European Journal of Cancer 101 (2018) 201–209

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

Safety and clinical activity of atezolizumab monotherapy in metastatic non-small-cell lung cancer: final results from a phase I study

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Received 7 June 2018; accepted 20 June 2018

KEYWORDS
Atezolizumab;
Non-small-cell lung cancer;

Abstract ***Introduction:*** Atezolizumab, an anti-programmed death-ligand 1 (PD-L1) antibody, inhibits PD-L1:PD-1 and PD-L1:B7.1 interactions, restoring anticancer immunity. Here, we report final analyses from the non-small-cell lung cancer (NSCLC) cohort of the first atezolizumab phase I study.

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https://doi.org/10.1016/j.ejca.2018.06.031

PD-L1;
Immune checkpoint inhibitor

Methods: Patients with NSCLC received atezolizumab 1–20 mg/kg or 1200 mg intravenously every 3 weeks. Baseline PD-L1 expression on tumour cells (TCs) and tumour-infiltrating immune cells (ICs) was assessed (VENTANA SP142 immunohistochemistry assay). Exploratory subgroup analyses investigated responses by baseline PD-L1 expression and oncogenic mutational status.

Results: Eighty-nine patients, 98% of whom had received previous systemic therapy, were evaluable for safety and antitumour activity. Atezolizumab was well tolerated, with grade III/IV treatment-related adverse events (TRAEs) observed in 10 patients (11%). All-grade TRAEs occurring in >10% of patients were fatigue, nausea and decreased appetite; grade III/IV TRAEs occurring in >2% of patients were fatigue, dyspnoea, hyponatremia and hypoxia. One patient died from treatment-unrelated pneumonia. Objective response rate (ORR) was 50% (95% confidence interval [CI], 28%–72%), 33% (20%–48%), 29% (18%–41%) and 11% (1%–35%) for the TC3 or IC3, TC2/3 or IC2/3, TC1/2/3 or IC1/2/3 and TC0 and IC0 subgroups, respectively. All-patient ORR was 23% (95% CI, 14%–33%). Median duration of response was 16.4 months (range, 7.2–53.4+). One-, 2-, and 3-year survival rates were 63% (95% CI, 53%–73%), 37% (26%–47%) and 28% (18%–38%), respectively.

Conclusions: Single-agent atezolizumab was well tolerated with long-term clinical benefits, including durable responses and survival, in pretreated NSCLC. Improved responses and survival rates were seen with increasing baseline PD-L1 expression.

ClinicalTrials.gov identifier: NCT01375842.

1. Introduction

Programmed death-ligand 1 (PD-L1) is expressed on tumour cells (TCs) and tumour-infiltrating immune cells (ICs) in many cancers, including non-small-cell lung cancer (NSCLC) [1–5] and binds to programmed death-1 (PD-1) and B7.1, thus inhibiting anticancer T-cell activity [6]. Antibodies targeting the PD-L1:PD-1 pathway have demonstrated remarkable efficacy in a wide range of cancers, including NSCLC, and are now standard of care for patients with advanced NSCLC in several countries [7,8]. Unlike anti–PD-1 antibodies, atezolizumab (an anti-PD-L1–engineered humanised monoclonal antibody) does not disrupt the PD-1:PD-L2 interaction, which may be important in preserving immune homeostasis [9,10]. In the phase III OAK study, atezolizumab showed significant survival benefit regardless of PD-L1 expression and was well tolerated, with a favourable safety profile versus docetaxel, supporting its approval for previously treated metastatic NSCLC [11].

The efficacy of atezolizumab in patients with NSCLC from the first phase I trial, PCD4989g (NCT01375842), was initially reported by Herbst et al. [2] at the data cut-off of 30th April 2013. Here, we report the long-term follow-up data from the NSCLC cohort of this trial with a cut-off of 31st December 2016.

2. Materials and methods

2.1. Study design and treatments

PCD4989g is an ongoing phase I study investigating single-agent atezolizumab in advanced or metastatic solid tumours and haematologic malignancies. It consists of dose-escalation cohorts, followed by enrichment of patients with PD-L1 expression within multiple tumour-specific expansion cohorts [2]. This first-in-human study was approved by local institutional review boards and was conducted in accordance with Good Clinical Practice and the Helsinki Declaration. All patients provided written informed consent.

2.2. Objectives

The primary objective was to evaluate safety and tolerability of atezolizumab. During the dose-escalation phase, primary objectives included evaluation of dose-limiting toxicities, determination of a maximum tolerated dose and identification of a recommended phase II dose. Secondary objectives included assessment of pharmacokinetics and preliminary clinical activity. Exploratory objectives included analyses of pharmacodynamic and/or predictive biomarkers of atezolizumab activity and overall survival (OS).

2.3. Treatment

The dose-escalation phase was previously described [2], and no dose-limiting toxicities were observed. Patients in the NSCLC cohort, therefore, received atezolizumab at a dose of 1, 10, 15 or 20 mg/kg or 1200 mg every 3 weeks. Initially, all patients enrolled were treated until disease progression or for a maximum of 16 cycles or 1 year, whichever came first. After protocol amendments, patients could be retreated if they progressed during follow-up and could continue atezolizumab treatment