Expert Review of Anticancer Therapy

ISSN: 1473-7140 (Print) 1744-8328 (Online) Journal homepage: http://www.tandfonline.com/loi/iery20

Nivolumab for advanced non-small cell lung cancer: an evaluation of a phase III study

Ruxandra Ulmeanu, Ileana Antohe, Ecaterina Anisie & Sabina Antoniu

To cite this article: Ruxandra Ulmeanu, Ileana Antohe, Ecaterina Anisie & Sabina Antoniu (2016): Nivolumab for advanced non-small cell lung cancer: an evaluation of a phase III study, Expert Review of Anticancer Therapy, DOI: 10.1586/14737140.2016.1127760

To link to this article: http://dx.doi.org/10.1586/14737140.2016.1127760

Accepted author version posted online: 03 Dec 2015.
Published online: 12 Jan 2016.

EXPERT REVIEW OF ANTICANCER THERAPY, 2016
http://dx.doi.org/10.1586/14737140.2016.1127760

Taylor & Francis
Taylor & Francis Group

Nivolumab for advanced non-small cell lung cancer: an evaluation of a phase III study

Ruxandra Ulmeanu[a,b], Ileana Antohe[c], Ecaterina Anisie[d] and Sabina Antoniu[c]

[a]Marius Nasta Institute, Bucuresti, Romania; [b]Faculty of Medicine, University of Medicine Oradea, Bucuresti, Romania; [c]Department of Interdisciplinarity and Preventive Medicine, University of Medicine and Pharmacy Gr T Popa, Iasi, Romania; [d]Immunology Laboratory, Sf Spiridon University Hospital, Iasi, Romania

ABSTRACT

Lung cancer still remains associated with a high mortality rate and more efficacious therapies are needed in order to improve the disease outcome. Nivolumab is a monoclonal antibody which blocks the programmed death-1 receptor which is currently evaluated in phase III clinical trials in advanced lung cancer. Here, we evaluate the results of a phase III study in which nivolumab efficacy and safety were compared to those of docetaxel. Nivolumab was able to improve survival and progression-free survival and exhibited a very good safety profile. Further clinical data are needed in order to better position this therapy among the existing methods. The promising results support the use of this therapy as a stand-alone approach.

ARTICLE HISTORY
Received 20 July 2015
Accepted 28 October 2015
Published online 05 January 2016

KEYWORDS
Nivolumab; PD-1; monoclonal antibody; lung cancer

Lung cancer is the solid tumor associated with the highest clinical and economic burden.[1] The existing therapies including pharmacological antitumor agents, radiotherapy and surgery applied according to the oncological stage, histopathological variant and therapy availability have increased the survival rate over the last decades. However, in a significant percentage of cases lung tumors still progress despite aggressive management and rapidly lead to death. In such cases newer therapies targeting relevant pathogenic pathways are needed in order to achieve a therapeutic response.

One such pathway might be represented by the programmed death pathway 1 which currently is under investigation in oncology for the therapeutic value of inhibiting its receptors or its ligands.[2] Nivolumab (ONO- 4538, MDX-1106, BMS-936558) is a fully humanized monoclonal antibody of IgG4 type directed against PD-1 receptor. Unlike conventional cytotoxic therapies which inhibit directly the tumor cells, nivolumab blocks the tumor related mechanisms of immune tolerance represented by the immune checkpoints.[3] With this blockade the T regulator cells which exert antitumor activities are derepressed and innate tumoricidal mechanisms are activated.[3,4] Nivolumab is currently approved in the USA and Japan for the treatment of advanced melanoma and of advanced lung cancer and is evaluated in clinical trials for various other indications including the non-small cell lung cancer (NSCLC).[5–7] At the time of publication of this paper nivolumab had also received marketing authorization in the EU (Nivolumab BMS®) for the therapy of advanced lung cancer.[8]

Methods and results

This was an open-label randomized phase III study evaluating the efficacy and the safety of intravenous nivolumab 3 mg/kg every 2 weeks versus intravenous docetaxel 75 mg/m^2 of surface area every 3 weeks in patients with advanced NSCLC.[9] Each therapy was given until the first signs of disease progression or signs of major toxicity (requiring drug discontinuation) were documented. The study included patients with advanced (IIIB or IV) NSCLC (squamous cells) with a prior disease recurrence after a platinum containing chemotherapy regimen and with an Eastern Cooperative Oncology Group score of 0 or 1.

The primary endpoint was represented by the overall survival, whereas the secondary endpoints included the rate of investigator-assessed confirmed objective response (based on RECIST criteria), progression-free survival, patient-reported outcomes (lung cancer-related symptoms, health status), efficacy and safety. An analysis of PD-L1 biomarker of lung cancer biopsy specimens of the enrolled patients was also performed in order to clearly identify the subset with the best efficacy for nivolumab. There were 272 patients

CONTACT Sabina Antoniu Sabina.antoniu@outlook.com

enrolled, mean age 63, all current or former smokers, most of them (206) men, 135 in the nivolumab treatment arm and 137 in the docetaxel treatment arm. Most of them (217) were stage IV NSCLC patients (105 for nivolumab, 112 for docetaxel). There were 91 patients (48 patients in the nivolumab arm and 43 patients in the docetaxel arm) with complete or partial response to the previous regimen, 80 patients (33 patients in nivolumab arm and 47 patients in docetaxel arm) with stable disease, 85 patients (44 patients in the nivolumab arm and 41 patients in the docetaxel arm) with progressive disease, whereas in 16 patients (10 patients in the nivolumab and 6 patients in the docetaxel arm) the previous therapeutic response status was unknown. The minimum follow up duration was 11 months and about 34% of the patients previously received paclitaxel. Nivolumab therapy was associated with a better median survival (9.2 months versus 6 months with docetaxel), with a hazard ratio of 0.59 (95% CI 0.44–0.79, $p < 0.001$). The response rate was higher with nivolumab (20 vs. 9% with docetaxel, $p = 0.008$), with comparable time intervals to achieve it (2.2 vs. 2.1 months). The median progression-free survival was 3.5 months for nivolumab versus 2.8 months for docetaxel (hazard ratio 0.62, 95% CI 2.1–3.5 months, $p < 0.001$). The progression-free survival rate was 21 versus 6%. Complete response was achieved in one patient in the nivolumab group and in no patient in the docetaxel arm, partial response was achieved in 26 patients in the nivolumab arm and 12 cases in the docetaxel group. Stable disease was detected in 39, respectively 47 patients, whereas progressive disease was identified in 56 versus 48 patients.

In the nivolumab arm 28 patients received the study medication after initial progression was confirmed with RECIST criteria, and nine of them met the criteria on non-conventional therapeutic benefit (defined as regression from baseline or stabilization of the target lesions after an initial increase in number). PD-L1 was not found to significantly impact the response rates in both study arms. The patient reported outcomes were not analyzed in this paper. The incidence of adverse events was 58% in the nivolumab group versus 86% in the docetaxel group. The adverse events most commonly reported in the nivolumab group were fatigue, anorexia and asthenia (16, 11 and 10%, respectively). In docetaxel treated patients adverse effects included neutropenia, fatigue, alopecia and nausea (33, 33, 22 and 23%, respectively). The incidence of the serious adverse events was 7% for nivolumab and 24% for docetaxel.

Discussion and conclusions

Nivolumab was able to significantly prolong survival in patients with advanced NSCLC and to delay disease progression as compared with docetaxel. This paper does not provide information on the antibody's efficacy, lung cancer symptoms and health-related quality of life. These data would have been very useful, especially in the advanced stages of lung cancer.

The results are backed up by those of a phase II single arm study, performed in 117 patients to evaluate the effects of a similar dose of nivolumab in patients with refractory NSCLC: in this study clinical response was detected in 17 patients and disease stabilization (with a median duration of the effect about 6 months) in 30 patients.[10] Grade 3–4 toxic effects including fatigue, diarrhea and pneumonitis were reported in 20 patients.[10] A phase III study (CheckMate-057) comparing the efficacy of nivolumab with that of docetaxel in non-scuamous NSCLC found that the antibody therapy was associated with a significantly higher overall survival, with a better response rate and a PD-1 expression driven response.[11] Unlike the evaluated paper the population in CheckMate-057 was different from a histological point of view and this might be related to a more clear relationship between the therapeutic benefit and the PD-1 expression.

Expert commentary and five year view

Nivolumab is a promising immune therapy in NSCLC and this is confirmed by the results of the present study. This antibody, alike ipilimumab, belongs to the so called checkpoint inhibitors, which have proven their potent effects in aggressive cancers, as melanoma or refractory non-Hodgkin lymphoma. Such antibodies have the ability to restore the innate immune surveillance mechanisms against the presence of the tumor through inhibiting the immune checkpoints. In the case of nivolumab, these targets are represented by programmed death 1(PD-1) receptor and ligand, which are both overexpressed and dysfunctional in lung cancer, leading to the inability of the immune system to limit the tumor invasiveness.[12]

The existing clinical data strongly support the use of nivolumab in patients with advanced NSCLC; currently the therapeutic value of this drug is under investigation in further phase III studies, in which this therapy is evaluated as a stand-alone strategy or in combination with the conventional chemotherapy, other checkpoint blockers (ipilimumab) or other antibodies (bevacizumab).[9]

Key issues

- Lung cancer is still associated with a high mortality worldwide and the existing therapies are not always able to improve significantly disease outcome.
- Some of the therapies are effective at the first therapeutic attempt and then are no longer able to interfere significantly with disease progression.
- Programmed death pathway was demonstrated to be involved in the pathogenesis of various cancers such as lung, melanoma, especially in the most advanced stages.
- Nivolumab is a monoclonal antibody against the PD-1 receptor which is approved in the USA for the therapy of metastasized or unresectable melanoma and for that of advanced non-squamous lung cancer
- In phase III studies in lung cancer nivolumab given as a single therapy was demonstrated to improve disease survival and progression free survival compared with platinum-based conventional therapies.
- Further clinical studies would help to better position this therapy within the existing therapeutic approach.

This therapeutic positioning can also be helped if the role of PD-1 pathway in the tumor progression is further deciphered. The existing data come from the adenocarcinoma subset of the NSCLC and demonstrate that the up-regulation of this pathway is associated with a more advanced stage of cancer and a poorer overall survival.[13] However, this analysis should be extended to other histological subsets of NSCLC, in order to get a clearer picture of the prognostic value of this biomarker pathway. This should also be prompted by the fact that the above study failed to demonstrate that the upregulation of PD-1 was associated with a better therapeutic response in a subset of squamous NSCLC. Such data would also help to find out if such a therapy like nivolumab would not be better given as an add-on to existing chemotherapy regimen even in earlier NSCLC stages in order to obtain a quicker and more sustained therapeutic response.

Financial & competing interests disclosure

Ruxandra Ulmeanu has received speaker's fees and congress fee from Angelini Pharmaceuticals, Astra Zeneca, Novartis, Pfizer, Boehringer Ingelheim, Servier, Lilly Oncology, Chiesi. Sabina Antoniu has received congress fees Angelini Pharmaceuticals. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References

1. Alberg AJ, Brock MV, Ford JG, et al. Epidemiology of lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e1S–29S.
2. Brahmer JR, Hammers H, Lipson EJ. Nivolumab: targeting PD-1 to bolster antitumor immunity. Future Oncol. 2015;11(9):1307–1326.
3. Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. J Clin Oncol. 2015;33(17):1974–1982.
4. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12(4):252–264.
5. Gettinger SN, Horn L, Gandhi L, et al. Overall survival and long-term safety of nivolumab (anti-programmed death 1 antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non-small-cell lung cancer. J Clin Oncol. 2015;33(18):2004–2012.
6. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012;366(26):2455–2465.
7. Administration, F.a.D. FDA expands approved use of Opdivo to treat lung cancer. 2015; Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436534.htm.
8. Agency EM Nivolumab BMS. 2015; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003840/human_med_001887.jsp&mid=WC0b01ac058001d124.
9. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015;373(2):123–135.
10. Rizvi NA, Mazieres J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncol. 2015;16(3):257–265.
11. Paz-Ares L, Horn L, Borghaei H, et al. Phase III, randomized trial (CheckMate 057) of nivolumab (NIVO) versus docetaxel (DOC) in advanced non-squamous cell (non-SQ) non-small cell lung cancer (NSCLC). ASCO Meet Abstr. 2015;33(15_suppl):LBA109.
12. Sundar R, Soong R, Cho BC, et al. Immunotherapy in the treatment of non-small cell lung cancer. Lung Cancer. 2014;85(2):101–109.
13. Zhang Y, Wang L, Li Y, et al. Protein expression of programmed death 1 ligand 1 and ligand 2 independently predict poor prognosis in surgically resected lung adenocarcinoma. Onco Targets Ther. 2014;7:567–573.