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Practical clinical guide on the use of talimogene laherparepvec monotherapy in patients with unresectable melanoma in Europe

Talimogene laherparepvec, a herpes simplex virus type 1-based intralesional oncolytic immunotherapy, is approved in Europe for the treatment of adults with unresectable stage IIIB-IVM1a melanoma, with no bone, brain, lung or other visceral disease. It has direct oncolytic effects in injected lesions, leading to the release of tumour-derived antigens and systemic immune effects mediated by the induction of anti-tumour immunity, which is enhanced by the production of granulocyte macrophage colony-stimulating factor. Responses (which occur in >40% of stage IIIB-IVM1a patients) are often durable (>50% last ≥6 months) and occur in injected and uninjected lesions (in stage IIIB-IVM1c patients, 64%/34% of evaluable injected/uninjected non-visceral lesions, respectively, decreased in size by ≥50%). As with other immunotherapies, responses may be delayed or can arise after pseudoprogression. The pattern of treatment-emergent adverse events is distinct, being mostly grade 1/2, easy to manage, and rarely leading to treatment discontinuation. Systemic therapy represents the backbone of care for many metastatic melanoma patients. Nonetheless, the potential for durable locoregional control with a locally injected agent may make talimogene laherparepvec suitable for selected patients with stage IIIB/C disease, for whom surgery is not possible (*e.g.* with in-transit metastases, multiple melanoma lesions at different body sites, or those relapsing rapidly after repeated rounds of surgery) and slowly progressing disease. Here, we discuss which patients could be suitable for talimogene laherparepvec monotherapy based on the European indication, review the patterns/timing of response, and discuss the incidence/management of adverse events. Its potential use combined with immune checkpoint inhibitors is also discussed.

Key words: intralesional injection, melanoma, oncolytic immunotherapy, talimogene laherparepvec, tolerability, tumour response

An innovative treatment approach for melanoma is oncolytic immunotherapy, such as talimogene laherparepvec, which is designed to replicate in and kill tumour cells without harming normal tissue, while increasing the host immune cell recognition of tumour-derived antigens released during oncolysis [1, 2]. Talimogene laherparepvec is a herpes simplex virus type 1 (HSV-1)-based agent that is injected directly into tumoural lesions, and which, due to its various genetic modifications, is able to selectively infect and destroy tumour cells. The genetic modifications include deletion of the gene for infected cell protein 34.5 (*ICP34.5*), which attenuates viral pathogenicity and enhances tumour-selective replication [3, 4]. *ICP34.5* is also known as a "neurovirulence factor" because it counteracts the interferon-induced block on viral replication that is mediated by protein kinase R. This is a process that is frequently already disabled in tumour cells. Therefore, while antiviral responses defend normal cells following infection with *ICP34.5*-deficient talimogene laherparepvec, tumour cells are susceptible to injury and death [3]. Another genetic modification of the virus is the deletion of *ICP47*. This prevents downregulation of antigen presentation molecules and increases the expression of HSV US11, thereby enhancing viral replication in tumour cells [3, 4]. Furthermore, insertion of two copies of the gene encoding human granulocyte macrophage colony-stimulating factor (GM-CSF) results in local GM-CSF production and an enhanced anti-tumour immune response, due to the capacity of GM-CSF to activate antigen-presenting cells and thereby help induce a tumour-specific T-cell response [4, 5].

Clinical development of talimogene laherparepvec has, so far, primarily focused on evaluating its efficacy and safety in patients with melanoma. In the phase III OPTiM trial (NCT00769704), intralesional talimogene laherparepvec significantly improved the durable response rate (DRR;

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rate of response lasting six months or more) *versus* subcutaneous GM-CSF in patients with unresectable stage IIIB-IVM1c melanoma (DRR: 16.3% *versus* 2.1%, respectively; $P < 0.001$) [5]. Treatment options for melanoma were limited when the OPTiM trial was initiated in 2009. GM-CSF was considered a suitable option for the control arm based on its immune-mediated mechanism of action, its good tolerability, and on evidence that it provided clinical benefit as adjuvant therapy in some patients with resectable stage III-IV melanoma [6]. Median overall survival (OS) was 4.4 months longer with talimogene laherparepvec than with GM-CSF (hazard ratio [HR]: 0.79; 95% confidence interval [CI]: 0.62-1.00; $P = 0.051$), an effect that persisted in a planned final analysis conducted at a median follow-up of 49 months [7]. Of note, six patients in the talimogene laherparepvec arm converted from unresectable to resectable status during treatment [8]. In Europe, talimogene laherparepvec monotherapy is indicated for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease [3]. Studies evaluating the potential use of talimogene laherparepvec in combination with immune checkpoint inhibitors are currently ongoing for melanoma and other solid tumours [9].

The aim of this narrative, non-systematic review is to provide practical recommendations on the use of talimogene laherparepvec monotherapy in patients with melanoma in Europe, based on the available published evidence to date and the clinical experience of the authors. We aim to provide suggestions for healthcare professionals on which melanoma patients may be best suited for treatment with talimogene laherparepvec, handling and administration, incidence, timing and management of adverse events (AEs), as well as criteria for assessing response.

Factors to consider when selecting the appropriate therapeutic for a patient

In addition to intralesional talimogene laherparepvec, several systemic agents have recently been approved for the treatment of unresectable and metastatic melanoma and many different treatment options are currently available [10]. These include BRAF inhibitors (*e.g.* vemurafenib, encorafenib and dabrafenib) and MEK inhibitors (*e.g.* binimetinib, cobimetinib and trametinib) which can be used in patients with *BRAF* V600 mutant tumours, and the immune checkpoint inhibitors, which target cytotoxic T-lymphocyte antigen 4 (CTLA4, *e.g.* ipilimumab) or programmed cell death protein 1 (PD-1, *e.g.* nivolumab and pembrolizumab) [11]. In line with international melanoma treatment guidelines [10, 12], these systemic agents are considered the backbone of treatment for the majority of patients with unresectable and metastatic melanoma [13, 14]. For patients with unresectable, early metastatic melanoma (stage IIIB-IVM1a), other alternatives could be considered for selected patients. Intralesional therapy with an agent such as talimogene laherparepvec is one option [10].

Patient- and tumour-related characteristics are of importance when deciding between the different treatments for unresectable stage IIIB-IVM1a melanoma, including selecting the most appropriate locoregional or systemic treatment option. For instance, patient age, performance status, comorbidities, previous treatments (including prior response and any side effects encountered), as well as patient preference may influence treatment choice. Furthermore, disease stage [15], including the size, site(s) and number/type of melanoma lesions (including in-transit metastases [16]) and number and type (macro, micro, palpable, matted) of lymph node metastases present, are important factors. Biomarkers such as serum lactate dehydrogenase and S100 levels can provide additional prognostic information [17-19]. The presence/absence of *BRAF, c-KIT* and *NRAS* mutations or potentially programmed cell death ligand 1 (PD-L1) expression [10, 20] can also play a role in the treatment selection. For instance, *BRAF* V600 mutations are present in approximately half of patients with metastatic melanoma [21], and in such patients, combination treatment with BRAF and MEK inhibitors could be an option [22], although immune checkpoint inhibitors also have a role [10]. Furthermore, disease kinetics (*i.e.* whether there is slowly or fast-progressing melanoma) can impact on the aim and choice of treatment [23].

Table 1. Potential clinical scenarios in patients with unresectable stage IIIB-IVM1a melanoma in whom talimogene laherparepvec could be considered a suitable treatment option.

Potential scenario
When surgery is not or is no longer an option e.g. in patients
With cutaneous head and neck melanoma or other body sites where surgery could be disfiguring
With in-transit metastases or multiple small injectable melanoma metastases at different body sites
At increased risk of surgical complications
With repeated disease recurrence despite multiple surgical interventions
When systemic immune checkpoint therapy or BRAF/MEK inhibitors are contraindicated/inappropriate/undesirable e.g. in patients
With a history of adverse events during immune checkpoint inhibitor therapy
Requiring first-line treatment after relapsing on adjuvant immune checkpoint inhibitor therapy
With slowly progressing disease who wish to avoid systemic therapy
Concerned about immune-related side effects such as colitis, pneumonitis, etc.
Who are elderly, with comorbidities or poor performance status

Which patients could be candidates for talimogene laherparepvec treatment?

Systemic therapies are considered the backbone of care for the majority of patients with unresectable and metastatic melanoma; however, there are potential clinical scenarios in which talimogene laherparepvec could be considered a new alternative treatment option (*table 1*). A description of these scenarios is provided below. The choice of treatment option to use in any particular scenario should be based on discussions within the multidisciplinary team (MDT).

A key difference *versus* systemic therapy is that any patient who is treated with talimogene laherparepvec must have injectable disease, as talimogene laherparepvec can only be administered into cutaneous, subcutaneous and nodal lesions that are visible, palpable or detectable by ultrasound.

Use of talimogene laherparepvec for stage IIIB-IVM1a, unresectable melanoma

Talimogene laherparepvec could be considered as a new treatment option for patients with unresectable stage IIIB-IVM1a disease. In this respect, efficacy in the phase III OPTiM trial was most pronounced in patients with early metastatic (stage IIIB-IVM1a) melanoma (*table 2*). Based on an exploratory analysis of OPTiM patients with stage IIIB-IVM1a disease, OS was improved in the talimogene laherparepvec arm *versus* GM-CSF (HR: 0.57 [95% CI: 0.40-0.80]; $P < 0.001$ [descriptive]; *table 2*) [24]. No difference between treatments was observed for OS in patients with stage IVM1b-c disease (HR: 1.07 [95% CI: 0.75-1.52]) [5]. In stage IIIB-IVM1a disease, talimogene laherparepvec also significantly improved overall response rate (ORR; 40.5% *versus* 2.3%) and complete response (CR) rate (16.6% *versus* 0%) *versus* GM-CSF. Among talimogene laherparepvec-treated patients achieving an objective response, estimated five-year OS was 78% [24]. Based on analyses performed for the intent-to-treat (ITT) population, OS was found to be most prolonged in patients achieving a CR [25] and the achievement of durable response (DR) was associated with improved OS [26].
Based on the results of the randomised phase III OPTiM trial, talimogene laherparepvec monotherapy was approved in Europe for the treatment of adults with unresectable stage IIIB-IVM1a melanoma, with no bone, brain, lung or other visceral disease [3]. Importantly, the stage IIIB-IVM1a unresectable population from the OPTiM study ($n = 249$; talimogene laherparepvec: $n = 163$; GM-CSF: $n = 86$ [24]) is the largest phase III dataset currently reported with a therapeutic in this group of melanoma patients.

Use of talimogene laherparepvec when surgery is impractical or unsuitable

Talimogene laherparepvec may be considered an option in patients for whom surgery is not an option due to the location of the tumour. This is quite frequently the case for cutaneous head and neck melanoma, for example, scalp melanoma, for which it may be difficult to achieve appropriate surgical margins [27, 28]. In one retrospective analysis from the phase III OPTiM trial, talimogene laherparepvec showed promising activity in 61 patients with stage IIIB-IVM1c cutaneous head and neck melanoma (*i.e*. patients with melanoma located in the scalp, face and neck at initial diagnosis), compared with 26 GM-CSF-treated patients [29]. Here, the DRR was 36.1% *versus* 3.8% ($P = 0.001$) and the CR rate was 29.5% *versus* 0% in talimogene laherparepvec- *versus* GM-CSF-treated patients, respectively (*table 2*). Local and systemic effects of talimogene laherparepvec were also noted specifically in this subgroup of patients with head and neck melanoma ($n = 87$) [29]. In this subpopulation, lesion-level responses were observed in 63.8%, 7.9% and 10.8% of injected, uninjected non-visceral and uninjected visceral lesions, respectively.
If surgery is deemed unsuitable, talimogene laherparepvec could be considered a new option in patients who have an elevated risk of surgical complications or in the case of repeated recurrence despite multiple surgical resections. Furthermore, in the case of in-transit melanoma [16, 30] or when there are multiple small melanoma lesions in different body sites, excision may not be possible or the result may be disfiguring (*e.g.* in the case of amputation).
The potential for a systemic immune response with talimogene laherparepvec, as evidenced by regression of uninjected locoregional or distant lesions (the bystander effect; see later section on patterns of clinical response) may be particularly attractive in such scenarios.

Use of talimogene laherparepvec prior to systemic therapy or after adjuvant systemic therapy

Data from the OPTiM ITT population support administration of talimogene laherparepvec first line, prior to other therapies. This is due to the observed improvements in DRR (24% *versus* 10%) and ORR (38% *versus* 17%, respectively) for treatment-naive patients (those with no prior systemic non-adjuvant melanoma treatment) compared with patients receiving talimogene laherparepvec as their second or greater line of melanoma therapy [5]. However, that line of therapy was not retained as an independent predictor for DR in a multivariate analysis taking into account disease stage [24]. It should also be noted that in 2009-2011, when the OPTiM study was open to enrolment, standard first-line systemic therapy was often chemotherapy-based, with current first-line options more likely to be used as subsequent treatment. For example, for stage IIIB-IVM1a patients receiving talimogene laherparepvec in the OPTiM study, only 4% received previous treatment with an anti-CTLA4 agent, 1% received prior vemurafenib, and no patients received prior anti-PD-1 therapy. In contrast, 37% of patients received subsequent ipilimumab, 9% subsequent vemurafenib, and 1% received subsequent anti-PD-1 therapy [24]. Similar treatment distributions were also noted in the GM-CSF arm. Nonetheless, the potential for durable locoregional control with a locally injected, well-tolerated treatment option could be desirable in some patients – in such cases, systemic treatments could be preserved for later use if the disease progresses. Although there are limited data available on the sequencing of immunotherapies, it has been suggested that pre-treatment of tumours with an oncolytic immunotherapy such as talimogene laherparepvec may improve the efficacy of anti-PD-1 therapy by changing the tumour microenvironment [31, 32]. This is because non-inflamed tumours are not readily amenable to immunotherapy, and talimogene laherparepvec can potentially increase inflammation in both injected and uninjected lesions by increasing tumour T-cell infiltration [31, 32].
Based on positive results from several recent well-designed adjuvant trials of ipilimumab, nivolumab or dabrafenib plus trametinib [33-35], patients with resectable stage III melanoma at high risk of recurrence may now receive systemic adjuvant therapy following resection. Talimogene laherparepvec may be an appropriate first-line option for some patients relapsing following systemic adjuvant treatment. This may especially be the case if the relapse occurred on or shortly after (within six months of) systemic adju-

Table 2. Overview of key efficacy data from the OPTiM study.

	Stage IIIB-IVM1a population [24]			Stage IIIB-IVM1c (ITT) population [5, 7]			Head and neck melanoma population [26]		
	Talimogene laherparepvec (*n* = 163)	**GM-CSF (*n* = 86)**	***P*-value[a]**	**Talimogene laherparepvec (*n* = 295)**	**GM-CSF (*n* = 141)**	***P*-value**	**Talimogene laherparepvec (*n* = 61)**	**GM-CSF (*n* = 26)**	***P*-value[a]**
Overall response, % (95% CI)[d]	40.5 (32.9-48.4)	2.3 (0.3-8.1)	<0.0001	26.4 (21.4-31.5)	5.7 (1.9-9.5)	<0.001	47.5 (34.6-60.7)	7.7 (1.0-25.1)	0.0004
Best response, %[d]			–						
Complete response (CR)	16.6	0		10.8	<1		29.5	0	
Partial response (PR)	23.9	2.3		15.6	5.0		18.0	7.7	
Stable disease (SD)[e]	34.4	50.0		45.4	50.4				
Disease control rate (CR/PR/SD)[e]	79.1	54.7		76.3	56.7				
Durable response, % (95% CI)[d]	25.2 (18.5-31.8)	1.2 (0.0-3.4)	<0.0001	16.3 (12.1-20.5)	2.1 (0-4.5)	<0.001	36.1 (24.2-49.4)	3.8 (0.1-19.6)	0.001
Overall survival–median, months (95% CI)	41.1 (30.6-NE)[b]	21.5 (17.4-29.6)[b]	<0.001	23.3 (19.5-29.6)[c]	18.9 (16.0-23.7)[c]	0.0494[a,c]	NE (29.7-NE)[f]	25.2 (12.8-37.4)[f]	
HR (95% CI)	0.57 (0.40-0.80)[b]			0.79 (0.62-1.00)			0.57 (0.32-1.03)		0.062
Estimated survival probability, %[b]									
At 12 months	87.0	76.8		73.7	69.1				
At 24 months	64.8	46.2		49.8	40.3		67.2	50.0	
At 36 months	54.7	34.3		38.6	30.1				
At 48 months	45.6	23.4		32.6	21.3		52.9	29.6	

CI: confidence interval; GM-CSF: granulocyte macrophage colony-stimulating factor; HR: hazard ratio; ITT: intent-to-treat; NE: not evaluable; OS: overall survival.

[a] *Descriptive P-value.*

[b] *Data derived from an exploratory analysis of the primary OS snapshot (data cut-off March 31, 2014).*

[c] *Data derived from the final OS analysis snapshot (data cut-off: September 5, 2014).*

[d] *Response per investigator and then evaluated by a blinded endpoint assessment committee (EAC).*

[e] *Based on investigator assessment, and not centrally confirmed by EAC; Amgen data on file.*

[f] *Interquartile ranges reported rather than CIs.*

vant therapy, in which rechallenge would not be a preferred option. However, it should be noted that data on the use of talimogene laherparepvec following systemic adjuvant treatment are currently lacking and trials in this setting are warranted.

Use of talimogene laherparepvec in slowly progressing disease

Due to its mechanism of action and the potential for delayed response, talimogene laherparepvec treatment would be expected to be best suited to patients with more slowly progressing disease. Two successive measures of total tumour burden while the patient is not undergoing treatment, ideally four to 12 weeks before treatment initiation, can provide an objective measure of disease kinetics [36]. For instance, patients with oligometastatic disease are more likely to have slow disease kinetics and so could be appropriate candidates for talimogene laherparepvec. For disease that is rapidly progressing, such as in cases of rapid decline in performance status or organ function, a large increase (*e.g.* doubling) in serum lactate dehydrogenase levels, or direct evidence of fast disease kinetics/progressive disease (PD) based on comparison of computed tomography scans performed within two months of each other, systemic therapy is more suitable. Potential algorithms to more objectively characterise such scenarios (*i.e.* whether there is slow- or fast-progressing disease) have recently been proposed [23]. Further data are warranted to determine the efficacy of talimogene laherparepvec in patients with different disease kinetics.

Use of talimogene laherparepvec when a systemic therapy is not feasible

There are situations in which systemic therapy may not always be the preferred option for patients with stage IIIB-IVM1a melanoma. These could include, for example, those who have poor performance status or a history of significant AEs during treatment with other agents [37]. Its favourable toxicity profile also makes talimogene laherparepvec a potential option for elderly patients, especially for those with pre-existing comorbidities. Of note, patients up to the age of 94 years received talimogene laherparepvec in the OPTiM ITT population, and 48% of patients were at least 65 years [5].

Patients with active/uncontrolled autoimmune disease (*i.e.* on high-dose steroids) or on immunosuppressive therapy were excluded from the OPTiM trial [5] as they were already participating in trials for immune checkpoint inhibitors. Consequently, there is currently no evidence to support the use of talimogene laherparepvec in such situations.

Handling, preparation and administration of talimogene laherparepvec

As talimogene laherparepvec is a genetically modified virus and classified as an advanced therapy medicinal product, a system that permits the complete traceability of the patient and product is required [38]. As a result, talimogene laherparepvec is currently only available in Europe through a special controlled distribution programme, which ensures that healthcare professionals using this agent are adequately trained. Procedures for gaining permission to use talimogene laherparepvec might differ between countries and local regulations should be followed.

Practical information about the handling, preparation, and administration of talimogene laherparepvec has recently been reviewed in depth by Harrington *et al*. [38] and others [39-41]. In brief, the handling of talimogene laherparepvec needs attention due to its deep freeze, cold-chain requirements, its administration by direct intralesional injection, and its potential for viral shedding [38]. During preparation and administration, protective gowns, safety glasses or a face shield and gloves should be worn and any exposed wounds covered. It is important to allow sufficient time ahead of administration to measure all injectable lesions, to determine the required talimogene laherparepvec volume to be injected. After thawing, talimogene laherparepvec should be administered as soon as practically feasible. The storage times and temperature ranges are described in the summary of product characteristics (SmPC) [3].

Talimogene laherparepvec is administered by intralesional injection into cutaneous, subcutaneous and/or nodal lesions that are visible, palpable, or detectable by ultrasound [3]. As a maximum total volume of 4 mL can be injected at each treatment visit, it may not be possible to inject all lesions during any one visit. It is recommended, therefore, that lesions to be injected should be prioritised based on lesion size with the largest lesion injected first and then the remaining lesions injected in size order, until the maximum injection volume is reached or all lesions are injected [3]. For subsequent injections, any new lesions that have developed since the previous treatment should be injected first, with the remainder prioritised in size order, as per the initial injection. To minimise the risk of viral shedding, each injection site and its surrounding area should be swabbed with alcohol and covered with an absorbent pad and a dry occlusive dressing [3].

Patients with lesions that cannot be clearly palpated (*e.g.* those with deeper subcutaneous or nodal lesions) may require ultrasound-guided talimogene laherparepvec administration [37]. In this way, it is possible to visualise the lesion, needle insertion, and drug delivery. Ultrasound may also permit a more accurate determination of lesion size and thereby the volume of talimogene laherparepvec to be injected ahead of administration.

Local institutional guidelines should be followed regarding the preparation and administration of talimogene laherparepvec. The use of a single room to prepare and administer this agent and scheduling all injections to be given on the same day of the week may facilitate workflow in the clinic [40]. A talimogene laherparepvec treatment visit may last up to approximately two hours. During this time, lesions to be injected are measured and compared with any measurements available from the previous visit – a lesion-tracking sheet and/or high-resolution photographs may be useful for this purpose. The required volume of talimogene laherparepvec should then be requested from the pharmacy and while this is thawing (for approximately 30 minutes), local anaesthetic can be applied or painkillers offered, as needed [40].

Healthcare professionals preparing or administering talimogene laherparepvec should avoid contact with skin, mucosa, and eyes. If accidental exposure occurs, the area should be flushed with water for at least 15 minutes. In the event of needle stick injury, the area should be cleaned thoroughly with soap and water and/or disinfectant [38]. Any spillages should be cleaned up using absorbent materials along with a virucidal agent (*e.g.* 2.5% bleach, 70% isopropyl alcohol, or 0.8% vesphene) and disposed of according to local guidelines [42]. All materials that have been in contact with talimogene laherparepvec should be disposed of in accordance with local institutional procedures.

Incidence, timing and management of adverse events during talimogene laherparepvec treatment

Incidence of adverse events

Talimogene laherparepvec was well tolerated in both the ITT and early-stage metastatic (stage IIIB-M1a) populations in the OPTiM trial [5, 24]. The most common treatment-emergent AEs, grade 3/4 AEs and the frequency of AEs leading to discontinuation in stage IIIB-IVM1a melanoma patients, are shown in *table 3*, and also described below [24]. Most AEs were low-grade, constitutional symptoms and local injection site reactions; the most commonly reported were fatigue, chills and pyrexia. Some AEs were more common in patients who were HSV-1 seronegative at baseline (*e.g.* fatigue in 56% *versus* 48% and diarrhoea in 31% *versus* 18% in HSV-1 seronegative *versus* seropositive patients, respectively) [43]. Grade ≥3 AEs and AEs leading to treatment discontinuation occurred in 32.5% and 8.6% of talimogene laherparepvec-treated patients, respectively [24]. Oral herpes (any grade) occurred in 3.1% of patients receiving talimogene laherparepvec compared with 1.3% of those receiving GM-CSF [44]. Notably, these rates of herpetic infection are similar to the expected prevalence of symptomatic herpes infections in a general adult population. As PCR testing was not performed, it could not be confirmed whether the herpetic infections reported in the OPTiM trial were caused by talimogene laherparepvec or wild-type HSV-1 infection.

Five patients experienced immune-related AEs in the talimogene laherparepvec treatment arm: glomerulonephritis/renal papillary necrosis (grade 2), glomerulonephritis/renal failure (grade 3), vasculitis (grade 2), pneumonitis (two episodes in one patient; grades 2 and 3), and psoriasis (two episodes in one patient; grades 1 and 3). Vitiligo also occurred in 12 (7%) patients, among these, three (25%) had a DR and all 12 were alive at more than 12 months [43]. Although there was a non-significant trend for the association of vitiligo and OS based on a nine-month landmark analysis (HR: 0.30 [95% CI: 0.07-1.22]; $P = 0.09$ [descriptive]), it was not associated with overall response or DR.

Timing and duration of adverse events

The incidence of the most common events (fatigue, chills, pyrexia, influenza-like illness, and nausea) was highest during the first three treatment cycles and decreased over time, being ≤10% for each event by cycle 6 (*figure 1*) [43]. Aside from influenza-like illness (which occurred after a median of three days), the first occurrence of most of these events coincided with the second talimogene laherparepvec injection. This may be related to the fact that the initial dose of talimogene laherparepvec is given at a lower concentration (10^6 plaque-forming units [PFU]/mL) than subsequent booster doses (10^8 PFU/mL) [3]. The median duration of the most common AEs during talimogene laherparepvec treatment was two to four days (*table 4*).

Table 3. Incidence of the most common adverse events (AEs), grade 3/4 AEs and AEs leading to discontinuation during talimogene laherparepvec treatment (based on a stage IIIB-IVM1a subpopulation from the OPTiM trial) [24, 43].

	Talimogene laherparepvec arm (*n* = 163)
Most common AEs (all grades)[a], n (%)	
Fatigue	84 (51.5)
Chills	81 (49.7)
Pyrexia	65 (39.9)
Nausea	56 (34.4)
Influenza-like illness	55 (33.7)
Injection site pain	50 (30.7)
Diarrhoea	35 (21.5)
Most common grade 3/4 AEs[b], n (%)	
Pain in extremity	4 (2.5)
Fatigue	3 (1.8)
Hypokalaemia	3 (1.8)
Cellulitis	3 (1.8)
Deep vein thrombosis	3 (1.8)
Dehydration	3 (1.8)
Infected neoplasm	3 (1.8)
Injection site pain	3 (1.8)
AEs leading to discontinuation, n (%)	
All	14 (8.6)
Serious	8 (4.9)
Non-serious	6 (3.7)
Fatal AEs during the study, n (%)	1[c] (0.6)

AEs (coded using MedDRA version 15.1) include all those that began between the first administration of study treatment and 30 days after the last administration of study treatment. AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities.
[a] AEs occurring in 20% or more of patients treated with talimogene laherparepvec.
[b] AEs occurring in three or more patients treated with talimogene laherparepvec.
[c] Not attributed to treatment.

Management of adverse events

As mentioned above, most AEs occurring during talimogene laherparepvec treatment are grade 1/2, relatively short-lived and, therefore, may not require active treatment. If treatment is required, over-the-counter medications can be used for many low-grade AEs. For instance, patients with pyrexia, chills, and influenza-like illness may be given acetaminophen (paracetamol) and non-steroidal anti-inflammatory drugs (NSAIDs). Nausea can be treated with metoclopramide or domperidone, and diarrhoea with

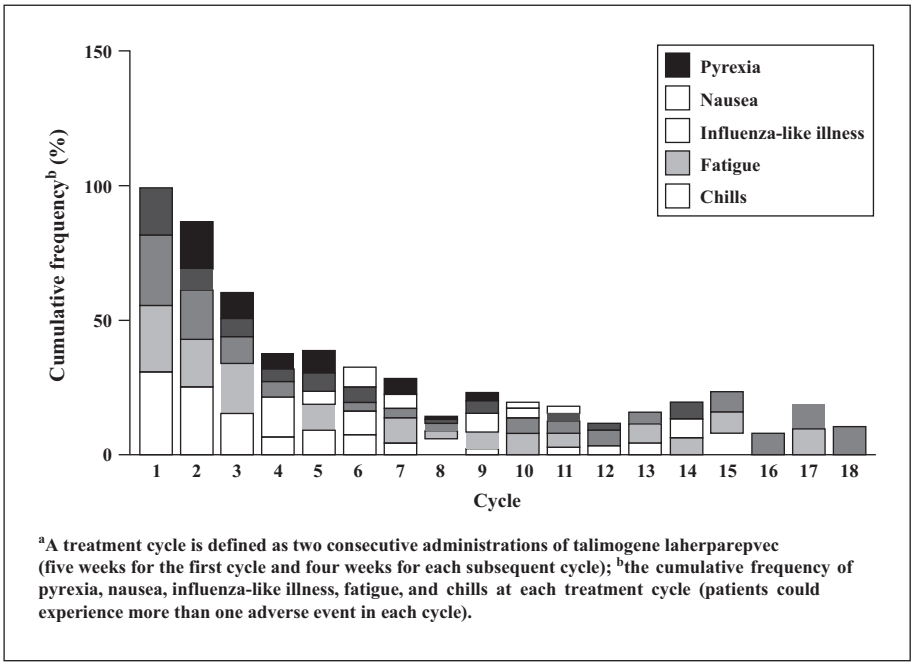

Figure 1. Incidence of the five most common treatment-emergent adverse events with talimogene laherparepvec, by treatment cycle[a] (based on a stage IIIB-IVM1a subpopulation from the OPTiM trial) [43].

Table 4. Time to occurrence and duration of the five most common treatment-emergent adverse events with talimogene laherparepvec (based on a stage IIIB-IVM1a subpopulation from the OPTiM trial) [43].

Adverse event	Talimogene laherparepvec arm ($n = 163$)	
	Median time to first occurrence (IQR) (days)	Median duration of first adverse event (IQR) (days)
Fatigue	36 (8-76)	4 (2-14)
Chills	23 (8-41)	2 (1-2)
Pyrexia	22 (3-35)	2 (2-3)
Influenza-like symptoms	3 (2-25)	3 (2-3)
Nausea	26 (6.5-113.5)	2 (1-6)

IQR: interquartile range.

rehydration and/or loperamide. Careful wound care is important to help avoid skin infections, particularly if tissue necrosis is present and results in open wounds. Injection site reactions (*e.g.* pain, erythema or swelling) may occur after talimogene laherparepvec administration, but these tend to resolve quickly (within 24-48 hours).

Grade 3/4 AEs that occurred in stage IIIB-IVM1a patients during talimogene laherparepvec treatment included pain in the extremities (2.5%), injection site pain (1.8%), and cellulitis (1.8%) [24] (*table 3*). Acetaminophen, combined acetaminophen/codeine or NSAIDs can be used to manage pain, while any sign of bacterial skin infection should be treated with appropriate antibiotics. Ice bags, anaesthetic patches or topical anaesthetic (*e.g.* 1% lidocaine) may be used if a patient has previously experienced injection site pain [37]. However, if local anaesthetic is injected, care must be taken to inject around the lesion (not directly into the tumour) to prevent altering the pH, which can affect talimogene laherparepvec stability.

Risk of viral shedding

Early clinical studies with talimogene laherparepvec suggested that seroconversion of HSV-1-negative patients occurs after approximately three to four weeks of treatment [45]. In three studies reporting shedding data, a low incidence of virus was detectable on swabs from the injection site (detectable in 3/17 [46], 1/19 [47], and 7/60 patients [48]), but no live, replication-competent virus was detected on the exterior of dressings [46, 48]. Interim results from a phase II trial (NCT02014441), specifically investigating the potential for shedding of talimogene laherparepvec in 60 patients with melanoma, indicate that transmission from treated patients to healthcare professionals and close contacts is unlikely [48]. There was one report of an investigator developing a cold sore while treating a patient in the study, but after swabbing, this was found not to contain talimogene laherparepvec DNA. Nonetheless, healthcare professionals who are immunocompromised or pregnant should not prepare or administer this agent or come into direct contact with the injection site(s) or body fluids of treated patients, as outlined in the SmPC.

Patients should be informed that, although the risk of transmission of talimogene laherparepvec is very low, they should avoid touching or scratching the injection site and use a latex condom during sexual contact for 30 days after treatment to avoid risk of transmission *via* bodily fluids [38]. Due to the relatively small number of patients who

have been treated with talimogene laherparepvec to date outside of clinical studies, recommendations in the SmPC [3] and elsewhere follow a cautious approach to avoid any potential risk. The final analysis from the study evaluating biodistribution and shedding will provide additional data. More data will also be collected in future clinical studies and through surveillance of patients undergoing treatment in clinical practice. A prospective post-marketing study (NCT02910557) aiming to characterise the risk of herpetic infection in melanoma patients treated with talimogene laherparepvec is currently open for enrolment.
Importantly, if herpes infection does occur in a patient treated with talimogene laherparepvec or following accidental exposure, this can be treated with an antiviral agent, such as aciclovir [38] or ganciclovir. Since talimogene laherparepvec retains the endogenous thymidine kinase gene, it is still sensitive to antiviral agents.

Patterns, timing and duration of response during talimogene laherparepvec treatment

Responses in injected and uninjected lesions

The anti-tumour activity of talimogene laherparepvec is in part mediated by direct oncolytic effects in injected lesions, which results in the release of tumour-derived antigens [3]. The induction of systemic anti-tumour immunity is enhanced by GM-CSF, which can help the recruitment and activation of dendritic cells [2, 49]. Dendritic cells can process and present tumour-derived antigens to promote a T-cell response against melanoma [4, 50]. Notably, in recent clinical and preclinical studies, there was evidence of a systemic increase in circulating CD4+ and CD8+ T cells [31] and increased CD8+ T-cell infiltration in uninjected tumours with talimogene laherparepvec [31, 51]. This has the potential to result in regression of uninjected lesions harbouring the same antigen as the injected tumour [52]. Indeed, patterns of response data for the ITT stage IIIB-IVM1c population of the OPTiM trial have demonstrated the local oncolytic and systemic immune effects of talimogene laherparepvec [52]. Overall, 64% (1361/2116) of evaluable injected lesions from 277 patients reduced in size by ≥50%, with 47% (995/2116) resolving completely. Of 981 uninjected non-visceral lesions from 177 patients, 34% (331/981) decreased in size by ≥50% (48% [159/331] of these were located in the same body site as injected lesions) and 22% (212/981) resolved completely. Responses were also noted in uninjected visceral lesions. Of 177 evaluable lesions from 79 patients, 15% (27/177) reduced in size by ≥50%, of which 9% (16/177) resolved completely; 81% (22/27) of responding visceral lesions were in the lung. Responses in individual injected and uninjected lesions during talimogene laherparepvec treatment are shown in *figure 2*.

Pseudoprogression

Responses to talimogene laherparepvec may occur after growth of existing lesions and/or the development of new lesions or an increase in lesion size due to a local influx of inflammatory cells [52, 53]. This phenomenon is often reported as "pseudoprogression" and such tumour dynamics have previously been noted with systemic immunotherapies, such as ipilimumab [53], nivolumab [54] or pembrolizumab [55]. In contrast, the directly cytotoxic effect of chemotherapy or the anti-proliferative effects of targeted therapies often result in measurable tumour shrinkage within a few weeks. An increase in the size of lesions during chemotherapy usually signals PD, indicating treatment failure [53].
In the stage IIIB-IVM1a subpopulation of the OPTiM study, 20 of 41 (48.8%) patients who went on to achieve a DR experienced pseudoprogression (defined as the appearance of a new lesion or ≥25% increase in total baseline tumour area) [24]. Of the 20 patients experiencing pseudoprogression, seven (35.0%) had growth of an existing lesion(s) and 13 (65.0%) developed new lesions. Importantly, data from the OPTiM trial indicate no impact of pseudoprogression on OS (*figure 3*) [56]. Furthermore, for those patients who experienced a DR during talimogene laherparepvec treatment, 80% (16/20) of those who had pseudoprogression and 86% (18/21) of subjects without pseudoprogression were still responding to treatment (*i.e.* maintaining a CR or partial response [PR]) at the time of data cut-off). Photographic images are presented in *figure 4* showing pseudoprogression in a patient receiving talimogene laherparepvec in the OPTiM trial, who subsequently achieved a DR [57].
Considering this phenomenon, it is important to try to distinguish pseudoprogression from true progression in order to avoid discontinuing or changing treatments unnecessarily. This is probably easier to ascertain in rapidly progressing, symptomatic melanoma than in slowly progressing, asymptomatic disease. According to the clinical experience of the authors, the increases in lesion size or the development of "new" lesions could be due to transient T-cell infiltration (with/without oedema) into existing measurable or non-measurable lesions [53]. This results in inflammation that although actually forms part of the therapeutic effect, could be misinterpreted as PD, which could lead to premature treatment discontinuation in a patient who might benefit from continued treatment. In line with this, some authors feel that pseudoprogression is mainly observed in injected lesions and is notably inflammatory in nature (*i.e.* may be a clinical expression of reactive inflammation). In contrast, true PD tends to be non-inflamed and associated with the rapid development of new lesions. Potential factors to aid distinguishing pseudoprogression from true progression are shown in *table 5*. Because of the potential for pseudoprogression, duration of therapy should be carefully discussed with the patient and not only based on any lesion changes/development, but also on any changes in the patient's performance status and biomarkers, for example, their serum lactate dehydrogenase and S100 levels.

Time to response and duration of treatment

The direct effects of talimogene laherparepvec mediate more rapid responses in injected lesions, whereas induction of systemic immunity *via* priming of specific T-cell responses often requires more time. In the OPTiM study, the median time to response was approximately four months

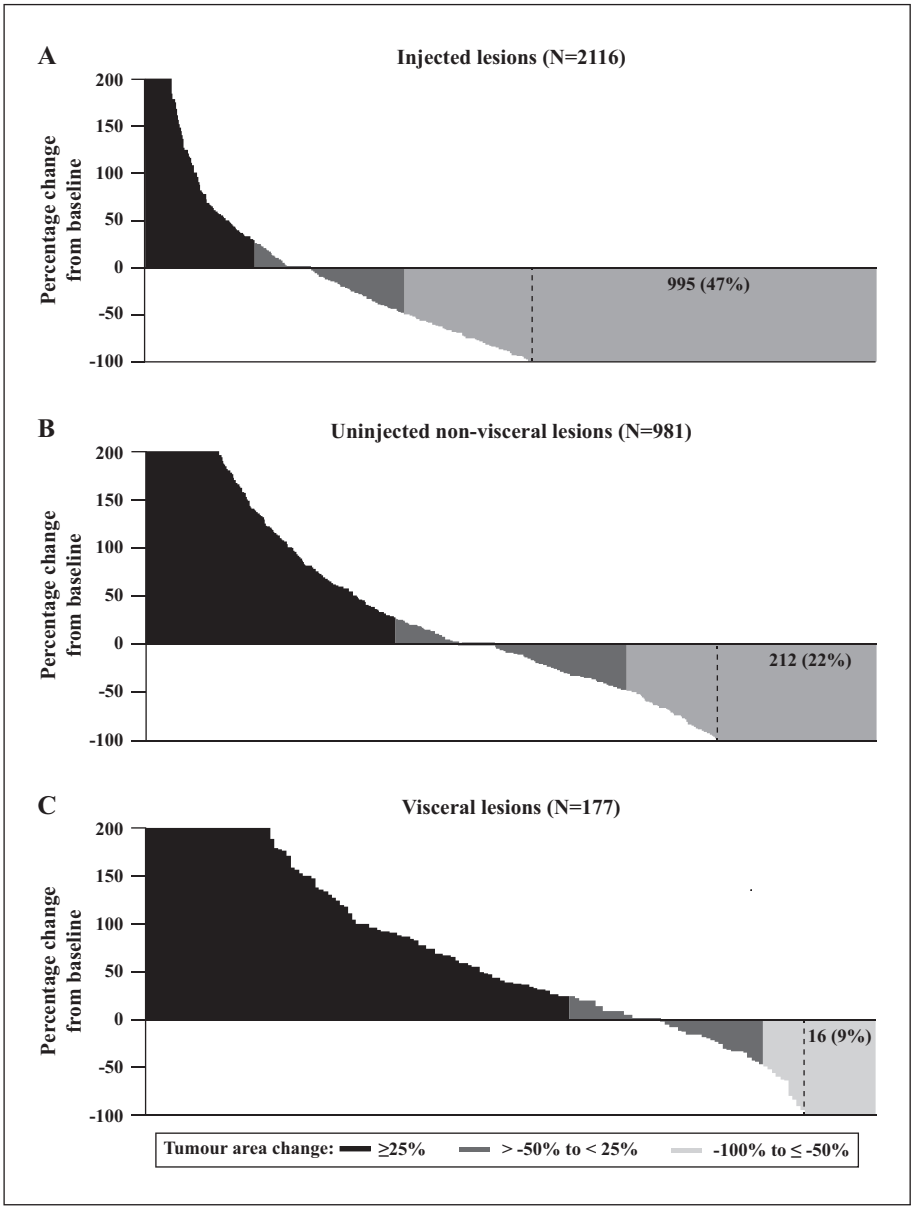

Figure 2. Responses in injected and uninjected lesions during talimogene laherparepvec treatment for individual **(A)** injected lesions; **(B)** uninjected lesions; and **(C)** visceral lesions (also uninjected) (based on a stage IIIB-IVM1c intent-to-treat population from the OPTiM trial). Vertical axis depicts maximal change in individual tumour lesion size (products of the two large perpendicular diameters) from baseline [52] (originally published under the terms of the Creative Commons Attrition 4.0 International License [https://creativecommons.org/licenses/by/4.0/]).

[5, 24]. However, the median time to response was approximately three weeks shorter in injected (9.3 weeks) *versus* uninjected non-visceral (12.9 weeks) and uninjected visceral (12.3 weeks) lesions. Time to DR onset was also delayed with talimogene laherparepvec in those with pseudoprogression (responses being initiated after five to six months compared with approximately three months in those without pseudoprogression) (*table 6*) [52, 56].

Because of this effect and its mode of action, the talimogene laherparepvec SmPC [3] states that treatment should continue for at least six months to allow for delayed immune-mediated anti-tumour activity to occur. For example, the median time to CR in the OPTiM ITT population was 8.6 months (range: 2.1-42.3) (*table 6*, *figure 5*) [25]. In line with this, treatment should be continued for at least six months as long as there are injectable lesion(s), unless the physician considers that a patient is not benefitting from talimogene laherparepvec treatment or that other treatment is required, as described in the SmPC [3]. However, the authors acknowledge that response is assessed every 12 weeks as standard-of-care, and in clinical practice, observations noted at these patient visits will provide guidance on management. For patients with bulky disease or those showing clinical deterioration, a decision to discontinue or switch treatment may be made before six months. Treating physicians, in conjunction with the MDT, should use their clinical judgement to decide when to stop talimogene laherparepvec therapy, based on how the patient tolerates

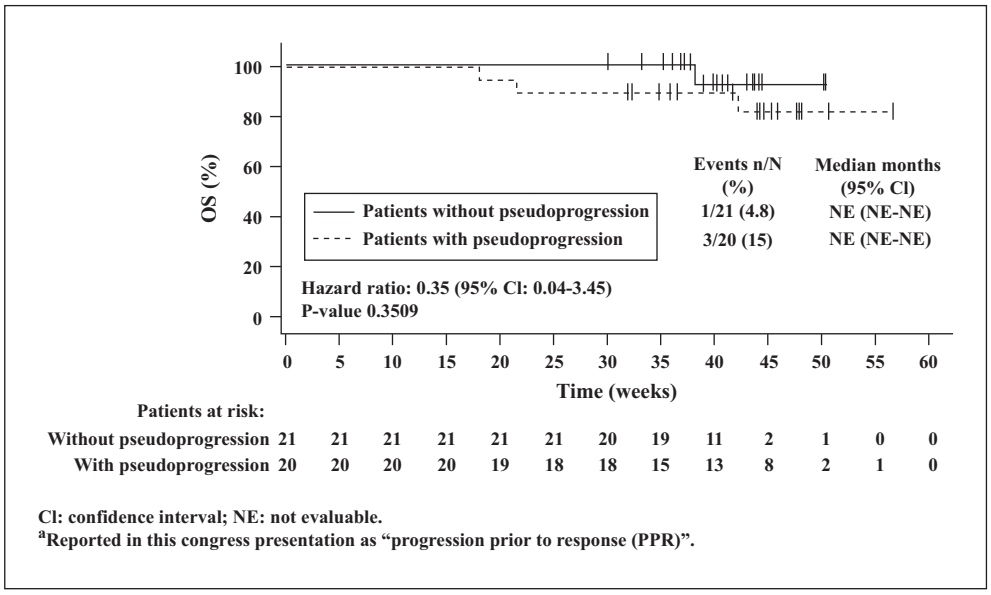

Figure 3. Overall survival (OS) by pseudoprogression[a] status in patients experiencing a durable response (based on a stage IIIB-IVM1a subpopulation from the OPTiM trial) [56].

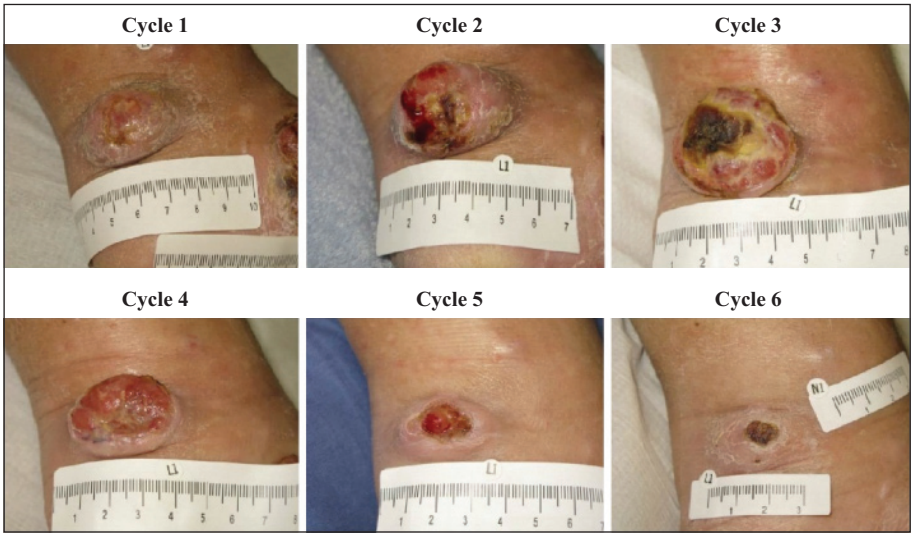

Figure 4. Photographic images demonstrating pseudoprogression in an injected lesion in a patient receiving talimogene laherparepvec, who subsequently achieved a durable response [57]. Images reproduced with the permission of Professor Kevin Harrington, NIHR Biomedical Research Centre, The Royal Marsden Hospital/The Institute of Cancer Research, London, UK, and with informed consent of the patient. A treatment cycle is defined as two consecutive administrations of talimogene laherparepvec (five weeks for the first cycle and four weeks for each subsequent cycle).

Table 5. Potential factors to aid distinguishing pseudoprogression from true disease progression.

Pseudoprogression	True progression
Minor increase in lesion size (<30%)	Major increase in lesion size (>30%)
Inflammatory reaction with oedema	Increased lesion firmness
Few new small lesions (<1 cm)	Multiple new large lesions (>1 cm)
Stable serum S100 levels[a]	Increasing serum S100 levels[a]
Stable serum LDH levels[a]	Increasing serum LDH levels[a]
Stable performance status	Deteriorating performance status

LDH: lactate dehydrogenase.
[a] Serum S100 and LDH levels should be assessed before treatment and then according to local institutional guidelines.

Table 6. Median time to overall response, complete response and durable response in talimogene laherparepvec-treated patients from the OPTiM trial.

	Stage IIIB-IVM1a subpopulation ($n = 163$) [24, 56], median (months)	Stage IIIB-IVM1c (ITT) population ($n = 295$) [5, 25], median (months)
Time to overall response (95% CI)	4.0 (3.2-5.0)	4.1 (1.2-16.7)
Time to complete response (range)	Data not available	8.6 (2.1-42.3)
Time to durable response (range)		
Without pseudoprogression[a]	3.1 (1.2-8.5)	3.1 (1.2-9.5)
With pseudoprogression[a]	5.1 (1.3-10.2)	5.8 (1.3-10.6)

CI: confidence interval; ITT: intent-to-treat.
[a] *Reported in this congress presentation as "progression prior to response" (PPR).*

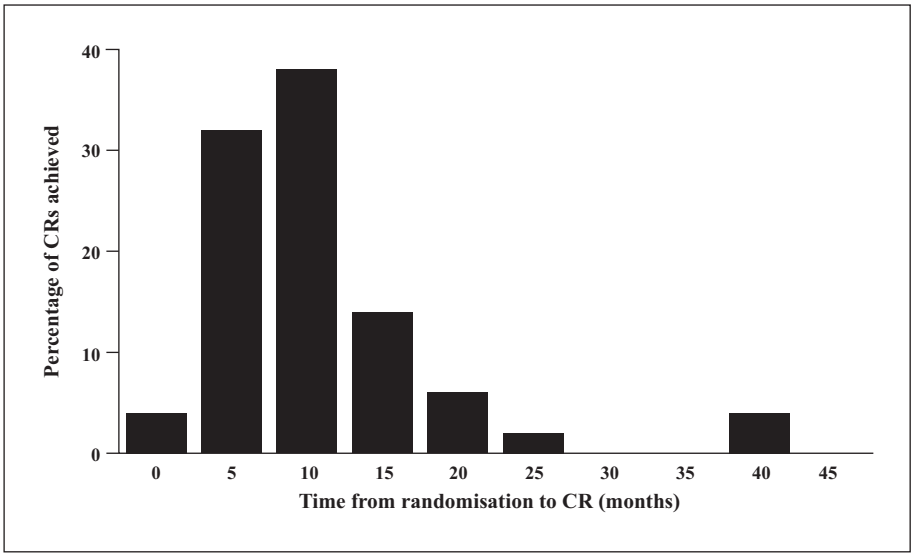

Figure 5. Time to complete response (CR) in patients treated with talimogene laherparepvec (based on a stage IIIB-IVM1c intent-to-treat population from the OPTiM trial) [25]. Median time to CR was 8.6 months (range: 2.1-42.3).

treatment and an overall assessment of their disease status, including any signs of clinical deterioration.

Duration of response

The duration of response (DoR) with talimogene laherparepvec can be prolonged. In the phase III OPTiM trial, more than 50% of responders with stage IIIB-IVM1a melanoma had a continuous DR lasting six months or longer [24]. At the time of data cut-off, 34/41 (83%) patients with DR were still in response [52]. The median DoR and duration of CR were not reached in this early metastatic population. In patients with stage IIIB-IVM1c melanoma (ITT population) who achieved a CR per investigator ($n = 50$) based on the final analysis, 41 CRs were still ongoing at the time of the last visit and the probability of remaining in CR after 18 months from the start of CR was 78% (95% CI: 59-89%) [25].

Assessment of response

In the clinic, response to talimogene laherparepvec (and other immunotherapies) is currently assessed by clinical examination of cutaneous lesions and/or tumour pathology (biopsies) alongside the imaging techniques used to evaluate other anticancer therapies *e.g.* positron emission or computed tomography/magnetic resonance imaging and ultrasound.

Conventional criteria for response, such as the Response Evaluation Criteria in Solid Tumours (RECIST) [58, 59] or World Health Organization (WHO) [60] criteria, were originally designed to detect early anti-tumour activity of cytotoxic agents. Immunotherapy, however, is associated with pseudoprogression, which would be classified as PD according to RECIST or WHO criteria. As pseudoprogression does not always signal treatment failure, new criteria for assessing response have been developed [59] and utilised, which allow for the patterns of response seen with immunotherapy to be better evaluated [53, 61-64]. For example, immune-related response criteria (irRC) were developed in an attempt to overcome these issues and may potentially be useful in guiding clinical care [53]. The main differences between irRC and RECIST or WHO criteria are the inclusion of measurable new lesions in the total tumour burden, a comparison of this with bidimensional baseline, and nadir (minimum recorded tumour burden) measure-

ments and confirmation of PD (irPD) at least four weeks after the date when PD was first documented [53]. More recently, irRC have been used to adapt the more commonly used and simpler RECIST 1.1, which requires tumour imaging measurements across only one dimension instead of two [61, 63]. The first adaptation of RECIST (irRECIST) aimed to allow for treatment evaluations and assessments that better meet investigator/patient needs, as well as reduce ambiguity of assessment criteria and minimise discordance between investigator and central independent image review [61]. As with irRC, irRECIST incorporates new lesions into the total tumour burden and includes two consecutive imaging assessments to account for delayed response, but unlike irRC, its thresholds for PD and PR are aligned with RECIST 1.1. The latest iteration of these criteria (iRECIST) was recently published [64].

Summary and future directions

Talimogene laherparepvec monotherapy is an effective and well-tolerated treatment option for patients with unresectable, early metastatic (stage IIIB-IVM1a) melanoma who have lesions that are accessible for intratumoural injection. Its novel mechanism of action includes both a local oncolytic and a systemic immune effect leading to responses in injected and uninjected lesions and the potential for durable disease control. Importantly, in the early metastatic, unresectable population, the high CR rate (16.6%) and sustainable responses (>50% lasting for ≥6 months) observed also appear to translate into OS benefits, with the estimated five-year survival for responders being 78% [24].

Although systemic treatment may be preferred for patients with unresectable melanoma, there are some clinical situations in which the MDT may consider talimogene laherparepvec or locoregional therapy as additional treatment options for selected groups of patients. For example, talimogene laherparepvec may be suitable for patients in whom surgery is not an option (*e.g.* for cutaneous head and neck melanoma for which surgery is technically challenging and the cosmetic effects are likely to be undesirable, or in patients with in-transit metastases or multiple metastases at different body locations) as well as in patients with slow disease kinetics. Furthermore, the favourable toxicity profile of talimogene laherparepvec may make it well suited to some patients with a poor performance status, elderly patients with comorbidities, and those who cannot tolerate systemic therapy. The pattern of AEs during treatment with talimogene laherparepvec is distinct and contrasts with that seen with other immuno-oncology products. Treatment-emergent AEs seen with talimogene laherparepvec are mostly low grade, easy to manage, and rarely lead to treatment discontinuation. Although there are specific requirements for the storage, handling, administration, and disposal of talimogene laherparepvec, these can be efficiently managed in the clinic through the implementation of training programmes and by establishing straightforward institutional guidelines. Furthermore, the risk of viral shedding is low if SmPC guidance [3] is followed.

The favourable tolerability profile of talimogene laherparepvec and its likely complementary mode of action mean that it may be particularly well suited to use in combination with other agents. As talimogene laherparepvec treatment leads to increased T-cell infiltration in both injected and uninjected lesions, it could potentially make non-inflamed tumours more amenable to treatment with systemic immunotherapy. Studies are currently evaluating this agent in combination with the immune checkpoint inhibitors, ipilimumab (NCT01740297) and pembrolizumab (NCT02263508), for melanoma as well as other solid tumours [9]. Results so far for stage IIIB-IVM1c melanoma suggest that combination therapy has greater efficacy than either ipilimumab [65] or pembrolizumab [31] alone, and that these combination treatments are well tolerated. Analyses according to disease stage have been predefined in these studies and results have so far demonstrated benefits in ORR for combination *versus* ipilimumab treatment for both stage IIIB-IVM1a (44% *versus* 19%) and stage IV1b-c (33% *versus* 16%) populations [65].

In conclusion, talimogene laherparepvec – the first approved oncolytic immunotherapy – represents an effective, well tolerated, and innovative treatment option for patients with unresectable, early metastatic melanoma (stage IIIB-IVM1a). Ongoing studies will further define which patients may be best suited to treatment with this agent as well as optimal use in the clinic, for instance, when it should be used within the sequence of treatments and its potential use in combination with other therapies. ■

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consulting and/or advisory relationships with Amgen, BMS, MSD, Novartis, Pierre Fabre, Roche, and Takeda, outside the submitted work.

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