Maintenance Therapy in the Management of Non-Small Cell Lung Cancer

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Scott Taylor Chair in Lung Cancer Research
Princess Margaret Hospital, Professor of Medicine, University of Toronto

Maintenance Therapy Options

• Chemotherapy
  • Continue same doublet chemotherapy
  • Continue same single agent chemotherapy
  • Switch to new single agent chemotherapy

• Targeted agents
  • Continue targeted agent used with chemotherapy
  • Switch to a new targeted agent
  • Add a new (2nd) targeted agent

Maintenance Chemotherapy

Continuing Same First-Line Single Agent Induction Chemotherapy Without the Platinum Analogue
**Advanced NSCLC**

**Gemcitabine Maintenance Therapy**

Stage IV NSCLC (n=352)
- CR / PR / SD after cisplatin/gemcitabine (n=206)

Maintenance gemcitabine 1250 mg/m² day 1, 8 Q3W
- (No cisplatin)

BSC only

Primary endpoint: median time to progression

Brodowicz et al, Lung Cancer 2006; 52: 155-163

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**Advanced NSCLC**

**Gemcitabine Maintenance Therapy**

Progression-Free Survival

PFS from the date of starting first-line chemotherapy P<0.001

Overall survival: 13.0 mos vs 11.0 mos, p= 0.19

Brodowicz et al, Lung Cancer 2006; 52: 155-163

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**POI-01-003-050: Phase III Study of Maintenance Gemcitabine after Standard First-Line Therapy in Advanced NSCLC**

Stage IIIb/IV NSCLC
- PS 0 - 2
- N=332

Gem d 1.8 + carbo AUC 5 d1 X 4 cycles or SD

PD / Off study

Gemcitabine 1000 mg/m² d1 + BSC 21 day cycle

N=600

Primary endpoint: OVERALL Survival

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Progression-Free Survival

HR = 1.09 (0.81-1.45)  
P = 0.575

Belani et al. Proc ASCO, 2010

Slide 8

Overall Survival

HR = 0.97 (0.72-1.30)  
P = 0.838

Belani et al. Proc ASCO, 2010

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IFCT-GFPC 0502 Study Design

Progression:
2nd line
Primary endpoint: PFS

Arm A: Cisplatin 80 mg/m² d1 + gemcitabine 1.250 mg/m² d1, d8
Arm B: gemcitabine 1.250 mg/m² d1, d8 Q3wks
Arm C: erlotinib 150 mg PO daily
**Slide 10**

**PFS by Independent Review**

<table>
<thead>
<tr>
<th></th>
<th>Observation</th>
<th>Gemcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR</strong></td>
<td>1.0</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>Log-rank test, p</strong></td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>152</td>
<td>149</td>
</tr>
<tr>
<td><strong>Median PFS, months</strong></td>
<td>1.9</td>
<td>3.8</td>
</tr>
<tr>
<td><strong>PFS at 3 months, %</strong></td>
<td>30.3</td>
<td>55.0</td>
</tr>
<tr>
<td><strong>PFS at 6 months, %</strong></td>
<td>8.6</td>
<td>22.1</td>
</tr>
</tbody>
</table>

Perol et al. Proc ASCO, 2010

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**Slide 11**

**PARAMOUNT Study Design**

- **Induction treatment period (unblinded):** Four cycles of pemetrexed (500 mg/m², Day 1) + cisplatin (75 mg/m², Day 1)*(approximately 900 patients)
- **Blinded maintenance period:** 2:1 randomization
- **Time to documented response of CR, PR, or SD and have an ECOG PS of 0 or 1**

*Patients received folic acid, vitamin B₁₂, and dexamethasone.

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**PARAMOUNT: Investigator Assessed PFS (from Maintenance)**

- **Pemetrexed:** median = 4.1 mos (3.2-4.6)
- **Placebo:** median = 2.8 mos (2.6-3.1)
- **Log-rank P = 0.00006**
- **Unadjusted HR: 0.62 (0.49-0.79)**

**PARAMOUNT: Independently Reviewed PFS (472/539)**

**Survival Probability**

- **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)


**PARAMOUNT: Subgroup PFS HRs**

- Favors Pemetrexed
- Favors Placebo

**PARAMOUNT: Independently Reviewed PFS (472/539)**

**Survival Results Awaited**

- P=0.0002
- Unadjusted HR: 0.64 (0.51-0.81)

Survival Results Awaited

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**PointBreak: Pem/Carbo/Bev Followed by Maintenance Pem/Bev vs Paclitaxel/Carbo/Bev in Stage IIIB or IV Nonsquamous NSCLC**

- Determination of eligibility
- Pem 500mg/m² q 21 D
- Carb AUC 6 q 21 D
- Bev 15 mg/kg q 21 D
- Vitamin Supplement as per label
- N=450

- Pac 200 mg/m² q21 D
- Carb AUC 6 q 21 D
- Bev 15 mg/kg q 21 D
- Premedication as per label
- N=450

- Post-Discontinuation
- Follow-up
- Pts with PD: FU every 90 days until death
- Pts without PD: FU every 6 weeks until PD; thereafter, follow-up every 90 days until death

- Induction Therapy: Up to 4 21 day cycles
- Pts CR, PR, or SD after 4 cycles of induction therapy continue on maintenance therapy

- Maintenance Therapy: Until PD or treatment discontinuation


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**Maintenance Chemotherapy**

Switching to a New Chemotherapy Agent in Responding and Stable Patients

(Usually a Single Agent)

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**Immediate versus Delayed Docetaxel**

- Chemotherapy
  - Stage IIIb/IV NSCLC
  - ORR 22%
  - GC Phase N = 552
  - ORR randomization
  - OR Study N = 242
  - Immediate Treated N = 153
  - Immediate Treated N = 142
  - Randomized
  - Delayed Treated N = 154
  - Delayed Treated N = 91

Progression-Free Survival
Total Randomized Population

Immediate (n=153)          Delayed (n=154)

LR p-Value
Significant

Median PFS
(months)
95% CI
Immediate 6.5 (4.4, 7.2)
Delayed 2.8 (2.6, 3.4)

12-month PFS %
Immediate 20% (13, 26)
Delayed 9% (5, 14)

Overall Survival
Total Randomized Population

Overall Survival Time (in Months)
Survival Probability

Immediate (n=153)          Delayed (n=154)

LR p-Value
Significant

Median OS, months
95% CI
Immediate 11.9 (10.0, 13.7)
Delayed 9.1 (8.0, 11.2)

12-month survival
95% CI
Immediate 48.5% (39.9, 57.1)
Delayed 38.3% (30.0, 46.5)

Is this negative for survival benefit or under-powered??

JMEN: Phase III Study of Maintenance Pemetrexed after Standard First-Line Therapy in Advanced NSCLC

Stage IIIB or IV NSCLC who has not progressed after 4 cycles of standard chemotherapy

Pemetrexed 500 day 1

N = 660 Patients

Primary objective: PFS, Superiority design

Secondary objectives: RR, OS, TTPD, TWQ (Time to Worsening QOL), QOL based on LCSS
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**JMEN: Progression-Free Survival**

- **N=581**
- **HR=0.599 (95% CI: 0.49–0.73)**
- **p <0.00001**

Pemetrexed: 4.04 mos (95% CI: 3.06–4.44)
Placebo: 1.97 mos (95% CI: 1.54–2.76)

Ciuleanu, et al. Presented at: Annual Meeting of the American Society of Clinical Oncology, June 2, 2008; Chicago, IL.

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**Overall Survival, All Randomized Patients**

- **Ciulanu et al. Lancet, 2009**
- **HR 0.79, CI 0.67-0.95, p=0.012**

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**Non-Squamous Subset**

- PFS and OS in the non-squamous subset
- **PFS HR 0.44, p<0.0001**
- **OS HR 0.70, p=0.002**
- **16.4 vs 11.7 months for adeno**

Ciulanu et al. Lancet, 2009
Meta-Analysis of Continuation vs Switch Maintenance

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<tr>
<th>Population</th>
<th>HR PFS</th>
<th>P</th>
<th>HR OS</th>
<th>P</th>
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<tr>
<td>All</td>
<td>0.84</td>
<td>&lt;0.0001</td>
<td>0.87</td>
<td>0.0003</td>
</tr>
<tr>
<td>Switch</td>
<td>0.77</td>
<td>&lt;0.0001</td>
<td>0.86</td>
<td>0.0005</td>
</tr>
<tr>
<td>Continuation</td>
<td>0.92</td>
<td>&lt;0.0007</td>
<td>0.92</td>
<td>0.33</td>
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<tr>
<td>Chemotherapy</td>
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<td>0.006</td>
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Behera M. Proc ASCO, Abst 7553, 2011
ATLAS: Bevacizumab +/- Erlotinib Maintenance After First-Line Treatment

**Chemotherapy naïve stage IIIb/IV non-squamous NSCLC**

- Bevacizumab + placebo
- Erlotinib

- Off-study
- Off-study

- Primary endpoint: PFS

**PI:** Dr W Navarro (USA)

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**PointBreak: Pem/Carbo/Bev Followed by Maintenance Pem/Bev vs Paclitaxel/Carbo/Bev in Stage IIIB or IV Nonsquamous NSCLC**

**Induction Therapy**

- Up to 4 21 day cycles
- Pts CR, PR, or SD after 4 cycles of induction therapy continue on maintenance therapy

**Maintenance Therapy**

- Until PD or treatment discontinuation


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**Maintenance Therapy With Oral Angiogenesis Inhibitors**

- Randomized trials performed with numerous agents administered with chemotherapy
- All continued oral AI when chemotherapy stopped (in the absence of toxicity)
- Until there is a positive trial of an oral AI, this question is of academic interest only
CALGB 30607: Sunitinib Maintenance Therapy Post Chemotherapy

- Phase III, randomized, placebo-controlled trial
- Planned randomization: 156 patients
- Continuous until disease progression†
- Planned follow-up: 1 year

Sunitinib 37.5 mg/day
Placebo

Randomization of responding patients or patients with stable disease stratified by prior treatment with/without bevacizumab

Patients with untreated stage IIIB/IV NSCLC and ECOG PS 0–1

Four cycles of platinum-based chemotherapy*

*Platinum-based regimen may include carboplatin/cisplatin plus paclitaxel, docetaxel, vinorelbine or gemcitabine with or without bevacizumab (bevacizumab discontinued after four cycles)

†At progression, patients receiving placebo may cross over to the sunitinib arm

EORTC 08092: Pazopanib Maintenance Therapy Post Chemotherapy

- Phase III, randomized, placebo-controlled trial
- Planned randomization: 540 patients
- Continuous until disease progression†
- Planned follow-up: 1 year

Pazopanib 800mg/day
Placebo

Randomization of responding patients or patients with stable disease stratified by prior treatment with/without bevacizumab

Patients with untreated stage IIIB/IV NSCLC and ECOG PS 0–2

Four cycles of platinum-based chemotherapy*

*Platinum-based regimen may include carboplatin/cisplatin plus paclitaxel, docetaxel, vinorelbine or gemcitabine with or without bevacizumab (bevacizumab discontinued after four cycles)

†At progression, patients receiving placebo may cross over to the sunitinib arm

Continuation of the Molecularly Targeted Agent After Chemotherapy is Completed

EGFR Monoclonal Antibodies
Cetuximab
Introduction of Switch Maintenance Therapy with EGFR TKIs

ATLAS
SWOG 0023
WJTOG-0203
(EORTC 08021)
SATURN
INFORM

ATLAS: Bevacizumab +/- Erlotinib Maintenance After First-Line Treatment

Bevacizumab + placebo
Chemotherapy naïve stage IIIb/IV non-squamous NSCLC
Erlotinib Non-PD
1:1 Bevacizumab plus chemotherapy*
PD or significant toxicity
• Primary endpoint: PFS
PI: Dr W Navarro (USA)

ATLAS: Progression-Free Survival
(ITT population, investigator assessment)

No. of patients at risk:
Bev + Placebo
Bev + Erlotinib

Progression-Free Survival (months)

Proportion without event

HR=0.722 (0.592 - 0.881)
Log-rank P =0.0012
October 15, 2009, Roche has communicated to OSI that an exploratory ATLAS data sweep for survival was not positive. OS was a 2nd endpoint and the study was not powered for OS!!!!!
**Slide 40**

**SWOG 0023 (Update): Survival**

Progression-Free Survival

Overall Survival

Kelly K et al. J Clin Oncol 26: 2450, 2008

**Slide 41**

**WJTOG -0203: Maintenance with Gefitinib in Patients with NSCLC**

IIIB/IV NSCLC PS 0-1 (n=604)

Stratify Institution Histology Stage Chemo

1st-line platinum-based chemotherapy x 6 cycles

1st-line platinum-based chemotherapy x 3 cycles Gefitinib 250 mg/d

1st Endpoint Overall Survival Designed to detect a 3 mo difference from 9 to 12 mos

**Slide 42**

**WJTOG-0203: Survival Results**

Overall Survival

MST: 12.9 m vs 13.7 m

HR: 0.86, p=0.11

Median PFS

MST: 4.3 m vs 4.6 m

HR: 0.67, p<0.001

**WJTOG-0203: Post-Study Therapy**

**EGFR TKI at any time**

54%

75%

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**MST in Non-smoking patients with adenocarcinoma**

Arm A 23.5 months
Arm B 25.1 months

>75% of these patients on Arm A received an EGFR TKI at the time of progression

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**SATURN: First-line Phase III Erlotinib Maintenance Trial in Patients with NSCLC**

1st-line III/IV NSCLC (n=1,700)

1st-line platinum-based chemotherapy x 4 cycles

1st Endpoint

- PFS
- Overall: 25% better
- EGFR IHC+: 30% better

PFS patients enter the 2nd-line study TITAN
Slide 46

SATURN: PFS in All Patients (ITT)

PFS probability

HR=0.71 (0.62–0.82)
Log-rank p<0.0001

Erlotinib (n=437)
Placebo (n=447)
PFS at 12 wks (%) 53 40
PFS at 24 wks (%) 31 17

Log-rank p<0.001

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Saturn: OS in all patients (ITT)

OS probability

HR=0.81 (0.70–0.95)
Log-rank p=0.0088

Erlotinib (n=438)
Placebo (n=451)

OS is measured from time of randomisation into the maintenance phase;
ITT = intent to treat population

*Closed early

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EORTC 08021

Advanced NSCLC stage IV, # PD 80 (UICC 0)
PE 5.2

Any patients containing radical chemotherapy
(int. 2 – int. 3, 4 cycles)

OR RR = 93
Randomisation in 173

Erlotinib 250mg daily
for 4 weeks

Progression free survival


•Closed early
**Slide 49**

**EORTC 08021**

- HR = 0.61, p = 0.002
- HR = 0.81, p = 0.20

*Gafaar et al. J Clin Oncol 28: (Suppl) Abst 7518, 2010*

**Slide 50**

**IFCT- GFPC 0502 study design**

- IFCT- GFPC 0502 study design
- Progression:
- 2nd line
- Primary endpoint: PFS
- Maintenance treatment
- PD

**Induction chemo:**
- Cisplatin 80 mg/m² d1 + gemcitabine 1,250 mg/m² d1, d8
- Arm B: gemcitabine 1,250 mg/m² d1, d8 every 3 weeks
- Arm C: erlotinib 150 mg PO daily

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**IFCT- GFPC 0502 : PFS**

- Erlotinib vs Observation
- Observation N=152
- Erlotinib N=153
- Median PFS, 1.9 mo vs 2.6 mo
- PFS at 3 months, 36.3% vs 36.3%
- PFS at 6 months, 18.8% vs 16.3%
- HR = 0.82 (0.73–0.93)
- Log-rank test, p = 0.002

*PFS is measured from time of randomisation into the maintenance phase.*
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**INFORM: Study Design**

**Gefitinib**
(250 mg/day)

**Placebo**
(once daily)

1:1 randomization

**Patients**
- Age ≥18 years
- Completed 4 cycles of first-line platinum-based chemotherapy without PD or unacceptable toxicity
- Life expectancy ≥12 weeks
- WHO PS 0–2
- Measurable Stage IIIB/IV disease

**Endpoints**
- **Primary**
  - Progression-free survival (PFS)
- **Secondary**
  - Objective response rate (ORR)
  - Disease control rate (DCR)
  - Overall survival (OS)
  - Quality of life
  - Safety and tolerability
- **Exploratory**
  - Biomarkers
    - EGFR mutation

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**INFORM: Progression-Free Survival**

HR 0.42 (0.33, 0.55); p<0.0001

Gefitinib
(n=148)

Placebo
(n=148)

Median PFS,† months
6

- 12-month PFS rate, %
  - Gefitinib: 47.3%
  - Placebo: 33.2%

- No. events, n (%)
  - Gefitinib: 144 (97.3%)
  - Placebo: 124 (83.8%)

**Zhang et al. Proc ASCO, 2011 LBA 7511**

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**Slide 54**

**ORR & DCR (RECIST; ITT Population)**

<table>
<thead>
<tr>
<th>ORR (%)</th>
<th>Gefitinib (n=148)</th>
<th>Placebo (n=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>71.6%</td>
<td>23.6%</td>
<td>0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DCR (%)</th>
<th>Gefitinib (n=148)</th>
<th>Placebo (n=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>71.6%</td>
<td>23.6%</td>
<td>0%</td>
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</tbody>
</table>

Odds ratio >1 implies a greater chance of response on gefitinib

Odds ratio (95% CI) = 2.69 (1.62, 4.46); p=0.0001

**Zhang et al. Proc ASCO, 2011 LBA 7511**
**Slide 55**

**Post-discontinuation Treatments**

- **Gefitinib**
  - None: 43.3%
  - Targeted therapy: 4.1%
  - Chemotherapy: 35.3%
  - Others: 24.4%

- **Placebo**
  - None: 33.1%
  - Targeted therapy: 31.8%
  - Chemotherapy: 53.4%
  - Others: 23.7%

Zhang et al. Proc ASCO, 2011 LBA 7511

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**INFORM: Overall Survival**

- Gefitinib
  - Median OS: 6 months
  - 12-month survival rate: 79%

- Placebo
  - Median OS: 4 months
  - 12-month survival rate: 53.4%

HR: 0.84 (0.62, 1.14); p=0.2608

Zhang et al. Proc ASCO, 2011 LBA 7511

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**Phase III H3E-CR-S131 Study Schema**

- **Eligibility**
  - NSCLC: Non-squamous histology
  - Stage IIIb/IV
  - Chemo-naïve (1st line)
  - PS: 0-1
  - Never smoker or light ex-smoker
  - Unknown, untested, inconclusive EGFR mutation status

- **Randomization (Stratification) Factors**
  - Gender
  - Smoking History (Never smoker/light ex-smoker)
  - Performance status
  - Adenocarcinoma/Non-adenocarcinoma

- **Primary Endpoint:** Superiority in PFS
  - HR: 0.68

- **Secondary Endpoints:**
  - OS, RR, Safety, Biomarkers

- **Translational Research:** Analysis of outcomes by EGFR mutation status

**Pharmacodynamic Analysis:**
- Determined by IGEP-002
- Assessed by objective tumor response

**Pharmacokinetic Analysis:**
- Determined by IGEP-002
- Assessed by plasma concentration

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**Note:**
- Light ex-smoker: quit from smoking for 5 years and ≤10 pack year.
**Slide 58**

**Meta-Analysis of Continuation vs Switch Maintenance**

<table>
<thead>
<tr>
<th>Population</th>
<th>HR PFS</th>
<th>P</th>
<th>HR OS</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>All</td>
<td>0.84</td>
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<td>0.77</td>
<td>&lt;0.0001</td>
<td>0.86</td>
<td>0.0006</td>
</tr>
<tr>
<td>Continuation</td>
<td>0.92</td>
<td>0.007</td>
<td>0.92</td>
<td>0.33</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>0.87</td>
<td>&lt;0.0001</td>
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</tbody>
</table>

Behera M. Proc ASCO, Abst 7553, 2011

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**Slide 59**

**Why Was There Such a Dramatic Difference Among The Three Trials of Maintenance Gemcitabine ???
Are There Clues to Patient Selection?**

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**Slide 60**

**Potential Predictors of Benefit From Maintenance Therapy**

- Chemotherapy
  - PS
  - Response to first-line treatment
  - Histology
- EGFR TKIs
  - EGFR expression
  - EGFR copy
  - EGFR mutation
  - Histology
Survival by Performance Status

<table>
<thead>
<tr>
<th>Trial</th>
<th>Median Survival (m)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>QG</td>
<td>11.2</td>
<td>8.8-13</td>
</tr>
<tr>
<td>GC</td>
<td>12.2</td>
<td>9.8-14</td>
</tr>
</tbody>
</table>

Patient Demographics

Maintenance Phase

<table>
<thead>
<tr>
<th></th>
<th>GEM</th>
<th>BSC</th>
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</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>67.2</td>
<td>67.4</td>
</tr>
<tr>
<td>Age ≥65 years /&lt;65 years</td>
<td>61/39</td>
<td>59/41</td>
</tr>
<tr>
<td>Stage III/IV disease</td>
<td>22/78</td>
<td>9/91</td>
</tr>
<tr>
<td>Male/Female</td>
<td>60/40</td>
<td>67/33</td>
</tr>
<tr>
<td>Caucasian/AA/Other</td>
<td>83/13/4</td>
<td>88/6/6</td>
</tr>
<tr>
<td>ECOG PS 0/1/2/3</td>
<td>0/44/52/4</td>
<td>0/43/54/4</td>
</tr>
</tbody>
</table>

Belani et al. Proc ASCO, 2010

Performance Status in Other Trials

- JMEN - PS 2 patients *not eligible*
- IFCT 0502 - PS 2 patients *not eligible*; only 5% of randomized patients PS 2
- SATURN - PS 2 patients *not eligible*
- PARAMOUNT - PS 2 patients *not eligible*

*All the above trials were Positive!!!*

- PointBreak - PS 2 patients *not eligible*
Response to First-Line Chemotherapy
CR/PR versus SD

Survival by Response to First-Line Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>CR/PR</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>JMEN (Non-Squam)</td>
<td>0.81</td>
<td>0.61</td>
</tr>
<tr>
<td>IFCT 0502 (PFS)</td>
<td>0.44</td>
<td>0.68</td>
</tr>
<tr>
<td>Belani</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>IFCT 0502 (PFS)</td>
<td>0.80</td>
<td>0.85</td>
</tr>
<tr>
<td>SATURN</td>
<td>0.94</td>
<td>0.72</td>
</tr>
</tbody>
</table>

JMEN: Effect of Response to Induction Rx on OS (Non-Squamous)

Pem 14.4 months  Plac 8.6 months
HR=0.61, p=0.0017

Pem 16.6 months  Plac 8.6 months
HR=0.61, p=0.198

Eli Lilly data on file
### Survival by Response to First-Line Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>CR/PR</th>
<th>SD</th>
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<tbody>
<tr>
<td>JMEN (Non-Squam)</td>
<td>0.81</td>
<td>0.61</td>
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<tr>
<td>PARAMOUNT</td>
<td>0.48</td>
<td>0.74</td>
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<td>IFC 0502 (PFS)</td>
<td>0.44</td>
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<tr>
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### Selection by Histology

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### PFS by Histology

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Continued Doublet Chemotherapy vs Maintenance Gefitinib


Selection by Biomarkers

EGFR
SATURN: PFS According to Biomarker Status

**All**

- **EGFR IHC+**
  - HR (95% CI): 0.71 (0.62–0.82)
  - N: 884

- **EGFR IHC–**
  - HR (95% CI): 0.69 (0.58–0.82)
  - N: 618

- **EGFR FISH+**
  - HR (95% CI): 0.77 (0.51–1.14)
  - N: 121

- **EGFR FISH–**
  - HR (95% CI): 0.68 (0.51–0.90)
  - N: 231

- **KRAS mutation+**
  - HR (95% CI): 0.81 (0.62–1.07)
  - N: 255

- **KRAS wild-type**
  - HR (95% CI): 0.77 (0.50–1.19)
  - N: 90

- **EGFR CA-SSR1 low**
  - HR (95% CI): 0.68 (0.55–0.85)
  - N: 403

- **EGFR CA-SSR1 high**
  - HR (95% CI): 0.75 (0.60–0.92)
  - N: 385

**0.4 0.6 0.8 1.0 1.2**

- **Favours erlotinib**
- **Favours placebo**

---

SATURN: PFS According to EGFR Mutation Status

**All**

- **EGFR mutation+**
  - HR (95% CI): 0.78 (0.63–0.96)
  - N: 328

- **EGFR wild-type**
  - HR (95% CI): 0.10 (0.04–0.25)
  - N: 49

**0.025 0.1 0.2 0.4 0.6**

- **Favours erlotinib**
- **Favours placebo**

---

SATURN OS Subgroup Analyses for EGFR IHC & EGFR Mutations

**All**

- **EGFR IHC+**
  - HR (95% CI): 0.73 (0.62–0.85)
  - N: 889

- **EGFR IHC–**
  - HR (95% CI): 0.83 (0.34–2.02)
  - N: 49

- ***EGFR mutation+**
  - HR (95% CI): 0.45 (0.27–0.76)
  - N: 889

- **EGFR wild-type**
  - HR (95% CI): 1.81 (1.03–3.16)
  - N: 49

**0.4 0.6 0.8 1.0 1.2**

- **Favours erlotinib**
- **Favours placebo**

---

*67% of patients with EGFR mutation+ disease in the placebo arm received a second-line EGFR TKI.

Cappuzzo et al. Proc IASLC, 2009

Quantitative not qualitative interaction

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* 47% of patients with EGFR mutation+ disease in the placebo arm received a second-line EGFR TKI.

Cappuzzo et al. Proc IASLC, 2009
**Slide 76**

*OS in EGFR Wild-Type Groups*

HR = 0.77 (0.61–0.97)

Log-rank p = 0.0243

**Slide 77**

*SATURN: OS in EGFR Wild-Type Group With SD on 1st-line Chemotherapy*

HR = 0.65 (0.48–0.87)

Log-rank p = 0.0041

OS is measured from time of randomisation into the maintenance phase.

**Slide 78**

*IFCT-GFPC 0502: Effect of Maintenance in EGFR IHC-ve Patients*

Erlotinib vs observation

HR = 0.86 (0.63–1.18)

Gemcitabine vs observation

HR = 0.42 (0.23–0.78)

464 randomized, 204 evaluable samples

127 EGFR IHC+; 77 EGFR IHC-
PERFORM: PFS by EGFR Mutation Status

- **EGFR mutation-positive**
  - Gefitinib (n=15) Median PFS †, 16.6 months
  - Placebo (n=15) Median PFS †, 2.8 months

- **EGFR mutation-negative**
  - Gefitinib (n=25) Median PFS †, 2.7 months
  - Placebo (n=24) Median PFS †, 1.5 months

Zhang et al. Proc ASCO, 2011 LBA 7511

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**Summary**

- There is no evidence to support prolonged administration of platinum-based doublet chemotherapy
- Preliminary evidence suggests a possible role for maintenance docetaxel, and perhaps gemcitabine in unselected patients
- Pemetrexed is approved as maintenance therapy in patients with non-squamous cell cancer

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**Summary (2)**

- SATURN and the WJTOG-0203 suggest a possible role for maintenance EGFR TKI therapy
- Major effect on PFS in patients with EGFR mutations with only modest effect on OS
- Although current practice is to continue monoclonal antibody therapy after completion of chemotherapy, there are no data to support this