Intratumoral delivery of tavokinogene telseplasmid (plasmid IL-12) and electroporation induces local and systemic enhancement of CD8 T cells and sensitizes to anti-PD1 therapy

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Background

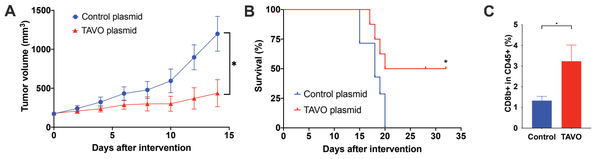
- Sustained disease control and prolonged survival in patients with TNBC is uncommon, highlighting the need for improved immune-based strategies particularly in poorly immunogenic tumors
- Interleukin-12 (IL-12) is involved in the generation of innate and adaptive immune responses, an inflammatory tumor microenvironment and is critical in eliciting a productive anti-tumor immune response[1,2]
- Intratumoral injection of plasmid IL-12 (tavokinogene telseplasmid; TAVO™) followed by electroporation (EP) (IT-TAVO-EP, collectively designated TAVO) is a gene therapy approach that drives local and immunologically relevant exposure of IL-12 with minimal systemic immune-related toxicity[3-5]

Methods

- Murine TNBC (JC-HER3) cells were orthotopically implanted into mice and allowed to establish prior to treatment with TAVO or control plasmid
- On days 0, 4 and 7, the mice underwent IT administration of plasmid, followed by *in vivo* electroporation
- Tumors were digested and CD45+ cells sorted for flow cytometry
- Flow cytometry for activated T cell populations and MDSCs and IHC summary data are from PMBCs and tumors from OMS-I140; data from this study were reported previously[6]
- Fold change in CD8 T cells following TAVO treatment was calculated and a fold change of >2 is shown in red (**Table 1**)
- Spotlight patient from OMS-I140 had previously failed to respond to atezolizumab

Results

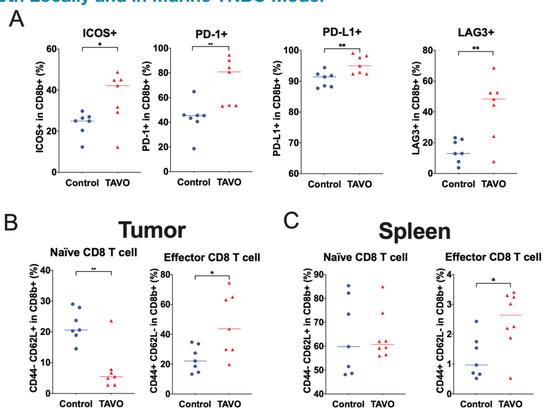
Figure 1. IL-12 Treatment Inhibits Tumor Growth and Enhances Immune Cell Infiltration in a Murine Model of TNBC



A. Growth inhibition of JC-HER3 tumors by intratumoral TAVO plasmid administration. Murine JC-HER3 cells were subcutaneously implanted to the flank of HER3 transgenic mice with BALB/c background. When the tumor size reached 6-7 mm in diameter, mice were randomized into two groups (day 0) and received intratumoral injections of plasmid followed by in vivo electroporation on days 0, 4, and 7. Tumor sizes were measured every other day and shown by Mean ± SEM (TAVO group: 8 mice, control group: 7 mice). **B.** Survival curves of JC-HER3 tumor-bearing mice. **C.** Flow Cytometric Analysis of tumor-infiltrating leukocytes in JC-HER3 tumors. JC-HER3 tumor-bearing mice (n=7 for each group) underwent interventions described in A, and the tumors were harvested on day 14. $^*P < 0.05$

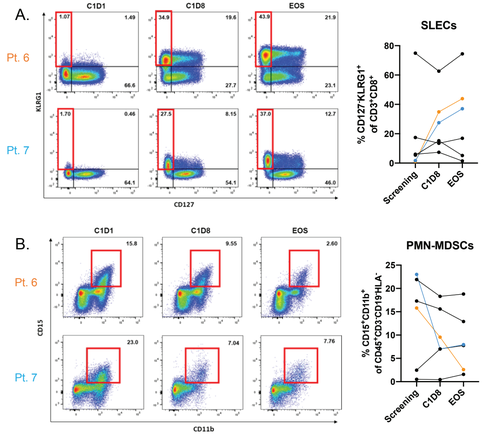
Results

Figure 2. TAVO Treatment Expands an Effector CD8 T cell Population Both Locally and in Murine TNBC Model



A. The expression of activation/exhaustion markers on CD45+CD3+CD8b+ cells from JC-HER3 tumors. **B.** Naïve and effector T cells in CD45+CD3+CD8b+ cells from JC-HER3 tumors. **C.** Naïve and effector T cells in CD45+CD3+CD8b+ cells from spleens from JC-HER3 tumor bearing mice. $^*P < 0.05$. $^{**}P < 0.01$

Figure 3. Systemic Response to TAVO in TNBC Patients



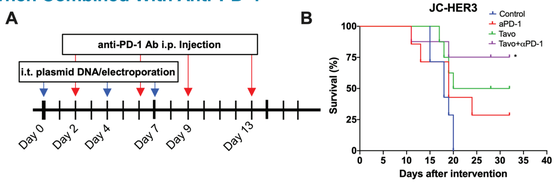
Flow cytometric analysis at cycle 1 day 1 (C1D1), cycle 1 day 8 (C1D8), or end of study (EOS) was performed on PBMCs. Representative flow plots for indicated patients and summary data for **A.** SLECS ($CD3^+CD8^+KLRG1^+CD127^-$) or **B.** PMN-MDSC ($CD45^+Lin\text{-}HLA\text{-}CD15^+CD11b^+$).

Table 1. Summary of mIHC Quantification for Matched Lesions at Screening and EOS

Patient	Treated	CD8+ at S (cells/mm²)	CD8+ at EOS (cells/mm²)	Fold change to CD8s	CD163+ at S (cells/mm²)	CD163+ at EOS (cells/mm²)	FoxP3+ at S (cells/mm²)	FoxP3+ at EOS (cells/mm²)	Total PD-L1 at S (cells/mm²)	Total PD-L1 at EOS (cells/mm²)	Fold change in PD-L1	Ratio at S CD8/FoxP3	Ratio at EOS CD8/FoxP3	Fold change CD8:FoxP3	Ratio at S CD8/CD163	Ratio at EOS CD8/CD163	Fold change CD8:CD163
1	N	NA*	NA*		NA*	NA*	NA*	NA*	NA*	NA*							
2	Y	635.31	410.79	0.65	2934.46	1542.39	74.40	104.21	5880.09	5818.34	0.99	8.54	3.94	0.46	0.22	0.27	1.23
3	Y	8.24	199.98	24.26	509.24	1102.63	8.24	28.73	1768.04	3645.96	2.06	1.00	6.96	6.96	0.02	0.18	11.20
4	N	91.74	66.00	0.72	1181.13	986.80	28.37	2.46	386.86	74.05	0.19	3.23	26.82	8.29	0.08	0.07	0.86
6	Y	97.57	458.59	4.7	1429.45	1018.55	62.04	142.56	2578.75	753.61	0.29	1.57	3.22	2.05	0.07	0.45	6.60
7	Y	50.77	78.90	1.55	2339.25	1236.81	56.91	44.63	5.01	139.03	27.73	0.89	1.77	1.98	0.02	0.06	2.94
8	N	159.44	277.12	1.74	1736.01	4983.88	158.59	77.30	6.80	295.57	43.48	1.01	3.59	3.57	0.09	0.06	0.61
10	N	78.94	24.96	0.32	504.38	3163.62	12.52	27.46	4258.22	6.39	0.001	6.30	0.91	0.14	0.16	0.01	0.05
11	Y	46.10	2444.31	53.02	2729.52	1792.39	2.46	406.59	281.36	2051.24	7.29	18.74	6.01	0.32	0.02	1.36	80.74
12	N	0.00	1626.32	>1626.32**	2310.30	4750.41	2.52	351.85	6869.22	668.08	0.10	NA	4.62	>4.62**	NA	0.34	>0.34**

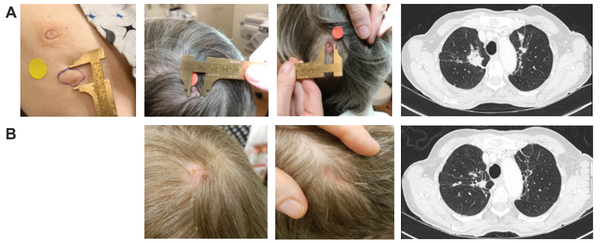
* Slides from patient 1 did not contain enough tissue to complete the analysis
**Divided by zero
Red indicates patients that had a >2 fold change in CD8 T cells following therapy.

Figure 4. TAVO Treatment Enhances Survival of Tumor-Bearing Mice When Combined With Anti-PD-1



A. 4T1 or JC-HER3 cells were subcutaneously implanted to the flank of BALB/c mice or HER3 transgenic mice, respectively. When the tumor size reached 6-7 mm in diameter, mice were randomized into four groups (day 0). Mice received intratumoral administration of TAVO or control plasmid on days 0, 4 and 7, and intraperitoneal injection of anti-PD-1 mAb or rat IgG2a isotype control on days 2, 6, 9 and 13. **B.** Survival curves of JC-HER3 tumor-bearing mice. All error bars represent mean ± SEM $^*P < 0.05$

Figure 5. Clinical Data Demonstrates That TAVO Treatment Converts a Previous ICB Non-Responder



A. Baseline breast nodule (treated), scalp metastases (untreated) and lung metastases (untreated). **B.** After 1 cycle of TAVO and 3 months of IV nivolumab therapy.

Summary & Conclusions

- TAVO treatment overcomes an immunologically 'cold' tumor microenvironment by expanding and activating T cells locally and systemically and by minimizing the infiltration of potentially suppressive granulocytic cells in both pre-clinical models and TNBC patients
- There is an increase in expression of PD-1/PD-L1 following TAVO therapy that may sensitize a patient to subsequent checkpoint inhibitor therapy
- Combined treatment of TAVO and PD-1/PD-L1 blockade enhanced anti-tumor efficacy and prolonged survival in preclinical models of TNBC
- These data are supportive of ongoing trial OMS-I141 (KEYNOTE-890), a phase 2, multi-cohort, open-label, multicenter study
  - Cohort 1 will be a single-arm study of intratumoral tavokinogene telseplasmid (TAVO) plus electroporation (EP) in combination with pembrolizumab therapy
  - Cohort 2 will be a single-arm study of intratumoral TAVO-EP plus pembrolizumab with nab-paclitaxel (Abraxane®) chemotherapy
  - Patients with TNBC and EP accessible cutaneous/subcutaneous disease will be enrolled

References

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Abbreviations:
BC, breast cancer; EOS, end of study; ICB, immune checkpoint blockade; IHC, immunohistochemistry; IL-12, interleukin-12; IT, intratumoral; mAB, monoclonal antibody; MDSC, myeloid derived suppressor cells; PD-1, programmed cell death receptor 1; PD-L1, programmed cell death ligand 1; PMBC, peripheral blood mononuclear cells; S, screening; TAVO, tavokinogene teleplasmid; TNBC, triple-negative breast cancer.