Idera Pharmaceuticals

ASCO 2018 Annual Meeting
Investor/Analyst Event

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Tilsotolimod Clinical Trials

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Featured Speakers

Adi Diab, M.D. – Lead Trial Investigator, Assistant Professor, Department of Melanoma Medical Oncology, Division of Cancer Medicine, University of Texas, MD Anderson Cancer Center

Vincent Milano
Idera CEO

Joanna Horobin, M.B., Ch.B.
Idera CMO

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Tilsotolimod Clinical Trials

A Phase 1/2 study to evaluate the safety and efficacy of intratumoral injection of the TLR9 agonist tilsotolimod (IMO-2125) in combination with ipilimumab in PD-1 inhibitor refractory metastatic melanoma

Adi Diab[1], Haymaker Cara[1], Chantale Bernatchez[1], Marihella James[1], Robert Andtbacka[2], Douglas Johnson[3], Joseph Markowitz[4], Ravi Murthy[1], Igor Puzanov[5], Monte Shaheen[6] Shah Rahimian[7], James Geib[7], Srinivas Chunduru[7], Suzanne Swann[7] and Patrick Hwu[1]

[1]University of Texas MD Anderson Cancer Center, Houston, TX, [2]University of Utah, Huntsman Cancer Institute, Salt Lake City, UT, [3]Vanderbilt University Nashville, TN, [4]Moffitt Cancer Center, Tampa, FL, [5]Roswell Park Cancer Institute, Buffalo, NY,[6]University of Arizona Cancer Center, Tucson, AZ, [7]Idera Pharmaceuticals, Inc., Exton, PA

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Tilsotolimod Clinical Trials

Background:

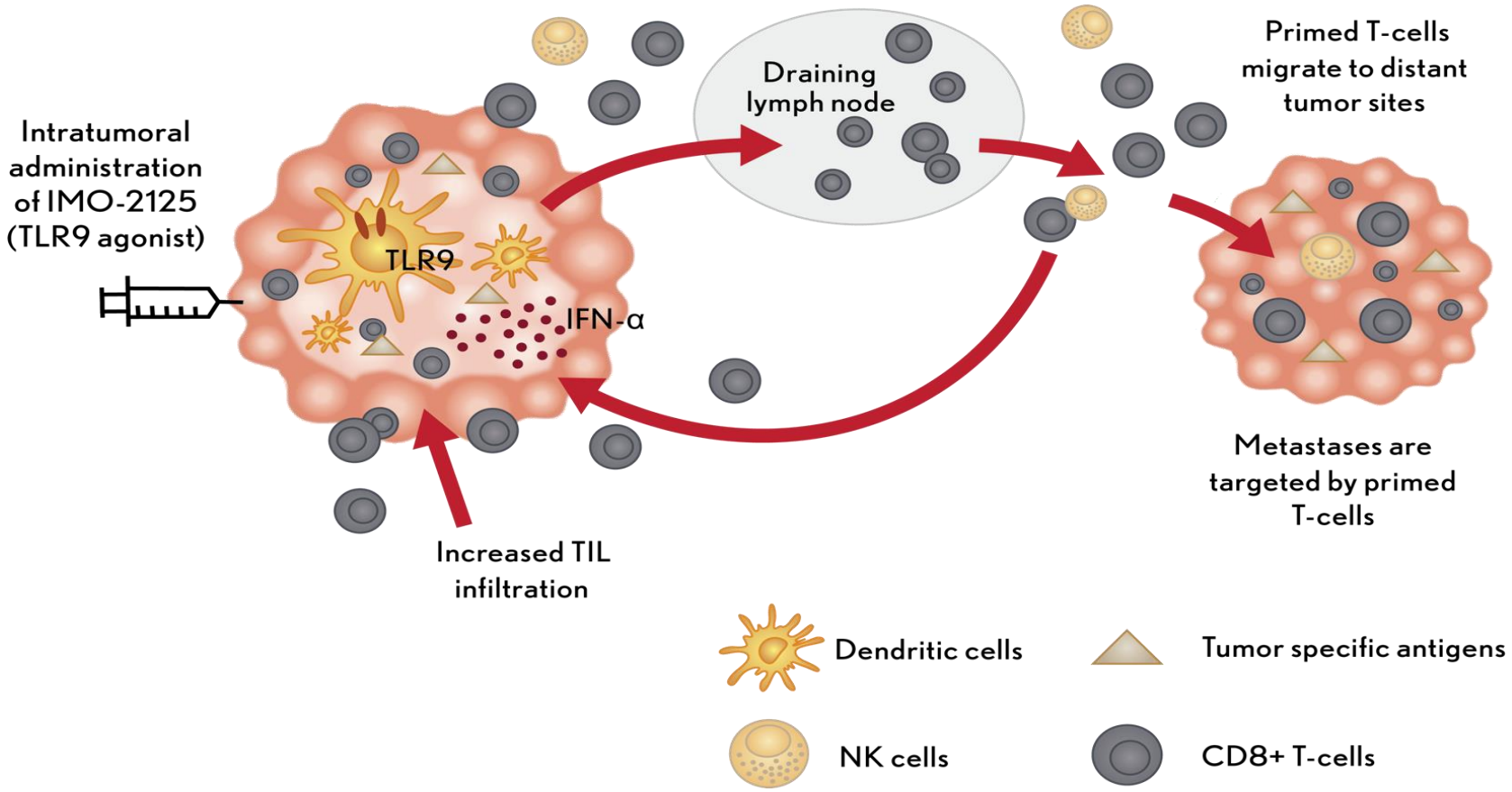
- Tilsotolimod (IMO-2125) is an investigational synthetic oligonucleotide which binds to TLR9, altering the tumor microenvironment by improving antigen presentation of dendritic cells and macrophages with subsequent proliferation of antigen specific cytotoxic T lymphocytes (CD8+ T-cells) in both injected and uninjected tumors resulting in tumor cell death (Haymaker, SITC 2017);

- There is a high unmet medical need in metastatic melanoma for patients who progress after PD-1 inhibitors, as treatment options are very limited;

- Post PD-1 inhibitor failure, standard of care (single agent ipilimumab) offers only modest benefit (10-13% ORR) (Long, *Society for Melanoma Research* 2016), (Bowyer S, et al. *Br. J Cancer*, 2016);

- Initial clinical experience with 8 mg tilsotolimod + ipi is promising. This report is an analysis of the first 26 subjects (21 evaluable for disease assessment) in a multi-center study who received 1+ doses of the treatment combination and at least one disease assessment.

Modulating the tumor microenvironment through intratumoral administration of tilsotolimod (TLR 9 agonist)



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ILLUMINATE-204 Trial Objectives

Primary Objective

To assess preliminary clinical activity of tilsotolimod in combination with ipilimumab at the respective recommended phase 2 dose (RP2D) in patients with metastatic melanoma that is not responsive to PD-1 inhibitor therapy, using Response Evaluation Criteria in Solid Tumors (RECIST v1.1) with a target of ORR of 35%

Secondary Objective

To further assess the safety and tolerability of tilsotolimod in combination with ipilimumab

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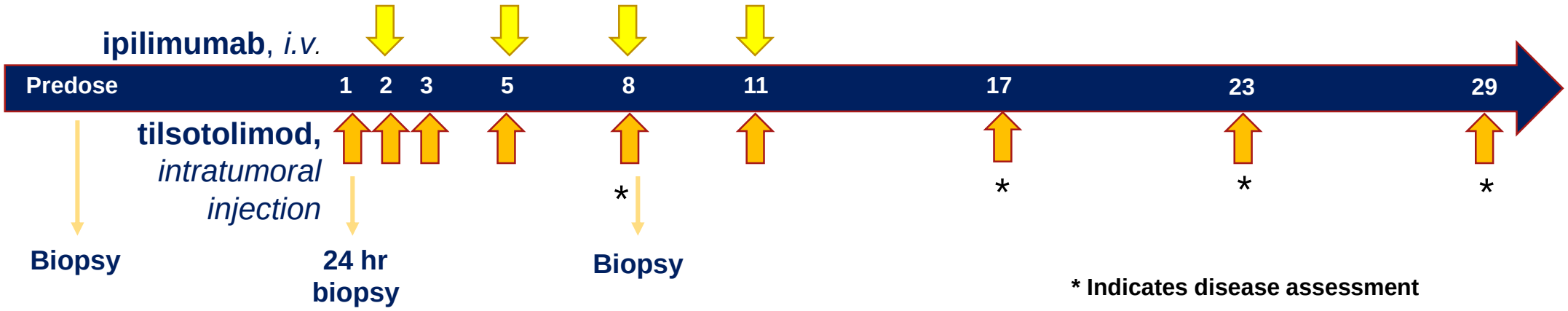
Illuminate 204 key eligibility criteria and study design

Patients:	Adults with unresectable or metastatic melanoma

- Radiologic (RECIST v1.1) or symptomatic progression on or after a PD-1 inhibitor
- ≥21d from most recent aPD-1
- Prior ipilimumab allowed
- BRAFwt: 2 lines systemic therapy
- BRAF^{V600}: 3 lines systemic therapy
- Ocular melanoma excluded

Phase 1 dose-finding (n=18)
tilsotolimod (4, 8, 16, 32 mg) + ipilimumab
DOSE SELECTION COMPLETED

Phase 2 (n ≈ 60)
tilsotolimod 8mg + ipilimumab
OPEN



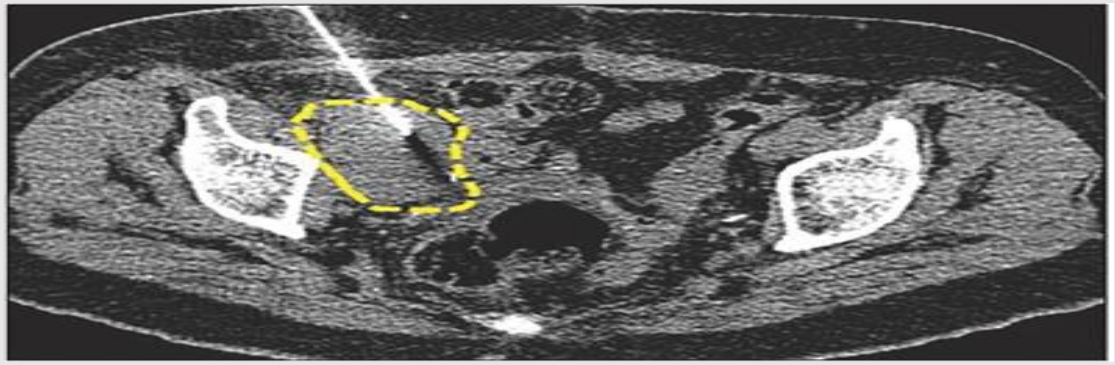
Illuminate 204 patient and baseline disease characteristics

Characteristic	n (%)	Prior Treatment	n (%)
Median Age (range)	**68.5 (39, 91)**	**Any previous PD-1 inhibitor***	**26 (100%)**
ECOG PS 0	16 (66.7%)	CTLA-4 inhibitor	6 (23.1%)
Mucosal	2 (7.7%)	PD-1 inhibitor monotherapy	17 (65.4%)
Elevated LDH	9 (34.6%)	CTLA-4 + PD-1 combo	5 (19.2%)
$BRAF^{v600}$ mutation	11 (42.3%)	Other PD-1 combo	8 (30.8%)
Stage IV **M1c**	**23 (88.5%)** **11 (42.3%)**	BRAFi	1 (3.8%)
Brain metastasis	3 (11.5%)	MEKi	1 (3.8%)

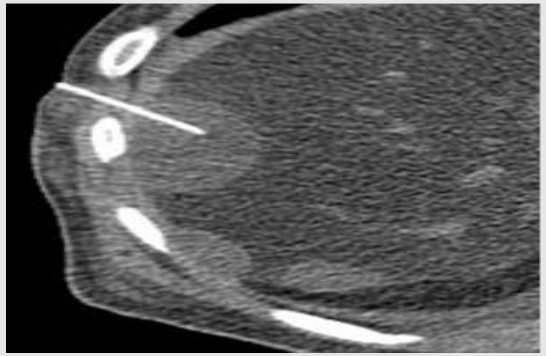
***PD-1 refractory requirement added May 2016**

58% of Patients Had Lesions only Accessible by Image Guided Injection

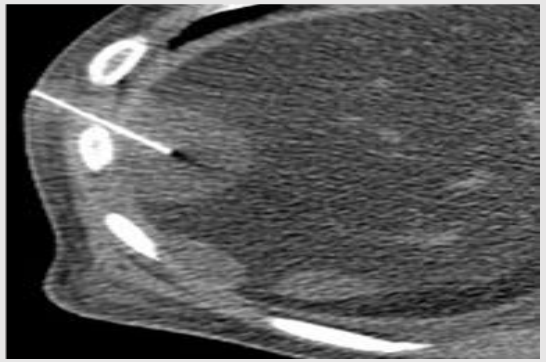
Liver Lesion Injection



Oct. 16, 2017



Oct. 26, 2017



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Safety Analysis	Subjects treated with tilsotolimod + ipilimumab (N=26)
At Least One AE	25 (96.2%)
At Least One Serious AE	9 (34.6%)
At Least One Grade ≥3 AE	13 (50.0%)
AE Leading to tilsotolimod Withdrawn	2 (7.7%)
AE Leading to Study Discontinuation	**0 (0.0%)**
Death	**0 (0.0%)**
Maximum Severity[1]	
Grade 1	2 (7.7%)
Grade 2	10 (38.5%)
Grade 3	11 (42.3%)
Grade 4	2 (7.7%)
Grade 5	0 (0.0%)
Relationship to Study Drugs	
Related	22 (84.6%)
Unrelated	3 (11.5%)

Safety population (n=26 as of 9 April 2018)

Immune-Related AE's Consistent with Ipilimumab

AE preferred term	8 mg tilsotolimod/ipilimumab N=26
Patients Reporting at Least One Adverse Event	6 (23.1%)
Autoimmune hepatitis	2 (7.7%)
Hypophysitis	2 (7.7%)
Adrenal insufficiency	1 (3.8%)
Colitis	1 (3.8%)
Enterocolitis	1 (3.8%)
Guillain-Barre syndrome	1 (3.8%)

No safety events associated with deep injections (liver, adrenal)

Safety population (n=26 as of 9 April 2018)

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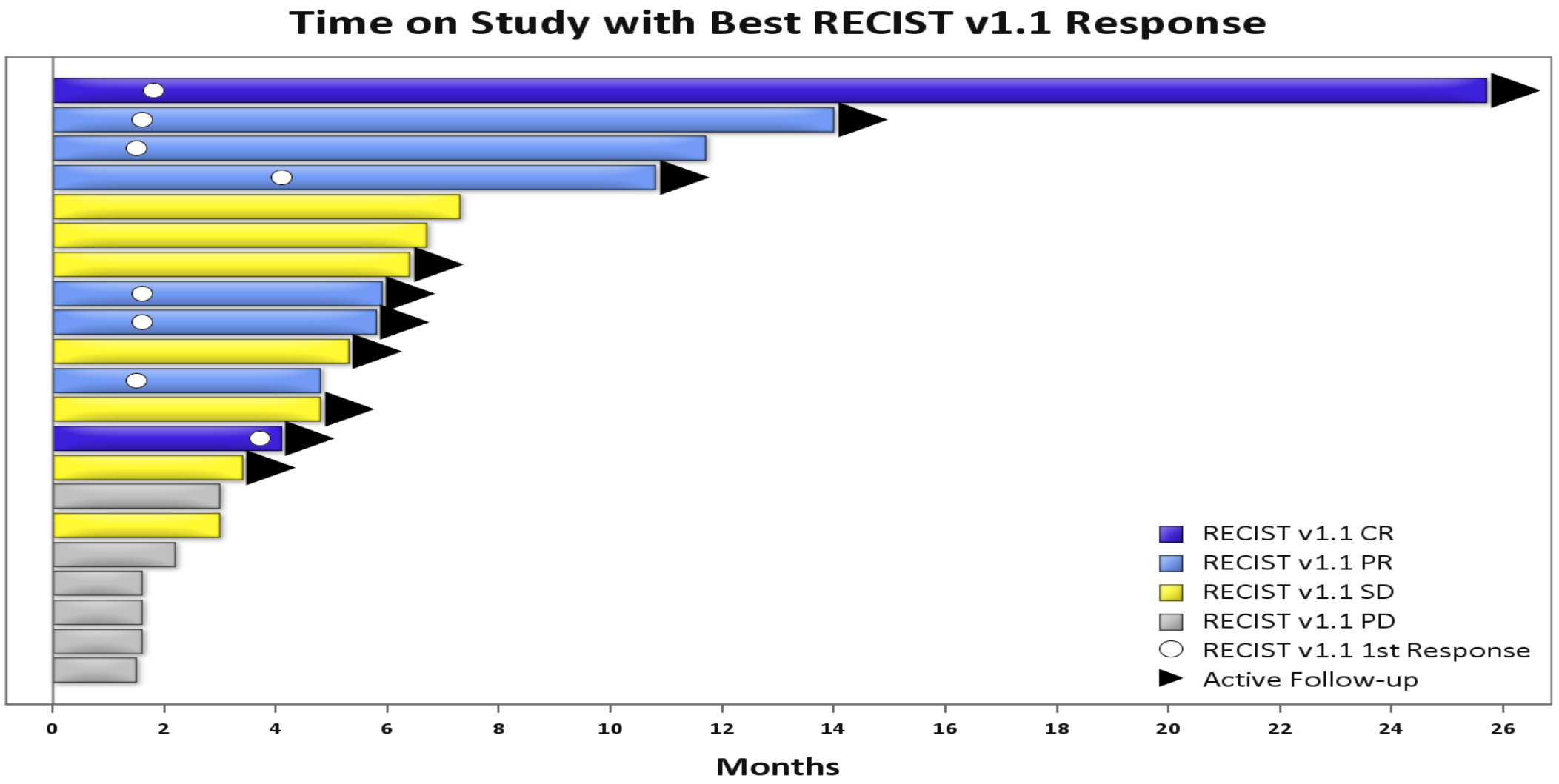
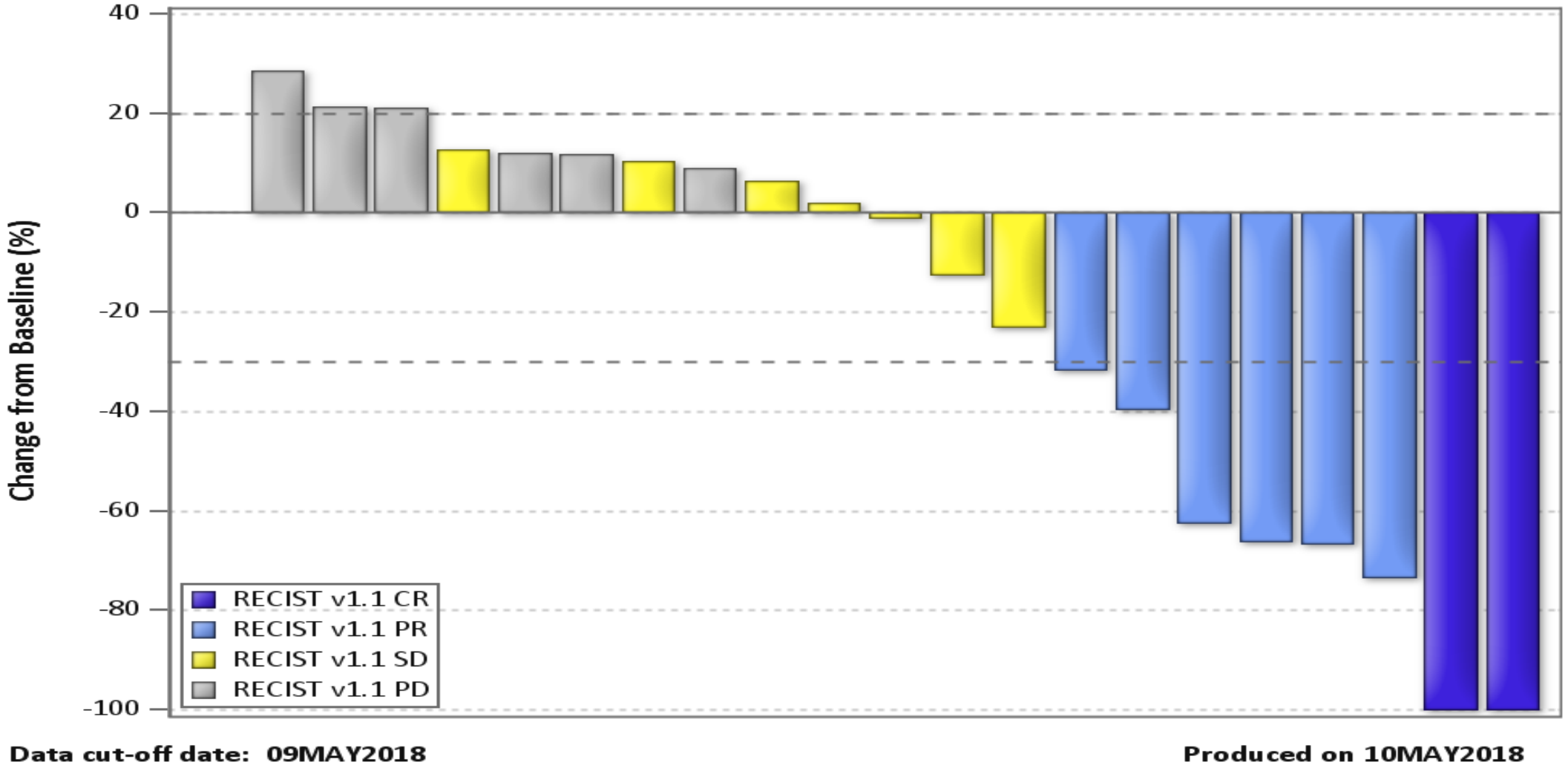
RECIST v1.1 Objective Response Rate: 38.1%; Disease Control Rate: 71.4%



Maximum Percent Decrease in Target Lesion Diameters



Data cut-off date: 09MAY2018

Produced on 10MAY2018

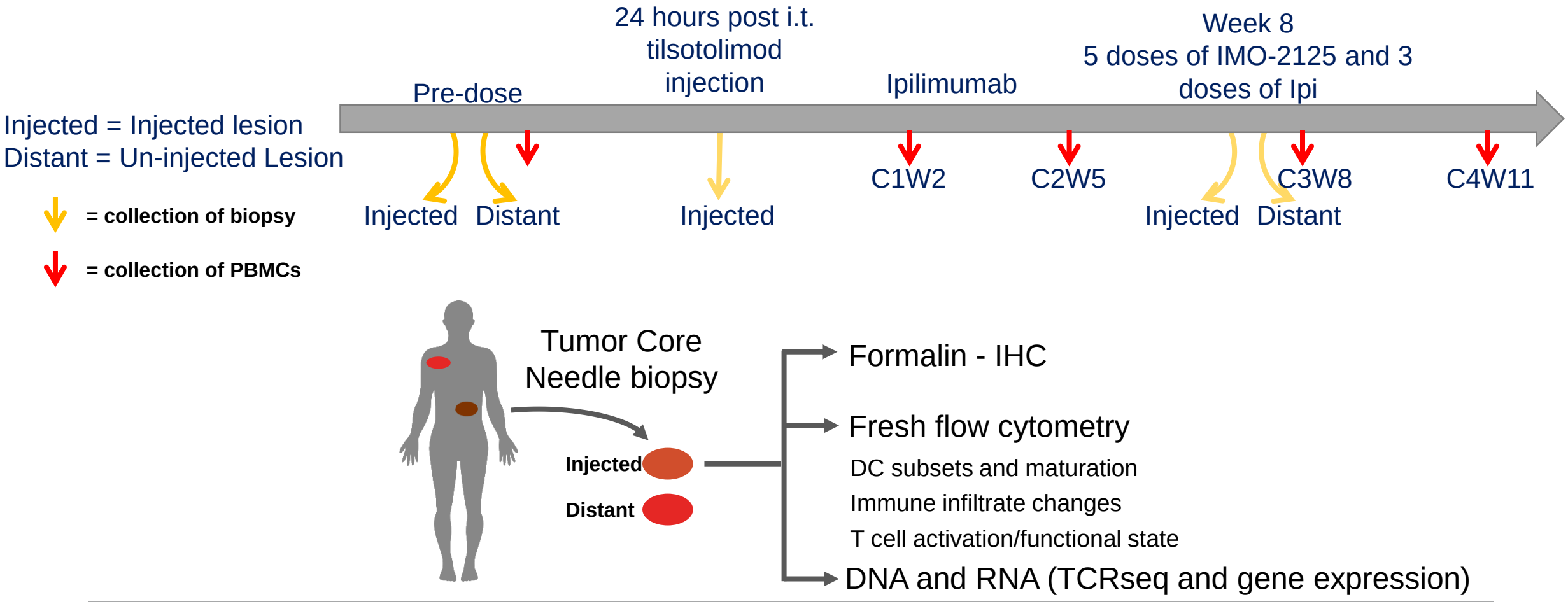
Best overall response

	tilsotolimod + ipilimumab (N=21)[1]
	Response Rate
Best Overall Tumor Response	
Complete Response (CR)	2 of 21 (9.5%)[2]
Partial Response (PR)	6 of 21 (28.6%)
Stable Disease (SD)	7 of 21 (33.3%)
Progressive Disease (PD)	6 of 21 (28.6%)
Overall Response Rate (CR, uCR, or PR)	8 of 21 (38.1%)
Disease Control Rate (CR, PR, or SD)	15 of 21 (71.4%)

As of 9 May 2018

[1] 21 of 26 subjects had a least 1 post-baseline disease assessment at time of data cut
[2] One CR unconfirmed

Immune response monitoring to correlate with mechanism of action



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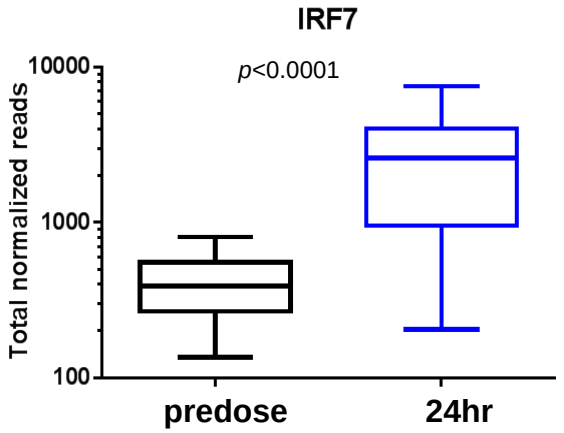
Tilsotolimod activates local IFNα-response gene signature and combination with ipilimumab therapy induces proliferation of T-cells in distant lesion

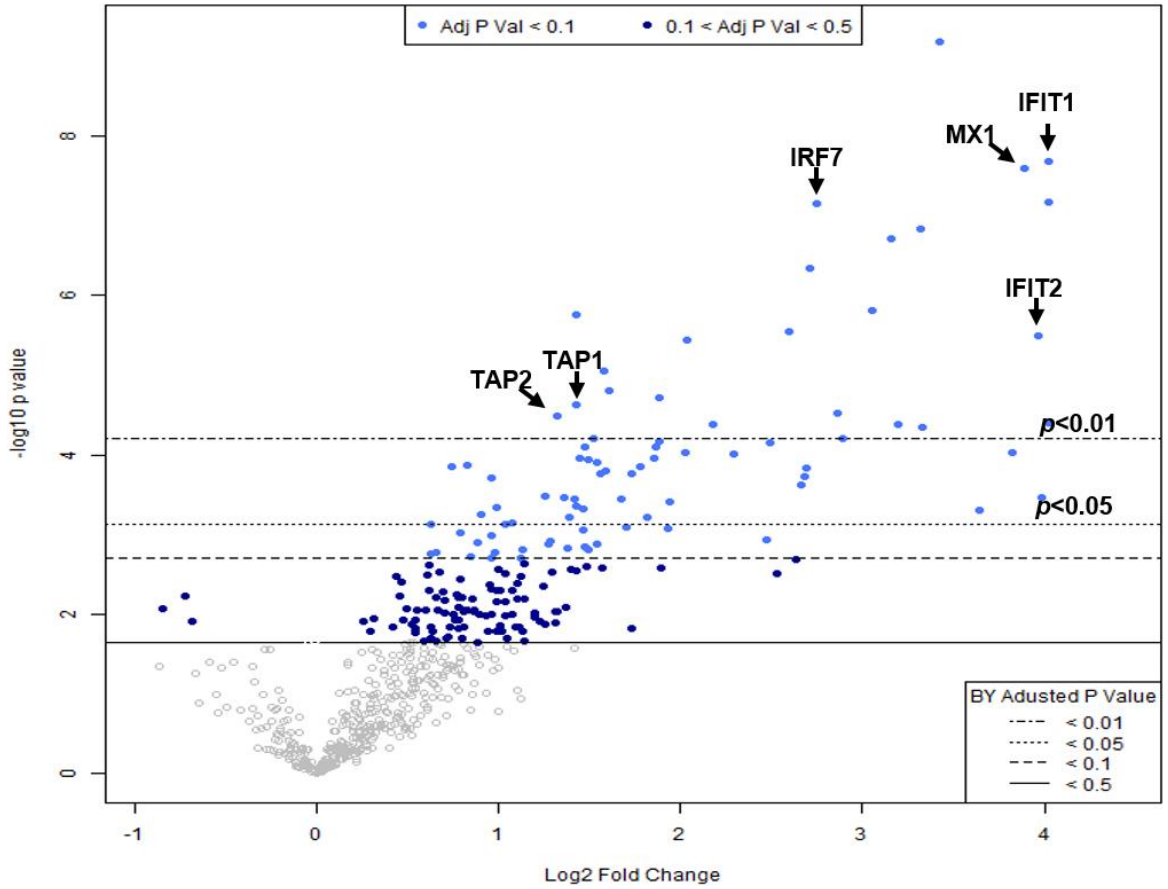
tilsotolimod only
(prior to ipilimumab)



n=15

Injected Lesion

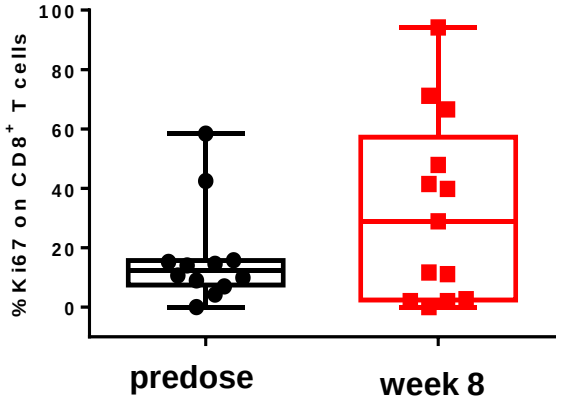
tilsotolimod only
(prior to ipilimumab)



n=15

Injected Lesion

tilsotolimod + ipilimumab



n=12

Distant Lesion

Illuminate-204

Responding Patient Case Studies

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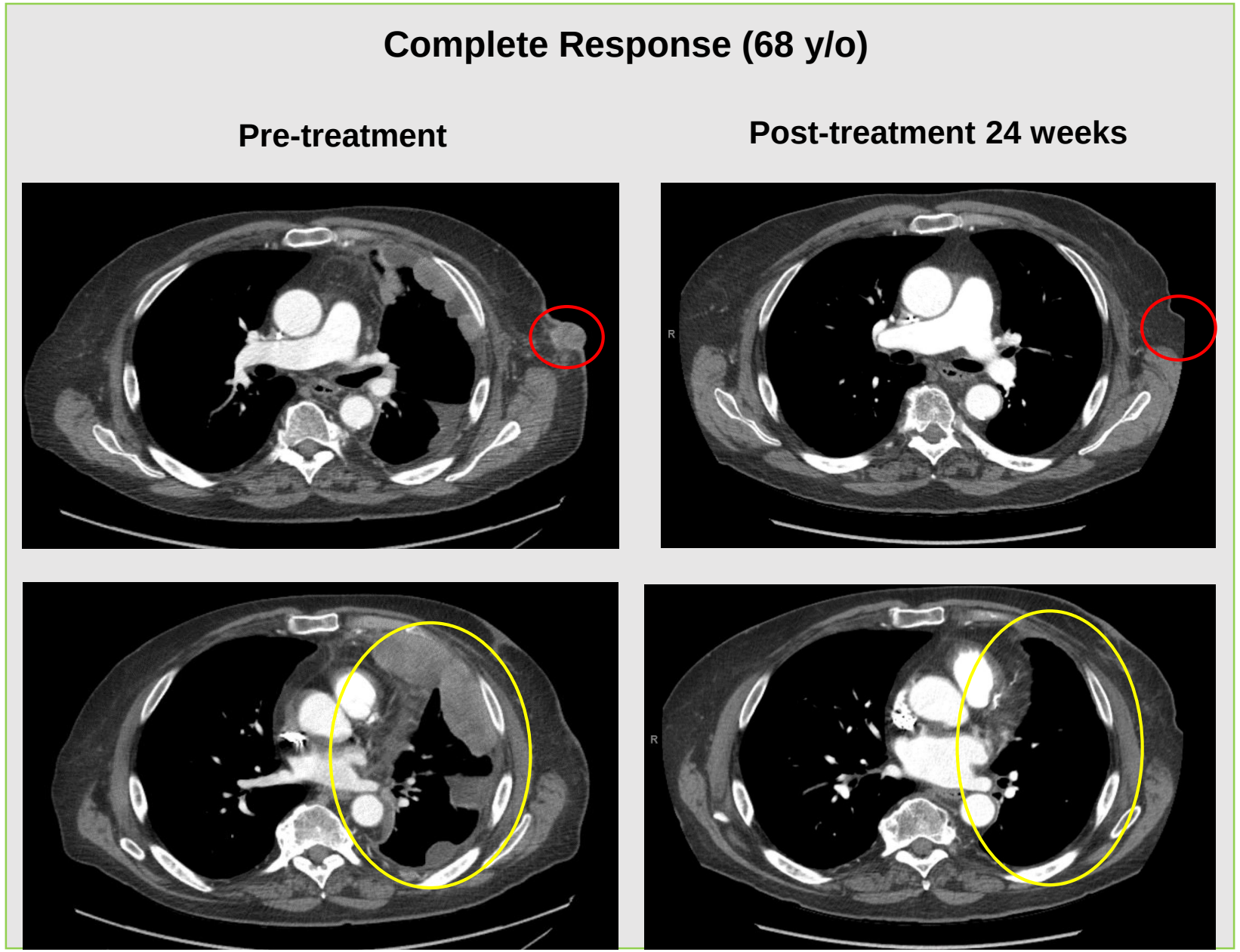
Patient – 001-004

- 68 y/o male with Stage IV cutaneous melanoma
  - $BRAF^{+}$
  - Metastatic to lung (bulky), LN, soft tissue
- Prior therapy
  - 6 months interferon → progression
  - 4 doses Nivo + Urelumab (anti-4-1BB)
    - Marked progression as best response
- Received tilsotolimod x 6; ipi x 4
  - Treatment continued thru AE of hypophysitis
- CR (> 24 mos), beginning W6

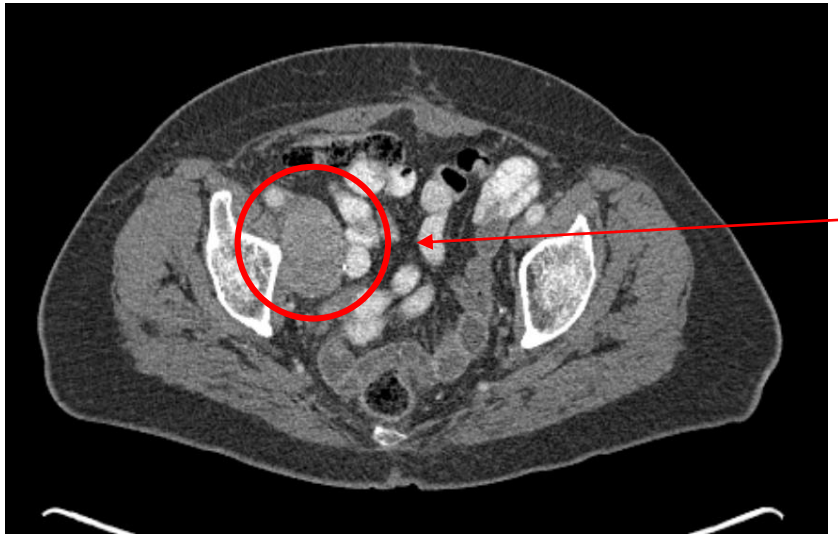
Patient 001-004 – Complete Response



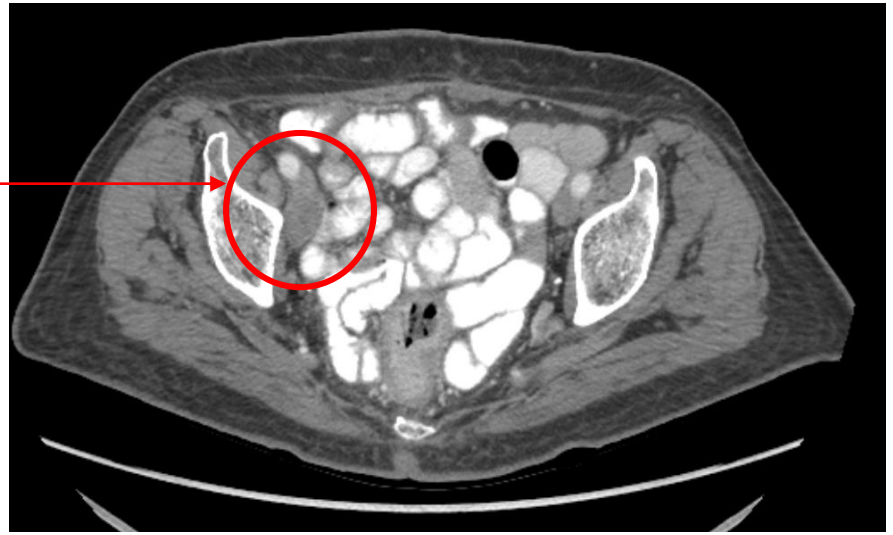
Patient – 001-023

- 70 y/o WF with Stage IV cutaneous melanoma
  - Elevated LDH
  - Unknown BRAF status
  - Metastatic to pelvis and LN
- Prior therapy with interferon + tamoxifen; pembrolizumab (~9 months)
- Received IMO x 5; ipi x 3.
  - Discontinued due to SAE of autoimmune hepatitis
- Confirmed PR at Week 8

Patient 001-023 – Partial Response

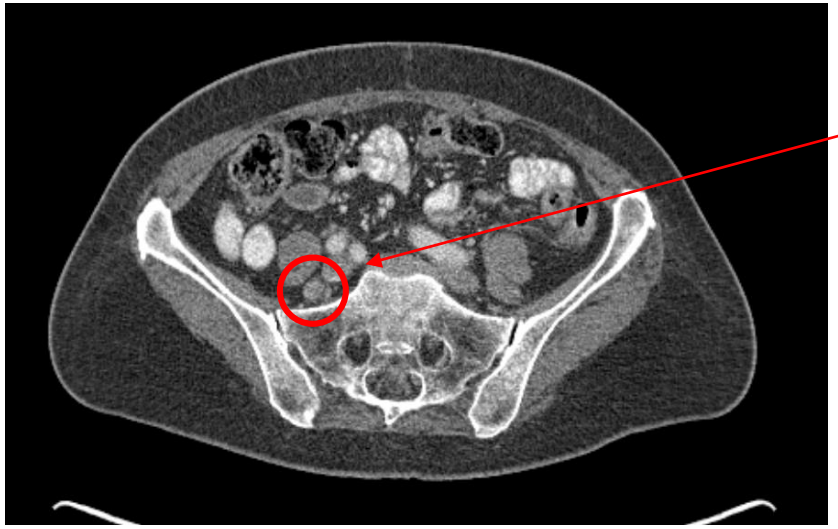


Site A – Inj Site

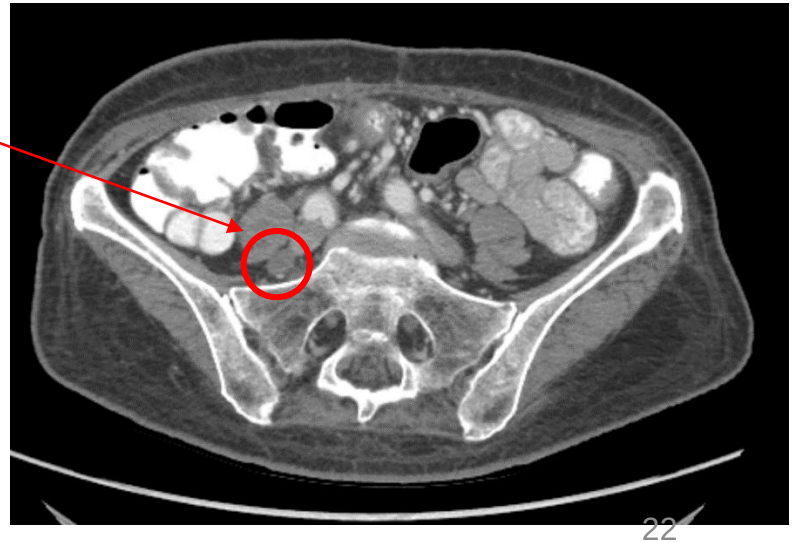


Pre-Treatment

Week 24



Target Lesion

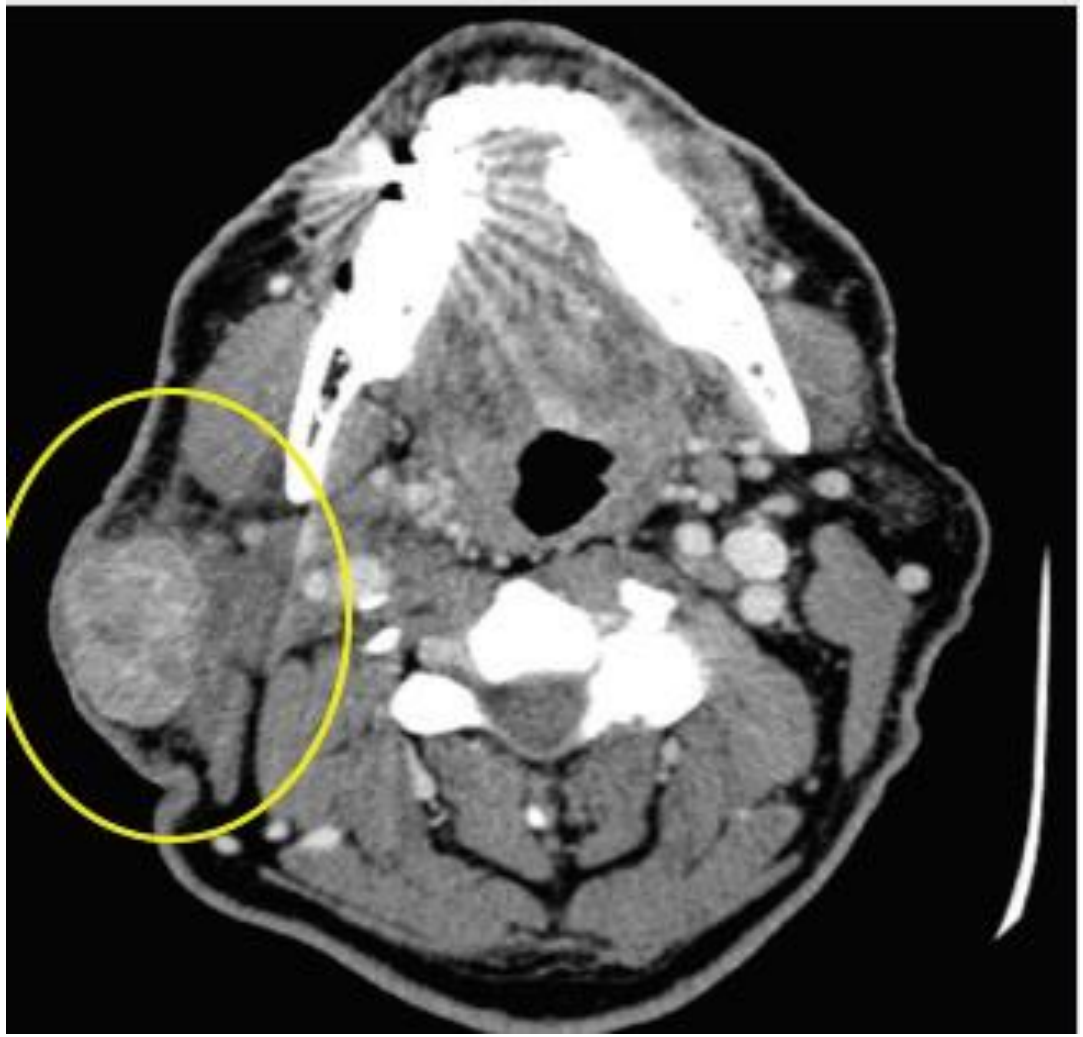


Patient – 001-025

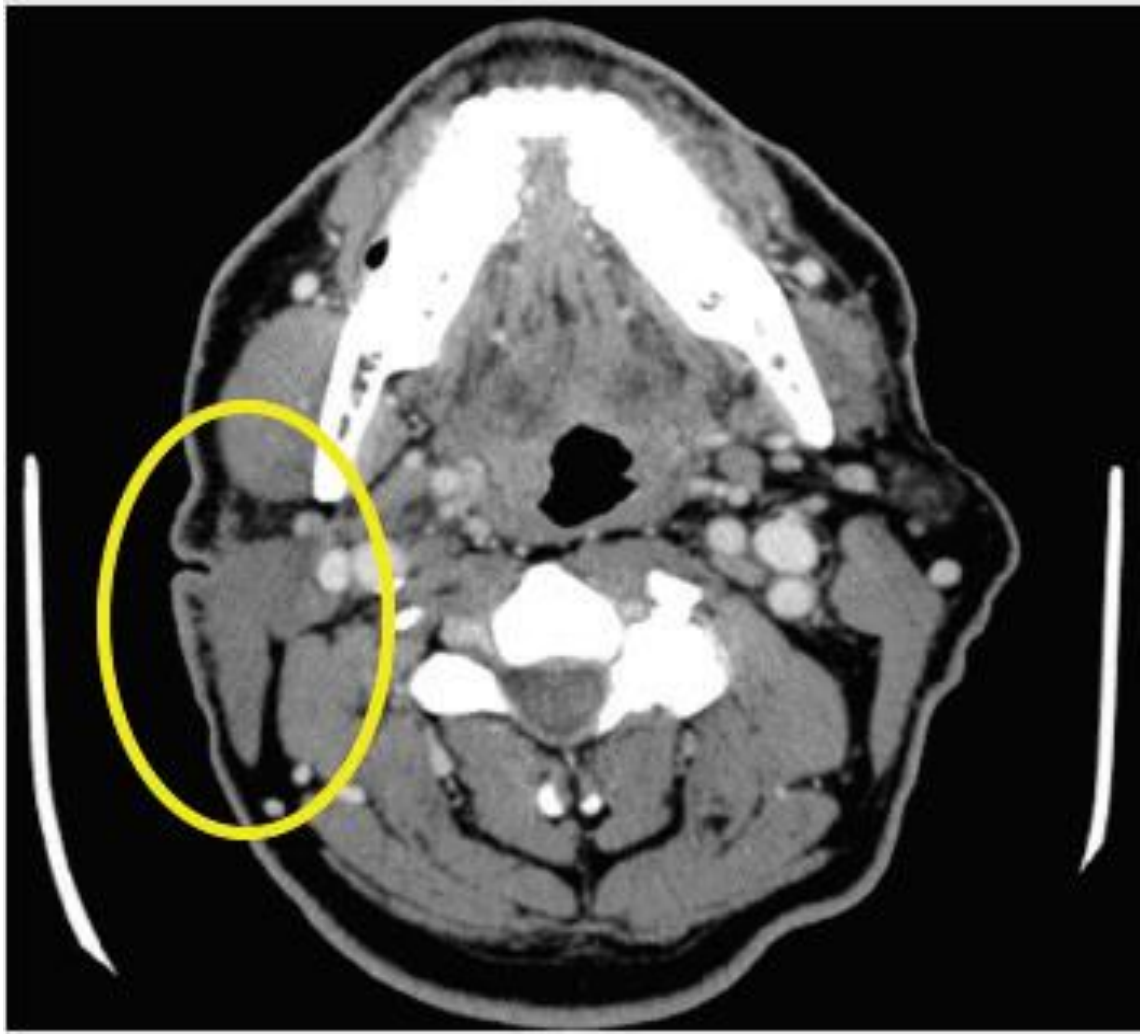
- 62 y/o WM with Stage IIIc cutaneous melanoma
  - BRAF wt
  - Head and neck LN and soft tissue mets
- Prior treatment with pembrolizumab (~3 months)
  - Progression
- Received tilsotolimod x 6; ipi x 4
- Confirmed PR (~9 mos) beginning Week 8

Patient 001-025 – Partial Response

Pre-treatment Injected Tumor

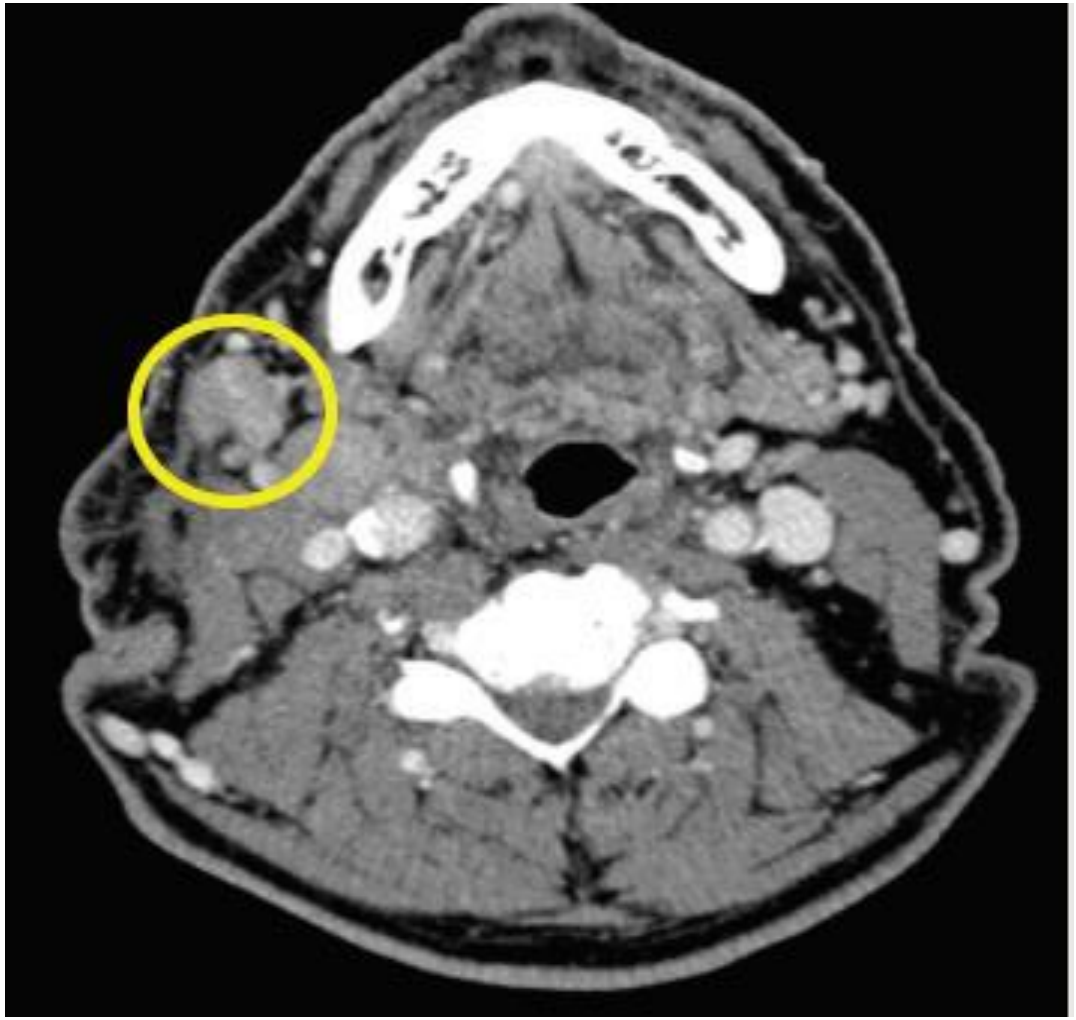


Post-treatment – 56 Weeks

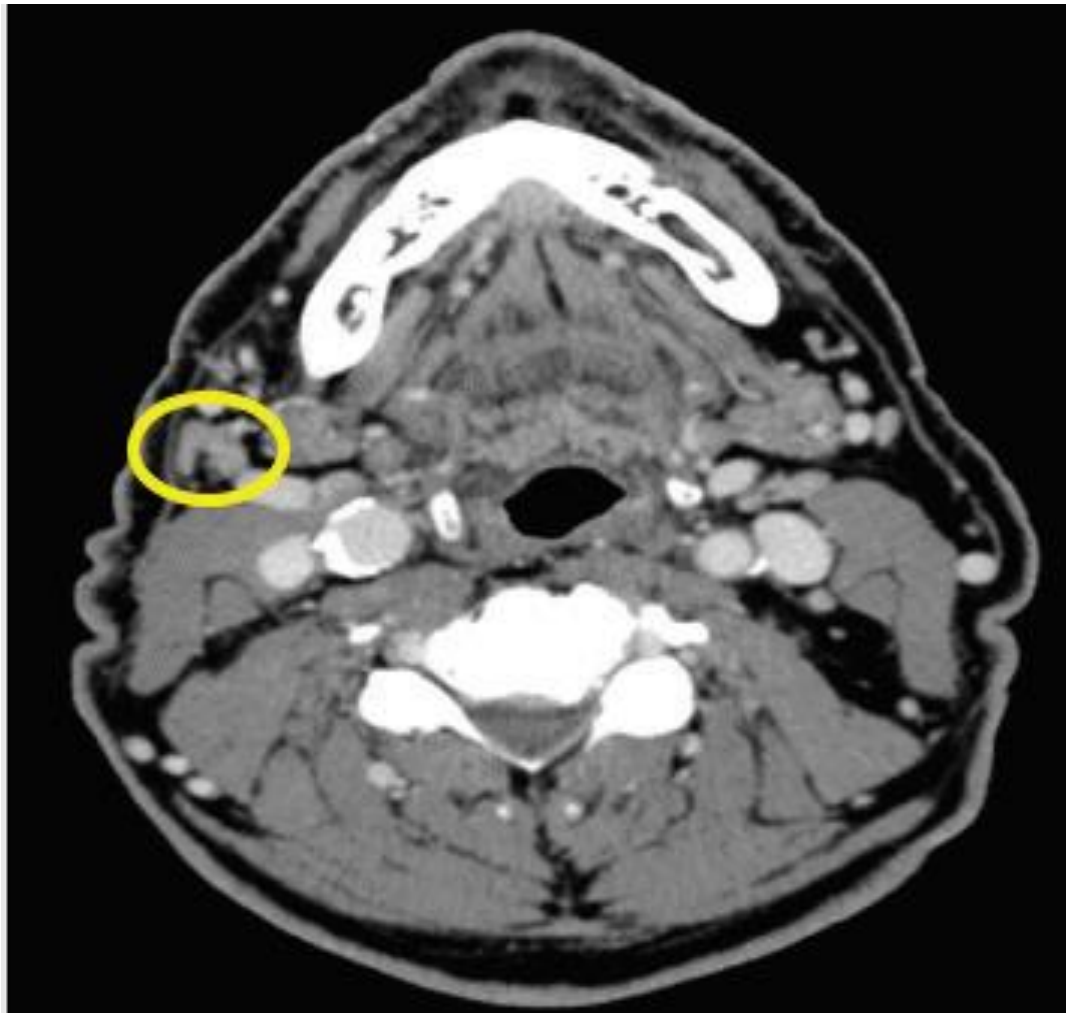


Patient 001-025 – Partial Response

Pre-treatment Un-injected Tumor



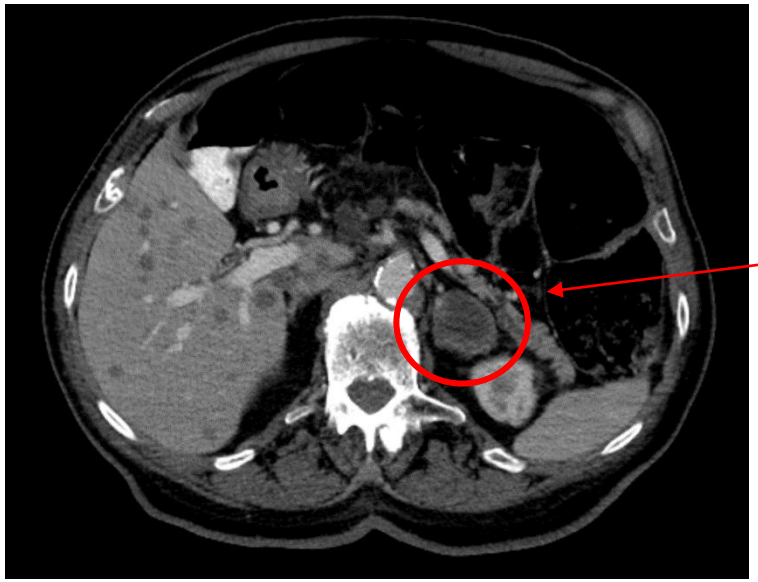
Post-treatment – 56 Weeks



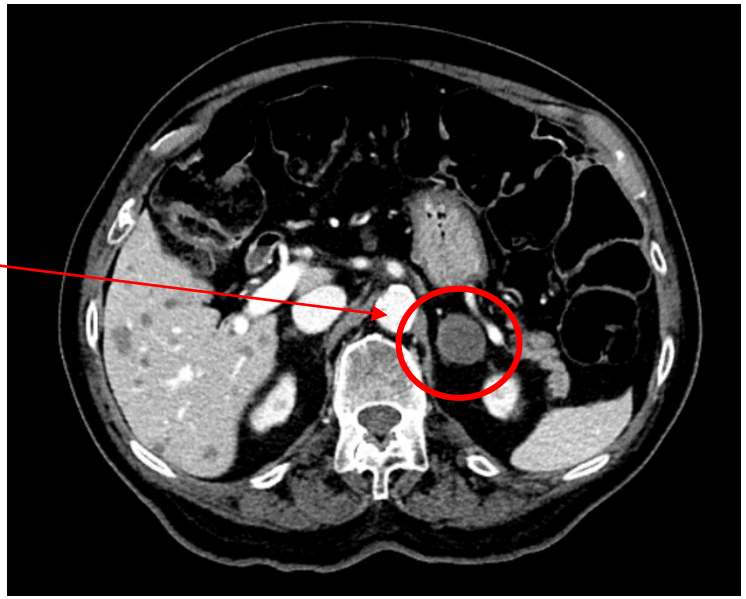
Patient – 001-029

- 91 y/o male with Stage IV visceral melanoma
  - BRAF wt
  - Metastatic to liver, adrenal gland, lungs (M1c)
- Prior treatment
  - Pembrolizumab (~3 mos) → progression
- Received tilsotolimod x 8; ipi x 4
- Confirmed PR (~6 mos) beginning W17

Patient 001-029 – Partial Response

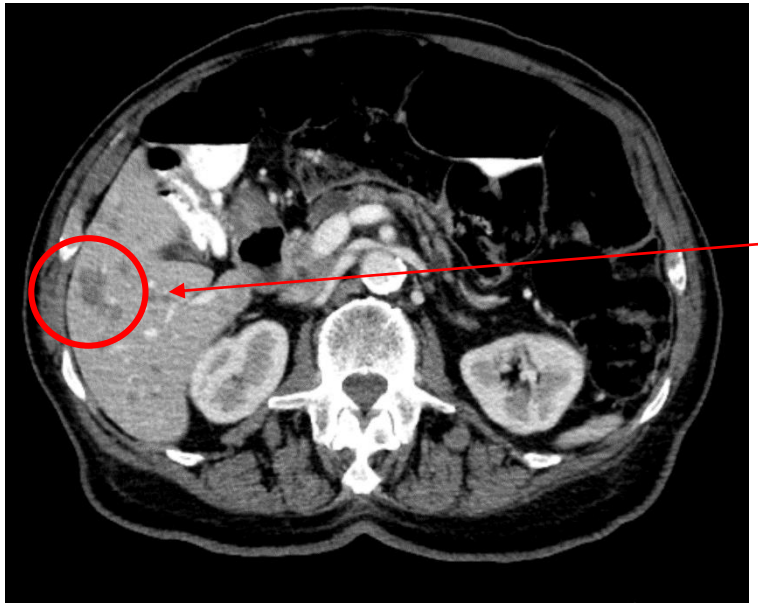


Site A – Inj Site

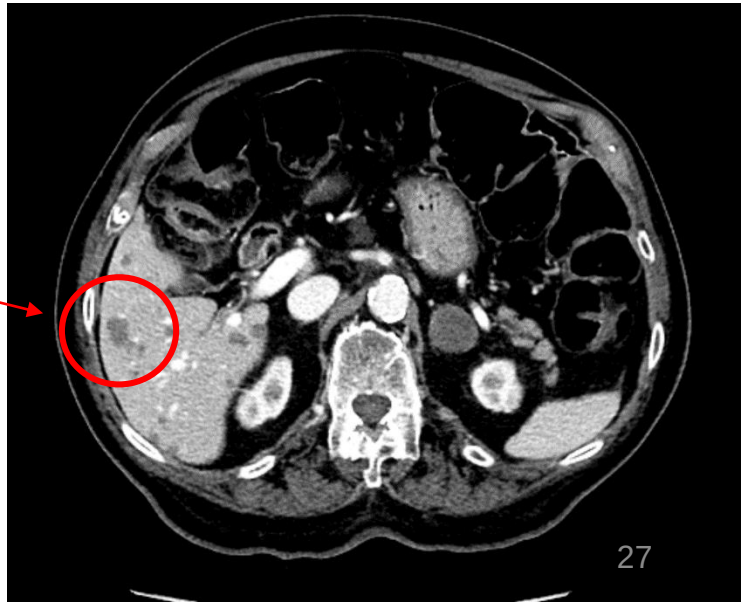


Pre-Treatment

Week 45



Target Lesion

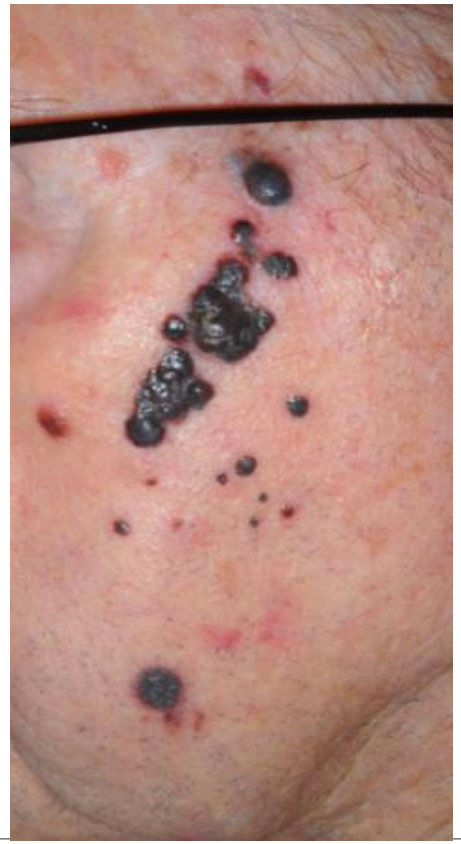


Patient – 004-002

- 91 y/o male with Stage IIIC cutaneous melanoma
  - BRAF wt
  - Metastatic to lung and pleura
- Prior treatment
  - Pembrolizumab (~2 months) → progression
- Received tilsotolimod x 4; ipi x 3
  - Tilsotolimod ongoing, ipi discontinued due to AE
- Unconfirmed CR beginning W16

Patient – 004-002 – Complete Response

1.4.2018



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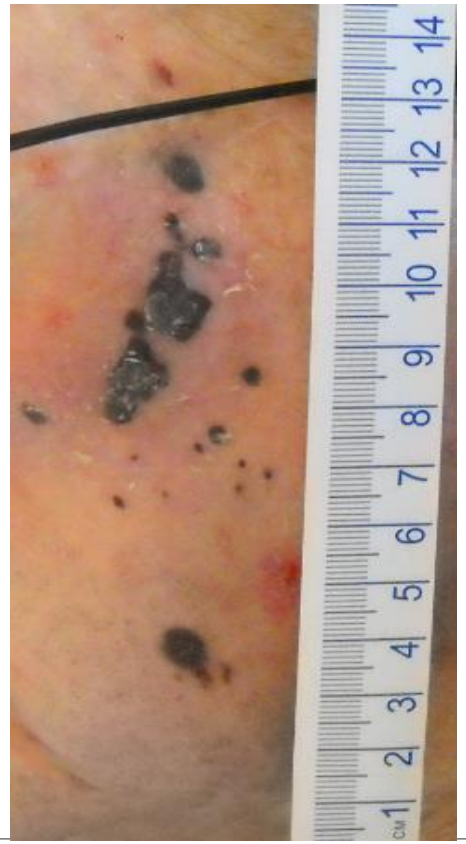

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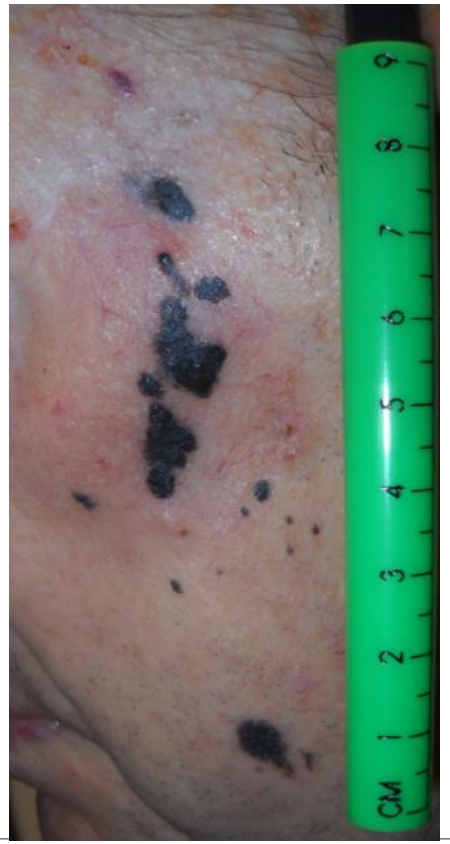

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Conclusions

- Tilsotolimod (IMO-2125) + ipilimumab revives the immune response in anti-PD-1-resistant tumors resulting in altering the tumor microenvironment and conversion of cold (noninflamed) to hot (inflamed) tumors;
- This combination treatment has produced durable responses and demonstrates substantial disease control rate in this clinically challenging population, including subjects with Stage IV M1c disease and BRAF mutations;
- The combination regimen is generally well tolerated and no synergistic toxicity was observed. Six subjects (23%) had immune-related toxicities. The safety profile indicates that tilsotolimod plus ipilimumab does not appear to add toxicity versus ipilimumab alone.

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IMO-2125 Clinical Trials
2125-MEL-301

Phase 3 Trial Design

Unresectable or metastatic melanoma w/ confirmed radiologic progression on or after a PD-1 inhibitor:

- **≥21d from most recent aPD-1 and no intervening systemic Tx**
- **No prior ipi (except adjuvant)**
- **Ocular melanoma excluded**

N~300

Ipilimumab 3 mg/kg Q3wks for 4 doses

No cross-over

Ipilimumab (same, beginning wk 2)
+
intratumoral IMO-2125,
wks 1, 2, 3, 5, 8, 11, 16, 20, 24

1^0 endpoint family:
- OS
- ORR (RECIST v1.1)

Questions & Answers

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