Phase 2 Study of PD-1 Inhibitor, Pimivalimab (JTX-4014) Alone and in Combination with Vopratelimab, an ICOS Agonist, in Biomarker-selected Subjects with Metastatic NSCLC After One Prior Platinum-containing Regimen (SELECT)

ABSTRACT# TPS9137

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Background

Immune checkpoint inhibitors have led to durable remissions for some patients with advanced malignancies, including non-small cell lung cancer (NSCLC); however, only a minority of patients benefit. The field of oncology is addressing this via the development of novel therapies, combinations and identification of biomarkers to select patients most likely to derive clinical benefit.

ICOS is a costimulatory molecule upregulated on activated T cells, and vopratelimab is an investigational IgG1 ICOS agonist monoclonal antibody that results in activation and proliferation of primed CD4 T effector cells but does not lead to a significant reduction in CD4 T regulatory cells, CD8 T cells, other T effector cells or natural killer cells as demonstrated in the Phase 1/2, first in human trial investigating vopratelimab, ICONIC (NCT02904226).

The preliminary efficacy of vopratelimab +/- nivolumab was assessed in the ICONIC study in which durable responses were observed in a subset of patients who demonstrated on treatment emergence of peripheral ICOS high (hi) CD4 T effector cells. Patients with peripheral ICOS hi CD4 T cells achieved significantly greater clinical benefit than patients whose CD4 T cells remained ICOS lo (Figure 1A).

Tumor inflammation score (TIS) is an RNA signature comprised of 18 genes associated with immune cell activity, including CD8 T cell activation and was previously identified as a predictive biomarker of response to PD-1 inhibitors (PD-1i; Ayers 2017). TIS also contains genes related to CD4 T cell activation and was found to be associated with ICOS hi CD4 T cell emergence in the ICONIC study. A specific threshold applied to pre-treatment tumor TIS scores, TIS^{vopra}, was established to optimize prediction for ICOS hi CD4 T cell emergence and was more predictive of clinical benefit than PD-L1 IHC in ICONIC (ASCO-SITC 2020). In ICONIC, TIS^{vopra} positive patients had improved investigator-assessed RECIST response, PFS, and OS compared to those with a TIS^{vopra} negative score (Figure 1B). As such, TIS^{vopra} has been identified as a biomarker to identify both patients who will display emergence of ICOS hi CD4 T cells and importantly, improved clinical outcomes when treated with vopratelimab, as well as patients more likely to respond to a PD-1i such as pimivalimab (JTX-4014; a novel PD-1i in development) in this study.

SELECT (JTX-4014-202; NCT04549025) is a multicenter study evaluating vopratelimab at two different dose levels in combination with pimivalimab versus pimivalimab alone in TIS^{vopra} eligible patients with locally advanced or metastatic NSCLC.

Study Rationale

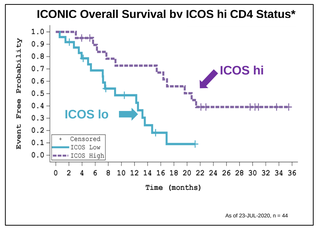
Figure 1: TIS^{vopra} Predicts for ICOS hi CD4 T Cells and Potential Clinical Benefit

Pharmacodynamic Biomarker: ICOS hi T cells

A Treatment emergent **ICOS hi CD4 T cells** associated with improved survival

Predictive Biomarker: TIS^{vopra}

B **TIS^{vopra}** predicts for on treatment emergence of ICOS hi CD4 T cells and OS



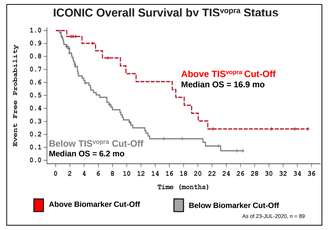


Figure 1. A) An ICONIC retrospective analysis demonstrated that a subset of 44 patients with on treatment emergence of ICOS hi CD4 T cells (purple) demonstrated an improved overall survival as compared with those who remained ICOS lo throughout treatment (blue).
B) TIS^{vopra} positive patients (those with a TIS score above the identified threshold) demonstrated improved overall survival as compared with those patients with a TIS score below the TIS^{vopra} cut-off in a retrospective analysis from the ICONIC study.

Figure 2: TIS^{vopra} Selects for Potential Clinical Benefit From Treatment with Vopratelimab & PD-1i

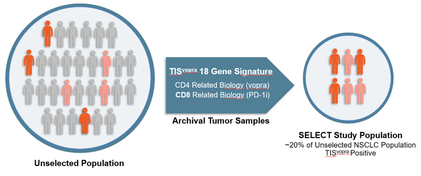


Figure 3: TIS^{vopra} Selected Patients are Hypothesized to Have Improved Clinical Outcomes After Treatment with Pimivalimab +/- Vopratelimab Compared to an Unselected NSCLC Population Treated with PD-1i monotherapy

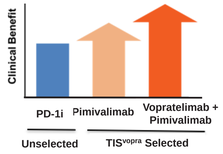
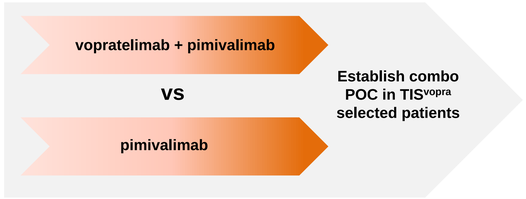


Figure 3. It is hypothesized that with TIS^{vopra} selection clinical outcomes to PD-1i such as pimivalimab may be enhanced compared to those of a non-selected population as it has been demonstrated that lung cancer patients with high TIS scores have improved clinical responses to PD-1i (Damotte 2019). Furthermore, combining vopratelimab with pimivalimab may lead to further clinical benefit since TIS^{vopra} may also identify those subjects who will have emergence of peripheral ICOS hi CD4 T cell populations and are therefore more likely to derive clinical benefit from vopratelimab.

Study Design



- IO naïve, 2L NSCLC in ~75 patients selected with TIS^{vopra}
- Powered to demonstrate statistical superiority of vopratelimab + pimivalimab (JTX-4014) versus pimivalimab
- Two different dose levels of vopratelimab with distinct profiles of pulsatile target engagement are being evaluated

Key Objectives

Primary Objective

- To demonstrate superiority of the combination of vopratelimab with pimivalimab (JTX-4014) over pimivalimab monotherapy in biomarker-selected subjects

Secondary Objectives

- Evaluate efficacy: RECIST v1.1 objective response rate (ORR), progression free survival (PFS), landmark PFS at 9 months, disease control rate (DCR), duration of response (DoR), and overall survival (OS)
- Evaluate safety and tolerability of vopratelimab in combination with pimivalimab and pimivalimab alone
- Evaluate pharmacokinetics (PK) of vopratelimab and pimivalimab
- Evaluate association of baseline TIS score with clinical outcomes

Key Endpoints

- Primary endpoint: mean percent change from baseline tumor size of all measurable existing and new lesions averaged over 9 and 18 weeks (Gao 2018; Wang 2009; Wang 2019)
- Secondary endpoints: RECIST v1.1 ORR, PFS, 9 month landmark PFS, disease control rate, duration of response, safety, OS

Key Eligibility Criteria

- Histologically or cytologically confirmed NSCLC with evaluable or measurable disease according to RECIST v1.1
- Confirmed TIS^{vopra} score above the established threshold
- Negative test for activating EGFR mutations
- Previously treated for locally advanced or metastatic NSCLC with 1 prior systemic antineoplastic platinum-containing regimen with or without bevacizumab
- No biologics (including immunotherapies), investigational agents/devices or targeted therapy in the metastatic setting with the exception of bevacizumab in 1L
- No concurrent anti-cancer treatment
- No prior whole brain radiation
- No active disease, including primary or acquired immunodeficiency (with exceptions allowed upon discussion with the medical monitor), requiring systemic immunosuppressive therapy

Summary

- In ICONIC, on-treatment emergence of peripheral ICOS hi CD4 T cells driven by vopratelimab was associated with improved clinical outcomes; TIS^{vopra} predicts for ICOS hi CD4 T cell emergence
- SELECT is a phase 2, open-label, multicenter study designed to demonstrate the statistical superiority of vopratelimab in combination with pimivalimab versus pimivalimab monotherapy in TIS^{vopra} selected patients with locally advanced or metastatic NSCLC after one prior platinum-containing regimen
- With TIS^{vopra}-selection, clinical outcomes with pimivalimab may be better than those of unselected patients treated with PD-1i; further, combining vopratelimab and pimivalimab may further improve clinical outcomes as CD4 T cells will be engaged in addition to restored CD8 T cell activity
- Patients must be PD-(L)1 inhibitor naïve, have a TIS^{vopra} eligible score and negative EGFR activating mutation status
- Additional referral sites were selected to refer eligible patients to main study sites; all sites are located in Russia and Central & Eastern Europe (list available upon request)
- SELECT has a target enrollment goal of 75 patients; the first patient was dosed October 2020
- Clinical data expected in 2022

References

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