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Efficacy of atezolizumab to treat non-small-cell lung cancer: a meta-analysis based on randomized clinical trials

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Purpose: Atezolizumab, an immunoglobulin G1 monoclonal antibody against PD-L1, is accepted to treat advanced non-small-cell lung cancer (NSCLC). Our systematic review aims to evaluate survival efficacy of atezolizumab, overall and in subgroups defined by PD-L1 expression. *Materials and Methods:* Search the trials on efficacy of atezolizumab in advanced NSCLC based on online electronic databases from their dates of inception up to June 2019, including PubMed, Embase and Cochrane library databases. After rigorous reviewing of quality, the data of the PFS and OS were measured as outcomes. *Results:* Six trials including seven researches were included. Overall, 4722 subjects involving 2488 patients received atezolizumab and 2234 patients received investigator's choice chemotherapy were retrieved. For the intention-to-treat (ITT) population, the pooled ORs for overall survival (OS) was 0.81 (95 % confidence interval [CI] 0.75–0.87; P<0.00001) and progression-free survival benefit (PFS) was 0.65 (95 % CI 0.59–0.73; P<0.00001), respectively. For the subgroups PD-L1 expression (negative and high), there were benefits both observed in the PFS and OS in two sub-groups with atezolizumab (P 0.05). However, in the low expression of PD-L1 group, the subjects who received atezolizumab achieved PFS (OR 0.70; 95% CI: 0.58–0.84, P=0.0002) advantage but OS advantage (OR 0.91; 95% CI: 0.62–1.33, P=0.62). *Conclusion:* In low expression of PD-L1 subgroups, a benefit was observed for PFS but OS. However, the status of PD-L1 expression cannot be recommend as prognostic biomarker to support the decision who will benefit from atezolizumab.

1. Introduction

The evaluation of the effect of treatment options for advanced non-small-cell lung cancer patients remains poor despite significant progress in therapy (Stinchcombe and Socinski 2008). Recently, developments in cancer immunotherapy led to novel approaches (Zappa and Mousa 2016). Immune checkpoint inhibitors (ICIs) target the pathway of the programmed death ligand 1 (PD-L1) /programmed death-1 (PD-1) that inhibit activation of T-cells (Butte et al. 2007; Yang et al. 2011).

Atezolizumab is a humanised monoclonal antibody against PD-L1 (Zou and Chen 2008; Chen et al. 2012; Chen and Mellman 2013). This antibody showed improvements in overall survival in the POPLAR trial (Fehrenbacher et al. 2016) and OAK trial (Rittmeyer et al. 2016), which led to its approval for the therapy for advanced NSCLC.

Some studies revealed that the status of PD-L1 expression on tumor-infiltrating immune cells identified as a viable biomarker can be affected by the relation of T-effector and interferon γ gene, which has superior effects on overall survival (Fehrenbacher et al. 2016). In POPLAR, patients received atezolizumab harboring high PD-L1 expression achieved OS benefit. However, low or negative PD-L1 expression patients also achieved OS benefit in the OAK trial (Blair and Hannah 2018).

Therefore, this meta-analysis is done to address the survival efficacy of atezolizumab in patients with advanced NSCLC.

2. Investigations and results

2.1. Retrieval strategy

Two independent researchers conducted a systematic search of the PubMed, Embase and Cochrane library electronic databases up to June 2019 with the free key words and Medical Subject Heading (MeSH) terms: "non-small cell lung cancer " AND "atezolizumab", AND "Programmed cell ligand 1", in English language. Further material was also searched from reference materials.

2.2. Eligibility criteria

The eligible publications were related to the following inclusion criteria: (1) random control trials (RCT); (2) patients with advanced NSCLC; (3) articles comparing atezolizumab-added therapy and chemotherapy; (4) PFS and OS as outcomes addressed.

2.3. Quality assessment

The risk of bias of the retrieved articles were rated by two investigators independently based on the Cochrane Handbook for Systematic Reviews.

2.4. Data selection and extraction

Data were extracted from the published studies independently by two investigators. In case of disagreement, the differences were resolved through discussion. The main categories contents including: trial name, histology, the status of PD-L1 expression, treatment regimen, patient's number, the outcomes of interest.

2.5. Statistical analysis

The I^2 statistic was conducted to assess the significance of heterogeneity between-study (Higgins et al. 2011). Articles with an I2 ≥ 50% were regarded to have moderate and high degrees of heterogeneity, while I2<50% was thought to indicate a low degree of heterogeneity (Higgins and Thompson 2002). If the degree of heterogeneity was low, we chose the fixed-effect model. The

random-effect model was conducted if the degree of heterogeneity was moderate and high.
A p value <0.05 was defined as statistically significant difference. The Review Manager version 5.3 software was conducted for statistical analysis.

2.6. Results

2.6.1. Study selection process

Through the literature search, 136 studies were initially identified. Ten articles were assessed by reading the full text based on the criteria, but some were further eliminated. Finally, six RCTs including seven articles (Fehrenbacher et al. 2016; Rittmeyer et al. 2016; Jotte et al. 2018; Papadimitrakopoulou et al. 2018; Socinski et al. 2018; West et al. 2019; von Pawel et al. 2019) addressed the addition of atezolizumab to chemotherapy (Fig. 1). The Table presents a brief description of the included articles in more detail.

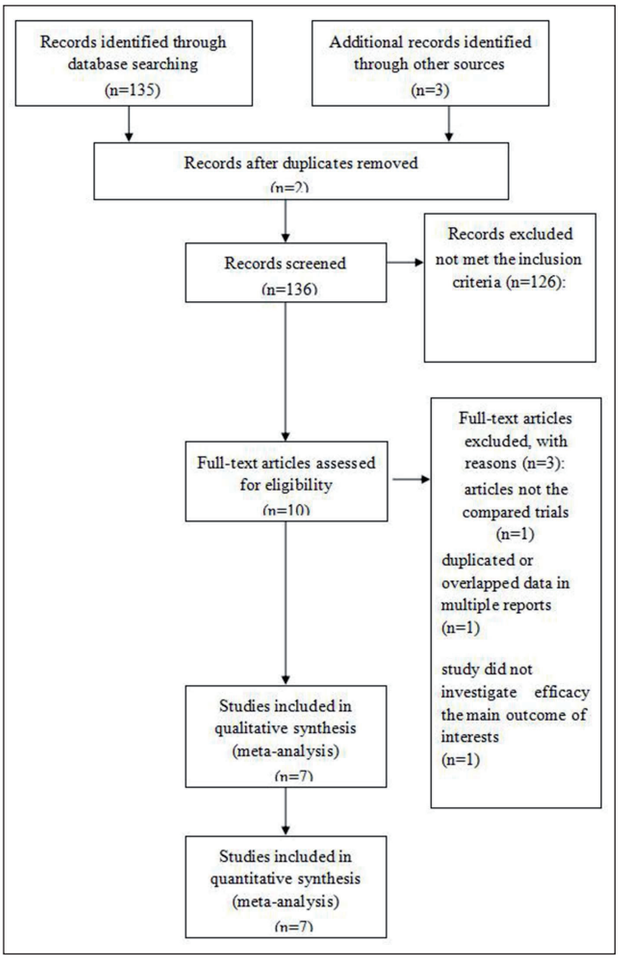

Fig. 1: PRISMA flow chart of selection process to identify studies eligible for pooling

2.6.2. Pooled analysis in the ITT population

As no statistical heterogeneity was seen in OR of articles (I^2 = 0%) in terms of the ITT population, the fixed effect model was used. Pooling data revealed that the addition of atezolizumab to chemotherapy can lead to a survival advantage both in PFS (OR=0.65,95%CI=0.59-0.73, *P*<0.00001) (Fig. 2) and OS (OR=0.81,95%CI=0.75-0.87, *P*<0.00001) (Fig. 3) versus the control group.

2.6.2. Sub-group analysis in the negative expression of PD-L1 patients

As pooled estimates of effect sizes suggested no statistical heterogeneity in OR of studies (P=0.33, I^2 = 9%), the fixed effect model was appropriate. In the analysis of PFS when comparing two groups, benefits were seen with atezolizumab treatment (OR=0.75,95%CI=0.63-0.88, *P*=0.0006) (Fig. 4). Also, we conducted the fixed effect model to pool the OS data due to the high degree of heterogeneity of articles (P=0.83, I^2 = 0%). Pooled data showed that OS was superior in the atezolizumab group versus the control group (OR=0.82,95%CI=0.72-0.93, *P*=0.002). (Fig. 5)

2.6.3. Sub-group analysis in the high expression of PD-L1 patients

No statistical heterogeneity was seen in OR of articles, so the fixed-effects model was conducted (P=0.87, I^2 = 0%). The pooled data showed that adding atezolizumab offers a PFS benefit (OR=0.47,95%CI=0.37-0.59, *P*<0.00001) (Fig. 6). The random-effects model was used to pool the OS data (P=0.08, I^2 = 52%), t shows that the atezolizumab group offers an OS advantage (OR=0.62,95%CI=0.45-0.85, P=0.003) (Fig. 7).

2.6.4. Sub-group analysis in the low expression of PD-L1 patients

A fixed-effects model was available (P=0.57, I^2 = 0%). PFS was superior with atezolizumab compared with chemotherapy (18, 25-26) (OR=0.70,95%CI=0.58-0.84, *P*=0.0002) (Fig. 8). When the random-effect model was applied to merge the OS data (P=0.02, I^2 = 73%) no OS advantage was observed in patients receiving atezolizumab compared to the control group (OR=0.91,95%CI=0.62-1.33, *P*=0.62) (Fig. 9).

3. Discussion

Immunotherapies offered novel approaches to treat advanced NSCLC. The Food and Drug Administration (FDA) approved atezolizumab (TECENTRIQTM), an immune checkpoint inhibitor targeting PD-L1, to treat advanced NSCLC as second-line treatment in 2015 (Akamine et al. 2018). Despite several studies have been published, the status of PD-L1 expression is still under discussion. Due to the studies' design, debates remain considering different expression subgroups of PD-L1.
As shown in our results, patients in all groups showed improvements in PFS regardless of PD-L1 status. However, there are OS benefits in the overall ITT population and subgroups PD-L1 expression (negative and high) but the low expression of PD-L1 population.
To our knowledge, the OAK trial reported that increased immune infiltration stimulates the first increase in tumor volume or continued treatment process the anti-tumor immune activation beyond progression may lead to the significant difference between PFS and OS (Wolchok et al. 2019). This difference has been commonly found in our analysis. For low expression of PD-L1 populations, these findings shown that PFS findings underestimate the OS benefit for atezolizumab.
The relationship between the expression of PD-L1 on tumor-infiltrating immune cells and the T-effector and interferon-γ gene signature further predicts that there are different mechanisms in NSCLC affecting PD-L1 expression: tumor cell-intrinsic mechanisms and an adaptive immune system mechanism (Herbst 2014). Many previous studies have demonstrated that the adaptive immune mechanism is consistent with adaptive PD-L1 regulation in highly inflamed tumors (Taube et al. 2012). In addition, a latest meta-analysis (Xian and Bin 2018) indicated that PD-L1 expression and many unrelated characteristics have effect on the result of PD-1 or PD- L1 blockade treatment. Furthermore, the expression of PD-L1 in tumors was not in accordance, and the location of sampling may influence the status of PD-L1 expression; and various molecular mechanisms might affect the expression of PD-L1 in various tumor histology. The heterogeneity within the low PD-L1 expression subgroup was significantly high, which has insufficient statistical power to support the conclusions.
We acknowledge that there are important limitations in our study. First, as the meta-analysis was based on study-level, clinical

Table: Atezolizumab NSCLC

Trial	Treatment regimen		Patients number		Histology
	Atezolizumab-based group	Chemotherapy group	Atezolizumab	Chemotherapy	
IMPower130	Atezolizumab plus chemotherapy	Chemotherapy	483	240	NonSq
IMPower131	Carbo-nabPac+atezolizumab	Carbo-nabPac	342	340	Sq
IMPower132	Pemetrexed+carboplatin or Cisplatin+atezolizumab	Pemetrexed+carboplatin or cisplatin	292	286	NonSq
IMPower150(1)	Carbo-Pac-Beva+atezolizumab	Carbo-Pac-Beva	400	400	NonSq
IMPower150(2)	Atezolizumab + Carbo-Pac	Carbo-Pac-Beva	402	400	NonSq
POPLAR	Atezolizumab	Docetaxel	144	143	NonSq+Sq
OAK	Atezolizumab	Docetaxel	425	425	NonSq+Sq

Beva, bevacizumab; Carbo, carboplatin;
NonSq, non-squamous;Sq, squamous

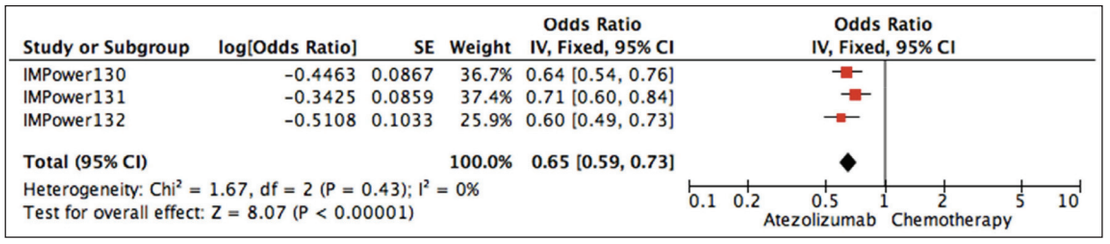

Fig. 2: PFS ITT

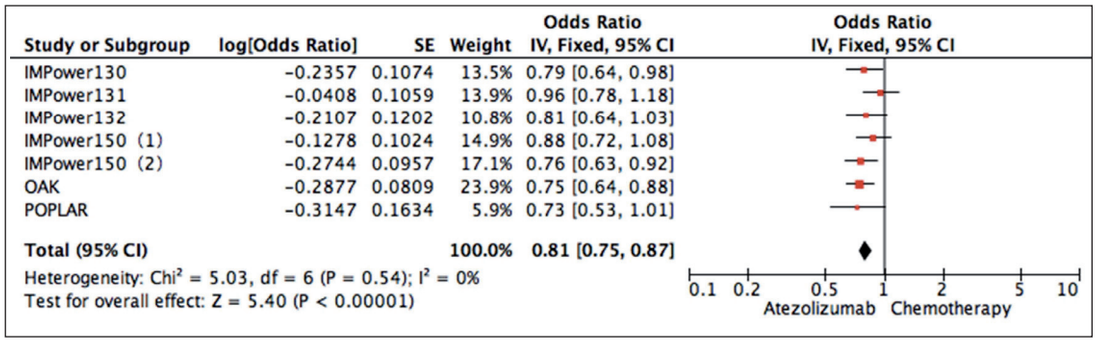

Fig. 3: 3 OS ITT

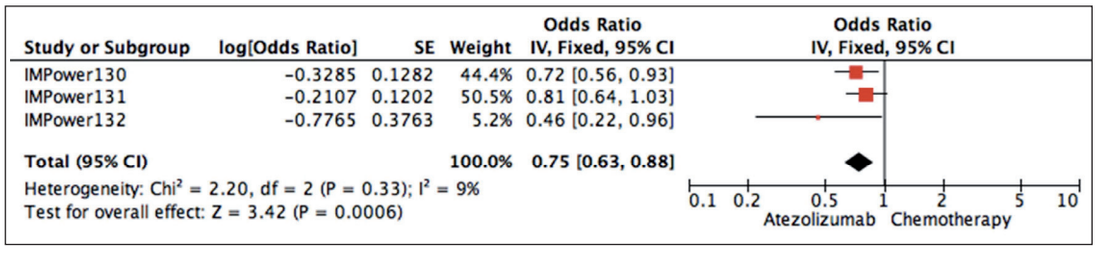

Fig. 4: PFS (-)

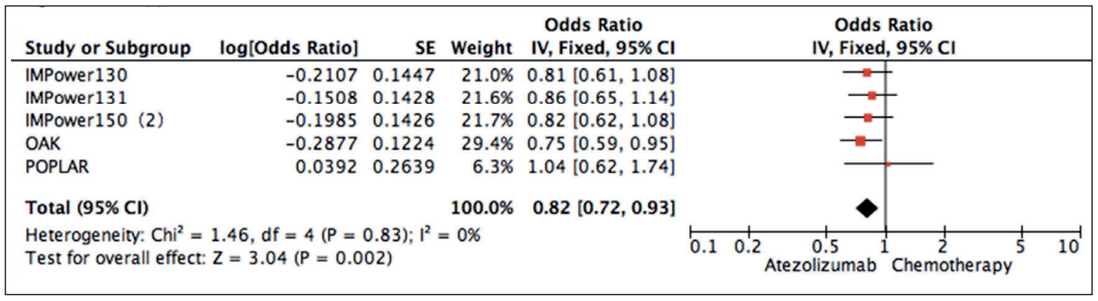

Fig. 5: OS (-)

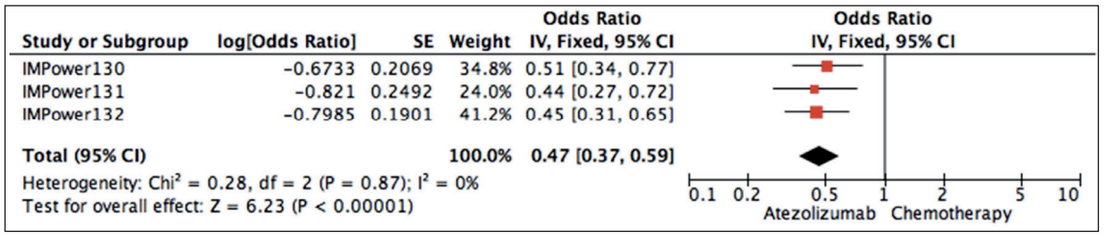

Fig. 6: PFS high

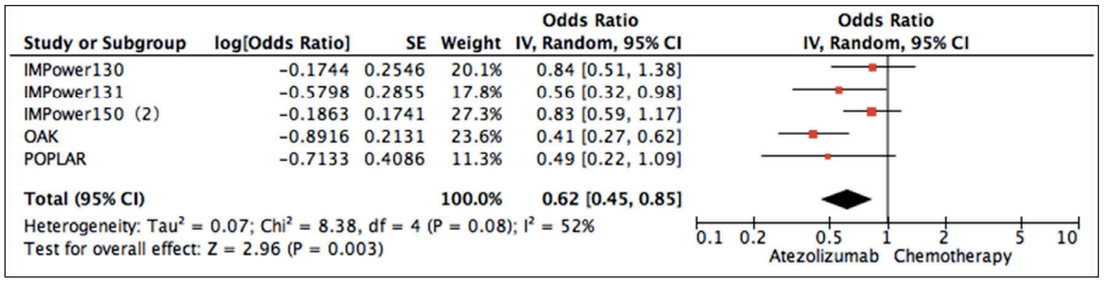

Fig. 7: OS high

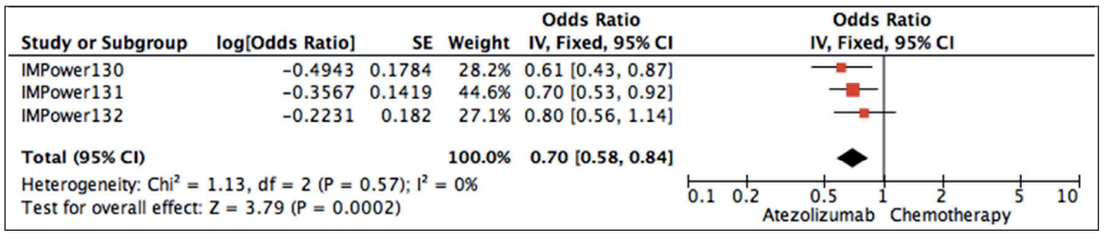

Fig. 8: PFS Low

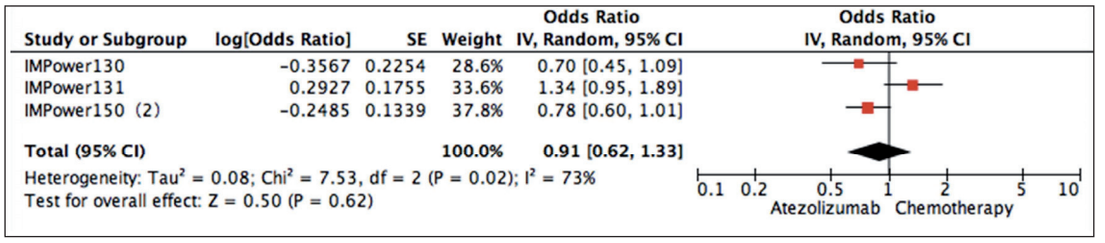

Fig. 9: OS Low

heterogeneity among studies should not be neglected, which may impact the interpretation of our results, even though all the included studies were randomized clinical trials. Second, the cutoff value for positive expression of PD-L1 was different, the benefit of anti-PD-1/PD-L1 treatment still needs further assessment.

Taken together, these findings reported that atezolizumab prolonged survival efficacy in PD-L1 expression (negative and positive). Whether the expression status of PD-L1 can be identified as prognostic biomarker to help in decision-making who will benefit from atezolizumab and a strict cut-off value to definite the PD-L1 expression will need further discussion.

Ethics approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study is approved by relevant Ethics Committee.

Authors' Contributions: Caihong Hu carried out the guarantor of integrity of the entire study, manuscript preparation and manuscript editing; Zhengbo Liang was dedicated to the study design, data analysis and statistical analysis; Ping Lai was involved in the definition of intellectual content, data acquisition; Xiaofang Wang was dedicated to experimental studies; Changming Zhao carried out the study concepts, literature research, clinical studies and manuscript review. All authors have read and approved this article.

Conflict of Interest: The authors declare that they have no competing interest.

References

Akamine T, Toyokawa G, Tagawa T, Seto T (2018) Atezolizumab in non-squamous non-small cell lung cancer. J Thorac Dis 10(Suppl 26): S3155-S3159.

Blair HA (2018) Atezolizumab: a review in previously treated advanced non-small cell Lung cancer. Targeted Oncol 13: 399–407.

Butte MJ, Keir ME, Phamduy TB, Sharpe AH, Freeman GJ (2007) Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 27: 111–122.

Chen DS, Daniel S, Mellman I (2013) Oncology meets immunology: the cancer-immunity cycle. Immunity 39: 1–10.

Chen DS, Irving BA, Hodi FS (2012) Molecular pathways: next-generation immunotherapy--inhibiting programmed death-ligand 1 and programmed death-1. Clin Cancer Res 18: 6580–6587.

Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, Park K, Smith D, Artal-Cortes A, Lewanski C, Braiteh F, Waterkamp D, He P, Zou W, Chen DS, Yi J, Sandler A, Rittmeyer A (2016) Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet. 387: 1837–1846.

Higgins JPT, Altman DG, Gøtzsche PC, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JAC (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343: 889–893.

Higgins JPT, Thompson SG., 2002. Quantifying heterogeneity in a meta-analysis. Statistics Med 21: 1539–1558.

Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, Sosman JA, McDermott DF, Powderly JD, Gettinger SN, Kohrt HE, Horn L, Lawrence DP, Rost S, Leabman M, Xiao Y, Mokatrin A, Koeppen H, Hegde PS, Mellman I, Chen DS, Hodi FS (2014) Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 515(7528): 563–567.

Jotte RM, Cappuzzo F, Vynnychenko I, Stroyakovskiy D, Abreu DR, Hussein MA (2018) IMpower131: primary PFS and safety analysis of a randomized phase III study of atezolizumab + carboplatin + paclitaxel or nab-paclitaxel vs carboplatin + nab-paclitaxel as 1L therapy in advanced squamous NSCLC. J Clin Oncol. 36: LBA9000-LBA9000.

Papadimitrakopoulou V, Cobo M, Bordoni R, Dubray-Longeras P, Szalai Z, Ursol G, et al. IMpower132: PFS and safety results with 1L Atezolizumab + Carboplatin/ Cisplatin + Pemetrexed in stage IV non-squamous NSCLC. In: International Association for the Study of Lung Cancer's (IASLC) 2018 World Conference on Lung Cancer (WCLC); 2018 Sept 23-26. Toronto, ON (2018).

Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, Gadgeel SM, Hida T, Kowalski DM, Dols M, Cortinovis DL, J, Polikoff J, Barrios C, Kabbinavar F, Arén Frontera O, De Marinis F, Turna H, Lee J, Ballinger M, Kowanetz MK, He P, Chen DS, Sandler A, Gandara DR (2016) Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 387: 1837–1846.

Socinski MA, Jotte RM, Cappuzzo F, Orlandi FJ, Stroyakovskiy D, Nogami N, Rodriguez-Abreu D, Moro-Sibilot D, Thomas CA, Barlesi F, Finley GG, Kelsch C, Lee A, Coleman S, Shen Y, Kowanetz M, Lopez-Chavez A, Sandler A, Reck M (2018) Overall survival (OS) analysis of IMpower150, a randomized Ph 3 study of atezolizumab (atezo) + chemotherapy (chemo) ± bevacizumab (bev) vs chemo + bev in 1L nonsquamous (NSQ) NSCLC. J Clin Oncol 36 (15) Suppl: 9002.

Stinchcombe TE, Socinski MA (2008) Considerations for second-line therapy of non-small cell lung cancer. Oncologist 13: 28–36.

Taube JM, Anders RA, Young GD, Xu H, Sharma R, McMiller TL, Chen S, Klein AP, Pardoll DM, Topalian SL, Chen L (2012) Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. Sci Transl Med 28:127ra37.

von Pawel J, Bordoni R, Satouchi M, Fehrenbacher L, Cobo M, Han JY, Hida T, Moro-Sibilot D, Conkling P, Gandara DR, Rittmeyer A, Gandhi M, Yu W, Matheny C, Patel H, Sandler A, Ballinger M, Kowanetz M, Park K (2019) Long-term survival in patients with advanced none small-cell lung cancer treated with atezolizumab versus docetaxel: Results from the randomised phase III OAK study. Eur J Cancer 107: 124–132.

West H, McCleod M, Hussein M, Morabito A, Rittmeyer A, Conter HJ, Kopp HG, Daniel D, McCune S, Mekhail T, Zer A, Reinmuth N, Sadiq A, Sandler A, Lin W, Ochi Lohmann T, Archer V, Wang L, Kowanetz M, Cappuzzo F (2002) Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 20: 924–937.

Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, Maio M, Binder M, Bohnsack O, Nichol G, Humphrey R, Hodi FS (2009) Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 15: 7412–7420.

Xian S, Bin Z (2018) Efficacy of PD-1 or PD-L1 inhibitors and PD-L1 expression status in cancer: meta-analysis. BMJ: k3529.

Yang J, Riella LV, Chock S, Liu T, Zhao X, Yuan X, Paterson AM, Watanabe T, Vanguri V, Yagita H, Azuma M, Blazar BR, Freeman GJ, Rodig SJ, Sharpe AH, Chandraker A, Sayegh MH (2011) The novel costimulatory programmed death ligand 1/B7.1 pathway is functional in inhibiting alloimmune responses in vivo. J Immunol 187: 1113–1119.

Zappa C, Mousa SA (2016) Non-small cell lung cancer: current treatment and future advances. Transl Lung Cancer Res 5: 288–300.

Zou W, Chen L (2008) Inhibitory B7-family molecules in the tumor microenvironment. Nat Rev Immunol 8: 467–477.