METASTATIC NON-SMALL CELL LUNG CANCER: IMMUNOTHERAPY

CLINICAL CASE PRESENTATION

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DISCLOSURES

• Advisory Board for Merck Sharp and Dohme
• Travel Grant Pfizer
History and clinical presentation

• Social history
51 years old man, manager
Current smoker (~20 pack-years), stopped at diagnosis

• Past and family medical history
No family history of cancer
Moderate COPD (FEV1 60%)

• Clinical presentation
Progressive onset of exertional dyspnea and diffuse left thoracic pain
ECOG performance status: 1

COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; FEV1, forced expiratory volume in 1 second
Initial assessment and diagnosis

- **Whole body CT scan**
  Large left lung mass (≈12 cm), metastatic lesion right adrenal gland (≈10 cm), **multiple metastatic liver lesions**.

- **Transthoracic biopsy of the lung lesion**
  Histology: **lung adenocarcinoma**, *EGFR* (ex 18,19,20,21) wild type, *BRAF* wild type, *ALK* and *ROS1* not rearranged.
  PDL-1 (IHC 22C3 Dako) tumour proportion score = 60%

- **Staging**: cT4N2M1c stage IVb (8th edition TNM). **High disease burden**.
Q1: Which treatment strategy would you recommend?

1. Single agent Pembrolizumab 200 mg every 3 weeks

2. Pembrolizumab 200 mg q3 weeks plus 4 cycles of platinum-pemetrexed (followed by pemetrexed/pembrolizumab maintenance)

3. Atezolizumab 1200 mg q3 weeks plus 4-6 cycles of carboplatin and nab-paclitaxel

4. Atezolizumab 1200 mg q3 weeks plus carboplatin-paclitaxel and bevacizumab (followed by atezolizumab/bevacizumab maintenance)

5. Atezolizumab 1200 mg q3 weeks plus 4-6 cycles of platinum-pemetrexed

6. Platinum-based chemotherapy (+/- bevacizumab)
ESMO Guidelines: first-line non-squamous NSCLC

Stage IV NSCC: Molecular tests negative (ALK/BRAF/EGFR/ROS1)

- PD-L1 expression
- Any expression of PD-L1

- PS 0-1
  - High TMB (≥ 10 mutations/Mb)
    - Pembrolizumab/pemetrexed and platinum [I, A, MCB15]
  - Pembrolizumab/pemetrexed and bevacizumab [II, B]
  - Atezolizumab/ platinum-based ChE: Carboplatin/pemetrexed [II, A]
  - Atezolizumab/ bevacizumab [II, B]

- < 70 years and PS 2 or selected ≥ 70 years and PS 0-2
  - 4-6 cycles Carboplatin-based ChE: Carboplatin/pemetrexed [II, B]
  - BSC [I, B]

- PS 3-4

Partial response or stable disease

- Maintenance treatment:
  - Pemetrexed (continuation) [I, A]
  - Gemcitabine (continuation) [I, B]
  - Pemetrexed (switch) [I, B]

ICI, immune-checkpoint inhibitor

Preferential role of chemotherapy+ICI in high tumour burden disease?
Q2: Would the presence of multiple liver lesions influence your treatment choice?

1. No, I would not preclude ICI due to the maintained benefit in patients with liver metastases

2. Yes, I would not give immunotherapy, in fact the benefit of ICI is inferior in patients with liver metastases

3. Yes, I would prefer a combination including an antiangiogenetic treatment (for example carboplatin+paclitaxel+bevacizumab+atezolizumab)

PD-1, programmed-cell death 1; PD-L1, programmed death ligand 1
Treatment evaluation

- Patient included in KEYNOTE 189 trial (platinum-pemetrexed +/- pembrolizumab; double blind)
  - After 2 cycles: clinical amelioration and onset of acneiform dermatitis and hypothyroidism

Clinical case 1

- Patient included in KEYNOTE 189 trial (platinum-pemetrexed +/- pembrolizumab; double blind)
  - After 2 cycles: clinical amelioration and onset of acneiform dermatitis and hypothyroidism

<table>
<thead>
<tr>
<th>Baseline</th>
<th>2 cycles of chemo +/- pembrolizumab</th>
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<tbody>
<tr>
<td>Adrenal</td>
<td>RECIST v1.1: partial response</td>
</tr>
<tr>
<td>Liver</td>
<td>(&gt;70% reduction in SLD of target lesions)</td>
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<tr>
<td>Lung</td>
<td>Response maintained after 4 cycles of chemotherapy +/- ICI and maintenance treatment.</td>
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<tr>
<td>Lung</td>
<td>Now patient is in the follow up phase of the study.</td>
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CT, computed tomography; ICI, immune-checkpoint inhibitor; SLD, sum of longest diameters
Q3: Would you continue ICI beyond 2 years if the patient could received anti-PD-1/PD-L1 agents outside clinical trials?

1. No, the evidence of continuing anti-PD-1/PD-L1 treatment beyond 2 years is not available
2. Yes, I would be afraid that after stopping anti-PD-1/PD-L1 treatment, patients may lose the obtained response
3. I would discuss with the patient the PROs and CONs and the evidence available for stopping anti-PD-1/PD-L1 agents after 2 years

PD-1, programmed-cell death 1; PD-L1, programmed death ligand 1
Clinical case 2
History and clinical presentation

• Social history
67 years old man, lawyer
Ex-smoker (~30 pack-years); stopped 5 years ago

• Past and family medical history
No family history of cancer
**Crohn disease** (right hemicolecction in 2013 and sulfasalazine therapy from 2014 to 2017, since 2017 asymptomatic and not in immunosuppressive treatment)
**History of psoriasis** treated with topical corticosteroids (no flares since 2014)

• Clinical presentation
2 months history of back and left hip pain and mild dyspnea/cough
ECOG performance status = 1
Initial assessment

• Lumbar spine CT scan
  Large left paravertebral lesion (>7 cm)
  involving L1 and L2 with spinal compression

• Whole body CT and FDG-PET scans
  Left hypermetabolic mesenteric lesion (≈4cm)
  left hypermetabolic paravertebral lesion, right subcutaneous nodule, Barety adenopathies (≈3cm), small nodule in left upper lung lobe

No brain metastases
Diagnosis and initial management

- Biopsy of paravertebral lesion

Histology: Lung adenocarcinoma, concomitant enteric differentiation CDX2+

Molecular and PD-L1 status: KRAS mut (G12C), EGFR (ex 18,19,20,21) wild type, ALK and ROS1 not rearranged, PD-L1 (IHC 22C3 Dako) tumour proportion score >50%

Staging: cT1aN3M1c (subcutaneous, soft tissue, mesenteric) stage IVb (8th edition TNM)

- Lumbar spine arthodesis and palliative radiotherapy on left paravertebral lesion (25 Gy dose)
Q4. Which treatment strategy would you recommend?

1. Single agent Pembrolizumab 200 mg every 3 weeks

2. Pembrolizumab 200 mg q3 weeks plus 4 cycles of platinum-pemetrexed (followed by pemetrexed/pembrolizumab maintenance)

3. Atezolizumab 1200 mg q3 weeks plus 4-6 cycles of carboplatin and nab-paclitaxel

4. Atezolizumab 1200 mg q3 weeks plus carboplatin-paclitaxel and bevacizumab (followed by atezolizumab/bevacizumab maintenance)

5. Atezolizumab 1200 mg q3 weeks plus 4-6 cycles of platinum-pemetrexed

6. Platinum-based chemotherapy (+/- bevacizumab) due to the history of autoimmune diseases

7. Clinical trial with a KRAS G12C inhibitor.
Treatment evaluation

Clinical case 2

- After 2 cycles of single agent Pembrolizumab: worsening of dyspnoea, back pain and onset of dysarthria

Baseline

After 2 cycles of pembrolizumab

RECIST v1.1 progression (>50% increase in SLD of target lesions) compared to baseline CT scan

Multisites progression: brain (left frontal brain lesion), lung, subcutaneous, mesenteric, paravertebral

= Fast/Hyperprogressive disease

CT, computed tomography; SLD, sum of longest diameters
Post-progression management and treatment

- Biopsy of subcutaneous lesion (right axillary line)

**Histology:** Lung adenocarcinoma, rare tumour infiltrating lymphocytes

**Molecular and PD-L1 status:** *KRAS* mut (G12C), *EGFR* (ex 18,19,20,21) wild type, *ALK* and *ROS1* not rearranged, *PD-L1* (IHC 22C3 Dako) tumour proportion score >50%, *RET* not rearranged, *BRAF*, *HER2*, *MET* ex14 wild type, *p53* mut, *LKB1* mut (Next Generation Sequencing)

- Stereotactic brain RT (25 Gy) on left frontal brain lesion

- Initiation of carboplatin-pemetrexed treatment (currently ongoing)
Q5. If you had known the presence of LKB1 mut before first line initiation, what would have been your treatment strategy?

1. The same: Pembrolizumab 200 mg q3 weeks
2. Chemotherapy plus anti-PD1/PD-L1 agents
3. Platinum-based chemotherapy
4. Clinical trials (for example with drugs targeting metabolic checkpoints)
Points of discussion

• Factors influencing the choice of ICI alone or in combination with chemotherapy in PD-L1 >50% NSCLC (beyond reimbursement from regulatory agencies)

• Treatment duration with ICI in first-line

• Clinical and molecular predictors of benefit or lack response to PD-1/PD-L1 inhibitors alone or in combination with chemotherapy in NSCLC
THANK YOU