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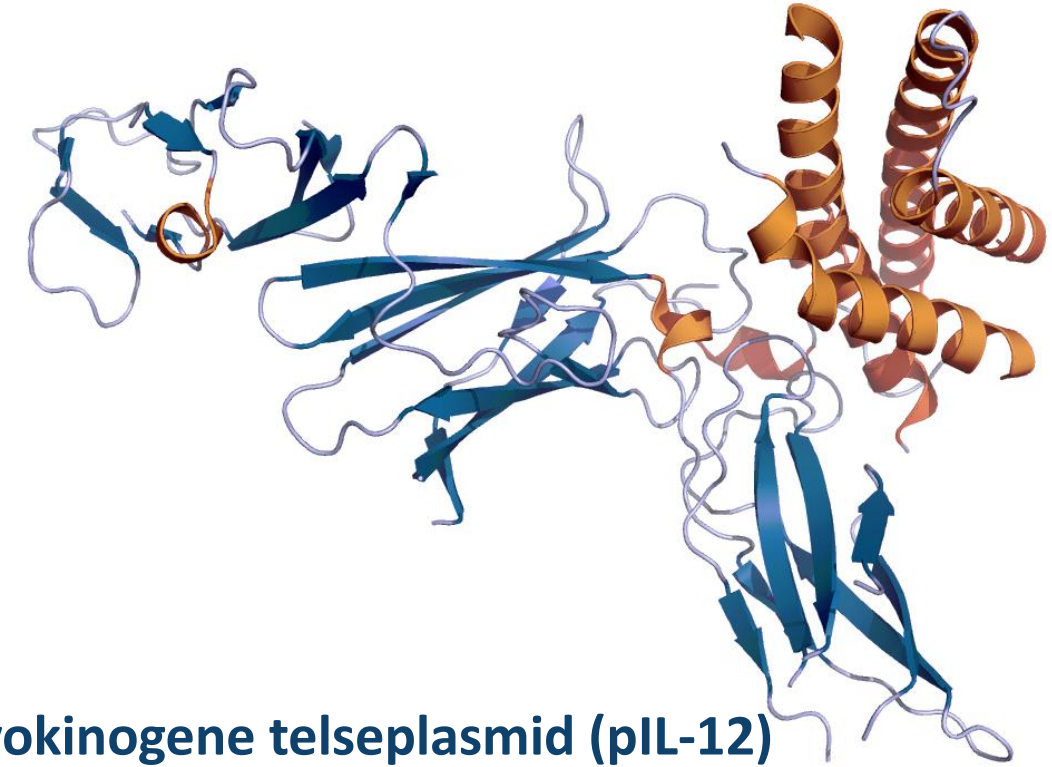


Intra-tumoral delivery of tavokinogene telseplasmid (pIL-12) by electroporation: immunomodulation in melanoma and triple negative breast cancer

Sharron Gargosky PhD

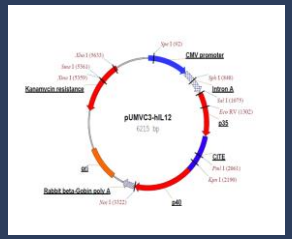
Presentation Topics

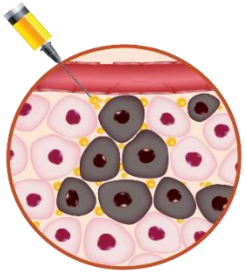
- Rationale of cytokine choice and electroporation delivery
- Clinical data in metastatic melanoma
- Clinical data in metastatic TNBC

Therapy and Terms

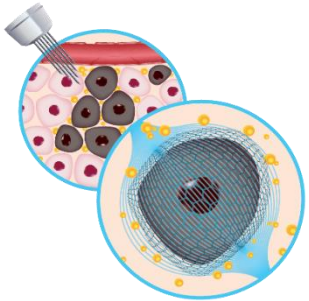
- Plasmid IL-12 INN name: tavokinogene telseplasmid; aka “TAVO”
- Device = OncoSec Medical System = OMS

○ The gene is human IL-12 cDNA, and is cloned into the bacterial plasmid pUMVC3.
○ IL-12 is a 70 kilodalton protein consisting of two subunits, 40 kD and 35 kD, stabilized by a disulfide bond.

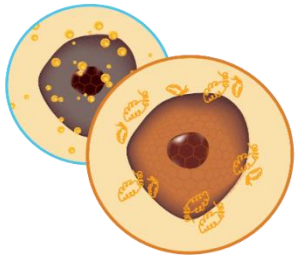




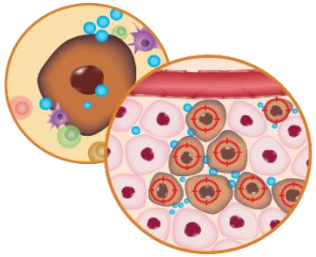
① Injection of tavokinogene telseplasmid **(tavo)**



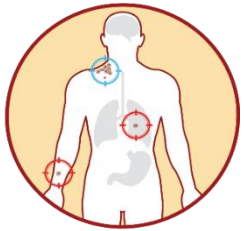
② Intratumoral electroporation delivers tavo into the cells



③ IL-12 is expressed & secreted



④ Innate and cellular responses



⑤ Systemic anti-tumor immune response

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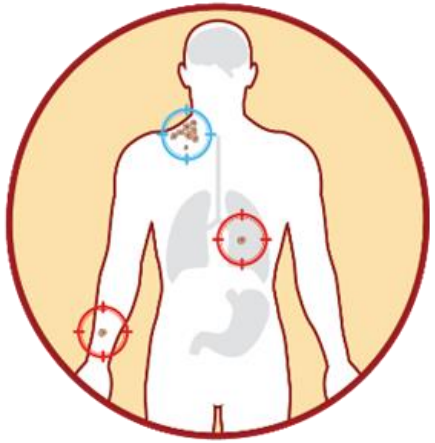
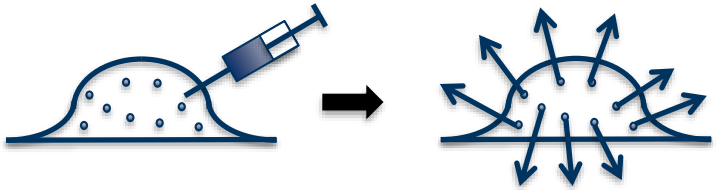
Prior approaches to cytokine delivery



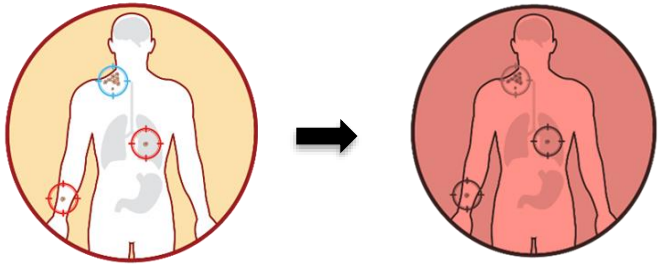
Accessible lesions
Systemic disease

IT



- Transient Exposure
- Regression of treated lesions
- No systemic effect

IV



- Sepsis-like side effects
- 3-5% long-term remission

Plasmid
TAVO

- Intra cellular
- Tumor makes IL-12
- 1 week exposure / tx

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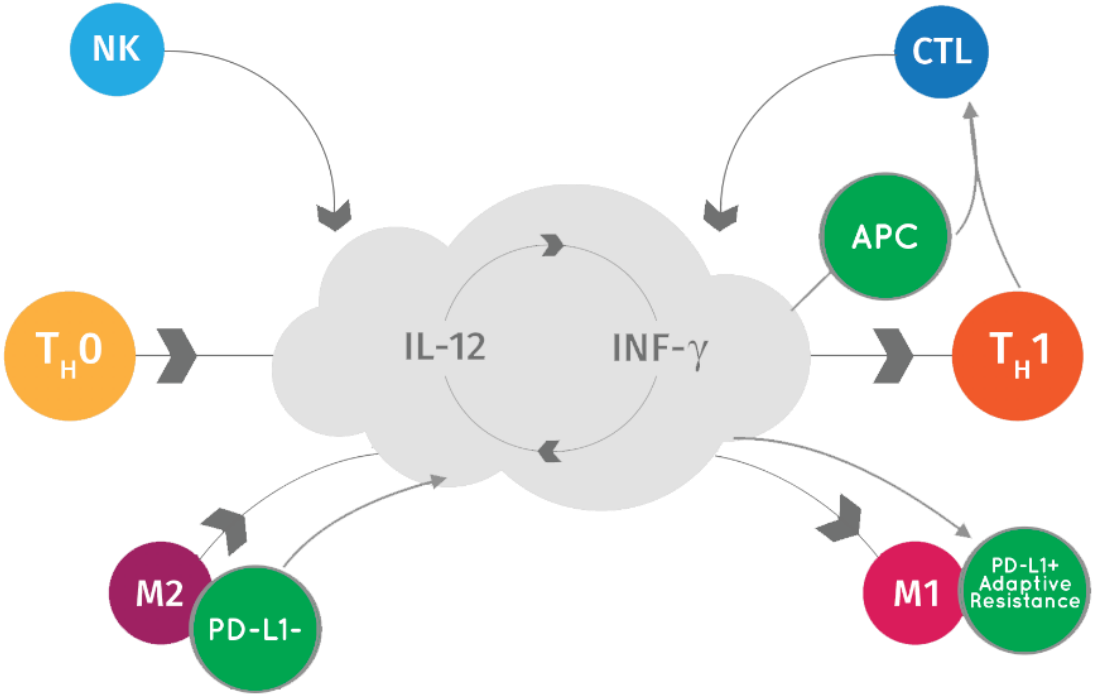
Why interleukin -12 (IL-12)
tavokinogene telseplasmid



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Agenda

- Rationale of cytokine choice and Electroporation delivery
- Clinical data in metastatic melanoma
- Clinical data in metastatic TNBC

Clinical data in Metastatic Melanoma

OMS-100 Phase 2 Repeat Dose:
Abscopal tumor response and continued safety

OMS-100 Phase 2 Repeat Dose Retrospective Analysis:
Evidence of priming for anti-PD-1 response and continued safety

OMS-102 Phase 2 Combination Study with Pembrolizumab:
Evidence of efficacy in predicted anti-PD-1 non-responder population and continued safety

Phase 2 (OMS-I100): Metastatic Melanoma monotherapy tavo

Phase 2 open label, multicenter study of IT-tavo-EP in metastatic melanoma

Dose and administration

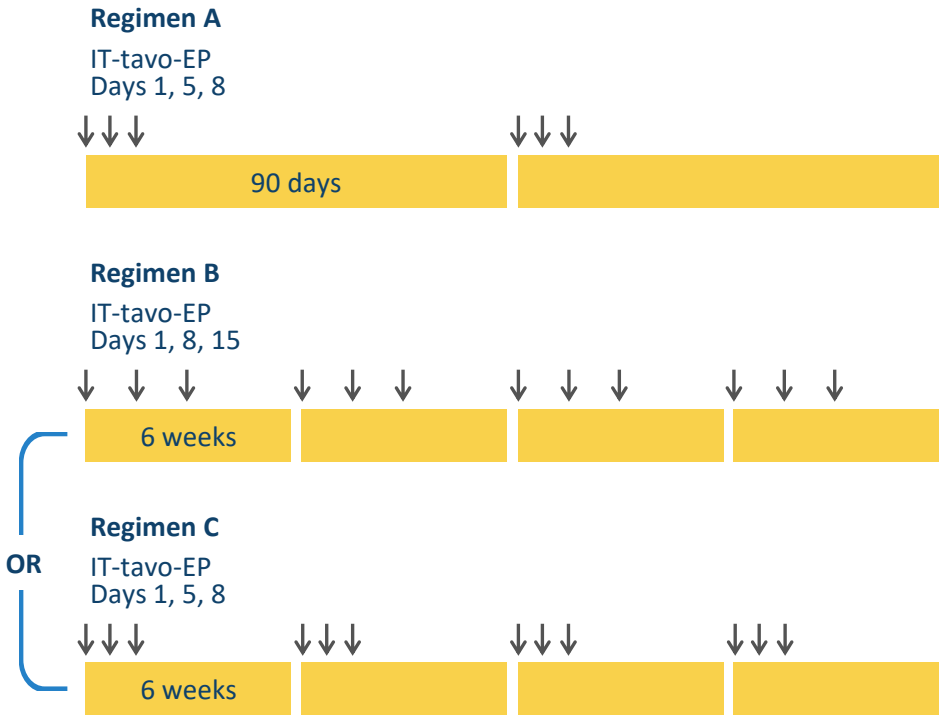
- Intratumoral injection of tavo (0.5 mg/mL) at a dose-volume of one-fourth the calculated lesion volume

Regimen A (part 1)

- One cycle of treatment; additional cycles may be administered at 3-month intervals up to a max of 4 total cycles
- Tumor response evaluation: days 90, 180, and 270

Regimens B and C (part 2)

- Up to 9 cycles of treatment at 6-week intervals
- Tumor response evaluation: weeks 12, 24, 36, and 48 or more frequently, if clinically indicated



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IT-tavo-EP, intratumoral injection of tavo with electroporation; tavo, plasmid interleukin-12.

Phase 2 (OMS-100): Demographics

Schedule		A	B	C	Overall
N		**30**	**17**	**4**	51
Age	Mean (SD)[a]	66.8 (10.19)	68.4 (13.47)	58.8 (3.30)	66.7 (11.18)
Gender	Male	16 (53.3%)	13 (76.5%)	4 (100%)	33 (64.7%)
	Female	14 (46.7%)	4 (23.5%)	0	28 (35.3%)
ECoG PS	0	21 (70.0%)	7 (41.2%)	3 (75.0%)	31 (60.8%)
	1	9 (30.0%)	10 (58.8%)	1 (25.0%)	20 (39.2%)
Stage	III b	6 (20.0%)	3 (17.6%)	0	9 (17.6%)
	III c	13 (43.3%)	5 (29.4%)	2 (50.0%)	20 (39.2%)
	IV M1a	8 (26.7%)	5 (29.4%)	1 (25.0%)	14 (27.5%)
	IV M1b	3 (10.0%)	2 (11.8%)	0	5 (9.8%)
	IV M1c	0	2 (11.8%)	1 (25.0%)	3 (5.9%)
BRAF Status	Mutant	10 (33.3%)	5 (29.4%)	2 (50.0%)	17 (33.3%)
	Wild type	13 (43.3%)	9 (52.9%)	1 (25.0%)	23 (45.1%)
	Unknown	7 (23.4%)	3 (17.7%)	1 (25.0%)	11 (21.5%)

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BRAF, proto-oncogene B-raf

Phase 2 (OMS-100): Treatment History

Prior Therapy	Cytokine	13 (43.3%)	7 (41.2%)	0	20 (39.2%)
	CTLA4	9 (26.7%)	7 (41.2%)	2 (50%)	17 (33.3%)
	PD-1 / PD-L1	4 (13.3%)	7 (41.2%)	2 (50%)	13 (25.5%)
	Cytokine+CTLA4	1 (3.3%)	1 (5.9%)	0	2 (3.9%)
	BRAF/MEK	3 (10%)	3 (17.6%)	1 (25%)	7 (13.7%)
	Other	5 (16.7%)	6 (35.3%)	0	11 (21.6%)
Prior lines	0	10 (33.3%)	4 (23.5%)	2 (50%)	16 (31.4%)
	1	10 (33.3%)	3 (17.6%)	0	13 (25.5%)
	2+	10 (33.3%)	10 (58.8%)	2 (50%)	22 (43.1%)

BRAF, proto-oncogene B-raf; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; MEK, mitogen-activated protein kinase ; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

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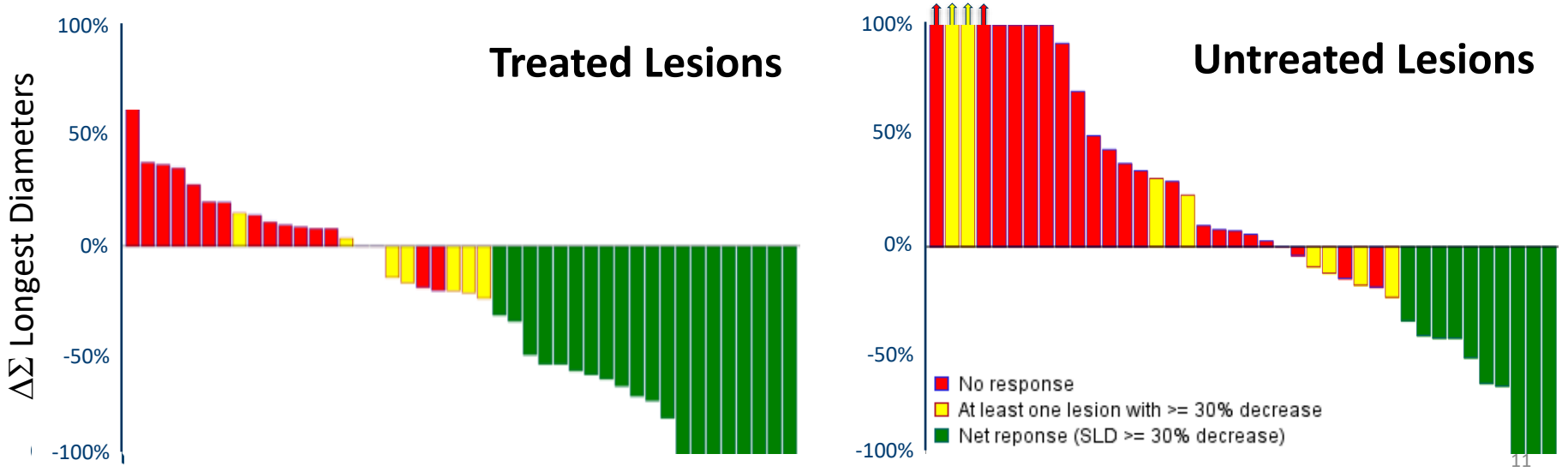
Phase 2 (OMS-100) Demonstrated Clinical Monotherapy Activity in Advanced Melanoma Patients

30%
Best Overall Response Rate*

21%
Complete Response Rate*

50%
Patients with regression of >1 non-treated lesion

77%
Disease Control Rate*



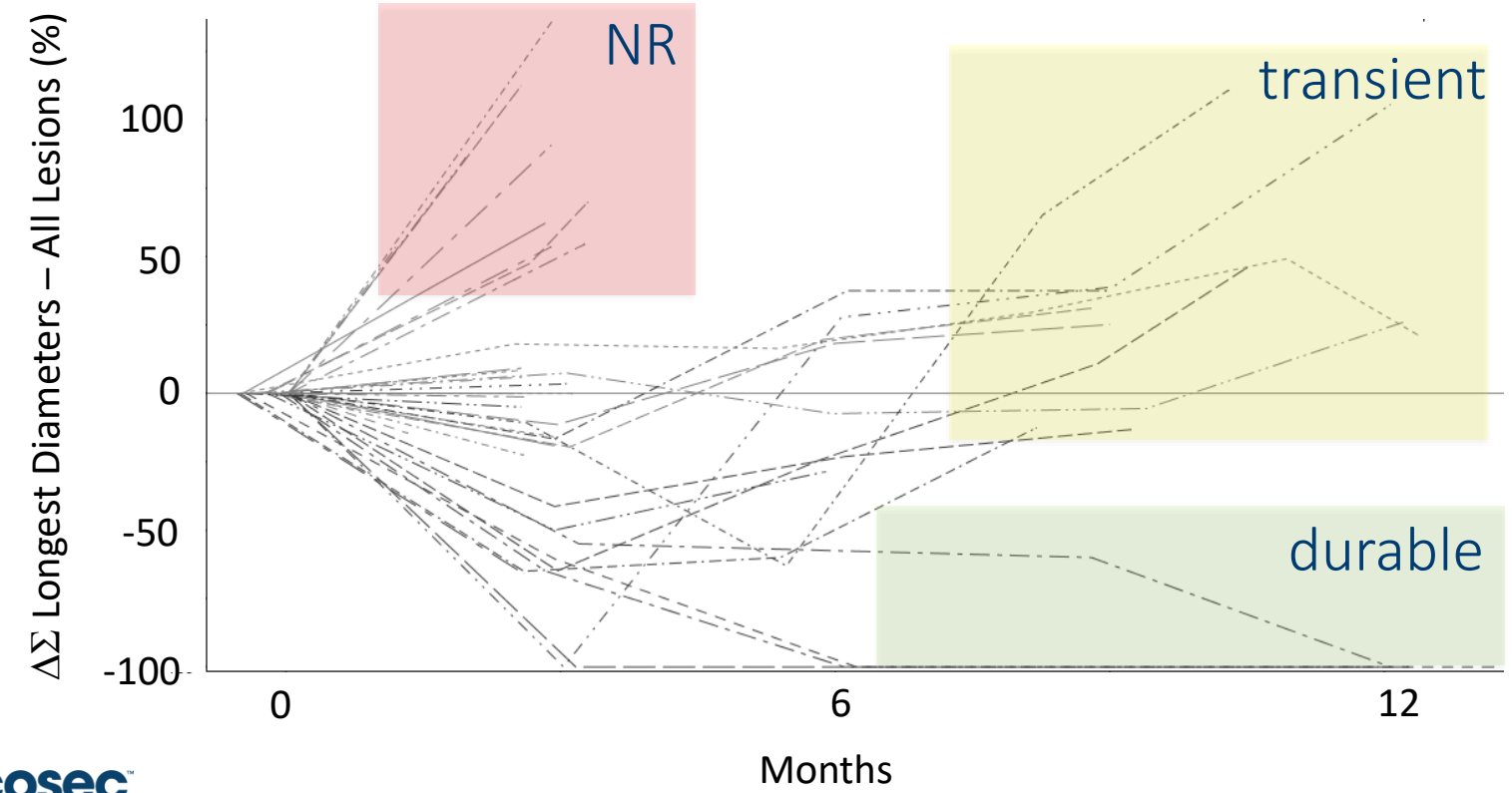
Phase 2 (OMS-I100)

SAFETY: TEAE

Treatment related
All seen in > 1 patient
All grade ≥ 3

Category	*Event*	*All grades (%)*	*Grade 3 (%)*
Any	Any	45 (88.2%)	6 (11.8%)
Procedural	Procedural pain	37 (72.5%)	4 (7.8%)
Injection site reactions	Injections site discoloration	6 (11.8%)	
	Regional pain	6 (11.8%)	
	Injection site inflammation	5 (9.8%)	
	Injection site pain	2 (3.9%)	1 (2.0%)
	Injection site discharge	2 (3.9%)	
	Ecchymosis	2 (3.9%)	
	Injection site erythema	2 (3.9%)	
Skin	Rash	4 (7.8%)	
	Cellulitis	4 (7.8%)	1 (2.0%)
	Skin disorder NOS	2 (3.9%)	
Constitutional	Fatigue	7 (13.7%)	
	Pyrexia	2 (3.9%)	
	Chills	2 (3.9%)	
Psychiatric	Anxiety	2 (3.9%)	

Phase 2 (OMS-100) – Overall response over time (N = 48)



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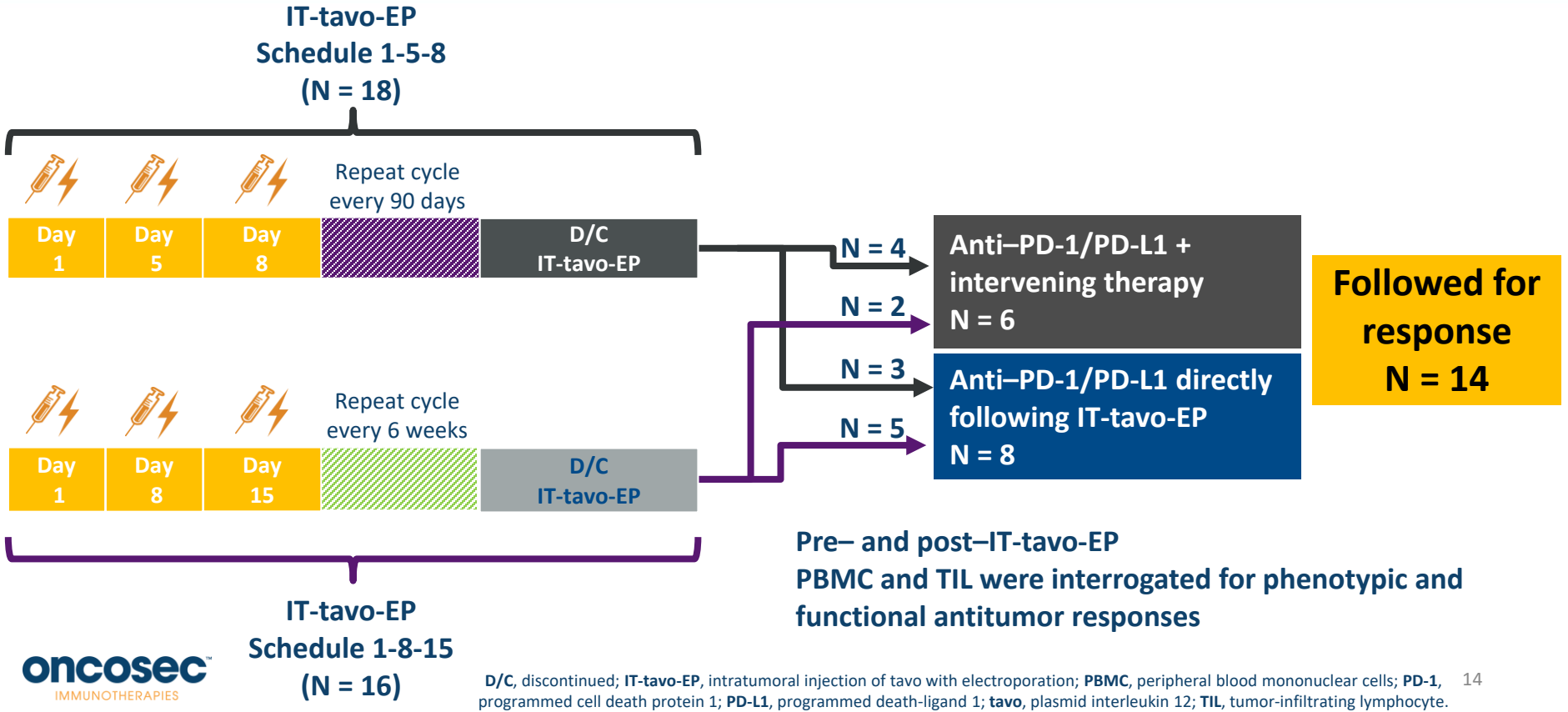
Phase 2 (OMS-100) Retrospective analysis of patients who received subsequent PD-1/PD-L1 inhibitors



D/C, discontinued; **IT-tavo-EP**, intratumoral injection of tavo with electroporation; **PBMC**, peripheral blood mononuclear cells; **PD-1**, programmed cell death protein 1; **PD-L1**, programmed death-ligand 1; **tavo**, plasmid interleukin 12; **TIL**, tumor-infiltrating lymphocyte.

Phase 2 (OMS-I100): IT-TAVO Followed by Anti-PD-1 Therapy

IT-TAVO alone: ORR = 31%

Anti-PD-1 alone: ORR = 20-40%

IT-TAVO followed by anti-PD-1 (n=14):
ORR = 64%

IT-TAVO followed by anti-PD-1 with NO intervening therapy (n=8):

ORR = 75%

Best Overall Response	Without Intervening Therapy N=8	With Intervening Therapy N=6
CR	**4 (50%)**	**1 (17%)**
PR	**2 (25%)**	**2 (33%)**
SD	1 (12.5%)	1 (17%)
PD	1 (12.5%)	2 (33%)

Higher Response Rates Than Those from Either Monotherapy

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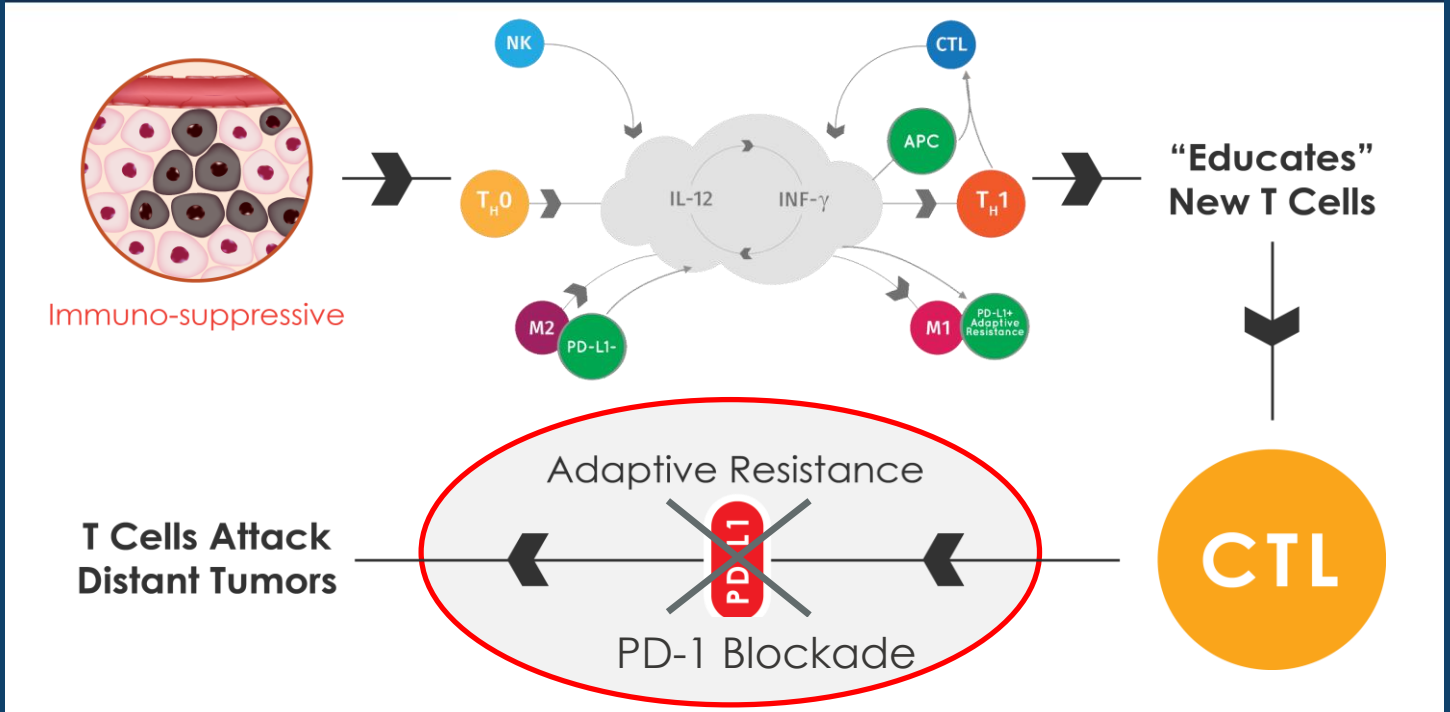
Rationale for Combination of TAVO and Anti-PD-1 Blockade



Hypothesis: **Activation of the PD-1 checkpoint in distant, untreated tumors blunts the effectiveness of TILs generated by tavo**

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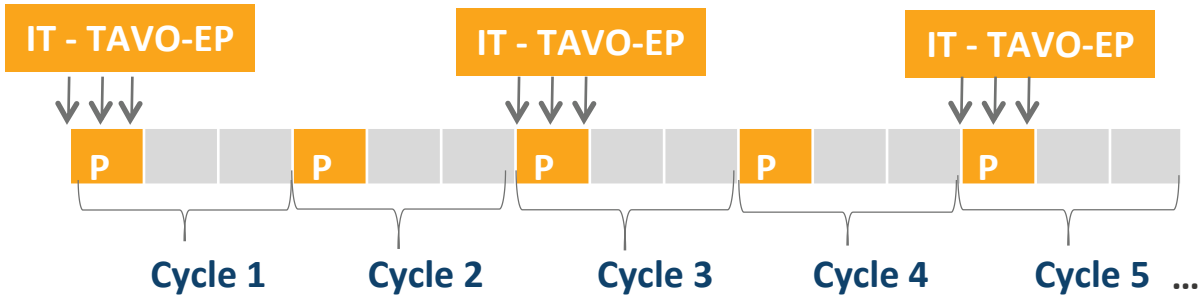
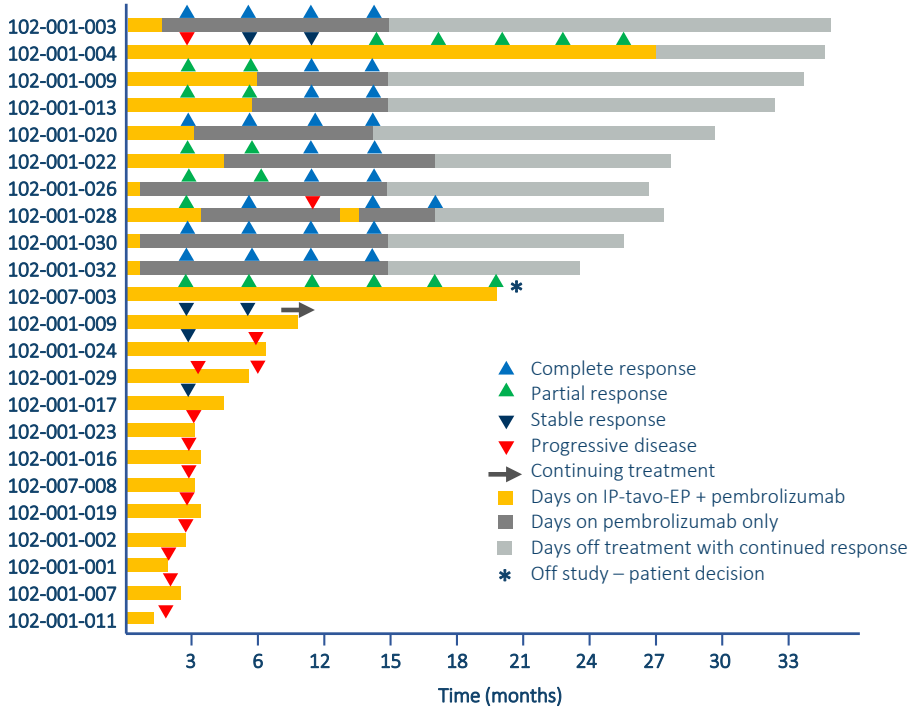
Phase 2 (OMS-102) Metastatic Melanoma Combination (tavo + pembro) Trial Design

- **Patients were selected using CTLA4^{hi}PD1^{hi} TIL phenotype**
- 3 week treatment cycles with pembro administered as a 30-minuted IV infusion at Day 1 of every cycle (flat dose of 200 mg)
- Patients treated with IT-TAVO-EP on days 1, 5 and 8 of every 6 weeks

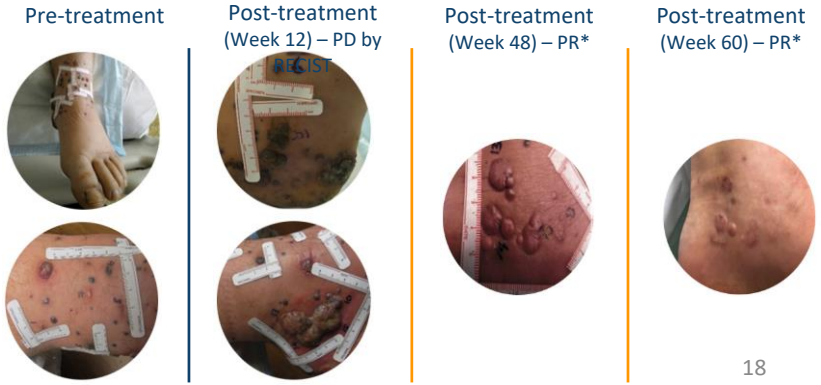


P = Pembrolizumab treatment

Phase 2 (OMS-102): ORR of combination (tavo + pembro)



	Clinical	RECIST
Best Overall Response Rate (BORR = CR + PR)	11/22 (50%)	9/21 43%
Disease Control Rate (DCR = CR + PR + SD)	13 /22 (59.0%)	12/21 57%
Complete Response (CR)	9/22 (41.0%)	8/21 38%
Partial Response (PR)	2/22 (9.0%)	1/21 5%
Stable Disease (SD)	2/22 (9.0%)	2/21 10%
Progressive Disease (PD)	9/22 (41.0%)	9/21 43%



*PR by clinical assessment

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Agenda

- Rationale of cytokine choice and Electroporation delivery
- Clinical data in metastatic melanoma
- Clinical data in metastatic TNBC

Metastatic Triple Negative Breast Cancer (TNBC)

Patients are ineligible for HER2 and ER-targeted therapies

Disease progression is rapid, and chemotherapy responses are not durable

Novel targeted therapies (e.g., PARP inhibitors) are only suitable for select patient segments

Checkpoint inhibition with PD-(L)1 monotherapy is only effective in a minority of patients

Urgent need for additional therapeutic options in TNBC

Poor overall survival for metastatic patients

Unmet need is likely to endure

Need for IO combos

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Phase 1 (OMS-I140) TNBC Study design and intervention

KEY ELIGIBILITY CRITERIA

- Adult patients (≥18 years) with histologically confirmed diagnosis of locally advanced, inoperable, metastatic and/or treatment-refractory TNBC (ER/PR <10%)
- At least 2 anatomically distinct lesions accessible for biopsy
- ECOG 0–1
- Life expectancy ≥6 months

Primary Endpoint: (immunology)

Evaluation of pre- & post-treatment changes in intratumoral lymphocyte subsets by immunohistochemistry and gene expression

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Phase 1 (OMS-I140) Patient demographics and baseline characteristics

- (July) 10 patients have been enrolled in the study.
- As of 23 January 2018:
  - 5 patients completed all study-related procedures and have correlative data available
  - 6 patients have complete safety data available
- The IT-TAVO dose delivered per patient per day ranged between 1.36–20 mL

Characteristic	All patients (N = 7)
Age, years	
Mean (SD)	58.7 (15.89)
Median (min, max)	59 (35–84)
Age group, n (%)	
<65 years	4 (57.1)
≥65 years	3 (42.9)
Sex, n (%)	
Male	0 (0.0)
Female	7 (100.0)
Race, n (%)	
White	4 (57.1)
Asian	3 (42.9)
Distant metastases at enrollment, n (%)	7 (100)

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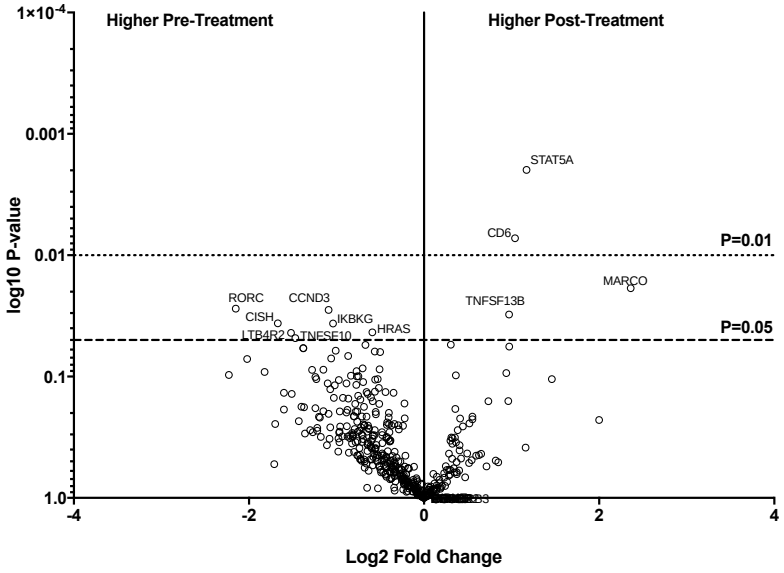
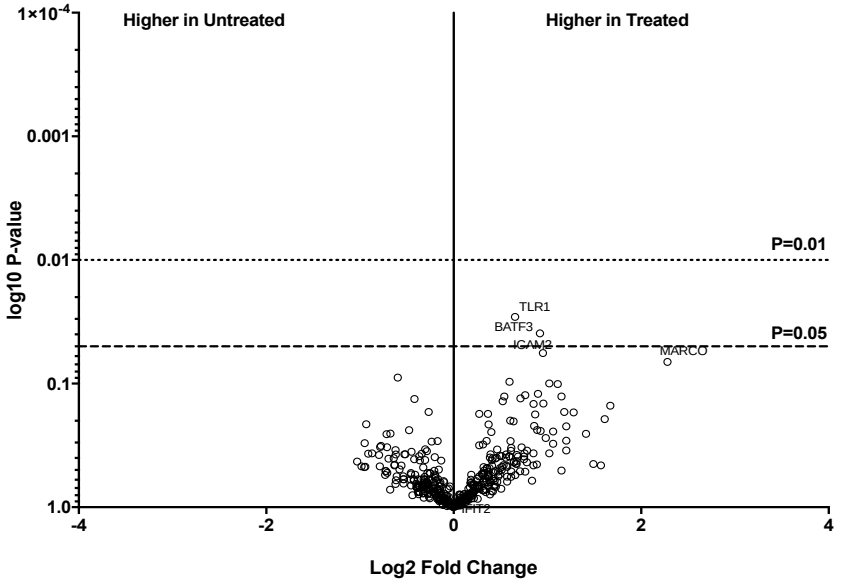
Phase 1 (OMS-I140) NanoString gene expression profiles

NanoString analysis suggests that 1 cycle of IT-tavo-EP did not globally impact intratumoral immune-related gene expression (n = 5 patients; 594 genes)

Treated lesions (pre- vs post-treatment)



Treated vs untreated lesions (post-treatment)



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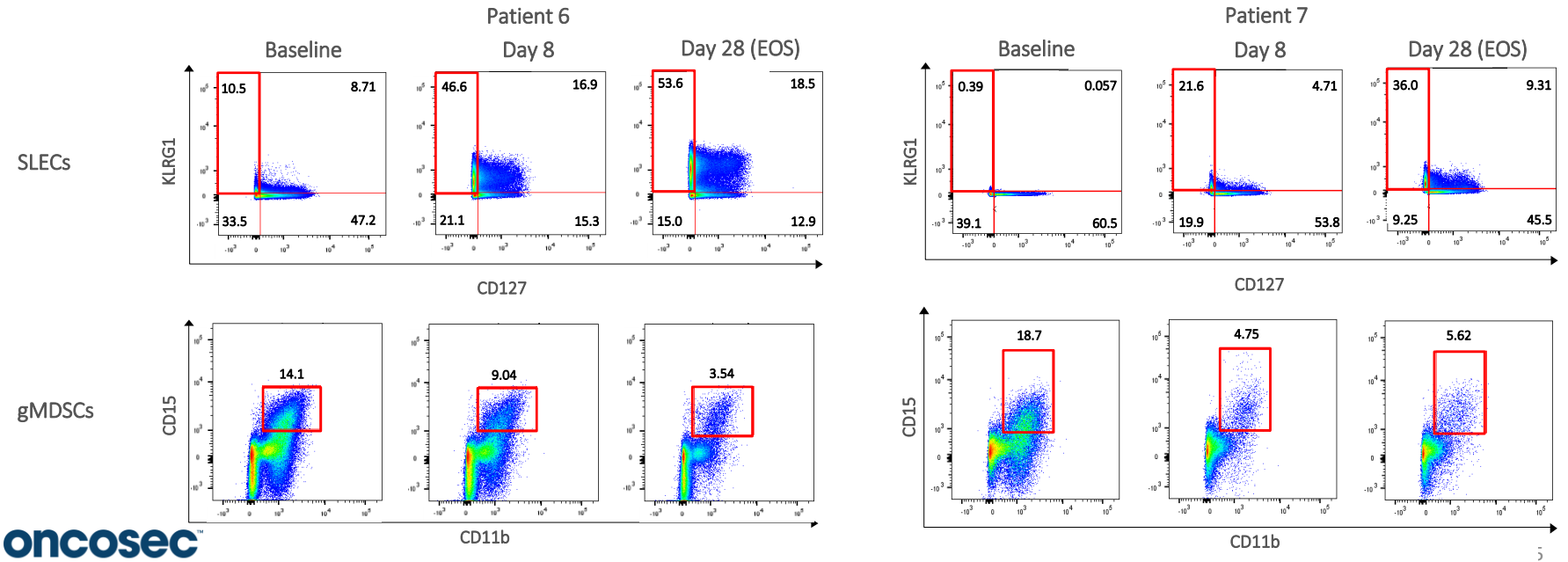
IT-tavo-EP, intratumoral IL-12 plasmid administration followed by electroporation; log, logarithm; vs, versus.

Phase 1 (OMS-I140) Proinflammatory signature

From screening to EOS, a dramatic increase in **short-lived effector cells (SLECs; $CD3^+CD8^+CD127^-KLRG1^+$)** was recorded in the PBMCs of patients treated with 1 cycle of IT-tavo-EP. A gradual increase in proliferating **partially exhausted T cells, and naïve and central memory/effector memory RA T cells** was also observed (data not shown). Consequently, a gradual decrease in the levels of **granulocytic myeloid-derived suppressor cells (gMDSCs; $CD45^+Lin^-HLA^-CD15^+CD11b^+$)** was also recorded following IT-tavo-EP treatment



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Phase 1 (OMS-I140) Safety: TEAEs recorded in the safety population (n = 6)

Adverse event, n (%)	Grade 1	Grade 2	Grade 3
Hypoalbuminemia		2 (28.6)	
Anemia	1 (14.3)		
AST increased*	1 (14.3)	1 (14.3)	
Hypercalcemia	1 (14.3)		
ALT increased	1 (14.3)		
ALP increased		2 (28.6)	
Pain in RUQ	1 (14.3)		
Fatigue	1 (14.3)	1 (14.3)	
Decreased appetite	1 (14.3)		
Confusion	1 (14.3)		

*Both grade 1 and grade 2 TEAEs were recorded in the same patient.

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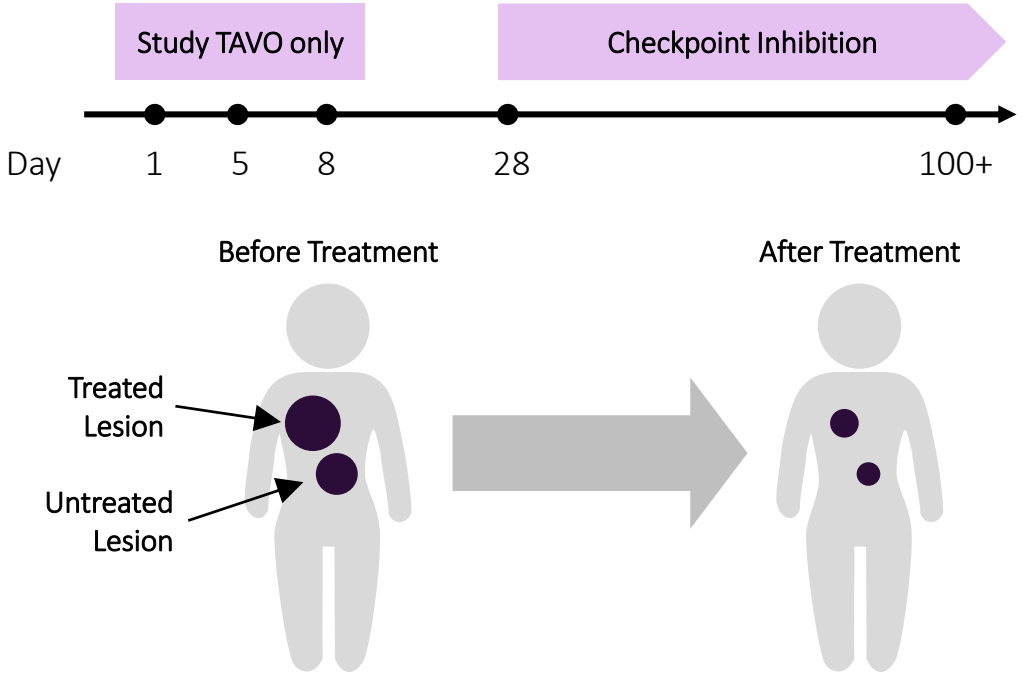
Phase 1 (OMS-I140) and Post Protocol

OMS-I140 Trial

Therapy:	TAVO followed by checkpoint inhibition in select patients
Patients:	Patients with advanced or metastatic TNBC (2L+)
Timeline:	Ongoing 9 TAVO only 6 TAVO + checkpoints
Results:	Tumor reduction observed



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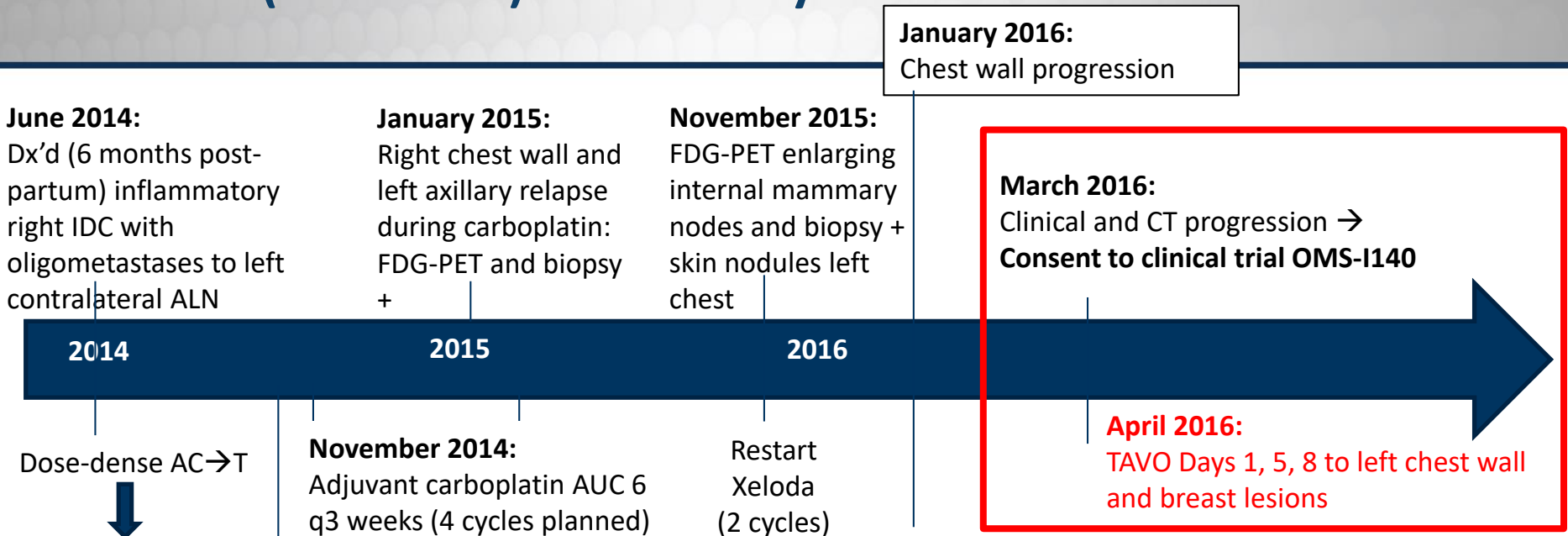
Phase 1 (OMS-I140) Case 1: 46-year-old T4dN3M1 TNBC



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Phase 1 (OMS-I140) Case 1: Protocol and Post-Protocol

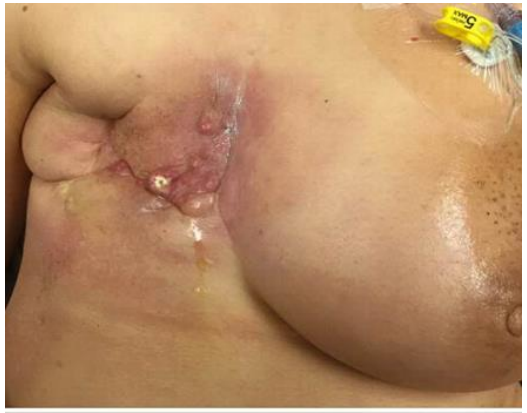
April 4, 2016 – May 2, 2016:
Cycle 1, Day 1 – Day 28 (post Bx)
Patient received all 3 per-protocol injections

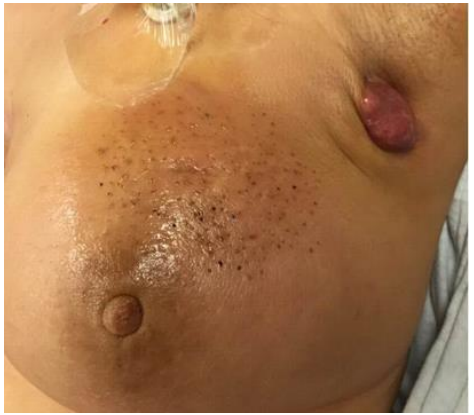
- Left axillary nodule (control) - UNTREATED
- Right chest wall and Left breast - TREATED

May 5, 2016:
Off-protocol checkpoint

October, 2016:
Disease progression (PD) in mediastinal nodes, but observed no PD at sites present when TAVO administered

May 5, 2016:





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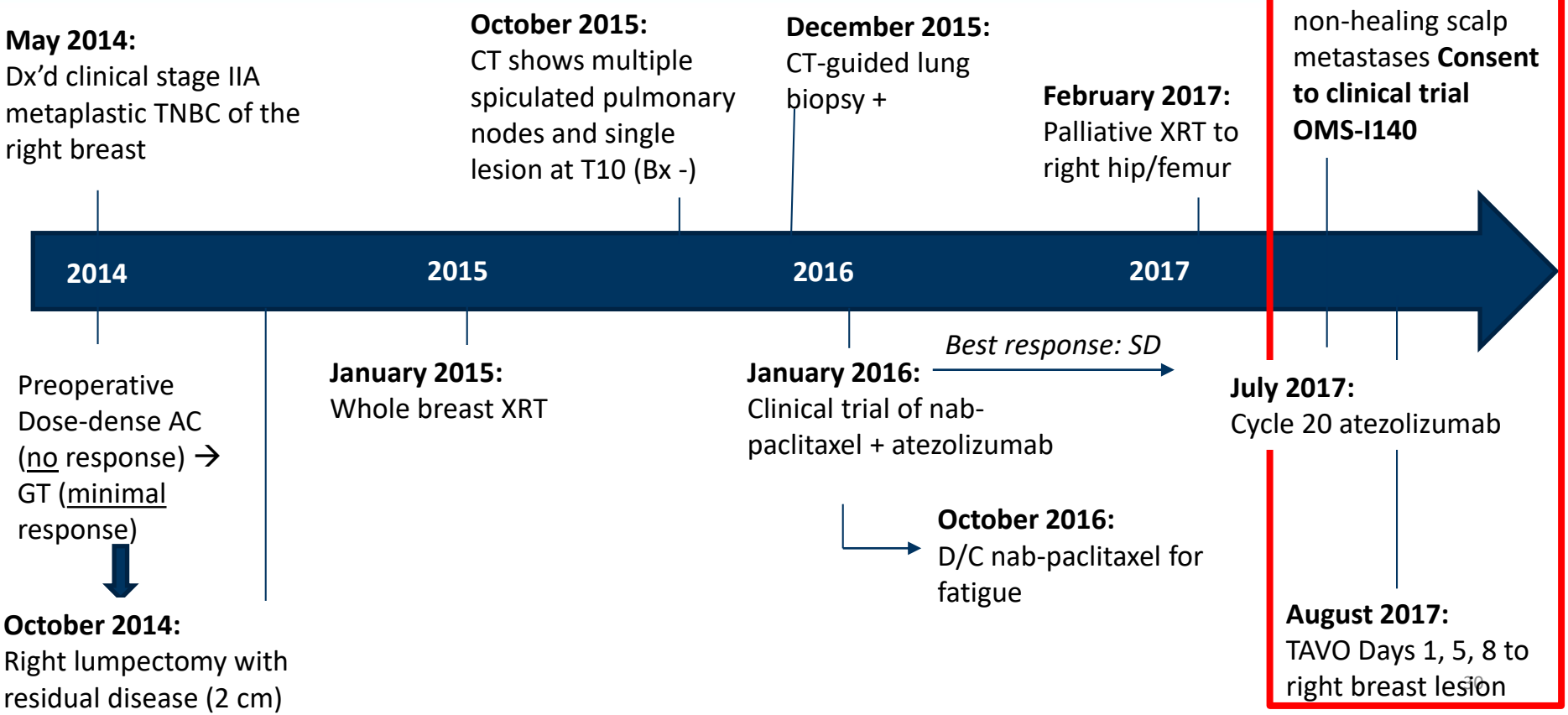
Phase 1 (OMS-I140)
Case 2: 64-year-old T2N0M0 TNBC

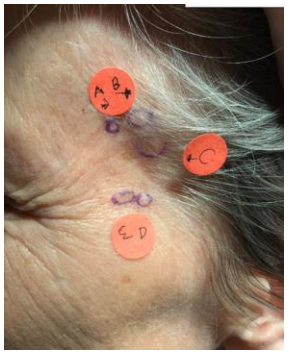


Phase 1 (OMS-I140) Case 2: Protocol and post-Protocol Treatment

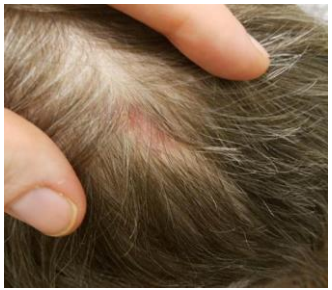
August 14, 2017 – September 14, 2017:
Cycle 1, Day 1 – Day 28 (post Bx)
Patient received all 3 per-protocol injections

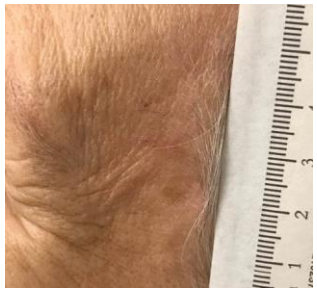
- Left scalp skin mets (control) - UNTREATED
- Right breast lesion - TREATED

August 14, 2017:



December 14, 2017:





September 21, 2017:
Off-protocol Nivolumab IV q 2 weeks
Rapid clinical and imaging response (decreased size of breast nodule, pulmonary nodules and sclerosis of osseous metastases; resolution of scalp metastases)

June 2018:
Surgery on right sacral tumor- confirmed PD

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Conclusions

- Immunological signals of systemic immune responses (2/2 patients) and CD 8 increases IT (not shown in 2/5)
- Well tolerated: Grade 1-2 TEAE of transient pain and fatigue
- Post TAVO with a checkpoint(s) may show benefit

These results suggest that IT-tavo-EP is a safe and tolerable TIL-stimulating therapy of skin and subcutaneous TNBC tumors

- Thus a study of this therapy in combination with pembrolizumab is underway

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A Phase 2, Open-Label Study of Intratumoral Tavokinogene Telseplasmid Plus Electroporation in Combination with Intravenous anti-PD-1 Therapy in TNBC Patients

OMS-I141 / Keynote 890

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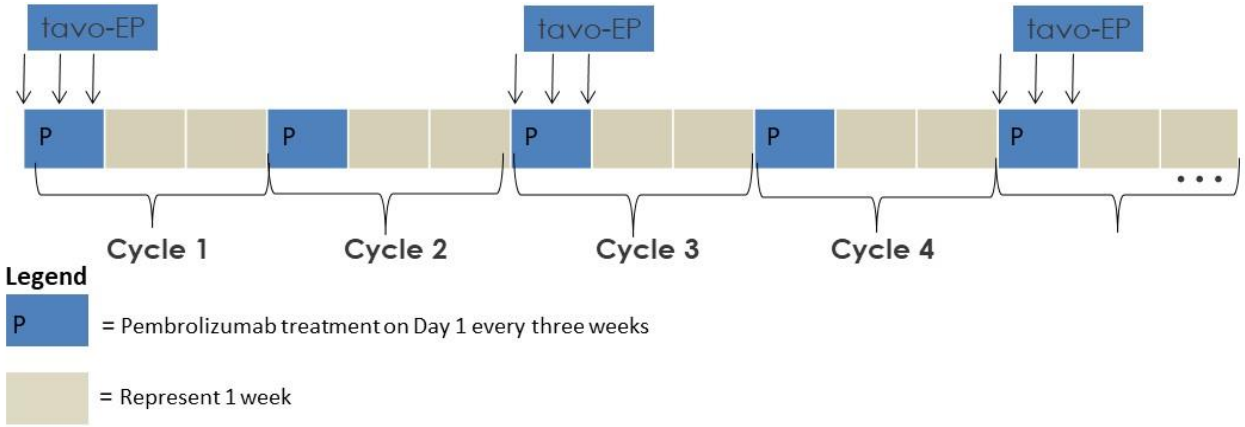
OMS-I141 / Keynote 890 Trial Design

- **3 wk treatment cycles with pembrolizumab and 6 wk cycles IT-TAVO on days 1, 5 and 8**
- **Subjects with histologically confirmed diagnosis of inoperable locally advanced or metastatic TNBC and at least 1 prior line approved systemic chemotherapy or immunotherapy.**
- **Primary Endpoint: RECIST v1.1 ORR**
- **Simon 2 Stage (>/= 1 of 15, add 10 for >/= 6/25)**

NCT03567720



tavo-EP = intratumoral tavokinogene telseplasmid injections followed by electroporation on days 1, 5 and 8 every 6 weeks

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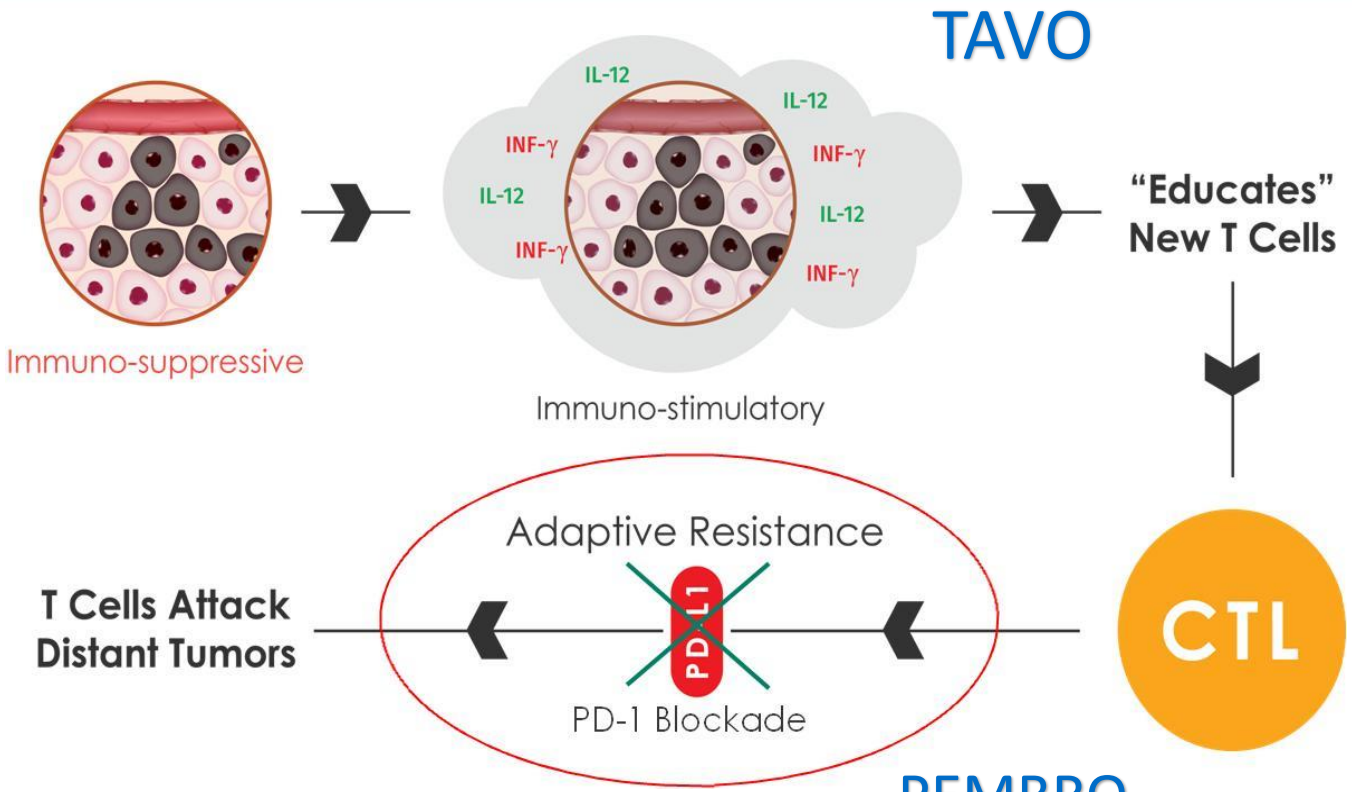
Rationale for TAVO and PD-1 blockade in TNBC



SUMMARY

- Intratumoral delivery of plasmid IL-12 (TAVO) is
  - Well tolerated
  - Efficacious as a monotherapy (treated and untreated)
  - In melanoma, in combination with pembrolizumab, TAVO may change anti-PD-I non responders into responders (trials underway)
  - In TNBC, sequential treatment of TAVO and checkpoints has led to encouraging clinical observations warranting a further trial
  - More to come…..

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