In Favour of

Immunotherapy in maintenance treatment of all unresectable Stage 3 NSCLC

NSCLC: Non Small Cell Lung Cancer

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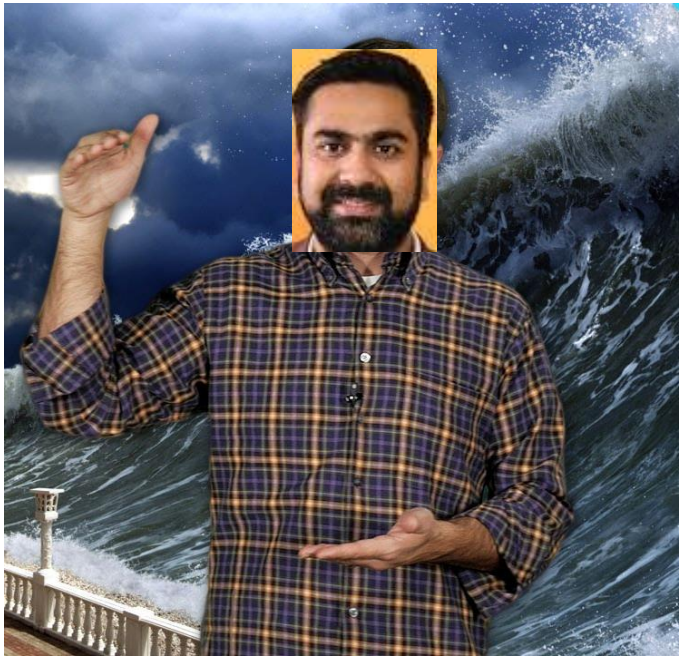
Apollo Delhi

Date	10 October 2016
Event	ESMO 2016 Congress
Session	The earthquake of immunotherapy in lung cancer
Topics	**Non-Small-Cell Lung Cancer, Metastatic Cancer Immunology and Immunotherapy**

PACIFIC A DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE III STUDY OF DURVALUMAB AFTER CHEMORADIATION THERAPY IN PATIENTS WITH STAGE III, LOCALLY ADVANCED, UNRESECTABLE NSCLC

A tsunami …

Since It's a Debate



- Setting: unresectable stage III NSCLC
- PACIFIC: was overall design appropriate ?
- PACIFIC: what risk/benefit ratio did we see ?
- PACIFIC: open questions
- Conclusion: what kind of a tsunami is this ?

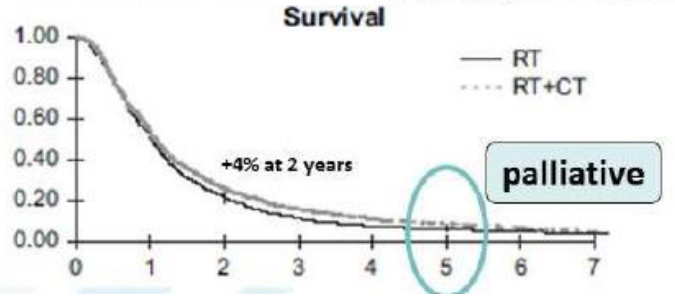
unresectable stage III NSCLC

- **1980: radiotherapy alone: median OS 10 m**
- **1990: chemotherapy added: median OS 14 m**

Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): A meta-analysis of individual data from 1764 patients

A. Aupérin[1]*, C. Le Péchoux[2], J. P. Pignon[1], C. Koning[4], B. Jeremic[5], G. Clamon[6], L. Einhorn[7], D. Ball[8], M. G. Trovo[9], H. J. M. Groen[10], J. A. Bonner[11], T. Le Chevalier[3] & R. Arriagada[2,12]
On behalf of the Meta-Analysis of Cisplatin/carboplatin based Concomitant Chemotherapy in non-small cell Lung Cancer (MACS-LC) Group

Annals of Oncology 17: 473–483, 2006



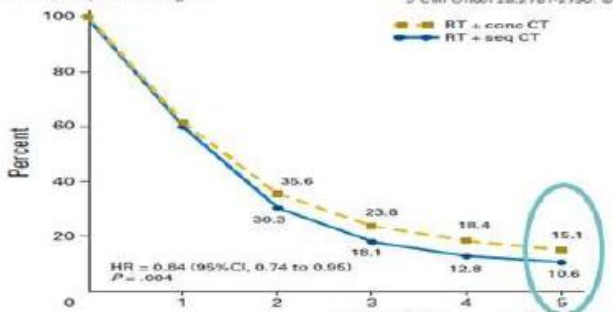
palliative

- **2000: concurrent chemoradiotherapy: median OS 18 m**

Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non–Small-Cell Lung Cancer

Anne Aupérin, Cecile Le Péchoux, Estelle Rolland, Walter J. Curran, Kiyoyuki Furuse, Pierre Fournel, Jose Belderbos, Gerald Clamon, Hakki Cuneyt Ulutin, Rebecca Paulus, Takeharu Yamanaka, Marie-Cecile Bozonnat, Apollonia Uitterhoeve, Xiaofei Wang, Lesley Stewart, Rodrigo Arriagada, Sarah Burdett, and Jean-Pierre Pignon

J Clin Oncol 28:2181-2190. © 2010



cure

unresectable stage III NSCLC

2 cycles of cis-etoposide

Radiotherapy 60 / 2 Gy

1/ Improve local therapy ?

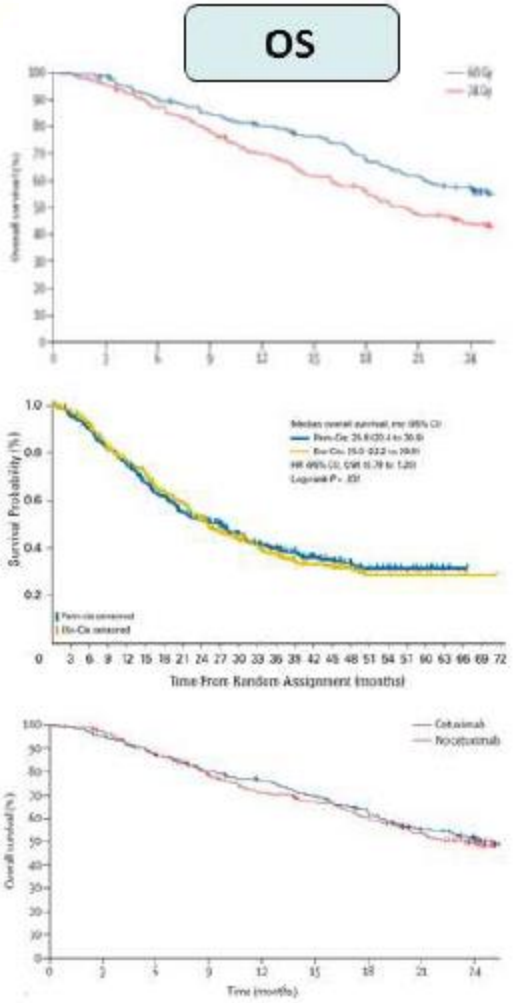
- Failure of RTOG 0617 (ASCO 2013) [1]
  - 74 Gy not better than 60 Gy

2/ Improve chemotherapy ?

- Failure of PROCLAIM (ASCO 2015) [2]
  - Cis-pemetrexed no better OS

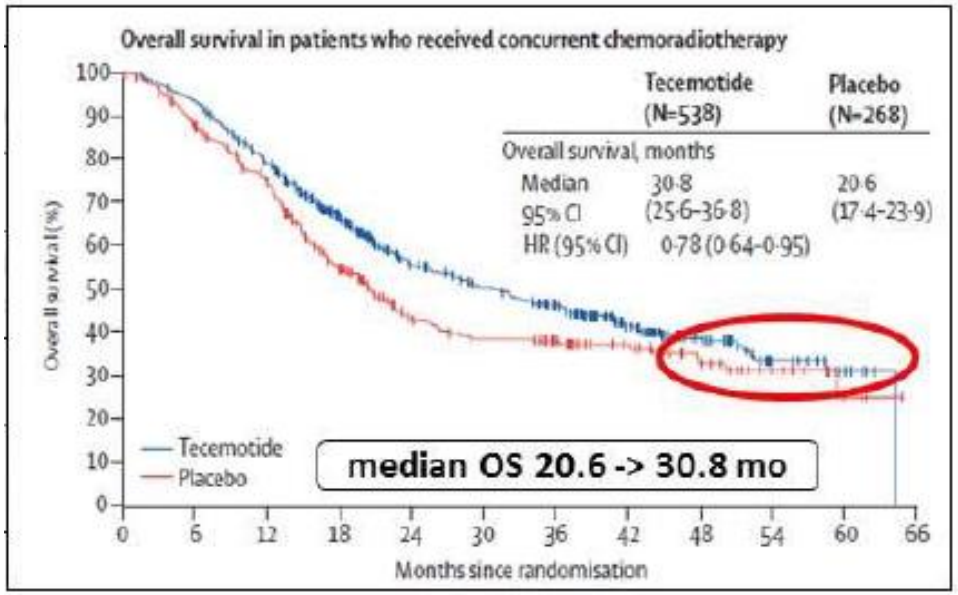
3/ Targeted therapy ?

- Failure of RTOG 0617 (WCLC 2013) [3]
  - Cetuximab not better than placebo



1 Bradley et al, ASCO 2013 *and* Lancet Oncol 16:187-199, 2015
2 Senan et al, ASCO 2015 and J Clin Oncol
3 Bradley et al, WCLC 2013 *and* Lancet Oncol 16:187-199, 2015

unresectable stage III NSCLC



4/ Immuno-therapy ?

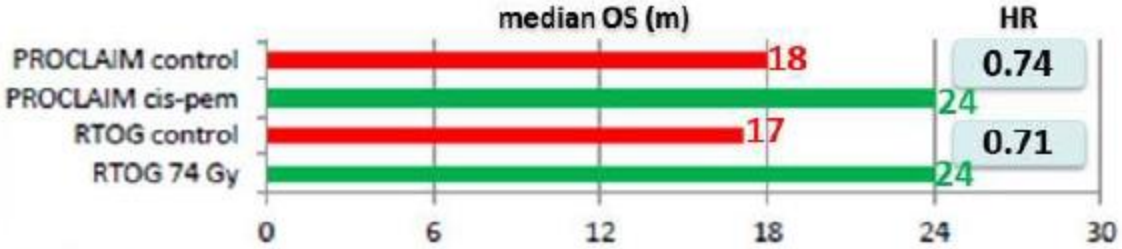
- **START: MUC1 immunotherapy** [4]

➢ **Development stopped**

4 Butts et al, ASCO 2013 *and* Lancet Oncol 15:59-68, 2014

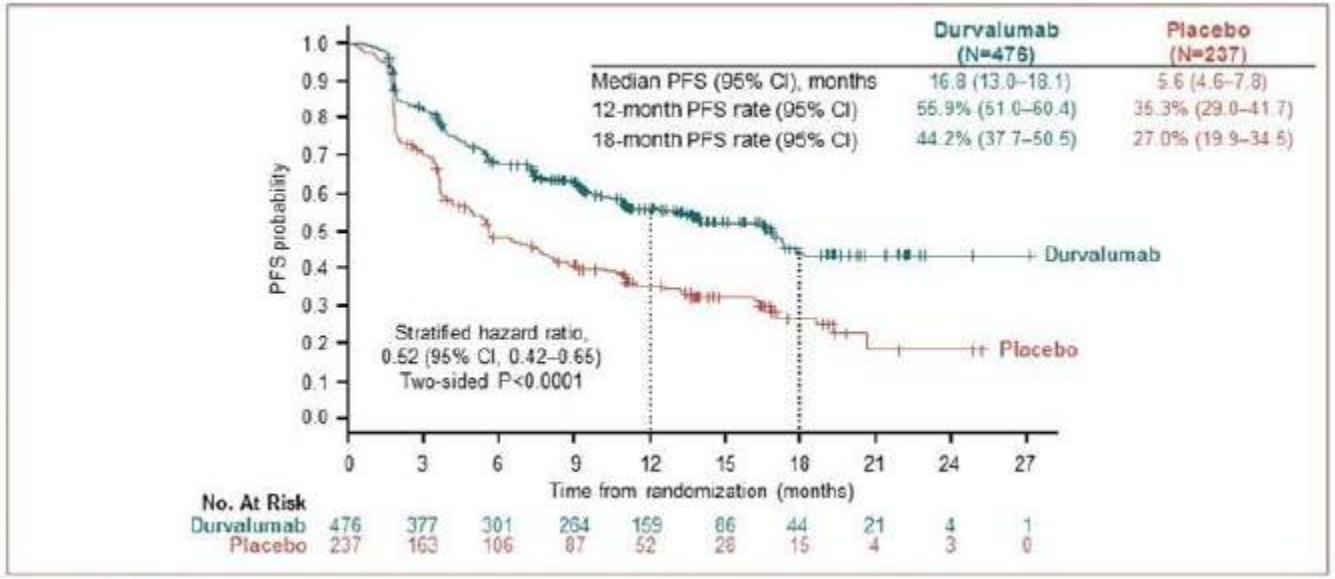
PACIFIC – overall design appropriate ?

- **Unmet medical need** √
- **PACIFIC OS hypothesis in line with disease setting**
  - **≥85% power to detect an OS HR of 0.73** (median from 22 to 30 m) √



- **Appropriate endpoints**
  - **PFS, in co-primary with OS** √
- **Study flow**
  - **2:1 randomization**
  - **Very well balanced patient groups** √

PACIFIC –
> benefit

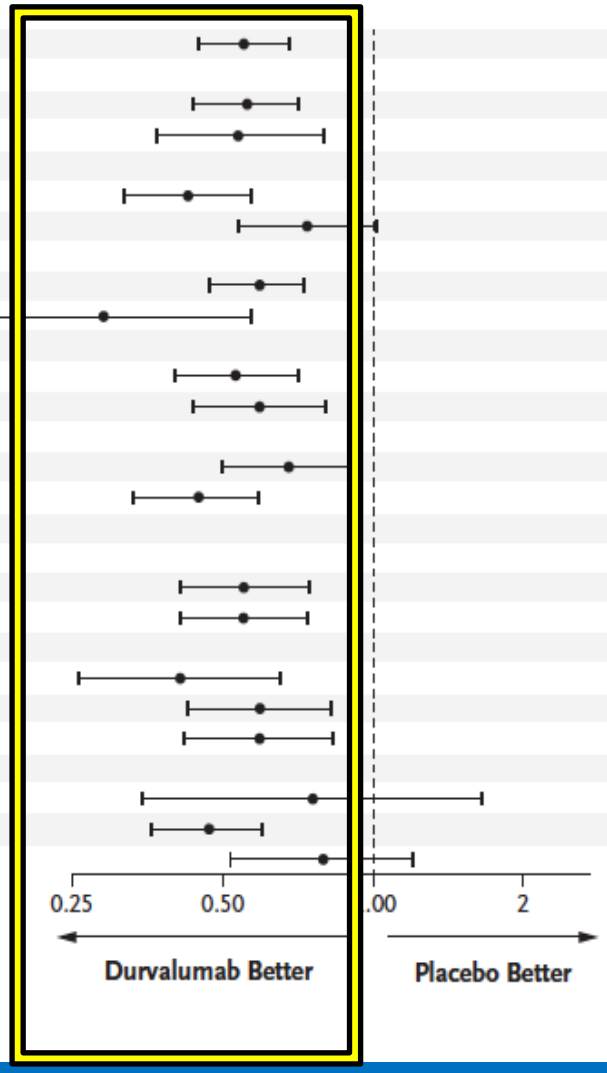


PFS by BICR (Primary Endpoint; ITT)

Interim report at 371 PFS events – median FU 14.5 m

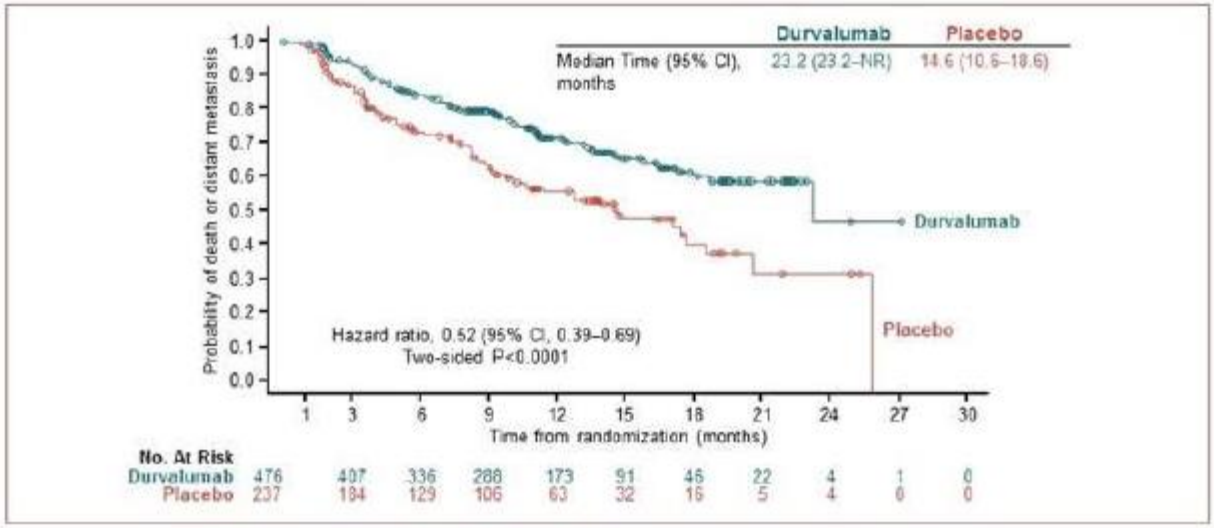
PFS benefit was seen across all subgroups with Durvalumab

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)

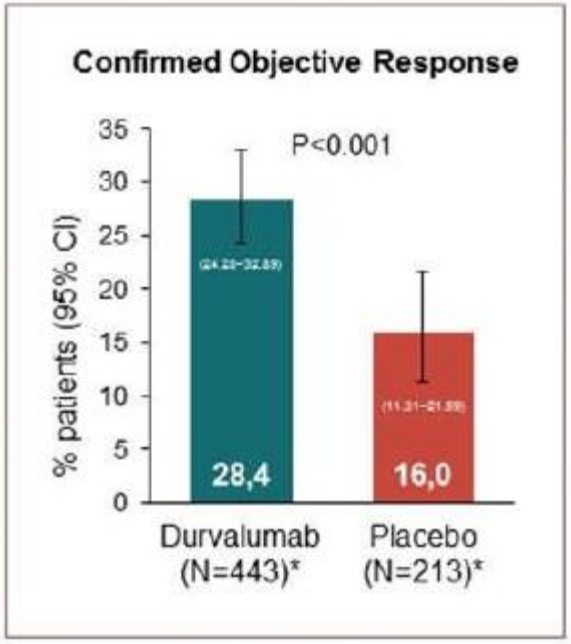


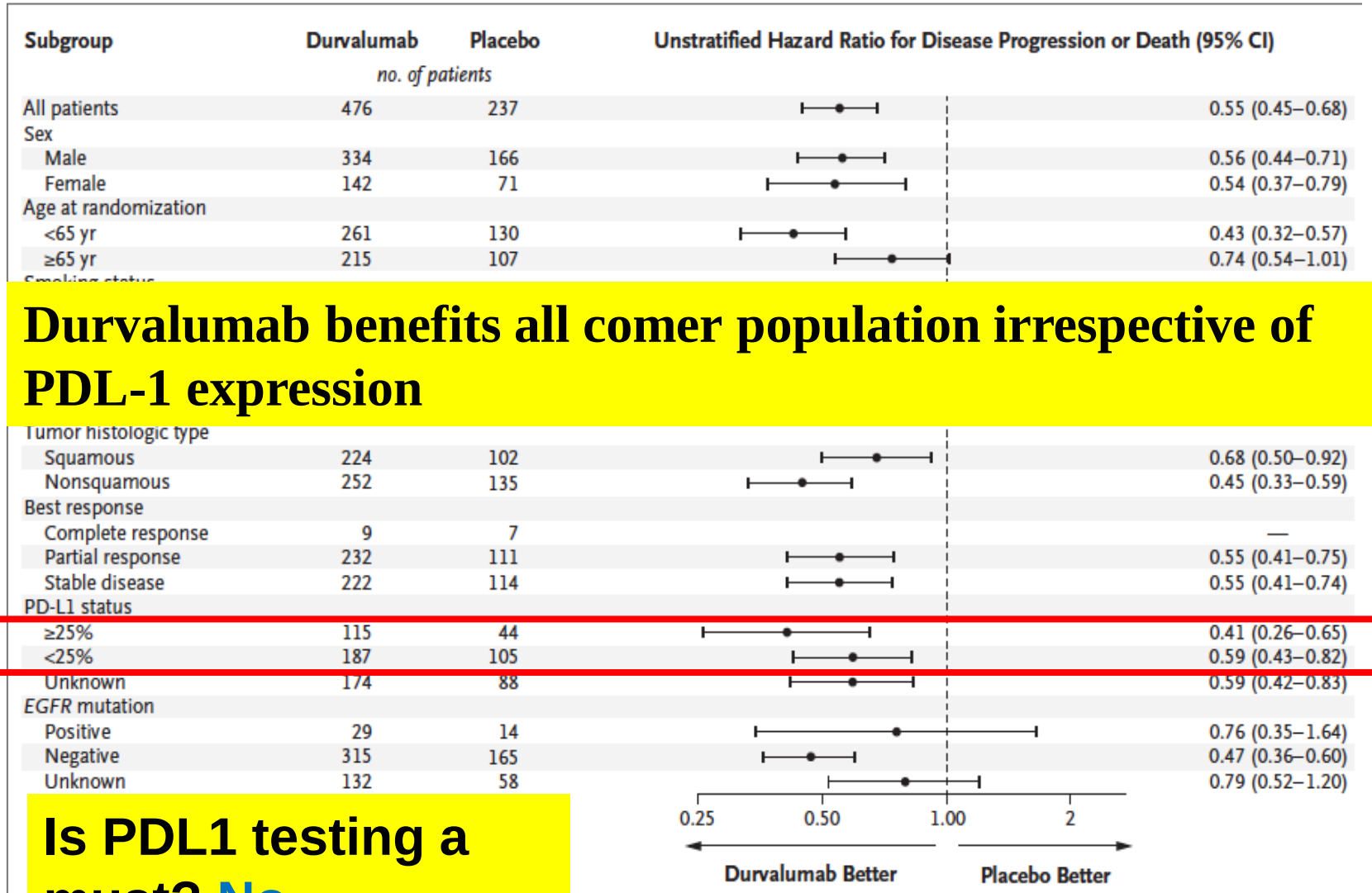
1. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer. New England Journal of Medicine [Internet]. 2017 Nov 16 [cited 2018 Mar 30];377(20):1919–29. Available from: https://doi.org/10.1056/NEJMoa1709937

PACIFIC – > benefit



Time to Death or Distant Metastasis by BICR (ITT)





Durvalumab benefits all comer population irrespective of PDL-1 expression

Is PDL1 testing a must? No

1. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer. New England Journal of Medicine [Internet]. 2017 Nov 16 [cited 2018 Mar 30];377(20):1919–29. Available from: https://doi.org/10.1056/NEJMoa1709937

PACIFIC – risk/benefit ratio

> risk

	Durvalumab (N=475)	Placebo (N=234)
Any-grade all-causality AEs, n (%)	460 (96.8)	222 (94.9)
Grade 3/4	142 (29.9)	61 (26.1)
Grade 5	21 (4.4)	13 (5.6)
Leading to discontinuation	73 (15.4)	23 (9.8)
Any-grade treatment-related AEs, n (%)	322 (67.8)	125 (53.4)
Any-grade all-causality AESIs, n (%)	311 (65.5)	114 (48.7)
Grade 3/4	39 (8.2)	9 (3.8)
Grade 5	4 (0.8)	4 (1.7)
Requiring concomitant treatment	200 (42.1)	40 (17.1)
Any-grade immune-mediated AEs, n (%)	115 (24.2)	19 (8.1)
Grade 3/4	16 (3.4)	6 (2.6)
Grade 5	4 (0.8)	3 (1.3)

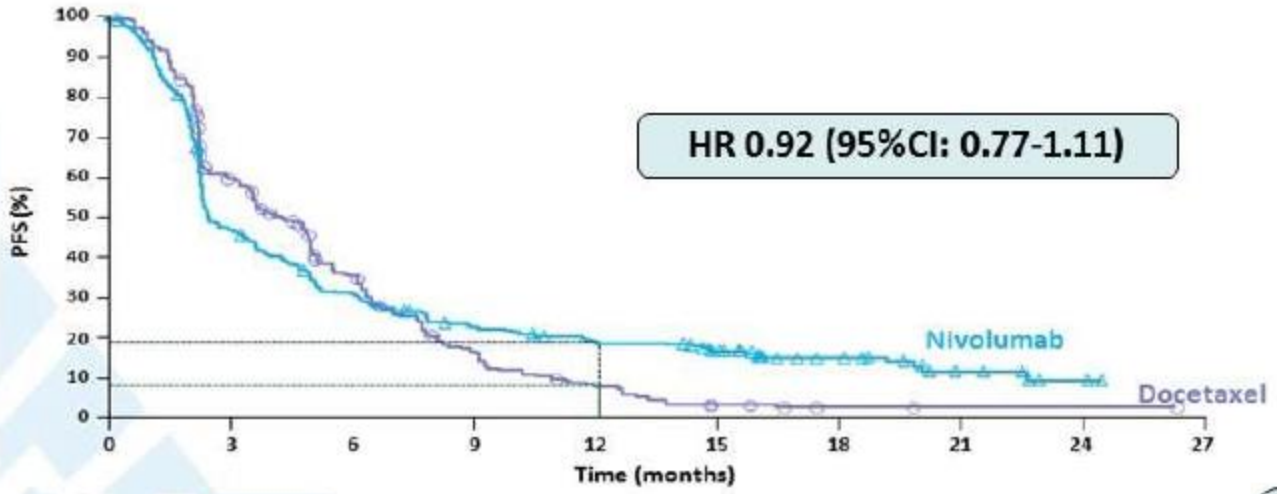
PACIFIC – risk/benefit ratio

> risk

Event	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any event, n (%)	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/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
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)

PACIFIC – open questions
(1) PFS *vs.* OS

- **PFS often has been a poor read-out for CPI immunotherapy**

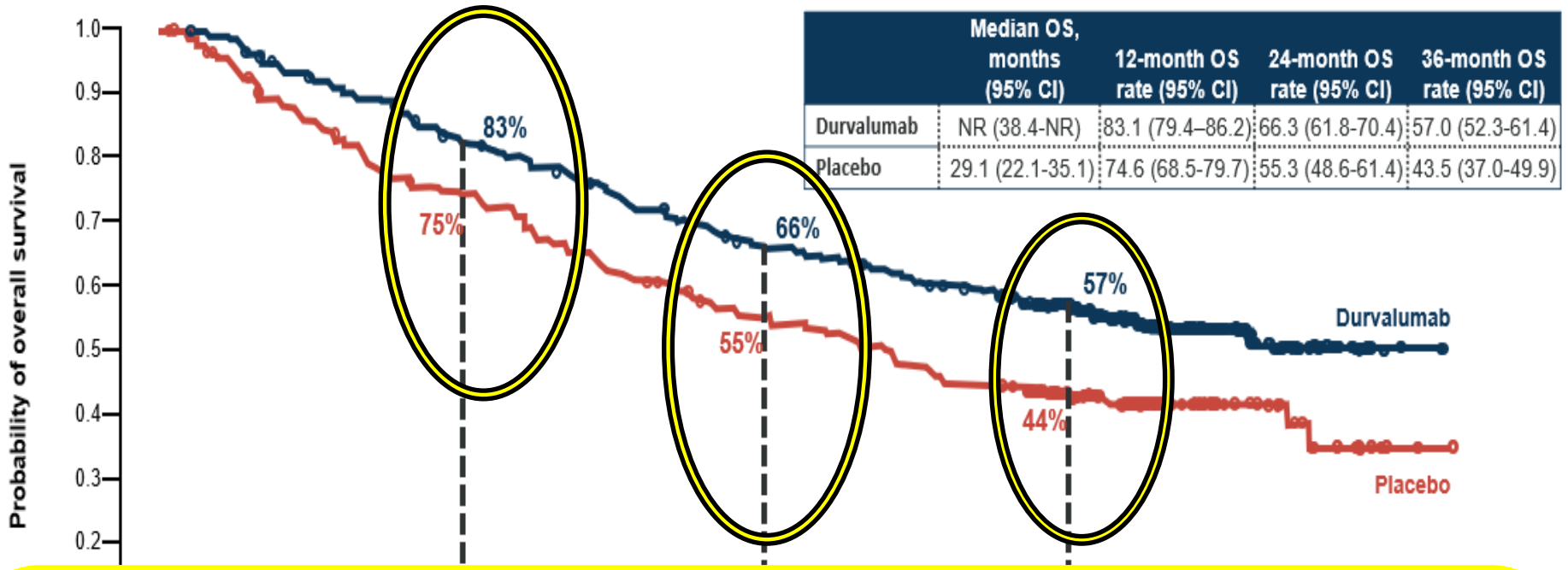


HR 0.92 (95%CI: 0.77-1.11)

Checkmate 057
PFS

N Engl J Med 373:1627-1639, 2015

Finally, Success In Locally Advanced Disease in Consolidation setting!



	Median OS, months (95% CI)	12-month OS rate (95% CI)	24-month OS rate (95% CI)	36-month OS rate (95% CI)
Durvalumab	NR (38.4-NR)	83.1 (79.4–86.2)	66.3 (61.8-70.4)	57.0 (52.3-61.4)
Placebo	29.1 (22.1-35.1)	74.6 (68.5-79.7)	55.3 (48.6-61.4)	43.5 (37.0-49.9)

mOS with Durvalumab =NR mOS with cCRT alone= 29.1 months

HR: 0.69 (95% Cl, 0.55-0.86)
31% reduction in the risk of death in Durvalumab arm compared to cCRT alone arm

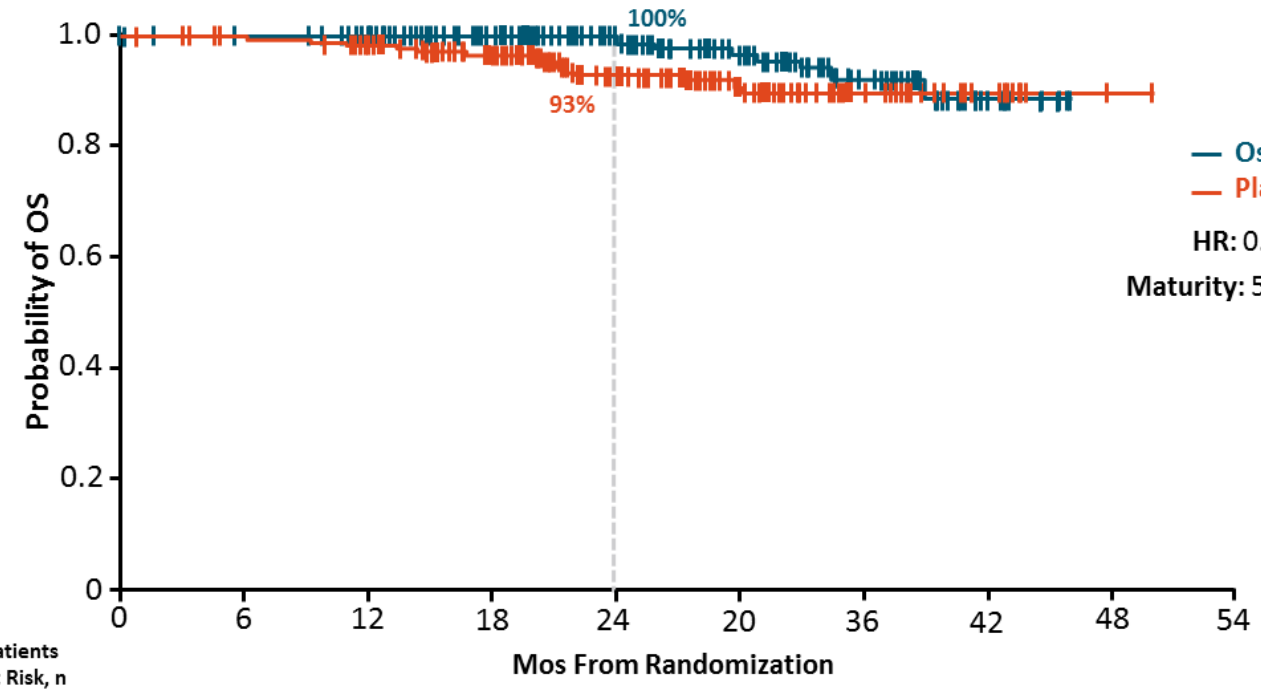
Table 1. Updated Incidence of New Lesions, as Assessed by Blinded Independent Central Review, in the Intention-to-treat Population.*

New Lesion Site	Durvalumab Group (N=476)	Placebo Group (N=237)
	no. of patients (%)	
Any site	107 (22.5)	80 (33.8)
Lung	60 (12.6)	44 (18.6)
Lymph nodes	31 (6.5)	27 (11.4)
Brain	30 (6.3)	28 (11.8)
Liver	9 (1.9)	8 (3.4)
Bone	8 (1.7)	7 (3.0)
Adrenal gland	3 (0.6)	5 (2.1)

In Pacific Study- Onset of new lesions reduced by ~50% in Durvalumab arm compared to control group

https://doi.org/10.1056/NEJMoa1709937

ADAURA: Early OS in Patients With Stage II/IIIA NSCLC



Median OS, Mos

Osimertinib	NR
Placebo	NR

HR: 0.40 (95% CI: 0.18-0.90)

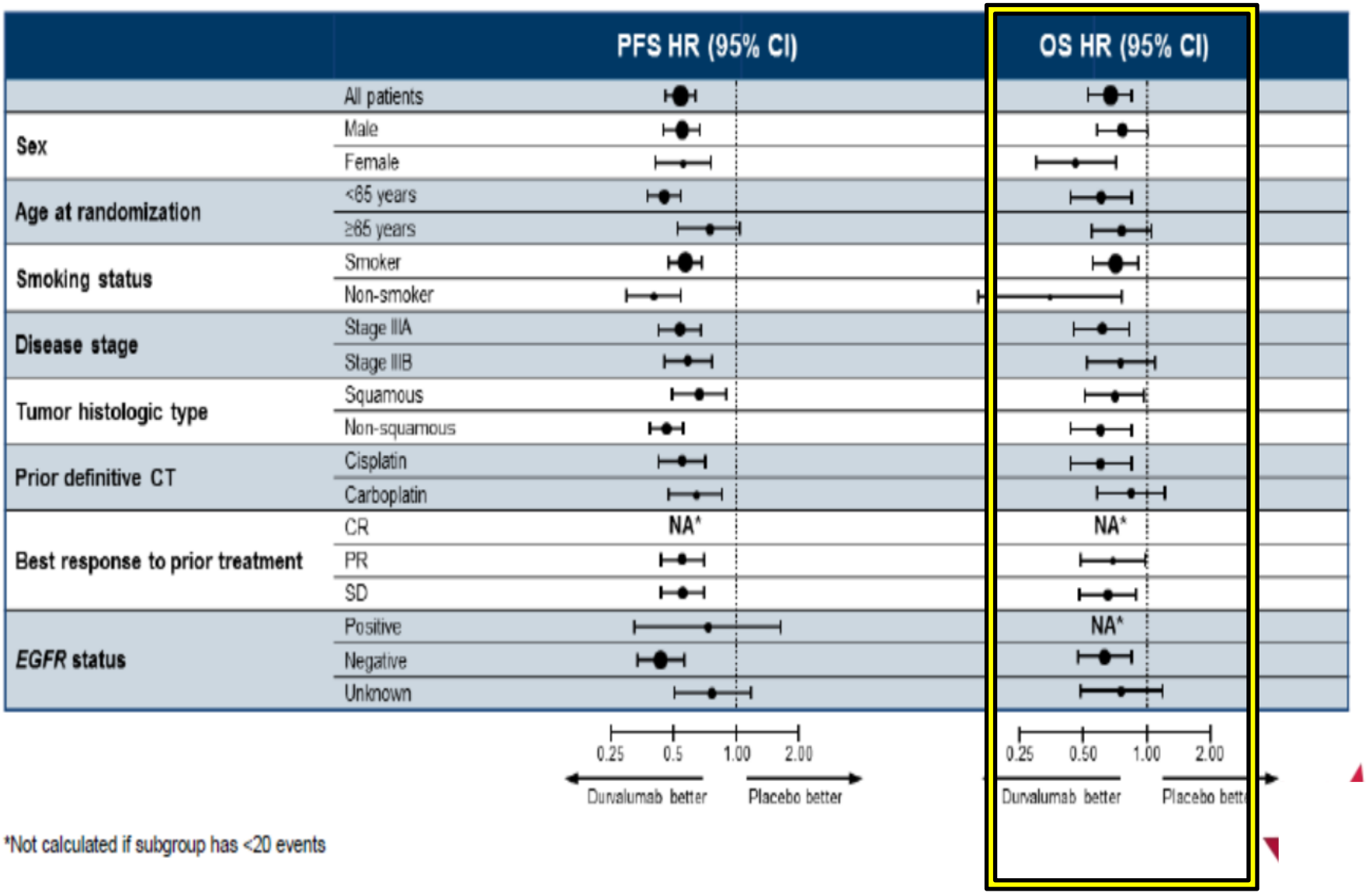
Maturity: 5% (osimertinib: 3%; placebo: 7%)

Herbst. ASCO 2020. Abstr LBA5. Reproduced with permission.

Slide credit: clinicaloptions.com

➢ **Benefits in stage IV are NOT translated in stage III**

Survival benefit was seen across all subgroups With Durvalumab



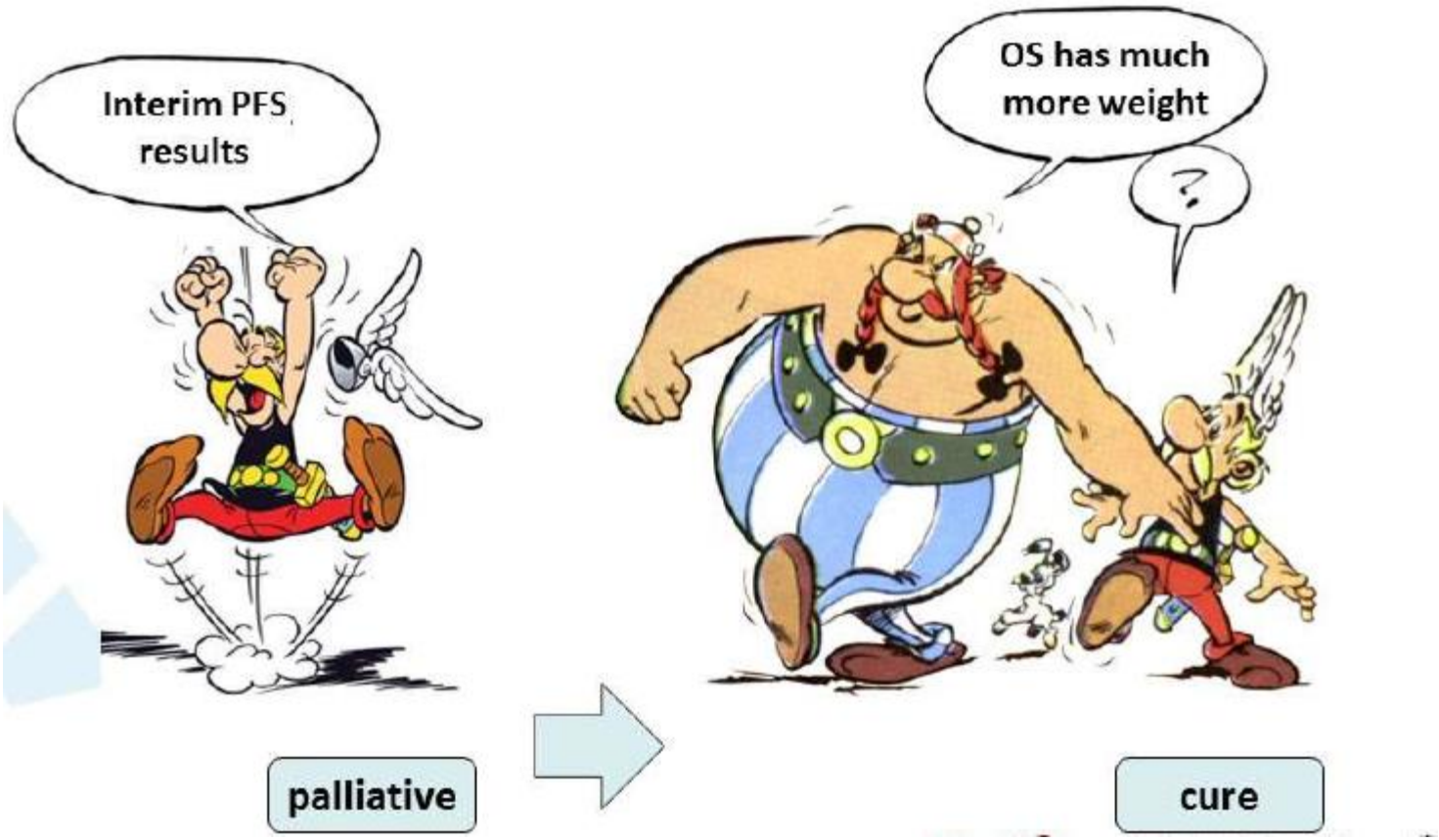
Note: PFS data based on data cutoff of Feb 13, 2017, and OS data based on data cutoff of March 22, 2018, NA, not available

SJ Antonia et al. N Engl J Med 2018. DOI: 10.1056/NEJMoa1809697

PACIFIC – open questions

- **Part of the overall earthquake "CPI immunotherapy in NSCLC": stage IV benefits now translated in stage III**
- **Radiotherapy and CPI immunotherapy can be excellent partners**
  - **RT has a priming effect by immunogenic cell death**
  - **RT promotes release of danger signals/chemokines that inflame the tumor microenvironment**
  - **RT promotes release of neo-antigens** *(irradiated cancer as an in-situ vaccine)*
  - **RT upregulates PD-1 and PD-L1**
  - **RT has been shown to have abscopal effects (rare)**

PACIFIC – what kind of a tsunami is this ?



after the previous tsunami of negative results ?

It’s a clear Knock Out Tsunami!!

Rx