Final Results from ILLUMINATE-204, a Phase 1/2 Trial of Intratumoral Tilsotolimod in Combination with Ipilimumab in PD-1 Inhibitor Refractory Advanced Melanoma

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DISCLOSURE INFORMATION

S.R. and S.C. are employees of Idera Pharmaceuticals, Inc. and own company stock; A.D. received research funding and consultation fees from Idera Pharmaceuticals, Inc.; C.L.H. received consultation fees from Idera Pharmaceuticals and is on the advisory board for Briacell, Inc.; D.B.J. received research funding from Bristol Myers Squibb and Incyte and is on the advisory board for Array Biopharma, Bristol Myers Squibb, Janssen, Iovance, Merck, and Novartis; R.H.I.A. is on the advisory board for Aduro, Merck, Novartis, OncoSec, Pfizer, and Takara Bio; M.A.D. has served on advisory boards for BMS, GSK, Roche/Genentech, and Novartis and has been the PI of grants to his institution from GSK and Roche/Genentech; J.M is on the advisory board for Newlink Genetics, has served on an advisory board for Array Biopharma in the past two years, and has been PI of grants/funding to his institution from Morphogenesis Inc, Navigate Biopharma, Merck, Macrogenics, and Reata Pharmaceuticals; other authors declare no competing interests.
Highly unmet need in post-PD-1 advanced melanoma

Patients with advanced melanoma that progressed on or after PD-1 inhibitor therapy have a poor prognosis.

Resistance to checkpoint inhibitors may be overcome by combining them with other immune modulators.

Tilsotolimod is an investigational TLR9 agonist that has been shown to activate innate and adaptive immune responses and rapidly upregulate type 1 IFN and dendritic cell activation following intratumoral injection.
ILLUMINATE-204: Study Design and Methods

A phase 1/2 clinical trial of intratumoral tilsotolimod in combination with ipilimumab in patients with advanced melanoma who progressed on or after anti-PD-1 therapy

Patient selection
Adults with unresectable or metastatic melanoma that progressed on or after a PD-1 inhibitor, an accessible tumor for intratumoral administration of tilsotolimod, and ≤ 2 lines of prior therapy (≤ 3 if BRAF-mutant) were eligible

Prior ipilimumab was allowed

Treatments
Tilsotolimod was administered to a single tumor during weeks 1, 2, 3, 5, 8, 11, 17, 23, and 29

Ipilimumab was administered per the product label

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Phase 1</th>
<th>Phase 2</th>
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<tbody>
<tr>
<td>Primary</td>
<td>Safety and determine a recommended Phase 2 dose</td>
<td>Clinical activity (objective response per RECIST v1.1)</td>
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<tr>
<td>Secondary</td>
<td>Determine plasma pharmacokinetics and assess clinical activity</td>
<td>Safety, landmark overall survival and progression-free survival at 6 and 12 months, and duration of response</td>
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<tr>
<td>Exploratory</td>
<td>Assess patient-reported outcomes and exploratory biomarkers</td>
<td>Assess patient-reported outcomes and exploratory biomarkers</td>
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</tbody>
</table>
Patient Characteristics

- All patients had received PD-(L)1 inhibitor therapy
- 22 patients received prior ipilimumab therapy
- 43.5% of patients had stage M1c disease
- Approximately half of patients (48.4%) had BRAF mutation
Safety Data

- Grade 3 or 4 treatment emergent adverse events (TEAEs) was reported in 48.4% of patients

- The most common serious TEAEs were autoimmune hepatitis, hyponatremia, and hypophysitis (n=2 for each)

- Immune-related toxicities were reported in 25.8% of patients, suggesting that tilsotolimod + ipilimumab does not add immune-related toxicity versus ipilimumab alone

- There were no TEAEs leading to study discontinuation or death
Clinical activity (8 mg intratumoral tilsotolimod with ipilimumab)

**Maximum Percent Tumor Reduction**

**Response Assessment**

<table>
<thead>
<tr>
<th>Best overall response</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>CR</td>
<td>2 (4.1)</td>
</tr>
<tr>
<td>PR</td>
<td>9 (18.4)</td>
</tr>
<tr>
<td>SD</td>
<td>24 (49.0)</td>
</tr>
<tr>
<td>PD</td>
<td>14 (28.6)</td>
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**ORR (95% CI), %**

22.4 (11.8-36.6)

**DCR (95% CI), %**

71.4 (56.7-83.4)

**Median DOR (IQR), months**

11.4 (4.2-NE)
Kaplan-Meier (8 mg tilsotolimod + ipilimumab)

Median follow-up 13.4 months (range, 3.0 - 47.0)

Overall Survival

Progression-free Survival

Median OS: 21.0 months
95% CI: 9.79 months-NE

Median PFS: 5.1 months
95% CI: 3.65 months-7.00

CI, confidence interval; NE, not evaluable; OS, overall survival; PFS, progression-free survival
Early Induction of IFNα-response gene signature and Innate immune activation after i.t Tilsotilomod
TIL activation and proliferation on treatment correlates with response to combination therapy.

Responses despite low HLA-ABC expression at baseline.
Extensive biopsy time course supports proposed MOA for intratumoral tilsotolimod with ipilimumab

All biopsies were collected at baseline 24 hrs (injected lesion only) and at 8 weeks from 25 patients

• At 24 hrs, the injected lesions in all tested patients (n=23) demonstrated a rapid, robust type 1 IFN response and maturation of dendritic cells

• Presence of local dendritic cells, but not T cells, was associated with clinical response

• Responses were observed in patients with low baseline HLA-ABC expression, which is a resistance marker for ipilimumab monotherapy

• On treatment, T cell activation and expansion of existing high-frequency T cell clones in both injected and non-injected lesions correlated with response
Conclusions

- Intratumoral tilsotolimod in combination with ipilimumab was generally well tolerated.
- In this single arm study, the combination demonstrated efficacy in PD-1 inhibitor refractory advanced melanoma, including durable responses.
- Intratumoral tilsotolimod induced a robust type 1 interferon signature at 24 hours.
- Response to therapy was associated with increased T cell activation and proliferation and the expansion of dominant T-cell clones that are shared between injected and non-injected lesions.
- ILLUMINATE-301, a randomized phase 3 clinical trial of tilsotolimod at 8 mg in combination with ipilimumab compared to ipilimumab alone in PD-1 refractory advanced melanoma patients, is ongoing (NCT03445533).
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