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

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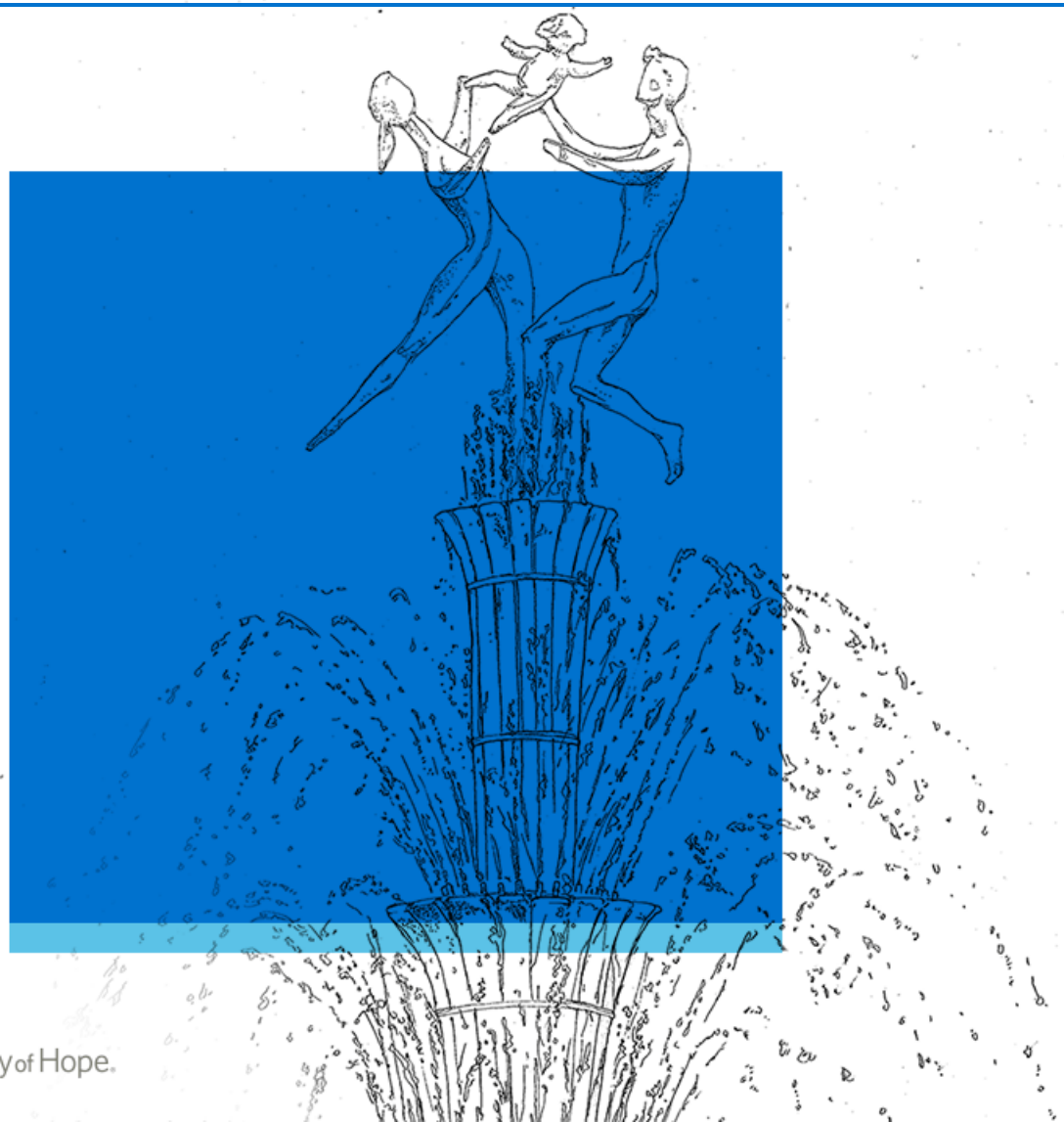
Disclosures

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

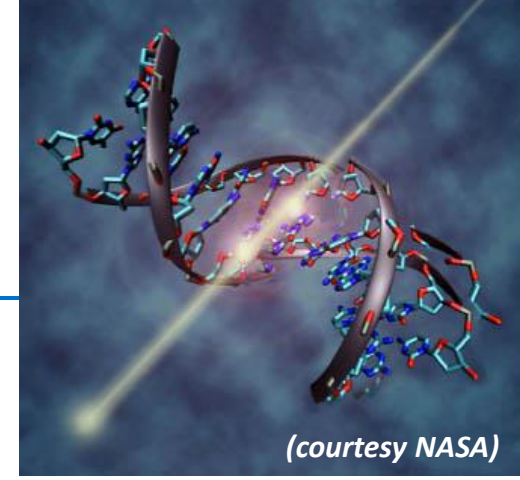
Outline

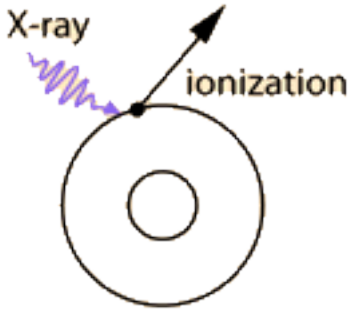


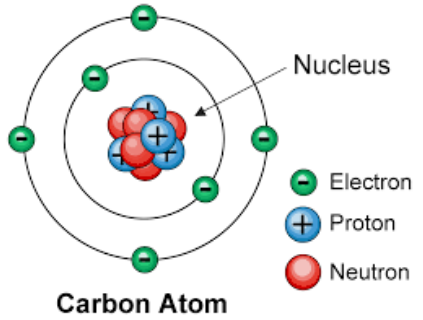
1. Radiation Therapy and the Therapeutic Index
2. Locally-advanced NSCLC
3. Early-stage NSCLC
4. Stage IV NSCLC (oligometastatic)
5. SCLC

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 or charged particles
- 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 modality or in combination with surgery or systemic therapies (e.g. chemotherapy, immunotherapy, etc.)

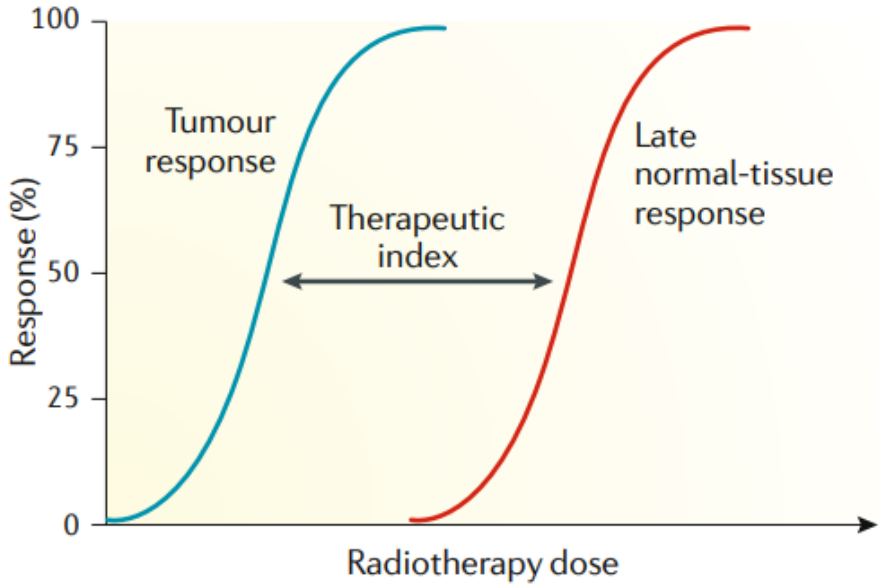






Therapeutic Index of Radiotherapy

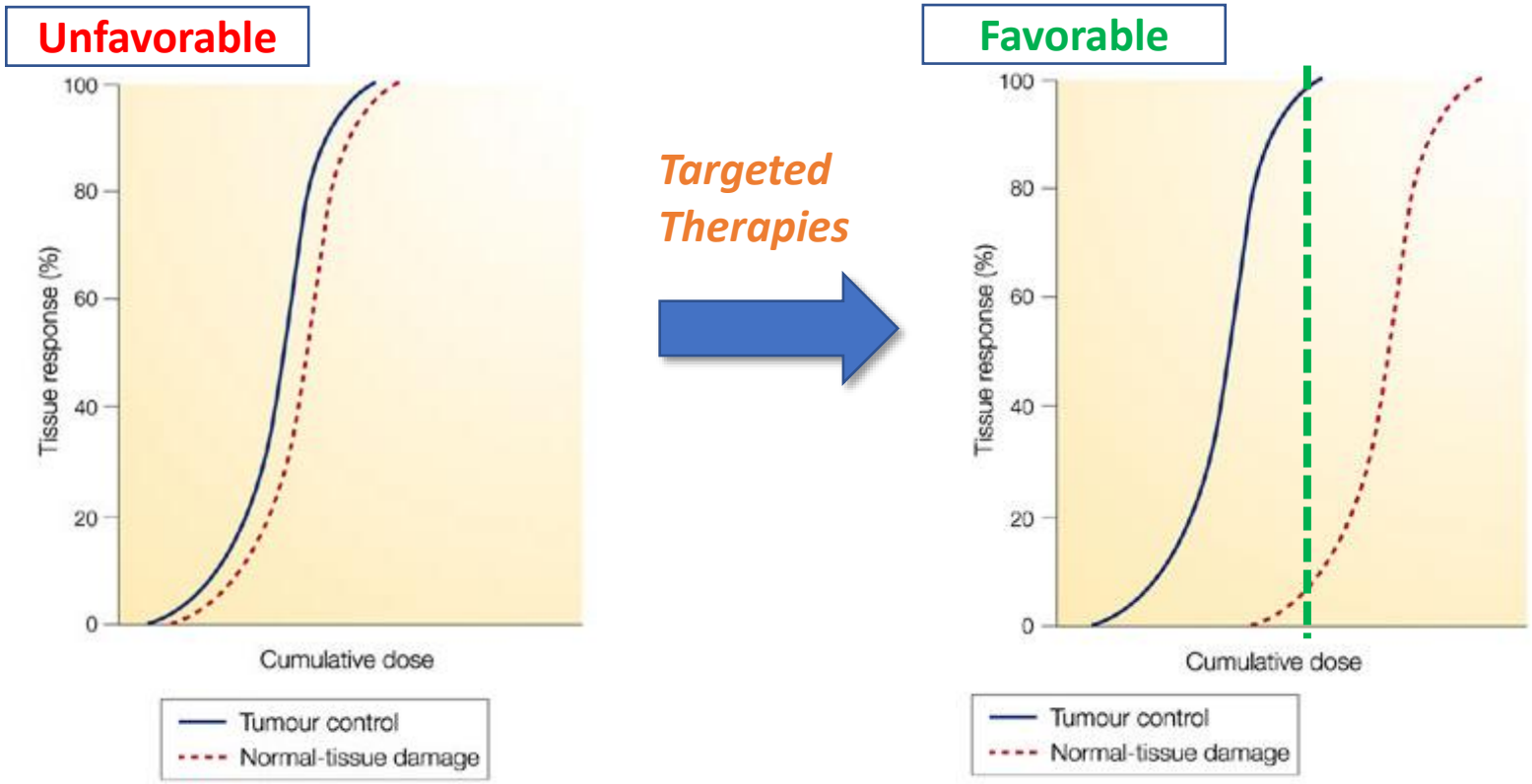
- Ratio between the effects on tumor tissue versus the effects on normal tissues (organs at risk)
- Index is favorable if response of tumor tissue is greater than the surrounding normal tissue
- Therapeutic index can be increased by biological or physical methods
  - **Physical**: improved tumor targeting
  - **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.

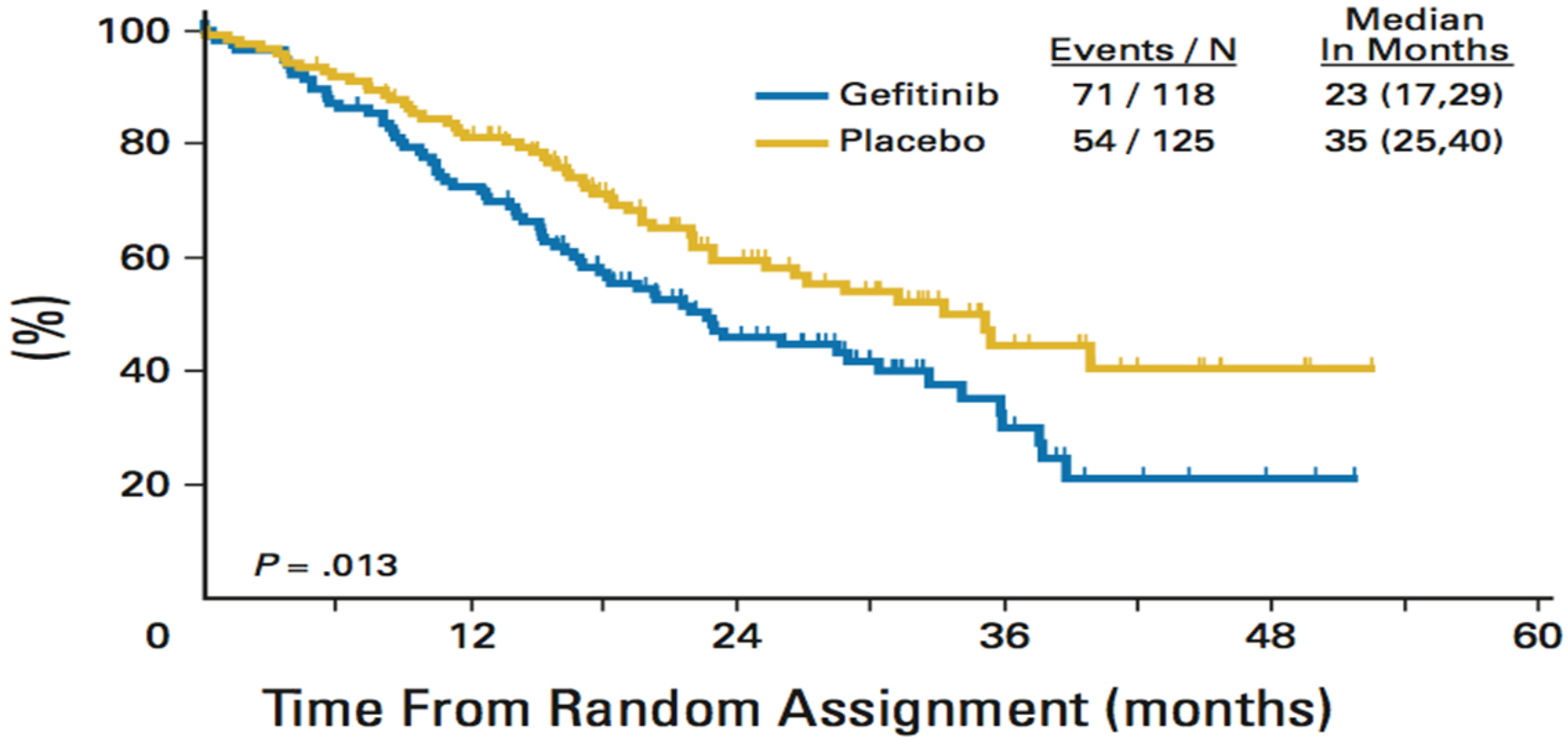


LOCALLY-ADVANCED NSCLC

Failures of Targeted Therapies – Example 1 (Gefitinib)

(Maintenance gefitinib in unselected patients)

SWOG 0023 - EGFR TKI after chemo/RT



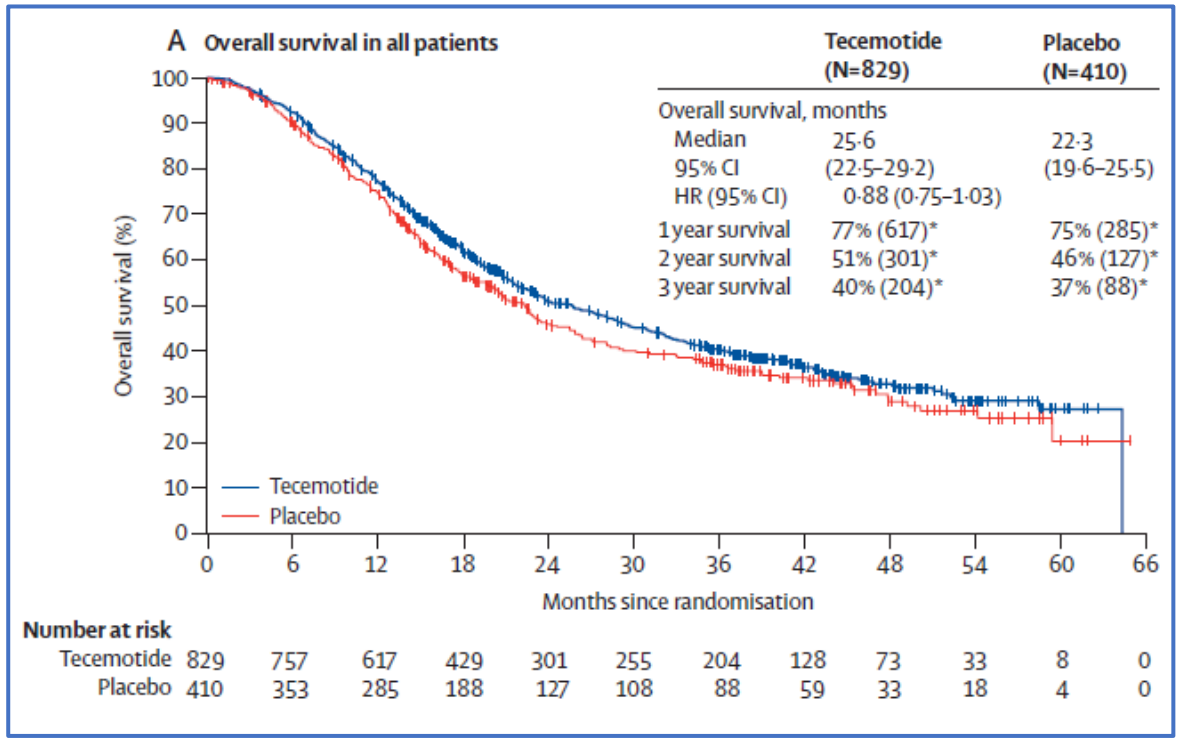
K Kelly, et al., JCO, 2008

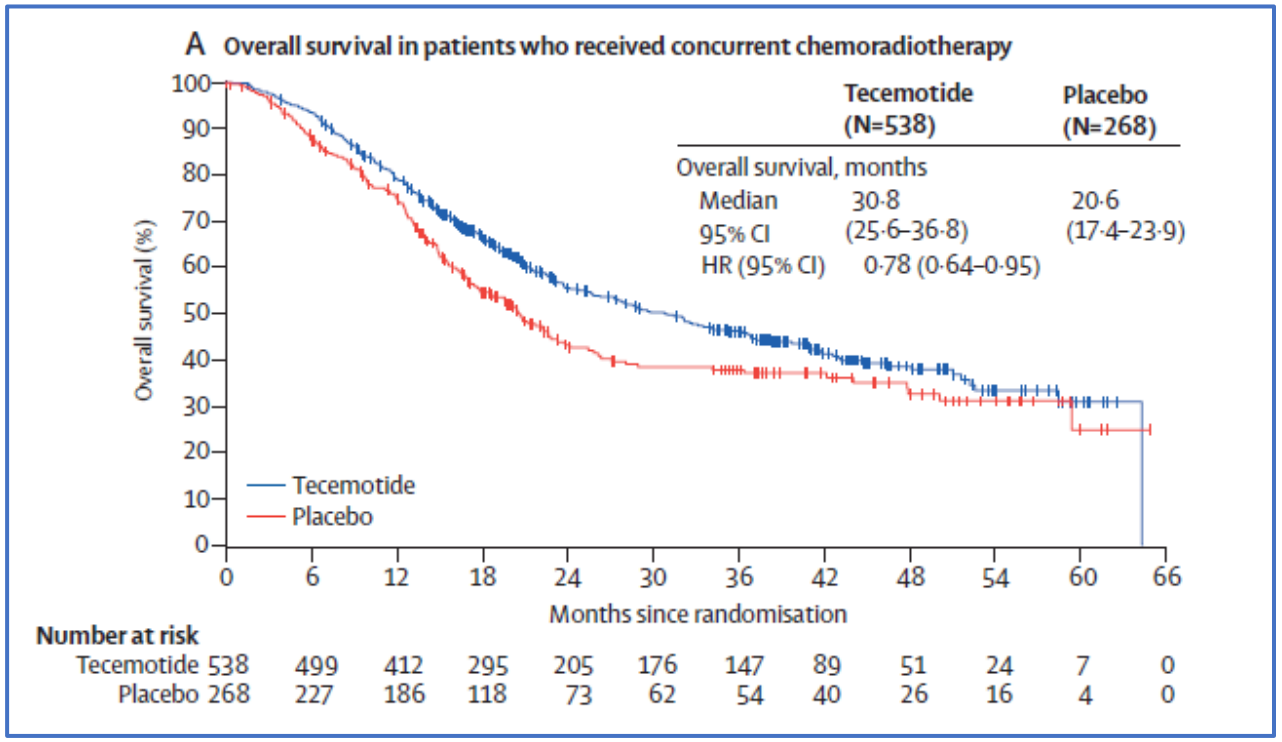
Failures of Targeted Therapies – Example 2 (Bevacizumab)

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)





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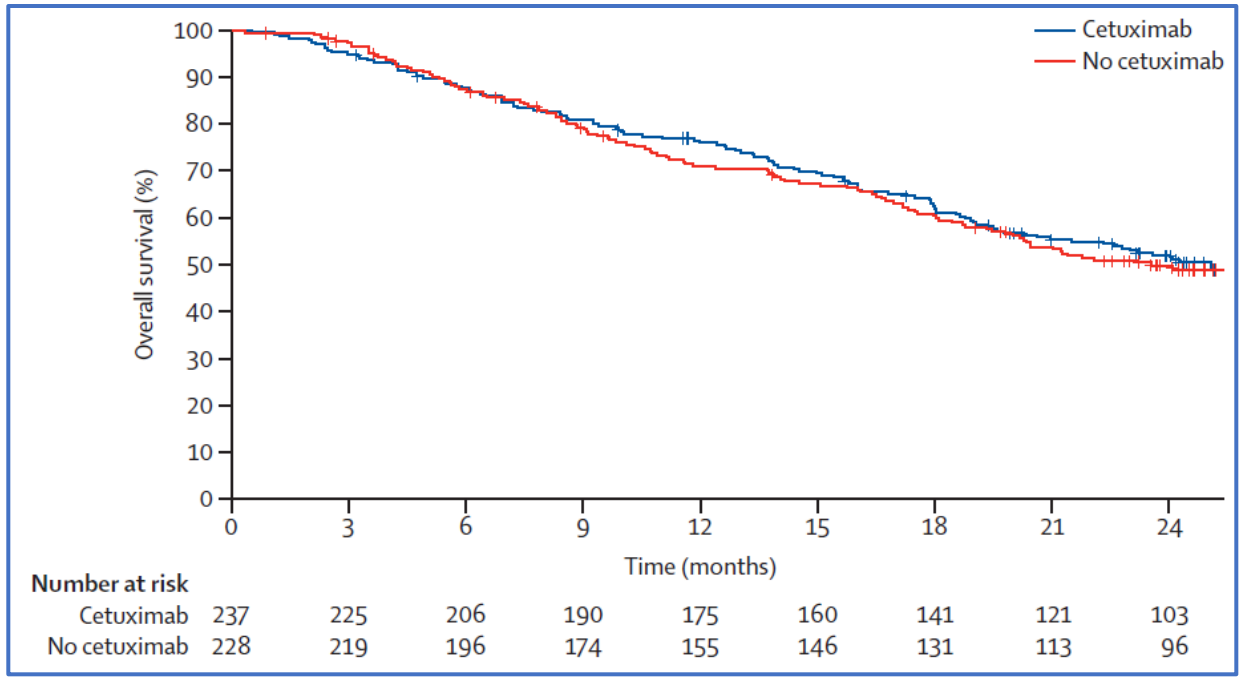
C Butts, et al., Lancet Oncol, 2014

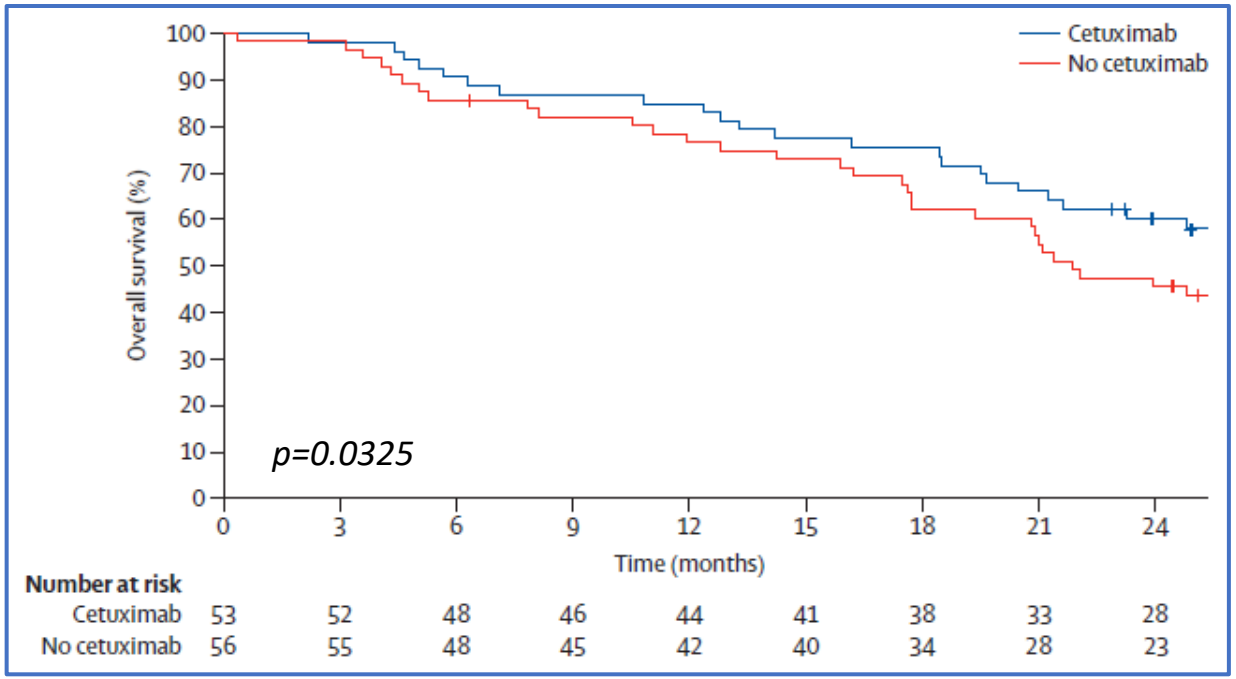
Failures of Targeted Therapies- Example 4 (Cetuximab)

RTOG 0617: Cetuximab vs. no Cetuximab

All patients



Tumors with high EGFR expression (H score≥ 200)



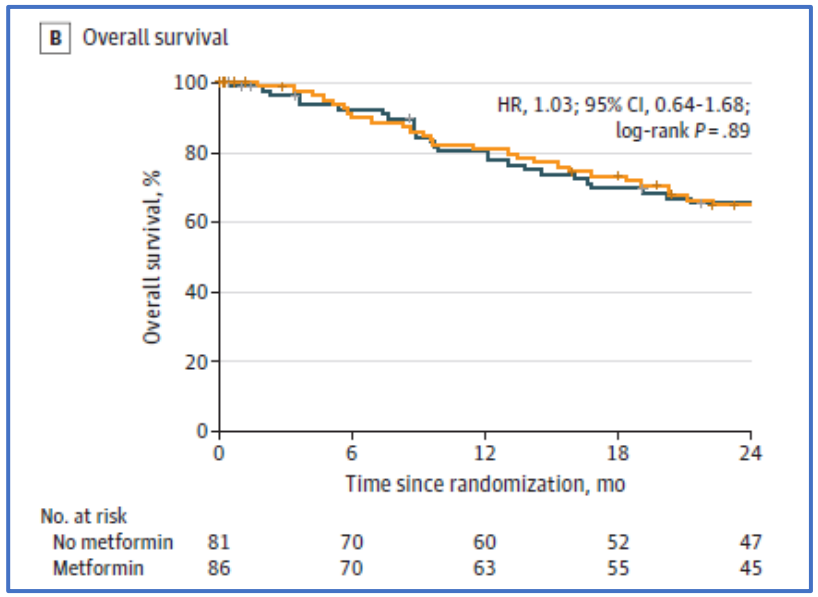
J Bradley, et al., Lancet Oncol, 2015

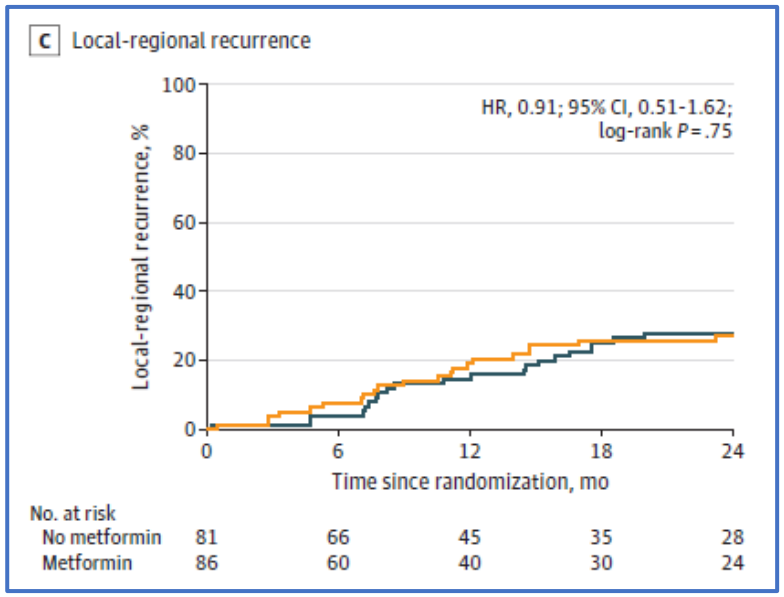
Failures of Targeted Therapies – Example 5 (Metformin)

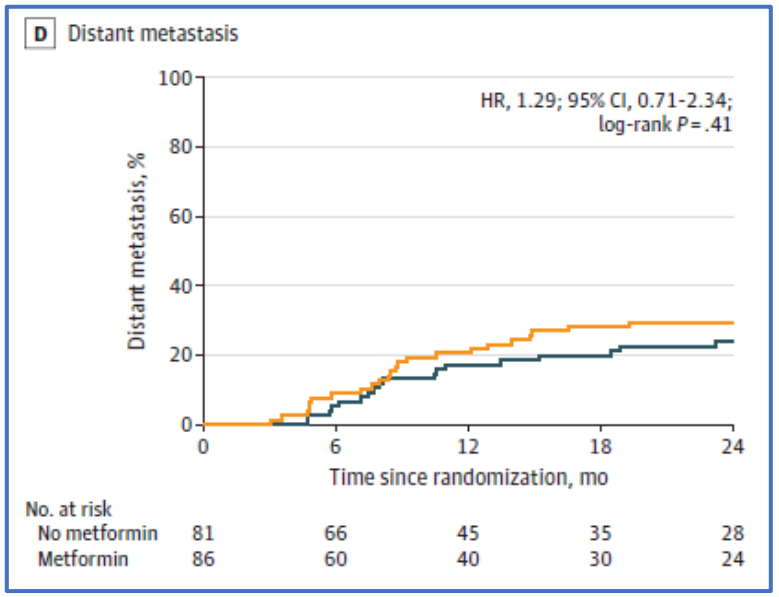
JAMA Oncology | Original Investigation

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

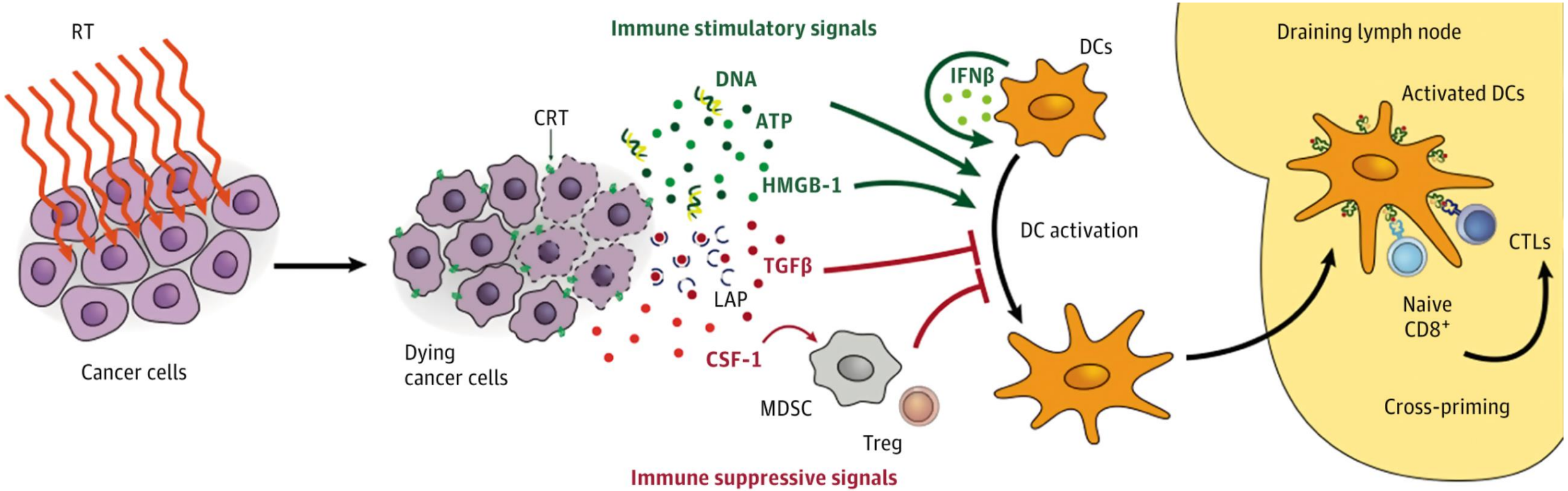
R A N D O M I Z E

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

Arm 2: Concurrent chemotherapy and radiation, 60Gy

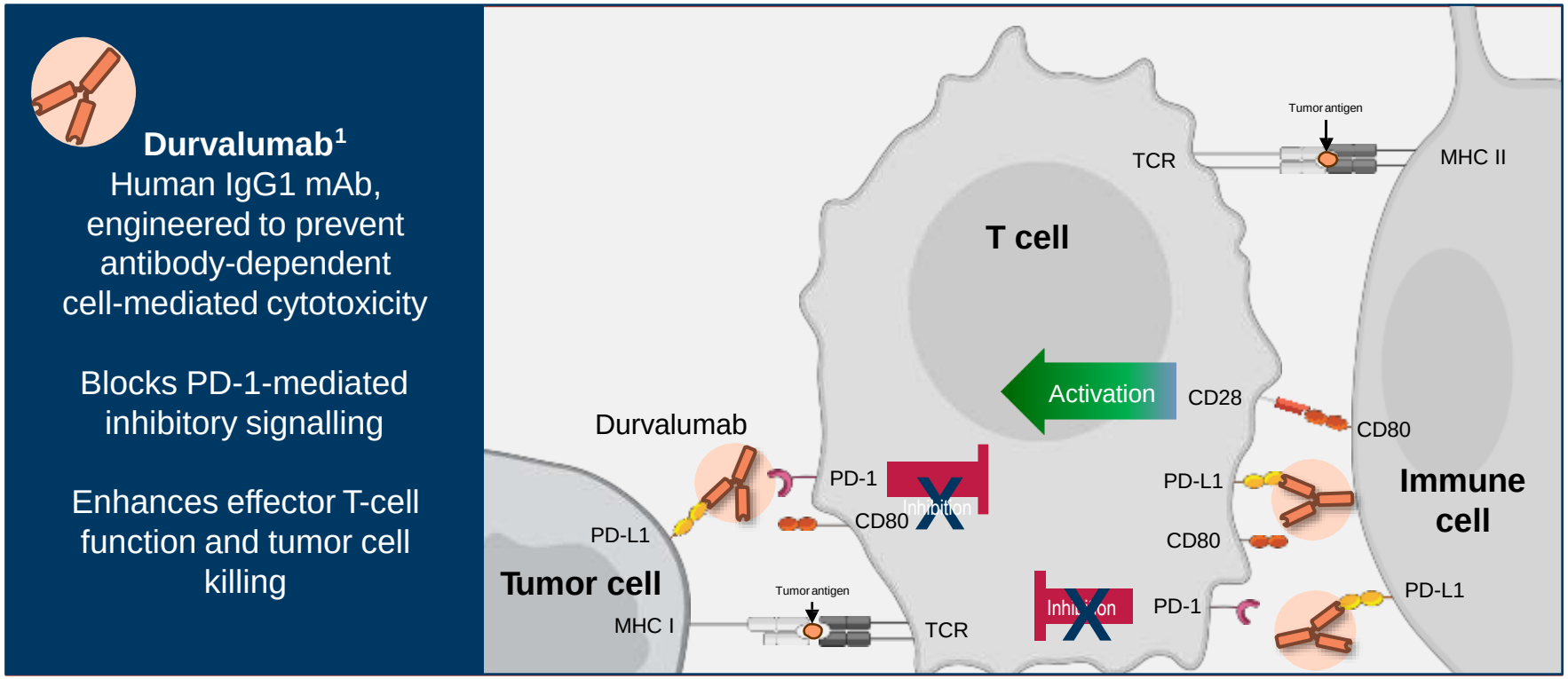
THEN CAME IMMUNOTHERAPY….

Role of Local Radiation Therapy in Cancer Immunotherapy



S Demaria, et al., JAMA Onc, 2015

Durvalumab Blocks PD-L1 Binding to PD-1

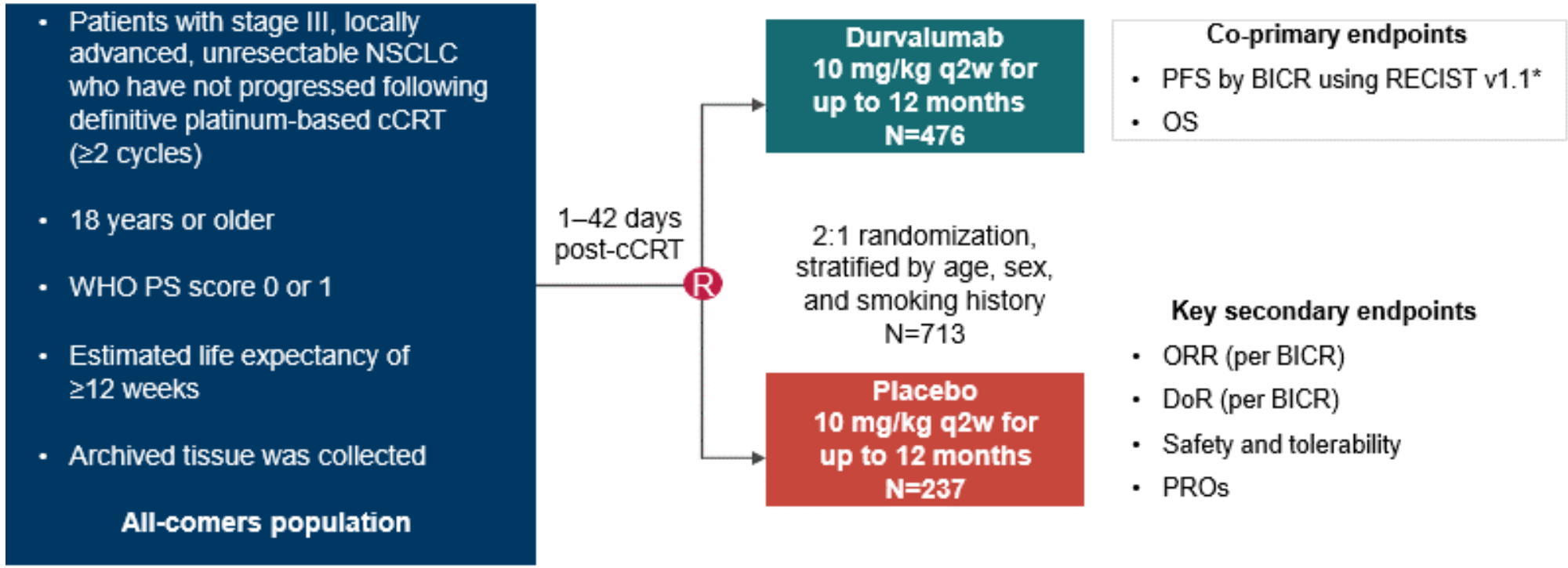


mAb, monoclonal antibody; MHC, major histocompatibility complex; PD-1, programmed cell dealth-1; PD-L1, programmed cell death ligand-1; TCR, T-cell receptor

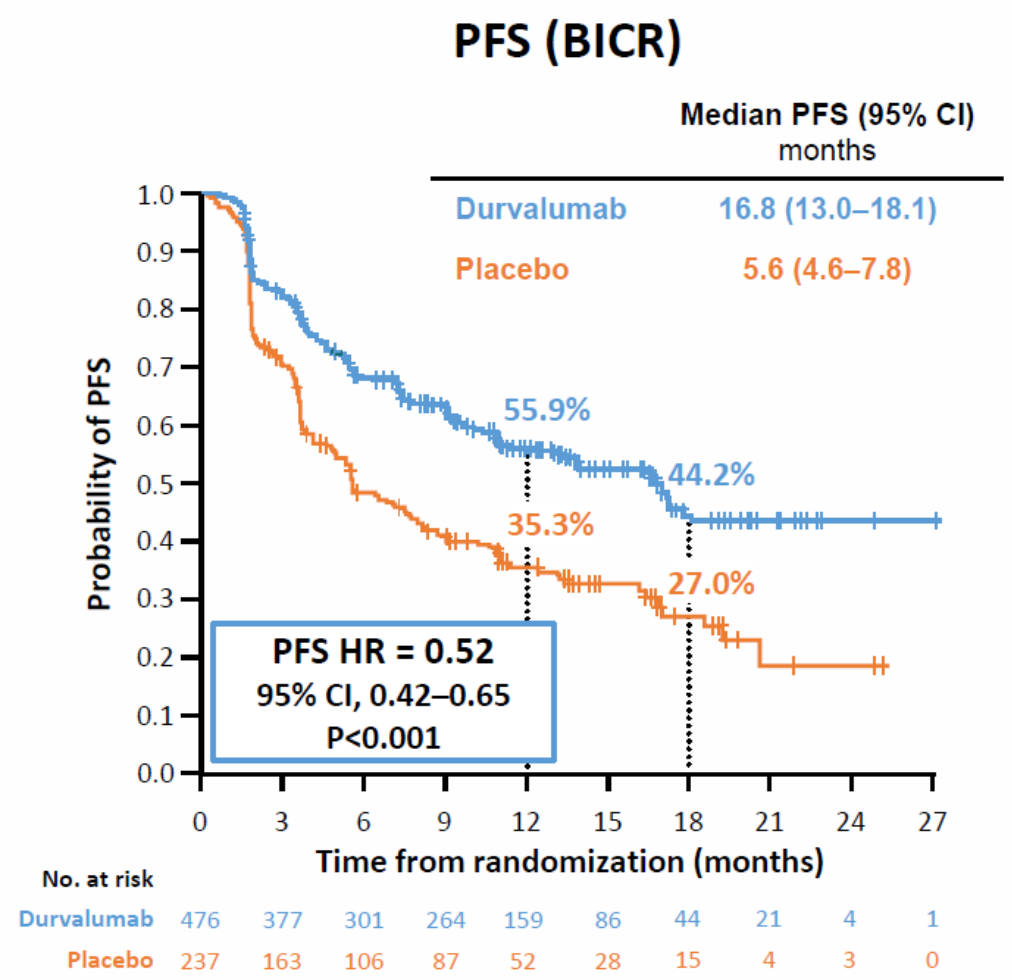
Stewart R, et al. Cancer Immunol Res 2015;3:1052-62

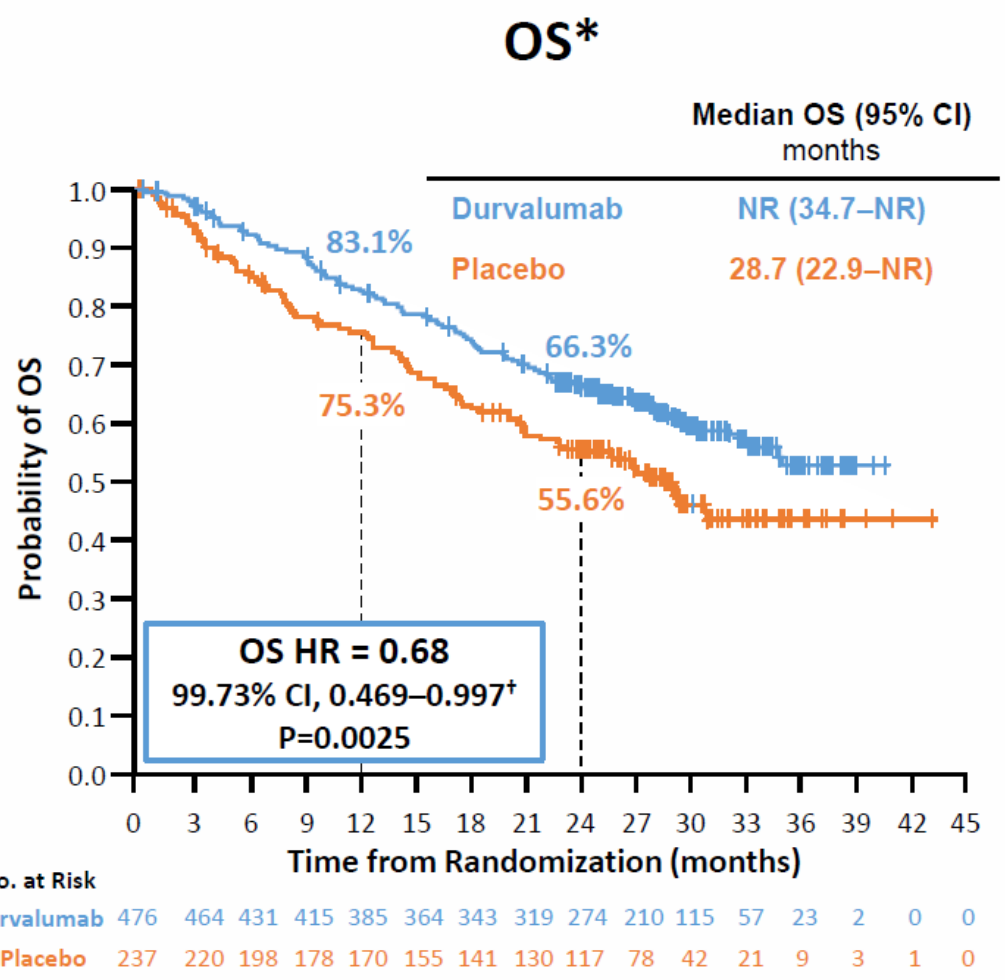
PACIFIC: Study Design

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



Durvalumab Blocks PD-L1 Binding to PD-1

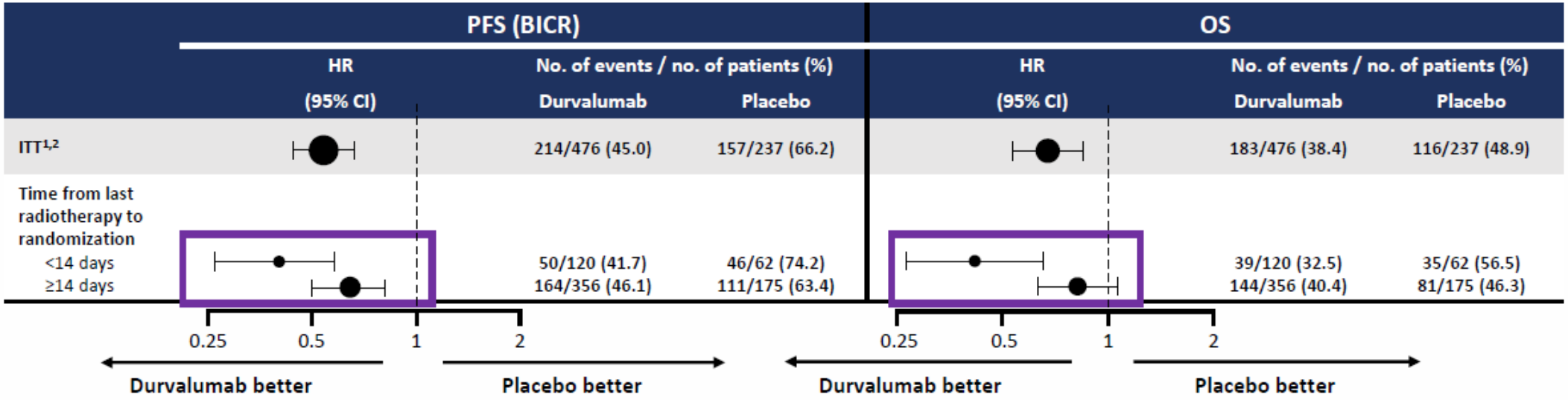




*Median duration of follow-up was 25.2 months (range 0.2–43.1); †Adjusted for interim analysis; NR, not reached.
Note: PFS data based on data cutoff of Feb 13, 2017, and OS data based on data cutoff of Mar 22, 2018.

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

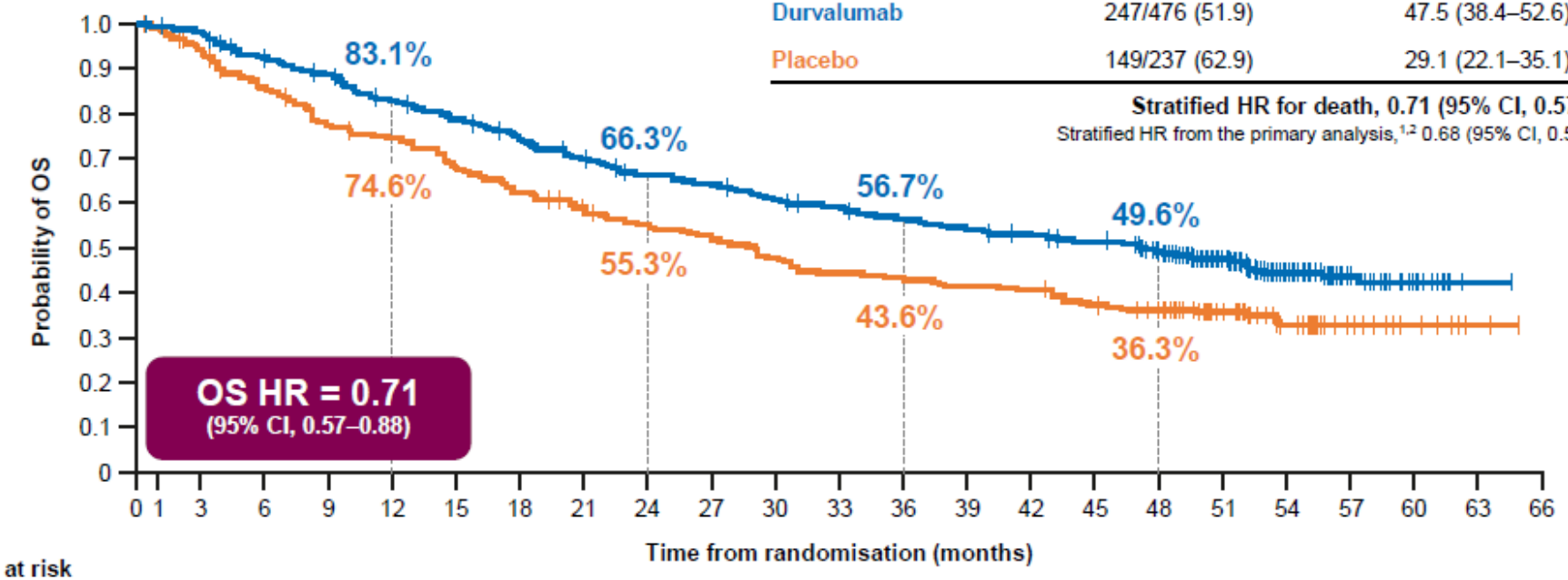
VIRTUAL 2020 ESMO congress

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

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

PACIFIC: 4 yr Survival Update

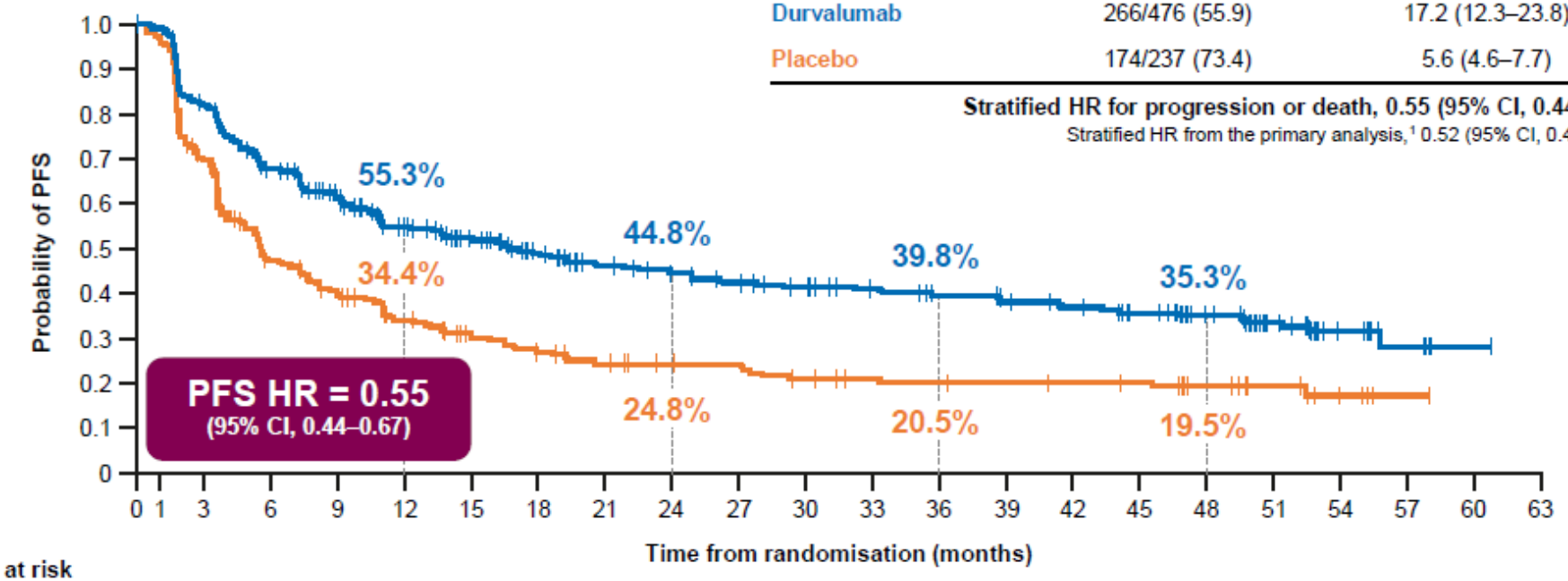
VIRTUAL 2020 ESMO congress

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

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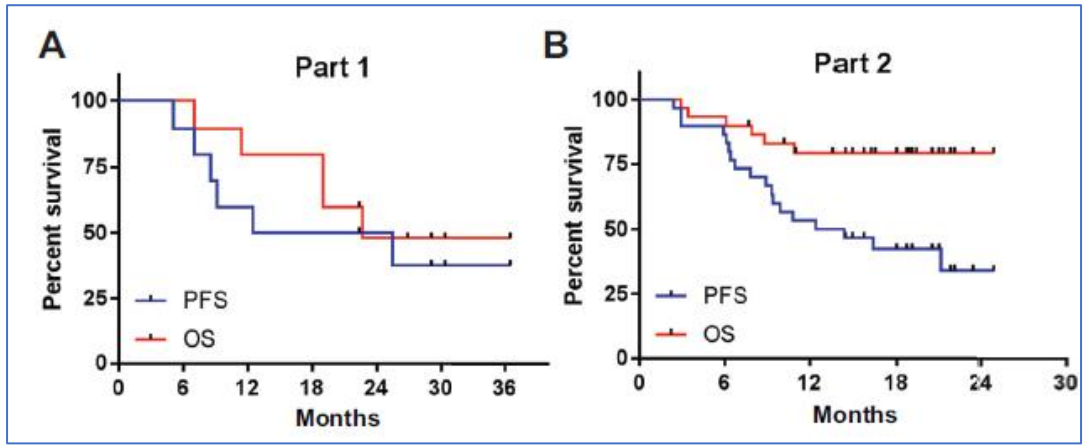
C Faivre-Finn, et al., ESMO and JTO, 2020

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

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S Lin, et al., JTO, 2019

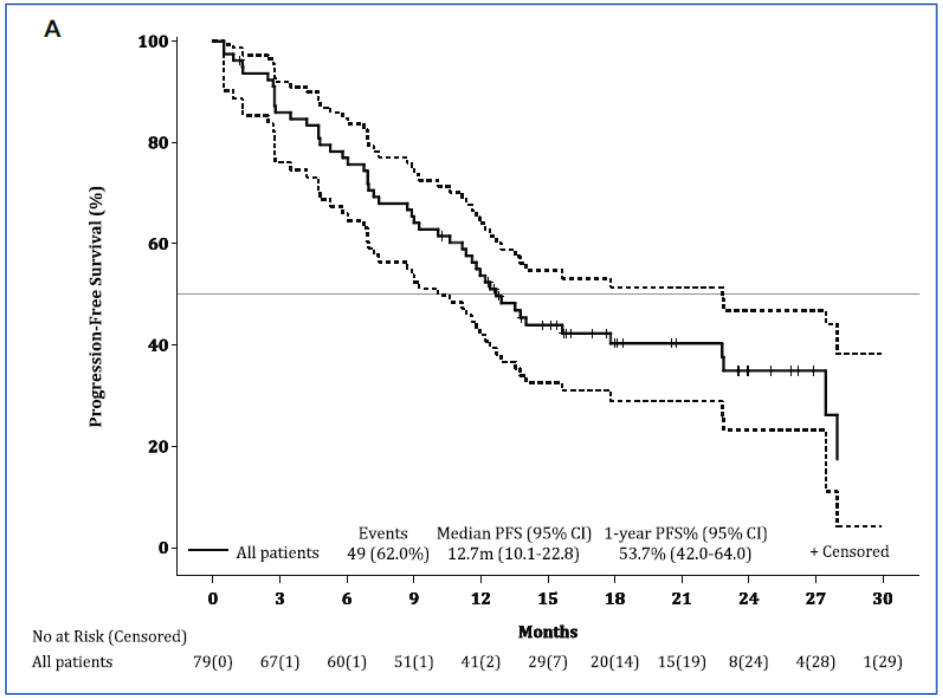
NICOLAS Trial: Phase II Concurrent Nivolumab with Chemoradiation for Unresectable NSCLC

- 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.



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S Peters, et al., JTO, 2020

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

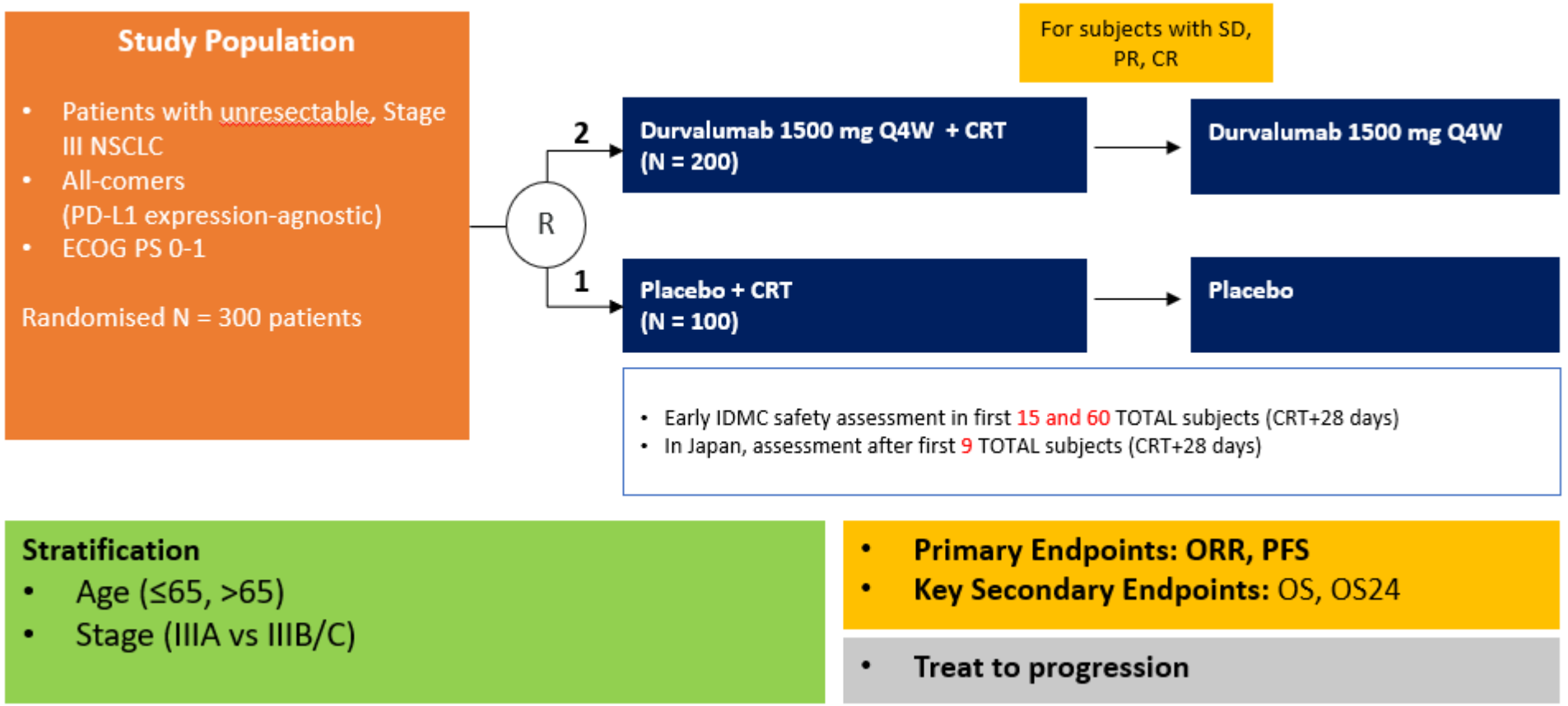
- Cohort A: 1 cycle of induction chemo + pembro → CRT +pembro; chemo was **carboplatin/paclitaxel**
- Cohort B: 1 cycle of inuction chemo + pembro → CRT + pembro; chemo was **cisplatin/pemetrexed**
- 112 patients cohort A, 102 patients in cohort B
- ORR: ~70% in both cohorts
- Gr3-5 treatment-related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

S Jabbour, et al., JAMA Onc, 2021

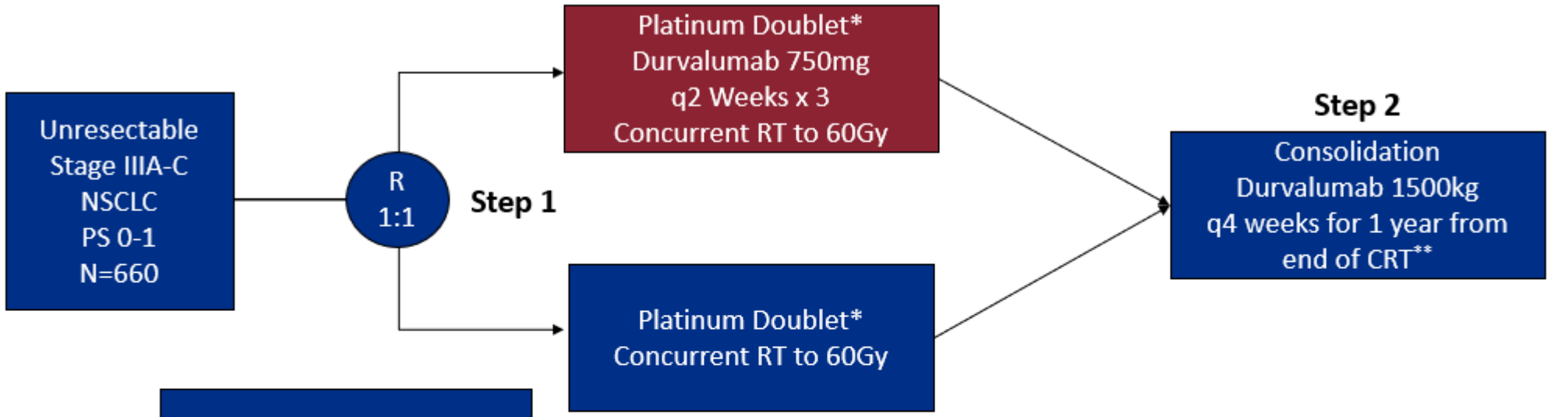
Ongoing Phase III Studies

- **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

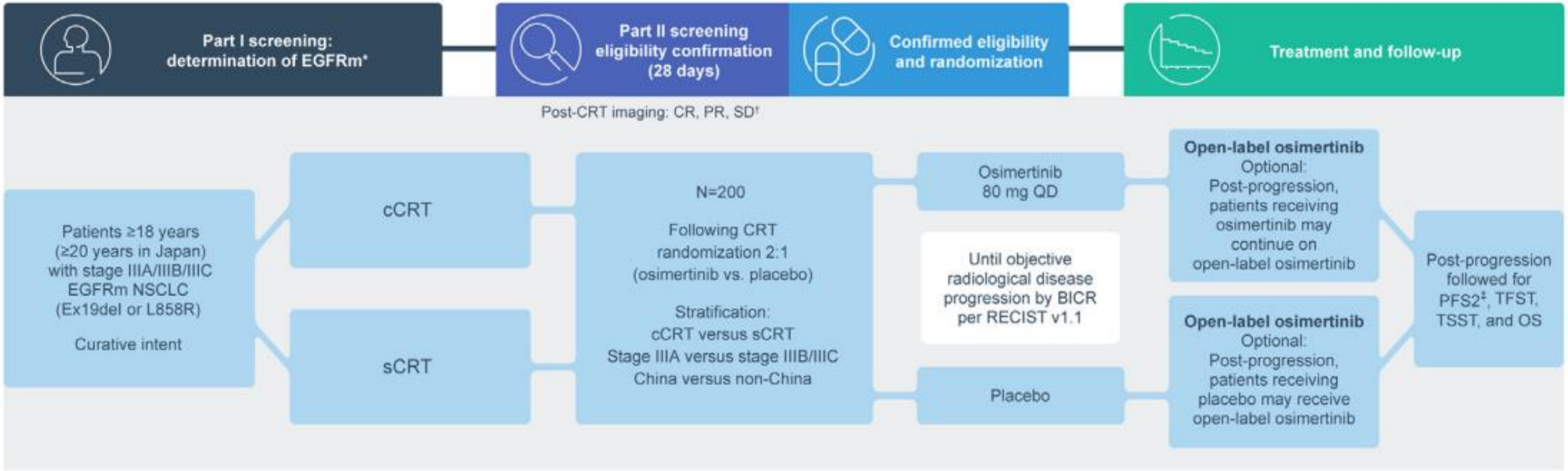


*__Investigator choice__

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

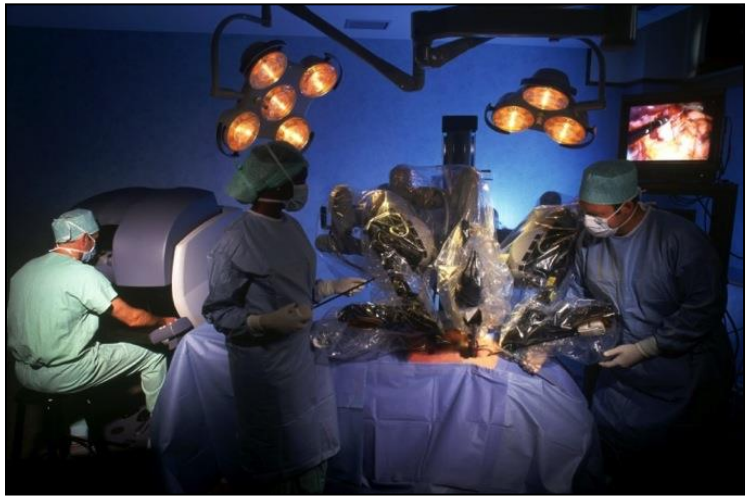
Ongoing Phase III Studies: LAURA



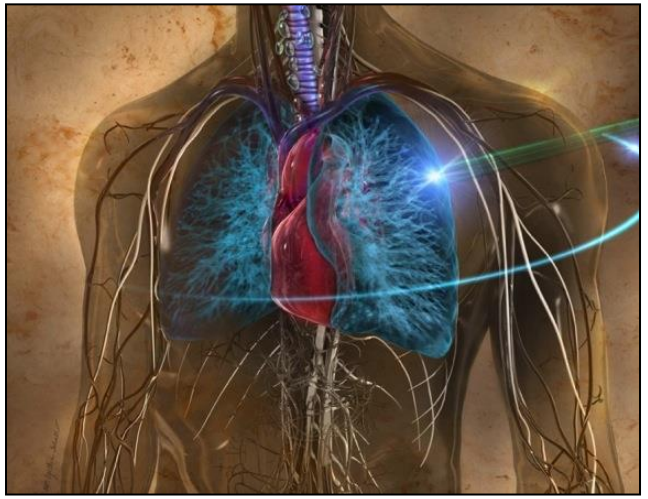
S Lu, et al., Clin Lung Cancer, 2021

EARLY STAGE NSCLC

SURGERY VERSUS SBRT



VS



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)…*

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

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

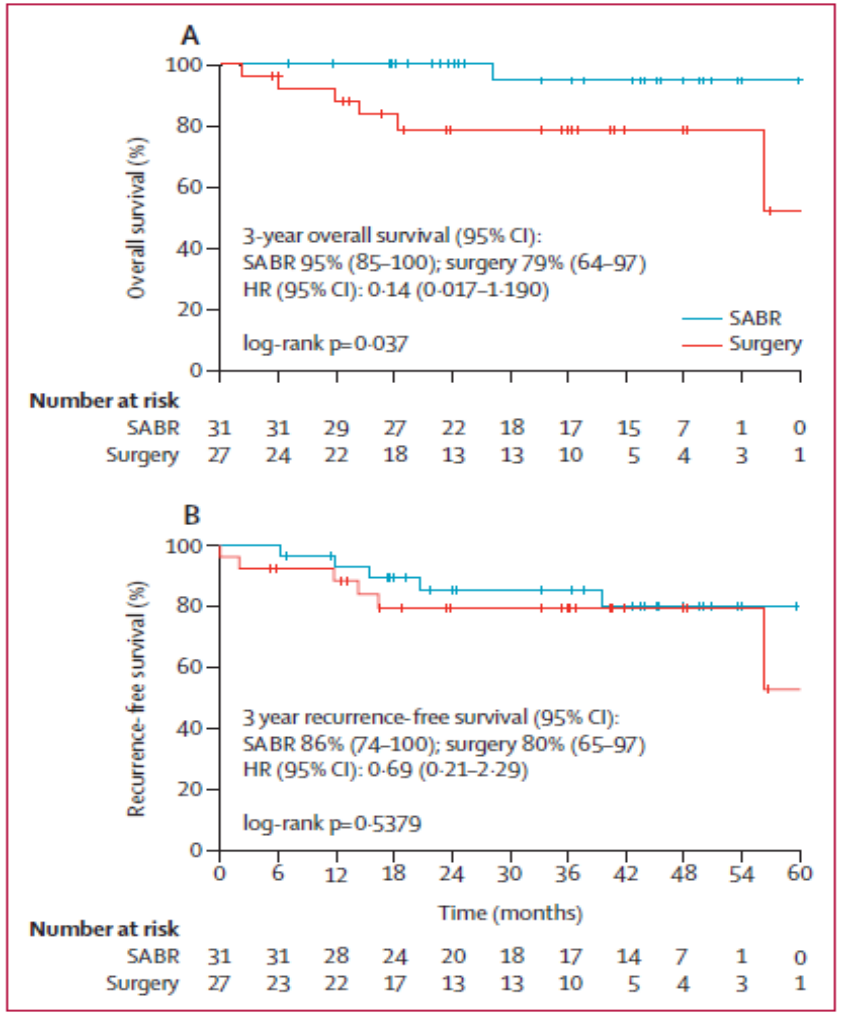
Joe Y Chang, Suresh Senan*, Marinus A Paul, Reza J Mehran, Alexander V Louie, Peter Balter, Harry J M Groen, Stephen E McRae, Joachim Widder, Lei Feng, Ben E E M van den Borne, Mark F Munsell, Coen Hurkmans, Donald A Berry, Erik van Werkhoven, John J Kresl, Anne-Marie Dingemans, Omar Dawood, Cornelis 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)

Chang, 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%

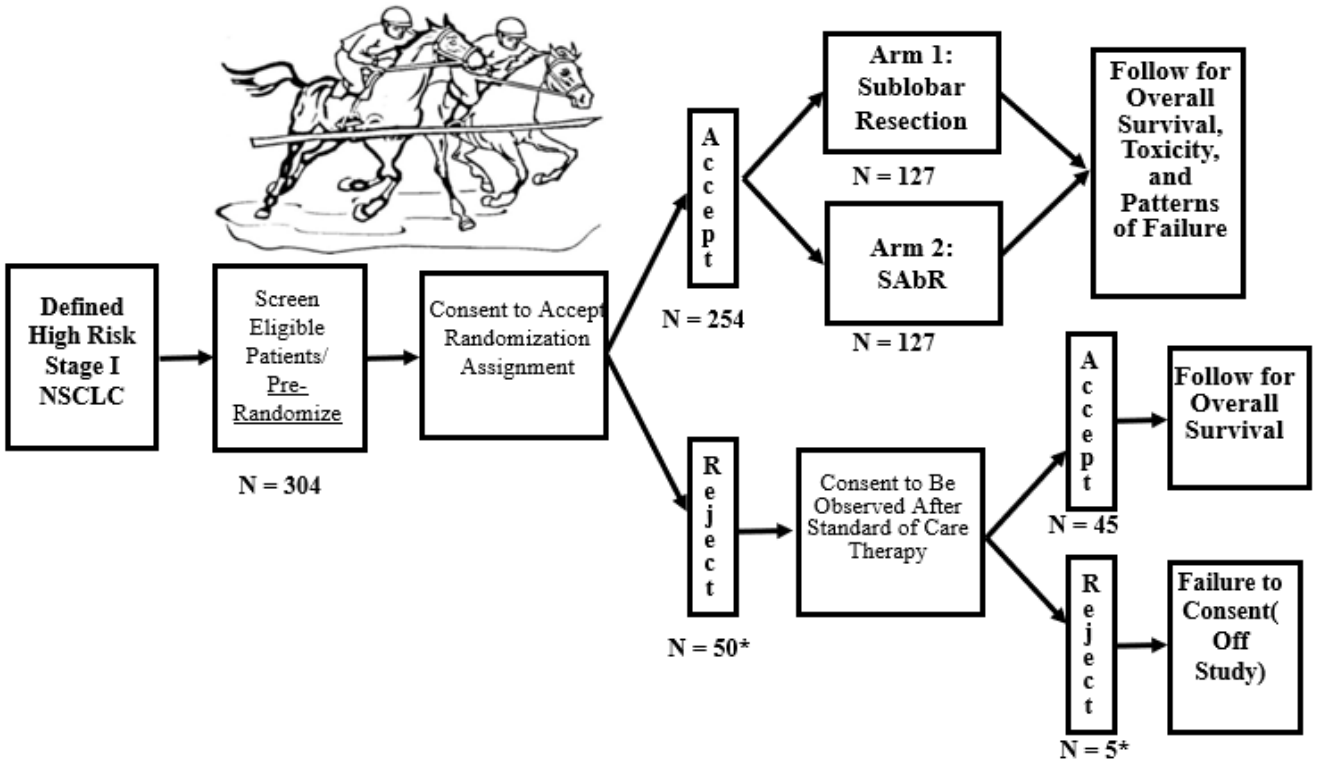


Chang, Senan et al., Lancet Oncol 2015

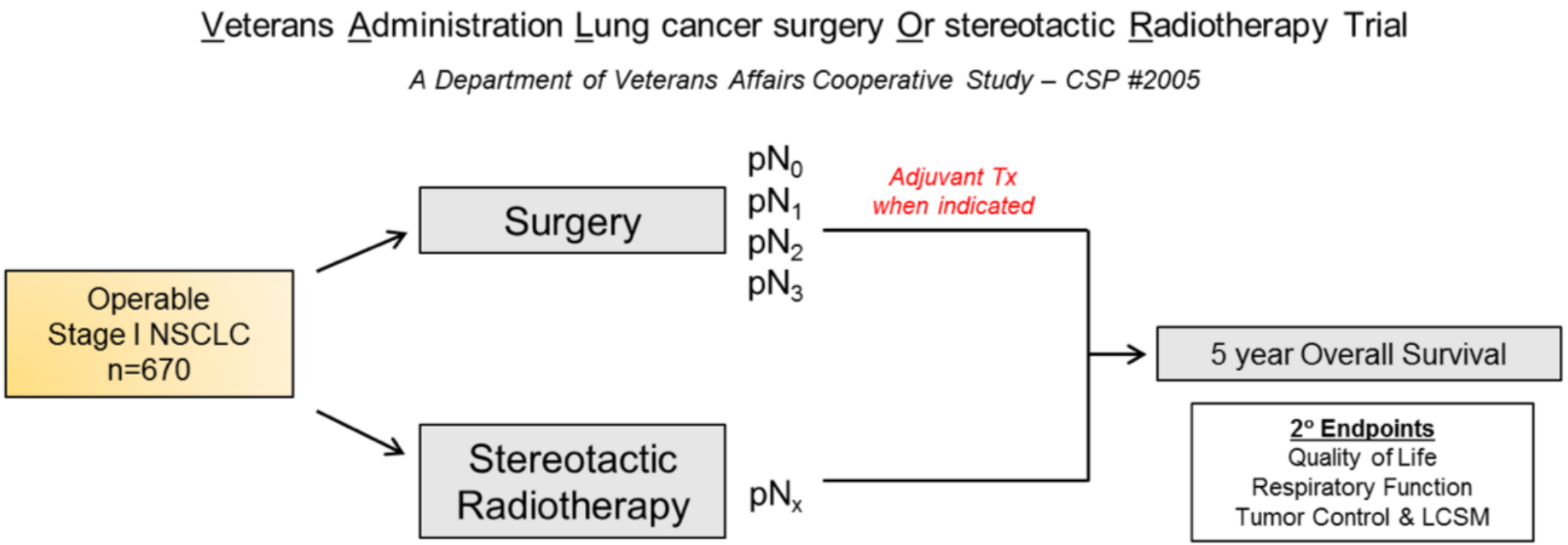
The STABLEMATES Trial

(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**

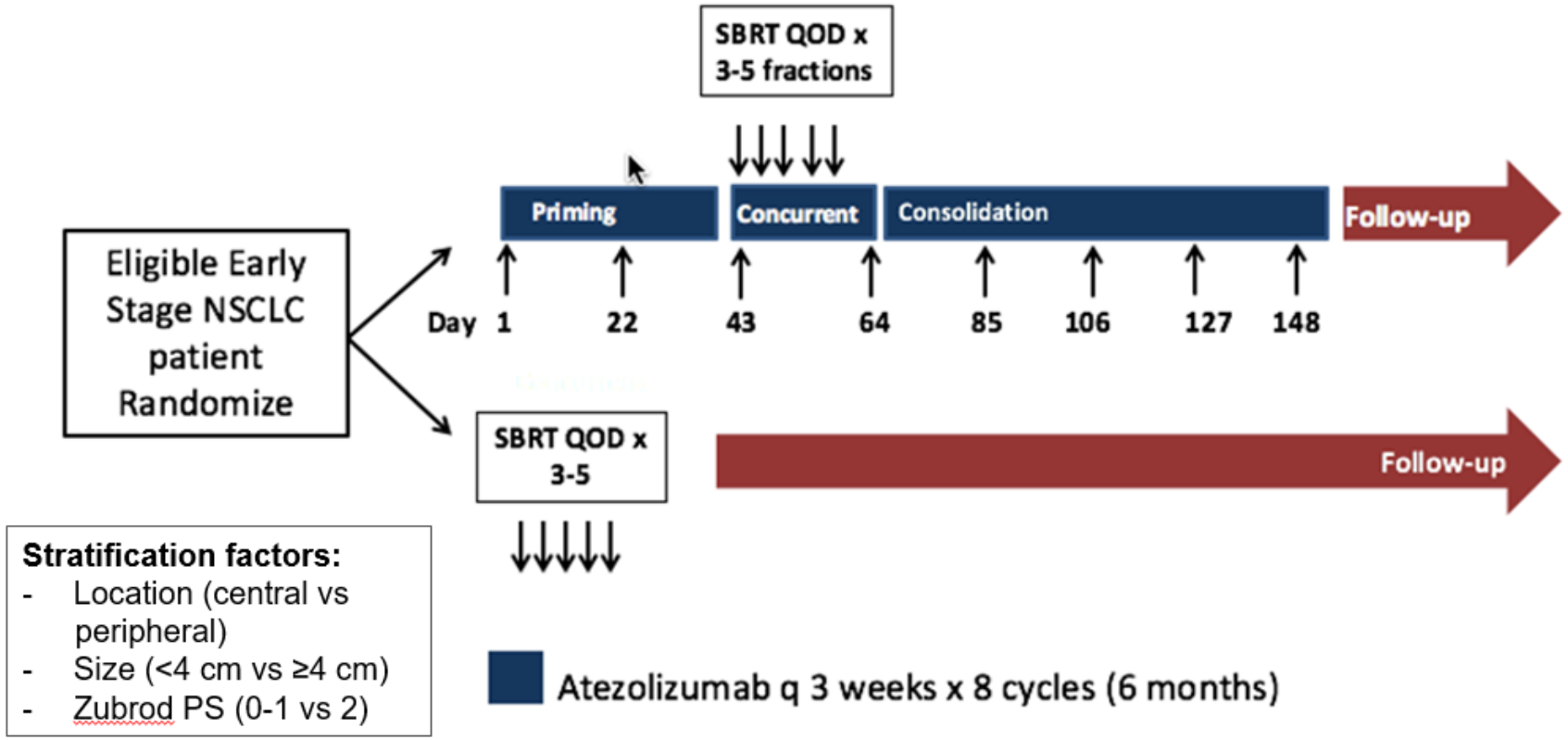
VALOR

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



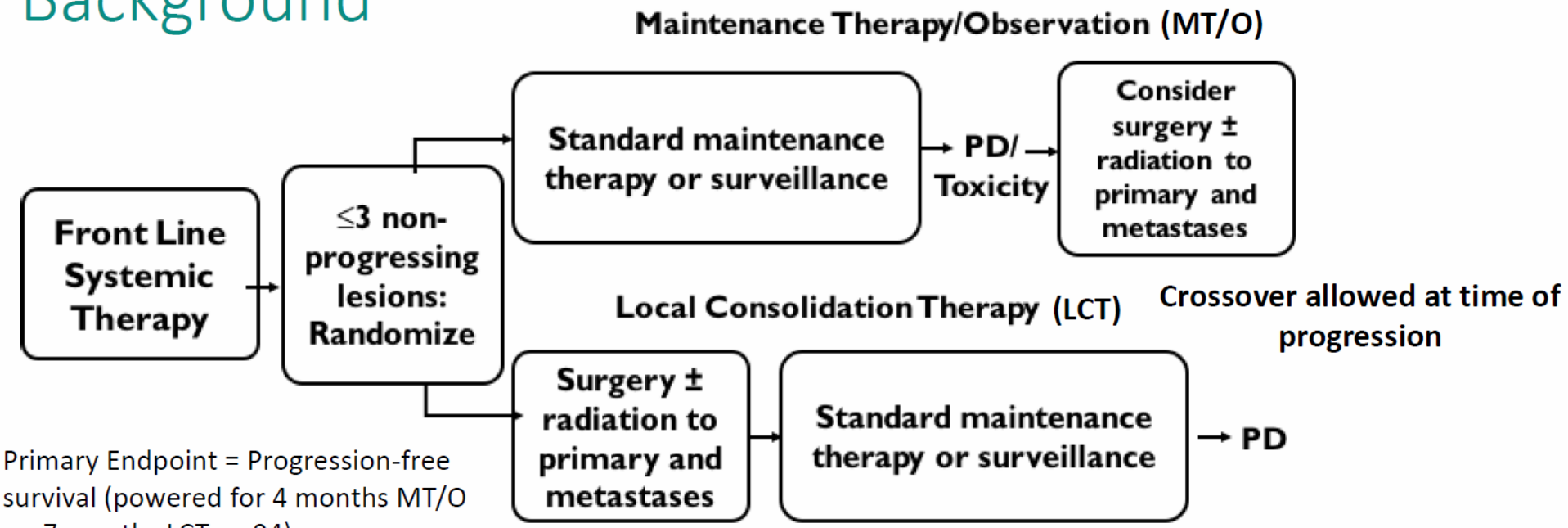
STAGE IV NSCLC

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

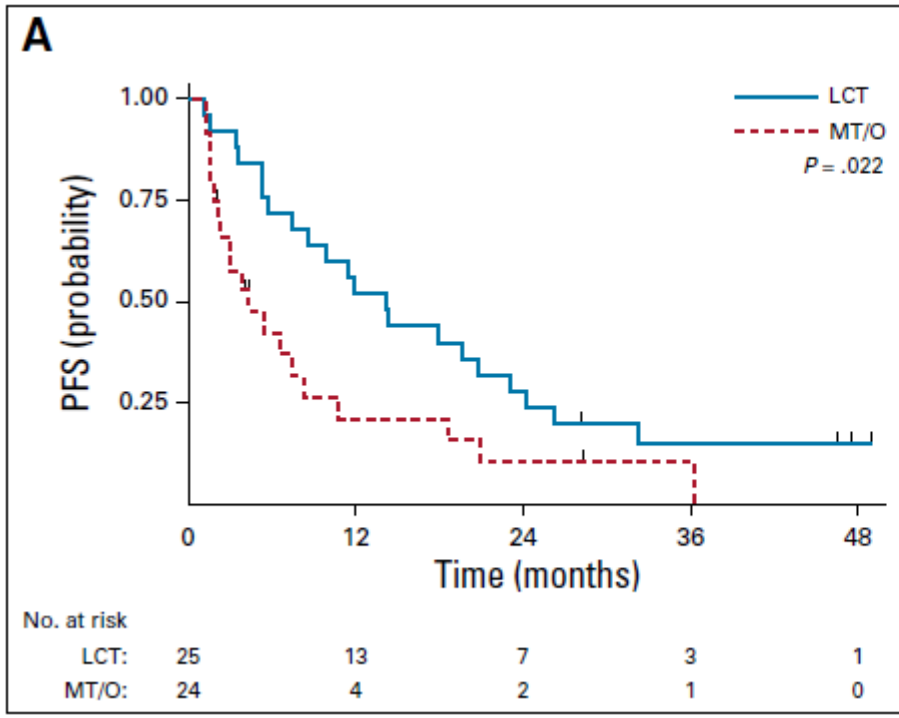
Balanced randomization: 1) Number of metastases (0-1 vs. 2-3), 2) Response to first-line systemic therapy (stable disease vs. partial response), 3) N0-N1 vs. N2-N3, 4) CNS vs. no CNS metastases, 5) EGFR/ALK alteration vs. wild type

D Gomez, ASTRO, 2018

Oligometastatic NSCLC

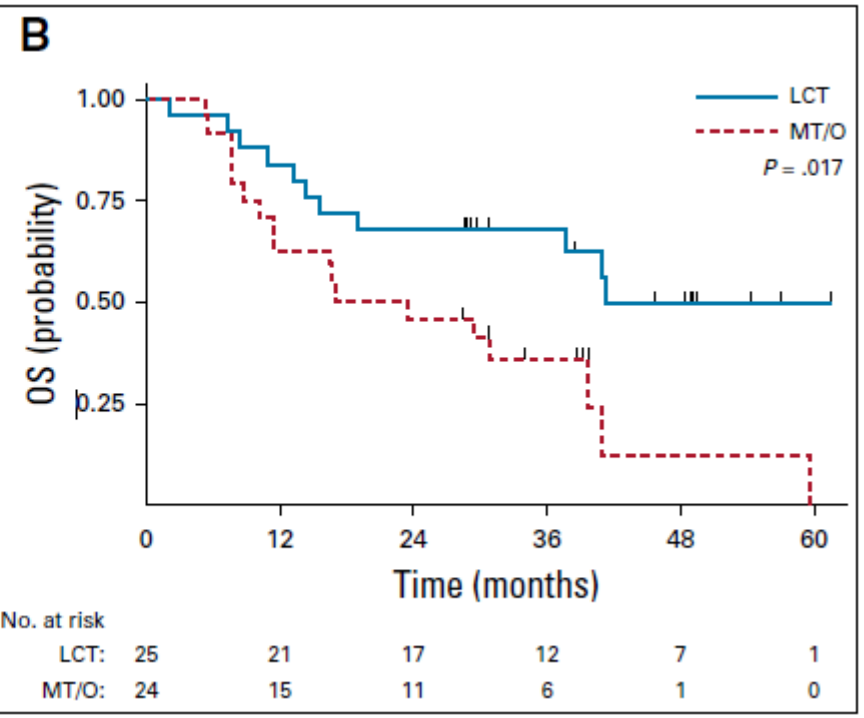
DSMB recommended early closure after 49 patients

Progression-Free Survival



Median PFS 4.4 months vs 14.2 months

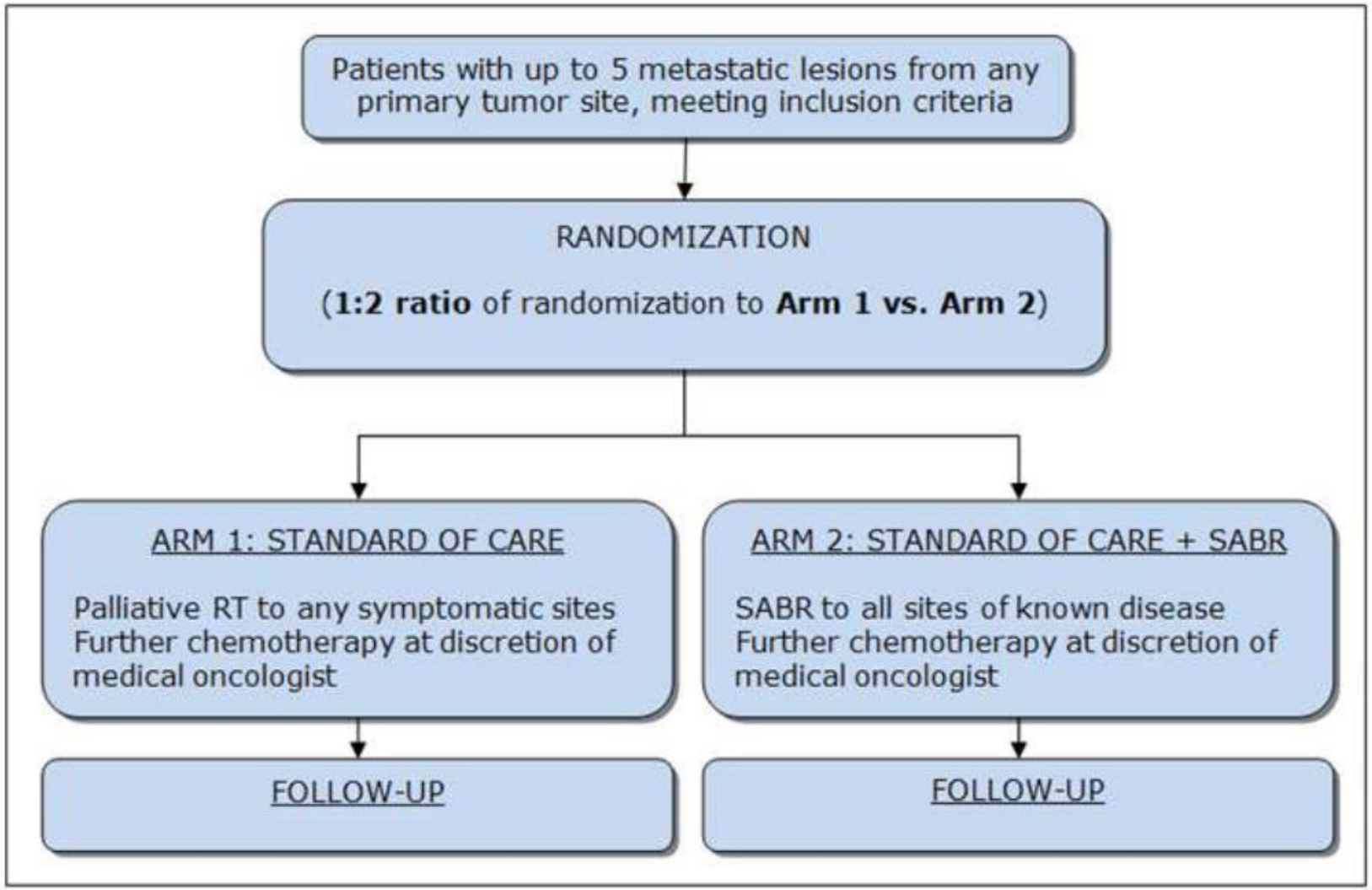
Overall Survival



Median OS 17.0 months vs 41.2 months

D Gomez, JCO, 2019

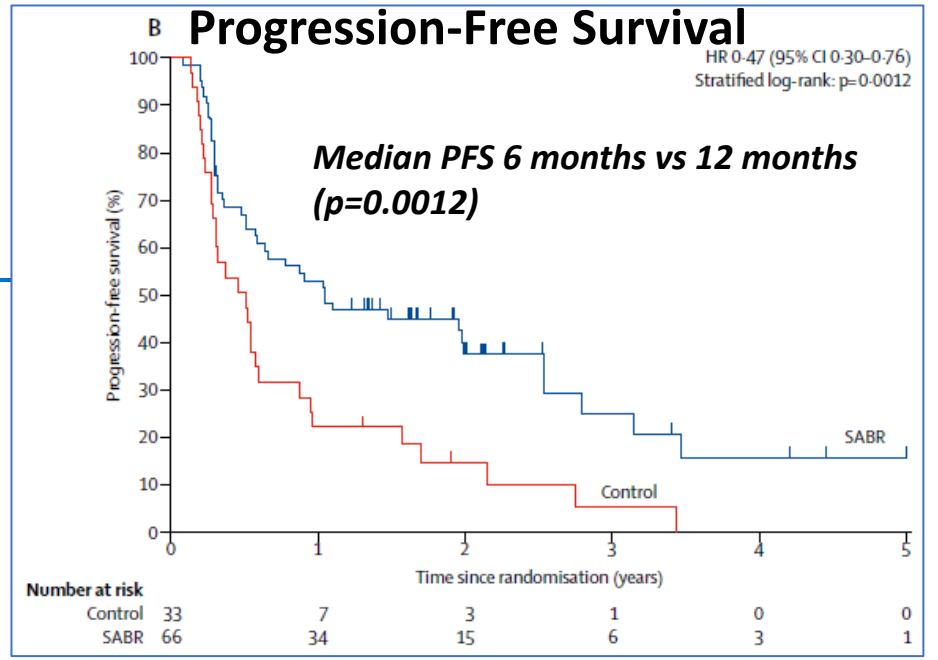
SABR-COMET

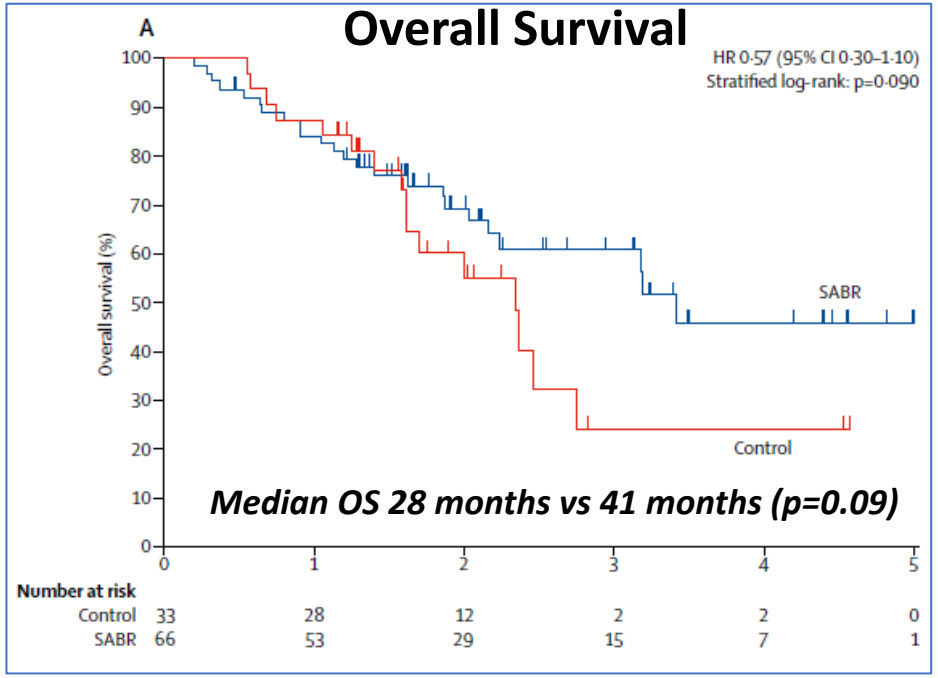


D Palma, ASTRO, 2018

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

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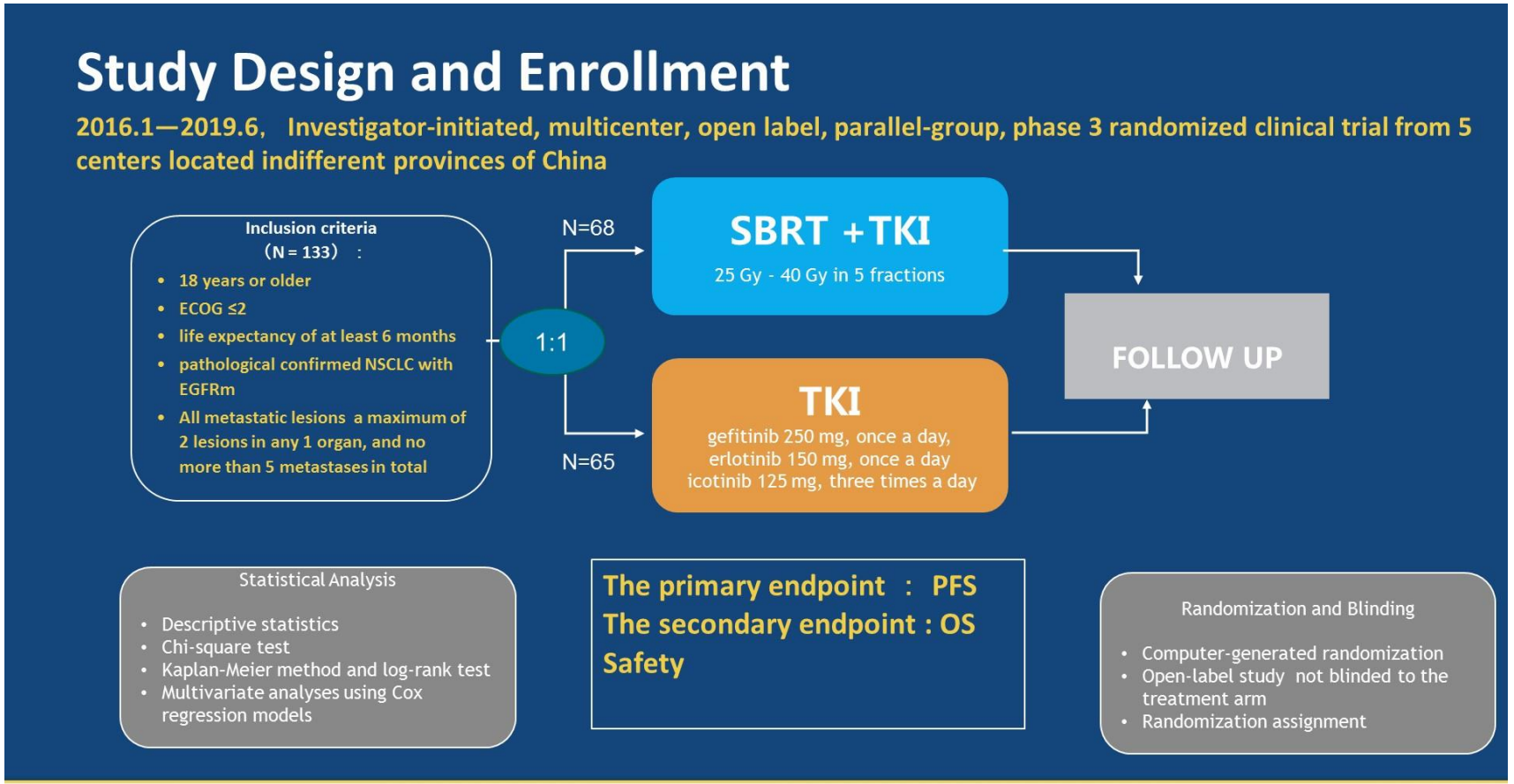
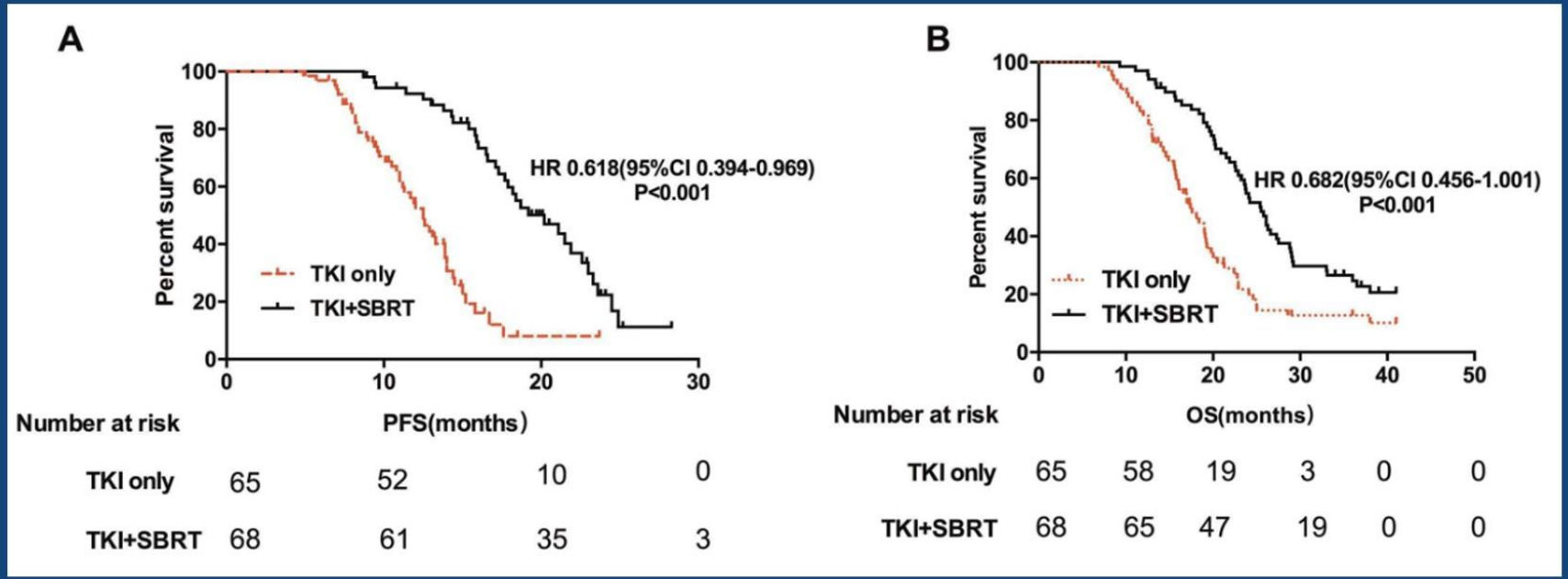
SINDAS trial (ASCO 2020)

- 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

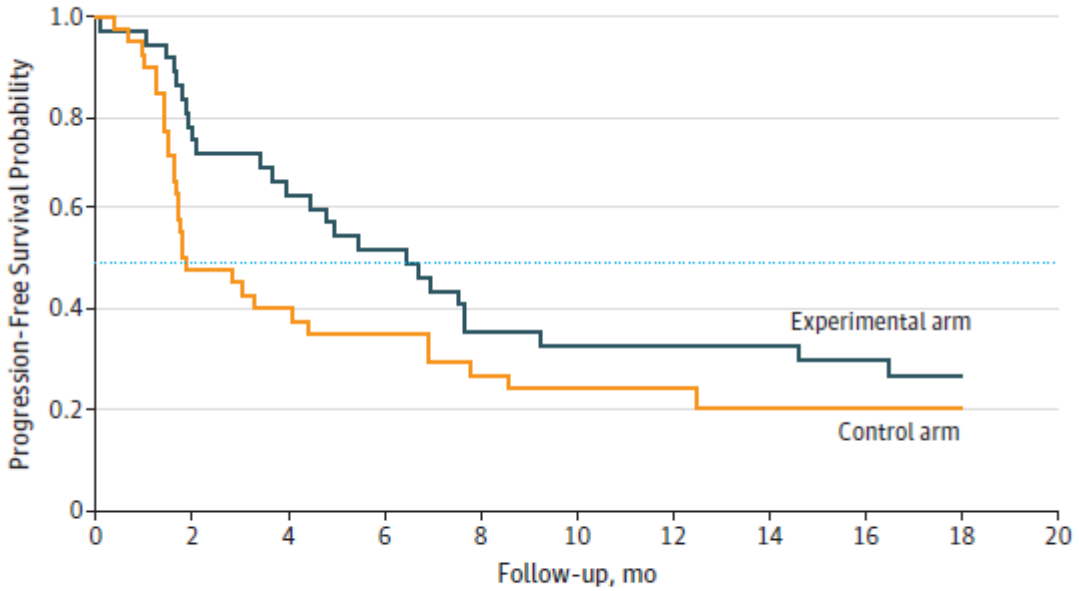
PEMBRO-RT

- **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

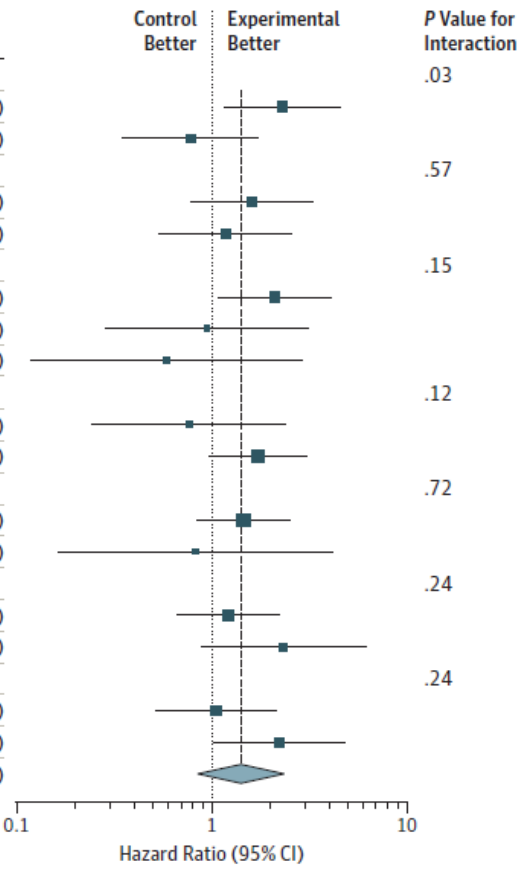


No. at risk

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)	



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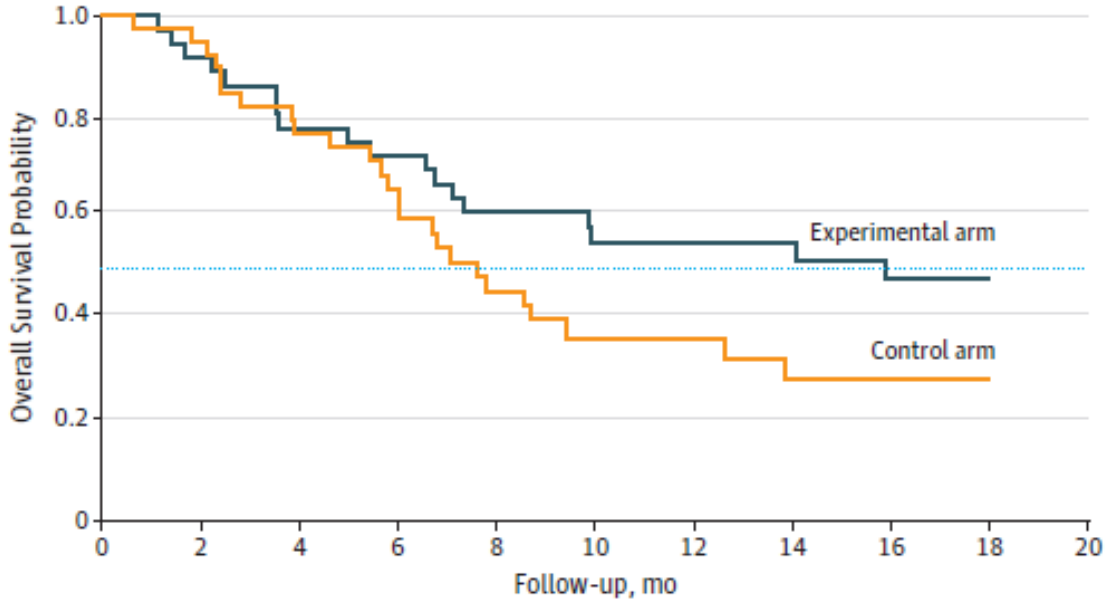
W Theelen et al., JAMA Onc, 2019

PEMBRO-RT

A Overall survival

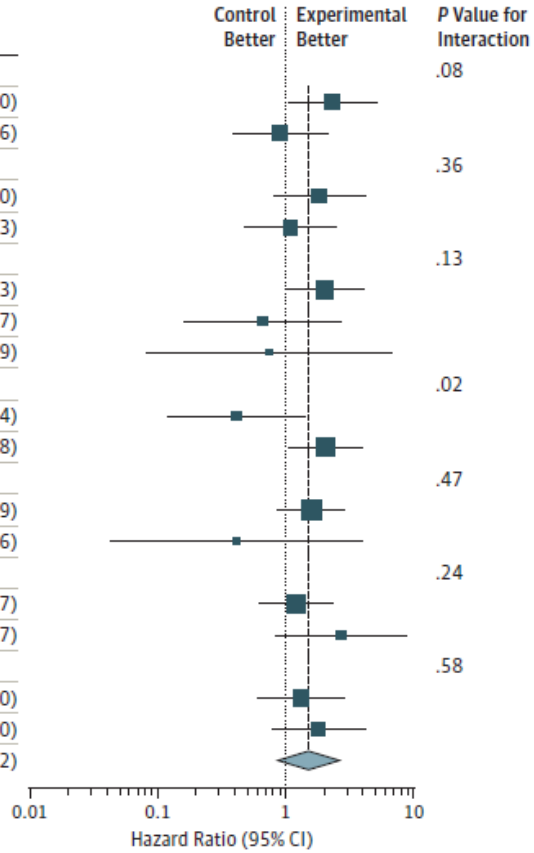


No. at risk

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)	



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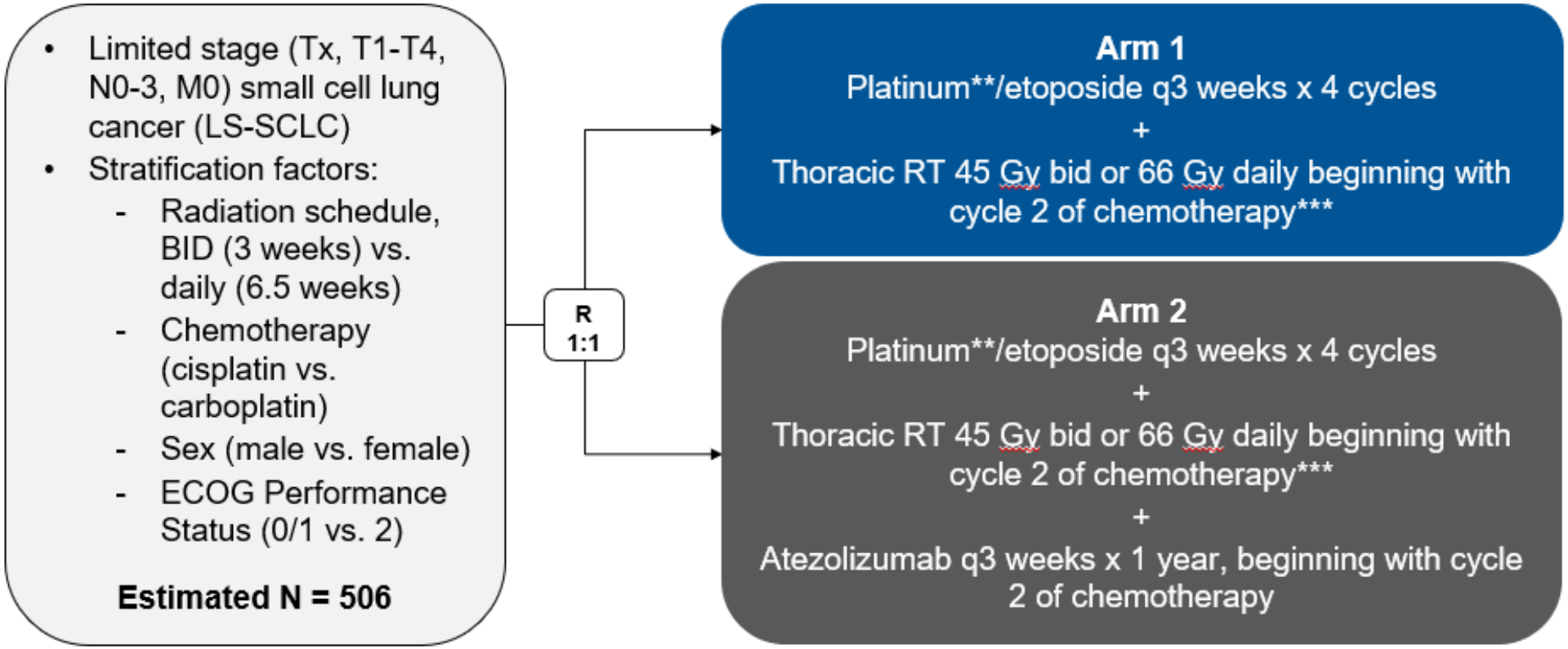
W Theelen et al., JAMA Onc, 2019

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!!

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