

Editor's Note:

In the era of personalized medicine, a critical appraisal new developments and controversies are essential in order to derived tailored approaches. In addition to its educative aspect, we expect these discussions to help younger researchers to refine their own research strategies.

Controversies on Lung Cancer: Pros and Cons

Cons: should immunotherapy be incorporated in the treatment of oncogene-driven lung cancer?

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We agree with Dr. Addeo and Dr. Banna when they emphasize that the biology of non-small cell lung cancer (NSCLC) is complex, and that a single biomarker is probably not exhaustive in order to optimally predict (either positively or negatively) the potential efficacy of immune checkpoint inhibitors. However, in our opinion, a clear distinction should be made between open areas of interest for clinical research and the use of drugs that can be recommended in routine clinical practice. At the moment, in fact, the evidence supporting the use of immune checkpoint inhibitors in patients with epidermal growth factor receptor (EGFR)- or anaplastic lymphoma kinase (ALK)-positive NSCLC in clinical practice is honestly weak.

Oncogene-driven NSCLC cases can show both innate and adaptive resistance to immunotherapy (1,2). As for

innate resistance, compared to typical smoking-associated cases, EGFR- or ALK-positive tumors are characterized, on average, by a lower somatic mutational burden, and this might imply that tumors are less immunogenic, with scarcity of tumor infiltrating lymphocytes and presence of tumor-infiltrating regulatory T cells (3). As for adaptive resistance, treatment with a tyrosine kinase inhibitor (TKI) can induce apoptosis of tumor cells, leading to tumor infiltration by immune cells and cytokine production, including cytotoxic enzymes (perforin and granzyme) and pro-inflammatory cytokines that could interfere with immune response.

Of course, we acknowledge that this “immune-challenging” biological scenario could substantially change when the disease becomes no longer sensitive to tyrosine kinase inhibition. Pretreated, resistant disease is reasonably characterized by changes in tumor dominant pathways,

along with changes in the interplay between tumor cells, immune cells and surrounding microenvironment (4). Consequently, we believe that preclinical and clinical research aimed to better define the role of immune checkpoint inhibitors (both as single-agents and as part of combination) in patients with oncogene-addicted NSCLC should be especially encouraged in pretreated patients.

So, we agree with Dr. Addeo and Dr. Banna conclusions, when they state that immune checkpoint inhibitors deserve further investigation. However, we believe that not all trial designs are equally worthwhile. Trials investigating the role of immune checkpoint inhibitors in patients that would be still eligible for targeted drugs as part of their standard management (for instance, the trial NCT02879994, testing the anti-PD-1 pembrolizumab in patients with *EGFR*-mutated, TKI-naïve, PD-L1-positive advanced NSCLC) do not seem particularly intriguing, and are not necessarily a valuable opportunity for participating patients (5). On the contrary, we look with interest at several ongoing trials, testing immune checkpoint inhibitors in pretreated, *EGFR*-mutated cases. For instance, Checkmate 722 (NCT02864251) is a phase 3 trial testing the role of two combination regimens (platinum-based chemotherapy + nivolumab and nivolumab + ipilimumab) in patients with *EGFR*-mutated T790M-negative cases, who have failed treatment with a TKI. The trial compares the two above mentioned experimental combinations with the current standard for these patients, that is platinum-based chemotherapy. Another randomized trial (NCT03091491) is comparing single-agent nivolumab with a combination of nivolumab plus ipilimumab in patients with advanced *EGFR*-mutated NSCLC who have failed one line of standard *EGFR*-TKI treatment and no more than one line of chemotherapy regimen, allowing the administration of a third generation *EGFR*-TKI for patients with acquired T790M mutation. Consequently, these patients have already received the targeted treatments available in clinical practice. Considering that biology and mechanisms of resistance of these tumors are different from naïve cases, there is room to explore the potential efficacy of immunotherapy.

On the other hand, if the aim of this controversy is to give an educational message for current clinical practice and not for investigational issues, we should honestly admit that, at least to date, the evidence supporting the role of immune checkpoint inhibitors in oncogene-driven NSCLC is disappointing (6). We perfectly agree with Dr.

Addeo and Dr. Banna that objective responses have been described in a minority of these subjects, but unfortunately, at the moment, we completely lack predictive biomarkers of sensitivity to PD-1-/PD-L1-inhibitors in NSCLC cases with *EGFR* mutations (7). Therefore, we strongly believe that sustainability should be a priority guiding treatment choices in clinical practice, and every effort should be made to identify the best candidates for each therapy.

In 2018, looking at the whole body of evidence, single-agent immune checkpoint inhibitors currently available in clinical practice are definitely not the best choice in oncogene-driven NSCLC patients.

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Footnote

Conflicts of Interest: M Di Maio received honoraria and acted as consultant for Bristol Myers Squibb, Merck Sharp & Dohme, AstraZeneca. G Metro has no conflicts of interest to declare.

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