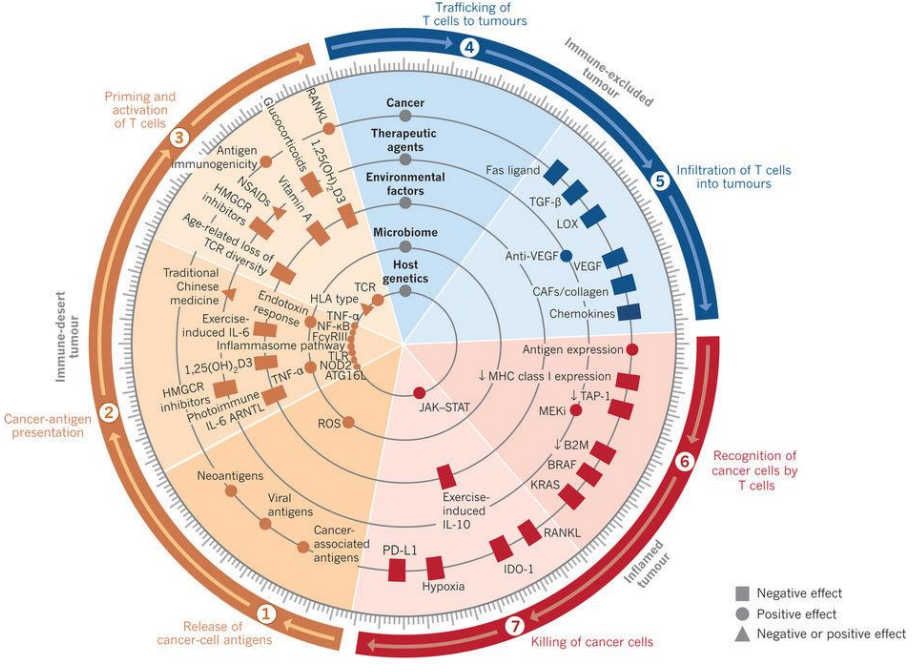
Combination Oncolytic Virus Immunotherapy

Howard L. Kaufman

Disclosures

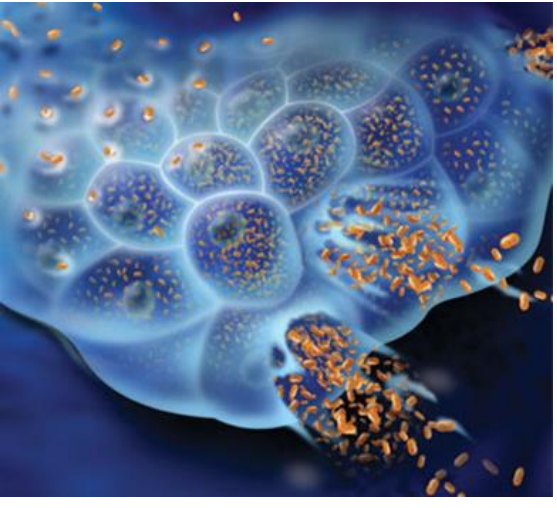
- Replimune, Inc.

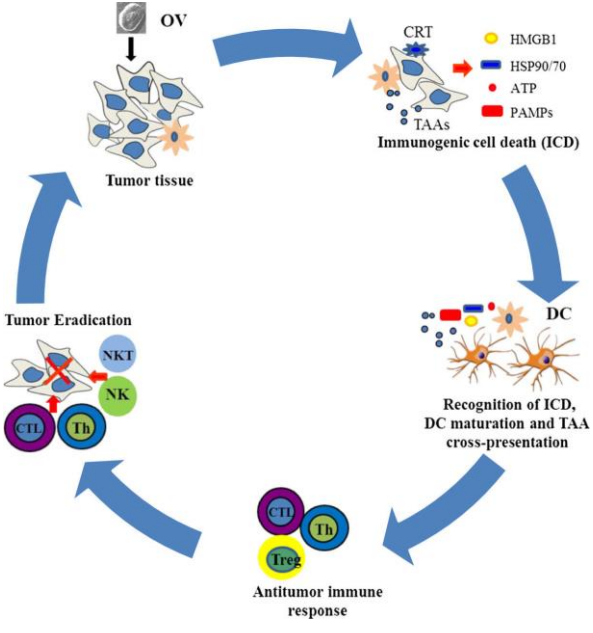
Immunologic Landscape of Established Tumors

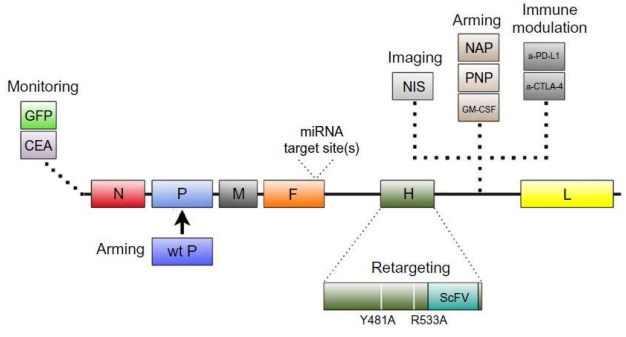


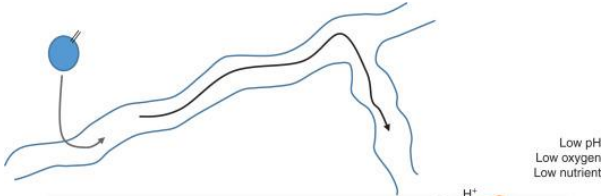
Chen and Mellman, Nature 2017

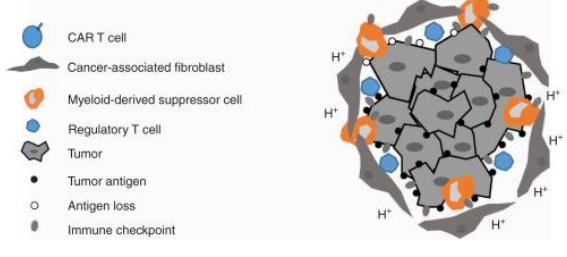
OVs mediate anti-tumor activity via multiple MOAs

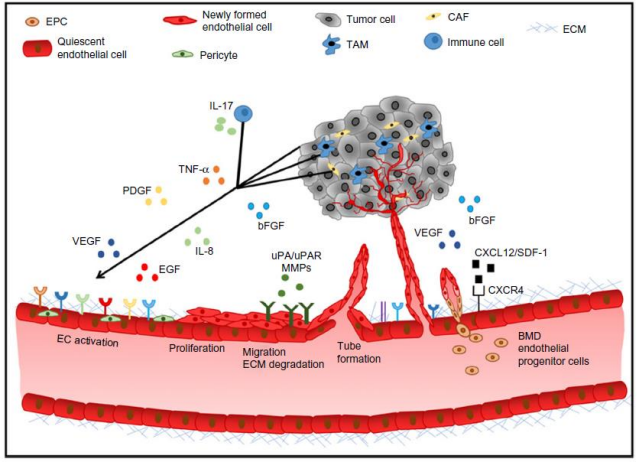






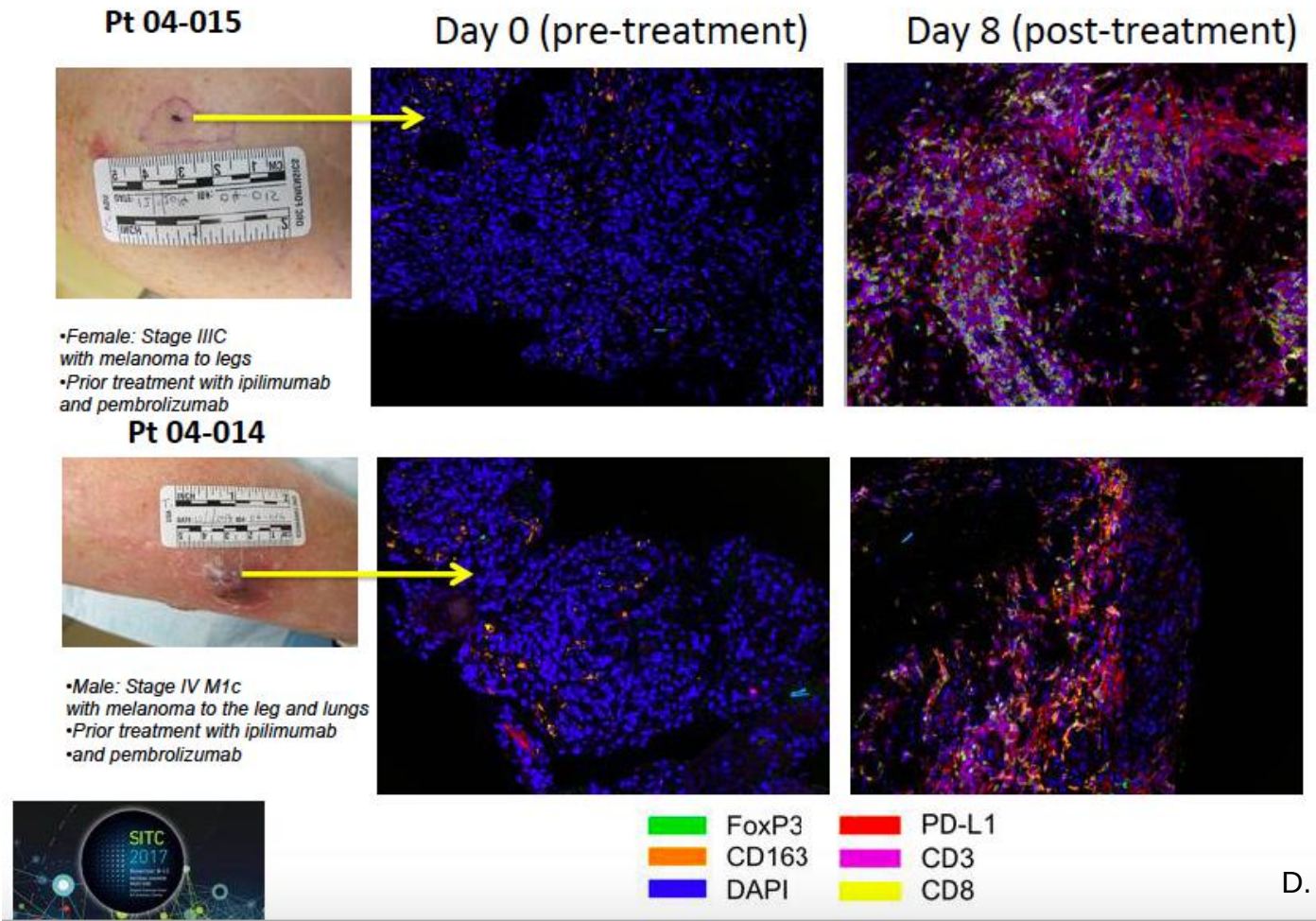






Bartlett et al. Mol Ther 2013
Newick et al. Mol Ther Oncol 2016
Hutzen et al. Oncol Virotherapy 2015
Bejarano and Merchan Oncol Virotherapy 2015

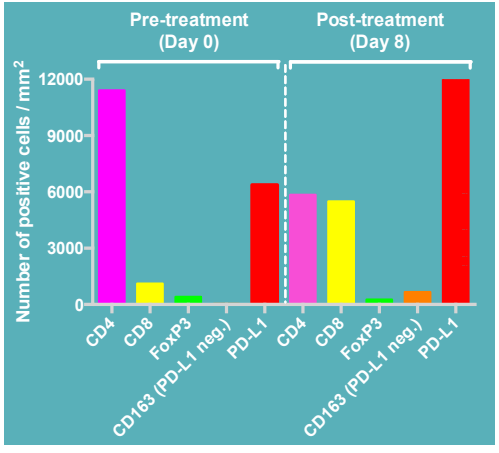
Oncolytic CVA21 increased PD-L1 expression and CD8+ T cell recruitment to the TME



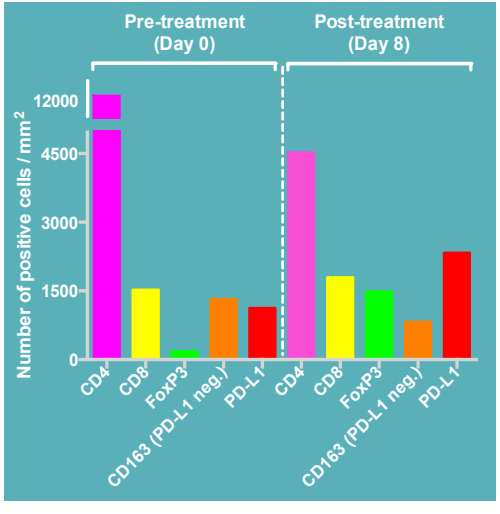
D. Shafren, Viralytics

Oncolytic CVA21 induces Type 1IFN response

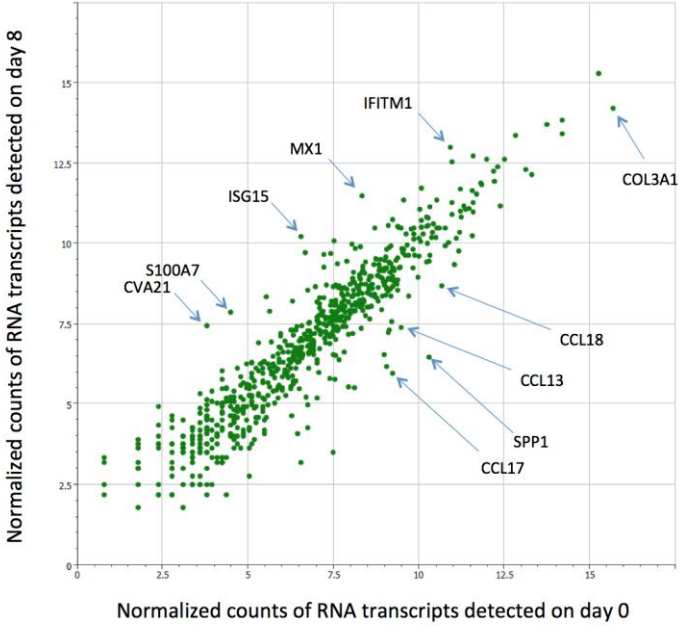
Injected



Non-injected



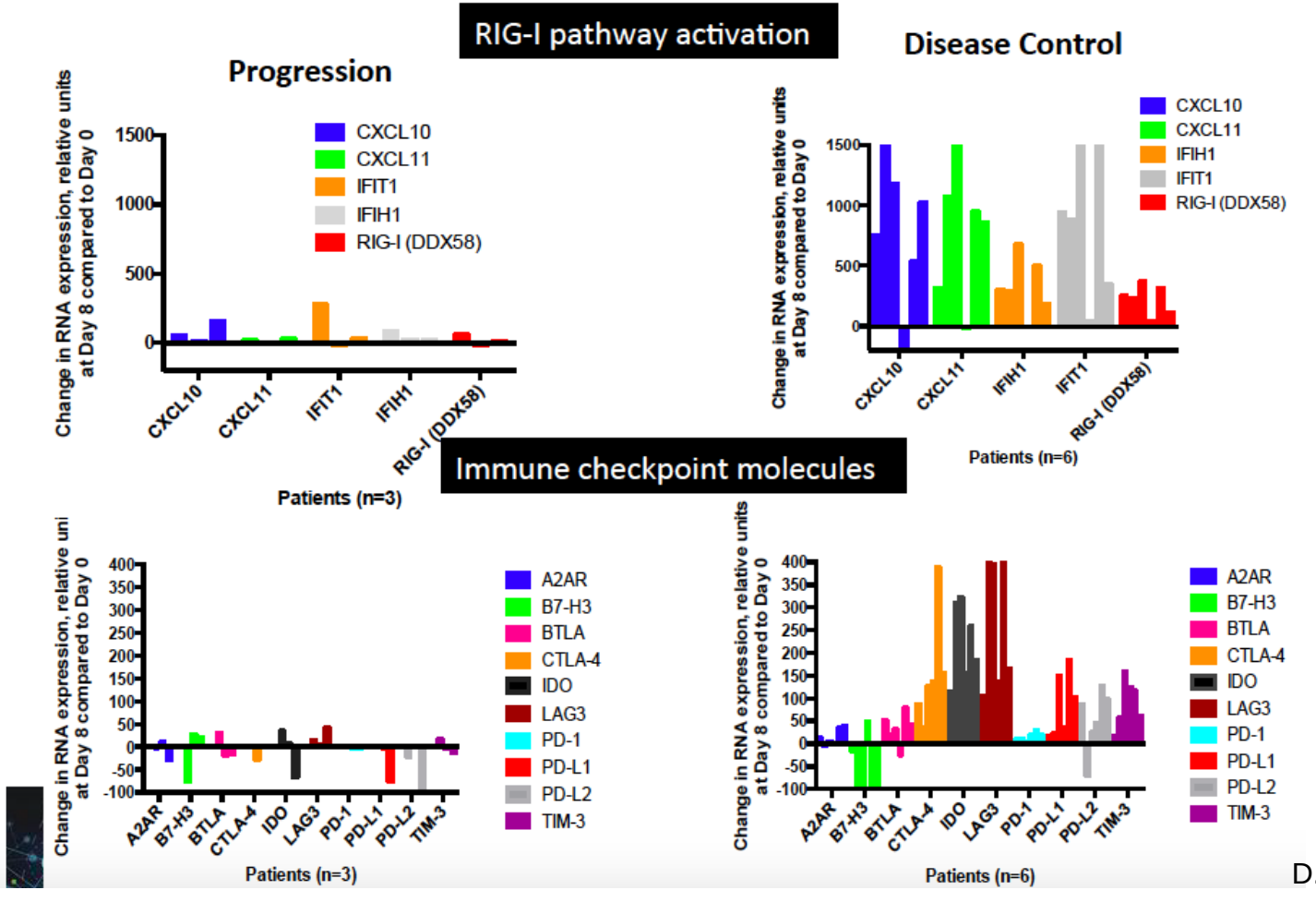
NanoString analysis:
Immune profiling panel



This patient's treated lesion exhibited a Th1-shift, with interferon-induced genes (ISG15, MX1 and IFITM1) upregulated by day 8 and Th2/regulatory associated transcripts (CCL13 and CCL18) down-regulated by day 8.

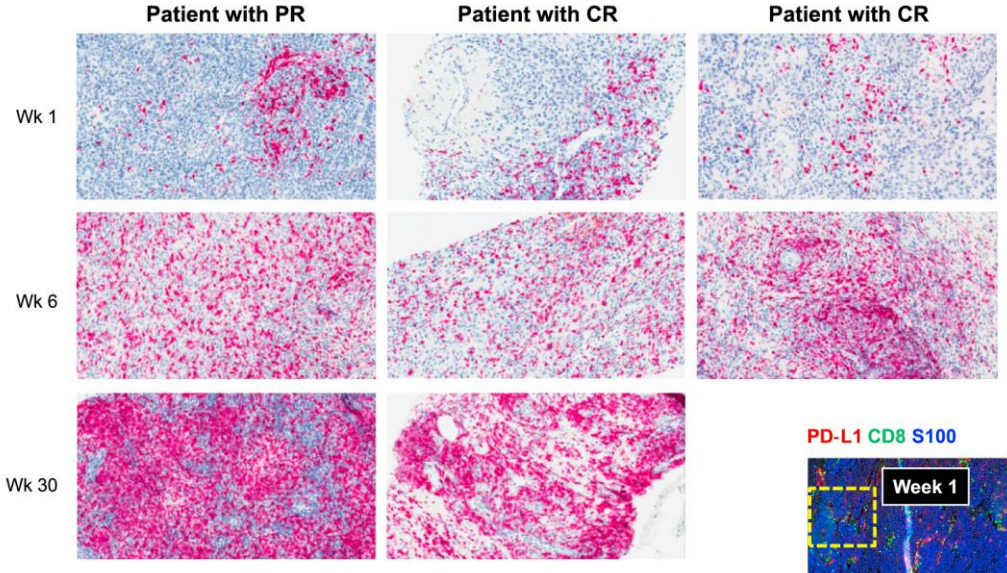
Andtbacka et al. ASCO 2015

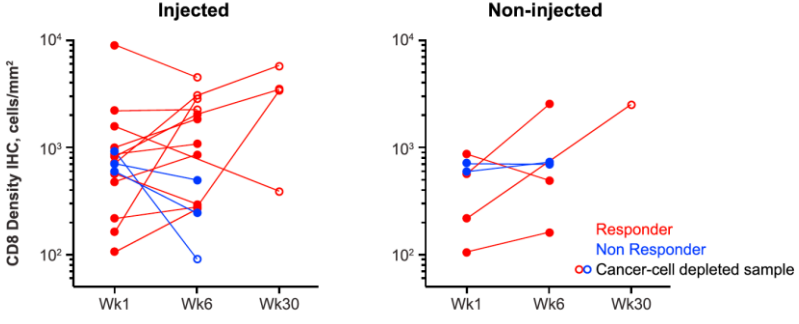
CVA21 promotes RIG-I pathway activation and increased immune checkpoint expression in responding patients

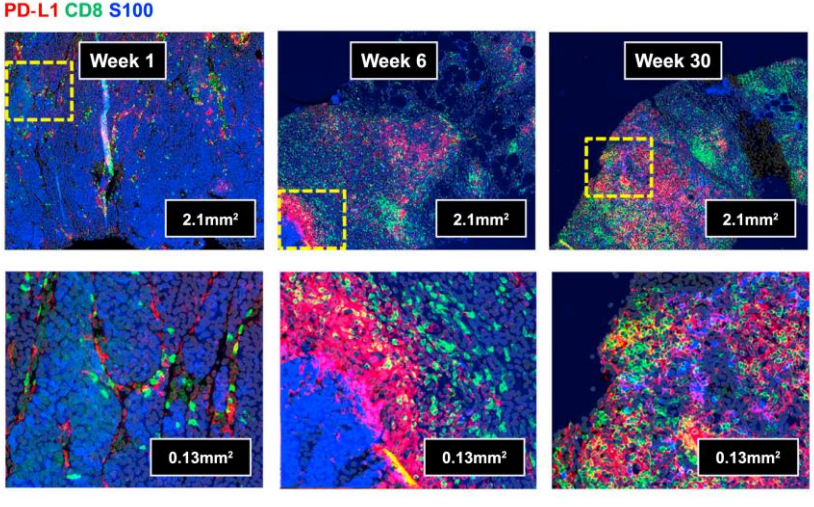


D. Shafren, Viralytics

cell density and PD-L1 in the TME of responding lesions

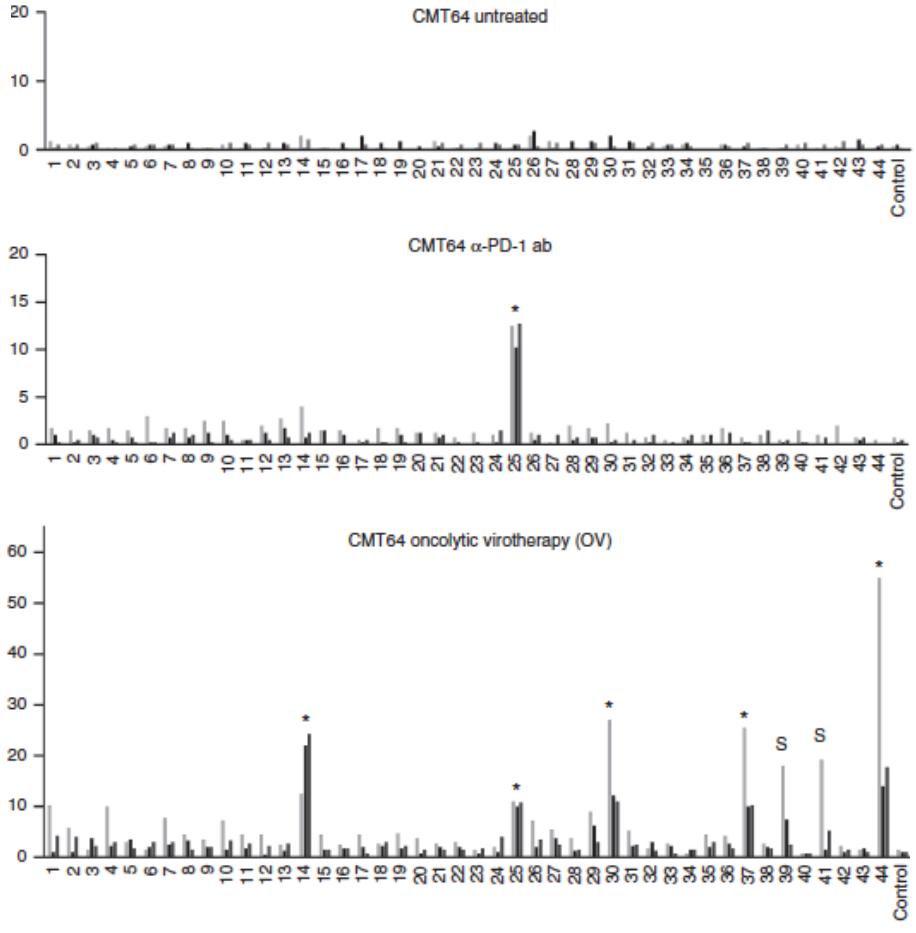






Ribas et al. Cell 2017

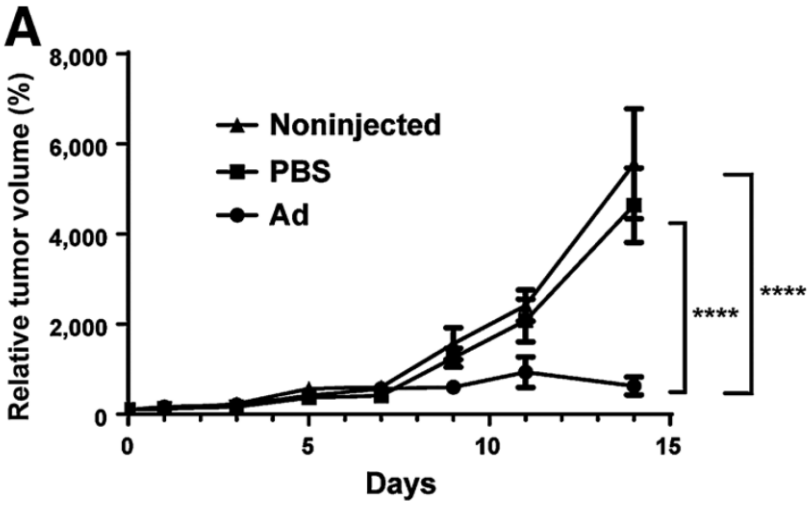
neoantigen-specific CD8+ T cells in PD-1 refractory tumor cells

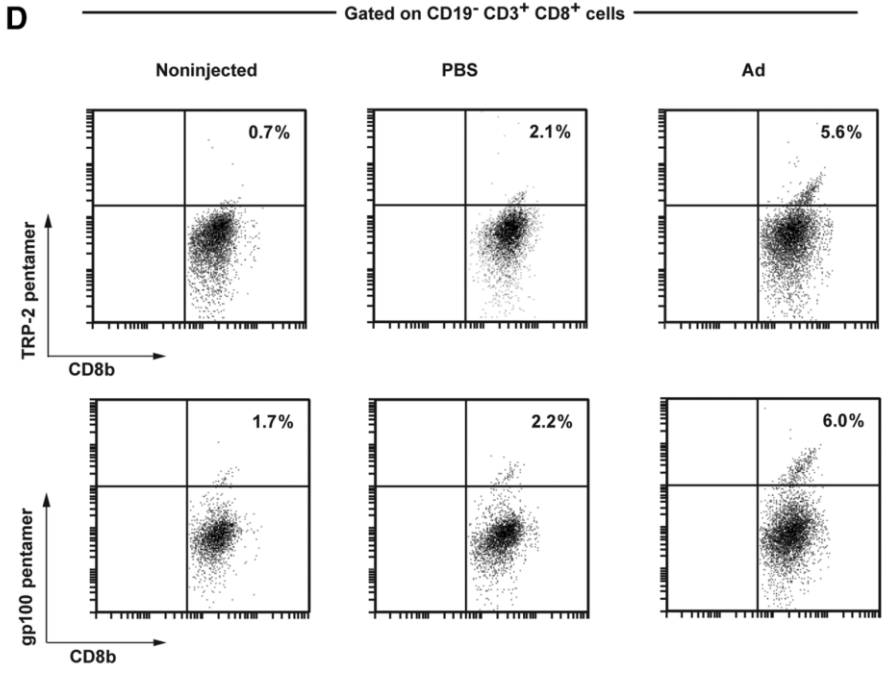


Woller et al. Mol Ther 2015

OVs may synergize with tumor immunotherapy

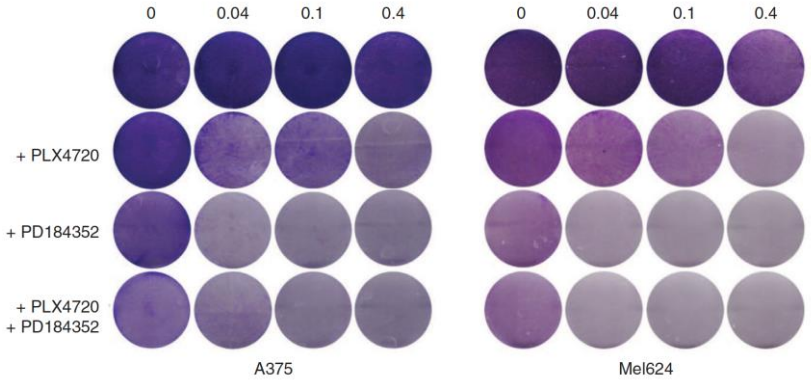
Combination adeno-OV enhances adoptive T cell therapy in OT-1 B16-OVA melanoma tumor model and increases TRP-2- and gp100-specific T cell responses

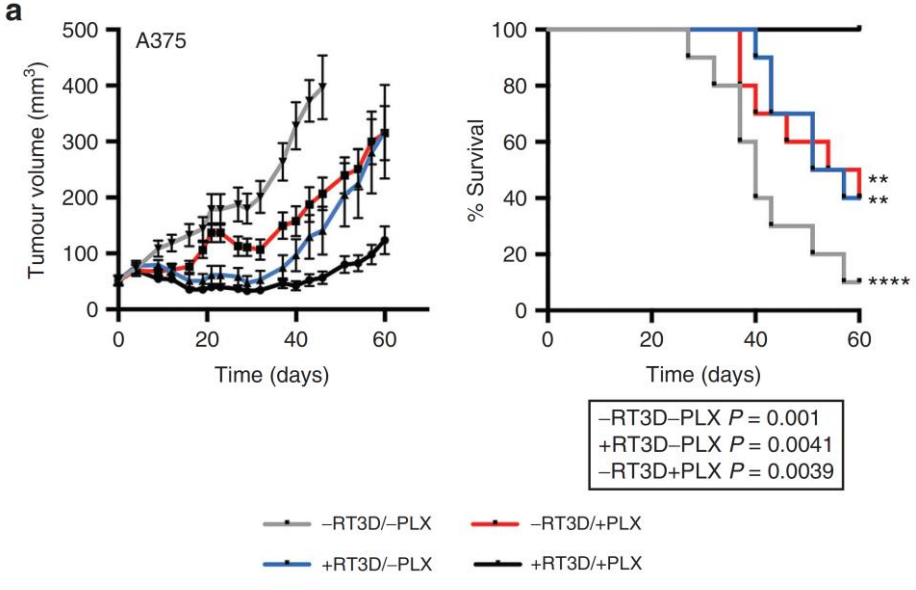




Tahtinen et al. CIR 2015

OVs may synergize with targeted therapy

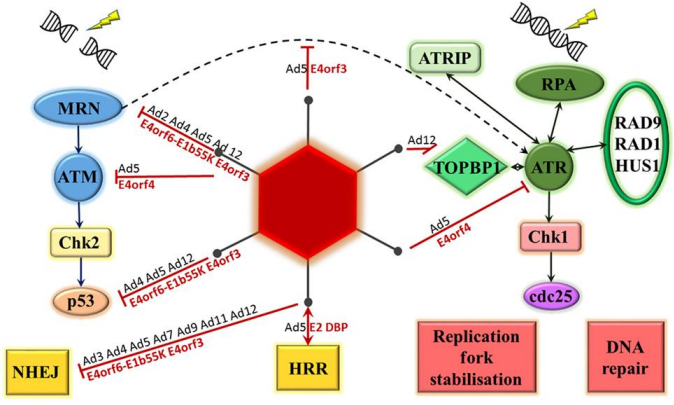


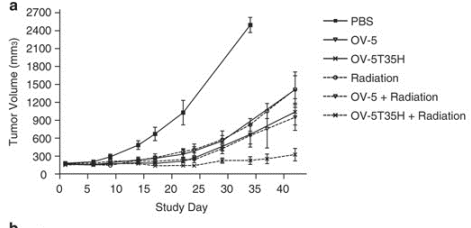


Roulstone et al. Mol Ther 2015

OVs cooperate with radiation therapy

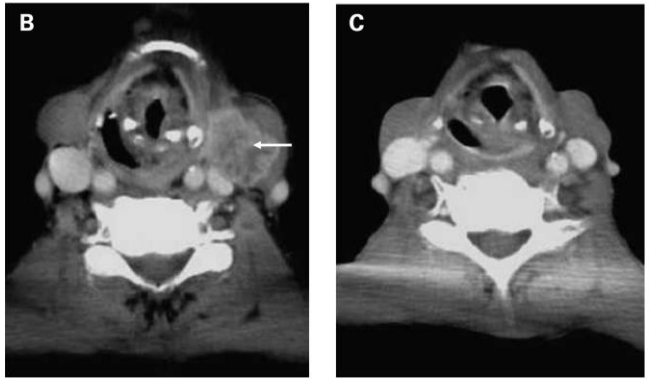
OV may block DNA repair in radiated tumor cells

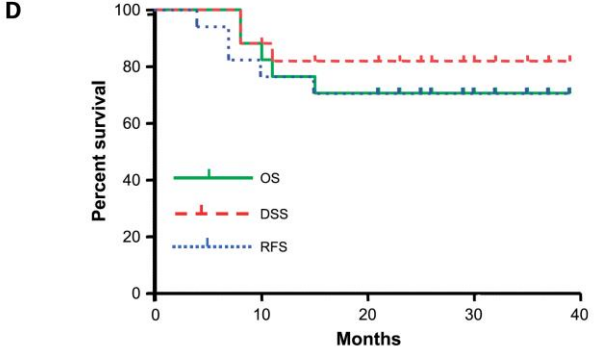




Chimeric adeno-OV and radiation in murine head and neck tumor model

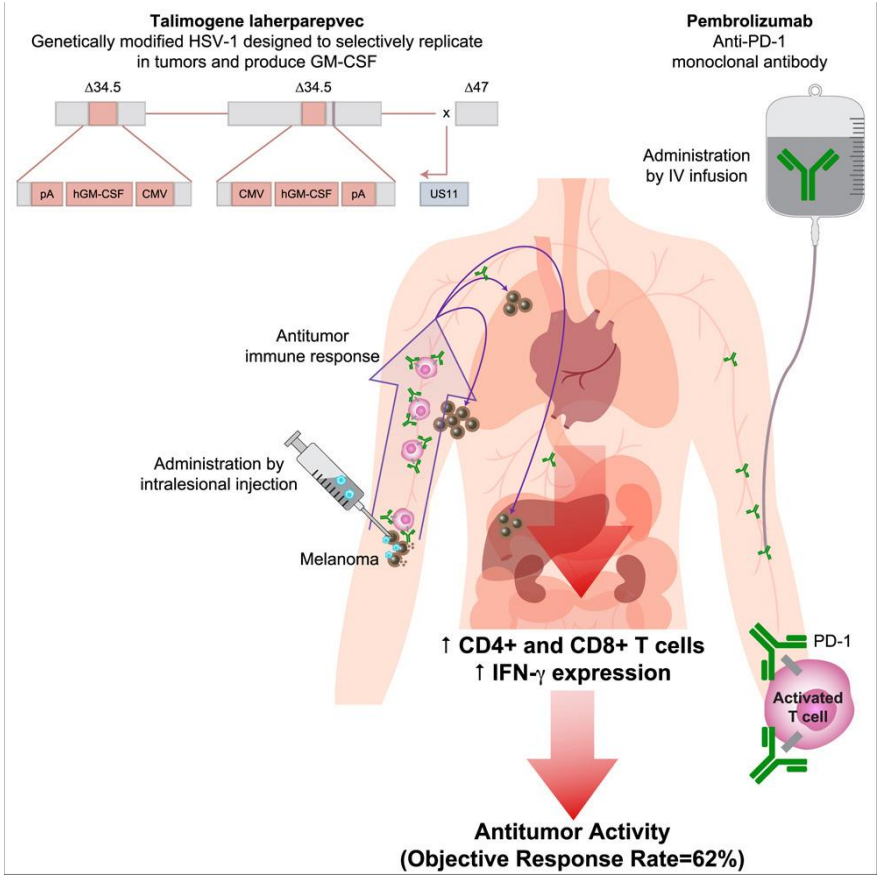
T-VEC + chemoradiation in head & neck cance



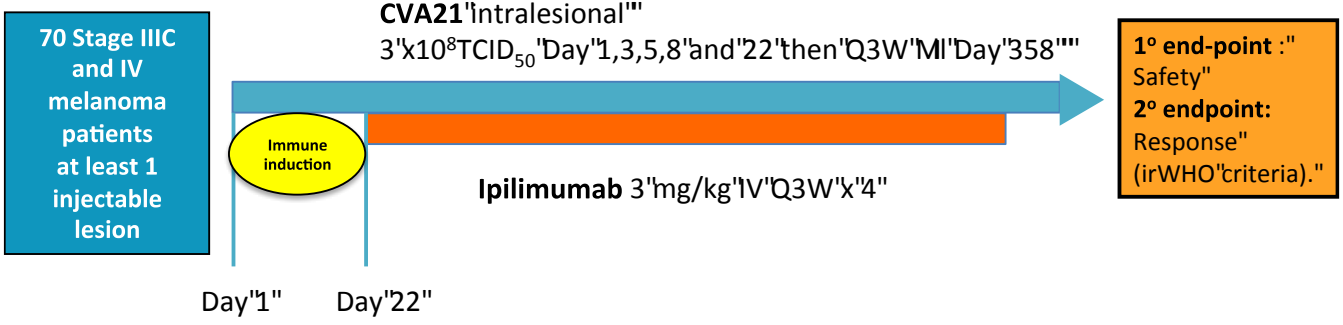


O'Cathail et al. Front Oncol 2017
Ganesh et al. Cancer Gene Ther 2008
Harrington et al. Clin Cancer Res 2010

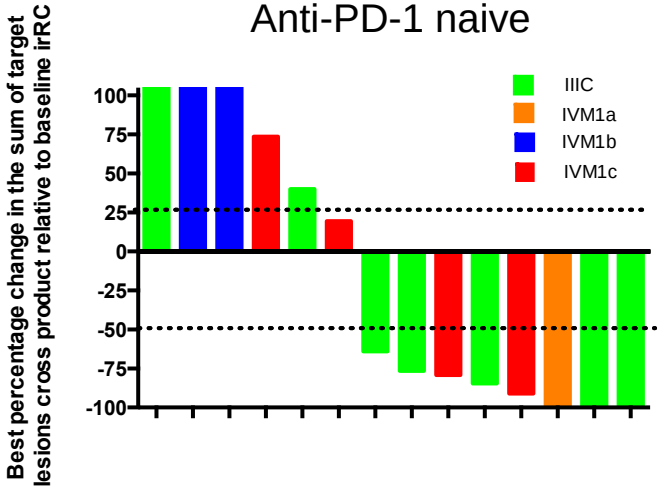
Oncolytic immunotherapy and immune checkpoint inhibitors

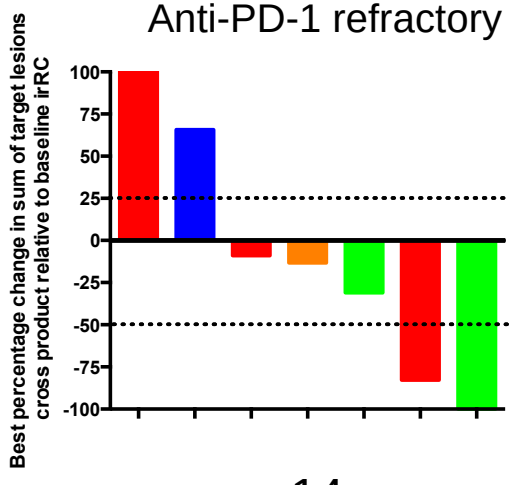


Intratumoral CVA21+ ipilimumab
(MITCI study : NCT02307149)



Preliminary Best percentage change in the sum of target les

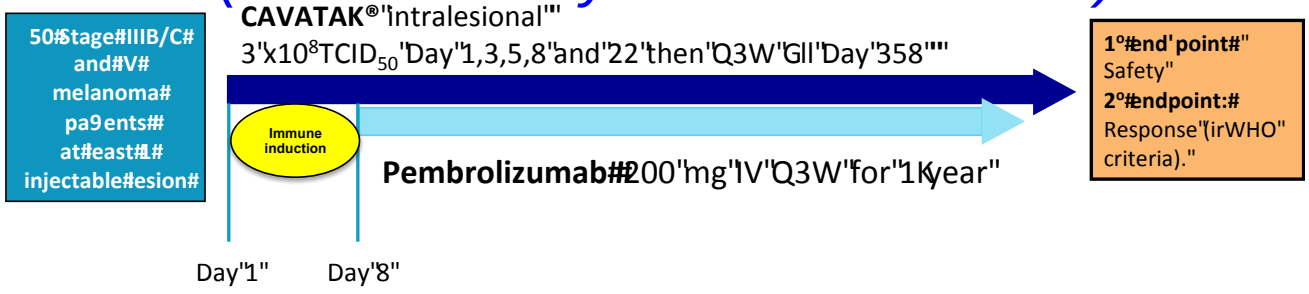




*, Preliminary data , investigator assessed

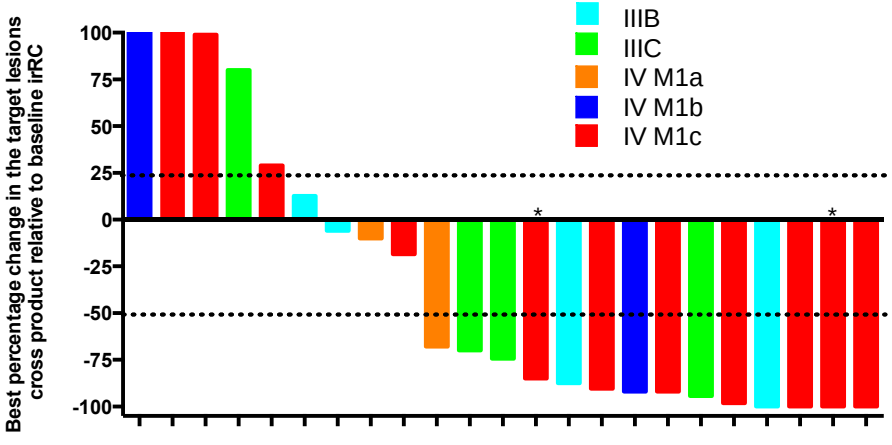
Intratumoral CVA21+ pembrolizumab

(CAPRA study : NCT02565992)



Preliminary Best percentage change in the sum of target les

Anti-PD-1 naive

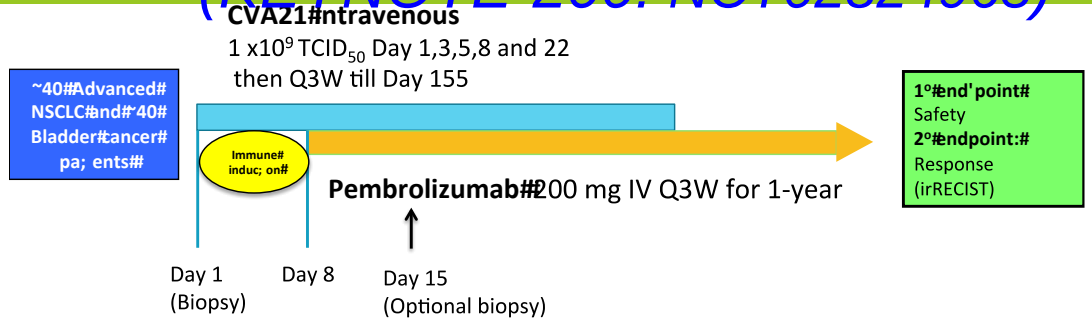


* **Prior ipilimumab treatment**

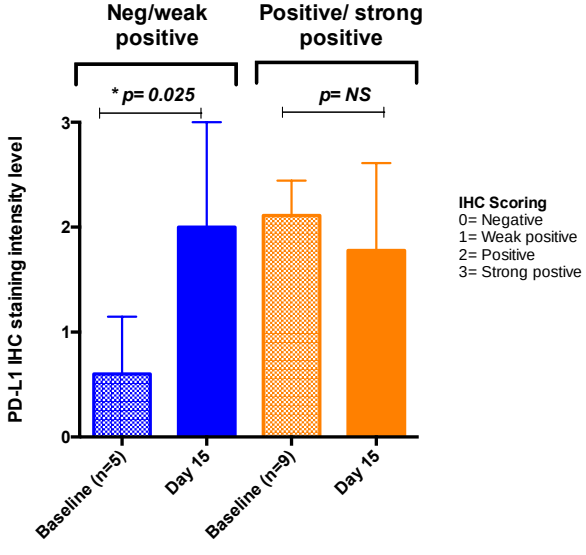
+, Preliminary data , investigator assessed

Intravenous CVA21+ pembrolizumab

(KEYNOTE-200: NCT02824965)



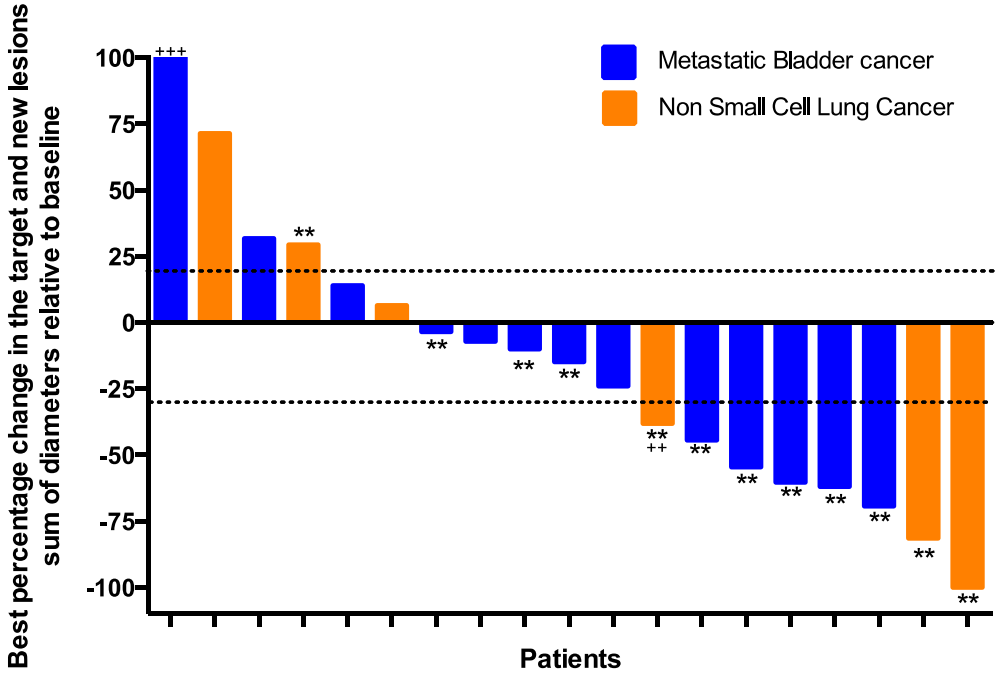
Preliminary PD-L1 expression levels (IHC) on paired tumor



Intravenous CVA21+ pembrolizumab

(KEYNOTE-200: NCT02824965)

Best percentage change in the sum of target lesion



At present 11% (7 of 64) pts have displayed treatment related ≥Gr 3 adverse events

+, Preliminary first investigator assessment of best percentage change in target and new lesions within the first 92 days of combination treatment in checkpoint naive patients, Data cutoff 8 November 2017;

**, Not evaluable due to early disease progression prior to first response assessment, 4 NSCLC pts + 5 Bladder cancer pts;*

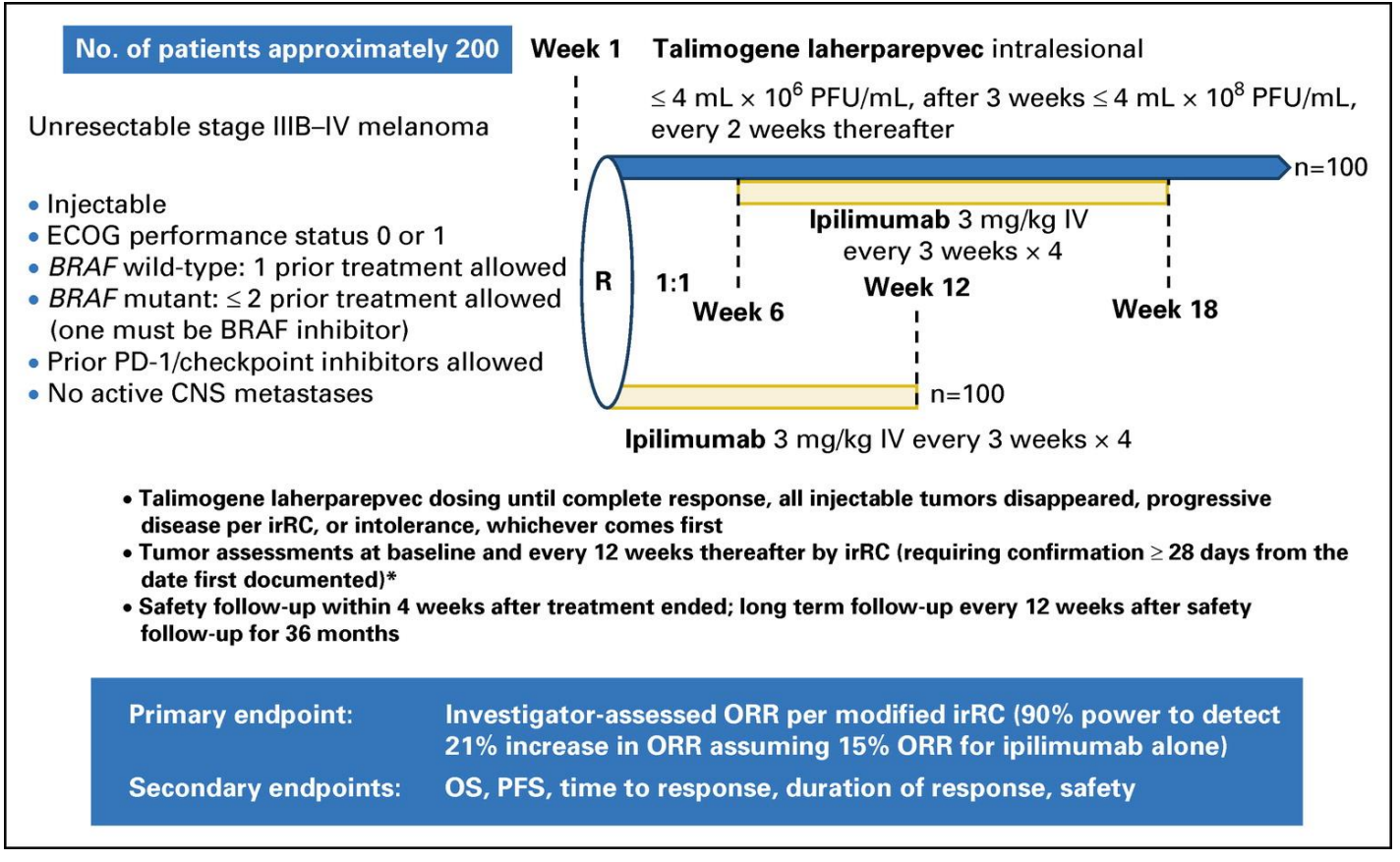
***, Patient currently on study;*

++, Day 176 response assessement;

+++, Day 43 response assessement.

Schema of T-VEC and ipilimumab randomized clinical trial

274 screened
198 enrolled



Chesney et al. JCO 2017

Baseline demographics in T-VEC + IPI clinical trial

Table 1. Baseline Demographic Data and Clinical Characteristics

Characteristic	Talimogene Laherparepvec Plus Ipilimumab (n = 98)	Ipilimumab (n = 100)
Sex		
Female	36 (37)	45 (45)
Male	62 (63)	55 (55)
Median age, years (range)	65 (23-93)	64 (23-90)
Race		
White	97 (99)	92 (92)
Black	0	3 (3)
Other	1 (1)	5 (5)
ECOG performance status		
0	69 (70)	73 (73)
1	29 (30)	27 (27)
Disease substage, AJCC classification		
IIIB	5 (5)	9 (9)
IIIC	29 (30)	31 (31)
IVM1a	16 (16)	17 (17)
IVM1b	20 (20)	10 (10)
IVM1c	28 (29)	33 (33)
BRAF status		
Mutant	35 (36)	34 (34)
Wild-type	62 (63)	60 (60)
Missing/unknown	1 (1)	6 (6)
Baseline LDH		
≤ 1 × ULN	79 (81)	74 (74)
> 1-2 × ULN	10 (10)	20 (20)
> 2 × ULN	7 (7)	5 (5)
Unknown	2 (2)	1 (1)
Visceral disease at baseline	39 (40)	46 (46)
Median SPD* of all index lesions, mm^2 (range)	930 (49-26,138)	589 (36-15,802)
Prior surgery	93 (95)	89 (89)
Prior anticancer therapy†	25 (26)	29 (29)
Radiotherapy	12 (12)	13 (13)
Immunotherapy	10 (10)	16 (16)
PD-1 inhibitors	2 (2)	3 (3)
Chemotherapy	4 (4)	4 (4)
Targeted small molecules	2 (2)	0 (0)
BRAF inhibitors	2 (2)	0 (0)
MEK inhibitors	1 (1)	0 (0)
Biochemotherapy	2 (2)	1 (1)
Isolated limb perfusion	0 (0)	2 (2)
Other	3 (3)	2 (2)

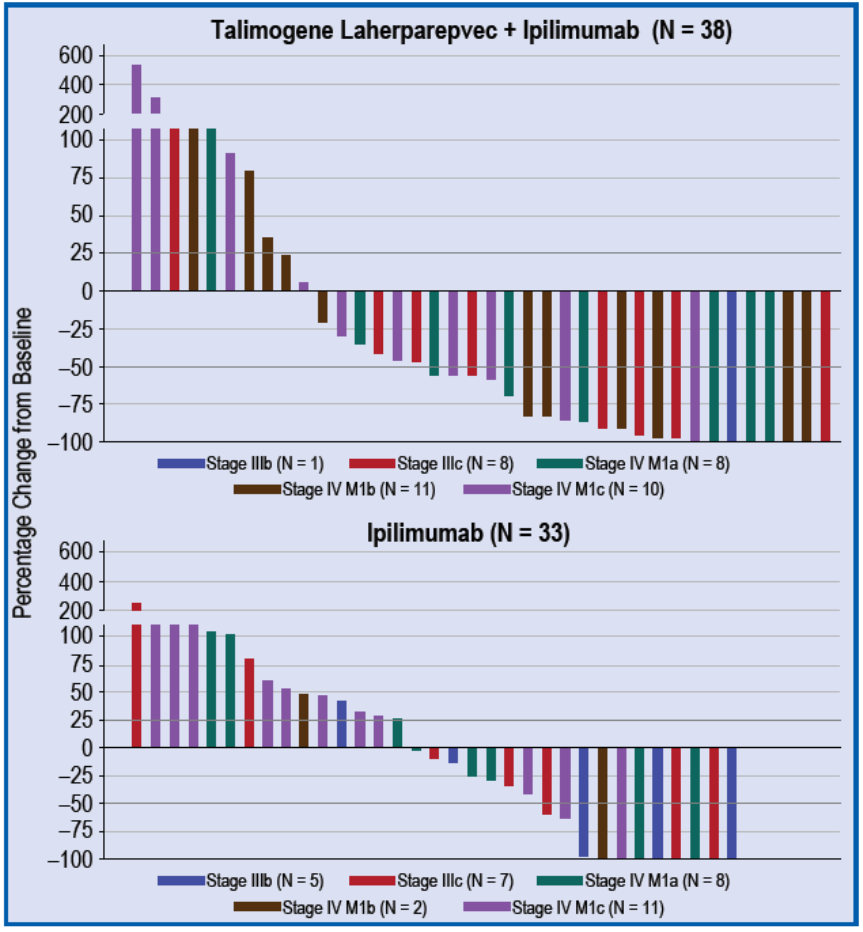
NOTE. Data presented as number (%) unless specified otherwise.
Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PD-1, programmed death-1; ULN, upper limit of normal.
*SPD refers to the sum of the products of the two longest perpendicular diameters.
†Among patients who had previously received anticancer therapy, seven had received systemic therapy for advanced melanoma.

Chesney et al. JCO 2017

Waterfall plot of responses in T-VEC + ipi vs. ipi alone melanoma trial

- Response rates (N=198) more than doubled with T-VEC + ipilimumab vs. ipilimumab alone (38% vs. 18%)
- No additional toxicity as compared to ipilumumab alone

- For visceral lesions (none injected), the response rate was 35% for T-VEC+ipilimumab vs. 14% for ipilimumab alone [vs. 15% in OPTiM]



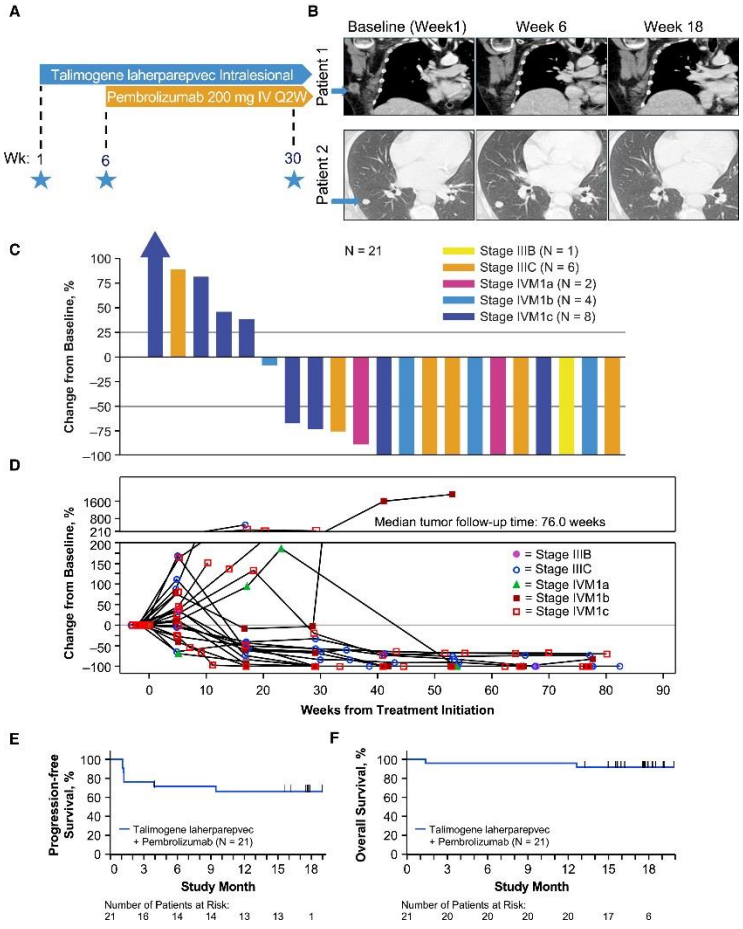
Chesney et al ESMO 2016, ASCO 2017 poster presentations
Chesney et al. JCO 2017
Andtbacka et al. Ann Surg Oncol. 2016

Stepwise regression model of ORR per irRC

- **Stage IIIB-IVM1a**
  - 44% vs. 19% (OR, 3.3; 95% CI, 1.4-7.8; P=0.007)
- **Stage M1b/c**
  - 33% vs. 16% (OR, 2.6; 95% CI, 0.9-7.0; P=0.09)
- **BRAF wild-type**
  - 42% vs. 10% (P<0.001)
- BRAF-mutated
  - 34% vs. 32% (P=1.0)

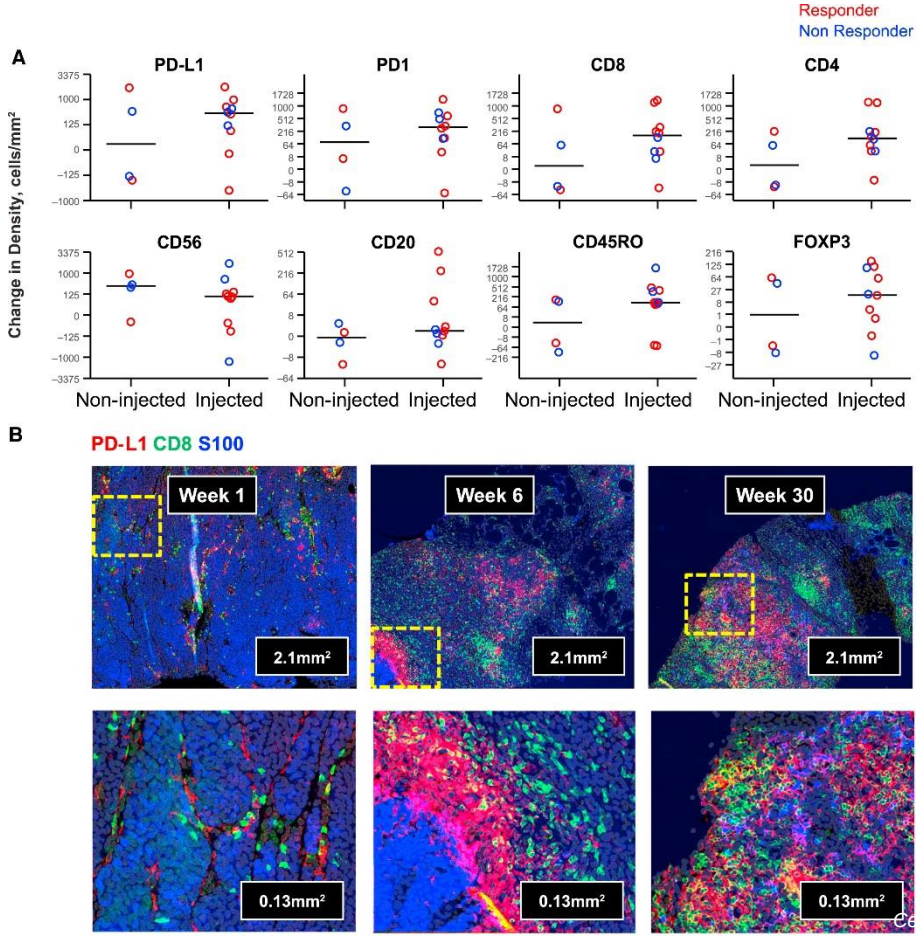
Chesney et al. JCO 2017

T-VEC and pembrolizumab Phase 1 study



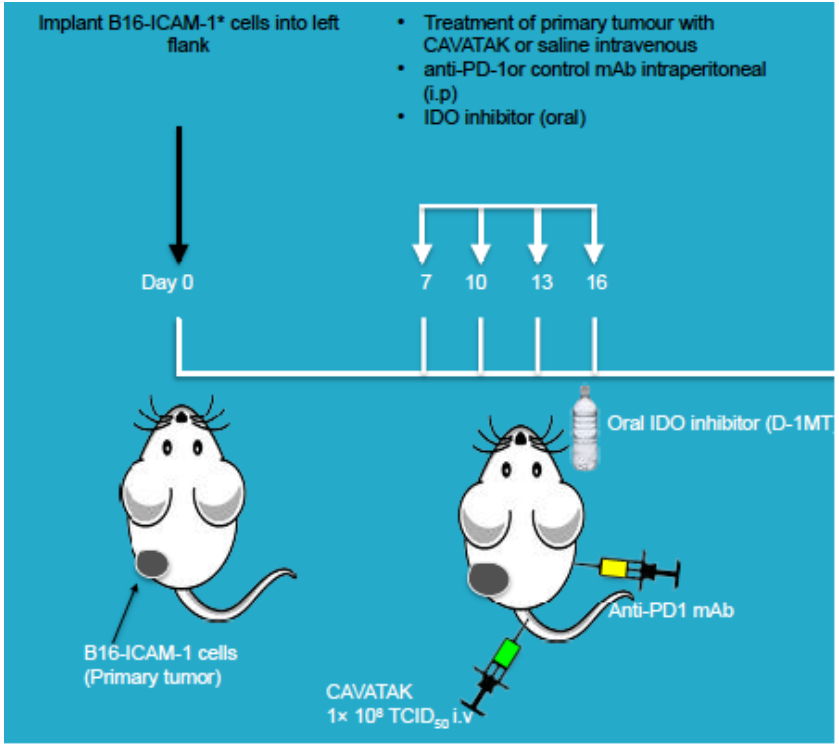
Ribas et al. Cell 2017

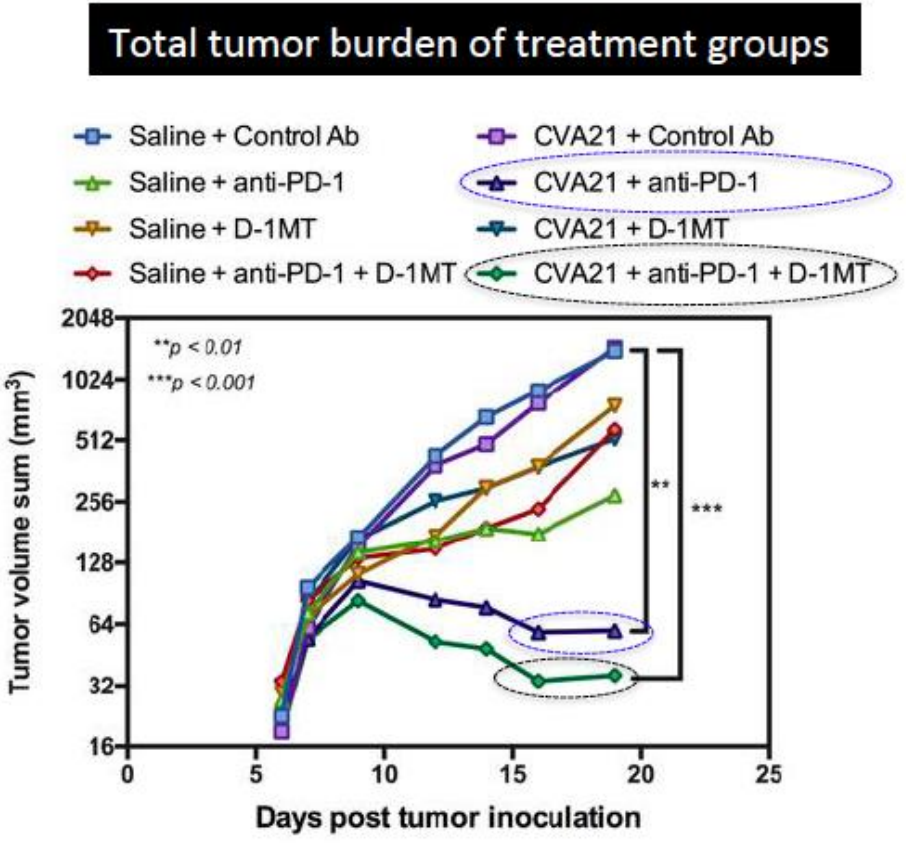
T-VEC + pembrolizumab increases CD8+ T cells and PD-L1 expression



Ribas et al. Cell 2017

CVA21 OV in triple immunotherapy regimen





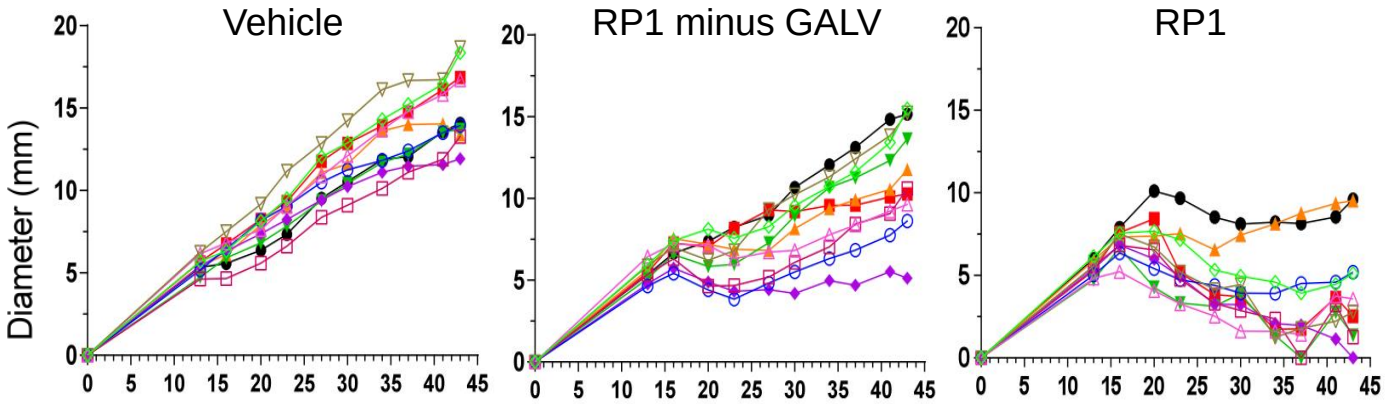
Courtesy Darren Shafren, Viralytics

Replimune oncolytic immunotherapy

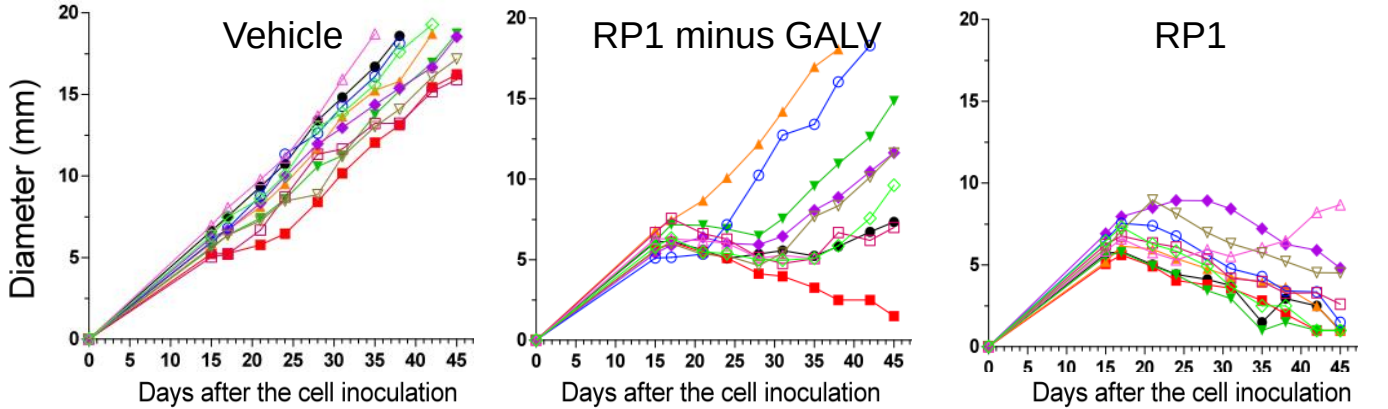
1. A potent underlying HSV strain
   - There is great diversity among clinical strains of HSV
   - Replimune tested 30 new clinical strains & selected the most effective
2. Further increased direct tumor cell killing, antigen release & spread
   - In addition to GM-CSF, a potent fusogenic protein (GALV) is expressed
     - Large bystander effect, highly immunogenic cell death
     - Provides a 10-100 fold increase in direct tumor killing potency
3. This virus (RP1) is then used to deliver additional potent immune stimulatory proteins directly to the tumor
   - Focuses on pathways where systemic engagement is sub-optimal
   - CTLA-4 blockade, immune-costimulatory pathway activation

GALV expression enhances efficacy

A549 lung cancer



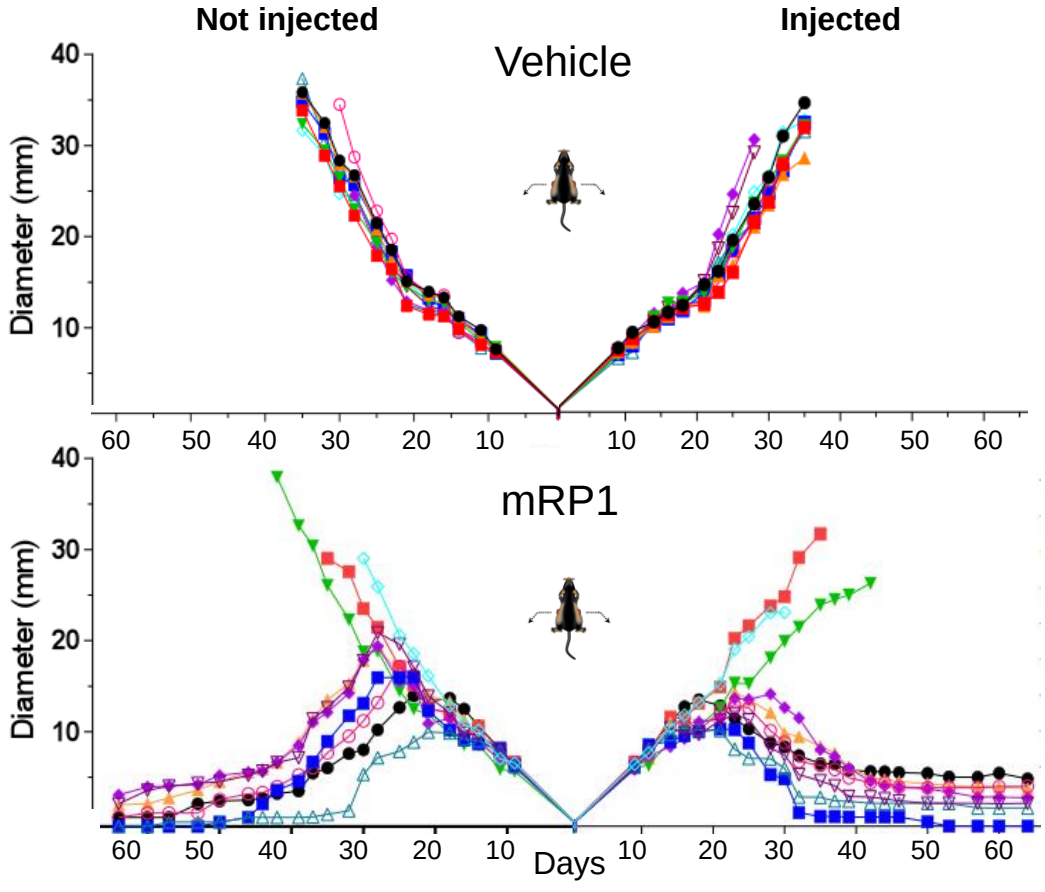
MDA-MB-231 breast cancer



3 injections over 1wk. Virus dose: $5x10^3$ pfu (very low: subtherapeutic for RP1 minus GALV)

Nude mice: No immune effect. GALV is not active in mice so immune competent mouse models can't be used

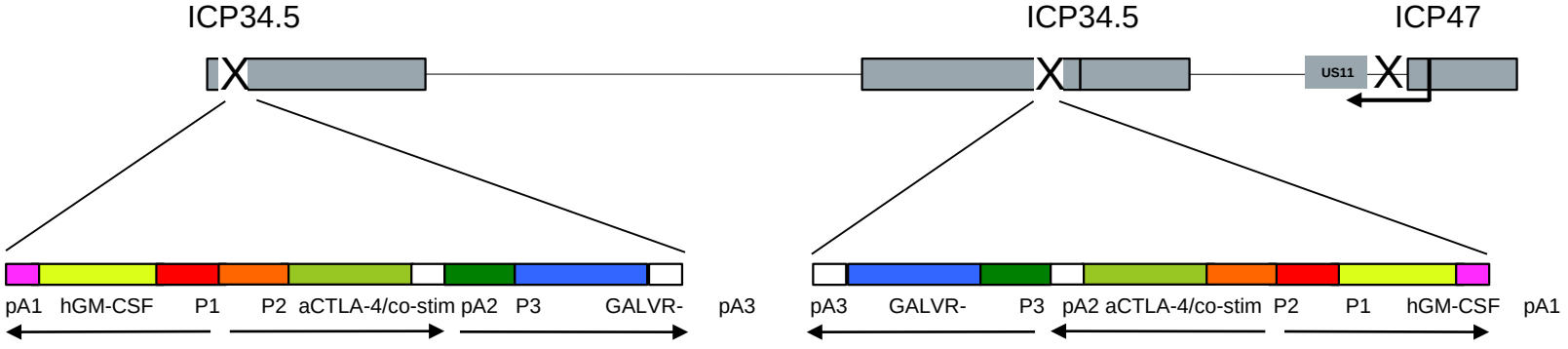
RP1 treats large injected & uninjected tumors



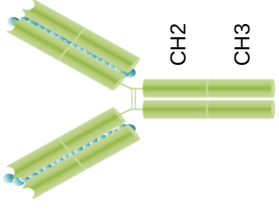
Immune competent rat 9L glioma model (dual flank)

GALV is active in rats

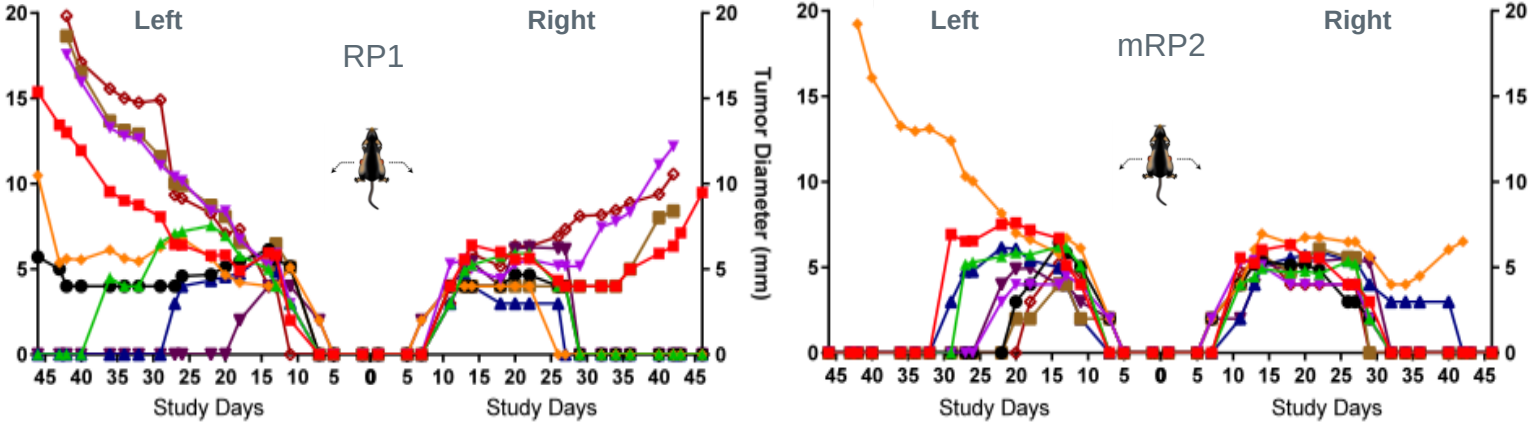
RP2/3 – Express anti-CTLA-4 and/or co-stim ligands



Anti-mouse or anti-human CTLA-4 constructs are codon optimized secreted scFv molecules linked to human or mouse IgG1 Fc regions. Co-stim viruses express membrane bound or secreted multimeric CD40L, 4-1BBL, GITRL, OX40L or ICOSL

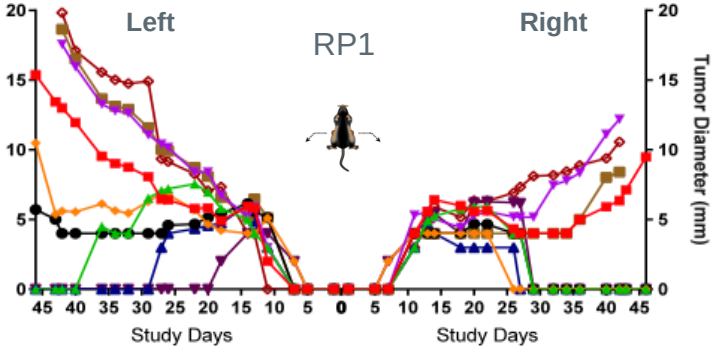


Expression of αmCTLA4 from RP1 enhances efficacy

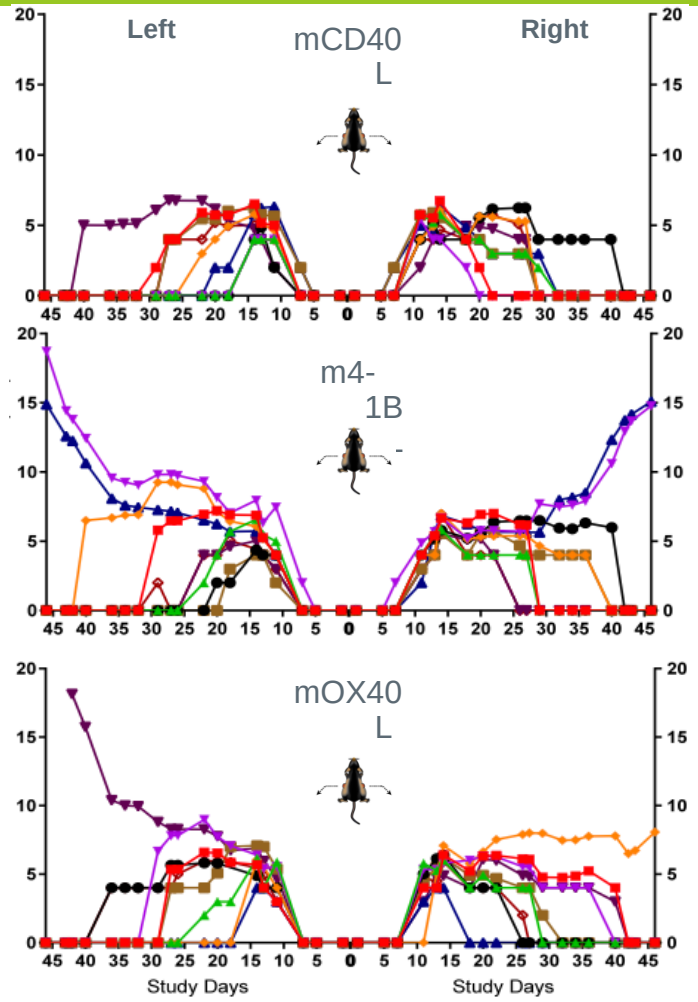


Immune competent mouse model
Subtherapeutic dose for RP1 injected into the right tumor only

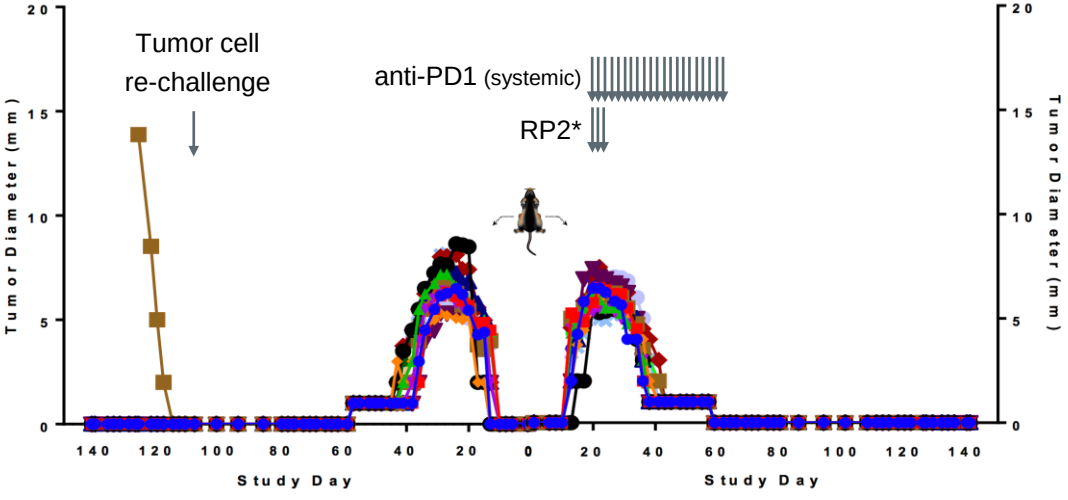
Expression of co-stimulatory ligands from RP1 enhances efficacy



Immune competent mouse model
Subtherapeutic dose for RP1 injected into the right tumor only

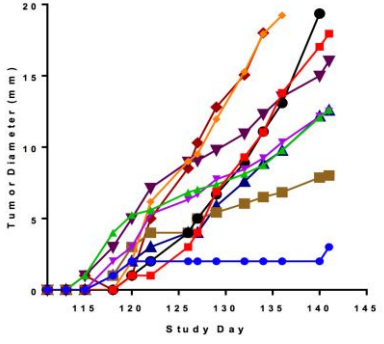


Responses are durable & cured mice are protected from re-challenge

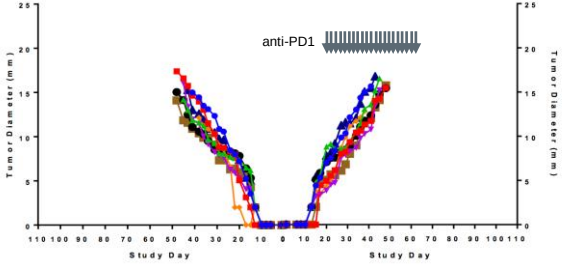


15 mice previously cured of bilateral tumors by treatment with RP2 + anti-PD1 were re-challenged with tumor cells on the left (uninjected) flank on Day 108 and followed for a further 32 days. Fourteen of the fifteen mice were completely protected from re-challenge.

** = RP1 additionally expressing anti-CTLA4*



10 tumor & virus naïve mice challenged with tumor cells on the same day all grew tumors



Mice treated with anti-PD1 alone do not respond

Conclusions

- Oncolytic viruses are uniquely positioned to serve as the foundation for combination immunotherapy regimens
  - Able to induce T cell recruitment and activation (“cold” tumors become “hot”)
  - Able to induce Type 1 IFN (reverse suppression in resistant “hot” tumors)
  - Induces immunogenic cell death and neoantigen spreading
- Clinical data supports the combination of oncolytic immunotherapy and immune checkpoint blockade
- New generation oncolytic immunotherapies can be engineered to further enhance tumor cell immunogenic death and deliver specific immune modulators to further enhance anti-tumor immunity
- Oncolytic viruses are well suited for multi-regimen combination approaches

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