

Nivolumab for advanced non-small cell lung cancer: an immunologically-mediated tumor checkout

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Non-small cell lung cancer (NSCLC) is associated with high mortality especially in the most advanced stages and when tumor is not responsive to the first line, conventional platinum-based chemotherapy or to newer compounds such as pemetrexed or erlotinib. Therefore newer agents with different mechanisms of action are needed and nivolumab is a relevant example of the kind.

Nivolumab is a monoclonal antibody of IgG4 type which targets the programmed death-1 (PD-1) receptor. PD-1 mediated pathway acts as an immune checkpoint aimed at maintaining self-tolerance by inhibiting the T cells. In cancers including NSCLC this mechanism is overexpressed in order to induce apoptosis of the activated T cells and consequently to allow tumor expansion (1).

Nivolumab was evaluated in various cancers including metastatic malignant melanoma, kidney or NSCLC and was found to be effective (2). Nivolumab is currently authorized in both European Union and the USA for the therapy of the NSCLC.

Several phase II and III studies were performed in advanced NSCLC comparing the efficacy and safety of nivolumab with that of second-line chemotherapy agents such as docetaxel.

The phase II study (CheckMate 063) was a single arm efficacy and safety study enrolling NSCLC 117 patients who received nivolumab 3 mg/kg every 2 weeks until signs of disease progression or signs of major toxicity were identified. Efficacy was measured with tumor objective response and was reported in 17 patients, and median time to response being 3.3 months, whereas disease stabilization was reported in 30 patients. Safety analysis found grade 3–4 treatment-related adverse events such as fatigue,

pneumonitis or diarrhea (five, four respectively three patients) (3).

The phase III study was an open-label randomized study enrolling patients with stage IIIB or IV NSCLC with failure to platinum-based first line therapy. They were randomized to receive nivolumab 3 mg/kg every 2 weeks or intravenous docetaxel 75 mg/m² every 3 weeks given until signs of disease progression or of major toxicity were reported (4). The primary endpoint was represented by the overall survival, whereas among the secondary endpoints patient-related outcomes, progression-free survival and safety were included. A sample of 272 patients [most of them of male gender (n=206)] was included in the analysis, 135 receiving nivolumab and 137 docetaxel. Patients receiving nivolumab had a significantly better survival (9.2 *vs.* 6 months with docetaxel (hazard ratio 0.59, P<0.001). Therapeutic response rate was significantly higher with nivolumab (20%) *vs.* 9% with docetaxel (P=0.008). Nivolumab therapy was also associated with better progression-free survival (median value 3.5 *vs.* 2.8 months with docetaxel, hazard ratio 0.62 P<0.001). In terms of safety, the incidence of adverse events was 58% in patients receiving nivolumab versus 86% in those receiving docetaxel. The most commonly adverse events reported by patients receiving nivolumab were represented by fatigue and anorexia (incidences of 16% respectively 11%), whereas in patients receiving docetaxel these were neutropenia and fatigue (33% each).

Another phase III study (CheckMate 057) had a similar design, endpoints, dosing regimen and NSCLC population (in terms of disease staging) but enrolled a larger sample of patients. A sample of 582 patients underwent randomization, 292 being in nivolumab arm

and 290 in the docetaxel arm. Nivolumab therapy was again associated with a significantly longer survival (median survival 12.2 *vs.* 9.4 months, hazard ratio 0.73, $P=0.002$). One-year survival rate was also found to be higher with nivolumab (51% *vs.* 39% with docetaxel). Therapeutic response rate was significantly higher with nivolumab (19% *vs.* 12% with docetaxel, $P=0.02$). There was no significant difference in the progression free survival (median survival 2.3 *vs.* 4.2 months), but the 1-year progression free survival rate was higher with nivolumab when compared to docetaxel (19% *vs.* 8%). Unlike the previous study which performed a secondary analysis according to the levels of PD-1 expression but failed to show any differences between nivolumab and docetaxel, this study demonstrated that for all PD-1 expression levels ($\geq 1\%$, $\geq 5\%$, $\geq 10\%$) the differences in efficacy versus docetaxel were even bigger. Safety analysis demonstrated that treatment-related adverse events (grade 3 or 4) were reported by 10% of the patients treated with nivolumab compared to 54% of those in docetaxel group (5).

The adverse events the most commonly reported in the nivolumab group irrespective of their severity were fatigue, nausea and decreased appetite (16%, 12% or 10%), whereas in the docetaxel group these were represented by neutropenia (31%), fatigue (29%) and alopecia (25%). The incidence of treatment-related serious adverse events was lower in nivolumab group compared to docetaxel group (7% *vs.* 20%), the most frequently reported serious adverse event being rash (9% in nivolumab group and 3% in docetaxel group) followed by pruritus (8% respectively 1%) and erythema (1% respectively 4%). The median time to onset of a treatment-related adverse event irrespective of their severity ranged from 0.9 to 31.1 weeks in the nivolumab group. Median time to resolution of 44–100% of the treatment related adverse events ranged from 0.1 to 12.1 weeks (5).

Such data demonstrate that in patients with advanced, refractory NSCLC nivolumab is able to improve the overall survival and to interfere with disease progression without

major safety issues.

Other clinical studies involving nivolumab as an add-on therapy to other checkpoint inhibitors (ipilimumab), other antibodies (bevacizumab) or to conventional chemotherapy are currently performed.

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Footnote

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