

20th ANNUAL

ATLANTA

LUNG CANCER SYMPOSIUM

Targeting EGFR mutations

November 07, 2026.

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Disclosures

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Classical EGFR Mutations

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Outline

- Exon 19 and 21 mutations
  - First line options- risk-adapted therapy
  - Salvage therapy
  - - EGFR + MET inhibition (SACHI, SAFFRON)
  - - 4th Gen TKI
  - - HER-3 ADCs
- Early state- ADAURA update
- Exon 20
  - Zipalertinib
  - Sunvozertinib

First-line therapy for metastatic NSCLC

- Combination therapy has emerged as the standard approach based on improved PFS and OS
- Monotherapy limited to low-risk patients
- Risk-adapted approaches have demonstrated utility
- Toxicity management is a key part of patient care

Overcoming Adverse Events with Amivantamab-Lazertinib

Regimen

Oral Tetracycline X 24 weeks

Ceramide-based moisturizer

Oral Zinc gluconate

Anticoagulation ~ 4 months

Lead-in with lazertinib only for cycle 1

Results:

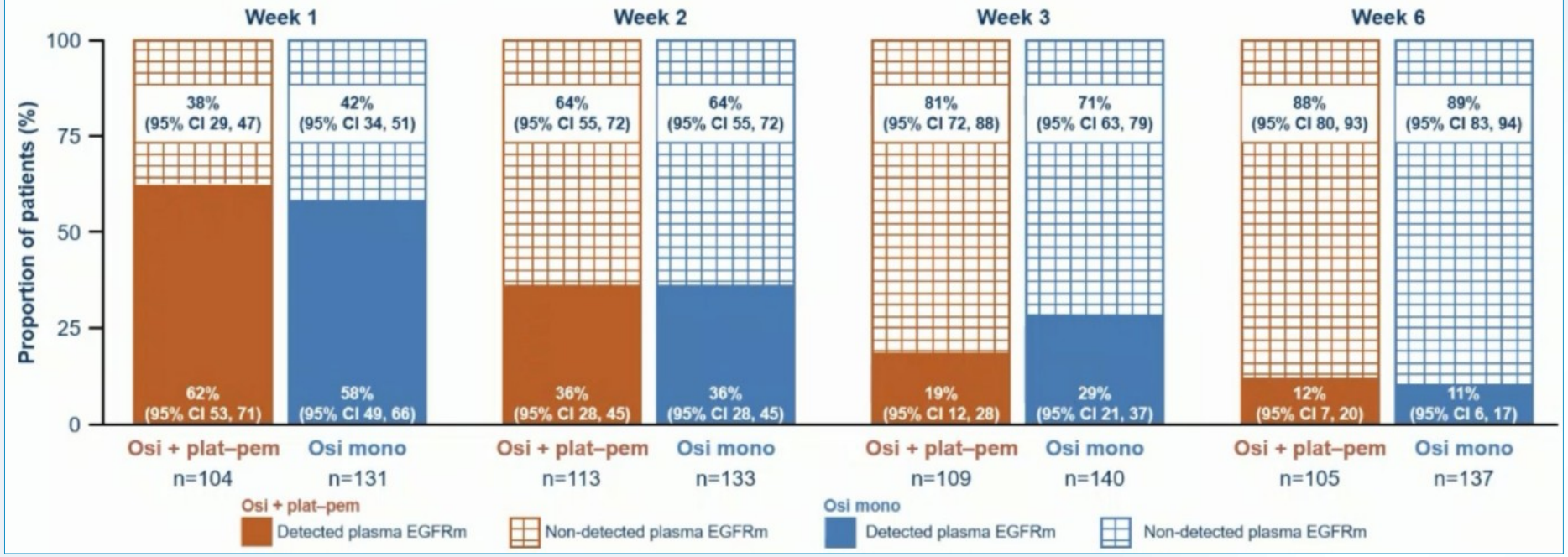
Grade 1/2 skin events 18%; VTE 15%; Peripheral edema 32%

Cho BC et al, ESMO 2026.

FLAURA2: Ct-DNA clearance

421 / 557 (76%) patients enrolled in FLAURA2 had an evaluable baseline plasma EGFRm ddPCR result (ctDNA analysis set)[1]

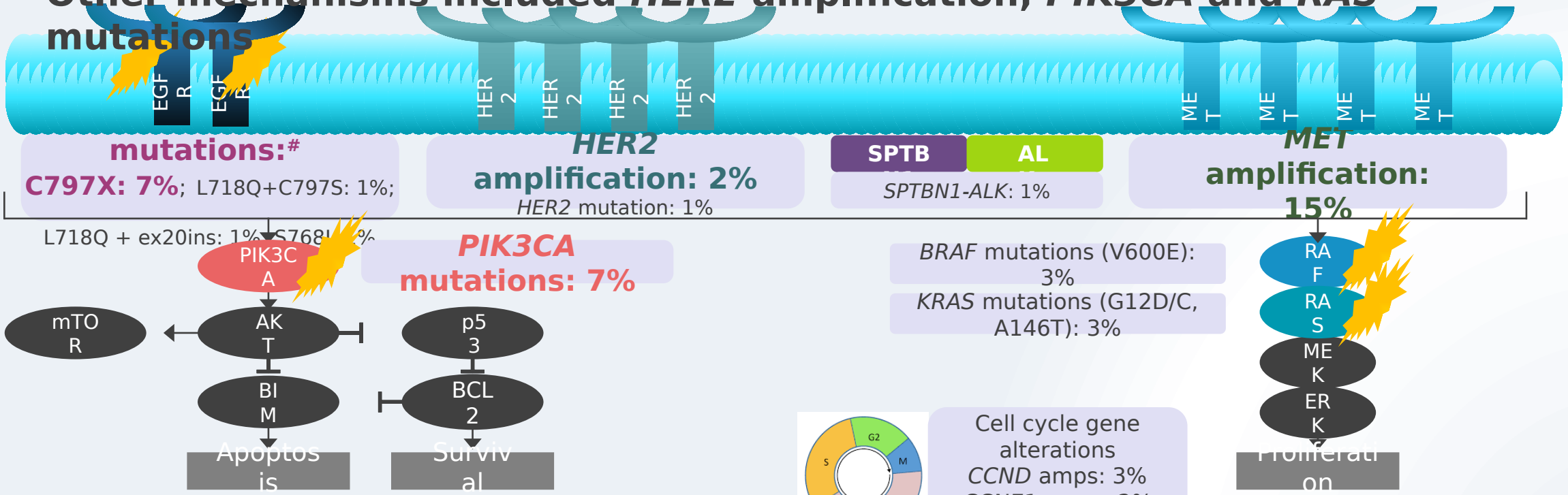
Of those patients included in the ctDNA analysis set, plasma EGFRm at baseline was detected in 147 / 212 (69%) patients in the osi + plat–pem arm and 161 / 209 (77%) patients in the osi mono arm[1]



Planchard D et al, ESMO 2026

Osimertinib Candidate Resistance Mechanisms

- **No evidence of acquired EGFR T790M**
- **The most common resistance mechanisms were *MET* amplification and *EGFR* C797S mutation**
  - **Other mechanisms included *HER2* amplification, *PIK3CA* and *RAS* mutations**



Ramalingam S et al, ESMO 2018; Chmielecki et al, Nat Comm, 2023.

Options for patients with acquired resistance

- Local therapy with continuation of TKI for oligoprogression
- Chemotherapy
- Chemotherapy + Amivantamab
- Datopotamab deruxtecan
- Consider histological transformation to SCLC or squamous histology
- Test for mechanism of acquired resistance

SAFFRON: Osimertinib + Savolitinib in MET+ EGFR^{MT} NSCLC

Setting: Treatment of acquired resistance to EGFR TKI

Biomarker: MET IHC 3+ or FISH >10 copies in post-progression biopsy

Regimen: Osimertinib + Savolitinib (300 mg BID) vs. Chemo

N= 338 patients (out of 1746 screened)

mPFS: 7.6 m vs. 5.4 m

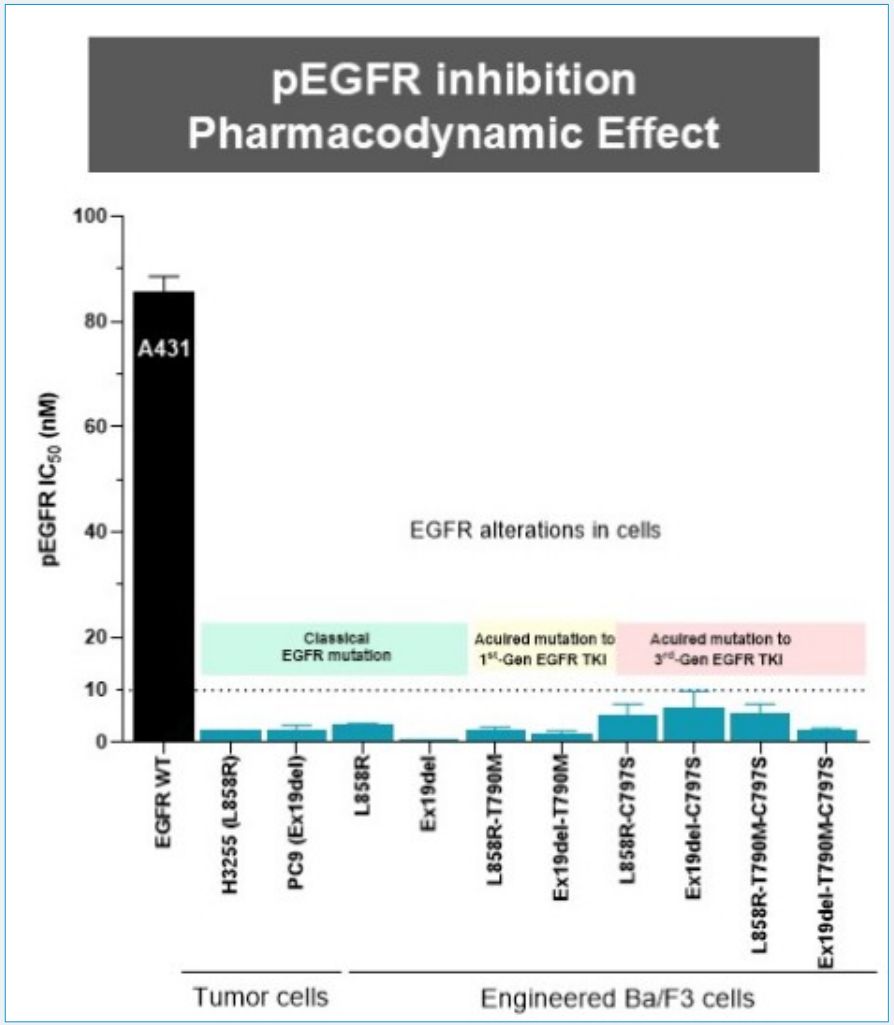
mOS: 17.8 m vs. 12.9 m

Response rate: 51% vs. 27%

Salient AEs: Peripheral edema, anemia, diarrhea, nausea & elevated CPK

Lu S et al, NEJM, 2026

4th Gen TKI (DZD 6008): Inhibiting classical and resistance mutations



	40 mg QD (n = 17)	60 mg QD (n = 21)
ORR, n (%) [95% CI]	7 (41.2) (18.4, 67.1)	9 (42.9) (21.8, 66.0)
DCR, n (%) [95% CI]	16 (94.1) (71.3, 99.9)	19 (90.5) (69.6, 98.8)
BOR, n (%)		
PR	7 (41.2)	9 (42.9)
SD	9 (52.9)	10 (47.6)
PD	1 (5.9)	2 (9.5)
PFS rate at 6 mo, % (95% CI)	70.6 (38.9, 88.0)	61.8 (35.8, 79.8)
Median follow-up, mo	6.1	5.7

Wang M et al, ASCO 2026.

Targeting HER3 for Salvage Therapy of EGFR^{MT} NSCLC

Study	PANKU-Lung01		HERON-Lung01	
Regimen	Iza-Bren*	Chemo	Ruzaltatug Rezetecan**	Chemotherapy
mPFS	11.1 m	5.7 m	8.3 m	5.4 m
RR	60%	34%	60%	34%
Survival HR (Prelim)	0.66		0.70	
Salient AE with ADC	Febrile neutropenia, Asthenia		Neutropenia, Anemia, Nausea, Transaminitis	

*Iza-Bren: Anti-EGFR and HER3 ADC
**Ruzaltatug Rez: Anti-HER3 ADC

Zhang L et al, ESMO 2026; Xu, C et al, Lancet 2026.

ADAURA: 8-Year Update

- ADAURA trial demonstrated efficacy of osimertinib as adjuvant therapy
- Improvement in DFS and OS for stages IB, II and IIIA
- Update at WCLC 2026
- 8-years survival rate 79% vs. 64%

Stage	8-year OS
IB	91% vs. 77%
II	78% vs. 63%
IIIA	70% vs. 52%

Herbst R et al, WCLC 2026.

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EGFR Exon 20 Insertion Mutation

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PAPILLON: Amivantamab + Chemotherapy

Setting: 1st line EGFR Ex 20 insertion

Regimen: Chemotherapy with or without amivantamab

N= 308 patients

mPFS: 11.4 m vs. 6.7 m (reported previously)

mOS: 34 m vs. 28 m, HR 0.87, NS

High proportion of cross over in control arm

Kim C et al, WCLC 2026.

REZILIENT 3: Zipalertinib + Chemotherapy

Setting: 1st line therapy for pts with metastatic EGFR Ex 20 insertion

Design: Chemotherapy with or without zipalertinib (100 mg PO BID)

N=279 pts

mPFS: 14.5 m vs . 8.5 m (HR 0.50)

Response rate: 65% vs. 40%

Preliminary survival results: 0.72

Adverse events: Anemia, neutropenia, rash (Gr 3 11%), stomatitis (Gr 3 5%) and pneumonitis (5.7%)

Tan D et al, WCLC 2026

WU-KONG 28: Sunvozertinib Vs. Chemotherapy

Setting: 1st line therapy for pts with EGFR Ex 20 insertion

Regimen: Sunvozertinib 300 mg QD vs. chemotherapy

N= 324 pts

mPFS: 10.3 m vs. 7.5 m

Response rate: 59% v. 31%

Salient AEs: Diarrhea (GR 3 14%), Skin rash, elevated CPK (Gr 3 20%), paronychia and anemia.

Zhou C et al, NEJM, 2026.

Recommendations for EGFR Ex 20 Insertion

- Multiple choices for 1st line therapy
  - Chemo + Amivantamab
  - Chemo + Zipalertinib
  - Sunvozertinib
- Pro-active toxicity management
- Need studies to define optimal sequencing

Conclusions

- Increasing therapeutic options for patients with EGFR mutation
- Outcomes have improved steadily with survival exceeding 4 years for patients with classical mutations
- Emerging novel options are poised to improve outcomes
- Exon 20 insertion mutation is a distinct biological sub-type with new treatment options