Editorial

Efficacy and safety of nivolumab combined with standard therapies for first-line therapy of advanced non-small cell lung cancer

Martin Metzenmacher, Daniel C. Christoph

Department of Medical Oncology, West German Cancer Center, University Hospital Essen, University Duisburg-Essen, 45122 Essen, NW, Germany
Correspondence to: Daniel C. Christoph, MD, PhD. Department of Medical Oncology, West German Cancer Center, University Hospital Essen, University Duisburg-Essen, Hufelandstr. 55, 45122 Essen, NW, Germany. Email: daniel.christoph@uk-essen.de.

Submitted Aug 28, 2016. Accepted for publication Aug 31, 2016.
doi: 10.21037/jtd.2016.10.26
View this article at: http://dx.doi.org/10.21037/jtd.2016.10.26

In the last 10 years treatment of advanced non-small cell lung cancer (NSCLC) improved and progressed dramatically. Although platinum-based doublet is still state of the art as first-line therapy in most cases (1), patients experience prolonged progression-free survival (PFS) and extended overall-survival (OS) by adding maintenance therapy (2) and/or antiangiogenic drugs (in first- or second-line (3,4) to the cytostatic regime. NSCLC harboring an EGFR-"driver" mutation can be treated effectively, with moderate adverse events, by an oral tyrosine kinase inhibitor (TKI) (5,6) or a combination of TKI with the antiangiogenic drug bevacizumab (7), resulting in improved PFS and OS [in case of an exon 19 deletion (6)].

Recently inhibitors of the programmed-death ligand 1 (PD-L1) pathway widened the range of agents in the fight against NSCLC. The PD-L1 ligand can be expressed on cancer cells, macrophages, and on other cells of the cancer microenvironment. Its expression helps the cancer to escape the immune response, especially the destruction by T lymphocytes. Blocking the PD-L1 signal transduction by immune checkpoint inhibitors, e.g., nivolumab, can lead to a superior PFS and OS (at least for patients with PD-L1 expressing tumors) when compared to docetaxel (8,9) and was therefore approved in the USA and Europe for the treatment of squamous and non-squamous NSCLC after platinum-based first-line therapy. The mentioned CheckMate trials showed a response for patients with strong as well as low or even lacking expression of PD-L1 (in case of squamous cell carcinoma patients). However, patients with a strong expression of PD-L1 on the cancer cells showed a much stronger response and improved median survival times (PFS/OS) compared to patients with a PD-L1 expression of <1% on cancer tissue.

The PD-L1 expression and lymphocyte infiltration of the tumors differs from patient to patient (or is volatile like PD-L1 expression). Therefore, the idea of a kind of an epigenetic approach by the combination of a PD-L1 inhibitor and classical cytostatic agents which bring the immune system in contact with cancer antigens and induce PD-L1 expression in cancer cells to escape the immune response, is attractive and discussed in literature and clinical trials (10-12).

Second-line therapy with nivolumab improved PFS and OS when compared to the cytostatic drug docetaxel. Due to its efficacy, nivolumab may also play a role in a first-line setting. In the CheckMate Trials 017 and 057 nivolumab showed a preferable profile of adverse events in comparison to docetaxel. So nivolumab could be an interesting drug in a first-line setting especially for patients not eligible for cis- or carboplatin based chemotherapy.

The report about the subgroup of NSCLC patients treated in the clinical trial CheckMate 012, which we discuss here, demonstrates the feasibility of adding nivolumab to the first-line treatment with generally accepted and performed, platinum based, doublet chemotherapies. Although the dose of nivolumab in the 10 mg/kg arm (administered every 21 instead of every 14 days) was higher than the clinical standard of 3 mg/kg, there were no additional adverse events due to nivolumab as it had been reported in the clinical trials from the second-line setting. Especially, the grade III–IV adverse events summarized in their report could regarded to be almost completely caused by the conventional cytostatic drugs, but not by the immune checkpoint inhibitor nivolumab.

In the CheckMate 017 trial (8) 10% of all patients treated with nivolumab developed an adverse event of grade III–IV. The most frequent adverse events caused by nivolumab (of any grade) in this trial were hypothyroidism (4%), diarrhea (8%) and pneumonitis (5%) (8).

Ten percent of all patients treated with nivolumab in the CheckMate 057 trial (9) developed a grade III–IV adverse event. The most common adverse events of any grade caused by nivolumab were fatigue (16%), nausea (12%), decreased appetite (10%) and asthenia (10%) (9).

Grade III–IV adverse events were higher in the report published by Rizvi and colleagues (45%), but were mostly caused by the platinum-based doublet chemotherapy and not by nivolumab. Adverse events typically known to be caused by nivolumab compared favorably to other CheckMate trials; e.g., hypothyroidism (any grade) occurred in a range from 0–8% in diverse subgroups, and pneumonitis (all grades) was distributed from 0–17% in the subgroups. Therefore, the most common adverse events of nivolumab shouldn't be significantly different in the discussed report from Rizvi and colleagues in comparison to the CheckMate 017 & 057 trials (8,9).

We conclude that in the development and preparation of future trials there should be no reason to worry about increased or additional adverse events by adding nivolumab to the back bone chemotherapy.

The CheckMate 012 is a phase I multicohort trial limiting the value of the reported results. As a matter of fact, control groups are lacking and historical controls were engaged. However, compared to historical controls the PFS- and OS-rates demonstrated by Rizvi and colleagues are encouraging to further investigate the role of nivolumab in a first-line setting, respectively in a setting following the combination of platinum based chemotherapy and antiangiogenic drugs. Although the number of patients enrolled was rather small due to the character of a phase I trial, the improvement of PFS and OS in relationship to historical control groups demonstrated a hopeful hint that the outcome of systemic antitumor therapy could be significant optimized by adding checkpoint inhibitors to the current standard of care. But the results of further clinical trials investigating nivolumab in the first-line setting combined with chemotherapy or other check point inhibitors such as ipilimumab (e.g., CheckMate 227) are eagerly awaited.

An important point to mention is the divergent efficacy of 10 *vs.* 5 mg/kg body weight nivolumab in combination with carboplatin and paclitaxel. The group of patients who received 5 mg/kg nivolumab showed compared to the arm with 10 mg/kg nivolumab (each in combination with carboplatin and paclitaxel) a better objective response rate (43% *vs.* 27%), a lower rate of progressive disease (7% *vs.* 27%), an increased PFS at 24 weeks (51% *vs.* 38%) and an improved OS after 2 years (62% *vs.* 27%). These findings may be due to the fact that there was a higher rate of patients with a NSCLC harboring a K-ras-mutation in the arm with 5 mg/kg than in the arm with 10 mg/kg nivolumab. Subgroup analyses in the CheckMate 057 Trail (9) showed that patients with K-ras-mutations are more likely to benefit from a therapy with nivolumab in terms of an improved overall survival. From a mechanistic point of view, NSCLCs harboring K-ras mutations are regarded to have higher mutational load and are more immunogenic. To point out, the difference in the percentage of patients with K-ras mutations might contribute to the divergent efficacy of nivolumab in combination with carboplatin und paclitaxel to the higher expression of PD-L1.

Assessment of the PD-L1 status was not possible in 21% of all NSCLC patients in the CheckMate 012 trial. Similar rates were observed in the CheckMate 017 and 057 trials. Unfortunately, expression of PD-L1 was not associated with response and outcome in the report by Rizvi and colleagues, but this might be influenced by the small number of patients and worsened by the lacking PD-L1-status in 21% of the patients. Maybe future clinical trials can clarify the value of the PD-L1 status.

The role of PD-L1 expression and the finding of biomarkers predicting the response to an immune-checkpoint-inhibitor therapy remains an unmet need and should urgently be investigated, not at least because of the costs of an anti PD-L1 therapy (in addition to the cost for the backbone chemotherapy).

Summarizing one can say that the data presented by Rizvi and colleagues are a very interesting signal demonstrating the feasibility and potential role for nivolumab in a first-line setting.

Acknowledgements

None.

Footnote

Provenance: This is an invited Editorial commissioned by the Section Editor Long Jiang (Second Affiliated Hospital, Institute of Respiratory Diseases, Zhejiang University

School of Medicine, Hangzhou, China).

Conflicts of Interest: DC Christoph received honoraria for advisory boards and lectures from Bristol-Myers Squibb. The other author has no conflicts of interest to declare.

Comment on: Rizvi NA, Hellmann MD, Brahmer JR, *et al.* Nivolumab in Combination With Platinum-Based Doublet Chemotherapy for First-Line Treatment of Advanced Non-Small-Cell Lung Cancer. J Clin Oncol 2016;34:2969-79.

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Cite this article as: Metzenmacher M, Christoph DC. Efficacy and safety of nivolumab combined with standard therapies for first-line therapy of advanced non-small cell lung cancer. J Thorac Dis 2016;8(10):E1254-E1256. doi: 10.21037/jtd.2016.10.26

