MedicalXpress

First line combination therapy improves progression-free survival in advanced lung cancer

December 7 2017

A new combination therapy for the first line treatment of advanced non-squamous non-small-cell lung cancer (NSCLC) improves progression-free survival (PFS), according to results of the phase III IMpower150 trial presented at the ESMO Immuno Oncology Congress 2017.

"This is the first phase III trial to report on the combination of chemotherapy, antiangiogenic treatment and immunotherapy as first line treatment for advanced non-squamous NSCLC," said lead author Professor Martin Reck, chief oncology physician, Department of Thoracic Oncology, Lung Clinic Grosshansdorf, Germany. "The trial met its co-primary endpoint of PFS and the preliminary results of the co-primary endpoint of overall survival (OS), although immature, look encouraging."

There is a scientific rationale to support the combinations that have been explored in the trial. Bevacizumab may enhance the ability of atezolizumab to restore anti-cancer immunity by inhibiting vascular endothelial growth factor (VEGF)-related immunosuppression and other mechanisms while chemotherapy may induce immune responses. The chemotherapy used in the trial was carboplatin plus paclitaxel. Atezolizumab is a monoclonal antibody that inhibits programmed death-ligand 1 (PD-L1), while bevacizumab is a biologic antiangiogenic drug.

IMpower150 enrolled 1,202 patients who were randomised to one of

three arms: A) chemotherapy plus atezolizumab; B) chemotherapy plus atezolizumab plus bevacizumab; or C) chemotherapy plus bevacizumab.

The PFS survival comparison was made between arms B and C and showed that the combination of atezolizumab, bevacizumab and chemotherapy was superior to bevacizumab and chemotherapy alone with a median PFS of 8.3 versus 6.8 months (hazard ratio [HR] 0.62; 95% confidence interval [CI] 0.52, 0.74; P

The corresponding median PFS in the Teff-WT population, which included patients with defined expression of a T-effector gene signature in the tumour tissue, was 11.3 versus 6.8 months (HR 0.51; 95% CI 0.38, 0.68; P

There were no new safety signals with the combination therapy. Due to prespecified testing hierachy, Arm A versus C has not been formally tested yet.

Reck said: "There was a significant and clinically relevant improvement in progression-free survival favouring the addition of atezolizumab to bevacizumab and chemotherapy. The results show that there is a way to improve the efficacy of platinum-based chemotherapy in patients with advanced non-squamous NSCLC. There were no new safety signals or toxicity issues with this combination so it appears to be a feasible approach for this group of patients."

Commenting on treatment for advanced non-squamous NSCLC for ESMO, Professor Solange Peters, Head of Medical Oncology, Department of Oncology, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland, said: "Immunotherapy is a standard of care treatment after platinum-based chemotherapy in patients with advanced NSCLC. Frontline immunotherapy alone is beneficial in those with a high PD-L1 expression, who make up less than a third of NSCLC

patients. (3) The combination of immunotherapy and platinum-based chemotherapy showed positive response rates in unselected non-squamous patients (without PD-L1 selection) in a hypothesis-generating phase II trial, which led to US Food and Drug Administration (FDA) approval." (4)

"IMpower150 is the first phase III randomised trial to formally evaluate the combination of immunotherapy and chemotherapy versus chemotherapy frontline," she continued. "The backbone therapy includes bevacizumab which might, by targeting VEGF, facilitate the immune response and the trafficking of T cells. Median PFS for the immunotherapy arm in patients without EGFR mutations or ALK rearrangements had a promising hazard ratio of 0.62 and a median PFS improvement of a little less than two months."

Peters said the benefit of immunotherapy is best observed at later time points. "When you look at the 12-month PFS, you double the number of patients who have not progressed from 18% without immunotherapy to 37% when you add the immunotherapy," she said. "This is very, very promising. Doubling PFS at one year is something we have not seen with any targeted therapy in unselected patients to date."

Even more important was that the combination of chemotherapy and immunotherapy was beneficial regardless of expression of PD-L1 or a T-effector gene signature. It was also beneficial in patients with alterations in EGFR and ALK, who usually do not do well with immunotherapy. Peters said: "We know that for immunotherapy monotherapy, we need to highly select patients for PD-L1 expression. This trial shows that by combining chemotherapy and immunotherapy you completely delete any need for patient selection according to a particular biomarker. This strategy has the potential to benefit large numbers of patients with advanced NSCLC without the practical difficulties of biomarker testing."

Peters concluded: "These exciting results pave the way for a new standard of care in advanced non-squamous NSCLC. The initial overall survival data looks encouraging, but we must wait for it to mature. We will also need to understand the impact of this combination in patients who have already received other immunotherapies. In the next year, other trials will report results in frontline treatment-naïve NSCLC patients using the combination of chemotherapy and immunotherapy or the combination of two immunotherapy drugs. The challenge will then be to judge which strategy is the best."

More information: 1. Abstract LBA1_PR 'Primary PFS and safety analyses of a randomized phase III study of carboplatin + paclitaxel +/− bevacizumab, with or without atezolizumab in 1L non-squamous metastatic NSCLC (IMpower150)' will be presented by Martin Reck during the Proffered Paper session 'Combining immune checkpoint inhibitors and VEGF targeted therapies in cancer treatment' on Thursday, 7 December, 18:15 to 19:15 (CET) in Room A. *Annals of Oncology*, Volume 28, 2017 Supplement 11.

2. PD-L1 expression was assessed on both tumour cells (TC) and tumour-infiltrating immune cells (IC); and patients were scored as TC 0, 1, 2, or 3 and IC 0, 1, 2, or 3 with an immunohistochemistry test.

3. Reck M, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer.N Engl J Med. 2016; 375:1823–1833.

4. Langer CJ, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol. 2016;17(11):1497–1508.