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ASO PERSPECTIVES

Talimogene Laherparepvec in Combination with Immunotherapy, A Viable Option?

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Talimogene laherparepvec (TVEC) is an oncolytic virus that has been proven to be effective in treating metastatic disease from melanoma via intralesional injection. The randomized, open-label, phase III OPTiM trial in patients with unresectable stage IIIB–IVM1c melanoma reported that the final overall survival (OS) analysis showed a median OS of 23.3 months in the TVEC group versus 18.9 months in the granulocyte macrophage colony-stimulating factor (GM-CSF)-alone arm ($p = 0.0494$ [descriptive]). Durable response rates (DRRs) were 19.0 (TVEC) and 1.4% (GM-CSF) [$p < 0.0001$], while overall response rates (ORRs) were 31.5 (TVEC) and 6.4% (GM-CSF). Fifty (16.9%) and one (0.7%) patients in the TVEC and GM-CSF arms, respectively, achieved a complete response (CR). Among patients with a CR, 88.5% were estimated to survive at a 5-year landmark analysis. The ORR benefit was more pronounced within the substage of patients with stage IIIB–IVM1a, with injectable nodal, subcutaneous, or soft tissue lesions.[1]

There are numerous theoretical advantages to combining this locally delivered oncolytic immunotherapy (IO) with systemic immunotherapeutic agents. One theory is that some tumors are 'cold', meaning they do not harbor a robust tumor-infiltrating lymphocyte (TIL) population and that injection of TVEC, or any other locally delivered oncolytic agent, can cause an influx of TIL as the tumor undergoes lysis, therefore turning these tumors 'hot'. This local release of antigens, along with local GM-CSF, results in a local increase of dendritic cells recognizing the antigens. Emerging preclinical and clinical findings confirm that oncolytic viruses act in a multimodal scheme, triggering lyses, immunogenic cell death, and finally inducing anticancer immune responses. Combining this with systemic IO seems to be a natural way of increasing a systemic immune-mediated response to antigens.[2,3]

The publication by Chesney et al. reported on a phase III randomized controlled trial that examined the combination of TVEC with pembrolizumab.[4] In that study, patients with stage IIIB–IVM1c unresectable melanoma, naïve to anti-programmed cell death protein-1 (PD-1), were randomly assigned 1:1 to TVEC/pembrolizumab or placebo/pembrolizumab. Primary endpoints were progression-free survival (PFS) and OS. Overall, 692 patients were randomly assigned (346 TVEC/pembrolizumab patients and 346 placebo/pembrolizumab patients). In the study, TVEC/pembrolizumab did not significantly improve PFS compared with placebo/pembrolizumab (hazard ratio 0.86, 95% confidence interval 0.71–1.04, $p = 0.13$).[4] It should be noted that 18 patients with stage IIIB were included in the TVEC/pembrolizumab group and 20 in the placebo/pembrolizumab group; similarly, low patient numbers were seen with stage IIIC, i.e. 66 versus 53 patients in the TVEC/pembrolizumab and placebo/pembrolizumab groups, respectively.

However, it is important to note that the objective response rate was 48.6% for TVEC/pembrolizumab, with a CR of 17.9%, versus an objective response rate of 41.3% for placebo/pembrolizumab, with a CR of 11.6%; the DRR

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was 42.2% and 34.1% for the two arms, respectively, showing there was an approximately 7% higher objective response rate and DRR in favor of TVEC/pembrolizumab, with an 8% improvement in DRR in favor of TVEC/pembrolizumab, although not statistically significant.[4]

Part of the possible non-statistically significant but numerically different difference in favor of the TVEC/pembrolizumab group could be that the trial was conducted to include stage IVb and IVc patients. We know from the OPTiM phase III trial that when the subgroup of stage IIIB–IVa patients is analyzed, there was a clear clinical benefit in favor of TVEC, with a median ORR in this population of 41.1 months for TVEC versus 21.5 months for GM-CSF ($p < 0.001$).[5,6] This represents the group of patients who led to the US FDA and European Medicines Agency approval and current indication for use and injection of lesions with TVEC monotherapy. Post-approval real-world evidence (RWE) series confirm this high efficacy in 'early' metastatic melanoma.[7–11] These multi-institutional RWE reports have shown efficacy in the stage IIIB–IVA population, with ORRs of 57–79%, with the highest response rates in patients with the lowest tumor burden.[6–10] Perhaps if the TVEC/pembrolizumab trial was conducted in the stage IIIB–IIIC populations only, we might have seen a larger difference in activity in favor of the combination group. If you drill down and look at the data in the TVEC/pembrolizumab study, there was a 7–8% benefit in ORR, CR, and DRR in favor of the TVEC/pembrolizumab group, which is not statistically different. Furthermore, the forest plots seem to indicate that the stage IIIB–IVA patients benefitted the most from the combination; however, this does not take into consideration the number and size of the lesions. Patients with normal lactate dehydrogenase (LDH) and sum of largest diameter (SLD) less than or equal to the median also seemed be in favor of the combination on the forest plot, although this was not statistically powered to show a difference. This supports the observations from real-world practice that TVEC is most effective in patients with fewer cutaneous satellite and/or in-transit lesions, and appears to become less effective with increasing tumor burden or larger/deeper lesions.

Additional data also suggest that TVEC alone or in combination might be effective in salvaging patients with stage IIIB–IVA melanoma after failure of systemic IO. Carr et al. reported on a group of 112 patients who had not responded to systemic IO for metastatic melanoma. Before TVEC, 57% of patients received one IO regimen and 42% received two or more regimens of IO. Most patients ($n = 74$, 66%) received TVEC sequential to IO, while the remaining 34% of patients received TVEC in addition to their current regimen of IO monotherapy. Most were stage IIIc ($n = 51$, 46%) at TVEC initiation and 29 (26%) received injections to nodal disease. Over a median follow-up of 14 months, in-field response at final TVEC injection showed an ORR of 51%, with 37% showing a CR and 14% showing a partial response. TVEC initiation sequentially after IO, or adding TVEC to systemic IO after failure of IO alone, did not significantly affect in-field response. The median in-field PFS was 15 months, with a median overall DFS after CR of 32 months.[12]

Finally, as surgical oncologists, it is our opinion that oncolytic viruses, even if they did not improve survival, either as a single agent or in combination, are clearly effective in locoregional control of morbid melanoma satellite/in-transit metastases (stage IIIB–IIIC melanoma) that would otherwise require extensive and mutilating surgery. This issue is often overlooked by regulators and payers who do not have good processes to assess this type of benefit. For these reasons we would not abandon the premise of using the combination of intralesional oncolytic injections and systemic IO just yet.

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REFERENCES

1. Andtbacka RHI, Collichio F, Harrington KJ, Middleton MR, Downey G, Öhrling K, 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 Immunother Cancer*. 2019;7(1):145. https://doi.org/10.1186/s40425-019-0623-z.
2. Ribas A, Dummer R, Puzanov I, VanderWalde A, Andtbacka RHI, Michielin O, et al. Oncolytic virotherapy promotes intratumoral T cell infiltration and improves anti-PD-1 immunotherapy. *Cell*. 2018;174(4):1031–2. https://doi.org/10.1016/j.cell.2018.07.035.Erratumfor:Cell.2017Sep;170(6):1109-1119.e10.
3. Garofalo M, Pancer KW, Wieczorek M, Staniszewska M, Salmaso S, Caliceti P, et al. From immunosuppression to immunomodulation—turning cold tumours into Hot. *J Cancer*. 2022;13(9):2884–92. https://doi.org/10.7150/jca.71992.
4. Chesney JA, Ribas A, Long GV, Kirkwood JM, Dummer R, Puzanov I, et al. Randomized, double-blind, placebo-controlled, global phase III trial of talimogene laherparepvec combined with pembrolizumab for advanced melanoma. *J Clin Oncol*. 2022;1:2. https://doi.org/10.1200/JCO.22.00343.

5. Andtbacka RH, Ross M, Puzanov I, Milhem M, Collichio F, Delman KA, et al. Patterns of clinical response with talimogene laherparepvec (T-VEC) in patients with melanoma treated in the OPTiM phase III clinical trial. *Ann Surg Oncol*. 2016;23(13):4169–77. https://doi.org/10.1245/s10434-016-5286-0.
6. Andtbacka RH, Kaufman HL, Collichio F, Amatruda T, Senzer N, Chesney J, et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. *J Clin Oncol*. 2015;33(25):2780–8. https://doi.org/10.1200/JCO.2014.58.3377.
7. Stahlie EHA, Mulder EEAP, Reijers S, Balduzzi S, Zuur CL, Klop WMC, et al. Single agent Talimogene Laherparepvec for stage IIIB-IVM1c melanoma patients: a systematic review and meta-analysis. *Crit Rev Oncol Hematol*. 2022;175:103705. https://doi.org/10.1016/j.critrevonc.2022.103705.
8. Stahlie EHA, Franke V, Zuur CL, Klop WMC, van der Hiel B, Van de Wiel BA, et al. T-VEC for stage IIIB-IVM1a melanoma achieves high rates of complete and durable responses and is associated with tumor load: a clinical prediction model. *Cancer Immunol Immunother*. 2021;70(8):2291–300. https://doi.org/10.1007/s00262-020-02839-7.
9. Stahlie EHA, Carr MJ, Zager JS, van Akkooi ACJ. External validation of a dutch predictive nomogram for complete response to T-VEC in an independent American patient cohort. *Ann Surg Oncol*. 2022;29(3):1637–44. https://doi.org/10.1245/s10434-021-11111-w.
10. Louie RJ, Perez MC, Jajja MR, Sun J, Collichio F, Delman KA, et al. Real-world outcomes of talimogene laherparepvec therapy: a multi-institutional experience. *J Am Coll Surg*. 2019;228(4):644–9. https://doi.org/10.1016/j.jamcollsurg.2018.12.027.
11. Perez MC, Miura JT, Naqvi SMH, Kim Y, Holstein A, Lee D, et al. Talimogene Laherparepvec (TVEC) for the treatment of advanced melanoma: a single-institution experience. *Ann Surg Oncol*. 2018;25(13):3960–5. https://doi.org/10.1245/s10434-018-6803-0.
12. Carr MJ, Sun J, DePalo D, Rothermel LD, Song Y, Straker RJ, et al. Talimogene laherparepvec (T-VEC) for the treatment of advanced locoregional melanoma after failure of immunotherapy: an international multi-institutional experience. *Ann Surg Oncol*. 2022;29(2):791–801. https://doi.org/10.1245/s10434-021-10910-5.