Pan-Asian adapted Clinical Practice Guidelines for the management of patients with metastatic Non-small Cell Lung Cancer:

a CSCO-ESMO initiative endorsed by JSMO, KSMO, MOS, SSO and TOS

DISCLOSURE INFORMATION
YI-LONG WU

Personal financial interests - Consulting and advisory services, speaking engagements:
Roche, AstraZeneca, Eli Lilly, Boehringer Ingelheim, Sanofi, MSD, BMS

Non-financial interests - Leadership roles:
Chinese Thoracic Oncology Group (CTONG), Past President of Chinese Society of Clinical Oncology (CSCO)
“Pan-Asian Adapted ESMO Guidelines for the management of patients with Metastatic Non-Small Cell Lung Cancer. A CSCO-ESMO initiative endorsed by JSMO, KSMO, MOS, SSO and TOS”

**Expert F2F meeting**

on August 5th 2018 at Guangzhou in China
BACKGROUND

- There are no comprehensive guidelines for the treatment of metastatic NSCLC (mNSCLC) in Asia
  - Japan has its own lung cancer treatment guidelines
  - China has the Chinese Society of Clinical Oncology (CSCO) Lung Cancer Practice guidelines stratified by resource availability and treatment values

- A decision was taken by CSCO, the Chinese Thoracic Oncology Group (CTONG) and European Society of Medical Oncology (ESMO) to develop guidelines adapted from the most recent 2016 and 2018 versions of the ESMO Clinical Practice Guidelines for the treatment and management of Asian patients with mNSCLC
COMPOSITION OF EXPERT PANEL

- The international panel of experts from the ESMO
  - David Planchard (Gustave Roussy, Villejuif, France)
  - Jean-Yves Douillard (Chief Medical Officer, ESMO and Centre René Gauducheau, France)
  - Solange Peters (Lausanne University Hospital, Switzerland)

- 12 experts from Asia
  - China (CSCO):
    - Yi-Long Wu (Guangdong Lung Cancer Institute)
    - Shun LU (Shanghai Chest Hospital)
  - Japan (JSMO):
    - Nobuyuki Yamamoto (Wakayama Medical University)
    - Tetsuya Mitsudomi (Kinki University Faculty of Medicine)
  - Korea (KMSO):
    - Dong-Wan Kim (Seoul National University Hospital)
    - Keunchil Park (Samsung Medical Center)
  - Malaysia (MOS):
    - Muhammad Azrif (Prince Court Medical Centre)
    - Adlinda Alip (University of Malaya)
  - Singapore (SSO):
    - Daniel Tan (National Cancer Centre Singapore)
    - Ross Soo (National University Hospital)
  - Taiwan (TOS):
    - Wen-Cheng Chang (Chang Gung Memorial Hospital)
    - James Yang (National Taiwan University Hospital)

- Only Asian expert members were allowed to vote on the recommendations.
Prior to the meeting 24 recommendations were circulated to each of the 12 Asian experts to gather their comments and input on each of the recommendations.

With specific emphasis being placed on the current practice in their countries and the data available from studies in Asian patients.

- ‘Is this recommendation adaptable for use in your country?’
- Provide details of the reasoning behind their responses and the relevant references to support their decisions.

A second survey was circulated shortly prior to the face-to-face meeting.

- The opinion of the experts on the updates to the recent ESMO Clinical Practice Guidelines submitted to Annals of Oncology July 2018.
<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIAGNOSIS</td>
<td>1</td>
</tr>
<tr>
<td>PATHOLOGY/MOLECULAR BIOLOGY</td>
<td>2</td>
</tr>
<tr>
<td>STAGING AND RISK ASSESSMENT</td>
<td>3</td>
</tr>
<tr>
<td>MANAGEMENT OF ADVANCED METASTATIC DISEASE</td>
<td>4</td>
</tr>
<tr>
<td>FIRST-LINE TREATMENT OF NSCLC WITHOUT DRUGGABLE ONCOGENE DRIVER</td>
<td>5</td>
</tr>
<tr>
<td>MAINTENANCE</td>
<td>6</td>
</tr>
<tr>
<td>PS 2 AND BEYOND</td>
<td>7</td>
</tr>
<tr>
<td>ELDERLY PATIENTS</td>
<td>8</td>
</tr>
<tr>
<td>SECOND-LINE TREATMENT OF NSCLC WITHOUT DRUGGABLE ONCOGENE DRIVER</td>
<td>9</td>
</tr>
<tr>
<td>FIRST-LINE TREATMENT OF EGFR MUTATED NSCLC</td>
<td>10</td>
</tr>
<tr>
<td>SECOND-LINE OF EGFR-MUTATED NSCLC</td>
<td>11</td>
</tr>
<tr>
<td>FIRST LINE TREATMENT ALK-REARRANGED NSCLC</td>
<td>12</td>
</tr>
<tr>
<td>SECOND-LINE TREATMENT OF ALK-REARRANGED NSCLC</td>
<td>13</td>
</tr>
<tr>
<td>PATIENTS WITH ROS1 REARRANGEMENT NSCLC</td>
<td>14</td>
</tr>
<tr>
<td>PATIENTS WITH BRAF MUTATED NSCLC</td>
<td>15</td>
</tr>
<tr>
<td>PATIENTS WITH NSCLC WITH OTHER DRUGGABLE ONCOGENE DRIVERS</td>
<td>16</td>
</tr>
<tr>
<td>ROLE OF RT IN STAGE IV</td>
<td>17</td>
</tr>
<tr>
<td>BRAIN METASTASES</td>
<td>18</td>
</tr>
<tr>
<td>LM CARCINOMATOSIS</td>
<td>19</td>
</tr>
<tr>
<td>TREATMENT OF OLIGOMETASTATIC DISEASE</td>
<td>20</td>
</tr>
<tr>
<td>BONE METASTASES</td>
<td>21</td>
</tr>
<tr>
<td>ROLE OF MINIMAL INVASIVE PROCEDURES IN STAGE IV NSCLC</td>
<td>22</td>
</tr>
<tr>
<td>PALLIATIVE CARE IN STAGE IV NSCLC</td>
<td>23</td>
</tr>
<tr>
<td>FOLLOW-UP</td>
<td>24</td>
</tr>
</tbody>
</table>
VOTING PROCESS

- A modified Delphi process was used to develop each individual statement prior to the final discussion and final voting process at the face-to-face working meeting in Guangzhou.
- The 12 Asian experts were asked to vote based on the evidence available, on a scale of A to E:
  - A = accept completely
  - B = accept with some reservation
  - C = accept with major reservation
  - D = reject with some reservation and
  - E = reject completely
- An adapted version of the ‘Infectious Diseases Society of America-United States Public Health Service Grading System’ was used to define the level of evidence and strength (grade) of each recommendation proposed by the group, as for all of the ESMO Consensus and ESMO Clinical Practice Guidelines and are given in the text in square brackets after each recommendation together with details of the levels of agreement.
- Whenever possible, the score of the ESMO Magnitude of Clinical Benefit Scale (MCBS) was provided for the most recently approved drugs. (All MCBS scores are available in Open Access at https://www.esmo.org/score/cards).
- The Asian experts were asked to make their decisions based on the available ‘scientific evidence’ rather than on some of the current practices in their respective countries, and also, independently of the approval and reimbursement status of certain drugs in their individual countries.
- The two experts, from ESMO (JYD and DP) were present at the face-to-face meeting in Guangzhou, China to offer their expert opinion if and as required.
A consensus was considered to have been achieved when ≥80% of experts voted to accept completely or accept with reservation a specific recommendation.

A recommendation was considered to have been rejected when >80% of the voting members indicated ‘reject completely’ or ‘reject with reservation’.

For recommendations where a consensus was not reached initially:

- The panel of Asian experts was invited to discuss and modify the recommendation(s) at the face-to-face meeting.
- A second round of voting was conducted.
- If still no consensus could be reached, the recommendation could be modified one more time, and a third and last vote was conducted to determine the definitive acceptance or rejection of a recommendation.
RESULTS

- Prior to the face-to-face meeting the 12 experts reported on the applicability of 137 recommendations from the 2016 ESMO NSCLC Clinical Practice Guidelines and subsequently the updated ESMO 2018 Clinical Practice Guidelines for the diagnosis treatment and follow-up of mNSCLC
Figure 1

Treatment algorithm for stage IV lung SCC.

Never/former light smoker or long-time ex-smoker (<15 packs/year)\(^4\)

Molecular test (ALK/EGFR/ROS1/BRAF)

Positive

Targeted therapy

Negative

follow recommended treatment depending on PD-L1 expression level

PS 0–1

Pembrolizumab [I, A; MCBS 5]

PD-L1 ≥50%

Pembrolizumab + carboplatin/paclitaxel or nab-PC (4 cycles) followed by pembrolizumab [I, A]

Atezolizumab + carboplatin + nab-PC (4-6 cycles) followed by atezolizumab [I, B]

Any expression of PD-L1\(^b\)

High TMB (≥10 mutations/Mb)

Nivolumab /ipilimumab [I, A]\(^c\)

PS 0–1

Platinum-based chemotherapy (see first-line treatment for PD-L1 <50%; PS 0–1)

Disease progression

PS 0–1

Platinum-based chemotherapy

PS 0–2

Nivolumab [I, A; MCBS 5]

Atezolizumab [I, A; MCBS 5]

Pembrolizumab if PD-L1 >31% [I, A; MCBS 5]

Docetaxel [I, B]

Ramucirumab/docetaxel [I, B; MCBS 1]

Erlotinib [II, C]

Afatinib [I, C; MCBS 2]

PS 3–4

BSC [II, B]

Disease progression

<70 years and PS 2 or Selected ≥70 years and PS 0–2

4–6 cycles: Carboplatin-based doublets: <70 years and PS 2 [II, A]

≥70 years and PS 0–2 [I, A]

Single-agent chemotherapy:

Gemcitabine, vinorelbine or docetaxel [I, B]

Stage IV SCC

PS 3–4

BSC [II, B]

BSC

Molecular testing is not recommended in SCC, except in those rare cases of never/former light smokers or long-time ex-smokers (<15 packs/year).

\(^4\)In absence of contraindications and conditioned by the registration and accessibility of anti-PD-L1 combinations with platinum-based chemotherapy, this strategy will be favoured to platinum-based chemotherapy in patients with PS 0–1 and PD-L1 >50%.

\(^b\)Depending on approval status and reimbursement.

ALK, anaplastic lymphoma kinase; BSC, best supportive care; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; Mb, megabase; MCBS, Magnitude of Clinical Benefit Scale; nab-PC, albumin-bound paclitaxel and carboplatin; PD-L1, programmed death-ligand 1; PS, performance status; SCC, squamous cell carcinoma; TMB, tumour mutation burden.

\(^c\)Depending on approval status and reimbursement.
**Treatment algorithm for stage IV lung NSCC negative for ALK/BRAF/EGFR/ROS1 alterations**

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

- **PD-L1 ≤50%**
  - PS 0–1: Pembrolizumab [I, A; MCBS 5]
  - High TMB (≥10 mutations/Mb): Nivolumab [I, A]
  - Disease progression: Pembrolizumab/pemetrexed and platinum-based chemotherapy (4 cycles) followed by pembrolizumab/pemetrexed [I, A]

- **4-6 cycles:**
  - Atezolizumab/bevacizumab with carboplatin and paclitaxel (4-6 cycles) followed by atezolizumab/bevacizumab [I, A]

- **PS 0–1**

- **Any expression of PD-L1**
  - <70 years and PS 2 or Selected ≥70 years and PS 0–2
    - 4–6 cycles: Carboplatin-based doublets: Cisplatin/gemcitabine [I, A]
      - Carboplatin/docetaxel [I, A]
      - Carboplatin/paclitaxel [I, A]
      - Carboplatin/vinorelbine [I, A]
      - Carboplatin/pemetrexed [II, A]
      - Carboplatin/pemetrexed nab-PC [I, B]
      - +/- bevacizumab [I, A with carboplatin/paclitaxel, otherwise III, B]

- **Partial response or stable disease**

- **Maintenance treatment:**
  - Pemetrexed (continuation) [I, A]
  - Gemcitabine (continuation) [I, B]
  - Pemetrexed (switch) [I, B]
  - +/- bevacizumab (if given before)

- **PS 0–2**

- **PS 3–4**

- **<70 years and PS 2 or Selected ≥70 years and PS 0–2**

- **BSC [II, B]**

**In absence of contraindications and conditioned by the registration and accessibility of anti-PD-L1 combinations with platinum-based chemotherapy, this strategy will be favoured to platinum-based chemotherapy in patients with PS 0–1 and PD-L1 <50%.

**Depending on approval status and reimbursement.**

ALK, anaplastic lymphoma kinase; BSC, best supportive care; EGFR, epidermal growth factor receptor; Mb, megabase; MCBS, Magnitude of Clinical Benefit Scale; nab-PC, albumin-bound paclitaxel and carboplatin; NSCC, non-squamous cell carcinoma; PD-L1, programmed death-ligand 1; PS, performance status; TMB, tumour mutation burden.

Figure 2
Treatment algorithm for stage IV lung carcinoma with an EGFR-activating mutation

Stage IV lung carcinoma with EGFR-activating mutation

- **PS 0–4 [I, A]**
  - (PS 3–4 for all following options [II, A])

  - Gefitinib [I, A]
  - Erlotinib [I, A]
  - Erlotinib +/- bevacizumab [II, A; MCBS 3]
  - Afatinib [I, A]
  - Dacomitinib [I, A]
  - Osimertinib [I, A; MCBS 4]
  - Gefitinib/carboplatin/pemetrexed [I, B]

Disease progression

- Oligoprogression
  - Local treatment (surgery or RT) and continue targeted systemic treatment [IV, C]

- Systemic progression
  - **Exon 20 T790M mutation testing:**
    - Re-biopsy or cfDNA plasma testing, with re-biopsy if plasma test is negative [II, A]

Exon 20 T790M mutation testing:

- Exon 20 T790M mutation positive
  - Osimertinib [I, A; MCBS 4]

- Exon 20 T790M mutation negative or re-biopsy indicated but not feasible
  - Platinum-based doublet [I, A]
  - Carboplatin/paclitaxel/bevacizumab/atezolizumab (PS 0–1) [IV, C]

*Depending on approval status and reimbursement.

cfDNA, cell-free DNA; EGFR, epidermal growth factor receptor; MCBS, Magnitude of Clinical Benefit Scale; PS, performance status; RT, radiotherapy.
Treatment algorithm for stage IV lung NSCC positive for **ALK/BRAF/ROS1** alterations

**Stage IV NSCC: Molecular tests positive (ALK/BRAF/ROS1)**

- **ALK translocation**
  - Crizotinib [I, A; MCBS 4]
  - Alectinib [I, A; MCBS 4]
  - Ceritinib [I, B; MCBS 4]
  - Brigatinib**

- **BRAF V600 mutation**
  - Dabrafenib/trametinib [III, A; MCBS 2]

- **ROS1 translocation**
  - Crizotinib [III, A; MCBS 3]

**Disease progression**

- Local treatment (surgery or radiotherapy) and continue targeted systemic treatment [IV, C]

**Oligoproggression**

- **Systemic progression**
  - Re-biopsy (recommended)

**Ceritinib [III, A]**
**Alectinib [III, A]**
**Brigatinib or lorlatinib [III, C]**
**Carboplatin/paclitaxel/bevacizumab/atezolizumab (PS 0–1) [V, C]**

- Disease progression

**Platinum-based chemotherapy [IV, A]**

**for crizotinib-naive patients**

- Crizotinib [III, A] or ceritinib [II, C]**

**Not approved for first-line treatment.**

**Depending on approval status and reimbursement.**


Figure 4
Pan-Asian adapted
Clinical Practice
Guidelines

Summary of drug approvals and reimbursement according to Asian country
<table>
<thead>
<tr>
<th>DRUG NAMES</th>
<th>CSCO</th>
<th>JSMO</th>
<th>KSMO</th>
<th>MOS</th>
<th>SSO</th>
<th>TOS</th>
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</thead>
<tbody>
<tr>
<td>Pemetrexed 1st L</td>
<td></td>
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<td></td>
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<tr>
<td>Pemetrexed Maintenance</td>
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<td>Pemetrexed 2nd L</td>
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<tr>
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<td>Ramucirumab</td>
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<td>Cetuximab</td>
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<td>Osimertinib</td>
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<tr>
<td>Crizotinib</td>
<td></td>
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<td></td>
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<tr>
<td>Alectinib 1stL</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Alectinib 2ndL</td>
<td></td>
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<td>Ceritinib 1stL</td>
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<tr>
<td>Nivolumab 2ndL</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab 1stL</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Pembrolizumab 2ndL</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Atezolizumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2nd line</td>
</tr>
<tr>
<td>Denzumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoledronic acid</td>
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</table>
I would thank:

• All 12 experts from Asia
• The societies of CSCO, JSMO KSMO, MOS, SSO and TOS
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