Advanced disease NSCLC: the state of the art before the advent of immunotherapy

Giorgio V. Scaglioni
University of Torino
Dipartment of Oncology
giorgio.scagliotti@unito.it
Advanced NSCLC, PS 0-1, cytology or histology

TTF-1, p63 (p40), PDL-1

EGFR, ALK, ROS1, (NGS)

NS-NSCLC

Diagnosis box

Molecular tests positive

NS-NSCLC

PDL-1 + < 50%

Cis/carbo/pem for 4-6 cycles
(± Bevacizumab)

Approximate targeted agent until progression

≈ 20%

Pemetrexed maintenance until progression

≈ 40%

NS & SQ NSCLC

PDL-1 + > 50%

Pembrolizumab until progression**

≈ 15-20%

SQ NSCLC

PDL-1 + < 50%

Cis/carbo doublets for 4-6 cycles
or Necitumumab plus Cis/gem

≈ 25%

*Consider molecular tests if SQ-NSCLC is diagnosed in a never smoker or ≤ 40 years

** according to the eligibility criteria of KEYNOTE 024
EGFR, ALK, ROS1, (NGS)

NS-NSCLC

Molecular tests positive

Appropriate targeted agent until progression

≈ 20%

Advanced NSCLC, PS 0-1, cytology or histology

TTF-1, p63 (p40), PDL-1

EGFR, ALK, ROS1, (NGS)

EGFR Inhibitors:
First & second generation
Third generation?

ALK inhibitors:
Crizotinib
Alectinib? Ceritinib?

ROS1 inhibitors:
Crizotinib
Clinical trials

B-raf inhibitors (clinical trials)
Ex14 MET (clinical trials)
HER-2 (clinical trials)
RET inhibitors (clinical trials)

Progression of the disease

*Consider molecular tests if SQ-NSCLC is diagnosed in a never smoker or <40 years
** according to the eligibility criteria of KEYNOTE 024
Advanced NSCLC, PS 0-1, cytology or histology

TTF-1, p63 (p40)

EGFR, ALK, ROS1, (NGS)

NS-NSCLC

Cis/carbo/pem for 4-6 cycles (± Bevacizumab)

Pemtrexed maintenance until progression

≈ 50%

SQ-NSCLC*

Cis/carbo doublets for 4-6 cycles or Necitumumab plus Cis/gem

≈ 30%

Progression of the disease

*Consider molecular tests if SQ-NSCLC is diagnosed in a never smoker or ≤ 40 years
** according to the eligibility criteria of KEYNOTE 024
Advanced NSCLC, PS 0-1, cytology or histology

**NS-NSCLC**

Diagnostic box

TTF-1, p63 (p40), PDL-1

**EGFR, ALK, ROS1, (NGS)**

SQ-NSCLC*

SQ NSCLC PDL-1 + < 50%

Cis/carbo/pem for 4-6 cycles (± Bevacizumab)

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≈ 40%

Progression of the disease

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*Consider molecular tests if SQ-NSCLC is diagnosed in a never smoker or ≤ 40 years
** according to the eligibility criteria of KEYNOTE 024
Front line strategies according to histology
Maintenance approaches
Second line treatments
Future treatment opportunities
2000-2017 – Changes in the therapeutic landscape of stage IV lung cancer
2000-2017 – The Role of Histology
### Subtyping NSCLC

<table>
<thead>
<tr>
<th>Squamous Cell Carcinoma</th>
<th>Versus</th>
<th>Small Cell Carcinoma</th>
</tr>
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<tbody>
<tr>
<td>p63/p40</td>
<td>+++/+++ (~100%)</td>
<td>-/-</td>
</tr>
<tr>
<td>TTF-1</td>
<td>-</td>
<td>++ (~80%)</td>
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<tr>
<td>Chromogranin</td>
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<td>++ (dot-like)</td>
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<th>Adenocarcinoma</th>
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[Image of immunohistochemical stains for TTF-1, p63, p40, ADC, SqC, n.o.s.]
Patients who get benefit from molecular diagnosis
2000-2017 – Treatment Decisions in Patients without oncogenic drivers and not candidate for front-line Pembrolizumab
The Superior Efficacy of Pemetrexed in Non-Squamous NSCLC

Role of Thymidilate Synthase

Adenocarcinoma

Squamous

Potential Surrogate Markers for the Evaluation of Anti-VEGF Agents

- **Invasive**
  - Tissue biopsy
  - Interstitial fluid pressure measurement
  - Measurement of tissue oxygenation
  - Skin wound healing

- **Minimally Invasive**
  - Circulating endothelial cells
  - Circulating progenitor cells
  - Protein levels in plasma
  - VEGF polymorphisms

- **Non-Invasive**
  - Imaging
    - CT imaging
    - PET imaging $^{15}$O FDG
    - MRI
  - Clinical
    - HTN
    - Gender
    - Urine protein (MMP, VEGF)

*Jain RK. Nat Clin Practice 2006;3:24–40; Davis DW. Br J Cancer 2003;89:8–14*
Decreasing incidence, mirrors transition (in demographic and geographic populations) from unfiltered to filtered cigarettes, with 2-3 decade lag time

Arises from proximal airways, gives rise to more central cancers, more co-morbidities

Higher mutational burden

**Therapy**

- Cis/carbo doublets x 4-6 courses
- No role for maintenance
- Ipilimumab plus carbo/paclitaxel some activity
- Nab-paclitaxel superior ORR compared to carbo/paclitaxel
- Necitumumab in combination with cis/gem improved survival over cis/gem

Nab-paclitaxel In NSCLC

Squamous

<table>
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<tr>
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<th>nab-P/C</th>
<th>P/C</th>
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<tbody>
<tr>
<td>Independent Radiologic Review</td>
<td>41%</td>
<td>24%</td>
</tr>
<tr>
<td>Investigator Assessment</td>
<td>37%</td>
<td>29%</td>
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Non-squamous

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<tbody>
<tr>
<td>Independent Radiologic Review</td>
<td>26%</td>
<td>25%</td>
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<tr>
<td>Investigator Assessment</td>
<td>37%</td>
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* Not a pre-specified endpoint

Nab-paclitaxel in NSCLC – OS

HR = 0.922
95% CI (0.797 to 1.066)
P = .271

Nab-PC
N/Events: 521/360
Median OS: 12.1 months
95% CI: 10.8 to 12.9

Sb-PC
N/Events: 531/384
Median OS: 11.2 months
95% CI: 10.3 to 12.6

HR = 0.890
95% CI (0.719 to 1.101)
P = .284

Nab-PC
N/Events: 229/170
Median OS: 10.7 months
95% CI: 9.4 to 12.5

Sb-PC
N/Events: 221/173
Median OS: 9.5 months
95% CI: 8.6 to 11.6

SQUIRE: Necitumumab in Squamous Cell Lung Cancer

HR (95% CI) = 0.84 (0.74 - 0.96); P = .012

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<th>Median OS (95% CI), mo</th>
<th>Median Follow-up Time, mo</th>
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<tr>
<td>Gem-CIs + Neci</td>
<td>11.5 (10.4-12.6)</td>
<td>25.2</td>
</tr>
<tr>
<td>Gem-CIs</td>
<td>9.9 (8.9-11.1)</td>
<td>24.8</td>
</tr>
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Overall Survival, %

1-y OS: 47.7%
2-y OS: 19.9%

Patients/events:
- Gem-CIs + Neci: 545/418
- Gem-CIs: 548/442

No. at risk
- Gem-CIs + Neci 545 496 450 407 358 291 243 208 176 130 101 84 61 42 32 20 11 3 3 0 0
- Gem-CIs 548 494 435 379 308 254 219 182 153 115 80 63 49 33 27 19 9 7 3 1 0

• Extremely similar agent; extremely similar results
• Should there be a distinction between statistical and clinical significance?

• Front line strategies according to histology
• Maintenance approaches
• Second line treatments
• Future treatment opportunities
Goal

- To extend progression-free and overall survival of patients with advanced NSCLC already treated with induction chemotherapy
- To extend symptom-free survival of advanced NSCLC patients

Therapeutic Action

- Continuous administration of single agents/combos of cytotoxic agents and/or targeted agents

Which target population?

- Those with CR, PR or SD following induction and minimal cumulative toxicity
Continuation Maintenance

Switch Maintenance

7 trials report no detrimental effect on QOL

Previously untreated stage IIIB–IV nsNSCLC

First-line induction
4 cycles, q3w

Continuation maintenance
q3w until PD

Arm A: bevacizumab
Arm B: bevacizumab + pemetrexed

Follow-up

CR/PR/SD per RECISTe

N=376

N=253

N=125

N=128

Primary objective: progression-free survival
Secondary objectives: Overall survival, response rate, disease control rate, duration of response, duration disease control, safety, QOL

Stratification factors:
- Gender
- Smoking status
- Response at randomization

AVAPEARL : Bevacizumab + Pemetrexed

- **Progression-Free Survival (%)**
  - Yellow line: Maintenance bevacizumab + pemetrexed (n=128)
  - Blue line: Maintenance bevacizumab (n=125)
  - Bevacizumab + pemetrexed: 7.4 months
  - Bevacizumab: 3.7 months
  - HR, 0.48
  - 95% CI, 0.35 to 0.66
  - *P* < .001

- **Overall Survival (%)**
  - Yellow line: Maintenance bevacizumab + pemetrexed (n=128)
  - Blue line: Maintenance bevacizumab (n=125)
  - Bevacizumab + pemetrexed: NR (12.8 months)
  - Bevacizumab: 12.8 months
  - HR, 0.75
  - 95% CI, 0.47 to 1.19
  - *P* = .219

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**Induction Phase**
4 cycles, q21d

- Pemetrexed + (folic acid & vitamin B₁₂)
- Carboplatin + Bevacizumab

**Maintenance Phase**
q21d until PD

- Pemetrexed + (folic acid & vitamin B₁₂)
- Bevacizumab

Stratified for:
- PS (0 vs. 1); sex (M vs. F); disease stage (IIIB vs. IV); measurable vs. non-measurable disease

Inclusion:
- No prior systemic therapy for lung cancer
- ECOG PS 0/1
- Stage IIIB-IV NS-NSCLC
- Stable treated brain mets allowed

Exclusion:
- Peripheral neuropathy ≥ Grade 1
- Uncontrolled pleural effusions

R 1:1

450 patients each

POINTBREAK : Bevacizumab + Pemetrexed

**Figure A**

- **OS median (95% CI), mo**: PemCBev (n = 472) - 12.6 (11.3 to 14.0); PacCBev (n = 467) - 13.4 (11.9 to 14.9)
- **HR (95% CI); P**: PemCBev - 1.00 (0.86 to 1.16); PacCBev - .949
- **Survival rate (%)**
  - 1-year: PemCBev - 52.7; PacCBev - 54.1
  - 2-year: PemCBev - 24.4; PacCBev - 21.2

**Figure B**

- **OS median (95% CI), mo**: PemCBev (n = 292) - 17.7 (16.6 to 20.5); PacCBev (n = 298) - 15.7 (14.9 to 17.7)
- **Survival rate (%)**
  - 1-year: PemCBev - 71.7; PacCBev - 66.5
  - 2-year: PemCBev - 34.5; PacCBev - 26.5

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**Progression during or after platinum therapy**

- **Chemotherapy**
  - Docetaxel
  - Pemetrexed
  - If not given previously
  - Not suitable for squamous NSCLC

- **EGFR TKI**
  - Erlotinib
  - May be inferior to chemotherapy in WT patients
  - Only approved for squamous NSCLC

- **Antiangiogenics**
  - Nintedanib (+ docetaxel)
  - If docetaxel not given previously
  - Only approved for squamous NSCLC

- **Immune checkpoint inhibitors**
  - Ramucirumab (+ docetaxel)
  - Only approved for adenocarcinoma
  - Nivolumab
  - Pembrolizumab
  - Atezolizumab
  - Only approved for patients whose tumors express PD-L1

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*Approved in EU only; †Approved in US only*
DNA Repair and Cancer

Health

Prevents cancer development

Disease/Cancer

DNA repair

Anti-cancer therapy

Interferes with anti-cancer therapy

DNA repair
Identifying BRCAness through genetic testing, functional assays or array-based procedures can potentially widen the therapeutic span of PARP-targeted strategies.
Comprehensive analyses of cancer genome sequencing data

Catalog of driver and passenger mutations
- Driver: TP53, BRCA1, PTEN,...
- Passenger: HBB, ORA1A1,...

Signatures of DNA damage and repair
- NCG → NTG → Deamination of 5mC
- NGC → NAC

Molecular clock-like signature

Tumor heterogeneity and clonal architecture

Model of tumor evolution

Molecular classification of cancer
- Stratification
- Targeted therapy
- Probability of emergence of resistance
- Immunotherapy
- Other clinical management options
- Mutagens and cancer risk
- Precursor lesions and initiating events

De S., Ganesan S. Ann. Oncol. 2016; ahead of print
In the majority of patients with advanced NSCLC histological subtyping remains the major determinant for treatment decisions.

Pemetrexed-based therapies (± bevacizumab) are preferred treatments for Non-squamous NSCLC.

Cisplatin-doublets remains the SOC for SCCL.

In non-squamous NSCLC maintenance therapy may be considered on individual basis.

Emerging therapeutic options in second and front line.

A more comprehensive understanding of tumor heterogeneity and tumor microenvironment through NGS will pave the way to new treatment opportunities.