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Abstract TPS2689

ELEPHAS-01, ELEPHAS-02 and ELEPHAS-04: Multi-institutional observational prospective clinical trials to assess the accuracy of an ex vivo live tumor fragment platform for predicting immunotherapy response

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Introduction

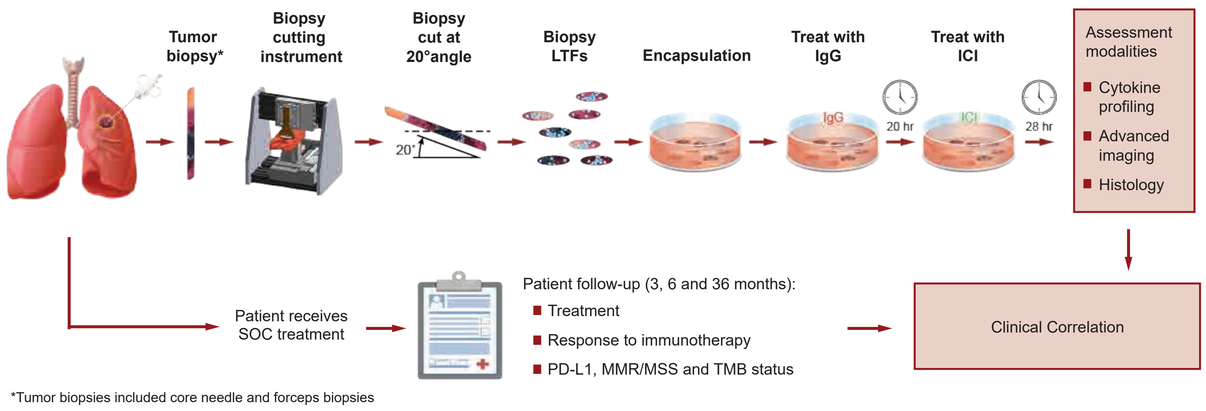
- FDA-approved companion diagnostic biomarkers for immune checkpoint inhibitors (ICIs) (PD-L1, MMR/MSI, and TMB) have low accuracy in predicting response (Chen, et al. Front. Oncol. 2021; Wang, et al. Front. Oncol. 2019)
- Ex vivo cytokine profiling of live tumor samples has shown promise to increase the accuracy of predicting response to PD-1 blockade (Voabil, et al. Nat Med. 2021), but this approach has been limited to tumor resections given the need for large amounts of tissue
- Here, we present the study design and background for three clinical trials that leverage a novel approach using the tissue obtained from as little as one core needle biopsy (CNB) of 20 gauge or larger
- A sequential ex vivo treatment strategy is used, eliminating the need for a separate control arm and addressing challenges with tumor heterogeneity, particularly in CNBs where tissue is limiting
- Using an automated proprietary instrument, biopsies are cut into live tumor fragments (LTFs) which are viable in culture and retain the native tumor microenvironment, enabling cytokine profiling in response to ICI treatment ex vivo
- This platform provides a scalable approach with the potential to change clinical practice for cancer patients being considered for treatment with immunotherapy
- These trials compare radiological response (RECIST v1.1 and iRECIST) or pathological response to ICI with the readout of our platform using cytokines and advanced imaging

Objectives

- **Primary objective:** Determine the sensitivity and specificity of the LTF Platform for predicting in vivo clinical response based on pathological response, RECIST v1.1 or iRECIST for neoadjuvant and locally advanced/metastatic patients, respectively
- **Secondary objective:** Compare the LTF Platform with established FDA-approved biomarkers using area under the receiver operating characteristics curve (AUROC)
- **Exploratory objectives:** Evaluate difference between LTF Platform predicted responders and non-responders for objective response rate, disease control rate, duration of treatment, duration of response, time to relapse, event free survival, progression free survival and overall survival

Study Design

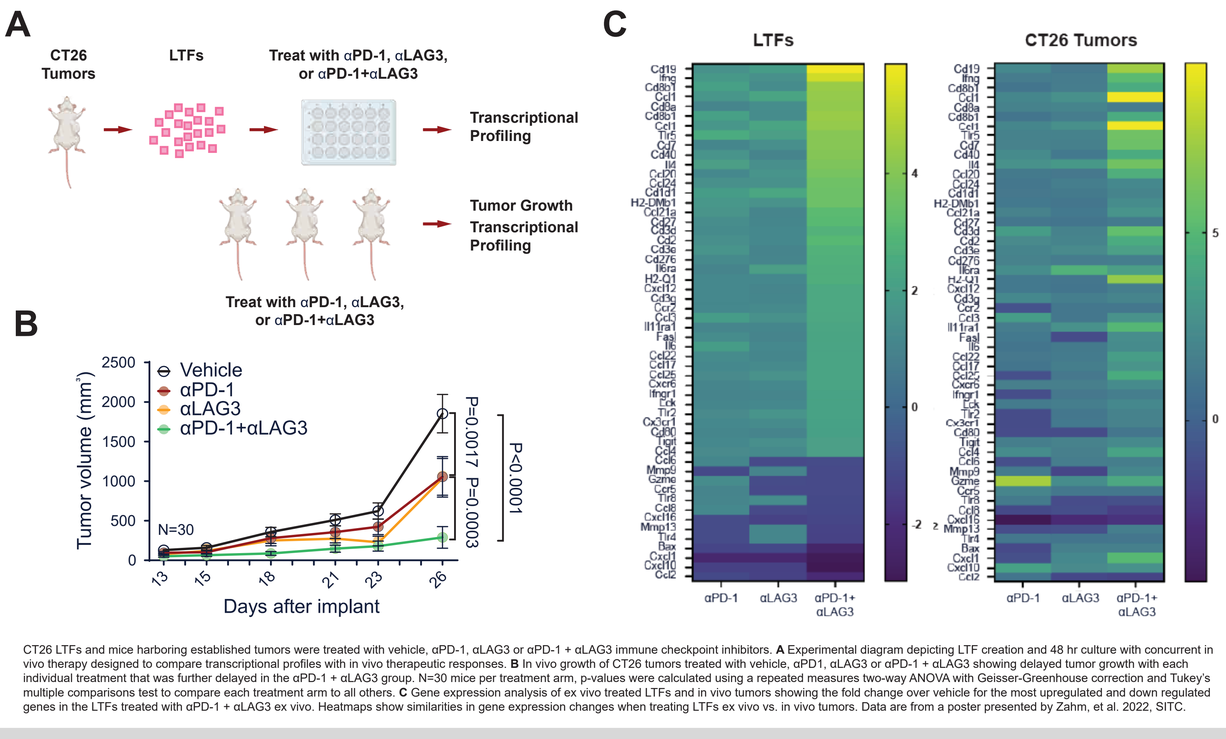
Live Tumor Fragment (LTF) Platform



*Tumor biopsies included core needle and forceps biopsies

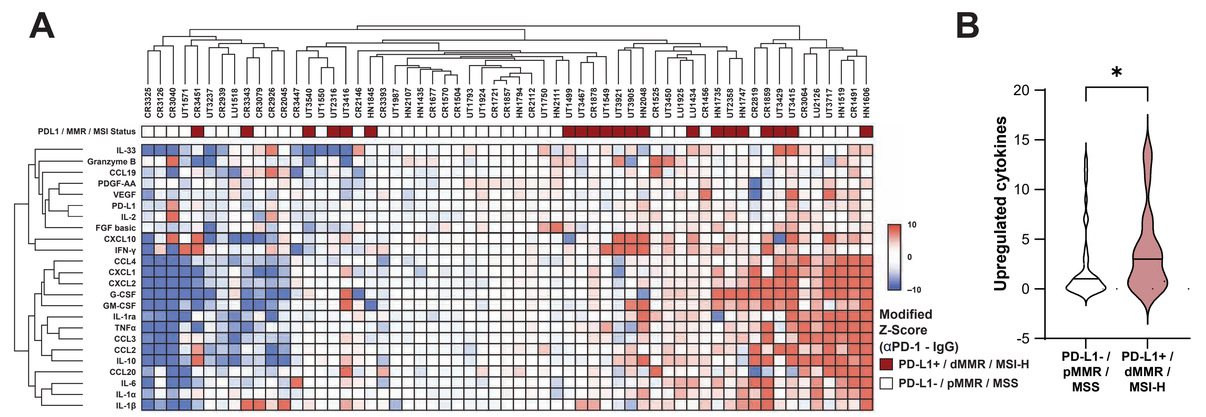
Fresh, live CNBs are collected prior to treatment start and processed within 24 hrs enabling prediction of results within 72 hrs of receipt. CNBs are cut into biopsy LTFs using a proprietary cutting instrument. LTFs are encapsulated in a proprietary hydrogel and treated using a strategy where control (IgG) and SOC ICI treatments are performed sequentially on the same tissue in a single well. Changes in the cytokine production rates are then compared between ICI and control to characterize immunotherapy response. Additionally, tissue viability and tumor content measurements are used to assess tissue quality. Clinical response is measured using pathologic response in patients receiving neoadjuvant ICI therapy, while RECIST v1.1 is used in all other patients. Ex vivo cytokine response to ICI treatment is then correlated with clinical response to ICI therapy.

In vivo vs. Ex vivo Alignment in ICI Response



CT26 LTFs and mice harboring established tumors were treated with vehicle, αPD-1, αLAG3 or αPD-1 + αLAG3 immune checkpoint inhibitors. **A** Experimental diagram depicting LTF creation and 48 hr culture with concurrent in vivo therapy designed to compare transcriptional profiles with in vivo therapeutic responses. **B** In vivo growth of CT26 tumors treated with vehicle, αPD1, αLAG3 or αPD-1 + αLAG3 showing delayed tumor growth with each individual treatment that was further delayed in the αPD-1 + αLAG3 group. N=30 mice per treatment arm, p-values were calculated using a repeated measures two-way ANOVA with Geisser-Greenhouse correction and Tukey's multiple comparisons test to compare each treatment arm to all others. **C** Gene expression analysis of ex vivo treated LTFs and in vivo tumors showing the fold change over vehicle for the most upregulated and down regulated genes in the LTFs treated with αPD-1 + αLAG3 ex vivo. Heatmaps show similarities in gene expression changes when treating LTFs ex vivo vs. in vivo tumors. Data are from a poster presented by Zahm, et al. 2022, SITC.

Cytokine Response Enriched in PD-L1+/dMMR/MSI Tumors



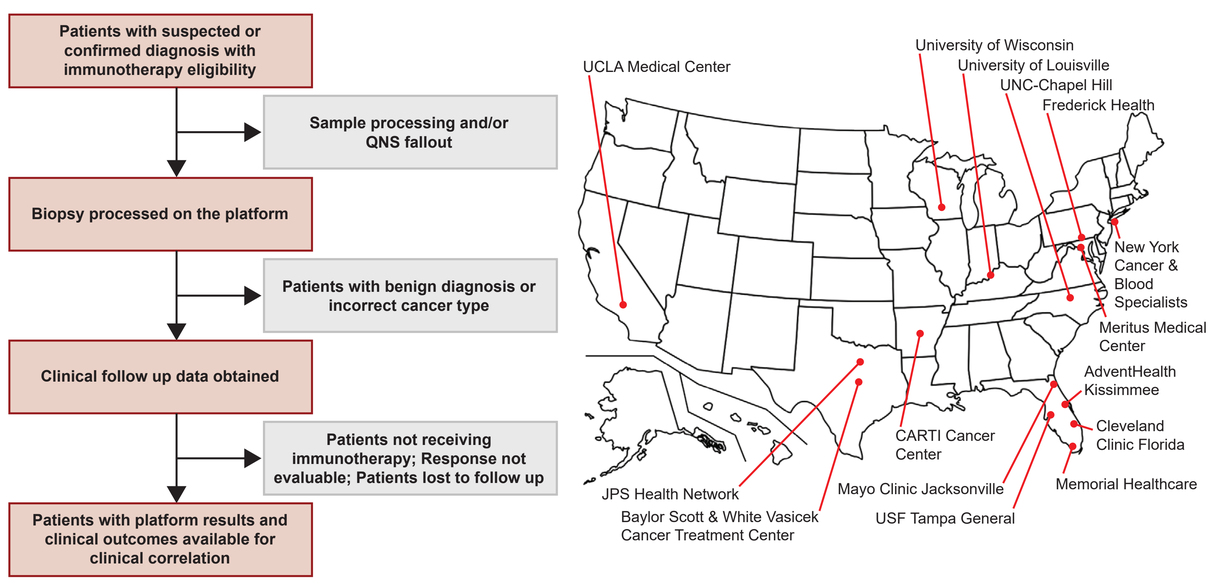
A Unsupervised hierarchical clustering of cytokine profiles from patient tumor resections using modified z-scores of the difference in cytokine concentrations between the αPD-1- and IgG-treated groups. To account for variability across wells, replicate wells for each treatment group were run when sufficient tissue was available (n=3 for 48 specimens, n=2 for 6 specimens and n=1 for 5 specimens). Positive modified z scores (capped at 10) are depicted in shades of red and negative modified Z-scores (capped at -10) are depicted in shades of blue. Samples with Z-scores of 0 are depicted in white. PD-L1+, dMMR, and MSI-H specimens are annotated with dark red boxes in the upper track. PD-L1-, pMMR, and MSS specimens are annotated in white. N=59 specimens. **B** The number of upregulated cytokines for individual specimens, defined by a modified Z-score ≥5, is significantly higher in the PD-L1+ / dMMR / MSI-H cohort compared to the PD-L1- / pMMR / MSS cohort. * p<0.05. Data are from a poster presented by Adstamongkonkul, et al. 2024, SITC.

Background on Three Observational Trials

Trial ID (clinicaltrials.gov)	NCT05478538	NCT05520099	NCT06349642
	ELEPHAS-01	ELEPHAS-02	ELEPHAS-04
Setting	Metastatic and recurrent	Metastatic and recurrent	Metastatic, recurrent and neoadjuvant
Tumor type	Lung	Bladder, kidney, colorectal, head and neck, lung, melanoma, endometrial	Metastatic/recurrent: lung, skin, esophageal, cervical, endometrial, colon, liver, kidney, bladder Neoadjuvant: lung, breast-TNBC
Enrollment (as of 5/9/2025)	34	72	20
Estimated total enrollment*	216	216	324
Clinical endpoints	RECIST v1.1 and iRECIST	RECIST v1.1 and iRECIST	RECIST v1.1, iRECIST and pathologic response at surgery

*Power calculations indicate a confidence interval of ≤0.3 per study for the AUROC evaluation.

Patient Enrollment Flowchart and Clinical Sites



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- Data supporting figure titled "Cytokine Response Enriched in Biomarker + Samples":
  - Most tissue samples were provided by the Cooperative Human Tissue Network which is funded by the National Cancer Institute.
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- Some figures were created in BioRender.com.

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