Background
ICS (inducible co-stimulator of T cells) is a co-stimulatory molecule expressed primarily on T lymphocytes. Clinical data identified ICS as a potentially key molecule in providing optimal anti-tumor benefit following anti-CTLA-4 therapy, with preclinical data confirming that engagement of the ICS pathway plays a significant role in mediating anti-CTLA-4 driven anti-tumor responses. JTX-2011 is an ICS agonist antibody that will be entering early phase clinical development for the treatment of advanced solid tumors in the ICONIC trial. JTX-2011 is designed to generate an anti-tumor immune response through stimulation of T effector cells and preferential reduction of intratumoral T regulatory (Treg) cells. Efficacy of an ICS agonist in mouse syngeneic tumor models is greatest in tumors with the highest levels of intra-tumoral ICS, suggesting a potential predictive biomarker approach for clinical development. In this study we report assessment of indications for enrollment in the clinic trial using in silico and IHC analyses across multiple tumor types.

Methods
Integrated analyses of RNA, DNA, and clinical data from the Cancer Genome Atlas (TCGA) were performed within multiple indications to understand the context in which ICS is expressed. Using a proprietary ICS IHC assay, ICS expression analysis was performed on a subset of indications based on ranking from in silico analysis. ICS expression was also compared to histology and molecularly defined indication subtypes as well as signatures of immune cell infiltrates to understand context of ICS positivity.

Results
We analyzed ICS mRNA expression in ~10,000 solid tumors samples across ~30 indications. These data were used to rank indications, and ICS expression in key indications was orthogonally confirmed using IHC. Consistent with previous data showing ICS protein expression on Treg cells, ICS RNA expression significantly correlated with Treg marker expression across multiple indications in TCGA tumor samples. Based on frequency of high ICS expression, we determined non-small cell lung cancer, head and neck squamous cell carcinoma, triple negative breast cancer, gastric adenocarcinoma, and melanoma to be potential indications for JTX-2011 therapy. We further compared ICS expression to PD-L1 expression to understand if there is a distinct population within an indication that is not a candidate for PD-1/PD-L1 therapy but could benefit from JTX-2011 therapy. A subset of patients in multiple indications exhibit high ICS levels but low PD-L1 expression.

Conclusions
In conclusion, these data support the prioritization of specific tumor types for treatment with JTX-2011 in the ICONIC trial.

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Increased antibody and T cell responses to neoepeitope site peptides following combination immunotherapy with a complex cell-derived cancer vaccine
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Background
Here, we report novel correlations between the antibody and T cell responses that develop to tumor-specific molecular targets following complex cancer vaccination. Further investigation of these correlations might lead to new methods of monitoring T cell immune responses via their corresponding antibody responses.

Methods
This study involves a complex autophagosome-enriched vaccine (DRibbles) made from 4T1 murine mammary carcinoma cells combined with poly-IC adjuvant. Animals pre-treated with 4T1 DRibbles and poly-I:C responded to tumor-specific molecular targets following complex cancer vaccination. Further investigation of these correlations might lead to new methods of monitoring T cell immune responses via their corresponding antibody responses.

Results
We designed an array of 150 paired mutant neoepitope and wild-type 4T1 variant site 15mer peptides; this array included all single-nucleotide polymorphism (SNP) variant sites which were an exact match between a published 4T1 sequence and variants identified from sequencing our own 4T1 cell bank. In pooled data from three independent biological experiments, we observed an increase in normal tissue using machine learning. Statistical hypothesis testing was used to investigate immune cell proportion differences (1) between tumor and normal tissues and (2) between tumor types. Prostate tumors were further investigated to determine whether particular cell types (1) were associated with androgen receptor (AR) signaling or (2) could serve as prognostic markers.

References