How to Combine RT and Immunotherapy without Compromising Anti-Tumor Effect?

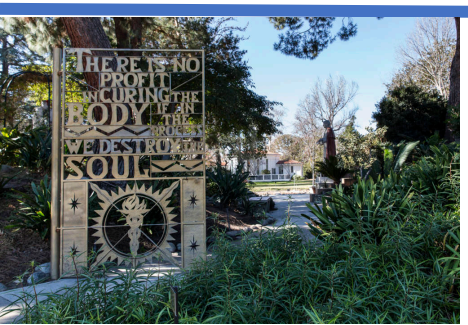
New Orleans Summer Cancer Meeting

Percy Lee, M.D.

Professor and Vice-Chair

City of Hope National Medical Center

@PercyLeeMD



City of Hope
ORANGE COUNTY

Outline

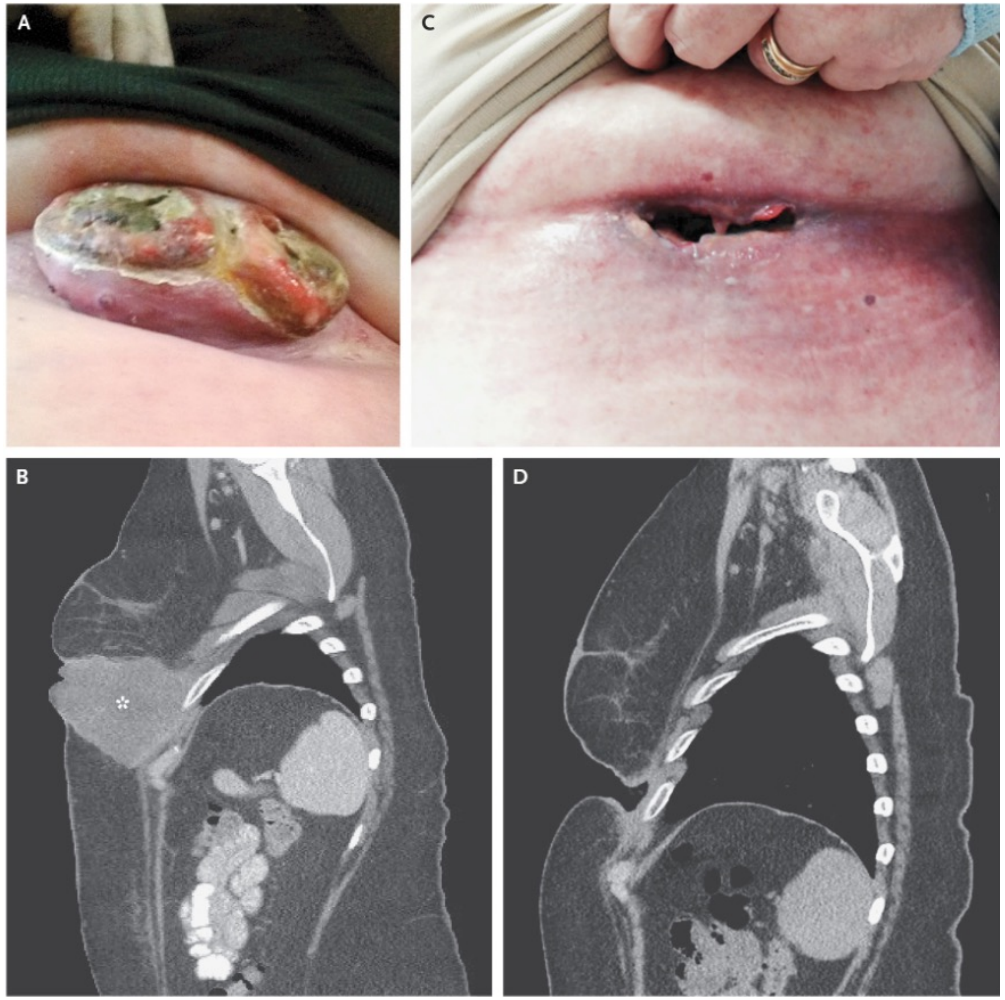
Basis of combining RT and IO

Clinical data combining RT and IO

Factors that affect Efficacy of RT and IO Combination

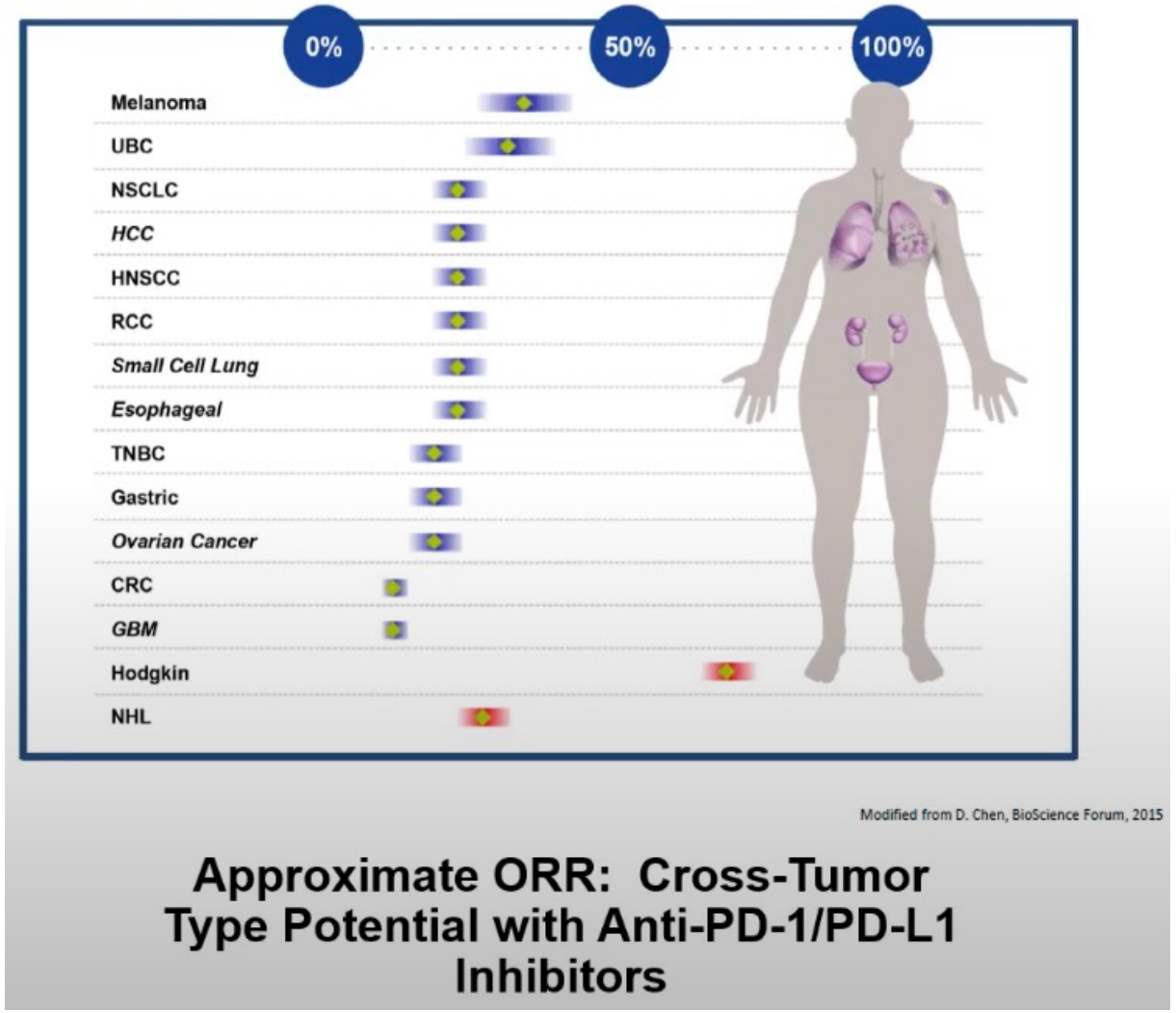
Ongoing trials and recently completed trial combining RT and IO

Immune Checkpoint Therapy



Response of Melanoma to a single dose
Dose of Ipilmumab plus Nivolumab

Chapman et al. NEJM 2015

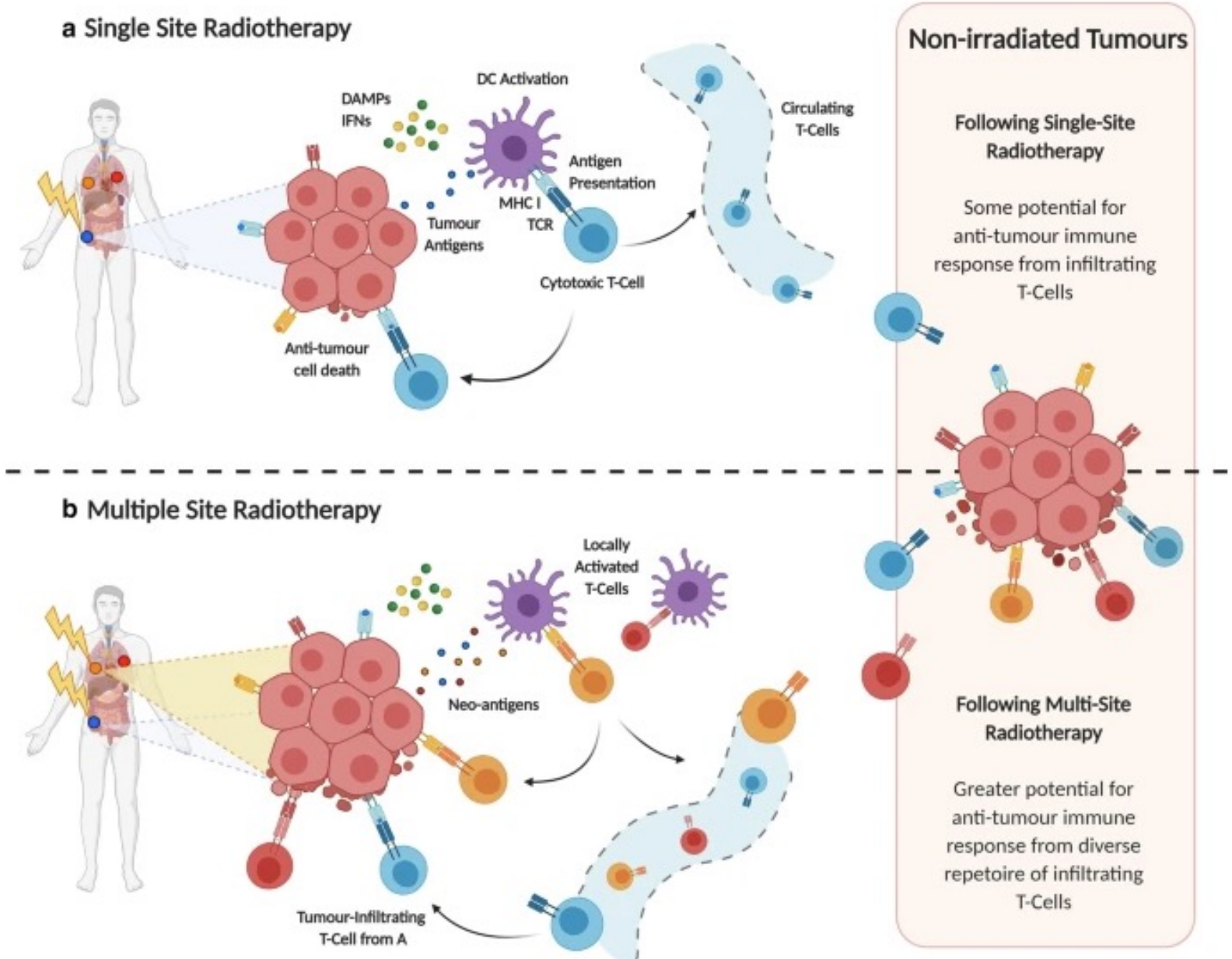


Approximate ORR: Cross-Tumor Type Potential with Anti-PD-1/PD-L1 Inhibitors

How to integrate radiotherapy in the immunotherapy era?

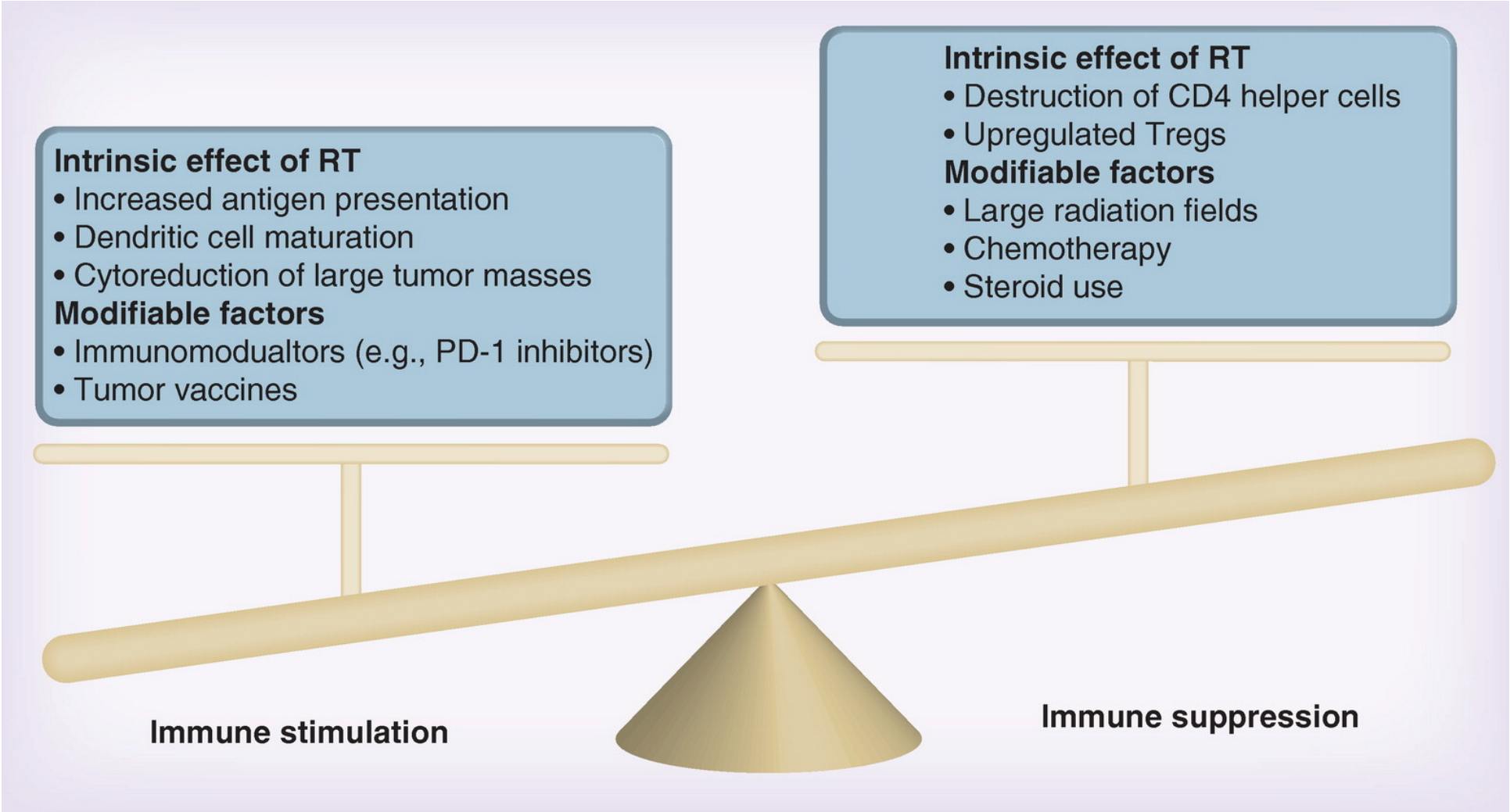
- Emphasis on multimodality therapy
- Sequence and timing of radiation therapy may be critically important
- Variation may depend on cancer types
- Molecular considerations may impact response
- Importance of clinical trials to tease all of this out

Reprogram of tumor microenvironment by RT



Colton, BMC 2020

Balance Immune stimulatory effects and suppressive effects of RT



Lawrence, Future Medicine 2014

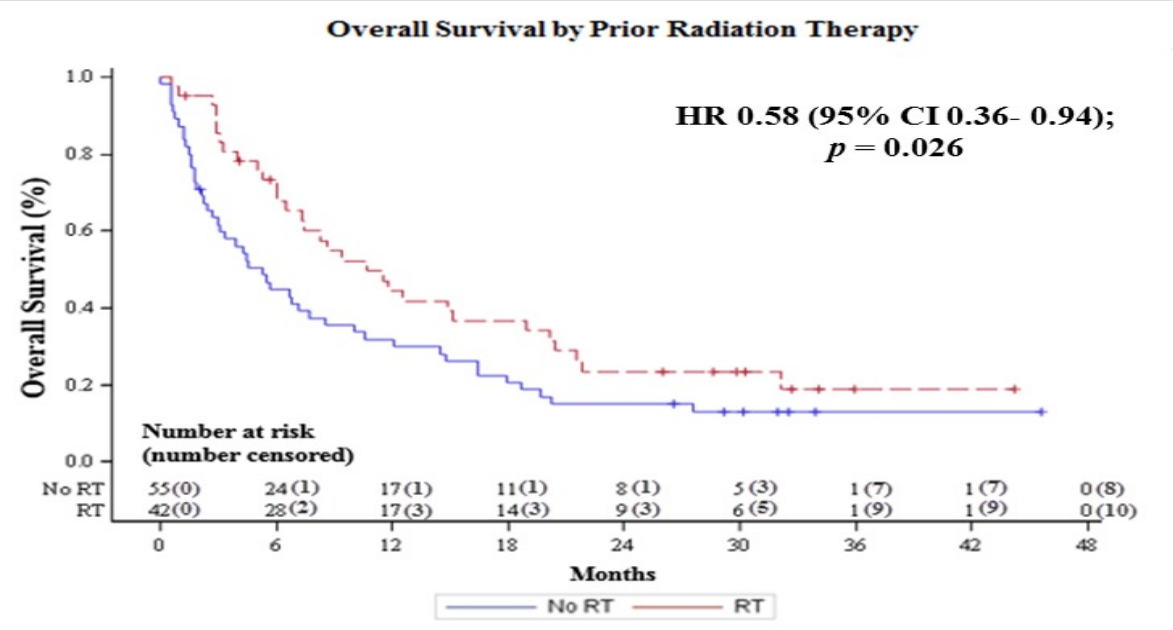
Clinical evidence for RT and IO synergy

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

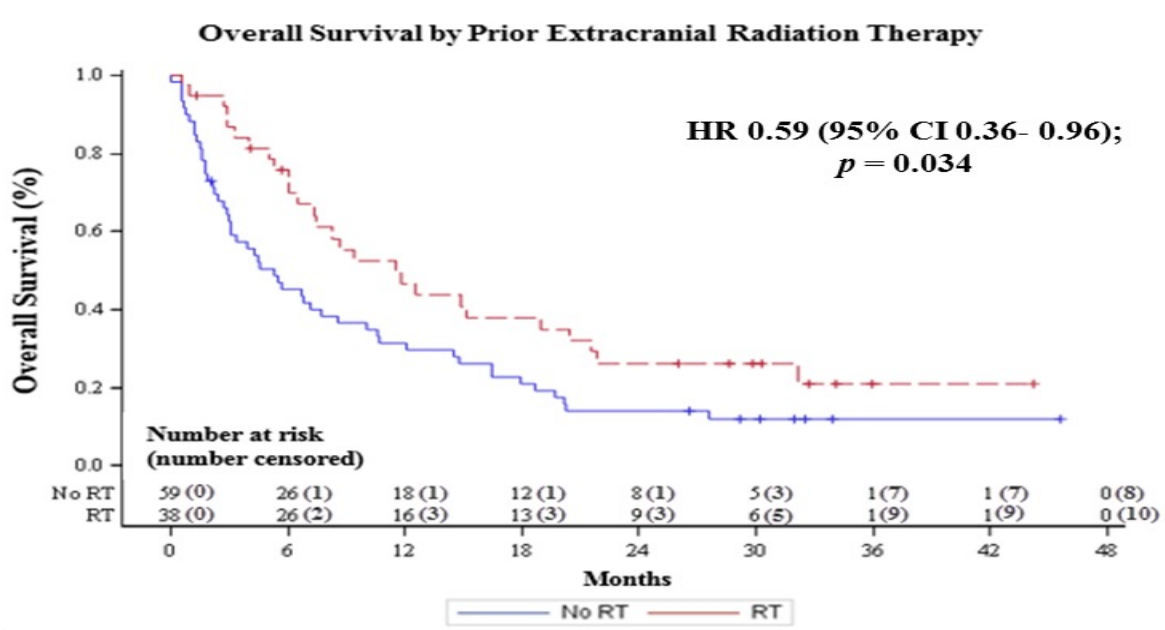
Narek Shaverdian, Aaron E Lisberg*, Krikor Bornazyan, Darlene Veruttipong, Jonathan W Goldman, Silvia C Formenti, Edward B Garon†, Percy Lee†*

- KEYNOTE-001
  - Phase I study of 495 patients with advanced NSCLC
  - Eligible patients had progressive disease and most were heavily pretreated
  - Primary objective was safety and antitumor activity of pembrolizumab
  - Overall response rate 19.4% and median PFS 3.7 months
  - PDL1 expression ≥ 50% correlated with improved efficacy
- Secondary analysis
  - To determine if patients with advanced NSCLC treated with pembrolizumab on the phase I KEYNOTE-001 trial who previously received radiation therapy had improved progression-free and overall survival with pembrolizumab treatment
  - To determine if prior thoracic radiation therapy influenced the rates of pulmonary toxicity with pembrolizumab

Impact of any radiation on overall survival



Median OS: 10.7 vs 5.3 months



Median OS: 11.6 vs 5.3 months

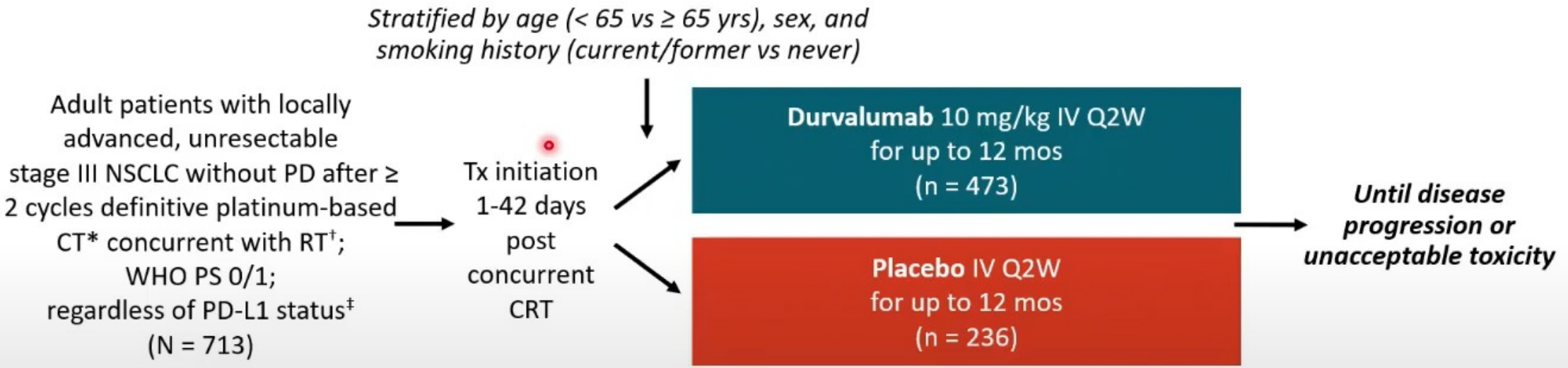
Immunotherapy and Radiation

- Cooperative effects at site of treatment
  - Neoadjuvant
  - Concurrent
  - Adjuvant

- Abscopal effect (very rare)

PACIFIC: Study Design

- Randomized, double-blind, placebo-controlled phase III trial



*Platinum-based CT contained etoposide, vinorelbine, paclitaxel, docetaxel, vinblastine, or pemetrexed.
†92% of patients received 54 Gy to 66 Gy RT dose. ‡If available, archived pre-cCRT tumor tissue tested for PD-L1.

- Co-primary endpoints: PFS by BICR per RECIST v1.1, OS
- Secondary endpoints including: ORR, DoR, TTDM by BICR, PFS2 by investigator, safety, PROs

Antonia. N Engl J Med. 2017;377:1919. Antonia. WCLC 2018. Abstract PL02.01. Antonia. N Engl J Med. 2018;379:2342.

Slide credit: clinicaloptions.com

PACIFIC

Durvalumab After Chemoradiotherapy in Stage III NSCLC – 5-Year Survival Update[1]

Unresectable stage III NSCLC without progression after definitive platinum-based cCRT (≥2 cycles)

- WHO PS 0-1
- If available, archived pre-cCRT tumor tissue for PD-L1 testing

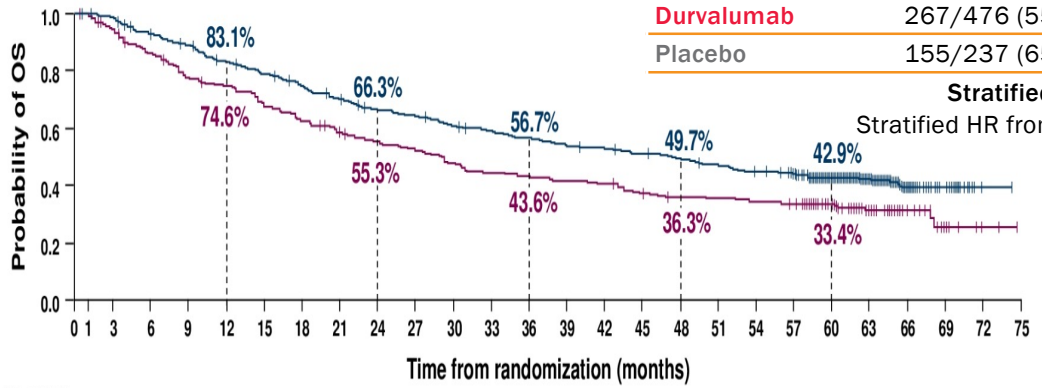
N=713

R 2:1

- Durvalumab n=476
- Placebo n=237

Stratified by age, sex, smoking history

Updated OS (ITT)



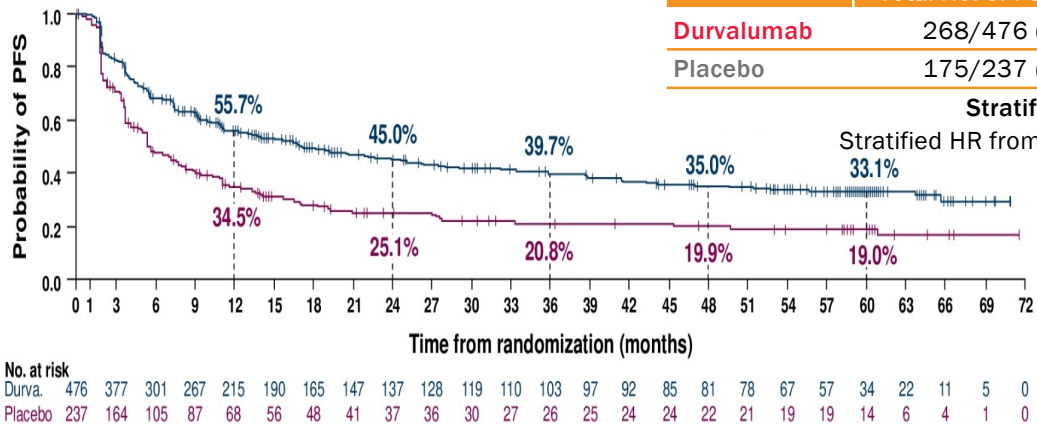
	No. of Events/ Total No. of Patients (%)	Median OS (95% CI), mo
Durvalumab	267/476 (55.5)	47.5 (38.5-52.6)
Placebo	155/237 (65.4)	29.1 (22.1-35.1)

Stratified HR, 0.72 (95% CI, 0.59-0.89)

Stratified HR from PA, 0.68 (95% CI, 0.53-0.87)

- Of patients surviving up to 5 years with durvalumab, **75%** had **no disease progression**[2]

Updated PFS (ITT; BICR)



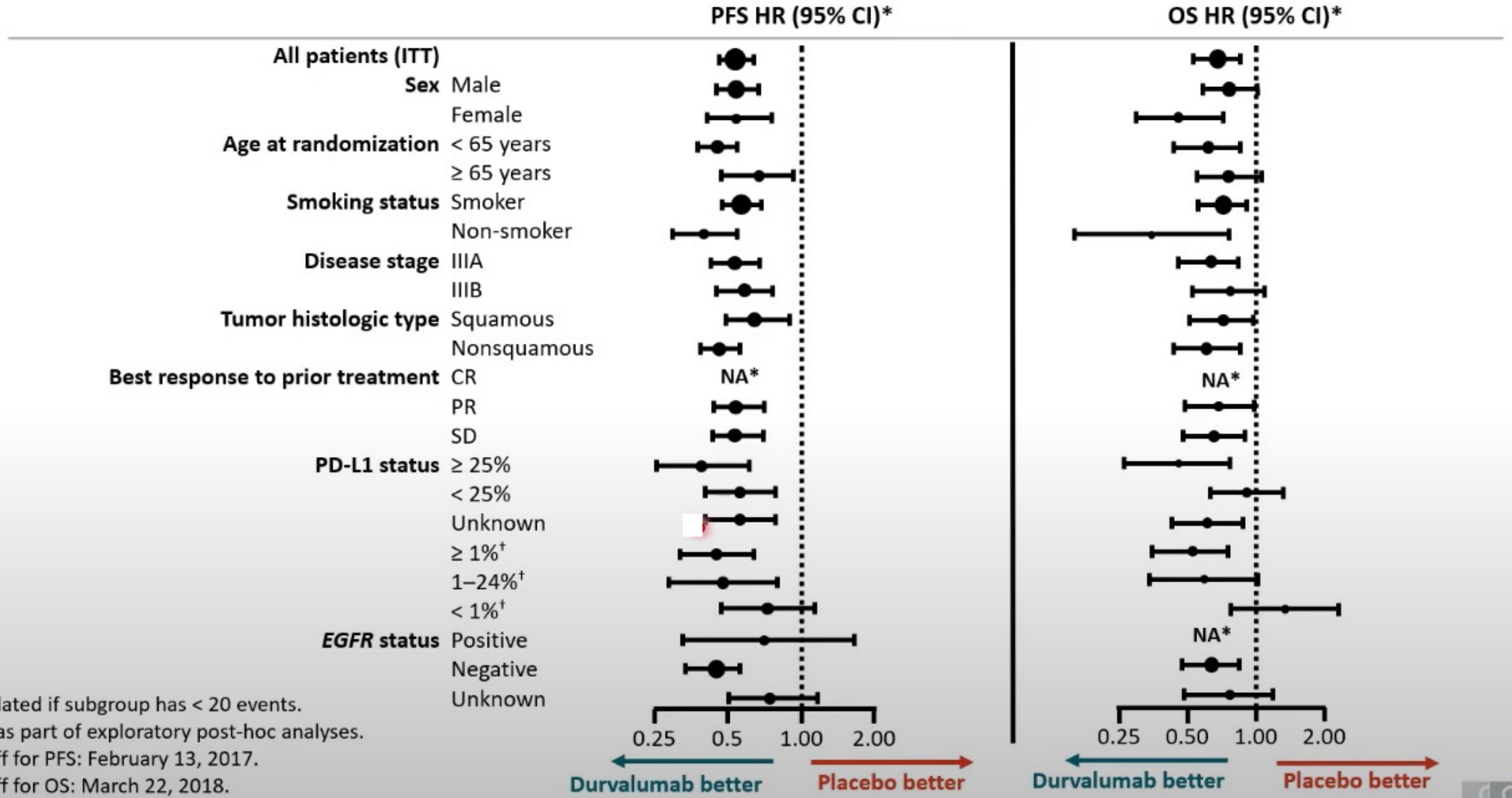
	No. of Events/ Total No. of Patients (%)	Median PFS (95% CI), mo
Durvalumab	268/476 (56.3)	16.9 (13.0-23.9)
Placebo	175/237 (73.8)	5.6 (4.8-7.7)

Stratified HR, 0.55 (95% CI, 0.45-0.68)

Stratified HR from the PA, 0.52 (95% CI, 0.42-0.65

1. Spigel DR, et al. Presented at ASCO 2021. Abstract 8511. 2. Imfinzi demonstrated unprecedented survival in unresectable, Stage III lung cancer with 43% of patients surviving five years. June 4, 2021. Accessed June 9, 2021. https://www.astrazeneca.com/media-centre/press-releases/2021/imfinzi-demonstrated-unprecedented-survival-in-unresectable-stage-iii-lung-cancer-with-43-percent-of-patients-surviving-five-years.html.

PACIFIC: PFS and OS by Subgroup (ITT)



*Not calculated if subgroup has < 20 events.
†Assessed as part of exploratory post-hoc analyses.
Data cut-off for PFS: February 13, 2017.
Data cut-off for OS: March 22, 2018.

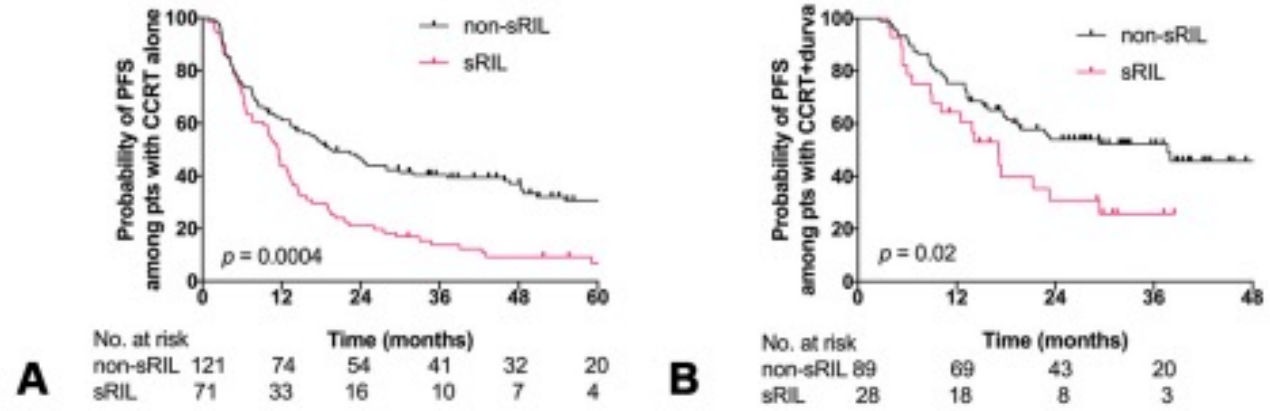
Antonia. WCLC 2018. Abstract PL02.01. Antonia. N Engl J Med. 2018;379:2342. Antonia. N Engl J Med. 2017;377:1919.

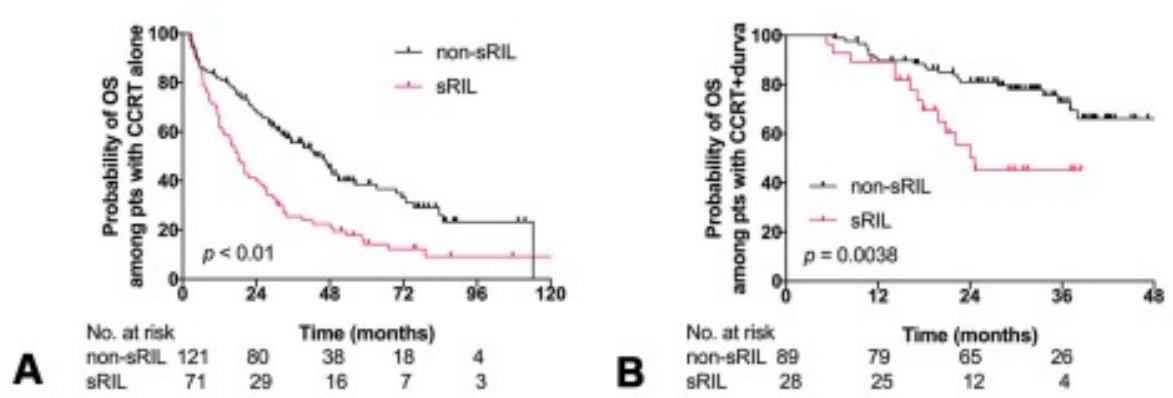
Slide credit: clinicaloptions.com

Lymphopenia and Benefit of IO after CRT

Severe Radiation-Induced Lymphopenia Attenuates the Benefit of Durvalumab After Concurrent Chemoradiotherapy for NSCLC

Wang Jing, MD,[a,b] Ting Xu, PhD,[a] Lirong Wu, MD,[a,c] Pablo B. Lopez, MD,[a] Clemens Grassberger, PhD,[d] Susannah G. Ellsworth, MD,[e] Radhe Mohan, PhD,[f] Brian P. Hobbs, PhD,[g] George R. Blumenschein, MD,[h] Janet Tu, MD,[h] Mehmet Altan, MD,[h] Percy Lee, MD,[a] Zhongxing Liao, MD,[a] Steven H. Lin, MD, PhD[a,*]





Proton Therapy Reduces High-Grade RT Induced Lymphopenia

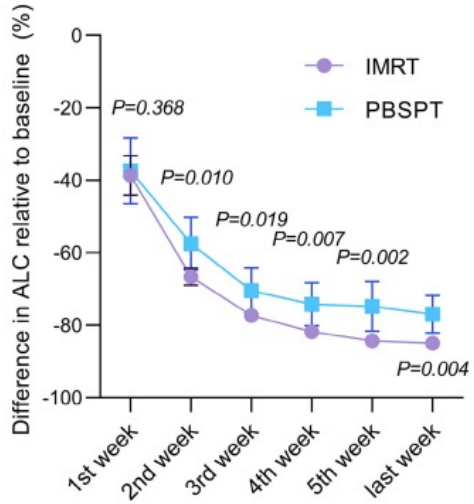
Original Article

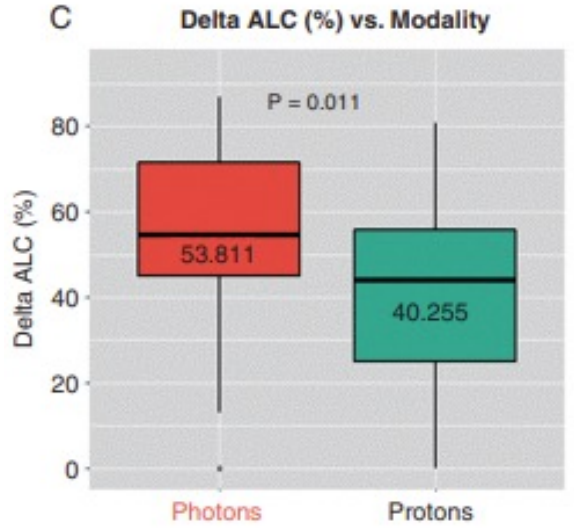
Proton beam therapy reduces the risk of severe radiation-induced lymphopenia during chemoradiotherapy for locally advanced non-small cell lung cancer: A comparative analysis of proton versus photon therapy

Nalee Kim, Jae Myoung Noh, Woojin Lee, Byoungsuk Park, Heejoo Park, Ji Young Park, Hongryull Pyo *

Proton therapy reduces the likelihood of high-grade radiation-induced lymphopenia in glioblastoma patients: phase II randomized study of protons vs photons

Radhe Mohan, Amy Y. Liu, Paul D. Brown, Anita Mahajan, Jeffrey Dinh, Caroline Chung, Sarah McAvoy, Mary Frances McAleer, Steven H. Lin, Jing Li, Amol J. Ghia, Cong Zhu, Erik P. Sulman, John F. de Groot, Amy B. Heimberger, Susan L. McGovern, Clemens Grassberger, Helen Shih, Susannah Ellsworth, and David R. Grosshans





Esophageal Cancer: Checkmate 577

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 1, 2021 VOL. 384 NO. 13

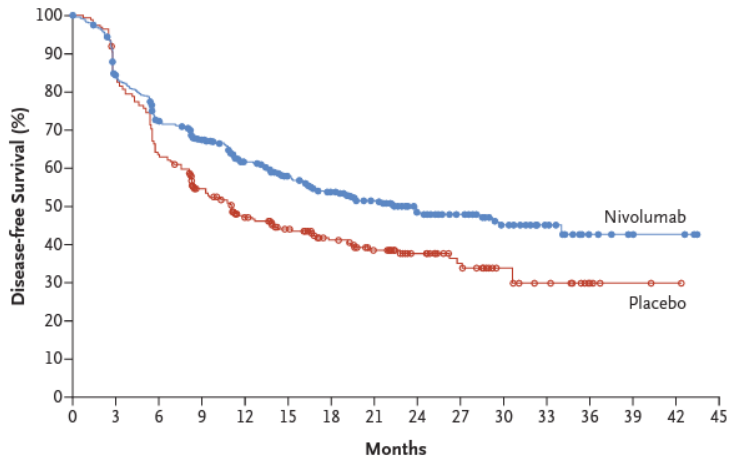
Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer

R.J. Kelly, J.A. Ajani, J. Kuzdzal, T. Zander, E. Van Cutsem, G. Piessen, G. Mendez, J. Feliciano, S. Motoyama, A. Lièvre, H. Uronis, E. Elimova, C. Grootscholten, K. Geboes, S. Zafar, S. Snow, A.H. Ko, K. Feeney, M. Schenker, P. Kocon, J. Zhang, L. Zhu, M. Lei, P. Singh, K. Kondo, J.M. Cleary, and M. Moehler, for the CheckMate 577 Investigators*

Phase III

Neoadjuvant chemoRT → Surgery → Nivolumab up to 1 year

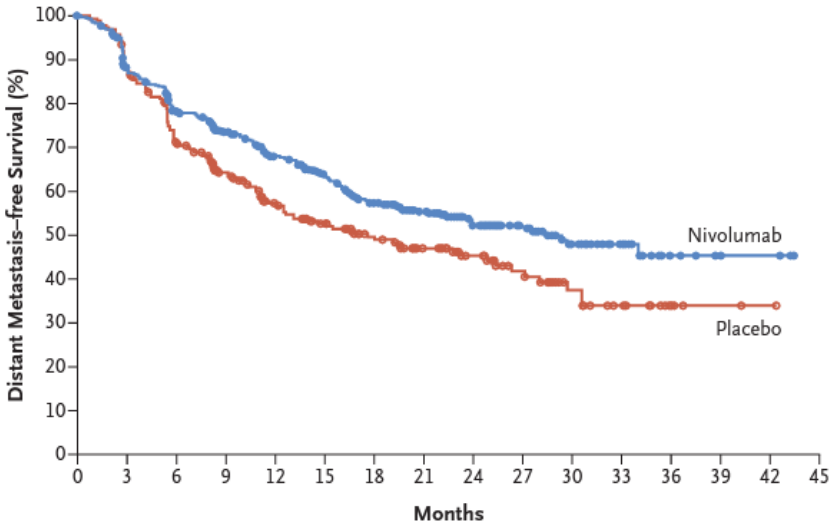
A Disease-free Survival in the Overall Population



	No. of Patients	Median
		mo
Nivolumab	532	22.4
Placebo	262	11.0

Hazard ratio for disease recurrer
0.69 (96.4% CI, 0.56–0.86)
P<0.001

No. at Risk																
Nivolumab	532	430	364	306	249	212	181	147	92	68	41	22	8	4	3	0
Placebo	262	214	163	126	96	80	65	53	38	28	17	12	5	2	1	0



	No. of Patients	Median Distant Metastasis–free Survival
		mo (95% CI)
Nivolumab	532	28.3 (21.3–NE)
Placebo	262	17.6 (12.5–25.4)

Hazard ratio for distant recurrence or death, 0.74 (95% CI, 0.60–0.92)

No. at Risk																
Nivolumab	532	449	392	332	276	235	195	160	102	75	44	23	8	4	3	0
Placebo	262	226	180	142	113	93	77	64	46	33	21	14	5	2	1	0

HNCC and Cervical CA

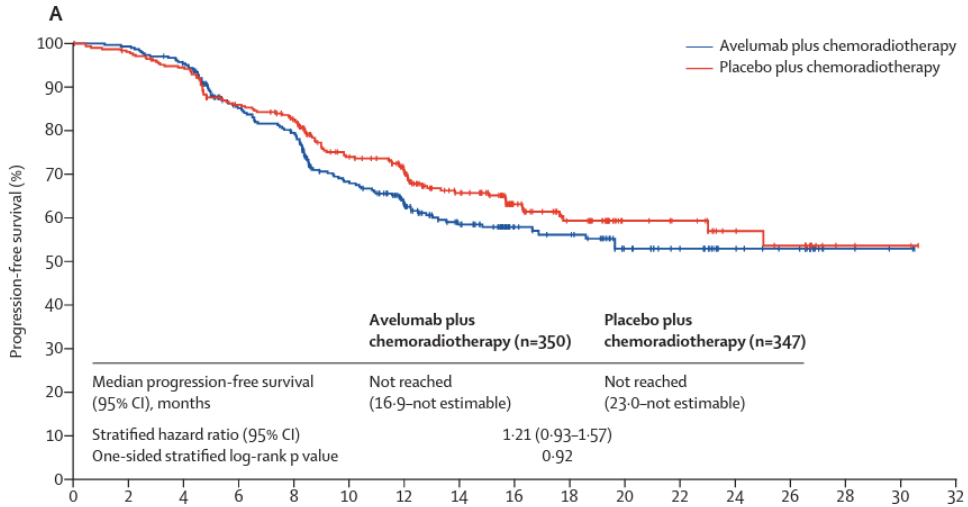
- No improvement with concurrent (+/- adjuvant ICI + RT
  - JAVALIN HNSCC 100 – phase III, avelumab + chemoRT vs. chemoRT
  - GORTEC-REACH- phase III, avelumab + cetuxmab RT vs. SOC (cis or cetuxmab + RT)
  - KEYNOTE 412 – phase III, pembro + chemoRT vs. chemoRT
  - CALLA – phase III, concurrent/adjuvant durvalumab + chemoRT vs. chemoRT

- What is the difference compared to PACIFIC?
  - Concurrent IO and chemoRT
  - Future questions include who benefits?
  - Fractionation/ dose/fraction?
  - Sequencing?
  - Which checkpoint inhibitors?

JAVELIN HNSCC 100

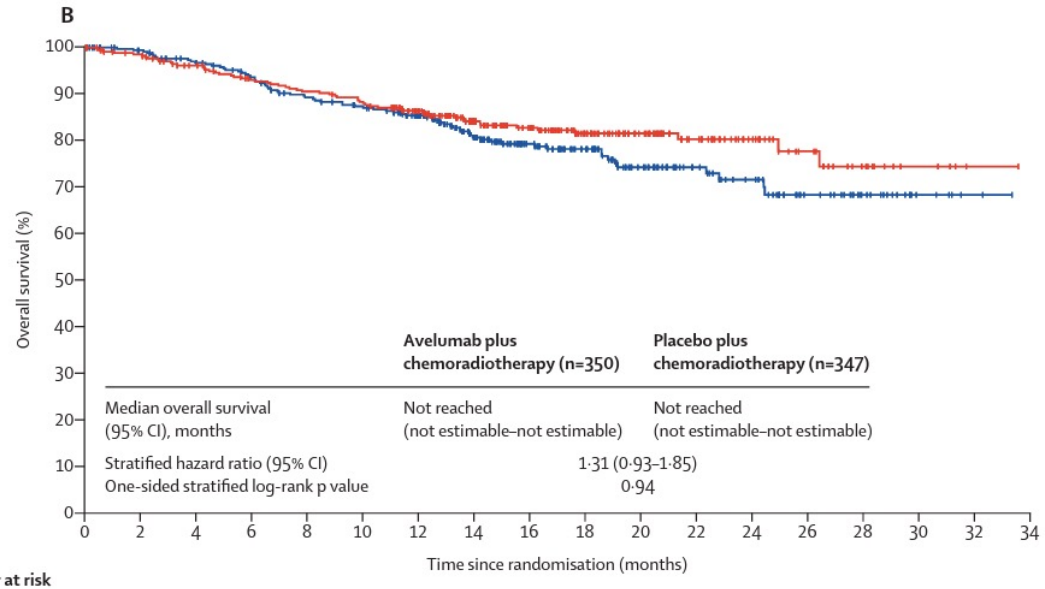
Avelumab plus standard-of-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial

Nancy Y Lee, Robert L Ferris*, Amanda Psyrri, Robert I Haddad, Makoto Tahara, Jean Bourhis, Kevin Harrington, Peter Mu-Hsin Chang, Jin-Ching Lin, Mohammad Abdul Razaq, Maria Margarida Teixeira, József Lövey, Jerome Chamois, Antonio Rueda, Chaosu Hu, Lara A Dunn, Mikhail Vladimirovich Dvorkin, Steven De Beukelaer, Dmitri Pavlov, Holger Thurm, Ezra Cohen**



Number at risk (number censored)																		
Avelumab plus chemoradiotherapy	350	303	289	239	222	176	143	107	69	63	41	33	22	18	4	2	0
	(0)	(45)	(47)	(67)	(68)	(84)	(105)	(131)	(168)	(172)	(191)	(199)	(210)	(214)	(228)	(230)	(232)
Placebo plus chemoradiotherapy	347	303	291	257	241	200	172	121	75	56	31	28	18	15	3	2	0
	(0)	(38)	(39)	(47)	(53)	(70)	(90)	(130)	(172)	(187)	(212)	(215)	(224)	(226)	(238)	(239)	(241)

Phase III, LA HNSCC
ChemoRT vs. ChemoRT + avelumab



Number at risk (number censored)																			
Avelumab plus chemoradiotherapy	350	336	319	303	284	273	244	190	148	118	82	59	47	29	18	6	2	0
	(0)	(12)	(20)	(26)	(31)	(36)	(59)	(101)	(140)	(168)	(199)	(222)	(232)	(248)	(259)	(271)	(275)	(277)
Placebo plus chemoradiotherapy	347	334	315	298	290	282	252	193	160	115	86	58	39	26	13	5	1	0
	(0)	(8)	(19)	(26)	(26)	(27)	(51)	(104)	(134)	(177)	(206)	(233)	(252)	(264)	(276)	(284)	(288)	(289)

SRS and Immune Checkpoint Blockade

- SRS for brain metastases is safe to give concurrent with anti-PD1 and anti-CTLA4
- Pseudoprogression may occur. May look like limited bleed
- Radionecrosis rates may be higher but difficult to distinguish from pseudoprogression
- Can be treated symptomatically, and does not need to be taken to the OR (16% vs. 5%) (Kim et al., European Radiology 2020)

SRS and ICI for Brain Metastases

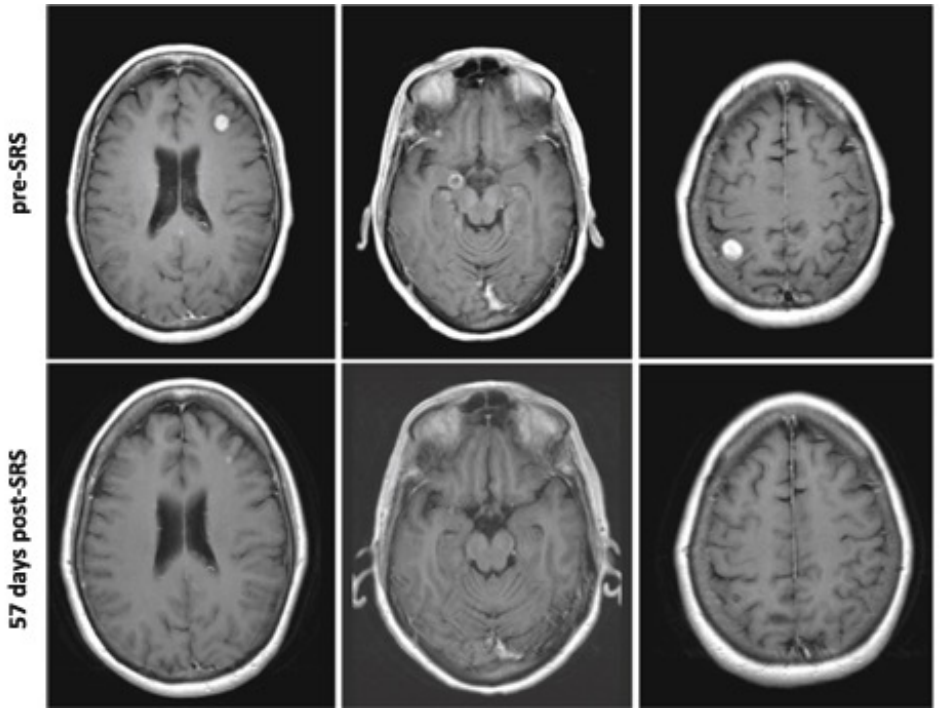
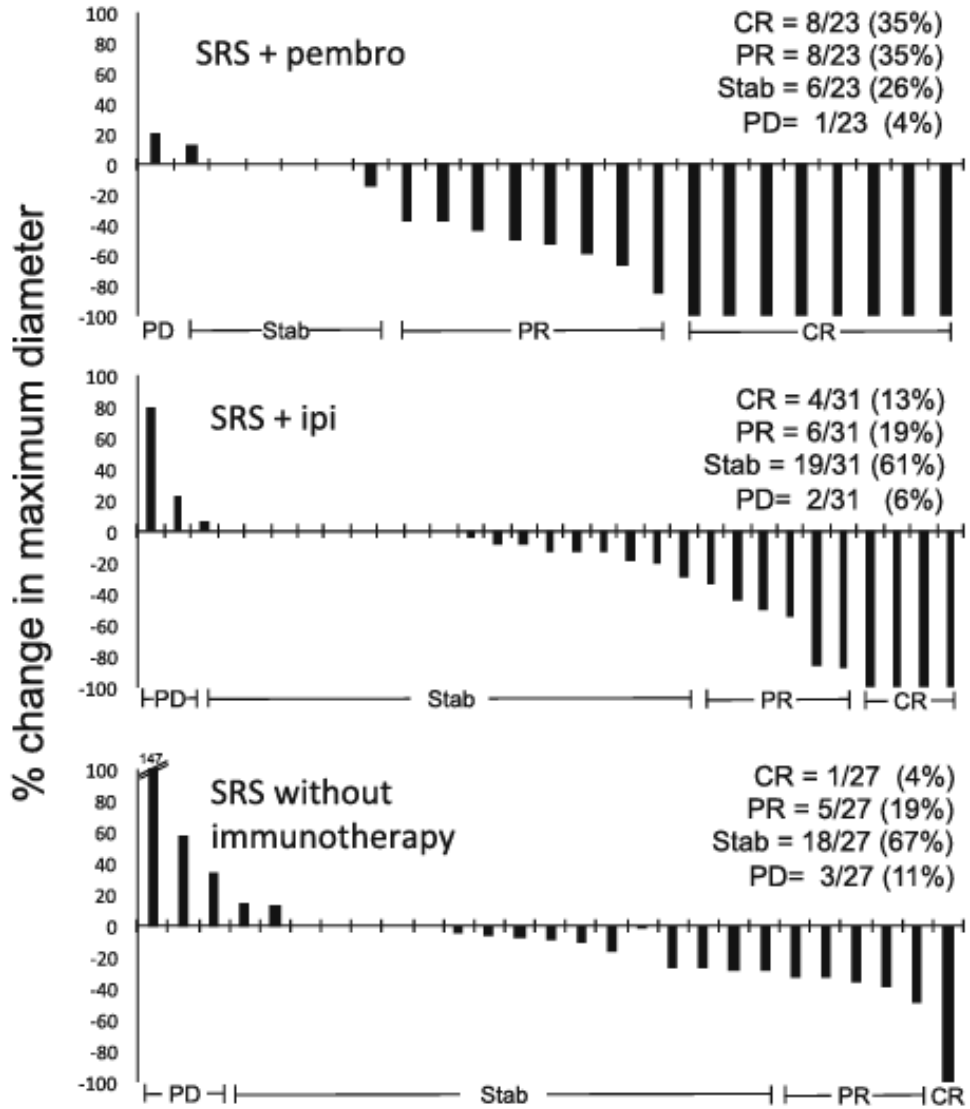


Table 3 SRS Response rate at follow-up MRI

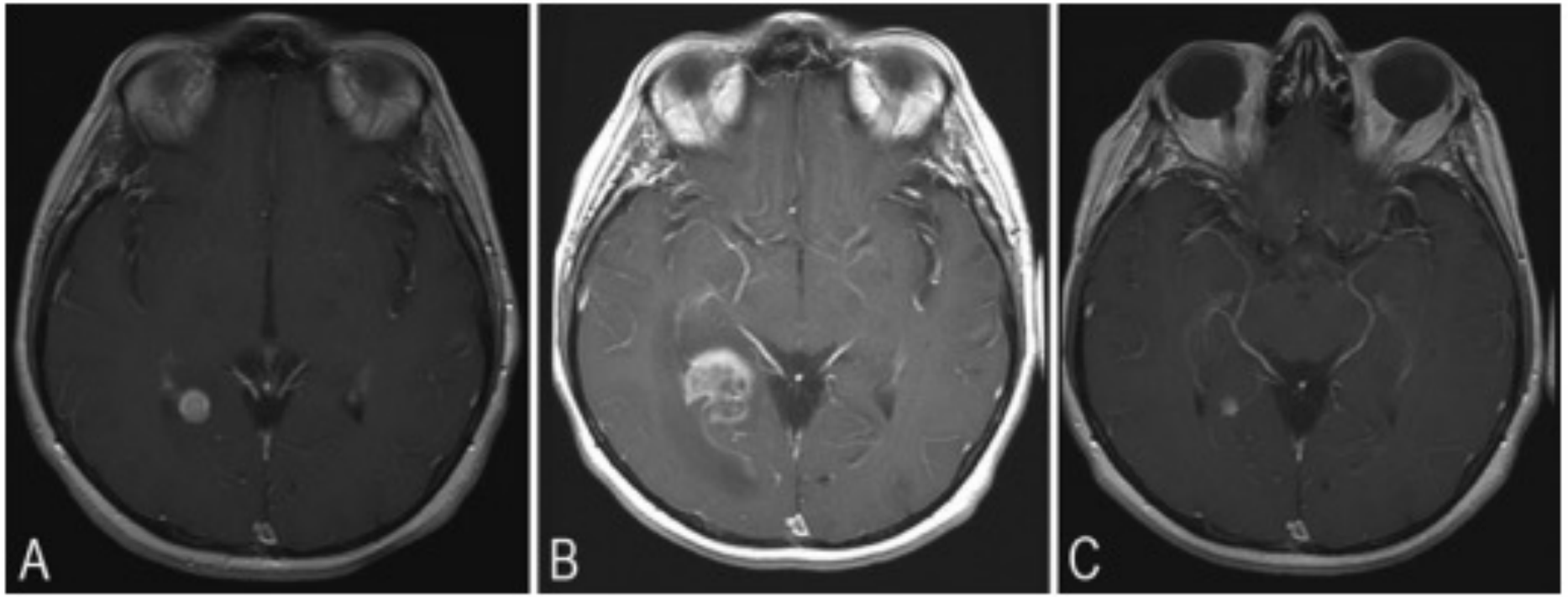
Treatment	Scan interval, d (range)	CR	PR	Stable	PD
SRS + pembro (n = 23)	57 (39-118)	8 (35%)	8 (35%)	6 (26%)	1 (4%)
SRS + ipi (n = 31)	53 (41-95)	4 (13%)	6 (19%)	19 (61%)	2 (6%)
SRS (n = 27)	51 (28-130)	1 (4%)	5 (19%)	18 (67%)	3 (11%)



Anderson, JIC 2017

SRS and ICI Induced Inflammatory Changes

- Frequently self-resolving



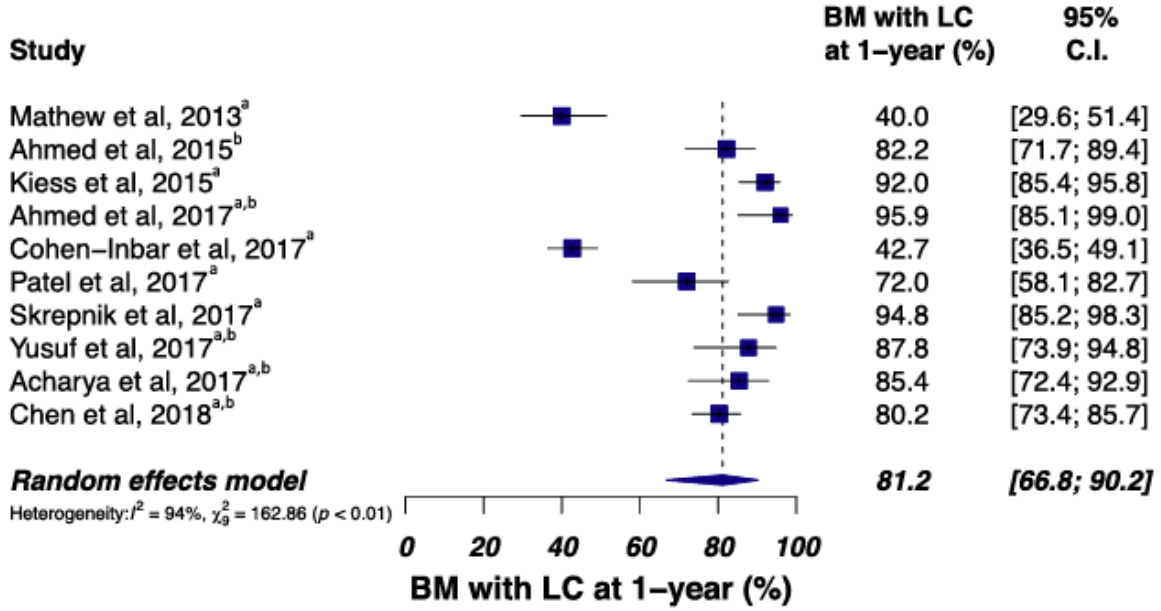
Colaco, JNS 2016

SRS and ICI for Brain Metastases

Systematic Review

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

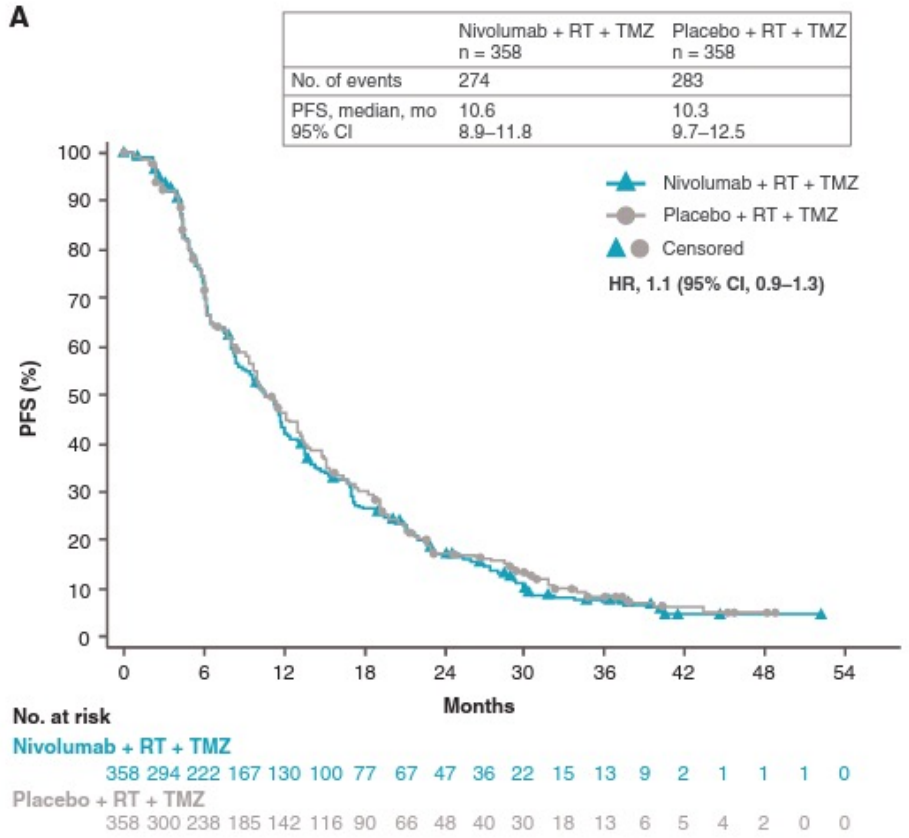
Eric J. Lehrer [a], Jennifer Peterson [b,c], Paul D. Brown [d], Jason P. Sheehan [e], Alfredo Quiñones-Hinojosa [c], Nicholas G. Zaorsky [f,1], Daniel M. Trifiletti [b,c,*,1]



- Meta-analysis of 17 studies across 15 institutions
- Local control 1 year: 89.2% with concurrent vs. 67.8% non-concurrent (p=0.09)

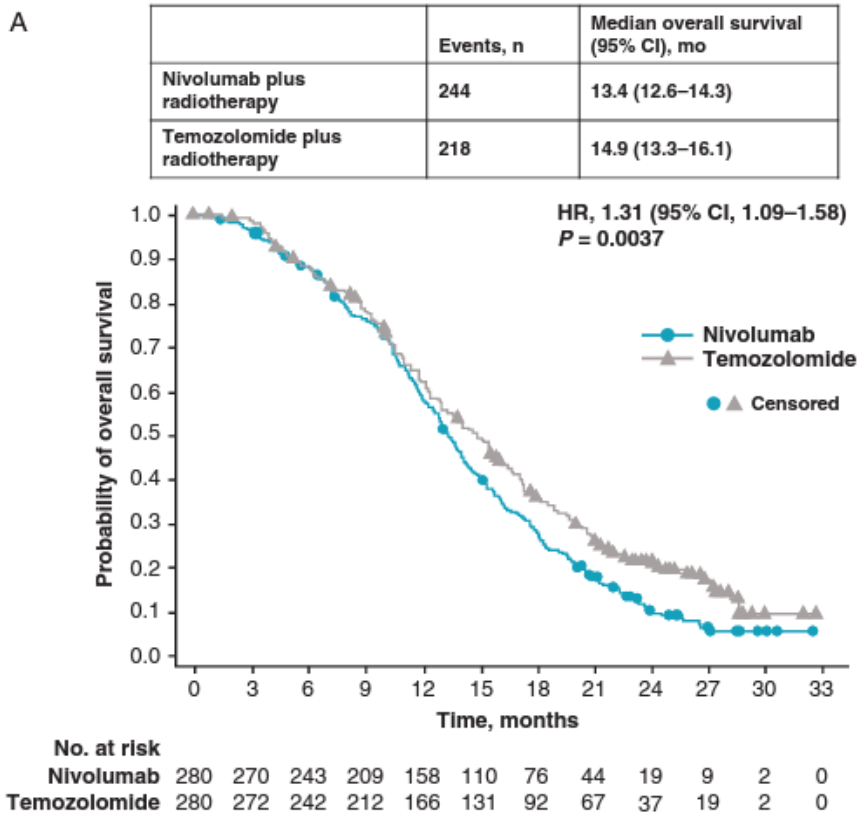
CRT with Anti-PD1 in primary GBM

Checkmate 548: Temozolomide + Nivo and RT vs. Temozolomide and RT w/ methylated MGMT



Lim, Neuro-Oncology 2022

Checkmate 498: Nivo and RT vs. Temozolomide and RT w/ unmethylated MGMT

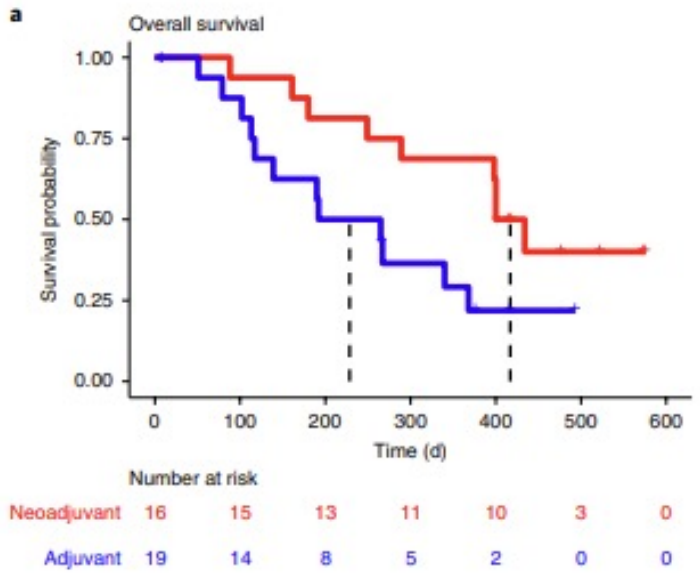


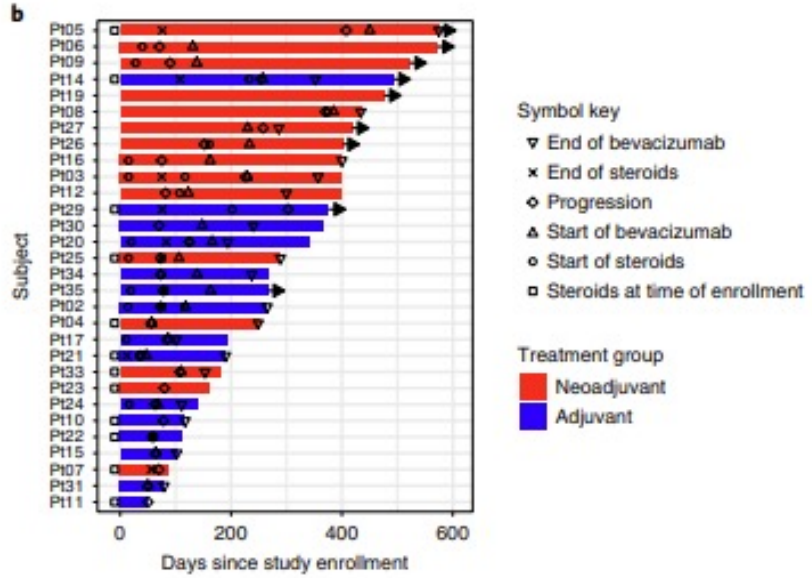
Omuro, Neuro-Oncology 2022

Neoadjuvant anti-PD1 and GBM

Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma

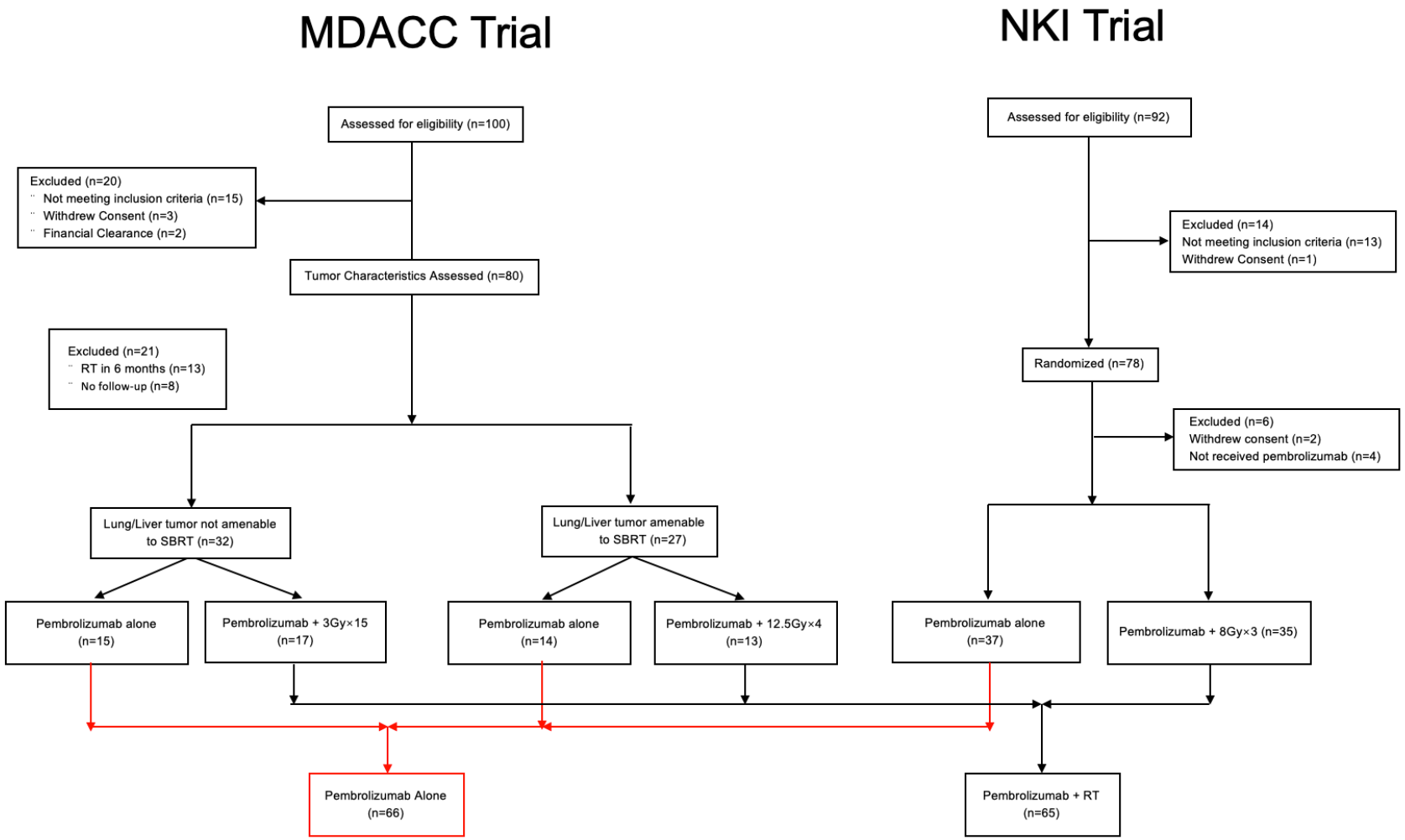
Timothy F. Cloughesy[1,2,3,18*], Aaron Y. Mochizuki[4,18], Joey R. Orpilla[5], Willy Hugo[6], Alexander H. Lee[2,5], Tom B. Davidson[3,4], Anthony C. Wang[5], Benjamin M. Ellingson[3,7], Julie A. Rytlewski[8], Catherine M. Sanders[8], Eric S. Kawaguchi[9], Lin Du[9], Gang Li[3,9], William H. Yong[10], Sarah C. Gaffey[11], Adam L. Cohen[12], Ingo K. Mellinghoff[13], Eudocia Q. Lee[11], David A. Reardon[11], Barbara J. O'Brien[14], Nicholas A. Butowski[15], Phioanh L. Nghiemphu[1], Jennifer L. Clarke[15], Isabel C. Arrillaga-Romany[16], Howard Colman[12], Thomas J. Kaley[13], John F. de Groot[14], Linda M. Liau[3,5], Patrick Y. Wen[11,19] and Robert M. Prins[2,3,5,17,19*]





Pembrolizumab +/- RT

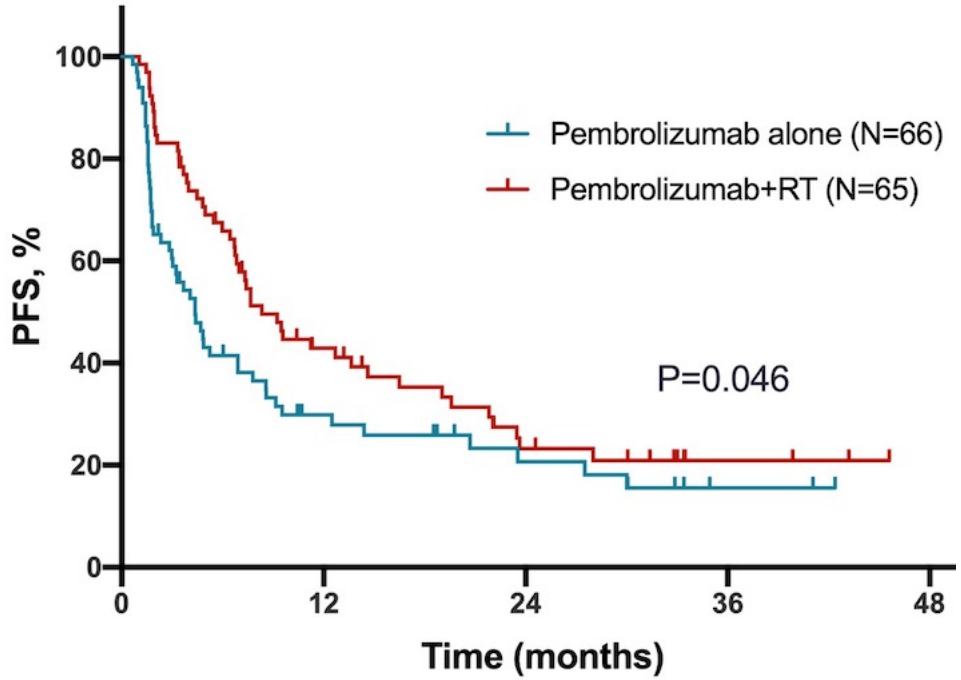
- Pooled two completed randomized studies of Pembrolizumab +/- RT in mNSCLC (MDACC and NKI)
- 131 pts (n=66 pembro alone, n=65 pembro/RT)
- MDACC: newly dx, 1-4 sites radiated, 50 in 4fx or 45 in 15 fx
- NK: previously tx, 1 site radiated, 24 Gy in 3 fx



Theelen W and Welsh J.W. Lancet Respiratory Medicine 2020

Pembrolizumab +/- RT

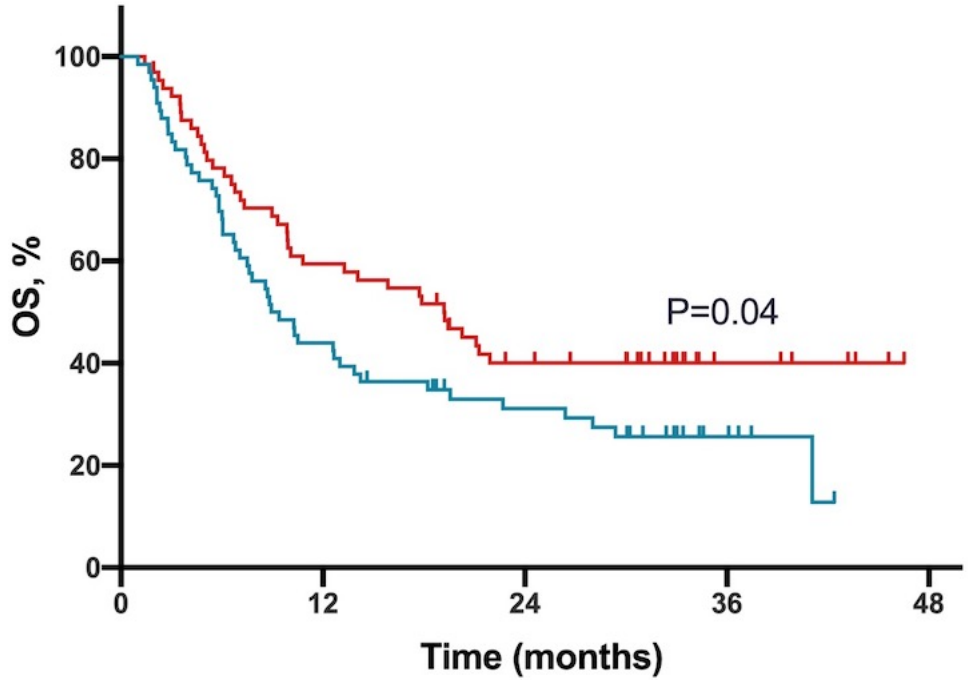
A



No. at risk					
Pembrolizuamb alone	66	16	9	3	0
Pembrolizumab+RT	65	25	12	4	0

PFS 8.3 vs. 4.4 months (+/- RT)

B

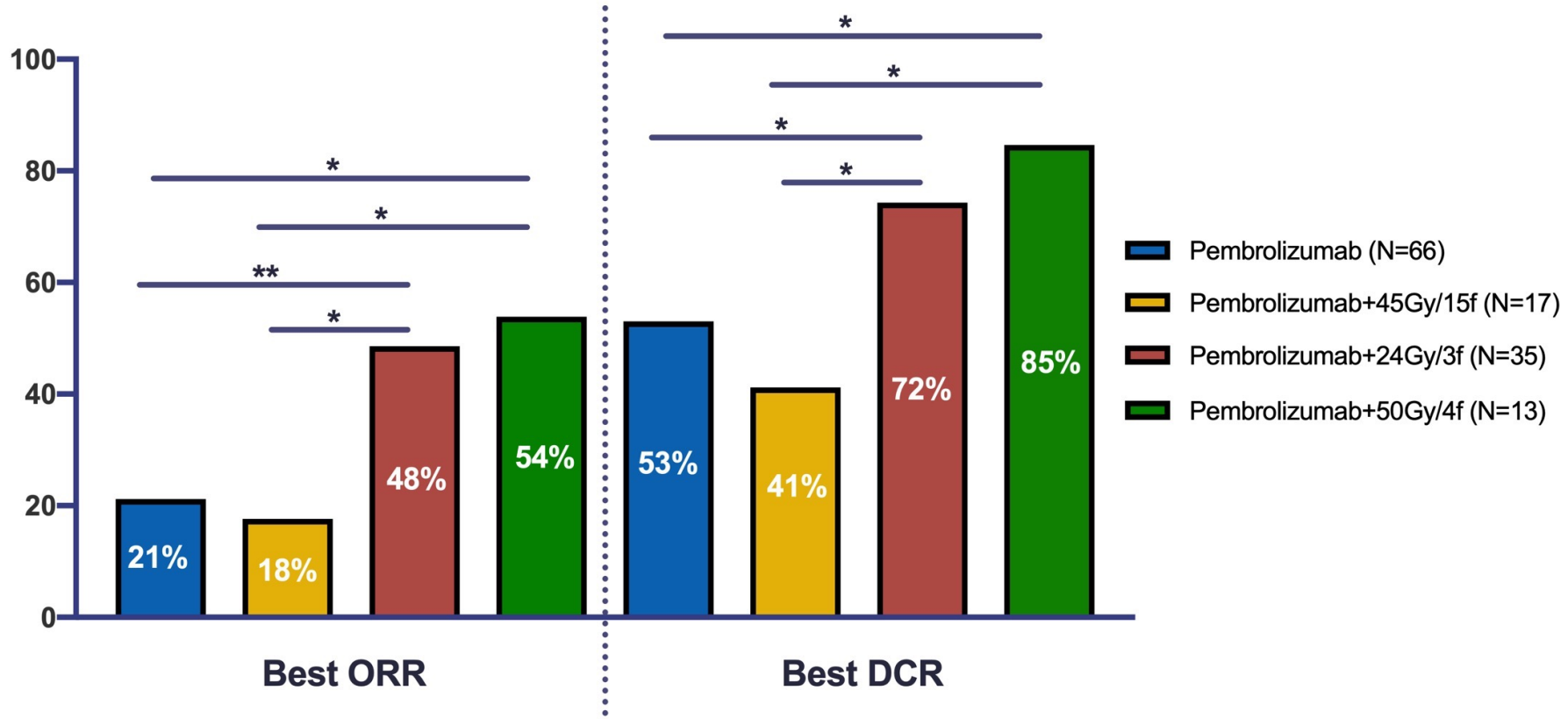


No. at risk					
Pembrolizuamb alone	66	29	18	6	0
Pembrolizumab+RT	65	39	24	7	0

OS 19.2 vs. 9.2 months(+/- RT)

Ablative RT doses achieved better outcomes

Figure. 4

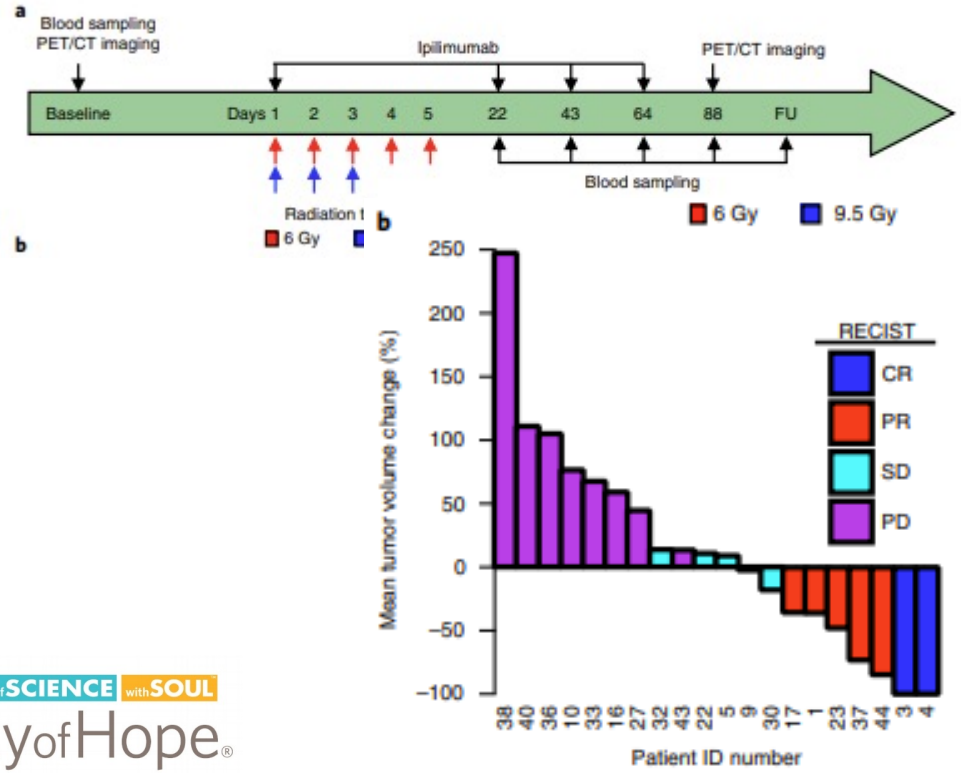


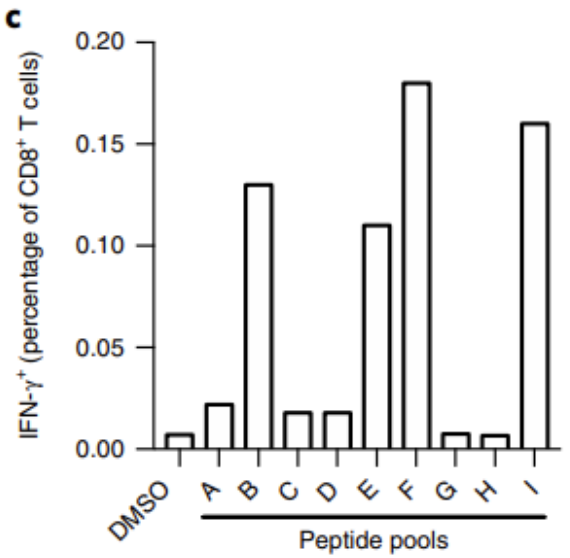
Radiotherapy and ICI Synergy via Immunoediting

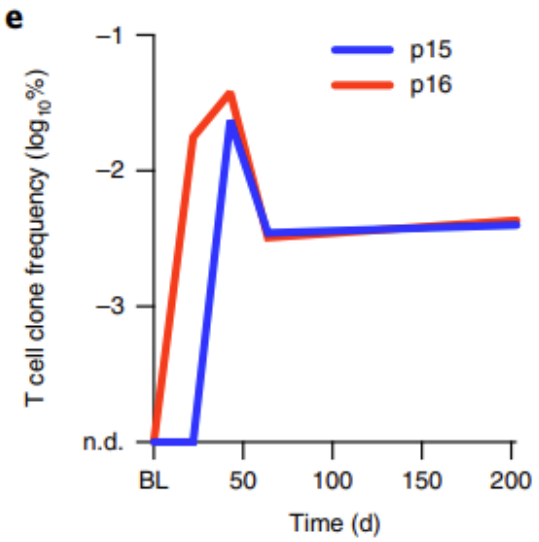
nature medicine
LETTERS
https://doi.org/10.1038/s41591-018-0232-2

Radiotherapy induces responses of lung cancer to CTLA-4 blockade

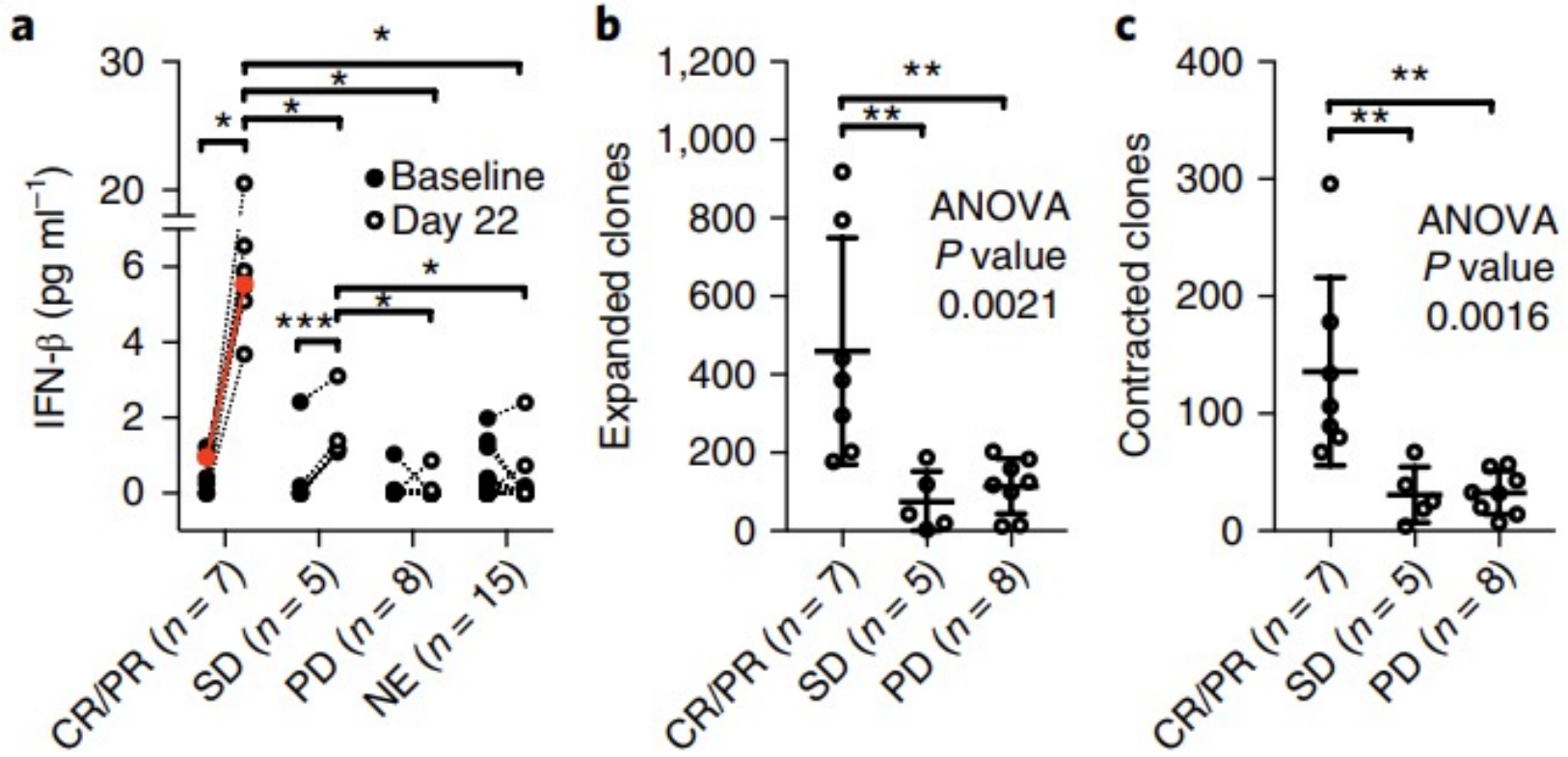
Silvia C. Formenti[1,15]*, Nils-Petter Rudqvist[1,15], Encouse Golden[1,14,15], Benjamin Cooper[2], Erik Wennerberg[1], Claire Lhuillier[1], Claire Vanpouille-Box[1], Kent Friedman[3], Lucas Ferrari de Andrade[4,5], Kai W. Wucherpfennig[4,5], Adriana Heguy[6,7], Naoko Imai[8], Sacha Gnjatic[8], Ryan O. Emerson[9], Xi Kathy Zhou[10], Tuo Zhang[11], Abraham Chachoua[12] and Sandra Demaria[1,13]*





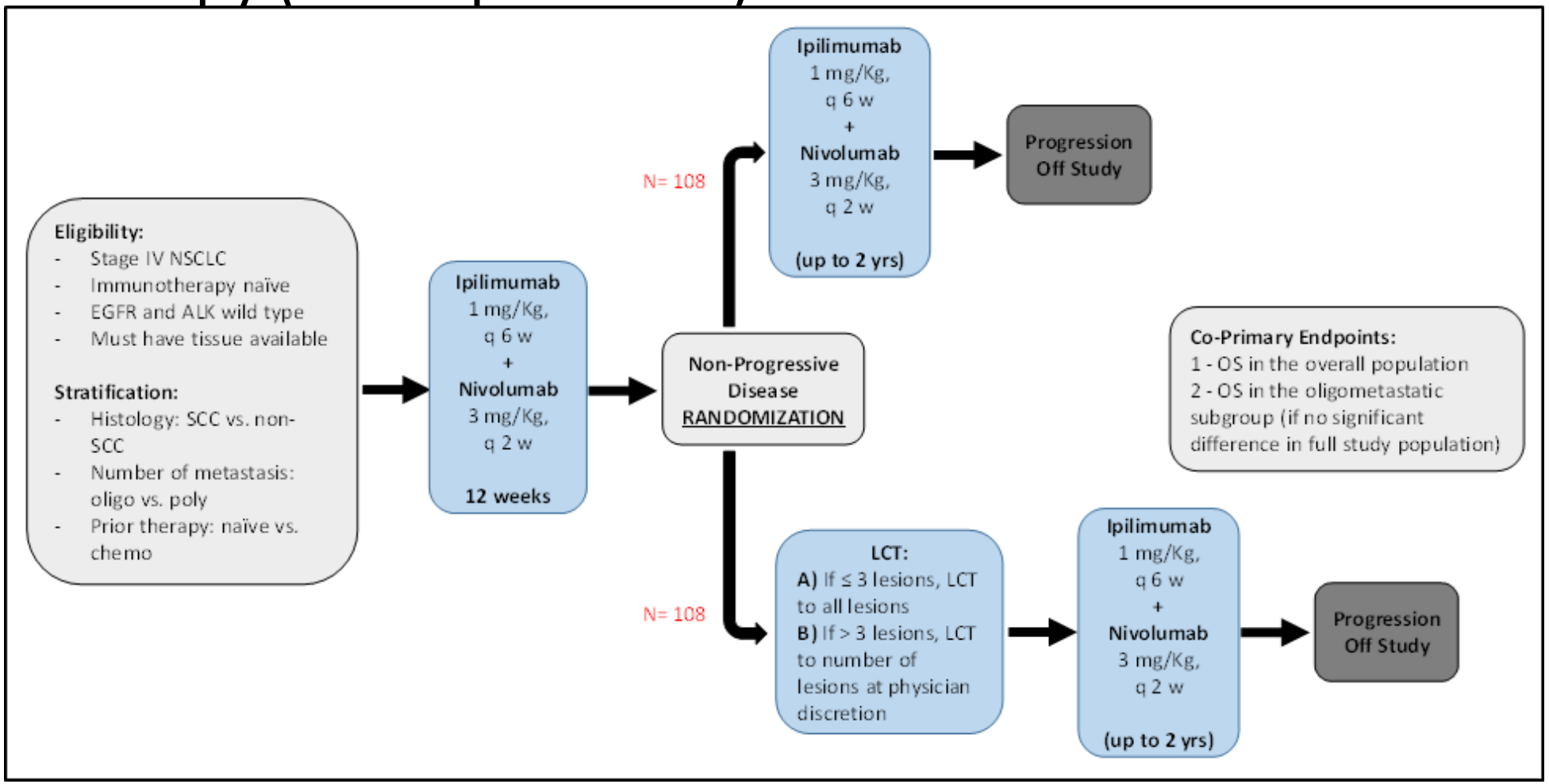


CD8 T cells in patients with CR/PR are active



Increase in interferon-beta and TCR clonal dynamics predict response to treatment

MDACC LONESTAR Trial - Local consolidative therapy after immunotherapy (BMS Sponsored)

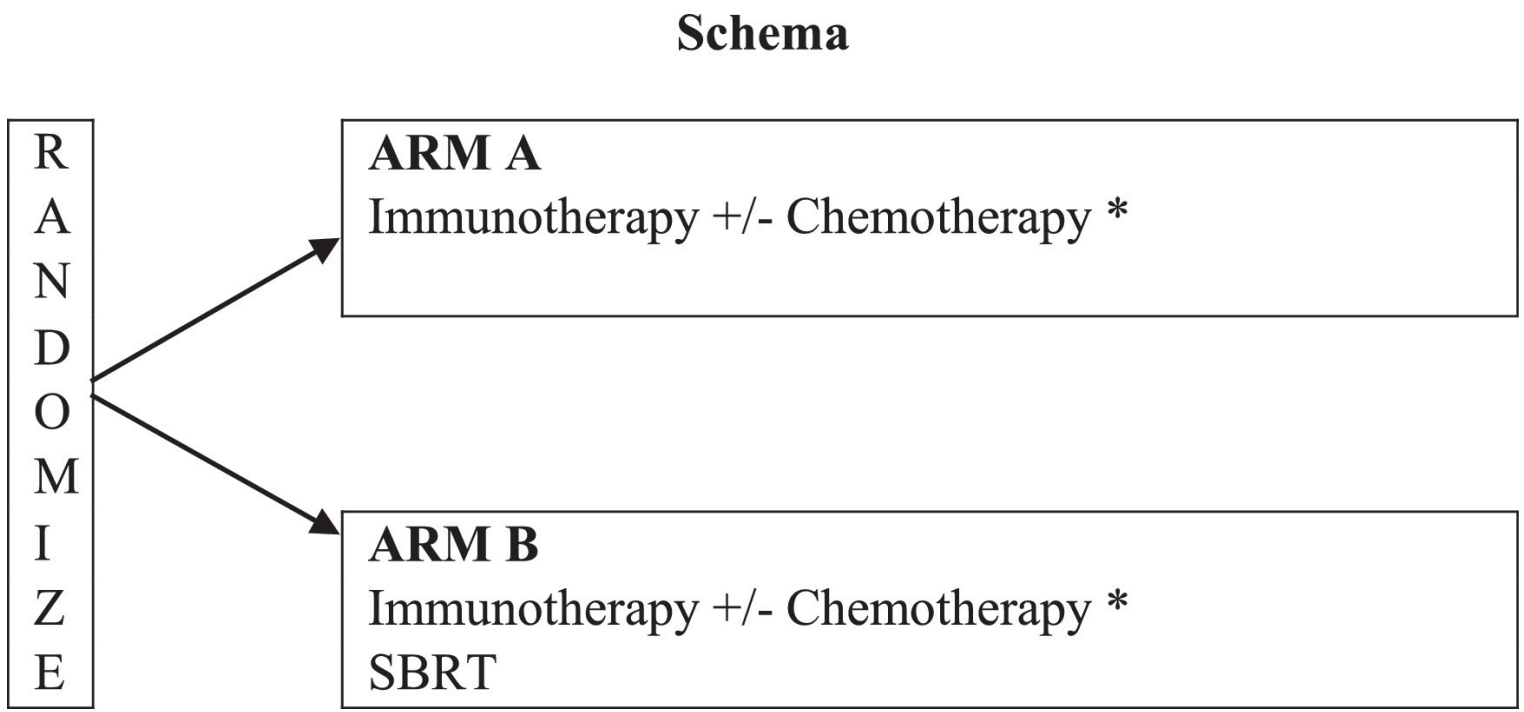


PI: John Heymach, MD PhD
Co-PI: Saumil Gandhi, MD PhD
Stephen Swisher, MD

the MIRACLE of SCIENCE with SOUL City of Hope

City of Hope ORANGE COUNTY

Alliance/SWOG A082002 for PDL1-negative stage IV NSCLC



Frontline metastatic NSCLC
PDL1 negative
SBRT 8 Gy x 3

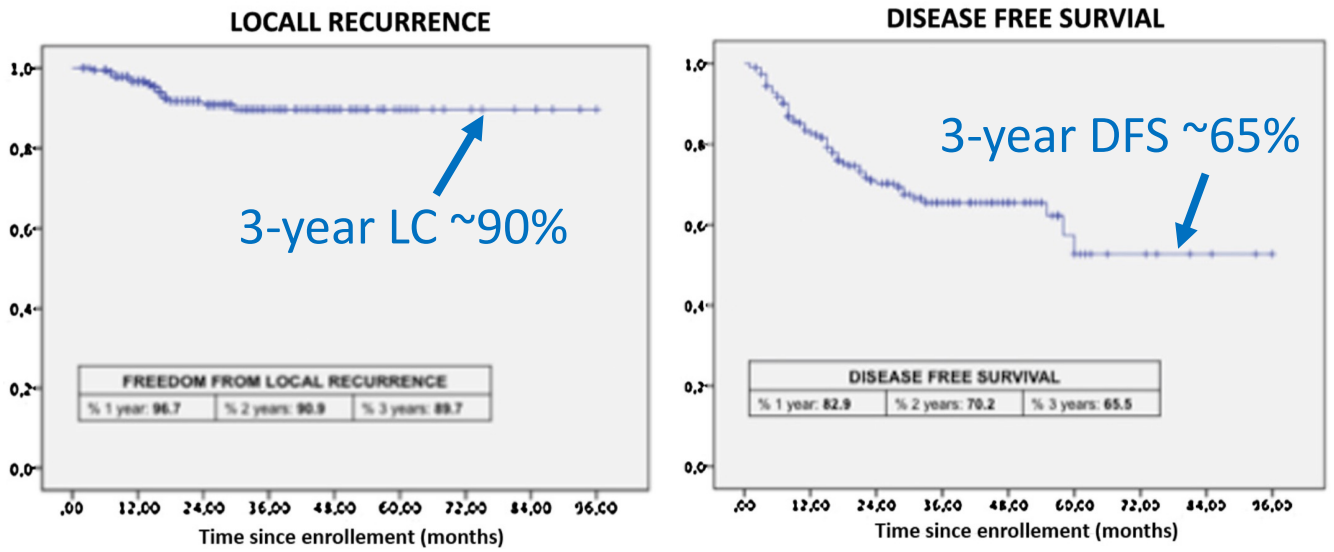
What about in earlier stage disease? Stage I NSCLC

RTOG 0236 5-year update

- Regional recurrences
  - 7 patients with regional failure
    - 2 patients in the original report
    - 5 year local-regional recurrence rate 38%
- Distant recurrences
    - 15 patients with disseminated failure
    - 5-year distant recurrence rate 31%
- 5-year disease-free survival only 26%

Timmerman R, ASTRO 2014

Multicenter Italian Study (n= 196)

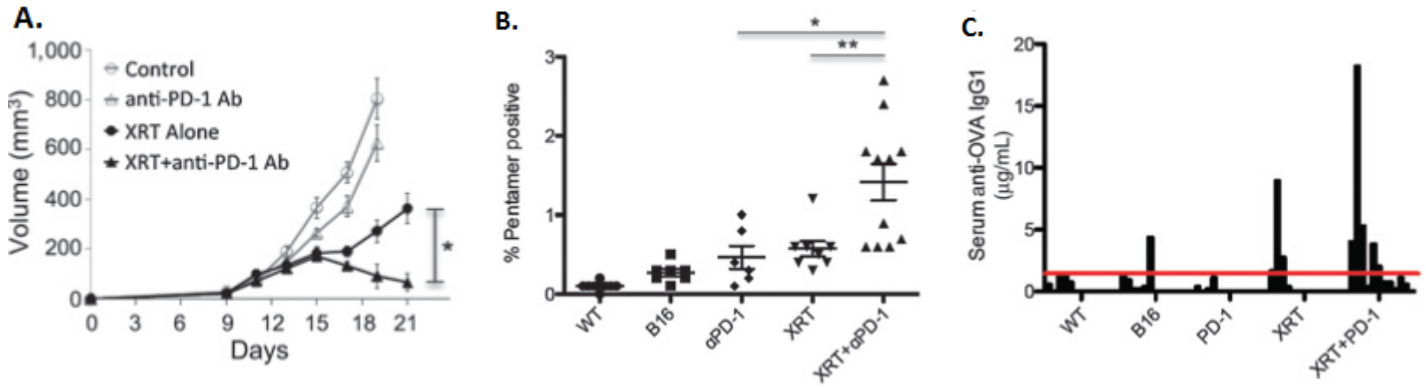


Ricardi U et al., Lung Cancer 2014

Combining SABR and checkpoint inhibition

- Rationale for combining SABR and anti-PDL1 therapy for early-stage NSCLC
  - No current proven role for adjuvant therapy in early-stage NSCLC after surgery or SABR except for EGFR+ patients after surgery
  - Anti-PD-1 therapies have shown excellent activity in advanced NSCLC with less toxicity than standard chemotherapy
  - High rates of out-of-field failure after lung SABR for early-stage NSCLC and anti-PD therapies in combination with SABR may be effective at sterilizing subclinical disease and therefore increase cure rates

Stereotactic XRT combined with anti PD-1 significantly improves tumor control and enhances development of T cell and B cell antitumor responses

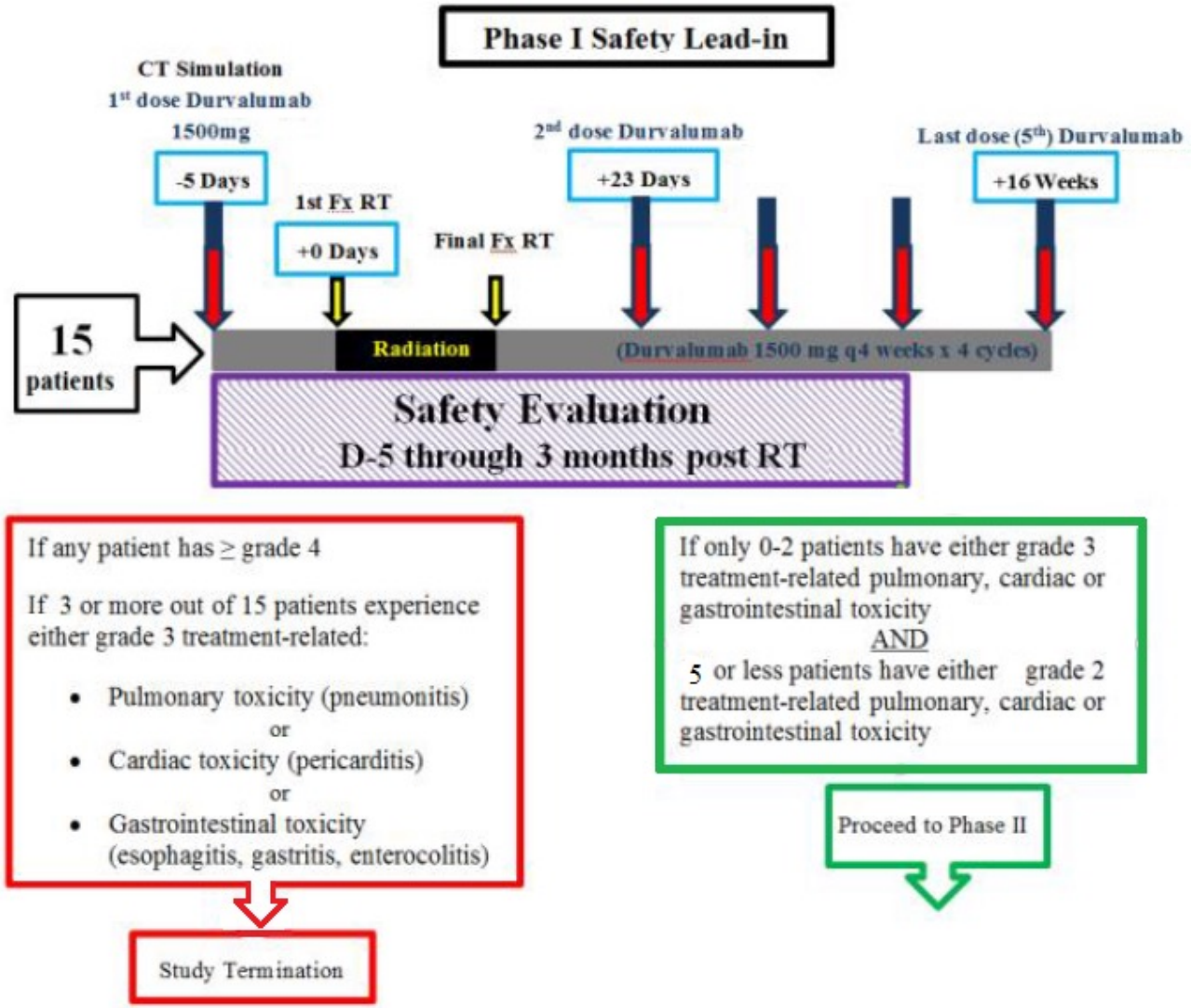


Mice inoculated with tumor cells and irradiated (12Gy x1) on D12 and/or injection with anti-PD-1 antibodies starting 1 day before RT then Q3 days

A. Tumor volumes
B. Antigen-specific CD8 T- cells
C. Concentration of antigen-specific IgG1 in sera

Sharabi, A, Cancer Immunology Research 2014

iSABR - Phase I Safety Lead in: SABR with Durvalumab



Eligibility

- Biopsy proven, stage I, IIA (AJCC 7th)
- Medically inoperable, refuse surgery
- ECOG 0-1
- Adequate organ/marrow function

UCLA Health

University of Colorado Hospital
UNIVERSITY OF COLORADO HEALTH

Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

the MIRACLE of SCIENCE with SOUL
City of Hope

City of Hope
ORANGE COUNTY

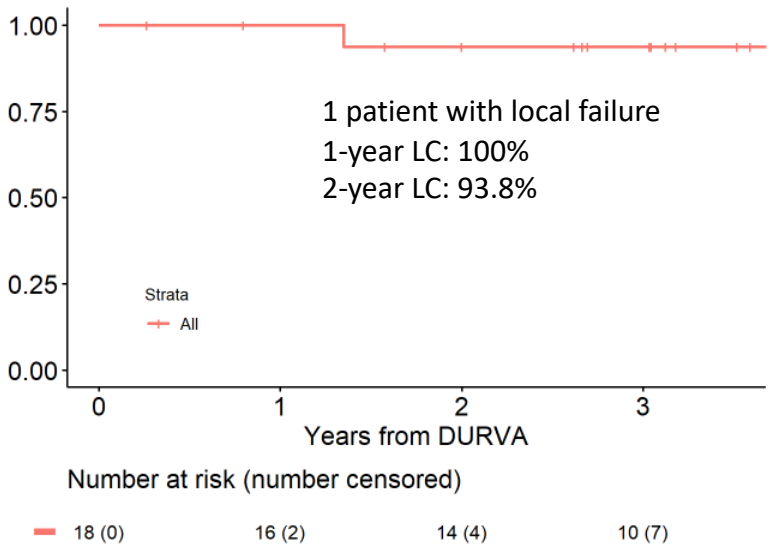
Patient characteristics

Patients	N = 18	
Age		79
	Range	57 – 96
Gender	Male.	11 (61)
	Female	7 (39)
Histology	Adenocarcinoma	18 (64)
	Squamous	10 (36)
Smoking status	Yes	16 (89)
	No	2 (11)
Stage	T1	13 (72)
	T2	5 (28)
GTV size		7.9 cc
	Range	0.6 – 270 cc

Median follow-up: 3 yrs.
Range: 0.7 – 4.7 yrs.

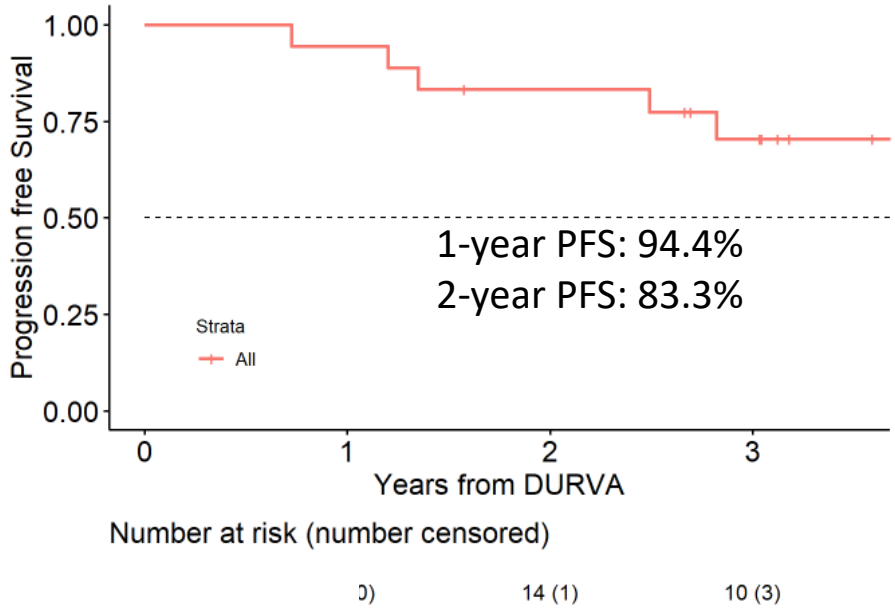
Outcomes

Local Control



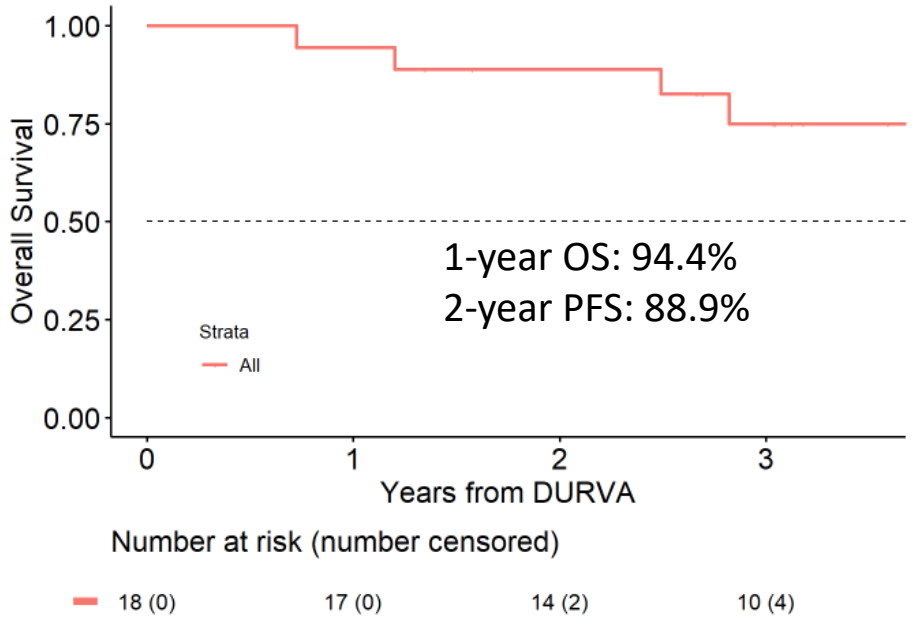
1 patient with local failure
1-year LC: 100%
2-year LC: 93.8%

PFS



1-year PFS: 94.4%
2-year PFS: 83.3%

OS



1-year OS: 94.4%
2-year PFS: 88.9%

On-going Phase II/III trials

NCT number	Title	Sponsor/ Recruitment	Study endpoint	Phase
NCT03110978	I-SABR: Clinical Trial Comparing Immunotherapy Plus Stereotactic Ablative Radiotherapy (I-SABR) Versus SABR Alone for Stage I, Selected Stage IIa or Isolated Lung Parenchymal Recurrent Non-Small Cell Lung Cancer (nivolumab)	MD Anderson; Accrual completed: N=140	EFS, OS, toxicity	II
NCT03833154	PACIFIC 4/RTOG 3515: Durvalumab vs Placebo With Stereotactic Body Radiation Therapy in Early Stage Unresected Non-small Cell Lung Cancer (NSCLC) Patients/Osimertinib Following SBRT in Patients With Early Stage Unresected NSCLC Harboring an EGFR Mutation	N=733	PFS, OS, LCSS	III
NCT04214262	SWOG S1914: A Randomized Phase III Trial of Induction/Consolidation Atezolizumab (NSC #783608) + SBRT versus SBRT Alone in High Risk, Early Stage NSCLC	NCI; N=480	OS, PFS, DF, LRF, LF, Toxicity	III
NCT03924869	MK-3475-867/KEYNOTE-867: Efficacy and Safety Study of Stereotactic Body Radiotherapy (SBRT) With or Without Pembrolizumab (MK-3475) in Adults with Unresected Stage I or II Non-Small Cell Lung Cancer (NSCLC)	N=530	EFS, OS, TTDM, AE, QOL	III

Radiotherapy and Immunotherapy Combinations

- Radiotherapy can potentially be synergistic with immunotherapy by several mechanism including releasing antigens, cytoreduce large bulky tumors, and acting as a in-situ vaccine

- The optimal radiotherapy dose, site of radiotherapy, sequence, schedule, and delivery techniques are yet to be determined and optimized

- Many ongoing trials addressing these questions in various disease sites and indications