SITC 2019

Gaylord National Hotel
& Convention Center

Nov. 6-10

NATIONAL HARBOR, MARYLAND

sitc

Society for Immunotherapy of Cancer

Clinical Assessment of Intratumoral Immunomodulation

Jianda Yuan MD, PhD, Anuradha Khilnani MD

On behalf of IT Biomarker Team

Translational Oncology

Early Oncology Development/Merck & Co., Inc.

Washington DC, USA, 7 November 2019

Conflict of Interest- Disclosure

I am currently a full time employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

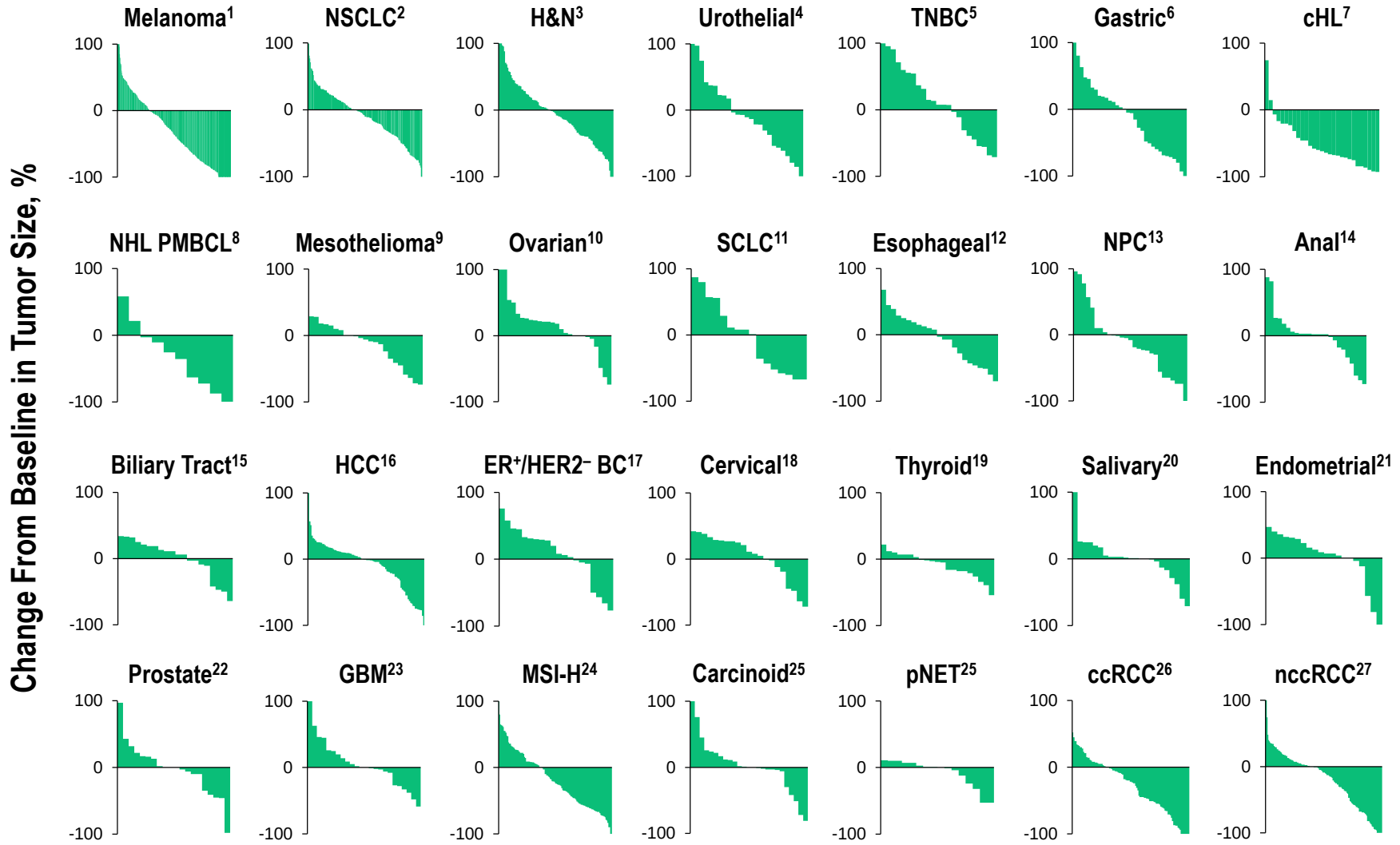
Outline

- Immune checkpoint inhibitors (CPI) as monotherapy and combination therapy have changed the landscape for standard of care in cancer treatment, which has highlighted the challenge of immunotherapy resistance

- Principles of intratumoral (IT) immunotherapy in evolving CPI landscape
  - Mechanisms of resistance to immunotherapy
  - GEP/TMB analysis reveals patterns of resistance biology
  - Advantages of IT immunotherapy to potentially overcome resistance
  - Growing landscape of IT immunotherapy

- Key biomarker strategy for IT immunotherapies
  - IT biomarkers of PD response to inform dose
  - IT biomarker scope of assessment
  - Potentially inform patient selection for optimal IT therapies

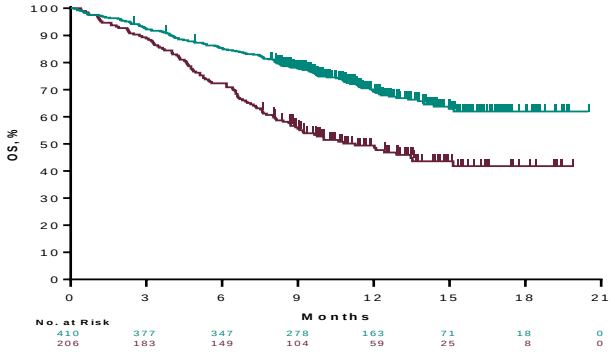
Pembrolizumab Monotherapy has Broad Antitumor Activity Demonstrated in >25 Cancers Types



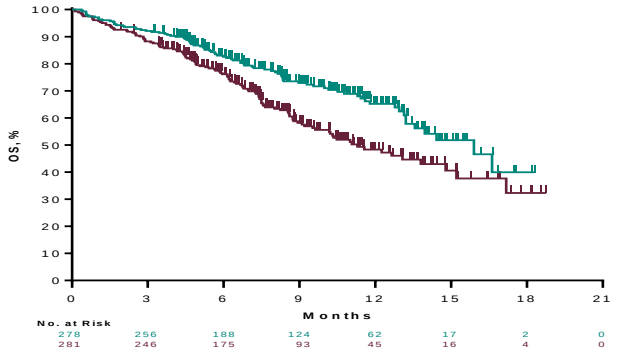
1. Daud A et al. ASCO 2015; 2. Garon EB et al. ESMO 2014; 3. Seiwert T et al. ASCO 2015; 4. Plimack E et al. ASCO 2015; 5. Nanda R et al. SABCS 2014; 6. Bang YJ et al. ASCO 2015; 7. Moskowitz C et al. ASH 2014; 8. Zinzani PL et al. ASH 2015; 9. Alley EA et al. AACR 2015; 10. Varga A et al. ASCO 2015; 11. Ott PA et al. 2015 ASCO; 12. Doi T et al. ASCO 2015; 13. Hsu C et al. ECC 2015; 14. Ott PA et al. ECC 2015; 15. Bang Y-J et al. ECC 2015; 16. Zhu A et al. Lancet Oncol. 2018;19:940-952; 17. Rugo HS et al. SABCS 2015; 18. Frenel JS et al. ASCO 2016; 19. Mehnert JM et al. ASCO 2016; 20. Cohen R et al. ASCO 2016; 21. Ott PA et al. ASCO 2016; 22. Hansen AR et al. ESMO 2016; 23. Reardeon D et al. SNO 2016; 24. Diaz L et al. ASCO 2017, updated 09Oct2018; 25. Mehnert J et al. ESMO 2017; 26. McDermott DF et al. ASCO 2018; 27. McDermott DF et al. ASCO-GU 2018.

CPI Combination Therapies Showing Great OS Benefit

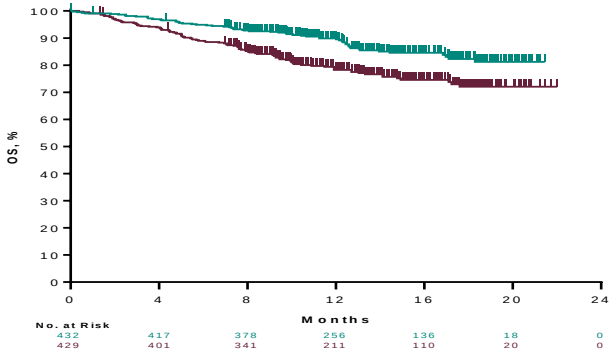
1L Nonsquamous NSCLC, Any PD-L1
KEYNOTE-189[1]
Pembro + Pemetrexed/Platinum vs Placebo + Pemetrexed/Platinum



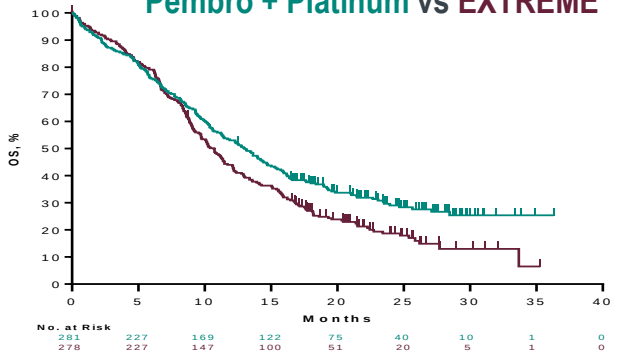
1L Squamous NSCLC, Any PD-L1
KEYNOTE-407[2]
Pembro + Carboplatin/Taxane vs Placbo + Carboplatin/Taxane



1L RCC, Any PD-L1
KEYNOTE-426[4]
Pembro + Axitinib vs Sunitinib



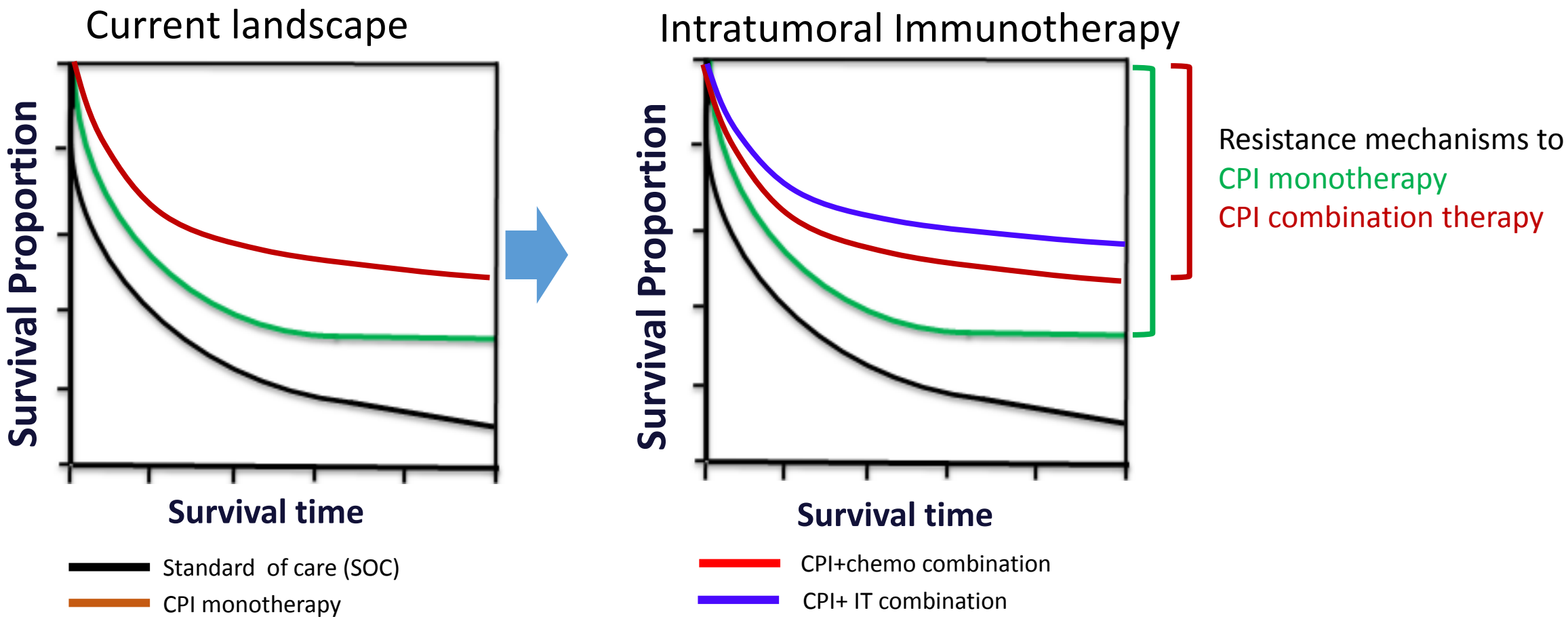
1L HNSCC, CPS ≥1
KEYNOTE-048[3]
Pembro + Platinum vs EXTREME



OS benefit demonstrated as part of combination therapy in 4 phase 3 studies and 3 cancer types

1. Gandhi L et al. *N Engl J Med* 2018;378:2078-92; **2.** Paz-Ares L et al; *N Engl J Med* 2018;379:2040-51;
3. Rini BI et al. *N Engl J Med* 2019; doi: 10.1056/NEJMoa1816714; **4.** Burtness B et al. ESMO 2018.

Intratumoral Immunotherapy may Overcome Resistance and Improve Clinical response



Resistance Mechanisms to Immunotherapy

Terminology for different resistance mechanisms to immunotherapy

Term	Description
Primary resistance	A clinical scenario where a cancer does not respond to an immunotherapy strategy. The mechanistic basis of lack of response to immunotherapy may include adaptive immune resistance
Adaptive immune resistance	A mechanism of resistance where a cancer is recognized by the immune system but it protects itself by adapting to the immune attack. Given the evolving nature of the immune/cancer cell interaction, this could clinically manifest as primary resistance, mixed responses or acquired resistance
Acquired resistance	A clinical scenario in which a cancer initially responded to immunotherapy but after a period of time it relapsed and progressed

Mechanisms of primary and adaptive resistance to immunotherapy

Term	Mechanisms
Tumor cell-intrinsic	Absence of antigenic protein
	Absence of antigen presentation
	Genetic T cell exclusion
	Insensibility to T cells
Tumor cell-extrinsic	Absence of T cells
	Inhibitory immune checkpoints
	Immunosuppressive cells

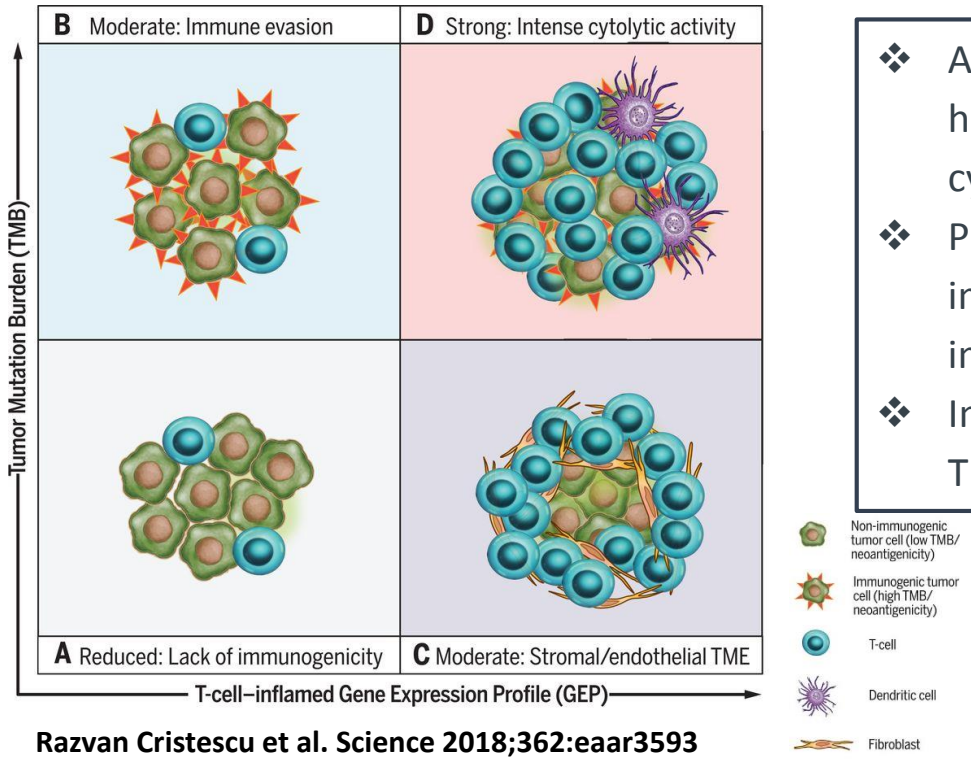
Modified from Sharma, Hu-Lieskovan, Wargo, Ribas. Cell, 2017

TMB and GEP/PD-L1 Reveal Different Patterns of Resistance Biology in Different Groups

Noninflamed tumor vs Inflamed tumor

Priming an immune response against tumors without pre-existing immunity
Boosting inadequate antitumor immunity

- Few or no immune cells and cytotoxic T cells with low TCR clonality
- Lack pre-existing antitumor immunity
- Lack of chemokines essential for T-cell homing, or vascular factors or barriers



Razvan Cristescu et al. Science 2018;362:eaar3593

- A TME that contains immune cells, high expression of proinflammatory cytokines with high TCR clonality
- Pre-existing T-cell–mediated immunity that is restrained by immunosuppressive pathways
- Immunosuppressive cytokines in the TME

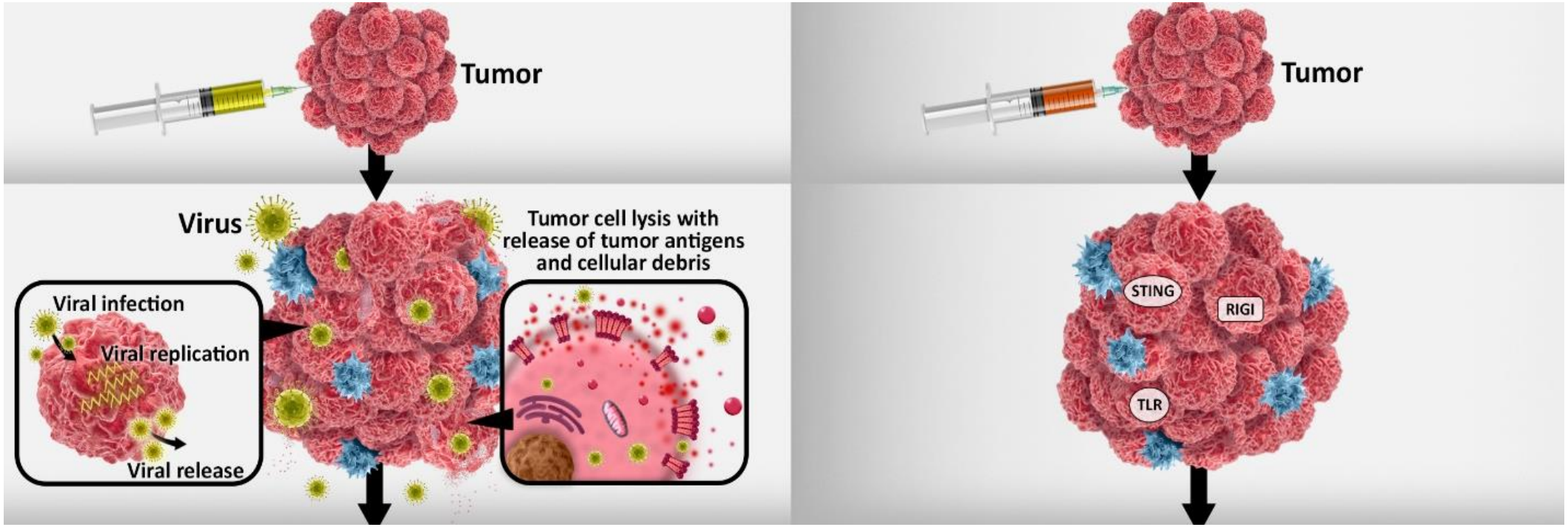
Potential Advantages of Intratumoral Immunotherapy

- Allow for efficacious dose exposure in the tumor microenvironment while limiting systemic exposure and thereby minimizing systemic adverse events
- Enable testing of potent immunostimulators that may otherwise have prohibitive systemic toxicity
- Expand options for potential synergistic combination therapy
- Combine as dual or triple combination therapy to target multiple resistance mechanisms while minimizing systemic toxicity

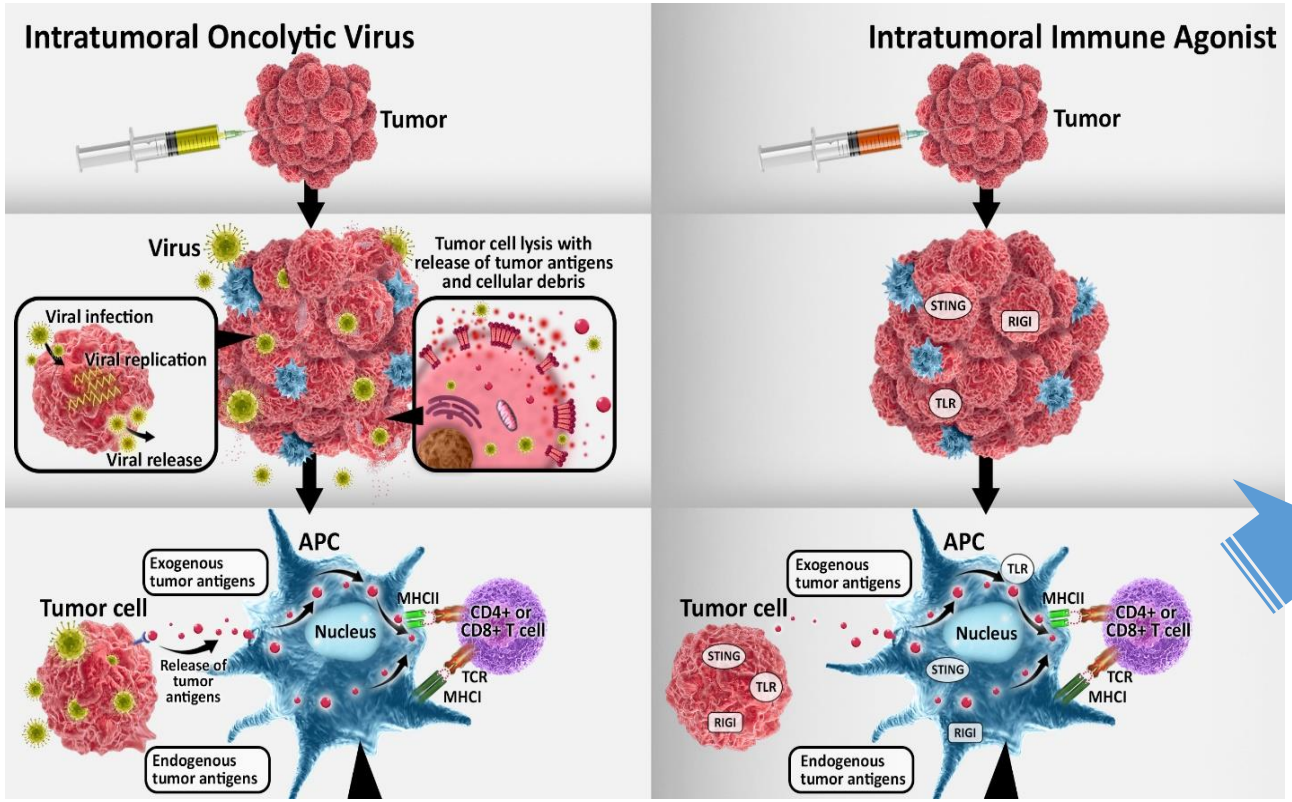
Current Landscape of IT Immunotherapy (Selected Examples)

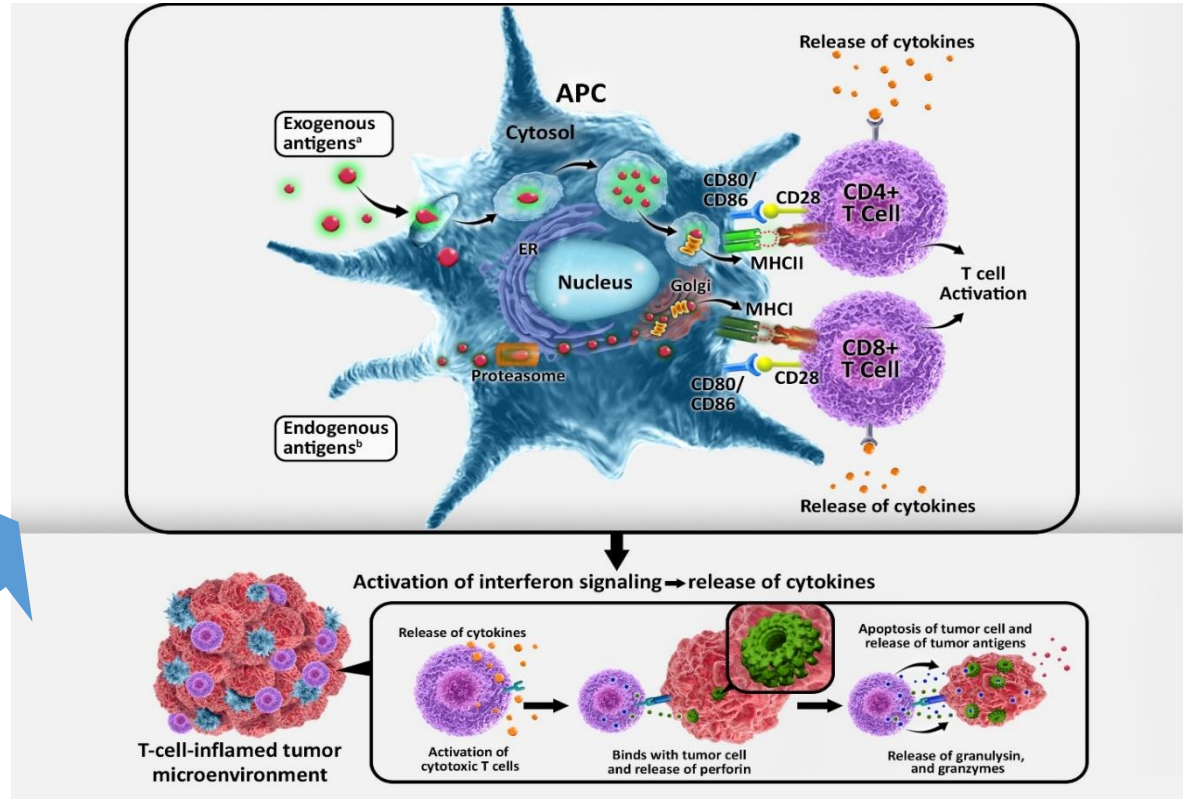
Oncolytic Viruses:
- T-VEC (HSV-1/GM-CSF)
- Coxsackievirus A21
- NDV (New Castle Disease Virus)
- Canerpaturev (C-REV, HF10)
- more

Immune Agonists:
- TLR Agonists, MDA-5, Bacillus Calmette-Guerin (BCG)
- STING Agonists, RIG-I Agonists,
- Anti-CD40 Agonists
- Cytokines (Interferon, Interleukin-2, GM-CSF)
- more

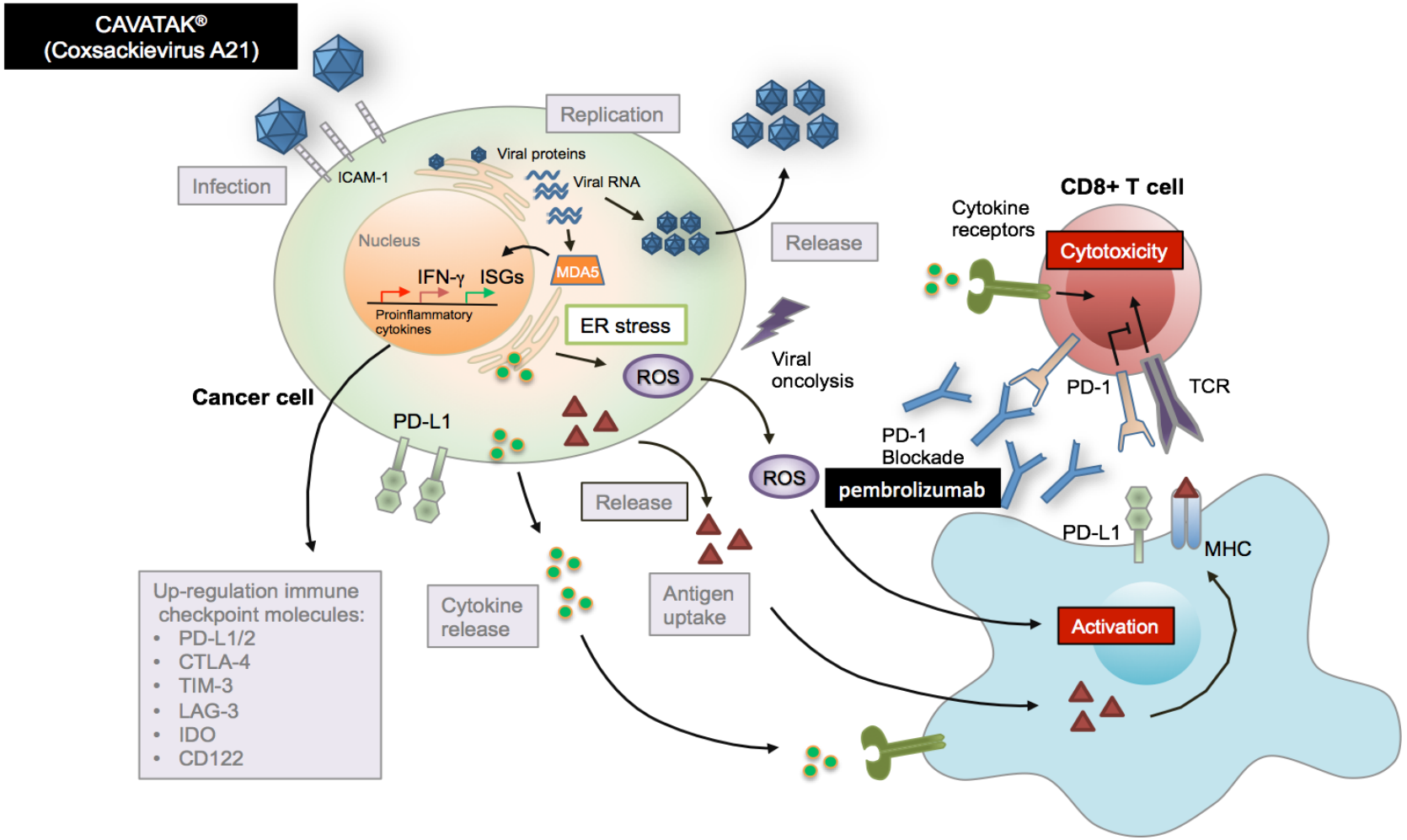


Intratumoral Administration of Immune Stimulatory Products





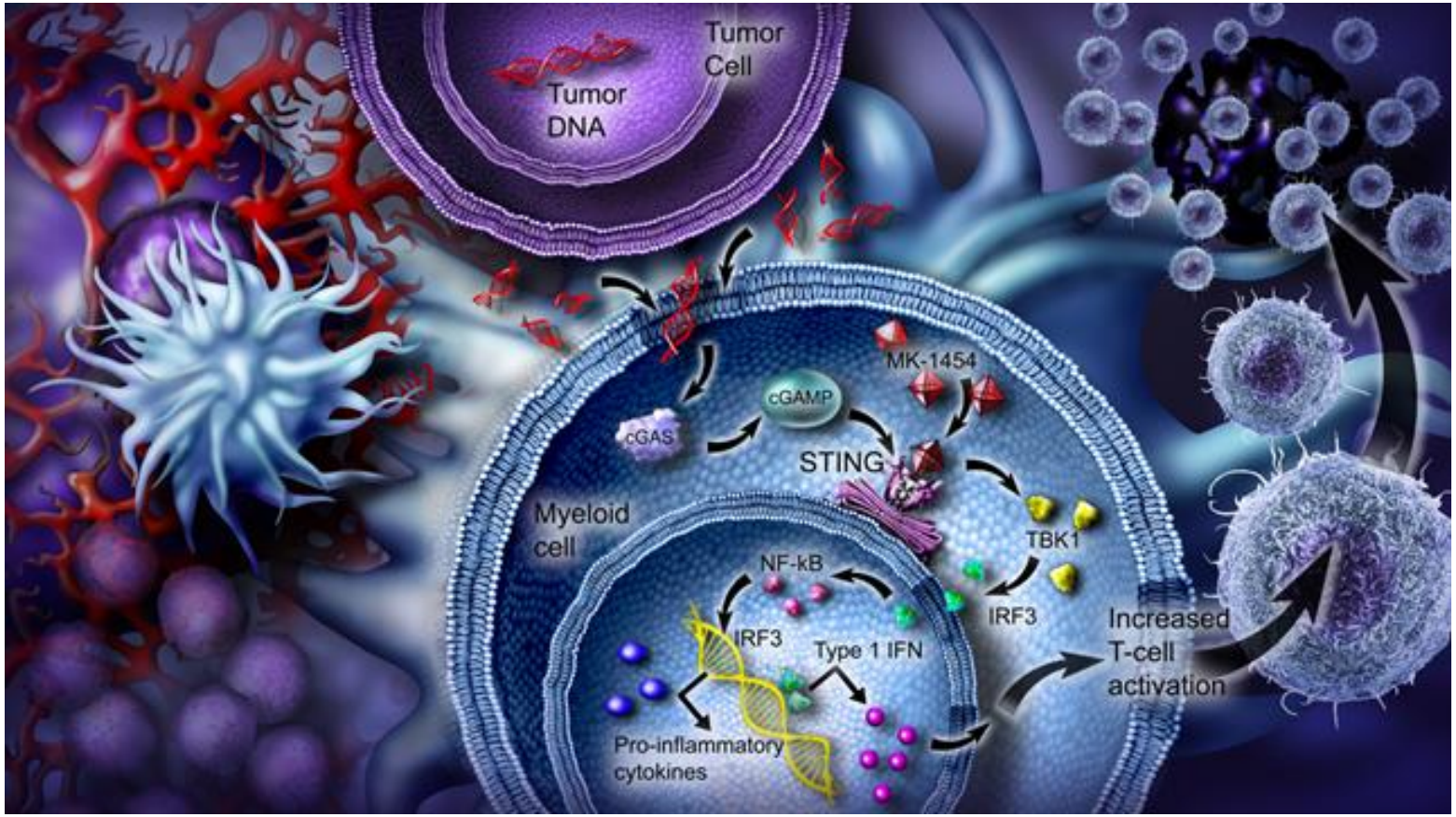
Current Landscape of IT Immunotherapy (Coxsackievirus A21)



Pandha HS et al 2018 the International Oncolytic Conference at Oxford (UK)

STING Mechanism of Action

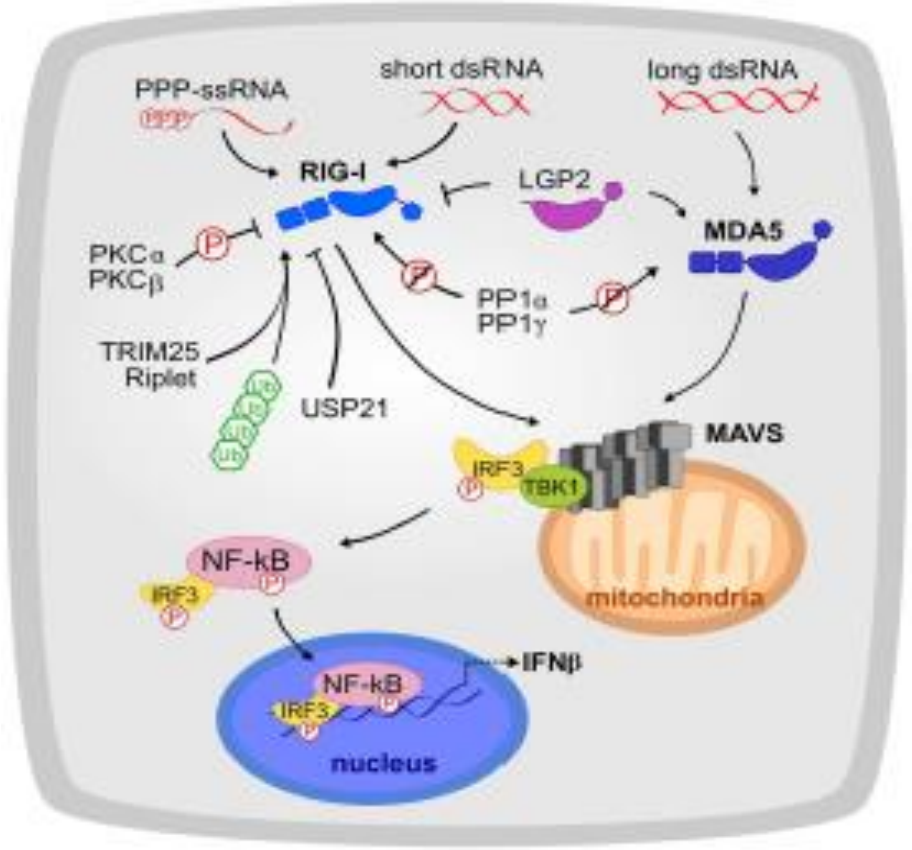
- Intratumoral (IT) injection of STING agonist leads to the production of type-I interferons (IFNs) and proinflammatory cytokines
- IFN-β strongly enhances cross-presentation of tumor antigens by CD8α+ CD103+ DCs either in the tumor or in tumor-draining lymph nodes
- Activated tumor-specific CD8+ T cells proliferate and mediate tumor killing at injected and non-injected lesions
- Potential to augment anti-tumor immunity stimulated by checkpoint blockade



Harrington KJ et al ESMO 2018

Current Landscape of IT Immunotherapy (RIG-I)

- Ubiquitously expressed cytosolic RNA receptor[1,2]
- Recognizes double-stranded RNA bearing a 5'-triphosphate, and plays a key role in antiviral defense[1,2]
- Activation of RIG-I triggers apoptosis, preferentially in tumor cells, and activation of the innate immune system via type I interferon (IFN) signaling in preclinical model[1,3]



Reproduced from Reikine S, et al. *Front Immunol*. 2014;5:342.

1. Elion DL, Cook RS. *Oncotarget.* 2018;9:29007-17. 2. Kell AM, Gale M Jr. *Virology.* 2015;479-80.
3. Besch R et al. *J Clin Invest*. 2009;119(8):2399-411.

IT Immunotherapy Key Clinical Questions

- A few key questions need to be addressed in order to determine doses and schedules to maximize benefits of combination regimens:
  - Dose-schedule determination
  - Identify and validate biomarkers for proof of mechanism of action
  - Assess immune response
  - Evaluate injected and noninjected effects
  - Patient selection

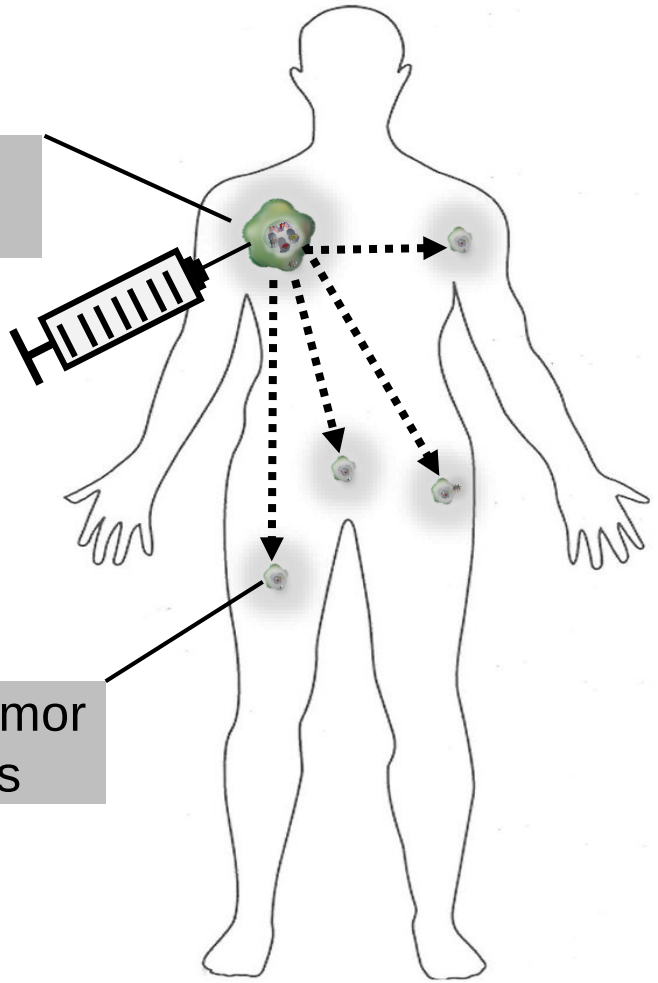
Dose Schedule Determination

Bioavailability	❖ Volume and concentration of agent ❖ Ratio between tumor size and volume of injection ❖ Local metabolism of agent ❖ Tumor vasculature ❖ Tumor interstitial pressure ❖ Expression of the target in the tumor
Frequency of injection	❖ Variable across agents with different mechanisms of action ❖ Half-life of the agent ❖ Time course of pharmacodynamic effects ❖ Biomarkers, as continued priming of T cells may be needed to replenish and maintain an antitumor immune response

Intratumoral Immunotherapy Dose Finding

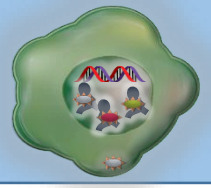
- Tumor PK/PD analysis including GEP RNA signature informs efficacious dose range
- Injected and non-injected lesion level response analyses to inform efficacious dose
- Dose level overall response analysis to determine dose response curve. Some IT immune agonists may have demonstrated a bell shaped dose response curve, with decreased efficacy at higher dose levels

Intratumoral Biomarker Assessment Strategy



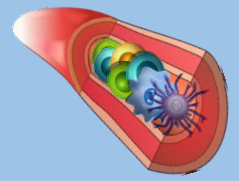
Immune assessment (pre- and post-treatment)

Injection tumor site



- Baseline immune profile
- Post-treatment immune activation

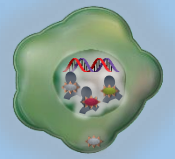
Peripheral blood



Evidence of induced systemic immunologic T cell response

- Peripheral T cell activation
- Peripheral immune profile
- Tumor antigen specific T cell

Non-injection tumor site



Evidence of induced systemic immunologic T cell response

- Baseline immune profile
- Post-treatment immune activation

Standardization of irRECIST and IT technique

- **Standardization of Intratumoral Response Assessment – itRECIST**
- **Standardization of Intratumoral Technique**
  - Optimize safety and create a technique guidance

Key Takeaways for Clinical Assessment of Intratumoral Immunomodulation

- Immune checkpoint inhibitors are changing the landscape of standard of care in cancer treatment with emerging immunotherapy resistance mechanisms.
- IT immunotherapy may overcome CPI resistance mechanisms, when administered as combination therapy.
- IT biomarker data will inform dose decisions for IT immunotherapy, provide deeper understanding of mechanism of action, and allow for selection of patients best suited for specific IT therapies

Acknowledgements

ITBiomarker team

Anuradha Khilnani
Joshua Brody
Robert Andtbacka
Siwen Hu-Lieskovan
Jason J. Luke
Adi Diab
Aurelien Marabelle
Alex Cao
Alexandra Snyder
F. Stephen Hodi

Merck

Eric Rubin
Elliot Chartash
Scott Pruitt
Vincent L. Giranda
Konstantin Dobrenkov
Anlong Li
Viola Jin Chen
Kapil Mayawala
Gretchen Baltus
Uyen Phan
Greg Goldmacher
Amy Calamari

Apothecom

Alexandra Lindsey
Dana Francis
Holly Cappelli
Michele Leo
Matt Grzywacz

Our patients