Lung Cancer UPDATES
ESMO HIGHLIGTHS
19-21 SEPTIEMBRE 2020

VIRTUAL

Iniciativa científica de: GECP lung cancer research

CARCINOMA DE PULMÓN NO MICROCÍTICO. ESTADIOS LOCALMENTE AVANZADOS

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PRESENTACIONES RELEVANTES EN ESMO DE CPCNP LOCALMENTE AVANZADO

- Gefitinib + RT torácica concurrente en CPCNP LA EGFR +
- QT + RT → Durvalumab. PACIFIC seguimiento a 4 años
- PACIFIC R: El Real-World del PACIFIC

A single-arm phase II study of gefitinib with concurrent thoracic radiotherapy in unresectable locally-advanced non-small cell lung cáncer patients with EGFR mutation (West Japan Oncology Group 6911L). J. Shimizu. 1236 MO

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Background, Study design and Patients' characteristics

- For unresectable, locally advanced non-small cell lung cancer (NSCLC) patients, chemoradiotherapy followed by durvalumab is the standard.
- Among them, about 30% have EGFR mutation and they seemed to be less likely to benefit from durvalumab .
- Preclinical study showed radio-sensitizing effect between EGFR-TKI plus radiotherapy.

Akamatsu H, Am J Clin Oncol 2014
Tanaka K, J Thorac Oncol 2015
Antonia SJ, NEJM 2018
Das AK, Cancer Res 2006

<WJOG6911L> Key Inclusion Criteria

- Treatment-naïve
- Unresectable, locally advanced NSCLC
- With EGFR mutation (19del or L858R)
- Age < 75 y.o.
- ECOG PS 0-1

↓

Gefitinib 250 mg/day, 2 years
+
Concurrent thoracic radiotherapy 64Gy / 32frs
(N = 27)

- **Primary endpoint**: Progression-free survival (PFS) rate at 2 years
  Hypothesis and statistical consideration
  - ✓ Study treatment will improve PFS rate at 2 years from 20 to 40%, one-sided α; 0.05 and β; 0.25
  >> 27 patients were required
- **Secondary endpoints**: Overall response rate (ORR), PFS, overall survival (OS) and adverse events (AEs)

	N = 27
Age	
Median (range)	67 (45-74)
Sex-no.	
Male / Female	7 / 20
Smoking status-no.	
Never / (ex-) smoker	15 / 12
ECOG performance status-no.	
0 / 1	19 / 8
Histology	
Adenocarinoma	27
Types of EGFR mutation-no.	
Exon 19del / exon 21 L858R	13 / 14
Clinical stage-no.	
IIIA / IIIB	14 /13
Location of the primary site-no.	
Right lobe (upper / middle / lower)	10 / 2 / 5
Left lobe (upper / lower)	6 / 4
Clinical N stage-no.	
N 0 / 1 / 2 / 3	1 / 2 /12 /12

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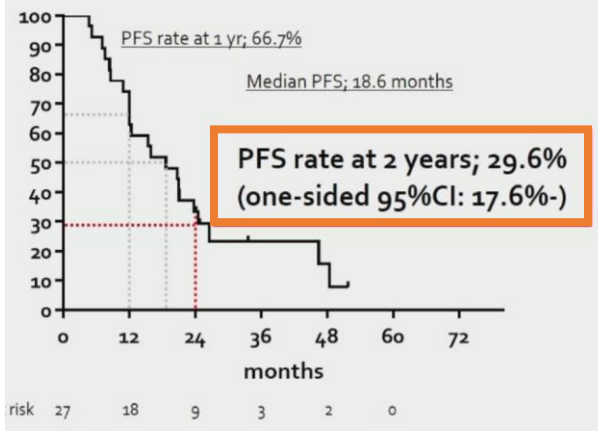
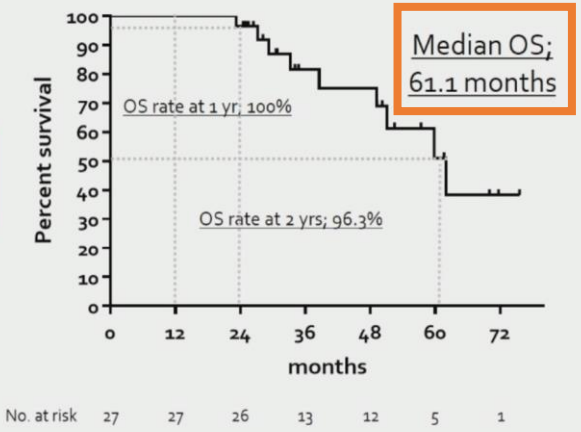
Progression-Free Survival by independent review and Overall survival





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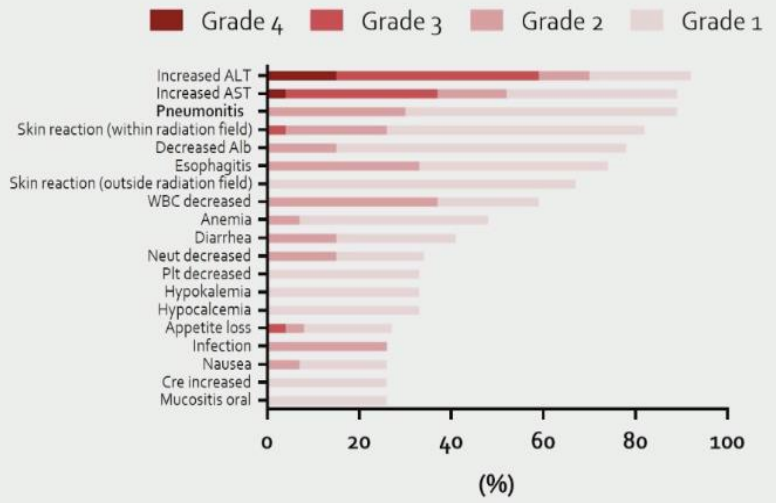
Sites of initial relapse and Adverse events

	N = 27
Within radiation field-no.	2
Primary site	1
Lymph node	1
Outside radiation field-no.	23
Intra-thoracic sites	9
Lymph nodes	2
Lung	3
Pleura, or pleural effusion	4
Extra-thoracic sites	14
Brain (Brain only)	**12 (11)**
Liver	1
Bone	1



A single-arm phase II study of gefitinib with concurrent thoracic radiotherapy in unresectable locally-advanced non-small cell lung cáncer patients with EGFR mutation (West Japan Oncology Group 6911L). J. Shimizu. 1236 MO

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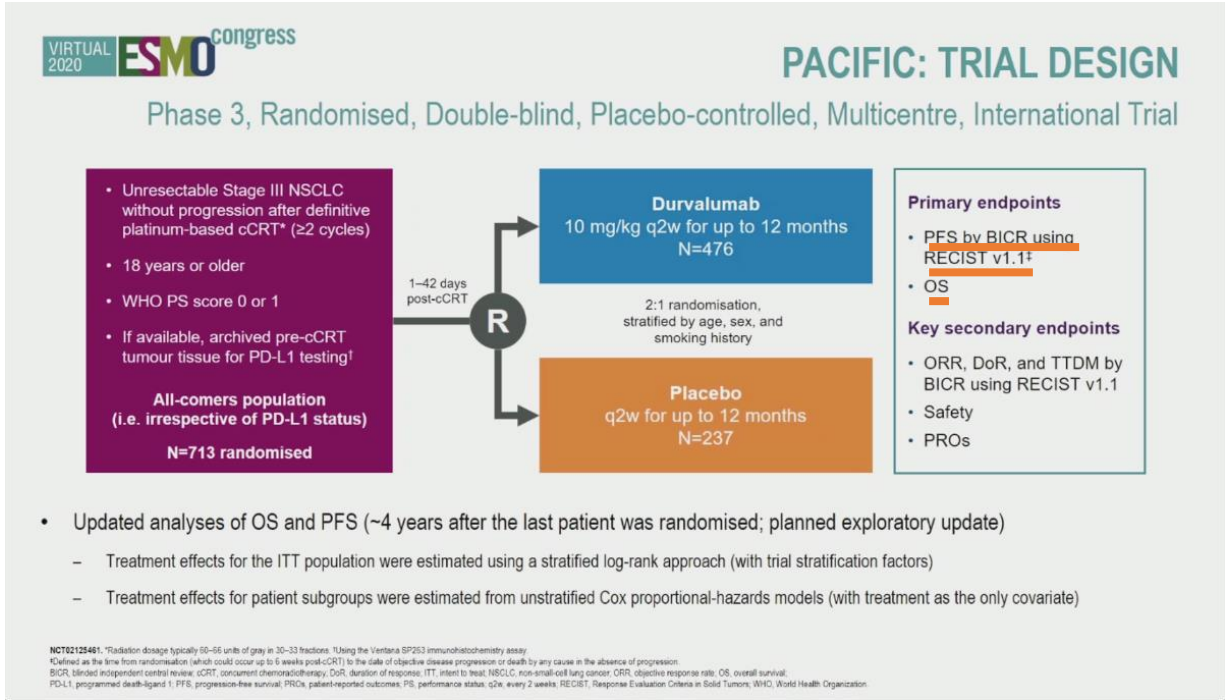
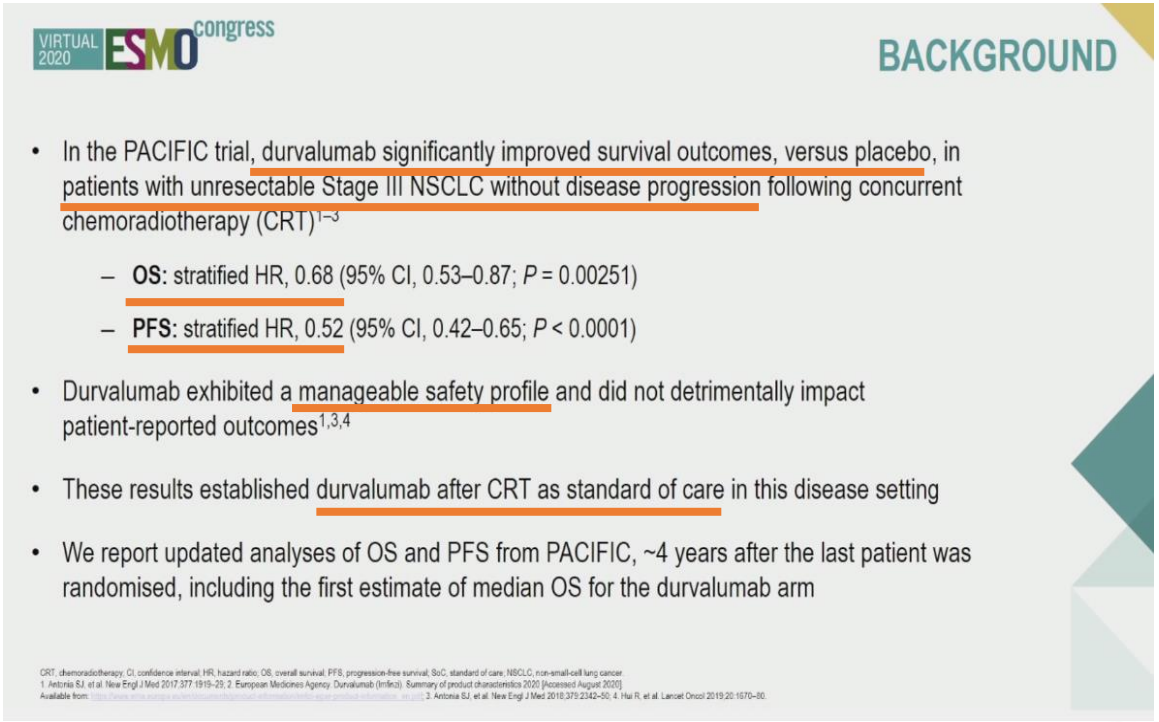
Conclusion

Among unresectable locally-advanced NSCLC patients *with EGFR mutation*, gefitinib with concurrent TRT showed favorable efficacy with manageable safety although this study did not meet the primary endpoint.

Novel strategy to prevent brain metastasis will be warranted.

Durvalumab after Chemoradiotherapy in Stage III NSCLC: 4-year survival update from the Phase 3. PACIFIC trial. C.Faivrer-Finn. LAB_49





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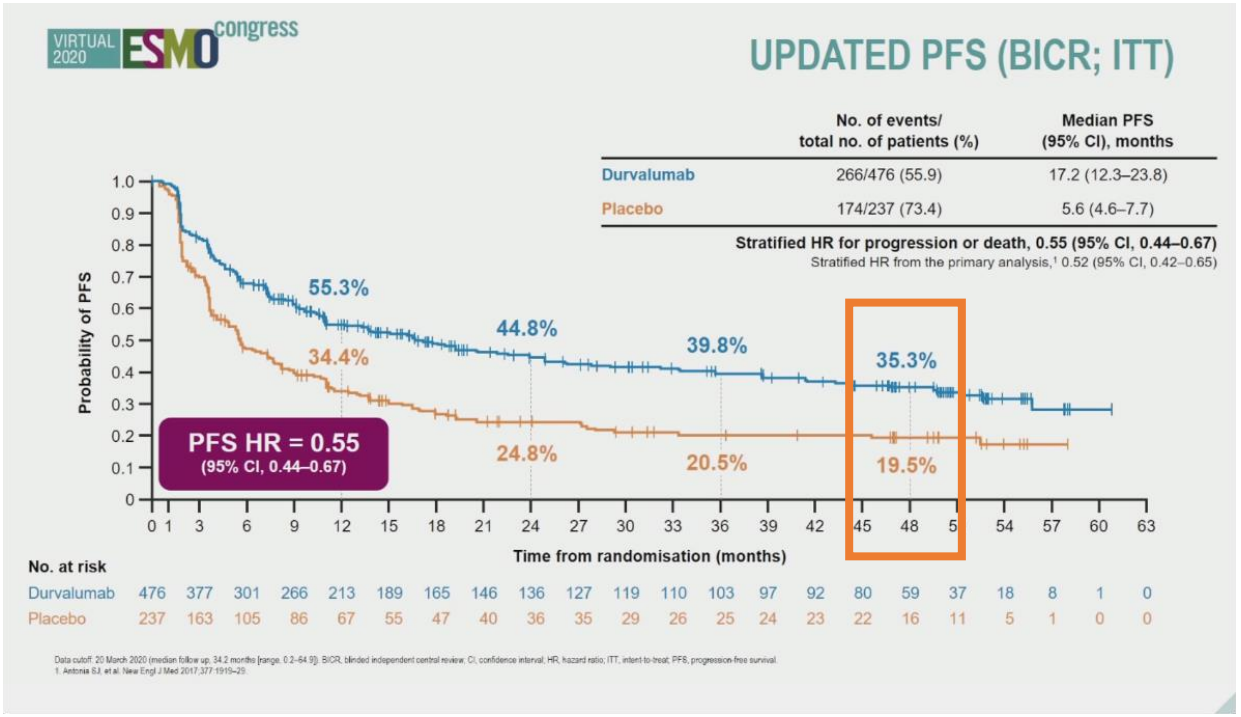

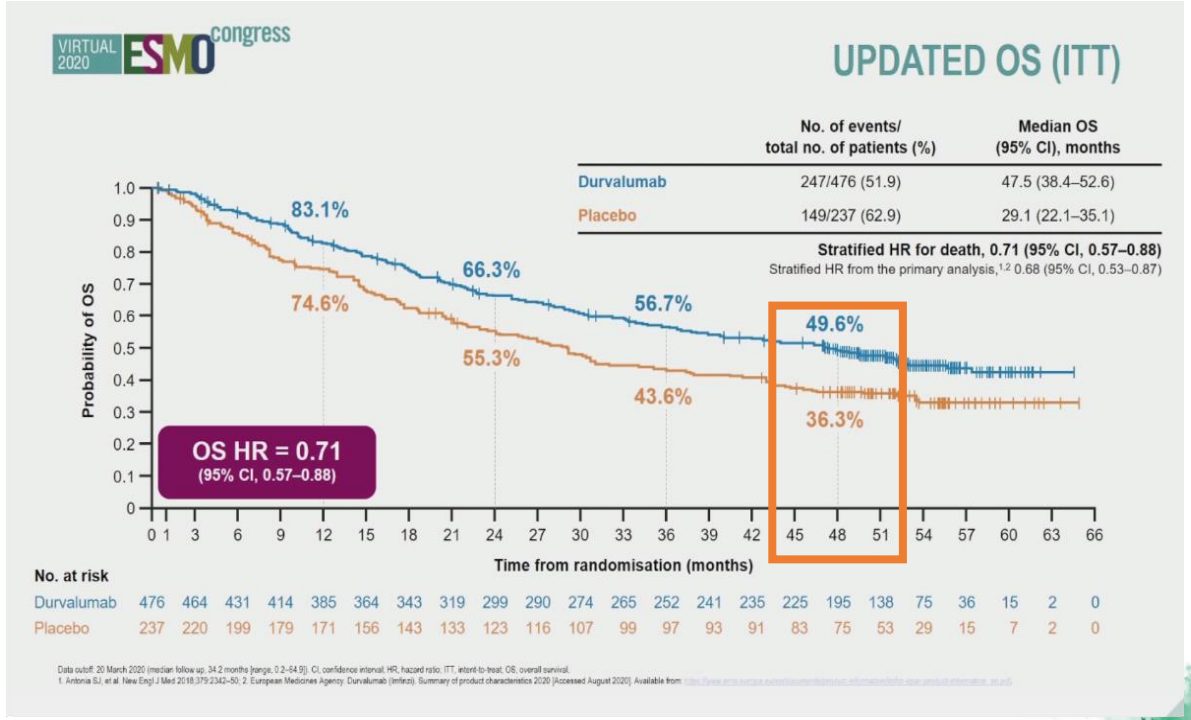

Durvalumab after Chemoradiotherapy in Stage III NSCLC: 4-year survival update from the Phase 3. PACIFIC trial. C.Faivrer-Finn. LAB_49

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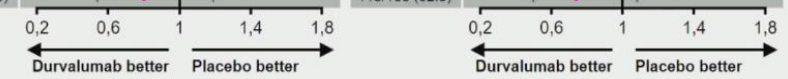
UPDATED OS AND PFS IN PRE-SPECIFIED SUBGROUPS

		OS		PFS (BICR)	
		# events / # patients (%)	HR and 95% CI	# events / # patients (%)	HR and 95% CI
All patients		396/713 (55.5)		440/713 (61.7)	
Sex	Male	290/500 (58.0)		313/500 (62.6)	
	Female	106/213 (49.8)		127/213 (59.6)	
Age at randomisation	<65 years	195/391 (49.9)		235/391 (60.1)	
	≥65 years	201/322 (62.4)		205/322 (63.7)	
Smoking status	Smoker	361/649 (55.6)		401/649 (61.8)	
	Non-smoker	35/64 (54.7)		39/64 (60.9)	
NSCLC disease stage	Stage IIIA	216/377 (57.3)		223/377 (59.2)	
	Stage IIIB	170/319 (53.3)		208/319 (65.2)	
Tumour histologic type	Squamous	192/326 (58.9)		212/326 (65.0)	
	All other	204/387 (52.7)		228/387 (58.9)	
Prior definitive CT	Cisplatin	203/395 (51.4)		238/395 (60.3)	
	Carboplatin	179/301 (59.5)		189/301 (62.8)	
Best response to prior therapy	Complete response	8/16 (50.0)	NA*	9/16 (56.3)	NA*
	Partial response	177/349 (50.7)		211/349 (60.5)	
	Stable disease	203/338 (60.1)		214/338 (63.3)	
EGFR mutation	Positive	24/43 (55.8)		32/43 (74.4)	
	Negative	261/482 (54.1)		290/482 (60.2)	
	Unknown	111/188 (59.0)		118/188 (62.8)	



*Hazard ratio and 95% CI not calculated if the subgroup has less than 20 events.
Data cutoff: 20 March 2020. BICR, blinded independent central review; CI, confidence interval; CT, chemotherapy; EGFR, epidermal growth factor receptor; HR, hazard ratio; ITT, intent-to-treat; NA, not applicable; OS, overall survival; PFS, progression-free survival.

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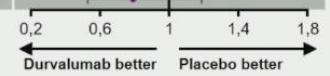
UPDATED OS AND PFS IN PD-L1 SUBGROUPS

		OS		PFS (BICR)	
		# events / # patients (%)	HR and 95% CI	# events / # patients (%)	HR and 95% CI
All patients		396/713 (55.5)		440/713 (61.7)	
PD-L1 status (pre-specified)	≥25%	76/159 (47.8)		92/159 (57.9)	
	<25%	164/292 (56.2)		181/292 (62.0)	
	Unknown	156/262 (59.5)		167/262 (63.7)	
PD-L1 status (post-hoc)	1–<25%	75/144 (52.1)		85/144 (59.0)	
	≥1%	151/303 (49.8)		177/303 (58.4)	
	<1%	89/148 (60.1)		96/148 (64.9)	



- Important facts regarding PD-L1 status:
  - PD-L1 testing was not required and 37% of all randomised patients had unknown PD-L1 status
  - PD-L1 status was determined from tumour tissue obtained pre-CRT (getting a sample post-CRT medically not feasible)
  - PD-L1 expression-level cutoff of 1% was part of an unplanned post-hoc analysis requested by the EMA

Data cutoff: 20 March 2020. BICR, blinded independent central review; CRT, chemoradiotherapy; CI, confidence interval; CR, complete response; EMA, European Medicines Agency; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

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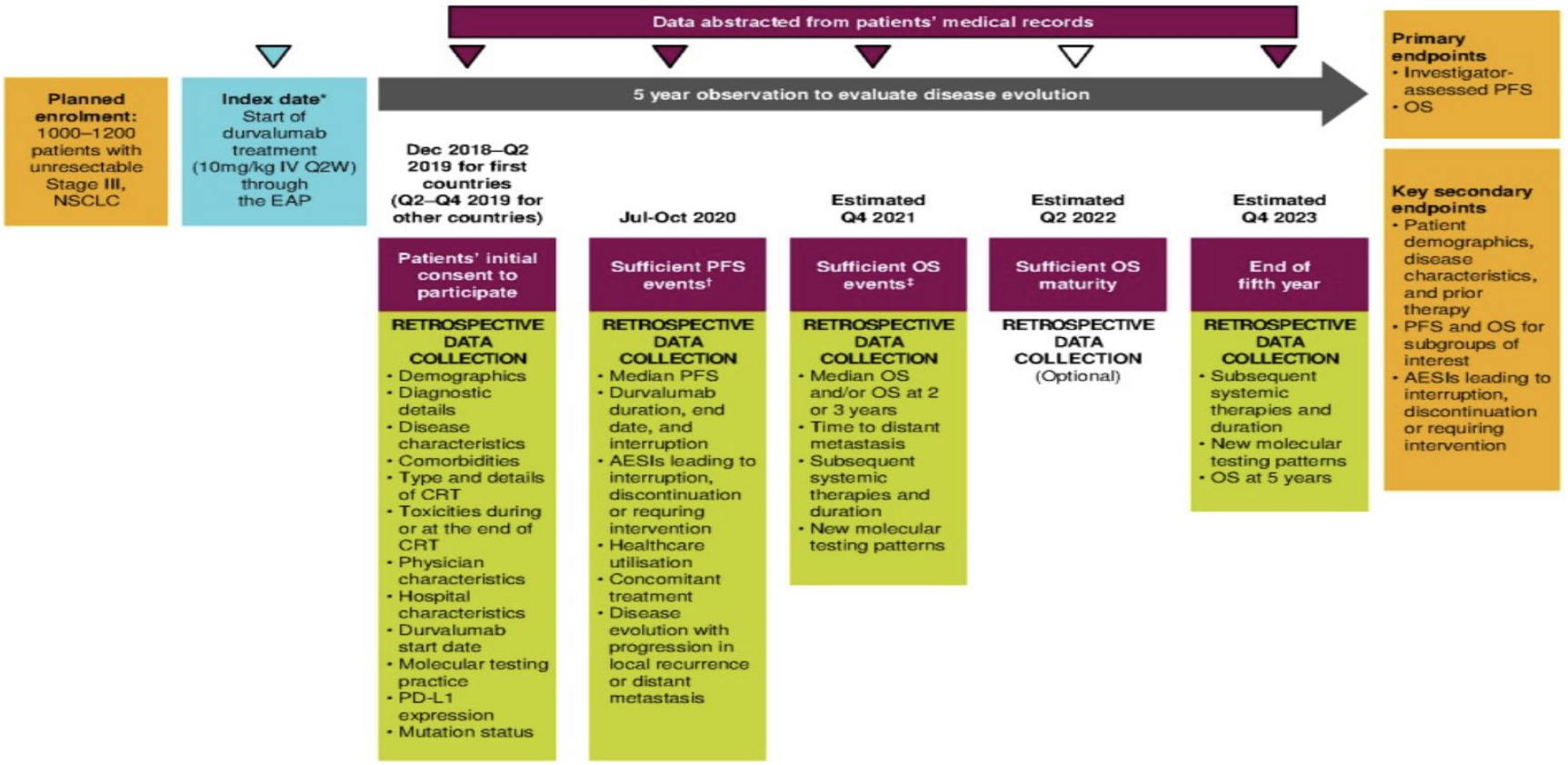
CONCLUSIONS

- The PACIFIC standard-of-care regimen, durvalumab consolidation after CRT, continues to demonstrate durable PFS and sustained OS benefit in this pre-planned exploratory update at 4 years, consistent with the significant benefit for these endpoints reported at the time of the primary analyses[1,2]
- The median OS for the durvalumab arm was reached for the first time at this update (KM estimates: durvalumab arm, 47.5 months; placebo arm, 29.1 months)
- The updated results demonstrate an estimated 4-year OS rate of 49.6% for the durvalumab arm vs 36.3% for placebo arm, and an estimated 4-year PFS rate of 35.3% vs 19.5%, respectively (KM estimates)
- Ongoing clinical trials are investigating concurrent ICI + CRT regimens and may further transform the treatment landscape for patients with unresectable Stage III NSCLC

CRT, chemoradiotherapy; ICI, immune checkpoint inhibition; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival.
1. Antonia SJ, et al. New Engl J Med 2018;379:2342–50; 2. Antonia SJ, et al. New Engl J Med 2017;377:1919–29.

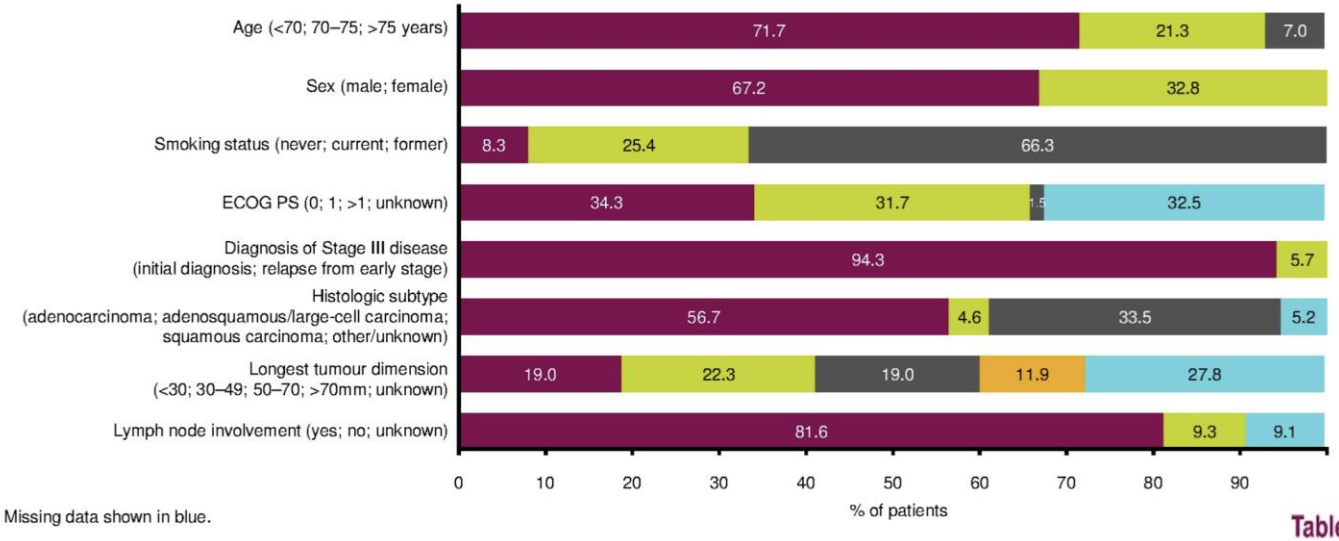
Characteristics of the first 615 patients enrolled in PACIFIC R: A study of the first real-world data on unresectable stage III NSCLC patients treated with durvalumab and chemoradiotherapy. N. Girard. 1242 P

Figure 1. Study Design



Characteristics of the first 615 patients enrolled in PACIFIC R: A study of the first real-world data on unresectable stage III NSCLC patients treated with durvalumab and chemoradiotherapy. N. Girard. 1242 P

Figure 2. Patient demographics and disease characteristics at EAP inclusion



Missing data shown in blue.

Table 1. Tumour biomarkers

Biomarker evaluated	Tested, n (%)	Positive*, n (%)	Inconclusive*, n (%)
PD-L1 expression†	442 (71.9)	324 (73.3)	27 (6.1)
EGFR mutation	262 (42.8)	19 (7.3)	7 (2.7)
ALK translocation	256 (41.9)	6 (2.3)	12 (4.7)
BRAF mutation	164 (26.8)	14 (8.5)	5 (3.0)
KRAS mutation	180 (29.5)	44 (24.4)	6 (3.3)

*Percentages are calculated using the total number of patients tested as the denominator.
†Threshold for PD-L1 expression: ≥1% of tumour cells. Positive status is derived from data collected, which was inconsistent for 27 patients.

Characteristics of the first 615 patients enrolled in PACIFIC R: A study of the first real-world data on unresectable stage III NSCLC patients treated with durvalumab and chemoradiotherapy. N. Girard. 1242 P

Table 2. Details of combination CRT regimens received prior to durvalumab

Prior regimens, n (%)	Total (N=615)
Patients who received cCRT	480 (78.0)
Patients who received CRT with induction chemotherapy	237 (38.5)
Patients who received sequential CRT	76 (12.4)
Most common combination chemotherapy regimens	
Cisplatin & vinorelbine	167 (27.2)
Carboplatin & paclitaxel	155 (25.2)
Cisplatin & etoposide	101 (16.4)
Carboplatin & vinorelbine	64 (10.4)
Cisplatin & pemetrexed	62 (10.1)
Carboplatin & pemetrexed	44 (7.2)
Carboplatin & etoposide	32 (5.2)
Cisplatin & docetaxel	25 (4.1)
Carboplatin & docetaxel	16 (2.6)
Cisplatin & paclitaxel	10 (1.6)
Other combinations	24 (3.9)
RT dosage	
≤60 Gy	239 (38.9)
>60–≤66 Gy	319 (51.9)
>66–≤70 Gy	26 (4.2)
>70–≤74 Gy	4 (0.7)
>74 Gy	3 (0.5)
Missing	24 (3.9)

Categories of CRT (concurrent, concurrent with induction, sequential) have been programmatically derived for consistency among sites and countries.
Combination chemotherapy regimens are not mutually exclusive as patients could switch from one combination to another.

Toxicities during CRT

- In total, 117/615 (19.0%) patients experienced toxicities during CRT which resolved at the end of CRT among 70 (59.8%) of these patients.
  - These were considered mild, moderate or severe in 45 (7.3%), 53 (8.6%), and 17 (2.8%) patients respectively; severity was not specified in 2 (0.3%) patients.
- AEs most frequently reported during CRT were oesophagitis (n=69, 11.2%) and dysphagia (n=24, 3.9%).
  - Oesophagitis was reported as mild (n=34, 5.5%), moderate (n=29, 4.7%), and severe (n=5, 0.8%); these events were resolved by the end of CRT in 36 patients, and lasted for a median duration of 52.0 days.
  - Dysphagia was reported as mild (n=10, 1.6%), moderate (n=10, 1.6%), and severe (n=4, 0.7%); these events were resolved by the end of CRT in 18 patients, and lasted for a median duration of 44.0 days.
  - Radiation-induced cutaneous toxicity and peripheral neuropathy were reported in 13 (2.1%) and 4 (0.7%) patients, respectively.

Conclusions

- This preliminary analysis of a Stage III unresectable NSCLC population provides a valuable insight into this patient population in the real world and into the makeup of the PACIFIC-R cohort.
- Future analyses will focus on progression-free survival, overall survival, duration of durvalumab and adverse events of special interest, such as, pneumonitis and interstitial lung disease.