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New data: new options for front-line therapy in NSCLC?

Niels Reinmuth

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Thoracic Oncology, Asklepios Clinics Munich-Gauting, Gauting, Germany

Correspondence to
Dr Niels Reinmuth; n.reinmuth@asklepios.com

Non-small cell lung cancer (NSCLC) is a deadly disease that still accounts among the most cancer deaths worldwide. Since characteristic symptoms are lacking, the majority of patients is diagnosed in an advanced tumour stage. In recent years, we have learnt a lot about the diversity of NSCLC and the need for different treatment strategies. For example, the identification of selected molecular alterations offers the chance of specific tyrosine kinase inhibitors or antibodies that result on substantially prolonged overall survival. However, only the minority of stage IV patients carry these molecular alterations, while the majority does not benefit from these drugs.

Recently, another novel approach, the modulation of the immune system by checkpoint inhibitors, has been developed. For the first time, clinical trials have demonstrated that treatment with various programmed death receptor (PD-1) and PD-ligand (PD-L1) inhibitors can yield into long-term survival for a subset of patients, a phenomenon that has rarely been observed in patients treated only with chemotherapy.[1] While monotherapy with PD-1 or PD-L1 inhibitors is generally well tolerated, it also challenges physicians with a wide spectrum of side effects that is very different to those known from chemotherapy or tyrosine kinase inhibitors. Consequently, to date, various PD-1 and one PD-L1 antibodies have been licenced for therapy of pretreated NSCLC. In addition, untreated NSCLC patients with high PD-L1 expression have shown superior progression-free and overall survival for first-line pembrolizumab monotherapy compared with platinum-based chemotherapy.[2]

Currently, clinical trials evaluate various combinational therapy approaches including chemotherapy and immune modulating agents. One major focus is the increase and early identification of the subset of patients with a long-term control of their cancer disease resulting in long-term survival. As the first of many approaches, data from the phase III IMpower150 study have been released at the European Society of Medical Oncology Immuno Oncology Congress end of last year.[3] In this study, 1202 untreated patients with stage IV or recurrent metastatic non-squamous NSCLC were treated with atezolizumab in combination with chemotherapy (carboplatin and paclitaxel) with or without bevacizumab and compared with chemotherapy with bevacizumab alone (control arm). So far, only data from the comparison of patients without an activating anaplastic lymphoma kinase (ALK) or epidermal growth factor receptor (EGFR) genetic mutation treated with the quadruplet combination versus the control arm have been presented. The study showed that the addition of atezolizumab to chemotherapy with bevacizumab resulted in an improvement of progression-free survival (PFS) (HR=0.62; p<0.0001; 95% CI 0.52–0.74; median PFS=8.3 months vs 6.8 months) and a doubling of the 12-month PFS rate (37% vs 18%). In addition, the overall response rate, a secondary endpoint of the study, was higher in the atezolizumab-containing arm (64% vs 48%). Importantly, no new safety signals were identified with the quadruplet combination.

These data open the window for multiple questions that will dominate the discussion on first-line therapy of NSCLC within this year: is this improvement of PFS clinically meaningful and what is the consequence of my treatment choice in stage IV NSCLC? Which patients benefit most? Apparently, data on overall survival need to be awaited in order to draw firm conclusions. In earlier studies including patients not selected for PD-L1 expression, PFS was often not significantly different to the control arm. In contrast, overall survival is seen as the most important end-point for studies evaluating the efficacy of immune modulating agents.[4] However, the unique survival kinetics of immunotherapy agents pose a specific challenge for statistical planning of clinical trials due to dependencies on statistical power and study duration.

Also, mature data from the first study arm, carboplatin, paclitaxel and atezolizumab are still to be published. So far, we do not know the benefit of adding an inhibitory vascular endothelial growth factor (VEGF) antibody to the combination of platinum-based chemotherapy and a PD-L1 inhibitor. Since long, VEGF has been known to interact with the immune response by multiple ways. For example, VEGF stimulates recruitment of immature dendritic cells (DCs) from the bone marrow and peripheral tissues and also blocks DC differentiation thereby harbouring the presentation of tumour antigens inefficient.[5] In addition, the vascular endothelium plays a barrier function and expresses various adhesion molecules such as CD34, intracellular cell adhesion molecule 1 and vascular cell adhesion molecule 1 that are downregulated by VEGF.[5 6] In turn, these adhesion molecules directly interact with macrophages, natural killer cells, granulocytes, B and T cells for antigen recognition, rolling, adhesion and extravasation during immune responses.[6] The IMpower150 study is the first phase III trial to add an antiangiogenic therapy with a checkpoint inhibitor that will provide very helpful information about the clinical impact of such a combination in stage IV NSCLC. Similar combinations are also being tested in other cancer entities such as mesothelioma.

As a consequence due to the increasing arsenal of therapeutic options, a preselection of patients is of utmost relevance. In fact, the assessment of tumour cell expression of PD-L1 performing immunohistochemistry has been incorporated into the diagnostic routine at least for patients with advanced NSCLC. Multiple phase III trials including the IMPower150 trial confirmed the predictive value of PD-L1 expression for patients with a PD-L1 expression of at least 50% of the tumour cells that have the best chance for clinical response to PD-1 or PD-L1 inhibitors and long-term survival. However, in the IMPower150 study, even patients with no detectable PD-L1 expression had a significant benefit from the addition of atezolizumab in regards to improvement of PFS compared with the control arm (HR 0.77). In addition to PD-L1 expression, a T-effector (Teff) gene signature was evaluated that has been defined by assessment of mRNA expression of three genes (*PD-L1*, *CXCL9* and *IFNγ*). Similar to PD-L1 expression assessed with immunohistochemistry, patients with a high expression of a Teff gene signature had a more pronounced improvement of PFS (HR 0.505; 95% CI 0.377 to 0.675; p<0.0001; median PFS=11.3 months vs 6.8 months) than patients with a low Teff signature (HR=0.76). Since no combinational data on PD-L1 expression and Teff signature have been presented, no conclusion on a benefit of assessing the Teff signature in addition to PD-L1 can be drawn so far.

Another candidate predictive marker represents the determination of high tumour mutational burden (TMB) as a surrogate for high intratumoural neoantigen load. TMB has been correlated with favourable outcome for patients treated with the PD-1 antibody nivolumab in an exploratory analysis of a randomised trial comparing of nivolumab monotherapy versus platinum doublet chemotherapy.[7] Importantly, TMB might be a factor that is independent from PD-L1 expression. Recently, a press release indicated that another phase III study demonstrated a highly statistically significant PFS benefit for patients with advanced NSCLC and high TMB treated with first-line therapy of nivolumab plus the CTLA-4 antibody ipilimumab versus platinum-based chemotherapy.[8]

Multiple phase III trials evaluating different first-line regimen in NSCLC are about to be published. Besides the above mentioned study Checkmate-227, the phase III keynote-189 study pronounced positive results for the combination of the PD-1 antibody pembrolizumab in combination with cisplatin or carboplatin and pemetrexed.[9] This combination showed longer progression-free and overall survival than pemetrexed plus platinum chemotherapy alone. Earlier, data from a randomised phase II cohort with similar design enrolling 123 patients to either front-line pembrolizumab combined with carboplatin and pemetrexed or chemotherapy alone indicated an improvement of the response rate (55% vs 26%) in the pembrolizumab containing arm.[10] Similarly, in the IMPower150 trial, an improvement of the response rate was noted for the quadruplet arm.

In general, the efficacy of combination regimens will need to be carefully weighed against increased toxicity, especially for those patients with high PD-L1 expression in whom PD-1 or PD-L1 monotherapy might be highly active.[3 10] Also, some chemotherapy regimen might be more appropriate for combination in regards to safety and efficacy than others. Importantly, for a true comparison of efficacy of different therapeutic approaches, mature data on overall survival are needed. Since therapeutic options are likely to be vastly increased, predictive markers and careful planning of subsequent treatment strategies is necessary. In this regard, the individual patient request needs to be taken into account. Since some patients may experience a long-term benefit from these regimens, the question of treatment duration, especially of checkpoint inhibitors, will need to be addressed. These and further questions will have to be discussed as more data will be available. As indicated by the already presented results, checkpoint inhibitors will become a firm part of front-line therapy in advanced NSCLC, at least for a good subset of patients. Hence, the standard therapy of NSCLC is about to change in its entirety.

However, we as the treating physicians should handle these treatment opportunities with carefulness since further questions such as applicability of promising study data on the majority of patients that would have been ineligible for inclusion into these trials, practicability of assessment of predictive factors and financial challenges for our health systems will also need to be addressed. To increase the benefit of immune modulating agents as part of a therapeutic approach, patients should be included into clinical trials wherever feasible. Moreover, clinical data should be reported to register databases. With the combined evaluation of large clinical and preclinical

data, the development of new hypotheses for preclinical and clinical research may be facilitated as well as sharpen our current understanding on how these agents work best in our patients. Nevertheless, a new era of front-line NSCLC treatment has already begun.

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