NASDC
NCI Awardee Skills Development Consortium

Radiographic Endpoints for Immunotherapy Clinical Trial Design

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Disclosures

Advisory Board:

» Array BioPharma, Aduro, BMS, Incyte, Merck, NewLink Genetics, Novartis, Eisai, Pfizer

Honoraria:

» BMS and Merck

Institutional Support:

» RGenix, Infinity, BMS, Merck, Array BioPharma, Novartis

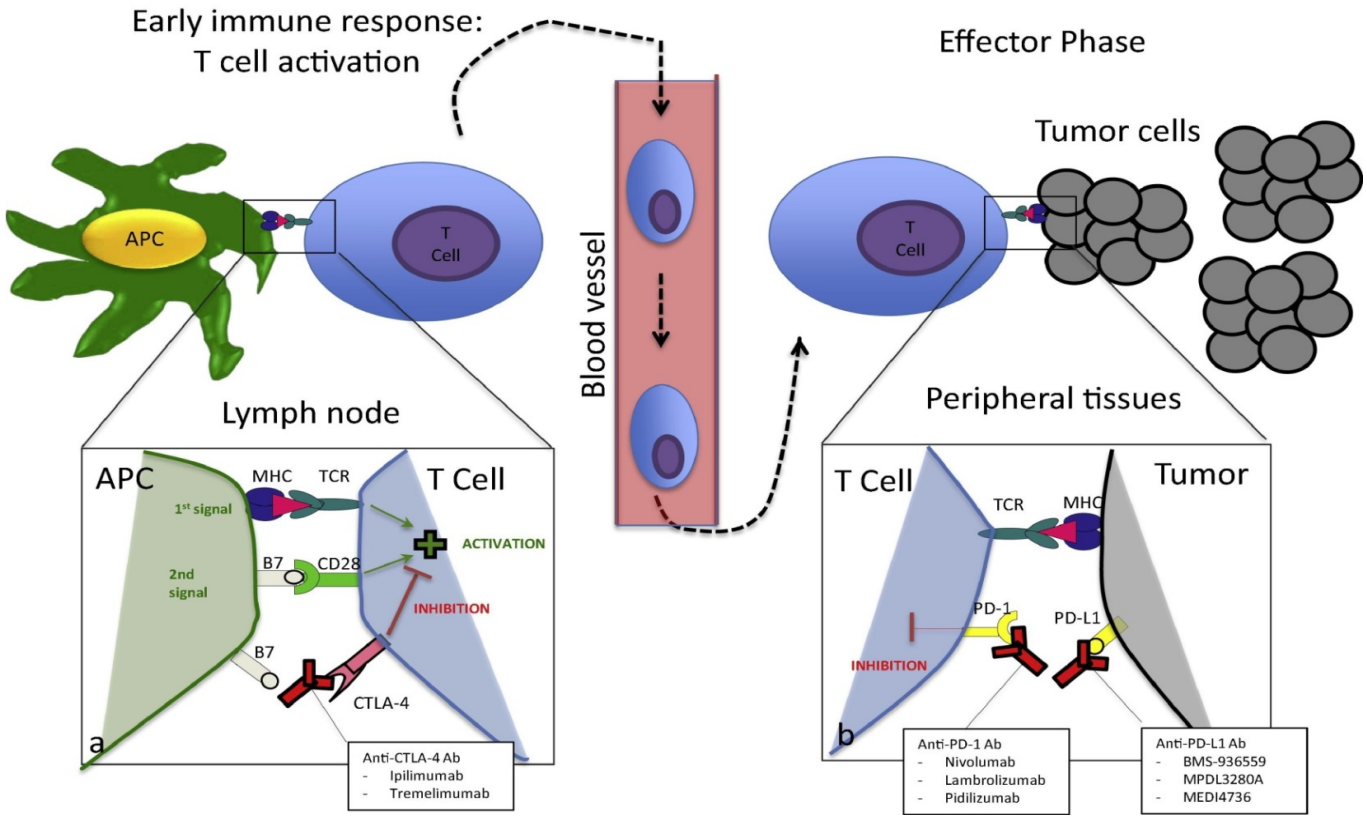
Overview

1. Types of immunotherapy under consideration

2. Difference radiographically with immunotherapy

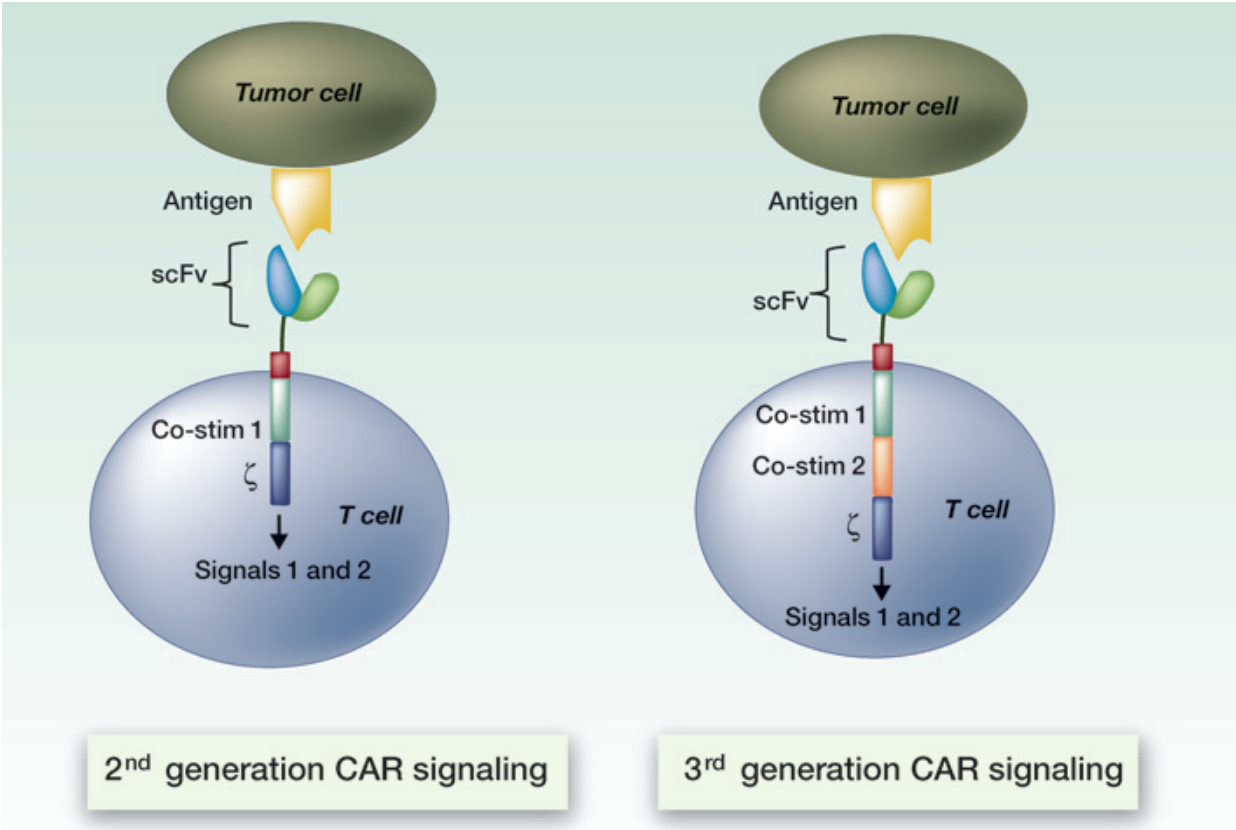
3. New ways to consider radiographic assessment

Immune Checkpoints



Kyi and Postow FEBS Letters 2014

CAR T Cells



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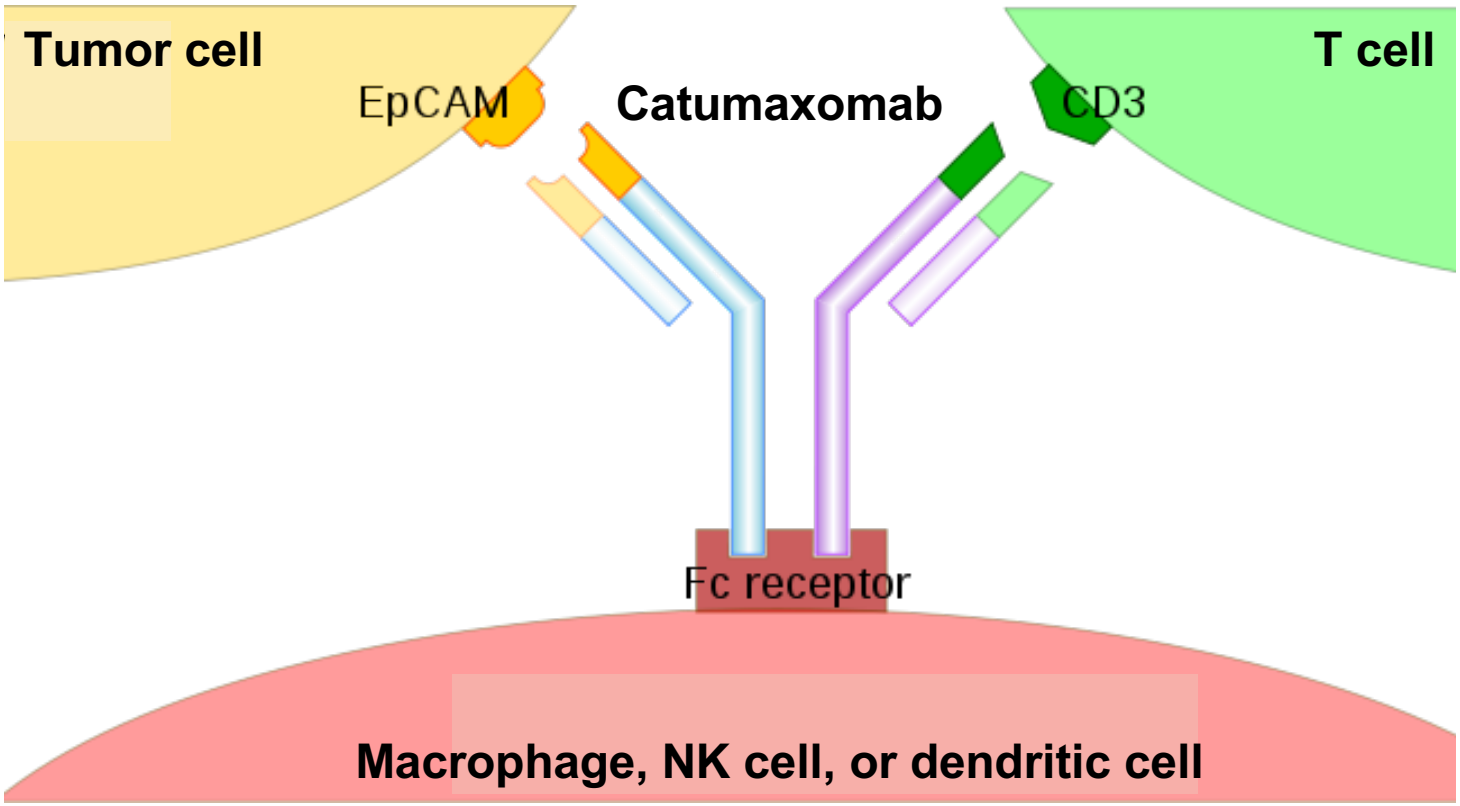
Bispecific Antibodies



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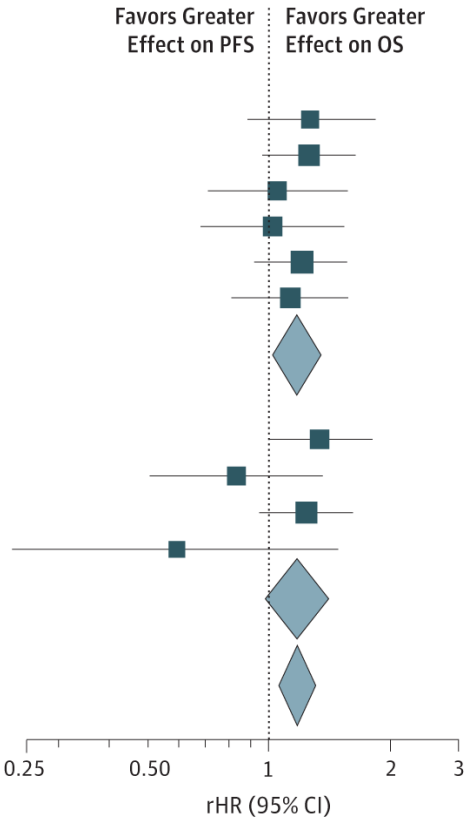
Assessing Efficacy

1. **Some immunotherapy does not directly treat the tumor, is watching a tumor grow or shrink appropriate?**

2. **What radiographic endpoints are appropriate?**

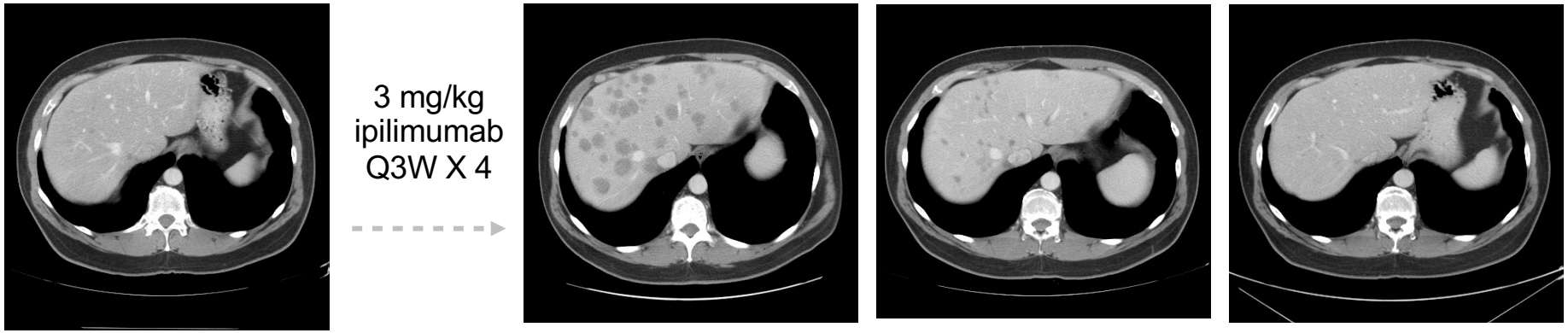
Immunotherapy has a stronger effect on OS than PFS

Study	rHR (95% CI)
Nivolumab	
Ferris et al,[8] 2016 (Checkmate 141)	1.27 (0.89-1.83)
Borghaei et al,[9] 2015 (Checkmate 057)	1.26 (0.97-1.64)
Brahmer et al,[10] 2015 (Checkmate 017)	1.05 (0.71-1.56)
Robert et al,[11] 2015 (Checkmate 066)	1.02 (0.68-1.54)
Motzer et al,[12] 2015 (Checkmate 025)	1.21 (0.93-1.56)
Carbone et al,[13] 2017 (Checkmate 026)	1.13 (0.81-1.57)
Overall	**1.18 (1.03-1.34)**
Pembrolizumab	
Bellmunt et al,[14] 2017 (Keynote 045)	1.34 (1.00-1.80)
Reck et al,[15] 2016 (Keynote 024)	0.83 (0.51-1.36)
Herbst et al,[16] 2016 (Keynote 010)	1.24 (0.95-1.62)
Langer et al,[17] 2016 (Keynote 021)	0.59 (0.23-1.49)
Overall	**1.18 (0.98-1.41)**
Overall	**1.18 (1.06-1.31)**



Gyawali et al. JAMA Netw Open 2018

Immunotherapy (ipilimumab) responses can be delayed

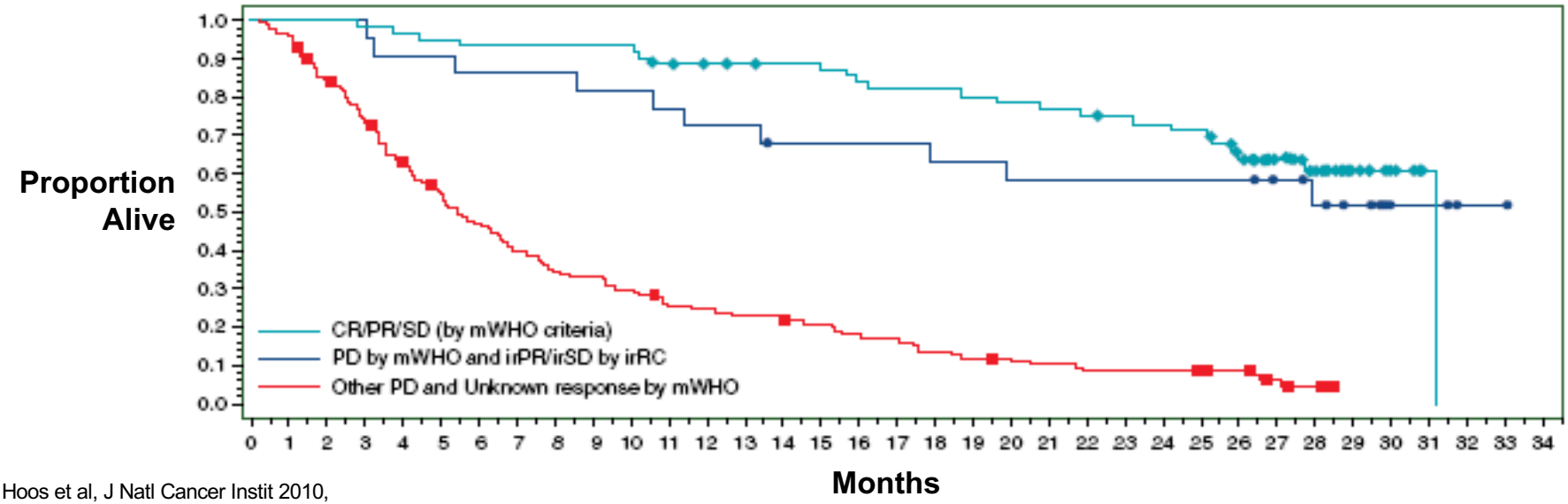


Pre-Treatment | **Week 12: Progression** | **Week 20: Regression** | **Week 36: Still Regressing**

Wolchok ASCO 2008

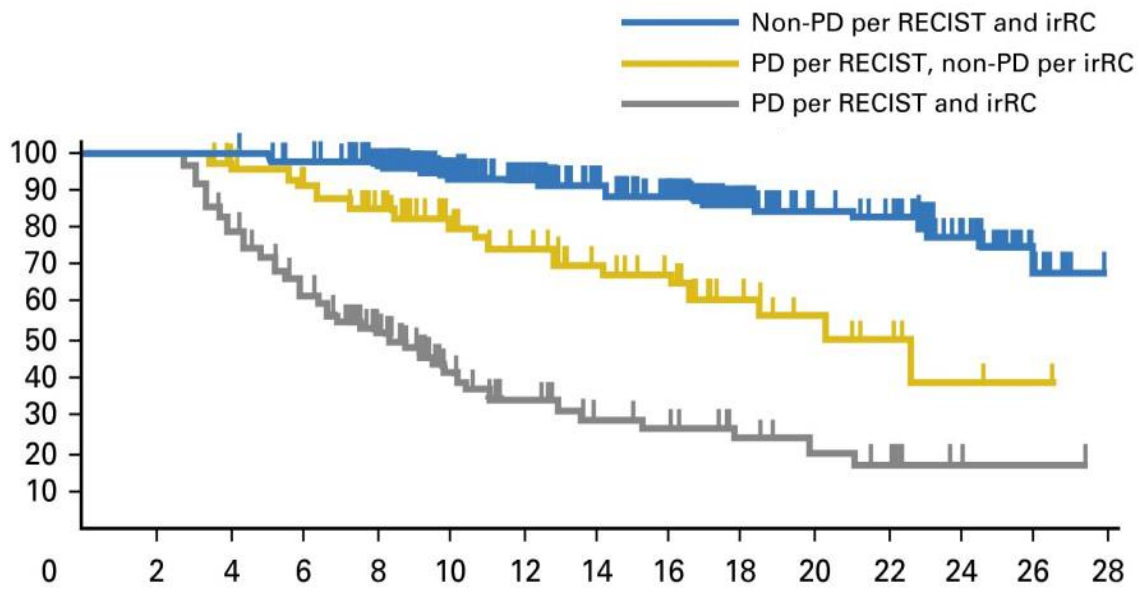
Some patients who “progress” do well

Pooled data from phase II studies of ipilimumab monotherapy at 10mg/kg (n=227)



Hoos et al, J Natl Cancer Instit 2010,
Wolchok et al, Clin Cancer Res 2009

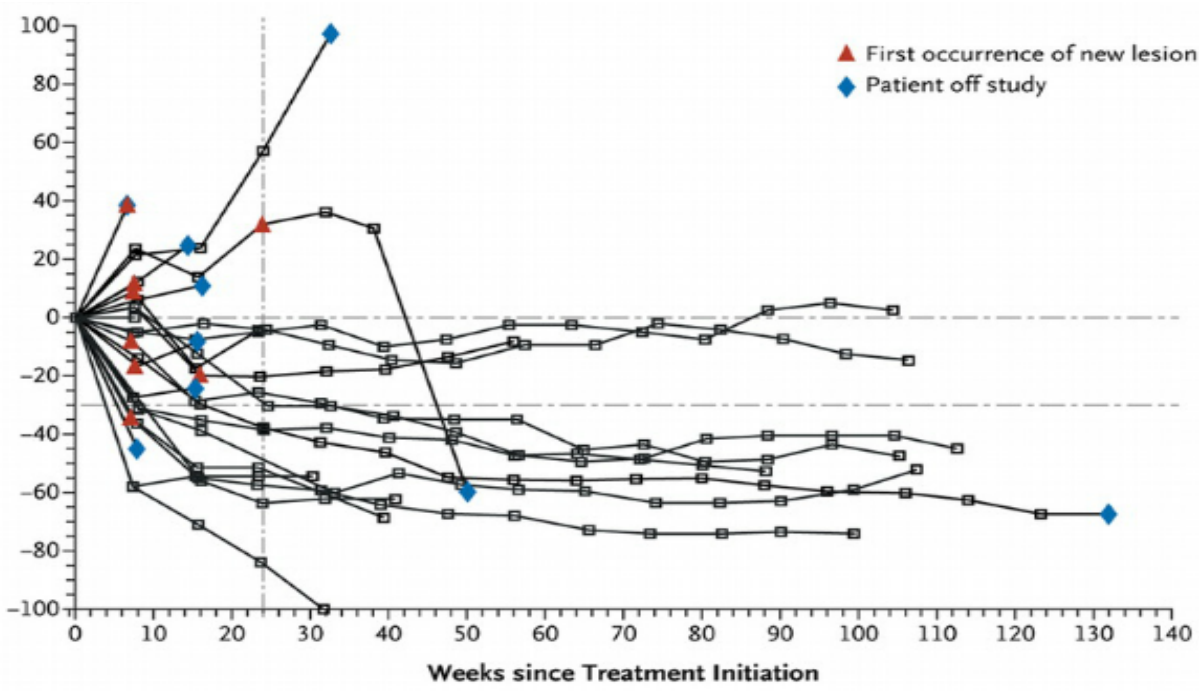
PD by RECIST very heterogeneous



No. at risk															
Non-PD per RECIST and irRC	331	331	329	321	301	219	192	159	136	79	60	55	31	8	0
PD per RECIST, non-PD per irRC	84	84	79	71	60	44	37	28	22	13	9	6	3	2	1
PD per RECIST and irRC	177	177	139	109	75	48	33	23	20	15	10	8	1	1	0

Hodi et al.
JCO 2016

What about PD-1 pseudoprogression?



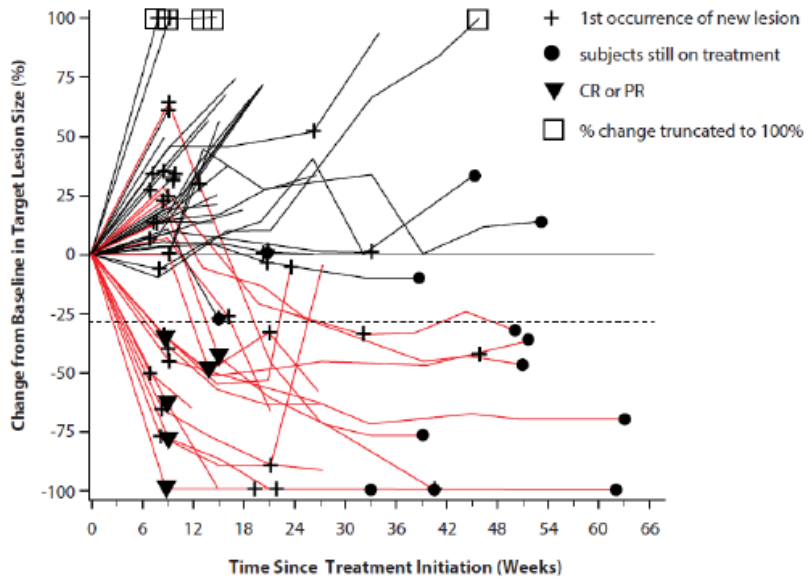
Topalian et al,
NEJM 2012

Pseudoprogression with PD-1 is rare (approximately 5-10%)

Weber et. al Lancet Oncol 2015, Hodi et al. JCO 2016, Beaver et al. Lancet Oncol 2018

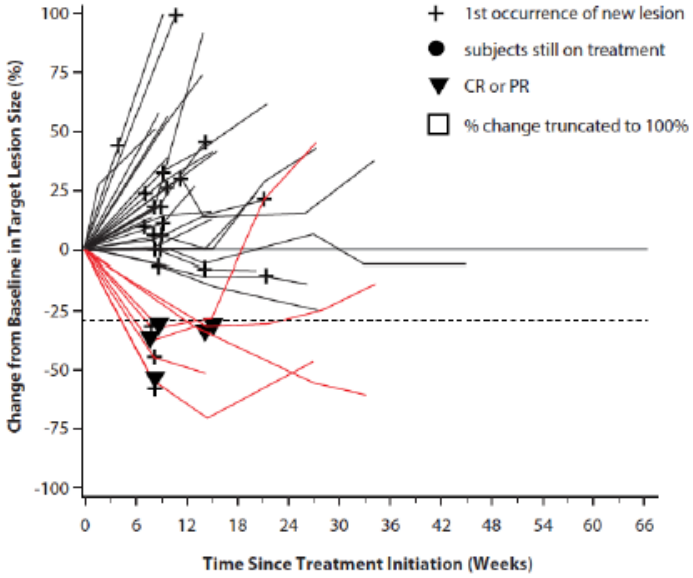
54 nivolumab patients treated beyond POD

17 (8% of total pts) eventually had 30% reduction



49 dacarbazine patients treated beyond POD

8 (4% of total pts) eventually had 30% reduction



Robert et al, NEJM 2015

Major effect of immune criteria is on progression free survival not overall response rate

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Main differences between RECIST and iRECIST is declaration of progression

Outcome	RECIST*	Immune RECIST**
Complete Response	Disappearance of targets	Disappearance of targets
Partial Response	≥30% decrease in targets	≥30% decrease in targets
Stable Disease	Everything else	Everything else
Progressive Disease	≥20% increase in targets **Any new lesion**	≥20% increase in targets requiring confirmation

*Eisenhauer et al. Eur J Cancer 2009
**Seymour et al. Lancet Oncol 2018

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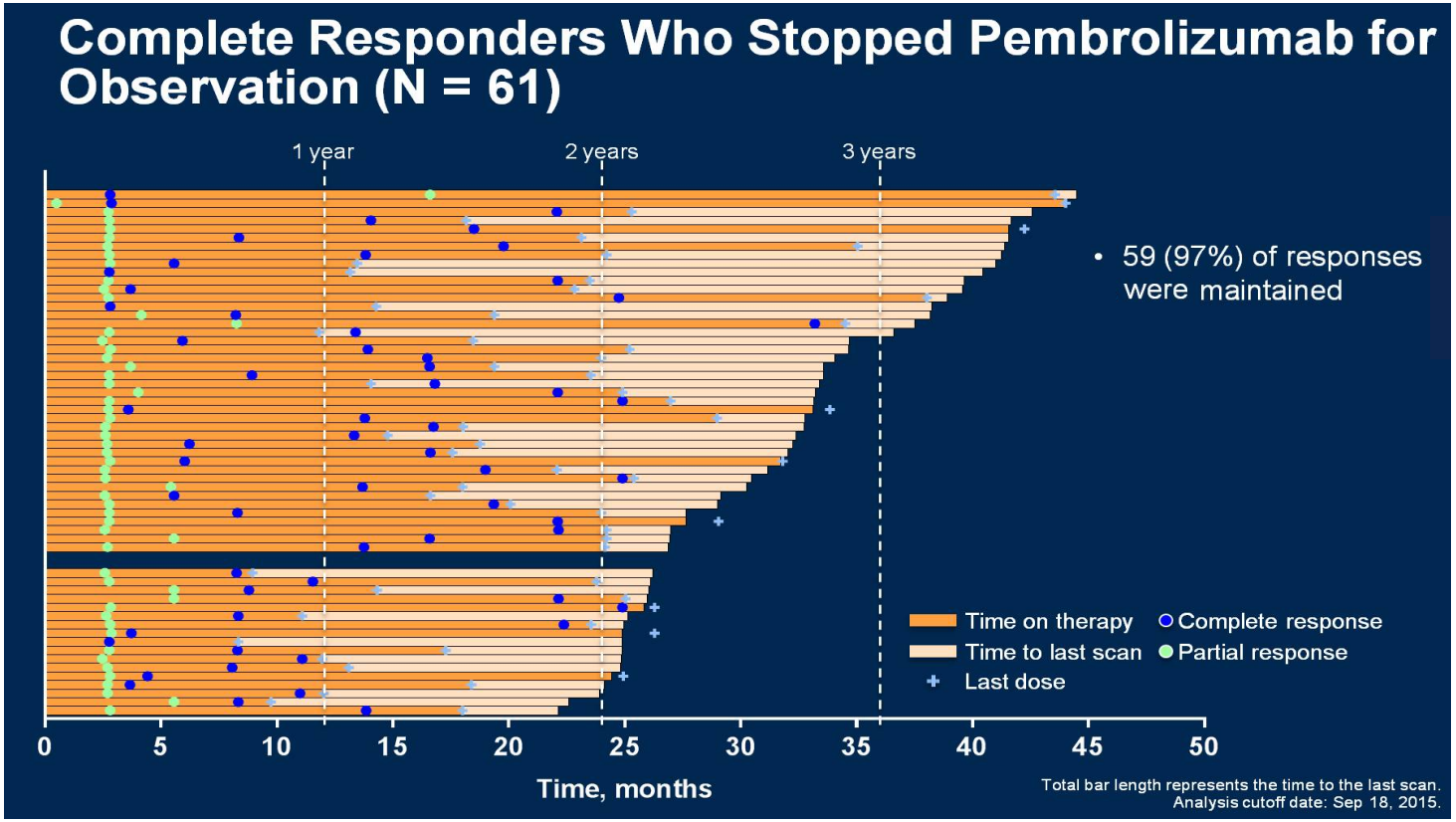
Possibility of late response is different from pseudoprogression

Most PD-1 responses occur early but some are late



Robert ASCO 2016

Summary of Standard IO Response Criteria

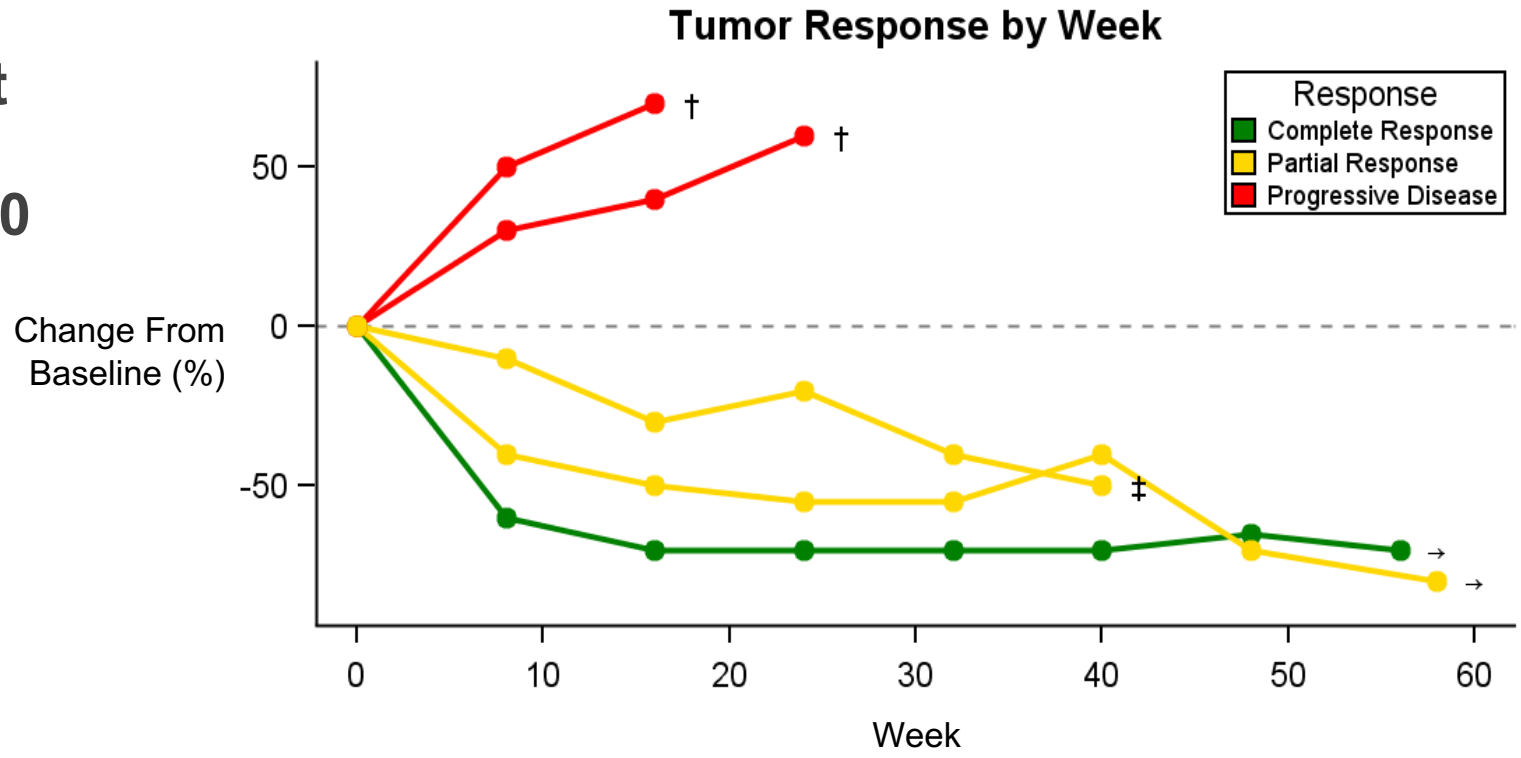
1. **Pseudoprogression rarely happens with PD-1 and PD-1 combos and is distinct from late response**

2. **Immune response criteria redefine PFS**
   - » Immune related response criteria (irRC)– Bidirectional*
   - » Immune RECIST (iRECIST)-- Newest/Unidimensional**

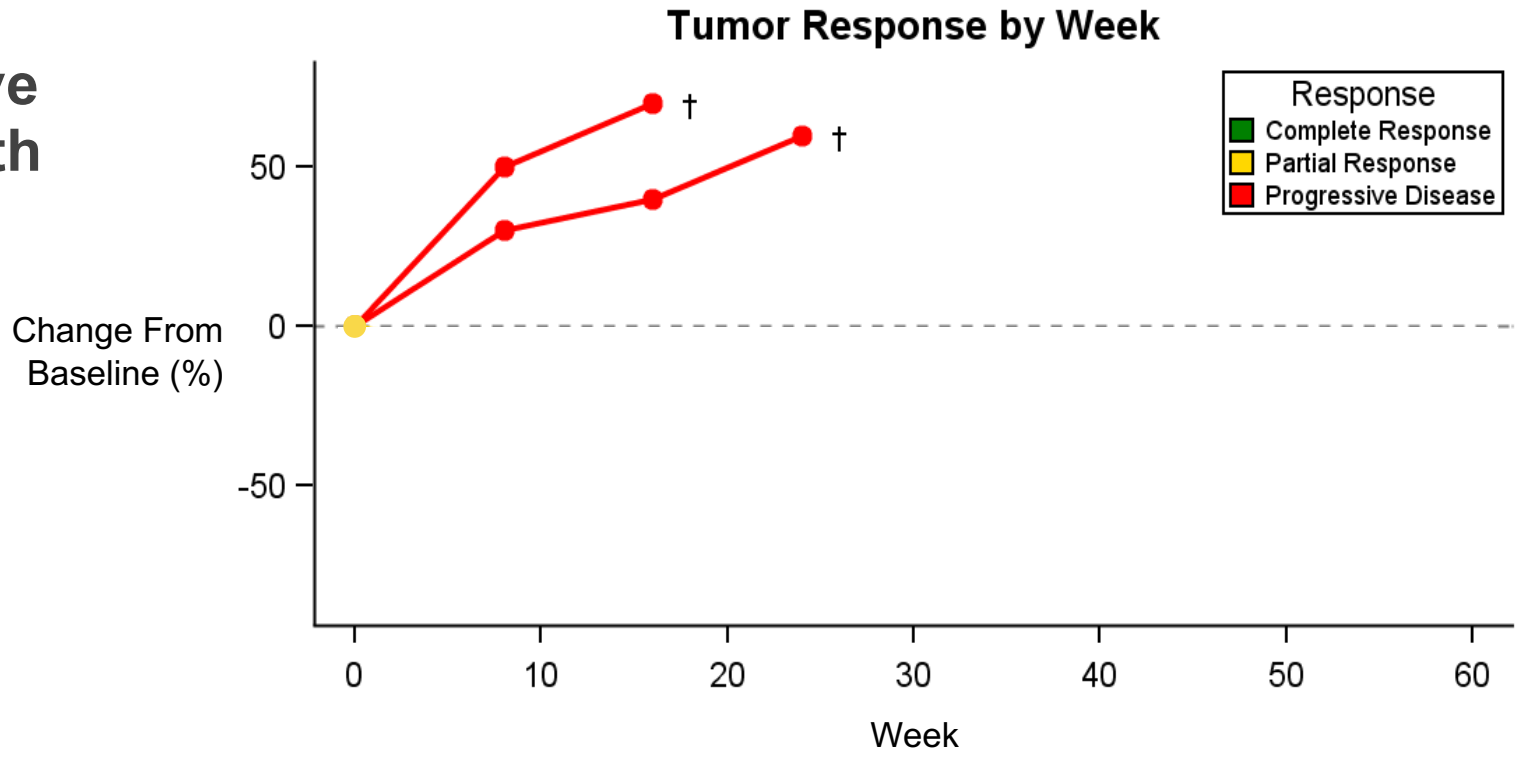
*Wolchok et al. Clin Cancer Res 2009
**Seymour et al. Lancet Oncol 2018

What if you cannot run a randomized study?

Traditional Spider Plot Measures from Time 0



Does drug "X" improve prior growth kinetics?



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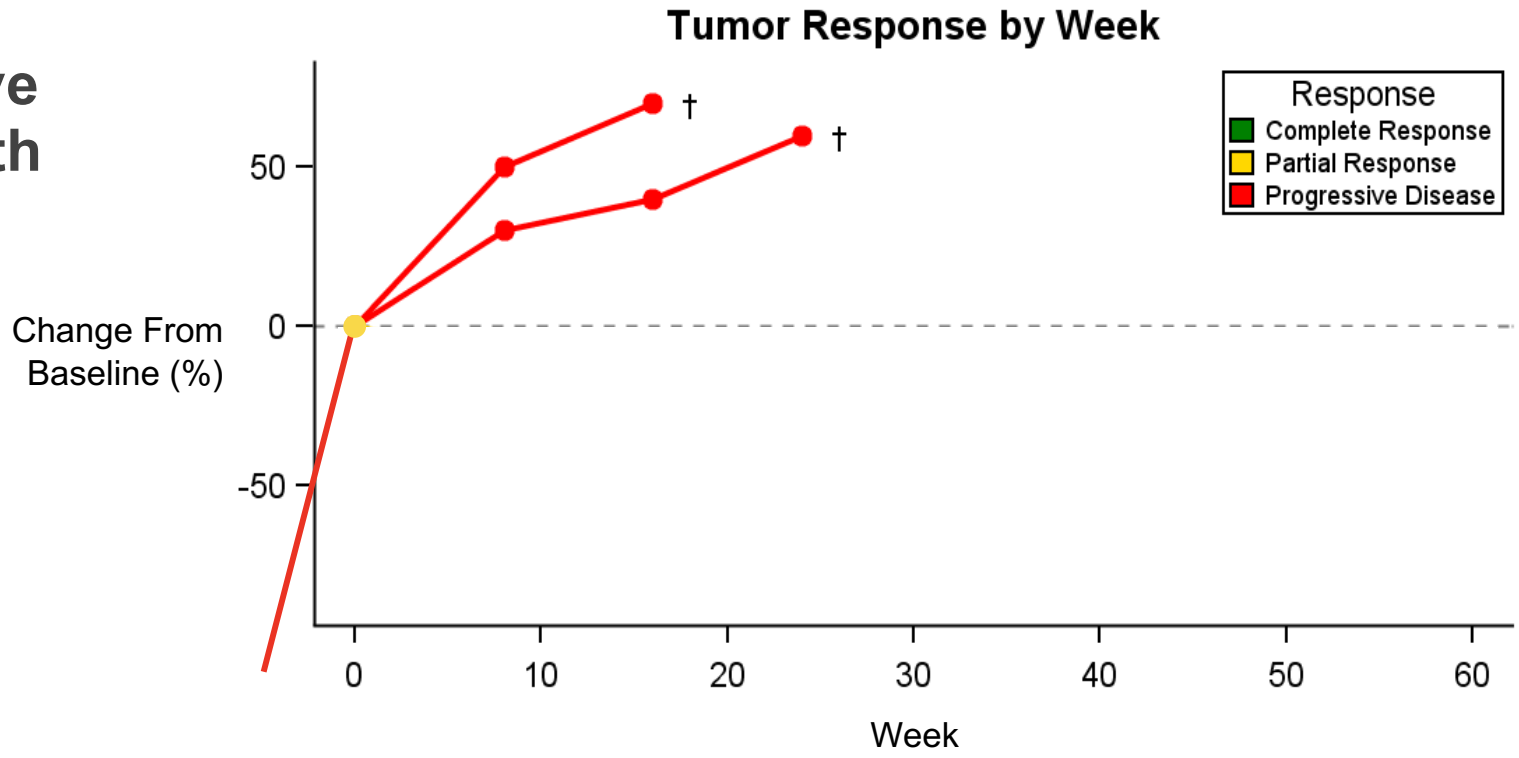

Exploring New Ways To Image Patients

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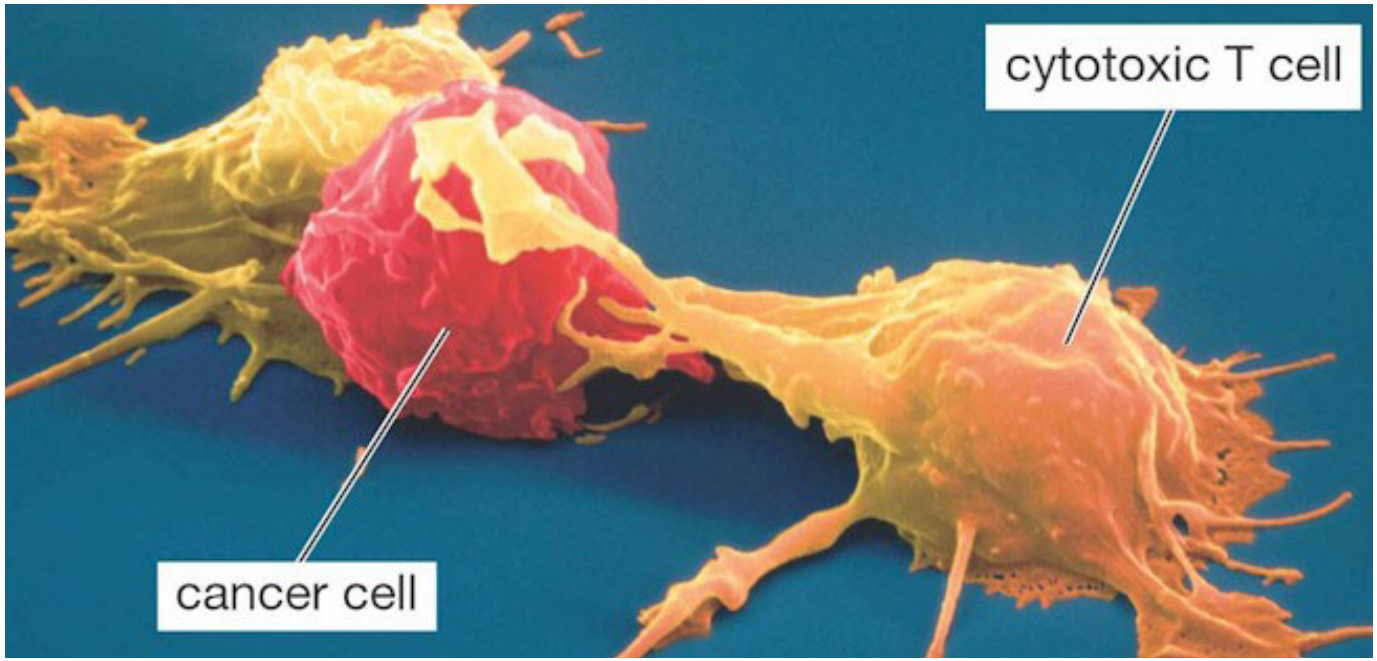
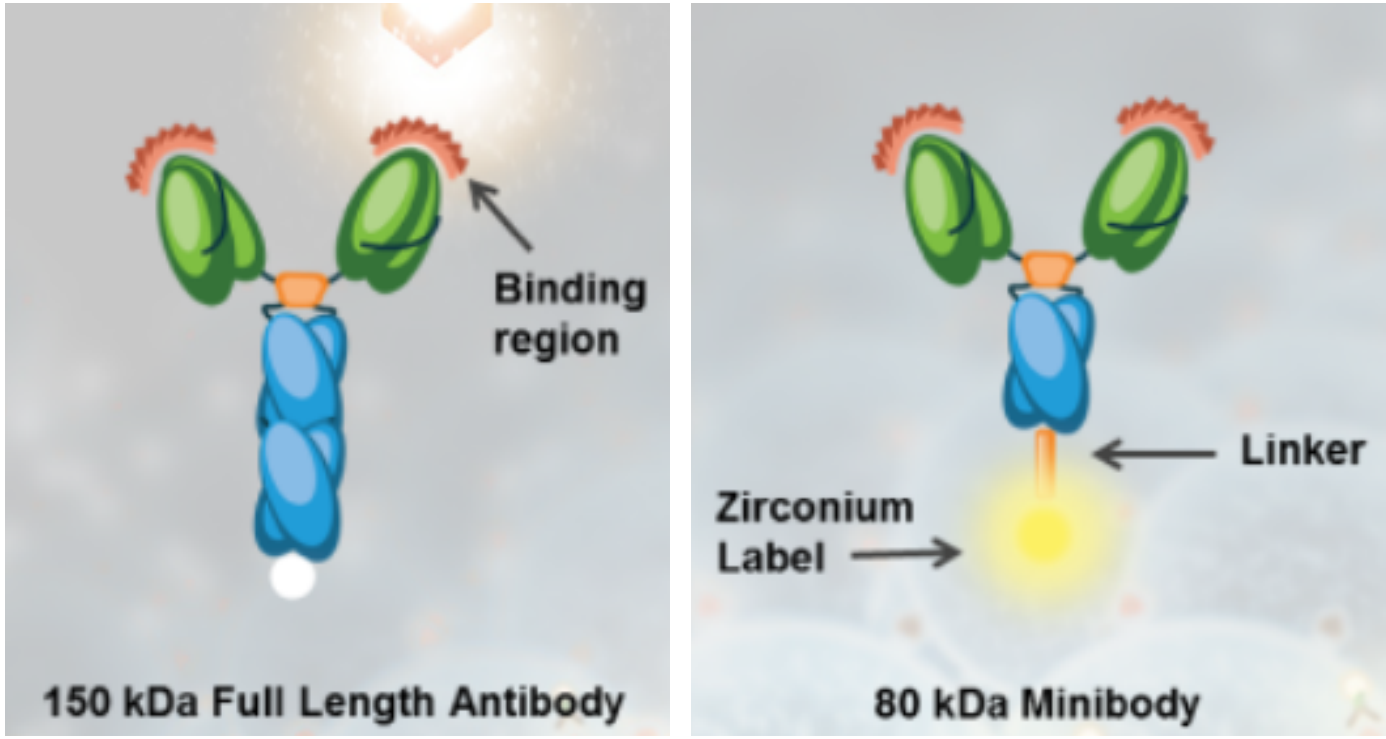
Immunotherapy = Immune cell kills a cancer cell

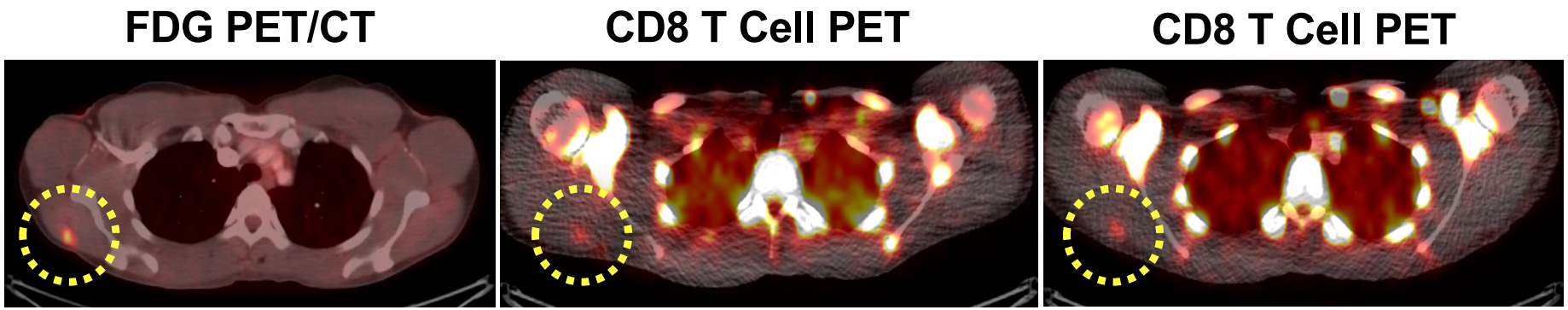


What about directly imaging CD8 T cells?



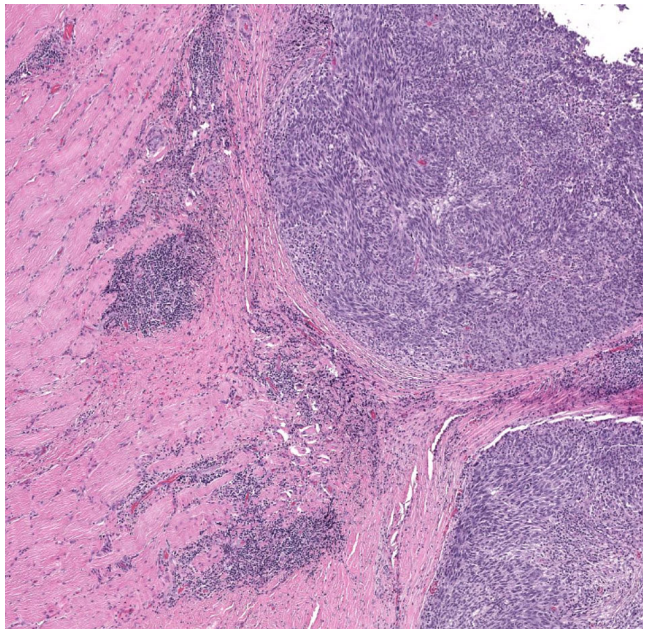
Non-invasive CD8 T Cell Imaging

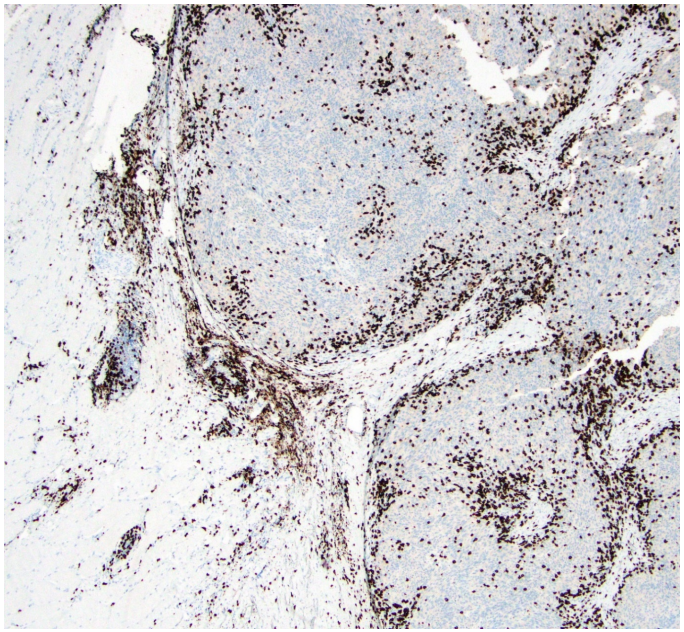
37 year old woman with metastatic melanoma on pembrolizumab for 2 years



Pandit-Taskar, Postow, Hellmann et. al J Nucl Med 2019

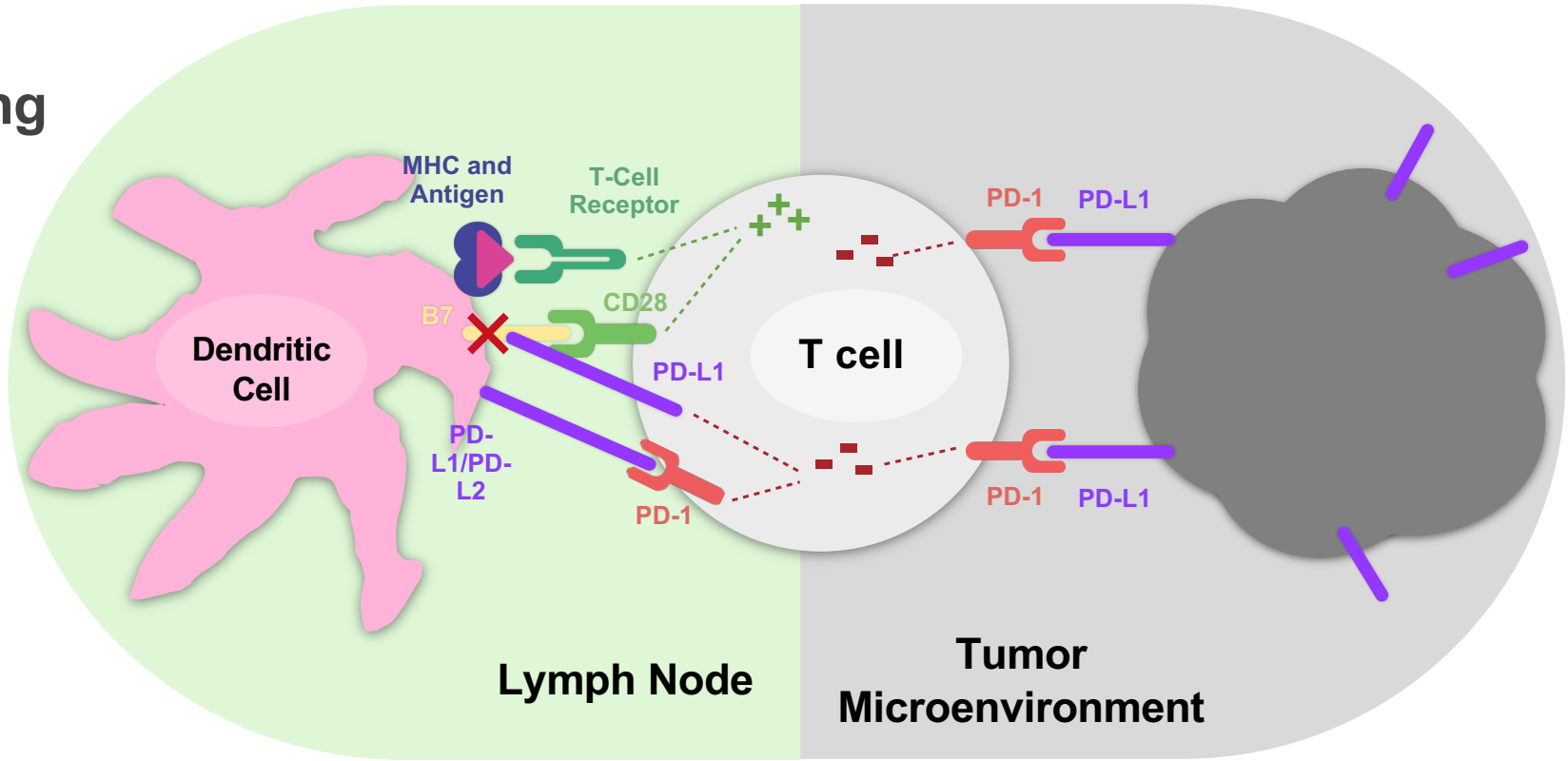
CD8 T cells seen on immunohistochemistry





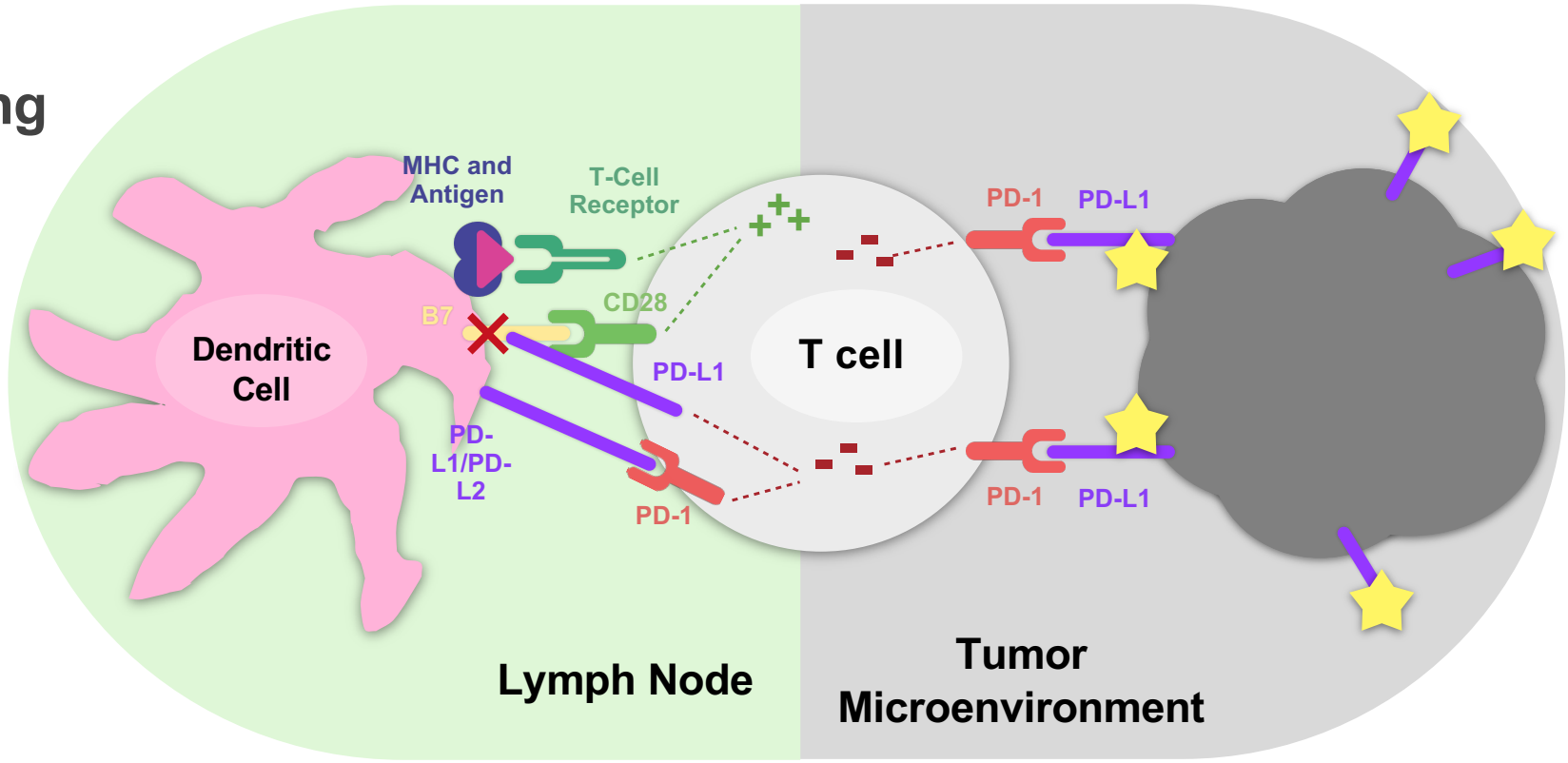
Pandit-Taskar, Postow, Hellmann et. al J Nucl Med 2019

PD-L1 Imaging



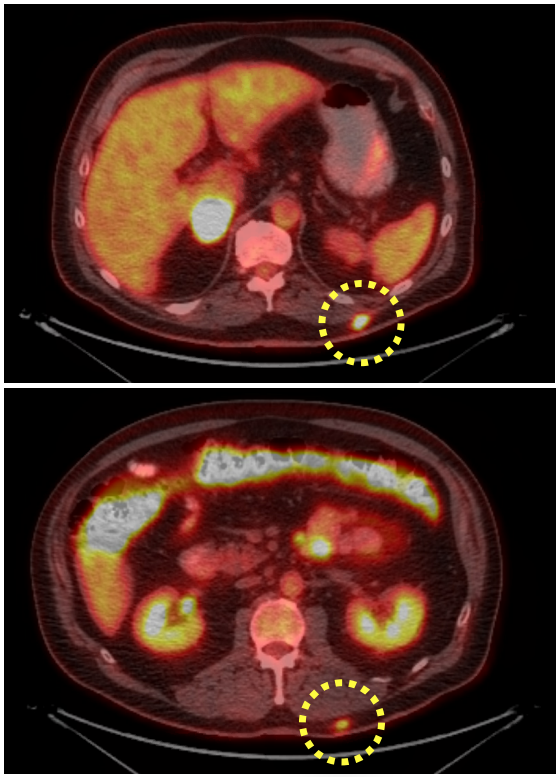
Postow et. al J Clin Oncol 2015

PD-L1 Imaging

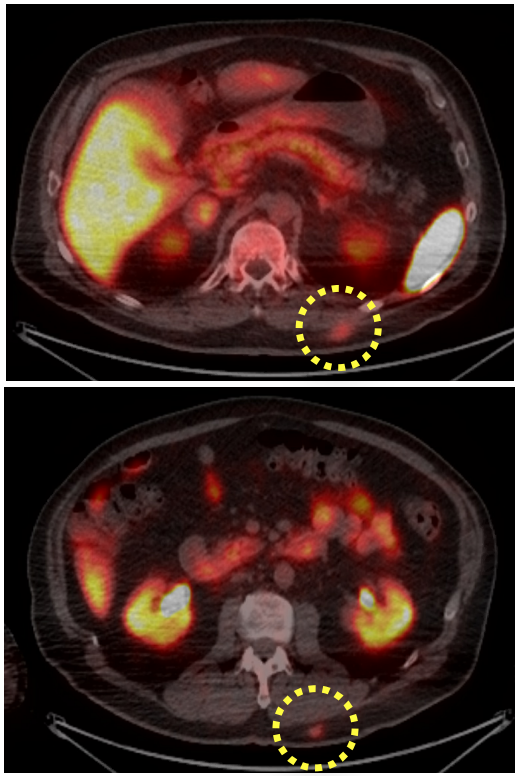


Postow et. al J Clin Oncol 2015

Non-invasive PD-L1 Imaging

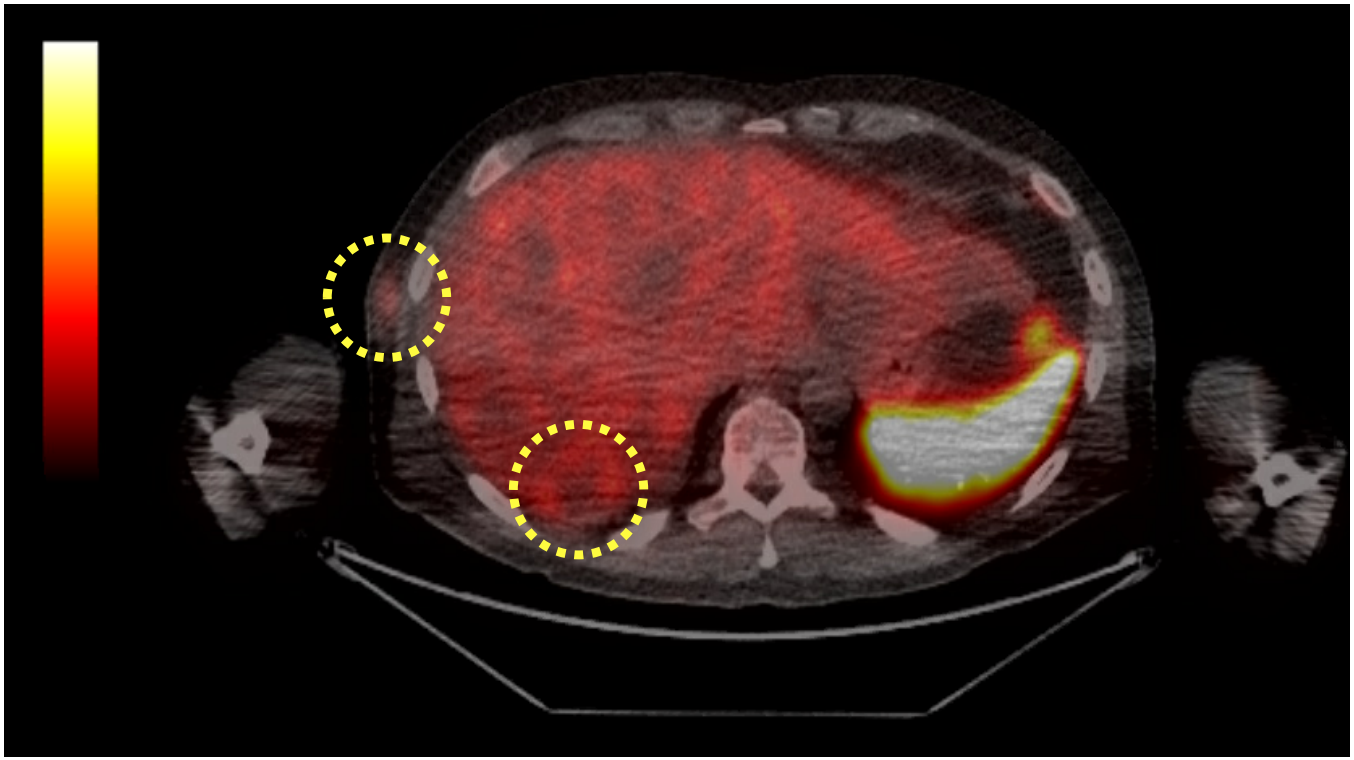


FDG PET



[18F]-BMS-986229 (PD-L1)

Non-invasive PD-L1 Imaging



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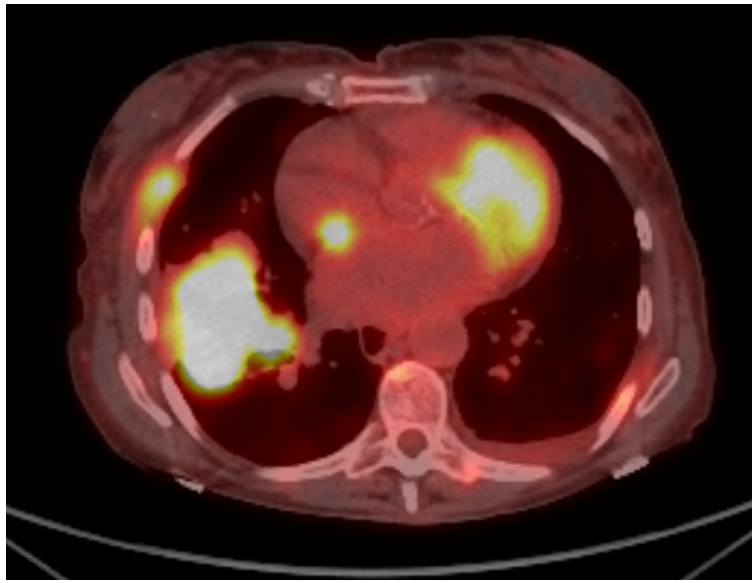
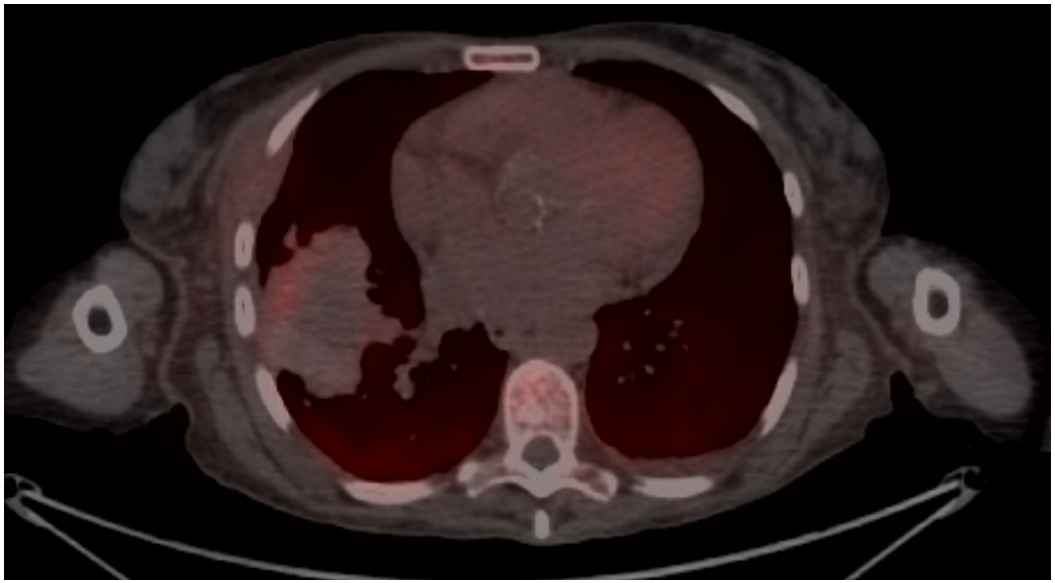
Non-invasive PD-L1 Imaging



FDG PET



[18F]-BMS-986229 (PD-L1)

Summary

1. **RECIST has limitations but remains standard for registrational trials**

2. **New ways of imaging patients will hopefully help**

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Radiographic Endpoints for Immunotherapy Clinical Trial Design

Questions