Editorial

# Targeting gene fusions in non-small cell lung cancer—a ceaseless success story?

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Lung cancer associates with most cancer-related deaths worldwide. Approximately 85% of all lung cancer cases classifies as non-small cell lung cancer (NSCLC) (1). During the past decade, we have experienced an incredible advancement in therapeutic compounds targeting subgroups of NSCLC, driven by specific genetic alterations, resulting in a substantial fraction of all NSCLC patients, as of today, being amenable for treatment with targeting therapies. Targeted therapies in NSCLC involve tyrosine kinase inhibitors (TKIs) as well as RAS GTPase family inhibitors. Despite the early Food and Drug Administration (FDA)-approval of gefitinib in 2003, a TKI targeting epidermal growth factor receptor (EGFR), it took several years until targeted therapies confirmed a clinical benefit compared to chemotherapy in sub-groups of NSCLC. This was due to a lag of biomarker awareness to properly select NSCLC patients for targeted therapy (2).

In addition to *EGFR*-mutant NSCLC and Kirsten rat sarcoma viral oncogene homolog (*KRAS*)-mutant NSCLC, numerous gene-fusions may act as drivers in NSCLC. In a recent review-article by Chen *et al.*, the authors summarize the evolvement of targeting gene fusions and the corresponding clinical efficacy in NSCLC (3). A relatively small portion of NSCLC consists of gene-fusions that are targetable in the clinic. The most common targetable gene-fusions in NSCLC are fusions involving the anaplastic lymphoma kinase (*ALK*), followed by fusions of ROS proto-oncogene 1 (*ROS1*), and rearranged during transfection proto-oncogene (*RET*). Together they account for up to 10% of NSCLC cases (4). The first targeted therapy reaching FDA-approval for NSCLC with gene fusions was crizotinib in 2011. Crizotinib was approved for patients with locally advanced or metastatic NSCLC displaying positivity for ALK (5). Since then, multiple ALK-inhibitors, including ceritinib, alectinib, brigatinib, lorlatinib, and ensartinib have been FDA-approved for treatment of ALK-positive NSCLC patients following resistance to crizotinib, or in the first-line setting. The remarkable development of agents targeting *ALK* fusions in NSCLC has propelled progression-free survival from only a few months with chemotherapy to more than 30 months with specific ALK targeted therapies (6). Moreover, the majority of ALK-positive NSCLC patients receiving second-generation ALK TKIs in the first-line setting are still alive 5 years after treatment initiation, which is a substantial survival improvement for this patient group compared to a decade ago (7).

*ROS1* fusions are more rare than *ALK* fusions and only account for 1–2% of NSCLC cases. As with the case of ALK-positive NSCLC, crizotinib was the first TKI to be FDA-approved for targeting ROS1-positive NSCLC. Other TKIs evaluated in the clinical setting for ROS1-positive NSCLC include lorlatinib, ceritinib, entrectinib and talatrectinib. Median progression-free survival is

reported up to 20 months in ROS1-positive NSCLC patients receiving ceritinib or entrectinib (8).

Like *ROS1* fusions, *RET* fusions occur in approximately 1–2% of NSCLC patients. Two TKIs have been FDA-approved for NSCLC with *RET* fusions, selpercatinib and pralsetinib with median progression-free survival reported around 16 months (9).

Among the even less common gene fusions in NSCLC, there are targeted therapies, including larotrectinib and entrectinib, being used in neurotrophic tropomyosin-receptor kinase (*NTRK*)-positive NSCLC. Like other studies investigating the clinical efficacy of agents targeting gene fusions in NSCLC, overall response rates and median progression-free survival looks promising with the latter approaching 30 months (10). Other gene fusions of potential interest include neuregulin 1 (*NRG1*) fusions, fibroblast growth factor receptor (*FGFR*) fusions, mesenchymal-to-epithelial transition (*MET*) fusions, *EGFR* fusions, and B-type Raf kinase (*BRAF*) fusions. However, data of clinical efficacy from targeting NSCLC with these fusions is still too immature to draw any solid conclusions (3).

While there is no doubt that the introduction of targeted therapies in gene fusion positive NSCLC has dramatically improved treatment efficacy with relatively limited adverse events, there are still numerous unanswered questions related to optimal treatment schedules in individual patients. In ALK-positive NSCLC, crizotinib was recommended as first-line therapy until the results of the global phase III ALEX trial revealed a more than three times improved progression-free survival in patients receiving alectinib compared to patients receiving crizotinib (11). In addition to alectinib, other ALK TKIs, such as brigatinib and lorlatinib, may also be considered in the first-line treatment setting of ALK-positive NSCLC. The shift from crizotinib to second- and third-generation ALK TKIs is likely to significantly improve survival also in the real-world setting, which is supported by recently reported data (7). Although this is encouraging news, the long-term impact in relation to resistance mechanisms is only partially mapped and raise challenges when deciding on subsequent therapies following disease progression on first-line ALK TKI. There are numerous TKI resistance mutations in the ALK kinase domain and different ALK TKIs have various potencies in targeting these mutations. The most common mutation following second-generation ALK TKIs alectinib and brigatinib is G1202R, occurring in 29% and 43% of patients, respectively. Lorlatinib displays potency to G1202R, at least *in vitro*, making lorlatinib a reasonable choice following disease progression on alectinib or brigatinib with emergence of G1202R. There are also mutations reported to confer resistance to lorlatinib, including L1198F. Interestingly, L1198F has further been reported to re-sensitize cancer cells to crizotinib due to conformational changes resulting in altered binding affinities to ALK TKIs (12). This emphasizes the extreme complexity in resistance mechanisms to ALK TKIs and the necessity to longitudinally monitor patients for ALK TKI kinase domain mutations. A detailed and longitudinal mapping of new mutations in the ALK kinase domain should likely aid in clinical decision making on ALK TKI sequence and potential ALK TKI re-challenge. However, we should keep in mind that various genetic alterations in the ALK kinase domain only account for a fraction of all ALK TKI resistance cases in NSCLC, highlighting the need of additional biomarkers of ALK TKI resistance, including biomarkers in the RNA and protein landscape.

Another aspect that may impact decision on ALK TKI sequence is location and magnitude of metastasis along the course of treatment since the potency of crossing the blood-brain barrier varies across ALK TKIs. Moreover, there is limited knowledge of a potential impact on the efficacy of different ALK TKIs in relation to various ALK fusion partners. The fusion of 5' echinoderm microtubule-associated protein-like 4 (EML4) and 3' ALK is the most common fusion event for ALK-positive NSCLC. However, this fusion type alone contains numerous variants contributing to a complex biology in ALK-positive NSCLC. There is contradictory data on whether the ALK fusion event impacts disease prognosis with some studies suggesting that shorter fusion variants may correlate with more aggressive disease potentially arguing for customized treatment (13). ALK fusions occur in approximately 5% of NSCLC cases and constitute the most common gene fusion event in NSCLC amenable for targeted therapies. There is a substantially larger amount of clinical data from patients being treated with ALK TKIs compared to TKIs targeting other gene fusions in NSCLC. Decision making on optimal targeted therapy in cases with rarer fusion events may be even more challenging due to limited clinical data. Moreover, for all targetable gene fusion events in NSCLC, we need to take the geographical aspect into account, which likely impacts preference and availability of specific targeted therapies. Finally, we await additional targeted therapies for gene fusions not yet targeted in clinical practice. Until then, the review-article by Chen *et al.*, provides an important

asset to aid decision making of clinicians when facing NSCLC patients with gene fusion events (3).

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