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EDITORIAL

The expanding scenario of advanced non-small-cell lung cancer between emerging evidence and clinical tasks

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This Editorial by De Giglio, Ricciuti and Metro introduces the series *Treatment of advanced non-small-cell lung cancer: one size does not fit all*: https://www.drugsincontext.com/special_issues/treatment-of-advanced-non-small-cell-lung-cancer-one-size-does-not-fit-all/

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Editorial

Lung cancer still represents the first cause of oncological death worldwide, primarily because more than 80% of diagnoses are performed in unresectable settings. Non-small-cell lung cancers (NSCLC) encompass 60% of diagnoses, mainly lung adenocarcinomas or squamous cell carcinomas. A shift from a histology-driven to a biomolecular-driven personalized therapy significantly improved survival outcomes and tolerability profile compared with standard chemotherapies. Thus, we have greatly enriched the therapeutic algorithm and treatment alternatives for advanced diseases in the last decade. Against this background, we elaborated a special collection entitled '*Treatment of advanced non-small-cell lung cancer: one size does not fit all*' to help oncologists navigate therapeutic approvals, ongoing clinical trials and specific clinical tasks.

The elucidating of immune-escape cancer mechanisms led to the development of immunotherapeutic agents such as monoclonal antibodies directed against the programmed death 1 (PD-1) receptor or its ligand (PD-L1) or the CTLA4 receptor.[1] Therefore, immunotherapy progressively became the backbone of upfront strategy as single agents or in combination with other agents (immunotherapy, chemotherapy) for advanced NSCLC without oncogenic driver alterations.[1] In this context, the rapidly expanding armamentarium and lack of predictive biomarkers other than PD-L1 intratumoural expression poses a challenge to physicians in daily practice and fosters the debate about translational studies. Notably, no clinical or molecular characteristics have been sufficiently demonstrated to influence immunotherapy outcomes and drive the need for combination strategies.[1] Conversely, frail patients may be exposed to unnecessary toxicities connected to chemotherapy or immunotherapy combinations with two agents. In the absence of randomized clinical trials, clinical decisions depend on cross-trial comparisons, meta-analyses or observational studies.

In parallel, the definition of oncogene-addicted NSCLC progressively includes an expanding rate of molecular alterations predictive of response to tyrosine kinase inhibitors (TKIs) or monoclonal antibodies.

The upfront treatment of advanced NSCLC with *EGFR* common mutations (del 19, L858R) still relies on osimertinib based on the results of the FLAURA trial.[2] At the same time, new third-generation TKIs offered encouraging progression-free survival benefits but overall-survival data are still immature.[3] Other than standard platinum-based doublets, the subsequent therapeutical decision should be driven by tissue or blood-based genotyping for novel targeted agents within clinical trials. Treatment of *ALK*-rearranged disease overcame the first-generation TKI crizotinib.[3] An appropriate sequential strategy starts with second-generation TKIs alectinib or brigatinib based on affordable clinical results and a good tolerability

profile. Lorlatinib represents a suitable subsequent clinical choice for disease progression due to its remarkable efficacy on typical *ALK*-resistance mutation during second-generation treatment and need of mature survival data as upfront treatment.

Moreover, the *KRAS* gene mutation has been considered the Cinderella of oncogenic driver alterations due to the hardly targetable GTP/GDP binding pocket.[4] The advent of sotorasib and adagrasib changed this concept, with remarkable results in pretreated advanced *KRAS*-positive disease. Clinical trials of combination or comparison strategies will further assess the interplay between anti-KRAS agents and immunotherapy or optimal clinical indication according to clinical characteristics and genomic profiling. Finally, several phase II trials are promisingly expanding the therapeutic scenario of rare driver alterations amenable to targeted therapy and, recently, the approbation of agnostic drugs reverted the hierarchy between histology and molecular targets.[3,5–8]

Interestingly, the actual dichotomic distinction between a disease with oncogenic addiction and that without is progressively smoothing. The road we are on seems to lead to the progressive abandonment of large categories of patients in favour of a personalized and dynamic profile composed of genomic and clinical characteristics because, as suggested in our title, one size does not fit all.

In conclusion, the navigation across the NSCLC sea may offer several challenges for clinicians and researchers, with a rapidly growing amount of evidence that can neither be efficiently registered within official international guidelines or be readily applicable in real-life contexts. The recently released special issue represents a comprehensive but practical hand guide aimed at answering the 'how to manage' question.

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