Tepotinib in second line NSCLC treatment

Dr Antonio Passaro (European Institute of Oncology, Milan, Italy) and Prof Raffaele Califano (The Christie and Manchester University Hospital, Manchester, UK) discuss the role of tepotinib as second-line treatment for patients with stage IV non-small cell lung cancer (NSCLC) harbouring a MET exon 14 skipping mutation.

Using a real-world clinical case, Prof Califano outlines treatment sequencing following disease progression on first-line chemo-immunotherapy, highlighting the importance of rebiopsy and comprehensive molecular testing. The case demonstrates a sustained clinical response to tepotinib with a manageable safety profile.

Context and aim of discussion

- Expert forum discussion on the role of **tepotinib as second-line treatment** for stage IV non-small cell lung cancer (NSCLC) with **MET exon 14 skipping mutation.**
- Case-based format to highlight real-world efficacy, safety, and testing challenges.

Clinical case overview

- Patient: 78-year-old Caucasian woman, former smoker, good baseline performance status (PS 1), limited comorbidities.
- Presentation: progressive dyspnoea and haemoptysis; imaging revealed right lower lobe lung mass with liver metastases (T2N1M1c).
- Diagnosis: lung adenocarcinoma, TTF-1 positive; initial molecular testing negative for EGFR, ALK, ROS1; PD-L1 expression 45%.
- NGS could not be performed initially due to insufficient tissue.

First-line management and outcome

- Patient declined re-biopsy to avoid treatment delay.

- Treated with **carboplatin, pemetrexed, and pembrolizumab**, achieving partial response.
- Maintenance pemetrexed plus pembrolizumab continued with manageable toxicity.
- Disease progression occurred after ~10 months, mainly in the liver.

Importance of re-biopsy and molecular testing

- Re-biopsy via EBUS performed at progression.
- NGS revealed a **MET exon 14 skipping mutation**, highlighting the risk of missing actionable drivers without comprehensive profiling.
- Speakers stress that **complete molecular testing is mandatory**, regardless of smoking history or PD-L1 status.

Second-line tepotinib treatment

- Tepotinib initiated December 2022.
- Achieved partial radiological response after three months.
- Treatment well tolerated; adverse events included mild peripheral oedema, diarrhoea, and nausea.
- Patient remained on tepotinib for ~20–21 months before CNS and systemic progression.

Safety and management insights

- Peripheral oedema identified as the key class toxicity for MET inhibitors.
- Most cases are grade 1–2 and manageable with supportive care, mobility advice, and dose reduction if needed.
- Proactive toxicity management is essential to maintain long-term treatment benefit.

Key conclusions

- MET exon 14 mutations occur across smoking statuses and histologies.
- Tepotinib provides superior outcomes versus standard chemotherapy in pre-treated patients.
- **Early, comprehensive molecular testing is critical** to optimise sequencing and avoid suboptimal or harmful treatment choices.