Lung Cancer UPDATES
IASLC HIGHLIGHTS
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Iniciativa científica de:
GECP
lung cancer research

CNMP Localmente Avanzado

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TERAPIAS DIRIGIDAS

Interim Analysis of the Phase III POLESTAR Study: Aumolertinib after CRT unresectable Stage III NSCLC EGFRm after definitive CRT

PL 04.1. Meng X, et al

Iniciativa científica de: GECP lung cancer research

2024 World Conference on Lung Cancer | SEPTEMBER 7-10, 2024 | SAN DIEGO, CA USA | #WCLC24 wclc2024.iaslc.org

Screening Period

Key inclusion criteria:
- ≥18 years
- ECOG score 0 / 1
- EGFR Ex19del / L858R
- Locally advanced, unresectable stage III* NSCLC
- No progression during or following definitive CRT# treatment
- Interval between last dose of CRT and randomization: ≤6 weeks

Treatment Period

2 : 1

Aumolertinib 110mg QD; (N=94)

Placebo 110mg QD; (N=53)

N=147
Stratification by
- Ex19del vs L858R
- Stage IIIA vs Stage IIIB/IIIC
- cCRT vs sCRT

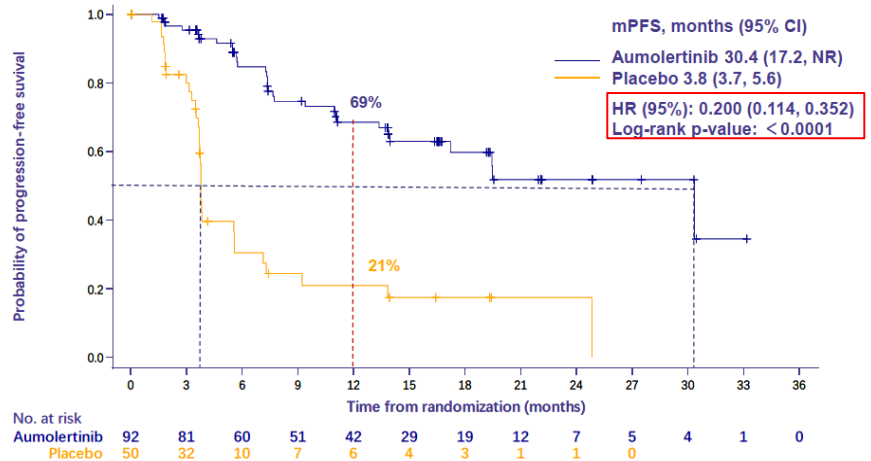
- Treatment duration until BICR-assessed progression (per RECIST v1.1), toxicity, or other discontinuation criteria
- Tumor assessment: every 8 weeks to week 48, then every 12 weeks until progression
- Crossover[5] is allowed for patients in placebo arm

- **Primary endpoint:** PFS assessed by BICR (sensitivity analysis: PFS assessed by Investigator)
- **Secondary endpoints:** OS, ORR, DCR, DoR, CNS PFS, TTDM, Safety

* According to AJCC / UICC staging (8th edition)

PFS by BICR Assessment

- Median follow-up of PFS was 16.36 months (0–33.2) for aumolertinib and 13.93 months (0–24.8) for placebo.
- PFS HR (95% CI) by BICR analyzed with Cox proportional hazards regression was 0.200 (0.114, 0.352).
- PFS HR (95% CI) by BICR analyzed with a log rank test was 0.135 (0.070, 0.258), which is a sensitivity analysis.

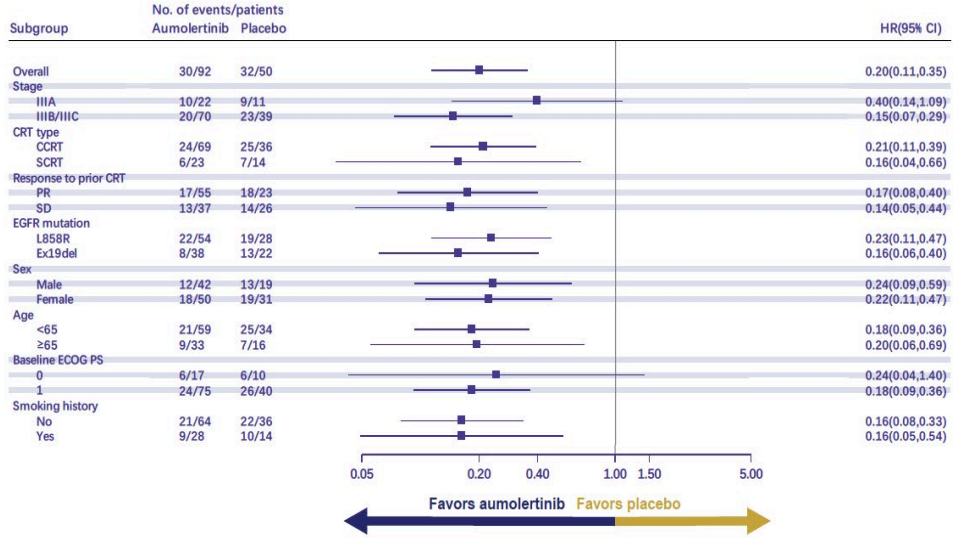


Abbreviations: PFS, progression free survival; BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NR, not reach.

Data cut-off: February 5, 2024.

PFS by BICR Across Subgroups

- PFS benefit favoring aumolertinib was consistent across predefined subgroups.



Abbreviations: CCRT, concurrent chemoradiotherapy; SCRT, sequential chemoradiotherapy

Data cut-off: February 5, 2024.

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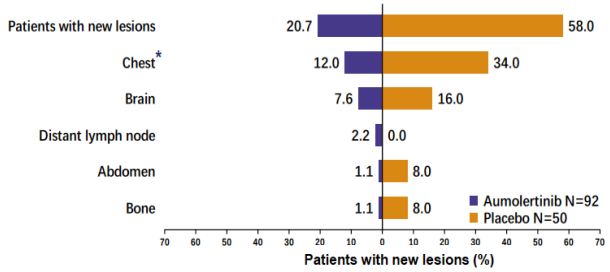
OS and New lesions by BICR

- Median follow-up of OS was 16.6 months (range 1.5–33.2) for aumolertinib and 14.9 months (range 0.4–31.4) for placebo.
- Median OS (9.8% maturity for aumolertinib and 6.0% maturity for placebo) was not reached in either group.
- Lower incidences of CNS lesions and distant metastases were observed in aumolertinib arm than in the placebo arm.



Endpoint	Aumolertinib (N=92)	Placebo (N=50)	HR, 95% CI) p value
Median CNS PFS#, months (95% CI)	NR (NR, NR)	NR (NR, NR)	0.33 (0.12-0.92) p=0.0270
Median TTDM§, months (95% CI)	NR (NR, NR)	NR (3.84, NR)	0.21 (0.09, 0.49), p<0.0001

CNS PFS: survival without progression of CNS disease.

§ TTDM: time to death or distant metastasis.

* Chest: including lungs and N1~N3 regional lymph node lesions.

Abbreviations: OS, overall survival; CI, confidence interval; NR, not reach; HR, Hazard ratio.

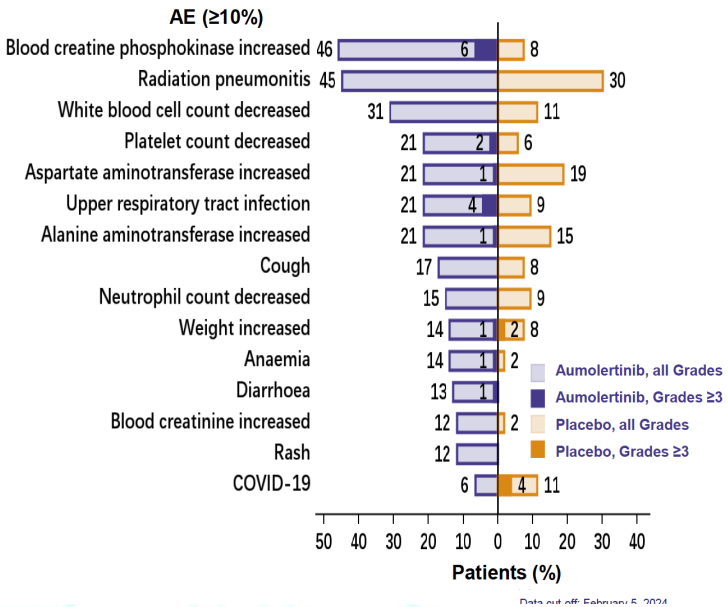
Data cut-off: February 5, 2024.

Safety

- The most common AE for aumolertinib was blood creatine phosphokinase increased; majority of the AEs were <Grade 3.
- Radiation pneumonitis was reported in 45% vs 30% for aumolertinib vs placebo, with none being Grade ≥3.
- Interstitial lung disease was not reported for aumolertinib, but reported in 1 patient (Grade 3) for placebo.

TRAE*, n (%)	Aumolertinib (N=94)	Placebo (N=53)
Any AE	79 (84.0)	23 (43.4)
Any Grade≥3 AE	9 (9.6)	1 (1.9)
Any SAE	6 (6.4)	1 (1.9)
AE leading to death	0	0
AE leading to treatment interruption	13 (13.8)	0
AE leading to treatment reduction	4 (4.3)	0
AE leading to treatment discontinuation	2 (2.1)	1 (1.9)

* TRAE: treatment-related adverse event.



CONCLUSIONES

- Aumolertinib mostró un aumento significativo en PFS comparado con placebo: mPFS (30.4 m vs 3.8 m; HR 0.200 (95% CI 0.114, 0.352), p<0.0001.
- El Beneficio en PFS fue consistente en todos los subgrupos predefinidos
- Aumolertinib fue bien tolerado y la toxicidad fue manejable
- Aumolertinib es una nueva opción para pacientes con CNMP estadio III irresecable EGFRm tras el tratamiento con quimioradioterapia

TERAPIAS DIRIGIDAS

Phase 3 LAURA study: Osimertinib after definitive CRT in unresectable stage III EGFRm NSCLC: Safety outcomes. OA12.3. Kato T, et al

Iniciativa científica de: GECP lung cancer research

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LAURA Phase 3 double-blind study design (NCT03521154)

Patients with locally advanced, unresectable stage III* EGFRm NSCLC with no progression during / following definitive CRT†

Key inclusion criteria:
- ≥18 years old (Japan: ≥20 years)
- WHO PS 0 / 1
- Confirmed locally advanced, unresectable stage III* NSCLC
- Ex19del / L858R‡
- Max 6 weeks from last dose of CRT to randomization
- **Patients with asymptomatic radiation pneumonitis / pneumonitis post-CRT were eligible**

Osimertinib 80 mg, QD

Randomization 2:1 (N=216)

Stratification by:
cCRT vs sCRT
Stage IIIA vs stage IIIB / IIIC
China vs non-China

Placebo, QD

Treatment until BICR-assessed PD (per RECIST v1.1), toxicity, or other discontinuation criteria met

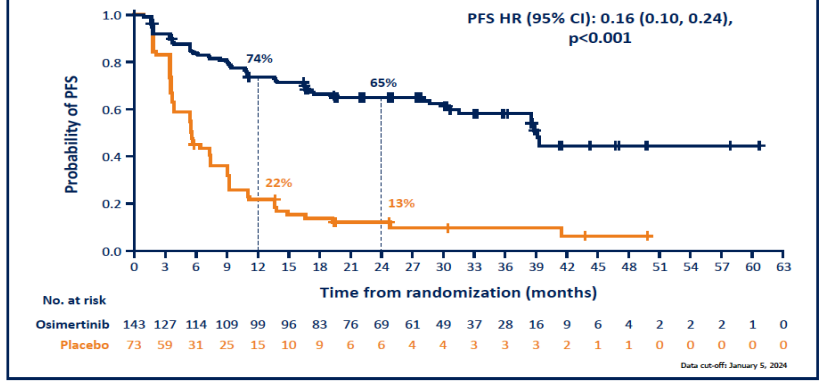
Open-label osimertinib offered to both treatment arms after BICR-confirmed PD§

Tumor assessments
- Chest CT / MRI and brain MRI
- Baseline, Q8W to Week 48, then Q12W until BICR-assessed progression

Safety assessments
- Baseline, Weeks 2, 4 and Q4W to Week 24, Q8W to Week 48, then Q12W until treatment discontinuation
  - Reporting of AEs and causality were investigator-assessed
- All AEs, SAEs and AESIs reported from screening to 28-day follow-up post-discontinuation

Endpoints
- **Primary endpoint:** PFS assessed by BICR per RECIST v1.1
- **Secondary endpoints included:** OS, CNS PFS, **safety**

LAURA primary analysis[7]



Safety summary by age

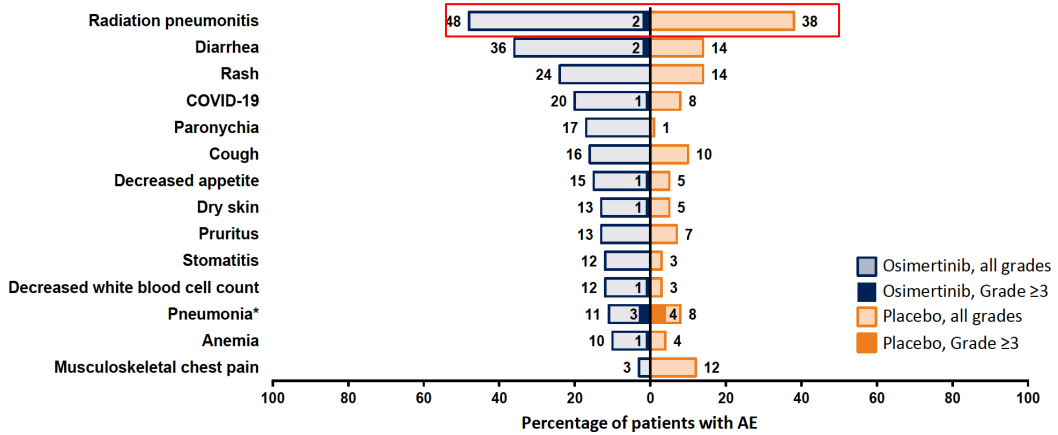
- At data cut-off, median total and actual exposures were 24.0 and 23.7 months (osimertinib) and 8.3 and 7.9 months (placebo)
  - This indicated that frequency and duration of dose interruptions had little impact on osimertinib exposure
- The safety profile between younger (<65 years) and older (≥65 years) patients was similar across treatment arms

	Osimertinib (n=143)			Placebo (n=73)		
AE, any cause,* n (%)	**Overall (n=143)[1]**	**<65 years (n=81)**	**≥65 years (n=62)**	**Overall (n=73)[1]**	**<65 years (n=39)**	**≥65 years (n=34)**
Any AE	140 (98)	79 (98)	61 (98)	64 (88)	32 (82)	32 (94)
Any AE Grade ≥3	50 (35)	27 (33)	23 (37)	9 (12)	5 (13)	4 (12)
Any AE leading to death	3 (2)	1 (1)	2 (3)	2 (3)	0	2 (6)
Any SAE	55 (38)	30 (37)	25 (40)	11 (15)	6 (15)	5 (15)
Any AE leading to dose interruption	80 (56)	47 (58)	33 (53)	18 (25)	11 (28)	7 (21)
Any AE leading to dose reduction	12 (8)	3 (4)	9 (15)	1 (1)	0	1 (3)
Any AE leading to discontinuation	18 (13)	7 (9)	11 (18)	4 (5)	1 (3)	3 (9)

Data cut-off: January 5, 2024.
Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the discontinuation of study treatment and on or before starting subsequent cancer therapy.
*Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.
1. Lu et al. N Engl J Med 2024;391:585-597.
AE, adverse event; SAE, serious AE

All-causality AEs (≥10%)

- Most common AEs were as expected for patients who had received prior CRT (radiation pneumonitis) or osimertinib treatment (diarrhea and rash)



Data cut-off: January 5, 2024.
AEs with incidence of ≥10% in either arm shown. Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.
Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the discontinuation of study treatment and before starting subsequent cancer therapy.
*One Grade 5 AE of pneumonia was reported in a patient in the osimertinib arm.
Lu et al. N Engl J Med 2024;391:585-597.
AE, adverse event; COVID-19, coronavirus disease 2019; CRT, chemoradiotherapy

Terufumi Kato | Osimertinib after definitive CRT in unresectable stage III EGFRm NSCLC: Safety outcomes from the Phase 3 LAURA study

TERAPIAS DIRIGIDAS

Phase 3 LAURA study: Osimertinib after definitive CRT in unresectable stage III EGFRm NSCLC: Safety outcomes. OA12.3. Kato T, et al

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Pneumonitis in LAURA Study in context

Radiation pneumonitis, n (%)	Osimertinib (n=143)	Placebo (n=73)
Total	69 (48)	28 (38)
Grade 1	22 (15)	14 (19)
Grade 2	44 (31)	14 (19)
Grade 3	3 (2)	0
CTCAE Grade ≥3	3 (2)	0
SAE	15 (10)	2 (3)
Discontinuations	7 (5)	2 (3)

Rates of Radiation Pneumonitis

Trial	Grade 1-2	Grade ≥ 3
LAURA (Osi Arm)	46%	2%
RTOG 0617: 3D-CRT	-	7.9%
RTOG 0617: IMRT	-	3.5%
Pacific (Control)	15.4%	0.4%
Pacific (Test)	18.7%	1.5%

Chun SG, et al. J Clin Oncol 35:56-62
Antonia SJ, et al. N Engl J Med 2018;379:2342-50

Pneumonitis vs ILD in LAURA

Radiation pneumonitis, n (%)	Osimertinib (n=143)	Placebo (n=73)
Total	69 (48)	28 (38)
Grade 1	22 (15)	14 (19)
Grade 2	44 (31)	14 (19)
Grade 3	3 (2)	0
CTCAE Grade ≥3	3 (2)	0
SAE	15 (10)	2 (3)
Discontinuations	7 (5)	2 (3)

ILD, n (%)	Osimertinib (n=143)	Placebo (n=73)
Total	11 (8)	1 (1)
Grade 1	4 (3)	1 (1)
Grade 2	4 (3)	0
Grade 3	2 (1)	0
Grade 5	1 (1)	0
CTCAE Grade ≥3	3 (2)	0
SAE	3 (2)	0
Discontinuations	3 (2)	0

- La mayoría EAs con osimertinib fueron leves o moderados y no condujeron a discontinuación del tratamiento
- Neumonitis por radiación fueron mayoritariamente de Grado 1/2 y resueltos con interrupción de dosis, no hubo neumonitis grado 4/5.
- La mayoría de los pacientes pudieron continuar o reiniciar el tratamiento con osimertini,b con bajas tasas de recurrencia
- Enfermedad pulmonar intersticial fue leve y manejable

Estudios Fase III con TKI tras QT-RT Estadio III irresecables CPNM EGFR +

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Trial (Patient no.)	POLESTAR		LAURA	
	CRT (92)	CRT +TKI (50)	CRT (73)	CRT +TKI(43)
Median PFS (months)	3.8	30.4	5.6	39.1
2-year PFS (%)	NA	NA	13	65
PET Staging (%)	50.3 overall		Not formally reported	Not formally reported
Follow-up Median Surviving (M)	14.9	16.6	5.6	22.0
Start for follow-up	From end RT		From end RT	

Pendientes de resultados de Supervivencia

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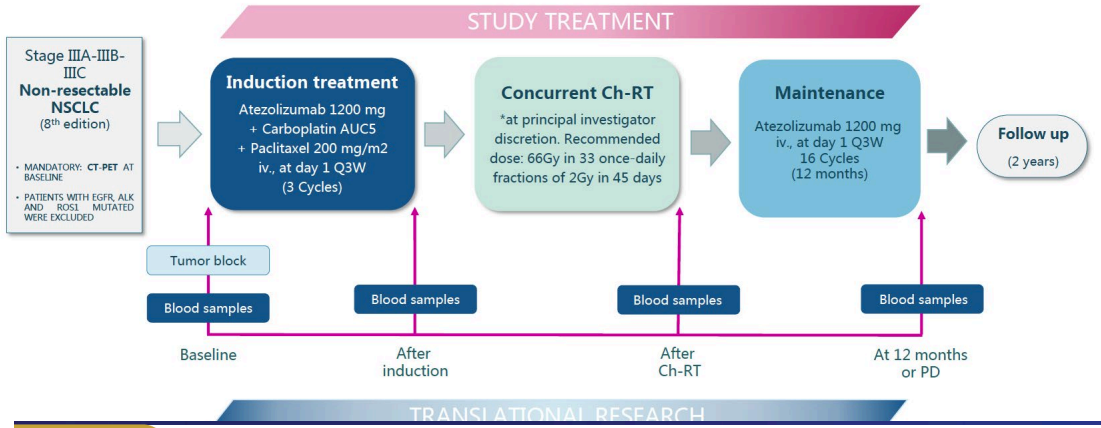
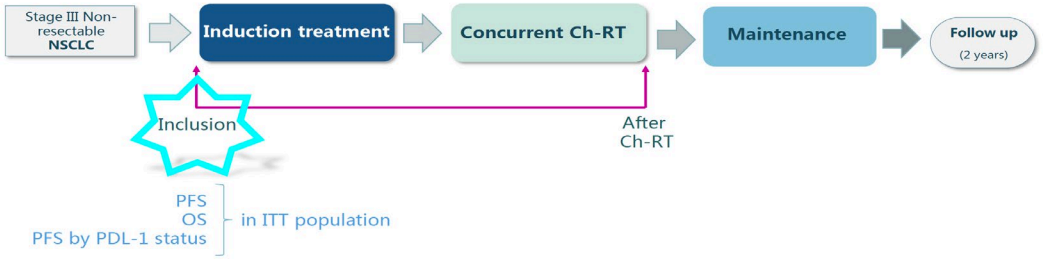
APOLO TRIAL: Atezolizumab + induction chemotherapy (Ch) + chemo-radiotherapy (Ch-RT) and atezolizumab maintenance in non-resectable stage IIIA-IIIB-IIIC non-small cell lung cancer (NSCLC) OA12.5 .Provencio M, et al

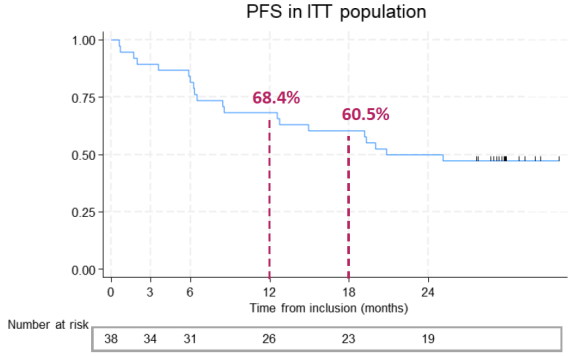
APOLO STUDY DESIGN



APOLO RESULTS



APOLO PRIMARY ENDPOINT – PFS in ITT population



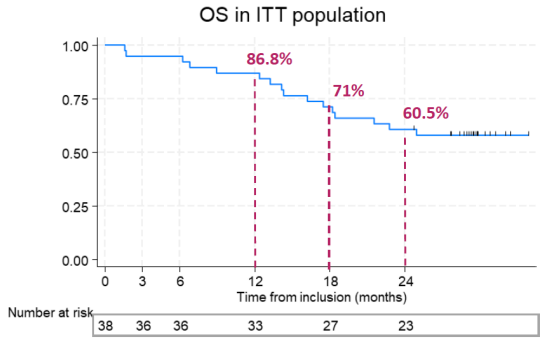
PFS 20.8 (95%CI 12.6; NR) months.

PFS in ITT population was **68.4%** (95%CI: 51.1-80.6%) **at 12 months** and **60.5%** (95%CI: 43.3-74%) **at 18 months.**

Median for follow-up: 29.6 months (95%CI: 28.8-29.8)

PFS, progression free survival; ITT, intention to treat

APOLO SECONDARY ENDPOINT – OS in ITT population



The median OS was not reached.

OS in ITT population was **86.8%** (95%CI: 71.2-94.3%) **at 12 months** and **60.5%** (95%CI: 43.3-74%) **at 24 months.**

99% maturity at 24 months.

Median for follow-up: 29.6 months (95%CI: 28.8-29.8)

PFS, progression free survival; ITT, intention to treat

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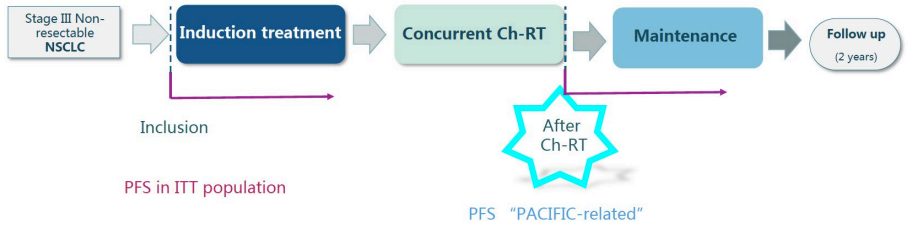
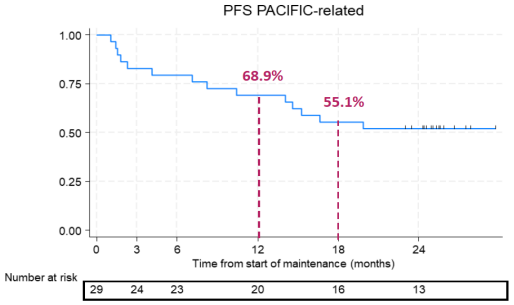
APOLO TRIAL: OA12.5. Provencio M, et al

APOLO RESULTS



IIIA: 36.8% IIIB/IIIC. 63.2%

APOLO PFS "PACIFIC-related"

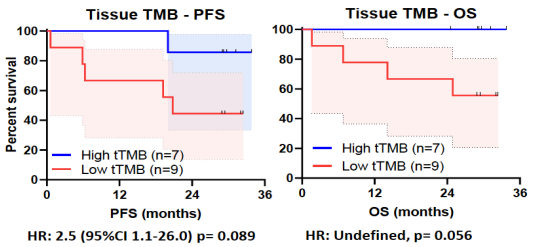


PFS from the start of maintenance treatment starting time in ITT population was **68.9%** (95%CI: 48.8-82.4%) **at 12 months** and **55.1%** (95%CI: 35.6-71%) **at 18 months.**

Median for follow-up: 29.6 months (95%CI: 28.8-29.8)

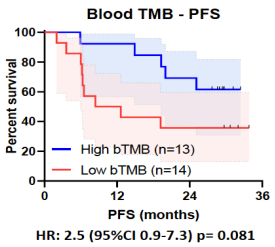
APOLO SECONDARY ENDPOINTS – TMB analysis – ITT population

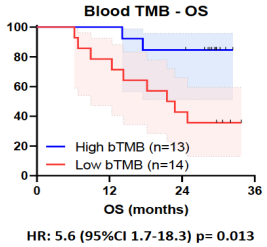
Tissue TMB[1] at baseline (n=16)



Patients with High Tissue TMB showed better PFS (p=0.089), and OS (p=0.056).

Blood TMB[2] at baseline (n=27)





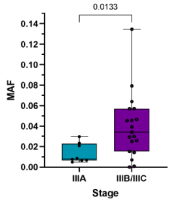
Patients with High Blood TMB showed better PFS (p=0.081), and OS (p=0.013).

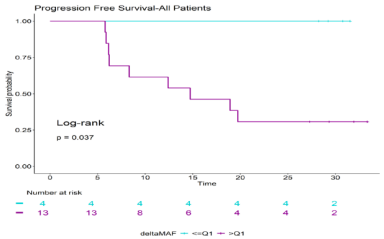
[1]Oncomine Tumor Mutation Load Assay on Ion S5 sequencer (ThermoFisher) was used for FFPE tissueTMB. DNA was extracted from 10 µm-thick paraffin sections using the truXTRAC® FFPE kit (Covaris). 16 out of 26 available samples (62%) passed final QC. ROC was used to select the best *exitus* cutoff, (High tTMB ≥ 9,89 mut/Mb) Log-rank pvalue and HR are shown.

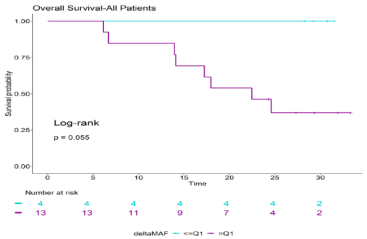
[2]TruSight Oncology ctDNA NGS assay on a NovaSeq sequencer (Illumina) was used for blood TMB. cfDNA was isolated from 4-6 mL plasma using the QIAamp Circulating Nucleic Acid Kit. ctDNA (minimum input: 30ng) was analyzed. 27 out of 36 (75%) samples passed QC. ROC curve was used to select the best cutoff value for *exitus* status, (High bTMB ≥ 16,5 mut/Mb.)

APOLO SECONDARY ENDPOINTS – ctDNA analysis

- ctDNA baseline levels were significantly associated with clinical stage (P=0.0133).
- Neither baseline ctDNA levels nor clinical stage were of prognostic significance.
- None of the patients who exhibited a reduction of at least 93% (upper quartile) in ctDNA levels died or experienced disease progression







APOLO muestra resultados excelentes: PFS a 12m: 68.4%, Mayor beneficio que otros ensayos: PACIFIC-related PFS 12 m 68.9% vs 55.9% *(Antonia SJ, al.NEJM 2017)*
Toxicidad tolerable, manejable y esperable, ctDNA clearance tras inducción fue un buen predictor de PFS y OS.
APOLO: abre una nueva estrategia de tratamiento para el tratamiento de estadios III irresecable: inducción con QT + IO puede se superior a QT + RT + IO de consolidación

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Iniciativa científica de: GECP lung cancer research

PACIFIC-BRAZIL (LACOG 2218): Intensified chemo-immuno-radiotherapy with durvalumab for stage III NSCLCs: a single arm phase II study. OA12.6 .Williams WN, et al

Study design

- **Phase 2, single-arm, multi-center (8 Brazilian research sites) study conducted through LACOG (NCT04230408)**

ELIGIBILITY CRITERIA

- ✓ Non-small cell lung cancer
- ✓ Stage III (TNM 8th ed.)†
- ✓ PS 0-1
- ✓ FEV1 ≥ 1.2 liters/second (or ≥ 50% predicted value)
- ✓ Predicted lung V20 <35%, cardiac V50 ≤25%
- ✓ No previous local or systemic therapy

INDUCTION CHEMO-IMMUNOTHERAPY

Carboplatin AUC 6 IV+ **Paclitaxel** 200mg/m² IV+ **Durvalumab** 1500mg/m² IV q3w **for 2 cycles**

CONCURRENT CHEMO-IMMUNO-RADIOTHERAPY

Carboplatin AUC 2 IV weekly **for 6 weeks** + **Paclitaxel** 50 mg/m² IV weekly **for 6 weeks** + **Durvalumab** 1500mg/m² q3w **for 2 cycles** + **Intensity-modulated radiation therapy** to 60 Gy in 30 fractions over 6 weeks‡

CONSOLIDATION IMMUNOTHERAPY

Durvalumab 1500mg/m² IV q4w **for 12 cycles**

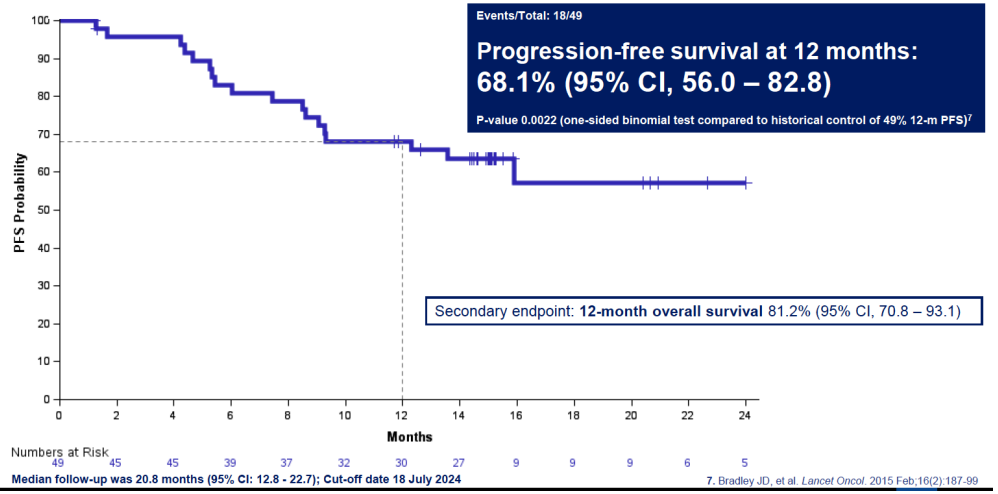
PRIMARY ENDPOINT:	**12-month progression-free survival**
SECONDARY ENDPOINTS:	Overall survival, overall response rate, duration of response, patterns of failure, efficacy (iRECIST as opposed to RECIST version 1.1), toxicity (CTCAE version 5)
EXPLORATORY ENDPOINTS:	Predictive biomarkers of response/survival

N= 49

†PET-CT was mandatory, invasive mediastinal staging was strongly encouraged. ‡Image guided radiation therapy (IGRT) was strongly encouraged.

IIB: 2% IIIA: 57% IIIB: 37% IIIC. 8%

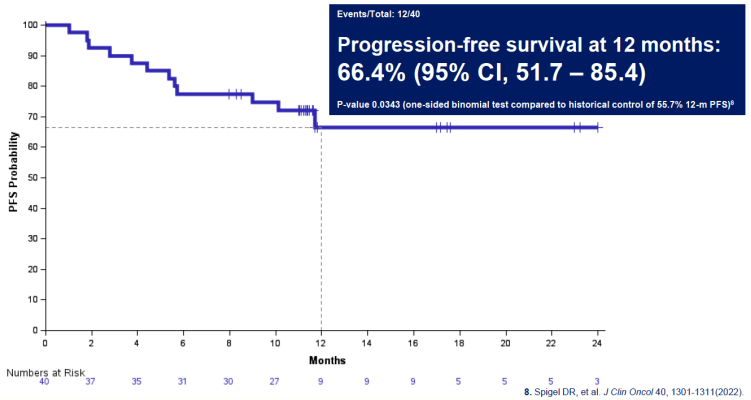
Primary endpoint: Pogression-free survival



Median follow-up was 20.8 months (95% CI: 12.8 - 22.7); Cut-off date 18 July 2024

7. Bradley JD, et al. *Lancet Oncol*. 2015 Feb;16(2):187-99

Pre-planned sensitivity landmark analysis: Progression-free survival from consolidation immunotherapy



8. Spigel DR, et al. *J Clin Oncol* 40, 1301-1311(2022).

- LACOG: muestra: PFS a 12m: 68.1%,
- PACIFIC-related PFS 12 m 66.4%
- Toxicidad tolerable, manejable y esperable
- Este estudio apoya la investigación adicional de la estrategia de inducción con quimio-inmunoterapia previa al tratamiento con quimiradioterapia concurrente

New Multimodality Therapies in unresectable Stage III NSCLC

Induction Chemo-Inmmunotherapy. → *Concurrent Chemoradiotherapy* → *Inmmunotherapy*

Iniciativa científica de: GECP lung cancer research

Paper	Patient Population	Study Phase (endpoint)	Treatment Setting	Investigational Agent	Key Outcome Data	Patients Completing Definitive Treatment (Sx or RT)
Provencio et al (APOLO)	N=38 Unresectable Stage III	PFS at 12 mths	ChemoIO→ CRT →IO	Atezolizumab	12m-PFS=68.4% (Pacific12m-PFS=68.9%)	84.2% (32)
William et al (PACIFIC-BRAZIL)	N=49 Stage IIB to IIIC	Single Arm Phase 2 (12 mth PFS)	ChemoIO→ ChemoIO+RT→ IO	Durvalumab	12m-PFS=68.1% (null hypothesis that 12m-PFS was ≤49%)	94% (46)

Resumen

Interim Analysis of the Phase III POLESTAR Study: Aumolertinib after CRT unresectable Stage III NSCLC EGFRm after definitive CRT
PL 04.1. Meng X, et al

- Aumolertinib Inhibidor EGFR 3ª generación mostró un aumento significativo en mPFS (30.4 m vs 3.8 m; HR 0.200 en Estadios III EGFR+ irresecables. Nueva opción de tratamiento

- LAURA: Osimertinib en Estadios III EGFR+ irresecables: La mayoría EAs con osimertinib fueron leves o moderado. Discontinuación 5%. Lo mas frecuente neumonitis por radiación. Grado≧ 3: 2%. EPI:2%.

- NUEVA ESTRATEGIA EN ESTADIOS III LOCALMENTE AVANZADO: Inducción QT + I0 seguido de QT+RT concurrente + IO consolidación
  - APOLO (IIIA- IIIC irresecables): mPFS 12m: 68.4%. mPFS 12 m desde consolidación con IO: 68.9% ATEZOLIZUMAB
  - LACOG (IIB- IIIC): mPFS 12m: 68.1%. mPFS 12 m desde consolidación con IO: 66.4% DURVALUMAB