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Review

Immunotherapy revolutionises non-small-cell lung cancer therapy: Results, perspectives and new challenges

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Abstract Immune checkpoint inhibitors (ICIs) are antibodies that target key signalling pathways such as programmed death 1 (PD1)/programmed death-ligands 1 and 2 (PDL1 and PDL2) to improve anti-tumour immune responses. Until recently, nivolumab was the only ICI validated for advanced non-small-cell lung cancer (NSCLC) in a second-line treatment setting. Results from recent phase II and phase III randomised trials testing other ICIs have been presented. In Keynote-024, pembrolizumab, an anti-PD1 antibody, was reported to have great efficacy in the first-line treatment of PDL1 $\geq$ 50% tumours (30% of screened tumours), with a progression-free survival (PFS, median) of 10.4 months versus 6.0 months with chemotherapy (CT; hazard ratio [HR] = 0.50; 95% confidence interval [95% CI] 0.37–0.68, $P < 0.001$), overall response rate (ORR) of 45% versus 28% with CT ($P = 0.0011$), and a 1-year overall survival (OS) of around 70%. In contrast, Checkmate-026 reported that nivolumab failed to show any benefit compared with standard platinum-based CT, with a PFS (median) in the PDL1 $\geq$ 5% NSCLC group of 4.2 months (nivolumab) versus 5.9 months (CT; HR = 1.15: 95% CI 0.91–1.45, $P = 0.25$). No benefit was observed in the PDL1 $\geq$ 50% subgroup. An encouraging report of the efficacy of pembrolizumab in addition to CT in first-line treatment in unselected NSCLC was also presented (Keynote-021) with an ORR of 55% versus 29% with CT alone ($P = 0.0016$). Atezolizumab, an anti-PDL1 antibody, showed efficacy for second-line treatment compared with docetaxel (OAK phase III study) with an OS (median) of

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13.8 months versus 9.6 months with docetaxel. These results suggest a new paradigm for the treatment of advanced NSCLC using pembrolizumab for the first-line treatment of PDL1 ≥ 50% tumours.

1. Introduction

Non-small-cell lung cancer (NSCLC) is the primary cause of cancer death worldwide [1]. Recently, new drugs called immune checkpoint inhibitors (ICIs) have been developed. Cancer cells can inhibit the immune system through inhibitor pathways such as cytotoxic T-lymphocyte-associated protein 4 or programmed death 1 (PD1)/programmed death-ligands 1 and 2 (PDL1 and PDL2). The activation of these pathways blocks the immune response of tumour-infiltrating lymphocytes, allowing the proliferation of tumour cells. Monoclonal antibodies such as anti-PD1 or anti-PDL1 antibodies have recently been developed to target these pathways (Fig. 1). Nivolumab, an anti-PD1 antibody, was the first agent to show efficacy in patients with NSCLC in two recent phase III trials that confirmed its benefit for second-line treatment [2,3]. The Checkmate-017 study was a randomised trial that compared nivolumab with docetaxel as a second-line treatment in advanced squamous-cell lung carcinoma [2]. Overall survival (OS, primary end-point) was better with nivolumab with a median of 9.2 months versus 6.0 months with docetaxel: hazard ratio (HR) for death at 0.59; 95% confidence interval (95% CI) 0.44–0.79; $P < 0.001$. No predictive effect of PDL1 status was observed. The Checkmate-057 study was also a randomised trial comparing nivolumab with docetaxel as a second-line treatment in advanced non-squamous-cell lung carcinoma [3]. The OS, which was the primary end-point, was better with nivolumab, with a median of 12.2 months versus 9.4 months with docetaxel (HR = 0.73; 95% CI 0.59–0.89; $P = 0.002$). A differential effect according to PDL1 status was detected in this trial, with a better response to nivolumab in PDL1-positive NSCLC (cutoff at 1% or 5%), but definitive conclusions were difficult to determine because no stratification was performed according to PDL1 expression at randomisation. These promising findings resulted in the Food and Drug Administration and the European Medicines Agency approving nivolumab as a second-line treatment for squamous-cell lung carcinoma and epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) wild-type (WT) adenocarcinoma in 2015.

In 2016, results from randomised phase II and III trials were published or presented in medical congresses, extending the potential indications of ICIs in NSCLC. Here, we present these results and discuss new perspectives and challenges of NSCLC treatment with ICIs in the future.

2. Beyond nivolumab: other ICIs for second-line treatment

2.1. Pembrolizumab

Pembrolizumab is an anti-PD1 antibody that showed promising results in a phase Ib trial (Keynote-001 study), especially for cases of PDL1 staining ≥50% tumour cells (22C3 clone) [4]. The Keynote-010 study was an open-label phase II–III randomised trial comparing pembrolizumab with docetaxel in advanced NSCLC with progression after at least one prior treatment line [5]. Patients had a performance status (PS) of 0 or 1, had no active brain metastasis or chronic immune disease, their tumour exhibited PDL1 staining ≥1% and a tumour proportion score (TPS) ≥1%. Patients were randomised between pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg, or docetaxel 75 mg/m^2, intravenously (IV) every 3 weeks. Stratification was performed according to the PS, country of patient origin and—after the inclusion of 441 patients—PDL1 staining (TPS 1–49% and TPS ≥ 50%). No crossover from docetaxel to pembrolizumab was allowed. Primary end-points were progression-free survival (PFS) and OS in the whole population and in patients with PDL1 ≥ 50% tumours. Secondary end-points were overall response rate (ORR), duration of response (DOR) and toxicity. A total of 1034 patients were randomised (442 patients with PDL1 ≥ 50%). Most patients (70%) were included after one line of treatment. The main results are presented in Table 1. The OS in the overall population was better with pembrolizumab compared with docetaxel: HR = 0.71 (95% CI 0.58–0.88, $P = 0.0008$) with 2 mg/kg and HR = 0.61 (95% CI 0.49–0.75, $P < 0.0001$) with 10 mg/kg. The PFS was significantly improved only in the overall population with pembrolizumab 10 mg/kg: HR = 0.79 (95% CI 0.66–0.94), $P = 0.004$. For the subgroup of patients with PDL1 ≥ 50% tumours, the improvement of OS was more marked: HR = 0.54 (95% CI 0.38–0.77, $P = 0.0002$) with 2 mg/kg pembrolizumab and HR = 0.50 (95% CI 0.36–0.70, $P < 0.0001$) with 10 mg/kg pembrolizumab. Similar results were obtained for the PFS: HR = 0.59 (95% CI 0.44–0.78, $P = 0.0001$) with 2 mg/kg pembrolizumab and HR = 0.59 (95% CI 0.45–0.78, $P < 0.0001$) with pembrolizumab 10 mg/kg compared with docetaxel. No significant difference was observed in other subgroup analyses for OS. No statistically significant benefit with pembrolizumab was observed for PFS in women (HR = 1.02; 95% CI 0.78–1.32), in patients with