MOVING THE NEEDLE FORWARD IN LUNG CANCER WITH RADIATION: COMBINATIONS WITH TARGETED THERAPIES

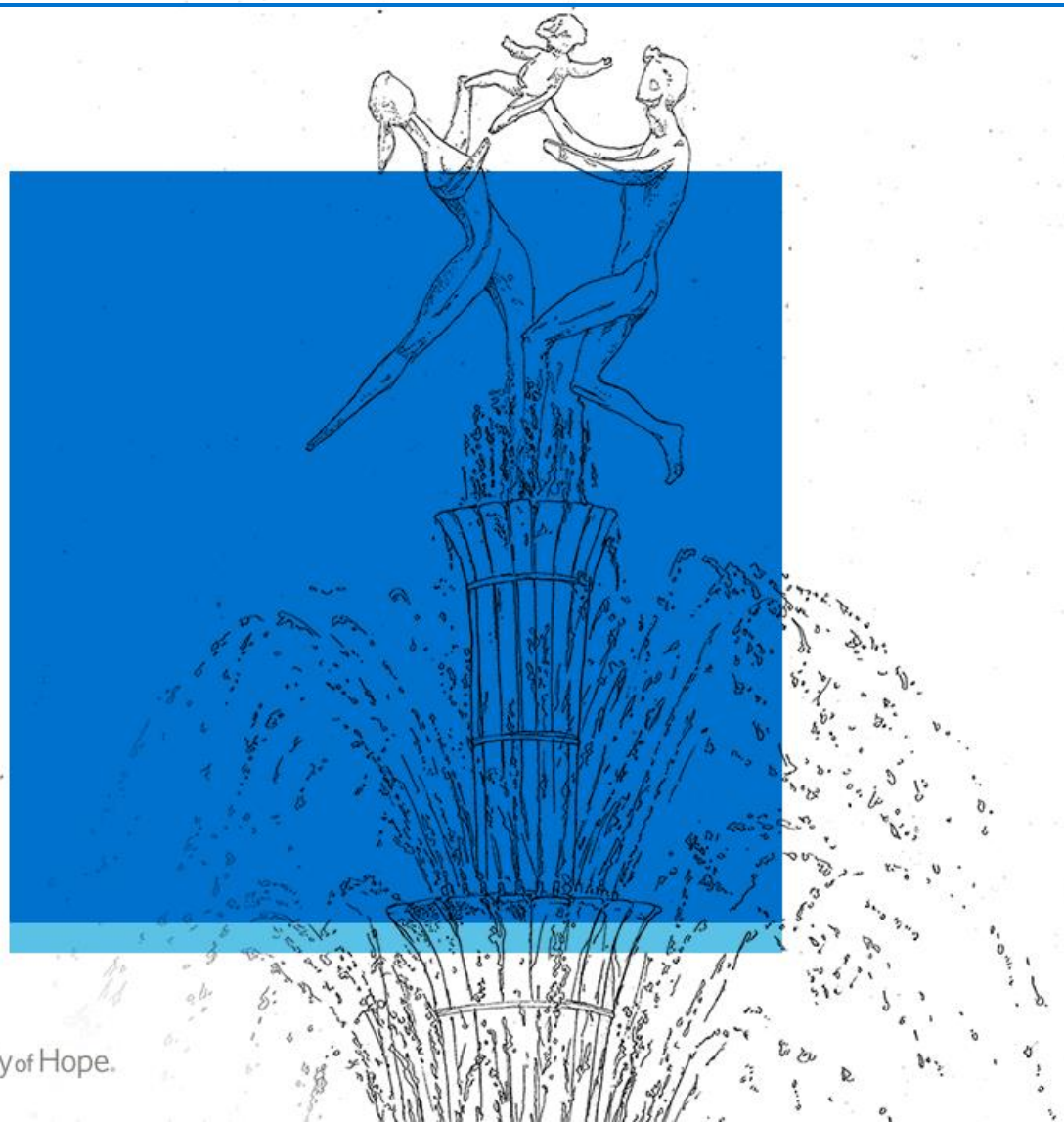
TERENCE WILLIAMS, MD, PHD

Chair and Professor, Department of Radiation Oncology
Adjunct Professor, Department of Cancer Genetics and Epigenetics
City of Hope National Medical Center

Disclosures

- Consulting/Advisory Board: Novocure, Accuray, January Therapeutics, Candel Therapeutics
- Research Funding: National Institutes of Health, American Cancer Society

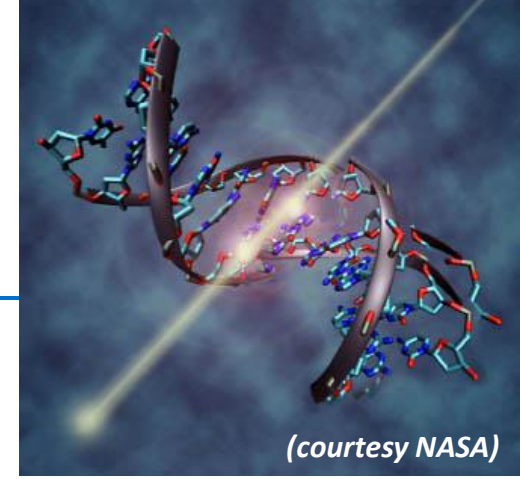
Outline

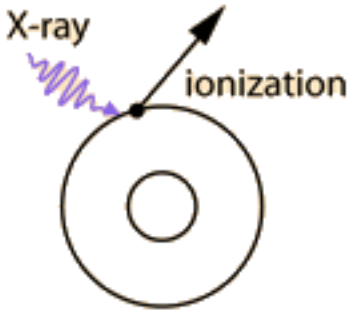


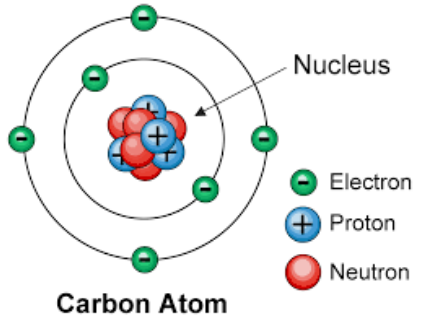
1. Radiation Therapy and the Therapeutic Index
2. Locally-advanced NSCLC
3. Early-stage NSCLC
4. Stage IV NSCLC (oligometastatic)
5. SCLC

What is Radiation?

- The most common prescribed single therapeutic agent for cancer treatment (~50-60% of cancer patients receive it at one point)
- Ionizing photons, charged particles (proton/electron), heavy particles (carbon), neutron
- 100-1,000x more energy than radiation used in Xrays or CT scans
- Target is typically DNA in cells (e.g. double-strand breaks)
- Most commonly delivered as external beam radiation
- Curative as a single modality or in combination with surgery or systemic therapies (e.g. chemotherapy, immunotherapy, etc.)

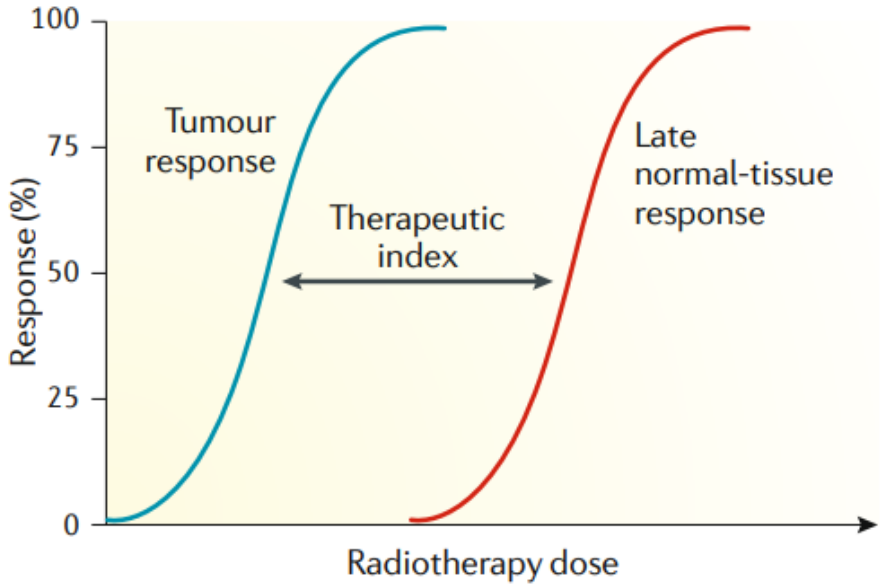






Therapeutic Index of Radiotherapy

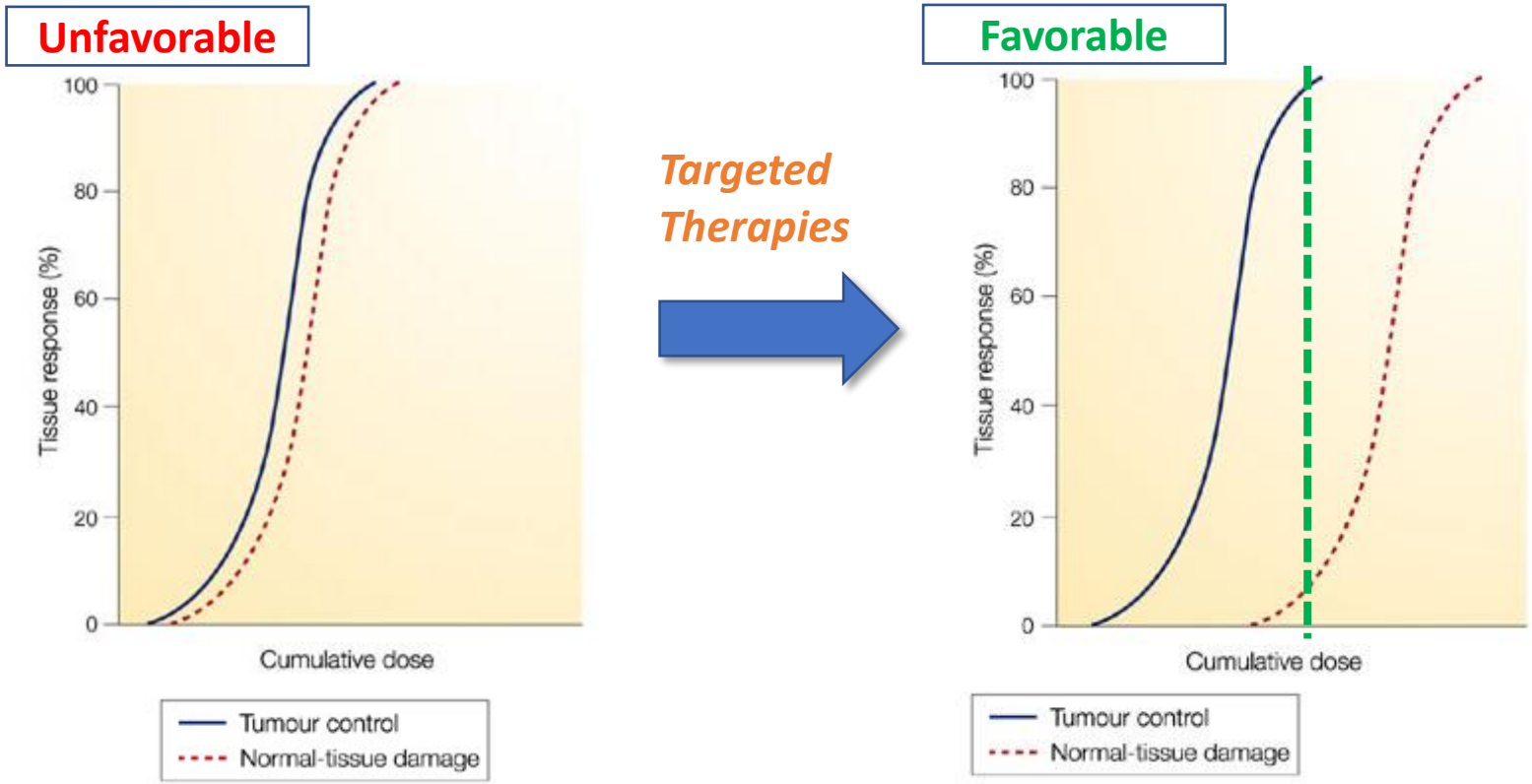
- Ratio between the effects on tumor tissue versus the effects on normal tissues (organs at risk)
- Index is favorable if response of tumor tissue is greater than the surrounding normal tissue
- Therapeutic index can be increased by biological or physical methods
  - **Physical**: improved tumor targeting
  - **Biological**: fractionation, radioprotectors, biomarkers to select dose escalation/de-escalation, **<u>tumor-specific radiosensitizers or modifiers</u>**



De Ruysscher et al., Nature Reviews, 2019, 5:13.

Enhancing Radiation Therapeutic Index with Tumor-Targeted Therapies

- Identify therapeutic agents which widen the therapeutic index with radiation, by selectively killing tumor cells while minimizing normal tissue toxicity.

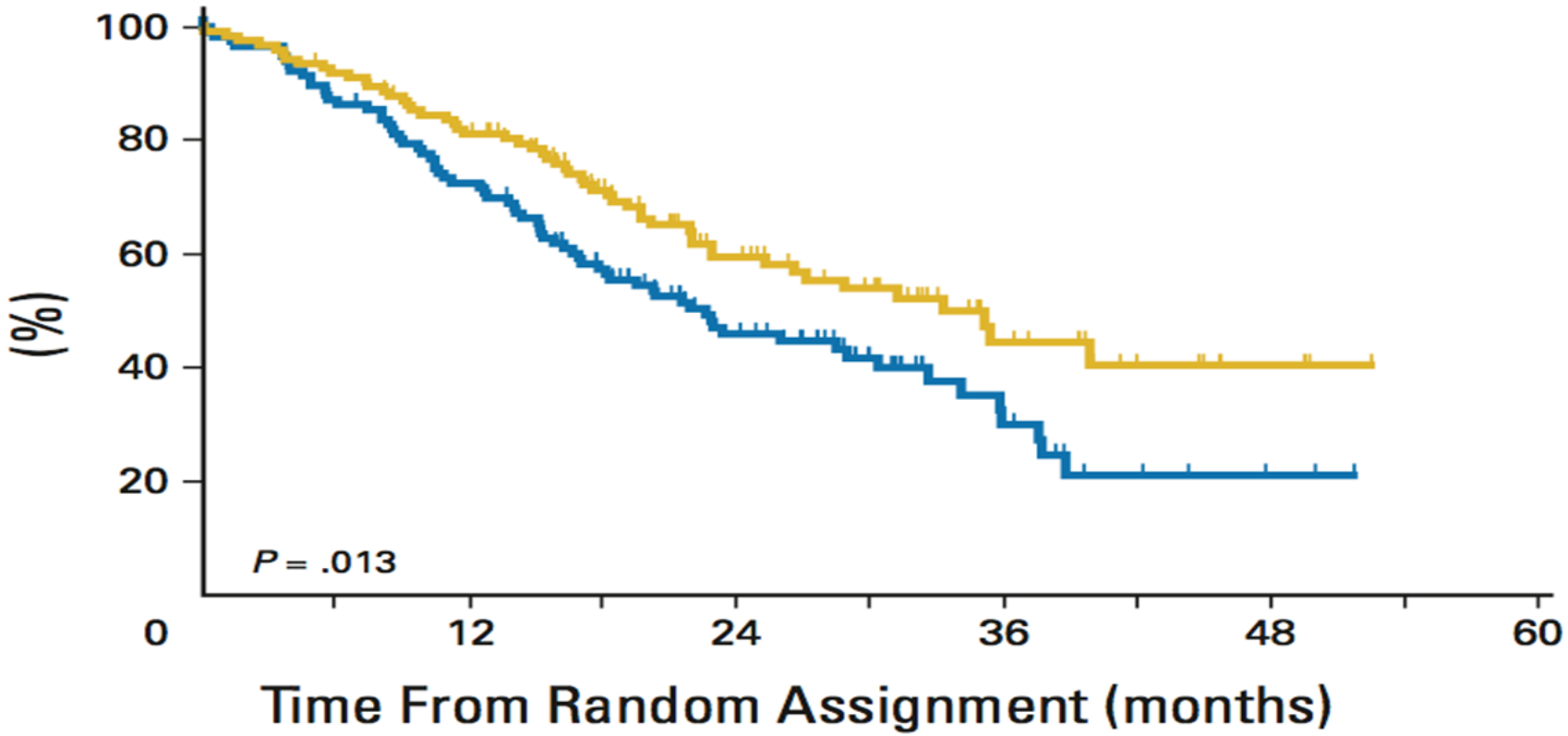


LOCALLY-ADVANCED NSCLC

Failures of Targeted Therapies – Example 1 (Gefitinib)

(Maintenance gefitinib in unselected patients)

SWOG 0023 - EGFR TKI after chemo/RT



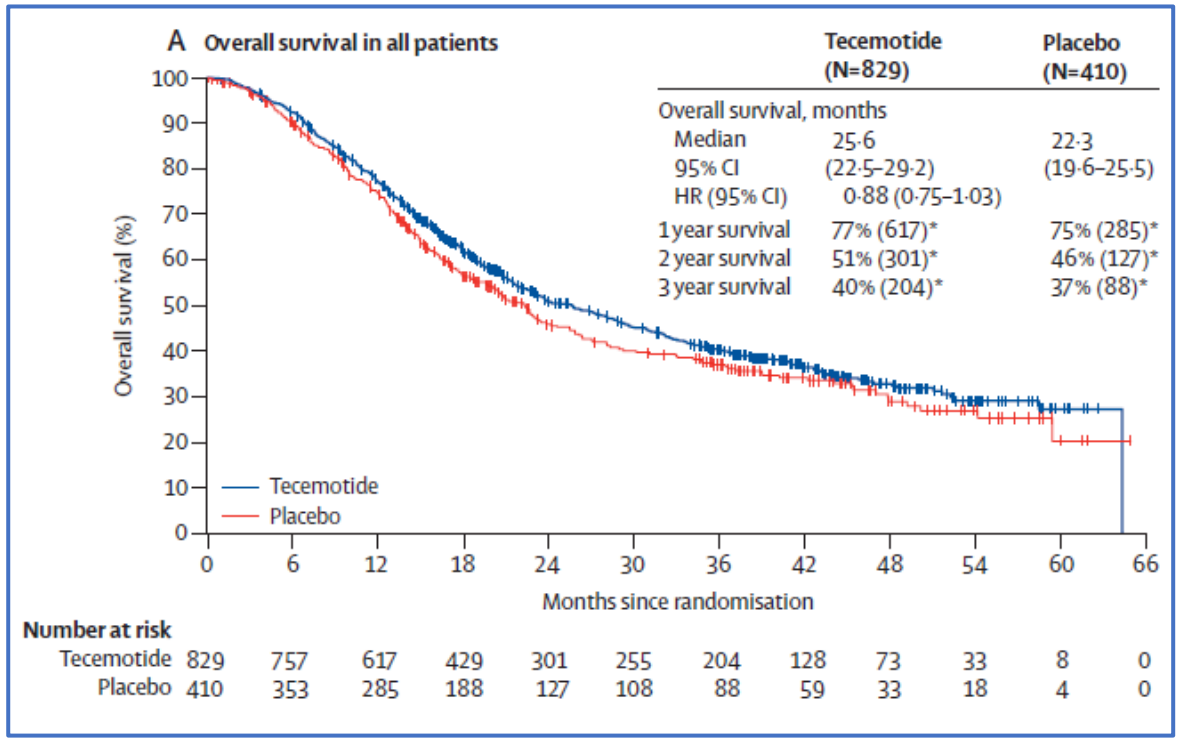
K Kelly, et al., JCO, 2008

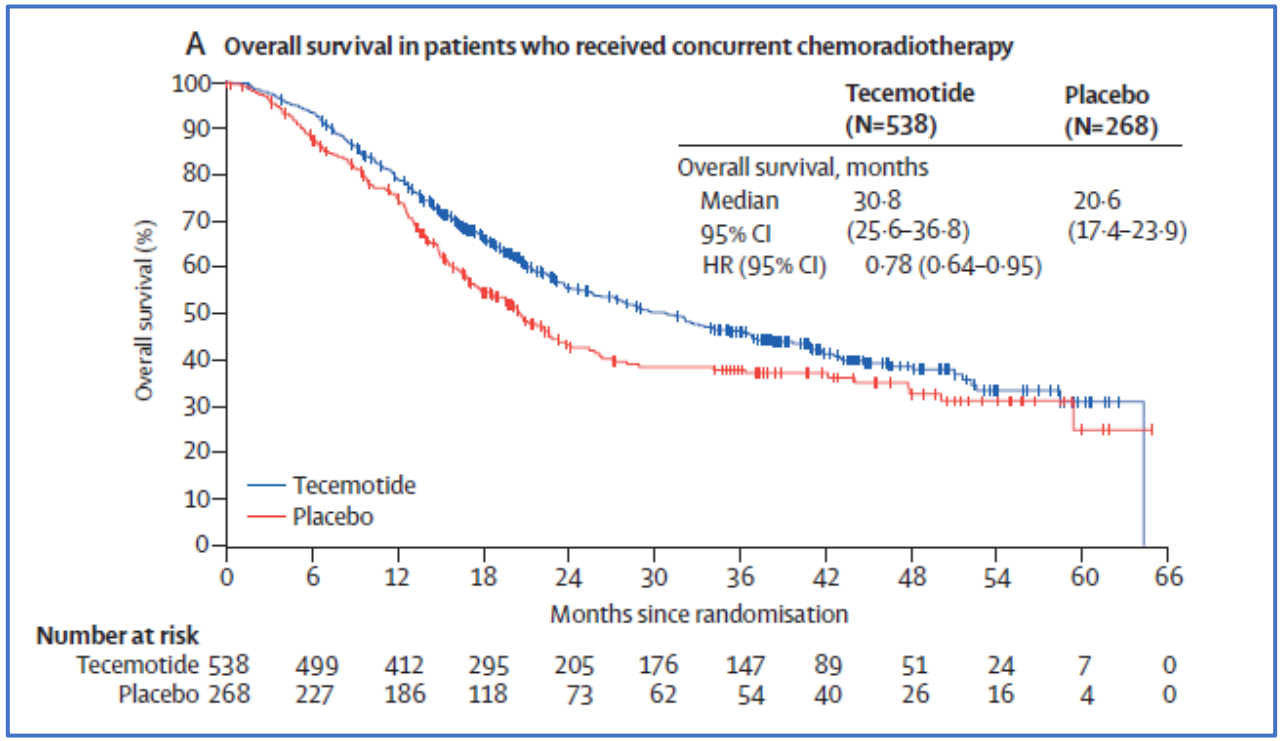
Failures of Targeted Therapies – Example 2 (Bevacizumab)

Trial/Institution	Regimen	Status
Ca Consortium (IIIB/IV)	RT → CP/Bev	Closed - 1 gr 5 **hemorrhage**
Northwestern (IIIB/IV)	RT → CP/Bev	Never Opened
Dana Farber	CP wkly + Bev q3 wk + RT → CP/Bev q3 wk → Bev x 1 yr	Closed 4 pt – 1 gr 5 **hemorrhage**, 1 PE
NCI 7213 (Vokes)	C/P/Bev/RT	Closed; 1 pt accrued
Sarah Cannon (Spigel)	Carbo/Pem/Bev/RT → Carbo/Pem/Bev → Bev	Closed – 5 pt – **2 TE fistulas**
UNC (Socinski)	CP/Bev → CP/Bev/RT → Bev/Erlotinib	After 21 pt – 1 gr 5 and 1 gr **3 hemorrhage**

Failures of Targeted Therapies – Example 3 (Tecemotide)

START trial: Maintenance Tecemotide/L-BLP25 (MUC1-targeted liposomal peptide vaccine)





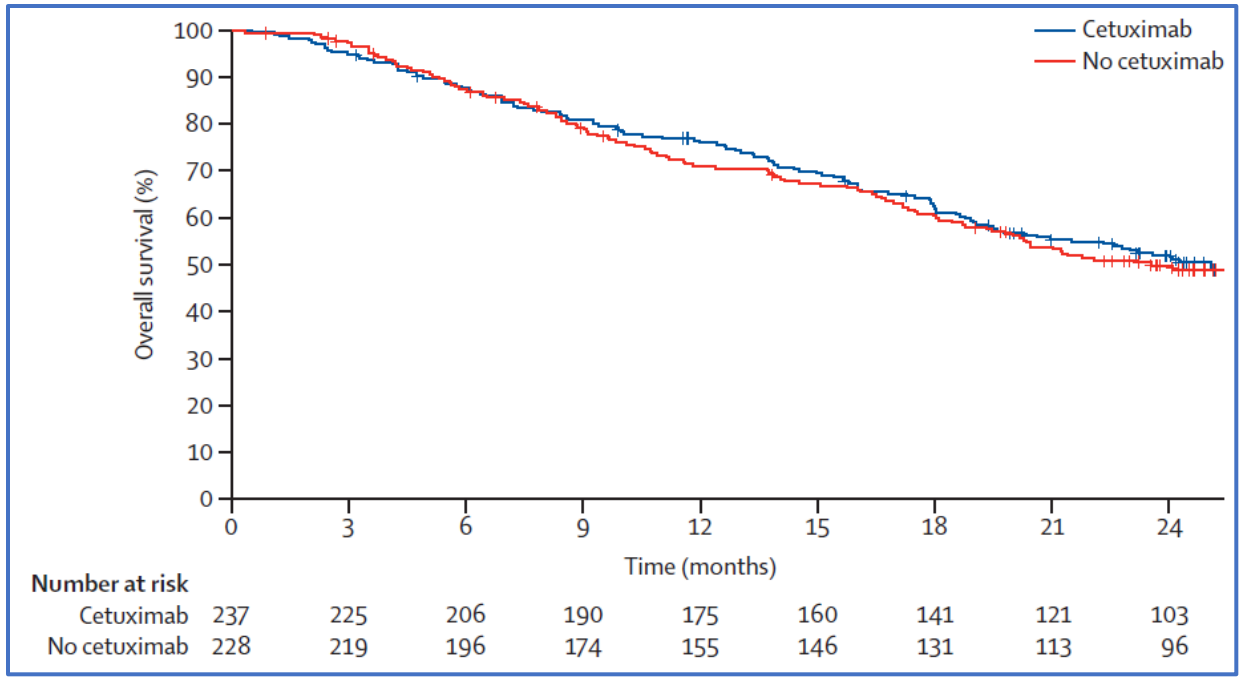
City of Hope

C Butts, et al., Lancet Oncol, 2014

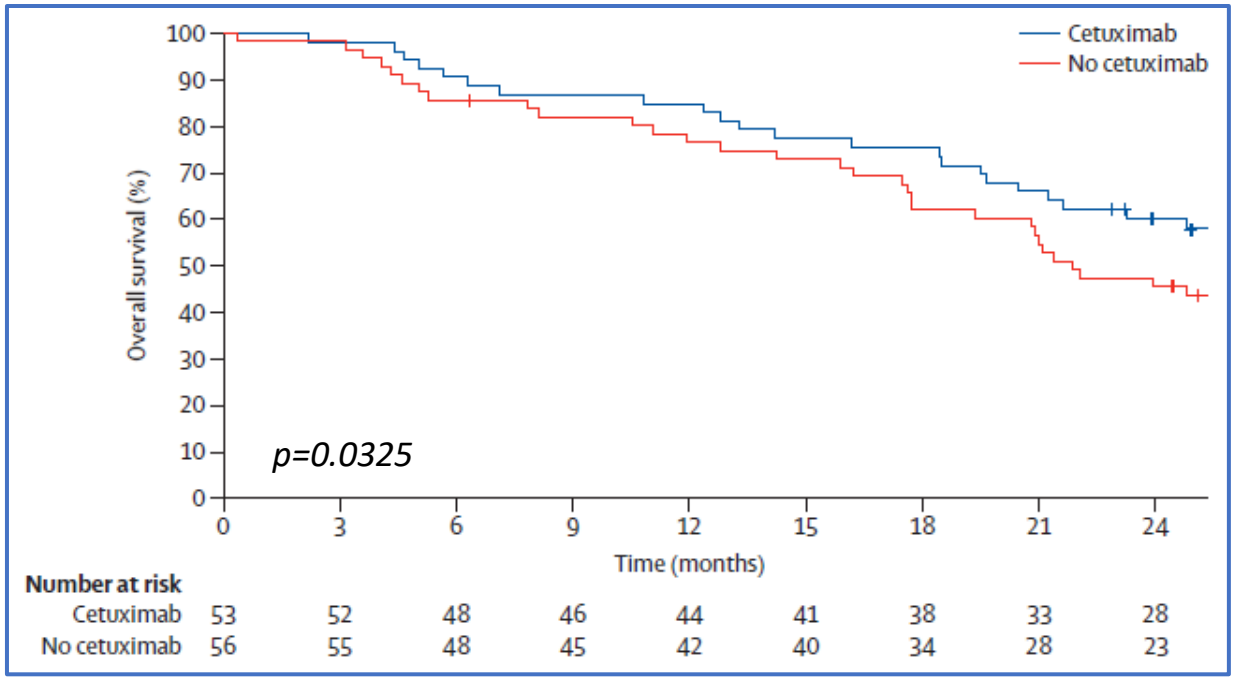
Failures of Targeted Therapies- Example 4 (Cetuximab)

RTOG 0617: Cetuximab vs. no Cetuximab

All patients



Tumors with high EGFR expression (H score≥ 200)



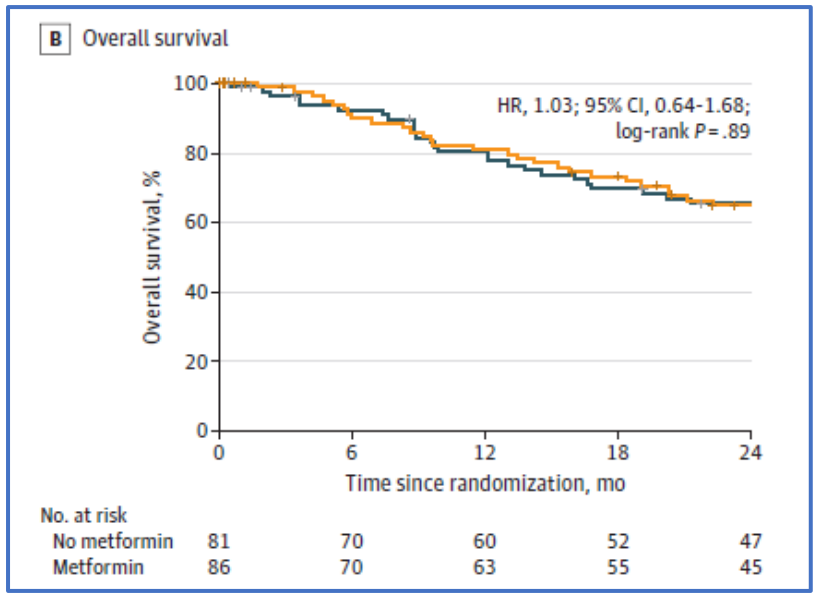
J Bradley, et al., Lancet Oncol, 2015

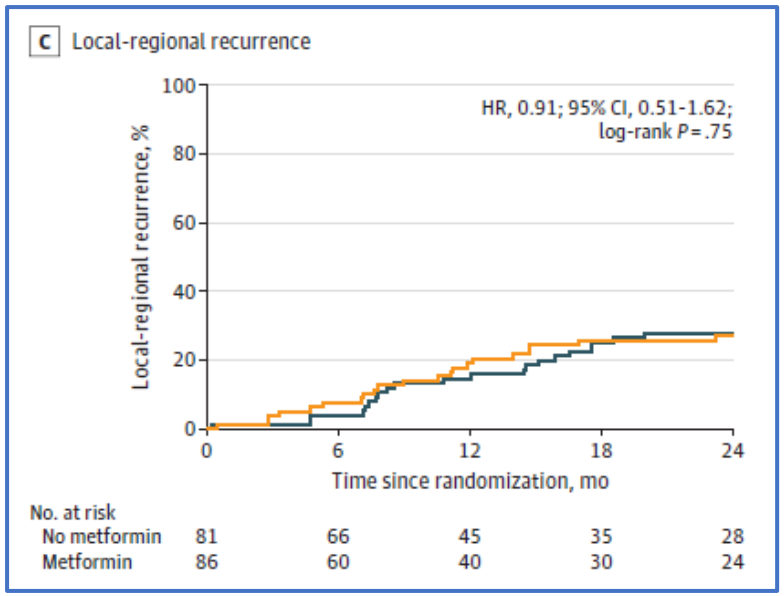
Failures of Targeted Therapies – Example 5 (Metformin)

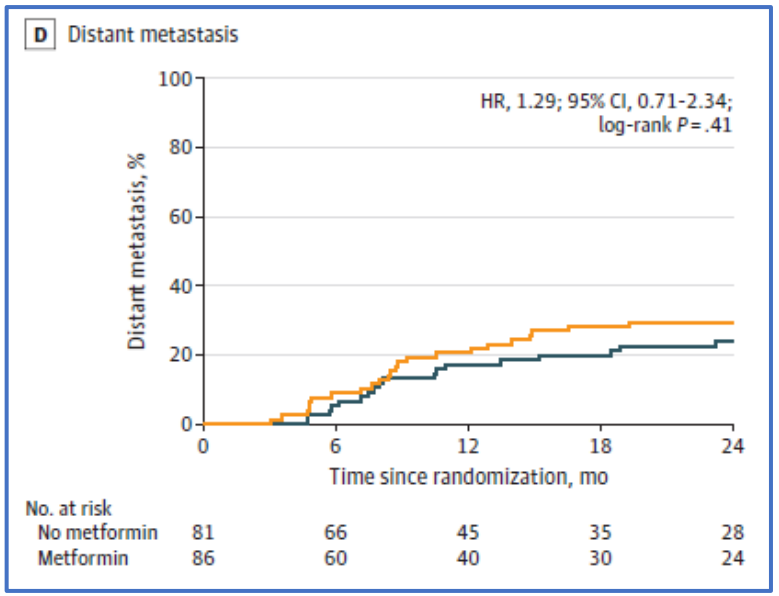
JAMA Oncology | Original Investigation

Addition of Metformin to Concurrent Chemoradiation in Patients With Locally Advanced Non–Small Cell Lung Cancer

The NRG-LUO01 Phase 2 Randomized Clinical Trial







H Skinner, et al., JAMA Onc, 2021

Individualized Combined Modality Therapy for Stage III Non-small Cell Lung Cancer (NSCLC) - RTOG 1306/Alliance 31101

EGFR TK Mutation Cohort

R A N D O M I Z E

Arm 1: Erlotinib, 150 mg/day for 12 weeks → Concurrent chemotherapy and radiation, 60 Gy

Arm 2: Concurrent Chemotherapy

CLOSED DUE TO POOR ACCRUAL

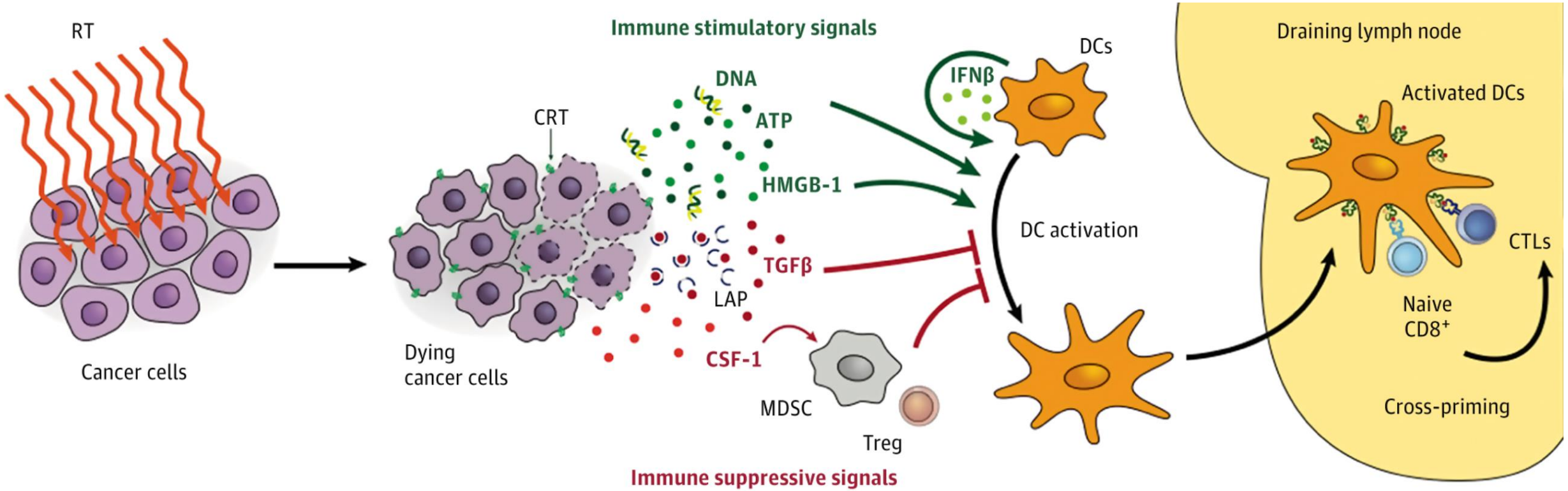
R A N D O M I Z E

Arm 1: Crizotinib, 250 mg/bid for 12 weeks → Concurrent chemotherapy and radiation, 60 Gy

Arm 2: Concurrent chemotherapy and radiation, 60Gy

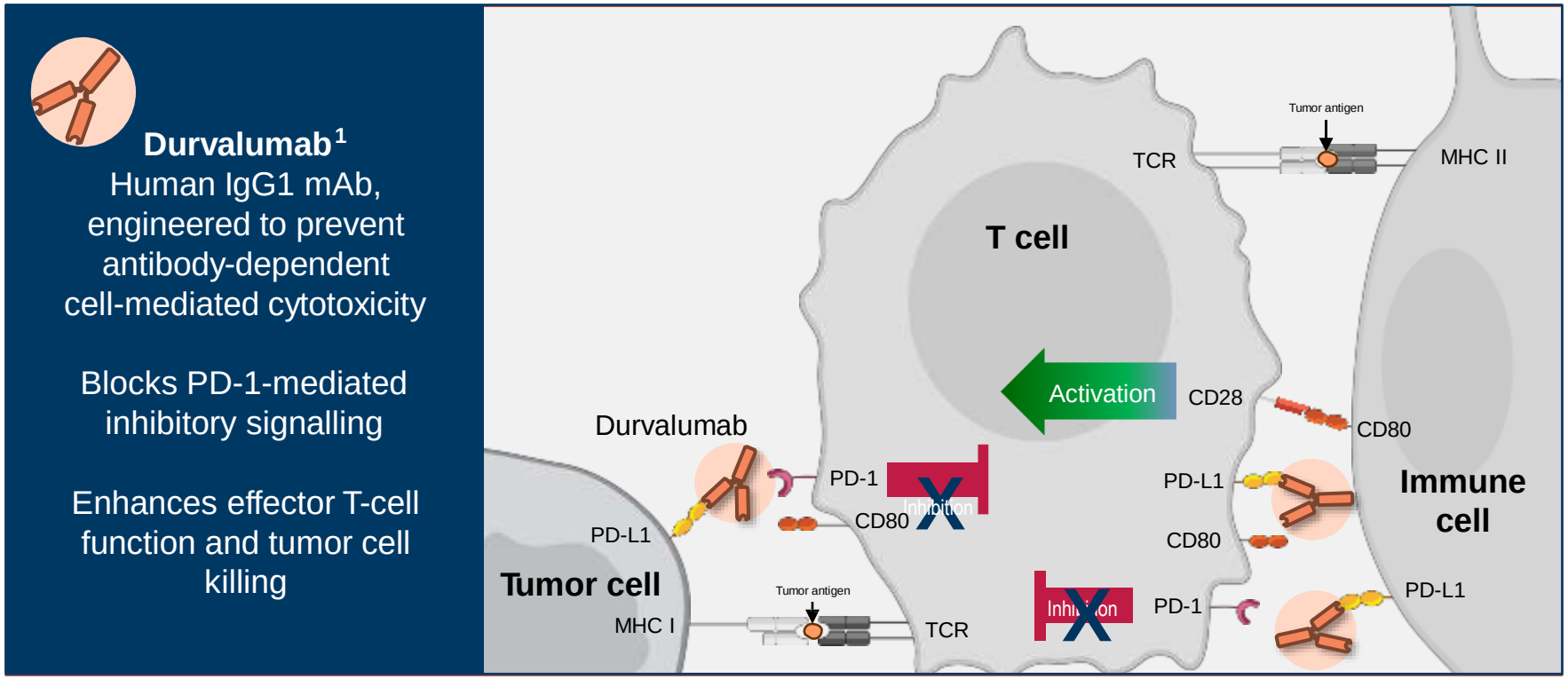
THEN CAME IMMUNOTHERAPY….

Role of Local Radiation Therapy in Cancer Immunotherapy



S Demaria, et al., JAMA Onc, 2015

Durvalumab Blocks PD-L1 Binding to PD-1

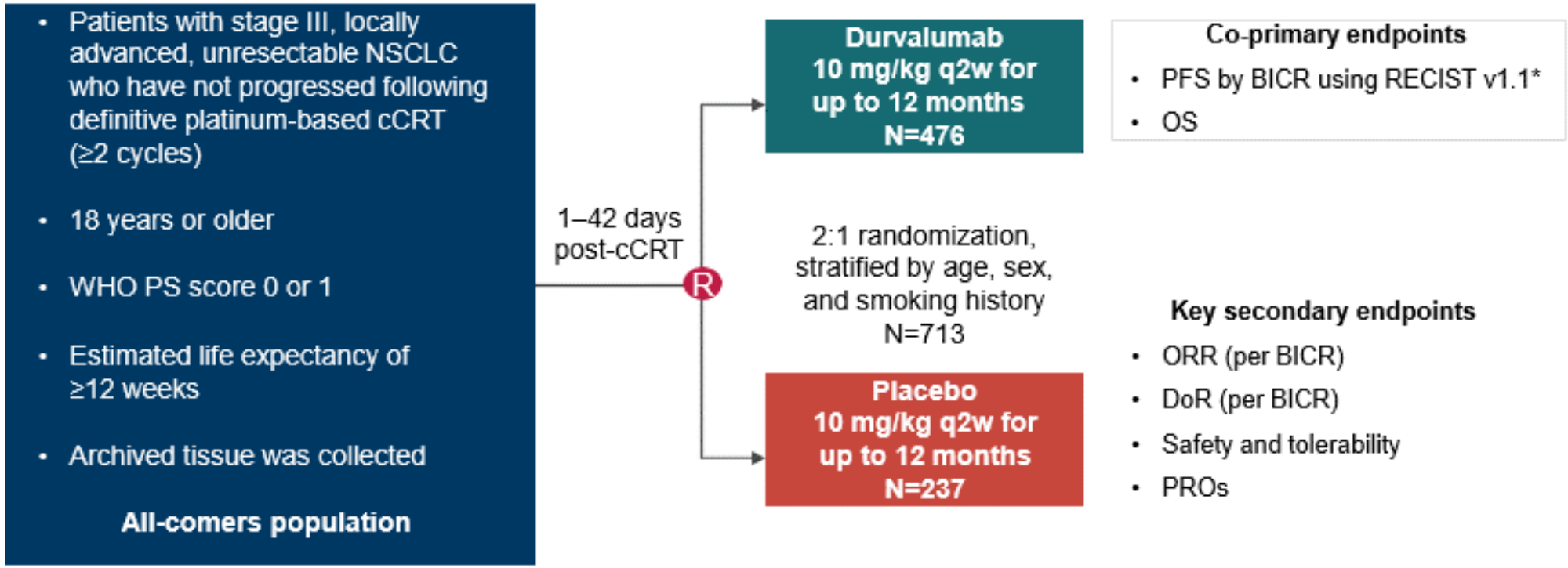


mAb, monoclonal antibody; MHC, major histocompatibility complex; PD-1, programmed cell dealth-1; PD-L1, programmed cell death ligand-1; TCR, T-cell receptor

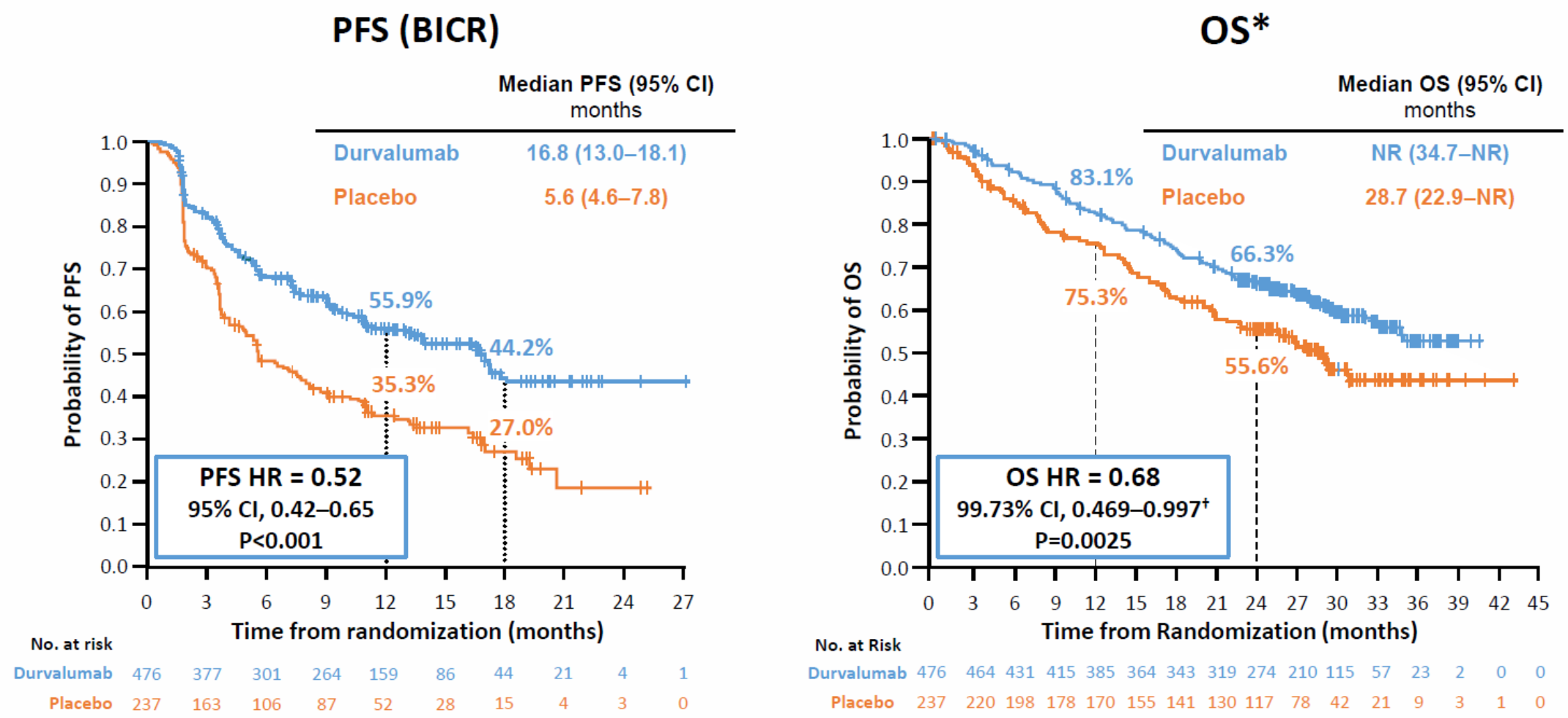
Stewart R, et al. Cancer Immunol Res 2015;3:1052-62

PACIFIC: Study Design

Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study



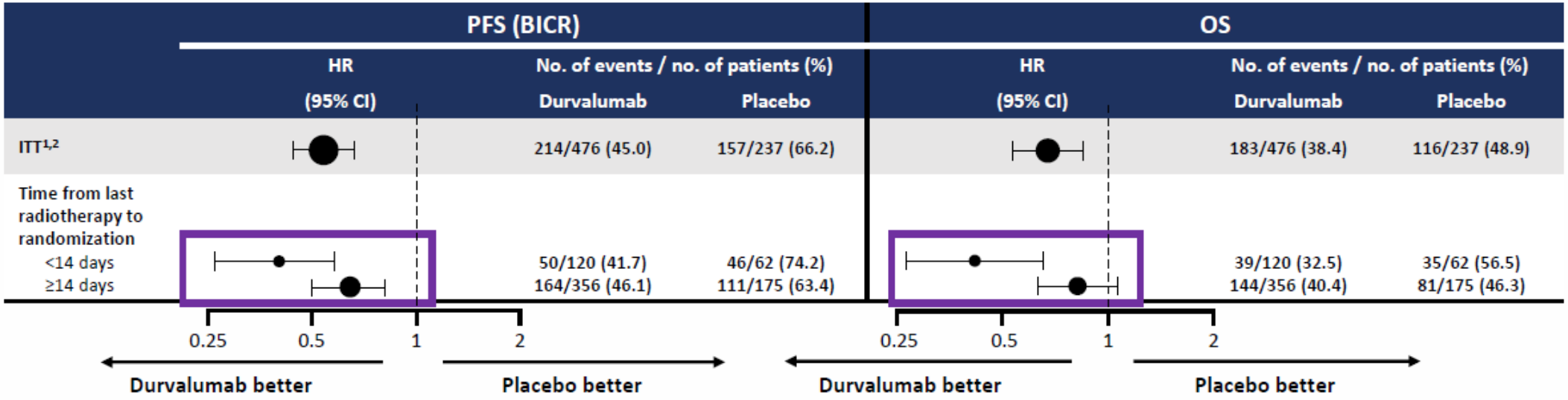
Durvalumab Blocks PD-L1 Binding to PD-1



*Median duration of follow-up was 25.2 months (range 0.2–43.1); †Adjusted for interim analysis; NR, not reached.
Note: PFS data based on data cutoff of Feb 13, 2017, and OS data based on data cutoff of Mar 22, 2018.

1. Antonia SJ, et al. N Engl J Med 2017;377:1919–29;
2. Antonia SJ, et al. N Engl J Med 2018; Epub Sep 25.

Impact of Time from Prior RT to Randomization



	TTDM (BICR)			ORR (BICR)	
	HR (95% CI)	No. of events / no. of patients (%) Durvalumab	Placebo	% Durvalumab	Placebo
ITT[1]	0.52 (0.39, 0.69)	131/476 (27.5)	98/237 (41.4)	28.4	16.0
Time from last radiotherapy to randomization					
<14 days	0.33 (0.20–0.55)	30/120 (25.0)	34/62 (54.8)	34.2	16.4
≥14 days	0.70 (0.51–0.95)	101/356 (28.4)	64/175 (36.6)	26.5	15.8

*Not calculated if subgroup has <20 events; NA, not available.
Note: PFS, TTDM, and ORR data based on data cutoff of Feb 13, 2017, and OS data based on data cutoff of Mar 22, 2018

1. Antonia SJ, et al. N Engl J Med 2017;377:1919–29;
2. Antonia SJ, et al. N Engl J Med 2018; Epub Sep 25.

Similar Toxicity Profiles Regardless of Time from Prior RT to Randomization

	<14 days		≥14 days	
	Durvalumab (N=120)	Placebo (N=60)	Durvalumab (N=355)	Placebo (N=174)
Any-grade all-causality AEs, n (%)	118 (98.3)	57 (95.0)	342 (96.3)	165 (94.8)
Grade 3/4	37 (30.8)	18 (30.0)	108 (30.4)	43 (24.7)
Outcome of death	6 (5.0)	7 (11.7)	15 (4.2)	8 (4.6)
Leading to discontinuation	16 (13.3)	9 (15.0)	57 (16.1)	14 (8.0)
Serious AEs, n (%)	36 (30.0)	20 (33.3)	102 (28.7)	34 (19.5)
Any-grade pneumonitis/radiation pneumonitis, n (%)	47 (39.2)	10 (16.7)	114 (32.1)	48 (27.6)
Grade 3/4	5 (4.2)	1 (1.7)	12 (3.4)	5 (2.9)
Outcome of death	0	2 (3.3)	5 (1.4)	3 (1.7)

Note: Data based on data cutoff of Mar 22, 2018.
Patients with multiple AEs are counted once at the maximum reported CTCAE grade.

PACIFIC: 4 yr Survival Update

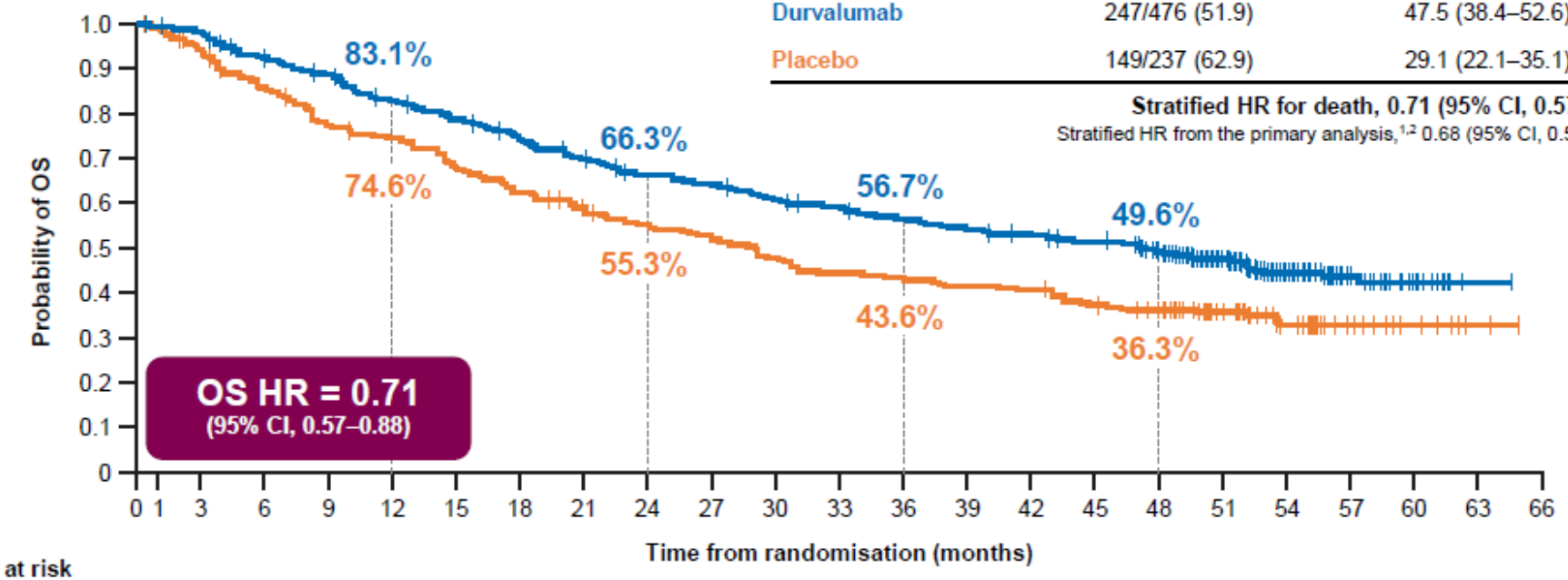
VIRTUAL 2020 ESMO congress

UPDATED OS (ITT)

	No. of events/ total no. of patients (%)	Median OS (95% CI), months
Durvalumab	247/476 (51.9)	47.5 (38.4–52.6)
Placebo	149/237 (62.9)	29.1 (22.1–35.1)

Stratified HR for death, 0.71 (95% CI, 0.57–0.88)

Stratified HR from the primary analysis,[1,2] 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

City of Hope

C Faivre-Finn, et al., ESMO and JTO, 2020

PACIFIC: 4 yr Survival Update

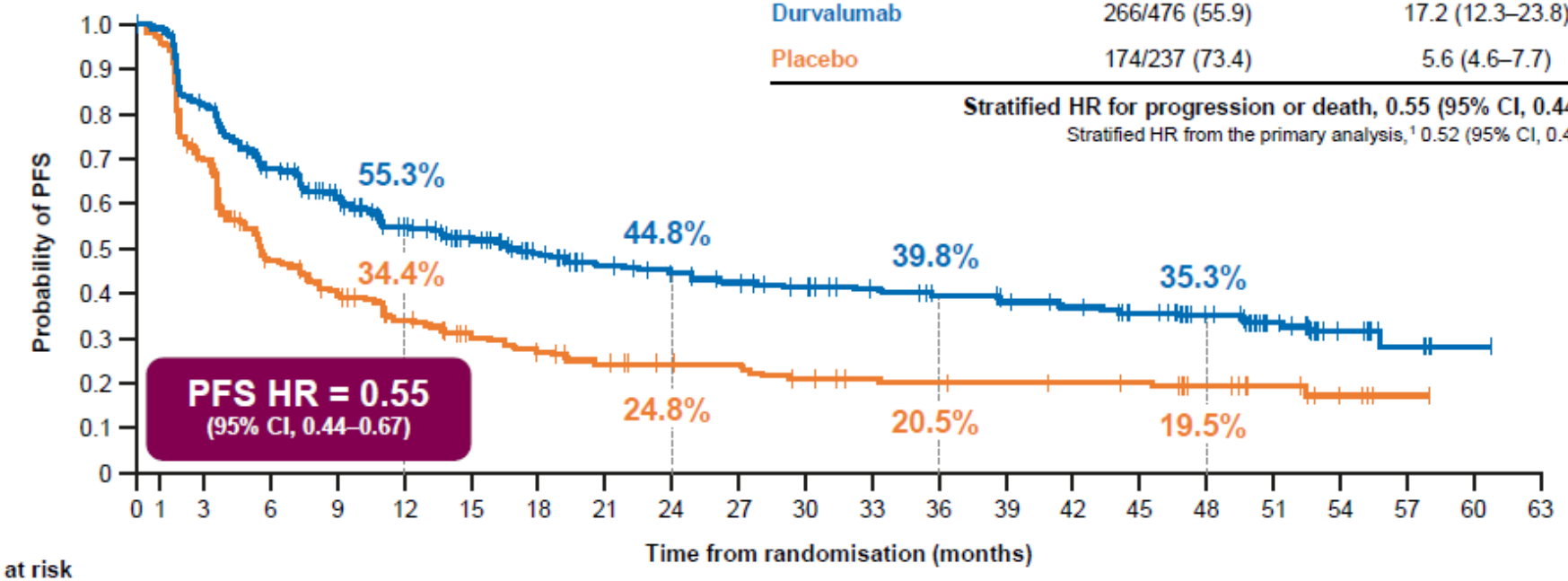
VIRTUAL 2020 ESMO congress

UPDATED PFS (BICR; ITT)

	No. of events/ total no. of patients (%)	Median PFS (95% CI), months
Durvalumab	266/476 (55.9)	17.2 (12.3–23.8)
Placebo	174/237 (73.4)	5.6 (4.6–7.7)

Stratified HR for progression or death, 0.55 (95% CI, 0.44–0.67)

Stratified HR from the primary analysis,[1] 0.52 (95% CI, 0.42–0.65)



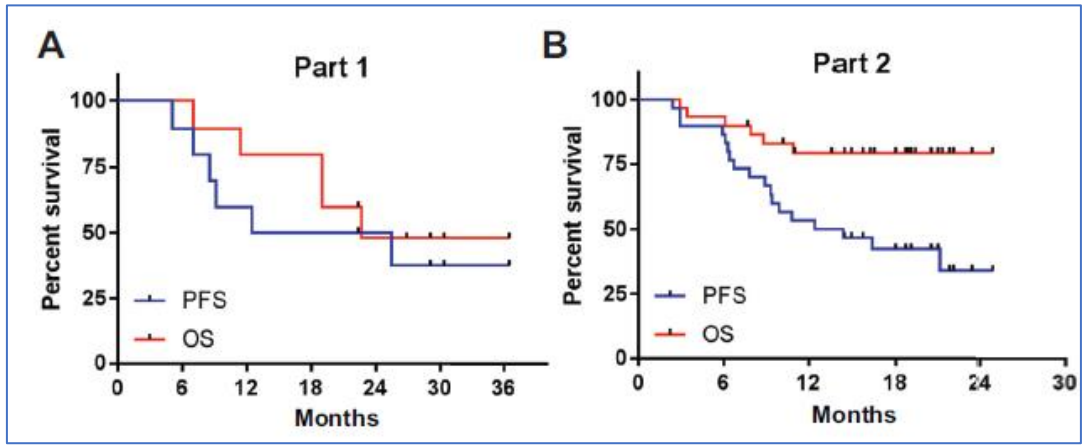
No. at risk																						
Durvalumab	476	377	301	266	213	189	165	146	136	127	119	110	103	97	92	80	59	37	18	8	1	0
Placebo	237	163	105	86	67	55	47	40	36	35	29	26	25	24	23	22	16	11	5	1	0	0

City of Hope.

C Faivre-Finn, et al., ESMO and JTO, 2020

DETERRED: Phase II Concurrent Atezolizumab with Chemoradiation for Unresectable NSCLC

- Part 1 (n=10): CRT followed by consolidation chemo and maintenance atezolizumab (median f/u 22.5 mo)
- Part 2 (n=30): concurrent CRT **with atezolizumab** followed by same consolidation chemo and maintenance atezolizumab (median f/u 15.1 mo)
- Median PFS:
  - Part 1= 18.6 months Part 2= 13.2 months
- Median OS:
  - Part 1= 22.8 months Part 2= not reached



- Toxicity: 80% of patients experienced at least 1 grade 3+ adverse event
  - Part 2= 20% grade 3+ immune-related toxicity; 20% treatment discontinuation
  - No immune-related grade 5 toxicities

City of Hope

S Lin, et al., JTO, 2019

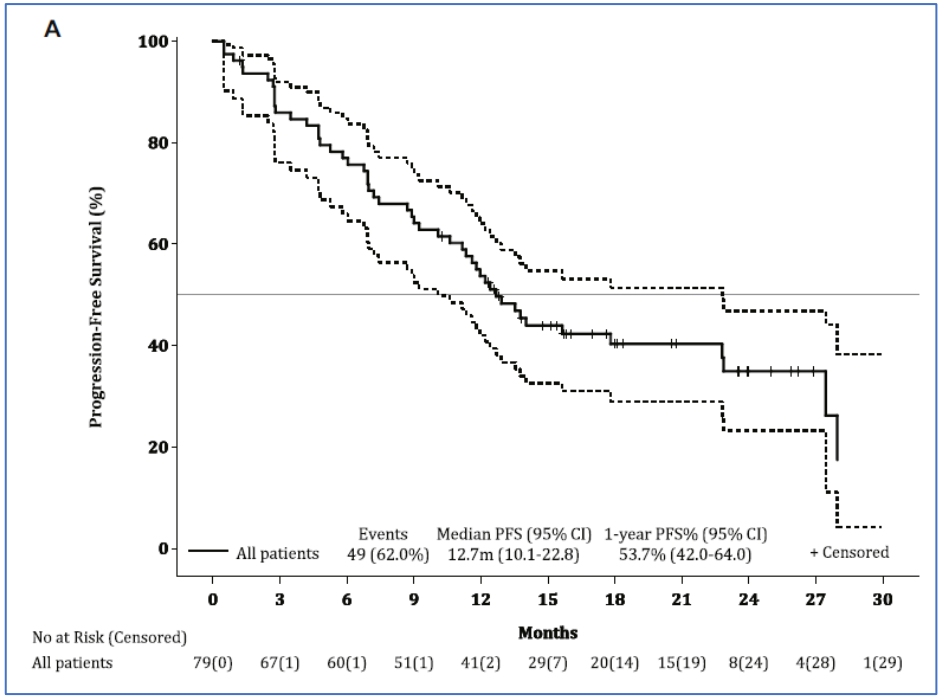
NICOLAS Trial: Phase II Concurrent Nivolumab with Chemoradiation for Unresectable NSCLC

- 79 patients with concurrent cisplatin-based chemoradiation with **concurrent nivolumab**, followed by nivolumab maintenance
- Median PFS (median f/u 21.0 mos)= 12.7 months
- Median OS (median f/u 32.6 mos)= 38.8 months

Table 2. Treatment-Related AEs (Safety Cohort; N = 77)

Information on Treatment-Related AEs	Radiotherapy	Nivolumab
Safety cohort: number of patients	77	76
Any AE (SAE)	780 (61)	
Treatment-related AEs (SAEs)	168 (14)	249 (26)
Treatment-related AEs (SAEs) grade 3-5	32 (9)	44 (18)
Treatment-related AEs (SAEs) leading to death	2 (1)	7 (6)
Treatment-related AEs (SAEs) leading to permanent discontinuation of treatment	6 (-)	16 (-)

AE, adverse event; SAE, severe adverse event.



S Peters, et al., JTO, 2020

KEYNOTE-799: Phase II Concurrent Pembrolizumab with Chemoradiation for Unresectable NSCLC

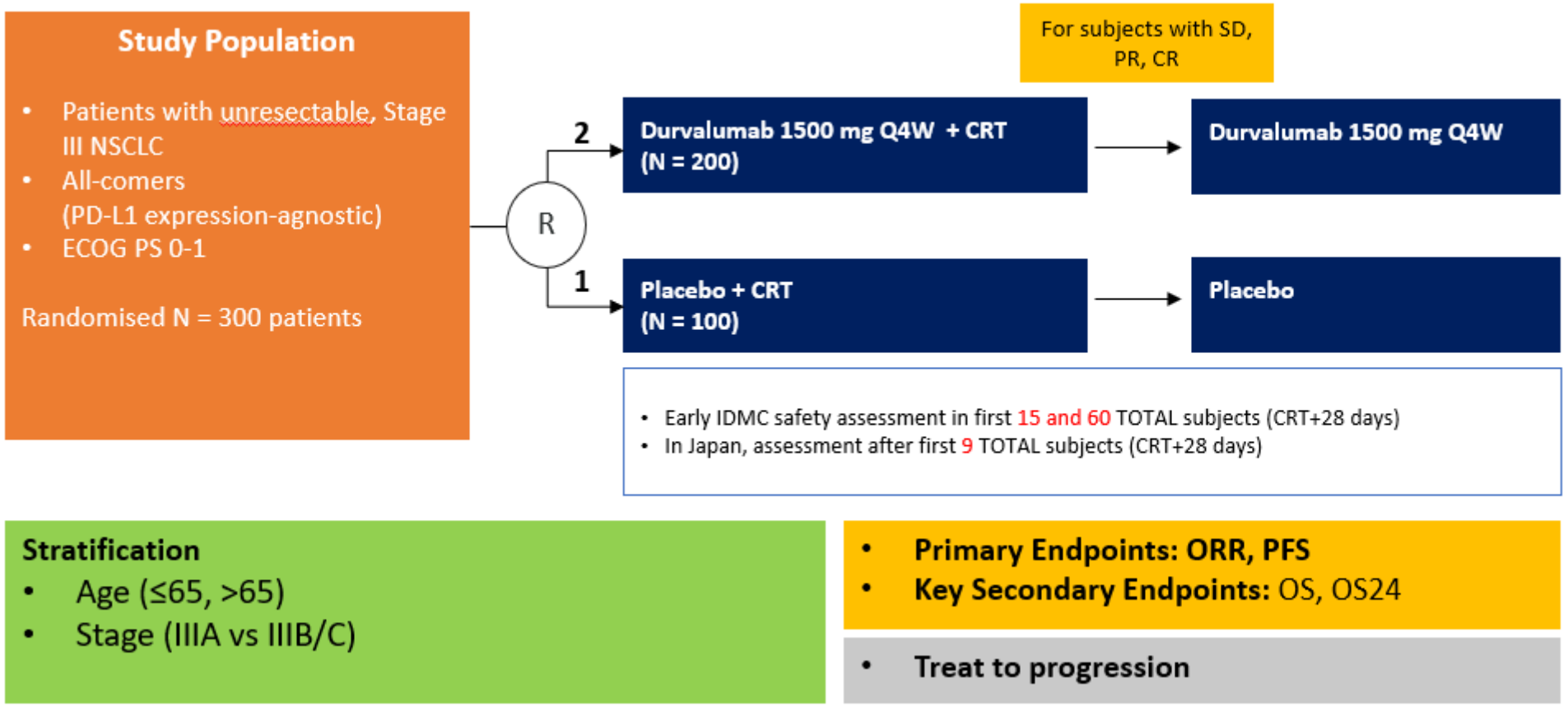
- Cohort A: 1 cycle of induction chemo + pembro → CRT +pembro; chemo= **carboplatin/paclitaxel**
- Cohort B: 1 cycle of induction chemo + pembro → CRT + pembro; chemo= **cisplatin/pemetrexed**
- 112 patients cohort A, 102 patients in cohort B
- ORR: ~70% in both cohorts
- Gr3-5 treatment-related AEs occurred in 50-64%
- Gr3+ pneumonitis 7-8%
- Conclusions: promising activity and manageable toxicity

S Jabbour, et al., JAMA Onc, 2021

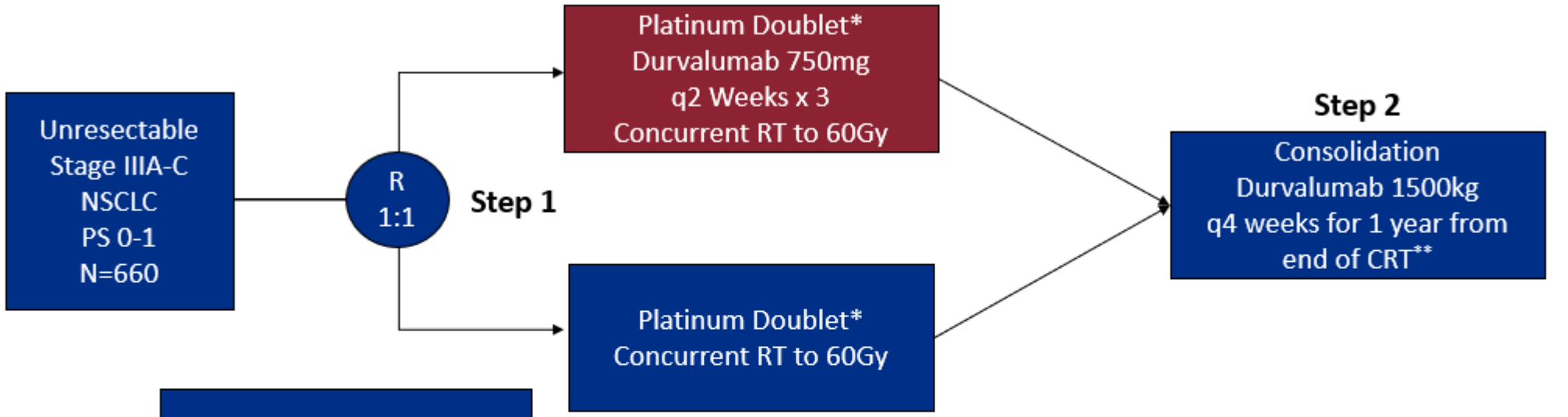
Ongoing Phase III Studies

- **PACIFIC-2**: Durvalumab + CRT → Durva vs. CRT
- **EA 5181**: Durvalumab + CRT→ Durva vs. PACIFIC regimen
- **Checkmate 73L**: Nivo + CRT→ Nivo + Ipi (or Nivo + CRT→ Nivo) vs. PACIFIC regimen
- **LAURA**: Osimertinib Maintenance (or placebo) After Definitive Chemoradiation in Patients with Unresectable EGFRm-Positive Stage III NSCLC

Ongoing Phase III Studies: PACIFIC-2



Ongoing Phase III Studies: EA 5181

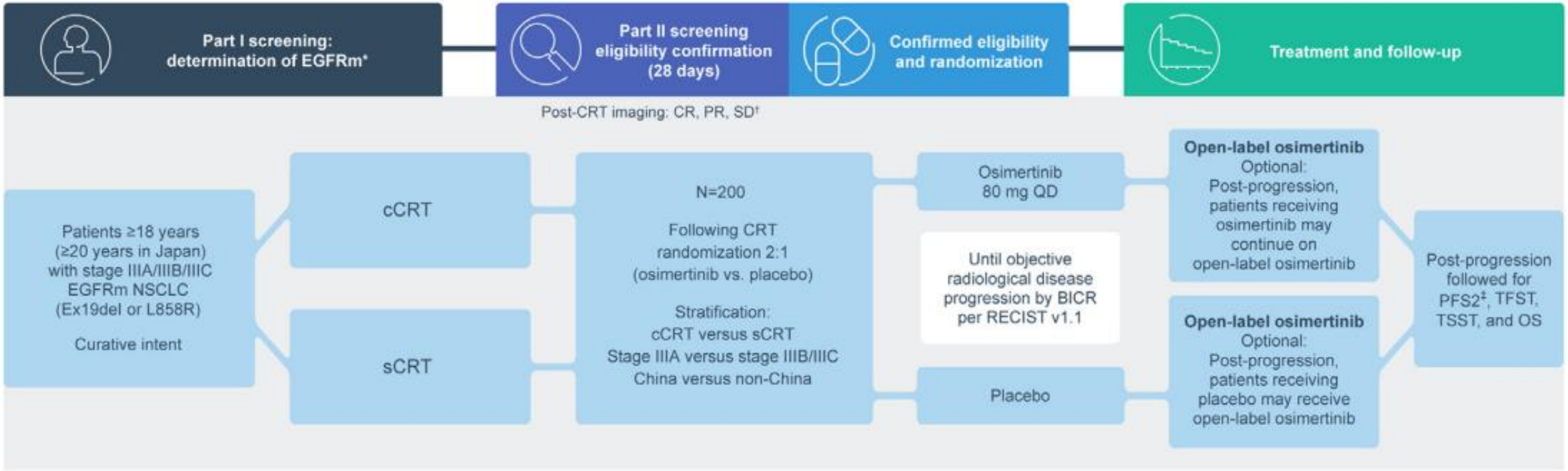


*__Investigator choice__

Cisplatin 50 mg/m2 D1, 8, 29, 36; etoposide 50 mg/m2 D1-5, 29-33
Cisplatin 75 mg/m2 D1, 22; pemetrexed 500 mg/m2 D1, 22 (nonsquamous only)
Carboplatin AUC 2 D1, 8, 15, 22, 29, 36; paclitaxel 45 mg/m2 D1, 8, 15, 22, 29, 36

**Starting within 14 days of CRT unless toxicity has not resolved to ≤ grade 2, but not later than 45 days post-CRT

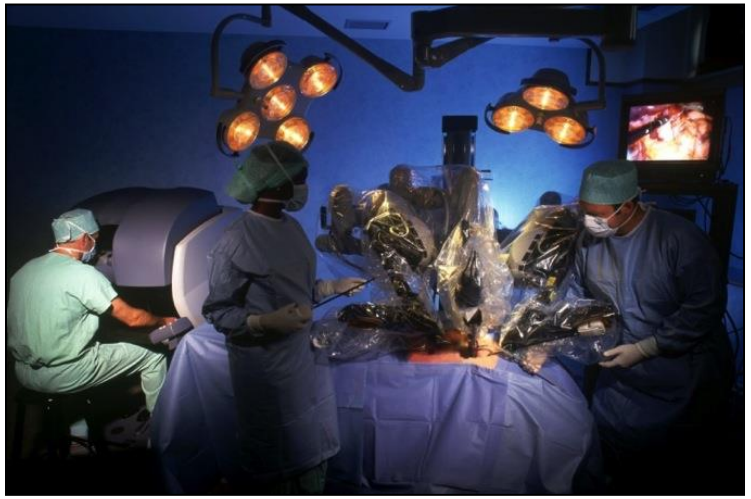
Ongoing Phase III Studies: LAURA



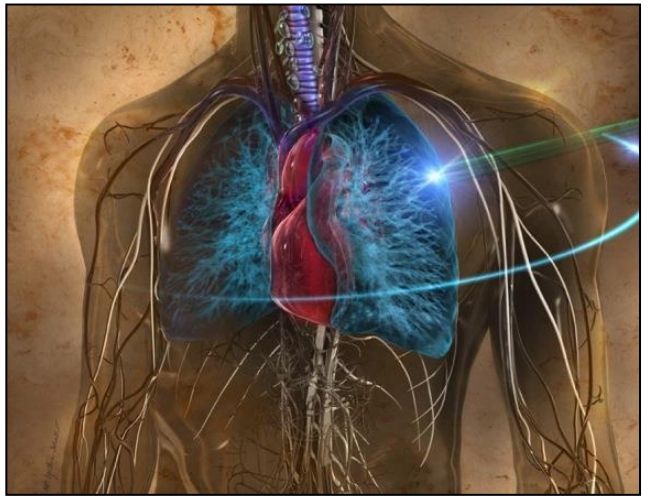
S Lu, et al., Clin Lung Cancer, 2021

EARLY STAGE NSCLC

SURGERY VERSUS SBRT



VS



High-risk operable patients have similar 3 yr survival rates whether receiving surgery or SBRT

SAbR Data	Stage	3-Year Survival	
SAbR- Dutch [7]	T1-T2N0	85%	*Lagerwaard et al., IJROBP, 83(1), 348-353 (2012)*
SAbR-Japan(JCOG 0403) [8]	T1N0	76%	*Nagata et al., IJROBP, 78(3), S27-28 (2010)*
SAbR-Japan [9]	T1-T2N0	86%	*Uematsu et al., IJROBP, 51(3), 666-670 (2001)*
SAbR-Japan [10]	T1-T2N0	80%	*Onishi et al., IJROBP, 81(5), 1352-1358 (2011)*
SAbR-Dutch [6]	T1-T2N0	80%	*Verstegen et al., Annals of Onc, 24(6), 1543-48 (2013)*
RTOG 0618	T1-T3N0	77%	
Randomized Sublobar Data			
ACOSOG -Z4032 [4]	T1N0	71%	*Fernando et al., JCO, 32(23), 2456-62 (2014)*
Non-Randomized Sublobar Data [11-13]	T1-T2N0	60-80%	*Birdas et al., Ann of Thor Surg, 81(2), 434-38 (2006)* *Fernando et al., J Thor & CV Surg, 129(2), 261-67 (2005)* *Santos et al., Surgery, 134(4), 691-97 (2003)*

Timmerman, Fernando et al., Stablemate's protocol

Randomized Trials Comparing SBRT versus Surgery for Early Stage, Operable NSCLC

- ROSEL (Netherlands/EORTC)
  - Stage IA
  - Randomized to Lobectomy versus 3-5 fraction SBRT (20 Gy x 3 or 12 Gy x 5)
  - Closed due to poor accrual
- STARS Trial (US multi-institutional, MD Anderson)
  - Randomized to surgery versus Cyberknife (60 Gy in 3-4 fx)
  - Closed due to poor accrual
- RTOG 1021/ACOSOG Z4099 (U.S.)
  - Phase III Study of Sublobar Resection (+/- Brachytherapy) versus Stereotactic Body Radiation Therapy in High Risk Patients with Stage I Non-Small Cell Lung Cancer (NSCLC)
  - Accrual goal 400 patients
  - Closed due to poor accrual
- *Many retrospective studies supporting equipoise between SBRT and Surgery (especially wedge or sublobar resection)…*

Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials

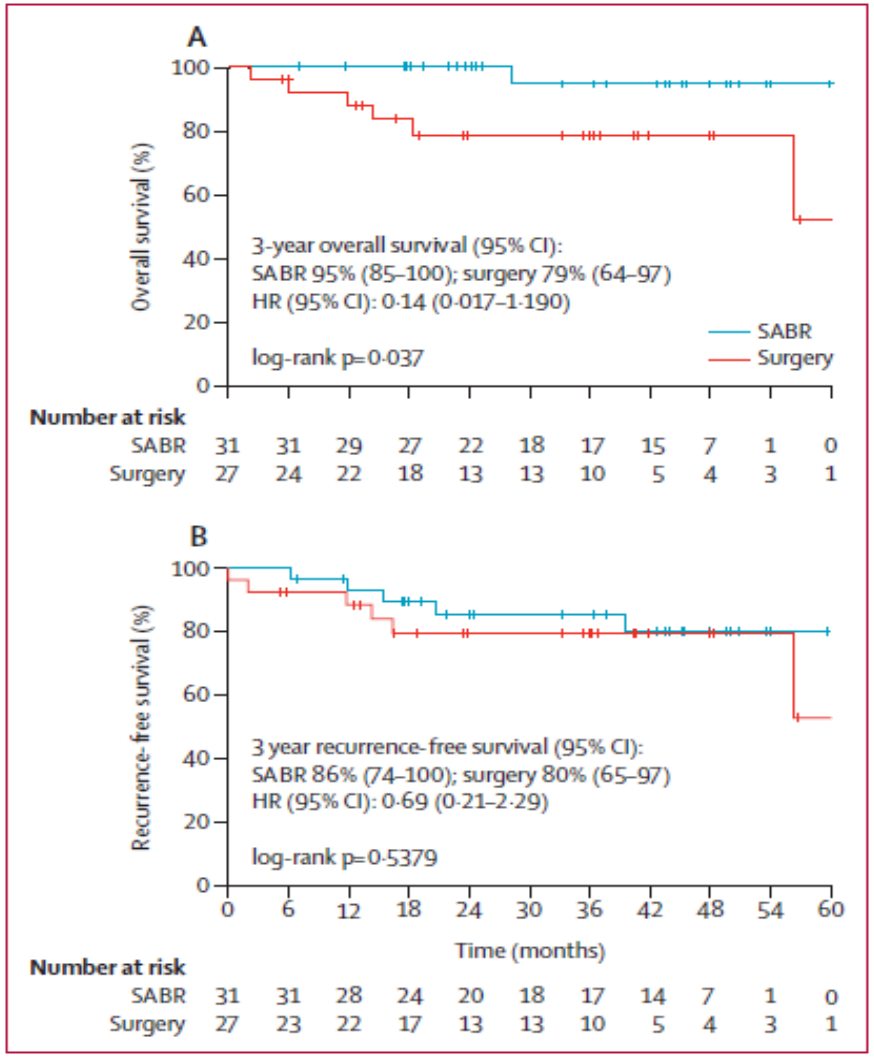
Joe Y Chang, Suresh Senan*, Marinus A Paul, Reza J Mehran, Alexander V Louie, Peter Balter, Harry J M Groen, Stephen E McRae, Joachim Widder, Lei Feng, Ben E E M van den Borne, Mark F Munsell, Coen Hurkmans, Donald A Berry, Erik van Werkhoven, John J Kresl, Anne-Marie Dingemans, Omar Dawood, Cornelis J A Haasbeek, Larry S Carpenter, Katrien De Jaeger, Ritsuko Komaki, Ben J Slotman, Egbert F Smit†, Jack A Roth†*

- Pooled analysis of STARS and ROSEL trials
- cT1-2a (<4 cm)N0M0 NSCLC, operable
- Randomized 1:1 to SABR vs lobectomy + mediastinal LND
- 58 patients (31 SABR, 27 surgery)
- Median follow-up: 40.2 months (SABR) and 35.4 months (surgery)

J Chang, S Senan et al., Lancet Oncol 2015

Results (STARS and ROSEL pooled analysis)

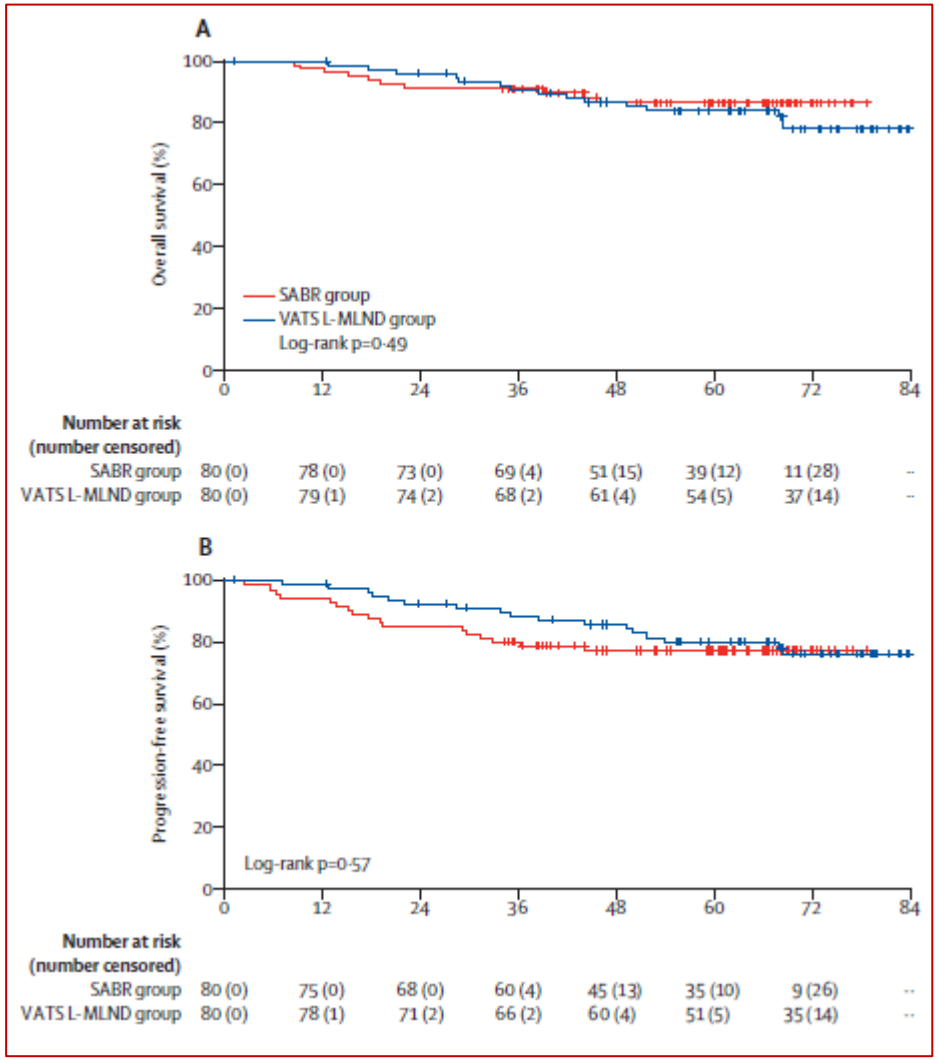
- 3 yr overall survival (estimated): 95% SABR vs. 79% surgery (p=0.037)
- 3 yr RFS : 86% SABR vs. 80% surgery (p = NS)
- Toxicity
  - SABR: grade 3= 10%, grade 4= 0%, grade 5= 0%
  - Surgery: grade 3-4= 44%, grade 5= 4%



J Chang, S Senan et al., Lancet Oncol 2015

REVISED STARS Trial

- 80 patients with Stage I operable NSCLC (patients not included in the initial STARS trial)
- 54 Gy/3 fractions (peripheral) or 50 Gy/4 fractions (central with SIB to GTV to 60 Gy)
- Pre-planned comparison to propensity matched surgical cohort who underwent VATS lobectomy with mediastinal LND, with non-inferiority statistics
- Median f/u time 5.1 yrs
- Overall survival:
  - SABR: 91% at 3 yrs and 87% at 5 yrs
  - VATS: 91% at 3 yrs, and 84% at 5 yrs
- Toxicity: No grade 4-5 toxicity; grade 3: 1% dyspnea
- **Conclusions**: Long-term survival of SABR is non-inferior to VATS lobectomy + mLND for operable Stage I NSCLC

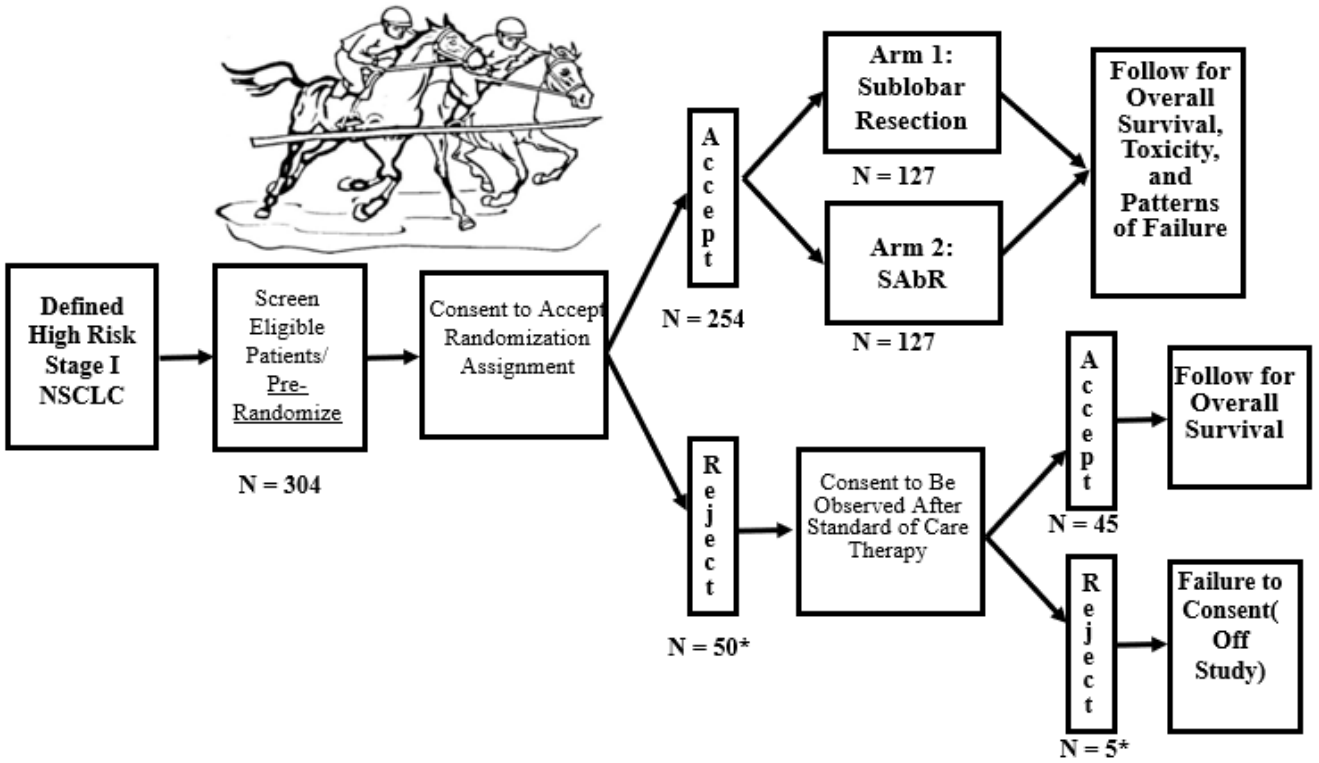


J Chang, et al., Lancet Oncol 2021

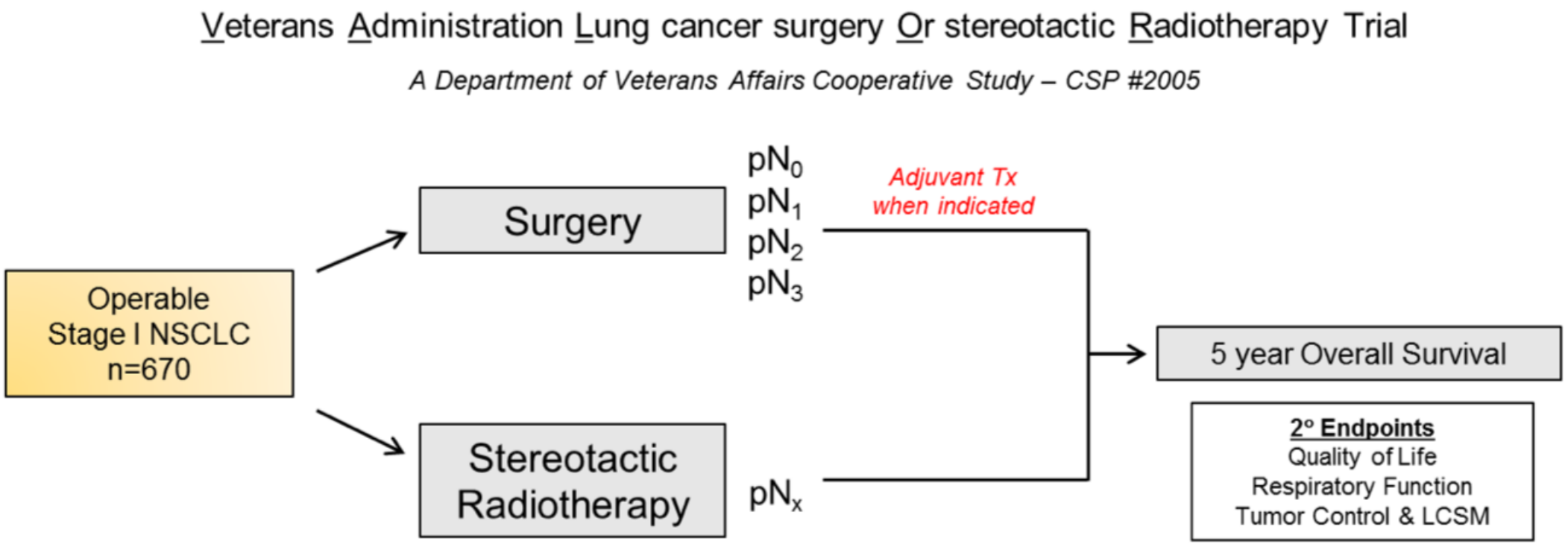
The STABLEMATES Trial

(formerly RTOG 1021/ACOSOG Z4099)

A Randomized Phase III Study of Sublobar Resection (SR) versus Stereotactic Ablative Radiotherapy (SAbR) in High Risk Patients with Stage I Non-Small Cell Lung Cancer (NSCLC)



VALOR Trial



Stratified by
- **Facility**
- **IA vs IB**
- **Central v Peripheral**

Surgery
- **Lobectomy or anatomic seg**
- **Lymph node sampling**
- **VATS/Robotic**

RT
- **Central: 10 Gy x 5**
- **Peripheral: 18 Gy x 3, 14 Gy x 4, 11.5 Gy x 5**

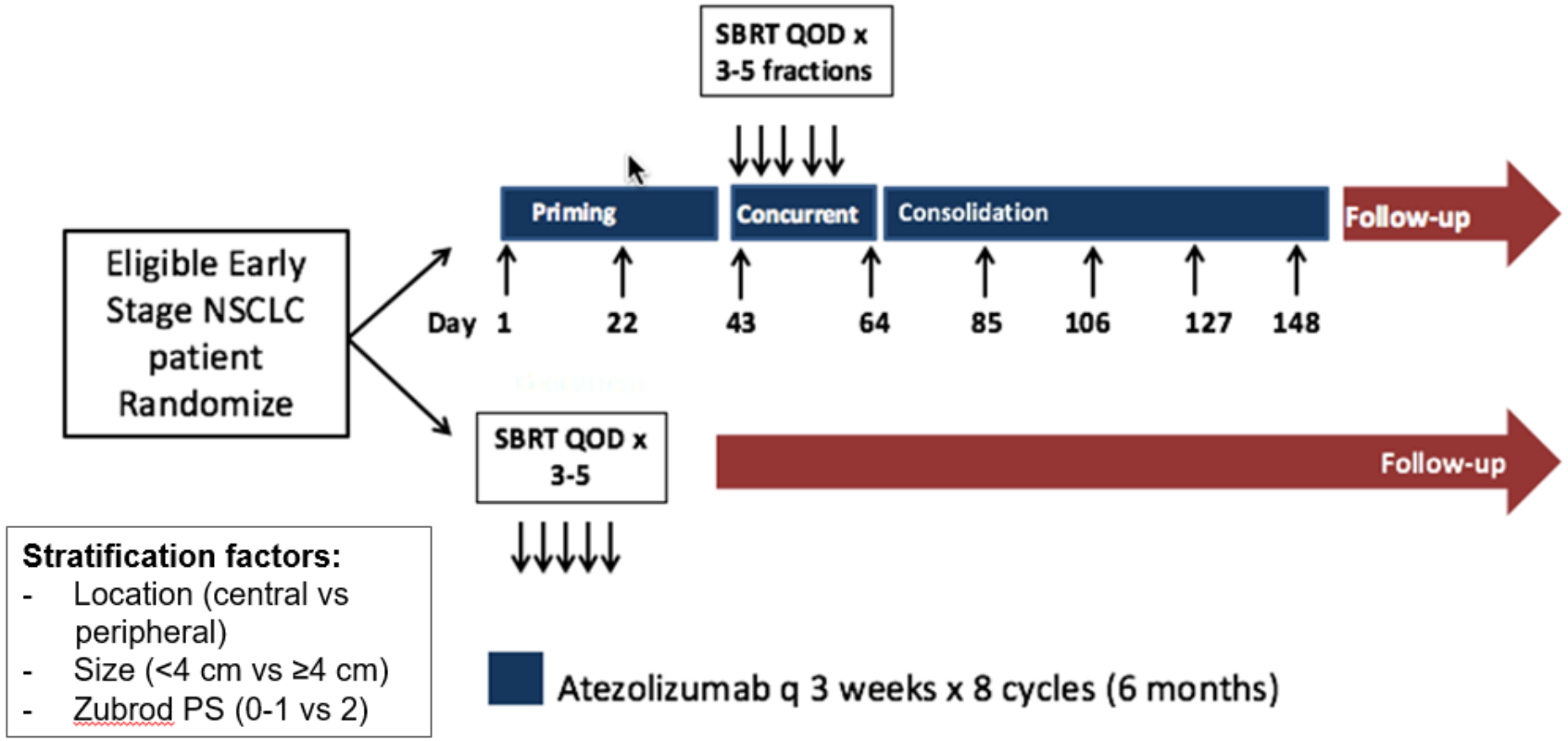
VALOR

PI: D. Moghanaki

WHAT ABOUT TARGETED AGENTS IN EARLY STAGE DISEASE?

Ongoing Phase 3 Trials

- **PACIFIC-4**: SBRT vs durvalumab after SBRT (1500 mg durva q4 wks)
- **NRG/SWOG S1914:** SBRT vs atezolizumab before/during/after SBRT



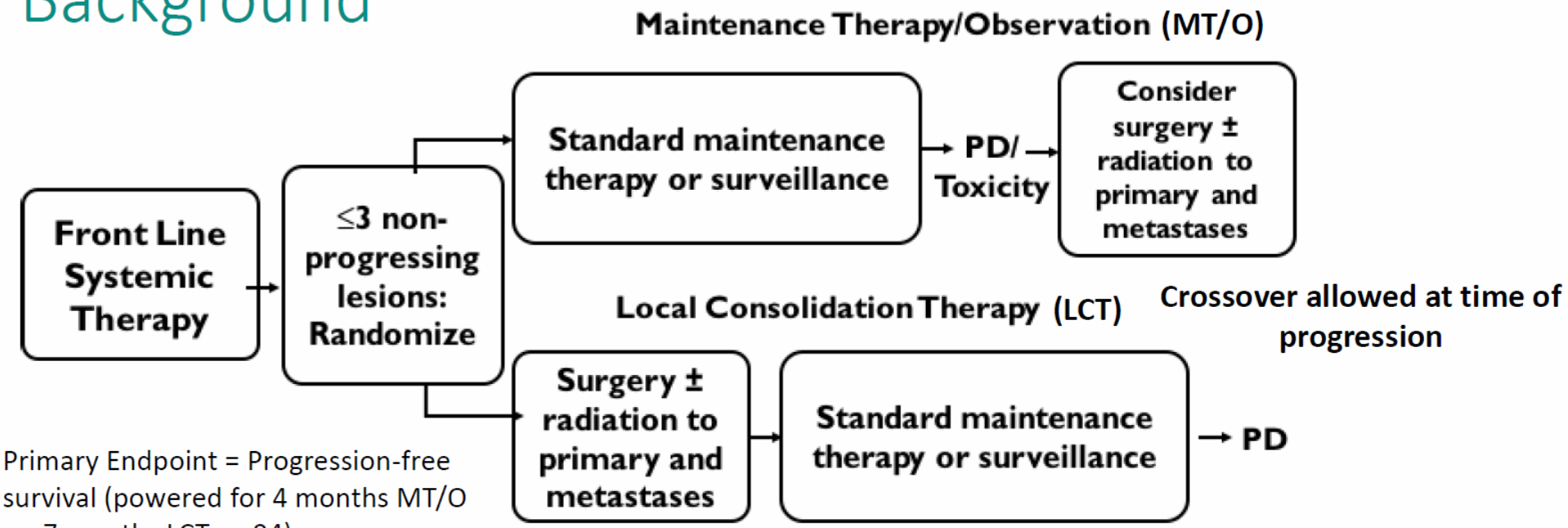
STAGE IV NSCLC

ROLE OF RADIATION BECOMING INCREASINGLY IMPORTANT IN STAGE IV DISEASE

Local Consolidative Therapy for Oligometastatic NSCLC

Randomized phase II trial

Background



Primary Endpoint = Progression-free survival (powered for 4 months MT/O vs. 7 months LCT, n=94)

Secondary Endpoints: Overall survival, safety/toxicity, time to appearance of new lesions

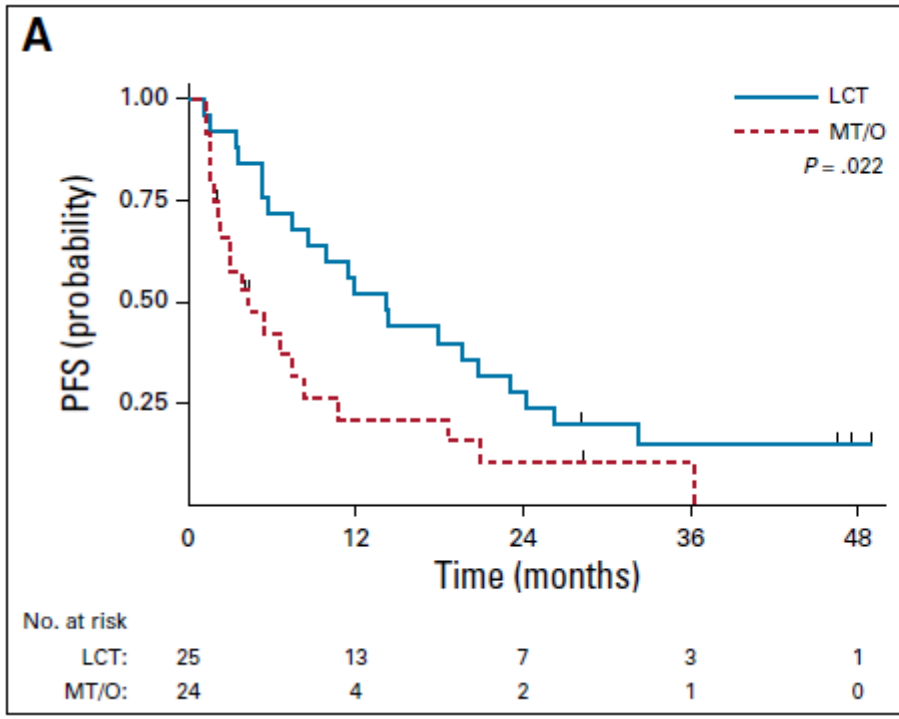
Balanced randomization: 1) Number of metastases (0-1 vs. 2-3), 2) Response to first-line systemic therapy (stable disease vs. partial response), 3) N0-N1 vs. N2-N3, 4) CNS vs. no CNS metastases, 5) EGFR/ALK alteration vs. wild type

D Gomez, ASTRO, 2018

Oligometastatic NSCLC

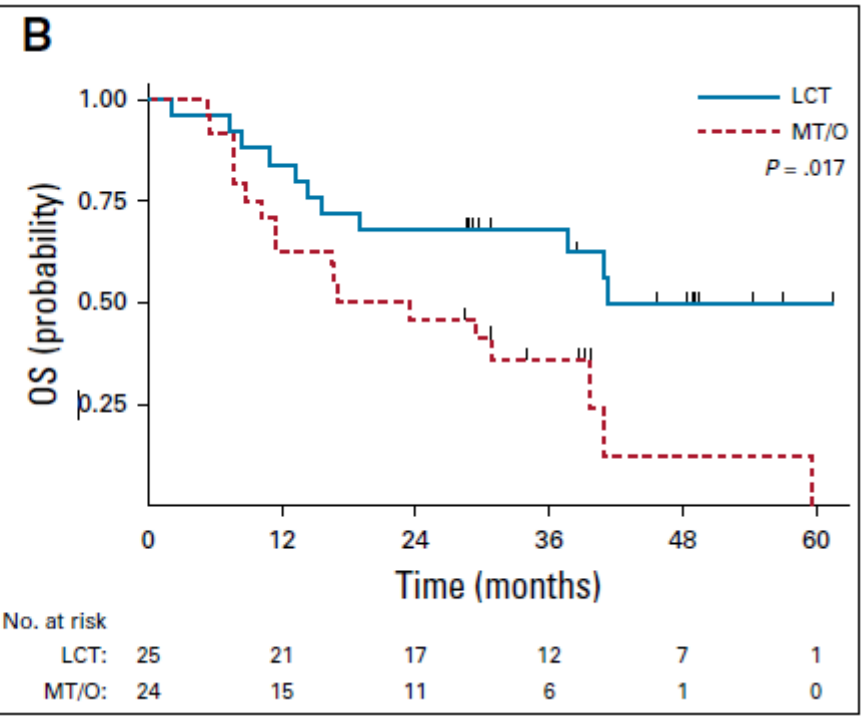
DSMB recommended early closure after 49 patients

Progression-Free Survival



Median PFS 4.4 months vs 14.2 months

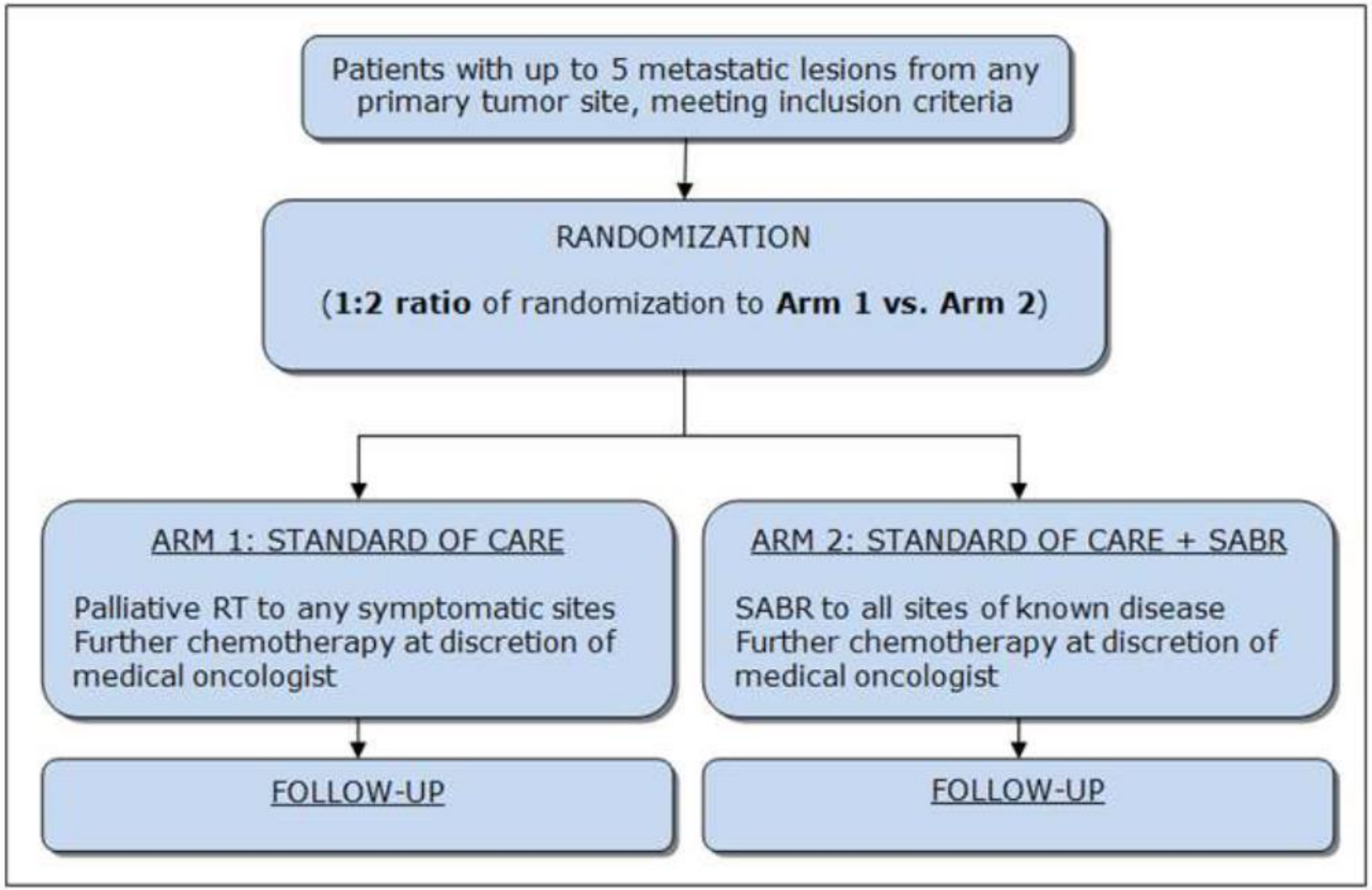
Overall Survival



Median OS 17.0 months vs 41.2 months

D Gomez, JCO, 2019

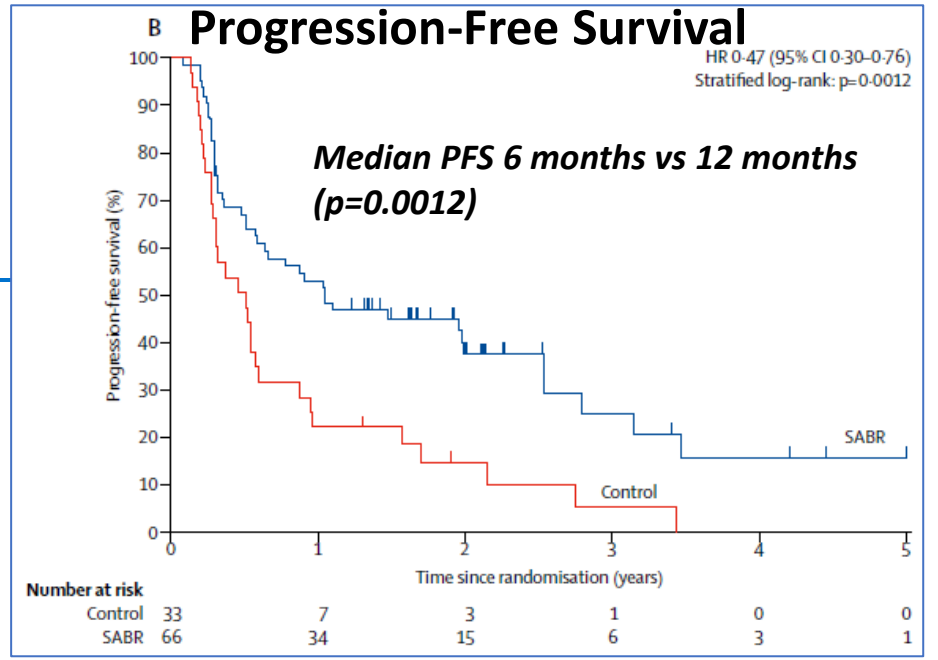
SABR-COMET

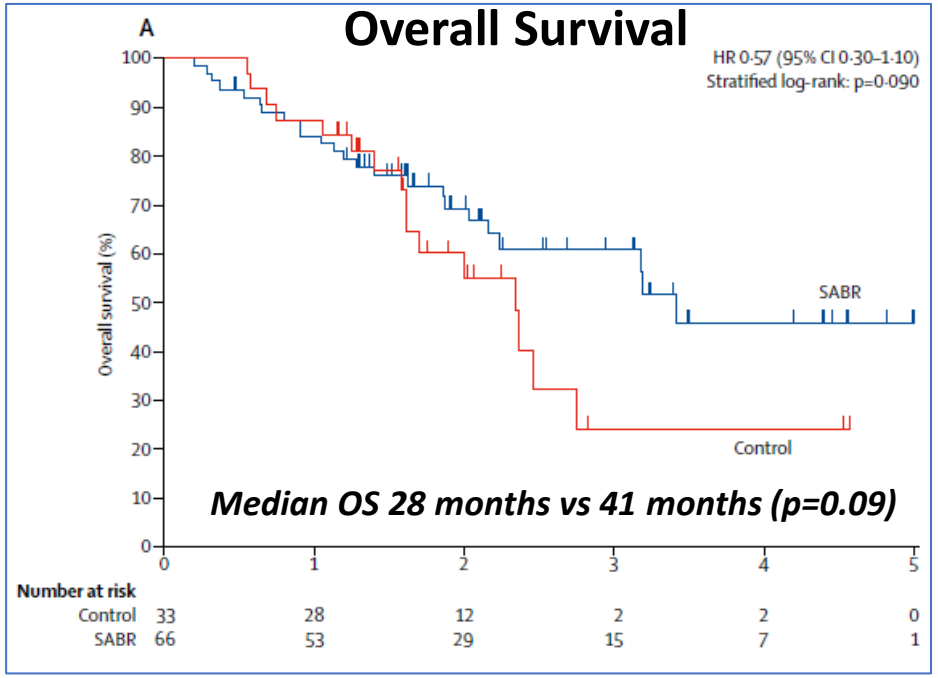


D Palma, ASTRO, 2018

SABR-COMET

	Control group (n=33)	SABR group (n=66)
Age	69 (64–75)	67 (59–74)
Sex		
Men	19 (58%)	40 (61%)
Women	14 (42%)	26 (39%)
Site of original primary tumour		
Breast	5 (15%)	13 (20%)
Colorectal	9 (27%)	9 (14%)
Lung	6 (18%)	12 (18%)
Prostate	2 (6 %)	14 (21%)
Other	11 (33%)	18 (27%)
Time from diagnosis of primary tumour to randomisation (years)	2·3 (1·3–4·5)	2·4 (1·6–5·3)
Number of metastases		
1	12 (36 %)	30 (46%)
2	13 (40%)	19 (29%)
3	6 (18%)	12 (18%)
4	2 (6%)	2 (3%)
5	0 (0%)	3 (5%)
Location of metastases		
Adrenal	2/64 (3%)	7/127 (6%)
Bone	20/64 (31%)	45/127 (35%)
Liver	3/64 (5%)	16/127 (13%)
Lung	34/64 (53%)	55/127 (43%)
Other*	5/64 (8%)	4/127 (3%)



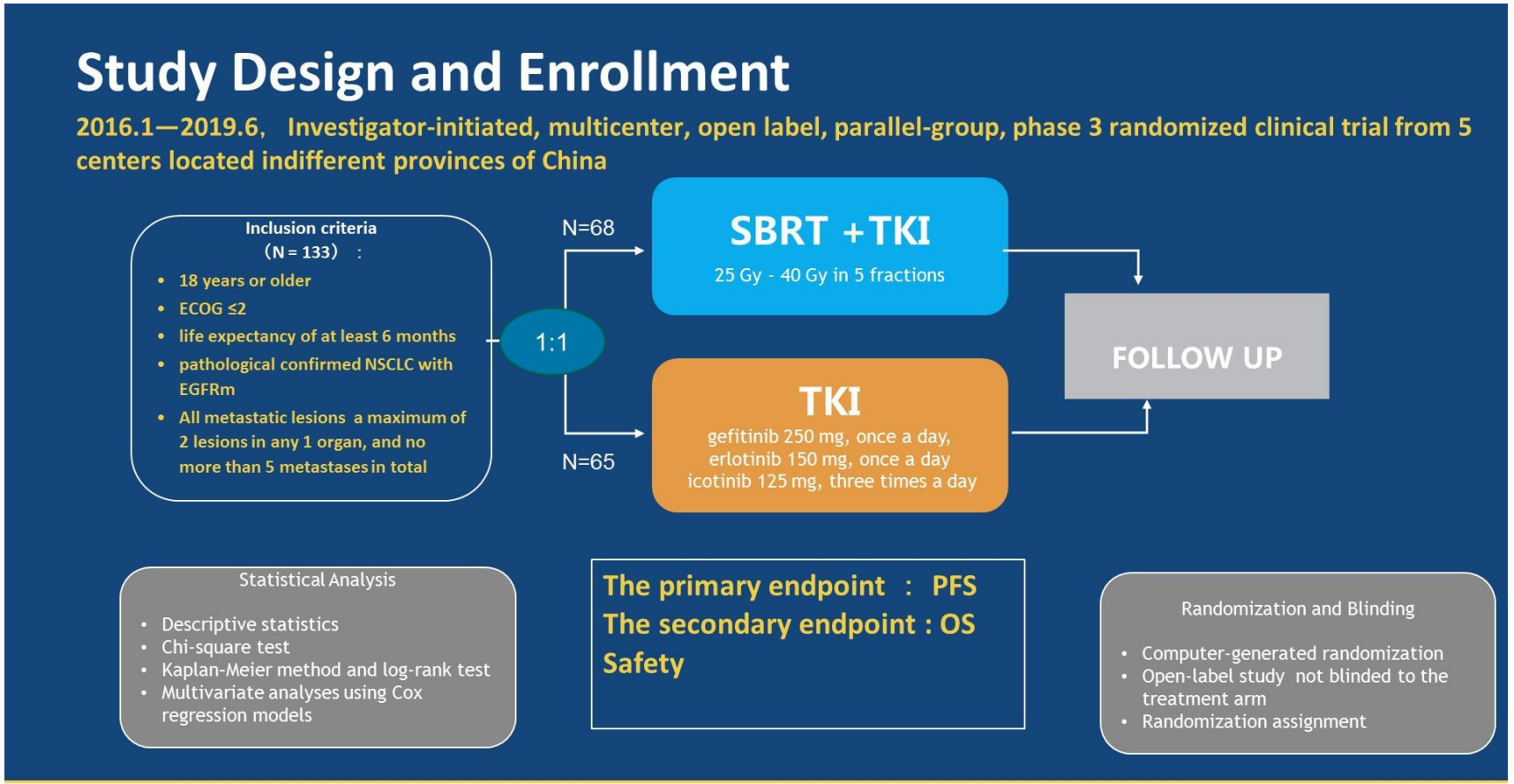


D Palma, Lancet, 2019

City of Hope

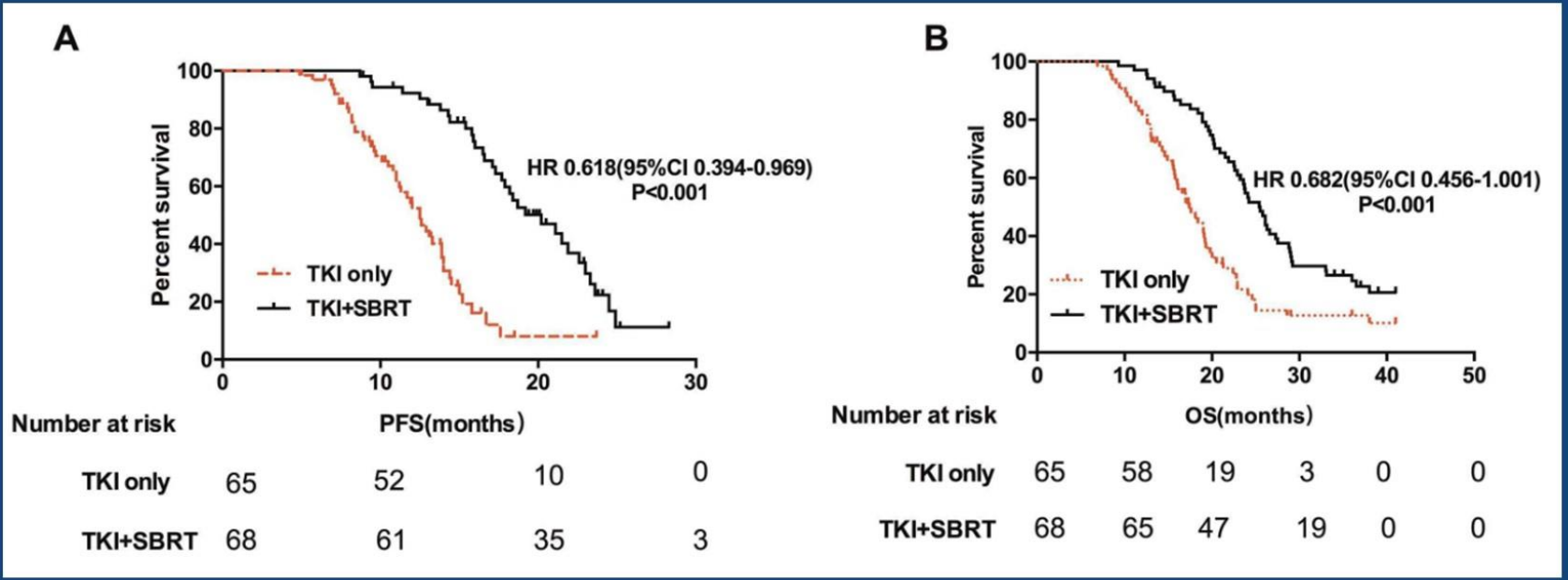
SINDAS trial (ASCO 2020)

- First-Line TKI With or Without Aggressive Upfront Local Radiation Therapy in Patients with EGFRm Oligometastatic NSCLC



SINDAS Trial: Outcomes

Kaplan-Meier plot of PFS (A) and OS (B)



SBRT=stereotactic body radiotherapy. HR=hazard ratio. (A) PFS and (B) OS. PFS,=progression-free survival; OS,=overall survival; C= confidence interval

SINDAS Trial: Toxicity

Toxicity （Grade 3 adverse events）

	TKI and SBRT arm (20 incidences)	TKI arm (13 incidences)	P
grade skin rash	10（50%）	8（62%）	0.423
severe liver injury	0	1（8%）	0.208
pneumonitis	6（30%）	2（15%）	0.338
Esophagitis	3 (15%)	2（15%）	0.976
Pathological rib fracture	1（5%）	0	0.413

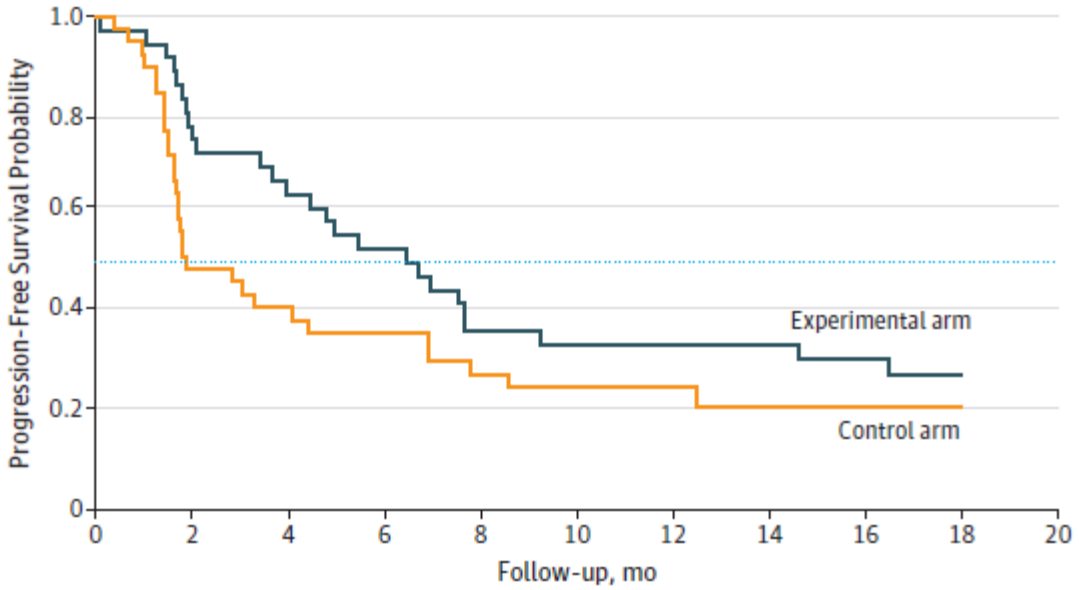
PEMBRO-RT

- **Randomized phase 2 study** of 76 patients with advanced NSCLC
- **Pembro vs RT followed by pembro** (**8 Gy x 3**; **single tumor site**)
- ORR (12 weeks)= 18% pembro vs. 36% pembro+RT (p=0.07)
- DCR (12 weeks)= 40% pembro vs. 64% pembro+RT (**p=0.04**)
- Median PFS= 1.9 mos pembro vs. 6.6 mos pembro+RT (p=0.19)
- Median OS= 17.6 mos pembro vs. 15.9 mos pembro+RT (p=0.16)
- Subgroup: **largest benefit to PD-L1 negative tumors**
  - HR for PFS 0.49, p=0.03
  - HR for OS 0.48, p=0.046

W Theelen et al., JAMA Onc, 2019

PEMBRO-RT

A Progression-free survival

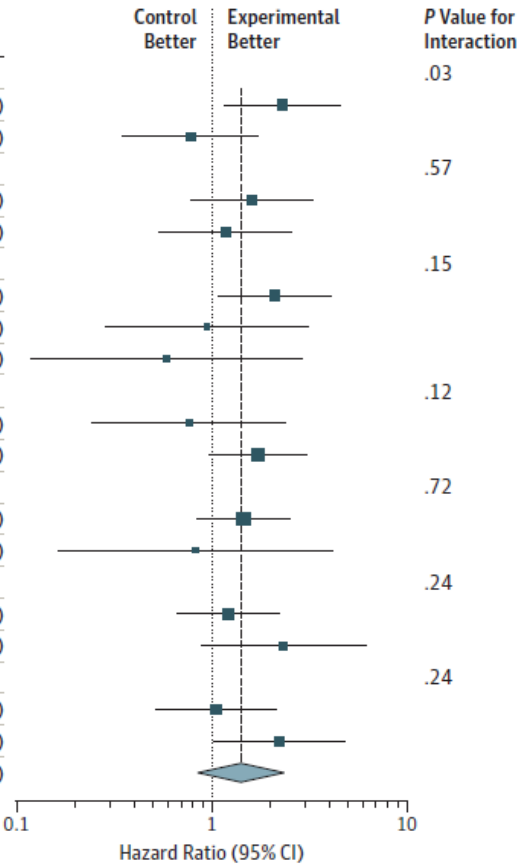


No. at risk

Experimental arm	36	28	23	19	13	12	12	11	10	9
Control arm	40	19	15	13	10	6	6	5	5	5

B Subgroup analysis

Subgroup	Control Events, No./ Total No.	Experimental Events, No./ Total No.	Hazard Ratio (95% CI)	*P* Value for Interaction
Sex				.03
Male	20/23	14/20	2.31 (1.15-4.62)	
Female	10/17	15/16	0.78 (0.35-1.74)	
ECOG performance score				.57
0	18/22	13/16	1.61 (0.78-3.32)	
1	11/17	15/19	1.18 (0.54-2.57)	
PD-L1, %				.15
0	22/25	17/18	2.11 (1.08-4.11)	
1-49	5/8	6/8	0.95 (0.28-3.14)	
≥50	2/5	6/10	0.58 (0.12-2.91)	
Smoking, pack-years				.12
<10	5/8	7/7	0.76 (0.24-2.41)	
≥10	25/32	22/29	1.73 (0.97-3.09)	
Histology				.72
Nonsquamous	27/36	26/31	1.45 (0.84-2.51)	
Squamous	3/4	3/5	0.82 (0.16-4.16)	
Lines of previous chemotherapy				.24
1	22/31	20/26	1.22 (0.66-2.24)	
≥2	8/9	9/10	2.35 (0.88-6.24)	
Age at randomization, y				.24
<65	14/22	17/21	1.06 (0.52-2.15)	
≥65	16/18	12/15	2.24 (1.03-4.86)	
Total	30/40	29/36	1.41 (0.85-2.36)	

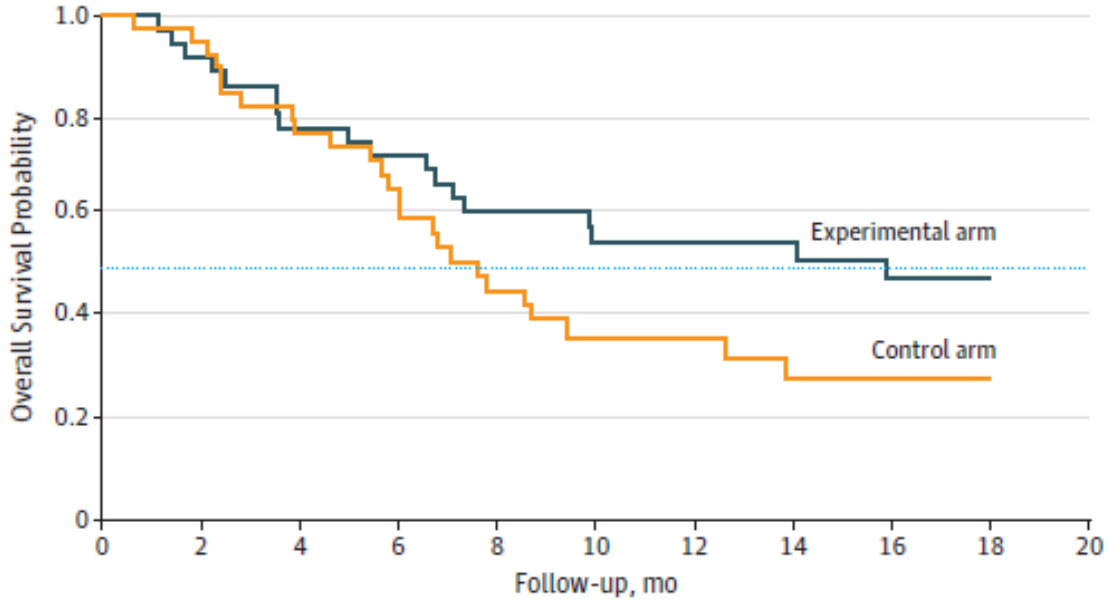


City of Hope

W Theelen et al., JAMA Onc, 2019

PEMBRO-RT

A Overall survival

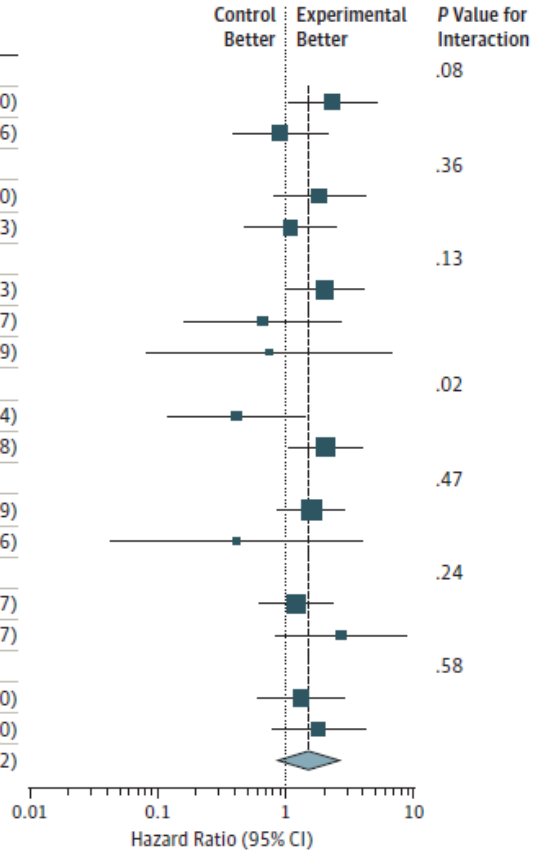


No. at risk

Experimental arm	36	33	28	26	20	18	18	16	14	14
Control arm	40	37	29	23	16	9	9	7	7	7

B Subgroup analysis

Subgroup	Control Events, No./ Total No.	Experimental Events, No./ Total No.	Hazard Ratio (95% CI)	P Value for Interaction
Sex				.08
Male	17/23	9/20	2.37 (1.04-5.40)	
Female	9/17	12/16	0.90 (0.38-2.16)	
ECOG performance score				.36
0	15/22	9/16	1.85 (0.80-4.30)	
1	10/17	12/19	1.09 (0.47-2.53)	
PD-L1, %				.13
0	21/25	13/18	2.06 (1.00-4.23)	
1-49	3/8	5/8	0.65 (0.15-2.77)	
≥50	1/5	3/10	0.74 (0.08-7.09)	
Smoking, pack-years				.02
<10	4/8	6/7	0.40 (0.11-1.44)	
≥10	22/32	15/29	2.09 (1.07-4.08)	
Histology				.47
Nonsquamous	24/36	18/31	1.61 (0.86-2.99)	
Squamous	2/4	3/5	0.40 (0.04-4.06)	
Lines of previous chemotherapy				.24
1	19/31	16/26	1.21 (0.62-2.37)	
≥2	7/9	5/10	2.77 (0.83-9.27)	
Age at randomization, y				.58
<65	13/22	12/21	1.31 (0.59-2.90)	
≥65	13/18	9/15	1.81 (0.77-4.30)	
Total	26/40	21/36	1.52 (0.85-2.72)	



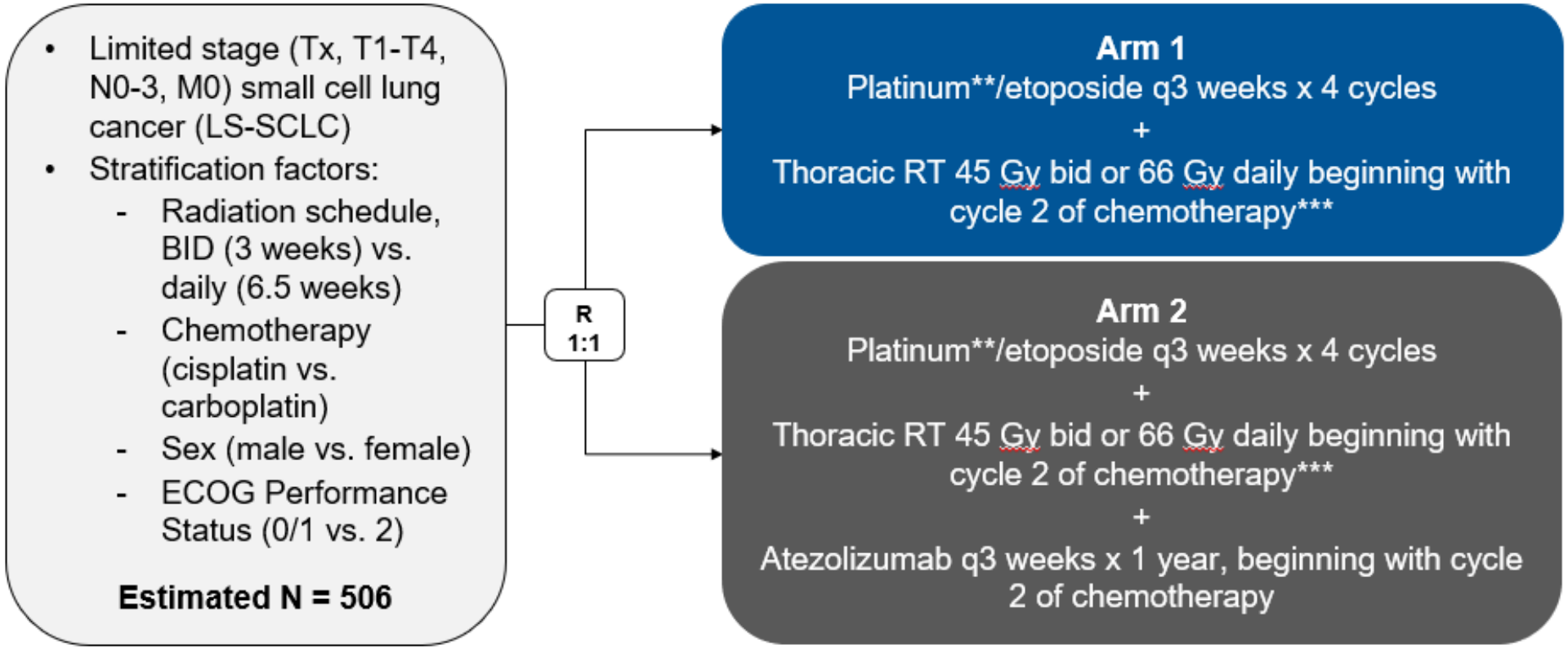
City of Hope

W Theelen et al., JAMA Onc, 2019

SMALL CELL LUNG CANCER

NRG LU005

- Multiple trials in extensive-stage SCLC show benefit with adding anti-PD-L1 drugs to chemotherapy (e.g. CASPIAN-durvalumab, IMpower133- atezolizumab)



CONCLUSIONS

- A potential strategy to improve outcomes in lung cancer with radiation is through the use of targeted therapies, including checkpoint inhibitor (CPI) immunotherapy
- Many trials combining targeted agents with radiation or chemoradiation have failed
- The PACIFIC trial established that maintenance durvalumab after chemoradiation for Stage III locally-advanced NSCLC dramatically improved PFS and OS (a breakthrough)
- Initial results of phase I & II clinical trials demonstrate the relative feasibility and safety of combining immunotherapy with chemoradiation for Stage III NSCLC
- Radiation has an emerging role in the management of oligometastatic lung cancer
- Future trials in locally-advanced, early-stage, and oligometastatic NSCLC (and limited-stage SCLC) will further solidify potential roles for targeted therapies, including CPI, in combination with radiation or chemoradiation

THANK YOU!!

Terence Williams, MD, PhD

Professor and Chair, Department of Radiation Oncology

Adjunct Professor, Department of Cancer Genetics and Epigenetics

City of Hope National Medical Center

Email: terwilliams@coh.org

@TeWilliamsMD @COH_RadOnc