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Maintenance and Duration of Therapy for Nonsmall Cell Lung Cancer

Is this an historical and outdated approach to NSCLC treatment?

- As a result of cumulative toxicity, patients receive a limited number of cycles of chemotherapy.

- According to ASCO guidelines, those with stable disease or better will be observed, with regular follow-up to check for disease progression – “Watch and Wait” approach.1


CR = complete response; NSCLC = nonsmall cell lung cancer; PD = progressive disease; PR = partial response; SD = stable disease.


"I need to believe that something extraordinary is possible...!"

"A Beautiful Mind"

Maintenance Therapy: Strategies

- Continuation of a doublet beyond 4 cycles
- Continuation of a targeted agent
  - Carboplatin/paclitaxel/bevacizumab followed by bevacizumab or cisplatin/vinorelbine and cetuximab followed by cetuximab
- Continuing one of the same agents from the original combination
  - Cisplatin and pemetrexed followed by pemetrexed as maintenance or carboplatin or cisplatin and gemcitabine followed by gemcitabine
  - Carboplatin and paclitaxel followed by paclitaxel
- Initiating a new agent ("switch")
  - Platinum-based combos followed by pemetrexed
  - Carboplatin and gemcitabine followed by docetaxel
  - Platinum-based doublets followed by erlotinib, bevacizumab, gefitinib

NONE with an improvement in OS in ITT pop.

ITT = intent-to-treat; OS = overall survival.
Randomized Phase III Trial: Point Break – Study Design

[Diagram of study design]

**Primary endpoint**
Overall Survival

Randomized Phase III Trials:
ECOG 5508: Study Design

IIB/IV nonsquamous NECLC PS0/1
No Prior Tx
N = 1338

Primary endpoint

Carboplatin
Paclitaxel
Bevacizumab
X 4 cycles

Bevacizumab
Pemetrexed

Bevacizumab
Pemetrexed

Overall

NCT 00948675: Study Design

IIB/IV nonsquamous NECLC
N = 360

Primary endpoint

Carboplatin
Paclitaxel
Bevacizumab
X 4 cycles

Bevacizumab
Pemetrexed

Overall

PFS without grade 4 toxicity

NCT 00948675: Study Design

Primary endpoint

Carboplatin
Paclitaxel
Bevacizumab
X 4 cycles

Bevacizumab
Pemetrexed

Overall

PFS without grade 4 toxicity

**Notes:**
- Bevacizumab in Lung: CP + carboplatin + paclitaxel; CG = cisplatin + gemcitabine; EGFR = epidermal growth factor receptor; PS0/1 = PS0 or PS1; PS2 = PS2;
- IHC = immunohistochemistry.

**Randomized Phase III Trial: Point Break – Study Design**

**Primary endpoint**
Overall Survival

**Randomized Phase III Trials:**

**ECOG 5508: Study Design**

IIB/IV nonsquamous NECLC PS0/1
No Prior Tx
N = 1338

Primary endpoint

Carboplatin
Paclitaxel
Bevacizumab
X 4 cycles

Bevacizumab
Pemetrexed

Bevacizumab
Pemetrexed

Overall

PFS without grade 4 toxicity

**Notes:**
- Bevacizumab in Lung: CP + carboplatin + paclitaxel; CG = cisplatin + gemcitabine; EGFR = epidermal growth factor receptor; PS0/1 = PS0 or PS1; PS2 = PS2;
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**Randomized Phase III Trial: Point Break – Study Design**

**Primary endpoint**
Overall Survival

**Randomized Phase III Trials:**

**ECOG 5508: Study Design**

IIB/IV nonsquamous NECLC PS0/1
No Prior Tx
N = 1338

Primary endpoint

Carboplatin
Paclitaxel
Bevacizumab
X 4 cycles

Bevacizumab
Pemetrexed

Bevacizumab
Pemetrexed

Overall

PFS without grade 4 toxicity

**Notes:**
- Bevacizumab in Lung: CP + carboplatin + paclitaxel; CG = cisplatin + gemcitabine; EGFR = epidermal growth factor receptor; PS0/1 = PS0 or PS1; PS2 = PS2;
- IHC = immunohistochemistry.
Randomized Phase III Trials: AVAPERL1: Study Design

- Median follow-up time for this analysis was 7.6 months
- Median age of the safety population was 60.0 years, and
the majority of patients (92.2%) had stage IV disease at
study entry

AVAPERL1: Study Design

Primary endpoint
Progression Free Survival

- Carboplatin
Paclitaxel
Bevacizumab
X 4 cycles

CR
PR
SD
N = 244

Bevacizumab
(Pem) N = 119

Bevacizumab
(Pem) N = 125

Carboplatin
Paclitaxel
Bevacizumab

Continuation of a doublet beyond 4 cycles

Continuation of a targeted agent

• Carboplatin and paclitaxel followed by paclitaxel

Initiating a new agent (“switch”)

• Platinum-based combos followed by pemetrexed
• Carboplatin and gemcitabine followed by docetaxel
• Platinum-based doublets followed by erlotinib, bevacizumab, gefitinib

Maintenance Therapy: Strategies

Work in Progress

AVAPERL1: Interim Safety Data

Median follow-up time for this analysis was 7.6 months
Median age of the safety population was 60.0 years, and
the majority of patients (92.2%) had stage IV disease at
study entry

AVAPERL1 = A Study of Bevacizumab With or Without Pemetrexed as Maintenance Therapy After Induction of a Doublet in Patients With Non-Squamous NSCLC.
Phase III Trial of “Maintenance”
Gemcitabine in Nonprogressing Advanced
NSCLC Following 4 Cycles of CG

- Primary endpoint: TTP (OS secondary)
- 352 patients entered
  - 257 “nonprogressors” after 4 cycles
  - 206 randomized (61%)
- TTP significantly increased in those randomized to GEM (6.6 vs 5.0 months, P<.001)
- OS not significantly different (13.0 vs 11.0, P=.2). In good PS pts, a worse survival in BSC arm (8.3 vs 22.9, HR = 2.1)
- Toxicity: maintenance GEM well tolerated but more transfusions required

IFCT-GFPC 0502: Study Design

- Primary endpoint: independent review with 80% power to detect 50% improvement in median PFS. PFS by each comparison (Gem vs Obs and Erl vs Obs).
- Secondary endpoints: OS, safety, symptom control, prognostic and predictive effect of tumor EGFR status (IHC, EGFR mut)

IFCT-GFPC 0502: Results

- Patients who received second-line pemetrexed: 73% (Obs), 55% (Gem), and 60% (Erl)
- Grade 3–4 treatment-related AEs were more common in Gem (27%) and Erl (14%) than in Obs (2%).

BSC = best supportive care only arm; GEM = best supportive care arm; PS = performance status; TTP = time to progression.


IFCT-GFPC 0502: Study Design

- Objective response rates at ends of cycles 1-2:
  - Stage IA n=8, IF (n=1), NS (n=7), A (n=2)
  - Stage IB n=2, IF (n=1), NS (n=1), A (n=1)
  - Stage IIA n=13, IF (n=3), NS (n=4), A (n=6)
  - Stage IIB n=25, IF (n=5), NS (n=7), A (n=13)

- Objective response rates at ends of cycles 4-6:
  - Stage IB n=2, IF (n=1), NS (n=1)
  - Stage IIA n=20, IF (n=5), NS (n=5), A (n=10)
  - Stage IIB n=15, IF (n=4), NS (n=5), A (n=6)

- Progression-free survival (PFS) by each comparison (Gem vs Obs and Erl vs Obs).

- Secondary endpoints: OS, safety, symptom control, prognostic and predictive effect of tumor EGFR status (IHC, EGFR mut)

- Toxicty: maintenance GEM well tolerated but more transfusions required
PARAMOUNT: Study Design

Study Treatment Period

**Primary Endpoint**
Progression-Free Survival

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

- Folic acid and vitamin B12 administered to both arms

**PARAMOUNT**: Phase III study of maintenance pemetrexed (pem) plus best supportive care (BSC) versus placebo plus BSC immediately following induction treatment with pem plus cisplatin for advanced nonsquamous non-small cell lung cancer (NSCLC).


**Patient Characteristics**

Continuation of a doublet beyond 4 cycles
Continuation of a targeted agent
- Carboplatin/paclitaxel/bevacizumab followed by bevacizumab or cetuximab
- Carboplatin/paclitaxel/bevacizumab or carboplatin/paclitaxel/gemcitabine and cetuximab
  
A Treatment Opportunity
- Carboplatin/paclitaxel/bevacizumab followed by bevacizumab or cisplatin/vinorelbine and cetuximab
- Continuing one of the same agents from the original combination
- Cisplatin and pemetrexed followed by pemetrexed as maintenance or carboplatin (or cisplatin) and gemcitabine followed by gemcitabine
- Carboplatin and paclitaxel followed by paclitaxel
  
Initiating a new agent (“switch”)
- Platinum-based combos followed by pemetrexed
- Carboplatin and gemcitabine followed by docetaxel
- Platinum-based doublets followed by erlotinib, bevacizumab, gefitinib

“...It is said that the slightest flutter of a butterfly is able to cause a hurricane halfway around the world.”
“...The Butterfly Effect”
Immediate versus Delayed Second-Line Docetaxel in Advanced NSCLC

- Chemo-naïve
- Stage IIIIB/IV NSCLC
- Gemcitabine 1,000 mg/m² d1, 8 × 4 cycles (N = 398)
- Carboplatin (AUC = 5), day 1, every 21 days

Primary endpoint: OS measured from date of randomization until death
Secondary endpoints: tumor response rate, PFS, toxicity, quality of life

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Maintenance Used</th>
<th>PFS mo (HR)</th>
<th>OS mo (HR)</th>
<th>2nd Line Rx in Control Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fidias</td>
<td>2008</td>
<td>Docetaxel</td>
<td>6.71</td>
<td>12.3</td>
<td>63%</td>
</tr>
<tr>
<td>Culeanu</td>
<td>2009</td>
<td>Pemetrexed</td>
<td>4.0</td>
<td>13.4</td>
<td></td>
</tr>
<tr>
<td>Cappuzzo</td>
<td>2009</td>
<td>Erlotinib</td>
<td>12.0</td>
<td>12.0</td>
<td>72%</td>
</tr>
<tr>
<td>Wilke</td>
<td>2009</td>
<td>Erlotinib</td>
<td>0.72</td>
<td>0.90</td>
<td>56%</td>
</tr>
<tr>
<td>Perli</td>
<td>2010</td>
<td>Erlotinib</td>
<td>2.9</td>
<td>3.8</td>
<td>82%</td>
</tr>
<tr>
<td>Takeda</td>
<td>2010</td>
<td>Gefitinib</td>
<td>0.68</td>
<td>0.86</td>
<td>72%</td>
</tr>
<tr>
<td>Zhang</td>
<td>2011</td>
<td>Gefitinib</td>
<td>2.6</td>
<td>18.7</td>
<td>72%</td>
</tr>
</tbody>
</table>

HR = hazard ratio; pem = pemetrexed; Rx = prescription; wks = weeks.
The Relevance of Second Line

<table>
<thead>
<tr>
<th></th>
<th>Randomized Pts (Median OS)</th>
<th>Pts who Actually Received Docetaxel (Median OS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed Docetaxel</td>
<td>9.7 m</td>
<td>13.2 m</td>
</tr>
<tr>
<td>Immediate Docetaxel</td>
<td>12.3 m</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systemic Anticancer Therapy</th>
<th>Pemetrexed</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any systemic anticancer therapy</td>
<td>51%</td>
<td>63%</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>&lt;1%</td>
<td>18%</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>22%</td>
<td>29%</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>22%</td>
<td>21%</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>13%</td>
<td>10%</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>13%</td>
<td>17%</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>9%</td>
<td>14%</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>4%</td>
<td>6%</td>
</tr>
</tbody>
</table>


The Relevance of Second Line/Cross-over

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>Cross-over %</th>
<th>Any agent %</th>
</tr>
</thead>
</table>

INFORM = Assess the Efficacy, Safety and Tolerability of Gefitinib (250mg) as Maintenance Therapy in Locally Advanced or Metastatic (Stage IIIB/IV) Non Small Cell Lung Cancer.

Personalized Therapy in Maintenance?
- PS
- Response to Induction
- I stology
- EGFR Mutational Status
PS in Maintenance

- PS is a variable associated with worsened survival

### Maintenance: Response to Induction

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>Responder (CR/PR)</th>
<th>Stable Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fidias</td>
<td>Docetaxel</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>JMEN</td>
<td>Pemetrexed</td>
<td>81 (p=n.s.)</td>
<td>81 (P &lt; .05)</td>
</tr>
<tr>
<td>SATURN</td>
<td>Erlotinib</td>
<td>94 (p=.618)</td>
<td>72 (P = .0019)</td>
</tr>
<tr>
<td>Belani</td>
<td>Gemcitabine</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>IFCT</td>
<td>Gemcitabine</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>PARAMOUNT</td>
<td>Pemetrexed</td>
<td>48 (significant)</td>
<td>7</td>
</tr>
<tr>
<td>INFORM</td>
<td>Gefitinib</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR = no response.

### Meta-analysis Belani/Ramalingam

**ASCO 2011**

Scorecard for Maintenance in NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>PFS</th>
<th>OS</th>
<th>Adeno</th>
<th>Wome</th>
<th>Never smoke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fidias</td>
<td>Docetaxel</td>
<td>+++</td>
<td>trend</td>
<td>47%</td>
<td>38%</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Immediate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciuleanu</td>
<td>Placebo</td>
<td>++++</td>
<td>++</td>
<td>48%</td>
<td>28%</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td>Pemetrexed</td>
<td></td>
<td></td>
<td>50%</td>
<td>26%</td>
<td>27%</td>
</tr>
<tr>
<td>SATURN</td>
<td>Placebo</td>
<td>++++</td>
<td>+</td>
<td>44%</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>Erlotinib</td>
<td></td>
<td></td>
<td>47%</td>
<td>18%</td>
<td>18%</td>
</tr>
<tr>
<td>CIUULEANU</td>
<td>Bevacizumab</td>
<td>++++</td>
<td>-</td>
<td>81%</td>
<td>48%</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>Erlotinib</td>
<td></td>
<td></td>
<td>82%</td>
<td>48%</td>
<td>18%</td>
</tr>
<tr>
<td>IPTEC</td>
<td>Observation</td>
<td>+++ (G)</td>
<td>(E)</td>
<td>67%</td>
<td>27%</td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine</td>
<td></td>
<td></td>
<td>66%</td>
<td>27%</td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td>Erlotinib</td>
<td></td>
<td></td>
<td>63%</td>
<td>27%</td>
<td>38%</td>
</tr>
</tbody>
</table>

Adeno = adenocarcinoma.

EGFR Mutations and Maintenance

- All studies that involve patients with EGFR mutations and EGFR TKIs demonstrate substantial PFS advantage.
- Conversely, almost no benefit in EGFR mutation-negative patients.

Quality of Life in Maintenance Therapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Instrument</th>
<th>Overall</th>
<th>Specific Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fidias</td>
<td>2008</td>
<td>LCSS</td>
<td>Better (not sig)</td>
<td>-</td>
</tr>
<tr>
<td>Ciuleanu</td>
<td>2009</td>
<td>LCSS</td>
<td>No difference</td>
<td>Delayed time to pain &amp; haemoptysis</td>
</tr>
<tr>
<td>Cappuzzo</td>
<td>2009</td>
<td>FACT-L</td>
<td>No difference</td>
<td>Delayed time to pain &amp; analgesic use</td>
</tr>
<tr>
<td>Miller</td>
<td>2009</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Perol</td>
<td>2010</td>
<td>-</td>
<td>nr</td>
<td>NR</td>
</tr>
<tr>
<td>Paz Ares</td>
<td>2011</td>
<td>EG5D</td>
<td>No difference</td>
<td>-</td>
</tr>
<tr>
<td>Zhang</td>
<td>2011</td>
<td>-</td>
<td>nr</td>
<td>NR</td>
</tr>
</tbody>
</table>
Conclusions (1)

- There is no evidence to support prolonged administration of doublet first line chemotherapy beyond 4–6 cycles.
- Even more than in other settings, during maintenance therapy, it is essential that the selection of the right patient population and “treatment-free interval” after first line REMAINS an option.
- Maintenance approach is ONLY another treatment possibility that we may consider in those patients who tolerated platinum-based therapy, with PS 0 or 1, without relevant clinical toxicities and who desire to continue therapy.

Conclusions (2)

- Considering maintenance approach as a treatment for your patient, remember:
  - It’s unlikely that all patients will benefit from it
  - Fix a second line therapy could be successful
  - Monitor with criteria and timing properly
  - Use a drug that works
  - Check also grade 1 and 2 toxicities, because it also impacts the patients’ quality of life in a disease where the primary goal is palliative care and OS remains modest.


“I’m too serious to be an amateur, and not serious enough to become a professional.”

— "La Dolce Vita," Federico Fellini