Combining Immunotherapy and Radiation Therapy

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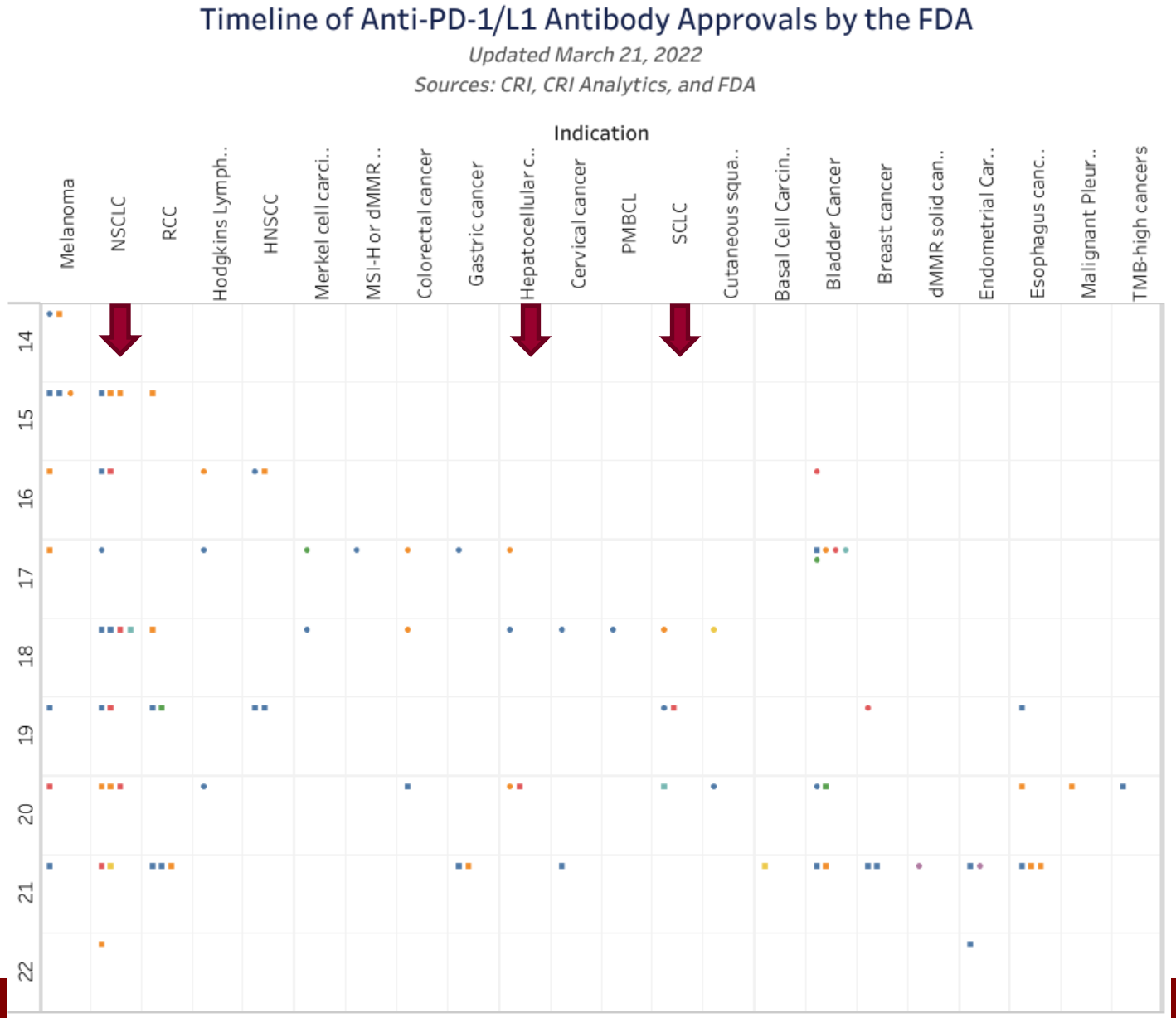
Disclosures

- Consultant – AstraZeneca, Genentech, Merck
- Research Support – AstraZeneca, Celldex, Merck

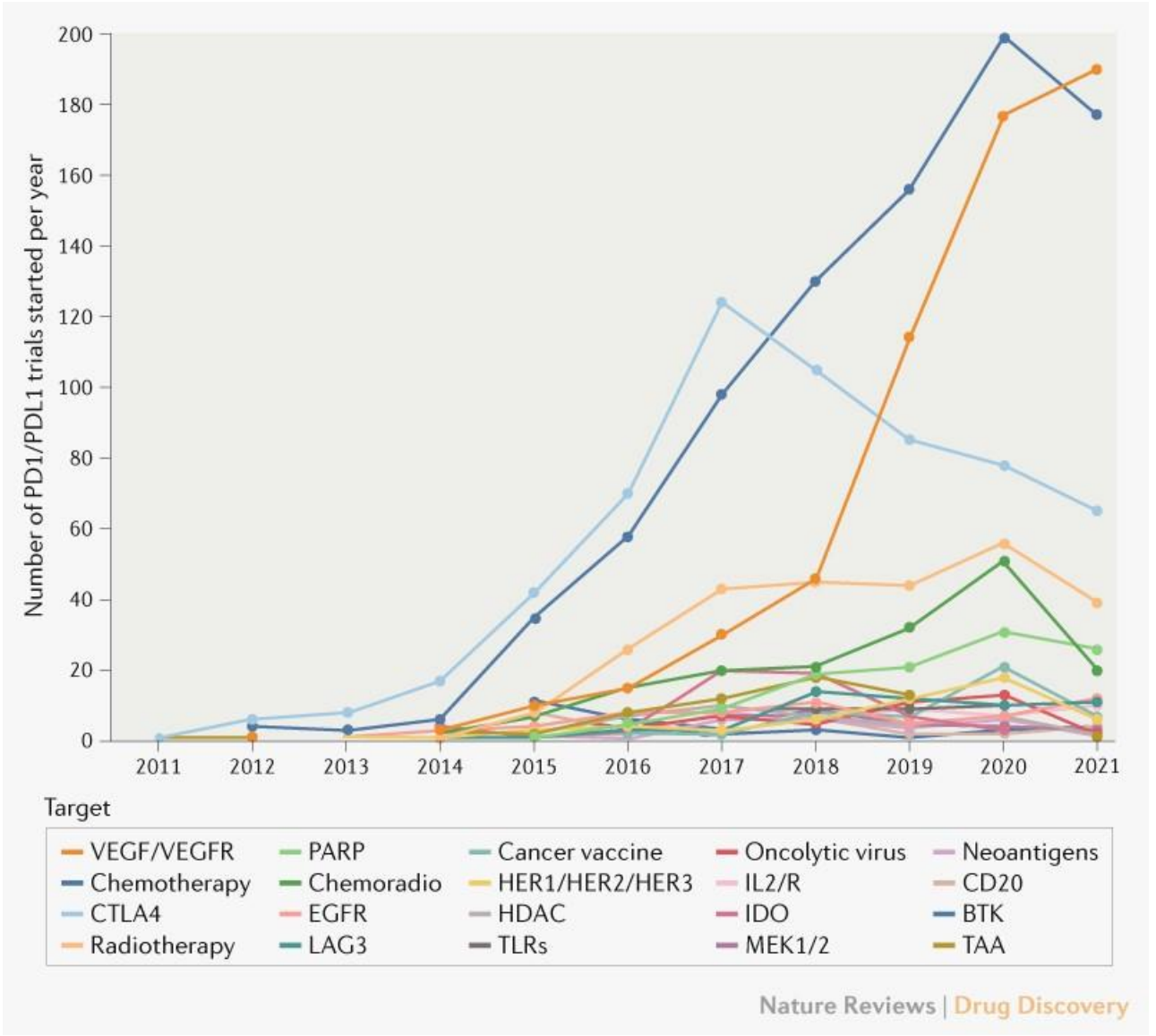
My Background

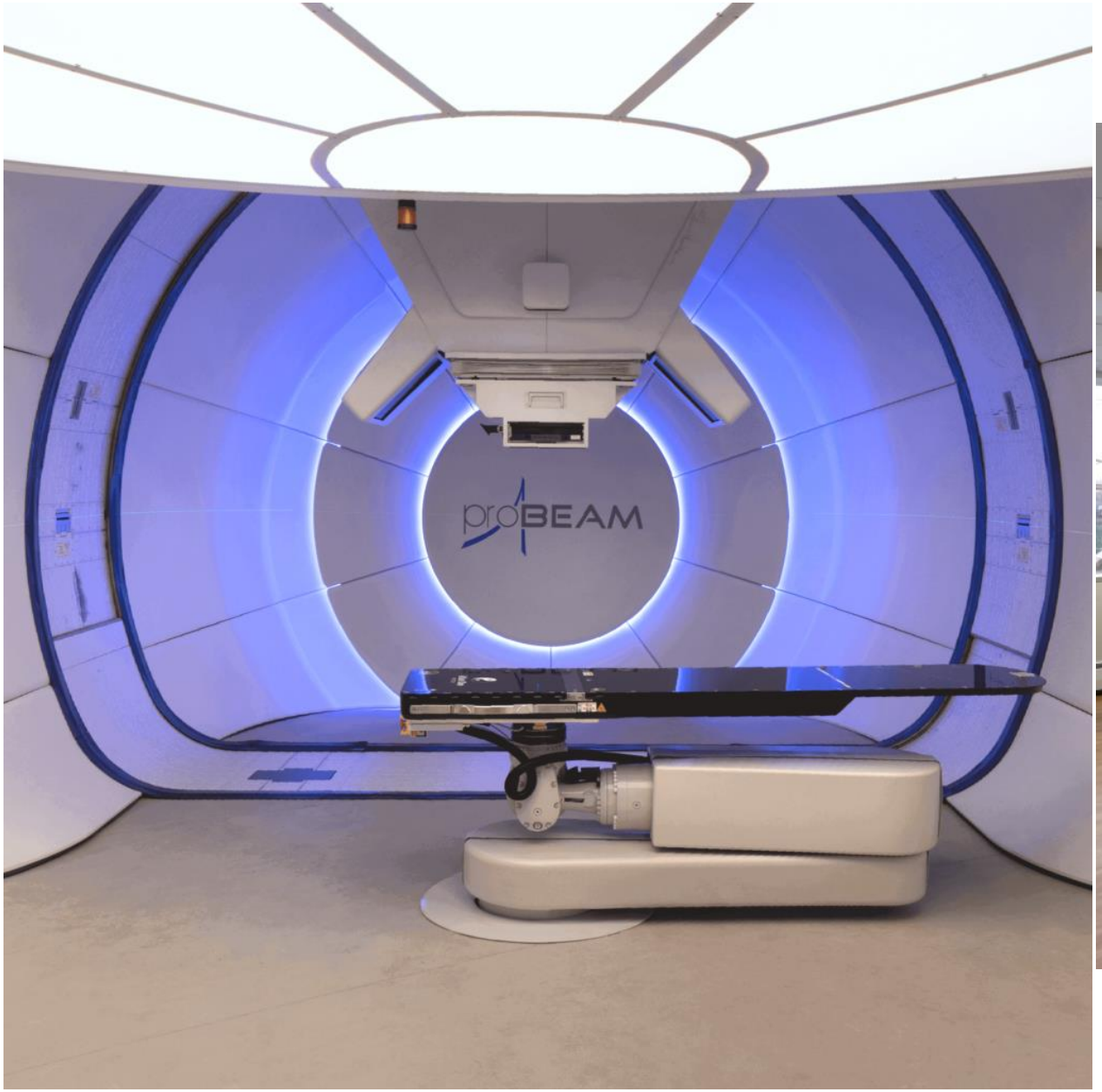
- I started practicing at Montefiore/Einstein in 2012, with a clinical focus on treating lung and hepatobiliary cancers.



My Background

- I lead our Department's clinical research team, I chair our Cancer Center's Protocol Review and Monitoring Committee, and I serve on several NRG Oncology committees.




proBEAM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Outline

- Safety of combining immunotherapy and radiotherapy
- Indications for combining immunotherapy and radiotherapy
- Adapting radiotherapy practices in the immunotherapy era
  - Who we treat
  - How we treat

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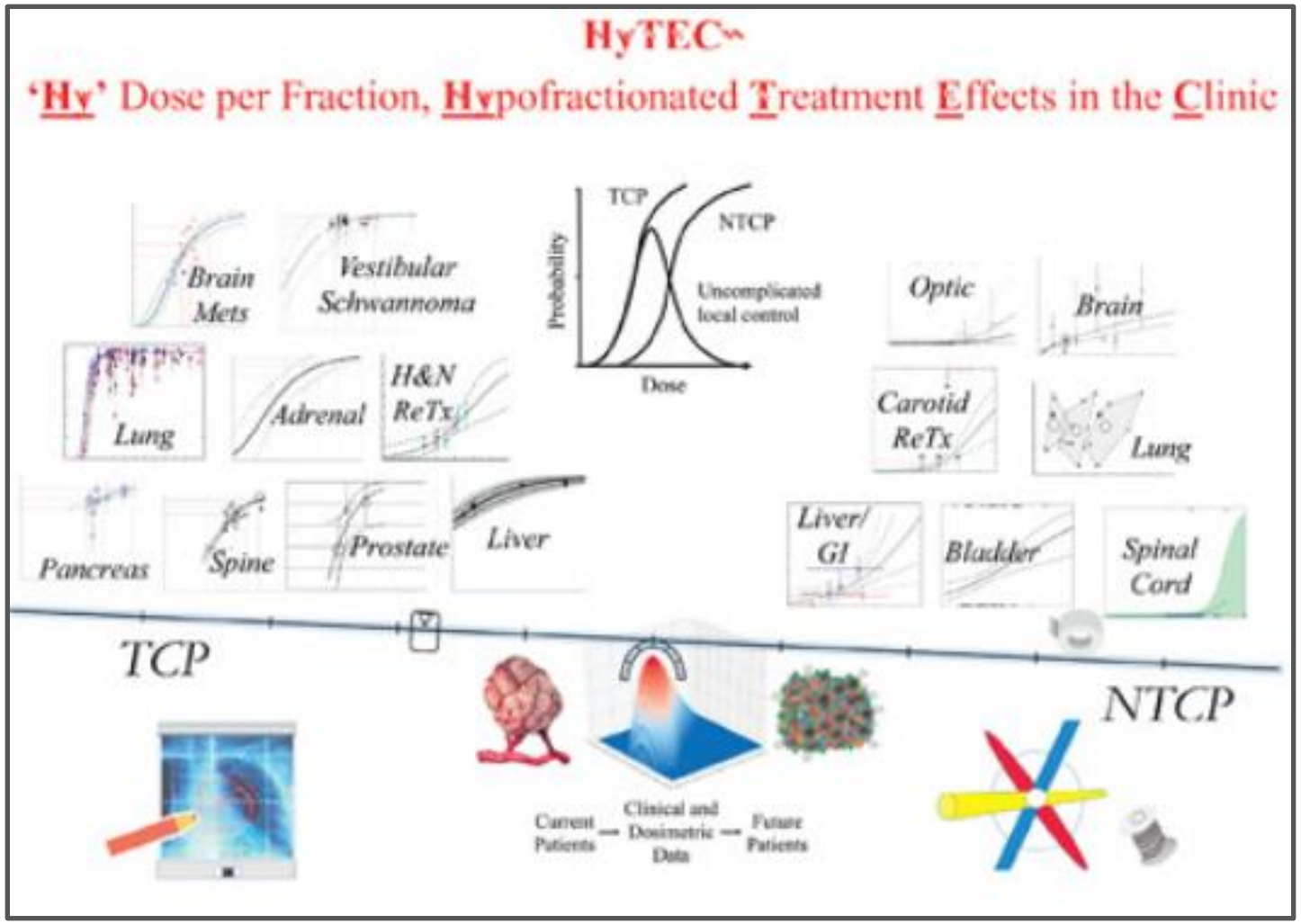
Grade ≥3 Immunotherapy-related Toxicities

- Pneumonitis: ≈1% (higher in lung cancer)
- Colitis/Diarrhea: ≈1%
- Hepatitis: <1%

JAMA Oncol. 2016;2(12):1607-1616. Oncoimmunology. 2017 Jul 5;6(10):e1344805. Am Soc Clin Oncol Educ Book. 2018 May 23;38:13-19.

Radiotherapy Toxicities



It's complicated

Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

- Unresectable, Stage III NSCLC without progression after definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- If available, archived pre-cCRT tumor tissue for PD-L1 testing*

(54-66 Gy)
Lung V20 < 35% or
Lung mean < 20 Gy

All-comers population
(i.e. irrespective of PD-L1 status)

N=713 randomized

1–42 days post-cCRT

R

2:1 randomization, stratified by age, sex, and smoking history

Durvalumab
10 mg/kg q2w for up to 12 months
N=476

Placebo
q2w for up to 12 months
N=237

Primary endpoints

- PFS by BICR using RECIST v1.1†
- OS

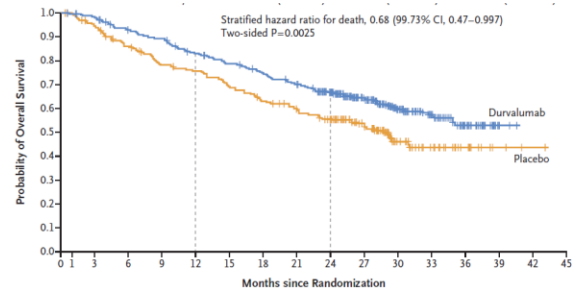
Key secondary endpoints

- ORR, DoR and TTDM by BICR
- PFS2 by investigator
- Safety
- PROs

"PACIFIC" Trial

N Engl J Med. 2017 Nov 16;377(20):1919-1929.

Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC

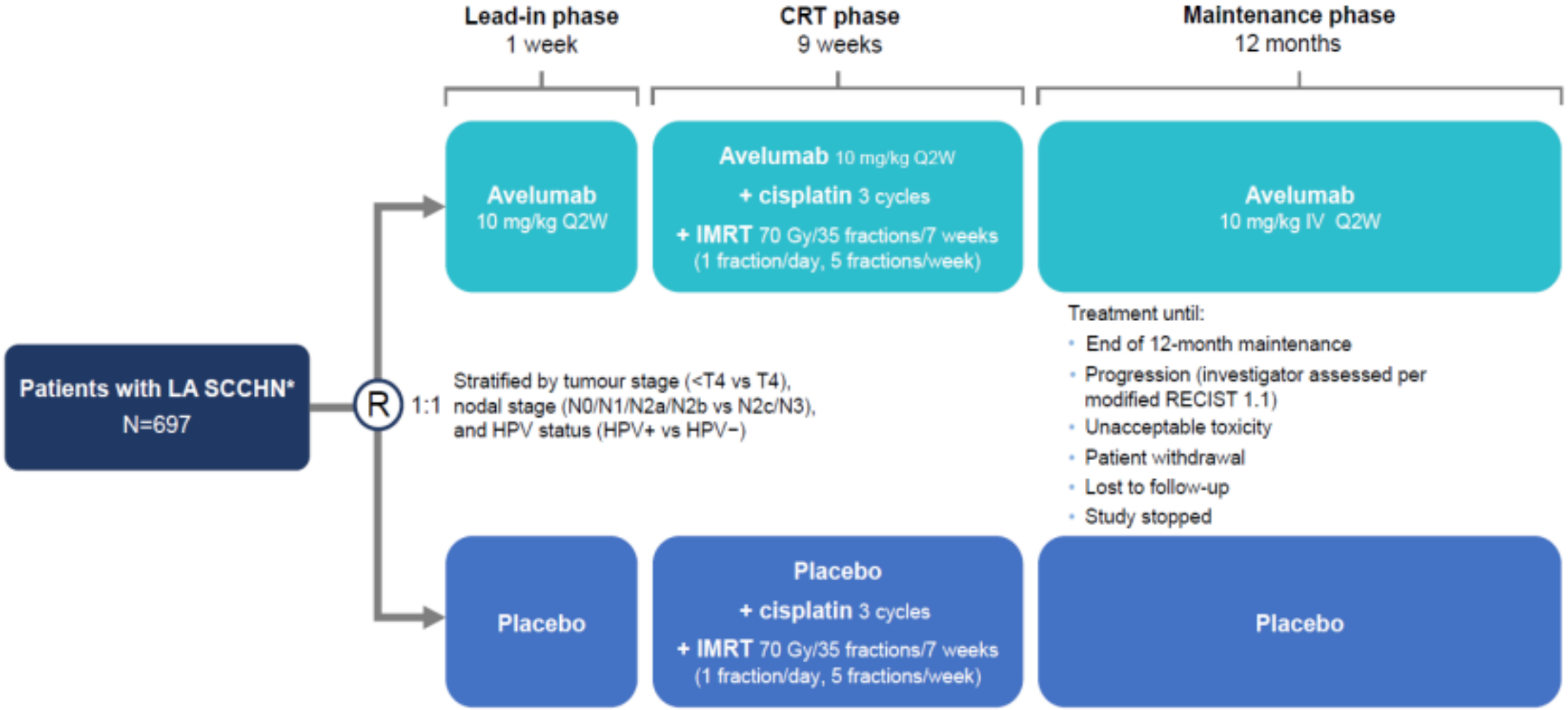


- Discontinuation of study therapy: 15% with durvalumab v. 10% with placebo
  - 5% due to pneumonitis with durvalumab v. 3% with placebo
- Serious adverse events: 29% with durvalumab v. 23% with placebo

Adding immunotherapy after chemoRT → No unexpected toxicity increase

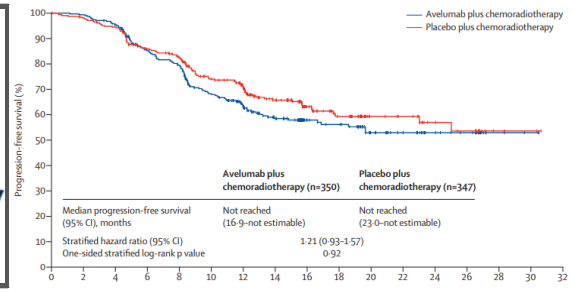
N Engl J Med 2018;379:2342-50.

Avelumab plus standard-of-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial



Lancet Oncol 2021; 22: 450–62

Avelumab plus standard-of-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial



- Grade ≥3 adverse events occurred in 88% of patients in the avelumab group and in 82% of patients in the placebo group.
- Grade ≥3 immune-related adverse events occurred in 5% of patients in the avelumab group.

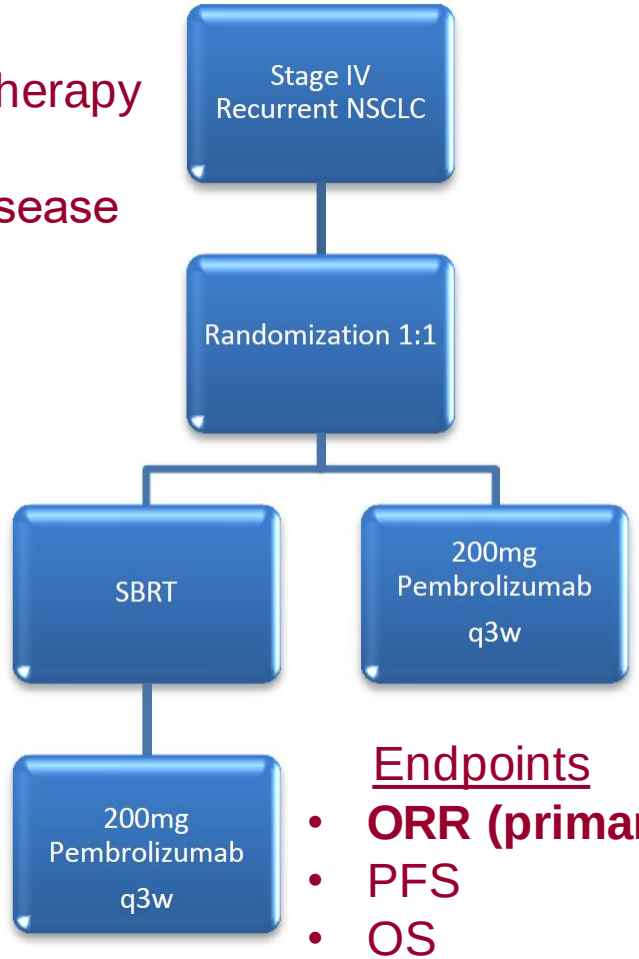
Adding immunotherapy to chemoRT → No unexpected toxicity increase

Lancet Oncol 2021; 22: 450–62

Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non-Small Cell Lung Cancer
Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial

Eligibility

- Post-chemotherapy
- I/O-naïve
- ≥2 sites of disease



8 Gy x 3

Response	Experimental Arm, No./Total No. (%) (n = 36)[a]	Control Arm, No./Total No. (%) (n = 40)[b]
Objective response rate at 12 wk		
Overall[c]	13/36 (36)	7/40 (18) p=0.07
PD-L1 TPS, %		
0	4/18 (22)	1/25 (4)
1-49	3/8 (38)	3/8 (38)
≥50	6/10 (60)	3/5 (60)
Disease control rate at 12 wk[d]	23/36 (64)	16/40 (40) p=0.04

Endpoints

- **ORR (primary)**
- PFS
- OS

SBRT before immunotherapy → No unexpected toxicity increase

JAMA Oncol. 2019;5(9):1276-1282.

Randomized Phase II Trial of Nivolumab With Stereotactic Body Radiotherapy Versus Nivolumab Alone in Metastatic Head and Neck Squamous Cell Carcinoma

- 62 immunotherapy-naïve patients with metastatic HNSCC and ≥2 measurable lesions
  - Both arms: nivolumab 3 mg/kg every 2 weeks for up to 96 weeks
  - Experimental arm: SBRT (9 Gy x 3) to a single lesion between cycles 1 and 2 of nivolumab
- Similar adverse event rates across arms:
  - Any grade - 87% in SBRT arm v. 70% in control arm (p=0.12)
  - Grade ≥3 - 10% in SBRT arm v. 13% in control arm (p=0.70)

SBRT during immunotherapy → No unexpected toxicity increase

J Clin Oncol. 2021 Jan 1;39(1):30-37.

Association of Radiation Therapy With Risk of Adverse Events in Patients Receiving Immunotherapy

A Pooled Analysis of Trials in the US Food and Drug Administration Database

- Data from >25,000 patients in 68 trials of immune checkpoint inhibitors
- 1,662 patients with no RT history were matched to 1,662 patients who received RT within 90 days.
- Recent RT was associated with increased rates of grade 1-2 fatigue (8%) and pneumonitis (2%).
- Recent RT was not associated with grade ≥3 adverse events.

RT before immunotherapy → No unexpected toxicity increase

JAMA Oncol. 2022;8(2):232-240.

Ongoing large RCTs

- ***EA5181*** - Randomized Phase III Trial of Durvalumab as Concurrent and Consolidative Therapy or Consolidative Therapy Alone for Unresectable Stage 3 NSCLC
- ***NRG-LU002*** - Maintenance Systemic Therapy Versus Local Consolidative Therapy (LCT) Plus Maintenance Systemic Therapy for Limited Metastatic Non-Small Cell Lung Cancer (NSCLC): A Randomized Phase II/III Trial
- ***NRG-LU005*** - Limited Stage Small Cell Lung Cancer (LS-SCLC): A Phase III Randomized Study of Chemoradiation Versus Chemoradiation Plus Atezolizumab

No concerning safety signals

Does immunotherapy increase the rate of radiation necrosis after radiosurgical treatment of brain metastases?

Tumor histology		
Melanoma	56	31.1
Lung	71	39.4
Renal cell	16	8.9
Breast	27	15.0
Colorectal	7	3.9
Other	3	1.7

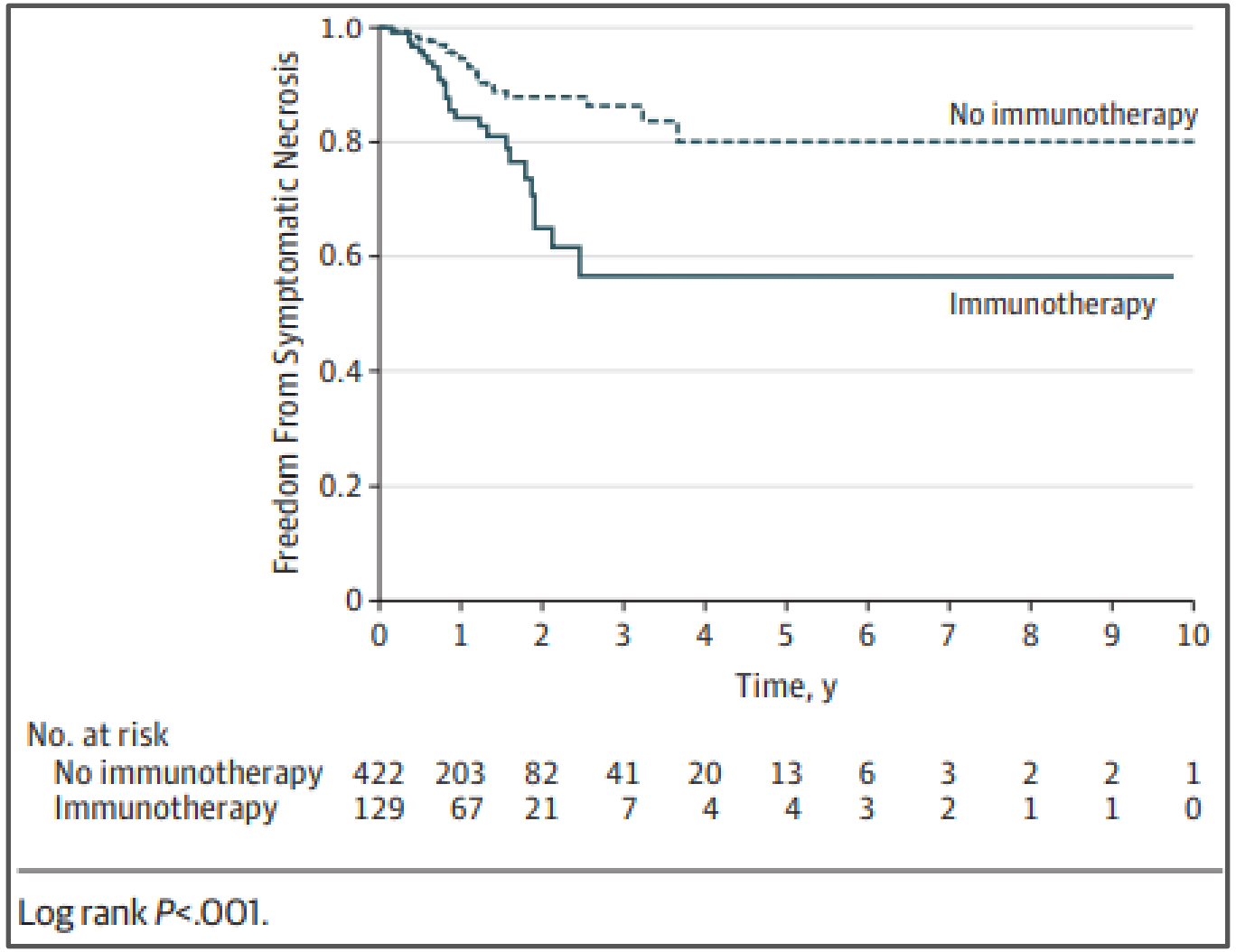
TABLE 3. Rates of RN according to systemic therapy type

Systemic Therapy	Total No. of Patients (n = 180)	Total w/ RN (n = 39)	%
IT only	32	12	37.5
TT only	20	5	25.0
CT only	83	14	16.9
IT + TT	4	2	50.0
IT + CT	4	0	0.0
TT + CT	31	5	16.1
IT + TT + CT	2	0	0.0
None	4	1	25.0

- Median overall survival was significantly longer in patients who developed radionecrosis compared to other patients (24 v. 10 months)

Biologic effect, or artifact of reduced competing risks?

Immunotherapy and Symptomatic Radiation Necrosis in Patients With Brain Metastases Treated With Stereotactic Radiation



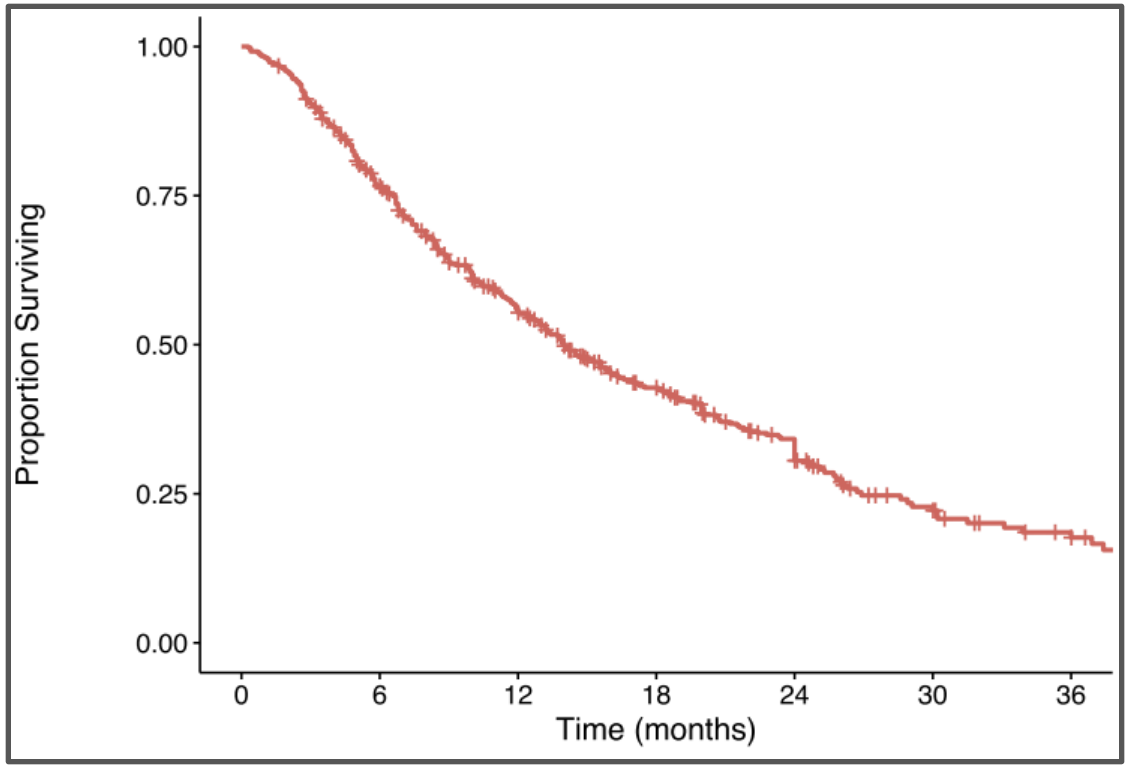
No. at risk											
No immunotherapy	422	203	82	41	20	13	6	3	2	2	1
Immunotherapy	129	67	21	7	4	4	3	2	1	1	0

Log rank $P<.001$.

JAMA Oncol. 2018 Aug 1;4(8):1123-1124.

Treatment of brain metastases with stereotactic radiosurgery and immune checkpoint inhibitors: An international meta-analysis of individual patient data

- 534 patients with 1,570 brain mets treated with SRS
- 5% radionecrosis rate
- Median OS only 13 months



Safety of combining radiotherapy and immunotherapy

- Hundreds of thousands of cancer patients have likely been treated with some sequence of immune checkpoint inhibitors and radiotherapy.
- There is no convincing evidence of synergistic toxicity.
- We should still be cautious with new agents.

U.S. Food and Drug Administration Approves First LAG-3-Blocking Antibody Combination, Opdualag™ (nivolumab and relatlimab-rmbw), as Treatment for Patients with Unresectable or Metastatic Melanoma

03/18/2022

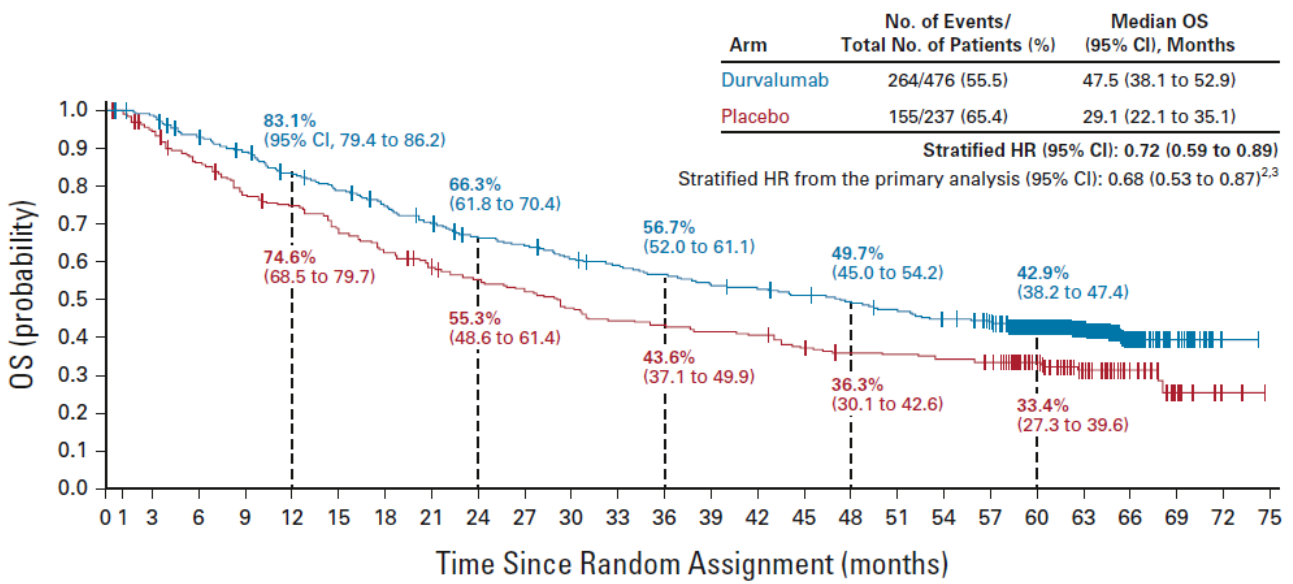
CATEGORY: Corporate/Financial News

REACTION — a phase Ib pilot study of nivolumab or nivolumab in combination with relatlimab after targeted radiation in patients with advanced esophagogastric cancer

Outline

- Safety of combining immunotherapy and radiotherapy
- **Indications for combining immunotherapy and radiotherapy**
- Adapting radiotherapy practices in the immunotherapy era
  - Who we treat
  - How we treat

Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer



- Landmark trial that transformed practice for *most* NSCLC patients treated with ChemoRT
- Not exactly an indication for *combining* immunotherapy and RT (EA5181 ongoing)
- We now know that LA-NSCLC patients treated with resection can also benefit from immunotherapy (IMpower010, CheckMate 816)

J Clin Oncol. 2022 Apr 20;40(12):1301-1311.

Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer

Key eligibility criteria
- Stage II/III EC/GEJC
- Adenocarcinoma or squamous cell carcinoma
- Neoadjuvant CRT + surgical resection (R0,[b] performed within 4-16 weeks prior to randomization)
- Residual pathologic disease
  - ≥ ypT1 or ≥ ypN1
- ECOG PS 0-1

Stratification factors
- Histology (squamous vs adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 vs ypN0)
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[c])

N = 794

R 2:1

n = 532 → **Nivolumab** 240 mg Q2W × 16 weeks then 480 mg Q4W

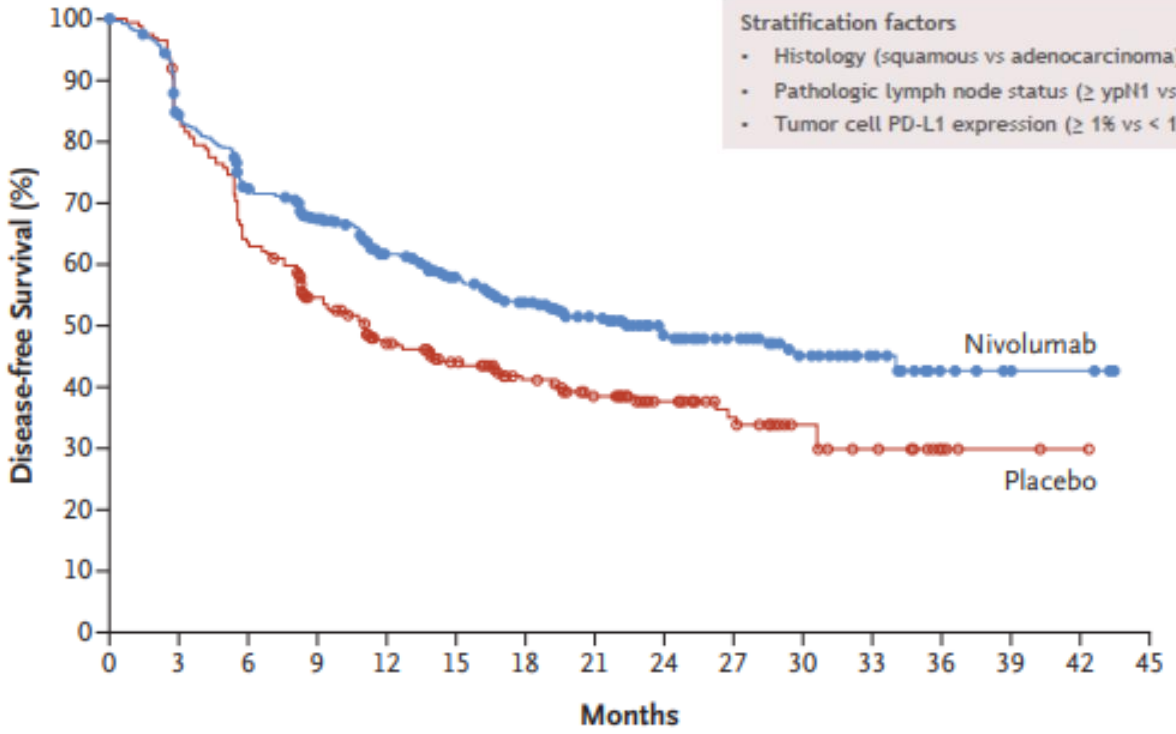
n = 262 → **Placebo** Q2W × 16 weeks then Q4W

Total treatment duration of up to 1 year[d]

Primary endpoint:
- DFS[e]

Secondary endpoints:
- OS[f]
- OS rate at 1, 2, and 3 years

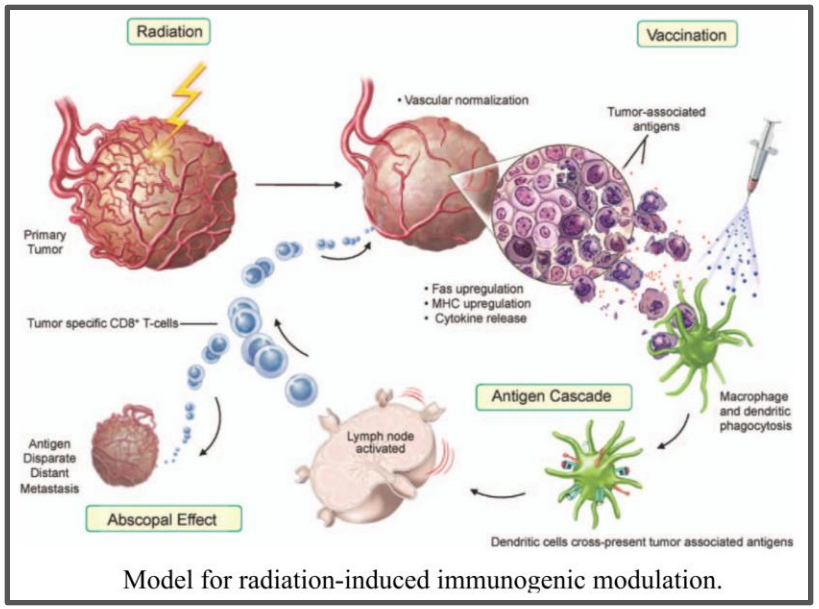
A Disease-free Survival in the Overall Population



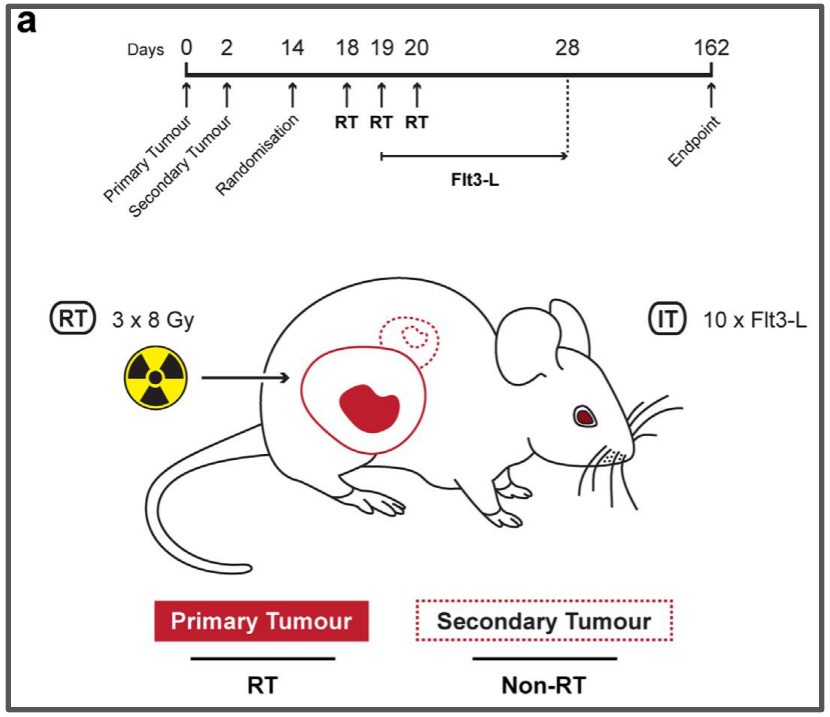
- Similar to PACIFIC
- Synergy or salvage?

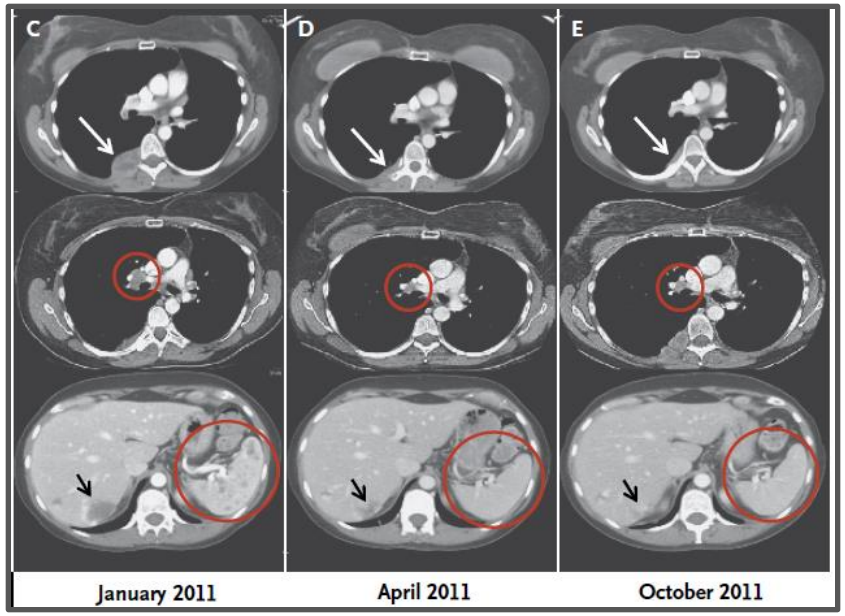
N Engl J Med 2021;384:1191-203.

Combining Radiotherapy and Immunotherapy: Mechanistic Rationale, Preclinical Models, Case Reports



Model for radiation-induced immunogenic modulation.





We now have some clinical trial data!

Radiat Res. 2014 August ; 182(2): 123–125.

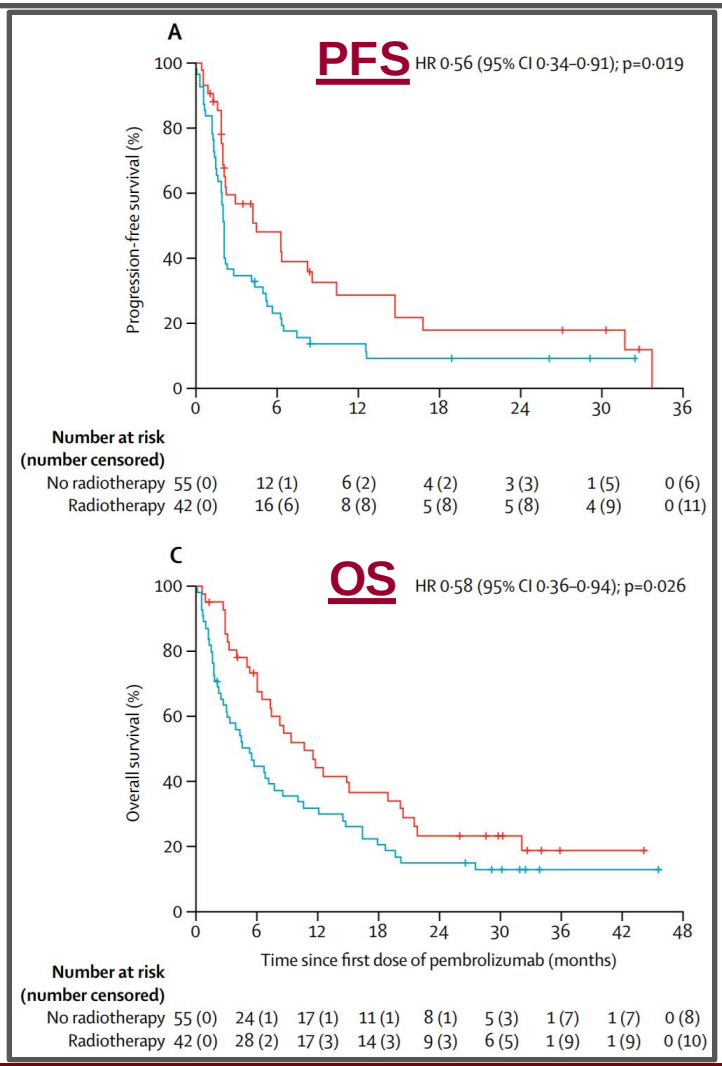
PLoS One. 2016 Jul 18;11(7):e0159515.

N Engl J Med 2012;366:925-31.

Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial

Narek Shaverdian, Aaron E Lisberg*, Krikor Bornazyan, Darlene Veruttipong, Jonathan W Goldman, Silvia C Formenti, Edward B Garon†, Percy Lee†*

	Previous radiotherapy		
	No (n=55)	Yes (n=42)	p value
Age (years)	66 (32·0–83·0)	65 (36·0–77·0)	0·36
Sex			0·79
Male	29 (53%)	21 (50%)	
Female	26 (47%)	21 (50%)	
ECOG performance status			0·82
0	21 (38%)	17 (40%)	
1	34 (62%)	25 (60%)	
Histology			0·24
Squamous cell	8 (15%)	11 (26%)	
Adenocarcinoma or other	47 (85%)	31 (74%)	
Time from initial diagnosis (months)	17·3 (0·9–98·2)	25·9 (2·6–107·0)	0·042
History of brain metastases	0	8 (19%)	0·0026
Number of previous unique systemic therapies	2 (0–5)	3 (0–5)	0·024
No previous systemic therapies	11 (20%)	2 (5%)	0·061
PD-L1 status*			0·75
Positive	44 (80%)	30 (71%)	
Negative	6 (11%)	5 (12%)	
Unknown	5 (9%)	7 (17%)	



- Cohorts not balanced
- Multivariable analyses supported benefits of prior RT

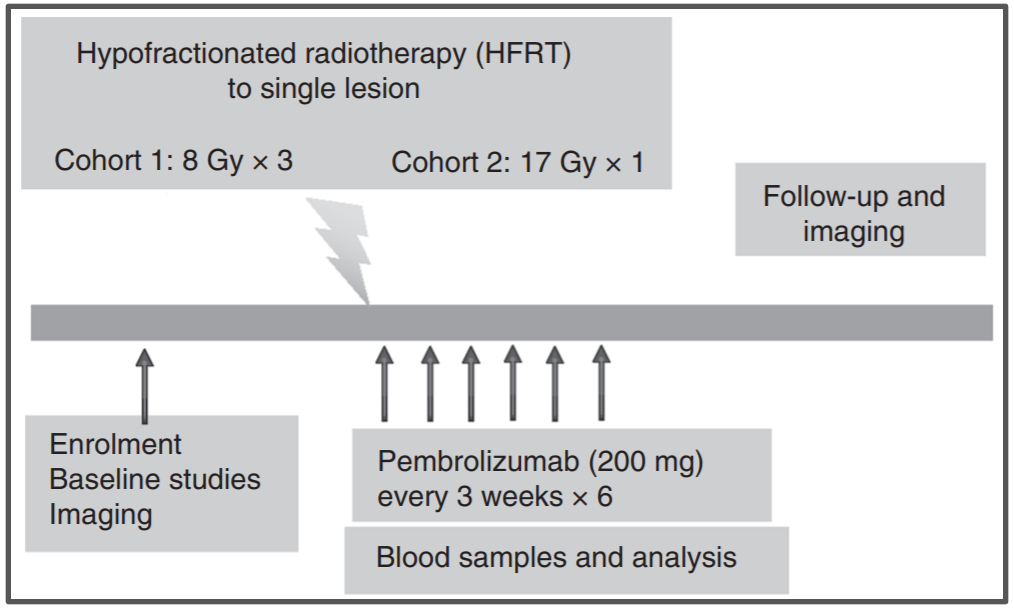
- Where are the validation studies?

Lancet Oncol 2017; 18: 895–903

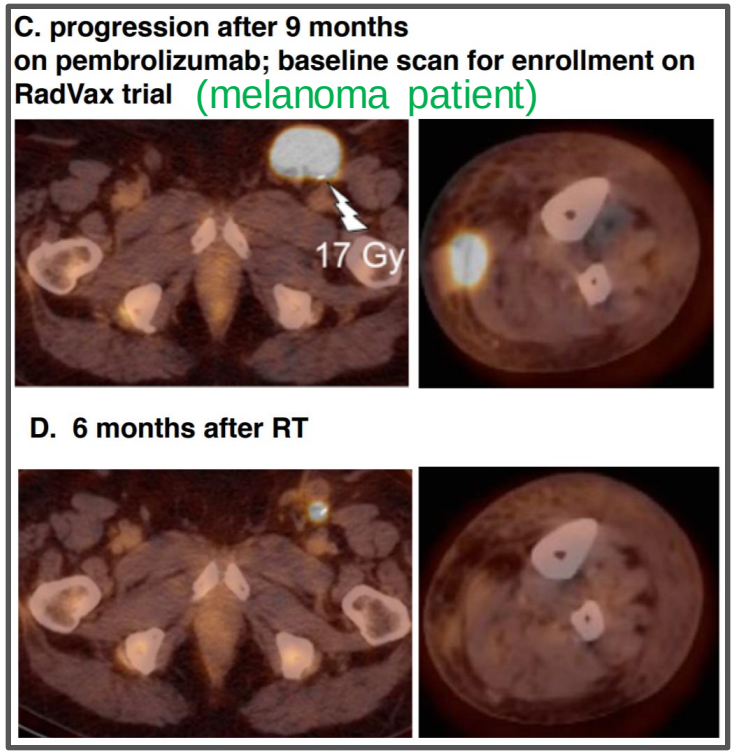
A phase I trial of pembrolizumab with hypofractionated radiotherapy in patients with metastatic solid tumours

Amit Maity[1,2], Rosemarie Mick[2,3], Alexander C. Huang[4,5], Sangeeth M. George[4,5], Michael D. Farwell[2,6], John N. Lukens[1], Abigail T. Berman[1,2], Tara C. Mitchell[2,4], Josh Bauml[2,4], Lynn M. Schuchter[2,4], Mark O'Hara[2,4], Lilie L. Lin[7], Angela Demichele[2,4], John P. Christodouleas[1], Naomi B. Haas[2,4], Dana M. Patsch[1], Stephen M. Hahn[7], Andy J. Minn[1,2,5], E. John Wherry[2,5,8] and Robert H. Vonderheide[2,4,5]

	Cohort 1	Cohort 2	Total
Stratum 1: melanoma/NSCLC progressed on prior anti-PD-1	6	6	12
Stratum 2: pancreas, breast, other; no prior anti-PD-1	6	6	12
Total	12	12	24



- No grade 3-5 treatment-related adverse events
- Excluding RT targets, 3/24 (13%) subjects had responses

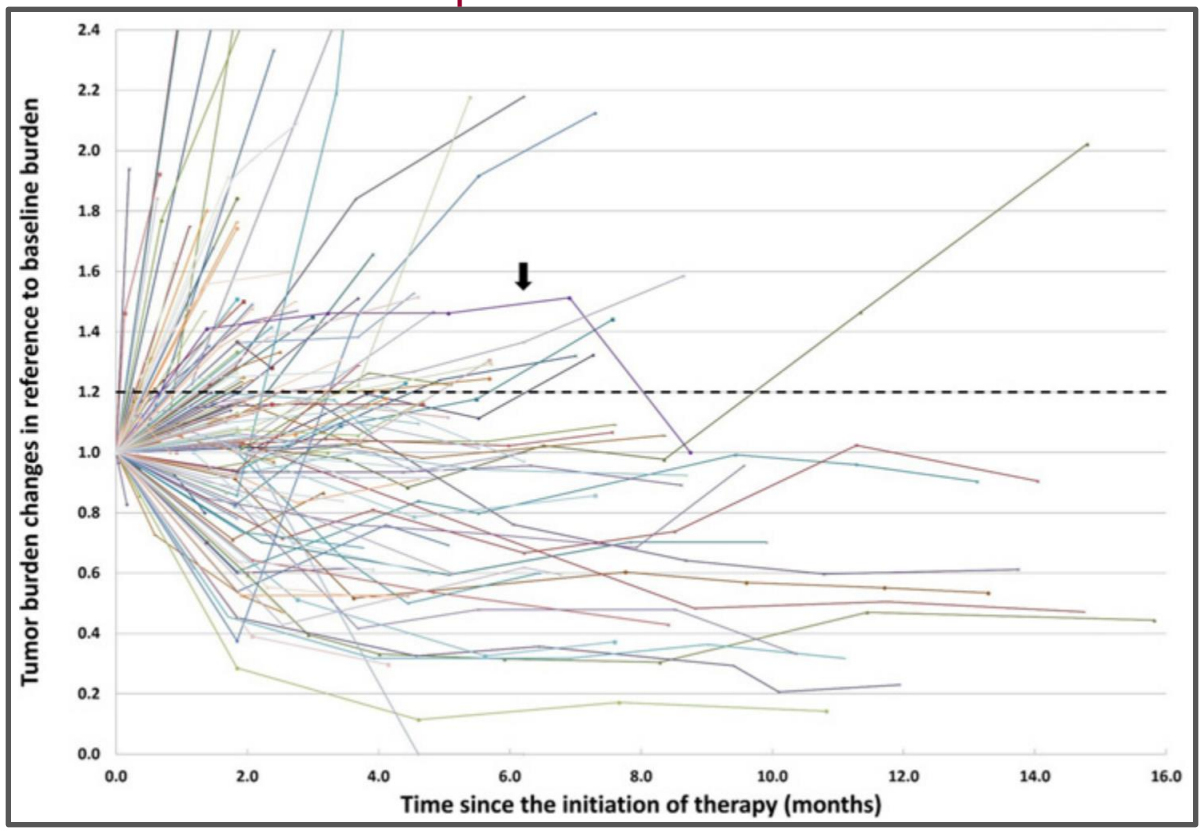


"abscopal" response?

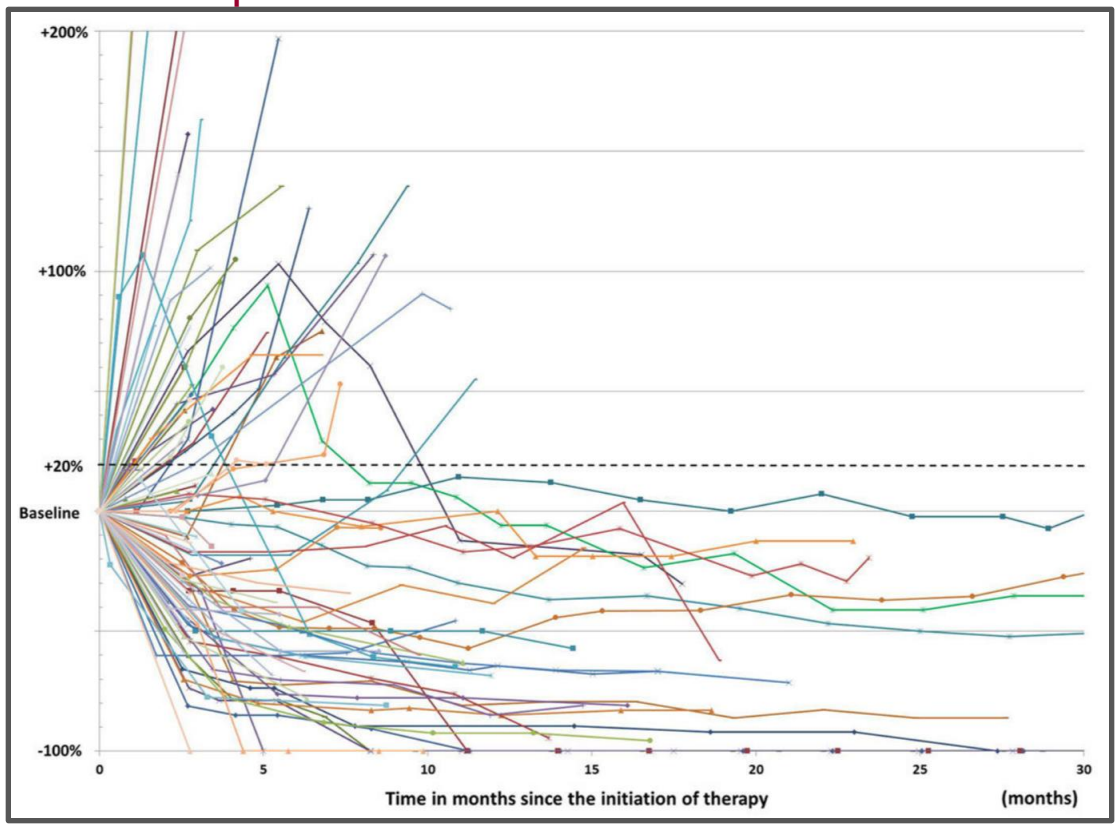
British Journal of Cancer (2018) 119:1200–1207

Immunotherapy: Delayed/Unexpected Responses

nivolumab or pembrolizumab for NSCLC



pembrolizumab for melanoma



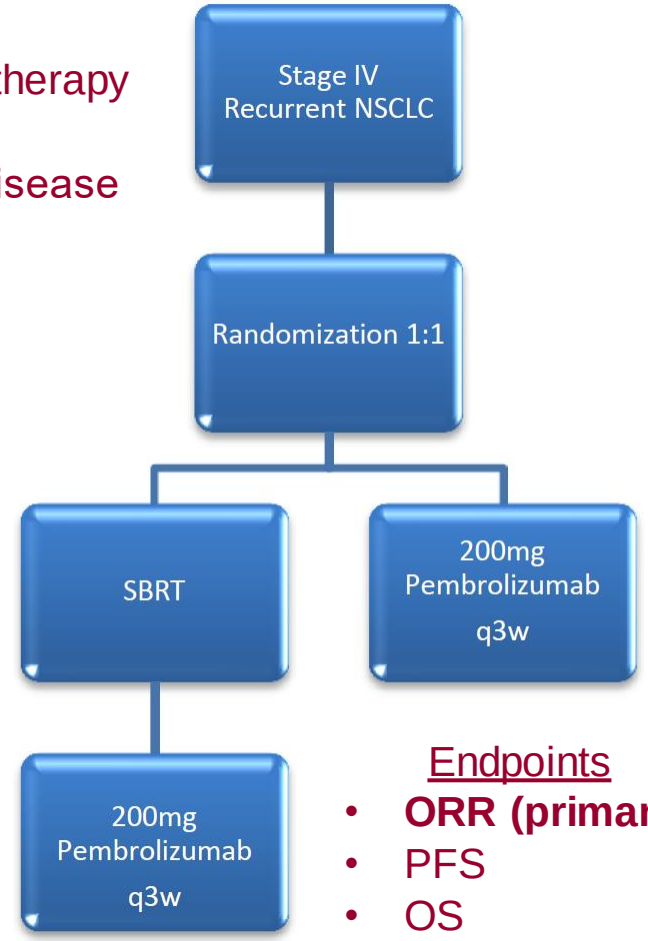
We need RCTs to quantify "abscopal" responses when RT is given with active immunotherapeutic agents

Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non–Small Cell Lung Cancer

Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial

Eligibility

- Post-chemotherapy
- I/O-naïve
- ≥2 sites of disease



Endpoints

- **ORR (primary)**
- PFS
- OS

Selected Patient Characteristics

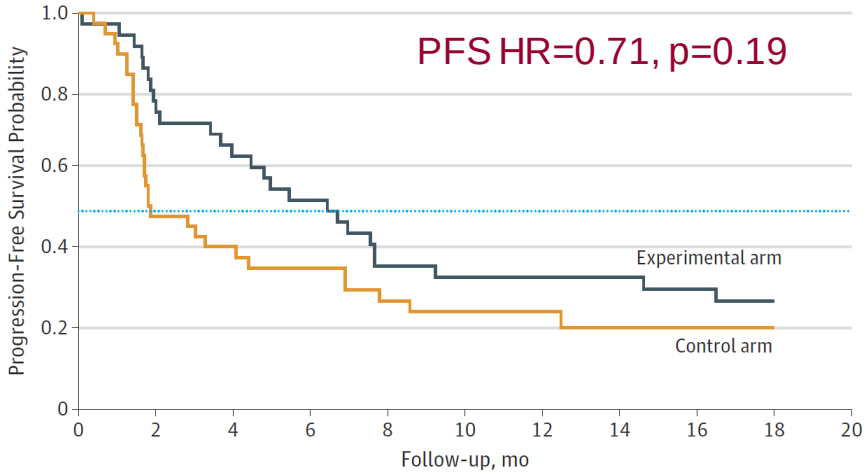
	Experimental arm n = 36	Control arm n = 40
Previous radiotherapy	15 (42%)	17 (43%)
Number of previous lines of systemic treatment		
1	26 (72%)	31 (78%)
2	6 (17%)	8 (20%)
3	4 (11%)	1 (3%)
PD-L1 TPS		
0%	18 (50%)	25 (66%)
1-49%	8 (22%)	8 (21%)
≥50%	10 (28%)	5 (13%)

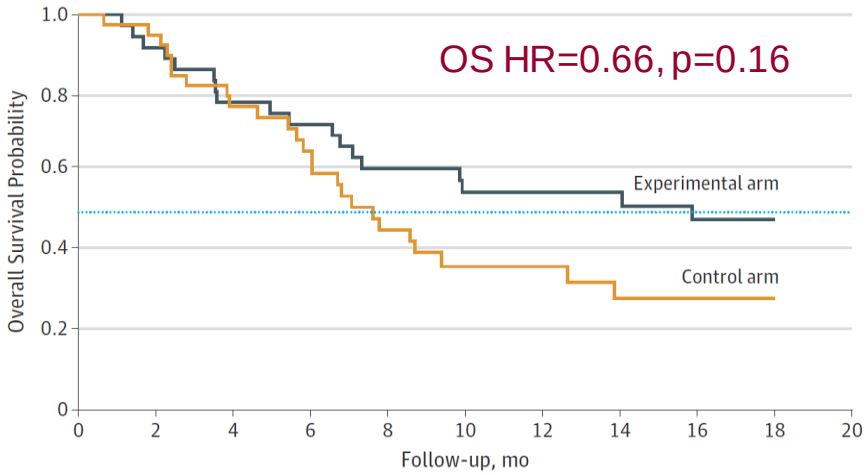
JAMA Oncol. 2019;5(9):1276-1282.

Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non–Small Cell Lung Cancer

Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial

Response	Experimental Arm, No./Total No. (%) (n = 36)[a]	Control Arm, No./Total No. (%) (n = 40)[b]	
Objective response rate at 12 wk			
Overall[c]	13/36 (36)	7/40 (18)	p=0.07
PD-L1 TPS, %			
0	4/18 (22)	1/25 (4)	
1-49	3/8 (38)	3/8 (38)	
≥50	6/10 (60)	3/5 (60)	
Disease control rate at 12 wk[d]	23/36 (64)	16/40 (40)	p=0.04



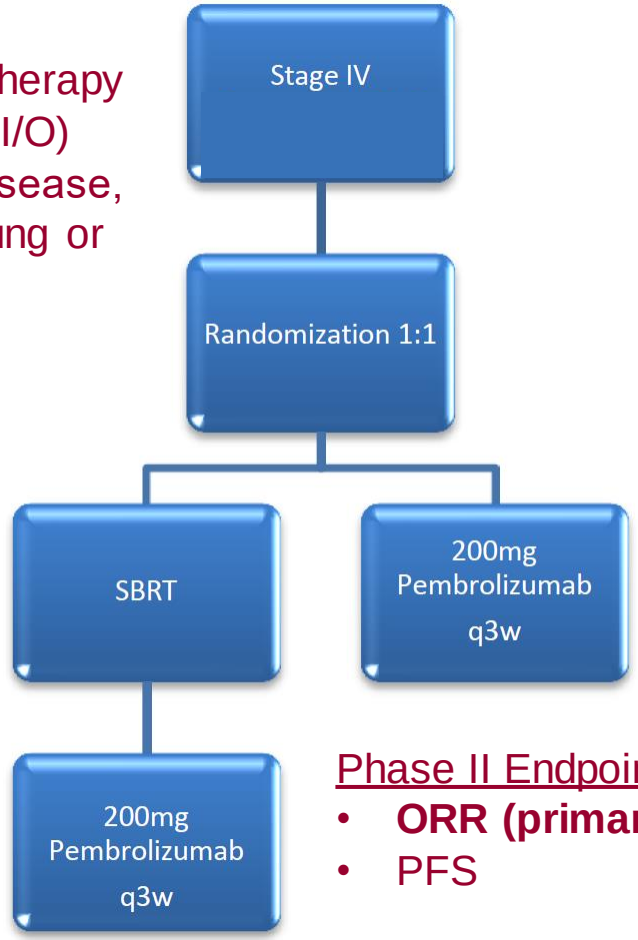


JAMA Oncol. 2019;5(9):1276-1282.

Pembrolizumab with or without radiation therapy for metastatic non-small cell lung cancer: a randomized phase I/II trial

Eligibility

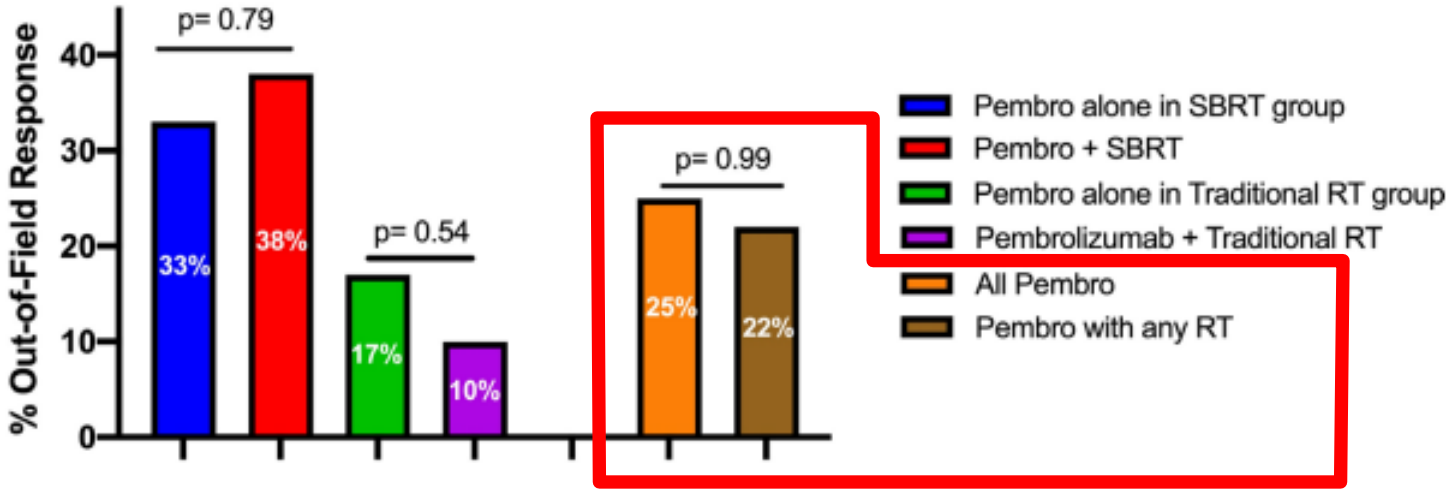
- Prior chemotherapy allowed (not I/O)
- ≥2 sites of disease, including a lung or liver lesion

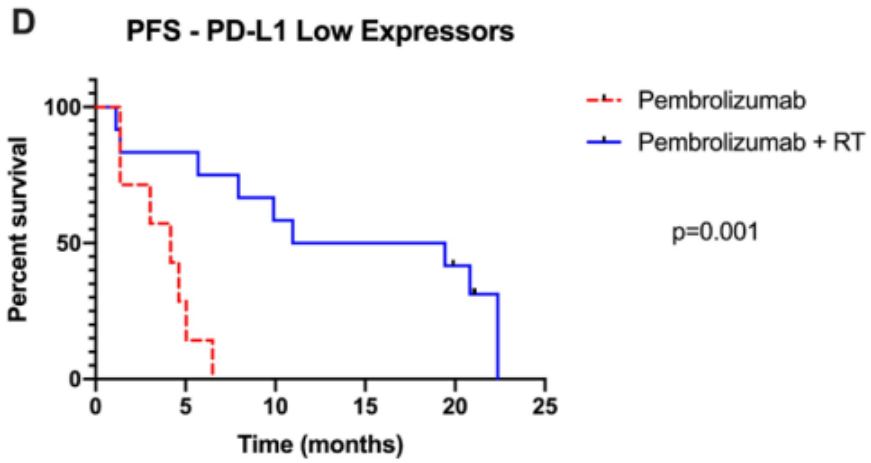


12.5 Gy x 4 or
3 Gy x 15,
Concurrent with pembro

Phase II Endpoints

- **ORR (primary)**
- PFS



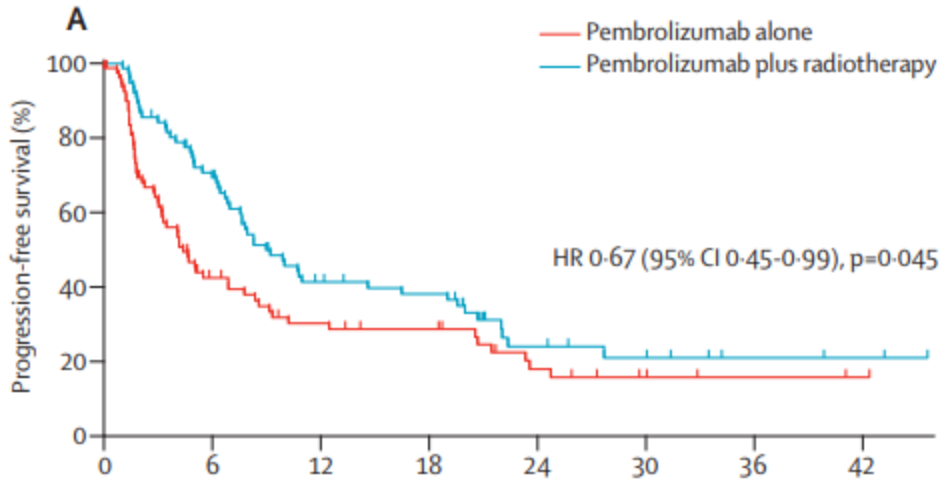


J Immunother Cancer. 2020 Oct;8(2):e001001.

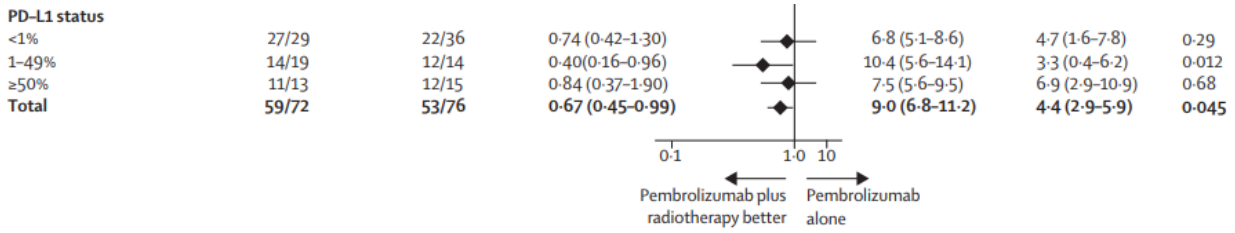
Pembrolizumab with or without radiotherapy for metastatic non-small-cell lung cancer: a pooled analysis of two randomised trials

	Pembrolizumab alone (n=76)	Pembrolizumab plus radiotherapy (n=72)	Number needed to treat	Odds ratio (95% CI)	p value
Best overall response					
Abscopal response rate	15/76 (19·7%)	30/72 (41·7%)	2·00	2·96 (1·42–6·20)	0·0039
Abscopal control rate	33/76 (43·4%)	47/72 (65·3%)	4·58	2·51 (1·28–4·91)	0·0071

Progression-free Survival

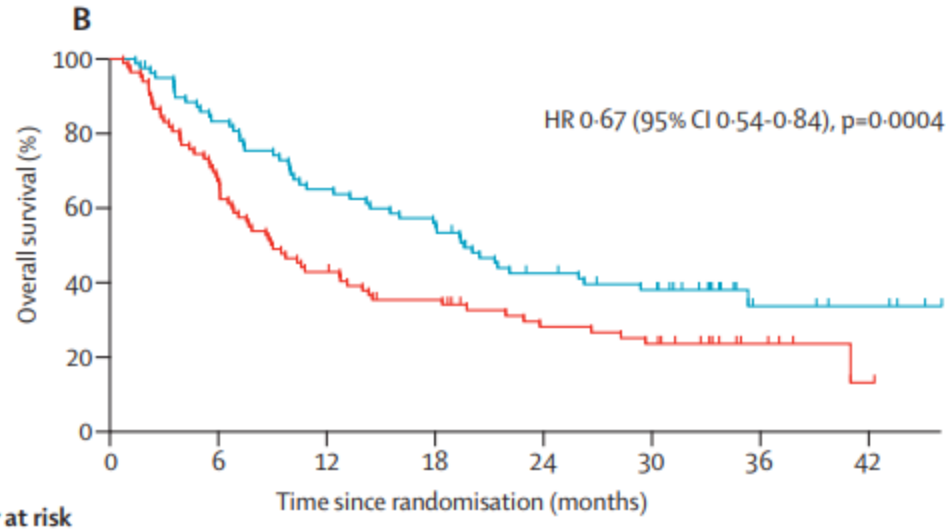


Number at risk (number censored)								
Pembrolizumab alone	76 (0)	30 (7)	20 (9)	17 (11)	9 (14)	5 (17)	3 (19)	2 (21)
Pembrolizumab plus radiotherapy	72 (0)	53 (2)	28 (5)	25 (7)	11 (14)	8 (16)	4 (20)	3 (21)

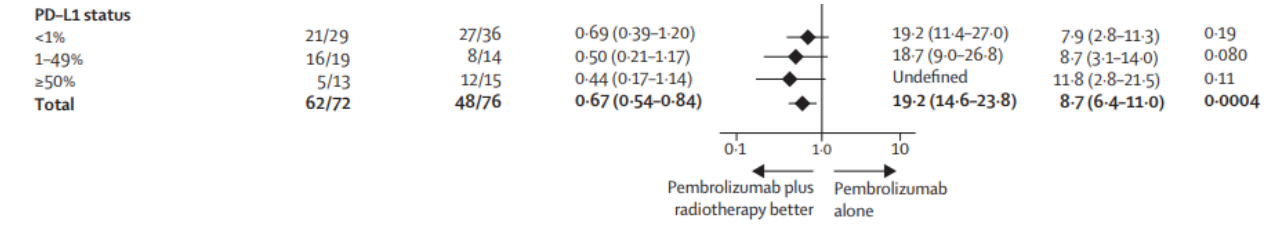


PD-L1 status						
<1%	27/29	22/36	0·74 (0·42–1·30)	6·8 (5·1–8·6)	4·7 (1·6–7·8)	0·29
1–49%	14/19	12/14	0·40(0·16–0·96)	10·4 (5·6–14·1)	3·3 (0·4–6·2)	0·012
≥50%	11/13	12/15	0·84 (0·37–1·90)	7·5 (5·6–9·5)	6·9 (2·9–10·9)	0·68
Total	**59/72**	**53/76**	**0·67 (0·45–0·99)**	**9·0 (6·8–11·2)**	**4·4 (2·9–5·9)**	**0·045**

Overall Survival



Number at risk (number censored)								
Pembrolizumab alone	76 (0)	54 (0)	33 (1)	26 (2)	18 (5)	15 (5)	6 (14)	2 (17)
Pembrolizumab plus radiotherapy	72 (0)	63 (1)	49 (1)	40 (1)	29 (4)	23 (7)	7 (12)	5 (14)

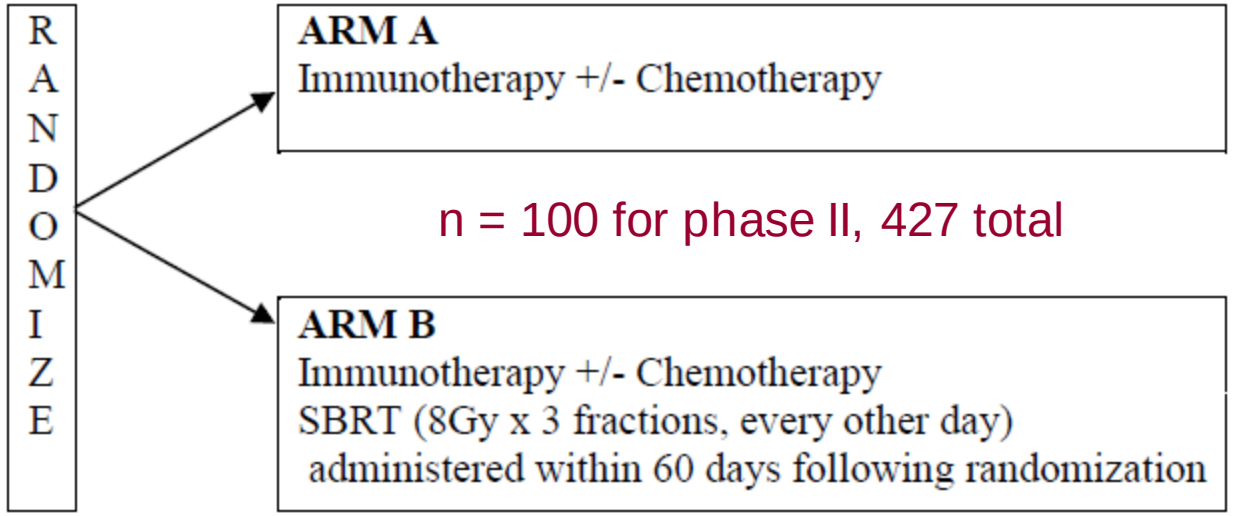


PD-L1 status						
<1%	21/29	27/36	0·69 (0·39–1·20)	19·2 (11·4–27·0)	7·9 (2·8–11·3)	0·19
1–49%	16/19	8/14	0·50 (0·21–1·17)	18·7 (9·0–26·8)	8·7 (3·1–14·0)	0·080
≥50%	5/13	12/15	0·44 (0·17–1·14)	Undefined	11·8 (2·8–21·5)	0·11
Total	**62/72**	**48/76**	**0·67 (0·54–0·84)**	**19·2 (14·6–23·8)**	**8·7 (6·4–11·0)**	**0·0004**

Lancet Respir Med. 2021 May;9(5):467-475.

A082002

A RANDOMIZED PHASE II/III TRIAL OF MODERN IMMUNOTHERAPY BASED SYSTEMIC THERAPY WITH OR WITHOUT SBRT FOR PD-L1-NEGATIVE, ADVANCED NON-SMALL CELL LUNG CANCER



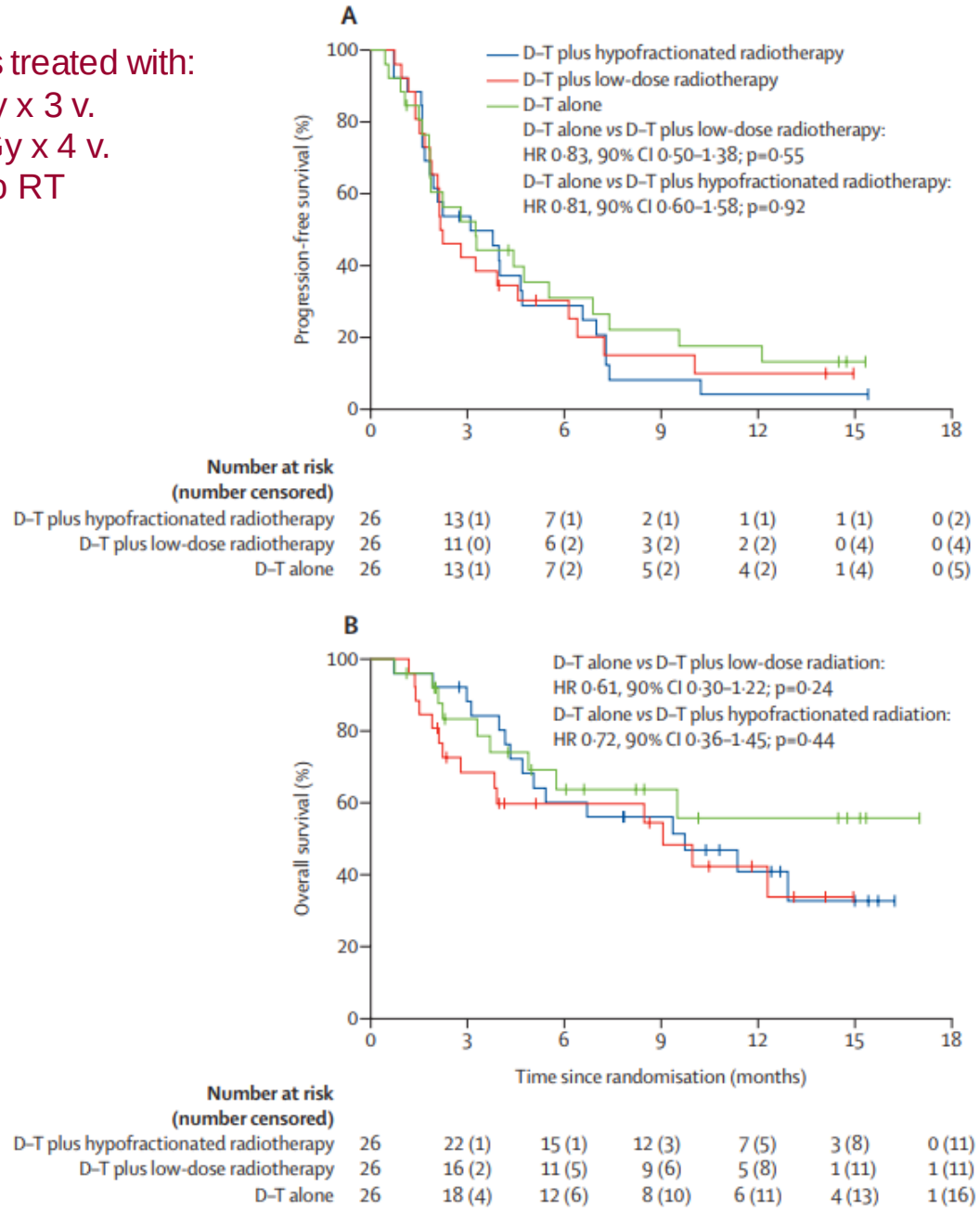
Immunotherapy options:
ipi/nivo +/- chemo
pembro + chemo

- "For the phase II portion, we hypothesize a [PFS] hazard ratio (HR) of 0.55 to warrant continuing to the phase III trial."
- "We are interested in testing a HR of 0.70… increase in median OS from 17 months to 24.3 months."

Durvalumab plus tremelimumab alone or in combination with low-dose or hypofractionated radiotherapy in metastatic non-small-cell lung cancer refractory to previous PD(L)-1 therapy: an open-label, multicentre, randomised, phase 2 trial

1-2 lesions treated with:
8 Gy x 3 v.
0.5 Gy x 4 v.
No RT

- Median #3 lines of prior therapy
- Primary endpoint: response rate of non-irradiated lesions
  - ≈10% in all arms



Randomized Phase II Trial of Nivolumab With Stereotactic Body Radiotherapy Versus Nivolumab Alone in Metastatic Head and Neck Squamous Cell Carcinoma

- 62 immunotherapy-naïve patients with metastatic HNSCC and ≥2 measurable lesions
  - Both arms: nivolumab 3 mg/kg every 2 weeks for up to 96 weeks
  - Experimental arm: SBRT (9 Gy x 3) to a single lesion between cycles 1 and 2 of nivolumab
- Similar adverse event rates across arms:
  - Any grade - 87% in SBRT arm v. 70% in control arm (p=0.12)
  - Grade ≥3 - 10% in SBRT arm v. 13% in control arm (p=0.70)

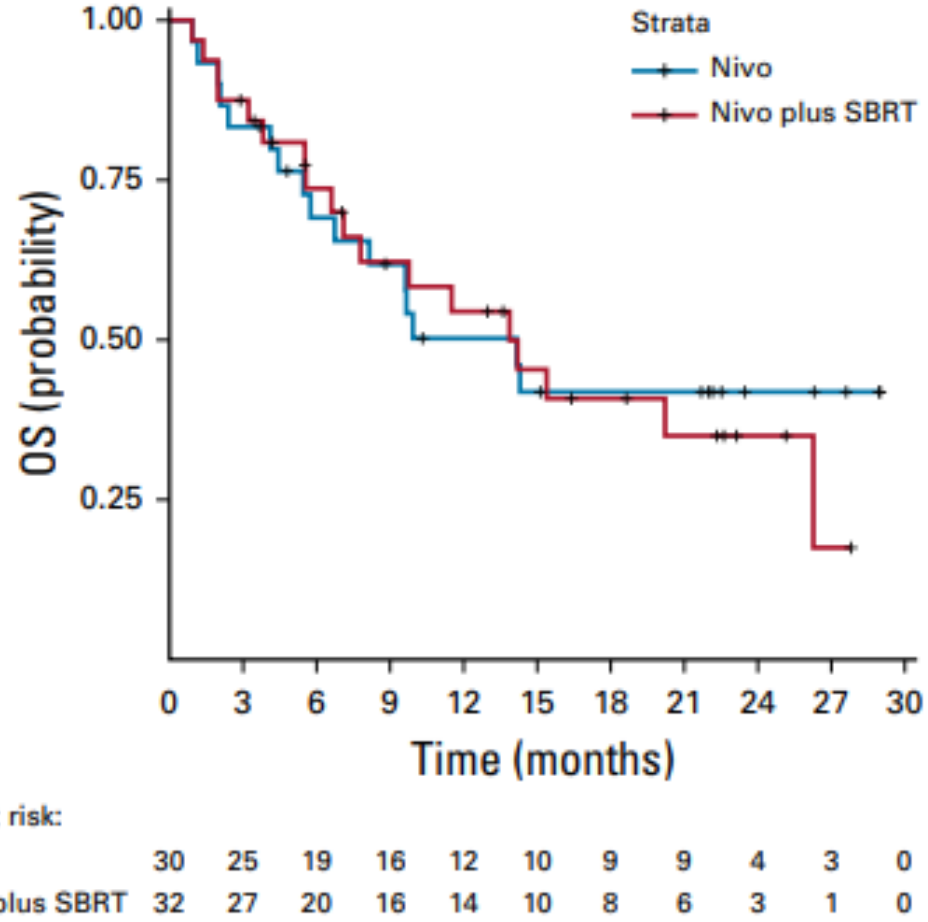
SBRT during immunotherapy → No unexpected toxicity increase

J Clin Oncol. 2021 Jan 1;39(1):30-37.

Randomized Phase II Trial of Nivolumab With Stereotactic Body Radiotherapy Versus Nivolumab Alone in Metastatic Head and Neck Squamous Cell Carcinoma

TABLE 4. Multivariable Logistic Model With Objective Response Rate as the Outcome

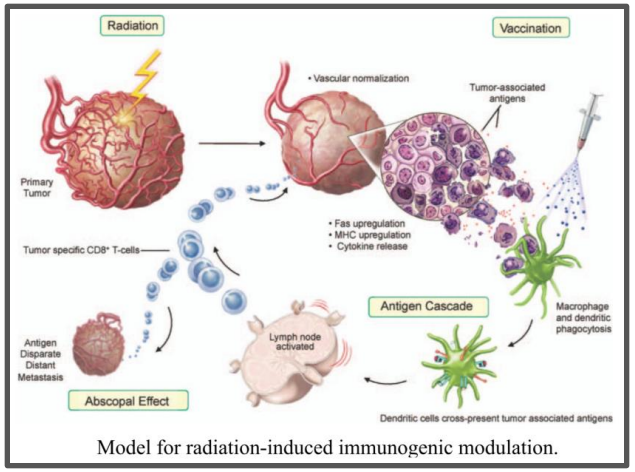
Variable	OR (95% CI)	*P*
PD-L1 status	3.08 (0.94 to 10.04)	.06
Viral status	2.70 (0.81 to 9.02)	.11
Treatment arm	0.80 (0.24 to 2.61)	.71



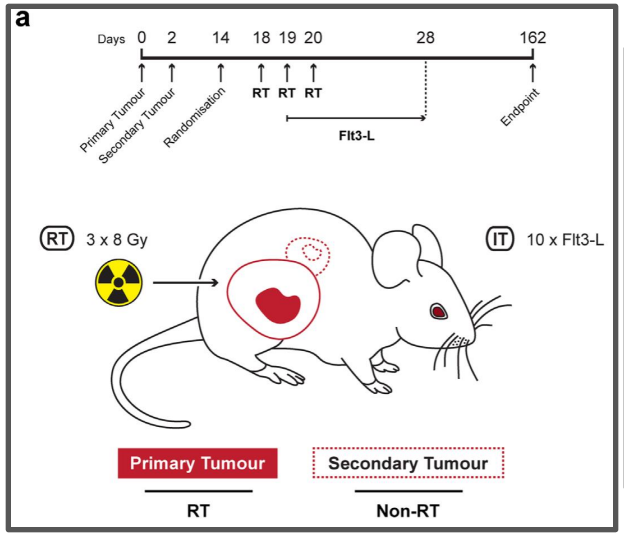
SBRT during immunotherapy → No clinical benefit

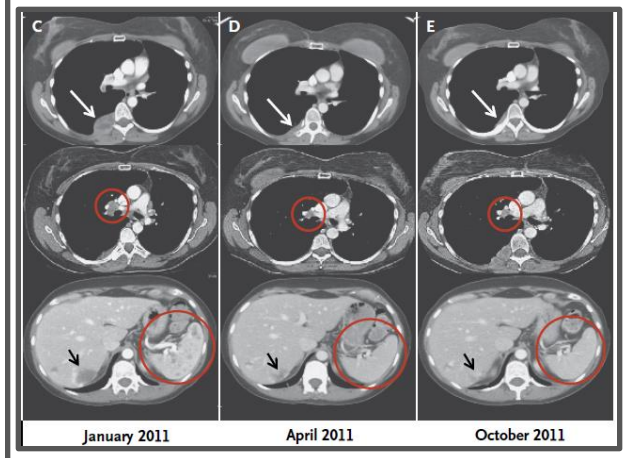
J Clin Oncol. 2021 Jan 1;39(1):30-37.

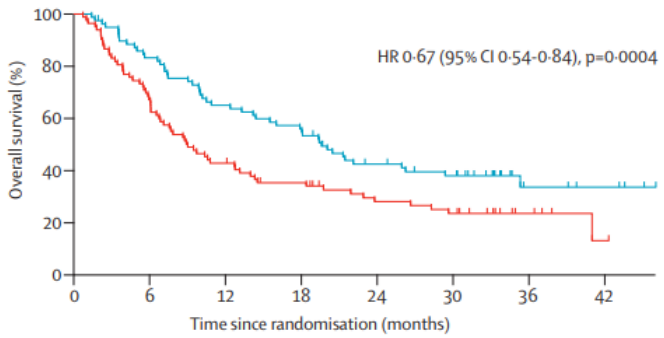
Utilizing Radiotherapy to Induce Abscopal Effects:
Mechanistic Rationale, Preclinical Models, Case Reports, Early-phase Trials



Model for radiation-induced immunogenic modulation.







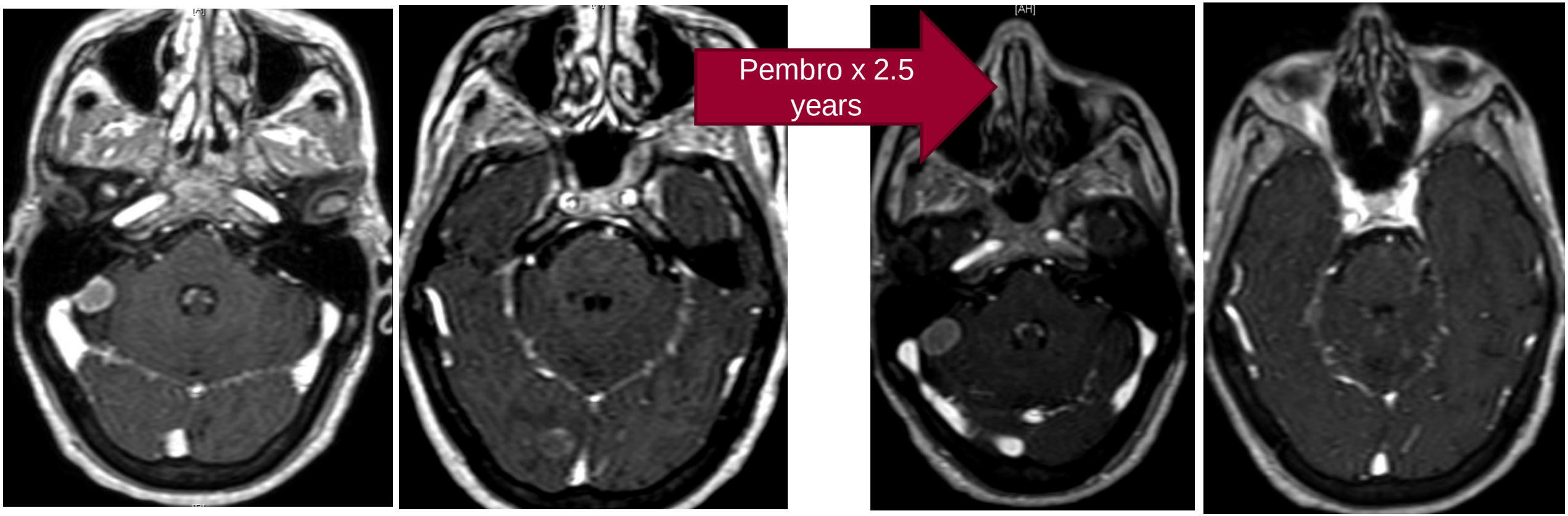
Use of RT with the specific intent of inducing abscopal effects is not yet supported by high-level data

Radiat Res. 2014 August ; 182(2): 123–125. PLoS One. 2016 Jul 18;11(7):e0159515. N Engl J Med 2012;366:925-31. Lancet Respir Med. 2021 May;9(5):467-475.

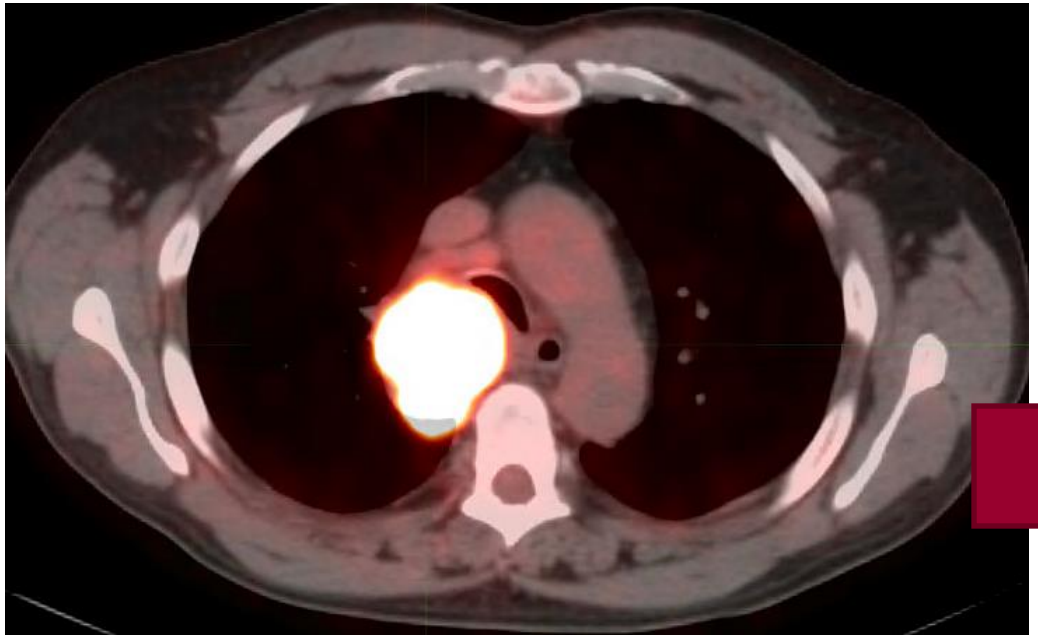
Outline

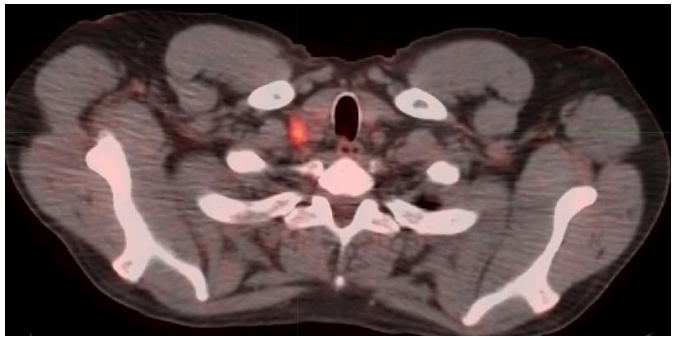
- Safety of combining immunotherapy and radiotherapy
- Indications for combining immunotherapy and radiotherapy
- **Adapting radiotherapy practices in the immunotherapy era**
  - **Who we treat**
  - How we treat

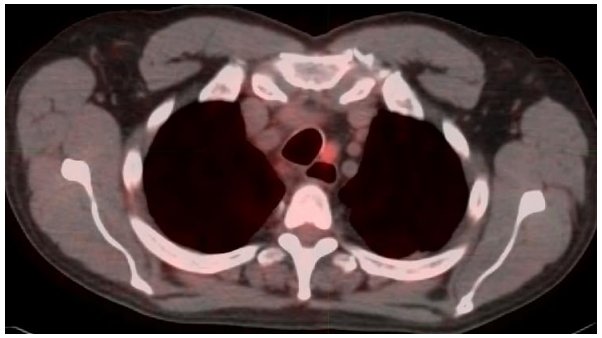
73-year-old female with metastatic lung adenocarcinoma (PD-L1 TPS 100%) involving the brain



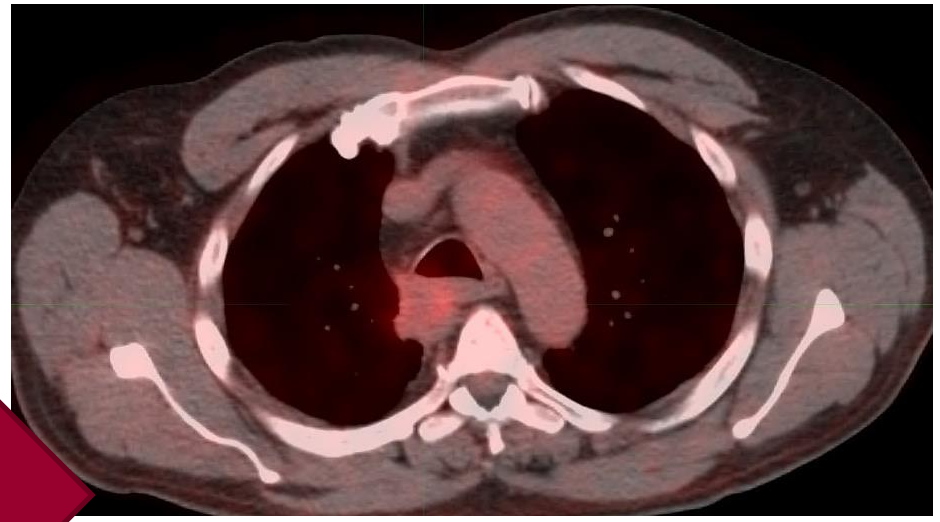
53-year-old male with right lung adenocarcinoma (EGFR/ALK/ROS-negative, PD-L1 TPS 90%), stage cT4N3M0, IIIC

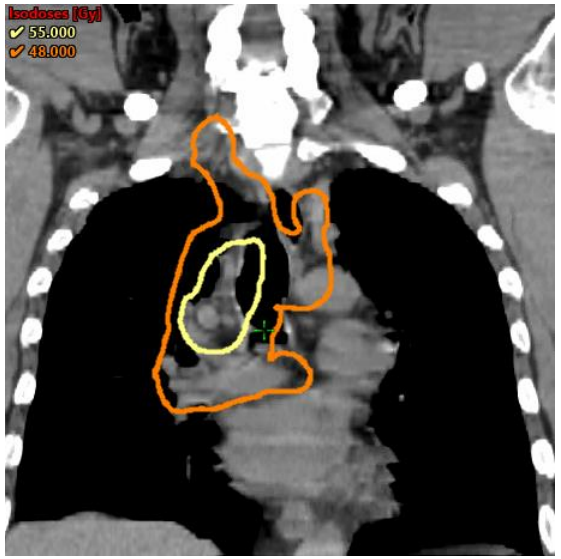




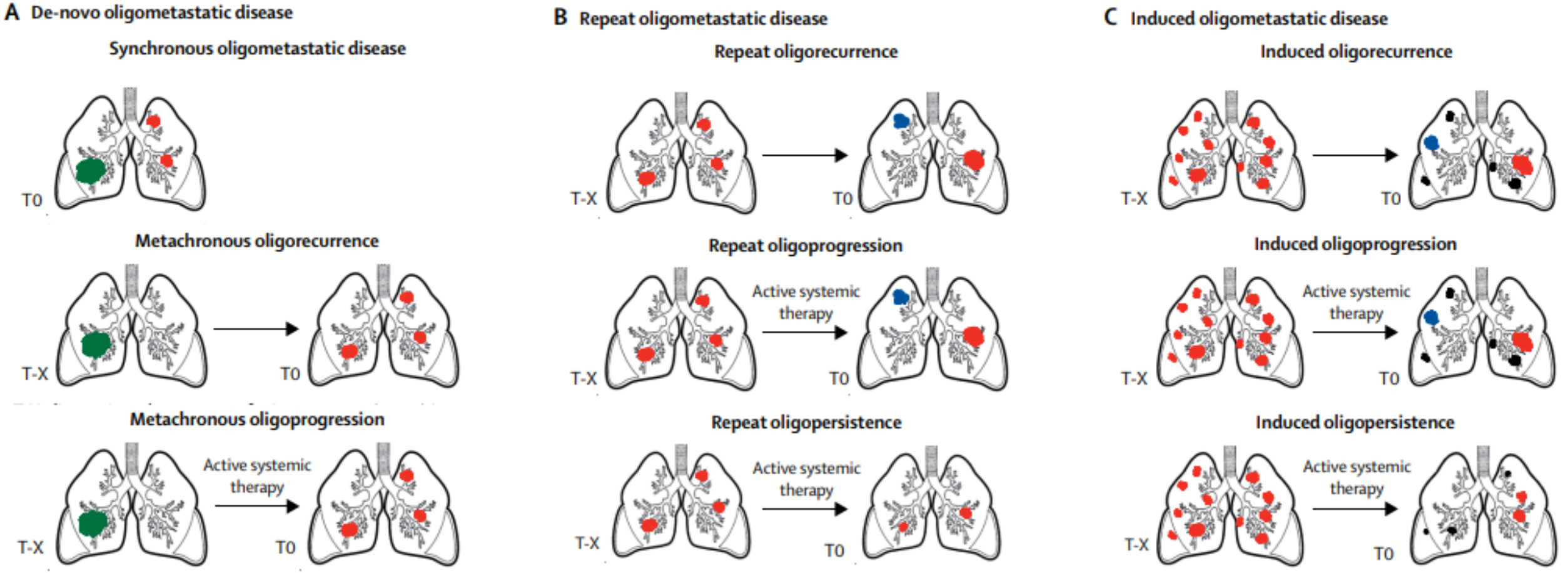


Pembro x 3 cycles





Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation



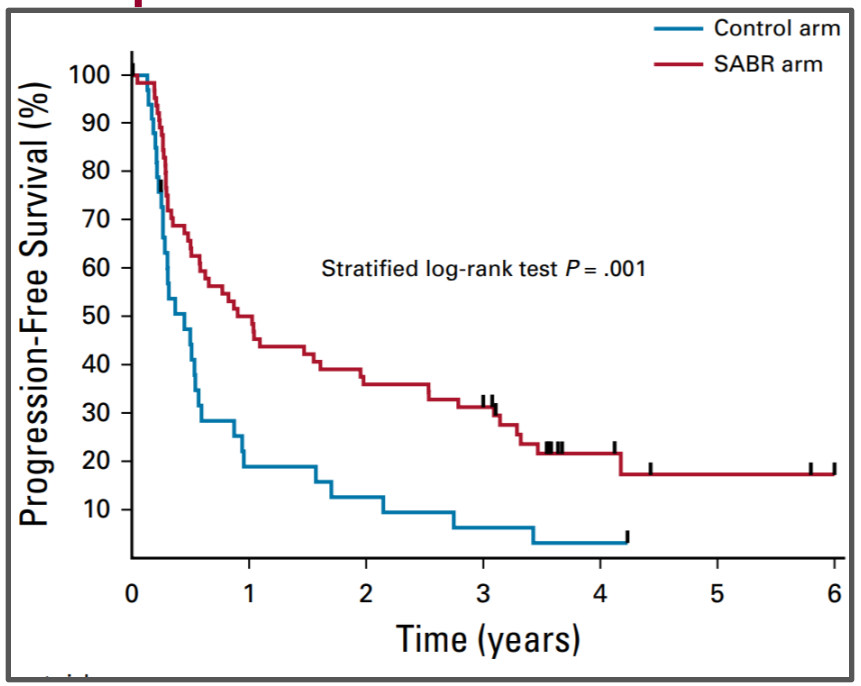
Lancet Oncol 2020; 21: e18–28

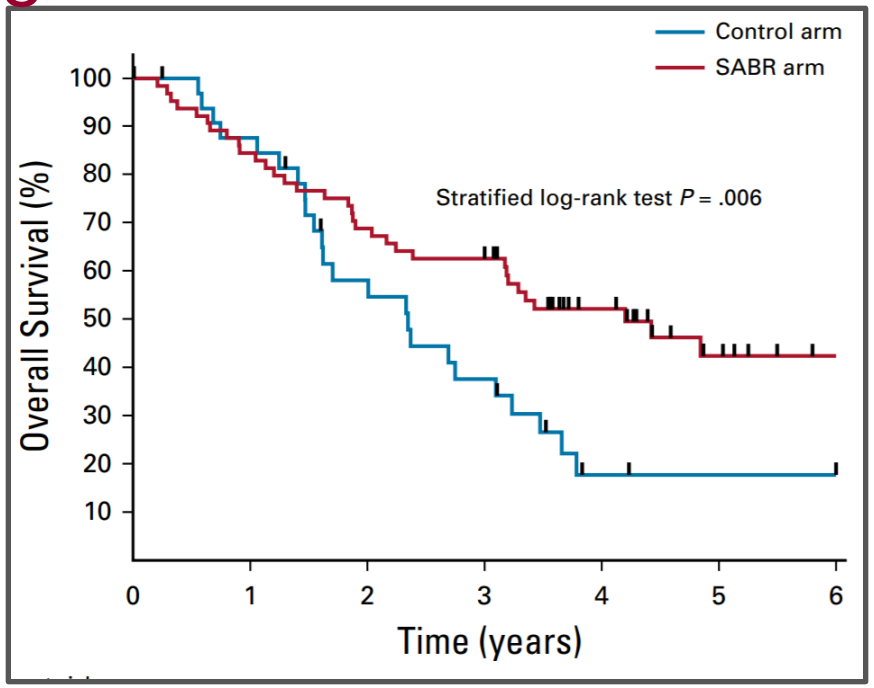
Could local therapy improve outcomes in oligometastatic disease?

Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial

J Clin Oncol. 2020 Jun 2;

Controlled primaries
75% had 1-2 metastases
All disease treated
(multiple cancer types)

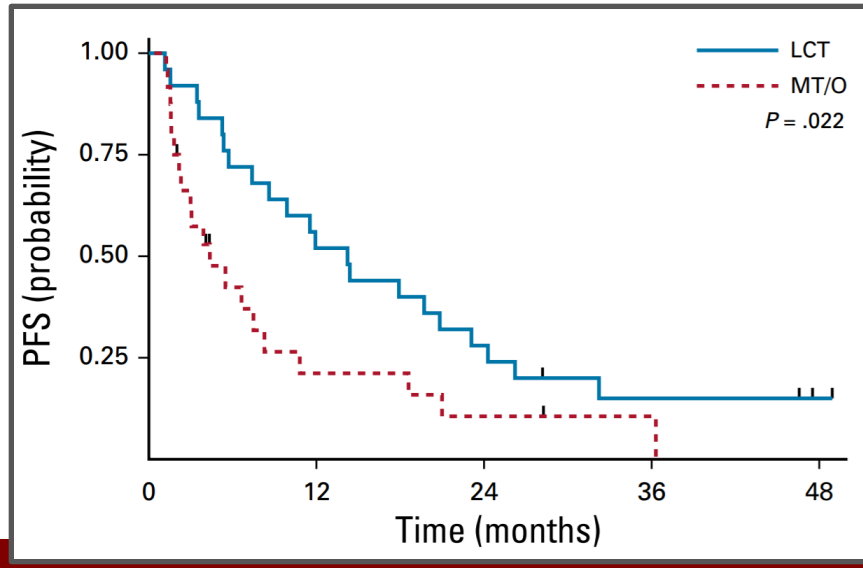


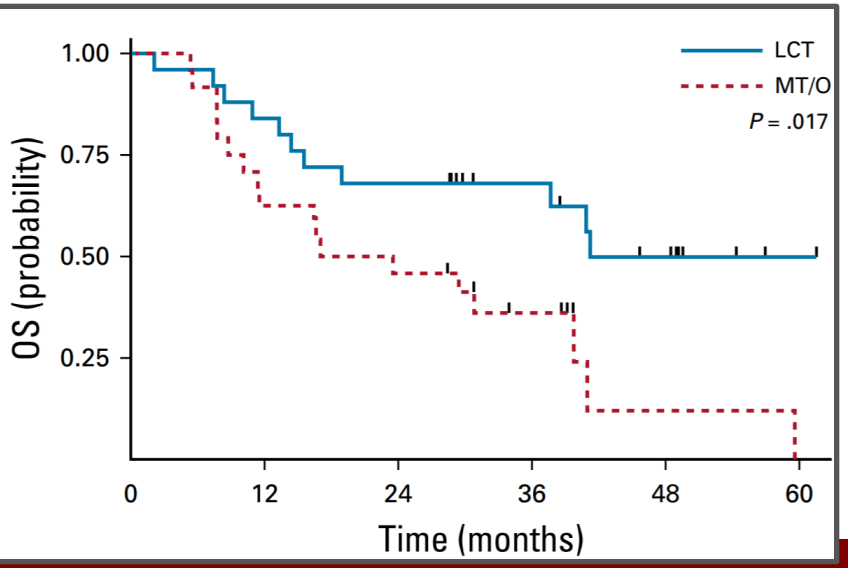


Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non–Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study

J Clin Oncol. 2019 Jun 20;37(18):1558-1565.

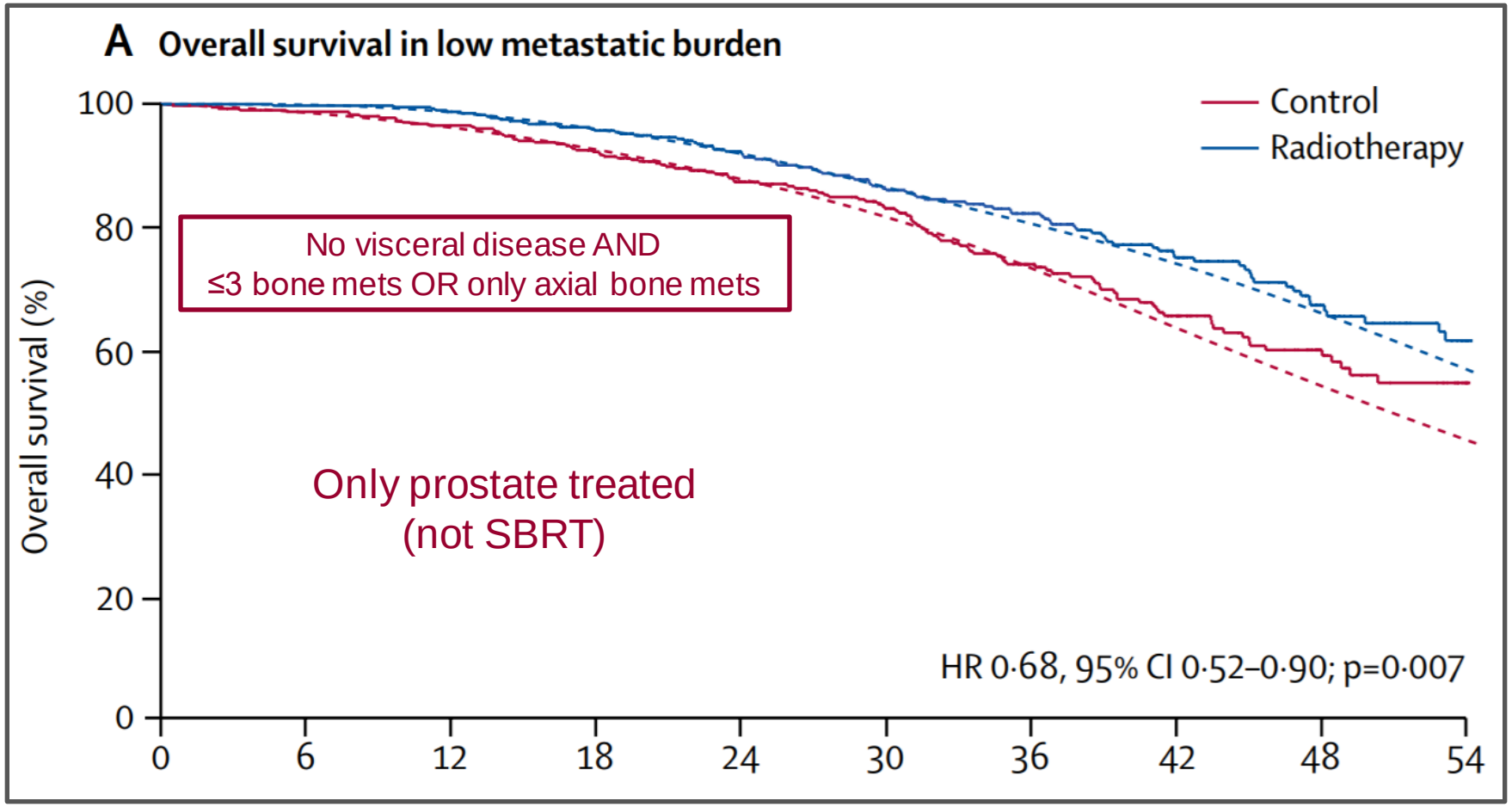
68% had 0-1 metastases
All disease treated





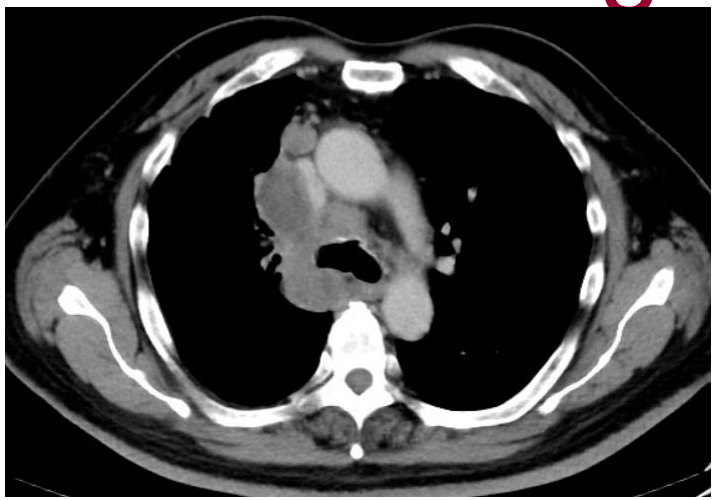
Could local therapy improve outcomes in oligometastatic disease?

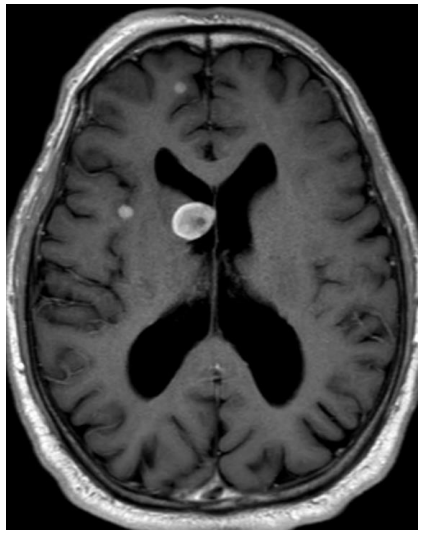
Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial



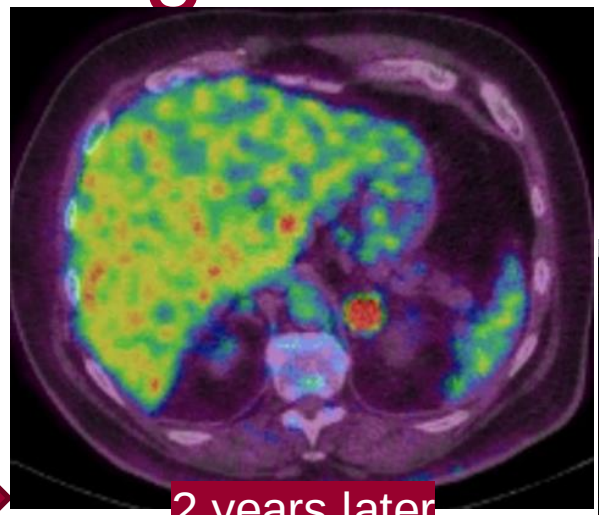
Lancet 2018; 392: 2353–66

61-year-old with metastatic small cell carcinoma involving the brain, stage cT4N3M1c, IVB

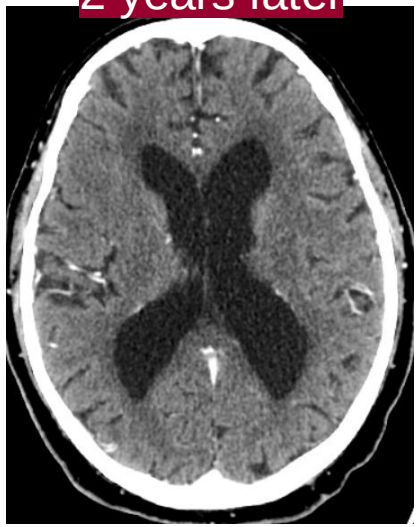


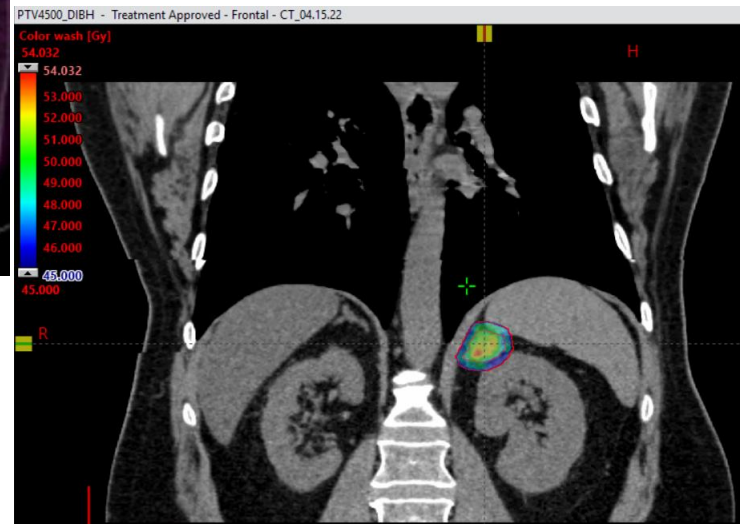


Whole brain RT, carbo/etopo/atezo

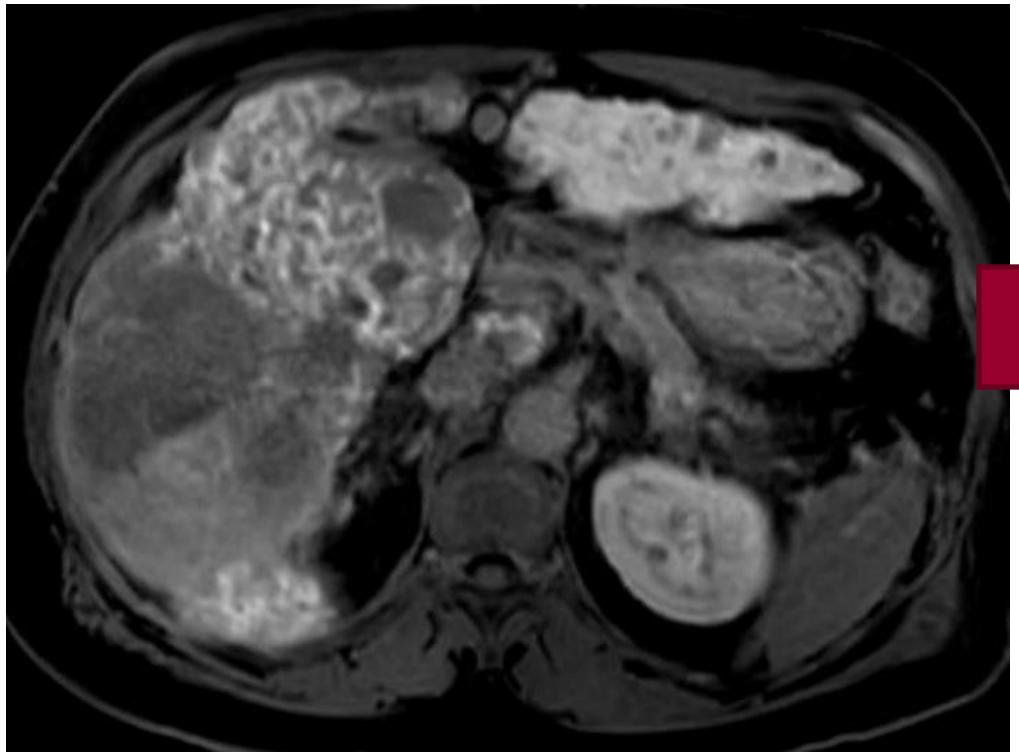


2 years later

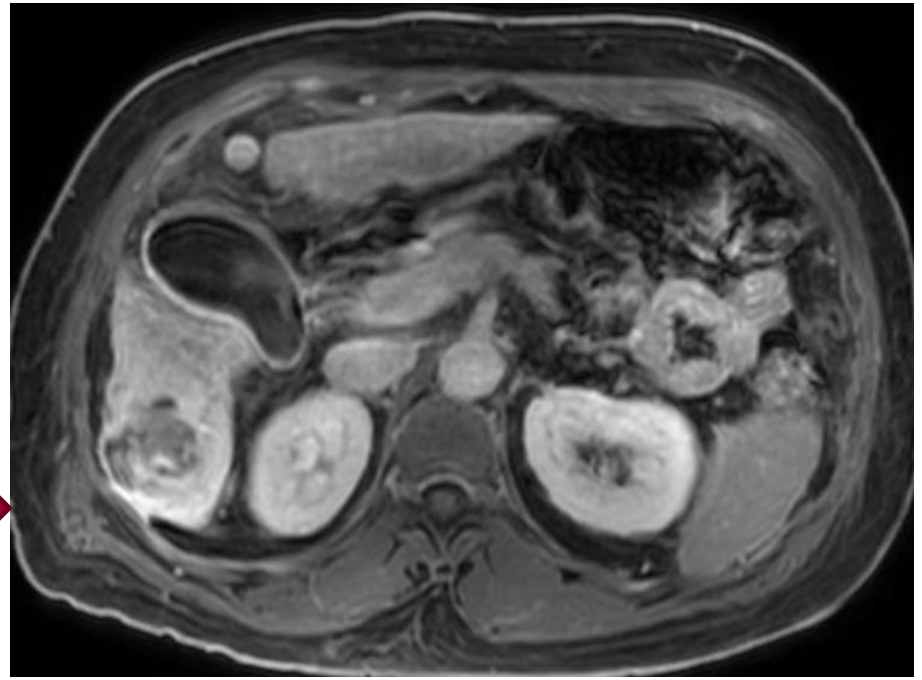


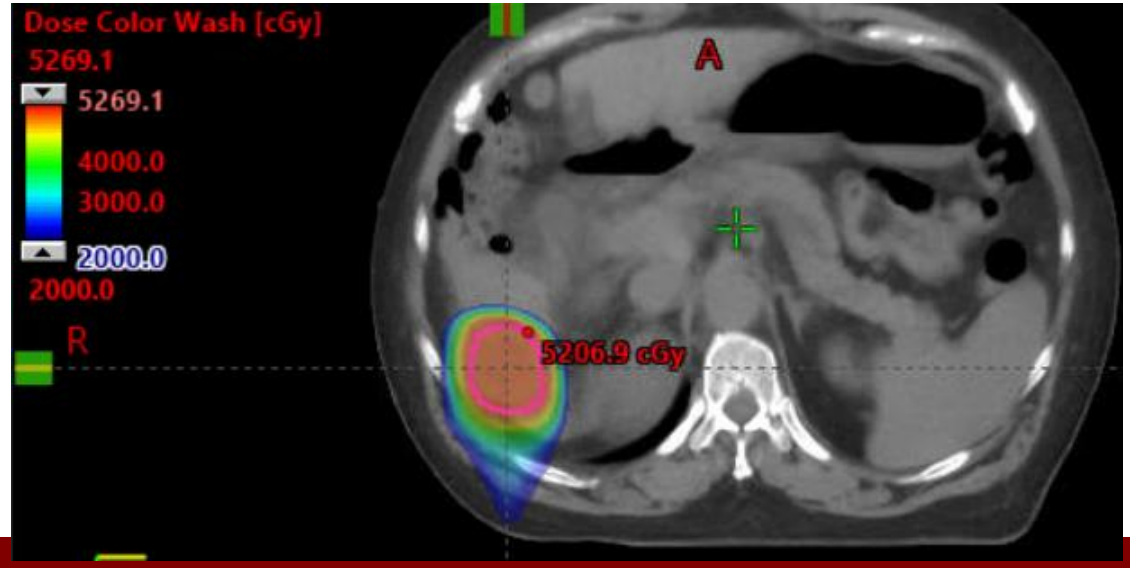


59-year-old male with hepatitis C and alcoholic cirrhosis and multifocal HCC



atezo/bev x 13 cycles

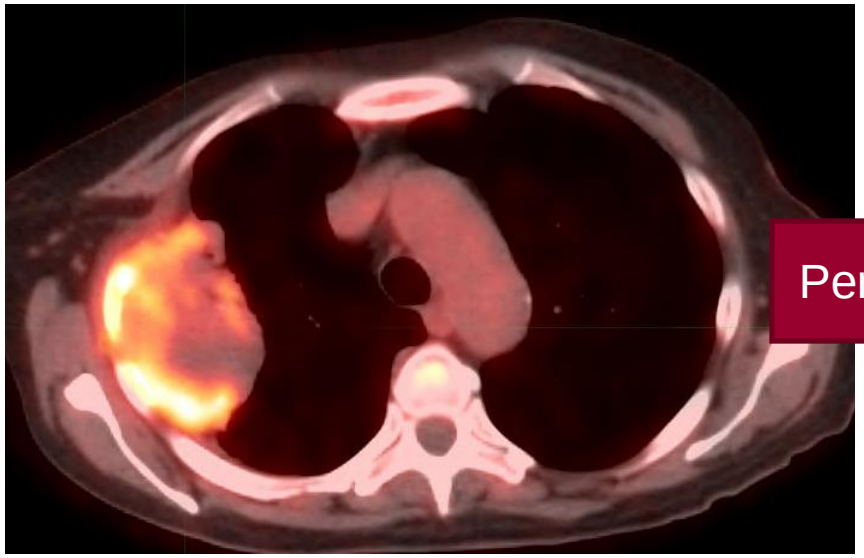




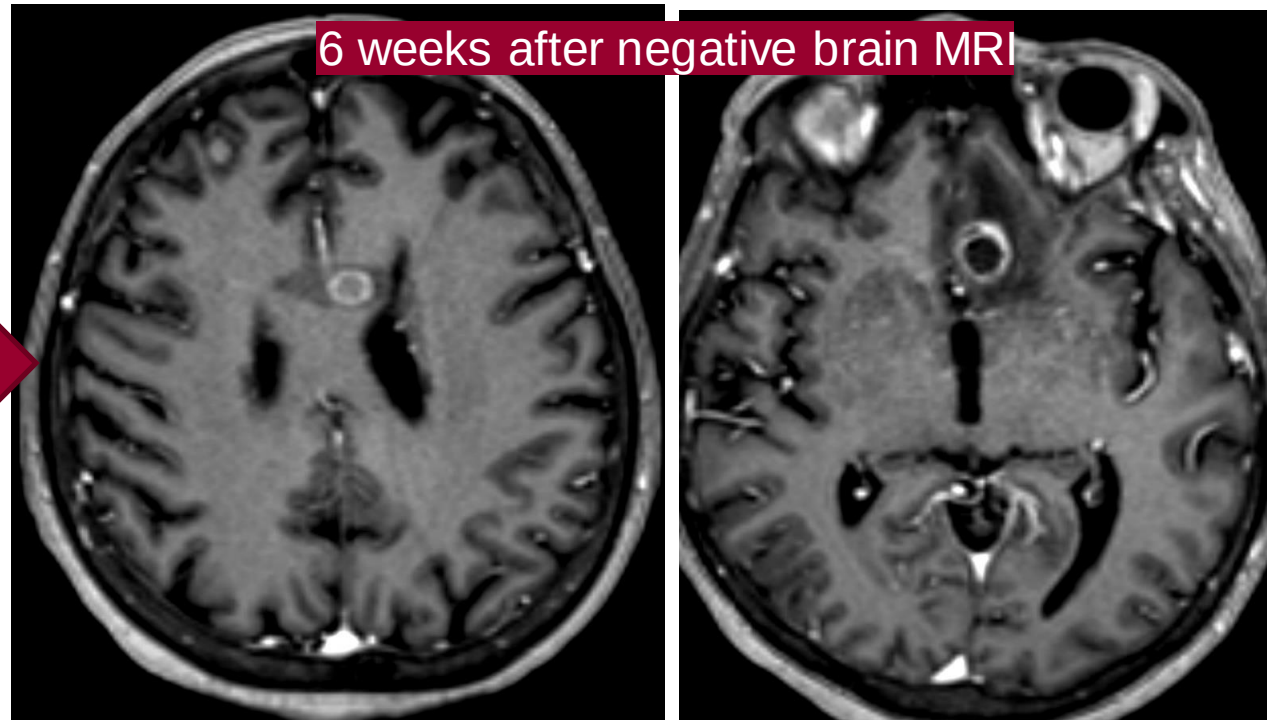
Outline

- Safety of combining immunotherapy and radiotherapy
- Indications for combining immunotherapy and radiotherapy
- Adapting radiotherapy practices in the immunotherapy era
  - Who we treat
  - **How we treat**

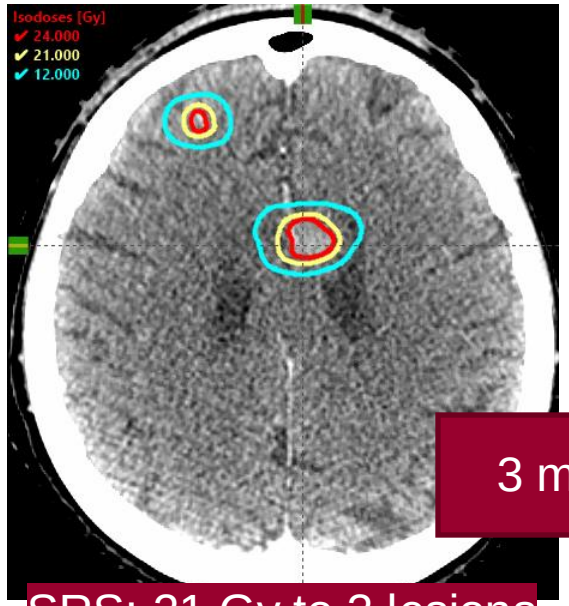
64-year-old female with right lung adenocarcinoma (EGFR/ALK/ROS-negative, PD-L1 TPS 60%), stage cT4N0M0, IIIA



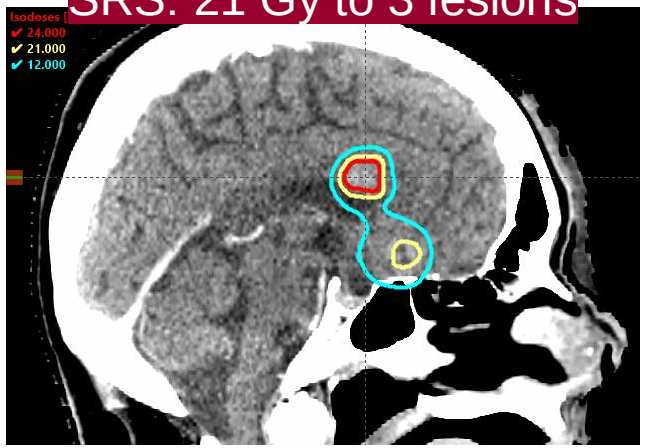
Pembro x 1 cycle



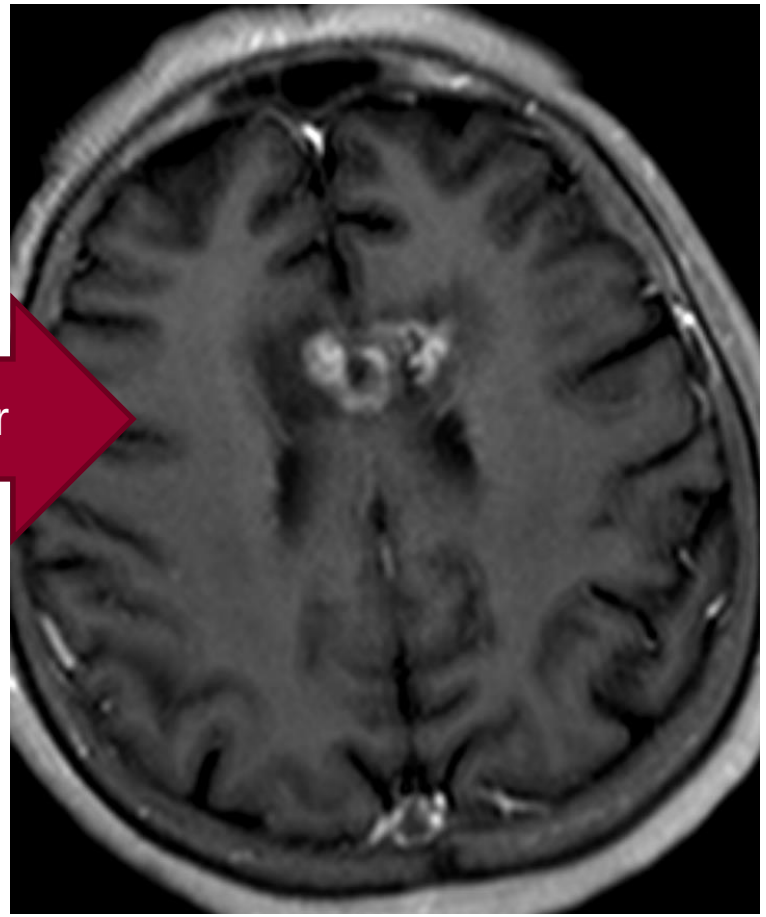
64-year-old female with right lung adenocarcinoma (EGFR/ALK/ROS-negative, PD-L1 TPS 60%), stage cT4N0M0, IIIA

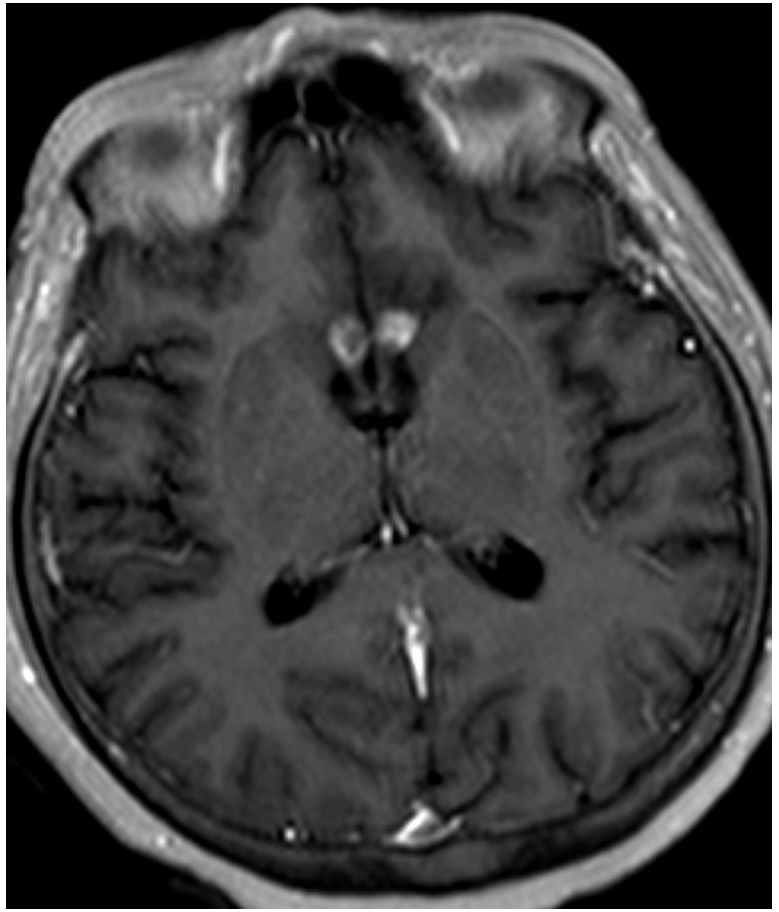


SRS: 21 Gy to 3 lesions



3 months later

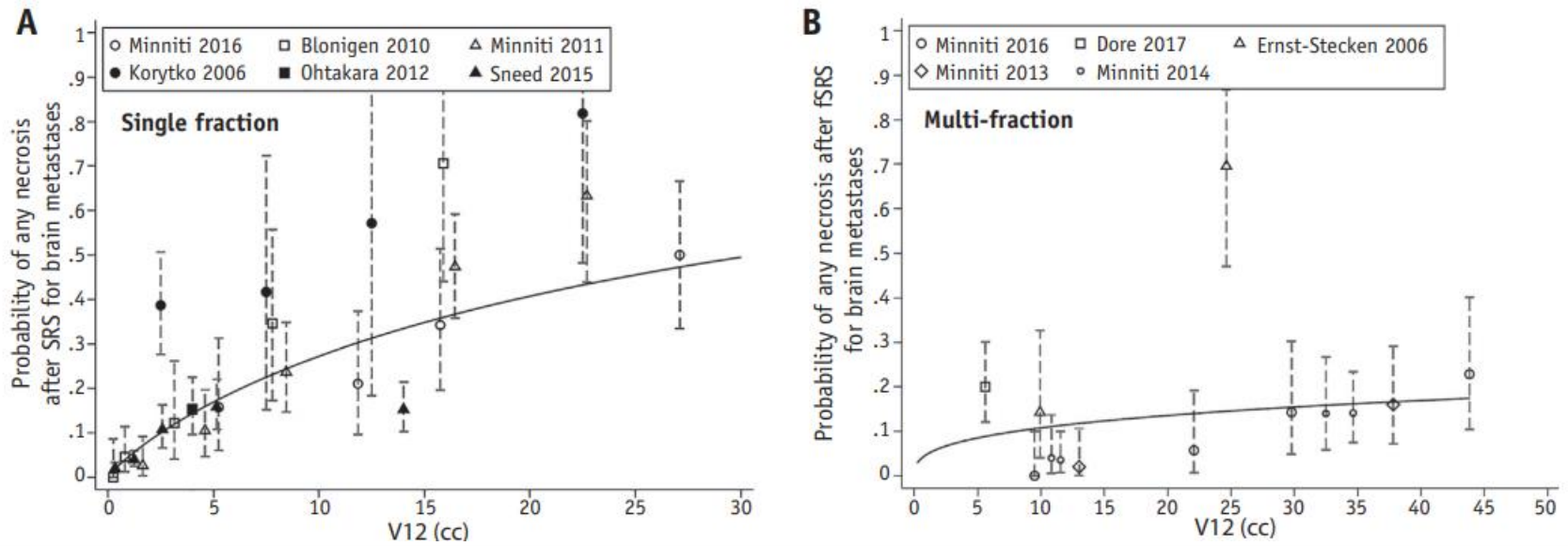




Now NED and doing well after steroids, pembrolizumab x 2 years, and thoracic RT

My thoughts about RT for brain metastases

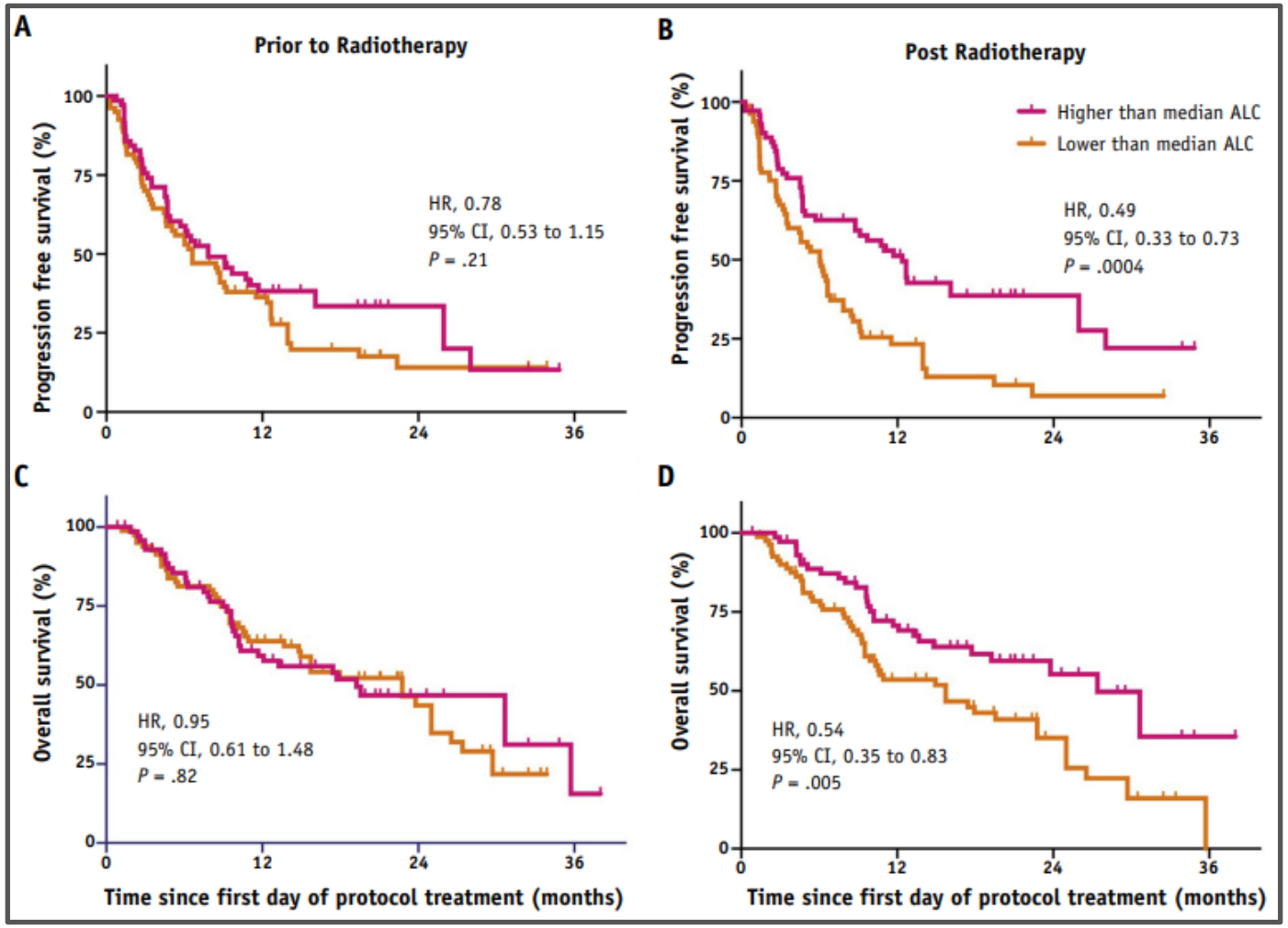
- Many modern systemic agents have CNS activity.
  - Wait for molecular testing, try to avoid whole brain RT.
- I believe radionecrosis is now far more common than local progression after SRS.
  - Consider moderate doses, fractionation.



Int J Radiation Oncol Biol Phys, Vol. 110, No. 1, pp. 68–86, 2021

Absolute Lymphocyte Count Predicts Abscopal Responses and Outcomes in Patients Receiving Combined Immunotherapy and Radiation Therapy: Analysis of 3 Phase 1/2 Trials

Primary tumor	
NSCLC	62
SCLC	25
HN	16
RCC	13
HCC	5
GYN	7
CRC	6
Pancreatic	4
Prostate	4
Esophageal	3
Bone	3
Other	5
Immunotherapy drug	
Ipilimumab	98
Pembrolizumab	55
RT scheme	
12.5 Gy × 4 fractions	99
6 Gy × 10 fractions	20
3 Gy × 15 fractions	34



Int J Radiation Oncol Biol Phys, Vol. 108, No. 1, pp. 196–203, 2020

Lymphocyte-Sparing Radiotherapy: The Rationale for Protecting Lymphocyte-rich Organs When Combining Radiotherapy With Immunotherapy

Philippe Lambin, MD, PhD,[*,1] Relinde I.Y. Lieverse, MD,[*,1] Franziska Eckert, MD,[†,1] Damiënne Marcus, MSc,[*] Cary Oberije, PhD,[*] Alexander M.A. van der Wiel, MSc,[*] Chandan Guha, MD PhD,[‡] Ludwig J. Dubois, PhD,[*] and Joseph O. Deasy, PhD[§]

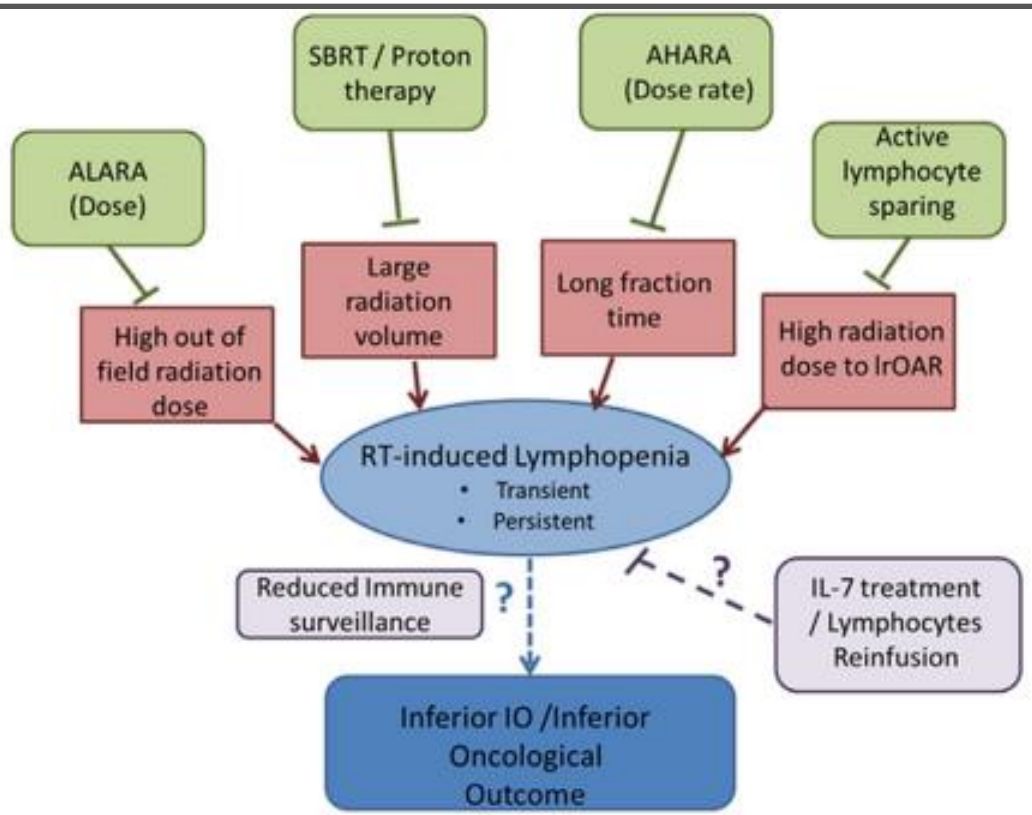


Figure 3 Hypothetical model linking radiation to lymphopenia and to inferior oncological outcomes.

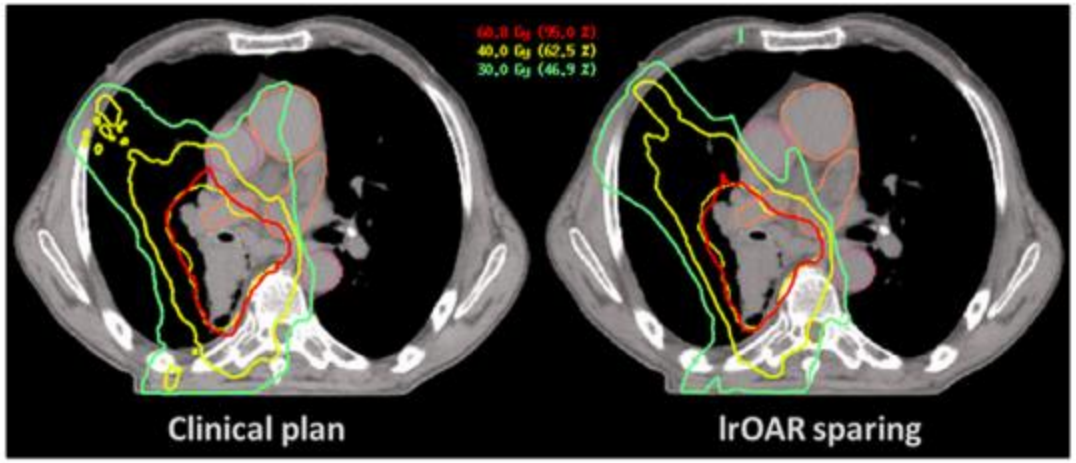


Figure 2 A standard dose distribution of a clinically applied radiation treatment plan (left), and an example of an optimised radiation plan applying the As Low As Reasonably Achievable (ALARA) principle (right), demonstrating that sparing of LOAR is feasible without compromising dose coverage of the target volume or increasing dose to OARs important in clinical radiotherapy planning.

Who Benefits the Most From Adjuvant Durvalumab After Chemoradiotherapy for Non-small Cell Lung Cancer? An Exploratory Analysis

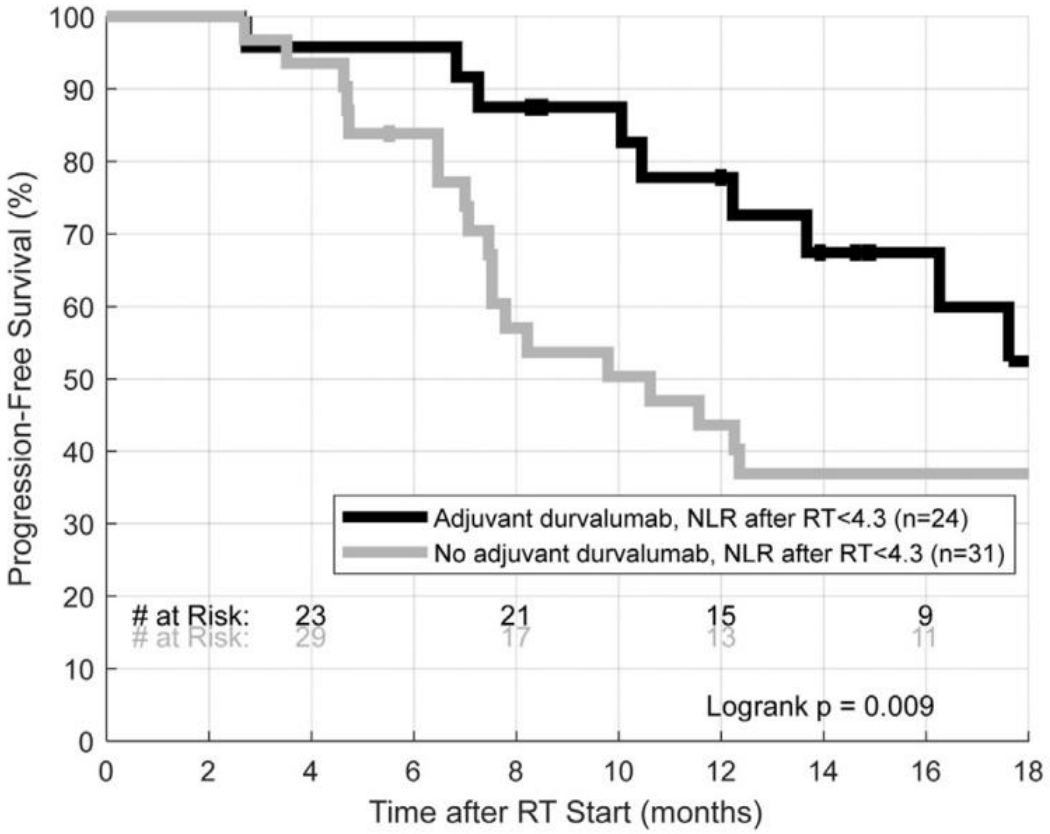


Figure 4 Kaplan-Meier curves for progression-free survival for patients with neutrophil-to-lymphocyte ratios lower than the cohort median, grouped by durvalumab receipt.

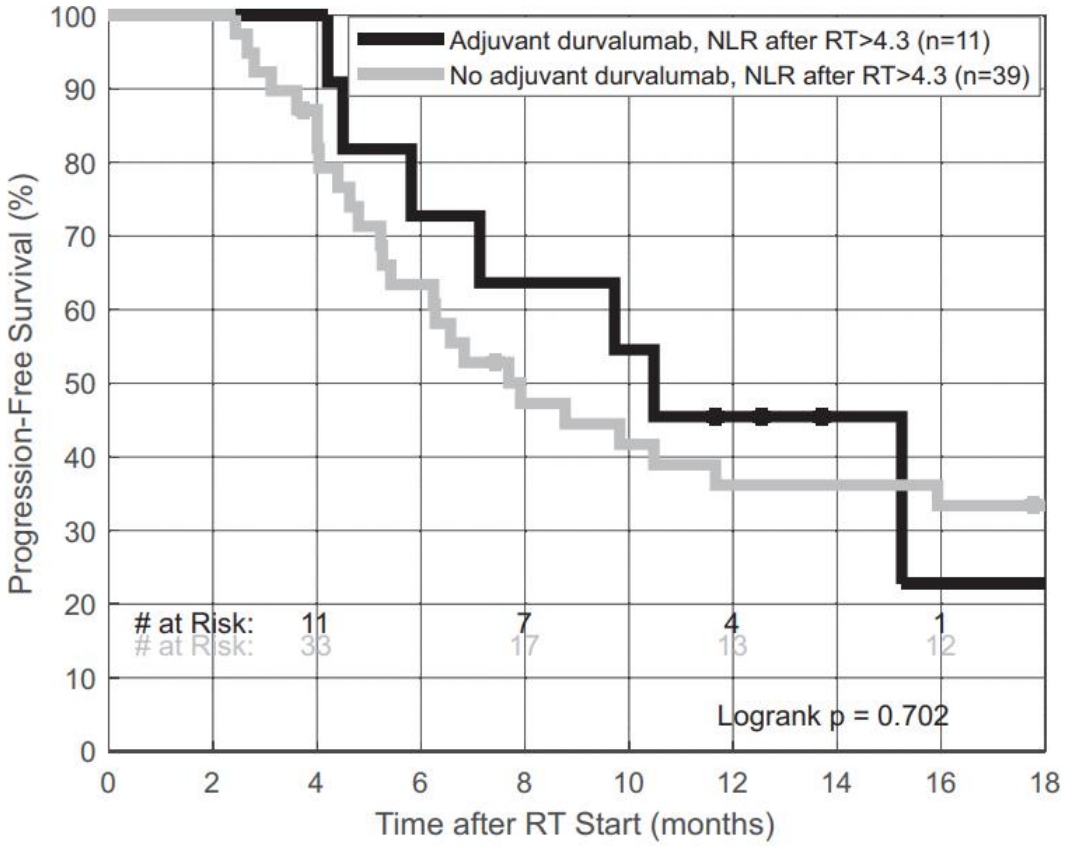


Figure 5 Kaplan-Meier curves for progression-free survival for patients with neutrophil-to-lymphocyte ratios greater than the cohort median, grouped by durvalumab receipt.

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Predictors of Early Durvalumab Discontinuation After Chemoradiotherapy for Non-Small Cell Lung Cancer

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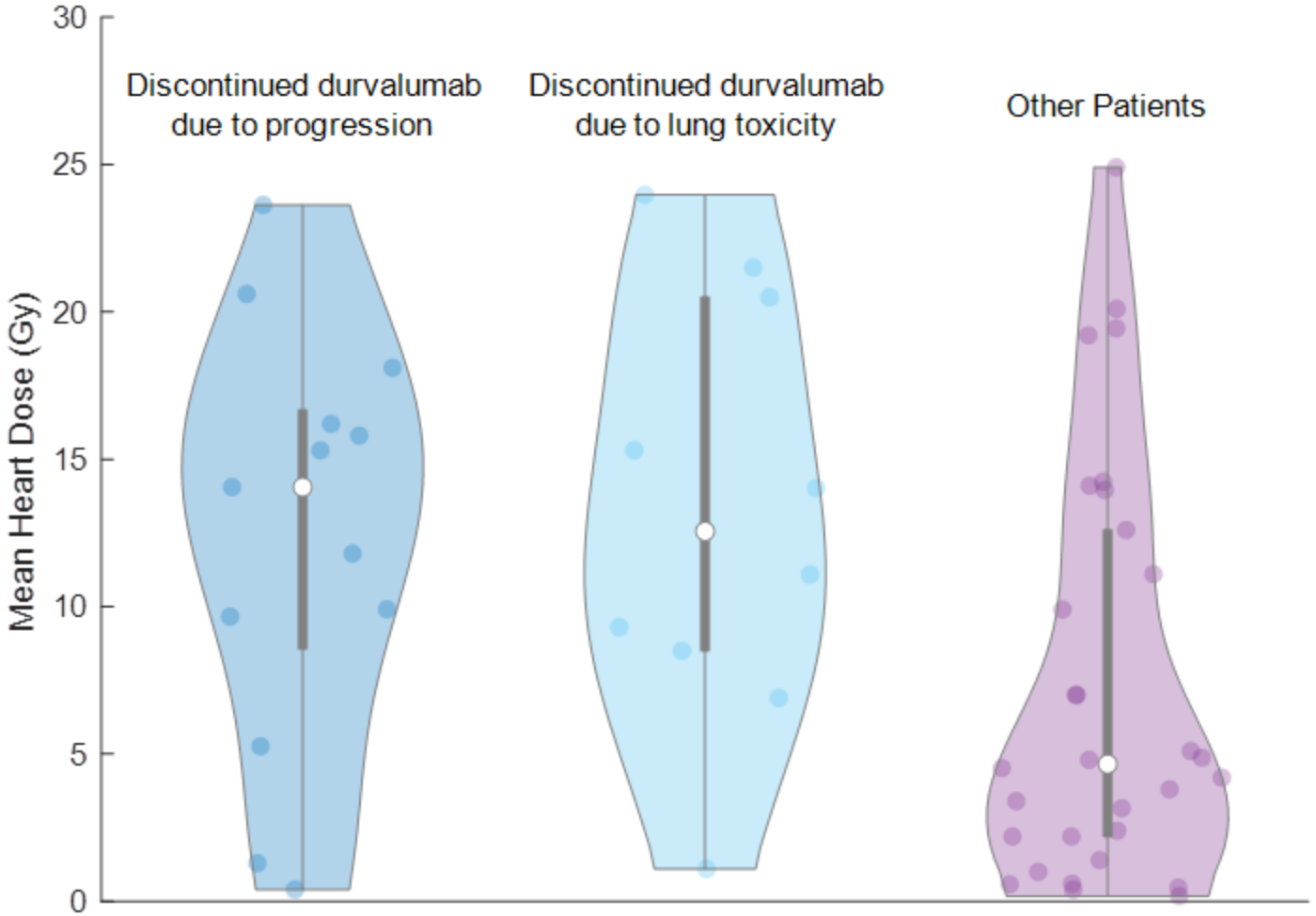

Evolving RT in the Immunotherapy Era

- RT-induced lymphopenia may detract from immunotherapy efficacy
- RT toxicities (e.g., pneumonitis) may lead to immunotherapy interruption
- Long-term survival for some metastatic cancer patients is possible

These factors all favor short RT courses and highly conformal treatment techniques

Questions?