

What's Next for Cancer Immunotherapy?

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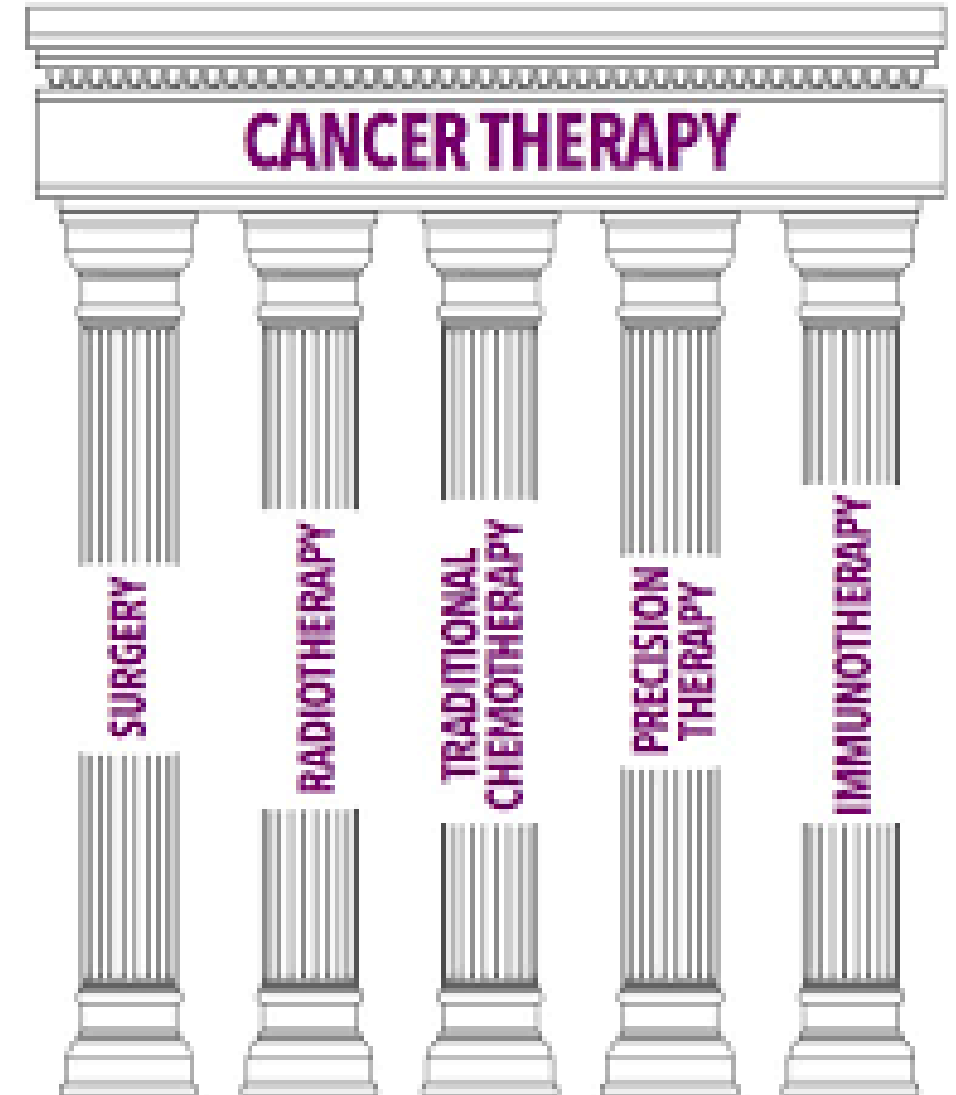
CMO, Replimune, Inc.

Disclosures

- I am an employee of Replimune, Inc.
- I will not be discussing non-FDA approved indications during my presentation.

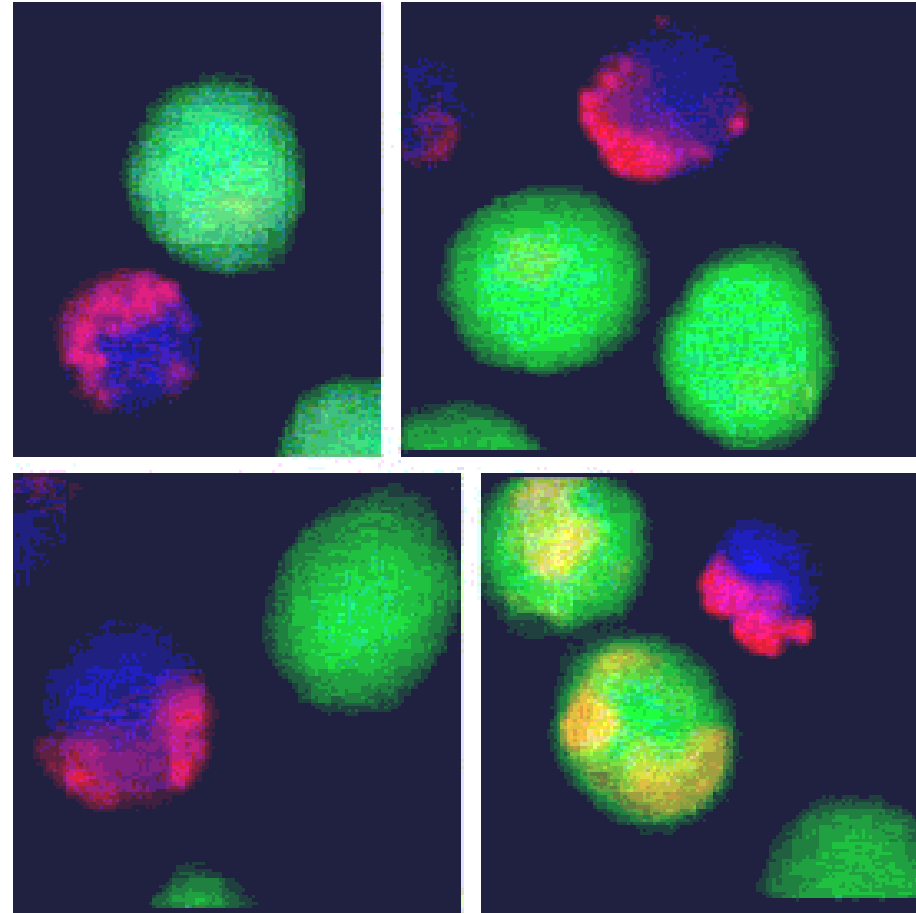
History of Cancer Therapy

- Surgery 1600 BC
- Radiation therapy 1895
- Chemotherapy 1942
- Targeted Therapy 2004
- Immunotherapy 2015



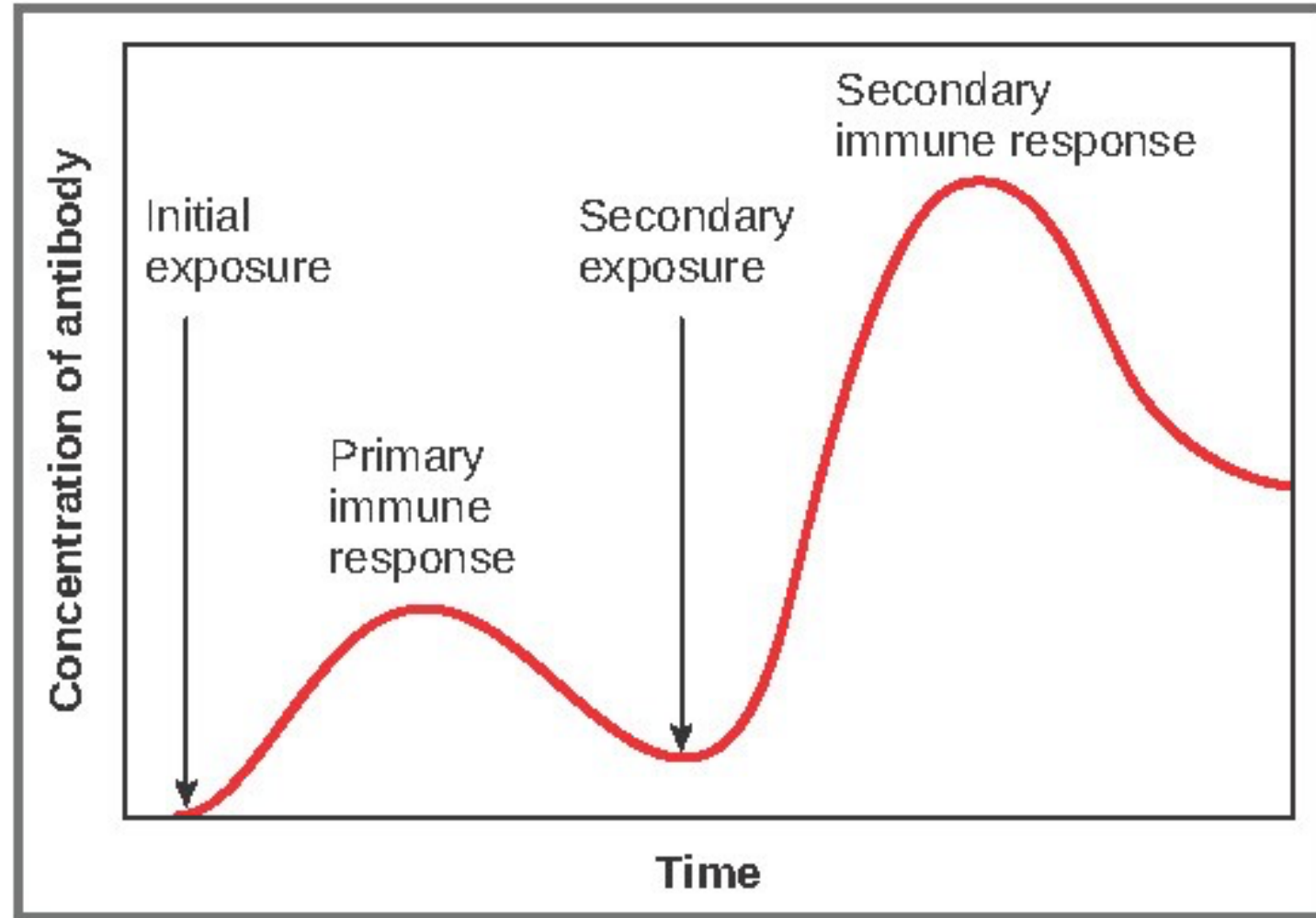
Why Immunotherapy?

- Specificity
- Memory
- Adaptability

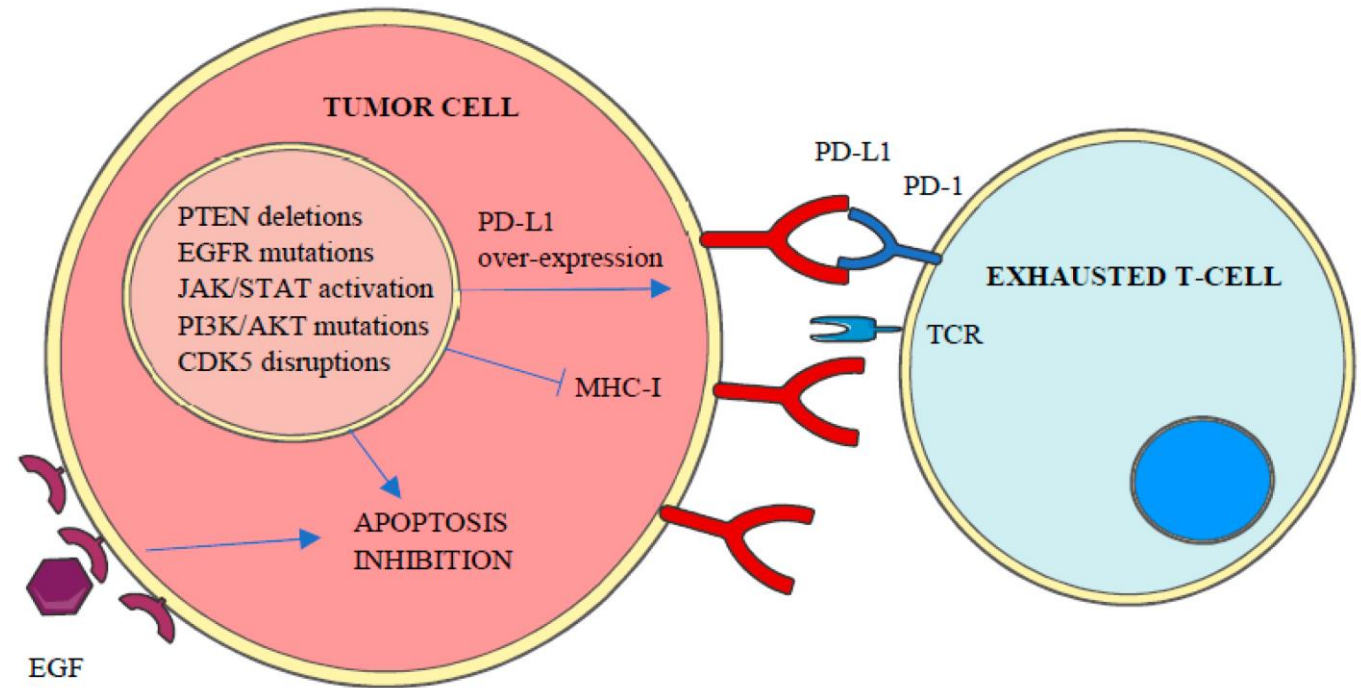
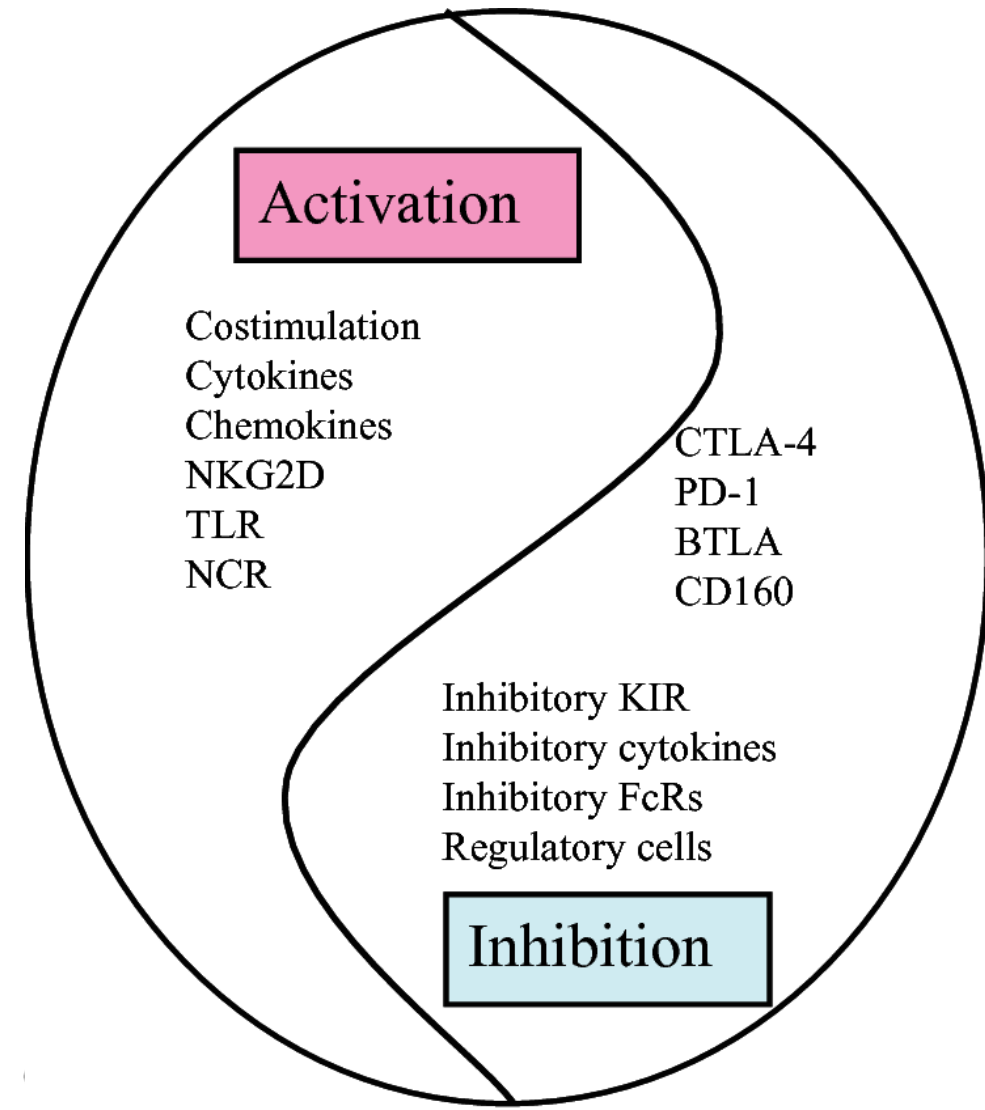


Credited Jim Allison, PhD

The kinetics of immune responses

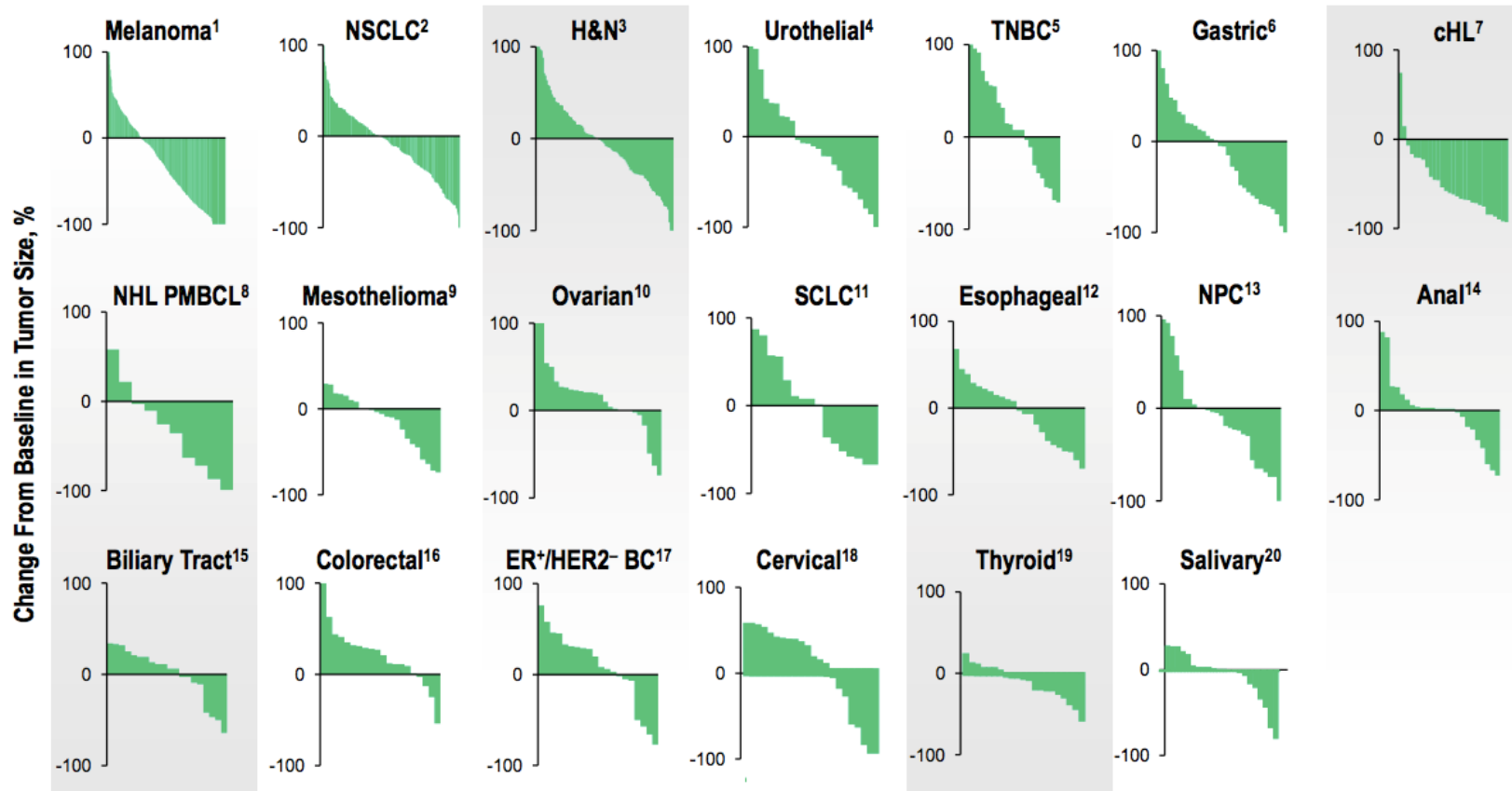


The immune system is highly regulated



Zheng et al Cell Mol Immunol 2009
 Garcia-Aranda and Redondo IJMS 2019

Immune checkpoint blockade has revolutionized cancer treatment



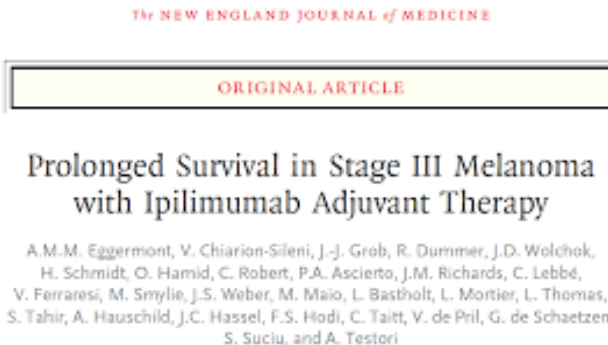
- Overall ORR 15-40%
- Innate and acquired resistance occur
- So, what's next?

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. O'Neill B et al. ECC 2015; 17. Rugo HS et al. SABCS 2015.

Unresolved clinical issues associated with immune checkpoint blockade

KEYNOTE-006 provides the best, though admittedly indirect, evidence that you don't need to continue to treat patients forever who respond or are stable.— *Jeffrey S. Weber, MD, PhD, ASCO 2018*

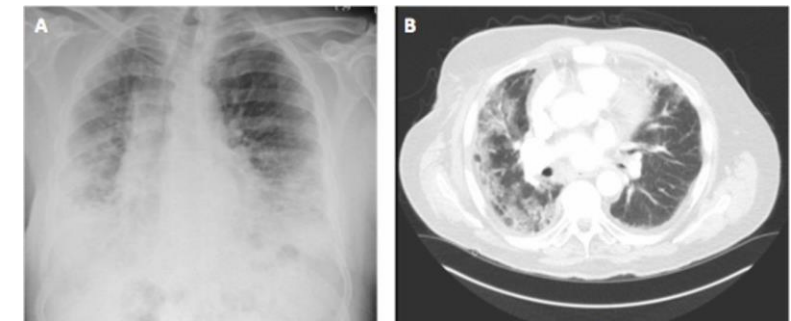
- How long should patients be treated?



- What is the natural history of patients treated with adjuvant checkpoint blockade?



- How to manage toxicity?

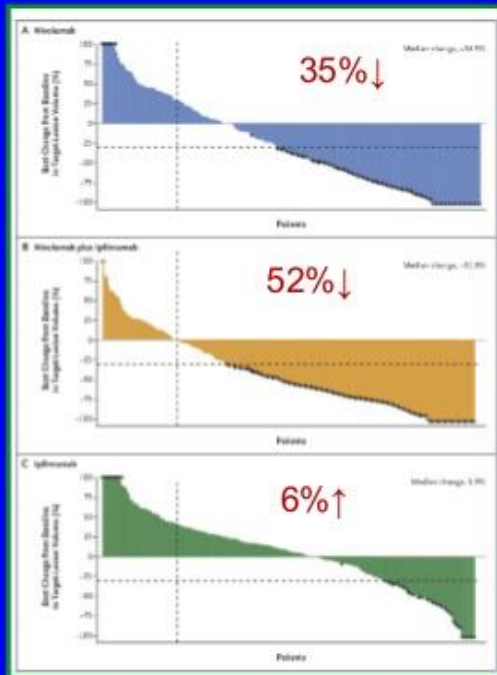


Combination checkpoint blockade

Nivo

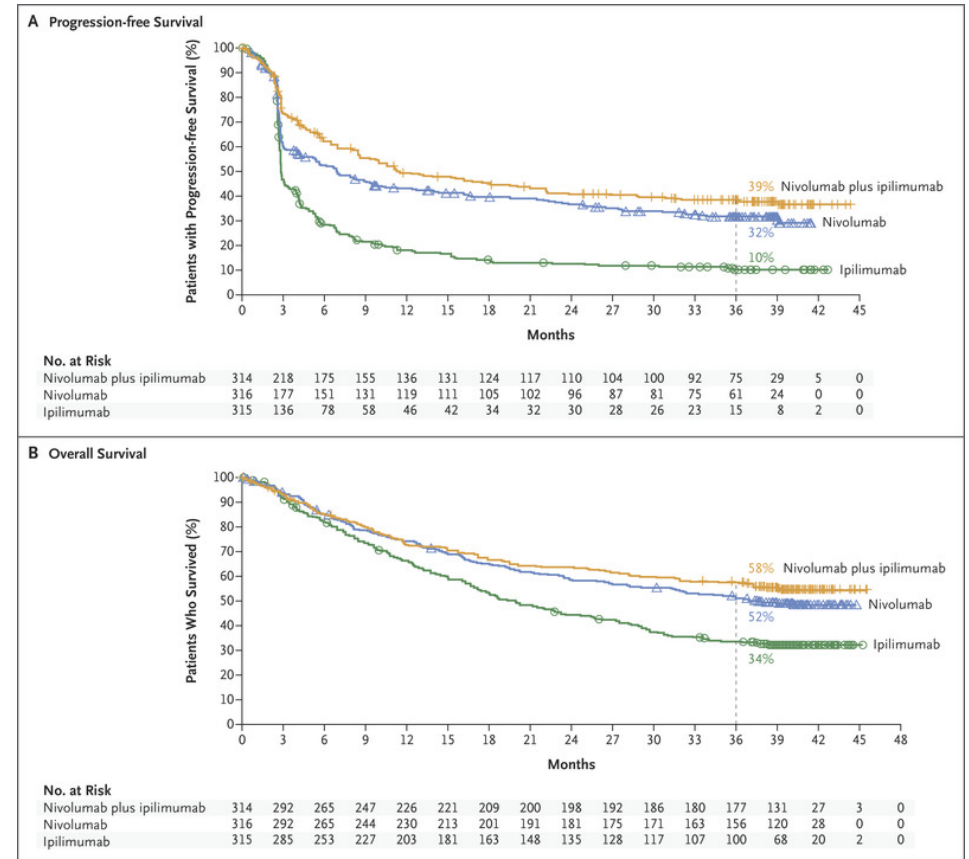
Nivo & Ipi

Ipi



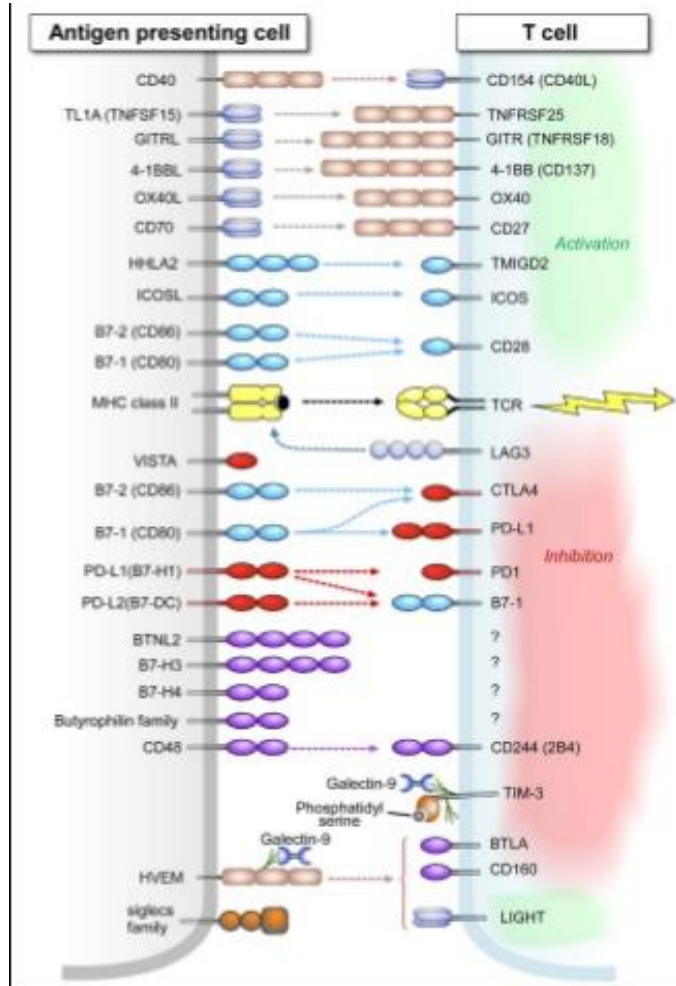
Tumor-burden
change
from baseline

Larkin, NEJM
373:23, 2015



Wolchok et al. NEJM 2017

Other checkpoints and potential combination therapy approaches



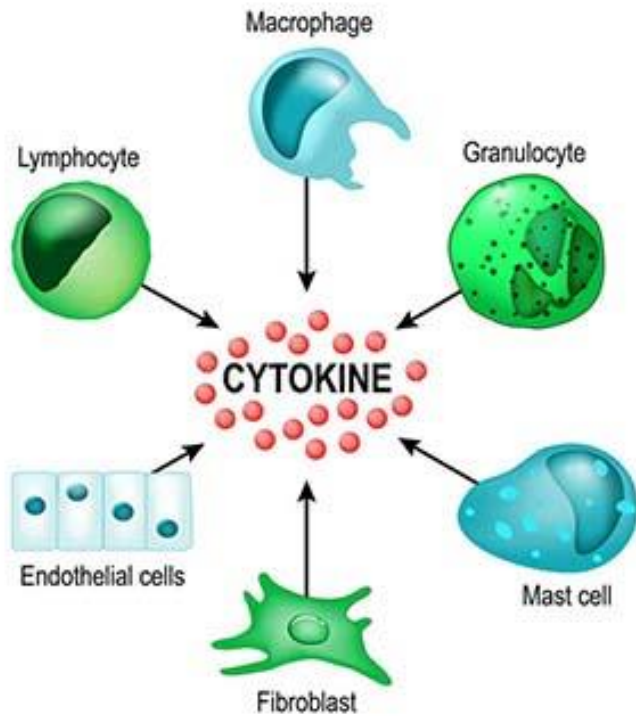
ICI Combinations

- Where to begin?
- Diverse targets and cell types
- Inhibitory and activating pathways
- Known and unknown biology

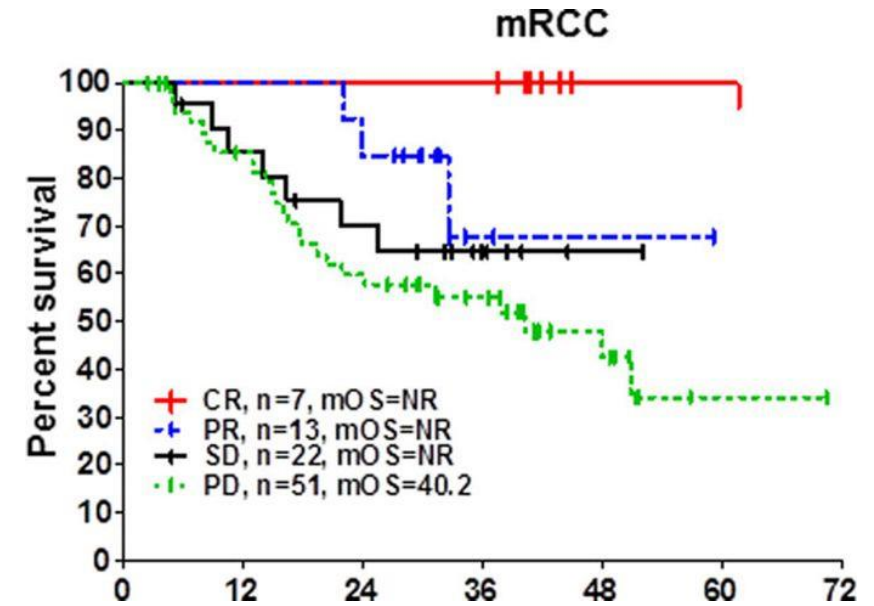
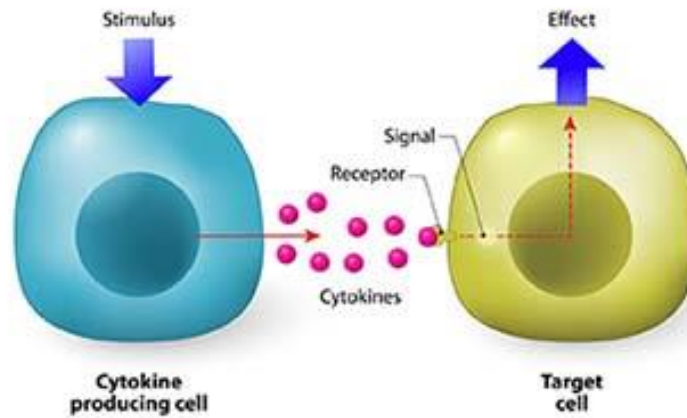
How do you approach this complexity?

Arasanz et al. Oncotarget 2017

What about cytokines?

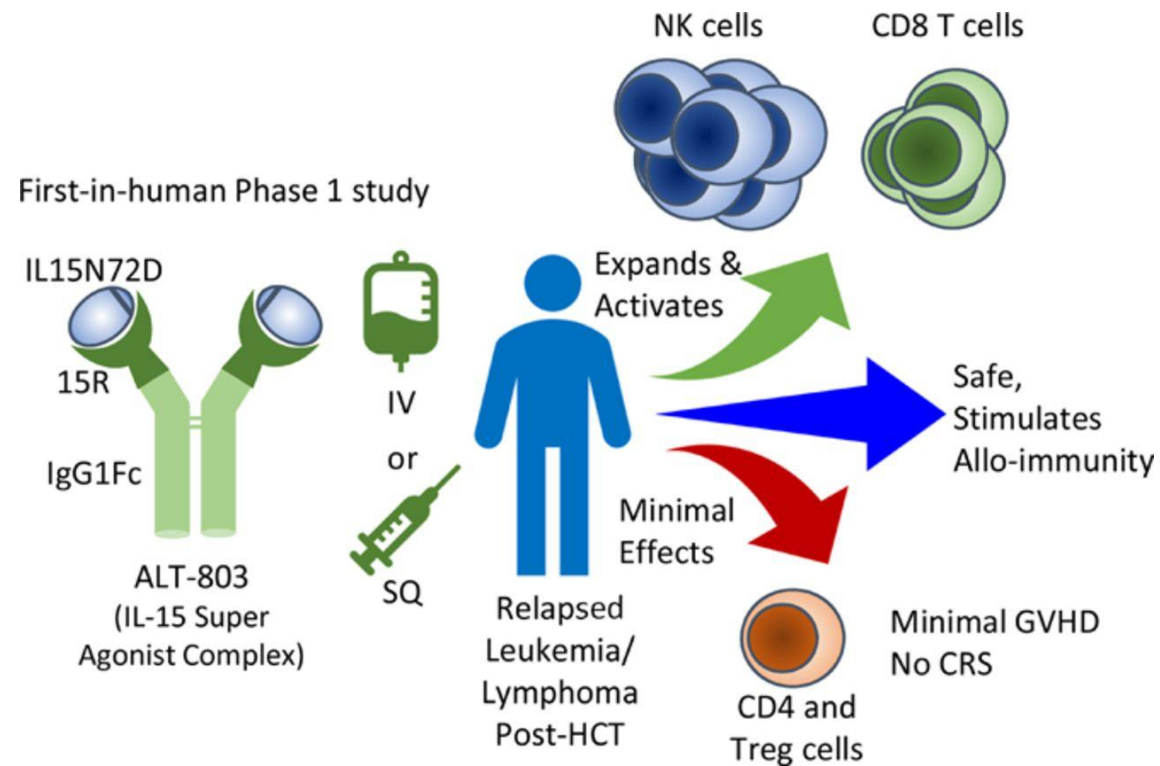
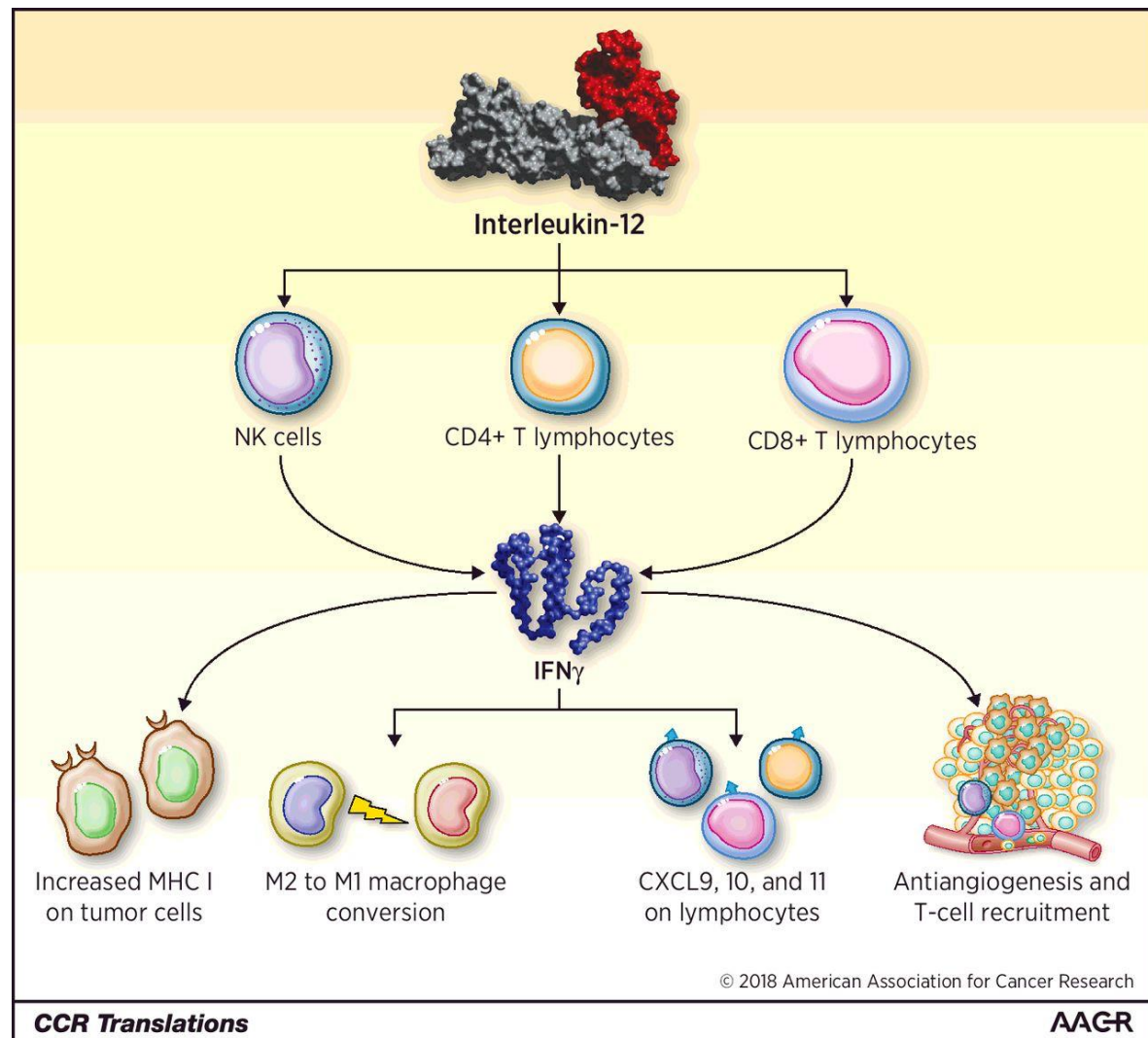


Cytokines



Biomedicine 2018
 Kaufman et al. JTC 2014

Interleukin-12 and Interleukin-15



Berraondo et al. CCR 2018

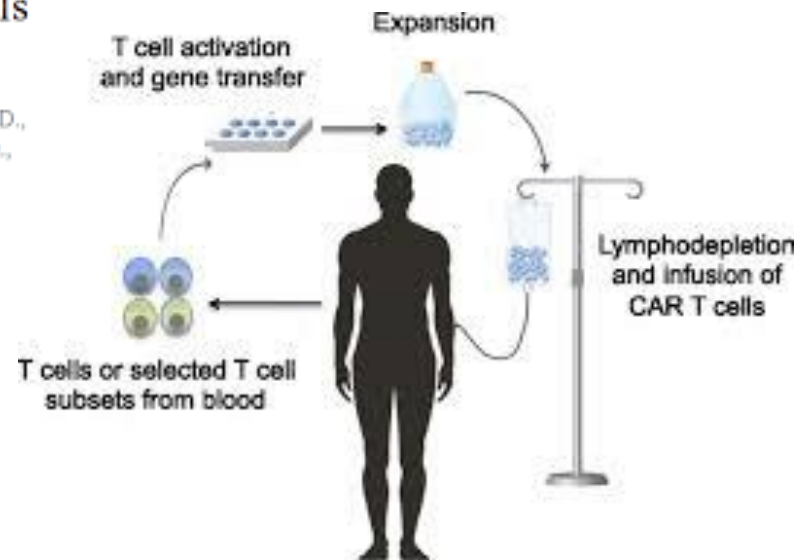
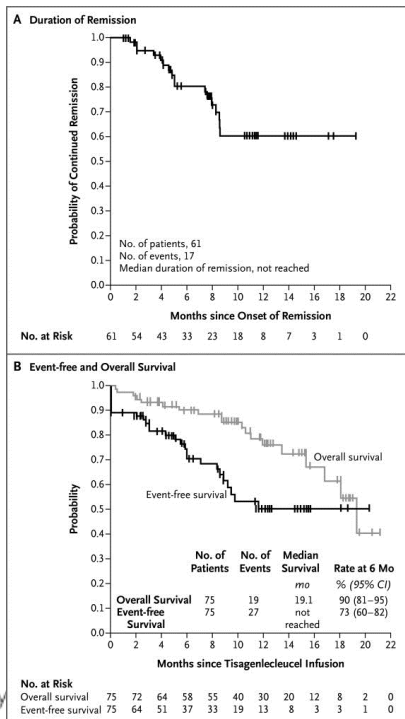
Romee et al. Blood 2018

CAR T cells and adoptive T cell therapy for cancer

BRIEF REPORT

Chimeric Antigen Receptor–Modified T Cells for Acute Lymphoid Leukemia

Stephan A. Grupp, M.D., Ph.D., Michael Kalos, Ph.D., David Barrett, M.D., Ph.D., Richard Aplenc, M.D., Ph.D., David L. Porter, M.D., Susan R. Rheingold, M.D., David T. Teachey, M.D., Anne Chew, Ph.D., Bernd Hauck, Ph.D., J. Fraser Wright, Ph.D., Michael C. Milone, M.D., Ph.D., Bruce L. Levine, Ph.D., and Carl H. June, M.D.



Rosenberg and Dudley Curr Opin Immunol 2009
Grupp et al. NEJM 2013
Srivastava and Riddell J Immunol 2018
Maude et al. NEJM 2018

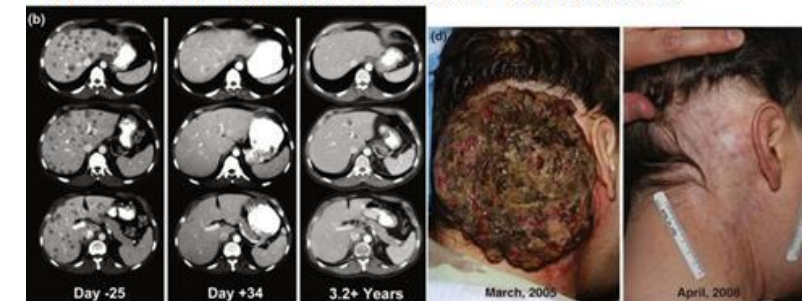
Tumor-infiltrating lymphocyte (TIL) adoptive therapy is promising therapy for melanoma, in case with adequate expansion of active T-cell *ex vivo*
Melanoma might have many mutations, which could be recognized by CTLs

Development of strong immune cell therapy for various cancer in Japan

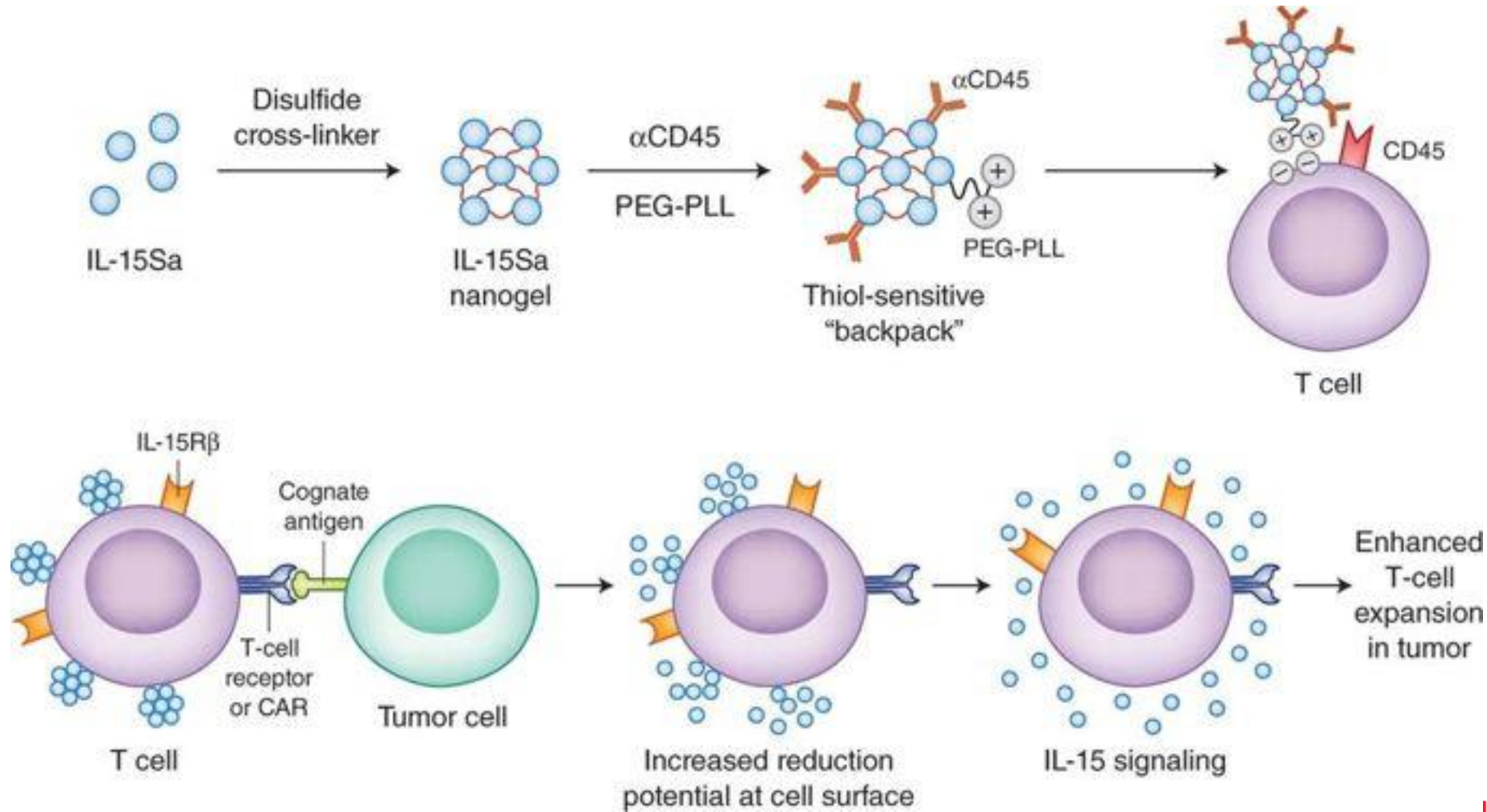
Adoptive cell therapy for the treatment of patients with metastatic melanoma

Steven A Rosenberg and Mark E Dudley (Current Opinion in Immunology 2008, 21:233–240)

TIL adoptive therapy + lymphodepletion (chemotherapy + total body irradiation)



T cell backpack technology



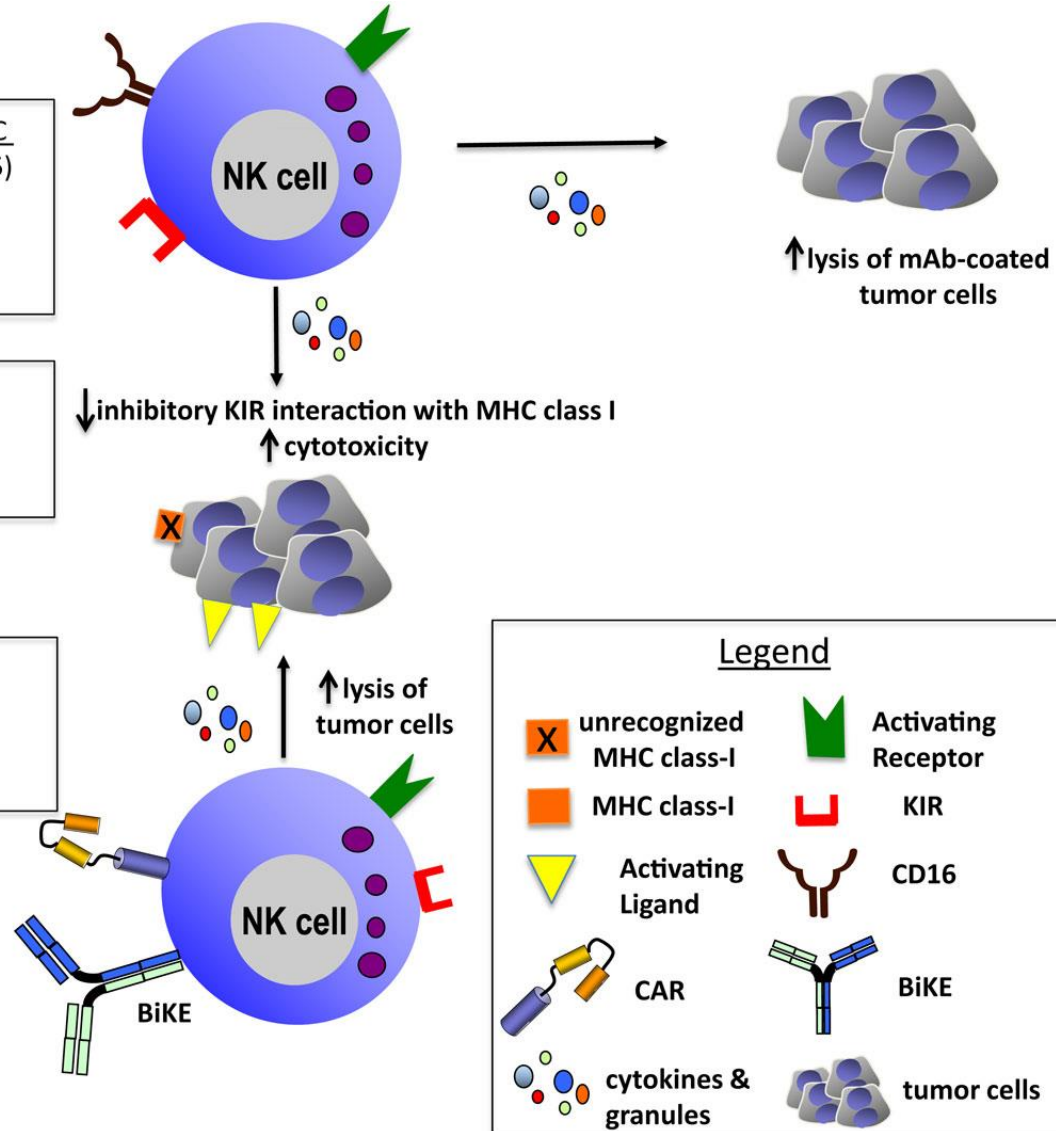
Shum and Heslop Nature Biotechnol 2018

Is there a role for NK cells?

- Enhanced CD16-mediated ADCC
- Engineered Fc Ab (DLE-HuM195)
 - Mogamulizumab
 - anti-CD137 mAb + Rituximab
 - Obinutuzumab

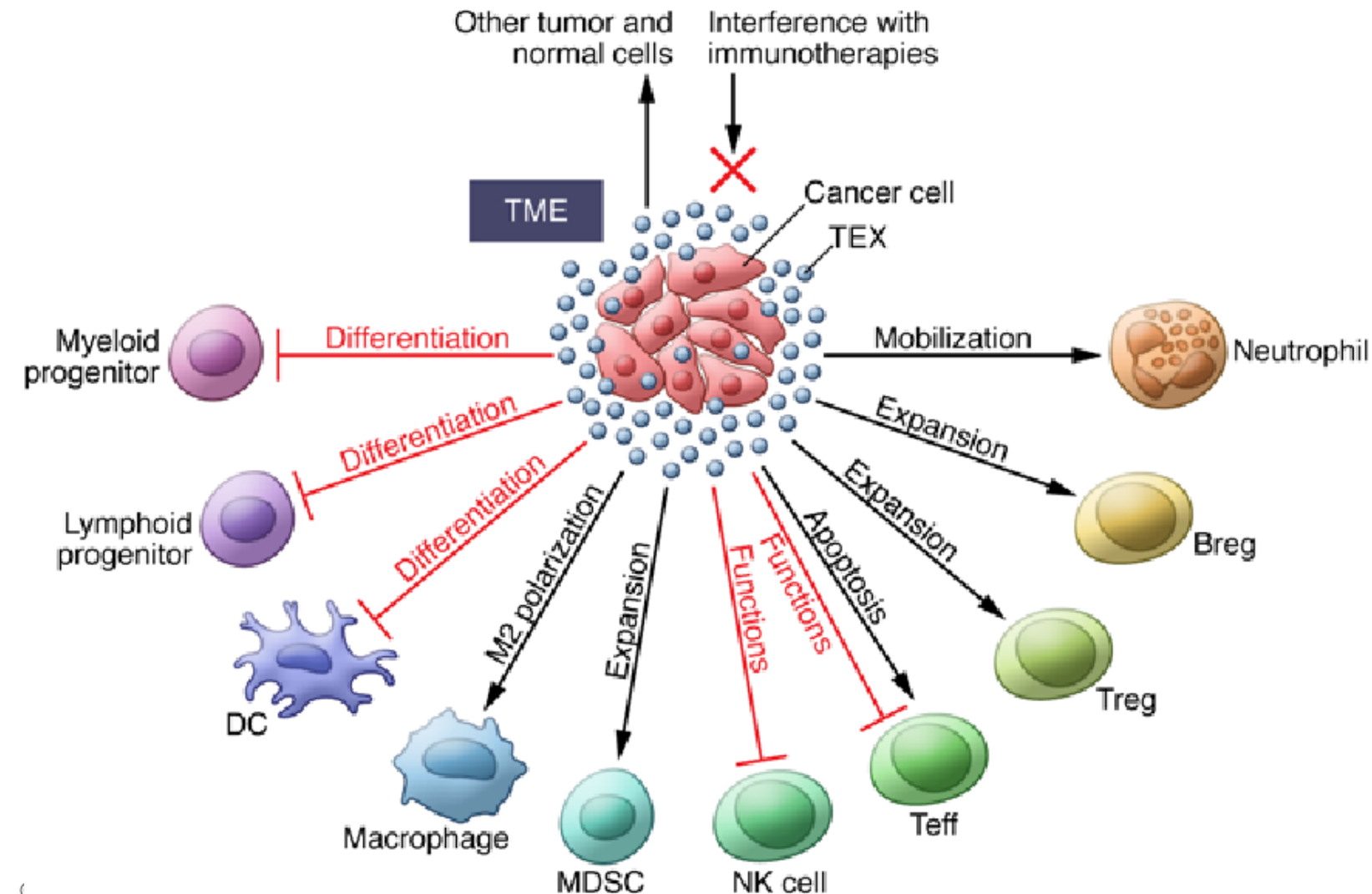
- Inhibitory KIR blockade
- Anti-KIR mAb
 - Anti-KIR mAb + Lenalidomide

- Genetic Modification
- Chimeric Antigen Receptors
 - Bi/Tri-specific Engagers
 - NK-92 cell line



Rezvani and Rouse Front Immunol 2015

Dealing with immune suppression



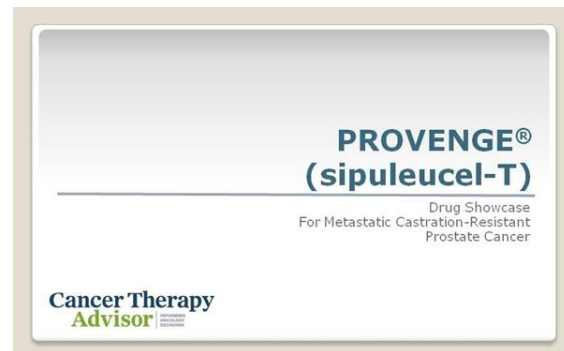
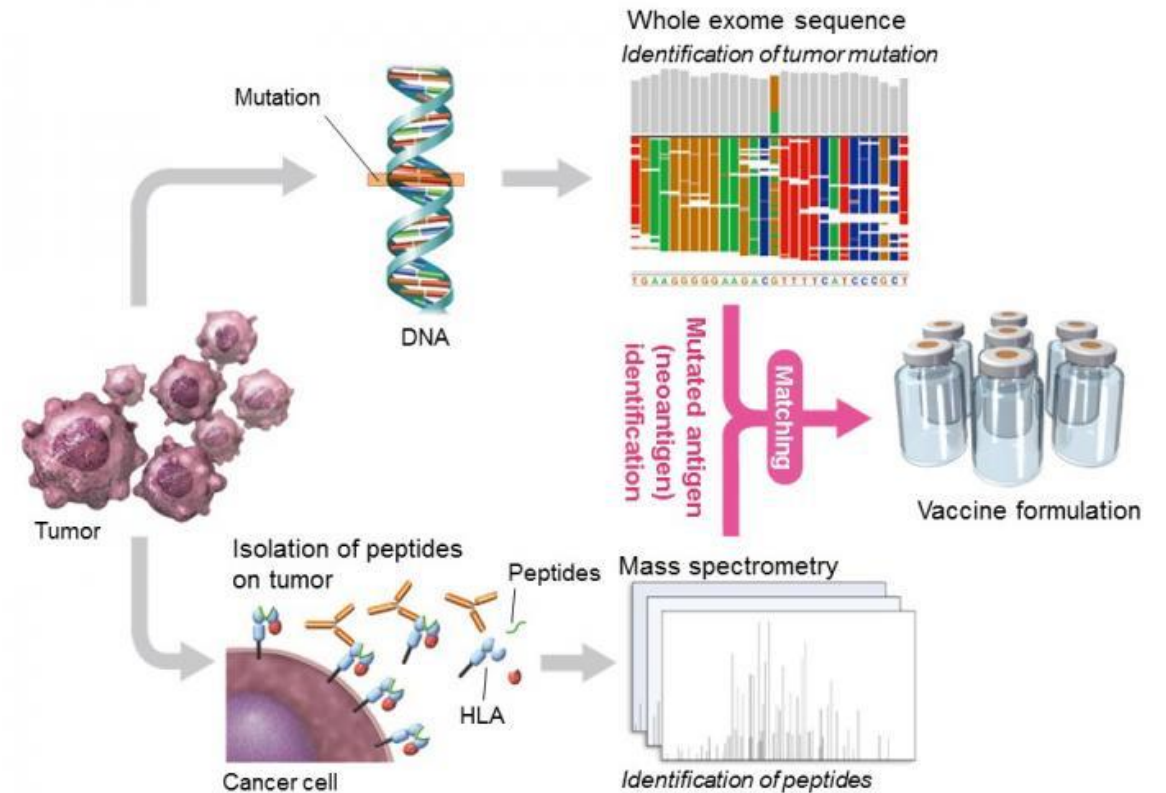
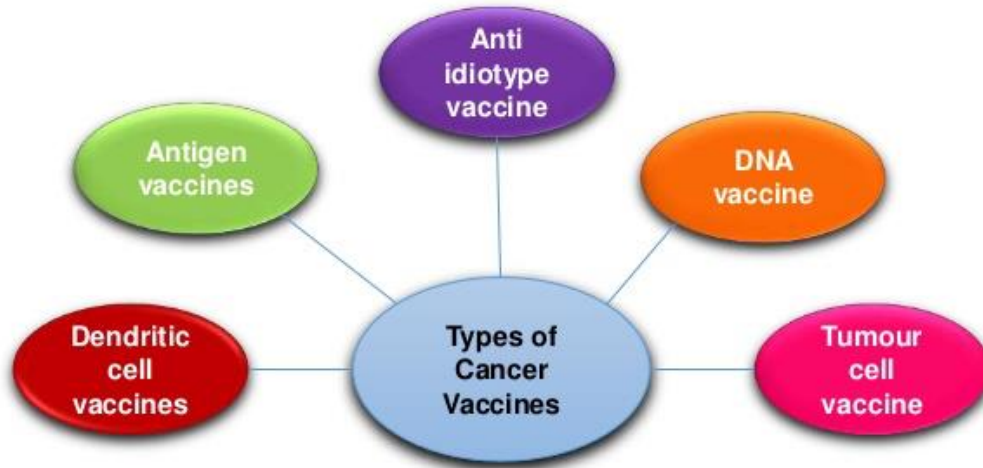
Soluble factors:

- IL-10
- TGF-beta
- VEGF
- Exosomes

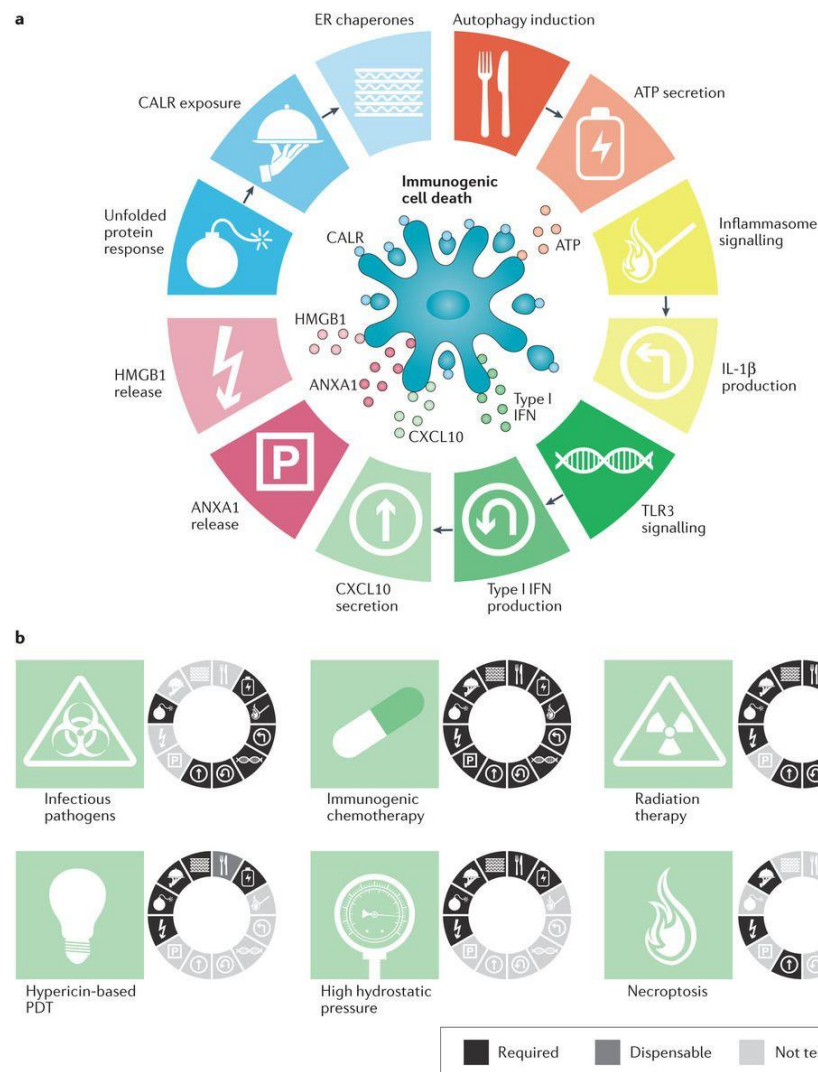
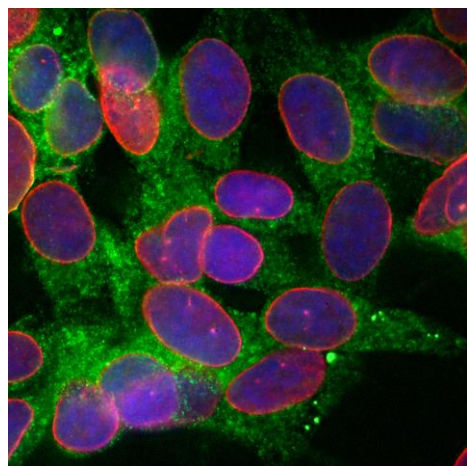
Whiteside JCI 2016

Vaccines: The new (and old) frontier

TYPES OF CANCER VACCINES:



Immunogenic Cell Death

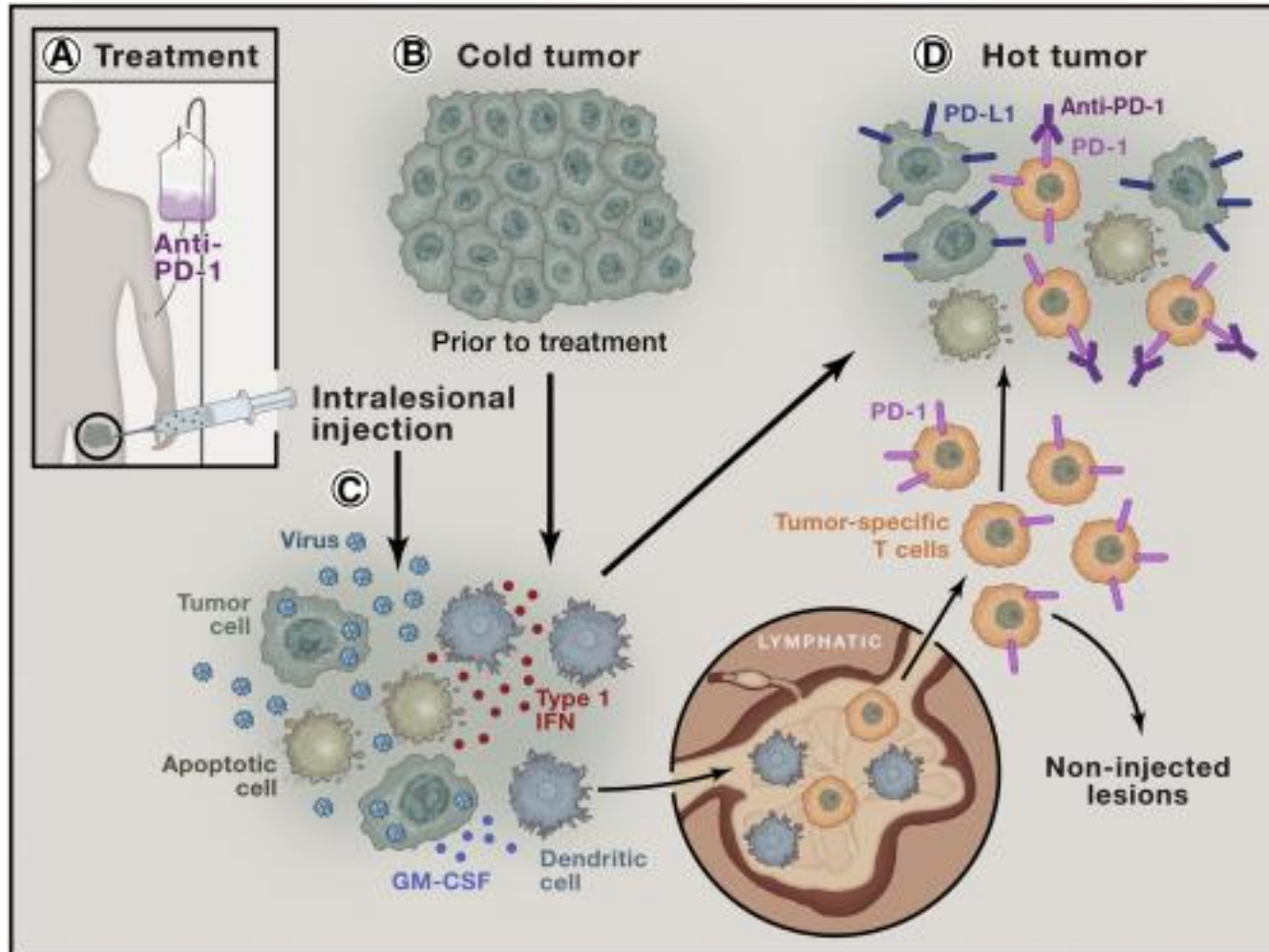


“How is your cancer cell dying?”



Galluzzi et al. Nature Rev Immunol. 2017

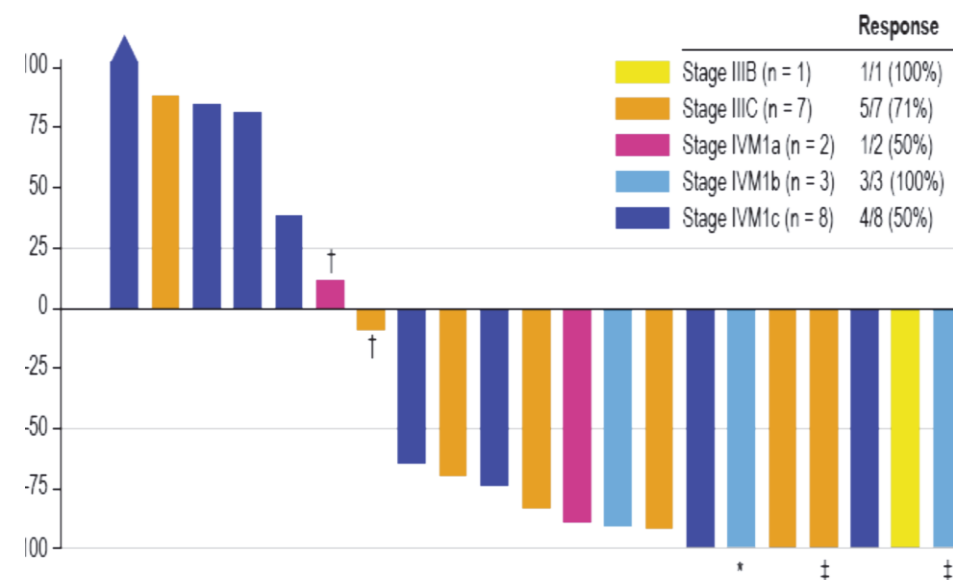
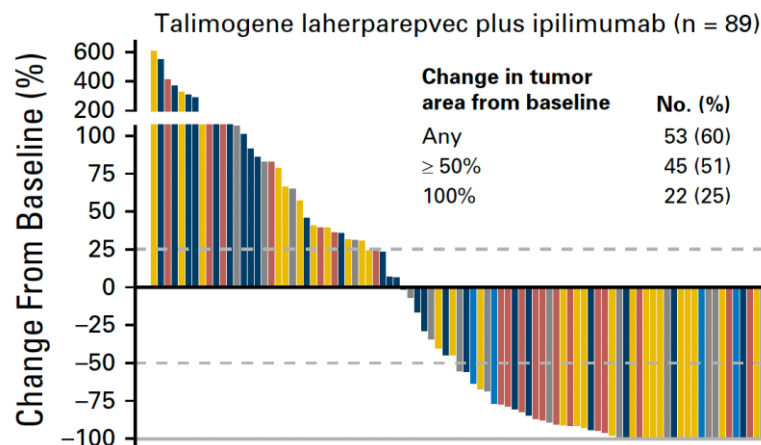
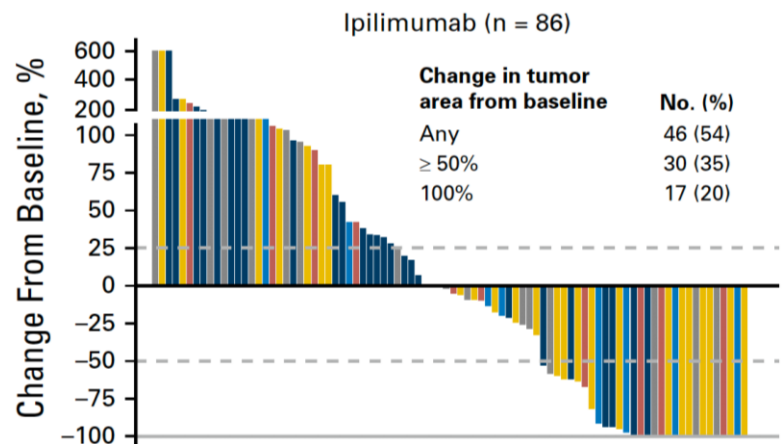
Intra-lesional cancer therapy



- Oncolytic viruses
- TLR agonists
- STING agonists
- Cytokines
- Monoclonal antibodies
- Electroporation

Haanen Cell 2017

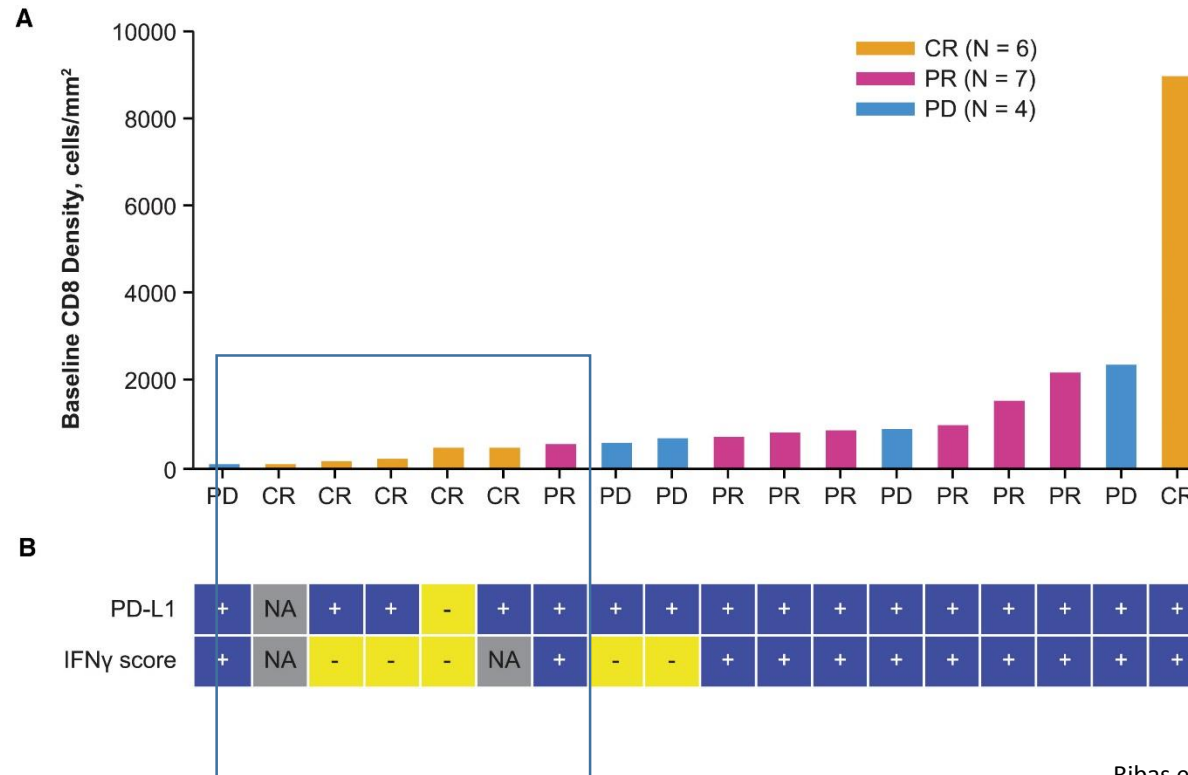
T-VEC and immune checkpoint blockade



Chesney et al. JCO 2017

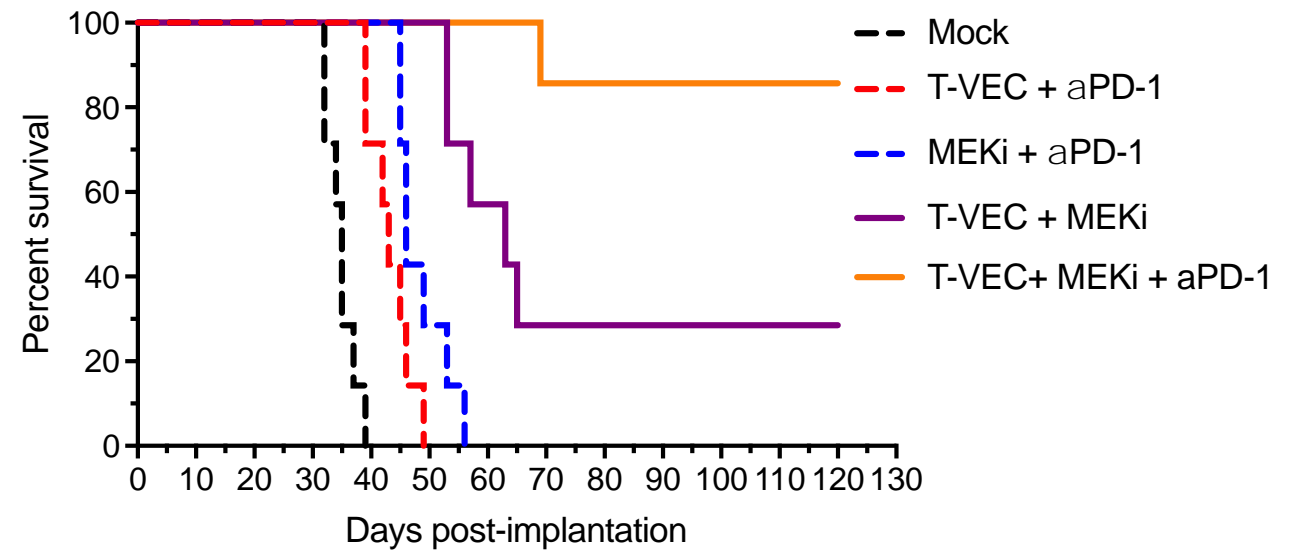
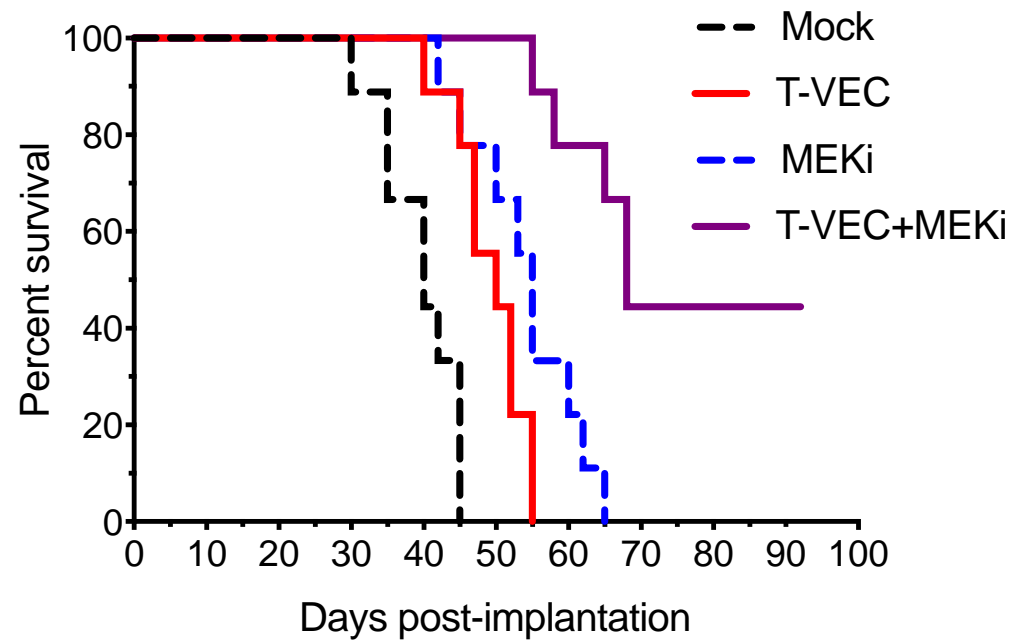
Ribas et al. Cell 2017

T-VEC + pembrolizumab induces CR in immunologically deserted tumors



Ribas et al. Cell 2017

Triple Combination Therapy for Cancer



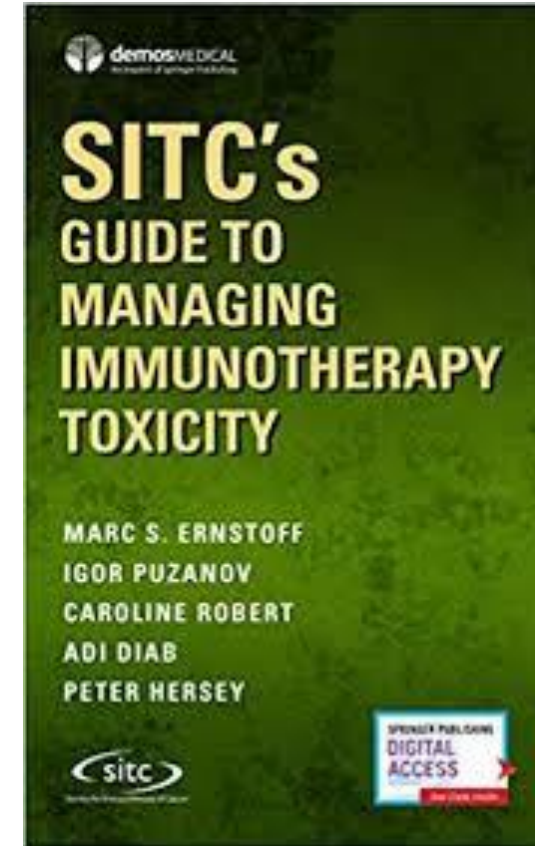
Bommareddy et al. Science Transl Med 2018

Managing IO-related toxicity

TABLE 1. Immune-Related Adverse Reactions

Common (> 10%)	Rare (< 5%)
Dermatitis, pruritus	Arthritis
Fevers, chills, fatigue	Dermatomyositis
Diarrhea/colitis	Diabetes type 1
	Encephalitis
Infrequent (5%–10%)	Episcleritis/uveitis
Hepatitis/liver enzyme abnormalities	Myocarditis
Endocrinopathies: hypophysitis, thyroiditis, adrenal insufficiency	Nephritis
Vitiligo	Neuropathies, Guillain-Barré, myasthenia gravis
	Pancreatitis
	Pericarditis
	Pneumonitis
	Thrombocytopenia
	Toxic epidermal necrolysis, Stevens-Johnson syndrome
	Vasculitis

Note. Information from Champiat et al. (2016).

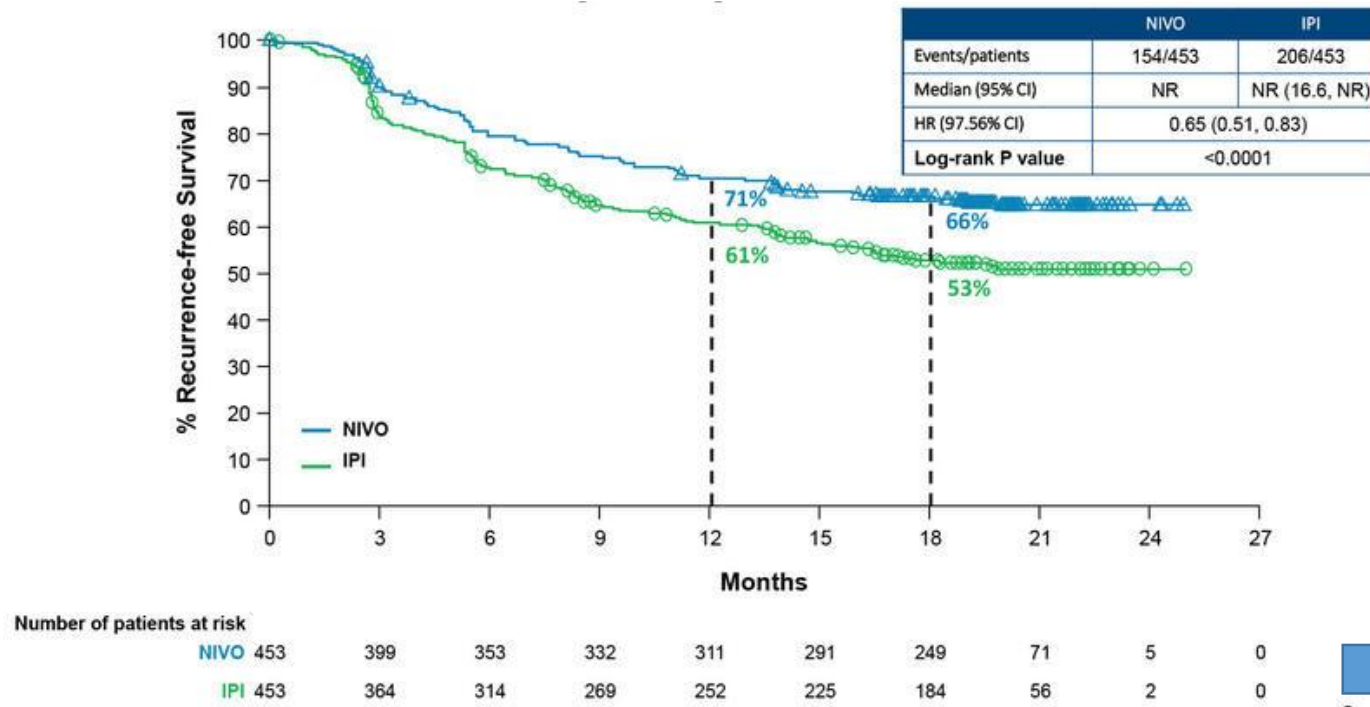


Adjuvant immunotherapy

December 20, 2017

FDA Approves Adjuvant Nivolumab for Melanoma

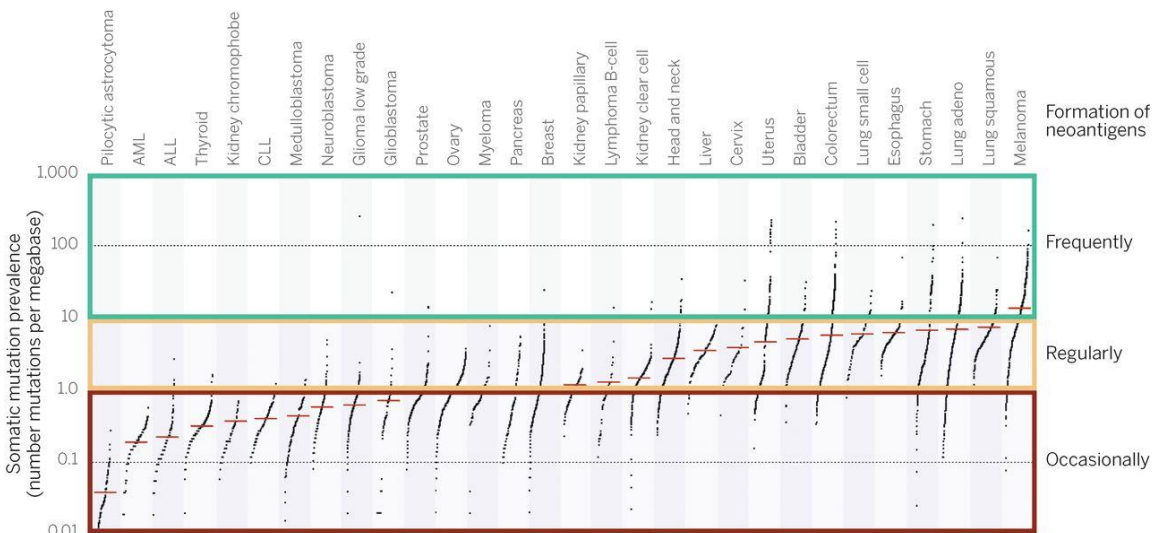
The FDA has approved nivolumab as an adjuvant treatment for patients with completely resected melanoma with lymph node involvement or metastatic disease.



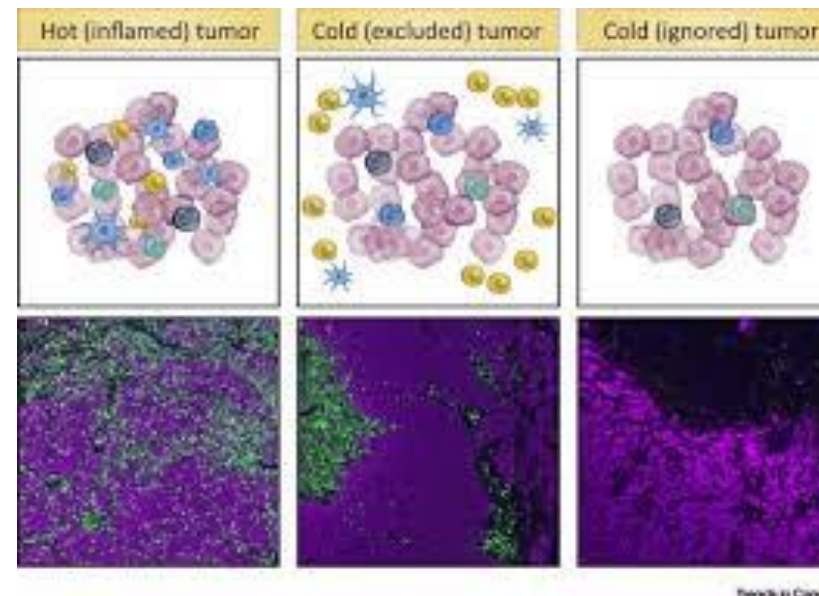
- Neoadjuvant immunotherapy?
- How does this change the natural history?

Weber et al. NEJM 2017

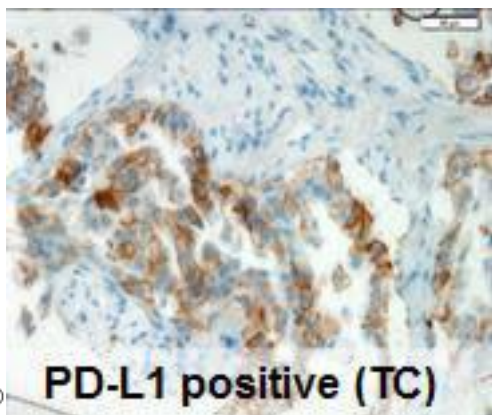
Validating Biomarkers for Immunotherapy



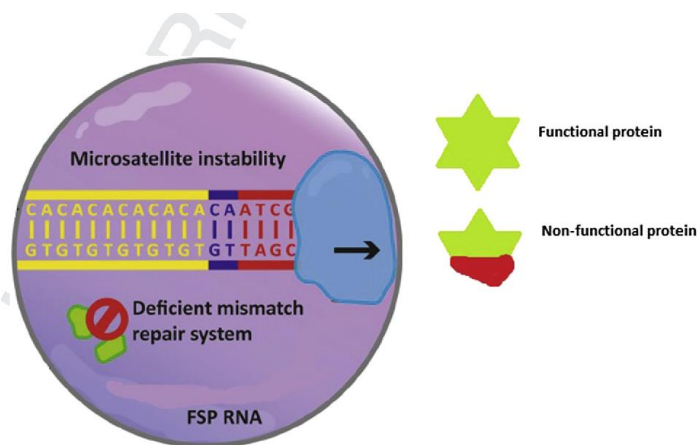
Tumor mutation burden
Neoantigen repertoire



Tumor lymphocyte infiltration



PD-L1 expression



Microsatellite instability

Yarchoan et al. NEJM 2017
Van der Woude et al. Trends Cancer 2017
Westdorp et al. Cancer Letters 2017

Conclusions

- Immunotherapy has revolutionized cancer therapy
- Multiple types of immunotherapy are approved (and in development)
- Promising approaches for activating anti-tumor immunity
 - Cytokines, vaccines, intra-lesional approaches, T cell therapy
- Strategies for blocking immune suppression are needed
 - Cells (M2 macrophages, MDSC, Tregs, etc.)
 - Soluble factors (IL-10, TGF-beta, VEGF, exosomes, etc.)
- Impact of agents on tumor cell ICD may guide immunotherapy
- Combination strategies are a high priority for investigation
- Many questions remain:
 - When should immunotherapy start and stop?
 - What mediates toxicity and how should it be managed?
 - What are the best predictive biomarkers?
 - What are the optimal combinations or sequences?