Initial results from a phase 1a/b study of Etigilimab (OMP-313M32), an anti-T cell immunoreceptor with Ig and ITIM domains (TIGIT) antibody, in advanced solid tumors

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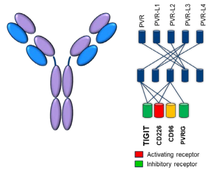
Abstract (updated)

Background: TIGIT is an immune-checkpoint expressed on T and NK cells. Etigilimab is a novel IgG1 anti-TIGIT antibody that has inhibitory as well as ADCC characteristics. Anti-TIGIT demonstrates preclinical *in-vivo* anti-tumor effects as a single agent and with anti-PD-1. Initial results from the phase 1a dose escalation portion of the study are presented.
Methods: This phase 1a/b study enrolled subjects with advanced solid tumors into either a Ph 1a single-agent portion (dose escalation in all comers + expansion in selected tumor types) or a Ph 1b combination [PD-(L)1 refractory] portion in selected tumor types with nivolumab (dose escalation). Objectives included safety, maximum tolerated dose (MTD), determining the recommended Ph 2 dose (RP2D), pharmacokinetics, immunogenicity, efficacy and biomarkers. Dose escalation followed a modified 3+3 framework.
Results: 18 subjects were treated in the dose escalation portion of the Phase 1a with doses ranging from 0.3 to 20 mg/kg Q2W. Tumor types included colorectal cancer (6), endometrial cancer (2), pancreatic cancer (2), and 8 other tumor types (1 each). No dose-limiting toxicities were observed; thus, the recommended phase 2 dose was 20 mg/kg Q2W. The most frequent treatment-related AEs were rash (27.8%), fatigue (16.7%), nausea (16.7%), pruritus (16.7%), and cough (11.1%). Immune-related adverse events included rash (27.8%), pruritus (16.7%), autoimmune hepatitis (5.6%) and stomatitis (5.6%). Grade 3 or higher treatment-related AEs included rash (16.7%), and abdominal pain, embolism, hypertension, and pulmonary embolism (11.1% each). 7 (38.9%) subjects had stable disease as best response (longest durations were 205 and 225 days), 10 had progressive disease, and 1 was not evaluable. The expansion cohort in phase 1a and dose-escalation in phase 1b are ongoing. Data cut-off: 10/3/18.
Conclusions: TIGIT is a potential therapeutic target against cancer. Etigilimab has been well tolerated at doses up to 20 mg/kg Q2W. Evidence of immune activation was shown in multiple subjects with immune-related AEs. Early signs of potential efficacy have been observed in subjects with prolonged stable disease.
Trial Registration: clinicaltrials.gov NCT03119428

Background

T cell immunoreceptor with Ig and ITIM domains (TIGIT)

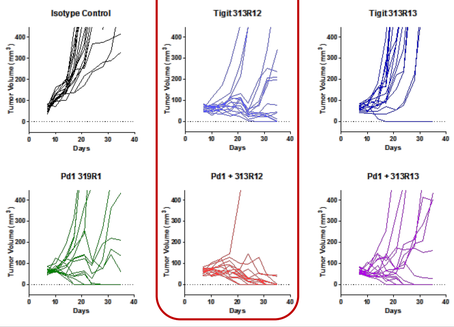


- TIGIT is a receptor similar to PD1 in both structure and expression
- TIGIT is expressed on CD4, CD8 and NK cells and is elevated upon activation
- TIGIT expression is pronounced on Tregs
- TIGIT mediates an inhibitory signal

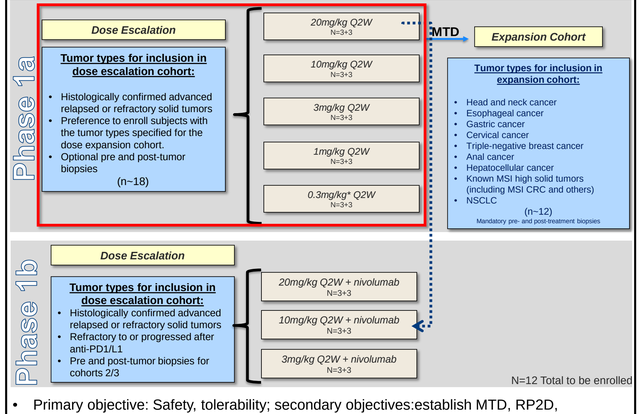
- Pre-clinical models demonstrate single-agent and combination (PD-1) efficacy
- Effector function is an important component of efficacy

313R12 = IgG2a

313R13 = IgG2a without effector function



Methods, Study Schema, and Objectives



- Primary objective: Safety, tolerability; secondary objectives:establish MTD, RP2D, PK/immunogenicity, preliminary efficacy; exploratory objectives: PD and predictive biomarkers
- Data presented today represents the dose escalation cohorts from the Phase 1a portion of the study (red box)
- Data cut-off: 10/3/18

Disposition and DLTs

	Dose Escalation					
	0.3 mg/kg Q2W (N=3)	1.0 mg/kg Q2W (N=3)	3.0 mg/kg Q2W (N=4)	10.0 mg/kg Q2W (N=3)	20.0 mg/kg Q2W (N=8)	Phase 1a Overall (N=21)*
Intent-to-Treat (ITT) Population[1]	3	3	4	3	8	21
Safety Population[2]	3 (100%)	3 (100%)	3 (75.0%)	3 (100%)	6 (75.0%)	18 (85.7%)
Pharmacokinetic (PK) Population[3]	3 (100%)	3 (100%)	3 (75.0%)	3 (100%)	6 (75.0%)	18 (85.7%)
DLT	0	0	0	0	0	0
Reason for Study Treatment Discontinuation						
Disease Progression	2 (66.7%)	3 (100%)	3 (75.0%)	3 (100%)	5 (62.5%)	16 (76.2%)
Adverse Event	0	0	0	0	1 (12.5%)	1 (4.8%)
Other	1 (33.3%)	0	0	0	1 (12.5%)	2 (9.5%)
Clinical Progression	1 (33.3%)	0	0	0	0	1 (4.8%)
Not Eligible For Treatment	0	0	0	0	1 (12.5%)	1 (4.8%)

* 3 subjects were enrolled and not treated

Baseline Characteristics

	Dose Escalation					
	0.3 mg/kg Q2W (N=3)	1.0 mg/kg Q2W (N=3)	3.0 mg/kg Q2W (N=3)	10.0 mg/kg Q2W (N=3)	20.0 mg/kg Q2W (N=6)	Phase 1a Overall (N=18)
Age (years)[1]						
<65	2 (66.7%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	5 (83.3%)	10 (55.6%)
>=65 - <75	1 (33.3%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	1 (16.7%)	8 (44.4%)
>=75	0	0	0	0	0	0
Missing	0	0	0	0	0	0
Sex						
Male	1 (33.3%)	2 (66.7%)	1 (33.3%)	1 (33.3%)	2 (33.3%)	7 (38.9%)
Female	2 (66.7%)	1 (33.3%)	2 (66.7%)	2 (66.7%)	4 (66.7%)	11 (61.1%)
Initial Diagnosis (Cancer Type)						
Colorectal cancer	2 (66.6%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (16.7%)	6 (33.3%)
Endometrial cancer				1 (33.3%)	1 (16.7%)	2 (11.1%)
Pancreatic cancer				1 (33.3%)	1 (16.7%)	2 (11.1%)
Uterine cancer		1 (33.3%)			1 (16.7%)	2 (11.1%)
Adenoid cystic carcinoma					1 (16.7%)	1 (5.6%)
Anal Cancer						1 (5.6%)
Ewing sarcoma			1 (33.3%)			1 (5.6%)
Fallopian tube cancer			1 (33.3%)			1 (5.6%)
Gallbladder cancer	1 (33.3%)					1 (5.6%)
Head and neck cancer		1 (33.3%)				1 (5.6%)
Triple-negative breast cancer					1 (16.7%)	1 (5.6%)
Microsatellite Status						
MSI (Microsatellite Instability)					1 (16.7%)	1 (5.6%)
MSS (Microsatellite Stable)	2 (66.7%)	1 (33.3%)		1 (33.3%)	1 (16.7%)	5 (33.3%)
Unknown	1 (33.3%)	2 (66.7%)	3 (100.0%)	2 (66.7%)	4 (66.6%)	12 (66.7%)

Treatment Exposure

	Dose Escalation					
	0.3 mg/kg Q2W (N=3)	1.0 mg/kg Q2W (N=3)	3.0 mg/kg Q2W (N=3)	10.0 mg/kg Q2W (N=3)	20.0 mg/kg Q2W (N=6)	Phase 1a Overall (N=18)
Total Number of Infusions Administered per Subject						
n	3	3	3	3	6	18
Mean (SD)	5.3 (4.16)	8.0 (6.93)	7.7 (6.35)	6.0 (2.00)	4.8 (3.60)	6.1 (4.30)
Median	4	4	4	6	4	4
25th, 75th Percentile	2.0, 10.0	4.0, 16.0	4.0, 15.0	4.0, 8.0	3.0, 4.0	4.0, 8.0
Min, Max	2.0, 10.0	4.0, 16.0	4.0, 15.0	4.0, 8.0	2.0, 12.0	2.0, 16.0
Total Dose Administered (mg) per Subject						
n	3	3	3	3	6	18
Mean (SD)	123.0 (106.65)	716.3 (640.70)	1,462.3 (879.95)	7,157.3 (4,599.85)	9,694.6 (10,403.12)	4,808.0 (7,257.13)
Median	84	356	1,292.00	7,308.00	5,895.00	2,449.50
25th, 75th Percentile	41.4, 243.7	336.8, 1,456.0	680.0, 2,415.0	2,484.0, 11,680.0	5,208.0, 8,008.0	356.0, 6,438.0
Min, Max	41.4, 243.7	336.8, 1,456.0	680.0, 2,415.0	2,484.0, 11,680.0	2,548.0, 30,613.8	41.4, 30,613.8

Adverse Events (all Grades ≥10%)

Preferred Term (group)	Grade (Maximum per subject) 1	2	3	Total
Rash	4 (22.2%)		3 (16.7%)	7 (38.9%)
Nausea	6 (33.3%)			6 (33.3%)
Pruritus	4 (22.2%)			4 (22.2%)
Constipation	4 (22.2%)			4 (22.2%)
Abdominal pain	2 (11.1%)		2 (11.1%)	4 (22.2%)
Vomiting	3 (16.7%)			3 (16.7%)
Fatigue		3 (16.7%)		3 (16.7%)
Dyspnoea		3 (16.7%)		3 (16.7%)
Cough	3 (16.7%)			3 (16.7%)
Chills	3 (16.7%)			3 (16.7%)
Abdominal distension	3 (16.7%)			3 (16.7%)
Urinary tract infection		2 (11.1%)		2 (11.1%)
Pyrexia		2 (11.1%)		2 (11.1%)
Pulmonary embolism			2 (11.1%)	2 (11.1%)
Productive cough	2 (11.1%)			2 (11.1%)
Pleural effusion	2 (11.1%)			2 (11.1%)
Hypokalaemia	2 (11.1%)			2 (11.1%)
Hypertension			2 (11.1%)	2 (11.1%)
Headache		2 (11.1%)		2 (11.1%)
Embolism			2 (11.1%)	2 (11.1%)
Dysuria	2 (11.1%)			2 (11.1%)
Dizziness	2 (11.1%)			2 (11.1%)
Diarrhoea	2 (11.1%)			2 (11.1%)
Dehydration	2 (11.1%)			2 (11.1%)
Decreased appetite	2 (11.1%)			2 (11.1%)
Chest pain	2 (11.1%)			2 (11.1%)
Blood creatinine increased	2 (11.1%)			2 (11.1%)

Adverse Events (Grade ≥3)

Preferred Term (group)	Grade (Maximum per subject) 3	5	Total
Rash	3 (16.7%)		3 (16.7%)
Pulmonary embolism	2 (11.1%)		2 (11.1%)
Hypertension	2 (11.1%)		2 (11.1%)
Embolism	2 (11.1%)		2 (11.1%)
Abdominal pain	2 (11.1%)		2 (11.1%)
Vomiting	1 (5.6%)		1 (5.6%)
Pleural effusion	1 (5.6%)		1 (5.6%)
Pancreatic carcinoma metastatic		1 (5.6%)	1 (5.6%)
Pain (non-cardiac)	1 (5.6%)		1 (5.6%)
Oedema peripheral	1 (5.6%)		1 (5.6%)
Nausea	1 (5.6%)		1 (5.6%)
Malignant neoplasm progression		1 (5.6%)	1 (5.6%)
Hypoxia	1 (5.6%)		1 (5.6%)
Hypophosphataemia	1 (5.6%)		1 (5.6%)
Hyponatraemia	1 (5.6%)		1 (5.6%)
Hypokalaemia	1 (5.6%)		1 (5.6%)
Fatigue	1 (5.6%)		1 (5.6%)
Endometrial cancer metastatic		1 (5.6%)	1 (5.6%)
Decreased appetite	1 (5.6%)		1 (5.6%)
Chronic myeloid leukaemia	1 (5.6%)		1 (5.6%)
Blood alkaline phosphatase incre..	1 (5.6%)		1 (5.6%)
Back pain	1 (5.6%)		1 (5.6%)
Autoimmune hepatitis	1 (5.6%)		1 (5.6%)
Aspartate aminotransferase incr..	1 (5.6%)		1 (5.6%)
Alanine aminotransferase increa..	1 (5.6%)		1 (5.6%)

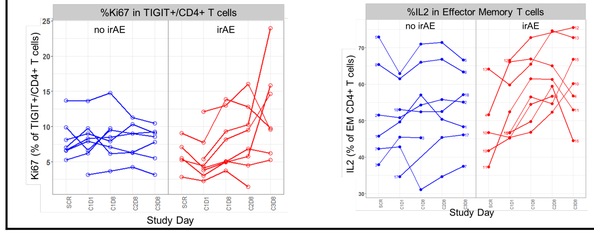
Adverse Events (Treatment-Related)

Preferred Term (group)	Grade (Maximum per subject) 1	2	3	Total
Rash	2 (11.1%)		3 (16.7%)	5 (27.8%)
Pruritus	3 (16.7%)			3 (16.7%)
Nausea	3 (16.7%)			3 (16.7%)
Fatigue	1 (5.6%)	1 (5.6%)	1 (5.6%)	3 (16.7%)
Cough	2 (11.1%)			2 (11.1%)
Vomiting	1 (5.6%)			1 (5.6%)
Thrombocytopenia	1 (5.6%)			1 (5.6%)
Stomatitis	1 (5.6%)			1 (5.6%)
Pain		1 (5.6%)		1 (5.6%)
Influenza like illness	1 (5.6%)			1 (5.6%)
Hypophosphataemia			1 (5.6%)	1 (5.6%)
Headache		1 (5.6%)		1 (5.6%)
Chills	1 (5.6%)			1 (5.6%)
Autoimmune hepatitis			1 (5.6%)	1 (5.6%)
Aspartate aminotransferase incr..			1 (5.6%)	1 (5.6%)
Alanine aminotransferase increa..			1 (5.6%)	1 (5.6%)
Abdominal pain	1 (5.6%)			1 (5.6%)

Immune-Related Adverse Events

Preferred Term (group)	Dose Cohort / Max. Grade (Maximum per subject) 1.0 mg/kg 3	3.0 mg/kg 1	3.0 mg/kg 3	10.0 mg/kg 1	10.0 mg/kg 3	20.0 mg/kg 1	20.0 mg/kg 3	Subjects Total
Rash	1 (5.6%)		1 (5.6%)		3 (16.7%)			5 (27.8%)
Pruritus		1 (5.6%)		1 (5.6%)		1 (5.6%)		3 (16.7%)
Autoimmune hepatitis							1 (5.6%)	1 (5.6%)
Stomatitis						1 (5.6%)		1 (5.6%)

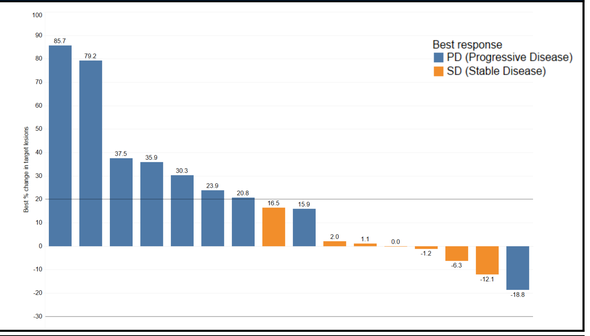
Etigilimab enhances activation of T cells more predominately in pts with immune-related adverse effects



Best Overall Tumor Response

	Dose Escalation 0.3 mg/kg Q2W (N=3)	1.0 mg/kg Q2W (N=3)	3.0 mg/kg Q2W (N=3)	10.0 mg/kg Q2W (N=3)	20.0 mg/kg Q2W (N=6)	Total
Best Overall Tumor Response						
Complete Response (CR)	0	0	0	0	0	0
Partial Response (PR)	0	0	0	0	0	0
Stable Disease (SD)	1 (5.6%)	2 (11.1%)	1 (5.6%)	1 (5.6%)	2 (11.1%)	7 (38.9%)
Progressive Disease (PD)	1 (5.6%)	1 (5.6%)	2 (11.1%)	2 (11.1%)	4 (22.2%)	10 (55.6%)
Not Evaluable (NE)	1 (5.6%)	0	0	0	0	1 (5.6%)
Overall Response Rate (CR or PR)	0	0	0	0	0	0

Waterfall Plot

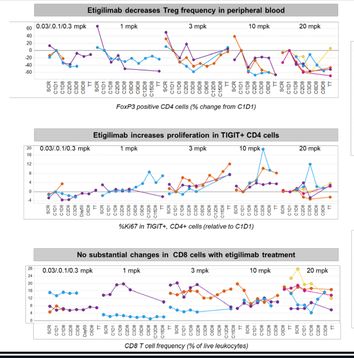


Swim lanes

Dose Cohort	Diagnosis	MSI Status	Prior PD-(L)1	Best Response	
0.3 mg/kg	Colorectal cancer	MSS	N	SD (Stable Disease)	113.0
	Colorectal cancer	MSS	N	PD (Progressive Disease)	58.0
	Uterine cancer	Unknown	Y	SD (Stable Disease)	85.0
1.0 mg/kg	Head and neck cancer	Unknown	N	SD (Stable Disease)	225.0
	Colorectal cancer	MSS	N	PD (Progressive Disease)	52.0
	Ewing sarcoma	Unknown	Y	PD (Progressive Disease)	51.0
3.0 mg/kg	Colorectal cancer	Unknown	N	PD (Progressive Disease)	53.0
	Fallopian tube cancer	Unknown	Y	SD (Stable Disease)	205.0
	Endometrial cancer	Unknown	N	SD (Stable Disease)	112.0
10.0 mg/kg	Colorectal cancer	MSS	N	PD (Progressive Disease)	51.0
	Pancreatic cancer	Unknown	N	PD (Progressive Disease)	50.0
	Pancreatic cancer	MSS	N	PD (Progressive Disease)	50.0
	Colorectal cancer	Unknown*	Y	SD (Stable Disease)	165.0
20.0 mg/kg	Triple-negative breast cancer	Unknown	N	PD (Progressive Disease)	58.0
	Adenoid cystic carcinoma	Unknown	N	SD (Stable Disease)	37.0**
	Uterine cancer	Unknown	N	PD (Progressive Disease)	44.0
	Endometrial cancer	MSI	Y	PD (Progressive Disease)	53.0

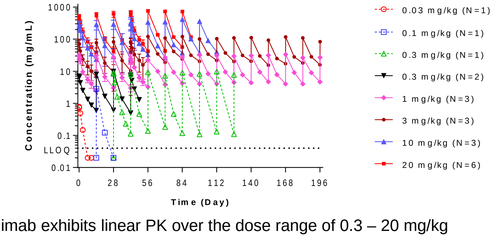
* Subject noted to be MSI post data-cut for this presentation
** Subject discontinued treatment due to AE (autoimmune hepatitis) but subsequently had the Day 56 CT scan with stable disease

Biomarkers



PBMC flow cytometry
Each line represents one subject

Pharmacokinetics and Immunogenicity



- Etigilimab exhibits linear PK over the dose range of 0.3 – 20 mg/kg
  - Clearance estimate is ~8-10 mL/day/kg
  - Half-life estimate is ~6 days
- No confirmed ADA+ patients through cycle 4

Conclusions

- Etigilimab can be safely administered up to 20 mg/kg Q2W dose level
- Immune-related adverse events were observed in several subjects, consistent with activation of the immune system
- Blood-based biomarker analysis reveals significant reduction in Tregs and increases in proliferation and activation signals in CD4 T-cells
- 38.9% (7/18) of subjects had stable disease as best response. 2 subjects had PFS of 205 and 225 days.