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**Case 37**

# PD-L1 negative NSCLC patient – which treatment is advisable?

## SUMMARY

### Diagnosis: stage IV adenocarcinoma of the lung

This case is an example of the advances that have been made concerning the treatment for patients with this diagnosis. As a result, there is an increase in quality of life for those affected, and importantly, also survival parameters have substantially ameliorated.

## STATUS AT FIRST PRESENTATION

### October 2020

A 60-year-old, early retired architect sees his doctor because he has suffered from dry cough and chest pain for the last five months. He has recently quit smoking due to these symptoms but has a smoking history of 40 pack years. Over the last three months, he had an involuntary weight loss of 4–5 kg. The architect complains of an overall weakness/fatigue during the previous year. He describes that he can generally care for himself, but his day-to-day routine has become somewhat tiresome, so he sometimes requires help from his wife.

### Clinical findings

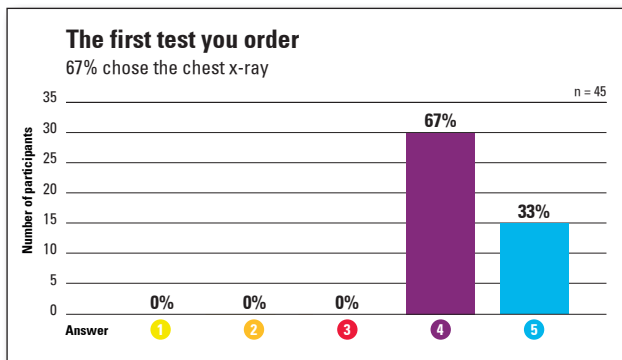
178 cm, 65 kg, blood pressure 130/80, pulse 70, no fever, ECG normal, CRP 16 mg/l, BSG > 40 mm, haemoglobin 11,8 g/dl

Eastern Co-operative Oncology Group performance status (ECOG PS) 1

### Previous medical history

2017 and 2019 posttraumatic deep vein thrombosis with consecutive anticoagulation.

2020 surgery for benign prostate hypertrophy with transurethral resection.



**Figure 1** – poll results first question of the case report: «Which diagnostic step should the general physician take first in this situation?»

- 1 Cardiac stress test
- 2 Pulmonary function test
- 3 Allergy testing for Asthma
- 4 Chest X-ray
- 5 CT-Scan

## EVALUATION AND EXPERT OPINIONS

### What is your primary diagnostic action?

More than two third of the participants decided to start diagnostics with an x-ray. 33% would have performed a CT-scan right away (**figure 1**).

### The right answer is 4

Early stages of lung cancer (LC) often don't present with symptoms, but the described patient demonstrates various signs that often occur and point to the possibility of a malignancy: cough, weakness and involuntary weight loss.<sup>1,2</sup> Furthermore, even though he has lately quit, there is a long-standing history of smoking, which is still the number one risk factor for LC.<sup>1,2</sup>

A chest x-ray is recommended as the first diagnostic tool in case of a suspected LC, and it can, of course, additionally shed light on possible differential diagnoses that could also cause our patient's symptoms. With regard to LC, the chest x-ray can reveal direct or indirect signs such as rounded masses, pleural effusions or atelectasis.<sup>1</sup> Positive findings are indications for further investigations, but negative results cannot definitely exclude a lung malignancy. So, in the presence of typical clinical signs, more extended diagnostic measures are recommended nevertheless.<sup>1</sup>

## FURTHER COURSE

### October 2020

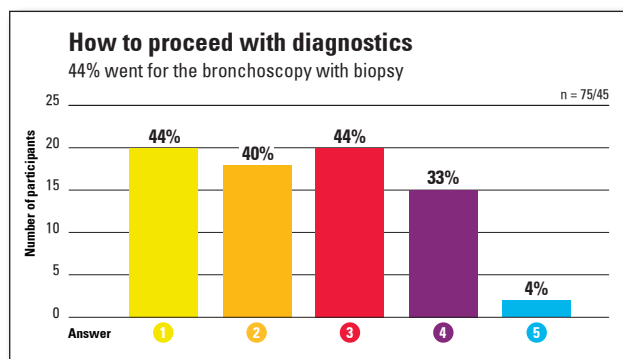
- Chest x-ray shows suspicion of tumour in right lower lobe with possible lymphangiosis (**figure 2**)
- Patient is transferred to a local cancer centre for further evaluation



**Figure 2:** suspicion of tumour in right lower lobe with possible lymphangiosis.

### What are the next investigations after these x-ray findings?

44% opted for a bronchoscopy with biopsy and an equivalent rate for a thoracoabdominal CT scan. 40% were in favour of performing a PET-CT and one third picked the endobronchial ultrasound (**figure 3**).



**Figure 3** – poll results second question of the case report: «Which further diagnostic steps should be taken in light of the x-ray results?»

(Multiple choices eligible)

- 1 Thoracoabdominal CT scan
- 2 PET-CT
- 3 Bronchoscopy with biopsy
- 4 Endobronchial ultrasound (EBUS)
- 5 Mediastinoscopy

### The right answers are 2 and 3

Especially in the case of central masses, a bronchoscopy with biopsy is a key method to ascertain a diagnosis of lung cancer with diagnostic significance in 65%-88%.<sup>1,3</sup> When the bronchoscopy is combined with endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA), its reliability is even greater and non-inferior to the more invasive mediastinoscopy.<sup>3</sup> The collected material not only serves for typing and grading of the tumour, but also for molecular testing that is of substantial importance in treatment planning.<sup>1,3</sup> Furthermore, if a lymph node involvement is suspected EBUS-guided biopsies are among the recommended procedures.<sup>4</sup> It should be noted that if the EBUS TBNA is negative, mediastinoscopy should be performed prior to an operative treatment if CT or PET scans are positive.<sup>4</sup>

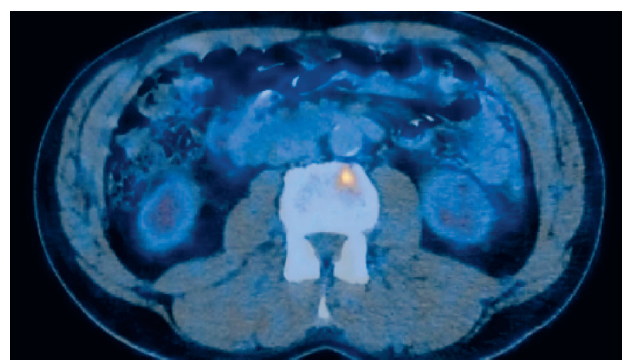
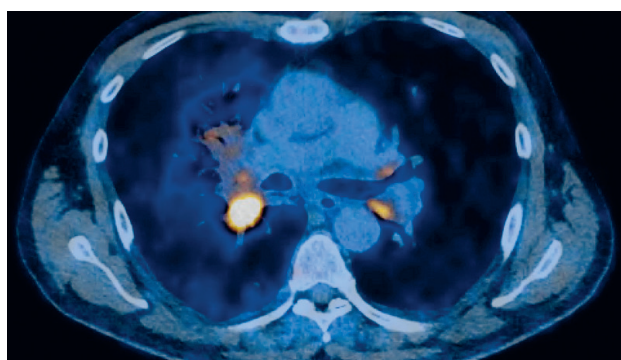
Besides making a definite diagnosis and differentiating the type of lung cancer, staging is very important.<sup>2</sup> In non-small cell lung cancer (NSCLC), metastases are found most commonly in lymph nodes, bones, liver as well as the central nervous system.<sup>2</sup>

A fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan yields important insights into lymph node staging as well as organ metastases.<sup>1</sup> Using a PET scan for staging can reduce the need for more invasive tests.<sup>1</sup> To detect skeletal filiae, a PET-CT is superior to bone scans.<sup>3</sup> Importantly, a PET-CT can guide an EBUS- bronchoscopy to the most relevant sites for biopsy, thus, it is recommended to perform the PET-CT before the bronchoscopy.

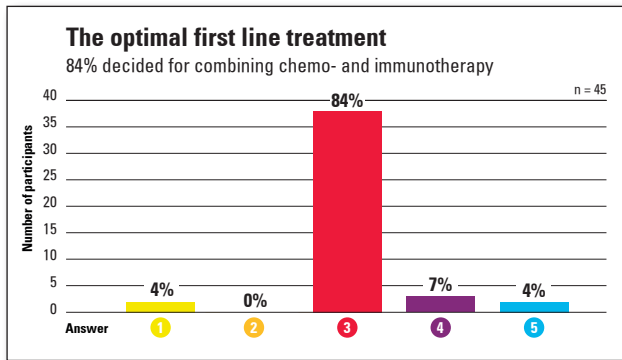
### FURTHER COURSE

#### October 2020

- PET-CT scan is performed
- Findings: central tumour at the right hilum (2,3 cm), atelectasis, bilateral mediastinal/hilar lymph node metastases, possible small pulmonary metastases in both lungs (also same lobe), bone metastases in ribs on right side 4, 7 and 11. Lymphangiosis of lower and middle lobe. Stage cT3 cN3 M1 (pul, oss) (**figures 4a and 4b**)



**Figures 4a and 4b:** PET scan in October 2020 with a) visible mass at the right hilum along with enlarged lymph nodes (metastases) and b) suspicion of bone and liver (not shown here) filiae



**Figure 5** – poll results third question of the case report: «What treatment option would you choose for this patient?» (multiple choices eligible)

- 1 The information is insufficient; input from the molecular board is necessary.
- 2 Standard chemotherapy is the best choice of first-line treatment.
- 3 A combination of standard chemo- and immunotherapy is the best choice of first line treatment.
- 4 A single HER2-directed agent is the best choice of first-line treatment.
- 5 The best choice is to look for a suitable trial, as no available treatment fits the patient's needs.

- EBUS-bronchoscopy with transbronchial needle aspiration biopsy is executed. Tumour cells are found in lymph nodes 11R, 4 and 11L, as well as in the primary tumour
- Histological findings are in line with an undifferentiated adenocarcinoma of the lung
- Immunohistochemistry: CK7/TTF1 positive, CK 5/6 negative, p63 negative, programmed death-ligand 1 (PD-L1) negative (< 1%)
- Next generation sequencing: p.Y772\_A775dup in ERBB2 (HER2), no driver mutations were found (EGFR, ALK, BRAF, ROS1, Met exon 14 skipping, KRAS, NTRK)

### How would you treat this patient?

The great majority selected a combination of standard chemo- and immunotherapy as the best choice in this situation. 7% thought of a single HER2 agent to treat the described patient (**figure 5**).

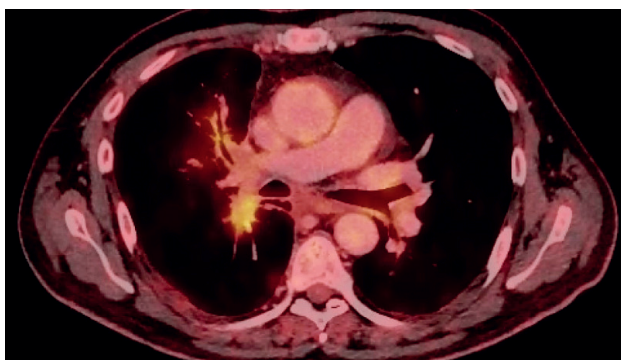
### The right answer is 3

Most lung cancer cases (85%) are NSCLC, the greater part not suitable for operative treatment due to advanced stages at first diagnosis.<sup>5</sup> Therefore, immunotherapy plays an increasingly important role.<sup>5</sup>

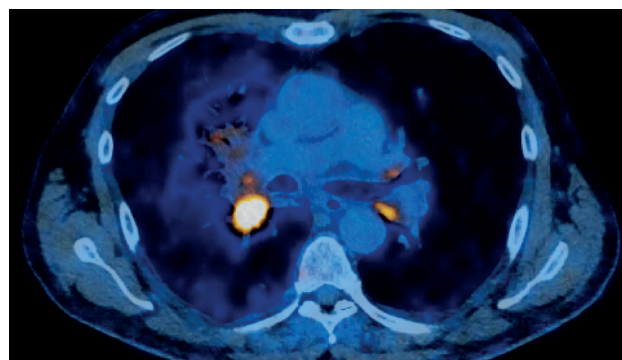
The negative results from testing for PD-L1 and driver mutation excludes a variety of potential agents in our patient with adenocarcinoma. Previously, those patients were generally treated with double chemotherapy.<sup>6</sup> This approach was changed by the KEYNOTE-189 trial. Regardless of PD-L1 expression, it found that adding pembrolizumab to the first line

therapy with pemetrexed and a platinum-based agent resulted in significant benefit for nonsquamous (nonSCC) NSCLC patients who did not present EGFR/ALK mutations.<sup>7,8,9</sup>

In the patients previously untreated for metastatic non-SCC NSCLC, the addition of pembrolizumab to standard chemotherapy of pemetrexed and a platinum-based drug resulted in significantly longer overall survival (OS) and progression-free survival (PFS) than chemotherapy alone.<sup>7,9</sup> The OS in the pembrolizumab group of patients with a PD-L1 tumour proportion score (TPS) under 1% at twelve months was 61.7% in comparison to 52.2% in the placebo combination group. This led to a significantly lowered hazard ratio (HR) for death of 0.59 (95% CI 0.38–0.92).<sup>7</sup> A current 4-year follow-up of KEYNOTE-189 also demonstrated very encouraging results in the subgroup with < 1% PD-L1 TPS: HR for OS 0.52 (95% CI 0.37–0.72), 2-year OS rate 23.3% (pembrolizumab) versus 5.3% (placebo), HR of PFS 0.49 (95% 0.35–0.68).<sup>8</sup> The results of KEYNOTE-189 led to a change in recommendations for first-line treatment of advanced non-SCC NSCLC patients with ECOG PS 0-1 and without the presence of PD-L1.<sup>3,10,11</sup> Presently, the combination with pembrolizumab/pemetrexed/platinum-based chemotherapy is a preferred first-line option in many guidelines.<sup>2–4,10</sup>



**Figure 6a:** PET-CT scan after three cycles of chemo-immunotherapy.



**Figure 6b:** PET-CT scan at baseline

## FURTHER COURSE

### November 2020 until January 2021

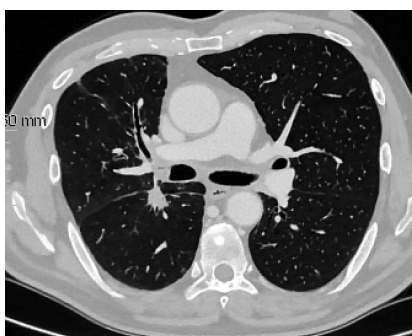
- In this case of advanced, undifferentiated adenocarcinoma, a combination of chemo- and immunotherapy is decided.
- The choice of first-line treatment is: four cycles of carboplatin plus pemetrexed and pembrolizumab.
- The patient experienced moderate nausea that was manageable with medication, mild anaemia and transient fatigue that subsided after one week of each cycle.
- During treatment, the patient's physical abilities soon start ameliorating and improved to ECOG PS1 at the end.
- The control PET-CT scan after three cycles demonstrated partial remission: metabolic normalisation of lymph node metastases in 11R and L, but lymph nodes still enlarged morphologically. Regression of the primary tumour in the right lower and middle lobe, but persisting lymphangiosis. Metabolic normalisation of bone metastases in ribs, new sclerotic lesions in multiple vertebrae, without metabolic activity (**figures 6a and 6b**)

### February 2021

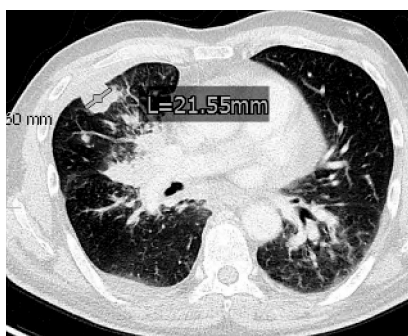
- Further controls confirm partial remission: normalisation of lymph nodes, further regression of primary tumour, persisting but less prominent lymphangiosis, no new metastases (**figures 7a–7c**)
- A maintenance therapy with pemetrexed and pembrolizumab is indicated and well-tolerated
- The patient achieves an ECOG PS of 0
- He subjectively feels a lot better than before the treatment: he started yoga again, is skiing several hours and can do 5-hour hikes. He can also look after his three grandchildren on a regular basis

### October 2021

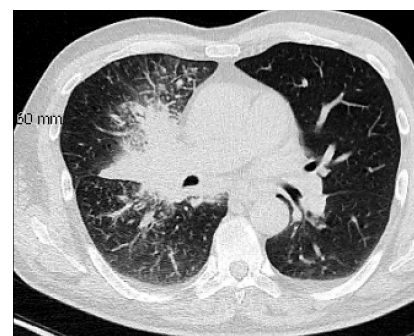
The patient continues to be in partial remission with ongoing maintenance treatment. His ECOG PS has stayed at 0, and he reports overall well-being.



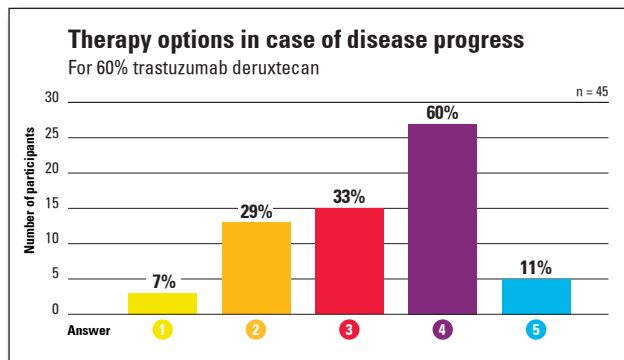
**Figure 7a:** CT scan from April 2021: after four cycles of chemo-immunotherapy.



**Figure 7b:** CT scan February 2021: after two cycles of chemo-immunotherapy.



**Figure 7c:** CT scan October 2020 at diagnosis.



**Figure 8** – poll results fourth question of the case report: «What options for further (experimental/trial) treatment would you consider if the patient's tumour is progressing?» (multiple choices eligible)

- 1 Afatinib
- 2 Chemotherapy plus trastuzumab
- 3 Treatment with ado-trastuzumab emtansine (T-DM1)
- 4 Trastuzumab deruxtecan
- 5 Poziotinib

### What could be possible further lines of treatment?

More than half of the participants selected trastuzumab deruxtecan. 33% picked ado-trastuzumab emtansine, and 29% leaned towards chemotherapy plus trastuzumab. 11% would have considered poziotinib (**figure 8**).

### Possible suggestions\* are 1, 2, 3, 4 and 5

A HER2 alteration can be detected in 2–4% of NSCLC-patients. The change found in our patient is also known under the name A775\_G776insYVMA and it is the most frequent type of HER2 mutation in NSCLC.<sup>12,13</sup> Three older trials on the combination of trastuzumab with chemotherapy have shown some benefit in patients with HER2 lung cancer.<sup>12</sup>

Afatinib, an irreversible EGFR inhibitor, has been tested for advanced NSCLC treatment in smaller studies with moderate success: e.g. of the 13 patients in the phase 2 NICHE trial, the median OS was 56 weeks and PFS 15.6, and a little over half reached disease control at week 12.<sup>13,14</sup>

The antibody-toxin conjugate ado-trastuzumab emtansine has been evaluated in small studies as a potential therapy for advanced adenocarcinoma patients with HER2 mutation.<sup>13</sup> Among 18 patients, 44% yielded partial response and a median PFS of 5 months.<sup>15</sup> In another trial with 22 patients, the objective response rate (ORR) to treatment was 38.1%, PFS 2.8 months and OS 8.1 months.<sup>16</sup> The agent is listed as one possible option by the current NCCN-Guideline.<sup>4</sup>

Most recently, positive phase 2 outcomes were published on poziotinib for refractory exon 20 mutated NSCLC: confirmed ORR 27%, median PFS 5.5 months and median OS 15 months. Of note, grade 3 adverse events were noted in up to 47% (skin rash), no grade 4, however one death due to pneumonitis was recorded.<sup>17</sup>

To date, the most promising results for the second-line setting have been seen with trastuzumab deruxtecan. The multicentre, phase 2 DESTINY-Lung01 study included 91 patients with non-SCC NSCLC, all refractory or relapsing with standard treatment. Patients were followed over a median time of 13.1 months, objective response was detected in 55%, and lasted over a median of 9.3 months. Median OS and PFS was 17.8 and 8.2 months, respectively. 46% of study participants experienced grade 3 or higher drug-related adverse events, among them two deaths due to interstitial lung disease.<sup>18</sup> In May 2020 trastuzumab deruxtecan received the U.S. Food and Drug Administration breakthrough therapy designation for HER2-mutant metastatic NSCLC.<sup>13</sup>

\*The listed agents in off-label use are personal suggestions by the author.

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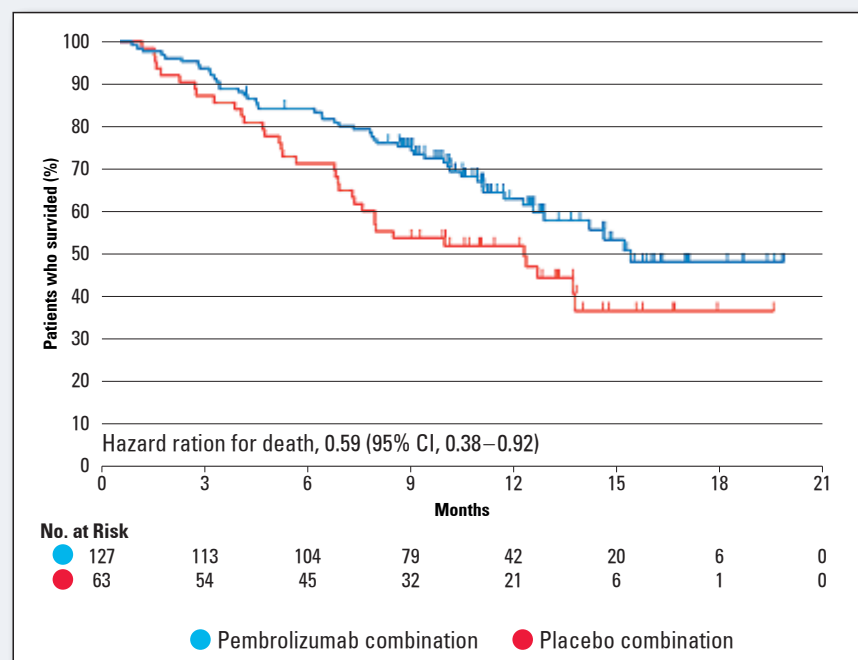
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### KEY-MESSAGE

#### The possibilities for the treatment of advanced NSCLC have substantially evolved within the last years

- Although the therapeutic aim in most cases of metastatic NSCLC is palliative, targeted therapy can be very beneficial<sup>1,3</sup>
- Immunohistochemistry and genetic testing play an important role in determining the optimal personalised treatment<sup>1,2</sup>
- In the subgroup\* of patients with nonSCC NSCLC, negative PD-L1 status and an ECOG PS 0/1 (Keynote-189) the addition of pembrolizumab to pemetrexed plus platinum-based chemotherapy leads to numerically increased OS and PFS (**figure 9**)<sup>7</sup>

\*Subgroup analysis was not statistically powered.



**Figure 9:** Kaplan-Meier curves comparing overall survival of combination therapy with and without pembrolizumab in the subgroup of patients with a PD-L1 tumour proportion score < 1%. Adapted according to <sup>7</sup>. The hazard ratio of the primary outcome of OS in the entire study cohort was 0.49 (95% CI 0.38–0.64).

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