

Effect of JAK/STAT or PI3K δ Plus PD-1 Inhibition on the Tumor Microenvironment: Biomarker Results From a Phase 1b Study in Patients With Advanced Solid Tumors

John M. Kirkwood,¹ Nicholas Iannotti,² Daniel Cho,³ Steven O'Day,⁴
Geoffrey Gibney,⁵ F. Stephen Hodi,⁶ Pamela Munster,⁷ Paul Hoyle,⁸
Sherry Owens,⁸ Michael Smith,⁸ and Niharika Mettu⁹

¹UPMC Hillman Cancer Center Melanoma and Skin Cancer Program, Pittsburgh, PA; ²Hematology-Oncology Associates of Treasure Coast, Port St Lucie, FL; ³NYU Laura & Isaac Perlmutter Cancer Center at NYU Langone, New York City, NY; ⁴John Wayne Cancer Institute of Providence, Saint John's Health Center, Santa Monica, CA; ⁵Georgetown Lombardi Comprehensive Care Center, Washington, DC; ⁶Dana Farber Cancer Institute, Boston, MA; ⁷UCSF Medical Center, Mt. Zion Campus, San Francisco, CA; ⁸Incyte Corporation, Wilmington, DE; ⁹Duke Cancer Institute, Durham, NC

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Disclosures

Kirkwood: Consultant work where honorarium was received – *Amgen, Array Biopharma, BMS, Incyte, Merck, Novartis, Roche and Immunocore LLC*; **Iannotti:** Nothing to disclose; **Cho:** Consultancy (>2 years ago) – *Pfizer, BMS, Exelixis, Genentech, Prometheus Pharmaceuticals*; **O'Day:** Clinical trial research support – *Incyte, Merck*; Consultant work where honorarium was received – *Incyte*; **Gibney:** Consultancy – *Genentech, Novartis, Newlink Genetics, Incyte*; Speaker's bureau participation – *Merck, Genentech*; **Hodi:** Commercial institutional grant – *Bristol Myers Squibb*; Consultancy – *Bristol Myers Squibb*; Consultant work where honorarium was received – *Incyte*; **Munster:** Research support – *Incyte, Merck*; **Hoyle:** Employment – *Incyte*; **Owens:** Employment – *Incyte*; **Smith:** Employment – *Incyte*; **Mettu:** Nothing to disclose.

I will discuss the following off-label use and/or investigational use in my presentation:

- Itacitinib (JAKi) or INCB050465 (PI3K δ i) plus pembrolizumab in patients with advanced tumors

Background

- Inhibitory immune pathway blockade is a key therapeutic modality for cancer
- Tumors escape immune surveillance through multiple mechanisms
 - Targeting distinct immunosuppressive pathways within the tumor microenvironment may maximize therapeutic benefit¹
- Clinical trials are needed to efficiently evaluate novel IO combinations

Modulation of the Tumor Microenvironment to Promote Anti-tumor Immunity

Signaling through the JAK/STAT pathway promotes tumor growth¹

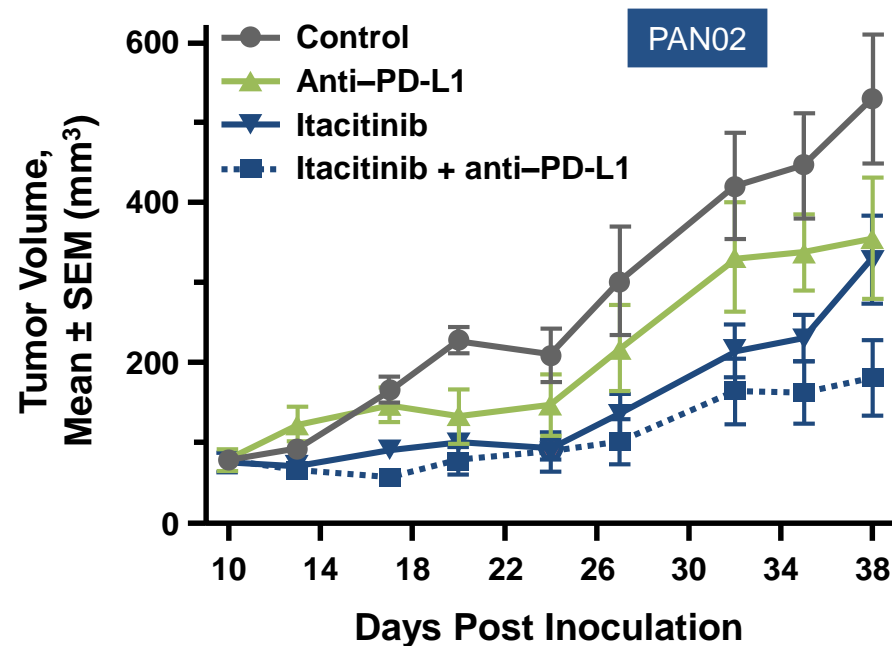
- Provides proliferative/survival signals
- Shapes the antitumor immune response
 - Promotes the accumulation and activity of negative regulatory cells
 - Upregulates PD-1/PD-L1 expression to promote T cell “exhaustion”
 - Pathway modulation shown to enhance T cell activity and T cell-dependent inhibition of tumor growth
 - Average IL-6 inhibition with itacitinib (JAKi) 300 mg QD is 40%

Published data demonstrate that inactivation of PI3K δ in preclinical models²⁻⁴:

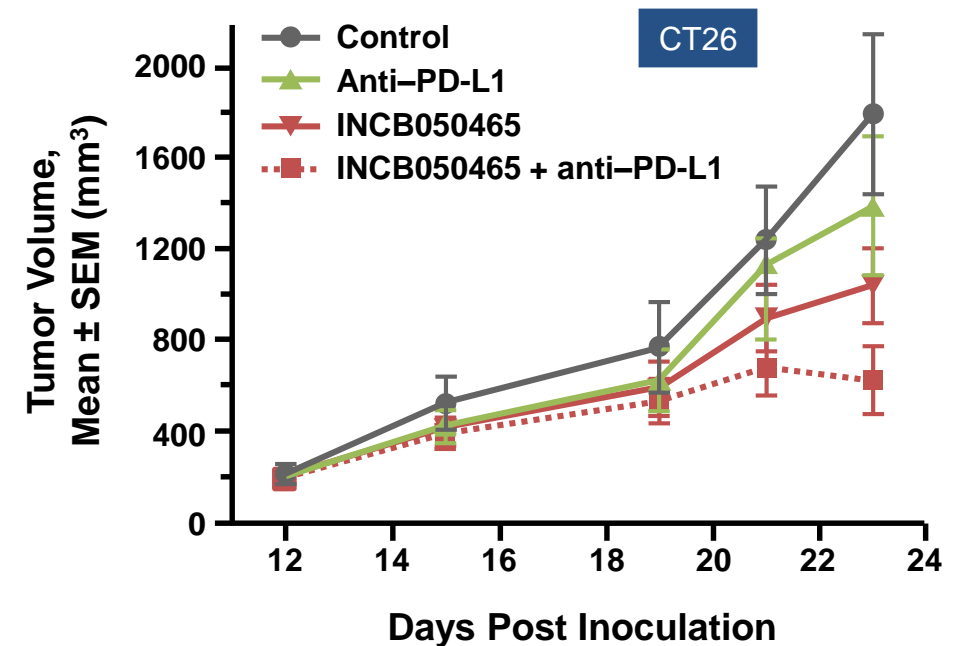
- Inhibits solid tumor growth and metastasis and prolongs survival
- Shapes the tumor microenvironment in favor of antitumor immunity by
 - Reducing T_{reg} function
 - Reducing levels of MDSCs
 - Enhancing activity of CD8+ effector T cells
 - INCB050465 IC₅₀ for:
 - T_{reg} function: 1.5 nM
 - T_{eff} proliferation: 2000 nM

JAK Inhibitor (Itacitinib; INCB039110) and PI3K δ Inhibitor (INCB050465) Synergize With anti-PD-L1 in Mouse Tumor Models

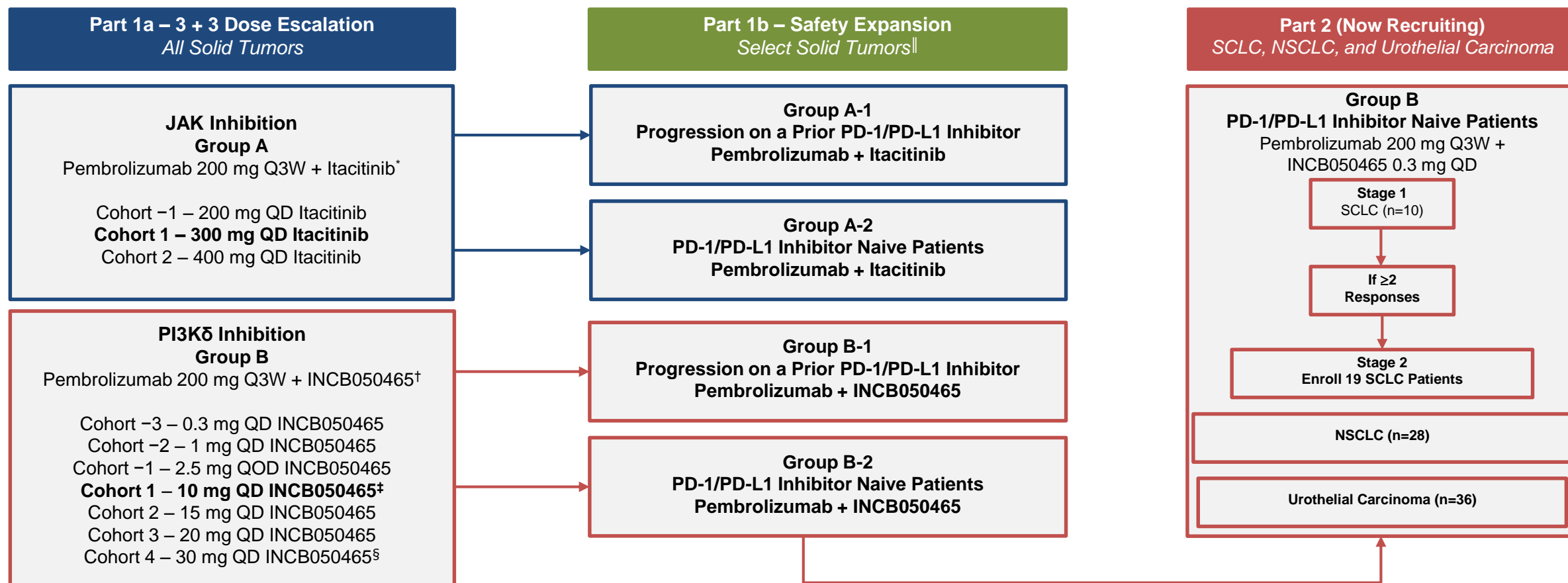
JAK inhibition synergizes with anti-PD-L1 antibodies to block tumor growth¹



PI3K δ inhibition synergizes with anti-PD-L1 antibodies to block tumor growth²



Study Design: Phase 1b, 2-Part, Open-Label Study



* Cohort 1 will initially be evaluated. Cohort –1 will be evaluated if the Cohort 1 dose proves intolerable.

† Cohort 1 will initially be evaluated. Further dose exploration may be evaluated based on emerging PK/PD or safety data. Subsequent increases in the dose of INCB050465 will be limited to ≤50% and will not exceed the dose level tested as monotherapy.

‡ Patients treated at ≥10 mg should switch to a once weekly dosing schedule at Cycle 4 Day 1 and beyond.

§ Based on the review of safety data from the INCB050465 program, patients receiving 30 mg QD of INCB050465 should have the dose reduced to 20 mg QD.

¶ Select solid tumor types include endometrial cancer, gastric cancer, melanoma, MSI-CRC or other mismatch repair-deficient tumors, NSCLC, SCCHN, RCC, TNBC, urothelial carcinoma, or PDAC.

Patient Enrollment for Part 1

Study Part	Patients Enrolled
Itacitinib (JAKi) + Pembrolizumab	
Group A – dose escalation	8
Group A-1 (progression on prior PD-1/PD-L1 inhibitor) – safety expansion	20
Group A-2 (PD-1/PD-L1 inhibitor naive) – safety expansion	21
INCB050465 (PI3Kδi) + Pembrolizumab	
Group B – dose escalation	34
Group B-1 (progression on prior PD-1/PD-L1 inhibitor) – safety expansion	24
Group B-2 (PD-1/PD-L1 inhibitor naive) – safety expansion	24

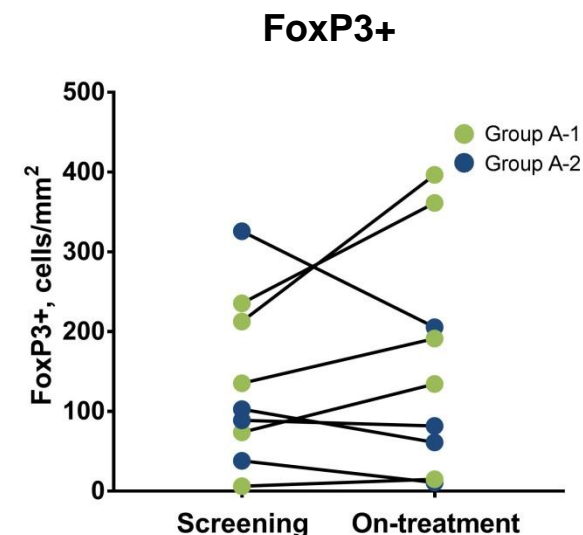
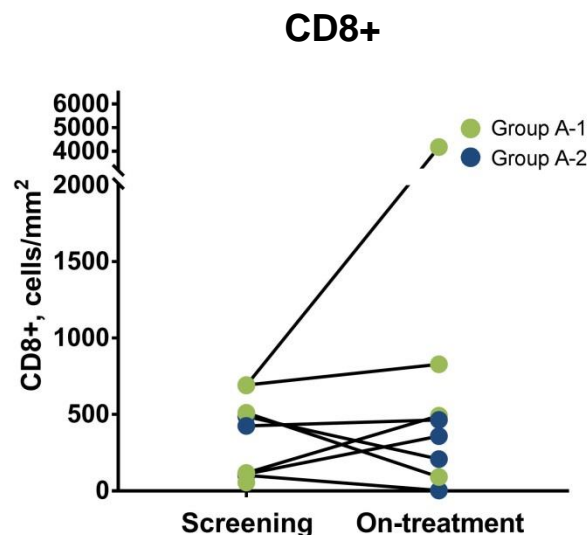
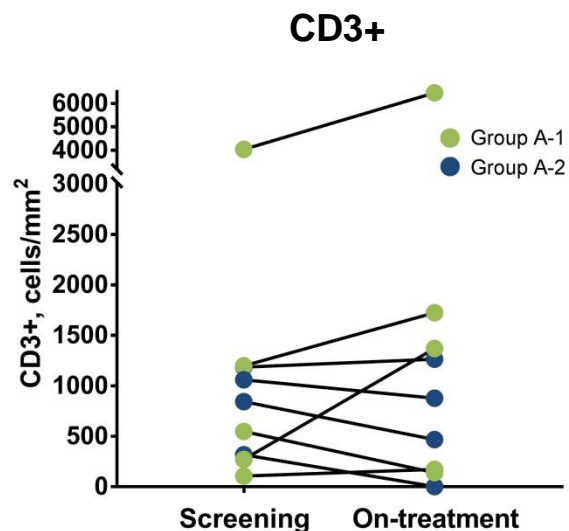
Biomarker Assessments

- Biomarker analysis performed on patient samples from Part 1 of study
- Core biopsies were obtained at screening and between week 3 and 5 on treatment
 - Presence of CD3+, CD8+, and FoxP3+ cells determined by chromogenic IHC and expressed as cells/mm² in tumor
- Flow cytometry was performed on fresh peripheral blood samples within 48 hours of blood draw
- Multiplexed plasma protein analysis performed using Proximity Extension Assay (PEA) at Olink Proteomics
 - Select plasma cytokines measured by ELISA using commercially available kits to validate the PEA results

Paired Biopsy Study: CD3+, CD8+, and FoxP3+ Cells/mm²

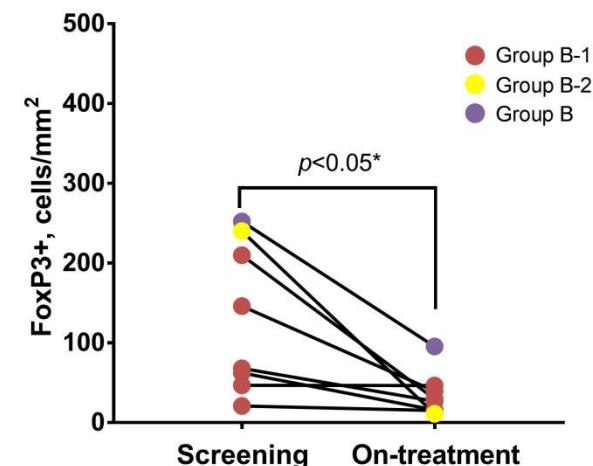
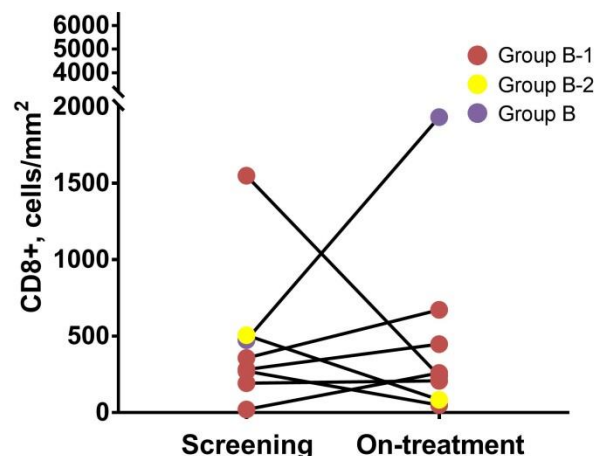
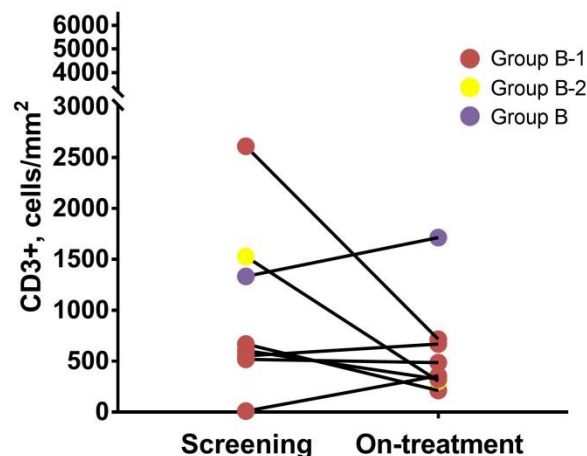
INCB050465 (PI3K δ i) + pembrolizumab treatment decreased intratumoral T_{reg} cells

Itacitinib
(JAKi)



n=9 pairs

INCB050465
(PI3K δ i)

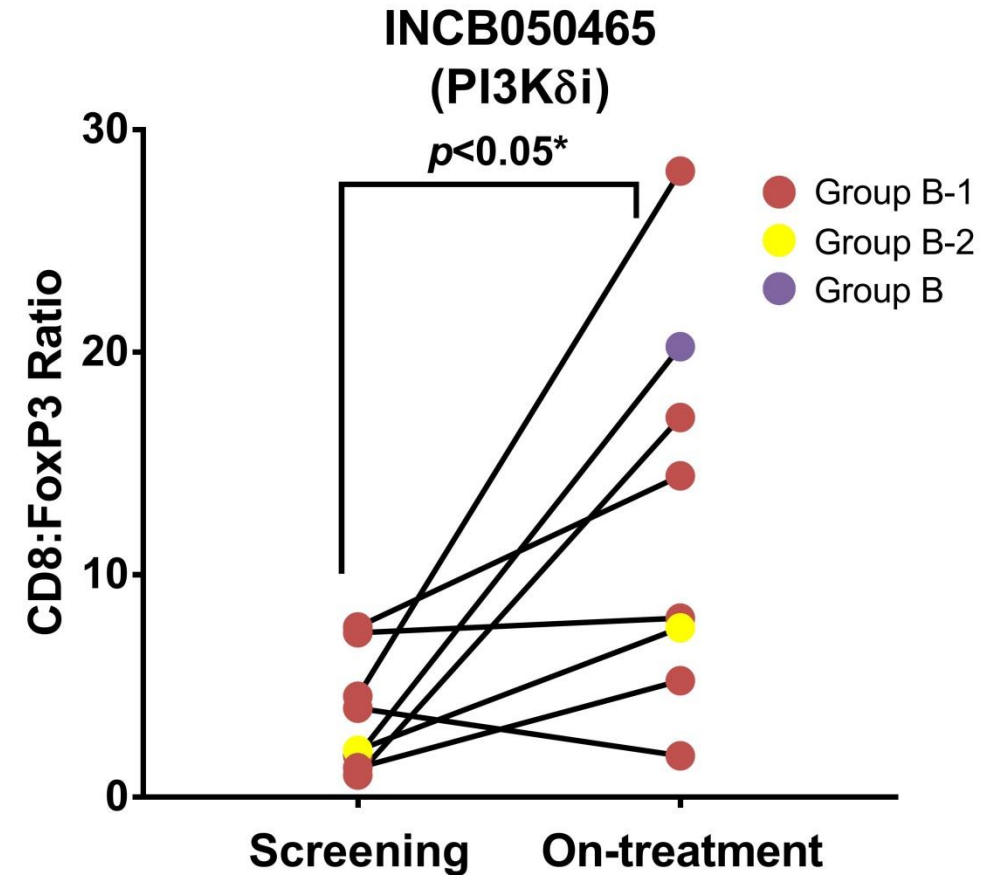
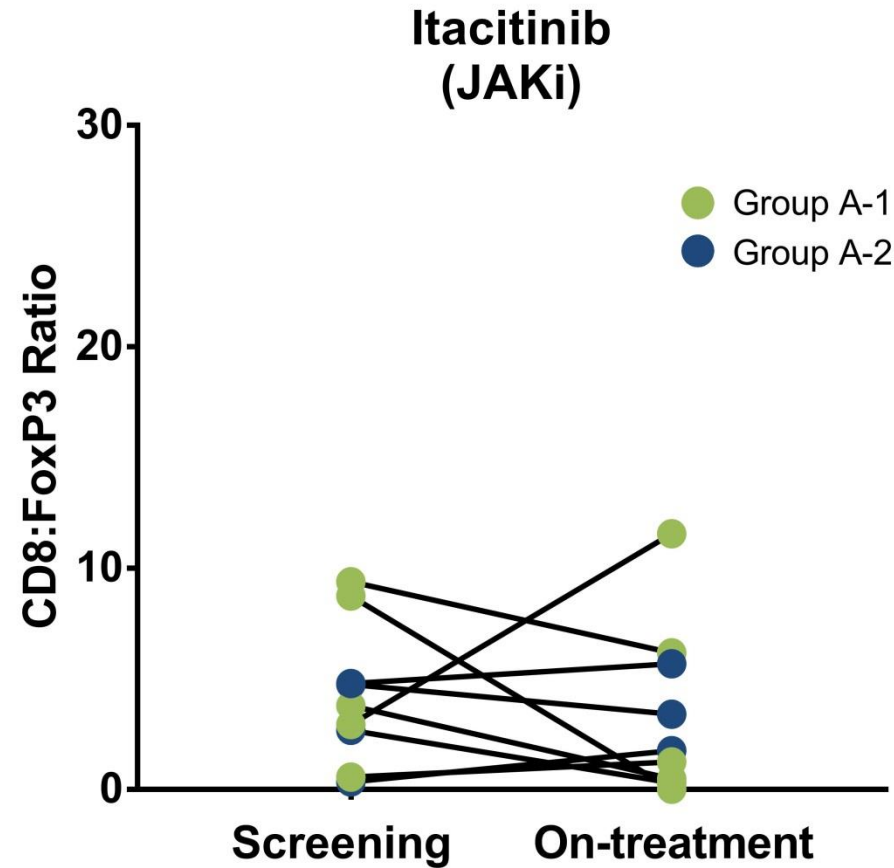


n=8 pairs

*Paired t-test.

Paired Biopsy Study: CD8:FoxP3 Ratio

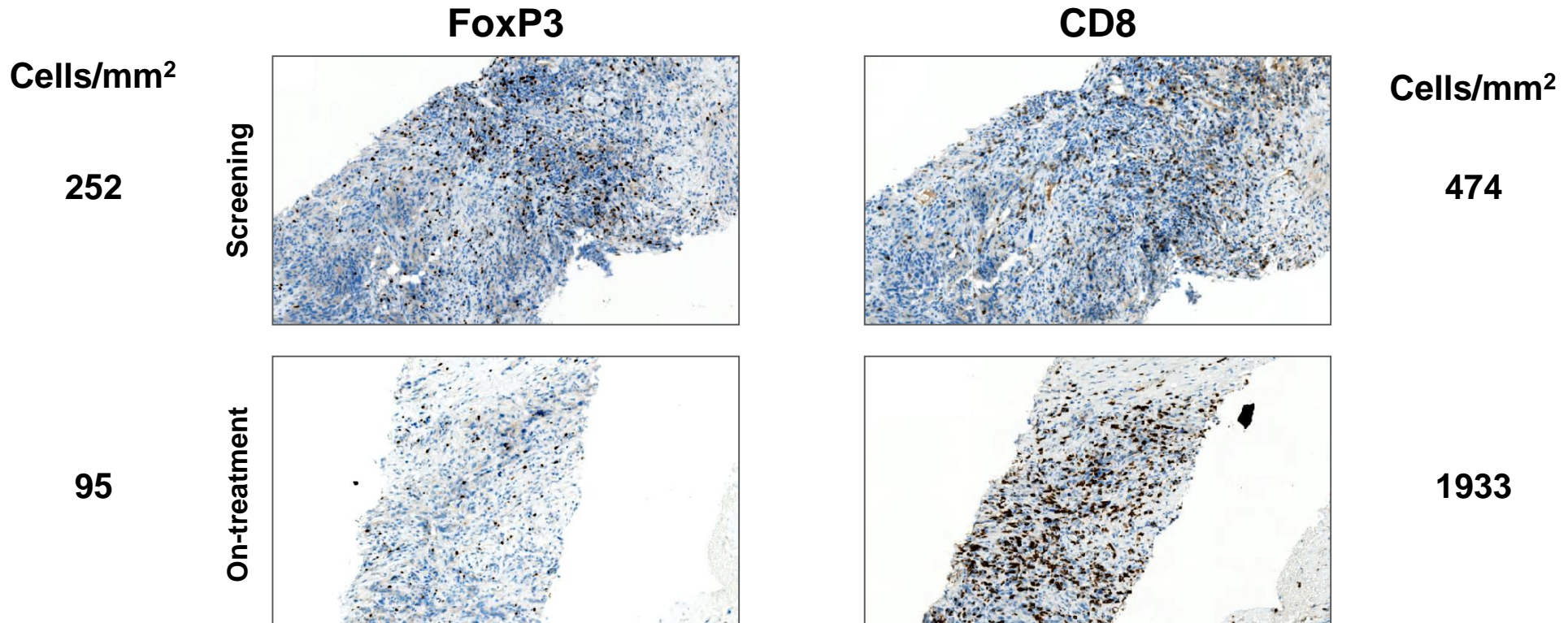
INCB050465 (PI3K δ i) + pembrolizumab treatment increased intratumoral CD8: T_{reg} ratio



*Paired t-test.

Immunohistochemistry: Metastatic Melanoma

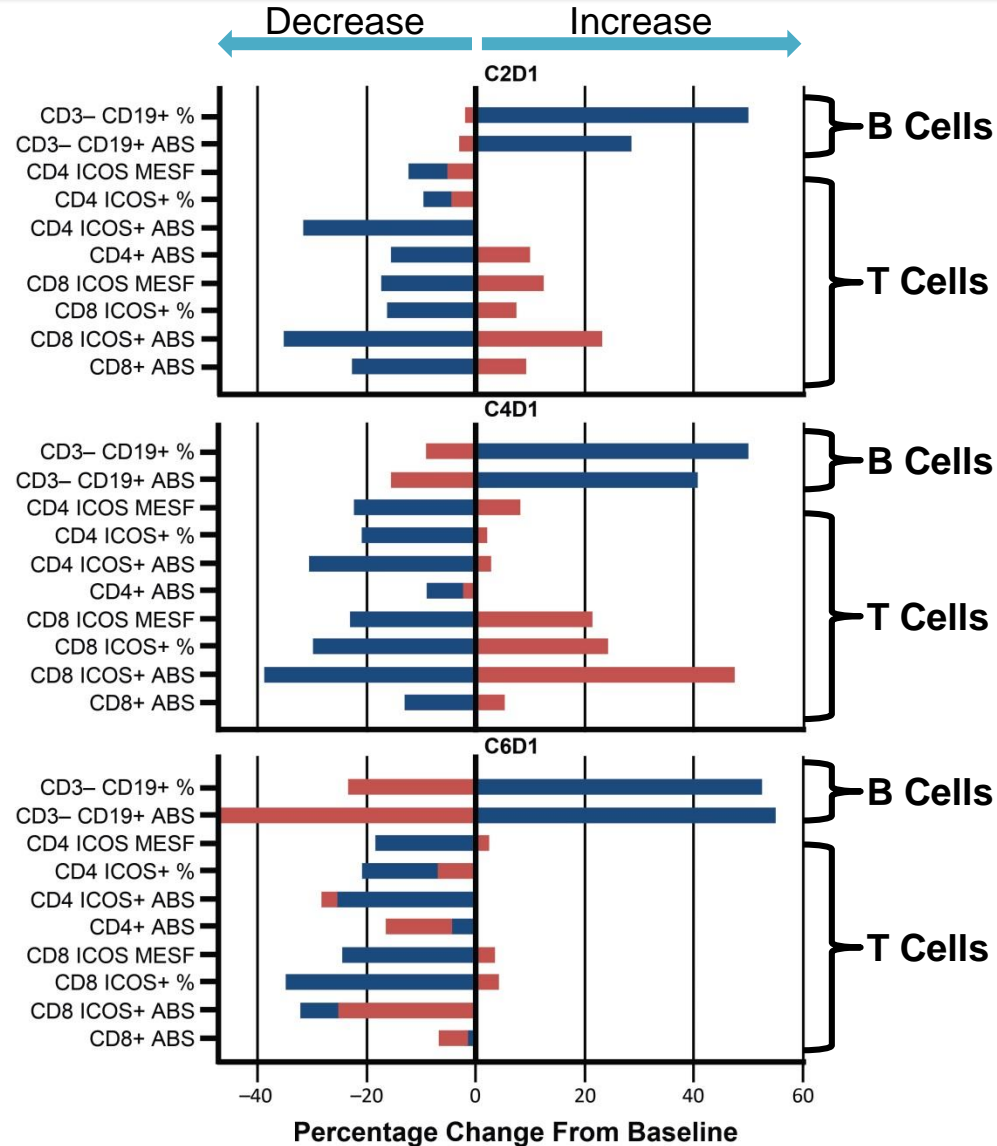
INCB050465 (PI3K δ i) + pembrolizumab



IHC analysis of tumor tissue from a patient with metastatic melanoma receiving INCB050465 (PI3K δ i) + pembrolizumab demonstrating decreased intratumoral T_{regs} and increased CD8+ cells compared with baseline

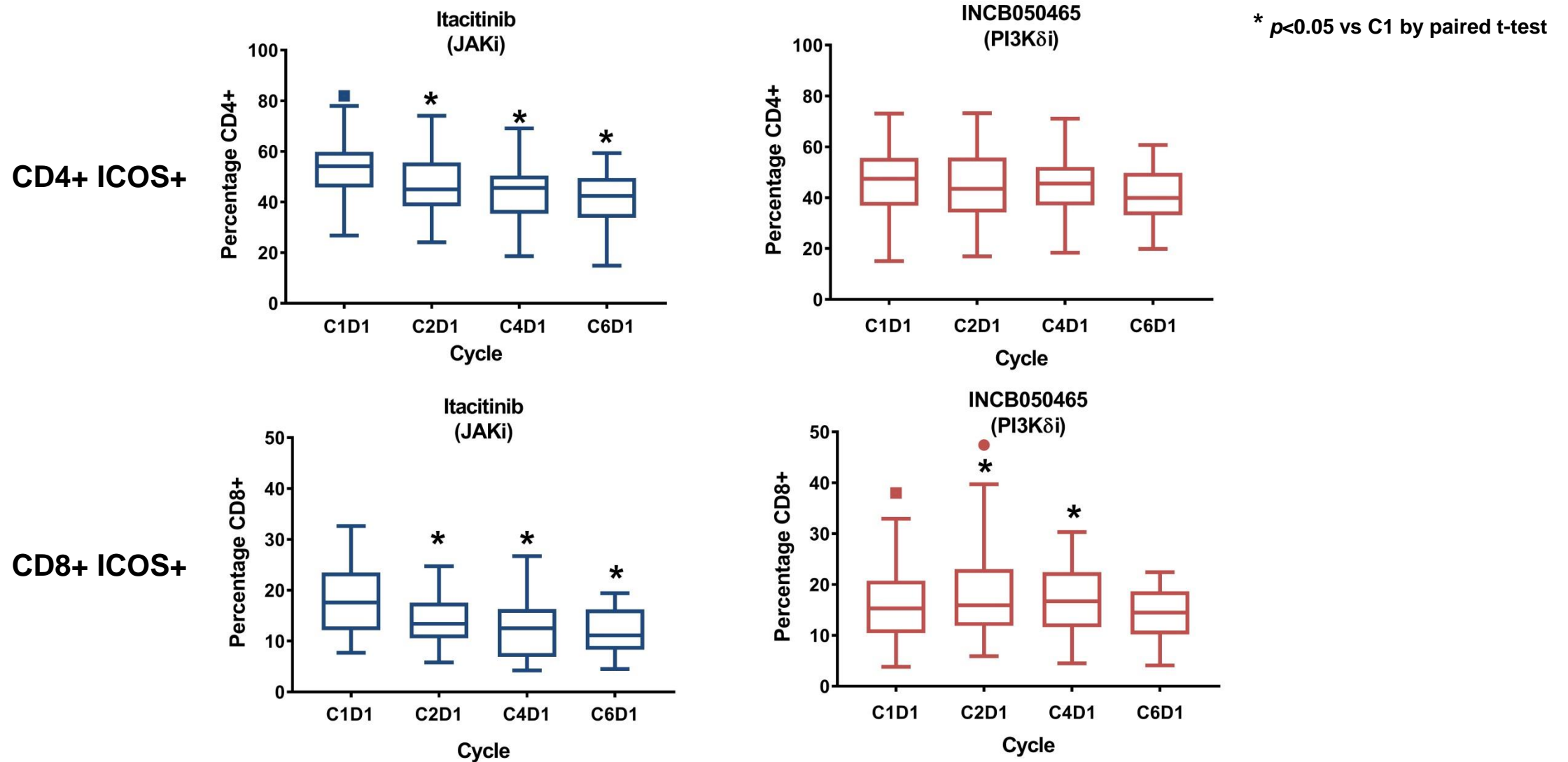
Peripheral Blood Flow Cytometry

Comparison of baseline with C2D1, C4D1, or C6D1



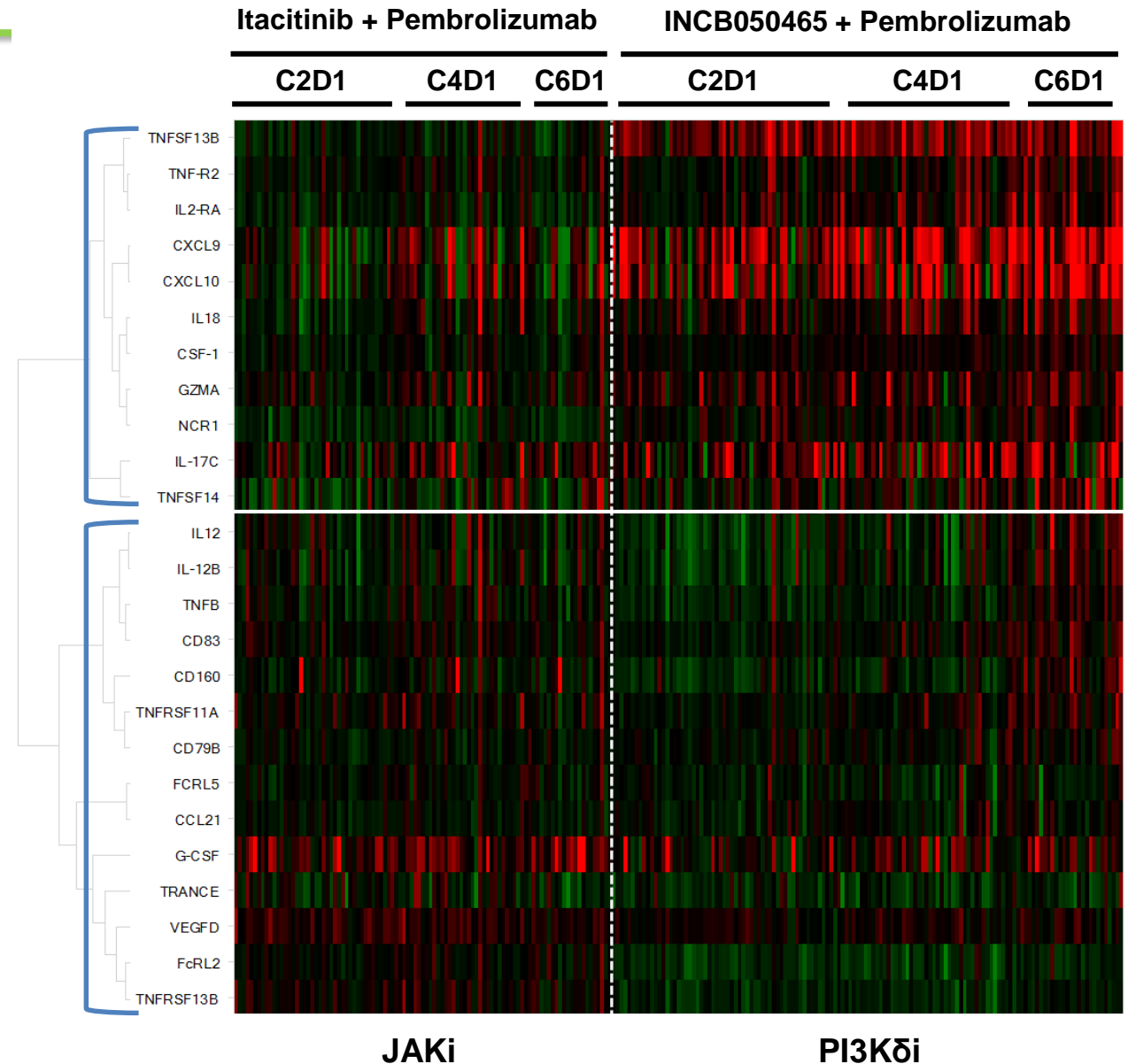
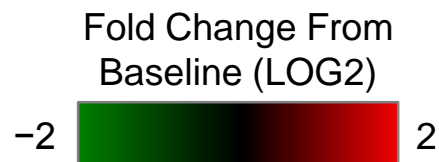
- JAK inhibition with itacitinib resulted in a generalized decrease in T-cell activation and increased B cells
- PI3Kδ inhibition with INCB050465 decreased B cells but retained T-cell activation

FACS Analysis of T-cell Activation



Plasma Cytokine Analysis

- Proximity extension assay
 - >1000 plasma proteins analyzed
 - Changes in expression levels from baseline (C1D1) determined by paired t-test ($p < 0.05$)
- Plasma cytokines and chemokines were differentially regulated by itacitinib (JAKi) and INCB050465 (PI3K δ i)
- Enriched for proteins involved in:
 - Lymphocyte proliferation (adj. p value 6×10^{-8})
 - IFN γ signaling (adj. p value 2.4×10^{-3})

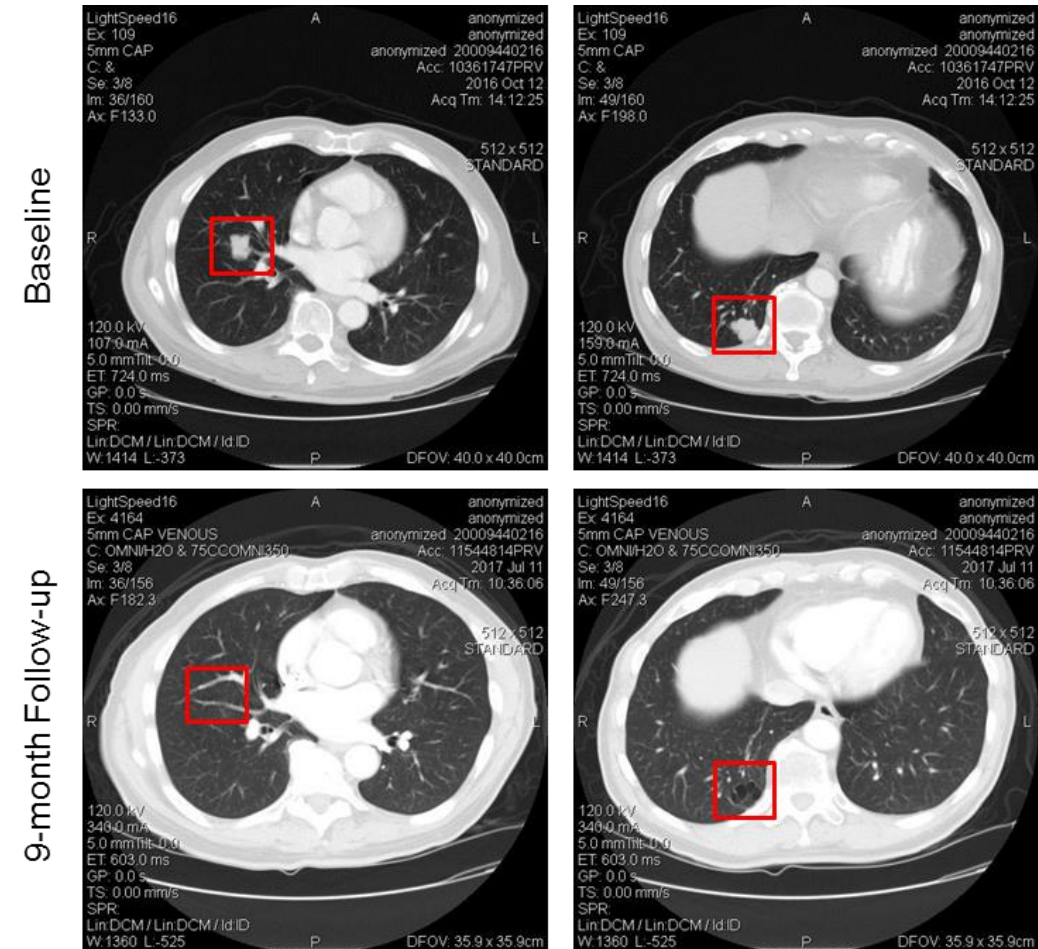


Preliminary Efficacy* by RECIST v1.1

- INCB050465 (PI3K δ i) + pembrolizumab
 - Relapsed SCLC: 2/4 responses (both PR; 2/3 responses in ICI naive)
 - Relapsed NSCLC: 3/14 responses (1 CR; 3/10 responses in ICI naive)
 - Relapsed urothelial carcinoma: 2/5 responses (2 CR; 2/3 responses in ICI naive)
 - Relapsed melanoma: 1 CR in ICI refractory
- Itacitinib (JAKi) + pembrolizumab
 - Relapsed disease, multiple tumor types: 4/49 responses (all PR; 3/21 responses in ICI naive)

Complete Response in a Patient With Urothelial Carcinoma Treated With INCB050465 (PI3K δ i) + Pembrolizumab

- CR was achieved by a 72 year-old white male former smoker with urothelial carcinoma
 - Previously treated with adjuvant Bacillus Calmette-Guérin therapy (best response, CR) followed by adjuvant gemcitabine plus carboplatin
 - Enrolled with target lesions in the lung and nontarget lesions in the lung, lymph node, and brain
 - Initially received INCB050465 30 mg QD, reduced to 20 mg QW
 - All adverse events were grade ≤ 2 ; dose was interrupted for 5 days for absolute neutrophil count decrease



Summary

- In the paired biopsy study, in contrast to itacitinib (JAKi) + pembrolizumab, INCB050465 (PI3K δ i) + pembrolizumab led to:
 - Decreased intratumoral T_{reg} cells
 - Increased intratumoral CD8:T_{reg} ratio
- Analysis of peripheral blood demonstrated that, in contrast to itacitinib (JAKi) + pembrolizumab, INCB050465 (PI3K δ i) + pembrolizumab resulted in a generalized increase in markers of effector T-cell activation
- Treatment with itacitinib (JAKi) or INCB050465 (PI3K δ i) + pembrolizumab differentially regulated proteins involved in lymphocyte proliferation and IFN γ signaling in the peripheral blood

Conclusions

- The combination of INCB050465 (PI3K δ i) + pembrolizumab was associated with favorable changes in the tumor microenvironment and peripheral T-cell activation
 - This combination is under further exploration in Part 2 of this study in patients with small cell lung cancer, non-small cell lung cancer, and urothelial carcinoma
- Itacitinib (JAKi) combined with pembrolizumab was associated with unfavorable changes in the tumor microenvironment and peripheral immune profile, and will not be investigated further in this study

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