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The Role of T-VEC and Other Oncolytic Viruses in Priming the Tumor Microenvironment for Immunotherapy

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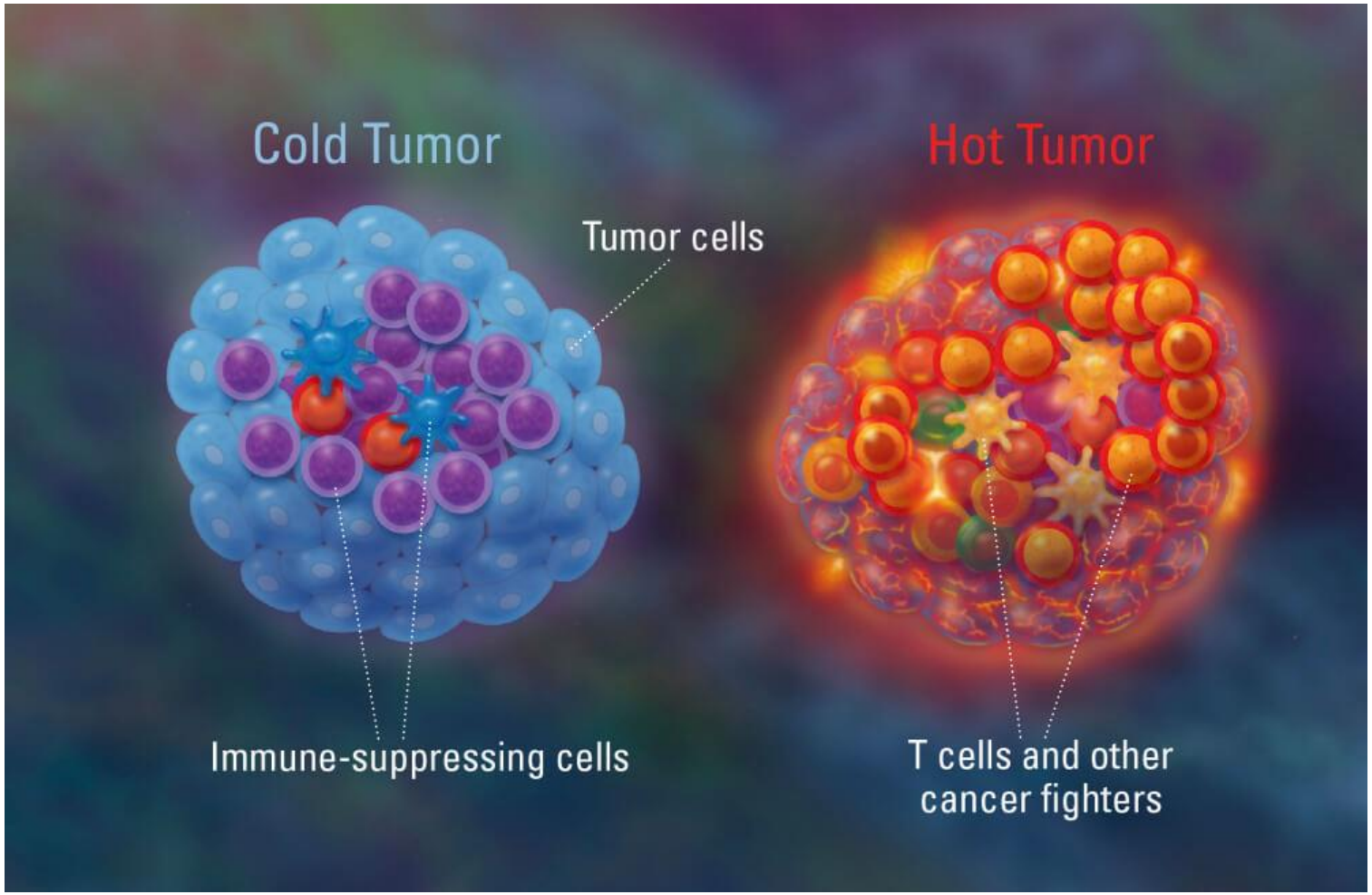
Disclosures

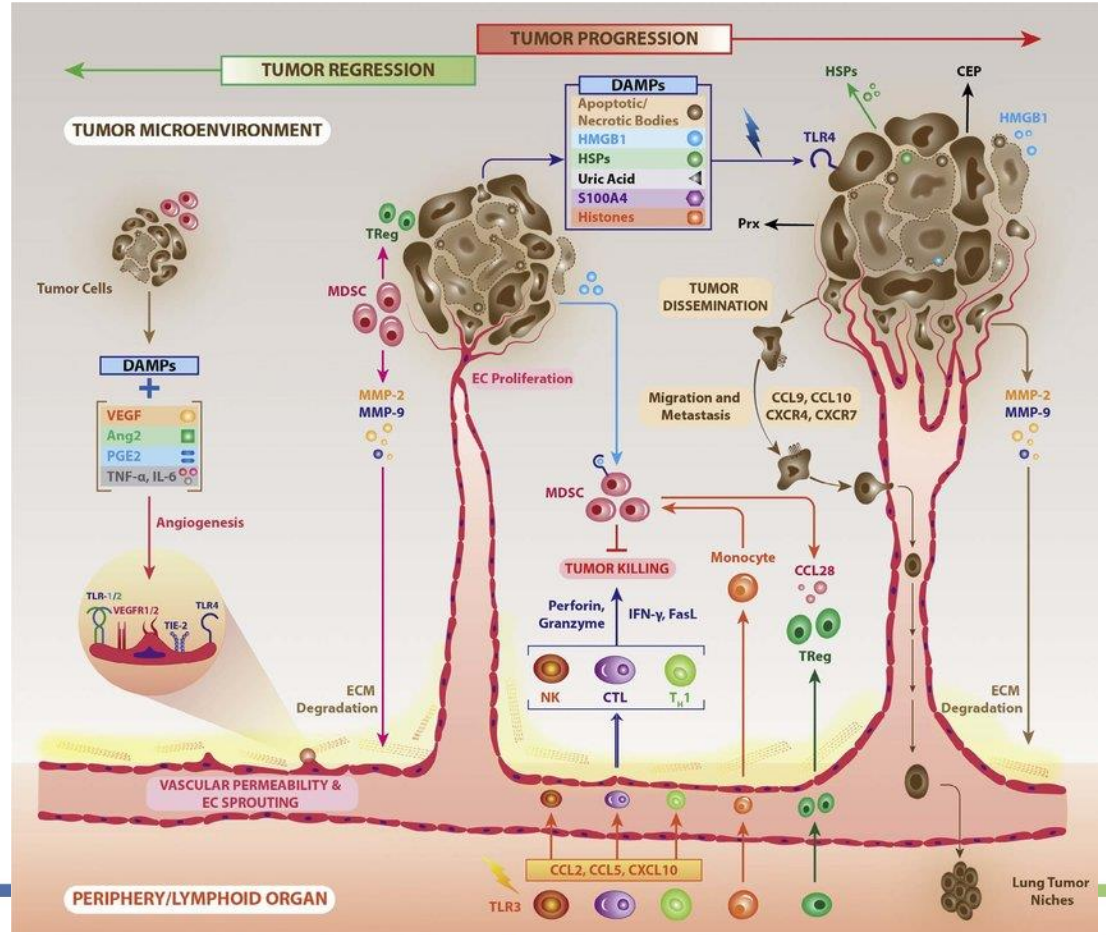
- I am an employee of Replimune, Inc.
- I served on advisory board for SapVax
- Data relating to T-VEC relates to prior work from MGH & at Rutgers University prior to joining Replimune, Inc

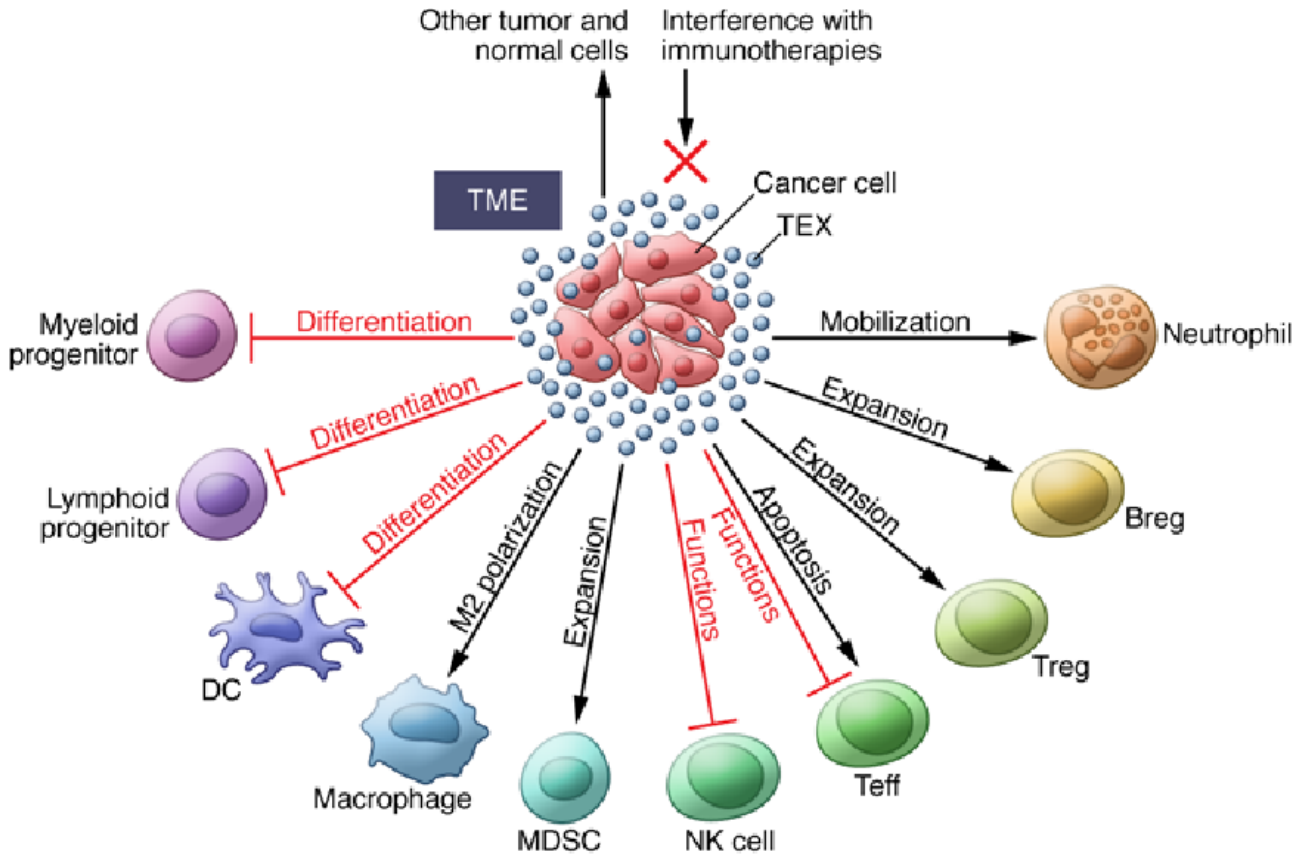
Cold vs. Hot Tumor Microenvironment



Courtesy Gordon Freeman, DFCI

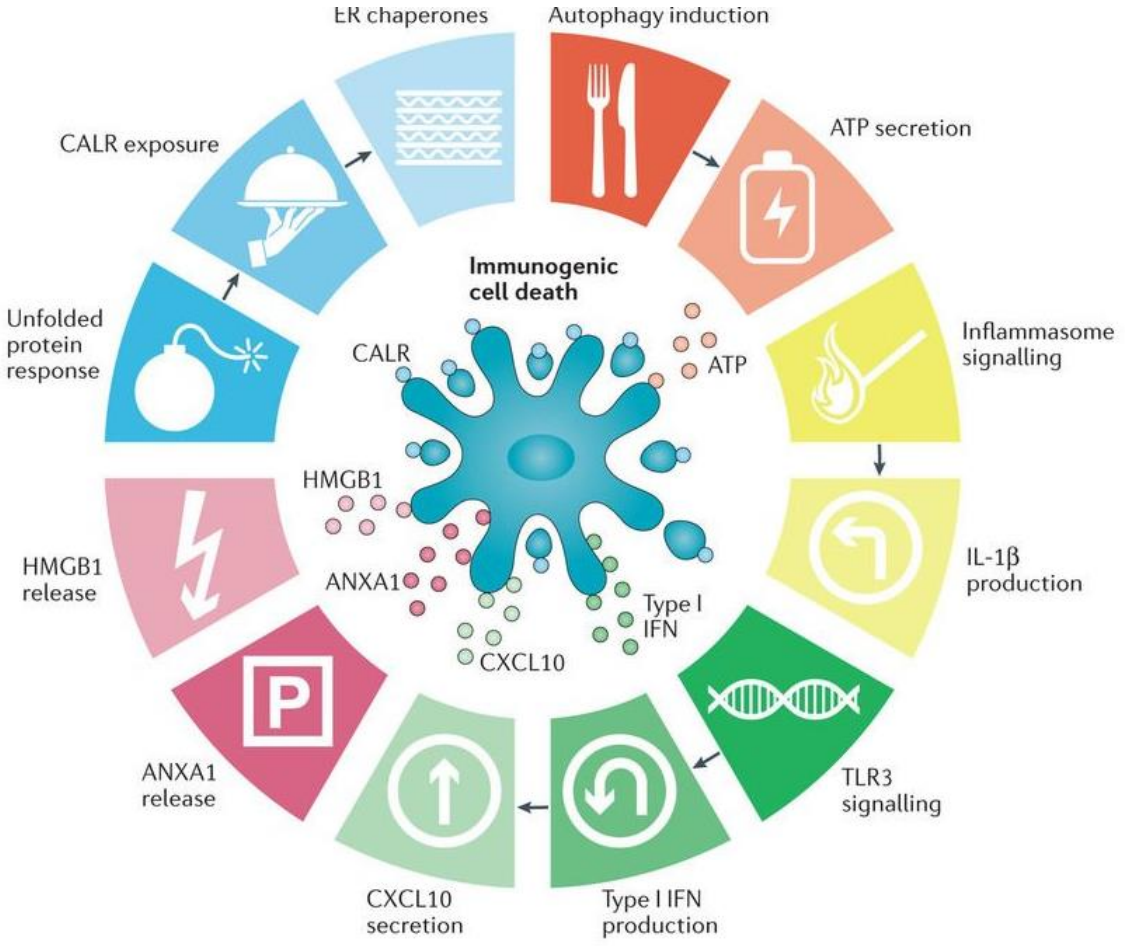
The Tumor Microenvironment is Complex and Inhibits Anti-tumor Immunity





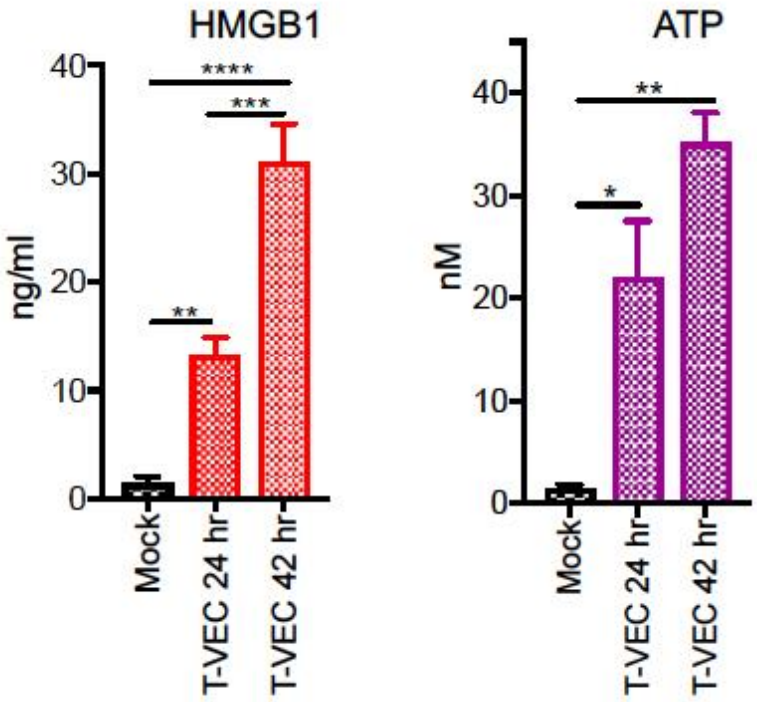
Malinovskaya et al. Front Oncol 2019
Whiteside JCI 2016

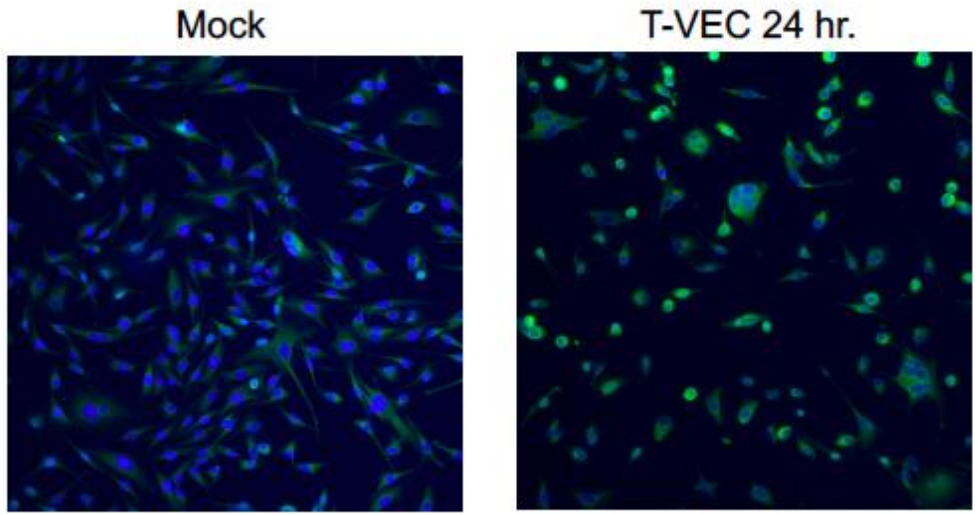
Immunogenic cell death



Galluzzi et al. Nature Immunol. 2017

T-VEC induces ICD in SK-MEL-28 melanoma cell lines

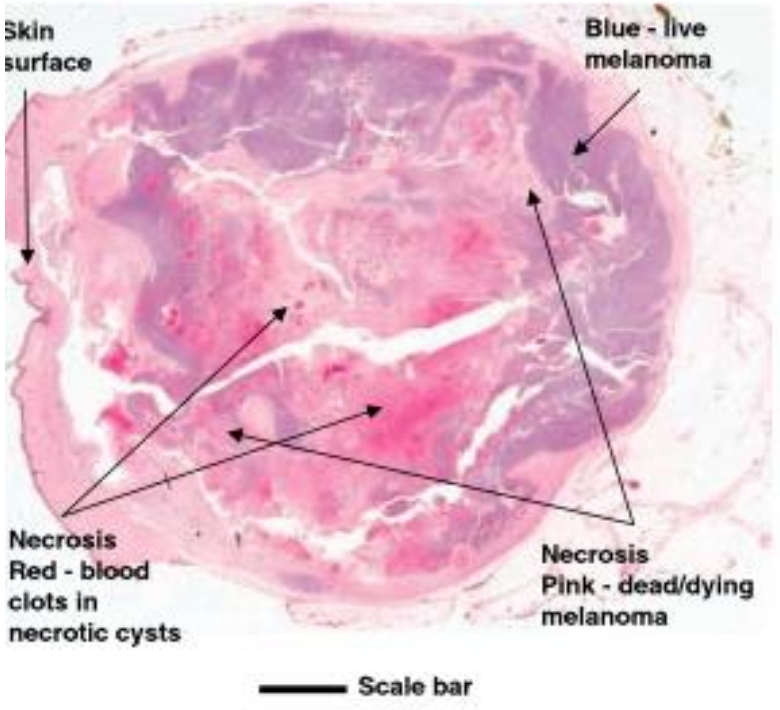


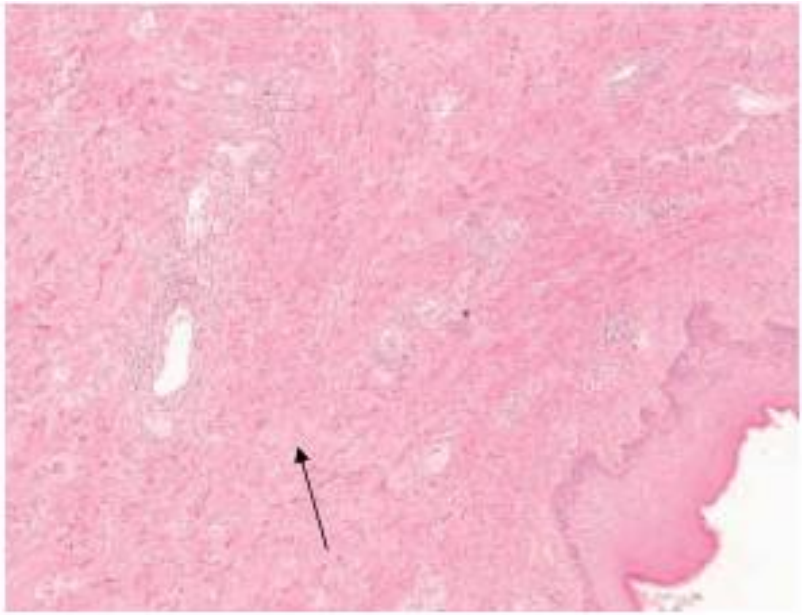


Ecto-calreticulin (green)

Bommareddy et al. In press, 2019

T-VEC induces central necrosis following injection





Liu et al. Clin Cancer Res 2006

T-VEC improves objective and durable response rate

ITT Set	GM-CSF (N=141)	T-VEC (N= 295)	**Treatment Difference (T-VEC – GM-CSF)**
Overall Response Rate (95% CI)	5.7% (1.9, 9.5)	26.4% (21.4, 31.5)	20.8% (14.4, 27.1) *P* < 0.0001[a] descriptive
CR	0.7%	10.8%	
PR	5.0%	15.6%	

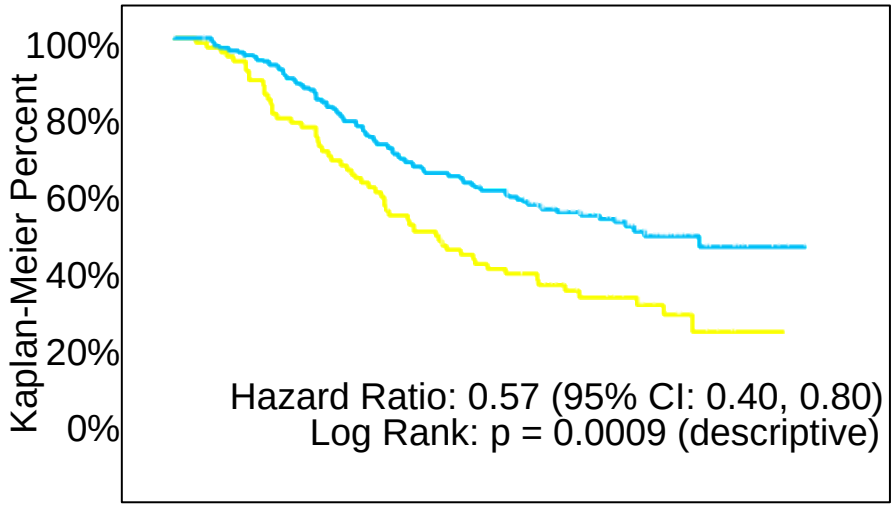
ITT Set	GM-CSF (N=141)	T-VEC (N= 295)	**Treatment Difference (T-VEC – GM-CSF)**
Durable Response Rate	2.1%	16.3%	14.1% 95% CI: (8.2, 19.2) *P* < 0.0001[a]

Final analysis of OPTiM study (median follow-up of 49 months)

- DRR 19% vs. 1.4% (unadjusted odds ratio 16.6; 95% CI, 4.0-69.2; p<0.0001)
- ORR 31.5% vs. 6.4%

Exploratory OS subgroup analysis by disease stage

Stage IIIB/C, IVM1a

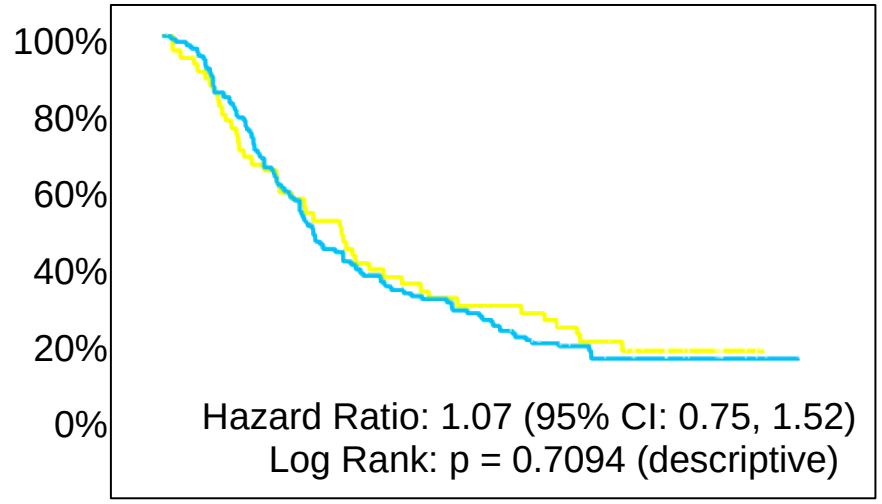


Risk set, n

T-VEC	163	157	146	129	113	104	93	73	51	23	10	1	0
GM-CSF	86	78	65	55	43	35	30	22	17	10	2	0	0

	Events / N (%)	Median (95% CI), mos
T-VEC	60 / 183 (49)	41.1 (30.6, NE)
GM-CSF	57 / 86 (66)	21.5 (17.4, 29.6)

Stage IVM1b/c



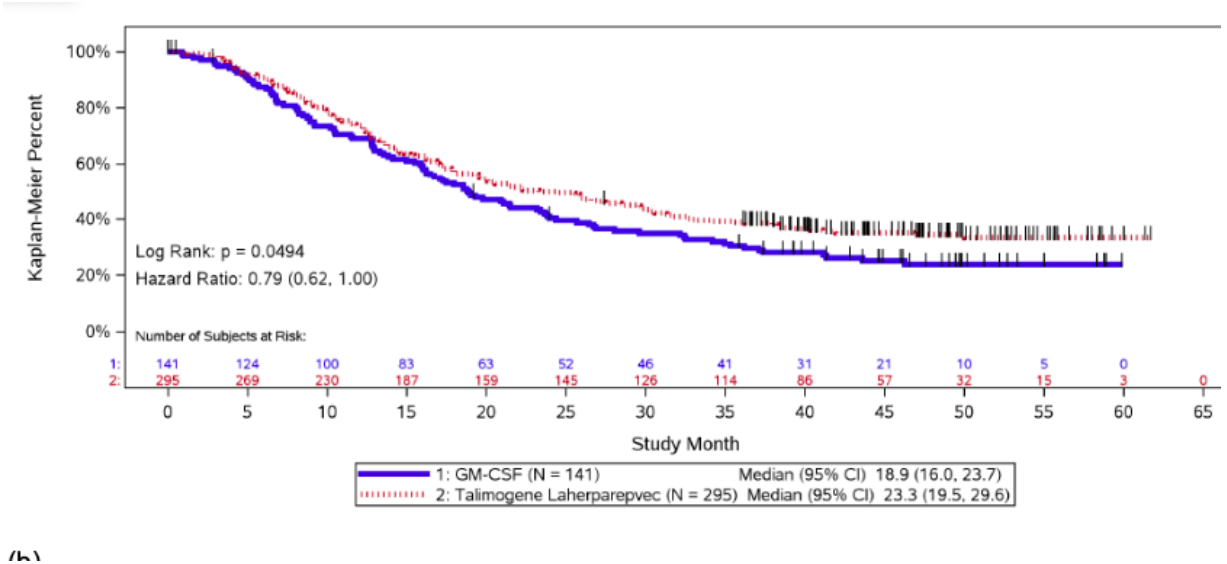
Risk set, n

T-VEC	131	112	84	58	46	41	32	22	15	13	6	1	0
GM-CSF	55	46	35	28	20	17	16	14	10	5	3	0	0

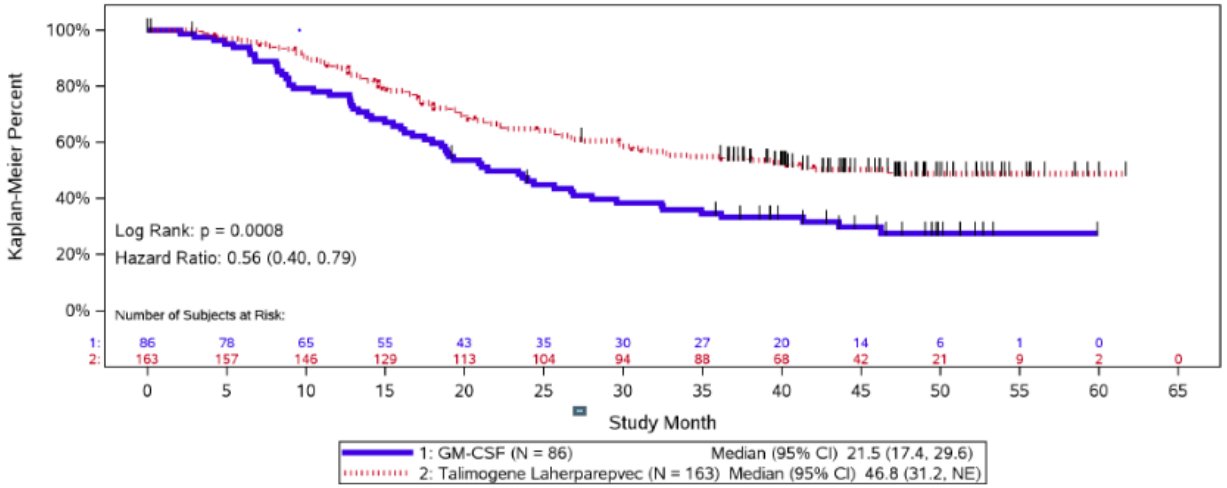
	Events / N (%)	Median (95% CI), mos
T-VEC	109 / 131 (83)	13.4 (11.4-16.2)
GM-CSF	44 / 55 (80)	15.9 (10.2-19.7)

Andtbacka Kaufman, et al. JCO 2015

T-VEC improves OS in final analysis (median follow-up 49 months)



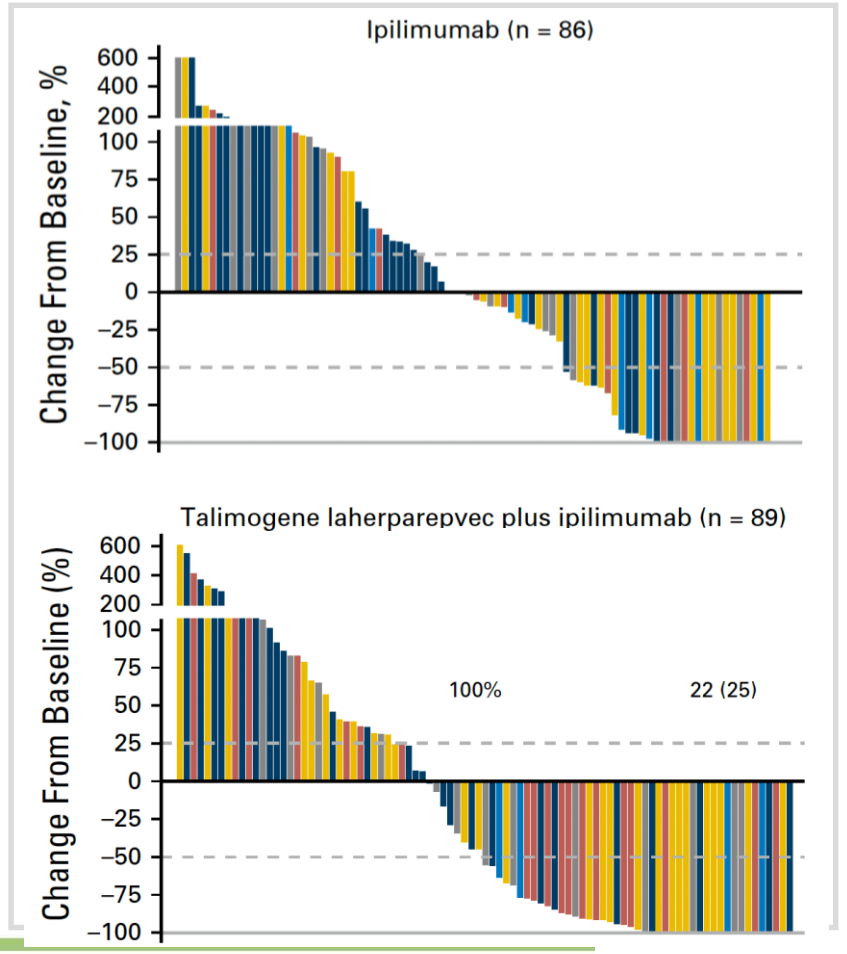
ITT population



Stage III—IVM1a population

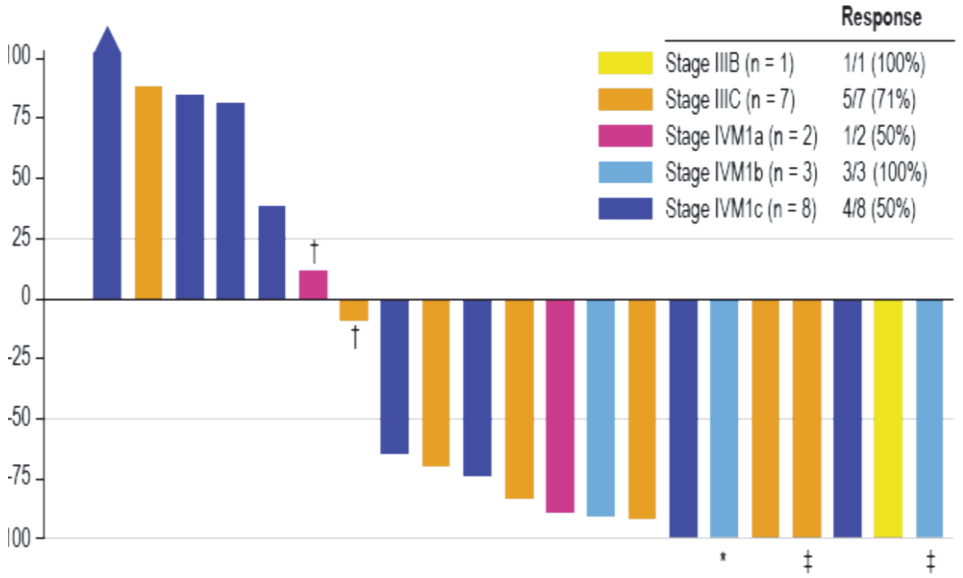
Randomized Phase 2 Clinical Trial: T-VEC + ipilimumab improves ORR

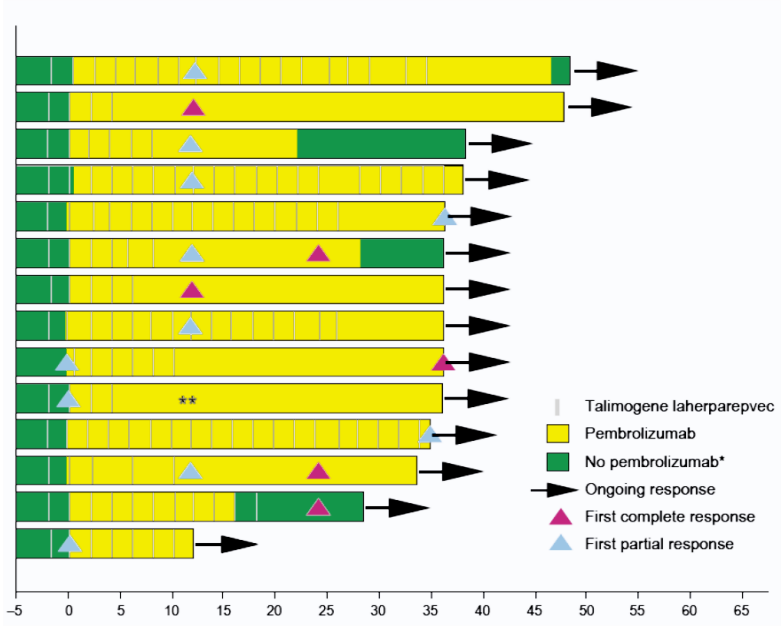
- T-VEC + ipilimumab vs. ipilimumab alone Stage IIIb-IVM1c melanoma
- Response rates (N=198) more than doubled with T-VEC + ipilimumab vs. ipilimumab alone (38% vs. 18%)
- For visceral lesions (none injected), the response rate was 35% for T-VEC +ipilimumab vs. 14% for ipilimumab alone
- No additional toxicity as compared to ipilumumab alone



Chesney et al JCO, 2017

Phase 1 clinical trial of T-VEC and pembrolizumab in melanoma

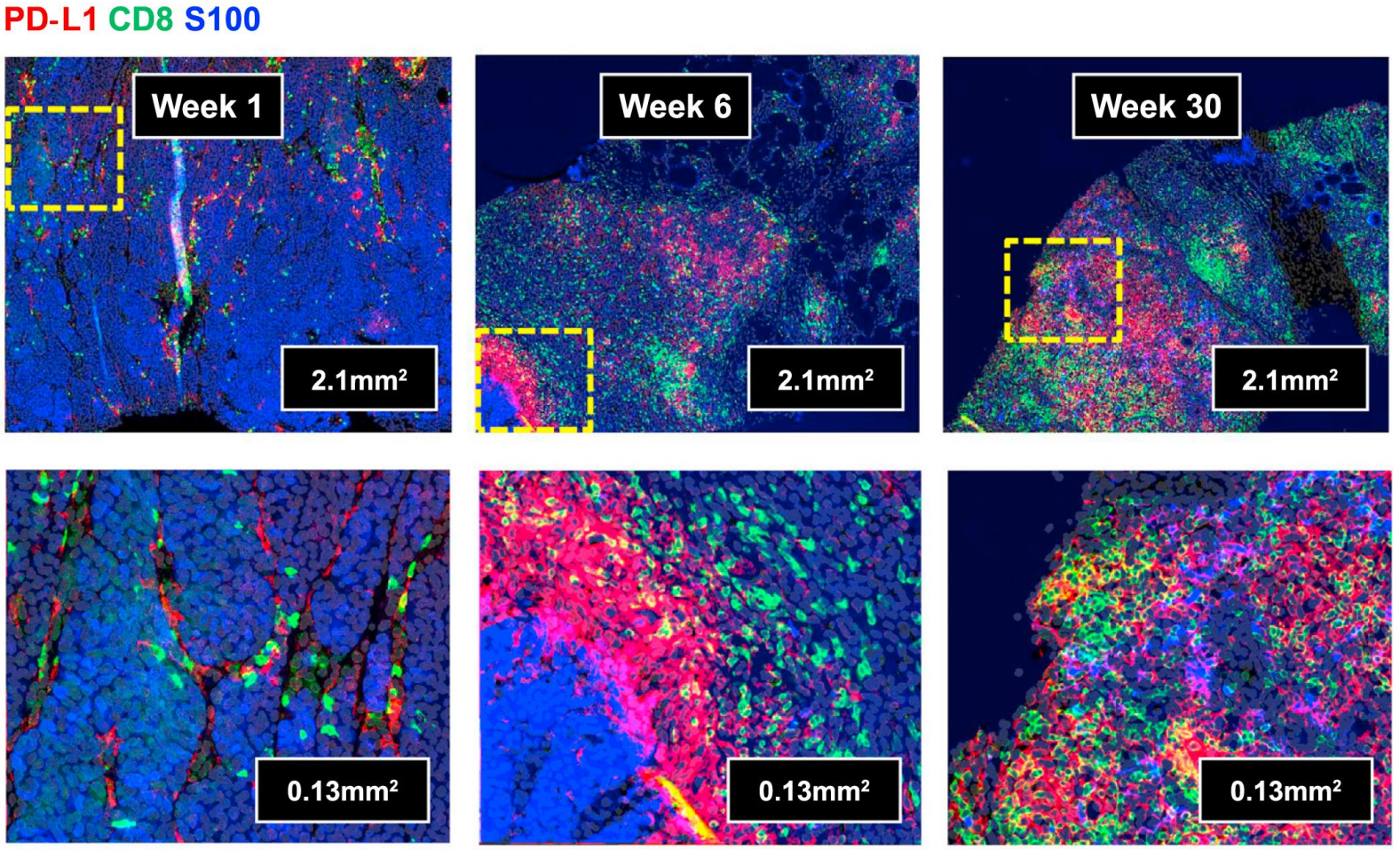




Without added toxicity

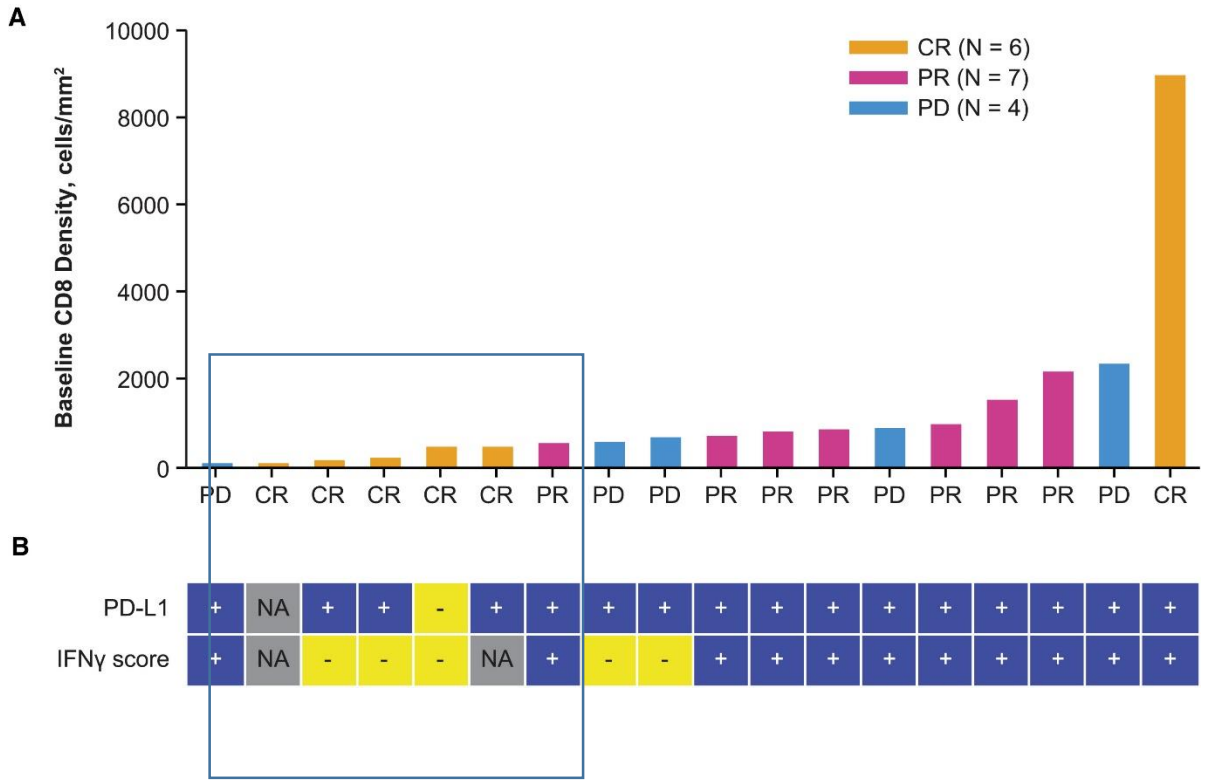
Ribas et al. Cell 2017

T-VEC induces CD8+ T cell recruitment and PD-L1 expression in the TME



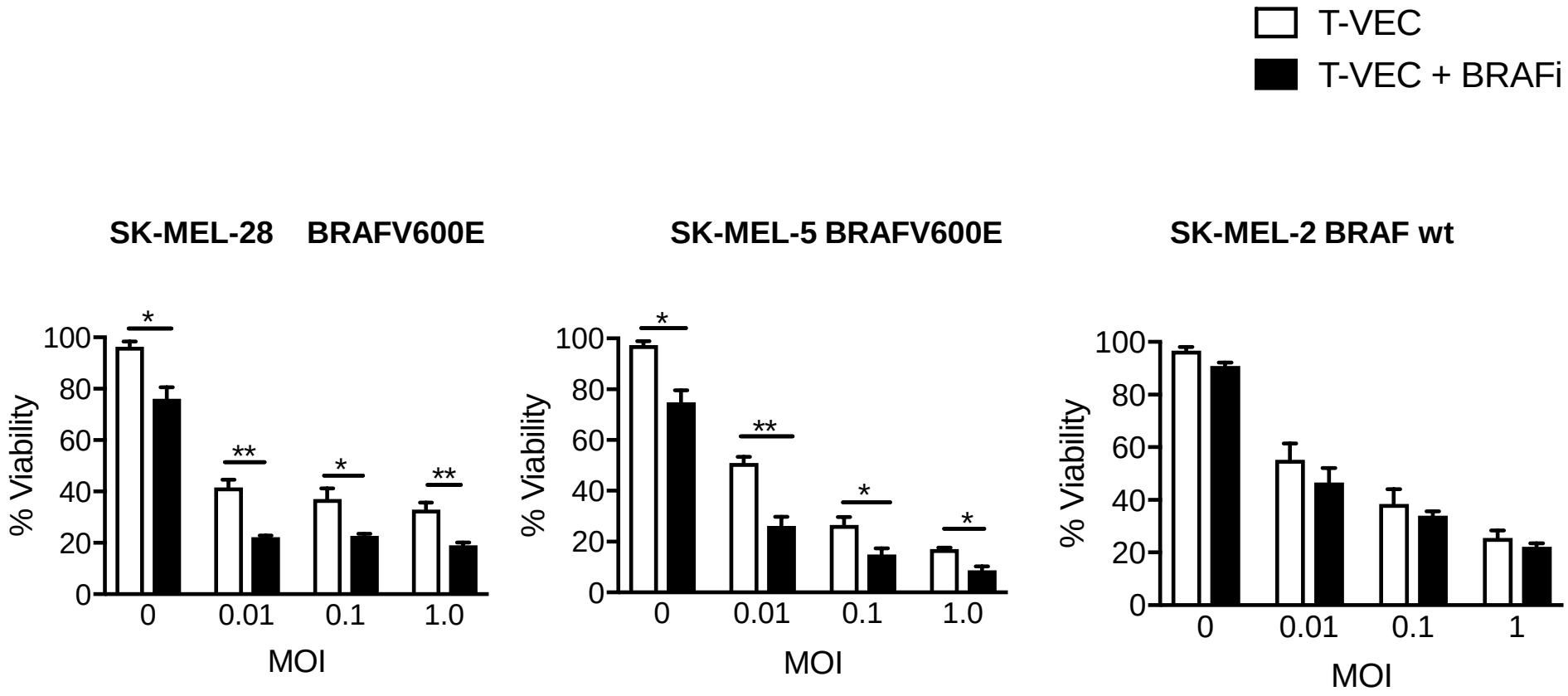
Ribas et al. Cell 2017

T-VEC + pembrolizumab induces CR in immunologically deserted tumors



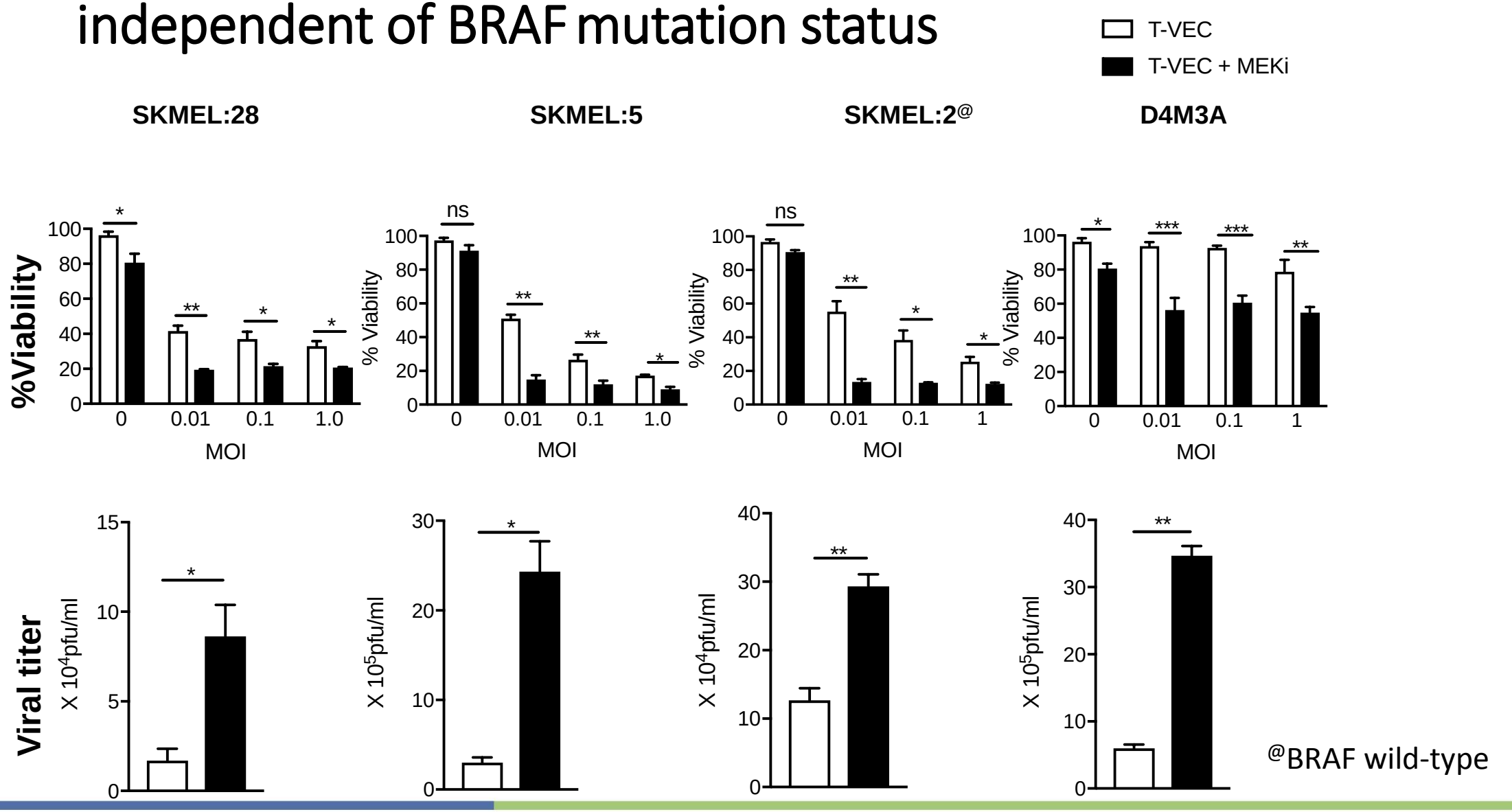
Ribas et al. Cell 2017

Vemurafinib augments T-VEC mediated oncolysis in BRAF^{V600E} melanoma cells



Bommareddy PK et al, Sci Trans Med. 2018

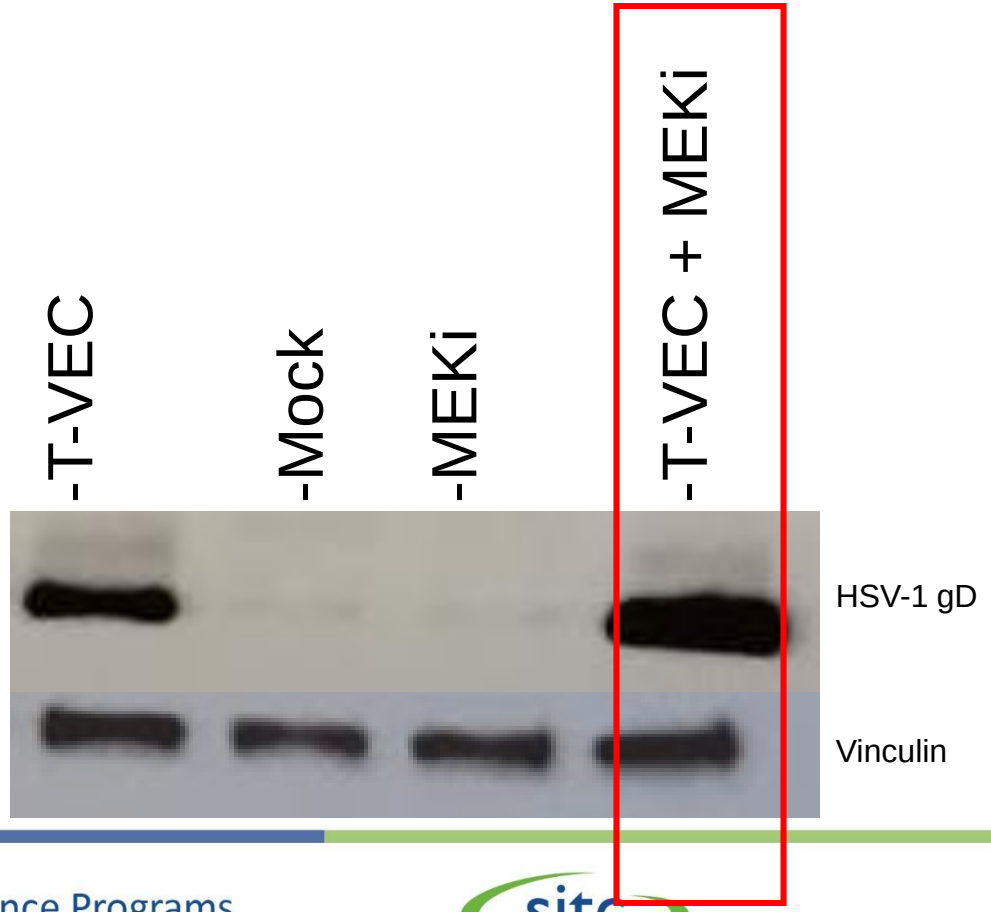
Trametinib augments T-VEC mediated oncolysis independent of BRAF mutation status



@BRAF wild-type

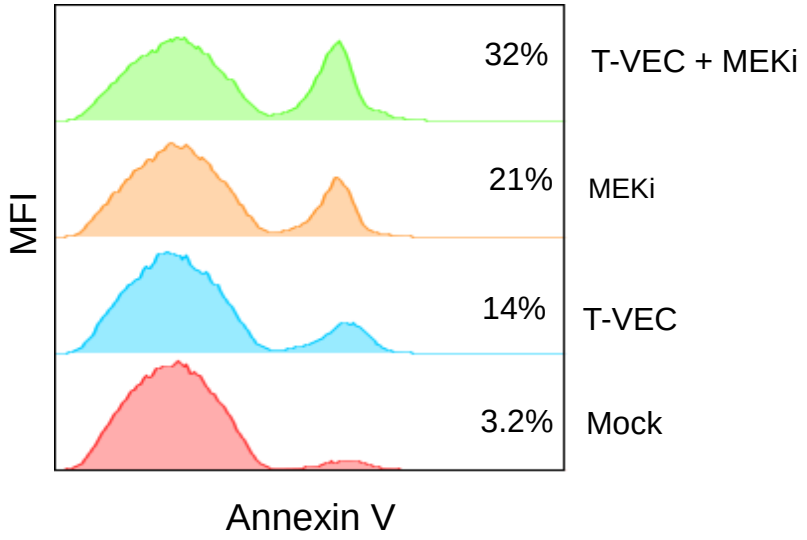
Bommareddy PK et al, Sci Trans Med. 2018

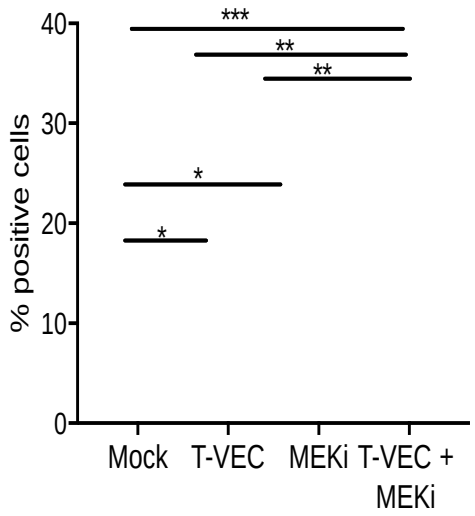
MEK inhibition enhances T-VEC protein production



Bommareddy PK et al, Sci Trans Med. 2018

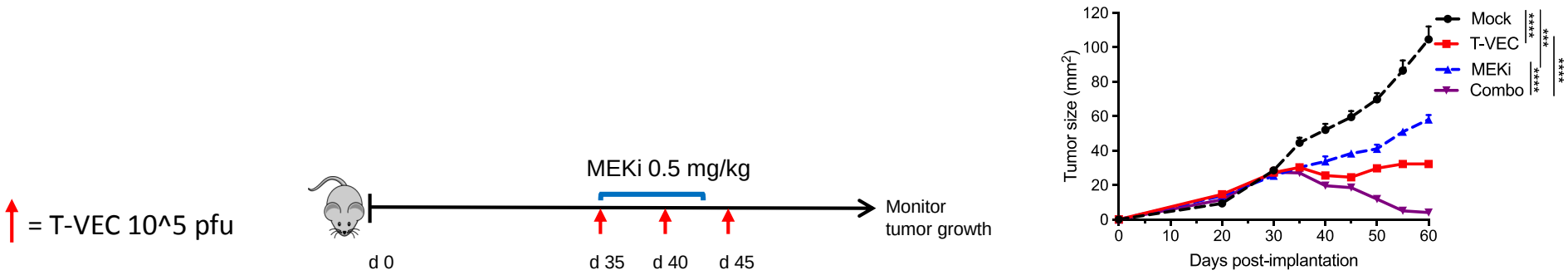
MEKi augments apoptosis induced by T-VEC in SK-MEL-28 melanoma cells

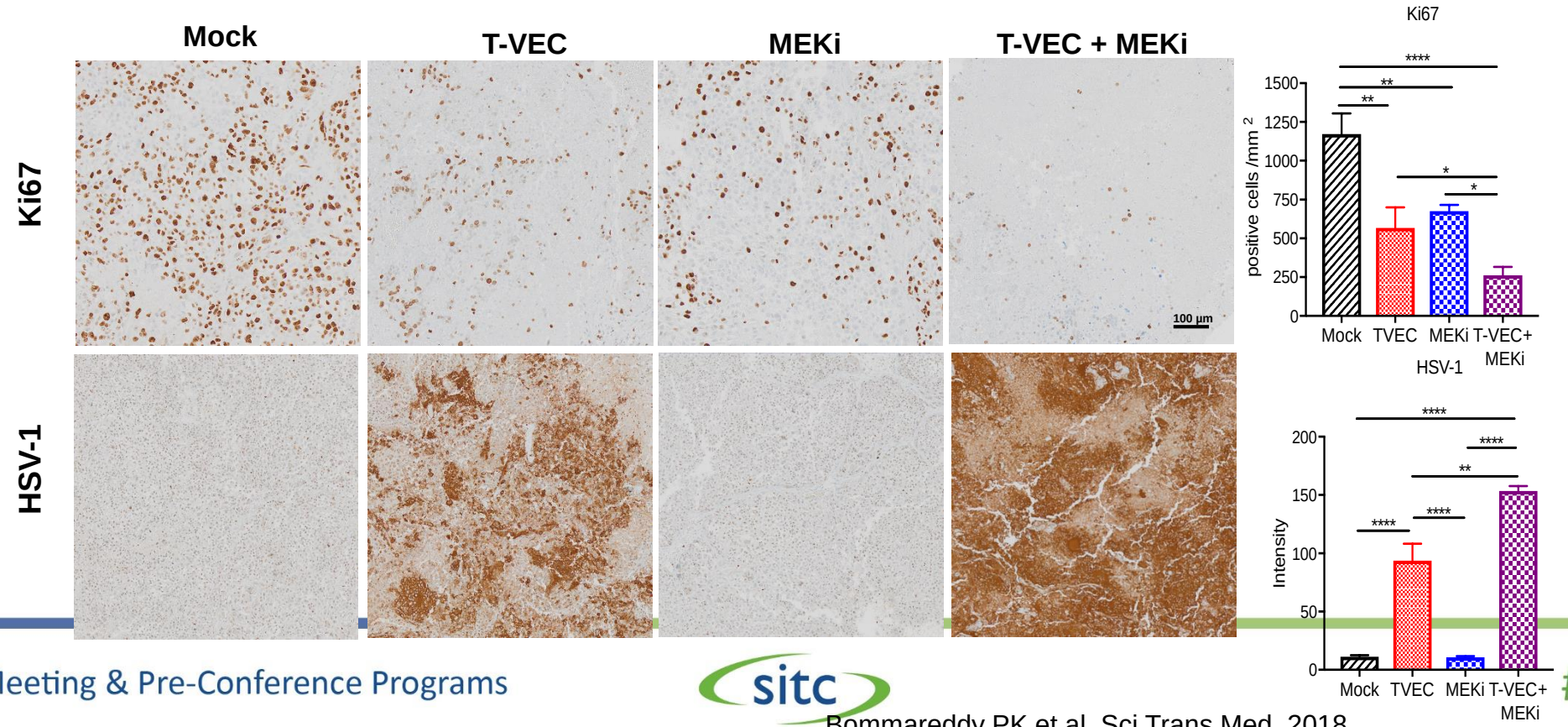




Bommareddy PK et al, Sci Trans Med. 2018

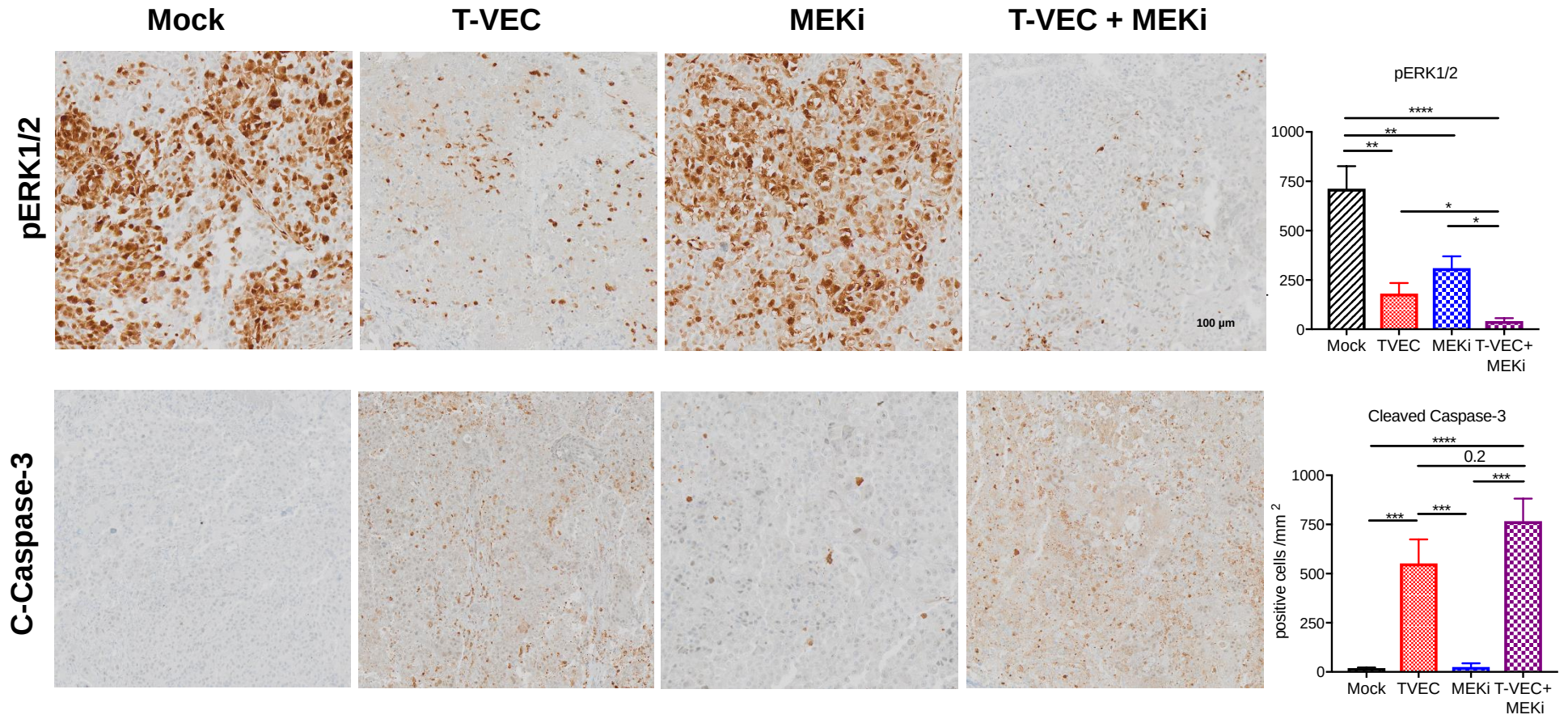
Trametinib (MEKi) augments T-VEC mediated oncolysis in SKMEL-28 human Melanoma xenograft model





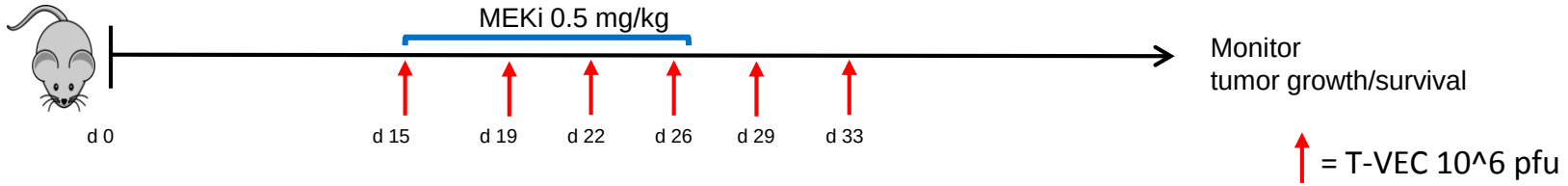
Bommareddy PK et al, Sci Trans Med. 2018

Combination of T-VEC and MEKi increased apoptosis *in vivo*

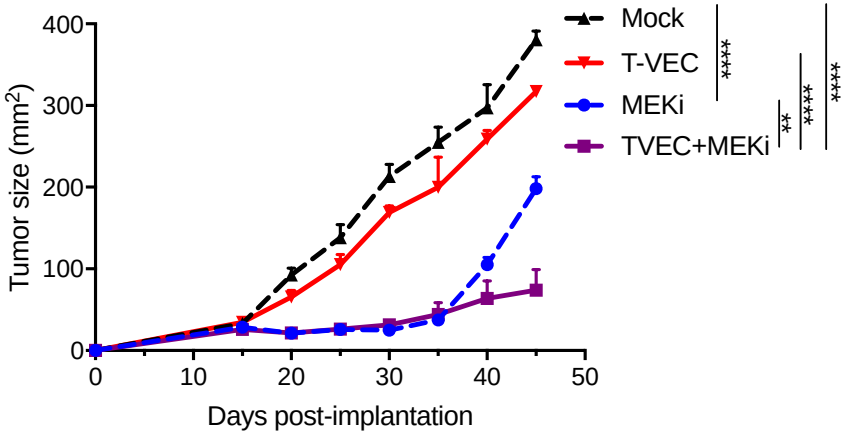


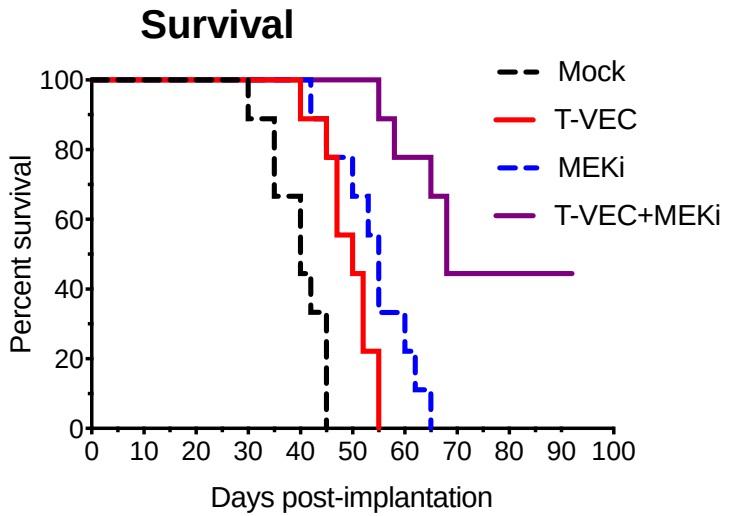
Bommareddy PK et al, Sci Trans med. 2018

TVEC and MEKi reduces tumor growth in syngeneic murine melanoma model (D4M3A)



N = 9





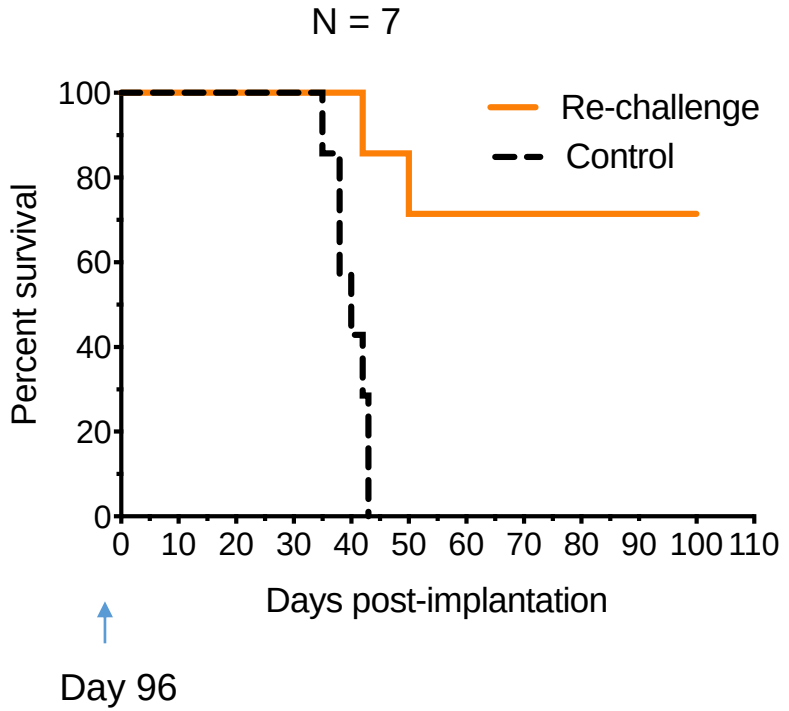
Bommareddy PK et al, Sci Trans Med. 2018

T-VEC and MEKi induces immune memory

Mice rejected primary tumor

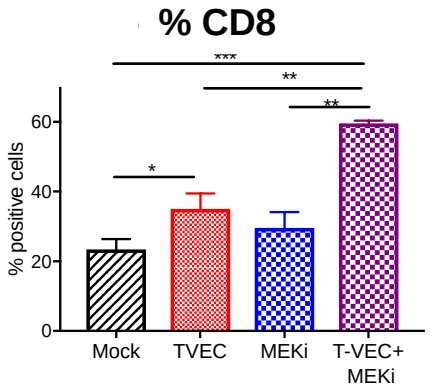
Re-challenge mice D4M 600K

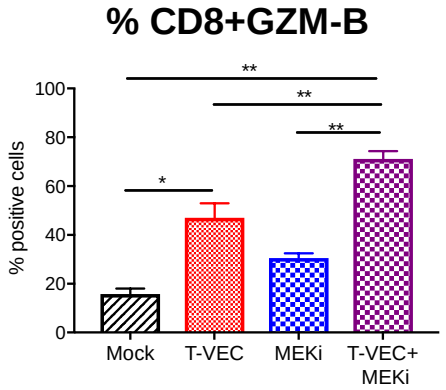
Monitor tumor growth/survival

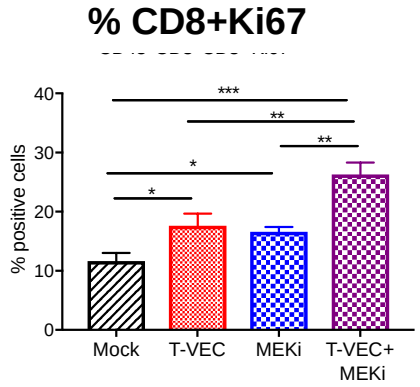


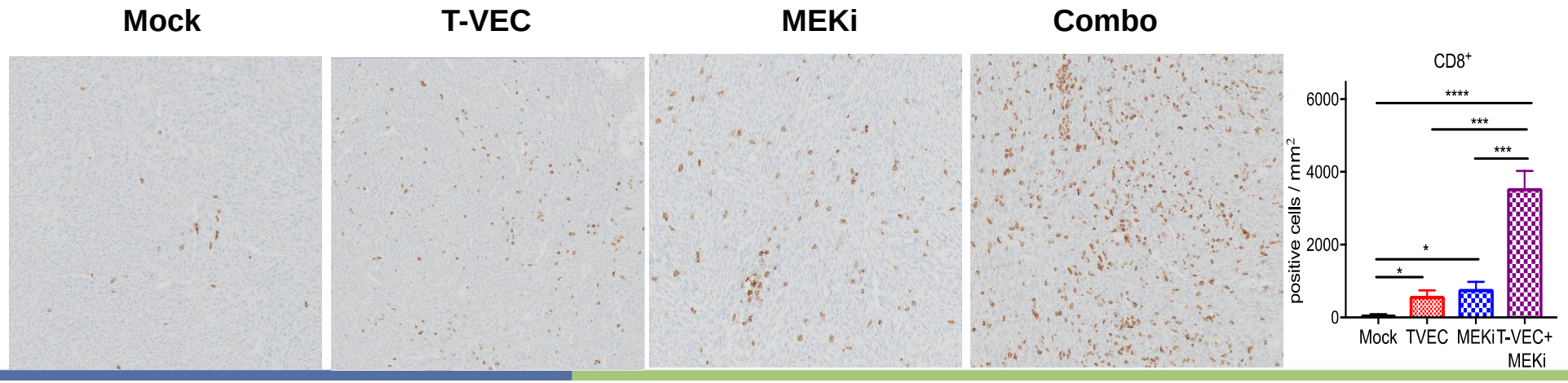
Bommareddy PK et al, Sci Trans Med. 2018

T-VEC and MEKi enhances T cell activation



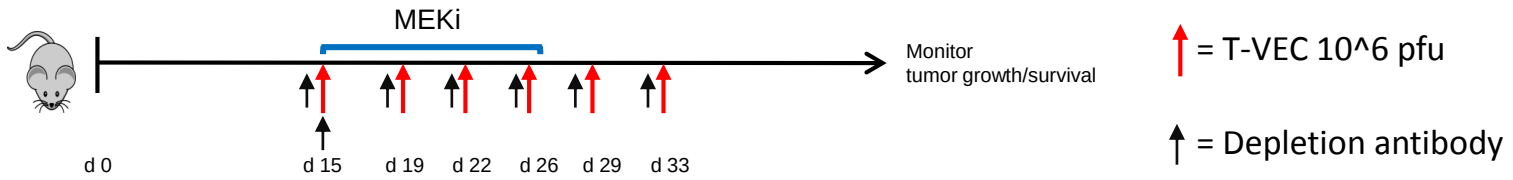


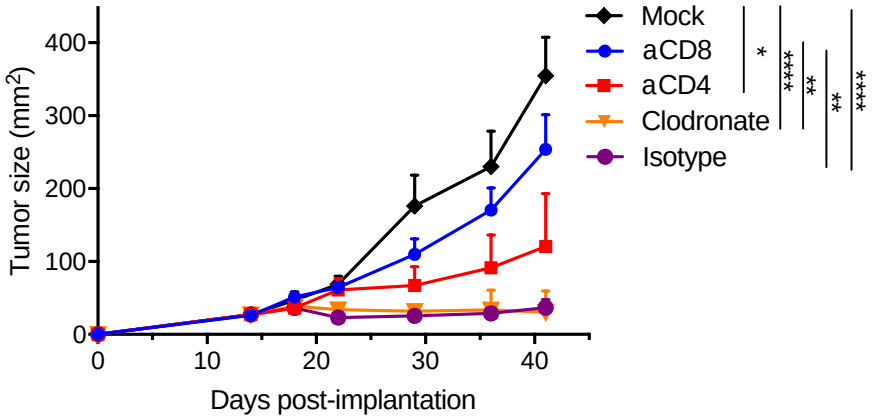


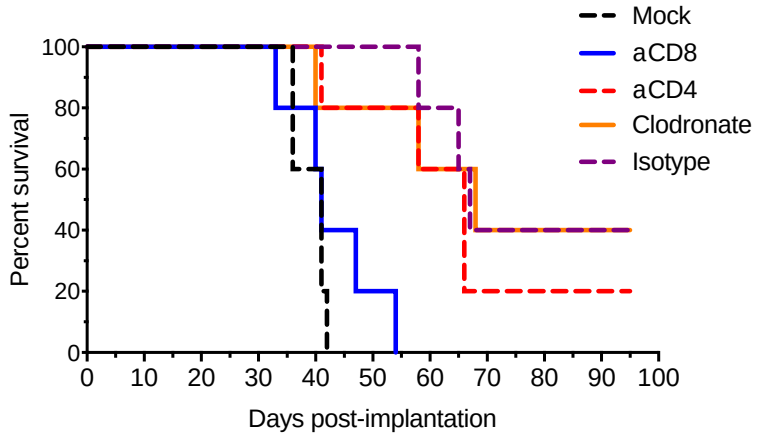


Bommaredddy et al. STM 2018

T-VEC and MEKi effects are CD8+ T cell dependent

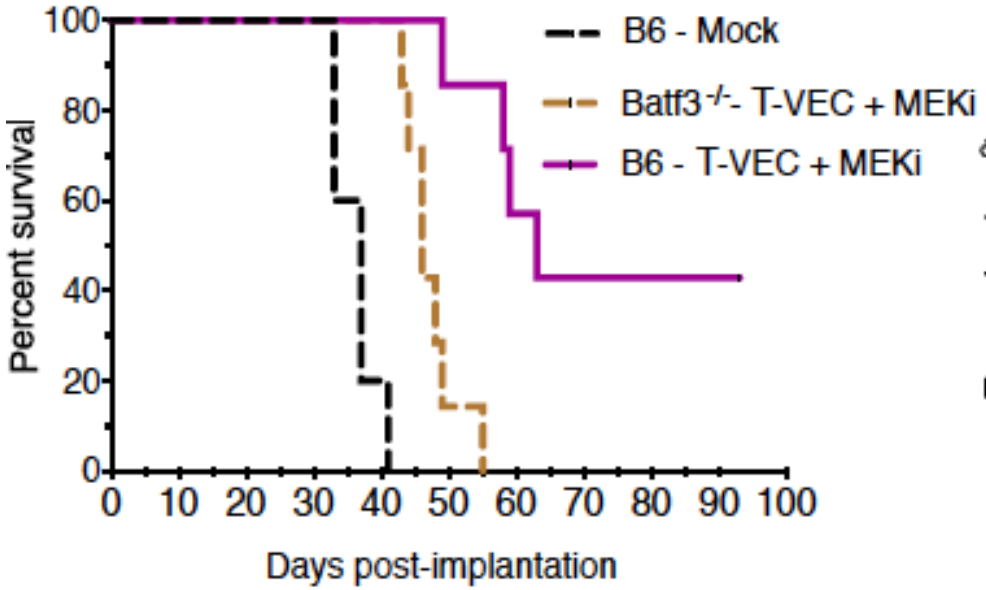


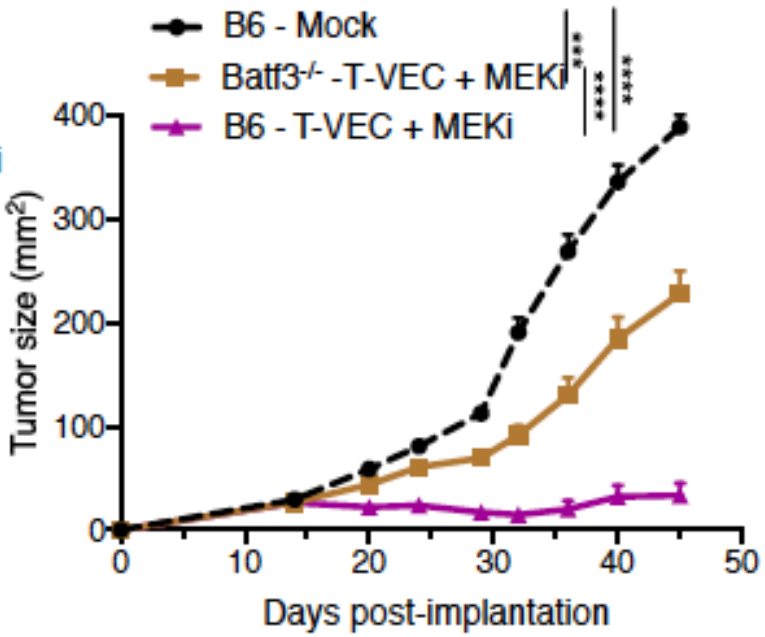




Bommareddy PK et al, Sci Trans Med. 2018

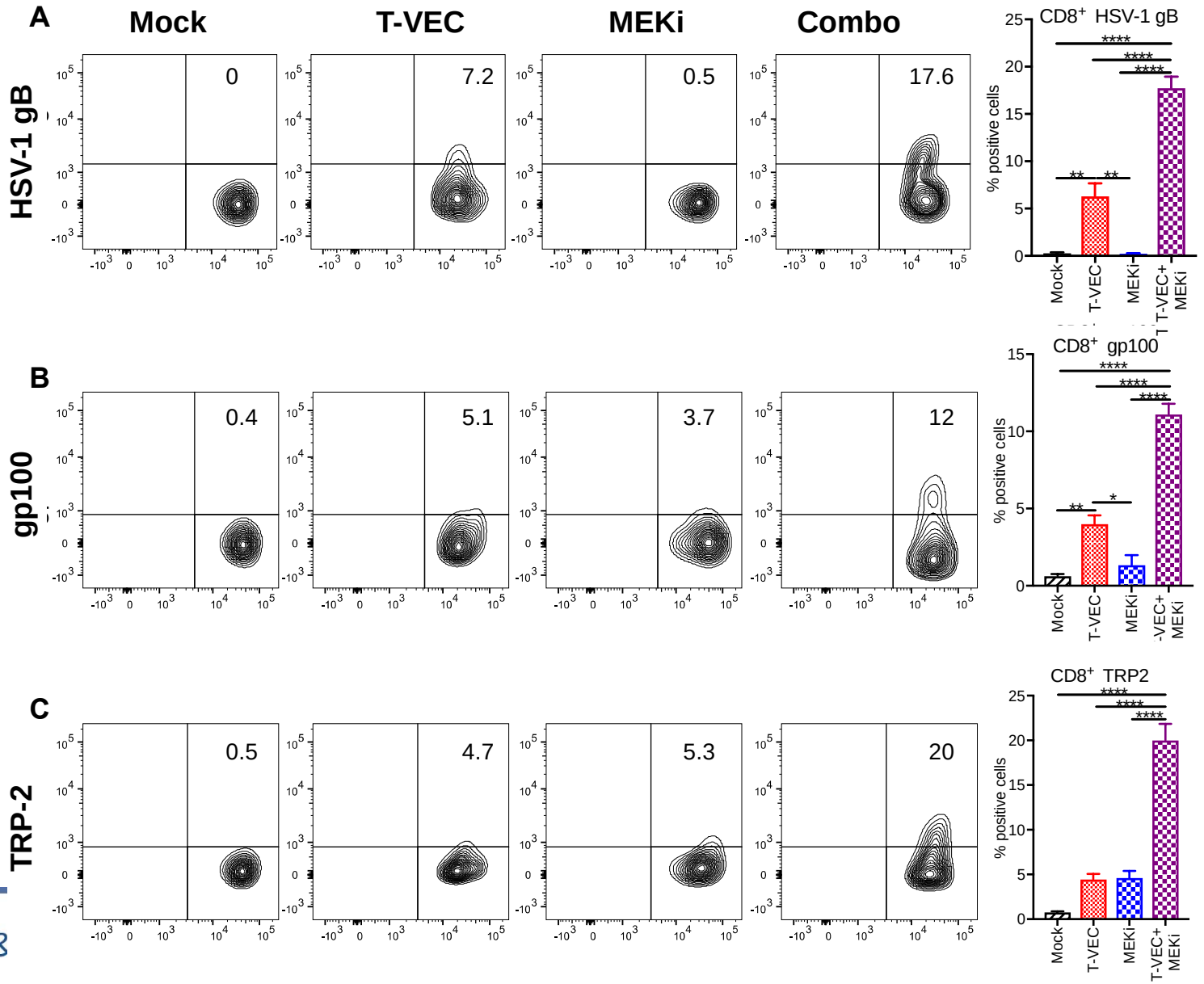
T-VEC and MEKi anti-tumor activity depend on Batf3 dendritic cells





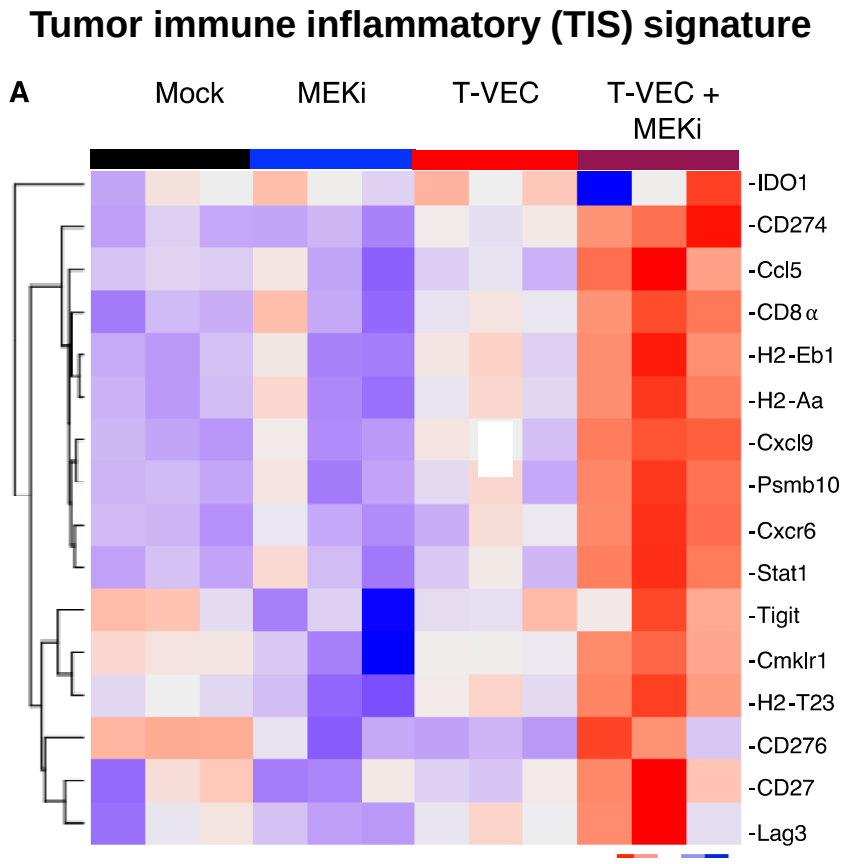
Bommareddy et al. Science Transl Med 2018

Combination enhances HSV-1 and melanoma antigen specific T cell responses



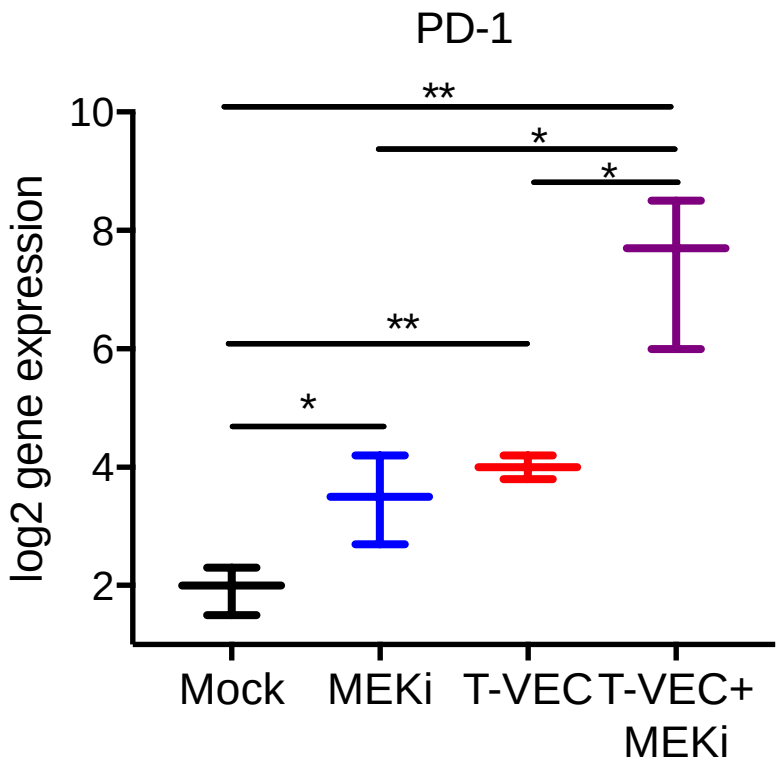
Single-Live+ CD45+CD3+CD8

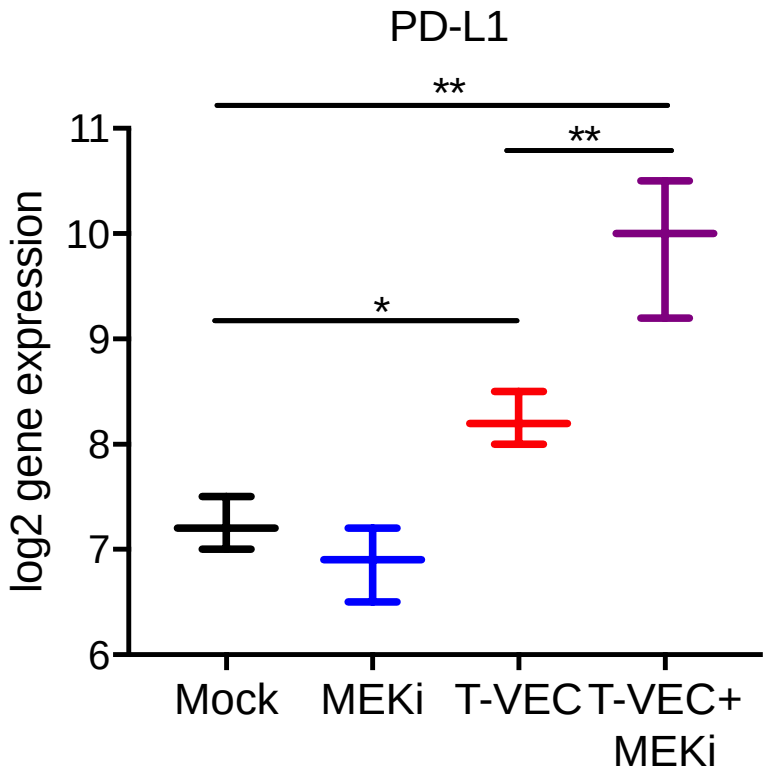
T-VEC and MEKi reprograms TME and increases PD-1 and PD-L1 expression



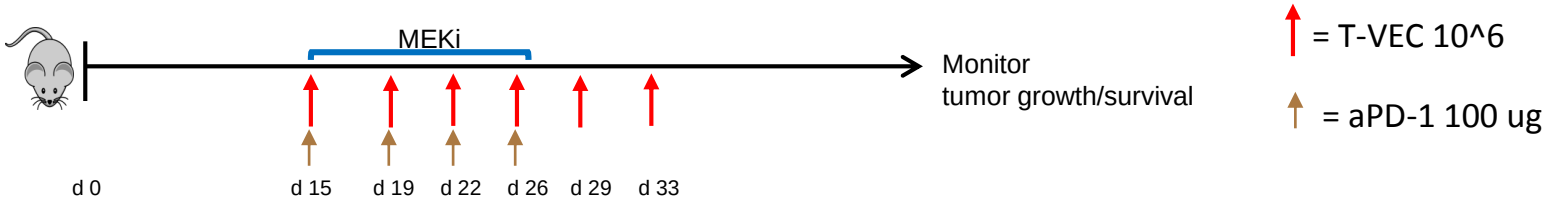
Bommareddy et al. Science Transl Med 2018

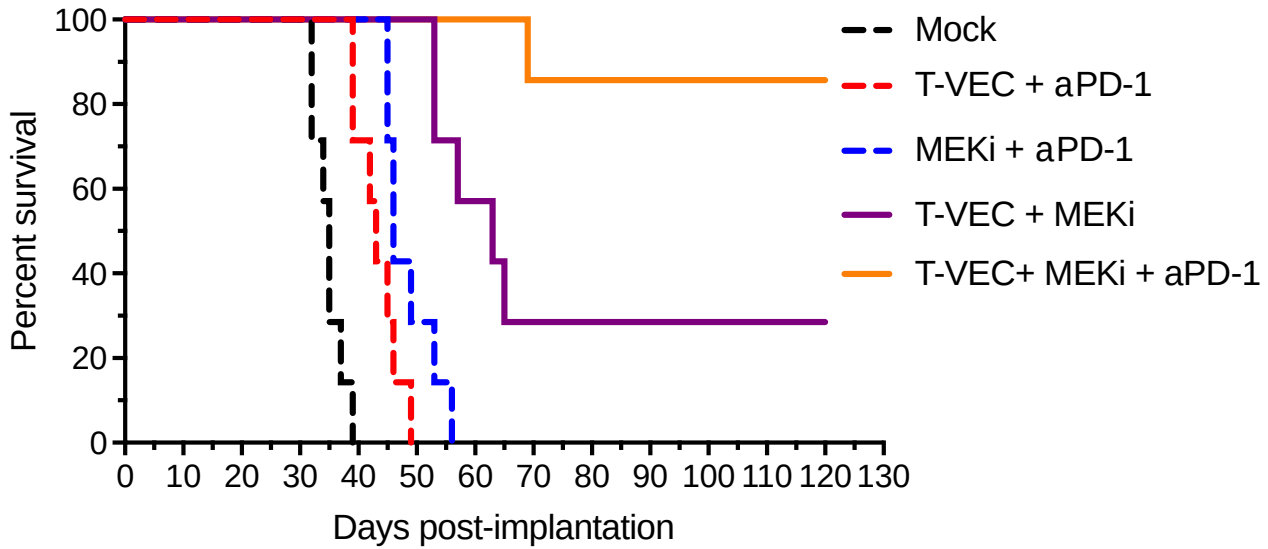
PD-1/PD-L1 expression is increased by treatment with T-VEC and MEK inhibition



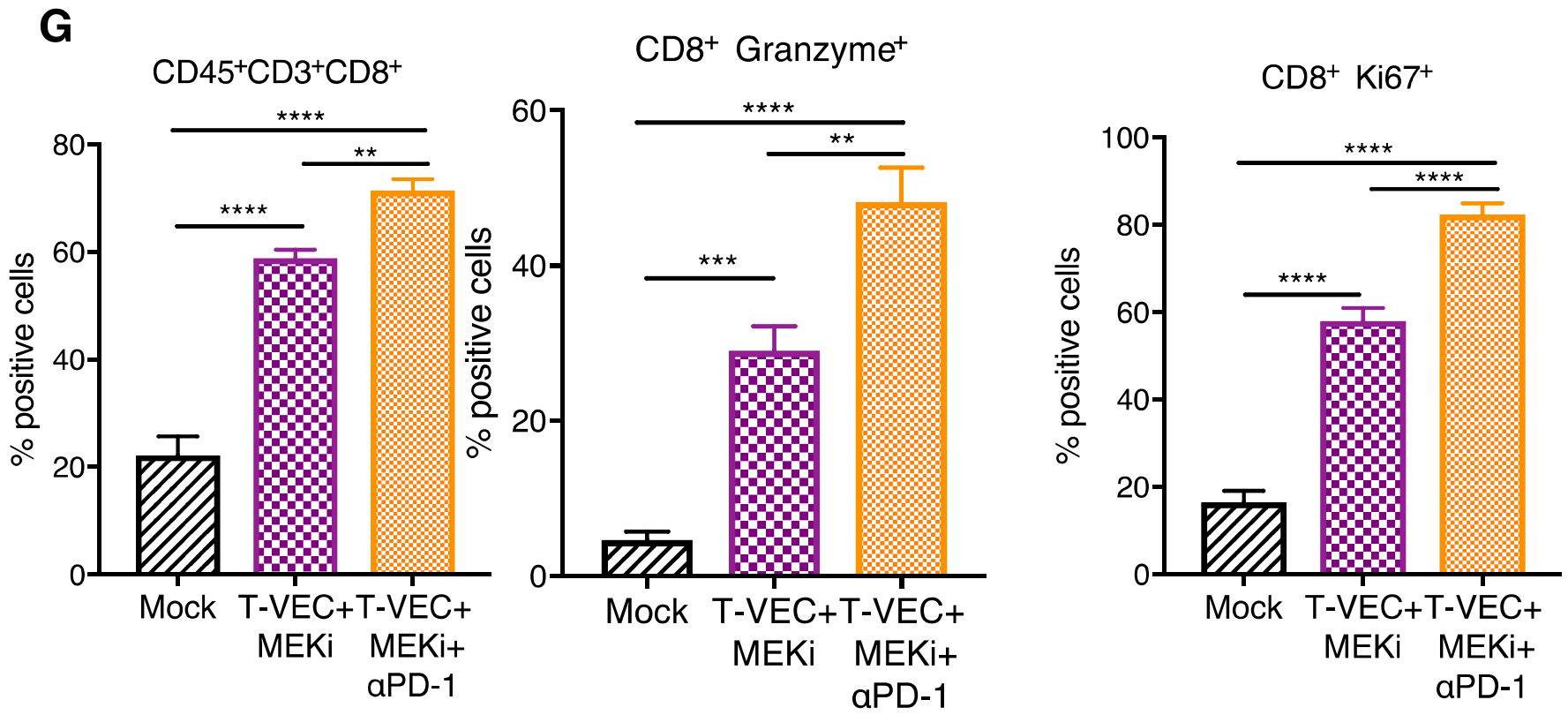


PD-1 blockade augments T-VEC + MEKi combination treatment



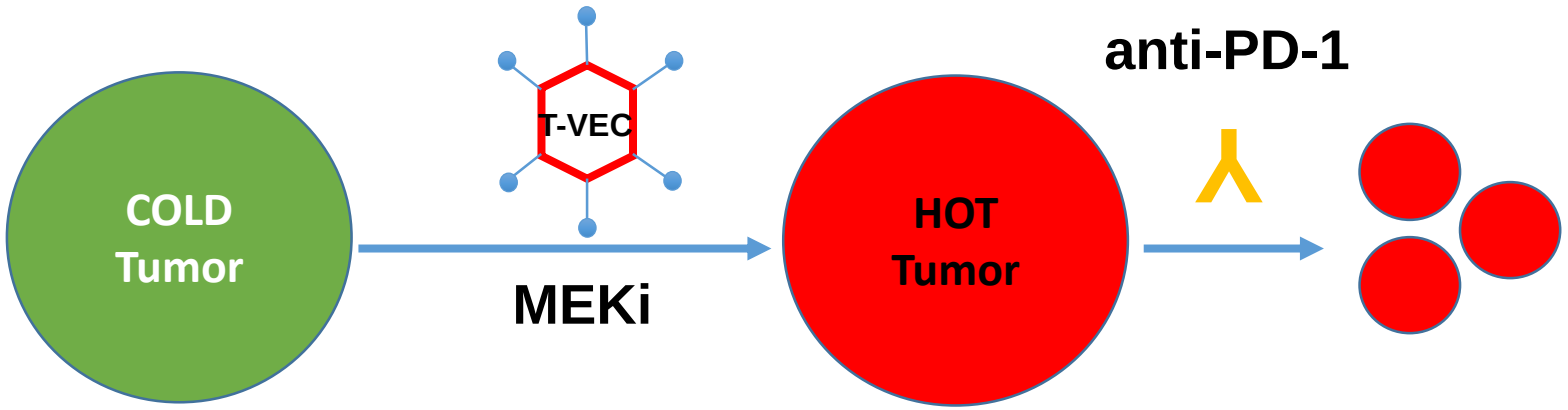


Triple therapy further drives effector T cell recruitment



Bommareddy PK et al, Sci Trans Med. 2018

Triple combination therapy: a more rational approach to tumor immunotherapy



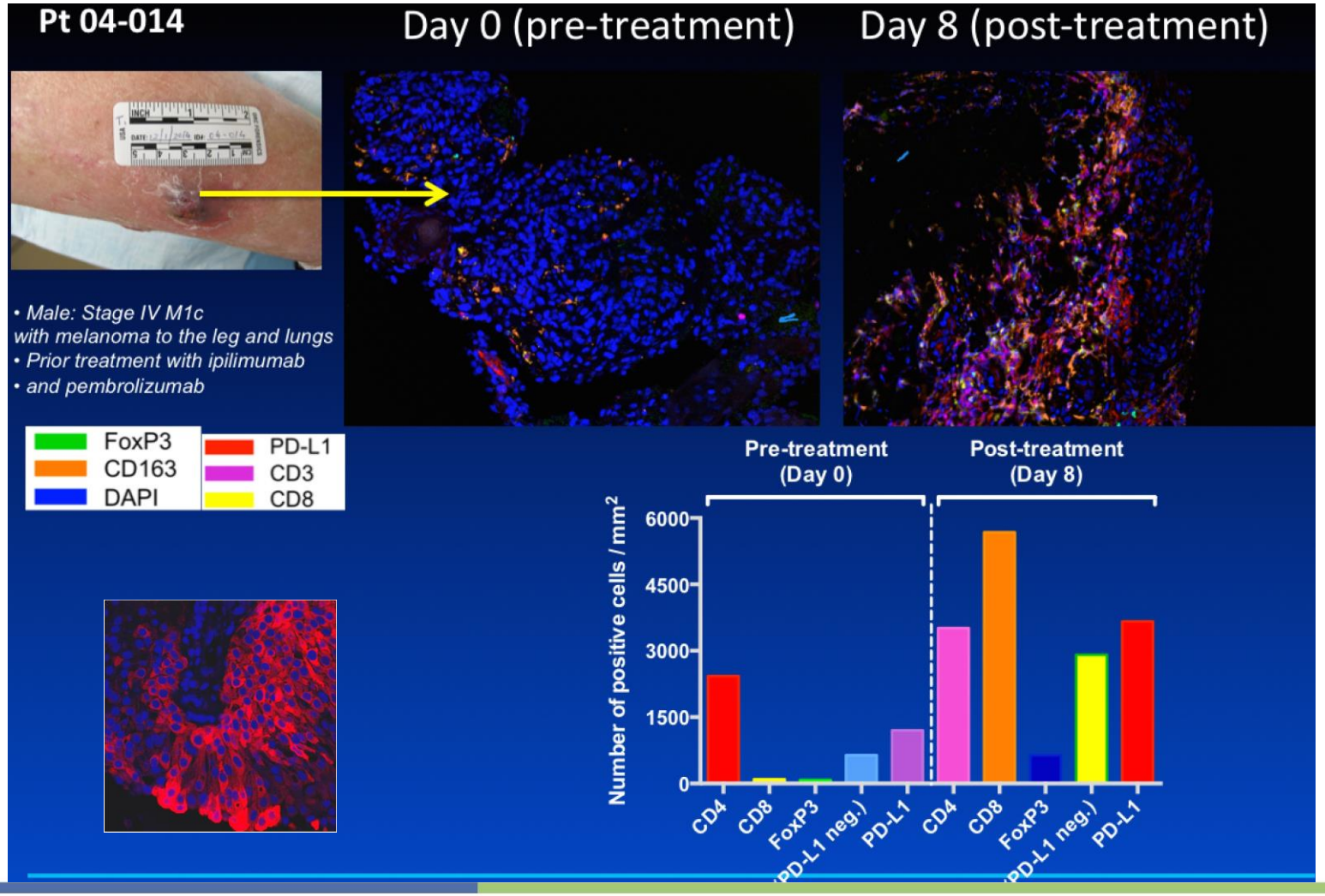
No response to immunotherapy*

Respond to PD-1 blockade

Tumor clearance

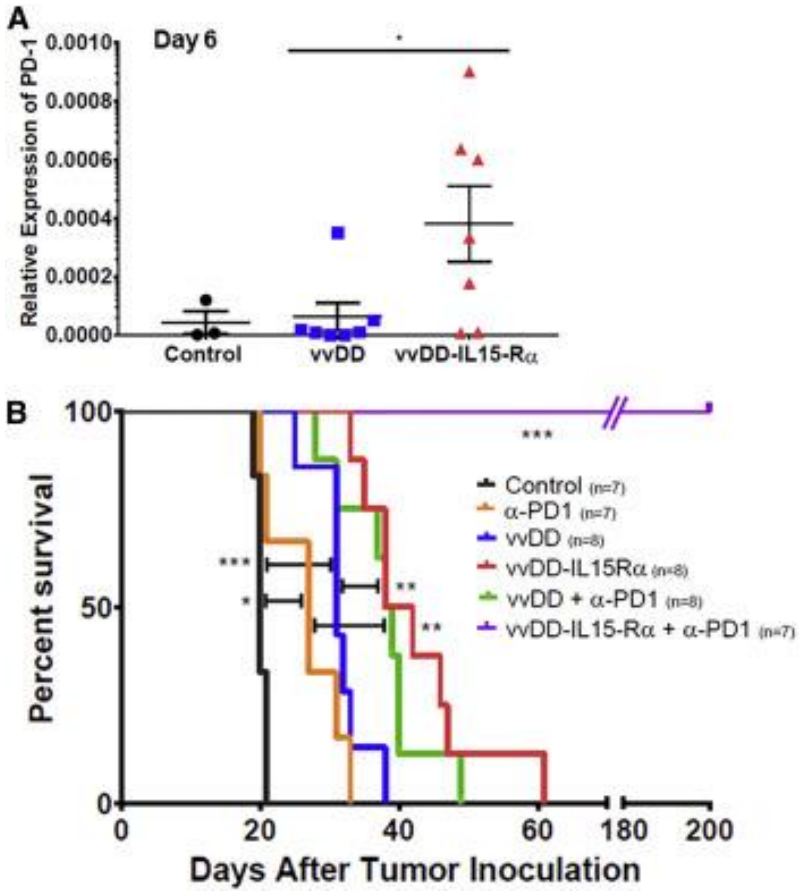
Bommareddy PK et al, Sci Trans. Med. 2018

Oncolytic coxsackievirus, CVA21, also induces immune cell infiltrates and increased PD-L1 expression



Courtesy B. Fox

Oncolytic VV encoding superagonist IL-15 induces PD-1 expression and has anti-tumor activity with PD-1 blockade in the MC38 murine model



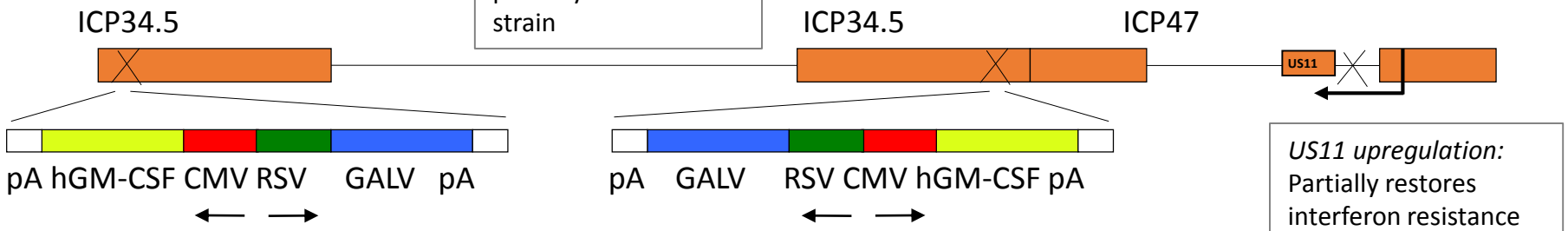
Kowalsky et al. Mol Ther. 2019

Replimune's Immulytic HSV-based backbone - RP1

ICP34.5 deletion: Provides tumor selectivity by deleting functions including the ability to block IFN-mediated antiviral responses

Strain RH018A: High potency new clinical strain

ICP47 deletion: Prevents blocking of antigen presentation in tumor cells



US11 upregulation: Partially restores interferon resistance as compared to deletion of ICP34.5 alone

Fusogenic GALV expression: Increases immunogenic cell death, tumor killing and spread

GM-CSF expression: Stimulates dendritic cell activity in the tumor

RP1- HSV1, high potency new clinical strain (RH018A), ICP34.5 deleted, ICP47 deleted, US11 upregulated, codon optimized GM-CSF expressed, codon optimized GALV-GP *R*- expressed

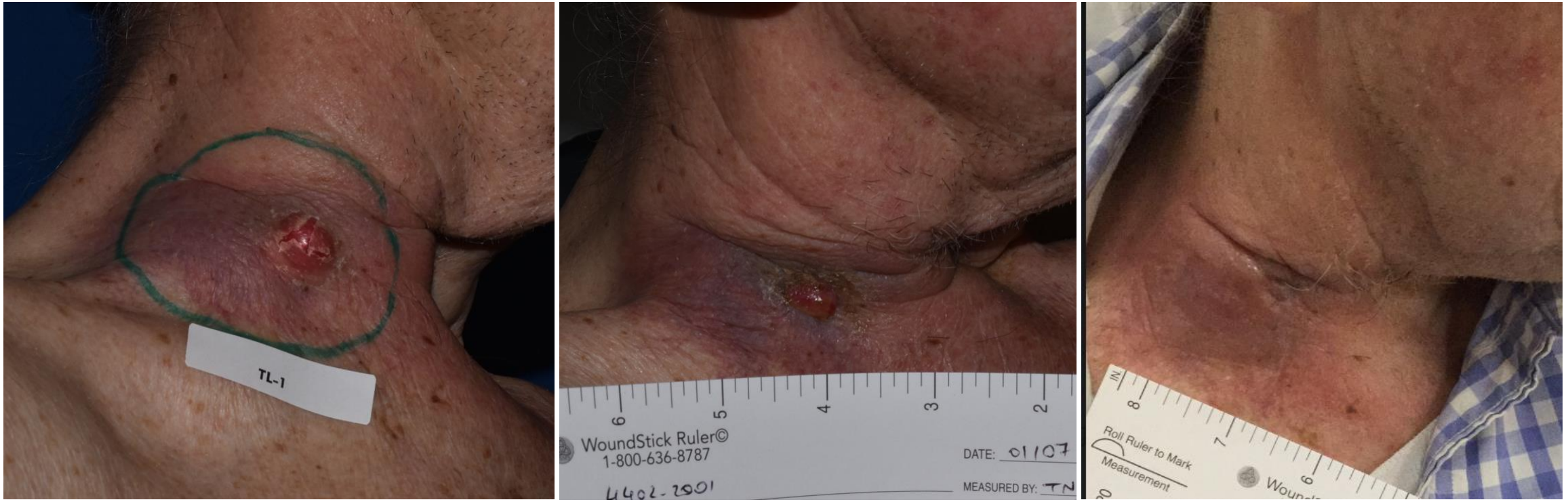
Not to scale – the HSV genome is 152Kb

RP1 clinical efficacy in CSCC (RP1+nivolumab phase 1/2 clinical trial)

16th June 2019
(baseline)

1st July 2019
(post one dose of RP1, no Opdivo)

16th July 2019
(post 2 doses of RP1 & 1 dose of Opdivo)



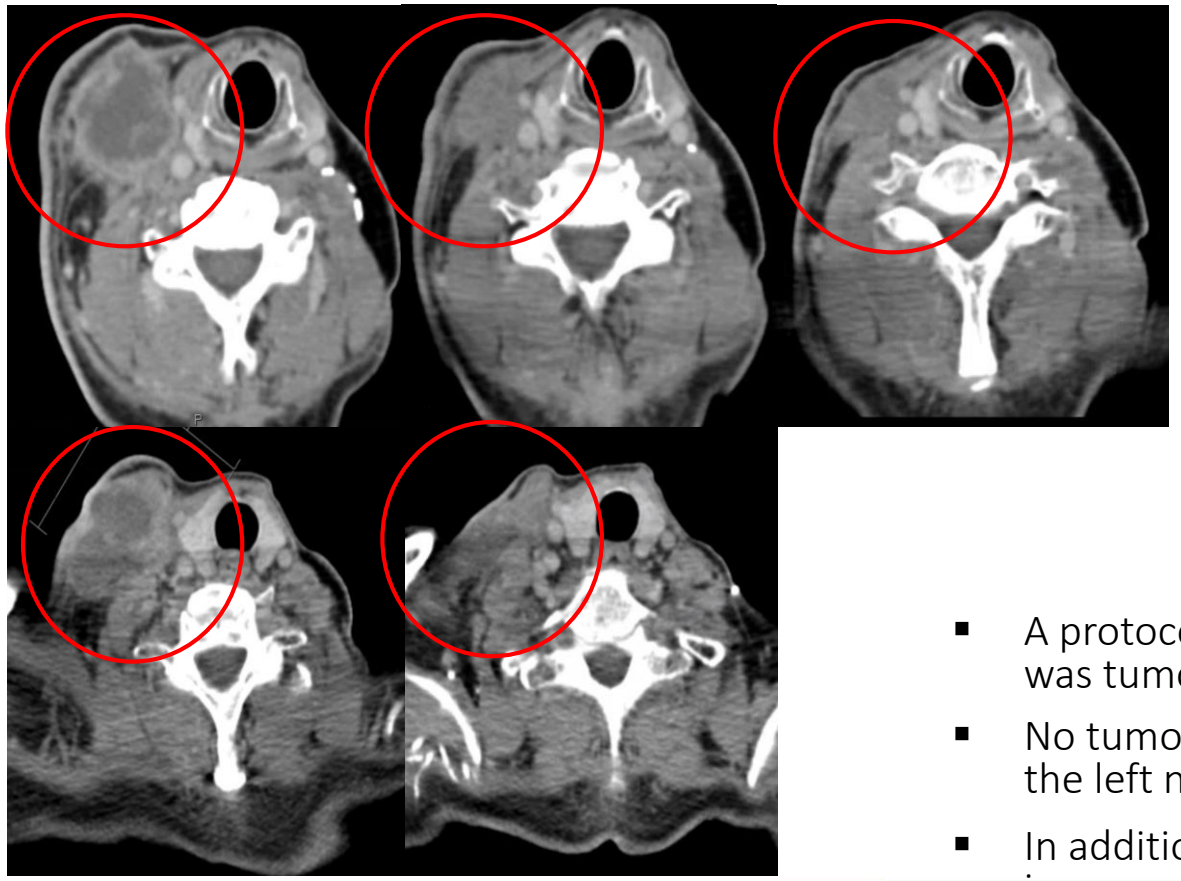
- Patient with recurrent CSCC of the neck (bilateral), previously treated with cisplatin-based chemoradiation & six cycles of carboplatin/5-FU, prior to entering the clinical trial
- Both the large injected tumor & the smaller contralateral tumor in the neck reduced considerably before the first Opdivo dose, i.e. after the first dose of RP1

Unpublished, Replimune Inc 2019

RP1 clinical efficacy in CSCC (RP1+nivolumab phase 1/2 clinical trial)

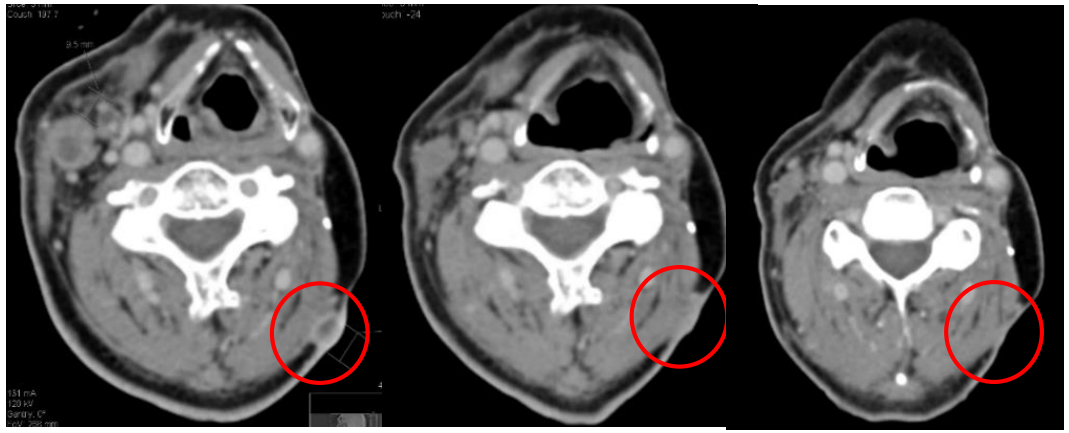
Right neck (injected)

Baseline 8 weeks 16 weeks



Left neck (not injected)

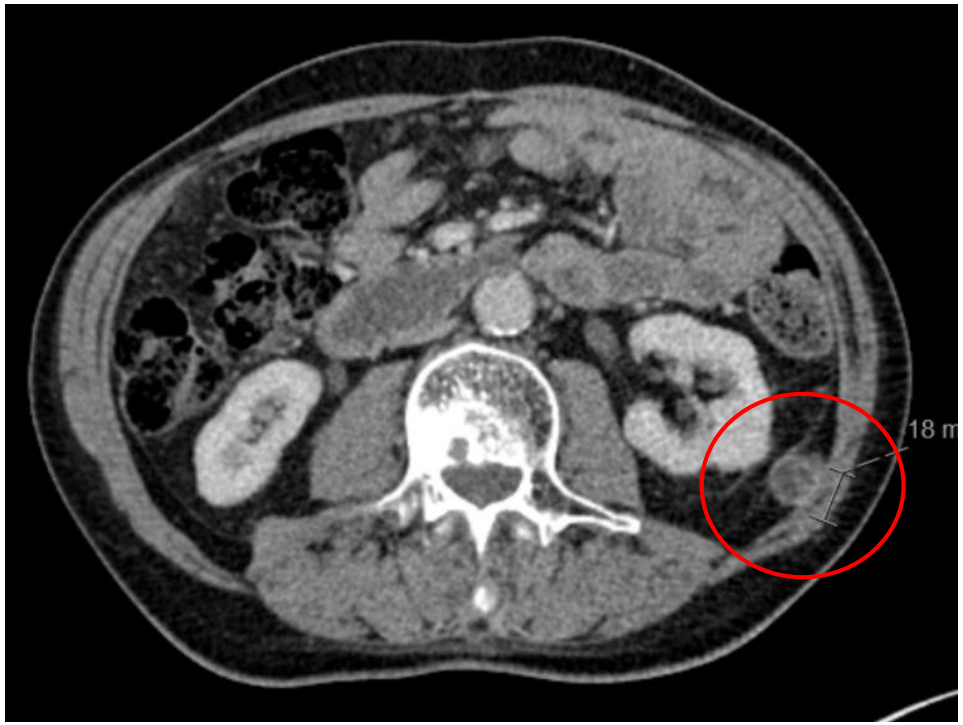
Baseline 8 weeks 16 weeks



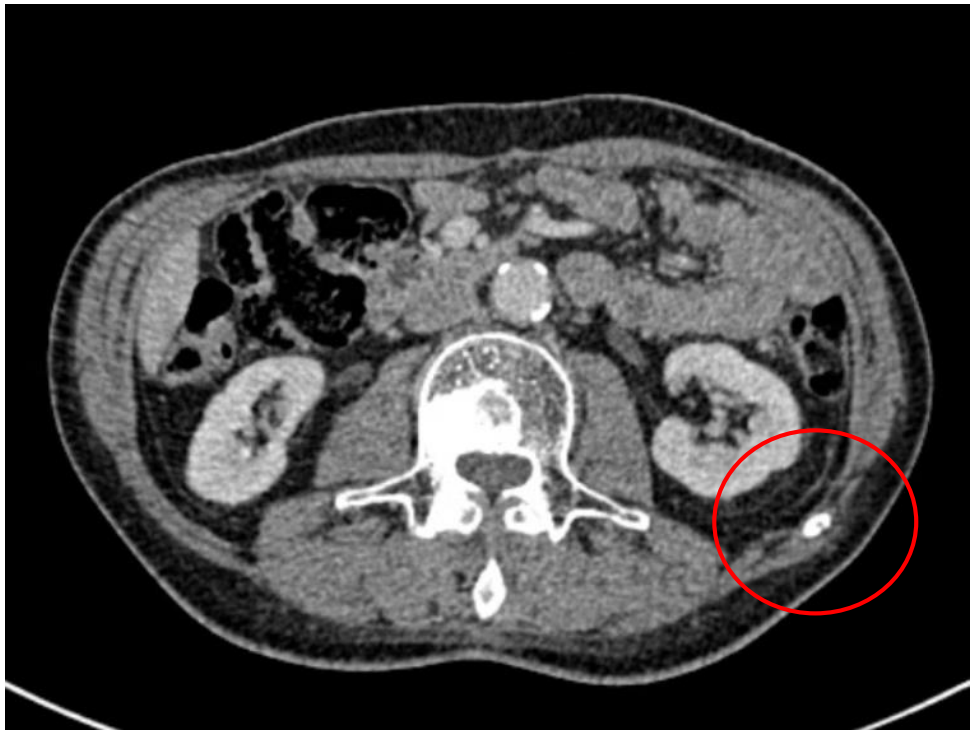
- A protocol mandated biopsy of the injected tumor taken at day 43 was tumor free
- No tumor was found to remain when a biopsy was attempted from the left neck
- In addition to the tumor response, this patient has had a dramatic improvement in quality of life & is now off pain medication

RP1 clinical efficacy in CSCC (RP1+nivolumab phase 1/2 trial)

Baseline



16 weeks



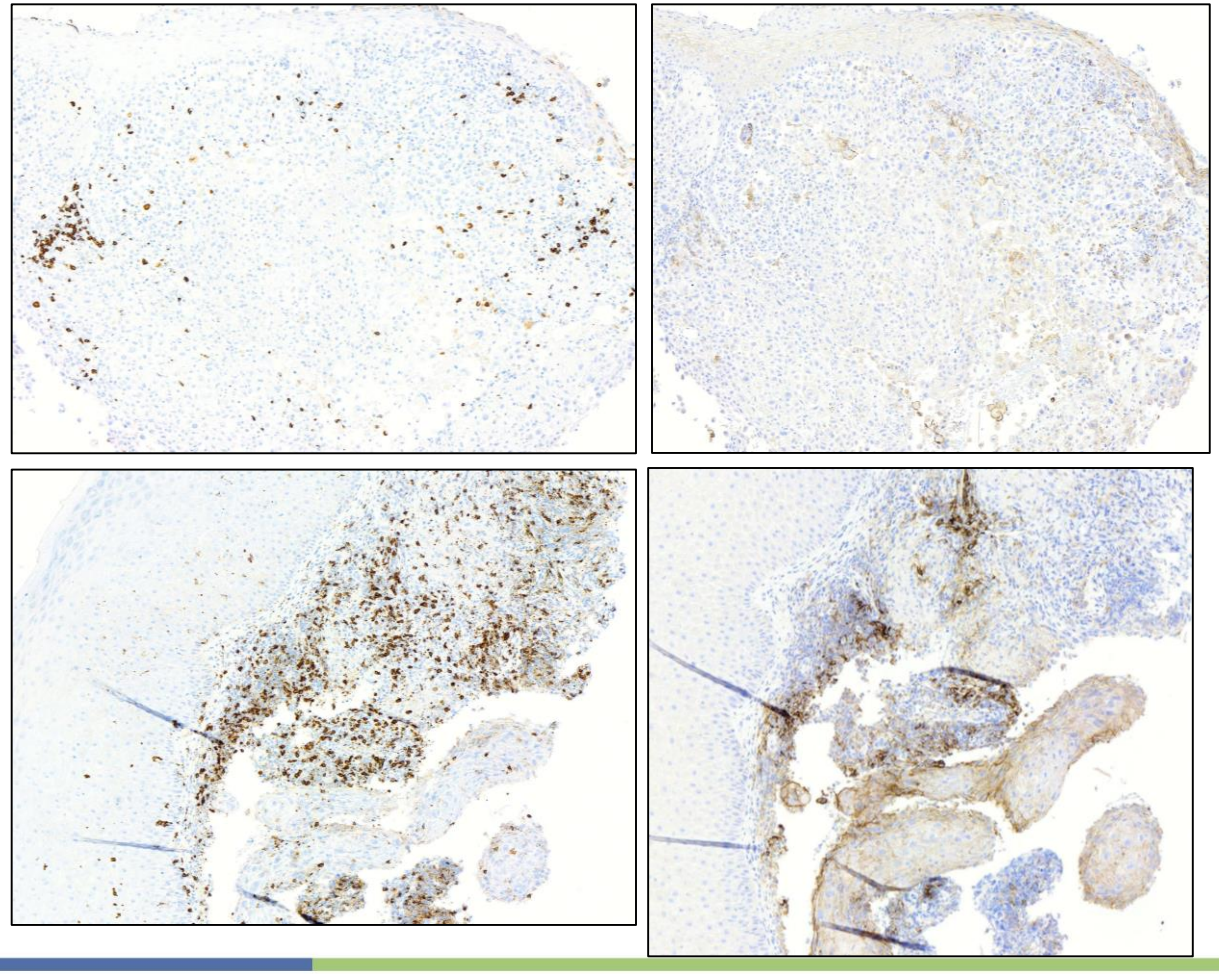
- The patient also had baseline retroperitoneal tumors which have completely resolved
- The only remaining disease are a number of non-measurable bone metastases, which were the main source of the cancer pain which has now resolved. These are now sclerotic, also suggestive of a treatment response

Unpublished, Replimune Inc 2019

RP1 and nivolumab induces CD8+ T cell recruitment and PD-L1 expression

Baseline

Day 43



Unpublished, Replimune Inc 2019

Conclusions

- T-VEC is the first oncolytic virus - approved for advanced melanoma
- T-VEC kills melanoma cells through immunogenic cell death
- T-VEC induces systemic immunity and local T cell recruitment
  - Depends on CD8+ T cells and Batf3+ DC
  - Promotes antigen spreading
- MEK inhibition enhances T-VEC-induced PD-1/PD-L1 expression; and anti-tumor activity is further improved with PD-1 blockade
- Other oncolytic viruses also appear to enhance immunity and therapeutic activity in combination with other cancer therapeutics
- Clinical combination studies with T-VEC, and other OVs, are warranted in melanoma and perhaps other cancers as well

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Study Participants

& Supporters

- Patients and Families

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- Andrew Zloza, MD, PhD
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