LUNG CANCER UPDATES

ESMO HIGHLIGHTS

19-23 DE OCTUBRE 2018, MUNICH

ESTADIOS TEMPRANOS Y LOCALMENTE AVANZADOS

Dra. Virginia Calvo

Iniciativa científica de:

GECP

Grupo Español de Cáncer de Pulmón

Spanish Lung Cancer Group

NEO-ADJUVANT THERAPY IN NSCLC

- **Is EGFR TKI effective as pre-operative therapy for IIIA (N2) NSCLC?**
  - CTONG 1103: Erlotinib versus Gemcitabine plus Cisplatin as Neo-adjuvant Treatment for stage IIIA-N2 EGFR mutation non-small-cell lung cancer (EMERGING): a randomised study (Zhong et al, LBA48)

- **What is the biological role of immune checkpoint inhibition in early stage NSCLC?**
  - Neoadjuvant Nivolumab or Nivolumab plus Ipilimumab for resectable non-small cell lung cancer (Cascone et al, LBA49)

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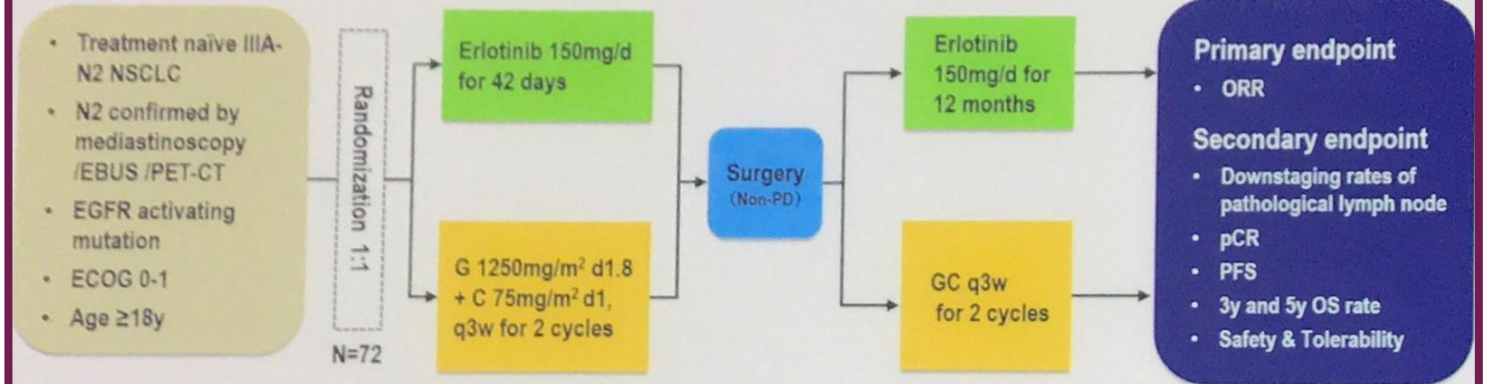
Erlotinib versus Gemcitabine plus Cisplatin as Neoadjuvant Treatment for Stage IIIA-N2 EGFR-mutation Positive Non-small-cell Lung Cancer (EMERGING-CTONG 1103): multicentre phase 2 randomized study

Wen-zhao Zhong,[1] Yi-long Wu,[1] Ke-neng Chen,[2] Chun Chen,[3] Chun-dong Gu,[4] Jun Wang,[5] Xue-ning Yang,[1] Wei-min Mao,[6] Qun Wang,[7] Gui-bin

EMERGING-CTONG 1103 Study Design



- Stratification by lymph node status, histology, smoking status and sex.

ECOG PS, Eastern Cooperative Oncology Group Performance Status; G, gemcitabine ; C, cisplatin;
ORR, objective response rate; pCR, pathological complete response; PFS, progression free survival; OS, overall survival.

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Data cut-off: April 2018 ; NCT01407822; PI:Yi-long Wu

LBA48. EMERGING-CTONG 1103: Erlotinib versus Gemcitabine plus Cisplatin as Neoadjuvant Treatment for Stage IIIA-N2 EGFR-mutation Positive Non-small-cell Lung Cancer: multicentre phase 2 randomized study

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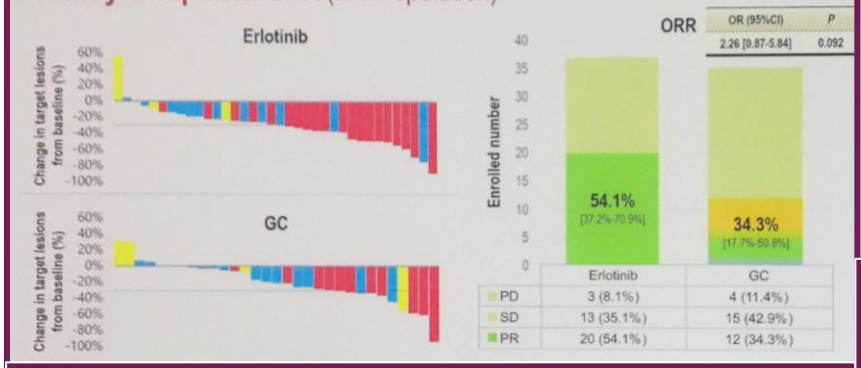
Primary Endpoint: ORR (ITT Population)



ORR 54% vs 34%, p=0.092

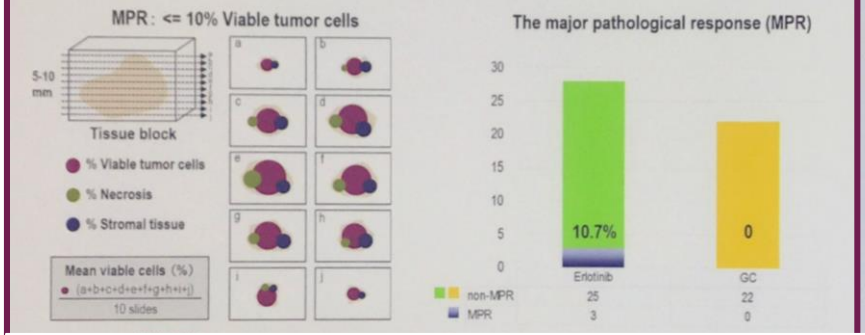
Secondary Endpoint: Complete Resection and Lymph Node Downstage

	Erlotinib group (n=37)	GC group (n=35)	P value
Surgery, n (%)	31 (83.8)	24 (68.6)	0.129
Complete resection, n (%)	27 (73.0)	22 (62.9)	
R0	27 (73.0)	22 (62.9)	0.358
R1	1 (2.7)	1 (2.9)	
R2	3 (8.1)	1 (2.9)	
Lymph node downstage,n (%)	4 (10.8)	1 (2.9)	

Operation rate 83.8% vs 68.6%
R0 resection 73.0 vs 62.9%
LN Down staging: 10.8 vs 2.9%

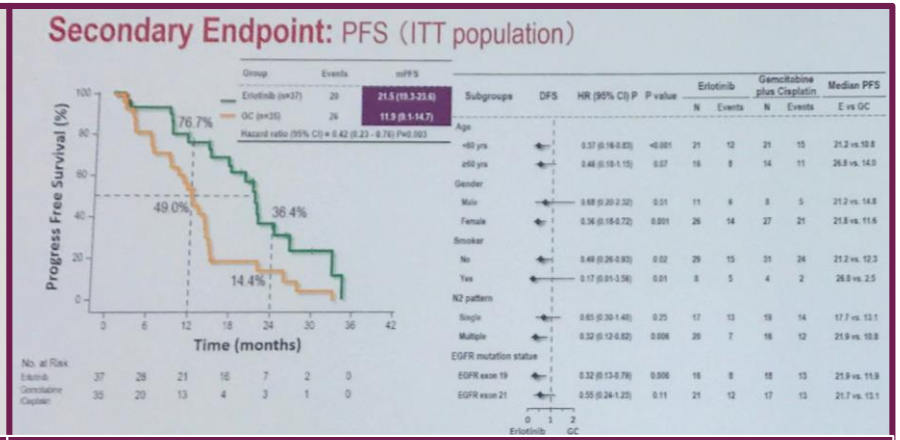
Secondary Endpoint: Pathological Complete Response (pCR) Rate

50 surgical resected specimens were available, No pCR cases in both groups.



No pathological CR was observed
MPR: 10.7% vs 0%

Secondary Endpoint: PFS (ITT population)



mPFS: 21.5 VS 11.9 MONTHS (HR 0.42, p=0.003)

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LBA48. EMERGING-CTONG 1103: Erlotinib versus Gemcitabine plus Cisplatin as Neoadjuvant Treatment for Stage IIIA-N2 EGFR-mutation Positive Non-small-cell Lung Cancer: multicentre phase 2 randomized study

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AEs Associated with Neoadjuvant therapy (≥10%, Safety Population)

AEs, n (%)	Erlotinib group (n=37)		GC chemotherapy group (n=34)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any event, n (%)	28 (75·7)	0 (0·0)	30 (88·2)	10 (29.4)
Rash	25 (67·6)	0	10 (29·4)	0
Diarrhoea	9 (24·3)	0	0	0
Cough	6 (16·2)	0	2 (5·9)	0
Oral ulcers	4 (10·8)	0	2 (5·9)	0
Vomiting	0	0	15 (44·1)	1 (2·9)
Anorexia	0	0	14 (41·2)	0
Neutropenia	0	0	13 (38·2)	6 (17·6)
Decreased white blood cell	0	0	13 (38·2)	0
Nausea	0	0	11 (32·4)	0
Fatigue	0	0	9 (26·5)	0
Anaemia	0	0	7 (20·6)	0
Hoarseness	0	0	6 (17·6)	0
Hair loss	0	0	6 (17·6)	0
Thrombocytopenia	0	0	5 (14·7)	0

AEs Associated with Postoperative Adjuvant Therapy (≥10%, Safety Population)

AEs, n (%)	Erlotinib group (n=37)		GC chemotherapy group (n=34)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any event, n (%)	26 (70·3)	5 (13·5)	20 (58·8)	10 (29.4)
Rash	16 (43·2)	2 (5·4)	3 (8·8)	0
Diarrhoea	9 (24·3)	1 (2·7)	2 (5·9)	0
Cough	9 (24·3)	0	6 (17·6)	0
Shortness of breath	5 (13·5)	1 (2·7)	3 (8·8)	0
Expectoration	5 (13·5)	0	2 (5·9)	0
Elevated total bilirubin	4 (10·8)	1 (2·7)	0	0
Elevated aminotransferases	4 (10·8)	1 (2·7)	0	0
Chest pain	4 (10·8)	0	2 (5·9)	0
Anorexia	4 (10·8)	0	9 (26·5)	0
Decreased white blood cell	2 (5·4)	1 (2·7)	11 (32·4)	4 (11·8)
Neutropenia	0	0	13 (38·2)	10 (29·4)
Vomiting	0	0	9 (26·5)	1 (2·9)
Nausea	0	0	8 (23·5)	1 (2·9)
Anaemia	0	0	4 (11·8)	1 (2·9)
Fatigue	0	0	4 (11·8)	0
Thrombocytopenia	0	0	4 (11·8)	0
Dizziness	0	0	4 (11·8)	0

Postoperative Complications

Postoperative complications, n (%)	Erlotinib group (n=31)	GC chemotherapy group (n=24)
Sinus tachycardia/Arrhythmia	2 (6·5)	0 (0)
Lung infection	2 (6.5)	0 (0)
Mechanical ventilation	0 (0)	1(4·2)
Poor incision healing	2 (6·5)	0 (0)
Injury to the recurrent laryngeal nerves	0 (0)	1(4·2)
Lung infection/Left-sided pneumothorax	1 (3·2)	0 (0)
Lung infection / Chest tube drainage for more than 7 days / Leakage of water-sealed drainage bottle for more than 7 days / Surgical stress response	1 (3·2)	1(4·2)

No perioperative mortality in both group.

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Safety results consistent with prior studies

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Conclusions

- CTONG 1103 is the first phase II, randomized controlled trial comparing EGFR-TKI versus doublet chemo in neoadjuvant setting;
- Neoadjuvant Erlotinib improved ORR (although not significantly), MPR, operation rate, R0 resection and LN down staging in stage IIIA-N2 *EGFR*m;
  - *ORR: 54.1% vs 34.3%(P=0.092); Operation rate: 83.8% vs 68.6%; R0 resection: 73.0% vs 62.9%;*
  - *LN Down staging: 10.8% vs 2.9%; MPR: 10.7% vs 0% ;*
- Erlotinib has longer PFS compared with GC chemo in the neoadjuvant/adjuvant setting of stage IIIA-N2 EGFRm NSCLC. OS data is immature.
  - *mPFS: 21.5 vs 11.9 months (HR 0.42, P=0.003)* NSCLC
- The AEs profile were in line with that reported previously;
- The promising biomarker-guided treatment regimens for stage IIIA-N2 NSCLC warrants further exploration in neoadjuvant setting.

LBA49. NEOSTAR: Neoadjuvant Nivolumab (N) or Nivolumab plus Ipilimumab (NI) for resectable non-small cell lung cancer (NSCLC)

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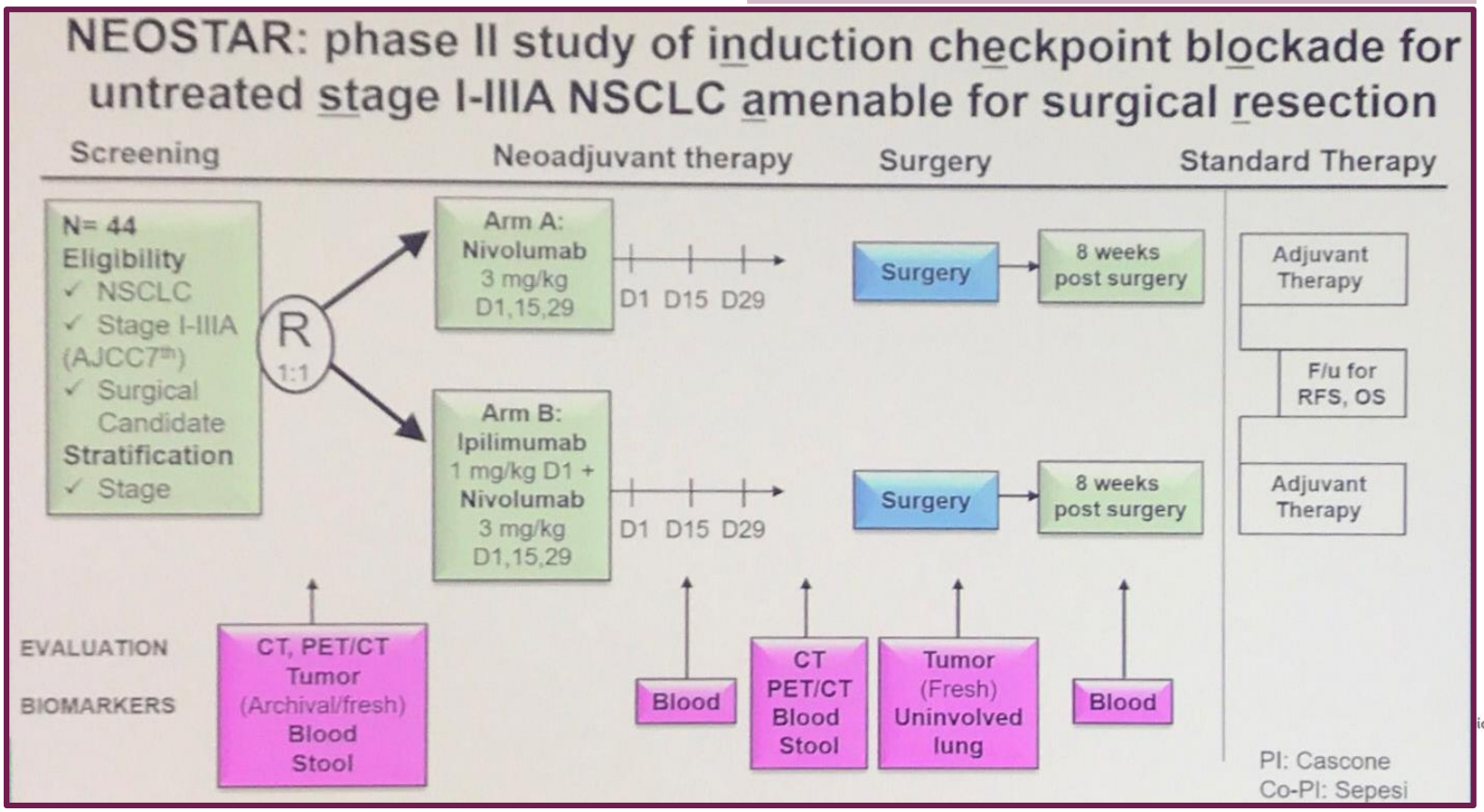
NEOSTAR: NEOADJUVANT NIVOLUMAB (N) OR NIVOLUMAB PLUS IPILIMUMAB (NI) FOR RESECTABLE NON-SMALL CELL LUNG CANCER (NSCLC)

T. Cascone[1], W.N. William Jr.[1], A. Weissferdt[2], C.H. Leung[3], L. Federico[4], C. Haymaker[4], C.

N=36 patients
26 evaluable for efficacy analysis
5 patients out of 31 could not have surgery (16%)



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Study design, hypothesis and endpoints

Design and Statistical plan:

- Single center, open label, phase 2, multi-arm, randomized study
- Primary hypothesis: Induction N and/or NI will produce a MPR rate of at least 40%, which is greater than the MPR rate to induction platinum-based chemotherapy (as compared to historical controls, 15%). The trial has 90% power when the MPR rate is 40%.

Primary endpoint

MPR rate in patients treated with induction N and NI

Secondary endpoints

- Toxicity, peri-operative morbidity and mortality
- ORR, RFS, OS
- To correlate MPR and RECIST responses with RFS and OS
- Complete resection rate; pathologic complete response (pCR)
- $CD8^+$ TILs in resected tumors; to correlate tissue, blood, and stool biomarkers with efficacy and toxicity

Exploratory endpoints

Blood, tissue and stool biomarkers and their modulation by treatment

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Major pathologic response (≤10% viable tumor cells)

Evaluable* (Resected)	n=26	N n=14	NI n=12
MPR + pCR	8 (31%)	4 (28%)	4 (33%)
0% viable tumor cells (pCR)	5 (19%)	2 (14%)	3 (25%)
1-10% viable tumor cells	3 (11%)	2 (14%)	1 (8%)

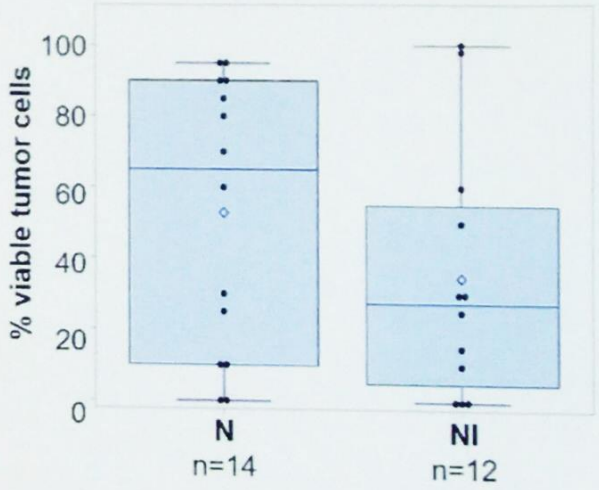
*5 no surgery (2 N, 3 NI)

Overall** Resected + unresectable	n=31	N n=16	NI n=15
MPR + pCR	8 (26%)	4 (25%)	4 (27%)
0% viable tumor cells (pCR)	5 (16%)	2 (13%)	3 (20%)
1-10% viable tumor cells	3 (10%)	2 (13%)	1 (7%)
Path response pending	5**	2	3

**5 pending (2 N, 3 NI)

Evaluable (resected)	N n=14*	NI n=12**	p-value
	Median (min, max)	Median (min, max)	
% viable tumor cells	65 (0, 95)	27.5 (0, 100)	0.364

* 2 no surgery; 1 awaiting surgery; 1 on therapy
** 3 no surgery; 1 awaiting surgery; 2 on therapy



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pCR is 16%
MPR is 10%

LBA49. NEOSTAR: Neoadjuvant Nivolumab (N) or Nivolumab plus Ipilimumab (NI) for resectable non-small cell lung cancer (NSCLC)

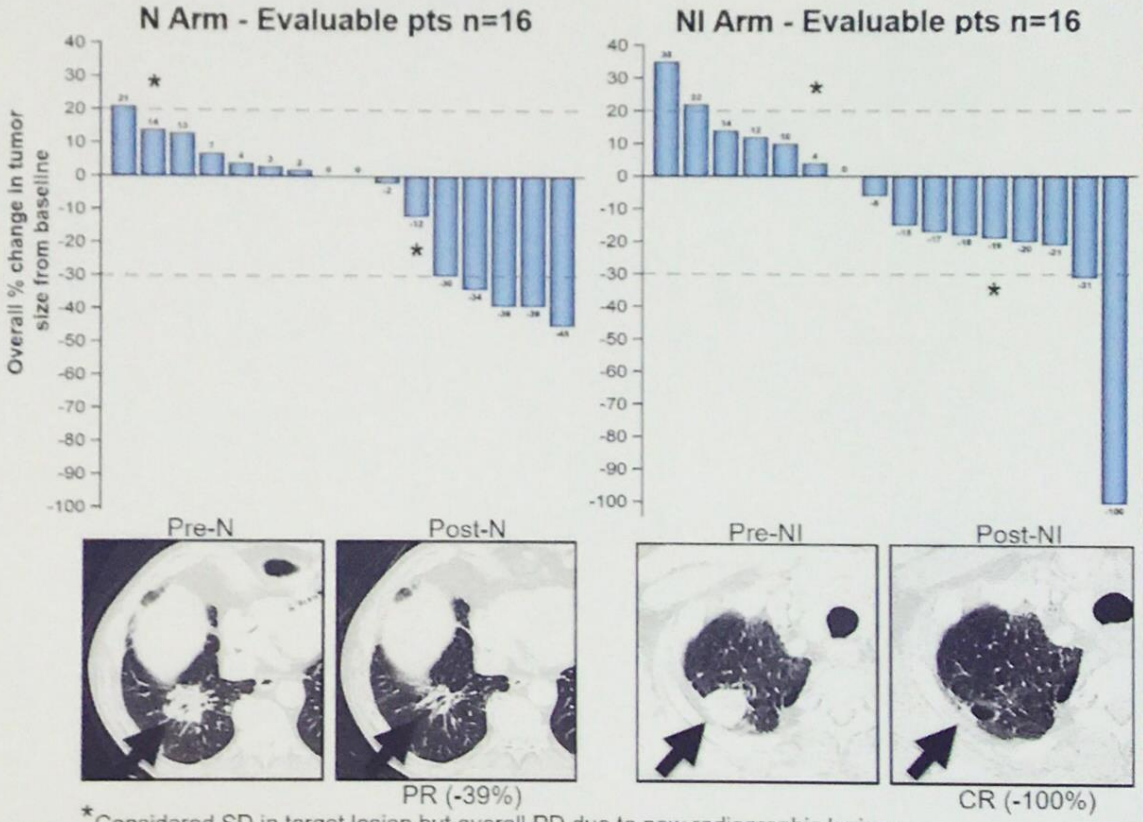
Radiographic responses

Evaluable*	n=32*	N n=16	NI n=16
Response (RECIST)	n (%)	n (%)	n (%)
CR	1 (3)	0 (0)	1 (6)
PR	6 (19)	5 (31)	1 (6)
SD	19 (59)	8 (50)	11 (69)
PD	6 (19)	3 (19)	3 (19)
Not yet evaluable	4	2*	2**

* 1 pending, 1 on therapy; ** 2 on therapy

ORR (CR+PR): 22%(7/32)

ORR by Arm:
N: 31% (5/16)
NI: 12% (2/16)



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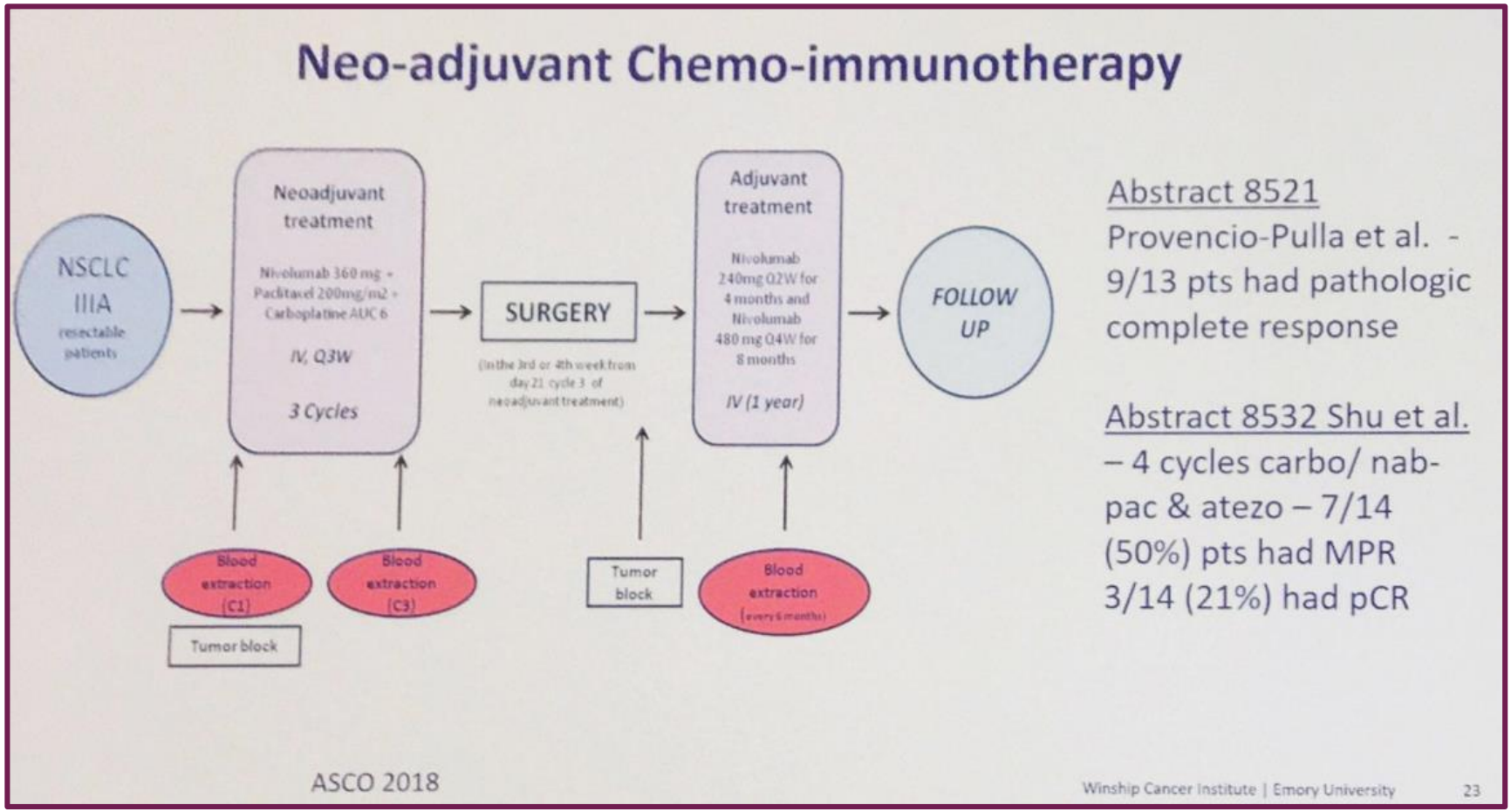
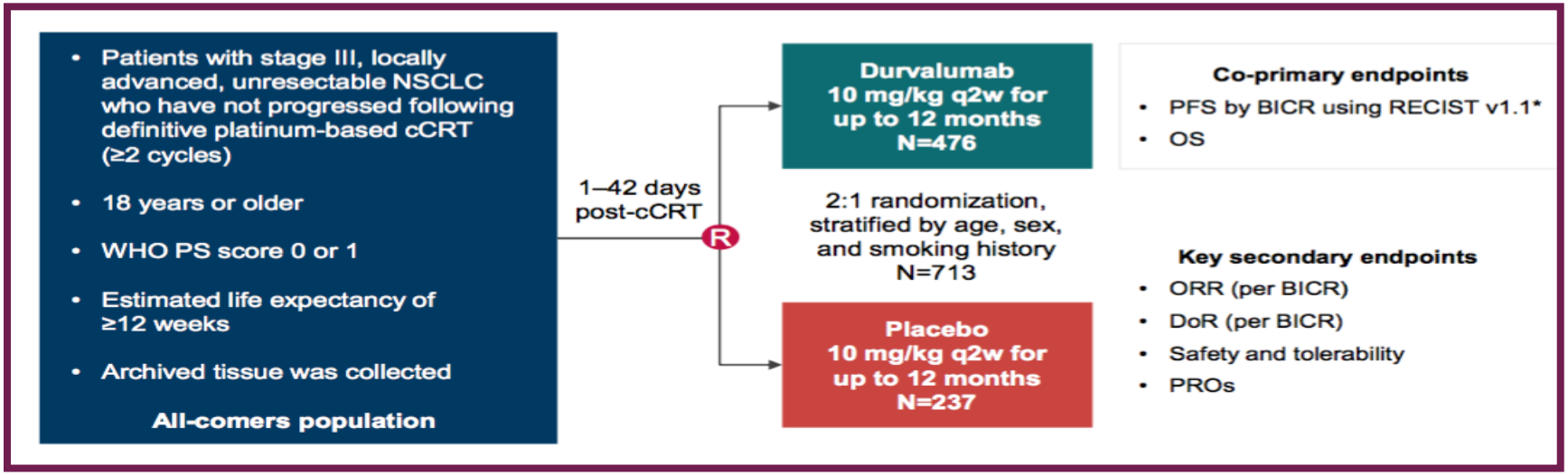


13630. Exploratory analyses of overall survival in PACIFIC

PACIFIC: study design
Phase 3, randomised, double-blind, placebo-controlled, multicentre, international study



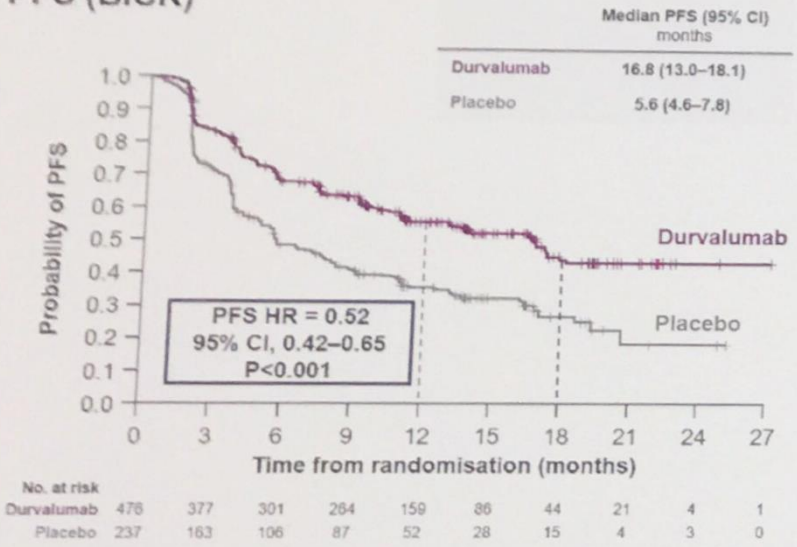
13630. Exploratory analyses of overall survival in PACIFIC

PACIFIC: PFS and OS in the ITT population

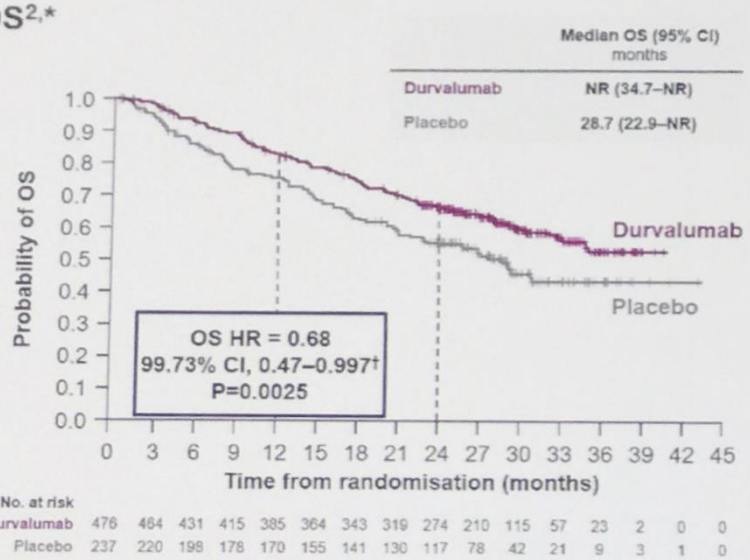
mPFS 16.8 vs 5.6 months

mOS NR vs 28.7 months

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

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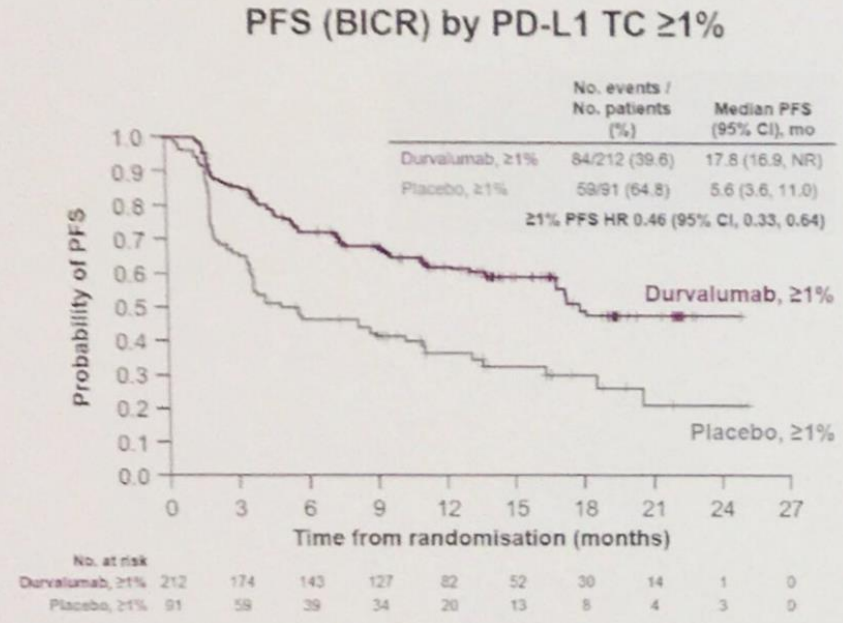
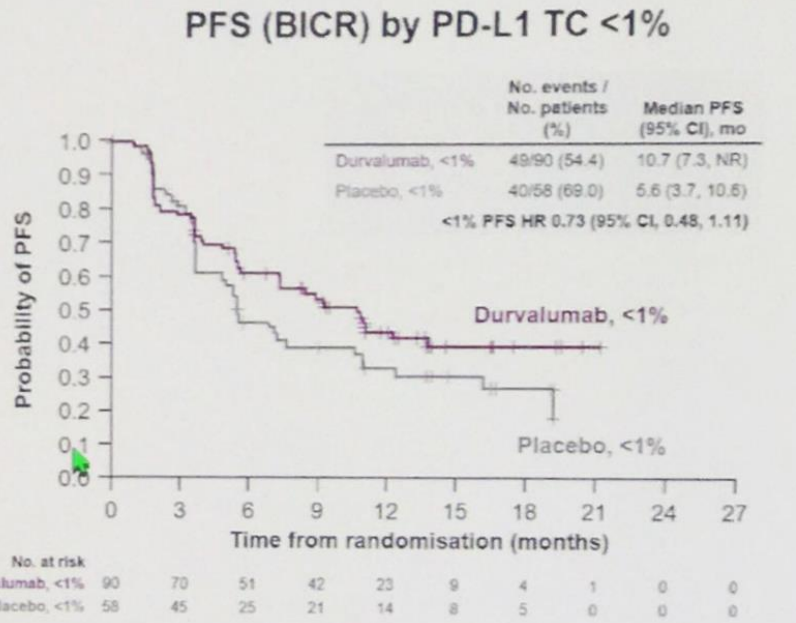
1. Antonia SJ, et al. N Engl J Med 2017;377:1919–29;
2. Antonia SJ, et al. N Engl J Med 2018; Epub Sep 25
PFS DCO: 13 February 2017; OS DCO: 22 March 2018

13630. Exploratory analyses of overall survival in PACIFIC

Improvement in PFS by PD-L1 TC ≥1% and <1%

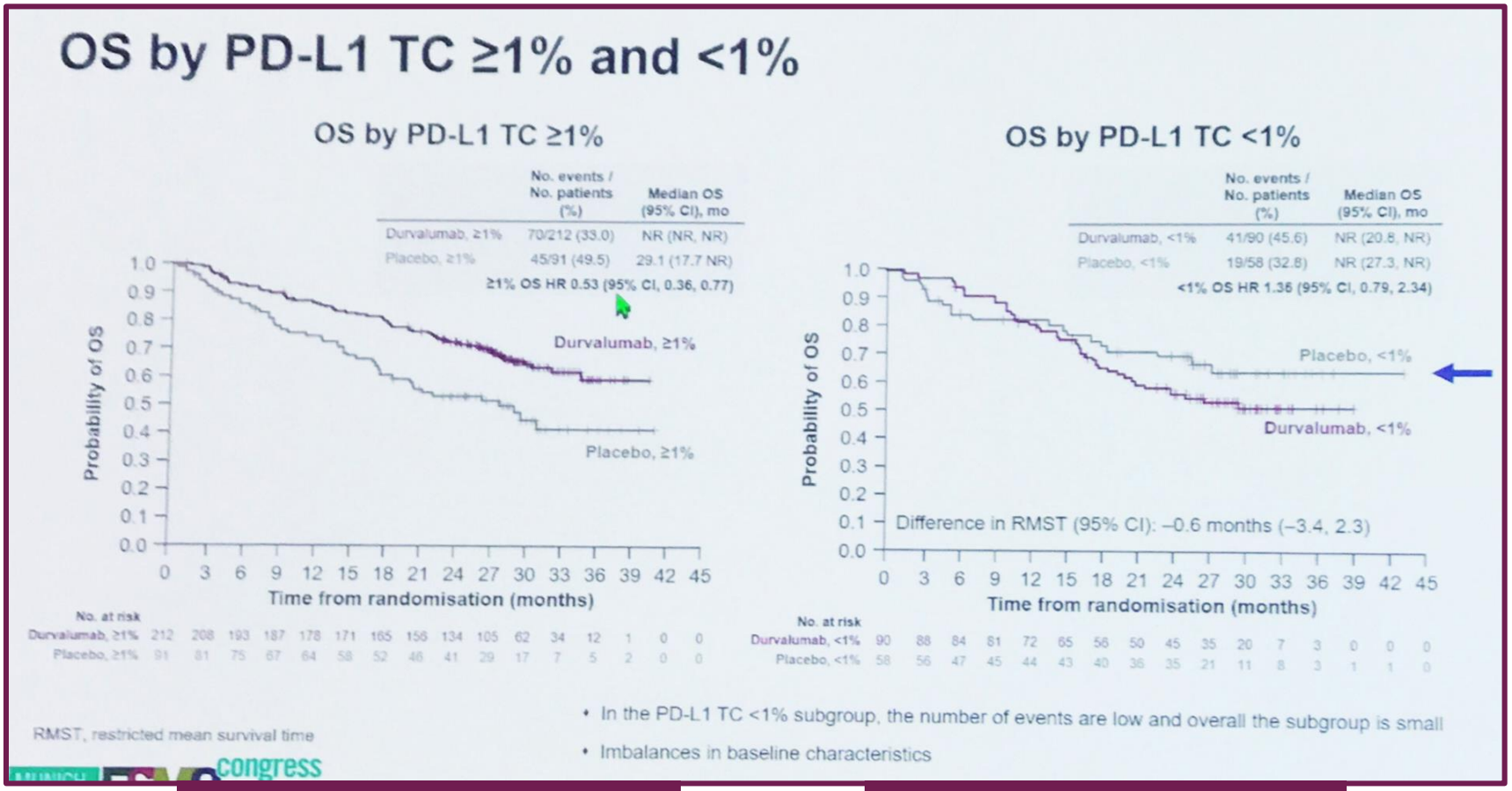




mPFS ≥ 1%: 17.8 vs 5.6 months
HR 0.46 (95% CI, 0.33-0.64)

mPFS < 1%: 10.7 vs 5.6 months
HR 0.73 (95% CI, 0.48-1.11)

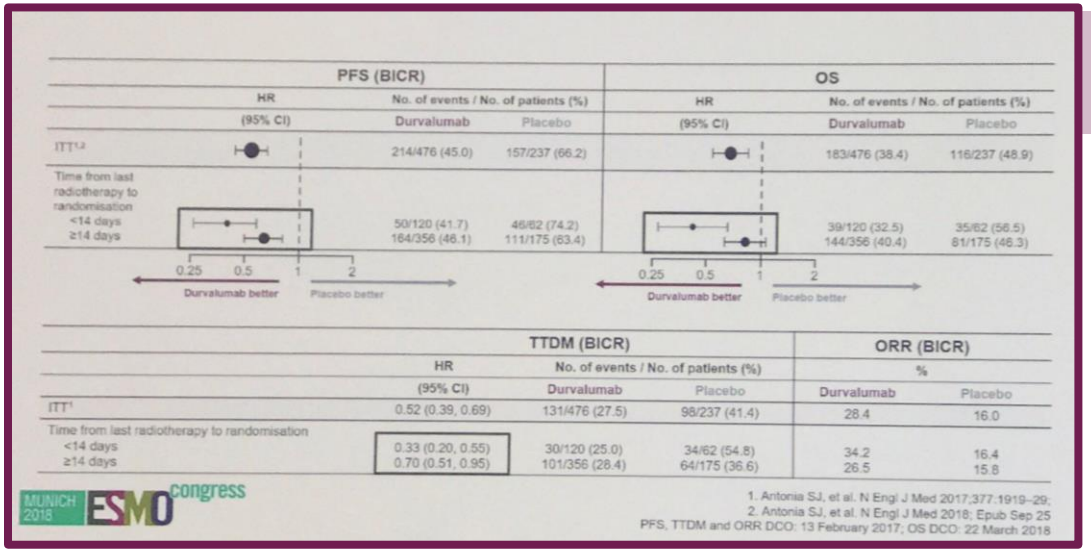
13630. Exploratory analyses of overall survival in PACIFIC



mOS ≥ 1%: NR vs 29.1 months
HR 0.53 (95% CI, 0.36-0.77)

mOS < 1%: NR vs NR months
HR 1.36 (95% CI, 0.79-2.34)

13630. Exploratory analyses of overall survival in PACIFIC



	PFS (BICR)			OS		
	HR (95% CI)	No. of events / No. of patients (%) Durvalumab	Placebo	HR (95% CI)	No. of events / No. of patients (%) Durvalumab	Placebo
ITT[1,2]		214/476 (45.0)	157/237 (66.2)		183/476 (38.4)	116/237 (48.9)
Time from last radiotherapy to randomisation						
<14 days		50/120 (41.7)	46/82 (74.2)		39/120 (32.5)	35/82 (56.5)
≥14 days		164/356 (46.1)	111/175 (63.4)		144/356 (40.4)	81/175 (46.3)

0.25 0.5 1 2
Durvalumab better | Placebo better

	TTDM (BICR) HR (95% CI)	No. of events / No. of patients (%) Durvalumab	Placebo	ORR (BICR) % 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 randomisation					
<14 days	0.33 (0.20, 0.55)	30/120 (25.0)	34/82 (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

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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
PFS, TTDM and ORR DCO: 13 February 2017; OS DCO: 22 March 2018

Improved outcomes irrespective 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

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DCO: 22 March 2018

Similar toxicity profiles regardless of time from radiation

13630. Exploratory analyses of overall survival in PACIFIC

Conclusions

- PACIFIC study was designed to evaluate the benefit of durvalumab in an all-comers population
- Post-hoc exploratory subgroup analyses have shown
  - For PD-L1 by TC 1% subgroups
    - ≥1% subgroup – PFS and OS improvement
    - <1% subgroup – PFS benefit, OS confounded by performance of placebo arm
    - Similar safety across all PD-L1 subgroups
  - Improved PFS and OS with durvalumab regardless of type of chemotherapy, radiation dose used or time from radiation to randomisation
  - These analyses have known limitations that preclude definitive conclusions
- These data support the PACIFIC regimen of durvalumab following CRT as the new standard of care in the treatment of patients with unresectable, Stage III NSCLC

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PFS DCO: 13 February 2017; OS DCO: 22 March 2018

- **PACIFIC was designed to evaluate Durvalumab in the ITT (all-comers)**
- **PD-L1 testing was not mandatory and status was unknown for 37% of patients**