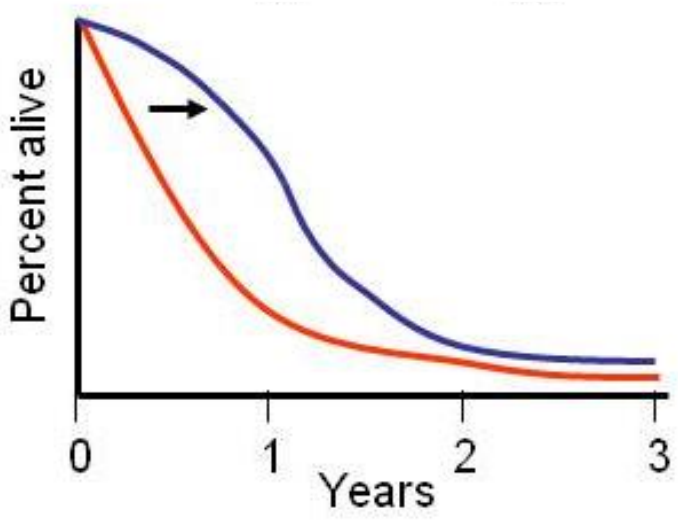
Immunotherapy for Cancer: Where are we now?

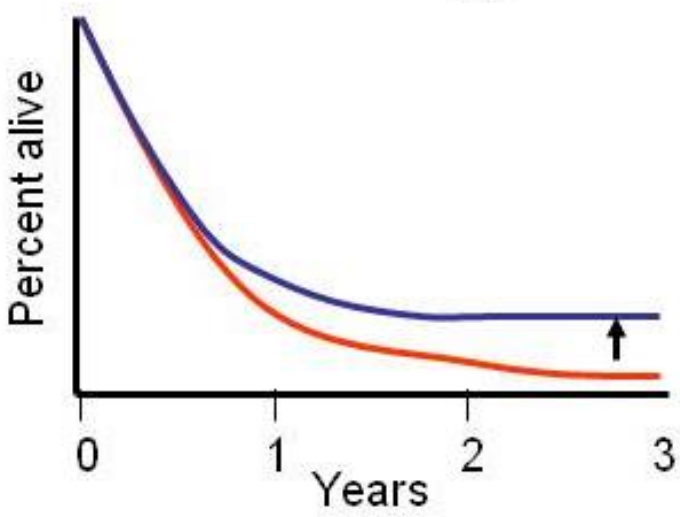
Marcus O. Butler
Princess Margaret Cancer Centre

Goals for the Treatment of Metastatic "Incurable" Cancer

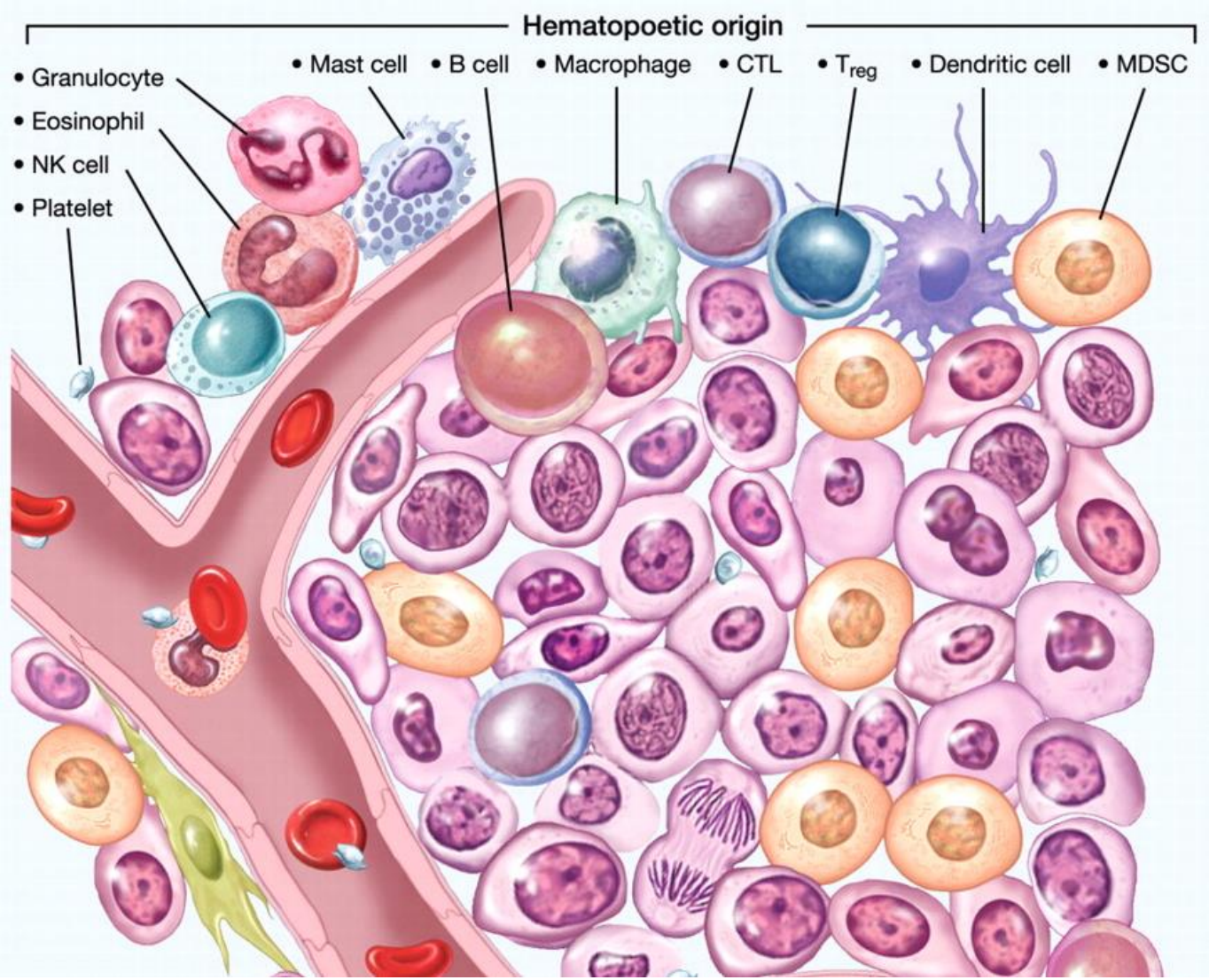
Standard Therapy



Immunotherapy



Tumor microenvironment – immune cells

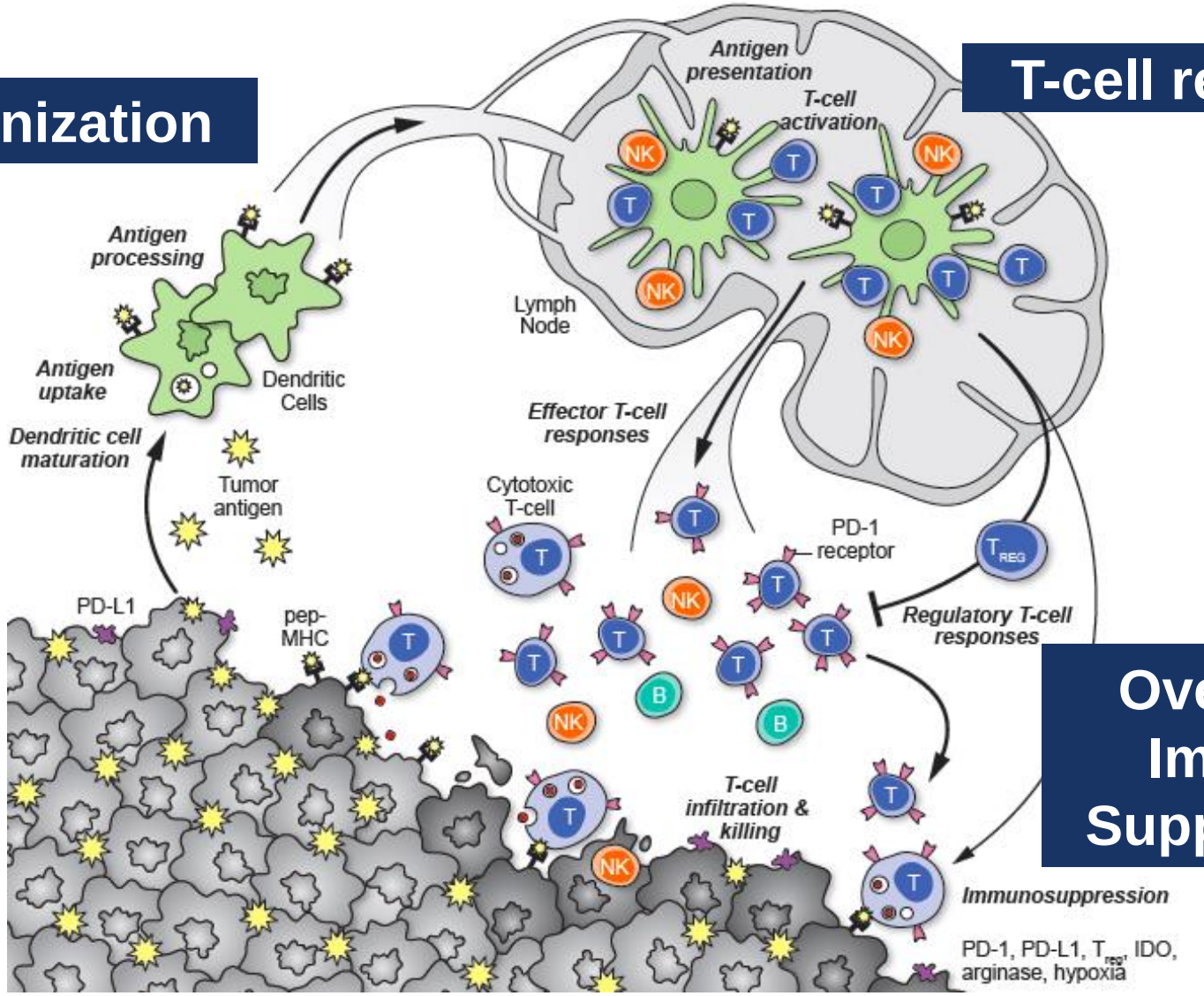


Kerkar and Restifo, Cancer Res 2012

Three Requirements for Spontaneous or Therapeutic Immune Response

Immunization

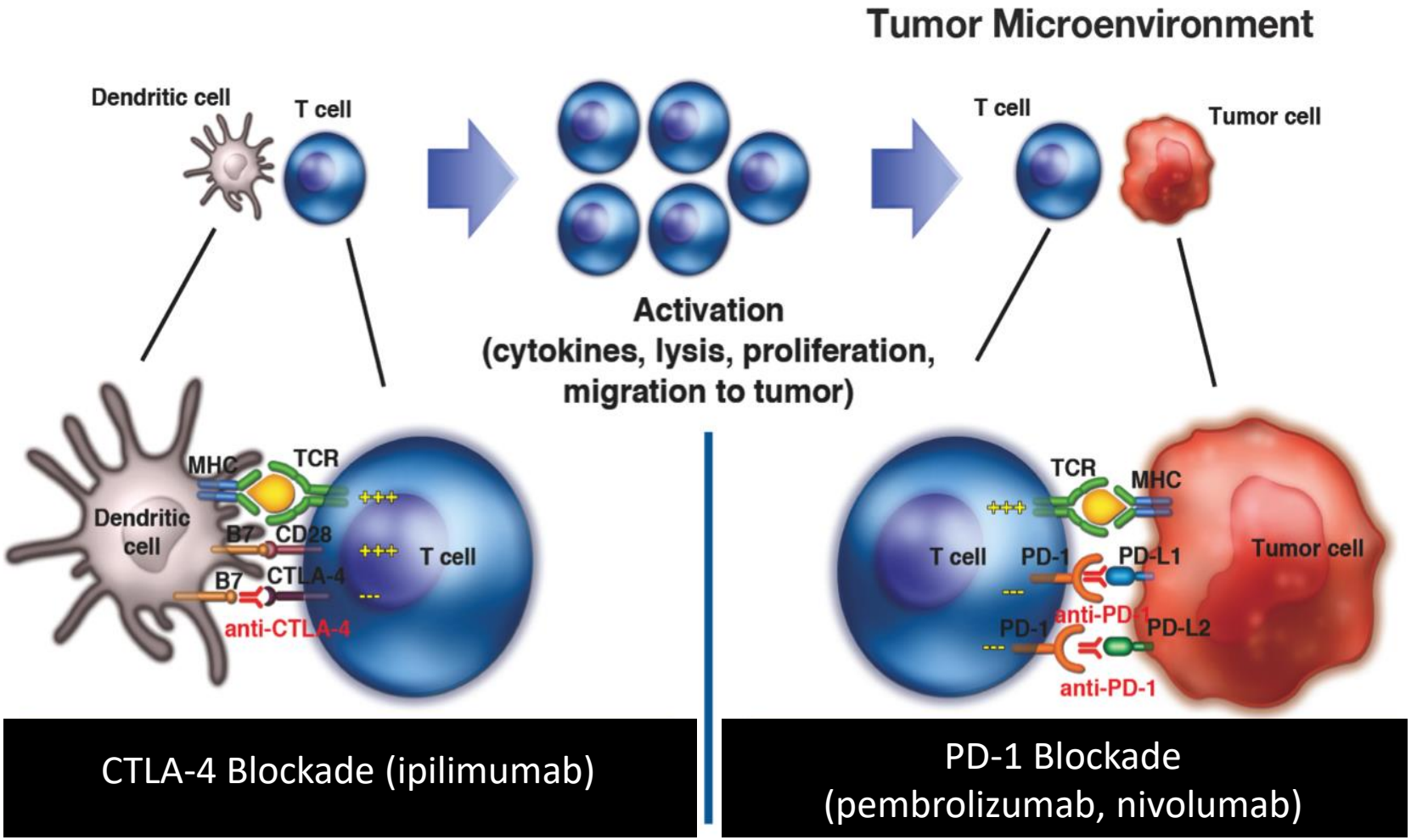
T-cell response



Overcome Immune Suppression

Mellman, Coukos, Dranoff. Nature 2011;480:480-489

Immune Checkpoint Antibodies

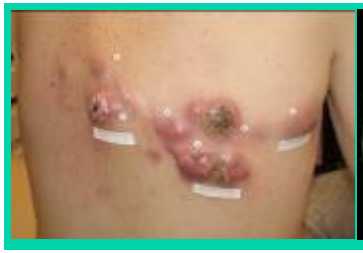
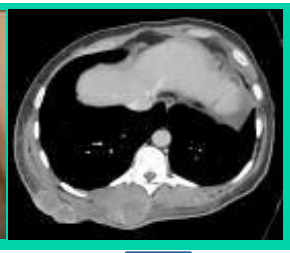


CTLA-4 Blockade (ipilimumab)

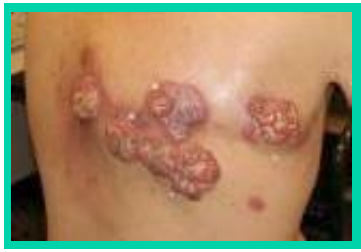
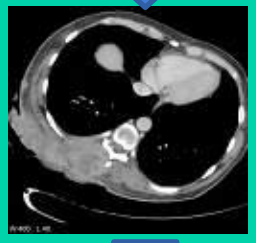
PD-1 Blockade
(pembrolizumab, nivolumab)

Presented By Jedd D. Wolchok, MD, PhD at 2013 ASCO Annual Meeting

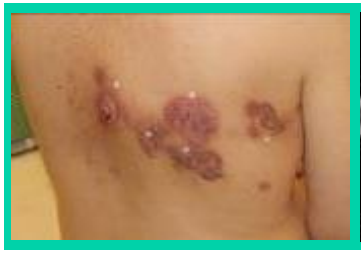
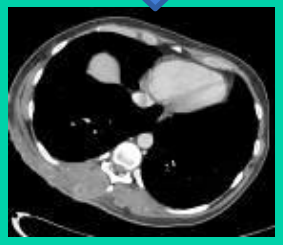
The power of immunotherapy

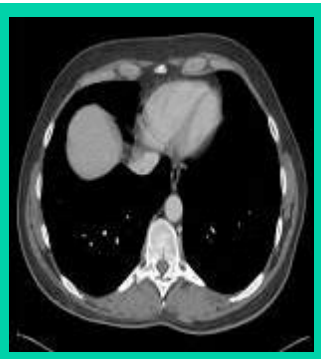
Screening

Week 12:
Initial increase in total tumor burden (mWHO PD)

Week 16:
Responding

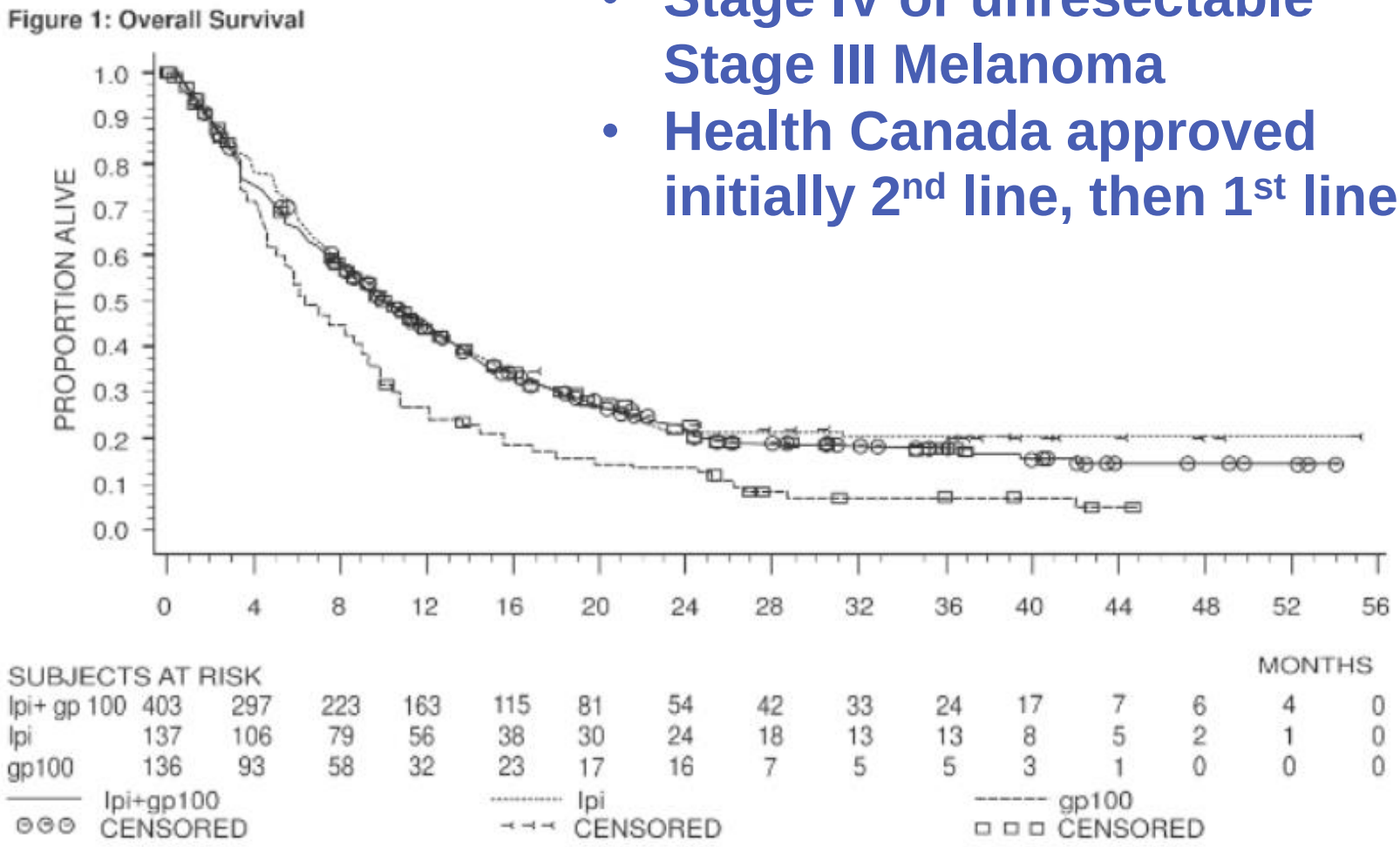



Week 96:
Durable & ongoing response without signs of IRAEs

Harmankaya K, et al: Presented at EADO 7th World Congress of Melanoma 2009, Vienna, Austria

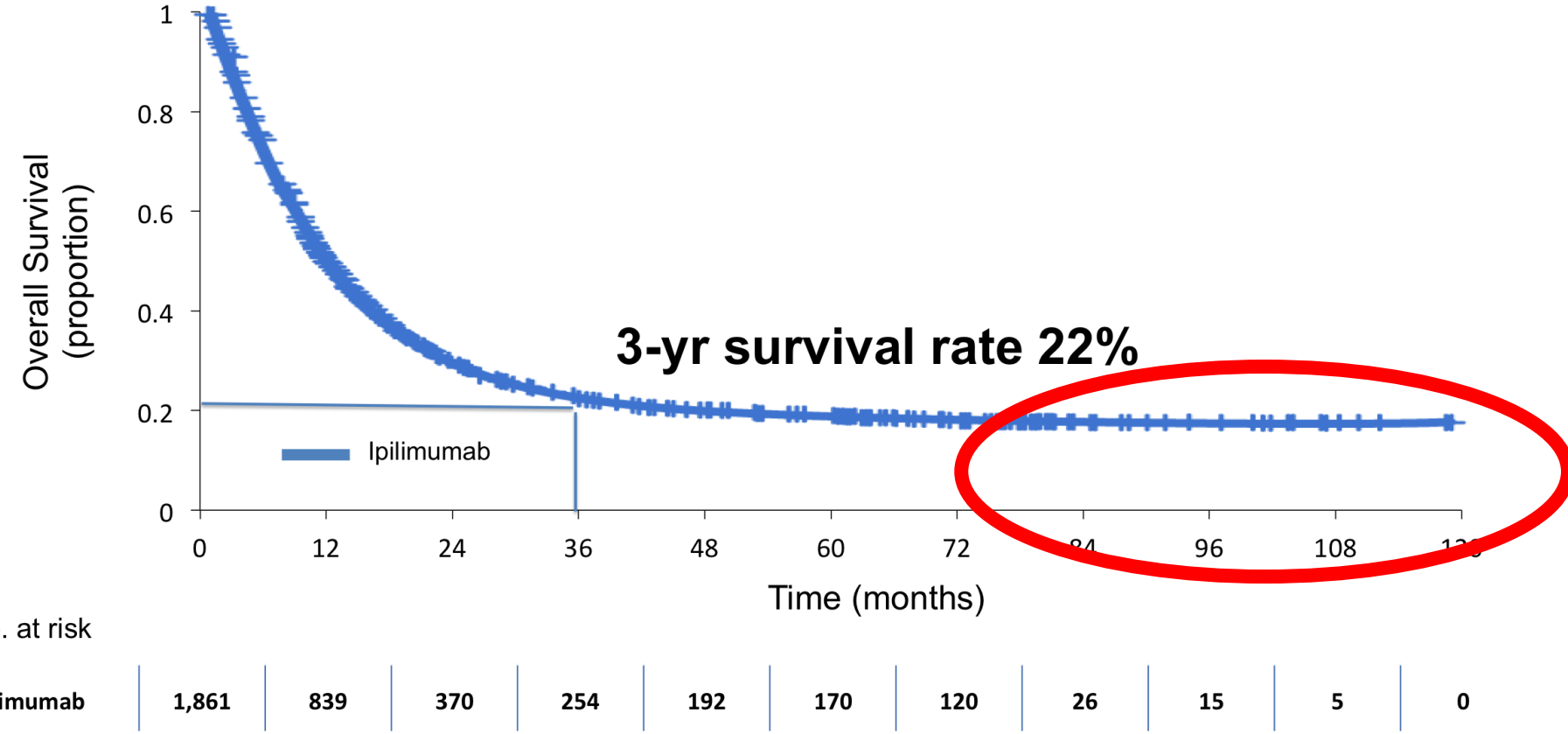
Improved Survival with Ipilimumab (Anti-CTLA-4)

- **Stage IV or unresectable Stage III Melanoma**
- **Health Canada approved initially 2nd line, then 1st line**



Metastatic Melanoma Survival: Ipilimumab Therapy

Durability of 10 year long-term survival after 3 years

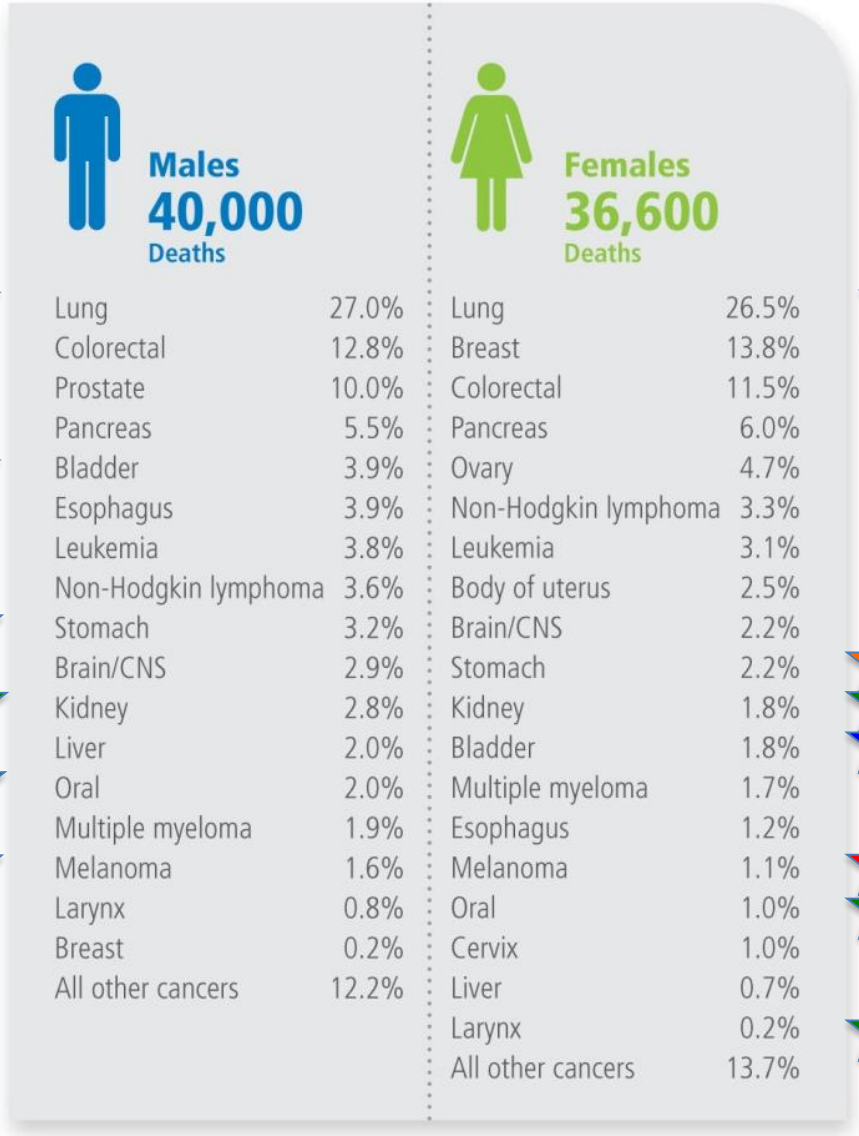


No. at risk

Ipilimumab	**1,861**	**839**	**370**	**254**	**192**	**170**	**120**	**26**	**15**	**5**	**0**

Schadendorf D et al. *J Clin Oncol* 2015; Feb 9: doi 10.1200/JCO.2014.56.2736

Immune Checkpoint Inhibitor Monotherapy



Males
40,000
Deaths

Lung	27.0%
Colorectal	12.8%
Prostate	10.0%
Pancreas	5.5%
Bladder	3.9%
Esophagus	3.9%
Leukemia	3.8%
Non-Hodgkin lymphoma	3.6%
Stomach	3.2%
Brain/CNS	2.9%
Kidney	2.8%
Liver	2.0%
Oral	2.0%
Multiple myeloma	1.9%
Melanoma	1.6%
Larynx	0.8%
Breast	0.2%
All other cancers	12.2%

Females
36,600
Deaths

Lung	26.5%
Breast	13.8%
Colorectal	11.5%
Pancreas	6.0%
Ovary	4.7%
Non-Hodgkin lymphoma	3.3%
Leukemia	3.1%
Body of uterus	2.5%
Brain/CNS	2.2%
Stomach	2.2%
Kidney	1.8%
Bladder	1.8%
Multiple myeloma	1.7%
Esophagus	1.2%
Melanoma	1.1%
Oral	1.0%
Cervix	1.0%
Liver	0.7%
Larynx	0.2%
All other cancers	13.7%

*

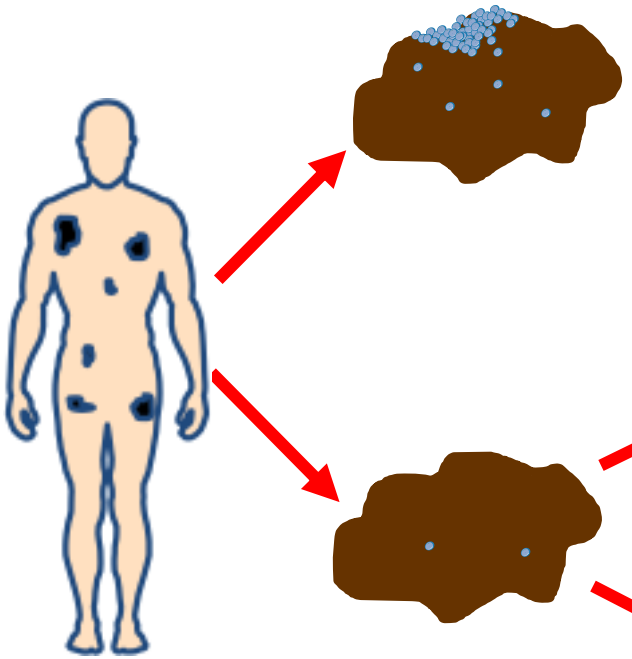
Canadian Cancer Statistics 2014

Overall Response Rate

30-40%	PD-1/PD-L1
20-30%	PD-1/PD-L1
10-20%	PD-1/PD-L1
10%	CTLA-4

*TNBC subtype only

Management of cancer in the post-anti-PD-1/L1 era



Anti-PD-1/anti-PD-L1

Bring T cells into tumors:

+ anti-CTLA4
+ radiation/SBRT
+ immune activating antibodies or cytokines
+ TLR agonists or oncolytic viruses
+ IDO or macrophage inhibitors
+ targeted therapies
+ Bispecific molecules

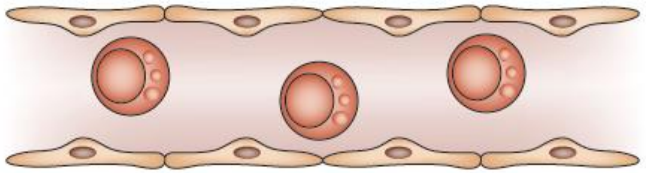
Generate/Expand T cells:

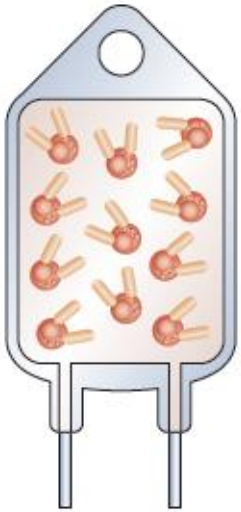
Vaccines/radiation
TCR engineered ACT
CAR engineered ACT
Expanded T cells/TIL

ACT with Gene-Engineered T Cells

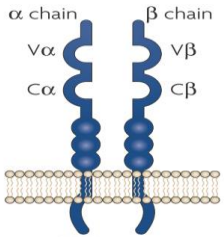
Infuse the T cells into the patient

Isolate lymphocytes from patient's blood



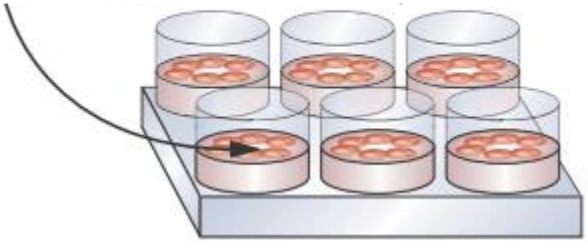


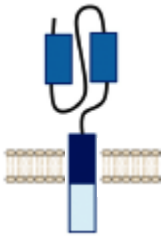
Expand the genetically engineered T cells



TCR genes

Transduction of the peripheral T cells





CAR

Redirect the T cells toward tumor cells

Antitumor TCR/CAR genes

(Rosenberg, Nat Rev Clin Oncol. 2011)

Summary

- Oncologists have become Immunotherapists
  - We have made great strides for many patients
  - However, most do not have long-term benefit
- Ways to make it better:
  - New combinations
    - Searching for better response rates, lower toxicity
    - Cell therapies, vaccines, radiation to focus the immune response
  - New strategies
    - Better selection– identify who can easily respond to therapy and who needs a faster approach

Challenges

- Treating patients with the best therapies tailored to their tumor and immune system
- Understand the **value** of these new therapies
  - Response rate
  - Reduction of pain and suffering
  - Long-term benefit
- Managing the health care system
  - Access to treatments through partnerships with patients, industry, government, and the healthcare system