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## A case of the third-line treatment of lung adenocarcinoma using nivolumab combined with anlotinib

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Lung adenocarcinoma, a subtype of non-small cell lung cancer (NSCLC), is the most common lung cancer that considerably threatens humans' life. In recent years, the treatment of lung cancers has largely evolved, in which programmed cell death protein 1 (PD-1) together with its ligand PD Ligand-1 (PD-L1) has become a prevalent target of interest. Being effective to improve the survivability of cancer patients, monoclonal antibody-based immunotherapy that inhibits PD-1 and PD-L1 is playing a vital role in treating a wide spectrum of cancers. Increasing cases of using diversified monoclonal antibodies combined with anlotinib for the treatment of NSCLC have been reported. Herein, we report a case of treating advanced lung adenocarcinoma with the combination of nivolumab and anlotinib. After two cycles of the combination therapy, the patient's condition was effectively improved, demonstrated that this therapy might be effective in treating lung adenocarcinoma.

### 1. Introduction

Lung adenocarcinoma, a subtype of non-small cell lung cancer (NSCLC), is the most common type that accounts for about 40% of lung cancers. Lung adenocarcinoma usually grows along the periphery of the lung, where it occurs in glandular cells and develops in small airways. Compared with other types of lung cancers, lung adenocarcinoma tends to grow slower (Zappa and Mousa 2016).

The programmed cell death protein (PD)-1 signaling pathway negatively regulates T cell-mediated immune responses and serves as a mechanism for tumors to evade an antigen-specific T cell immunologic response. The axis of PD-1 together with its ligand PD Ligand-1 (PD-L1) has attracted researchers' attention and becomes a novel therapeutic target of interest for cancer treatment in recent years (Meyers et al. 2018; Akinleye and Rasool 2019). Monoclonal antibodies that target and inhibit the PD-1/PD-L1 axis have proved successful in clinical trials in different tumors.

In contrast to the severe side effects of chemotherapy that damage patients' healthy cells, immunotherapy using monoclonal antibodies is tolerated much better (Weiner et al. 2009). Moreover, immunotherapy mainly relies on patients' own immune system, which facilitates the activation of patients' immune response in the body to guide the immune system to identify and kill cancer cells (Farkona et al. 2016). VEGF (vascular endothelial growth factor), a cytokine that promotes angiogenesis, induces tumor-associated immunodeficiency and plays an important regulatory role in the immunosuppressive microenvironment in which tumor cells evade immune surveillance (Qiang et al. 2020). Herein, we report a case of nivolumab combined with anlotinib for the third-line treatment of advanced lung adenocarcinoma. In this case, after the patient received two cycles of the therapy his conditions had been largely improved.

### 2. Case Presentation

A 58-year old male patient with a history of long heavy smoking was admitted to our hospital due to cough and tightness of breath on Oct 23rd, 2018. Before admission, the whole-body PET/CT showed: 1. Cancer in the upper lobe of the left lung was found with obstructive inflammation (range: ~52×38 mm) 2. Ipsilateral hilar and mediastinal lymph node metastases (the largest one was

about 14 mm in width). Percutaneous lung biopsy was conducted for pathological immunohistochemistry, which suggested a small amount of poorly differentiated adenocarcinoma. The expression of PD-L1 was tested negative using SP142 antibody. NGS gene detection analysis was performed by checking 56 gene mutations related to lung cancers and a frameshift mutation of TP53 in exon 9 was detected. On admission, an imaging examination was performed by using the enhanced CT scan of the chest. The results were shown as follows: 1. Irregular soft tissue masses were found in the posterior apex of the left upper lobe, embedding the left pulmonary artery trunk and the pulmonary artery in the upper lobe, which was accompanied by distal obstructive atelectasis and inflammation; 2. Several of the left axillary and left hilar lymph nodes were enlarged, most of which were originated from metastases. The patient was therefore diagnosed with lung adenocarcinoma (T3N2M1b, Stage IVA).

The patient received a cycle of chemotherapy of pemetrexed and carboplatin on October 27th, 2018, but a new mass (about 15 mm ×

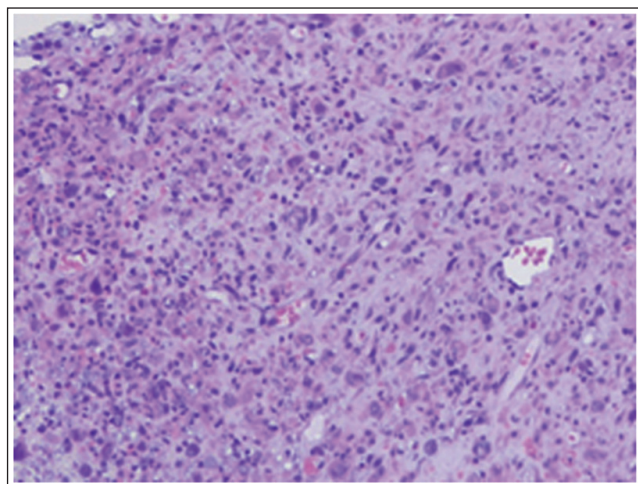


Fig. 1: The pathology of abdominal wall mass biopsy. The result was consistent with lung adenocarcinoma metastasis

10 mm in diameter) on the left lower abdominal wall appeared three days after the chemotherapy. The pathology of the mass biopsy was consistent with lung adenocarcinoma metastasis (Fig. 1). On November 16<sup>th</sup>, 2018, the patient was re-examined in our hospital by a CT scan of the chest and the full abdomen for assessing treatment efficacy, which was evaluated to be PD based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The patient began to switch to one cycle of treatment of combining recombinant human endostatin (Endostar) with vinorelbine and carboplatin on November 23<sup>rd</sup>, 2018. After chemotherapy, the chest and full abdominal was rechecked by CT, and the efficacy was evaluated to be PD (RECIST, version 1.1). The patient started to orally use anlotinib (12 mg qd) for targeted therapy on December 29<sup>th</sup>, 2018 followed by the first infusion of nivolumab on January 7<sup>th</sup>, 2019. After two cycles of the combination therapy, the chest and full abdomen were rechecked by using CT, and the efficacy was evaluated to be partial response (PR), based on iRECIST(-modified RECIST 1.1 for immune-based therapeutics) (Fig. 2). The patient was still receiving treatment with nivolumab (3 mg/kg, q2w) and anlotinib, and the effect of regular review remained PR. The adverse reactions in patient during the treatment included diarrhea, fatigue, and hand-foot skin reactions. In June 2019, because of adverse reactions intolerance, the dose of anlotinib was reduced to 10 mg p.o qd. The reduction of the anlotinib dose improved the status of the hand-foot skin reactions but not diarrhea and fatigue. In October 2019, the patient was intolerant of diarrhea and fatigue, and the dose of anlotinib was reduced to 8 mg p.o qd. After the second dose reduction, the patient's diarrhea and fatigue were improved with good compliance. The efficacy evaluation remained PR. Till the day of preparing this report, the patient is still using nivolumab and anlotinib.

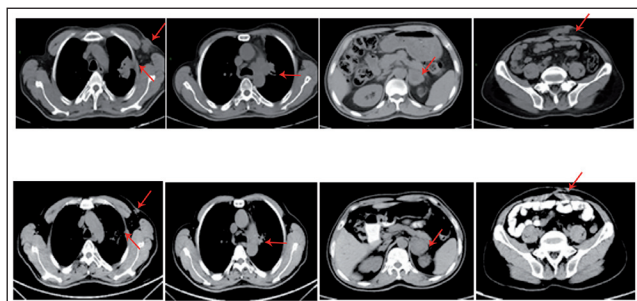


Fig. 2: Evaluation of the efficacy of the combination therapy of nivolumab and anlotinib before and after treatment. Upper panel: CT scan of the patient's lung before the treatment (December 14<sup>th</sup>, 2018). Lower panel: CT scan of the patient's lung after 2 cycles of treatment with nivolumab plus anlotinib (February 11<sup>th</sup>, 2019).

### 3. Discussion

At present, the curative effect of antiangiogenic therapy combined with immunotherapy has been well established and verified. Based on the results of IMpower 150, atezolizumab plus BCP (bevacizumab plus carboplatin plus paclitaxel) have become a novel direction in the first-line treatment of NSCLC (Socinski et al. 2018). However, chemotherapy, a conventional cancer treatment, has been criticized due to the toxicity and side effects. In the exploration of the chemo-free cancer treatment, antiangiogenesis combined with immunotherapy has become a research focus. Professor Baohui Han reported on the efficacy and safety of sintilimab combined with anlotinib in the first-line treatment of advanced NSCLC without mutations of driver genes at the 2019 World Conference on Lung Cancer (Han et al. 2019). The results showed that among the 22 enrolled patients, the overall response rate (ORR) of all patients was 72.7%, in which 8 patients had PD-L1 expression <1% with an ORR of 75%. The disease control rate (DCR) of all patients was 100%. Professor Caicun Zhou reported at the 2019 American Society of Clinical Oncology annual meeting that camrelizumab combined with

apatinib in the treatment of EGFR and ALK wild-type non-squamous NSCLC also exhibited good anti-tumor effects (Zhou et al. 2019). It was revealed that among 91 evaluable patients, ORR was 30.8%, DCR was 81.3%, and the median PFS was 5.9 months. Herein, our study reports a case of third-line treatment of NSCLC. Our clinical experience indicates that the more the treatment goes to the late-line stage, the lower the efficacy of treatment is. However, nivolumab plus anlotinib caused rapid remission of the tumour in our case. The current PFS has been more than 23 months. It has been observed that the adverse reactions of anti-angiogenic drugs combined with immunotherapy are mainly related to anti-angiogenic drugs. Professor Zhou's team has investigated the efficacy and safety of camrelizumab combined with apatinib in the treatment of EGFR and ALK wild-type non-squamous NSCLC. In the first phase of the trial, the efficacy and safety of camrelizumab (200 mg q2w) combined with different apatinib doses (375 mg qd vs 250 mg qd) were investigated. Compared with apatinib (375 mg qd), apatinib (250 mg qd) combined with camrelizumab exhibited better tolerability and compliance, and the incidence of Grade 3/4 adverse events (AE) was lower (Zhou et al. 2019). The results of the Professor Han's study on the efficacy and safety of sintilimab combined with anlotinib showed that among the 22 patients enrolled, there were 6 cases of Grade 3 or higher treatment-related AEs (incidence rate: 27.3%) and a total of 7 AEs that caused dose adjustment or interruption (incidence rate: 31.8%) (Han et al. 2019). Similarly, the patient in this report had to reduce the dose of anlotinib twice due to adverse reactions, but the treatment was still effective even after decreasing the dose. Considering the adverse effects of anti-angiogenic drugs, whether the dose of anti-angiogenic drugs should be adjusted when combined with PD1 inhibitors requires further clinical trials to verify.

The National Comprehensive Cancer Network (NCCN) guidelines proposed that PD-L1 detection could be performed in newly diagnosed advanced NSCLC patients without clear driver gene mutations. According to the results of previous studies (Reck et al. 2016; Mok et al. 2019), for the advanced NSCLC patients with PD-L1 $\geq$ 50%, it is recommended to choose pembrolizumab monotherapy. Previous studies have confirmed that the immunotherapy combined with chemotherapy is better than chemotherapy alone for the first-line treatment of advanced NSCLC with any expression level of PD-L1 (Gandhi et al. 2018; Paz-Ares et al. 2018; West et al. 2019; Jotte et al. 2020). Currently, it is not fully clear whether immunotherapy combined with antiangiogenesis therapy has an efficacy predictor based on the available findings. In Professor Han's study on sintilimab combined with anlotinib in the first-line treatment (Han et al. 2019), regardless of the expression of either PD-L1 or TMB, all subgroups of patients achieved higher remission rates. In Professor Zhou's study, 83 patients were tested for bTMB. The cut-off value, calculated based on the receiver operating characteristic curve, was 1.54 muts/Mb (Zhou et al. 2019). The ORR of patients with high bTMB was 52.6%, and the ORR of patients with low bTMB was only 17.1%. Further studies are required to substantiate the results and the effectiveness of bTMB as an efficacy predictor. In our report, PD-L1 was negative by using SP142 antibody test but the therapy still exhibited a good effect.

However, it remains mysterious why patients with negative PD-L1 expression still respond to PD-1/PD-L1 inhibitors. This may be due to the intratumoral heterogeneity of PD-L1 expression. Studies have shown that the expression of PD-L1 in the same tissue slices could be inconsistent (McLaughlin et al. 2016; Velcheti et al. 2014), and the expression of PD-L1 would change dynamically with treatment (Sharma and Allison 2015). In addition, different detection antibodies and platforms, different threshold standards, and subjective interpretation may also interfere with PD-L1 detection. The Blueprint Project Phase 1 (BP1) study showed that the three reagents 22C3, 28-8, and SP263 had higher consistency in the staining of PD-L1 in tumor cells, while positive tumor cells using the SP142 staining were fewer than the other three reagents (Hirsch et al. 2017).

#### 4. Conclusion

In general, the treatment with nivolumab combined with anlotinib for lung adenocarcinoma reported here was effective. The current PFS has been more than 23 months. Although the patient had twice lowered the dose of anlotinib due to adverse reactions during the treatment, the overall adverse reactions were tolerable. Judging by the results available, this treatment model is worth expecting. We hope that the efficacy and safety of the combination therapy can be verified in a larger sample study and provide more evidence for future clinical practice.

Conflicts of interest: None declared.

#### References

- Akinleye A, Rasool Z (2019) Immune checkpoint inhibitors of PD-L1 as cancer therapeutics. *J Hematol Oncol* 12:92.
- Farkona S, Diamandis EP, Blasutig IM (2016) Cancer immunotherapy: the beginning of the end of cancer? *BMC Med* 14:73.
- Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Domine M, Clingan P, Hochmair MJ, Powell SF, Cheng SY, Bischoff HG, Peled N, Grossi F, Jennens RR, Reck M, Hui R, Garon EB, Boyer M, Rubio-Viqueira B, Novello S, Kurata T, Gray JE, Vida J, Wei Z, Yang J, Raftopoulos H, Pietanza MC, Garassino MC (2018) Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 378: 2078–2092.
- Han BH CT, Zhong RB, et al. (2019) Efficacy and safety of Sintilimab with Anlotinib as first-line therapy for advanced non-small cell lung cancer (NSCLC). In *WCLC2019*.
- Hirsch FR, McElhinny A, Stanforth D, Ranger-Moore J, Jansson M, Kulangara K, Richardson W, Towne P, Hanks D, Vennapusa B, Mistry A, Kalamegham R, Averbuch S, Novotny J, Rubin E, Emancipator K, McCaffery I, Williams JA, Walker J, Longshore J, Tsao MS, Kerr KM (2017) PD-L1 Immunohistochemistry assays for lung cancer: Results from phase 1 of the blueprint PD-L1 IHC assay comparison Project. *J Thorac Oncol* 12: 208–222.
- Jotte R, Cappuzzo F, Vynnychenko I, Stroyakovskiy D, Rodriguez-Abreu D, Hussein M, Soo R, Conter HJ, Kozuki T, Huang KC, Graupner V, Sun SW, Hoang T, Jessop H, McClelland M, Ballinger M, Sandler A, Socinski MA (2020) Atezolizumab in combination with carboplatin and nab-paclitaxel in advanced squamous NSCLC (IMpower131): Results from a randomized phase III trial. *J Thorac Oncol* 15: 1351–1360.
- McLaughlin J, Han G, Schalper KA, Carvajal-Hausdorf D, Pelekanou V, Rehman J, Velcheti V, Herbst R, LoRusso P, Rimm DL (2016) Quantitative assessment of the heterogeneity of PD-L1 expression in non-small-cell lung cancer. *JAMA Oncol* 2: 46–54.
- Meyers DE, Bryan PM, Banerji S, Morris DG (2018) Targeting the PD-1/PD-L1 axis for the treatment of non-small-cell lung cancer. *Curr Oncol* 25: e324–e334.
- Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, Castro G, Jr., Srimuninnimit V, Laktionov KK, Bondarenko I, Kubota K, Lubiniecki GM, Zhang J, Kush D, Lopes G (2019) Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet* 393: 1819–1830.
- Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gumus M, Mazieres J, Hermes B, Cay Senler F, Csoszi T, Fülöp A, A, Rodríguez-Cid J, Wilson J, Sugawara S, Kato T, Lee KH, Cheng Y, Novello S, Halmos B, Li X, Lubiniecki GM, Piperdi B, Kowalski DM (2018) Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med* 379: 2040–2051.
- Qiang H, Chang Q, Xu J, Qian J, Zhang Y, Lei Y, Han B, Chu T (2020) New advances in antiangiogenic combination therapeutic strategies for advanced non-small cell lung cancer. *J Cancer Res Clin Oncol* 146: 631–645.
- Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leiby MA, Lubiniecki GM, Shentu Y, Rangwala R, Brahmer JR (2016) Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* 375: 1823–1833.
- Sharma P, Allison JP (2015) The future of immune checkpoint therapy. *Science* 348: 56–61.
- Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, Rodriguez-Abreu D, Moro-Sibilot D, Thomas CA, Barlesi F, Finley G, Kelsch C, Lee A, Coleman S, Deng Y, Shen Y, Kowanetz M, Lopez-Chavez A, Sandler A, Reck M (2018) Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med* 378: 2288–2301.
- Velcheti V, Schalper KA, Carvajal DE, Anagnostou VK, Strygros KN, Sznol M, Herbst RS, Gettinger SN, Chen L, Rimm DL (2014) Programmed death ligand-1 expression in non-small cell lung cancer. *Lab Invest* 94: 107–116.
- Weiner LM, Dhodapkar MV, Ferrone S (2009) Monoclonal antibodies for cancer immunotherapy. *Lancet* 373: 1033–1040.
- 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 (2019) 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.
- Zappa C, Mousa SA (2016) Non-small cell lung cancer: current treatment and future advances. *Transl Lung Cancer Res* 5: 288–300.
- Zhou CC GG, Ren SX, et al. (2019) Efficacy of PD-1 monoclonal antibody SHR-1210 plus apatinib in patients with advanced non-squamous NSCLC with wild-type EGFR and ALK. In 2019 ASCO Annual Meeting.