Phase 1 Study of the Arginase Inhibitor INCB001158 (1158) Alone and in Combination with Pembrolizumab (PEM) in Patients (Pts) with Advanced/Metastatic (Adv/Met) Solid Tumors

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- On advisory board of CytomX Therapeutics and Novartis
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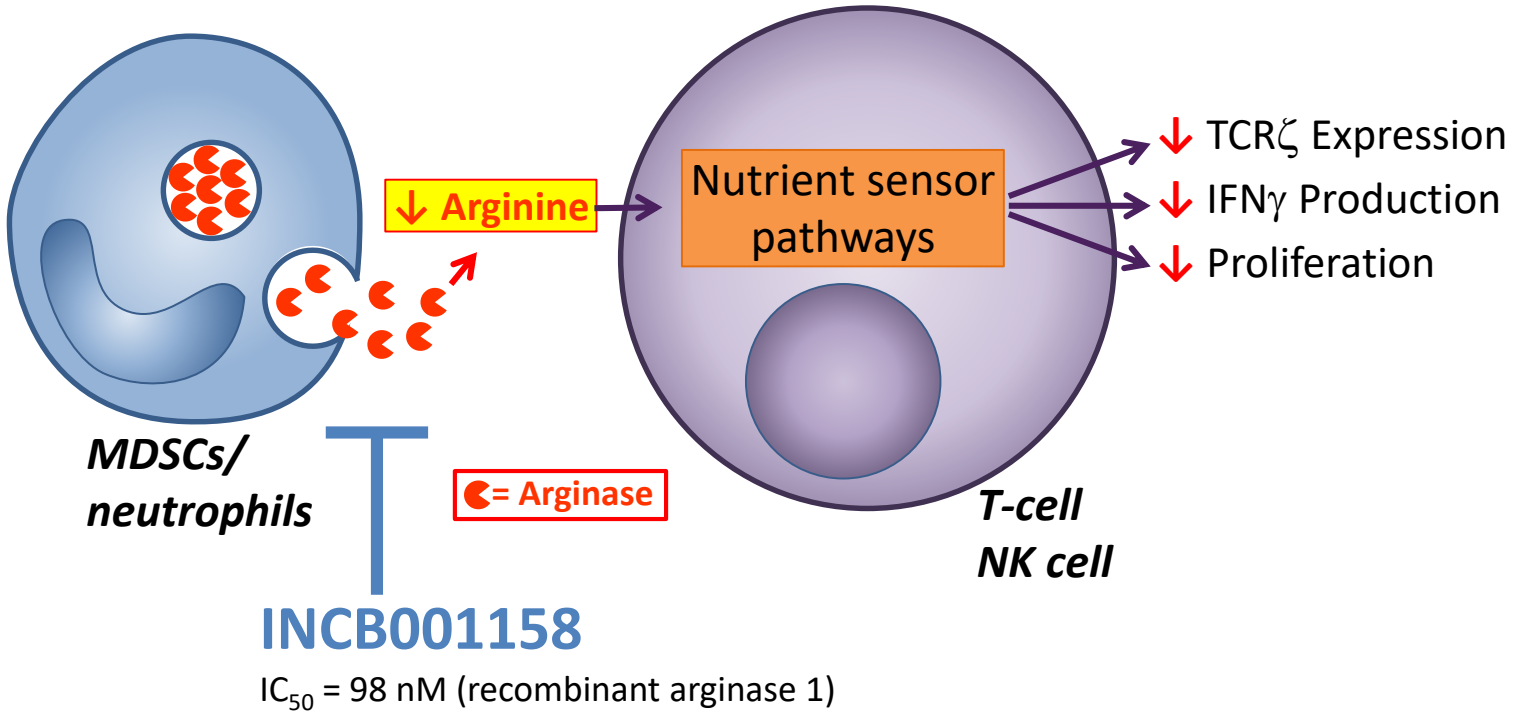
Arginase is a Key Immunosuppressive Enzyme in Tumors

Blocks T- and NK cell function

- Myeloid cells infiltrate tumors, secrete arginase, and deplete arginine[1,2]
- INCB001158 is an oral inhibitor of arginase that restores tumor arginine in preclinical studies[3]
- INCB001158 offers a novel strategy to relieve tumor immunosuppression and enhance checkpoint inhibitor activity
- INCB001158 is being explored in several clinical studies in solid tumors and hematologic malignancies[4]



IC_{50}, half maximal inhibitory concentration; IFNγ, interferon-γ; MDSC, myeloid-derived suppressor cells; NK, natural killer; TCR, T cell receptor

[1]Rodriguez et al. Front Immunol. 2017;8:93; [2]Morris. Br J Pharmacol 2009;157(6):922-930; [3]Steggerda et al. J Immunother Cancer 2017;5:101; [4]NCT02903914; NCT03314935; NCT03837509.

Study Design (NCT02903914)

Key Eligibility Criteria

- Metastatic or locally advanced cancer not amenable to local therapy
- ECOG PS 0-1
- Measurable disease per RECIST 1.1

3+3 Dose Escalation[a]

MONOTHERAPY

INCB001158 (50-1000 mg BID)
Solid Tumors (All-Comers)

→ **MTD/ RP2D**

COMBINATION THERAPY

INCB001158 (50-100 mg BID)
+ Pembrolizumab (200 mg IV q3w)
Expansion Cohort Populations

→ **MTD/ RP2D**

Tumor Expansion (Simon 2-Stage)

- Non-Small Cell Lung Cancer[a]
- Colorectal Carcinoma[a]
- Other Solid Tumors ('Basket')[a,c]

PD-(L)1-naive

- MSS Colorectal Carcinoma
- SCCHN
- Gastric/GEJ
- Mesothelioma

PD-(L)1 refractory[b]

- Non-Small Cell Lung Cancer
- Urothelial Carcinoma
- Melanoma
- MSI Colorectal Carcinoma

Primary endpoint: Safety/tolerability
Secondary endpoints: Recommended phase 2 dose (RP2D), anti-tumor effects
Other: PK, PD, biomarkers

[a]Disease progression following treatment with all available therapies known to confer clinical benefit.
[b]Actively progressing on immediately preceding anti-PD-(L)1 or no better than stable disease for 6 months on pembrolizumab.
[c]Not included in Simon 2-Stage
BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; IV, intravenous; MSI, microsatellite instable; MSS, microsatellite stable; MTD, maximum tolerated dose; q3w,every 3 weeks; RP2D, recommended phase 2 dose; SCCHN, squamous cell carcinoma of the head & neck

Demographics and Patient Characteristics

Baseline Characteristics		INCB001158 Monotherapy N=107	INCB001158 + Pembrolizumab N=138	
			PD-(L)1-naïve n=86	PD-(L)1-exposed n=52
Median age, years (range)		64 (39-87)	62 (32–92)	62.5 (34–79)
Male, n (%)		53 (50)	58 (67)	31 (60)
Median lines prior therapies in advanced/metastatic setting, n (range)		3 (0–11)	2 (0–11)	2 (0–8)
ECOG PS, n (%)	0	23 (22)	25 (29)	20 (38)
	1	84 (79)	61 (71)	32 (62)

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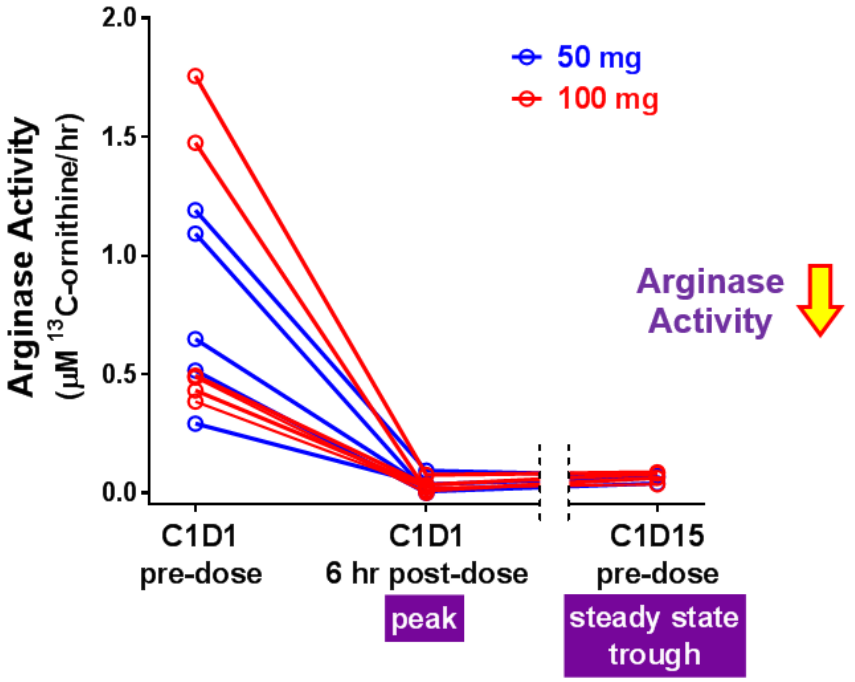
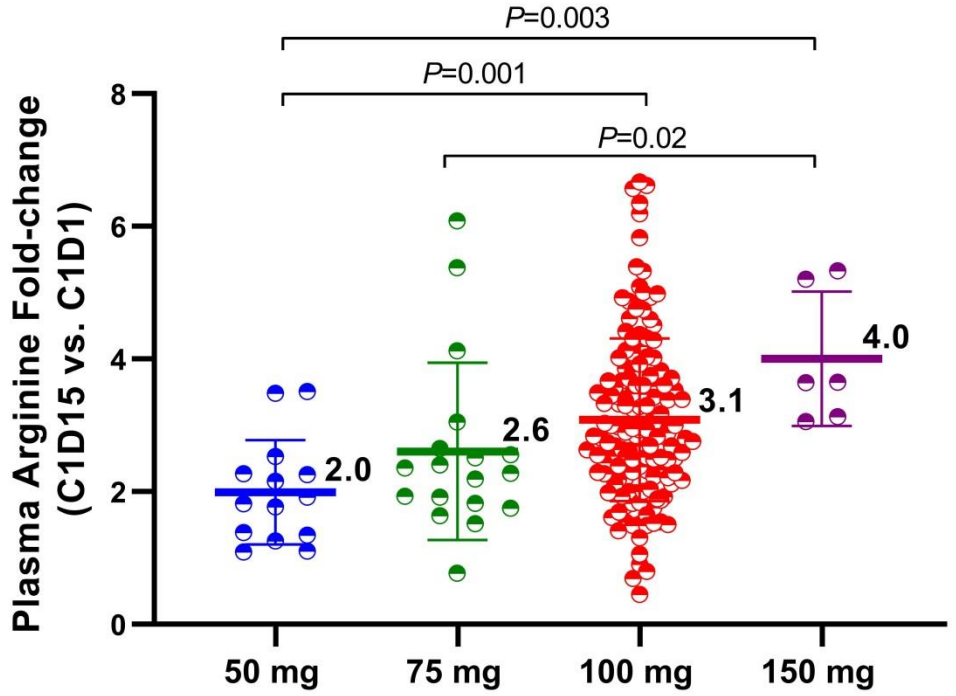
NOTE: Additional patients were enrolled during dose escalation at safe dose levels for biomarker assessments.
ECOG PS, Eastern Cooperative Oncology Group performance status

Arginase Inhibition and Increase in Plasma Arginine Post-Dosing with INCB001158 Monotherapy

Potent Target Inhibition at All Doses Evaluated[a]



Dose-Related Increases in Plasma Arginine[a]



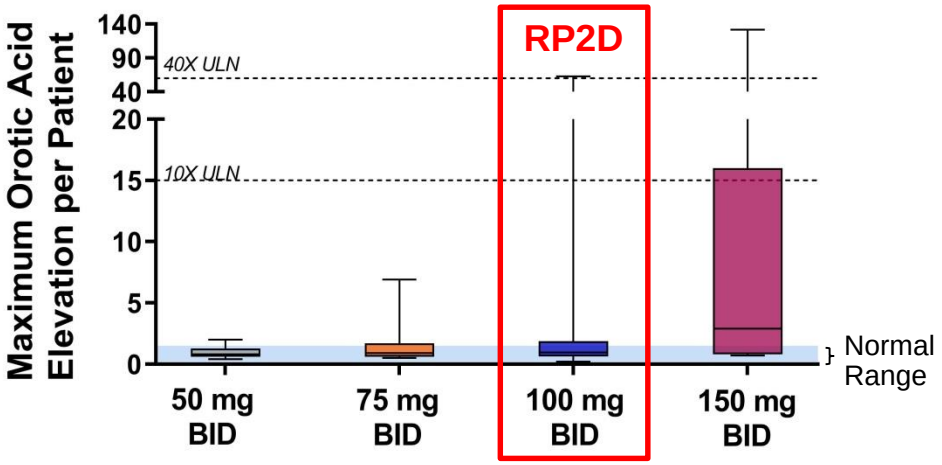
- Steady-state INCB001158 pharmacokinetics at trough exceeded the arginase IC_{90} at all doses
- INCB001158 inhibited plasma arginase activity
- INCB001158 induced dose-related increases in mean plasma arginine

[a]Effects on arginase inhibition and plasma arginine levels were similar in patients receiving INCB001158 in combination with pembrolizumab (data not shown).
BID, twice daily; C, cycle; D, day RP2D, recommended phase 2 dose

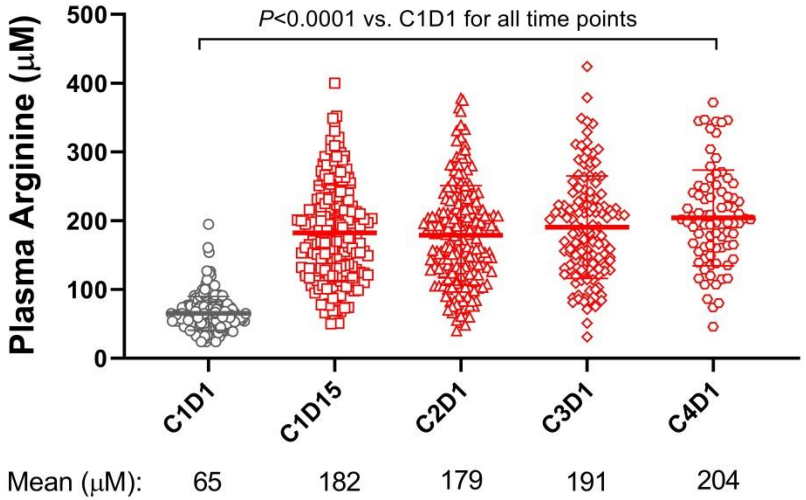
Dose Escalation and RP2D Selection

- Doses of 50–150 mg BID were explored during dose escalation
- MTD was not reached
  - Monotherapy: 1 DLT (Gr 2 malaise) at 150 mg BID
  - Combination: 1 DLT (Gr 3 pneumonitis) at 75 mg BID
- No clinically significant urea cycle inhibition[a] at any dose
  - Urinary orotic acid (uOA) is a highly sensitive biomarker of urea cycle inhibition
- RP2D of 100 mg BID was selected for monotherapy and combination based on:
  - Strong pharmacodynamic inhibition of arginase and durable elevation in plasma arginine[b]
  - Absence of clinically significant urea cycle inhibition

INCB001158 Monotherapy
Dose-Related Effects on Urea Cycle



Effect on Plasma Arginine at RP2D (100 mg BID)[b]



NOTE: In bar graphs, the line represents the median; the box represents the 25%-75% range, and whiskers represent range.
[a]Defined as concomitant elevations in plasma ammonia, uOA
[b]Effects on plasma arginine levels were similar in patients receiving INCB001158 in combination with pembrolizumab (data not shown)
BID, twice daily; C, cycle; CNS, central nervous system; D, day; DLT, dose-limiting toxicity; Gr, grade;
MTD, maximum-tolerated dose; RP2D, recommended phase 2 dose

Safety Summary

INCB001158 Monotherapy and Combination with Pembrolizumab

Treatment-related AEs occurring in ≥5% of patients receiving INCB001158 at RP2D (100 mg BID)

(A) Monotherapy

AE, n (%)	INCB001158 Monotherapy (n=85)	
	Any Grade	Grade 3-4
Any AE	28 (33)	3 (4)
Fatigue	8 (9)	1 (1)
Constipation	6 (7)	0
Decreased appetite	6 (7)	1 (1)
Nausea	5 (6)	0

(B) Combination with Pembrolizumab

AE, n (%)	INCB001158 + Pembrolizumab (n=114)	
	Any Grade	Grade 3-4
Any AE	70 (61)	15 (13)
Diarrhea	18 (16)	1 (1)
AST increased	13 (11)	2 (2)
Fatigue	13 (11)	1 (1)
Rash	10 (9)	0
Nausea	9 (8)	0
ALT increased	8 (7)	2 (2)
Constipation	8 (7)	0
Anemia	6 (5)	2 (2)
Hyponatremia	6 (5)	1 (1)
Hypothyroidism	6 (5)	0

- No treatment-related Grade 5 AEs
- Immune-related AEs
  - Monotherapy: Gr 3 colitis (n=1), Gr 2 malaise (n=1)
  - Combination: Consistent w/ pembrolizumab safety profile

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AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Gr, grade;

Tumor Expansion Cohorts – Current Status

Tumor Type		Current Simon 2-Stage Status
Monotherapy	**Colorectal carcinoma (n=37)[a]**	**Stage 2 completed**
	Non-small cell lung cancer (n=15)	Stage 1 ongoing
	Other solid tumors (n=55)	Completed
Combination w/ Pembrolizumab: PD-(L)1-Naïve	**MSS colorectal carcinoma (n=43)**	**Stage 2 ongoing**
	SCCHN (n=17)	**Stage 2 enrolling**
	Gastric/GEJ (n=13)	Stage 1 ongoing
	Mesothelioma (n=11)	Stage 1 ongoing
Combination w/ Pembrolizumab: PD-(L)1-Refractory	Non-small cell lung cancer (n=16)	Stage 1 ongoing
	Urothelial carcinoma (n=12)	Stage 1 ongoing
	Melanoma (n=14)	Stage 1 ongoing
	MSI colorectal carcinoma (n=7)	Stage 1 ongoing

[a]Not selected based on MSI/MSS status; n=33 with known MSS CRC

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GEJ, gastroesophageal junction; MSI, microsatellite instable; MSS, microsatellite stable; SCCHN, squamous cell carcinoma of the head & neck

MSS CRC Monotherapy and Combination Cohorts

Demographics and Patient Characteristics

Baseline Characteristics		INCB001158 Monotherapy n=33	INCB001158 + Pembrolizumab n=43
Median age, years (range)		56 (42–87)	57 (35–80)
ECOG PS, n (%)	0	7 (21)	12 (28)
	1	26 (79)	31 (72)
Median prior lines of therapy in advanced/metastatic setting, n (range)		3 (0–5)	3 (1-11)
Median time since diagnosis, years (range)		3.2 (0.6–13)	3.0 (0.4–15)
Liver metastases, n (%)		24 (73)	28 (65)
Prior anti-PD-(L)1, n (%)		7 (21)	0
KRAS status, n (%)	Mutant	21 (64)	29 (67)
	Wild-type	10 (30)	12 (28)
BRAF status, n (%)	Mutant	2 (6)	4 (9)
	Wild-type	23 (70)	26 (60)

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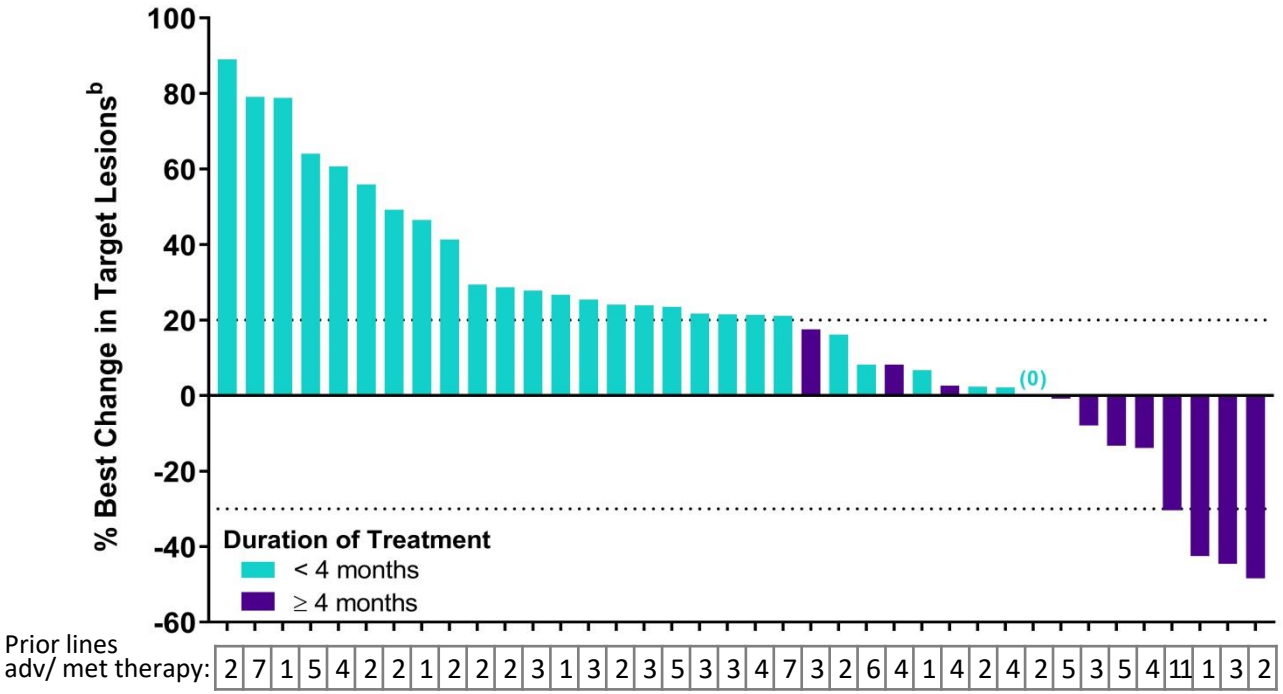
ECOG PS, Eastern Cooperative Oncology Group Performance Status

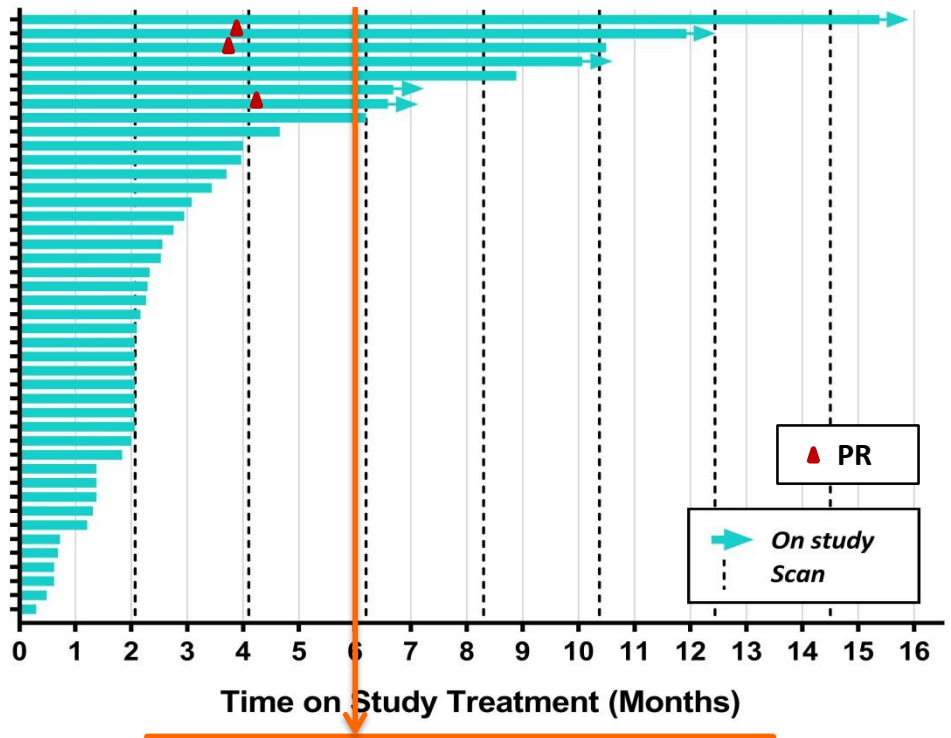
Objective Responses and Treatment Duration with INCB001158 in MSS CRC

- **INCB001158 Monotherapy (N=33[a]):** 3% ORR, 27% DCR
- **INCB001158 + Pembrolizumab (N=43[a]):** 7% ORR, 30% DCR

Combination with Pembrolizumab



Historic ORR with CPI therapies in 2L/3L MSS CRC: 0-1%[1-4]



6-month PFS rate: 20%
Historic CPI 6-month PFS rate: ~10%[1-4]

[a]Response evaluable patients include those who discontinued treatment without a postbaseline scan for reasons other than unrelated toxicity, death, or withdrawal of consent
[b]37 of 43 response-evaluable patients per protocol had postbaseline scans
CPI, checkpoint inhibitor; CRC, colorectal carcinoma; DCR, disease control rate = ORR + stable disease ≥ 56 days; MSS, microsatellite stable; ORR, objective response rate; PFS, progression-free survival; PR, partial response
[1]Le et al, NEJM 2015;372:2509-2520; [2]Eng et al, Lancet Oncol 2019; 20:849-861; [3]Brahmer et al. NEJM 2012;366(26):2455-65; [4]Chen et al JCO 2019;37(suppl):abstr 3512

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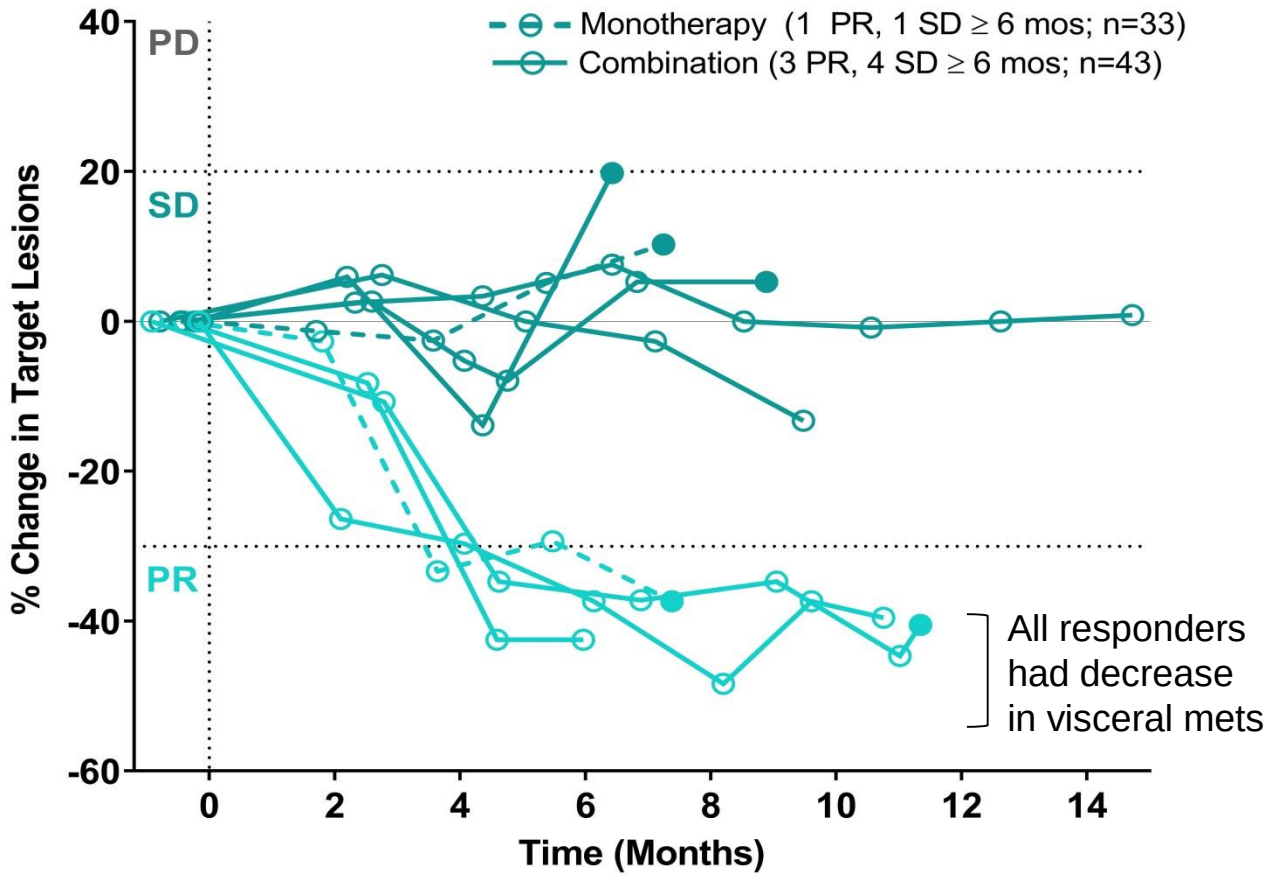
Disease Characteristics of MSS CRC Patients with Response or Prolonged Stable Disease

Disease Features

Disease Feature	PR or SD ≥ 6 months	
	Monotherapy (n=2/33)	Combination (n=7/43)
≥2 prior lines of therapy	2/2	7/7
Progressed within 6 on prior therapy	2/2	5/7
≥4 RECIST-evaluable lesions	2/2	4/7

Change in Target Lesions Over Time



Closed circle: off study

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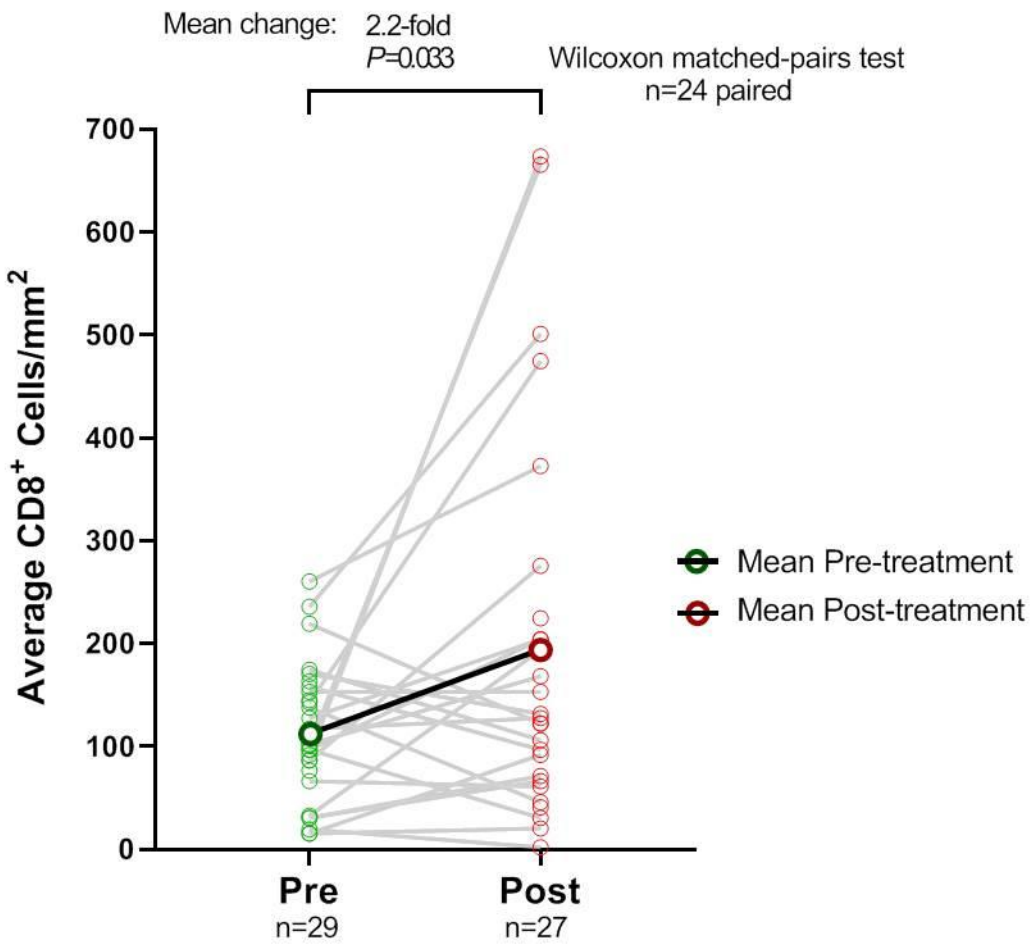
CRC, colorectal carcinoma; MSS, microsatellite stable; PR, partial response; RECIST, response-evaluable criteria in solid tumors; SD, stable disease; VEGF, vascular endothelial growth factor

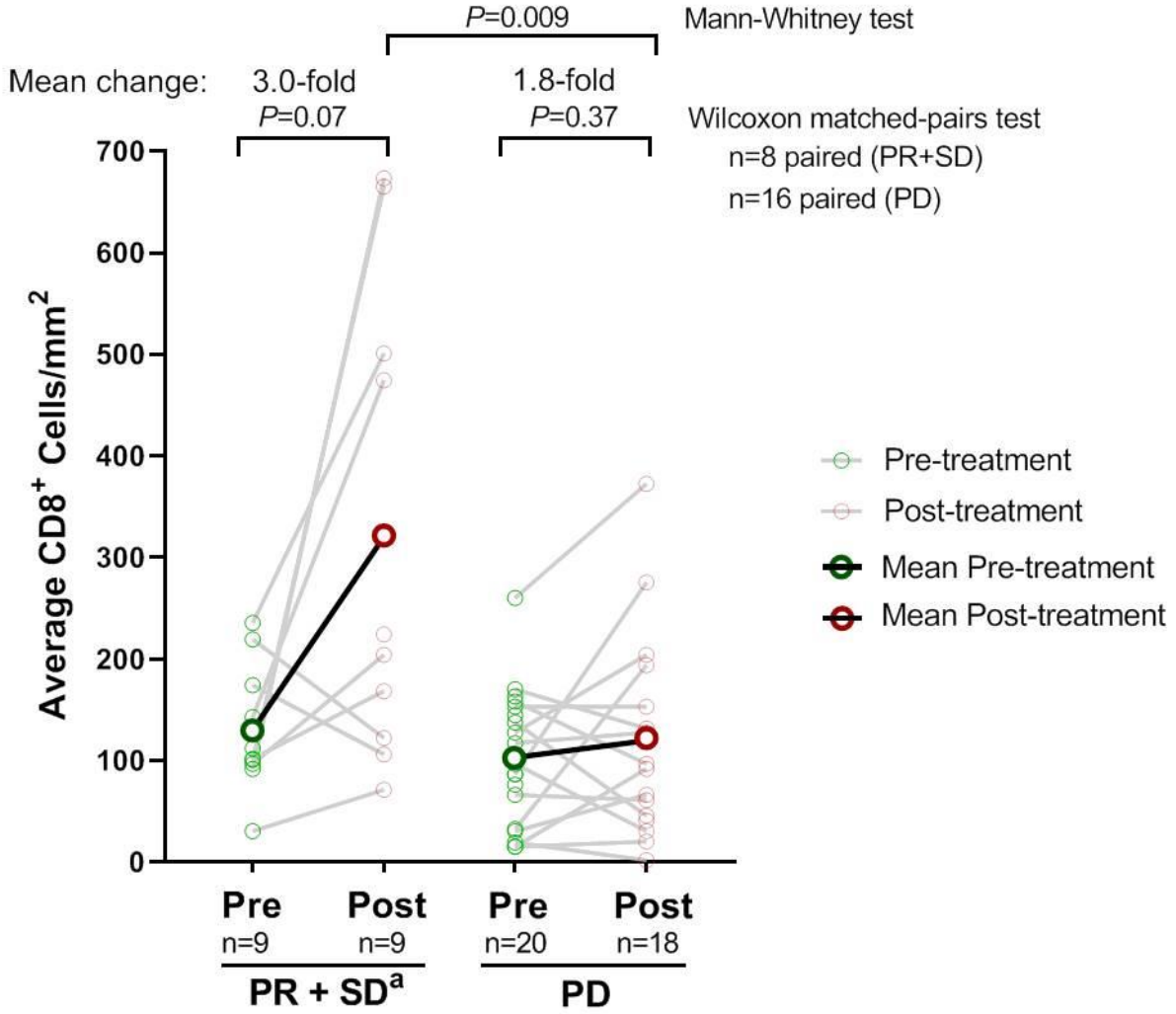
Biomarker Analysis: INCB001158 + Pembrolizumab in MSS CRC

Pharmacodynamic increases in total intratumoral CD8⁺ cells post-treatment

Increase in CD8⁺ cells post-treatment



Trend towards greater CD8⁺ increase in patients with PR or SD[a]



[a]SD ≥56 days

NOTE: Mean pre- and post-treatment (Day 29) values include non-paired samples; non-evaluable patients excluded from the analysis. *P*-values are provided for descriptive purposes only.

CRC, colorectal carcinoma; MSS, microsatellite stable; PR, partial response; PD, progressive disease; SD, stable disease

Conclusions

- INCB001158 is the first arginase inhibitor in clinical trials
- INCB001158 was well tolerated alone and in combination with pembrolizumab
- RP2D of 100 mg BID based on strong pharmacodynamic effect and lack of significant urea cycle inhibition
- Responses were observed in MSS CRC, a tumor type refractory to PD-(L)1 therapy
  - 1 monotherapy response (n=33) in a patient who had progressed on immediate prior PD-(L)1 exposure
  - 3 responses in combination with pembrolizumab (n=43); 6-month PFS rate of 20%
- Pharmacodynamic increases in total intratumoral $CD8^+$ cells were seen post-treatment with INCB001158 + pembrolizumab in MSS CRC patients
- Clinical studies of arginase inhibition with INCB001158 in solid tumors and hematologic malignancies are ongoing

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