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EGFR-MUTATED NSCLC: ACQUIRED RESISTANCE

When first-line therapy stops working

How ctDNA, real-world data, and emerging regimens are reshaping resistance management.

Mechanisms of Acquired Resistance

Only 35% of evaluable patients on frontline osimertinib had a detectable acquired resistance mechanism—meaning that for the majority of patients, the cause of acquired resistance is unexplained.

16%
***MET* Amplification**

10%
***EGFR* Mutations**

14%
Had more than 1 Resistance Mechanism

Catching Resistance Early

In FLAURA, ctDNA signals of disease progression preceded or co-occurred with radiographic progression in **nearly two-thirds of patients**—offering a window to act before imaging catches up.

64%
of patient's ctDNA progression preceded or co-occurred with RECIST-defined progression

3.4 Months
median lead time from ctDNA progression to radiographic progression (osimertinib arm)

ctDNA as an early warning system

- Median time from ctDNA progression to first subsequent treatment: **6.0 months (osimertinib) vs 4.7 months (comparator)**
- ctDNA can signal molecular relapse before clinical or imaging changes are apparent
- Tissue biopsy and liquid biopsy at progression are both recommended —they don't always yield the same information

How the Combination Regimens Compare

Amivantamab + lazertinib (MARIPOSA)

***MET* amplification rate:**
3.4% vs 13.1% with osimertinib alone

Secondary *EGFR* resistance mutations:
1.4% vs 7.6%

Mechanisms vs Monotherapy:
roughly a 4–5x reduction in key resistance

Osimertinib + chemotherapy (FLAURA 2)

Most common mechanisms:
MET amplification (**16%**)
and small cell cancer transformation (**13%**)

Median time from treatment start to tissue biopsy:
14.5 months
Resistance mechanisms were similar across both treatment arms; no novel mechanisms

Local Consolidative Therapy (LCT) as an Early Intervention

25.3
MONTHS
Median PFS LCT + osimertinib (NorthStar trial)

17.5
MONTHS
Median PFS osimertinib alone (HR 0.66)

- **Higher radiation dose (BED ≥75 Gy) dramatically extended PFS: 49.1 months vs. 22.3 months (HR 0.31)**
- Disease recurrence after LCT occurred primarily at new distant sites—not within the radiation field
- Postinduction clearance of thoracic nodes and pleural effusion may predict who will benefit most from LCT

Emerging therapies after resistance

Most second-line strategies under investigation involve some form of chemotherapy — but novel mechanisms are entering the picture.

Amivantamab + chemotherapy ± lazertinib

After osimertinib progression · MARIPOSA-2

PFS vs chemo alone:

- **Amivantamab + chemo: HR 0.48**
- **Amivantamab + lazertinib + chemo: HR 0.44**

Sacituzumab tirumotecan (sac-TMT)

TROP2-directed ADC · OptiTROP-Lung04

Median PFS:
8.3 months vs. 4.3 months
(chemo; HR 0.49)

Median OS:
Not reached vs. 17.4 months
(HR 0.60)

Ivonescimab + chemotherapy

VEGF–PD1 bispecific antibody · HARMONi trial

Median PFS:
6.8 months vs. 4.4 months
(chemo alone; HR 0.52)

Median OS:
16.8 months vs. 14.0 months
(HR 0.79)

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