Defining optimal oncolytic virus treatment and diagnostics in high risk melanoma patients

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CHAPTER 4

Single agent Talimogene Laherparepvec for stage IIIB-IVM1c melanoma patients: a systematic review and meta-analysis

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ABSTRACT

Single-agent Talimogene Laherparepvec(T-VEC) was developed for treatment of unresectable and injectable stage III-IV melanoma. Since its approval and reimbursement, studies have reported varying response rates. The purpose of this systematic review and meta-analysis was to investigate the efficacy and safety of T-VEC. Of 341 publications that were identified, eight studies with a total of 642 patients were included. In patients with stage IIIB-IVM1a, the pooled complete- and overall response rate(CRR and ORR) were 41% and 64%, respectively. In patients with stage IIIB-IVM1c, the pooled CRR and ORR were 30% and 44%, respectively. In patients with stage IVM1b and IVM1c, the pooled CRR and ORR were 4% and 9%, respectively. Adverse events(AEs) were seen in 41 – 100% of all patients and 0 – 11% of AEs were severe. In conclusion, single agent T-VEC achieves the highest response rates in patients with early metastatic melanoma and is well-tolerated with generally only mild toxicities.

INTRODUCTION

Over the past decade, significant advances have been made in anti-cancer therapy for patients with metastatic melanoma. Successful results have been reported for the use of immune checkpoint inhibitors that block programmed death-1 (PD-1, pembrolizumab and nivolumab) or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4, ipilimumab), first for stage IV patients, and only recently for adjuvant treatment of patients with stage III disease[1-4]. Relatively new and derived from herpes simplex virus type-1 is treatment with Talimogene Laherparepvec (T-VEC), which has a dual mechanism of action: a direct oncolytic effect as well as an immunotherapeutic effect. It is administered intralesionally and used in melanoma patients with cutaneous, subcutaneous and nodal metastases. After injection, it is designed to selectively replicate in tumor cells, causing cell lysis and cell death. In Addition to this this local effect, the release of replicated viruses subsequently promotes the release of tumor-derived antigens and production of granulocyte-macrophage colony stimulating factor (GM-CSF), which in turn also stimulates the systemic anti-tumor response[5-8]. Efficacy can therefore be observed in both injected and non-injected lesions[9].

The OPTiM trial, a randomized phase III trial comparing intralesional T-VEC with subcutaneous GM-CSF in patients with unresectable stage IIIB-IV melanoma, was the first to report that treatment with T-VEC resulted in a prolonged median overall survival (OS, 23.3 vs. 18.9 months; p=0.051) and improved overall response rate (ORR, 26% vs. 6%, p<0.001), compared to those treated with GM-CSF. Also, subgroup analysis demonstrated more pronounced effects of T-VEC versus GM-CSF in stage IIIB-IVM1a melanoma (ORR 46% vs. 5% and OS 46.8 vs. 21.5 months) compared to stage IVM1b-c melanoma (ORR 14% vs. 9% and OS 13.4 vs. 15.9 months). In this trial, T-VEC was well tolerated and the most reported adverse events (AEs) were fatigue, chills, pyrexia, influenza-like illness, and nausea; most of which were self-limiting[10, 11]. Based on these results, its use was approved by the Food and Drug Administration (FDA) at the end of 2015. Subsequently, T-VEC was also approved by the European Medicines Agency (EMA) for patients with stage III-IVM1a disease, as this subgroup had the best results.

Since its approval, the real-world response- and AEs to T-VEC have been investigated in several (mostly non-randomized) studies performed in research centers across the United States of America (USA) and Europe. Although these studies seem alike (they all investigate single agent T-VEC therapy in stage III and/or IV disease), study results differ[12-14]. Moreover, most studies have only limited patient numbers, making it difficult to draw significant conclusions.

Therefore, we performed a systematic review and meta-analysis for treatment with single agent T-VEC in patients with stage IIIB-IV melanoma, in order to objectively assess clinical efficacy- and toxicity outcomes of prospective clinical trial(s) and real-world (non-randomized) cohort studies.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were used for this systematic review and meta-analysis[15]. There was no protocol prepared for this study.

Eligibility criteria

Studies investigating single agent T-VEC in patients with stage IIIB to IV disease were included. Patients had to be treated according to the manufacturer's (AMGEN Inc, Thousand Oaks, CA) therapy guidelines and recommendations. Included were phase III randomized controlled trials (RCT), prospective and retrospective studies, and case series providing efficacy-, survival with or without safety outcomes, using the English language.

Exclusion criteria were phase I and II clinical trials, case reports, studies investigating uveal and mucosal melanoma and studies that included patients that were concurrently treated with T-VEC and other drugs. If more than one publication referred to the same study, presenting either more follow-up data or results from a larger population, only the most recent publication was included. Unpublished manuscripts and conference abstracts were excluded.

Search strategy and study selection

Studies were identified by a search in the PubMed and Embase database. In Pubmed a combination of Medical Subject Headings (MeSH) and keywords related to our literature search was used: ("Melanoma"[MeSH Terms] OR "Melanoma" [tiab]) AND "Talimogene Laherparepvec"[tiab] AND ("Treatment Outcome"[MeSH Terms] OR "Survival Analysis"[MeSH Terms] OR "response"[All Fields] OR "survival"[All Fields] OR "OS"[All Fields] OR "toxicit*"[All Fields] OR "adverse event*"[All Fields] OR "safety"[All Fields]). In Embase, the following search was used: ("Melanoma"/exp OR "Melanoma":ti,ab,kw) AND ("Talimogene Laherparepvec":ti,ab,kw) AND ("treatment outcome"/exp OR "Survival Analysis"/exp OR ("response" OR "survival" OR "OS" OR "toxicit*" OR "adverse event*" OR "safety")) NOT ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it). Both searches took place on the 23rd of April 2021.

All duplicate records found in PubMed and Embase were excluded. Titles and abstracts were screened by one reviewer, for all articles identified by PubMed

or Embase. Only those articles that met the inclusion criteria or where a clear decision could not be made were fully reviewed. Subsequently, the full text of the remaining studies was reviewed. In case of doubt, a second reviewer was asked for an opinion.

Data analyses and outcome measures

To assess the eligibility and methodological quality (risk of bias) of the selected papers prior to inclusion, two independent reviewers (EM and ES) used the Joanna Briggs Institute (JBI) Critical Appraisal Checklist[16]. Disagreements were discussed until a consensus was reached.

Efficacy outcomes included response- and survival rates to T-VEC, including: complete response rate (CRR), partial response rate (PRR), stable disease rate (SDR), progressive disease rate (PDR), ORR and durable response rate (DRR). The ORR was the sum of CRR and PRR. ORR was calculated for studies that yielded a PRR and CRR, but reported no ORR. DRR is the percentage of patients with a complete response (CR) or partial response (PR) for at least 6 months, starting within 12 months after treatment initiation. CRR, PRR, SDR, PDR, ORR, and DRR are expressed as proportions or percentages. Survival outcomes included OS and progression-free survival (PFS).

CRR and ORR were further analyzed using both the 7th and 8th editions of the American Joint Committee on Cancer (AJCC) disease staging system. Safety outcomes included all reported AEs. When graded, we also report grade 3 – 4 AEs.

Meta-analyses of CRR and ORR were performed, in order to obtain pooled estimates of these outcomes, both overall (i.e. stage IIIB-IVM1c), and by stage (i.e. stage IIIB-IVM1a and stage IVM1b&IVM1c).). Studies' results were pooled through the inverse variance method (a sensitivity analysis was conducted considering a different pooling method, i.e. generalized mixed model). A random effects model, allowing for between-study variation, was adopted, and heterogeneity was assessed through I^2 and τ^2[16, 17]. A 0% value indicated no heterogeneity, and higher values represented an increase in heterogeneity; an I^2 bigger than 75% indicates a considerable heterogeneity. The R package meta was used to perform the meta-analyses[18].

RESULTS

A total of 342 publications were identified, of which 151 were duplicates and were therefore excluded. After screening the abstract and title, 173 additional publications were excluded. Most studies were found the be ineligible because

the outcomes of interest were not measured. For the remaining 18 publications, full-text reviews were performed. Eight studies, with a total of 642 patients (range: 14 – 295), met the inclusion criteria and were included in this review. An overview of the in- and excluded articles is provided in a flow diagram in Figure 1. Questions and results of the JBI checklist are provided in the supplementary file.

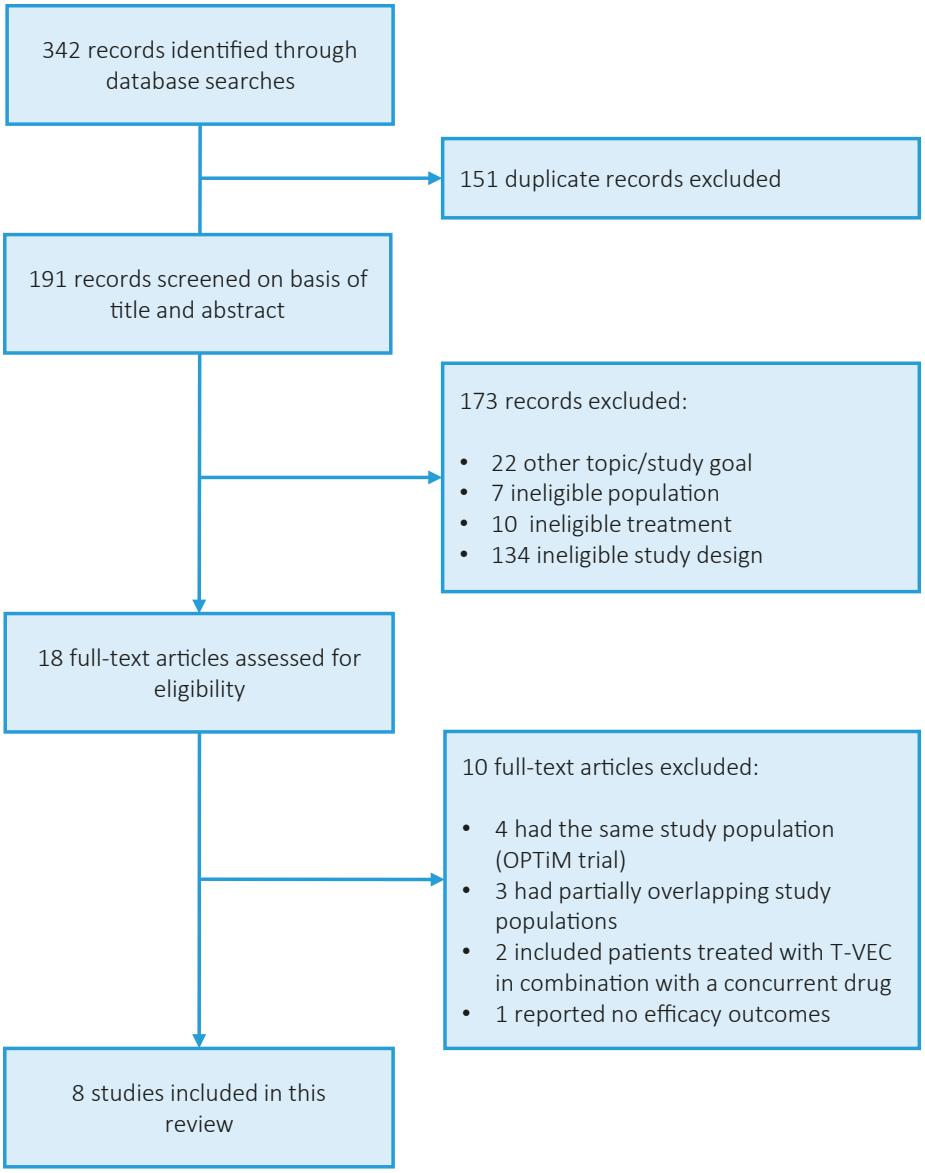

Figure 1. *An overview of the in- and excluded articles*

The extracted data, comprising study and patient characteristics and efficacy, survival and safety outcomes, are outlined in Table 1. All studies were published between 2015 and 2021. Most studies were retrospective cohort studies (n=6), one was a prospective cohort study and one was a randomized phase III trial. Studies were either performed in Europe or in the USA. Median age of patients was 70 years and the median follow-up was 10 months (range 7 – 49 months). Study populations were heterogeneous; in all but two studies, patients were staged according to the AJCC 7thedition, three studies included only patients with IIIB-IVM1a disease and five also included patients with >IVM1a. In addition, studies included both treatment-naïve and pre-treated patients with metastatic melanoma (47% of patients were treated with systemic therapy prior to T-VEC treatment).

All studies presented a low risk of bias. The question: 'Was there clear reporting of the presenting site(s)/clinic(s) demographic information?' was considered not applicable for six studies because they did not address this specific information (except for women vs. men) (table S1.)

Due to the small number of included studies, an assessment of a small-studies effect (and publication bias) with formal tests or with funnel plots was not possible[19].

Response rates

In three studies, efficicacy was assessed according to the World Health Organization criteria (Andtbacka, Perez, Stahlie) and in one study according to the Response Evaluation Criteria In Solid Tumors (RECIST) v1.1, which is a radiological assessment (Zhou)[20, 21]. The other studies did not describe how they assessed response rates. In two studies (Mohr, van Akkooi), part of the included patients was still on treatment at the time of response analysis, so efficacy outcomes were calculated over those who had completed treatment with T-VEC or discontinued T-VEC for other reasons (progression or toxicity).

In all included studies, median CRR was 40% (range 14 – 62%), median PRR was 14 (range 5 – 43%), median SDR was 20.5% (7 – 45%), and median PDR was 28% (20 – 53%). Median ORR was 52.5% (range 32 – 79%). Median DRR, with responses lasting for more than 6 months, was 38% (range 19 – 51%). The randomized phase III trial published by Andtbacka et al. was the only study with a control group, comparing T-VEC with subcutaneous GM-CSF, in stage III-IV disease. All efficacy results, including CRR (16.9% vs. 0.7%) and PRR (14.6% vs. 5.7%), were higher in the T-VEC arm. Also, ORR (31.5% vs. 6.4%) and DRR (19.3% vs. 1.4%) were significantly higher in the T-VEC arm (both $p < 0.001$).

Study and patient characteristics							
First author and year	**Study design**	**Population treated with T-VEC**	**Location**	**Median age**	**Stage (AJCC)**	**Prior treatment with systemic therapy**	**Median follow-up months**
Andtbacka [10, 35] (2015) #, @	Randomized phase III study (OPTiM trial)	n = 295	UK	63	IIIB - IV (7^{th})	157 (53%)	49
Perez [14] (2018)#	Retrospective	n = 27 *n = 23 (analyses)*	US	75	IIIB - IV (7^{th})	9 (34%)	8.6
Zhou [23] (2019)*, @	Retrospective	n = 40	US	73	IIIB - IV (7^{th})	22 (55%)	14
Louie [13] (2019)	Retrospective	n = 80 *n = 79 (analyses)*	US	69	IIIB - IV (8^{th})	59 (74%)	9
Frohlich [24] (2020)@	Retrospective, case series	n = 14	Germany	73	IIIB - IV (7^{th})	8 (57%)	10
Andtbacka [10, 35] (2015)	Randomized phase III study	n = 163	UK	-	IIIB-IVM1a (7^{th})		-
Mohr [36] (2019)	Retrospective	n = 27 *n = 14 (analyses)*	Germany	68	IIIB - IVM1a (7^{th})	10 (37%)	7
Van Akkooi [37] (2020)	Retrospective	n = 66 *n = 47 (analyses)*	Netherlands, Germany, UK, Austria	69	IIIB - IVM1a (7^{th})	23 (35%)	-
Stahlie [25] (2021)#	Prospective	n = 93	Netherlands	69	IIIB - IVM1a (8^{th})	16 (17%)	16.6

Table 1. *Study characteristics, efficacy, survival and safety outcomes. Above the line are shown all studies that included stage IIIB-IV disease, below the line all studies that included stage IIIB-IVM1a disease. Efficacy outcomes were calculated over the population groups without italic style. [3] response lasting for more than 3 months instead of 6 months, [5] calculated over total group. Abbreviations: AJCC: American Joint Cancer Committee; CRR: complete response rate; PRR: partial response rate; SDR: stable disease rate; PDR: progressive disease rate; non-RR: non-response rate; Non-R: non-response; ORR: overall response rate; DRR: durable response rate; OS: overall survival; PFS: progression-free survival; AE: adverse event; NR: Not reached. #used the WHO criteria as efficacy assessment, *used the RECIST criteria as efficacy assessment, @used the CTCAE criteria as safety assessment.*

	Efficacy						Survival			Safety	
	CRR	**PRR**	**SDR**	**PDR/ Non-RR**	**ORR**	**DRR**	**Median OS months**	**1-year OS**	**Median PFF months**	**All grades AEs/toxicities**	**Grade 3 - 4**
	50 (17%)	43 (15%)	132 (45%)	62 (21%)	32%	19%	23.3	50%	-	292 (99%)	33 (11%)
	10 (44%)	3 (13%)	5 (22%)	5 (22%)	57%	-	NR	80%	-	11 (41%)[5]	-
	17 (43%)	2 (5%)	-	21 (53%)	48%	40%	NR	+/- 70%	10.5	32 (80%)	3 (7.5%)
	29 (37%)	6 (8%)	15 (19%)	25 (30%)	45%	47%[3]	-	-	-	34 (43%)	-
	2 (14%)	6 (43%)	1 (7%)	5 (36%)	57%	36%	-	-	4.5	9 (64%)	0 (0%)
	46 (28%)	29 (18%)	-	-	46%	29%	46.8	+/- 65%	-	-	-
	3 (21%)	-	-	7 (50%)		-	-	-	-	-	-
	26 (55%)	-	-	12 (26%)			-	-	-	47 (71%)	-
	58 (62%)	22 (17%)	-	19 (20%)	79%	51%	NR	+/- 95%	17	+/- 93 (100%)	1 (1%)

For patients with stage IIIB-IVM1a disease, median CRR was 38% (range 21 – 62%), median ORR was 61% (range 46 – 79%) and median DRR was 40% (range 29 - 51%). The pooled CRR for patients with stage IIIB-IVM1a disease was obtained from six studies (n=344 patients) and was 41% (95% confidence interval [CI], 25 – 58%). The pooled ORR in this group was obtained from four studies (n=283 patients) and was 64% (95% CI, 41 – 82%) (Figure 2a).

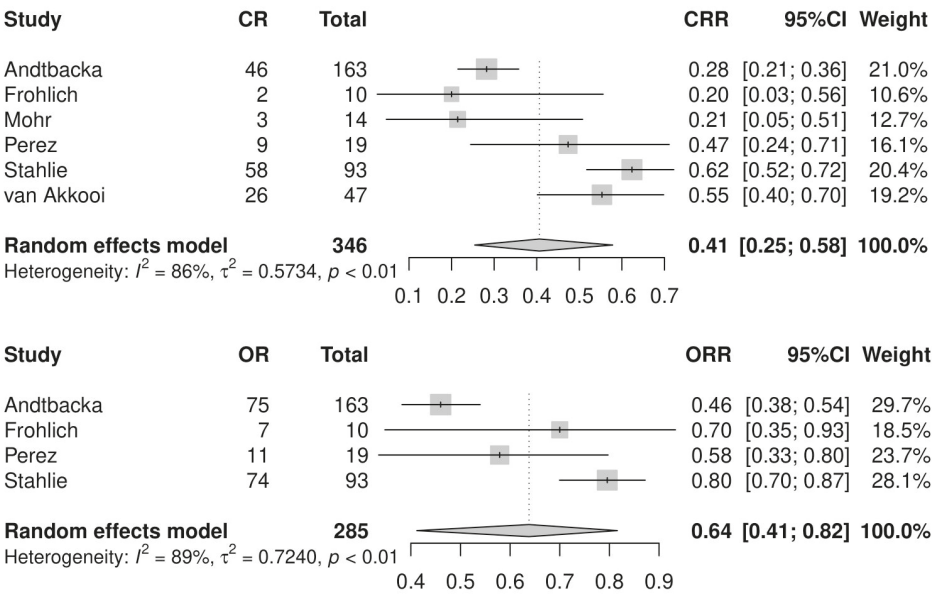

Figure 2a. *Forest plot of the CRR and ORR of patients with stage IIIB-IVM1a. Abbreviations: CRR: complete response rate; ORR: overall response rate.*

For patients with stage IIIB-IVM1c disease, median CRR was 37% (range 14 – 43%), median ORR was 48% (range 32 – 57%), and median DRR was 36% (range 19 – 40%). The pooled CRR and ORR for patients with stage IIIB-IVM1c disease were obtained from five studies (n=450 patients) and were 30% (95% CI, 18 – 46%) and 44% (95% CI, 34 – 55%), respectively (Figure 2b).

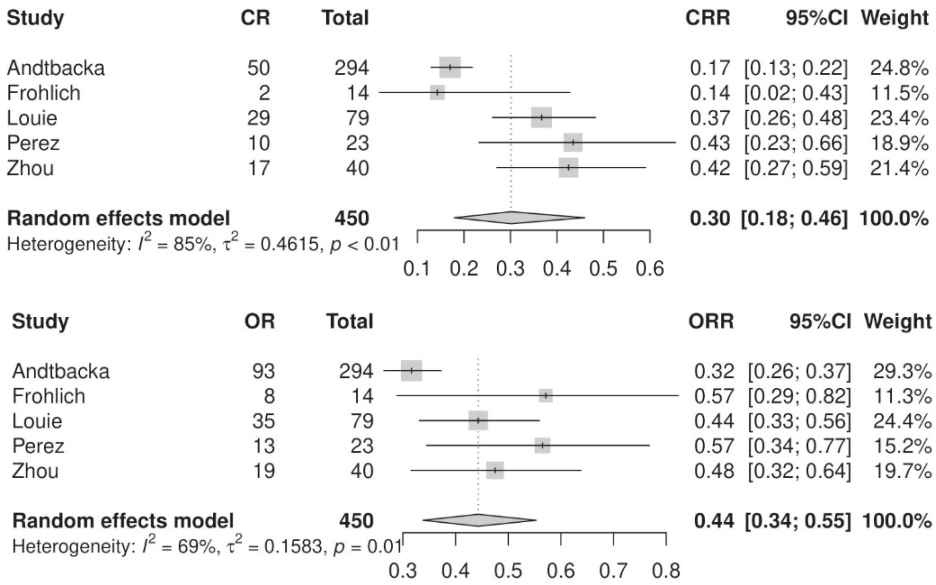

Figure 2b. *Forest plot of the CRR and ORR of patients with stage IIIB-IVM1c. Abbreviations: CRR: complete response rate; ORR: overall response rate.*

For patients with stage IVM1b-c disease, median CRR was 3% (range 0 – 6%) and median ORR was 16% (range 7 – 25%). No DRR was reported for patients with stage IVM1b-c disease. The pooled CRR for patients with stage IVM1b-d disease was obtained from three studies (n=151 patients) and was 4% (95% CI, 2 – 9%). The pooled ORR in this group was obtained from two studies (n=135 patients) and was 9% (95% CI, 3 – 27%) (Figure 2c).

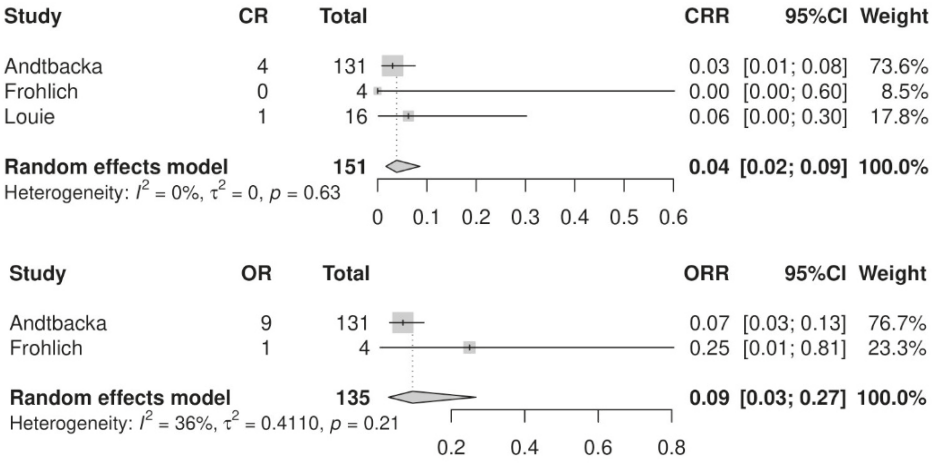

Figure 2c. *Forest plot of the CRR and ORR of patients with stage IVM1b-IVM1c. Abbreviations: CRR: complete response rate; ORR: overall response rate.*

Meta-analyses reported similar results with a different pooling method (i.e. generalized mixed model). High heterogeneity was reported for the studies with subgroups IIIB-IVM1a (CRR: I^2=86%, p<0.01 and ORR: I^2=89%, p<0.01) and IIIB-IVM1c (CRR: I^2=85%, p<0.01 and ORR: I^2=69%, p=0.01). The heterogeneity in studies with subgroups IVM1b-c were low (CRR: I^2=0%, p=0.63) and moderate (ORR: I^2=36%, p=0.21).

Survival

Only one study (Andtbacka), including patients with stage IIIB-IVM1c melanoma patients, reported a median OS (23.3 months). Median OS was not reached in three studies (Perez, Zhou, Stahlie). The 1-year OS ranged from 50 – 92%. Two studies (Zhou, Frohlich) including patients with stage IIIB-IVM1c disease, reported a PFS of 4.5 and 10.5 months. One study including only patients with stage IIIB-IVM1a disease reported a PFS of 17 months (Stahlie).

Safety

Three studies assessed adverse events according to the Common Terminology Criteria for Adverse Events (Andtbacka, Zhou and Frohlich)[22]. Andtbacka et al. subdivided the AEs between treatment-related or not. All other studies did not report their methods of assessing AEs and Mohr et al. did not describe the incidence of AEs at all. In the seven studies reporting on the AE incidence, AEs were seen in 41 – 100% of all patients. Most AEs were grade 1 or 2, with the most commonly reported AEs being fatigue, pyrexia, and chills. In four studies grade 3 - 4 AEs were reported (in 0 – 11% of the patients, with an average of 8%). Most reported grade 3 - 4 AEs were fatigue, cellulitis and vomiting. Of the 642 patients included, 21 (3%) discontinued treatment due to treatment-related AEs. No treatment-related grade 5 AEs (death) were reported.

DISCUSSION

To our knowledge, this is the first systematic review investigating the efficacy and safety profile of T-VEC monotherapy in stage IIIB-IV melanoma. Response and AE rates of one clinical trial and seven real-world prospective and retrospective cohort studies were assessed.

More than half of the included studies treated patients with cutaneous, subcutaneous and nodal metastases (stage IIIB-IVM1a disease) as well as patients with lung and visceral metastases (stage IVM1b and IVM1c disease, respectively). A clear difference in response rates between these patient groups was shown; the pooled CRR and ORR were higher in patients with stage IIIB - IVM1a disease (CRR 41%; 95% CI, 25 – 58% and ORR 64%; 95% CI, 41 – 82%) compared to patients with stage IVM1b - IVM1c disease (CRR 4%; 95% CI, 2 – 9% and ORR 9%; 95% CI, 3 – 27%). These results are supported by the OPTiM trial, which concluded that T-VEC efficacy was most pronounced in patients with stage IIIB - IVM1a disease (ORR of 53% [stage IIIB-C], 27% [IVM1a], 6% [IVM1b], and 12% [IVM1c])[9]. Moreover, Louie et al. found that patients with stage IIIB disease were more likely to achieve a CR to T-VEC than patients with stage IIIC, IIID, and IV disease (68% vs. 26%, 0% and 6%, respectively)[13]. We can thus conclude that T-VEC achieves the best responses in patients with early metastatic disease.

The OPTiM trial was the only clinical trial included, in which patients were randomly assigned to intralesional T-VEC or subcutaneous GM-CSF. Notably, Andtbacka et al. reported the lowest ORR and second lowest CRR of all studies that included stage IIIB-IVM1c patients. This is most likely explained by the fact that OPTiM included a higher percentage of patients with stage IVM1b - IVM1c disease (45%) than the other studies in this pool (Frohlich: 31%, Louie: 20%, Zhou: 15%, Perez: 4%)[9, 13, 23, 24]. Further patient selection might also be of influence: in-

and exclusion criteria for studies lead to homogenous groups of patients, often different from the real-world.

In addition to disease stage, two studies have noticed an association between tumor load and response to T-VEC. Bulky tumors and/or tumor lesions with a large diameter appear to be negatively associated with the clinical response to T-VEC[23, 25]. Unfortunately, patient tumor size and corresponding response to T-VEC were not specifically reported. Therefore, it was not possible to perform a comparable pooled analysis as we did for disease stages. Nevertheless, tumor size appears to be an important predictive factor (in addition to disease stage) and should be taken into account when selecting patients for treatment with T-VEC.

DRR were reported by four studies and ranged between 29 – 51% (IIIB-IVM1a) and 19 – 40% (IIIB-IVM1c disease)[9, 23-25]. Louie et al. only reported the number of patients that remained disease-free at the time of last follow-up (47%). They did show a statistically significant difference in DRR between stage III and IV disease (56% vs. 6% for stage IIIB-D and IV, respectively), which corresponds to the findings of the OPTiM trial (33% vs. 16% for stage IIIB – IIIC and IV, respectively)[9, 13]. Similar to CRR and ORR, durable responses belonged to the patients treated with T-VEC early in the course of the disease.

As the median follow-up of most studies was relatively short, median OS was either not reported or was not yet reached. OPTiM was the only study with comprehensive survival analyses, with a median OS of 23.3 months and an estimated 5-year survival rate of 33.4% for the T-VEC arm, increasing to 48.9% for stage IIIB - IVM1a patients. Of the patients who achieved a CR, approximately 90% were estimated to be alive at 5 years[9]. The latter is supported by Stahlie et al., who reported a 1-year survival of +/- 95% in the CR-group (in stage III - IVM1a patients)[25].

Nearly half of the patients were treated with systemic immunotherapy prior to treatment with T-VEC. A negative association between T-VEC as second-line therapy and response has been suggested, highlighting the need for further research[10, 25]. Two studies were excluded as they also included patients (mostly patients with >stage IVM1a disease) treated with T-VEC in combination with a concurrent drug[26, 27]. In these studies, the response to T-VEC monotherapy was not reported separately and therefore a systematic comparison with the outcomes of other studies could not be made. Although this review did not focus on T-VEC combined with immunotherapy, the combination is being investigated. A phase 2 study that treated patients with either ipilimumab or T-VEC and ipilimumab, reported significantly higher response rates for the combination group (ORR 18% vs. 39%, respectively)[28]. The phase 1b MASTERKEY-265 study,

investigating the combination of T-VEC and pembrolizumab, found that T-VEC had the potential to improve the efficacy of pembrolizumab by changing the tumor microenvironment[29]. However, recently, the randomized, double-blind phase 3 sequel did not confirm this potential synergistic effect[30].

Most patients treated with single agent T-VEC experienced some AEs, but the vast majority were categorized as grade 1 - 2 or mild. In the studies that distinguished between grade 1 – 4 AEs occurring in patients receiving T-VEC, 8% had grade 3 - 4 AEs (notably, most were reported in the OPTiM trial). This is lower than the rate of AEs reported in patients treated with systemic immunotherapies; 9 – 21% in patients receiving nivolumab or pembrolizumab, 20 – 28% in patients receiving ipilimumab, and 59% in patients receiving combination therapy with nivolumab plus ipilimumab[2, 31-33]. These AEs are often immune-related and affect tissues such as the skin, bowel, liver (e.g. hepatitis), and endocrine glands (e.g. hypophysitis), sometimes requiring (lifelong hormone replacement) therapy. In addition, these AEs can be serious or even life-threatening and occasionally lead to treatment discontinuation[34]. Although 3% of patients treated with T-VEC discontinued treatment due to treatment-related AEs, these were rarely immune-related and patients did not need life-long hormone replacement. No treatment-related deaths were reported either. Local treatment with T-VEC therefore seems to be a milder alternative.

Our review has several limitations. First, the heterogeneity was high among the studies with various subgroups (IIIB-IVM1c), making it difficult to be conclusive on the results of these meta-analyses. Also, the limited number of included studies preclude an appropriate assessment of the risk of publication bias (for which at least 10 studies should be included). We assume that our search was sensible enough to include all relevant studies and we are not aware of studies on the topic (that we should have included) that were conducted but not published. Other limitations of this review were the English language restriction, the exclusion of grey literature, that the samples of participants in most of the studies reviewed were relatively small and that half of the included patients were from a single study (OPTiM). And while this was the only prospective randomized trial to be included, and such trials tend to yield better outcomes than pro- and retrospective real-world studies, it was actually the opposite. This raises the question whether trial and retrospective study outcomes should be combined. Moreover, real-world studies may be limited by their heterogeneous patient population, but at the same time it could be argued that this actually reflects patients currently eligible for T-VEC treatment. Another difference was how response rates and AEs were assessed between the RCT and cohort studies: our results would have been more powerful if all studies used the same criteria for assessing responses (WHO or RECIST) and adverse events (CTCAE). Finally, several studies had a relatively

short follow-up period. While no reasons have been given for not addressing outcomes such as OS or PFS, these data may still be immature.

Despite these limitations, our results show that patients with early metastatic disease (stage IIIB-IVM1a) achieve far superior responses (pooled CRR of 42% and pooled ORR of 58%) to single agent T-VEC treatment than patients who also harbor distant visceral metastases (stage IVM1b-c). In addition, T-VEC is generally well-tolerated with only mild toxicity.

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SUPPLEMENTARY MATERIAL

JBI Critical Appraisal Checklist for randomized controlled trials
Was true randomization used for assignment of participants to treatment groups?
Was allocation to treatment groups concealed?
Were treatment groups similar at the baseline?
Were participants blind to treatment assignment?
Were those delivering treatment blind to treatment assignment?
Were outcomes assessors blind to treatment assignment?
Were treatment groups treated identically other than the intervention of interest?
Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?
Were participants analyzed in the groups to which they were randomized?
Were outcomes measured in the same way for treatment groups?
Were outcomes measured in a reliable way?
Was appropriate statistical analysis used?
Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

JBI Critical Appraisal Checklist for Case Series
Were there clear criteria for inclusion in the case series?
Was the condition measured in a standard, reliable way for all participants included in the case series?
Were valid methods used for identification of the condition for all participants included in the case series?
Did the case series have consecutive inclusion of participants?
Did the case series have complete inclusion of participants?
Was there clear reporting of the demographics of the participants in the study?
Was there clear reporting of clinical information of the participants?
Were the outcomes or follow up results of cases clearly reported?
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
Was statistical analysis appropriate?

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13
Andtbacka*	Y	N	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y
Perez#	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y			
Zhou#	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y			
Louie#	N	Unclear	Unclear	Y	Y	Y	Y	Y	NA	Y			
Mohr#	Y	N	N	Y	Y	Y	Unclear	Unclear	NA	Y			
Frohlich#	Y	Unclear	N	Y	Y	Y	Y	Y	NA	Y			
Van Akkooi#	Y	Unclear	Unclear	Y	Y	Y	Y	Y	Y	Y			
Stahlie#	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y			

Table S1. *Critical appraisal of the included studies using the JBI checklists for randomized control trials* and case series#.*