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Monotherapy Dose Escalation Clinical and Translational Data from the First-in-Human Study in Advanced Solid Tumors of IPI-549, an Oral, Selective PI3K-γ Inhibitor Targeting Tumor Macrophages

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Presenter Disclosure Information

David S. Hong, MD

The following relationships exist related to this presentation:

- ***Scientific Advisory Boards:*** Adaptimmune, OncoResponse
- ***Research/Grant Funding:*** Adaptimmune, AbbVie, Astra-Zeneca, Bayer, BMS, Lilly, Genentech, Genmab, Kywoya, LOXO, Pfizer, Amgen, Mirati, Ignyta, Merck, Medimmune, Novartis, Infinity, Daiichi-Sankyo, Eisai, Takeda, Molecular Template, Kite
- ***Travel, Accommodations, Expenses:*** MiRNA, LOXO
- ***Consulting or Advisory Roles:*** Amgen, Bayer, Baxter, Guidepoint Global, Janssen
- ***Other Ownership Interests:*** OncoResponse (Founder), Molecular Match (Advisor)

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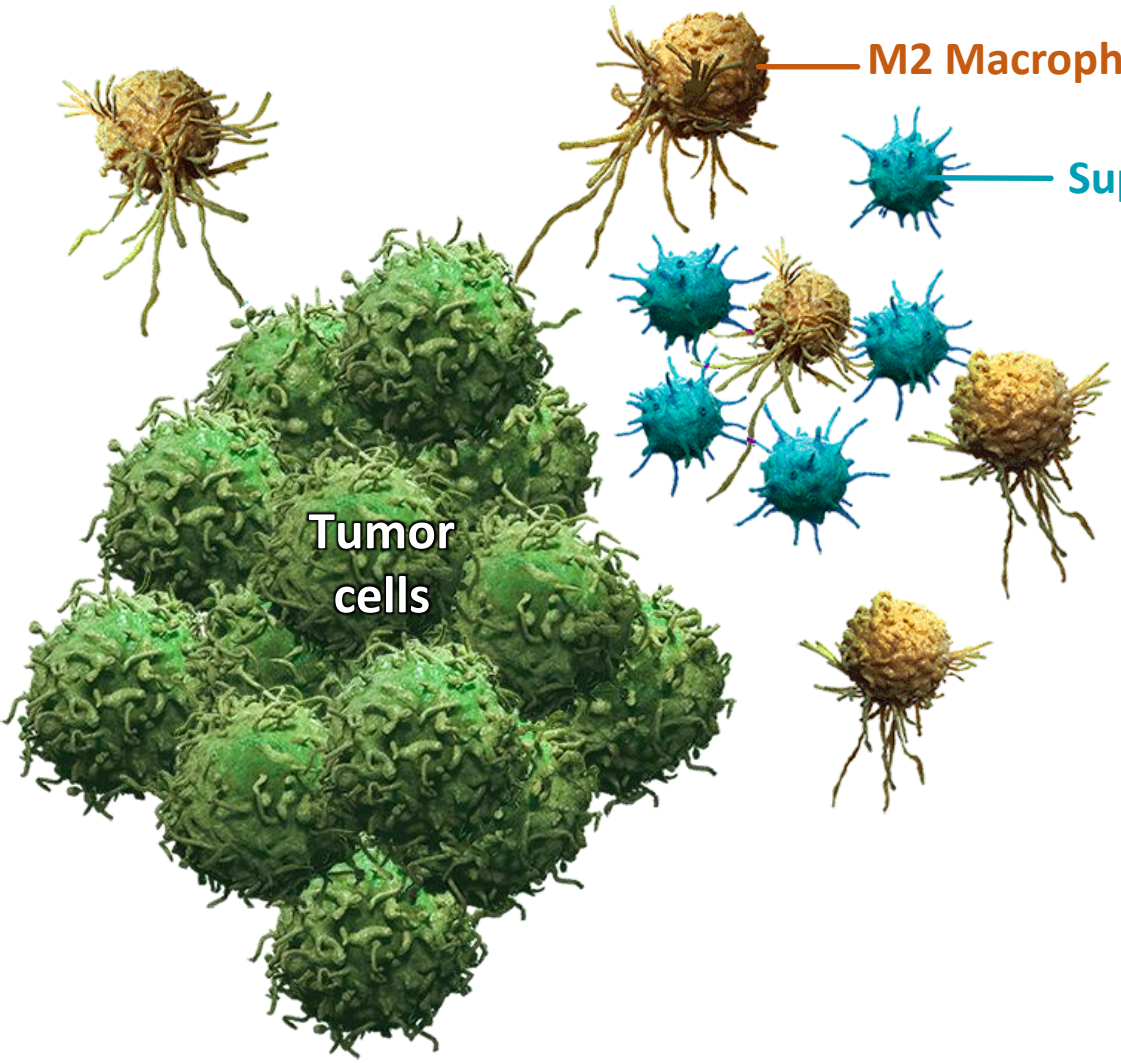
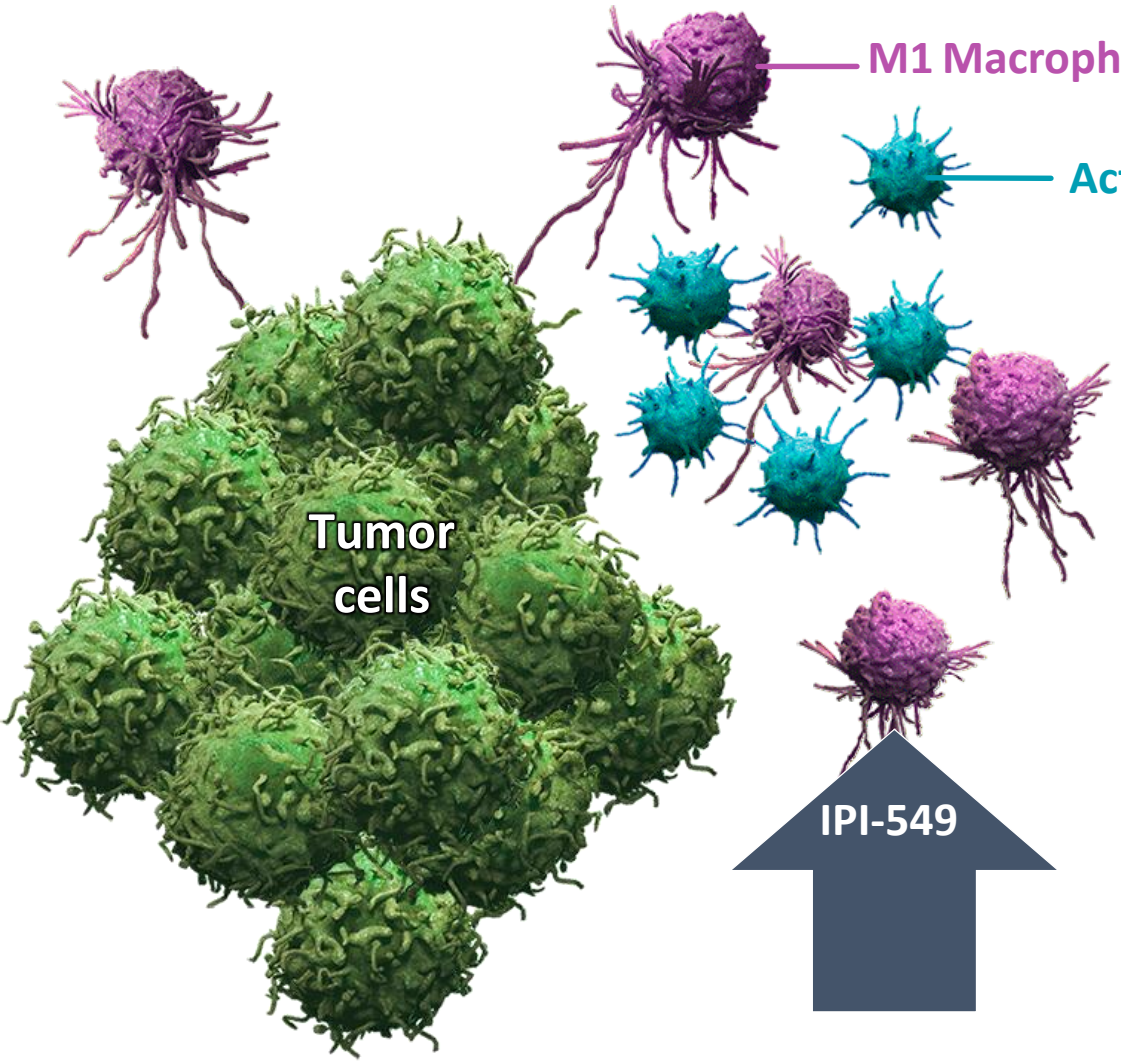
PI3K-γ Inhibition by IPI-549 Activates an Anti-Tumor Immune Response



- Tumors maintain an immunosuppressive microenvironment through interactions with multiple cell types
- PI3K-γ signaling in macrophages/MDSCs plays a key role in maintaining this immunosuppressive tumor microenvironment
- Targeting macrophages/MDSCs may enhance T cell approaches and more fully restore anti-tumor immune response

Kaneda, et al. Nature. 2016 Nov;539:437-442;
De Henau, et al. Nature. 2016 Nov;539:443-447.

PI3K-γ Inhibition by IPI-549 Activates an Anti-Tumor Immune Response



- Inhibition of PI3K-γ by IPI-549 reprograms macrophages from the M2 (pro-tumor) to the M1 (anti-tumor) type, which ultimately:
  - Overcomes immune suppression
  - Promotes immune stimulation
  - Results in anti-tumor immune response

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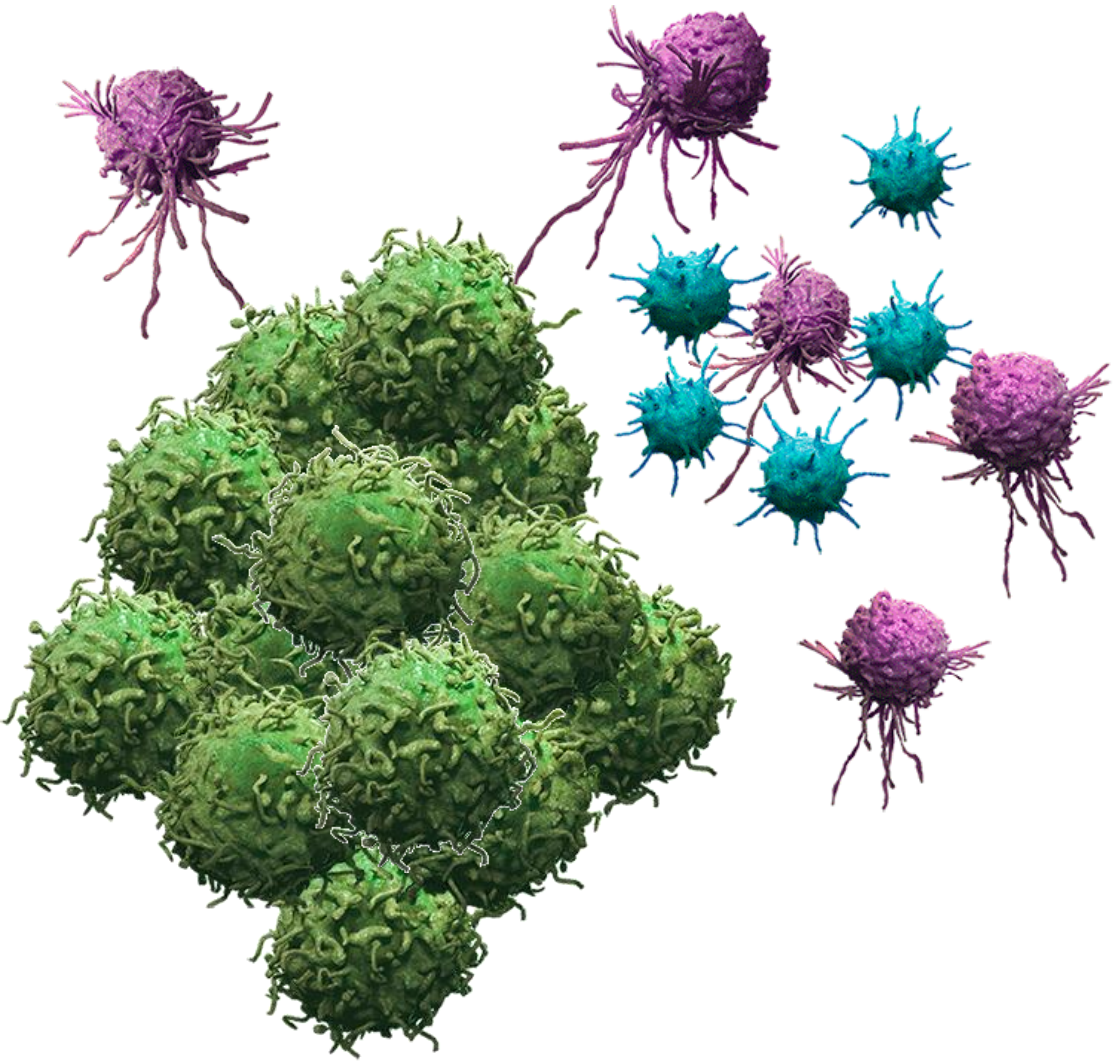

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  - Overcomes immune suppression
  - Promotes immune stimulation
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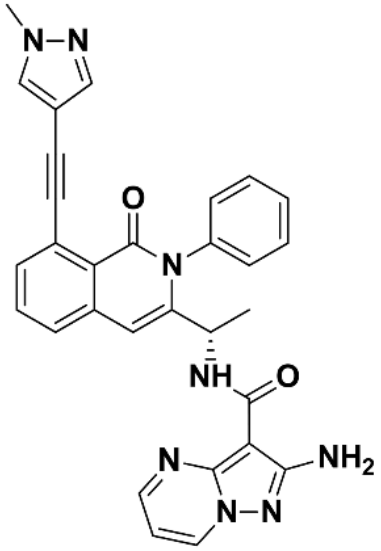
IPI-549: A Potent, First-in-Class, Oral, Selective PI3K-γ Inhibitor

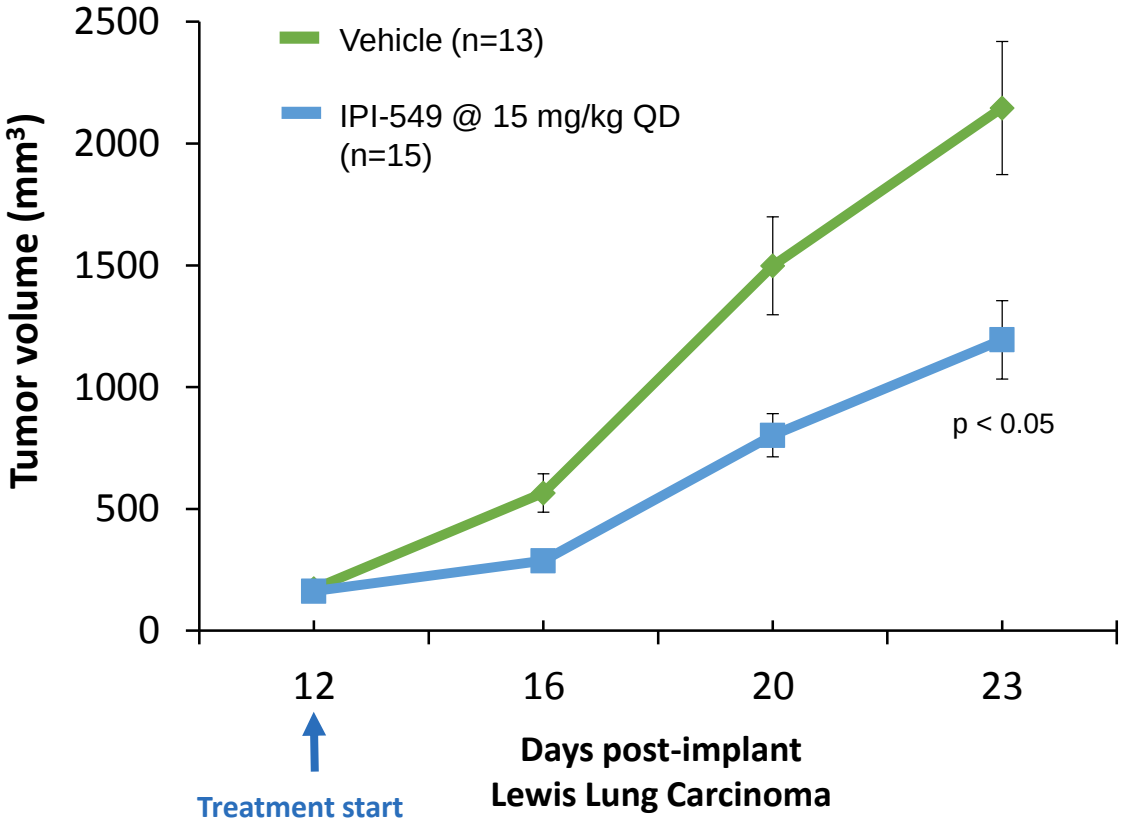
Chemical Structure of IPI-549



Assay	PI3K-γ	PI3K-α	PI3K-β	PI3K-δ
Binding Affinity Kd (nM)	0.29	17	82	23
Biochemical IC_{50} (nM)	15.7	3241	3468	>8421
Cellular IC_{50} (nM)	1.2	248	241	176

> 100 × selectivity in cellular assay

Strong Preclinical Rationale for Developing IPI-549 for the Treatment of Solid Tumors



Evans, et al. ACS Med Chem Lett. 2016;
Kutok, et al. immune Microenvironment: Transforming the Future of Cancer Therapies Meeting, 2015.

IPI-549-01: Trial Design (N~200)

DOSE ESCALATION COHORTS

Solid Tumors

Peripheral Blood Samples

COMPLETED

Monotherapy
10 mg to 60 mg QD

3+3 design

ONGOING → *ONGOING*

ONGOING

Combination
IPI-549 + Nivolumab*

6+6 design

PENDING →

*Flat-dose Nivolumab 240 mg Q2W
28-day cycles

EXPANSION COHORTS

Peripheral Blood Samples

Mandatory Pre-Treatment and On-Treatment Biopsies

All Solid Tumors

NSCLC

SCCHN

Melanoma

*Checkpoint inhibitor-resistant***

** Must have de novo or acquired resistance to immediately prior anti-PD-1/anti-PD-L1 therapy

TNBC

Checkpoint inhibitor-naïve

Mesothelioma

Adrenocortical Carcinoma

Checkpoint inhibitor-independent

IPI-549-01: Monotherapy Dose Escalation

DOSE ESCALATION COHORTS
Solid Tumors

- Monotherapy 60 mg QD → *COMPLETED*
  - No DLTs: MTD was not identified
  - Expansion initiated based on PK/PD
- Monotherapy 40 mg QD
- Monotherapy 30 mg QD
- Monotherapy 20 mg QD
- Monotherapy 15 mg QD
- Monotherapy 10 mg QD

3+3 design
N=19 total, 18 evaluable

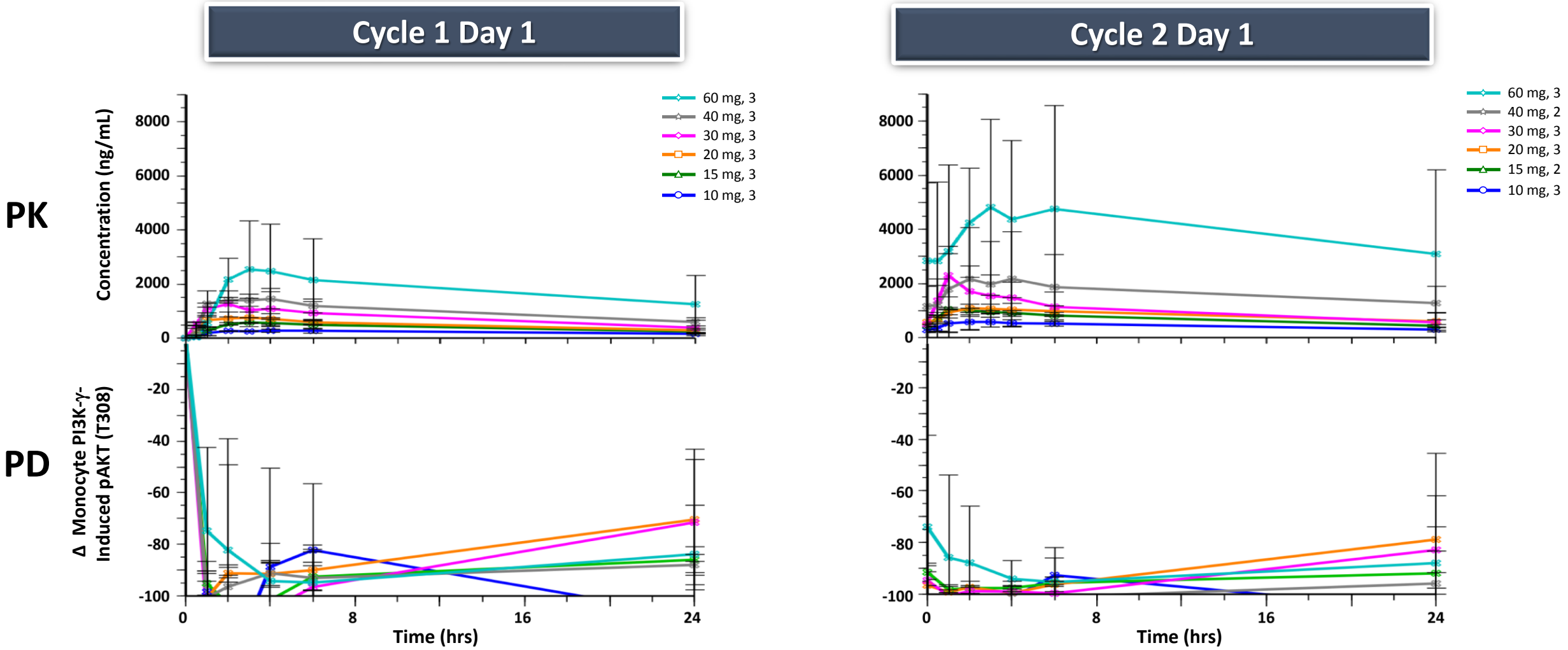
Endpoints:
- PK/PD
- Safety
- Activity
- Peripheral Blood Samples for Translational Analysis

Patient Demographics

Baseline Characteristics	All Patients N=19
Age (years), median (range)	63 (42-83)
Male, n (%)	7 (37)
Female, n (%)	12 (63)
ECOG Performance Status, n (%)	
0	7 (37)
1	11 (58)
# of Prior Lines of Therapy, median (range)	4 (0-11)
Prior PD-1/PD-L1 Therapy, n (%)	2 (11)

Data as of 18 October 2017

PK/PD Time Profile



Linear PK, limited accumulation; sustained inhibition of PI3K-γ at doses ≥ 20 mg QD

Safety Summary (N=19)

- IPI-549 monotherapy has been well tolerated (doses up to 60 mg QD)
- No DLTs - MTD was not identified
- Majority of reported AEs have been Grade 1-2 per NCI CTCAE
- No treatment-related SAEs or treatment-related deaths
- 2 patients discontinued study drug due to treatment-related AEs:
  - Grade 2 rash and Grade 2 ALT/AST increase
  - Grade 3 ALT/AST increase

Data as of 18 October 2017

TEAEs ≥15% of Patients (All Causality; All Grades and Grade ≥3)

TEAE	All Grades n (%)	Grades ≥3 n (%)
Alanine aminotransferase increased	5 (26)	1 (5)
Aspartate aminotransferase increased	5 (26)	1 (5)
Anaemia	5 (26)	2 (11)
Fatigue	4 (21)	0
Diarrhoea	4 (21)	0
Cough	4 (21)	0
White blood cell count decreased	3 (16)	1 (5)
Rash maculo-papular	3 (16)	0
Nausea	3 (16)	0
Headache	3 (16)	0
Hypomagnesaemia	3 (16)	0
Pyrexia	3 (16)	0

Data as of 18 October 2017

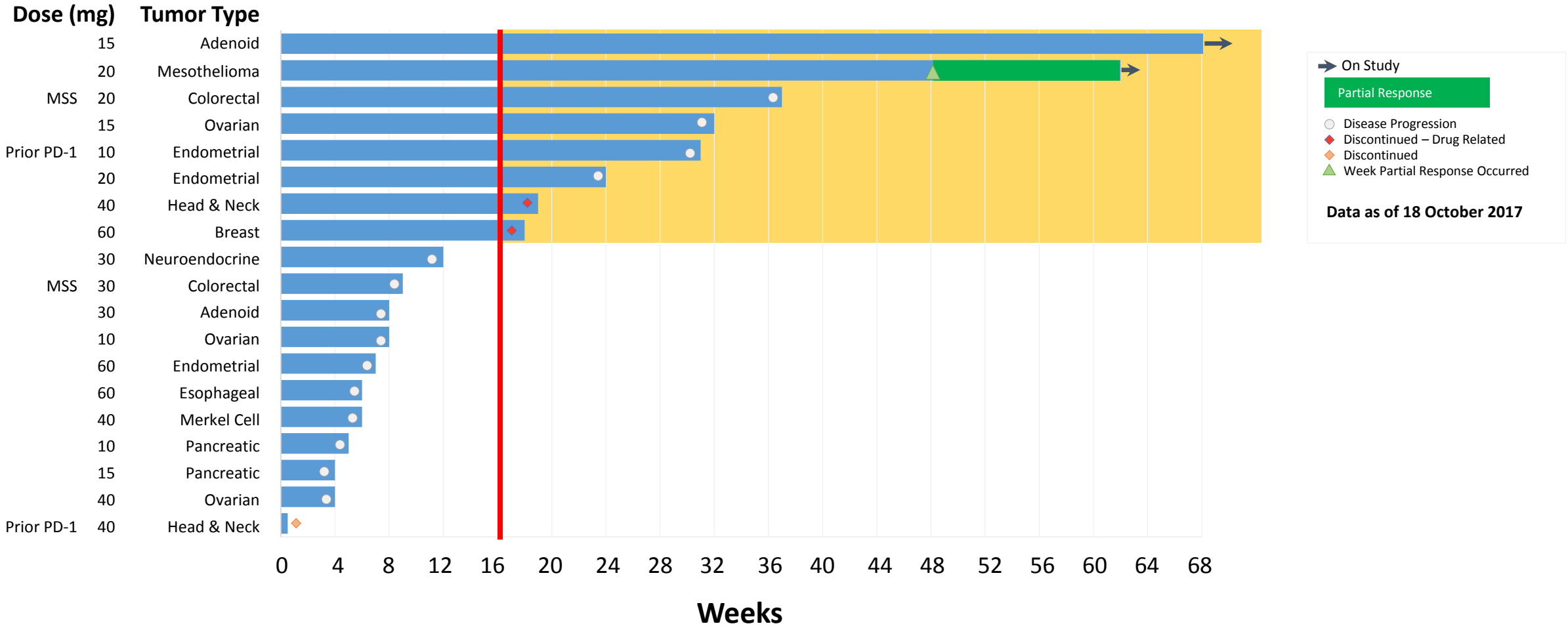
Treatment-Related* TEAEs (All Grades and Grades ≥3)

Treatment-Related* TEAE	All Grades n (%)	Grades ≥3 n (%)
Alanine aminotransferase increased	3 (16)	1 (5)
White blood cell count decreased	2 (11)	0
Rash maculo-papular	2 (11)	0
Aspartate aminotransferase increased	2 (11)	1 (5)
Headache	2 (11)	0
Dysaesthesia	1 (5)	0
Gamma-glutamyltransferase increased	1 (5)	0
Hypomagnesaemia	1 (5)	0
Paraesthesia oral	1 (5)	0
Nausea	1 (5)	0
Blepharospasm	1 (5)	0
Dizziness	1 (5)	0
Neuropathy peripheral	1 (5)	0
Eye swelling	1 (5)	0
Hypoalbuminaemia	1 (5)	0
Diarrhoea	1 (5)	0
Blood cholesterol increased	1 (5)	0
Hyponatraemia	1 (5)	0
Ocular hyperaemia	1 (5)	0
Anaemia	1 (5)	0
Fatigue	1 (5)	0
Pruritus	1 (5)	0
Hypercalcaemia	1 (5)	0

Data as of 18 October 2017

***As assessed by Investigator**

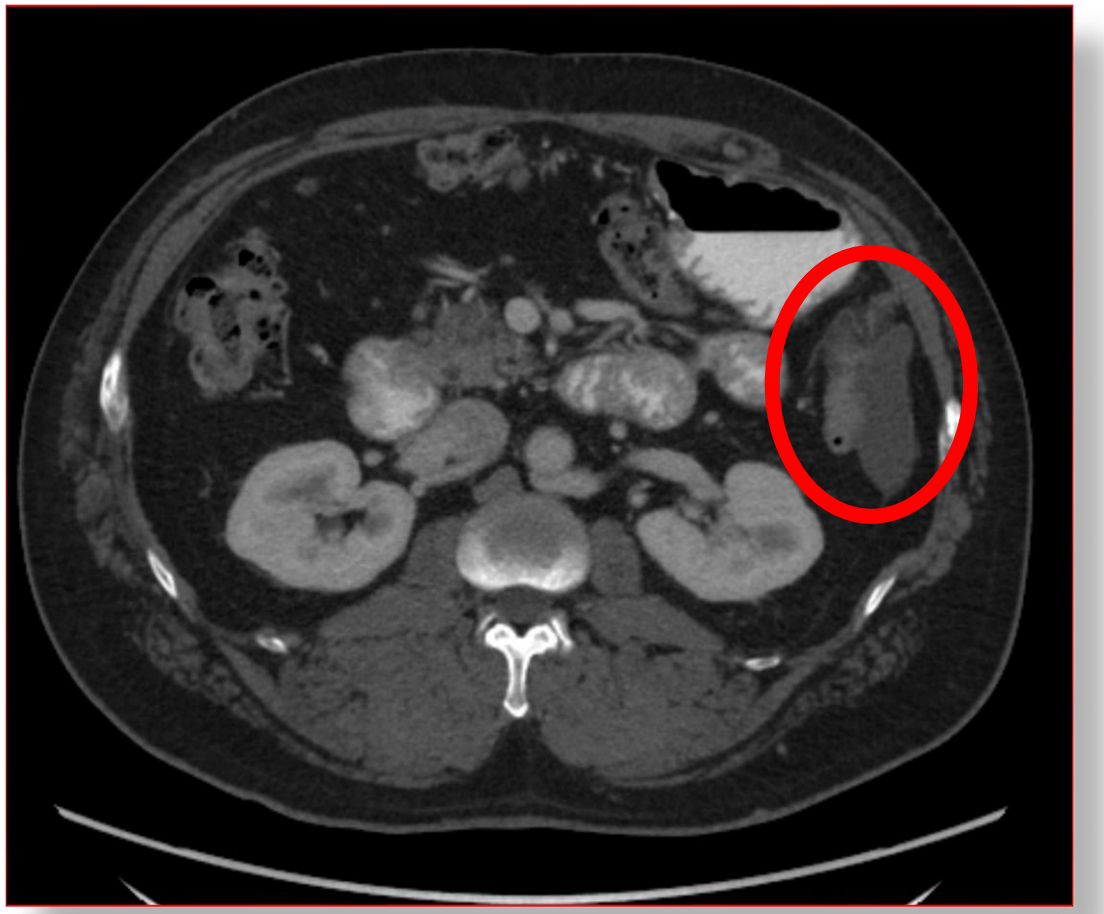
Time on Study (N=19)



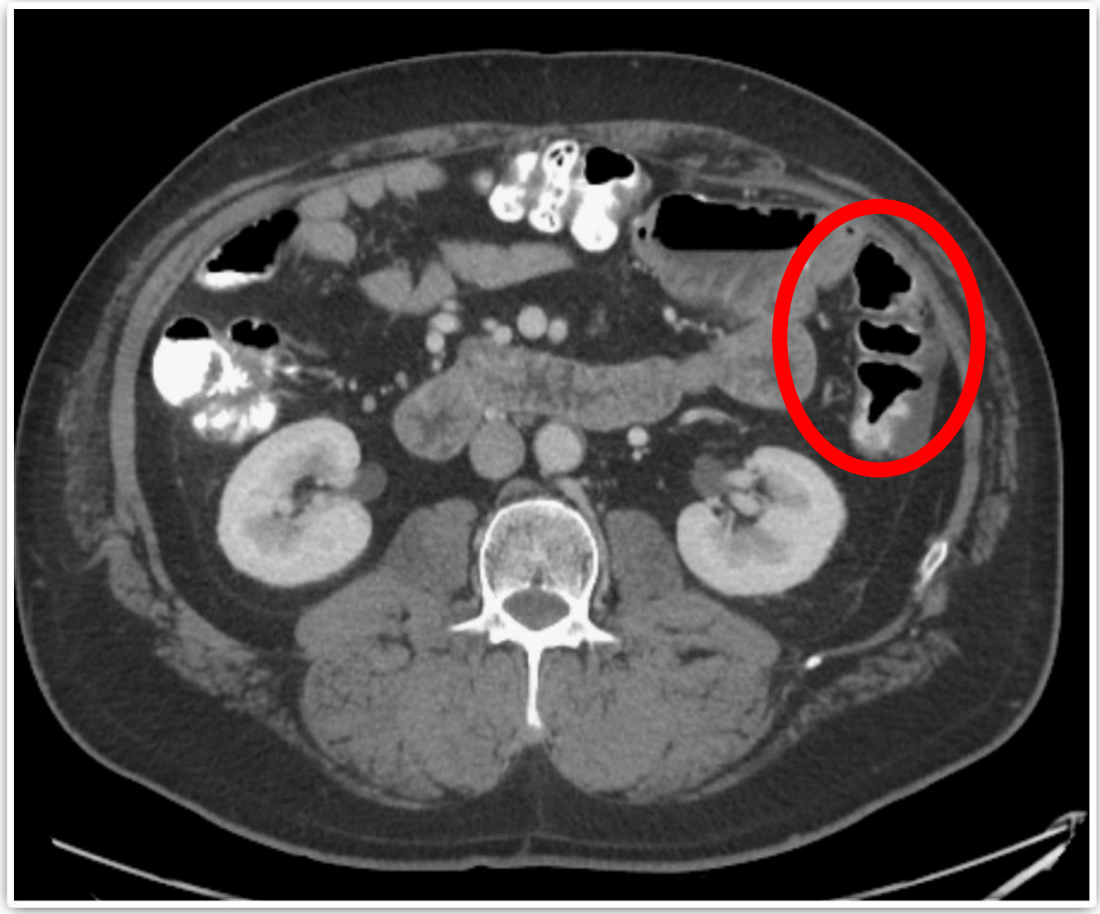
Clinical benefit defined as patients who have not progressed at 16 weeks (8/18 evaluable patients)

Partial Response in a Patient with Advanced Peritoneal Mesothelioma

- Original dx: October 2013
- 4 prior regimens, last regimen pemetrexed/carboplatin (DOT 2.5 mo)
- Patient remains on treatment >1 year



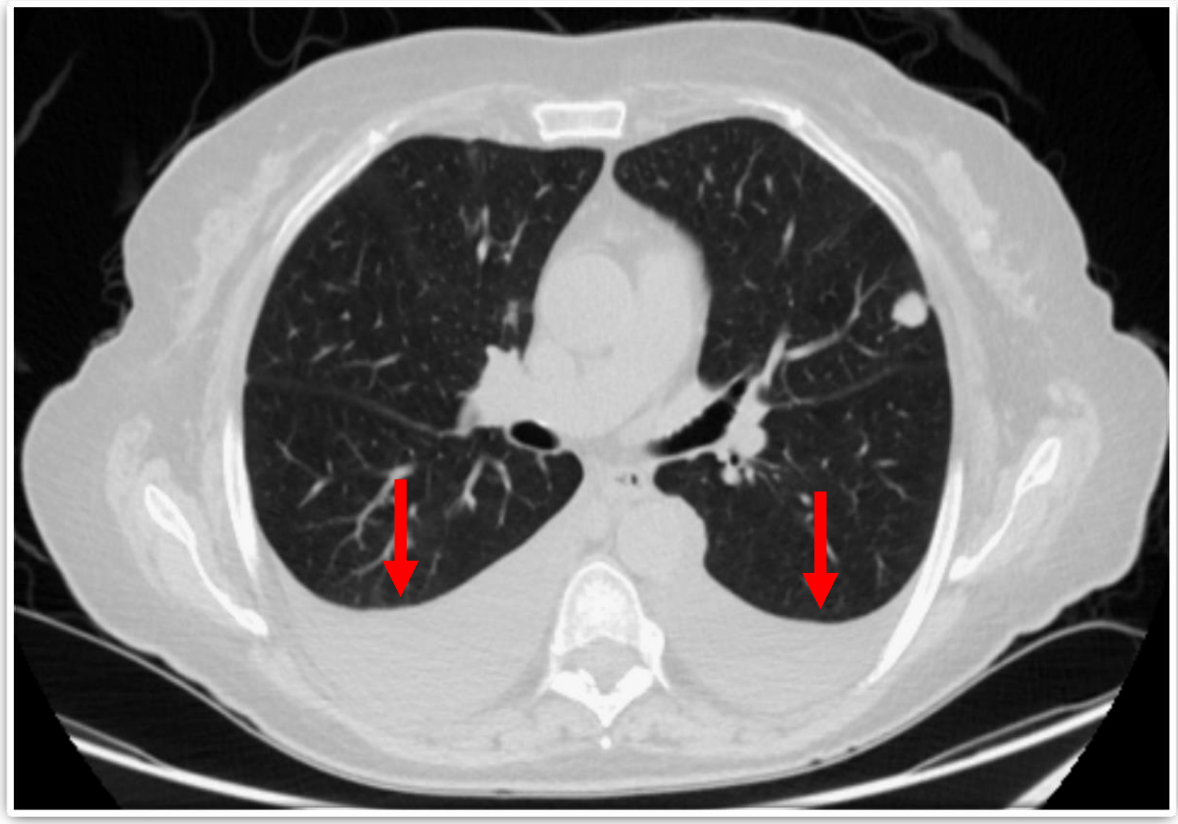
Baseline



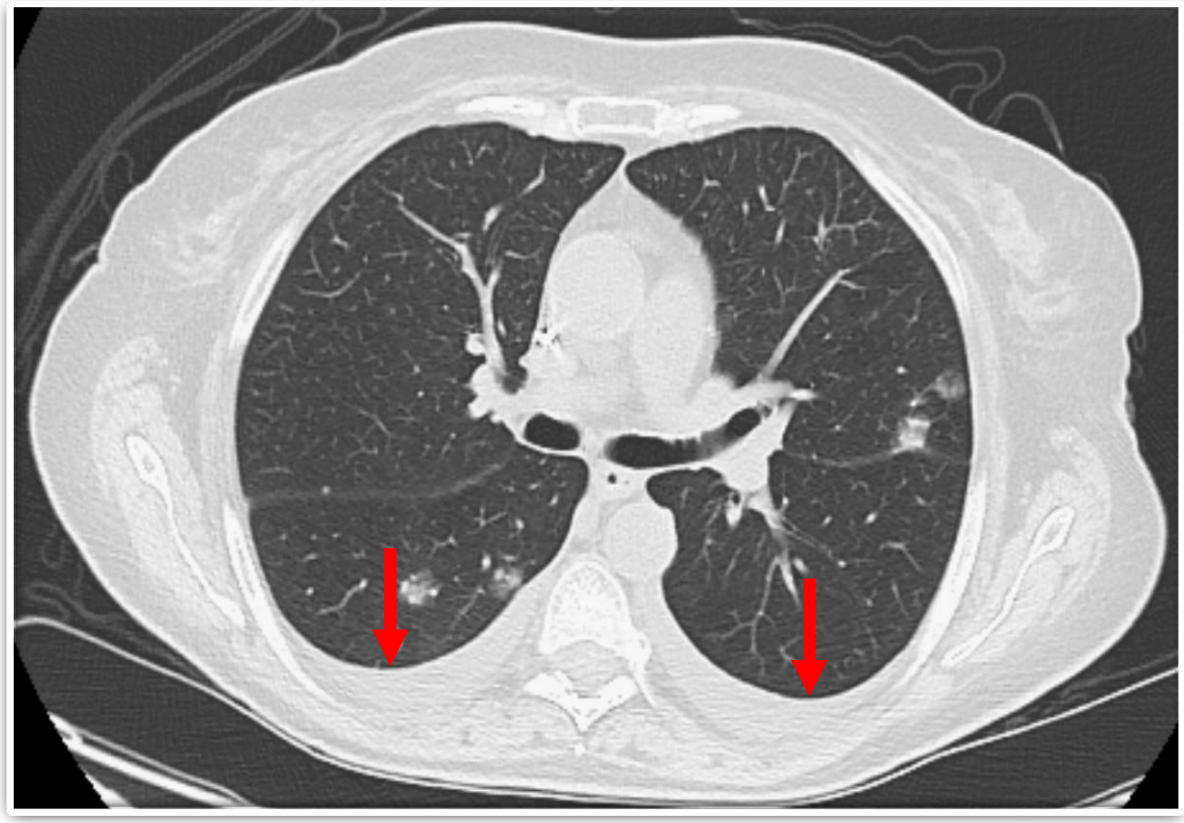
End of Cycle 15

Improvement of Malignant Pleural Effusions in Heavily Pre-Treated Patient with KRAS+ MSS CRC

- Stage IV dx: July 2012 with 8 prior regimens (duration of last prior therapy: ~2 mos.)
- Extensive peritoneal carcinoma with ascites; bilateral pleural effusion, as well as liver and lung lesions
- On Monotherapy Tx for 36 weeks



Baseline



End of Cycle 2

Translational Data in Peripheral Blood

- Monotherapy treatment enables demonstration of IPI-549-specific immune-modulatory activity

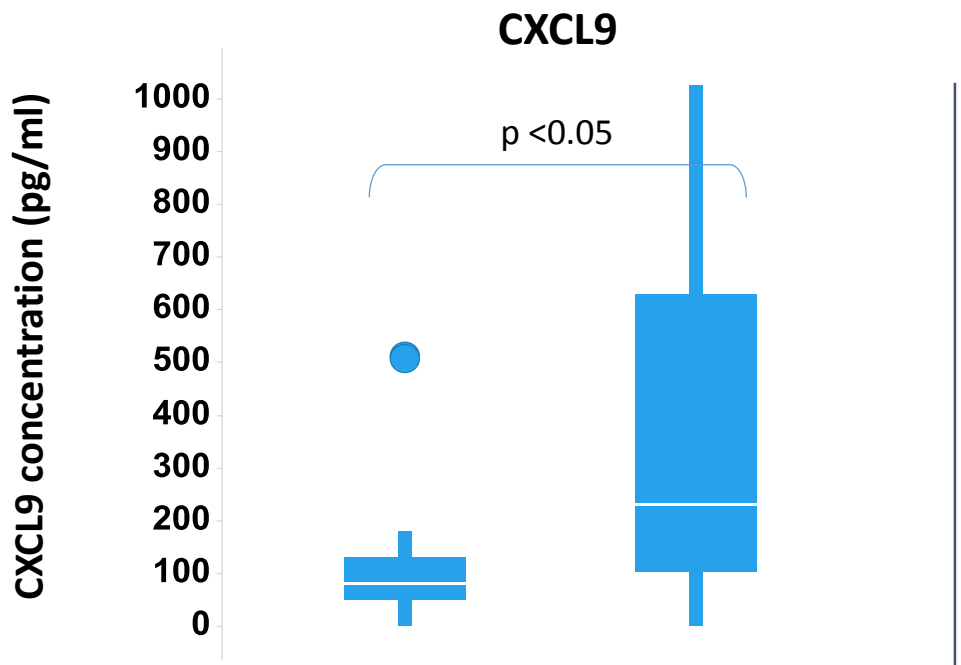
- Monotherapy dose escalation translational studies using peripheral blood include:
    - Serum cytokine/chemokine analysis (Milliplex luminex 61 analyte panel)
    - Immune subset analysis (Flow cytometry)
    - Gene Expression Profiling (RNA seq)

Initial Translational Data in Peripheral Blood Support IPI-549 On-Mechanism Immune Stimulation

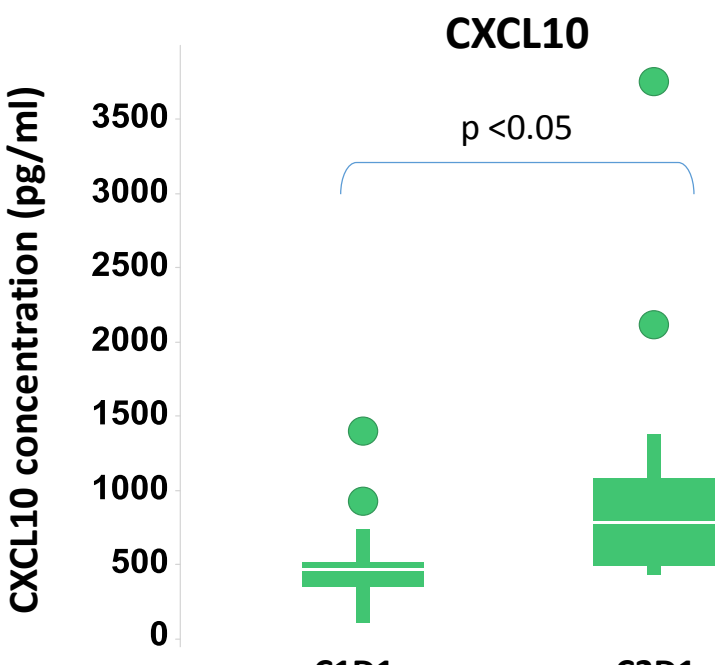
- Evidence of immune stimulation
  - **Up-regulation of interferon-gamma (γ) responsive factors**
  - Reinvigoration (proliferation) of exhausted CD8+ T-cells

- Clinical benefit associated with markers of increased monocyte/ myeloid cell activation

Increase in Interferon-γ-Responsive Serum M1 Chemokines[1], Consistent with IPI-549-Induced Immuno-Stimulatory State



	C1D1	C2D1
N	17	17
Median	81	229
Avg	129	335



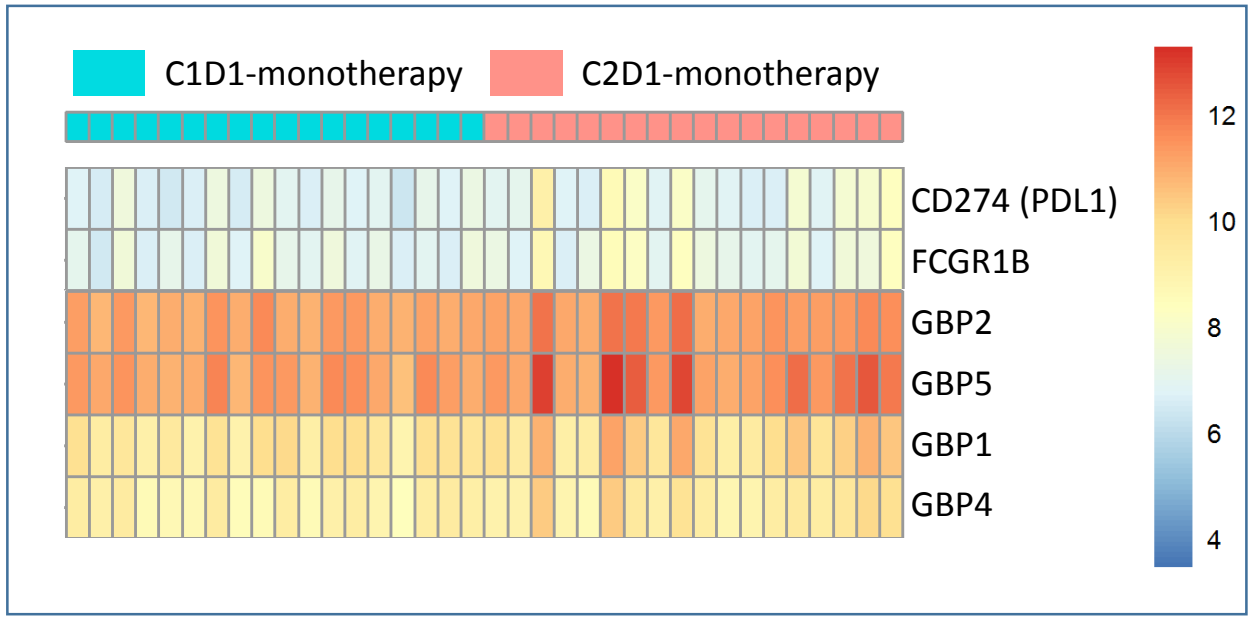
	C1D1	C2D1
N	17	17
Median	467	783
Avg	518	994

Similar increases in CXCL9 and CXCL10 were reported in patients receiving anti-PD-1 therapy [2]

1. Goswami, et al. Cellular Immunology. 2017
2. Choueiri, et al. Clin Cancer Res. 2016

Up-Regulation of Interferon-γ-Responsive Gene Expression, Consistent with IPI-549-Induced Immuno-Stimulatory State

IFN-γ -responsive genes	Fold increase at C2D1	P value
CD274 (PDL1)	2.4	3.5×10^{-5}
FCGR1B	1.8	1.5×10^{-3}
GBP2	1.5	5.6×10^{-4}
GBP5	2.3	1.3×10^{-4}
GBP1	2.0	1.9×10^{-4}
GBP4	1.7	9.4×10^{-4}



RNA Seq peripheral blood across all dose levels

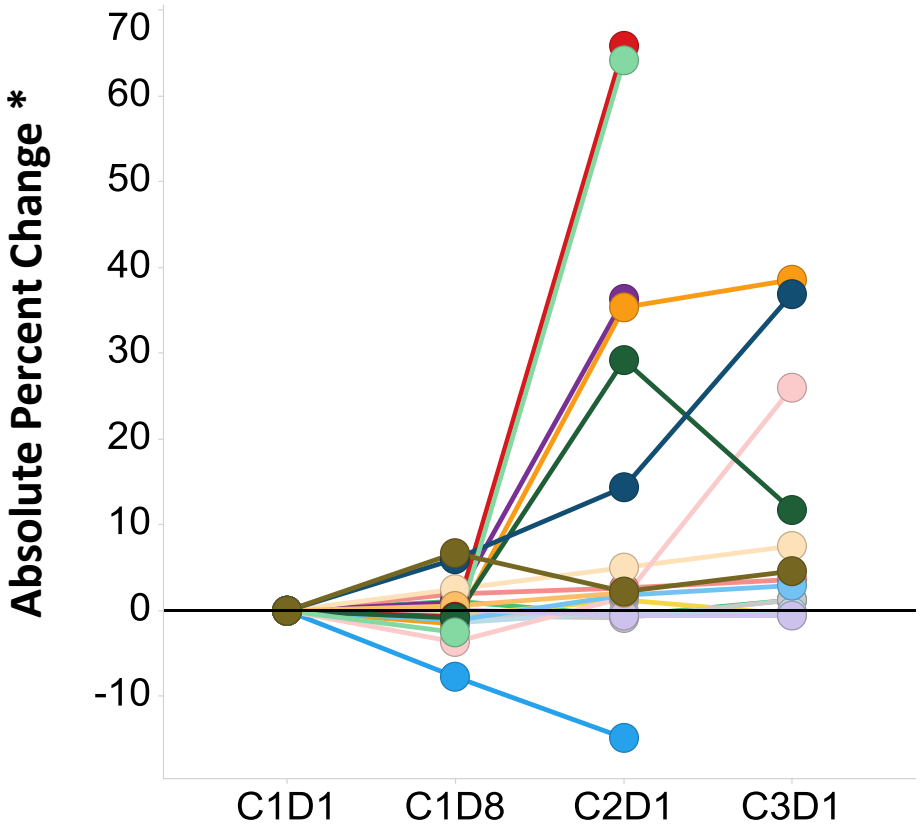
The above interferon-γ-responsive genes were among the top 30 most significantly differentially expressed genes

Initial Translational Data in Peripheral Blood Support IPI-549 On-Mechanism Immune Stimulation

- Evidence of immune stimulation
  - Up-regulation of interferon- γ -responsive factors
  - **Reinvigoration (proliferation) of exhausted CD8+ T cells**
- Clinical benefit associated with markers of increased monocyte/myeloid activation

Reinvigoration of Exhausted CD8+ Memory T cells

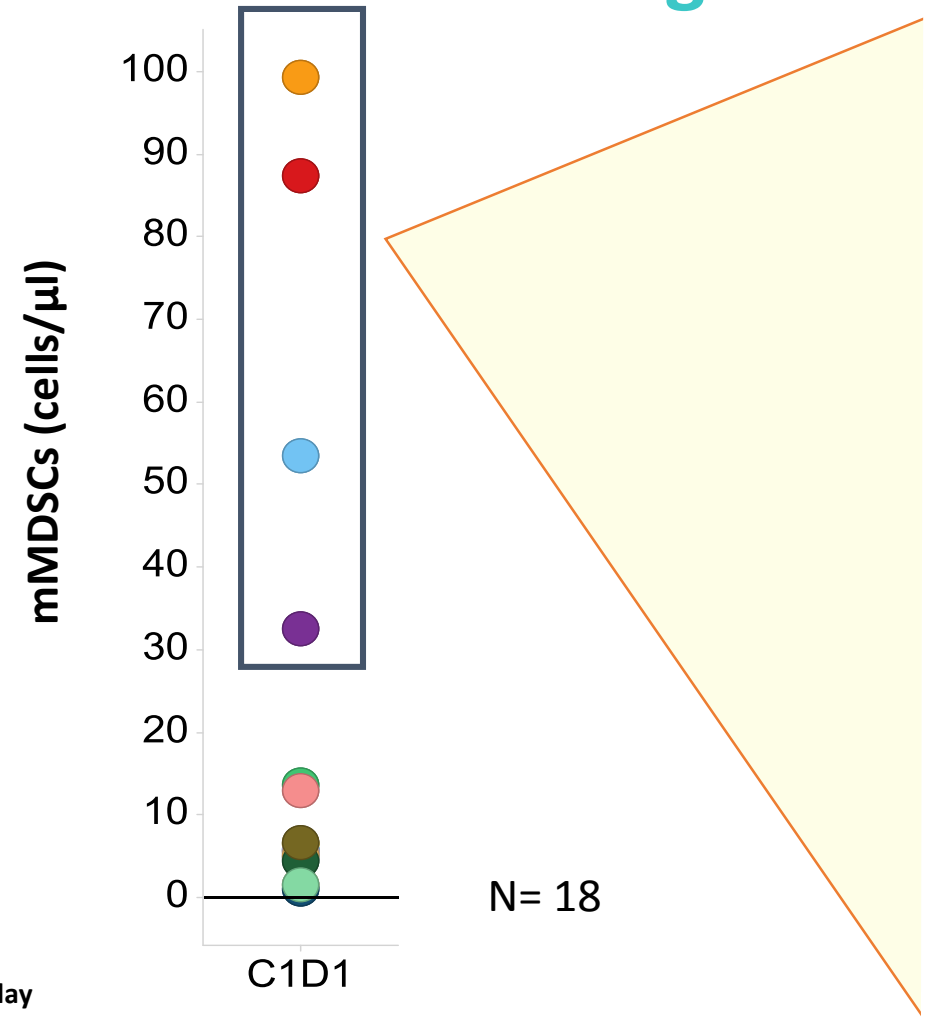
Proliferating PD1+ memory CD8+ T cells

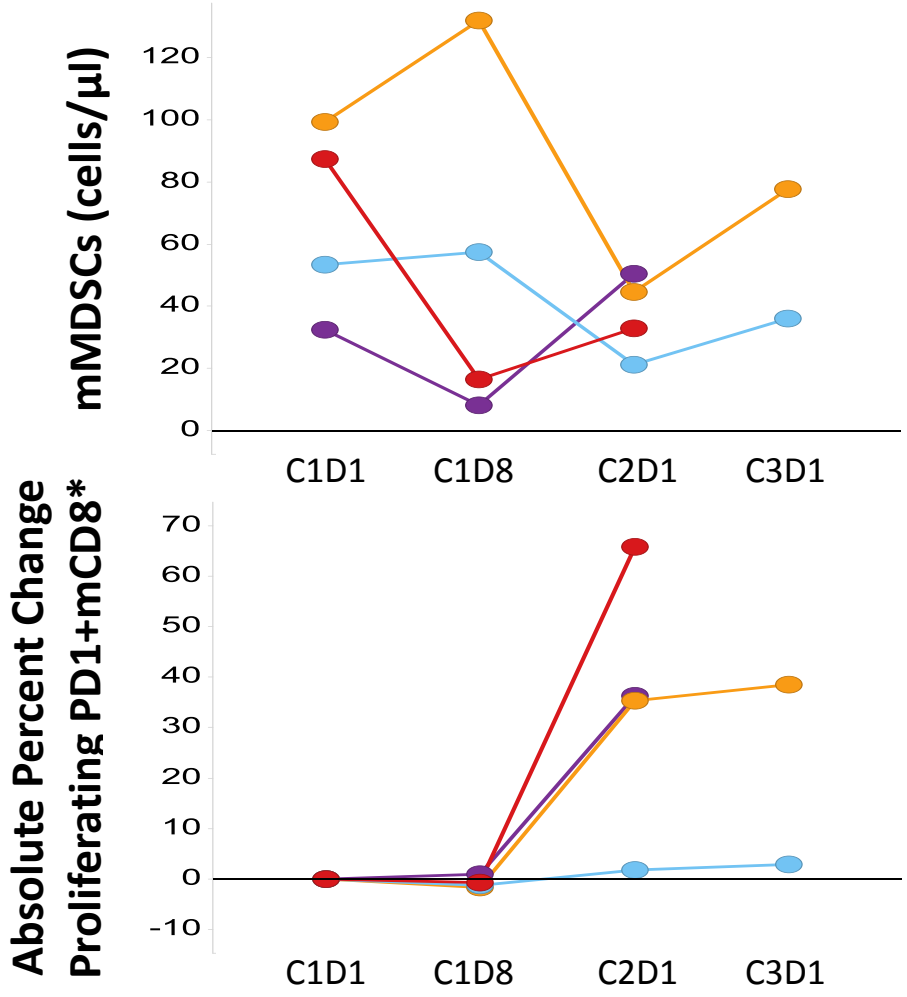


- Increases in proliferating CD8+ T cells appear specific to PD1+ memory subset.
- Similar increases in proliferating PD1+ CD8+ memory T cells reported in melanoma patients receiving anti-PD-1 therapy.
  (Huang et al. Nature. 2017;545:60-65)

C=cycle, D=day
***Difference in % from C1D1 of Ki-67+ PD1+CD8+ memory T cells of total PD1+ CD8+ memory T cells (CD3+ CD8+ CD45RA-)**

Decrease in High Basal Monocytic MDSCs with IPI-549 Treatment is Associated with Reinvigoration of Exhausted Memory CD8+ T cells





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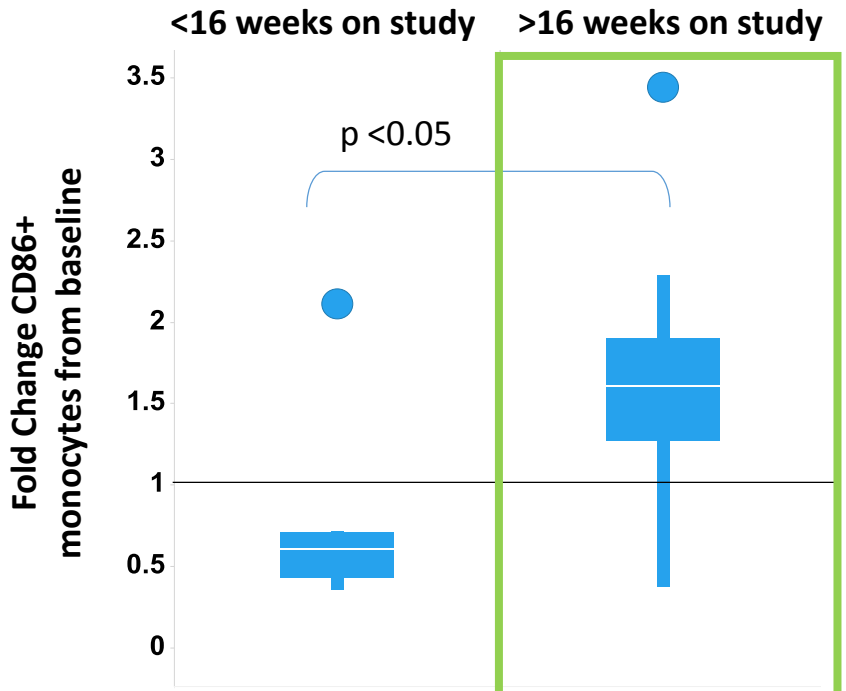
*Difference in % from C1D1 of Ki-67+ PD1+CD8+ memory T cells of total PD1+ CD8+ memory T cells (CD3+ CD8+ CD45RA-)

Initial Translational Data in Peripheral Blood Support IPI-549 On-Mechanism Immune Stimulation

- Evidence of immune stimulation
  - Up-regulation of interferon-γ-responsive factors
  - Reinvigoration (proliferation) of exhausted CD8+ T cells
- **Clinical benefit associated with increased numbers of activated monocytes**

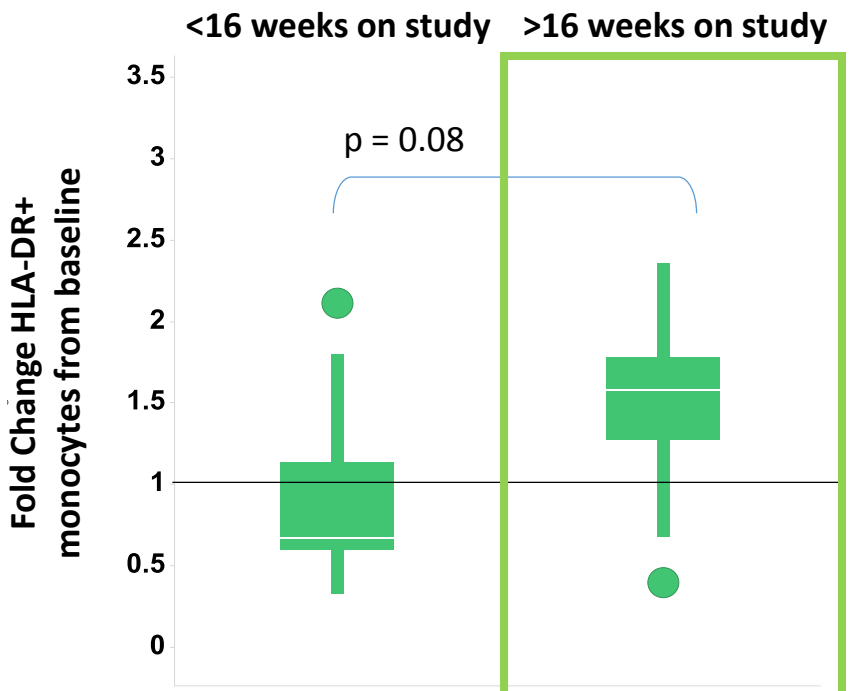
Patients with Clinical Benefit Show Increased Numbers of Activated Monocytes (>16 Weeks on Study)

CD86



	Max change	Max change
N	10	8
Median	0.6	1.6
Avg	0.7	1.7

HLA-DR



	Max change	Max change
N	10	8
Median	0.7	1.6
Avg	0.9	1.5

Max change = Maximum change observed among C1D8, C2D1, C3D1.

Conclusions

- IPI-549 has been well tolerated at all doses studied (10 mg to 60 mg QD); expansion at 60 mg QD is ongoing
  - No DLTs, treatment-related SAEs, or treatment-related deaths
- IPI-549 as monotherapy demonstrates evidence of clinical activity
  - 44% of patients on treatment over 16 weeks
  - Partial response in mesothelioma; expansion cohort in combination with nivolumab being initiated
- Encouraging evidence of IPI-549-induced immune activation in peripheral blood across multiple tumor types and dose levels, including evidence of biomarkers that correlate with clinical benefit (>16 weeks on study)
  - Pre- and on-study biopsies in currently enrolling monotherapy expansion patients will enable further characterization of intra-tumoral, immune-activating effects

Acknowledgments

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THANK YOU