Lung cancer...
What’s next after diagnosis?

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Disclosures

- Advisor/Speaker Bureau: Eli Lilly, Astra Zeneca, Roche, BMS, MSD, BI, Takeda, Celgene.
Step one: knowing my patient

- Comorbidities, smoking habit assessment, weight loss, performance status
- Physical examination
- Laboratory tests (routine hematology, renal and hepatic function, bone biochemistry).
- Neutrophil to lymphocyte ratio (NLR) as potential prognostic marker
  
  *(Mezquita L, JAMA Oncol 2018)*

*D. Planchard et al, 2018*
Step two: determine the stage (imaging studies)

Contrast-enhanced CT scan of the chest and upper abdomen
Including complete assessment of liver, kidneys and adrenal glands

Bone scan
• If bone metastases are clinically suspected
  (the routine use is not recommended)

Positron emission tomography (PET), ideally coupled with CT
• In case of patients potentially suitable for treatment with curative intent
• In case of intra-thoracic pathological lymph nodes in locally advanced disease
• If bone metastases are clinically suspected (the most sensitive modality)
Step two: determine the stage (imaging studies)

PET-CT vs Bone scan

Meta-analysis: Comparison of F-18 Fluorodeoxyglucose-Positron Emission Tomography and Bone Scintigraphy in the Detection of Bone Metastasis in Patients with Lung Cancer

**PET/PET-CT**

- **Sensitivity**: 0.93
- **Specificity**: 0.95

**Bone scan**

- **Sensitivity**: 0.87
- **Specificity**: 0.82

Chang MC; Acad Radiol 2012
Lung cancer represents the most common cause of brain dissemination.

Brain metastases are present at diagnosis in approximately 25% of patients with advanced NSCLC.

The incidence of leptomeningeal carcinomatosis in NSCLC ranges between 5 and 10%.

Oncogene-addicted NSCLCs are characterized by a particularly high incidence of brain metastases: above 20% and 30–40% in EGFR-mutated and ALK-rearranged cases at presentation.

The cumulative incidence of post-diagnosis BM increased over time.
CNS imaging: when?

Screening for brain metastases by MRI might be useful in patients considered for curative therapy [III, B].

Imaging of CNS should be considered at diagnosis for all patients with metastatic disease [IV, B] and is required for patients with neurological symptoms or signs [IV, A].

Brain MRI with contrast to rule out asymptomatic metastases is recommended for patients with stage II, III and IV disease.

In patients with stage IB MRI is optional and can be considered in selected high risk patients (tumor > 5 cm, central location..)

Consider MRI or CT of the head in patients selected for treatment with curative intent, especially in stage III disease.

Consider brain imaging in stage III/IV and symptomatic patients.
Step two: determine the stage (imaging studies)

CNS imaging: when?

Early stage non-small cell lung cancer patients need brain imaging regardless of symptoms (Ando et al, 2018)

- 46 out of 124 cases had brain metastasis at presentation.
- 21 of 35 adenocarcinoma cases with brain metastasis had EGFR mutations.
- 29 patients (63%) were asymptomatic, 6 of 46 cases with brain metastasis (13%) were clinical T1-2aN0.
- In clinical T1-2aN0 cases, only one patient had neurological symptoms at presentation.

Lymph Node Size Predicts for Asymptomatic Brain Metastases in Patients With Non–small-cell Lung Cancer at Diagnosis (Rice et al, 2018)

5.7% prevalence of asymptomatic brain metastases at diagnosis :
- 2.4% of stage IA
- 5.6% of stage IB
- 6.1% of stage IIIA
- 20% of stage IIIB
Step two: determine the stage (imaging studies)

CNS imaging: what? CT scan vs MRI

Screening for brain metastases by MRI might be useful in patients considered for curative therapy [III, B].

Imaging of CNS should be considered at diagnosis for all patients with metastatic disease [IV, B] and is required for patients with neurological symptoms or signs [IV, A]. MRI is more sensitive than CT scan [III, B].

Brain MRI with contrast to rule out asymptomatic brain metastases for patients with stage II, III and IV. If brain MRI cannot be done, then CT of the head with contrast in an option.
Screening for brain metastases (BM) in patients (pts) with stage III non-small cell lung cancer (NSCLC), magnetic resonance imaging (MRI) or dedicated contrast-enhanced computed tomography (dCE-CT)? A prospective observational study *(J J A O Schoenmaekers et al JTO 2018)*

- Observational prospective multicentre study
- Primary endpoint: % of patients with BM on MRI without suspect lesions on dCE-CT. 118 pts were needed to show a clinically relevant considered difference of 2%. In total 7/154 pts (4.5%) had a BM on MRI without suspect lesions on dCE-CT

**MRI brain detected BM in an additional 4.5% of patients**

- Secondary endpoints:
  - % of pts with BM on dCE-CT → 7%
  - % of pts with BM ≤ 1 year of a negative staging MRI → 8.5%
**Step two: determine the stage**

*In case of locoregional disease:*

- For patients with abnormal mediastinal and/or hilar lymph nodes at CT and/or PET, endosonography is recommended over surgical staging [I, A].

- If EBUS and/or EUS does not reveal nodal involvement in a situation of high clinical suspicion, mediastinoscopy is indicated [I, A].

- Mediastinoscopy is the test with the highest negative predictive value to rule out mediastinal lymph node disease [I, A].

- For peripheral tumours without mediastinal involvement on CT or PET-CT, mediastinal staging is advised in case of no uptake of FDG by the primary tumour and/or a tumour size > 3 cm [II, C]

*Postmus 2017*

*Block MI, Tarrazzi FA. YSTCS. 2013;25(3):218-227.*
Step two: determine the stage

Algorithm for locoregional lymph node staging in patients with non-metastatic NSCLC.

CT and PET or PET-CT

- Mediastinal LNs negative
  - cN0 and peripheral tumour (outer third of the lung) and tumour ≤ 3 cm
  - Mediastinal LNs negative
    - Tissue confirmation: EBUS/EUC or VAM (B)
      - Mediastinal LNs negative
      - Multimodality treatment
        - Surgery

- Mediastinal LNs positive
  - Mediastinal LNs positive
  - Mediastinal LNs negative on EBUS/EUS
    - VAM (D)
      - Mediastinal LNs positive
      - Mediastinal LNs negative
### TNM 8th Edition: news in the T stage

**T1** split into three subgroups based on size (T1a < 1 cm; T1b > 1 cm to < 2 cm; T1c > 2 cm to < 3 cm).

**T2** (T2a > 3 cm to < 4 cm; T2b > 4 cm to < 5 cm). The T2 category was further enriched by adding the previous T3 classifiers, atelectasis/pneumonitis and/or involvement of main bronchus.

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>AJCC 7th</th>
<th>AJCC 8th</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1 cm</td>
<td>T1a</td>
<td>T1a</td>
</tr>
<tr>
<td>&gt;1-2 cm</td>
<td>T1a</td>
<td>T1b</td>
</tr>
<tr>
<td>&gt;2-3 cm</td>
<td>T1b</td>
<td>T1c</td>
</tr>
<tr>
<td>&gt;3-4 cm</td>
<td>T2a</td>
<td>T2a</td>
</tr>
<tr>
<td>&gt;4-5 cm</td>
<td>T2a</td>
<td>T2b</td>
</tr>
</tbody>
</table>

Note: If the tumour is associated with atelectasis or pneumonitis, it is T2a if lesion ≤ 4 cm or if tumour size cannot be measured; it is T2b if lesion > 4 cm, ≤ 5 cm.
Step two: determine the stage (TNM classification)

TNM 8th Edition: news in the T stage

**T3** (>5 cm to < 7 cm)

Invasion of the diaphragm was found to have a similar prognosis as other T4 tumours and has therefore been added to this category.

**T4** (>7 cm)

Invasion of the diaphragm was found to have a similar prognosis as other T4 tumours and has therefore been added to this category.

<table>
<thead>
<tr>
<th>Tumor size</th>
<th>AJCC 7th</th>
<th>AJCC 8th</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5 cm &lt; 7 cm</td>
<td>T2b</td>
<td>T3</td>
</tr>
<tr>
<td>&gt; 7 cm</td>
<td>T3</td>
<td>T4</td>
</tr>
<tr>
<td>Invasion of the diaphragm</td>
<td>T3</td>
<td>T4</td>
</tr>
</tbody>
</table>

IASLC 8th Edition Staging
Measurement of Tumour Size in Part-Solid Non-Mucinous Adenocarcinomas

- For part-solid tumours, the size of the invasive component should be used to assign the T category for clinical staging [III, A]

- Subsolid lesions need dedicated radiological expertise for evaluating the lung lesion composition [V, A].

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### Step two: determine the stage (TNM classification)

**TNM 8th Edition: news in the T stage**

**Lung Cancers with Multiple Sites of Involvement**

<table>
<thead>
<tr>
<th>Second Primary Lung Cancer</th>
<th>Separate Tumour Nodule (intrapulmonary metastasis)</th>
<th>Multifocal GG/L Nodules</th>
<th>Pneumonic-Type of Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging features</td>
<td>Two or more distinct masses</td>
<td>Typical lung cancer</td>
<td>Patchy areas of ground glass and consolidation</td>
</tr>
<tr>
<td></td>
<td>with imaging characteristics</td>
<td>(e.g. solid, spiculated)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>of lung cancer (e.g.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>spiculated)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathologic features</td>
<td>Different histotype or different morphotype by comprehensive histologic assessment</td>
<td>Distinct masses with the same morphologic features by comprehensive histologic assessment</td>
<td>Adenocarcinomas with prominent lepidic component (typically varying degrees of AIS, MIA, LPA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Same histologic features throughout (most often invasive mucinous adenocarcinoma)</td>
</tr>
<tr>
<td>TNM classification</td>
<td>Separate CTNM and pTNM for each cancer</td>
<td>Location of separate nodule relative to primary site determines if T3, T4 or M1a; single N and M</td>
<td>T based on highest T lesion with (#/m) indicating multiplicity; single N and M</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T based on size or T3 if in single lobe, T4 or M1a if in different ipsilateral or contralateral lobes; single N and M</td>
</tr>
<tr>
<td>Conceptual view</td>
<td>Unrelated tumours</td>
<td>Single tumour, with intrapulmonary metastasis</td>
<td>Separate tumours, albeit with similarities</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Single tumour, diffuse pulmonary involvement</td>
</tr>
</tbody>
</table>

(AIS, adenocarcinoma in situ; GG/L, ground glass/lepidic; LPM, lepidic-predominant adenocarcinoma; MIA, minimally invasive adenocarcinoma; p, pathologic; TNNM, tumour, node, metastasis.)
Step two: determine the stage (TNM classification)

Evaluation of the 7th and 8th editions of the AJCC/UICC TNM staging systems for lung cancer in a large North American cohort: survival curves among different T stages

Improvement in discriminatory ability appears mainly for the advanced stages.

Better discriminatory ability compared to the 7th edition.
Step two: determine the stage (TNM classification)

TNM 8th Edition: the N stage

Quantification of Nodal Disease (based on N of nodal stations involved)

- N1a: single station N1
- N1b: multiple station N1
- N2a1: single station N2 without N1 disease (skip metastasis)
- N2a2: single station N2 with N1 disease
- N2b: multiple station N2

IASLC 8th Edition Staging

The 5-year survival rates according to the cN and pN status

- cN0 60%  pN0 75%
- cN1 37%  pN1 49%
- cN2 23%  pN2 36%
- cN3 9%  pN3 20%
In the presence of a solitary metastatic lesion on imaging studies, including pleural and pericardial effusion, efforts should be made to obtain a cytological or histological confirmation of stage IV disease [IV, A].

<table>
<thead>
<tr>
<th>Distant metastasis</th>
<th>AJCC 7th</th>
<th>AJCC 8th</th>
</tr>
</thead>
<tbody>
<tr>
<td>No distant metastasis</td>
<td>M0</td>
<td>M0</td>
</tr>
<tr>
<td>Separate nodules in a contralateral lobe, pleural/pericardial nodules/effusion</td>
<td>M1a</td>
<td>M1a</td>
</tr>
<tr>
<td>Single extrathoracic metastasis in a single organ</td>
<td>M1b</td>
<td>M1b</td>
</tr>
<tr>
<td>Multiple extrathoracic metastases in one or several organs</td>
<td>M1b</td>
<td>M1c</td>
</tr>
</tbody>
</table>

Overall survival (OS) for subgroups of the M category of the 7th and 8th editions

Step two: determine the stage (TNM classification)

<table>
<thead>
<tr>
<th>Table 3. Staging and stage grouping UICC TNM 8 [79]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occult carcinoma</td>
</tr>
<tr>
<td>Stage 0</td>
</tr>
<tr>
<td>Stage IA</td>
</tr>
<tr>
<td>Stage IA1</td>
</tr>
<tr>
<td>Stage IA2</td>
</tr>
<tr>
<td>Stage IA3</td>
</tr>
<tr>
<td>Stage IB</td>
</tr>
<tr>
<td>Stage IIA</td>
</tr>
<tr>
<td>Stage IIB</td>
</tr>
<tr>
<td>Stage IIIA</td>
</tr>
<tr>
<td>Stage IIIB</td>
</tr>
<tr>
<td>Stage IIIC</td>
</tr>
<tr>
<td>Stage IVA</td>
</tr>
<tr>
<td>Stage IVB</td>
</tr>
<tr>
<td>Stage IV</td>
</tr>
<tr>
<td>Stage IVa</td>
</tr>
<tr>
<td>Stage IVb</td>
</tr>
</tbody>
</table>

TNM, tumour, node and metastasis; UICC, Union for International Cancer Control.

Overall survival by clinical stage according to the seventh (A) and the eighth edition

Goldstraw JTO 2016

The IASLC Lung Cancer Staging Project: A Renewed Call to Participation

Dorothy J. Giroux, MS, Paul Van Schil, MD, Hisao Asamura, MD, Ramón Rami-Porta, MD, Kari Chansky, MS, John J. Crowley, PhD, Valerie W. Rusch, MD, Kemp Kernstine, MD, PhD, on behalf of the International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee.
Step three: molecular profiling

Molecular alterations in lung adenocarcinoma

Target therapy vs Non Target Therapy


M Kris et al, JAMA 2014
EGFR tyrosine kinase inhibitors (TKIs) are established effective therapies in patients who have activating and sensitizing mutations in exons 18–21 of EGFR.

- Prevalence is around 10%–20% of a Caucasian population with adenocarcinoma but much higher in Asian population.
- Deletions in exon 19 and L858R substitution mutation in exon 21 are the most common mutations.
Step three: molecular profiling

EGFR

- EGFR mutation status should be systematically analysed in advanced non-squamous NSCLC[I, A].

- Molecular testing is not recommended in SCC, except in those rare circumstances when SCC is found in a never-, long-time ex- or light-smoker (<15 pack-years) [IV, A].

- Test methodology should have adequate coverage of mutations in exons 18–21, including those associated with resistance to some therapies [III, B].

- At a minimum, when resources or material are limited, the most common activating mutations (exon 19 deletion, exon 21 L858R point mutation) should be determined [I, A].

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Step three: molecular profiling

ALK

- Fusion genes involving ALK and a number of partners (most commonly EML4) account for around 2%–5% of lung adenocarcinomas. (Tsao, 2016)

- ALK driven adenocarcinoma is very sensitive to several ALK TKIs

First line treatment

**PROFILE 1014**

**ASCEND-4**

**J-ALEX**

**ALTA1**

Hida et al 2017

Soria et al 2017

Camidge et al 2018

Peters et al 2017
Step three: molecular profiling

ALK

- Testing for ALK rearrangement should be systematically carried out in advanced non-squamous NSCLC [I, A]

- ALK testing is not recommended in patients with a confident diagnosis of SCC, except in unusual cases, e.g. never/former light smokers or long-time ex-smokers [IV, A]

- Detection of the ALK translocation by FISH remains a standard, but IHC with high-performance ALK antibodies and validated assays may be used for screening [III, A] and have recently been accepted as an equivalent alternative to FISH for ALK testing.

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• ROS1 fusion genes are yet another addictive oncogenic driver that occurs in 1%–4% of the same testing population.

• Testing for ROS1 rearrangement should be systematically carried out in advanced NSCLC [III, A]. Detection of the ROS1 translocation by FISH remains a standard; IHC may be used as a screening approach [IV, A]

**Step three: molecular profiling ROS**

- **Crizotinib**
  - Shaw 2014

- **Ceritinib**
  - Sun Min Lim 2017

- **Entrectinib**
  - Doebele WCLC 2018
BRAF mutation testing is now required in many countries after the approval of BRAF and MEK inhibitors for BRAF V600-mutant NSCLC.

The V600E mutation is the most common of the BRAF V600 family and, overall, these BRAF mutations are found in 2% of cases.

BRAF V600 mutations appear mutually exclusive to EGFR and KRAS mutations, ALK and ROS1 rearrangements and are similarly much more common in adenocarcinoma.

BRAF V600 mutation status should be systematically analysed in advanced non-squamous NSCLC for the prescription of BRAF/MEK inhibitors [II, A].
Step three: molecular profiling
Walking to the future

BLU-667 in NSCLC with **RET fusion** Results from the ARROW phase I trial

Activity and Safety of Crizotinib in Patients with **MET Exon 14**-Altered Advanced NSCLC

- Targeting RET is not currently routinely recommended and recruitment into open trials is encouraged [III, C].

- Targeting HER2 dysregulation is not currently recommended and recruitment into open trials is encouraged [III, C].

- For METex14 variants recruitment into open trials is encouraged [III, C].
For many laboratories, testing for EGFR and BRAF mutations and ALK and ROS1 rearrangements involves individual standalone tests.

NGS of various sorts is rapidly being adopted as the standard approach to screening adenocarcinomas for oncogenic targets [III, A]

Whatever testing modality is used, it is mandatory that adequate internal validation and quality control measures are in place and that laboratories participate in, and perform adequately, external quality assurance schemes for each biomarker test [III, A].

Step three: molecular profiling

NGS

- Multiplexed genetic sequencing panels (e.g. NGS) are preferred over multiple singlegene tests to identify other treatment options beyond EGFR, ALK, and ROS1, however single gene assays are still acceptable.
- In addition to small mutations, NGS assays have the capability to detect fusions/rearrangements and copy number changes in the examined genes.
- NGS also enables the use of small specimens (e.g., fine needle aspirates) that are standard of care and help avoid the risks to the patient associated with obtaining surgical biopsies.
- When NGS is performed, several other genes are also recommended – BRAF, ERBB2, MET, RET, and KRAS. However, these genes are not essential when only single gene tests are performed.

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Step three: molecular profiling
Liquid biopsy

Liquid Biopsy for Advanced Non-Small Cell Lung Cancer (NSCLC): A Statement Paper from the IASLC.

No Recommendation: There is currently insufficient evidence to support the use of circulating cell-free plasma DNA (cfDNA) molecular methods for the diagnosis of primary lung adenocarcinoma.

Recommendation: In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cell-free plasma DNA (cfDNA) assay to identify EGFR mutations.

* EGFR, ALK, ROS1, and BRAF at minimum, but a panel if available

# Strongly suggest tissue sparing to facilitate participation in clinical trials

+ While NGS is preferred, based on availability, other validated assays are acceptable

Rollo C, JTO 2018
### Step three: molecular profiling

**Walking to the future: liquid biopsy**

<table>
<thead>
<tr>
<th>Tissue Biopsy</th>
<th>Liquid Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of complication</td>
<td>Least invasive or noninvasive.</td>
</tr>
<tr>
<td>High cost</td>
<td>Removes costs associated with procedure and complications.</td>
</tr>
<tr>
<td>Difficult tumor site</td>
<td>Blood, cerebrospinal fluid, or urine can be easily collected.</td>
</tr>
<tr>
<td>Specimens quality varies</td>
<td>More control over quantity and quality of specimen.</td>
</tr>
<tr>
<td>Lengthy turnaround time</td>
<td>Turnaround time is significantly less.</td>
</tr>
<tr>
<td>Tumor heterogeneity</td>
<td>Better captures the molecular state of tumours and metastases.</td>
</tr>
</tbody>
</table>

Goldman, *Ann Oncol* 2018

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**Incorporating blood-based liquid biopsy information into cancer staging: time for a TNMB system?**

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>Lymph Node</th>
<th>Metastasis</th>
<th>Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>B0</td>
</tr>
<tr>
<td>Tumor size/local invasion: no regional lymph node invasion. No distant metastasis. No cDNA mutations in blood.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>N1</td>
<td>M1</td>
<td>B1</td>
</tr>
<tr>
<td>Tumor size/local invasion: tumor spread to a single or small number of regional lymph nodes. Distant metastasis. cDNA mutations in blood. (Can be better defined with more detailed quantification in the future.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>N2</td>
<td>M2</td>
<td></td>
</tr>
<tr>
<td>Tumor size/local invasion: tumor spread to a single or small number of regional lymph nodes. Distant metastasis.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>N3</td>
<td>M3</td>
<td></td>
</tr>
<tr>
<td>Tumor of any size that invades to other organs.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Yang, *Ann Oncol* 2018
Step three: PD-L1 testing

Keynote 024 study showed that treatment naïve NSCLC patients with PD-L1 tissue proportion score (TPS) ≥ 50% had superior OS with pembrolizumab compared to chemotherapy.

- PD-L1 IHC should be systematically determined in advanced NSCLC [I, A]
- Testing is required for pembrolizumab therapy but may also be informative when nivolumab or atezolizumab are used [I, A]
- Other biomarkers, such as tumor mutational burden (TMB), are under investigation.
- Although TMB has been shown to be associated with immune checkpoint inhibitor efficacy and seems to be independent of PD-L1 staining, it remains experimental and is not routinely recommended outside of clinical trials.

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Reck et al, 2016

Kowanetz et al, 2017
Step four: beware of the time!

- Reducing time to treatment may improve survival above all for patients with early stage disease at diagnosis. *Gomez et al, Radiother Oncol. 2015*

- A multidisciplinary team approach has to be used to ensure the quality of care and to reduce delays in treatment. *Ost DE et al, Chest.2013*

- A close collaboration with pathologists is required to ensure a turnaround time for biomarker testing up to 10 working days. *Lindeman NI, Arch Pathol Lab Med. 2018*
Step five: choosing the best treatment

Stage IV NSCC

Molecular test
(ALK/GPR/ROS/EGFR)

PD-L1 expression

PD-L1 ≥ 50%

PD-L1 < 50%

Stage IV NSCC: Molecular tests negative (ALK/GPR/ROS/EGFR)

Any expression of PD-L1

< 70 years and PS 0-1

Selected ≥ 70 years and PS 0-2

Stage IV NSCC: Molecular tests positive (ALK/GPR/ROS/EGFR)

ALK translocation
(refer to Figure 5)

BRAF V600 mutation
(refer to Figure 7)

EGFR mutation
(refer to Figure 4)

ROST translocation
(refer to Figure 6)

Crizotinib [I; A; MCB5 4]
Alecinib [I; A; MCB5 4]
Ceritinib [I; B; MCB5 4]
Brigatinib [I; B]*

Dabrafenib/trametinib
[BRAF/MTAL; MCB5 2]

Gefitinib [I; A]
Erlotinib [I; A]
+/- bevacizumab [II; B; MCB5 3]*
Alatibin [I; A]
Moxatinib [I; A]*
Osimertinib [I; A]*
Gefitinib/carboplatin/pemetrexed [I; A]*

Crisitinib
[III; A; MCB5 3]

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Lung cancer... What’s next after diagnosis?

- Improved staging methods
- Appropriate diagnostic tests
- Tissue is still the tissue
- Growing exciting molecular information
- Tailoring the treatment
- Multidisciplinarity
What’s next after diagnosis: can we do it better?

- Solving the controversy between existing guidelines of evaluating the presence of brain metastases by brain magnetic resonance imaging (MRI)

- Overcoming some criticism of the 8th TNM edition (Van Schil et al, Ann Transl Med 2018):
  - Few prospective data (5.1%)
  - Study population mainly from Europe and Asia (insignificant participation from North America)
  - Few data on advanced metastatic disease

- Further analysis of prospective data and incorporation of detailed immunohistochemical information, biomarkers and mutational analysis will allow better refinement of prognostic categories.

- Current challenges as NGS represent an opportunity for a wide information: a close collaboration with pathologists is required to select patients and to interpret results.

- Simplify the access to treatment in the different health systems.
What’s next after diagnosis: drawing the strands together

• Improved staging methods and accurate characterization of microscopic disease allow the definition of a homogeneous group of patients with similar characteristics and tumor-related prognostic factors. Selecting appropriate diagnostic tests is crucial.

• Tissue preservation for molecular profiling is fundamental, particularly in advanced NSCLC. Non-invasive methods are emerging to overcome the potential limits of biopsies or aspirates.

• New technologies can provide relevant information for standard-of-care treatments and investigational ones. In this scenario biomarker selection and frontline strategies continue to evolve rapidly.

• Cooperation and a multidisciplinary approach is essential to maximize the efforts for a more efficient management of lung cancer from the diagnosis to the treatment.