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

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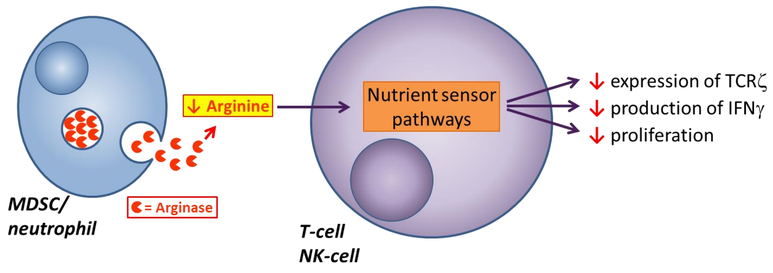
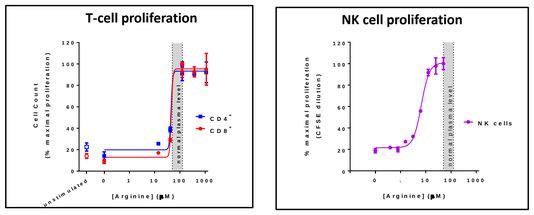
Background and Rationale for Targeting Arginase

- Arginase-expressing myeloid-derived suppressor cells (MDSC) and neutrophils infiltrate many tumor types and are associated with poor prognosis
- Arginase is an immunosuppressive enzyme
  - Depletes arginine, required for the activation and proliferation of T- and NK-cells
- Inhibition of arginase in the tumor microenvironment should restore arginine levels leading to T- and NK-cell activation and proliferation



Arginine Depletion Blocks T-cell and NK cell Activation

Arginine levels below the normal plasma levels (50 -130 uM) in healthy donors suppress T-cell (<40 uM) and NK cells (<10 uM) proliferation respectively

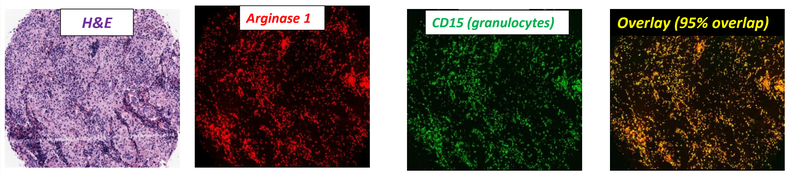


Human T-cells stimulated with anti-CD3/CD28

Human NK cells stimulated with IL-2

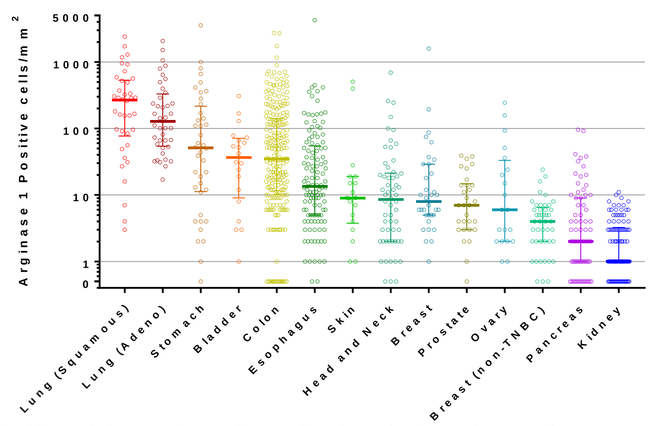
Granulocytic Myeloid Derived Suppressor Cells are the Primary Source of Tumor Arginine

Arginase 1 localizes with granulocyte marker CD15



Immunofluorescent staining of a head and neck tumor labeled with α–arginase 1 and α–CD15

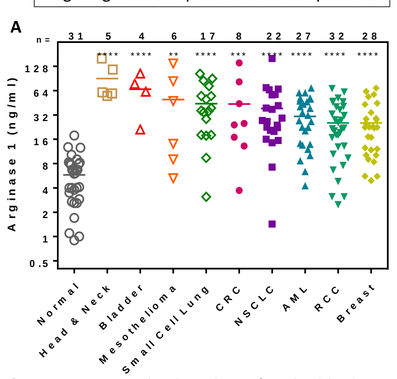
Arginase 1-expressing Myeloid Cells Infiltrate Many Tumor Types



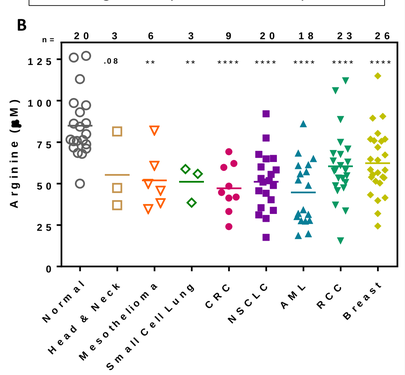
Digital histopathology quantitation of immunohistochemical staining with α–Arg1 of tumor tissues. The number of Arg1+ positive cells per field is plotted for each tumor types

High Plasma Arginase 1 and Low Plasma Arginine in Cancer Patients

High Arginase 1 in plasma of cancer patients



Low arginine in plasma of cancer patients



A) Arginase 1 protein levels in plasma from healthy donors and cancer patients as determined by ELISA. B) Plasma arginine concentrations in healthy donor and cancer patient samples determined by LC/MS.

Preclinical Data Supporting Development of CB-1158

CB-1158 is a Orally Bioavailable, Selective Inhibitor of Human Arginase

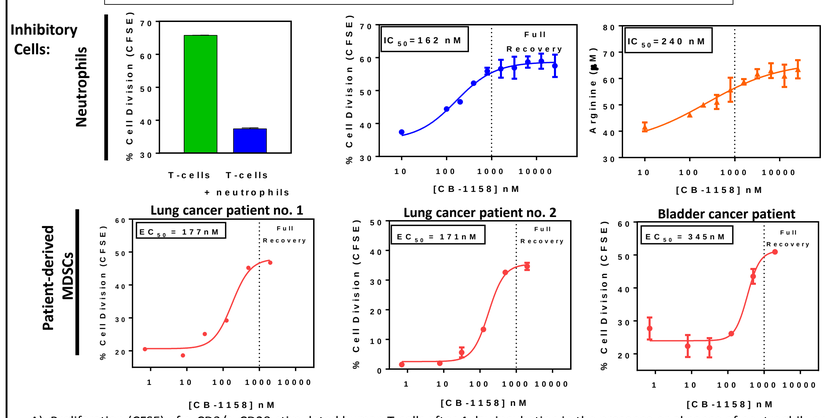
CB-1158 inhibits recombinant arginase, arginase in hepatocyte lysates, neutrophils and RBCs, and arginase in cancer patient plasma

Human Arginase Source	IC_{50}
Arginase 1 (recombinant)	98 nM
Arginase 2 (recombinant)	274 nM
Neutrophil lysate	162 nM
Red blood cell lysate	116 nM
Hepatocyte lysate	139 nM
RCC patient plasma #1	127 nM
RCC patient plasma #2	174 nM

CB-1158 Reverses MDSC-mediated T-cell Suppression

MDSCs and Neutrophils suppress T-cell proliferation in co-culture

CB-1158 maintains arginine levels and reverses neutrophils and patient-derived MDSC suppression of T-cell proliferation

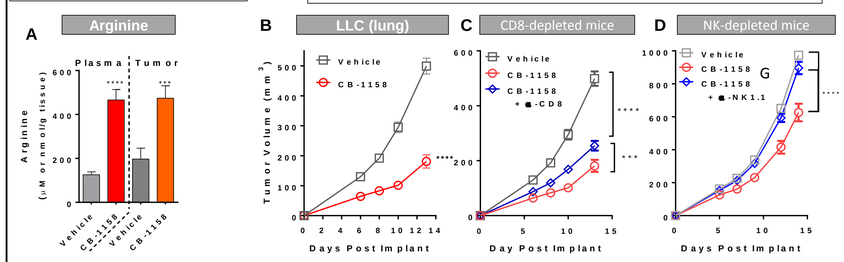


A). Proliferation (CFSE) of α-CD3/α-CD28-stimulated human T-cells after 4 day incubation in the presence or absence of neutrophils or CB-1158 (1.6 μM). B) Human T-cells from a healthy donor were cultured in media pre-conditioned for 2 days with granulocytes isolated from a patient with head & neck cancer. The media was collected and analyzed for the indicated analytes by Cytometric Bead Array.

CB-1158 Increases Arginine Levels and has Single-Agent Anti-Tumor Efficacy in Animal Models

CB-1158 increases arginine levels in tumor and plasma

CB-1158 has antitumor activity in a syngeneic lung model that is mediated by CD8 and NK cells

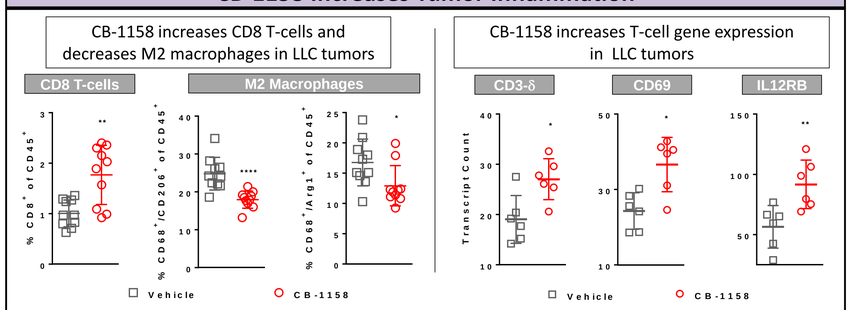


(A) Concentration of arginine in plasma or LLC tumor lysates after oral dosing of CB-839. B-D) Tumor volume in the LCC model with either no depletion (B), CD8 depletion (C) or NK cell depletion (D) and dosed with CB-1158 (100 mg/kg BID)

CB-1158 Increases Tumor Inflammation

CB-1158 increases CD8 T-cells and decreases M2 macrophages in LLC tumors

CB-1158 increases T-cell gene expression in LLC tumors

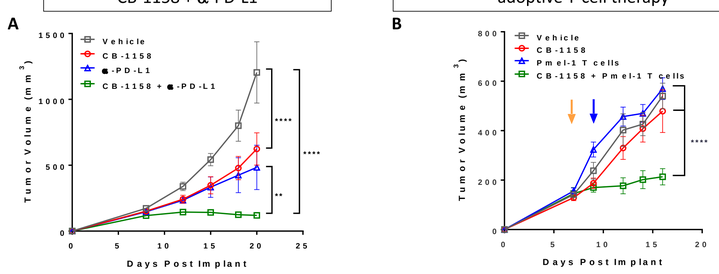


Levels of immune cell subsets determined by flow cytometry *(left)* or levels of mRNA transcripts determined by Nanostring *(right)* in LLC tumors from mice treated with vehicle or 100 mg/kg CB-1158 twice daily for 14 days

CB-1158 Combines with Anti-PD-L1 and Adoptively-Transferred Antigen-Specific T-cells to Inhibit Tumor Growth

Enhanced antitumor activity with CB-1158 + α-PD-L1

Enhanced antitumor activity with CB-1158 + adoptive T-cell therapy

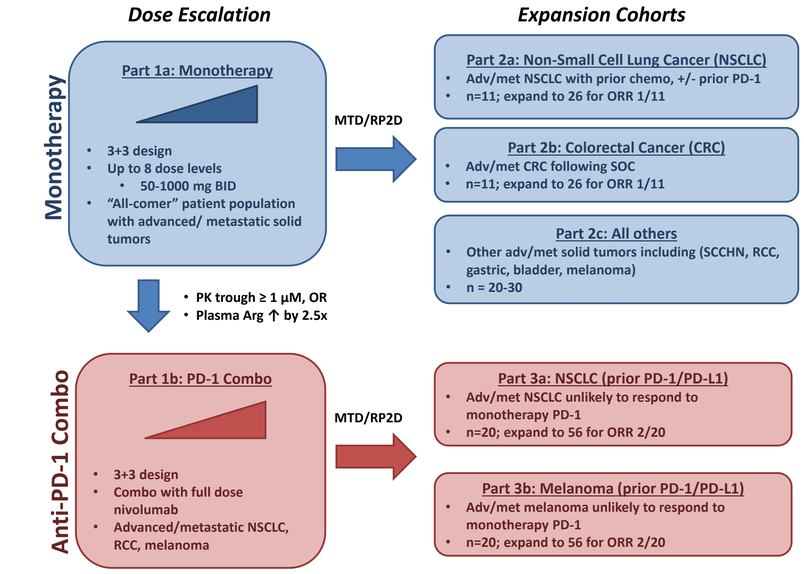


A) Tumor volumes were measured in syngeneic colorectal model (CT26) dosed with CB-1158,(200 mg/kg BID), a-PD-L1 (10F.9G2) (5 mg/kg IP on days 5, 7, 9, 11, 13, 15) or the combination. B) Tumor volumes measured in syngeneic melanoma model (B16F10) that underwent non-myeloablative chemotherapy and then dosed CB-1158 (200 mg/kg BID), Pme1CD8 T-cells (1c10^6 on day 7) or the combination.

CX-1158-101: Study Design

- First-in-Human Phase 1 of CB-1158 in advanced cancer patients
- Evaluates monotherapy CB-1158 and the combination of CB-1158 with anti-PD-1
- Evaluates safety, tolerability, PK, PD and anti-cancer activity

Schematic of CX-1158-101 Study Design

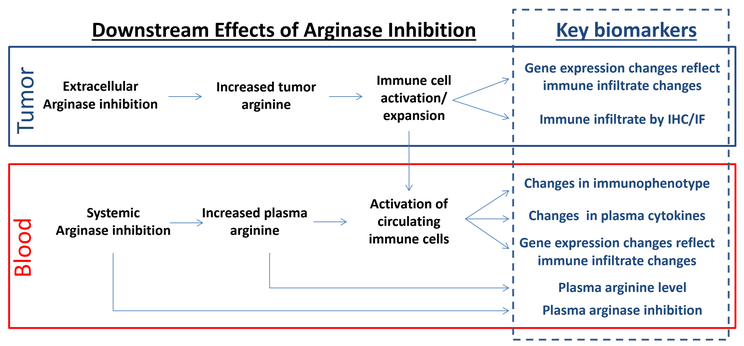


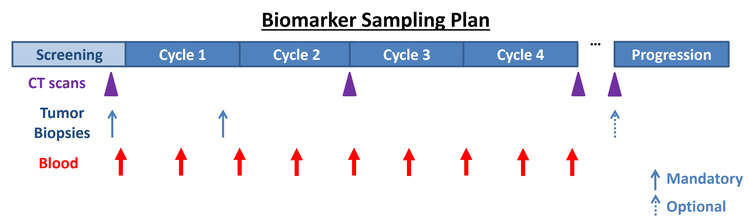
Key Inclusion/Exclusion Criteria

- Metastatic or locally advanced disease not amenable to local therapy
- ECOG 0-1
- Washout prior anti-cancer therapy
  - Prior PD-1/PD-L1 allowed
- Previously treated brain mets allowed if stable
- PD-1 combo Expansion Cohorts ONLY:
  - Received or were ineligible for standard therapy for NSCLC or melanoma
  - Received prior PD-1/PD-L1 therapy and either:
    - Progressed or SD ≥ 24 weeks in most recent line of therapy ("Add on")
    - Best response of SD in any prior line

Clinical Biomarker Plan

- Key pharmacodynamic biomarkers include:
  - Plasma arginine and arginase activity
  - Alterations in gene expression profile of immune cells in tumor and in peripheral blood
  - Changes in immune cell immuno-phenotype in peripheral blood
  - Changes in TIL infiltrate in tumors
- Potential biomarkers predictive of clinical activity include:





Summary

- **CX-1158-101 (NCT02903914) is a First-in-Human Ph1 study evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of CB-1158 as monotherapy and in combination with anti-PD-1 therapy**
- **Arginase is an immunosuppressive enzyme secreted by MDSCs**
- **CB-1158 is a potent, orally bioavailable inhibitor of Arginase**
- **CB-1158 reverses arginine depletion and T-cell inhibition by MDSCs**
- **CB-1158 has monotherapy activity in syngeneic mouse models and is synergistic with anti-PD-L1 and adoptive T-cell therapy**