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Perspectives on *EGFR*-mutant and wildtype NSCLC: Tailoring treatment advances in late-stage disease

Clinical summary for Module 1: *EGFR*-mutant NSCLC

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Advances in *EGFR*-mutant NSCLC to address unmet needs

Research to focus on more personalized and effective therapies

"More than half of patients will develop brain metastases or leptomeningeal disease and these are sites of metastatic disease that are associated with a lot of morbidity and mortality in our patients, so understanding how effective novel therapies are is key."

Faculty and topics

Dr Helena Yu, CD presented on how the clinical trial landscape is evolving to address unmet needs in the metastatic setting

Key areas for research

Overcoming resistance mechanisms[1]

- Understand specific resistance mutations
- Role of dual inhibitor approaches

Novel therapeutic strategies[1]

- Role of upfront combination strategies
- Assessment of risk-benefit ratio (e.g. ↑ toxicities)

Biomarker development[2]

- Identify markers to monitor/ predict treatment response
- Methods to detect resistance early

Addressing CNS metastases[3]

- Inclusion of patients with CNS metastases in clinical trials to assess intercranial activity

Key takeaways for ongoing research

- Ensure inclusion of diverse patient populations in clinical trials to improve generalizability of results
- Apply advances in risk stratification to inform risk-adaptive treatment strategies

EGFR-mutant NSCLC: Key clinical trial data in the first line

Combination approaches

Phase III: FLAURA2[4]

Osimertinib ± Pt-ChT
vs osimertinib

- **Overall PFS was significantly longer in** the **combination** group vs monotherapy (HR 0.62; 95% CI, 0.49–0.79; p<0.001)
- **PFS benefit** with the combination was **consistent across subgroups, including CNS metastases**
- There was a **higher incidence of grade ≥3** adverse events and haematological effects in the **combination group** vs osimertinib

Phase III MARIPOSA[5,6]

Amivantamab + lazertinib
vs osimertinib

- **Median PFS** was **improved** in the **combination** group vs osimertinib alone (HR 0.70; 95% CI, 0.58–0.85; p<0.001)
- **PFS benefit** with the combination was **consistent across all subgroups, including CNS metastases**
- There were **higher incidences of grade ≥3** adverse events and VTE in the **combination group** vs osimertinib

OS data outstanding for both combination approaches

Faculty and topics

Dr Antonio Passaro presented on key clinical trial results reported in the last 12 months in both the first and second line

Secondary analysis: mPFS in high-risk groups[7]

- **PFS outcomes were better among high-risk patients** (including brain and liver metastases, and *TP53* co-mutations) who received amivantamab + lazertinib vs osimertinib

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EGFR-mutant NSCLC: Key clinical trial data in second and later line

Novel agents

Phase II
HERTHENA-Lung01[8]
Patritumab deruxtecan
(post osimertinib and ChT)

- **Overall response rate** in patients with **CNS disease was similar** to that in **all patients** (28.7% vs 29.8%)
- Most common **grade ≥3** adverse events were **haematological toxicities**

- **HERTHENA-Lung02**[9] phase II trial ongoing in patients progressing on a third-generation EGFR TKI

Phase III
HARMONi-A[10*]
Ivonescimab + ChT vs ChT
(post EGFR-TKI)

- **PFS was significantly improved** in the **combination arm** vs ChT (HR 0.46; 95% CI, 0.34–0.62; p<0.0001)
- **PFS benefit** also observed in patients who: **progressed on a third-generation EGFR TKI;** had **brain metastases;** possessed an ***EGFR* deletion 19** or ***T790*M mutation**
- Incidences of **grade ≥3** adverse events **higher** in the **combination group** vs ChT

Combination approaches

Phase III
MARIPOSA-2[12]
IV amivantamab + Pt-ChT
± lazertinib vs Pt-ChT
(post osimertinib)

- **PFS was significantly longer with amivantamab + ChT** vs Pt-ChT (HR 0.48; 95% CI, 0.36–0.64; p<0.001) and in patients with **intracranial disease** (HR 0.52; 95% CI, 0.35–0.78)
- Incidence of **grade ≥3** adverse events **higher** in the **amivantamab + Pt-ChT group** vs Pt-ChT

Phase III
PALOMA-3[13]
SC vs IV amivantamab
+ lazertinib
(post osimertinib and ChT)

- **SC administration** demonstrated **noninferiority pharmacokinetics** compared to IV administration: the change in C_{trough} and $AUC_{D1\text{-}D15}$ remained similar between groups
- **Higher incidences** of **any grade IRRs and VTEs** in IV group vs SC

*Study conducted in China (Asian population).[11]

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EGFR-mutant NSCLC: Implications of latest data for clinical practice

Evolving therapeutic options in advanced/metastatic *EGFR*-mutant NSCLC

"I think in the near future, there will be more complexity in the various options that we might have… It is key to continue to follow closely new data as it comes out and to figure out what would be the appropriate biomarkers to help us pick which patients for which different combination therapies."

Faculty and topics

Dr Helena Yu, CD presented a clinical case and discussed the current and evolving treatment options for improved outcomes

Current and future strategies

NCCN/ESMO Guidelines[14,15]

- Osimertinib is the preferred 1L option
- In 2L, treat based on resistance mechanisms (clinical trial) or standard of care Pt-ChT

Novel 1L strategies[1]

- Know when to escalate or de-escalate treatment according to adaptive response
- Role of prognostic markers

Novel 2L strategies[8,10,11]

- Amivantamab + ChT
- Ivonescimab + ChT
- Patritumab deruxtecan (HER3-DXd)

High-risk groups[4–6]

- Assess CNS efficacy (and efficacy in high-risk subgroups) evaluated in clinical trials for novel therapies

Key takeaways for clinical practice

- Clinical trials in the first line focus on combination therapies
- Clinical trials in the second line focus on adding agents to the standard of care, chemotherapy

Abbreviations and references

Abbreviations

1/2L, first-/second-line; AUC_{D1-D15}, area under the curve from cycle-2 day-1 to day-15; CD, course director; ChT, chemotherapy; CI, confidence interval; CNS, central nervous system; C_{trough}, trough concentrations; EGFR, epidermal growth factor receptor; HR, hazard ratio; IRR, infusion-related reaction; IV, intravenous; m, median; NSCLC, non-small cell lung cancer; OS, overall survival; Pt-ChT, platinum-based ChT; PD, progressive disease; PFS, progression-free survival; SC, subcutaneous; TKI, tyrosine kinase inhibitor; VTE, venous thromboembolism.

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