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Real-World Use of Talimogene Laherparepvec in German Patients with Stage IIIB to IVM1a Melanoma: A Retrospective Chart Review and Physician Survey

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ABSTRACT

Introduction: Talimogene laherparepvec is a first-in-class oncolytic immunotherapy for intratumoral injection with proven efficacy and tolerability in patients with unresectable early metastatic melanoma (stage IIIB–IVM1a) in the pivotal phase III OPTiM study. The objective was to characterize melanoma patients treated with talimogene laherparepvec in routine clinical practice in Germany.

Methods: A retrospective chart review was conducted in unresectable stage IIIB–IVM1a melanoma patients. Data on demographics, disease and medical history, and use of talimogene laherparepvec were collected. A survey was also conducted to understand physician treatment decisions.

Results: Data for 27 patients who initiated talimogene laherparepvec between June 2016 and July 2017 were analyzed (median age 68; stage IIIB/C disease 56%). All patients had prior surgery, and over half had repeated resections for recurrent disease (median 3). Overall, 48% of patients received at least one prior local treatment, mainly radiation therapy or electrochemotherapy. Talimogene laherparepvec was first-line systemic therapy in 63% of patients. The most frequent prior systemic treatment was immunotherapy (7/27 patients). At end of follow-up, 13 patients were still on

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talimogene laherparepvec and 14 patients had discontinued treatment. Among those who discontinued, 8 (57%) did not receive subsequent systemic therapy. Only one patient receiving first-line talimogene laherparepvec received a subsequent systemic therapy. Three patients stopped treatment because of no remaining injectable lesions. Median treatment duration was 22.1 weeks overall and 27.9 weeks in stage IIIB/C disease patients. Nearly all cutaneous lesions (93%) were injected with talimogene laherparepvec compared to subcutaneous (83%) and nodal lesions (77%). No new safety signals were reported. The main reasons given in the physician survey for treating with talimogene laherparepvec were good tolerability, overall efficacy, and lack of contraindications.

Conclusion: Talimogene laherparepvec is now included as a routine treatment option for unresectable early metastatic melanoma in Germany. This study characterizes the first patients treated with talimogene laherparepvec in Europe and confirms the good tolerability observed in clinical trials.

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INTRODUCTION

In 2014, there were over 21,000 newly diagnosed cases of melanoma and over 3000 deaths from melanoma in Germany [1]. Over the past decade, new treatment options have been introduced for unresectable and metastatic melanoma. These include targeted therapy with BRAF (v-raf murine sarcoma viral oncogene homolog B1) and MEK (mitogen-activated

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protein kinase) inhibitors, and immunotherapy with anti-CTLA4 (cytotoxic T lymphocyte-associated protein 4) agent ipilimumab or the anti-PD1 (programmed cell death 1) therapies pembrolizumab and nivolumab [2–4]. While targeted agents and systemic immunotherapies are now considered the backbone of care for patients with unresectable or metastatic melanoma, locoregional options could be considered for patients with early metastatic disease (stage IIIB–IVM1a), including isolated limb perfusion, cryotherapy, laser therapy, radiotherapy, electrochemotherapy, and intratumoral interleukin-2 (IL-2) [3, 4]. Intratumoral talimogene laherparepvec is another recently approved well-tolerated treatment option that may be preferable in some groups of patients and could help to prevent or delay disease progression.

Talimogene laherparepvec is a first-in-class oncolytic immunotherapy that is injected into melanoma lesions. It is based on a herpes simplex type 1 virus (HSV1) that has been genetically engineered to replicate selectively in tumor cells and to produce granulocyte–macrophage colony-stimulating factor (GM-CSF). Selective replication of talimogene laherparepvec results in the lysis of tumor cells releasing tumor-associated antigens [5]. Local expression and production of GM-CSF maximizes the immune response and the recruited antigen-presenting cells (including dendritic cells) may take up the released tumor antigens for presentation to T cells [5]. These local effects lead to a systemic immune response that may confer additional distal antitumor effects [5, 6].

In the pivotal phase III randomized, multinational, open-label OPTiM trial in 436 patients with unresectable stage IIIB–IVM1c melanoma [7], intratumoral talimogene laherparepvec significantly ($P < 0.001$) improved the durable response rate (continuous response for at least 6 months) over subcutaneous GM-CSF control (16.3% vs 2.1%) [8]. The most commonly reported adverse events were fatigue, chills, pyrexia, influenza-like illness, and nausea [9]. A greater benefit was observed in a subanalysis of 249 patients with stage IIIB–IVM1a disease. The overall response rates were 40.5% and 2.3% ($P < 0.0001$) for talimogene laherparepvec and GM-CSF, respectively, and median overall

survival times were 41.1 vs 21.5 months ($P < 0.001$; descriptive) [9]. These results from OPTiM led to European approval in October 2015 of talimogene laherparepvec for the treatment of adults with regionally or distantly metastatic unresectable melanoma (stage IIIB–IVM1a) with no bone, brain, lung, or other visceral disease [10, 11]. Talimogene laherparepvec subsequently became available for use in Germany on 15 June 2016 following assessment by the German Institute for Quality and Efficiency in Health Care and is supplied under a controlled distribution program.

Despite its proven efficacy in clinical trials, real-world data in Europe on use of talimogene laherparepvec are still limited. These types of data are important to support clinicians in patient selection and their understanding of the best treatment pathway to achieve optimal outcomes in routine clinical practice [12]. In this setting, patients may likely have different disease courses, medical histories, and comorbidities compared with those patients included in clinical trials [13].

The aim of the study was to carry out a retrospective medical chart review to characterize use of talimogene laherparepvec in routine clinical practice in Germany. Specifically, the objectives were to characterize patients with melanoma at the time of initiating talimogene laherparepvec in terms of patient characteristics (demographics, melanoma disease and treatment history, and clinical characteristics), use of talimogene laherparepvec, treatment patterns before and after talimogene laherparepvec, and the tolerability of talimogene laherparepvec treatment. In addition, a physician survey was conducted to understand the physician's decision-making process and rationale for prescribing talimogene laherparepvec.

METHODS

Study Design

This was a multicenter, observational, retrospective chart review study at sites treating stage IIIB–IVM1a melanoma patients with talimogene laherparepvec in Germany. Physicians at participating sites also completed a survey about their decision-making process of prescribing talimogene laherparepvec.

Study Site Selection

In Europe, talimogene laherparepvec is authorized under a controlled distribution program [10]. Only sites that are trained and qualified for safe handling and administration of talimogene laherparepvec can prescribe the drug. Among the qualified sites in Germany, those that had treated a minimum of two to five patients in routine clinical practice were invited to participate in the study.

Study Population

Patients aged 18 years or more who were diagnosed with unresectable melanoma stage IIIB, IIIC, or IVM1a with no bone, brain, lung, or visceral disease and received at least one dose of talimogene laherparepvec, as per the European marketing authorization label, were included. Staging of disease was based on the 7th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual [7]. Patients were excluded if they had received talimogene laherparepvec in a clinical trial or expanded access program.

Data Collection

Anonymized data were abstracted from patient charts and entered into an electronic case report form between 31 July and 22 November 2017. Data were collected on patient demographics (sex and age), melanoma history (primary melanoma diagnosis, diagnosis prior to first talimogene laherparepvec dose, body site of disease, number and size of lesions), clinical characteristics [Eastern Cooperative Oncology Group (ECOG) performance status, *BRAF* status, and lactate dehydrogenase (LDH)], tumor characteristics [type of lesion, anatomical region, diameter of lesion, and lesion injected (yes/no)], concomitant medications during treatment, and information on other melanoma treatments prior to and after talimogene

laherparepvec (surgery, locoregional treatment, systemic therapies). Information on use of talimogene laherparepvec was collected in terms of date of injection, dose, injected volume, reason for discontinuation (if applicable), and select events of interest (e.g., tolerability). All retrospective data available for each individual patient, spanning from primary melanoma diagnosis to date of chart abstraction (e.g., end of study period) were collected.

A physician from each participating study center completed a web-based survey after retrospective chart review abstraction was completed to capture physician characteristics, treatment practices for the management of unresectable stage IIIB–IVM1a melanoma, and clinical practices with talimogene laherparepvec.

Statistical Analysis

Descriptive statistics of the study population were carried out to describe continuous (mean, standard deviation, median, quartiles, minimum and maximum) and categorical (numbers and percentages) variables. Kaplan–Meier (KM) methods were used to estimate treatment persistence (i.e., median duration of treatment). Patients were censored if the study ended before a treatment discontinuation event occurred. The estimation of treatment persistence took into account the 14-day interval period after the last dose was administered (i.e., permissible gap between dose administrations [14]) in which a patient could go without a talimogene laherparepvec 10^8 PFU/mL dose.

Ethics

This study was performed in accordance with the standards of the institutional ethic committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. The study was registered with the EUPAS registry as EUPAS17410.

RESULTS

Chart Review

Study Population

Data were abstracted for 28 German patients, of whom 27 patients who initiated talimogene laherparepvec between June 22, 2016 and July 6, 2017 were eligible for analysis. One patient was excluded as the patient had stage IVM1b melanoma. At the time of chart abstraction (i.e., end of study period), 13 patients had ongoing treatment and 14 patients had discontinued treatment (Fig. 1). Reasons for discontinuation include no remaining injectable lesions, progressive disease, patient decision, and known side effect/toxicity (nausea) (see Fig. 1 for details). The patients who discontinued treatment because of no remaining injectable lesions
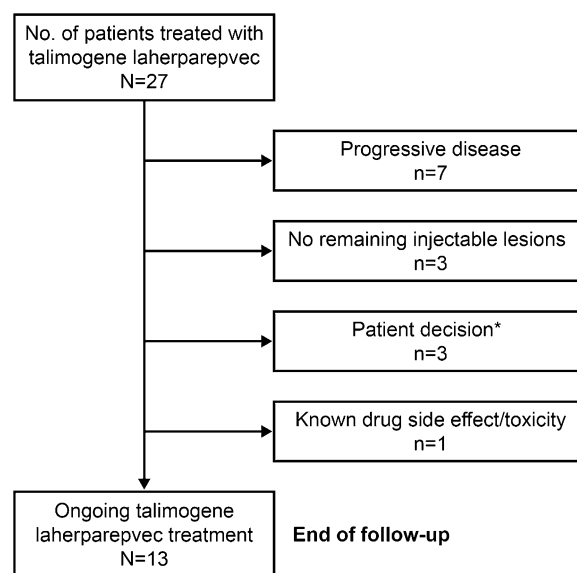
Fig. 1 Flowchart of patient follow-up and end of study status. Thirteen (48%) patients were still undergoing treatment with talimogene laherparepvec at the end of the study and 14 (52%) had discontinued treatment. Asterisk indicates the patients who discontinued treatment because of patient decision: one patient had a mixed response in which five tumors had a complete response and two were growing and were resected; another patient discontinued because of distance from the center; the third patient discontinued because of unwillingness to comply with the treatment schedule

(potentially due to response; $n = 3$) had received talimogene laherparepvec as first-line systemic therapy and had melanoma on the extremities (Supplementary Online Table S1). Two of these patients did not receive any subsequent therapy after discontinuation; and the third patient had a resection for recurrent disease, but had no further locoregional or systemic therapy.

Table 1 describes the patient and disease characteristics. Median duration of follow-up since primary melanoma diagnosis was 3.8 years. Median age was 68 years (range 26–87 years) and 37% were aged over 70 years. There was an even distribution of men and women. Over half the patients (56%) had stage IIIB/C and the remaining had stage IVM1a (44%) disease. Nearly half of the patients had missing ECOG performance status information, but one-third reported an ECOG performance status of 0. Approximately one-third of patients had raised levels of LDH according to local laboratory test cutoff of upper limit of normal (ULN). However, no patients had LDH $> 1.5 \times$ ULN cutoff. Two-thirds of patients had wild-type *BRAF* mutation status.

Prior Treatments

Table 2 summarizes treatment received prior to talimogene laherparepvec. All patients had surgery of their primary melanoma. More than half of the patients had a sentinel biopsy performed, and/or had lymphadenectomy, and/or experienced excision of recurrent locoregional disease. The median number of recurrent excisions was 3 and the median time from the last recorded resection was 10 months prior to receiving talimogene laherparepvec. Eleven patients had received adjuvant treatment with interferon-alfa. About half of the patients received one or more local treatments prior to receiving talimogene laherparepvec and the most common was radiation therapy, followed by electrochemotherapy, intralesional injection of IL-2 or interferon-alfa, and local ablation therapy. Two patients previously received regional treatment with isolated limb perfusion. Figure 2a describes the ten patients who received systemic therapy before talimogene

Table 1 Baseline patient demographic and clinical characteristics

Patient characteristic	
Total no. of patients	27
Median duration of follow-up since primary diagnosis, years (range)[a]	3.8 (0.9–19.3)
Age (years)	
Median (range)	68.0 (26.0–87.0)
Sex, *n* (%)	
Male	13 (48)
Female	14 (52)
Disease stage[a], *n* (%)	
IIIB/C	15 (56)
IVM1a	12 (44)
ECOG performance status, *n* (%)	
0	9 (33)
1	6 (22)
Missing	12 (44)
Lactate dehydrogenase, *n* (%)	
$\leq$ ULN	16 (59)
$>$ ULN	8 (30)
$< 1.5 \times$ ULN	24 (89)
$\geq 1.5 \times$ ULN	0
Unknown	3 (11)
BRAF status, *n* (%)	
Mutated	7 (26)
Wild-type	17 (63)
Not tested	3 (11)
Unknown or missing	0

ECOG Eastern Cooperative Oncology Group, *IQR* interquartile range, *ULN* upper limit of normal range
[a] American Joint Committee on Cancer, Cancer Staging Manual, 7th edition [7]

laherparepvec, of whom seven patients received immunotherapy, which were mainly ipilimumab, pembrolizumab, and nivolumab.

Table 2 Treatment history prior to talimogene laherparepvec administration

Treatment history prior to talimogene laherparepvec	
Surgery, n (%)	27 (100)
Type of surgery, n (%)	
Sentinel biopsy	16 (59)
Lymphadenectomy	15 (56)
Recorded resection of recurrent disease	14 (52)
No. of resections for recurrent disease per patient, median (IQR; range)	3.0 (1.0–5.0; 1–11)
Months from resection for recurrent disease to initiating talimogene laherparepvec, median (range)	10.0 (2–77)
Adjuvant therapy (with interferon-alfa), n (%)	11 (41)
Local treatment, n (%)	14 (52)
Local treatments received, n (%)	
1	4 (15)
2+	9 (33)
Type of local treatments, n (%)	
Electrochemotherapy	4 (15)
Radiation therapy	11 (41)
Local ablation therapy	1 (4)
Intralesional therapy injection of IL-2 or interferon-alfa	3 (11)
Regional therapy, n (%)	2 (7)
Type of regional therapy	
Isolated limb infusion	0
Isolated limb perfusion	2 (7)
Systemic therapy, n (%)	10 (37)
Patients receiving immunotherapy	7 (26)
Ipilimumab	6 (22)
Pembrolizumab	4 (15)
Nivolumab	3 (11)
Patients receiving other systemic therapies	6 (22)

Table 2 continued

Treatment history prior to talimogene laherparepvec	
IL-2	2 (7)
Trametinib/dabrafenib	1 (4)
Chemotherapy (e.g., dacarbazine, temozolamide, taxanes)	5 (19)
Other systemic therapy[a]	1 (4)

IL interleukin, *IQR* interquartile range

[a] Received treatment in a clinical trial

Talimogene Laherparepvec

Around two-thirds of patients received talimogene laherparepvec as first-line systemic therapy. Of the 14 patients who discontinued talimogene laherparepvec during the study period (Fig. 1), more than half did not receive subsequent systemic therapy. Figure 2b describes the six patients who received subsequent systemic treatment after talimogene laherparepvec, of whom four patients received one subsequent line of therapy and two patients received two subsequent lines of therapy during the study period. Subsequent therapies received included targeted therapy (BRAF/MEK inhibitor combination, $n = 2$; and MEK inhibitor monotherapy, $n = 1$), immunotherapy (ipilimumab/nivolumab, $n = 2$; pembrolizumab, $n = 1$), and chemotherapy ($n = 2$). Only one patient who received first-line talimogene laherparepvec received a subsequent systemic therapy (nivolumab/ipilimumab).

The median treatment duration of talimogene laherparepvec treatment was 22.1 weeks (Fig. 3a), but was longer in patients with stage IIIB/C disease (27.9 weeks) than in those with stage IVM1a (22.0 weeks). Furthermore, the treatment duration was longer in patients receiving first-line (23.1 weeks) and second-line (22.1 weeks) talimogene laherparepvec vs third-line or later (15.9 weeks). Of the 13 patients with ongoing treatment at the end of the study, about two-thirds had received treatment for less than 20 weeks (62%) (Fig. 3b). Median time from discontinuing talimogene laherparepvec to end of study was 21.4 weeks. Median

A

Patient number	Line of treatment				
	1st	2nd	3rd	4th	5th
1	Chemotherapy*	Ipilimumab	Talimogene laherparepvec		
2	Ipilimumab	Nivolumab	Talimogene laherparepvec		
3	Ipilimumab	Pembrolizumab	Talimogene laherparepvec		
4	Chemotherapy*	Talimogene laherparepvec			
5	Targeted therapy (trametinib/dabrafenib)	Talimogene laherparepvec			
6	Ipilimumab	Nivolumab	Chemotherapy*	Pembrolizumab	Talimogene laherparepvec
7	Ipilimumab	Pembrolizumab	Talimogene laherparepvec		
8	Other systemic therapy**	Talimogene laherparepvec			
9	Chemotherapy*	Ipilimumab	Nivolumab	Talimogene laherparepvec	
10	Chemotherapy*	Pembrolizumab	Talimogene laherparepvec		

B

| Patient number	Line of treatment				
	1st	2nd	3rd	4th	5th
1	Ipilimumab	Nivolumab	Talimogene laherparepvec	Chemotherapy*	
2	Targeted therapy (trametinib/dabrafenib)	Talimogene laherparepvec	Pembrolizumab	Targeted therapy (vemurafenib/cobimetinib)	
3	Ipilimumab	Pembrolizumab	Talimogene laherparepvec	Targeted therapy (trametinib)	Chemotherapy*
4	Other systemic therapy**	Talimogene laherparepvec	Ipilimumab/Nivolumab		
5	Chemotherapy*	Ipilimumab	Nivolumab	Talimogene laherparepvec	Targeted therapy (trametinib)
6	Talimogene laherparepvec	Ipilimumab/Nivolumab			

Fig. 2 Melanoma systemic treatments received **a** before talimogene laherparepvec ($n = 10$) during chart review period and **b** after talimogene laherparepvec among patients who discontinued treatment during the study period ($n = 6$). Patient numbers are for illustrative purposes only. The patient numbers in **a** do not correspond to the same patient numbers in **b**. *Administered chemotherapy included dacarbazine, temozolamide, and taxanes; **Clinical trial of systemic therapy

duration of follow-up from initiating talimogene laherparepvec to end of study was 30.6 weeks.

Lesion Characteristics

Table 3 describes the melanoma lesion characteristics at first administration of talimogene laherparepvec at the patient (a) and lesion level
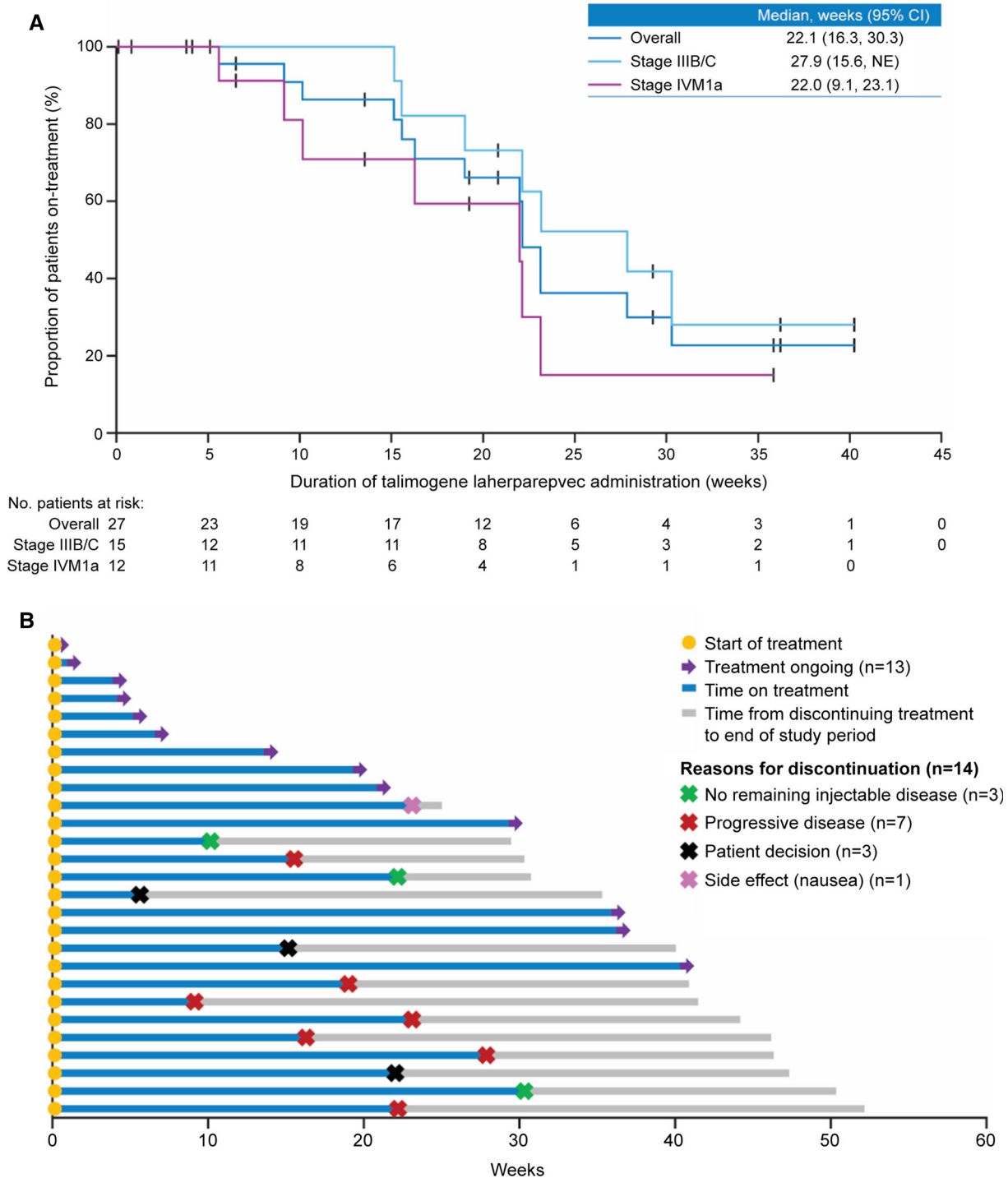
Fig. 3 Duration of talimogene laherparepvec treatment. **a** Kaplan–Meier analysis of time to talimogene laherparepvec treatment discontinuation. **b** Swimmer plot showing time on talimogene laherparepvec treatment up until initiation of chart review. Median duration of follow-up from initiating talimogene laherparepvec to end of study was 30.6 weeks and median time from discontinuing talimogene laherparepvec to end of study was 21.4 weeks. *CI* confidence interval, *NE* not estimable

Table 3 Melanoma lesion characteristics at first administration of talimogene laherparepvec and subsequent talimogene laherparepvec lesion injectability at the patient level and lesion level

Overall	[a]Patient level			[b]Lesion level		
	Total patients	Lesions injected with talimogene laherparepvec	Lesions not injected with talimogene laherparepvec	Total lesions	Lesions injected with talimogene laherparepvec	Lesions not injected with talimogene laherparepvec
	($N = 27$)	($N = 27$)	($N = 8$)	($N = 153$)	($N = 134$)	($N = 19$)
Cutaneous lesions, n (%)	17 (63)	17 (63)	4 (50)	89 (58)	83 (62)	6 (32)
Head/neck	1/17 (6)	1/17 (6)	0	1/89 (1)	1/83 (1)	0
Trunk	3/17 (18)	3/17 (18)	1/4 (25)	7/89 (8)	6/83 (7)	1/6 (17)
Inguinal	1/17 (6)	1/17 (6)	0	1/89 (1)	1/83 (1)	0
Upper extremity	2/17 (12)	1/17 (6)	1/4 (25)	2/89 (2)	1/83 (1)	1/6 (17)
Lower extremity	14/17 (82)	14/17 (82)	2/4 (50)	78/89 (88)	74/83 (89)	4/6 (67)
	Number of lesions			Diameter of lesions (mm)		
	17[c]	17[c]	4[c]	67	66	1
Mean (SD)	5.2 (3.9)	4.9 (4.0)	1.5 (1.0)	6.5 (4.9)	6.6 (4.9)	3.3 (–)
Median (IQR; range)	5.0 (2, 8; 1–12)	3.0 (1, 8; 1–12)	1.0 (1, 2; 1–3)	5.0 (3, 8; 1–22)	5.0 (3, 8; 1–22)	3.3 (–)
Subcutaneous lesions, n (%)	10 (37)	9 (33)	3 (38)	41 (27)	34 (25)	7 (37)
Head/neck	1/10 (10)	1/9 (11)	0	10/41 (24)	10/34 (29)	0
Trunk	0	0	0	0	0	0
Inguinal	0	0	0	0	0	0
Upper extremity	2/10 (20)	2/9 (22)	0	3/41 (7)	3/34 (9)	0
Lower extremity	7/10 (70)	6/9 (67)	3/3 (100)	28/41 (68)	21/34 (62)	7/7 (100)
	Number of lesions			Diameter of lesions (mm)		
	10[c]	9[c]	3[c]	31	26	5
Mean (SD)	4.1 (3.7)	3.8 (3.4)	2.3 (2.3)	8 (5.8)	8.3 (6.2)	6.2 (2.6)

Table 3 continued

Overall	[a]Patient level			[b]Lesion level		
	Total patients (N = 27)	Lesions injected with talimogene laherparepvec (N = 27)	Lesions not injected with talimogene laherparepvec (N = 8)	Total lesions (N = 153)	Lesions injected with talimogene laherparepvec (N = 134)	Lesions not injected with talimogene laherparepvec (N = 19)
Median (IQR; range)	2.0 (1, 8; 1–10)	2 (1, 6; 1–10)	1 (1, 5; 1–5)	5 (4.4, 10; 2–25)	5.2 (4.6, 10; 2–25)	4.6 (4.4, 8; 4–10)
Nodal lesions, n (%)	4 (15)	3 (11)	2 (25)	13 (8)	10 (7)	3 (16)
Axillary	1/4 (25)	1/3 (33)	1/2 (50)	5/13 (38)	4/10 (40)	1/3 (33)
Cervical	0	0	0	0	0	0
Inguinal	2/4 (50)	1/3 (33)	1/2 (50)	5/13 (38)	3/10 (30)	2/3 (67)
Trunk	1/4 (25)	1/3 (33)	0	1/13 (8)	1/10 (10)	0
Lower extremity	1/4 (25)	1/3 (33)	0	2/13 (15)	2/10 (20)	0
	Number of lesions			Diameter of lesions (mm)		
	4[c]	3[c]	2[c]	11	10	1
Mean (SD)	3.3 (1.3)	3.3 (0.6)	1.5 (0.7)	9.2 (5.8)	8.3 (5.3)	18 (–)
Median (IQR; range)	3 (2.5, 4; 2–5)	3 (3, 4; 3–4)	1.5 (1, 2; 1–2)	8 (3, 16; 3–18)	7 (3, 11; 3–17)	18 (–)

[a] Median number of lesions per patient was 6 and median number of lesions injected was 4

[b] Information on the location and injectability of 10 lesions was missing

[c] Number of subjects with evaluable data for lesion diameter

IQR interquartile range, *SD* standard deviation

(b). Two-thirds of patients had cutaneous lesions, with the majority located in the lower extremity (82%) (Table 3). Approximately one-third of patients had subcutaneous lesions (37%) and 15% had nodal lesions.

In total, 153 lesions were identified: 58% were cutaneous [most frequent in lower extremity (78/89; 88%)], 27% were subcutaneous [most frequent in lower extremity (28/41; 68%)], and 8% were nodal [mainly axillary or inguinal (5/13; 38% for both)] (Table 3). The location of ten lesions was unknown. The median number of lesions each patient had was 6.

Overall, the majority of lesions (88%; 134/153) were injected with talimogene laherparepvec. The median number of lesions injected was 4 for each patient. Compared with cutaneous lesions (93%), fewer subcutaneous (83%) and nodal lesions (77%) were injected (Table 3). The mean diameter of the cutaneous lesions that were injected was 6.6 mm and 8.3 mm for subcutaneous and nodal lesions. The median injection volumes were 2 mL for the first injection, 2 mL for the 2–5th, 1.2 mL for 6–7th, and 1 mL for the 8–13th injections (Supplementary Online Table S2).

Table 4 Events of interest observed during talimogene laherparepvec treatment

Events[a]	No. of patients (%)
Administration site conditions	
Injection-site complications	2 (7)
Injection-site pain[b]	2 (7)
Erythema	1 (4)
Pruritus left leg	1 (4)
Wateriness left shank	1 (4)
General disorders	
Fever	3 (11)
Ague (fever and chills)	2 (7)
Hot flush/sweating	1 (4)
Gastrointestinal disorders	
Nausea	4 (15)
Vomiting	1 (4)
Physician-defined immune-mediated events[c]	3 (11)
Other	
Headache	1 (4)
Increase in liver enzymes	1 (4)

[a] Multiple events may have been reported from the same patient

[b] Pain left foot, pain left shank

[c] Physician-defined immune-mediated events were eczema, increased 2-deoxy-2-fluoro-D-glucose (FDG) uptake in distant nodes without progression, and vitiligo. Only one event (vitiligo) appeared to be associated with talimogene laherparepvec

Tolerability

Table 4 shows the events of interest during talimogene laherparepvec treatment. The most frequently reported event of interest was nausea ($n = 4$). Fever ($n = 3$) was the second most frequently reported event of interest. There were three physician-defined immune-mediated events reported in three patients, but only one event, vitiligo, appeared to be associated with talimogene laherparepvec. No herpetic events or deaths were recorded among studied patients.

Physician Survey

This survey was conducted among six physicians treating melanoma patients at academic/university/teaching hospitals in Germany. All physicians were dermato-oncologists with a median of 15 years of treating melanoma patients. The median number of months of experience treating with talimogene laherparepvec was 12. Two physicians also reported experience of treating patients with talimogene laherparepvec in clinical trials.

Table 5 describes factors that influence management of patients with unresectable stage IIIB–IVM1a melanoma. Physicians reported that multiple tumor sites, previous resections in the same area, and tumor size are the three most important factors that would make stage IIIB–IVM1a melanoma unresectable. When considering locoregional treatment options for unresectable melanoma, physicians responded that they were less likely to use electrochemotherapy and isolated limb perfusion in patients with stage IVM1a disease than in those with stage IIIB/C (data not shown). Physicians reported that the majority of their unresectable stage IIIB–IVM1a melanoma cases are eligible for systemic treatment and less than 10% were considered ineligible. The main reasons for not treating patients with systemic therapy were patient choice, poor performance status, comorbidities, and toxicity.

Physicians reported using talimogene laherparepvec to treat approximately 5–30% of patients with stage IIIB/C and 3–30% of those with stage IVM1a unresectable melanoma. The three most common attributes for choosing to treat with talimogene laherparepvec were good safety profile, overall efficacy, and few contraindications (Table 5); the three most common reasons that made patients ineligible for treatment with talimogene laherparepvec were non-injectable disease, patient decision, and rapidly progressing disease. In terms of administration of talimogene laherparepvec, the three

Table 5 Physician survey

Treatment of patients with unresectable stage IIIB–IVM1a melanoma, *n* (%)	
Factors making stage IIIB–IVM1a melanoma unresectable	$N = 5^a$
Multiple tumor sites	5 (100)
Previous resections in the same area	5 (100)
Size of the tumor	5 (100)
Tumor location	4 (80)
Patient choice	3 (60)
Old age	2 (40)
Comorbidities	2 (40)
Stage of disease	2 (40)
Aesthetic/cosmetic outcome	1 (20)
Reasons for not using systemic treatment in unresectable stage IIIB–IVM1a melanoma	
Patient choice	3 (60)
Poor performance status	2 (40)
Comorbidities	2 (40)
Toxicity/side effects	2 (40)
Old age	1 (20)
Other: no evidence of tumor	1 (20)

Talimogene laherparepvec treatment, *n* (%)	
Attributes most commonly selected (by ≥ 50% of respondents) as reasons for choosing talimogene laherparepvec treatment	$N = 6$
Has a good safety profile	6 (100)
Overall efficacy	5 (83)
Has few contraindications	5 (83)
Clinical data regarding overall response rate	3 (50)
Can be reimbursed	3 (50)

Table 5 continued

Talimogene laherparepvec treatment, *n* (%)	
Attributes most commonly selected (by ≥ 50% of respondents) that make patients ineligible for talimogene laherparepvec treatment	
Non-injectable disease	5 (83)
Patient request	4 (67)
Rapid progression of disease	4 (67)
Tumor ulceration	4 (67)
High-risk patient with suspected poor prognosis	3 (50)

[a] Of the six physicians participating in the survey, only five responded to this specific question

main factors influencing the number of lesions to be injected were size/extent of melanoma lesions, lesion location, and ulceration drainage. The majority of physicians ($n = 4/6$ for each factor) reported that they would consider depth of lesion, lymph node metastases, and proximity to major blood vessels as factors for determining if ultrasound would be used to guide talimogene laherparepvec injections.

DISCUSSION

To our knowledge, this is the first post-approval analysis of the real-world use of talimogene laherparepvec in Europe. This chart review study provides insights into the first patients treated with talimogene laherparepvec in routine clinical practice in Germany.

Generally, the patient characteristics in this retrospective chart review study were similar to those who participated in the phase III OPTiM randomized clinical trial [9]. The distribution of stage IIIB/C and IVM1a disease stages were similar to OPTiM: 56% vs 54% and 44% vs 46%,

respectively. The main difference in this study vs OPTiM was that patients were generally older (median age 68 vs 63 years) [9]. This is not surprising as patients participating in clinical trials are different from those treated in routine practice, where there are stricter inclusion and exclusion criteria [13]. Another key difference in this study compared to OPTiM was the use of BRAF testing. Most patients in this study (89%) were tested for BRAF mutation according to German guidelines [15], whereas the majority of those enrolled in OPTiM (conducted in 2009–2011) had either missing or unknown BRAF status (69%) [9].

Talimogene laherparepvec is approved for unresectable melanoma, so it was not unexpected to find that all patients had undergone surgery. Over half had received surgery for recurrent locoregional disease with a median of three recurrent excisions, which suggests that, in practice, patients may be resected three times before they are determined as unresectable. However, to date, there is no consensus on the definition of unresectability (e.g., lesions are almost always considered resectable by surgeons, whereas dermato-oncologists may have a different clinical opinion). Patients with unresectable stage IIIB–IVM1a melanoma who are considered eligible for talimogene laherparepvec may differ depending on the specialty of the physician treating the patient. The resectability and eligibility of patients to be treated with talimogene laherparepvec should be considered in multidisciplinary team discussions taking into account patient preferences and disease characteristics, such as the site, burden of disease, and disease kinetics. The sites included in this study were all certified skin cancer centers, in which all patients receiving a systemic therapy were discussed in the multidisciplinary tumor board.

Prior to talimogene laherparepvec, about half of patients had received at least one prior local treatment option (mainly radiation therapy and electrochemotherapy), 7% had received regional therapy with isolated limb perfusion, and 37% had received a prior systemic therapy. Compared with OPTiM [9], a higher proportion of patients in this real-world setting received checkpoint inhibitors or targeted therapies prior to talimogene laherparepvec (6% vs 30%, respectively). This is not unexpected as most of these therapies were unavailable when the OPTiM study was conducted. Despite the availability of newer and less toxic treatments, 18.5% of patients in this German chart review study previously received chemotherapy. This finding is consistent with a retrospective cancer treatment database study reporting physician-entered case histories in Germany in 2014–2015 which found that 40% of unresectable or metastatic melanoma patients with BRAF wild-type disease received dacarbazine as first-line therapy [16].

The overall median duration of talimogene laherparepvec treatment of patients with stage IIIB–IVM1a disease was slightly shorter in this German study than in OPTiM: 22.1 weeks vs 25.7 weeks, respectively [9]. However, the median duration of treatment specifically for patients with stage IIIB/C disease in our study was similar to OPTiM (27.9 weeks vs 25.7 weeks). This duration of treatment corresponded to the European SmPC guideline of continuing talimogene laherparepvec for at least 24 weeks [10]. Duration of treatment was also longer in our study when talimogene laherparepvec was used first line vs second line or later. This is unsurprising given that patients who have already received prior lines of systemic therapy may have more aggressive, rapidly progressing disease than first-line patients. Most patients in this study received talimogene laherparepvec as first-line therapy.

Nearly half of patients remained on talimogene laherparepvec treatment at the end of the study. Among the 14 patients who discontinued talimogene laherparepvec, three discontinued treatment because of no remaining injectable lesions. Of these three patients, none had subsequent locoregional or systemic therapy following talimogene laherparepvec during the study period; and one patient had a subsequent resection for recurrent disease. Interestingly, half of the patients who discontinued treatment did not receive subsequent systemic therapy and only one patient who was treated with talimogene laherparepvec as first line received a subsequent systemic therapy. These findings suggest that a subgroup of patients may

benefit from intratumoral talimogene laherparepvec alone and will not require subsequent systemic therapy or the need for subsequent therapy may be delayed. This is supported by data from the OPTiM trial in patients with stage IIIB–IVM1a melanoma [9]. Compared with GM-CSF control, fewer patients in the talimogene laherparepvec group required subsequent systemic therapy (50% vs 41%, respectively), and time to treatment failure (defined as time to first clinically relevant disease progression or death) was longer with talimogene laherparepvec (3.3 vs 13.1 months, respectively) [9]. This indicates that there may be some systemic benefit associated with talimogene laherparepvec, which may be supported by the 20-month difference in overall survival in the talimogene laherparepvec vs GM-CSF treated groups (41.1 months vs 21.5 months) [9].

The tolerability profile of talimogene laherparepvec was similar in this real-life study compared with OPTiM [9]. Talimogene laherparepvec was well tolerated. No new or unexpected safety concerns were raised. Influenza-like symptoms and injection-site complications were the most frequently reported events. Severity of these events was not recorded in the patient charts. Only one patient discontinued talimogene laherparepvec because of nausea compared with 18.5% (14 of 163) patients in OPTiM [9]. No herpetic events were recorded in this study. It should be noted that while injection-site reactions, immune-mediated events, and herpetic events were systematically abstracted in this chart review study, some of the more general events (fever and sweating) and gastrointestinal (GI) disorders (nausea and vomiting) known to be associated with talimogene laherparepvec may have been underestimated as they were not systematically collected in the physician's case report form. This may explain the lower incidence of these events when compared to OPTiM. Nevertheless, the events of interest reported were consistent with the adverse events collected in OPTiM [9].

Talimogene laherparepvec is dosed per volume depending on the size of the lesions, with a maximum of 4 mL injected per administration visit. During the first five courses of treatment, the median dosage in the current study was

2 mL compared with 3 mL in OPTiM [17]. This suggests that patients treated in the real-life setting may have had a lower tumor burden than in the OPTiM trial.

The proportions of patients with cutaneous lesions were similar between our study and OPTiM (63% vs 67%) [9]. However, our patients presented with lower proportions of subcutaneous and nodal lesions compared with the OPTiM trial (37% and 15% compared with 48% and 43%, respectively). The study population may have had lower disease burden compared to OPTiM or this may reflect the use of whole-body computed tomography (CT), positron emission tomography (PET), or PET-CT scans used in OPTiM as part of the screening process to identify injectable lesions. Although German guidelines recommend these imaging procedures for staging melanoma [15], these sensitive methods for detecting extracerebral metastases (e.g., PET-CT) may not always be accessible as they are not reimbursed as part of routine clinical care. Furthermore, while ultrasound is as sensitive as PET-CT and CT [18] and widely used in Germany for staging melanoma [19], it may not have been systematically used in all centers and all patients, and therefore, the number of subcutaneous and nodal lesions eligible for injection may have been potentially underestimated. With the introduction of talimogene laherparepvec and future intratumoral therapies [20, 21], the use of more sensitive scanning methods at diagnosis might become more important in identifying and mapping cutaneous/subcutaneous/nodal lesions suitable for intratumoral treatment.

In our physician survey, the three main factors that influenced the number of lesions that were injected were size/extent of melanoma lesions, lesion location, and ulceration drainage. These findings were consistent with a survey study of 122 physicians in Germany, France, and the UK, which found that the anatomical site of a lesion strongly influenced its perceived injectability in patients with stage IIIB to IVM1a–c melanoma [22]. In addition, the study also reviewed 1193 melanoma case histories and found that 76–77% of cutaneous or subcutaneous, 65% of regional lymph nodes,

and 46% in distant lymph nodes were considered to be injectable.

There were several limitations in this study. The sample size was small; nevertheless, it represented approximately 25% of the entire talimogene laherparepvec-treated population in Germany at the time of the study. The study did not collect data on treatment efficacy as the main objective was to characterize patient characteristics and to describe drug utilization in real-life. However, we note that three patients discontinued talimogene laherparepvec because of no remaining injectable lesions, which may have been due to response as these patients did not receive subsequent locoregional or systemic therapy during the follow-up period. In addition, we did not collect data on comorbidities, which may have influenced treatment and management of these patients. The generalizability of these results should be cautioned as most patients included in this study initiated treatment in 2016, which is shortly after marketing authorization of talimogene laherparepvec in Europe. Therefore, data reported are likely to reflect early use, which may potentially evolve over time with more clinical experience.

Talimogene laherparepvec is now included as a routine treatment option for unresectable early metastatic melanoma in Germany, with the majority of patients receiving it as first-line therapy. Although this study characterizes the first patients treated with talimogene laherparepvec in Europe, additional long-term data are needed to assess its effectiveness over time in the real-world setting.

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Data Availability. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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