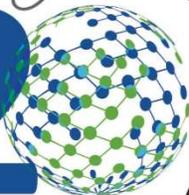




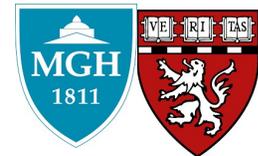
*Reimagined*  
**20** **SITC**   
NOVEMBER 9-14 



Society for Immunotherapy of Cancer

# How a surgeon can influence immuno-oncology drug development

Howard L. Kaufman  
Division of Surgical Oncology  
Massachusetts General Hospital  
Boston, MA  
and  
Immuneering Corporation  
Cambridge, MA



# Disclosures

- I am an employee of Immuneering Corp.
- I serve as a consultant to Replimune and as an advisory board member of SapVax

## Challenges to becoming a surgical scientist

Surgical training is long

Surgical care more comprehensive

Technical aspects of surgery mandate focus and time

Laboratory opportunities and time may be limited

Basic and clinical research strategies largely developed by non-surgeons

# Surgical training brings unique opportunities

Surgical training is more comprehensive

Surgeons better trained for anatomy-related research

Tissue access

Earlier relationship with patients

Strong culture of mentorship

Capable of adding to multi-disciplinary approaches

# Vaccinia virus encoding human CEA



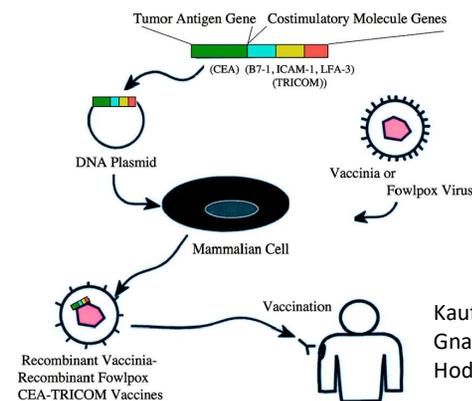
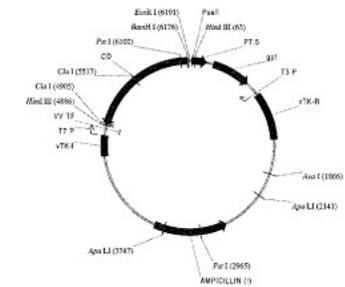
Article

## A recombinant vaccinia virus expressing human carcinoembryonic antigen (CEA)

Howard Kaufman, Jeffrey Schlom, Judy Kantor

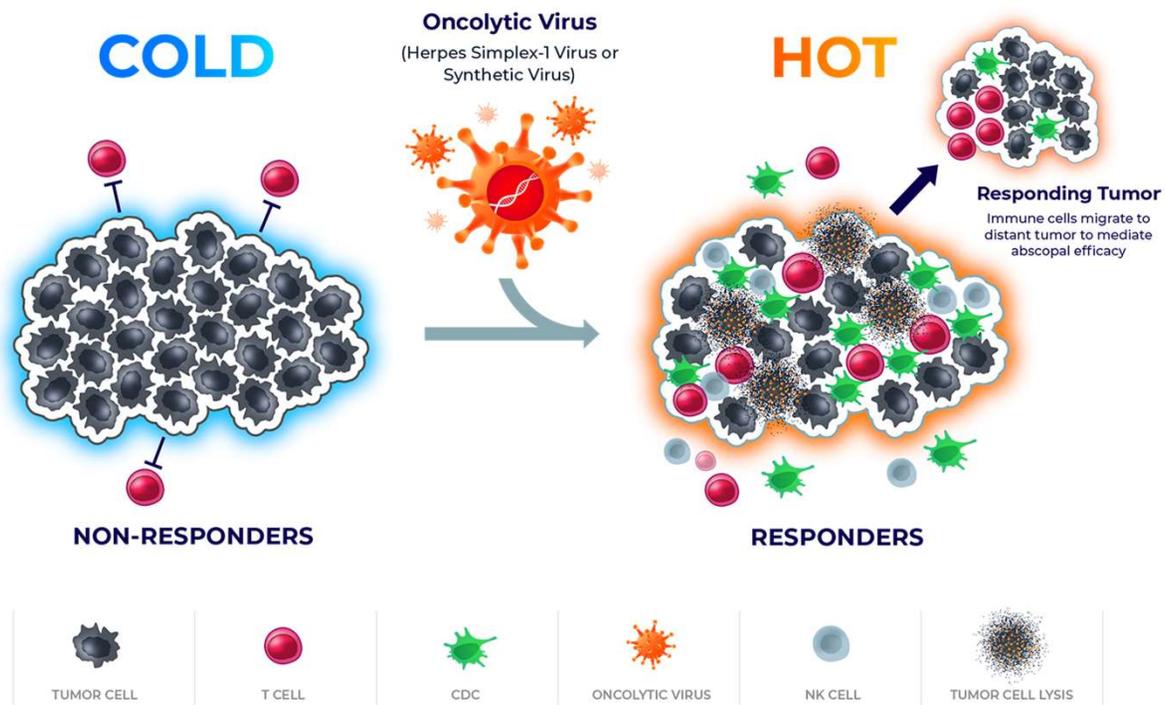
First published: 30 July 1991 | <https://doi.org/10.1002/ijc.2910480618> | Citations: 51

- Recombinant viruses can express human antigens
- Vaccination was safe
- Vaccination induces CEA-specific immunity
- Vaccination did not induce clinical responses

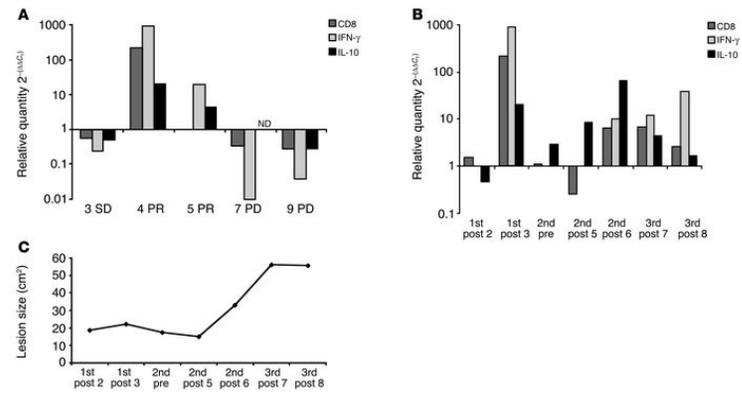
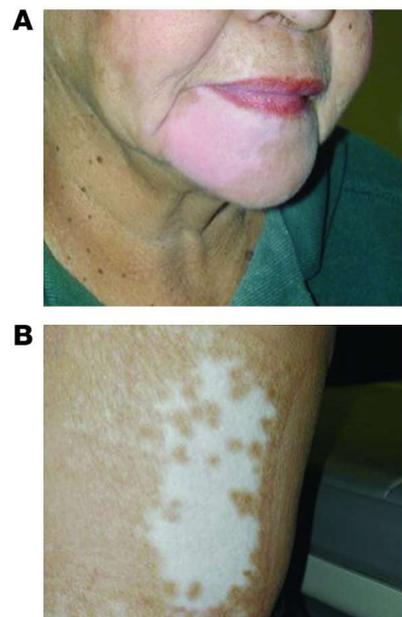


Kaufman et al. Int J Cancer 1991  
 Gnat et al. Cancer Res 1999  
 Hodge et al. Front Bioscience 2006

# Viral infection tumor as a strategy to overcome limited efficacy of recombinant viral vaccines



# Oncolytic vaccinia virus encoding B7.1



- Oncolytic vaccinia-B7.1 well tolerated
- Demonstrated 25% ORR
- Associated with ag-specific immunity
- Associated with autoimmune vitiligo

Kaufman et al. J Clin Invest. 2005

# Can other viruses be used as oncolytic therapeutic agents? HSV-1-GM-CSF

VOLUME 27 · NUMBER 34 · DECEMBER 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

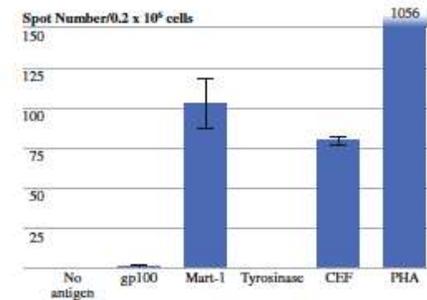
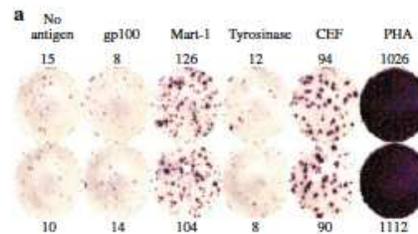
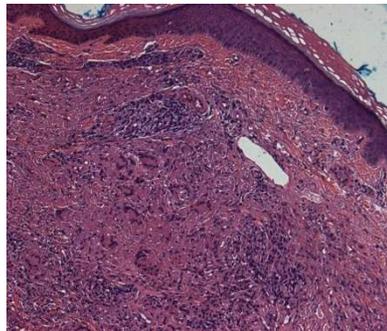
**Objective Responses 13 (26%)**

**Complete Response 8 (16%)**

**Partial Response 5 (10%)**

Phase II Clinical Trial of a Granulocyte-Macrophage Colony-Stimulating Factor–Encoding, Second-Generation Oncolytic Herpesvirus in Patients With Unresectable Metastatic Melanoma

*Neil N. Senzer, Howard I. Kaufman, Thomas Amatruda, Mike Nemunaitis, Tony Reid, Gregory Daniels, Rene Gonzalez, John Glaspy, Eric Whitman, Kevin Harrington, Howard Goldswieg, Tracey Marshall, Colin Love, Robert Coffin, and John J. Nemunaitis*



Senzer et al. J Clin Oncol. 2009

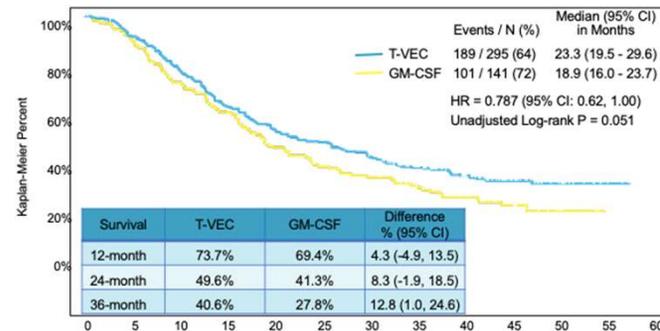
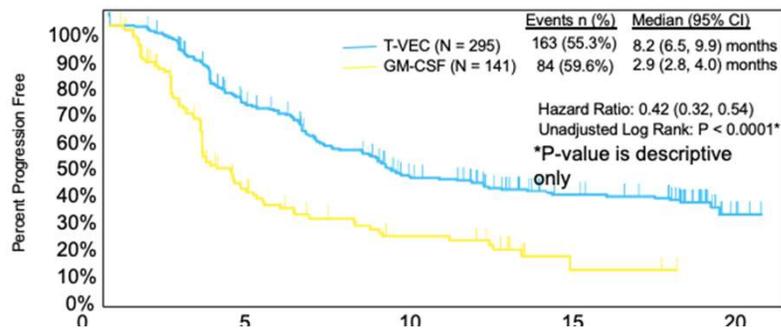
Kaufman et al. Ann Surg Oncol. 2010

# Talimogene laherparepvec: OPTiM

FDA Approves IMLYGIC™ (Talimogene Laherparepvec) As First Oncolytic Viral Therapy In The US

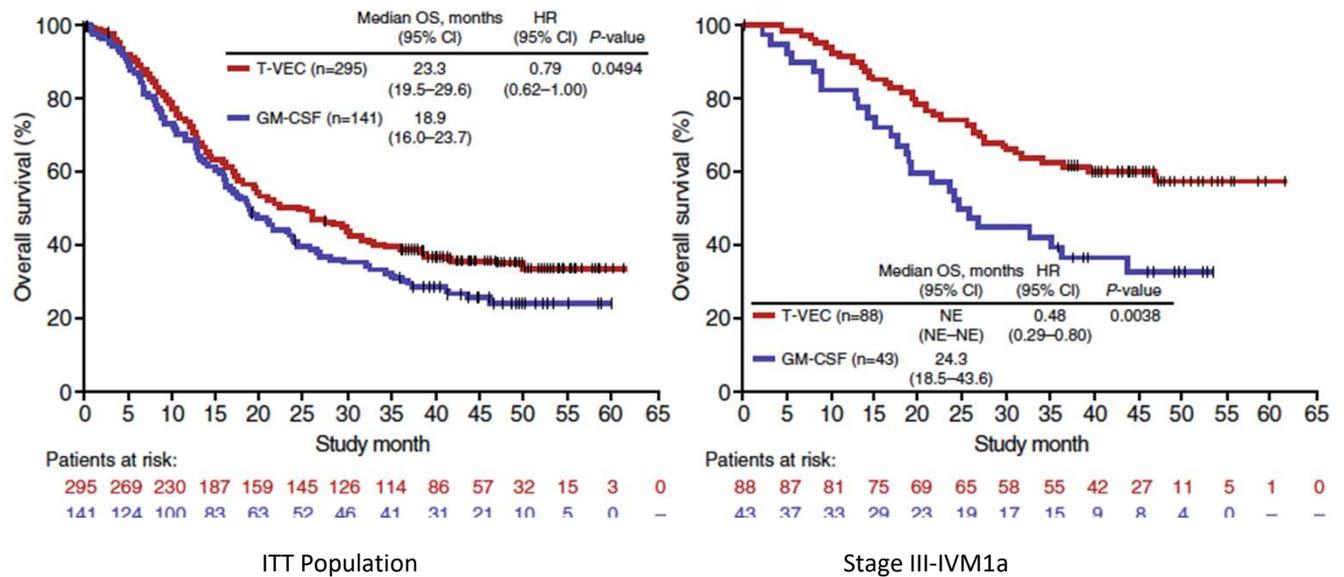
IMLYGIC Indicated for the Local Treatment of Unresectable Cutaneous, Subcutaneous and Nodal Lesions in Patients With Melanoma Recurrent After Initial Surgery

Patients Treated With IMLYGIC Achieved a Significant Increase in Durable Response Rate in Pivotal Study



Andtbacka, Kaufman, et al. J Clin Oncol 2015

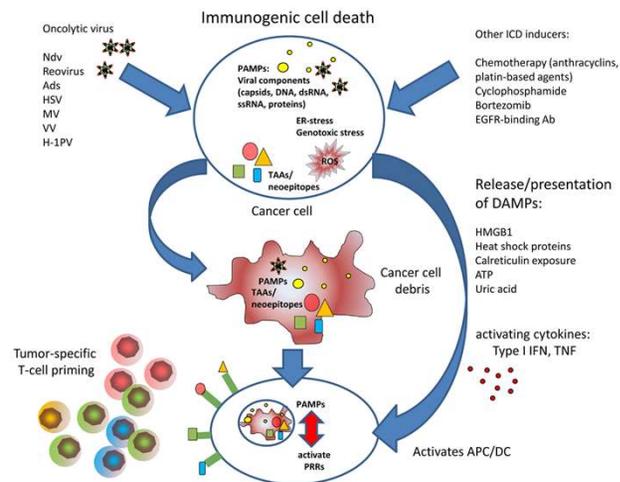
# OPTiM shows sustained OS benefit at 49 months median follow-up



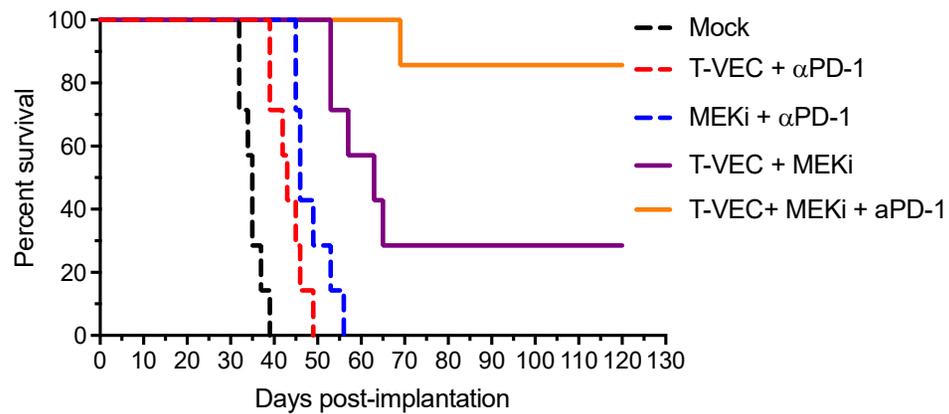
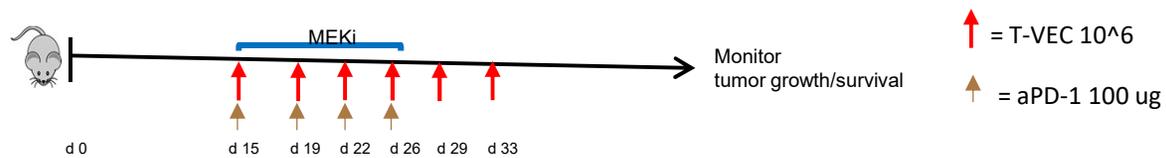
Final ORR 31.5% (vs. 6.4% and DRR 19.1% (vs. 1.4%))

# Why Oncolytic Viruses?

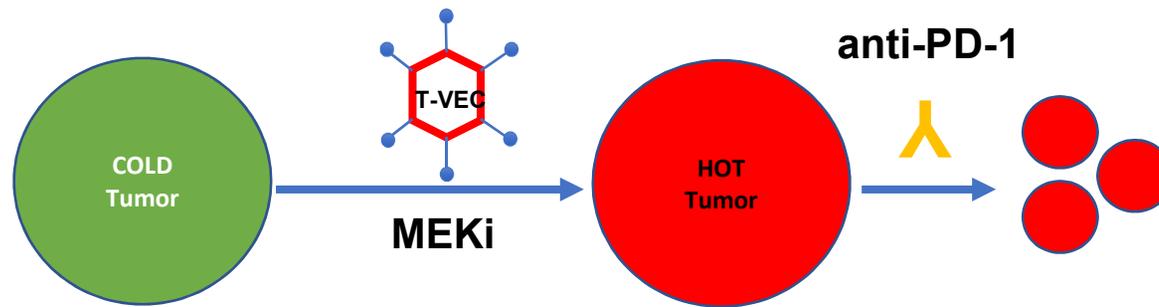
- Selective cytotoxicity
  - Immunogenic cell death
- Immunity
  - Recruits DC and T cells
  - Systemic anti-tumor immunity
- Safety
  - Well tolerated
  - Non-overlapping toxicity profile with other drugs



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



T-VEC replicates better in STING<sup>lo</sup> tumors, is enhanced by MEKi and sensitizes to PD-1 blockade

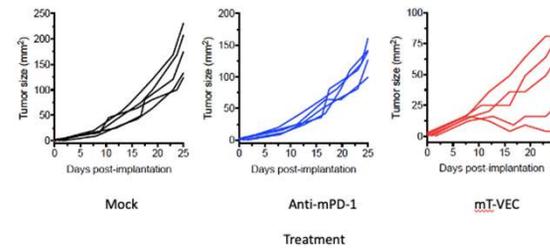


No response to immunotherapy\*

Respond to PD-1 blockade

Tumor clearance

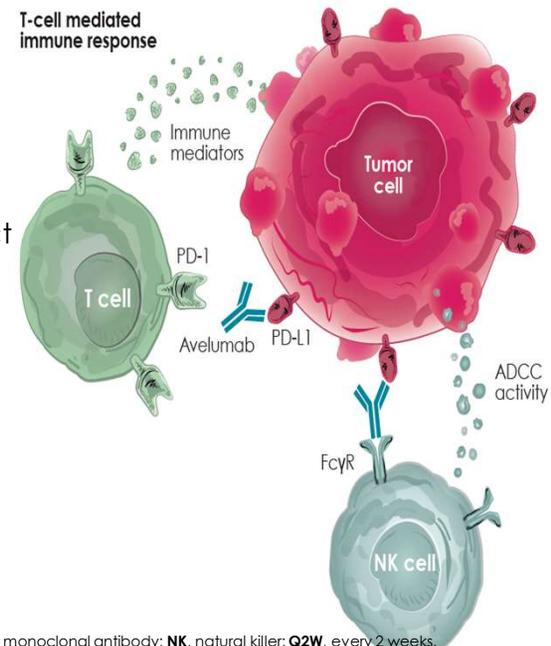
\*STING<sup>lo</sup>



Bommareddy PK et al, Sci Trans. Med. 2018  
 Bommareddy PK et al, Oncoimmunology 2019

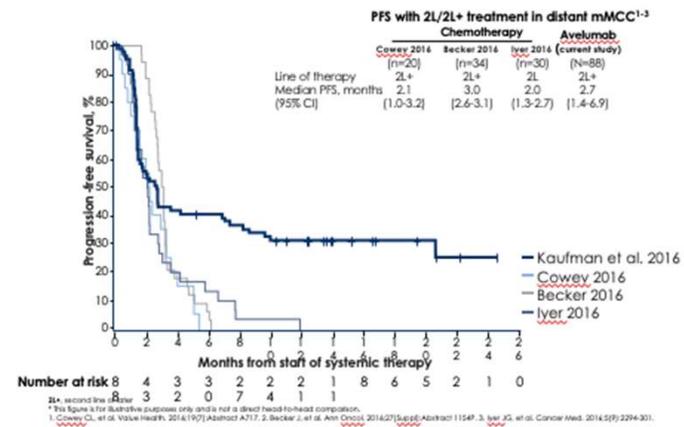
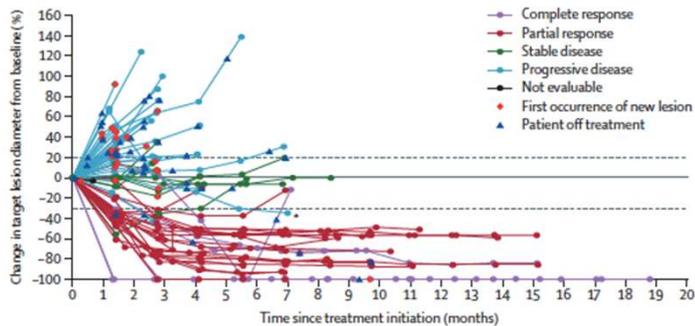
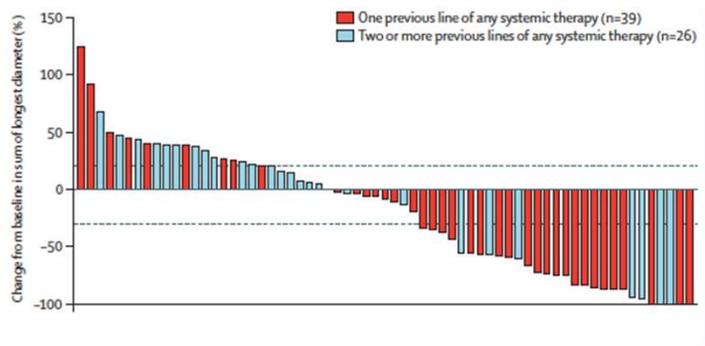
# Avelumab, a novel anti-PD-L1 mAb

- Human IgG1 mAb<sup>1</sup>
- Binds PD-L1<sup>1,2</sup>
  - Inhibits PD-1/PD-L1 interactions
  - Leaves PD-1/PD-L2 pathway intact
- Half-life ≈4 days
- >90% target occupancy<sup>2</sup>
- Dosing Q2W (10 mg/kg)<sup>2</sup>
- Induces ADCC in preclinical models<sup>3</sup>
- Antitumor activity in multiple malignancies<sup>4-9</sup>



**ADCC**, antibody-dependent cell-mediated cytotoxicity; **mAb**, monoclonal antibody; **NK**, natural killer; **Q2W**, every 2 weeks. 1. Heery CR, et al. J Clin Oncol. 2014;32(Suppl):Abstract 3064. 2. Heery CR, et al. J Clin Oncol. 2015;33(Suppl):Abstract 3055. 3. Boyerinas B, et al. Cancer Immunol Res. 2015;3(10):1148-57. 4. Gulley JL, et al. J Clin Oncol. 2015;33(Suppl):Abstract 8034. 5. Chung HC, et al. Eur J Cancer. 2015;51(Suppl S3):Abstract 2364. 6. Disis ML, et al. J Clin Oncol. 2015;33(Suppl):Abstract 5509. 7. Apolo AB, et al. J Clin Oncol. 2016;34(Suppl):Abstract 4514. 8. Disis ML, et al. J Clin Oncol. 2016;34(Suppl):Abstract 5533. 9. Larkin J, et al. Ann Oncol. 2016;27(Suppl):Abstract 775PD.

# Avelumab induces therapeutic responses in 32% of previously treated MCC patients



FDA NEWS RELEASE

**FDA approves first treatment for rare form of skin cancer**

March 23, 2017

Kaufman et al. Lancet Oncol. 2016



# Conclusions

- Oncolytic viruses are a new class of cancer therapeutics
- T-VEC was the first OV to be approved in melanoma
- Current work is supporting new combination strategies and potential biomarkers
- Surgeons were integral to both pre-clinical and clinical development of T-VEC
- Avelumab was the first FDA approved treatment for advanced MCC
- An understanding of the MCC academic community allowed for rapid subject accrual
- An understanding of the disease allowed for input into the regulatory process

The logo for Amgen, consisting of the word "AMGEN" in a bold, blue, sans-serif font.The logo for EMD Serono, consisting of the words "EMD" and "SERONO" stacked vertically in a red, sans-serif font.

## My advice for [surgical] investigators

- Be passionate
- Be persistent
- Identify your mentors early
- Spend time in other disciplines
- Focus on specific elements at dedicated times
- Collaborate
- Network
- Communicate with your chair
- Explore other avenues of support (e.g., Cancer Center)

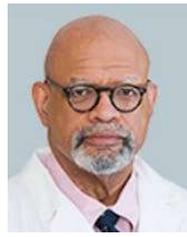
# Thanks to my (surgical)mentors



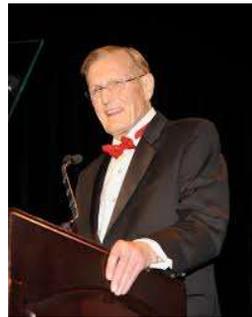
Charles Balch, Kim Lyerly, David Ota



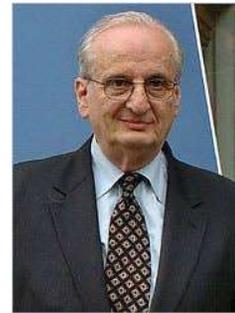
Jim Menzoian.



Mike Watkins



Don Morton.



Judah Folkman



Eric Rose



Steve Rosenberg



Franco Marincola



Mike Lotze



Mike Zenilman.



TJ Ravikumar