Targeting chimeras fusion proteins in non-small cell lung cancer: where are we going?

The advent of precision medicine has revolutioned the therapeutic landscape of non-small cell lung cancer (NSCLC), leading to a significant increase of patients' life expectancy and quality of life, with a 5-year survival rate of 21.7% nowadays, compared to 17.2% ten years ago (1). Since the discovery of the *epidermal growth factor receptor* (*EGFR*) sensitizing mutations in 2004 (2), the number of targetable alterations detected in lung cancer patients has progressively increased, thus extending the percentage of potential candidates to personalized treatment strategies. Alongside *EGFR*, *BRAF (v-Raf murine sarcoma viral oncogene homolog B)*, *KRAS (kirsten rat sarcoma 2 viral oncogene homolog)* and c-*MET* (*hepatocyte growth factor receptor*)-exon 14 mutations, different chromosomal rearrangements involving *ALK* (*anaplastic lymphoma kinase)*, *ROS1 (v-ros avian UR2 sarcoma virus oncogene homolog 1)*, *RET (rearranged during transfection)*, and *NTRK (tropomyosin receptor kinase A)* genes, have been recently identified as druggable targets in a relevant subgroup of metastatic NSCLC patients, with both old and new-generation tyrosine-kinase inhibitors (TKIs) already available or coming soon in the clinical setting (3). Crizotinib represented the first example of successful targeted therapy available for the treatment of metastatic NSCLC patients harboring either *ALK* or *ROS1* chromosomal rearrangements (4,5). The subsequent introduction of more effective and better tolerated second/third-generation TKIs into clinical practice has dramatically improved patients' outcomes (6-8), leading to unprecedent long-term survival, even compared with other oncogene-addicted NSCLC subgroups. The NTRK inhibitors Entrectinib (9) and Larotrectinib (10) were the first targeted agents receiving a tissue agnostic approval by the Food and Drug Administration (FDA), for the clinical treatment of patients with NTRK gene fusion positive advanced solid tumors, including lung cancer. More recently the community of thoracic oncologists has celebrated the advent of new selective TKIs effectively targeting RET-rearranged metastatic disease (11). Despite the great efficacy of the new generation TKIs available for the clinical treatment of a relevant subgroup of NSCLC patients harbouring oncogenic rearrangements, however the histological and biological heterogeneity are well-known phenomena with significant impact on patients' response and survival outcomes, thus questioning the best upfront TKI to be selected in order to delay the occurrence of disease progression. The series "Looking for chimeras in NSCLC: Widen Therapeutic Options Targeting Oncogenic Fusions", published in *Translational Lung Cancer Research* (*TLCR*) addresses the actual and controversial topic of the best treatment sequences across the different subgroups of NSCLC harboring oncogenic fusions (*ALK*, *ROS1*, *RET*, *NTRK*, *NRG1*), including also the optimal strategies for the clinical management of oligo-metastatic/progressive diseases.

A deeper understanding of innate/acquired resistance to the different TKIs already available for clinical use and the development of new effective treatment strategies to overcome it, represent a current area of intense investigation and has been extensively debated within different papers published in the series.

Since we are now moving towards genomic-driven therapeutic sequences in order to identify the best candidate to tailored strategies (12), a non-invasive detection/monitoring of genomic alterations through circulating tumor DNA/RNA analysis is emerging as a reasonable approach to guide treatment decision during the disease course. Two different specific papers will discuss current evidence and technical issue related to both tissue and plasma genotyping methods for detecting oncogenic rearrangements in NSCLC patients. Finally the role of immune-checkpoint inhibitors in the treatment algorithm of fusion driven metastatic NSCLC, the potential application of targeted therapies in the early stage setting, as well as the future perspectives emerging from pre-clinical models, have been specifically discussed in dedicated literature reviews.

In conclusion the series "Looking for chimeras in NSCLC: Widen Therapeutic Options Targeting Oncogenic Fusions" addresses the most relevant questions related to the clinical management of NSCLC patients harboring oncogenic rearrangements, reporting an updated and detailed overview of current available evidence and providing critical discussions by key experts in the field.

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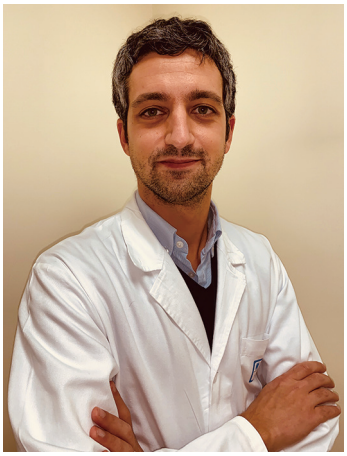

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