The Evolving Management of Advanced Lung Cancer

CAGPO
October 19th, 2013

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Thoracic & GI MDT
London Regional Cancer Program

Professor
(Senate Stream)
Dept. of Oncology

Western

London Health Sciences Centre
CONFLICT OF INTEREST

• CEO:
  Sarissa, Inc.

• Scientific Advisory Boards:
  YM BioSciences
  Critical Outcomes Technology Inc.
  Capital Royalty, Inc.

• Board of Directors:
  Lorus Therapeutics Inc.

• Speaker’s Bureau
  Bristol Myers Squibb
  Eli Lilly, Inc.

• Honoraria:
  Amgen
  Astra Zeneca
  Bristol Myers Squibb
  Eli Lilly Inc.
  Hoffman La Roche
  Sanofi-Aventis
  Boehringer-Ingelheim

• Research Funding:
  Hoffman La Roche
OBJECTIVES

• Clear overview of both A-NSCLC and SCLC

• Explore areas of research and interest in Small Cell Lung Cancer

• Emphasize biomarker testing & $R_x$ decision impact

• Intro www.MyOncologyResource.com, online A-NSCLC $R_x$ guide

• Case Study
Suspected Stage IV (based on scans and/or patient history)

Sufficient Tissue Sample for Histological and Molecular Diagnosis, via Path of Least Resistance (e.g., least invasive, most accessible and most likely to up-stage the patient)
Lung Cancer: Histology

- **Adenocarcinoma**: 40%
- **Squamous cell carcinoma**: 25% to 30%
- **Large-cell carcinoma**: 10% to 15%
- **Small-cell carcinoma**: 10% to 15%

Sensitivity........87%
Specificity........98%

Sensitivity........93%...........94%
Specificity........87%...........97%

Histopathology, 61:1017
Figure 1. Immunomarkers for adenocarcinomatous differentiation. The total percentage rates are given for all occurring marker combinations when all three markers were applied [n = 530 adenocarcinomas (ADCs)]. Additionally, respective diagnostic test indices are provided. NPV, negative predictive value; PPV, positive predictive value.

<table>
<thead>
<tr>
<th>ADC</th>
<th>Specificity</th>
<th>Sensitivity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK7</td>
<td>0.79</td>
<td>0.66</td>
<td>0.84</td>
<td>0.94</td>
</tr>
<tr>
<td>TTF-1</td>
<td>0.98</td>
<td>0.87</td>
<td>0.98</td>
<td>0.87</td>
</tr>
<tr>
<td>Napsin A</td>
<td>0.99</td>
<td>0.73</td>
<td>0.99</td>
<td>0.76</td>
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</tbody>
</table>

Figure 2. Immunomarkers for squamous differentiation. The total percentage rates are given for all occurring marker combinations when all three markers were applied [n = 436 squamous cell carcinomas (SQCcs)]. Additionally, respective diagnostic test indices are provided. NPV, negative predictive value; PPV, positive predictive value.

<table>
<thead>
<tr>
<th>SCC</th>
<th>Specificity</th>
<th>Sensitivity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK5/6</td>
<td>0.97</td>
<td>0.94</td>
<td>0.97</td>
<td>0.95</td>
</tr>
<tr>
<td>p63</td>
<td>0.87</td>
<td>0.93</td>
<td>0.86</td>
<td>0.94</td>
</tr>
<tr>
<td>Desmocollin-3</td>
<td>0.99</td>
<td>0.84</td>
<td>0.98</td>
<td>0.88</td>
</tr>
</tbody>
</table>
Lung Cancer: Biomarkers in Adenocarcinoma

Lung Cancer Mutation Consortium: Incidence of Driver Mutations

- MEK1: <1%
- NRAS: 1%
- MET: 1%
- PIK3CA: 1%
- BRAF: 2%
- HER2: 3%
- Mutation in >1 gene: 3%
- EGFR (other): 4%
- ALK: 8%
- EGFR (sensitizing): 17%
- KRAS: 25%
- No oncogenic driver detected: 36%

ASCO 2013, Abstr # 8019
EGFR Mutations Associated with Sensitivity to EGFR-TKIs

a | Simplified illustration of signal transduction through the epidermal growth factor receptor (EGFR). Ligand binding causes receptor dimerization. This leads to receptor autophosphorylation, which is inhibited by gefitinib.

b | Structure of gefitinib and its in vitro inhibitory activity against various tyrosine kinases. Gefitinib was originally identified from structure-activity studies based around a 4-anilinoquinazoline lead series. MAPK
CASE REPORT: Response to an EGFR-TKI
A RARE EVENT IN AN UNSELECTED CAUCASIAN

2003, June 12  
2003, Nov. 28

This was at a time *before* the mutation was recognised
FISH Assay for ALK Rearrangement*

[Diagram showing ALK29.3 and EML442.3 with Telomere, 2p23 region, and Centromere labeled.]

- ALK break-apart FISH assay
  [Courtesy John Iafrate, Massachusetts General Hospital]

- "Split signal"
- "Non-split signal"

- "Break-apart FISH assay for ALK-fusion genes" (Shaw AT et al. J Clin Oncol)

- "Genetic rearrangements can be detected in ≥15% of cells"

FISH = fluorescence in situ hybridization
Crizotinib in the ALK ATP binding pocket
Rapid Response to Crizotinib

Pre-Treatment

Crizotinib x 12 weeks
SO, HOW DO WE RECONCILE HISTOLOGY WITH MOLECULAR BIOMARKERS?
First, we need an approach to histopathology

A-NSCLC

Non-Squamous

Squamous

AdenoCa

Large

Non-N-E

Neuro-endocrine

"Nested Sets"
Acinar Adenoca
(±13% EGFR mt)

Papillary Adenoca
(±35% EGFR mt)

Cribiform
80% ALK +

Micropapillary
(35% EGFR mt+)

Solid Adenoca with Mucin
(Never EGFR mt+)

Signet Ring
65% ALK +

Bronchioloalveolar Adenoca, Non-mucinous
(50% EGFR mt+)

Bronchioloalveolar Adenoca, Mucinous
(Never EGFR mt+)
A-NSCLC: Algorithm Scaffold

Non-Squamous
- NOS
- Adenoca

Squamous
- Large

<table>
<thead>
<tr>
<th></th>
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<th>ALK+</th>
<th>WT/WT</th>
<th>UNKNOWN</th>
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<td></td>
<td></td>
</tr>
<tr>
<td>1LM</td>
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<td>2L</td>
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<td>3L</td>
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<tr>
<td>1L M</td>
<td><strong>Red</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2L</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>3L</td>
<td></td>
<td></td>
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## Adenocarcinoma –
Estimated Genomic Probabilities of KRAS and EGFR Mutations

<table>
<thead>
<tr>
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<th>East Asia (Japan, Korea, Taiwan, HK)</th>
<th>West (USA, Australia)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>6 studies n = 814</td>
<td>2 studies n = 116</td>
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<tr>
<td>Neversmokers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR mt</td>
<td>70%</td>
<td>37%</td>
</tr>
<tr>
<td>KRAS mt</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>neither</td>
<td>29%</td>
<td>63%</td>
</tr>
<tr>
<td>Ever-smokers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR mt</td>
<td>29%</td>
<td>8%</td>
</tr>
<tr>
<td>KRAS mt</td>
<td>17%</td>
<td>41%</td>
</tr>
<tr>
<td>neither</td>
<td>54%</td>
<td>51%</td>
</tr>
</tbody>
</table>

*Shigematsu, Sakema, Takema, Bae, Tam*
IPASS Study design

Patients
- Age ≥18 years
- Life expectancy ≥ 12 weeks
- Adenocarcinoma histology
- Never smokers or light ex-smokers*
- PS 0-2
- Stage IIIB/IV
- Measurable disease

Gefitinib 250 mg/day
1:1 randomization
Carboplatin AUC 5 or 6 and Paclitaxel 200mg/m² 3 wkly

Endpoints
Primary
- Progression free survival (non-inferiority)

Secondary
- Objective response rate
- Quality of life
- Disease related symptoms
- Overall survival
- Safety and tolerability

Exploratory
- Biomarkers
  - EGFR mutation
  - EGFR gene copy number
  - EGFR protein expression

*Never smokers:<100 cigarettes in lifetime; light ex-smokers: stopped ≥15 years ago and smoked ≤10 pack yrs
Carboplatin/paclitaxel was offered to gefitinib patients upon progression
PS, performance status; EGFR, epidermal growth factor receptor
Objective response rate in EGFR mutation positive and negative patients

- **Gefitinib**
- Carboplatin / paclitaxel

EGFR M+ odds ratio (95% CI) = 2.75 (1.65, 4.60), p=0.0001

EGFR M- odds ratio (95% CI) = 0.04 (0.01, 0.27), p=0.0013

Overall response rate (%)

- Mutation positive patients: 71.2% (n=132), 47.3% (n=129)
- Mutation negative patients: 1.1% (n=91), 23.5% (n=85)

Odds ratio >1 implies greater chance of response on gefitinib

*Mok et al, Chicago 2008*
Progression-free survival in EGFR mutation positive and negative patients

EGFR mutation positive

**Gefitinib** (n=132)
Carboplatin / paclitaxel (n=129)

HR (95% CI) = 0.48 (0.36, 0.64)
p<0.0001

EGFR mutation negative

**Gefitinib** (n=91)
Carboplatin / paclitaxel (n=85)

HR (95% CI) = 2.85 (2.05, 3.98)
p<0.0001

Treatment by subgroup interaction test, p<0.0001

Mok et al, Chicago 2008
Overall Survival in EGFR mutation positive and negative patients

Fukuoka et al. JCO 2011
TARCEVA™ (erlotinib)

- Quinazolinamine-derived small-molecule inhibitor of the EGFR kinase
- TARCEVA inhibits the intracellular phosphorylation of the tyrosine kinase associated with EGFR
**EURTAC study design**

- Stage IIIb/IV NSCLC
- *EGFR* exon 19 deletion or exon 21 L858R mutation (DNA sequencing/Genoscan and Taqman)
- Chemonaive
- ECOG PS 0–2
- Measurable or evaluable disease

**Primary endpoint**
- Progression-free survival (PFS)

**Secondary endpoints**
- Objective response rate
- Overall survival (OS)
- Location of progression
- Safety
- *EGFR* mutation analysis in serum
- Quality of life

*Erlotinib 150 mg/day → PD*

**Stratification**
- Mutation type
- ECOG PS (0 vs 1 vs 2)

**Platinum-based doublet chemotherapy q3wks x 4 cycles* → PD**

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ECOG = Eastern Cooperative Oncology Group, PS = performance status, PD = progressive disease

*Cisplatin 75mg/m² d1 / docetaxel 75mg/m² d1; cisplatin 75mg/m² d1 / gemcitabine 1250mg/m² d1,8; carboxplatin AUC6 d1 / docetaxel 75mg/m² d1; carboplatin AUC5 d1 / gemcitabine 1000mg/m² d1,8
EURTAC: 1L CHEMO vs ERLOTINIB

Primary endpoint: PFS in ITT population (updated analysis 26 Jan 2011)

HR=0.37 (0.25–0.54)
Log-rank p<0.0001

Patients at risk
Erlotinib 86 63 54 32 21 17 9 7 4 2 2 0
Chemotherapy 87 49 26 8 5 4 3 1 0 0 0 0

Data cut off: 25 Jan 2011
EURTAC: 1L CHEMO vs ERLOTINIB

Overall survival in ITT population (updated analysis 26 Jan 2011)

HR=1.04 (0.65–1.68)
Log-rank p=0.8702

- Erlotinib (n=86; 44% with event)
- Chemotherapy (n=87; 36% with event)

N.B. 59 pts in chemotherapy arm had PFS event; 51 of these had second-line treatment, of whom 49 had EGFR TKI

Patients at risk
Erlotinib 86 72 64 53 46 32 25 15 12 7 6 1 1 1 1 1
Chemotherapy 87 69 59 47 38 31 19 11 8 3 3 2 1 1 0
Afatinib: an irreversible ErbB Family Blocker

- Afatinib is an orally available, irreversible ErbB Family Blocker, with high efficacy potential
  - Inhibition of ErbB Family receptor heterodimerization
  - In vitro activity against EGFR-resistant T790M mutation


*III.W 2992 (afatinib) is an investigational compound undergoing clinical development and is not approved for use in Canada.*
**Study design**

Stage IIIB (wet)/IV lung adenocarcinoma (AJCC version 6)

- EGFR mutation in tumor
  (central lab testing; Therascreen EGFR20/ RQ PCR)

Randomization 2:1
Stratified by:
- EGFR mutation (Del19/L858R/other)
- Race (Asian/non-Asian)

- Afatinib 40 mg/day
- Cisplatin + Pemetrexed
  75 mg/m² + 500 mg/m²
  i.v. q21 days, up to 6 cycles

Primary endpoint: PFS (RECIST 1.1, independent review)
Secondary endpoints: ORR, DCR, DoR, tumor shrinkage, OS, PRO, safety, PK

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1. EGFR20 deletions in exons 19, 3 insertions in exons 20, L858R, L858Q, T790M, G719S, G719A and G719C (E1 G719X), S768L.
2. Dose escalated to 50 mg if limited AE observed in cycle 1. Dose reduced by 10 mg decrements in case of related G3 or prolonged G2 AE.
3. Tumor assessments: q6 weeks until Week 48 and q12 weeks thereafter until progression/start of new therapy.
4. Patient-reported outcomes: Q-SD, EORTC QLQ-C30 and QLQ-LC13 at randomization and q3 weeks until progression or new anti-cancer therapy.

III/III2 2992 (afatinib) is an investigational compound undergoing clinical development and is not approved for use in Canada.
Primary endpoint: PFS
Independent review – all randomized patients

Afatinib  n=230  Cis/pem  n=115
PFS event, n (%)  152 (66)  69 (60)
Median PFS (months)  11.1  6.9
Hazard ratio (95% confidence interval)  0.58 (0.43–0.78)  p=0.0004

Number at risk
Afatinib  230  180  151  120  77  50  31  10  3  0
Cis/Pem  115  72  41  21  11  7  3  2  0  0
### Most frequent related adverse events

>20% difference between treatment arms

<table>
<thead>
<tr>
<th></th>
<th>Aftinib (n=229)</th>
<th>Cis/pem (n=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Gr (%)</td>
<td>Gr 3 (%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>218 (95.2)</td>
<td>33 (14.4)</td>
</tr>
<tr>
<td>Rash/acne*</td>
<td>204 (89.1)</td>
<td>37 (16.2)</td>
</tr>
<tr>
<td>Stomatitis/mucositis*</td>
<td>165 (72.1)</td>
<td>19 (8.3)</td>
</tr>
<tr>
<td>Paronychia</td>
<td>130 (56.8)</td>
<td>26 (11.4)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>67 (29.3)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>41 (17.9)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>47 (20.5)</td>
<td>7 (3.1)</td>
</tr>
<tr>
<td>Fatigue*</td>
<td>40 (17.5)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>39 (17.0)</td>
<td>7 (3.1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 (0.9)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Anemia</td>
<td>7 (3.1)</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

*Grouped term.

*No grade 5 events for the presented AEs.
EGFR M+

<table>
<thead>
<tr>
<th>1L + 1LM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iressa ... IPASS</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>Tarceva ... EURTAC</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>Tomtovok ... LUX-Lung 3</td>
</tr>
</tbody>
</table>
A-NSCLC

Non-Squamous

NOS

Adenoca

Squamous

Large

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>1L + 1LM</td>
<td>Iressa or Tarceva or Tomtovok</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2L</td>
<td>Platinum doublet → Alimta</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3L</td>
<td>TKI re-challenge?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1L

2L

3L

1LM

Iressa or Tarceva or Tomtovok

Platinum doublet

TKI re-challenge?
Retreatment with erlotinib: Regain of TKI sensitivity following a drug holiday for patients with NSCLC who initially responded to EGFR-TKI treatment


* Department of Pulmonary Disease, VU University Medical Center, Amsterdam, The Netherlands
** Department of Pathology, VU University Medical Center, Amsterdam, The Netherlands

Table 2 – Results of TKI retreatment.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of TKI ‘holiday’ (months)</td>
<td>9.5 (3–36)</td>
</tr>
<tr>
<td>Follow-up after retreatment (months)</td>
<td>9 (1.5–16)</td>
</tr>
<tr>
<td>Progression free survival (months)</td>
<td>6.5 (1–16)</td>
</tr>
<tr>
<td>Number (%) of patients</td>
<td></td>
</tr>
<tr>
<td>Response to reintroduction of TKI</td>
<td></td>
</tr>
<tr>
<td>Partial remission</td>
<td>5 (36)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>7 (50)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Toxicity</td>
<td></td>
</tr>
<tr>
<td>Skin rash grade 1–3</td>
<td>6 (43)</td>
</tr>
<tr>
<td>Hair loss grade 2</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Diarrhoea grade 1</td>
<td>3 (21)</td>
</tr>
<tr>
<td>Esophagitis grade 1</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Paronychia</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>3 (21)</td>
</tr>
</tbody>
</table>

TKI Re-Challenge:
May be a realistic option

Chemotherapy Alimta-based
A-NSCLC: Algorithm Scaffold

Non-Squamous

NOS  Adenoca

Squamous

Large

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<tr>
<td>3L</td>
<td></td>
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Consistent Tumor Response to Crizotinib Across Studies

Study 1001 - ORR 61%, n=116

Current Study - ORR 51%, n=133

Camidge DR et al. ASCO 2011
<table>
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<td>1L</td>
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</tr>
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<td>1LM</td>
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<tr>
<td>Xalkori (crizotinib)</td>
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<td>US FDA 26/8/11</td>
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**PROFILE 1007: PFS of 2L Crizotinib vs Pemetrexed or Docetaxel**

<table>
<thead>
<tr>
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<th>Crizotinib (n=172a)</th>
<th>Pemetrexed (n=99a)</th>
<th>Docetaxel (n=72a)</th>
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<tr>
<td>Events, n (%)</td>
<td>100 (58)</td>
<td>72 (73)</td>
<td>54 (75)</td>
</tr>
<tr>
<td>Median, mo</td>
<td>7.7</td>
<td>4.2</td>
<td>2.6</td>
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<tr>
<td>HRb (95% CI)</td>
<td>0.59 (0.43 to 0.80)</td>
<td>0.30 (0.21 to 0.43)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.0004</td>
<td>&lt;0.0001</td>
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**Graphical Representation:**

- **Graph Title:** PROFILE 1007: PFS of 2L Crizotinib vs Pemetrexed or Docetaxel
- **X-axis:** Time (months)
- **Y-axis:** Probability of survival without progression (%)
- **Legend:**
  - Crizotinib
  - Pemetrexed
  - Docetaxel
- **Key Data Points:***
  - Events, n (%): 100 (58), 72 (73), 54 (75)
  - Median, mo: 7.7, 4.2, 2.6
  - HRb (95% CI): 0.59 (0.43 to 0.80), 0.30 (0.21 to 0.43)
  - P: 0.0004, <0.0001

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</table>

**Note:**
- As-treated population: excludes 1 patient in crizotinib arm who did not receive study treatment and 3 patients in chemotherapy arm who did not receive study treatment; b vs crizotinib
ORR\textsuperscript{a} by Independent Radiologic Review

ORR ratio: 3.4 (95% CI: 2.5 to 4.7); P<0.0001

\textbullet\ Crizotinib (n=173\textsuperscript{b})
\textbullet\ Chemotherapy (n=174\textsuperscript{c})

\textbullet\ Crizotinib (n=172\textsuperscript{c})
\textbullet\ Pemetrexed (n=99\textsuperscript{c})
\textbullet\ Docetaxel (n=72\textsuperscript{c})

\textsuperscript{a}RECIST v1.1; \textsuperscript{b}ITT population; \textsuperscript{c}as-treated population
# A-NSCLC: alternative schema for ALK +

<table>
<thead>
<tr>
<th>Stage</th>
<th>EGFR M+</th>
<th>ALK+</th>
<th>WT/WT</th>
<th>UNKNOWN</th>
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<td>Alimta→PD</td>
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<td>Xalkori→PD…and beyond?</td>
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A-NSCLC: Algorithm Scaffold

Non-Squamous

NOS

Adenoca

Squamous

Large

<table>
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<tr>
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# NON-SMALL CELL LUNG CANCER

<table>
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<tr>
<th>1st generation</th>
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<th>3rd generation</th>
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<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>Ifosfamide</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Docetaxel</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Mitomycin C</td>
<td>Gemcitabine</td>
</tr>
<tr>
<td>Cisplatin (low dose)</td>
<td>Cisplatin (high dose)</td>
<td>Oxaliplatin</td>
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<tr>
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<td>Carboplatin</td>
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<td>Vincristine</td>
<td>Vinblastine</td>
<td>Vinorelbine</td>
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<tr>
<td></td>
<td>Vindesine</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Etoposide</td>
<td>Irinotecan</td>
</tr>
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<td></td>
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</tr>
</tbody>
</table>

“No evidence existed that any group of patients specified by … histological type … benefited more or less from chemotherapy”.

![Graph showing survival rates](image)
## NON-SMALL CELL LUNG CANCER

<table>
<thead>
<tr>
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</tbody>
</table>
Hitting the Wall
First-line chemotherapy options in NSCLC (E1594): comparable efficacy with platinum doublets

Therapeutic plateau: overall survival <12 months

NSCLC = non-small cell lung cancer

Schiller, et al. NEJM 2002
ECOG 1594: Efficacies by Histology

- Log-rank test for comparing
  - OS and PFS distributions among different histology groups
  - Survival in each histology group for different chemotherapy regimen
- Results:
  - No difference in OS and PFS between the four histology groups
  - No survival difference between the four chemotherapy regimens in each histology group

Regardless of histology types, OS and PFS were similar in chemonaive NSCLC patients treated with standard platin-based doublets involving paclitaxel, docetaxel, or gemcitabine!

WCLC 2009 – Hoang et al, Abstract # PD6.4.1
JMDB:
Cis/Pem vs. Cis/Gem in First-Line NSCLC: Study Design

Randomization Factors
- Stage
- Performance status (PS) (0 vs 1)
- Gender
- Histologic vs cytologic diagnosis
- History of brain metastases

Cisplatin 75 mg/m² day 1 + Pemetrexed 500 mg/m² day 1
Each cycle repeated every 3 weeks up to 6 cycles
Cisplatin 75 mg/m² day 1 + Gemcitabine 1250 mg/m² days 1 & 8

Vitamin B₁₂, folate, and dexamethasone given in both arms

Cis/Pem, cisplatin/pemetrexed; Cis/Gem, cisplatin/gemcitabine
Cis/Pem vs. Cis/Gem in First-line NSCLC: Overall Survival in Squamous Cell Carcinoma and Adenocarcinoma / Large Cell

Overall Survival Median (95% CI)
- Cis/Pem in Ad or La (N=512) 11.8 mos (10.4, 13.2)
- Cis/Gem in Ad or La (N=488) 10.4 mos (9.6, 11.2)
- Cis/Pem in Sq (N=244) 9.4 mos (8.4, 10.2)
- Cis/Gem in Sq (N=229) 10.8 mos (9.5, 12.1)

Overall Survival Time (months) in Squamous Patients

Overall Survival Probability
- 0.0
- 0.1
- 0.2
- 0.3
- 0.4
- 0.5
- 0.6
- 0.7
- 0.8
- 0.9
- 1.0

0 6 12 18 24 30
Figure 1. Kaplan–Meier overall survival curves for the pemetrexed versus docetaxel study for each of the histologic subgroups: adenocarcinoma, large cell carcinoma, squamous cell carcinoma, and other NSCLC/NOS histologies.
<table>
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<tr>
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</tr>
<tr>
<td>3L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Adenoca/NOS/Large Cell: UNKNOWN, WT/WT

Platinum doublet x 4-6:
- Cisplatin/gemcitabine
- Cisplatin/docetaxel
- Carboplatin/paclitaxel
- Carboplatin/gemcitabine

But also consider Cisplatin/pemetrexed
J MEN: Study Design

Double-blind, Placebo-controlled, Multicenter, Phase III Trial

- Stage III B/IV NSCLC
- ECOG PS 0-1
- 4 prior cycles of gem, doc, or tax + cis or carb, with CR, PR, or SD
- Randomization factors:
  - gender
  - PS
  - stage
  - best tumor response
  - non-platinum drug
  - brain mets

- Pemetrexed 500 mg/m^2 (d1,q21d) + BSC (N=441)*
- Placebo (d1, q21d) + BSC (N=222)*

Primary Endpoint = PFS

* B12, folate, and dexamethasone given in both arms
Progression-free Survival by Histology

Non-squamous

HR = 0.47 (95% CI: 0.37-0.6)

P < 0.00001

Squamous

HR = 1.03 (95% CI: 0.77-1.5)

P = 0.896

Pemetrexed 4.4 mos

Placebo 1.8 mos

Pemetrexed 2.4 mos

Placebo 2.5 mos
Overall Survival by Histology

**Non-squamous (n=481)**

- HR = 0.70 (95% CI: 0.56-0.88)
- P = 0.002

**Squamous (n=182)**

- HR = 1.07 (95% CI: 0.49-0.73)
- P = 0.678

Survival Probability

- **Placebo**: 10.3 mos
- **Pemetrexed**: 15.5 mos

Time (months)
## Treatment-related Toxicities

<table>
<thead>
<tr>
<th></th>
<th>Pemetrexed (N = 441) %</th>
<th>Placebo (N = 222) %</th>
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<tr>
<td>Grade 3/4</td>
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<tr>
<td>Neutropenia‡</td>
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<tr>
<td>Anemia</td>
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<tr>
<td>Leukopenia</td>
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<td>Fatigue‡</td>
<td>5</td>
<td>1</td>
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<tr>
<td>Anorexia</td>
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<td>1</td>
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<tr>
<td>Vomiting</td>
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<td>0</td>
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<tr>
<td>Sensory neuropathy</td>
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<td>0</td>
</tr>
<tr>
<td>Mucositis/ Stomatitis</td>
<td>1</td>
<td>0</td>
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</tbody>
</table>

*NCI CTC version 3.0
‡ P < 0.05 for grade 3/4 rates of neutropenia and fatigue
Tarceva maintenance therapy after first-line chemotherapy treatment – SATURN

- Tumour samples
- Stage IIIb/IV NSCLC (n=1,700*)
- 4 cycles of a first-line standard platinum-based doublet
- EGFR protein expression (IHC) results
- Non-PD
- 1:1
- Tarceva 150mg/day
- PD → Off study
- Placebo
- PD → Off study
- TITAN or Off study

*planned; PD = progressive disease
OS in patients with non-squamous disease

HR=0.79 (0.64–0.96)
Log-rank p=0.0194

Cappuzzo et al. ESMO 2009
OS according to response to first-line chemotherapy (ITT population)

SD

HR=0.72 (0.59–0.89)
Log-rank p=0.0019

CR/PR

HR=0.94 (0.74–1.20)
Log-rank p=0.6181

Multivariate HR for OS in SD population
0.71, p=0.0019

Measured from time of randomisation into the maintenance phase
OS in patients with SD on first-line chemotherapy according to histology

- **Squamous-cell**
  - HR=0.67 (0.48–0.92)
  - Log-rank p=0.0116
  - Erlotinib (n=97)
  - Placebo (n=93)

- **Non-squamous**
  - HR=0.76 (0.59–1.00)
  - Log-rank p=0.0457
  - Erlotinib (n=155)
  - Placebo (n=142)

Measured from time of randomisation into the maintenance phase
A-NSCLC

Non-Squamous

NOS

Adenoca

Squamous

Large

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<tr>
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<tr>
<td>2L</td>
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</tbody>
</table>

Platinum doublet x 4

Pemetrexed
(or erlotinib)
### A-NSCLC: Algorithm Scaffold

#### Non-Squamous
- NOS
- Adenoca

#### Squamous
- Large

<table>
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<td>Platinum Doublet (non-pemetrexed)</td>
<td>Surveillance (erlotinib)</td>
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Survival – TAX 317B
Docetaxel 75mg/m² vs BSC: Superior in 2nd Line

- Median 7.5 mo vs. 4.6 mo
- Log-rank p = 0.010
- 1-year 37% vs. 12%
- Chi-square p = 0.003
BR.21: Erlotinib vs Placebo in 2/3L
Overall Survival


*HR 0.71, p <0.0001
## Analysis of Survival

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<th>Factor</th>
<th>No. of Patients</th>
<th>Univariate Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>Multivariate Hazard Ratio (95% CI)</th>
<th>P Value</th>
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<td>Complete response or partial</td>
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<td>&lt;0.001</td>
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<td>0.8 (0.7–0.9)</td>
<td>0.01</td>
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</table>

* CI denotes confidence interval. NA not included in the final model, and NA not applicable as a stratification factor.
1 The univariate hazard ratio was derived from a Cox model with a right truncation interval.
2 The hazard ratio between levels of respective covariates was derived from the final stratified Cox regression model.
3 If values are for the comparison of patients who had never smoked and those whose history of smoking was unknown with those who were smokers.
BR21: A large subgroup benefit in pts with zero EGFR mutations

HR=0.67, p=0.0007

Squamous patients (Smokers)

### A-NSCLC

#### Non-Squamous
- **NOS**
- **Adenoca**

#### Squamous
- **Large**

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<tr>
<th>Stage</th>
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<td>Alimta (or erlotinib) (Or Surveillance)</td>
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<td>2L</td>
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<td></td>
<td></td>
<td>Erlotinib (docetaxel not funded, no data)</td>
</tr>
</tbody>
</table>
A-NSCLC: Algorithm Scaffold

Non-Squamous

- NOS
- Adenoca

Squamous

- Large

<table>
<thead>
<tr>
<th></th>
<th>EGFR M+</th>
<th>ALK+</th>
<th>WT/WT</th>
<th>UNKNOWN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1LM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1L: Platinum Doublet (non-pemetrexed)
1LM: Surveillance (erlotinib)
2L: Erlotinib Or Docetaxel
3L: Docetaxel Or Erlotinib
### A-NSCLC

#### Non-Squamous

<table>
<thead>
<tr>
<th></th>
<th>EGFR M+</th>
<th>ALK+</th>
<th>WT/WT/WT</th>
<th>UNKNOWN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1L</td>
<td>Gefitinib or Erlotinib or Afatinib</td>
<td>Platinum doublet x 4</td>
<td>Platinum doublet x 4</td>
<td>Platinum Doublet (non-pemetrexed)</td>
</tr>
<tr>
<td>1LM</td>
<td>Pemetrexed</td>
<td></td>
<td>Pemetrexed (or erlotinib)</td>
<td>Surveillance or erlotinib</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>EGFR M+</th>
<th>ALK+</th>
<th>WT/WT/WT</th>
<th>UNKNOWN</th>
</tr>
</thead>
<tbody>
<tr>
<td>2L</td>
<td>Platinum doublet X 4</td>
<td>Crizotinib</td>
<td>Erlotinib</td>
<td>Erlotinib or docetaxel</td>
</tr>
<tr>
<td>3L</td>
<td>TKI re-challenge</td>
<td>Erlotinib</td>
<td>Palliative RT, BSC or clinical trial</td>
<td>Docetaxel or erlotinib</td>
</tr>
</tbody>
</table>
Early Palliative Care for Patients with Metastatic Non–Small-Cell Lung Cancer


Figure 3. Kaplan-Meier Estimates of Survival According to Study Group.
Survival was calculated from the time of enrollment to the time of death, if it occurred during the study period, or to the time of censoring of data on December 1, 2000. Median estimates of survival were as follows: 2.8 months (95% confidence interval [CI], 7.9 to 11.7) in the entire sample (151 patients), 11.6 months (95% CI, 6.4 to 16.9) in the group assigned to early palliative care (77 patients), and 8.9 months (95% CI, 6.3 to 11.4) in the standard care group (74 patients) (P = 0.02 with the use of the log-rank test). After adjustment for age, sex, and baseline Eastern Cooperative Oncology Group performance status, the group assignment remained a significant predictor of survival (hazard ratio for death in the standard care group, 1.70; 95% CI, 1.14 to 2.54; P = 0.01). Tick marks indicate censoring of data.

Table 2: Bivariate Analyses of Quality-of-Life Outcomes at 12 Weeks.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard Care (N=47)</th>
<th>Early Palliative Care (N=60)</th>
<th>Difference between Early Care and Standard Care (95% CI)</th>
<th>P Value†</th>
<th>Effect Size‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT-L score</td>
<td>91.5±15.8</td>
<td>98.0±15.1</td>
<td>6.5 (0.5–12.4)</td>
<td>0.03</td>
<td>0.42</td>
</tr>
<tr>
<td>LCS score</td>
<td>19.3±4.2</td>
<td>21.0±3.9</td>
<td>1.7 (0.1–3.2)</td>
<td>0.04</td>
<td>0.41</td>
</tr>
<tr>
<td>TOI score</td>
<td>53.0±11.5</td>
<td>59.0±11.6</td>
<td>6.0 (1.5–10.4)</td>
<td>0.009</td>
<td>0.52</td>
</tr>
</tbody>
</table>

* Plus-minus values are means ±SD. Quality of life was assessed with the use of three scales: the Functional Assessment of Cancer Therapy–Lung (FACT-L) scale, on which scores range from 0 to 136, with higher scores indicating better quality of life; the lung-cancer subscale (LCS) of the FACT-L scale, on which scores range from 0 to 28, with higher scores indicating fewer symptoms; and the Trial Outcome Index (TOI), which is the sum of the scores on the LCS and the physical well-being and functional well-being subscales of the FACT-L scale (scores range from 0 to 84, with higher scores indicating better quality of life).

† The P value was calculated with the use of two-sided Student’s t-tests for independent samples.

‡ The effect size was determined with the use of Cohen’s d statistic, which is a measure of the difference between two means [in this case, the mean in the group assigned to early palliative care group minus the mean in the group assigned to standard care] divided by a standard deviation for the pooled data. According to the conventional classification, an effect size of 0.20 is small, 0.50 moderate, and 0.80 large.

Met plays an important role in normal cellular physiology

- Met (c-Met, HGFR) is a cell surface RTK that functions as a dimer
- Binding of HGF (scatter factor) causes receptor dimerisation
- Dimerisation activates multiple cell signalling cascades leading to
  - Cell proliferation, survival, motility, invasion and migration


HGFR= hepatocyte growth factor receptor; RTK = receptor tyrosine kinase; HGF = hepatocyte growth factor
The Met Pathway in Lung Cancer

• In non–small cell lung cancer (NSCLC) studies1–6
  – Met overexpression was detected in up to 67% of patient samples
  – MET gene amplification has been observed in 1–7% of NSCLC patients samples surveyed
  – Mutations in MET have been identified in patient samples and NSCLC cell lines
• Met activation has been reported in up to 5–20% of patients with EGFR tyrosine kinase inhibitor (TKI)-resistant NSCLC1,7–9
  – In preclinical studies, inhibition of Met signaling was capable of restoring sensitivity to treatment in EGFR TKI-resistant NSCLC cells

Prognostic value of Met
High Met expression is linked with lower OS in NSCLC

- Retrospective study; 88 NSCLC tumours assessed by IHC*
  - Adenocarcinoma (n=46)
  - Squamous cell carcinoma (n=29)
  - Large-cell carcinoma (n=13)
- 36/88 were intratumoural Met positive (40.9%)
- Intratumoural Met expression was a significant prognostic factor
  - RR=2.642; p=0.0029

OS = overall survival; NSCLC = non-small-cell lung cancer
*IHC: rabbit polyclonal anti-Met antibody (sc10), Santa Cruz Biotechnology
†5-year survival rate, based on 52 Met negative tumours and 36 Met positive tumours
MET IHC as a companion diagnostic in NSCLC

- ‘MET Positive’ was defined as majority (≥50%) of tumor cells with moderate or strong staining intensity

- MET diagnostic status was assessed after randomization and prior to unblinding
- 93% of patients had adequate tissue for evaluation of MET by IHC
- 52% patients with evaluable tissue were “MET Positive”

Ventana’s CONFIRM (SP44 mAb clone)

IHC: immunohistochemistry
Roche data on file
One-Armed (Monovalent) antibody binds MET, but does not lead to dimerization and activation.

- Onartuzumab prevents HGF binding and avoids MET “homodimerization” and activation. 1

Cross-talk between Met and EGFR pathways
Scientific rationale for dual inhibition of Met and EGFR

ERLOTINIB THERAPY
Erlotinib is a small molecule inhibitor (SMI) of EGFR used to treat NSCLC and pancreatic cancer1

EGF
EGFR
Erlotinib
No activity

SMI RESISTANCE VIA MET—EGFR CROSS-TALK
Tumour resistance to EGFR SMIs can occur via multiple mechanisms including cross-talk between Met and EGFR2,3
Evidence of Met amplification is seen in ~20–22% of EGFR mutant NSCLC tumours4

EGF
EGFR
Erlotinib
Motility, invasion, survival, migration, proliferation

DUAL INHIBITION
Dual inhibition of Met and EGFR may overcome tumour resistance5

EGF
EGFR
Onartuzumab
Erlotinib
No activity

EGFR = epidermal growth factor receptor
Phase II: Erlotinib +/- MetMAb in 2nd/3rd-line NSCLC

**Key eligibility:**
- Stage IIIB/IV NSCLC
- 2nd/3rd-line NSCLC
- Tissue required
- PS 0–2

**Co-primary objectives:**
- PFS in ‘Met Diagnostic Positive’ patients (est. 50%)
- PFS in overall ITT population

**Other key objectives:**
- OS in ‘Met Diagnostic Positive’ pts
- OS in overall ITT patients
- Overall response rate
- Safety/tolerability

- Placebo (IV Q3W) + erlotinib (150 mg daily)
- Add MetMAb (15 mg/kg IV Q3W) + erlotinib (150 mg daily)

**Stratification factors:**
- Tobacco history
- Performance status
- Histology

- **Arm A:** n=69
- **Arm B:** n=68
- **PD:** n=27

Data presented includes >5 additional months of follow-up
MetMAb plus erlotinib in Met Dx+ patients

**PFS: HR=0.53**
- Placebo + erlotinib: Median (mo) 1.5, HR 0.53 (0.28–0.99), Log-rank p-value 0.04, No. of events 27
- MetMAb + erlotinib: Median (mo) 2.9

**OS: HR=0.37**
- Placebo + erlotinib: Median (mo) 3.8, HR 0.37 (0.19–0.72), Log-rank p-value 0.002, No. of events 26
- MetMAb + erlotinib: Median (mo) 12.6

Probability of progression free
- Time to progression (months)

Probability of survival
- Overall survival (months)
MetLung (OAM4971g): A RANDOMIZED, PHASE III, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING ONARTUZUMAB IN COMBINATION WITH ERLOTINIB IN PATIENTS WITH MET DIAGNOSTIC-POSITIVE mNSCLC WHO AFTER STANDARD CHEMOTHERAPY

**Stratification criteria**
- EGFR mutation status
- Met 2+ or 3+ score
- Number of prior lines of therapy
- Histology

**Key eligibility criteria**
- Stage IIIb or IV Met+ NSCLC
- 1–2 prior lines of treatment
- No prior EGFR inhibitor
- ECOG PS 0 or 1

**Erlotinib + onartuzumab**
- Treat until PD
- Survival follow-up

**Erlotinib + placebo**
- No crossover tx

**Primary endpoint:**
- OS

**Secondary endpoints:**
- PFS
- ORR
- Quality of life
- Safety

ECOG = Eastern Cooperative Oncology Group; PFS = progression-free survival; ITT = intent-to-treat; OS = overall survival; ORR = overall response rate; PD = progressive disease

Erlotinib: 150mg p.o. qd
Onartuzumab/placebo: 15mg/kg i.v. q3w

2L/3L NSCLC Met-positive
(1 prior platinum-based line of therapy)
Central testing for:
- Met status
- EGFR mutation status
(N=490)
## SMALL CELL LUNG CANCER: ALGORITHM

<table>
<thead>
<tr>
<th></th>
<th>Limited Disease</th>
<th>Extensive Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1L</td>
<td>Cisplatin/Etoposide x 4-6 cycles</td>
<td>Carboplatin/Etoposide x 4-6 cycles</td>
</tr>
<tr>
<td></td>
<td>Concurrent thoracic RT</td>
<td>± Palliative RT</td>
</tr>
<tr>
<td></td>
<td>Prophylactic Cranial RT</td>
<td>Prophylactic Cranial RT</td>
</tr>
<tr>
<td>1LM</td>
<td>Surveillance</td>
<td>Surveillance</td>
</tr>
<tr>
<td>2L</td>
<td>Re-challenge with Carboplatin/Etoposide or Topotecan single-agent</td>
<td></td>
</tr>
</tbody>
</table>
A systematic review of the role of etoposide and cisplatin in the chemotherapy of small cell lung cancer with methodology assessment and meta-analysis


* Service de Médecine, Institut Jules Bordet, 1 rue Higuer-Bordet, 1000 Bruxelles, Belgium
* Service de Pneumo-phthisiologie, CHU Calmette, Lille, France

Received 5 November 1999; revised in revised form 2 February 2000; accepted 17 February 2000

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of trials</th>
<th>Comparison</th>
<th>Survival HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>1</td>
<td>± Cisplatin (no etoposide)</td>
<td>0.70</td>
</tr>
<tr>
<td>Group 2</td>
<td>17</td>
<td>± Etoposide (no cisplatin)</td>
<td>0.72</td>
</tr>
<tr>
<td>Group 3</td>
<td>9</td>
<td>Cis/Etop vs Other</td>
<td><strong>0.57</strong></td>
</tr>
<tr>
<td>Group 4</td>
<td>9</td>
<td>Cis/Etop vs Etop/other</td>
<td>0.74</td>
</tr>
</tbody>
</table>
“It was decided to remove the reference that Etoposide-carboplatin was biologically equivalent to etoposide-cisplatin, and to discuss the limited amount of data on this issue.”
Sequencing and schedule effects of cisplatin plus etoposide in small-cell lung cancer: results of a North Central Cancer Treatment Group randomized clinical trial.

Saskatchewan Cancer Foundation-Saskatoon Cancer Centre, Canada.

Abstract
PURPOSE: The combination of etoposide (E) and cisplatin (P) is an accepted standard therapy for small-cell lung cancer (SCLC); however, the optimal sequencing and administration schedule has not been defined. This study was designed to evaluate different sequencing and administration schedules of E and P in the treatment of SCLC.

PATIENTS AND METHODS: Five hundred fifty-two eligible patients with limited (LD) and extensive-stage (ED) SCLC were randomized to receive one of the following regimens: arm A: P 35 mg/m² by intravenous (IV) bolus followed by E 130 mg/m² bolus; arm B: E 130 mg/m² bolus followed by P 30 mg/m² bolus; arm C: E 130 mg/m² by 24-hour infusion and P 30 mg/m² bolus at the end of each 24-hour infusion of E; arm D: E 130 mg/m² by 24-hour infusion and P 45 mg/m² by 24-hour infusion on day 2 and 3 only. Two 3-day induction cycles of IV EP were administered 4 weeks apart. Subsequent therapy was the same for all arms, consisting of four cycles of cyclophosphamide, doxorubicin, and vincristine (CAV) at 4-week intervals. Consolidative thoracic radiation therapy (TRT) and prophylactic cranial irradiation (PCI) were administered to responders.

RESULTS: The overall response rate (84%) was similar in all treatment arms. Treatment arm A was associated with the best complete response (CR) rate (52%), the most favorable median survival time (MST) of 15 months, and a 26% 2-year survival rate. Patients with LD on arm A had a MST of 20 months and a 42% 2-year survival rate. Multivariate analysis indicated that extent of disease, performance status, arm of therapy, and sex were significant independent factors influencing survival. Toxicity of the four regimens was similar, except for greater thrombocytopenia on arm D.

CONCLUSION: The bolus administration of EP with E following P for the first two cycles of chemotherapy was the most effective regimen, with especially encouraging survival for LD patients.

PMID: 6270593 [PubMed - indexed for MEDLINE]
Original article

Superiority of cisplatin or carboplatin in combination with teniposide and vincristine in the induction chemotherapy of small-cell lung cancer. A randomized trial with 5 years follow up

U Lassen,1 P.E.G. Krøjgaard,1 K. Østerlund,1 B. Bergman,2 T.C Siggaard,2 F.R. Hirsch,3 M. Hansen,4 P. Døvbergsby,4 H. H. Hansen5

1Thoracic Oncology Department, Rigshospitalet, Copenhagen. 2Department of Oncology, Herlev University Hospital, Herlev. 3Department of Respiratory Medicine and Allergology, St James University Hospital, Leeds. 4Medical Department E, Rigshospitalet, Copenhagen. 5Medical Department C, Hillerød Sygehus, Hillerød, Denmark. *Department of Respiratory Medicine and Allergology, St James University Hospital, Leeds, UK.

Table 1. Study design.

<table>
<thead>
<tr>
<th>Randomization:</th>
<th>Arm I</th>
<th>Arm II</th>
<th>Arm III</th>
</tr>
</thead>
<tbody>
<tr>
<td>A:</td>
<td>D1</td>
<td>D1</td>
<td>D1</td>
</tr>
<tr>
<td>B:</td>
<td>A</td>
<td>C</td>
<td>A</td>
</tr>
<tr>
<td>C:</td>
<td>B</td>
<td>B</td>
<td>C</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Combos:</th>
<th>A: Cyclophosphamide</th>
<th>B: Adriamycin</th>
<th>C: Cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 1</td>
<td>Day 1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>8 months</td>
<td>8 months</td>
<td>8 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3 months</th>
<th>8 months</th>
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</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Etoposide</th>
<th>Vindesine</th>
<th>Hexamethylmelamin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 3-6 incl.</td>
<td>Days 1 + 14</td>
<td>Days 8-22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D1: Cisplatin</th>
<th>Teniposide</th>
<th>Vincristine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 2 + 3</td>
<td>Day 1</td>
<td>Day 1 (+ day 8 and 15, 1. cycle)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D2: Carboplatin</th>
<th>Teniposide</th>
<th>Vincristine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 2 + 3</td>
<td>Days 1-5 incl.</td>
<td>Day 1 (+ day 8 and 15, 1. cycle)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Objective response rates.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Complete (CR)</td>
</tr>
<tr>
<td>Partial (PR)</td>
</tr>
<tr>
<td>CR+PR</td>
</tr>
<tr>
<td>CR+PR, after 3 months</td>
</tr>
<tr>
<td>Stable disease/no response</td>
</tr>
<tr>
<td>Progression</td>
</tr>
<tr>
<td>Early death</td>
</tr>
<tr>
<td>Not assessable for response</td>
</tr>
</tbody>
</table>

* None of the differences are statistically significant.

<table>
<thead>
<tr>
<th>Table 4. Long-term follow up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
</tr>
<tr>
<td>%</td>
</tr>
<tr>
<td>2-Year survival</td>
</tr>
<tr>
<td>Limited disease</td>
</tr>
<tr>
<td>Extensive disease</td>
</tr>
<tr>
<td>5-Year survival</td>
</tr>
<tr>
<td>Limited disease</td>
</tr>
<tr>
<td>Extensive disease</td>
</tr>
</tbody>
</table>

* Kruskal–Wallis.

^ Not significant (P > 0.05).
Compared to patients in arm III patients treated in arms I and II survived longer with median survivals of 336 days (95% CI 275-397), 340 days (95% CI 290-390), and 293 days (95% a 266-320), respectively. The overall survival difference between the three arms was statistically significant ($P = 0.04$, Figure 1). Pairwise comparison by the logrank test showed that the difference in survival between arm II and III was statistically significant ($P = 0.02$, logrank test), while the $P$-value of the difference between arm I and arm III was 0.07.

Kosmidis P1, Samantas P, Fountzilas G, Pavlidis N, Apostolopoulou P, Skarlos D.

Department of Medical Oncology, Metaxa Cancer Hospital, Piraeus, Greece.

Abstract

The efficacy and toxicity of cisplatin/etoposide and carboplatin/etoposide combinations along with thoracic irradiation were prospectively assessed in patients with small cell lung cancer. Both combinations were equally effective. However, the carboplatin/etoposide regimen caused significantly less nausea, vomiting, nephrotoxicity, and neurotoxicity, and it was easier to administer. Dose intensity and treatment delays were similar in both groups. Thoracic irradiation given concurrently with chemotherapy is feasible and seems to offer a survival advantage. The relapse rate also is lower among patients who have received radiation therapy, and recurrences tended to be outside of the lung. Overall, a survival benefit was identified for patients aged between 50 and 65 years who had limited disease, good performance status, and only one metastatic site. Prophylactic brain irradiation in a subset of patients reduced brain metastasis, but the difference did not reach significance. From this trial, it is concluded that carboplatin/etoposide combination therapy is highly effective and is well tolerated by patients with small cell lung cancer. In limited disease, this combination can be given concurrently with thoracic irradiation and offers a survival advantage.

PMID: 3052870 [PubMed - indexed for MEDLINE]
Topotecan Versus Cyclophosphamide, Doxorubicin, and Vincristine for the Treatment of Recurrent Small-Cell Lung Cancer


Similar survival, superior symptom relief, slightly better response rates; but more anemia, thrombocytopenia on topotecan.
However, we have identified seven studies (192 patients altogether) employing so-called non-cross-resistant chemotherapy in clearly distinguishable relapsed patients. Their response rates (CR + PR) range from 6% to 31%, and the median survival of responding patients was usually only 3-4 months. Thus, results with re-challenge chemotherapy, although poor, appear to be no worse than with alternative second-line chemotherapy.

**Table 2. Likelihood of a good second response is a function of duration of first response ($P = 0.02$)**

<table>
<thead>
<tr>
<th>First response</th>
<th>&lt;8 months</th>
<th>&gt;8 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>NR or second response &lt;2 months, or NR</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Second response &gt;2 months</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>
PCI in ED-SCLC:
Cumulative Incidence of Symptomatic Brain Metastases

PCI in ED-SCLC:
Overall Survival

Bone Metastases:

Zoledronate vs Placebo

**FIGURE 1.** Zoledronic acid significantly extended (A) the time to first skeletal complication compared with placebo and (B) the time to first pathologic fracture compared with placebo. NR: no response.
XGEVA™: Targets and Inhibits RANK Ligand to Break the Vicious Cycle of Bone Destruction and Prevent SREs

- XGEVA™ targets and binds to RANK Ligand, preventing activation of its receptor, RANK, on osteoclasts.
- By binding to RANK Ligand, XGEVA™ inhibits osteoclast formation, function, and survival.
- XGEVA™ prevents the maturation of osteoclasts, decreasing bone resorption and breaking the vicious cycle of bone destruction.

Overall Survival Improvement in Patients With Lung Cancer Treated With Denosumab Versus Zoledronic Acid: Results From a Randomized Phase 3 Study

G Scagliotti¹, V Hirsh², S Siena³, D Henry⁴, P Woll⁵, C Manegold⁶, P Solal-Celigny⁷, G Rodriguez⁸, M Krzakowski⁹, ND Mehta¹⁰, L Lipton¹¹, JA García-Sáenz¹², J Pereira¹³, K Prabhash¹⁴, C Tudor-Eliade¹⁵, V Kanarev¹⁶, A Feng¹⁷, I Jacobs¹⁷

¹University of Turin, Orbassano, Italy; ²McGill University Health Centre, Montreal, Canada; ³Ospedale Niguarda Ca’ Granda, Milan, Italy; ⁴Joan Kornell Cancer Center, Philadelphia, PA, USA; ⁵Weston Park Hospital, University of Sheffield, Sheffield, UK; ⁶Klinikum Mannheim, Mannheim, Germany; ⁷Clinique Victor Hugo, Le Mans, France; ⁸South Texas Oncology and Hematology, San Antonio, TX, USA; ⁹The Maria Skłodowska-Curie Institute of Oncology, Warsaw, Poland; ¹⁰Oncology Hematology Associates of Northern Illinois, Gurnee, IL, USA; ¹¹Western Hospital, Footscray, Vic, Australia; ¹²Hospital Clínico San Carlos, Madrid, Spain; ¹³Instituto do Cancer Arnaldo Vieira de Carvalho, Sao Paolo, Brazil; ¹⁴Tata Memorial Hospital, Mumbai, India; ¹⁵Institutul Oncologic I, Chișinău, Moldova, Romania; ¹⁶Regional Oncology Dispensary with Inpatient Sector, Plovdiv, Bulgaria; ¹⁷Amgen Inc., Thousand Oaks, CA, USA
Study Design: Lung Cancer Subgroup of International, Randomized, Double-Blind, Active-Controlled, Phase 3 Trial

Key Inclusion
- Adults with lung cancer and bone metastases

Key Exclusion
- Current or prior intravenous bisphosphonate administration

1:1

Densumab 120 mg SC and Placebo IV* Q4W (N = 411)

Calcium (500 mg) and Vitamin D (400 IU) strongly recommended

Zoledronic Acid 4 mg IV* and Placebo SC Q4W (N = 400)

<table>
<thead>
<tr>
<th>Lung Cancer Type</th>
<th>Zoledronic Acid</th>
<th>Denosumab</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>352 (88)</td>
<td>350 (85)</td>
<td>702 (100)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>211 (60)</td>
<td>189 (54)</td>
<td>400 (57)</td>
</tr>
<tr>
<td>Squamous Cell</td>
<td>75 (21)</td>
<td>88 (25)</td>
<td>163 (23)</td>
</tr>
<tr>
<td>Other</td>
<td>66 (19)</td>
<td>73 (21)</td>
<td>139 (20)</td>
</tr>
<tr>
<td>SCLC</td>
<td>48 (12)</td>
<td>61 (15)</td>
<td>109 (100)</td>
</tr>
</tbody>
</table>

Values are n (%)

*IV product dose adjusted for baseline creatinine clearance and subsequent dose intervals determined by serum creatinine (per Zometa® label)
### Baseline Characteristics for Patients with Lung Cancer

<table>
<thead>
<tr>
<th>Characteristic, n (%) or median (range)</th>
<th>Zoledronic Acid (N = 400)</th>
<th>Denosumab (N = 411)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>272 (68)</td>
<td>303 (74)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61</td>
<td>60</td>
</tr>
<tr>
<td>Ethnicity – Caucasian</td>
<td>353 (88)</td>
<td>364 (89)</td>
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<tr>
<td>ECOG performance status of 0 – 1</td>
<td>321 (80)</td>
<td>350 (85)</td>
</tr>
<tr>
<td>Time from diagnosis of cancer to first bone metastasis, months</td>
<td>1.0 (-9, 117)</td>
<td>0.8 (-13, 111)</td>
</tr>
<tr>
<td>Time from diagnosis of bone metastasis to randomization, months</td>
<td>1.6 (0, 119)</td>
<td>1.5 (0, 55)</td>
</tr>
<tr>
<td>Prior systemic anticancer therapy</td>
<td>356 (89)</td>
<td>367 (89)</td>
</tr>
<tr>
<td>Prior SRE</td>
<td>197 (49)</td>
<td>191 (46)</td>
</tr>
</tbody>
</table>
Overall Survival: Patients with Lung Cancer

KM Estimate of Median (months)
- Denosumab: 8.9
- Zoledronic acid: 7.7

HR: 0.80 (95% CI: 0.67–0.95)
P = 0.01

Patients at Risk:
- Zoledronic acid: 400, 309, 207, 135, 96, 43, 24, 13
- Denosumab: 411, 323, 233, 164, 120, 71, 43, 26
Overall Survival: Patients with NSCLC

- KM Estimate of Median (months):
  - Denosumab: 9.5
  - Zoledronic acid: 8.1

HR: 0.78 (95% CI: 0.65–0.94)
P = 0.0104

Patients at Risk:
- Zoledronic acid: 352, 275, 185, 123, 91, 40, 23, 12
- Denosumab: 350, 278, 203, 148, 110, 66, 39, 24
Overall Survival: NSCLC by Histological Types

Adenocarcinoma

Squamous Cell Carcinoma

Patients at Risk

Zoledronic acid
Denosumab

Patients at Risk

Zoledronic acid
Denosumab
Overall Survival: Patients with SCLC

KM Estimate of Median (months)
- Denosumab: 7.8
- Zoledronic acid: 5.1

Proportion of Patients Survived

HR: 0.81 (95% CI: 0.52 – 1.26)
P = 0.3580

Patients at Risk:
- Zoledronic acid: 48 34 22 12 7 3 1 1
- Denosumab: 61 45 30 16 10 5 4 2
## Adverse Events Among Patients with Lung Cancer

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>Zoledronic Acid (N = 395)</th>
<th>Denosumab (N = 406)</th>
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<tbody>
<tr>
<td>All AEs</td>
<td>377 (95.4)</td>
<td>393 (96.8)</td>
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<tr>
<td>Serious AEs</td>
<td>288 (72.9)</td>
<td>268 (66.0)</td>
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<td>Fatal AEs</td>
<td>189 (47.8)</td>
<td>183 (45.1)</td>
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<td>AEs of Interest</td>
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<tr>
<td>Hypocalcemia</td>
<td>15 (3.8)</td>
<td>35 (8.6)</td>
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<td>ONJ</td>
<td>3 (0.8)</td>
<td>3 (0.7)</td>
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</table>
Hypotheses for Longer Survival Observed With Denosumab Treatment in Patients With Lung Cancer

- **Indirect effect on tumor cells:**
  - Reduction in NSCLC tumor growth in skeleton through modulation of bone microenvironment is observed in a mouse model upon RANKL inhibition\(^1\)

- **Direct effect on tumor cells:**
  - RANK and RANKL are expressed in the tumor epithelium of primary human NSCLC samples
    - Among 16 samples with adenocarcinoma histotype: 56% expressed RANK, 75% expressed RANKL, and 37% expressed both
    - Among 26 samples with squamous cell carcinoma histotype: 34% expressed RANK, 19% expressed RANKL, and 8% expressed both

---

SUMMARY

• In this exploratory analysis of a large subgroup of patients with NSCLC or SCLC and bone metastases, denosumab treatment is associated with significantly improved overall survival versus zoledronic acid.

• Preclinical investigation underway to evaluate if RANKL inhibition has indirect (via osteoclast inhibition) and/or direct anti-tumor effects on lung cancer cells (e.g., apoptosis, inhibition of cancer migration/invasion).

• These findings warrant further clinical investigation.
EXPERIMENTAL TARGETS IN SMALL CELL LUNG CANCER

Teicher B. Biochemical Pharmacology 2013
ABSTRACT

Recurrent small cell lung cancer is a recalcitrant malignancy. The application of genomic technologies has begun to elucidate the large number of genetic abnormalities in SCLC. Several cell surface receptors are known to be overexpressed by SCLC in clinic specimens and cell in culture including GPCRs such as the bradykinin receptor, the chemokine receptor CXCR4, the vasopression receptor and the three bonebsin receptors. The glucose transporter GLUT1, the tetraspanin family member PETA/CD151 and the immunoglobulin superfamily member ALCAM/CD166 are also overexpressed by SCLC. NCAM/CD56 is overexpressed by nearly all SCLC and is currently the target for an antibody drug conjugate in Phase II trial. Although SCLC is not considered a RTK driven disease, IGF1R and FGFRs are often overexpressed by SCLC. SCLC aberrantly expresses several developmental transcription factors including ASCL1, SOX2, 4, and 11, OCT4, NANOG, PAX5; however, overexpression of MYC may be a driver in SCLC. Like other cancers, SCLC expresses survival factors and uses aerobic glycolysis as a major source of ATP. The drawback of many potential targets overexpressed by SCLC is expression of the same proteins by normal tissues. We are slowly learning more about the molecular abnormalities that occur in SCLC; however, therapeutic impact from new findings remains a goal to work toward.
Welcome to My Oncology Resource, our mission was to develop and deliver a comprehensive web-based, online tool specifically tailored to meet the needs of healthcare professionals involved in the management of lung cancer patients. This tool will provide an overview of evidence-based treatment options for advanced NSCLC patients, which will serve not only as a treatment guide, but also a resource and teaching tool for healthcare providers.
Logging in
Premise behind the website

Recent progress in the understanding of lung cancer biology, combined with a proliferation of new drug options, have considerably brightened the prospects for the thousands of patients. At the same time, however, these new opportunities pose considerable challenges to every level of service: diagnostic, delivery, educational, financial, and, not least, the evidentiary process that must evaluate these options, put them in context, and substantiate their use. What is new is that patients with advanced NSCLC will probably require serial treatments over an extended lifespan, each decision potentially constraining the choice of what follows, and each needing to be carefully weighed amongst the expanding list of competing possibilities.

Gratifyingly, a level of personalized care is now achievable that could not have been contemplated before. Its realization requires a combination of sophisticated tissue diagnosis and biomarker assessment, with traditional parameters such as PS, co-morbidities, organ function, age, demographics, cognition, patient values, social support and drug access potential. Although the basic goals (symptom control, survival prolongation, and toxicity minimization) have not changed, it is clear that their optimal realization through this personalized approach will require an informational framework that exceeds anything that has gone before it, that incorporates but goes beyond the usual Guideline approach.

Oncologists, and their lung cancer patients, need a tool that meets their informational needs in a convenient, ready-to-hand manner. What is approved in Canada? What is funded in my province? What other access options exist? What is appropriate in this line of therapy? Are there different sets of recommendations? What is the evidence, and how do I access it? What toxicities are important? What supportive care and accessory products can ease the journey?

While we do not claim to be comprehensive, nor is anything we present intended to substitute for physician judgement, we hope this computer aid will provide efficiencies for the oncologist, and options for the patients, and assist in the process of truly informed consent.
Resources – available to view without signing in or logging in

Resources

- BCCA NSCLC Guidelines
- CCD NSCLC Guidelines
- Cisplatin/Permutrexed Toxicity Table
- Cis/Vin vs Carbop/ Tax (Kelly et al, 2001)
- Crizotinib Study (Shaw et al, 2011)
- Docetaxel 2nd line: (Shepherd et al., 2001)
- E4599 for Carbop/Tax + Bev (Sandler et al, 2010)
- Erlotinib 1st Line: (Rosell et al., EURTAC Study)
- Erlotinib 1st Line: (Zhou et al., Optimal Study)
- Erlotinib 2nd/3rd Line: (Shepherd et al., 2005 BR.21)
- Erlotinib Maintenance: (Capuzzo et al, 2010 Satum ITT)
- Erlotinib Maintenance: (Coudert et al, 2011 Satum SD)
- Gefitinib 1st Study (IPASS Mok et al, 2009)
- NCCN NSCLC Guidelines
- Oncology Review of EGFR Inhibitors
- Ontario Cancer Trials
- Permutrexed 1LM (Ciuleanu et al., 2009 JMEM trial)
Resources include a link to the actual trial, granted the computer you are working from has access (i.e., hospital).

Docetaxel 2nd line: (Shepherd et al., 2001)

Source: http://jco.ascopubs.org/content/18/10/2095.long

(Shepherd et al.)

**Purpose:** To evaluate whether treatment with single-agent docetaxel would result in longer survival than would best supportive care in patients with non-small-cell lung cancer who had previously been treated with platinum-based chemotherapy. Secondary end points included assessment of response (docetaxel arm only), toxicity, and quality of life.

**Patients and Methods:** Patients with performance statuses of 0 to 2 and stage IIIIB/IV non-small-cell lung cancer with either measurable or evaluable lesions were eligible for entry onto the study if they had undergone one or more platinum-based chemotherapy regimens and if they had adequate hematology and biochemistry parameters. They were excluded if they had symptomatic brain metastases or if they had previously been treated with paclitaxel. Patients were stratified by performance status and best response to cisplatin chemotherapy and were then randomized to treatment with docetaxel 100 mg/m² (49 patients) or 75 mg/m² (50 patients) or best supportive care. Patients in both arms were assessed every 3 weeks.

**Results:** One hundred four patients (100 of whom were eligible for entry onto the study) were well balanced for prognostic factors. Of 94 patients with measurable lesions, six (7.1%) achieved partial responses (three patients at each dose level). Time to progression was longer for docetaxel patients than for best supportive care patients (10.6 v 6.7 weeks, respectively; P < .001), as was median survival (7.0 v 4.6 months; log-rank test, P = .047). The difference was more significant for docetaxel 75 mg/m² patients, compared with corresponding best supportive care patients (7.5 v 4.6 months; log-rank test, P = .010; 1-year survival, 37% v 11%; p² test, P = .003). Febrile neutropenia occurred in 11 patients treated with docetaxel 100 mg/m², three of whom died, and in one patient treated with docetaxel 75 mg/m². Grade 3 or 4 nonhematologic toxicity, with the exception of diarrhea, occurred at a similar rate in both the docetaxel and best supportive care groups.
Welcome to My Oncology Resource; our mission was to develop and deliver a comprehensive web based, online tool specifically tailored to meet the needs of healthcare professionals involved in the management of lung cancer patients. This tool will provide an overview of evidence-based treatment options for advanced NSCLC patients, which will serve not only as a treatment guide, but a resource and teaching tool for healthcare practitioners.

Table of Contents

1. Sign Up .................................................................
   Enter Registration Info .............................................

2. Login .................................................................
   Log In ..............................................................

3. Resources ..........................................................
New patient (can be saved) vs sample patient (teaching or review opportunity)

<table>
<thead>
<tr>
<th>Title</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
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### Overview field

#### My Oncology Resource

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<th>ALK+</th>
<th>WT/WT or Unknown/Not Available</th>
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<td>Cisplatin Doublet</td>
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<tr>
<td>Ercitinib</td>
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<tr>
<td>Surveillance</td>
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<tr>
<td><strong>Comments</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Overview

- A-NSCLC Systemic Rx
- Squamous or NOS (favor squame)
  - Non-Squamous
    - Adenoca
    - Large Cell
    - NOS or NOS Favor Adenoca
      - EGFR M
      - ALK +
      - WT/WT
Entering patient characteristics allows for a personalized treatment guide

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<thead>
<tr>
<th></th>
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<th>ALK+</th>
</tr>
</thead>
<tbody>
<tr>
<td>1L</td>
<td>☐ Erlotinib</td>
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<tr>
<td></td>
<td>Cisplatin Doublet</td>
<td>Cisplatin Doublet</td>
</tr>
</tbody>
</table>

Click here for an overview
### Patient Characteristics

**Histology**
- □ Adenocarcinoma
- □ Large Cell
- □ NOS
- □ Squamous

**Biomarker status**
- □ ALK +
- □ EGFR M+
- □ NA/Unknown
- □ WT/WT

**Medical Details**
- Age
- Gender

**Prior Therapy Considerations**
- Line
  - L

[Update Patient]
### Medical details

**My Oncology Resource**

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Medical Details</th>
<th>Prior Therapy Considerations</th>
<th>Toxicity concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECOG PS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Smoking Status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Hemoptysis**
  - Yes
  - No

- **Pre Existing Conditions**
  - COPD/pneumonectomy
  - Hemoptysis
  - Hepatic dysfunction
  - Open wound/recent fix
  - Pregnant
  - Recent Myocardial Infarction
  - Recent Thrombi-embolism
  - Renal impairment
  - Uncontrolled Hypertension
  - Unstable Angina

- **Metastatic**
  - Bone
  - Brain
  - Leptomeninges

- **Toxicity concerns**
  - Abnormal LFTs
  - Alopecia
  - Anemia
  - Arthritis
  - Bleeding
  - Bone Marrow Suppression
  - Cardiac Abnormalities
  - Diarrhea
  - Dyspnea
  - Edema
  - Fatigue
  - Febrile Neutropenia
  - Fluid retention
  - GI Toxicity
  - Haematologic
  - Hearing
  - Hepatotoxicity
Prior therapy considerations

- Had radiation before?
  - Yes
  - No

- Have you used Cisplatin in prior treatment?
  - Yes
  - No
Specific notes that pertain to patient characteristics

- There is Health Canada approval for both Zometa as well as Xgeva for delay in time to next skeletal-related event in patients with a proven bone met in lung cancer.
Drug details

Gefitinib Funded Publically

**Name:** Iressa

**Indications:** IRESSA (gefitinib) is indicated for the first line treatment of patients with locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) who have activating mutations of the EGFR-TK.

**Contraindications:** Patients who are hypersensitive to gefitinib or to any ingredient in the formulation or component of the container EGFR mutation status unknown or negative.

**Considerations:** Renal and hepatic impairment CYP 3A4 and 2D6 interactions Contains lactose.

**Dosage:** 250mg QD (no dose modifications)

**Toxicity Concerns:** Diarrhea Rash

**Links**
- IPASS Study
Warning symbols

Prior to treatment with Alimta initiate supplementation with oral folic acid and intramuscular Vitamin B12 to reduce the severity of haematologic and gastrointestinal toxicity associated with Alimta.

ALIMTA is primarily eliminated unchanged by renal excretion. No dosage adjustment is needed in patients with creatinine clearance $\geq 45$ mL/min. Insufficient numbers of patients have been studied with creatinine clearance $<45$ mL/min to give a dose recommendation. Therefore, ALIMTA should not be
Choosing a drug eliminates subsequent choices in later lines

<table>
<thead>
<tr>
<th>1L</th>
<th>Erlotinib</th>
<th>Crizotinib</th>
<th>Carboplatin Doublet</th>
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</table>
Comment Boxes

Comments

Bevacizumab as maintenance monotherapy beyond 4-6 cycles of Carbo/Pac/Bev
Patients on the PCB arm of the E4599 trial stopped the PC after 6 cycles and continued on Bev alone until disease progression.

Crizotinib: Rx to PD
Proceed until progression.
CASE REPORT (1)

An overview: Current systemic therapies for advanced non-small cell lung cancer

Ong M and Vincent M. Lung Cancer, In Press
• 54 yr Caucasian male
• Never-smoker
• Dyspnea, large pleural effusion
• FNA: “adenocarcinoma lung”
• Chest tube drainage, pleurodthesis
• EGFR “inconclusive” (scant 6x material)
• 6 cycles carbo/paclitaxel – minor response
• Relapsed within 3/12
• Refractory to 3 cycles pemetrexed
• Multiple brain mets, O₂ dependent
• Whole brain RT
CASE REPORT (cont) … (3)

• Rx erlotinib 150 mg po od
Disease burden before (Panels A, B, C) and 8 months after (Panels D, E, F) initiation of third-line erlotinib for metastatic A-NSCLC.
CASE REPORT (cont) … (4)

- Eventual PD on erlotinib (± 1 year remission)
- Unresponsive to trial of afatinib
- Dies rapidly of respiratory failure
- EGFR ? But almost certainly M+
TAILOR Study Design

- Advanced/recurrent
- Previous platinum based doublet
- EGFR wild-type
- KRAS determined
- ECOG PS 0-2

DOCETAXEL
75 mg/m2 iv day 1,21 OR 35 mg/m2 iv day 1,8,15,28

ERLOTINIB
150 mg po, daily

CROSS OVER NOT ALLOWED

Stratification minimization approach
- Centre
- Recurrent/progressed
- Type of prior chemotherapy regimen (pem vs gem vs vnb)
- ECOG-PS (0-1 vs 2)
- Adequacy of tissue sample (optimal vs suboptimal)
## Baseline patients demographic

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<thead>
<tr>
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<th><strong>ERLOTINIB</strong> (n=109)</th>
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<tr>
<td><strong>Median Age, years (range)</strong></td>
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<td>66 (40-81)</td>
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<tr>
<td><strong>Gender</strong></td>
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<tr>
<td>Male</td>
<td>66.4%</td>
<td>70.6%</td>
</tr>
<tr>
<td>Female</td>
<td>33.6%</td>
<td>29.4%</td>
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<tr>
<td><strong>ECOG PS</strong></td>
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<tr>
<td>0</td>
<td>48.2%</td>
<td>47.7%</td>
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<td>1</td>
<td>45.5%</td>
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</tr>
<tr>
<td>2</td>
<td>6.3%</td>
<td>8.3%</td>
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<tr>
<td><strong>Histology</strong></td>
<td></td>
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</tr>
<tr>
<td>Squamous</td>
<td>20.9%</td>
<td>28.4%</td>
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<tr>
<td>Adenocarcinoma</td>
<td>75.5%</td>
<td>63.4%</td>
</tr>
<tr>
<td>Others</td>
<td>3.6%</td>
<td>8.2%</td>
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<tr>
<td><strong>Smoking Habit</strong></td>
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</tr>
<tr>
<td>Smokers (also ex)</td>
<td>71.8%</td>
<td>81.7%</td>
</tr>
<tr>
<td>Never-smokers</td>
<td>28.2%</td>
<td>18.3%</td>
</tr>
<tr>
<td><strong>KRAS status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutated</td>
<td>22.7%</td>
<td>23.9%</td>
</tr>
<tr>
<td>Wild-type</td>
<td>77.3%</td>
<td>76.1%</td>
</tr>
</tbody>
</table>
## Major reported toxicities

<table>
<thead>
<tr>
<th>TOXICITY</th>
<th>DOCETAXEL (n = 104)</th>
<th>ERLOTINIB (n = 107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non haematological toxicity</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Nausea &amp; Vomiting</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Asthenia</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Alopecia (all grades)</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>Dermatological toxicity</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Neurological</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Haematological toxicity</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>
PFS [ITT]

HR 0.69 (95% CI 0.52-0.93)  p=0.014

<table>
<thead>
<tr>
<th></th>
<th>Median mos.</th>
<th>6-mos PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>3.4</td>
<td>28.9%</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>2.4</td>
<td>16.9%</td>
</tr>
</tbody>
</table>

Patients at risk:

<table>
<thead>
<tr>
<th></th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>110</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>109</td>
</tr>
</tbody>
</table>
## Response Rate

<table>
<thead>
<tr>
<th></th>
<th>DOCETAXEL</th>
<th>ERLOTINIB</th>
<th>$\chi^2$ test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=94 %</td>
<td>n=92 %</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>4.3</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>9.6</td>
<td>2.2</td>
<td>p=0.002</td>
</tr>
<tr>
<td>SD</td>
<td>27.6</td>
<td>20.6</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>58.5</td>
<td>77.2</td>
<td></td>
</tr>
<tr>
<td>RR (CR+PR)</td>
<td>13.9</td>
<td>2.2</td>
<td>p=0.004</td>
</tr>
<tr>
<td>DCR (CR+PR+SD)</td>
<td>41.5</td>
<td>22.8</td>
<td>p=0.007</td>
</tr>
</tbody>
</table>