Lung Cancer UPDATES
ESMO HIGHLIGTHS
17-21 SEPTIEMBRE 2021

Iniciativa científica de:
GECP lung cancer research

Estadios localmente avanzados
Carcinoma no microcítico

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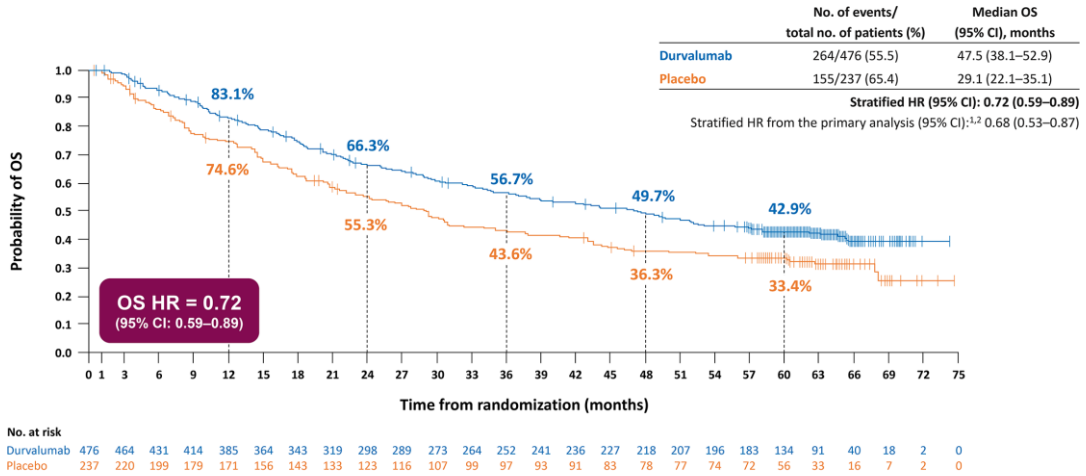
De la investigación a la calidad asistencial



Data cutoff: 11 January 2021 (median follow-up: all patients, 34.2 months [range, 0.2–74.7]; censored patients, 61.6 months [range, 0.4–74.7]).
1. Antonia SJ, et al. New Engl J Med 2018;379:2342–50; 2. European Medicines Agency. Durvalumab (Imfinzi). Summary of product characteristics 2020. Available from: https://www.ema.europa.eu/en/documents/product-information/imfinzi-epar-product-information_en.pdf 5. [Accessed April 2021]

RESULTS

Table 1: Baseline and treatment characteristics

	N = 150 (%)
Median FU (mo)	15 (IQR 7-22)
ECOG Score	
0	57 (38.0)
1	73 (48.7)
2	20 (13.3)
Histology	
Squamous cell	74 (49.3)
Adenocarcinoma	70 (46.7)
Other	6 (4.0)
Group Stage	
I	7 (4.7)
II	10 (6.7)
III	132 (88.0)
IV	1 (0.7)
Chemo	
Carbo/taxol	125 (83.3)
Cis/etop	16 (10.7)
Other	9 (6.0)
RT Dose (Gy)	
<60	2 (1.3)
60	143 (95.3)
>60	5 (3.3)
Durva Cycles	12 (IQR 4-22)

- 36 pneumonitis events
  - 11 grade 3, 2 grade 5
  - 1-year risk: 25.7%
- OS at 1- and 3-years 88.7% and 55.5%, respectively

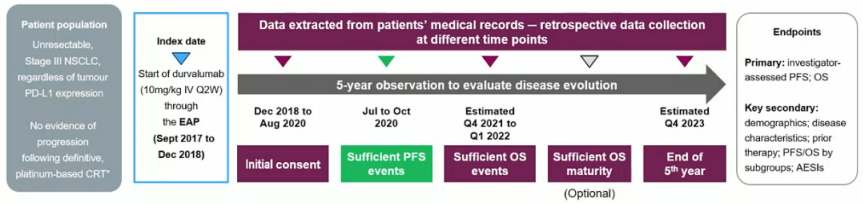
Table 2: Significant predictors of pneumonitis

UNIVARIATE	HR
Durva cycles	0.92
Total lung	
Volume	0.68
Mean dose	2.66
Ipsilateral lung	
Volume	0.51
Mean dose	1.71
V5Gy (%)	1.24
V10Gy (%)	1.26
V10Gy (cc)	9.85
V20Gy (%)	1.28
V40Gy (%)	1.30
Contralateral lung	
Volume	0.52
Mean dose	2.42
V40Gy (%)	2.34
MULTIVARIATE	**HR**
Durva cycles	0.92
Contralateral lung	
Mean dose	4.75

Poster 1175P

Study Design & Status (NCT03798535)

PACIFIC-R: An International, Observational Study



- **1,399 patients** included in the **full analysis set (FAS)** from **290 active sites** in **11 participating countries**
  - France (n=342), Spain (244)†, Australia (165), Netherlands (155), Belgium (118), Italy (116), Israel (92), Germany (62), UK (54), Norway (36), and Switzerland (15)

*Patients had completed platinum-based chemotherapy concurrent or sequential to radiotherapy within the previous 12 weeks without evidence of disease progression; †Spanish data are from an externally sponsored study integrated in April 2021
AESI, adverse event of special interest; CRT, chemoradiotherapy; EAP, expanded access programme; IV, intravenously; NSCLC, non-small-cell lung cancer; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; Q2W, every 2 weeks

Patient Characteristics & Durvalumab Treatment

Characteristics		FAS (N=1,399)
Age at EAP inclusion (years)	Median (range)	66.0 (26–88)
Age categories, %	≤75 years / >75 years	89.6 / 10.4
Sex, %	Male / Female	67.5 / 32.5
Smoking status at EAP inclusion, %	Never / Current / Former	7.9 / 32.6 / 59.5
Stage at diagnosis, %*[A]	Stage IIIA	43.2
	Stage IIIB/C	51.0
Histological subtype, %*[B]	Squamous	35.5
	Non-squamous	63.1
	Unknown	1.4
ECOG/WHO PS at EAP inclusion, %	0 / 1 / 2 / 3	51.4 / 46.6 / 1.9 / 0.1
CRT type, %*[C]	Concurrent	76.6
	Sequential	14.3
	Other	9.1
PD-L1 expression, %*[D] (Based on n=967 tested patients)	≥1%	72.5
	<1%	17.9
	Inconsistent†	9.6

- **Median time to durvalumab initiation** from the end of RT = **56 days**
- Overall **median durvalumab treatment duration =** 335 days (**~11 months**)
  - >12 months' treatment: 20.1%
  - >14 months' treatment: 4.4%
- Patients received a **median of 22 durvalumab infusions**
  - 7.1% received >26 infusions

Cut-off date for data extraction: 8 April 2021
*Percentages based on patients for whom the data were available; †PD-L1 expression tested but not clearly reported.
[A]Disease stage was missing for n=7 and n=74 had were diagnosed at a stage <IIIi; [B]Histology was missing for n=2; [C]CRT type was missing for n=2; [D]PD-L1 was not tested for n=432
CRT, chemoradiotherapy; EAP, expanded access programme; ECOG/WHO PS, Eastern Cooperative Oncology Group/World Health Organization performance status; FAS, full analysis set; PD-L1, programmed cell death-ligand 1; RT, radiotherapy

Real-world PFS (FAS) – Median Follow-up Duration = 23.0 Months*

- Median rwPFS in PACIFIC-R was higher than the median PFS reported for the durva. arm of the PACIFIC trial[1†]
- Challenges with collecting rwPFS data limit comparisons between PACIFIC-R and PACIFIC
- RwPFS is likely overestimated as:
  - Germany and UK sites did not collect deaths that occurred prior to study enrolment‡ (50 early deaths not counted)
  - RECIST criteria for tumour assessments is used heterogeneously across countries
  - Assessments for progression in the real world may not occur as frequently or consistently as in clinical trials; the COVID-19 pandemic may also have resulted in fewer hospital visits

	PACIFIC-R FAS	PACIFIC trial (durva. arm)[1]
PFS	N=1,399	N=476
Total events, N (%)	737 (52.7)	268 (56.3)†
Progression per RECIST	456 (32.6)	
Progression per physician assessment	170 (12.2)	
Progression, assessment unknown	30 (2.1)	
Deaths in absence of progression	81 (5.8)	
Median PFS, months	**21.7**	**16.9**
95% CI	19.2–24.5	13.0–23.9
PFS rate, %		
12 months	62.4	55.7
24 months	48.2	45.0

*Range for median follow-up duration = 0–35.6 months; †In the PACIFIC trial, PFS was assessed by blinded independent central review per RECIST v1.1; ‡Per local regulations
CI, confidence interval; FAS, full analysis set; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; rw, real-world; UK, United Kingdom

1. Spigel DR, et al. J Clin Oncol 2021;39(15_suppl):8511

Durvalumab Treatment Discontinuation

FAS (N=1,399)	Discontinuation reason, n (%)*	Median time from durva. start to discontinuation
Patient decision	20 (1.4)	6.1 months
AE	233 (16.7)	2.8 months
Completed treatment†	659 (47.1)	12.0 months
Disease progression	377 (26.9)	5.1 months
Death	21 (1.5)	1.9 months

- **Pneumonitis/interstitial lung disease (ILD)** was the most common AE leading to (% of FAS):
  - **Permanent** discontinuation: 133 (**9.5%**)‡
  - **Temporary** interruption: 73 (**5.2%**)‡

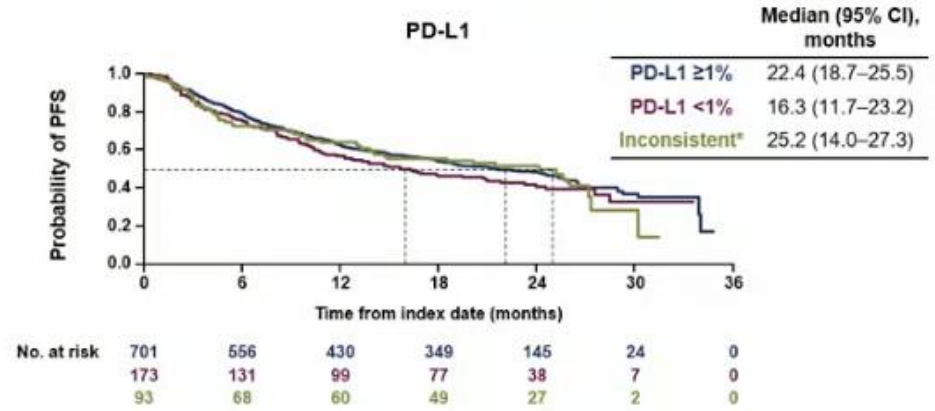
Pneumonitis/ILD

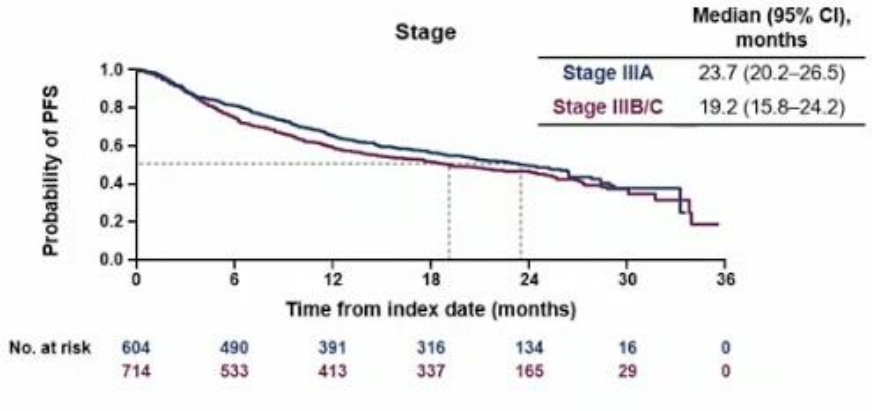
	FAS (N=1,399)
Patients with any pneumonitis/ILD, n (%)§	250 (17.9)
Mild event¶	56 (4.0)
Moderate event¶	118 (8.4)
Severe event¶	41 (2.9)
Life-threatening or fatal event¶	5 (0.4)

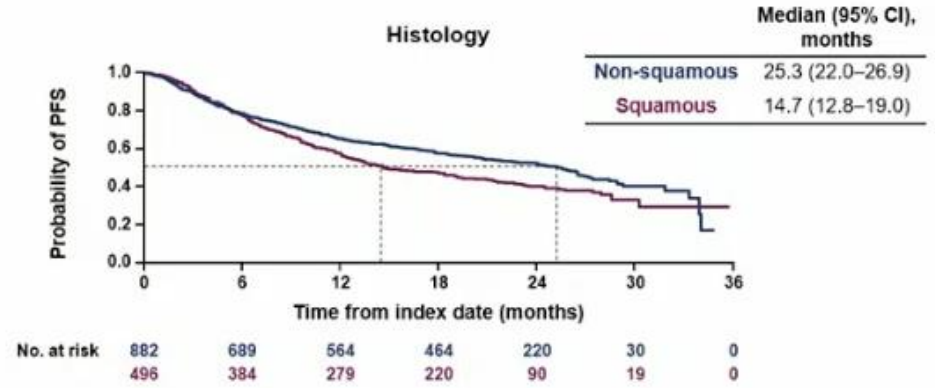
- Median **time to onset** of pneumonitis/ILD from durvalumab initiation: **2.5 months**
- **Corticosteroid** administration was required in **71.3%** of events#

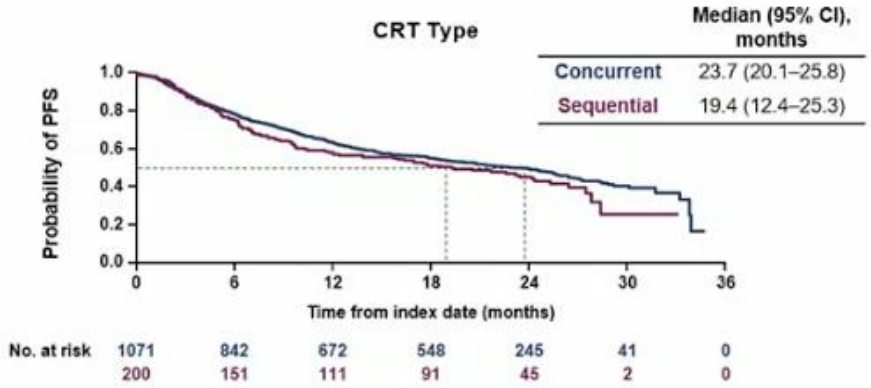
*Other discontinuation reason: missing (n=2), 'other' reasons (n=68), lost to follow-up (n=3), and ongoing durvalumab at time of data extraction (n=16); †Investigator's decision per country protocol and, where applicable, was after >12 months' treatment; ‡Categories are not mutually exclusive (i.e. a single patient could both interrupt and permanently discontinue durvalumab due to pneumonitis/ILD); §37/1,399 patients (2.6%) had pneumonitis/ILD events of unknown severity; ¶Categories are not mutually exclusive – patients experiencing ≥2 events of different severity can be counted under both categories. #A total of 279 pneumonitis/ILD events were reported among the 250 patients who experienced pneumonitis/ILD
AE, adverse event; FAS, full analysis set; ILD, interstitial lung disease

Real-world PFS by Subgroup



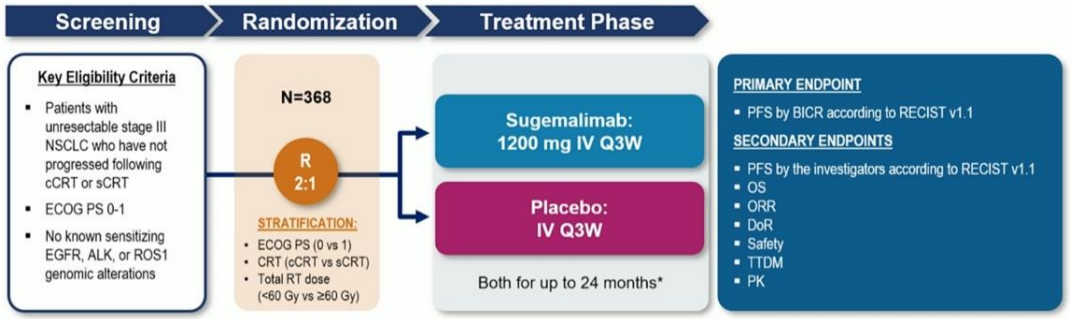






*PD-L1 expression tested but not clearly reported
CI, confidence interval; CRT, chemoradiotherapy; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival

GEMSTONE-301 Study Design



Statistical Considerations

- PFS is tested first at a two-sided alpha of 0.05; if PFS is significant, then OS would be tested at a two-sided alpha of 0.05
- Interim and final PFS analysis were planned when approximately 194 and 262 PFS events occurred, respectively. O'Brien-Fleming method was used to control the type I error
- Interim and final OS analysis were planned when approximately 175 and 260 OS events occurred, respectively.

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*First dose administered within 1–42 days after cCRT or sCRT (including at least 2 cycles of platinum-based chemotherapy) was completed.
BICR, blinded independent central review; cCRT, concurrent chemoradiotherapy; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous administration; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; RT, radiotherapy; sCRT, sequential chemoradiotherapy; TTDM, time to death/distant metastasis

GEMSTONE-301 VS PACIFIC

	GEMSTONE-301	PACIFIC[1]
Patient area	China	Non-China
Prior CRT	cCRT or sCRT	cCRT only
Treatment period	24 months*	12 months
EGFR/ALK/ROS1	Exclude EGFR/ALK/ROS1+	Not exclude EGFR/ALK/ROS1+
Disease Stage	IIIA: 29%	IIIA: 53%
Histology	SCC:69%	SCC:46%

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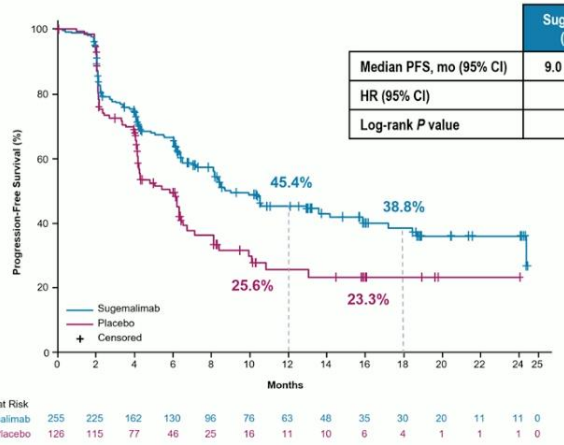
*if subject can benefit from sugemalimab, treatment period can extend
SCC, Squamous cell carcinoma
[1]Antonia SJ, et al. N Engl J Med 2017;377:1919–29

PFS by BICR

	Sugemalimab (N=255)	Placebo (N=126)
Median PFS, mo (95% CI)	9.0 (8.1–14.1)	5.8 (4.2–6.6)
HR (95% CI)	0.64 (0.48–0.85)	
Log-rank *P* value	0.0026	



Patients at Risk

Sugemalimab	255	225	162	130	96	76	63	48	35	30	20	11	11	0
Placebo	126	115	77	46	25	16	11	10	6	4	1	1	1	0

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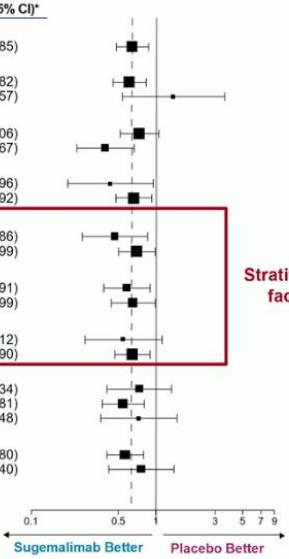
Interim PFS analysis (reviewed by iDMC) with median follow-up of 14 months; observed 197 PFS events with two-sided alpha of 0.0195

Data cutoff date: March 8, 202

Subgroup Analyses of PFS

	Sugemalimab No. patients	Placebo No. patients	Hazard Ratio (95% CI)*
All patients	255	126	**0.64** (0.48–0.85)
Sex			
Male	236	115	**0.61** (0.45–0.82)
Female	19	11	**1.40** (0.55–3.57)
Age			
<65 years	182	94	**0.75** (0.52–1.06)
≥65 years	73	32	**0.40** (0.23–0.67)
Smoking history			
Never	42	16	**0.44** (0.20–0.96)
Former or current	213	110	**0.67** (0.49–0.92)
ECOG PS			
0	78	38	**0.47** (0.26–0.86)
1	177	88	**0.71** (0.51–0.99)
CRT type			
Sequential	86	41	**0.59** (0.39–0.91)
Concurrent	169	85	**0.66** (0.44–0.99)
Radiotherapy dose			
<60 Gy	43	20	**0.55** (0.27–1.12)
≥60 Gy	212	106	**0.66** (0.48–0.90)
Cancer stage# before CRT			
Stage IIIA	74	32	**0.74** (0.41–1.34)
Stage IIIB	146	65	**0.55** (0.37–0.81)
Stage IIIC	33	28	**0.73** (0.36–1.48)
Pathologic type			
Squamous cell carcinoma	177	86	**0.57** (0.41–0.80)
Nonsquamous cell carcinoma	76	40	**0.77** (0.42–1.40)



Stratification factors

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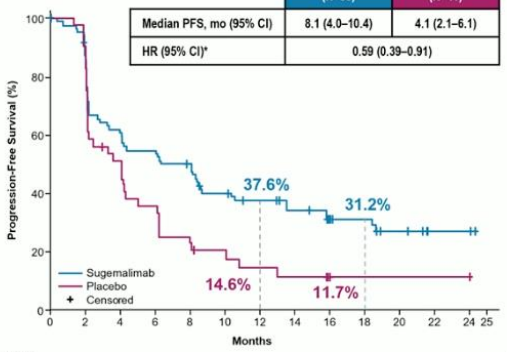
*Stratified for all patients, unstratified for the subgroups.
#Staged according to the IASLC classification, version 8.

Data cutoff date: March 8, 2021

PFS by CRT Type

Sequential CRT

	Sugemalimab (N=86)	Placebo (N=41)
Median PFS, mo (95% CI)	8.1 (4.0–10.4)	4.1 (2.1–6.1)
HR (95% CI)*	0.59 (0.39–0.91)	

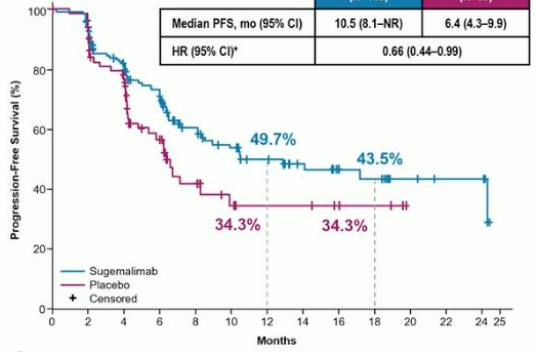


Patients at Risk

Sugemalimab	86	73	51	46	41	32	28	22	17	15	11	6	6	0
Placebo	41	37	20	14	10	7	5	4	2	1	1	1	1	0

Concurrent CRT

	Sugemalimab (N=169)	Placebo (N=85)
Median PFS, mo (95% CI)	10.5 (8.1–NR)	6.4 (4.3–9.9)
HR (95% CI)*	0.66 (0.44–0.99)	



Patients at Risk

Sugemalimab	169	152	111	84	55	44	35	26	18	15	9	5	5	0
Placebo	85	78	57	32	15	9	6	6	4	3	0	0	0	0

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*Unstratified HR.

Data cutoff date: March 8, 2021

AEs leading to treatment discontinuation:
11.4% vs 4.8%

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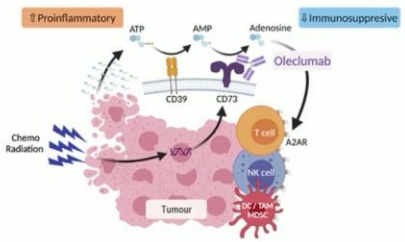
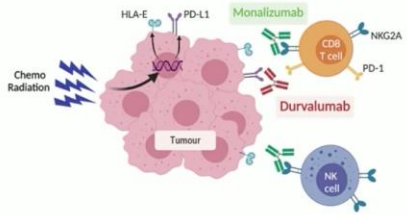
COAST: an open-label, Phase 2, multidrug platform study of durvalumab alone or in combination with novel agents in patients with locally advanced, unresectable, Stage III NSCLC

Alex Martinez-Marti[1], Margarita Majem[2], Fabrice Barlesi[3], Enric Carcereny[4], Quincy Chu[5], Isabelle Monnet[6], Alfredo Sanchez-Hernandez[7], Shaker Dakhil[8], D. Ross Camidge[9], Peng He[10], Yee Soo-Hoo[10], Zachary A. Cooper[10], Rakesh Kumar[10], John Bothos[10], Charu Aggarwal[11], Roy S. Herbst[12]

[1]Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Barcelona, Spain; [2]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [3]Gustave Roussy, Villejuif, France; [4]Institut Català d'Oncologia, Badalona-Hospital Germans Trias i Pujol, Barcelona, Spain; [5]Cross Cancer Institute, Edmonton, AB, Canada; [6]Centre Hospitalier Intercommunal de Créteil, Créteil, France; [7]Consorcio Hospitalario Provincial de Castellón, Castellón, Spain; [8]Cancer Center of Kansas, Wichita, KS, USA; [9]University of Colorado Anschutz Medical Campus, Aurora, CO, USA; [10]AstraZeneca, Gaithersburg, MD, USA; [11]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [12]Yale Cancer Center, New Haven, CT, USA

Rationale for combining durvalumab with oleclumab (anti-CD73) or monalizumab (anti-NKG2A)





- RT induces expression of CD73 and HLA-E (NKG2A ligand), which inhibit antitumour immune response[1-4]
- Oleclumab inhibits CD73 to reduce extracellular adenosine production, thereby promoting antitumour immunity.[5] Oleclumab combined with durvalumab produced durable responses with manageable safety in a Ph I study of advanced *EGFR*m NSCLC[6]
- Monalizumab blocks NKG2A to reduce inhibition of NK and CD8+ T cells.[7] Monalizumab combined with cetuximab had promising activity with manageable safety in a Ph I/II trial of patients with R/M HNSCC[8]
- Combinations of RT and anti-CD73/NKG2A ± anti-PD-(X) show increased antitumour activity in preclinical models[1,2,4]

ATP, adenosine triphosphate; AMP, adenosine monophosphate; DC, dendritic cell; *EGFR*m, epidermal growth factor receptor mutant; MDSC, myeloid-derived suppressor cell; NK, natural kille PD-(L)1, programmed cell death (ligand) 1; R/M HNSCC, recurrent/metastatic head and neck squamous cell carcinoma; RT, radiotherapy; TAM, tumour-associated macrophage

1. Wennerberg E, et al. Cancer Immunology Res 2020;8:465-478. 2. Tsukui H, et al. BMC Cancer 2020;20:411. 3. Nguyen AM, et al. Mol Cell Proteomics, 2020;19:375-38 4. Battaglia NG, et al. J Immunol 2020;204:241.24. 5. Geoghegan JC, et al. MAbs 2016;8:454-467. 6. Bendell J, et al. J Clin Oncol 2021;39:no. 15_suppl:904 7. André P, et al. Cell 2018;175:1731–1743.e13. 8. Cohen RB et al. J Clin Oncol 38: 2020 (suppl, abstr 6516). Figures created with BioRender.com.

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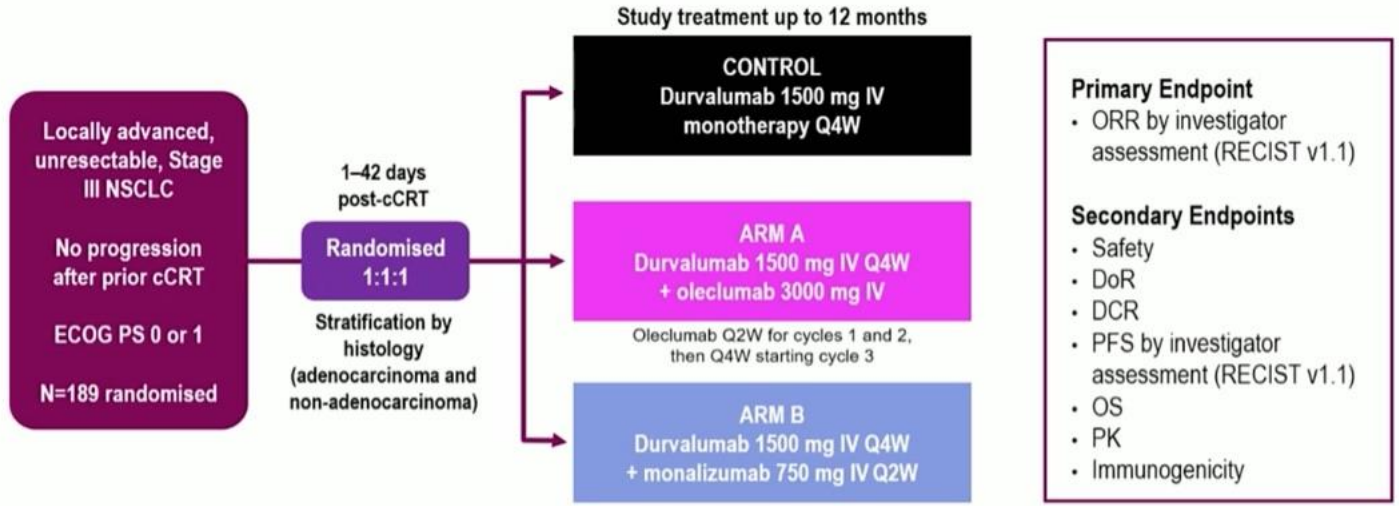
COAST: Phase 2, randomised open-label study



- A planned sample size of 60 patients per arm was designed to provide acceptable precision in estimating antitumour activities in an early phase setting
- Between Jan 2019 and Jul 2020, 189 patients were randomised of whom 186 received D (n=66), D+O (n=59) or D+M (n=61)
- As of 17 May 2021, all patients had a minimum of 10 months potential follow-up and the median actual follow-up was 11.5 months (range, 0.4–23.4; all patients)

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D, durvalumab; DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; IV, intravenously; M, monalizumab; O, oleclumab; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumours

Antitumour activity by investigator assessment
(interim analysis; ITT population)

Antitumour activity	D (N=67)	D+O (N=60)	D+M (N=62)
Confirmed ORR (95% CI),[b] %	**17.9 (9.6, 29.2)**	**30.0 (18.8, 43.2)**	**35.5 (23.7, 48.7)**
[n]	[12]	[18]	[22]
Confirmed + unconfirmed ORR (95% CI),[b] %	**25.4 (15.5, 37.5)**	**38.3 (26.1, 51.8)**	**37.1 (25.2, 50.3)**
[n]	[17]	[23]	[23]
ORR odds ratio (95% CI)[a,b]	–	**1.83 (0.80, 4.20)**	**1.77 (0.77, 4.11)**
Objective responses by RECIST,[a] n (%)			
CR	2 (3.0)	1 (1.7)	3 (4.8)
PR	15 (22.4)	22 (36.7)	20 (32.3)
SD	27 (40.3)	25 (41.7)	27 (43.5)
PD	15 (22.4)	7 (11.7)	7 (11.3)
NE	8 (11.9)	5 (8.3)	4 (6.5)
DCR at 16 weeks (95% CI),[a,c] %	**58.2 (45.5, 70.2)**	**81.7 (69.6, 90.5)**	**77.4 (65.0, 87.1)**
[n]	[39]	[49]	[48]
Median DoR (95% CI),[a] months	**NR (2.3, NA)**	**12.9 (6.7, NA)**	**NR (9.0, NA)**
Range	0.0+, 17.5+	0.0+, 16.9+	1.9+, 18.4+

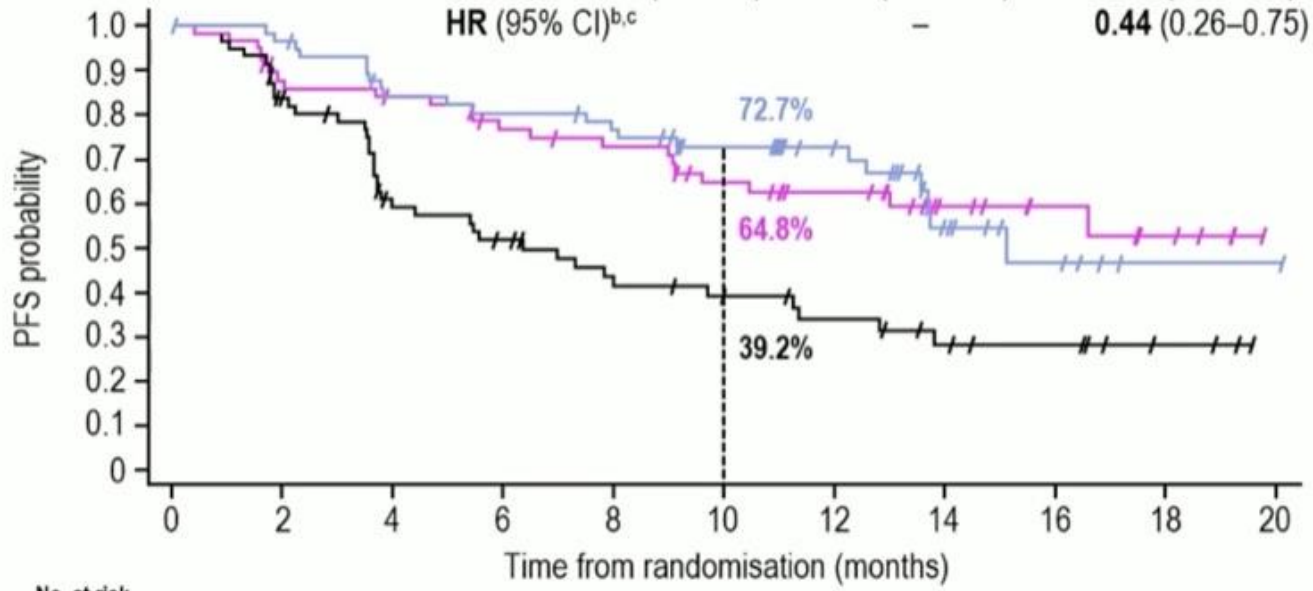
Data cutoff: 17 May 2021 (median follow-up of 11.5 months; range, 0.4–23.4)

[a]Confirmed and unconfirmed responses; [b]95% CI by Clopper-Pearson exact method; [c]DCR at 16 weeks = CR + PR + SD for ≥16 weeks

CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; NA, not applicable; NE, not evaluable; NR, not reached; ORR, objective response rate; PR, partial response; PD, progressive disease; SD, stable disease

PFS by investigator assessment
(interim analysis; ITT population)

	D	D+O	D+M
Events/patients, n	38/67	22/60	21/62
mPFS, months (95% CI)[a]	**6.3** (3.7–11.2)	**NR** (10.4–NE)	**15.1** (13.6–NE)
HR (95% CI)[b,c]	–	**0.44** (0.26–0.75)	**0.65** (0.49–0.85)



No. at risk											
D	67	50	32	32	20	16	13	9	7	3	0
D+O	60	49	46	40	37	30	22	13	9	5	0
D+M	62	55	46	44	41	35	25	11	6	1	1

Data cutoff: 17 May 2021 (median follow-up of 11.5 months; range, 0.4–23.4)

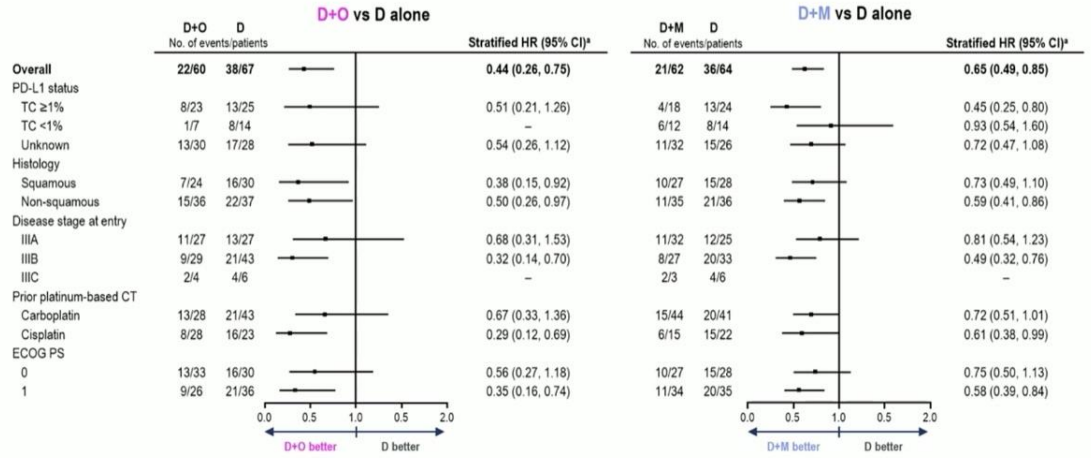
[a]Interim analysis was performed when all patients had a 10-month minimum potential follow-up; Kaplan-Meier estimates for PFS, PFS rate and 95% CIs

[b]PFS HR and 95% CI estimated by Cox regression model, stratified by histology (adenocarcinoma and non-adenocarcinoma)

[c]Compared with the 67 and 64 patients in the D arm enrolled concurrently with patients in the D+O and D+M arms, respectively

CI, confidence interval; HR, hazard ratio; ITT, intention to treat; mPFS, median PFS; NE, not estimable; NR, not reached

PFS subgroup analysis by investigator assessment
(interim analysis; ITT population)



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Data cutoff: 17 May 2021 (median follow-up of 11.5 months; range, 0.4–23.4)
[a]PFS HR and 95% CI estimated by Cox regression model, stratified by histology (adenocarcinoma and non-adenocarcinoma)

Safety summary
(as-treated population)

Incidence, n (%)	D (N=66)	D+O (N=59)	D+M (N=61)
Any TEAEs	65 (98.5)	57 (96.6)	61 (100)
Grade ≥3 TEAEs	26 (39.4)	24 (40.7)	17 (27.9)
Study drug-related AEs	49 (74.2)	46 (78.0)	50 (82.0)
Study drug-related SAEs	6 (9.1)	7 (11.9)	5 (8.2)
AEs leading to discontinuation	11 (16.7)	9 (15.3)	9 (14.8)
Deaths[a,b]	7 (10.6)	4 (6.8)	3 (4.9)

[a]All reported deaths within 90 days post-last dose, regardless of relationship to study drug
[b]In total, 4 deaths were related to study drug, 2 (pneumonitis and radiation pneumonitis) in the D arm, 1 (pneumonitis) in the D+O arm, and 1 (myocardial infarction) in the D+M arm

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Data cutoff: 17 May 2021 (median follow-up of 11.5 months; range, 0.4–23.4)
AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Pneumonitis:
D 18.2% vs D+0 20.3% vs D+M 18%

Real World Data: CANTO

To generate knowledge about a disease

Ines Vaz-Luis, ESMO Open. 2019; 4(5): e000562. Published online 2019 Sep 8. doi: 10.1136/esmoopen-2019-000562

Academia to generate data in a format meant for drug development

And not assume that medical care format is the sole driver of how data are generated, captured, and made accessible -

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GRACIAS

GECP lung cancer research

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