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Original Research

Long-term survival follow-up of atezolizumab in combination with platinum-based doublet chemotherapy in patients with advanced non–small-cell lung cancer

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Abstract ***Background:*** Before the availability of immunotherapy, chemotherapy was standard first-line therapy for non–small-cell lung cancer (NSCLC) lacking actionable gene alterations. Preclinical evidence suggests chemotherapy is immunomodulatory, supporting chemotherapy/immunotherapy combinations. Atezolizumab, anti-programmed death ligand-1 (PD-L1) antibody, blocks programmed cell death protein-1 and B7.1 interaction with PD-L1. GP28328 (NCT01633970) assessed atezolizumab with chemotherapy in multiple tumours; we report results for advanced, treatment-naïve NSCLC.
Methods: Patients received atezolizumab plus carboplatin with paclitaxel (Arm C: atezo/cb/pac), pemetrexed (Arm D: atezo/cb/pem, maintenance pemetrexed permitted), or nab-

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paclitaxel (Arm E: atezo/cb/nab-pac), four–six cycles, then atezolizumab maintenance. Primary end-point was safety; secondary end-points were objective response rate (ORR), progression-free survival (PFS) and overall survival (OS).

Results: Seventy-six NSCLC patients were enrolled (n = 25, 25 and 26 for Arms C, D and E, respectively). Common treatment-related grade III/IV adverse events were neutropenia (36% atezo/cb/pac, 36% atezo/cb/pem, 42% atezo/cb/nab-pac) and anaemia (16% atezo/cb/pac, 16% atezo/cb/pem, 31% atezo/cb/nab-pac). Confirmed ORRs were 36% atezo/cb/pac, 68% atezo/cb/pem (one complete response [CR]) and 46% atezo/cb/nab-pac (four CRs). Median PFS was 7.1 months, (95% confidence interval [CI]: 4.2–8.3), 8.4 months (95% CI: 4.7–11) and 5.7 months (95% CI: 4.4–14.8), respectively. Median OS was 12.9 months (95% CI: 8.8–21.3), 18.9 months (95% CI: 9.9–27.4) and 17.0 months (95% CI: 12.7–not evaluable), respectively.

Conclusion: Atezolizumab with chemotherapy was well tolerated with encouraging efficacy, though the analysis was limited by small numbers. NSCLC chemotherapy combination studies are ongoing.

ClinicalTrials.gov identifier: NCT01633970.

1. Introduction

Before the availability of immunotherapy, platinum-doublet chemotherapy with or without bevacizumab was standard first-line therapy for patients with advanced non–small-cell lung cancer (NSCLC) whose tumours lacked actionable gene alterations (e.g., epidermal growth factor receptor [*EGFR*] mutations/*ALK* rearrangements). Despite advances, survival outcomes with chemotherapy remain poor, with median overall survival (OS) of approximately 12 months [1–4], progression-free survival (PFS) less than 6 months [4–6] and objective response rates (ORRs) around 30% [6].

Aberrant programmed death ligand-1 (PD-L1) expression on tumour cells (TCs) impedes anti-tumour immunity, permitting tumour immune evasion [7]. Pembrolizumab, an antibody targeting programmed cell death protein-1 (PD-1), is approved for use as first-line monotherapy for metastatic NSCLC in patients whose tumours have high (≥50%) PD-L1 expression [8], after improving outcomes versus platinum-doublet chemotherapy. Only about 30% of tumours highly express PD-L1. In mouse models, chemotherapy demonstrated synergy with anti–PD-L1 treatment to induce durable anti-tumour responses [9]. Treatment with platinum- or taxane-based agents, combined with anti–PD-L1 treatment, increased the number of tumour-infiltrating CD8+ T cells. The phase III KEYNOTE-189 trial showed that addition of pembrolizumab to platinum-doublet chemotherapy (carboplatin and pemetrexed) improved ORR (47.6% with pembrolizumab versus 18.9% with chemotherapy alone) and OS (hazards ratio = 0.49, 95% confidence interval [CI] = 0.38–0.62) [10]. Pembrolizumab received US Food and Drug Administration approval for first line non-squamous NSCLC treatment, combined with carboplatin and pemetrexed, irrespective of tumour PD-L1 expression [10].

Atezolizumab is a humanised monoclonal antibody that targets PD-L1 and inhibits binding with PD-1 and B7.1 to restore anti-tumour T-cell activity [11]. In the phase III OAK trial, atezolizumab prolonged OS compared with docetaxel in patients with previously treated, metastatic NSCLC [12]. Here we report results of a phase IB study evaluating the combination of atezolizumab with three different carboplatin-based chemotherapy regimens in patients with advanced, treatment-naïve NSCLC, to assess the safety and preliminary clinical activity of these combinations.

2. Material and methods

2.1. Study design

GP28328 (NCT01633970) was a multicenter, multiarm, non-randomised, open-label phase IB study examining atezolizumab with chemotherapy (and/or bevacizumab) combinations in multiple tumour types. Three treatment arms (Arms C, D and E) evaluated first-line atezolizumab regimens for advanced NSCLC. Results from other arms will be reported separately.

2.2. Patients

Key inclusion criteria for the NSCLC cohorts were histologically or cytologically confirmed stage IIIB/IV NSCLC, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1 and no prior chemotherapy for advanced disease, except patients with *EGFR*+/*ALK* + disease who must have progressed on tyrosine kinase inhibitor therapy. Eligible patients had adequate haematologic and end-organ function. Patients with known active central nervous system (CNS) metastases or significant autoimmune disease were excluded.