

Frontline Choice Anchors Sequencing Decisions in *EGFR*-Mutated NSCLC

Frontline treatment determines later-line options

Patients who receive:



Osimertinib alone

Retain the widest range of second-line options



Osimertinib + chemotherapy

Fewer sequencing options remain



Amivantamab + lazertinib

Those agents are no longer available later, narrowing future treatment choices

Best Available Evidence After Frontline Osimertinib

MARIPOSA-2 (Phase 3)

Median PFS

HR = 0.48

chemotherapy alone

4.2
Months

amivantamab +
chemotherapy

6.3
Months

Median PFS

HR = 0.44

amivantamab +
lazertinib + chemotherapy

8.3
Months

Overall survival data
remain immature

Emerging Later-Line Option

Datopotamab Deruxtecan (Dato-DXd)

A chemotherapy-sparing option after *EGFR* TKI progression



Response Rate

43%



Median PFS

5.8 Months



Median Overall Survival

15.6 months

Responses observed across:

- Common *EGFR* mutations
- Uncommon *EGFR* mutations
- Multiple resistance mechanisms

COMPEL Trial

Median PFS

HR = 0.43

osimertinib + chemotherapy

8.4
Months

chemotherapy + placebo

4.4
Months



Potential Advantage:

Similar efficacy with potentially improved tolerability compared with amivantamab-based combinations (study was small).

Additional Emerging Therapies

Median PFS

HR = 0.53

ivonescimab + chemotherapy

6.8
Months

chemotherapy alone

4.4
Months



Currently under FDA review:

Did not yet meet the OS end point at interim analysis

Sacituzumab Tirumotecan (Sac-TMT)



- TROP2-directed ADC
- Approved in China; not yet FDA approved
- Improved both PFS and OS vs chemotherapy

Clinical Practice Pearls



Frontline treatment determines later-line sequencing



Efficacy and tolerability should both guide treatment selection



Repeat liquid/tissue biopsy at progression may identify:

- *MET* amplification
- Small cell transformation
- Other actionable resistance mechanisms

Treatment sequencing begins with the frontline regimen

The growing number of effective therapies—including targeted combinations, ADCs, and novel immunotherapy approaches—makes selecting the optimal first-line treatment increasingly important because it directly shapes future treatment options.