Systemic therapy for non-oncogene addicted NSCLC

Dr Ross Soo, MB BS, PhD, FRACP
Department Haematology-Oncology, National University Hospital
National University Cancer Institute, Singapore
National University Health System

ESMO Preceptorship Programme, Non-small cell lung cancer, Singapore, 21-22 November 2018
Disclosures

• **Advisory Board:** Astra-Zeneca, BMS, Boehringer Ingelheim, Celgene, Ignyta, Lilly, Merck, Novartis, Pfizer, Roche, Taiho, Yuhan

• **Research grant:** Astra-Zeneca
1\textsuperscript{st} line chemotherapy and contribution of targeted agents in non-driver addicted NSCLC

- Historical management
- 1\textsuperscript{st} line management of non-squamous NSCLC
  - The treatment strategy should consider the histology, molecular pathology, age, PS, comorbidities and the patient’s preferences
  - Systemic therapy should be offered to all stage IV patients with PS 0–2
- 1\textsuperscript{st} line management of squamous NSCLC

---

**Clinical practice guidelines**

*Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up*
In the beginning...role of 1st line chemotherapy

ESMO guidelines:
Chemotherapy with platinum doublets should be considered in all stage IV NSCLC patients without an actionable oncogenic driver, without major comorbidities and PS 0–2.
Platinum-based doublets are the recommended chemotherapy option in all stage IV NSCLC patients with no contraindications to platinum compounds.

NSCLC Meta-Analyses Collaborative Group. JCO 2008
Platinum doublet with 3rd generation drugs

ECOG1594

TAX 326

FACS:
IP, TC, GP, NP

nab-Paclitaxel and Carboplatin in Advanced NSCLC

ESMO Guidelines:
Nab-paclitaxel combination can be considered an option in advanced NSCLC patients, particularly in patients with:
- greater risk of neurotoxicity
- preexisting hypersensitivity to paclitaxel
- or contraindications to standard paclitaxel premedication

Socinski JCO 2012
1L treatment of advanced non-Squamous NSCLC without driver oncogenes (NSCC)

• Pemetrexed-based chemotherapy is preferred to gemcitabine- or docetaxel-based combinations in patients with non-squamous tumours
• Pemetrexed is restricted to NSCC in any line of treatment line
• Carboplatin and pemetrexed can be an option in patients with a contraindication to cisplatin
Impact of histology as a biomarker on treatment selection: efficacy

JMDB: Phase III cisplatin/gemcitabine vs cisplatin/ pemetrexed

Pemetrexed platinum and gemcitabine platinum have differential efficacy based on histology: JMDB

Intention to treat (all histologies): no difference between CP and GC

Scagliotti J Clin Oncol 2008
Addition of bevacizumab to chemotherapy: ECOG 4599

Stage 4, NSCLC
Treatment naive
ECOG PS=0-1
N=878

Paclitaxel + carboplatin + bevacizumab x6 cycles q3w

Paclitaxel + carboplatin q3w x6 cycles

Bevacizumab until PD, intolerable toxicity

OS
Safety

Sandler NEJM 2006
ECOG4599: addition bevacizumab to carboplatin/paclitaxel improves OS

HR (95% CI) = 0.79 (0.67, 0.92), p=0.003
OS= 12.3 vs 10.3 months

PFS: 6.2m vs 4.5m
ORR: 35% vs 15%

Sandler NEJM 2006
Other issues with bevacizumab

• Can I give it in the elderly?
• Is CNS mets a contraindication?
The survival benefit for bevacizumab added to chemotherapy seems limited to patients aged less than 75 years.

<table>
<thead>
<tr>
<th>Study</th>
<th>Age cutoff</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laskin</td>
<td>65 years</td>
<td>OS benefit</td>
</tr>
<tr>
<td>Leighl</td>
<td>65 years</td>
<td>OS benefit</td>
</tr>
<tr>
<td>Zhu</td>
<td>65 years</td>
<td>No OS benefit</td>
</tr>
<tr>
<td>Ramalingam</td>
<td>70 years</td>
<td>No OS benefit, more AEs</td>
</tr>
<tr>
<td>Langer</td>
<td>75 years</td>
<td>No OS benefit, more AEs</td>
</tr>
</tbody>
</table>

**CNS mets**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Besse</td>
<td>retrospective exploratory analysis</td>
<td>CNS metastases: risk of CNS bleed independent of bevacizumab</td>
</tr>
<tr>
<td>Socinski</td>
<td>PASSPORT Phase II, prior treated CNS mets</td>
<td>No grade ≥2 cerebral hemorrhage was observed</td>
</tr>
<tr>
<td>Lynch</td>
<td>SEER 65 years</td>
<td>Similar to other studies</td>
</tr>
<tr>
<td>Zhu</td>
<td>SEER 65 years</td>
<td>No OS benefit</td>
</tr>
</tbody>
</table>

EMA removed label restriction on March 25, 2009, to allow patients with untreated CNS metastases to receive bevacizumab

Meta-analysis of 1st Bevacizumab+ chemotherapy

ESMO Guidelines:
The combination of bevacizumab and other platinum-based chemotherapies may be offered in the absence of contraindications in eligible patients with advanced NSCC

significant improvement in OS and PFS for the combination of bevacizumab and platinum-based chemotherapy

Soria Ann Oncol 2013
1\textsuperscript{st} line chemotherapy + VEGF receptor TKIs...too high a mountain?

- Sorafenib (ESCAPE, NExUS)
- Motesanib (MONET 1)
- Cediranib (BR29)
- AMG-706
- Axitinib
- ABT-869
How about using 1\textsuperscript{st} line EGFR TKIs in unselected patients?

In unselected patients, 1\textsuperscript{st} line erlotinib followed by chemotherapy is inferior to 1\textsuperscript{st} line chemotherapy followed by erlotinib.
Maintenance therapy: the uninterrupted continuation of therapy for patients who have not progressed after 1L chemotherapy

• Factors to be considered:
  • Histology
  • Residual toxicity after 1L chemotherapy
  • Response to platinum doublet
  • Performance status
  • Patient preference
Continuation maintenance therapy: pemetrexed after x4 cycles cisplatin/ pemetrexed (PARAMOUNT)

ESMO guidelines:
Pemetrexed continuation maintenance should be considered in patients having disease control following four cycles of cisplatin/pemetrexed
Switch maintenance therapy: pemetrexed after x4 cycles platinum based chemotherapy (JMEN).

OS and PFS more pronounced in non-squamous subset

Ciuleanu Lancet 2009
Switch maintenance

ESMO guidelines:
NSCC and PS 0–1, pemetrexed switch maintenance should be considered in patients with disease control after x4 non-pemetrexed containing platinum-based chemotherapy

Continuation maintenance with gemcitabine is an option in NSCLC patients treated with x4 cycles of cisplatin/gemcitabine

Fidias JCO 2009, Cappuzzo Lancet Oncol 2010, Perol JCO 2012
How about maintenance EGFR TKIs in unselected patients?

<table>
<thead>
<tr>
<th>Study</th>
<th>Induction</th>
<th>Maintenance</th>
<th>PFS (HR, p value)</th>
<th>OS (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SATURN</td>
<td>Platinum doublet x4</td>
<td>Erlotinib Placebo</td>
<td>12.3w (0.71, p&lt;0.001)</td>
<td>12.0m (0.81, p=0.0088)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>11.1w</td>
<td>11m</td>
</tr>
<tr>
<td>WJTOG</td>
<td>Platinum doublet x3</td>
<td>Gefitinib Observation</td>
<td>4.6m (0.68 p&lt;0.001)</td>
<td>13.7m (p=ns)</td>
</tr>
<tr>
<td></td>
<td>Platinum doublet x6</td>
<td></td>
<td>4.3m</td>
<td>12.9m</td>
</tr>
<tr>
<td>INFORM</td>
<td>Platinum doublet x4</td>
<td>Gefitinib Placebo</td>
<td>4.8m (0.69, p=0.003)</td>
<td>18.7m (p=ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.6m</td>
<td>16.9m</td>
</tr>
</tbody>
</table>

IUNO: 1L maintenance vs 2L erlotinib in NSCLC without \textit{EGFR} mutations.

ESMO guidelines:
Maintenance treatment with erlotinib is only recommended for NSCC patients with an EGFR-sensitising mutation

Cicenas Lung Cancer 2016
1L treatment of advanced Squamous NSCLC

- Platinum-based doublets with a third-generation cytotoxic agent (gemcitabine, vinorelbine, taxanes) are recommended in advanced SCC patients without major comorbidities and PS 0–2
Phase III 1\textsuperscript{st} line Gem/ CDDP +/- necitumumab in SCC (SQUIRE)

ESMO guidelines:
the addition of necitumumab to cisplatin
and gemcitabine has not been adopted as a standard...and
its use should be carefully evaluated

Thatcher Lancet Oncol 2015
Docetaxel standard 2\textsuperscript{nd} line therapy until recently

- 2\textsuperscript{nd} line combination chemo has no OS benefit over single-agent.
- Docetaxel:
  - Improvement in OS vs BSC
  - Similar efficacy, but more favourable tolerability for weekly docetaxel schedule
- Pemetrexed:
  - Comparable OS to docetaxel
  - Lower rates of neutropenia, alopecia and GI toxicity
- Docetaxel + antiangiogenic therapy
  - LUME Lung 1
  - REVEL
  - ULTIMATE
- Immune checkpoint inhibitors

Shepherd JCO 2000, Hanna JCO 2004
2\textsuperscript{nd} line therapy: docetaxel +/- nintedanib (LUME LUNG 1) \( n=1314 \)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Nintedanib + docetaxel</th>
<th>Placebo + docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, mo</td>
<td>12.6</td>
<td>10.3</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.83 (0.70–0.99)</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.0359</td>
<td></td>
</tr>
</tbody>
</table>

Reck Lancet Oncol 2014
2\textsuperscript{nd} line therapy: docetaxel +/- nintedanib (LUME LUNG 1) (ADC, n=658)

ESMO guidelines:
Docetaxel + nintedanib is a treatment option for patients with adenocarcinoma progressing after previous chemotherapy or immunotherapy

Reck Lancet Oncol 2014
2nd line therapy: docetaxel + ramucirumab (REVEL) (n=1253)

ESMO guidelines:
Docetaxel + ramucirumab is treatment option for patients with NSCLC progressing after previous chemotherapy or immunotherapy, with PS 0–2
2\textsuperscript{nd} line therapy: weekly paclitaxel + bevacizumab vs docetaxel (ULTIMATE)

<table>
<thead>
<tr>
<th></th>
<th>docetaxel</th>
<th>wPB</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>5.5%</td>
<td>22.5%</td>
</tr>
</tbody>
</table>

Improved PFS

HR = 0.62 [0.44-0.87]  
$p = 0.006$

No OS benefit

HR = 1.18 [0.81-1.72]  
$p = 0.40$

Cortot WCLC 2016
Is 2\textsuperscript{nd} line EGFR TKIs effective in WT \textit{EGFR} NSCLC?

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Treatment</th>
<th>Primary endpoint</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTEREST</td>
<td>EGFR unselected</td>
<td>Gefitinib v Docetaxel</td>
<td>OS non inferiority of gefitinib</td>
<td>Gefitinib non inferior to docetaxel</td>
</tr>
<tr>
<td>TITAN</td>
<td>EGFR unselected</td>
<td>Erlotinib v Docetaxel or pemetrexed</td>
<td>OS</td>
<td>No statistical difference</td>
</tr>
<tr>
<td>KCSG-LU08-01</td>
<td>Never smoker, ADC</td>
<td>Gefitinib v Pemetrexed</td>
<td>PFS</td>
<td>Gefitinib better (P = .0006)</td>
</tr>
<tr>
<td>TAILOR</td>
<td>WT EGFR</td>
<td>Erlotinib v Docetaxel</td>
<td>OS</td>
<td>Docetaxel better (p=0.05)</td>
</tr>
<tr>
<td>HORG</td>
<td>EGFR unselected</td>
<td>Pemetrexed v erlotinib</td>
<td>TTP</td>
<td>No statistical difference</td>
</tr>
<tr>
<td>DELTA</td>
<td>EGFR unselected</td>
<td>Erlotinib v Docetaxel</td>
<td>PFS</td>
<td>No statistical difference</td>
</tr>
<tr>
<td>CTONG-0806</td>
<td>WT EGFR</td>
<td>Pemetrexed v gefitinib</td>
<td>PFS</td>
<td>Pemetrexed better (p &lt; 0.001)</td>
</tr>
</tbody>
</table>

When there’s controversy, let’s do a meta-analysis...

ESMO Guidelines

Erlotinib represents a potential second/third-line treatment option in particular for patients not suitable for immunotherapy or 2L chemotherapy in unknown EGFR status or EGFR WT NSCLC.
2L SCC: afatinib vs erlotinib (LUX Lung 8)

<table>
<thead>
<tr>
<th></th>
<th>Afatinib (n=398)</th>
<th>Erlotinib (n=397)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients died</td>
<td>307 (77.1%)</td>
<td>325 (81.9%)</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>7.92 (7.19, 8.74)</td>
<td>6.77 (5.85, 7.79)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, p-value</td>
<td>0.808 (0.691, 0.946)</td>
<td>0.0077</td>
</tr>
</tbody>
</table>

ESMO Guidelines
In patients with advanced SCC with PS 0–2 unfit for chemotherapy or immunotherapy, afatinib is a potential option with unknown EGFR status or EGFR WT patients.
Conclusions

- Non-squamous NSCLC:
  - Doublet chemotherapy ± bevacizumab
  - Carboplatin based doublet, monotherapy
  - Maintenance erlotinib not recommended for WT EGFR

- Squamous NSCLC
  - Platinum-based doublets with a third-generation cytotoxic agent (gemcitabine, vinorelbine, taxanes) for PS 0-2

- Developing novel therapeutic agents (immune checkpoint inhibitors)
- Identifying biomarkers in oncogene WT NSCLC