Real-Life Use of Talimogene Laherparepvec in Centers in Austria and Switzerland

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Objective

Talimogene Laherparepvec (TVEC), a genetically modified GM-CSF expressing HSV1 Virus that preferentially replicates in tumor cells is approved in Europe for use in melanoma patients with injectable metastatic lesions in stage III-IVM1a. Approval was based on the OPTIM study(1) which did also include patients with distant metastases and demonstrated a ORR of 40.5% and a CR rate of 16.6%. The aim of this study was to assess the outcome of melanoma patients treated with TVEC in a real life clinical setting outside of clinical studies.

Patients and Methods

A retrospective chart review was conducted in 7 melanoma centres in Austria and 1 centre in Switzerland and anonymized data on disease stage, treatment duration, treatment response by investigator assessment following RECIST 1.1, tolerability as well as data on follow up therapies was collected. Due to the nature of a retrospective study not all data points were available for every patient.
A total of 62 patients received TVEC since December of 2016 in the participating centres. Two thirds of the patients had stage III melanoma. Among those with stage IV the majority had M1a disease with only soft tissue or lymph node lesions. Two patients with stage IV M1b and M1d who had complete control of their distant metastases and a locoregional progression were treated in parallel with a PD-1 antibody in one case and in parallel with a BRAF/MEK inhibitor combination in the other. In 3 other cases TVEC was used in combination with a PD-1 inhibitor as first line of therapy. Baseline characteristics are presented in Table 1.

Results

Data cut off for this analysis was May 2019, the median follow up was 15.5 months (95% CI 11.7-20.6). The median number of intralesional injection cycles was 10 (Range 1-27). Response assessment was available for 59 of the 62 patients and showed an ORR of 67,7% with 50% of patients achieving a complete remission (Table 2). Median time to response among 38 responders was 4.7 months (95% CI 4.2-11.9, Figure 1). Median PFS was 25.8 months (95% CI 18.5-26,8) and median OS was not reached (Figure 2 A, C). Patients achieving a CR had a favourable long term outcome with a low likelihood of relapse and median PFS and OS was not reached in this group of patients (Fig. 2 B, D). 9 of 48 patients initially responding to TVEC had a subsequent progression with an equal distribution of locoregional and distant relapse. Among 17 patients with PD as their best response to TVEC 64% had a local relapse at the time of progression. The first follow-up therapy was a PD-1 blocking antibody in the majority of patients. 1 of the TVEC responders and 2 of the TVEC progressors showed a response to subsequent immunotherapy (Table 3). Of note one patient was retreated with TVEC after an initial CR and a relapse after 11 months of observation and did again show a complete remission, which is ongoing at the cut-off date. A detailed graphic showing detailed information on treatments, treatment duration and time point of response is shown in Figure 3.

Table 1: patient Characteristics

Patient Characteristics	n	%
Total no of patients	62	100
Age (median) years	73 (53-94)	-
Stage (AJCC 8th ed.) at start of TVEC		
III B/C/D	7/28/1	11/13/2
IV M1a/b/c/d	15/3/2/1	24/5/3/2
Not available	5	8
Mutational Status		
BRAF V600 mut.	17	27
NRAS mut	7	11
c-KIT mut	1	2
Not available	16	26

Table 3: Progression and subsequent therapy

Response to first follow up therapy	Relapse after PR or CR on TVEC n/%	PD on TVEC n/%
Total no of patients	9	17
Type of relapse		
locoregional	5/56%	11/64%
distant	4/44%	3/18%
locoregional + distant	-	3/18%
anti PD-1	4/44%	9/53%
CR/PR	1	2
PD	2	4
not available	1	3
BRAF/MEK Inhibitor	0	2/12%
CR/PR	-	1
not available	-	1
Talimogene Laherparepvec	1/11%	0
CR/PR	1	-
Electrochemotherapy	0	1/6%
Surgery (R0)	2/22%	2/12%
No further therapy	2/22%	0

A detailed graph showing individual patient information on treatments, treatment duration and time point of response is shown in Figure 3.
TVEC was well tolerated and only 2 out of 62 patients stopped TVEC because of side effects (Fever and consecutive cardiac decompensation, aseptic meningo-encephalitis). The only side effect observed in more than 10% of the patients was fever and chills (Table 4).

Table 2: Investigator assessed response

Investigator assesed response	n	%
CR	31	50,0
PR	11	17,7
SD	1	1,6
PD	16	25,8
NA	3	4,8

Figure 1: Time to response

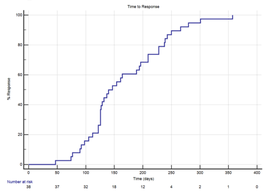

Figure 2: Progression free and Overall survival

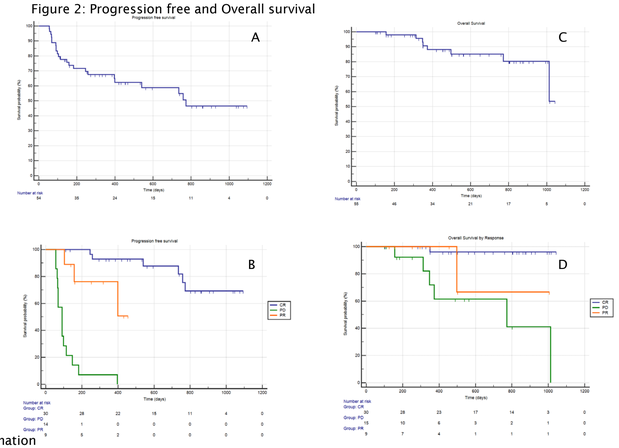

Figure 3: Individual patient information

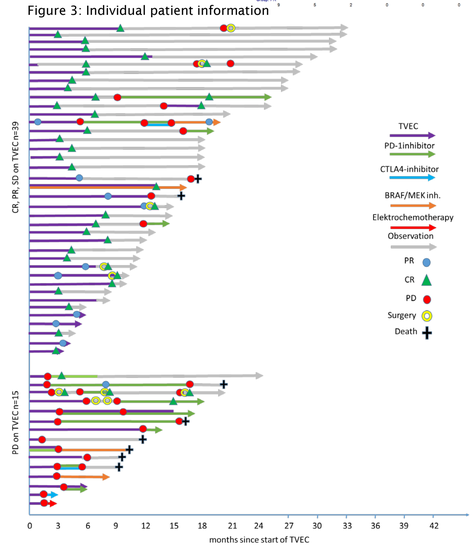

Table 3: Side effects during therapy with TVEC

Adverse Events	n	%
Chills/Fever	19	30,6
Erythema	4	6,5
Pain	4	6,5
Diarrhea	3	4,8
Cellulitis	3	4,8
Fatigue	2	3,2
Nausea/Vomiting	2	3,2
Loss of Appetite	2	3,2
Rash	1	1,6
Myalgia	1	1,6
Astenia	1	1,6
Vitiligo	1	1,6
Aseptic Meningo-Encephalitis	1	1,6
Infection	1	1,6
Vertigo	1	1,6
agrrav. of underlying disease	2 DM, 1 Card Insuff.	

Conclusion

In this real life cohort treatment with TVEC leads to a high overall and complete remission rate which is most likely due to selection of patients most likely to benefit from this treatment. This high response rate is in line with a previous, smaller cohort reported (2). The majority of responses was durable supporting the idea of induction of a systemic immune-response by TVEC. While the majority of patients was treated within the approved indication, a minority of patients with stage IV M1b-d disease was also treated with TVEC - mostly in patients with stable systemic disease but locoregional progression - with responses observed in some of those patients. TVEC was well tolerated in this real-life cohort with only 2 of 62 patients stopping treatment because of side effects. Although documentation of side effects is usually less stringent outside of a clinical study, those side effects recorded do more likely represent clinically meaningful events. If pretreatment with TVEC can alter the response to a subsequent systemic immunotherapy cannot be answered due to the low number of patients requiring these follow up treatment. In summary this real-life cohort study demonstrates that TVEC is a well-tolerated and highly effective intralesional therapy that can be successfully used in patients with injectable lesions that do not require immediate systemic therapy.

References

1 Andtbacka RHI et al., J Clin Oncol. 2015 Sep 1;33(25):2780-8
2 Franke V et al., Int J Cancer. 2019 Aug 15;145(4):974-978

Conflicts of Interest:

CH speaker/consultancy Amgen, BMS, MSD, Novartis, Pierre Fabre, Roche; OM speaker/consultancy BMS, Roche, Amgen, MSD, Novartis, GSK, Pierre-Fabre, research funding Amgen, BMS, MSD; all other authors do declare no COI in regard to the work presented.