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REVIEW

The European Medicines Agency review of the initial application of atezolizumab and the role of PD-L1 expression as biomarker for checkpoint inhibitors

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Immune checkpoint inhibitors have revolutionised cancer therapeutics. Translational research evaluating the role of biomarkers is essential to identify the ideal target population for these drugs. From a regulatory perspective, the identification of biomarkers and diagnostic assays is strongly encouraged by the European Medicines Agency (EMA). The aim of this article is to analyse the role of programmed death-ligand 1 (PD-L1) expression as a predictive biomarker in relation to the data submitted for the initial assessment of atezolizumab, a monoclonal antibody targeting human PD-L1. On 20 July 2017, atezolizumab was granted a marketing authorisation valid throughout the European Union (EU) for adult patients with (i) locally advanced or metastatic non-small-cell lung cancer (NSCLC) after chemotherapy and (ii) locally advanced or metastatic urothelial carcinoma (UC) after chemotherapy or cisplatin-ineligibility. Initially, these indications were not restricted by the level of PD-L1 expression, but preliminary data from an ongoing phase III trial in patients with UC led to a restriction in the UC indication to cisplatin-ineligible patients whose tumours have $\geq$5% PD-L1 expression. Still, the role of PD-L1 expression as predictive biomarker for atezolizumab therapy remains inconclusive and further research is needed. Data in this paper came from the scientific review leading to the initial regulatory approval of atezolizumab in the EU and its complementary application for indication (EMEA/H/C/004143/II/0010). The full scientific assessment report and product information are available on the EMA website (www.ema.europa.eu).

Key words: atezolizumab, TECENTRIQ, biomarkers, lung cancer, bladder cancer, PD-L1 expression, EMA

INTRODUCTION

The immune system has a protective function against cancer through its ability to recognise and eliminate incipient cancer cells. Malignant cells can evade immune destruction, and major efforts have been devoted to the understanding of this process and how it can be blocked.[1,2] To that effect, monoclonal antibodies targeting specific immune checkpoints, such as cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) have been developed. These agents constitute a breakthrough in cancer therapeutics, being authorised for different indications such as melanoma,[3] non-small-cell lung cancer (NSCLC),[4,5] urothelial carcinoma (UC),[6] renal cell carcinoma,[7] and head and neck cancer.[8] Of note, their efficacy varies across different tumour types with a relatively low proportion of responders in some settings. Immune biomarkers are needed to identify those patient subpopulations more likely to benefit from these agents. One of the biomarkers studied was PD-L1 expression in both tumour and immune cells.

Atezolizumab (TECENTRIQ®) is a humanised monoclonal antibody that targets PD-L1 and inhibits its interaction with PD-1. PD-L1 is one of two ligands that regulate the activity of PD-1, an inhibitory receptor whose expression on T cells is induced in sites of chronic stimulation such as the tumour microenvironment.[9] On 20 July 2017, a marketing authorisation valid through the European Union (EU) was issued

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for atezolizumab for the treatment of adult patients with (i) locally advanced or metastatic NSCLC after chemotherapy or (ii) locally advanced or metastatic UC after chemotherapy or ineligibility for cisplatin therapy.

At that time, agents approved for the treatment of NSCLC in second line and beyond (2L+) included docetaxel, pemetrexed, and erlotinib. The therapeutic index of these agents was restricted by both limited survival benefit and significant toxicity such as myelosuppression and neuropathy (docetaxel), diarrhoea (pemetrexed, erlotinib), and rash (erlotinib).[10] Moreover, pembrolizumab and nivolumab had been recently approved for this indication.[11-13] With regard to UC, cisplatin-based chemotherapy was the preferred therapy for previously untreated patients,[14] but there were no approved options for patients ineligible for this treatment. Responses to cisplatin-based regimens were of limited duration, with nearly all patients eventually experiencing progressive disease (PD). Moreover, vinflunine was the only drug approved in the EU for patients with relapsed disease, although taxanes (paclitaxel and docetaxel) were also commonly used in this setting.

The aim of this article is to analyse the role of PD-L1 expression as a predictive biomarker in relation to the data submitted for the initial assessment of atezolizumab (TECENTRIQ) and the complementary application for a variation (EMEA/H/C/004143/II/0010) to the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA).

SCIENTIFIC ASSESSMENT

NSCLC

The OAK study (GO28915) was submitted in support of the claimed indication for NSCLC.[15] Additional data from POPLAR (GO28753), BIRCH (GO28754), and FIR (GO28625) were also provided.[16-18] OAK was a phase III, open-label, multicentre, randomised study to evaluate the efficacy and safety of atezolizumab versus docetaxel in patients with locally advanced or metastatic NSCLC who had failed prior platinum-containing chemotherapy. The main inclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance status $\leq$1, life expectancy $\geq$12 months, locally advanced or metastatic NSCLC, and PD following treatment with platinum-based chemotherapy. Patients harbouring a sensitising epidermal growth factor receptor (EGFR) mutation or an anaplastic lymphoma kinase (ALK) fusion oncogene were additionally required to have experienced PD after treatment with an EGFR tyrosine kinase inhibitor or ALK inhibitor, respectively.

Patients were stratified by PD-L1 expression by immunohistochemistry, number of prior chemotherapy regimens and histology, and were randomised to receive either atezolizumab or docetaxel. PD-L1 expression was assessed in tumour-infiltrating immune cells (ICs) or tumour cells (TCs). Four levels of IC expression (IC0, IC1, IC2, IC3) and four levels of TC expression (TC0, TC1, TC2, TC3) were assigned, corresponding to PD-L1 staining in $<$1%, $\geq$1% to $<$5%, $\geq$5% to $<$10%, and $\geq$10% of ICs, and $<$1%, $\geq$1% to $<$5%, $\geq$5% to $<$50%, and $\geq$50% of TCs, respectively, according to the SP142 IHC assay. Atezolizumab was administered intravenously (i.v.) at a fixed dose of 1200 mg every 3 weeks until unacceptable toxicity or symptomatic deterioration attributed to PD. Docetaxel (75 mg/m^2) was administered IV every 3 weeks. The primary endpoint was overall survival (OS), the main secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and duration of response (DOR).

At the clinical cut-off date (CCOD) of 7 July 2016, the OS was significantly better for patients assigned to atezolizumab [hazard ratio (HR) 0.73; 95% confidence interval (CI): 0.62-0.87]. Subgroup analyses by PD-L1 expression showed an improved OS in all subpopulations treated with atezolizumab, including TC0 and IC0 (Figure 1). The results in PD-L1 expression subpopulations according to histology (non-squamous versus squamous) were also in line with the primary results. The ORR was 13.4% (95% CI: 10.32% to 17.02%) versus 13.6% (95% CI: 10.53% to 17.28%) for the docetaxel and atezolizumab arms, respectively, but was higher for atezolizumab compared with docetaxel in those subgroups with a higher PD-L1 expression (Table 1).

The safety database for NSCLC included 1636 patients. Overall, 65.7% of patients reported at least one treatment-related adverse event, of which 13.3% were of grade $\geq$3. The most common immune-related events in this population were hypothyroidism (4.6%) and pneumonitis (3.4%). Safety was also evaluated across all TC/IC subpopulations, but no noteworthy differences were observed.

Urothelial cancer

The claimed indication of atezolizumab in UC was supported by the clinical trials IMvigor 210 (GO29293) and IMvigor 211 (Study GO29294).

IMvigor 210 (GO29293). This was a multicentre single-arm phase II study in patients with locally advanced or metastatic UC.[19,20] The study included patients with a representative tumour specimen evaluable for PD-L1 expression, measurable disease, and a life expectancy $\geq$12 weeks. Treatment-naive cisplatin-ineligible patients were allocated to cohort 1 (1L)[20] and those that had received a least one platinum-containing regimen were allocated to cohort 2 (2L+).[19] Patients were classified based only on PD-L1 expression in IC due to the large overlap in PD-L1 expression between TCs and ICs. The scores of IC0, IC1, and IC2/3 were assigned to tumour samples with PD-L1 staining in $<$1%, $\geq$1% to $<$5%, and $\geq$5% of ICs, respectively. Atezolizumab was administered i.v. at a flat dose of 1200 mg every 3 weeks until PD or beyond if patients obtained clinical benefit (cohort 2 only). The primary endpoint was ORR, and key secondary endpoints included DOR, PFS, and OS.

In cohort 1, results showed an ORR of 22.7% (95% CI: 15.5% to 31.3%), ranging from 20.5% to 28.1% across PD-L1 expression subgroups, and the median DOR had not been reached at the CCOD of 4 July 2016. When compared with historical data using carboplatin and gemcitabine as the best available treatment option for cisplatin-ineligible

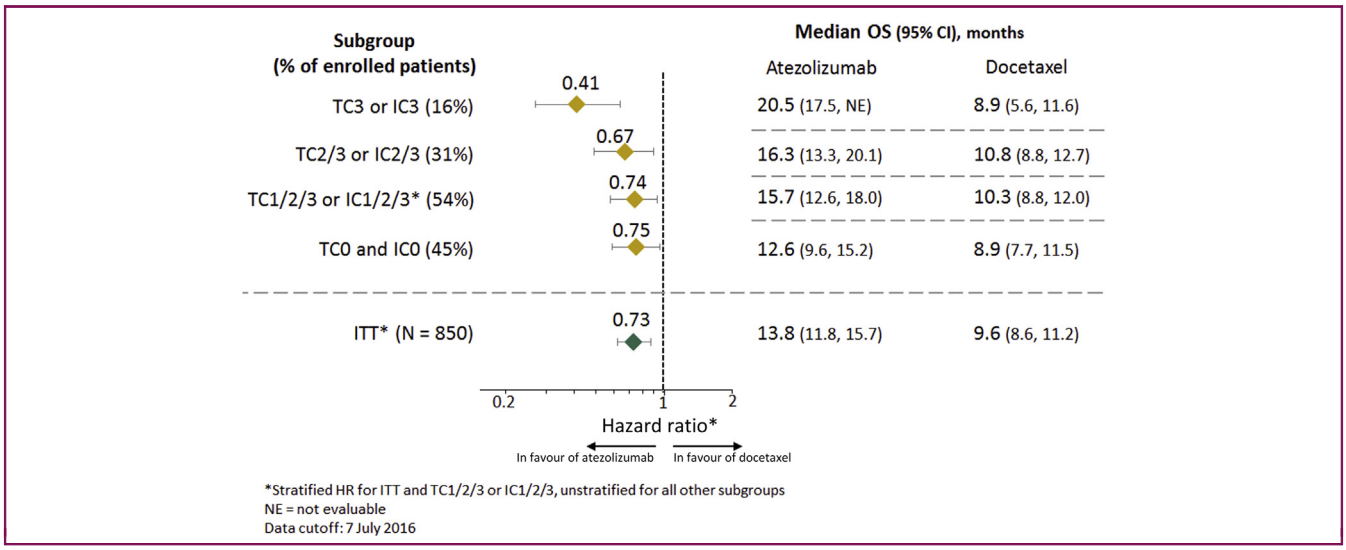

Figure 1. Forest plot of overall survival by PD-L1 expression in patients with non-small-cell lung cancer in second line (OAK study).
IC, immune cells; TC, tumour cells; ITT, intention to treat.

patients, the ORR was less favourable for atezolizumab (22.7% versus 36.1%), but responses were still ongoing in 70% of patients with a median follow-up of 17.2 months compared with a median DOR of 5.3 months for carboplatin and gemcitabine. The estimated 12-month OS was 57.2%, with a trend towards a longer OS in subgroups with low PD-L1 expression: 62.2%, 56.3%, 52.4%, and 54.8% for IC0, IC1, IC2/3, and IC1/2/3, respectively. In cohort 2, the ORR was 15.8% (95% CI: 11.9% to 20.4%), being higher for IC2/3 (28.0%) and IC1/2/3 (19.3%) subgroups. The median DOR had not been reached, and the estimated OS at 12 months was 36.9% in the overall population: 30.0%, 49.9%, and 40.2% for IC0, IC2/3, and IC1/2/3 expression subgroups, respectively (Table 2).

IMvigor 211 (GO29294). This was a randomised phase III study comparing atezolizumab with chemotherapy (investigator's choice of vinflunine or paclitaxel/docetaxel) for locally advanced or metastatic UC after a platinum-containing regimen.[21] Randomisation was stratified by chemotherapy (vinflunine versus taxane), PD-L1 expression, presence of liver metastasis, and number of baseline prognostic risk factors. The primary endpoint was OS but tested in a hierarchical fixed sequence in prespecified populations: IC2/3, followed by IC1/2/3, followed by the entire population. Statistical significance was required at each step before formal testing of the subsequent population. The main secondary endpoints included ORR, PFS, and DOR.

At the CCOD of 13 March 2017, the HR for OS in the IC2/3 population was 0.87 (95% CI: 0.63-1.21), precluding further formal statistical comparisons. The exploratory analysis of the entire population showed a HR of 0.85 (95% CI: 0.73-0.99), which was maintained (HR below 1) in all PD-L1 expression subgroups (Table 2). The ORR was 13.4% in both treatment arms.

The safety profile of atezolizumab in UC patients was assessed with data from 524 patients. Overall, 69.1% of the patients reported at least one treatment-related adverse event (16.0% grade $\geq$3). Safety was also evaluated according to PD-L1 expression without notable differences.

The benefit of atezolizumab in 1L cisplatin-ineligible patients was considered established based on durable responses and promising OS data. Moreover, and based on a positive OS trend and a more favourable safety profile, the

Table 1. Objective response rate by PD-L1 expression in patients with non-small-cell lung cancer in second line (OAK study)

	Docetaxel	Atezolizumab
TC3 or IC3	*n* = 65	*n* = 72
Responders (%)	7 (10.8%)	22 (30.6%)
95% CI (Clopper—Pearson)	4.44% to 20.94%	20.24% to 42.53%
TC2/3 or IC2/3	*n* = 136	*n* = 129
Responders (%)	17 (12.5%)	29 (22.5%)
95% CI (Clopper—Pearson)	7.45% to 19.26%	15.60% to 30.66%
TC0 and IC0	*n* = 199	n = 180
Responders (%)	21 (10.6%)	14 (7.8%)
95% CI (Clopper—Pearson)	6.65% to 15.68%	4.32% to 12.71%

CI, confidence interval; IC, immune cells; PD-L1, programmed death-ligand 1; TC, tumour cells.

Table 2. Overall survival of patients with urothelial carcinoma in second line after a platinum-containing regimen according to PD-L1 expression (IMvigor 210 and IMvigor 211 studies)

	IMvigor 210	IMvigor 211		
	Cohort 2[a] (*n* = 310)	Atezolizumab[a] (*n* = 467)	Chemotherapy[a] (*n* = 467)	Hazard ratio (95% CI)
All patients	7.9 (36.9%)	8.6 (39.2%)	8.0 (32.4%)	0.85 (0.73-0.99)
IC1/2/3	9.0 (40.2%)	8.9 (40%)	8.2 (33.2%)	0.87 (0.71-1.05)
IC2/3	11.9 (49.9%)	11.1 (46.4%)	10.6 (41.2%)	0.87 (0.63-1.21)
IC1	6.7 (31.2%)	8.4 (36.3%)	7.5 (28%)	0.85 (0.68-1.08)
IC0	6.5 (30%)	7.2 (37.6%)	6.7 (30.9%)	0.82 (0.63-1.07)

CI, confidence interval; IC, immune cells.
[a] Median overall survival in months (12-month rate).

clinical benefit of atezolizumab over chemotherapy was also considered established in the 2L setting. Of note, the applicant was recommended to provide results of a 'biomarker analysis plan' in order to solve uncertainties regarding the efficacy of atezolizumab according to PD-L1 expression status. The applicant was also requested to submit the results of the post-authorisation efficacy study (PAES) IMvigor 130, a phase III randomised study evaluating the safety and efficacy of atezolizumab monotherapy versus atezolizumab plus carboplatin/gemcitabine versus cisplatin/gemcitabine in previously untreated patients. The motivation for requesting this PAES was the inferior ORR of atezolizumab compared with historical data with carboplatin and gemcitabine, despite its longer DOR, and to fully evaluate PFS and OS.

On 19 March 2018, the independent data monitoring committee for the IMvigor 130 study met to review the interim results (CCOD: 12 March 2018) and their recommendation was to close the atezolizumab monotherapy arm for patients with IC0-1 PD-L1 expression. In this subgroup, patients treated with atezolizumab showed a decreased OS compared with the control platinum-based chemotherapy arm. This unfavourable OS could not be attributed to higher rates of adverse events or withdrawals or differences in baseline characteristics. As a result, on 31 May 2018, the indication of atezolizumab was amended to "Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (1) after prior platinum-containing chemotherapy, or (2) who are considered cisplatin ineligible and whose tumours have a PD-L1 expression of 5% or greater". The applicant was also requested to submit the final results of the IMvigor 130 study.

DISCUSSION

Immune checkpoint inhibitors have improved the outlook of patients diagnosed with a variety of malignancies, but it would be desirable to possess biomarkers able to identify those patients likely to benefit from these therapies. From a regulatory perspective, biomarkers are considered essential to identify the proper target population for a given therapy, specifically in the oncology setting. Thus, the development of biomarkers and diagnostic assays during drug development is strongly encouraged by the EMA.[22]

Atezolizumab targets PD-L1 and, hence, PD-L1 expression has been extensively evaluated as a predictive biomarker.[23,24] The drug was approved for patients with NSCLC, regardless of PD-L1 expression, based on a phase III randomised trial in which a survival benefit was documented for all PD-L1 expression subgroups. Despite all subgroups benefiting from atezolizumab therapy, there was a trend towards a better treatment effect of atezolizumab in the higher PD-L1 expression groups (HR for OS: 0.41 versus 0.75 for TC3/IC3 versus TC0/IC0 patients, respectively).

In patients with UC, atezolizumab was approved based on two different trials with conflicting results regarding the value of PD-L1 expression. In the IMvigor 210 study (cohort 1), the ORR ranged from 20.5% to 28.1% across all PD-L1 expression subgroups, but there was a trend towards a longer OS in those with a low PD-L1 expression. In cohort 2, the ORR was higher and the OS longer for patients with higher PD-L1 expression compared with the overall population. In the IMvigor 211 study, the survival benefit was not statistically significant in the population with high PD-L1 expression and, indeed, PD-L1 expression proved to have prognostic rather than predictive value in this trial. Overall, the benefit of atezolizumab was considered established in both the 1L (cisplatin-ineligible patients) and 2L settings. Whilst response rates were in the same range as for chemotherapy and consistent across all patients, the DOR was substantially longer.

Of note, there was a divergent position from several members of the CHMP regarding the population of patients with previously untreated disease who were ineligible for cisplatin. This divergent position stated that, although OS appeared longer for atezolizumab compared with historical data, the lack of direct comparative data with standard first-line therapy precluded its full evaluation. Because of the low ORR of atezolizumab in patients with UC compared with historical data with carboplatin/gemcitabine (22.7% versus 36.1%), the applicant was requested to submit the results of study IMvigor 130, a phase III randomised trial in frontline therapy. The interim analysis of this trial concluded that the OS for atezolizumab monotherapy was inferior to that of conventional chemotherapy for patients with low PD-L1 expression (IC0/1). Accordingly, the study was amended so that this arm was closed for patients with low PD-L1 expression, and the approved indication was also amended to exclude these patients. Final results from the IMvigor 130 and other clinical trials (e.g. JAVELIN Bladder 100[25]) will help to establish the best place for PD-1/PD-L1 inhibitors, in relation to conventional chemotherapy, in the treatment of patients with UC and high PD-L1 expression.

CONCLUSION

The role of predictive biomarkers cannot be overemphasised in modern oncology. Despite many attempts by the applicant, the role of PD-L1 expression as a predictive biomarker was unclear in all pivotal trials, even with conflicting results in patients with UC. As a result, atezolizumab was approved in patients with locally advanced or metastatic UC after chemotherapy or those considered ineligible for cisplatin therapy regardless of PD-L1 expression. This approval was based on sustained responses, promising OS results and a favourable safety profile. However, emerging data from an ongoing phase III trial led to a revision of the approved indication to exclude patients ineligible for cisplatin with a low PD-L1 expression. From a regulatory perspective, the development of biomarkers and diagnostic assays during drug development is highly encouraged. To promote this, EMA is developing a guideline that could help to optimise the co-development of medicinal products and companion diagnostics. Interested parties are advised to

consult the 'Concept paper on predictive biomarker-based assay development in the context of drug development and lifecycle (EMA/CHMP/800914/2016)'.

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DISCLOSURE

The authors declare no conflict of interest.

DISCLAIMER

This publication is based on the European Public Assessment Report of TECENTRIQ, the summary of product characteristics, and other product information as published on the EMA website (www.ema.europa.eu). For the most current information on this marketing authorisation, please refer to the EMA website. The views expressed in this article are the personal views of the author(s) and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agency/agencies or organisations with which the author(s) is/are employed/affiliated.

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