Radiation Induced Immune Responses in NSCLC

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Trials using IO (or chemo+IO) with RT in NSCLC

Reported Randomized Phase II or III Trials

• Early-stage NSCLC:	Chang et. Al
• Operable Locally-advanced NSCLC:	Altorki et. Al
• Locally-advanced Unresectable NSCLC:	Antonia et. Al Spigel et al
• Oligometastatic NCSLC:	Theelen et. al Welsh et. Al

Stereotactic ablative radiotherapy with or without immunotherapy for early-stage or isolated lung parenchymal recurrent node-negative non-small-cell lung cancer: an open-label, randomised, phase 2 trial

Joe Y Chang, Steven H Lin, Wenli Dong, Zhongxing Liao, Saumil J Gandhi, Carl M Gay, Jianjun Zhang, Stephen G Chun, Yasir Y Elamin, Frank V Fossella, George Blumenschein, Tina Cascone, Xiuning Le, Jenny V Pozadzides, Anne Tsao, Vivek Verma, James W Welsh, Aileen B Chen, Mehmet Altan, Reza J Mehran, Ara A Vaporciyan, Stephen G Swisher, Peter A Balter, Junya Fujimoto, Ignacio I Wistuba, Lei Feng, J Jack Lee, John V Heymach

- N= 156 patients (141 receiving assigned therapy) with treatment naïve Stage I-II NSCLC (<7cm, N0) or isolated recurrence (<7cm)
- 1:1 randomization to SBRT +/- nivolumab (480 mg once every 4 weeks) x 4 cycles starting within 36 hours of 1st SBRT
- Primary endpoint: 4-year event-free survival
- 50Gy/4 fractions (84% & 89%) or 70 Gy/10 fractions (16% & 11%)

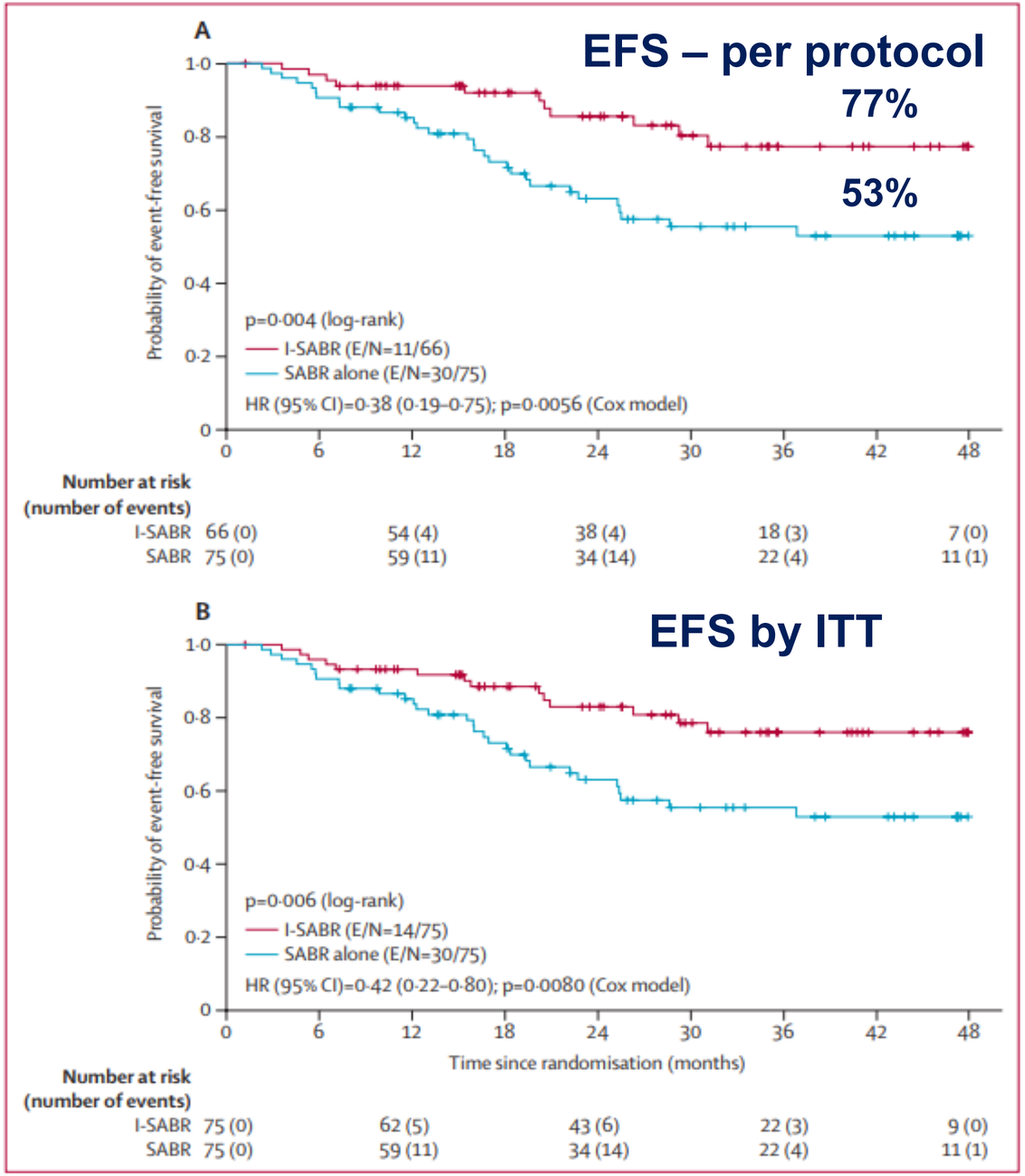


Figure 2: **Kaplan-Meier plot of event-free survival**
(A) Event-free survival for the randomly assigned per-protocol population (n=141). (B) Event-free survival for the randomly assigned intention-to-treat population (n=156). E/N=events/number of participants. HR=hazard ratio. I-SABR=stereotactic ablative radiotherapy with immunotherapy. SABR=stereotactic ablative radiotherapy.

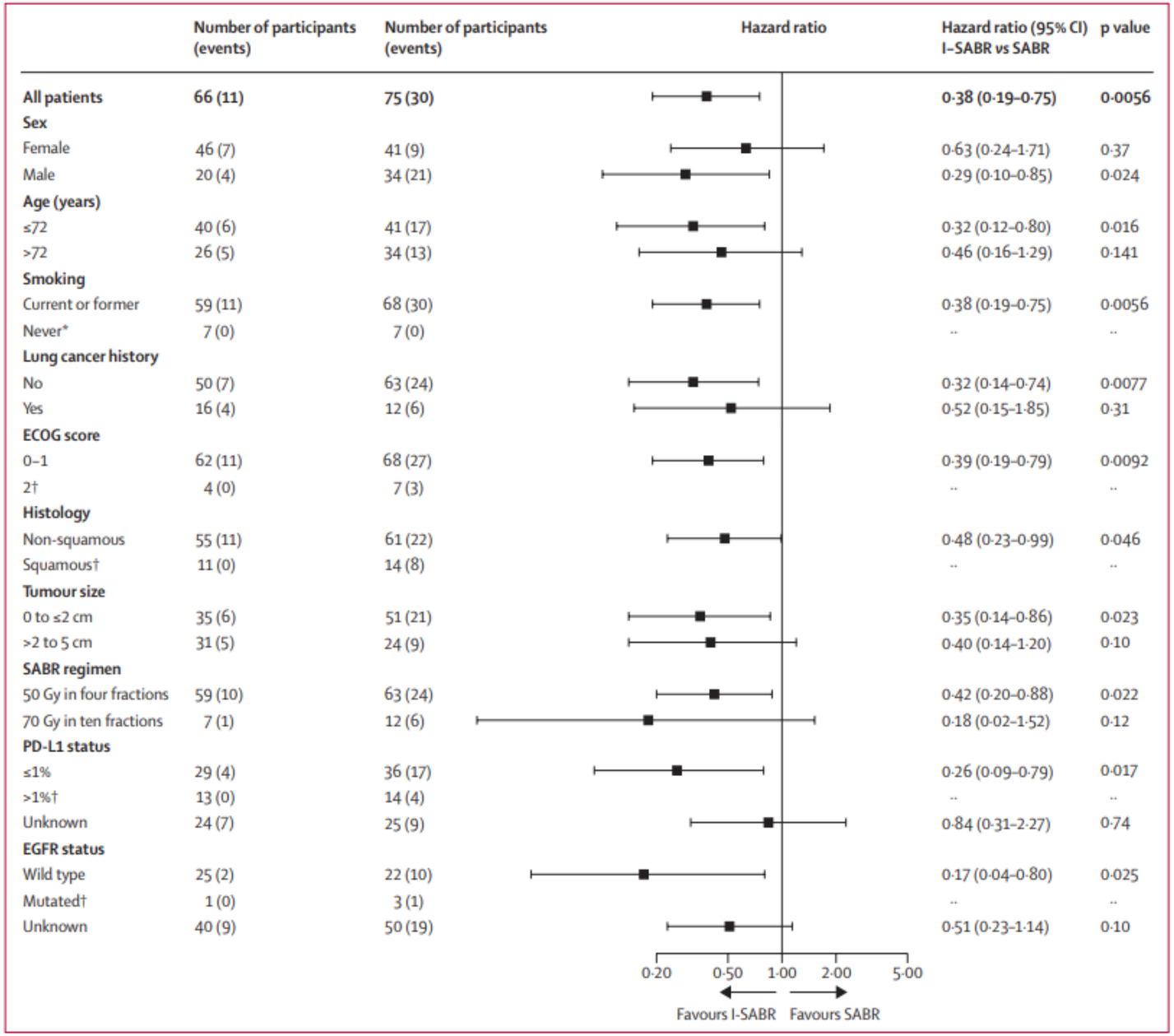
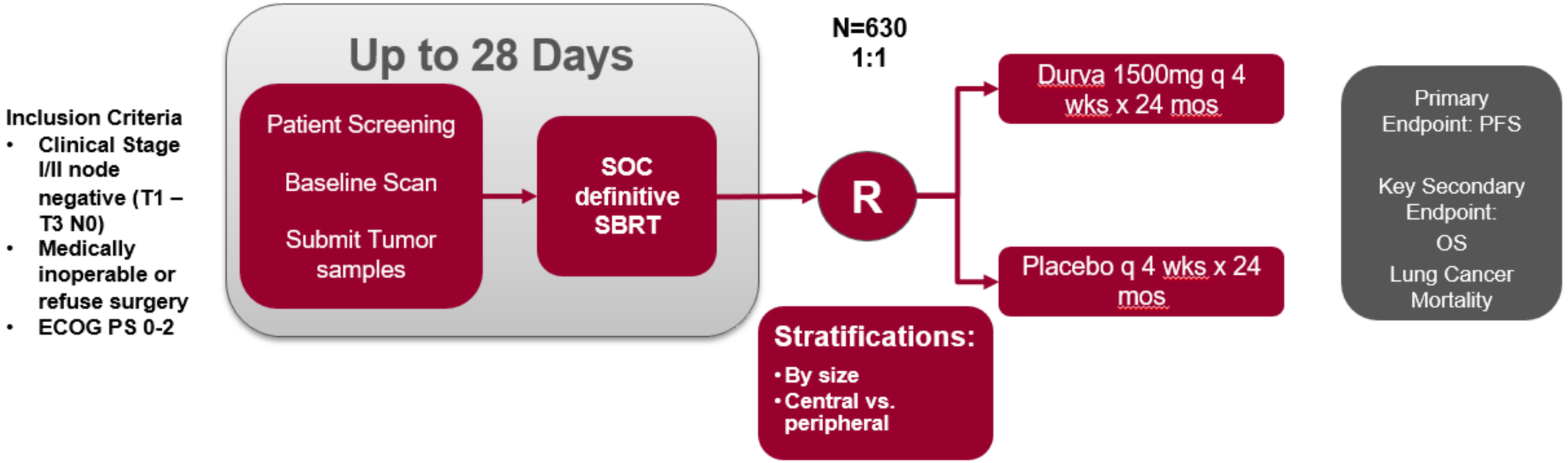


Figure 3: **Forest plot of I-SABR versus SABR for event-free survival in subgroup analysis**

Role for Adjuvant Therapy after SBRT

PACIFIC 4 / RTOG 3515 Schema

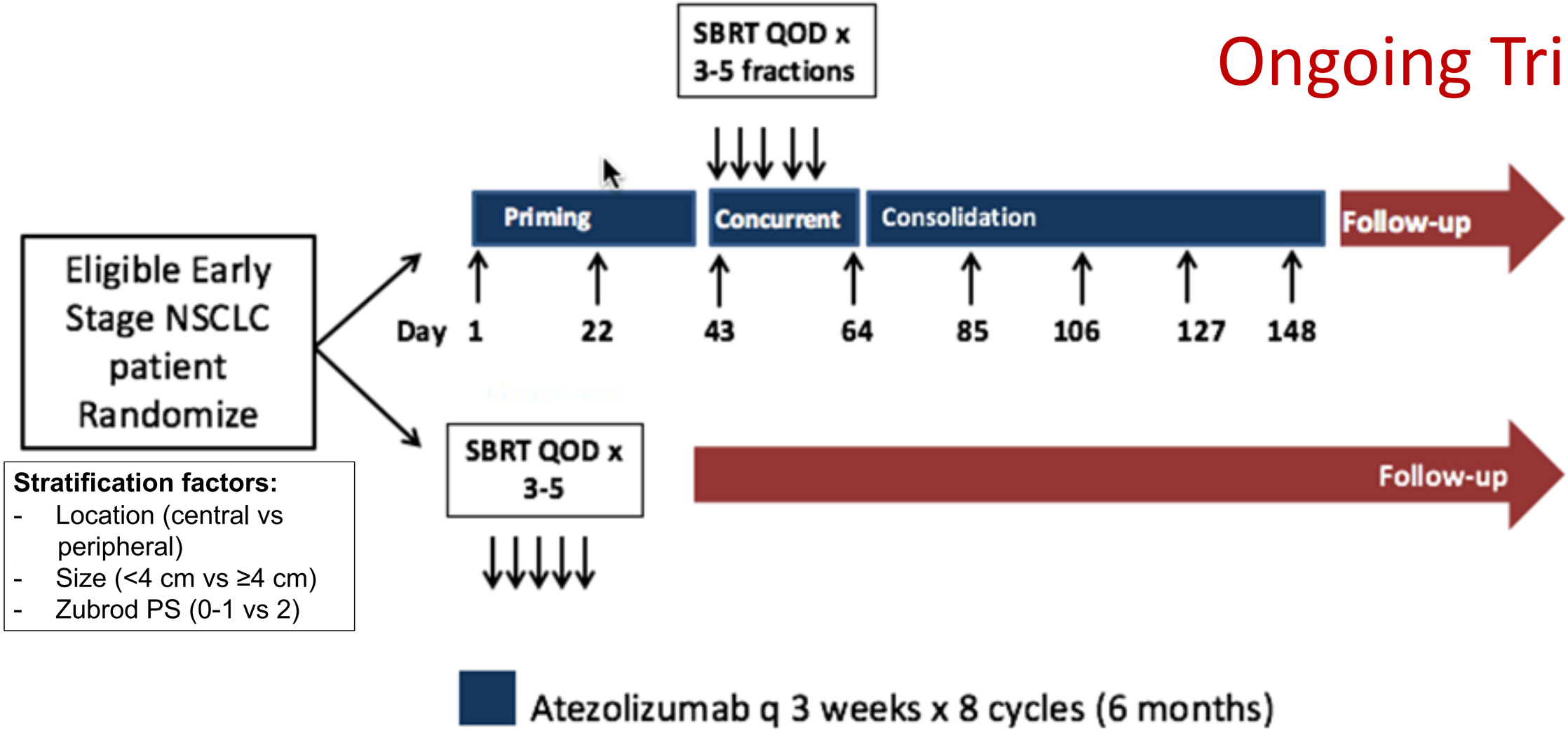


Ongoing Trial

PI: Dr. Clifford Robinson

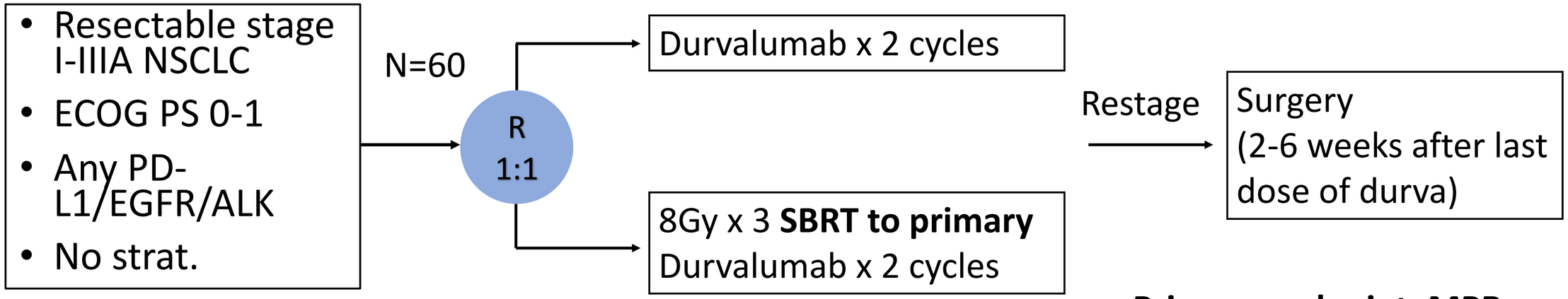
SWOG/NRG S1914 Schema – Early-stage NSCLC SBRT +/- Neoadjuvant Atezo

Ongoing Trial



Stratification factors:
- Location (central vs peripheral)
- Size (<4 cm vs ≥4 cm)
- Zubrod PS (0-1 vs 2)

Neoadjuvant durvalumab with or without stereotactic body radiotherapy in patients with early-stage non-small-cell lung cancer: a single-centre, randomised phase 2 trial

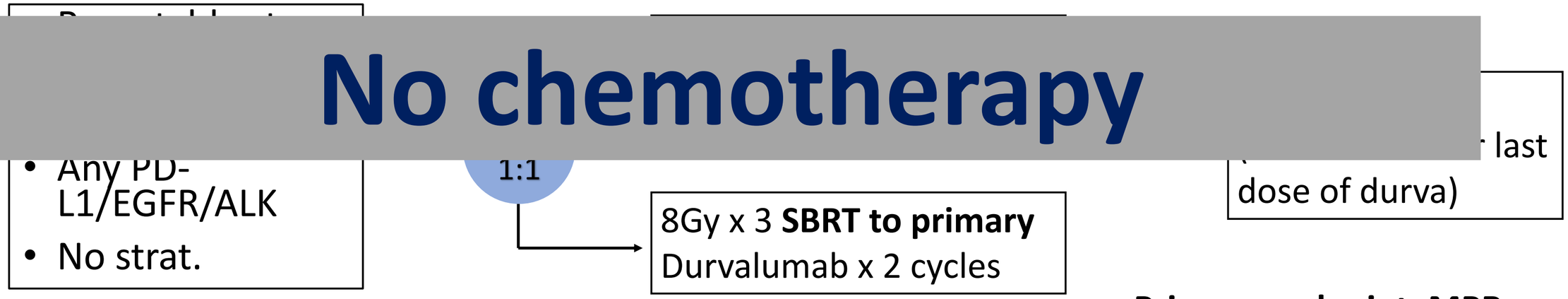


Primary endpoint: MPR (major pathologic response)

Endpoint	Arm A (Durva x2)	Arm B (Durva + RT)
MPR	6.7%	53.5%
pCR	0%	26.7%
Nodal downstaging	14% (1/7)	66% (4/6)

Altorki et al. *Lancet Oncol* 2021 Jun;22(6):824-835

Neoadjuvant durvalumab with or without stereotactic body radiotherapy in patients with early-stage non-small-cell lung cancer: a single-centre, randomised phase 2 trial



No chemotherapy

No lymph node irradiation

MPR	6.7%	53.5%
pCR	0%	26.7%
Nodal downstaging	14% (1/7)	66% (4/6)

Altorki et al. *Lancet Oncol* 2021 Jun;22(6):824-835

Patient Demographics – Altorki et al

	Durvalumab monotherapy group (n=30)	Durvalumab plus SBRT group (n=30)
Age, years	71·0 (65·2–75·0)	70·0 (64·2–74·0)
Sex		
Male	16 (53%)	15 (50%)
Female	14 (47%)	15 (50%)
ECOG performance status		
0	21 (70%)	23 (77%)
1	9 (30%)	7 (23%)
Smoking status		
Current	7 (23%)	10 (33%)
Former	17 (57%)	16 (53%)
Never	6 (20%)	4 (13%)
Clinical stage		
IA	3 (10%)	1 (3%)
IB	8 (27%)	7 (23%)
IIA	1 (3%)	6 (20%)
IIB	4 (13%)	4 (13%)
IIIA	14 (47%)	12 (40%)
Invasive mediastinal staging	12 (40%)	13 (43%)
Cell type		
Adenocarcinoma	16 (53%)	18 (60%)
Squamous	11 (37%)	12 (40%)
Sarcomatoid	1 (3%)	0
Not otherwise specified	2 (7%)	0
PD-L1 expression status		
≥1%	13 (43%)	23 (77%)
<1%	15 (50%)	6 (20%)
Unknown	2 (7%)	1 (3%)
EGFR mutation		
Positive	5 (17%)	7 (23%)
Negative	25 (83%)	23 (77%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. SBRT=stereotactic body radiotherapy.

Table 1: **Demographic and disease characteristics**

Altorki et al Lancet Oncology 2021

Tumor Responses - Altorki et al

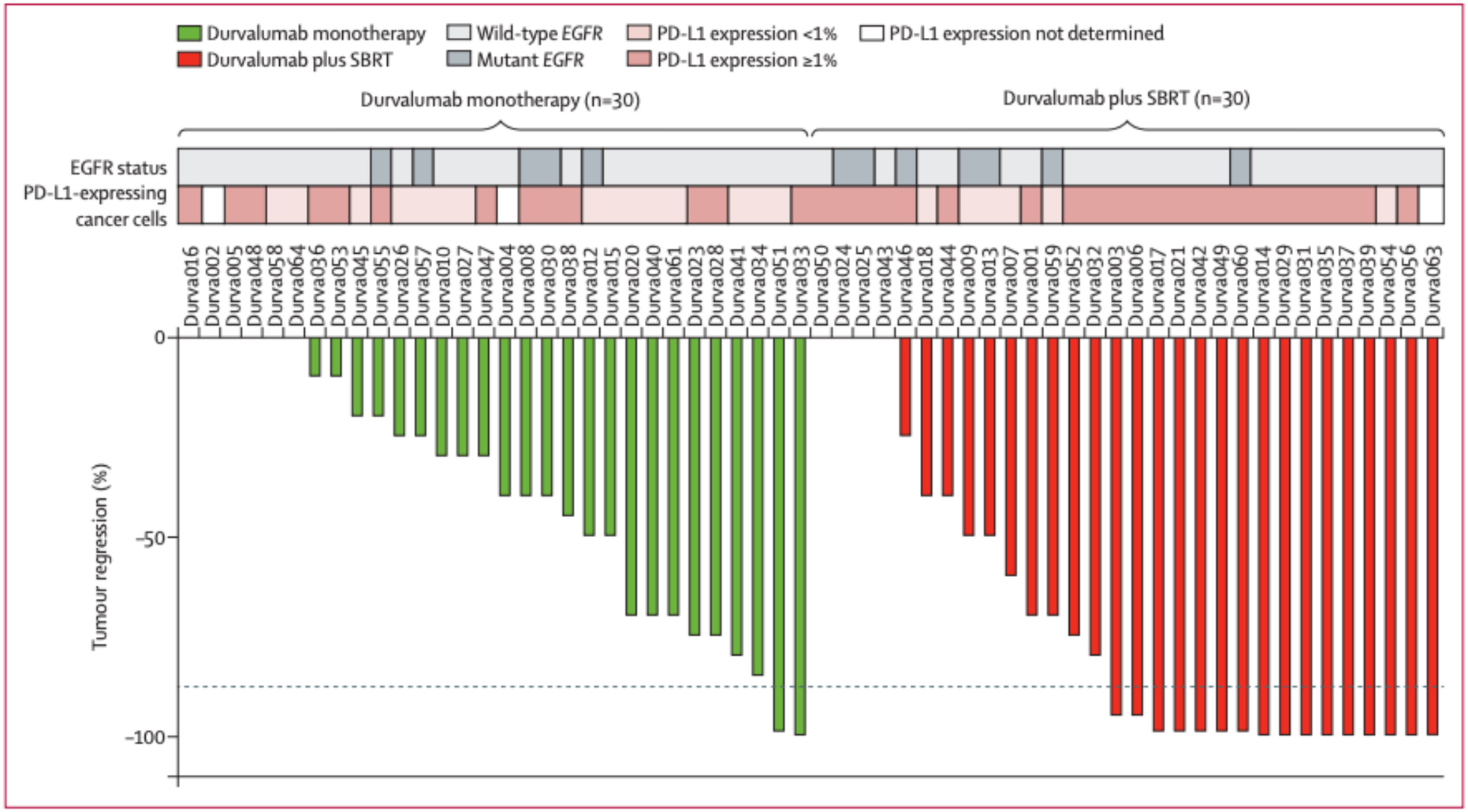


Figure 2: **Waterfall plot of tumour regression**

The dashed line indicates the threshold for achieving a major pathological response (≤10% viable tumour cells in the primary tumour). Tumour regression was determined as the negative of 100 minus the residual tumour percentage. EGFR status and percentage of PD-L1-positive cancer cells are reported. For the purpose of this analysis, tumours that progressed were assigned a value of 0 for tumour regression. One patient from each group (ie, Durva016 and Durva050) died before surgery and they were also assigned a value of 0 for tumour regression. SBRT=stereotactic body radiotherapy.

Ongoing Phase II Study – Brendan Stiles, MD

RECRUITING

An Open Label, Randomized Study of Neoadjuvant Nivolumab and Chemotherapy, With or Without Sub-ablative Stereotactic Body Radiation Therapy, for Resectable Stage IIA to IIIB Non-small Cell Lung Cancer (CA209-6K6)

ClinicalTrials.gov ID NCT05500092

Sponsor Montefiore Medical Center

Information provided by Montefiore Medical Center (Responsible Party)

Last Update Posted 2023-03-06

Study Overview

Brief Summary

An open label, randomized study of neoadjuvant nivolumab and chemotherapy, with or without sub-ablative stereotactic body radiation therapy, for resectable stage IIA to IIIB non-small cell lung cancer

Detailed Description

Primary Objective

- To compare the complete pathological response rate after 3 cycles of neoadjuvant nivolumab and platinum-based doublet chemotherapy vs. the same regimen with the addition of sub-ablative stereotactic radiation therapy (8 Gy x 3) directed at the primary lung tumor.

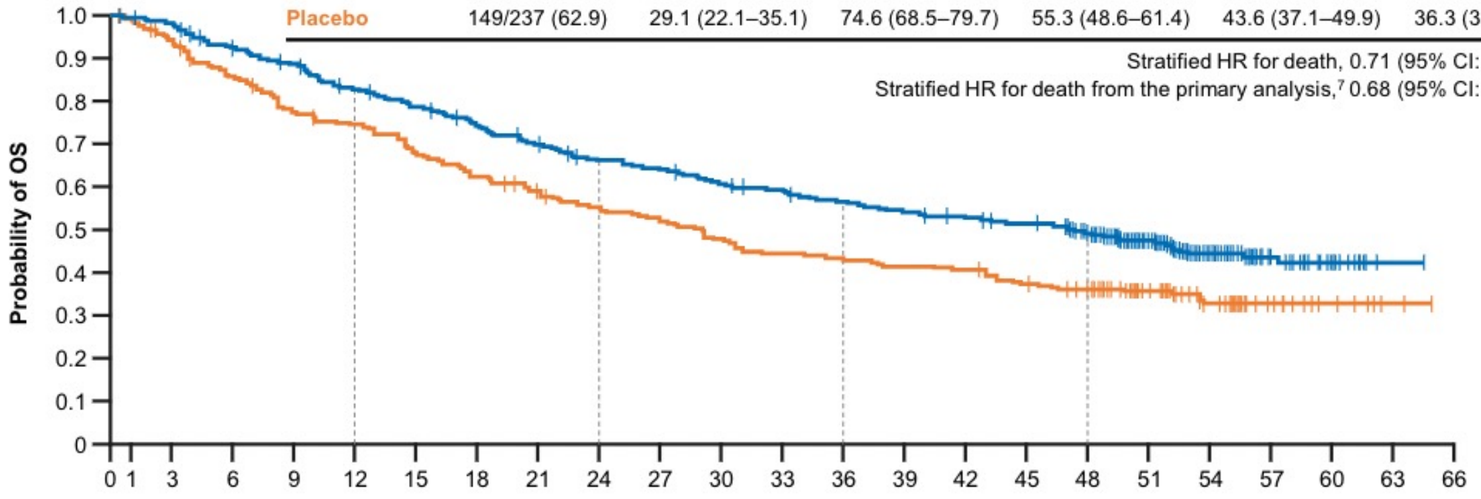
PACIFIC Trial: 5-Year Survival Outcomes With Durvalumab After Chemoradiotherapy in Stage III NSCLC

Median overall survival was 47.5 months (95% CI = 38.1–52.9 months) in the durvalumab group vs 29.1 months (95% CI = 22.1–35.1 months) in the placebo group (stratified HR = 0.72, 95% CI = 0.59–0.89).

A

	No. of events/ total no. of patients (%)	Median OS (95% CI), months	12-month OS rate (95% CI) %	24-month OS rate (95% CI) %	36-month OS rate (95% CI) %	48-month OS rate (95% CI) %
Durvalumab	247/476 (51.9)	47.5 (38.4–52.6)	83.1 (79.4–86.2)	66.3 (61.8–70.4)	56.7 (52.1–61.1)	49.6 (44.9–54.1)
Placebo	149/237 (62.9)	29.1 (22.1–35.1)	74.6 (68.5–79.7)	55.3 (48.6–61.4)	43.6 (37.1–49.9)	36.3 (30.1–42.6)

Stratified HR for death, 0.71 (95% CI: 0.57–0.88)
Stratified HR for death from the primary analysis,[7] 0.68 (95% CI: 0.53–0.87)



No. at risk

Durvalumab	476	464	431	414	385	364	343	319	299	290	274	265	252	241	235	225	195	138	75	36	15	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	75	53	29	15	7	2	0

Antonia et. al NEJM 2017; Spigel et al JCO 2022

Other studies testing concurrent CRT + IO for Unresectable LA-NSCLC

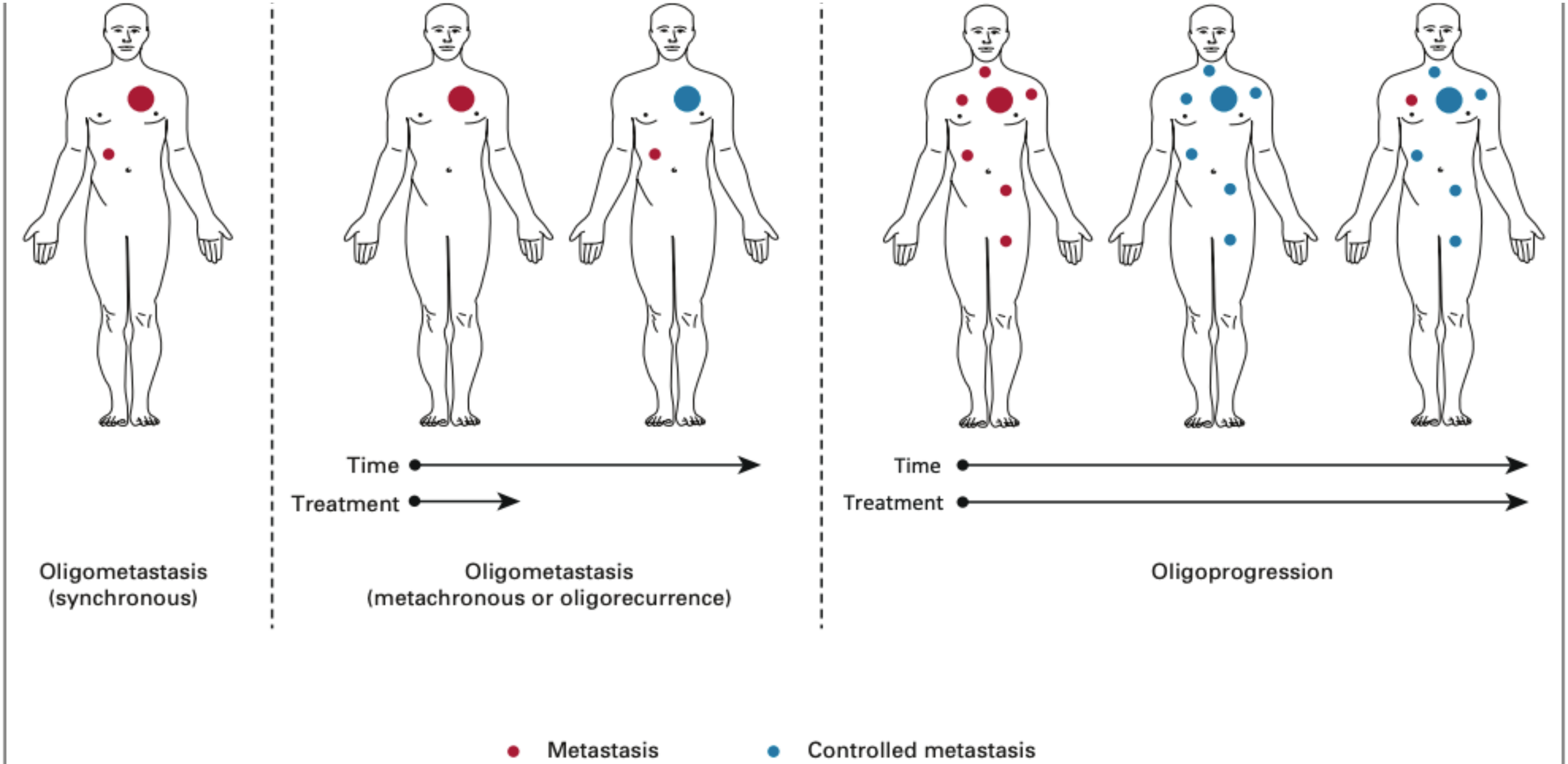
PACIFIC 2

Initial report pending

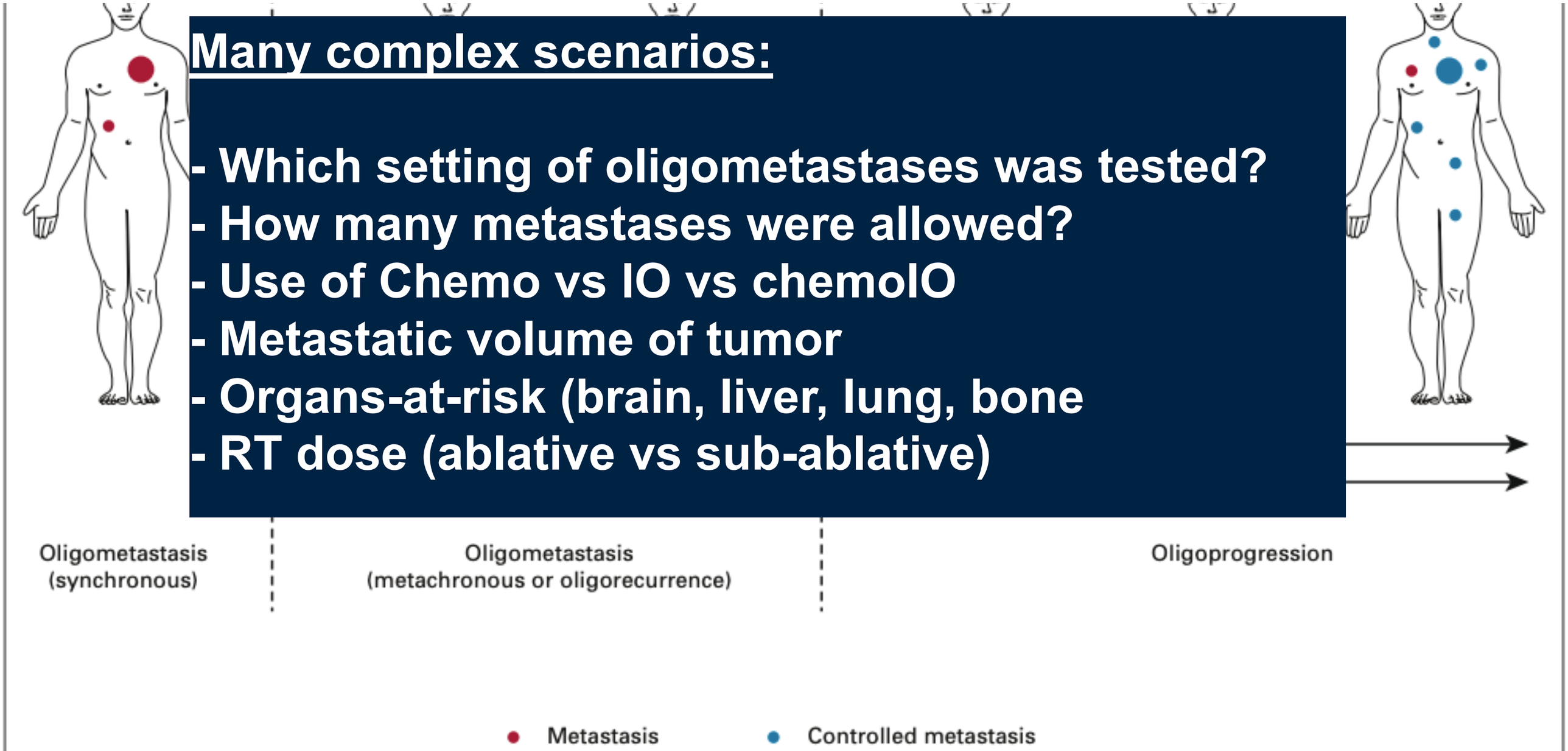
ECOG-ACRIN 5181

Accrual completed

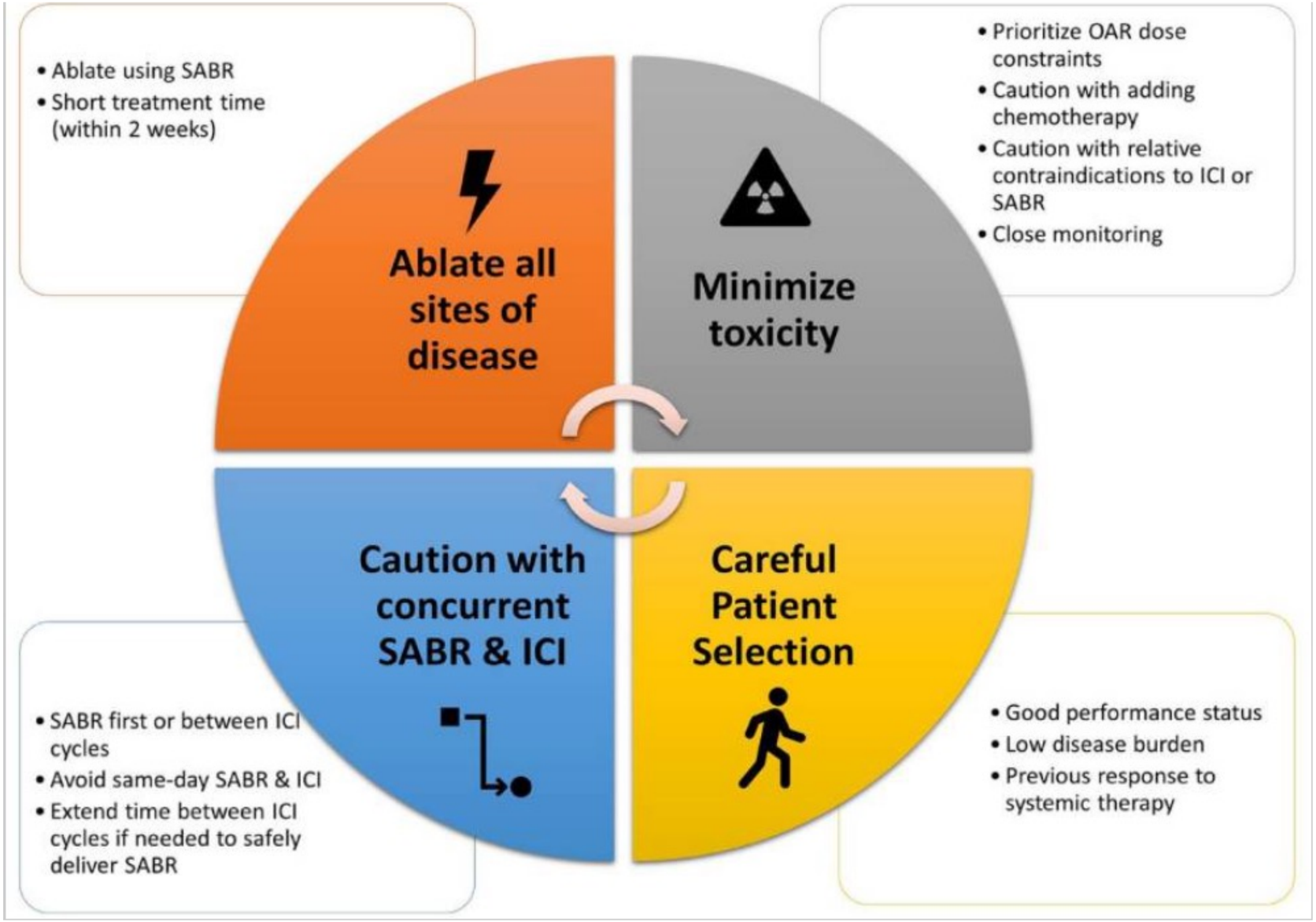
Oligometastases



Oligometastases



Oligometastatic NSCLC – SBRT principles



Original Investigation

FREE

July 11, 2019

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

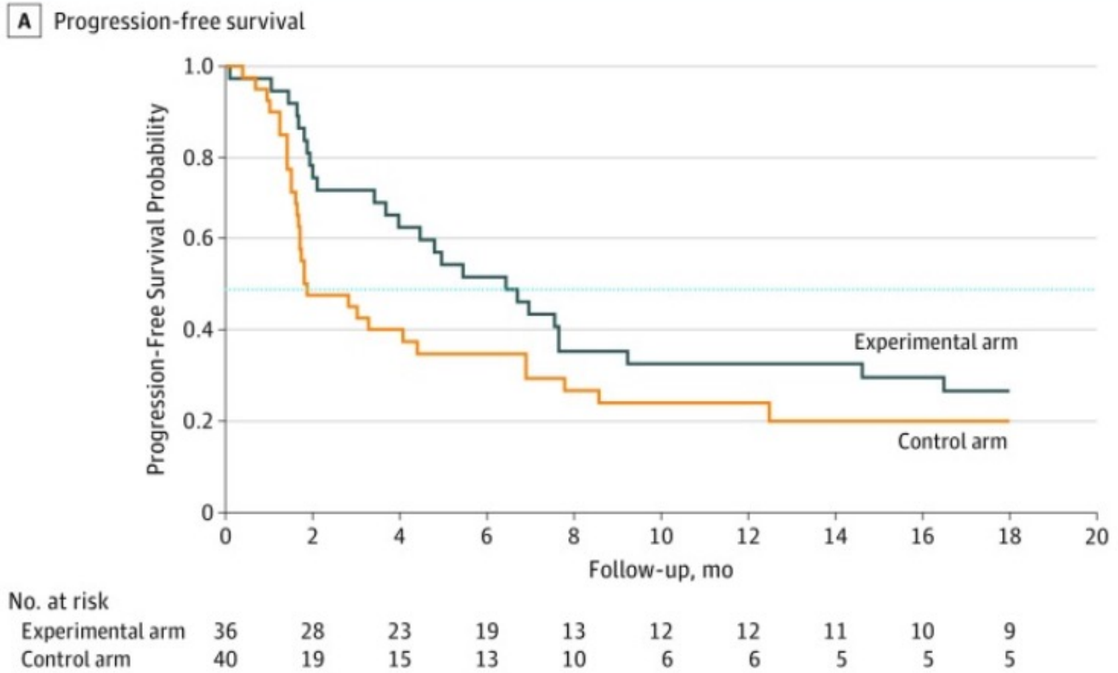
Willemijn S. M. E. Theelen, MD[1]; Heike M. U. Peulen, MD, PhD[2,3]; Ferry Lalezari, MD[4]; Vincent van der Noort, PhD[5]; Jeltje F. de Vries, PhD[5]; Joachim G. J. V. Aerts, MD, PhD[6]; Daphne W. Dumoulin, MD[6]; Idris Bahce, MD, PhD[7]; Anna-Larissa N. Niemeijer, MD[7]; Adrianus J. de Langen, MD, PhD[1]; Kim Monkhorst, MD, PhD[8]; Paul Baas, MD, PhD[1]

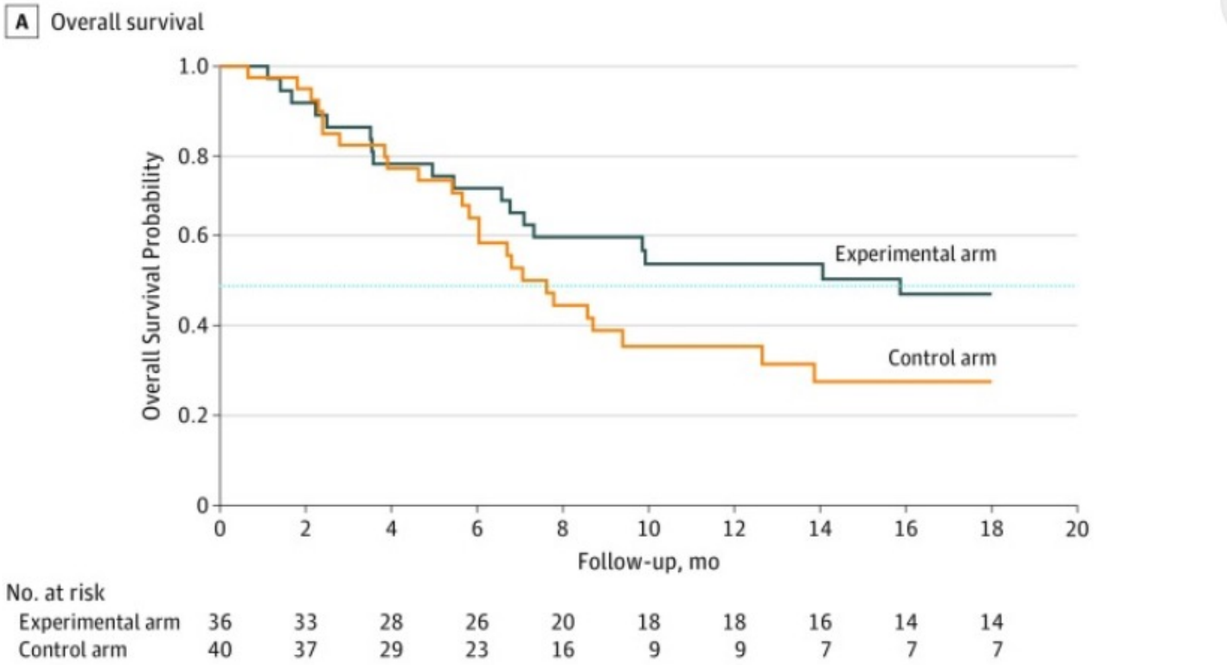
» Author Affiliations | Article Information

JAMA Oncol. 2019;5(9):1276-1282. doi:10.1001/jamaoncol.2019.1478

N= 76 patients with recurrent NSCLC at a single tumor site

RT dose was 3 x 8 Gy



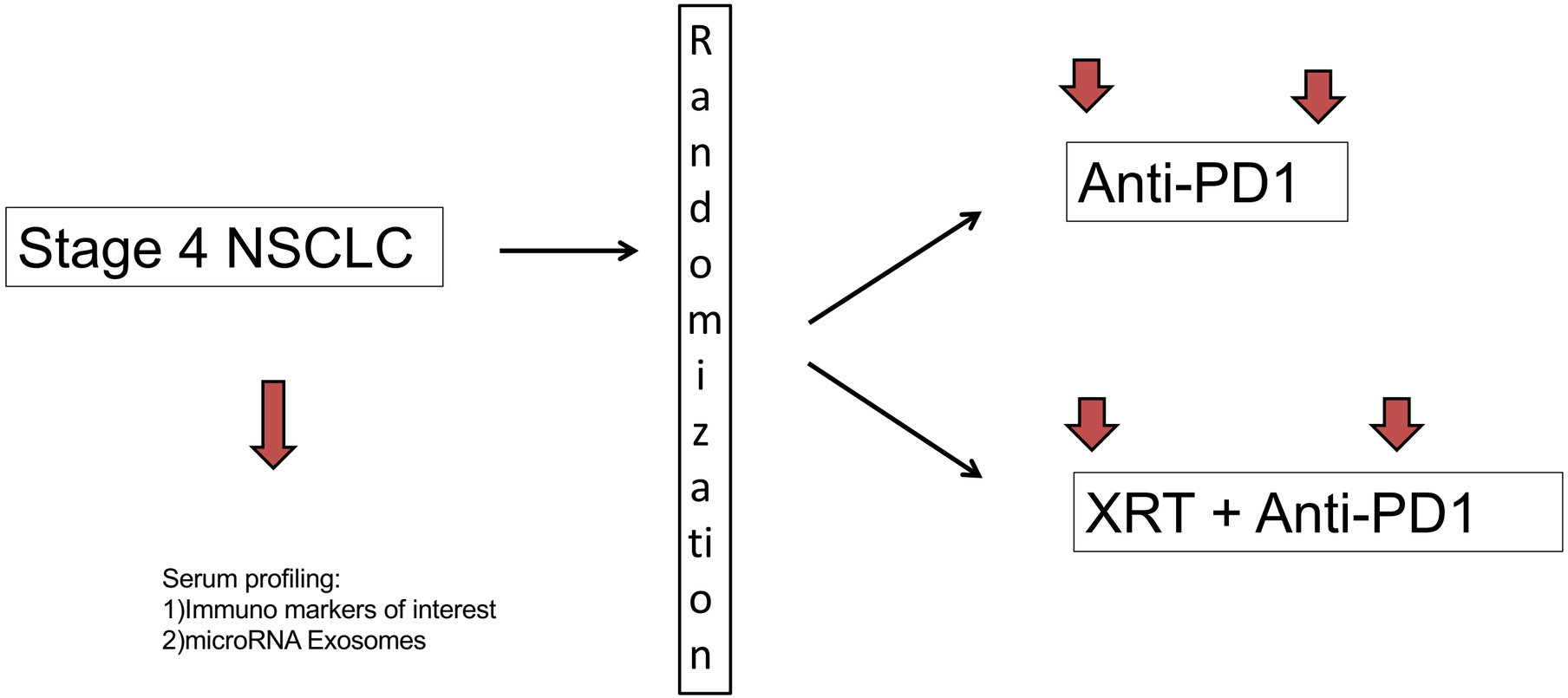


J Immunother Cancer. 2020; 8(2): e001001.
Published online 2020 Oct 13. doi: 10.1136/jitc-2020-001001
PMCID: PMC7555111
PMID: 33051340

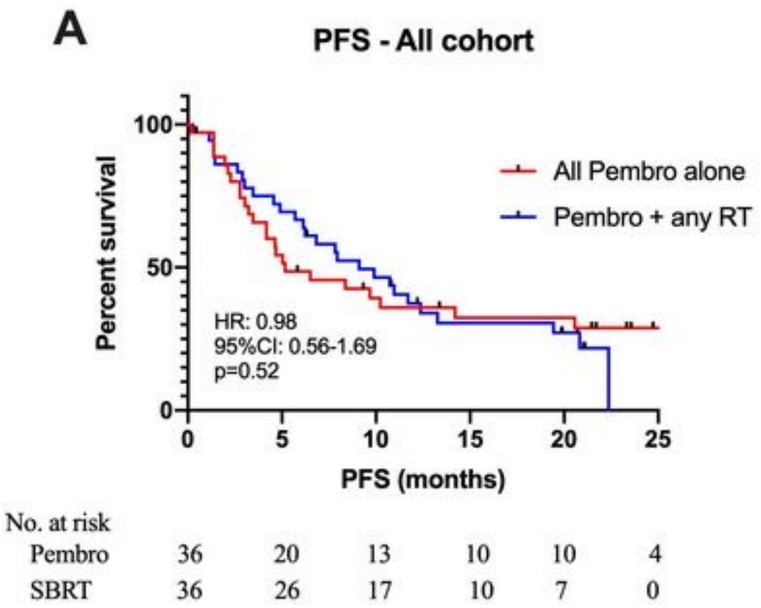
Original research

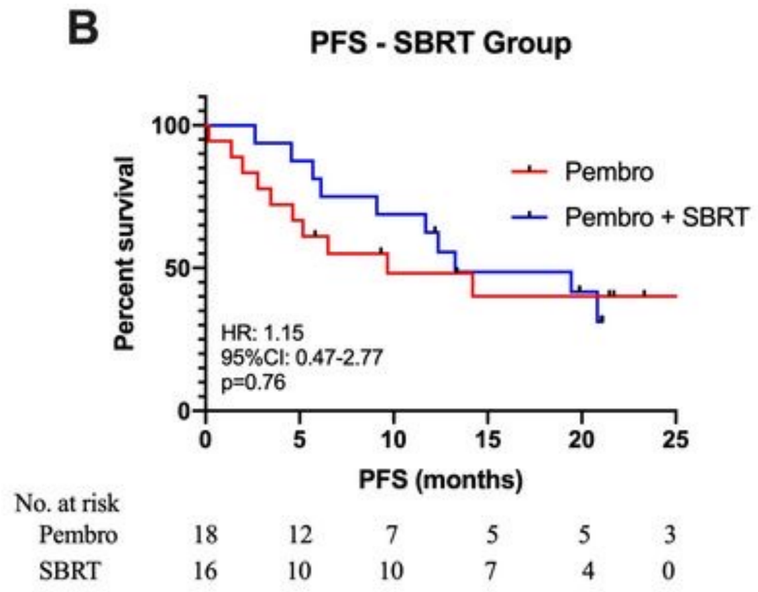
Pembrolizumab with or without radiation therapy for metastatic non-small cell lung cancer: a randomized phase I/II trial

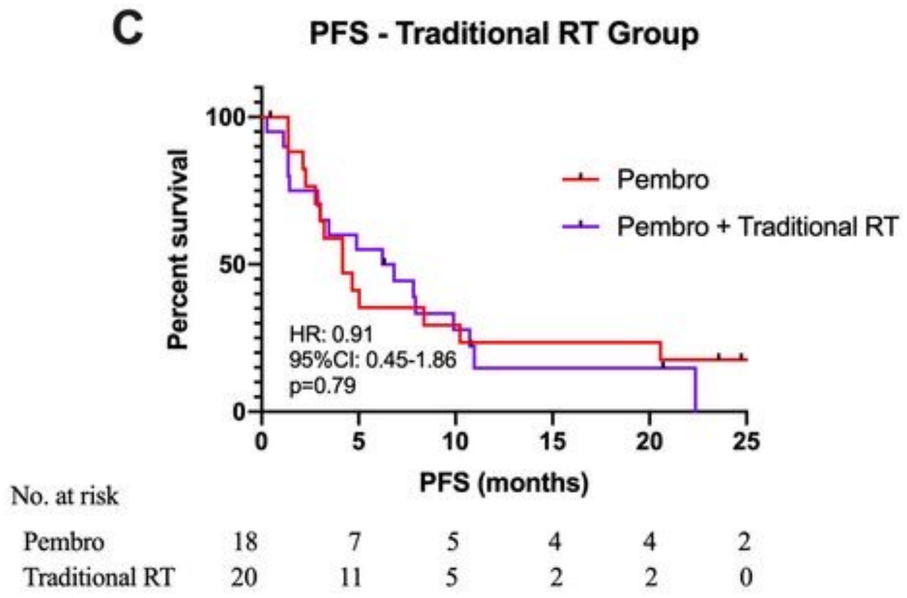
James Welsh,[✉#1] Hari Menon,[#1] Dawei Chen,[#2] Vivek Verma,[3] Chad Tang,[1] Mehmet Altan,[4] Kenneth Hess,[5] Patricia de Groot,[6] Quynh-Nhu Nguyen,[1] Rejani Varghese,[1] Nathan I Comeaux,[1] George Simon,[1] Ferdinandos Skoulidis,[4] Joe Y Chang,[1] Vasiliki Papdimitrakopoulou,[1] Steven H Lin,[1] and John V Heymach[4]



Progression-free survival (PFS) times in (A) all patients, (B) patients with disease amenable to stereotactic body RT (SBRT) and (C) patients with disease requiring traditional radiotherapy (RT).







James Welsh et al. J Immunother Cancer 2020;8:e001001

Journal for ImmunoTherapy of Cancer

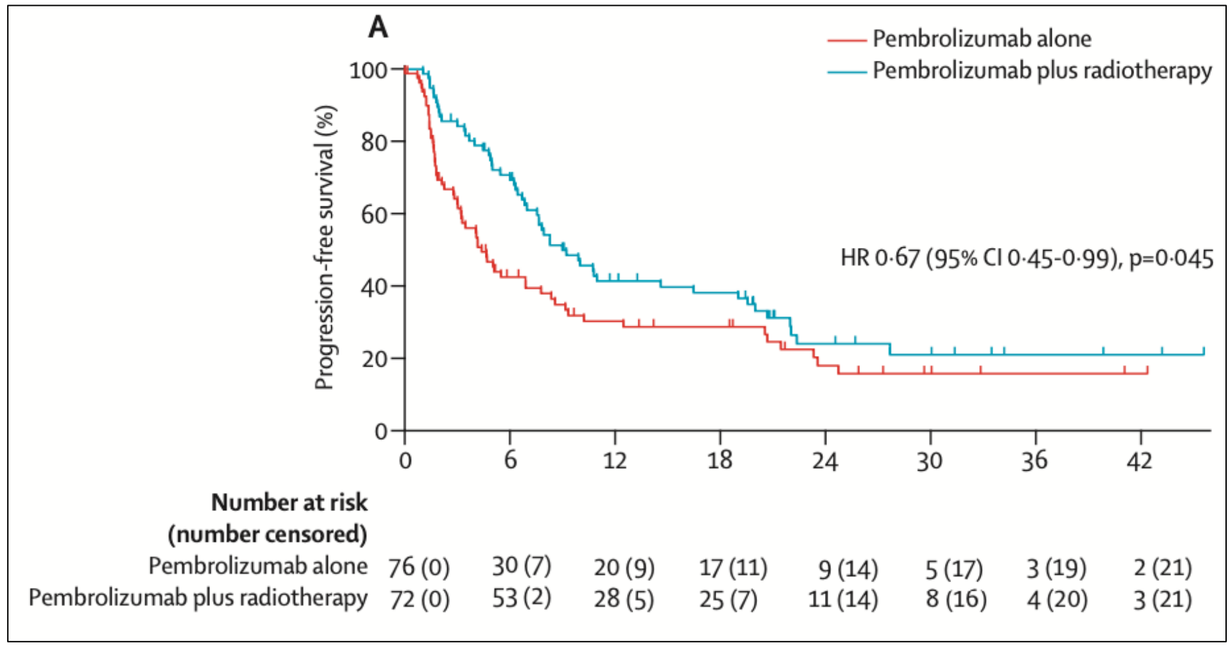
Pembrolizumab with or without radiotherapy for metastatic non-small-cell lung cancer: a pooled analysis of two randomised trials

Willemijn S M E Theelen, Dawei Chen*, Vivek Verma, Brian P Hobbs, Heike M U Peulen, Joachim G J V Aerts, Idris Bahce, Anna Larissa N Niemeijer, Joe Y Chang, Patricia M de Groot, Quynh-Nhu Nguyen, Nathan I Comeaux, George R Simon, Ferdinandos Skoulidis, Steven H Lin, Kewen He, Roshal Patel, John Heymach†, Paul Baas†, James W Welsh†*

Progression-Free Survival

-4.4 m with anti PD1

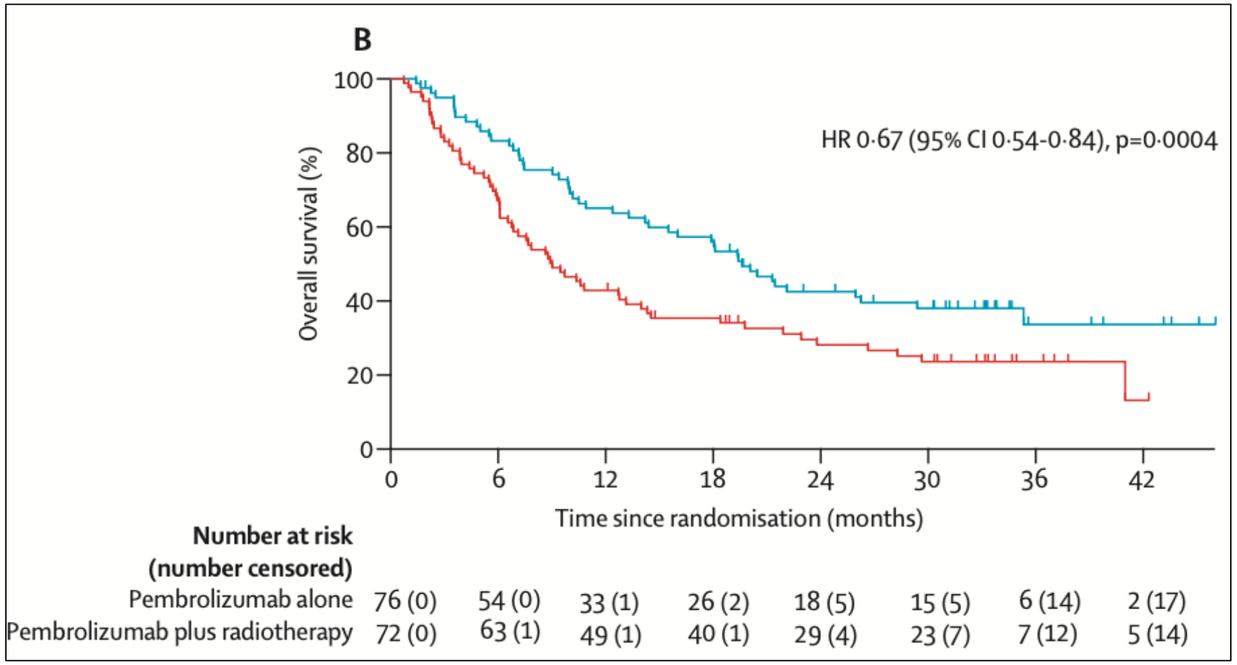
-9.0 m with SBRT + anti PD1



Overall Survival

-8.7 m with anti PD1

-19.2 m with SBRT + anti PD1



Toxicity concerns with RT

Metastases-directed stereotactic body radiotherapy in combination with targeted therapy or immunotherapy: systematic review and consensus recommendations by the EORTC–ESTRO OligoCare consortium

Stephanie G C Kroeze, Matea Pavic*, Karin Stellamans, Yolande Lievens, Carlotta Becherini, Marta Scorsetti, Filippo Alongi, Umberto Ricardi, Barbara Alicja Jereczek-Fossa, Paulien Westhoff, Jasna But-Hadzic, Joachim Widder, Xavier Geets, Samuel Bral, Maarten Lambrecht, Charlotte Billiet, Igor Sirak, Sara Ramella, Ivaldi Giovanni Battista, Sergi Benavente, Almudena Zapatero, Fabiola Romero, Thomas Zilli, Kaouthar Khanfir, Hossein Hemmatazad, Berardino de Bari, Desiree N Klass, Shaukat Adnan, Heike Peulen, Juan Salinas Ramos, Michiel Strijbos, Sanjay Popat, Piet Ost, Matthias Guckenberger*

Consensus of 28 experts; 26 RO and 2 MO

Lancet Oncology 2023: 24; e21-32

Patients treated by agent and location

	Head and neck	Thorax	Abdomen	Bone	Body
Immune checkpoint inhibitors					
Anti-CTLA-4	..	145	86	12	13
Anti-PD-L1 and anti-PD-1	3	375	276	147	29
Anti-PD-L1 plus anti-CTLA-4 or anti-PD-1 plus anti-CTLA-4	..	38	12	12	..
Monoclonal antibodies					
Anti-VEGF	14	..	34	..	..
Anti-EGFR	235	..	..	..	..
Anti-HER2	..	..	..	..	..
Small molecules					
mTKI or mTOR	1	59	175	333	41
EGFR inhibitor	..	360	61	75	22
ALK inhibitor	..	7	2	5	2
ROS1 inhibitor	..	..	..	..	..
NTRK inhibitor	..	..	..	..	..
RET inhibitor	..	..	..	..	..
MET inhibitor	..	..	..	..	..
BRAF inhibitor and MEK inhibitor	..	..	..	5	..
PARP inhibitor	..	..	..	..	..
HER2 inhibitor	..	..	..	..	..
CDK4/6 inhibitor	..	1	..	5	..

In the body group, location was not further specified. 0–10 patients is defined as limited data, 11–50 patients is defined as few data, and >50 cumulative patients in all studies is defined as relevant data. SBRT=stereotactic body radiotherapy.

Table 1: **Systematic review with total number of SBRT-treated metastases per targeted agent group and anatomical location of SBRT-treated metastases**

Risk of ≥ grade 3 toxicity

	Head and neck	Thorax	Abdomen	Bone	Body
Immune checkpoint inhibitors					
Anti-CTLA-4	..	12%	10%	8%	23%
Anti-PD-L1 and anti-PD-1	0%	6%	5%	1%	3%
Anti-PD-L1 plus anti-CTLA-4 or anti-PD-1 plus anti-CTLA-4	..	26%	0%	8%	..
Monoclonal antibodies					
Anti-VEGF	0%	..	12%	..	..
Anti-EGFR	15%	..	..	..	..
Anti-HER2	..	..	..	..	..
Small molecules					
mTKI	0%	0%	22%	1%	0%
mTOR inhibitor	..	0%	0%	0%	0%
EGFR inhibitor	..	7%	0%	1%	0%
ALK inhibitor	..	0%	0%	0%	0%
ROS1 inhibitor	..	..	..	..	..
NTRK inhibitor	..	..	..	..	..
RET inhibitor	..	..	..	..	..
MET inhibitor	..	..	..	..	..
BRAF inhibitor and MEK inhibitor	..	..	..	0%	..
PARP inhibitor	..	..	..	..	..
HER2 inhibitor	..	..	..	..	..
CDK4 or CDK6 inhibitor	..	0%	..	0%	..

In the body group, location was not further specified. 0–10% of toxicity is defined as low risk, 11–20% of toxicity is defined as intermediate risk, and >20% of toxicity is defined as increased risk. SBRT=stereotactic body radiotherapy.

Table 2: **Percentage of systematic review with severe in-field toxicity events (toxicity ≥grade 3) per SBRT treated lesion by targeted agent group and anatomical location of SBRT-treated metastases**

Summary

- The trials in RT + IO (or chemo + IO) for NSCLC are stacking up positively in the early stage, perioperative, LA-NSCLC, and oligo-metastatic settings

- Many, many trials are ongoing in each of these settings

- Questions still being addressed – concurrent vs sequential IO, RT dose, oligmetastatic settings, 1 vs 2 IO agents, RT doses, RT volumes