SELECT: A Phase 2 Randomized Trial Evaluating 2 doses of Vopratelimab + Pimivalimab in TIS^{vopra} Selected Patients

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ABSTRACT

Background

ICOS is a costimulatory molecule induced on T cells after TCR activation. Vopratelimab (vopra) is an ICOS agonist monoclonal antibody that amplifies CD4 T cell proliferation and may boost immune response and anti-tumor activity. SELECT is a Phase 2 randomized study of pimivalimab (pimi), an investigational PD-1 inhibitor (PD-1i) plus vopra vs pimi monotherapy in TIS^{vopra} selected, immunotherapy naïve, 2nd line non-small cell lung cancer (NSCLC). Tumor inflammation signature (TIS) at and above a designated cut-off, termed TIS^{vopra}, was previously associated with improved clinical outcomes in patients treated with vopra +/- nivolumab. SELECT was designed to demonstrate superiority of pimi + vopra in TIS^{vopra} selected patients (pts) and evaluate 2 doses of vopra with different pulsatile target engagement (TE) profiles intended to reduce T cell exhaustion.

Methods

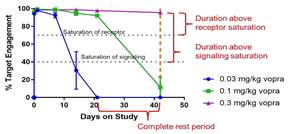
69 TIS^{vopra} positive patients with metastatic NSCLC after 1 prior platinum-containing regimen were randomized 2:1:1 to pimi 1000 mg (MC1, n=36), pimi + vopra 0.1 mg/kg (CC1, n=18) or pimi + vopra 0.03 mg/kg (CC2, n=15) q6w. The primary endpoint was mean % change from baseline size of all measurable lesions averaged over 9 & 18 weeks by independent central radiology review (ICR); the study was powered to compare MC1 vs pooled CC1+CC2. Overall response rate (ORR) per RECIST v1.1 by ICR, progression free survival (PFS), and overall survival (OS) were secondary endpoints. Safety, TE and association between PD-L1 status and efficacy were evaluated.

Results

Both doses of vopra demonstrated distinct patterns of pulsatile target engagement; vopra 0.03 mg achieved a shorter duration of TE where a meaningful rest period from receptor saturation and signaling was observed. The primary endpoint was numerically better in CC1+CC2 vs MC1 but not statistically significant. CC2 trended favorably for primary endpoint, ORR, and PFS. ORR (95% confidence interval [CI]) was 40% (16, 68) for CC2, 28% (14, 45) for MC1, 17% (4, 41) for CC1. 6 month (mo) PFS rate (95% CI) was 80% (50, 93) for CC2, 36% (20, 53) for MC1, 31% for CC1 (11, 52). Data continue to mature. PD-L1 expression was evenly distributed across TIS^{vopra} patients with no evidence suggesting association with efficacy. No meaningful differences were observed in patient baseline characteristics across cohorts. Study treatment was well tolerated across all cohorts with 7.2% of patients reporting Grade ≥3 treatment related adverse events (TRAEs). Most common TRAEs in ≥5% were Grade 1/2 hyperthyroidism and hypothyroidism.

BACKGROUND AND STUDY DESIGN

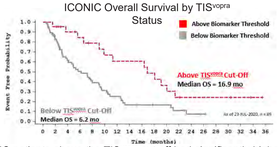
Figure 1. SELECT is Evaluating 2 Doses of Vopra With Different Pulsatile Patterns of Target Engagement: 0.1 mg/kg and 0.03 mg/kg



*Data from previous study (ICONIC)

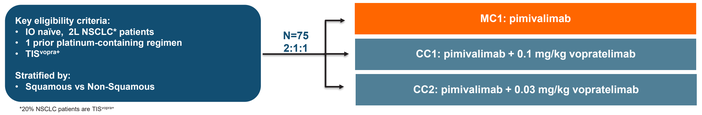
- Constant ICOS signaling achieved by continuous TE may lead to T cell exhaustion.
- A lower dose and less frequent schedule provide a period of receptor saturation followed by a period of receptor occupancy below saturation which allows T cell recovery (Figure 1, Pachinski et al. 2019) and thus may be optimal for an agonist.

Figure 2. SELECT is Prospectively Evaluating TIS^{vopra} as a Predictive Biomarker



- ICONIC patients above the TIS^{vopra} cut-off had significantly higher median OS (p-value 0.0062) compared to those below the cut-off (Figure 2, Yap et al. 2022).
- Tumor Inflammation Signature (TIS) is an RNA signature that includes genes associated with antigen presentation, lymphocyte/monocyte abundance and immune cell activation, including CD4 T cell activation (Ayers et al. 2017).
- TIS at a specific cut-off, TIS^{vopra}, may identify patients more likely to have T cell inflamed tumors and result in improved clinical outcomes after treatment with vopra + a PD-1 inhibitor.

Figure 3. SELECT was Designed to Demonstrate Superiority of 2 Pooled Doses of Vopra + Pimi vs Pimi Monotherapy in TIS^{vopra} Selected 2L NSCLC Patients



*20% NSCLC patients are TIS^{vopra+}

- Primary Endpoint - mean percent change from baseline in tumor size in all measurable lesions, averaged over 9 and 18 weeks
- Secondary Endpoints: RECIST v1.1 ORR, PFS and OS

PRELIMINARY EFFICACY RESULTS

A Favorable Trend Was Observed With Vopra 0.03mg/kg + Pimi For All Efficacy Endpoints

Table 1. A Trend Toward Improved Tumor Response is Observed With Pimi + Vopra 0.03 mg/kg vs Pimi Monotherapy

	MC1: pimi monotherapy (N=36)	CC1+CC2: pooled pimi + vopra doses (n=33)	CC1: pimi + vopra 0.1 mg/kg (n=18)	CC2: pimi + vopra 0.03 mg/kg (n=15)
RECIST v1.1				
Overall Response Rate (ORR), n (%) 95% CI	10 (27.8) 14.20, 45.19	9 (27.3) 13.30, 45.52	3 (16.7) 3.58, 41.42	6 (40.0) 16.34, 67.71
Complete Response (CR), n (%)	2 (5.6)	1 (3.0)	0	1 (6.7)
Partial Response (PR), n (5)%	8 (22.2)	8 (24.2)	3 (16.7)	5 (33.3)
Stable Disease (SD), n (%)	13 (36.1)	15 (45.5)	8 (44.4)	7 (46.7)
Progressive Disease (PD), n (%)	10 (27.8)	6 (18.2)	5 (27.8)	1 (6.7)
Not Evaluable[1], (NE), n (%)%	3 (8.3)	3 (9.1)	2 (11.1)	1 (6.7)
Disease Control Rate (DCR), n (%) 95% CI	23 (63.9) 46.22, 79.18	24 (72.7) 54.48, 86.70	11 (61.1) 35.75, 82.70	13 (86.7) 59.54, 98.34
Duration of Response (DOR), months	0.0*-16.4+	2.1*-14.3*	2.1-12.2*	2.1*-14.3*
Primary Endpoint[2]				
Mean % change from baseline in all measurable lesions averaged over 9 & 18 weeks **95% CI**	5.38 -14.11, 24.87	0.15 -20.21, 20.52	8.17 -20.15, 36.50	-7.87 -37.20, 21.45
Difference between combo and pimi monotherapy, absolute 95% CI		-5.23 -33.36, 22.90	2.80 -31.55, 37.14	-13.25 -48.41, 21.91

Data cut September 13, 2022

Table 1. Summary of RECIST v1.1 ORR and the primary endpoint as assessed by Independent Central Review (ICR). There was no statistically significant difference between pimi monotherapy and pimi + the pooled doses of vopra for the primary endpoint. Data continue to mature.

No meaningful differences between baseline characteristics across cohorts: age, gender, tumor histology, ECOG score, smoking status, PD-L1 expression, tumor burden or neutrophil to lymphocyte ratio

[1] NE: Not Evaluable, Not Reported/Unknown/Missing and Early Death Termination;
[2] Repeated Measures Analysis (MMRM); *Censored observation

Figure 4. Pimi + Vopra 0.03 mg/kg Demonstrates Numerically Improved RECIST v1.1 Tumor Responses per ICR Compared to Pimi Monotherapy With a Greater Proportion of Patients Still on Treatment

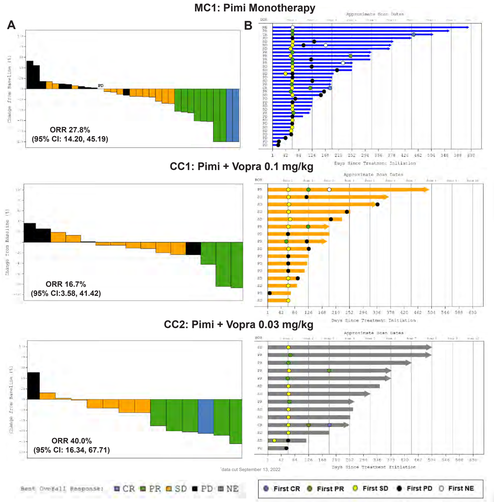
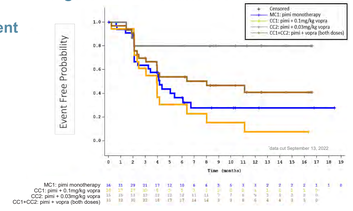


Figure 4. A) Percent change in target lesion tumor size for patients who had baseline and at least one post-baseline tumor assessment up to initial RECIST v1.1 PD per Independent Central Review (ICR).
B) Swimmer plots showing time on treatment per cohort. **53% of patients remain on study treatment in CC2 vs 39% in MC1 vs 28% in CC1.**

Figure 5. A Favorable Trend in PFS is Observed With Pimi + Vopra 0.03 mg/kg vs Pimi Monotherapy



	MC1 Pimi mono (n=36)	CC1+CC2 pimi + vopra (n=33)	CC1 pimi + vopra 0.1mg/kg (n=18)	CC2 pimi + vopra 0.03 mg/kg (n=15)
Events, n (%)	22 (61.1)	18 (54.5)	15 (83.3)	3 (20.0)
Censored, n (%)	14 (38.9)	15 (45.5)	3 (16.7)	12 (80.0)
Median PFS, months (95% CI)	4.2 (2.1,6.1)	8.0 (3.1,-)	3.9 (2.1,6.4)	NE[1] (2.1,-)
Hazard Ratio vs MC1 (95% CI)		0.72 (0.38, 1.36)	1.39 (0.71, 2.68)	0.21 (0.05, 0.62)
6 mo PFS rate (95% CI)	36% (20%,53%)	54% (35%, 69%)	31% (11%, 52%)	80% (50%, 93%)

Data continue to mature.
[1]NE = non-estimable (median has not been reached)

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Table 4. Vopra and Pimi are Well Tolerated

	SELECT TRAEs N=69							
	MC1: pimi monotherapy N=36		CC1: pimi + vopra 0.1 mg/kg N=18		CC2: pimi + vopra 0.03 mg/kg N=15		Total (N=69)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Total TRAEs, n (%)	13 (36.1)	2 (5.6)	7 (38.9)	0 (0.0)	7 (46.6)	3 (20.0)	27 (39.1)	5 (7.2)
Most common TRAEs (≥5% of patients)								
Hypothyroidism, n (%)	3 (8.3)*	0	2 (11.1)**	0	1 (6.7)**	0	6 (8.7)	0 (0.0)
Hyperthyroidism, n (%)	2 (5.6)*	0	2 (11.1)**	0	0	0	4 (5.8)	0 (0.0)
Serious TRAEs								
Diarrhoea, n (%)	0	0	0	0	1 (6.7)**	1 (6.7)**	1 (1.4)	1 (1.4)
Diabetic ketoacidosis*, n (%)	1 (2.8)*	1 (2.8)*	0	0	0	0	1 (1.4)	1 (1.4)
Hypersensitivity*, n (%)	1 (2.8)*	1 (2.8)*	0	0	0	0	1 (1.4)	1 (1.4)

Data cut September 13, 2022

Table 4. Summary of all Treatment Related Adverse Events (TRAEs) and Serious TRAEs observed in each cohort and relationship to pimi and/or vopra. Vopra does not add to the toxicity of pimi.
*related to pimivalimab only;**related to vopratelimab and pimivalimab.

TARGET ENGAGEMENT (TE) DURATION: CLINICAL AND *IN VITRO* ANALYSES

Shorter TE May Prevent T Cell Exhaustion and Allow for Optimal Anti-Tumor Activity

Table 2. Two Doses of Vopra Provide Distinct Patterns of Pulsatile TE in SELECT

Target Engagement Over 6 week Cycle Median %				
	Week 1	Week 2	Week 3	Week 6
CC1: pimi + 0.1 mg/kg vopra	91.70 (n=9)	91.20 (n=6)	77.60 (n=8)	0.90 (n=8)
CC2: pimi + 0.03 mg/kg vopra	95.00 (n=7)	57.80 (n=8)	16.10 (n=8)	2.50 (n=7)

Data cut September 13, 2022

Table 2. Cycle 1 shown. Vopra 0.1 mg/kg saturates peripheral TE for approximately 3 weeks while vopra 0.03 mg/kg saturates for approximately 1 week of the 6 week cycle.

Table 3. *In Vitro* Studies Demonstrate No Signs of T Cell Exhaustion or T Reg Induction with Shorter Periods of TE

Readout	Long Vopra Target Engagement	Short Vopra Target Engagement
PD-1 induction on CD4 and CD8 T cells (exhaustion)	++	-
Treg emergence and IL-10 secretion (anti-inflammatory response)	++	-

Table 3. PBMCs from 8 healthy donors were treated with different concentrations and duration of vopra. For long treatment, PBMCs were treated with aCD3 + vopra for continuous 96h, and for short treatment PBMCs were treated with aCD3+ vopra for 24h + 72h washout. Simulations were plate bound. Readouts measured at 96 hr post-treatment (for both groups) included: viability, CD4, CD8, FOXP3, Ki-67, PD-1, via FACS and IL-10 from supernatants via cytometric bead array.

CONCLUSIONS

- SELECT assessed 2 doses of vopra with distinct target engagement profiles in a TIS^{vopra} -selected population, intended to identify patients more likely to have T cell inflamed tumors
- A favorable trend towards clinical benefit was observed in the pimi + vopra 0.03 mg/kg cohort for all efficacy endpoints including the primary endpoint, ORR and PFS
- No meaningful differences were observed in patient baseline characteristics across cohorts that could affect clinical outcomes, including PD-L1 score
- Both study drugs are well tolerated
- Shorter duration of target engagement with vopra 0.03 mg/kg may allow T cell recovery and lead to clinical benefit
- Vopra 0.03 mg/kg + a PD-1 inhibitor warrants further exploration

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1. Pachinski et al., SITC Annual Meeting (2019) #P438
2. Yap et al., Clin Cancer Res (2022) 28 (17):3695-3708
3. Ayers et al., The Journal of Clinical Investigation (2017) 127(8) 2930:2940

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