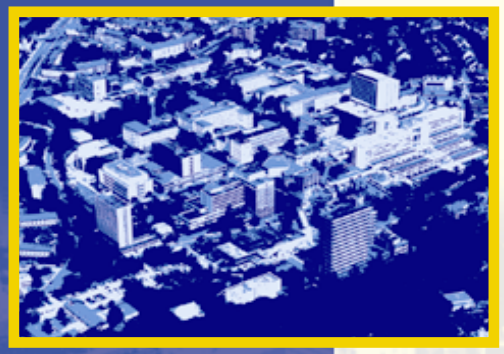
Universitätsklinikum Essen



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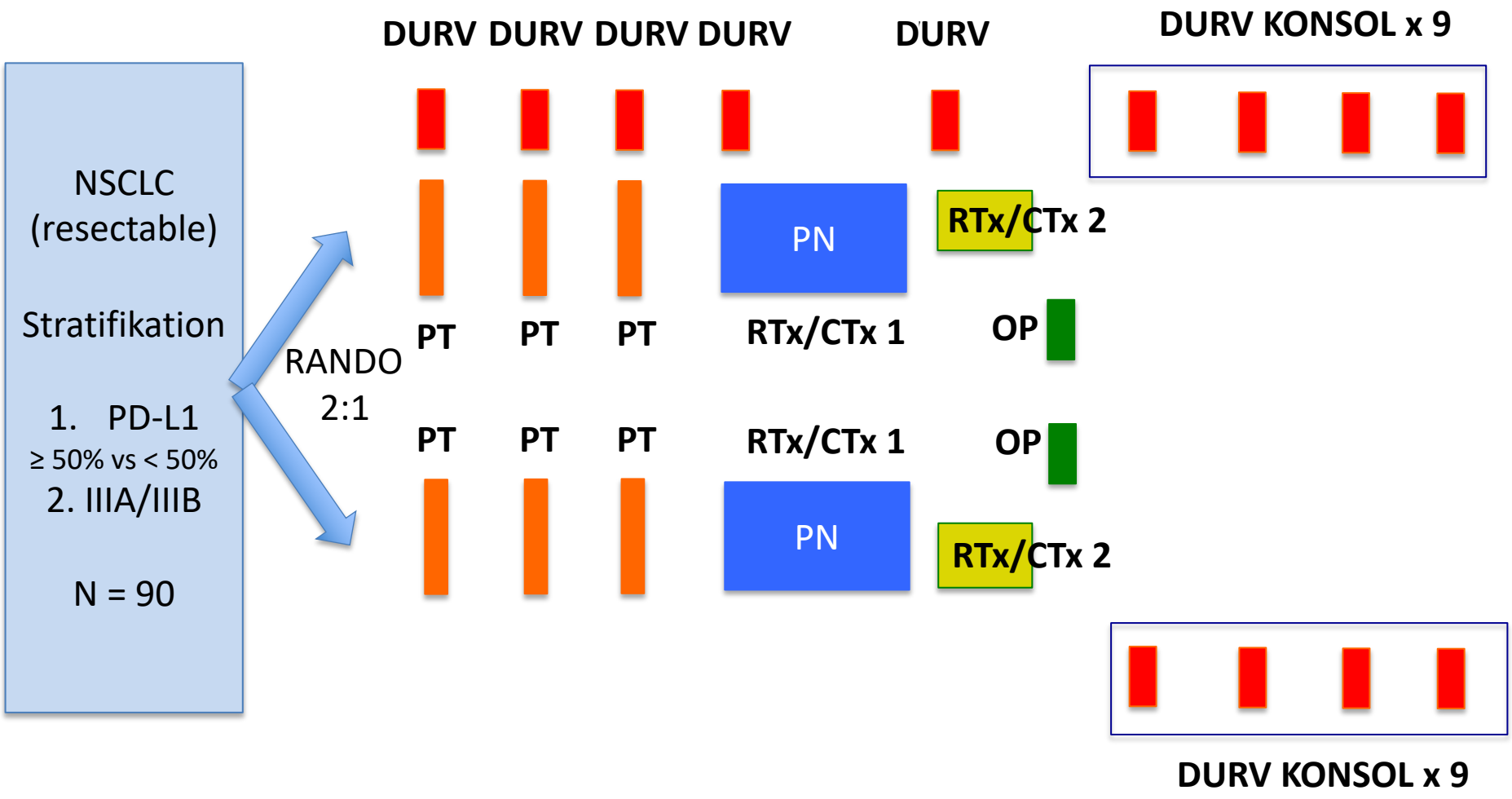
ESPADURVA (PI PD Dr. WEE Eberhardt)



PT = Cis Pacli PN Cis Nav Durv = Durvalumab 1200 mg q d 21 Konsol = 1500 mg q d 28
RTx/CTx 1 = 45 Gy HF RTx RTx/CTx 2 = 20 Gy

Therapiesequenzen

Kombinierter primärer Endpunkt:

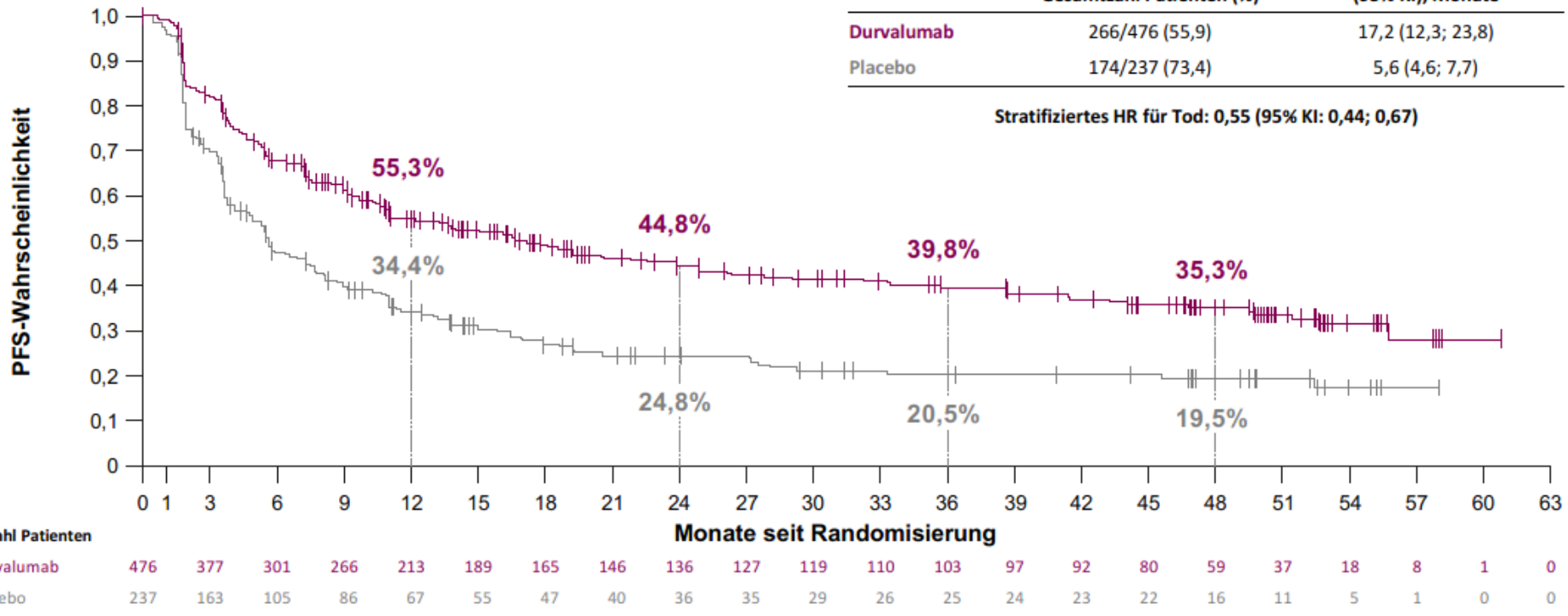
H0a: PFS nach 2 Jahren in beiden Armen zusammen ist ≤ 35%
H0a wird abgelehnt bei ≥39 von 84 Patienten mit PFS nach 2 Jahren (α<0.025)

H0b: PFS Arm A = Arm B
H0b wird abgelehnt mit einer power > 80% bei einem HR < 0.5

Sekundärer Endpunkt
Histopath. Remission

exploratorisch
Präsenz, Phänotyp und Klonalität von TILs vor und nach neoadjuvanter Therapie
Expression Immunmodulatorischer Moleküle im Tumor
Immunantwort im peripheren Blut und den drainierenden Lk

Pacific trial on anti-PD-L1 antibody for up to 12 m as consolidation after concurrent radiochemotherapy, 4 J survival at 34 M median follow-up

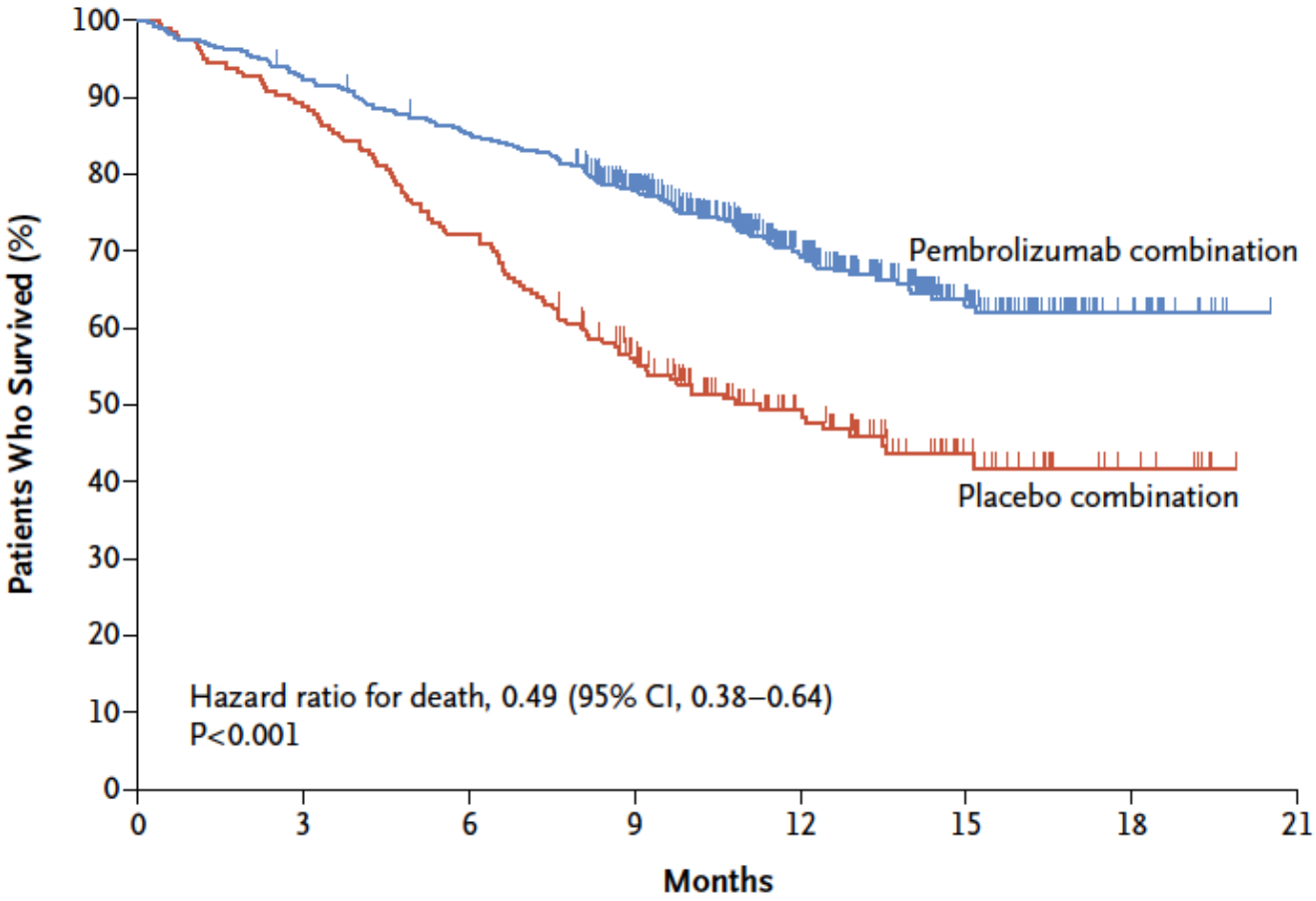


	Anzahl der Ereignisse/ Gesamtzahl Patienten (%)	Medianes PFS (95% KI), Monate
Durvalumab	266/476 (55,9)	17,2 (12,3; 23,8)
Placebo	174/237 (73,4)	5,6 (4,6; 7,7)

Stratifiziertes HR für Tod: 0,55 (95% KI: 0,44; 0,67)

Faivre-Finn C et al. Ann Oncol (2020) 31 (suppl_4); S1142-S1215

First line stage IV Adenokrazinome der Lunge: KEYNOTE-189
Cis/CarboPem + Pembro vs. Cis/CarboPem + Placebo



No. at Risk								
Pembrolizumab combination	410	377	347	278	163	71	18	0
Placebo combination	206	183	149	104	59	25	8	0

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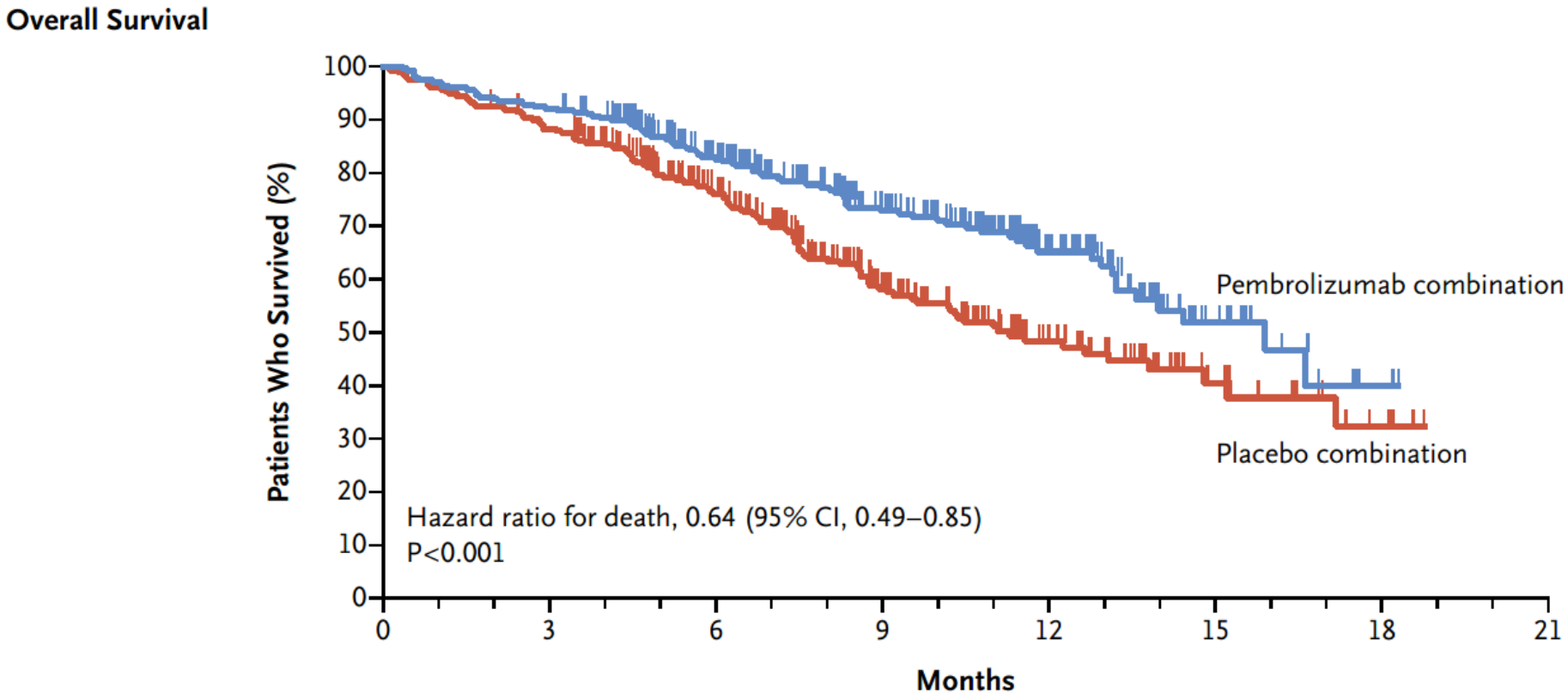
Gandhi et al. NEJM 2018

First line stage IV für SCC der Lunge: KEYNOTE-407
CarboTaxan + Pembro vs. CarboTaxan + Placebo



No. at Risk

Pembrolizumab combination	278	256	188	124	62	17	2	0
Placebo combination	281	246	175	93	45	16	4	0

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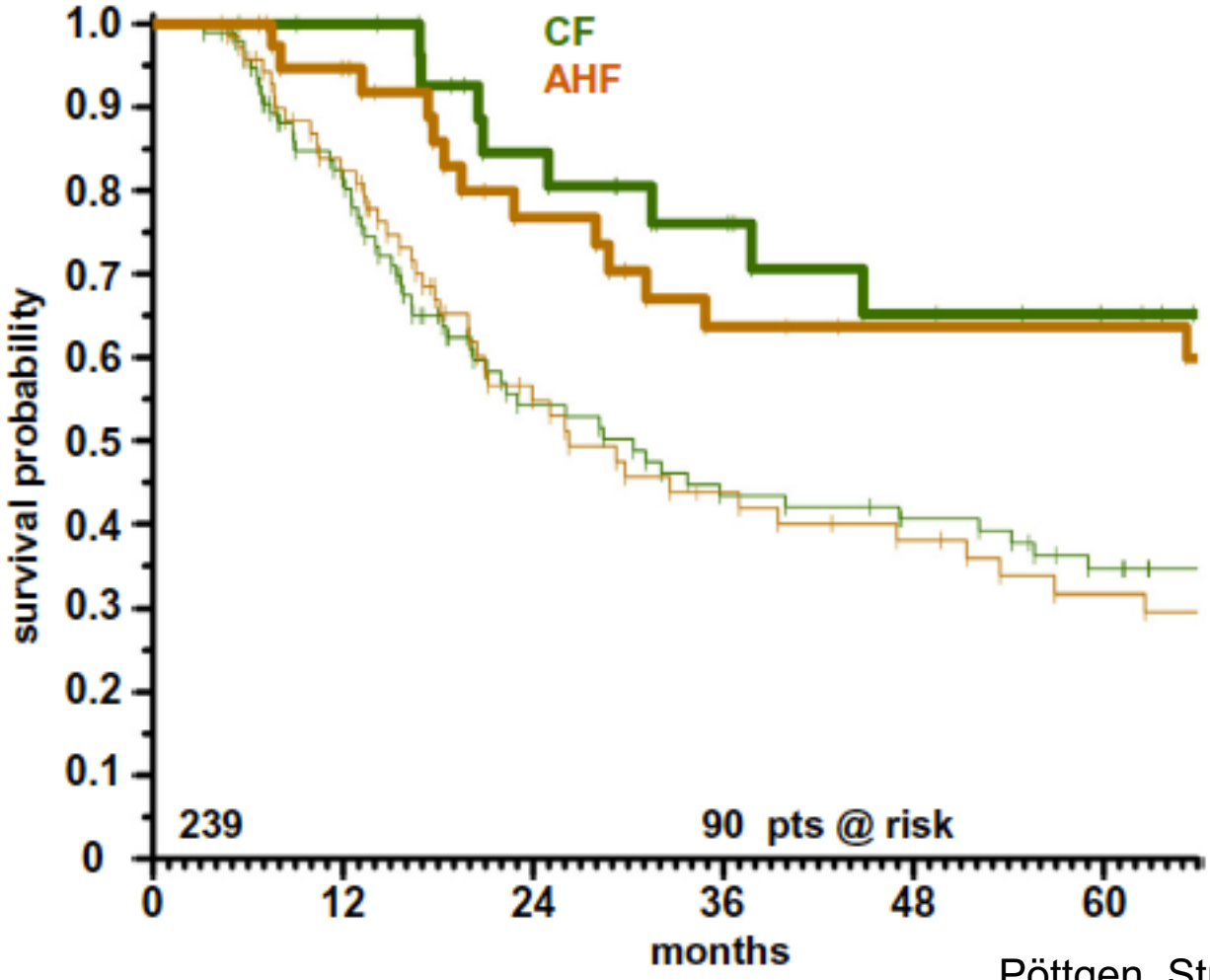
Paz-Ares et al. NEJM 2018

Survival according to pCR and fractionation schedule

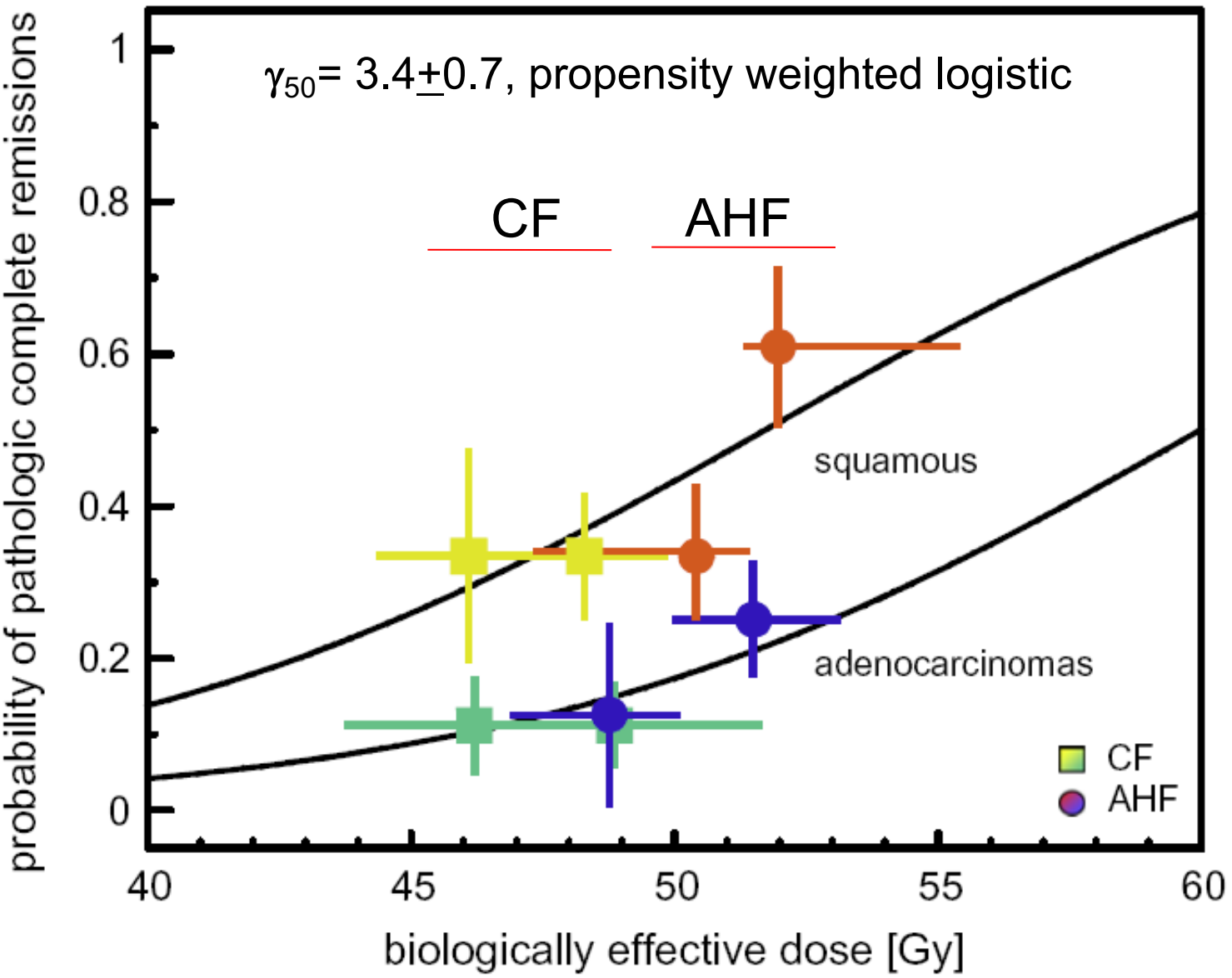


pCR

¬ pCR

Pöttgen, Stuschke Eberhardt, Stamatis, Eur J Cancer 2013

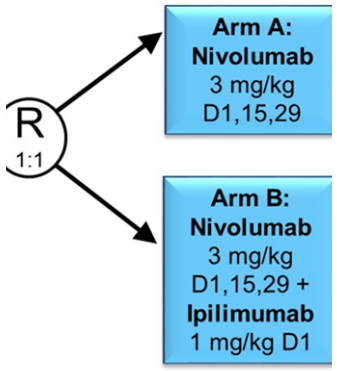
Dose-effect relation of neoadjuvant RT/CTx in NSCLC histopathologic complete response in 239 patients



Pöttgen, Stuschke Eberhardt, Stamatis Eur J Cancer 2013

IO als neoadjuvante Therapie

ASCO Meeting Library



Neoadjuvant nivolumab (N) or nivolumab plus ipilimumab (NI) for resectable non-small cell lung cancer (NSCLC): clinical and correlative results from the NEOSTAR study

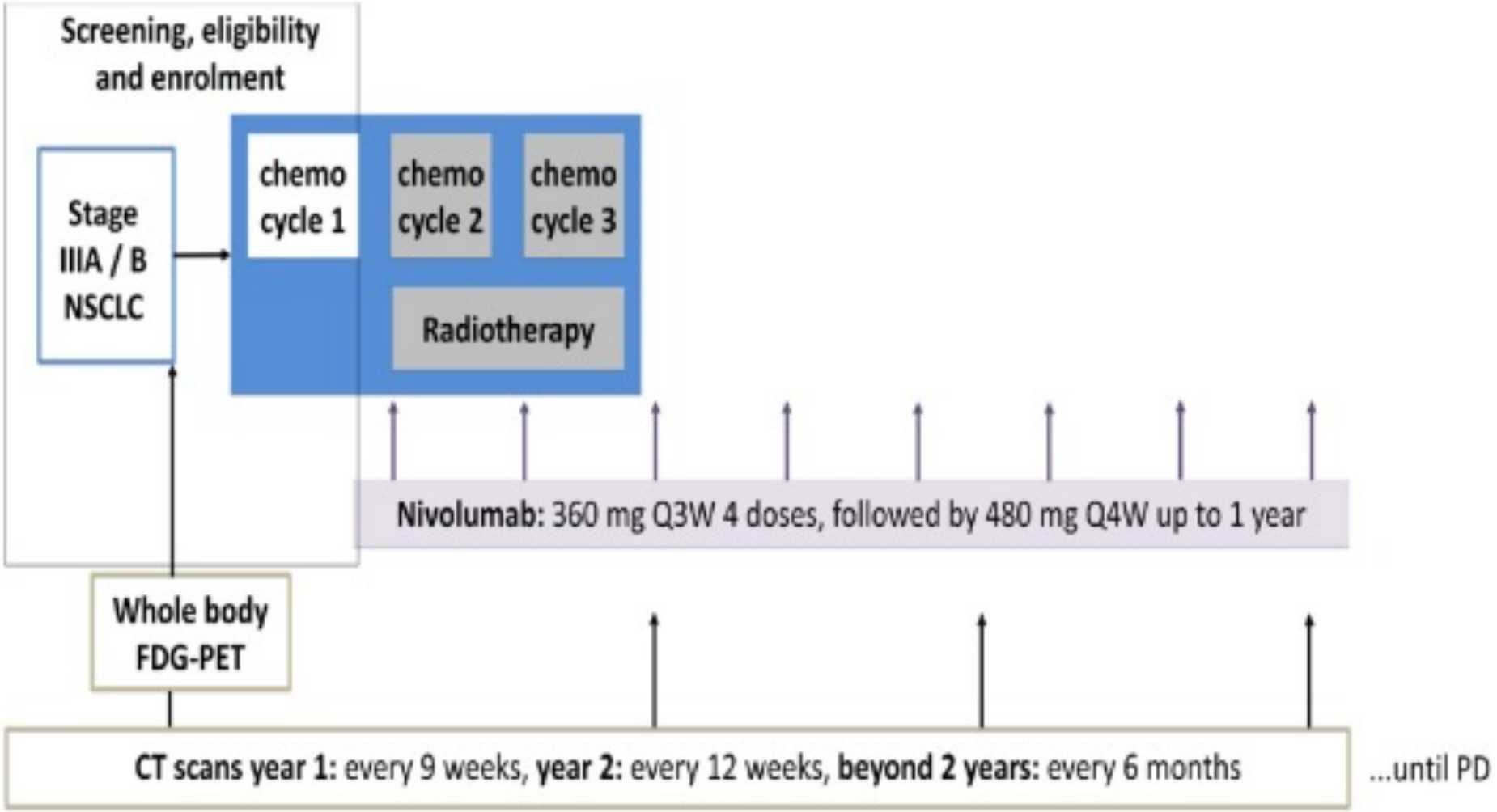
Tina Cascone[1], William N. William Jr.[1], Annikka Weissferdt[2], Heather Lin[3], Cheuk H. Leung[3], Brett W.

June 1, 2019, # 8504

	alle	N	NI
Anzahl Patienten	44	23	21
operierte Pat.	34		
MpR (alle)		17%	33%
pCR (alle)		9%	29%
Recist PD (alle)		13%	14%
Toxizität		1xG5 Pneumonitis	1xG3 Diarrhoe
		1xG3 Hypoxie	1xG3 Hyponatriämie
Therapie PD-L1	war prädiktiv		

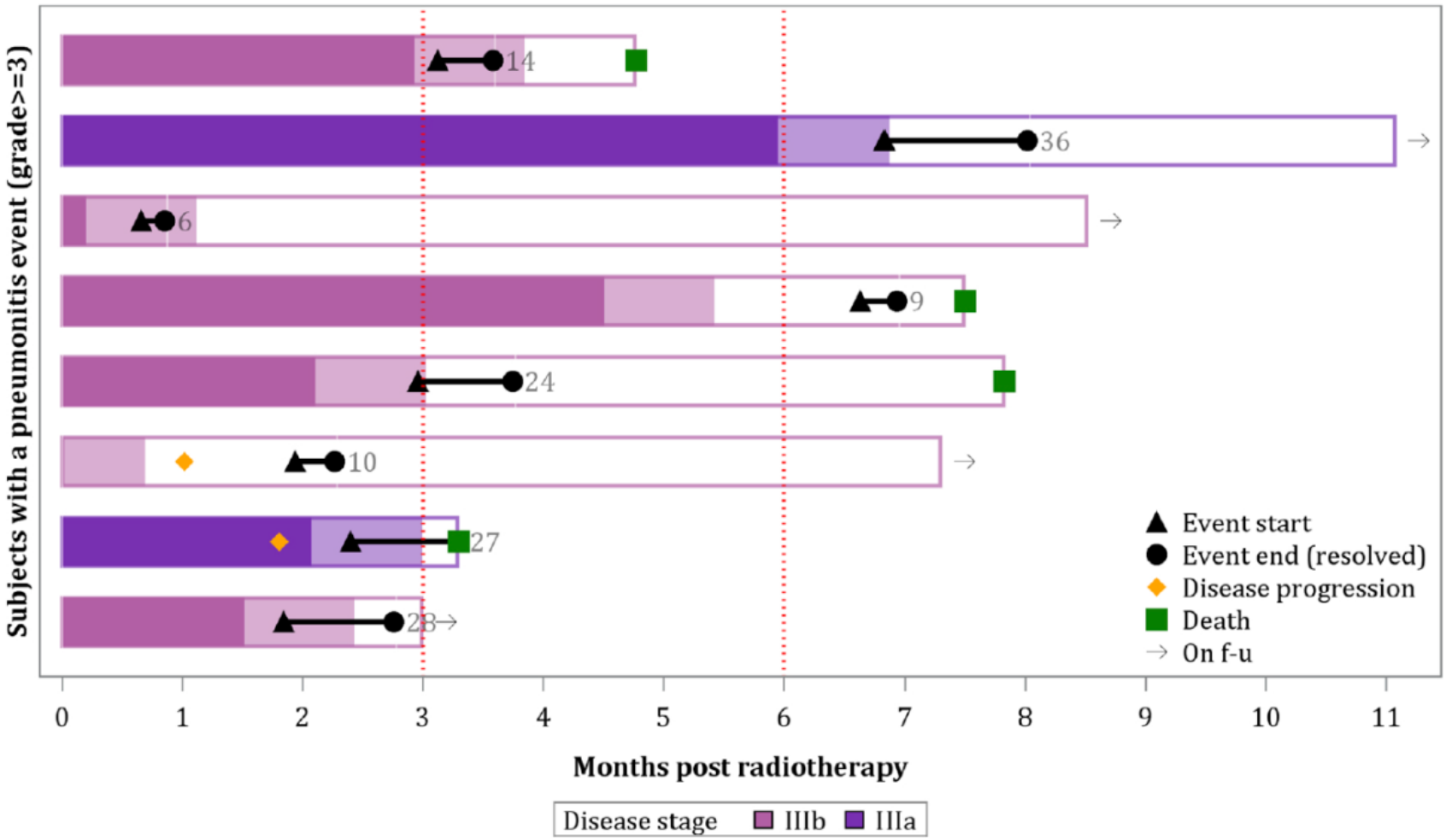
wtz westdeutsches tumorzentrum

ETOP Nicolas Trial: Safety of Nivolumab and simultaneous Standard-Radiochemotherapy for locally advanced NSCLC



Peters, Lung Cancer 2019

ETOP Nicolas Trial, Primary End point: pneumonitis Grade 3 in the safety cohort of 80 pts. within 6 months



pneumonitis grade 3: 8 / 80

Peters, Lung Cancer 2019

DETERRED trial „PD-L1 blockadE To Evaluate the safety of Lung CanceR therapy using Carboplatin, Paclitaxel, and Radiaton combined with Atezolizumab“

Immune-related adverse events in patients who have received at least one dose of atezolizumab N=24

	Part 2			
	Grade 1-2	Grade 3	Grade 4	Grade 5
Any event	24 (80%)	5 (17%)	1 (3%)	0
Dyspnea	3 (10%)	0	0	0
Pneumonitis*	4 (13%)	1 (3%)	0	0
Lung infection	0	0	0	0
Respiratory failure	0	0	1 (3%)	0
Nephritis	1 (3%)	1 (3%)	0	0
Heart failure	0	1 (3%)	0	0

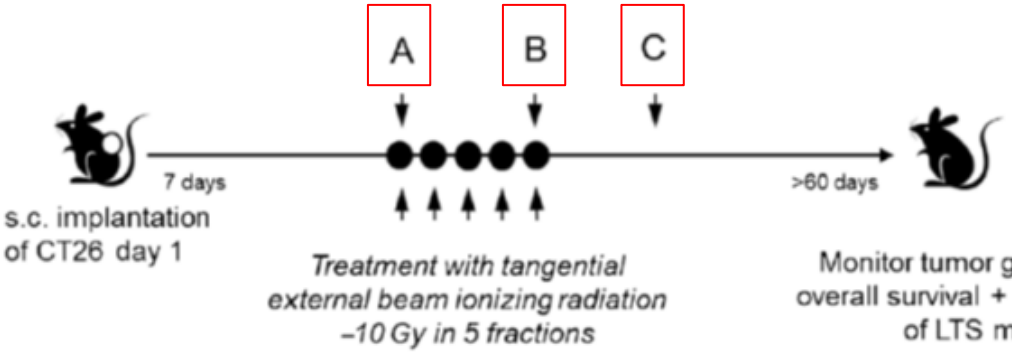
Lin et al., JTO 2019

Pacific trial on anti-PD-L1 antibody consolidation: Adverse events according to incidence rate

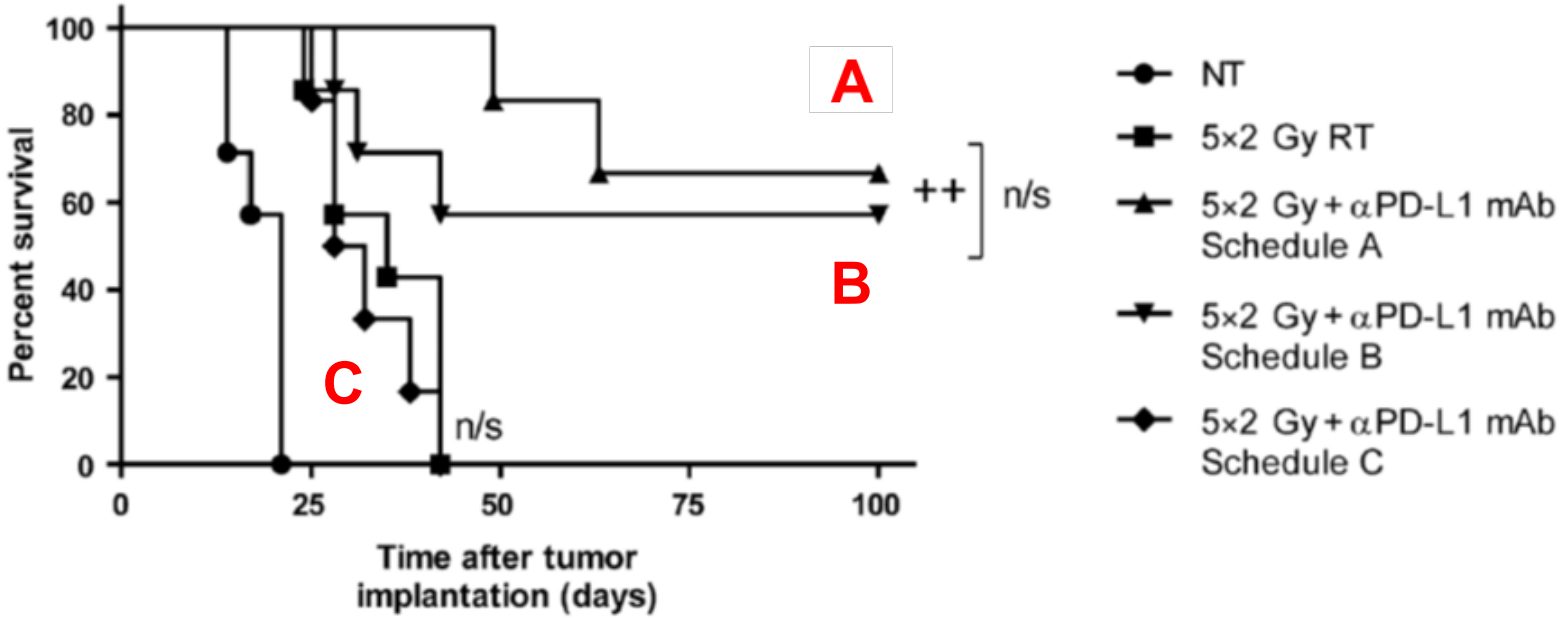
Event	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade*	Grade 3 or 4	Any Grade*	Grade 3 or 4
	number of patients with event (percent)			
Any event	460 (96.8)	145 (30.5)	222 (94.9)	61 (26.1)
Cough	167 (35.2)	2 (0.4)	59 (25.2)	1 (0.4)
Fatigue	114 (24.0)	1 (0.2)	48 (20.5)	3 (1.3)
Dyspnea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Radiation pneumonitis†	96 (20.2)	7 (1.5)	37 (15.8)	1 (0.4)
Diarrhea	88 (18.5)	3 (0.6)	46 (19.7)	3 (1.3)
Pyrexia	72 (15.2)	1 (0.2)	22 (9.4)	0
Nausea	68 (14.3)	0	31 (13.2)	0
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Pneumonia	63 (13.3)	21 (4.4)	18 (7.7)	9 (3.8)
Pneumonitis†	60 (12.6)	9 (1.9)	18 (7.7)	4 (1.7)

Antionia et al. N Engl J Med; 2018

Resistance to fractionated radiotherapy can be overcome **by concurrent but not sequential** PD-L1 Blockade

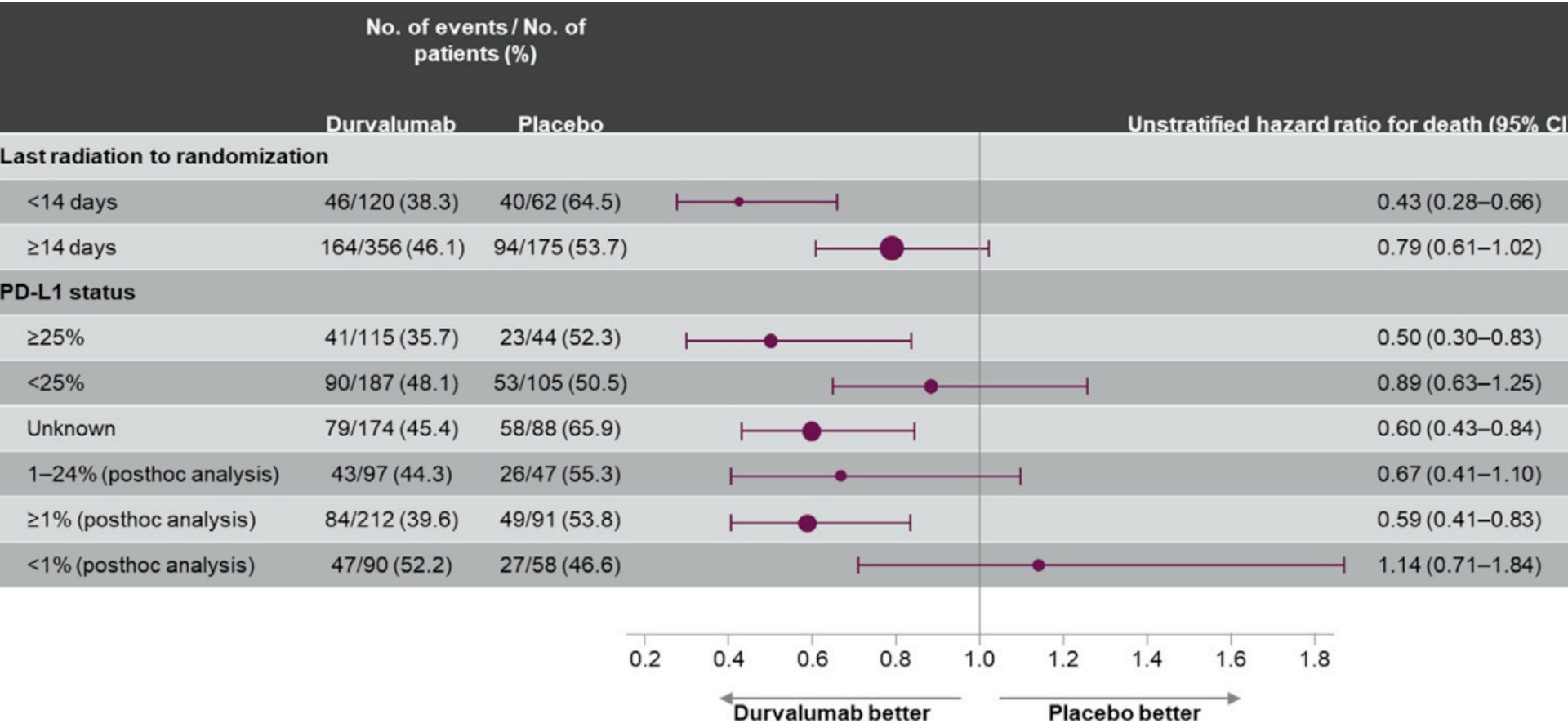


A. *αPD-L1 mAb starting on day 1 of RT*
B. *αPD-L1 mAb starting on day 5 of RT*
C. *αPD-L1 mAb starting 7 days after the last dose of RT*



Dovedi et al.
Cancer Res 2014

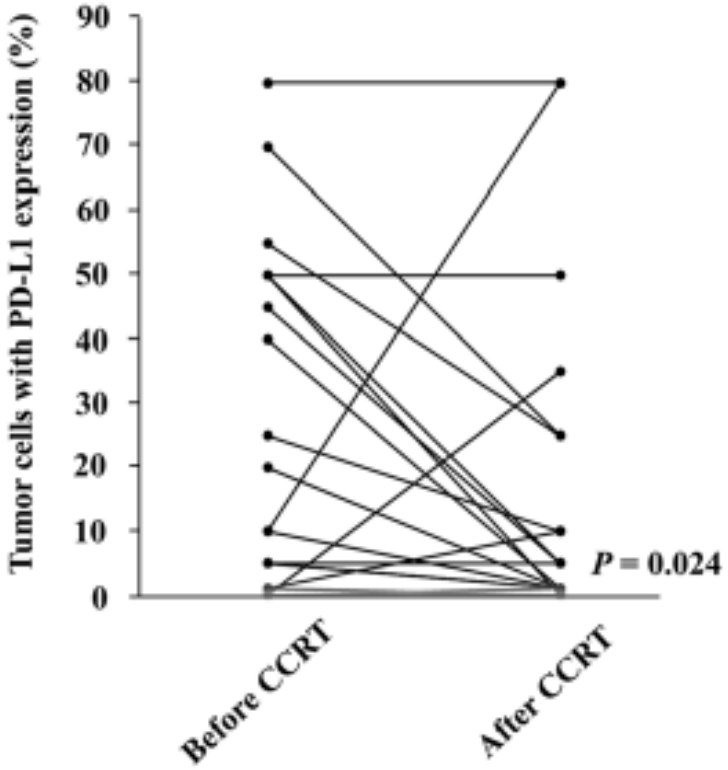
Updated post-hoc overall survival analyses of the Pacific Trial inexploratory subgroups

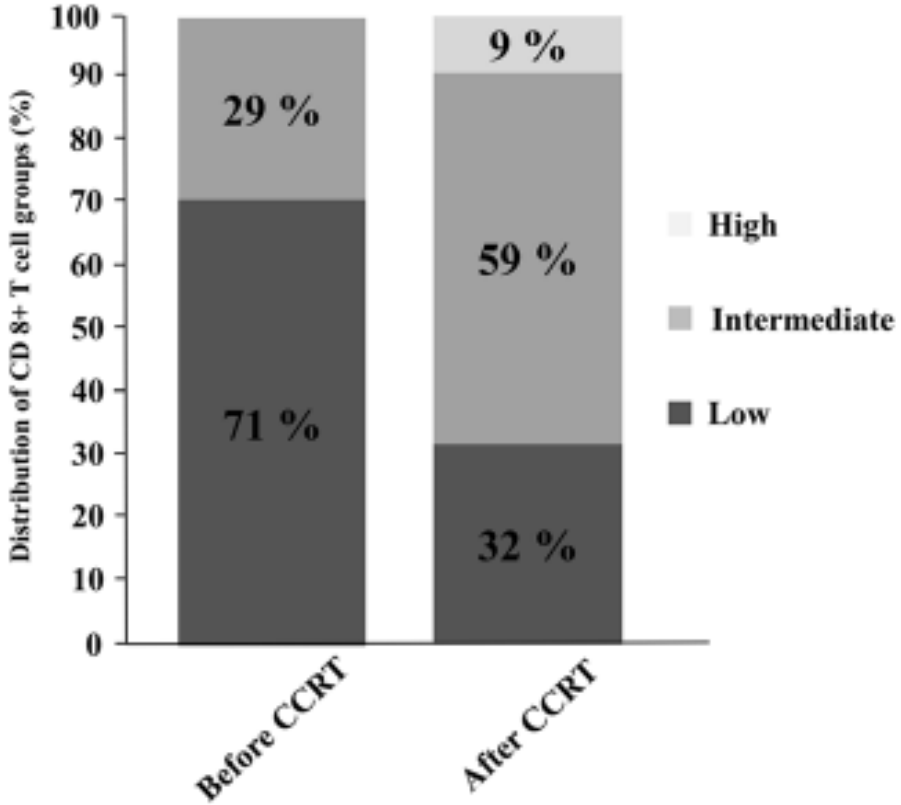


	No. of events / No. of patients (%)		Unstratified hazard ratio for death (95% CI
	Durvalumab	Placebo	
Last radiation to randomization			
<14 days	46/120 (38.3)	40/62 (64.5)	0.43 (0.28–0.66)
≥14 days	164/356 (46.1)	94/175 (53.7)	0.79 (0.61–1.02)
PD-L1 status			
≥25%	41/115 (35.7)	23/44 (52.3)	0.50 (0.30–0.83)
<25%	90/187 (48.1)	53/105 (50.5)	0.89 (0.63–1.25)
Unknown	79/174 (45.4)	58/88 (65.9)	0.60 (0.43–0.84)
1–24% (posthoc analysis)	43/97 (44.3)	26/47 (55.3)	0.67 (0.41–1.10)
≥1% (posthoc analysis)	84/212 (39.6)	49/91 (53.8)	0.59 (0.41–0.83)
<1% (posthoc analysis)	47/90 (52.2)	27/58 (46.6)	1.14 (0.71–1.84)

Gray and Antionia JTO, Oct 2019

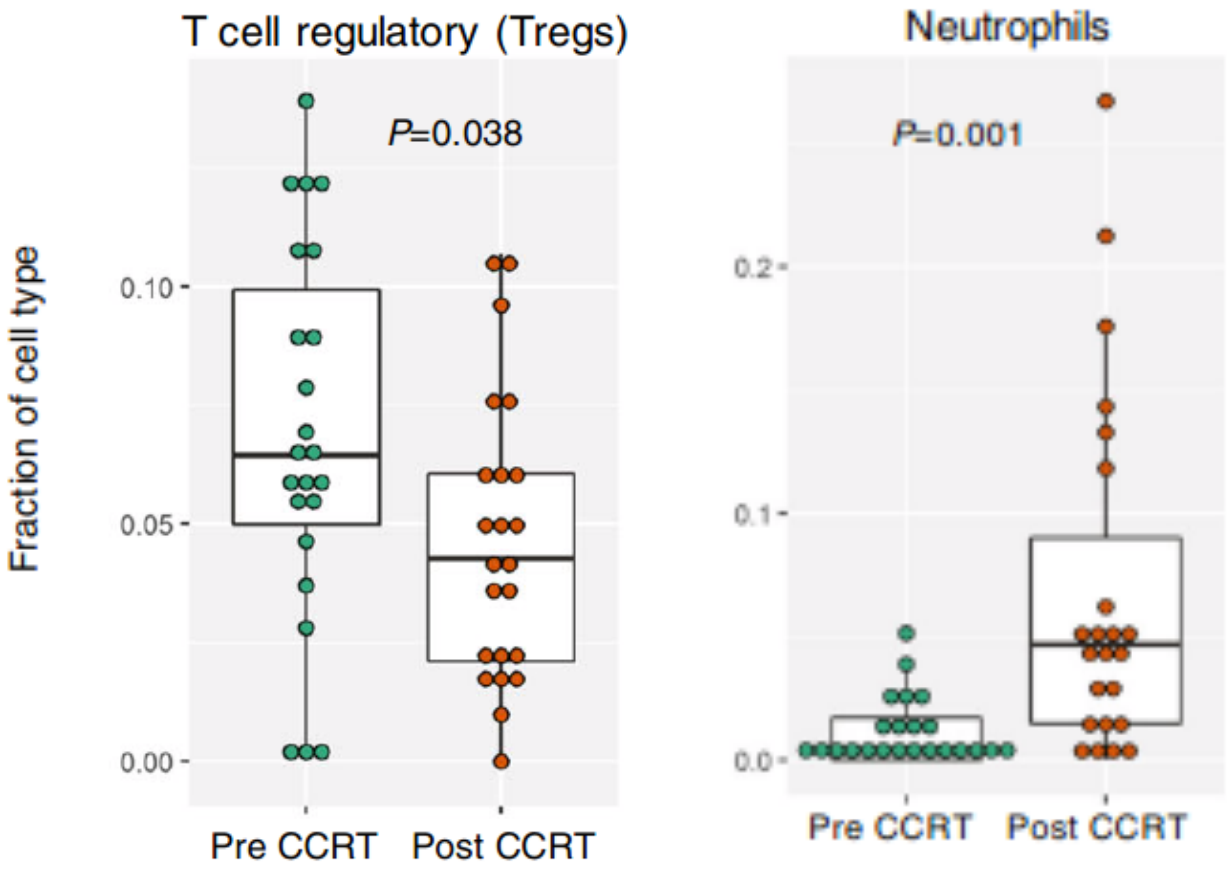
Alterations of PD-L1 expression on tumor cells after neoadjuvant concurrent RT/CTx in 35 NSCLC Patients





Fujimoto Sci Rep 2017

Immungenomic changes during following neoadjuvant chemoradiotherapy in esophageal squamous cell carcinoma



Park et al.
J Immunother Cancer 2019

SAKK 16/18

- Neoadjuvant chemotherapy with cisplatin and docetaxel: 3 cycles of 21 days
- Neoadjuvant immunotherapy with durvalumab: 1 cycle
- Neoadjuvant immune-modulatory radiotherapy
  - Concurrent with neoadjuvant immunotherapy
  - Random assignment to one of the following fractionation regimens:
    - 20x2 Gy (weekdaily, 4 weeks)
    - 5x5 Gy (weekdaily, 1 week)
    - 3x8 Gy (on alternate days, 1 week)
- Surgery

o Between 4 and 6 weeks after the application of durvalumab

- If indicated: Postoperative radiotherapy (should start between 3 to 6 weeks after surgery)
- Adjuvant immunotherapy with durvalumab: 13 cycles of 28 days

www.clinicaltrials.gov 8/2020

Zusammenfassung ESPADURVA

- Charakterisierung von Effektivität und Toxizität der 4-modalen Therapie

- Translationale Begleitforschung zu immunologischer Resistenzmechanismen

Wir danken den Sponsoren