Durable responses and immune activation with intratumoral electroporation of pIL-12 plus pembrolizumab in actively progressing anti-PD-1 refractory advanced melanoma: KEYNOTE 695 interim data

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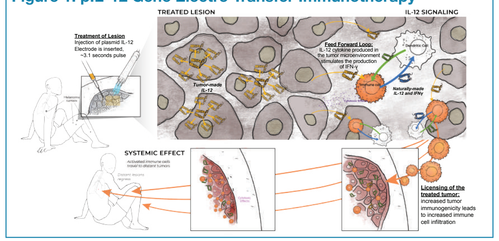
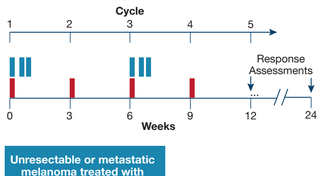
Background

- IL-12 is an immunoregulatory cytokine that promotes communication between innate (dendritic cells, macrophages and natural killer cells) and adaptive immune subsets (T and B cells)
- Importantly, IL-12 expression, working in concert with IFN-γ, productively alters the tumor microenvironment (**Figure 1**) and is critical for successful anti-tumor immunity including anti-PD-1 immunotherapy[1]
- While this IL-12/IFN-γ axis is often absent in advanced melanoma, intratumoral electroporation of plasmid IL-12 (TAVO™ or tavokinogene telseplasmid) can re-establish this axis, leading to both single agent and anti-PD-1 combination activity in predicted non-responders[2,3]
- These data provided the rationale to extend this intratumoral IL-12 platform to treat a rigorously defined anti-PD-1 refractory patient population with a TAVO and pembrolizumab combination

Figure 1. pIL-12 Gene Electro Transfer Immunotherapy



KEYNOTE-695 Trial Design



IT-TAVO-EP days 1, 5, 8
Pembro 200 mg day

Unresectable or metastatic melanoma treated with anti-PD-1 (alone or in combination) for 12 weeks prior to study entry

- Must have confirmed RECIST v1.1 progression with no intervening therapy prior to study entry
- RECIST v1.1 measurable disease and at least one anatomically distinct lesion accessible for electroporation

Planned Enrollment N=100

- Pembrolizumab 200 mg IV every 3 week
- pIL12 (TAVO) administered to at least one accessible lesion(s) on days 1, 5, and 8 every 6 weeks until no more lesions to treat

All Responses are by RECIST v1.1
Primary Endpoint: ORR by blinded independent review
Secondary Endpoints: Investigator assessed ORR, DOR, PFS, iPFS, iORR, OS

References

1. Garris CS, et al. *Immunity*. 2018;49(6):1148-1161.e7.
2. Algazi A, et al. *Ann Oncol*. 2020;31(4):532-540.
3. Algazi AP, et al. *Clin Cancer Res*. 2020;26(12):2827-2837.
4. Tickotsky N, et al. *Bioinformatics*. 2017;33(18):2924-2929.

Abreviations

BL SLD, baseline sum of the longest diameters; **C**, cycle; **D**, day; **Dab**, dabrafenib; **DOR**, duration of response; **ECOG**, Eastern Cooperative Oncology Group; **EOT**, end of treatment; **FFPE**, formalin fixed paraffin embedded; **iORR**, immune objective response rate; **iPFS**, intracranial progression-free survival; **Ipi**, ipilimumab; **LDH**, lactate dehydrogenase; **LN**, lymph node; **LTFU**, long-term follow-up; **Nivo**, nivolumab; **mo**, month(s); **ORR**, overall response rate; **OS**, overall survival; **Pembro**, pembrolizumab; **PFS**, progression-free survival; **PMN-MDSC**, polymorphonuclear myeloid-derived suppressor cells; **Rt**, right; **SC**, subcutaneous; **TCR**, T-cell receptor; **TIL**, tumor infiltrating lymphocyte; **TME**, tumor microenvironment; **Tram**, trametinib; **wk**, week(s)

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Results

Table 1. Patient Demographics and Disease Characteristics

	N=56
Sex	
Female	25 (44.6%)
Male	31 (55.4%)
Age (years)	
Median (Range)	66 (30, 86)
ECOG Performance Status	
0	35 (62.5%)
1	21 (37.5%)
BRAF Status	
Mutant (V600E, V600K)	12 (21.4%)
Wild-Type or non-V600 mutation	44 (78.6%)

	N=56
LDH[1]	
Normal	42 (75.0%)
Elevated >ULN*	11 (19.6%)
Unknown	3 (5.4%)
Stage	
III (B,C,D)	9 (16%)
IV (a,b)	30 (53.6%)
IV (c,d)	17 (30.4%)
Number of Target + Non Target Lesions at Baseline	
>3	43 (76.8%)
Mean	8.9 (range 1, 169)
Number of Prior Therapies	
1 line	28 (50%)
2-3 lines	13 (23.2%)
≥ 4 lines	15 (26.8%)
Median	1.5
Mean	2.9 (range 1, 17)
No. of Pts with Prior Ipilimumab	15 (27%)
Median time of anti-PD-1 exposure prior to study entry with no more than a 12 week gap in between treatments	5.3 months
Median time from last dose of anti-PD-1 to study treatment (Cycle 1 Day 1)	1.2 months

[1]Based on maximum value prior to dosing 2 patients with > 2x ULN

Table 2. Treatment-Related Adverse Events (TRAEs) > 5% of Patients

	All Grades n (%) (N=56)	Grade 1/2	Grade 3	Grade 4	Grade 5
Patients with at least one TRAE	43 (76.8%)	40 (71.4%)	3 (5.4%)	–	–
Fatigue	15 (26.8%)	15 (26.8%)	–	–	–
Procedural pain	13 (23.2%)	13 (23.2%)	–	–	–
Diarrhea	11 (19.6%)	11 (19.6%)	–	–	–
Nausea	6 (10.7%)	6 (10.7%)	–	–	–
Rash	6 (10.7%)	6 (10.7%)	–	–	–
Abdominal pain	4 (7.1%)	4 (7.1%)	–	–	–
Arthralgia	4 (7.1%)	4 (7.1%)	–	–	–
Injection site pain	4 (7.1%)	4 (7.1%)	–	–	–
Myalgia	4 (7.1%)	4 (7.1%)	–	–	–
Pruritus	4 (7.1%)	4 (7.1%)	–	–	–
Administration site reaction	3 (5.4%)	3 (5.4%)	–	–	–
Aspartate aminotransferase increased	3 (5.4%)	3 (5.4%)	–	–	–
Cellulitis	3 (5.4%)	2 (3.6%)	1 (1.8%)	–	–
Dysgeusia	3 (5.4%)	3 (5.4%)	–	–	–
Upper respiratory tract infection	3 (5.4%)	3 (5.4%)	–	–	–
Enteritis	1 (1.8%)	–	1 (1.8%)	–	–
Lichen planus	1 (1.8%)	–	1 (1.8%)	–	–

Patients who experienced the same TEAE on more than one occasion (based on the specific category) are counted once in each relevant category (n). Adverse event terms are coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0.

- The median time for pIL-12 (TAVO™) electroporation treatment was 11 minutes (range 1,76)

Figure 2. Best Overall Response

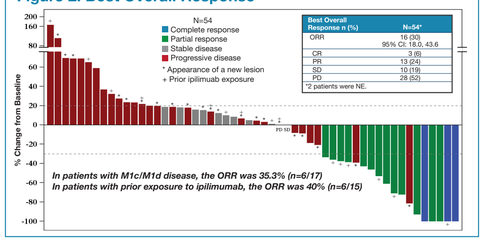


Figure 3. Percent Change in Tumor Size Over Time

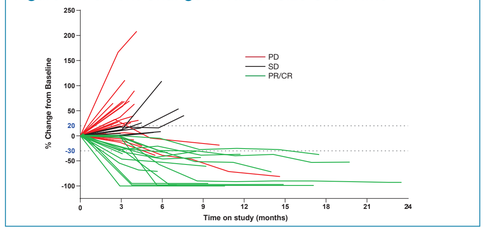


Figure 4. Treated and Untreated Lesions from 16 Responding Patients

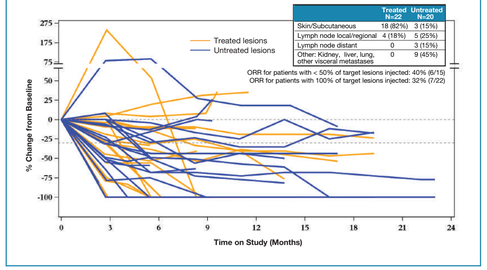


Figure 5. Actively Progressing Patients and Short Interval Between the Last Dose of Anti-PD-1 and Study Treatment

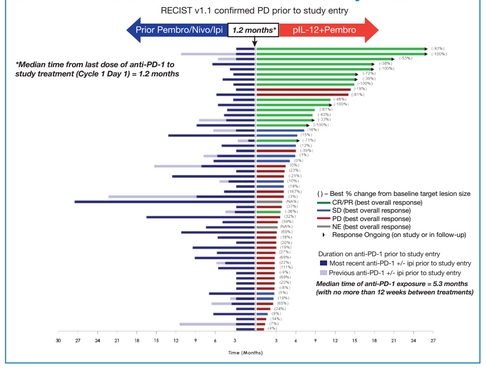


Figure 6. Actively Growing Lesions Significantly Reduce in Size After pIL-12 + Pembrolizumab Treatment

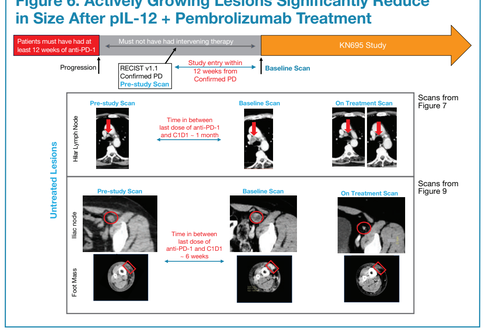


Figure 7. Pseudo Progression in Target Lesion Followed by Tumor Response (Stage IVB; PR [-93%])

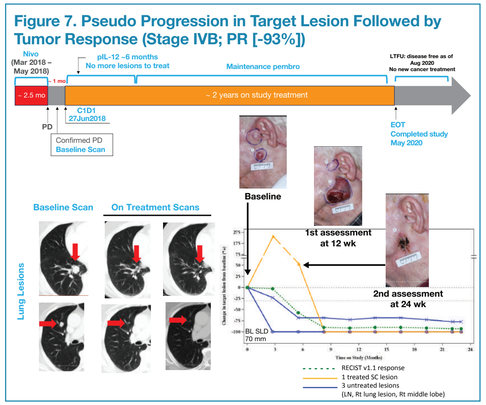


Figure 8. Progression on Ipi/Nivo Followed by Tumor Response (Stage IVC; PR [-53%])

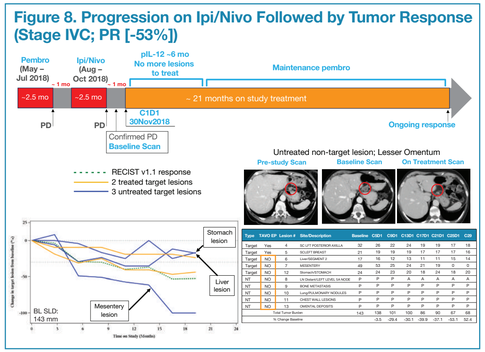


Figure 9. Progression on Ipi/Nivo Followed by Tumor Response (Stage IVC; PR [-71%])

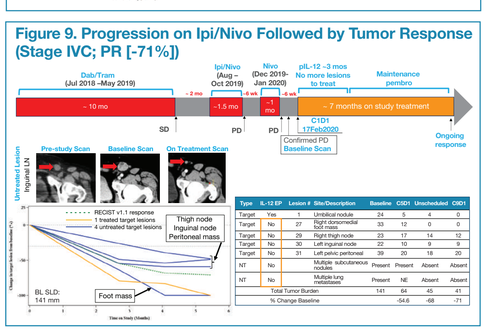
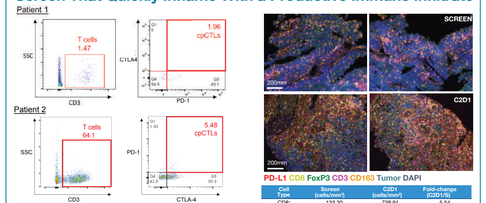


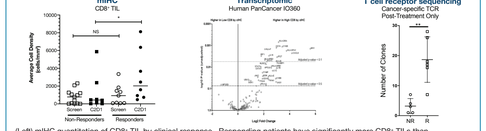
Figure 10. Patients Have Immunologically Quiescent Lesions at Screen That Quickly Inflame With a Productive Immune Infiltrate



Cell Type	Screen (cells/mm²)	C2D1 (cells/mm²)	Fold-change (C2D1/S)
CD8⁺	133.30	738.91	5.54
CD4⁺	376.24	260.57	0.69
CD163⁺	789.02	1135.15	1.44
FoxP3⁺	53.84	35.69	0.66
PD-L1⁺	173.01	3655.78	21.13

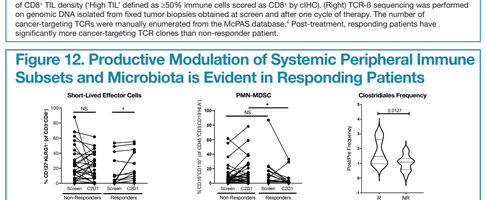
Fresh tumor biopsies (left) were dissociated and analyzed by flow cytometry (cpCTL = 'checkpoint' or 'partially exhausted' cytotoxic lymphocytes). Gating: singles> live>CD45⁺>CD3⁺CD8⁺>CTLA-4⁺ PD-1⁺. FFPE-fixed biopsies (right) were stained as shown, imaged on a Vectra Polaris system, and enumerated as cells per mm².

Figure 11. On-treatment Increase of CD8⁺ T cells in TME is Associated With an Active Transcriptomic Profile With Increased Intratumor Clonality After a Single Cycle of Treatment



(Left) mIHC quantitation of CD8⁺ TIL by clinical response. Responding patients have significantly more CD8⁺ TILs than non-responders after 1 cycle of treatment. (Middle) Transcriptomic analysis of FFPE tumor RNA grouped by differential expression of CD8⁺ TIL density ('High TIL' defined as ≥50% immune cells scored as CD8⁺ by cIHC). (Right) TCR-δ sequencing was performed on genomic DNA isolated from fixed tumor biopsies obtained at screen and after one cycle of therapy. The number of cancer-targeting TCRs were manually enumerated from the McPAS database.* Post-treatment, responding patients have significantly more cancer-targeting TCR clones than non-responder patient.

Figure 12. Productive Modulation of Systemic Peripheral Immune Subsets and Microbiota is Evident in Responding Patients



Patient PBMCs taken at screen and after 2 cycles of treatment were analyzed by flow cytometry. (Left, middle) Responding patients show significant on-treatment increases in short-lived effector cells (Gating: singles>live>CD3⁺CD8⁺>CD127⁻KLRG1⁺) with significantly fewer PMN-MDSCs compared to non-responders (Gating: singles>live>CD45⁺>CD3⁻>CD19⁻>HLA>>CD15⁺CD11b⁺). (Right) Genomic DNA was extracted from 2g of patient fecal material and whole genome sequencing was performed at a depth of 6M reads. Responding patients show a significant on-treatment increase in the frequency of Clostridiales compared to non-responding patients (fold-change C2D1/Screen).

Summary

1. The addition of pIL-12-EP (TAVO) to PD-1 antibody therapy induced several complete responses and numerous deep systemic durable responses in a clinically proven PD-1 antibody refractory patient population as determined by rigorous enrollment criteria
   - ORR was 30% (95%CI [18.0%, 43.6%]) (16/54), Investigator-assessed RECIST v1.1
   - 6% (3/54) complete response rate
   - 9% (5/54) of patients had 100% reduction of target lesions
   - All responses are confirmed
   - ORR was 35.3% (n=6/17) in patients with M1c/M1d disease
   - ORR was 40% (n=6/15) in patients with prior exposure to ipilimumab
   - Tumor responses were observed in distant and visceral lesions
   - Median duration of response (mDOR) is currently 12.2 months (95% CI, 5.6-NE) (11 patients censored before 12 months)
     - Median study follow-up was 13.5 months
     - Two patients completed the 2 year study duration with responses ongoing
     - Of 16 responding patients, 3 relapsed as of September 11, 2020
2. Nominal toxicity
   - Grade 3 Treatment-related AEs were seen in 5.4% of patients
   - No grade 4/5 treatment-related AEs
3. Actively progressing patients with a short interval of 1.2 months between last dose of anti-PD-1 and study treatment
4. On-treatment biomarker signatures demonstrate that this combination treatment licenses immunologically quiescent tumors to yield productive local and systemic immune responses

Acknowledgments

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