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Association Between Complete Response and Survival in Advanced Melanoma Treated With Talimogene Laherparepvec (T-VEC) Plus Ipilimumab

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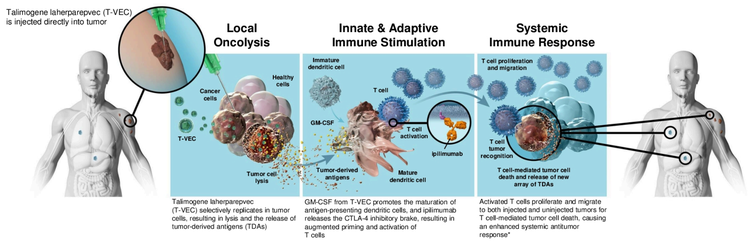
INTRODUCTION

- T-VEC is a genetically modified, oncolytic HSV-1 designed to selectively replicate within tumors and produce GM-CSF to enhance systemic antitumor immunity[1]
- Ipilimumab is an inhibitory antibody specific for cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) to enhance systemic antitumor immunity[2]
- This is the first randomized trial testing the addition of an oncolytic virus, T-VEC, to an immune checkpoint inhibitor, ipilimumab, for advanced, unresectable melanoma
  - The primary analysis was conducted approximately 6 months after the last patient was enrolled[3]
    - The objective response rate (ORR) was significantly higher with T-VEC plus ipilimumab versus ipilimumab alone (39% of the patients in the T-VEC + Ipi arm and 18% in the Ipi arm had an ORR; odds ratio, 2.9; 95% confidence interval (CI), 1.5 to 5.5; p=.002)
    - Combination treatment was tolerable and not associated with unexpected AEs or increase in incidence or severity of AEs for either agent
  - At the 3-year follow-up, the T-VEC plus ipilimumab combination demonstrated durable and statistically superior ORR over ipilimumab alone (36.7% vs 16.0%; odds ratio, 3.0; 95% CI, 1.6–6.0; P = 0.002)[4]
    - Complete response (CR) rate was 21.4% with the T-VEC plus ipilimumab combination and 6.0% with ipilimumab alone
    - Median overall survival (OS) was not reached in either arm
- In this post hoc analysis, we utilized the 3-year landmark data to explore the relationship between CR and OS in the T-VEC plus ipilimumab combination arm

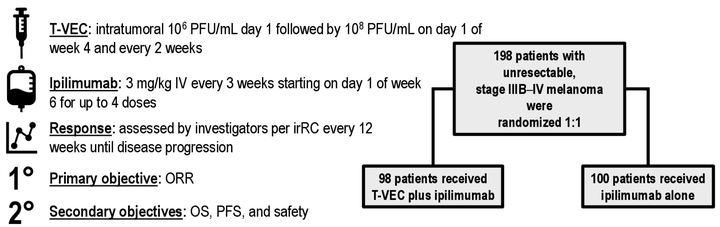
METHODS

Figure 1: Proposed MOA for T-VEC Plus Ipilimumab Combination



*This figure depicts the proposed mechanism of action and is not meant to imply clinical efficacy
CTLA-4: cytotoxic T-lymphocyte-associated protein 4; GM-CSF: granulocyte-macrophage colony-stimulating factor; MOA: mechanism of action; TDA: tumor-derived antigen; T-VEC: talimogene laherparepvec.

Figure 2: Methods, Treatment, Objectives, and Patients



irRC: immune-related response criteria; IV: intravenous; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PFU: plaque-forming unit

CONCLUSIONS

- CR rate was higher with T-VEC plus ipilimumab combination than with ipilimumab alone in patients with advanced melanoma (21.4% vs 6.0%)
- Achievement of CR was associated with prolonged OS
- Patients with CR tended to have better ECOG performance status, earlier-stage disease, and lower baseline tumor burden, as compared with those with non-CR
- CR was durable in both arms (95% ongoing in T-VEC plus ipilimumab combination arm, 100% ongoing in ipilimumab arm)

Acknowledgements

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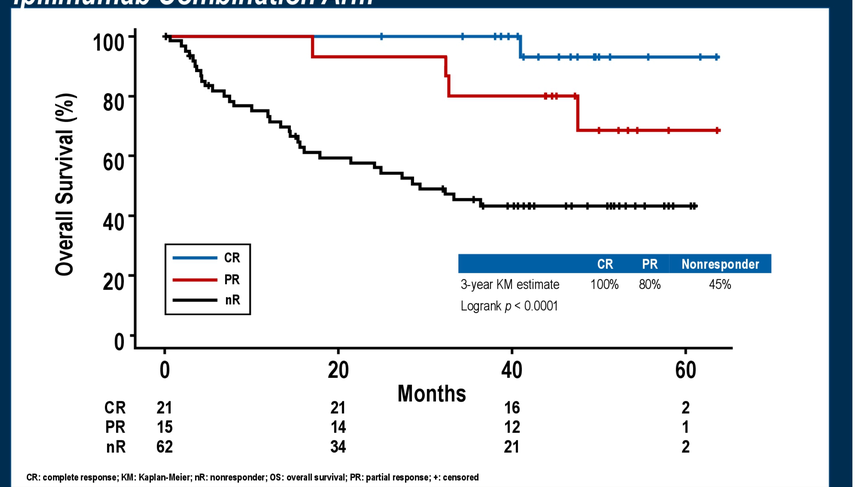
References

1. Liu BL, et al. *Gene Ther.* 2003;10:292-303.
2. Hodi FS, et al. *N Engl J Med.* 2010;363:711-723.
3. Chesney JA, et al. *J Clin Onc.* 2018;36:1658-1667.
4. Chesney JA, et al. *Ann Oncol.* 2019;30(suppl_5):mdz394-067.

In patients with advanced melanoma:

- ***CR rate was higher with T-VEC plus ipilimumab*** than with ipilimumab alone
- ***CR was associated with prolonged OS in both arms***

Figure 5: CR Correlated With Improved OS in the T-VEC Plus Ipilimumab Combination Arm



CR: complete response; KM: Kaplan-Meier; nR: nonresponder; OS: overall survival; PR: partial response; +: censored

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RESULTS

Table 1: Baseline Patient Characteristics by Arms and Response

	Ipilimumab With CR (N = 6)	Ipilimumab Without CR (N = 94)	T-VEC + Ipilimumab With CR (N = 21)	T-VEC + Ipilimumab Without CR (N = 77)	Total (N = 198)
ECOG PS – n (%)					
0	6 (100.0)	67 (71.3)	17 (81.0)	52 (67.5)	142 (71.7)
1	0 (0.0)	27 (28.7)	4 (19.0)	25 (32.5)	56 (28.3)
Baseline LDH – n (%)					
≤ 1xULN	3 (50.0)	71 (75.5)	20 (95.2)	59 (76.6)	153 (77.3)
> 1-2xULN	3 (50.0)	17 (18.1)	0 (0.0)	10 (13.0)	30 (15.2)
> 2xULN	0 (0.0)	5 (5.3)	1 (4.8)	6 (7.8)	12 (6.1)
Unknown	0 (0.0)	1 (1.1)	0 (0.0)	2 (2.6)	3 (1.5)
BRAF V600 mutation status – n (%)					
Mutation	4 (66.7)	30 (31.9)	8 (38.1)	27 (35.1)	69 (34.8)
Wild-type	2 (33.3)	58 (61.7)	13 (61.9)	49 (63.6)	122 (61.6)
Missing/unknown	0 (0.0)	6 (6.4)	0 (0.0)	1 (1.3)	7 (3.5)
Baseline HSV-1 status – n (%)					
Negative	2 (33.3)	7 (7.4)	1 (4.8)	5 (6.5)	15 (7.6)
Positive	1 (16.7)	16 (17.0)	3 (14.3)	11 (14.3)	31 (15.7)
Unknown	3 (50.0)	71 (75.5)	17 (81.0)	61 (79.2)	152 (76.8)
Prior surgical procedures (CRF) – n (%)	6 (100.0)	83 (88.3)	21 (100.0)	72 (93.5)	182 (91.9)
Prior anticancer therapy (CRF) – n (%)	3 (50.0)	26 (27.7)	7 (33.3)	18 (23.4)	54 (27.3)
Time from initial histological diagnosis of melanoma to enrollment date (years) – median (range)	3.56 (0.5–22.7)	2.00 (0.0–35.5)	2.29 (0.0–21.3)	0.93 (0.0–22.4)	1.62 (0.0–35.5)
Visceral disease at baseline – n (%)	2 (33.3)	44 (46.8)	5 (23.8)	33 (42.9)	84 (42.4)
Baseline SPD of all index lesions (mm^2) – median (range)	442.8 (70.0–2,340.0)	604.0 (36.0–15,802.0)	594.0 (49.0–2,611.7)	1008.8 (72.0–26,137.5)	836.0 (36.0–26,137.5)
Stage (current) – n (%)					
IIIB	1 (16.7)	8 (8.5)	3 (14.3)	2 (2.6)	14 (7.1)
IIIC	1 (16.7)	30 (31.9)	9 (42.9)	20 (26.0)	60 (30.3)
IV M1a	2 (33.3)	15 (16.0)	4 (19.0)	12 (15.6)	33 (16.7)
IV M1b	1 (16.7)	9 (9.6)	2 (9.5)	18 (23.4)	30 (15.2)
IV M1c	1 (16.7)	32 (34.0)	3 (14.3)	25 (32.5)	61 (30.8)

CR: complete response; CRF: case report form; ECOG PS: Eastern Collective Oncology Group performance status; LDH: lactate dehydrogenase; SPD: sum of the products of the two largest perpendicular diameters; ULN: upper limit of normal

Table 2: More Patients Achieved CR in the T-VEC Plus Ipilimumab Combination Arm

	T-VEC + Ipilimumab (N = 98)	Ipilimumab (N = 100)
BOR – n (%)		
CR	21 (21.4)	6 (6.0)
PR	15 (15.3)	10 (10.0)
SD	19 (19.4)	24 (24.0)
PD	30 (30.6)	35 (35.0)
UE	7 (7.1)	16 (16.0)
ND	6 (6.1)	9 (9.0)

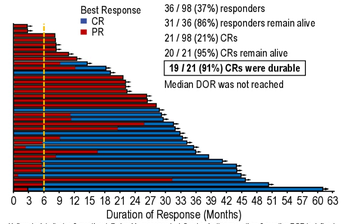
Response criteria per irRC. BOR: best overall response; CR: complete response; ND: not determined; PD: progressive disease; PR: partial response; SD: stable disease; UE: unevaluable;

Table 3: Most CR Lasting More Than 6 Months Occurred in Earlier Stage Patients

	T-VEC + Ipilimumab (N = 19)	Ipilimumab (N = 6)
Current stage (at baseline) of durable responders – n (%)		
IIIB	2 (10.5)	1 (16.7)
IIIC	9 (47.4)	1 (16.7)
IV M1a	3 (15.8)	2 (33.3)
IV M1b	2 (10.5)	1 (16.7)
IV M1c	3 (15.8)	1 (16.7)
Response duration, median - months (range)	28.8 (6.0-58.2)	30.7 (22.9-46.5)

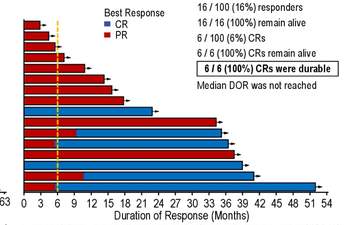
Durable response is defined as lasting more than 6 months

Figure 3: Responses Were Durable In the T-VEC Plus Ipilimumab Combination Arm



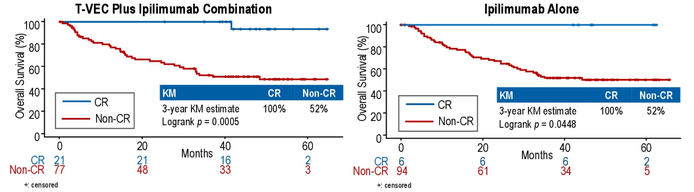
Yellow dash indicates 6-month cutoff; durable response is defined as lasting more than 6 months; DOR is defined as the time from the first confirmed CR or PR to the confirmed disease progression per modified irRC or death, whichever occurs earlier
CR: complete response; DOR: duration of response; PR: partial response

Figure 4: Responses Were Durable In the Ipilimumab Arm



Yellow dash indicates 6-month cutoff; durable response is defined as lasting more than 6 months; DOR is defined as the time from the first confirmed CR or PR to the confirmed disease progression per modified irRC or death, whichever occurs earlier
CR: complete response; DOR: duration of response; PR: partial response

Figure 6: CR Correlated With Improved OS Compared With Non-CR



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