Molecular profiling and targeted therapies for older patients with advanced NSCLC

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Disclosures

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• Travel Grants: Roche, MSD
NSCLC: more than one disease!!

2019 Targets EGFR, ALK, ROS1, BRAF, NTRK, MET AND PDL1
Future: RET, KRAS G12C; EGFR exon 20 insertions, ....

Reck et al Lancet 2013
NSCLC more than one disease

- Histological AND Molecular differentiation
NSCLC: more than one disease!

- Accurate identification of genetic alterations is crucial
  - Both at baseline and at progression
  - Need for tissue

- Tissue biopsies may be sometimes problematic
  - Tumor localisation or medical condition
  - Risk of complications
  - Scarcity of tumor cells in biopsy

- Liquid biopsy
  - If insufficient tissue or too high risk or too much burden
  - Faster turn-around time
  - False negatives

Rolfo et al. JTO 2018
# Targeted drugs for molecular alterations

## Approved targeted drugs

<table>
<thead>
<tr>
<th>Target</th>
<th>FDA</th>
<th>EMA</th>
<th>Drugs</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>X</td>
<td>X</td>
<td>Gefitinib/Erlotinib, Afatinib, Osimertinib</td>
<td>RR 70-80%; mPFS 10-12 mo RR 80%; mPFS 18 mo</td>
</tr>
<tr>
<td>ALK</td>
<td>X</td>
<td>X</td>
<td>Crizotinib, Alectinib, Brigatinib</td>
<td>RR 75%; mPFS 11 mo RR 75%; mPFS 34.8 mo</td>
</tr>
<tr>
<td>ROS-1</td>
<td>X</td>
<td>X</td>
<td>Crizotinib Entrectinib (FDA)</td>
<td>RR 70%; mPFS 19 mo RR 77%; mPFS 19 mo</td>
</tr>
<tr>
<td>BRAF</td>
<td>X</td>
<td>X</td>
<td>Dabrafenib+Trametinib</td>
<td>RR 64%; mPFS 11 mo</td>
</tr>
<tr>
<td>MET ex14</td>
<td>X</td>
<td>X</td>
<td>Capmatinib (1st line) Tepotinib (2nd line)</td>
<td>RR 60-70%; mPFS 9-10 mo</td>
</tr>
<tr>
<td>NTRK</td>
<td>X</td>
<td>X</td>
<td>Larotrectinib, Entrectinib</td>
<td>RR 70%; mPFS 15 mo</td>
</tr>
</tbody>
</table>
## Targeted drugs for molecular alterations

### Promising targeted drugs

<table>
<thead>
<tr>
<th>Target</th>
<th>Drugs</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>RET</td>
<td>Pralsetinib, Selpercatinib</td>
<td>RR 70%; mPFS 18 mo</td>
</tr>
<tr>
<td>KRAS G12C</td>
<td>AMG510</td>
<td>RR 48%</td>
</tr>
<tr>
<td>EGFR exon 20 insertions</td>
<td>Poziotinib, TAK-788</td>
<td>RR 43%; mPFS 7.3 mo</td>
</tr>
</tbody>
</table>
EGFR mutations

- 10% of NSCLC
  - Higher frequency in adenocarcinoma, never smokers, females, Asian patients

- EGFR TKI 1\textsuperscript{st}/2\textsuperscript{nd} generation:
  - Higher ORR, improved PFS and better QoL compared to chemotherapy

Hsu WH et al. Ann Oncol 2018
EGFR mutations in older patients

- Phase III trials: median age 60 yrs
  - Efficacy in combination with favorable toxicity profile and improved QOL compared to chemotherapy is attractive for older patients

- In meta-analysis: PFS benefit did not differ by age
  - HR 0.40 for ≥65 and HR 0.34 for <65; p=0.27

- Smaller prospective studies confirm benefit in older patients
  - Even in the “oldest old” 80+

Lee CK et al. J Clin Oncol 2015; Maemondo M et al. JTO 2012; Corre R et al. Oncotarget 2018
EGFR mutations in patients with ‘bad’ PS

- Phase III trials most patients had good PS 0/1
  - Rapid responses, favorable toxicity, ...

- In meta-analysis: PFS benefit did not differ by PS
  - HR 0.34 for 2 and HR 0.36 for 0-1; p=0.85

- In ECOG-PS>2: rapid response and improvement of PS

EGFR mutations

- Choice of TKI may depend on toxicity profile

Hsu WH et al. Ann Oncol 2018
EGFR mutations

- Osimertinib: $3^{rd}$ generation EGFR TKI vs $1^{st}$ generation (FLAURA)
  - Improvement of ORR, PFS (HR 0.46), OS (HR 0.79)
  - Improvement of QoL
  - CNS activity
  - Better toxicity profile: less grade $\frac{3}{4}$ toxicity
- Median age 64 yrs, HR 0.49 for $\geq65$ yrs

MET exon 14 skipping mutations

- 3-4% of non-squamous NSCLC and 20-30% of sarcomatoid lung cancers
- More frequent in older patients and in smokers
- Aggressive tumor behaviour and poor prognosis
- Crizotinib: ORR 39% and mPFS 8 months

Reungwetwattana T et al. Lung Cancer 2017
MET exon 14 skipping mutations

- Selective MET inhibitors Capmatinib and Tepotinib

- In phase II trials (Geometry and Vision)
  - Median age 71 yrs and 74 yrs resp
  - ORR 60% in first line
  - mPFS 10 months
  - Intracranial activity

- Toxicity issues
  - 40-50% peripheral edema with 8% grade ¾
  - 20-30% nausea, mainly grade ½
  - 10-20% increase in blood creatinin mainly grade ½
  - Fatigue

Wolf et al. AND Paik et al  ASCO 2019
NTRK fusions

- Rearrangements involving either NTRK 1, 2 or 3 genes and various unrelated partners

- 0.2% of NSCLC
  - Mutually exclusive with other oncogenic drivers
  - Irrespective of age, smoking history and histology

Vaishnavi et al. Cancer Discov 2015; Farago et al. JCO Precis Oncol 2018
NTRK fusions

- Larotrectinib and Entrectinib:
  - Small number of NSCLC patients (12 and 10 resp)
  - Median age resp 49 yrs and 62.5 yrs
  - ORR 70-75%
  - Toxicity:
    - Fatigue 35%
    - Dizziness 25% (careful for falls)
    - Nausea 15-29%
    - Constipation 25%

Farago AF et al. WCLC 2019; Paz-Ares et al. ELCC 2019