

# Immunotherapy 101 in the Radiation Context

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# Disclosures

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- Consulting/SAB/DMB for LEK, Catenion, ACI Clinical, Debiopharm, Immunitas



# Outline

- What makes immunotherapy unique?
- Why are radiotherapy combinations appealing?
- Toxicity and response



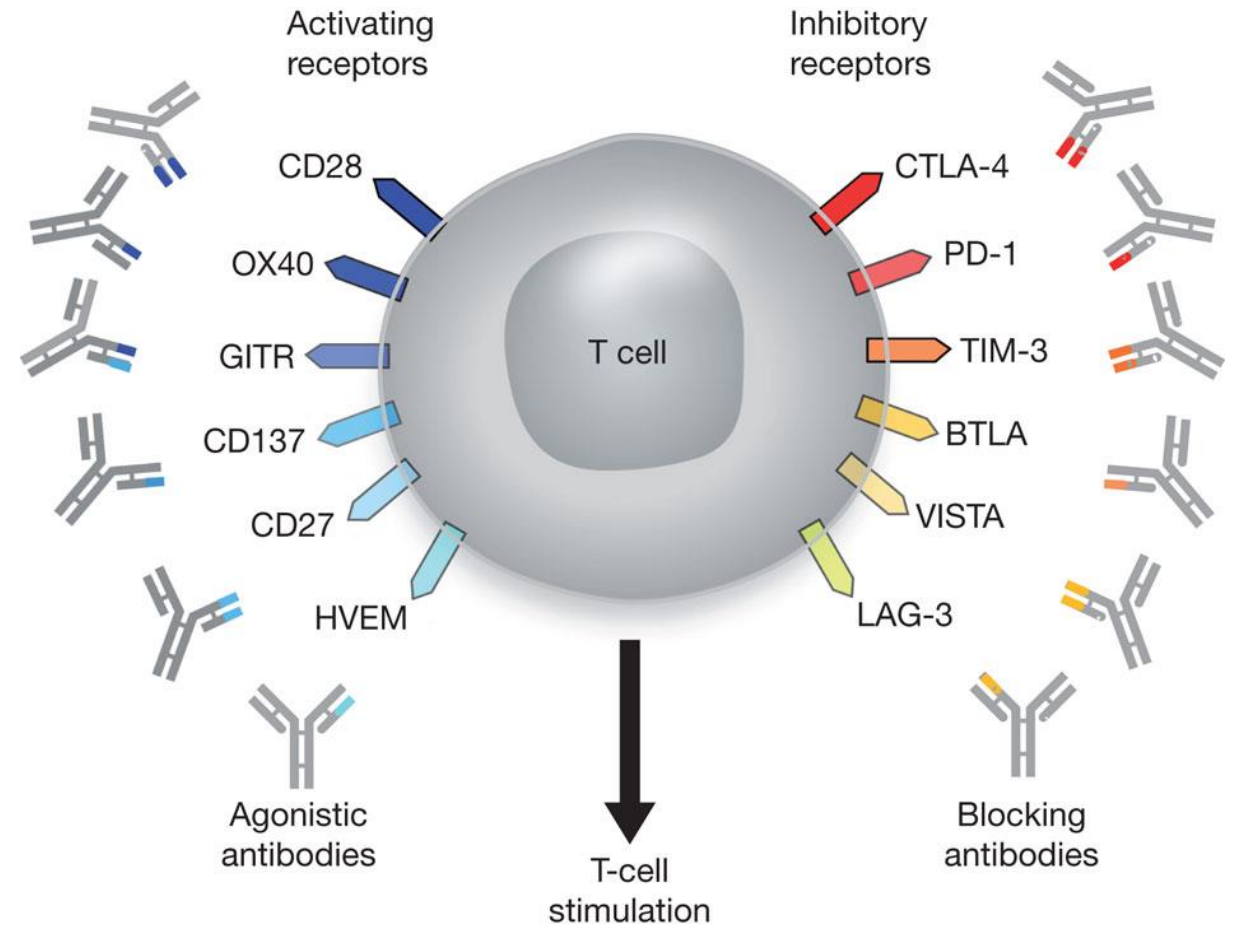
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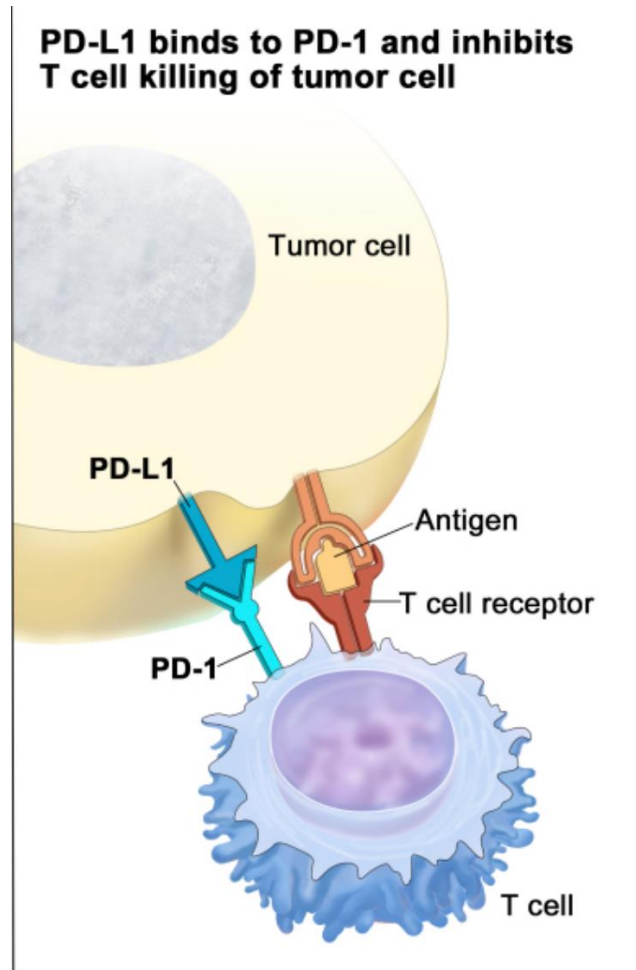
# Understanding of T-cell biology and identification of “immune checkpoints” paved the way for modern tumor immunotherapy

- Activating receptors
  - Respond to danger signals
- Inhibitory receptors
  - Immune Checkpoints

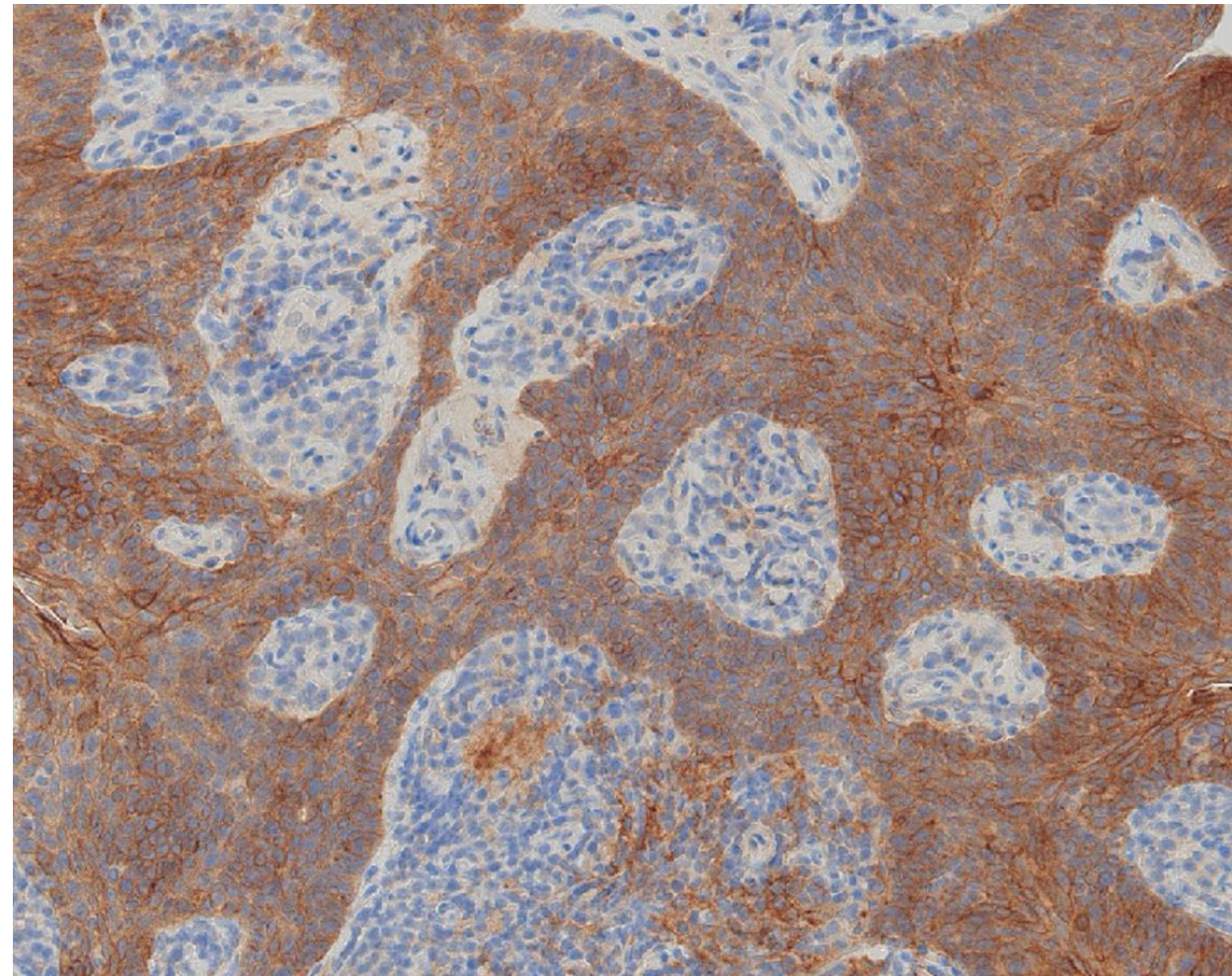




# Cancer exploits immune checkpoints such as PD-1



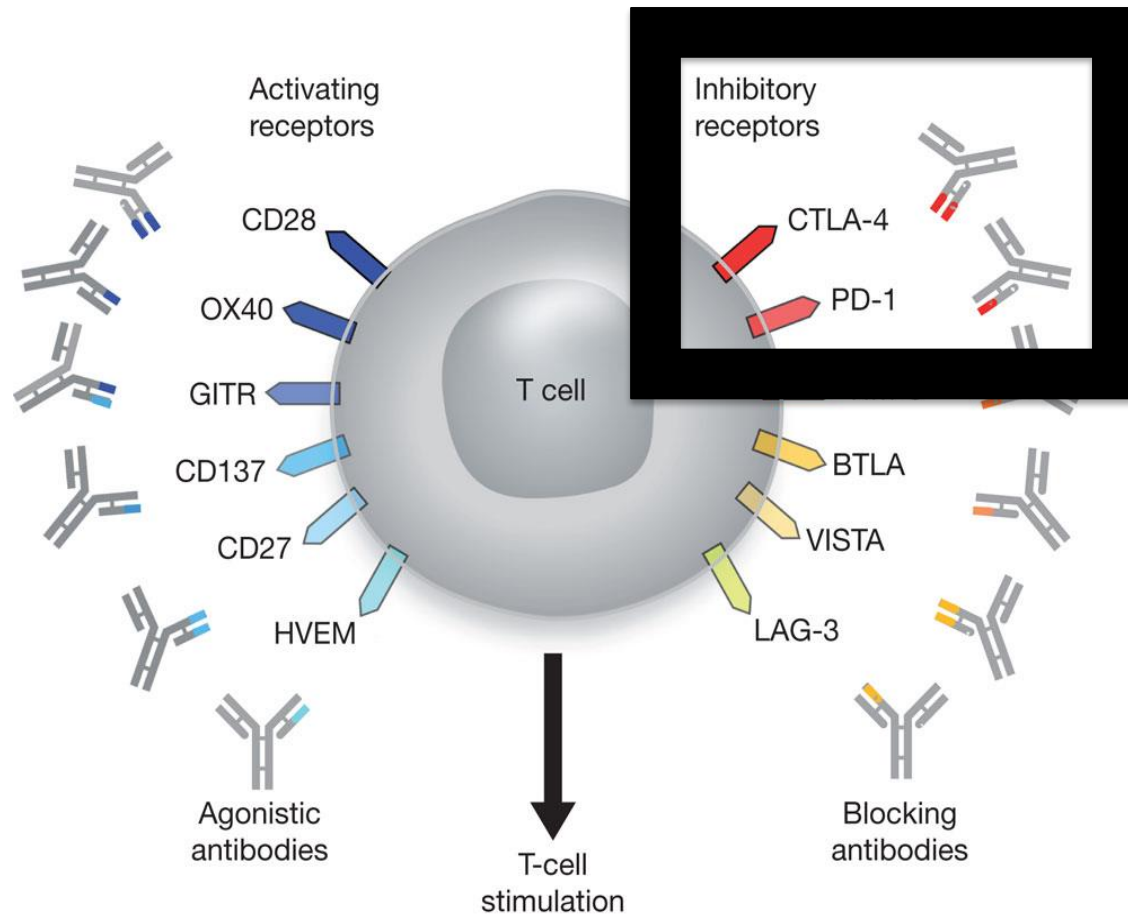
<https://www.ncbi.nlm.nih.gov/books/NBK65917>



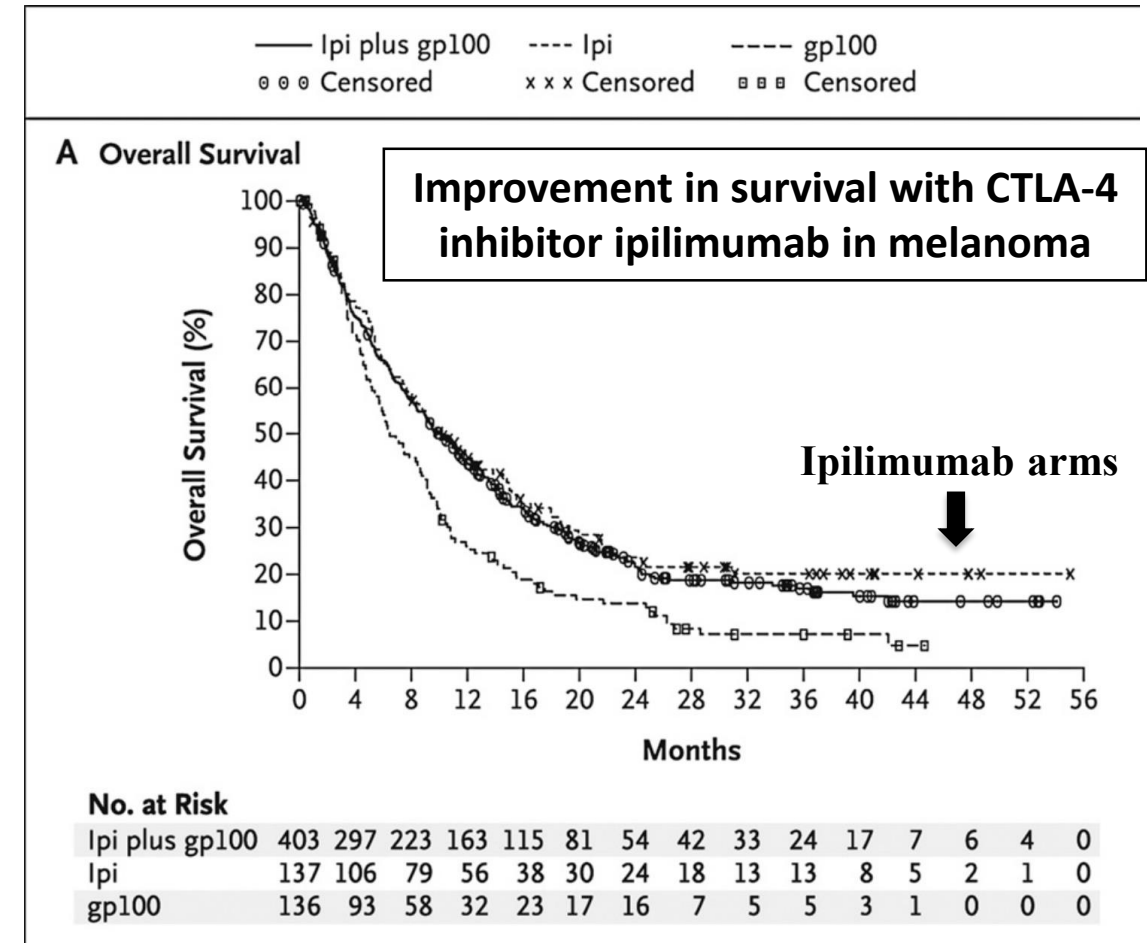
PD-L1 expression (brown) in squamous cell head and neck cancer  
Schoenfeld et al. IJROBP 2018



# Immune checkpoints have been targeted by blocking antibodies



I Mellman *et al. Nature* **480**, 480-489 (2011)  
doi:10.1038/nature10673



Hodi *et al. NEJM* 2010

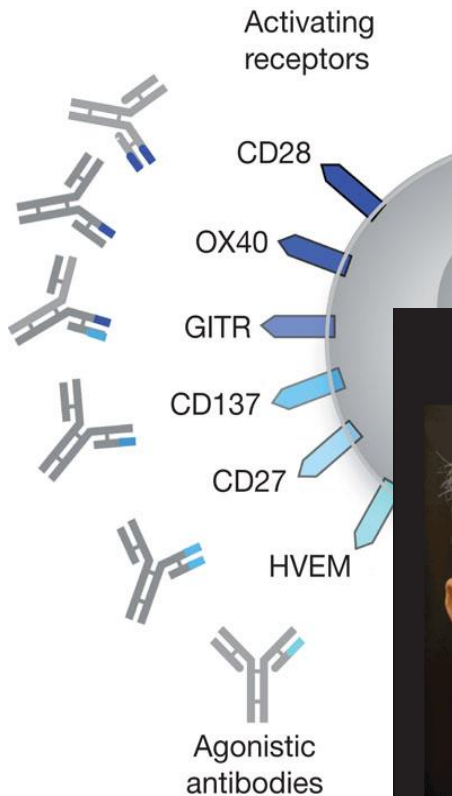
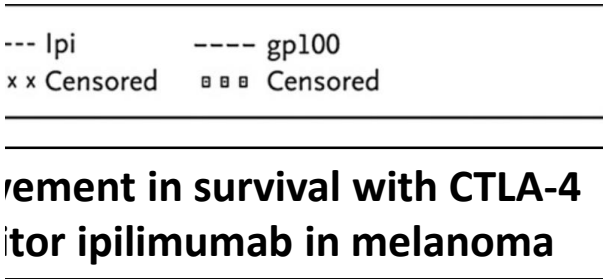






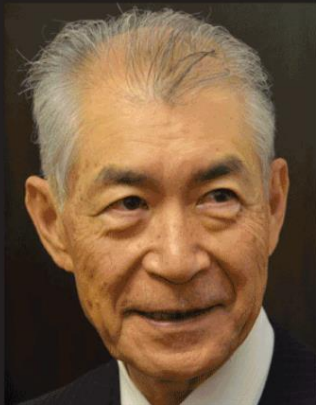
# Immune checkpoints have been targeted by blocking antibodies

Immune checkpoint inhibitors have led to improved outcomes across multiple different malignancy types (including melanoma, RCC, NSCLC, SCCHN, Merkel cell carcinoma, MSI high tumors, urothelial ca, cervical ca, gastric ca, TNBC, lymphoma, and others)

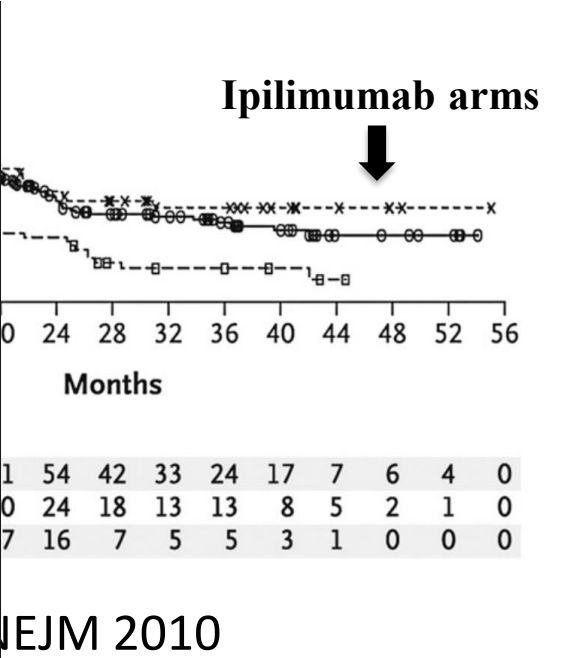
**Nobel Prize for medicine awarded in 2018**



**Nobel Prize in Medicine**



**James P. Allison (USA) and Tasuku Honjo (JPN) have won the 2018 Nobel Prize in Medicine for their discovery that the body’s immune system can be harnessed to attack cancer cells**

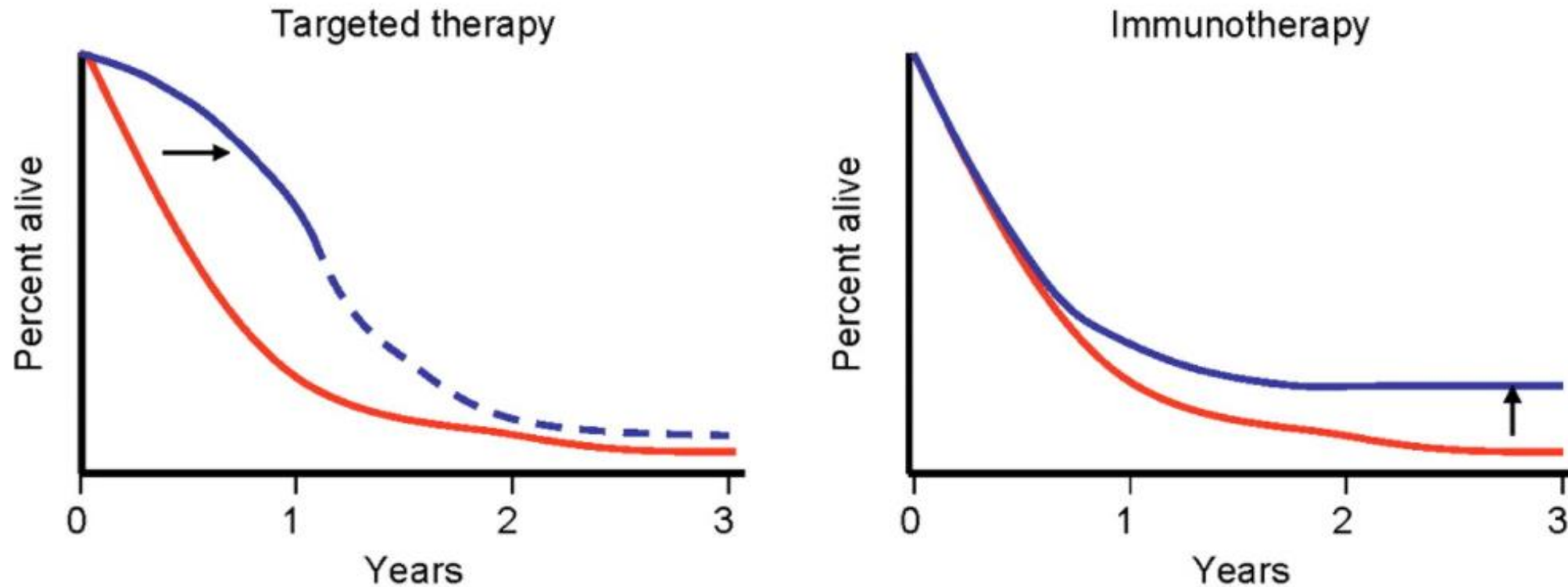


I Mellman et al. Nature 480  
doi:10.1038/nature10698





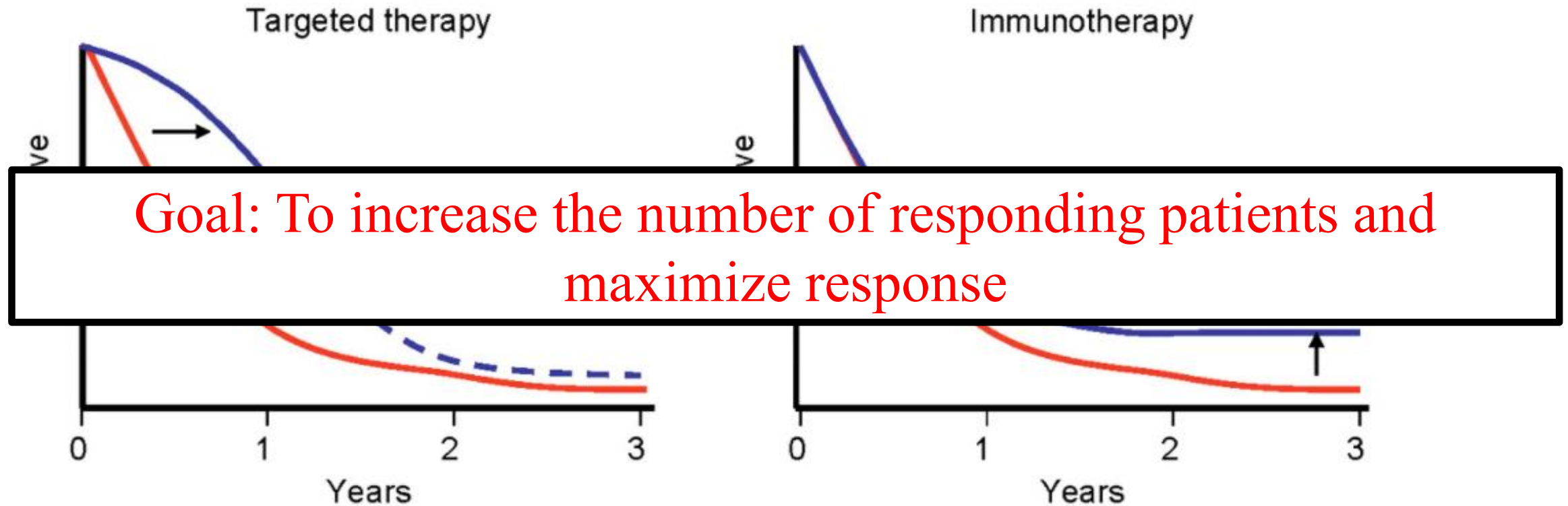
# Immunotherapy impacts long-term survival



In contrast to other therapies, only a minority of patients demonstrate any response  
**However, responding patients can respond for long periods of time, or indefinitely**



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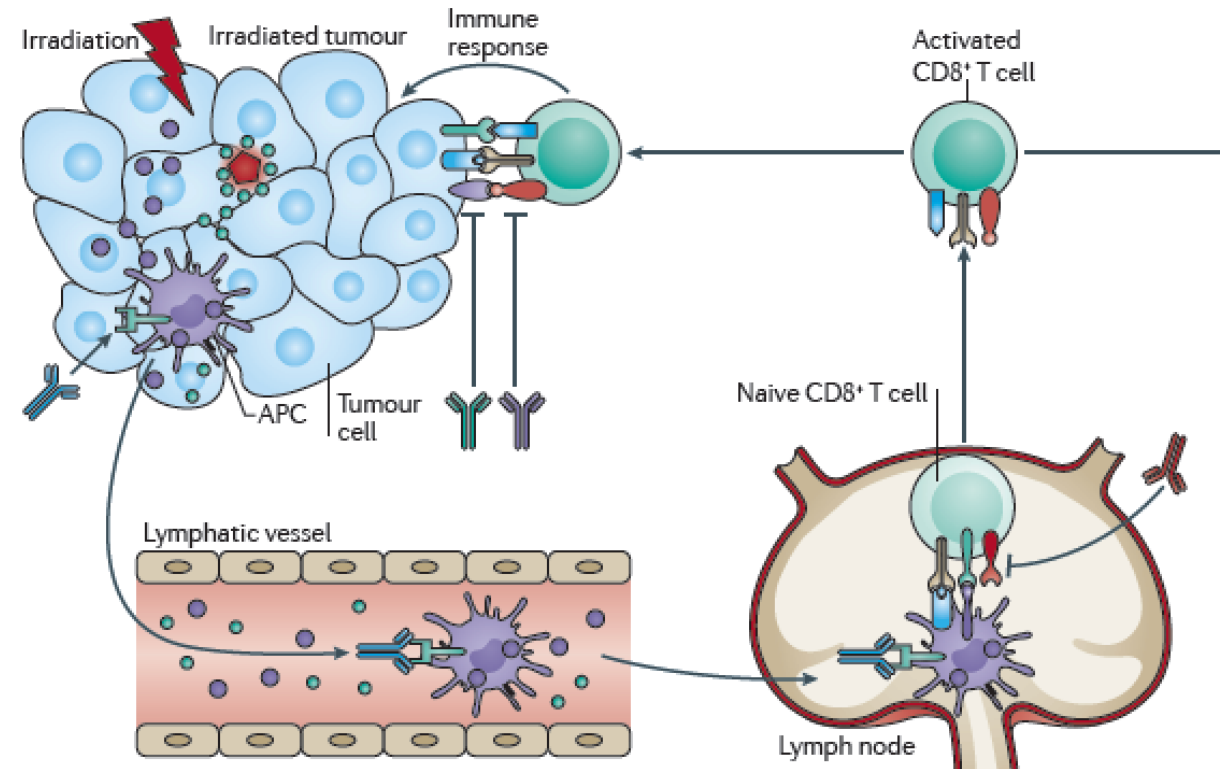
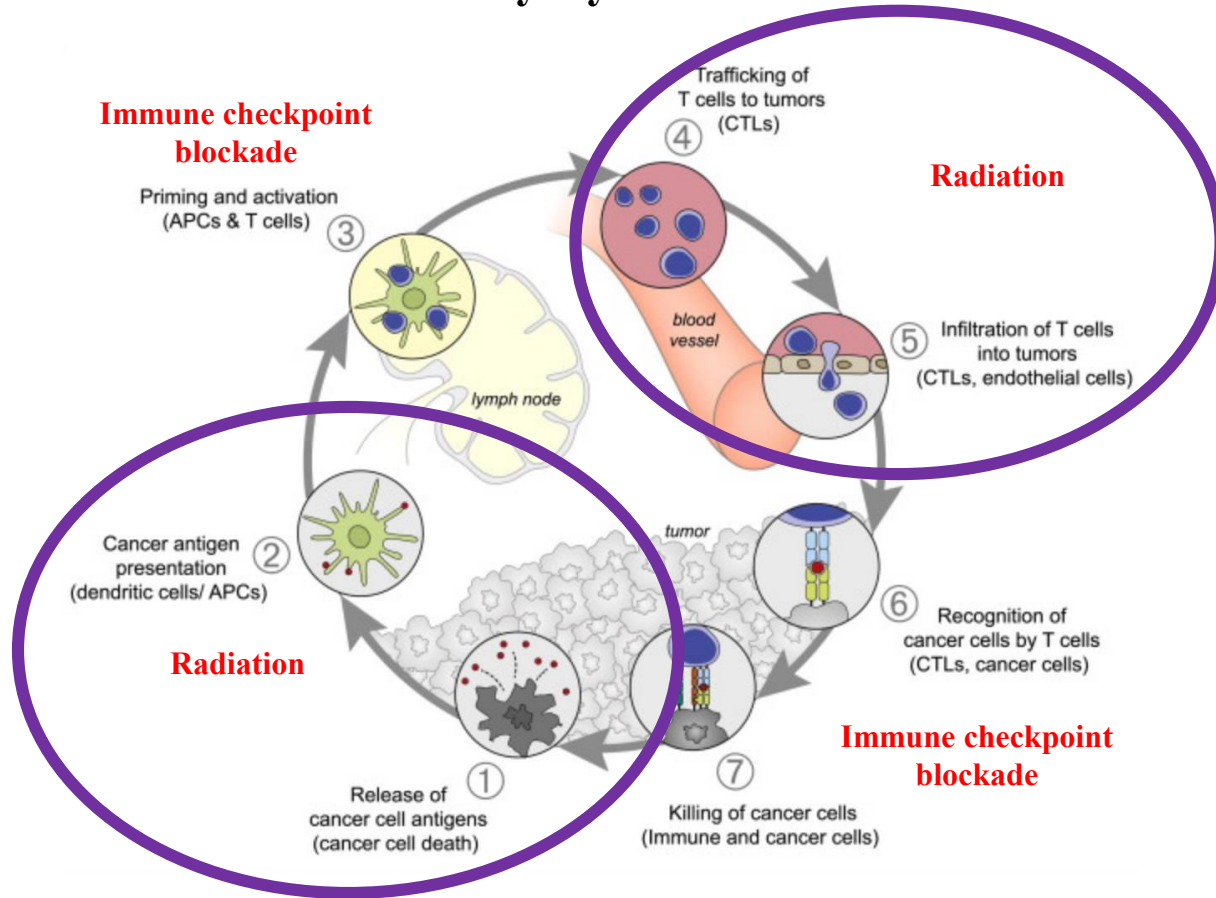
# Outline

- What makes immunotherapy unique?
- Why are radiotherapy combinations appealing?
- Relevant study endpoints



# Improving systemic response rates in patients with metastastatic disease

## Tumor Immunity Cycle



Chen and Mellman, Immunity 2013

Ngwa, Irabor, Schoenfeld et al. Nature Reviews Cancer 2018

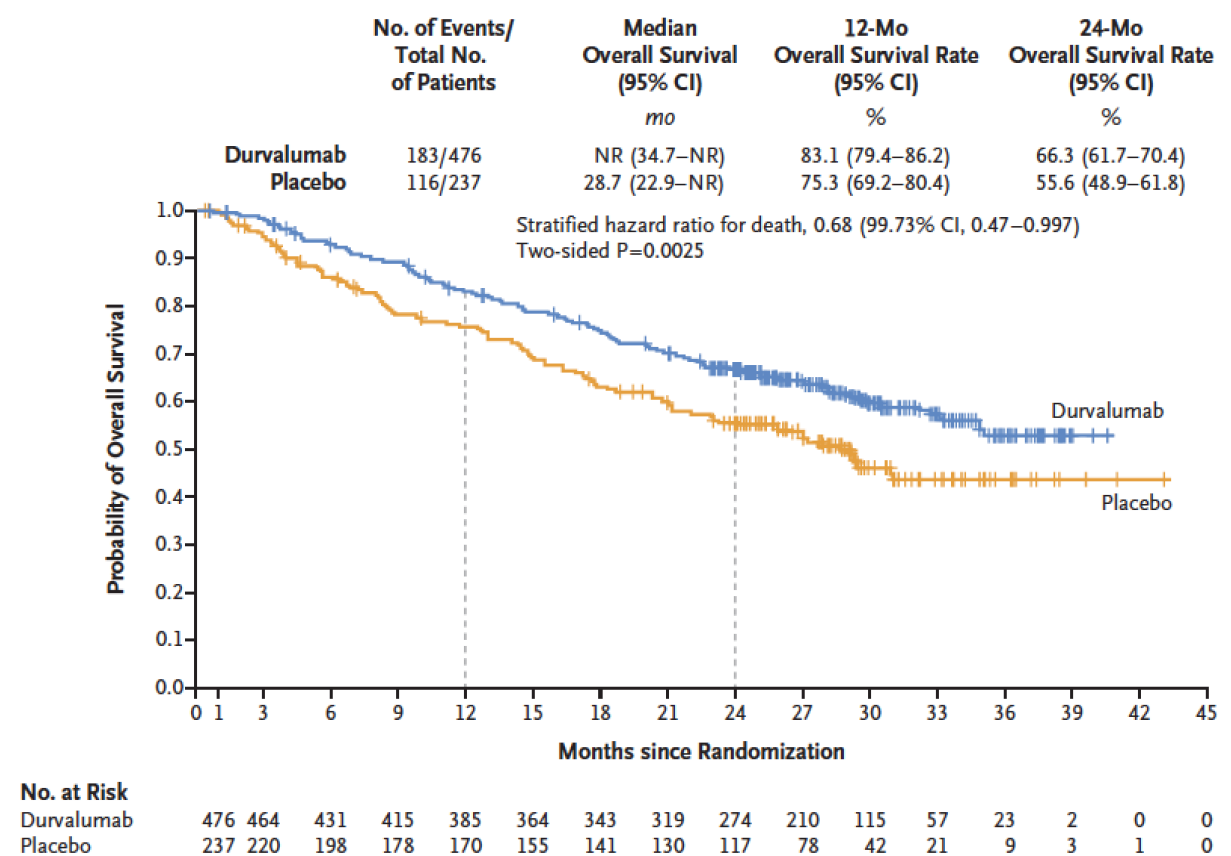
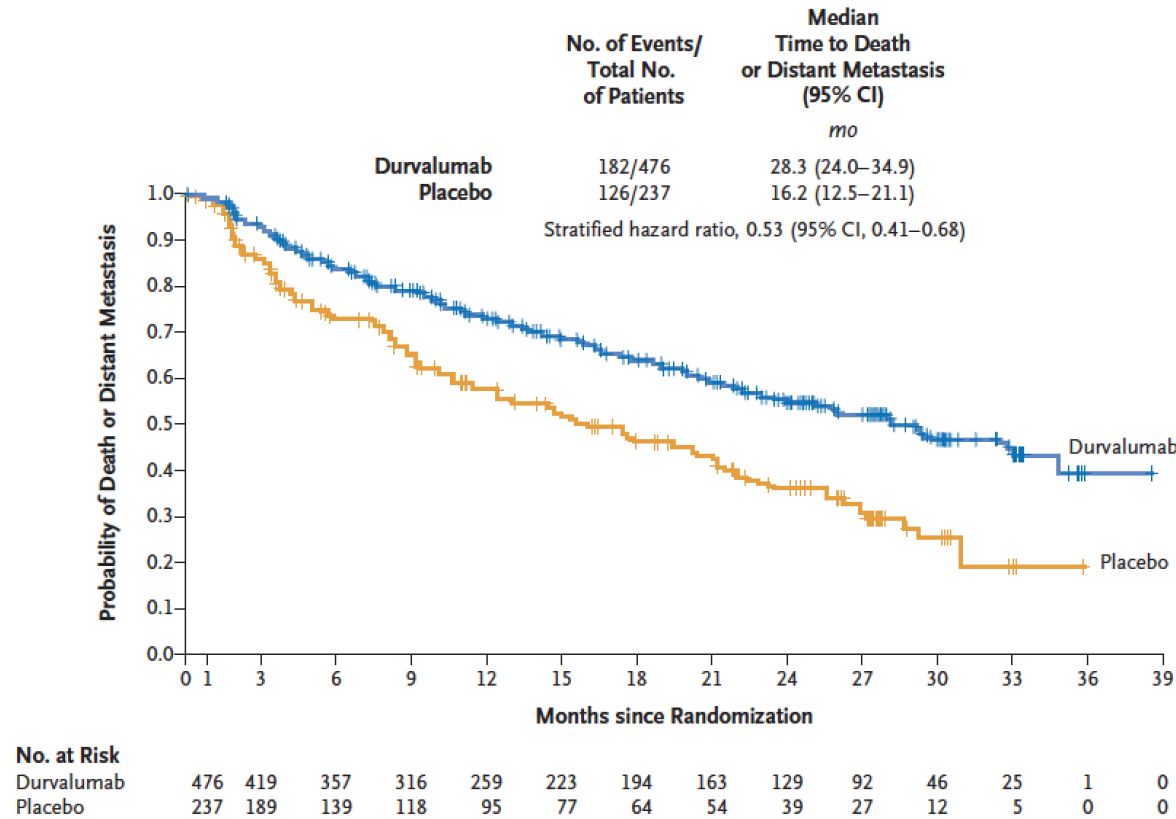




# Improving Outcomes in Locally Advanced Disease

## PACIFIC Trial – Stage 3 NSCLC

### Patients Treated with Chemoradiation +/- PD-L1 Inhibition

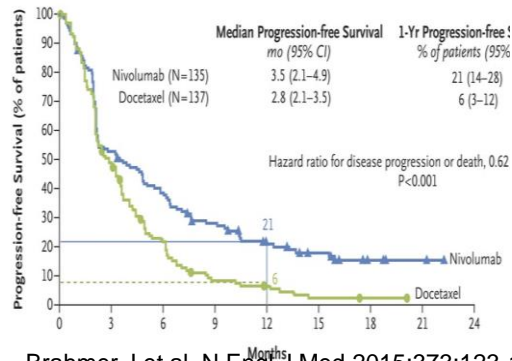


**Durvalumab Associated with Hazard Ratio for Progression of **0.53****  
**(Response rate 10-20% in unselected metastatic NSCLC population)**



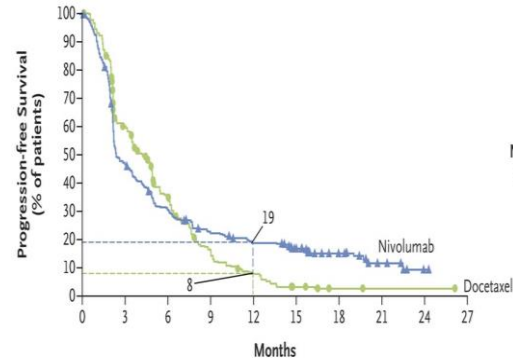
# Why might the benefit of PD-L1 blockade be greater in locally advanced disease following chemoradiation?

**Checkmate 017**



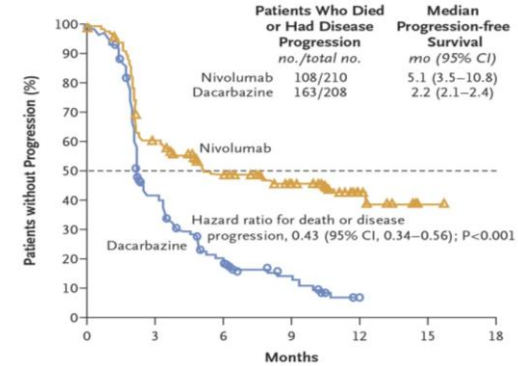
Brahmer J et al. N Engl J Med 2015;373:123-135

**Checkmate 057**



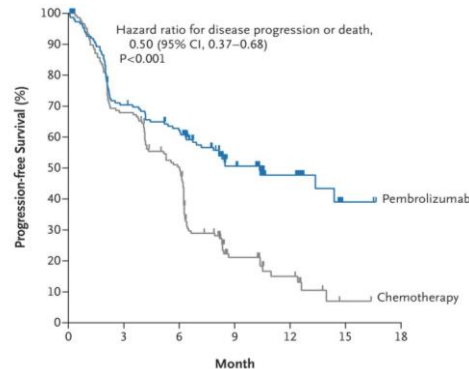
Borghaei H et al. N Engl J Med 2015;373:1627-1639

**Checkmate 066**



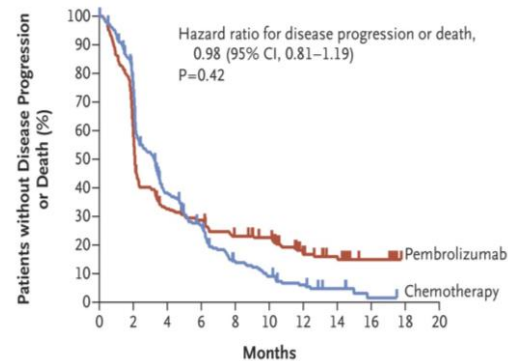
Robert C et al. N Engl J Med 2015;372:320-330

**Keynote 024**



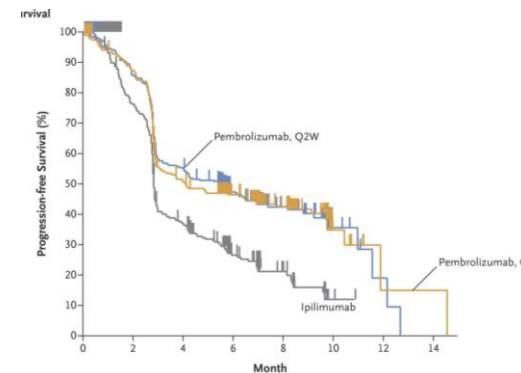
Reck M et al. N Engl J Med 2016;375:1823-1833

**Keynote 045**



Bellmunt J et al. N Engl J Med 2017;376:1015-1026

**Keynote 006**



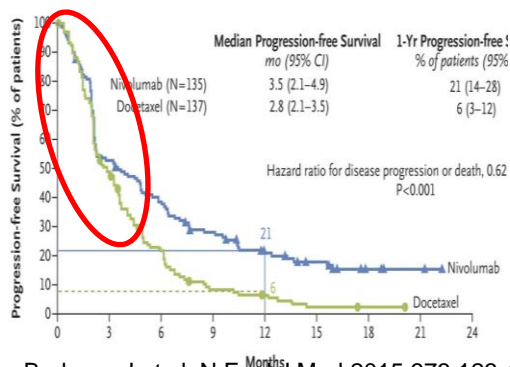
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**Landmark Immunotherapy Trials Demonstrate Durable Benefit in a Limited Percentage of Patients**



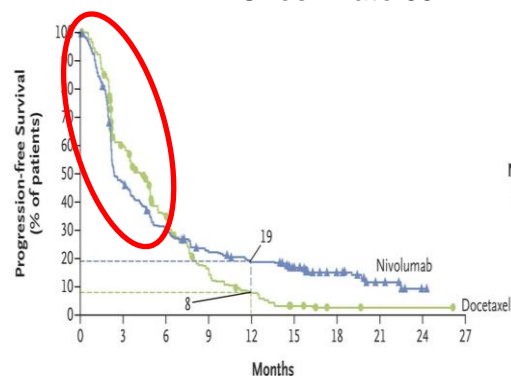
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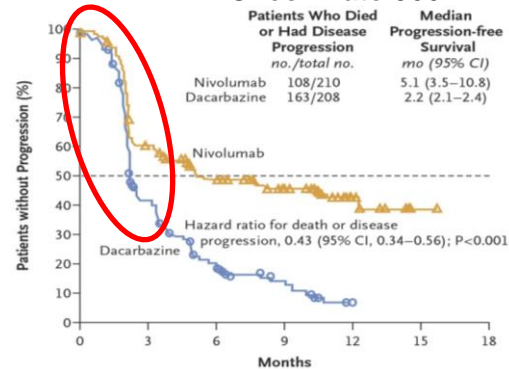
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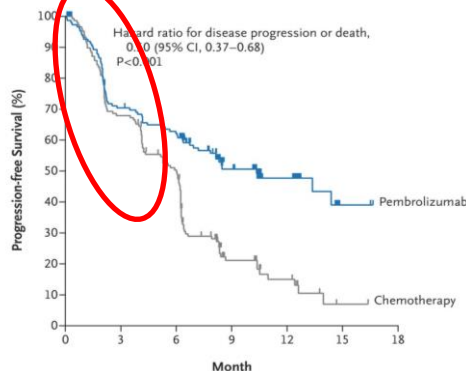
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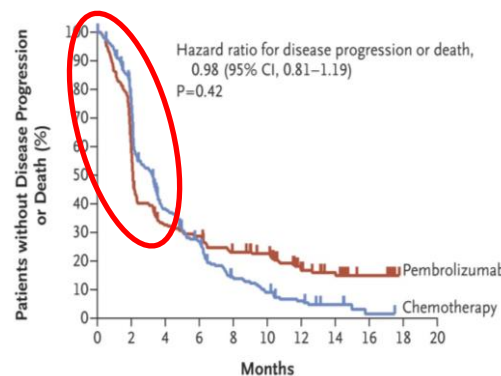
**Deviation from proportional hazards, with a population of early progressors that don't derive benefit from immunotherapy**

**Keynote 024**



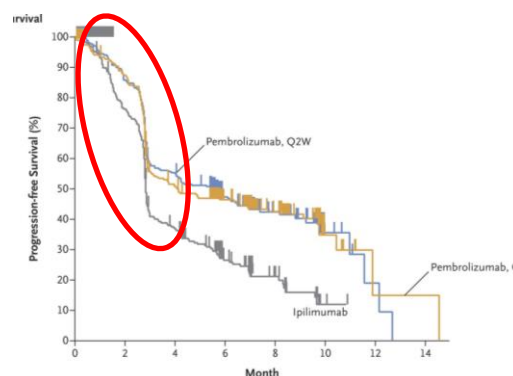
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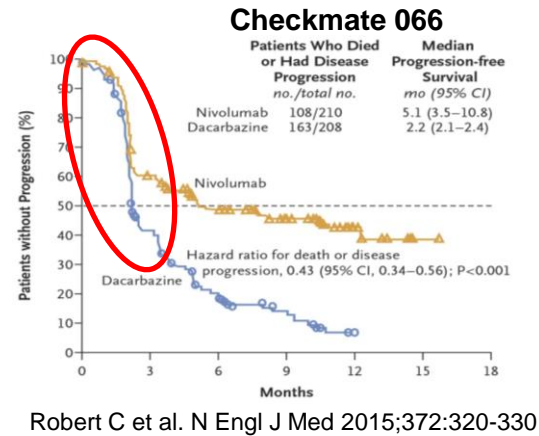
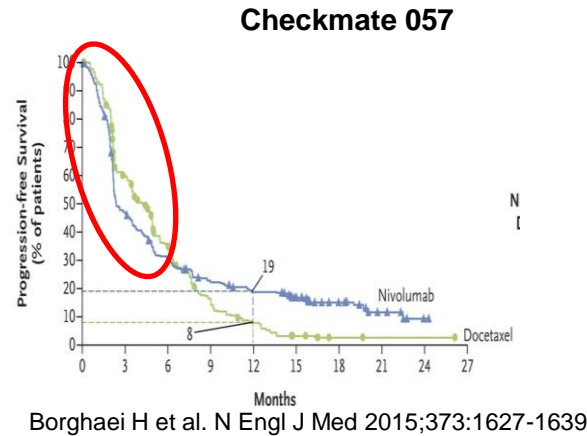
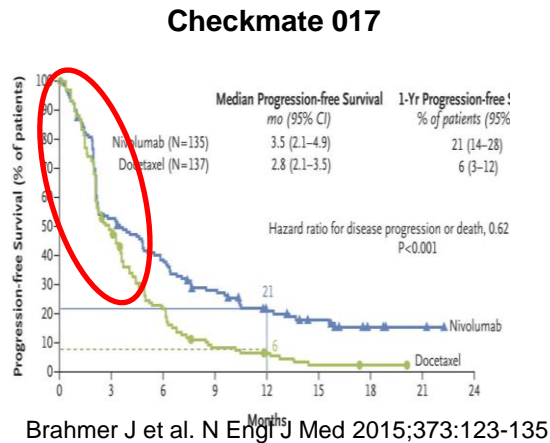


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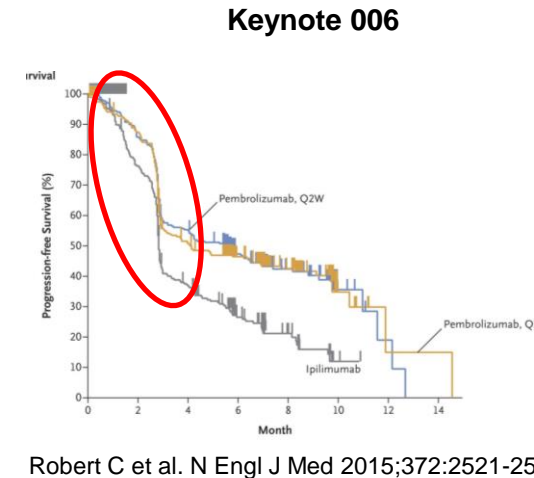
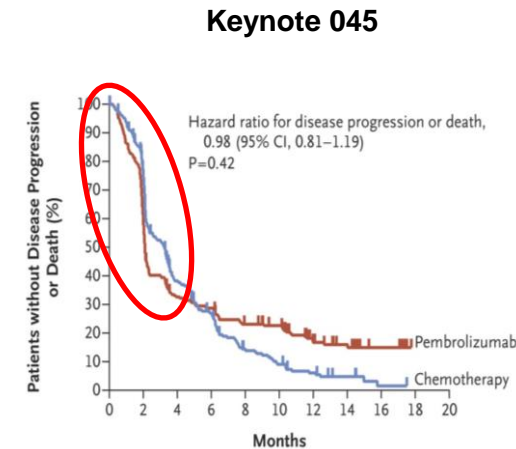
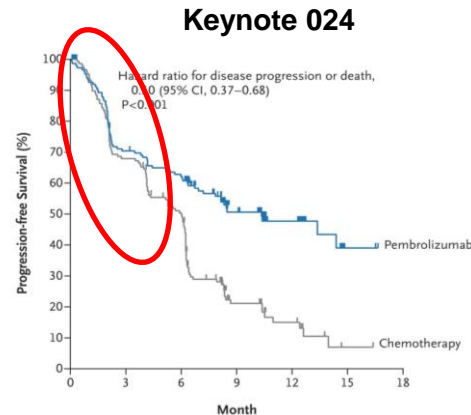
**Landmark Immunotherapy Trials Demonstrate Durable Benefit in a Limited Percentage of Patients**



# Why might the benefit of PD-L1 blockade be greater in locally advanced disease following chemoradiation?



**Deviation from proportional hazards, with a population of early progressors that don't derive benefit from immunotherapy**



**Immunosuppressive disease burden?**  
Huang et al. Nature 2017

**Landmark Immunotherapy Trials Demonstrate Durable Benefit in a Limited Percentage of Patients**







## Immunosuppressive tumor burden (ants)







**Immunosuppressive tumor burden (ants)  
plus T-cells (ant traps)**







**Immunosuppressive tumor burden (ants) plus T-cells (ant traps) minus irradiated immunosuppressive tumor burden**





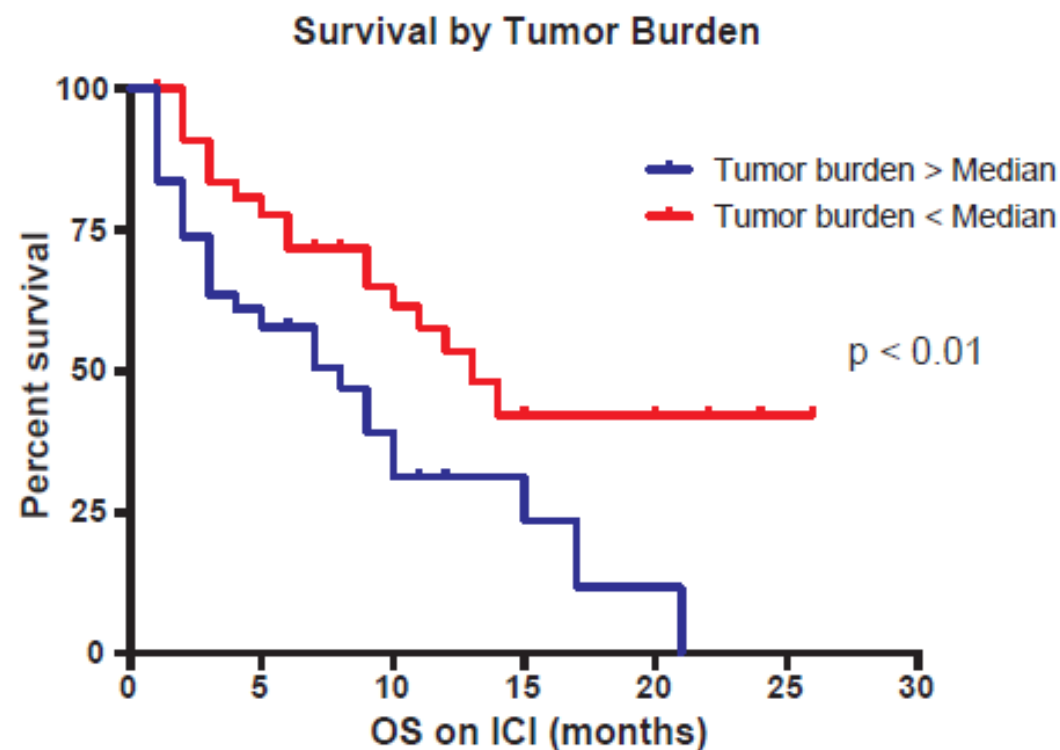


**= Durable Response**





# Emerging Data Suggests Lower Burden of Disease is Associated with Greater Benefit for Immune Checkpoint Blockade



**eTable 3. Association Between Baseline Sum of Target Lesion Diameters and 5-Year Survival in All Patients Receiving Nivolumab (N = 270)<sup>a</sup>**

Sum of Target Lesion Diameters (mm)	5-Year Survivors	All Other Patients	P value
Melanoma Median (IQR) Range	n = 30 75 (48-134) 22-374	n = 77 111 (69-189) 10-377	.0427
RCC Median (IQR) Range	n = 9 98 (89-110) 42-236	n = 25 139 (88-191) 43-615	.0542
NSCLC Median (IQR) Range	n = 16 83 (62.5-117) 11-291	n = 113 95 (59-147) 10-292	.5084
All 3 tumor types Median (IQR) Range	n = 55 88 (52-116) 11-374	n = 215 109 (65-165) 10-615	.0244

<sup>a</sup> Analysis is based on t tests for comparing the 2 subsets of baseline sum of target lesion diameters. IQR indicates interquartile range.

Topalian et al. JAMA Oncol 2019.

**Fig. 3B.** Patients whose TB was lower than the median showed improved OS.

Sridharan et al. Oral Oncology 2018.

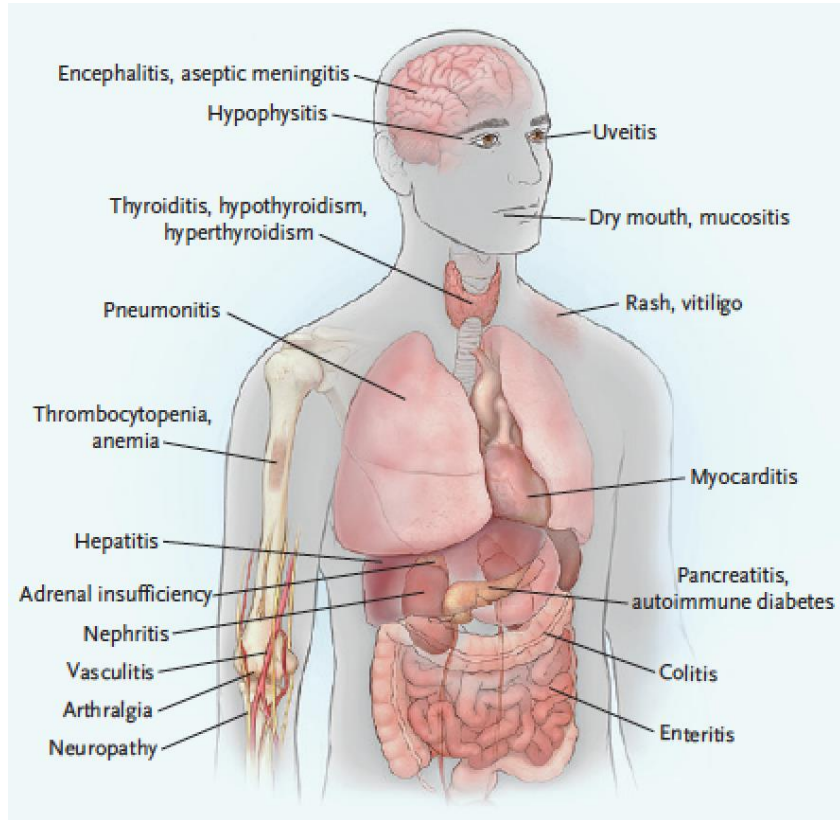


# Outline

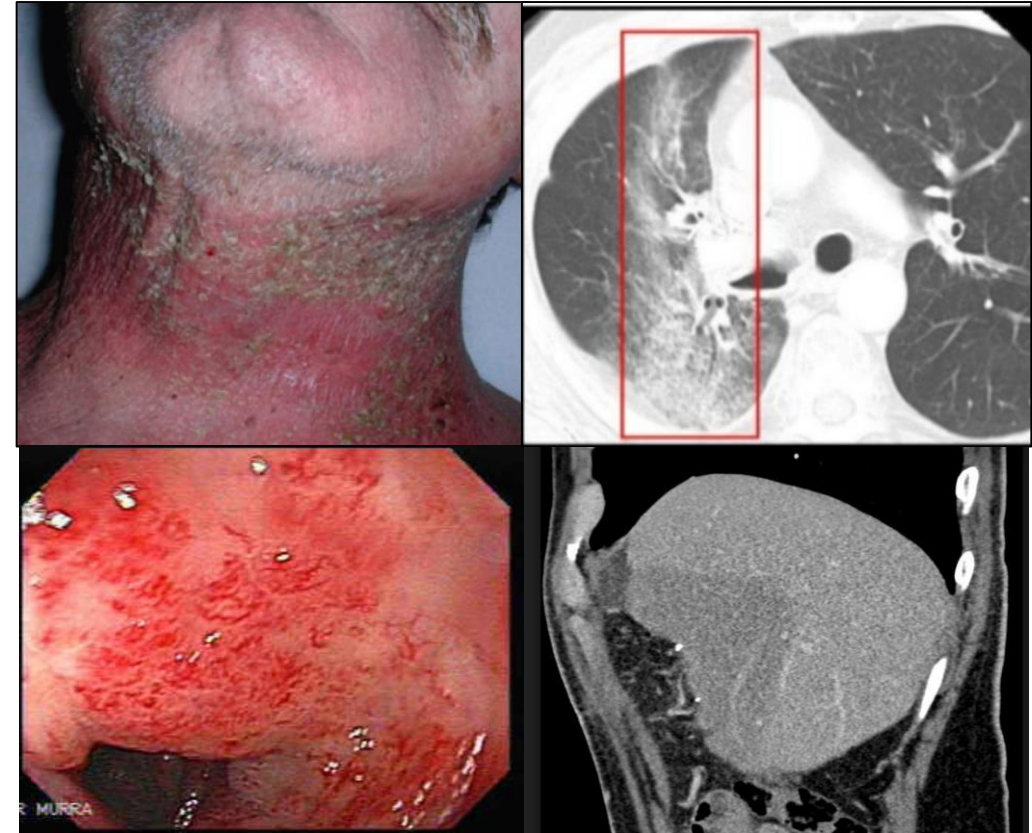
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- Why are radiotherapy combinations appealing?
- Toxicity and response



# Clinical Data: Safety Concerns Regarding Overlapping Toxicities



Toxicities of Immune Checkpoint Blockade  
Postow, Sidlow and Hellman. NEJM 2017



Common Toxicities Associated with  
Radiation Therapy



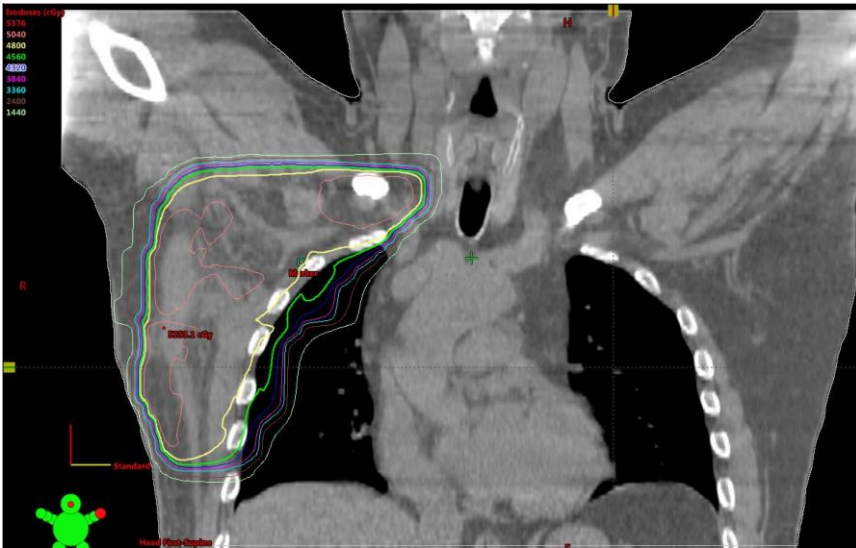
# Toxicity Endpoints

- Initial data from clinical practice and multiple studies suggests that radiation and immune checkpoint blockade are generally well tolerated administered together (Bang and Schoenfeld Ann Pall Med 2018)
- There remain concern about long-term toxicities (including recall) and specific and overlapping toxicities (e.g. pneumonitis, lymphopenia)
- It is important but can be challenging to try to identify the etiology of toxicity in patients treated with immunotherapy radiation





# Challenging to Attribute Toxicity with Combined Treatment



Right axillary radiotherapy for melanoma



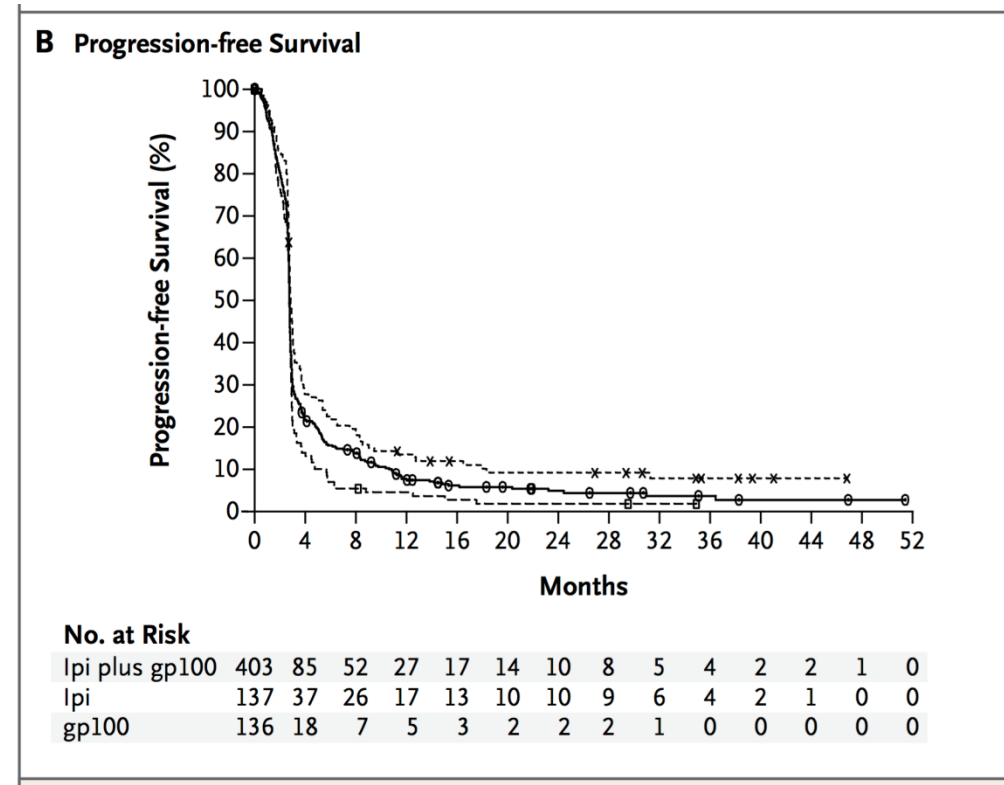
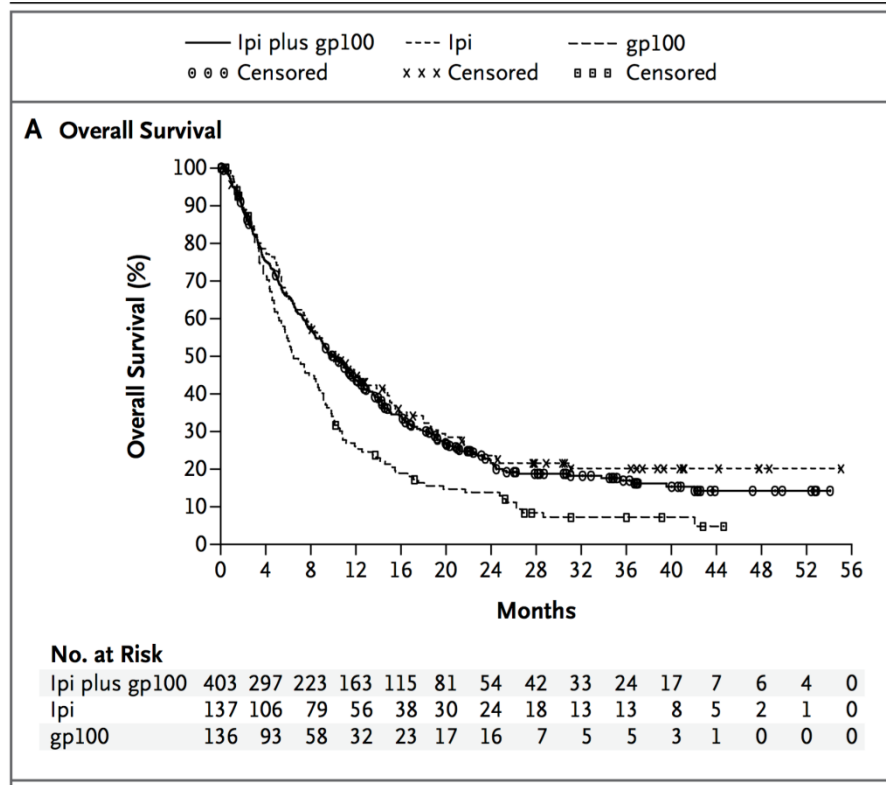
Symptomatic pneumonitis 5 months following RT and 1.5 months following nivolumab therapy



Evolving change demonstrates consolidation and ground glass opacities outside of the radiation treatment field confined to the ipsilateral lung

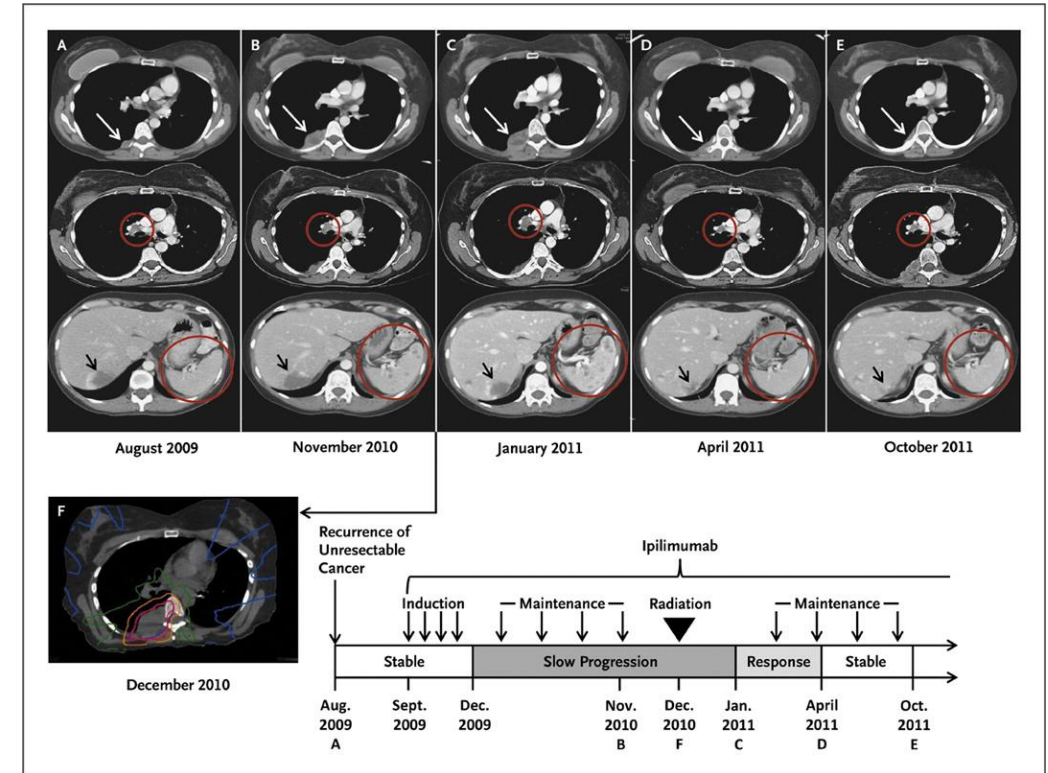


# Response Underestimates Benefit



# Efficacy Parameters in Radiation Immunotherapy Studies

- Systemic Response (may be hard to interpret and correlate with clinical benefit in all cases)
  - RECIST, irRECIST, irRC
  - Out of field, “abscopal” response (Golden et al. Lancet Oncol 2015)
- Local response
- **Overall survival**



“Abscopal” responses following radiation in a patient progressing on anti-CTLA-4 therapy

Postow MA et al. N Engl J Med 2012;366:925-931.



# Summary

- Immunotherapy provides durable improvement in survival in a limited number of solid tumor patients
- Radiation / immunotherapy combinations are being explored to help improve local or systemic responses and generate anti tumor immunity
- Immunotherapy response can be unique, and patterns of response and toxicity are important considerations with combined radiation / immune therapy





# Thank you!!

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