A lung adenocarcinoma patient with *ROS1* fusion and *NBN* germline mutation achieves long progression-free survival from sintilimab combined with niraparib after failure of *ROS1* inhibitors: a case report

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Background: Lung cancer is a malignant tumor with high morbidity and mortality worldwide. At present, the main treatment methods for patients with advanced non-small cell lung cancer (NSCLC) include molecular targeted therapy and immunotherapy. The efficacy rate of immune checkpoint inhibitor (ICI) monotherapy is relatively low. Studies have confirmed that some combination therapies have better anti-tumor efficacy and higher response rates, such as PD-1/PD-L1 inhibitors combined with chemotherapy or targeted therapy. Poly (ADP-ribose) polymerase (PARP) inhibitors have become a new line of cancer therapy in ovarian and breast cancer, but it's not approved in lung cancer. Some reports show that homologous recombination repair (HRR) gene variants may be potential biomarkers for immunotherapy. However, whether lung cancer with HRR gene variants can be benefit from ICIs combined with PARP inhibitors is unknown.

Case Description: We present a case of a 30-year-old man who was admitted to hospital with several months of cough and the chest computed tomography (CT) scan showed a mass about 2.6 cm × 2.1 cm in the left lung. Then he was diagnosed with lung adenocarcinoma (LUAD). Next generation sequencing (NGS) revealed that he harbors *ROS1* fusion and *NBN* germline mutation. So, he received platinum-based chemotherapy and *ROS1* inhibitors, but the disease continued to progress. Ultimately, the patient was switched to sintilimab combined with niraparib and the efficacy was evaluated as stable disease (SD), with a progression-free survival (PFS) of more than 12 months, and the overall survival (OS) is 23 months up to now. During the treatment, the major adverse events (AEs) observed were lymphopenia, nausea, vomiting, and edema. The AEs were tolerable.

Conclusions: This case shows that the combination of small-molecule inhibitors and immunotherapy may improve survival in NSCLC patients with driver genes, and sintilimab combined with niraparib provides a successful clinical case for the treatment of refractory tumors HRR gene mutation, which can be used as a reference for personalized treatment. Of course, more clinical trials are needed to confirm this combination treatment strategy.

Keywords: Lung adenocarcinoma; *ROS1* and *NBN*; sintilimab; niraparib; case report

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Introduction

Almost one-quarter of all cancer deaths are due to lung cancer according to the Cancer Statistics, 2021 (1). In recent years, the utility of next generation sequencing (NGS) for the selection of clinical treatment options has gradually been realized. Genetic testing for oncogenic driver gene alterations has become standard in the clinical treatment of lung cancer. At present, the main treatment methods for patients with advanced non-small cell lung cancer (NSCLC) include molecular targeted therapy and immunotherapy. A study has revealed that genetic mutations of some DNA repair genes are involved in lung cancer susceptibility (2), which highlights the molecular mechanisms underlying carcinogenesis. Patients with the homologous recombination repair (HRR) gene mutations are particularly sensitive to certain poly (ADP-ribose) polymerase (PARP) inhibitors, such as niraparib, olaparib, and rucaparib (3). Although the US Food and Drug Administration (FDA) has approved PARP inhibitors in ovarian, breast cancer and other cancers, but it has not been approved in lung cancer. For advanced NSCLC patients, immune checkpoint inhibitors (ICIs) have been approved for first-line or later-line treatment. The efficacy rate of ICI monotherapy is relatively not enough. It has been validated that some combination therapies, such as PD-1/PD-L1 inhibitors combined with chemotherapy or targeted therapy, have superior anti-tumor efficacy and higher response rates (4). However, there are currently few data on the treatment of PARP inhibitors combination with ICIs in NSCLC, especially lung adenocarcinoma. Herein, we report a case of a lung adenocarcinoma patient with *ROS1* fusion and *NBN* germline mutation. After failure of *ROS1* inhibitor therapy, the patient was subsequently treated with sintilimab combined with niraparib and achieved a response of SD for more than 12 months. We present the following article in accordance with the CARE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3582/rc).

Case presentation

A 30-year-old non-smoking Chinese male was admitted to the First Affiliated Hospital of Nanjing Medical University on April 2020 presenting with several months of cough. Chest CT scans showed nodules in the lower left lung, indicating a high possibility of malignancy. On May 13, 2020, the chest CT scan showed a high-density mass in the left lower lung lobe, with a size of 2.6 cm × 2.1 cm. No obvious lymph nodes were observed in mediastinum, hilum of lung and axilla. Then, thoracoscopic left lower lobectomy with lymph node dissection was performed at the First Affiliated Hospital of Nanjing Medical University. Postoperative pathology showed that it was invasive adenocarcinoma with a mass size of 3.5 cm × 2.5 cm × 2.0 cm, stage IIIA (pT2N2M0) (*Figure 1*). The results of immunohistochemistry (IHC) were CK7 (+), TTF-1 (+), Napsin A (+), P40 (–), and Syn (–). However, a month later, brain magnetic resonance imaging (MRI) showed brain metastases. The patient then received first-line chemotherapy based on pemetrexed (900 mg d1) and nedaplatin (60 mg d1,2) on June 2020. With informed consent, DNA based 1021-gene panel sequencing was performed for lung tissue and paired leukocytes. A total of 6 somatic mutations were detected (*Table 1*), including *SLC34A2-ROS1* fusion and *NBN* gene germline mutation. Thus, the patient received crizotinib in combination with pemetrexed and nedaplatin from July to August 2020. On September 2020, whole-body emission computed tomography (ECT) showed multiple bone metastases throughout the body, while the brain MRI showed the size of brain lesions was reduced. The overall efficacy was evaluated as progressive disease (PD). Then, the therapeutic regimen was switched from crizotinib to ceritinib, a second-generation ALK tyrosine kinase inhibitor. The patient received ceritinib combined with docetaxel as second-line therapy. After 2 cycles, the disease was assessed as slight progression. Due to sintilimab being approved for NSCLC, the patient requested to be treated with sintilimab. Considering the results of a large clinical study of sintilimab combined with chemotherapy in the first-line treatment for locally advanced or metastatic NSCLC (5), the regimen was adjusted to ceritinib, docetaxel, and sintilimab for 1 cycle on November 2020. On January 2021, cervicothoracic and abdominal CT and liver MRI showed multiple intrahepatic metastases. The condition was assessed as PD (*Figure 2A*). Considering that this patient carried *ROS1* fusion and *NBN* germline mutation, and the literature review suggested that niraparib could be effective against tumor cells with HRR gene mutation and improve the efficacy of PD-1 inhibitors, we fully communicated with the patient before signing the off-label consent, then the regimen was adjusted to niraparib (200 mg/day) combined with docetaxel and sintilimab (200 mg Q3W) for 6 cycles. The patient was evaluated for efficacy in the second, fourth, and sixth cycles. The best curative effect was that the brain lesion was

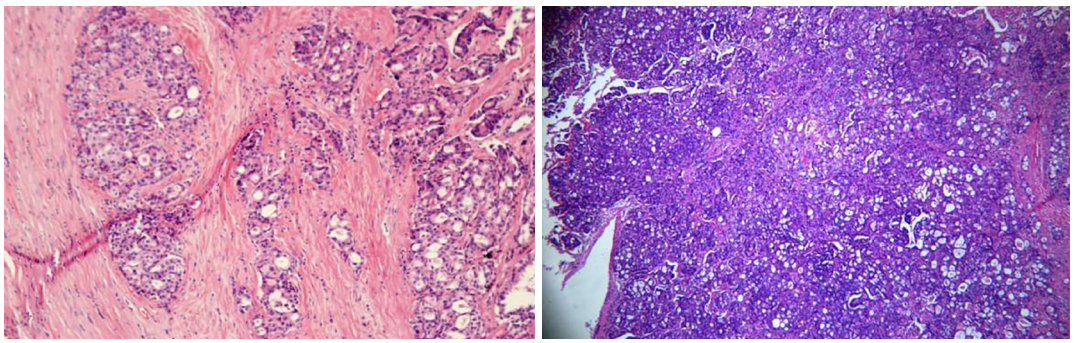

Figure 1 Postoperative pathological examination of the reported case (hematoxylin-eosin staining, 100× and 40×, respectively).

Table 1 Somatic and germline variant mutations detected by next-generation sequencing

Gene	Transcript	c.HGVS	p.HGVS	Functional region	Allele frequency	Homo/heterozygous
Single-nucleotide variants and small insertions/deletions						
MLL2	NM_003482.3	c.1336G>A	p.E446K	EX10	15.00%	–
PIK3CA	NM_006218.2	c.3012G>A	p.M1004I	EX21	10.70%	–
SMARCB1	NM_003073.3	c.568C>T	p.R190W	EX5	2.40%	–
RPTOR	NM_020761.2	c.1042C>T	p.R348*	EX9	1.90%	–
Fusions						
SLC34A2-ROS1	NM_006424.2;NM_002944.2	–	–	EX13E:EX32	26.80%	–
Germline variant mutations						
NBN	NM_002485.4	c.1480_1481delCA	p.Q494Tfs*10	EX11	–	Heterozygous

reduced by 18%, multiple lymph nodes around the bilateral axilla, neck and abdominal aorta were roughly similar than before. So, the overall efficacy evaluation was SD. (*Figure 2B*). He subsequently received sintilimab combined with niraparib maintenance treatment until November 2021, and the disease progressed at this time (*Figure 2C*). The 12-month landmark PFS rate was observed with the combination of sintilimab and niraparib. His treatment was then switched to sintilimab combined with niraparib, albumin-bound paclitaxel, and recombinant endostatin, and is currently still ongoing at the time of writing. In other words, at the end of the 23-month follow-up, the patient was still alive, during which CT and MRI scans were reviewed every 2 months. The major AEs observed were lymphopenia, nausea, vomiting, and edema. The treatment processes of this patient are shown in *Figure 3*.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

The emergence of small molecule targeted drugs has changed the therapeutic strategies for NSCLC with positive driver genes. Our patient was identified as having *ROS1* fusion-positive NSCLC. According to the guideline of the National Comprehensive Cancer Network (NCCN), he immediately started therapy with crizotinib and ceritinib, which target *ROS1* fusions. After failure of *ROS1* inhibitors, the combination of sintilimab, niraparib, and docetaxel followed by sintilimab and niraparib maintenance

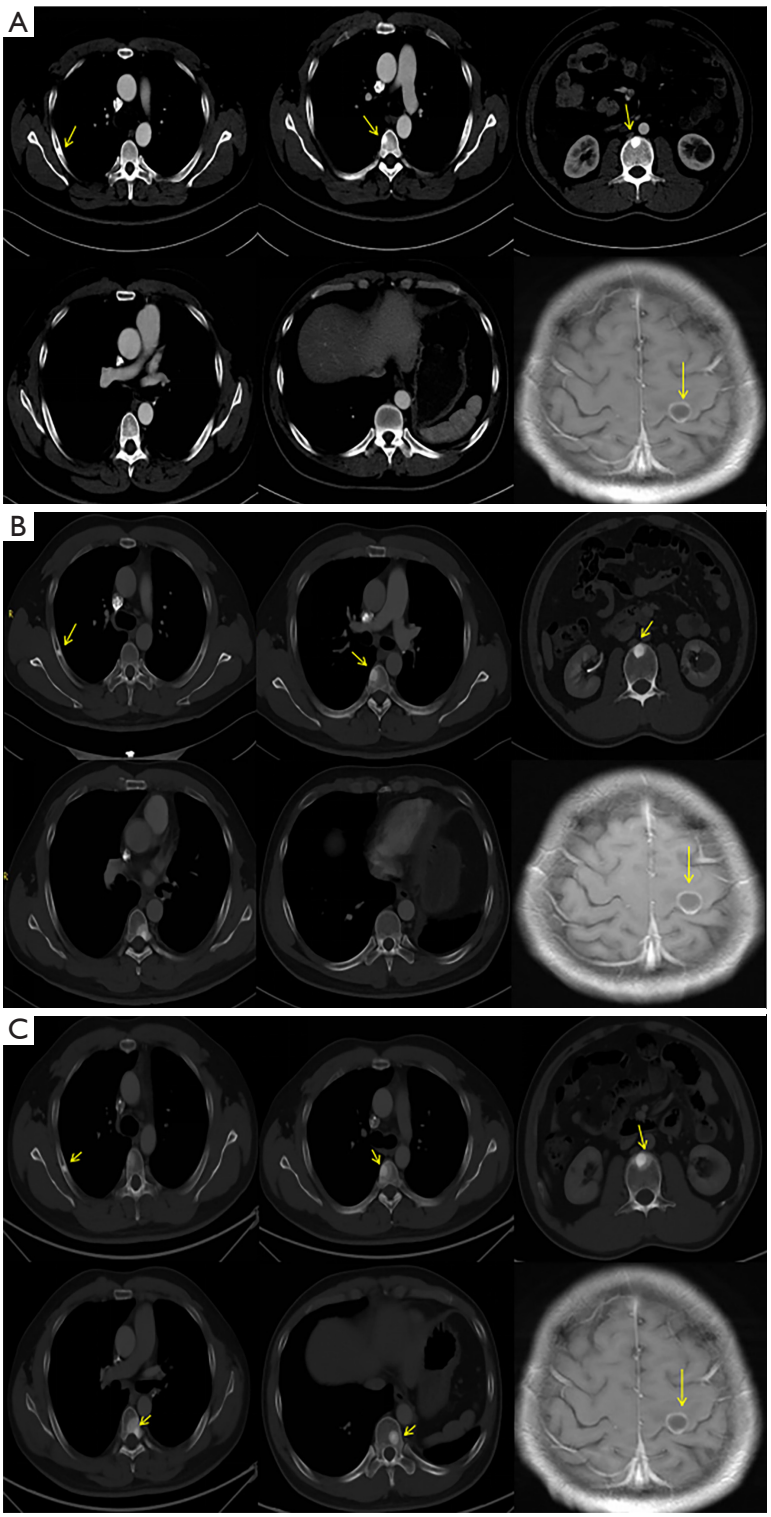

Figure 2 CT and brain MRI scans during therapy. (A) CT and MRI scans before the combination of niraparib and sintilimab treatment; (B) brain metastases PR and bone metastases SD after niraparib and sintilimab treatment was administered; (C) brain metastases PR and bone metastases PD after sintilimab and niraparib maintenance treatment. The arrows indicate changes in the lesions during treatment. CT, computed tomography; MRI, magnetic resonance imaging; PR, partial response; SD, stable disease; PD, progressive disease.

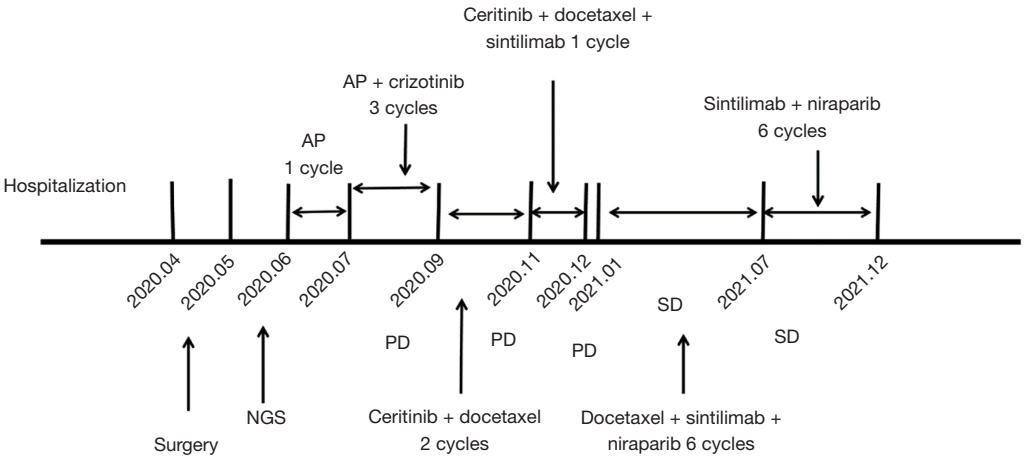

Figure 3 Timeline of the treatment processes. AP, pemetrexed and nedaplatin; PD, progressive disease; SD, stable disease; NGS, next generation sequencing.

treatment was adopted, achieving SD with a PFS of more than 12 months. The OS is 23 months up to now. Because treatments were used in combination, we cannot pinpoint the exact response for either chemotherapy or sintilimab/niraparib. However, our case suggests that maintenance treatment of sintilimab combined with niraparib can provide a durable response of 5 months. It also proved that sintilimab combined with niraparib is an effective and safe treatment option.

NGS revealed a germline mutation of *NBN*. Nijmegen breakage syndrome protein 1 (*NBS1*; also known as *NBN*) plays a key role in maintaining genome stability and tumor development. The variation of *NBN* rs1805794G>C (p.Glu185Gln) was found in multiple association studies, showing that rs1805794G>C of *NBN* may be a functional lung cancer gene marker (6). In humans, the repair of double-strand breaks (DSBs) involves two main repair pathways, namely, homologous recombination and non-homologous end-joining pathway (NHEJ) (7). Cells with homologous recombination repair deficiency (HRD) can only use alternative DNA repair pathways which have lower fidelity than HRR, resulting in a cascade of effects on the genome and increased mutation rates. *NBN* is an HR effector gene potentially presumed as being associated with HRD status (8). *NBN* has no DNA binding region but carries a combination of the fork-head associated (FHA) domain and the *BRCA1* C-terminal (BRCT) domain. A study has shown that PARP inhibitors (PARPi) can comprehensively kill tumor cells with homologous recombination defects (9). Although the BRCA mutated population is still the main beneficiary of PARPi, recent clinical trials indicated the therapeutic potential of PARPi in the non-BRCA mutated population, especially in the HRD-positive population. A previous study has reported that genotoxic stress and stalled DNA replication forks induce the expression of ligands for the NKG2D receptor found in natural killer cells, suggesting that PARP inhibition may act synergistically with checkpoint inhibitors (10).

Sintilimab is a Chinese anti-PD-1 monoclonal antibody and has been approved for NSCLC. Compared with nivolumab and pembrolizumab, sintilimab has a similar anti-tumor effect, a better safety profile, and economic advantages. Niraparib is an oral selective PARP-1/2 inhibitor approved for the treatment of advanced or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. A phase III study concluded that among the HRD-positive patients, the median PFS (mPFS) was significantly longer in the niraparib group compared with the placebo group (21.9 *vs.* 10.4 months; HR 0.43; 95% CI: 0.31–0.59; P<0.001) (3). The results of a prospective phase II study revealed the safety and anti-tumor activity of the combination of niraparib and dostarlimab in the treatment of advanced NSCLC with PD-L1 positive expression and mutations in the HRR genes (11). Another phase II trial of niraparib combined with pembrolizumab in the first-line treatment of patients with advanced NSCLC demonstrated that combined therapy has clinical activity in advanced or metastatic NSCLC patients (12). The changes in the tumor microenvironment induced by niraparib facilitate its combination with anti-PD-1 therapy. In BRCA mutant

and BRCA wild-type tumor models, both niraparib and anti-PD-1 have synergistic anti-tumor activities. Niraparib activates interferon signaling and potentiates anti-PD-1 antibody efficacy in tumor models, and may provide clinical activity for patients with recurrent ovarian cancer through tumor shrinkage and disease stabilization (13,14). Given the clinical evidence that PARP and ICIs may have different therapeutic effects with complementary and synergistic roles in tumor suppression, we hypothesized that niraparib combined with sintilimab would show promising clinical activity in the patient in this case. Eventually, our patient achieved a PFS lasting for 12 months. The hematological AEs included lymphopenia, while the non-hematological AEs were nausea, vomiting, and edema. Our findings provide clinical evidence for the potential efficacy of the combined therapy of niraparib and sintilimab in advanced NSCLC.

In this report, several limits exist. Despite the guide of NGS targeted treatment, our patient still developed TKI resistance. Therefore, a second biopsy after recurrence combined with NGS is necessary, which unfortunately our patient refused. Collectively, we hope this information furthers our understanding of the treatment options for NSCLC patients, suggesting the importance of secondary biopsy after each relapse combined with NGS, to permit the individualized selection of treatment regimens.

Conclusions

In summary, our study provides clinical evidence that the combination of niraparib and sintilimab is an effective and safe treatment option for advanced NSCLC. Our case also highlights the importance of NGS in guiding treatment.

Questions to be further discussed and considered

What is the prospect for the use of PARP inhibitors in lung cancer, and which patients may benefit from PARP inhibitors?

Roberto Chalela: They are not routinely used treatments for lung cancer, unlike breast or ovarian cancer. But it is clearly an interesting option in the medium term, especially in patients with *BRCA1* or *BRCA2* mutations or in combination with anti-PD-L1 treatments. The problem right now is that we need a biomarker in order to obtain better results. Preclinical studies suggest that PARP inhibitors can act as sensitizers of targeted therapies and immunotherapy.

Ken Masuda: The effect of PARP inhibitors has been expected for small cell lung cancer (SCLC) because SCLC shows high PARP expression in comparison with normal lung epithelial cells and other histologic subtypes of lung cancer. Further, PARP inhibition also enhances anticancer agents that exert their cytotoxic effect through DNA damage induction. However, the expected clinical trial results have not been obtained in SCLC. As the authors show, it is expected to be used in combination with other anticancer drugs such as immunotherapy and ATR inhibitors (15,16). I would like to expect an effect on lung cancer, but I consider that the effect cannot be expected so much without a BRCA gene mutation or HRR mutation, as in ovarian cancer and breast cancer. Therefore, novel biomarkers are greatly needed.

Paola Ulivi: PARP inhibitors are currently not used in the clinical practice. They could potentially have a use in patients who, following NGS analysis, are found to be carriers of mutations at the level of genes involved in repairing DNA damage (i.e., BRCA ...).

In clinical practice, how is the optimal combination of drugs to benefit patients chosen?

Roberto Chalela: I think the treatment chosen for the patient was correct. Probably with the results of the latest evidence, the initial treatment with Entrectinib could be a valid option.

Ken Masuda: In Japan, crizotinib and entrectinib as monotherapy have been approved as a standard treatment in *ROS1*-NSCLC. After progression, platinum-doublet ± ICIs or docetaxel ± ramucirumab are commonly used. The treatment system in the United States is almost the same as in Japan. In this paper, I consider the treatment you gave was generally acceptable. However, the reviewer may ask why you chose the combination therapies, "crizotinib and platinum-doublet" or "ceritinib and docetaxel".

Paola Ulivi: A molecular characterization of the tumor has been made before any treatment decision. If an oncogene addicted mutation is present, a targeted treatment will be started. In case of non-oncogene addicted mutation, an immunotherapy-based treatment is start. In particular, monoimmunotherapy for patients with PDL1 ≥50%, and a combination of chemo-immunotherapy for patients with PDL1 <50%.

In ROS1 fusion-positive NSCLC, after the failure of crizotinib, can other ROS1 inhibitors be used? How should the order of ROS1 inhibitors be chosen for ROS1-positive patients?

Roberto Chalela: I'm a pulmonologist and we help to oncologist in the prognosis evaluation of patients. We also give our opinion in order to try of-label treatments. In *ROS1* for us the first line option is Entrectinib or Crizotinib. If Crizotinib is used and fail, of-label treatment with ceritinib or entrectinib can be an option (as clinical trial).

Ken Masuda: In Japan, entrectinib can be used after the failure of crizotinib. *ROS1* inhibitors are basically used in first-line treatment and are recommended as a monotherapy. However, I consider it is also reasonable to use *ROS1* inhibitors after platinum-doublet.

Paola Ulivi: To date, there are no approved *ROS1* inhibitors after progression after crizotinib. We are awaiting the results of studies on the role of Lorlatinib in this setting.

In lung cancer, can patients with driver mutations try immunotherapy when they are resistant to targeted drugs and have no better treatment options?

Roberto Chalela: Yes. Actually, with the biomarkers available, we can try immunotherapy in some cases.

Ken Masuda: The use of ICIs for driver gene-positive lung cancer is generally not strongly recommended in Japan. However, they are one of the options when they are resistant to targeted drugs. Some NSCLC patients with driver mutation may benefit from these treatments. In this paper, I consider the treatment you gave was generally acceptable.

Paola Ulivi: Immunotherapy is not the standard of treatment for oncogene-addicted patients. The IMPOWER 150 study has showed activity of the combination of atezolizumab plus bevacizumab plus carboplatin and paclitaxel in patients at progression after a TKI.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3582/coif). WS and YH are from Beijing GenePlus Clinical Laboratory Co., Ltd. RC received honoraria as speaker from GlaxoSmithKline, Chiesi and TEVA, not related with the manuscript. KM received honoraria as speaker from ONO, AstraZeneca, Chugai, Bristol Myers Squibb and Healios, not related with the manuscript. The other authors have 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. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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