

Radiotherapie en combinatie immunotherapie

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Oncologisch Netwerk
Zuidoost-Nederland



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DISCLOSURE

Advisory board:

Merck Serono/ Pfizer

Bristol-Meyers-Squibb

Roche/ Genentech

Celgene

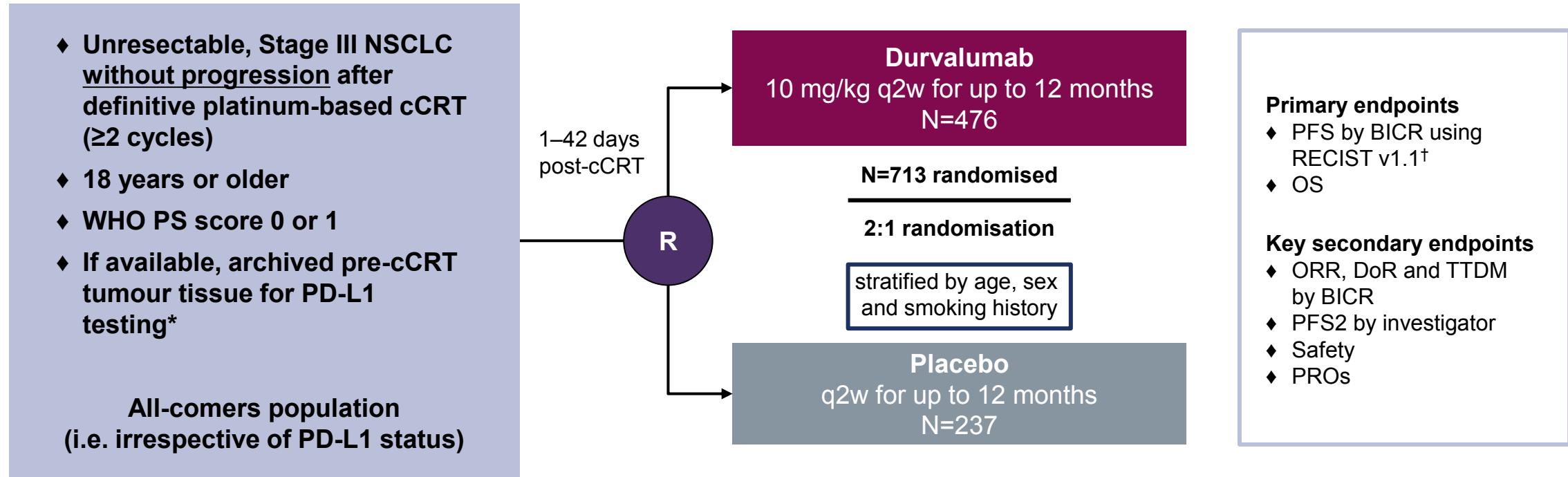
Astra Zeneca

Research support:

Bristol-Meyers-Squibb

PACIFIC: study design

Phase 3, randomised, double-blind, placebo-controlled, multicentre, international study¹

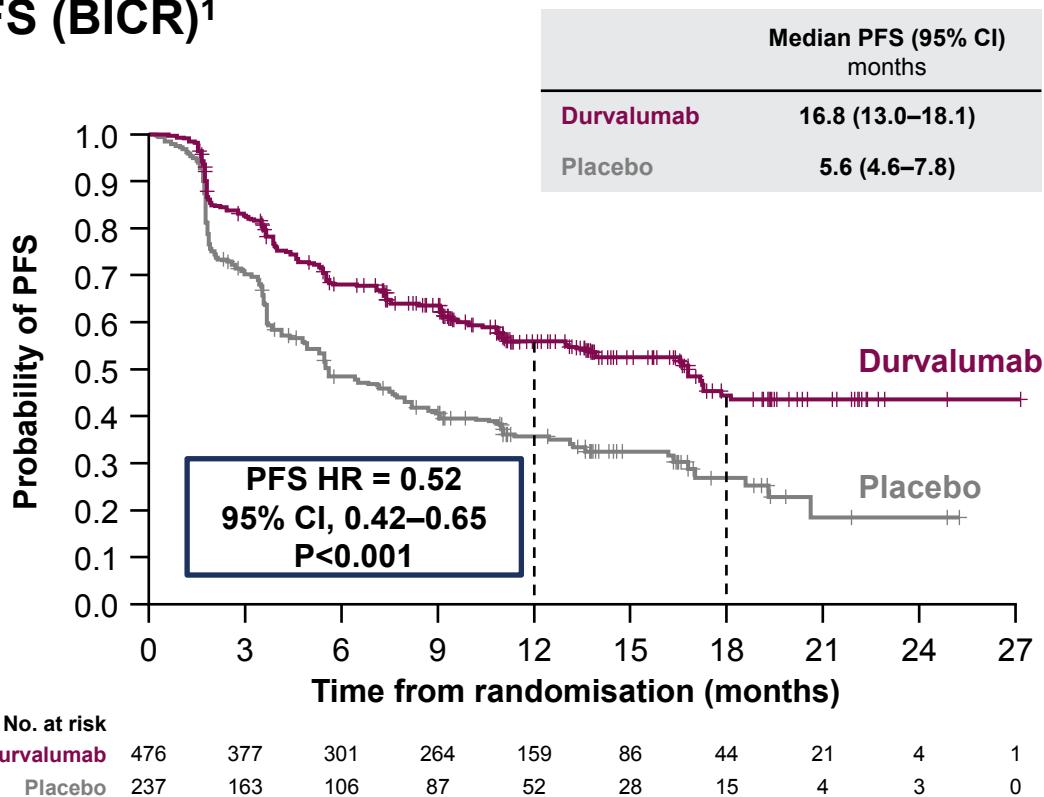


*Using the Ventana PD-L1 (SP263) assay; †defined as the time from randomisation until the date of objective disease progression or death by any cause in the absence of progression

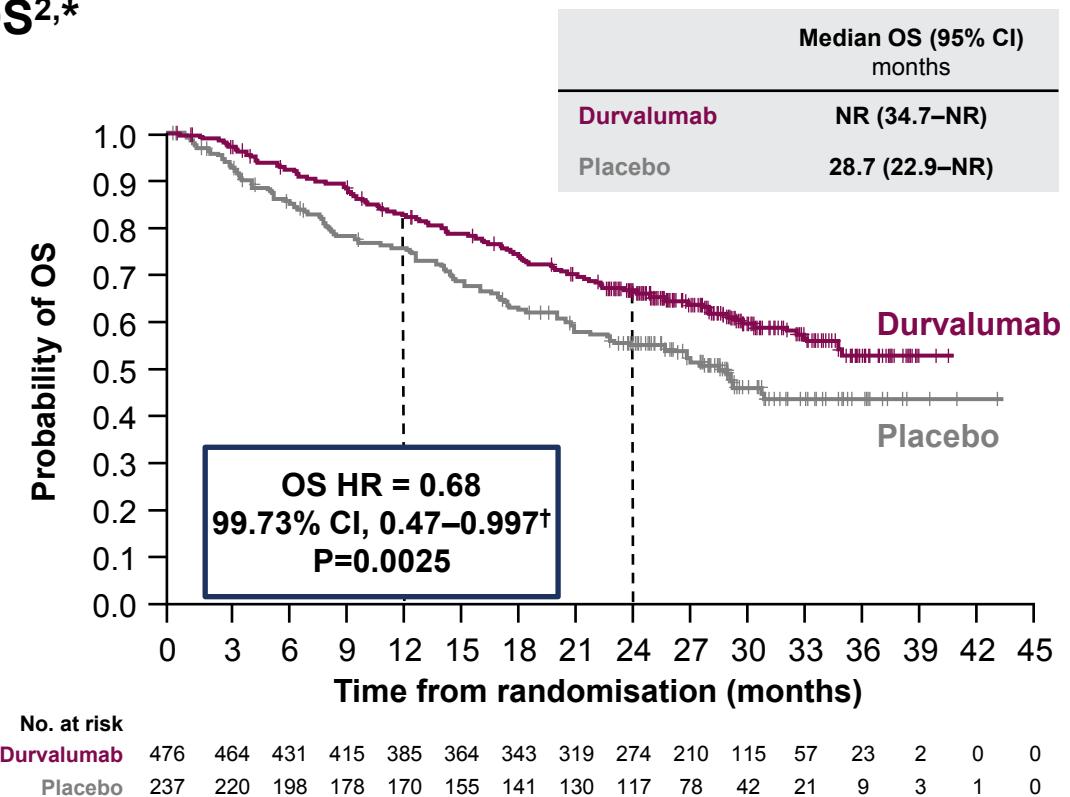
BICR, blinded independent central review; cCRT, concurrent CRT; DoR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, time to second progression; PRO, patient-reported outcome; q2w, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TTDM, time to death or distant metastasis; WHO PS, World Health Organization performance status

PACIFIC: PFS and OS in the ITT population

PFS (BICR)¹



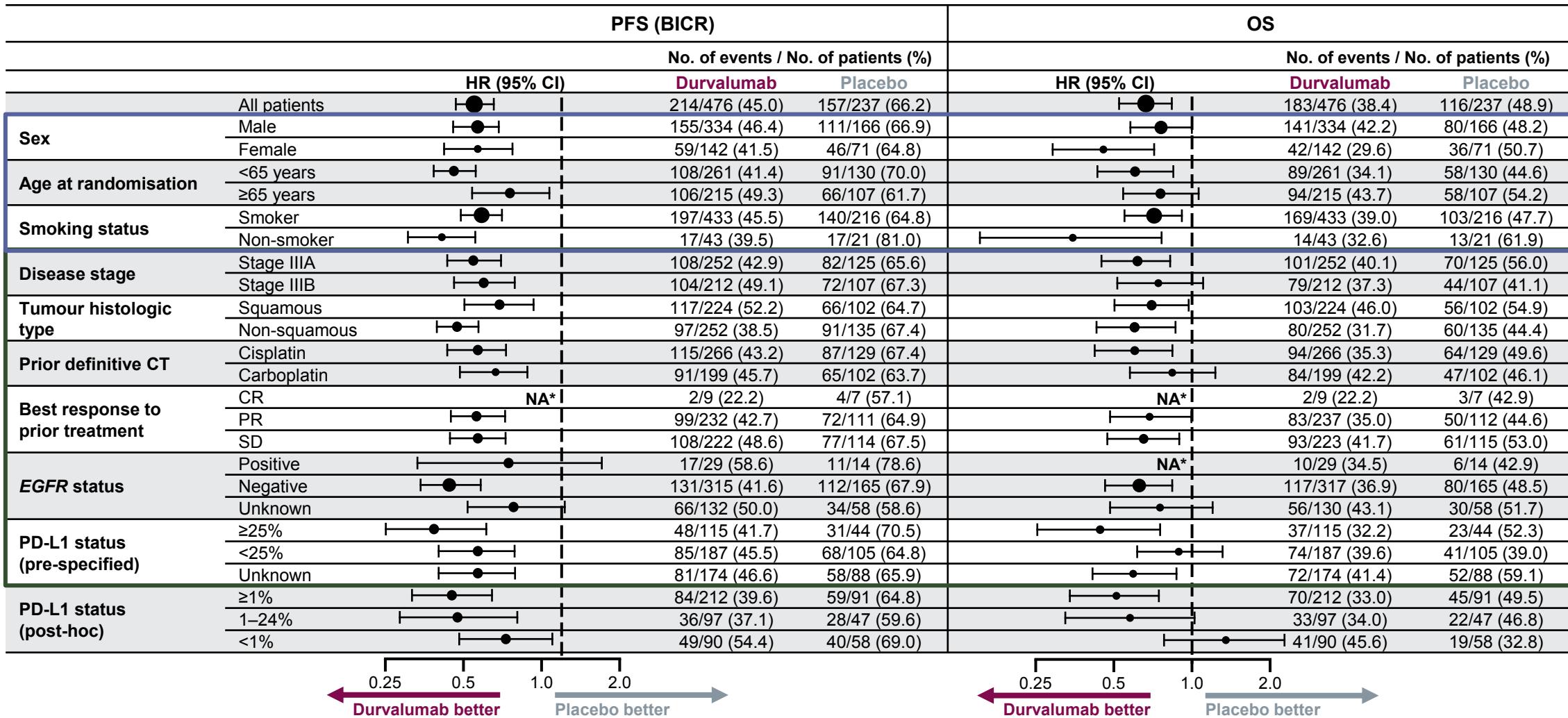
OS^{2,*}



*Median duration of follow-up was 25.2 months (range 0.2–43.1); †adjusted for interim analysis

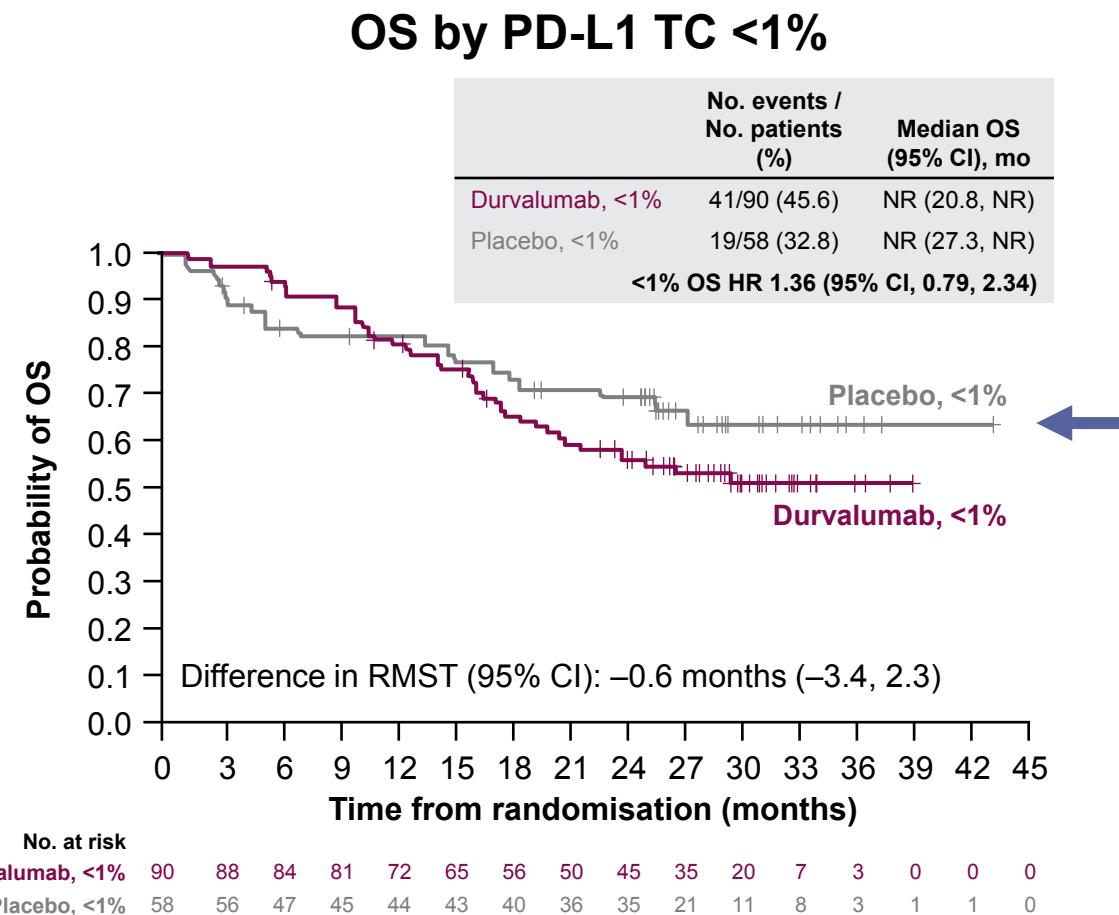
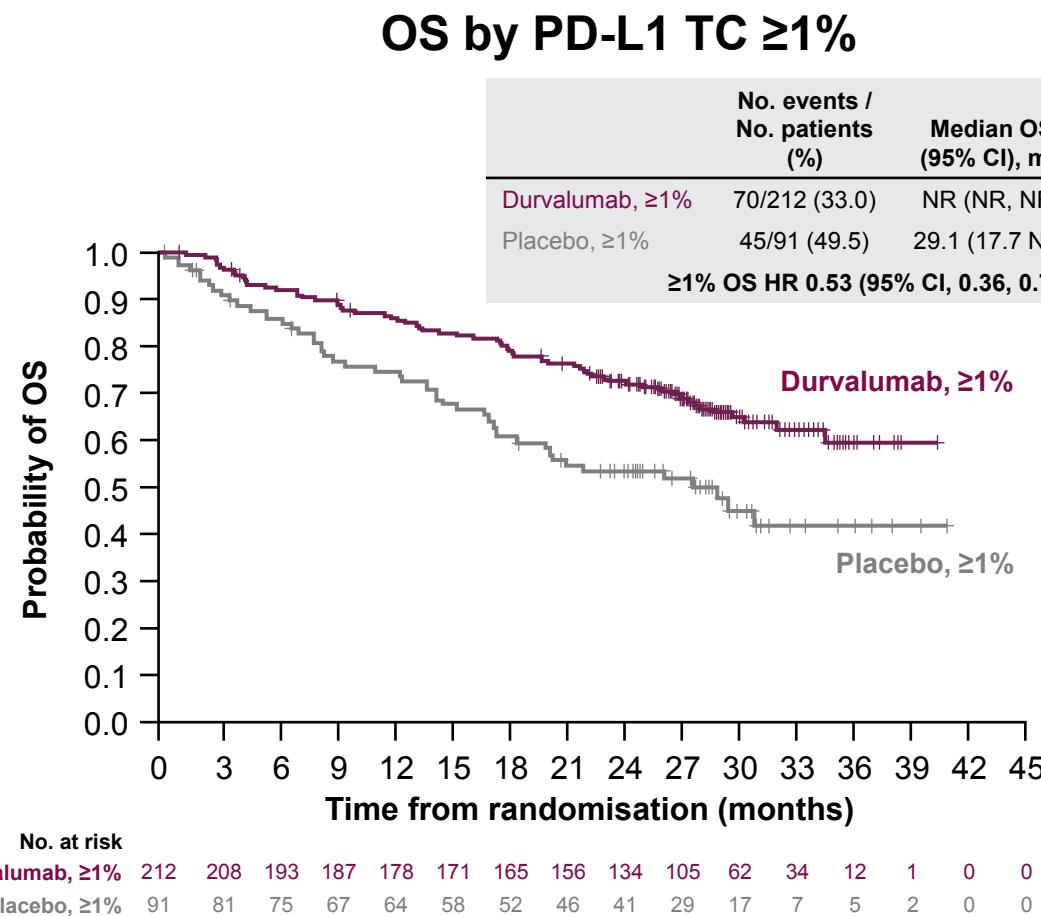
CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NR, not reached

PFS and OS by subgroup (ITT)



CR, complete response; EGFR, epidermal growth factor receptor; NA, not applicable PR, partial response; SD, stable disease

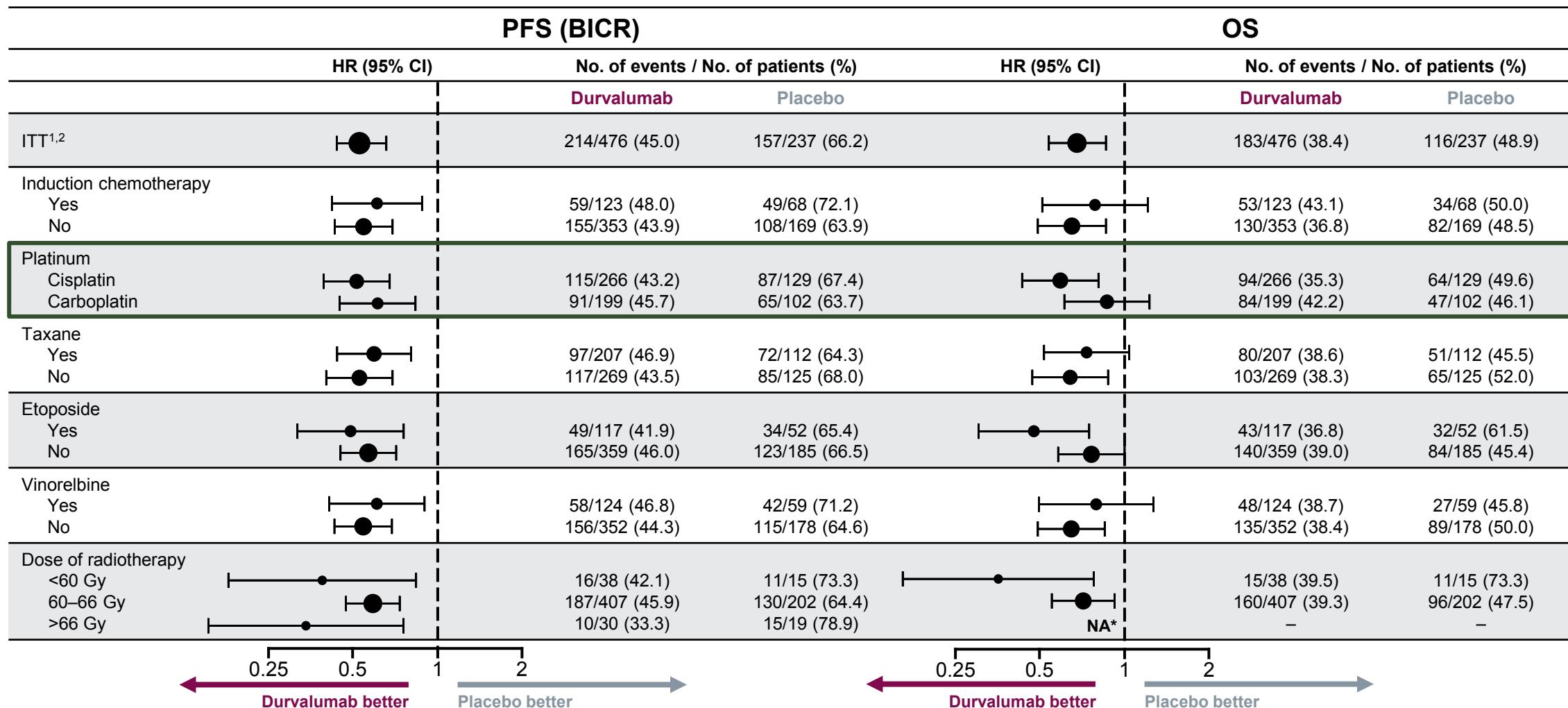
OS by PD-L1 TC $\geq 1\%$ and $<1\%$



RMST, restricted mean survival time

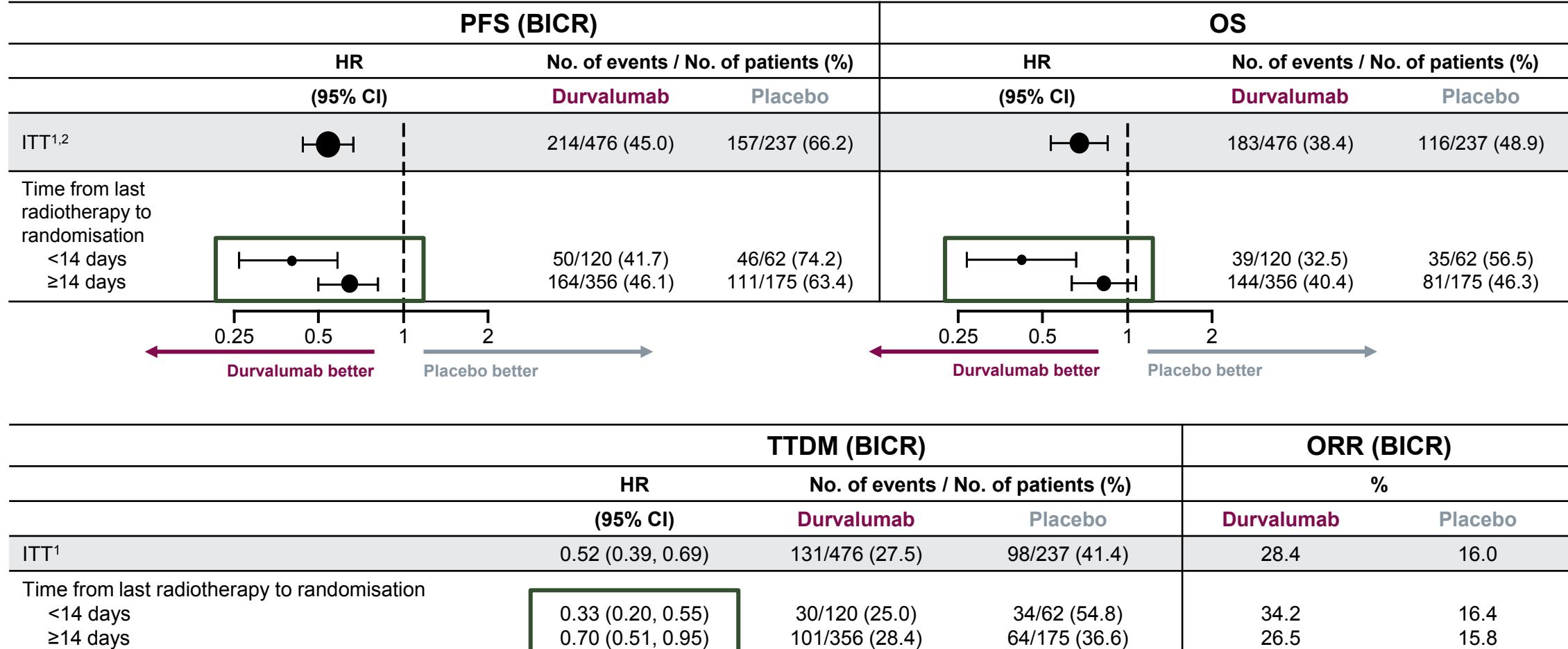
- ♦ In the PD-L1 TC $<1\%$ subgroup, the number of events are low and overall the subgroup is small
- ♦ Imbalances in baseline characteristics

Impact of preceding chemotherapy and radiation dose



*Not calculated if subgroup has <20 events

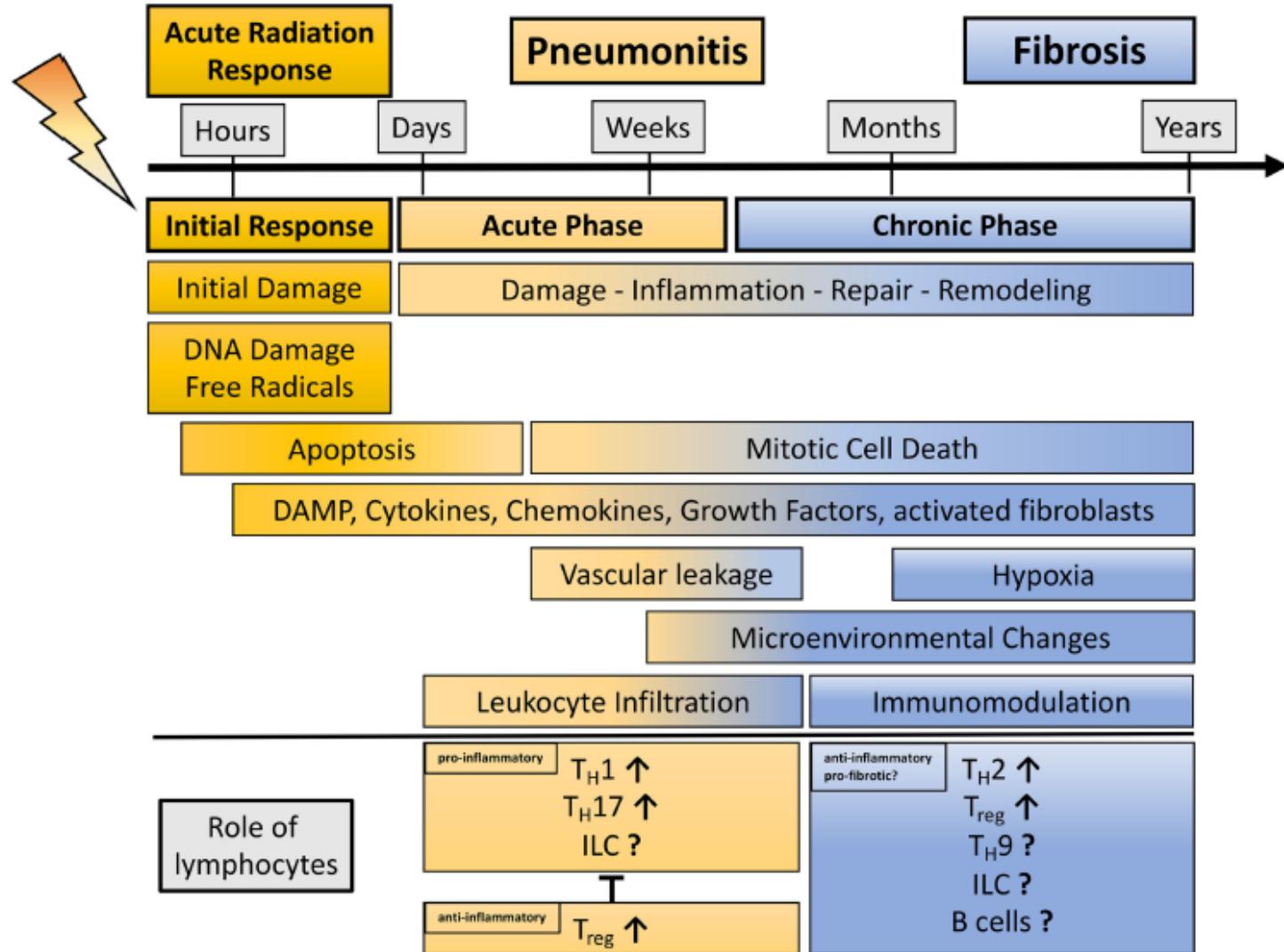
Improved outcomes irrespective of time from radiation



Similar toxicity profiles regardless of time from radiation

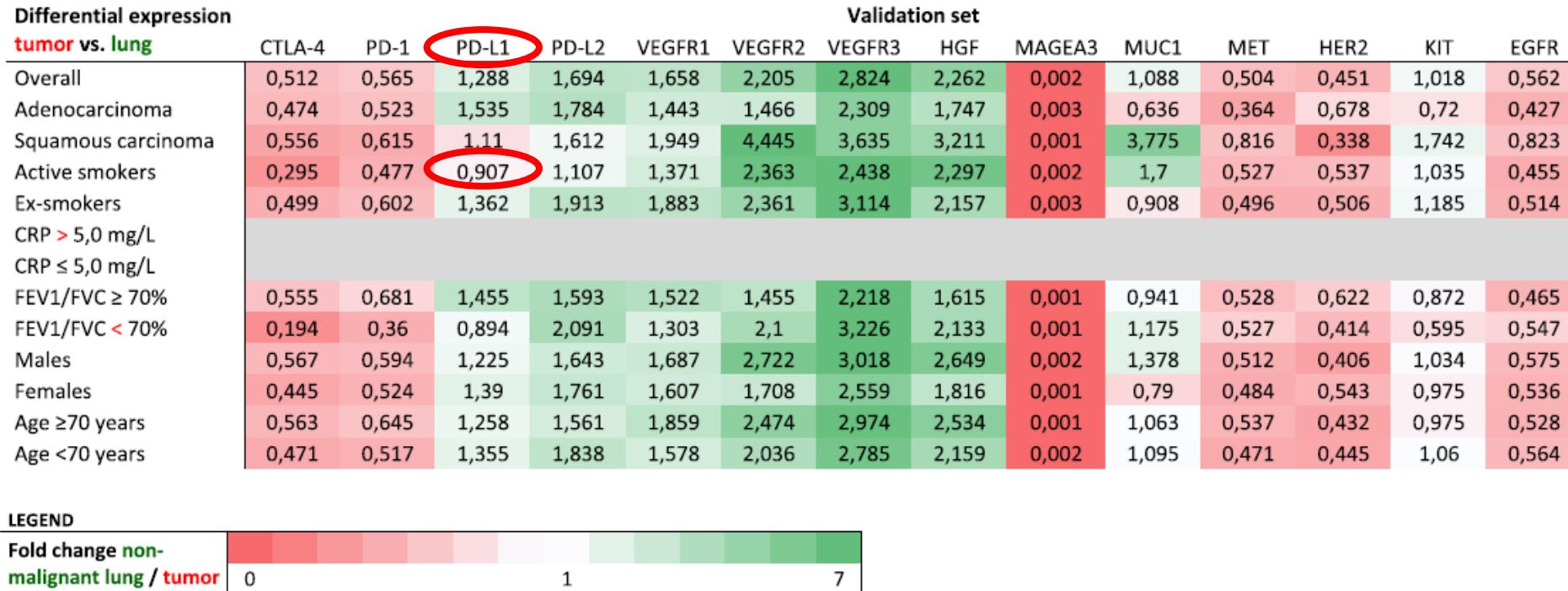
	<14 days		≥14 days	
	Durvalumab (N=120)	Placebo (N=60)	Durvalumab (N=355)	Placebo (N=174)
Any-grade all-causality AEs, n (%)	118 (98.3)	57 (95.0)	342 (96.3)	165 (94.8)
Grade 3/4	37 (30.8)	18 (30.0)	108 (30.4)	43 (24.7)
Outcome of death	6 (5.0)	7 (11.7)	15 (4.2)	8 (4.6)
Leading to discontinuation	16 (13.3)	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)

Patients with multiple AEs are counted once at the maximum reported CTCAE grade



RNA Seq tumor vs. surrounding lung (primary resection NSCLC)

Validation data set. n= 1122 with tumor and lung samples



Similar PD-L1 expression in non-malignant lung tissue and tumor in active smokers

PACIFIC

Table 3. Adverse Events of Any Cause.

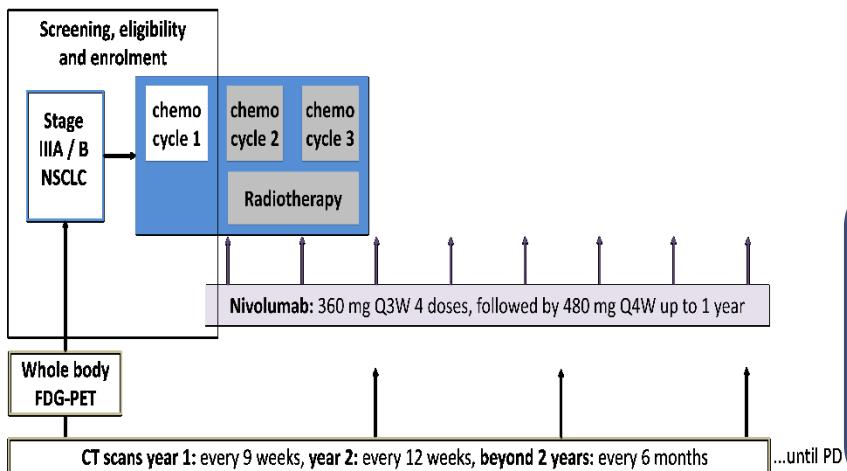
Event	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade*	Grade 3 or 4	Any Grade*	
			Grade 3 or 4	
	number of patients with event (percent)			
Any event	460 (96.8)	142 (29.9)	222 (94.9)	61 (26.1)
Cough	168 (35.4)	2 (0.4)	59 (25.2)	1 (0.4)
Pneumonitis or radiation pneumonitis†	161 (33.9)	16 (3.4)	58 (24.8)	6 (2.6)
Fatigue	113 (23.8)	1 (0.2)	48 (20.5)	3 (1.3)
Dyspnea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Diarrhea	87 (18.3)	3 (0.6)	44 (18.8)	3 (1.3)
Pyrexia	70 (14.7)	1 (0.2)	21 (9.0)	0
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Nausea	66 (13.9)	0	31 (13.2)	0
Pneumonia	62 (13.1)	21 (4.4)	18 (7.7)	9 (3.8)
Arthralgia	59 (12.4)	0	26 (11.1)	0
Pruritus	58 (12.2)	0	11 (4.7)	0
Rash	58 (12.2)	1 (0.2)	17 (7.3)	0
Upper respiratory tract infection	58 (12.2)	1 (0.2)	23 (9.8)	0
Constipation	56 (11.8)	1 (0.2)	20 (8.5)	0
Hypothyroidism	55 (11.6)	1 (0.2)	4 (1.7)	0
Headache	52 (10.9)	1 (0.2)	21 (9.0)	2 (0.9)
Asthenia	51 (10.7)	3 (0.6)	31 (13.2)	1 (0.4)
Back pain	50 (10.5)	1 (0.2)	27 (11.5)	1 (0.4)
Musculoskeletal pain	39 (8.2)	3 (0.6)	24 (10.3)	1 (0.4)
Anemia	36 (7.6)	14 (2.9)	25 (10.7)	8 (3.4)



Antonia et al. New Engl J Med 2017

ETOP NICOLAS phase II trial

Single-arm phase II trial assessing the safety and efficacy of the administration of nivolumab consolidation to standard first-line chemo-RT in unresectable locally advanced stage IIIA/B NSCLC.



Sequential administration of chemo-RT was allowed before amendment for efficacy

- Primary safety evaluation

Pneumonitis-free rate of grade ≥ 3 at 6 months post-RT

$$H_0: \pi_0 \leq 67\% \text{ vs } H_1: \pi_1 > 85\%$$

n=41 (1-sided alpha=5%, power=83%)

Success Rule: up to 8 events



Hierarchical design: IF safety proven →

- Key-secondary efficacy evaluation: 1-year PFS

$$Hs_0: PFS_0 \leq 45\% \text{ vs } Hs_1: PFS_1 > 60\%$$

n=74 (1-sided alpha=5%, power=83%).

Table 1: Patient baseline characteristics

Characteristic	Interim cohort (N=21)	Total cohort (N=62)
Gender		
Male	13 (61.9%)	42 (67.7%)
Female	8 (38.1%)	20 (32.3%)
Smoking history		
Current	-	15 (24.2%)
Former	19 (90.5%)	43 (69.4%)
Never	2 (9.5%)	3 (4.8%)
Missing	-	1 (1.6%)
ECOG Performance status		
0	11 (52.4%)	27 (43.5%)
1	10 (47.6%)	34 (54.8%)
Missing	-	1 (1.6%)
Histology		
Non-squamous	12 (57.1%)	24 (38.7%)
Squamous	9 (42.9%)	21 (33.9%)
Missing	-	17 (27.4%)
Stage		
IIIA	9 (42.9%)	21 (33.9%)
IIIB	12 (57.1%)	40 (64.5%)
Missing	-	1 (1.6%)
Age (years)		
Median (Min-Max)	62 (43 - 76)	62 (41 - 78)

- ♦ Up to February 20, 2018, 62 patients have been recruited (median follow-up 6.6 months, 95% CI: 5.6, 7.8)
- ♦ Safety cohort: 58 patients (with ≥1 dose of trial treatment)
 - 52 (89.7%) have experienced an adverse event (AE)
 - 24 (41.4%) have experienced a serious adverse event (SAE)
- No unexpected AEs or increased safety risk were observed.
- The most frequently observed AEs are:
 - Fatigue: N=24 (41.4%)
 - Anemia: N=24 (41.4%)
 - Nausea: N=18 (31.0%)

The ETOP NICOLAS phase II trial: Results of the Interim Safety Analysis

- ♦ Interim safety analysis (September 19, 2017)
 - Among the 21* patients reaching 3 months follow-up after completion of RT
 - NO pneumonitis grade \geq 3 was observed

Thus:

- Safety is proven
- Accrual continues to the total of 74 evaluable patients to assess efficacy of
- The 1-year PFS endpoint – Expected to be evaluated in 2019, Q3

* concurrent chemo-RT schedule: 18 pts

ETOP NICOLAS phase II trial: Results: Adverse events

Table 2: Adverse events for the safety cohort (N=58 patients)

Characteristic	Grade 1/2 (177/376)	Grade 3 (43/50)	Grade 4 (15/15)	Grade 5 (3/3)	N of which became SAE
Blood and lymphatic system disorders					
Anemia	21 (36.2%)	3 (5.2%)	-	-	1 G3
Neutrophil count decreased	7 (12.1%)	4 (6.9%)	9 (15.5%)	-	2 G4
Febrile neutropenia	-	5 (8.6%)	1 (1.7%)	-	5 G3 / 1 G4
Cardiac disorders					
Heart failure	1 (1.7%)	-	-	-	1 G2
Pericarditis	1 (1.7%)	-	-	-	1 G2
Gastrointestinal disorders					
Nausea	17 (29.3%)	1 (1.7%)	-	-	1 G2 / 1 G3
Dysphagia	14 (24.1%)	1 (1.7%)	-	-	
Esophagitis	9 (15.5%)	3 (5.2%)	-	-	1 G3
Enterocolitis	-	1 (1.7%)	-	-	1 G3
Esophageal fistula	-	-	-	1 (1.7%)	1 G5
General disorders and administration site conditions					
Fatigue	21 (36.2%)	3 (5.2%)	-	-	
Pain	9 (15.5%)	1 (1.7%)	-	-	1 G3
Fever	8 (13.8%)	1 (1.7%)	-	-	3 G2
Malaise	3 (5.2%)	-	-	-	2 G2

SAEs are presented.

Characteristic	Grade 1/2 (177/376)	Grade 3 (43/50)	Grade 4 (15/15)	Grade 5 (3/3)	N of which became SAE
Infections and infestations					
Bronchial infection	6 (10.3%)	1 (1.7%)	-	-	1 G3
Lung infection	4 (6.9%)	-	-	-	1 G2
Catheter related infection	-	1 (1.7%)	-	-	1 G3
Sepsis	-	-	1 (1.7%)	-	1 G4
Investigations					
White blood cell ↓	6 (10.3%)	2 (3.4%)	1 (1.7%)	-	
Lymphocyte count ↓	-	5 (8.6%)	1 (1.7%)	-	
Platelet count ↓	5 (8.6%)	-	1 (1.7%)	-	
Lipase ↑	1 (1.7%)	1 (1.7%)	1 (1.7%)	-	
Metabolism and nutrition disorders					
Hyponatremia	1 (1.7%)	1 (1.7%)	-	-	1 G3
Nervous system disorders					
Stroke	-	1 (1.7%)	-	2 (3.4%)	1 G3 / 2 G5
Respiratory, thoracic and mediastinal disorders					
Dyspnea	11 (19.0%)	1 (1.7%)	-	-	1 G2 / 1 G3
Pneumonitis	13 (22.4%)	6 (10.3%)	-	-	2 G2 / 6 G3
Cough	18 (31.0%)	-	-	-	
Pulmonary fibrosis	-	1 (1.7%)	-	-	1 G3
Respiratory insufficiency	1 (1.7%)	-	-	-	1 G2



PFS and OS Beyond 5 years of NSCLC Patients with Synchronous Oligometastases Treated in a Prospective Phase II Trial (NCT 01282450)

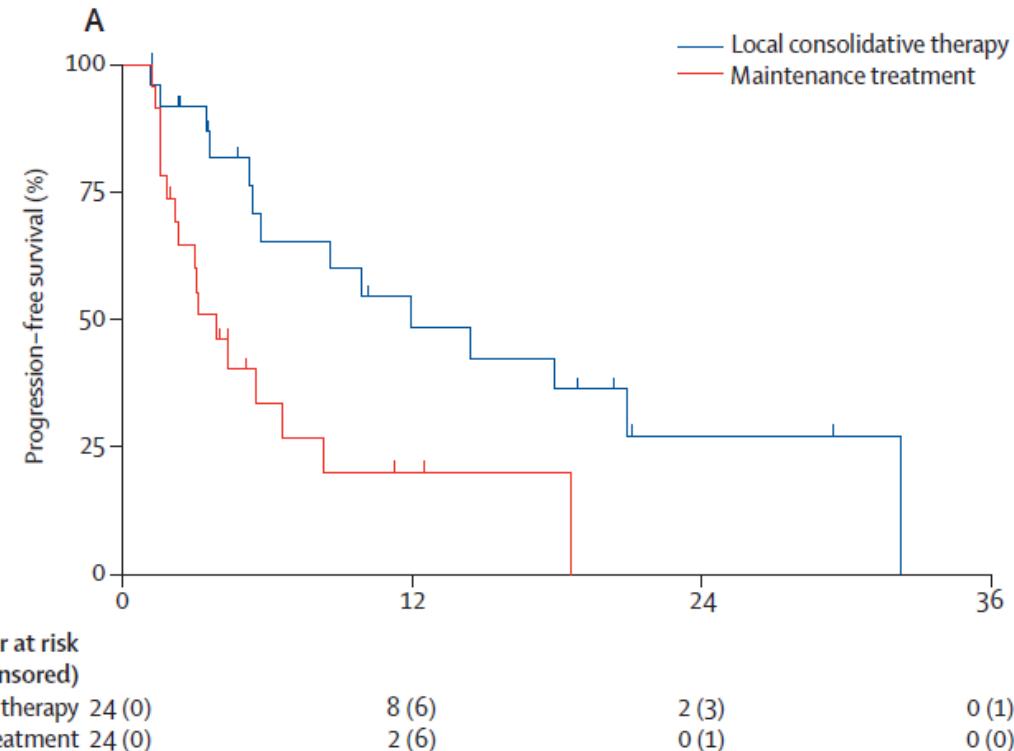
Dirk De Ruysscher¹, Rinus Wanders¹, Lizza Hendriks², Angela Van Baardwijk¹, Bart Reymen¹, Ruud Houben¹, Gerben Bootsma³, Cordula Pitz⁴, Anne-Marie C. Dingemans²

¹Maastricht University Medical Centre, Maastricht/Netherlands, ²Maastricht University Medical Center, Maastricht/Netherlands, ³Zuyderland MC, Heerlen/Netherlands, ⁴Laurentius MC, Roermond/Netherlands

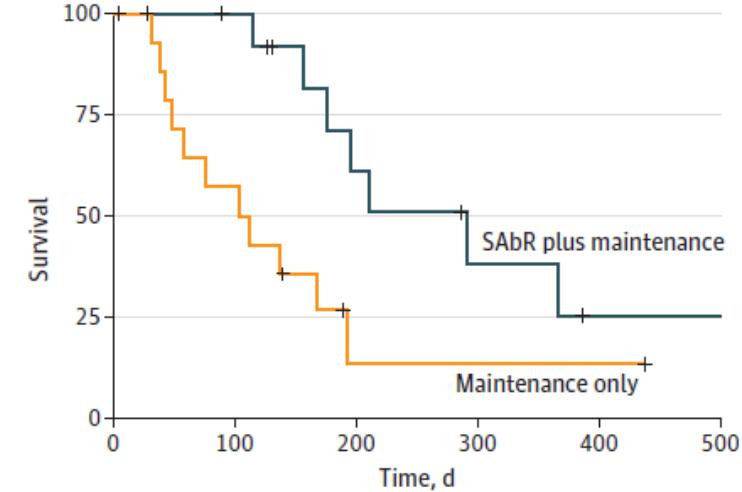


Background: Long-term OS and PFS in patients with synchronous oligometastases is largely unknown from prospective trials

Figure 2. Analysis of Progression-Free Survival



Gomez et al. Lancet Oncol 2016



No. at risk	SABR plus maintenance	Maintenance only
SABR plus maintenance	14	12
Maintenance only	15	8

Log-rank testing reveals a statistically significant benefit in progression-free survival for SABR-plus-maintenance chemotherapy (hazard ratio, 0.304; 95% CI, 0.113–0.815; $P = .01$). SABR indicates stereotactic ablative radiotherapy.

Iyengar et al. JAMA Oncol 2018

2018



6-year results of a prospective, single-arm trial

- July 27, 2006 until July 23, 2010
- N=40; with one patient being ineligible
- Inclusion criteria:
 - Histologically or cytologically proven NSCLC with less than five metastases at the time of diagnosis. Whole-body FDG-PET-CT scan and CT with iv contrast or MRI brain.
 - All tumor sites (local, regional, and distant) had to be amenable for radical treatment (surgery or radiotherapy to a biological dose of at least 60 Gy in 30 daily fractions of 2 Gy, except for brain metastases in which lower radiation doses were allowed).
 - Both surgery and radiotherapy were allowed in the same patient.
 - Systemic treatment was not mandatory.
 - WHO performance status 0 to 2
 - Any other malignancy in clinical complete remission





Age (yrs) (mean ± SD) (range)	62.1±9.2 (44–81)
Sex	
Male	18 (46.2%)
Female	21 (53.8%)
Comorbidity (modified Charlson)	
None	18 (46.2%)
1	20 (51.3%)
2	1 (2.6%)
WHO performance status	
0	12 (30.8%)
1	26 (66.7%)
2	1 (2.6%)
Pathology	
Adenocarcinoma	13 (33.3%)
Large cell carcinoma	7 (17.9%)
Large cell neuro-endocrine carcinoma	1 (2.6%)
Non-small-cell lung cancer (NOS)	8 (20.5%)
Undifferentiated carcinoma	2 (5.2%)
Squamous cell carcinoma	8 (20.5%)

➤ WCLC2018.IASLC.ORG

Local stage (ignoring M1 status)

I

II

IIIA

IIIB

Localization metastasis

Adrenal gland

Bone

Brain

Gastro-hepatic ligament

Liver

Lung

Lymph node

Muscle

Ovary

Pleura

Number metastases

1

2

3

4 (10.3%)

6 (15.4%)

9 (23.1%)

20 (51.3%)

4 (10.3%)

7 (17.9%)

17 (43.9%)

1 (2.6%)

1 (2.6%)

1 (2.6%)

2 (5.1%)

2 (5.1%)

1 (2.6%)

3 (7.7%)

34 (87.2%)

4 (10.3%)

1 (2.6%)



Updated OS and PFS

Time	Overall Survival (n=39)	Progression-Free Survival (PFS)
Median	13.5 months	12.1 months
1 year	56.4 %	51.3 %
2 year	23.3 %	13.6 %
3 year	12.8 %	12.8 %
4 year	10.3 %	7.7 %
5 year	7.7 %	7.7 %
6 year	5.1 %	2.5 %

Local Consolidative Therapy (LCT) Improves Overall Survival (OS) Compared to Maintenance Therapy/Observation in Oligometastatic Non-Small Cell Lung Cancer (NSCLC): Final Results of a Multicenter, Randomized, Controlled Phase 2 Trial

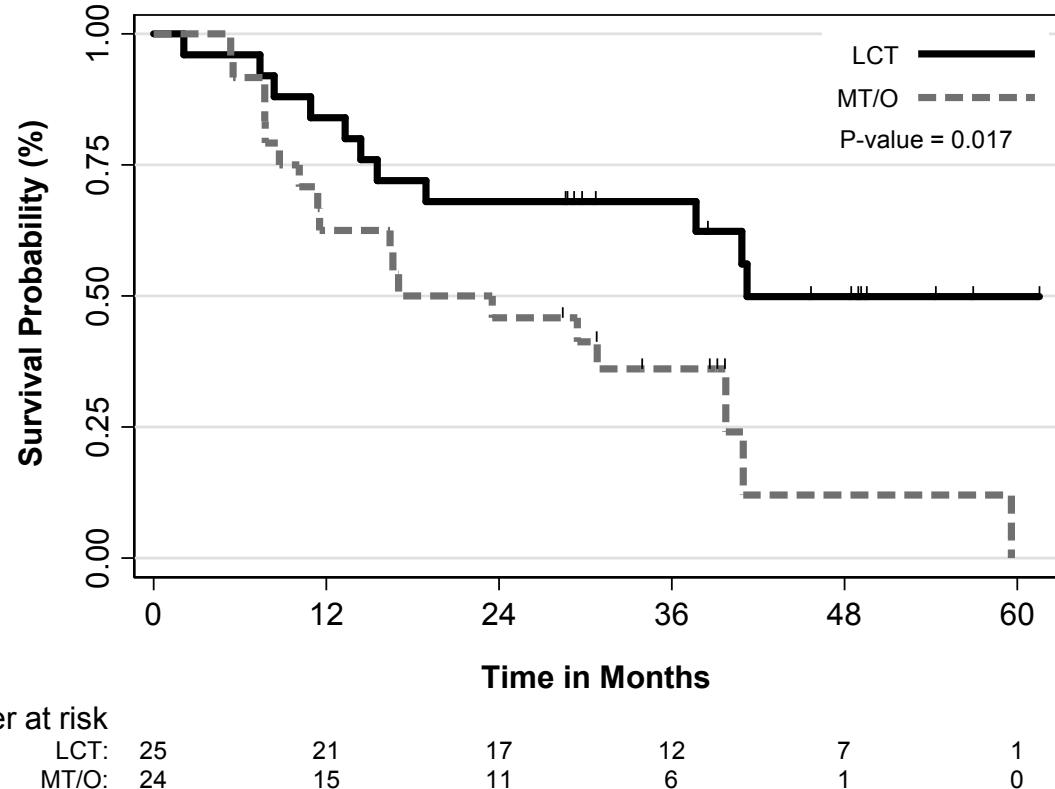
Daniel R. Gomez, MD, Chad Tang, MD, Jianjun Zhang, MD, PhD, George R. Blumenschein Jr, MD, Mike Hernandez, MS, J. Jack Lee, PhD, Rong Ye, MS, David A. Palma, MD, PhD , Alexander V. Louie, MD, PhD, D. Ross Camidge, MD, PhD, Robert C. Doebele, MD, PhD, Ferdinandos Skoulidis, MD, Laurie E. Gaspar, MD, James W. Welsh, M.D., Don L. Gibbons, MD, PhD, Jose A. Karam, MD, Brian D. Kavanagh, MD, Anne S. Tsao, MD, Boris Sepesi, MD, Stephen G. Swisher, MD,* John V. Heymach, MD, PhD*

*Dr. Swisher and Dr. Heymach contributed equally to this project.

ASTRO Clinical Trials Session
October 21, 2018

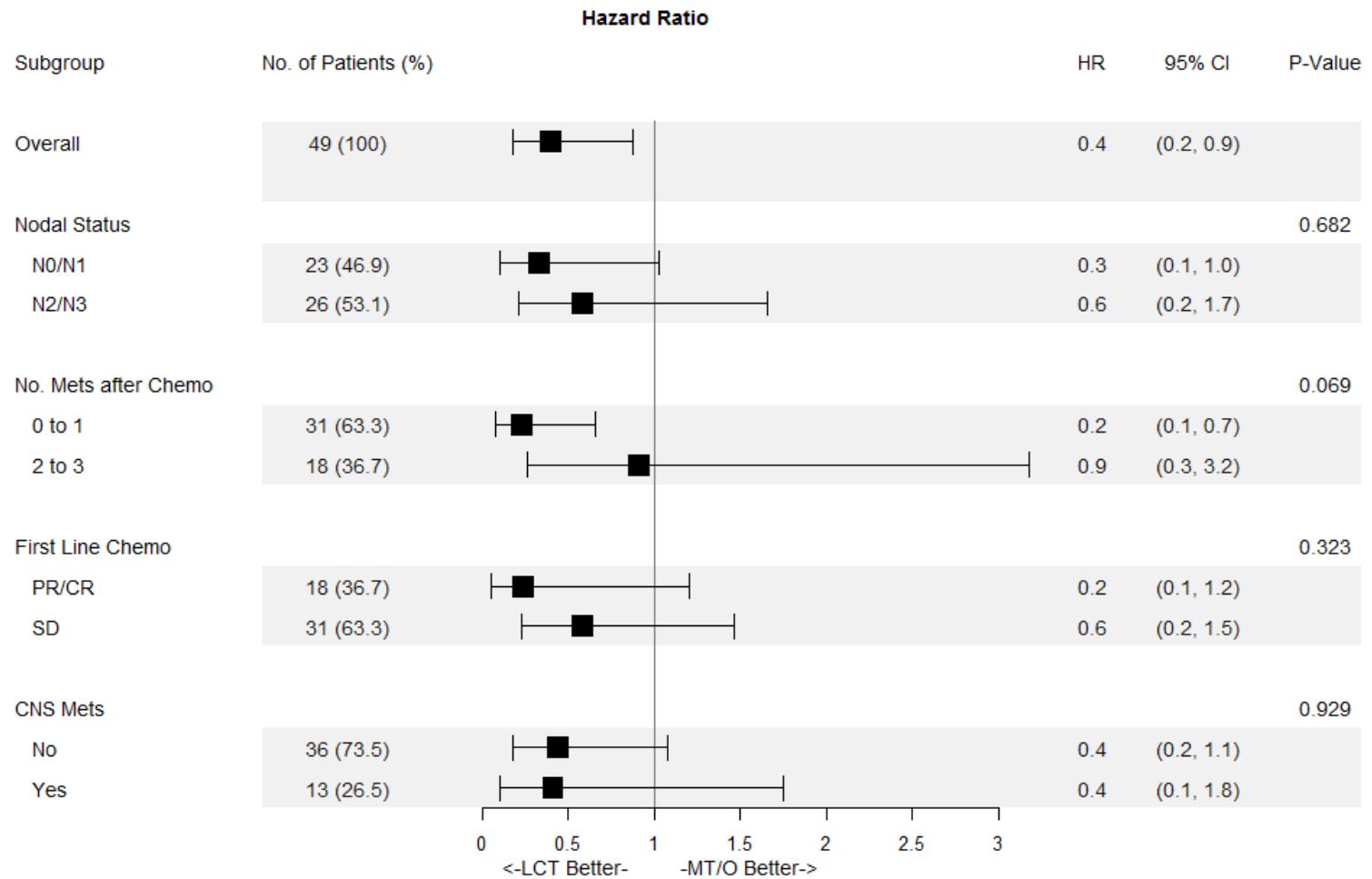


Overall Survival

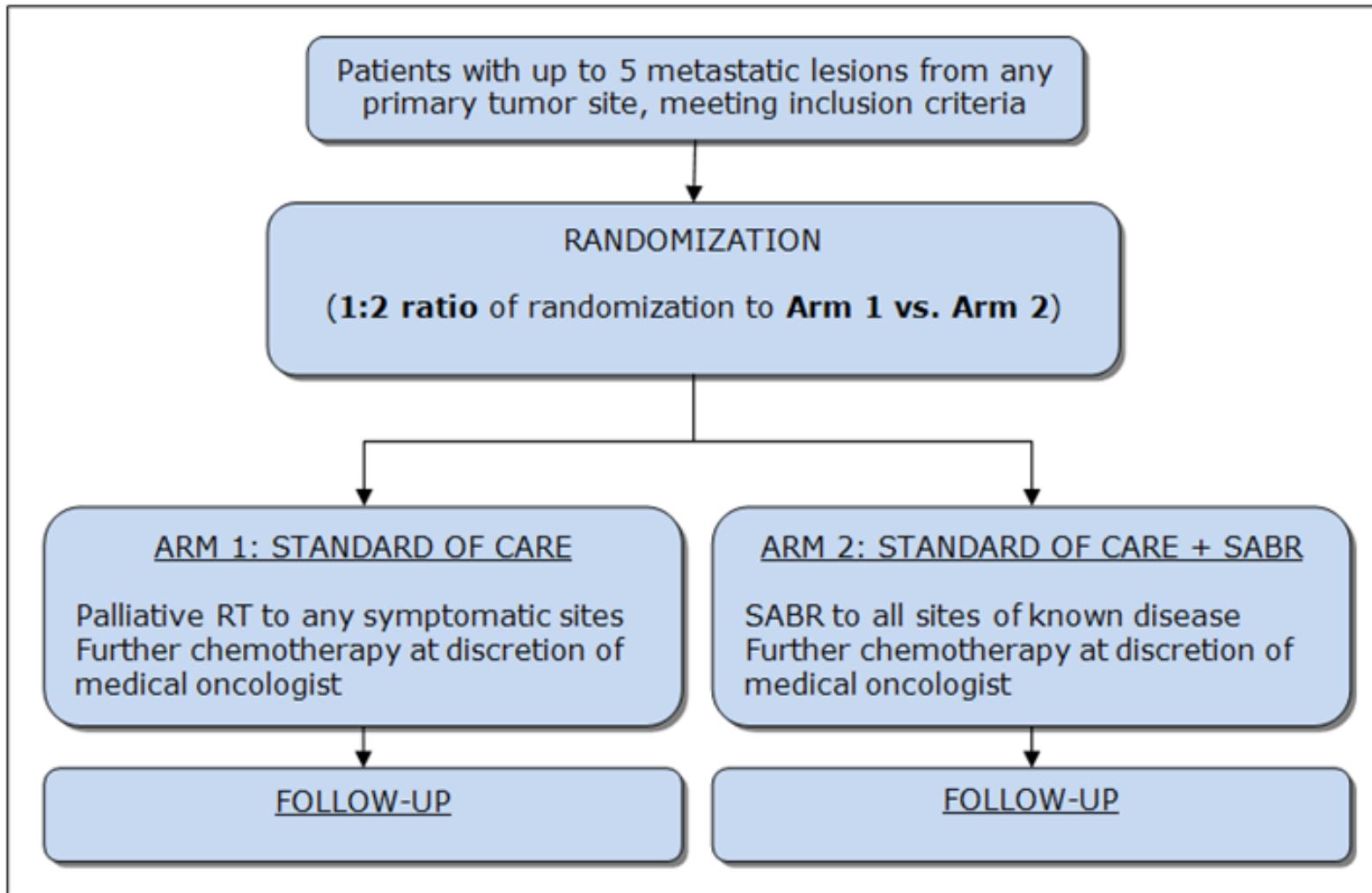


Median 17.0 months
MT/O [HR=0.40, 95% CI
10.1–39.8, $P=0.017$] vs.
41.2 months LCT [95%
CI 18.9–not reached]

Subgroup Analysis of Prognostic Factors on OS



SABR-COMET Schema



Main Inclusion Criteria

- Controlled primary tumor
 - defined as: at least 3 months since original tumor treated definitively, with no progression at primary site
- Up to 5 hematogenous metastases
- Maximum 3 metastases in any single organ system
- All sites of disease safely treatable

Baseline Characteristics

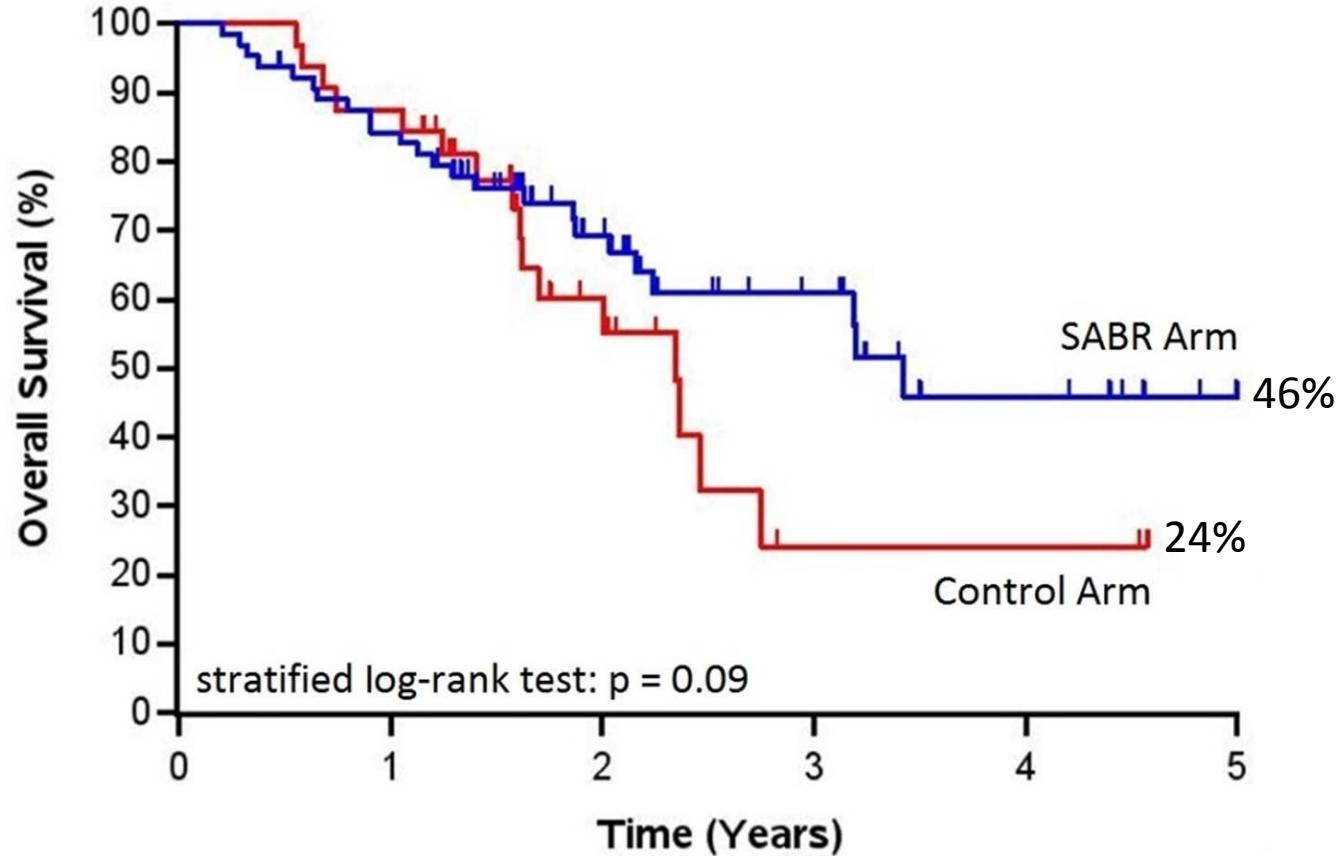
Between February 2012 and August 2016, 99 patients were randomized at centres in Canada, Scotland, Netherlands and Australia

<u>Characteristic</u>	<u>All Patients (n=99)</u>	<u>Control Arm (n=33)</u>	<u>SABR Arm (n=66)</u>	<u>p-value</u>
Age – median, (min, max)	68 (43, 89)	69 (44, 87)	67 (43, 89)	0.494
Sex – n(%)				0.772
Male	59 (59.6)	19 (57.6)	40 (60.6)	
Female	40 (40.4)	14 (42.4)	26 (39.4)	
Site of Original Primary Tumor – n(%)				0.204
Breast	18 (18.2)	5 (15.2)	13 (19.7)	
Colorectal	18 (18.2)	9 (27.3)	9 (13.6)	
Lung	18 (18.2)	6 (18.2)	12 (18.2)	
Prostate	16 (16.2)	2 (6.1)	14 (21.2)	
Other	29 (29.3)	11 (33.3)	18 (27.3)	

Baseline Characteristics

<u>Characteristic</u>	<u>All Patients</u> <u>(n=99)</u>	<u>Control Arm</u> <u>(n=33)</u>	<u>SABR Arm</u> <u>(n=66)</u>	<u>p-value</u>
Number of Metastases – n(%)				0.591
1	42 (42.4)	12 (36.4)	30 (45.5)	
2	32 (32.3)	13 (39.4)	19 (28.8)	
3	18 (18.2)	6 (18.2)	12 (18.2)	
4	4 (4.0)	2 (6.1)	2 (3.0)	
5	3 (3.0)	0 (0.0)	3 (4.6)	
Location of Metastases – n(%)				0.181
Adrenal	9 (4.7)	2 (3.1)	7 (5.5)	
Bone	65 (34.0)	20 (31.3)	45 (35.4)	
Liver	19 (10.0)	3 (4.7)	16 (12.6)	
Lung	89 (46.6)	34 (53.1)	55 (43.3)	
Other	9 (4.7)	5 (7.8)	4 (3.2)	

Overall Survival



Median OS

Control Arm: 28 months
(95% CI: 19-33 months)

SABR Arm: 41 months
(95% CI: 26 months to 'not reached')

Number at risk:

Control	33	28	12	2	2
SABR	66	53	29	15	7