Short Communication

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Melanoma Management

Observational study of talimogene laherparepvec use in the anti-PD-1 era for melanoma in the US (COSMUS-2)

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Aim: Talimogene laherparepvec (T-VEC) is an intralesional therapy for unresectable, metastatic melanoma. T-VEC real-world use in the context of anti-PD1-based therapy requires further characterization. **Materials & methods:** A retrospective review of T-VEC use from 1 January 2017 and 31 March 2018 for melanoma patients was conducted at seven US institutions. **Results:** Among 83 patients, three categories of T-VEC and anti-PD-1 therapy were identified: T-VEC used without anti-PD-1 (n = 29, 35%), T-VEC after anti-PD-1-based therapy (n = 22, 27%) and concurrent T-VEC and anti-PD-1-based therapy (n = 32, 39%). 25% of patients discontinued T-VEC therapy due to no remaining injectable lesions, 37% discontinued T-VEC due to progressive disease. Discontinuation of T-VEC did not differ by anti-PD-1-based therapy use or timing. **Conclusion:** In real-world settings, T-VEC may be used concurrently with or after anti-PD-1-based therapy.

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Talimogene laherparepvec (T-VEC) is an intralesional oncolytic virus that received US FDA approval in October 2015 for local (intralesional injection) treatment of unresectable cutaneous, subcutaneous and nodal lesions in patients with melanoma recurrent after initial surgery on the basis of the OPTiM trial [1]. This study compared intralesional T-VEC and GM-CSF and reported significantly improved overall response rate (ORR) and durable response rate (DRR) with T-VEC therapy. A recently published final update of the OPTiM trial reported an estimated 5-year survival of 33.4% for the T-VEC arm and confirmed that T-VEC is more effective in patients with early metastatic disease (stage IIIB–IVM1a) [2]. Furthermore, of the 17% of patients that achieved complete response (CR), the median duration of response and OS were not reached over a median follow-up time of greater than 4 years (49 months). Coupled with low rates of serious (grade $\geq$3) adverse events, these data demonstrate that T-VEC therapy is beneficial for patients with stage IIIB–IVM1a disease with durable response and continues to be an important treatment option.

Studies of real-world T-VEC use have reported similar response rates. One study reported a locoregional ORR of 57% (CR + partial response [PR], 39% + 18%) over a median follow-up time of 9 months [3]. A prior observational study, COSMUS-1, reported a CR in 20% of patients after T-VEC injections [4]. Both studies identify that the

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Table 1. Number of patients enrolled in study from each participating institution.

Institution	Enrolled patients, n
1	19
2	18
3	12
4	10
5	9
6	8
7	7
Total	83

majority of patients were treated with T-VEC as second- or later-line therapy in the clinical setting and that most patients have received prior systemic immunotherapy.

In the era of effective systemic immunotherapy, it is important to characterize the real-world use of T-VEC in relation to these therapies. Immunotherapies revolutionized the treatment of advanced melanoma with improvements in survival and are now standard of care for advanced disease [5]. The two major mechanisms are the inhibition of PD-1 and CTLA-4, which lead to the activation of T cells (see Bhandaru *et al.* and Marhelava *et al.* for detailed descriptions of mechanisms of action) [6,7]. Approximately 50% of patients do not respond to anti-PD-1 therapy, and mechanisms of resistance are due to lack of T-cell priming or T-cell infiltration into the tumor [8,9]. Combining T-VEC and immunotherapy can benefit from the mechanisms of action of both treatment modalities, which may have a synergistic effect [10–12]. Intratumoral T-VEC injection increases local T-cell recruitment, which augments immune-mediated anti-tumor responses [8,13,14]. Given the evidence that T-VEC and immunotherapy have synergistic effects, the goal of this study was to describe real-world patterns of T-VEC use and physician attitudes toward its role in current treatment regimens.

Materials & methods

Study design

COSMUS-2 is a retrospective chart review of melanoma patients treated with T-VEC at seven high-volume academic centers and specialty clinics in USA. The number of patients enrolled from each institution is described in Table 1. The primary objectives of this study were to describe the clinical characteristics of patients treated with T-VEC. The secondary objective was to describe T-VEC use, characterize the use of other therapies and evaluate other clinical outcome of T-VEC such as safety. Institutional Review Board approval was obtained at each of the seven participating institutions.

Patient selection

To be eligible for the study, patients must have started their first T-VEC treatment between 1 January 2017 and 31 March 2018. Patients were excluded if they received T-VEC in a clinical trial or expanded access program. Per the protocol, data were abstracted from medical records by trained abstractors at selected institutions that treat melanoma patients with T-VEC and agreed to participate in this chart review. Consecutive cases were identified within the defined study period to avoid selection bias. Sites were instructed to enroll all eligible patients treated with T-VEC within the study period. Data collected including patient demographics (age, sex), treatment details and clinical characteristics (Eastern Cooperative Oncology Group Performance Status [ECOG-PS], disease stage, and *BRAF* mutation status). Patients were restaged at study initiation according to the American Joint Commission on Cancer 8th edition staging manual [15].

Statistical analysis

We analyzed T-VEC use in relation to the use of checkpoint inhibitors. Patients were categorized into three groups: initiation of T-VEC after anti-PD-1 inhibitor therapy, initiation of T-VEC concurrently with anti-PD-1 inhibitor therapy, initiation of T-VEC without anti-PD-1 inhibitor therapy. A consecutive medical chart review was done at the seven US-based academic centers to provide patient-level descriptive data of patients administered with T-VEC during routine clinical practice with the first T-VEC dose given between 1 January 2017 and 31 March 2018. Charts were reviewed between 1 January 2017 and 31 March 2019. Patients with any history of being a subject in

Table 2. Demographic, pathologic and treatment characteristics of study cohort.

Characteristics	Overall cohort (n = 83)	T-VEC after PD-1 (n = 22)	T-VEC concurrent with PD-1 (n = 32)	T-VEC without PD-1 (n = 29)
Age (median, IQR)	67 years (58–76)	62 years (57–75)	64 years (58–74)	71 years (64–77)
Sex (%)				
– Males	41 (49)	9 (41)	20 (63)	12 (41)
– Females	42 (51)	13 (59)	12 (38)	17 (59)
ECOG (%)				
– 0	33 (40)	6 (27)	14 (44)	13 (45)
– 1	27 (33)	6 (27)	11 (34)	10 (34)
– 2	5 (6)	3 (14)	1 (3)	1 (3)
– Unknown	18 (22)	7 (32)	6 (19)	5 (17)
BRAF status (%)				
– Wild-type	49 (59)	12 (55)	18 (56)	19 (66)
– Mutant	19 (23)	6 (27)	8 (25)	5 (17)
– Unknown	15 (18)	4 (18)	6 (19)	5 (17)
Prior therapies to T-VEC initiation (%)				
– Anti-CTLA4	26 (33)	14 (64)	11 (34)	1 (3)
– BRAF/MEK	6 (7)	5 (23)	1 (3)	–
Concurrent therapies with T-VEC (%)				
– Anti-CTLA4	6 (7)	1 (5)	5 (16)	–
– BRAF/MEK	4 (5)	2 (9)	–	2 (7)
Disease stage† at first T-VEC injection (%)				
– IIIB	19 (23)	3 (14)	7 (22)	9 (31)
– IIIC	31 (37)	6 (27)	12 (38)	13 (45)
– IIID	1 (1)	–	1 (3)	–
– IVM1a	12 (14)	7 (32)	3 (9)	2 (7)
– IVM1b	4 (5)	–	2 (6)	2 (7)
– IVM1c	11 (13)	4 (18)	5 (16)	2 (7)
– IVM1d	1 (1)	–	–	1 (3)
– Unknown	4 (5)	2 (9)	2 (6)	–
T-VEC exposure				
– Cumulative volume T-VEC delivered (ml median, range)	12.1 (0.6–120.5)	9 (2–21)	16.5 (1.5–120.50)	14.7 (0.6–100.5)
– Treatment duration‡ (months, range)	3 (0–20)	2 (0–20)	5 (0–17)	3 (1–15)
– Number of visits (range)	7 (1–30)	5 (1–15)	8 (2–30)	7 (2–25)
T-VEC ongoing (%)	9 (11)	–	7 (22)	2 (7)
– T-VEC discontinuation	74 (89)	22 (100)	25 (78)	27 (93)
Reason for discontinuation (if known) (%)§				
– No remaining injectable disease	21 (25)	5 (23)	8 (25)	8 (28)
– Progressive disease	31 (37)	12 (55)	9 (28)	10 (34)
– Adverse event	8 (10)	4 (18)	3 (9)	1 (3)
– Death	8 (10)	2 (9)	5 (16)	1 (3)
– Patient preference	4 (5)	2 (9)	–	2 (7)

†Staging reflected either AJCC 7 or 8.
‡Among those whose treatment has ended.
§Patients could have more than one reason for discontinuation. Eight patients received an anti-PD-1 after T-VEC.
AJCC: American Joint Committee on Cancer; ECOG: Eastern Cooperative Oncology Group; IQR: Interquartile range; T-VEC: Talimogene laherparepvec.

a clinical trial or expanded access program for T-VEC were excluded. Only select adverse events in the categories of herpetic events, systemic and injection-site complications were collected. An additional survey was provided to each center to assess physician decision-making considerations toward T-VEC use. All analyses were descriptive, no formal comparisons were conducted. Analysis was performed using Stata v15.1 or higher (Stata Corp. [2017] Stata Statistical Software Release 15; StataCorp LLC, TX, USA).

Results

Eighty-three patients were eligible and included in the analysis. The median age was 67 years (interquartile range [IQR], 58–76 years); 49% (n = 41) were males. At T-VEC initiation, most patients had AJCC 8th edition disease stage IIIB (n = 19, 23%) or IIIC (n = 31, 37%); 28 patients (34%) had stage IV disease at the start of T-VEC treatment. Median follow-up time was 12 months (range: 0–25 months). Patients received a median of seven T-VEC treatments with median treatment duration of 3 months (range: 0–20 months) and a cumulative median volume of 12 ml. Forty-six of the 74 patients who discontinued treatment (62%) received subsequent treatment. Patient demographic and treatment characteristics are presented in Table 2.

Table 3. Incidence of adverse events among treated patients by treatment regimen.

	Overall cohort (n = 83)	T-VEC after PD-1 (n = 22)	T-VEC concurrent with PD-1 (n = 32)	T-VEC without PD-1 (n = 29)
Systemic AE[†]	9 (11%)	2 (9%)	3 (9%)	4 (14%)
– Fatigue	4 (5%)	–	1 (3%)	3 (10%)
– Flu-like symptoms	7 (8%)	2 (9%)	2 (6%)	3 (10%)
– Muscle ache	1 (1%)	–	–	1 (3%)
– Vomiting	3 (4%)	1 (5%)	–	2 (7%)
– Other[‡]	3 (4%)	2 (9%)	1 (3%)	–
Injection site AE[†]	13 (16%)	1 (5%)	4 (13%)	8 (28%)
– Rash	2 (2%)	–	–	2 (7%)
– Injection-site pain	3 (4%)	–	1 (3%)	2 (7%)
– Ulceration	1 (1%)	–	1 (3%)	–
– Erythema	1 (1%)	–	1 (3%)	–
– Inflammation	1 (1%)	–	1 (3%)	–
– Other[§]	6 (7%)	1 (5%)	1 (3%)	4 (14%)

[†]Patients may have more than one adverse event.
[‡]Others were weakness, nausea and hypopituitarism.
[§]Others were bleeding, pruritis, pressure sensation headache on top of scalp, shingles rash due to varicella zoster virus infection.
AE: Adverse event; T-VEC: Talimogene laherparepvec.

Patients were grouped into three categories: T-VEC initiated during or after anti-PD-1, T-VEC concurrent with anti-PD-1 and T-VEC without anti-PD-1. Patients in the first category started T-VEC at a median time of 3 months after the last anti-PD-1 therapy, with therapy starting as early as simultaneously with last anti-PD-1 (0 months) or as long as 19 months after last anti-PD-1.

Aside from anti-PD-1 therapy, 33% of patients received anti-CTLA4 and 7% received BRAF/MEK inhibition prior to initiation of T-VEC (Table 2). When T-VEC use was analyzed relative to treatment with anti-PD-1 inhibitor therapy, 22 patients (26.5%) received T-VEC after anti-PD-1 inhibitor therapy, 32 patients (38.6%) received T-VEC concurrently with anti-PD-1 therapy and 29 patients (34.9%) did not receive anti-PD-1 inhibitor therapy before or during T-VEC treatment. Among the 29 patients that did not receive anti-PD-1 inhibitor therapy, the median age was 71 years (range 64–77 years). Most (83%) had stage IIIB–IVM1a disease and 66% were *BRAF*-wild-type. Anti-PD-1 drugs, including pembrolizumab or nivolumab, were the most commonly used agents regardless of sequencing with T-VEC.

Study outcomes from the chart review were as follows: nine patients (10.8%) were still receiving T-VEC injections and 74 patients (89.2%) had discontinued at the end of the study. Twenty-one patients (25.3%) completed treatment with no remaining injectable lesions (local complete response.). Median time to no remaining injectable lesions was 4 months (range: 1–20 months). Twenty-six other patients (32.3%) had died; 19 died due to disease progression (73%) and the cause of death was not reported for seven patients (27%).

Reported select adverse events (AE) during treatment were divided into two categories: systemic and injection site AE as no herpetic events were reported (Table 3). The most common systemic AE was fever, chills, and rigors (seven patients, 8%). Other systemic AEs included fatigue, muscle aches and nausea/vomiting. The most commonly reported injection site AE was pain (three patients, 4%); other reported AEs included rash, ulceration, erythema and inflammation. Although variability across treatment groups was observed, no conclusions can be drawn due to the study design and small sample sizes.

A survey was provided to one physician at each institution to understand physician treatment decision-making related to T-VEC usage. Responses were received from all seven institutions (Table 4). Most physicians initiated T-VEC therapy for curative intent or to decrease the size of lesions to allow for resection. All of the surveyed physicians indicated that T-VEC should be administered in combination with systemic checkpoint inhibitors and all would consider discontinuing T-VEC injection when there are no injectable lesions or if patients experience AEs.

Discussion

Our study demonstrates that at high-volume academic and specialty centers in the real-world setting, over two-thirds of patients treated with T-VEC received it with immunotherapy – either concurrently or following immunotherapy. The select AE profile was similar in those patients that received T-VEC as a single agent or in combination with an immunotherapy. The majority of T-VEC use was in patients with local or regional disease (63/83). Although 39% (32/83) of patients in this study received T-VEC concurrently with PD-1 checkpoint inhibitors, physician surveys

Table 4. Physician perception of talimogene laherparepvec as a treatment option in the anti-PD-1 era.

Survey question and response statements[†]	n (%)
Number of institutions responding	7 (100)
What considerations led to T-VEC use in your patients?	
– Treatment of local lesions with curative intent	4 (57)
– Priming for future systemic immunotherapy	2 (29)
– For improvement of current systemic immunotherapy	5 (71)
– Reducing size of lesions to make patient resectable	4 (57)
– Reducing the size of the lesions for symptom control	2 (29)
– Other treatment strategy	0
When should systemic checkpoint inhibitors be used with T-VEC treatment?	
– Before T-VEC treatment	2 (29)
– In combination with T-VEC	7 (100)
– After T-VEC treatment	3 (43)
– Timing of checkpoint inhibitor administration is irrelevant to T-VEC treatment	0
– I do not believe checkpoint inhibitors should be used in a treatment regimen with T-VEC	0
– I do not have enough experience prescribing these treatments to provide a response	0
When would you consider stopping T-VEC treatment in a patient?	
– No injectable lesions	7 (100)
– Clinical complete response	6 (86)
– Pathological complete response	6 (86)
– First incidence of increasing lesions	1 (14)
– Increasing size of existing lesions	4 (57)
– Local progression	1 (14)
– Regional metastases	2 (29)
– Distant metastases	2 (29)
–Adverse events	7 (100)
– I have not yet discontinued T-VEC therapy in a patient	0

[†]Responders asked to evaluate each question and selected all responses reflected their use of T-VEC therapy.
T-VEC: Talimogene laherparepvec.

from these centers indicate that most clinicians feel that T-VEC is effective in combination with anti-PD-1 and anti-CTLA-4 antibodies and that there may be synergistic effect due to immune priming. The present COSMUS-2 study is a follow-up study to COSMUS-1 and characterizes the evolving landscape of melanoma treatment. COSMUS-1 reported 43% of T-VEC treated patients received any checkpoint inhibitor prior to or concurrently with T-VEC, and within 2 years, we observe an increase to 65% with anti-PD-1 treatment options specifically for melanoma patients [4].

Despite the observational nature of this study, we observed no remaining injectable tumors (local CR) in 25% across all treatment groups. In similar real-world chart review studies of T-VEC use, no remaining injectable were noted in 11–20% of patients [4,16]. Additionally, an ongoing study by Sun *et al.* of T-VEC as second- or later-line therapy after failure of immunotherapy reported no remaining injectable lesions in 25.5% of treated patients [SUN J ET AL. (2020) SUBMITTED], which is consistent with the data seen in COSMUS-2 and other similar real-world studies.

There are few published clinical studies investigating the combination of systemic immunotherapy and T-VEC. A case series of by Chesney *et al.* reported on two patients who had failed multiple lines of systemic therapy [17]. They reported a durable CR in one patient and a PR in the other and upon analysis of the tumor microenvironment, confirmed evidence of lymphocytic infiltration, leading the authors to conclude that T-VEC may induce tumor immunogenicity and be an effective treatment option in combination with systemic immunotherapy. Furthermore, a randomized Phase II study demonstrated superior objective response rate with T-VEC plus ipilimumab versus ipilimumab alone [18] and a Phase IB study of T-VEC plus pembrolizumab demonstrated a 43% CR rate by immune-related response criteria and a 71% OS rate at 3 years with evidence of T-cell infiltration and favorable tumor microenvironment with this combination [8,19].

Compared with our previous chart review study, the observed select AE profile in this study is consistent with that published in our previous chart review study, COSMUS-1 [1,3,4,20]. The most frequently reported systemic AE was flu-like symptoms and the most frequently reported injection-site AE was pain. The incidence of select AEs did not increase among patients treated after or concurrently with PD-1 therapy and immune-related AEs were not reported for any patients despite higher proportion of patients receiving T-VEC in combination with anti-PD-1 inhibitor in this study. However, among the eight patients that discontinued T-VEC due to AEs, a higher proportion were in the PD-1-treated treatment groups. AEs as reasons for discontinuation included grade

2 colitis (n = 1), weakness (n = 2), discomfort/pain (n = 2), chest pain (n = 1), flu-like symptoms (n = 1) and worsening functional status (n = 1). Autoimmune AEs, such as diabetes, hypothyroidism or myocarditis were not reported for any patients. Clinical studies of the combination of T-VEC and immune checkpoint inhibitor therapy have reported AEs profiles consistent with those seen with both agents individually [8,18,21]. Incidence of select AEs do not seem to differ between patients treated with combination therapy or T-VEC monotherapy. None of the studies, including this study, reported development of herpetic simplex lesions in patients treated with systemic immunotherapy prior to or concurrently with T-VEC.

The combination of T-VEC and systemic immunotherapy for the treatment of unresectable metastatic melanoma has been reported in published studies demonstrating efficacy of this treatment strategy. Our study provides support that physicians at high-volume treatment centers have recognized this as a potential treatment strategy and now use T-VEC to augment systemic immunotherapy in some of their patient cases. This study is limited by the observational and retrospective design, including some incomplete medical records. Selection bias was minimized by defining a time period wherein all patients treated with T-VEC were included. The findings of these studies should be confirmed by future studies designed to evaluate treatment efficacy.

Conclusion

In the real-world clinical setting, T-VEC is used concurrently with or after anti-PD-1 inhibitor-based therapy about two-thirds of the time. T-VEC remained tolerable when used with anti-PD-1 inhibitor therapy with few patients discontinuing T-VEC due to adverse events. Randomized studies are underway to confirm the efficacy and safety of T-VEC in combination with immunotherapy.

Summary points

- Talimogene laherparepvec (T-VEC) is an oncolytic virus approved for intralesional therapy of unresectable, cutaneous, subcutaneous and nodal metastatic melanoma recurrent after the initial surgery.
- Review of patients treated at seven high-volume academic centers demonstrated use of T-VEC primarily after or concurrently with systemic immunotherapy.
- 25% of patients completed treatment with no remaining injectable lesions (local complete response).
- In the select adverse events that were evaluated in this analysis, the T-VEC adverse event profile did not change due to combination therapy, with the most common being flu-like symptoms and injection-site pain.
- Physicians surveyed at these institutions indicated that T-VEC is best used in combination with systemic immunotherapy agents.
- T-VEC use among these high-volume melanoma centers is concurrent with or shortly after systemic immunotherapy.

Author contributions

J Sun, BR Gastman, EI Buchbinder, I Puzanov, JM Lewis, RD Carvajal, AM Desai, L Raskin, R Ismail and JS Zager were responsible for study conception and design. J Sun, L McCahon, M Nanni, S Singh-Kandah and A Desai were responsible for the acquisition of data. J Sun, CM Nielson, R Ismail, JS Zager were responsible for data analysis. J Sun and JS Zager were responsible for drafting of the manuscript. All authors were responsible for revision of the manuscript.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval.

Disclaimer

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References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Andtbacka RH, Kaufman HL, Collichio F *et al.* Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. *J. Clin. Oncol.* 33(25), 2780–2788 (2015).

• **Randomized trial demonstrating efficacy of talimogene laherparepvec (T-VEC) leading to US FDA approval.**

2. Andtbacka RHI, Collichio F, Harrington KJ *et al.* Final analyses of OPTiM: a randomized Phase III trial of talimogene laherparepvec versus granulocyte-macrophage colony-stimulating factor in unresectable stage III–IV melanoma. *J. Immunotherapy of Cancer* 7(1), 145 (2019).

• **COSMUS-1, a retrospective study identifying patterns of T-VEC use by physicians in USA.**

3. Louie RJ, Perez MC, Jajja MR *et al.* Real-world outcomes of talimogene laherparepvec therapy: a multi-institutional experience. *J. Am. Coll. Surg.* 228(4), 644–649 (2019).

•• **Phase IB results from MASTERKEY-265, a randomized trial that demonstrated immune priming effect of T-VEC in combination with immunotherapy.**

4. Perez MC, Zager JS, Amatruda T *et al.* Observational study of talimogene laherparepvec use for melanoma in clinical practice in the United States (COSMUS-1). *Melanoma. Manag.* 6(2), MMT19 (2019).

•• **First randomized clinical trial of combination T-VEC and ipilimumab.**

5. National Comprehensive Cancer Network Clinical Practice Guideslines in Oncology: Cutaneous Melanoma, Version 2.2020 (2020). https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf

• **Phase I study demonstrating the safety of combination T-VEC and ipilimumab.**

6. Bhandaru M, Rotte A. Monoclonal antibodies for the treatment of melanoma: present and future strategies. *Methods Mol. Biol.* 1904, 83–108 (2019).

7. Marhelava K, Pilch Z, Bajor M, Graczyk-Jarzynka A, Zagozdzon R. Targeting negative and positive immune checkpoints with monoclonal antibodies in therapy of cancer. *Cancers* 11(11), 1756 (2019).

8. Ribas A, Dummer R, Puzanov I *et al.* Oncolytic virotherapy promotes intratumoral T cell infiltration and improves anti-PD-1 immunotherapy. *Cell* 170(6), 1109.e1110–1119.e1110 (2017).

9. Weiss SA, Wolchok JD, Sznol M. Immunotherapy of melanoma: facts and hopes. *Clinical Cancer Research* 25(17), 519–520 (2019).

10. Reale A, Vitiello A, Conciatori V, Parolin C, Calistri A, Palu G. Perspectives on immunotherapy via oncolytic viruses. *Infectious Agents Cancer* 14, 5 (2019).

11. Sivanandam V, LaRocca CJ, Chen NG, Fong Y, Warner SG. Oncolytic viruses and immune checkpoint inhibition: the best of both worlds. *Mol. Therapy Oncolytics* 13, 93–106 (2019).

12. Bommareddy PK, Shettigar M, Kaufman HL. Integrating oncolytic viruses in combination cancer immunotherapy. *Nat. Rev. Immunol.* 18(8), 498–513 (2018).

13. Broman KK, Zager JS. An evaluation of talimogene laherparepvec for the treatment of melanoma. *Expert Opin. Biol. Ther.* 20(1), 9–14 (2020).

14. Gogas H, Samoylenko I, Schadendorf D *et al.* Talimogene laherparepvec (T-VEC) treatment increases intratumoral effector T-cell and natural killer (NK) cell density in noninjected tumors in patients (PTS) with stage IIIB–IVM1c melanoma: evidence for systemic effects in a Phase II, single-arm study. *Ann. Oncol.* 29(Suppl. 8), viii442–viii466 (2018).

15. Gershenwald JE, Scolyer RA, Hess KR *et al.* Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J. Clin.* 67(6), 472–492 (2017).

16. Mohr P, Haferkamp S, Pinter A *et al.* Real-world use of talimogene laherparepvec in German patients with stage IIIB to IVM1a melanoma: a retrospective chart review and physician survey. *Adv. Ther.* 36(1), 101–117 (2019).

17. Chesney J, Imbert-Fernandez Y, Telang S *et al.* Potential clinical and immunotherapeutic utility of talimogene laherparepvec for patients with melanoma after disease progression on immune checkpoint inhibitors and BRAF inhibitors. *Melanoma Res.* 28(3), 250–255 (2018).

18. Chesney J, Puzanov I, Collichio F *et al.* Randomized, open-label Phase II study evaluating the efficacy and safety of talimogene laherparepvec in combination with ipilimumab versus ipilimumab alone in patients with advanced, unresectable melanoma. *J. Clin. Oncol.* 36(17), 1658–1667 (2018).

19. Long G, Dummer R, Andtbacka R *et al.* Follow-up analysis of MASTERKEY-265 Phase 1b (ph1b) trial of talimogene laherparepvec (T-VEC) in combination (combo) with pembrolizumab (pembro) in patients (pts) with unresectable stage IIIB–IVM1c melanoma (MEL). *Pigment Cell Melanoma Res* 32(1), 133–134 (2019).

20. Perez MC, Miura JT, Naqvi SMH *et al.* Talimogene laherparepvec (TVEC) for the treatment of advanced melanoma: a single-institution experience. *Ann. Surg. Oncol.* 25(13), 3960–3965 (2018).

21. Puzanov I, Milhem MM, Minor D *et al.* Talimogene laherparepvec in combination with ipilimumab in previously untreated, unresectable stage IIIB–IV melanoma. *J. Clin. Oncol.* 34(22), 2619–2626 (2016).