Disease and symptom control with late-line PD-1 inhibitor treatment in NSCLC

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Presentation

A 66-year-old male with a long smoking history (about 20 cigarettes/day for almost 50 years) presented with pneumonia-like disease and haemoptysis in early August 2014. PET-CT revealed a 5.8 cm tumour over the upper lobe of the left lung abutting the pleura, as well as aortopulmonary window lymph node, precarinal lymph node and bilateral paratracheal lymph node enlargements. Staging MRI showed no signs of brain metastases.

Later that month, CT-guided core biopsy of the tumour in the left upper lobe of the lung revealed a moderately differentiated TTF1-positive, *EGFR/ALK/ROS-1* wild-type adenocarcinoma. However, a later mediastinoscopic biopsy to confirm the presence of N3 disease revealed a large-cell adenocarcinoma with neuroendocrine component that was negative for TTF1, positive for MNF116, and focally positive for synaptophysin, CD56 and CK7.

Management and response

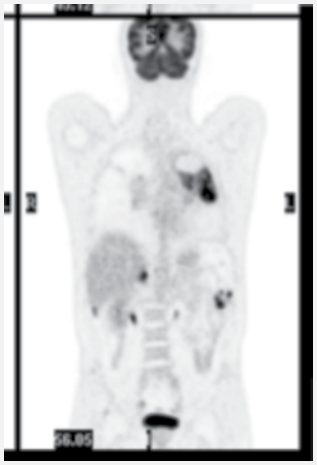
As the patient had no metastases and limited primary tumour invasion, radiotherapy (60 Gy in 30 fractions over 6 weeks) was administered concurrently with two cycles of etoposide/carboplatin chemotherapy. Chest X-ray in late January 2015 showed partial remission of the primary tumour. Reassessment PET-CT after another two cycles of doublet chemotherapy revealed a high probability of residual disease, and the patient was therefore switched to maintenance chemotherapy with pemetrexed. A second reassessment PET-CT in September 2015 showed morphological and metabolic deterioration of the tumour at the left upper lobe, as well as supraclavicular fossa and mediastinal lymph node metastases, new intra-abdominal peritoneal tumour deposits, and suspicious pleural metastases.

Given the radiological evidence of progressive disease, the patient was offered second-line treatment with docetaxel plus the VEGFR inhibitor nintedanib. Docetaxel was administered once weekly as monotherapy in the first 4 weeks (while awaiting the availability of nintedanib), and in combination with nintedanib for the next 2 weeks followed by 2 weeks of rest. During treatment, the patient experienced >10 episodes of watery diarrhoea per day along with dehydration, dark urine, fatigue and malaise, necessitating treatment termination.

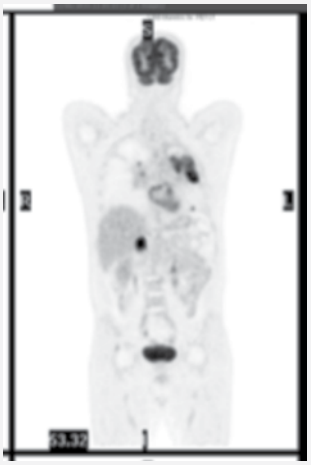
The patient agreed to start nivolumab monotherapy when it became available in late December 2015. Prior to initiation of nivolumab, his symptoms had worsened, with marked dyspnoea as well as poorly controlled pain on the left side of the chest requiring PRN oxygen therapy. His chest pain lessened after one cycle of nivolumab, and he reported no chest pain, dyspnoea or treatment-related adverse events (AEs) after the third cycle. After receiving the fourth cycle of nivolumab in early February 2016, the patient reported coughing up a piece of tissue on two occasions, which was presumed to originate from the primary tumour.

Nivolumab was continued in view of excellent symptom control and the lack of treatment-related AEs. However, reassessment PET-CT in mid March 2016 showed radiological progression with deterioration of the hypermetabolic tumour in the left upper lobe of the lung, mixed response of lymph node metastases at the lower neck and thorax, as well as new right adrenal metas-

Figure 1. PET scans at 4 months (A) and 7 months after initiation of nivolumab treatment (B), showing deterioration in right adrenal metastases and stable disease at multiple sites after 3 further months of treatment



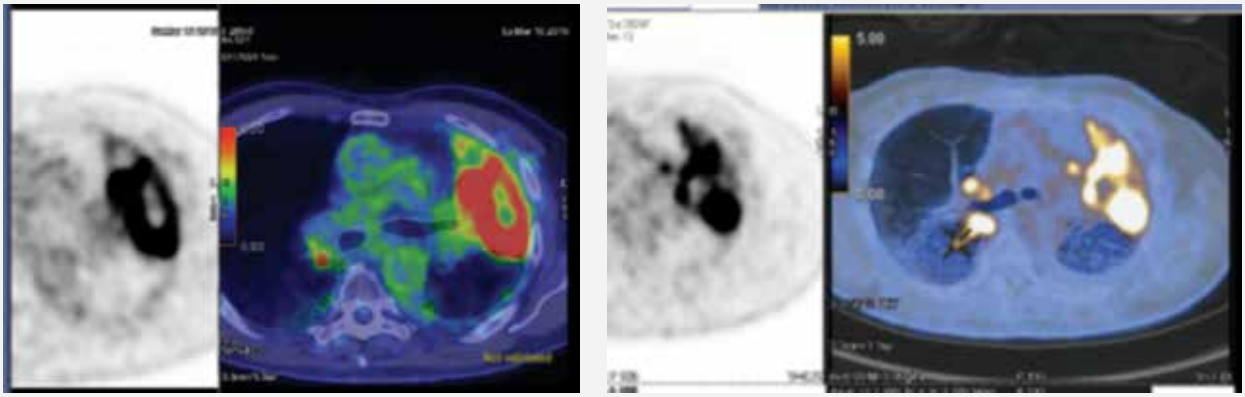
(A) March 2016



(B) June 2016

Figure 2. Thoracic PET-CT scans at 4 months (A) and 7 months after initiation of nivolumab treatment (B) showing stable disease after 3 further months of treatment

(A) March 2016 (B) June 2016



tases, while the peritoneal metastases remained static. (Figures 1A and 2A)

In view of the gross discrepancy between radiological assessment and clinical symptoms suggestive of psuedoprogression, nivolumab was continued further for 3 months. Reassessment PET-CT in late June 2016 showed radiological deterioration of the right adrenal metastases and the presence of new bilateral intrapulmonary metastases, but the lung primary tumour as well as the intrathoracic, supraclavicular fossa and peritoneal metastases remained stable. (Figures 1B and 2B) Metabolic deterioration was noted at the mediastinal and right hilar lymph node metastases, but their sizes remained static. Nivolumab was continued due to the slow progression of the disease and excellent control of clinical symptoms.

Discussion

Nivolumab is a PD-1 immune checkpoint inhibitor that blocks T cell inhibitory signalling pathways by preventing the engagement of PD-1 with its ligands (PD-L1/2), thereby restoring the patient's own antitumour immunity.[1]

The US FDA approved nivolumab for treatment of advanced or metastatic squamous NSCLC that progressed on or after platinum-based chemotherapy in March 2015 based on results of the phase III CheckMate 017 study, which showed superior efficacy of nivolumab vs docetaxel in patients with stage IIIb/IV squamous NSCLC.[1,2] The indication was expanded to include patients with metastatic nonsquamous NSCLC in October 2015 based on findings from the CheckMate 057 trial, which showed improved overall survival (OS) vs docetaxel in patients with nonsquamous NSCLC.[3,4]

Our present case showed clinically significant symptomatic improvement following nivolumab monotherapy. The reasons for continuing nivolumab therapy despite slow disease progression at the right adrenal metastases include good disease control at other metastatic sites, the lack of new or worsening symptoms at sites of progression, and the lack of other good treatment options.

References:
1. *The Oncologist* 2016;21:1-9. **2.** *N Engl J Med* 2015;373:123-135. **3.** NCCN clinical practice guidelines in oncology: non–small cell lung cancer version 4.2016. **4.** *N Engl J Med* 2015;373:1627-1639.

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