

Efficacy of Talimogene Laherparepvec (T-VEC) in Melanoma Patients (Pts) with Locoregional (LR) Recurrence, Including In-transit Metastases (ITM): Subgroup Analysis of the Phase 3 OPTiM Study

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INTRODUCTION

- Talimogene laherparepvec (T-VEC) is a first-in-class herpes simplex virus type-1 (HSV-1)–derived oncolytic immunotherapy designed to preferentially replicate in tumours, produce granulocyte-macrophage colony-stimulating factor (GM-CSF), and stimulate antitumor immune response¹
- In the OPTiM phase 3 study, T-VEC, injected into cutaneous/subcutaneous melanoma lesions or lymph node metastases, was compared (2:1) with subcutaneously administered GM-CSF in 436 patients with stage IIIB–IV unresectable melanoma²
- T-VEC was efficacious and well tolerated in OPTiM. An objective response rate (ORR) of 26% was reported in patients with unresectable stage IIIB–IVM1c melanoma (median follow-up: 44 months). Exploratory subgroup analysis demonstrated an improved ORR (40.5%) in patients with earlier metastatic disease (IIIB/C and IVM1a),^{3,4} which represented around half of the patients in OPTiM
- In-transit melanoma metastases (ITM) represent a distinct disease pattern, whereby the disease recurs as dermal or subcutaneous nodules between the primary melanoma site and the regional lymph node basin
- After surgical therapy for primary melanoma, approximately 4–10% of patients develop ITM⁵
- Preliminary real-world data suggest that T-VEC may have an improved effect in patients with ITM,⁵ however, data from controlled clinical trials are lacking
- This retrospective analysis of the phase 3, randomised, controlled OPTiM trial assessed T-VEC in patients with unresectable melanoma who had ITM (with or without regional lymph node metastases) as the first recorded recurrence after primary surgery

METHODS

Key Inclusion Criteria

- The full inclusion/exclusion criteria for OPTiM have ben reported previously²
- This retrospective analysis included patients from the OPTiM trial who had stage IIIB/C melanoma (per AJCC 7th edition) and ITM (defined as patients with in-transit disease, satellitosis or surgical scar as the site of first recurrence after primary surgery) or ITM and regional lymph node metastases
 - Regional lymph nodes could have been recorded as site of first recurrence or at baseline
- A difference from the submitted abstract is that this analysis excludes patients with distant lymph node metastases or visceral disease at the time of first recurrence or enrolment into OPTiM. As a consequence, versus the submitted abstract, this current analysis removes 39 patients (28 in the T-VEC arm; 11 in the GM-CSF arm) who were found to have distant lymph node metastases or visceral disease
- Analyses were conducted separately for the two following patient subgroups:
 - Patients with ITM as site of first recurrence only WITHOUT regional lymph node metastases
 - Patients with ITM as site of first recurrence AND regional lymph node metastases

Assessments

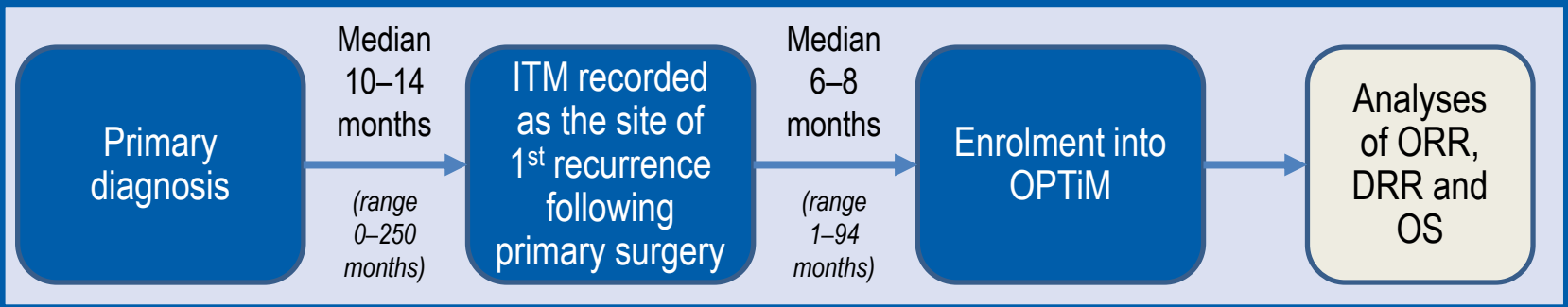
- Assessments reported here include analyses of ORR, durable response rate (response lasting ≥6 months) and overall survival (OS) using the primary OPTiM data set (cut-off March 31 2014 for OS)
- Clinical response was evaluated using the modified World Health Organization criteria. Patients with a response per investigator were evaluated by a blinded endpoint assessment committee
- OS was defined as the time from random assignment to death from any cause
- All efficacy analyses reported here are descriptive, as multiple comparisons were not controlled for. Patients were analysed per the intent-to-treat population (all patients randomised to study treatment)

RESULTS

Patient disposition

- Overall, 70 patients were included with ITM as the first recorded site of recurrence after primary surgery: 47 patients without nodal metastases and 23 patients with lymph node metastases (Table 1)
- Median time from diagnosis to the first recorded recurrence was 10–14 months across groups; median time from first recurrence to randomisation into OPTiM was 6–8 months across groups (Figure 1)

Figure 1. Timing of ITM Occurrence Following Diagnosis and prior to OPTiM



RESULTS (CONTINUED)

Table 1. Timing and Location of First Melanoma Recurrence after Primary Surgery

	ITM as site of 1st recurrence (NO lymph node involvement)		ITM as site of 1st recurrence AND regional lymph node metastases	
	T-VEC (n = 31)	GM-CSF (n = 16)	T-VEC (n = 20)	GM-CSF (n = 3)
Anatomic location of primary melanoma ^a – n(%)				
Scalp, face and neck	8 (26)	4 (25)	7 (35)	0
Trunk	5 (16)	2 (13)	2 (10)	1 (33)
Upper limb	4 (13)	1 (6)	2 (10)	1 (33)
Lower limb	14 (45)	9 (56)	9 (45)	1 (33)
Other	1 (3)	0	0	0
Time from initial diagnosis to first recurrence – median (range), months	11 (4, 250)	12 (0, 110)	14 (0, 144)	10 (5, 26)
Description of first recurrence – n (%)				
In-transit/satellitosis only	24 (77)	11 (69)	10 (50)	0
Surgical scar only	5 (16)	5 (31)	6 (30)	1 (33)
In-transit/satellitosis and surgical scar	2 (7)	0	1 (5)	0
In-transit/satellitosis and RLN	0	0	1 (5)	0
Surgical scar and RLN	0	0	1 (5)	0
In-transit/satellitosis and surgical scar and RLN	0	0	1 (5)	2 (67)
Time from date of first recurrence to randomisation into OPTiM – median (range), months	7 (1, 92)	6 (1, 35)	8 (1, 94)	7 (1, 16)

^aThe categories are not mutually exclusive. ITM, in-transit melanoma metastases; RLN, regional lymph node(s)

Baseline Characteristics

- Baseline characteristics of patients at the time of patient enrolment into OPTiM are shown in Table 2.

Table 2. Baseline Characteristics at Time of Enrolment into OPTiM

	ITM as site of 1st recurrence (NO lymph node involvement)		ITM as site of 1st recurrence AND regional lymph node metastases	
	T-VEC (n = 31)	GM-CSF (n = 16)	T-VEC (n = 20)	GM-CSF (n = 3)
Age – median (range), years	70 (36, 94)	75 (28, 91)	62 (41, 88)	60 (56, 68)
Male – n (%)	14 (45)	6 (38)	9 (45)	2 (67)
Disease stage per AJCC 7 – n (%)				
Stage IIIB	8 (26)	5 (31)	7 (35)	0
Stage IIIC	23 (74)	11 (69)	13 (65)	3 (100)
ECOG PS – n (%)				
0	24 (77)	12 (75)	17 (85)	2 (67)
1	7 (23)	4 (25)	3 (15)	1 (33)
LDH – n (%)				
≤ ULN	29 (94)	16 (100)	19 (95)	3 (100)
> ULN	1 (3)	0	0	0
Missing	1 (3)	0	1 (5)	0
BRAF mutation status – n (%)				
Mutation	6 (19)	4 (25)	0	1 (33)
Wildtype	5 (16)	2 (13)	3 (15)	1 (33)
Unknown	0	1 (6)	2 (10)	0
Missing	20 (65)	9 (56)	15 (75)	1 (33)
Line of therapy – n (%)				
First line	23 (74)	11 (69)	10 (50)	1 (33)
Second line or greater	8 (26)	5 (31)	10 (50)	2 (67)

AJCC: American Joint Committee on Cancer; ECOG PS: Eastern Cooperative Oncology Group performance status; ITM: in-transit melanoma metastases; LDH: lactate dehydrogenase; ULN: upper limit of normal.

Response Rates

- In patients with ITM, but no regional lymph node involvement, the ORRs were 81% versus 0% with T-VEC versus GM-CSF, respectively (p<0.001; Table 3). For T-VEC versus GM-CSF:
 - The complete response rate was 36% versus 0%, respectively (p=0.009)
 - The durable response rate was 52% versus 0%, respectively (p<0.001)
- In patients with ITM AND regional lymph node metastases, since the patient numbers were small (with just 3 patients receiving GM-CSF) it was not possible to conduct meaningful statistical comparisons of the treatment arms. Nevertheless, response rates were numerically higher for T-VEC versus GM-CSF (Table 3). No patients receiving GM-CSF achieved a complete or durable response. In contrast, 25% and 35% of T-VEC patients achieved a complete and durable response, respectively

Table 3. Response Rates

	ITM as site of 1st recurrence (NO lymph node involvement)			ITM as site of 1st recurrence AND regional lymph node metastases	
	T-VEC (n = 31)	GM-CSF (n = 16)	95% CI for difference ^a (p value ^b)	T-VEC (n = 20)	GM-CSF (n = 3)
Overall response rate – n (%)	25 (81)	0	67, 95 (p<0.001)	12 (60)	1 (33)
Complete response	11 (36)	0	19, 52 (p=0.009)	5 (25)	0
Partial response	14 (45)	0	–	7 (35)	1 (33)
Median time to response ^c , months (Q1, Q3)	4 (3, 6)	0	–	4 (3, 5)	2 (2, 2)
Durable response rate – n (%)	16 (52)	0	34, 69 (p<0.001)	7 (35)	0

^aBinomial proportion with asymptotic 95% CI; ^bCalculated using Fisher's Exact Test; ^cTime to response is calculated from the randomisation date to the date of an initial response (complete response + partial response); CI, confidence interval; ITM, in-transit melanoma metastases; Cut-off for response analyses was December 21, 2012

Overall Survival

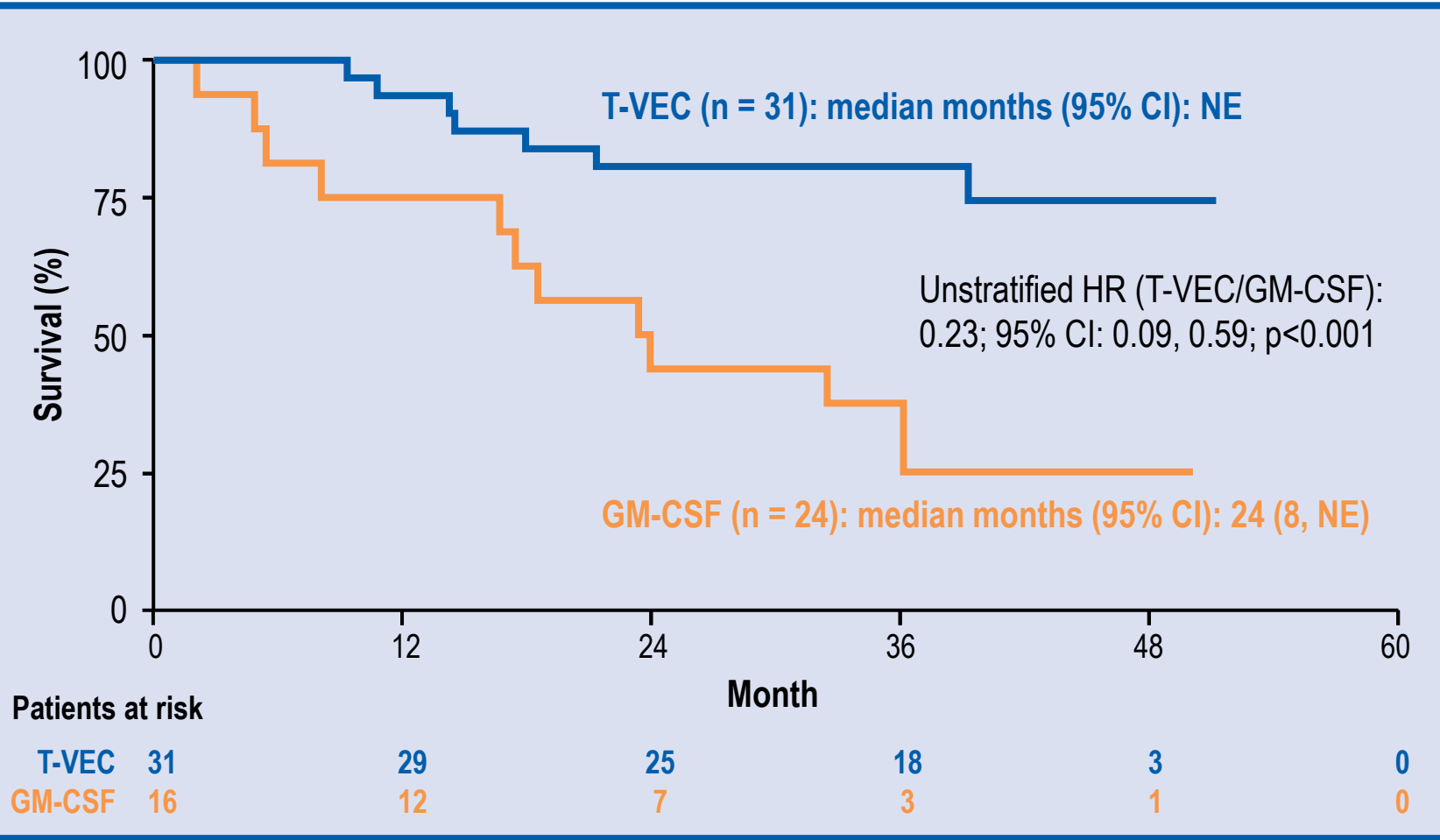
- In patients with ITM, but no regional lymph node involvement, median OS was not reached for T-VEC versus 24 months with GM-CSF, respectively. Reduction in the risk of death was 77% with T-VEC versus GM-CSF (hazard ratio [HR] 0.23; p<0.001; Figure 2)
 - Estimated 4-year survival was 74% versus 25% for T-VEC versus GM-CSF, respectively
- Patient numbers were limited in patients with ITM AND regional lymph node metastases. In this group, median OS was not estimable for either T-VEC or GM-CSF

Table 4. Kaplan-Meier Estimates of Overall Survival Probability at Landmark Times

	ITM as site of 1st recurrence (NO lymph node involvement)			ITM as site of 1st recurrence AND regional lymph node metastases		
	T-VEC (n = 31)	GM-CSF (n = 16)	Treatment difference	T-VEC (n = 20)	GM-CSF (n = 3)	Treatment difference
All values are %, 95% CI						
At 12 months	94 (77, 98)	75 (46, 90)	19 (–4, 42)	95 (70, 99)	100 (–)	–5 (–)
At 24 months	81 (62, 91)	44 (20, 66)	37 (9, 65)	85 (60, 95)	67 (5, 95)	18 (–37, 74)
At 36 months	81 (62, 91)	38 (15, 60)	43 (16, 71)	80 (55, 92)	67 (5, 95)	13 (–43, 70)
At 48 months	74 (52, 88)	25 (6, 52)	49 (19, 80)	64 (26, 86)	67 (5, 95)	–3 (–65, 59)

CI, confidence interval ; ITM, in-transit melanoma metastases

Figure 2. Kaplan-Meier Plot of Overall Survival in Patients with ITM as Site of First Recurrence Following Primary Surgery (NO Lymph Node Metastases)*



Patients not recorded as dead have been censored
^aData not shown for patients with ITM and regional lymph node metastases due to limited patient numbers
CI, confidence interval; HR, hazard ratio; ITM, in-transit melanoma metastases

CONCLUSIONS

- Although this retrospective analysis of the phase 3 OPTiM trial has limitations, the efficacy observed with T-VEC monotherapy in patients with ITM as the recorded site of first recurrence was higher than that observed with T-VEC in the overall population of OPTiM²
- In T-VEC-treated patients with ITM (without lymph node metastases) as site of first recurrence, we observed an ORR of 81% and complete response rate of 36%. In comparison, in the overall OPTiM population (stage IIIB-IV melanoma), the ORR was 26% and CR rate was 11%²
- Due to the small numbers of patients in our analysis, it is not possible to draw conclusions regarding patients with ITM as site first recurrence and regional lymph node metastases. Further investigation of T-VEC is required in this patient group
- This post-hoc analysis suggests that T-VEC may be of particular benefit in patients with ITM. Further investigation of T-VEC is warranted in patients with ITM as part of their disease journey

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DISCLOSURES

- Middleton M – has acted as a consultant for Amgen, AstraZeneca, Bristol-Myers Squibb, Eisai, GlaxoSmithKline, Immunocore, Lilly, Merck, Millennium, Novartis, Physiomics, Rigontec, and Roche; his institution has received research grants from Abbvie, Amgen, AstraZeneca, Bristol-Myers Squibb, Clovis, Eisai, GlaxoSmithKline, Immunocore, Merck, Millennium, Novartis, Pfizer, Rigontec, Roche, and Vertex
- Harrington K – has received consulting or advisory fees from Amgen, AstraZeneca, BMS, Merck, and Pfizer; his institution has received research grants from AstraZeneca and MSD; has served on speaker bureaus for Amgen, AstraZeneca, BMS, Merck, and MSD
- Ross M - honoraria from, consultant/advisor for, and travel expenses from Merck and Amgen; speakers' bureau for Merck; research funding from Amgen
- Öhrling K and Radcliffe H-S – employees and stock holders of Amgen
- Collichio F – her institution is receiving research support from Amgen, Merck and Novartis. A portion of this support is used for her salary

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