Phase IIIb safety results from an expanded-access protocol of talimogene laherparepvec for patients with unresected, stage IIIB–IVM1c melanoma

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Talimogene laherparepvec is a genetically modified herpes simplex virus-1-based oncolytic immunotherapy for the local treatment of unresectable cutaneous, subcutaneous, and nodal tumors in patients with melanoma recurrence following surgery. We aim to describe the safety of talimogene laherparepvec. Intralesional talimogene laherparepvec was administered at less than or equal to 4 ml × 10^6 PFU/ml at protocol day 1, then less than or equal to 4 ml × 10^8 PFU/ml 21 days later, and then every 14 days. Treatment continued until complete response, absence of injectable tumors, progressive disease, intolerance, or US Food and Drug Administration approval. Adverse events were graded during and 30 days after the end of treatment. Lesions suspected to have herpetic origin were tested for talimogene laherparepvec DNA by quantitative PCR (qPCR). Between September 2014 and October 2015, 41 patients were enrolled with stage IIIB (22%), IIIC (37%), IVM1a (34%), IVM1b (5%), and IVM1c (2%) melanoma. The median age was 72 (range: 32–96) years and 54% of the patients were men. Patients had an ECOG performance status of 0 (68%) or 1 (32%). The median treatment duration was 13.1 (3.0–41.1) weeks. Treatment-related adverse events of greater than or equal to grade 3 were reported in three (7.3%) patients and included vomiting, upper abdominal pain, chills, hyperhidrosis, nausea, pyrexia, and wound infection. Suspected herpetic lesions were swabbed in five (12%) patients. One of the five tested positive for talimogene laherparepvec DNA by qPCR, but this lesion had been injected previously with talimogene laherparepvec. During the study, five patients completed treatment because of complete response per investigators. In the clinical practice setting, talimogene laherparepvec has a safety profile comparable to that observed in previous clinical trials. Talimogene laherparepvec (IMLYGIC) is now approved in the US, European Union, and Australia. *Melanoma Res* **28:44–51**

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Introduction

Cutaneous melanoma is the fifth most common cancer in adult men and the seventh most common in adult women in the USA [1,2], and its incidence is increasing rapidly worldwide [3,4]. Patients with advanced melanoma have a very poor prognosis because the advanced disease often does not respond to older therapies and immunotherapeutic approaches. Historically, for those patients who have developed multiple metastases, the 5-year survival is 59% for stage IIIB and 40% for stage IIIC, and the 1-year survival is 62% for stage IVM1a, 53% for stage IVM1b, and 33% for stage IVM1c [5,6]. Previous therapies offered little survival benefit for most patients with metastatic melanoma; treatments such as dacarbazine, temozolomide [7,8], and interleukin-2 [9,10] usually offer at best limited, short-lived responses. The introduction of new therapies may improve the survival rates for patients with advanced melanoma.

Newly developed immunotherapies have been proven to be effective treatments as both monotherapy and

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combination therapy for patients with advanced melanoma. Since 2011, seven novel therapies have been approved by the Food and Drug Administration (FDA). Many target the serine/threonine protein kinase B-raf (BRAF)/mitogen-activated protein kinase kinase (MEK) pathway, and are limited to use in patients with mutations in the *BRAF* gene. Ipilimumab, a cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitor, leads to a 3-year survival of 22% in patients with advanced melanoma [11,12]. Two new immunotherapies target the programmed cell death 1 (PD-1) pathway: pembrolizumab and nivolumab. The recent application of PD-1 inhibitors in the treatment of melanoma has resulted in relatively long-term objective responses, particularly in advanced melanoma [13–15]. Most recently, long-term survival was reported in patients with advanced melanoma treated with the anti-PD-1 agent pembrolizumab [16]. Among patients with ipilimumab-naive advanced melanoma who received pembrolizumab in a phase 3 study (KEYNOTE-006), the 2-year overall survival (OS) rate was 55% [16]. In addition, whereas combination therapy with ipilimumab and nivolumab has yielded very high response rates, and 1- and 2-year survival rates were 79 and 65%, respectively [17], severe immune-related toxicity is an impediment to its use for all patients; thus, the need remains for additional treatment options for patients with advanced melanoma.

Talimogene laherparepvec, a first-in-class oncolytic immunotherapy, is designed to selectively replicate in tumors, first by direct infection through lysis of tumor cells, resulting in cell death, followed by the promotion of an antitumor immune response characterized by antigen release, and the production of granulocyte-macrophage colony-stimulating factor (GM-CSF), which can stimulate antigen-presenting cells to enhance the systemic antitumor immune response [18–20]. In the randomized phase III trial OPTiM, treatment with intralesional talimogene laherparepvec was compared with subcutaneous GM-CSF in 436 patients with unresectable stages IIIB/C and IV melanoma. In the primary analysis, talimogene laherparepvec significantly improved the durable response rate (rate of complete or partial response lasting continuously for $\geq$6 months) from 2.1 to 16.3% ($P < 0.0001$) versus GM-CSF [21]. The median OS was 23.3 months with talimogene laherparepvec versus 18.9 months with GM-CSF (hazard ratio: 0.79, 95% confidence interval: 0.62–1.00, $P = 0.051$) [21]. In an exploratory subgroup analysis, the treatment effect of talimogene laherparepvec was most pronounced among patients with stages IIIB, IIIC, and IVM1a melanoma, with a durable response rate of 25% (vs. 1%) and OS 41.1 months (vs. 21.5 months with GM-CSF; hazard ratio 0.57, 95% confidence interval: 0.40–0.80, $P < 0.001$) [21]. The most common adverse events (AEs) in OPTiM patients receiving talimogene laherparepvec were fatigue (50%), chills (49%), pyrexia (43%), nausea (36%), influenza-like illness (31%), and injection-site pain (28%). Additional evidence from OPTiM shows the potential systemic effect of talimogene laherparepvec in that 34% of uninjected nonvisceral lesions and 15% of uninjected visceral lesions reduced in size by at least 50%, thereby supporting the evidence of the systemic response observed in phase II [22,23] and in animal models [20].

On the basis of data from a phase IIIb, single-arm, expanded-access protocol (EAP) of talimogene laherparepvec, we aim to describe the use of talimogene laherparepvec in this study population from a safety perspective, including treatment-emergent and serious AEs. Furthermore, we will document the incidence of talimogene laherparepvec DNA detection in suspected herpetic lesions. Finally, we will discuss the responses to talimogene laherparepvec that were reported during the study.

Patients and methods

Patients

Patients who were eligible for or had access to ongoing talimogene laherparepvec clinical trials were not included in the study. Patients were included if they had stage IIIB–IVM1c histologically confirmed melanoma not suitable to resection; injectable cutaneous, subcutaneous, or nodal disease (at least one injectable lesion $\geq$10 mm longest diameter or multiple lesions with a longest diameter in aggregate $\geq$10 mm for patients who had not been treated previously with talimogene laherparepvec, at least one injectable lesion with no minimal size criteria for patients treated previously with talimogene laherpaprevec); and adequate organ function. Enrollment criteria were similar to those used for the OPTiM study; however, in this study, patients with Eastern Cooperative Oncology Group performance status 0, 1, or 2 were eligible. Additional criteria included stage IIIB–IVM1c histologically confirmed melanoma not suitable to resection; injectable cutaneous, subcutaneous, or nodal disease; and adequate organ function. Key exclusion criteria included clinically active central nervous system (CNS) metastases, primary uveal or mucosal melanoma, a history of symptomatic autoimmune disease, clinically significant immunosuppression, active herpetic lesions, treatment with systemic antiherpetic agents, or infection with HIV, hepatitis B virus, or hepatitis C virus. Patients were required to read and sign an informed consent form.

Trial design and treatment scheme

This phase IIIb open-label study was carried out at 15 centers in the USA. The primary endpoint was to provide access to talimogene laherparepvec until FDA approval. The secondary endpoints included safety by assessment of AEs and incidence of positive quantitative PCR (qPCR) for talimogene laherparepvec DNA detection. Talimogene laherparepvec was injected intralesionally into cutaneous, subcutaneous, and nodal tumors at up to $4\,ml \times 10^6$ PFU/ml on day 1, then up to $4\,ml \times 10^8$ PFU/ml 21 days later, and every 14 days

thereafter. Safety follow-up was completed 30 (+7) days after the last dose of talimogene laherparepvec. Treatment of visceral metastases was not allowed. Treatment continued until complete response, no remaining injectable tumors, disease progression beyond 6 months, intolerance, or US FDA approval.

Assessments

Vital signs, hematology, and chemistry were assessed at screening, at the 30-day safety follow-up, and at cycle 1, cycle 2, and every second cycle thereafter. AEs were assessed by Common Terminology Criteria for Adverse Events, version 3, from screening through to safety follow-up. Suspected herpetic lesions on patients as well as close contacts and caregivers were swabbed within 3 days of occurrence from screening to the 30-day safety follow-up. Suspected herpetic lesions in close contacts and caregivers could not necessarily be linked to treatment of any one patient or to a specific treatment date; therefore, intent to swab such lesions did not end after a specific safety follow-up appointment.

As efficacy was not an endpoint of the study, responses were not defined in the protocol. However, investigators noted the reason for completing and/or discontinuing the treatment with talimogene laherparepvec. Therefore, some instances of complete response and disease progression were captured during the study. These responses were based on investigator assessment.

Concomitant therapy

Any concomitant medications or treatments deemed necessary for supportive care could be administered, with the exception of other antitumor or experimental agents and antiherpetic drugs. All prescription and nonprescription medications administered from screening to 30 days after the last dose were recorded.

Statistical analysis

Patient characteristics and the statistical reporting of the safety endpoints and patient incidence of detectable talimogene laherparepvec DNA were analyzed using descriptive statistics, with no formal statistical hypothesis testing performed. The study sample size was based on patient recruitment between study protocol initiation and regulatory approval of talimogene laherparepvec. Analyses were carried out using SAS software (version 9.2; SAS Institute, Cary, North Carolina, USA).

Results

The demographics and baseline disease characteristics of patients treated with talimogene laherparepvec under the EAP are shown in Table 1. All 41 patients enrolled between September 2014 and October 2015 received talimogene laherparepvec, and 26 (63.4%) patients completed treatment with the investigational product (either completed because of complete response or remained on treatment until FDA approval). Of these 26 patients, five completed treatment because of complete response and 21 came off study once talimogene laherparepvec became available outside of the clinical trial setting following FDA approval. Of the 15 (36.6%) patients who discontinued treatment, nine discontinued because of disease progression, three because of requirement of alternative therapy, two because of AEs (one patient developed flu-like symptoms, the other experienced chest pain, dyspnea, and a fractured hip), and one related to therapeutic surgery (talimogene laherparepvec was withheld because of a necrotic melanoma lesion; following a subsequent surgery consultation, the patient underwent a successful complete lymphadenectomy).

Table 1 Baseline demographic and clinical characteristics of patients

	Talimogene laherparepvec ($N=41$) [n (%)]
Age [median (range)] years	72 (32–96)
<65	16 (39.0)
≥65	25 (61.0)
Sex	
Male	22 (53.7)
Female	19 (46.3)
Disease substage	
IIIB	9 (22.0)
IIIC	15 (36.6)
IVM1a	14 (34.1)
IVM1b	2 (4.9)
IVM1c	1 (2.4)
Line of therapy	
First	21 (51.2)
Second or later	20 (48.8)
ECOG performance status	
0	28 (68.3)
1	13 (31.7)
2	0 (0)
LDH	
≤ULN	32 (78.0)
>ULN	9 (22.0)
HSV serostatus	
Positive	24 (58.5)
Negative	14 (34.1)
Unknown	3 (7.3)

ECOG, Eastern Cooperative Oncology Group; HSV, herpes simplex virus; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Safety

Any adverse events and treatment-related adverse events

Any AEs as well as treatment-related AEs of any grade or greater than or equal to grade 3 reported during treatment with talimogene laherparepvec are shown in Tables 2 and 3, respectively. AEs were reported in 38 (93%) patients. Any AEs reported in at least 25% of patients included pyrexia (63%), chills (56%), fatigue (54%), influenza-like illness (27%), and myalgia (27%). Any AEs of greater than or equal to grade 3 were reported in 10 (24%) patients, and included vomiting (in two patients), pyrexia, chills, nausea, hyperhidrosis, diarrhea, upper abdominal pain, bradycardia, femur fracture, hip fracture, hypercalcemia, hyperkalemia, incision site infection, metastases to CNS, pneumonia, and wound

Table 2 Adverse events[a]

	Talimogene laherparepvec ($N=41$) [n (%)]	
	Any grade AEs	Grade ≥ 3 AEs
Number of patients reporting AEs	38 (92.7)	10 (24.4)
Pyrexia	26 (63.4)	1 (2.4)
Chills	23 (56.1)	1 (2.4)
Fatigue	22 (53.7)	0 (0)
Influenza-like illness	11 (26.8)	0 (0)
Myalgia	11 (26.8)	0 (0)
Nausea	10 (24.4)	1 (2.4)
Headache	9 (22.0)	0 (0)
Injection-site pain	8 (19.5)	0 (0)
Pain	7 (17.1)	0 (0)
Rash	7 (17.1)	0 (0)
Vomiting	6 (14.6)	2 (4.9)
Peripheral edema	5 (12.2)	0 (0)
Anxiety	4 (9.8)	0 (0)
Asthenia	4 (9.8)	0 (0)
Hyperhidrosis	4 (9.8)	1 (2.4)
Pruritus	4 (9.8)	0 (0)
Arthralgia	3 (7.3)	0 (0)
Back pain	3 (7.3)	0 (0)
Decreased appetite	3 (7.3)	0 (0)
Diarrhea	3 (7.3)	1 (2.4)
Pain in extremity	3 (7.3)	0 (0)
Hyperkalemia	2 (4.9)	1 (2.4)
Incision site infection	2 (4.9)	1 (2.4)
Wound infection	2 (4.9)	1 (2.4)
Upper abdominal pain	1 (2.4)	1 (2.4)
Bradycardia	1 (2.4)	1 (2.4)
Femur fracture	1 (2.4)	1 (2.4)
Hip fracture	1 (2.4)	1 (2.4)
Hypercalcemia	1 (2.4)	1 (2.4)
Metastases to the central nervous system	1 (2.4)	1 (2.4)
Pneumonia	1 (2.4)	1 (2.4)

AE, adverse event.
[a]AEs are included if they occurred in > 2 patients (first column) or any with grade ≥ 3 (second column).

Table 3 Treatment-related adverse events[a]

	Talimogene laherparepvec ($N=41$) [n (%)]	
	TRAEs in > 1 patient	Grade ≥ 3 TRAEs
Number of patients reporting TRAEs	37 (90.2)	3 (7.3)
Pyrexia	25 (61.0)	1 (2.4)
Chills	23 (56.1)	1 (2.4)
Fatigue	19 (46.3)	0 (0)
Influenza-like illness	11 (26.8)	0 (0)
Myalgia	10 (24.4)	0 (0)
Nausea	9 (22.0)	1 (2.4)
Headache	8 (19.5)	0 (0)
Injection-site pain	8 (19.5)	0 (0)
Pain	7 (17.1)	0 (0)
Vomiting	6 (14.6)	2 (4.9)
Hyperhidrosis	4 (9.8)	1 (2.4)
Pruritus	4 (9.8)	0 (0)
Decreased appetite	3 (7.3)	0 (0)
Asthenia	3 (7.3)	0 (0)
Rash	3 (7.3)	0 (0)
Peripheral edema	2 (4.9)	0 (0)
Arthralgia	2 (4.9)	0 (0)
Pain in extremity	2 (4.9)	0 (0)
Dizziness	2 (4.9)	0 (0)
Dyspnea	2 (4.9)	0 (0)
Erythema	2 (4.9)	0 (0)
Feeling cold	2 (4.9)	0 (0)
Hypersensitivity	2 (4.9)	0 (0)
Muscle spasms	2 (4.9)	0 (0)
Musculoskeletal pain	2 (4.9)	0 (0)
Night sweats	2 (4.9)	0 (0)
Vision blurred	2 (4.9)	0 (0)
Body temperature increased	2 (4.9)	0 (0)
Upper abdominal pain	1 (2.4)	1 (2.4)
Wound infection	1 (2.4)	1 (2.4)

AE, adverse event; TRAE, treatment-related adverse event.
[a]AEs are included if they occurred in > 1 patient (first column) or any with grade ≥ 3 (second column).

infection (each in one patient). Serious AEs were reported in seven (17%) patients, and included nausea, vomiting (each in two patients), pyrexia, chills, hyperhidrosis, upper abdominal pain, bradycardia, femur fracture, hip fracture, metastases to CNS, pneumonia, and wound infection (each in one patient). Treatment-related AEs were reported in 37 (90%) patients; those reported in more than 10% of patients included pyrexia (61%), chills (56%), fatigue (46%), influenza-like illness (27%), myalgia (24%), nausea (22%), headache (20%), injection-site pain (20%), pain (17%), and vomiting (15%). Treatment-related AEs of greater than or equal to grade 3 were reported in three (7%) patients, and included vomiting, pyrexia, chills, nausea, hyperhidrosis, upper abdominal pain, and wound infection. Treatment-related serious AEs were reported in three (7%) patients, and included nausea, vomiting (each in two patients), upper abdominal pain, chills, hyperhidrosis, pyrexia, and wound infection (each in one patient).

Talimogene laherparepvec DNA in suspected herpetic lesions

Lesions that were oozing or suspected to be of herpetic origin were swabbed and tested for talimogene laherparepvec DNA upon identification and at each subsequent treatment visit during which such lesions were still present. Five (12.2%) patients had lesions that were swabbed. One of the five tested positive for talimogene laherparepvec DNA by qPCR. This lesion was swabbed 9 days after the first talimogene laherparepvec injection, during cycle 1. It was confirmed that this lesion had been injected previously with talimogene laherparepvec and so would not be considered a suspected herpetic lesion. It was tested because it was oozing and was reported as nonserious grade 2 wound necrosis lasting 15 days (resolved on day 24 after injection), which was treated presumptively with antibiotics.

Previous anticancer therapies for current malignancy of melanoma

Of the total of 41 patients in the EAP study, 21 (51.2%) received talimogene laherparepvec as the first treatment of their recurrent melanoma and 20 (48.8%) received it as second-line-or-later treatment for their recurrence(s). In patients treated with talimogene laherparepvec as second line or later, previous therapies included immunotherapy and chemotherapy in 18 (43.9%)

and seven (17.1%) patients, respectively. The most common immunotherapies were ipilimumab (36.6%), interferon (12.2%), and pembrolizumab (12.2%). A further breakdown of specific previous therapies is shown in Table 4.

Table 4 Previous anticancer therapies for current malignancy of melanoma

	Talimogene laherparepvec ($N=41$) [n (%)]
Total patients reporting previous anticancer therapy	20 (48.8)
Immunotherapy	18 (43.9)
Ipilimumab	15 (36.6)
Interferon	5 (12.2)
Pembrolizumab	5 (12.2)
Interleukin-2	2 (4.9)
Nivolumab	2 (4.9)
Avelumab	1 (2.4)
Sargramostim	1 (2.4)
Chemotherapy	7 (17.1)
Dabrafenib	2 (4.9)
Trametinib	2 (4.9)
Vemurafenib	2 (4.9)
Adriamycin/ifosfamide	1 (2.4)
Carboplatin	1 (2.4)
Cisplatin	1 (2.4)
Dacarbazine	1 (2.4)
Sorafenib	1 (2.4)
Paclitaxel	1 (2.4)
Melphalan	1 (2.4)
Vinblastine	1 (2.4)
Other	1 (2.4)
Isolated limb perfusion	1 (2.4)

The subcategories within each category of previous anticancer therapy are not mutually exclusive. Patients are only included once within each subcategory.

Concomitant medication use

Documentation of concomitant medications began with the initiation of treatment and continued through 30 days after the last administration of talimogene laherparepvec. The most commonly used concomitant medications were acetaminophen, diphenhydramine, and ondansetron; most use occurred in the first three treatment cycles. The usage of these concomitant medications (acetaminophen, diphenhydramine, and ondansetron) by cycle of therapy is shown in Fig. 1.

Duration of exposure

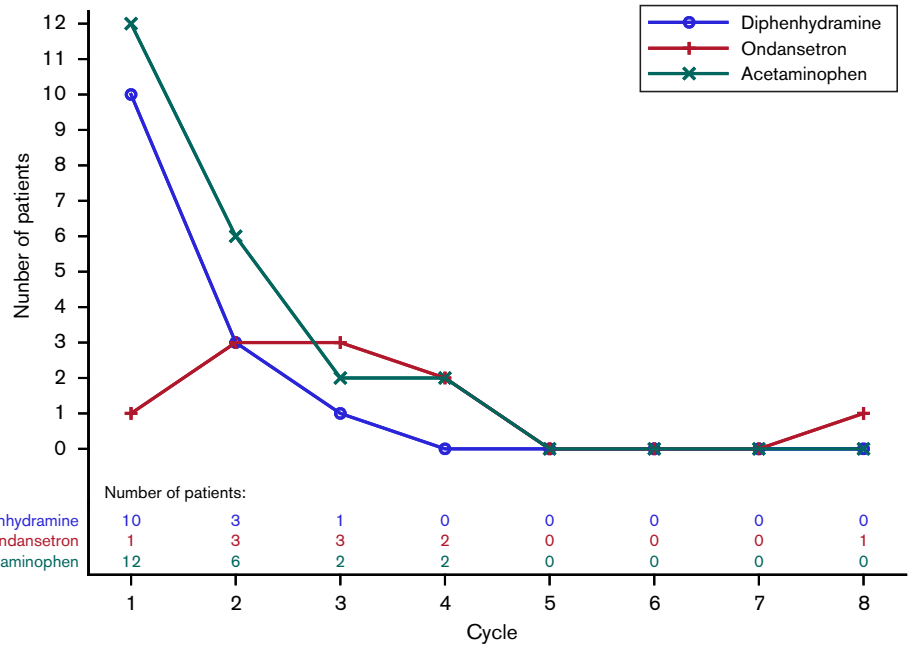
The exposure and swimmer plots for duration of exposure to treatment are shown in Fig. 2a and b. The median duration of treatment was 13.1 (range: 3.0–41.1) weeks.

Following FDA approval of talimogene laherparepvec on 27 October 2015, 21 patients came off the investigational product. As the study did not include follow-up after the completion of treatment with the investigational product, data on patients who continued treatment on the commercial product following FDA approval were beyond the scope of the protocol. Some patients were noted to continue on talimogene laherparepvec after approval, but this could not be confirmed for all 21 patients.

Treatment completion and discontinuation

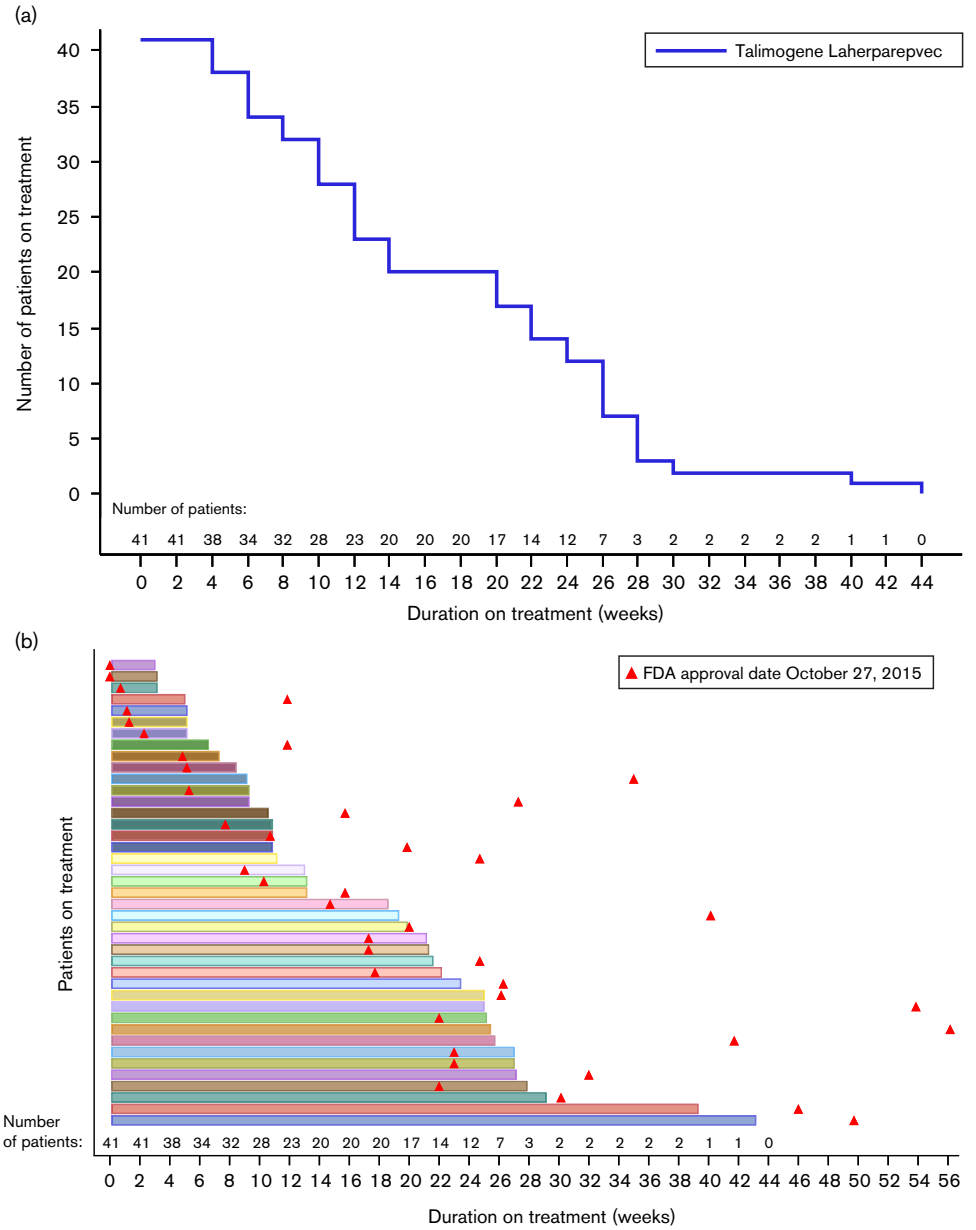
Although efficacy was beyond the scope of the protocol, limited information on complete response and progressive disease was collected for some patients per investigator assessment. Twenty-six of 41 (63.4%) patients completed treatment (either completed because of complete response

Fig. 1



Usage of concomitant medications acetaminophen, diphenhydramine, and ondansetron by cycle of therapy.

Fig. 2



(a) Exposure plot for duration of exposure to treatment; (b) swimmer plot for the duration of treatment.

or remained on treatment until FDA approval). Of 41 patients, five (12.2%) were reported to have completed treatment during the study because of complete response and 21 patients completed treatment following the approval of talimogene laherparepvec. Of the five with a reported complete response, three had received previous anticancer therapy for melanoma including pegylated interferon-α-2b, ipilimumab, and isolated limb perfusion ($n = 1$ each). Of the 15 (36.6%) patients who discontinued treatment during the study, nine (22.0%) were reported to have discontinued because of progressive disease, three (7.3%) because of requirement for alternative therapy, two (4.9%) because of AEs, and one (2.4%) related to therapeutic surgery.

Discussion

In patients with stages IIIB–IVM1c melanoma treated with intralesional talimogene laherparepvec under the EAP, the safety findings were consistent with the known safety profile of talimogene laherparepvec from published clinical trials. Influenza-like symptoms were the most commonly reported AEs. Reported AEs were

generally nonserious and mild or moderate. There were no additional safety signals compared with previously reported studies. Suspected herpetic lesions were reported in 12.2% of patients, and no uninjected lesions tested positive for talimogene laherparepvec DNA by qPCR.

AEs reported in patients treated with talimogene laherparepvec through the EAP were similar to those observed in OPTiM [21]. Pyrexia, chills, and fatigue were the most common AEs in the EAP, and they were also the most common AEs observed in the talimogene laherparepvec arm for the OPTiM trial. Greater than or equal to grade 3 AEs occurred in 36% of patients treated with talimogene laherparepvec in OPTiM and 24% of patients in the EAP. Fewer patients in the EAP reported diarrhea (7.3%) and arthralgia (7.3%) compared with OPTiM (18.8 and 17.1%, respectively). In the EAP, two (5%) patients had cellulitis of any grade, whereas 17 (6%) patients had cellulitis in OPTiM; in the EAP, no patients were reported to have greater than or equal to grade 3 cellulitis, whereas six (2.1%) patients had cellulitis in OPTiM. However, the small size of the EAP compared with the OPTiM trial could explain any difference in toxicity. In the EAP, 92.7% of patients (compared with 55% in OPTiM) had stage IIIB–IVM1a disease and 7.3% of patients (compared with 45% in OPTiM) had stage IVM1b/c disease.

In addition to the limited size, there are other limitations associated with these data. The study endpoints were limited to the safety profile. Five (12.2%) patients completed treatment because of complete response during the study, per investigators. In this small population, the reasons for completing treatment with talimogene laherparepvec were generally consistent with previously published results. As complete and partial responses were not defined in the EAP, clinical benefit data were determined by investigators and were not included in the study protocol. In addition, because many patients in the EAP presumably transitioned to commercially available talimogene laherparepvec at the time of US FDA approval, the duration of exposure as well as the incidence of AEs may be underestimated in the EAP compared with previous studies.

An observational study is currently ongoing in the USA, which will provide additional data on the patient characteristics and safety of talimogene laherparepvec in the postapproval setting. A registry study to evaluate the survival and long-term safety of patients with melanoma who have previously received talimogene laherparepvec is ongoing (ClinicalTrials.gov identifier: NCT02173171).

Conclusion

In the clinical practice setting, talimogene laherparepvec had a safety profile comparable to that observed in previously reported clinical trials, and there were no new safety signals in this expanded-access study. Talimogene laherparepvec is a treatment option for selected patients with melanoma recurrent after intitial surgery, both after previous chemotherapies and/or immunotherapies as well as in those who are treatment-naive. Talimogene laherparepvec (IMLYGIC) is now approved in the USA, European Union, and Australia.

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Conflicts of interest

Jason Chesney – consultant/advisor to Amgen Inc.; institution research funding from Amgen Inc.; Sanjay Awasthi – research support from Amgen Inc.; Russell Brown – research support from Amgen Inc.; John Nemunaitis – employed by Mary Crowley Cancer Research, consultant for AstraZeneca, speakers bureau for Amgen Inc., and shareholder in Gradalis and STRIKE Bio; Eric Whitman – consultant for Merck and Amgen Inc., and speakers bureau for BMS, Merck, Genentech, and Amgen Inc.; Jose Lutzky – speakers bureau for BMS; Gerald F. Downey – employed by Amgen Ltd.; Nicolas Batty – employed by and owns stock in Amgen Inc.; Thomas Amatruda – research support by Amgen Inc. For the remaining authors there are no conflicts of interest.

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