There is NO ROLE for Immunotherapy in stage III NSCLC

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Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Wadsworth, G. Melillo, H. Jiang, Y. Huang, P.A. Dennis, and M. Özgüroğlu, for the PACIFIC Investigators*

Durvalumab deemed the treatment of choice for patients not progressed on Chemoradiotherapy in stage III unresectable NSCLC –

1) irrespective of the PD-L1 status
2) irrespective of the mutational status
3) IO was administered within 42 days of last radiotherapy dose

Important thought on metoo IO drugs

- Too many IO similar drugs
- Each company pushing its drug for a different indication
- Each drug pushing to get a different biomarker done to carve out its own niche amongst various indications
- Waste of resources , funds , unnecessary increase in cost
- IO drugs are ruthlessly expensive whatever PAP assistance some companies may bring in, bottomline

PACIFIC: Baseline Patient Characteristics

Characteristic	Durvalumab (n = 476)	Placebo (n = 237)
Median age, yrs (range)	64 (31-84)	64 (23-90)
▪ Age ≥ 65 yrs, %	45.2	45.1
Male sex, %	70.2	70.0
WHO PS 0/1, %	49.2/50.4	48.1/51.5
Smoking status, %		
▪ Current	16.6	16.0
▪ Former	74.4	75.1
▪ Never	9.0	8.9
Disease stage, %		
▪ IIIA	52.9	52.7
▪ IIIB	44.5	45.1
▪ Other	2.5	2.1
Histology, squamous/ nonsquamous, %	47.1/52.9	43.0/57.0

Characteristic, %	Durvalumab (n = 476)	Placebo (n = 237)
PD-L1		
▪ < 25%	39.3	44.3
▪ ≥ 25%	24.2	18.6
▪ Unknown	36.6	37.1
Prior CT, induction/cCRT	25.8/99.8	28.7/99.6
Prior RT		
▪ < 54 Gy	0.6	0
▪ ≥ 54 to ≤ 66 Gy	92.9	91.6
▪ > 66 to ≤ 74 Gy	6.3	8.0
Best response to prior cCRT		
▪ CR	1.9	3.0
▪ PR	48.7	46.8
▪ SD	46.6	48.1

Antonia SJ, et al. N Engl J Med. 2017;377:1919-1929.

GLOBAL Approval labels for IO in stage III

Following these impressive results, the United States FDA, as well as regulatory agencies in Canada, Japan, Australia, Switzerland, Malaysia, Singapore, India and the United Arab Emirates have approved durvalumab as consolidation therapy after chemoRT in unselected unresectable stage III NSCLC. Unexpectedly, the European Medicines Agency (EMA) made the decision to limit the use of durvalumab for patients with PD-L1 expressing tumors. This was based on an unplanned post-hoc analysis, in a relatively small subset, that could not unequivocally establish an OS benefit in PD-L1 negative tumors, though the ITT population demonstrated a robust survival benefit[4,5].

EMA label/PI for Durvalumab in unresectable stage III NSCLC

PD-L1 status

Subgroup analysis by PD-L1 for PFS – NEJM main article

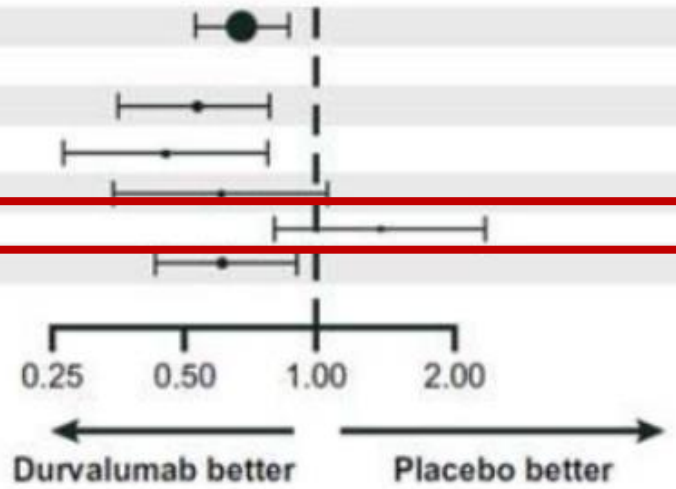
PD-L1 status				
≥25%	115	44		0.41 (0.26–0.65)
<25%	187	105		0.59 (0.43–0.82)
Unknown	174	88		0.59 (0.42–0.83)

PD-L1 status			
≥25%	37/115 (32.2)	23/44 (52.3)	0.46 (0.27–0.78)
<25%	74/187 (39.6)	41/105 (39.0)	0.92 (0.63–1.34)
Unknown	72/174 (41.4)	52/88 (59.1)	0.62 (0.43–0.89)

Antonio SJ et al. NEJM 2017; 377(20): 1919-29
Antonio SJ et al. Supplementary Appendix NEJM 2018; 379: 2342-50

Post-HOC Analysis for OS by PD-L1 positivity as requested by EMA

Subgroup	Durvalumab	Placebo	Unstratified Hazard Ratio for Death (95% CI)
	no. of events / no. of patients (%)		
All patients	183/476 (38.4)	116/237 (48.9)	0.68 (0.53–0.87)†
PD-L1 status			
≥1%	70/212 (33.0)	45/91 (49.5)	0.53 (0.36–0.77)
≥25%*	37/115 (32.2)	23/44 (52.3)	0.46 (0.27–0.78)
1–24%	33/97 (34.0)	22/47 (46.8)	0.60 (0.35–1.03)
<1%	41/90 (45.6)	19/58 (32.8)	1.36 (0.79–2.34)
Unknown	72/174 (41.4)	52/88 (59.1)	0.62 (0.43–0.89)



PD-L1 <1 % ,overall survival NOT favoring IO arm and patients doing much better with the placebo arm

Antonio SJ et al. NEJM 2017; 377(20): 1919-29
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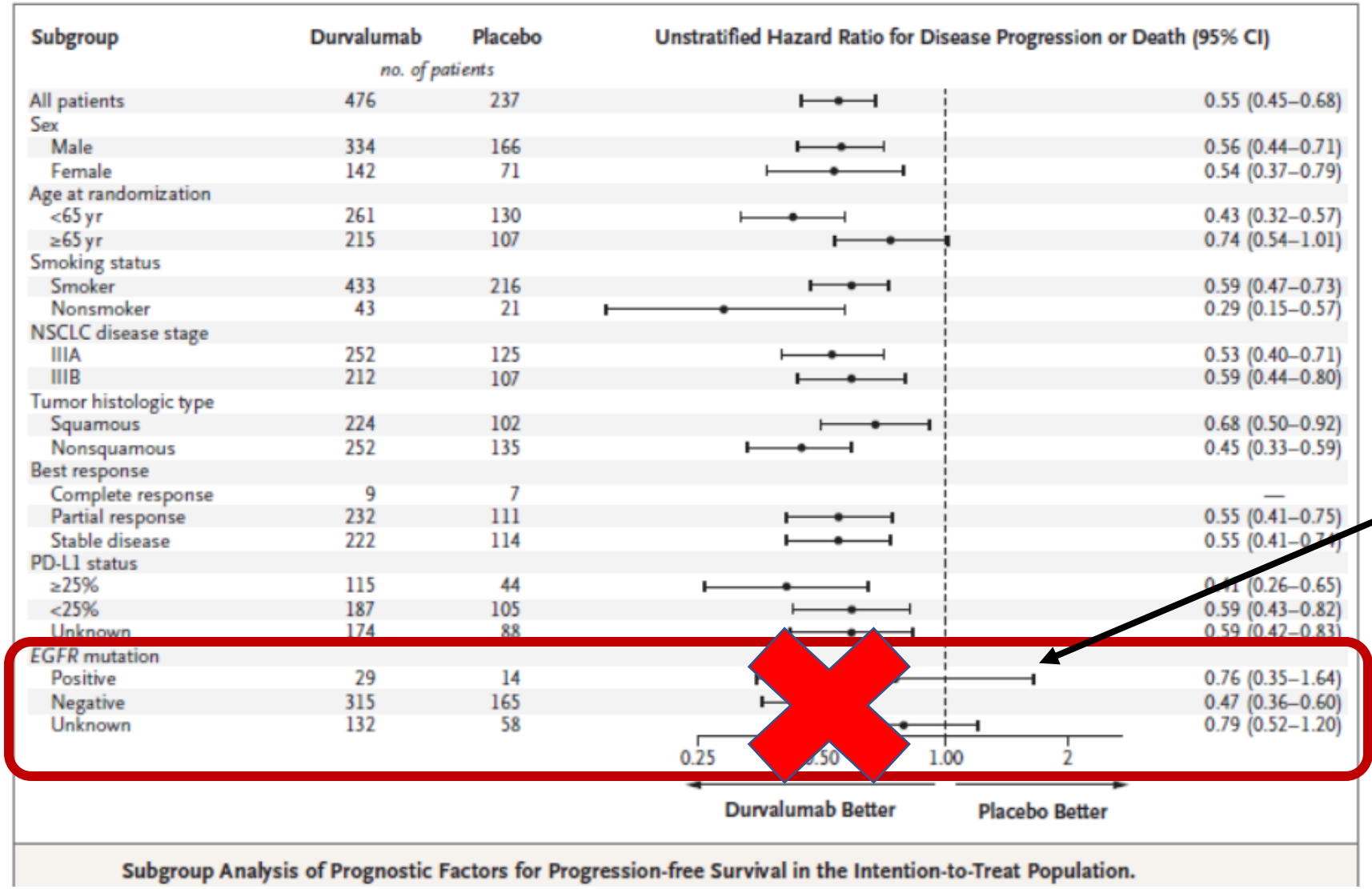
EGFR subgroup



Subgroup	Durvalumab	Placebo	Unstratified Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients		
All patients	476	237	0.55 (0.45–0.68)
Sex			
Male	334	166	0.56 (0.44–0.71)
Female	142	71	0.54 (0.37–0.79)
Age at randomization			
<65 yr	261	130	0.43 (0.32–0.57)
≥65 yr	215	107	0.74 (0.54–1.01)
Smoking status			
Smoker	433	216	0.59 (0.47–0.73)
Nonsmoker	43	21	0.29 (0.15–0.57)
NSCLC disease stage			
IIIA	252	125	0.53 (0.40–0.71)
IIIB	212	107	0.59 (0.44–0.80)
Tumor histologic type			
Squamous	224	102	0.68 (0.50–0.92)
Nonsquamous	252	135	0.45 (0.33–0.59)
Best response			
Complete response	9	7	—
Partial response	232	111	0.55 (0.41–0.75)
Stable disease	222	114	0.55 (0.41–0.74)
PD-L1 status			
≥25%	115	44	0.41 (0.26–0.65)
<25%	187	105	0.59 (0.43–0.82)
Unknown	174	88	0.59 (0.42–0.83)
EGFR mutation			
Positive	29	14	0.76 (0.35–1.64)
Negative	315	165	0.47 (0.36–0.60)
Unknown	132	58	0.79 (0.52–1.20)

Subgroup Analysis of Prognostic Factors for Progression-free Survival in the Intention-to-Treat Population.

*Small size also less in EGFR+ gp

Antonio SJ et al. NEJM 2017; 377(20): 1919-29

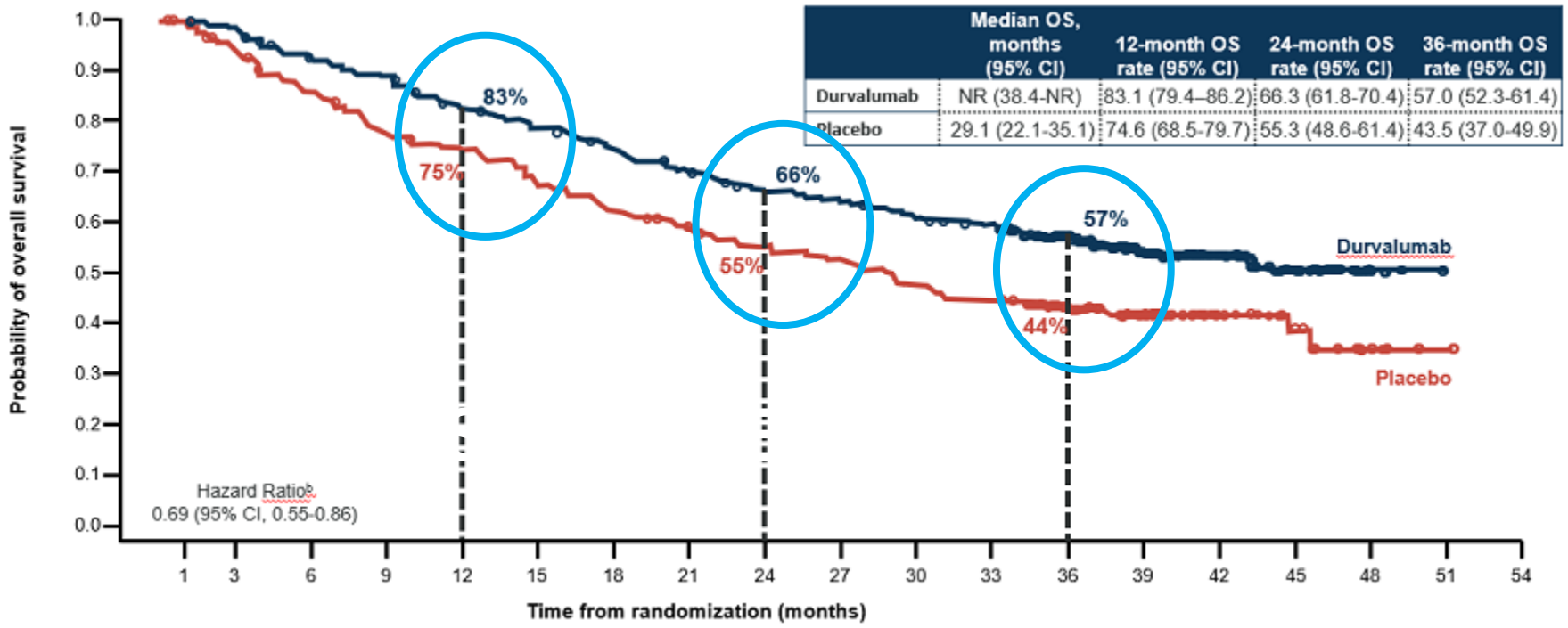
Administration on IO post CTRT ???

- IO had to be administered within 42 days post last dose of radiotherapy in a non-progressed patients with either CR/PR/SD
- Also, faster the administration, better be the responses & benefit due to the immunostimulatory effect of RT/CTRT for increased PD-1/PD-L1 expression !!!

- **How practical is it to assess response within 28-42 days of a therapy i.e CTRT ???**

Continuous administration of an IO agent !!!

- **Concerns of immune-mediated toxicities**
- **OVERALL Survival ???**



Gray et al. PACIFIC 3-year OS update *J Clin Oncol* 2019

There is NO ROLE of IO in all subsets of Stage III NSCLC

- PD-L1 negative subgroup – UNCERTAIN !!!

- EGFRm positive subgroup – role IO agents ???
- ALK/ROS1 not analysed
- How many of our patients are ECOG PS 0-1 ?
- **348/476 - DID NOT BENEFIT (73 %) (PD L1 <1 % + EGFRm or unknown)**
- Administration of IO agent within 42 days post CRTR is a practical problem

- 5 year Survival – Benefit vs Risk assessment DO NOT favor an IO considering the life threatening immune-mediated adverse events (imAEs)

Durvalumab Consolidation Therapy: Open Questions

- Would you consider durvalumab therapy for a patient with stage III NSCLC:
  - Following CRT and surgery?
  - Following sequential CT and RT due to frailty?
  - Who has evidence of asymptomatic pulmonary infiltrates following concurrent CRT?
  - Who is PD-L1 negative?
  - Who is *EGFR* mutation positive?
- Should we start biomarker and PD-L1 testing prior to initiation of immune checkpoint inhibitors in stage III disease?
- How would you treat a patient with stage III NSCLC who progresses to metastatic disease on or after durvalumab?

THANK YOU...!!!