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Randomized, Open-Label, Phase III Study of Tilsotolimod in Combination With Ipilimumab Versus Ipilimumab Alone in Patients With Advanced Refractory Melanoma (ILLUMINATE-301)

Adi Diab, MD¹ ; Paolo A. Ascierto, MD, PhD² ; Michele Maio, MD, PhD³ ; Reham Abdel-Wahab, MD, PhD^{1,4} ; Sylvie Negrier, MD, PhD⁵; Laurent Mortier, MD, PhD⁶; Petr Arenberger, MD⁷ ; Stephane Dalle, MD, PhD⁸; Ivana Krajsova, MD⁹ ; Luis de la Cruz, MD¹⁰ ; Marie-Therese Leccia, MD¹¹; Michele Guida, MD, PhD¹²; Celeste Lebbe, MD, PhD¹³ ; Jean-Jacques Grob, MD¹⁴ ; Marcus O. Butler, MD¹⁵ ; Gino K. In, MD¹⁶; Carmen Loquai, MD¹⁷; John W.T. Walker, MD, PhD¹⁸; Victoria Atkinson, MD¹⁹; Ellen Kapiteijn, MD, PhD²⁰; Sebastian Haferkamp, MD, PhD²¹ ; Srinivas Chunduru, MD, PhD²²; Shahram Rahimian, MD^{22,23}; Massimo Guidoboni, MD, PhD²⁴ ; and Caroline Robert, MD, PhD²⁵

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ABSTRACT

PURPOSE There are limited treatment options for advanced melanoma that have progressed during or after immune checkpoint inhibitor therapy. Intratumoral (IT) immunotherapy may improve tumor-specific immune activation by promoting local tumor antigen presentation while avoiding systemic toxicities. The phase 3 ILLUMINATE-301 study (ClinicalTrials.gov identifier: [NCT03445533](#)) evaluated tilsotolimod, a Toll-like receptor-9 agonist, with or without ipilimumab in patients with anti-PD-1 advanced refractory melanoma.

METHODS Patients with unresectable stage III-IV melanoma that progressed during or after anti-PD-1 therapy were randomly assigned 1:1 to receive 24 weeks of tilsotolimod plus ipilimumab or 10 weeks of ipilimumab alone. Nine IT injections of tilsotolimod were administered to a single designated lesion over 24 weeks. Intravenous ipilimumab 3 mg/kg was administered once every 3 weeks from week 2 in the tilsotolimod arm and week 1 in the ipilimumab arm. The primary end point was efficacy measured using objective response rate (ORR; independent review) and overall survival (OS).

RESULTS A total of 481 patients received tilsotolimod plus ipilimumab ($n = 238$) or ipilimumab alone ($n = 243$). ORRs were 8.8% in the tilsotolimod arm and 8.6% in the ipilimumab arm, with disease control rates of 34.5% and 27.2%, respectively. Median OS was 11.6 months in the tilsotolimod arm and 10 months in the ipilimumab arm (hazard ratio, 0.96 [95% CI, 0.77 to 1.19]; $P = .7$). Grade ≥ 3 treatment-emergent adverse events occurred in 61.1% and 55.5% of patients in the tilsotolimod and ipilimumab arms, respectively.

CONCLUSION Combining IT tilsotolimod with ipilimumab did not significantly improve the ORR or OS compared with ipilimumab alone in patients with anti-PD-1 advanced refractory melanoma.

ACCOMPANYING CONTENT

- Appendix
- Data Sharing Statement
- Protocol

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INTRODUCTION

Immune checkpoint inhibitors (ICIs) have transformed the treatment of melanoma. Nivolumab (alone or combined with ipilimumab) and pembrolizumab are standard-of-care first-line treatments of metastatic melanoma. However, patients may ultimately progress during or after treatment and require subsequent treatment options. The selection of second-line therapy is challenging as a result of the lack of data to guide treatment choice. For patients with advanced melanoma who

progressed on or after anti-PD-1 inhibitors, subsequent treatment with the anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) inhibitor is an option.^{1,2}

The efficacy of ICIs was found to be correlated with the presence of tumor-infiltrating T cells in the tumor micro-environment. Thus, manipulating the innate immune system within the tumor using intratumoral (IT) immunotherapy may induce a favorable immune environment, recruiting and activating immune cells and activating dendritic cells (DCs) at

CONTEXT

Key Objective

The ILLUMINATE-301 phase 3 trial is designed to assess the efficacy and clinical benefit of the combination of intratumoral tilsotolimod, a Toll-like receptor-9 agonist, with ipilimumab versus ipilimumab alone in patients with advanced or metastatic melanoma refractory to anti-PD-1 therapies.

Knowledge Generated

Combined tilsotolimod with ipilimumab did not significantly improve overall response rate, progression-free survival, or overall survival compared with ipilimumab monotherapy. However, this trial, to our knowledge, provides the largest data set to date on ipilimumab usage for treating this difficult-to-treat refractory population.

Relevance (G.K. Schwartz)

For patients with metastatic melanoma who progress on PD-1 checkpoint, the addition of ipilimumab remains the standard of care.*

*Relevance section written by JCO Associate Editor Gary K. Schwartz, MD, FASCO.

the tumor site capable of priming antitumor T cells, hence ensuring optimal local tumor antigen/neoantigen presentation while avoiding systemic toxicities. One such approach is through activation of Toll-like receptor-9 (TLR9), a pattern recognition receptor in plasmacytoid DCs, which induces the production of interferon (IFN)- α and tumor necrosis factor- α , which promotes downstream activation and maturation of antigen-presenting cells (APCs).³

Although TLR9 agonists share the common mechanism of TLR9 activation, they can differ significantly in their structure, potency, and biological effects. Tilsotolimod (IMO-2125) is a class B synthetic phosphorothioate oligonucleotide and a selective TLR9 agonist with potent immunostimulatory activity.⁴⁻⁶ In a murine animal model, tilsotolimod IT injection increased local APC maturation, CD3⁺ T cells, and expression of multiple immune checkpoints (PD-1 and CTLA-4) in both injected and noninjected distant tumors.⁷ Tilsotolimod has also been shown to augment ICI response in multiple tumor models, including melanoma.⁸⁻¹⁰ Results from a phase 1/2 clinical study of IT tilsotolimod plus ipilimumab for advanced melanoma showed the combination is tolerable with evidence of clinical activity in patients with anti-PD-1 advanced refractory melanoma. At the recommended phase 2 dose, 22% of patients had an objective response and an additional 49% of patients had stable disease. Furthermore, tilsotolimod IT injection induced a rapid, local production of type 1 IFN. When combined with ipilimumab, it activated more T cells, promoting clinical activity, including in distant lesions and patients who were not expected to respond to ipilimumab alone.¹¹

Given the absence of therapies that have demonstrated a survival advantage in patients who progressed on prior PD-1 blockade, along with the promising results from phase 1/2 ILLUMINATE-204 study, we conducted ILLUMINATE-301

(ClinicalTrials.gov identifier: [NCT03445533](https://clinicaltrials.gov/ct2/show/study/NCT03445533)), an international, randomized, phase 3, multicenter, open-label study to evaluate the efficacy of IT tilsotolimod combined with ipilimumab versus ipilimumab monotherapy in patients with advanced melanoma who had progressed during or after anti-PD-1 therapy.

METHODS

Patients

Eligible patients were of age 18 years and older with histologically confirmed unresectable stage III or stage IV melanoma, according to the American Joint Committee on Cancer, Seventh Edition. Patients were required to have ≥ 1 measurable lesion accessible for injection (superficial or visceral) and have confirmed progression during or after treatment with a PD-1 inhibitor (prior PD-1 targeted bispecific antibodies were not permitted). Confirmed progression was defined as radiological progression (confirmed at least 4 weeks after the initial scan showing progressive disease [PD] or confirmed at least 4 weeks after the initial scan for progression solely on the basis of worsening of nontarget or new, nonmeasurable disease). Patients were also required to have an Eastern Cooperative Oncology Group (ECOG) status ≤ 1 , adequate organ function, and known BRAF mutation status. Exclusion criteria included prior TLR agonists, prior ipilimumab (except adjuvant ≥ 12 weeks before progression), and CNS disease other than stable brain metastases.

The study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki. The institutional review board or ethics committee approved the study protocol (online only) at each site. All patients provided written informed consent.

Study Design

Patients were randomly assigned 1:1 to receive treatment with IT tilsotolimod combined with ipilimumab or ipilimumab alone. Random assignment was stratified by duration of prior anti-PD-1 (≥ 12 v < 12 weeks), stage (M1c v other), and BRAF status/prior targeted therapy (BRAF wild-type v BRAF mutant type with prior targeted therapy v BRAF mutant type without prior targeted therapy). Patients randomly assigned to the tilsotolimod arm received nine doses of IT injection on weeks 1, 2, 3, 5, 8, 11, 16, 20, and 24. Tilsotolimod was administered to a single designated lesion selected from (in order of priority) pathologic draining lymph nodes, superficial/subcutaneous metastases, or deep/visceral metastases using a single injection site and a fanning method to ensure even distribution. As outlined in the protocol, all deep lesion injections required image guidance, supported by interventional radiology, to ensure safe and accurate administration. Tilsotolimod was continued until disease progression.

Patients in both groups received ipilimumab at a dose of 3 mg/kg over 90 minutes. Ipilimumab was given on weeks 2, 5, 8, and 11 for patients in the tilsotolimod arm and on weeks 1, 4, 7, and 10 for patients in the monotherapy arm. Ipilimumab dose reductions were not permitted, although treatment could be delayed as a result of toxicity.

Study End Points and Assessments

The primary end points were objective response rate (ORR) by independent central review and overall survival (OS). Secondary end points included ORR by investigator assessment, time to response, disease control rate (DCR), duration of response (DoR), progression-free survival (PFS) by independent central review and investigator assessment, and safety. Tumor response was assessed at screening and week 12, then every 8 weeks for the first year, and then every 12 weeks in subsequent years. Investigators followed modified immune-related RECIST (irRECIST) guidelines for subject management, and both investigators and independent central reviewers used irRECIST and RECIST v1.1 guidelines for visit response assessments. Complete responses (CRs), partial responses (PRs), and PD determined using irRECIST were confirmed by imaging ≥ 4 weeks after the initial documentation of response, except progression solely on the basis of substantial, unequivocal worsening of nontarget or new, nonmeasurable disease accompanied by correlative symptoms. CRs and PRs determined using RECIST were also confirmed by imaging ≥ 4 weeks after the initial response documentation. Safety was summarized using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.03.

Statistical Analysis

Under the fallback method, $\alpha = 0.02$ is assigned to the one-sided ORR test and an alpha of 0.005 is saved for the one-sided OS test. The sample size was specified assuming a

hazard ratio (HR) of 0.677, equating to an increase in median OS from 11.4 months (historical control for ipilimumab alone) to 16.9 months with the addition of tilsotolimod. To provide 90% power at a one-sided 5% significance level, the sample size was calculated to be 454 patients. No interim analyses were planned. All efficacy analyses were performed in an intention-to-treat manner and included all randomly assigned patients. The safety analysis set included all patients who received at least 1 dose of the study treatment.

A hierarchical testing procedure was applied to control the type I error rate when analyzing the OS. Formal statistical testing for OS was only allowed if the difference in ORR was confirmed statistically significant. The comparison of ORR between treatment arms was calculated using Cochran-Mantel-Haenszel test. Analysis of OS was performed using stratified log-rank test controlling for the random assignment strata. DoR and PFS were estimated using Kaplan-Meier method. The HRs and corresponding 95% CIs were estimated using stratified Cox proportional hazards model. Median follow-up time was calculated using the reverse Kaplan-Meier method.

RESULTS

Patients

Between May 2018 and March 2020, 579 patients were screened, and 481 patients from 80 sites were randomly assigned to receive tilsotolimod plus ipilimumab ($n = 238$) or ipilimumab ($n = 243$; Fig 1). Baseline characteristics are presented in Table 1 and were generally balanced between the treatment arms. The median age (range) was 66 (28-89) years in the tilsotolimod arm and 67 (19-92) years in the ipilimumab arm. In both arms, most of the patients were male (55.9% and 52.3%, respectively) and had an ECOG status of 0 (63% and 60.1%, respectively).

Exposure

In the tilsotolimod arm, the median (range) duration of tilsotolimod treatment was 10 (0.1-56.6) weeks, median (range) number of tilsotolimod injections was 5 (1-9), median (range) cumulative dose of tilsotolimod was 40 (8-72) mg, and only 54 patients (23.1%) received all nine injections per protocol. Tilsotolimod was injected in superficial lesions for 76 patients and in deep lesions for 161 patients. In the same arm, the median (range) duration of ipilimumab treatment was 7.1 (0.1-61.4) weeks, median (range) number of ipilimumab infusions was 3 (0-4), median (range) cumulative dose of ipilimumab was 9.02 (2.8-13) mg, and 100 patients (42.7%) received the four infusions per protocol. In the ipilimumab arm, the median (range) duration of treatment was 8.9 (0.1-15.6) weeks, median (range) number of infusions was 3 (1-4), median (range) cumulative dose was 9.2 (3-12.8) mg, and 116 patients (49.2%) received the four infusions per protocol. Moreover, the median (range) follow-up time was

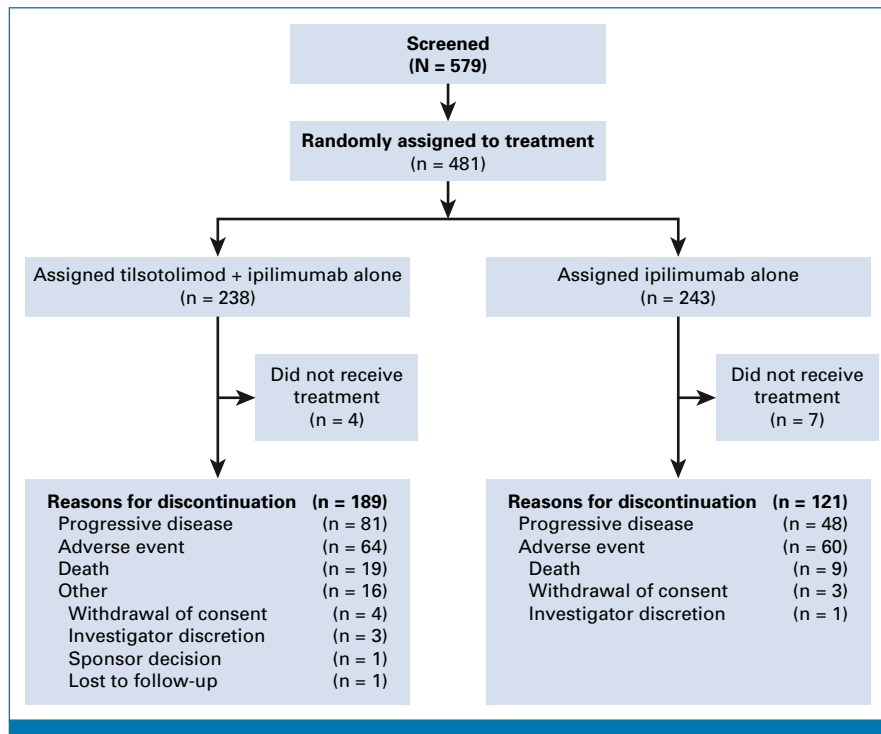


FIG 1. CONSORT diagram.

68 (0–156) weeks in the tilsotolimod arm and 58 (0–152) weeks in the ipilimumab arm (Appendix Table A1, online only).

Response Rate

The ORR was not significantly improved in the tilsotolimod arm (8.8%) versus the ipilimumab arm (8.6%; Table 2) by independent review. The findings were consistent in all prespecified subgroup analyses (Fig 2). The median time to respond was 2.7 months in the tilsotolimod arm and 2.6 months in the ipilimumab arm. The DCR was 34.5% in the tilsotolimod arm and 27.2% in the ipilimumab arm. The median DoR was 11.1 months in the tilsotolimod arm and not evaluable in the ipilimumab arm. The results were similar to the investigator assessment (Appendix Table A2). Additionally, in the tilsotolimod arm, a significant tumor reduction was observed in noninjected tumors (Appendix Fig A1).

Overall Survival

The median duration of follow-up for survival was 23.9 months (95% CI, 21.6 to 24.9) in the tilsotolimod arm and 22.4 months (95% CI, 21.4 to 24.2) in the ipilimumab arm. At the time of analysis, 331 patients had died (165 in the tilsotolimod arm and 166 in the ipilimumab arm). Median OS was 11.6 months (95% CI, 9.6 to 13.5) in the tilsotolimod arm and 10 months (95% CI, 8.1 to 11.5) in the ipilimumab arm and was not statistically significant (HR, 0.96 [95% CI, 0.77 to 1.19]; $P = .7$; Fig 3A). The findings were consistent in all prespecified subgroup analyses (Fig 3B). One-year survival rates were 48.6% (95% CI, 42 to 54.8) in the tilsotolimod

arm and 42.2% (95% CI, 35.9 to 48.5) in the ipilimumab arm; 2-year survival rates were 25.9% (95% CI, 19.8 to 32.4) and 27.5% (95% CI, 21.5 to 33.7), respectively.

Progression-Free Survival

Median PFS, as determined by independent central review, was 2.9 months (95% CI, 2.8 to 3.3) in the tilsotolimod arm and 2.7 months (95% CI, 2.6 to 2.8) in the ipilimumab arm (Fig 3C). The results were similar to the investigator assessment, with median PFS 2.8 months (95% CI, 2.6 to 3.1) determined in the tilsotolimod arm and 2.7 months (95% CI, 2.6 to 2.8) determined in the ipilimumab arm (Appendix Fig A2).

Safety

98.7% of patients in the tilsotolimod arm and 95.3% in the ipilimumab arm reported at least 1 treatment-emergent adverse event (TEAE), including 61.1% and 55.5% grade ≥ 3 , respectively. All TEAEs, regardless of causality, are provided in Table 3 and Appendix Table A3. General disorders and administration site conditions, as well as GI and skin and subcutaneous tissue disorders were the most frequently reported TEAEs in both treatment groups. These included pyrexia (46.2%), asthenia (34.6%), chills (32.1%), diarrhea (30.3%), pruritus (24.4%), nausea (23.5%), and fatigue (20.5%) in the tilsotolimod arm. While in the ipilimumab monotherapy group, the most frequently reported TEAEs were diarrhea (28%), pruritus (25.4%), asthenia (23.3%), and nausea (20.3%). In the tilsotolimod arm, 15% and 24.8% of patients had treatment-related TEAEs that led to the discontinuation of tilsotolimod or ipilimumab, respectively,

TABLE 1. Baseline Demographics and Clinical Characteristics (intention-to-treat analysis)

Characteristic	Tilsotolimod Plus Ipilimumab (n = 238)	Ipilimumab (n = 243)
Age, years, median (range)	66 (28-89)	67 (19-92)
Male	133 (55.9)	127 (52.3)
Race		
White	187 (96.4)	207 (95.8)
Asian	1 (0.5)	6 (2.8)
Black or African American	2 (1)	2 (0.9)
Other	4 (1.7)	1 (0.5)
Missing	44	27
ECOG performance status		
0	150 (63)	146 (60.1)
1	87 (36.6)	96 (39.5)
2	1 (0.4)	1 (0.4)
Enrollment location		
US	23 (9.7)	23 (9.5)
Non-US	215 (90.3)	220 (90.5)
Elevated serum LDH ^a	126 (52.9)	124 (51)
Disease stage ^{b,c}		
IIIA-IIIB	3 (1.2)	0
IIIC	35 (14.7)	20 (8.2)
IVM1a-IVM1b	48 (20.2)	82 (33.7)
IVM1C	147 (61.8)	137 (56.4)
Mutant <i>BRAF</i>	56 (23.5)	54 (22.2)
Prior lines of systemic therapy		
1 prior line of therapy	136 (57.1)	149 (61.3)
2 prior lines of therapy	65 (27.3)	67 (27.6)
>2 prior lines of therapy	28 (11.8)	21 (8.6)
Type of prior therapy		
PD-1 inhibitor	237 (99.6)	242 (99.6)
CTLA-4 inhibitor	6 (2.5)	5 (2.1)
Other immunotherapy	18 (7.6)	14 (5.8)
<i>BRAF</i> inhibitor	35 (14.7)	36 (14.8)
<i>MEK</i> inhibitor	33 (13.9)	36 (14.8)
Other targeted therapy	5 (2.1)	6 (2.5)
Oncolytic virus	5 (2.1)	6 (2.5)
Cytokine	10 (4.2)	14 (5.8)
Chemotherapy	11 (4.6)	8 (3.3)
Other therapy	38 (16)	27 (11.1)

NOTE. All presenting data are No. (%) unless otherwise specified.

Abbreviations: AJCC, American Joint Committee on Cancer; CTLA-4, cytotoxic T-lymphocyte antigen-4; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

^aLDH higher than the upper limit of normal.

^bDetermined using the AJCC Cancer Staging Manual, 7th Edition.

^cThe actual stage was not reported in five patients in the tilsoilomod plus ipilimumab arm and four patients in the ipilimumab monotherapy arm.

whereas it was 23.7% of patients in the ipilimumab-only arm. Additionally, serious treatment related adverse events occurred in 49.6% of patients in the tilsoilomod arm and 45.8% of patients in the ipilimumab arm (Appendix Table A4). Treatment-related deaths occurred in two and three patients in the tilsoilomod and ipilimumab arms, respectively.

DISCUSSION

In this phase III study of patients with anti-PD-1 advanced refractory melanoma, tilsoilomod plus ipilimumab demonstrated a low ORR and missed its coprimary end points of improving ORR and OS compared with ipilimumab

TABLE 2. Independent Reviewer–Assessed Responses (intention-to-treat analysis)

Response	Tilsotolimod Plus Ipilimumab (n = 238)	Ipilimumab (n = 243)
Best overall response		
CR	1 (0.4)	1 (0.4)
PR	20 (8.4)	20 (8.2)
SD	61 (25.6)	45 (18.5)
PD	89 (37.4)	110 (45.3)
Unevaluable	67 (28.2)	67 (27.6)
ORR (CR/PR)	21 (8.8)	21 (8.6)
95% CI	5.2 to 12.4	5.1 to 12.2
Rate difference (95% CI)	0.2 (−4.8 to 5.2) [<i>P</i> = .9]	
DCR (CR/PR/SD)	82 (34.5)	66 (27.2)
95% CI	28.4 to 40.5	21.6 to 32.8
Time to response, months, median (range)	2.7 (2.4–8.4)	2.6 (1.4–6.2)
DoR, months, median (range)	11.1 (6 to NE)	NE (9.3 to NE)

NOTE. All presenting data are No. (%) unless otherwise specified.

Abbreviations: CR, complete response; DCR, disease control rate; DoR, duration of response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

monotherapy. This is despite observations of clinical benefit in the earlier phase 1/2 ILLUMINATE-204 study of tilsotolimod plus ipilimumab in a relatively similar patient population.¹¹

This negative result cannot be attributed to a high performance of ipilimumab in the control arm. Indeed, although the observed ORR (8.6%) and DCR (27.2%) in the ipilimumab monotherapy arm were comparable with the

results of the SWOG S1616 (ORR, 9%; DCR, 22%),¹² it was lower than the ORR and DCR reported recently, in a phase III trial that compared tumor-infiltrating lymphocyte (TIL) therapy versus ipilimumab alone (21% and 36%, respectively).¹³ This could be attributed to the fact that in our trial, 51% of patients in the monotherapy arm have elevated serum lactate dehydrogenase (LDH) compared with 17% and that 36.2% versus none had received ≥ 2 prior lines of therapy. Moreover, the ORR was lower than the ones

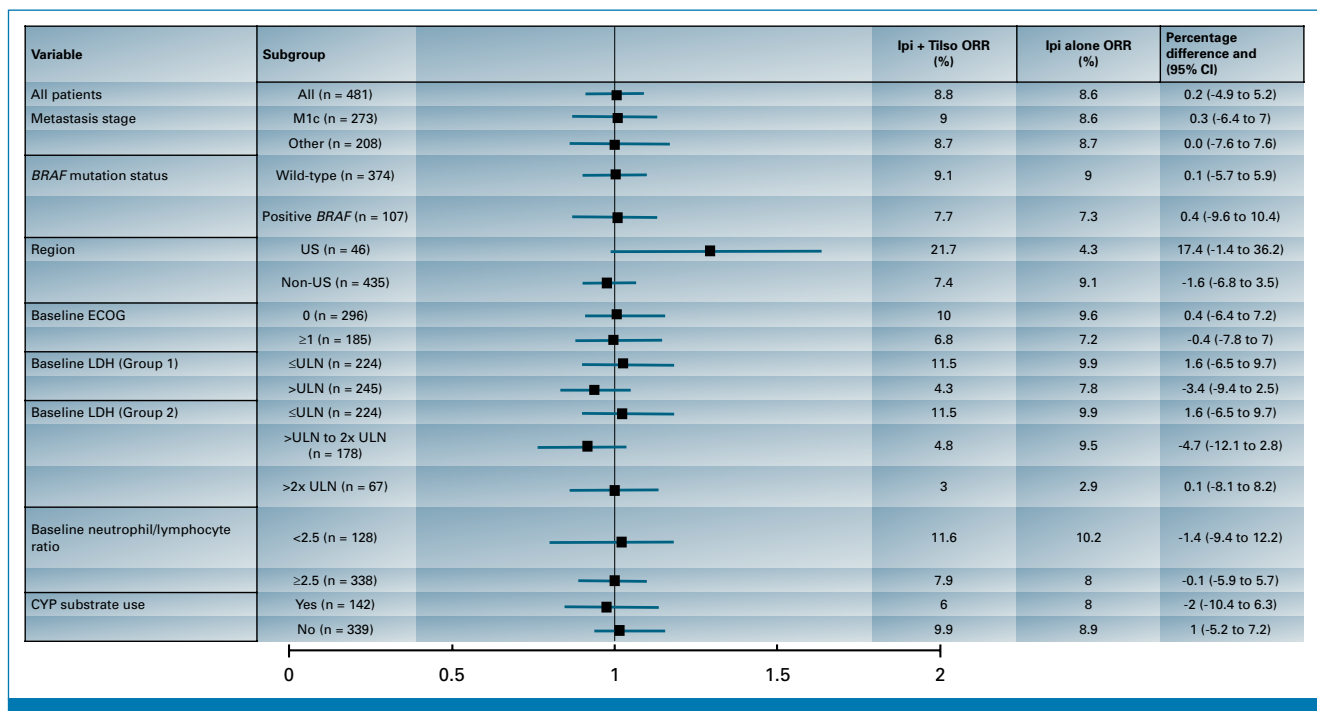


FIG 2. Forest plot of percentage of differences of ORR by subgroups assessed by independent reviewer. ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; ORR, objective response rate; ULN, upper limit of normal.

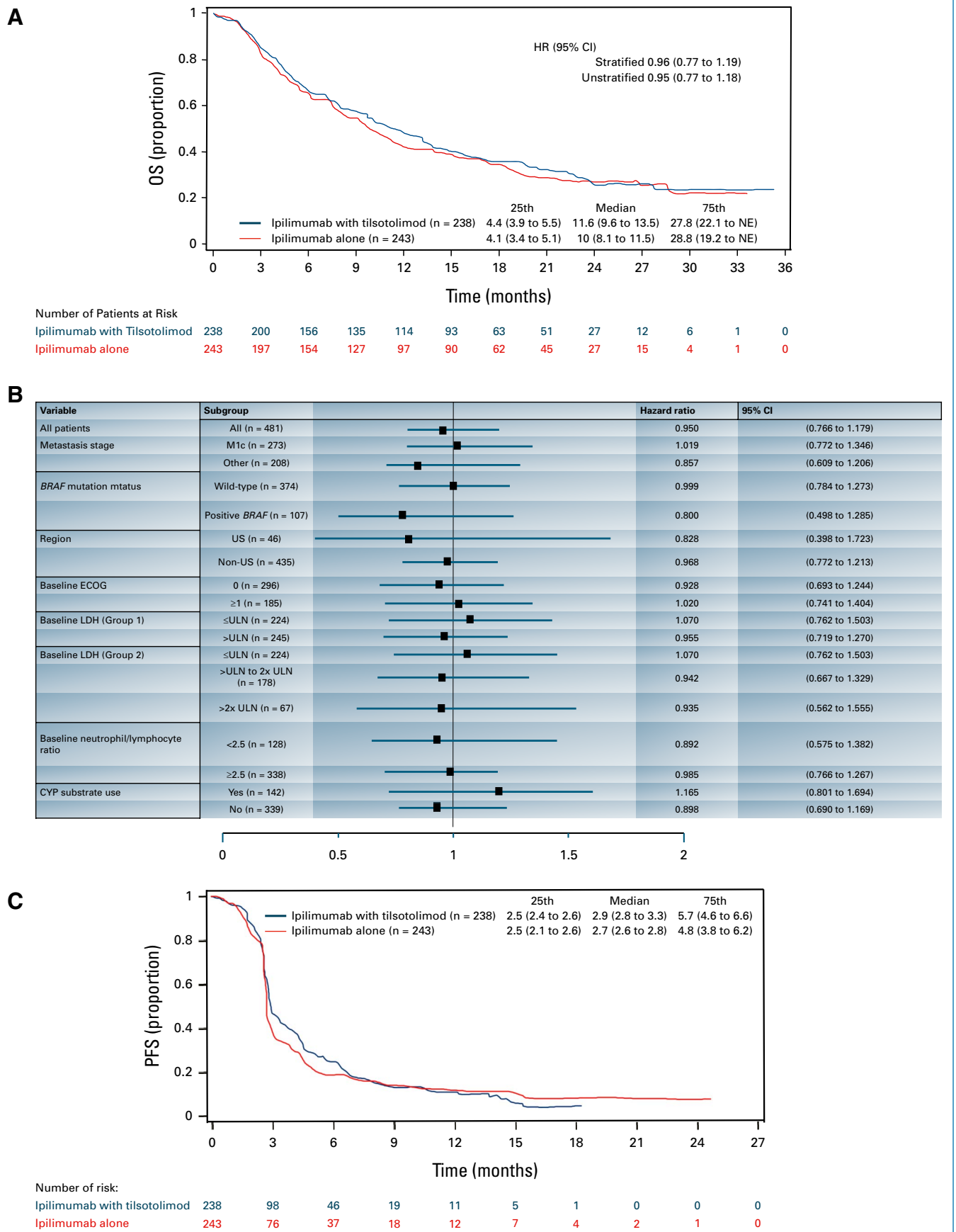


FIG 3. (A) Kaplan-Meier estimate of OS in all patients, (B) prespecified subgroup analysis according to baseline characteristics, and (C) Kaplan-Meier estimate of PFS in all patients by (continued on following page)

FIG 3. (Continued). blinded independent central assessment. ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; NE, not evaluable; OS, overall survival; PFS, progression-free survival; ULN, upper limit of normal.

observed in two retrospective studies, including ORR 16% and DCR 42% in one study¹⁴ but similar to results (ORR, 10%) reported in another retrospective study of patients with metastatic melanoma whose disease progressed during prior with anti-PD-1 therapy.¹⁵

Although several studies are investigating the potential of combining IT treatment with systemic immunotherapies, the only IT treatment approved for patients with unresectable melanoma and injectable metastases is talimogene laherparepvec (TVEC).¹⁶ The addition of this oncolytic virus to ipilimumab significantly improved ORR compared with ipilimumab monotherapy (39% v 18%; odds ratio, 2.9 [95% CI, 1.5 to 5.5]; $P = .002$) in a phase II trial. However, this benefit was primarily driven by the significant tumor reduction seen in the injected lesions only, whereas there was no significant difference between combined TVEC with ipilimumab versus ipilimumab alone in the tumor reduction rate of noninjected lesions.¹⁷ Furthermore, the addition of TVEC to pembrolizumab did not significantly improve PFS (14.3 v 8.5 months; HR,

0.86 [95% CI, 0.71 to 1.04]; $P = .13$) or OS (HR, 0.96 [95% CI, 0.76 to 1.24]; $P = .74$) compared with pembrolizumab monotherapy in the phase III MASTERKEY-265 study.¹⁸ Additionally, interleukin-2, a proinflammatory cytokine, has also been investigated as an IT treatment combined with ipilimumab in pretreated patients. However, it did not show DCR improvement in a phase II study compared with ipilimumab alone.¹⁹

In this trial, median PFS in the ipilimumab arm (2.7 months) was similar to the tilsotolimod arm (2.9 months) and to that reported for ipilimumab monotherapy in the SWOG S1616 (2.7 months)¹² and in the TIL therapy versus ipilimumab phase III trial (3.1 months).¹³ Also, median OS was not statistically different between the tilsotolimod and ipilimumab arms (11.6 v 10 months; HR, 0.96 [95% CI, 0.77 to 1.19]; $P = .7$). However, the median OS in the ipilimumab arm was less than that reported for ipilimumab in the SWOG S1616 (25.7 months) and a phase III trial (18.9 months).¹³ The survival rate at 1 year (42.2%) was less than that reported for ipilimumab both in SWOG S1616 (57%)¹² and in a

TABLE 3. Most Common TEAEs Grade 3 to 5 by Preferred Term (>2% of patients in either treatment group; safety set)

Preferred Term	Ipilimumab With Tilsotolimod (n = 234), No. (%)	Ipilimumab Alone (n = 236), No. (%)
Patients with at least 1 grade 3-5 TEAE ^a	143 (61.1)	131 (55.5)
Anemia	15 (6.4)	15 (6.4)
Immune-mediated hepatitis	10 (4.3)	5 (2.1)
Immune-mediated enterocolitis	9 (3.8)	10 (4.2)
ALT increased	8 (3.4)	5 (2.1)
Colitis	8 (3.4)	12 (5.1)
General physical health deterioration	7 (3)	4 (1.7)
Lipase increased	7 (3)	6 (2.5)
Pyrexia	7 (3)	5 (2.1)
AST increased	6 (2.6)	5 (2.1)
Hepatitis	6 (2.6)	3 (1.3)
Anaphylactic reaction	5 (2.1)	0
Asthenia	5 (2.1)	6 (2.5)
Cholestasis	5 (2.1)	5 (2.1)
Hypokalemia	3 (1.3)	5 (2.1)
Diarrhea	2 (0.9)	10 (4.2)
Hypophysitis	2 (0.9)	7 (3)
Fatigue	2 (0.9)	5 (2.1)
Pulmonary embolism	1 (0.4)	5 (2.1)

NOTE. All percentages were based on the number of patients in the safety set within each group. Adverse events were coded using MedDRA dictionary version 23.0. A patient was counted once per each unique preferred term.

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

^aTEAEs were defined as adverse events occurring or worsening in severity on or after the date of the first dose of study treatment.

retrospective study (54%)¹⁴; and the 2-year survival rate (27.5%) was less than that reported in the ipilimumab arm of the phase III trial with TIL therapy versus ipilimumab monotherapy (44.1%).¹³ These survival rate variations could again be because more patients had a high LDH (51%) in our trial compared with 26% in SWOG S1616 and 17% in the phase III trial. Geographical variations and subsequent differences in therapeutic strategies, available drugs, and selection of patients could also play a role, as most of our patients were enrolled in Europe compared with the SWOG, which enrolled only US patients.

Minimizing systemic exposure to cancer treatments can improve tolerability and is an integral part of the rationale for developing IT treatments. In this study, grade 3–4 TEAEs were common in both arms but more frequent in the combination arm (61.1% and 55.1%, respectively), suggesting that adding tilsotolimod increases the toxicity burden. Findings in the combination arm were comparable with those observed in ILLUMINATE-204,¹¹ during which 48% of patients had grade ≥ 3 TEAEs. Serious anaphylactic reactions that occurred in four patients (2%) and led to treatment discontinuation were also new signals in this study that have not been observed. The rate of grade ≥ 3 TEAEs in the monotherapy arm is similar to the reported toxicity rate with ipilimumab monotherapy in the phase III trial comparing the tumor-infiltrating lymphocytes with ipilimumab (57%),¹³ whereas it is higher than that observed in SWOG S1616 (approximately 35%).¹²

Although this study did not demonstrate an additive or synergistic effect from combining IT tilsotolimod with ipilimumab, it is important to acknowledge certain study

limitations that may have affected the performance of the combination arm. One major limitation is the suboptimal dosing/injection of tilsotolimod; only 23.1% of patients completed the nine doses of IT injections, while 51.2% received less than the median number of required tilsotolimod injections and continued receiving ipilimumab alone. Also, major baseline parameters were different from those of the phase 1/2 ILLUMINATE-204; for example, only 24.2% had elevated LDH, and 43% had stage IV M1C VS compared with 52.9% and 61.8%, respectively, in the phase III trial, and finally, all patients enrolled were from the United States. Understanding the impact of variations in the disease's nature and its genomic and immunological heterogeneity will be essential to identify patients who can benefit from IT therapy. The open-label design of the study, chosen because of ethical concerns about injecting a placebo into deep lesions, may also introduce potential bias; however, this bias would likely favor the combination arm rather than the monotherapy arm. OS data were immature at the time of this analysis, although given the hierarchical testing plan, this is unlikely to affect the study results.

To our knowledge, the results of ILLUMINATE-301 represent the largest data set currently available describing the use of ipilimumab in patients with advanced melanoma refractory to anti-PD-1 therapy. Although the tilsotolimod plus ipilimumab treatment did not meet its coprimary end point, these results are a valuable addition to the literature with respect to second-line treatment options in this disease area. Future studies are warranted to explore the ideal IT injection approaches and the most effective and safe combination therapy.

AFFILIATIONS

¹The University of Texas MD Anderson Cancer Center, Houston, TX

²Melanoma Cancer Immunotherapy and Development Therapeutics Unit Istituto Nazionale Tumori IRCCS Fondazione "G. Pascale," Napoli, Italy

³Italy and Center for Immuno-Oncology, Azienda Ospedaliero Universitaria Senese, University of Siena, Siena, Italy

⁴Clinical Oncology Department, Assiut University, Assiut, Egypt

⁵Centre Léon Bérard Lyon, University Lyon I, Lyon, France

⁶Inserm U1189, CHU Lille, University of Lille, Lille, France

⁷Fakultni nemocnice Kralovské Vinohrady, Vinohrady, Czechia

⁸Centre Hospitalier Lyon Sud, Pierre-Bénite, France

⁹Všeobecná fakultní nemocnice v Praze, Nové Město, Czechia

¹⁰Clinical Oncology Department, Cancer Immunotherapy, Biomedicine Institute of Seville (IBIS)/CSIC, University Hospital Virgen Macarena and School of Medicine, University of Seville, Seville, Spain

¹¹INSERM-UGA U1209/CNRS UMR5309, CHU Grenoble Alpes, Université Grenoble Alpes, Grenoble, France

¹²Istituto Tumori Giovanni Paolo II, Bari, Italy

¹³AP-HP Dermato-Oncology and CIC, Cancer Institute APHP Nord Paris Cité, INSERM U976, Université Paris Cité, Saint Louis Hospital, Paris, France

¹⁴Aix-Marseille University, APHM, Marseille, France

¹⁵Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada

¹⁶Norris Comprehensive Cancer Center, USC Keck School of Medicine, Los Angeles, CA

¹⁷Universitätsmedizin der Johannes Gutenberg Mainz, Mainz, Germany

¹⁸Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada

¹⁹Gallipoli Medical Research Foundation, University of Queensland, Brisbane, Australia

²⁰Leiden University Medical Center, Leiden, the Netherlands

²¹Universitätsklinikum Regensburg, Regensburg, Germany

²²Idera Pharmaceuticals, Inc, Exton, PA

²³Virogin Biotech, Richmond, BC, Canada

²⁴Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola, Italy

²⁵Gustave Roussy and Paris Saclay University, Villejuif, France

CORRESPONDING AUTHOR

Adi Diab, MD; e-mail: adiab@mdanderson.org.

EQUAL CONTRIBUTION

A.D. and C.R. contributed equally to this work.

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AUTHOR CONTRIBUTIONS

Conception and design: Adi Diab, Paolo A. Ascierto, Srinivas Chunduru, Shahram Rahimian, Caroline Robert

Financial support: Adi Diab

Administrative support: Adi Diab, Marcus O. Butler

Provision of study materials or patients: Adi Diab, Sylvie Negrier, Laurent Mortier, Luis de la Cruz, Marie-Therese Leccia, Michele Guida, Celeste Lebbe, Marcus O. Butler, Carmen Loquai, Victoria Atkinson, Ellen Kapiteijn, Srinivas Chunduru

Collection and assembly of data: Adi Diab, Michele Maio, Reham Abdel-Wahab, Petr Arenberger, Stephane Dalle, Ivana Krajsova, Luis de la Cruz, Marie-Therese Leccia, Michele Guida, Celeste Lebbe, Jean-Jacques Grob, Marcus O. Butler, Gino K. In, Carmen Loquai, John W.T. Walker, Victoria Atkinson, Ellen Kapiteijn, Sebastian Haferkamp, Shahram Rahimian, Massimo Guidoboni, Caroline Robert

Data analysis and interpretation: Adi Diab, Paolo A. Ascierto, Michele Maio, Reham Abdel-Wahab, Sylvie Negrier, Laurent Mortier, Luis de la Cruz, Celeste Lebbe, Jean-Jacques Grob, Gino K. In, John W.T. Walker, Victoria Atkinson, Ellen Kapiteijn, Sebastian Haferkamp, Shahram Rahimian, Caroline Robert

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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Adi Diab

Honoraria: Pfizer, Regeneron, Teva, CytomX Therapeutics, CureVac, Idera (Inst), Nektar (Inst), Genesis Therapeutics, Lytix Biopharma (Inst), Cullinan Oncology (Inst), Memgen

Consulting or Advisory Role: Nektar, CureVac, Celgene, Idera, Memgen, Regeneron, CytomX Therapeutics, Pfizer (Inst)

Research Funding: Nektar (Inst), Idera (Inst), Celgene (Inst), Pfizer (Inst), Apexigen (Inst), Lytix Biopharma (Inst), Cullinan Oncology (Inst)

Paolo A. Ascierto

Consulting or Advisory Role: Bristol Myers Squibb, Roche/Genentech, Merck Sharp & Dohme, Novartis, Pierre Fabre, Sun Pharma, Sanofi, Sandoz, Immunocore, Italfarmaco, Boehringer Ingelheim, Regeneron, Pfizer, Nouscom, Lunaphore Technologies, Medicenna, Bio-AI Health, ValoTx, Replimune, Bayer, Erasca, Inc, Philogen, BioNTech SE, Anaveon, Genmab, Menarini Silicon Biosystems

Research Funding: Bristol Myers Squibb (Inst), Roche/Genentech (Inst), Sanofi (Inst), Pfizer (Inst)

Travel, Accommodations, Expenses: Replimune, MSD Oncology, Pierre Fabre, Philogen

Michele Maio

Stock and Other Ownership Interests: Theravance, Epigen Therapeutics

Honoraria: Bristol Myers Squibb, AstraZeneca, Roche, MSD, Merck, Amgen, Pierre Fabre, Alfasigma, Sanofi, Lilly

Consulting or Advisory Role: Bristol Myers Squibb, Roche, AstraZeneca, MSD, Merck, Pierre Fabre, Alfasigma

Patents, Royalties, Other Intellectual Property: DNA Hypomethylating Agents for Cancer Therapy

Travel, Accommodations, Expenses: Bristol Myers Squibb, AstraZeneca, Roche, MSD, Merck, Amgen, Pierre Fabre, Alfasigma

Sylvie Negrier

Honoraria: Pfizer, Ipsen, Bristol Myers Squibb, MSD Oncology, Eisai

Consulting or Advisory Role: Ipsen, MSD Oncology, Eisai

Research Funding: Pfizer (Inst), Ipsen (Inst), MSD (Inst)

Travel, Accommodations, Expenses: Pfizer, Bristol Myers Squibb, Ipsen, MSD

Laurent Mortier

Honoraria: BMS France, MSD Oncology, Novartis, Sun Pharma

Consulting or Advisory Role: BMS GmbH & Co KG, Sun Pharma, Novartis

Research Funding: MSD Oncology (Inst), Pierre Fabre (Inst)

Travel, Accommodations, Expenses: Roche/Genentech, Novartis, Bristol Myers Squibb

Petr Arenberger

Honoraria: AbbVie, Bristol Myers Squibb/Pfizer, Merck, Pierre Fabre, La Roche-Posay, Sanofi/Aventis, Novartis, Janssen

Consulting or Advisory Role: Sanofi/Aventis, AbbVie

Research Funding: Pfizer

Stephane Dalle

Employment: Sanofi Pasteur

Stock and Other Ownership Interests: Sanofi

Consulting or Advisory Role: Bristol Myers Squibb (Inst), MSD (Inst)

Speakers' Bureau: Bristol Myers Squibb (Inst), MSD (Inst)

Research Funding: Bristol Myers Squibb (Inst), Merck Sharp & Dohme (Inst), Roche (Inst), Pierre Fabre (Inst)

Patents, Royalties, Other Intellectual Property: TRIM24 Regulation Pending Patent (Inst)

Travel, Accommodations, Expenses: Bristol Myers Squibb, MSD

Luis de la Cruz

Consulting or Advisory Role: Roche (Inst), MSD Oncology, Bristol Myers Squibb, Gilead Sciences, AstraZeneca, Incyte

Research Funding: Roche (Inst), Celgene (Inst)

Travel, Accommodations, Expenses: Roche

Michele Guida

Consulting or Advisory Role: Merck Sharp & Dohme, Bristol Myers Squibb, Novartis, Pierre Fabre

Celeste Lebbe

Honoraria: Bristol Myers Squibb, Novartis, MSD, Pierre Fabre, Pfizer, Sanofi

Consulting or Advisory Role: Bristol Myers Squibb, MSD, Novartis, Amgen, Merck Serono, Sanofi, Pierre Fabre, Inflax

Speakers' Bureau: Bristol Myers Squibb, Novartis, MSD, Pierre Fabre, Sanofi

Research Funding: Roche (Inst), Bristol Myers Squibb (Inst)

Travel, Accommodations, Expenses: Bristol Myers Squibb, MSD, Novartis, Sanofi, Pierre Fabre, Roche

Other Relationship: InflaRx, Sanofi, BMS, MSD, Pierre Fabre, Novartis, Jazz Pharmaceuticals

Jean-Jacques Grob

Consulting or Advisory Role: BMS, MSD Oncology, Roche/Genentech, Novartis, Amgen, Pierre Fabre, Sun Pharma, Merck KGaA, Sanofi, Roche, Philogen, Ultimovacs

Speakers' Bureau: Novartis, Pierre Fabre

Travel, Accommodations, Expenses: BMS, MSD Oncology, Novartis, Pierre Fabre

Marcus O. Butler

Honoraria: Roche, Merck, Bristol Myers Squibb, Novartis, Sanofi, Medison, Pfizer

Consulting or Advisory Role: Merck, Bristol Myers Squibb, Novartis, Immunovaccine, Immunocore, Adaptimmune, EMD Serono, GlaxoSmithKline, Genzyme, Sanofi, LaRoche Posay, Sun Pharma, Instil

Bio, Iovance Biotherapeutics, Pfizer, Medison, IDEAYA Biosciences, Regeneron

Research Funding: Merck (Inst), Takara Bio (Inst), Novartis Canada Pharmaceuticals Inc (Inst)

Expert Testimony: Merck

Gino K. In

Honoraria: Array BioPharma/Pfizer, Regeneron, Bristol Myers Squibb, Sanofi, Pfizer

Consulting or Advisory Role: Bristol Myers Squibb, Castle Biosciences, Novartis, Sanofi, Pfizer, Replimune, Replimune

Speakers' Bureau: Merck, Rockpointe CME, Regeneron, Targeted Oncology

Research Funding: Regeneron (Inst), Xencor (Inst), Checkmate Pharmaceuticals (Inst), Replimune (Inst), Instil Bio (Inst), Idera (Inst), Iovance Biotherapeutics (Inst), Pfizer (Inst), Bicara Therapeutics (Inst), Obsidian Therapeutics (Inst), Merck (Inst), Immunocore (Inst)

Travel, Accommodations, Expenses: Regeneron, Bristol Myers Squibb/Pfizer, Pfizer

Carmen Loquai

Consulting or Advisory Role: Bristol Myers Squibb (Inst), MSD (Inst), Biontech (Inst), Novartis (Inst), Sanofi (Inst), Pierre Fabre (Inst), Almirall Hermal GmbH (Inst), Sun Pharma (Inst), Merck (Inst), Roche (Inst), Kyowa Kirin International (Inst)

Travel, Accommodations, Expenses: Bristol Myers Squibb (Inst), MSD (Inst), Biontech (Inst), Novartis (Inst), Sanofi (Inst), Pierre Fabre (Inst), Almirall Hermal GmbH (Inst), Sun Pharma (Inst), Merck (Inst), Roche (Inst), Kyowa Kirin International (Inst)

John W.T. Walker

Honoraria: Bristol Myers Squibb, Merck, Regeneron, Pfizer, Medison

Consulting or Advisory Role: Merck Serono, Bristol Myers Squibb

Speakers' Bureau: Medison, Regeneron

Research Funding: Merck Serono

Victoria Atkinson

Honoraria: Bristol Myers Squibb, Novartis, Merck Sharp & Dohme, Pierre Fabre, Nektar, QBiotech, Provectus Biopharmaceuticals

Consulting or Advisory Role: Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Merck Serono, QBiotech, Immunocore

Speakers' Bureau: Roche/Genentech, Bristol Myers Squibb, Novartis, Merck Sharp & Dohme, Merck Serono

Expert Testimony: Bristol Myers Squibb/Celgene

Travel, Accommodations, Expenses: Bristol Myers Squibb, OncoSec, Merck Sharp & Dohme, Pierre Fabre, Novartis

Ellen Kapiteijn

Consulting or Advisory Role: Bristol Myers Squibb (Inst), Lilly (Inst), Delcath Systems (Inst), Immunocore (Inst)

Research Funding: BMS (Inst), Pierre Fabre (Inst), Delcath Systems (Inst), Novartis (Inst)

Sebastian Haferkamp

Honoraria: Novartis, Bristol Myers Squibb, Amgen

Consulting or Advisory Role: Bristol Myers Squibb, Novartis, Pierre Fabre, MSD, Sun Pharma

Srinivas Chunduru

Employment: EveryONE Medicines

Massimo Guidoboni

Consulting or Advisory Role: Pierre Fabre

Speakers' Bureau: BMS, Pierre Fabre

Caroline Robert

Stock and Other Ownership Interests: RiboNexus

Honoraria: Pierre Fabre, Sanofi, Bristol Myers Squibb, MSD, Novartis, Merck, Roche, Pfizer, Sun Pharma, Ultimovacs, Regeneron, Egle, Philogen, MaaT Pharma, IO Biotech

Consulting or Advisory Role: Bristol Myers Squibb, Roche, Novartis, Pierre Fabre, MSD, Sanofi, Pfizer, Sun Pharma, Merck, Ultimovacs, Regeneron, Egle, Philogen, MaaT Pharma

Travel, Accommodations, Expenses: Pierre Fabre

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APPENDIX

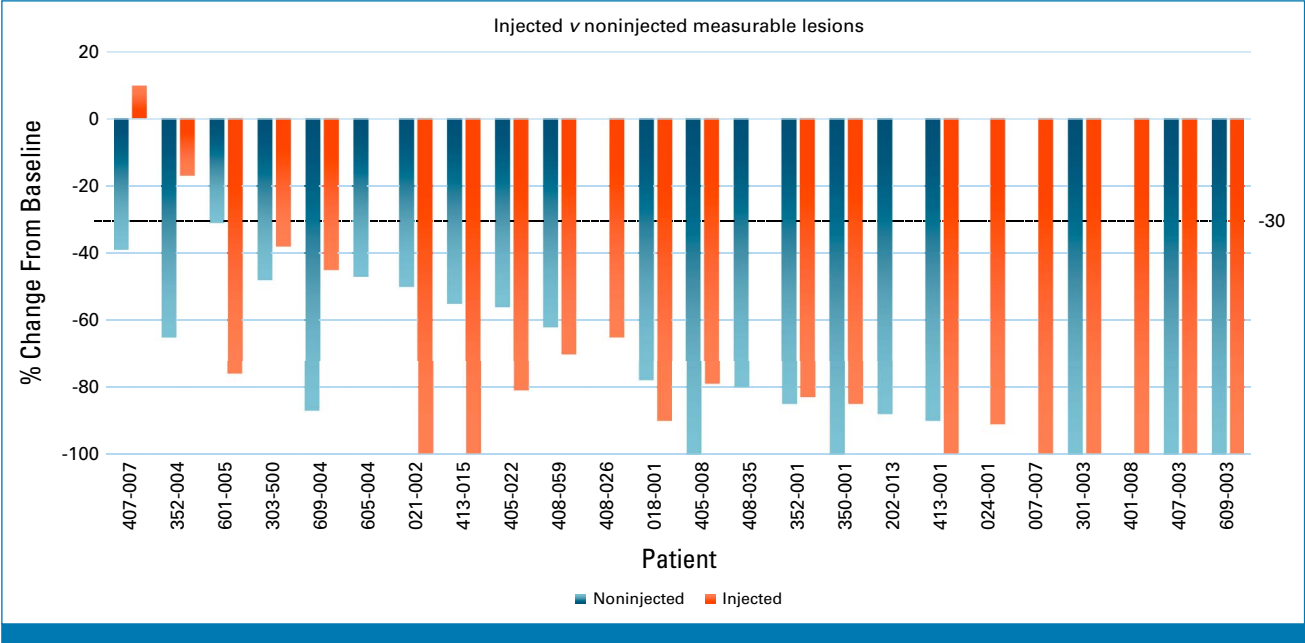


FIG A1. Tilsotolimod in combination with ipilimumab arm: Investigator assessed ORR. ORR, objective response rate.

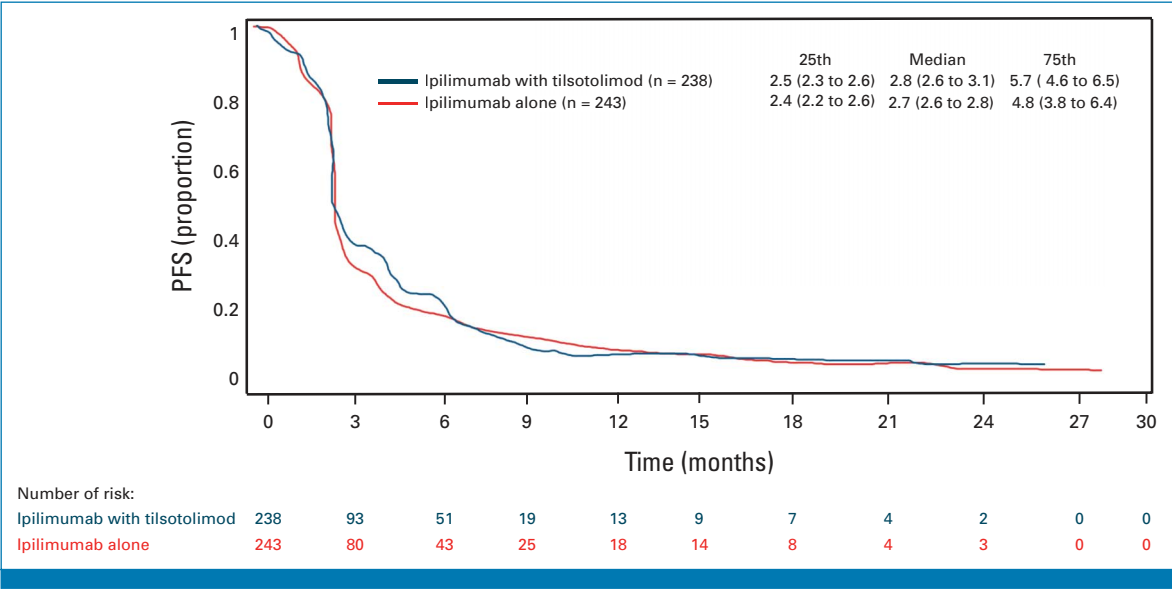


FIG A2. Kaplan-Meier estimates of PFS by investigator assessment. PFS, progression-free survival.

TABLE A1. Tilsotolimod Plus Ipilimumab Exposure

Injection/Infusion	Ipilimumab With Tilsotolimod (n = 234)	Ipilimumab Alone (n = 236)
Tilsotolimod injections		
1 injection	7 (3)	
2 injections	16 (6.8)	
3 injections	20 (8.5)	
4 injections	42 (17.9)	
5 injections	35 (15)	
6 injections	37 (15.8)	
7 injections	14 (6)	
8 injections	9 (3.8)	
9 injections	54 (23.1)	
Mean (standard deviation)	5.6 (2.38)	
Ipilimumab infusion		
0 infusion	6 (2.6)	0
1 infusion	36 (15.4)	22 (9.3)
2 infusions	49 (20.9)	59 (25)
3 infusions	43 (18.4)	39 (16.5)
4 infusions	100 (42.7)	116 (49.2)
Mean (standard deviation)	2.8 (1.21)	3.1 (1.06)

NOTE. Data are No. (%) unless otherwise specified.

TABLE A2. Investigator-Assessed Responses (intention-to-treat analysis)

Response	Tilsotolimod Plus Ipilimumab (n = 238)	Ipilimumab (n = 243)
Best overall response		
CR	2 (0.8)	2 (0.8)
PR	22 (9.2)	24 (9.9)
SD	54 (22.7)	37 (15.2)
PD	105 (44.1)	120 (49.4)
Unevaluable	55 (23.1)	60 (24.7)
ORR (CR/PR)	24 (10.1)	26 (10.7)
Rate difference (95% CI)	−0.6 (−6.1 to 4.8) [<i>P</i> = .8]	
DCR (CR/PR/SD)	78 (32.8)	63 (25.9)
Median (range) time to response, months	2.7 (2.3-4.4)	2.7 (1.6-8.2)
Median (95% CI) DoR, months	9.2 (5.6 to NE)	14.5 (7.4 to NE)

NOTE. All presenting data are No. (%) unless otherwise specified.

Abbreviations: CR, complete response; DCR, disease control rate; DoR, duration of response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

TABLE A3. Most Common TEAEs (>5% of patients in either treatment group; safety set)

System Organ Class Preferred Term	Ipilimumab With Tilsotolimod (n = 234), No. (%)	Ipilimumab Alone (n = 236), No. (%)
Patients reporting at least 1 TEAE ^a	231 (98.7)	225 (95.3)
General disorders and administration site conditions	197 (84.2)	124 (52.5)
Pyrexia	108 (46.2)	34 (14.4)
Asthenia	81 (34.6)	55 (23.3)
Chills	75 (32.1)	7 (3)
Fatigue	48 (20.5)	36 (15.3)
Influenza-like illness	31 (13.2)	6 (2.5)
Injection site pain	22 (9.4)	0
GI disorders	147 (62.8)	141 (59.7)
Diarrhea	71 (30.3)	66 (28)
Nausea	55 (23.5)	48 (20.3)
Vomiting	36 (15.4)	32 (13.6)
Abdominal pain	21 (9)	15 (6.4)
Constipation	21 (9)	23 (9.7)
Colitis	14 (6)	19 (8.1)
Immune-mediated enterocolitis	14 (6)	12 (5.1)
Dry mouth	13 (5.6)	13 (5.5)
Abdominal pain upper	8 (3.4)	16 (6.8)
Skin and subcutaneous tissue disorders	105 (44.9)	107 (45.3)
Pruritus	57 (24.4)	60 (25.4)
Rash	22 (9.4)	22 (9.3)
Vitiligo	15 (6.4)	3 (1.3)
Erythema	12 (5.1)	5 (2.1)
Investigations	90 (38.5)	69 (29.2)
AST increase	32 (13.7)	18 (7.6)
ALT increased	31 (13.2)	18 (7.6)
Weight decreased	25 (10.7)	12 (5.1)
Blood alkaline phosphatase increased	16 (6.8)	8 (3.4)
Gamma-glutamyltransferase increased	16 (6.8)	3 (1.3)
Metabolism and nutrition disorders	87 (37.2)	78 (33.1)
Decreased appetite	46 (19.7)	42 (17.8)
Hypokalemia	18 (7.7)	15 (6.4)
Hyponatremia	14 (6)	8 (3.4)
Nervous system disorders	74 (31.6)	42 (17.8)
Headache	43 (18.4)	15 (6.4)
Musculoskeletal and connective tissue disorders	70 (29.9)	63 (26.7)
Arthralgia	18 (7.7)	18 (7.6)
Back pain	13 (5.6)	18 (7.6)
Pain in extremity	12 (5.1)	12 (5.1)
Blood and lymphatic system disorders	67 (28.6)	51 (21.6)
Anemia	37 (15.8)	33 (14)
Respiratory, thoracic, and mediastinal disorders	54 (23.1)	49 (20.8)
Cough	19 (8.1)	14 (5.9)
Dyspnea	18 (7.7)	12 (5.1)

(continued on following page)

TABLE A3. Most Common TEAEs (>5% of patients in either treatment group; safety set) (continued)

System Organ Class Preferred Term	Ipilimumab With Tilsotolimod (n = 234), No. (%)	Ipilimumab Alone (n = 236), No. (%)
Hepatobiliary disorders	42 (17.9)	29 (12.3)
Hepatocellular injury	14 (6)	9 (3.8)
Cholestasis	13 (5.6)	7 (3)
Vascular disorders	32 (13.7)	19 (8.1)
Hypotension	14 (6)	0
Psychiatric disorders	26 (11.1)	29 (12.3)
Insomnia	11 (4.7)	14 (5.9)

NOTE. All percentages were based on the number of patients in the safety set within each group. AEs were coded using MedDRA dictionary version 23.0. A patient was counted once per each unique system organ class and unique preferred term.

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

^aTreatment-emergent AEs were defined as AEs occurring or worsening in severity on or after the date of the first dose of study treatment.

TABLE A4. Incidence of SAE (safety analysis)

Preferred Term	Ipilimumab With Tilsotolimod (n = 234), No. (%)	Ipilimumab Alone (n = 236), No. (%)
Patients reporting at least 1 SAE	116 (49.6)	108 (45.8)
Pyrexia	12 (5.1)	8 (3.4)
Immune-mediated enterocolitis	11 (4.7)	11 (4.7)
Colitis	10 (4.3)	13 (5.5)
General physical health deterioration	6 (2.6)	5 (2.1)
Immune-mediated hepatitis	6 (2.6)	5 (2.1)
Pneumonitis	5 (2.1)	2 (0.8)
Diarrhea	3 (1.3)	9 (3.8)
Hypophysitis	3 (1.3)	6 (2.5)
Erysipelas	2 (0.9)	5 (2.1)
Pulmonary embolism	0	5 (2.1)

Abbreviation: SAE, serious adverse event.