METASTATIC NON-SMALL CELL LUNG CANCER: IMMUNOTHERAPY

CLINICAL CASE DISCUSSION

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DISCLOSURE

- Personal financial interests:
  - Advisory Board/Consultancy/Speaker honoraria: Merck Sharp and Dohme, Roche, Boehringer Ingelheim, Guardant Health, Pfizer, Takeda, Novartis, Astra-Zeneca, Lilly
  - Research Funding: Pfizer, Novartis

- Institutional financial interests:
  those related to clinical trials and patient recruitment
How to choose?
ESMO Clinical Practice Guidelines

Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

D. Planchard†, S. Popat‡, K. Kerr§, S. Novello†, E. F. Smit§, C. Faivre-Finn§, E. F. Smit§, C. Faivre-Finn§, T. S. Mok††, M. Reck*, P. E. Van Schil†, M. D. Hellmann†† & S. Peters††, on behalf of the ESMO Guidelines Committee*
How to choose?
ESMO Clinical Practice Guidelines

Stage IV non-squamous NSCLC: Molecular tests negative (ALK, BRAF, EGFR, ROS1)

PD-L1 ≥50%

Any PD-L1 expression

Histology

PS

PS-L1 status

Driver Gene Negative


IO, immuno-oncology; PD-L1, programmed death-ligand 1; VEGF, vascular endothelial growth factor
How to choose?
ESMO Clinical Practice Guidelines

Stage IV non-squamous NSCLC: Molecular tests negative (ALK, BRAF, EGFR, ROS1)

**PD-L1 ≥50%**
- PS 0-1
  - Pembrolizumab ([A]; MO25 5)
  - Nivolumab/ ipilimumab ([A])

**Any PD-L1 expression**
- PS 0-1
  - Pembrolizumab/ nivolumab and platinum-based ChT ([4 cycles]
    followed by pembrolizumab/ nivolumab ([A]; MO25 4))
  - Atezolizumab/ bevacizumab and platinum-based ChT ([4-6 cycles]
    followed by atezolizumab/ bevacizumab ([A])
- PS 2-4
  - 4-6 cycles
    - Platinum-based ChT: Carboplatin/gemcitabine ([A])
    - Carboplatin/ docetaxel ([A])
    - Carboplatin/ navelitumab ([A])
    - Carboplatin/ pembrolizumab ([A])
    - Carboplatin/ bevacizumab ([A])
    - Carboplatin/ pembrolizumab ([A])
  - Maintenance Treatment:
    - Pembrolizumab (continuation) ([A])
    - Gemcitabine (continuation) ([B])
    - Pembrolizumab (switch) ([A])
    - Pembrolizumab ([A])

**Partial response or stable disease**
- IO alone
- IO + Chemo
- IO + Chemo + anti-VEGF
- Chemo
- IO/IO


IO, immuno-oncology; PD-L1, programmed death-ligand 1; VEGF, vascular endothelial growth factor
IO or IO/Chemo: a new SoC in advanced NSCLC

Nonsquamous, chemo alone vs chemo-IO

- KEYNOTE-189: Platinum + pemetrexed + pembrolizumab vs Platinum + pemetrexed
  - PFS: 8.8 vs 4.9
  - OS: NR vs 11.3

- IMpower 150: Carboplatin + paclitaxel + bevacizumab + atezolizumab vs Carboplatin + paclitaxel + bevacizumab
  - PFS: 8.8 vs 6.8
  - OS: 14.7 vs 18.2

- IMpower 130: Platinum + pemetrexed + atezolizumab vs Platinum + pemetrexed
  - PFS: 7 vs 5.5
  - OS: 13.9 vs 13.9

Squamous, chemo alone vs chemo-IO

- KEYNOTE-407: Carboplatin + (nab)-paclitaxel + pembrolizumab vs Carboplatin + (nab)-paclitaxel
  - PFS: 6.4 vs 4.8
  - OS: 15.9 vs 11.3

- IMpower 131: Carboplatin + (nab)-paclitaxel + atezolizumab vs Carboplatin + (nab)-paclitaxel
  - PFS: 6.3 vs 5.6
  - OS: 14 vs 13.9

Squamous and nonsquamous, chemo vs IO

- KEYNOTE-024: Platinum + pemetrexed or gemcitabine or paclitaxel
  - PFS: 10.1 vs 6
  - OS: 30 vs 14.2

- CheckMate 227: Nivolumab + ipilimumab vs Platinum + pemetrexed/platinum + gemcitabine
  - PFS: 7.2 vs 5.5
  - OS: 23 vs 16.7

Hazard ratio for disease progression or death:
- Favor IO alone/combination
- Favor chemo alone

Martínez et al. Clin Cancer Res 2019
Clinical Practice Guidelines: ESMO-MCBS v1.1

<table>
<thead>
<tr>
<th>Trial</th>
<th>HR-OS</th>
<th>LoE/GoR</th>
<th>MCBS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>KN-024</td>
<td>0.63</td>
<td>IA</td>
<td>5</td>
</tr>
<tr>
<td>KN-189</td>
<td>0.56</td>
<td>IA</td>
<td>4</td>
</tr>
<tr>
<td>IMpower 150 (B-C)</td>
<td>0.78</td>
<td>IA</td>
<td>3</td>
</tr>
<tr>
<td>IMpower 130</td>
<td>0.79</td>
<td>IA</td>
<td>3</td>
</tr>
<tr>
<td>IMpower 132*</td>
<td>0.81</td>
<td>IB</td>
<td>-</td>
</tr>
<tr>
<td>CM-227</td>
<td>0.58</td>
<td>IA</td>
<td>-</td>
</tr>
</tbody>
</table>

Yellow, EMA-approvals to date; SqCC squamous; IO, immunotherapy; *not statistically significant

Reck M. JCO 2019; Mok T. Lancet 2019; OA14.01; Gadgeel S.M, ASCO 2019; Socinski MA, NEJM 2018
Case number #1: Before starting, collect KEY information

1 Molecular

- PDL-1 TPS ≥ 50% (=60%)
- EGFR, ALK, ROS, BRAF wild type

2 Disease

- Adenocarcinoma
- High-liver tumour burden
- NO vascular infiltration

3 Patient

- Age 51
- Current smoking
- Good performance status (PS1)
- NO comorbidities
- NO immunosuppressants or underlying autoimmune disorders

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; PD-L1, programmed death-ligand 1; TPS, tumour proportion score
Can we spare IO?

**Molecular**
- PDL-1 TPS ≥ 50% (=60%)
- EGFR, ALK, ROS, BRAF wild type

**Disease**
- Adenocarcinoma
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ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; PD-L1, programmed death-ligand 1; TPS, tumour proportion score
First-line IO monotherapy in NSCLC PD-L1≥50%

Phase III trials overall survival

KEYNOTE-024: PD-L1 ≥ 50%

Overall Survival: Updated Analysis

Reck M. WCLC 2019, OA14.01

KEYNOTE-042 (subgroup PD-L1 ≥ 50%)

Mok T. ELCC 2019

IO, immuno-oncology; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1
First-line IO monotherapy in NSCLC PD-L1 ≥ 50%

Long term outcomes (5 years)

Among patients who received ≥ 2 years of pembrolizumab (11%)

5-year OS 78.6%
First-line IO monotherapy in NSCLC PD-L1≥50%
Toxicity profile

**KEYNOTE-024**
Treatment-Related AEs With Incidence >10%

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Pembrolizumab</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>50%</td>
<td>20%</td>
</tr>
<tr>
<td>vomiting</td>
<td>45%</td>
<td>10%</td>
</tr>
<tr>
<td>diarrhea</td>
<td>40%</td>
<td>5%</td>
</tr>
<tr>
<td>asthenia</td>
<td>35%</td>
<td>15%</td>
</tr>
<tr>
<td>anorexia</td>
<td>30%</td>
<td>5%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>25%</td>
<td>10%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>20%</td>
<td>5%</td>
</tr>
</tbody>
</table>

**KEYNOTE-042**
Treatment-Related AEs: Frequency ≥10%

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Pembrolizumab</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>40%</td>
<td>10%</td>
</tr>
<tr>
<td>Nausea</td>
<td>35%</td>
<td>5%</td>
</tr>
<tr>
<td>constipation</td>
<td>30%</td>
<td>5%</td>
</tr>
<tr>
<td>vomiting</td>
<td>25%</td>
<td>5%</td>
</tr>
<tr>
<td>anorexia</td>
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<td>5%</td>
</tr>
<tr>
<td>alopecia</td>
<td>15%</td>
<td>5%</td>
</tr>
</tbody>
</table>

AE, adverse event; IO, immuno-oncology; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1
The million dollar question: Do we need Chemo?

1. Molecular
   - PDL-1 TPS ≥ 50% (=60%)
   - EGFR, ALK, ROS, BRAF wild type

2. Disease
   - Adenocarcinoma
   - High-liver tumour burden
   - NO vascular infiltration

3. Patient
   - Age 51
   - Current smoking
   - Good performance status (PS1)
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ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; PD-L1, programmed death-ligand 1; TPS, tumour proportion score
### The million dollar question: Do we need Chemo?

Comparison of Phase III trials with pembrolizumab in PD-L1≥ 50%

<table>
<thead>
<tr>
<th></th>
<th>AEs ≥ 3 (study arm)</th>
<th>ORR (study arm)</th>
<th>OS (ITT)</th>
<th>PFS (ITT)</th>
<th>PFS2 (ITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pembrolizumab</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KN-024 (n=305)</td>
<td>31%</td>
<td>45%</td>
<td>0.63</td>
<td>0.50</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>Pembrolizumab and chemotherapy</strong></td>
<td>ITT</td>
<td>PD-L1≥50% (n=202)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KN-189 (n=616)</td>
<td>72%</td>
<td>62%</td>
<td>0.59</td>
<td><strong>0.36</strong></td>
<td><strong>0.47</strong></td>
</tr>
</tbody>
</table>

*percentages have been rounded

Median survival follow-up: KN-189 18 months; KN-024 25 months

Reck M., NEJM 2016; updated JCO 2019; Brahmer JR, ASCO 2017; Gadgeel S.M, ASCO 2019, abstr 9013

AE, adverse event; IO, immuno-oncology; ORR, overall response rate; OS, overall survival; PFS, progression-free survival
The million dollar question: Do we need Chemo?
Comparison of Phase III trials with pembrolizumab in PD-L1 ≥ 50%

**KEYNOTE-024: PD-L1 ≥ 50%**

Hazard ratio for disease progression or death, 0.50 (95% CI, 0.37–0.68)
P = 0.001

**KEYNOTE-189: PD-L1 ≥ 50%**

Hazard ratio for disease progression or death, 0.36 (95% CI, 0.25–0.52)

Reck M., NEJM 2016
Gandhi L., NEJM 2018

IO, immuno-oncology; PD-L1, programmed death-ligand 1
Do we need the antiangiogenics?

Liver metastasis

**IMpower 150 (with liver metastasis)**

Arm B vs Arm C

- Atezo+Bev+CP: 
  - HR*: 0.54 (95% CI: 0.33, 0.88)
- Bev+CP: 
  - Overall Survival (%)
  - Time (months)
  - 9.1 mo vs 13.2 mo

Arm A vs Arm C

- Atezo+CP: 
  - HR*: 0.85 (95% CI: 0.53, 1.38)
- Bev+CP: 
  - Overall Survival (%)
  - Time (months)
  - 7.0 mo vs 9.1 mo

**KEYNOTE-189**

With Liver Metastases

- Pembro/Pem/Plat: 43 (65.2)
- Placebo/Pem/Plat: 41 (63.7)
- HR: 0.62 (95% CI: 0.39-0.96)

Without Liver Metastases

- Pembro/Pem/Plat: 170 (49.4)
- Placebo/Pem/Plat: 167 (65.6)
- HR: 0.58 (95% CI: 0.45-0.74)

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Socinski MA, ASCO Meeting 2018, abstr 9002.; NEJM 2018

Garassino MC, AACR 2019

CP, carboplatin-paclitaxel; Bev, bevacizumab; Atezo, atezolizumab; Pembro, pembrolizumab; Pem, pemetrexed; Plat, platinum; HR, hazard ratio; OS, overall survival; CI, confidence interval
How long shall we treat with IO?
Worth continuing beyond 2 years (35 cycles)? KN-024

38/154 (24%) completed 35 cycles
ORR 82%
DoR ≥24 mo 25/38 (81%)

Reck M, WCLC 2019

OS, overall survival; CR complete response; PR partial response; SD, stable disease; PD progressive disease; ORR overall response rate; DoR duration of response
Case number # 2: Before starting, collect KEY information

1. **Molecular**
   - PDL-1 TPS ≥50%
   - KRAS(G12C), p53, STK11/LKB1 mut identified by NGS

2. **Disease**
   - Adenocarcinoma
   - NO visceral metastases

3. **Patient**
   - Former smoking
   - Good performance status (PS1)
   - NO immunosuppressants and history of stable autoimmune disorders

PD-L1, programmed death ligand 1; TPS, tumour progression score; NGS, next-generation sequencing
Case number # 2: Before starting, collect KEY information

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2. Disease
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Case report Roberto Ferrara, ESMO 2019

PD-L1, programmed death ligand 1; TPS, tumour progression score; NGS, next-generation sequencing
Clinical case # 2: How to choose? ESMO Clinical Practice Guidelines

Stage IV non-squamous NSCLC: Molecular tests negative (ALK, BRAF, EGFR, ROS1)

PD-L1 ≥50%  \[\text{High TMB (≥ 10 mutations/Mb)}\]
- Pembrolizumab [L, A; MSS 5]
- Nivolumab/palliative [L, A]

Any PD-L1 expression  \[\text{Any PD-L1 expression}\]
- Pembrolizumab/nervebrumab [L, A; MSS 4]
- Atezolizumab/pembrolizumab/nervebrumab [L, A]
- Atezolizumab/bevacizumab [L, A]

No other predictive biomarkers of IO recommended beyond PD-L1 or TMB….

Planchard, D et al. Annals Oncol 2018

IO, immuno-oncology; PD-L1, programmed death-ligand 1; TMB, tumour mutational burden
STK11/LKB1 alterations in KRAS\textsuperscript{mut} NSCLC

‘Cold’ microenviroment and Primary Resistance to IO

KL (co-occurring KRAS and STK11/LKB1 MUT); KP (co-occurring KRAS and TP53 MUT); K-only, KRAS MUT; IO, immunotherapy

Skoulidis F, Cancer Discovery 2015, 2018
**STK11/LKB1** and **KEAP1** alterations regardless of **KRAS**

Primary Resistance to Chemo-IO

WT, wild type; MUT, mutated; IO, immunotherapy; PR partial response; CR, complete response; PD, progressive disease; BOR, best objective response

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**STK11-mutant and chemo-IO**

<table>
<thead>
<tr>
<th>Group</th>
<th>PFS (months)</th>
<th>HR (95% CI)</th>
<th><strong>P</strong>-value</th>
<th>Log-rank test</th>
</tr>
</thead>
<tbody>
<tr>
<td>STK11/LKB1&lt;sup&gt;WT&lt;/sup&gt;</td>
<td>5.2m</td>
<td>0.99 (0.59-1.69)</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>STK11/LKB1&lt;sup&gt;MUT&lt;/sup&gt;</td>
<td>2.7m</td>
<td>0.36 (0.20-0.65)</td>
<td>0.0008</td>
<td></td>
</tr>
</tbody>
</table>

**KEAP1-mutant and chemo-IO**

<table>
<thead>
<tr>
<th>Group</th>
<th>PFS (months)</th>
<th>HR (95% CI)</th>
<th><strong>P</strong>-value</th>
<th>Log-rank test</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEAP1&lt;sup&gt;WT&lt;/sup&gt;</td>
<td>5.9m</td>
<td>2.83 (1.73-4.63)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>KEAP1&lt;sup&gt;MUT&lt;/sup&gt;</td>
<td>3.5m</td>
<td>0.99 (0.59-1.69)</td>
<td>0.84</td>
<td></td>
</tr>
</tbody>
</table>

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Skoulidis F, WCLC 2019
My ‘Take-Away’ messages for PD-L1 ≥ 50%

- **Immunotherapy** (alone or in combination) must **always be considered**.
- **WHEN can we spare IO?** Only if contraindications (severe autoimmune diseases, steroids, immune-suppression) or patients with poor PS ≥ 2.
- **WHEN can we consider chemo +/- anti-VEGF?** Aggressive biology, high symptom and disease burden, fitter patients.
- **WHICH chemo?** The same agent and schedule used in the phase III trial.
- **WHEN do we stop?** No clear evidence supporting the continuation of IO beyond 2 years, but preliminary data suggest activity of second-course pembrolizumab. Discuss PROs/CONs with patients and individualise.
- In a **data-free zone** of prospective trials, *STK11/LKB1* gene alterations must be taken into account when using IO, even when combined with chemotherapy.

IO, immuno-oncology; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1; PS, performance status; SoC, standard of care; VEGF, vascular endothelial growth factor
THANK YOU!!!