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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Targeting Cold Tumors with Immunotherapy: Focus on GI Malignancies

Filip Janku, MD, PhD

Associate Professor, Investigational Cancer Therapeutics
(Phase I Clinical Trials Program)

Medical Director, Clinical & Translational Research Center

Bench to Bedside & Back

Disclosures

- **Research Funding (through institution):** Agios, Asana, Astellas, Astex, Bayer, BioMed Valley Discoveries, Bristol-Myers Squibb, Cotinga, Ideaya, Deciphera, FujiFilm Pharma, Genentech, Novartis, Piqur, Plexxikon, Proximagen, Symphogen, Sotio, Sanofi, SynthoRx, SpringBank Pharma, Synlogic

- **Consulting:** Baush, Bicara, Deciphera, Guardant Health, Grail, Ideaya, IFM Therapeutics, Immunomet, Illumina, Jazz Pharmaceuticals, Novartis, Primmune Therapeutics, PureTech Health, Sotio, Synlogic, SpringBank Pharma, Tessa Therapeutics, Trovagene

- **Ownership Interests:** Trovagene

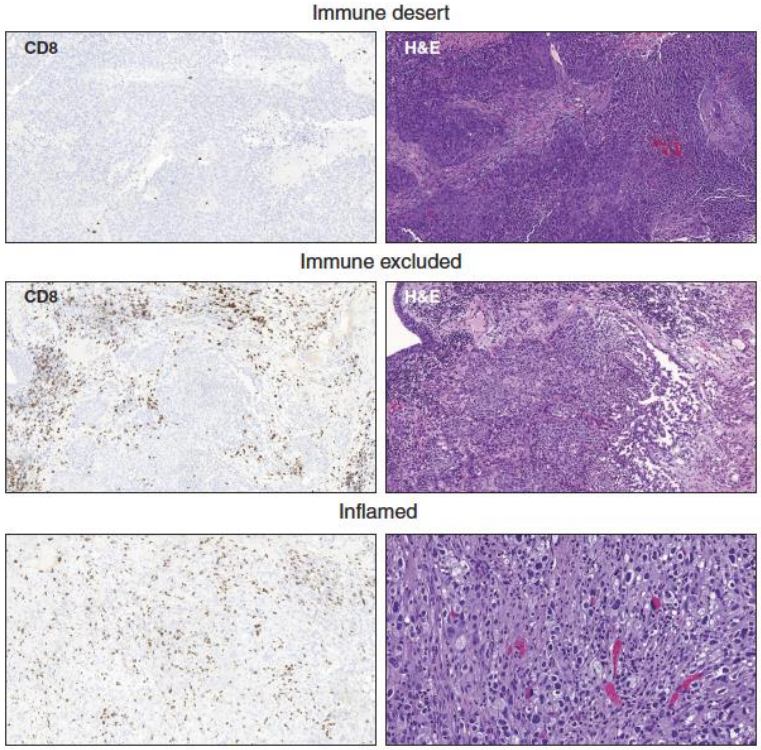
- **Other:** Bio-Rad, Biocartis

Response rates to immune checkpoint inhibitors in selected approved indications

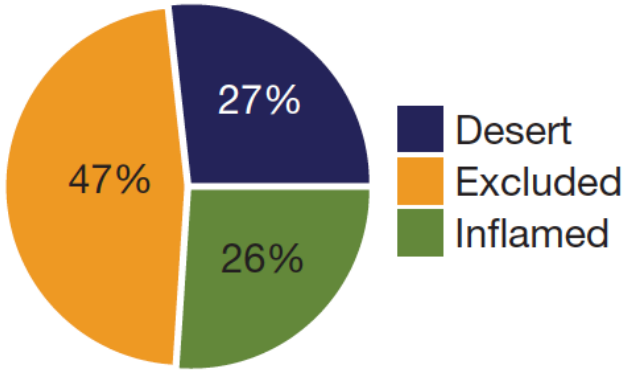
- **Melanoma**
  - Pembrolizumab: RR ~ **30%**
  - Nivolumab/ipilimumab: RR ~ **50%**
- **Non-small lung cancer**
  - Pembrolizumab: RR ~ **20%-40%**
  - Nivolumab: RR ~ **20%**
- **SCC of head and neck**
  - Pembrolizumab: RR ~ **18%**
  - Nivolumab: RR ~ **13%**
- **Urothelial cancer**
  - Pembrolizumab: RR ~ **21%**
  - Nivolumab: RR ~ **28%**
  - Atezolizumab: RR ~ **15%-26%**
- **Gastric cancer**
  - Pembrolizumab: RR ~ **10-15%**
  - Nivolumab: RR ~ **12%**
- **Colorectal cancer (unselected)**
  - Pembrolizumab: RR ~ **0-4%**
  - Nivolumab RR ~ **0%**

Robert NEJM 2015
Wolchok NEJM 2013
Garon NEJM 2015
Reck NEJM 2016
Ferris NEJM 2016
Chow J Clin Oncol 2016
Bellmunt 2017
Rosenberg 2016
Shah 2019
O'Neil 2017

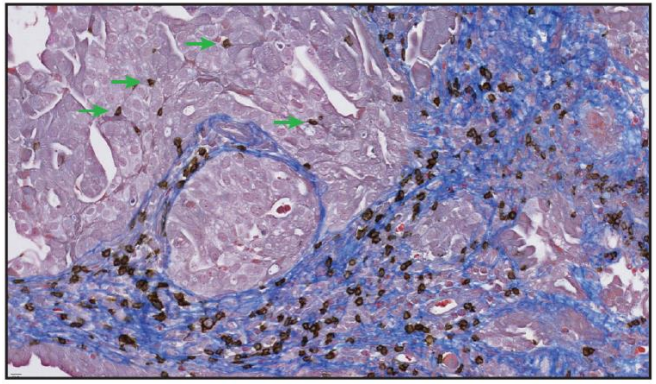
Classification by tumor immune phenotype



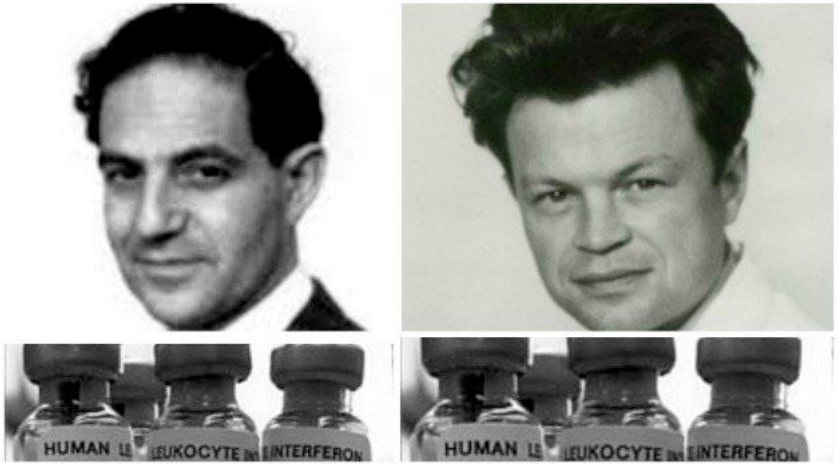
Mariathasan S. Nature 2018



Immune excluded (CD8 trichrome stain)

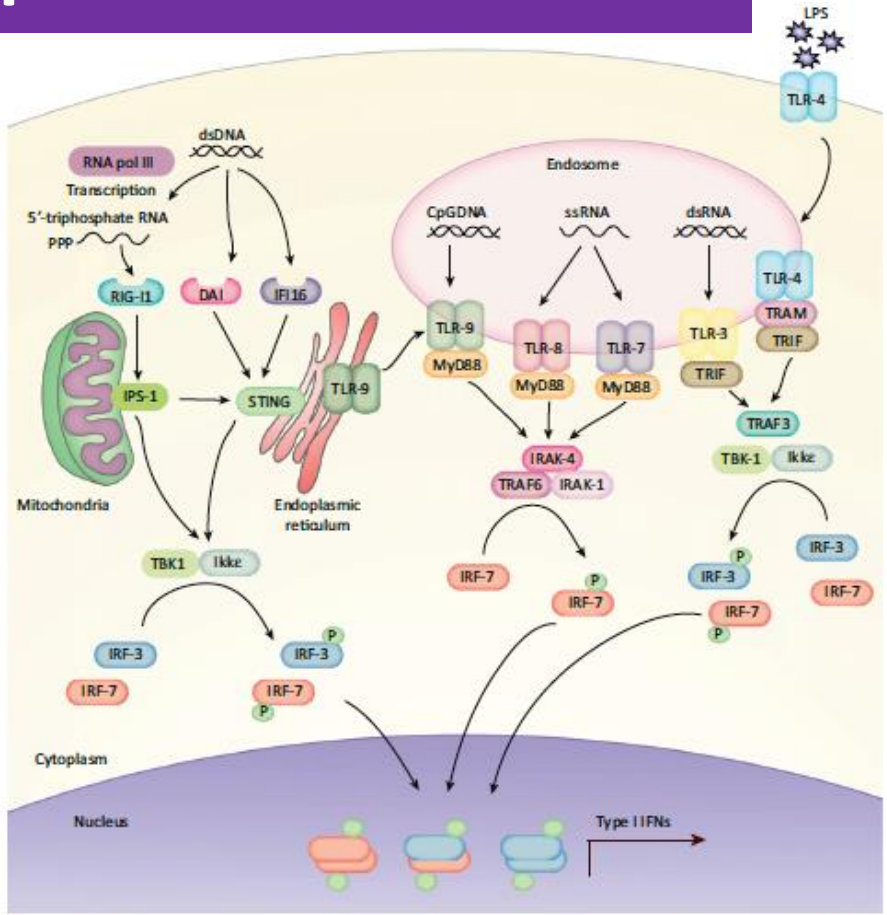


Type I Interferon Response and Cancer

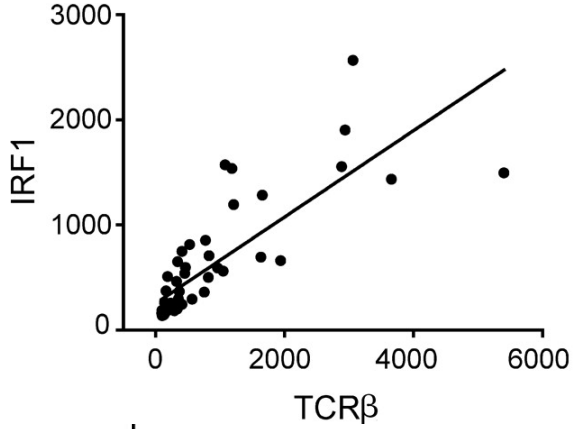


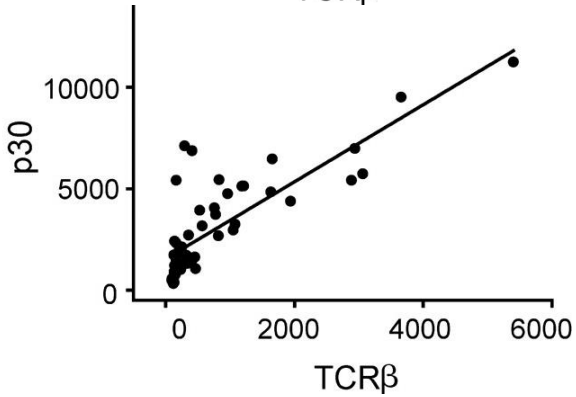
Alick Isaacs Jean Lindenmann

Isaacs, A, and Lindenmann, J. Proc Roy Soc B 1957
Fuertes MB. Trends Immunol 2013

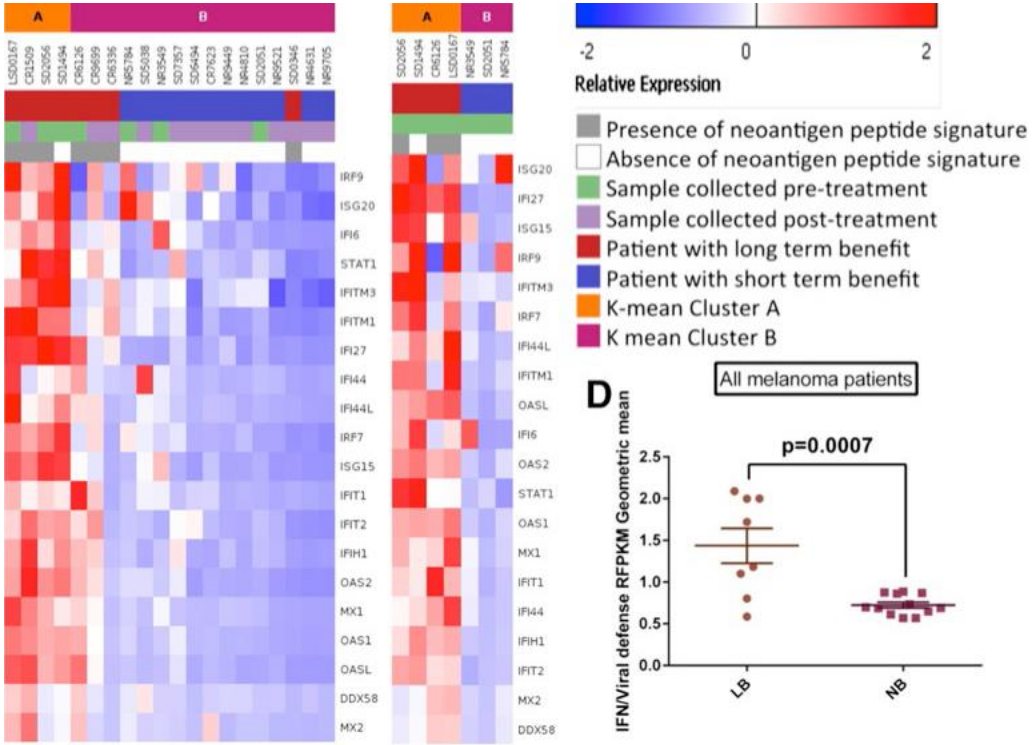


Type I Interferon Signature is Associated with benefit from Ipilimumab in Melanoma





Fuertes M.B. et al., JEM. 208:2005-16 (2011)



Chiappinelli et al., Cell 2015

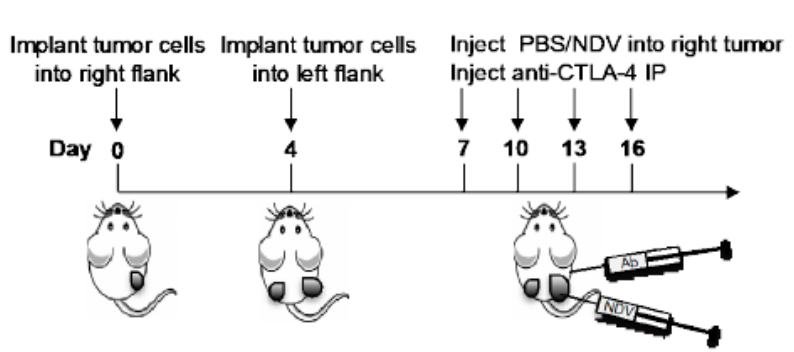
Therapeutic Strategies to Target Type I Interferon Response

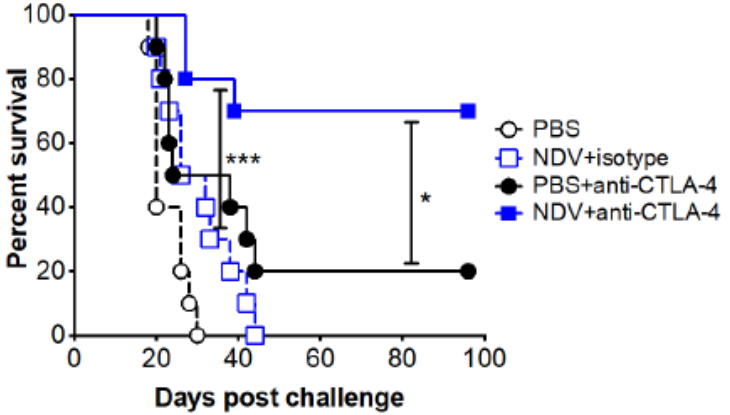
- **TLR agonists** (intratumor *and systemic*)
- **STING agonists** (intratumor *and systemic*)
- **Inflammasome stimulating agents** (intratumor)
- **Viruses** (intratumor)
- **Bacteria** (intratumor)
- **Engineered viruses** and **bacteria** (intratumor *and systemic*)

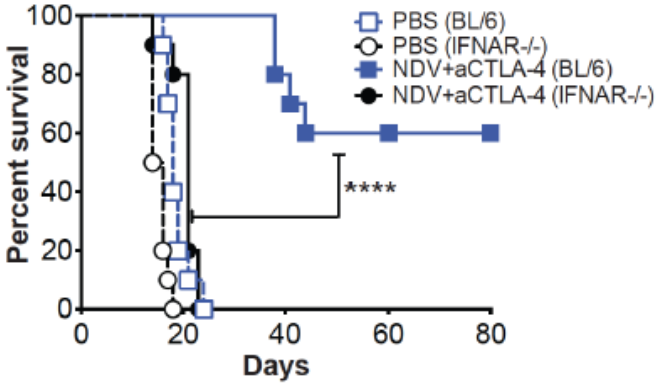
Type I Interferon Induced by Intratumor Oncolytic Virus Administration Can Overcome Resistance to Checkpoint Inhibitors

Newcastle Disease Virus (NDV):

- Replicates at injected site
- Delays tumor growth of local and distant tumors
- Increases local and distant tumor lymphocyte infiltration
- Increase expansion of tumor-specific lymphocytes
- Synergizes with ipilimumab

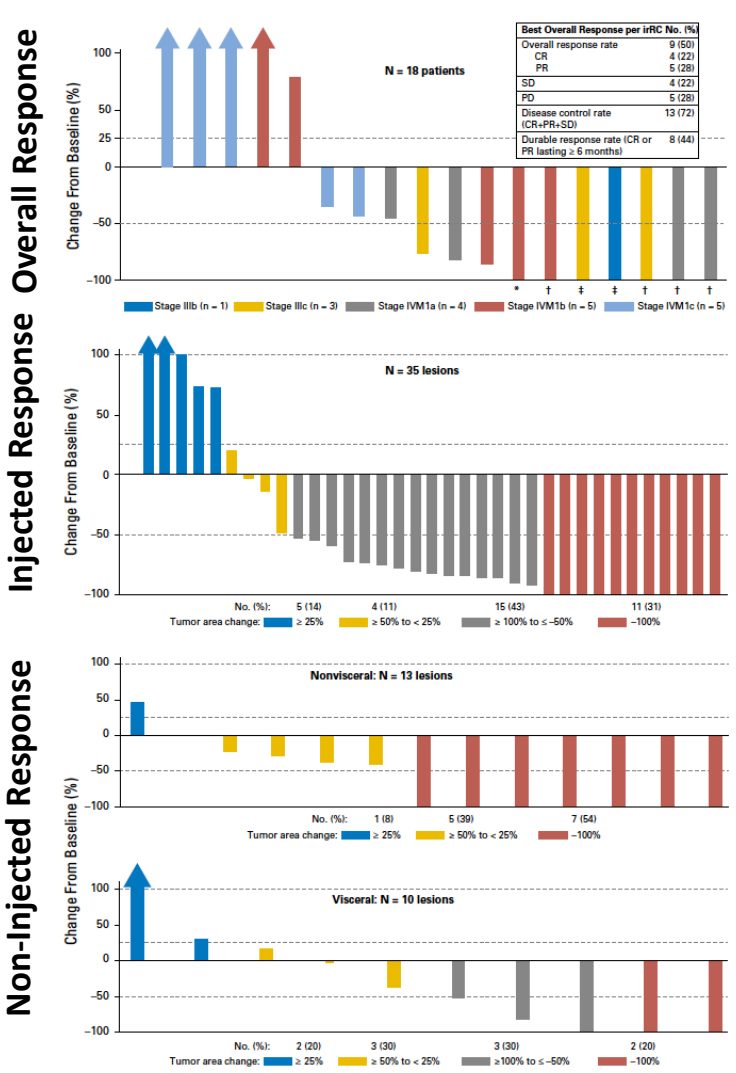


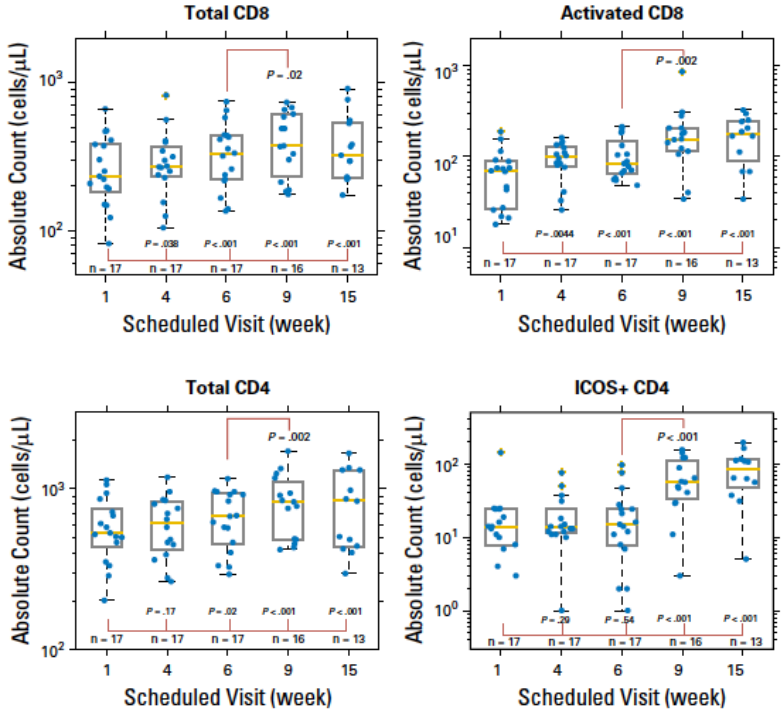




Zamarin et al., Sci Transl Med 2014

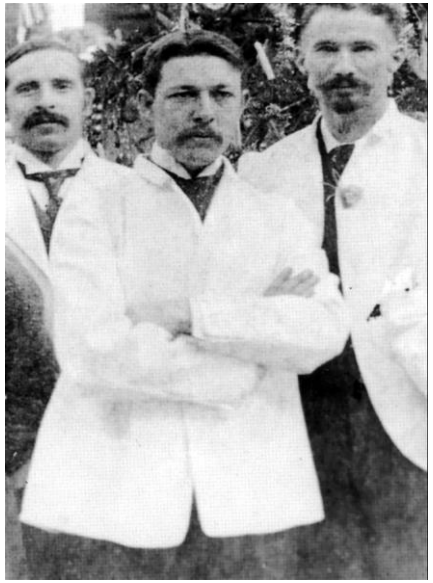
Talimogene Laherparepvec (T-VEC) in Combination with Ipilimumab in Untreated Advanced Melanoma





Puzanov, J Clin Oncol 2016

Treating Cancer with Bacteria



- Post-surgical infections can help to control cancer by inducing immune response
- Injection of *Streptococcus pyogenes* (Coley's Toxin) can induce anticancer response

W. B. Coley, The treatment of inoperable sarcoma by bacterial toxins (the mixed toxins of the Streptococcus erysipelas and the Bacillus prodigiosus). Proc. R. Soc. Med. 3, 1–48 (1910)

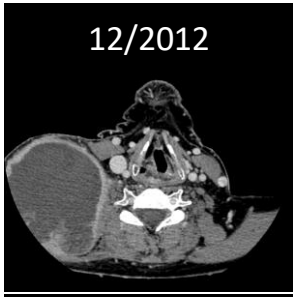
Spontaneous Regression of the Supraclavicular and Abdominal Wall Recurrence in a Patient with Malignant Peripheral Nerve Sheet Tumor

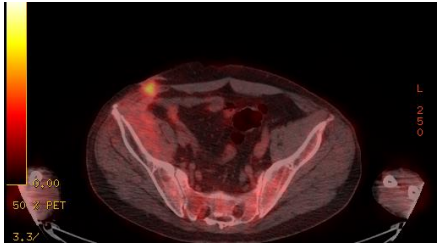
1/2013: prolonged neutropenia (after pemetrexed and crizotinib), infection (enterococcus and staph) and sepsis requiring 5 weeks of hospitalization

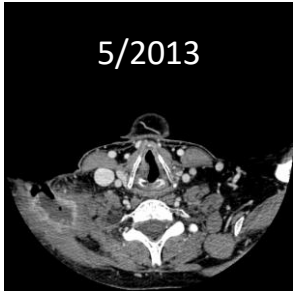
4/2013: tumor mass fell off and the patient presents with open wound and visible muscles

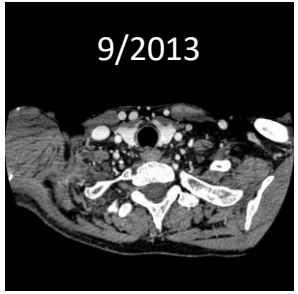
5/2013: surgical resection and debridement with no residual tumor

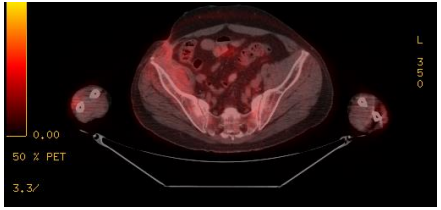
9/2013: imaging shows no evidence of disease





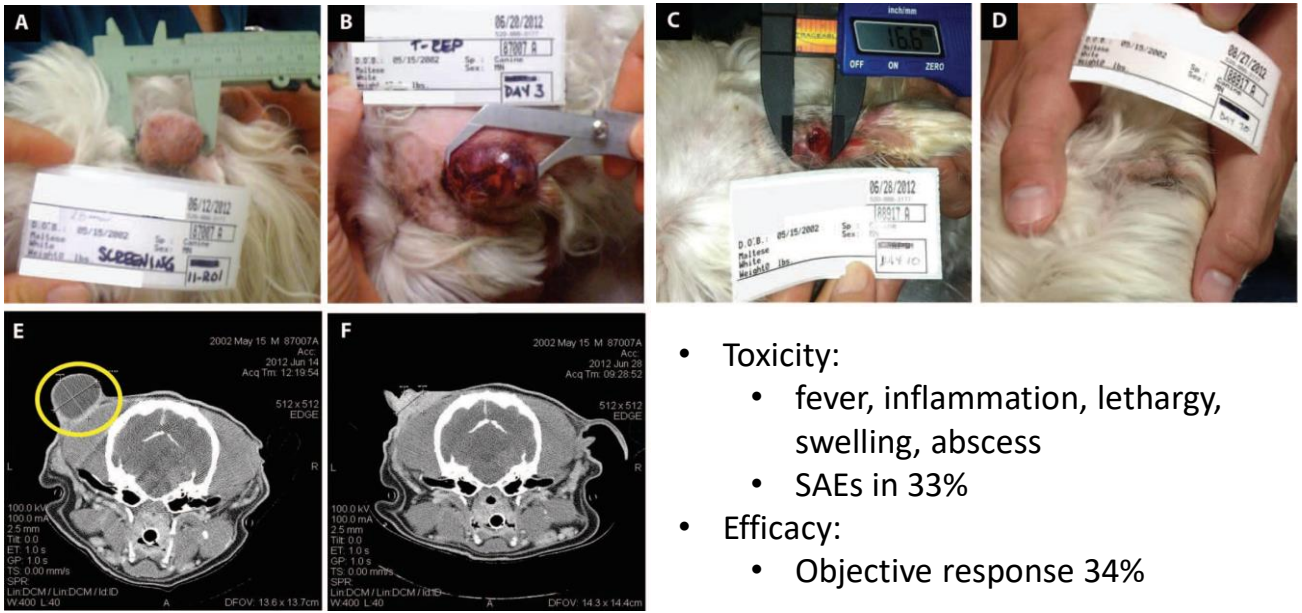






Dose Escalation with Intratumor Injection of *Clostridium novyi-NT* Study in Dogs with Spontaneous Tumors

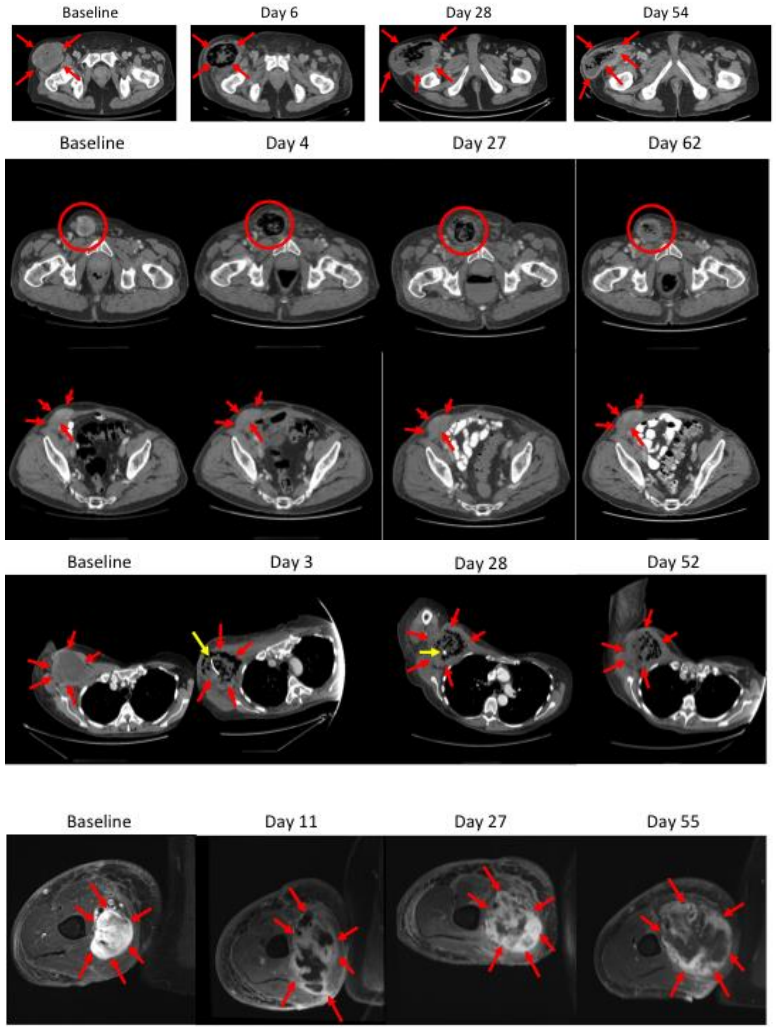
- Multicenter study (n=66), 4 dose levels
- 1-8 cycles of *Clostridium novyi-NT* administered
- At least 1 week between cycles



- Toxicity:
  - fever, inflammation, lethargy, swelling, abscess
  - SAEs in 33%
- Efficacy:
  - Objective response 34%

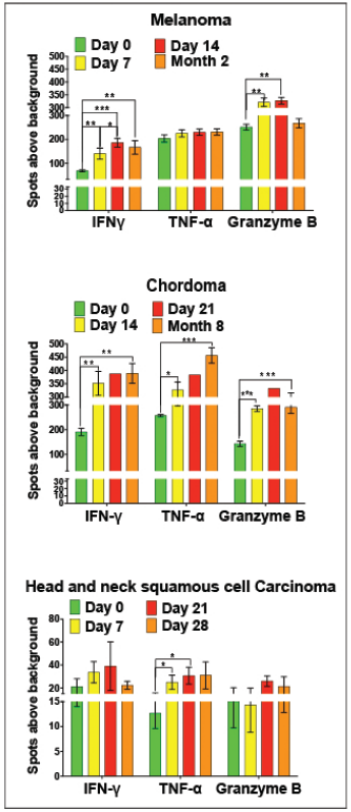
Roberts, Zhang, Janku. Sci Transl Med 2014

Anticancer activity of single intratumor injection of *Clostridium Novyi-NT* in advanced cancers

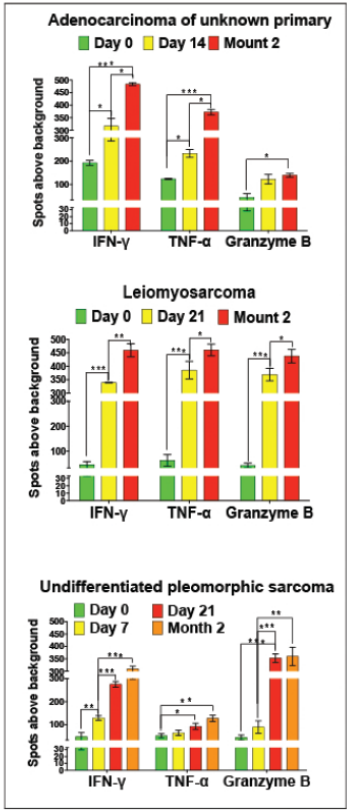


PBMCs

D. "+" cytokine response
"No" Clinical germination



E. "+" cytokine response
"+" Clinical germination

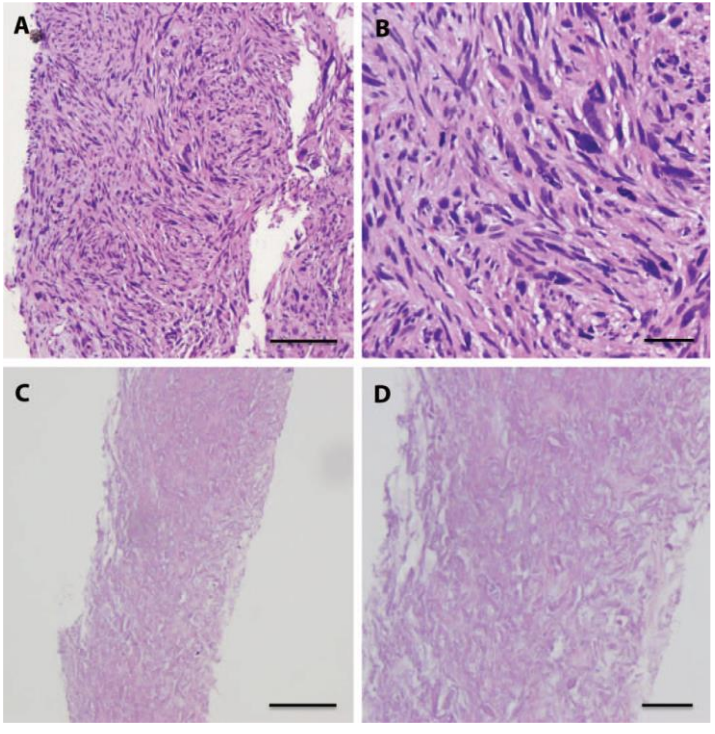


Janku CRI-CMIT-EATI-AACR 2018 & submitted

Phase I Clinical Study of Intratumoral Injection of *Clostridium novyi*-NT Spores in Patients with Advanced Cancer

53-year-old female with leiomyosarcoma treated at dose level 1

Extensive tumor necrosis after treatment with *C. novyi-NT* spores

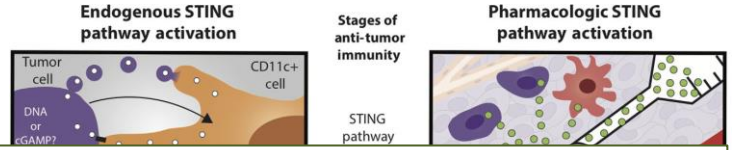


A and B: Pretreatment tumor biopsy showing viable tumor

C and D: Posttreatment tumor biopsy, 4 days after intratumoral injection of *C. novyi-NT* spores, showing extensive necrosis of tumor cells

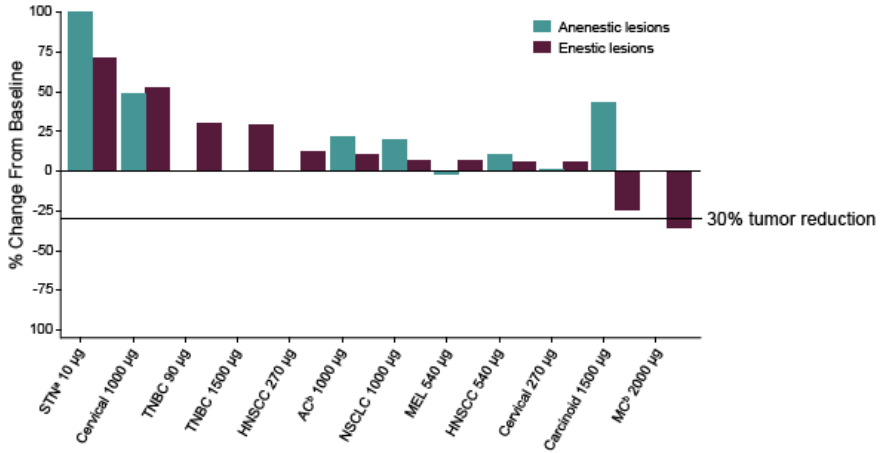
Roberts, Zhang, Janku. Sci Transl Med 2014

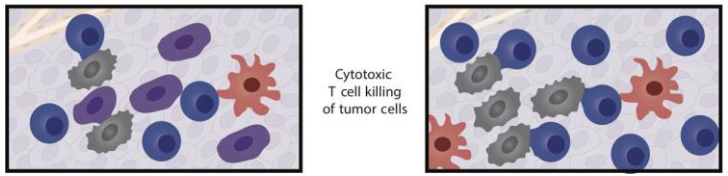
Intratumor STING agonist MK-1454 +/- pembrolizumab



MK-1454 single agent

Maximum change in %

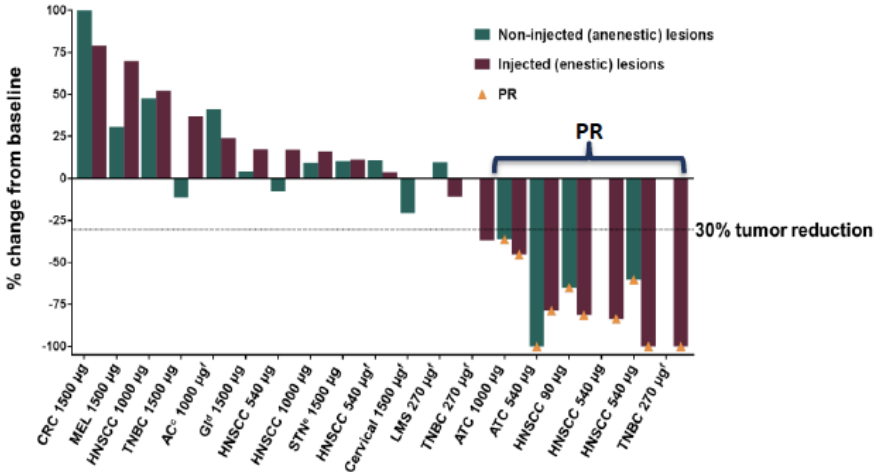




Flood et al. *Immunological Reviews.* 2019;290:24–38.

MK-1454 + pembrolizumab

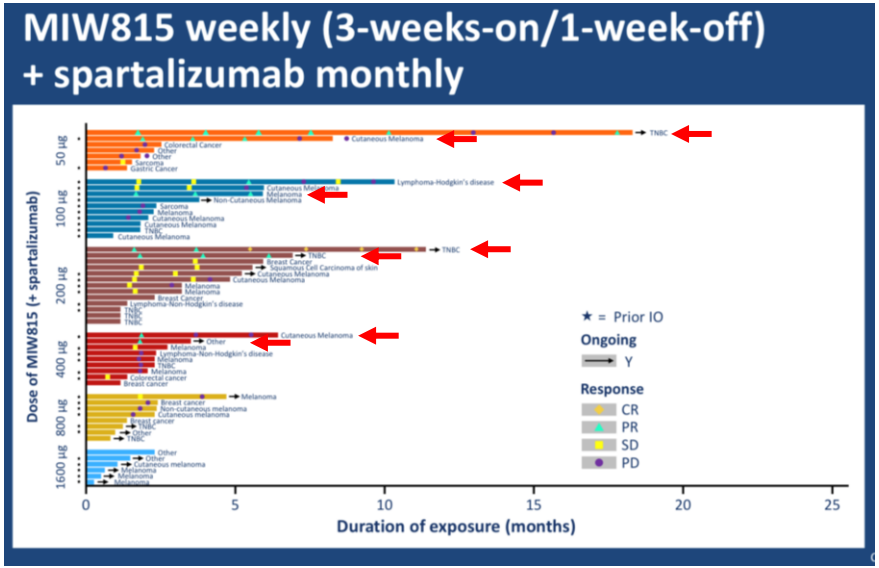
Maximum change from baseline in lesions[b]

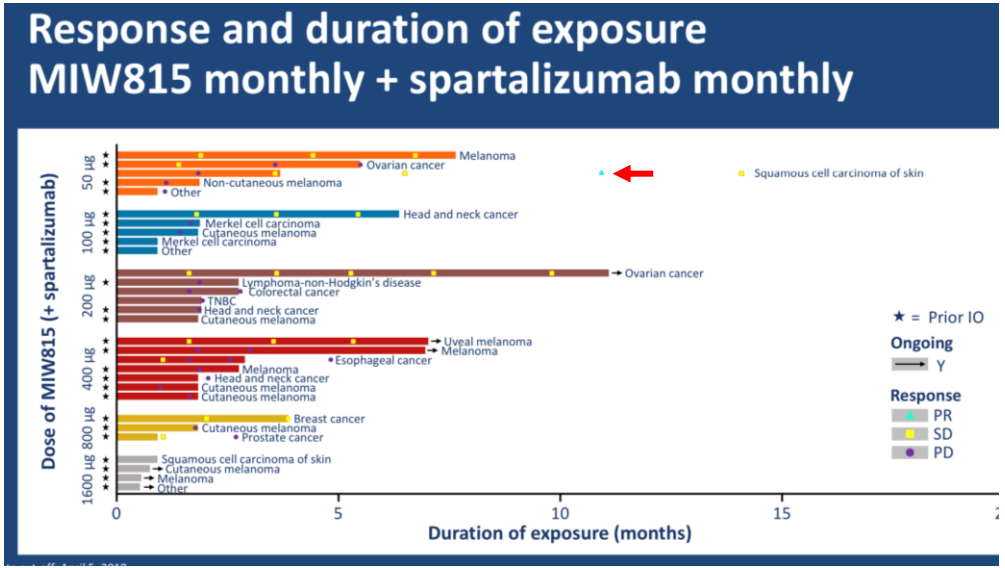


- **Median 83% reduction in size of target lesions for responders**

Harrington ESMO 2018

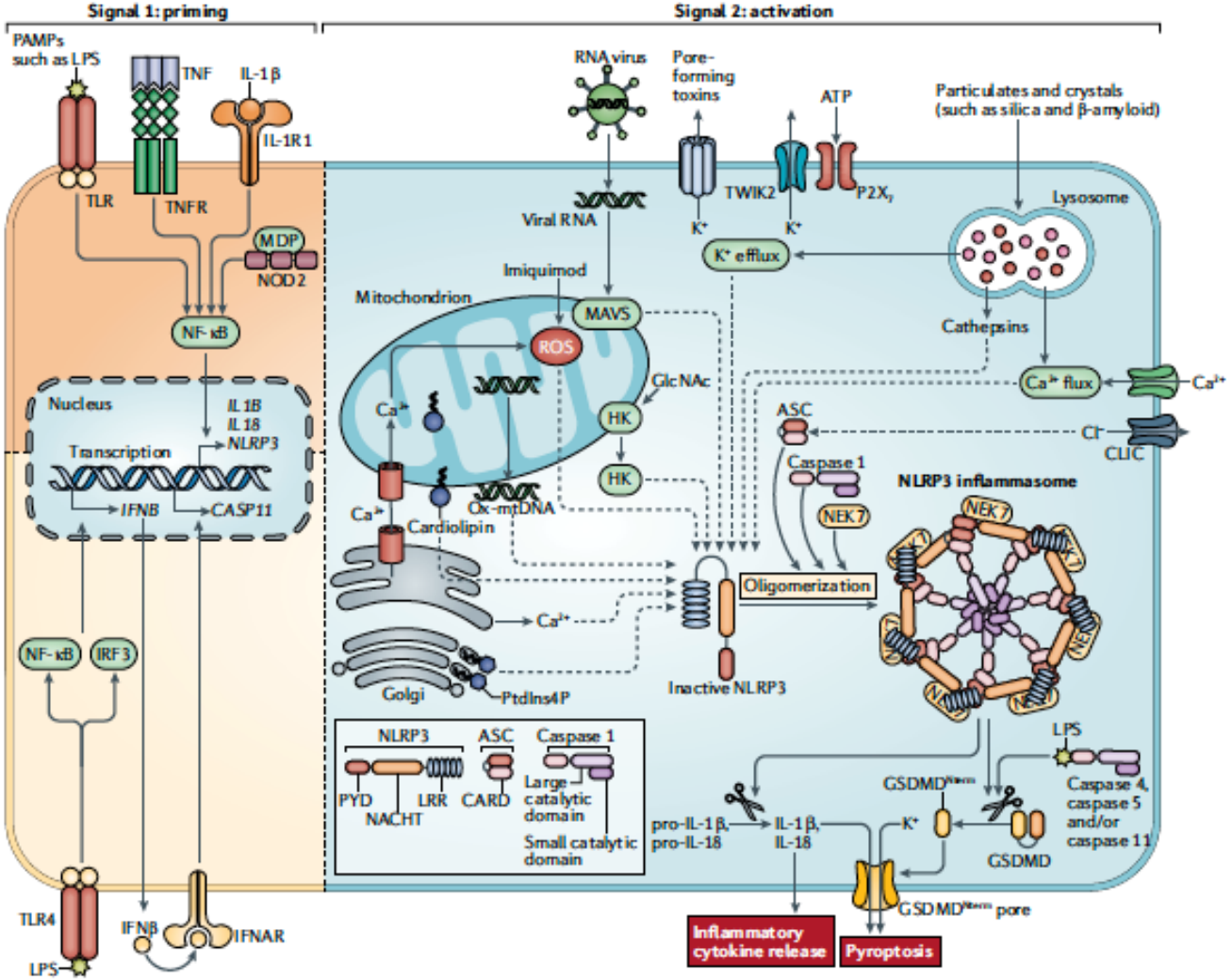
Phase I Dose-Finding Study of MIW815 (ADU-S100), an Intratumoral STING Agonist, and Spartalizumab in Patients With Advanced Solid Tumors or Lymphomas





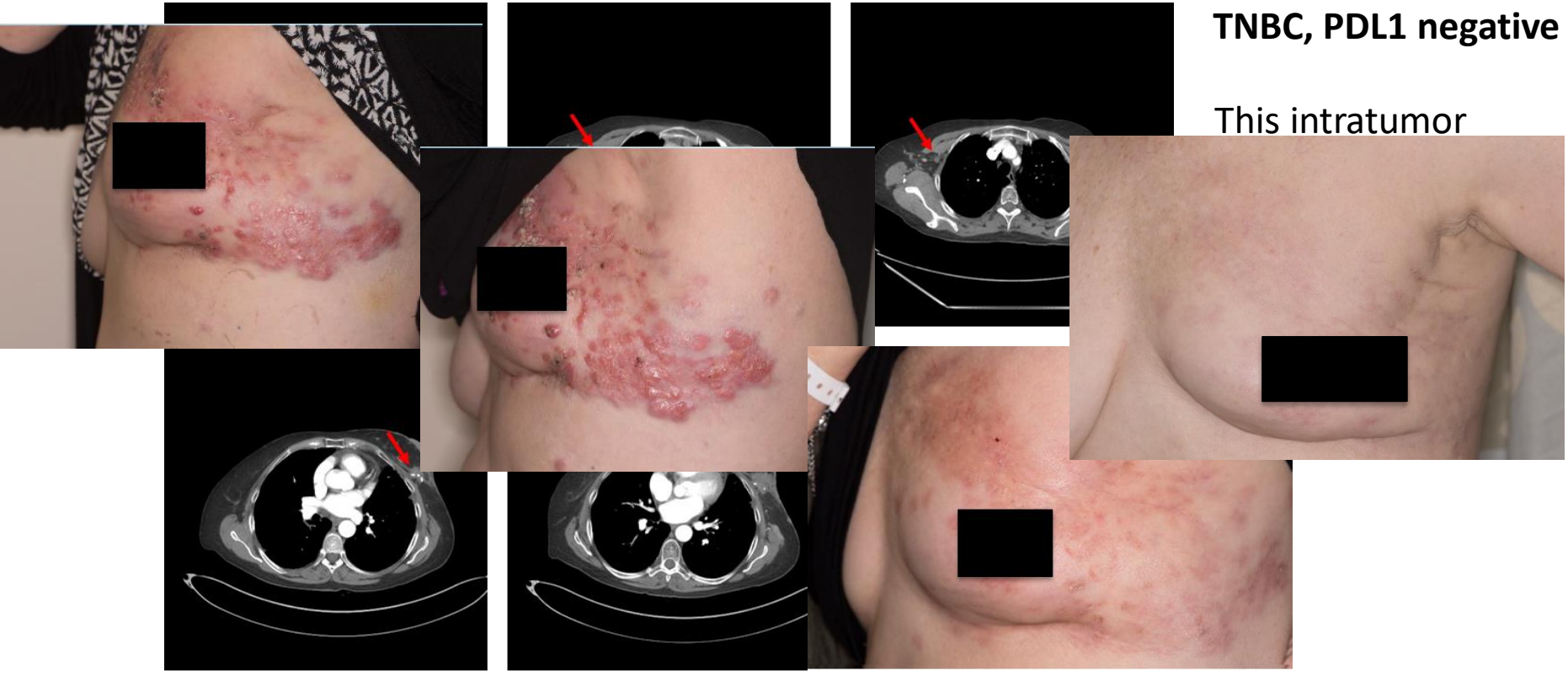
Meric-Bernstam F, Luke J. ASCO 2019

Targeting Inflammasome with NLRP3 agonists



Swanson Nat Rev Immunol 2019

Intratumor targeting of inflammasome +/- checkpoint inhibitors



TNBC, PDL1 negative

This intratumor

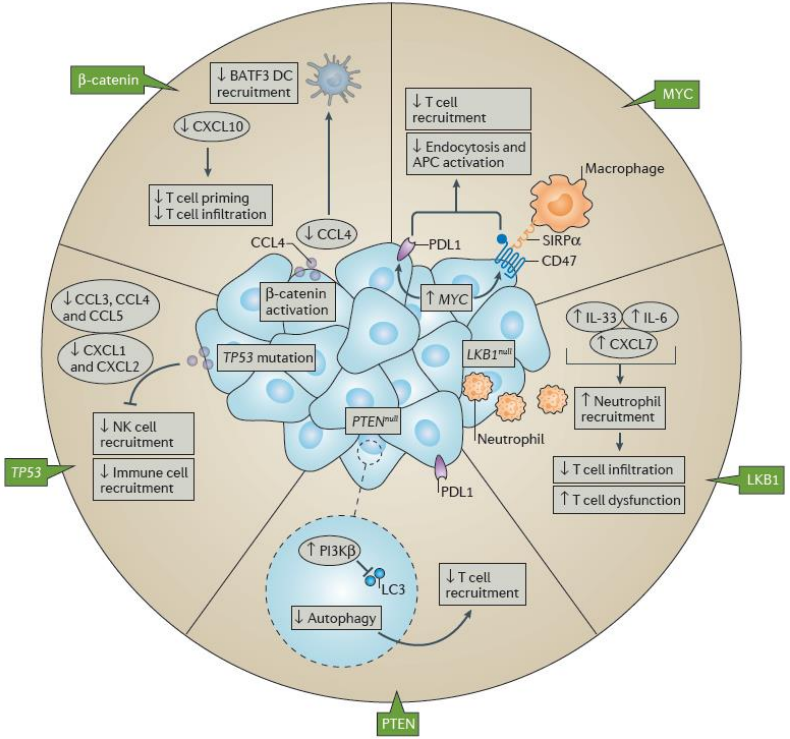
DO NOT POST

Intratumor therapies: challenges

- **Factors limiting intratumor delivery**
  - Needle device: single vs. multipronged device
  - Medication volume vs. tumor size/volume
  - Intratumor pressure
- **Intratumor PK**
- **Intratumor PD**

Targeted therapy and the immune response

- Response to immunotherapy has been linked to recruitment of CD8$^+$ T-cells to the tumor microenvironment[1]
- In addition to their roles in signaling and cell growth, some oncogenic pathways, including Wnt/β-catenin, also have immune modulatory effects[2]
  - Therapies targeting these pathways may be effective in priming tumors for immunotherapy



1. Tumeh PC, et al. Nature 2014;515:568–571;
2. Spranger S & Gajewski TF. Nat Rev Cancer 2018;18:139–147.

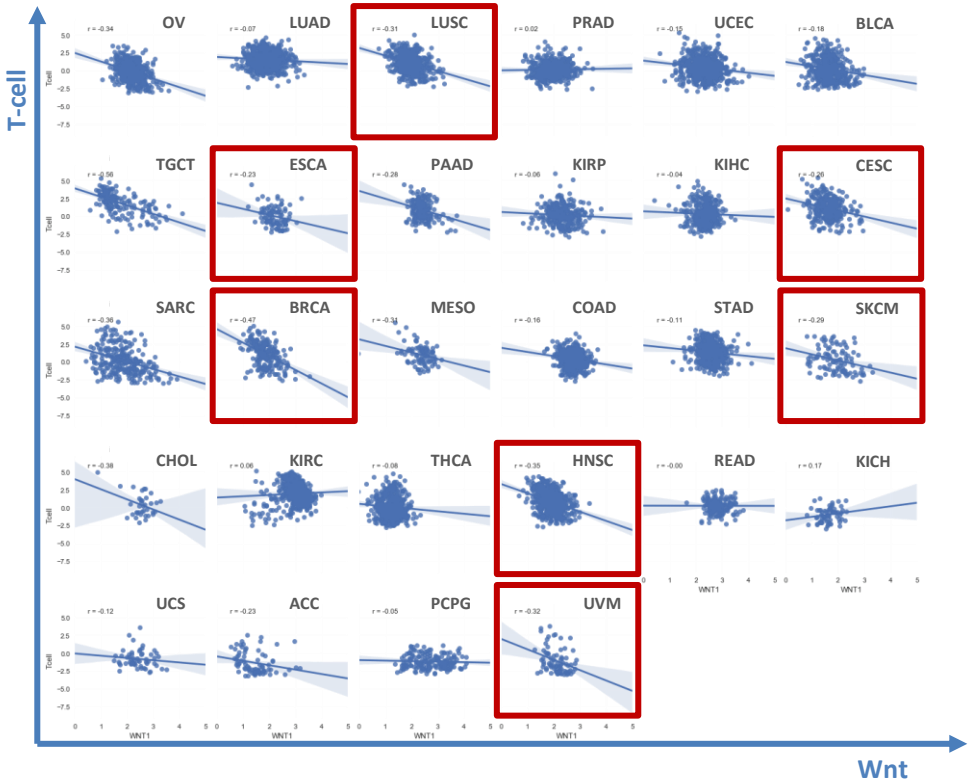
Figure reproduced with permission from Springer Nature;
Spranger S & Gajewski TF. Nat Rev Cancer 2018;18:139–147, © 2018.

Rodon J. AACR 2017

Inverse association between Wnt signature and T-cell signature

- TCGA samples (untreated) were examined for an association between Wnt/β-catenin gene signature and T-cell signature
- An inverse association was seen in melanoma, squamous cell cancers, and basal-like breast cancers

WNT signature[1]	T-cell signature	
EFNB3	CD8A	CD3D
APC2	CD8B	CD3E
HNF1A	PYHIN1	CD3G
MYC	TRAT1	CD247
TCF12	GZMK	CD2
VEGFA	SH2D1A	SIRPG
	CXCR6	



1. Spranger S, et al. Nature 2015;523:231–235.

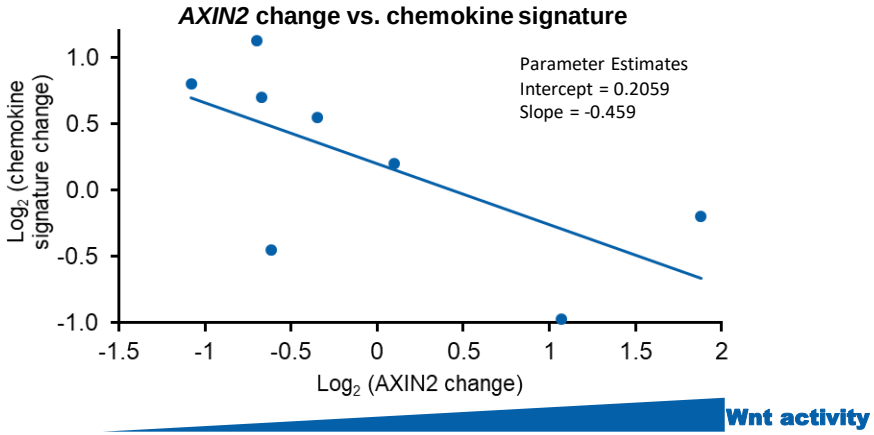
BRCA, basal-like breast cancer; CESC, cervical squamous cell cancer; ESCA, esophageal squamous cell cancer; HNSC, head and neck squamous cell cancer; LUSC, lung squamous cell cancer; SKCM, cutaneous melanoma; UVM, uveal melanoma.

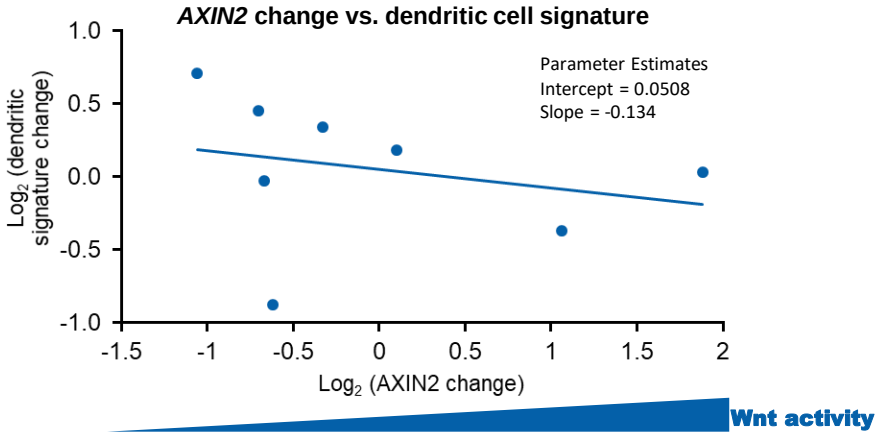
Rodon J. AACR 2017

Targeting Wnt in the Clinic with LGK974: Association between *AXIN2* change and immune signature change

- Tumor samples (n=8) were analysed pre- and on-treatment to assess changes in *AXIN2* expression and in immune signature
- An inverse association was seen between the *AXIN2* change and the change in:
  - Chemokine signature; dendritic cell signature

Chemokine signature[1]		Dendritic cell signature[2]		
CCL2	CCL5	BATF3	CCR5	CXCL1
CCL3	CXCL9	ITGAE	CCL3	
CCL4	CXCL10	IRF8	CCL4	

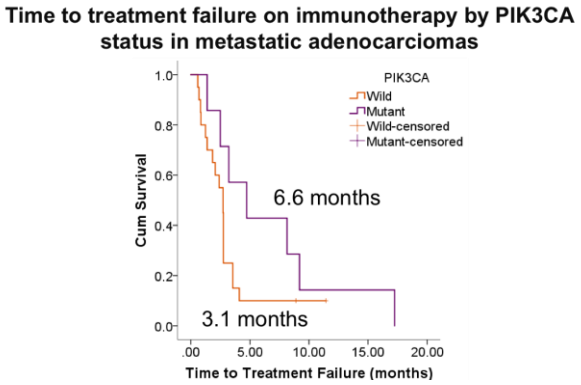


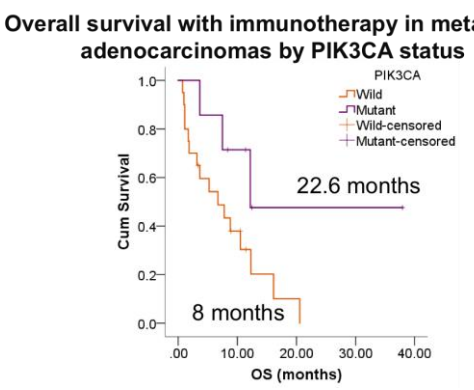


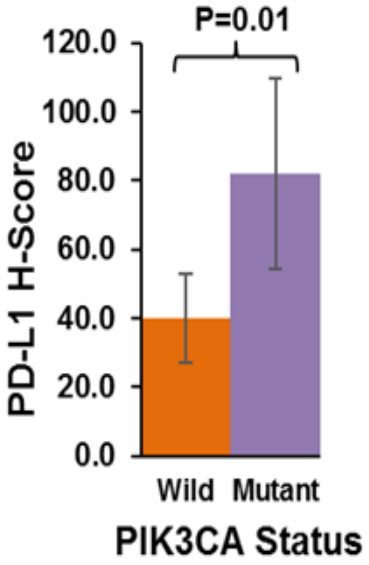
1. Harlin H, et al. Cancer Res 2009;69:3077–3085;
2. Spranger S, et al. Nature 2015;523:231–235.

Rodon J. AACR 2017

Targeting PD1/PDL1 in MSS Colorectal Cancers and Solid Tumors with *PIK3CA* mutations (N=27)







- Patients with PIK3CA mutations with prolonged disease control (SD ≥ 6 months had higher mean CD8 density than patients with SD < 6 months (630.3 vs 305.1 cells/mm3; p=0.06).

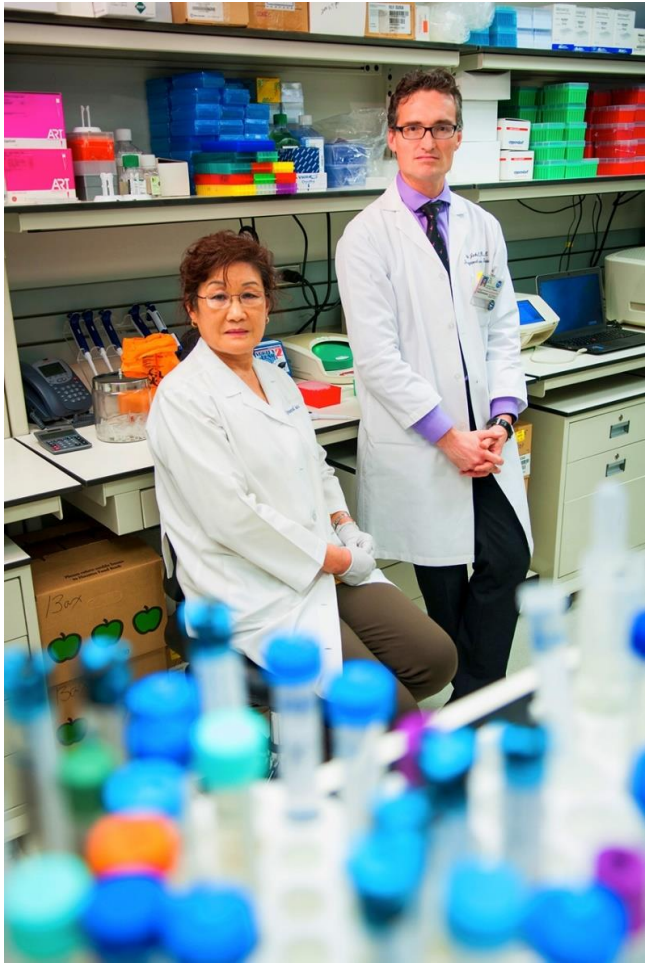
Nusrat, Tapia, Kopetz, Janku

DO NOT POST

Conclusions

- Immunotherapy with immune checkpoint inhibitors can be effective only in subsets of patients with MSI-high cancers , melanoma, lung cancer and other tumor types, while for many common cancers including breast, prostate, ovarian, MSS colorectal and sarcomas there is unmet need for novel immunotherapeutic approaches

- Turning cold tumors into hot with intratumor activators of innate immunity through the type I interferon response offers a new promising approach to increase efficacy of cancer immunotherapy



fjanku@mdanderson.org

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- Dr. Shubham Pant

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ICT Lab and Team Janku

- **Anjali Raina**
- **Dr. Abha Adat**
- **Dr. Kiran Madwani**
- **Thorunn Helgason**
- **Dr. Greg Call**

Intervention Radiology

- **Dr. Ravi Murthy**
- Dr. Steven Huang
- Dr. Rahul Seth

Division of Cancer Medicine

- Dr. Patrick Hwu
- Dr. Waun Ki Hong

GI, Melanoma Oncology

- Dr. Scott Kopetz
- Dr. Sapna Patel
- Dr. Husein Tawbi
- Dr. Michael Davies

Translational Pathology

- **Dr. Coya Tapia**

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