Therapeutic Advances in Medical Oncology
Review

Atezolizumab: feasible second-line therapy for patients with non-small cell lung cancer? A review of efficacy, safety and place in therapy

Ther Adv Med Oncol
2017, Vol. 9(12) 769–779
DOI: 10.1177/1758834017741074

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***Abstract*:** Advanced non-small cell lung cancer (NSCLC) prognosis is still poor and has recently been reformed by the development of immune checkpoint inhibitors and the approval of anti-PD-1 (programmed cell-death 1) treatments such as nivolumab and pembrolizumab in second line. More recently, atezolizumab (MDPL 3280A), a programmed cell-death-ligand 1 (PD-L1) inhibitor, was also studied in this setting. Here, we report a review of the literature assessing the efficacy, safety, and place of atezolizumab in the second-line treatment of advanced NSCLC. We performed a literature search of PubMed, American Society of Clinical Oncology, European Society of Medical Oncology and World Conference on Lung Cancer meetings. Atezolizumab showed a good tolerance profile and efficacy in comparison with docetaxel for second-line treatment of advanced NSCLC. Potential predictive biomarkers also have to be assessed.

Keywords: atezolizumab, immunotherapy, lung cancer, PD-L1, second-line

Received: 6 July 2017; revised manuscript accepted: 28 September 2017

Introduction

Lung cancer is the leading cause of cancer death worldwide.[1] Indeed, non-small cell lung Cancer (NSCLC) prognosis is poor with an overall survival rate at 5 years of 15% and until recently, treatment options in the second- or third-line setting for advanced diseases were limited.[2,3] However, in the last few years, comprehension of cell biology has improved, and mechanisms allowing cancer cells to avoid immune destruction,[4] relying both on innate and adaptive immunity, are better understood and addressed. Regarding adaptive immunity, there are two phases: during the first phase, dendritic cells interact with T cells which will then induce cancer cell destruction in the second phase. Inhibitory signals occur in both phases, involving membrane molecules of which the most important representative is the couple PD-1 (programmed cell-death 1) expressed by T cells with PD-L1 (programmed cell-death-ligand 1) on cancer cells. The last few years have seen the development and approval of anti-PD-1 therapies such as nivolumab in pretreated squamous[5] and nonsquamous[6] NSCLC, or pembrolizumab in previously treated, PD-L1-positive, advanced NSCLC.[7] Therefore, recent guidelines established new recommendations including anti-PD-1 immunotherapy for second line treatment of NSCLC.[8,9] However, PD-L1 blockade is distinct, since it allows PD-1 to bind its other ligand, PD-L2 which may be important in possibly preventing severe immune adverse effect events such as pneumonitis.[10–12] Atezolizumab (MDPL 3280A) is a humanised engineered IgG1 monoclonal antibody targeting PD-L1 usually used with its specific companion immunohistochemistry (IHC) diagnostic assay, SP142 (Ventana Medical Systems, Inc. Arizona, USA), assessing PD-L1 expression both on tumour cells (TCs) and on tumour-infiltrating immune cells (ICs).

The percentage of PD-L1-positive cells is expressed by a score including PD-L1 expression levels on both TCs and ICs. On TCs, TC3, TC2, TC1 and TC0 are respectively correlated with PD-L1 expression levels of $\geq$50%; $\geq$5% and $<$50%; $\geq$1%

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and <5%; and <1%. On tumour-infiltrating ICs IC3, IC2, IC1 and IC0 are respectively correlated with PD-L1 expression levels of ⩾10%; ⩾5% and <10%; ⩾1% and <5%; and <1%.[13–16]

In this article, we are proposing a review of the efficacy and safety of atezolizumab in locally advanced or metastatic NSCLC, focusing on its place as second-line treatment of NSCLC.

Methods

A literature search of PubMed, ASCO (American Society of Clinical Oncology), ESMO (European Society of Medical Oncology) and WCLC (World Conference on Lung Cancer) meeting abstracts, as well as a review of ClinicalTrials.gov was conducted using the following terms: 'Atezolizumab', 'MDPL3280A', 'lung cancer' or 'Non-Small Cell Lung Cancer'. We chose to include clinical trials, meta-analyses and communications from international congresses between 2015 and 2017, since no clinical data were available on atezolizumab before 2013.

Results

In PubMed, among 53 articles found, 4 were clinical trials. One phase I trial was excluded due to the lack of data compared with the others. Moreover, four articles were meta-analyses, including one with insufficient atezolizumab data, not reported here. Among congress reports, between 2015 and 2017, we found 19 abstracts. Two of them, being preliminary data further published in a larger trial or not reporting enough data about atezolizumab, were excluded. Figure 1 reports the flow chart of articles and reports included in this review.

Efficacy

Phase I

Herbst and colleagues conducted a phase I study[17] aiming to evaluate the single-agent safety and tolerability of MDPL3280A/atezolizumab administered by intravenous infusion every 3 weeks (q3w) to patients with locally advanced or metastatic solid tumours or haematological malignancies. A total of 277 patients were included, mostly suffering from NSCLC (31%), renal cell carcinoma (25%) and melanoma (16%). In the NSCLC subgroup, patients had a median age of 60 years and were mostly males (56%) performance status 0–1. A total of 76% had nonsquamous NSCLC, only 5% had central nervous system (CNS) metastasis, 80% had a tobacco history and 55% had received at least three prior systemic regimens.

In the dose-escalation phase of the study, patients received atezolizumab q3w from 0.01 mg/kg to 20 mg/kg and the expansion phase enrolled patients at 10 mg/kg, 15 mg/kg or 20 mg/kg q3w. Mean terminal serum half-life of 3 weeks was reached with a minimum dose of 1 mg/kg. A dose of 15 mg/kg q3w was sufficient to maintain target drug levels and the equivalent fixed dose of 1200 mg q3w was moved forward in clinical development of single-agent atezolizumab.

In this phase I study, 21% of patients with NSCLC showed a confirmed response according to Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST 1.1). The median progression-free survival (PFS) of all patients was 18 weeks. The association between response to atezolizumab and tumour-infiltrating ICs PD-L1 expression reached statistical significance in NSCLC ($p = 0.015$). These data were confirmed in a Japanese phase I study in 2016.[14]

Phase II – POPLAR trial

POPLAR[15] was a phase II clinical trial testing atezolizumab 1200 mg q3w *versus* docetaxel 75 mg/m² q3w in the treatment of stage IIIb–IV NSCLC patients previously treated with platinum-based first-line chemotherapy. Overall survival (OS) favoured atezolizumab *versus* docetaxel with a hazard ratio (HR) of 0.73 [95% confidence interval (CI) 0.53–0.99], $p = 0.040$ in the intent-to-treat (ITT) population. Increasing improvement in OS was correlated with increased PD-L1 expression. However, PFS was not significantly improved in the atezolizumab arm: HR = 0.94 (95% CI 0.72–1.23), $p = 0.645$ (ITT population).

An objective response rate (ORR) of 38% was noticed in the TC3 or IC3 subgroup. Objective responses with atezolizumab were durable, with a median duration of 14.3 months (11.6–nonestimable) compared with 7.2 months (5.6–12.5 months) for docetaxel. This gap between atezolizumab and docetaxel was even wider in updated data presented at ASCO congress in 2016.[18]

An ongoing phase II trial, BIRCH, is currently conducted in first or more lines of treatment in preselected patients with IC2/3 or TC2/3 PD-L1

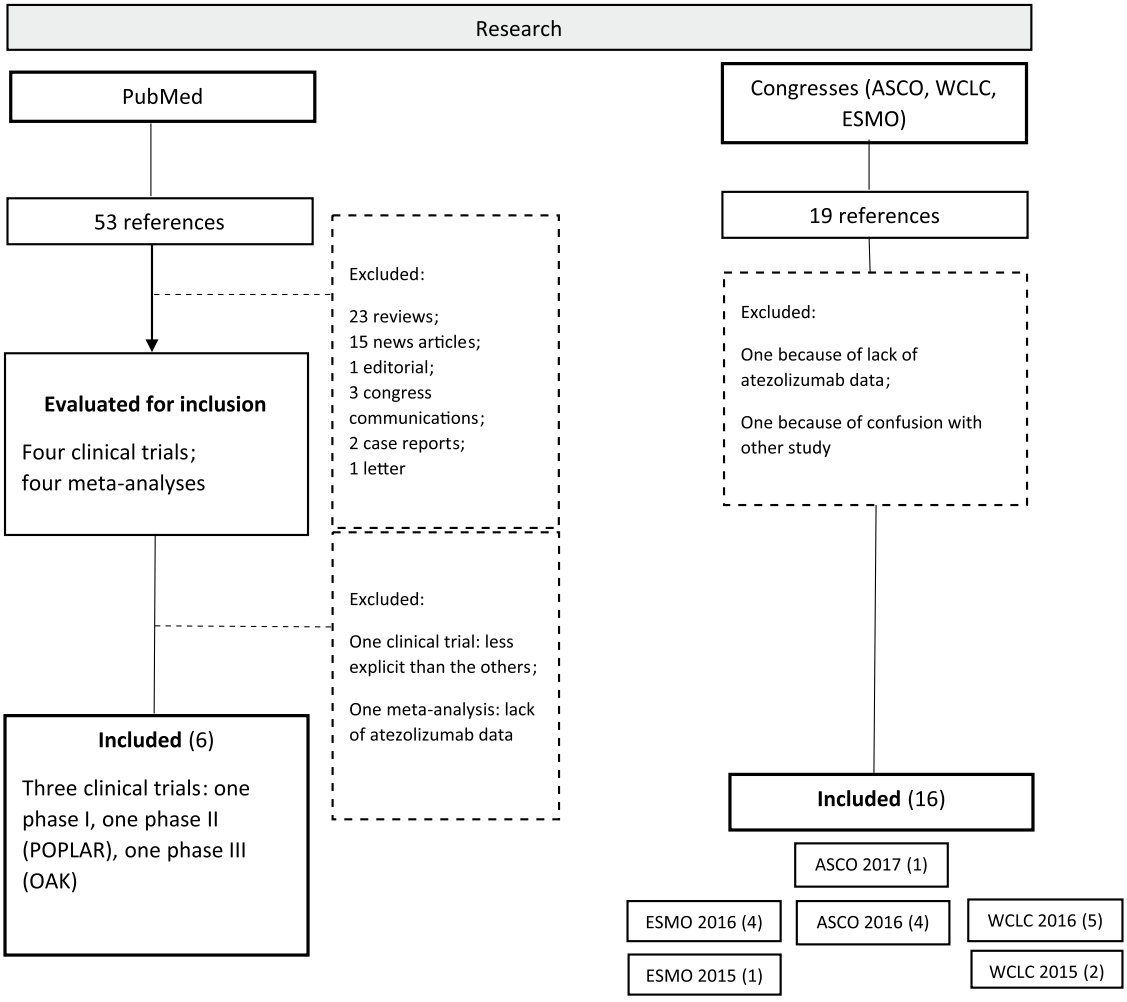

Figure 1. Flow chart.
ESMO, European Society for Medical Oncology; ASCO, American Society of Clinical Oncology; WCLC, World Conference on Lung Cancer.

expression profile [ClinicalTrials.gov identifier: NCT02031458].[19,20] In the first-line subgroup, ORR was 19%; 6-month PFS was 46%; 6-month OS was 82%; whereas in the second line subgroup, ORR was 17%; 6-month PFS was 29% and 6-month OS was 76%.[19]

Phase III – OAK trial

The following phase III trial, OAK,[16,21] highlighted the efficacy of atezolizumab in second-line treatment of NSCLC, with a median OS of 13.8 months in the atezolizumab arm (95% CI 11.8–15.7) *versus* 9.6 months in the docetaxel arm [(8.6–11.2); HR 0.73 (95% CI 0.62–0.87), p = 0.0003]. PFS was similar between treatment groups in the ITT population [HR 0.95 (95% CI 0.82–1.10)]. There was no difference regarding objective response between the two groups with an ORR of 14% with atezolizumab and 13% with docetaxel in the ITT population.

Characteristics of TC3 or IC3 population were: median age of 64 years, mostly males (64.2%), White (77.4%), previous (65%) or current (19.7%) smokers, *EGFR* wild type (73.7%) and with nonsquamous NSCLC (70.1%).

Treatment beyond progression (TBP) is authorized if the investigator deemed the patient to be receiving clinical benefit and if patients consented to continuation. Clinical benefit is defined by an absence of unacceptable toxicity, a symptomatic deterioration attributed to disease progression after an integrated assessment of radiographic data, biopsy results (if available) and clinical status. New data from the OAK trial[22] suggest that

TBP with atezolizumab is efficient, as presented in ASCO 2017, where a pool of patients continue to receive the anti-PD-L1 agent after disease progression if a clinical benefit was still present. Among 332 patients with PD while treated by atezolizumab, 51% (168) continued anti-PD-L1 therapy. A total of 7% achieved subsequent response from new baseline (at PD), 49% had stable target lesions and median of OS (mOS) was 12.7 months (95% CI 9.3–14.9) while those who received other anticancer therapy (chemotherapy or new line of immunotherapy) had an mOS of 8.8 months (95% CI 6.0–12.1). Safety profile seemed to be tolerable. Consequently, there would be an interest of using atezolizumab in postprogression prolongation of survival.

Subgroup analyses

PD-L1 expression

In the POPLAR study,[15] OS was correlated with PD-L1 expression level since OS in the TC1/2/3 or IC1/2/3 subgroups was higher in the atezolizumab [HR of 0.59 (95% CI 0.33–0.89), p = 0.014], whereas OS was not improved by atezolizumab in the TC0 and IC0 groups [HR 1.04 (0.62–1.75), p = 0.871].

Unlike in POPLAR, the OAK study[16,21,23] showed a survival advantage for atezolizumab *versus* docetaxel even in the TC0 or IC0 subgroups (45% of the patients) with an HR of 0.75 (95% CI 0.59–0.96), p = 0.0215. It was consistent with the PD-L1 gene expression results: OS was improved by atezolizumab regardless of PD-L1 gene level expression. The difference in the two trials may be due to a statistically larger female population in the docetaxel group in POPLAR, overestimating the OS.

These data were consistent with a meta-analysis of three clinical trials with anti-PD-1 or PD-L1 antibodies such as nivolumab or atezolizumab[24] and showing a significant improvement in OS, but not in PFS, except in the case of elevated levels of PD-L1 expression.

The main results of the OAK and POPLAR trials are showed in Table 2.

Clinical characteristics

The survival advantage of atezolizumab over docetaxel was statistically the same regardless of pathology subtype (squamous or nonsquamous),[16,21] the presence of CNS metastases at baseline, or tobacco smoking history.[16,21] However, a trend emerged, revealing that some subgroups benefited even more from atezolizumab than the global population, such as the elderly population (⩾65 years)[16,21] [median OS was 14.1 months *versus* 9.2 months respectively, HR = 0.66 (95% CI 0.52–0.83) *versus* 0.80 (95% CI 0.64–1.00)] or the CNS metastases population[19] [HR of 0.54 (95% CI 0.31–0.94) *versus* 0.75 (0.63–0.89)].

On the contrary, there was a disadvantage of atezolizumab *versus* docetaxel in the *EGFR* (epidermal growth factor receptor) mutant population [OS HR 1.24 (95% CI 0.71–2.18)],[21] as previously reported with other immune checkpoint inhibitors such as nivolumab or pembrolizumab [OS HR = 1.05 (95% CI 0.70–1.55), p < 0.81] in a meta-analysis recently published.[25]

Other biomarkers

In the phase II trial, POPLAR, OS in the atezolizumab population seemed to be correlated to higher gene level expression of PD-L1, PD-1, PD-L2, B7.1 and T-effector interferon gamma,[15] but since it was not confirmed for PD-L1 in OAK, further analyses should be performed based on tumour mutation burden researches as shown in Rizvi and colleagues' study: high nonsynonymous mutation burden was associated with clinical benefit of pembrolizumab.[26]

Safety

In the phase I study by Herbst and colleagues,[17] the maximum tolerated dose was not reached and no dose-limiting toxicities were observed.

The rates of adverse effect events in clinical trials of atezolizumab are reported in Table 1.

The most common side effects of any grade were fatigue (26.8%), decreased appetite (23.5%), cough (23.2%), asthenia (19%), dyspnoea (19%), nausea (17.7%), pyrexia (17.7%), constipation (17.6%), diarrhoea (15.4%) and arthralgia (12%).[16]

Pooled safety analyses were conducted on patients suffering from asymptomatic untreated CNS metastases or stable previously treated brain metastases at baseline[27] in several studies as POPLAR. A total of 27 patients were analysed: 44% had any neurological adverse event (AE) *versus* 28% in the population with no CNS metastasis, but there were no more AEs of any type and no discontinued treatment due to AE

Table 1. Adverse event rates in the POPLAR and OAK trials in intention-to-treat populations.

Trial name	Arms	Any grade adverse events (%)	Grade 3–4 adverse events (%)	Adverse events leading to dose modification, delay or interruption (%)	Immune-related adverse events (%)
Hervst et al.[13]	Atezo	94.9	39	–	–
POPLAR	Atezo	96	40	24	3.2*
	Doc	96	53	33	–
OAK	Atezo	94	37	25	10.5**
	Doc	96	54	36	–

*Pneumonitis: 6; colitis: 2; hepatitis: 2.
**Pneumonitis: 4; increased aspartate aminotransferase: 6; increased alanine aminotransferase: 6; colitis: 4; hepatitis: 1.
Atezo, atezolizumab; Doc, docetaxel.

in the subgroup of patients with CNS metastases.

PD-1/PD-L1 AEs compared with docetaxel in a meta-analysis had an odds ratio (OR) of 0.36 (95% CI 0.28–0.46); $p < 0.001$, all grades included and of 0.18 (95% CI 0.14–0.22), $p < 0.001$ for grade 3–5 AEs, showing a better tolerability profile of immune checkpoint inhibitors in comparison with chemotherapy by docetaxel.[28]

Another meta-analysis compared anti-PD-1 and anti-PD-L1 tolerance profile and did not show any difference on AE rates (including immune AE and pneumonitis) on a population of more than 4400 patients.[29]

In conclusion, phase I–III trials showed a good tolerance profile and efficacy of atezolizumab for the treatment of pretreated NSCLC patients, especially in comparison with standard chemotherapy with docetaxel.

Discussion

Based on clinical trials and meta-analyses, we report that atezolizumab is efficient and safe for second-line treatment of advanced NSCLC, irrespective of PD-L1 expression. But its place compared with other immune checkpoint inhibitors, including anti-PD-1 treatments already approved in this setting is still to be proven. Otherwise, relevance of PD-L1 expression according to SP142 IHC should be reassessed, since atezolizumab is effective in any PD-L1 expression group, and other predictive biomarkers should be studied.

Furthermore, there are remaining questions regarding potential combination of atezolizumab with other therapeutics, such as systemic treatment

Table 2. Efficacy data of POPLAR and OAK trials on atezolizumab in intention-to-treat and TC3 and IC3 populations.

	Phase	Population	Group	n	OS (months)	HR (95% CI)	p	PFS (months)	HR (95% CI)	p	ORR (%)
Fehrenbacher et al.[15] (POPLAR)	II	ITT	Atezo	144	12.6	0.73 (0.53–0.99)	0.04	2.7	0.94 (0.72–1.23)	0.645	14.6
			Docetaxel	143	9.7			3			14.7
		TC3 or IC3	Atezo	24	15.5	0.49 (0.27–1.07)	–	7.8	0.60 (0.31–1.16)	0.127	37.5
			Docetaxel	23	11.1			3.9			13
Rittmeyer et al.[16] (OAK)	III	ITT	Atezo	425	13.8	0.73 (0.62–0.87)	0.0003	2.8	0.95 (0.82–1.10)	0.49	14
			Docetaxel	425	9.6			4.0			13
		TC3 or IC3	Atezo	72	20.5	0.41 (0.27–0.64)	< 0.0001	4.2	0.63 (0.43–0.91)	0.0123	30.6
			Docetaxel	65	8.9			3.3			10.8

Atezo, atezolizumab; CI, confidence interval; HR, hazard ratio; IC3, immune cell 3; ITT, intention to treat; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; TC3, tumour cell 3.

(chemotherapy, other immunotherapy, and targeted therapy), radiotherapy or surgery; the existence of a targeted population of interest and biomarkers to guide atezolizumab use; the place of atezolizumab in the treatment strategy of advanced NSCLC; the potential extension of atezolizumab use to other histology like small cell lung cancer (SCLC) or in other settings such as adjuvant or neoadjuvant treatment of early-stage NSCLC.

All upcoming trials referring to atezolizumab are presented in Table 3. Atezolizumab is being tested alone in the neoadjuvant or adjuvant setting, in first-line treatment of NSCLC, in small SCLC or in association with other therapies.

Atezolizumab combined with other treatments

Atezolizumab is currently tested in association with chemotherapy, anti-VEGF, EGFR tyrosine kinase inhibitor, vaccine therapy, anti-CD38, anti-Cyclin Dependent Kinase (CDK)4/6 and radiation therapy (Table 2).

Combinations of atezolizumab with chemotherapy shouldn't convey more toxicities than chemotherapy alone as shown as in a phase Ib study examining safety of the anti-PD-L1 associated with either paclitaxel, pemetrexed or weekly nab-paclitaxel.[30]

Other trials should provide more information about the efficacy and safety of the combination with chemotherapy.[31,32]

Targeted population and potential biomarkers

Updated data from the BIRCH trial were presented at WCLC 2016,[20] where the ORR in the investigated group was 32% for TC3 or IC3 and 24% for TC2/3 or IC2/3. In this last subgroup, median duration of response was 13.1 months, median OS was 20.1 months. ORR was surprisingly better in the *EGFR* mutant subgroup (31%) than in the *EGFR* wild-type subgroup (20%) and ORR was also better in the *Kirsten rat sarcoma virus oncogene (KRAS)* mutant subgroup (27% *versus* 21% for *KRAS* wild-type NSCLC).

The FIR [ClinicalTrials.gov identifier: NCT01846416] study is currently assessing the efficacy of atezolizumab on preselected patients with CNS metastasis at baseline.

Companion diagnostic assays for anti-PD-1/PD-L1 therapies are discussed because of many differences and heterogeneity of measures and practical use. For instance, the nivolumab companion assay is Dako 28-8, targeting membrane tumour cells, with a threshold of positivity ⩾5%, pembrolizumab uses Dako 22C3 (Agilent, CA, United States), staining PD-L1 present on membrane tumour cells with a distinction for 'weak' expression (1–49%) and strong (⩾50%), SP142 attendant atezolizumab detect PD-L1 on tumour and tumour-infiltrating immune cells with a the positivity score TC1/2/3 or IC1/2/3.[33]

However, SP142, used with atezolizumab, is distinguishing itself due to its ability to detect PD-L1 expression on two different types of cells: TCs and tumour-infiltrating ICs. Furthermore, there is a strong correlation between PD-L1 IHC status and PD-L1 messenger RNA (mRNA) expression also with T-effector mRNA expression.[34]

One interesting fact in PD-L1 expression is that its intrapatient heterogeneity is low in metachronous tissues, indicating distinct types of tumour samples, including fresh or archival, can be reliably used to assess PD-L1 expression.[35]

The phase I study of atezolizumab[17] for the treatment of NSCLC, melanoma, renal cell carcinoma, other solid tumours and haematological malignancies showed that atezolizumab was more effective in patients with pre-existing immunity suppressed by PD-L1, thus immunotherapy helps to reinvigorate immune cells. Therefore, high levels of PD-L1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) expression at baseline, such as low levels of CX3CL-1 (fractalin) expression were correlated with a positive response, in all tumour types. In addition, in melanoma, great expression of interferon gamma and indoleamine 2,3-dioxygénase (IDO-1) or Chemokine (C-X-C motif) ligand 9 (CXCL-9) was correlated with a good response to anti-PD-L1. The authors of this phase I study proposed three models of nonresponders: (1) 'immunological ignorance' (little or no tumour-infiltrating immune cell infiltration); (2) 'nonfunctional immune response' (presence of an immune infiltrate with minimal to no expression of PD-L1); and (3) 'excluded infiltrate' (presence of an immune infiltrate that resided solely around the outer edge of the tumour cell mass).

Table 3. Expected atezolizumab (MDPL3280A) trials.

Histology	Stage	Histology subgroup	Therapeutic place	Phase	Experimental arm	Control arm	ClinicalTrials.gov identifier
NSCLC	Stage I			I	MDPL3280A + stereotaxic radiotherapy		NCT02599454
	Stage Ib-IIIa		After adjuvant cisplatin-based chemotherapy	III	MDPL3280A	Best supportive care	NCT02486718
			Neoadjuvant +/– adjuvant	II	MDPL3280A		NCT02927301
			Neoadjuvant	II	MDPL3280A + carboplatin + nab-paclitaxel		NCT02716038
	Stage IIIb–IV	Nonsquamous	First line	III	MDPL3280A + carboplatin + nab-paclitaxel	Carboplatin + nab-paclitaxel	NCT02367781
				III	MDPL3280A + carboplatin/cisplatin + pemetrexed	Carboplatin/ cisplatin + pemetrexed	NCT02657434
				III	MDPL3280A + carboplatin + paclitaxel +/– bevacizumab	Carboplatin + paclitaxel + bevacizumab	NCT02366143
			First line or higher in *EGFR* mutant	Ib–II	MDPL3280A + rociletinib		NCT02630186
		Squamous	First line	III	MDPL3280A + carboplatin + paclitaxel or nab-paclitaxel	Carboplatin + nab-paclitaxel	NCT02367794
				III	MDPL3280A + carboplatin/ cisplatin + gemcitabine	Carboplatin/ cisplatin + gemcitabine	NCT02409355
		Both	After previous treatment with PD-1-directed therapy	II	MDPL3280A		NCT03014648
			First line or higher	Ib	MDPL3280A + alectinib or erlotinib		NCT02013219
			First line or higher in preselected PD-L1 (+)	II	MDPL3280A		NCT02031458 or NCT01846416
			First line or higher in NY-ESO-1 (+)	II	CDX-1401 + MDPL3280A		NCT02495636
			Second line or higher	IB-II	MDPL3280A + daratumumab (anti-CD38)	MDPL3280A	NCT03023423

(Continued)

Table 3. (Continued)

Histology	Stage	Histology subgroup	Therapeutic place	Phase	Experimental arm	Control arm	ClinicalTrials.gov identifier
SCLC	Stage IIIb–IV		First line	I-II	MDPL3280A + carboplatin + etoposide	Carboplatin–etoposide	NCT02748889
				II	MDPL3280A + carboplatin + etoposide + trilaciclib	MDPL3280A + carboplatin + etoposide	NCT03041311
				I–III	MDPL3280A + carboplatin + etoposide	Carboplatin + etoposide	NCT027633579
			Second line	II	MDPL3280A	Carboplatin + etoposide or topotecan	NCT03059667

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; NY-ESO-1, cancer-testis antigen; PD-1, programmed cell-death 1; PD-L1, programmed cell-death-ligand 1; SCLC, small cell lung cancer.

However, atezolizumab has shown efficacy in phase II and III studies regardless of SP142 PD-L1 expression results, and other biomarkers should be investigated further. For example, tumour mutation load, which was quantified by Kowanetz and colleagues using the Fundation Medicine 1 (FM1) panel of 315 cancer-related genes on tumour specimens of patients from the POPLAR, BIRCH and FIR studies. OS, PFS and ORR were improved in patients with increased mutation load treated with atezolizumab in both unselected and PD-L1-positive patients.[36]

PD-L2 expression also seems to be correlated with atezolizumab efficacy in NSCLC, melanoma, renal cell carcinoma and urothelial carcinoma but further evidence is required.[37]

Moreover, PD-L1 staining is usually performed on tumour samples and sometimes leads to rebiopsy, but PD-1/PD-L1/PD-L2 expression on peripheral blood cells could be an easiest way to characterize PD-L1 expression and predict response to atezolizumab.[38]

The place of atezolizumab in therapy and potential extension of use

So far, atezolizumab was studied for second-line treatment of advanced NSCLC, such as previously approved other immune checkpoint inhibitors.

A phase II study of atezolizumab as neoadjuvant and adjuvant therapy in patients with resectable NSCLC is currently ongoing[39] aiming to enrol 180 patients with stage I, II and IIIa NSCLC prior to curative intent, who will receive two injections of atezolizumab 1200 mg before surgery. A second phase of this study will assess atezolizumab as an adjuvant therapy for patients who benefited from the neoadjuvant phase.

A multicentre phase III double-blinded, placebo-controlled study, IMpower133 [ClinicalTrials.gov identifier: NCT02763579],[40] will try to extend the indication of atezolizumab to SCLC treatment in first line and in association with standard chemotherapy: carboplatin–etoposide.

Conclusions

Atezolizumab (MDPL3280A) clearly is an added value in the treatment of advanced stage pretreated NSCLC. Its interest in contrast with other immune checkpoint inhibitors relies on its efficacy, even in low or no PD-L1 expression subgroups. Considering the efficacy of anti-PD-1 such as pembrolizumab or nivolumab is overall higher in PD-L1-positive patients, atezolizumab might be preferable in PD-L1-negative patients. It will be necessary to consider other variant methods of PD-L1 testing used for each therapy to further explore this hypothesis.

Nonetheless, toxicity profile does not seem to differ between anti-PD-1 and anti-PD-L1 treatments and, in order, there is no argument for choosing atezolizumab over pembrolizumab or nivolumab, based on toxicity profile.

We are still far from fully understanding cancer immunity and the mechanisms leading to the success or not of immunotherapy agents. For this reason, we should investigate to a greater level the factors of failure, such as *EGFR*-mutant tumours.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

Consultations for Astra-Zeneca, Bristol-Myers Squibb, Boehringer–Ingelheim, Clovis Oncology, Eli Lilly Oncology, F. Hoffmann–La Roche Ltd., Novartis, Merck, MSD, Pierre Fabre and Pfizer.

References

1. Stewart BW and Wild CP (eds). *World cancer report 2014*. Lyon, France: International agency for research on cancer.
2. Masters GA, Temin S, Azzoli CG, *et al*. Systemic therapy for stage IV non-small-cell lung cancer: American society of clinical oncology clinical practice guideline update. *J Clin Oncol* 2015; 33: 3488–3515.
3. Besse B, Adjei A, Meldgaard P, *et al*. 2nd ESMO consensus conference on lung cancer: non-small-cell lung cancer first line/second and further lines of treatment in advanced disease. *Ann Oncol* 2014; 25: 1475–1484.
4. Hanahan D and Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; 144: 646–674.
5. Brahmer J, Reckamp KL, Baas P, *et al*. Nivolumab vs docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015; 373: 123–135.
6. Borghaei H, Paz-Ares L, Horn L, *et al*. Nivolumab vs docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015; 373: 1627–1639.
7. 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: 1540–1550.
8. Novello S, Barlesi F, Califano R, *et al*. Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016; 27(Suppl. 5): V1–V27.
9. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology (NCCN guidelines). *Non-small cell lung cancer v6*.2017, shttps://www.nccn.org/professionals/physician_gls/PDF/nscl.pdf (2017, accessed 12 May 2017).
10. Xia B and Herbst RS. Immune checkpoint therapy for non-small-cell cancer: an update. *Immunotherapy* 2016; 8: 265–277.
11. Matsumoto K, Fukuyama S, Eguchi-Tsuda M, *et al*. B7-DC induced by IL-13 works as a feedback regulator in the effector phase of allergic asthma. *Biochem Biophys Res Commun* 2008; 365: 170–175.
12. Akbari O, Stock P, Singh AK, *et al*. PD-L1 and PD-L2 modulate airway inflammation and iNKT-cell-dependent airway hyperreactivity in opposing directions. *Mucosal Immunol* 2010; 3: 81–91.
13. Gaule P, Smithy JW, Toki M, *et al*. A quantitative comparison of antibodies to programmed cell death 1 ligand 1. *JAMA Oncol* 2016; 3: 256–259.
14. Mizugaki H, Yamamoto N, Murakami H, *et al*. Phase I-dose finding study of monotherapy with atezolizumab, an engineered immunoglobulin monoclonal antibody targeting PD-L1, in Japanese patients with advanced solid tumours. *Invest New Drug* 2016; 34: 596–603.
15. 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: 1837–1846.
16. 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: 255–265.
17. Herbst RS, Soria JC, Kowanetz M, *et al*. Predictive correlates of response to the anti-PD-L1 antibody MDPL3280A in cancer patients. *Nature* 2014; 515: 563–567.
18. Smith DA, Vansteenkiste JF, Fehrenbacher L, *et al*. *Updated survival and biomarker analyses of*

a randomized phase II study of atezolizumab vs docetaxel in 2L/3L NSCLC (POPLAR). Paper presented at 2016 American Society of Clinical Oncology, June 2016; Chicago, USA. Abstract 9028.

19. Besse B, Johnson M, Janne PA, *et al. Phase II, single-arm trial (BIRCH) of atezolizumab as first-line or subsequent therapy for locally advanced or metastatic PD-L1 selected non-small cell lung cancer (NSCLC)*. Paper presented at 2015 European Society of Medical Oncology, September 2015; Vienna, Austria. Abstract 16LBA.
20. Garassino M, Rizvi N, Besse B, *et al. Atezolizumab as 1L therapy for advanced NSCLC in PD-L1-selected patents: updated ORR, PFS and OS data from BIRCH study*. Paper presented at 2016 World Conference on Lung Cancer, December 2016; Vienna, Austria. S251–S252.
21. Barlesi F, Park K, Ciardiello F, *et al. Primary analysis from OAK, a randomized phase III study comparing atezolizumab with docetaxel in 2L/3L NSCLC*. Paper presented at 2016 European Society of Medical Oncology, October 2016; Copenhagen, Denmark. Abstract LBA44_PR.
22. Gandara DR, Pawel JV, Sullivan R, *et al. Impact of atezolizumab treatment beyond disease progression (TBP) in advanced NSCLC: results from the randomized Ph III OAK Study*. Paper presented at 2017 American Society of Clinical Oncology, June 2017; Chicago, USA. Abstract 9001.
23. Gadgeel SM, Ciardiello F, Rittmeyer A, *et al. OAK, a randomized phase III study of atezolizumab vs docetaxel in patients with advanced NSCLC: results from subgroup analyses*. Paper presented at 2016 World Conference on Lung Cancer, December 2016; Vienna, Austria. Plenary session 430.
24. Zhou GW, Xiong Y, Chen S, *et al.* Anti-PD-1/PD-L1 antibody therapy for pre-treated advanced non-small-cell lung cancer: a meta-analysis of randomized clinical trials. *Medicine* 2016; 95: e4611.
25. Lee CK, Man J, Lord S, *et al.* Checkpoint inhibitors in metastatic EGFR-mutated NSCLC – A meta-analysis. *J Thorac Oncol* 2017; 12: 403–407.
26. Rizvi NA, Hellmann MD, Snyder A, *et al.* Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science* 2015; 348: 124–128.
27. Lukas R, Gandhi M, O'Hear C, *et al. Atezolizumab in advanced NSCLC patients with baseline brain metastases: a pooled cohort safety analysis*. Paper presented at 2016 World Conference on Lung Cancer, December 2016; Vienna, Austria. Abstract P2.03b-014, Poster 5214.
28. Wang C, Yu X and Wang W. A meta-analysis of efficacy and safety of antibodies targeting PD-1/PD-L1 in treatment of advanced NSCLC. *Medicine* 2016; 95: e5539.
29. Pillai RN, Behera M, Owonikoko TK, *et al. Evaluation of toxicity profile of PD-1 versus PD-L1 inhibitors in NSCLC*. Paper presented at 2016 American Society of Clinical Oncology, June 2016; Chicago, USA. Abstract 9035.
30. Camidge R, Liu SV, Powderly J, *et al. Atezolizumab (MDPL3280A) combined with platinum-based chemotherapy in non-small cell lung cancer (NSCLC): a phase IB safety and efficacy update*. Paper presented at 2015 World Conference on Lung Cancer, September 2015; Denver, CO, USA. Oral session, S173–S260.
31. Reck M, Papadimitrakopoulou VA, Capuzzo F, *et al. Phase III clinical trials in chemotherapy-naive patients with advanced NSCLC assessing the combination of atezolizumab with chemotherapy*. Paper presented at 2016 European Society of Medical Oncology, October 2016; Copenhagen, Denmark. vi416–vi454.
32. Papadimitrakopoulou VA, Cappuzzo F, Jotte RM, *et al. Phase III clinical trials of atezolizumab combined with chemotherapy in chemotherapy-naive patients with advanced NSCLC*. Paper presented at 2016 American Society of Clinical Oncology, June 2016; Chicago, IL, USA. Abstract TPS9103.
33. Texido C, Karachaliou N, Gonzalez-Cao M, *et al.* Assays for predicting and monitoring responses to lung cancer immunotherapy. *Cancer Biol Med* 2015; 12: 87–95.
34. Williams J, Kowanetz M, Koeppen H, *et al. The SP142 PD-L1 IHC assay for atezolizumab reflects pre-existing immune status in NSCLC and correlates with PD-L1 mRNA*. Paper presented at 2016 European Society of Medical Oncology, October 2016; Copenhagen, Denmark. Abstract 1171P.
35. Chaft JE, Chao B, Akerley WL, *et al. Evaluation of PD-L1 expression in metachronous tumour samples and FDG-PET as a predictive biomarker in Ph2 study (FIR) of atezolizumab (MDPL3280A)*. Paper presented at 2015 World Conference on Lung Cancer, September 2015; Denver, CO, USA. 1556–0864.
36. Kowanetz M, Zou W, Shames DS, *et al. Tumour mutation load assessed by Foundation One (FM1) is associated with improved efficacy of atezolizumab in patients with advanced NSCLC*. Paper presented at 2016 European Society of Medical Oncology, October 2016; Copenhagen, Denmark. Abstract 77P.

37. Schmid P, Hegde PS, Zou W, *et al. Association of PD-L2 expression in human tumours with atezolizumab activity*. Paper presented at 2016 American Society of Clinical Oncology, June 2016; Chicago, USA. Abstract 11506.

38. Arrieta O and Montes-Servin E. *Evaluation of PD1/PDL1 expression on peripheral blood cells subpopulations in patients with NSCLC*. Paper presented at 2016 World Conference on Lung Cancer, December 2016; Vienna, Austria. Abstract MA 14.02.

39. Owen D, Bunn PJ, Johnson B, *et al. A phase II study of atezolizumab as neoadjuvant and adjuvant therapy in patients with resectable non-small-cell lung cancer (NSCLC)*. Paper presented at 2016 World Conference on Lung Cancer, December 2016; Vienna, Austria. S1082.

40. Horn L, Reck M, Mok TSK, *et al. A phase III study of atezolizumab with carboplatin plus etoposide in patients with extensive-stage small-cell lung cancer (IMpower 133)*. Paper presented at 2016 European Society of Medical Oncology, October 2016; Copenhagen, Denmark. vi493–vi496.