Editorial

Predictive molecular pathology in lung cancer: the oncologist point of view

Francesco Passiglia[#], Paolo Bironzo[#], Silvia Novello

Department of Oncology, University of Turin, San Luigi Hospital, Orbassano, Italy

[#]These authors equally contributed to this work.

Correspondence to: Silvia Novello, MD, PhD. Department of Oncology, University of Turin, San Luigi Hospital, Orbassano, TO, Italy.
Email: silvia.novello@unito.it.

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Lung cancer certainly represents a successful example of the predictive molecular pathology paradigm application in cancer care, since it has become clear that the routine testing for molecular alterations and the progressive introduction of targeted therapies allowed to significantly reduce patients' mortality (1). Following the initial identification of epidermal growth factor receptor *(EGFR)* activating mutations as molecular predictor of EGFR tyrosine kinase inhibitors (TKIs) activity (2) in non-small cell lung cancer (NSCLC) patients, the number of molecular biomarkers has rapidly increased over the last few years, leading to a radical shift from histological to molecular subtype of lung cancer. Tumor molecular profiling is now considered a crucial step of the diagnostic and therapeutic management of metastatic non-squamous NSCLC, allowing to personalize therapeutic strategies and ultimately improve patients' survival.

Novel, potent, and highly selective TKIs are progressively entering the treatment algorithm of lung cancer patients harboring oncogenic drivers, including both clinical approved biomarkers, such as EGFR (12–15%), ALK (3–8%), ROS1 (1–2%), BRAF (2–4%), and NTRK (0.5–1%), and emerging ones, like RET (1–2%), MET exon14 skipping (2–3%), KRASp.G12C (10–12%), HER2 (2–3%), with targeted agents available either in clinical trials or in the real-world scenario. The advent of the third-generation EGFR-TKI, osimertinib, established a new survival plateau approaching 40 months in metastatic patients harboring EGFR-common alterations (Del19 and L858R) included within the phase III randomized FLAURA trial (3), while we have recently celebrated the regulatory approval of novel agents targeting the EGFR exon20 insertions, amivantamab and mobocertinib, offering new targeted opportunities to this hard to treat subgroup of EGFR-positive patients. A series of new generation TKIs, characterized by high intracranial activity and optimal tolerability, is now available for the clinical treatment of both ALK- (alectinib, brigatinib, ceritinib, ensartinib, lorlatinib) and ROS1-rearranged (crizotinib, entrectinib) NSCLC patients, reaching unprecedented survival outcomes and quality of life (4). Whether dual BRAF-MEK targeted inhibition by dabrafenib and trametinib combination certainly represents the most effective therapy for BRAF-V600E mutant NSCLC (5), however there are some concerns regarding the best upfront treatment for both non-V600E and non-V600 BRAF-mutant disease, considering the very low certainty of evidence coming from available studies and the lack of randomized comparison versus chemo-immunotherapeutic regimens. The promising results of phase I/II ARROW and LIBRETTO studies (6,7) have recently prompted the clinical approval of novel selective RET inhibitors, Pralsetinib and Selpercatinib, for the clinical treatment of pre-treated advanced NSCLC harboring *RET*-fusions, while the potential role of these agents in first-line is currently being investigated. Similarly, the phase II VISION and GEOMETRY studies showed encouraging antitumor activity with two different small molecules, tepotinib and capmatinib, selectively targeting *MET* exon 14 skipping alterations (8,9). A third selective inhibitor, savolitinib, has shown its activity in patients with sarcomatoid histology harboring the same molecular alteration (10). The recent resolution of the KRASp.G12C

binding pocket has been crucial to developing a new class of mutant-directed inhibitors, able to covalently bind and trap KRASp.G12C in its inactive state. These pre-clinical proof of principle have broken down the dogma that mutant KRAS was undruggable, leading to the design of early phase clinical studies testing selective KRASp.G12C inhibitors in patients with previously treated advanced NSCLC harboring p.G12C mutation subtype. Preliminary activity data emerging from both CodeBreak 101 and KRYSTAL-1 studies, suggested that both sotorasib and adagrasib are potential effective targeted options to be offered to about 12% of advanced NSCLC patients harboring KRASp.G12C mutation (11,12), gathering further investigation in larger randomized confirmatory studies. Preliminary results from the phase II DESTINY-Lung01 study, demonstrated great and durable tumor responses with the new anti-HER2 antibody-drug conjugate (ADC), trastuzumab deruxtecan, in heavily pre-treated, advanced NSCLC patients harboring HER2-mutations, definitively interrupting the negative trend of HER2 inhibition in lung cancer (13). Finally, larotrectinib and entrectinib are two selective TRK-inhibitors recently approved by regulatory authorities as tissue agnostic therapeutic options for patients with metastatic solid tumors harboring *NTRK*-rearrangements, regardless of tumor histotypes and/or lines of therapy (14,15).

The identification of an increasing number of "rare" targetable molecular alterations favoured the accelerated approval of novel molecules, based on biomarker-driven, early phase clinical studies results. Innovative umbrella design, including the LUNG-MAP Master Protocol (16) and the Lung-Matrix Trial (17) explored novel clinical research infrastructure, allowing the simultaneous testing of different genotype-based targeted therapies in molecularly selected cohorts. International cancer scientific societies have recently endorsed next generation sequencing (NGS)-based molecular profiling as a key component of NSCLC patients' standard management and care (18), definitively ensuring adequate detection of some elusive targets, like EGFR exon 20 insertion variants and NTRK rearrangements. However national molecular testing guidelines are still too heterogeneous across different European countries, and several additional logistic, cultural, and socioeconomic barriers limited patients' access to NGS-based molecular profiling and matched targeted treatments (19).

Tissue still represents the main issue in the era of predictive molecular pathology, while the liquid biopsy is emerging as a non-invasive reliable alternative approach with possible applications in different scenarios. A series of diagnostic accuracy clinical studies have definitively demonstrated a high concordance between tissue and ctDNA NGS-based molecular profiling (20,21), leading to the recent approval of the first ctDNA NGS diagnostic assay for the molecular profiling of advanced NSCLC patients in the United States. The ctDNA NGS analysis has shown to accurately detect molecular mechanisms of acquired resistance under TKI therapy, allowing longitudinal tracking of somatic alterations during the treatment course (22). Since predictive molecular pathology is now considered as a standard approach in the clinical management of advanced disease, it's progressively moving also to the early stages setting. After several years of clinical research, the randomized ADAURA trial (23) showed that the adjuvant administration of osimertinib, produced a dramatic increase of disease-free recurrence rate in surgically resected NSCLC patients harboring common *EGFR*-mutations, suggesting that the application of predictive molecular pathology paradigm in the early stage disease is feasible and supporting the routine use of molecular profile and targeted treatments in oncogene addicted, surgically resected patients. Recent findings revealed that the post-surgical assessment and monitoring of minimal residual disease (MRD) could provide reliable information on patients' prognosis and risk of disease relapse (24), offering the opportunity to identify high-risk subgroups who are best candidates to adjuvant therapies. The prospective validation of MRD as prognostic biomarker within ongoing phase II-III clinical studies, will likely allow to further personalize treatment of early stage disease, overcoming traditional drug-development and regulatory procedures.

The application of predictive molecular pathology paradigm into the real-word clinical scenario is inevitably associated to the emergence of unavoidable challenges, including the safe and equal implementation of NGS-based molecular testing, the increased access of lung cancer patients to biomarker driven-clinical trials, the accurate preservation of the health systems' financial sustainability worldwide, requiring joined efforts at the global level.

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