Durable responses with intratumoral electroporation of plasmid interleukin 12 plus pembrolizumab in patients with advanced melanoma progressing on an anti-PD-1 antibody: updated data from Keynote 695

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ABSTRACT 383

Background & Introduction

To facilitate the evaluation of novel agents after progression on PD-1 antibodies, a SITC task force has established stringent criteria to minimize the possible contribution of delayed response to immunotherapy (pseudoprogression) to identify patients with ≤ 5% chance of delayed response if treatment was continued past progression.[1] These stringent criteria include confirmation of disease progression following a full course (~12 weeks) of anti-PD-1/L1 treatment. To our knowledge, the only reported phase 3 randomized trial that enrolled patients according to these stringent criteria was the ILLUMINATE 301 (TLR + ipi vs ipi) trial, which showed an objective response rate to ipilimumab of 8.6% in patients with immediate prior progression and PD-1 antibody therapy. These data suggest that an objective response rate of 8.6% to ipilimumab (in ipi naive patients) in a patient population with confirmed progression on prior anti-PD-1, is a true treatment effect and a new benchmark for this patient population.

The KEYNOTE-695 study is a single-arm, phase 2, open-label, multicenter study of intratumoral plasmid IL12-EP (TAVO) plus pembrolizumab in patients with unresectable or metastatic melanoma progressing on PD-1 antibodies who have met the stringent criteria to minimize any potential contribution of pseudoprogression.

Key eligibility criteria:

- PD-1 antibody therapy for at least 12 weeks
- Documented and confirmed disease progression within 12 weeks of last PD-1 antibody dose
- Any number of prior therapies, but not intervening treatment between last PD-1 antibody dose and initiation of treatment on study

Once a rigorously defined patient population is identified, the duration of response and survival are key factors in evaluating new agents. Here, we present response and survival duration data for the initial cohort of 56 patients treated on study based on a data cutoff of 9/30/21. Safety data are presented for all 105 patients enrolled.

Non-Viral Cytokine Gene Therapy: Using the Tumor to Safely Harness the Power of IL-12

1 Billions of IL-12 coded DNA plasmids are injected directly into the tumor to produce immune modulatory proteins

2 Intratumoral electroporation increases the permeability of cell membranes, facilitating uptake ("transfection") of IL-12 coded DNA plasmids into cells

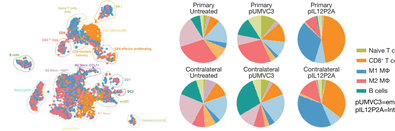
3 IL-12 transfected cells express and secrete IL-12 into the tumor microenvironment (TME)

4 IL-12 expression in the TME enhances immunomodulatory molecules to promote local tumor inflammation

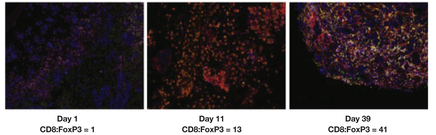
5 IL-12 expression in the TME endues systemic immune activation and T-cell education for a systemic anti-tumor immune response

IL-12 is a potent, well-characterized, pro-inflammatory cytokine
Intratumoral delivery of IL-12 may stimulate a safe but powerful systemic immune response

Intratumoral Electroporation of Plasmid IL-12 Increases Tumor Immunogenicity



Immune composition of B16-F10 murine melanoma tumors by scRNA-seq with intratumoral IL-12 with electroporation is associated with an increase in CD8+ T cells and M1 macrophage in both injected (primary lesion) and distal non-injected lesions (contralateral lesion).



Day 1
CD8:FoxP3 = 1

Day 11
CD8:FoxP3 = 13

Day 39
CD8:FoxP3 = 41

Stains: PD-L1 CD8 FoxP3 CD3 CD163 Tumor DAPI

IHC of tumors from a responding patient treated with pIL-12-EP (TAVO) monotherapy is associated with an increase in CD8+ T cells and an increase in the CD8+:FoxP3+ cells ratio.

Results

Figure 1. Confirmation of Disease Progression Is Required for Eligibility on KN695

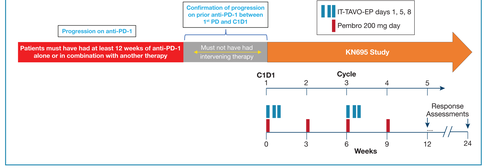
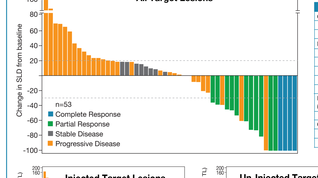


Table 1. Patient Demographics and Disease Characteristics

	Total N=56
Age (years)	
Median (range)	65.5 (30, 86)
Age Category, n (%)	
<65 years	26 (46.4)
≥65 years	30 (53.6)
Sex, n (%)	
Male	31 (55.4)
Female	25 (44.6)
Ethnicity, n (%)	
Hispanic or Latino	5 (8.9)
Not Hispanic or Latino	51 (91.1)
Race, n (%)	
White	52 (92.9)
Black or African American	1 (1.8)
Other	3 (5.4)
Number of Prior Therapies, n (%)	
1 line	29 (51.8)
2-3 lines	22 (39.3)
≥4 lines	5 (8.9)
Prior Ipilimumab, n (%)	
Yes	15 (26.8)
No	41 (73.2)
Prior BRAF/MEK, n (%)	
No	44 (78.6)
Yes	12 (21.4)
Duration of Last Anti-PD-1 Treatment (months)	
Median	4.70
BOR on Prior anti-PD-1 Therapy, n (%)	
CR	2 (3.6)
PR	7 (12.5)
SD	5 (8.9)
PD	35 (62.5)
Missing	7 (12.5)
Time from Last Anti-PD-1 Dose to C1D1 (months)	
Median	1.25
ECOG Performance Status, n (%)	
0	35 (62.5)
1	21 (37.5)
BRAF Status, n (%)	
Negative	44 (78.6)
Positive	12 (21.4)
Baseline Lactate Dehydrogenase (LDH), n (%)	
Normal	42 (75.0)
Elevated >ULN	11 (19.6)
≥2xULN	2 (3.6)
Missing	3 (5.4)
Stage Grouping at Screening, n (%)	
Stage III (B–D)	10 (17.9)
Stage IVA and IVB	29 (51.8)
Stage IVC and IVD	17 (30.4)

Figure 2. Reduction of Un-Injected Lesion(s) Demonstrates Systemic Response to TAVO + Pembrolizumab in Patients With Documented Confirmed Progression on Anti-PD-1 Therapy



Efficacy Evaluable Population N=54	
Objective Response Rate (CR + PRs, n (%))	15 (27.8)
95% Confidence Interval	16.5, 41.6
Best Overall Response, n (%)	
Complete Response (CR)	4 (7.4)
Partial Response (PR)	11 (20.4)
Stable Disease (SD)	9 (16.7)
Progressive Disease (PD)	30 (55.6)
Durable Objective Response Rate (CR + PR ≥24 weeks), n (%)	12 (22.2)
ORR of Subgroups, n (%)	
Prior Treatment With Ipilimumab	5/15 (33.3%)
Baseline Stage M1b/M1c/M1d	7/27 (25.9%)

Figure 3. Systemic Tumor Response in Visceral Lesion(s)

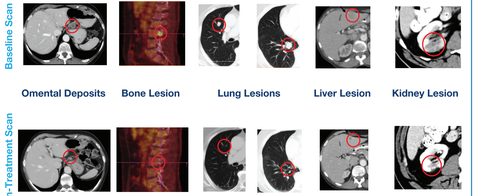
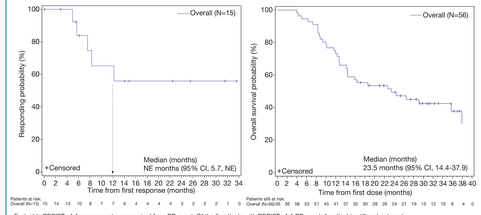


Figure 4. Patients With Documented Confirmed Progression on Prior Anti-PD-1 Therapy Have a Median DOR Not Reached and Median OS of 23.5 Months

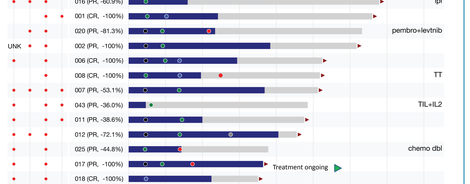


Evaluable RECIST v1.1 assessment was required for a PD event. Of the 5 patients with RECIST v1.1 PD event, 1 patient is still on treatment.

Patients were censored at last evaluable RECIST assessment, before the initiation of new systemic cancer treatment, or radiation or resection of target lesion.

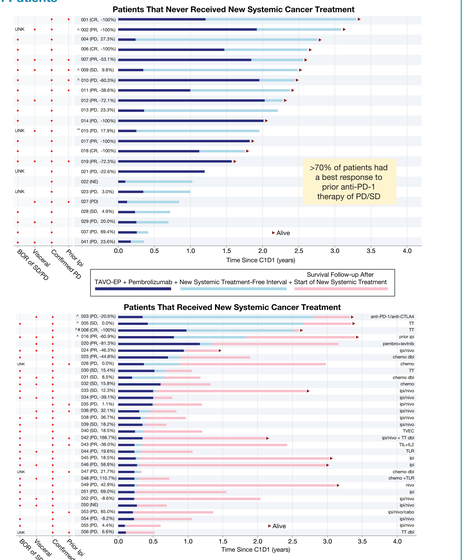
Of the 10 responding patients with a censored event, 6 responses are still ongoing; 1 patient (#43) had subsequent treatment with TIL therapy after TIL increase with TAVO treatment; 1 patient (#11) discontinued study treatment because of an AE and had 1 remaining target lesion resected; 1 patient (#12) had remaining lesion resected and remains disease-free; 1 patient (#16) discontinued treatment due to patient decision and started subsequent therapy. See corresponding patient numbers in Figure 6 for additional details.

Figure 5. 67% of Responding Patients (10/15) Did Not Have RECIST v1.1 Progression



See footnote in Figure 6.

Figure 6. Time to Initiation of Next Systemic Therapy Was ≥ 1 Year in 38% of Patients



Dark blue bar represents the length of TAVO+pembrolizumab treatment (C1D1 to EOT). The light blue bar represents new systemic treatment-free interval (if applicable). The pink bar is start of the first new systemic treatment to survival or last contact. Radiotherapy, surgery, maintenance pembrolizumab or retreatment with TAVO (expanded excess) were not counted as new systemic anti-cancer treatments.

*BOR of SD/PD" = patients that never responded to any prior anti-PD-1 treatment; "Visceral" = patients who had sites of metastasis in liver, lung, brain, bone, or kidney; "Confirmed PD"= patients who had documented confirmed progression on immediate prior anti-PD1 therapy; "Prior ipi" = exposure to prior ipilimumab.

^"new anti-cancer treatment was marked "unknown"

^patients that received maintenance pembrolizumab

^patient received compassionate use TAVO after new appearance of a lesion

Table 2. Minimal Cytokine-Associated Systemic Toxicity With Local Production of IL-12 Combined With Pembrolizumab

Grade 1/2 Treatment-Related Adverse Events (TRAEs) > 5% of Patients, and Grade 3-5 TRAEs in Any Patient (N=105)			
Preferred term, n (%)	All Grades	Grade 1/2	Grade 3
Patients with at least one TRAE	88 (83.8%)	81 (77.1%)	7 (6.7%)
Fatigue	29 (27.6%)	29 (27.6%)	–
Procedural pain	22 (21.0%)	22 (21.0%)	–
Diarrhea	19 (18.1%)	19 (18.1%)	–
Pruritus	11 (10.5%)	11 (10.5%)	–
Nausea	10 (9.5%)	10 (9.5%)	–
Rash	10 (9.5%)	9 (8.6%)	1 (1.0%)
Arthralgia	9 (8.6%)	8 (7.6%)	1 (1.0%)
Decreased appetite	6 (5.7%)	6 (5.7%)	–
Myalgia	6 (5.7%)	6 (5.7%)	–
Cellulitis	–	–	2 (1.9%)
Pneumonitis	–	–	1 (1.0%)
Enteritis	–	–	1 (1.0%)
Keratoacanthoma	–	–	1 (1.0%)
Lichen planus	–	–	1 (1.0%)
Musculoskeletal chest pain	–	–	1 (1.0%)

Adverse event terms are coded using the Medical Dictionary for Regulatory Activities (MedDRA) v24.0.

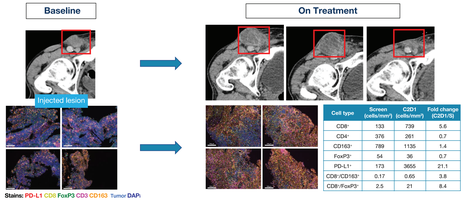
No treatment-related Grade 4 or 5 events reported

TRAE Leading to Drug Withdrawal (N=105)				
Preferred term, n (%)	All Grades	Grade 3	Related to Pembro	Related to TAVO-EP
Pneumonitis	2 (1.9%)	^1 (1.0%)	^2 (1.9%)	1 (1.0%)
Diarrhea	1 (1.0%)	0	1 (1.0%)	0
Dyspnea	1 (1.0%)	0	^1 (1.0%)	0
Electric shock sensation	1 (1.0%)	0	0	*1 (1.0%)
Enteritis	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)
Mental fatigue	1 (1.0%)	0	1 (1.0%)	*1 (1.0%)

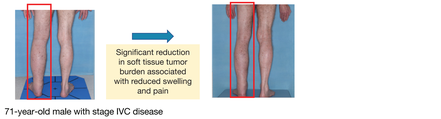
*One patient discontinued treatment for electric shock sensation and mental fatigue; 1 patient discontinued for pneumonitis and dyspnea.^^Denotes same patient.

Figure 7. Case Study: 71-Year-Old Male With RECIST v1.1 PR Experienced 1) Immune Infiltration With Tumor Flare 2) Symptomatic Improvement of Disease

Patient #20 on Figure 6



Cell type	Screen (cells/mm²)	C1D1 (cells/mm²)	Fold change (C1D1/0)
CD8+	133	739	5.6
CD4+	376	261	0.7
CD163+	789	1135	1.4
FoxP3+	54	36	0.7
PD-L1+	173	3655	21.1
CD8+/CD163+	0.17	0.65	3.8
CD8+/FoxP3+	2.5	21	8.4



- 71-year-old male with stage IVC disease
- 2 prior systemic treatments
- The duration from last dose of pembrolizumab to C1D1 on KN695 trial was 1 month
- Matching baseline and week 3 on-treatment tumor biopsies taken from an injected inguinal LN lesion, that increased in size, showed 5-fold increase in CD8+ T cells and productive effector:suppressor ratio in both CD163 macrophages and T regulatory cells

Summary

- KN695 study enrolled a population of melanoma patients with confirmed progression on prior anti-PD1 therapy, many of whom did not respond to any anti-PD-1 therapy (>70%)
- Intratumoral IL-12 (TAVO-EP) combined with pembrolizumab establishes and/or re-invigorates anti-tumor immune response in patients who definitively progressed on prior anti-PD-1 therapy
  - 100% of patients had documented confirmation of disease progression prior to study entry
  - ORR was 27.8% (95%CI [16.5%, 41.6%]) (15/54), investigator-assessed RECIST v1.1
  - ORR was 25.9% (n=7/27) in patients with M1b/M1c/M1d disease
- Patients who exhausted all approved standard-of-care immune checkpoint inhibitors responded to TAVO-EP combined with pembrolizumab
  - ORR was 33.3% in patients with prior ipilimumab treatment
- Systemic tumor responses were reported in patients with visceral lesions, including bone, brain, liver, lung, and kidney lesions
- Many ongoing responses out to 1, 2, and 3 years.
  - 47% of responding patients with durable responses lasting over 1 year
  - 20% of responding patients with durable responses lasting over 2 years
- Mature survival data compares favorably to historical rates in this patient population
  - Median OS 23.5 months; the expected mOS is 7-8 months[3,4]
- Minimal treatment-related toxicity
  - Grade 3 treatment-related AEs were seen in 6.7% of patients (N=105)
  - No grade 4/5 treatment-related AEs
  - 4.8% of patients discontinued treatment due to TRAEs
- 38% of patients experienced clinical benefit defined by "delay in administration of more toxic therapies"[2]

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Abbreviations

BOR, best overall response; cabo, cabozantinib; C1D1, cycle 1 day 1; chemo, chemotherapy; CR, complete response; dbl, doublet; ICI, immune checkpoint inhibitor; ipi, ipilimumab; levtnib, levatinib; nivo, nivolumab; PD, progressive disease; SLD, sum of longest diameters; SD, stable disease; TT, targeted therapy; TAVO, IL12-EP; TIL, tumor infiltrating lymphocyte; TLR, toll like receptor; TME, tumor microenvironment; ULN, upper limit of normal.