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Pembrolizumab versus docetaxel for previously treated PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomized controlled trial.


This study was a randomized, open-label, phase 2/3 study of 1034 previously treated, PD-L1 positive, advanced NSCLC patients from 202 academic medical centers in 24 countries. Patients with previously treated NSCLC with PD-L1 expression on at least 1% were randomly assigned (1:1:1) to received pembrolizumab 2mg/kg, pembrolizumab 10 mg/kg, or docetaxel 75 mg/m2 every 3 weeks. The primary endpoints were overall survival and progression-free survival in total population and in patients with PD-L1 expression on at least 50% of tumor cells. In all population, median overall survival was 10.4 months for pembrolizumab 2mg/kg, 12.7 months for pembrolizumab 10mg/kg and 8.5 months with docetaxel. In population with PD-L1 expression of at least 50% in the tumor cells, overall survival was significantly longer with pembrolizumab 2mg/kg than with docetaxel (median 14.9 months vs 8.2 months respectively, p=0.0002), and pembrolizumab 10mg/kg than with docetaxel (17.3 months vs 8.2 months, p<0.0001). This study showed pembrolizumab prolongs overall survival in previously treated advanced NSCLC. This study also validate the use of PD-L1 selection.

Safety and antitumour activity of durvalumab plus tremelimumab in non-small cell lung cancer: a multicentre phase 1b study

Antonia S, Goldberg SB, Balmanoukian A, Chaft JE, Sanborn RE, Rivzi NA et al.

Combinational treatment with anti PD-L1 antibody and anti-CTLA-4 antibody might provide better activity with single drug alone. This study is a randomized multicentre, open label phase 1b, dose-escalation phase study for locally advanced or metastatic squamous or non-squamous NSCLC for durvalumab plus tremelimumab. Durvalumab is an anti-PD-L1 antibody and tremelimumab is an anti-CTLA-1 antibody for NSCLC immunotherapy. The primary endpoint of this study was safety. 102 patients were enrolled into dose-escalation phase. Most frequent treatment-related grade 3 and 4 adverse effects were diarrhea, colitis, increased lipase. 27 (25% of 102 patients) discontinued treatments due to adverse events. Serious adverse events occurred in 35% of 102 patients, 3 of them were treatment-related deaths due to myasthenia gravis, pericardial effusion, neuromuscular disorders. By comparison, the similar study of pembrolizumab and nivolumab, grade 3 or 4 treatment-related adverse events were seen in 7-11% of patients, deaths related to study treatments were <1%. In this novel study, durvalumab 20mg/kg every 4 weeks plus tremelimumab 1 mg/kg showed a manageable tolerability profile, with antitumor activity irrespective of PD-L1 status.
Atezolizumab versus docetaxel for patients with previously treated non-small cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial

http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(16)00587-0.pdf

Atezolizumab is the anti programmed death-ligand 1 (PD-L1) antibody, clinically active against cancer including NSCLC, especially PD-L1 expressing on tumor or tumor-infiltrating immune cells NSCLC. In this study, 287 post platinum chemotherapy progressed NSCLC patients were recruited. A group of 142 patients received at least one dose of atezolizumab (1200mg) and 135 patients received docetaxel (75mg/m2) every 3 weeks. Baseline PD-L1 expression was scored by immunohistochemistry (as percentage of PD-L1 expressing tumor cells or PD-L1 expressing tumour-infiltrating immune cells). The primary endpoint was overall survival in the intention-to-treat population and PD-L1 subgroups at 173 deaths. Overall survival in the intention-to-treat population was 12.6 month (95%CI 9.7-16.4) for atezolizumab versus 9.7 months (8.6 -12.0) for docetaxel (p=0.04). Increasing overall survival was associated with increasing PD-L1 expression in tumour cells or in tumor-infiltrating cells. In different analysis, patient with pre-existing immunity, defined by high T-effector-interferon-γ-associated gene expression, had improved overall survival with atezolizumab. In conclusion, atezolizumab significantly improved survival compared with docetaxel in previously treated NSCLC, and the improvement were correlated with PD-L1 expression on tumor cells and tumor-infiltrating immune cells. PD-L1 expression is predictive marker for atezolizumab benefit.

Phase I study of ipilimumub in phased combination with paclitaxel and carboplatin in Japanese patients with non-small-cell lung cancer

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4491360/

Ipilimumab is an antibody targeting CTLA-4 to increase antitumor immunity. In this Phase I study, ipilimumab 10mg/kg and paclitaxel (PTX) and carboplatin (CBDCA) three weekly were given in advanced NSCLC patients. Some eligible patients were receiving maintenance ipilimumab once every 12 weeks. Primary endpoints included safety, tumor response, pharmacokinetics and immunogenicity. In this study the most common grade 3 or 4 adverse events were decreased hemoglobin, leucopenia, and neutropenia. The recommended dose for the patient in this study was 10mg/kg. Safety profile was similar to previously AE in immunotherapy trials.

More on this topic in Respirology:

**Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer**


This study is phase 3, randomized, open-label of Nivolumab, a fully human IgG4 programmed death-1 (PD-1) immune-checkpoint-inhibitor antibody at 3mg per kilogram of body weight every 2 weeks for nonsquamous NSCLC that had progressed during platinum doublet chemotherapy, compared to docetaxel (75mg per square meter of body-surface area) every 3 weeks. The primary endpoint of this study was overall survival. Median overall survival was 12.2 months in nivolumab vs 9.4 months in docetaxel (p=0.002), with overall survival rate at 18 months was 39% for nivolumab versus 23% in docetaxel. Progression-free survival 2.3 versus 4.2 months for nivolumab and docetaxel respectively. In this study, the PD-1 ligand expressions were associated with greater efficacy as compared to docetaxel.

**Predictive markers for the efficacy of anti-PD-1/PD-L1 antibodies in lung cancer**

J Thorac Oncol 2016, Mar 2 (Epub ahead of print)  
Shukuya T, Carbone DP  

This is a review article for predictive markers for the efficacy of immunotherapy in lung cancer, especially anti-PD-1/PD-L1. Programmed death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) blocking had resulted promising clinical responses and improved overall survival in patients with non-small cell lung cancer (NSCLC). The response rate of PD-1/PD-L1 was only 15-20% in unselected patients with NSCLC and cost of treatment is high. This articles provides review on existing data on anti-PD-1/PD-L1 predictive marker for efficacies in NSCLCs.

**Programmed cell death-ligand 1 expression is associated with a favourable immune microenvironment and better overall survival in stage I pulmonary squamous cell carcinoma.**

Yang CY, Lin MW, Chang YL, Wu CT, Yang PC.  

This study investigated the immune response in squamous cell carcinoma. The expression of PD-L1 in surgically resected stage I squamous cell carcinoma was investigated, and the correlation with TILs in tumor microenvironment, common driver mutation and clinical outcomes was measured. PD-L1 expression was not associated with status of EGFR mutation, KRAS, BRAF, ALK, PI3KCA, and FGFR1. PD-L1 tumor expression was associated with CD8 T cells and stromal CD4 T cells. In multivariate analysis, the PD-L1 expression is associated with favourable immune microenvironments and correlates with better clinical conditions.
Cellular immunotherapy as maintenance therapy prolongs the survival of the patients with small cell lung cancer

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4446113/

Despite the advancement of immunotherapy in NSCLC, this articles showed promising study of maintenance cellular immunotherapy in small cell lung cancer (SCLC). In this pilot prospective cohort study with autologous cellular immunotherapy (NK, γδT cells, and cytokine-induced killer cells. A total of 58 patients (29 patients each groups) were enrolled in this study, and followed-up without further treatments. The primary endpoint was progression free survival, overall survival and adverse effect. In the study group OS was significantly higher in the study group (20 vs 11.5 months, p=0.005). In patient with limited disease, the OS was higher as compared to control goups (26.5 vs 11.8 months respectively). Among patients with extensive-stage, PFS and OS were longer in study groups that control (5 vs 2.7 months P=0.037), and overall survival was 14.5 vs 9 moths. There was no significant adverse reaction during immunotherapy.

Dendritic cell vaccine and cytokine-induced killer cell therapy for the treatment of advanced non-small cell lung cancer

Zhang L, Yang X, Sun Z, Li J, Zhu H, Li J, Pang Y
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4812113/

This translational study was using autologous PBMC derived dendritic cells cocultured with tumor lysate antigen derived from human adenocarcinoma SPC-A-1 cell lines and human lung squamous cell carcinoma SK-MES-1 cells lines.

The dendritic cells were harvested and injected intradermally into forearms of NSCLC patients. The primary endpoint was delayed-type hypersensitivity (DTH) in patients, and the secondary endpoint was overall survival. In this experimental study, the overall survival of the patients with DC vaccination was significantly longer compared to conventional study. Although the study design was not clear for each group of patients, this study provides opportunity in autologous immunotherapy in NSCLC.

Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria.

http://clincancerres.aacrjournals.org/content/15/23/7412.full

This articles provides systematic, immune-related response criteria beyond described by Response Evaluation Criteria in Solid Tumor or WHO criteria.
The appearance of the measurable antitumor activities in immunotherapy may take longer compared to conventional cytotoxic therapy, response to immunotherapy may occur after conventional PD, and discontinuation of immunotherapy after conventional PD may not appropriate in some cases, durable SD may represent antitumor activity. In this article, the comparison between WHO criteria and the immune-related response criteria (iRC were presented).