Atezolizumab for previous treated advanced non-small-cell lung cancer: should it be worthy for the clinical practice?

Pedro Aguiar Jr[1], Hakaru Tadokoro[1], Ramon Andrade de Mello[2,3,4]

[1]Division of Medical Oncology, Federal University of Sao Paulo, Sao Paulo, Brazil; [2]Clatterbridge Cancer Centre NHS Foundation Trust, Birkenhead, UK; [3]Department of Biomedical Sciences and Medicine, [4]Algarve Biomedical Centre, University of Algarve, Faro, Portugal

Correspondence to: Ramon Andrade de Mello, MD, PhD. Clatterbridge Cancer Centre NHS Foundation Trust, Clatterbridge Health Park, Clatterbridge Road, Birkenhead, Wirral CH63 4JY, UK. Email: ramondemello@doctors.org.uk.

Comment on: Rittmeyer A, Barlesi F, Waterkamp D, *et al*. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389:255-65.

Received: 09 February 2017; Accepted: 20 February 2017; Published: 10 March 2017.

doi: 10.21037/amj.2017.02.06

View this article at: http://dx.doi.org/10.21037/amj.2017.02.06

Lung cancer is the leading cause of cancer-related death. American epidemiological data show that the incidence and mortality rate of lung cancer in the US is 57.3 and 46.0 per 100,000, respectively, with 224,390 new cases and 158,050 deaths estimated in 2016 (1,2). Globally, more than 1.5 million lung cancer-related deaths occurred in 2012 (2,3). Lung cancer has a significant economic burden. Its cost represents approximately 10% of the US cancer care expenditure, which was more than 12 billion dollars in 2010 (4).

Avoiding the immune system is one of the hallmarks of cancer (5). Tumor cells can inhibit the immune system through many mechanisms (6). The most important are the production of anti-inflammatory cytokines, stimulation of T-regulatory lymphocytes, and inhibition of T-effector lymphocytes (6). Antigen presenting cells, lymphocytes, and tumor cells interact through receptors. These receptors have complex interactions that lead to inhibition or activation of the immune system, for this reason they are also known as immune checkpoints (6).

Modern immunotherapy consists of monoclonal antibodies that bind to the immune checkpoint receptors and stimulate the immune system against the tumor (6). The most studied is the link between the lymphocytes membrane receptor, program cell death 1 (PD-1), and its ligand 1 or 2 (PD-L1 or PD-L2), which are expressed by some tumor cells. This interaction inhibits lymphocytes (6).

Nivolumab and pembrolizumab are anti-PD1 monoclonal antibodies that have showed a survival advantage over docetaxel for previously treated advanced non-small cell lung cancer (NSCLC) (7-9). The Food and Drug Administration (FDA) and the European Medical Agency (EMA) have approved both drugs.

Atezolizumab is a fully humanized IgG1 antibody against the PD-L1. The PD-1 blockade can enhance lymphocyte function in a diversity of organs, while PD-L1 blockade may stimulate lymphocytes mainly in the tumor microenvironment because PD-L1 is much more common in tumor cells than in normal cells (6). Atezolizumab is expected to have a more favorable toxicity profile because of its high specificity for PD-L1 blockade rather than PD-1 blockade.

Atezolizumab was initially studied in a dose escalation phase Ia trial that included 88 patients with advanced NSCLC (11% of them were previously untreated) (10). The overall response rate (ORR) for all patients was 23% and the median overall survival (OS) for all patients was 16 months (10). In this study, a PD-L1 expression of ≥50% in tumor cells or tumor infiltrating cells resulted in a higher ORR (48% versus 16%) and a longer median OS (18 versus 16 months) compared to patients without PD-L1 expression (10). Atezolizumab was well-tolerated in most patients. Eleven percent of patients experienced some grade 3 to 4 adverse events and four patients developed mild pneumonitis (10).

A randomized phase II trial (POPLAR) compared atezolizumab 1,200 mg every 3 weeks to docetaxel 75 mg/m² every 3 weeks for the treatment of patients

with NSCLC who had progressed on platinum-doublet chemotherapy (11). There were 287 patients included in this study, 144 were randomly allocated to receive atezolizumab, and 143 to allocated to receive docetaxel (11). Atezolizumab improved the median OS (12.6 months for atezolizumab versus 9.7 months for docetaxel), although the ORR was not improved in the overall population (15% for both groups) (11).

Cell surface PD-L1 expression of tumor cells and tumor infiltrating cells were assessed in all patient samples (11). The ORR with atezolizumab was directly proportional to the PD-L1 expression (from 8% ORR for patients with negative PD-L1 expression to 38% ORR for patients with ≥50% PD-L1 expression in the tumor or tumor infiltrating cells) (11).

In this study, PD-L1 positive patients were the only group who had a statistically significant improvement compared with docetaxel (11). The hazard ratio (HR) for OS for all patients was 0.77 (0.55–1.06) and the HR for PD-L1 with ≥50% expression was 0.46 (0.19–1.09). The median OS was not reached with atezolizumab but was 11.1 months with docetaxel and the HR for PD-L1 negative patients was 1.12 (0.64–1.93) and the median OS was 9.7 months in both treatment arms (11).

Recently, a randomized phase III trial (OAK) evaluated atezolizumab for the second-line treatment of NSCLC regardless of tumor histology or PD-L1 expression; however, there was a stratification according to PD-L1 expression (12). The OAK study enrolled 1,225 patients and randomized them to atezolizumab (1,200 mg every 3 weeks) or docetaxel (75 mg/m² every 3 weeks) (12).

In the preliminary analysis of data from 850 patients (425 included in each treatment arm), the OS improved by 27% in the patients receiving atezolizumab compared to those treated with docetaxel (median OS was 13.8 versus 9.6 months; HR 0.73; 95% CI: 0.62–0.87) (12). There was no improvement in ORR (14% for atezolizumab and 13% for docetaxel) (12).

When patients were stratified according to their level of PD-L1 expression, the OS was 59% greater among patients with PD-L1 expression ≥50% in the tumor cells or ≥10% in the tumor infiltrating cells who were treated with atezolizumab, compared to the docetaxel treatment (12). The median OS was 20.5 months for atezolizumab and 8.9 months for docetaxel (HR 0.41; 95% CI: 0.27–0.64) (12).

In contrast to previous randomized studies assessing NSCLC immunotherapy (7,8,13), atezolizumab improved the OS by 25% in patients with no PD-L1 expression (12). The median OS was 12.6 months for atezolizumab and 8.9 months for docetaxel (HR 0.75; 95% CI: 0.59–0.96) (12).

Interestingly, an anti-PD-L1 was the first immune checkpoint inhibitor to show a statistically significant improvement in OS in PD-L1 negative patients. A reason for this has not yet been identified. The main hypothesis is that differences in clones used for PD-L1 testing may explain the different results for each immune checkpoint inhibitor (14).

On the other hand, the ORR was higher in patients positive for PD-L1 (31% versus 8% in patients negative for PD-L1) (12).

In accordance with previous studies with nivolumab and pembrolizumab (8,9), patients with a mutated epidermal growth factor receptor (EGFR) showed no benefit with atezolizumab compared with docetaxel in terms of OS (median OS 10.5 months with atezolizumab versus 16.2 months with docetaxel, HR 1.24, P>0.05) (12).

Atezolizumab was expected to be tolerated better than anti-PD1, however, both drugs had similar toxicity profiles. Fewer patients had treatment-related grade 3 to 4 adverse events with atezolizumab compared to those treated with docetaxel (15% versus 43%) (12). In OAK trial, six cases of pneumonitis occurred, four of them were grade 3 to 4, but all cases were managed clinically (12).

These phase II and III trials led to the approval of atezolizumab by the FDA.

Table 1 summarizes the clinical findings of the atezolizumab studies.

Although atezolizumab had a good clinical efficacy, the cost of the treatment is a very important issue.

The cost of a vial of 1,200 mg of atezolizumab is approximately 12,500 dollars in the US. Treatment with atezolizumab for 6 months can cost 100,000 dollars while treatment with nivolumab or pembrolizumab for 6 months will cost approximately 70,000 dollars (30% less).

Our group estimated the economic burden of treating all previously treated advanced NSCLC with atezolizumab in the US and found that it could lead to an incremental cost of 2.4 billion dollars annually (15). This represents an improvement of $7.55 for each citizen to treat a population that represents no more than 10% of all cancer patients (15).

In conclusion, atezolizumab achieved good clinical efficacy for previously treated NSCLC. The survival gain compared with docetaxel represents a paradigm shift for PD-L1 negative patients. Atezolizumab will be the preferred immune checkpoint inhibitor for this population,

Table 1 Clinical findings of the atezolizumab studies

	PCD4989g (10)		POPLAR (11)	OAK (12)
ORR	23%	ORR *vs*. Doc	15% *vs*. 15%	14% *vs*. 13%
		Median PFS *vs*. Doc	2.7 *vs*. 3.0 m	2.8 *vs*. 4.0 m
Median OS	16 months	Median OS *vs*. Doc	12.6 *vs*. 9.7 m	13.8 *vs*. 9.6 m
		HR for OS (95% CI)	0.73 (0.53–0.99)	0.73 (0.62–0.87)

ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Doc, docetaxel; HR, hazard ratio; m, month.

although the economic issues must be discussed between the drug developers, policy makers, clinicians, and patients in order to improve the access for patients who will benefit the most from this treatment.

Acknowledgements

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Qing-Yuan Huang (Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China).

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037amj.2017.02.06). RA de Mello has received honoraria from AstraZeneca, Pfizer Advisory Board, Zodiac consulting, Novartis honoraria, National Science Centre, Krakow, Poland, and educational grant from Pierre Fabre, Amgen. RA de Mello is ad hoc consultant at Ministry of Health, Brasília, Brazil. P Aguiar Jr has received honoraria from Bristol Myers Squibb and Merck Sharp Dome. H Tadokoro has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Altekruse SF, Kosary CL, Krapcho M, et al. editors. SEER Cancer Statistics Review, 1975-2007, National Cancer Institute. Bethesda, MD, 2010.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7-30.
3. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86.
4. Mariotto AB, Yabroff KR, Shao Y, et al. Projections of the cost of cancer care in the United States: 2010-2020. J Natl Cancer Inst 2011;103:117-28.
5. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646-74.
6. Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy--inhibiting programmed death-ligand 1 and programmed death-1. Clin Cancer Res 2012;18:6580-7.
7. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:123-35.
8. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:1627-39.
9. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387:1540-50.
10. Horn L, Spigel DR, Gettinger SN, et al. Clinical activity, safety and predictive biomarkers of the engineered

antibody MPDL3280A (anti-PDL1) in non-small cell lung cancer (NSCLC): update from a phase Ia study. J Clin Oncol 2015;33:abstr 8029.
11. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837-46.
12. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389:255-65.
13. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372:2018-28.
14. Hirsch FR, McElhinny A, Stanforth D, et al. PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project. J Thorac Oncol 2017;12:208-22.
15. Aguiar PN, Tadokoro H, BARRETO CM, et al. Cost effectiveness of immune checkpoint inhibitors in NSCLC according to PD-L1 expression. J Clin Oncol 2016;34:abstr 9033.

doi: 10.21037/amj.2017.02.06
Cite this article as: Aguiar P Jr, Tadokoro H, de Mello RA. Atezolizumab for previous treated advanced non-small-cell lung cancer: should it be worthy for the clinical practice? AME Med J 2017;2:34.

