INTRATUMORAL IL-12 PLUS PEMBROLIZUMAB COMBINATION THERAPY IN TREATMENT REFRACTORY SOLID TUMORS: A SAFETY AND BIOMARKER ANALYSIS

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ABSTRACT

Background: Intratumoral inflammation is a requirement for response to anti-PD-1 therapies. Previously, we demonstrated that enhanced intratumoral IL-12 expression via injection of plasmid IL-12 (tavokinogene telseplasmid; TAVO) followed by electroporation (IT-tavo-EP) can increase TIL, ratios of $CD8^+$ T cell: suppressive immune subsets, and IFN-gamma gene signatures, converting weakly immunogenic tumors into highly inflamed, immunologically active lesions that regress with anti-PD-1 antibody therapy. Here, we present updated summary safety data and evidence of systemic immune modulation from our two KEYNOTE trials in TNBC and melanoma.

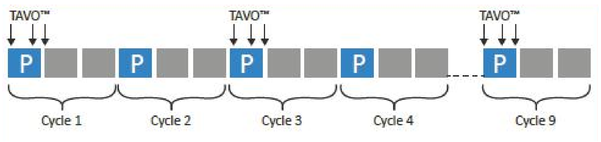
Methods: Melanoma (KEYNOTE-695) and mTNBC (KEYNOTE-890) patients were treated every six weeks with IT-tavo-EP on days 1, 5, and 8 of every odd numbered cycle. Clinical toxicity was assessed at 3-week intervals and graded by CTCAE v5. In addition, pre- and post-treatment tumor biopsies and peripheral blood samples were interrogated for treatment-related immunological changes in the frequency of $CD8^+$ TIL and other key IL-12-driven peripheral immune cell populations.

Results: 57 patients (TNBC and melanoma) were assessed including 44 patients with anti-PD-1 antibody-refractory melanoma, and 13 patients with chemotherapy-refractory mTNBC. TAVO in combination with pembrolizumab was well-tolerated with only 2 of 44 (4.5%) patients from KEYNOTE-695 (cellulitis and presyncope) experiencing grade 3 treatment related adverse events (TRAEs) and 3 of 13 (23%) from KEYNOTE-890 (acute renal failure, hyperglycemia, and increased fatigue) experiencing grade 3 treatment-related adverse events to combination therapy. Flow cytometry on matched fresh biopsies from the KEYNOTE-695 revealed significant increases in $CD8^+$ T cells after 1 cycle of treatment. Despite previous data demonstrating non-detectable circulating IL-12 levels after treatment with TAVO, paired peripheral blood analysis from both trials revealed a treatment-related increase of $KLRG1^+/CD127^-$ SLECs as well as a treatment-related reduction of MDSCs in the periphery predominantly in responding patients.

Conclusion: Updated cumulative safety data demonstrates that TAVO + pembrolizumab is well-tolerated in patients with advanced solid tumors. In multiple tumor settings peripheral blood analyses demonstrates both local and most importantly, systemic signals of IL-12 mediated anti-tumor immunity in the absence of systemic IL-12 exposure. Thus, TAVO acts as an *in situ* vaccine to further potentiate the anti-tumor activity of pembrolizumab with a favorable toxicity profile.

FIGURE 1: TRIAL DESIGN AND INCLUSION CRITERIA

A **Treatment Regimen for KEYNOTE-695 and KEYNOTE-890:**



Patients are treated with 0.5 mg/mL TAVO™ to the accessible lesions on days 1, 5, and 8 every 6 weeks, and with 200 mg IV pembrolizumab on day 1 of each 3-week cycle for 27 weeks.

TAVO™ is injected at a dose volume of ~ ¼ of the calculated lesion volume, with a minimum dose volume/lesion of 0.1 mL. An applicator with a hexagonal array of 6 microneedles is placed into and around the injected tumor, with the tip co-localized at the site(s) and depth of plasmid injection. Six pulses at a field strength of 1500 volt/cm and pulse width of 100µs at 300-msec intervals are delivered.

B **Trial Inclusion Criteria**

For both trials, patients must be >18 years with ECOG performance status of 0-1 and must have measurable disease based on RECIST v1.1 and at least one anatomically distinct lesion accessible for electroporation with a life expectancy of at least 6 months.

KEYNOTE-695

- Stage III/IV unresectable melanoma who progressed on pembrolizumab or nivolumab treatment
- Patients must have failed all available treatment options (BRAF inhibitors and other targeted therapies)
- Patients must be definitive anti-PD-1 non-responders:
  - Definitively progressed on a full course (4+ doses) of anti-PD-1 treatment with pembrolizumab or nivolumab
  - Progressive disease per RECIST v1.1 determined by radiologic assessment
  - Documented disease progression ≤24 weeks of the last dose of anti-PD-1
  - No intervening therapies between anti-PD-1 failure and TAVO™ + KEYTRUDA© (pembrolizumab)

KEYNOTE-890

- Histologically confirmed diagnosis of inoperable locally advanced or metastatic TNBC and at least 1 prior line of systemic chemotherapy or immunotherapy
- ER and PR receptor staining <10% and be HER2 negative defined as IHC 0 to 1+
- Subjects must not have disease that, in the opinion of the Investigator, is considered amenable to potentially curative treatment

C **Summary of Treatment-Emergent Treatment-Related Adverse Events**
Complete TAVO™ Clinical Trials Safety Population

Therapy	Maximum Grade: Grade 1,2 n (%)	Grade 3,4 n (%)	Grade 5 n (%)	All Grades n (%)
Monotherapy (N = 106)	89 (84.0%)	8 (7.5%)	0	97 (91.5%)
Combination Therapy (N = 97)	71 (73.2%)	8 (8.2%)	0	79 (81.4%)
Therapy Overall (N = 203)	160 (78.8%)	16 (7.9%)	0	176 (86.7%)

Note: Adverse events were mapped according to MedDRA. For studies OMS-I100, OMS-I102 (CC15-852) OMS-I103, and OMS-I110 MedDRA v19.0 was used. For study OMS-I120 MedDRA v19.1 was used. For study OMS-I130 MedDRA v18.1 was used. For study OMS-I090 (MCC-13244) MedDRA v18.0 was used. For study OMS-I140 MedDRA v21.0 was used. For study OMS-I141 MedDRA v21.1 was used. Treatment-related events are define as events where the relationship to study drug (pIL-12 and/or electroporation or pembrolizumab) was reported as 'unlikely', 'possibly', 'probably' or 'definitely' related to study drug. Patients were counted only once for each preferred term, at the highest grade for that term. Patients with one or more preferred terms within a system organ class were counted only once for that system organ class, at the highest grade of any event within that SOC. Percentages are calculated based on the number of patients in the Safety Population. The Monotherapy group comprises of pooled data from OMS-I090 (MCC-13244), OMS-I100, OMS-I100 Addendum, OMS-I110, OMS-I120, OMS-I130, and OMS-I140 and the Combination Therapy group comprise of pooled data from OMS-I102 (CC15-852), OMS-I103, and OMS-I141.

Figure 1: Treatment regimen (A) and trial inclusion criteria (B) for KEYNOTE-695 and KEYNOTE-890 trials. (C) Summary of Treatment-Emergent Treatment-Related Adverse Events.

Abbreviations: BRAF, B-Raf murine sarcoma viral oncogene homologue; ECOG, Eastern Cooperative Oncology Group; EP, electroporation; PD-1, programmed cell death protein 1; P, pembrolizumab; RECIST, Response Evaluation Criterial In Solid Tumors; TAVO™, intratumoral administration of interleukin-12 plasmid followed by electroporation, ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.

TABLE 1: PATIENT DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Characteristic	Overall Population (N = 57)	Population with at least one tumor assessment post- completion of 2 cycles of TAVO (N = 51)
Mean age, years (SD)	61 (13.6)	63 (12.1)
Gender n (%)		
Male	22 (38.6)	21 (41.2)
Female	35 (61.4)	30 (58.8)
Race n (%)		
Asian	1 (1.7)	1 (1.9)
Black African American	2 (3.5)	0 (0.0)
Hispanic or Latino	4 (7.0)	3 (5.8)
Native Hawaii or Pacific Islander	1 (1.7)	1 (1.9)
White	49 (85.6)	46 (90.1)
Disease Stage at enrollment n (%)		
IIA	1 (1.7)	0 (0.0)
IIB	2 (3.5)	1 (1.9)
IIIB	7 (12.3)	6 (11.7)
IIIC	9 (15.8)	9 (17.6)
IV	1 (1.7)	0 (0.0)
IVA	20 (35)	18 (35.2)
IVB	7 (12.3)	7 (13.7)
IVC	8 (14)	8 (15.6)
Not specified	2 (3.5)	2 (3.9)
Prior lines of therapy, n (%)		
1	25 (43.8)	22 (43.1)
2	13(22.8)	13 (25.4)
>2	19 (33.3)	16 (31.3)
Prior anti-PD-1 cycles		
Pembrolizumab IV	N 33 (3-18)	N 33 (3-18)
Nivolumab IV	N 20 (4-25)	N 18 (4-25)

FIGURE 2: ACTIVE CLINICAL SITES PER TRIAL

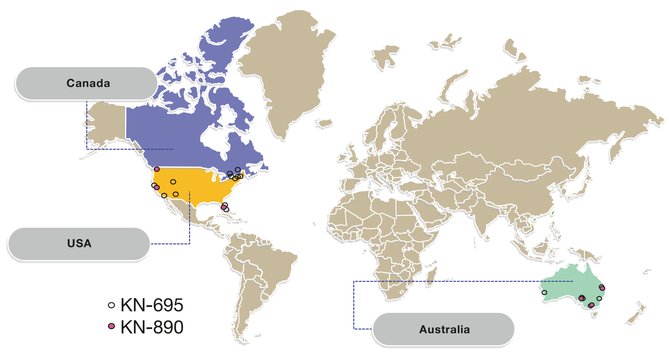
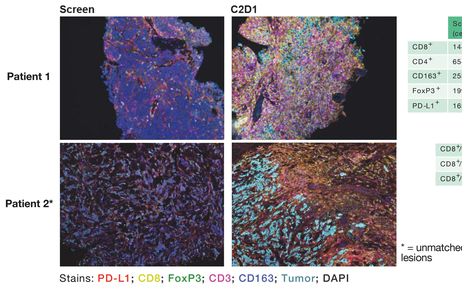


Figure 2: Clinical sites active or soon to be operational for KEYNOTE-695 and KEYNOTE-890.

FIGURE 3: MULTISPECTRAL IHC ANALYSIS

A Representative mIHC images from KEYNOTE-695 and KEYNOTE-890 patients



	Screen (cells/mm²)	C2D1 (cells/mm²)	Fold-change (C2D1/S)
$CD8^+$	1449.36	3668.04	2.53
$CD4^+$	654.23	1480.19	2.26
$CD163^+$	2537.09	1436.44	0.57
$FoxP3^+$	199.37	1265.11	6.35
PD-$L1^+$	1657.44	3913.14	2.36

	Screen	C2D1	Fold-change
$CD8^+/CD163^+$	0.57	2.55	4.47
$CD8^+/FoxP3^+$	7.27	2.90	0.40
$CD8^+/CD4^+$	2.22	2.48	1.12

* = unmatched lesions

Stains: PD-L1; CD8; FoxP3; CD3; CD163; Tumor; DAPI

B Fold-change $CD8^+$ T cells across KEYNOTE-695 and KEYNOTE-890 Patients

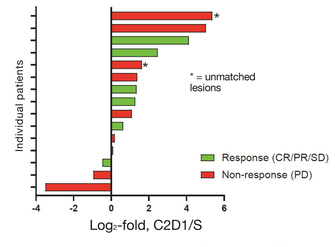
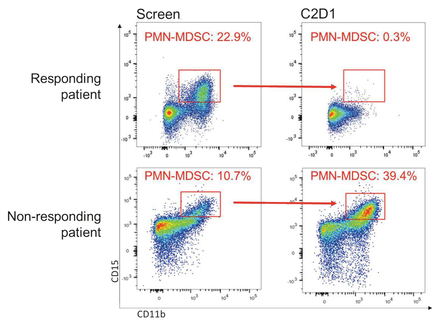


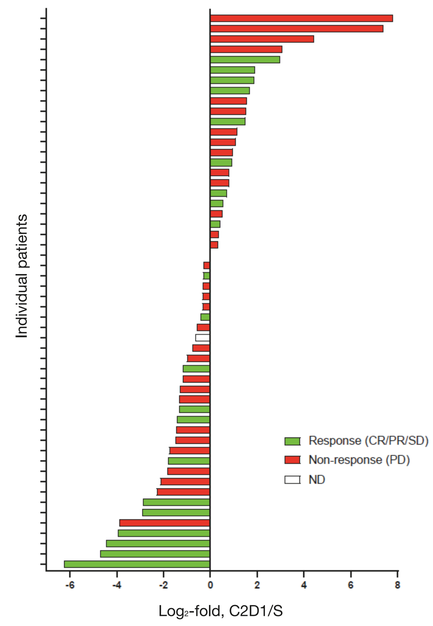
Figure 3: Following 1 cycle of combined therapy, treatment-related increases in TIL density were observed in patients from both KEYNOTE-695 and KEYNOTE-890 (subset of patients shown with matched pre- and post-treatment biopsies, unless otherwise noted). A) Representative mIHC images from two patients with quantitation. B) Fold-increase in $CD8^+$ T cells versus clinical response across both trials (C2D1 over S; Log2 scale).

FIGURE 4: ON-TREATMENT CHANGES IN PERIPHERAL IMMUNE SUBSETS

A Peripheral PMN-MDSCs:



B Change in peripheral PMN-MDSCs across KEYNOTE-695 and KEYNOTE-890:



C Change in proliferating central memory across KEYNOTE-695 and KEYNOTE-890:

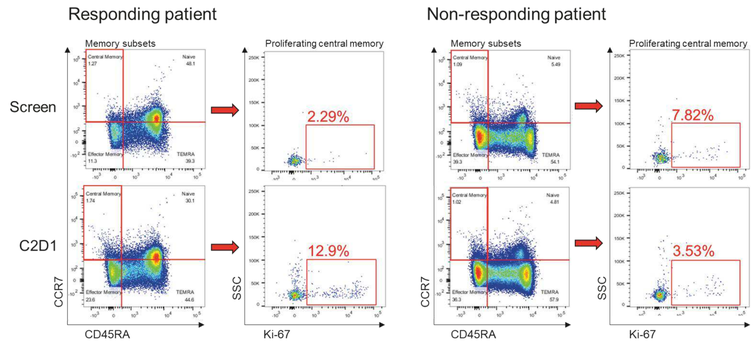


Figure 4: A) Peripheral PMN-MDSCs at screening (S) and on day 1 of cycle 2 of treatment for a representative responder and non-responder patient. B) Fold-change in PMN-MDSCs levels versus clinical response across both trials (C2D1 over Screen; Log2 scale). C) Changes in proliferating $CD8^+$ central memory cells are shown for a representative responding and non-responding patient.

SUMMARY AND CONCLUSIONS

- This interim analysis was limited to pre- and post-treatment matched samples (unless otherwise noted).
- Early analysis of peripheral blood and intratumoral biomarker data reveal that:
  - Increases in intratumoral $CD8^+$ T cells may correlate with improved clinical outcome in multiple solid tumor types
  - Decreased peripheral PMN-MDSCs may be associated with clinical response, both in melanoma and TNBC patients
- TAVO + pembrolizumab continues to be well-tolerated in patients with advanced solid tumors
- Across multiple indications, TAVO acts as an *in situ* vaccine to potentiate the anti-tumor activity of pembrolizumab
- Enrollment in both KEYNOTE-695 and -890 is ongoing

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