Systemic chemotherapy and targeted treatment in metastatic NSCLC

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CIOCC Barcelona – HM Delfos

@JordiRemon
Outline

• Introduction

• Chemotherapy, where we come from?
  – Squamous
  – Non-squamous

• Oncogenic addicted
  – $EGFR$ mutation
  – $ALK$ rearranged
  – $ROS1$ rearranged
  – $BRAF$ mutation

Fortunately family is expanding!!!
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# Therapy-predictive biomarker test

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Method</th>
<th>Use</th>
<th>LoE, GoR</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR mutation</td>
<td>Any appropriate, validated method, subject to external quality assurance</td>
<td>To select those patients with EGFR-sensitising mutations most likely to respond to EGFR TKI therapy</td>
<td>I, A</td>
</tr>
<tr>
<td>ALK rearrangement</td>
<td>Any appropriate, validated method, subject to external quality assurance. FISH is the historical standard but IHC is now becoming the primary therapy-determining test, provided the method is validated against FISH or some other orthogonal test approach. NGS is an emerging technology.</td>
<td>To select those patients with ALK gene rearrangements most likely to respond to ALK TKI therapy</td>
<td>I, A</td>
</tr>
<tr>
<td>ROS1 rearrangement</td>
<td>FISH is the trial-validated standard. IHC may be used to select patients for confirmatory FISH testing but currently lacks specificity. NGS is an emerging technology. External quality assurance is essential</td>
<td>To select those patients with ROS1 gene rearrangements most likely to respond to ROS1 TKI therapy</td>
<td>II, A</td>
</tr>
<tr>
<td>BRAF mutation</td>
<td>Any appropriate, validated method, subject to external quality assurance</td>
<td>To select those patients with BRAF V600-sensitising mutations most likely to respond to BRAF inhibitor, with or without MEK inhibitor therapy</td>
<td>II, A</td>
</tr>
<tr>
<td>PD-L1 expression</td>
<td>IHC to identify PD-L1 expression at the appropriate level and on the appropriate cell population(s) as determined by the intended drug and line of therapy. Only specific trial assays are validated. Internal and external quality assurance are essential</td>
<td>To enrich for those patients more likely to benefit from anti-PD-1 or anti-PD-L1 therapy. For pembrolizumab, testing is a companion diagnostic for nivolumab and atezolizumab, testing is complementary</td>
<td>I, A</td>
</tr>
</tbody>
</table>

Planchard- Ann Oncol 2018
But family is expanding

2016

Mr. Target

Mr. CT

2020

Mr. Target ICI

Mr. CT

2040 CT in 16,4% of Lung Cancer pts

Data from MSK-IMPACT (Jordan et al.\textsuperscript{a}) and FoundationOne (Frampton et al.\textsuperscript{c}) panels (n = 5262)

2nd ESMO Consensus Conference on Lung Cancer: non-small-cell lung cancer first-line/second and further lines of treatment in advanced disease

B. Besse¹*, A. Adjei², P. Baas³, P. Meldgaard⁴, M. Nicolson⁵, L. Paz-Ares⁶, M. Reck⁷, E. F. Smit⁸, K. Syrigos⁹, R. Stahel¹⁰, E. Felip¹¹, S. Peters¹² & Panel Members†

Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

Updated 2019

D. Planchard¹, S. Popat², K. Kerr³, S. Novello⁴, E. F. Smit⁸, C. Faivre-Finn⁶, T. S. Mok⁷, M. Reck⁸, P. E. Van Schil⁹, M. D. Hellmann¹⁰ & S. Peters¹¹, on behalf of the ESMO Guidelines Committee*

Systemic Therapy for Stage IV Non–Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

Stage IV SCC

4-6 cycles of platinum-based CT is the SoC

- Platinum-based ChT:
  - Cisplatin/gemcitabine [I, A]
  - Cisplatin/docetaxel [I, A]
  - Cisplatin/paclitaxel [I, A]
  - Cisplatin/vinorelbine [I, A]
  - Carboplatin/gemcitabine [I, A]
  - Carboplatin/docetaxel [I, A]
  - Carboplatin/paclitaxel [I, A]
  - Carboplatin/vinorelbine [I, A]
  - nab-PC [I, B]

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

4-6 cycles

- Cisplatin/gemcitabine [I, A]
- Cisplatin/docetaxel [I, A]
- Cisplatin/paclitaxel [I, A]
- Cisplatin/vinorelbine [I, A]
- Carboplatin/gemcitabine [I, A]
- Carboplatin/docetaxel [I, A]
- Carboplatin/paclitaxel [I, A]
- Carboplatin/vinorelbine [I, A]
- Cisplatin/pemetrexed [II, A]
- Carboplatin/pemetrexed [II, B]
  - 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)
Chemotherapy vs. BSC

- N=2714
- 16 trials
- 9 with platin.
- 1 yr absolute benefit: 9% (20% to 29%).

HR=0.77 [0.71-0.83]  
\[p=0.0001\]  

NSCLC Meta-Analyses Collaborative Group JCO 08
Number of cycles

PFS: 4 vs 6 cycles of cisplatin-based CT
In non-PD patients after 2 cycles

6 cycles vs fewer of cisplatin-based CT
In non-PD patients after 2 cycles

No OS benefit of six versus fewer cycles of first-line chemotherapy

Park – JCO 2007
Soon – JCO 2009
Rossi – Lancet Oncol 2014
Cisplatin vs. Carboplatin: CISCA-MA

9 trials. N=2968

Response Rate
CIS 30%
CARBO 24%
OR = 1.37 (1.16-1.61)
P <0.001

Overall survival
HR = 1.07
IC 95% = 0.99 to 1.15
P = .100

Survival benefit with cisplatin in non-squamous and 3rd generation combos

Adrizzoni – JNCI 2007 * De Castria – Cochrane review 2013
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  – ROS1 rearranged
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## Squamous cell carcinoma

<table>
<thead>
<tr>
<th>Classification</th>
<th>Characteristics</th>
</tr>
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<tbody>
<tr>
<td><strong>Non-squamous</strong></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma (AC) 30–50%*</td>
<td>- Malignant epithelial tumors with glandular differentiation</td>
</tr>
<tr>
<td></td>
<td>- IASLC classification of invasive AC:²</td>
</tr>
<tr>
<td></td>
<td>- Lepidic, acinar, papillary, micropapillary, or solid pattern predominant</td>
</tr>
<tr>
<td></td>
<td>- Variants: invasive mucinous AC, colloid, fetal, and enteric</td>
</tr>
<tr>
<td>Large cell carcinoma 10%*</td>
<td>- Involves large cells (subtypes are giant cell, clear cell) with large nuclei</td>
</tr>
<tr>
<td></td>
<td>- No evidence of squamous or glandular differentiation</td>
</tr>
<tr>
<td><strong>Squamous</strong></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma 30%†</td>
<td>- Involves cells of the squamous epithelium</td>
</tr>
<tr>
<td></td>
<td>- Two variants of clinicopathologic significance³</td>
</tr>
<tr>
<td></td>
<td>- Papillary variant</td>
</tr>
<tr>
<td></td>
<td>- Basaloid variant</td>
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</table>
First-line chemotherapy in squamous

![Graphs showing overall survival over months for different chemotherapy regimens in 2001, 2002, and 2002.]

<table>
<thead>
<tr>
<th>Study arm</th>
<th>OS (mo)</th>
<th>1 year (%)</th>
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</thead>
<tbody>
<tr>
<td>PCB</td>
<td>8.6</td>
<td>38</td>
</tr>
<tr>
<td>CV</td>
<td>8.1</td>
<td>36</td>
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</table>

Kelly et al. J Clin Oncol 2001

<table>
<thead>
<tr>
<th>Study arm</th>
<th>OS (mo)</th>
<th>1 year (%)</th>
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<tbody>
<tr>
<td>PC</td>
<td>7.8</td>
<td>31</td>
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<tr>
<td>GC</td>
<td>8.1</td>
<td>36</td>
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<tr>
<td>DC</td>
<td>7.4</td>
<td>31</td>
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<tr>
<td>PCB</td>
<td>8.1</td>
<td>34</td>
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<table>
<thead>
<tr>
<th>Study arm</th>
<th>OS (mo)</th>
<th>1 year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCB</td>
<td>9.9</td>
<td>43</td>
</tr>
<tr>
<td>GC</td>
<td>9.8</td>
<td>37</td>
</tr>
<tr>
<td>CV</td>
<td>9.5</td>
<td>37</td>
</tr>
</tbody>
</table>


Courtesy of Prof. Besse
Nab-paclitaxel in NSCLC

**First-line**
Stage IV
ECOG PS 0-2

**EndPoint:** ORR
N=1052

**Paclitaxel 100 mg/m² Q3W**
**CBDCA (AUC=6) Q3W**

**RR in SCC:** 41% vs. 24%, p < 0.001

**Nab-Paclitaxel 100 mg/m² QW**
**CBDCA (AUC=6) Q3W**

**Maximum of 6 cycles**

**RR in SCC:** 41% vs. 24%, p < 0.001

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**Events/N**

<table>
<thead>
<tr>
<th>nab-PC</th>
<th>sb-PC</th>
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</thead>
<tbody>
<tr>
<td>nab-PC</td>
<td>sb-PC</td>
</tr>
<tr>
<td>Events/N</td>
<td>HR</td>
</tr>
<tr>
<td>----------</td>
<td>----</td>
</tr>
<tr>
<td>639/896</td>
<td>0.999</td>
</tr>
<tr>
<td>105/156</td>
<td>0.583</td>
</tr>
<tr>
<td>343/450</td>
<td>0.890</td>
</tr>
<tr>
<td>401/602</td>
<td>0.950</td>
</tr>
</tbody>
</table>

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Socinski – JCO 2012 * Socinski – Ann Oncol 2013

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IO + Chemotherapy in Squamous

**KEYNOTE 407**

- **Key Eligibility Criteria**
  - Untreated stage IV NSCLC with squamous histology
  - ECOG PS 0 or 1
  - Provision of a sample for PD-L1 assessment
  - No symptomatic brain metastases
  - No pneumonitis requiring systemic steroids

- **Stratification Factors**
  - PD-L1 expression (TPS>1% vs <1%)
  - Choice of taxane (paclitaxel vs nab-paclitaxel)
  - Geographic region (east Asia vs rest of world)

- **End points**
  - Primary: PFS (RECURIST v1.1, BICR) and OS
  - Secondary: ORR and DOR (RECURIST v1.1, BICR), safety

- **Optional Crossover**
  - Pembrolizumab 200 mg Q3W for up to 35 cycles

- **N=559**

- **Results**
  - 31.7% Crossover

**IMPOWER 150**

- **Stage IV squamous NSCLC**
  - Chemotherapy naïve
  - ECOG PS 0 or 1
  - Any PD-L1 IHC status
- **Stratification factors**
  - Sex
  - PD-L1 IHC expression
  - Liver metastases

- **N=1021**

- **Co-primary endpoints**
  - TC0/IC0: 50%
  - TC3/IC3: 16%

- **Secondary endpoints**
  - PFS and OS in PD-L1 subgroups
  - ORR, DOR, safety

**Results**

- **OS: 12 months → 17 months**
- **Negative Trial OS: 13.5 mo. → 14.2 mo.**
- **TC3/IC3: 23.4 mo. vs. 10.2 mo., HR 0.48**

Paz-Ares – NEJM 2018

Cappuzzo – WCLC 2019
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Histology for treatment selection

1st L advanced NSCLC, mOS: ~ 8 mo
Cis/Pem vs. Cis/Gem (6 cycles)

All NSCLC patients (N=1725)

Non-squamous histology (N=1000, ADC+LCC) → Pemetrexed better

ADC histology (N=847): 12.6 vs. 10.9

Non inferiority. End Point: OS

Scaglioni- JCO 2008 * Li – PlosOne 2012
E4599: Bevacizumab pivotal phase III trial

Previously untreated stage IIIB, IV non-squamous NSCLC n=878

R 1:1

CP q3w x 6 (n=444)

BVZ (15mg/kg) + CP q3w x 6 (n=434)

Primary endpoint: OS

In ADC histology mOS: + 3.9 mo. (14.2 vs. 10.3)

HR (95% CI) 0.69 (0.58 to 0.83)

CP = carboplatin/paclitaxel. AUC=6 / 200 mg/m² Q3W

Sandler - NEJM 2006
AVAiL: Ph III Cis/Gem +/- Bevacizumab

Previously untreated, stage IIIB or IV, non-squamous NSCLC, PS 0–1 (n=1,043)

R 1:1

Up to 6 cycles

Gemcitabine + cisplatin + bevacizumab 7.5-15mg/kg q3w

bevacizumab 7.5 - 15mg/kg q3w

Treat to PD

No crossover allowed

Gemcitabine + cisplatin + placebo 7.5-15mg/kg q3w

Placebo 7.5 - 15mg/kg q3w

Treat to PD

Primary endpoint: OS amended to PFS

PFS BVZ 7.5 mg/kg vs. Placebo: 6.7 vs. 6.1, HR 0.75
PFS BVZ 15 mg/kg vs. Placebo: 6.5 vs. 6.1, HR 0.82

Bevacizumab: pooled analysis

Great effect in OS in ADC vs. others (p=0.02)
BRAIN: phase II trial of bevacizumab in patients with CNS metastases

Stage IV non-squamous NSCLC with untreated asymptomatic brain metastases (n=66)

Bevacizumab 15 mg/kg q3w + paclitaxel + carboplatin

6 cycles

First-line Pac + Carbo + Bev \(\rightarrow\) Bev

(n=67)

Summary of response rates for primary tumours and metastases (% and 95% CI; n=67) for Pac + Carbo + Bev \(\rightarrow\) Bev

Besse, Clin Cancer Res 2015
Pemetrexed: maintenance JMEN trial

- Stage IIIB/IV NSCLC*
- ECOG PS 0–1
- 4 prior cycles of gemcitabine, docetaxel or taxane plus cisplatin or carboplatin
- Prior Pemetrexed excluded

Non-PD (N=663)

- Pemetrexed 500mg/m² Q3W (n=441)
- Placebo# (n=222)

Primary endpoint: PFS

OS

PFS 4.3 vs. 2.6, HR 0.50 (0.42-0.61), p<0.0001

*ADC 50%, squamous 26%. #Only 18% received Pemetrexed at PD.

Ciuleanu – Lancet 2009
Pemetrexed maintenance: PARAMOUNT

**Induction Therapy**
- 4 cycles, Q21d

**Continuation Maintenance Therapy**
- Q21d until PD

- Pemetrexed + BSC
- Placebo + BSC

**Pemetrexed + Cisplatin**

CR/PR/SD per RECIST

R 2:1

- Previously untreated
- PS 0/1
- Stage IIIB-IV
- Stable Brain Mets
- NonSq-NSCLC

**Primary endpoint:** OS

Paz-Ares - JCO 2013
Pemetrexed maintenance: PARAMOUNT

PFS
Pemetrexed: median = 4.4 mos (4.1 to 5.7 mos)
Placebo: median = 2.8 mos (2.6 to 3.0 mos)
Log-rank $P < .001$
Unadjusted HR: 0.60 (0.50 to 0.73)

OS
Pemetrexed: median = 13.9 mos (12.8 to 16.0 mos)
Placebo: median = 11.0 mos (10.0 to 12.5 mos)
Log-rank $P = .0195$
Unadjusted HR: 0.78 (0.64 to 0.96)

OS maintenance pemetrexed: 13.9 months

Paz-Ares - JCO 2013
Double maintenance: AVAPERL

First-line induction
4 cycles, q3w

Continuation maintenance
q3w until PD

Bevacizumab
n=125

Bevacizumab + pemetrexed
n=128

Follow-up

Previously untreated stage IIIB–IV non-squamous NSCLC
n=376

Stratification factors
- Gender
- Smoking status
- Response at randomisation

CR/PR/SD per RECIST

R: 1:1

n=253
Double maintenance: AVAPERL

PFS from induction

10.2 months vs. 6.6 months
HR 0.58 (0.45-0.76); P <0.0001

OS from induction

19.8 months vs. 15.9 months
HR, 0.88 (0.64-1.22); P <0.32

Barlesi - Annals Oncol 2014
No OS benefit with 2 drugs as maintenance

**POINTBREAK**

**ECOG-ACRIN 5508**

**COMPASS (WJOG 5610L)**

Maintenance treatment with monotherapy (pemetrexed or BVZ) is SoC

2nd L: Nintedanib and Ramucirumab

**LUME-Lung1**
N=1314 (SQ ~42%)

PFS - Docetaxel +/- nindetanib (VEGFR TKI)

- **D+N** - Med PFS 3.4 m [95% CI 2.9–3.9]
- **D+PL** - Med PFS 2.7 m [2.6–2.8]
- HR = 0.79 [95% CI 0.68–0.92], p=0.0019

Previous BVZ: 4%
Never smoker: 24%

**OS benefit in ADC:** 12.6 vs. 10.3 (p=0.036)

**OS benefit in ADC / 9 mo:** 10.9 vs. 7.9 (p=0.0073)

**Not OS benefit in whole:** 10.1 vs 9.1 (p=0.272)

---

**REVEL**
N=1253 (~25% SQ)

OS - Docetaxel +/- ramucirumab (VEGFR2 Ab)

- Median (95% CI)
  - **RAM+DOC**
    - 10.5 (9.5-11.2)
  - **PL+DOC**
    - 9.1 (8.4-10.0)
- HR (95% CI) = 0.86 (0.75-0.98)
  - log-rank P = .023

Previous BVZ: 14%
Never smoker: 17%

**OS benefit in SCC and non SCC (HR 0.83)**

**PFS:** 4.5 vs. 3.0 (HR 0.76, p<0.001)

ICI 2nd Line NSCLC, still valid options?

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>PFS / OS (months)</th>
<th>HR OS</th>
<th>G ≥ 3 AE'S</th>
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</thead>
<tbody>
<tr>
<td>KEYNOTE 010</td>
<td>1034</td>
<td>Pembrolizumab</td>
<td>3,9</td>
<td>10,4</td>
</tr>
<tr>
<td></td>
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<td>Docetaxel</td>
<td>4,0</td>
<td>8,5</td>
</tr>
<tr>
<td>Check Mate 057</td>
<td>582</td>
<td>Nivolumab</td>
<td>2,3</td>
<td>12,2</td>
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<tr>
<td>All comers</td>
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<td>Docetaxel</td>
<td>4,2</td>
<td>9,4</td>
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<tr>
<td>Non-Squamous</td>
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<td>Check Mate 017</td>
<td>272</td>
<td>Nivolumab</td>
<td>3,5</td>
<td>9,2</td>
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<td>All comers</td>
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<td>Docetaxel</td>
<td>2,8</td>
<td>6</td>
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<tr>
<td>Squamous</td>
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<tr>
<td>OAK</td>
<td>1225</td>
<td>Atezolizumab</td>
<td>2,7</td>
<td>13,3</td>
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<tr>
<td>All comers</td>
<td></td>
<td>Docetaxel</td>
<td>3,8</td>
<td>9,6</td>
</tr>
</tbody>
</table>

JAVELIN Lung 200, avelumab no OS benefit vs. docetaxel (11.4 vs. 10.3) in PD-L1 positive NSCLC

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  – $BRAF$ mutation
**EGFR mutant NSCLC patients 2018**

![Barlesi – Lancet Oncol 2016 * Planchard – Ann Oncol 2018](image)

**EGFR mutation** (refer to Figure 4)

- Gefitinib \([I, A]\)
- Erlotinib \([I, A]\)
- +/- bevacizumab \([II, B; MCBS 3]^a\)
- Afatinib \([I, A]\)
- Dacomitinib \([I, A]^b\)
- Osimertinib \([I, A]^b\)
- Gefitinib/carboplatin/pemetrexed \([I, A]^b\)

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

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<table>
<thead>
<tr>
<th>Trial</th>
<th>TKI</th>
<th>Comparing Tx</th>
<th>ORR %</th>
<th>PFS (months)</th>
<th>HR</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPASS</td>
<td>Gefitinib</td>
<td>Cb/Pac</td>
<td>71 v 47</td>
<td>9.5 v 6.3</td>
<td>0.48 (0.36-0.64)</td>
<td>21.6 v 21.9</td>
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<tr>
<td>First-Signal</td>
<td>Gefitinib</td>
<td>Cis/Gem</td>
<td>55 v 46</td>
<td>8.0 v 6.4</td>
<td>0.54 (0.26-1.10)</td>
<td>27.2 v 25.6</td>
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<tr>
<td>WJTOG</td>
<td>Gefitinib</td>
<td>Cis/Doc</td>
<td>62 v 32</td>
<td>9.2 v 6.3</td>
<td>0.49 (0.34-0.71)</td>
<td>34.9 v 37.3</td>
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<td>NEJ002</td>
<td>Gefitinib</td>
<td>Cb/Pac</td>
<td>74 v 31</td>
<td>10.8 v 5.4</td>
<td>0.35 (0.22-0.41)</td>
<td>30.5 v 23.6</td>
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<tr>
<td>OPTIMAL</td>
<td>Erlotinib</td>
<td>Cis/Gem</td>
<td>83 v 36</td>
<td>13.1 v 4.6</td>
<td>0.16 (0.10-0.26)</td>
<td>22.8 v 27.2</td>
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<td>EURTAC</td>
<td>Erlotinib</td>
<td>Cis/Doc or Gem</td>
<td>58 v 15</td>
<td>10.4 v 5.1</td>
<td>0.34 (0.23-0.29)</td>
<td>19.3 v 19.5</td>
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<tr>
<td>LUX-Lung 3</td>
<td>Afatinib</td>
<td>Cis/Pem</td>
<td>62 v 22</td>
<td>13.6 v 6.9</td>
<td>0.47 (0.34-0.65)</td>
<td>31.6 v 28.2</td>
</tr>
<tr>
<td>LUX-Lung 6</td>
<td>Afatinib</td>
<td>Cis/Gem</td>
<td>68 v 23</td>
<td>11.0 v 5.6</td>
<td>0.25 (0.20-0.39)</td>
<td>23.6 v 23.5</td>
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<tr>
<td>LUX-Lung 7</td>
<td>Afatinib</td>
<td>Gefitinib</td>
<td>70 v 56</td>
<td>11.0 v 10.6</td>
<td>0.74 (0.57-0.95)</td>
<td>27.9 v 24.5</td>
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<tr>
<td>ARCHER 1050</td>
<td>Dacomitinib</td>
<td>Gefitinib</td>
<td>75 v 76</td>
<td>14.7 v 9.2</td>
<td>0.59 (0.47-0.74)</td>
<td>34.1 v 26.8</td>
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<td>FLAURA*</td>
<td>Osimertinib</td>
<td>Gefitinib/ Erlotinib</td>
<td>80 v 76</td>
<td>18.9 v 10.2</td>
<td>0.46 (0.37-0.57)</td>
<td>38.6 v 31.8</td>
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<td>NEJ 026</td>
<td>Erlotinib / BVZ</td>
<td>Erlotinib</td>
<td>72 v 67</td>
<td>16.9 v 13.3</td>
<td>0.60 (0.42-0.88)</td>
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<td>ARTEMIS</td>
<td>Erlotinib / BV.</td>
<td>Erlotinib</td>
<td>86 v 85</td>
<td>18.0 v 11.3</td>
<td>0.55 (0.41-0.75)</td>
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<td>RELAY*</td>
<td>Erlotinib / Ramuc.</td>
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<td>76 v 77</td>
<td>19.4 v 12.4</td>
<td>0.59 (0.46-0.76)</td>
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<td>NEJ009</td>
<td>Gefitinib /CG</td>
<td>Gefitinib</td>
<td>84 v 67</td>
<td>20.9 v 11.2</td>
<td>0.49 (0.39-0.62)</td>
<td>52.2 v 38.8</td>
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<td>Norohona*</td>
<td>Gefitinib /CG</td>
<td>Gefitinib</td>
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<td>16.0 v 8.0</td>
<td>0.51 (0.39-0.66)</td>
<td>NR v 17.0</td>
</tr>
</tbody>
</table>

*End point by investigator

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The best, first....FLAURA Trial

**Patients with locally advanced or metastatic NSCLC**

**Key inclusion criteria**
- ≥18 years
- WHO performance status 0 / 1
- Exon 19 deletion / L858R (enrolment by local or central EGFR testing)
- No prior systemic anti-cancer / EGFR-TKI therapy
- Stable CNS metastases allowed

**Stratification by mutation status (Exon 19 deletion / L858R) and race (Asian / non-Asian)**

**Osimertinib** (80 mg p.o. qd) (n=279)

Randomised 1:1

EGFR-TKI SoC:
- Gefitinib (250 mg p.o. qd) or
- Erlotinib (150 mg p.o. qd) (n=277)

**PFS**

- Osimertinib
- Comparator EGFR-TKI

**OS**

- Osimertinib
- Comparator EGFR-TKI

Soria – NEJM 2018 * Ramalingam – NEJM 2019
### Antiangiogenic and EGFR TKI 1st line

<table>
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<tr>
<th>Treatment</th>
<th>N</th>
<th>RR (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
<th>AE Gr 3 (%)</th>
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<td>72% vs 54%</td>
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</table>

*BM allowed. # PFS by BIRC

**Is there any ethnicity influence?**

**EGFR TKI and CT**

**NEJ009 Trial**

- Non-squamous NSCLC
- Previously untreated stage IIIb, IV, recurrence
- 20-75 years old
- PS 0-1
- Positive EGFR mutation

Stratified by sex, stage, type of EGFR mutation, and smoking history

~25% Brain Mets.

**Induction Phase**

- Gefitinib (daily)
- Carboplatin + Pemetrexed (4-6 cycles, q21d)
- Repeat until PD

**Maintenance Phase**

- Gefitinib (daily)
- Pemetrexed (q21d)
- Continue until PD

**Platinum-based regimen**

*Recommended by the protocol

**Indian Trial**

**Primary Endpoint: PFS by investigator**

**Eligibility Criteria**

- Age > 18 yrs
- Histologic/cytologic NSCLC
- Stage IIIB not amenable to radical therapy or Stage IV
- First-line palliative intent
- Activating EGFR mutation (exon 19/21/18)
- ECOG PS 0 to 2
- Adequate organ function
- No h/o ILD, radiation pneumonitis that required steroids or IPF

**Stratify**

- ECOG PS (0/1 v.2)
- EGFR mutation (exon 19 v. other)

**Randomized 1:1 Open Label**

- Gefitinib 250mg daily

- Gemcitabine 1000mg/m2 i.v. bolus d1, d8 + Cisplatin 75mg/m2 i.v. bolus d1
d2, d8

**Duration of Therapy**: until PD, unacceptable toxicity or consent withdrawal.

**Evaluation**: Clinical- Q 3 wks in Gef + C (pre-chemo), Q 2mth (gef); Radiologic-Q 2-3 mth

- 21% ECOG 2
- 18% BM
- ~5% uncommon *EGFR* mut.

**EGFR TKI and CT**

**NEJ009 Trial**

**PFS**
- RR: 84% vs. 67.5%, G ≥ 3 AEs: 65% vs. 31%
- HR: 0.494, 0.391-0.625, p<0.001
- Median (95%CI): Gefitinib 11.2 m (8.0-13.4) vs. Gefitinib+CBDCA+PEM 20.9 m (18.0-24.0)

**OS**
- Median (95%CI): Gefitinib 38.8 m (31.1-50.8) vs. Gefitinib+CBDCA+PEM 44.0-NA
- HR: 0.695, 0.520-0.927, p=0.013

**Indian Trial**

- 16 mo. vs. 8.0 mo. HR 0.51
- NR vs. 17.0 mo. HR 0.51
- RR: 75% vs. 62%, p=0.01. G ≥ 3 AEs: 75% vs. 49%, p<0.001
Outstanding PFS ~ 15-20 months

- Afatinib
- Erlotinib
- Gefitinib
- Icotinib
- Dacomitiib
- E+ BVZ / Ram.
- Osimertinib
- Gefitinib + CT

~7 mo.

Median PFS with 2nd G ALK TK ~35 months
Clinical & Molecular Heterogeneity of Acquired Resistance

Diverse Clinical Patterns of Progression

TREATMENT BEYOND PROGRESSION

- Erlotinib beyond PD: PFS for 3.9 mo.

TREATMENT BEYOND PROGRESSION + LOCAL THERAPIES

ASPIRATION study

PFS 1: 11 months
PFS 2: 14.9 months

Gandara - Clinical Lung Cancer 2014
Park - JAMA Oncol 2016
Weickhardt – J Thorac Oncol 2012
Clinical & Molecular Heterogeneity of Acquired Resistance

Diverse Molecular Mechanisms of Acquired Resistance

AURA 3

RR: 71% vs. 31%, p<0.001

Median PFS, months (95% CI)
Osimertinib 10.1 (8.3, 12.3)
Platinum-pemetrexed 4.4 (4.2, 5.6)

HR (95% CI) 0.30 (0.23, 0.41) p<0.001

60% cross over to osimertinib


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Switch to chemotherapy

**IMPRESS Phase III Trial**

- PD on Gefitinib by RECIST criteria
- Measurable stage IIIB / IV disease
- ECOG 0-1
- **activating EGFR mutations**

N=265

1:1 randomisation

Gefitinib + Cisplatin / Pem
Max 6 cycles
→ Gefitinib until PD

Placebo + Cisplatin / Pem
Max 6 cycles
→ Placebo until PD

**PFS:** 5.4 vs. 5.4
HR 0.86, p=0.273

**OS:** 13.4 vs. 19.5
HR 1.44, p=0.016

Soria – Lancet Oncol 2015 * Mok – JCO 2017
Outline

• Introduction

• Chemotherapy, where we come from?
  – Squamous
  – Non-squamous

• Oncogenic addicted
  – EGFR mutation
  – ALK rearranged
  – ROS1 rearranged
  – BRAF mutation
ALK rearranged NSCLC patients 2018

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

ALK translocation
(refer to Figure 5)

Crizotinib [I, A; MCBS 4]
Alectinib [I, A; MCBS 4]
Ceritinib [I, B; MCBS 4]
Brigatinib [I, B]

PROFILE 1014: Crizot. vs. CT

ALEX: Alectinib vs. Crizot.

J-ALEX: Alectinib vs. Crizot.

ALESIA: Alectinib vs. Crizot.

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2nd vs. 1st Generation ALK TKI

ALEX TRIAL  Alectinib vs. Crizotinib. Brain MRI/8w

ALTA1L TRIAL  Brigatinib vs. Crizotinib. Brain MRI/8w

Based on longer PFS and better intracranial RR, 2nd Generation ALK TKI (Alectinib) are the preferred option

icRR w/o RT (N=29): 79% vs. 40%
icRR (N=41): 78% vs. 26%
icPFS (N=96): 24 mo. vs. 5.6 mo.
Pending trials in 1st line setting

**EXALT3**

Advanced NSCLC, ALK+. PS 0-2. Asymptomatic CNS allowed
NCT02767804

Primary End Point: PFS

- Crizotinib 250 mg BID
- Ensartinib X-396 225 mg QD

N=402

PD
Toxicity
Or death

*Ensartinib phase I/II in ALK TKI-naïve patients: RR 80%, PFS 26.2 mo.

**CROWN**

Advanced NSCLC, ALK+
Asymptomatic CNS allowed
PS 0-2
NCT03052608

Primary End Point: PFS

- Crizotinib 250 mg BID
- Lorlatinib 100 mg QD

N=280

PD
Toxicity
Or death

*Lorlatinib phase II in ALK TKI-naïve patients (N=30): RR 90%, PFS Not reached.

Horn – CCR 2018 * Salomon – WCLC 2017
Understanding the resistance

Crizotinib
1st line

Next Gen.
1st line

Gainor – Cancer Disc 2016 (Courtesy of Prof. Besse, modified)
Ph III trials in crizotinib pretreated

ASCEND-5 (ceritinib) phase 3 study:
Primary Endpoint PFS by BICR

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<tr>
<th>Treatment</th>
<th>Median PFS (mo)</th>
<th>Events, n (%)</th>
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<td>Ceritinib 750 mg</td>
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<td>83 (72.2)</td>
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<tr>
<td>Chemotherapy</td>
<td>1.6 (1.4, 2.8)</td>
<td>89 (76.7)</td>
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</table>

HR 0.49 [95% CI 0.36, 0.67]; p<0.001

RR by BIRC 39.1% vs 6.9%

ALUR (alectinib) phase 3 study:
Primary Endpoint PFS by BICR

- Alectinib: Median 9.6 months [95% CI: 6.9–12.2]
- Chemotherapy: Median 1.4 months [95% CI: 1.3–1.6]

Post-crizotinib OS in phase II clinical trials with: Alectinib: 29 mo., and Brigatinib: 34 mo.

Ou – lung Cancer 2020 * Huber – JTO 2019 (Slide courtesy of Dr. Reguart, modified)
Are 2\textsuperscript{nd} G ALK TKI active after failure of a prior 2\textsuperscript{nd} G ALK TKI

Before ALEX Trial

1\textsuperscript{st} generation TKI
- crizotinib

2\textsuperscript{nd} generation TKI
- ceritinib
- alectinib
- brigatinib

Slide courtesy of Dr Shaw – ELCC 2019 (modified)
After 2\textsuperscript{nd} generation ALK TKI…

Alectinib $\rightarrow$ Brigatinib (N=22)

- RR 17%. PFS 4.4 mo.

- 17 patients $\geq$ 2 ALK TKI
- No efficacy in G1202R
- Post brigatinib, lorlatinib

Alectinib $\rightarrow$ Ceritinib (N=20)
ASCEND-9 phase II Trial

- RR 20%. PFS 3.7 mo.

Lin – JTO 2018
Remon – Clin Transl Oncol 2020
Hida- Cancer Sci 2018
3rd G ALK TKI active after failure of 2nd G ALK TKI

1st generation TKI
- crizotinib

2nd generation TKI
- ceritinib
- alectinib
- brigatinib

3rd generation TKI
- lorlatinib

2nd generation TKI
- ceritinib
- alectinib
- brigatinib

3rd generation TKI
- lorlatinib

Slide courtesy of Dr Shaw – ELCC 2019 (modified)
Lorlatinib after 2nd G ALK TKI

EXP3B (Non-crizotinib TKI +/- CT) N=28

RR: 32%. PFS 5.5 mo. icRR: 56%

EXP4 (2 ALK TKI +/- CT) + EXP5 (3 ALK TKI +/- CT) N=111

RR: 39%. PFS 6.9 mo. icRR: 53%

EXP 3-5: RR / icRR according to last ALK TKI: Alectinib (37%/43%), Ceritinib (40%/54%), Brigatinib (38%/40%)

Solomon – WCLC 2017 * Solomon – Lancet Oncol 2018
Outline

• Introduction

• Chemotherapy, where we come from?
  – Squamous
  – Non-squamous

• Oncogenic addicted
  – EGFR mutation
  – ALK rearranged
  – ROS1 rearranged
  – BRAF mutation
Clinicopathologic characteristics \textit{ROS1}

N=62 \textit{ROS1} NSCLC
(validation cohort of 166 \textit{ROS1} by FoundationOne)

\textit{ROS1} rearrangements are generally mutually exclusive with oncogenic drivers alterations
(Some \textit{EGFR} mutations coexist with \textit{ROS1})

\textbf{EGFR / TP53 (~60%) ALK / TP53 (~24%) ROS1 / TP53 (~9%)}

worse prognosis

Crizotinib / Entrectinib in ROS1 NSCLC

**Profile 1001 update**

N=53
13%, 0 prior regimens. BM not reported

ORR: 72%. PFS: 19.3 mo. mOS: 51 mo.

**Entrectinib**

N=53 (32%, 0 prior regimens. 43% BM)

RR: 77%. PFS: 19 mo. 1y OS: 85%
PFS w/o BM: 26.3 mo.
icRR: 55%. DoR: 12.9 mo.

FDA approval for ROS1 NSCLC and NTRK tissue-agnostic on 25th August 2019

Crizotinib approved for ROS1 NSCLC by FDA (11 March 2016) and EMA (21 July 2016)

Lorlatinib in **ROS1**

**Crizotinib pre treated (N=34)**
- 66% Crizotinib
- 6% Crizotinib + Ceritinib

**Lorlatinib in whole population (N=47).**
- ORR: 36%. PFS: 9.9 mo.

**Crizotinib naïve (N=13)**
- ORR: 27%. PFS: 8.5 mo.
  - Ic-RR: 53%. 6-mo ic-DOR: 60%

- ORR: 62%. PFS: 21 mo.
  - Ic-RR: 67%. 6-mo ic-DOR: 50%

**Not preclinical and clinical efficacy in ROS1 G2032R mutation**

Besse – ESMO 2017 *Ou – WCLC 2018 * Solomon – ESMO 2018
Outline

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**BRAF mutation**

**Europe¹**
All histology (Biomarkers France) 
(n = 9,911)

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR (sensitizing)</td>
<td>9.5%</td>
</tr>
<tr>
<td>EGFR (resistance)</td>
<td>0.8%</td>
</tr>
<tr>
<td>HER2</td>
<td>0.9%</td>
</tr>
<tr>
<td>UKN/Other</td>
<td>53.8%</td>
</tr>
<tr>
<td>KRAS</td>
<td>27%</td>
</tr>
<tr>
<td>BRAF</td>
<td>1.7%</td>
</tr>
<tr>
<td>ALK</td>
<td>3.7%</td>
</tr>
<tr>
<td>PI3K</td>
<td>2.6%</td>
</tr>
</tbody>
</table>

Most common **BRAF mutations in NSCLC**

Pathway and drugs

**BRAF** shorter OS compared wt. **BRAF**V600E “CDDP-resistant”

Dabrafenib and trametinib in BRAF$^{V600E}$ mutation

2nd Line (BRF113928, cohort B)

40 BRAF$^{V600E}$ NSCLC
ORR: 63%

PFS: 10.2 mo.  OS: 18.2 mo.
(investigator assessed)

1st Line (BRF113928, cohort C)

36 BRAF$^{V600E}$ NSCLC
ORR: 64%

PFS: 10.9 mo.  OS: 24.6 mo.
(investigator assessed. PFS 14.6 by BICR)

FDA and EMA approved

SEOM/SEAP Biomarkers guideline

Non-small cell lung carcinomas (advanced stage)

Squamous cell carcinomas
- Never- or light-smokers or < 50 years-old

Non-squamous cell carcinomas
(AC, tumors with an AC component or tumors where an AC cannot be reasonably excluded)

PD-L1 expression

EGFR mutation

ALK rearrangement

ROS1 rearrangement

BRAF V600E mutation

Garrido – Clin Transl Oncol 2019
Genomic profiling and agnostic approvals

Gainor – ASCO 2019 * Hyman – ASCO 2017
**RET-altered cancers**

Non-small cell lung cancer (2%)
- Thyroid cancers (10–20%)
- Pancreatic cancer (<1%)
- Salivary gland cancer (<1%)
- Spitz tumors (<1%)
- Colorectal cancer (<1%)
- Ovarian cancer (<1%)
- Myeloproliferative disorders (<1%)
- Many others (<1%)

**KIF5B** (most common in lung cancer)
GGCC6 or NCOA4 (most common in thyroid cancer)

**Dimerization domain**

**NSCLC**: 0.9%–1.8% as a whole to 6%–14% in WT ADK

IHQ not reliable RT-PCR

Specific RET TKI: BLU667 and LOXO 292

**BLU667: ARROW, part 2 Expansion**

N=120 NSCLC (40 CDDP-naïve, 40% BM)

- **RR:** 58% (60% Prior Platinum)
- **PFS:** not reached. ic-RR 78% (7/9)
- TKI-naïve (N=7): RR 71%

**LOXO 292: LIBRETTO-001, Phase I/II**

N=105 NSCLC (35% BM). 160 mg BD

- N=39 TKI-naïve (18% BM)
- **RR:** 68%
- **PFS:** 18.4. ic-RR 91% (10/11)
- TKI-naïve: RR 85%. PFS: NR

Gainor – ASCO 2019 * Drilon – WCLC 2019
Multiple $NTRK$ 1/2/3 fusions across multiple tumours

ESMO guidelines for detecting $NTRK$

Estimated 1,500–5,000 patients harbor TRK fusion-positive cancers in the United States annually.

**NTRK fusions** (0.23% in NSCLC)

**Larotrectinib (Updated Ph I)**

- Dose: 100 mg BD
- ORR: 81%. 1-y DoR: 81%
- First agnostic-tissue approval by EMA On 25th July 2019 (FDA 11/2018)

**Entrectinib Pooled Ph I&II trial**

- Dose: 600 mg QD
- ORR: 57.4%. PFS 11.2 mo. OS 20.9 mo
- 11 BM: icRR 54.5%. icPFS: 14.3 mo.

Retrospective cohort 11 NTRK+ (41-y/o. ADC, non-S) OS 41 mo. (73% received at least 1 NTRK TKI)

**KRAS G12C mutation: AMG510**

Best Tumor Response and Change in Tumor Burden From Baseline

<table>
<thead>
<tr>
<th>Efficacy outcomes</th>
<th>All evaluable patients N = 23</th>
<th>Evaluable patients treated with 960mg N = 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response – No. (%)</td>
<td>11 (48)</td>
<td>7 (54)</td>
</tr>
<tr>
<td>Stable disease – No. (%)</td>
<td>11 (48)</td>
<td>6 (46)</td>
</tr>
<tr>
<td>Progressive disease – No. (%)</td>
<td>1 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Objective response rate – %</td>
<td>48%</td>
<td>54%</td>
</tr>
<tr>
<td>Disease control rate(^p) – %</td>
<td>96%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Planned dose: 180 mg, 360 mg, 720 mg, 960 mg

\(^p\)Patient had complete response to the target lesions.

Govindan et al. OA02.02
Other biomarkers and genomic alterations

Constitutive PD-L1 expression

IMMUNOTARGET COHORT (N=551)

PD-L1≥ 50%#

Pre-treated:

EGFR KRAS ALK ROS1 BRAF HER2 RET MET

PD-L1≥ 50%: 5%-11% 17% 26% 0-36% 45% 13% 21% 41%

Pre-treated: 33% 52%
Other biomarkers and genomic alterations

**MET**
- RR=17%

**EGFR**
- RR=0%

**BRAF**
- RR=0%

ICI MUST NOT BE THE FIRST-TREATMENT OPTION IN ONCOGENIC ADDICTED NSCLC REGARDLESS OF HIGH PD-L1 EXPRESSION. IT COULD BE CONSIDERED AN OPTION AFTER ALL OPTIONS OF PERSONALISED TREATMENT.

Conclusions

• Platinum-based chemotherapy remains the SoC in advanced NSCLC without oncogenic driver and not suitable for ICI. ≤ 6 cycles.

• Maintenance treatment with 1 (pemetrexed or BVZ) is SoC in non-squamous NSCLC.

• TKI must be the 1\textsuperscript{st} Line treatment option in \textit{EGFR, ALK, ROS1} and \textit{BRAF} regardless of PD-L1 expression.

• New genomic alterations: \textit{NTRK, RET} have already agnostic-approval personalised treatments.