Plotting the course: optimizing treatment strategies in patients with advanced adenocarcinoma

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Disclosures

- **Advisor**
  - Bristol-Myers Squibb
  - AstraZeneca
  - Boehringer Ingelheim
  - Celgene
  - Roche
  - MerckSerono
  - Janssen
  - Clovis
  - Astellas
  - MSD
  - AbbVie
  - G1 Therapeutics

- **Speakers fee**
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  - Pfizer
  - AstraZeneca
  - Eli Lilly
  - MSD

- **Travel support**
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  - Boehringer Ingelheim
  - MSD
  - Celgene
After this presentation, participants will be able to

- describe current and emerging treatment modalities, such as immunotherapy and anti-angiogenic agents, for patients with advanced adenocarcinoma
- summarize the efficacy and safety of these treatment modalities in recent clinical trials
Question 1

Should every patient be treated with an immunotherapy agent as second-line treatment with adenocarcinoma?

1. Yes, regardless of PD-L1 status
2. No, only in patients who present with PD-L1 positive tumours
3. No, only in patients with PD-L1 positive tumours, EGFR wt, and ALK wt
The view on lung cancer is changing…

- **1990**: Lung cancer
- **2000**: Non-small-cell lung cancer and Small-cell lung cancer
- **2008**: Adenocarcinoma, Large-cell carcinoma, Squamous-cell carcinoma
- **Today (2013)**: Targets today (EGFR, ALK, ROS1) and Targets in the future (KRAS and others, BRAF, HER2, RET, DDR2, MET, FGR1, P13K)

Even guidelines have difficulty in keeping up to date...
Case discussion: WS, born 1945

- Healthy smoker with pain on right side of chest
- 40 pack-years
- CT/PET:
  - Mass RUL – SUV 20
  - SUV 16 in left adrenal gland
- CT-guided biopsy RUL; adenocarcinoma

- Molecular testing:
  - EGFR negative
  - ALK negative
  - PD-L1 65%
- CT-guided biopsy adrenal gland; NSCLC (not otherwise specified)

CT, computerized tomography; NOS, not otherwise specified; PET, positive-emission tomography; RUL, right upper lobe of lung; SUV, standardized uptake value.

Courtesy of P. Postmus.
Case: WS, born 1945 (continued)

Courtesy of P. Postmus.
Question 2

What treatment would you recommend?

1. Carboplatin-based doublet
2. Cisplatin + pemetrexed
3. Carboplatin + (nab-)paclitaxel + bevacizumab
4. PD-1/PD-L1 checkpoint inhibitors
5. PD-1/PD-L1 checkpoint inhibitors + chemotherapy
ESMO Guidelines: stage IV non-squamous cell carcinoma

Stage IV NSCC

ALK translocation

Crizotinib [I, A]

Molecular tests

No EGFR/ALK mutation

EGFR mutation

Gefitinib [I, A]
Erlotinib [I, A] ± bevacizumab
[I, A; MCBS 2]
Afatinib [I, A]

PS 0–1 < 70 years

PS 2 < 70 years or PS 0–2 > 70 years

PS 3–4

NSCC, non-squamous-cell carcinoma; MCBS, Magnitude of Clinical Benefit Scale, PS, performance status.

ESMO Guidelines: stage IV non-squamous cell carcinoma

Stage IV NSCC

- ALK translocation
  - Crizotinib [I, A]

Molecular tests

- No EGFR/ALK mutation
  - PS 0–1 < 70 years
  - PS 2 < 70 years or PS 0–2 > 70 years
  - PS 3–4

EGFR mutation

- Gefitinib [I, A]
- Erlotinib [I, A] ± bevacizumab
  - [I, A; MCBS 2]
- Afatinib [I, A]

ESMO Guidelines: stage IV non-squamous cell carcinoma

Stage IV NSCC

No testing for PD-L1...

PS 0–1 < 70 years
PS 2 < 70 years or PS 0–2 > 70 years
PS 3–4

EGFR mutation
Gefitinib [I, A]
Erlotinib [I, A]
± bevacizumab [I, A; MCBS 2]
Afatinib [I, A]

PS 2 < 70 years or PS 0–2 > 70 years

ALK translocation
Crizotinib [I, A]

PS 0–1 < 70 years
PS 2 < 70 years or PS 0–2 > 70 years
PS 3–4

ESMO Guidelines: stage IV non-squamous cell carcinoma (no driver mutations)

**PS 0–1 < 70 years**
- 4–6 cycles
  - Cisplatin + pemetrexed [II, A]
  - Cisplatin + gemcitabine [I, B]
  - Cisplatin + docetaxel [I, B]
  - Carboplatin + paclitaxel [I, B]
  - Carboplatin + nab-paclitaxel [I, B] ± bevacizumab

**PS 2 < 70 years or PS 0–2 > 70 years**
- 4–6 cycles
  - Carboplatin-based doublets [II, B]
  - Single-agent chemotherapy (gemcitabine, vinorelbine or docetaxel) [I, A]

**PS 0–1**
- Partial response or stable disease
- Maintenance treatment
  - Pemetrexed (switch) [I, B]
  - Pemetrexed (continuation) [I, A]
  - Erlotinib (EGFR-activating mutation) [I, B] ± bevacizumab (if given before)

The reality...

• > 80% of patients have no treatable oncogenic alterations\(^1\)
• Most patients are still in need of systemic treatment\(^2\)
• “Boundary” of efficacy reached for chemotherapy\(^2\)
• Impressive activity of immunotherapy in pretreated patients\(^2\)

2. Personal communication P. Postmus.
PD-L1 expression associated with a favourable outcome with pembrolizumab

[Images not shown]

• PD-L1 expression was assessed using 22C3 pharmDx, which is approved in the USA as a companion diagnostic for pembrolizumab\(^1\)

• For biomarker cutoff selection, PD-L1 expression was reported as the percentage of neoplastic cells indicating staining of PD-L1 in tumor samples from patients with NSCLC\(^2\)

• TPS \(> 50\%\) cutoff point was based on KEYNOTE-001
  – strict determination using independent training and validation sets\(^2\)

IHC, immunohistochemistry; PD-1, programmed cell death protein 1; TPS, tumour proportion score.

To be eligible for cross-over, progressive disease had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.

**KEYNOTE-024: study design**

**Patients**
- Untreated stage IV NSCLC
- Measurable disease
- ECOG PS 0–1
- PD-L1 TPS > 50%
- No sensitizing EGFR mutations or ALK translocations
- No treated brain metastases

**Randomized 1:1 N = 305**

**Primary endpoint:** PFS (RECIST v1.1 per blinded, independent central review)

**Secondary endpoints:** OS, ORR, safety

**Exploratory:** Duration of response

**Progressive disease**
- Pembrolizumab 200 mg every 3 weeks Up to 2 years
- Platinum doublet every 3 weeks, 4–6 cycles
  - Paclitaxel + carboplatin
  - Pemetrexed + carboplatin
  - Pemetrexed + cisplatin
  - Gemcitabine + carboplatin
  - Gemcitabine + cisplatin
  (non-squamous histology + pemetrexed maintenance)

**Progressive disease**
- Off study

**Crossover**
- Pembrolizumab 200 mg every 3 weeks Up to 2 years

---

*To be eligible for cross-over, progressive disease had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.*

ECOG: Eastern Cooperative Oncology Group; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TPS: tumour proportion score (% of patients with membranous PD-L1 staining on tumour cells).

KEYNOTE-024: PD-L1 screening

1,934 patients entered screening

1,729 submitted samples for PD-L1 assessment

1,653 samples evaluable for PD-L1

500 TPS ≥ 50% (30%)  1,153 TPS < 50%

KEYNOTE-024: PFS and OS (ITT population)

Median PFS (95% CI), months | HR (95% CI) | p value
--- | --- | ---
Pembrolizumab | 10.3 (6.7–NR) | 0.50 (0.37–0.68) | < 0.001
Chemotherapy | 6.0 (4.2–6.2) | - | -

Median OS (95% CI), months | HR (95% CI) | p value
--- | --- | ---
Pembrolizumab | NR | 0.60 (0.41–0.89) | 0.005
Chemotherapy | NR | - | -

Following the recommendation of the external DMC, this trial was terminated early, allowing patients who were previously being treated with chemotherapy to receive pembrolizumab.

Analysis cut-off date: 9 May 2016.

CI, confidence interval; DMC, data and safety monitoring committee; HR, hazard ratio; NR, not reached.

KEYNOTE-024: response (ITT population)$^{1,2}$

- In patients who had an OR:$^a$
  - The median time to response was 2.2 months in both pembrolizumab and chemotherapy groups.
  - The median duration of response was not reached in the pembrolizumab group and was 6.3 months in the chemotherapy group, with response ongoing at cut-off.

Analysis cut-off date: 9 May 2016.

$^a$ OR was a confirmed CR or PR; assessment was made in accordance with RECIST, version 1.1 by means of blinded, independent, central radiological review.

CR, complete response; OR, objective response; PR, partial response.

### KEYNOTE-024: PFS in key subgroups (ITT population)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Events, n/patients, n</th>
<th>HR for disease progression or death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>189/305</td>
<td>0.50 (0.37–0.68)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65 years</td>
<td>91/141</td>
<td>0.61 (0.40–0.92)</td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>98/164</td>
<td>0.45 (0.29–0.70)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>116/187</td>
<td>0.39 (0.26–0.58)</td>
</tr>
<tr>
<td>Female</td>
<td>73/118</td>
<td>0.75 (0.46–1.21)</td>
</tr>
<tr>
<td><strong>Region of enrolment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>East Asia</td>
<td>21/40</td>
<td>0.35 (0.14–0.91)</td>
</tr>
<tr>
<td>Non-East Asia</td>
<td>168/265</td>
<td>0.52 (0.38–0.72)</td>
</tr>
<tr>
<td><strong>ECOG PS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>59/107</td>
<td>0.45 (0.26–0.77)</td>
</tr>
<tr>
<td>1</td>
<td>129/197</td>
<td>0.51 (0.35–0.73)</td>
</tr>
<tr>
<td><strong>Histological type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>37/56</td>
<td>0.35 (0.17–0.71)</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>152/249</td>
<td>0.55 (0.39–0.76)</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>44/65</td>
<td>0.68 (0.36–1.31)</td>
</tr>
<tr>
<td>Former</td>
<td>133/216</td>
<td>0.47 (0.33–0.67)</td>
</tr>
<tr>
<td>Never</td>
<td>12/24</td>
<td>0.90 (0.11–7.59)</td>
</tr>
<tr>
<td><strong>Brain metastases at baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17/28</td>
<td>0.55 (0.20–1.56)</td>
</tr>
<tr>
<td>No</td>
<td>172/277</td>
<td>0.50 (0.36–0.68)</td>
</tr>
<tr>
<td><strong>Platinum-based chemotherapy regimen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Included pemetrexed</td>
<td>120/199</td>
<td>0.63 (0.44–0.91)</td>
</tr>
<tr>
<td>Did not include pemetrexed</td>
<td>69/106</td>
<td>0.29 (0.17–0.50)</td>
</tr>
</tbody>
</table>

Analysis cut-off date: 9 May 2016.

### KEYNOTE-024: exposure and AE summary (as-treated population)\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab (n = 154)</th>
<th>Chemotherapy (n = 150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of treatment (range)</td>
<td>7.0 months (1 day–18.7 months)</td>
<td>3.5 months (1 day–16.8 months)</td>
</tr>
<tr>
<td>Treatment-related AEs, %</td>
<td>Any grade</td>
<td>Grade 3–5</td>
</tr>
<tr>
<td>Any</td>
<td>73</td>
<td>27</td>
</tr>
<tr>
<td>Serious</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Leading to death</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Analysis cut-off date: 9 May 2016.

\(^a\) Included all patients who received at least one dose of a trial treatment; for patients in the chemotherapy group who crossed over to the pembrolizumab group after disease progression, only events that occurred during treatment with the assigned chemotherapy regimen are included.

AE, adverse event.

KEYNOTE-024: updated OS analysis in patients with advanced NSCLC

Data cut-off: 5 January 2017. NE, not estimable.

Nominal p value.

Brahmer JR. Presented at ASCO 2017; abstract 9000. Reproduced with permission.
Case: WS, born 1945 (continued)

April 2017

June 2017

Courtesy of P. Postmus.
Case: WS, 1945 (continued)

- No toxicity
- Still responding after 6 cycles

Unclear: if progressing, what is the best therapy?
Question 3

If disease progresses, which treatment would you start?

1. Platinum doublet
2. Docetaxel
3. Nintedanib + docetaxel
4. Pemetrexed
Case discussion: BU, born 1955

- Adenocarcinoma with pleural effusion
- Cytology positive
- Molecular testing:
  - ALK negative
  - EGFR negative
  - PD-L1 0%
- Response to cisplatin + pemetrexed
- Maintenance: pemetrexed 8 cycles
- Mass now growing in LLL

LLL, left lower lobe of lung.

Courtesy of P. Postmus.
Question 4

What would you do next? Perform another biopsy to re-evaluate for?

1. T790M
2. BRAF
3. ROS1
4. RET
5. PD-L1
6. None of the above
ESMO Guidelines: stage IV non-squamous cell carcinoma

Disease progression

PS 0–2
- Pemetrexed [I, B]
- Docetaxel [I, B]
- Nivolumab [I, B; MCBS 5]
- Pembrolizumab if PD-L1 > 1% [I, A; MCBS 3 if PD-L1 > 1%; MCBS 5 if PD-L1 > 50%]
- Ramucirumab + docetaxel [I, B; MCBS 1]
- Nintedanib + docetaxel [II, B]
- Erlotinib [II, C]

PS 3–4 ➔ BSC
- Pemetrexed (switch) [I, B]
- Pemetrexed (continuation) [I, A]
- Erlotinib (EGFR-activating mutation) [I, B] ± bevacizumab (if given before)

Maintenance treatment

Issues around second-line treatment

• No targetable mutation found?
• Access to immunotherapy?
• If yes, is marker analysis needed? Consider need for second biopsy if:
  — not tested
  — initially negative
• According to ESMO Guidelines, an anti-angiogenic agent, either ramucirumab or nintedanib, in combination with docetaxel is one of the second-line treatment options in patients with advanced adenocarcinoma
  — more likely to be active in early progressors after first-line chemotherapy

Anti-angiogenic agents as second-line therapy in advanced adenocarcinoma: nintedanib

Anti-angiogenic agents as second-line therapy in advanced NSCLC: ramucirumab

**REVEL: PFS**

- Ramucirumab + docetaxel
- Placebo + docetaxel

Stratified HR (95% CI) = 0.76 (0.68–0.86)
Stratified log-rank p < 0.0001

**REVEL: OS**

- Ramucirumab + docetaxel
- Placebo + docetaxel

Stratified HR (95% CI) = 0.86 (0.75–0.98)
Stratified log-rank p = 0.023

Summary

• Targeted therapy is an option for approximately 10–15% of patients; new developments are on the way

• Immunotherapy is first choice for second-line therapy, depending on PD-L1 expression levels for pembrolizumab or nivolumab

• Pembrolizumab is first choice in previously untreated patients with \( \geq 50\% \) PD-L1 positive tumours

• For PD-L1 0%, standard chemotherapy is still first choice
  — nintedanib + docetaxel for advanced non-squamous NSCLC
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