CX-1158-101: A First-in-Human Phase 1 Study of CB-1158, a Small Molecule Inhibitor of Arginase, as Monotherapy and in Combination with an anti-PD-1 Checkpoint Inhibitor in Patients with Solid Tumors

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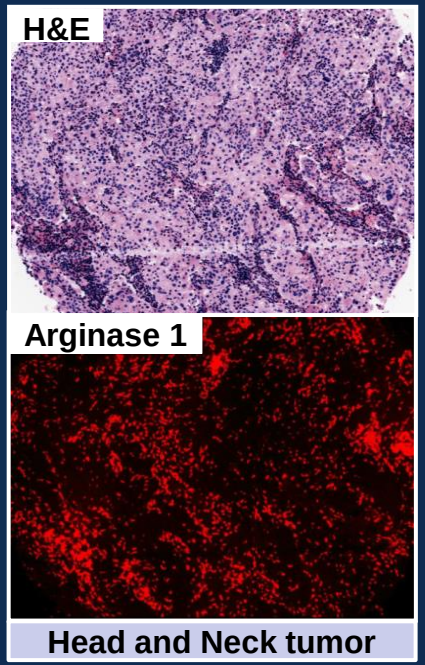
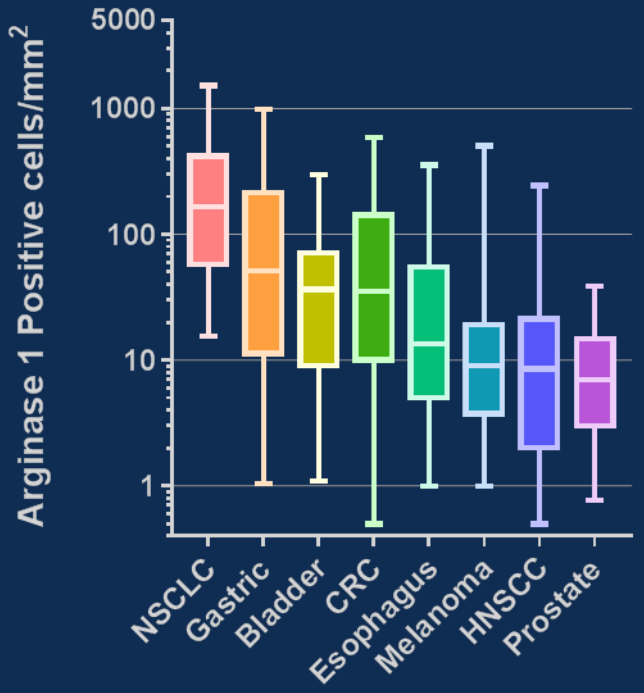
Immunosuppression in the Tumor Microenvironment

- Despite the important advances in immunotherapy, a limited number of patients derive significant benefit from checkpoint inhibitors
- Tumor-infiltrating myeloid cells suppress T-cell and NK cell function and can limit the activity of checkpoint inhibitors
- Arginase is a key immunosuppressive enzyme secreted by tumor-infiltrating myeloid cells
- Inhibiting arginase offers a novel strategy to relieve immunosuppression and to enhance checkpoint inhibitor activity
- CB-1158 is a first-in-class oral arginase inhibitor in a Phase 1 clinical study

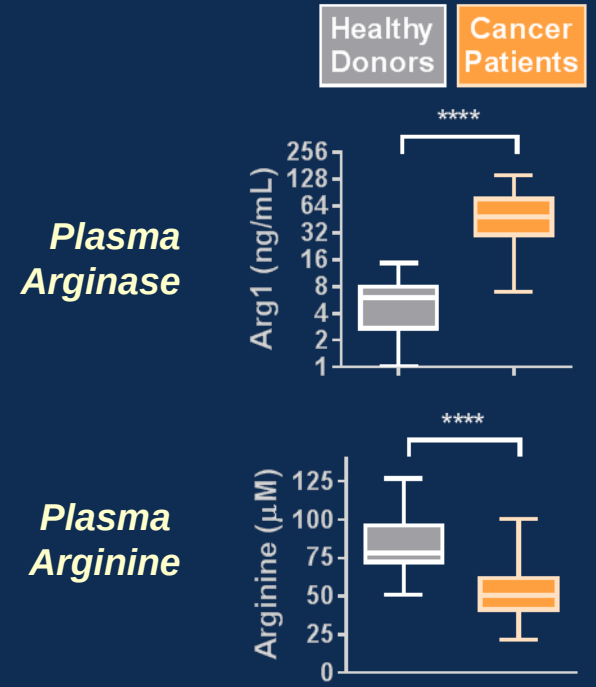
Arginase in Cancer Patients

Arginase-positive myeloid cell infiltrate in tumor tissues





High arginase and low arginine in patient plasma

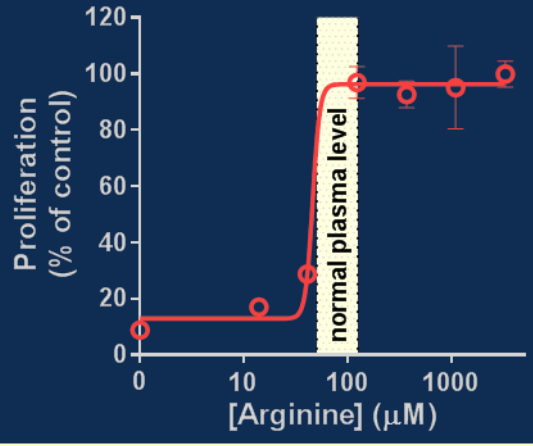


Arginase-Mediated Immune Suppression in Tumor Microenvironment

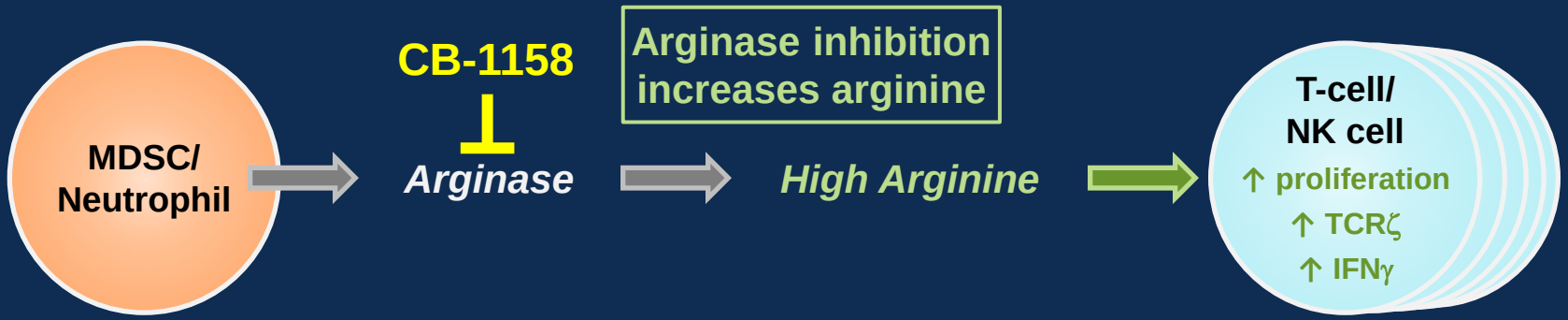
Arginase depletes arginine in tumor

MDSC/ Neutrophil → ***Arginase*** → ***Low Arginine*** → **T-cell/ NK cell**
- ↓ proliferation
- ↓ TCRζ
- ↓ IFNγ

Arginine is required for proliferation of activated CD8+ T-cells



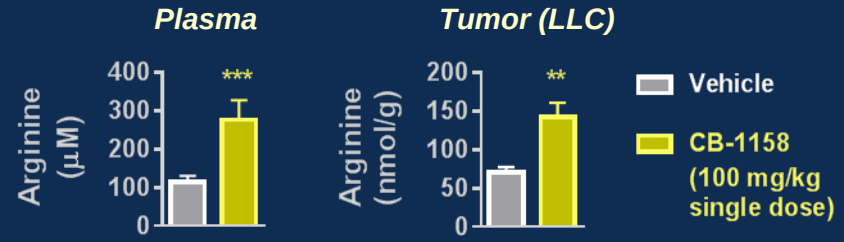
CB-1158 Inhibits Arginase and Overcomes T-cell Suppression



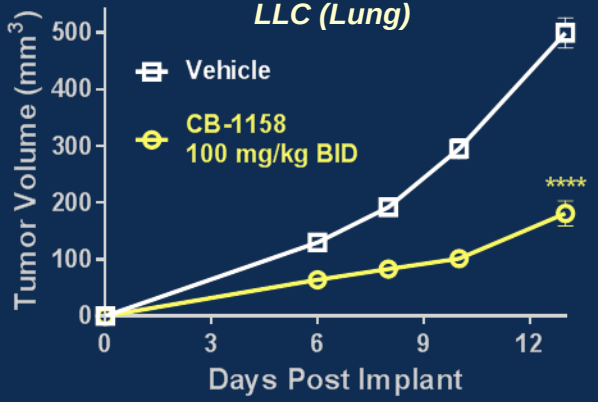
Arginase Assay	CB-1158 IC_{50}
Arginase 1 (recombinant)	98 nM
Reversal of neutrophil-mediated T-cell suppression	200 nM

CB-1158 Has Single Agent and Combination Activity in Syngeneic Tumor Models

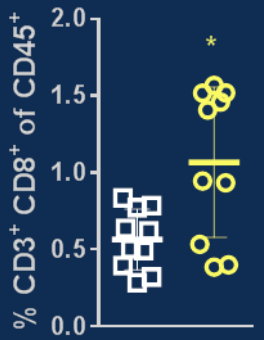
Increased plasma and tumor arginine



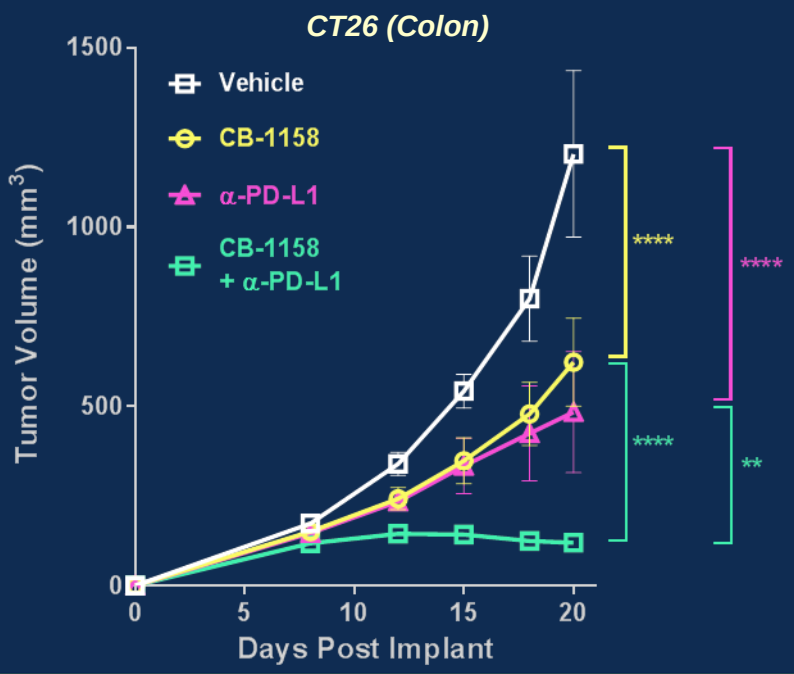
Monotherapy anti-tumor activity



Increased CD8+ TILs



Combination anti-tumor activity with checkpoint inhibitor



CX-1158-101 Phase 1 Study Objectives

- Primary
  - Evaluate the safety and tolerability of CB-1158 in patients with advanced/metastatic and/or treatment-refractory solid tumors
    - Monotherapy
    - Combination with anti-PD-1 therapy
- Secondary
  - Select the recommended Phase 2 dose (RP2D) of CB-1158
    - Monotherapy
    - Combination with anti-PD-1 therapy
  - Determine the PK of CB-1158
  - Evaluate the anti-tumor effect of CB-1158
- Exploratory
  - Evaluate the pharmacodynamic effects of CB-1158 and identify potential biomarkers

CX-1158-101 Phase 1 Study Design

Dose Escalation

Monotherapy

- All-comer patients with advanced/ metastatic solid tumors
- 3+3 design*
- PO dosing, BID schedule

MTD/ RP2D

Dose Expansion Cohorts

- NSCLC
- CRC
- SCCHN, RCC, Gastric, Bladder, Melanoma

Anti-PD-1 Combination Therapy

- Combo with full dose α-PD-1
- NSCLC, RCC, melanoma

MTD/ RP2D

- Prior α-PD-1/PD-L1 therapy
  - NSCLC
  - Melanoma

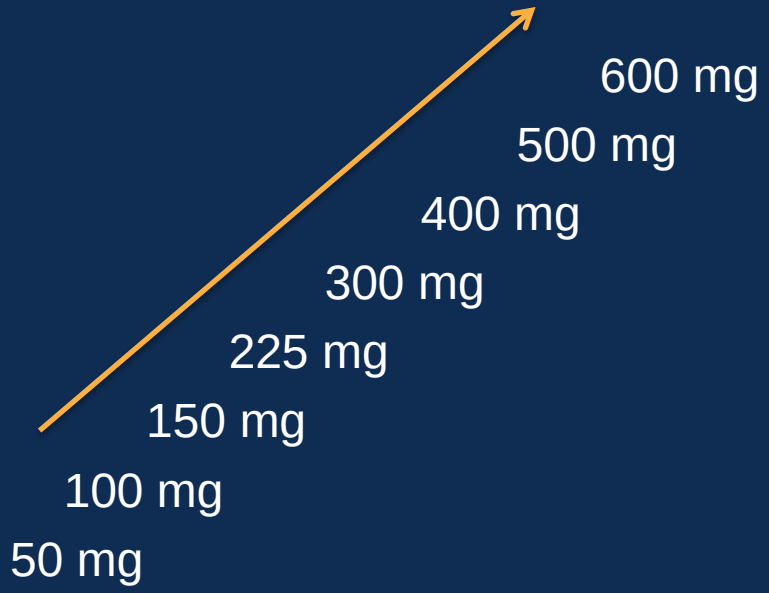
Additional naïve and α-PD-1/ α-PD-L1 refractory tumor types under consideration

*Additional patients enrolled into cleared dose levels for biomarker assessments

CX-1158-101 Phase 1 Patient Selection

- Inclusion:
  - Age ≥18
  - ECOG PS 0-1
  - Adequate renal, hepatic and hematologic function
  - Prior PD1/PDL-1 allowed.
- Exclusion:
  - Immunosuppression pred > 10 mg
  - Autoimmune disease
  - Valproic acid and xanthine oxidase inhibitors

- Dose Levels



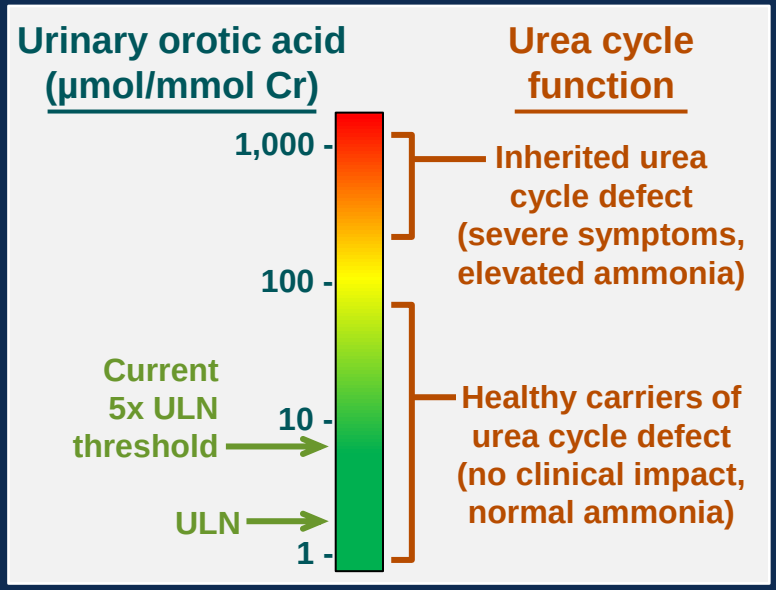
CX-1158-101 Phase 1 Study Assessments

- Safety
  - Standard adverse event (CTCAE) and laboratory monitoring
  - Markers of urea cycle inhibition (plasma ammonia, BUN)
- PK, pharmacodynamics and biomarkers
  - Plasma drug concentration
  - Plasma arginine and arginase activity
  - Arginase expression and immune modulation in the periphery and tumor
  - Urinary orotic acid
- Tumor response
  - Standard RECIST and immune-related RECIST criteria

Urinary Orotic Acid is a Sensitive Biomarker to Monitor Urea Cycle Inhibition

- Arginase is also a urea cycle enzyme
  - "Sequestered" location in hepatocytes
  - Therapeutic window observed in preclinical species
- Urinary orotic acid is a highly sensitive biomarker of urea cycle function
- Urinary orotic acid is being measured in this Phase 1 study
  - Elevations above 5x ULN triggers further evaluation of that dose level

Arginase Function	CB-1158 IC_{50}
Immunosuppression	0.2 µM
Urea cycle	260 µM



Study Demographics

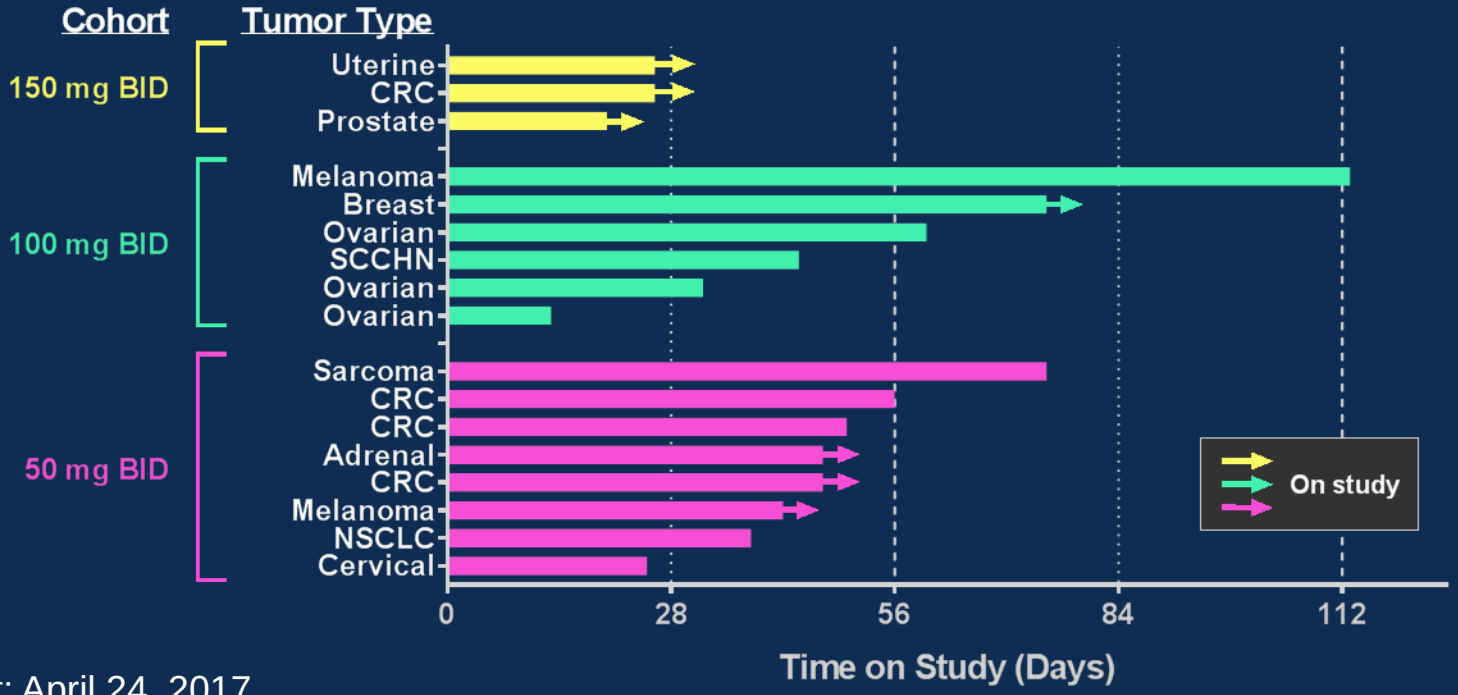
Baseline Characteristics		N=17*
	Age [median (range)]	61 (49-77)
	Female/Male [N (%)]	12 (71)/5 (29)
CB-1158 Dose [N]	50 mg BID	8^
	100 mg BID	6
	150 mg BID	3
Prior systemic regimens	Median (range)	4 (1-11)
	Prior α-PD-1/α-PD-L1 [N (%)]	5 (29)
ECOG [N (%)]	0	2 (12)
	1	15 (88)

*Data cut: April 24, 2017

^Additional patients enrolled for biomarker assessments

Time on Study

17 patients enrolled with 7 ongoing*



*Data cut: April 24, 2017

Safety: Treatment-Related Events

Treatment-related AEs* (N=17)		
Adverse Event	Total [N (%)]	≥Grade 3 [N (%)]
Patients with Any AE	3 (18)	0 (0)
Anemia	1 (5.9)	0 (0)
Fatigue	1 (5.9)	0 (0)
Increased AST	1 (5.9)	0 (0)
Myalgia	1 (5.9)	0 (0)

*Data cut: April 24, 2017

- No drug-related SAEs
- Reversible elevations of urinary orotic acid above 5X ULN threshold at 150 mg dose level (2 of 3 patients)
  - Patients asymptomatic without other evidence of urea cycle inhibition
  - Levels comparable to healthy heterozygous carriers for urea cycle defects
  - Additional evaluation of 150 mg dose level ongoing

Pharmacokinetics

Cohort (N)	$T_{1/2}$ (C1D1) (hr)	C_{max} (C1D15) (μM)	C_{min} (C1D15) (μM)	AUC_t (C1D15) (μM*hr)
50 mg BID (5^)	6.2 ± 1.0	3.3 ± 0.5	1.6 ± 0.6	30.2 ± 6.5
100 mg BID (6^)	6.0 ± 0.6	8.4 ± 1.4	4.1 ± 0.5	80.6 ± 12.2
150 mg BID (3)	5.0 ± 0.5	9.9 ± 2.4	4.4 ± 0.8	85.5 ± 7.6

^N=4 for steady state values on C1D15

Pharmacokinetics

Cohort (N)	$T_{1/2}$ (C1D1) (hr)	C_{max} (C1D15) (μM)	C_{min} (C1D15) (μM)	AUC_t (C1D15) (μM*hr)
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100 mg BID (6^)	6.0 ± 0.6	8.4 ± 1.4	4.1 ± 0.5	80.6 ± 12.2
150 mg BID (3)	5.0 ± 0.5	9.9 ± 2.4	4.4 ± 0.8	85.5 ± 7.6

^N=4 for steady state values on C1D15

- Six hour half-life:
  - Supports BID dose schedule
  - Consistent with renal clearance predicted from preclinical studies

Pharmacokinetics

Cohort (N)	$T_{1/2}$ (C1D1) (hr)	C_{max} (C1D15) (μM)	C_{min} (C1D15) (μM)	AUC_t (C1D15) (μM*hr)
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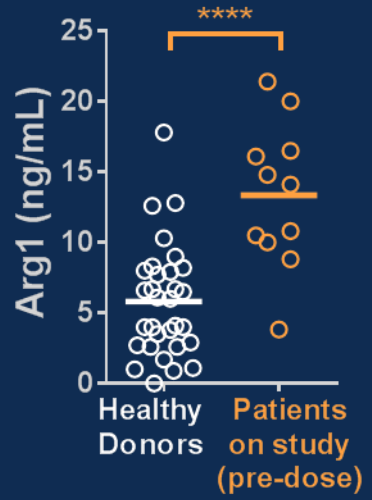
150 mg BID (3)	5.0 ± 0.5	9.9 ± 2.4	4.4 ± 0.8	85.5 ± 7.6

^N=4 for steady state values on C1D15

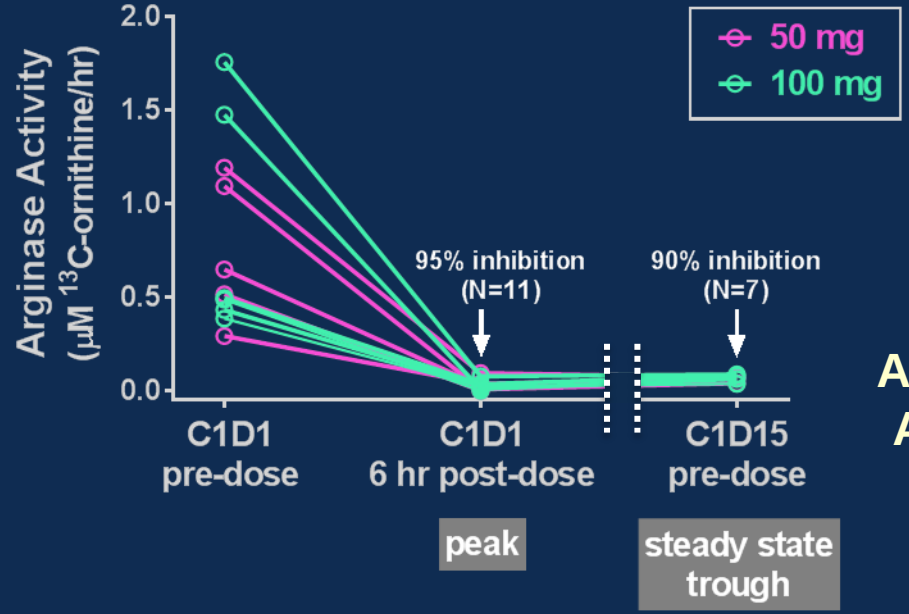
- Steady state trough levels above the IC_{90} for arginase inhibition at all dose levels

CB-1158 Inhibits Arginase in Patient Plasma

Pre-dose Plasma Arginase



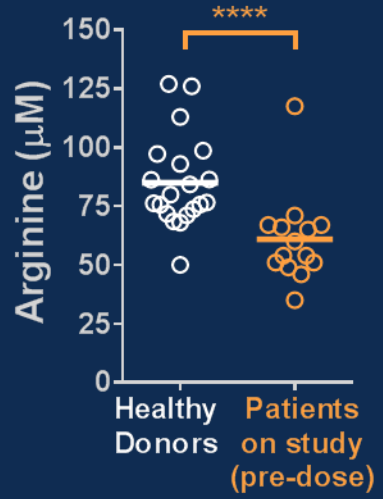
Post-dose Plasma Arginase Activity



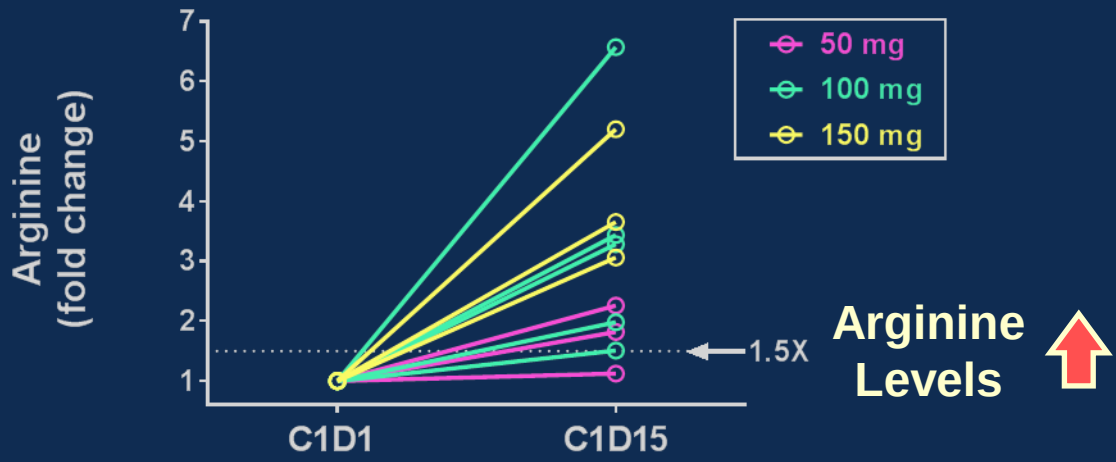
Arginase Activity ↓

CB-1158 Increases Arginine in Patient Plasma

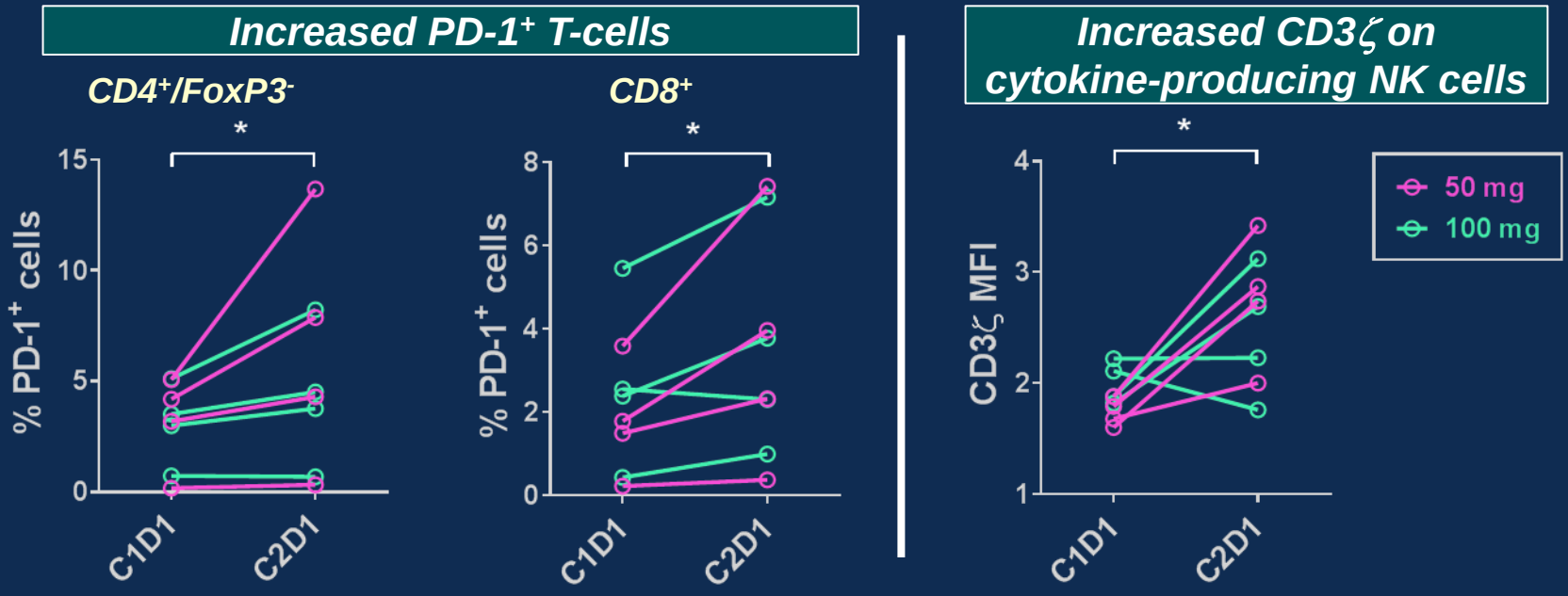
Pre-dose Plasma Arginine



Post-dose Plasma Arginine



Immune Biomarkers: Peripheral Blood



Sub-populations and activation state of T-cells and NK cells by flow cytometry

Conclusions

- CB-1158 is a first-in-class, potent, selective arginase inhibitor
- Oral dosing of CB1158 was well tolerated at all doses tested
- Steady state trough exposure >IC_{90} for arginase, with 90-95% arginase inhibition and increases in plasma arginine
- Preliminary evidence of peripheral immune modulation - to be further explored
- Ongoing Phase 1 study will continue to explore monotherapy as well as the combination with anti-PD-1 therapy in a variety of solid tumor indications

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