Lung Cancer 106 (2017) 70–75

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Review

Immune-checkpoint inhibition in first-line treatment of advanced non-small cell lung cancer patients: Current status and future approaches

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ARTICLE INFO

Article history:
Received 11 January 2017
Accepted 4 February 2017

Keywords:
Immunotherapy
Pembrolizumab
Nivolumab
First-line
Non-small cell lung cancer

ABSTRACT

Immune checkpoint inhibitors are considered standard second-line treatment in advanced non-small cell lung cancer patients. This strategy has also become standard in first-line setting for a subgroup of patients with strongly positive PD-L1 tumors; therefore, PD-L1 status might be considered a new biomarker that deserves upfront testing. New combinations of immune checkpoint inhibitors and with chemotherapy have been tested in first-line treatment. However, some questions remain unanswered such as the best treatment strategy or the real upfront efficacy of these therapeutic strategies in the whole lung cancer population. In this review we summarize the main results in the first-line setting of recent phase III trials with immune checkpoint inhibitors in advanced non-small cell lung cancer patients.

Contents

1. Introduction

Modulation of immune response to elicit antitumor activity has been achieved by development of immune checkpoint inhibitors, different monoclonal antibodies that bind either to PD-1 or its ligand the PD-L1 and anti-CTLA4 antibodies hampering immune evasion [1–3], changing the landscape treatment of non-small cell lung cancer (NSCLC) patients and other malignancies.

Four randomized phase III trials have reported significant overall survival (OS) benefit with immune checkpoint inhibitors (such as: nivolumab an anti-PD-1 in squamous [4] and non-squamous [5] patients; pembrolizumab another anti-PD1, restricted to patients with at least 1% PD-L1 expression on tumor cells [6] and atezolizumab an anti-PD-L1 [7]) compared with single-agent docetaxel as second-line treatment in advanced NSCLC patients. Of note, the magnitude of benefit with pembrolizumab was greater among patients with strong PD-L1 expression (at least 50% of tumour cells expressing PD-L1) [6]. Given the absence of head-to-head comparison, the lack of clear biological differences and

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http://dx.doi.org/10.1016/j.lungcan.2017.02.002
0169-5002/

the similarity in toxicity profile [8], one treatment cannot be recommended over another in this setting. Nivolumab and pembrolizumab have received US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval as second-line therapy, the latter restricted to tumours expressing PD-L1 (≥1%); and FDA has approved atezolizumab in the second-line setting.

The results of ATLANTIC phase 2 study recently showed the clear activity of durvalumab, an anti-PD-L1, as third-line treatment or beyond; higher PD-L1 expression levels correlated with improved response rate and OS [9]. All these results spurred numerous efforts to assess immunotherapies in the front-line setting.

First-line platinum-based chemotherapy still remains the standard of care in the majority of the advanced NSCLC patients [10] without oncogenic drivers alterations such as the epidermal growth factor receptor (*EGFR*) mutation (in almost 50% of patients of Asian ethnicity compared to 15% in the Caucasian population [11]) or the anaplastic lymphoma kinase (*ALK*) re-arrangement (in 5% patients independently of ethnicity [12]). However, efficacy of chemotherapy remains poor [10] and new strategies are awaited. In this review, we summarize recent advances and strategies with immune checkpoint inhibitors as first-line treatment in advanced NSCLC.

2. Anti-PD1 or anti-PD-L1 as monotherapy

2.1. Pembrolizumab

Tumours with strong PD-L1 expression (expression on at least 50% of tumour cells, regardless of the staining intensity with the 22C3 clone, which occurs in approximately 23% to 28% of advanced NSCLC [6,13]) has been reported as a predictive marker for better outcome in the pembrolizumab phase I KEYNOTE 001 [13] and phase III KEYNOTE 010 [6] trials, and improving this benefit when pembrolizumab was prescribed upfront [14], with a promising median progression-free survival (PFS) of 12.5 months [13].

On basis of these observations, the phase III KEYNOTE 024 trial [15] randomized 305 NSCLC patients with strong PD-L1 positivity to pembrolizumab (200 mg every 3 weeks up to 35 cycles or until documented progressive disease) versus 4–6 cycles of platinum-based chemotherapy as first-line treatment. Pemetrexed maintenance therapy was permitted for patients with non-squamous histology and pemetrexed induction chemotherapy. Pembrolizumab compared to standard first-line platinum-based chemotherapy significantly improved the median PFS (10.3 *vs.* 6.0 months, hazard ratio [HR] 0.50 [0.37–0.68], $p < 0.001$), response rate (RR) by RECIST (44.8% *vs.* 27.8%, $p < 0.001$), and OS (not reached in both arms, HR 0.60 [0.41–0.89], $p = 0.005$), with 1-year OS of 70% *vs.* 54%, despite 43.7% of patients in the control arm were allowed to crossover to pembrolizumab upon disease progression [15]. Quality of life [16] and grade ≥ 3 treatment-related adverse events (AEs) also favoured pembrolizumab (26.6% *vs.* 53.3%), with 9.7% of grade 3–4 immune-mediated AEs [15]. The magnitude of benefit in control arm is consistent with historic controls [17], suggesting that pembrolizumab efficacy was not related to infra-therapeutic control arm. Also, it remains unknown whether survival benefit is because pembrolizumab treatment is intrinsically more efficacious as first-line treatment or because more than 50% of the patients in control arm did not receive immune-checkpoint inhibitor at progression. Also, it remains unknown how strong is the tumor-immune addiction reported in KEYNOTE 024 trial and whether it is independent of PD-L1 expression. KEYNOTE 024 results prompted FDA approval of pembrolizumab on October 24, 2016, as the first-line treatment in NSCLC patients with strong PD-L1 positivity, and on December 15th, 2016, EMA CHMP also approved pembrolzizumab as monotherapy in the first-line setting of metastatic NSCLC in adults whose tumors express PDL1 in a tumor proportion score (TPS) ≥ 50% with no *EGFR*- or *ALK* positive tumor mutations. The ongoing phase III KEYNOTE 042 study (NCT02220894) will assess the survival benefit of pembrolizumab over standard first-line platinum-based chemotherapy as first-line treatment in treatment in NSCLC patients with PD-L1 expression of 1% or greater.

2.2. Nivolumab

The phase I, multicohort, CheckMate 012 trial evaluated nivolumab in the first-line setting among 52 NSCLC patients. Nivolumab reported a RR of 23%, median PFS of 3.6 months and median and 1-year OS of 21.8 months and 73%, respectively. Trend toward better outcome with nivolumab was reported among 12 patients with PD-L1 ≥ 50% (tumor cell membrane staining any intensity >50% with the 28-8 clone Epitomics) with a RR of 50%, median PFS of 8.4 months and 1-year OS of 83% [18].

The phase III CheckMate 026 trial compared nivolumab with standard first-line chemotherapy in 423 PD-L1-positive (≥5% of expression by 28-8 clone) advanced NSCLC patients [19]. Maintenance treatment was allowed and 38% of patients received pemetrexed-maintenance [19]. Nivolumab did not achieve benefit compared to control arm in terms of PFS (4.2 *vs.* 5.9 months, HR 1.15 [0.91–1.45], $p = 0.251$), OS (14.4 *vs.* 13.2 months, HR 1.02 [0.80–1.30]), or RR (26.1% *vs.* 33.5%), but reported better toxicity profile (grade ≥ 3 AEs: 17.6% *vs.* 50.6%) [19]. Imbalances in nivolumab arm compared to control arm according to post-discontinuation treatment (40% *vs.* 60%) and percentage of tumours with strong PD-L1 expression (53.2% *vs.* 74.1%) may explain the lack of survival benefit [19]. The high proportion of lack of post-discontinuation treatment at progression in nivolumab arm may suggest that for some patients upfront immune checkpoint inhibitors is not an appropriate strategy [20].

Differences in population characteristics, previous treatment with radiotherapy, and differences in biomarker tests and in PD-L1 expression cut-off point could partially justify the contrasting results between KEYNOTE 024 [15] and Checkmate 026 [19] trials. The ongoing phase III CheckMate 227 (NCT02477826) trial evaluates the best strategy for delivering nivolumab (as monotherapy, combined with ipilimumab or chemotherapy) compared with standard upfront platinum-based chemotherapy in PD-L1 positive advanced NSCLC patients.

2.3. Atezolizumab, avelumab and durvalumab

The phase II BIRCH trial tested the anti-PD-L1 atezolizumab (1200 mg iv every 3 weeks), in 142 treatment-naïve PD-L1 positive NSCLC patients. The RR was 25%, median PFS and OS was of 7.3 months and 23.5 months, respectively, with 33% of serious AE's, suggesting activity in first-line setting [21]. The ongoing IMpower110 (NCT02409342) and IMpower 111 (NCT02409355) phase III trials compare atezolizumab with chemotherapy in PD-L1 positive (≥1% on TC or IC with ventana SP142 assay) advanced treatment-naïve NSCLC patients.

In the phase I, multicohort, JAVELIN study, including 156 treatment-naïve advanced NSCLC patients and unselected for PD-L1 expression, avelumab (10 mg/kg iv biweekly), an anti-PD-L1, achieved a RR of 22.5% and median PFS of 4.4 months with an 11% grade 3 treatment-related AEs [22]. The ongoing phase III JAVELIN Lung 100 trial (NCT02576574) compares in first-line setting avelumab versus chemotherapy in advanced PD-L1 positive NSCLC patients.

The anti-PDL1 durvalumab (10 mg/kg every 2 weeks) tested as first-line treatment in 59 advanced NSCLC patients, obtained promising efficacy with a long-lasting RR of 25% irrespective of histologic subtype, and with grade 3 AEs in 9% of patients [23]. The