Treatment of advanced non-small cell lung cancer with driver mutations

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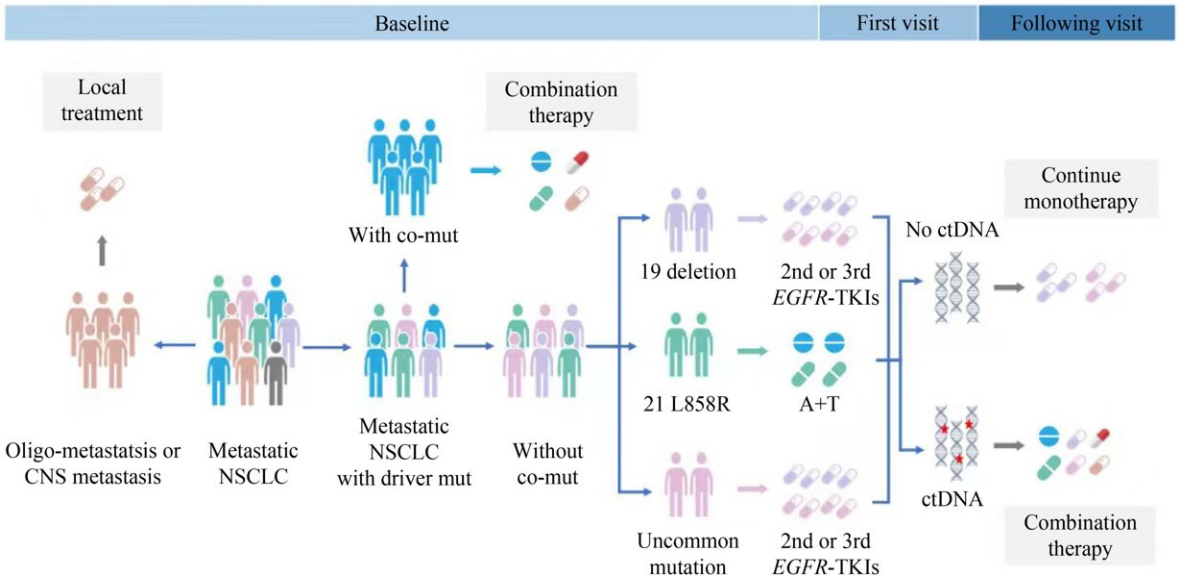

Graphical abstract. Credit: *Frontiers of Medicine* (2023). DOI: 10.1007/s11684-022-0976-4

Lung cancer is the leading cause of cancer-related death worldwide. Improved understanding of driver mutations of non-small cell lung cancer (NSCLC) has led to more biomarker-directed treatment for patients with advanced stages. The expanding number of drugs targeting these driver mutations offers more opportunity to improve patient's survival benefit.

A study titled "Treatment of advanced non-small cell lung cancer with driver mutations: current applications and future directions" has been published in the journal *Frontiers of Medicine*.

To date, NSCLCs, especially those with non-squamous histology, are recommended for testing epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) gene rearrangements, ROS proto-oncogene receptor tyrosine kinase 1 (ROS-1) rearrangements, B-raf proto-oncogene (BRAF) mutations, rearranged during transfection (RET) fusions, Met proto-oncogene (MET) amplification and exon 14 skipping alterations, neurotrophic receptor tyrosine kinase (NTRK) gene fusions, and immunohistochemistry (IHC) testing for the programmed death receptor-ligand 1 (PD-L1) expression.

EGFR-activating mutations are the most common driver mutations in NSCLC. Targeted therapies included first-generation epidermal growth factor inhibitor tyrosine kinase inhibitors (EGFR-TKIs), erlotinib, gefitinib, and icotinib; second-generation pan-human epidermal growth receptor (HER) family inhibitor, afatinib and dacotinib; and third-generation EGFR-TKI, osimertinib, that inhibits both EGFR-sensitive mutations and resistant mutation EGFR T790M.

ALK inhibitors included first-generation, crizotinib; second generation, ceritinib, alectinib, and brigatinib; and third-generation, lorlatinib, with increasing capacity for ALK inhibition generation-by-generation.

The resistance caused by secondary ALK mutations can be overcome by next-generation ALK-TKIs. Moreover, alectinib, brigatinib, and lorlatinib are all recommended as first-line treatment choice for ALK-rearranged NSCLC for their superior survival compared with crizontinb.

Crizotinib, ceritinib, brigatinib, and lorlatinib can also inhibit ROS-1. BRAF inhibitor dabrafenib combined with MEK inhibitor trametinib is

now the recommended treatment for BRAF V600E-mutated NSCLC attributing to improved outcomes compared with vemurafenib or dabrafenib monotherapy.

Drugs targeting MET aberrations with different binding modes included type Ia, crizotinib; type Ib, tepotinib, capmatinib, and savolitinib; and type II, cabozantinib. Entrectinib and larotrectinib are the current standard treatment for NTRK fusion-positive NSCLC.

Kirsten ratsarcoma viral oncogene homolog (KRAS) mutations occur in ~20%–30% of patients with NSCLC. Recently, several small molecules including sotorasib (AMG510), adagrasib (MRTX-849) have been developed to specifically target KRAS G12C.

Although drugs targeting oncogenic driver mutations have significantly improved survival, their long-term responses are still uncommon for most patients, and the emergence of acquired drug resistance is inevitable. Therefore, exploration and understanding of the resistance mechanism of target therapy are important to enhance the clinical outcomes and ultimately increase the treatment rate of NSCLC.

Improved understanding of biological characteristics in various molecular subtypes of each driver mutation helps explore new classified treatment strategies.

Until recently, multiomics analysis has ushered in a new era of precision targeted therapy in lung cancer and led to a deeper understanding of the underlying resistant mechanism. All these scientific and clinical progresses ultimately lead to improved survival in NSCLC and achieve more refined individualized treatment.

The discovery of oncogenic driver alterations and target therapy have brought significant clinical benefits and established an individualized

treatment approach. The management of advanced NSCLC has shifted from a histology based on a biomarker-driven process.

The treatment landscape of oncogenic-addicted NSCLC has become complex. On the one hand, more individualized treatment based on fine stratification has become the focus of research nowadays. The choice of optimal treatment strategy should consider gene subtype, concomitant mutation, dynamic gene alternation, and metastasis site. On the other hand, understanding primary and acquired resistance to targeted therapy provides an insight into the molecular evolution of tumor development.

The recognition of resistant mechanisms is the basis to design new drugs or combinatorial therapeutic strategies.

Combination strategies require integration with immunotherapy, and the immunosuppressive microenvironment should be reversed to improve the sensitivity of ICIs by the drug combination.

The authors say we should also be aware of the possible risk of combined toxicity and therefore explore the optimal timing and combined regimen of immunotherapy.

The interaction between driver mutations and immune-microenvironment is essential to uncover drug resistance and establish robust predictive biomarker for the NSCLC with driver mutations, in order to identify specific oncogenic driving patients with NSCLC who can benefit from immunotherapy.

More information: Jia Zhong et al, Treatment of advanced non-small cell lung cancer with driver mutations: current applications and future directions, *Frontiers of Medicine* (2023). DOI:

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