MAINTENANCE TREATMENT
CHEMO MAINTENANCE OR TARGETED OF BOTH?

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OUTLINE

• Background and Concept
• Switch Maintenance
• Continuation Maintenance
• Conclusions / Critical Remarks
HISTORICAL APPROACH TO NSCLC TREATMENT

First-line treatment: Platinum doublet chemotherapy (4–6 cycles)

‘Watch and wait’

Second and further lines of treatment

Diagnosis

CR/PR/SD

PD

PD

As a result of cumulative toxicity, patients receive a limited number of cycles of chemotherapy
Patients may not be eligible for further therapy upon progression after first-line chemotherapy.

In recent studies, approximately 50% of patients did not receive second-line therapy.
Patient eligibility
- Stage IIIB/IV
- Chemo-naïve
- ECOG PS 0-2
- CNS metastases allowed

Consolidation arm:
- docetaxel 75 mg/m² d1,
- q21d, until PD
- or max 6 cycles

GC phase:
- gemcitabine 1,000 mg/m² d1,8
- carboplatin AUC=5 d1
- q21d x 4 cycles

CR/PR/SD
n = 566

Endpoints
- Primary: OS
- Secondary: response, PFS, safety, QoL

Delayed arm:
- BSC to PD, then
- docetaxel 75 mg/m² d1,
- q21d, until PD
- or max 6 cycles

n = 145

n = 309
C: 153
D: 156

n = 98

Fidias PM et al. 2009 J Clin Oncol 27:591

AUC: area under the curve; CNS: central nervous system
Consolidated Versus Delayed Docetaxel: More Patients Get to Receive Treatment

<table>
<thead>
<tr>
<th></th>
<th>Consolidation (n = 156)</th>
<th>Delayed (n = 153)</th>
<th>Log-rank p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (95% CI)</td>
<td>5.7 months (4.4–6.9)</td>
<td>2.7 months (2.6–2.9)</td>
<td>0.0001</td>
</tr>
<tr>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median OS (95% CI)</td>
<td>12.3 months (10.4–15.2)</td>
<td>9.7 months (8.4–12.5)</td>
<td>0.0853</td>
</tr>
<tr>
<td>OS*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year OS (95% CI)</td>
<td>51.1% (43.0–59.3)</td>
<td>43.5% (35.5–51.3)</td>
<td></td>
</tr>
</tbody>
</table>

*From randomization

Fidias PM et al. 2009 J Clin Oncol 27:591
CONCEPTS OF MAINTENANCE

"Switch" maintenance

1st-line: Platinum doublet

CR, PR, SD

Progression

New maintenance monotherapy

J Men (Pemetrexed)\(^1\)

SATURN (Erlotinib)\(^2\)

4 cycles

Until progression

Further lines following progression monotherapy

"Continuation" maintenance

1st-line: Pemetrexed/Cisplatin

CR, PR, SD

Progression

Maintenance Pemetrexed monotherapy

PARAMOUNT\(^3\)

AVAPERL\(^4\)

4 cycles

Until progression

Further lines following progression monotherapy

Selection of patients with good prognosis

Quality of life

Symptom control

Tolerability

KEY OBJECTIVES OF MAINTENANCE THERAPY

PRIMARY OBJECTIVES

- Delay PD
- Increase OS

Secondary Objectives

- Prevent symptom deterioration
- Maintain performance status to allow further therapy
OUTLINE

• Background and Concept
• **Switch Maintenance**
  • Chemotherapy
  • Targeted Therapies
  • Checkpoint Inhibitors
• Continuation Maintenance
• Conclusions / Critical Remarks
THE SWITCH MAINTENANCE REGISTRATION TRIALS

<table>
<thead>
<tr>
<th>Study</th>
<th>PFS HR p</th>
<th>OS HR p</th>
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<tbody>
<tr>
<td>JMEN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pem</td>
<td>0.5</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.0001</td>
<td>0.012</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SATURN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td>0.71</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.0001</td>
<td>0.009</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Switch maintenance:
TKI and pemetrexed show improved PFS and OS

SWITCH MAINTENANCE: PEMETREXED RESPONSE TO PREVIOUS TREATMENT

Non-squamous cell carcinoma group

Induction response CR/PR
- HR: 0.81

Induction response SD
- HR: 0.61

Advantage in favour of Pemetrexed
Advantage in favour of placebo

Belani CP et al. 2009 J Clin Oncol 27(Suppl): Abs. CRA8000
SWITCH MAINTENANCE: ERLOTINIB
RESPONSE TO PREVIOUS TREATMENT AND EGFR MUTATION

Coudert B et al. 2010 J Thorac Oncol 5(Suppl): Abs. 204O.
## SWITCH-MAINTENANCE TRIALS

### GEFTINIB

<table>
<thead>
<tr>
<th>Trial</th>
<th>Schedule</th>
<th>Pat.</th>
<th>Med PFS (m)</th>
<th>Signific.</th>
<th>Med OS (m)</th>
<th>Sign.</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>WJTOG 604</td>
<td>3 cycles CT + gefitinib</td>
<td>302</td>
<td>4.6</td>
<td>HR 0.68 P&lt;0.001</td>
<td>12.9</td>
<td>NS</td>
<td>No assessment of EGFR mutation status</td>
</tr>
<tr>
<td></td>
<td>6 cycles CT</td>
<td>301</td>
<td>4.3</td>
<td></td>
<td>13.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INFORM</td>
<td>Gefitinib (after 4 cycles CT)</td>
<td>148</td>
<td>4.8</td>
<td>HR 0.42 P&lt;0.001</td>
<td>18.97</td>
<td>NS</td>
<td>Retrospective Assessment of EGFR mutation status</td>
</tr>
<tr>
<td></td>
<td>Placebo (after 4 cycles CT)</td>
<td>148</td>
<td>2.6</td>
<td></td>
<td>16.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC 08021</td>
<td>Gefitinib (after 4 cycles CT)</td>
<td>86</td>
<td>4.1</td>
<td>HR 0.61 P&lt;0.0015</td>
<td>10.9</td>
<td>NS</td>
<td>Closed due to poor accrual Primary EP: OS</td>
</tr>
<tr>
<td></td>
<td>Placebo (after 4 cycles CT)</td>
<td>87</td>
<td>2.9</td>
<td></td>
<td>9.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

INFORM
EGFR-MUTATION: PREDICTIVE FOR OS
**Study objective**

- To evaluate the effect on survival of sunitinib maintenance vs placebo in patients with advanced NSCLC who were stable or responding after 4 cycles of first-line platinum-based chemotherapy (with or without bevacizumab)

**Key patient inclusion criteria**

- Stage IIIB/IV
- ECOG PS 0–1
- Stable or responding disease after 4 cycles of platinum-based therapy
- No symptomatic or untreated brain metastases or cavitary lesions

**Primary endpoint**

- PFS after randomisation

**Secondary endpoints**

- OS, safety and QoL

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Socinski et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8040)
8040: Sunitinib (S) switch maintenance in advanced non-small cell lung cancer (NSCLC): An ALLIANCE (CALGB 30607), randomized, placebo-controlled phase III trial – Socinski MA et al

- **Key results**
  
  - Patients had a median age 66 (range 25–89) years, 55.7% male, 61.0% ECOG PS 1, 87.6% stage IV, 91.7% current/past smokers. 45.7% had adenocarcinoma, 33.2% squamous, 13.5% undifferentiated NSCLC and 4.3% large cell

- Significant improvement in PFS (but not OS) observed with sunitinib switch maintenance in patients with advanced NSCLC

Socinski et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8040)
Switch maintenance = efficacy due to change in treatment (SD) – early second-line therapy without progression established? Involves loss of a molecule option for a later line of treatment.

- Individual option
- Clear indication for switch to targeted therapies in patients with oncogenic alterations
- Interesting concept for checkpoint inhibitors
OUTLINE

• Background and Concept
• Switch Maintenance
  • Continuation Maintenance
    • Chemotherapy
    • Antiangiogenic therapies
• Conclusions / Critical Remarks
CONCEPTS OF MAINTENANCE

**“Switch” maintenance**

1st-line: Platinum doublet

- CR, PR, SD
- Progression
- Further lines following progression monotherapy

4 cycles

**“Continuation” maintenance**

1st-line: Pemetrexed/Cisplatin

- CR, PR, SD
- Progression
- Further lines following progression monotherapy

4 cycles

- Selection of patients with good prognosis
- Quality of life
- Symptom control
- Tolerability

Primary endpoint: PFS

Inclusion criteria:
- NSCLC
- Stage IIIIB/IV
- Chemonaive
- ECOG PS 0-1 (n = 939)

Stratification:
- PS
- Stage

Continuation Maintenance: Pemetrexed (PARAMOUNT) double-blind, placebo-controlled, multicentre, phase III study

Induction therapy (4 cycles)
- Cisplatin 75 mg/kg IV q21d
- Pemetrexed 500 mg/m² IV q21d

Maintenance therapy (until PD)
- Placebo N = 180
- Pemetrexed 500 mg/m² IV q21d N = 359

Progression
- PD

CR, PR, SD

Start of study medication

Paz-Ares LG et al, Lancet Oncology Published online February 16, 2012 DOI:10.1016/S1470-2045(12)70063-3.
Independent review of 88% of the patients (472/539)

**Pemetrexed**: Median 3.9 months (3.0–4.2)
**Placebo**: Median 2.6 months (2.2–2.9)
**Log-rank**: P = 0.0002
**HR, not adjusted**: 0.64 (0.51–0.81)
PARAMOUNT: Final survival (from induction)

Pemetrexed + BSC
359 335 276 234 200 164 138 106 77 42 15 2 0

Placebo + BSC
180 168 132 103 78 63 49 35 23 12 8 3 0

OS Propability
Time from induction (months)

Pemetrexed: Median OS = 16,9 Months
(95% KI) (15,8-19,0)
Placebo: Median OS = 14,0 Months
(95% KI) (12,9-15,5)
Log-Rank p=0,0191
HR (95% KI) 0,78 (0,64-0,96)

OS, overall survival, Gesamtüberleben; BSC, best supportive care

PARAMOUNT: OS; Subgroup Analysis

In favour of Pemetrexed
In favour of Placebo

Hazard Ratio (95% KI)

- All randomised patients (n=539)
  - Stage IV (n=490)
  - Stage IIIb (n=49)
- CR/PR after induction (n=234)
- SD after induction (n=285)
- PS 1 before randomisation (n=363)
- PS 0 before randomisation (n=173)
- CR/PR after induction (n=234)
- SD after induction (n=285)
- Non Smoker (n=117)
- Smoker (n=418)
  - Male (n=313)
  - Female (n=226)
- age <70 (n=447)
- age ≥70 (n=92)
- age <65 (n=350)
- age ≥65 (n=189)
- Other histology (n=32)
  - Large Cell NSCLC (n=36)
  - Adenocarcinoma (n=471)

Hazard Ratio

- All randomised patients (n=539)
  - CR, complete response: vollständiges Ansprechen; PR, partial response: teilweises Ansprechen; SD, stable disease: Krankheitsstabilisierung; PS, propensity score

Paramount: Results of additional analysis

- OS benefit is consistent across all subgroups
- Patients surviving longer periods had comparable baseline parameters as those surviving shorter periods
- No OS difference based on response to induction treatment
- No OS difference correlating with degree of tumor shrinkage
- No OS difference associated with shorter (<7 days) versus longer (7-30 days) between completion of induction therapy and start of maintenance treatment (median interval = 3 days).
- PS was confirmed as a prognostic factor; however, OS benefit by pemetrexed maintenance therapy was shown in both PS0 and PS1 patients.
## PARAMOUNT: CTCAEs Grade 3/4 Drug-Related Toxicities (Randomized Patients)

<table>
<thead>
<tr>
<th>Grade 3/4 Event</th>
<th>Pemetrexed N=359 (%)</th>
<th>Placebo N=180 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue*</td>
<td>4.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Anemia*</td>
<td>4.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>3.6</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1.7</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>Neuropathy-sensory</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Mucositis/stomatitis</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>ALT (SGPT)</td>
<td>0.3</td>
<td>0</td>
</tr>
</tbody>
</table>

*Statistically significant between arms (Fisher’s exact test $P \leq 0.05$)

Paz-Ares presentation on ASCO 2011 (Paz-Ares et al. J Clin Oncol 29: 2011; (suppl; abstr CRA7510)
AVAPERL: Patient Disposition

Patients screened (n=414) → First-line induction with Bev-cis-pem (n=376) → CR/PR/SD by RECIST → Patients randomized to maintenance\(^a\) (n=253)\(^b\) → Arm A: Bevacizumab (n=125) + bevacizumab + pemetrexed (n=128)

- 123 patients not randomized
  - 50 discontinued due to AEs
  - 49 discontinued due to PD
  - 9 patients died
  - 7 withdrew consent
  - 5 discontinued for other reasons
  - 3 did not start treatment

- Median follow-up time for this analysis: 11 months

\(^a\) RECIST-related end points measured from the preinduction phase.

\(^b\) Intent-to-treat population

Barlesi F; J Clin Oncol 2013
AVAPERL: PFS from Randomization

**Bev+pem** 7.4 months (81 events)
**Bev** 3.7 months (104 events)
HR, 0.48 (0.35–0.66); \( P < .001 \)

**Cont. maintenance bev+pem (n=128)**
**Cont. maintenance bev (n=125)**

* Median follow-up time in ITT population (excluding induction): 8.28 months (bev+pem arm), 7.95 months (bev arm)
bev, bevacizumab; cont., continuation; HR, hazard ratio; ITT, intent to treat; pem, pemetrexed; pts, patients.
AVAPERL: PFS Subgroup Analysis

ITT population (n=253)

- Favors combination
- Favors bevacizumab alone

- Hazard ratio: 0.54

Age <65 y (n=176)

- Hazard ratio: 0.53

Age ≥65 y (n=77)

- Hazard ratio: 0.57

ECOG PS 0 (n=118)

- Hazard ratio: 0.43

ECOG PS 1 (n=126)

- Hazard ratio: 0.60

Never smoker (n=64)

- Hazard ratio: 0.40

Current/past smoker (n=188)

- Hazard ratio: 0.59

Adenocarcinoma (n=225)

- Hazard ratio: 0.52

SD prior to randomization (n=116)

- Hazard ratio: 0.64

CR/PR prior to randomization (n=137)

- Hazard ratio: 0.46
Figure 4. Overall survival from the time of randomization

- OS measured from the start of induction was also numerically longer for bevacizumab + pemetrexed (19.8 vs 15.9 months, HR, 0.88 [0.64–1.22], P=.32) (Figure 5). However, the difference was also not significant.
PointBreak: Study Design

- Randomized, open-label, Phase III superiority study conducted in US
- Pemetrexed 500 mg/m²; Carboplatin AUC 6; Bevacizumab 15 mg/kg
- Paclitaxel 200 mg/m²; Carboplatin AUC 6; Bevacizumab 15 mg/kg

**Inclusion:**
- No prior systemic therapy for lung cancer
- PS 0/1
- Stage IIIB-IV NS-NSCLC
- Stable, treated brain metastasis

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

**Induction Phase**
- q21d, 4 cycles
- Pemetrexed (folic acid & vitamin B₁₂) + Carboplatin + Bevacizumab
- Paclitaxel + Carboplatin + Bevacizumab
- 450 patients each

**Maintenance Phase**
- q21d until PD
- Pemetrexed (folic acid & vitamin B₁₂) + Bevacizumab
- Bevacizumab

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

POINTBREAK RESULTS

- Negative trial
- No improvement for OS (primary endpoint)
- Improvement for Pem/Bev for PFS (5.6 vs 6.0 mts; p:0.012)

Patel J, J Clin Oncol 2013; 31: 4349-4357
OUTLINE

• Background and Concept
• Switch Maintenance
• Continuation Maintenance
• Conclusions / Critical Remarks
Conclusion

• Continuation maintenance = genuine maintenance
• Switch maintenance = efficacy due to change in treatment; individual option
• Symptomatic efficacy must be confirmed
• New challenges in daily routine …
Challenges

• Length of the induction therapy – how long can we give cisplatin?
• New treatment paradigm: no fixed number of treatment cycles
• New treatment to explain: Treatment as long as benefit is seen
• Different emphasis on adverse reactions: not every adverse reaction is included in the CTC – even CTC grade 2 fatigue can considerably influence quality of life.
• Principles of tumour measurement: How often? What should be done when progression is slow?
Continuation Maintenance – Clinical Factors

- Indication established case by case: most important prerequisites are the patient's wishes and response to first-line therapy
- Histology is important for deciding on therapy: Pemetrexed is the only chemotherapy option for non-squamous cell carcinoma
- No option available for squamous cell carcinoma
- Molecular screening: EGFR-TKI best option when evidence of EGFR mutation
Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

M. Reck¹,², S. Popat³,⁴, N. Reinmuth¹,², D. De Ruysscher⁵, K. M. Kerr⁶, S. Peters⁷ & on behalf of the ESMO Guidelines Working Group*  

¹Department of Thoracic Oncology, LungenClinic, Grosshansdorf; ²Member of the German Center for Lung Research (DZL), Germany; ³Royal Marsden Hospital NHS Foundation Trust, London; ⁴Royal Marsden Hospital NHS Foundation Trust, Surrey, UK; ⁵Department of Radiation Oncology, University Hospitals Leuven/ KU Leuven, Leuven, Belgium; ⁶Department of Pathology, Aberdeen Royal Infirmary and Aberdeen University Medical School, Aberdeen, UK; ⁷Department of Oncology, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

Maintenance treatment

- Maintenance chemotherapy should be offered only to patients with PS of 0–1 after first-line chemotherapy.
- In patients with a non-squamous histology and PS 0–1, improvements in PFS and OS were observed with pemetrexed switch maintenance versus placebo following four cycles of platinum-based chemotherapy [I, B].
- Switch maintenance with erlotinib versus placebo demonstrated PFS and OS benefit in all histologies, with the greatest benefit in patients with SD after first-line treatment [I, B].
- Decisions about maintenance must take into account the histology, response to platinum-doublet chemotherapy, remaining toxicity after first-line chemotherapy, PS, and patient preference [I, B].
- Continuing pemetrexed following four cycles of first-line cisplatin plus pemetrexed chemotherapy is recommended in patients with non-squamous histology [I, B].