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Targeting Cancer with Intratumor Immunotherapy

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Investigational Cancer Therapeutics
(Phase I Clinical Trials Program)



Disclosures

- **Research Funding:** Agios, Asana, Astellas, Astex, Bayer, BioMed Valley Discoveries, Bristol-Myers Squibb, Deciphera, FujiFilm Pharma, Genentech, Novartis, Piquor, Plexxikon, Proximagen, Symphogen
- **Consulting/Advisory Boards:** Deciphera, Guardant Health, Grail, IFM Therapeutics, Immunomet, Illumina, Novartis, PureTech Health, Sotio, Synlogic, Trovogene, Bausch Health (Valeant)
- **Ownership Interests:** Trovogene
- **Other:** Bio-Rad, Biocartis

Response rates to checkpoint inhibitors in 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%**

Robert NEJM 2015

Wolchok NEJM 2013

Garon NEJM 2015

Reck NEJM 2016

Ferris NEJM 2016

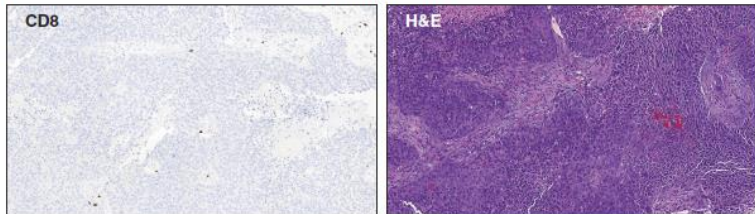
Chow J Clin Oncol 2016

Bellmunt 2017

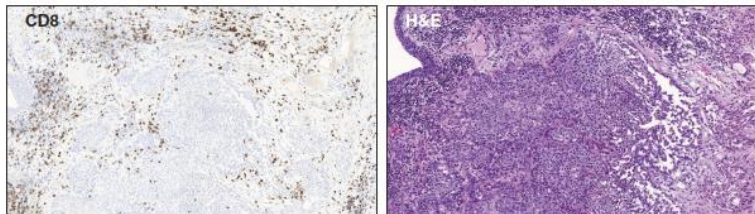
Rosenberg 2016

Classification by tumor immune phenotype in urothelial cancers

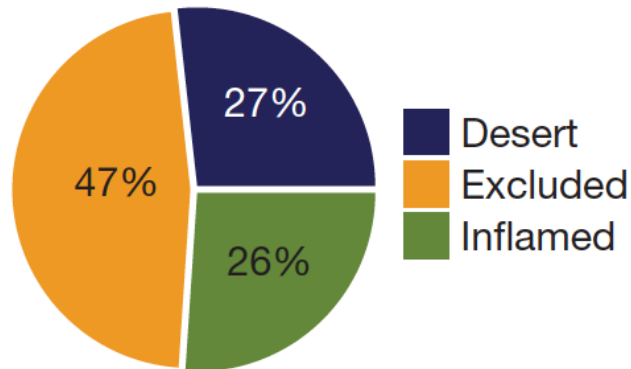
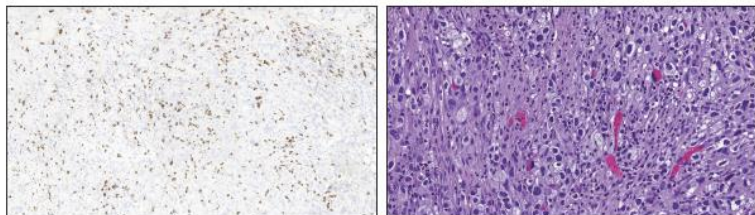
Immune desert



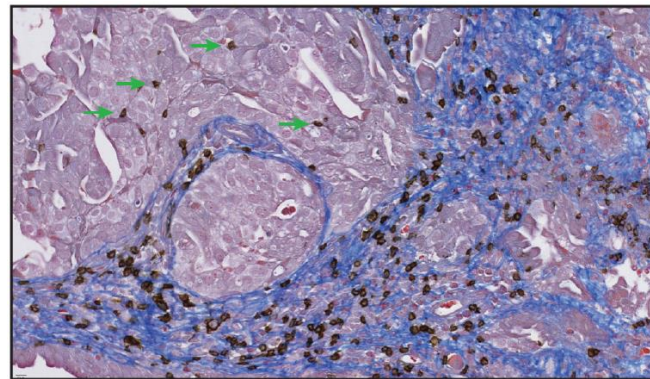
Immune excluded



Inflamed



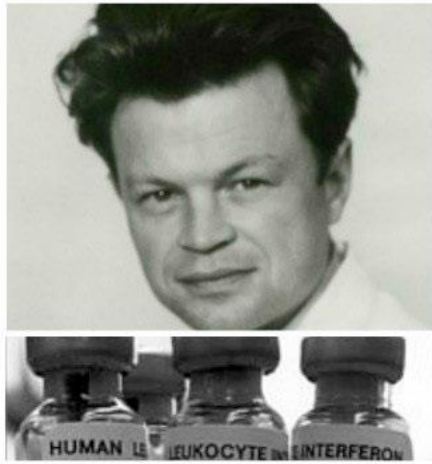
Immune excluded (CD8 trichrome stain)



Therapeutic Strategies to Target Type I Interferon Response



Alick Isaacs



Jean Lindenmann

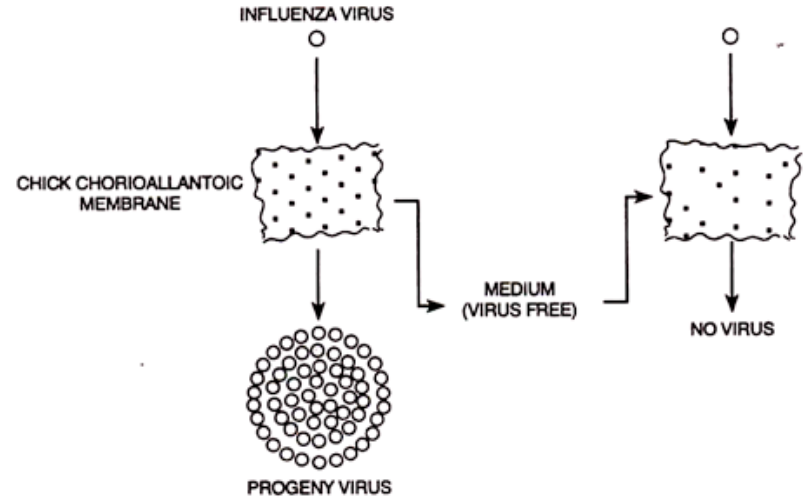
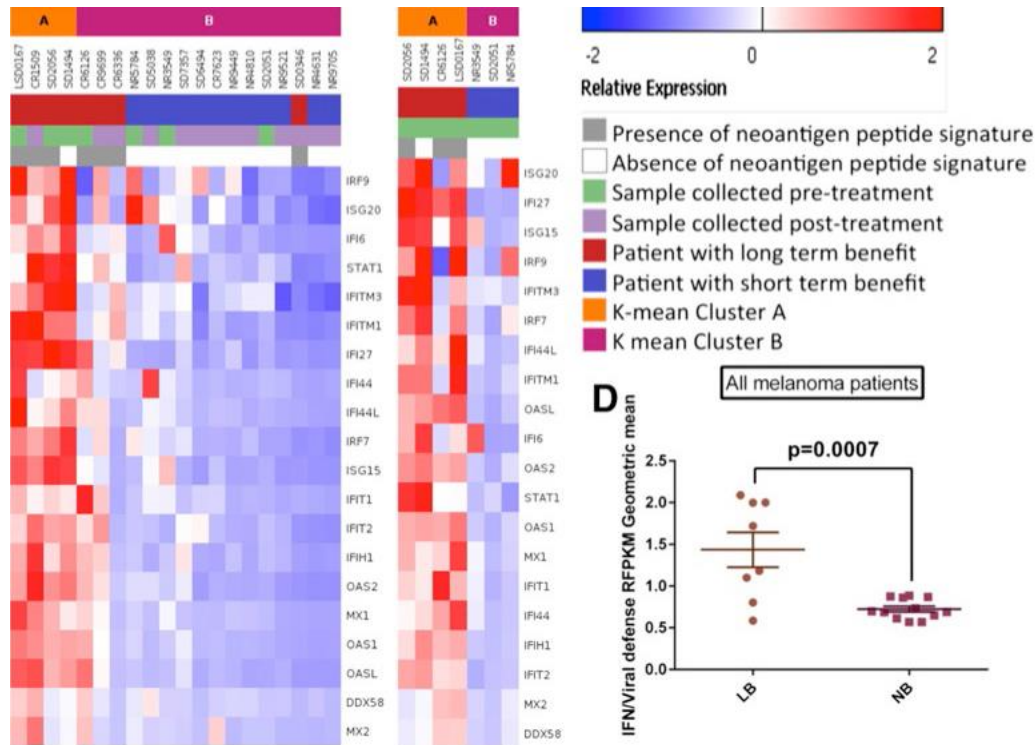
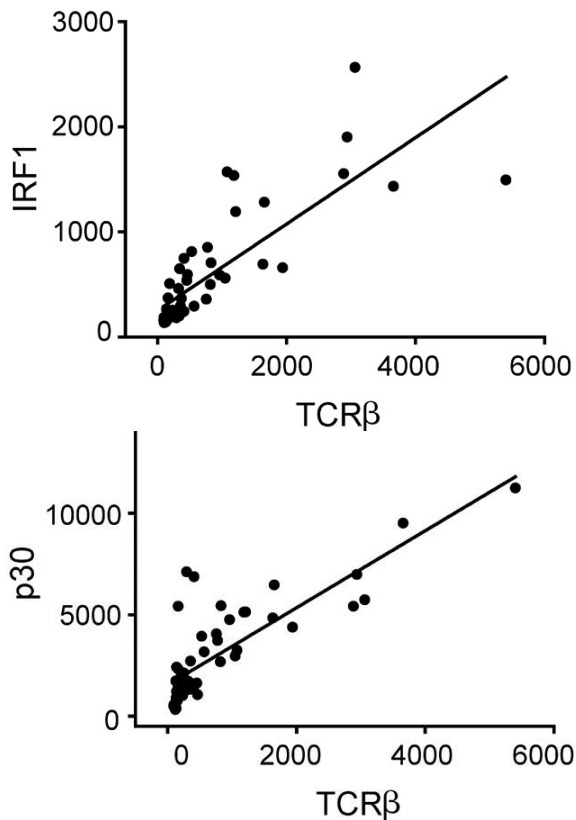


FIG. 11.14. Discovery experiment.

Isaacs, A., and Lindenmann, J., Proc. Roy. Soc., B, 147, 258 (1957)

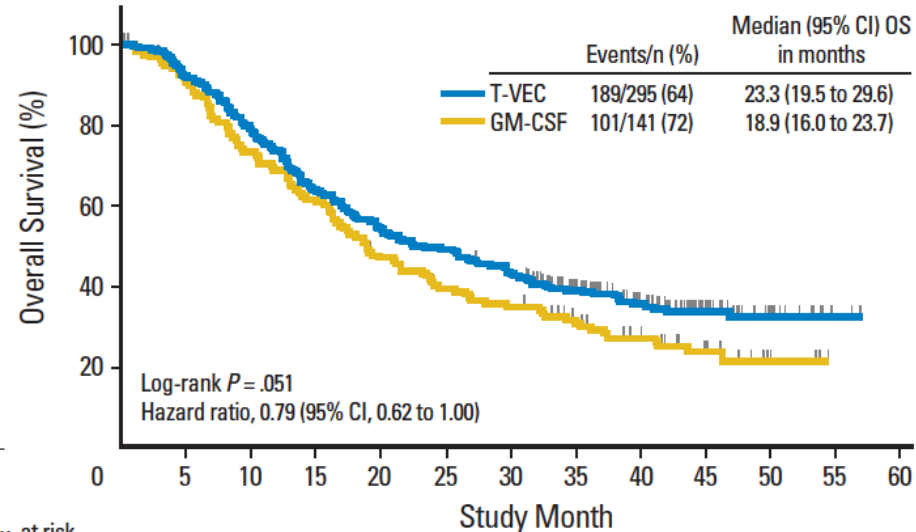
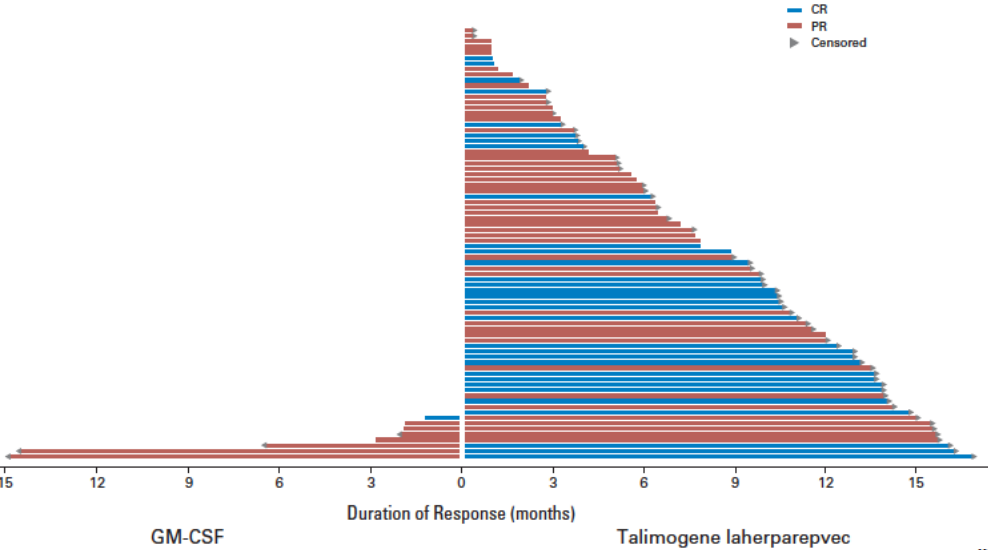
Type I Interferon Signature is Associated with benefit from Ipilimumab in Melanoma



Therapeutic Strategies to Target Type I Interferon Response

- **TLR agonists** (intratumor *and systemic*)
- **STING agonists** (intratumor *and systemic*)
- **NLRP3 agonists** (intratumor)
- **Viruses** (intratumor)
- **Bacteria** (intratumor)
- **Engineered viruses and bacteria** (intratumor *and systemic*)

Intratumor Talimogene Laherparepvec (T-VEC) vs. GM-CSF in Advanced Melanoma



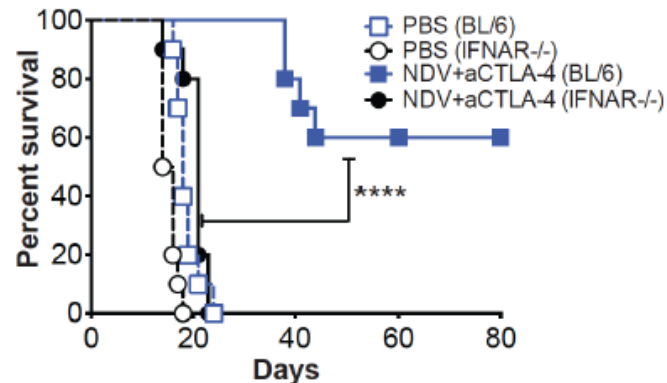
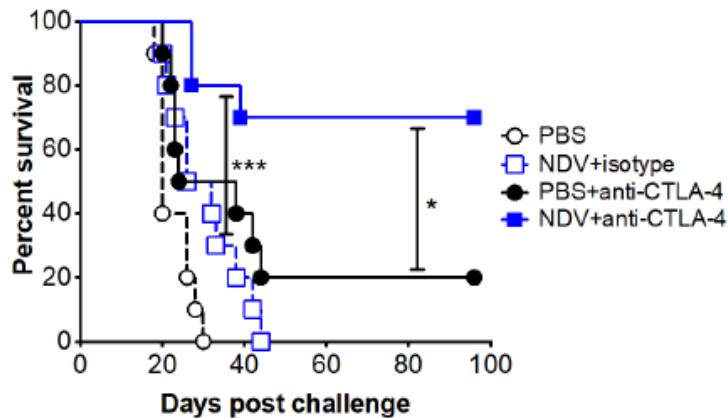
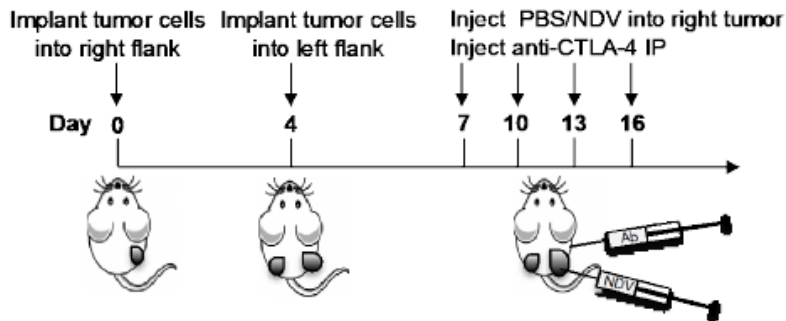
no. at risk												
GM-CSF	141	124	100	83	63	52	46	36	27	15	5	
T-VEC	295	269	230	187	159	145	125	95	66	36	16	2

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

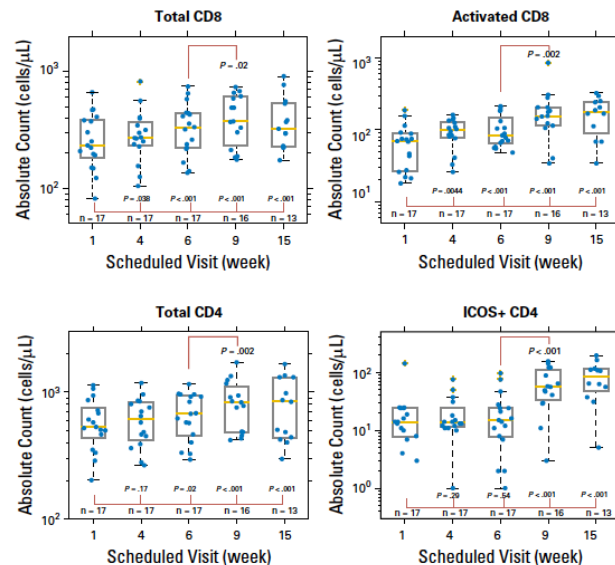
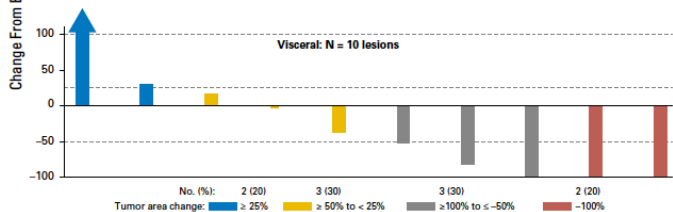
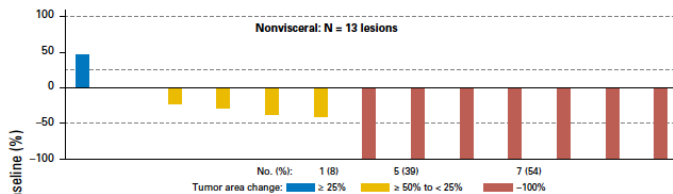
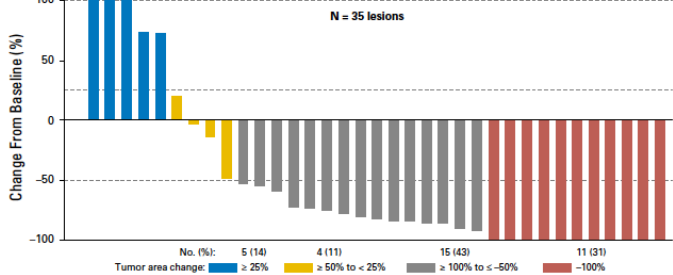
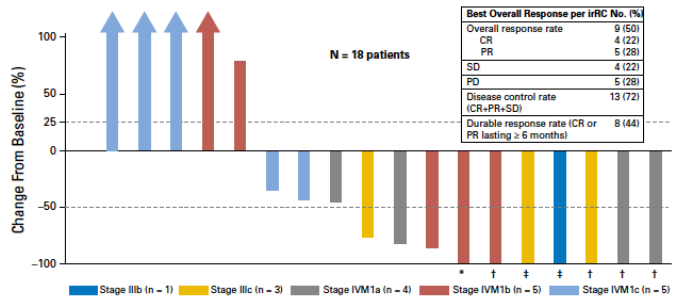
Newcastle Disease Virus (NDV):

- 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

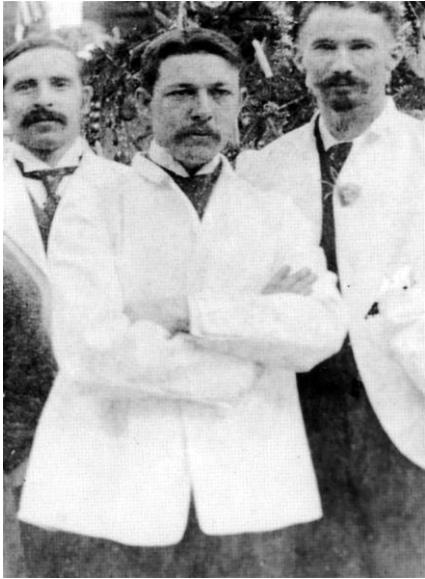
a.



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



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)

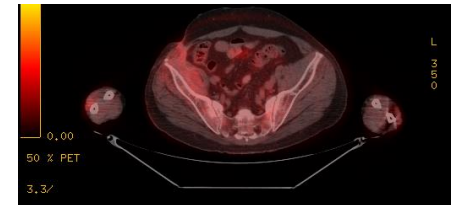
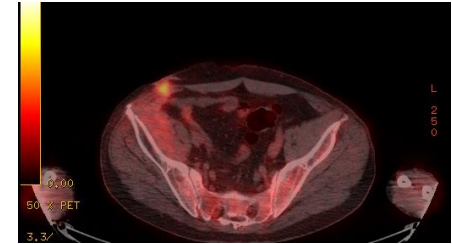
Spontaneous Regression of the Supraclavicular and Abdominal Wall Recurrence in a Patient with Malignant Peripheral Nerve Sheet Tumor

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



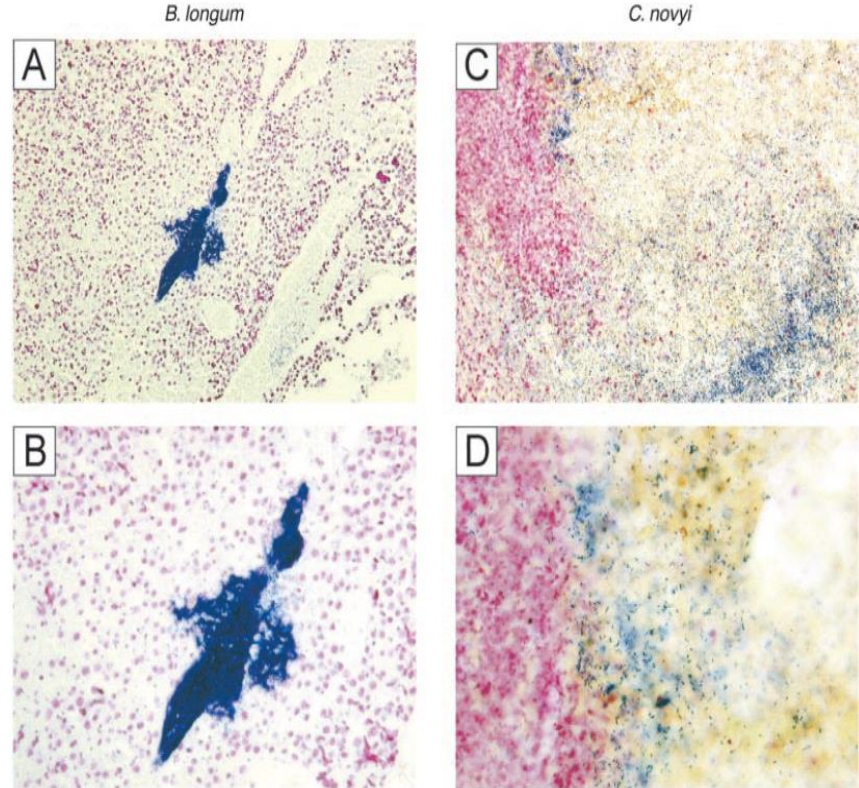
Combination bacteriolytic therapy for the treatment of experimental tumors

Long H. Dang, Chetan Bettegowda, David L. Huso, Kenneth W. Kinzler, and Bert Vogelstein*

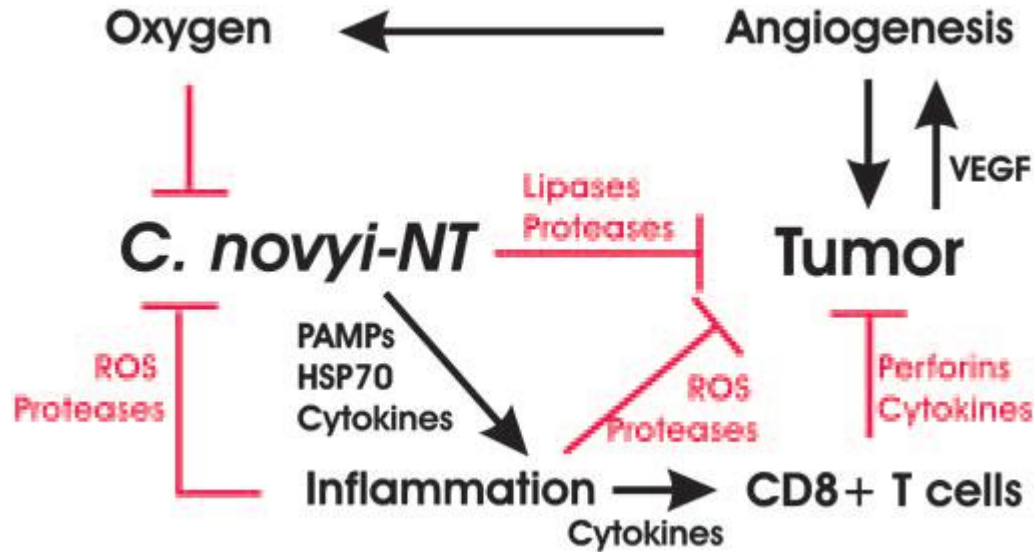
The Howard Hughes Medical Institute, Program in Cellular and Molecular Medicine, Division of Comparative Medicine, The Johns Hopkins School of Medicine, and The Johns Hopkins Oncology Center, 1650 Orleans Street, Baltimore, MD 21231

Contributed by Bert Vogelstein, October 12, 2001

- Spores of *Clostridium novyi* germinates in hypoxic tumor and lead to direct tumor destruction
- *Clostridium novyi-NT* (non-toxic) is a strain deprived of lethal toxin, which can be tested for therapeutic purposes

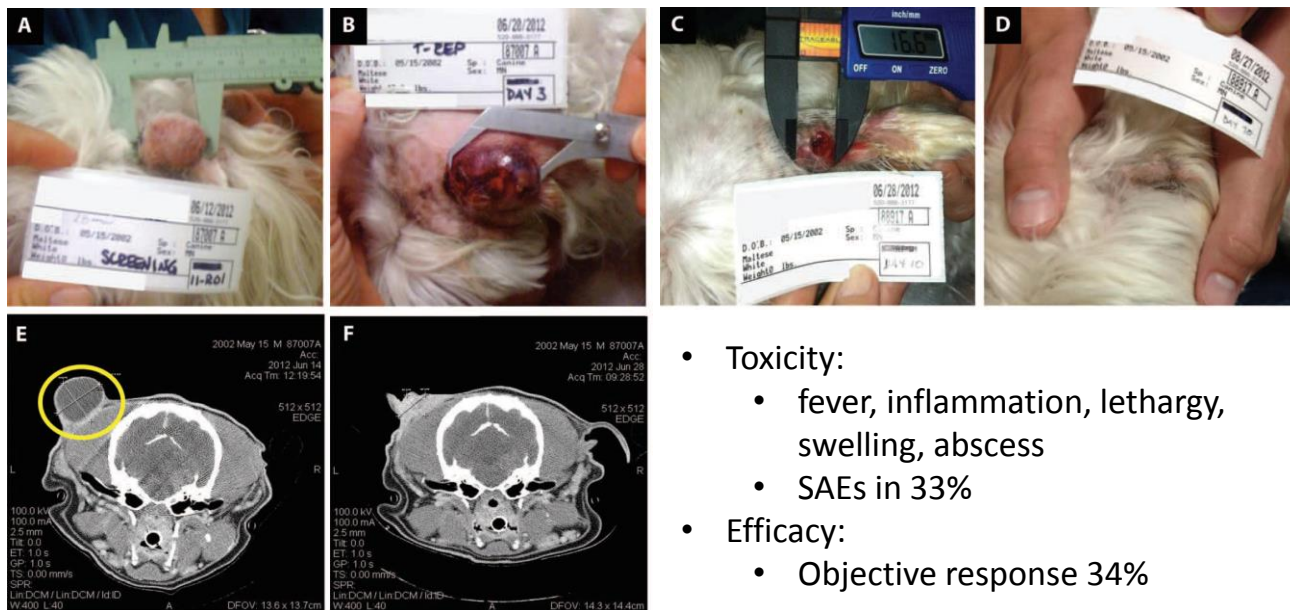


Clostridium novyi-NT induces inflammatory response



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

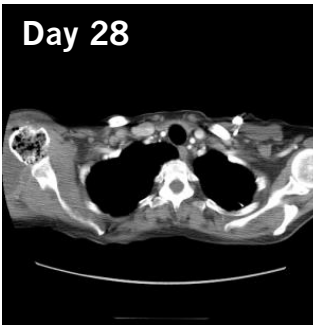
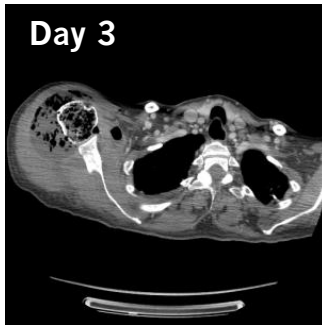
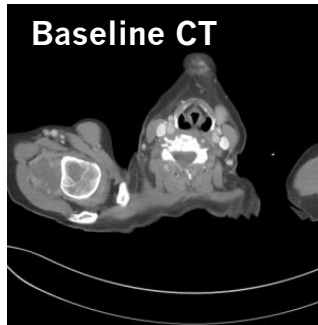
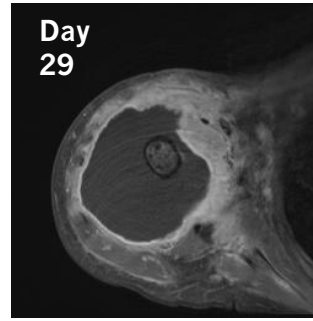
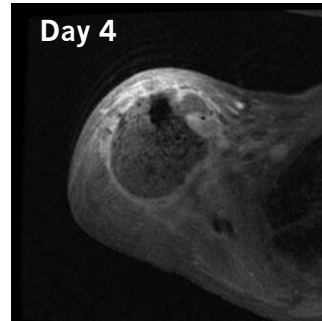
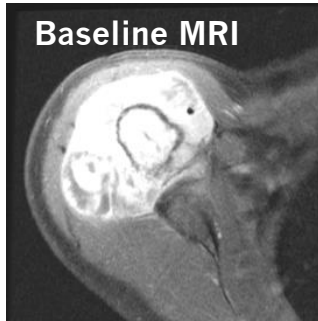
- Multicenter study (n=66), 4 dose levels
- 1-8 cycles of *Clostridium novyi-NT* administered
- At least 1 week between cycles



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

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

53-year-old female with metastatic leiomyosarcoma

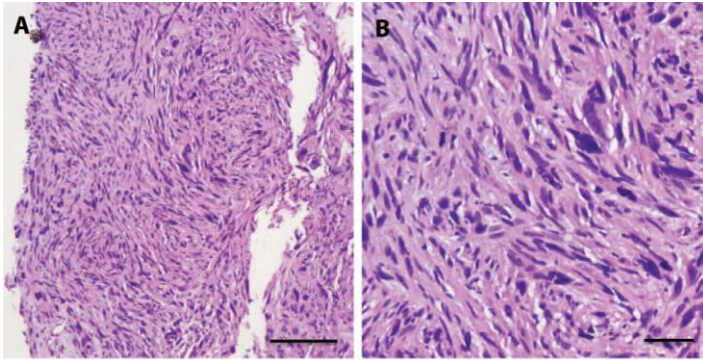


- Patient developed significant germination with rapid tumor destruction and systemic inflammatory symptoms
- Patient developed pathological fracture of the right humerus 8 weeks post injection, which required surgical intervention

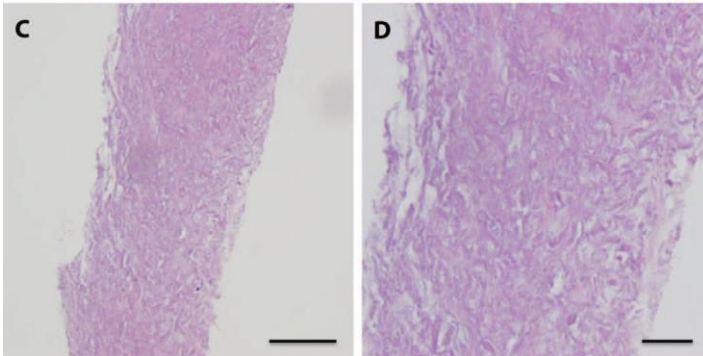
Phase I Clinical Study of Intratumoral Injection of *Clostridium novyi-NT* Spores in Patients with Advanced Cancer

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

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



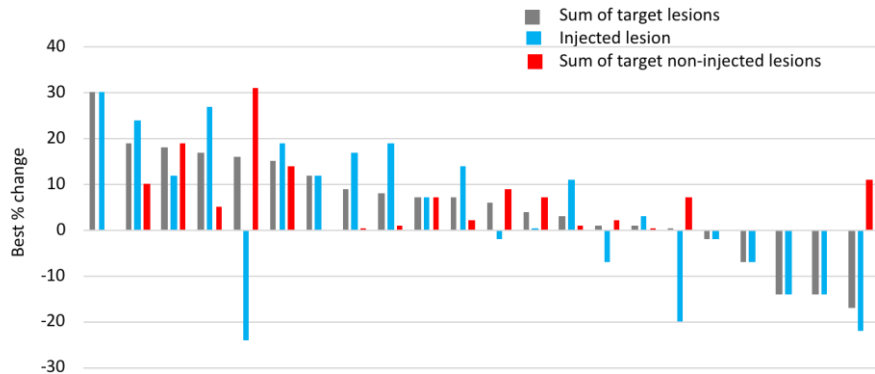
A and B: Pretreatment tumor biopsy showing viable tumor



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

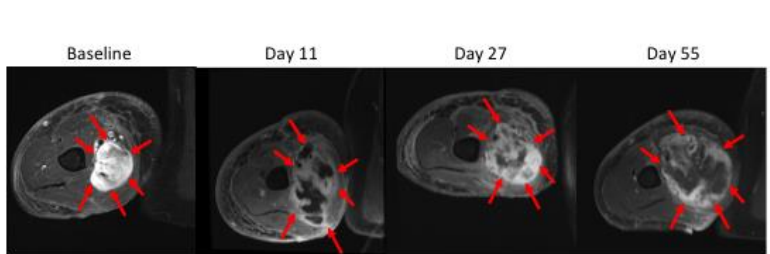
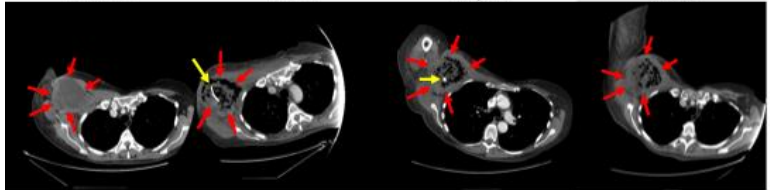
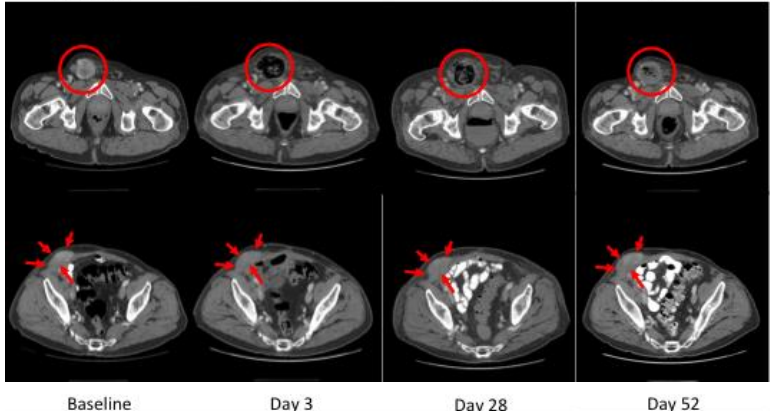
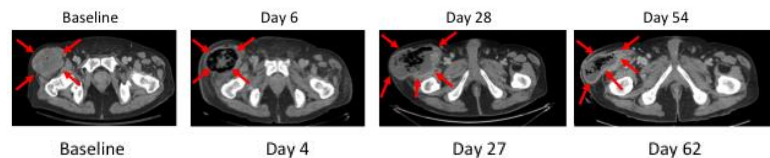
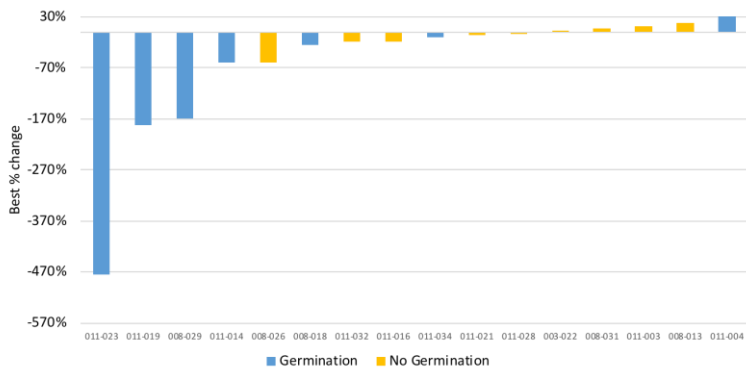
Anticancer activity of single intratumor injection of *Clostridium Novyi-NT*

Best change in size



Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Germination	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	Y	Y	Y
PFS (days)	95	56	34	54	77	43	81	26	59	43	137	58	56	59	240	54	29	54	223	96	91	57
Progression	Y	Y	Y	Y	N	Y	Y	N	N	Y	Y	N	N	Y	Y	Y	Y	N	N	Y	N	Y

Best change in density



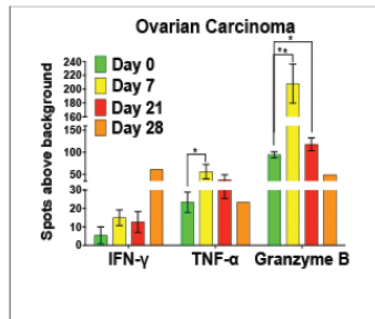
Cytokine response after single intratumor injection of *Clostridium Novyi-NT*

Paired tumor biopsies

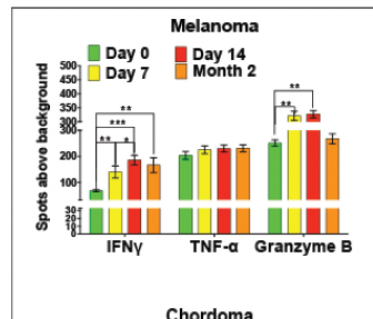
Case	Biopsy	Immune Surveillance				Tregs	Inflammation	
		CD3+	CD8+	Perforin	GZMB	FoxP3	MDSC	Mono cytes
Germination absent								
Melanoma	Day 0	2+	2+	1+	1+	1+	1+	2+
	Weeks 4-8	2+	2+	1+	1+	1+	1+	2+
Chordoma	Day 0	2+	2+	0	0	ND	1+	0
	Weeks 4-8	1+	1+	0	0	ND	1+	0
Endometrial Carcinoma	Day 0	1+	1+	1+	1+	0	1+	1+
	Weeks 4-8	1+	ND	ND	ND	1+	1+	1+
Germination present								
Adenocarcinoma of unknown primary	Day 0	1+	1+	0	0	1+	1+	0
	Weeks 4-8	2+	2+	1+	0	1+	2+	2+
Leiomyosarcoma	Day 0	1+	1+	0	0	0	1+	1+
	Weeks 4-8	3+	3+	1+	1+	1+	3+	2+
Myxofibrosarcoma	Day 0	1+	1+	0	0	0	2+	1+
	Weeks 4-8	2+	2+	1+	1+	1+	3+	2+
Uterine Carcinosarcoma	Day 0	2+	2+	1+	1+	1+	2+	2+
	Weeks 4-8	2+	2+	2+	2+	?	2+	1+
Osteosarcoma	Day 0	0	0	0	0	0	2+	0
	Weeks 4-8	0	0	0	0	0	2+	0

PBMCs

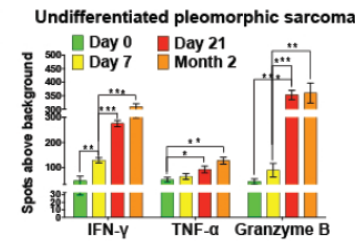
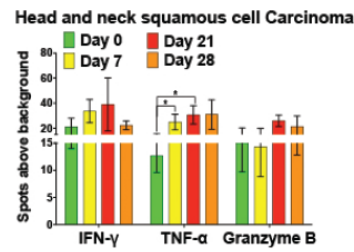
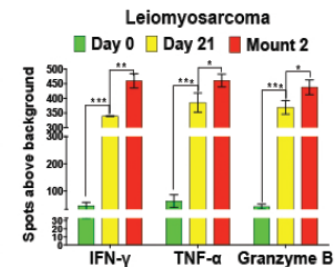
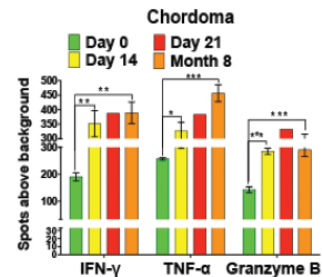
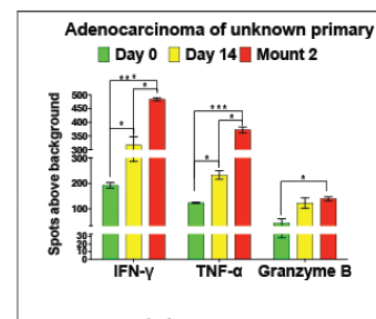
C. "No" cytokine response
"No" Clinical germination



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



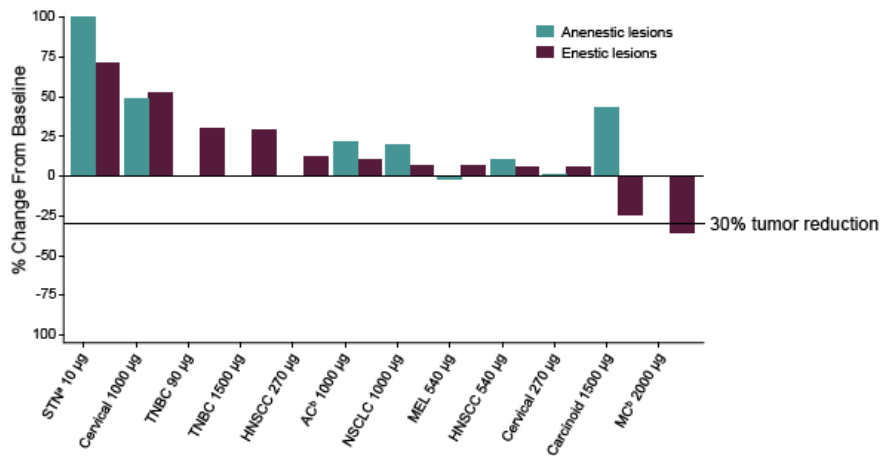
E. "+" cytokine response
"+" Clinical germination



Intratumor STING agonist MK-1454 +/- pembrolizumab

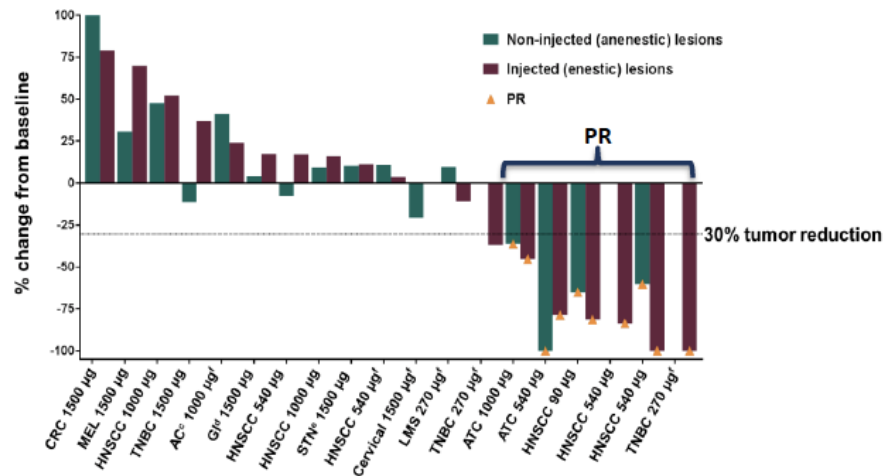
MK-1454 single agent

Maximum change in %



MK-1454 + pembrolizumab

Maximum change from baseline in lesions^b



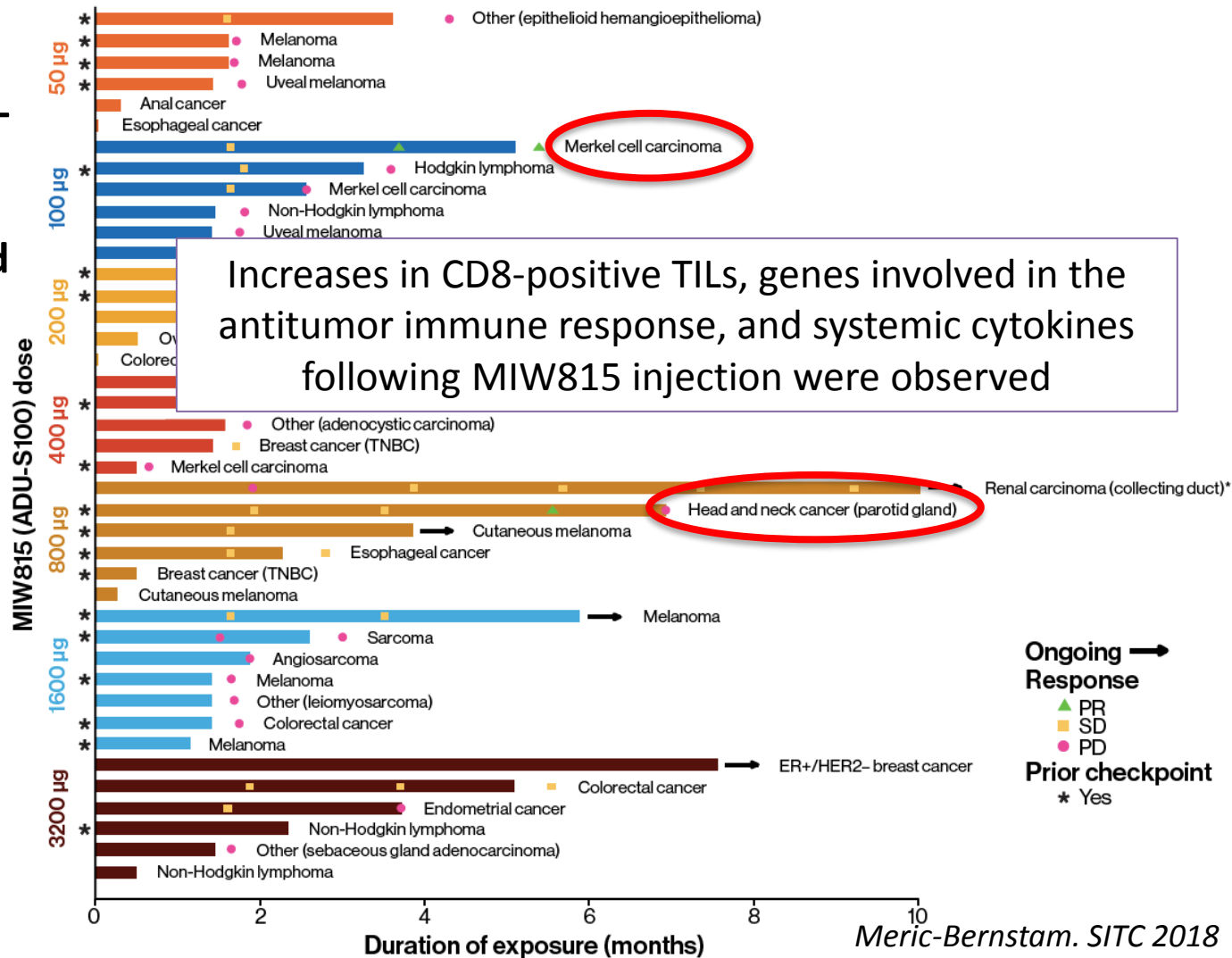
□ Median 83% reduction in size of target lesions for responders

Harrington ESMO 2018

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

Related AEs:

- 78.0% of patients (12.2% Grade 3/4 AEs. [lipase])
- headache, injection site pain, and pyrexia (14.6% each).
- No DLT



Conclusions

- Immunotherapy with immune checkpoint inhibitors can be effective only in subsets of patients with 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

Acknowledgements



OUR PATIENTS AND THEIR FAMILIES