Challenges in maintenance treatment in advanced NSCLC:

Do BENEFITS outweigh the COSTS?

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Disclosure slide

• Honoraria: Roche Hellas, Novartis Hellas
• Advisory: Amgen Hellas
Lung cancer: a global killer

Most common cancer worldwide
1.35 million new cases per year

Leading cause of cancer death
1.18 million deaths per year

- 85% of cases are non-small-cell lung cancer (NSCLC)
"Ideal" maintenance therapy

- Effective
  - Prevent symptom deterioration
  - Delays disease progression
  - Ideally prolong overall survival
- No life-threatening AEs
- Allows patient to recover from previous chemotherapy
- Maintain performance status to allow further therapy
- Well tolerated
- Positive risk : benefit ratio
- No negative impact on QoL
- Allows patients to live their lives as normally as possible
- COST-EFFECTIVE!!
Docetaxel Switch Maintenance: OS

- Median OS delayed vs immediate: 9.7 vs 12.3 mos ($P = .0853$)
- 1-yr survival delayed vs immediate: 43.5% vs 51.1%

Risk-benefit comments:

- Feeling of “never ending” chemotherapy
- Continuous exposure to additive toxicity
- Fatigue Grades 3-4 (Impairing quality of life)
  9.4% for immediate Docetaxel vs 4.1% for delayed
- Inability to use docetaxel as 2nd line treatment
- Without a significant survival benefit.....
PARAMOUNT: Final OS From Randomization

<table>
<thead>
<tr>
<th></th>
<th>Pemetrexed + BSC</th>
<th>Placebo + BSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS median (95% CI)</td>
<td>13.9 mos (12.8-16.0)</td>
<td>11.0 mos (10.0-12.5)</td>
</tr>
<tr>
<td>Survival rate, % (95% CI)</td>
<td>58 (53-63)</td>
<td>45 (38-53)</td>
</tr>
<tr>
<td>1 year</td>
<td>58 (53-63)</td>
<td>45 (38-53)</td>
</tr>
<tr>
<td>2 year</td>
<td>32 (27-37)</td>
<td>21 (15-28)</td>
</tr>
</tbody>
</table>

\[HR=0.78 \ (0.64–0.96)\]
\[\text{Log-rank } p=0.0195\]

Pearl:

- **EQ-5D** is a health-status questionnaire consisting of 2 parts:
  - Index score generated from 5 descriptive questions (relating to mobility, self-care, activities, discomfort, and anxiety).
  - Visual analog scale: patients rate their present health.

- **Administered at:**
  - Baseline (before induction).
  - Day 1 of each cycle of induction or continuation maintenance therapy (prior to treatment).
  - 30-day post-discontinuation visit.

- **Compliance at all time points during continuation maintenance phase was >80%.

- **No statistical differences in EQ-5D index score or visual analog scale were observed between treatment arms.**

- **The EQ-5D suggests that patients can tolerate long-term maintenance Pemetrexed without significant worsening of quality of life.**

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## Possible drug-related CTCAEs

<table>
<thead>
<tr>
<th>Event</th>
<th>PEMETREXED (n=359)</th>
<th>Placebo (n=180)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1/2 %</td>
<td>Grade 3/4 %</td>
</tr>
<tr>
<td><strong>Fatigue†</strong></td>
<td>17.5</td>
<td>4.7</td>
</tr>
<tr>
<td><strong>Anemia†</strong></td>
<td>11.7</td>
<td>6.4</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>13.4</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Neutropenia†</strong></td>
<td>5.0</td>
<td>5.8</td>
</tr>
<tr>
<td><strong>Mucositis/stomatitis‡</strong></td>
<td>5.8</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>7.5</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Neuropathy/sensory</strong></td>
<td>5.3</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Leukopenia</strong></td>
<td>2.8</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>ALT (SGPT)</strong></td>
<td>2.5</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Maintenance safety similar to known profile of single-agent Pemetrexed\(^2,3\)

\(\text{ALT} = \text{alanine transaminase}; \text{CTCAE} = \text{Common Technology Criteria for Adverse Events}; \text{SGPT} = \text{serum glutamate pyruvic transaminase.}\)

\(*\) Data derived from the March 2011 safety update. Toxicities occurring in ≥5% of patients in either arm are listed, along with some select toxicities.

\(\dagger\) \(P<0.05\) Fisher’s exact test of Gr 3/4 toxicities.

\(\ddagger\) Combined term.
### Possible drug-related CTCAEs

<table>
<thead>
<tr>
<th>CTCAE Grade 3/4/5 Term</th>
<th>&gt;10 Cycles PEMETREXED (n=275) (%)</th>
<th>≤10 Cycles PEMETREXED (n=84) (%)</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All laboratory</td>
<td>13.1</td>
<td>8.0</td>
<td>0.194</td>
</tr>
<tr>
<td>All non-laboratory</td>
<td>8.3</td>
<td>9.1</td>
<td>1.00</td>
</tr>
<tr>
<td>Neutropenia Grades 3/4†</td>
<td>9.3</td>
<td>3.9</td>
<td>0.062</td>
</tr>
<tr>
<td>Infections</td>
<td>1.2</td>
<td>2.9</td>
<td>0.691</td>
</tr>
</tbody>
</table>

*Note: † indicates possible drug-related CTCAEs.*

Paz-Ares et al, JCO 2013
Cost-Effectiveness of Pemetrexed as First-Line Maintenance Therapy for Advanced Nonsquamous Non-small Cell Lung Cancer

Robert Klein, MS.* Ron Wielage, MA. MPH.* Catherine Muehlenbein, MPH. MBA,† Astra M. Liepa, PharmD,† Steve Babineaux, MS, RPh,† Anthony Lawson, MA,† and Lee Schwartzberg, MD‡

Results: In the prespecified subset of patients with nonsquamous cell histology only, the incremental cost per life-year gained was $122,371 for Pem to observation and $150,260 for Pem to Erl, and Bev was dominated by Pem. In all patients with advanced NSCLC regardless of histologic subtype, using Pem as maintenance therapy led to an incremental cost per life-year gained of $205,597 compared with observation and $312,341 compared with Erl.

Conclusions: Compared with observation and other agents used and/or reimbursed for maintenance therapy in advanced NSCLC, Pem may be considered cost-effective, particularly in patients with nonsquamous cell histology. This analysis is the first to evaluate the cost-effectiveness of maintenance therapy in advanced NSCLC and emphasizes the importance of histology in identifying the appropriate patient for Pem maintenance therapy.

(J Thorac Oncol. 2010;5: 1263–1272)
Cost-Effectiveness of Maintenance Pemetrexed in Patients with Advanced Nonsquamous-Cell Lung Cancer from the Perspective of the Swiss Health Care System

Klazien Matter-Walstra, PhD1,*, Markus Joerger, MD2, Ursula Kühnel3, Thomas Szucs, PhD1, Bernhard Pestalozzi, PhD, MD4, Matthias Schwenkglenks, PhD1

1Institute of Pharmaceutical Medicine, University of Basel, Basel, Switzerland; 2Department of Oncology & Hematology, Cantonal Hospital, St. Gallen, Switzerland; 3Swiss Group for Clinical Cancer Research, Bern, Switzerland; 4Department of Medical Oncology, University Hospital, Zurich, Switzerland

Conclusions: Switch maintenance with pemetrexed in patients with advanced nonsquamous-cell lung cancer after standard first-line chemotherapy is not cost-effective. Uncertainties on the resource use and costs for BSC have a large influence on the cost-effectiveness calculation and should be reported in more detail.

Keywords: best supportive care, cost-effectiveness, health economics, lung cancer, pemetrexed, maintenance treatment.

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Cost-Effectiveness of Continuation Maintenance Pemetrexed After Cisplatin and Pemetrexed Chemotherapy for Advanced Nonsquamous Non–Small-Cell Lung Cancer: Estimates From the Perspective of the Chinese Health Care System

Xiaohui Zeng, PhD¹,²; Liubao Peng, BS²; Jianhe Li, MS¹,²; Gannong Chen, MS³; Chongqing Tan, PhD¹,²; Siying Wang, MS¹,²; Xiaomin Wan, PhD¹,²; Lihui Ouyang, MS¹,²; and Ziyong Zhao, MS¹,²

Conclusions: Continuation maintenance of pemetrexed after a CP strategy for patients with advanced nonsquamous NSCLC is not cost-effective based on a recent clinical trial. Decreasing the price or adjusting the dosage of pemetrexed may be a better option for meeting the treatment demands of Chinese patients

ClinicalTrials.gov identifier: NCT00789373. (Clin Ther. 2013;35:54–65) © 2013 Elsevier HS Journals, Inc. All rights reserved.
SATURN TRIAL

EGFR wild-type with SD following chemotherapy

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Time (months)

erlotinib (n=114)
placebo (n=103)

Overall survival

HR: 0.77 (0.61-0.97); p=0.0243

Number at risk
Erlotinib: 199 186 147 115 91 72 52 30 17 13 4 2 0
Placebo: 189 165 133 103 75 54 31 15 11 7 4 0
# SATURN, Toxicity Data

| Table 2: Treatment-related Adverse Events (grades 2-3 and grade 4) by body system reported in more than 5% of patients treated with erlotinib. |
|------------------------|-----------------|-----------------|-----------------|
|                        | Erlotinib (N = 9) | All (N = 11)    | None            |
| Patients with one or more treatment-related adverse events | | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash                      | 0 (0)           | ...             | ...             |
| Pruritus                  | ...             | ...             | ...             |
| Gastrointestinal disorders|                   |                  |                  |
| Diarrhoea                 | 14 (3)          | 0 (0)           | 0 (0)           |
| General disorders and adverse consequences | 13 (3) | 1 (<1) | 1 (<1) |
| Metabolism and nutrition  | 1 (<1)          | 10 (2)          | 1 (<1)          |
| Anorexia                  | 1 (<1)          | 10 (2)          | 1 (<1)          |
| Infections and infestations| 4 (1)          | 1 (<1)          | 0 (0)           |
| Data are not available for grade 4 adverse events. | | | |

Cappuzzo et al; The Lancet Oncology 2010; 11:521-529 (DOI:10.1016/S1470-2045(10)70112-1)
Risk-benefit comments:

• FACT QoL: No significant differences in overall quality of life
• 16% of patients required dose reduction
• 5% of patients permanent discontinuation
• Rash and diarrhea significantly more common in the erlotinib arm, albeit mostly moderate in severity (G1-2)
• Inability to use Erlotinib as second-line treatment
Erlotinib Monotherapy for the Maintenance Treatment of Non-Small Cell Lung Cancer after Previous Platinum-Containing Chemotherapy

A NICE Single Technology Appraisal

Rumona Dickson,1 Adrian Bagust,1 Angela Boland,1 Michaela Blundell,1 Helen Davis,2 Yenal Dundar,1 Juliet Hockenhull,1 Carlos Martin Saborido,1 James Oyee1 and Vidhya Sagar Ramani3

The ERG recalculated the base-case cost-effectiveness results in the manufacturer’s submission, considering nine key areas where corrections and/or adjustments were required, related to time horizon, discounting logic, costs of erlotinib and pemetrexed, cost of second-line chemotherapy, unit costs, utility values, PFS and OS. This resulted in ERG-revised ICERs for the stable disease squamous population of £44 812 per QALY gained, in the stable disease non-squamous population of £68 120 per QALY gained, and, when erlotinib was compared with pemetrexed, the result was £84 029 per QALY gained. All values were above NICE’s perceived willingness-to-pay threshold. After the second Appraisal Committee meeting, the Committee did not recommend the use of erlotinib in this patient population.
A cross-market cost comparison of erlotinib versus pemetrexed for first-line maintenance treatment of patients with locally advanced or metastatic non-small-cell lung cancer

Mark J.C. Nuijten, Javier de Castro Carpeño, Christos Chouaid, Alain Vergnenègre, Francesco Grossi, Helge Bischoff, David Heigener, Stefan Walzer

Fig. 2. Average monthly per-patient costs of treating adverse events associated with erlotinib or pemetrexed first-line maintenance therapy.
Comparison of treatment costs of grade 3/4 adverse events associated with erlotinib or pemetrexed maintenance therapy for patients with advanced non-small-cell lung cancer (NSCLC) in Germany, France, Italy, and Spain

Kurt Banz\textsuperscript{a,*}, Helge Bischoff\textsuperscript{b}, Matthias Brunner\textsuperscript{a}, Christos Chouaid\textsuperscript{c}, Javier de Castro Carpeño\textsuperscript{d}, Filippo de Marinis\textsuperscript{e}, Francesco Grossi\textsuperscript{f}, Alain Vergnenègre\textsuperscript{g}, Stefan Walzer\textsuperscript{h}

**Fig. 1.** Total average per-patient management costs of grade 3/4 adverse events associated with erlotinib or pemetrexed maintenance therapy in patients with advanced NSCLC.

Erlotinib maintenance therapy in patients with advanced NSCLC causes lower AE management costs than pemetrexed maintenance therapy indicating a potentially superior tolerability profile.

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Bevacizumab maintenance in NSCLC?

- Continuation of bevacizumab until disease progression was inherent in the design of all registration clinical trials of bevacizumab in advanced NSCLC (E4599, AVAIL).

- Clinical trial design does not allow a clear conclusion of whether the observed benefit is derived from the addition of bevacizumab in the induction phase or in the maintenance phase or in both.
Societal savings in patients with advanced non-squamous non-small-cell lung cancer receiving bevacizumab-based versus non-bevacizumab-based treatments in France, Germany, Italy, and Spain.
Conclusion: This analysis shows that bevacizumab-based treatment in non-small-cell lung cancer is associated with more savings to society compared to standard chemotherapy in terms of increased productivity and decreased social benefits paid to patients who are able to work in France, Germany, Italy, and Spain.
Bev+ Erlotinib: Not cost-effective in most health care systems

ATLAS: Progression-Free Survival

Proportion Without Event

Survival (months)

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>15</th>
<th>18</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bev</td>
<td>27</td>
<td>15</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Bev + Erlotinib</td>
<td>43</td>
<td>20</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>
Bev + Pem: Not cost-effective in most health care systems.

AVAPERL: PFS

Barlesi, et al. EMCC 2011
Issues to Consider Regarding Maintenance Therapy

- **The big question** about maintenance therapy is WHO to treat and WHEN to treat in a COST-EFFECTIVE way without compromising EFFICACY.
- **How do these trials relate** to the patients I am treating in my office?
- If **6 cycles of platinum chemotherapy** are given, are the maintenance data still relevant?
- If a patient achieves **stable disease (SD) and remains symptomatic**, is subsequent therapy “maintenance” or “early second-line therapy”?
- **What about the underlying molecular profile** of the individual patient?
- In the emerging era of personalized therapy, these decisions should be made on an individual basis: “One size does not fit all”
Conclusions

• Maintenance treatment in advanced NSCLC should be individualized taking into consideration efficacy outcomes, adherence to treatment, toxicity and impact on Quality of life.

• Cost-effectiveness of maintenance treatment largely depends on health care systems across Europe and the parameters taken into account in the pharmacoeconomic analysis.

• For maintenance treatment combinations of novel agents that prolong PFS but not OS, it is highly unlikely that they will represent cost-effective options for most European countries.
Ευχαριστώ πολύ...