Tilsotolimod engages the TLR9 pathway to promote antigen presentation and type I IFN signaling in solid tumors

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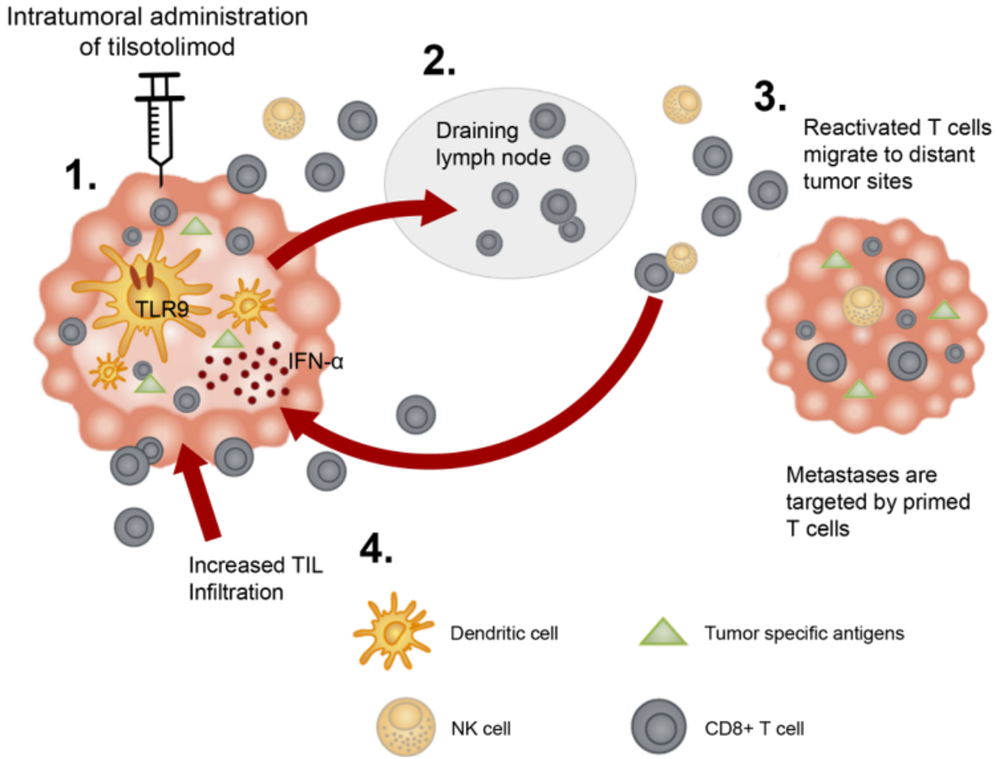
Background

- Tilsotolimod (IMO-2125) is an investigational, synthetic Toll-like receptor 9 (TLR9) agonist[1]
- In a phase 1/2 study of intratumoral tilsotolimod plus ipilimumab in anti–PD-(L)1–refractory advanced melanoma, durable responses in injected and noninjected lesions were observed[2]
- ILLUMINATE-101 (NCT03052205) was a phase 1b dose evaluation study of single-agent intratumoral tilsotolimod in patients with multiple refractory solid tumor types with a melanoma dose expansion cohort treated at the recommended phase 2 dose (RP2D)

Proposed Mechanism of Action



1. Wang D, et al. *Int J Oncol.* 2018;53(3):1193-1203. **2.** Diab A, et al. *Ann Oncol.* 2018;29(suppl 8):viii442.

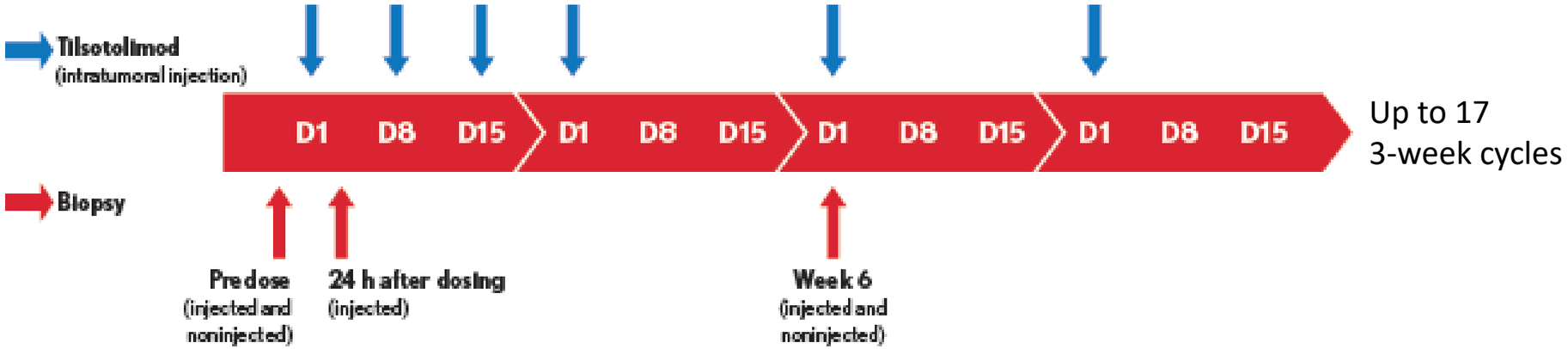
Methods

Eligibility criteria

- Adults with metastatic refractory solid tumors and an Eastern Cooperative Oncology Group performance status of ≤ 2 were eligible
- Patients with a diagnosis for which a PD-(L)1 inhibitor has been approved must have previously received treatment with one of these therapies

Objectives	Dose Escalation	Melanoma Dose Expansion
Primary	Safety	Clinical activity
Secondary	Establish RP2D, PK, clinical activity	Safety, PK, other clinical benefit measures
Exploratory	Immunologic assessment	Immunologic assessment

PK, pharmacokinetic; RP2D, recommended phase 2 dose



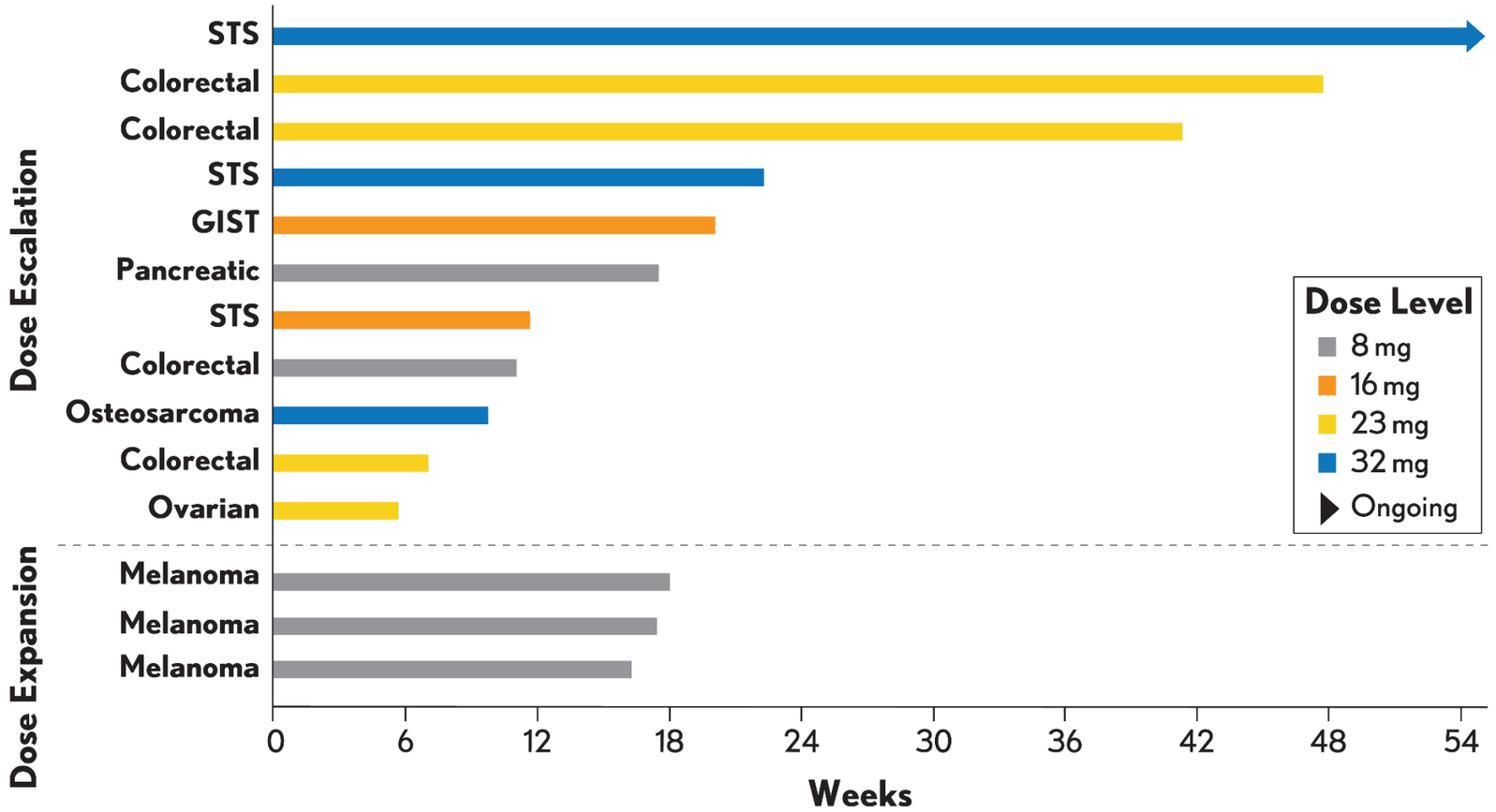
Patient Characteristics, Safety

- 54 patients were enrolled
  - 38 in the dose-evaluation portion received 8 (n=11), 16 (n=8), 23 (n=10), or 32 (n=9) mg tilsotolimod
  - 16 in a melanoma dose-expansion cohort received the 8 mg RP2D
- Most patients had advanced disease
  - Dose evaluation: 92% had metastatic disease
  - Melanoma expansion: All patients had metastatic disease, and 63% had elevated lactate dehydrogenase
  - 91% of patients had injections into deep, visceral lesions with image guidance
- Tilsotolimod was generally well tolerated
  - No dose-limiting toxicities were observed
  - No discontinuations or deaths due to treatment-emergent adverse events (TEAEs)

Adverse Event, n (%)	Dose Evaluation (N = 38)	Melanoma Dose Expansion (N = 16)
≥ 1 TEAE	38 (100)	16 (100)
≥ 1 Grade 3/4 TEAE	18 (47)	7 (44)
≥ 1 Grade 3 TRAE[a]	6 (16)	2 (13)
≥ 1 SAE	13 (34)	7 (44)
Most common grade 3/4 TEAEs		
Anemia	3 (8)	1 (6)
Fatigue	2 (5)	0
Sepsis	2 (5)	0
Hyponatremia	2 (5)	0
AST increased	2 (5)	0
Thrombocytopenia	2 (5)	0
Most common TRAEs[b]		
Pyrexia	23 (61)	12 (75)
Fatigue	13 (34)	6 (38)
Chills	13 (34)	3 (19)
Nausea	4 (11)	5 (31)
Vomiting	3 (8)	5 (31)

AST, Aspartate aminotransferase; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
[a]No grade 4 TRAEs were observed.
[b]Most common TRAEs observed in total population

Duration of Stable Disease



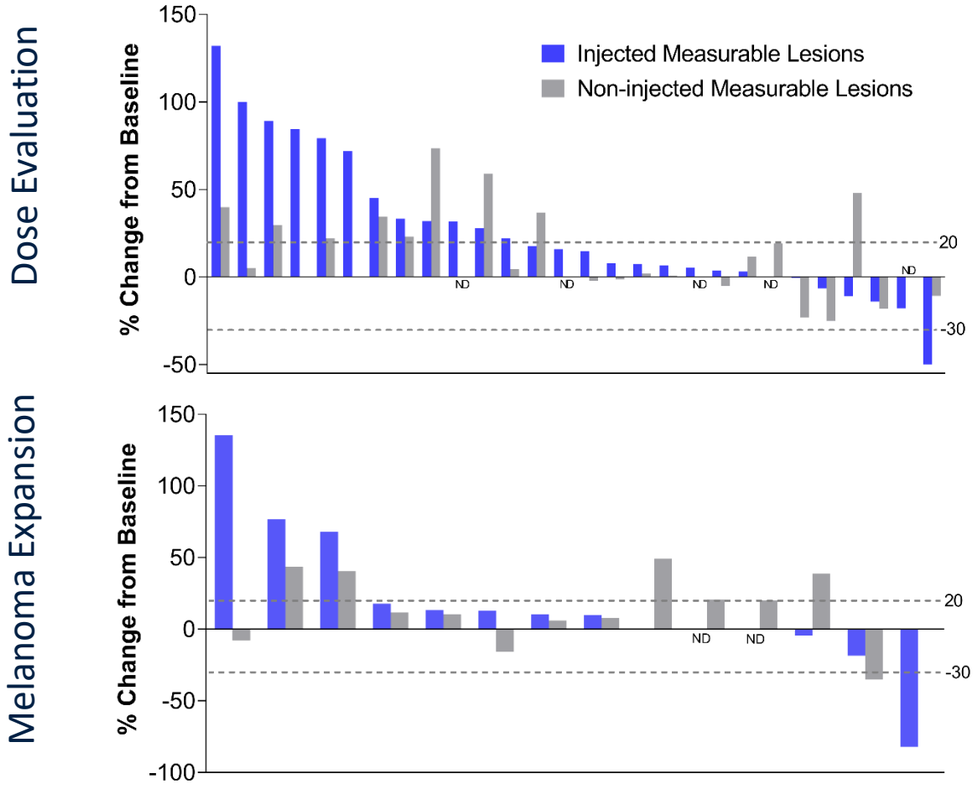
GIST, gastrointestinal stromal tumor; STS, soft tissue sarcoma.

One patient had an assessment of stable disease after discontinuing treatment due to clinical progression and is excluded from the figure.

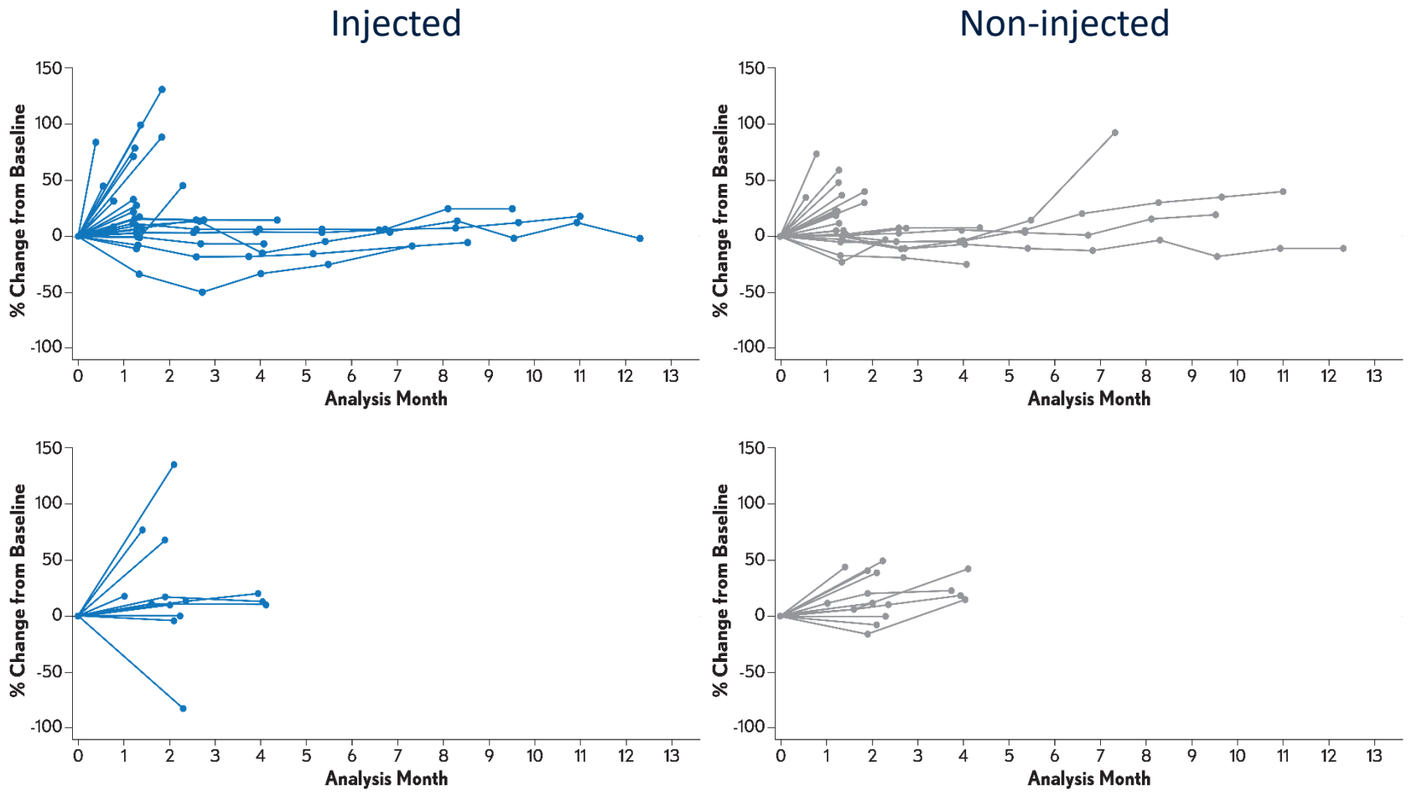
- 12 of 35 evaluable patients (34%) in the dose evaluation cohort and 3 of 16 (19%) in the melanoma cohort had stable disease

Tumor reduction in injected and non-injected lesions suggests a potential abscopal effect

Maximum Percent Reduction From Baseline in the Individual Sum of Longest Diameters by Injection Status[a]



Individual Change From Baseline in the Sum of Longest Diameters



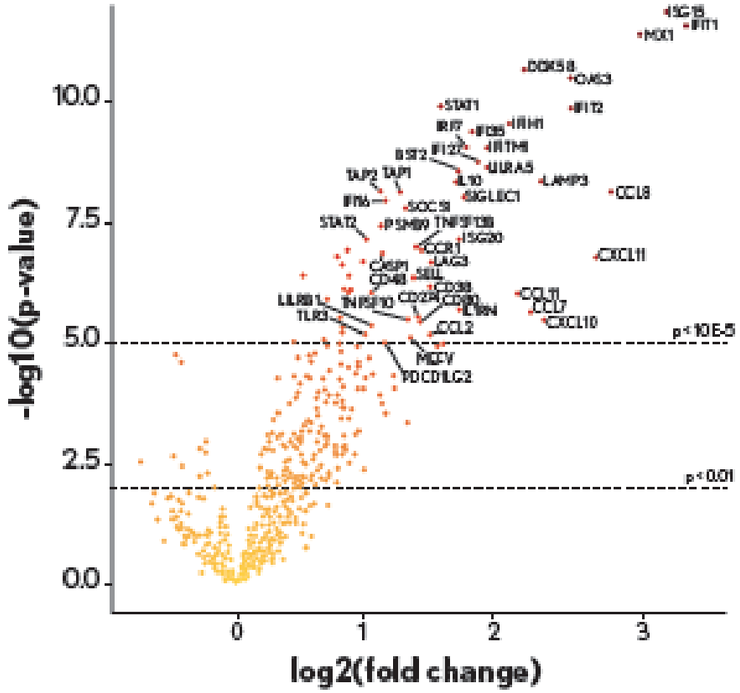
ND, not determined.

[a]Includes patients with at least 1 post-baseline assessment that includes measurements of all measurable lesions.

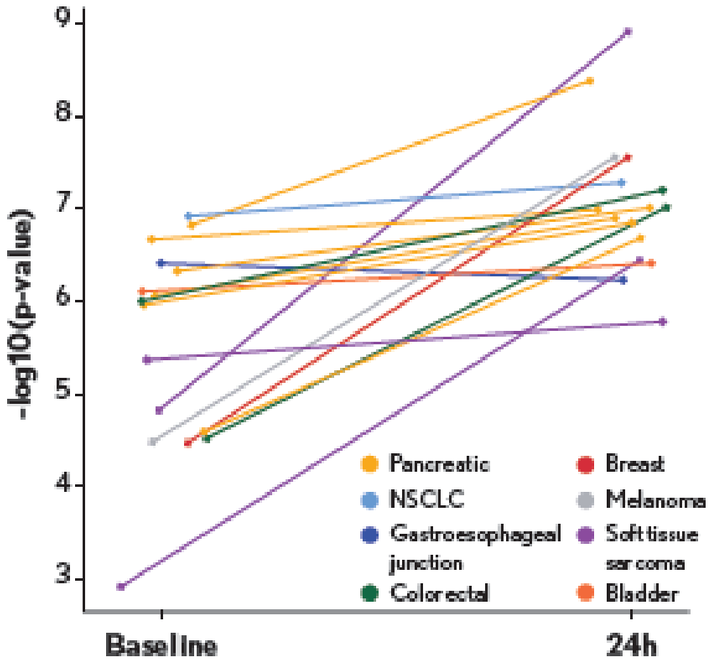
Translational Findings

Robust, early activation of the type I IFN pathway and evidence of DC activation in biopsies following intratumoral tilsotolimod injection

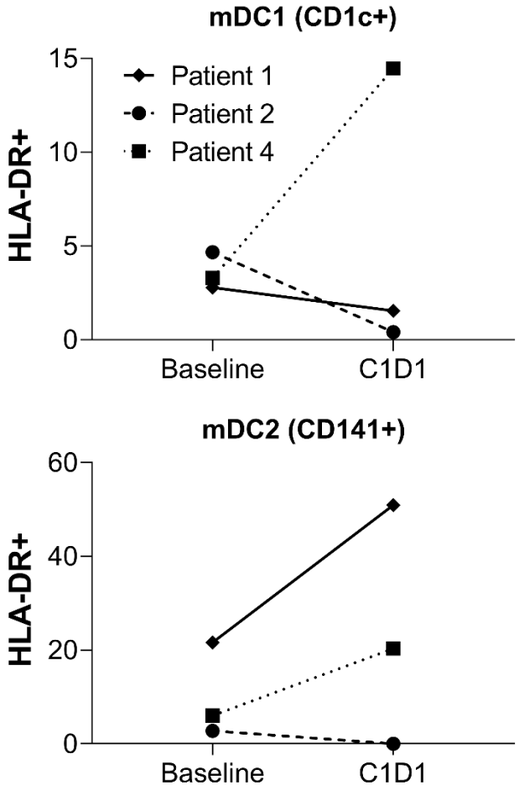
Gene Expression Change from Baseline to 24 Hours After Dosing



IFN-α Signaling Change from Baseline to 24 Hours After Dosing



MHC-II (HLA-DR) Upregulation from Baseline to 24 Hours After Dosing



Conclusions and Acknowledgements

- Intratumoral injection of single-agent tilsotolimod was generally well tolerated
- Preliminary evidence of clinical activity across multiple solid tumors, including those traditionally unresponsive to immunotherapy
- Tumor reduction was observed in injected and noninjected lesions, suggesting a potential abscopal effect
- Across multiple tumor types, tilsotolimod:
  - rapidly increased dendritic cell activation
  - upregulated MHC class II on dendritic cells
  - upregulated IFN-α signaling

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