

Intratumoral electroporation of plasmid interleukin-12: efficacy and biomarker analyses from a phase 2 study in melanoma (OMS-1100)

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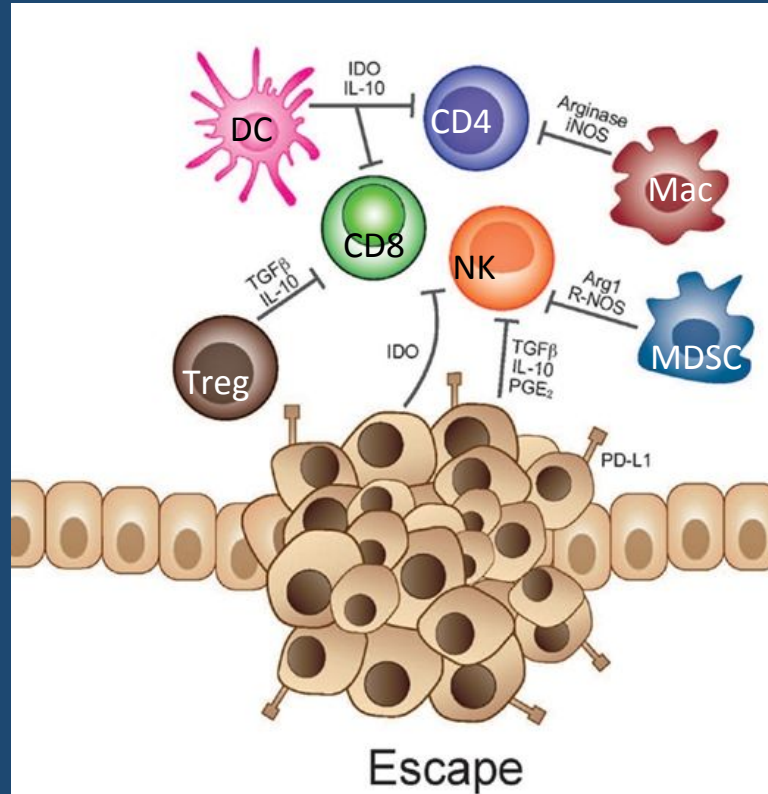
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Background: The Immunosuppressive Tumor Microenvironment

- Lack of immune stimulatory cytokines & chemokines
- Lack of co-stimulatory molecules
- Lack of tumor antigen processing & presentation



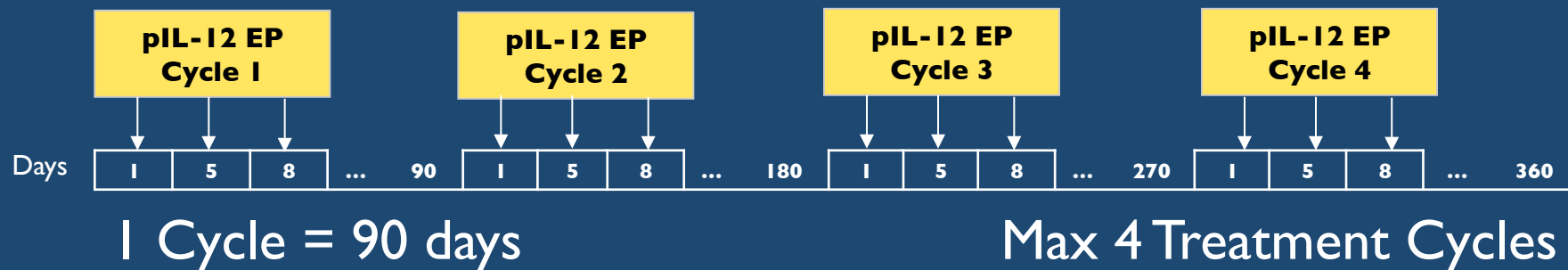
- High engagement of immune inhibitory molecules
- Low infiltration of cytotoxic T-cells (i.e. low TILs)
- High CD4 regulatory T-cell infiltration

Intratumoral Plasmid IL-12 Electroporation

Local Treatment, Systemic Results

- Intratumoral plasmid IL-12 (pIL-12) Electroporation (EP) leads to local IL-12 expression
- IL-12 promotes anti-tumor immune response
 - Cytotoxicity via CD8⁺ T-cell and NK cell activation
 - Converts myeloid-derived suppressor cells (MDSC) into immunostimulatory antigen-presenting cells (APCs)
- Phase I Study: Intratumoral pIL-12 EP was well-tolerated and achieve some complete responses after one treatment cycle

Phase 2 Study Design and Treatment Schedule



Primary Objective:

- Overall Response Rate by modified “skin” RECIST within 180 days (ORR = CR + PR)

Secondary Objectives

- Disease Control Rate (DCR = CR + PR+ SD)
- Distant Lesion Regression
- Duration of Response (DOR)
- Progression-Free Survival (PFS)
- Overall Survival (OS)
- Safety

Why Modify RECIST for Skin Metastatic Melanoma?

Occurrence of new skin lesions does not always constitute clinical progression or worsening of disease status

Response to immunotherapy may be delayed

Patients with mainly cutaneous metastatic melanoma may not have RECIST 1.1 “measurable” disease



Day 8

Day 39

6 Months

Per Protocol Modifications to Standard RECIST Criteria

Modified “Skin” RECIST	
Measurable Disease	≥0.3 cm in the longest dimension for lesions that can be measured by clinical exam
New Lesions	New lesions on skin permitted if sum total increase is <30% from nadir

IL-12 EP is Safe and Well-Tolerated Across Multiple Treatment Cycles

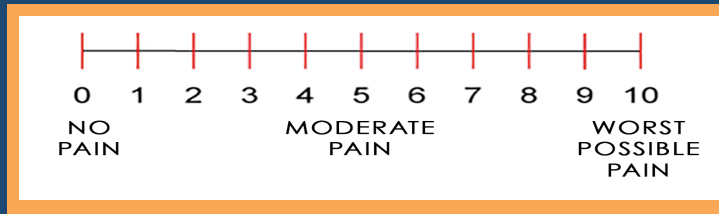
Adverse Event* (N=30)	All Grades N (%)	Grade 3 N (%)
Pain	26 (87%)	1 (3%)
Inflammation	5 (17%)	0(0%)
Skin Discoloration	4 (13%)	
Fatigue		
Ecchymosis	3 (10%)	
Edema		
Erythema		
Pruritus		
Rash		

*treatment-related

No Treatment-Related SAEs

No Treatment-Related
Grade 4 or 5 AEs

PAIN SCORE SUMMARY



Median Score

Immediately after	3.00 (0-10)
5 minutes after	0.00 (0-8)

Median Duration of Pain	1 minute
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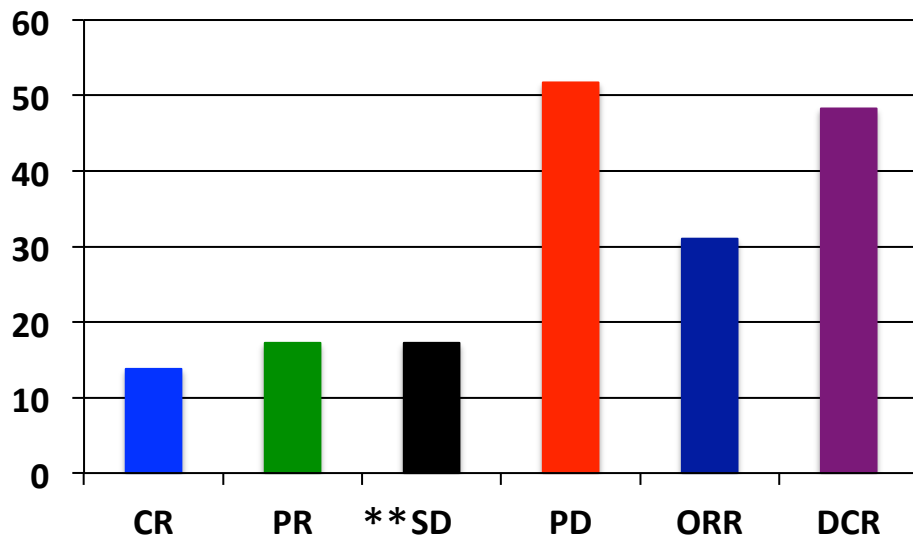
Baseline Characteristics

Characteristic	Patients (N = 30)
Gender (male)	16 (53.3%)
Age	Median 67 yr (44-88 yr)
AJCC Stage	
IIIB/C	19 (63.3%)
IVA	8 (26.7%)
IVB	2 (6.7%)
IVC	1 (3.3%)
Prior Immunotherapy* (Yes)	16/29** (55.2%)

*Immunotherapies included ipilimumab, anti-PD1, interferon, IL-12 and GM-CSF

**Prior therapies data remain outstanding for 1 patient

pIL-12 EP Monotherapy Demonstrates Anti-tumor Activity in Advanced Melanoma



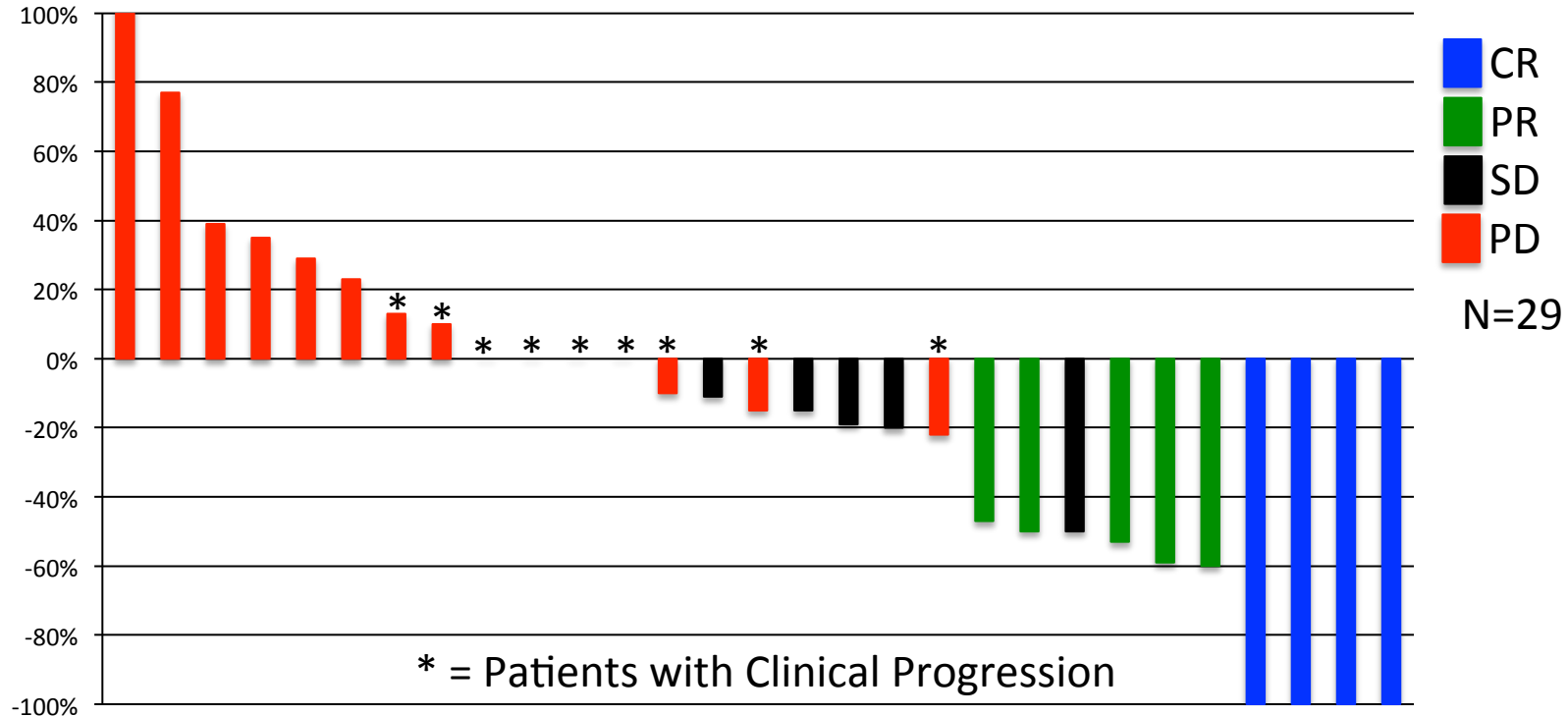
Response Category*	N (%)
Complete Response (CR)	4 (14%)
Partial Response (PR)	5 (17%)
**Stable Disease (SD)	5 (17%)
Progressive Disease (PD)	15 (52%)
Overall Response Rate (CR + PR)	9 (31%)
Disease Control Rate (CR + PR + SD)	14 (48%)

*by Modified "Skin" RECIST

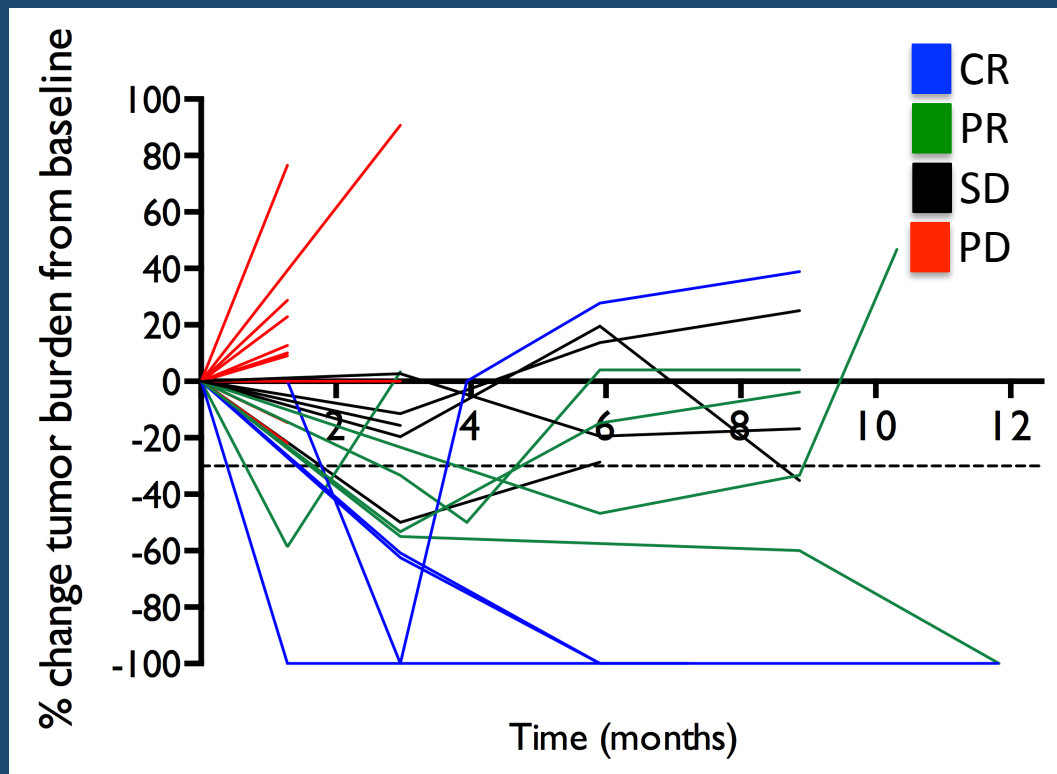
**SD required to last for at least 90 days

Evaluable for Objective Response , N=29

pIL-12 EP Monotherapy Demonstrates Antitumor Activity in Advanced Melanoma

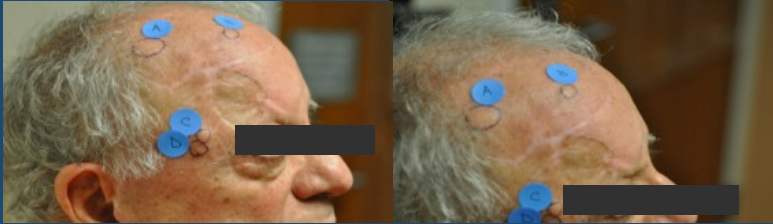


Intratumoral pIL-12 EP can lead to durable clinical responses

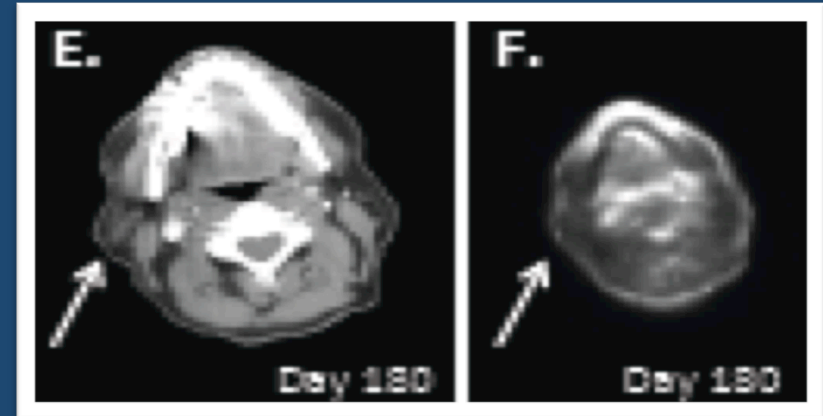
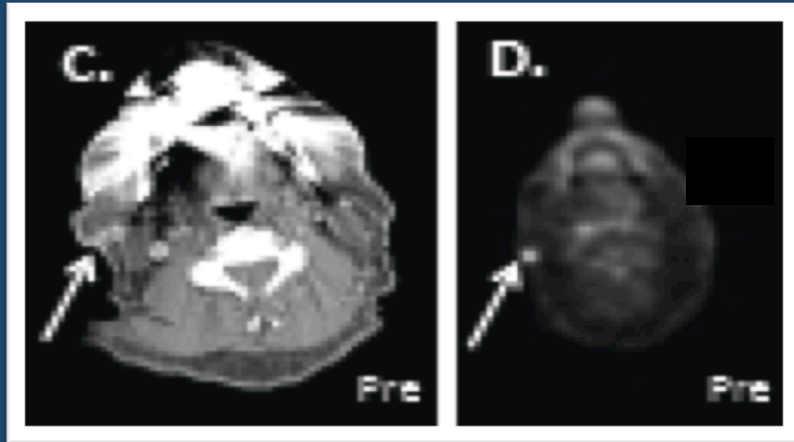


Complete Response with pIL-12 EP

Baseline



Day 180

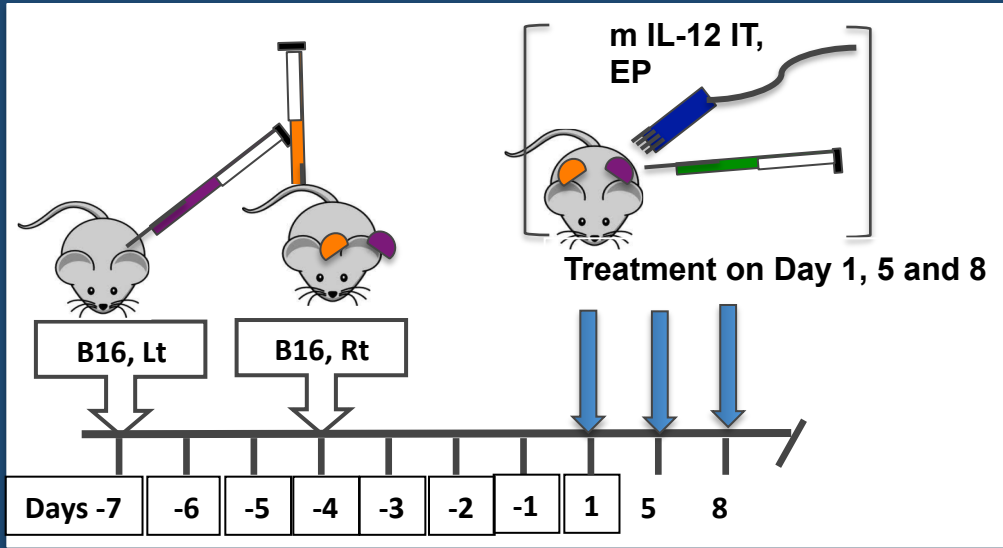


pIL-12 EP Promotes Local and Systemic Anti-Tumor Immunity

Distant Lesion Regression	
Evaluable patients	26
Patients with distant lesion regression	13 (50%)

Distant Lesion Regression: not injected/electroporated, anatomically distinct

Understanding the Systemic Response: The B16 Contralateral Mouse Model



- 30 mice were injected with B16 cells in the left flank (7 days prior to first treatment) and again on the right flank (4 days prior to first treatment) to establish contralateral tumors
- 30 mice were treated in the left flank on days 1, 5 and 8
- Treated and untreated tumors were harvested in 5 mice from each of 6 cohorts (baseline and 5 post-treatment time points)

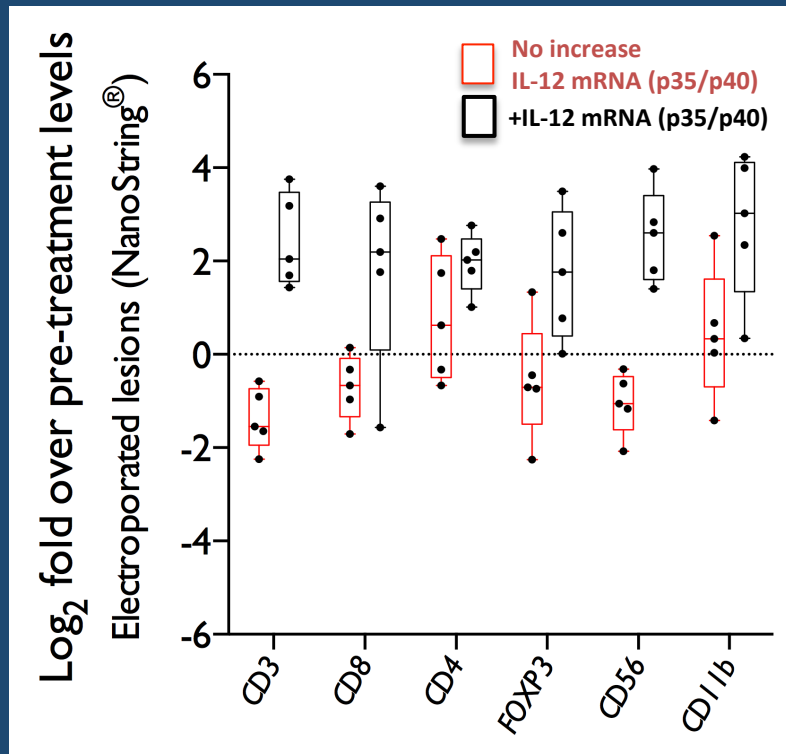
Endpoints: “Clinical” and pathologic assessment & transcriptional analysis (Nanostring).

B16 contralateral 2-tumor model:

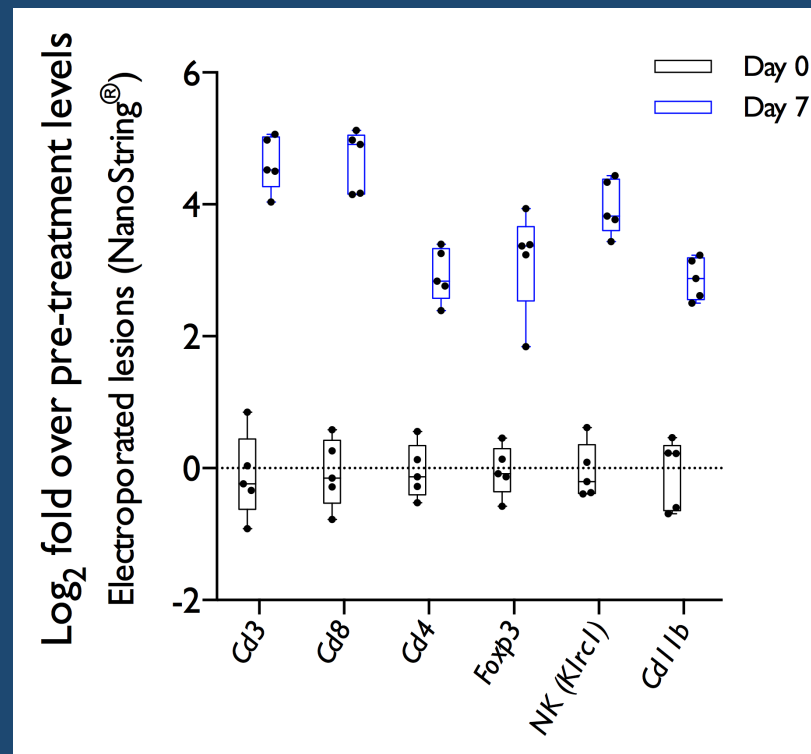
Clinical and Pathologic Observations

- By Day 11, all treated tumors were complete clinical responders with no pathologic evidence of tumor
- By Day 18, clinical and pathologic response in non-injected tumors was observed with 3/5 mice (partial response accompanied by significant TIL infiltrate in the non-injected tumor).
- By Day 22, 1/5 mice harvested showed persistent TILs and a complete response in the non-injected tumor; non-injected tumors in 4 out of 5 mice had no significant increase in TILs.

IL-12 Expression is Associated with Increased Tumor-Associated Inflammatory Cell Infiltrate in Electroporated Lesions in Patients and Mouse Model

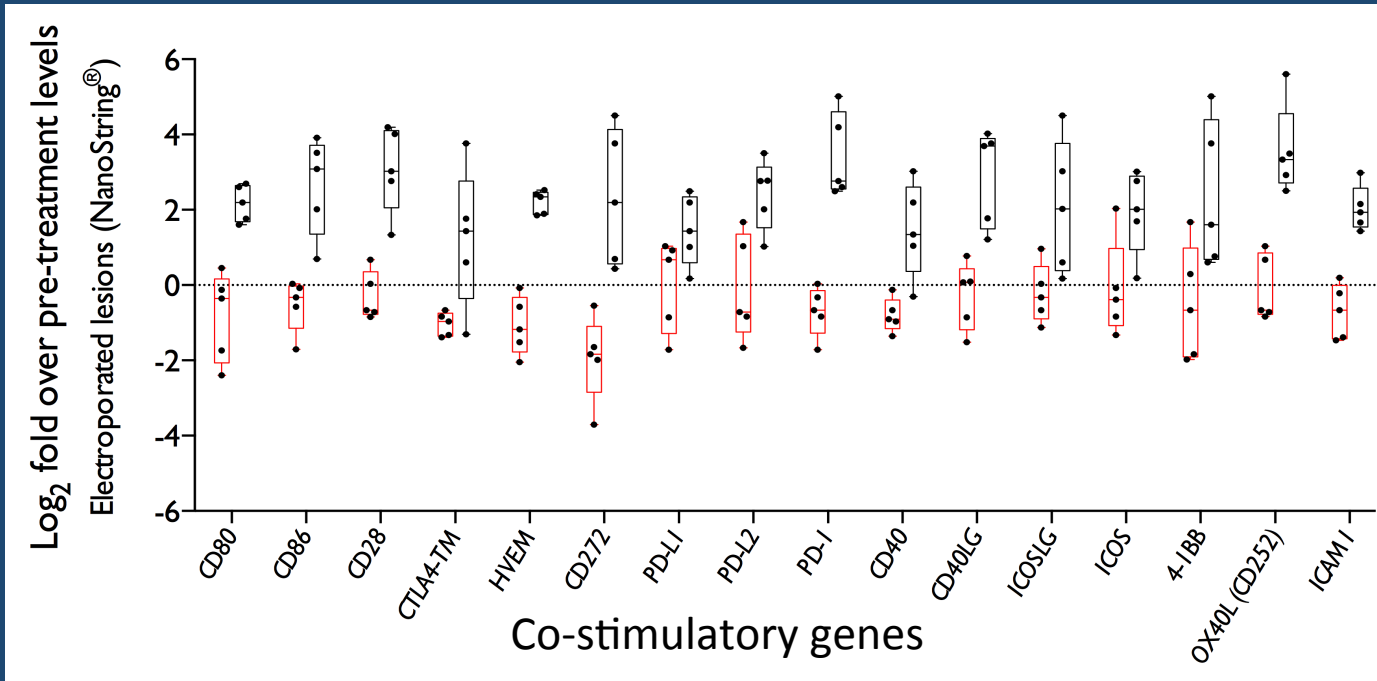


Patient Paired Biopsies, baseline versus Day 11 (N=10)



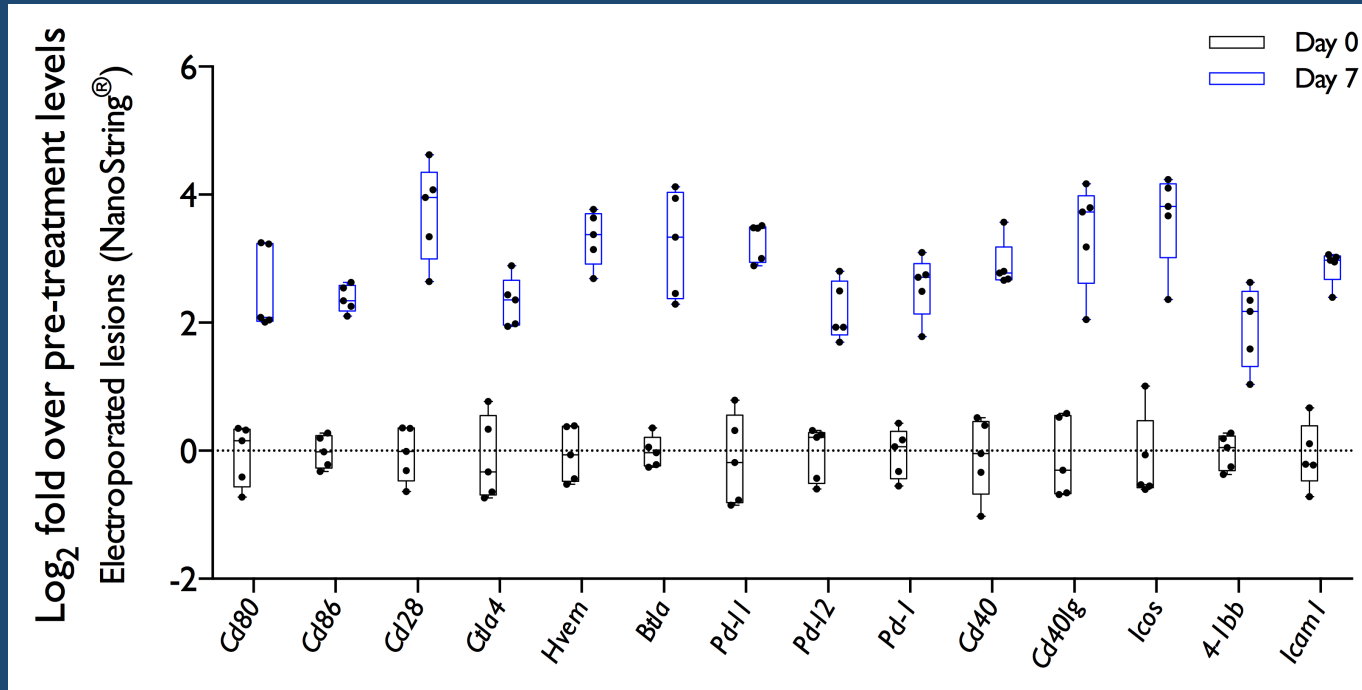
B16.F10 Mouse Melanoma Model

IL-12 Expression Results in Increased Expression of Co-Stimulatory Genes in Treated Lesions in Patients

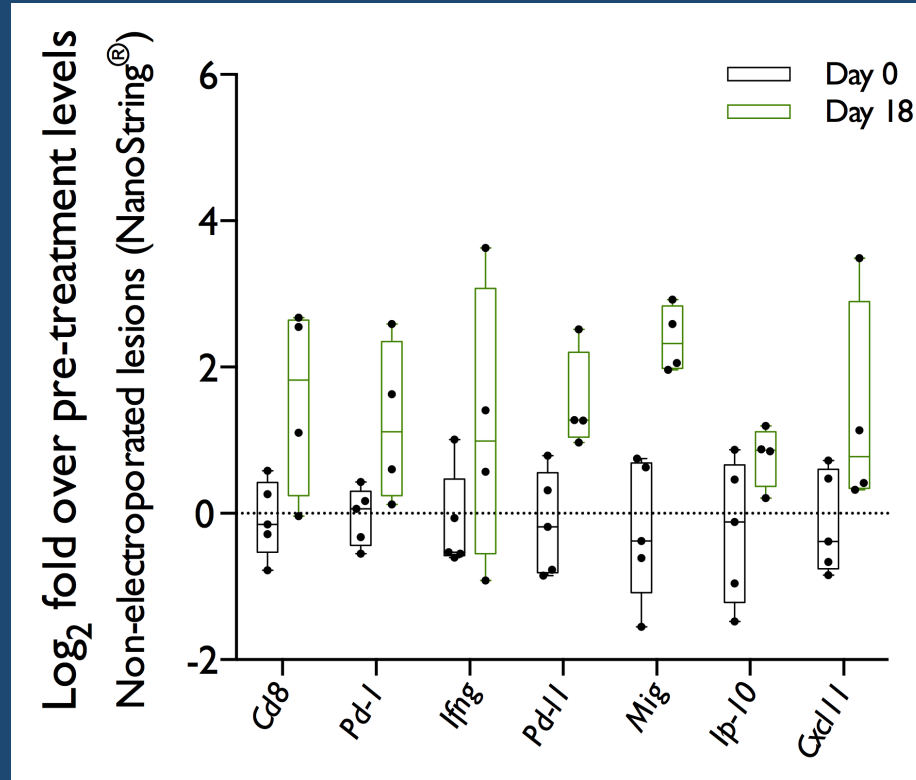


Patient Paired Biopsies, baseline versus Day 11 (N=10)

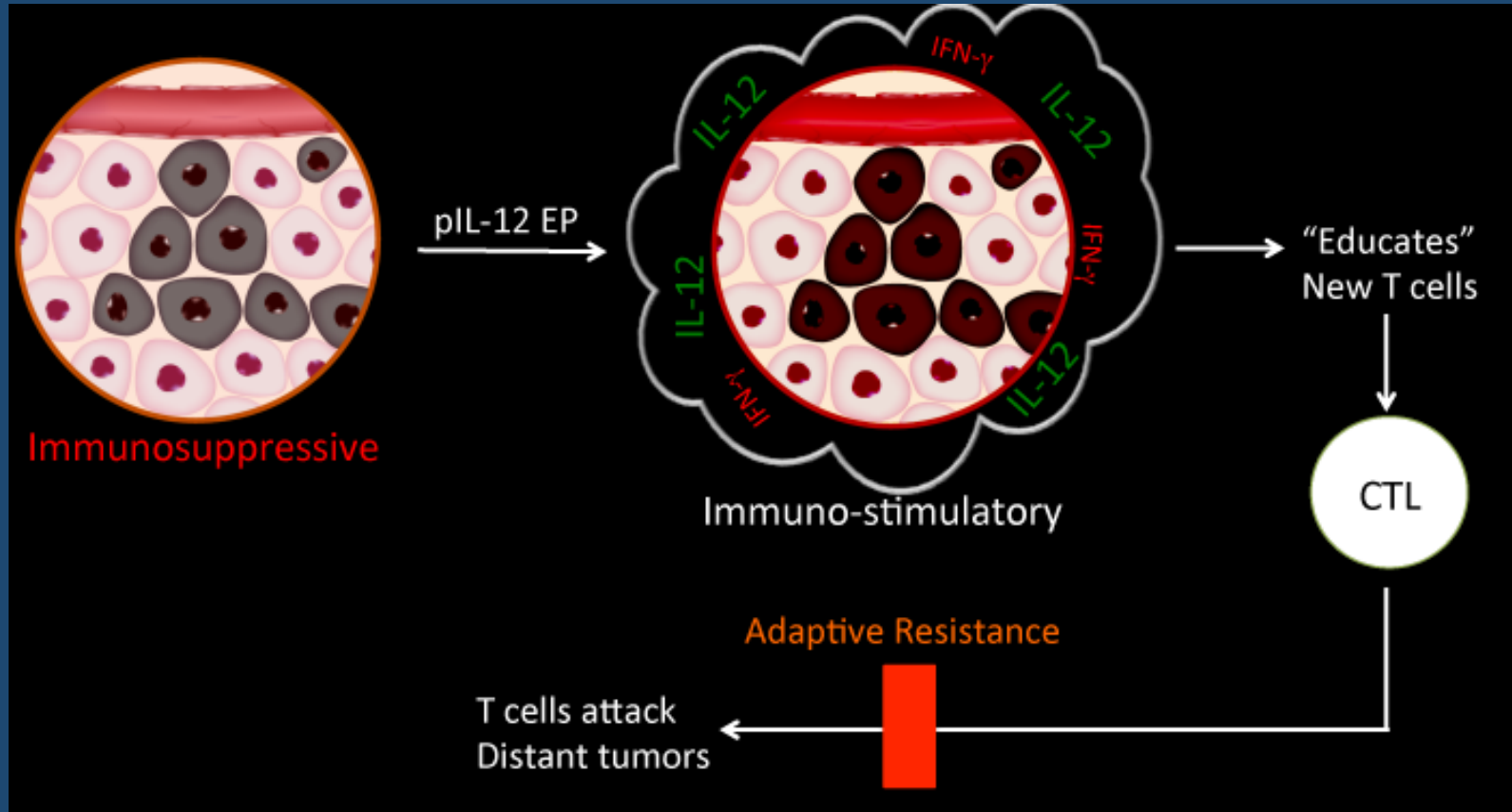
IL-12 Expression Results in Increased Expression of Co-Stimulatory Genes in Treated Lesions in B16.F10 Mice



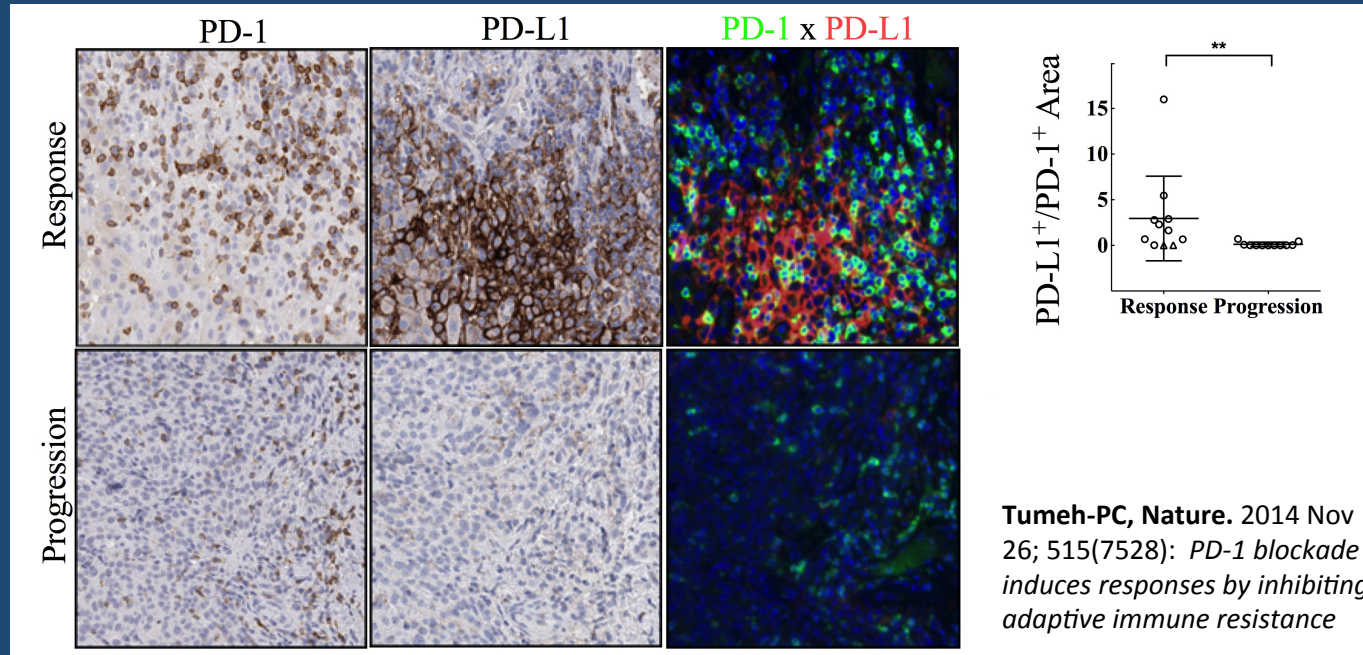
Induction of 'Adaptive Resistance' may limit systemic immune response induced by intratumoral pIL-12 electroporation



Intratumoral IL-12 and the Induction of Systemic Anti-Tumor Immunity



'Adaptive Resistance' phenotype predicts response to anti-PD-1 in melanoma



- pIL-12-induced TIL generation provides rationale for combination with PD-1/PD-L1 mAb
- UCSF Investigators to study combination of intratumoral pIL-12 and pembrolizumab in low TIL patients

Conclusions

- Intratumoral EP of pIL-12 demonstrates monotherapy activity in advanced cutaneous & in-transit melanoma
 - ORR 31% & DCR 48%
- Intratumoral EP of pIL-12 is safe and well-tolerated across multiple treatment cycles
 - No treatment-related Serious Adverse Events Reported
 - No treatment-related Grade 4 or 5 AEs Reported
- Local intratumoral treatment with pIL-12 EP achieves systemic tumor regression
 - 50% patients have regression of a distant lesion
- Preliminary data suggests that intratumoral pIL-12 EP drives tumor immunogenicity and is predicted to synergize with anti-PD1/PD-L1 therapies

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