Discovery and *in vivo* Activity of Potent and Selective Oral PD-L1 Antagonists

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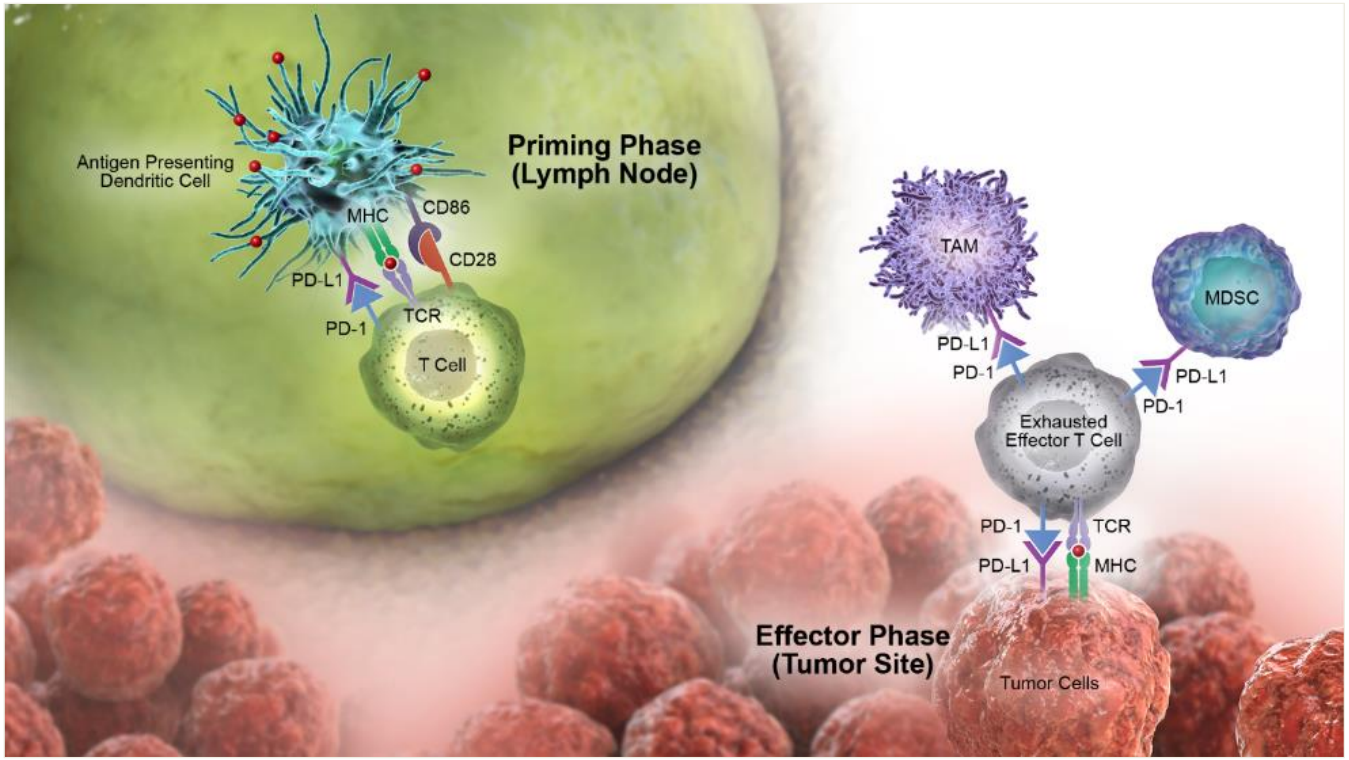
Disclosures

- All authors are current or previous employees of Incyte, and own stock of Incyte

Small-Molecule PD-L1 Inhibitors as a Novel Approach to Cancer Therapy

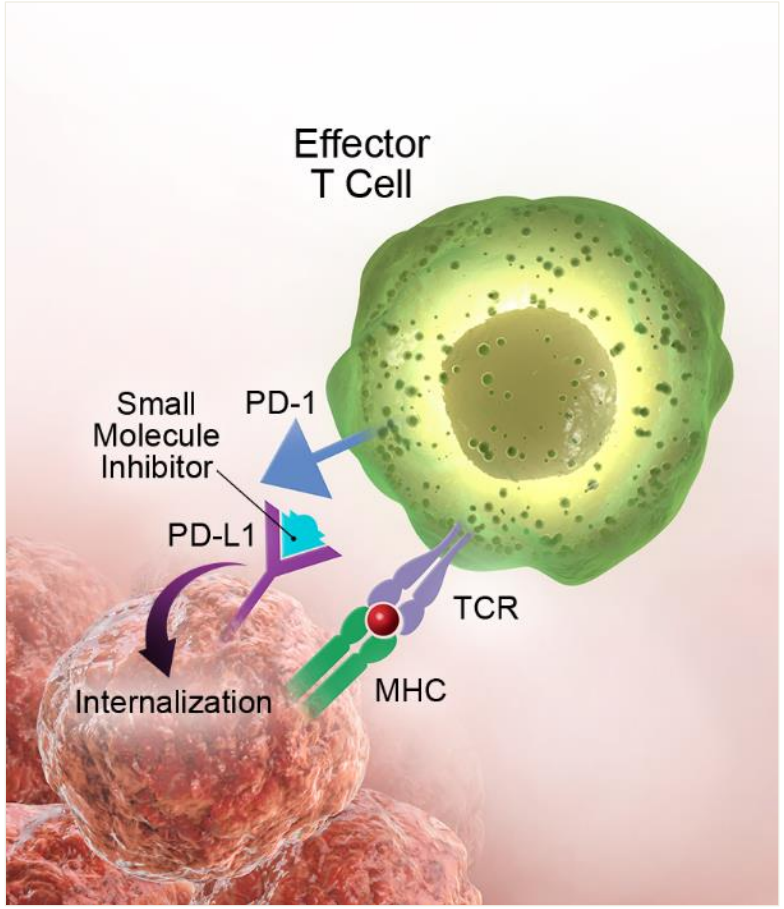


The interaction of PD-L1 with PD-1 reduces T-cell function
Tumor cells utilize this mechanism to evade immune surveillance

- Monoclonal antibodies against PD-L1 or PD-1 have been approved for the treatment of multiple tumor histologies[1,2]
- Oral, small-molecule PD-L1 inhibitors
  - Are potent and selective
  - Induce PD-L1 internalization
  - Exhibit antitumor efficacy as single agent
- The first-in-human phase 1 study of INCB086550 has been initiated (NCT03762447)

1. Ribas A and Wolchok JD. *Science.* 2018;359:1350–55. **2.** Sharpe AH and Pauken KE. *Nat Rev Immunol.* 2018;18:153–67.

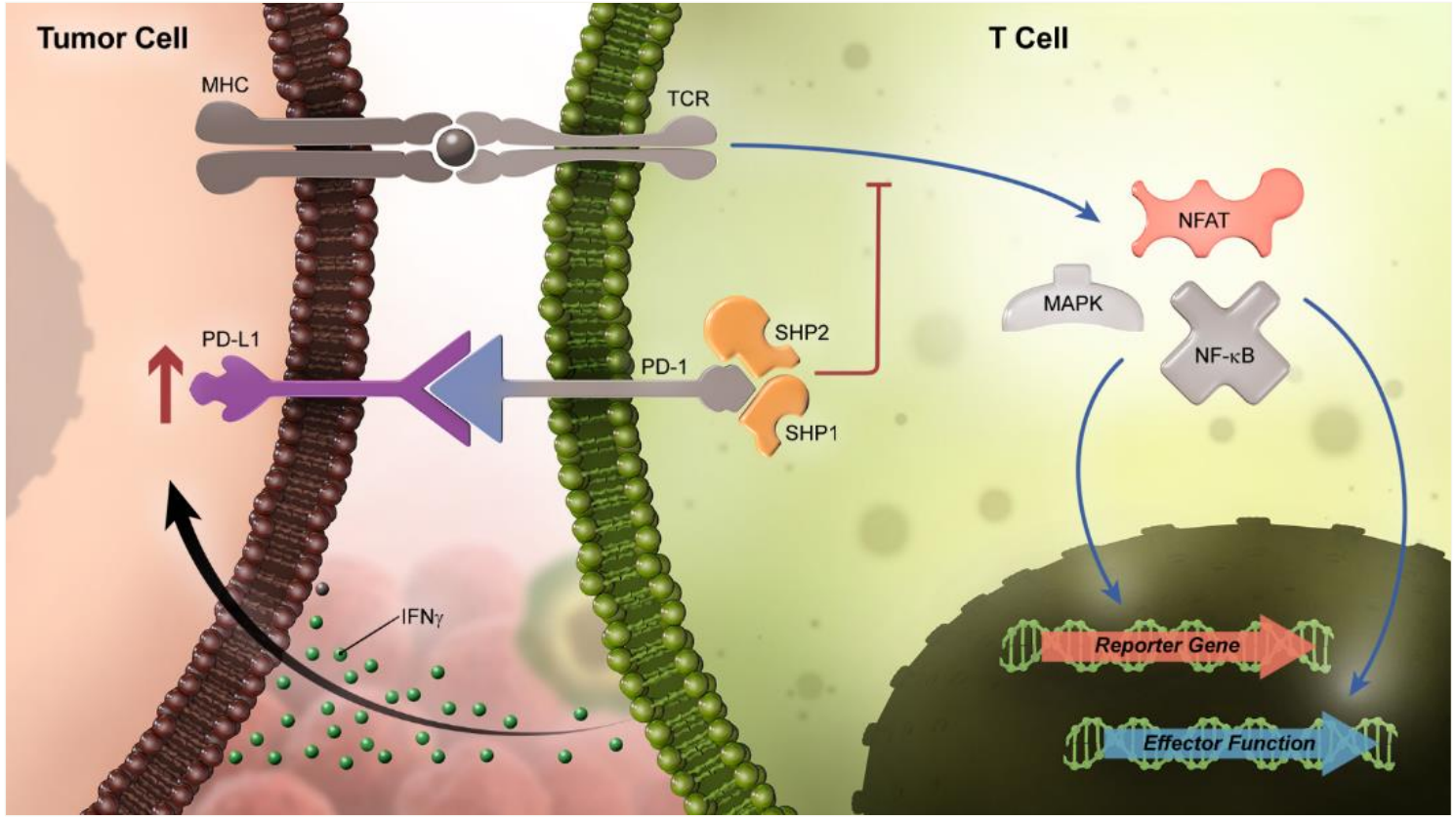
INCB090244 is a Potent and Selective PD-L1 Small-Molecule Inhibitor

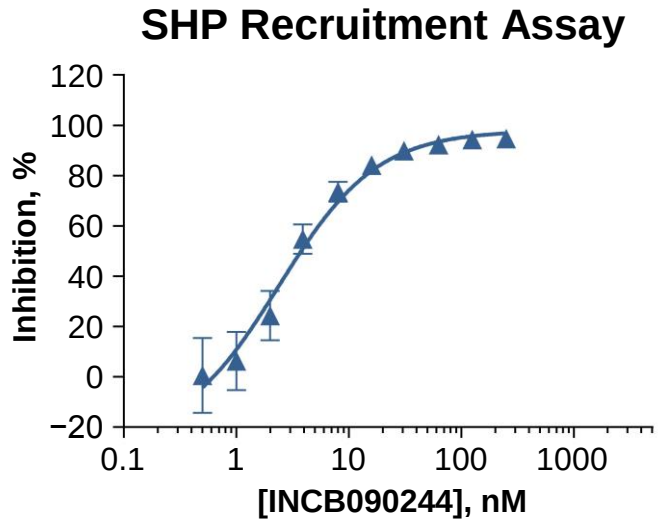


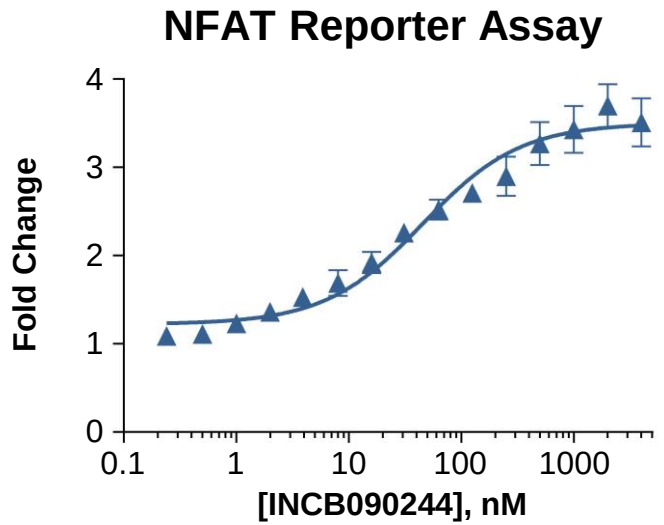
	INCB090244
PD-L1:PD-1 IC_{50}, nM	
Human	1.9
Mouse	No effect
Oral bioavailability in cynomolgus monkey, %	100

INCB090244 is an oral PD-L1 inhibitor with high selectivity against panels of kinases, ion channels and transporters

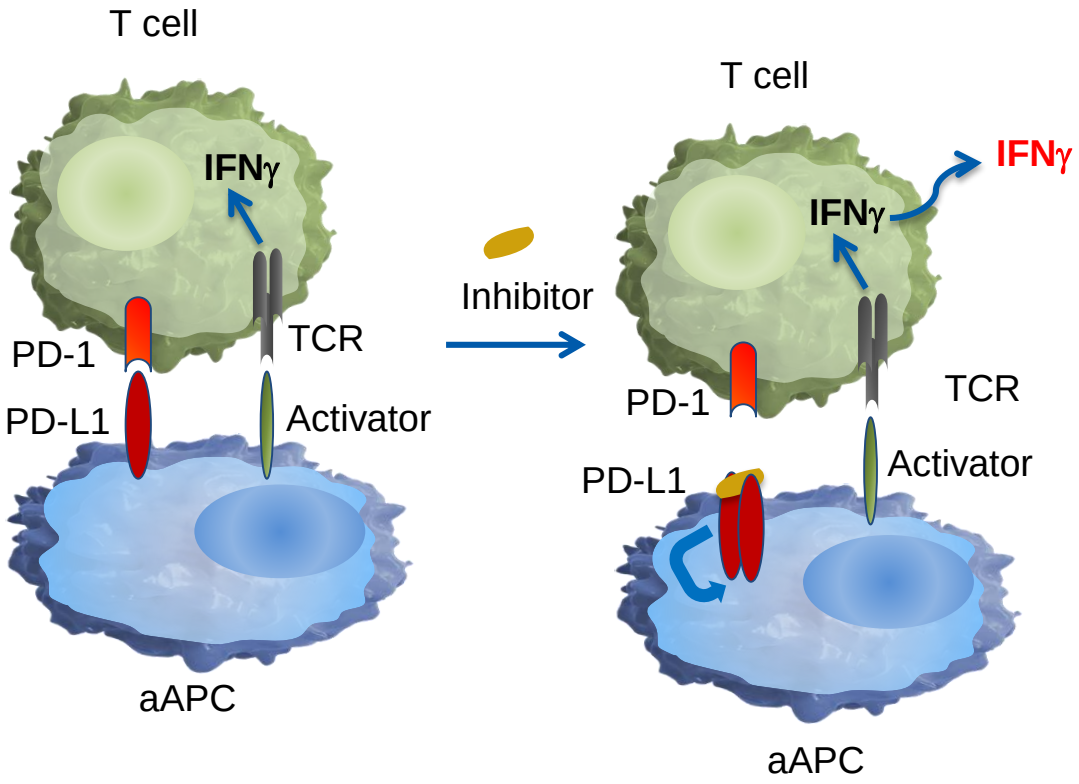
INCB090244 Decreases PD-1-mediated SHP Recruitment and Enhances NFAT Signaling

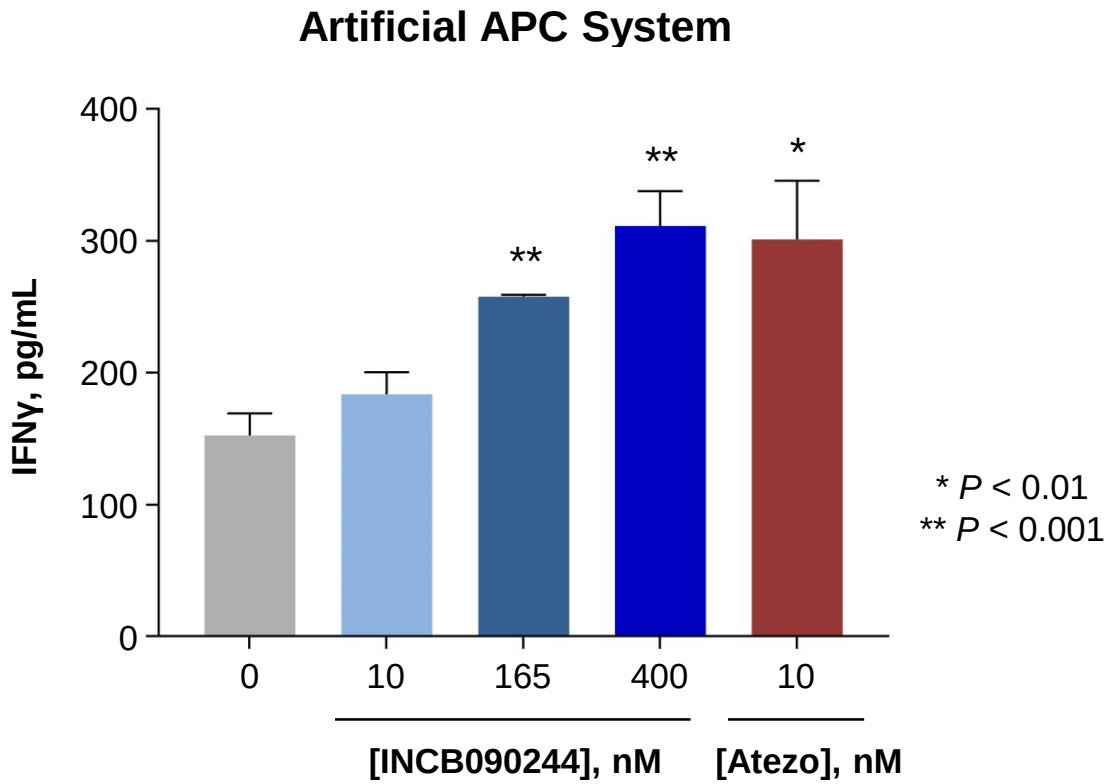






INCB090244 Enhances T Cell Cytokine Production





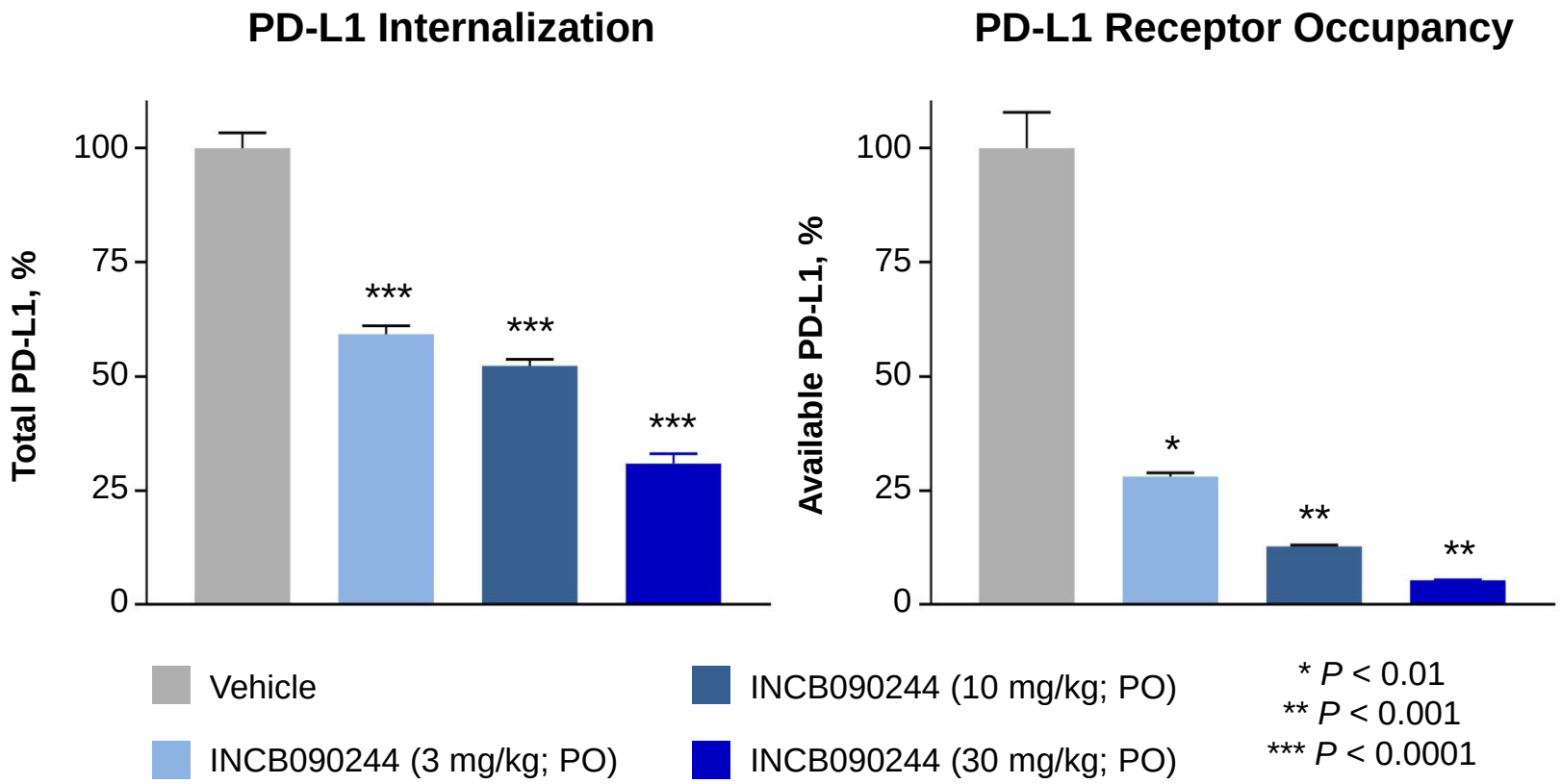
Similar finding with Staphylococcal enterotoxin B-stimulated whole blood assay

INCB090244 Binds to and Internalizes Tumor Cell PD-L1 in vivo

Day 0 C57BL/6 WT mice were inoculated with MC38-huPD-L1 tumors

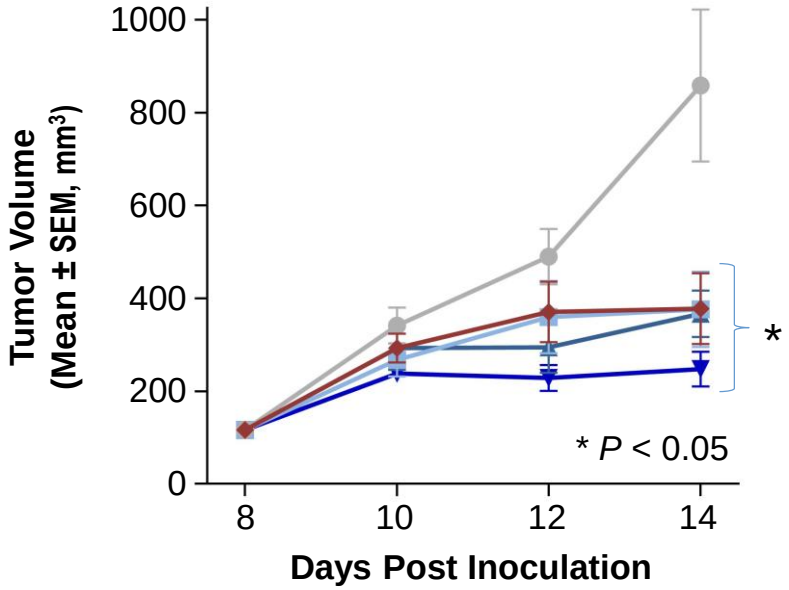
Day 8 When tumors reached ~100 mm^3, INCB090244 was given orally twice daily

Day 17 Tumors were harvested 9 days post-treatment, and PD-L1 receptor occupancy and internalization were determined by flow cytometry

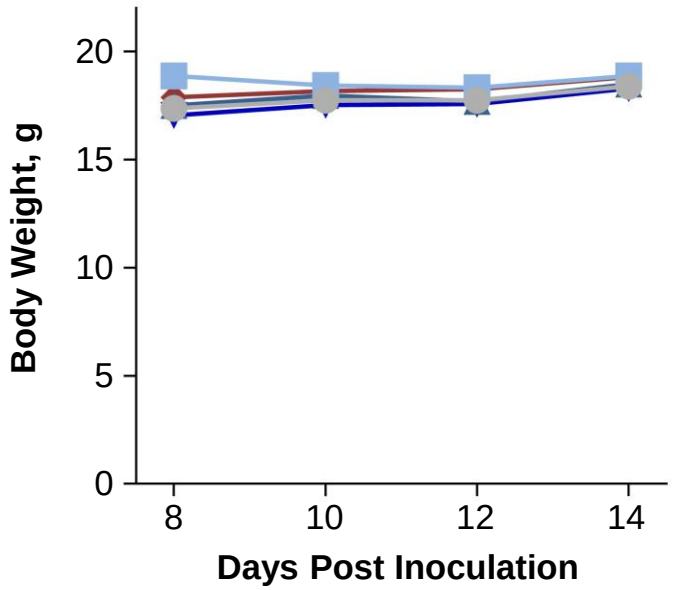


INCB090244 Inhibits the Growth of MC38-huPD-L1 Tumors in Immuno-competent, but not in Immunocompromised Mice

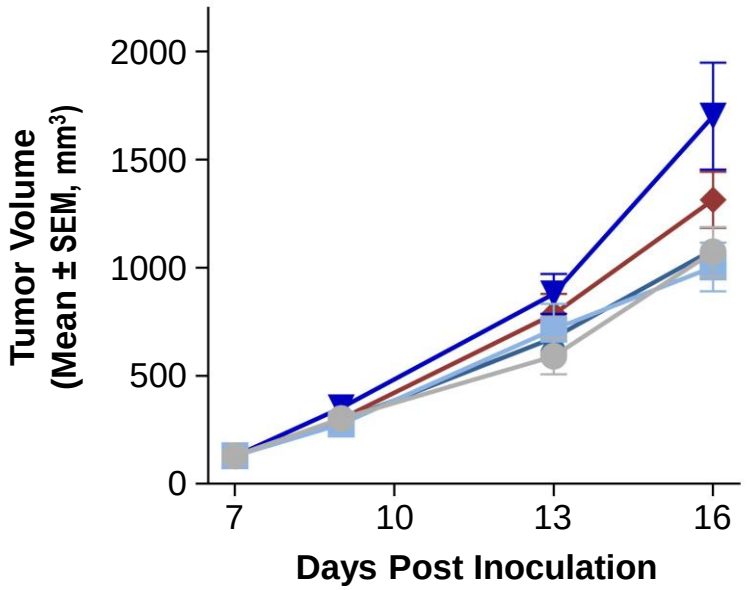
INCB090244 controls the growth of established tumors engineered to overexpress human PD-L1



No change in body weight

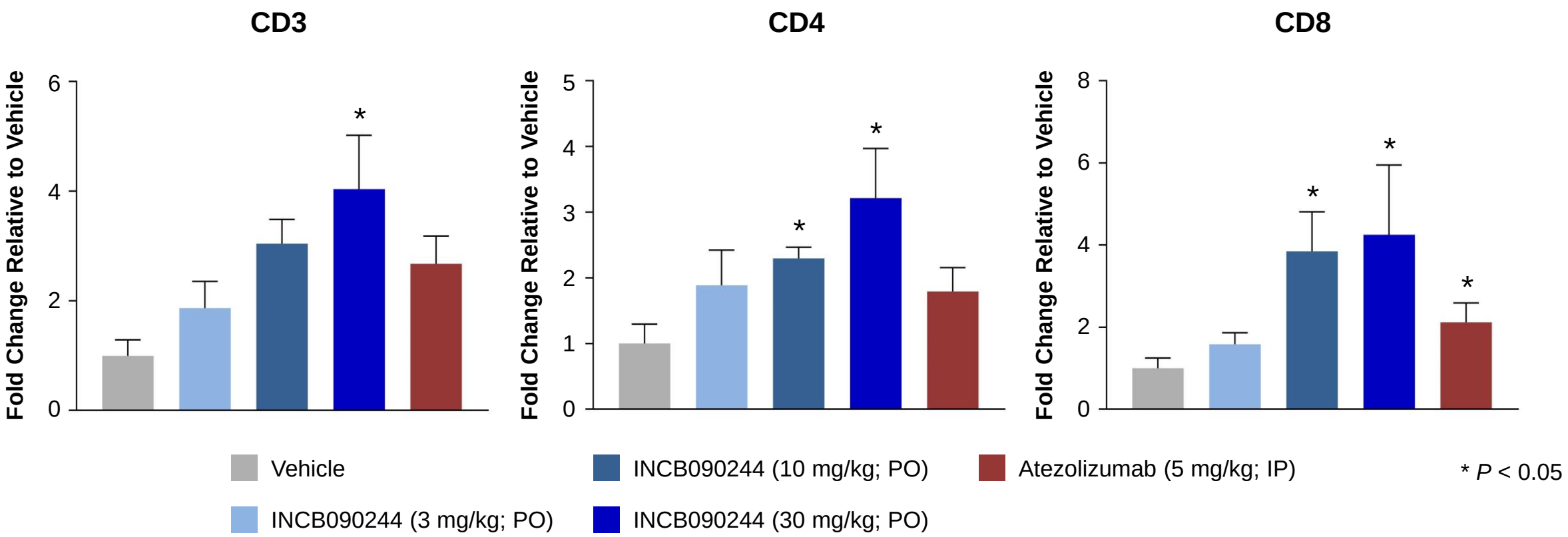


INCB090244 has no effect on the same tumor grown in immunocompromised mice



Vehicle
INCB090244 (10 mg/kg; PO)
Atezolizumab (5 mg/kg; IP)
INCB090244 (3 mg/kg; PO)
INCB090244 (30 mg/kg; PO)

INCB090244 Increases Infiltrating T Cells in MC38-huPD-L1 Tumors



Both atezolizumab and INCB090244 significantly increased number of infiltrating T cells above the control groups

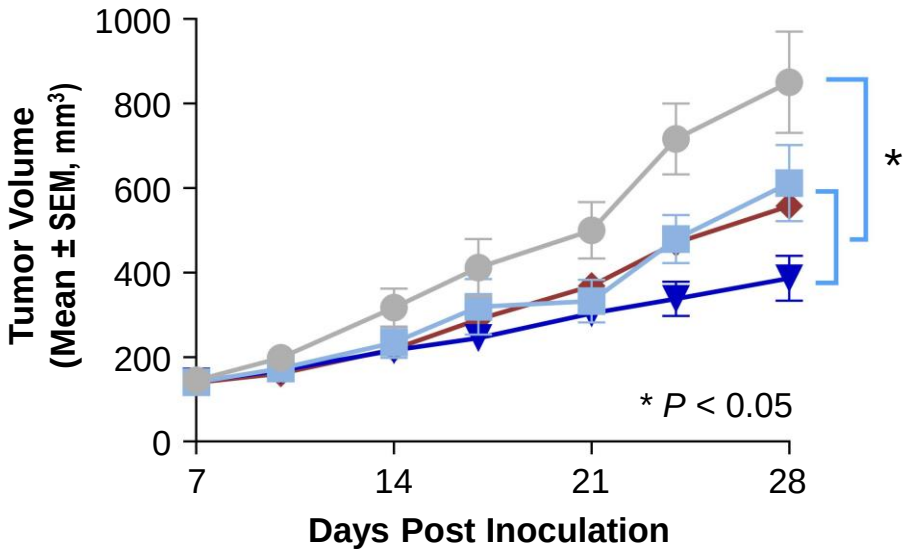
INCB090244 Inhibits Growth of MDA-MB-231 Tumors in Humanized CD34 NSG Mice and Increases Number of Infiltrating CD8+ T Cells

Day 0 huCD34+ NSG mice inoculated with MDA-MB-231 tumors

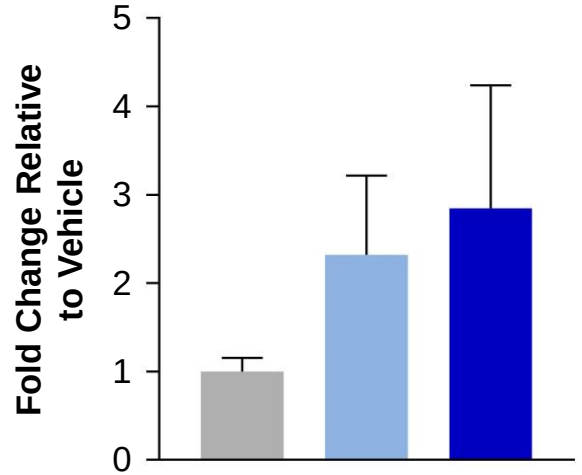
Day 7 When tumors reached ~100 mm^3, INCB090244 was given orally twice daily

Day 28 Tumors were harvested at terminal timepoints and immune profile was determined by flow cytometry

INCB090244 controls the growth of MDA-MB-231 tumors with endogenous PD-L1 expression in humanized mouse model



INCB090244 increases number of infiltrating CD8+ T cells



Vehicle

INCB090244 (30 mg/kg; PO)

INCB090244 (3 mg/kg; PO)

Atezolizumab (5 mg/kg; IP)

No significant change in body weight was observed

Summary

- INCB090244 is a novel, orally active small-molecule PD-L1 inhibitor
- INCB090244 potently activates $CD8^+$ T cells in culture
- INCB090244 binds and internalizes surface PD-L1 in vivo in a dose-dependent manner
- Orally dosed INCB090244 exhibits single agent activity and increases infiltrating T cells in 2 distinct humanized mouse models
  - Antitumor efficacy response only seen in immunocompetent mice
- INCB086550 is currently being evaluated in a first-in-human phase 1 study in patients with advanced solid tumors (NCT03762447)

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