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# *Design of Clinical Trials Integrating Radiation and Immunotherapy*

Jonathan Schoenfeld, MD MPH

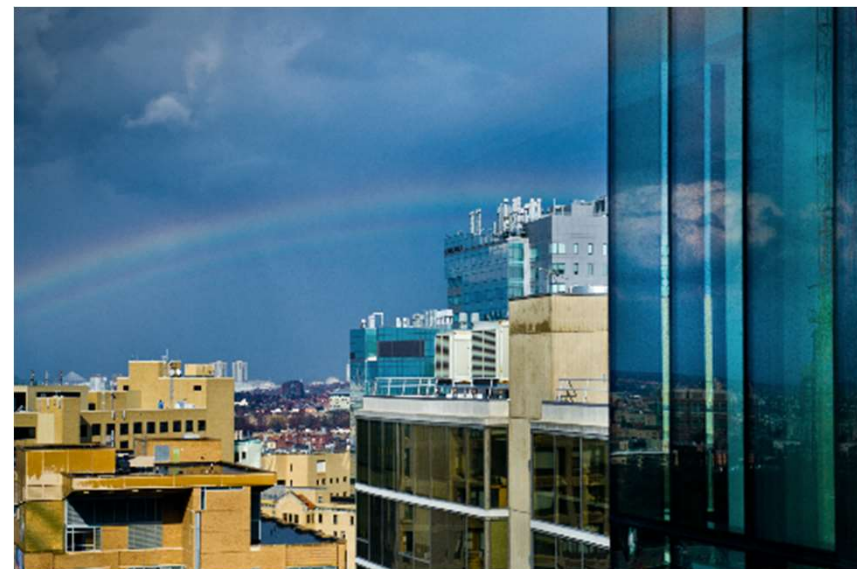
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# Disclosures

- Employment: BWPO, Boston, MA
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- Consulting/SAB/DMB for LEK, Catenion, ACI Clinical, Debiopharm, Immunitas, AstraZeneca, BMS, Nanobiotix. Expert witness fees.



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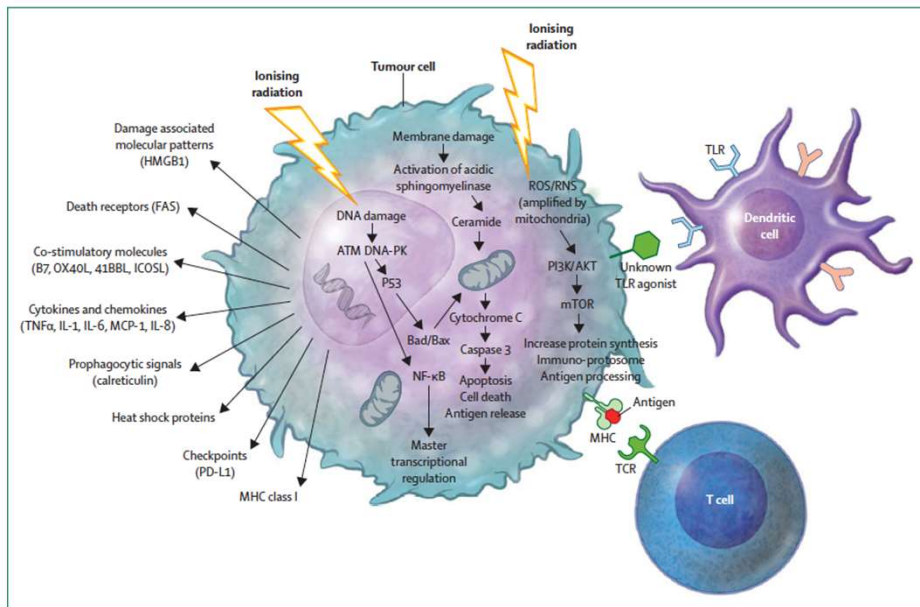


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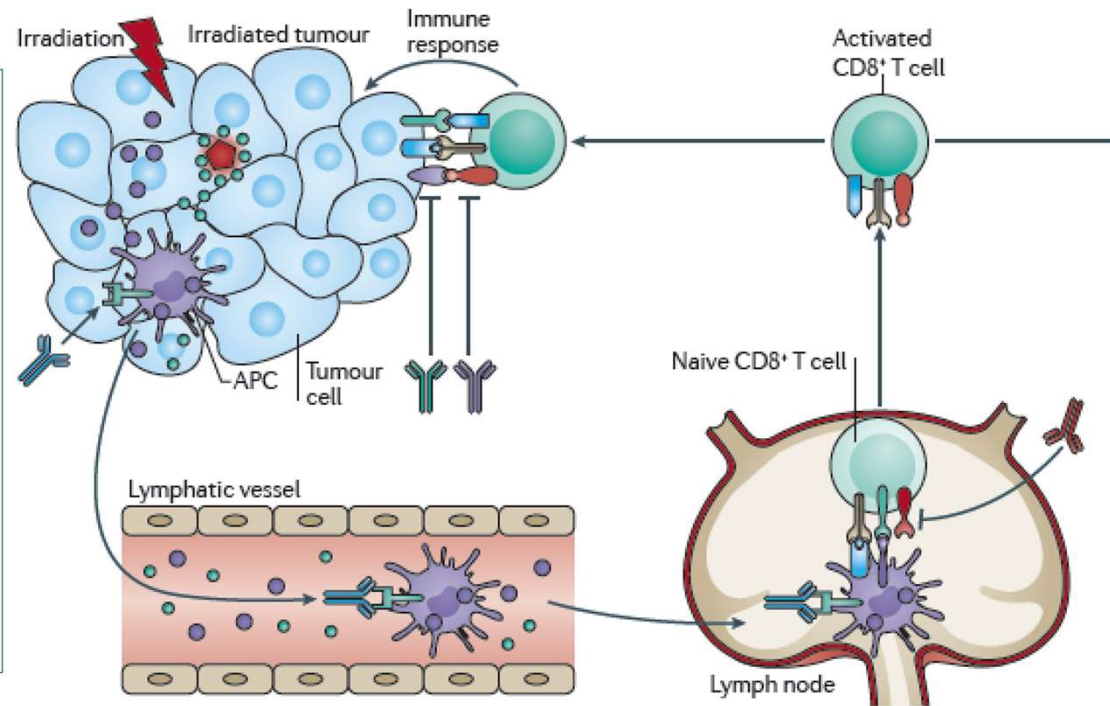


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# Introduction



Sharabi, Lim, Dewese, Drake. Lancet Oncology 2015



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



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# Trial Design: Choice of Clinical Trial Setting

- Can be guided by scientific rationale
- Novel combinations often tested in patients with more advanced disease
  - Prior lines of therapy and more extensive disease burden impair anti-tumor immunity

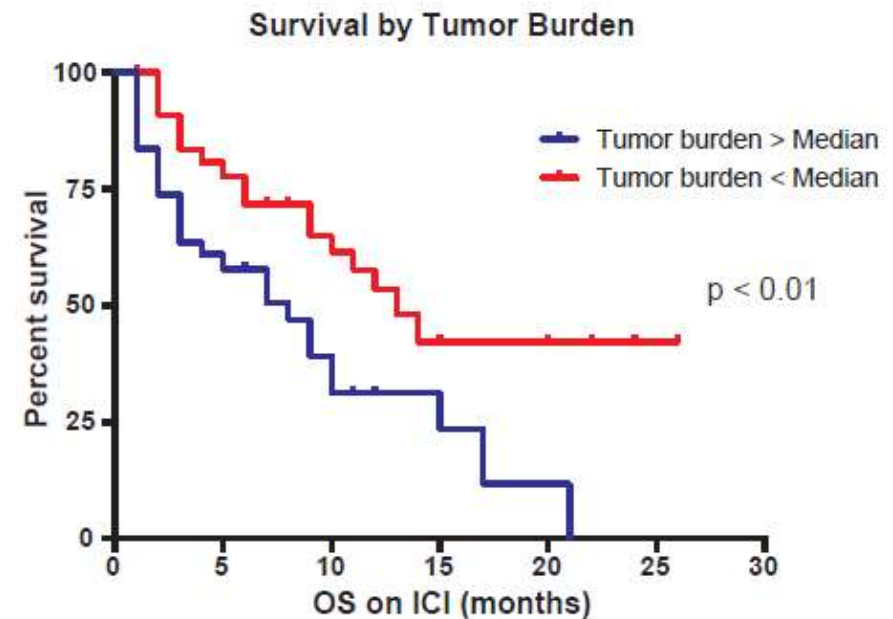


Fig. 3B. Patients whose TB was lower than the median showed improved OS.

Sridharan et al. Oral Oncology 2018.  
Also: Topalian et al. JAMA Oncol. 2019;  
Huang et al. Nature 2017



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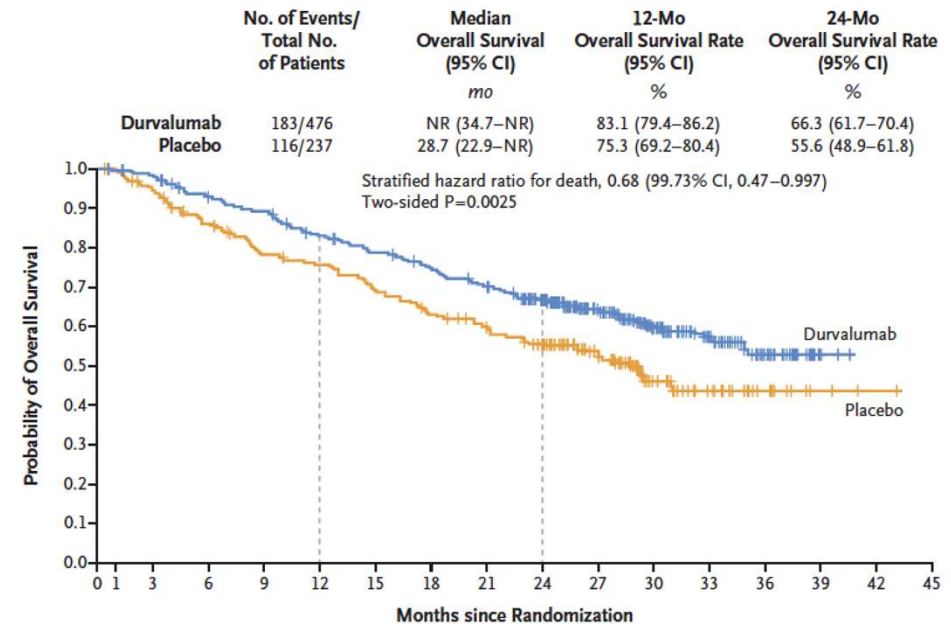
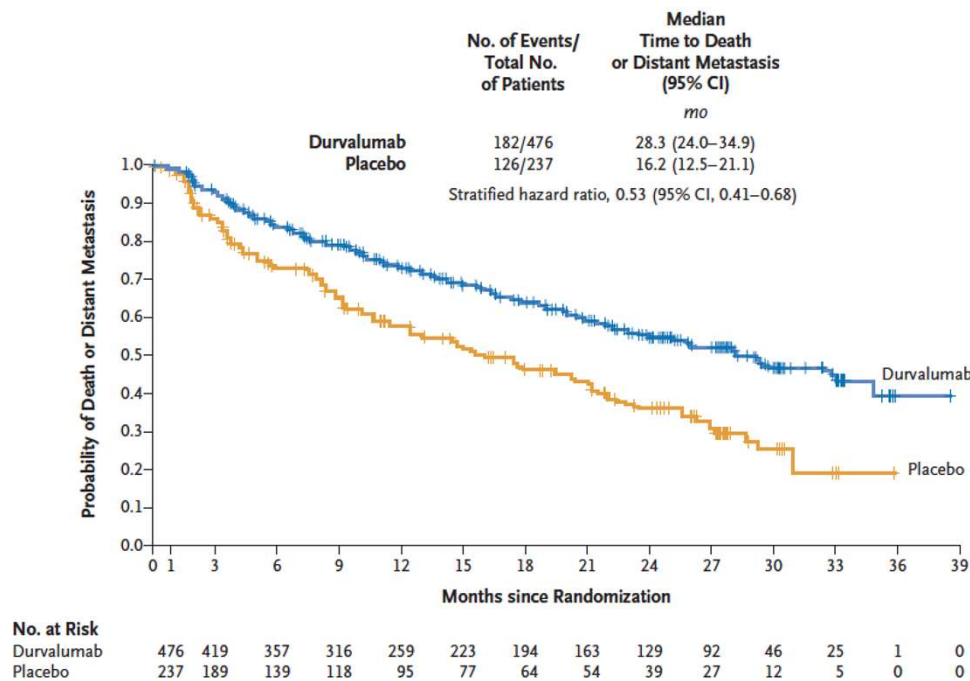
# Clinical Trial Setting

- There is rationale to move beyond the later line treatment for metastatic disease
- Radiation / immunotherapy can be tested as part of definitive therapy
  - Radiation commonly used as standard of care for patients with locally advanced disease, either prior to surgery, after surgery, or in lieu of surgery
- Combinations in earlier stage disease allow for treatment of visible disease with radiation, allowing immunotherapy to address micrometastatic 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)



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Antonia, Villegas, Daniel et al. NEJM 2018

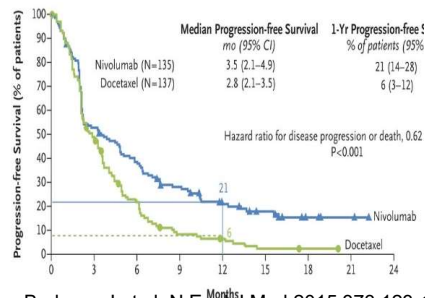


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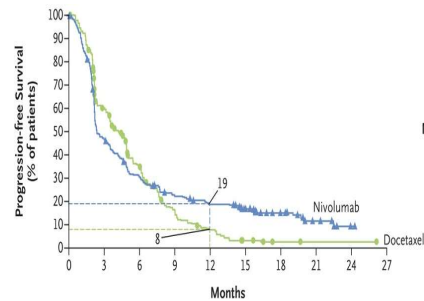
# Opportunities in Metastatic Disease

**Checkmate 017**



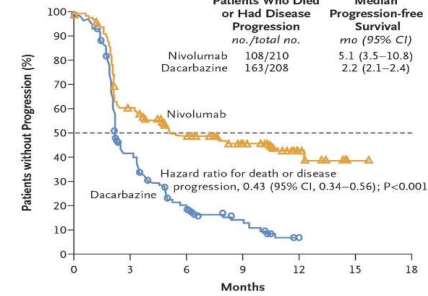
Brahmer J et al. N Engl J Med 2015;373:123-135

**Checkmate 057**



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

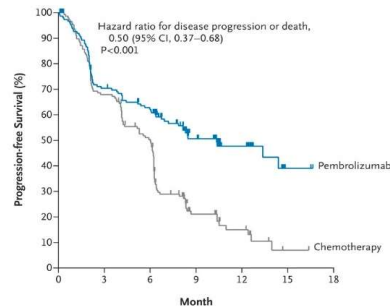
**Checkmate 066**



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

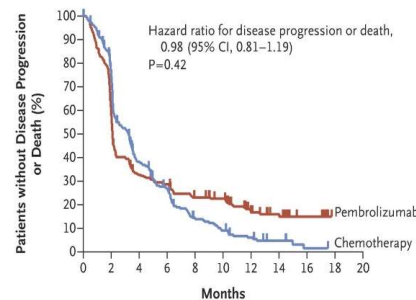
**Deviation from proportional hazards, with a population of early progressors that don't derive benefit from immunotherapy**

**Keynote 024**



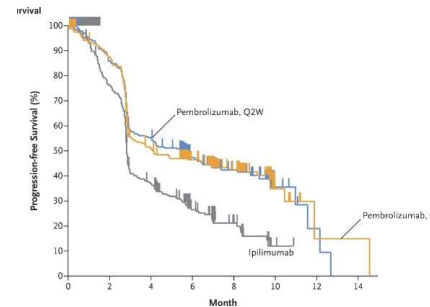
Reck M et al. N Engl J Med 2016;375:1823-1833

**Keynote 045**



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

**Keynote 006**



Robert C et al. N Engl J Med 2015;372:2521-2532



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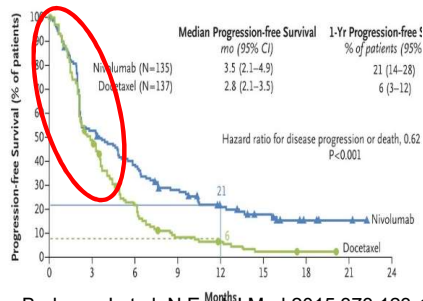
Alexander, Schoenfeld, Trippa NEJM 2018.



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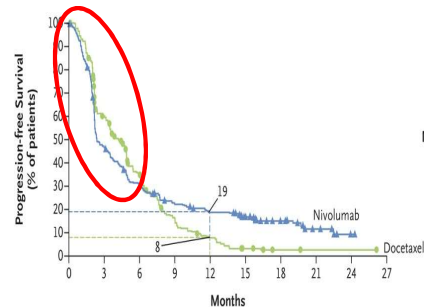
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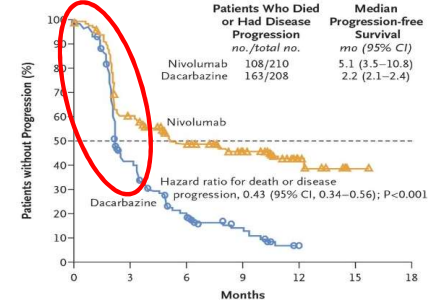
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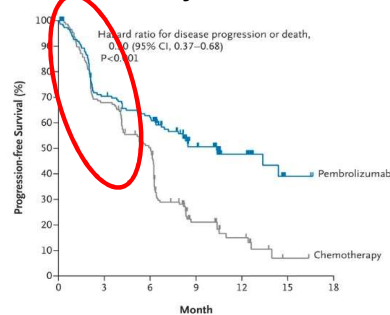
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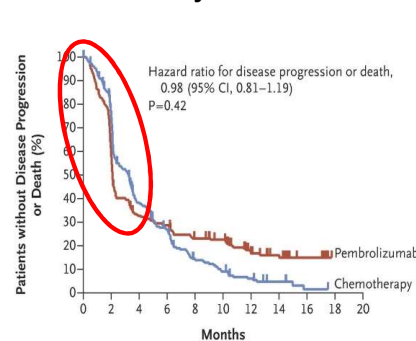
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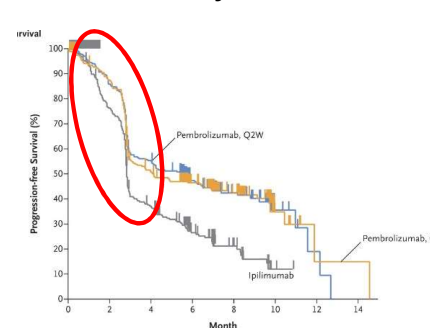
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**Keynote 006**



Robert C et al. N Engl J Med 2015;372:2521-2532

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

**Radiation (or chemotherapy) can potentially impact this non-responding population**



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Alexander, Schoenfeld, Trippa NEJM 2018.



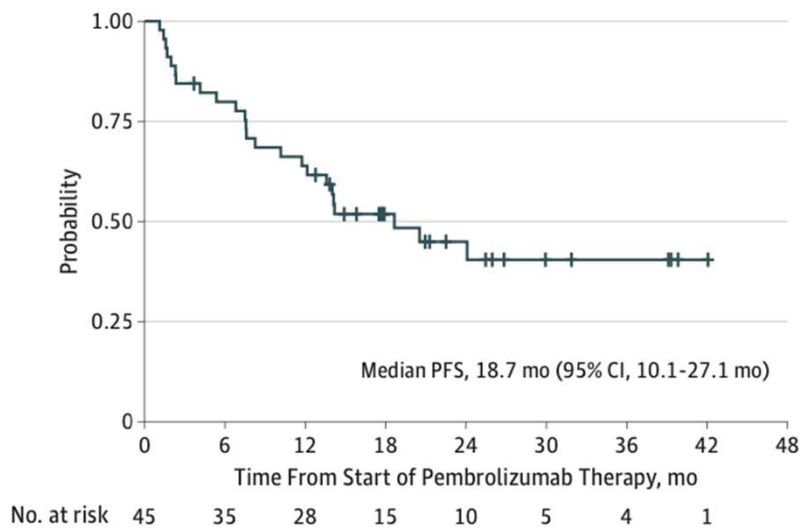
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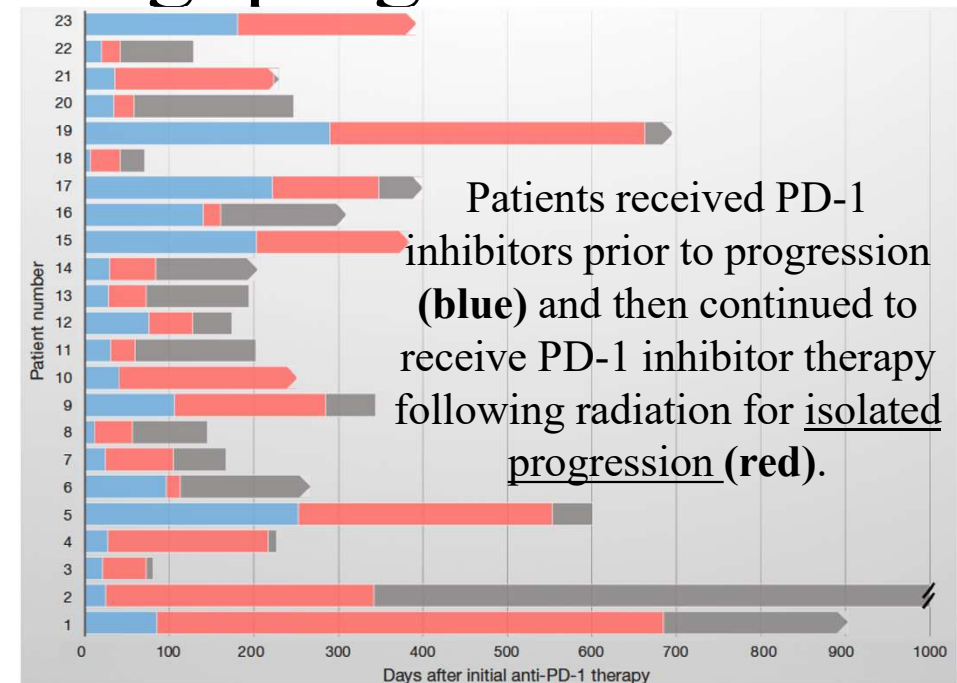
# Clinical Trial Setting

## Oligometastases and Oligoprogression

**B** Progression-free survival from start of pembrolizumab therapy



Baumli et al. JAMA Oncol. 2019; Pembro administered following local therapy to  $\leq 4$  metastases in patients with NSCLC. Improved median PFS of 18.7 months compared to 6.6 months for historical controls.



Bang and Schoenfeld, Ann Pall Med 2018; Pike et al. Radiotherapy and Oncology 2018. Also Klemen et al. JTC 2019.



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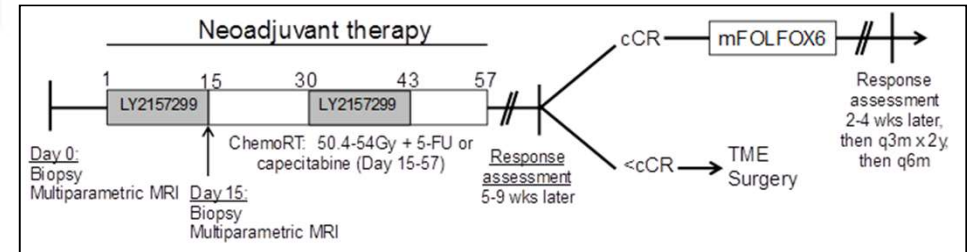
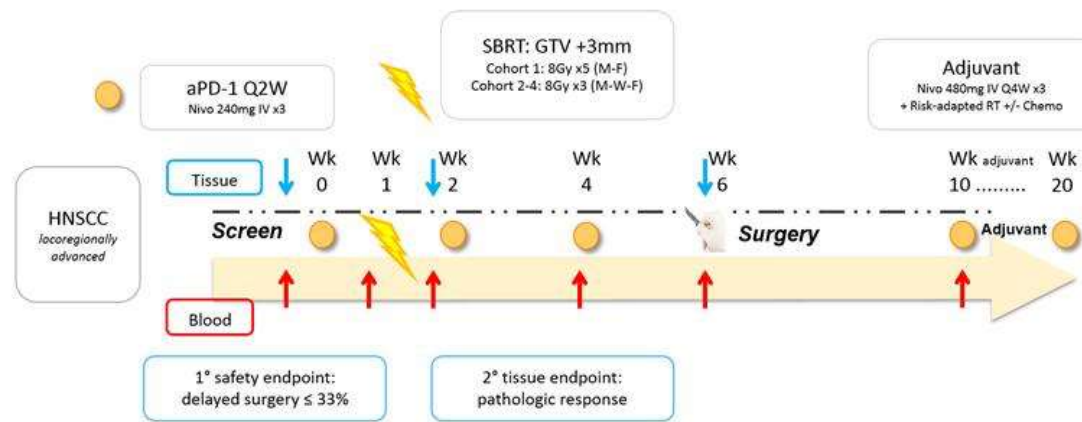


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# Clinical Trial Setting: Window of Opportunity Studies



Leidner AACR 2019:

Nivolumab (3 cycles) + SBRT (8 Gy x 3-5) prior to surgery  
for p16+ HNSCC

**100% pathologic CR with 8 Gy x 5**

**80% pathologic CR with 8 Gy x 3**

Opportunity to test novel agents in combination  
with radiation (e.g. TGF-beta pathway inhibitor)



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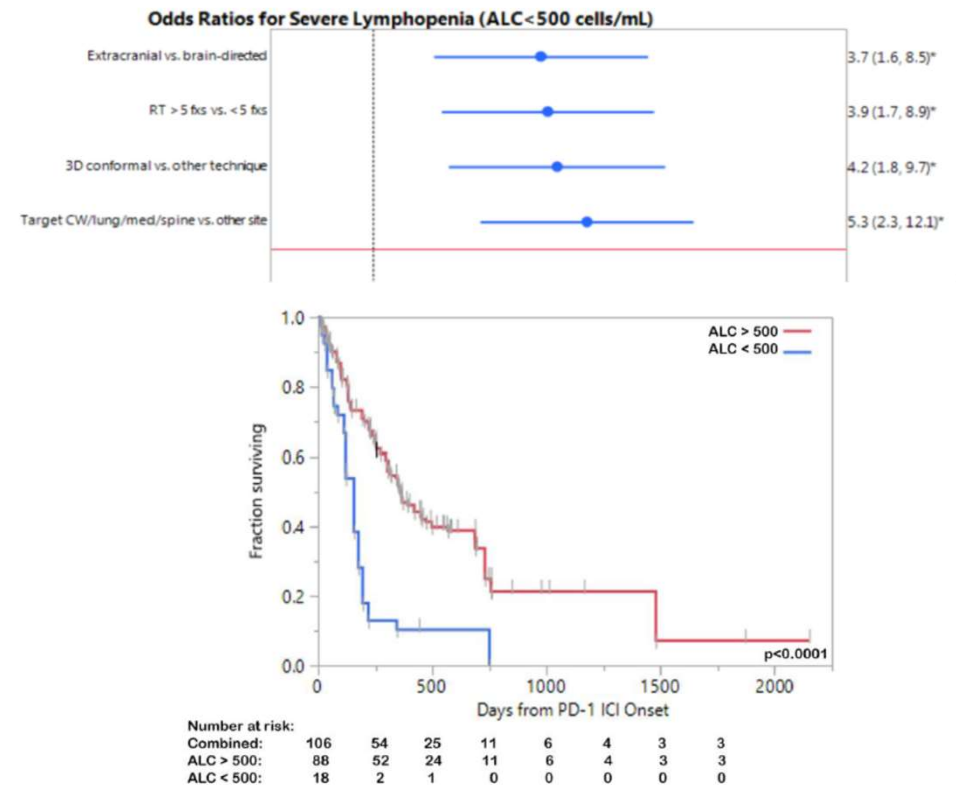
With thanks to Dr. Kristina Young



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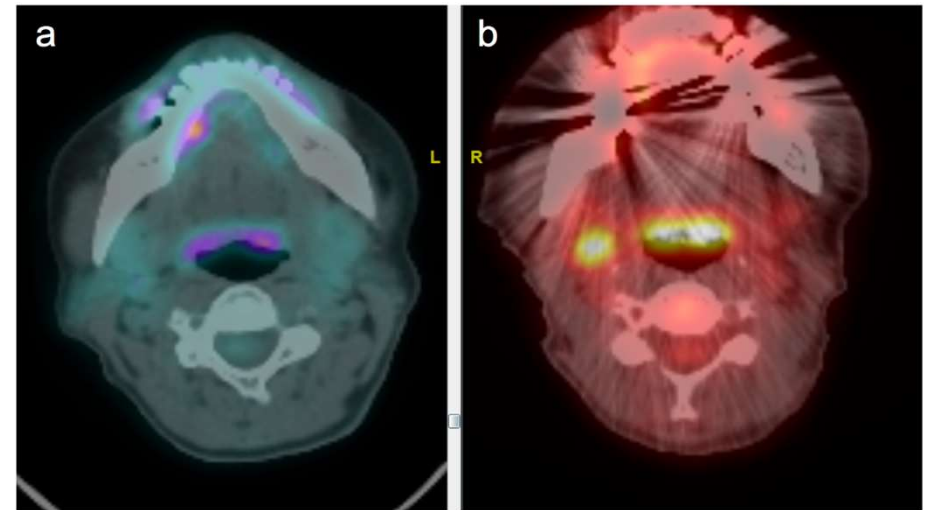
# Importance of Radiation Treatment Parameters

- **Dose / number of treatments (fractionation)**
- Radiation field
- Technique
  - Photons, protons, radioisotopes
- Radiation field quality control



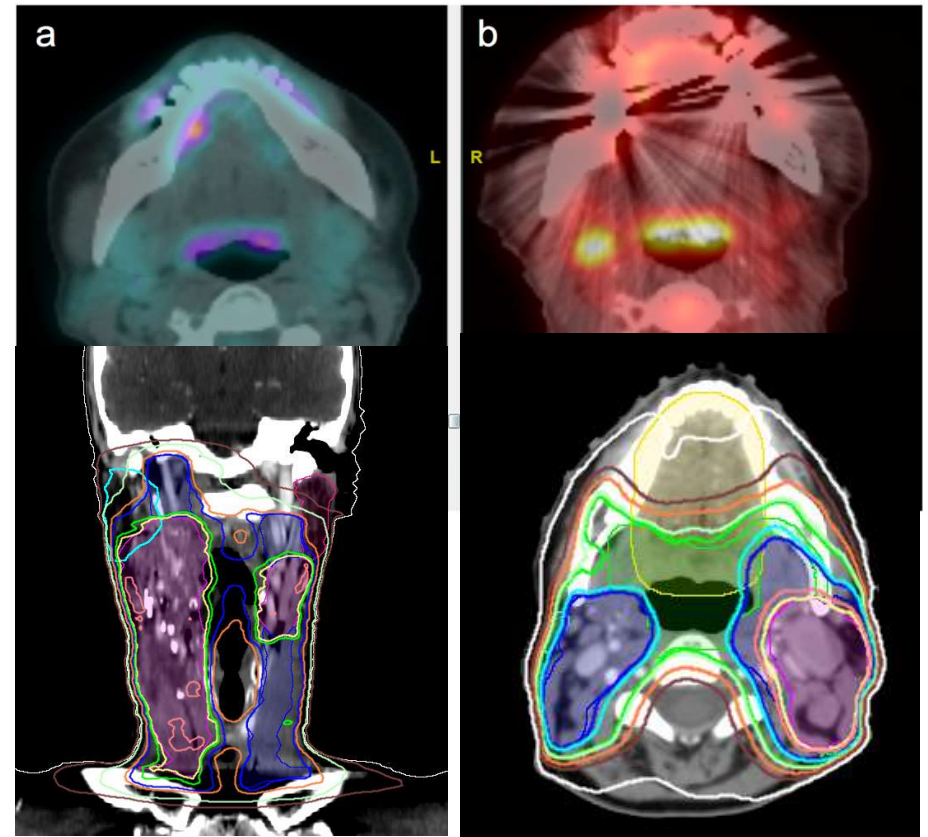
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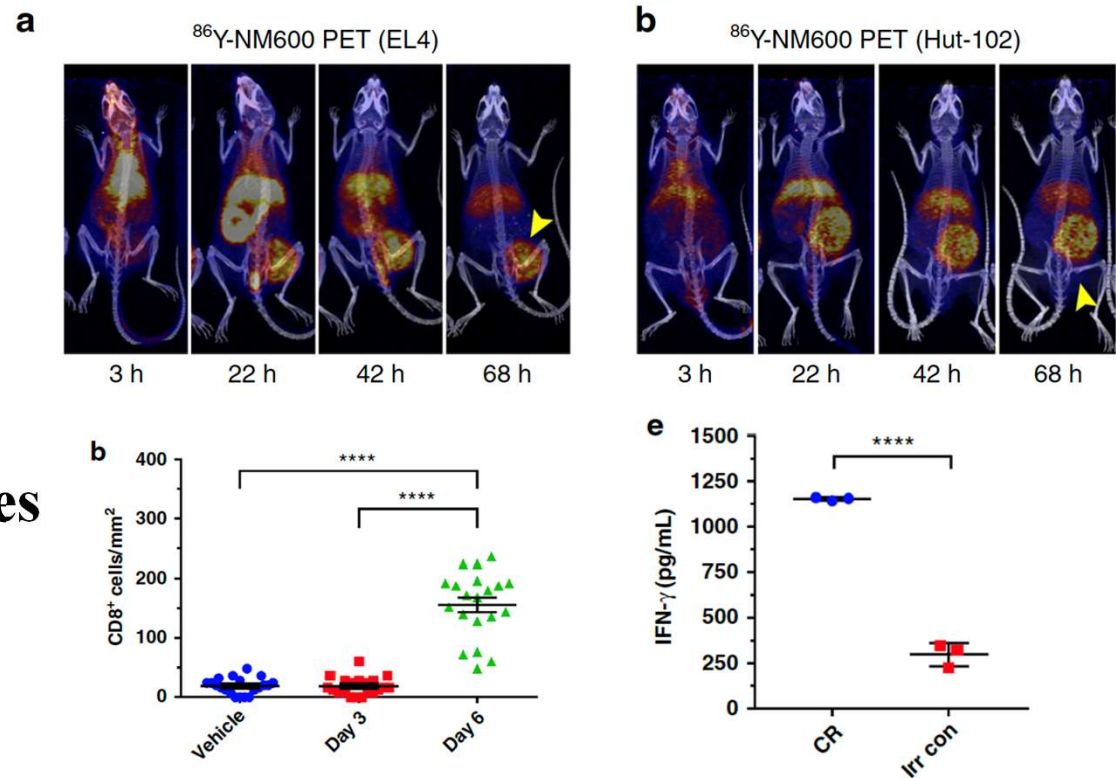
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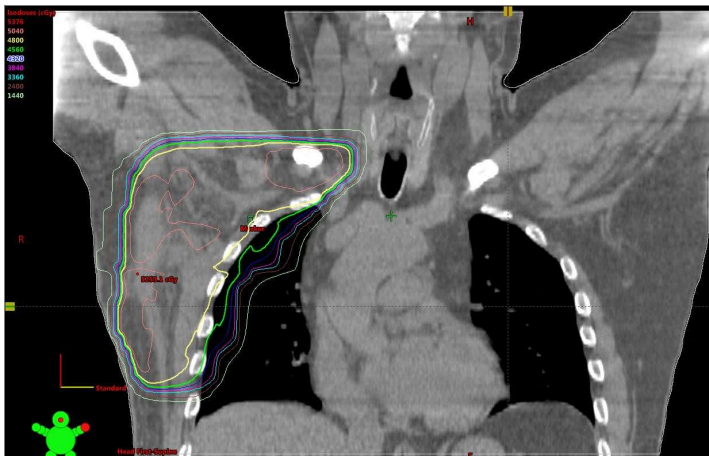
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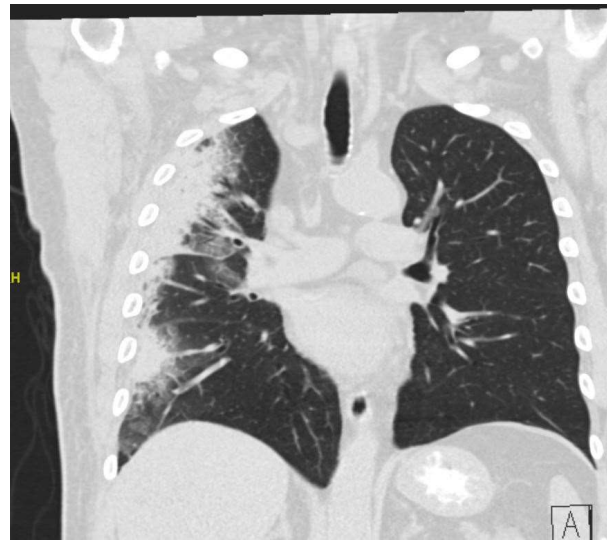




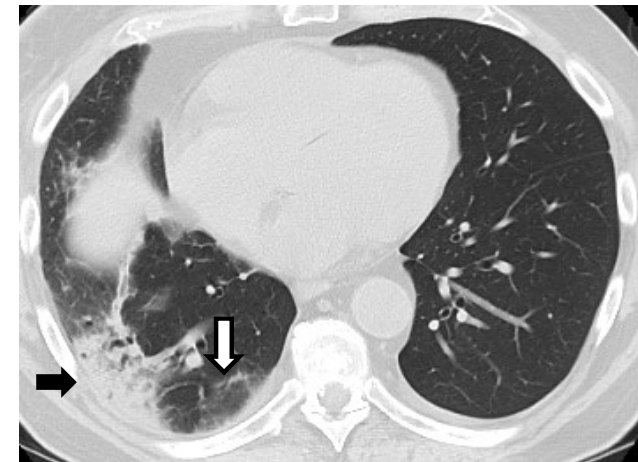
# Importance of collecting and evaluating radiation treatment data



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

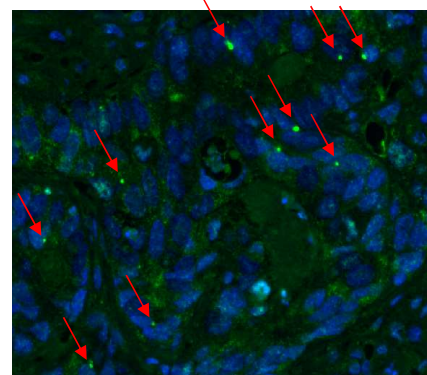
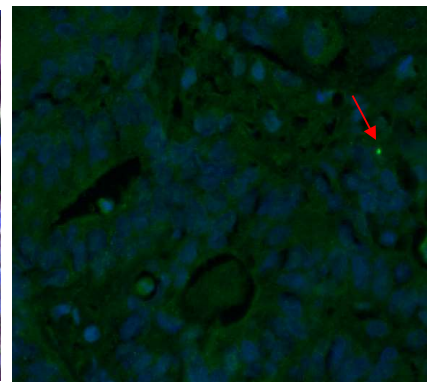
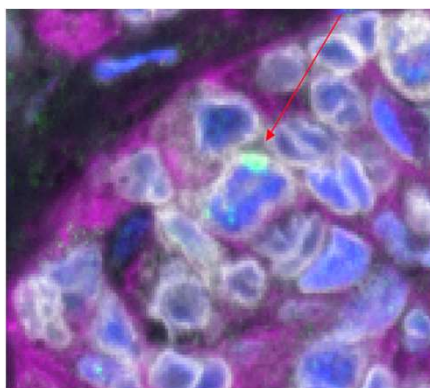
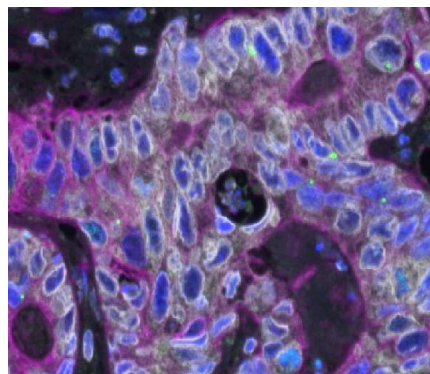
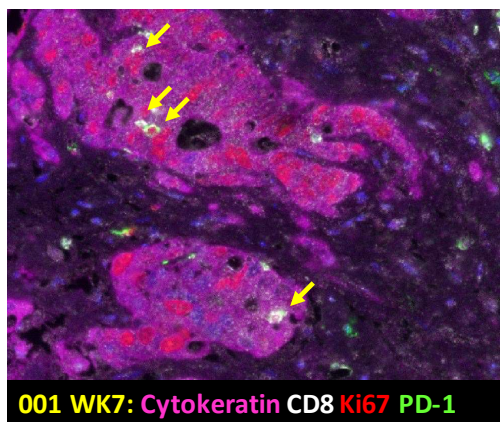
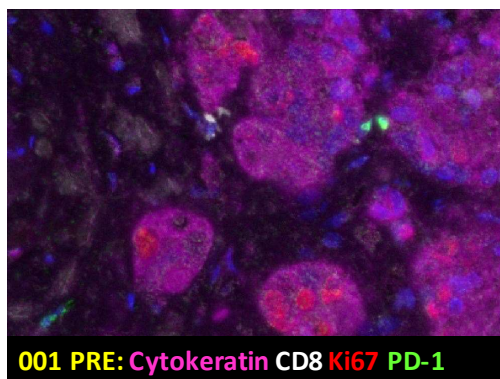


# Clinical Trial Endpoints

- Response
  - Overall response (RECIST, immune-related response criteria), and then specifically within radiation field (**local**), outside of radiation field (**abscopal**)
- Toxicity: both short- and long-term toxicities occur with both radiation and immune therapy
- Correlative endpoints



# Correlative Endpoints



Increased CD8+ T-cell infiltration (left) and micronuclei and foci of primary nuclear ruptures (red arrows) with the addition of either low-dose or hypofractionated radiation to PD-L1/CTLA-4 blockade. ETCTN 10021. ASCO SITC 2019

Above: cytokeratin (purple), DAPI (blue), cGAS (green) and Lamin B receptor (white) as shown (low power, top).



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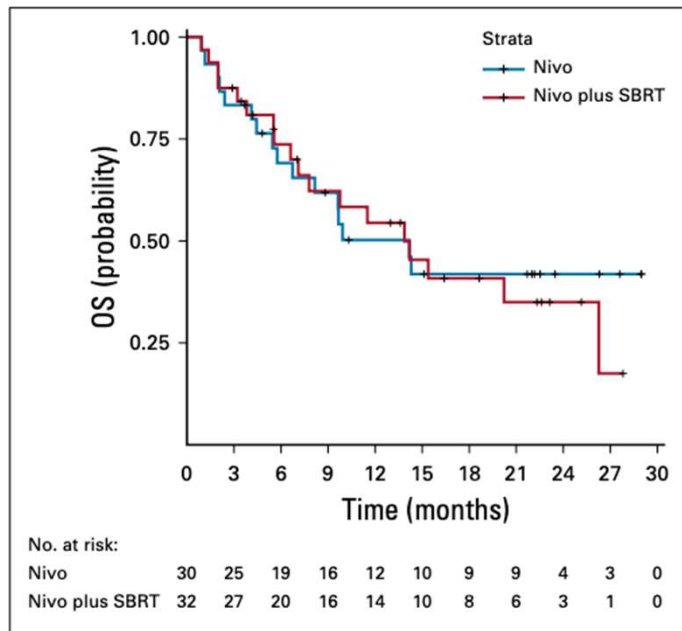


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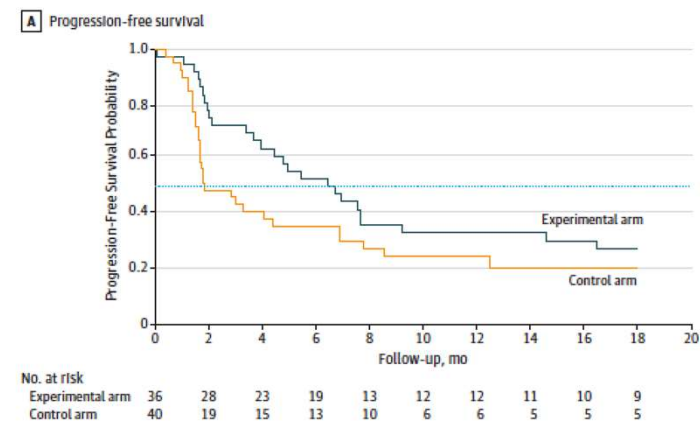
# Importance of randomization



**FIG 2.** Overall survival (OS) in the intention-to-treat population (n = 62). Nivo, nivolumab; SBRT, stereotactic body radiotherapy.

McBride et al. JCO 2020

**Figure 2. Progression-Free Survival in the Intent-to-Treat Population**



PembroRT study. NSCLC patients with trend towards improved ORR ( $p=0.07$ ), PFS and OS with the addition of hypofractionated RT to pembro.  
Theelen et al. JAMA Oncology 2019



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# Summary / Conclusions

- Hypothesis-driven, thoughtfully designed clinical trials important to future development of radiation / immune therapy combinations, with input from basic and translational scientists, clinical practitioners including medical and radiation oncologists
- Important considerations
  - Clinical setting (recurrent/metastatic, definitive, pre/post operative)
  - Radiation parameters: dose/fractionation, target, technique
  - Study endpoints and study design







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# Thank you!

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