Abstract: 1306TiP

A randomized phase 3 comparison of IMO-2125 with ipilimumab versus ipilimumab alone in subjects with anti-PD-1 refractory melanoma

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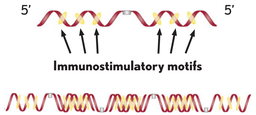
Trial details on EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-002454-36/SE).

BACKGROUND

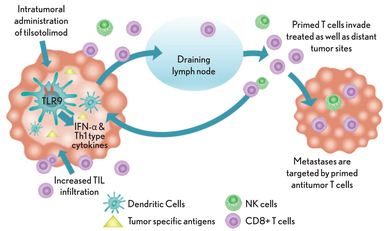
- Tilsotolimod (IMO-2125), an investigational synthetic oligonucleotide, is a toll-like receptor 9 (TLR9) agonist with potent immunostimulating activity

Chemistry of Tilsotolimod



- An ongoing phase 1/2 clinical study of intratumoral tilsotolimod plus ipilimumab (NCT02644967) shows the combination to be generally well-tolerated over the range of tilsotolimod doses tested, with evidence of dendritic cell activation and infiltration of tumor specific immune cells in subject samples
- Clinical responses (including durable complete response >26 months) have been seen in anti-PD-1-refractory subjects
- Because no therapy has been shown to prolong survival after failure of first-line anti-PD-1 immunotherapy, this phase 3 study is designed to show the superiority of tilsotolimod plus ipilimumab over ipilimumab alone
- This is a randomized phase 3 global, multicenter, open-label comparison of ipilimumab (3 mg/kg) with or without intratumoral tilsotolimod (8 mg) in subjects with advanced and progressing cutaneous or mucosal melanoma while receiving anti-PD-1 therapy

Graphic representation of intratumoral mechanism of action of tilsotolimod



OBJECTIVES

Primary objective

- To compare the efficacy, measured by overall survival and overall response rate, of intratumoral tilsotolimod in combination with ipilimumab versus ipilimumab alone

Secondary objectives

- To assess other measures of clinical safety, pharmacokinetics, and patient-reported outcomes

Exploratory objectives

- To investigate potential biomarkers and the incidence of antitilsotolimod antibodies

STUDY ENROLLMENT

Study Enrollment

Enrollment is planned to include 308 adult subjects with unresectable or metastatic melanoma with confirmed radiologic progression during or after PD-1 inhibitor therapy who

- were ≥21 days from the most recent anti-PD-1 treatment and underwent no intervening systemic treatment
- underwent no prior ipilimumab treatment except adjuvant
- underwent no BRAF mutation positive treatment or else declined it
- had no ocular melanoma

Key Eligibility Criteria

- 18 years of age or older
- Histologically confirmed stage III or IV metastatic melanoma
- A measurable lesion that is accessible for injection
- Eastern Cooperative Oncology Group (ECOG) performance status score of ≥1
- Adequate organ function
- No prior therapy with a TLR agonist, excluding topical agents
- No prior ipilimumab treatment with the exception of adjuvant treatment completed ≥6 months before enrollment
- No evidence of central nervous system, meningeal, or epidural metastatic disease other than stable (≥4 weeks) brain metastases

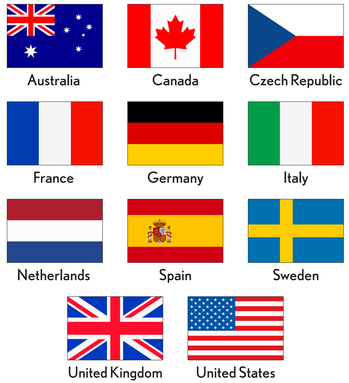
This study is currently recruiting in the United States, Canada, Europe, and Australia.

STUDY ENROLLMENT

308 subjects

80 centers

11 countries



METHODS

Study Design

Subjects will be randomized 1:1 to either study treatment arm A or arm B

	Arm A	Arm B
Study Design	• ipilimumab 3 mg/kg (4 doses: weeks 1, 4, 7, 10)	• ipilimumab 3 mg/kg (4 doses: weeks 2, 5, 8, 11) • intratumoral tilsotolimod 8 mg (9 doses: weeks 1, 2, 3, 5, 8, 11, 16, 20, 24)
Treatment duration	• 10 weeks	• 24 weeks

Subjects will be stratified by

Duration of prior anti-PD-1 therapy	Metastasis stage	BRAF mutation status and prior targeted therapy
• ≥12 weeks • Less than 12 weeks	• M1c • Other	• BRAF wild type • BRAF mutation positive with targeted therapy • BRAF mutation positive with no prior targeted therapy

Disease assessment and follow-up

Tumor assessments will be performed at

- Baseline
- Week 12
- Every 8 weeks during first year, then
- Every 12 weeks in subsequent years

Active follow-up

- If there is no disease progression or new cancer treatment
- Clinical and radiologic assessments for subjects who complete study treatment or discontinue it for reasons other than disease progression or starting new cancer treatment but remain in the study

Survival follow-up

- If there is disease progression or new cancer treatment
- Telephone interviews for subjects who discontinue study assessments in response to disease progression or for those with or without disease progression who start new cancer treatment

Endpoints

Primary endpoints

- Overall response rate by independent review of RECIST v1.1
- Overall survival (hazard ratio, 0.63)

Secondary endpoints

- Durable response rate
- Time to response
- Progression-free survival
- Patient-reported outcomes
- Safety

Study Analysis

Interim analysis

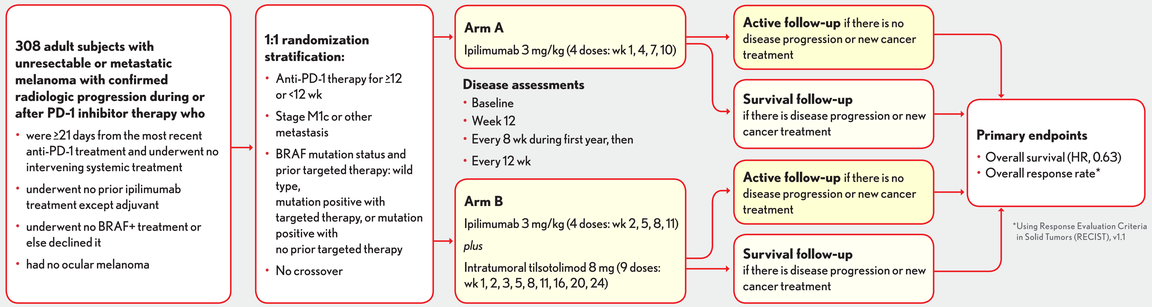
- Overall survival, after 110 deaths
  - $P<.001$
  - $Z>3.08963$

Final analysis

Overall response rate and overall survival, after 219 deaths

- Estimated at 36 months postrandomization
  - $P<.01967$
  - $Z>2.06066$

Illuminate 301 Study Design (N=308)



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