LUNG CANCER UPDATES

ESMO HIGHLIGHTS

19-23 DE OCTUBRE 2018, MUNICH

INMUNOTERAPIA II

Dra. Virginia Calvo

Iniciativa científica de:

GECP

Grupo Español de Cáncer de Pulmón

Spanish Lung Cancer Group

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IMpower130: efficacy and safety from a randomised phase 3 study of carboplatin and nab-paclitaxel with or without atezolizumab in 1L advanced non-squamous NSCLC

Federico Cappuzzo [1] Michael McCleod [2] Maen Hussein [3] Alessandro Morabito [4] Achim Rittmeyer [5]

IMpower130 study design

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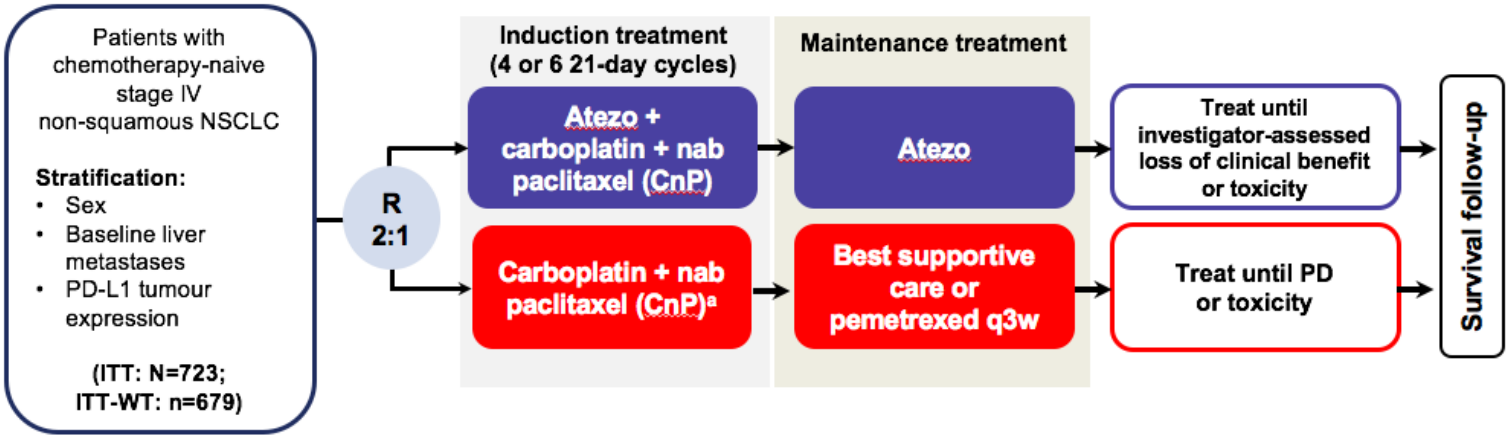

- **Co-primary endpoints:** investigator-assessed PFS
  - ITT-WT population: randomised patients excluding thos
- **Key secondary endpoints:** OS and PFS (ITT population and by PD-L1 expression), ORR and safety
  - ITT population could be formally tested for OS/PFS if ITT-WT OS was positive

20% Pemetrexed switch maintenance

Investigator-assessed PFS (ITT-WT)

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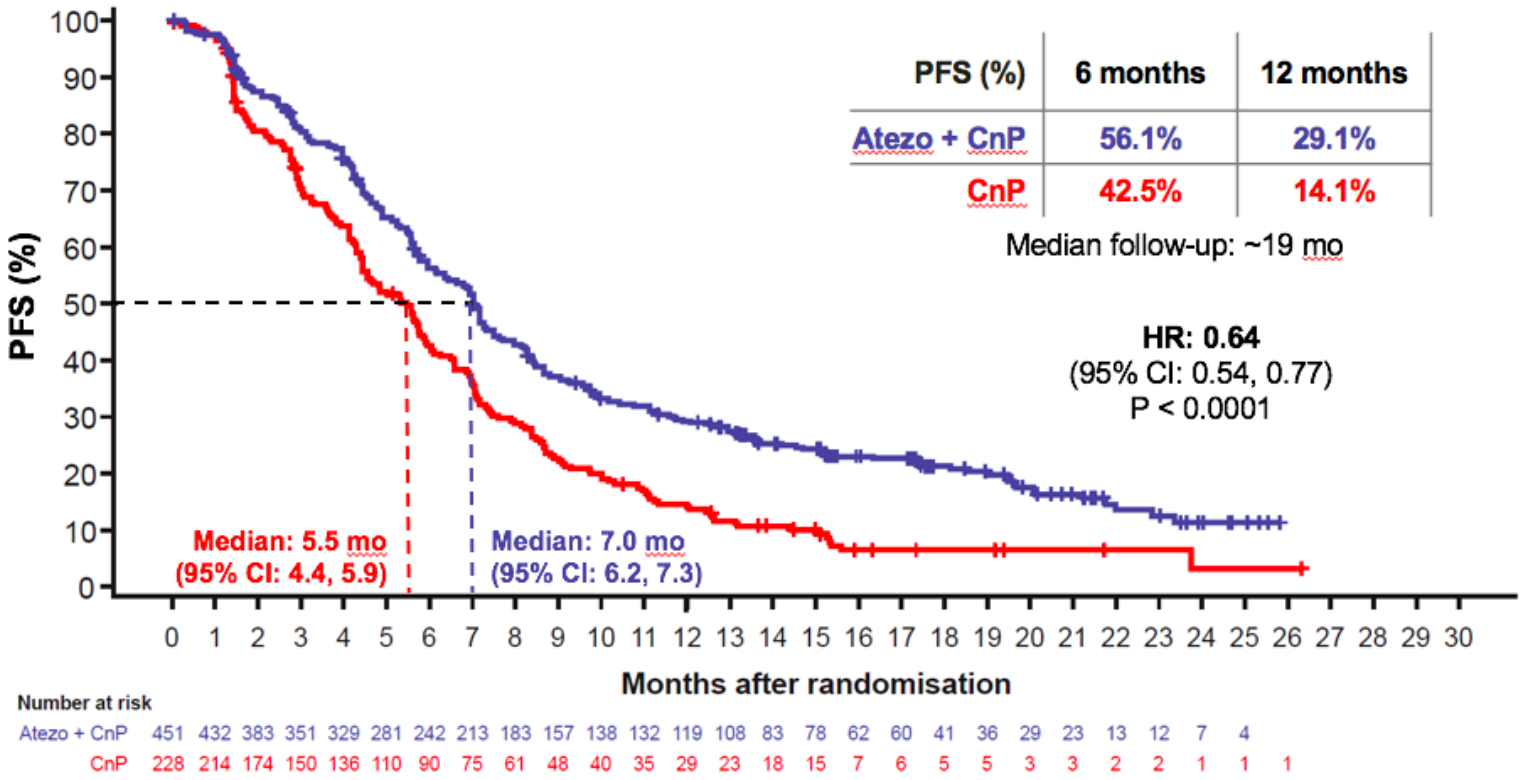

PFS (%)	6 months	12 months
Atezo + CnP	56.1%	29.1%
CnP	42.5%	14.1%

Median follow-up: ~19 mo

Cross over to immunotherapy 135 (59,2%)

OS (ITT-WT)

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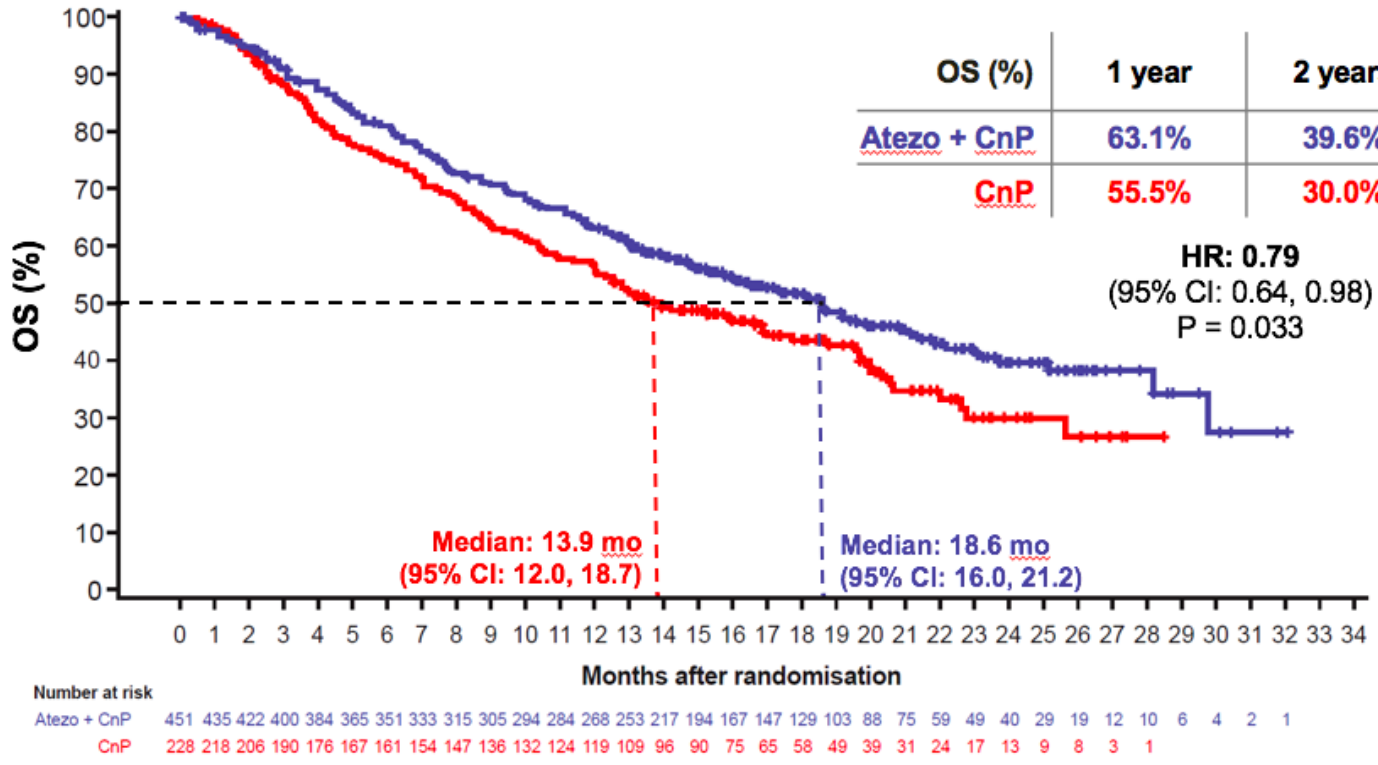

OS (%)	1 year	2 years
Atezo + CnP	63.1%	39.6%
CnP	55.5%	30.0%

Number at risk

Atezo + CnP	451	435	422	400	384	365	351	333	315	305	294	284	268	253	217	194	167	147	129	103	88	75	59	49	40	29	19	12	10	6	4	2	1
CnP	228	218	206	190	176	167	161	154	147	136	132	124	119	109	96	90	75	65	58	49	39	31	24	17	13	9	8	3	1				

LBA53. IMpower130. Progression-free survival (PFS) and safety analysis from a randomised phase 3 study of carboplatin + nab-paclitaxel (CnP) with o without atezolizumab (atezo) as first-line (1L) therapy in advanced non-squamous NSCLC

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PFS in key subgroups (ITT-WT)

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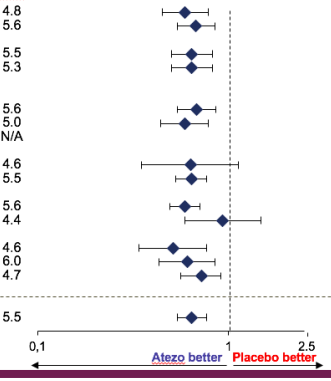
Population	n (%)	Median PFS (mo) Atezo + CnP	CnP	HR (95% CI)
Female	279 (41.1)	7.4	4.8	0.59 (0.45, 0.78)
Male	400 (58.9)	6.4	5.6	0.67 (0.54, 0.85)
<65 years	341 (50.2)	6.8	5.5	0.64 (0.5, 0.82)
≥65 years	338 (49.8)	7.2	5.3	0.64 (0.5, 0.82)
ECOG PS[a]				
0	280 (41.3)	7.9	5.6	0.59 (0.44, 0.78)
1	397 (58.6)	6.1	5.0	0.68 (0.54, 0.86)
2	1 (0.1)	N/A	N/A	N/A (N/A, N/A)
Never smoker	65 (9.6)	8.1	4.6	0.63 (0.35, 1.12)
Current/previous smoker	614 (90.4)	6.9	5.5	0.64 (0.53, 0.77)
No liver mets at enrolment	579 (85.3)	7.3	5.6	0.59 (0.49, 0.71)
Liver mets at enrolment	100 (14.7)	4.2	4.4	0.93 (0.59, 1.47)
PD-L1-high (TC3 or IC3)	130 (19.1)	6.4	4.6	0.51 (0.34, 0.77)
PD-L1-low (TC1/2 or IC1/2)	193 (28.4)	8.3	6.0	0.61 (0.43, 0.85)
PD-L1-negative (TC0 and IC0)	356 (52.4)	6.2	4.7	0.72 (0.56, 0.91)
ITT-WT	679 (100)	7.0	5.5	0.64 (0.54, 0.77)



OS in key subgroups (ITT-WT)

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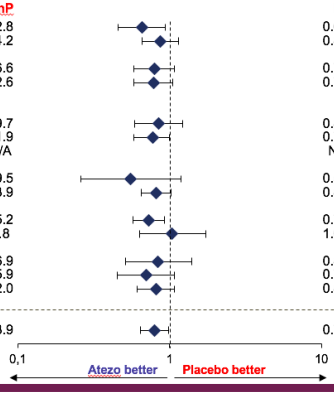
Population	n (%)	Median OS (mo) Atezo + CnP	CnP	HR (95% CI)
Female	279 (41.1)	21.4	12.8	0.66 (0.46, 0.93)
Male	400 (58.9)	16.0	14.2	0.87 (0.66, 1.15)
<65 years	341 (50.2)	19.2	16.6	0.79 (0.58, 1.08)
≥65 years	338 (49.8)	16.1	12.6	0.78 (0.58, 1.05)
ECOG PS[a]				
0	280 (41.3)	20.8	19.7	0.85 (0.59, 1.22)
1	397 (58.6)	15.2	11.9	0.77 (0.58, 1.00)
2	1 (0.1)	N/A	N/A	N/A (N/A, N/A)
Never smoker	65 (9.6)	28.2	19.5	0.55 (0.26, 1.19)
Current/previous smoker	614 (90.4)	18.1	13.9	0.81 (0.65, 1.02)
No liver mets at enrolment	579 (85.3)	21.1	15.2	0.73 (0.57, 0.92)
Liver mets at enrolment	100 (14.7)	10.0	8.8	1.04 (0.63, 1.72)
PD-L1-high (TC3 or IC3)	130 (19.1)	17.3	16.9	0.84 (0.51, 1.39)
PD-L1-low (TC1/2 or IC1/2)	193 (28.4)	23.7	15.9	0.70 (0.45, 1.08)
PD-L1-negative (TC0 and IC0)	356 (52.4)	15.2	12.0	0.81 (0.61, 1.08)
ITT-WT	679 (100)	18.6	13.9	0.79 (0.64, 0.98)



Confirmed ORR and DOR (ITT-WT)

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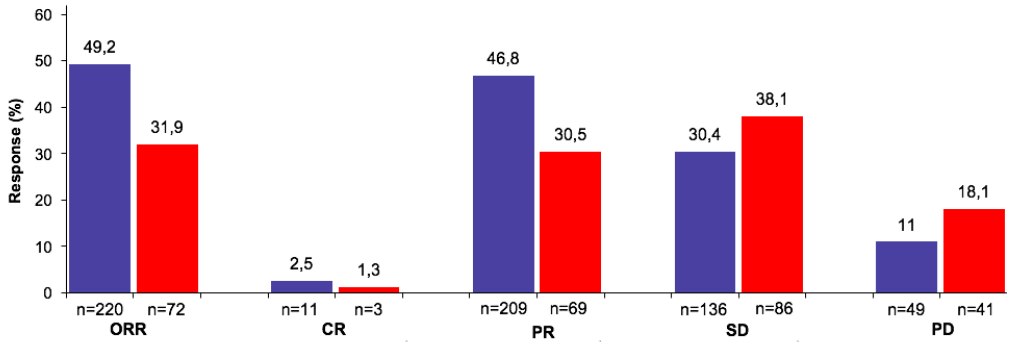

	Atezo+CnP (n=220)	CnP (n=72)
Median DOR, mo (95% CI)	8.4 (6.9, 11.8)	6.1 (5.5, 7.9)
P value (stratified)[a]	0.0004	
Ongoing response, n (%)	81 (36.8)	14 (19.4)

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Investigator-assessed PFS and OS in *EGFR/ALK*-positive subgroup

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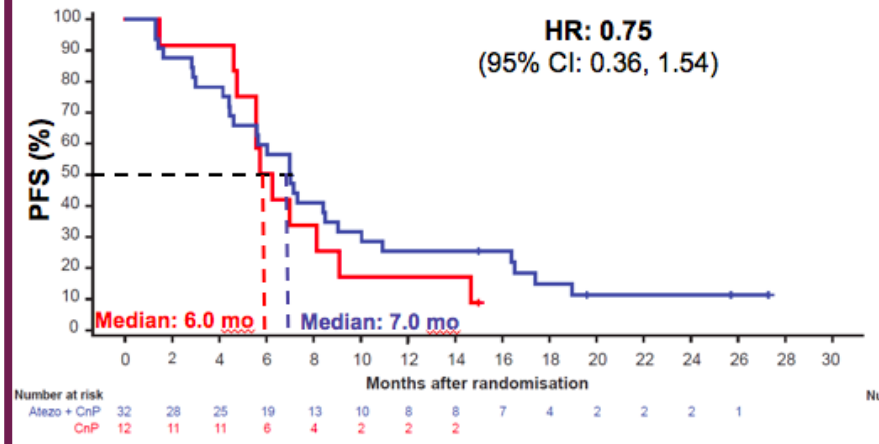

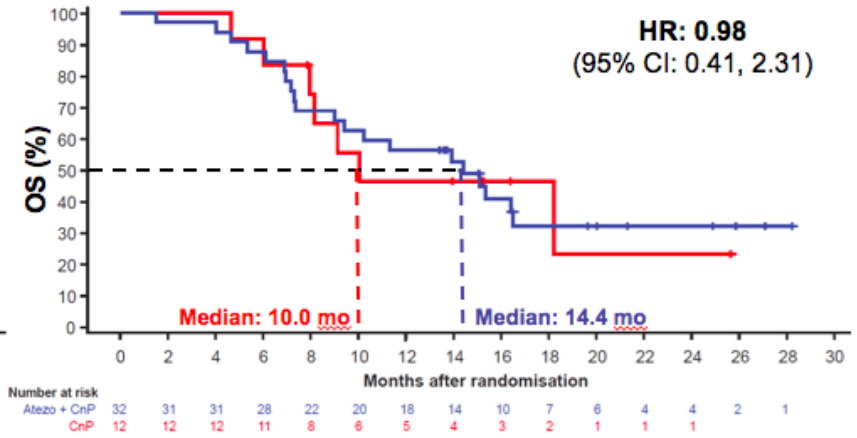

Benefit in this subgroup not confirmed

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PFS by baseline PD-L1 status (ITT-WT)

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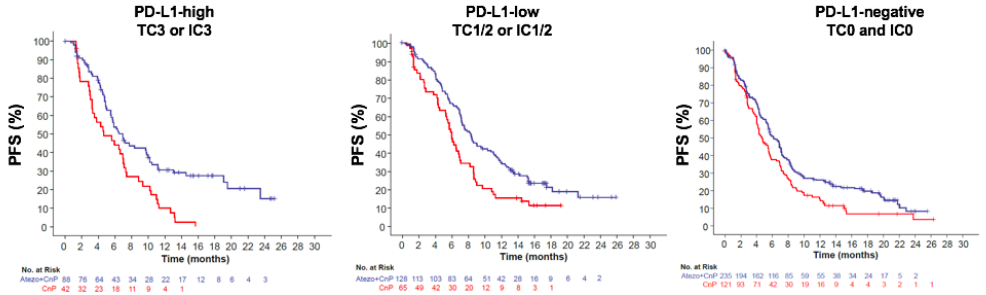

	Atezo + CnP (n=88)	CnP (n=42)	Atezo + CnP (n=128)	CnP (n=65)	Atezo + CnP (n=235)	CnP (n=121)
Median PFS, mo (95% CI)	6.4 (5.49, 9.76)	4.6 (3.22, 7)	8.3 (7.16, 10.35)	6.0 (5.29, 6.93)	6.2 (5.52, 7.16)	4.7 (4.11, 5.72)
HR (95% CI)	0.51 (0.34, 0.77)		0.61 (0.43, 0.85)		0.72 (0.56, 0.91)	

OS by baseline PD-L1 status (ITT-WT)

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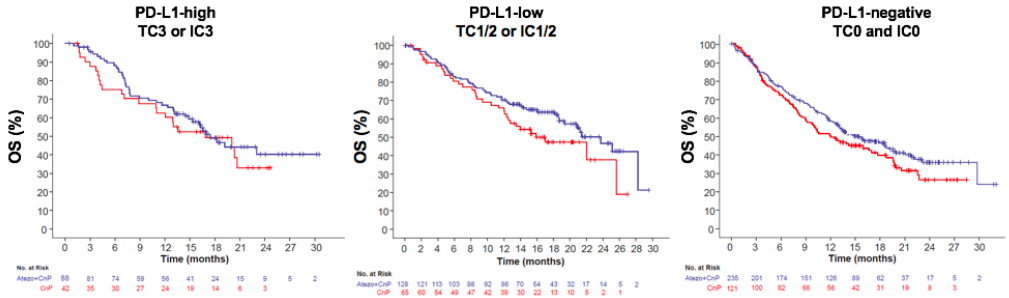

	Atezo + CnP (n=88)	CnP (n=42)	Atezo + CnP (n=128)	CnP (n=65)	Atezo + CnP (n=235)	CnP (n=121)
Median OS, mo (95% CI)	17.3 (14.78, N/A)	16.9 (10.94, N/A)	23.7 (18.63, N/A)	15.9 (12.32, 25.63)	15.2 (12.88, 19.15)	12.0 (8.97, 17.71)
HR (95% CI)	0.84 (0.51, 1.39)		0.70 (0.45, 1.08)		0.81 (0.61, 1.08)	

OS and PFS benefits were observed across all PD-L1 subgroups

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Safety summary

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	Atezo + CnP (n=473)	CnP (n=232)
Treatment duration, median (range), mo		
Nab-paclitaxel	2.8 (0–7)	2.7 (0–5)
Carboplatin	2.3 (0–6)	2.3 (0–5)
Atezolizumab	6.9 (0–32)	–
Pemetrexed	–	3.5 (0–16)
All-cause AE, n (%)	471 (99.6%)	230 (99.1%)
Grade 3–4	381 (80.5%)	164 (70.7%)
Grade 5	25 (5.3%)	13 (5.6%)
Treatment-related AE, n (%)[a]	455 (96.2%)	215 (92.7%)
Grade 3–4	346 (73.2%)	140 (60.3%)
Grade 5	8 (1.7%)	1 (0.4%)
Serious AE, n (%)	240 (50.7%)	88 (37.9%)
Treatment-related serious AE[a]	112 (23.7%)	30 (12.9%)
Treatment-related AEs of special interest, n (%)	168 (35.5%)	34 (14.7%)
Grade 3–4	24 (5.1%)	6 (2.6%)
Grade 5	3 (0.6%)	0
AE leading to any treatment withdrawal, n (%)	125 (26.4%)	51 (22.0%)
AE leading to any dose interruption or modification, n (%)	402 (85.0%)	186 (80.2%)

Atezo + CnP had a safety profile consistent with AEs associated with single-agent therapy
No new safety signals were identified

CONCLUSIONS

- IMpower130 met its co-primary PFS and OS endpoints and demonstrated a statistically significant and clinically meaningful benefit of 4.7 months' OS (and 1.5 months' PFS) for atezo plus chemotherapy in the ITT-WT population, compared with chemotherapy alone
  - OS and PFS benefits were observed across all PD-L1 subgroups
  - Outcomes in patients with *EGFR* or *ALK* genomic alterations suggest treatment benefit was mostly driven by the ITT-WT population
- Atezo plus chemotherapy had a safety profile consistent with AEs associated with single-agent therapy; no new safety signals were identified
- The IMpower130 results support atezo plus chemotherapy as a treatment option for patients with advanced non-squamous NSCLC, regardless of PD-L1 status

IMpower132: efficacy of atezolizumab + carboplatin/cisplatin + pemetrexed as 1L treatment in key subgroups with stage IV non-squamous NSCLC

Fabrice Barlesi,[1] Makoto Nishio,[2] Manuel Cobo,[3] Nicola Steele,[4] Victor Paramonov,[5]

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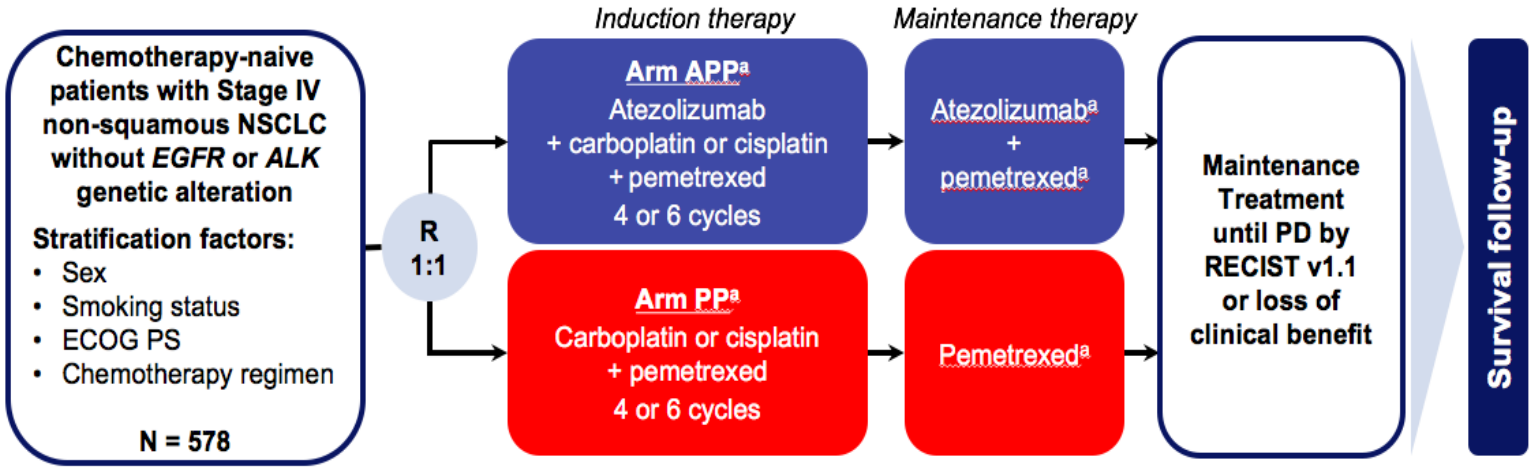
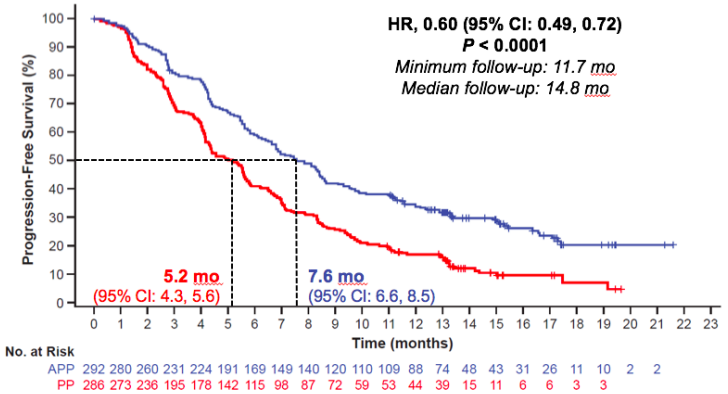
IMpower132 study design



- Co-primary endpoints: INV-assessed PFS and OS
- Secondary endpoints: INV-assessed ORR and DOR, PRO and safety measures
- Exploratory analyses: clinical and biomarker[b] subgroup analyses

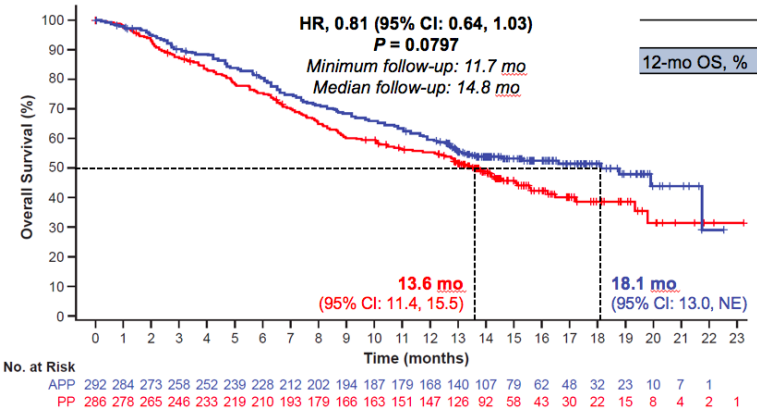
PFS in the ITT population[1]



	APP	PP
6-mo PFS, %	59%	41%
12-mo PFS, %	34%	17%
ORR, %	47%	32%
CR	2%	1%
PR	45%	32%
Median DOR, mo	10.1	7.2
Ongoing response, %	42%	30%

Clear improvement of PFS and OS adding Atezolizumab

Interim OS analysis in the ITT population[1]



	APP	PP
12-mo OS, %	59.6%	55.4%

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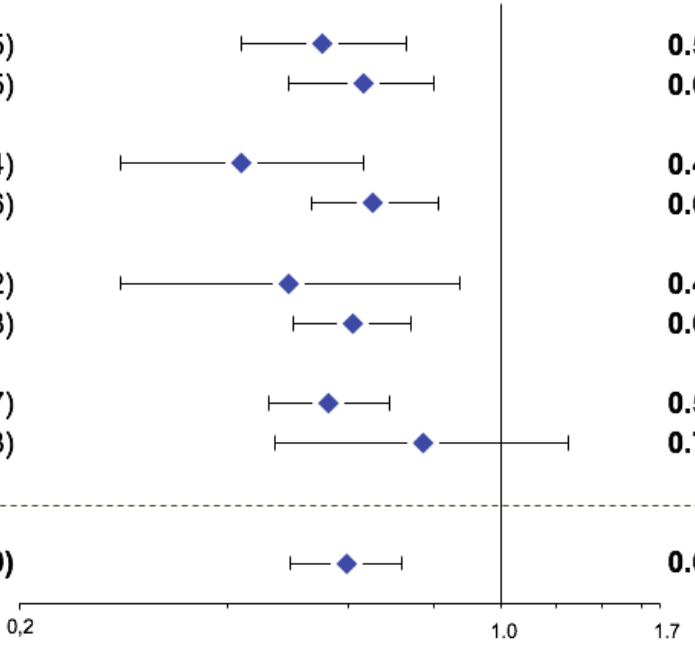
PFS in key patient subgroups[1]

Subgroup	n (%)	HR (95% CI)[a]	Median PFS, mo	
			APP	PP
≥ 65 years	258 (45)	**0.55** (0.42, 0.73)	8.4	5.6
< 65 years	320 (55)	**0.63** (0.49, 0.80)	6.9	4.4
Asian	136 (24)	**0.42** (0.28, 0.63)	10.2	5.3
Non-Asian	442 (76)	**0.65** (0.53, 0.81)	6.9	5.0
Never smoker	67 (12)	**0.49** (0.28, 0.87)	8.6	5.5
Current or former smoker	511 (88)	**0.61** (0.50, 0.74)	7.5	5.1
No liver metastases	505 (87)	**0.56** (0.46, 0.69)	8.4	5.5
Liver metastases	73 (13)	**0.77** (0.47, 1.25)	4.4	4.0
ITT population	**578 (100)**	**0.60 (0.49, 0.72)**	**7.6**	**5.2**



APP, atezolizumab + carboplatin/cisplatin + pemetrexed; PP, carboplatin/cisplatin + pemetrexed. [a] Stratified HR for ITT; unstratified for all other subgroups.

PFS in former/current and never smokers

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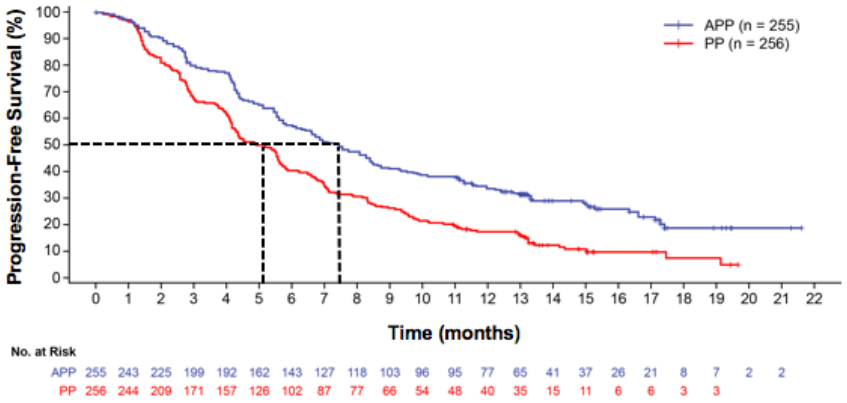
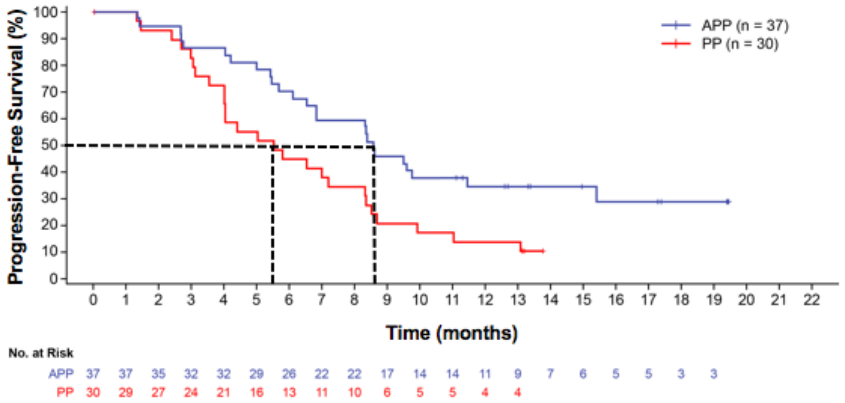
	Former/current smokers		Never smokers	
	APP	PP	APP	PP
Median PFS (95% CI), mo	7.5 (6.3, 8.4)	5.1 (4.3, 5.6)	8.6 (6.5, 15.4)	5.5 (4.0, 8.3)
HR (95% CI)	0.61 (0.50, 0.74)		0.49 (0.28, 0.87)	





The percentage of Asian patients was 21% among smokers and 40% among non-smokers

PFS in patients without/with liver metastases

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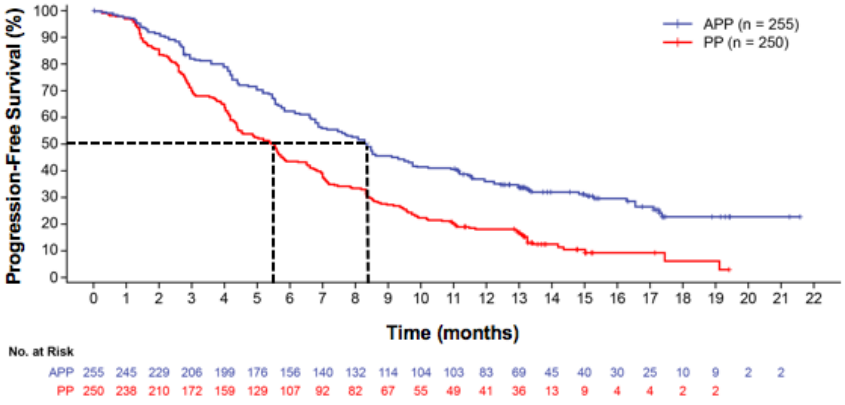
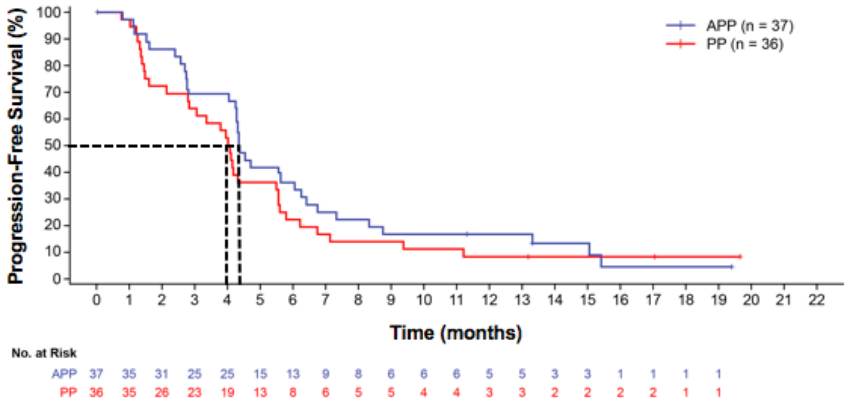
	Patients without liver metastases		Patients with liver metastases	
	APP	PP	APP	PP
Median PFS (95% CI), mo	8.4 (7.0, 9.5)	5.5 (4.4, 5.9)	4.4 (4.2, 6.0)	4.0 (2.8, 5.5)
HR (95% CI)	0.56 (0.46, 0.69)		0.77 (0.47, 1.25)	





CONCLUSIONS

- The addition of atezolizumab to carboplatin/cisplatin and pemetrexed resulted in statistical and clinically relevant improvement in PFS in the ITT population
- PFS improvements were observed in key clinical subgroups, including patients who were from Asia, never smokers, older and without liver metastases at baseline
- Although the efficacy boundary has not been crossed for OS, numerical improvements were observed in the ITT population (mOS improvement of 4.5 months) and in key subgroups
- Further analyses may provide insights into the causes underlying these results to improve knowledge and future treatment options for patients

B-F1RST: Study design

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Patients with stage IIIb-IVa[a] locally advanced or metastatic NSCLC (any histology; N = 152[b]) → **Atezolizumab 1200 mg IV q3w** → **Until PD, unacceptable toxicity or loss of clinical benefit**

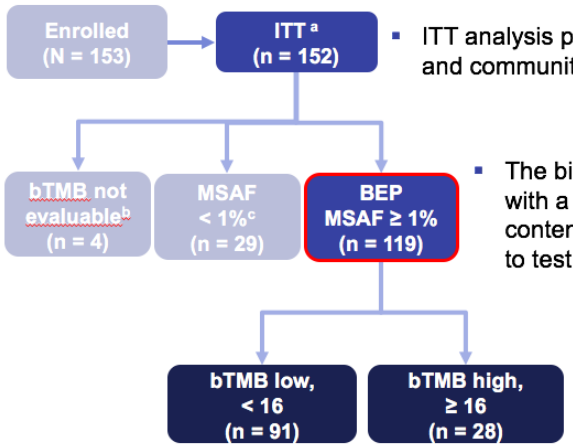
Inclusion Criteria
- Measurable disease per RECIST v1.1
- ECOG PS of 0 or 1
- Immunotherapy naive
- PD-L1 unselected
- Provision of blood[c]

Exclusion Criteria
- Sensitizing *EGFR* mutations or *ALK* rearrangements
- Active brain metastases requiring treatment

Primary analysis
- All enrolled patients with at least 6 months of follow-up
- Prespecified bTMB biomarker cutoff of 16

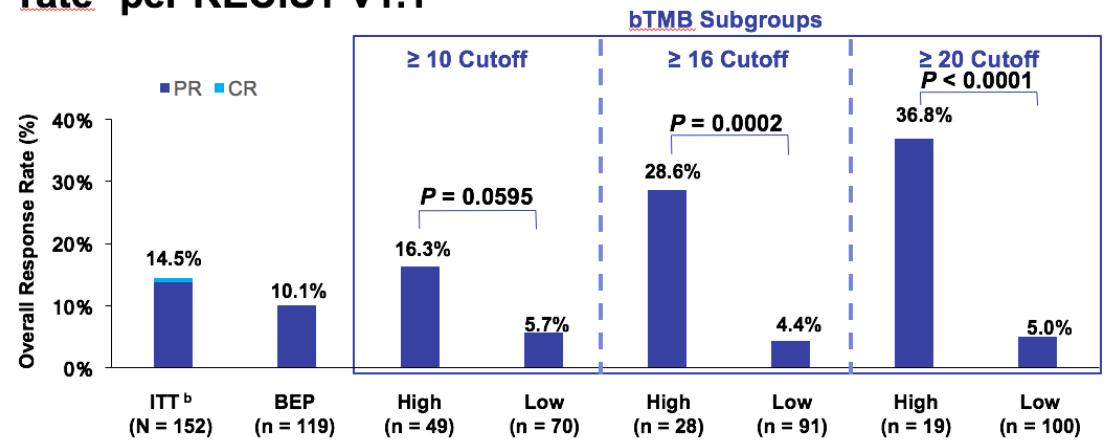
Co-Primary Endpoints
- Efficacy endpoint: INV-assessed ORR per RECIST v1.1
- Biomarker endpoint: INV-assessed PFS per RECIST v1.1

Secondary Objectives
- Safety and assessment of efficacy by INV-assessed DOR, OS



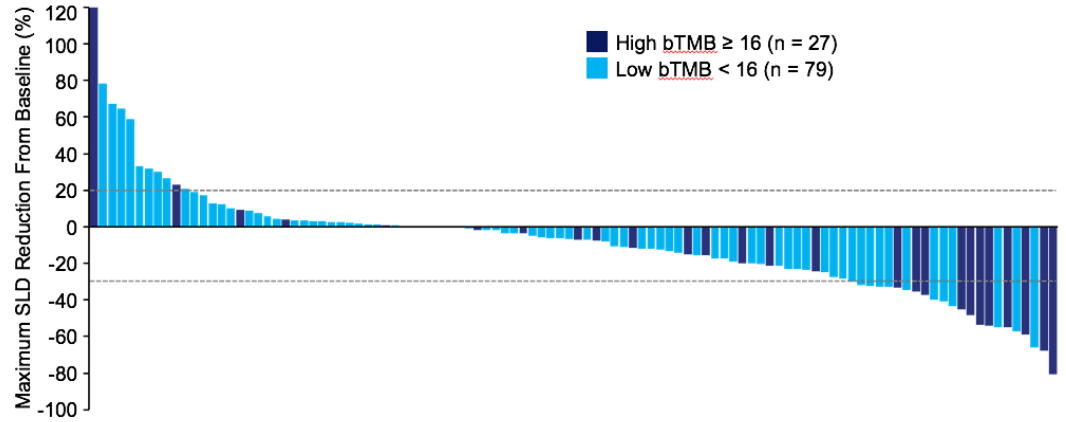
- ITT analysis population enrolled from 20 US regional and community practice sites
- The biomarker-evaluable population (BEP) included patients with a baseline evaluable blood sample with adequate tumour content (i.e., maximum somatic allele frequency [MSAF] ≥ 1%) to test on the FMI bTMB assay
- The bTMB cutoff score of 16 was prespecified to evaluate efficacy (bTMB high, ≥ 16; bTMB low, < 16)

B-F1RST: Atezolizumab overall response rate[a] per RECIST v1.1



Minimum follow-up: 6 months

B-F1RST: Maximum SLD reduction from baseline in bTMB ≥ 16 and bTMB < 16 subgroups



LBA55. Primary efficacy results from B-F1RST, a prospective phase II trial evaluating blood-based tumour mutational burden (bTMB) as a predictive biomarker for atezolizumab (atezo) in 1L non-small cell lung cancer (NSCLC)

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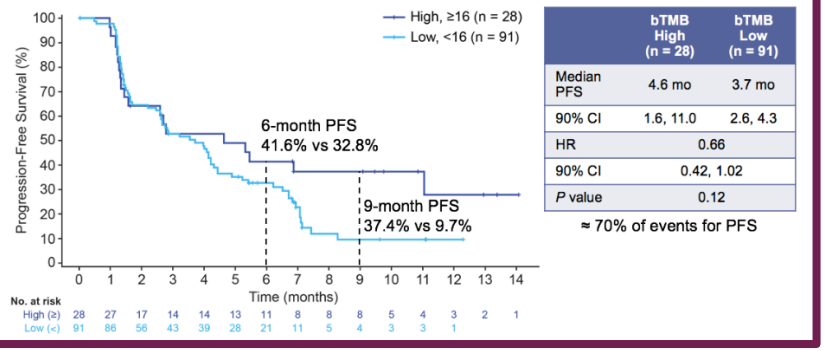
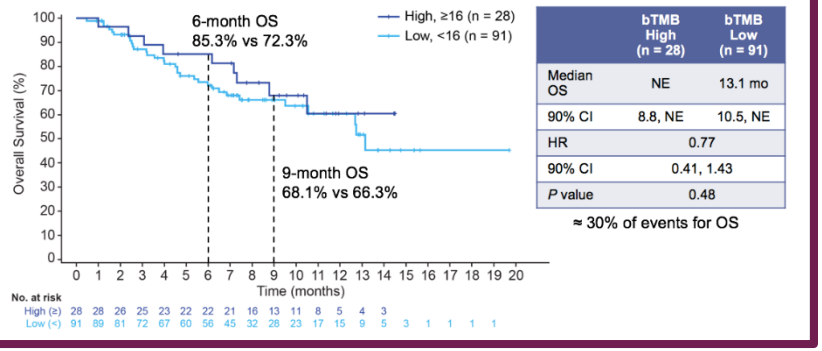
B-F1RST: PFS with atezolizumab in bTMB high (≥ 16) vs low (< 16) subgroups



	bTMB High (n = 28)	bTMB Low (n = 91)
Median PFS	4.6 mo	3.7 mo
90% CI	1.6, 11.0	2.6, 4.3
HR	0.66	
90% CI	0.42, 1.02	
P value	0.12	

≈ 70% of events for PFS

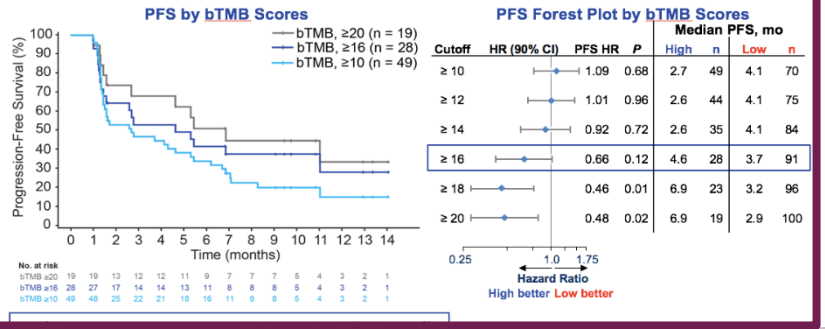
B-F1RST: OS with atezolizumab in bTMB high (≥ 16) vs low (< 16) subgroups



	bTMB High (n = 28)	bTMB Low (n = 91)
Median OS	NE	13.1 mo
90% CI	8.8, NE	10.5, NE
HR	0.77	
90% CI	0.41, 1.43	
P value	0.48	

≈ 30% of events for OS

B-F1RST: PFS by various bTMB cutoffs

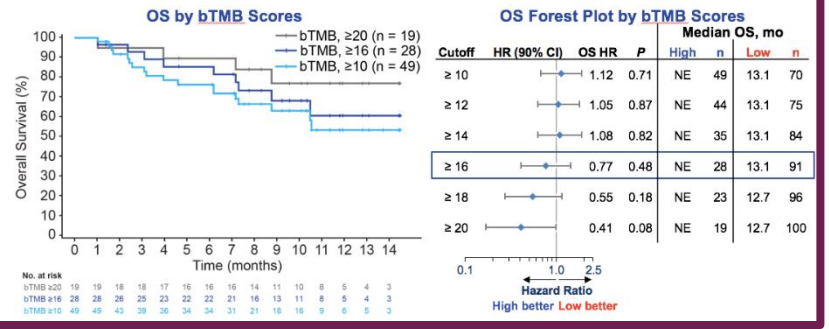


PFS Forest Plot by bTMB Scores

Cutoff	HR (90% CI)	PFS HR	*P*	Median PFS, mo High	n	Low	n
≥ 10		1.09	0.68	2.7	49	4.1	70
≥ 12		1.01	0.96	2.6	44	4.1	75
≥ 14		0.92	0.72	2.6	35	4.1	84
≥ 16		0.66	0.12	4.6	28	3.7	91
≥ 18		0.46	0.01	6.9	23	3.2	96
≥ 20		0.48	0.02	6.9	19	2.9	100

0.25 1.0 1.75
Hazard Ratio
High better Low better

B-F1RST: OS by various bTMB cutoffs



OS Forest Plot by bTMB Scores

Cutoff	HR (90% CI)	OS HR	*P*	Median OS, mo High	n	Low	n
≥ 10		1.12	0.71	NE	49	13.1	70
≥ 12		1.05	0.87	NE	44	13.1	75
≥ 14		1.08	0.82	NE	35	13.1	84
≥ 16		0.77	0.48	NE	28	13.1	91
≥ 18		0.55	0.18	NE	23	12.7	96
≥ 20		0.41	0.08	NE	19	12.7	100

0.1 1.0 2.5
Hazard Ratio
High better Low better

PFS and OS improvement were seen with increasing bTMB cutoffs

Iniciativa científica de:
GECP
Grupo Español de Cáncer de Pulmón
Spanish Lung Cancer Group

CONCLUSIONS

- B-F1RST is the first prospective evaluation of bTMB as a predictive biomarker for patients with NSCLC receiving 1L atezolizumab monotherapy
- These primary data suggest that a bTMB cutoff score of ≥ 16 showed a numerical improvement in clinical outcomes in patients with NSCLC treated with atezolizumab monotherapy:
  - Median PFS in bTMB high vs low subgroups, 4.6 vs 3.7 months (HR, 0.66 [90% CI: 0.42, 1.02]; *P* = 0.12)
  - Confirmed ORR of 28.6% and 4.4% (*P* = 0.0002) was observed in the bTMB high (≥ 16) and low (< 16) subgroups, respectively
  - Median OS in the bTMB high vs low subgroups was NE vs 13.1 months (HR, 0.77 [90% CI, 0.41-1.43]; *P* = 0.48) and will continue to be followed
- Atezolizumab was well tolerated, and no new safety signals were observed
- bTMB is being validated in a prospective, randomised Phase III study

13780. ARCTIC: Durvalumab + Tremelimumab and Durvalumab monotherapy vs SoC in ≥ 3L advanced NSCLC treatment

ARCTIC study design: a Phase 3, global, randomised, open-label, multicentre study

- Stage IIIB/IV NSCLC
- ≥2 prior systemic treatments, including platinum-doublet CT
- Immunotherapy-naïve
- WHO PS 0/1
- *EGFR/ALK* wildtype

Study A
PD-L1 TC ≥25%*

R 1:1

- **Durvalumab** 10 mg/kg q2w for up to 12 mo
- **SoC†** Erlotinib, gemcitabine or vinorelbine

Stratification:
- Planned SoC (erlotinib vs gemcitabine/ vinorelbine)
- Histology (squamous vs non-squamous)

R 3:2:2:1

Study B
PD-L1 TC <25%*

- **Durvalumab + tremelimumab** D 20 mg/kg + T 1 mg/kg q4w for 12 wks followed by D 10 mg/kg q2w for 34 wks
- **SoC†** Erlotinib, gemcitabine or vinorelbine
- **Durvalumab** 10 mg/kg q2w for up to 12 mo
- **Tremelimumab** 10 mg/kg q4w for 24 wks followed by q12w for 24 wks

Primary endpoints
- OS
- PFS‡

Key secondary endpoints
- 1-year OS and PFS‡ rates
- ORR‡
- Safety

CT, chemotherapy; D, durvalumab; DCO, data cut-off; i.v., intravenous; mo, months; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; q24-12w, every 24-12 weeks; QD, once daily; SoC, standard of care; T, tremelimumab; TC, tumour cell; WHO PS, World Health Organization performance status; wks, weeks

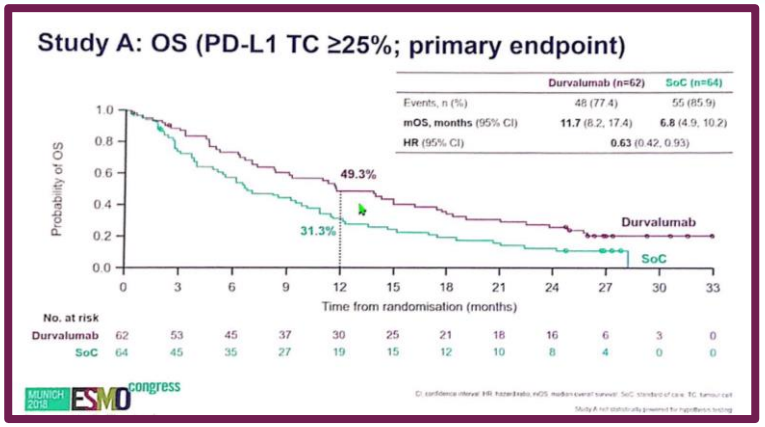
*Central assessment (Ventana PD-L1 [SP263] assay) of newly acquired or archival (≤3 years) tumour biopsy

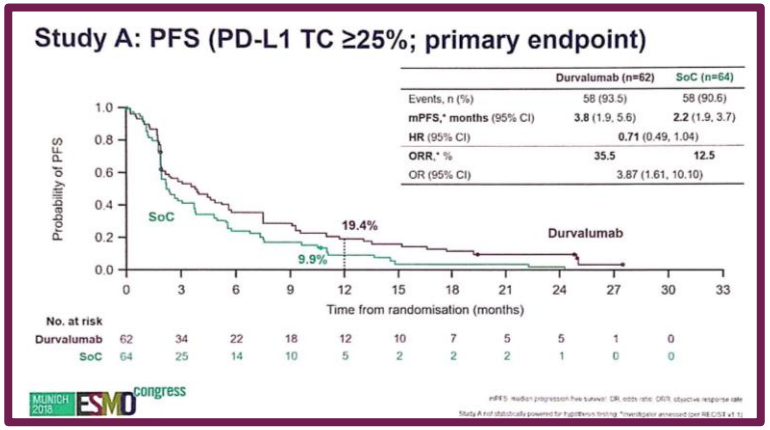
†Erlotinib 150 mg QD PO; gemcitabine 1000 mg/m² i.v. (days 1, 8 and 15 of a 28-day cycle) or vinorelbine 30 mg/m² i.v. (days 1, 8, 15 and 22 of a 28-day cycle) until progression; ‡investigator assessed (per RECIST v1.1); DCO 9 February 2018

MUNICH 2018 ESMO congress

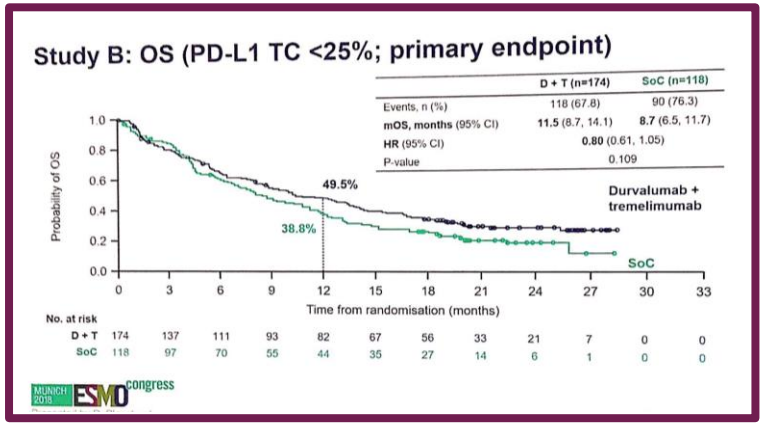
Presented by: D. Planchard

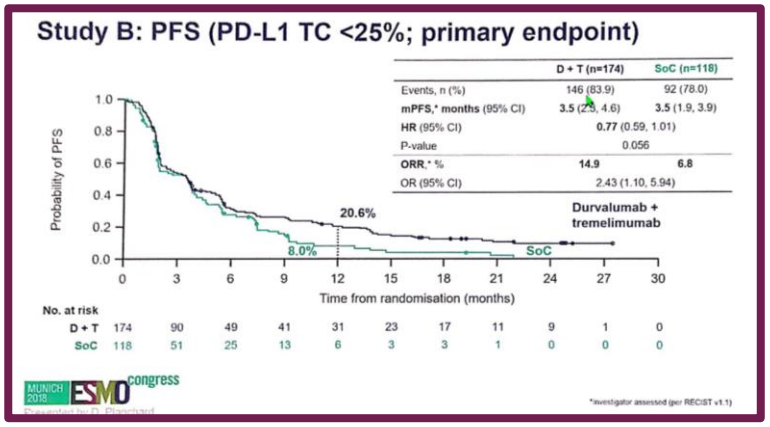
13780. ARCTIC: Durvalumab + Tremelimumab and Durvalumab monotherapy vs SoC in ≥ 3L advanced NSCLC treatment





PD-L1 TC ≥25%: Durvalumab monotherapy resulted in a clinically meaningful improvement in OS vs SoC with 49.3% vs 31.3% of patients alive at 1 year





PD-L1 TC <25%: Durvalumab + Tremelimumab demonstrated a non-significant numerical improvement in OS vs SoC with 49.5% vs 38.8% of patients alive at 1 year

CONCLUSIONS

- ARCTIC demonstrated activity with both Durvalumab and Durvalumab + Tremelimumab in a heavily pretreated patient population with advanced/metastatic NSCLC
- Durvalumab and Tremelimumab had an acceptable toxicity profile
- Incorporation of TMB along with PD-L1 in the assessment of benefit may be useful
- Await Phase 3 MYSTIC OS data