1st line chemotherapy and contribution of targeted agents

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Classification of advanced NSCLC based on therapy targets

- EGFR: 31%
- ALK
- ROS1
- PD-L1
- Wild
## Treatment Paradigm with Immunotherapy for advanced NSCLC in 2016

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<tr>
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*Note: PD-L1+ indicates PD-L1 expression ≥50%.*
Standard of care for patients without driver mutations

- **Nonsquamous**
  - Pemetrexed- or taxane-based doublets
  - Bevacizumab in selected patients
  - 4 cycles (6?)
  - Maintenance consideration after 4 cycles

- **Squamous**
  - Taxane- or gemcitabine-based doublets
  - 4 cycles (6?)
  - Maintenance consideration after 4 cycles

NCCN guideline 2016
Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

S. Novello¹, F. Barlesi², R. Califano³,⁴, T. Cufer⁵, S. Ekman⁶, M. Giaj Levra⁷, K. Kerr⁸, S. Popat⁹, M. Reck¹⁰, S. Senan¹¹, G. V. Simo¹², J. Vansteenkiste¹³ & S. Peters¹⁴ on behalf of the ESMO Guidelines Committee

First-line treatment of EGFR and ALK-negative disease (SCC and NSCC)

- Chemotherapy should be considered in all stage IV NSCLC patients with EGFR- and ALK-negative disease, without major co-morbidities and PS 0-2 [I, A].
- Platinum-based doublets are the recommended option in all stage IV NSCLC patients with no contraindications to platinum compounds [I, A].
- Four cycles of platinum-based doublets followed by less toxic maintenance monotherapy, or four up to a maximum of six cycles in patients not suitable for maintenance monotherapy, are currently recommended [I, A].
- In non-squamous tumours and in patients treated with third-generation regimens, cisplatin should be the treatment of choice [I, B].
- The nab-PC regimen could be considered a chemotherapeutic option in advanced NSCLC patients, particularly in patients with greater risk of neurotoxicity, pre-existing hypersensitivity to paclitaxel or contraindications for standard paclitaxel premedication [I, B].
- Platinum-based doublets with a third-generation cytotoxic agent (gemcitabine, vinorelbine, taxanes) are recommended in advanced SCC patients [I, A].
- Necitumumab plus gemcitabine and cisplatin represents a treatment option for advanced SCC expressing EGFR by IHC [I, B; ESMO-MCBS v1.0 score: 1].
- Pemetrexed is preferred to gemcitabine or docetaxel in patients with non-squamous tumours [II, A]. Pemetrexed use is restricted to NSCC in any line of treatment [I, A].
- The combination of bevacizumab and other platinum-based chemotherapies may be considered in eligible patients with NSCC and PS 0-1 [I, A].
1st line chemotherapy and contribution of targeted agents

- PD-L1 negative lung adenocarcinoma
- PD-L1 negative lung squamous carcinoma
Platinum Combos in Advanced NSCLC Around the Millennium

No significant difference in activity
Phase 3 trial: CP vs CG in advanced NSCLC

Chemotherapy-naïve stage IIIb/IV NSCLC
N=1725

CP
- Cisplatin 75 mg/m² day 1
- Pemetrexed 500 mg/m² day 1
- N=862
- Every 3 wk up to 6 cycles

CG
- Cisplatin 75 mg/m² day 1
- Gemcitabine 1250 mg/m² days 1, 8
- N=863
- Every 3 wk up to 6 cycles

Median OS (primary endpoint)
- 10.3 mo for both arms (adjusted HR, 0.94)
- Nonsquamous
  - 11.8 mo for CP vs 10.4 mo for CG (adjusted HR, 0.81)
- Squamous
  - 9.4 mo for CP vs 10.8 mo for CG (adjusted HR, 1.23)

Scagliotti GV et al. JCO 2008
# Pemetrexed Efficacy by Histology

<table>
<thead>
<tr>
<th>NSCLC Histologic Group</th>
<th>JMEI 2nd-line Pemetrexed vs Docetaxel</th>
<th>JMDB 1st-line Cis/Pem vs Cis/Gem</th>
<th>JMEN Maintenance Pemetrexed vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pem</td>
<td>Doc</td>
<td>Cis/Pem</td>
</tr>
<tr>
<td>Nonsquamous*</td>
<td>n = 205</td>
<td>n = 194</td>
<td>n = 618</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>9.3</td>
<td>8.0</td>
<td>11.0</td>
</tr>
<tr>
<td>Adjusted HR (95% CI) P-value</td>
<td>0.78 (0.61, 1.00) 0.048</td>
<td>0.84 (0.74, 0.96) 0.011</td>
<td>0.70 (0.56, 0.88) 0.002</td>
</tr>
<tr>
<td>Squamous</td>
<td>n = 78</td>
<td>n = 94</td>
<td>n = 244</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>6.2</td>
<td>7.4</td>
<td>9.4</td>
</tr>
<tr>
<td>Adjusted HR (95% CI) P-value</td>
<td>1.56 (1.08, 2.26) 0.018</td>
<td>1.23 (1.00, 1.51) 0.050</td>
<td>1.07 (0.77, 1.50) 0.678</td>
</tr>
</tbody>
</table>

* Nonsquamous: adenocarcinoma, large cell carcinoma, and other/indeterminate NSCLC histology; Cis/Pem: cisplatin/pemetrexed; Cis/Gem: cisplatin/gemcitabine; Pem: pemetrexed; Doc: docetaxel; HR: hazard ratio; OS: overall survival; CI: confidence interval

Scaglioni et al. WCLC 2009;B2.6
Maintenance treatment: PARAMOUNT: Study Design

**Study Treatment Period**

- **Induction Therapy (4 cycles 21 to 42 Days)**
- **Maintenance Therapy (Until PD)**

Patients enrolled if:
- Nonsquamous NSCLC
- No prior systemic treatment for lung cancer
- ECOG PS 0/1

- **Primary objective:** progression-free survival (PFS)

Randomized, placebo-controlled, double-blind, phase III study

Folic acid and vitamin B\textsubscript{12} administered to both arms

- **500 mg/m\textsuperscript{2} Pemetrexed + BSC, d1, q21d**
- **500 mg/m\textsuperscript{2} Pemetrexed + 75 mg/m\textsuperscript{2} Cisplatin, d1, q21d**

Stratified for:
- PS (0 vs 1)
- Disease stage (IIIB vs IV) prior to induction
- Response to induction (CR/PR vs SD)
PARAMOUNT: Independently Reviewed PFS (from Maintenance)

88% of patients were independently reviewed (472/539)

- Pemetrexed: median = 3.9 mos (3.0-4.2)
- Placebo: median = 2.6 mos (2.2-2.9)
- Log-rank P = 0.0002
- Unadjusted HR: 0.64 (0.51-0.81)

L. G. Paz-Ares ASCO 2011
PARAMOUNT: OS (from M)

- Pemetrexed (n=359): 13.9 months
- Placebo (n=180): 11.0 months

1 y OS: 58% vs. 45%
2 y OS: 32% vs. 21%

HR=0.78, 95%CI=0.64-0.96, P=0.0195

**Phase III ECOG 4599 trial**

**Paclitaxel/Carboplatin ± Bevacizumab**

- **PC**
  - Paclitaxel 200 mg/m²
  - Carboplatin AUC = 6 mg/mL/min (once every 3 weeks) x 6 cycles
  - (n = 433*)

- **PCB**
  - PC (once every 3 weeks) x 6 cycles + Bevacizumab 15 mg/kg (once every 3 weeks) until disease progression
  - (n = 417*)

*Eligible patients included in analysis.

**Treatment-naive patients with confirmed stage IIIB or IV cancer; adequate hematologic, hepatic, and renal function**

(N = 878)

**Median OS:** 12.3 m vs 10.3 m

**ORR**

**Median PFS:**

Phase III ECOG 4599 trial
Paclitaxel/Carboplatin ± Bevacizumab

Proportion surviving

Months

12 mo 24 mo
Pac/carbo + bev, n=434 51% 23%
Pac/carbo, n=444 44% 15%

HR: 0.79, 0.67-0.92
P = .003

BEYOND study design

Chinese patients with previously untreated, advanced, stage IIIB/IV non-squamous NSCLC n=276

Bevacizumab (B) 15 mg/kg d1
Carboplatin (C) AUC6 d1
Paclitaxel (P) 175 mg/m² d1
3-weekly cycle, n=138

6 cycles

CP + Placebo (Pl)
All on d1 3-weekly cycle, n=138

Primary endpoint: PFS
- to confirm efficacy in Chinese population through consistency with E4599 (HR threshold ≤0.83)

Secondary endpoints: OS, ORR, duration of response, safety, plasma biomarkers (VEGF-A, VEGFR-2)
Exploratory biomarkers: tissue and plasma EGFR mutation status
Stratification factors: gender, smoking status, age

Optional enrolment in post-progression phase of open-label B + approved 2nd-/3rd-line treatment for B+CP arm only

PD = disease progression; R = randomised; ORR = objective response rate; HR = hazard ratio; VEGF-A = vascular endothelial growth factor-A
VEGFR-2 = vascular endothelial growth factor receptor-2; EGFR = epidermal growth factor receptor
BEYOND study results

Zhou, JCO 2015
**Exploratory \textit{EGFR} biomarker analysis: OS**

- Median OS was 24.3 vs 27.5 months for B+CP vs PI+CP in the \textit{EGFR} mutation-positive subgroup (HR 0.90)

- In the \textit{EGFR} wild-type subgroup, median OS was 20.3 vs 13.8 months for B+CP vs PI+CP (HR 0.57)
NSCLC therapies associated with effectiveness and safety in particular histology

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Histologic subtype</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemetrexed</td>
<td>Nonsquamous NSCLC</td>
<td>Adenocarcinoma may be more susceptible because of lower thymidylate synthase levels.</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Predominantly nonsquamous NSCLC</td>
<td>Higher risk for fatal pulmonary hemorrhage with squamous cell histology; risk may be lower with small peripheral squamous tumors.</td>
</tr>
</tbody>
</table>

Adjusted from JOEL W. NEAL. *The Oncologist* 2010;15:3–5
Question 1:

JMDB and PARAMOUNT or ECOG4599 and BEYOND

Which is better?
PointBreak study Design

- Randomized, open-label, phase 3 superiority study conducted in the United States
- 939 patients with treatment-naïve stage IIIb/IV nonsquamous NSCLC randomized 1:1 to:
  - Pemetrexed 500 mg/m²; carboplatin AUC 6; bevacizumab 15 mg/kg
  - Paclitaxel 200 mg/m²; carboplatin AUC 6; bevacizumab 15 mg/kg
- Induction phase: 4 cycles every 21 d
- Maintenance phase: every 21 d until PD:
  - Pemetrexed plus bevacizumab, or bevacizumab
# PointBreak Efficacy Results

<table>
<thead>
<tr>
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<th>Pemetrexed, Carboplatin, Bevacizumab</th>
<th>Paclitaxel, Carboplatin, Bevacizumab</th>
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<tbody>
<tr>
<td>Median OS, mo</td>
<td>12.6</td>
<td>13.4</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1 (0.86, 1.16); P = .949</td>
<td></td>
</tr>
<tr>
<td>Survival rate, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 y</td>
<td>52.7</td>
<td>54.1</td>
</tr>
<tr>
<td>2 y</td>
<td>24.4</td>
<td>21.2</td>
</tr>
<tr>
<td>Median PFS, mo</td>
<td>6</td>
<td>5.6</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.83 (0.71, 0.96); P = .012</td>
<td></td>
</tr>
<tr>
<td>ORR, %</td>
<td>34.1</td>
<td>33.0</td>
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Patel et al. JCO 2013
Question 2:

Could we improve chemo outcome in driver gene and PD-L1 negative advanced NSCLC?
TS mRNA Results by Histology (N = 1671):
Squamous vs Adenocarcinoma

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>NSCLC: Total (N = 1671)</th>
<th>NSCLC: SCCA (n = 316)</th>
<th>NSCLC: AC (n = 649)</th>
<th>SCCA vs AC P Value</th>
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<tr>
<td>TS Median</td>
<td>2.71</td>
<td>4.1</td>
<td>2.5</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>Range</td>
<td>0.14-68.0</td>
<td>0.14-59.3</td>
<td>0.39-68.0</td>
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* Mann-Whitney test

TS (Reference < 2.33 for Pemetrexed) % Below Reference Level
- NSCLC: total 41.3
- NSCLC: adenoca 45.7
- NSCLC: SCCA 25.9

Is TS a predictive marker for pemetrexed?

This exploratory study is inconclusive about TS expression as a standard clinical assessment but indicate that with further studies it can potentially be of clinical relevance.
A new potential marker for pemetrexed: FR(+) - CTC

- FR-positive CTCs by LT-PCR has been approved by CFDA in 2016 as assistant diagnosis for NSCLC.

**Graph:**
- ORR: 75% vs 11%

**Table:**
- First-line pemetrexed-platinum
  - Overall: CTC=13.68, mPFS=9.3m, ORR=43%

- The patients with high expression of FR-positive CTCs appear to have superior response to pemetrexed than those with low expression.
- The change of CTC count can be used as a dynamic monitoring indicator in the treatment process to evaluate tumor burden and therapeutic outcomes.

[Xiaoxia Chen, et al., 2016 AACR. Abs. 2252]
• Pemetrexed is preferred to gemcitabine or docetaxel in patients with non-squamous tumours [II, A]. Pemetrexed use is restricted to NSCC in any line of treatment [I, A].

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**Note:**
- **PD-L1**: Programmed Death Ligand 1
- **EGFR**: Epidermal Growth Factor Receptor
- **ALK**: Anaplastic Lymphoma Kinase
- **ROS1**: Rearranged during Transfection
- **SCC**: Squamous Cell Carcinoma
- **TKIs**: Tyrosine Kinase Inhibitors
- **Chemo**: Chemotherapy
1st line chemotherapy and contribution of targeted agents

• PD-L1 negative lung adenocarcinoma

• PD-L1 negative lung squamous carcinoma
WJOG5208L: Study design

Chemo-naive
PS 0-1
Age 20-74
Stage IIIb/IV or recurrent
SqLC
N= 350

1:1

Docetaxel 60 mg/m² d1
Nedaplatin 100 mg/m² d1
q3w, 4-6 cycles
N= 175

Docetaxel 60 mg/m² d1
Cisplatin 80 mg/m² d1
q3w, 4-6 cycles
N= 175

Stratification factors:
Stage (IIIb, IV or recurrent)
Gender
Institutions

Presented By Takehito Shukuya at 2015 ASCO Annual Meeting

SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.
Nedaplatin plus docetaxel versus cisplatin plus docetaxel for advanced or relapsed squamous cell carcinoma of the lung (WJOG5208L)

Shukuya T, et al. 2015 Lancet Oncol
First-line chemotherapy + cetuximab in advanced NSCLC

Single-arm phase II studies
Thienelt CD et al. JCO 2005
Robert F et al. JCO 2005
Belani C et al. ASCO 2007
Barata F et al. Dresden 2008

Randomized phase II trials
Butts CA et al. JCO
Herbst RS et al. JCO 2010, 28, 4747

Phase III studies
FLEX
Pirker R et al. Lancet 2009, 373, 1525
BMS 099
Lynch TJ et al. JCO 2010, 28, 911

Meta-analysis
Pujol JL et al. ESMO 2009
FLEX survival: high EGFR expression
Squamous cell carcinoma (N=144)

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<tr>
<th>Survival</th>
<th>Median</th>
<th>1-year</th>
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<tr>
<td>CT + cetuximab</td>
<td>11.2 mo</td>
<td>44%</td>
</tr>
<tr>
<td>CT</td>
<td>8.9 mo</td>
<td>25%</td>
</tr>
</tbody>
</table>

HR=0.62 [95% CI 0.43–0.88]
SQUIRE & INSPIRE: Overall survival

Thatcher N et al. Lancet Oncol 2015, 16, 763

Paz-Ares L et al. Lancet Oncol 2015, 16, 328

SCC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients censored, n (%)</th>
<th>Median overall survival, months (95% CI)</th>
<th>Stratified p-value (log-rank)</th>
<th>Stratified HR (95% CI)</th>
</tr>
</thead>
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<tr>
<td>Necitumumab plus gemcitabine and cisplatin (n=545)</td>
<td>127 (23%)</td>
<td>11.5 (10.4-12.6)</td>
<td>0.01</td>
<td>0.64 (0.74-0.95)</td>
</tr>
<tr>
<td>Gemcitabine and cisplatin (n=540)</td>
<td>103 (19%)</td>
<td>9.9 (8.9-11.1)</td>
<td>0.64</td>
<td>0.74-0.95</td>
</tr>
</tbody>
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AD

Pemetrexed and cisplatin alone

SC10.03: Anti-EGFR monoclonal antibodies in squamous cell NSCLC – Robert Pirker
1\textsuperscript{st} line chemotherapy ± EGFR antibodies: Survival

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<tr>
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<th>Hazard ratio</th>
<th>p value</th>
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<td>Cetuximab</td>
<td></td>
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</tr>
<tr>
<td>FLEX ITT</td>
<td>0.87 (0.76-0.99)</td>
<td>0.04</td>
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<tr>
<td>BMS099 ITT</td>
<td>0.89 (0.75-1.05)</td>
<td>NS</td>
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<tr>
<td>Meta-Analysis ITT</td>
<td>0.88 (0.79-0.97)</td>
<td>0.009</td>
</tr>
<tr>
<td>Adeno</td>
<td>0.94 (0.82-1.09)</td>
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</tr>
<tr>
<td>Squamous</td>
<td>0.77 (0.64-0.93)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0.88 (0.72-1.08)</td>
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<tr>
<td>Necitumumab</td>
<td></td>
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<tr>
<td>SQUIRE</td>
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<td>Squamous</td>
<td>0.84 (0.74-0.96)</td>
<td>0.01</td>
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<td>INSPIRE</td>
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<tr>
<td>Adeno</td>
<td>1.01 (0.84-1.21)</td>
<td>NS</td>
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## Biomarkers

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Study</th>
<th>Subtype</th>
<th>Biomarker</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
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<td><strong>Cetuximab</strong></td>
<td>Meta-Analysis</td>
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<td></td>
<td>0.77 (0.64-0.93)</td>
</tr>
<tr>
<td></td>
<td>FLEX</td>
<td>ITT</td>
<td>High H score</td>
<td>0.73 (0.58-0.93)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Squamous</td>
<td>High H score</td>
<td>0.62 (0.43-0.88)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adeno</td>
<td>High H score</td>
<td>0.74 (0.48-1.14)</td>
</tr>
<tr>
<td></td>
<td>SWOG S0819</td>
<td>ITT</td>
<td>FISH positive</td>
<td>0.83 (0.67-1.04)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Squamous</td>
<td>FISH positive</td>
<td>0.56 (0.37-0.84)</td>
</tr>
<tr>
<td><strong>Necitumumab</strong></td>
<td>SQUIRE</td>
<td>Squamous</td>
<td>ITT</td>
<td>0.84 (0.74-0.96)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High H score</td>
<td>0.75 (0.60-0.94)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FISH positive</td>
<td>0.70 (0.50-1.0)</td>
</tr>
</tbody>
</table>
What do we learn from these trials?

Cetuximab added to first-line chemotherapy increased survival of patients with advanced squamous NSCLC with high EGFR expression.

Necitumumab added to cisplatin plus gemcitabine increased survival in patients with advanced squamous cell NSCLC.
• Platinum-based doublets with a third-generation cytotoxic agent (gemcitabine, vinorelbine, taxanes) are recommended in advanced SCC patients [I, A].

• Necitumumab plus gemcitabine and cisplatin represents a treatment option for advanced SCC expressing EGFR by IHC [I, B; ESMO-MCBS v1.0 score: 1]
In conclusions

• Pemetrexed is preferred to gemcitabine or docetaxel in patients with non-squamous tumours [II, A]. Pemetrexed use is restricted to NSCC in any line of treatment.

• The combination of bevacizumab and other platinum-based chemotherapies may be considered in eligible patients with NSCC and PS 0-1.

• Platinum-based doublets with a third-generation cytotoxic agent (gemcitabine, vinorelbine, taxanes) are recommended in advanced SCC patients.

• Necitumumab plus gemcitabine and cisplatin represents a treatment option for advanced SCC expressing EGFR by IHC [ESMO-MCBS v1.0 score: 1]
Thank You