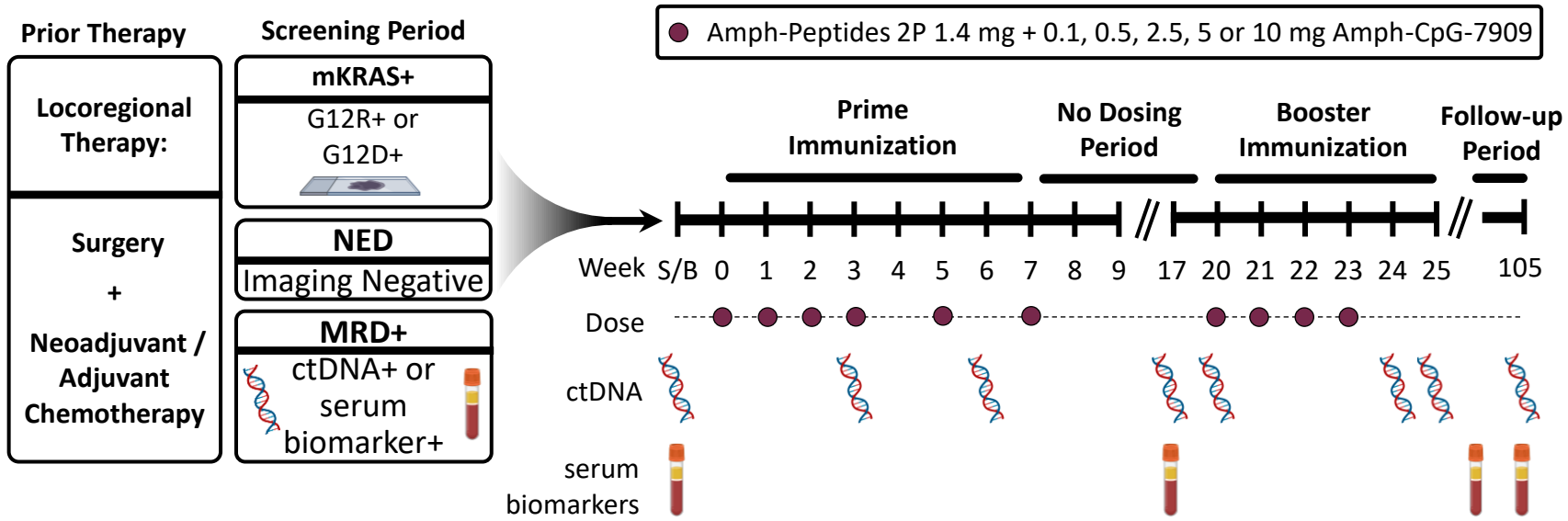


AMPLIFY-201 Study Design



Endpoint	Description
Primary	Safety, tolerability and RP2D
Secondary	Tumor Biomarker Reduction and Clearance *ctDNA and/or serum tumor antigens: CA19-9 or CEA*
Exploratory	Immunogenicity, Relapse Free Survival (iRECIST)

Cohort	Fixed Dose Amph-Peptides 2P	Ascending Dose Amph-CpG-7909
1	1.4 mg	0.1 mg
2	1.4 mg	0.5 mg
3	1.4 mg	2.5 mg
4	1.4 mg	5.0 mg
5	1.4 mg	10.0 mg

20/25 pancreatic, 5/25 colorectal enrolled at database cutoff (4/25/2023)

AMPLIFY-201 Baseline Characteristics

- High relapse risk population:
  - ctDNA+ pancreatic cancer exhibits 5-month median relapse free time post-surgery
- Two thirds of AMPLIFY-201 patients are stage III and IV
  - Oligometastatic stage IV (3 lesions in one organ) permitted if NED after resection

	Cohort 1 (0.1 mg) n=3	Cohort 2 (0.5 mg) n=6	Cohort 3 (2.5 mg) n=5	Cohort 4 (5.0 mg) n=5	Cohort 5 (10.0 mg) n=6	Overall n=25
Age (years)						
Median	50.0	54.5	67.0	67.0	59.0	61.0
Range	47–61	37–69	63–77	47–75	48–69	37–77
Female Sex, n (%)	2 (66.7)	5 (83.3)	4 (80.0)	3 (60.0)	1 (16.7)	15 (60.0)
Race, n (%)						
Asian	0	1 (16.7)	0	0	1 (16.7)	2 (8.0)
White	2 (66.7)	5 (83.3)	4 (80.0)	5 (100)	5 (83.3)	21 (84.0)
Not reported	1 (33.3)	0	2 (20.0)	0	0	2 (8.0)
ECOG PS, n (%)						
0	3 (100)	4 (66.7)	4 (80.0)	2 (40.0)	5 (83.3)	18 (72.0)
1	0	2 (33.3)	1 (20.0)	3 (60.0)	1 (16.7)	7 (28.3)
Initial Diagnosis, n (%)						
PDAC	1 (33.3)	4 (66.7)	5 (100)	4 (80.0)	6 (100)	20 (80.0)
CRC	2 (66.7)	2 (33.3)	0	1 (20.0)	0	5 (20.0)
Disease Stage at Screening						
Stage I, II	1 (33.3)	2 (33.3)	3 (60.0)	1 (20.0)	1 (16.7)	8 (32.0)
Stage III, IV*	2 (66.7)	4 (66.7)	2 (40.0)	4 (80.0)	5 (83.3)	17 (68.0)
Prior Anti-cancer Treatment:						
Systemic therapy	3 (100)	6 (100)	5 (100)	5 (100)	6 (100)	25 (100)
Surgery/Procedure	3 (100)	6 (100)	5 (100)	5 (100)	6 (100)	25 (100)
Radiation therapy	2 (66.7)	1 (16.7)	1 (20.0)	2 (40.0)	1 (16.7)	7 (28.0)

BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; PS: performance status; *Stage IV with NED on imaging after surgery for ≤ 3 oligometastatic sites was permitted

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AMPLIFY-201 Safety

- No Grade ≥3 related adverse events (AEs), no cytokine release syndrome, no DLTs
- 11/25 (44%) experienced Grade 1 or Grade 2 AEs
- 3/25 (12%) experienced injection site reactions
- No increase in adverse events was seen as Amph-CpG-7909 was dose escalated

	Cohort 1 (0.1 mg) n=3	Cohort 2 (0.5 mg) n=6	Cohort 3 (2.5 mg) n=5	Cohort 4 (5.0 mg) n=5	Cohort 5 (10.0 mg) n=6	Overall n=25
Adverse Event Term [a]						
Patients with Any Related TEAE, n (%)	1 (33.3)	3 (50.0)	2 (40.0)	3 (60.0)	2 (33.3)	11 (44.0)
Injection site reaction	0	1 (16.7)	1 (20.0)	1 (20.0)	0	3 (12.0)
Fatigue	0	1 (16.7)	2 (40.0)	0	1 (16.7)	4 (16.0)
Headache	1 (33.3)	1 (16.7)	0	0	1 (16.7)	4 (16.0)
Asthma	0	0	0	0	1 (16.7)	1 (4.0)
Dyspnoea	0	0	0	0	1 (16.7)	1 (4.0)
Nausea	1 (33.3)	0	0	1 (20.0)	0	2 (8.0)
Diarrhoea	0	0	0	0	1 (16.7)	1 (4.0)
Anemia	1 (33.3)	0	0	0	0	1 (4.0)
Contusion	1 (33.3)	0	0	0	0	1 (4.0)
Dry skin	0	1 (16.7)	0	0	0	1 (4.0)
Herpes simplex reactivation	0	1 (16.7)	0	0	0	1 (4.0)
Hot flush	0	1 (16.7)	0	0	1 (16.7)	2 (8.0)
Myalgia	0	0	0	1 (20.0)	0	1 (4.0)
Nasal congestion	0	1 (16.7)	0	1 (20.0)	0	2 (8.0)
Lymphadenopathy	0	0	0	0	1 (16.7)	1 (4.0)
Pruritus	0	0	0	1 (20.0)	0	1 (4.0)
Patient Summary						
KRAS Mutation	DDD	DDDDDD	DRDDD	DDRDD	RRDDRD	
Dose Limiting Toxicity	0	0	0	0	0	0
Biomarker Reduction / Clearance	2 (67)	5 (83)	3 (60)	4 (80)	3 (100) [b]	17 (77) [c]
T cell Response	2 (67)	5 (83)	4 (80)	5 (100)	4 (100)	20 (87) [d]

TEAE: Treatment Emergent Adverse Event
[a] Preferred terms per the Medical Dictionary for Regulatory Activities, version 25.0
[b] Measured among 19 evaluable patients
[c] Measured among 23 evaluable patients

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AMPLIFY-201 Waterfall Plot: Biomarker Reduction/Clearance

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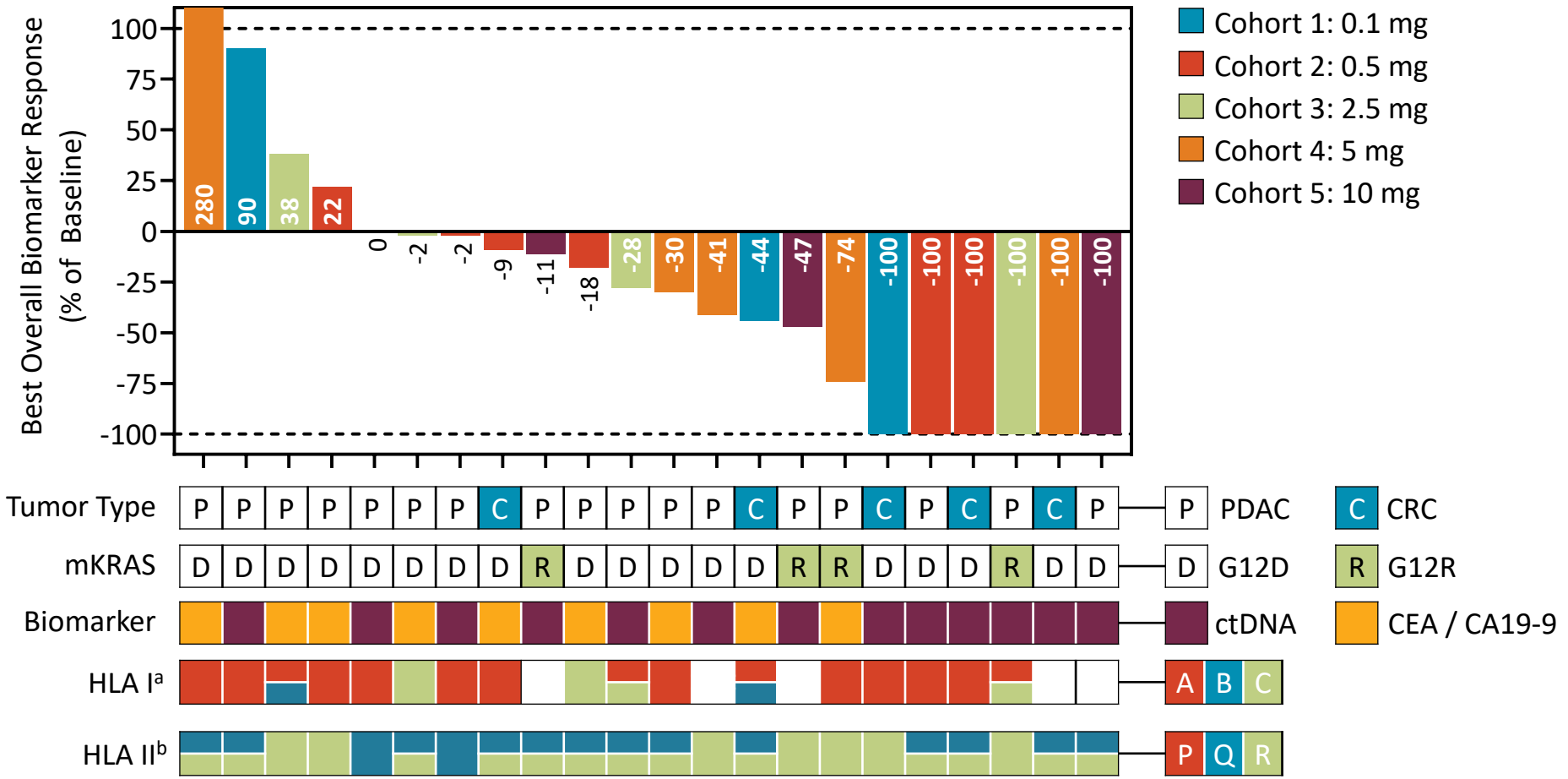

[a] Literature reported mKRAS-presenting Class I alleles: A*02:01, A*03:01, A*11:01, A*30:01, A*86:01; B*07:02; C*01:02 C*03:03 C*03:04 C*08:02

[b] Literature reported mKRAS-presenting Class II alleles: DRB3*02, DRB1*01:01, DRB1*03:01, DRB1*07:01, DRB5*01; DPB1*03:01; DQA1*05:01 DQA1*05:05 DQB1*03:01

AMPLIFY-201: mKRAS-specific T cell Induction

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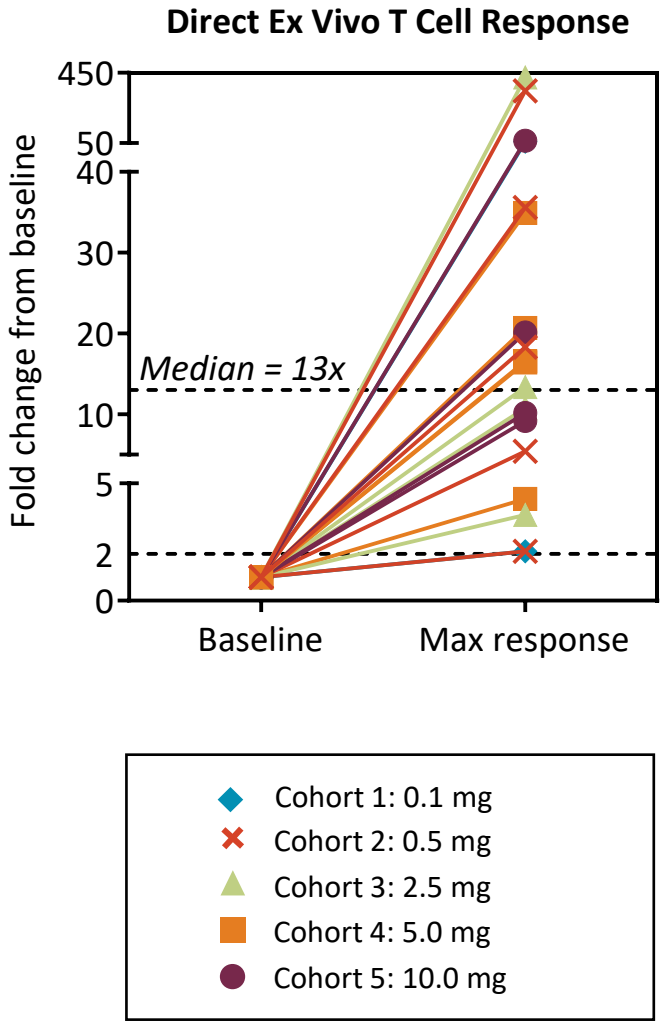
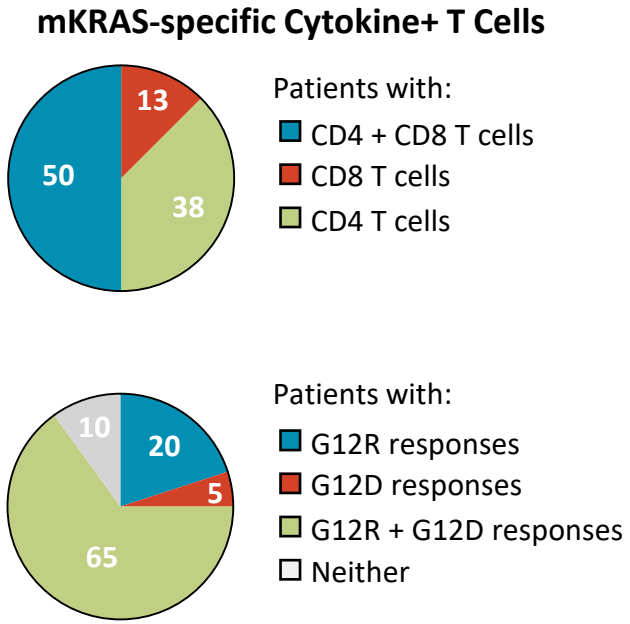
87% Direct Ex Vivo T Cell Response, Including CD4 and CD8, Polyfunctionality, Memory Phenotype

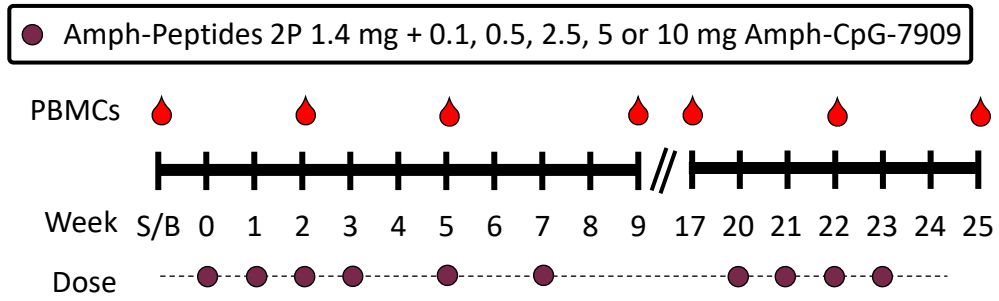


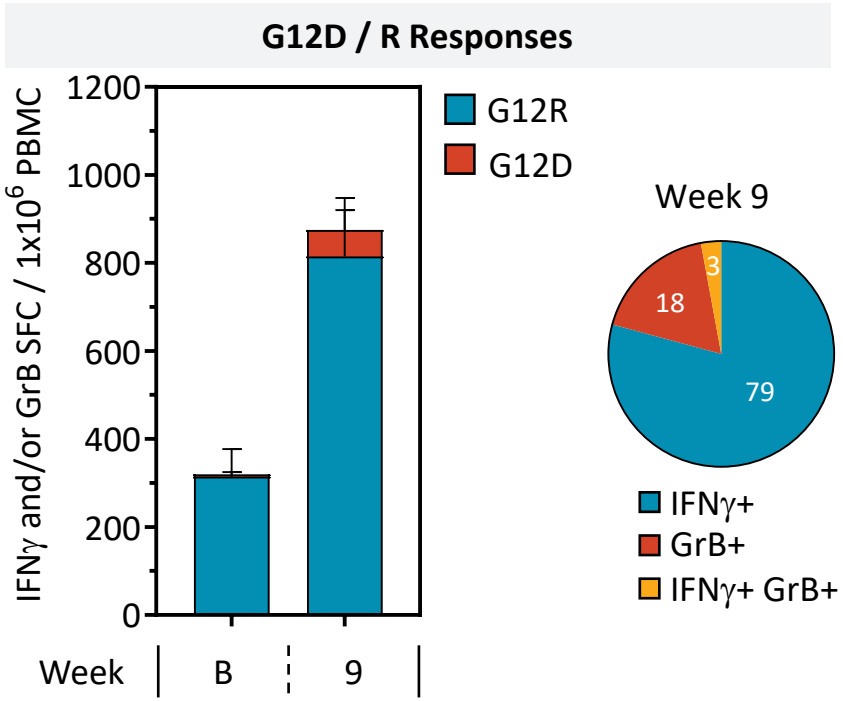
ELI-002-induced mKRAS T Cell Responses

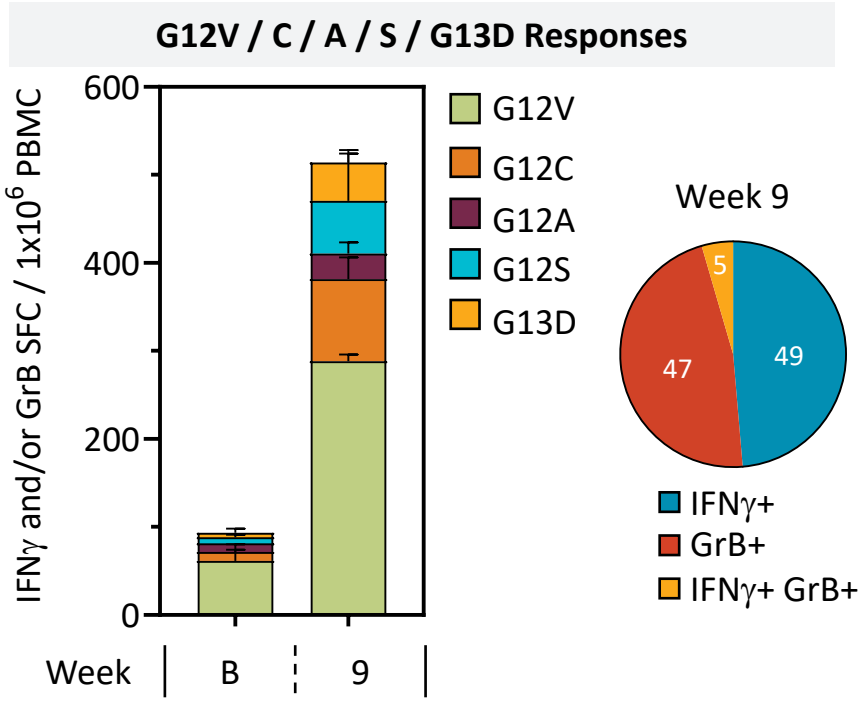
- **87% of patients had T cell responses**
- 100% in two highest dose cohorts, including at the RP2D (10 mg)
- 56x average fold-change in T cell numbers from baseline (**median 13x**; range 2-423x)
- T cells detectable by standard direct ex vivo FluoroSpot and flow cytometry, with no expansion required
- 50% of patients made both CD4+ and CD8+ T cells
- Both CD4+ and CD8+ had long-lasting central and effector memory T cell phenotype



Direct ex-vivo Assessment Indicates Robust Polyclonal T Cell Responses, Patient 11







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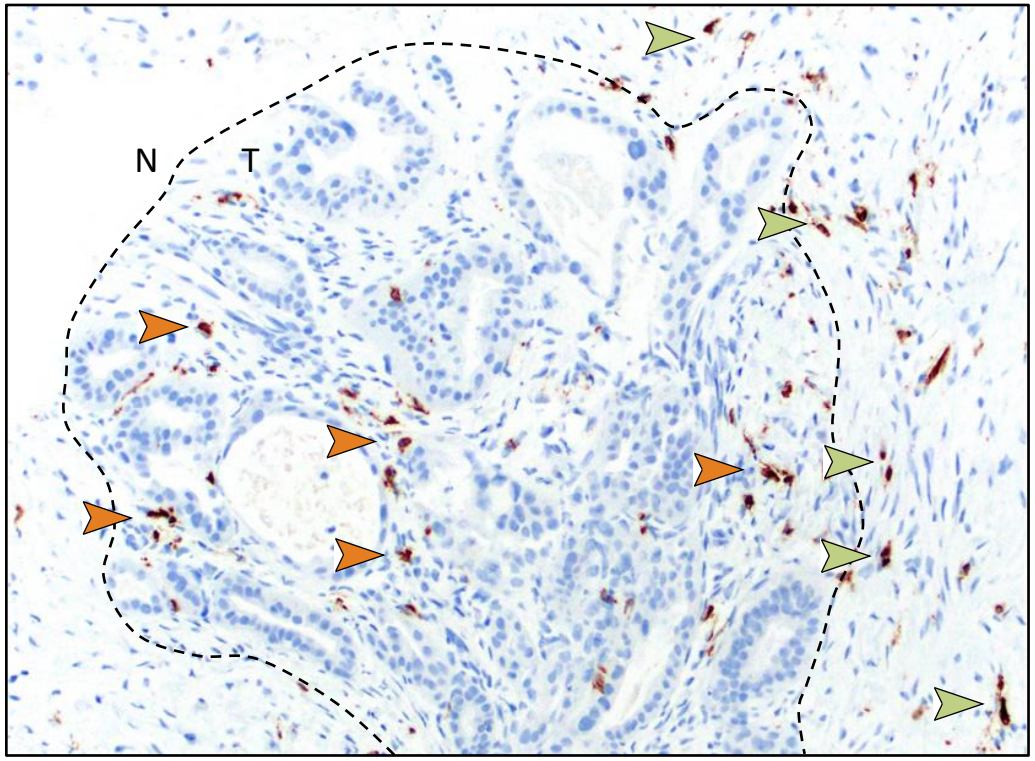
CD3+ T cell infiltration of pancreatic tumor, 0.1 mg dose level



N	Normal Tissue
T	Tumor
➤	Tumor Infiltrating CD3+
➤	Tumor Peripheral CD3+

002-001-102-003 (PDAC, Stage IVC)

- Preliminary clinical evidence that ELI-002 induced T cells penetrate tumors
- ctDNA doubling time progressively lengthening after initial flare:

Collection date	Timepoint	ctDNA Results	Tumor Growth Rate vs Baseline	Interval Doubling Time (days)
11-Oct-21	SCR	0.40	-	-
9-Nov-21	V3 (pre-dose)	0.63	Baseline	45 days
2-Dec-21	V6	1.20	187% (flare)	24 days
11-Jan-22	V9	2.37	93%	42 days
08-Mar-22	V11	4.18	73%	62 days

- Visit 6 (3 weeks on ELI-002) – CT liver with metastases bright on IV contrast
  - Radiologist reported these were enlargement of lesions present at screening, dark on IV contrast
- Therefore, liver biopsy obtained at Visit 8 (~7 weeks on ELI-002)
  - Pathologist reported "hot tumor" with **24** T cells/hpf
    - 10X increased vs expected **2-3**/hpf in PDAC literature[1]
  - T cells (brown stain) were PD1 negative - would resist PDL1
- Visit 10 (8 weeks on ELI-002) imaging showed no change
- Visit 11 (17 weeks on ELI-002) imaging showed iPD – eventual growth of liver mets

- Off study patient received subsequent investigational CTLA4-PD1 mAb, resulting in PR → XRT
- NED 12 months after initiating ELI-002 (expected survival of this group is a median 17 months)

[1]Ademmer 1988 Clin Exp Immunol 112:21

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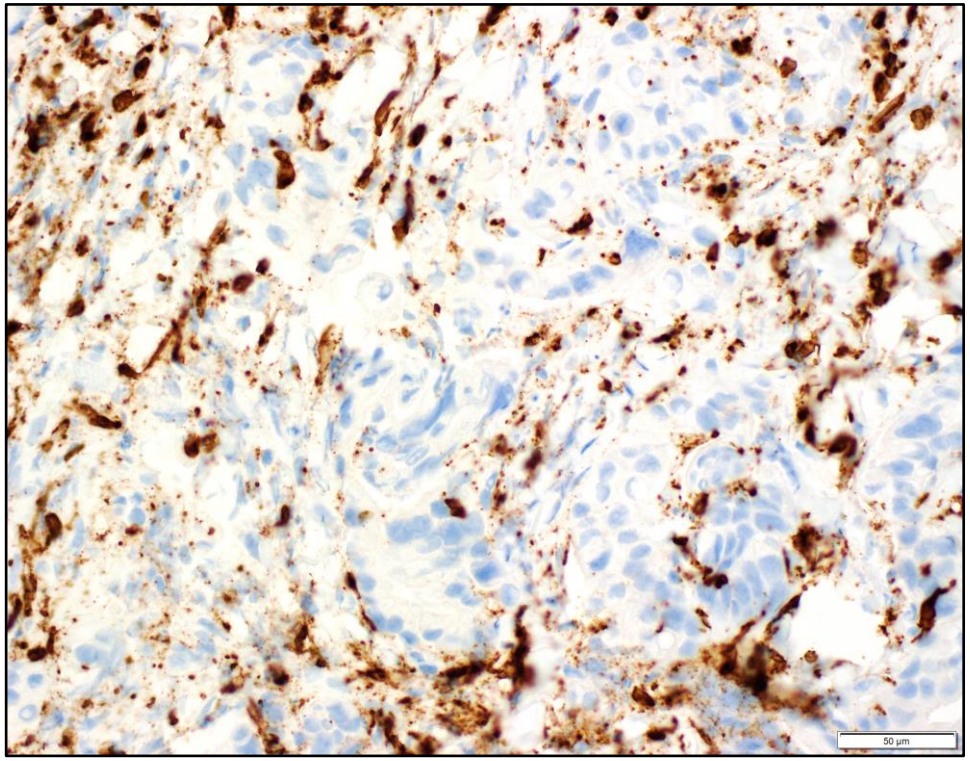
CD3+ T cell Infiltration and MRD Clearance, Pancreatic Tumor, 2.5 mg Dose Level



ctDNA clearance observed with 72 T cells/hpf observed at time of progression, patient received intermediate 2.5 mg dose level:

Collection date	Timepoint	ctDNA Results	Tumor Growth Rate vs Baseline	Interval Doubling Time (days)
13-Jul-22	SCR	13.26		
16-Aug-22	V4	0	34 days after screening	-100%
13-Sep-22	V7	0	28 days after V4 (35 days after 1st dose)	-100%
07-Dec-22	V11	0	85 days after V7	-100%
27-Dec-22	V12	0	105 days after V7	-100%
31-Jan-23	V16	0	140 days after V7	-100%
28-Feb-23	V17	8.66	168 days after V7	

- ctDNA increased prior to radiographic relapse
- T cell infiltration 72/hpf is 29-fold higher than median 2-3/hpf in pancreatic cancer literature[1]
- PDL1 expression 10% suggests a possible mechanism of resistance for ELI-002

[1]Ademmer 1988 Clin Exp Immunol 112:21

T Cell Fold Change Predicts Tumor Biomarker Response

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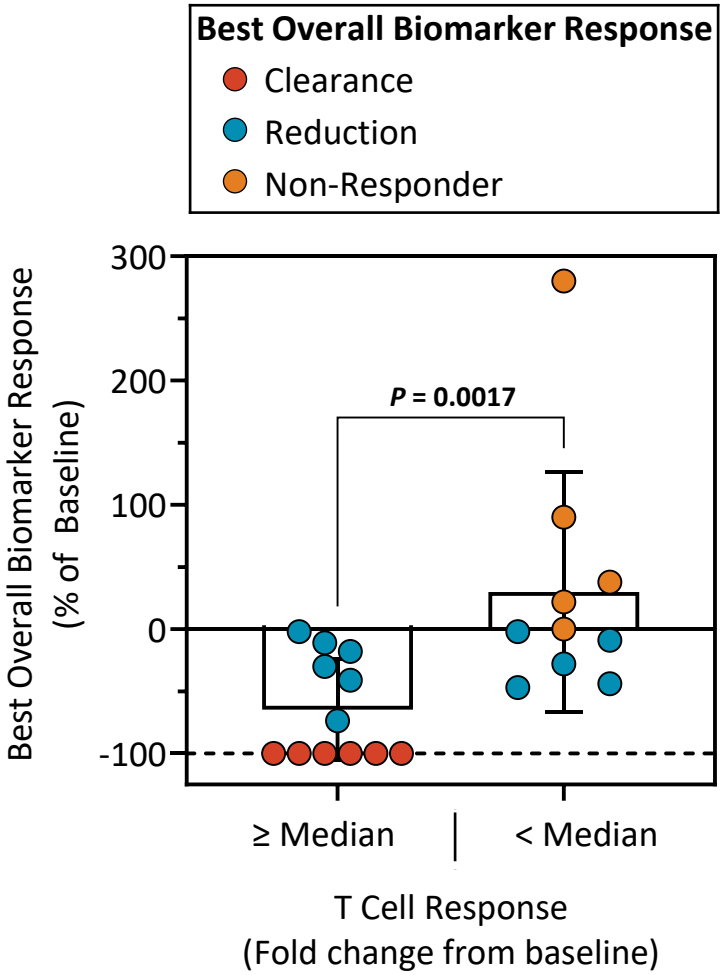
All Patients with T cell Responses Over Median (13x) Showed Tumor Biomarker Response

Strength of T cell response to ELI-002 is Strongly Correlated to Tumor Biomarker Response

- 100% of the above median T cell group responded to ELI-002; in the below median group 50% responded to ELI-002
- All (100%) of the observed tumor biomarker clearances (6/6) are in the above median T cell group
- Statistically significant, p-value per Mann Whitney Test (*P* = 0.0017)



Median Relapse-Free Survival of Above Median T Cell Responders was Significantly Prolonged

86% Reduction in the Risk of Progression or Death in Above Median T cell Responders

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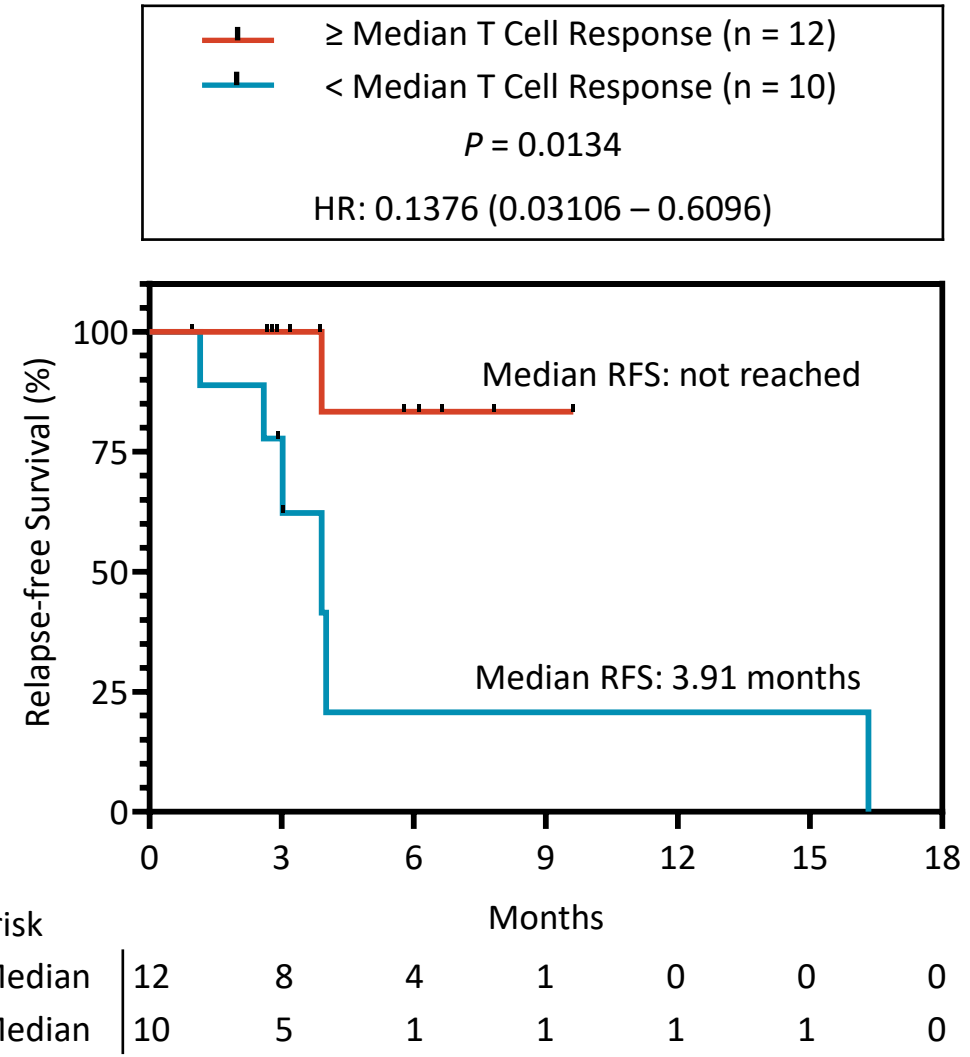
Strength of T Cell Response to ELI-002 is Strongly Correlated to Reduced Risk of Relapse or Death

- At a median follow up 7.6 months, median RFS was not reached for above median T cell responders compared to 3.91 months among below median T cell responders (**HR 0.1376**, 95% CI 0.03106-0.6096, *P* = 0.0134)
- **86% reduction in risk of progression or death in above-median T cell responders to ELI-002**
- Median overall survival was not reached for either group



Swimmer's Plot and ELI-002 2P-Induced Dual Positive CD4/8 T Cells

Above Median T Cell Response, Dual CD4 + CD8 Associated with Clinical Outcome

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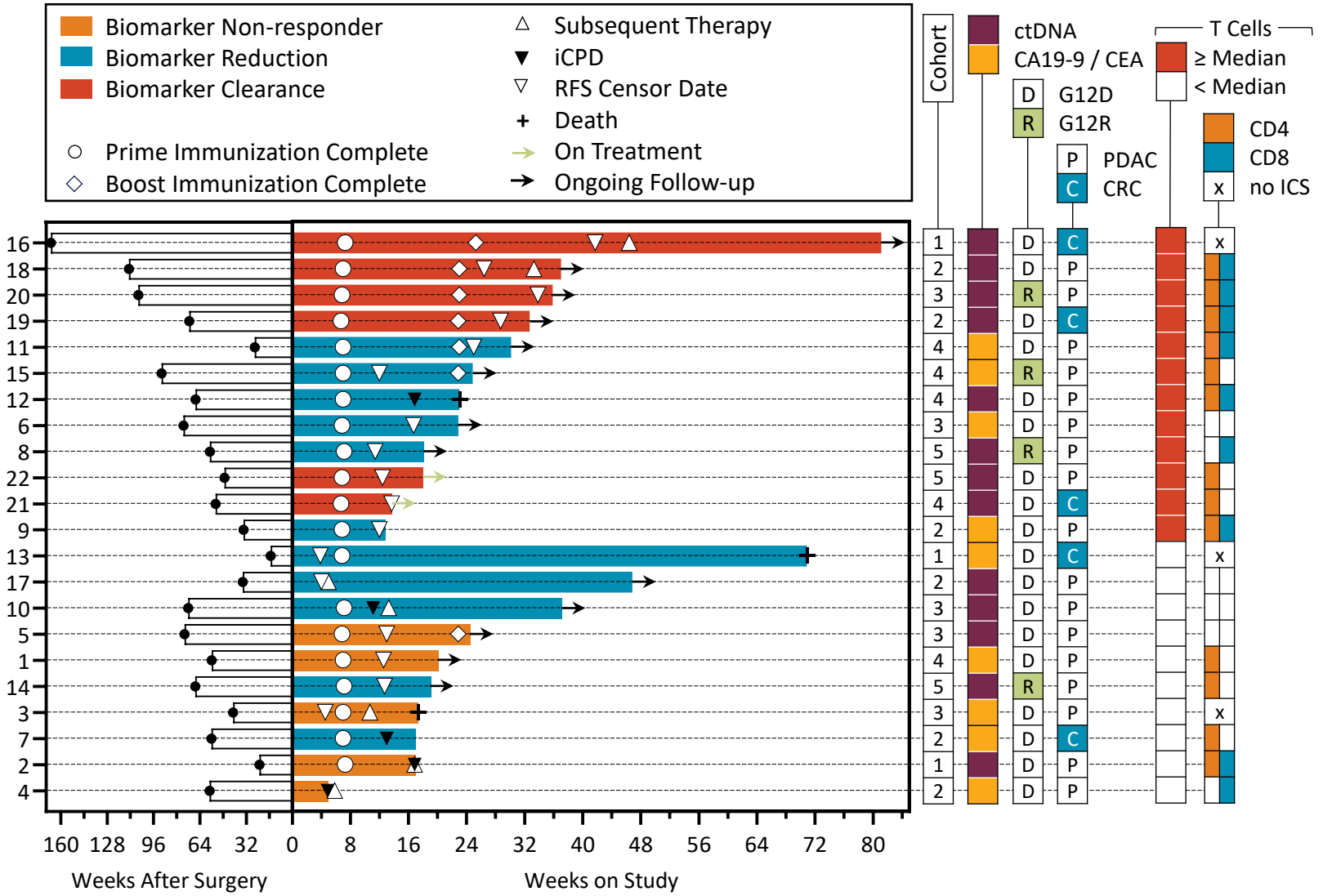
T Cell Response is Correlated to Tumor Response and Duration of ELI-002 Administration

- Strength of T cell response to ELI-002 is correlated to tumor response and completion of ELI-002 prime and boost dosing periods
- Patients with both CD4 and CD8 T cell responses have favorable clinical outcomes



No Effect of Tumor Stage on Median Relapse-Free Survival Analysis

Lymphocyte Recovery after Chemotherapy/Radiation to Normal Levels Required for ELI-002 response

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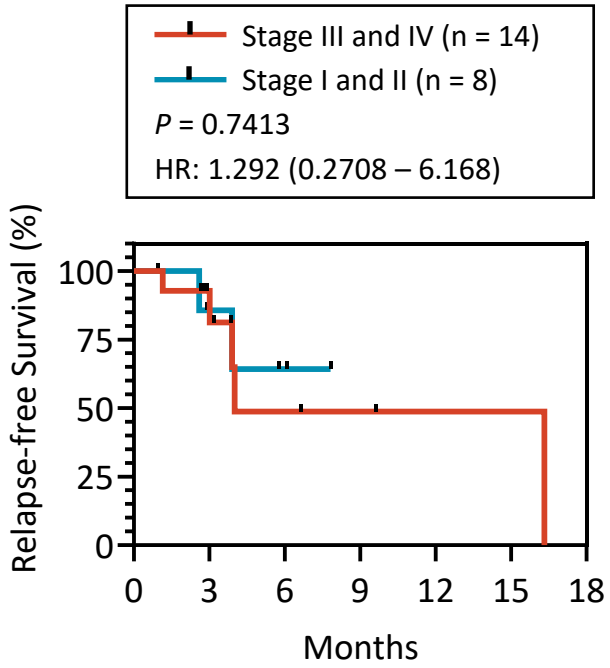
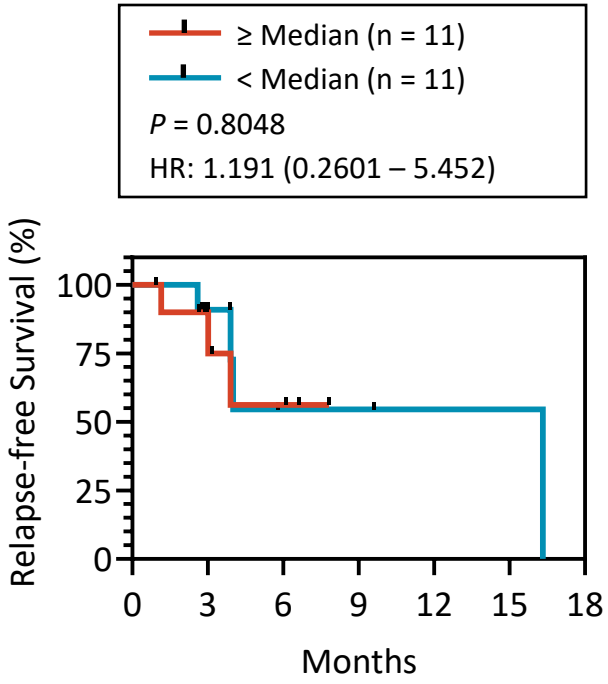
Tumor Stage



Absolute Neutrophil at Screening



Absolute Lymphocytes at Screening

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

Baseline Prognostic Factors Such as Tumor Stage, and Baseline Neutrophil Count did not Affect RFS

- Baseline lymphocyte count recovery following prior cytotoxic chemotherapy and/or radiation exhibited non-significant (*P*=0.1739) trend
  - Future protocols mandate lymphocyte recovery prior to ELI-002 initiation

Take Home Messages

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Monotherapy with Lymph node-Targeted Therapeutic mKRAS-specific Cancer Vaccine ELI-002:

Well-tolerated with No Dose-Limiting Toxicity

- No Grade 3/4 TEAEs, no CRS, no DLTs; 11/25 (44%) had Grade 1 or 2 AEs

Robust mKRAS-Specific T cell Responses

- Large Direct Ex Vivo T cell responses average 56-fold, median 13-fold [range 2-423-fold]
- Balanced CD4+ and CD8+ T cell response, development of memory T cells
- Tumor infiltration over 70 T cells per high powered field observed in pancreatic tumors

Robust mKRAS-Specific T cell Responses

- T cell responses predicted tumor biomarker reductions (77%) and clearance (27%)
- T cell responses correlated with 86% reduction in risk of relapse or death (HR 0.1376 95% CI 0.03106-0.6096, *P* = 0.0134)
- Baseline prognostic factors such as tumor stage did not predict response or relapse free survival

Next Steps

- ELI-002 7P trial **NCT05726864** activated for KRAS G12D, G12V, G12R, G12C, G12A, G12S, G13D in PDAC
- Patients with or without baseline biomarker elevation
- Lymphocyte recovery after prior cytotoxic therapy now required and may increase responses