First-In-Human Phase 1 Trial of IO-108, an Antagonist Antibody Targeting LILRB2 (ILT4), as Monotherapy and in Combination with Pembrolizumab in Adult Patients with Advanced Relapsed or Refractory Solid Tumors: Dose Escalation Data (NCT05054348)

Matthew H. Taylor, MD[1], Manish R Patel, MD[2], John Powderly, MD[3], Paul Woodard MD[4], Luke Chung, MD[4], Hongyu Tian, PhD[4], Hong Xiang, PhD[4], Kyu Hong, MS[4], Donna Valencia, PharmD[4], Tao Huang, PhD[4], Xiao Min Schebye, MD, PhD[4], X. Charlene Liao, PhD[4] and Aung Naing, MD[5]

[1] Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR; [2] Florida Cancer Specialists/ Sarah Cannon Research Institute, Sarasota, FL; [3] Carolina BioOncology Institute, Huntersville, NC; [4] Immune-Onc Therapeutics Inc., Palo Alto, CA; [5] UT MD Anderson Cancer Center, Houston, TX

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Disclosure Information

Matthew H. Taylor, MD

I have the following relevant financial relationships to disclose:

Consultant for: Bristol Myers Squibb, Eisai Inc, Bayer, Pfizer, Merck, Genzyme, Regeneron, Array Biopharma, Blueprint Medicines, Immune-Onc Therapeutics, Exelixis, Cascade Prodrug.

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LILRB2 Activation in Myeloid Cells Promotes Immune Inhibitory Signals

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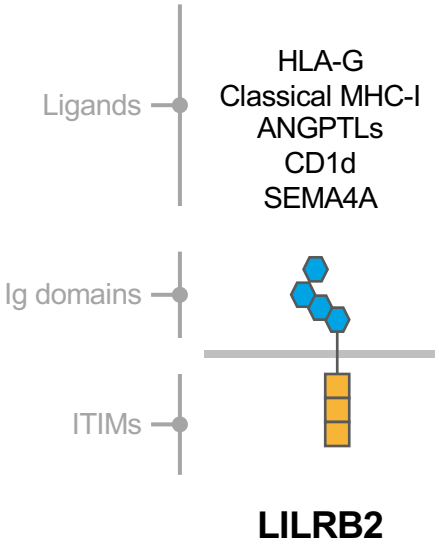

Mostly expressed on myeloid cells (monocyte, DC, macrophage, neutrophil)

Receptor with **dual immune inhibitory activity**

1. Inhibits Ca++ signaling through SHP-1 recruitment
2. Competes with CD8 for MHC class I binding

Promotes tumor immune evasion via interaction of LILRB2 with HLA-G and other ligands

High LILRB2 expression is associated with macrophage infiltration in many solid tumors*

ITIM = immunoreceptor tyrosine-based inhibition motif

*Ma J. et al. The American Association for Cancer Research (AACR) Annual Meeting 2022. April 8–13, 2022
Siu et al., *Clin. Cancer Res.*, 2021
Colonna et al., *Journal Immunol.*, 1998
Fanger et al., *Eur. J. Immunol.*, 1998
Chang et al., *Nat Immunol.*, 2002
Shiroishi et al., *PNAS*, 2003
Chen et al., *JCI*, 2018

IO-108 (Anti-LILRB2): Re-Programs Myeloid Cells to Activate T Cells

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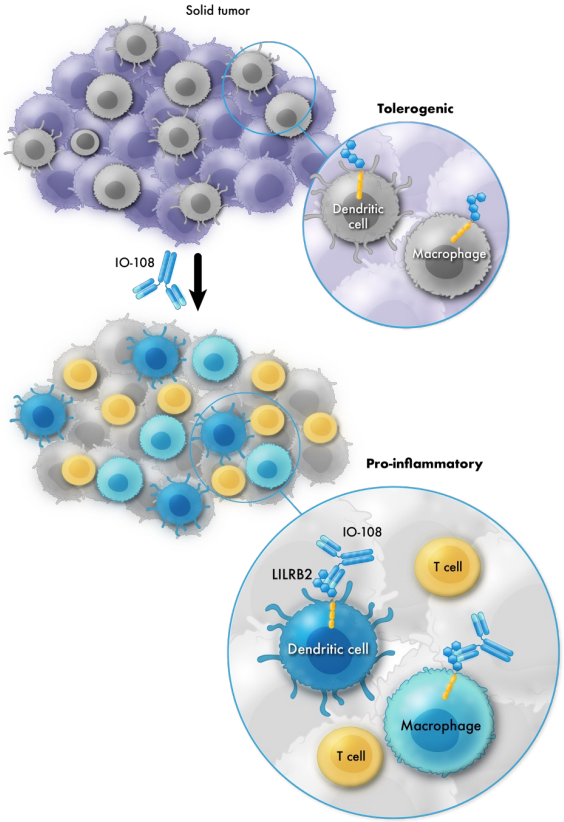

IO-108: LILRB2 (ILT4) Antagonist Antibody

IO-108 is a fully human IgG4 therapeutic antibody that binds to LILRB2 with high affinity and specificity, and blocks binding of LILRB2 to multiple cancer-relevant ligands (HLA-G, ANGPTL2, SEMA4A, CD1d)

Therapeutic Mechanism of Action

LILRB2 blockade causes **re-programming** of immune suppressive myeloid cells to pro-inflammatory in the tumor microenvironment leading to activation of T cells[1]

Global Clinical Development

Phase 1 in solid tumors as monotherapy and in combination with an anti-PD-1 (NCT05054348) completed dose escalation in the US; Expansion cohorts open in the US and China

1. J Clin Invest. 2018;128(12):5647–5662. https://doi.org/10.1172/JCI97570.

Open-Label Phase 1 Study of IO-108 as Monotherapy or in Combination With Pembrolizumab (NCT05054348)

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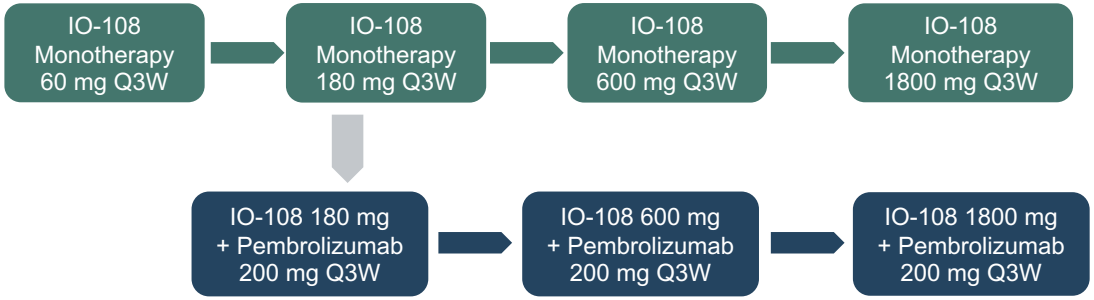
Key Eligibility Criteria

- Any histologically or cytologically confirmed advanced or metastatic solid tumor
- Received, has been intolerant to, or has been ineligible for standard systemic therapy known to confer clinical benefit
- Measurable disease per RECIST v1.1 as assessed by local clinical site
- Fresh pre- and on-treatment biopsies

Objectives

- **Primary:** Safety and tolerability
- **Secondary:** PK, efficacy, immunogenicity
- **Exploratory:** PD, biomarkers, long-term efficacy

Modified Toxicity Probability Interval



Cross-over allowed at PD
Intra-patient escalation allowed

Patient Disposition

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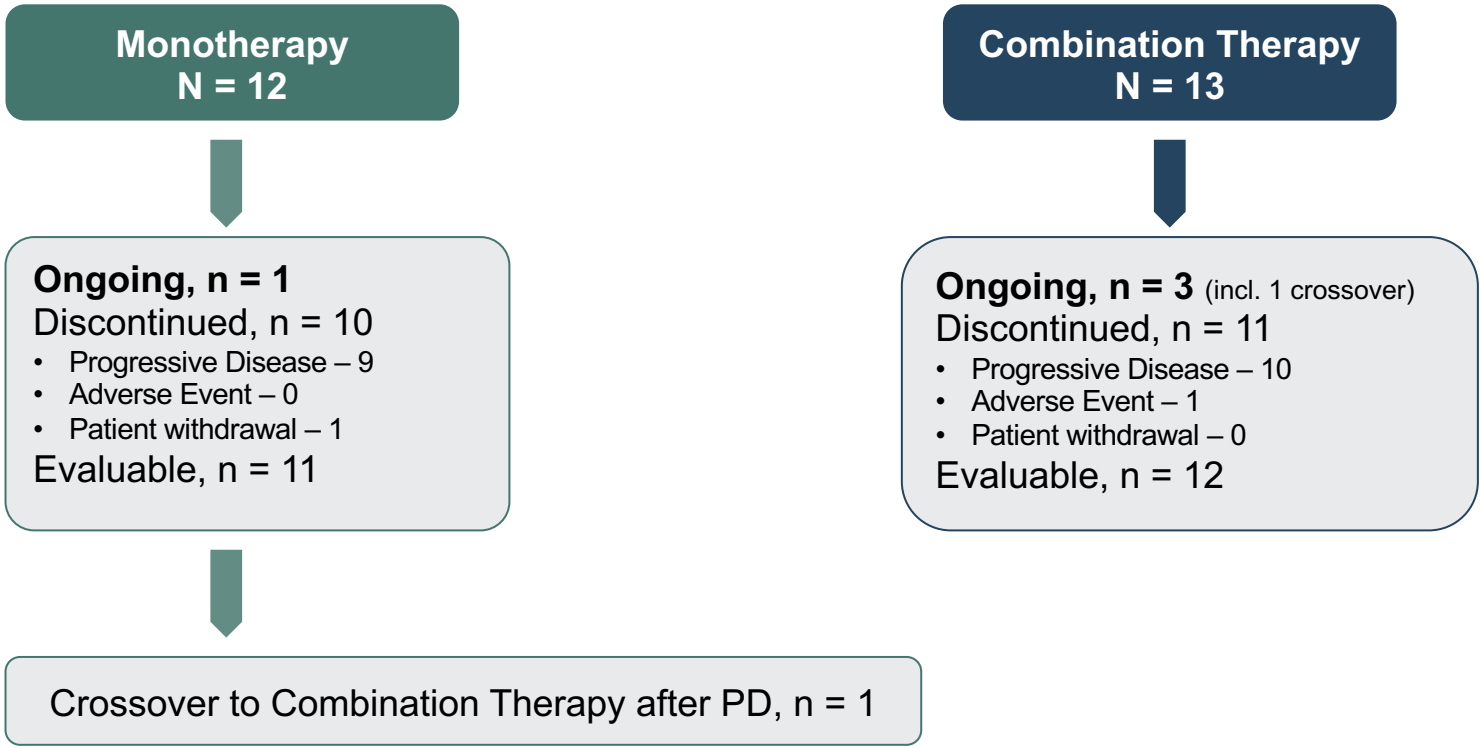

Data cut-off: 3/13/2023

Baseline Characteristics

		IO-108 Monotherapy N = 12	IO-108 + Pembrolizumab N = 13	Total N = 25
Age, median (range), years		54 (26 - 79)	66 (54 - 71)	66 (26 – 79)
Sex, F/M, n		9/3	6/7	15/10
ECOG PS, n	0	3	2	5
	1	9	11	20
Prior Line of Tx.		Median 4.5	Median 3.5	Median 4
1		0	0	0
2		4	4	8
3 or greater		8	9	17
Previous anti-PD-(L)1 Tx. (%)		4 (33%)	6 (46%)	10 (40%)
Tumor Types		Colorectal cancer		9
		Pancreas cancer		5
		Cholangiocarcinoma		2
		1 Each - Appendiceal ca., Adrenocortical ca., Breast ca., ccRCC, Unk primary ca., Merkel Cell Ca., Ovarian ca., Bladder ca., H&N ca.		9

Adverse Event Summary

AE, n (%)	IO-108 Monotherapy N = 12	IO-108 + Pembrolizumab N = 13
Any grade Treatment-Emergent AE	12 (100)	12 (92.3)
Grade 3-5	3 (25.0)	8 (61.5)
Led to discontinuation	1 (8.3)	2 (15.4)
Serious	1 (8.3)	8 (61.5)
Serious and led to discontinuation	1 (8.3)	2 (15.4)
Led to death	0	2 (15.4)
Any grade Treatment-Related AE	6 (50.0)	6 (46.2)
Grade 3-4 TRAE	0	0
TRAE led to discontinuation	0	0
Serious TRAE	0	0
Serious TRAE and led to discontinuation	0	0
Led to death	0	0

Data cut-off: 3/13/2023

- No serious adverse events (SAEs) or deaths were related to IO-108
- No dose limiting toxicities (DLTs) were observed
- Maximum tolerated dose (MTD) was not reached through the pre-planned highest dose (1800 mg)
- Frequent TRAEs - pruritus (n=4), myalgia (n=3) and diarrhea (n=2); all were Gr 1 or 2

BOR per Investigator- Assessed RECIST 1.1

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	IO-108 Monotherapy N = 12	IO-108 + Pembrolizumab N = 13
Efficacy Evaluable, n	11	12 +1 crossover
ORR (%)	1 (9.1)	3 (23.1)
CR	1 (9.1)	0 (0)
PR	0 (0)	3 (23.1)
SD	4 (36.4)	4 (30.8)
PD	6 (54.5)	6 (46.1)
Not Evaluable	1	1

Responses were observed in Merkel Cell Carcinoma, 2 cholangiocarcinoma (MSS) and colorectal ca (MSS) patients

Data cut-off: 3/13/2023

Durable Responses in IO-108 Dose Escalation

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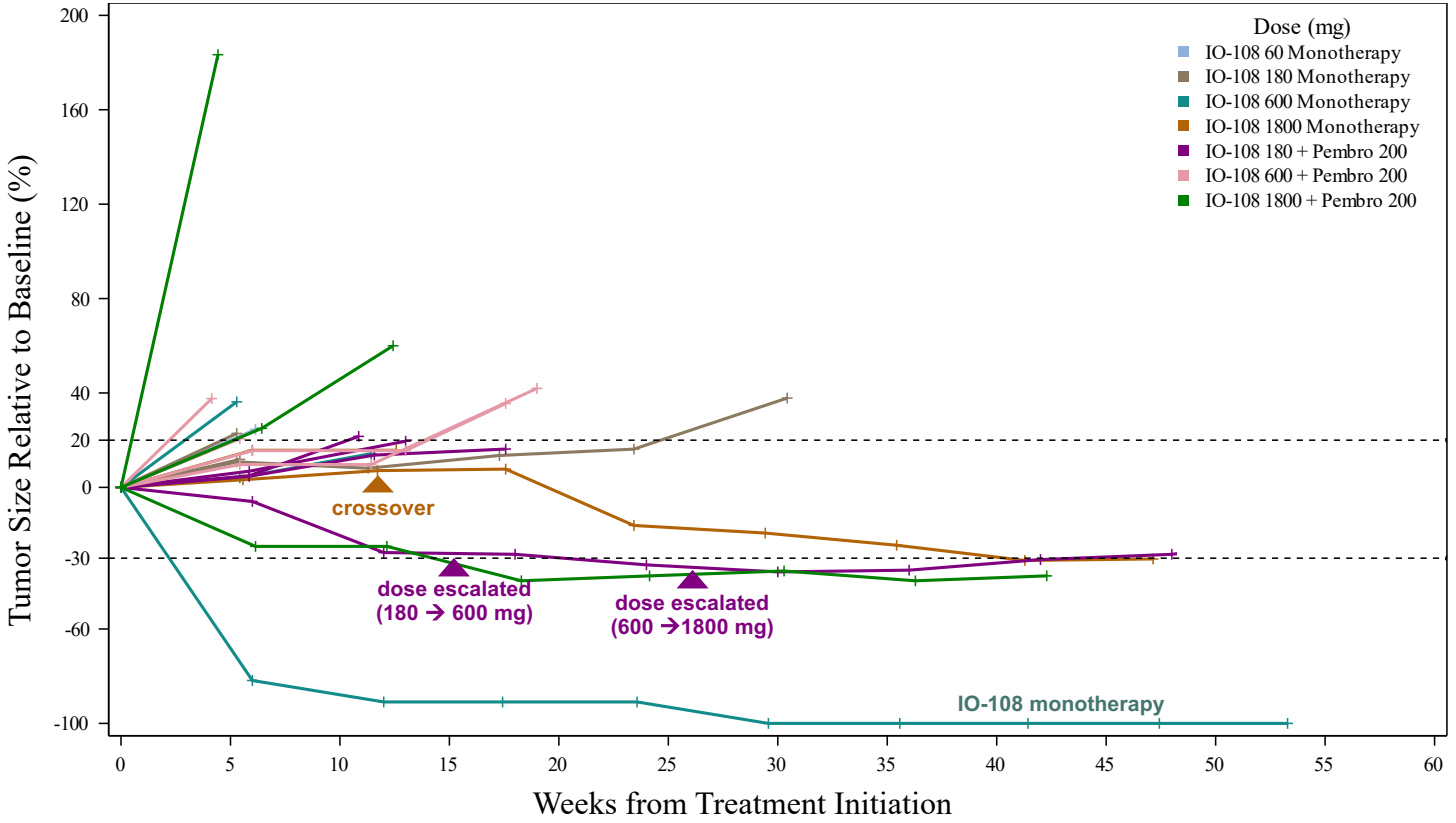

Data cut-off: 3/13/2023

Complete Response in a Merkel Cell Ca. Patient

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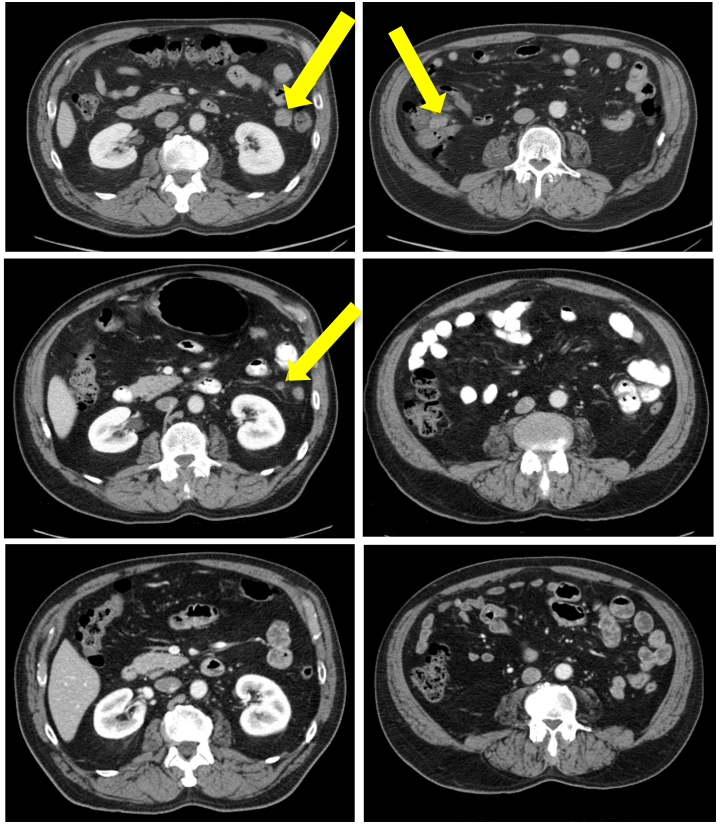
- **Initial therapy:**
  - Surgical resection and adjuvant RT
  - Positive for Merkel Cell Polyomavirus
- **Metastatic disease:**
  - Pembrolizumab
  - Ipilimumab/nivolumab
  - Palliative radiation therapy to metastatic sites (left upper arm, right supraclavicular lymph node, left tonsil metastases).
- **IO-108 monotherapy (600 mg) administered 82 days since stopping ipilimumab/nivolumab**
  - Achieved 82% reduction in sizes of targeted lesions by CT scan, after only 6 weeks on IO-108.
  - At 7 months, achieved a CR.
  - CR ongoing 13 months+ as of 3/2023

2/16/22 baseline CT

4/3/22 1st restaging CT

9/15/2022 restaging CT



Saturation of Clearance and LILRB2 Receptors Were Observed Following the First Dose at the Dose Range Tested

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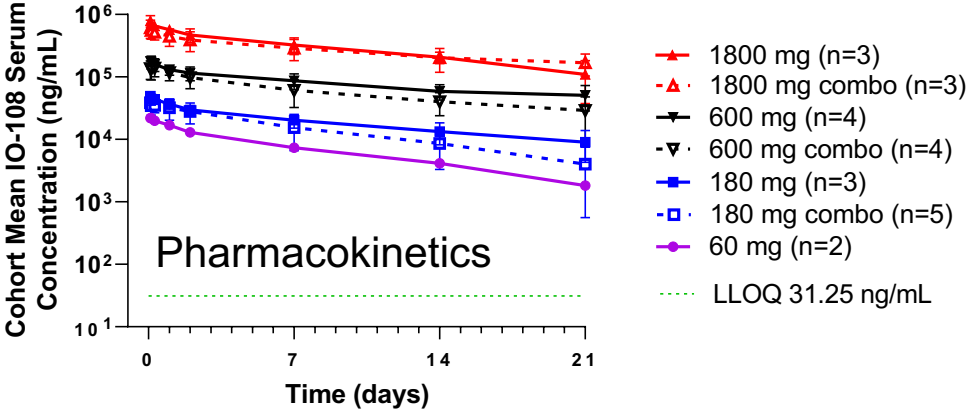

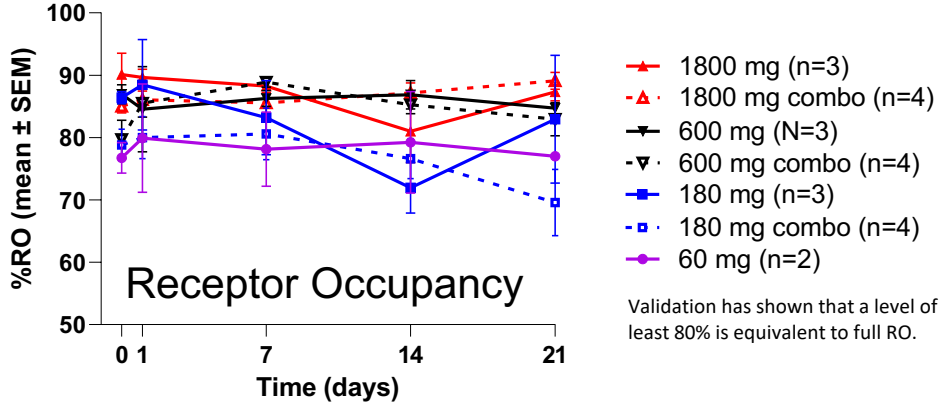

Validation has shown that a level of at least 80% is equivalent to full RO.

- At doses ranging from 180 mg to 1800 mg, IO-108 demonstrated a dose proportional increase in exposure
- Full receptor occupancy (RO) was achieved at doses ≥ 600 mg
- RP2D at 1200 mg is projected to achieve full RO at C_{trough} in ≥ 90% patients in blood circulation following first dose

A Trend of Increased T Cell Activation In Patients With Clinical Benefit (Monotherapy)

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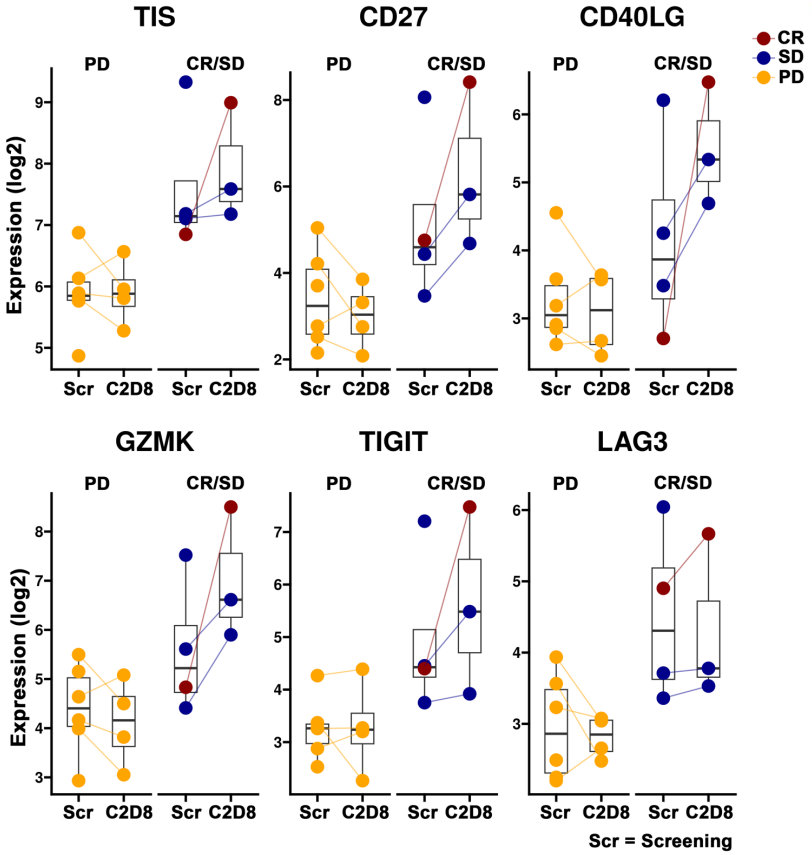

- NanoString profiling of tumor tissues at baseline and post IO-108 treatment at C2D8 as monotherapy (See figures on left)
  - Increased markers of T cell activation correlated with clinical benefit (similar trend observed in combination with pembrolizumab – data not shown)
  - Baseline tumor inflammation scores correlated with clinical benefit, both in monotherapy and in combination with pembrolizumab

- TIS: tumor inflammation signature (18 genes) enriches for clinical benefit to immune checkpoint blockade:
- CCL5, CD27, CD274, CD276, CD8A, CMKLR1, CXCL9, CXCR6, HLA-DQA1, HLA-DRB1, HLA-E, IDO1, LAG3, NK67, PDCD1LG2, PSMB10, STAT1, TIGIT
- CD27, CD40L, TIGIT, LAG3: T cell activation;
- GZMK: an effector molecule in NK or CD8 T cells

Summary and Conclusions

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- IO-108 was well tolerated up to 1800 mg, both in monotherapy and in combination with pembrolizumab
  - No DLT was observed, and the MTD was not reached
- Durable responses were observed in patients treated with both IO-108 monotherapy and IO-108 in combination with pembrolizumab
  - Merkel Cell Ca. patient who had PD on prior anti-PD-1/anti-CTLA4 therapies achieved CR on IO-108 monotherapy
  - 2 cholangiocarcinoma and 1 colorectal ca. patients (all MSS) achieved PR
- RP2D at 1200 mg is projected to achieve full receptor occupancy at C_{trough} in ≥ 90% patients
  - Full receptor occupancy (RO) was achieved at doses ≥ 600 mg
  - Clinical benefit correlated with baseline characteristics and post-treatment changes in PD biomarkers
- These encouraging data support the further development of IO-108 as monotherapy and in combination with an anti-PD-(L)1 therapy in patients with advanced solid tumors
  - Expansion cohorts are ongoing in various advanced solid tumors

Acknowledgments

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