SITC 2016

NATIONAL HARBOR, MD
NOVEMBER 9-13, 2016

Society for Immunotherapy of Cancer

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Reactivating the anti-tumor immune response by targeting innate and adaptive immunity in a phase I/II study of intratumoral IMO-2125 in combination with systemic ipilimumab in patients with anti-PD-1 refractory metastatic melanoma

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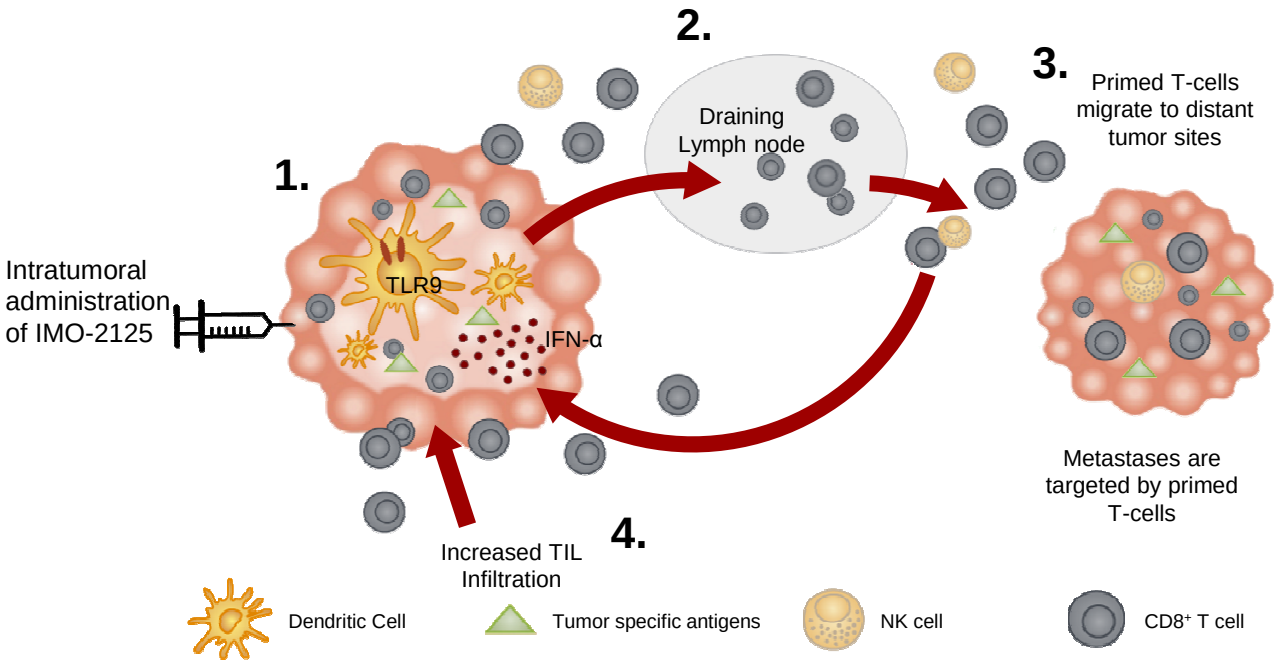
Presenter Disclosure Information

Cara Haymaker

The following relationships exist related to this presentation:

No Relationships to Disclose

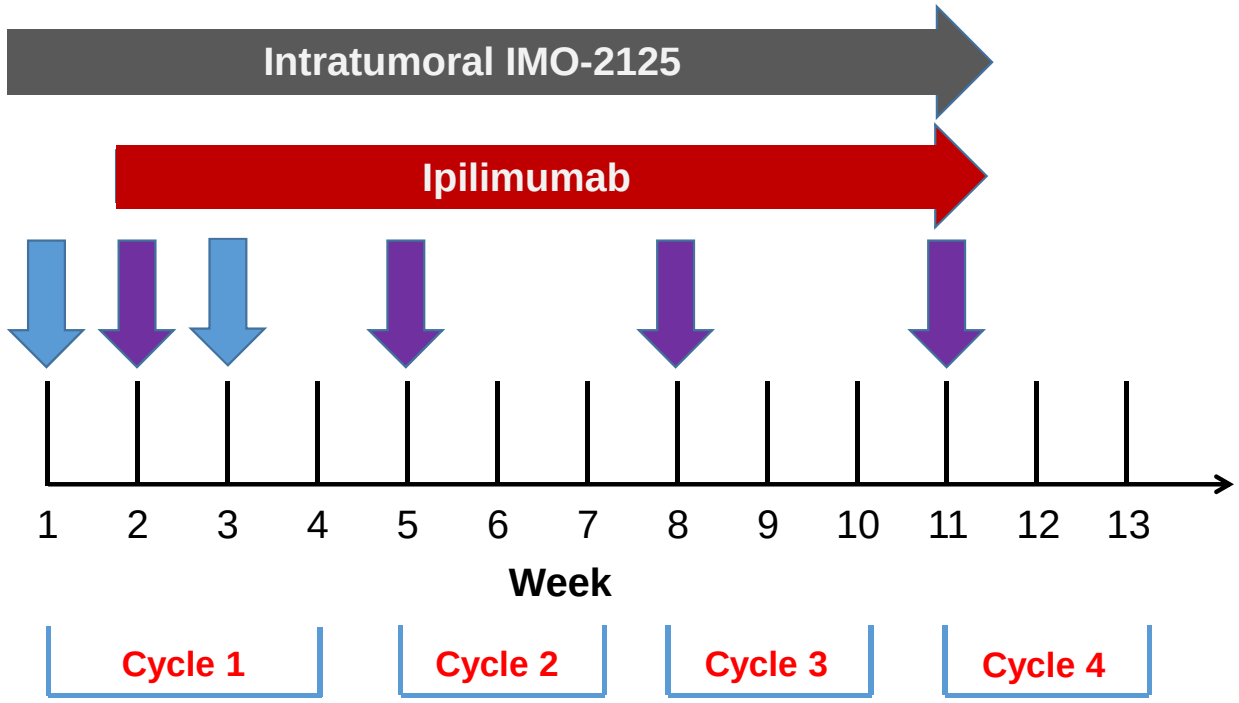
Modulation of the tumor microenvironment by intratumoral administration of the TLR9 agonist IMO-2125



Arm 1 Trial Design (NCT02644967)

i.t. IMO-2125 alone

i.t. IMO-2125 + Ipilimumab



Key Enrollment Criteria

Inclusion Criteria

- Diagnosis of metastatic melanoma with stage III (in transit lesions), IVA, IVB, or IVC disease
- **Progressive disease after treatment with PD-1 inhibitor**
- ≥ 2 measurable tumor lesions ≥ 1.0 cm
- ≥ 18 years
- ECOG ≤ 2
- Adequate renal, bone marrow, liver and cardiac function

Exclusion Criteria

- Received therapy with prior TLR agonist therapy
- Symptomatic, unstable or progressing CNS, meningeal, or epidural disease
- Concurrent systemic steroid therapy higher than physiologic dose (7.5 mg/day of prednisone)
- Active autoimmune disease requiring disease-modifying therapy

Patient Characteristics

Characteristics	N (%)
Age (yrs.) • Mean • Range	 55 39-76
Male Female	6 (60%) 4 (40%)
BRAF V600E (+)	3 (30%)
Mucosal Melanoma	2 (20%)
Visceral Disease	8 (80%)
Brain Metastases (treated)	1 (10%)
Received anti-PD-1	10 (100%)
Received anti-CTLA-4	5 (50%)
Duration on anti-PD-1 therapy	8-63 weeks

Data cut off: Oct 07, 2016

Most Frequent Adverse Events

AE Preferred Term	All, N (%)	Grade III, N (%)	Grade IV, N (%)
Any	10 (100)	5 (50)	1 (10)
Nausea	6 (60)	1 (10)	-
Vomiting	5 (50)	-	-
Anemia	4 (40)	1 (10)	-
Diarrhea	4 (40)	2 (20)	-
ALT increase	3 (30)	1 (10)	-
AST increase	3 (30)	-	1 (10)
Triglycerides increase	3 (30)	-	-
Chills	3 (30)	-	-
Fatigue	3 (30)	-	-
Pyrexia	3 (30)	1 (10)	-
Decreased WBC	3 (30)	-	-

Data cut off: Oct 07, 2016

Safety Summary (N=10)

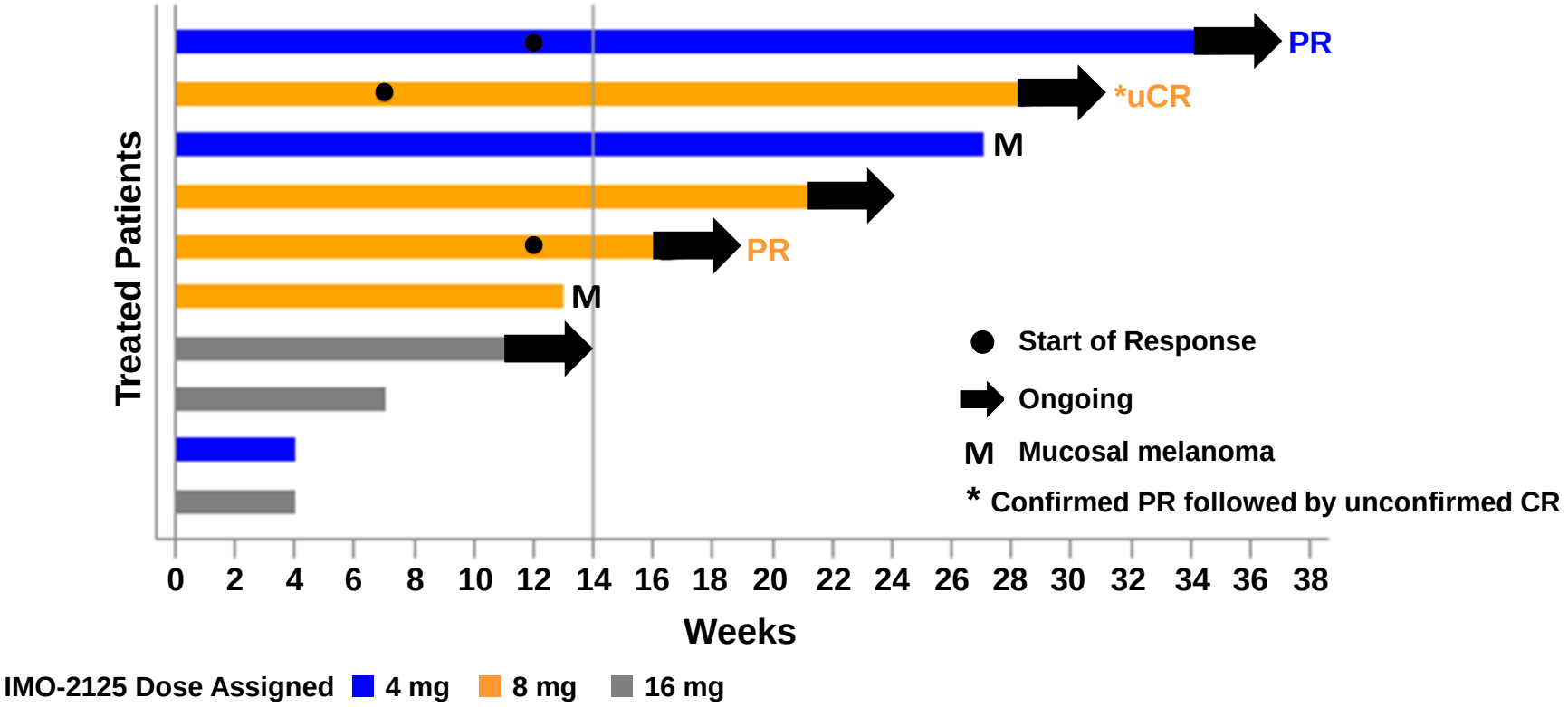
IMO-2125 dosing cohort (ipi 3 mg/kg x 4 doses)

N subjects with…	4 mg (N=3)	8 mg (N=4)	16 mg (N=3)	Total (N=10)
≥ 1 TEAE	3 (100)	4 (100)	3 (100)	10 (100)
Related TEAE	2 (67)	4 (100)	2 (67)	8 (80)
≥ 1 SAE	2 (67)	2 (50)	2 (67)	6 (60)^
Discontinue for AE	0	0	0	0
Death from AE	0	0	0	0
DLT	0	0	0	0

^related SAE (IMO or ipi): hypophysitis (2), fever, elevated LFT's, diarrhea, nausea

Data cut off: Oct 07, 2016

Early response data to IMO-2125 + Ipilimumab

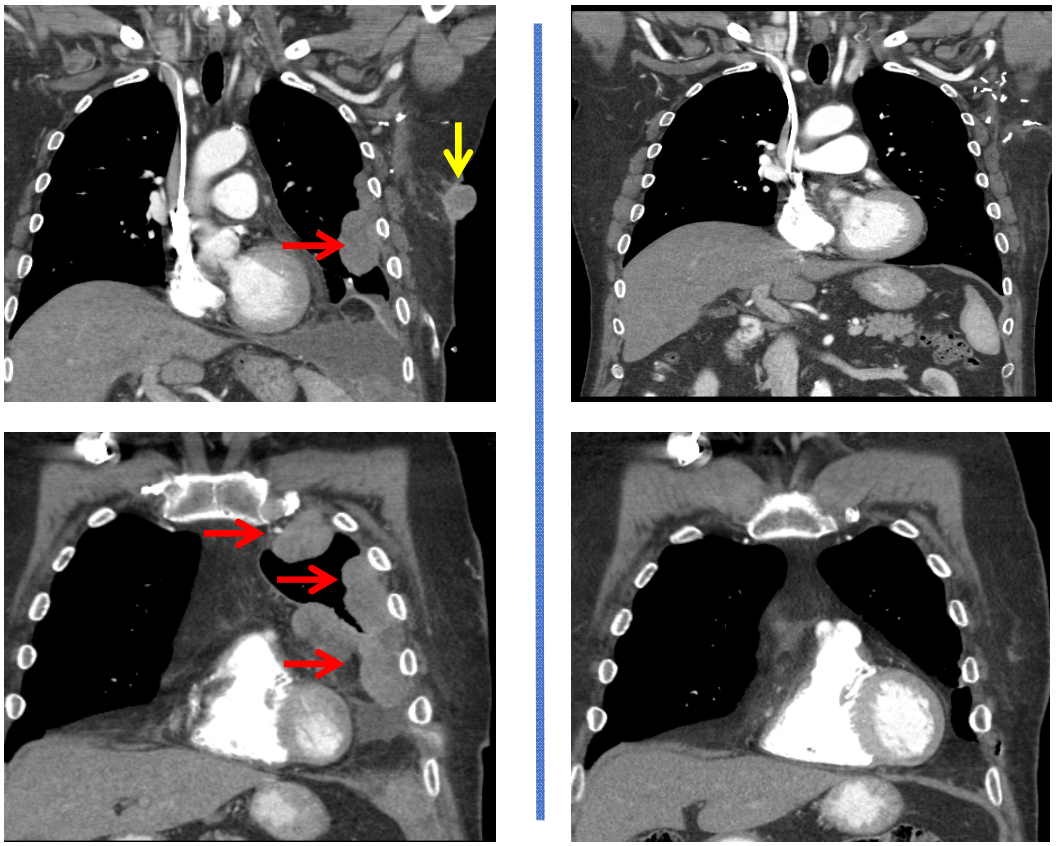


Data cut off: Nov. 7, 2016

Tumor Imaging of Patient with a Complete Response:

Ipilimumab 3mg plus i.t. IMO-2125 8 mg

Pre-Therapy 03/2016



Post-Therapy 08/2016

Injected Lesion

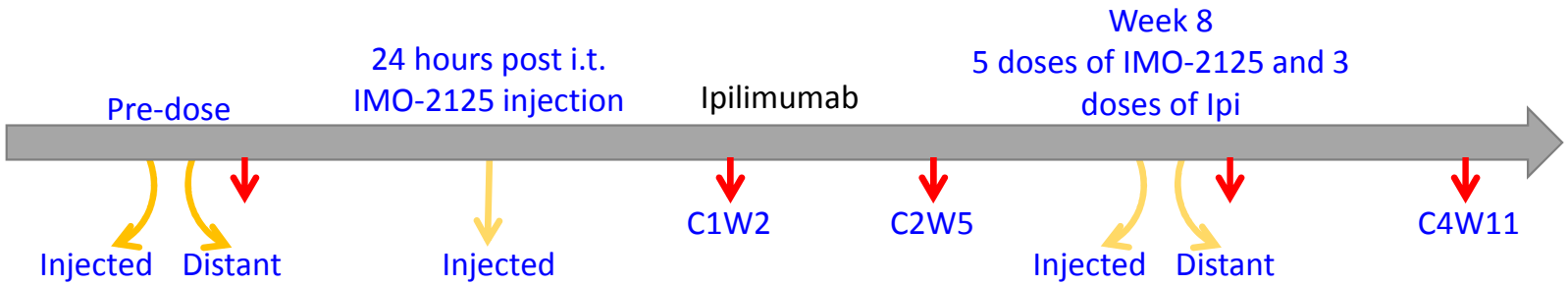
Distant Lesions

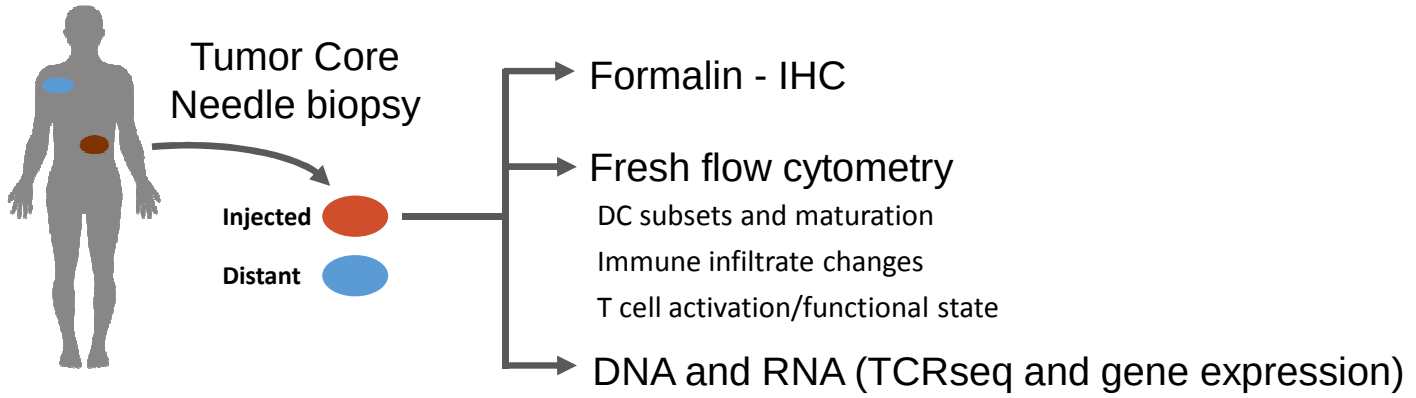
Study 2125-204: Immune response monitoring to correlate with mechanism of action

Injected = Injected lesion
Distant = Un-injected Lesion

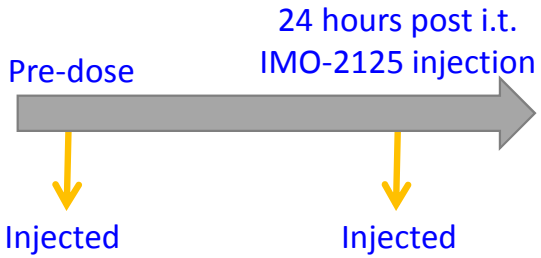
= collection of biopsy

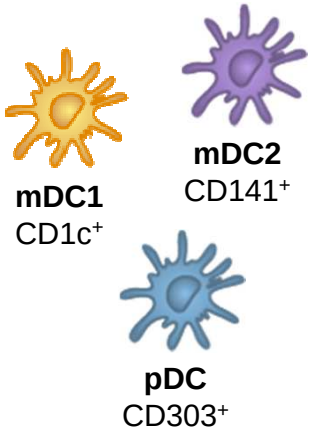
= collection of PBMCs



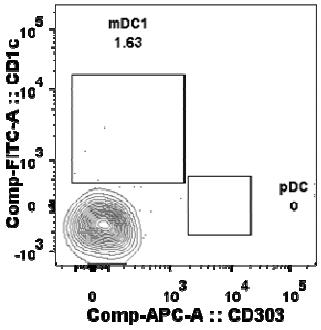


Rapid mDC1 maturation induced by IMO-2125 in the tumor

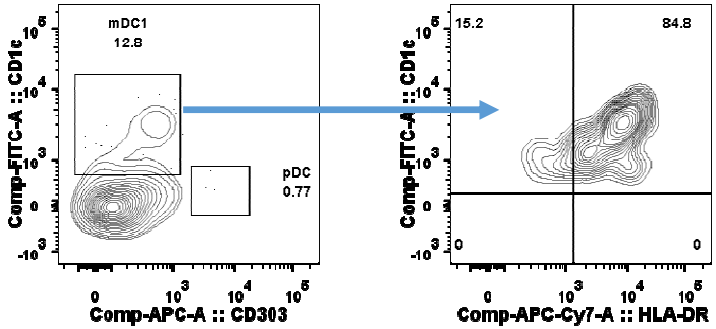


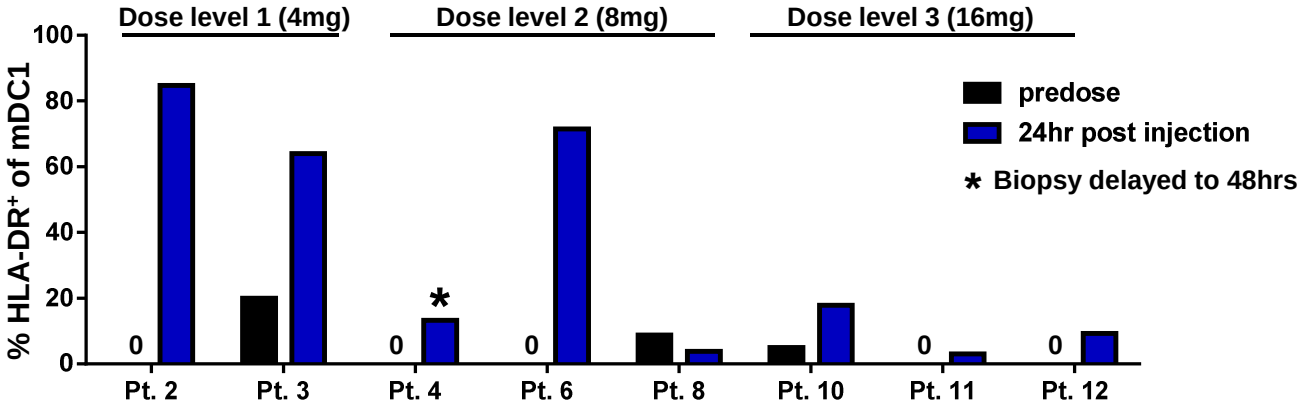


Pre-dose

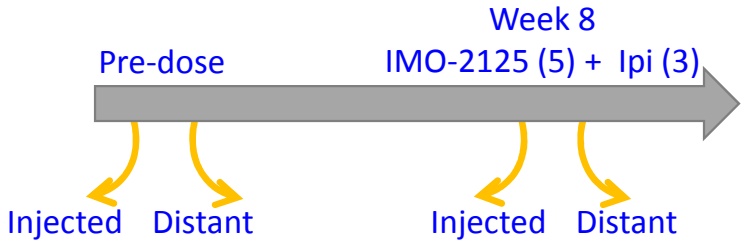


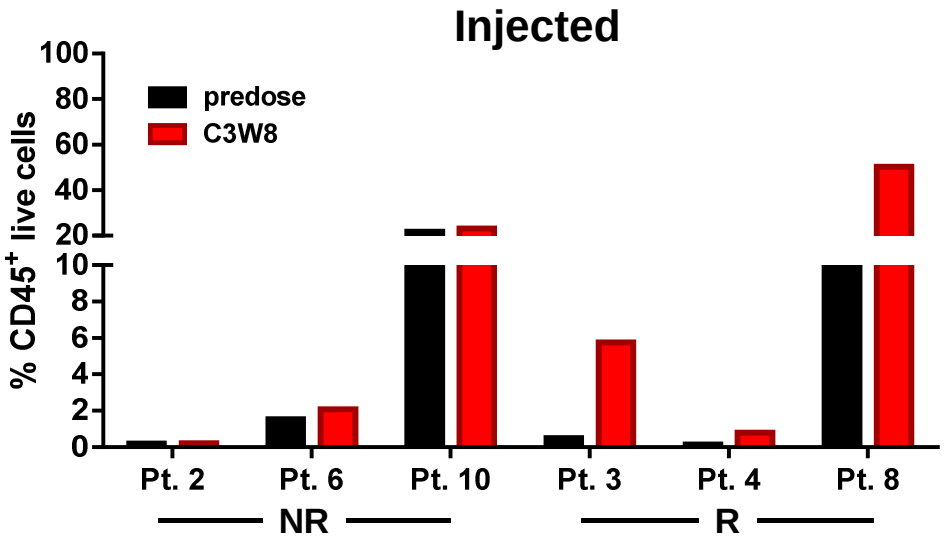
24 hours post i.t. IMO-2125 injection

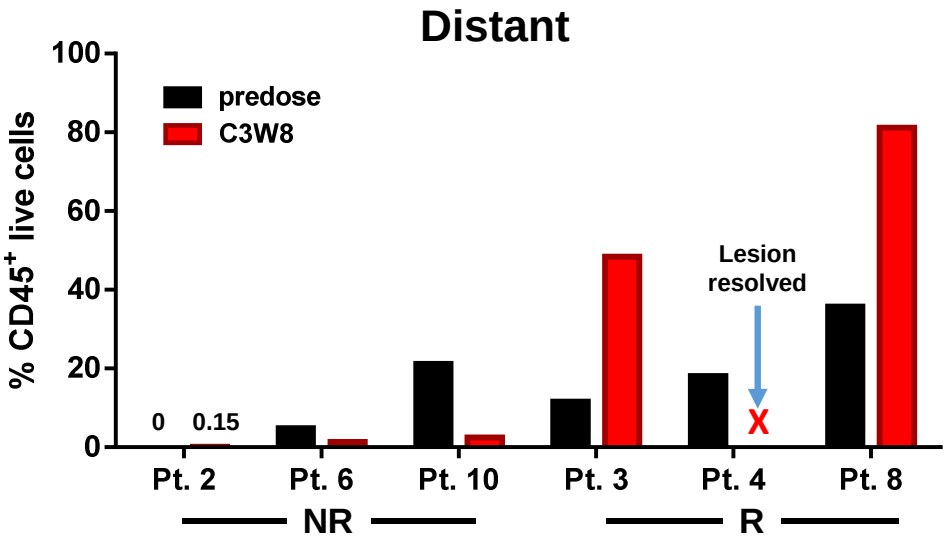




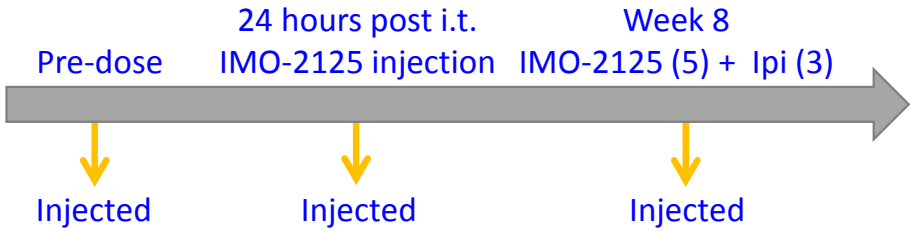
Combination therapy induces immune infiltration in distant lesions of responding patients





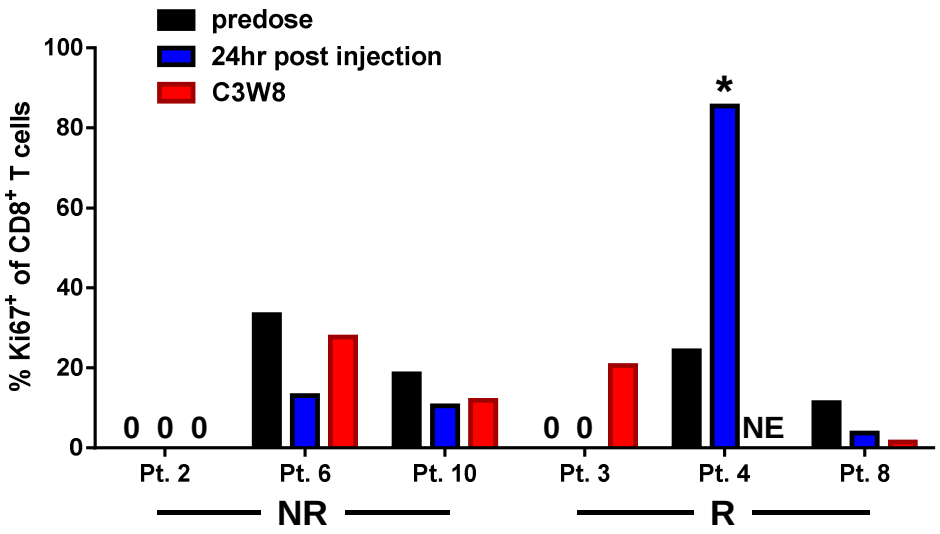


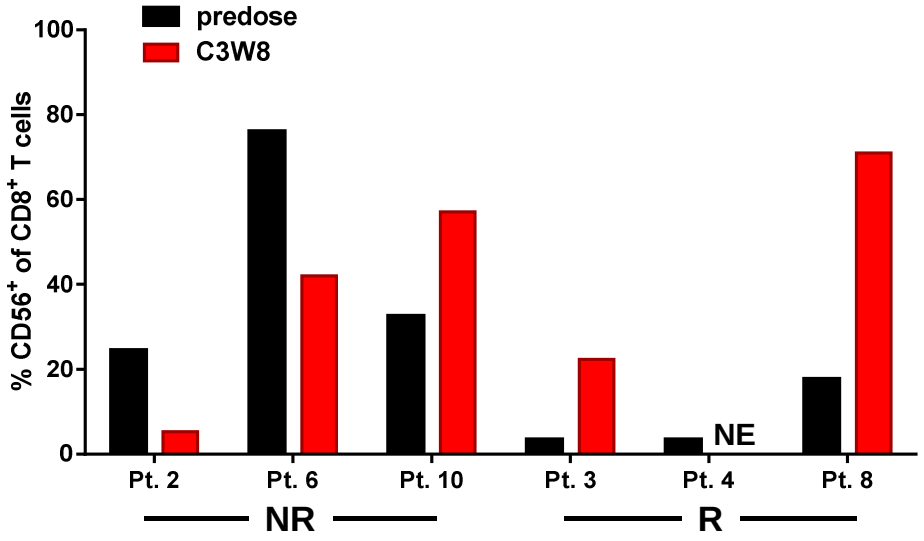
Combination therapy induces T cell expansion and activation



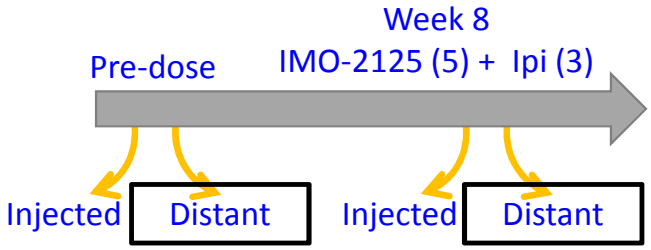
NE = not evaluable

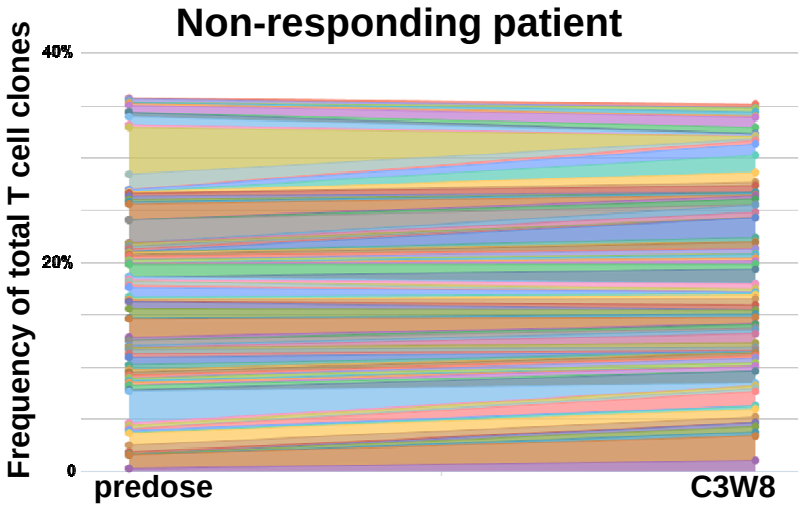
* Biopsy delayed to 48hrs

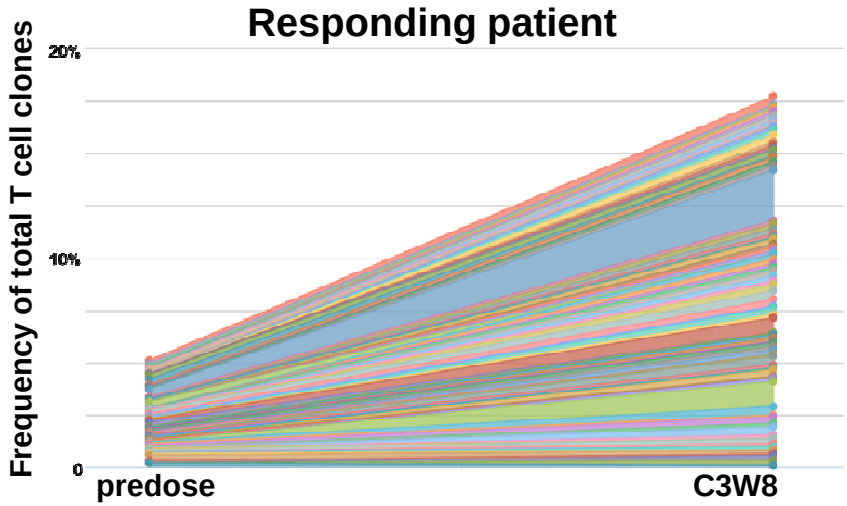




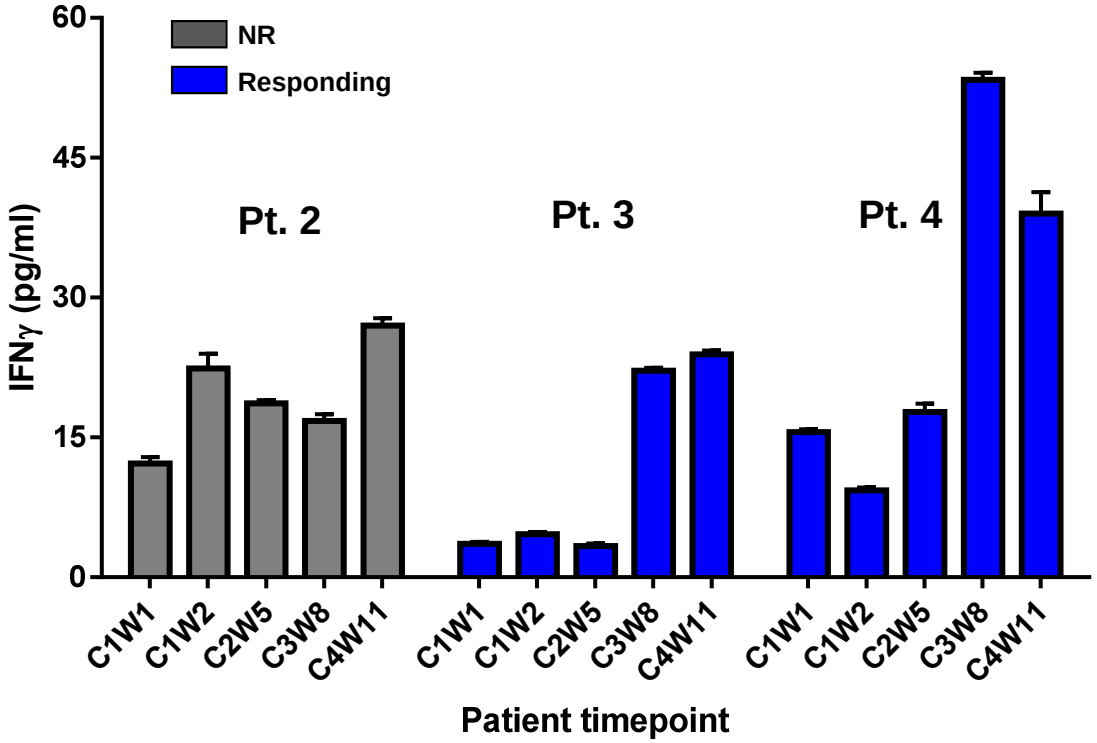
Expansion of top T cell clones in the distant lesion of responding patient







Late increase in IFNγ in patient plasma as a biomarker of response

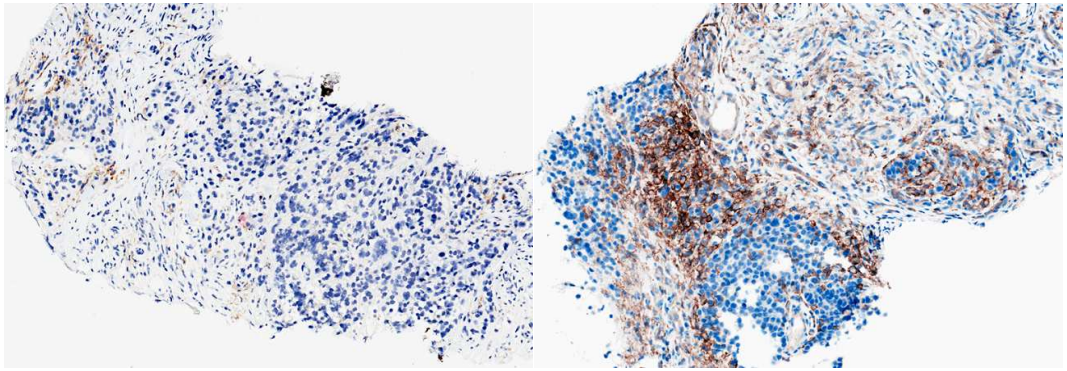


Additional cytokines assessed

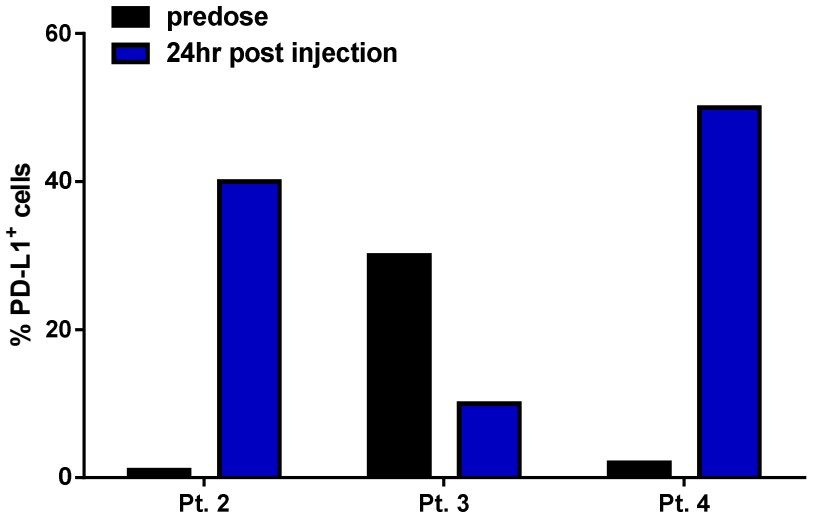
TNFα
IL-2
IL-10
IL-6
IL-8
IL-12p70
IL-13
IL-1β
IL-4

Where do we go from here?
Upregulation of PD-L1 early on therapy

Predose **24 hr post injection**



20x magnification



* Malignant cells only

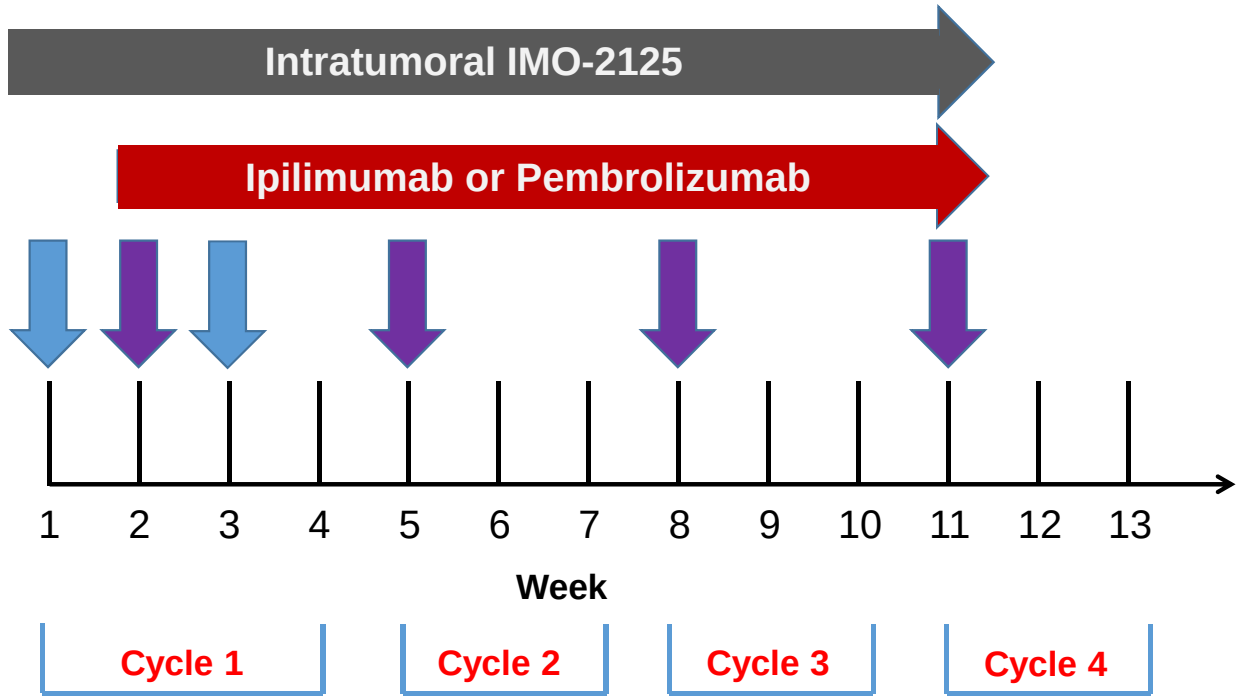
New Trial Design with addition of IMO-2125 + Pembro Arm

(NCT02644967)

i.t. IMO-2125 alone

i.t. IMO-2125 + ipi or pembro

* Pembro continues until time of progression



Lessons and Take Home Messages

- Key points
  - –IMO-2125 results in maturation of intratumoral mDC1 in injected lesion within 24h of drug administration
  - –Increased immune infiltration measured in distant lesions of responding patients at week 8
  - –Safety is acceptable through 3 dosing cohorts; MTD not yet reached
  - –Preliminary clinical activity with IMO-2125 + ipilimumab in this refractory population is encouraging
- Potential impact on the field
  - –Combining intra-tumoral DC activation to enhance T cell priming with checkpoint blockade may be key in IO refractory patient population
  - –A local tumor can be used as a vaccine itself and injection of one lesion results in regression of distant lesions that may not be easily accessible
- Lessons learned
  - –On-treatment biopsy timing is critical!!

Acknowledgements

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Patients and their families

MDACC Melanoma Medical Oncology Clinicians and Staff

MDACC Interventional Radiology Team

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