Systemic Therapy for Locally Advanced NSCLC

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Surbhi Singhal, MD
UC Davis Comprehensive Cancer Center

Key Abstracts

Stage III NSCLC with EGFR Mutation

- Phase 3 LAURA: Safety Outcomes of Osimertinib after Chemoradiotherapy
- Phase 3 POLESTAR: Aumolertinib after Chemoradiotherapy

Stage III NSCLC without Driver Mutation

- Phase 2 APOLO: Atezolizumab + Induction Chemotherapy + CRT and Atezolizumab Maintenance
- Phase 2 PACIFIC-BRAZIL: Intensified Chemo-Immuno-Radiotherapy with Durvalumab

Stage III NSCLC Treated with Surgery

- Phase 2 SQUAT: Concurrent Chemo-Immuno-RT Followed by Surgery for Stage III-N2 NSCLC

2024 World Conference on Lung Cancer
SEPTEMBER 7-10, 2024 | SAN DIEGO, CA USA

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

Terufumi Kato[1], Xiaorong Dong[2], Toshiaki Takahashi[3], Nopadol Soparattanapaisarn[4], Sarayut Lucien Geater[5], Khoi Van Nguyen[6], Chih-Liang Wang[7], Edurne Arriola[8], Fedor Moiseenko[9], Lucy Thompson[10], Susannah Harker[11], Ellie Grainger[12], Elena Armenteros-Monterroso[13], Ana Bolanos[14], Suresh Ramalingam[15], Shun Lu[16]

[1]Department of Thoracic Oncology, Kanagawa Cancer Center, Yokohama, Japan; [2]Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [3]Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan; [4]Mahidol University, Sriraj Hospital, Bangkok, Thailand; [5]Prince of Songkla University, Hat Yai District, Songkhla, Thailand; [6]Cho Ray Hospital, Oncology Department, Ho Chi Minh, Vietnam; [7]Division of Pulmonary Oncology and Interventional Bronchoscopy, Department of Thoracic Medicine, Chang Gung Memorial Hospital, Taoyuan, Taiwan; [8]Hospital del Mar Medical Research Institute, Barcelona, Spain; [9]Chemotherapy Department, Saint-Petersburg Clinical Scientific and Practical Center for Specialized Types of Medical Care (Oncological), Saint Petersburg, Russia; [10]Global Patient Safety, Oncology R&D, AstraZeneca, Cambridge, UK; [11]Global Patient Safety, Oncology R&D, AstraZeneca, Luton, UK; [12]Biometrics, Late-stage Development, Oncology R&D, AstraZeneca, Cambridge, UK; [13]Late-stage Development, Oncology R&D, AstraZeneca, Barcelona, Spain; [14]Late-stage Development, Oncology R&D, AstraZeneca, Mississauga, Canada; [15]Department of Hematology and Medical Oncology, Emory University School of Medicine, Winship Cancer Institute, Atlanta, GA, USA; [16]Shanghai Lung Cancer Center, Shanghai Chest Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

Phase 3 LAURA: Safety Outcomes of Osimertinib after Chemoradiotherapy

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

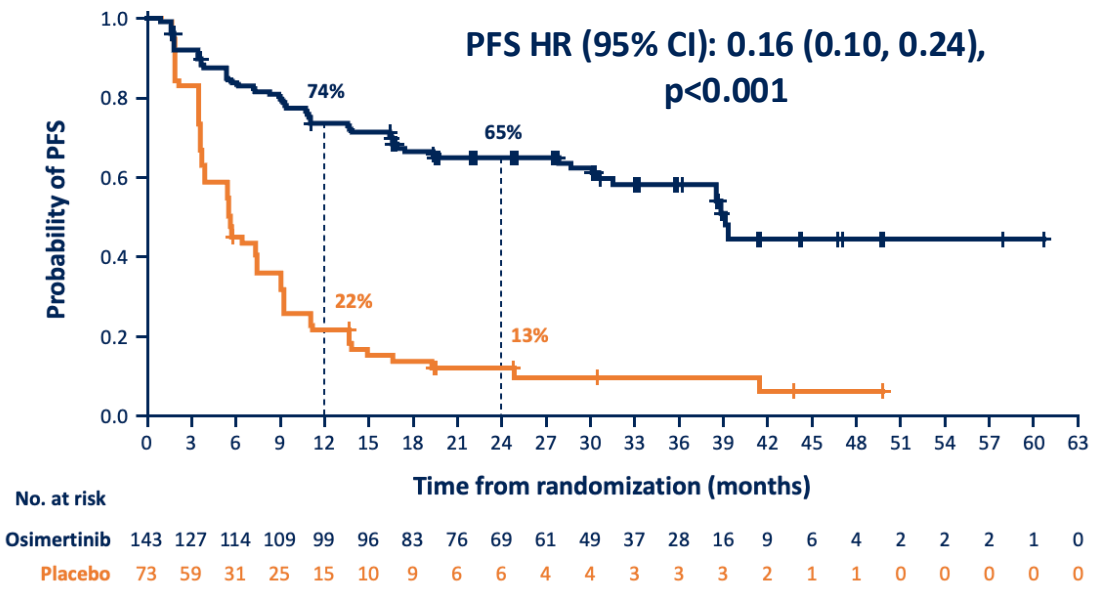
Open-label osimertinib offered to both treatment arms after BICR-confirmed PD§

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



- Also, trend for improved OS with osimertinib, but data not mature
- Incidence of Grade ≥3 adverse events: 35% osimertinib versus 12% in placebo group

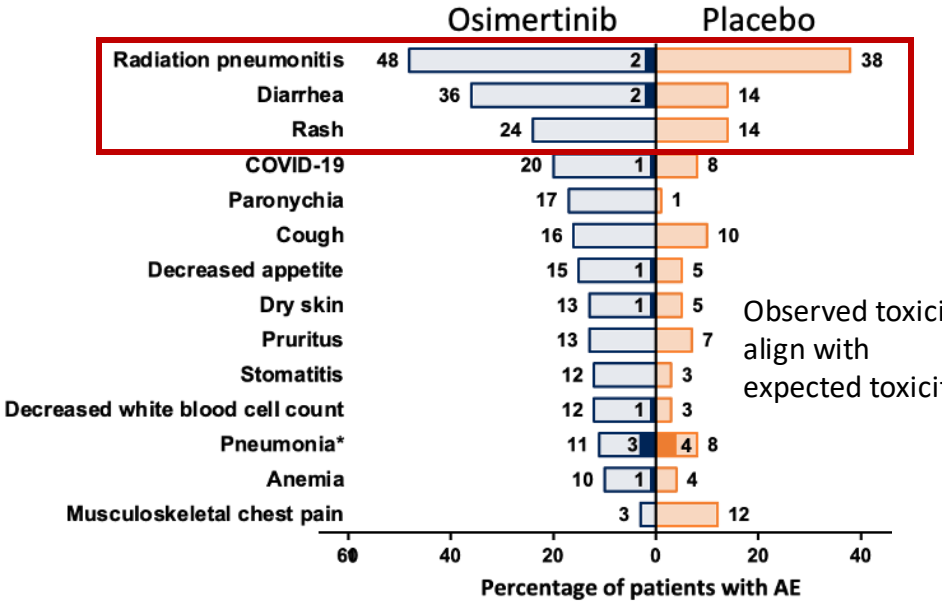
Phase 3 LAURA: Safety Outcomes of Osimertinib after Chemoradiotherapy

Overall Safety Summary

AE, any cause,* n (%)	Osimertinib (n=143)	Placebo (n=73)
Any AE	140 (98)	64 (88)
Any AE Grade ≥3	50 (35)	9 (12)
Any AE leading to death	3 (2)	2 (3)
Any SAE	55 (38)	11 (15)
Any AE leading to dose interruption	80 (56)	18 (25)
Any AE leading to dose reduction	12 (8)	1 (1)
Any AE leading to discontinuation	18 (13)	4 (5)

More SAE and AE leading to dose interruption in osimertinib group.

All Cause Adverse Events (≥10%)



Observed toxicities align with expected toxicities

Radiation Pneumonitis

Rates of RP

RP was more common in osimertinib group, but rarely grade 3.

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)

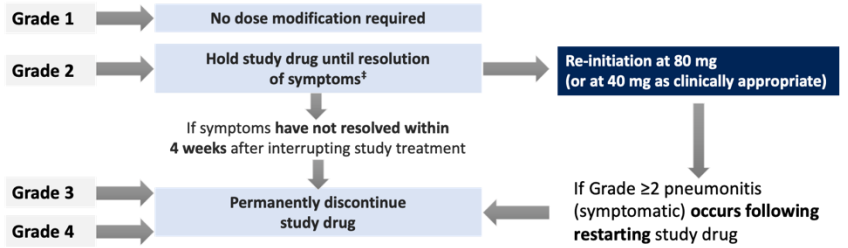
Median time to onset of radiation pneumonitis from first dose of study drug:

- Osimertinib: 52 days (range 10-676)
- Placebo: 54 days (range 15-113 days)

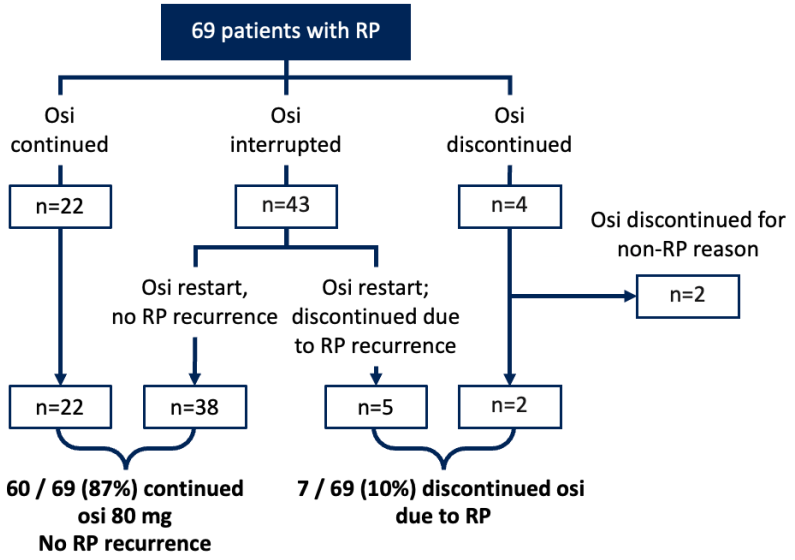
Of those who interrupted osi due to RP, most could restart without RP recurrence.

LAURA Management Guidelines of RP

Hold for Grade 2; Permanently discontinue for Grade 3



Osimertinib Restart After RP



Summary and conclusions (from the presenter at WCLC)

- Safety profile of osimertinib after definitive CRT was consistent with the established profile of osimertinib and CRT; **no new safety concerns** were identified
- Most AEs with osimertinib were **mild or moderate** in severity, and did not lead to treatment discontinuation
- Radiation pneumonitis events were primarily Grade 1 / 2, managed with dose interruptions per the mandated toxicity management guidelines; no Grade 4 / 5 events
- Most patients could continue or restart osimertinib following a radiation pneumonitis event; in both arms there were **low rates of radiation pneumonitis recurrence** after restart of study drug
- ILD events were mainly **low grade and manageable**

These safety data, together with efficacy data, support osimertinib given after definitive CRT as the new SoC for patients with unresectable stage III EGFRm NSCLC

2024 World Conference on Lung Cancer
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Aumolertinib after Chemoradiotherapy in Unresectable Stage III Non-Small-Cell Lung Cancer with EGFR Mutation: Interim Analysis of the Phase III POLESTAR Study

Xiangjiao Meng[1], Hong Ge[2], Qi Liu[3], Fangling Ning[4], Yufeng Cheng[5], Jun Wang[6], Xiaotao Zhang[7], Guowu Wu[8], Jianhua Chen[9], Yaping Xu[10], Xin Zhao[11], Kaihua Lu[11], Ou Jiang[12], Dongqing Lv[13], Conghua Xie[14], Xingya Li[15], Yi Yao[16], Xiaorong Dong[17], Baogang Liu[18], Jian Fang[19], Kunning Yang[20], Bo Zhu[21], Qin Lin[22], Jianhua Shi[23], Shucheng Ye[24], Anhui Shi[25], Shundong Cang[26], Jiancheng Li[27], Benhua Xu[28], Hui Li[29], Zhilong Zhang[30], Jie Yin[31], Gengming Wang[32], Chunling Liu[33], Xue Sun[34], Chuan Li[34], Yanhui Zhao[34], **Jinming Yu[1]***

*[1]**Shandong Cancer Hospital and Institute, Shandong First Medical University**, [2]Henan Cancer Hospital, Affiliated Cancer Hospital of Zhengzhou University, [3]Fudan University Shanghai Cancer Center, [4]Binzhou Medical University Hospital, [5]Qilu Hospital of Shandong University, [6]The Fourth Hospital of Hebei Medical University, [7]Qingdao Central Hospital, [8]Meizhou People's Hospital, [9]Hunan Cancer Hospital, [10]Shanghai Pulmonary Hospital, [11]Jiangsu Province Hospital, [12]Neijiang Second People's Hospital, [13]Taizhou Hospital of Zhejiang Province, [14]Zhongnan Hospital of Wuhan University, [15]The First Affiliated Hospital of Zhengzhou University, [16]Renmin Hospital of Wuhan University, [17]Union Hospital, Tongji Medical University, [18]Affiliated Tumor Hospital of Harbin Medical University, [19]Peking University Cancer Hospital, [20]Weifang Respiratory Disease Hospital, Weifang NO.2 people's Hospital, [21]Second Affiliated Hospital of Army Medical University, [22]First Affiliated Hospital of Xiamen University, [23]Linyi Cancer Hospital, [24]Affiliated Hospital of Jining Medical University, [25]Beijing Cancer Hospital, [26]Henan Provincial People's Hospital, [27]Fujian Provincial Cancer Hospital, [28]Union Hospital Affiliated to Fujian Medical University, [29]Linfen People's Hospital, [30]Anhui Cancer Hospital, [31]Nanjing General Hospital of Nanjing Military Region, [32]The First Affiliated Hospital of Bengbu Medical College, [33]Xinjiang Medical University Affiliated Cancer Hospital, [34]Shanghai Hansoh BioMedical Co., Ltd*

POLESTAR, Phase 3 double-blind study

Screening Period | **Treatment 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

2 : 1

Aumolertinib 110mg QD; (N=94)

N=147

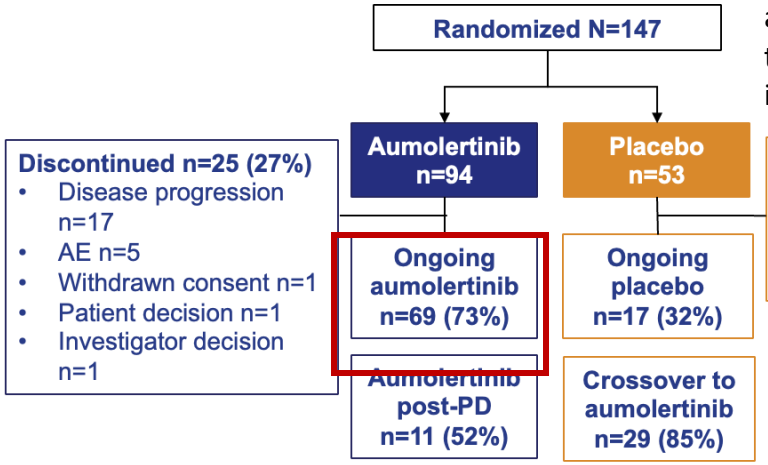
Stratification by
- **Ex19del vs L858R**
- **Stage IIIA vs Stage IIIB/IIIC**
- **cCRT vs sCRT**

Placebo 110mg QD; (N=53)

- 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§ 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

Randomized 147 patients



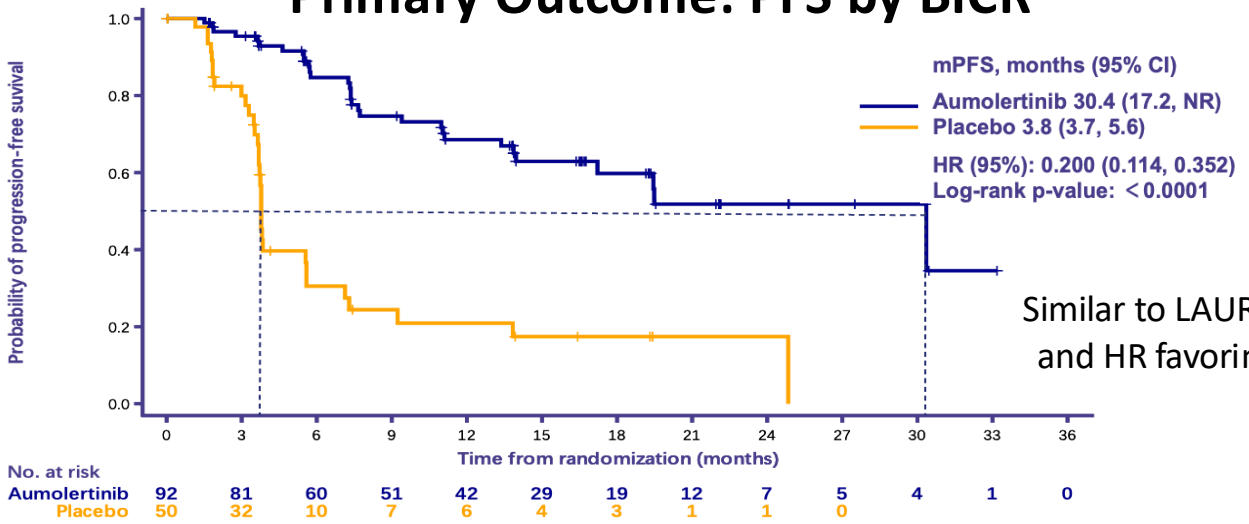
Most patients randomized to aumolertinib, continue to receive at time of this interim analysis

Characteristic, %	Aumolertinib (N=92)	Placebo (N=50)
Age, median (range),years	59 (39-76)	58 (36-77)
Gender: Male / Female	46 / 54	38 / 62
Smoking status: Never / Ever	70 / 30	72 / 28
AJCC staging: IIIA / IIIB / IIIC	24 / 60 / 16	22 / 62 / 16
CRT type: Concurrent / Sequential	75 / 25	72 / 28
EGFR mutation: Ex19del / L858R	41 / 59	44 / 56
Best response to prior CRT: PR / SD	60 / 40	46 / 52

Aumolertinib is a third-generation EGFR TKI with approval in China for the 1L treatment of patients with NSCLC harboring a classical EGFRm

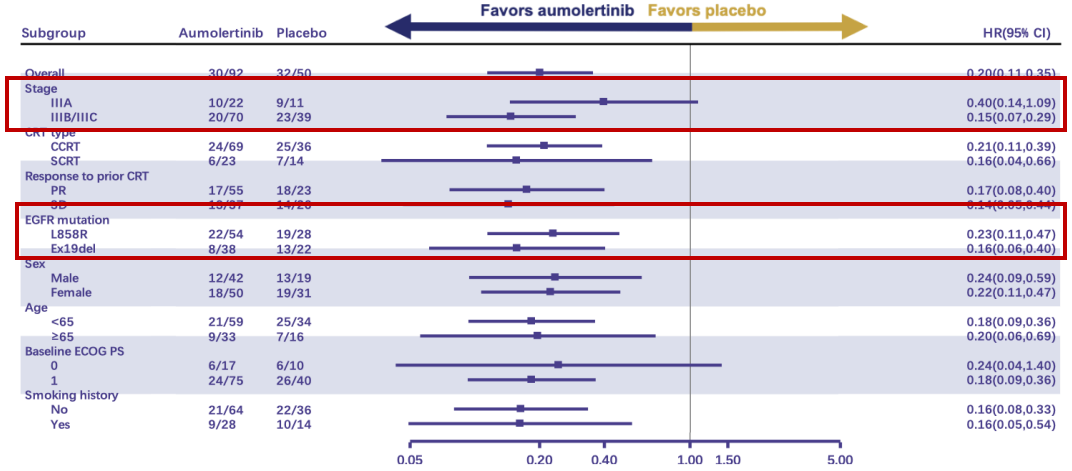
Phase 3 POLESTAR: Aumolertinib after Chemoradiotherapy

Primary Outcome: PFS by BICR



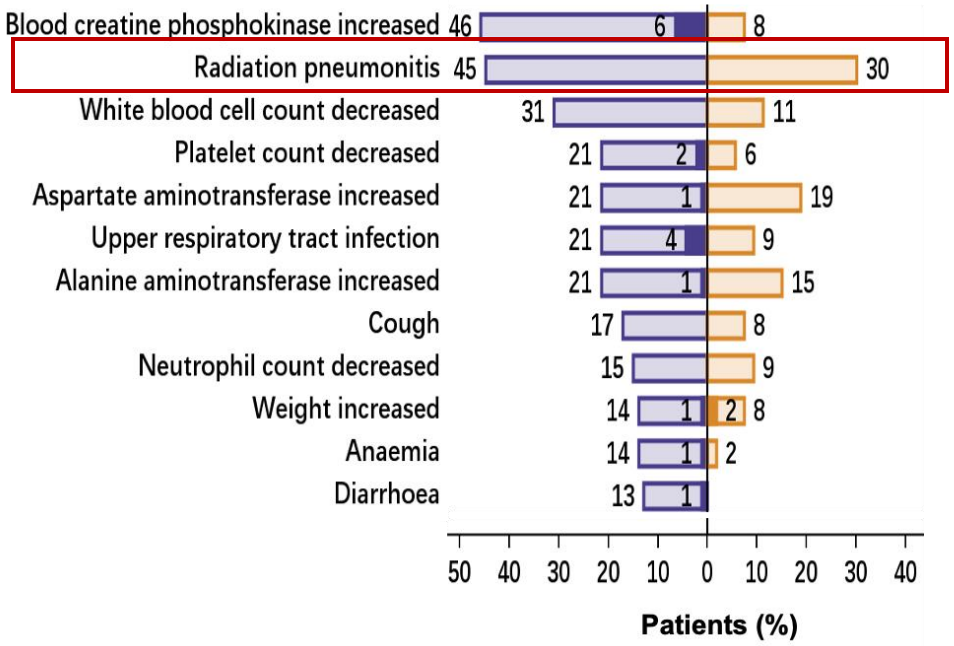
Similar to LAURA, PFS and HR favoring TKI

PFS Benefit Favored Aumolertinib Across Subgroups



Safety

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)



Conclusions (from the presenter at WCLC)

- In POLESTAR study, aumolertinib exhibited a statistically and clinically significant improvement in PFS compared to the placebo, as assessed by BICR, in patients with unresectable stage III EGFR-mutated NSCLC following definitive chemoradiotherapy.

  - Median PFS was 30.4 months for aumolertinib, 3.8 months for placebo; HR 0.200 (95% CI 0.114, 0.352), p<0.0001.

  - PFS benefit favoring aumolertinib was consistent across all predefined subgroups.

- The overall safety profile of aumolertinib after chemoradiotherapy was well tolerated and manageable with no new safety signal identified.

These findings demonstrate aumolertinib as a novel treatment option for patients with unresectable stage III EGFRm NSCLC after the CRT.

Data cut-off: February 5, 2024

Key Abstracts

Stage III NSCLC with EGFR Mutation

Safety and efficacy (PFS) data from Phase 3 studies establish EGFR TKI as standard of care after CRT for locally advanced NSCLC.

- Phase 3 LAURA: Safety Outcomes of Osimertinib after Chemoradiotherapy
- Phase 3 POLESTAR: Aumolertinib after Chemoradiotherapy

Stage III NSCLC without Driver Mutation

- Phase 2 APOLO: Atezolizumab + Induction Chemotherapy + CRT and Atezolizumab Maintenance
- Phase 2 PACIFIC-BRAZIL: Intensified Chemo-Immuno-Radiotherapy with Durvalumab

Stage III NSCLC Treated with Surgery

- Phase 2 SQUAT: Concurrent Chemo-Immuno-RT Followed by Surgery for Stage III-N2 NSCLC
- Phase 2 CHIO3: Chemotherapy + Immune Checkpoint Inhibitor for Operable Stage III NSCLC

Atezolizumab + induction chemotherapy (Ch) + chemo-radiotherapy (Ch-RT) and atezolizumab maintenance in non-resectable stage IIIA-IIIB-IIIC non-small cell lung cancer (NSCLC): APOLO trial

Mariano Provencio, MD, PhD.
Hospital Puerta de Hierro Majadahonda (Madrid), Spain
Spanish Lung Cancer Group

Phase 2 APOLO: Atezolizumab + Induction Chemotherapy + CRT and Atezo Maintenance

APOLO, Phase 2 single-arm study

Stage IIIA-IIIB-IIIC **Non-resectable NSCLC** (8th edition)

- MANDATORY: **CT-PET** AT BASELINE
- PATIENTS WITH EGFR, ALK AND ROS1 MUTATED WERE EXCLUDED

Induction treatment
Atezolizumab 1200 mg
+ Carboplatin AUC5
+ Paclitaxel 200 mg/m2
iv., at day 1 Q3W
(3 Cycles)

Concurrent Ch-RT
*at principal investigator discretion. Recommended dose: 66Gy in 33 once-daily fractions of 2Gy in 45 days

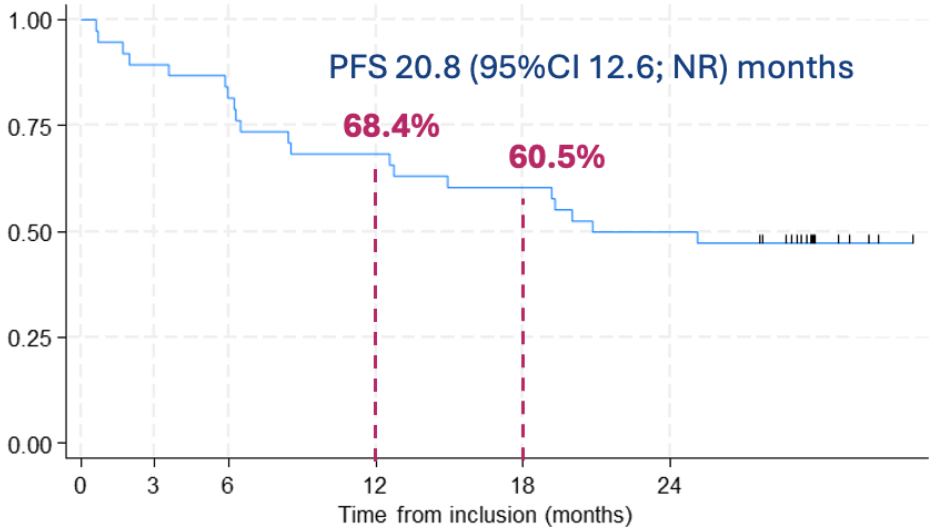
Maintenance
Atezolizumab 1200 mg
iv., at day 1 Q3W
16 Cycles
(12 months)

Primary Endpoint: PFS in ITT population, counted from time of inclusion

Study includes 2 different PFS measurements

PFS-PACIFIC, counted from time of maintenance therapy start

Primary Endpoint: PFS in ITT Population

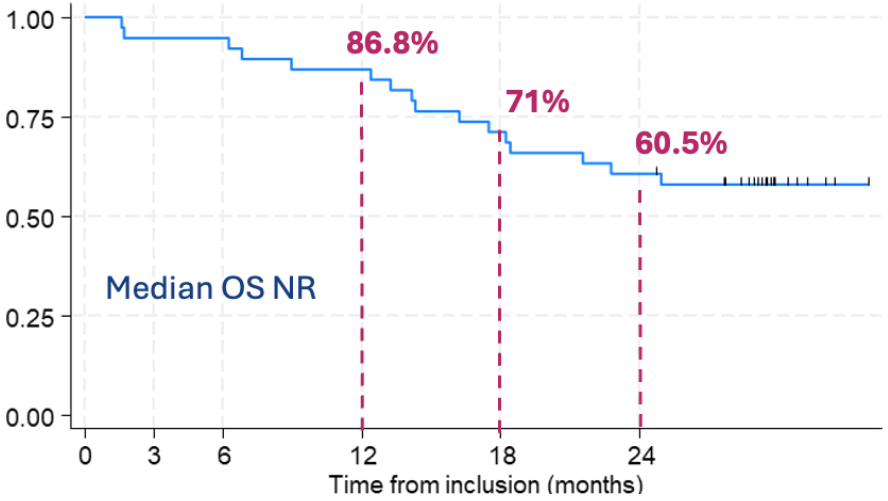


Enrolled 38 Patients

Baseline characteristics - ITT population (n = 38)	
Age – mean (SD), years	66.13 (7.81)
Female – No. (%)	11 (28.9)
History of tobacco use – No. (%)	
Former smoker (≥ 1 year)	25 (65.8)
Current smoker	13 (34.2)
Histology – No. (%)	
Adenocarcinoma	20 (52.6%)
Squamous	18 (47.4%)
TNM classification (AJCC 8th edition) – No. (%)	
IIIA	14 (36.8)
IIIB/IIIC	24 (63.2)
Clinical Stage T – No. (%)	
T4	25 (65.8)
Clinical Stage N – No. (%)	
N2	27 (71)
N3	4 (10.5)

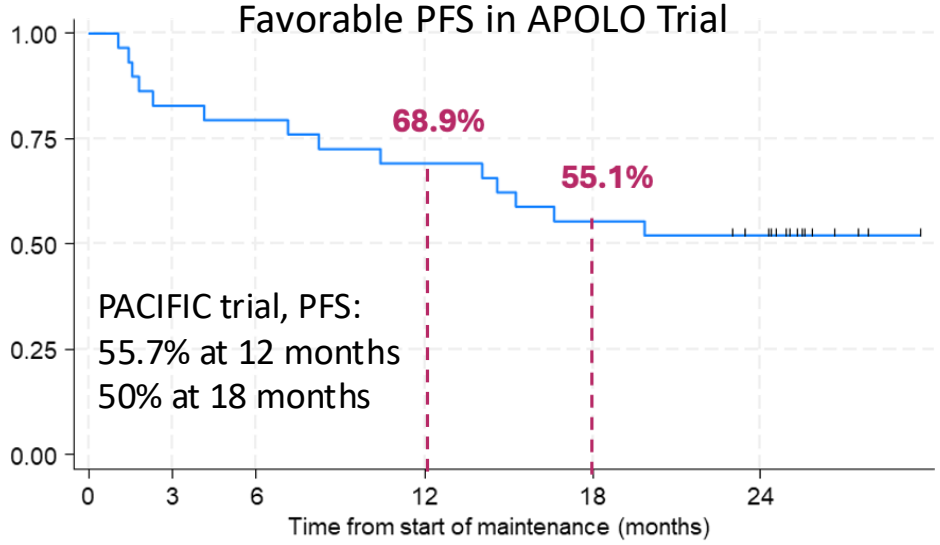
Phase 2 APOLO: Atezolizumab + Induction Chemotherapy + CRT and Atezo Maintenance

Secondary Endpoint, OS

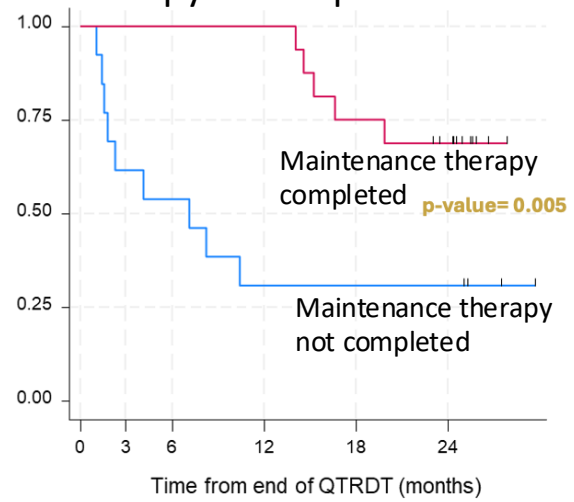


PFS "PACIFIC-related"

Favorable PFS in APOLO Trial



Those who completed maintenance therapy had improved PFS.



Selected Safety Data

TRAEs for induction treatment only shown

Induction tx (n= 38) Total events = 350	Atezolizumab Related			Carboplatin Related			Paclitaxel Related		
	Any Grade	Grd 1-2	Grd 3-4	Any Grade	Grd 1-2	Grd 3-4	Any Grade	Grd 1-2	Grd 3-4
	number of patients with TRAE (%)								
Any TRAE	26 (68.4)	24 (63.2)	6 (15.8)	34 (89.5)	32 (84.2)	9 (23.7)	36 (94.7)	34 (89.5)	9 (23.7)
Fatigue	10 (26.3)	10 (26.3)	1 (2.6)	19 (50.0)	19 (50.0)	2 (5.3)	18 (47.4)	18 (47.4)	2 (5.3)
Peripheral sensory neuropathy	1 (2.6)	1 (2.6)	0	9 (23.7)	9 (23.7)	0	19 (50.0)	19 (50.0)	0
Anemia	5 (13.2)	5 (13.2)	0	13 (34.2)	13 (34.2)	1 (2.6)	13 (34.2)	13 (34.2)	1 (2.6)
Nausea	1 (2.6)	1 (2.6)	0	7 (18.4)	7 (18.4)	0	6 (15.8)	6 (15.8)	0
Febrile neutropenia	2 (5.3)	0	2 (5.3)	4 (10.5)	0	4 (10.5)	4 (10.5)	0	4 (10.5)

Almost 1/4 of patients experienced a grade 3-4 treatment-related adverse event related to induction chemotherapy.

CONCLUSIONS (from the presenter at WCLC)

- APOLO shows encouraging results using induction with Atezolizumab plus chemotherapy (Ch) combination plus chemoradiotherapy (Ch-RT) and Atezolizumab maintenance in patients with unresectable stage IIIA-IIIB-IIIC NSCLC

  → Primary endpoint PFS rate 12m: 68.4% (95%CI: 51.1-80.6%)

- Compared to other trials, APOLO shows a major benefit:

  → "PACIFIC-related" PFS 12m: 68.9% (95%CI: 48.8-82.4%) vs 55.9% (95%CI: 51.0–60.4) (*SJ Antonia et al NEJM 2017)*

- There are no concerning safety data or treatment-related deaths.

- **ctDNA clearance** after induction treatment showed a **good prediction of PFS and OS**

- In light of these results, it seems reasonable to explore new research avenues to assess whether a chemo-immunotherapy induction approach may be superior to Ch-RT + consolidation immunotherapy.

Intensified chemo-immuno-radiotherapy with durvalumab for stage III NSCLCs: a single arm phase II study – PACIFIC-BRAZIL (LACOG 2218)

William N. William Jr [1, 2, 3], Gilberto Castro Junior [4,5], Danielli de Almeida Matias [6], Luiz Henrique de Lima Araújo [7], Tércia Vilasboas Reis [8], Victor Braga Gondim Teixeira [9], Gustavo Dix Junqueira Pinto [10], Lívia Alvarenga Fagundes Ferrigno [3], Suellen Nastri Castro [3], Cassio Murilo Trovo Hidalgo Filho [4], Daniel Kischinhevsky [7], Ana Caroline Zimmer Gelatti [11], Rafaela G. de Jesus[2], Taiane F. Rebelatto[2], Gustavo Werutsky[2]

1. Oncoclínicas&Co., São Paulo, Brazil; **2.** Latin American Cooperative Oncology Group (LACOG); **3.** Hospital Beneficência Portuguesa de São Paulo, São Paulo, Brazil; **4.** Instituto do Câncer do Estado de São Paulo (ICESP), São Paulo, Brazil; **5.** Hospital das Clínicas (HCFMUSP); Barretos Cancer Hospital, Barretos, Brazil. **6.** Liga Norte Riograndense Contra o Câncer, Natal, Brazil; **7.** Instituto Nacional do Câncer (INCA), Rio de Janeiro, Brazil; **8.** Santa Casa da Bahia, Salvador, Brazil; **9.** Instituto COI, Rio de Janeiro, Brazil; **10.** Barretos Cancer Hospital, Barretos, Brazil; **11.** CPO - Hospital São Lucas da PUCRS, Porto Alegre, Brazil; **12.** Grupo Oncoclínicas, Porto Alegre, Brazil.

PACIFIC-BRAZIL, Phase 2 single-arm study

2 cycles of induction in PACIFIC-BRAZIL compared to 3 cycles in APOLO

Inclusion of IO during CRT

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

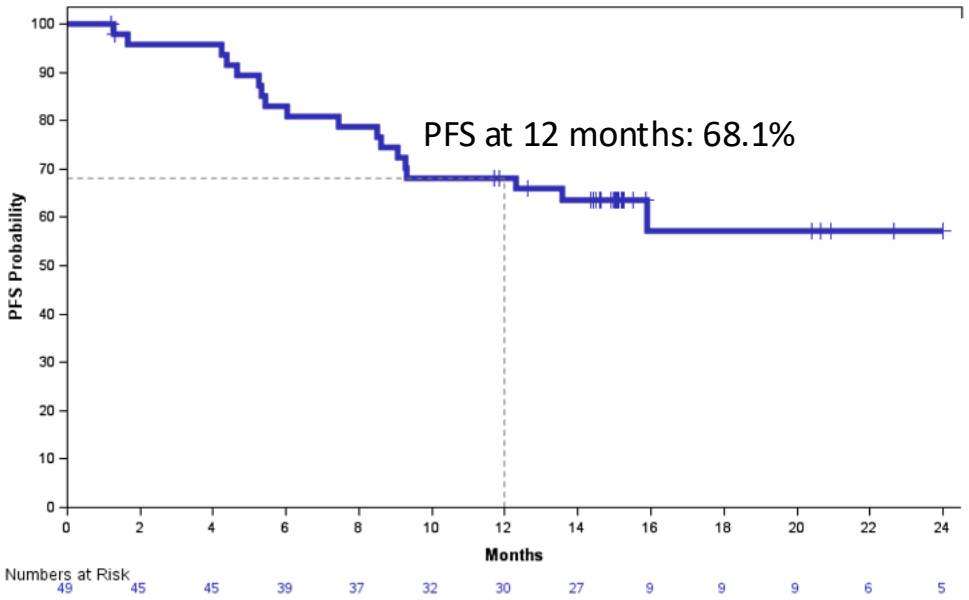
Fewer patients with Stage IIIB/IIIC disease compared to APOLO, proportions similar to PACIFIC

Enrolled 49 Patients

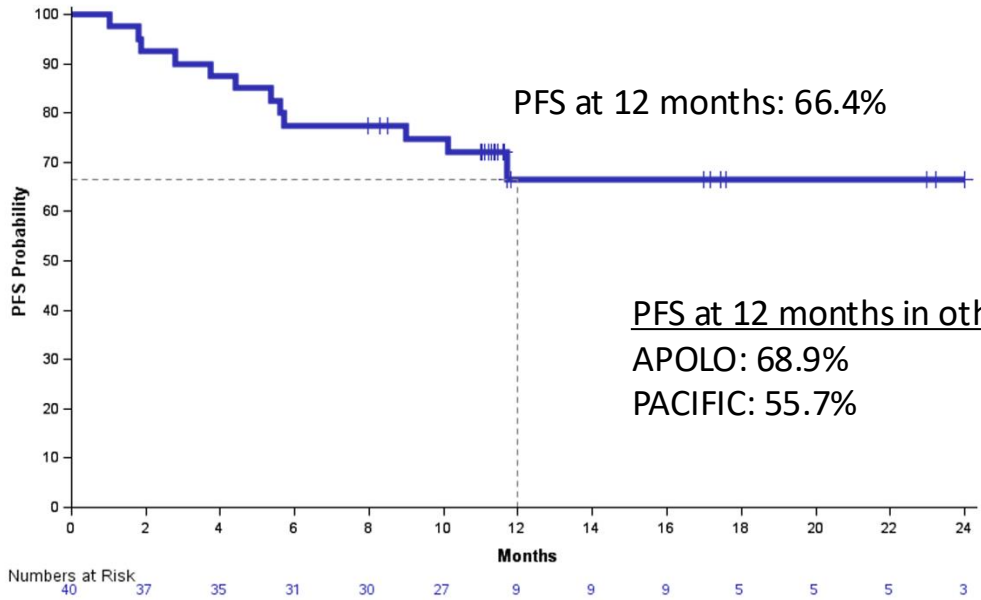
Demographic and disease characteristics	All Patients (N=49)
Age, in years — median (range)	67 (48 – 83)
Race or ethnic group	
White	25 (51%)
Black/Mixed	21 (43%)
Other	3 (6%)
Smoking status	
Current/Former	41 (84%)
Never	8 (16%)
Histology	
Squamous	18 (37%)
Non-squamous†	31 (63%)
Disease stage	
IIB	1 (2%)
IIIA	26 (53%)
IIIB	18 (37%)
IIIC	4 (8%)

Phase 2 PACIFIC-BRAZIL: Intensified Chemo-Immuno-Radiotherapy with Durvalumab

Primary Endpoint: PFS (from inclusion)



PFS (from time of start of maintenance durvalumab)



PFS at 12 months in other trials
APOLO: 68.9%
PACIFIC: 55.7%

Selected Treatment-Related Adverse Events

Adverse Event†	Overall N=49		Induction Chemo-immunotherapy N=49		Concurrent Chemo-immuno-radiotherapy N=46 [a]		Consolidation immunotherapy N=40 [b]	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any	48 (98%)	40 (82%)	46 (94%)	12 (25%)	46 (94%)	32 (65%)	33 (67%)	10 (20%)
Occurred in >20%								
Neutropenia	33 (67%)	16 (33%)	3 (6%)	2 (4%)	31 (67%)	15 (33%)	5 (13%)	0
Anaemia	32 (65%)	9 (18%)	10 (20%)	1 (2%)	29 (59%)	8 (17%)	11 (28%)	0
Fatigue	26 (53%)	2 (4%)	16 (33%)	1 (2%)	16 (35%)	1 (2%)	4 (10%)	0
Lymphopenia	21 (43%)	16 (33%)	3 (6%)	0	21 (46%)	16 (35%)	10 (25%)	2 (5%)
Nausea	20 (41%)	0	17 (35%)	0	11 (24%)	0	2 (5%)	0
Pain	13 (27%)	1 (2%)	12 (25%)	1 (2%)	2 (4%)	0	0	0
Pneumonitis	13 (27%)	7 (14%)	2 (4%)	1 (2%)	2 (4%)	2 (4%)	9 (23%)	4 (10%)

Overall, ≥82% of participants experienced a grade 3 treatment-related adverse event

Conclusions (from the presenter at WCLC)

- PACIFIC-BRAZIL met its primary endpoint (12m-PFS)
  - primary intention-to-treat analysis: 12m-PFS of 68.1% from treatment initiation
  - sensitivity landmark analysis: 12m-PFS of 66.4% from initiation of consolidation immunotherapy
- Although concurrent chemoradiotherapy followed by durvalumab remains the standard-of-care regimen for stage III unresectable NSCLC, our results may support further evaluation of induction chemo-immunotherapy prior to chemoradiotherapy
- Given toxicities observed herein and the negative PACIFIC-2 study, immunotherapy added concurrently during chemoradiation may not be warranted.

Key Abstracts

Stage III NSCLC with EGFR Mutation

Safety and efficacy (PFS) data from Phase 3 studies establish EGFR TKI as standard of care after CRT for locally advanced NSCLC.

- Phase 3 LAURA: Safety Outcomes of Osimertinib after Chemoradiotherapy
- Phase 3 POLESTAR: Aumolertinib after Chemoradiotherapy

Stage III NSCLC without Driver Mutation

Intensified regimens with induction prior to CRT demonstrate small PFS benefits compared to other trials (i.e., PACIFIC) at expense of increased toxicity.

- Phase 2 APOLO: Atezolizumab + Induction Chemotherapy + CRT and Atezolizumab Maintenance
- Phase 2 PACIFIC-BRAZIL: Intensified Chemo-Immuno-Radiotherapy with Durvalumab

Stage III NSCLC Treated with Surgery

- Phase 2 SQUAT: Concurrent Chemo-Immuno-RT Followed by Surgery for Stage III-N2 NSCLC

Neoadjuvant Concurrent Chemo-immuno-Radiation Therapy Followed by Surgery for Stage III-N2 NSCLC: SQUAT trial (WJOG 12119L)

Shinichi Toyooka,[a] Akira Hamada,[b,g] Junichi Soh,[b] Akito Hata,[c] Kiyoshi Nakamatsu,[d] Mototsugu Shimokawa,[e] Yasushi Yatabe,[f] Jun Suzuki,[g] Masahiro Tsuboi,[h] Hidehito Horinouchi,[i] Yuichi Sakairi,[j] Masayuki Tanahashi,[k] Hiromasa Yamamoto,[a] Morihito Okada,[l] Natsumi Matsuura,[m] Hisayuki Shigematsu,[n] Yasumasa Nishimura,[d] Nobuyuki Yamamoto,[o] Kazuhiko Nakagawa,[p] Tetsuya Mitsudomi,[b]

[a]Department of General Thoracic Surgery and Breast and Endocrinological Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan. [b]Division of Thoracic Surgery, Department of Surgery, Kindai University Faculty of Medicine, Osaka-Sayama, Japan. [c]Division of Thoracic Oncology, Kobe Minimally Invasive Cancer Center, Kobe, Japan. [d]Department of Radiation Oncology, Kindai University Faculty of Medicine, Osaka-Sayama, Japan. [e]Department of Biostatistics, Yamaguchi University Graduate School of Medicine, Yamaguchi, Japan. [f]Department of Diagnostic Pathology, National Cancer Center Hospital, Tokyo, Japan. [g]Department of Surgery II, Faculty of Medicine, Yamagata University, Yamagata, Japan. [h]Division of Thoracic Surgery, National Cancer Center Hospital East, Chiba, Japan. [i]Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan. [j]Department of General Thoracic Surgery, Chiba University Graduate School of Medicine, Chiba, Japan. [k]Division of Thoracic Surgery, Respiratory Disease Center, Seirei Mikatahara General Hospital, Hamamatsu, Japan. [l]Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan. [m]Department of General Thoracic, Breast and Endocrinological Surgery, Faculty of Medicine, Kagawa University, Kagawa, Japan. [n]Department of Thoracic Surgery, Shikoku Cancer Center, Matsuyama, Japan. [o]Department of Internal Medicine III, Wakayama Medical University, Wakayama, Japan. [p]Department of Medical Oncology, Kindai University Faculty of Medicine, Osaka-Sayama, Japan.

Phase 2 SQUAT: Concurrent Chemo-Immuno-RT Followed by Surgery for Stage III-N2 NSCLC

SQUAT, Phase 2 single-arm study

Key eligibility criteria
- Resectable Stage IIIA-B-N2 NSCLC (TNM8th)
- Discrete N2, pathologically confirmed
- ECOG PS 0-1

N=31

Neoadjuvant Chemo-Immuno-Radiation therapy
- PTX (40mg/m^2)+CBDCA (AUC=2) Day 1 8 15 22 29
- IFRT[a] 50Gy (2Gy × 25fr) Day 1–35
- Durvalumab (1500mg) Day 1, 29

Surgery

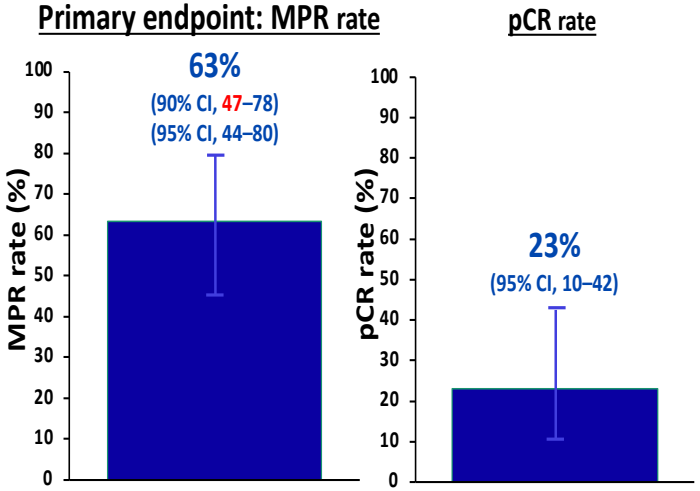
Adjuvant Immunotherapy
- Durvalumab (1500mg) 12 months

Enrolled patients with resectable, N2 disease

(+) radiation to the neoadjuvant chemoimmunotherapy

Secondary Endpoints: PFS, OS and safety

Primary Endpoint, Major Pathologic Response, previously reported



Enrolled 30 Patients

Age, median (range), years	64 (41-74)
Stage, n (%)	
IIIA	21 (70)
IIIB	9 (30)
N2 status, n (%)	
Single	25 (83)
Multiple	5 (17)
Histology, n (%)	
Squamous	11 (37)
Non-squamous	19 (63)
EGFR positive, n (%)	6 (20)
ALK fusion, n (%)	0 (0)

Phase 2 SQUAT: Concurrent Chemo-Immuno-RT Followed by Surgery for Stage III-N2 NSCLC

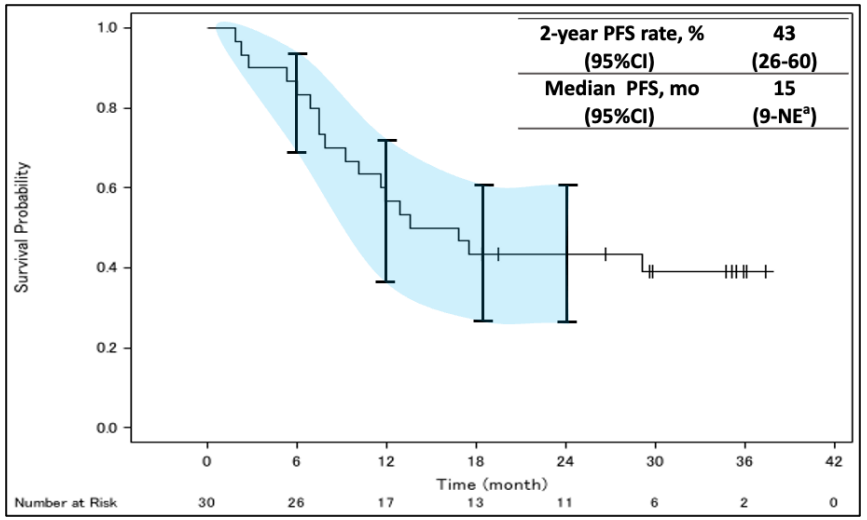
Treatment Summary

	N=30
Completed neoadjuvant therapy, n (%)	29 (97)
Discontinued neoadjuvant therapy, n (%)	1 (3)
Adverse event	1 (3)
Underwent definitive surgery, n (%)	27 (90)
Cancelled definitive surgery, n (%)	3 (10)
Disease progression	2 (7)
Adverse event	1 (3)
Delayed definitive surgery, n (%)	3 (10)
Delay due to radiation pneumonitis	2 (7)
Delay due to irAE (rash) and radiation pneumonitis	1 (3)

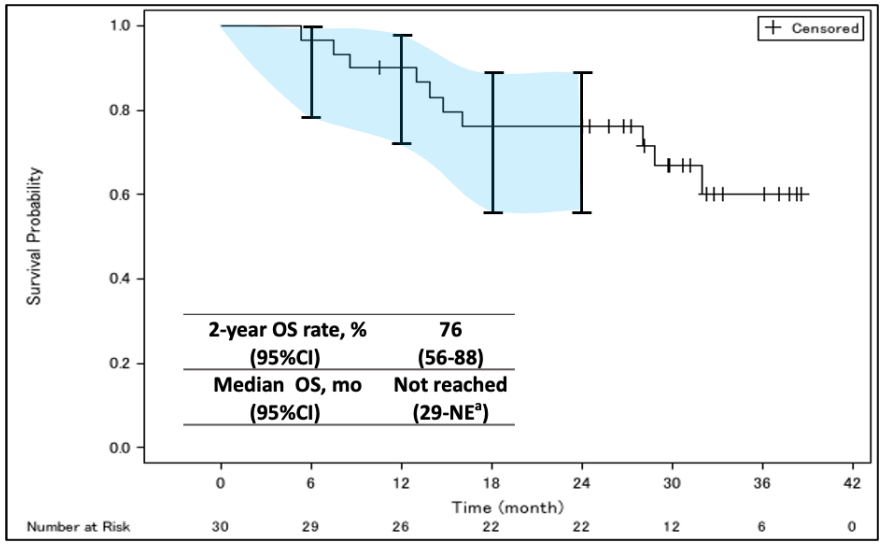
	N=27
Lobectomy, n (%)	27 (100)
Completeness of resection, n (%)	
R0	26 (96)
R2	1 (4)

Outcomes in the ITT population.

Progression-Free Survival



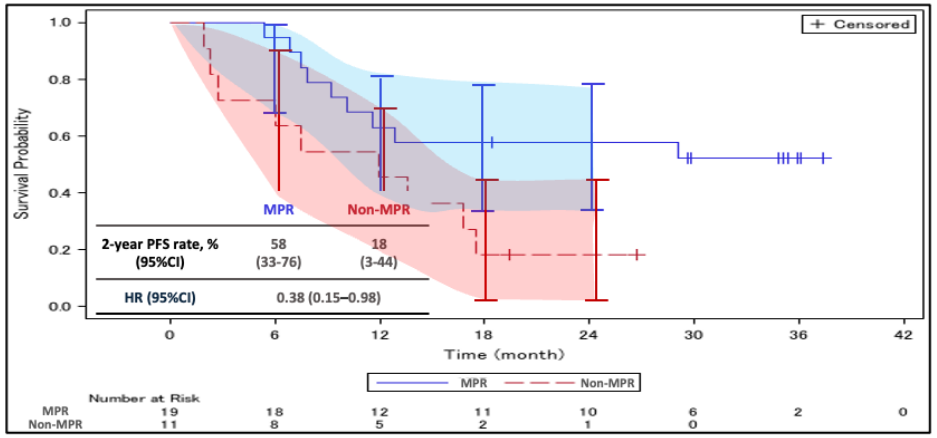
Overall Survival



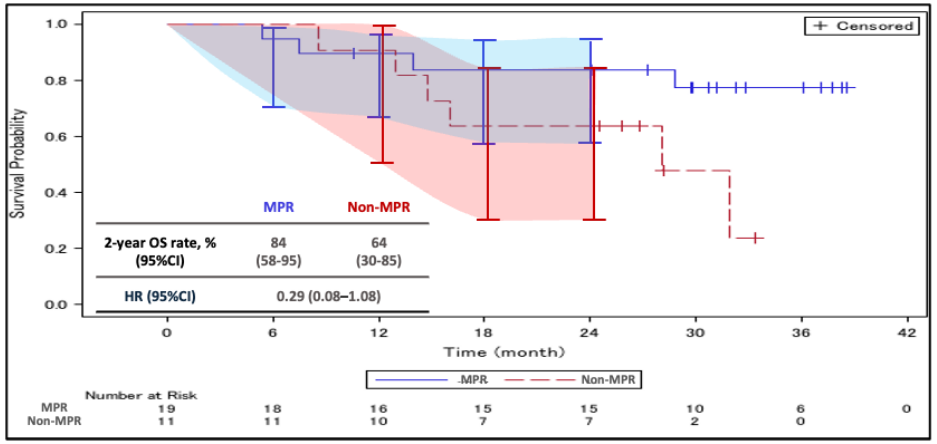
PFS and OS by MPR

Compared to those with no major pathologic response, those who had major pathologic response had improved 2-year PFS. No statistically significant differences observed in 2-year OS.

PFS



OS



Updated Adverse Event Summary

Event status (N=31)	Any Grade	Grade 3 or 4
Adverse events of any cause – no. (%)		
All	31 (100)	15 (48)
Leading to discontinuation of treatment	3 (10)	2 (7)
Serious	11 (36)	7 (23)
Treatment-related adverse events – no. (%)		
All	31 (100)	15 (48)
Leading to discontinuation of treatment	3 (10)	2 (7)
Serious	11 (36)	6 (19)
Death	1 (3)[a]	-
Surgery-related adverse events – no. (%)	22 (71)	4 (13)

Conclusions…SQUAT (from the presenter at WCLC)

- We conducted a single-arm phase II study of neoadjuvant chemo-immuno-radiation therapy for stage III N2 NSCLC followed by surgery and immunotherapy.
  - Efficacy
    - MPR 63%, pCR 23%.
    - 2-year PFS rate 43%, 2-year OS rate 76%.
  - Safety
    - Adverse events of any grade were observed in all patients (G3 ≤ 52%).
    - Treatment discontinuation in 10% of the patients.
    - Treatment-related death in 3% of patients.
    - Surgery-related adverse events occurred in 71% of patients (G3 ≤ 16%).
- Patients who achieved MPR or pCR had improved PFS and OS.
- Compared with recently published results of neoadjuvant chemo-immunotherapy trials, this treatment regimen tended to have higher MPR rate. However, this benefit did not necessarily translate into PFS or OS benefit.
- The benefit of adding radiation to neoadjuvant chemo-immunotherapy is questionable, although it warrants longer observation as well as verification by other studies.

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Stage III NSCLC Treated with Surgery

Compared to standard of care perioperative chemoimmuno approaches, addition of neoadjuvant radiation does not have favorable PFS or OS data.

- Phase 2 SQUAT: Concurrent Chemo-Immuno-RT Followed by Surgery for Stage III-N2 NSCLC

Unanswered Questions

Should all patients continue TKI indefinitely after CRT in absence of progression?

How do we identify patients who may safely discontinue TKI after CRT?

If intensified regimens explored in subsequent trials, can we better identify which patients may benefit from an intensified approach?

Should we be doing more trials with neoadjuvant radiation for stage III-N2 disease or stop here?