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Supplemental Information

Oncolytic Virotherapy Promotes Intratumoral T Cell Infiltration and Improves Anti-PD-1 Immunotherapy

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SUPPLEMENTAL TABLES

Supplemental Table 1 (Related to Figure 1). Patient Demographics and Baseline Clinical Characteristics

	Talimogene Laherparepvec Plus Pembrolizumab (N=21)
Sex, n (%)	
Female	13 (62)
Male	8 (38)
Median (range) age, years	58 (37–89)
ECOG performance status, n (%)	
0	19 (90)
1	2 (10)
Disease substage, n (%)	
IIIB	1 (5)
IIIC	6 (29)
IVM1a	2 (10)
IVM1b	4 (19)
IVM1c	8 (38)
LDH, n (%)	
≤ULN	16 (76)
>ULN to 2 × ULN	5 (24)
>2 × ULN	0
HSV serostatus, n (%)	
Positive	16 (76)
Negative	5 (24)
BRAF status, n (%)	
Mutant	4 (19)
Wild-type	17 (81)

PD-L1 status,[a] n (%)	
Positive	17 (81)
Negative	2 (10)
Unknown	2 (10)
Prior anticancer therapy, n (%)	7 (33)
Interferon	4 (19.0)
Isolated limb perfusion	1 (4.8)
Chemoembolization	0 (0.0)
Eyedrops	1 (4.8)
Topical immunotherapy	1 (4.8)

ECOG=Eastern Cooperative Oncology Group; HSV=herpes simplex virus; LDH=lactate dehydrogenase; PD-L1=programmed death ligand 1; ULN=upper limit of normal.

[a]Cutoff for positivity was ≥1% PD-L1 by immunohistochemistry.

Supplemental Table 2 (Related to Figure 1). Patient Incidence of Adverse Events

	Total		Attributed to Talimogene Laherparepvec		Attributed to Pembrolizumab		Attributed to Talimogene Laherparepvec and/or Pembrolizumab	
	Any Grade n (%)	Grade 3/4 n (%)[a]	Any Grade n (%)	Grade 3/4 n (%)[a]	Any Grade n (%)	Grade 3/4 n (%)[a]	Any Grade n (%)	Grade 3/4 n (%)[a]
Patient incidence of AEs irrespective of relationship to treatment	21 (100)	11 (52)	-	-	-	-	-	-
Patient incidence of treatment-related AEs	21 (100)	8 (38)	20 (95)	4 (19)	20 (95)	7 (33)	21 (100)	8 (38)
AEs occurring in ≥10% of patients irrespective of relationship to treatment[b]								
Fatigue	14 (67)	0	9 (43)	0	13 (62)	0	13 (62)	0
Fever	11 (52)	0	8 (38)	0	6 (29)	0	9 (43)	0
Chills	10 (48)	0	8 (38)	0	6 (29)	0	10 (48)	0
Diarrhea	10 (48)	1 (5)	4 (19)	0	5 (24)	0	6 (29)	0
Rash	9 (43)	2 (10)	6 (29)	0	7 (33)	2 (10)	8 (38)	2 (10)
Nausea	8 (38)	0	5 (24)	0	3 (14)	0	6 (29)	0
Headache	8 (38)	1 (5)	3 (14)	1 (5)	1 (5)	0	3 (14)	1 (5)
Cough	8 (38)	0	0	0	1 (5)	0	1 (5)	0
Arthralgia	7 (33)	0	3 (14)	0	7 (33)	0	7 (33)	0
Vomiting	7 (33)	0	4 (19)	0	3 (14)	0	5 (24)	0

Pruritus	6 (29)	0	4 (19)	0	6 (29)	0	6 (29)	0
Peripheral edema	5 (24)	0	0	0	1 (5)	0	1 (5)	0
Hypothyroidism	5 (24)	0	1 (5)	0	5 (24)	0	5 (24)	0
Influenza-like illness	5 (24)	0	4 (19)	0	2 (10)	0	4 (19)	0
Vitiligo	5 (24)	0	2 (10)	0	5 (24)	0	5 (24)	0
Constipation	4 (19)	0	0	0	0	0	0	0
Dyspnea	4 (19)	0	1 (5)	0	2 (10)	0	2 (10)	0
Alanine aminotransferase increased	3 (14)	2 (10)	1 (5)	0	3 (14)	1 (5)	3 (14)	1 (5)
Aspartate aminotransferase increased	3 (14)	1 (5)	1 (5)	0	2 (10)	1 (5)	2 (10)	1 (5)
Hyperglycemia	3 (14)	2 (10)	0	0	2 (10)	2 (10)	2 (10)	2 (10)
Hyperthyroidism	3 (14)	0	0	0	3 (14)	0	3 (14)	0
Myalgia	3 (14)	0	2 (10)	0	2 (10)	0	3 (14)	0
Back pain	3 (14)	0	0	0	0	0	0	0
Pain in extremity	3 (14)	0	0	0	0	0	0	0
Rash (maculopapular)	3 (14)	0	1 (5)	0	3 (15)	0	3 (14)	0
Squamous cell carcinoma	3 (14)	2 (10)	0	0	0	0	0	0
Alopecia	3 (14)	0	0	0	1 (5)	0	1 (5)	0

AE=adverse event.

[a]One grade 5 AE occurring during the study was attributed to disease progression. No grade 4 talimogene laherparepvec–related AEs occurred. One patient had grade 4 pembrolizumab-related pneumonitis; no other grade 4 pembrolizumab-related AEs occurred;

[b]no grade 4 events occurred in ≥10% of patients.

Supplemental Table 3 (Related to Figure 1). Summary of Best Change in Injected and Noninjected Nonvisceral Lesions

	Injected Lesions (n=16) n (%)	Noninjected Nonvisceral Lesions (n=10) n (%)
Any reduction	15 (93.7)	6 (60)
50% to <100% reduction	1 (6.3)	0
100% reduction	13 (81.3)	6 (60)
Never decrease	1 (6.3)	4 (40)

Supplemental Table 4 (Related to Figure 4). Cell Subset Changes Within the Tumor Between Injected Lesions at Week 6 and Baseline Lesions (Week 1)

Cell subset	Baseline Density Mean (cells/mm^2)	Week 6 Density Ratio to Baseline	*P* Value[b]
CD3+	204.21	2.57	2.28×10^{-23}
CD4+	68.96	2.73	7.56×10^{-21}
CD8+	126.15	2.47	3.70×10^{-20}
FOXP3	32.53	1.70	1.38×10^{-8}
PD-1	202.24	2.27	1.57×10^{-17}
PD-L1	172.28	2.73	1.99×10^{-16}
CD68+	71.01	1.09	0.41
CD45RO	204.57	1.56	6.86×10^{-6}
CD56+	339.99	1.31	1.30×10^{-3}
CD20+	1.58	5.33	2.03×10^{-9}
CTLA	22.49	0.77	0.09
CD3+CD8+	89.82	2.64	3.85×10^{-20}
CD3+CD8+PD-1	61.69	2.40	1.97×10^{-15}
CD3+CD4+	68.96	2.73	7.56×10^{-21}
CD3+CD4+PD-1	32.57	2.76	9.26×10^{-20}
CD3+CD4+FOXP3	13.00	1.90	1.46×10^{-7}

CD68+PD-L1	10.61	2.35	4.97×10^{-9}
CD3+CD4+PD-L1	8.43	4.74	1.70×10^{-20}
CD3+CD4+CD45RO	29.72	2.02	4.53×10^{-8}
CD3+CD8+CD45RO	40.52	1.94	1.49×10^{-7}
CD3+CD8+PD-L1	9.43	4.19	1.37×10^{-16}
CD3+CD8+CD56	1.01	3.34	2.53×10^{-6}
CD3+CD8+CD56+PD-L1	0.06	5.31	5.19×10^{-5}
CD3+CD4+PD1	32.57	2.76	9.26×10^{-20}
CD3+CD8+PD1	61.69	2.40	1.97×10^{-15}
CD3+CD20+	1.58	5.33	2.03×10^{-9}
CD3+CD20+PD-L1	0.16	6.35	1.15×10^{-7}