Non-Small Cell Lung Cancer
A REFERENCE GUIDE OF IMPORTANT CLINICAL TRIALS

Created by DAVA Oncology
2011 Standard of Care Reference Guide

- Navigate current treatment paradigm by stage, histology, biological subset, or line of treatment
- Review key trials that defined current treatment options and/or regulatory standards for each of the major markets (US, EU, Japan)

Clickable interface allows quick access to overview of SOC for desired patient subset or line of treatment
- Trials included in overview of SOC link to detailed descriptions of trial design & key data
- References included in trial descriptions link out to pubmed file

The main navigation buttons are at the bottom of the page. Click #1 to advance to the first introduction page with information about staging
## TNM STAGING SYSTEM FOR LUNG CANCER
### 7TH EDITION, 2009

<table>
<thead>
<tr>
<th>Stage</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>M</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
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<tbody>
<tr>
<td>I</td>
<td>• &lt; 3 cm</td>
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<td></td>
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<td>N0</td>
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<td>N1</td>
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<tr>
<td>II</td>
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<td>N1</td>
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<td>III</td>
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<td></td>
<td>N2</td>
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<tr>
<td>IV</td>
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<td></td>
<td></td>
<td></td>
<td>N3</td>
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</tbody>
</table>

#### Stage Distribution at Diagnosis:

- **I**: 16%
- **II**: 8%
- **IIIa**: 10%
- **IIIb/IV**: 37%
- **Ipsilateral peribronchial or perihilar lymph nodes**: 67%
- **Ipsilateral mediastinal or subcarinal lymph nodes**: 26%
- **Contralateral lymph nodes**: 12%

### Overview
- Non-Small Cell Lung Cancer

### Histology
- Standard of Care by Line of Treatment

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[Clicking on these links will provide the external reference.](http://seer.cancer.gov/)

[Sawabata et al., J Thorac Oncol. 2010; 5: p1369](http://www.ic.nhs.uk/)
IMPACT ON TREATMENT CHOICE:

- Safety: Pulmonary hemorrhage with bevacizumab in squamous histology
- Efficacy: Lack of benefit with pemetrexed in patients with squamous histology

HISTOLOGY DISTRIBUTION AT DIAGNOSIS:

Overview
Stage
Histology
Biology
Standard of Care by Line of Treatment
Impact on treatment choice:

- EGFR TKIs erlotinib and gefitinib active in EGFRmut pts
- ALK inhibitor crizotinib active in pts with EML4/ALK chromosomal rearrangement

Molecular subsets in non-squamous NSCLC:

<table>
<thead>
<tr>
<th>Subset</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>22%</td>
</tr>
<tr>
<td>EGFR</td>
<td>17%</td>
</tr>
<tr>
<td>EML4/ALK</td>
<td>7%</td>
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<tr>
<td>Double mut</td>
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<tr>
<td>BRAF</td>
<td></td>
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<tr>
<td>AKT</td>
<td></td>
</tr>
<tr>
<td>NRAS</td>
<td></td>
</tr>
<tr>
<td>MEK1</td>
<td></td>
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<tr>
<td>MET ampl</td>
<td></td>
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<tr>
<td>HER2</td>
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<tr>
<td>PI3K</td>
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</table>

Kris et al., ASCO. 2011; #CRA 7506
Non-Small Cell Lung Cancer

Localized

Advanced

Squamous

Non-Squamous

Overview

Stage

Histology

Biology

Standard of Care by Line of Treatment

This is the main landing page, which is broken down by line of therapy.

Click on one of the below circles to navigate to the regulatory page for 1L or 2L treatment.

You can return to the introduction pages by clicking on the text below.
Non-Small Cell Lung Cancer

Squamous

Overview

Histology

Standard of Care by Line of Treatment

Stage

Biology

You can click on the table to view the trial information.

The trials are divided into Pivotal (designed for regulatory approval), Key Cooperative/Key (important, changed practice pattern), and Ongoing.
### Ongoing Trials

<table>
<thead>
<tr>
<th>Sponsor (Trial Name)</th>
<th>N</th>
<th>Study Design</th>
<th>MoA</th>
<th>Primary Endpoint</th>
<th>Start Date</th>
<th>Estimated Completion Date</th>
<th>Id Number</th>
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</thead>
<tbody>
<tr>
<td>SWOG 0819</td>
<td>1546</td>
<td>Paclitaxel/Carboplatin/Bevacizumab (in Bev-Eligible) ± Cetuximab (1L)</td>
<td>VEGF mAb</td>
<td>OS/PFS</td>
<td>3Q2009</td>
<td>2Q2012</td>
<td>NCT00946712</td>
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<tr>
<td>NCIC (BR.29)</td>
<td>750</td>
<td>Cediranib/Paclitaxel/Carboplatin vs. Placebo/Paclitaxel/Carboplatin in 1L NSCLC</td>
<td>VEGF TKI</td>
<td>OS</td>
<td>4Q2008</td>
<td>1Q2013</td>
<td>NCT00795340</td>
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<tr>
<td>IMCLONE (SQUIRE)</td>
<td>947</td>
<td>Gemcitabine/Cisplatin ± Necitumumab in 1L, Squamous NSCLC</td>
<td>EGFR mAb</td>
<td>OS</td>
<td>1Q2010</td>
<td>2Q2013</td>
<td>NCT00981058</td>
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<tr>
<td>H. Lee Moffitt Cancer Center and Research Institute</td>
<td>267</td>
<td>1L Chemotherapy Based on ERCC1 and RRM1 Expression Levels</td>
<td>Genotype-directed therapy</td>
<td>PFS</td>
<td>2Q2007</td>
<td>2Q2015</td>
<td>NCT00499109</td>
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<td>BMS</td>
<td>800</td>
<td>Ipilimumab/Paclitaxel/Carboplatin vs. Placebo/Paclitaxel/Carboplatin in 1L, Squamous NSCLC</td>
<td>CTLA-4 mAb</td>
<td>OS</td>
<td>3Q2011</td>
<td>2Q2016</td>
<td>NCT01285609</td>
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<tr>
<td>SANOFI (ECLIPSE)</td>
<td>780</td>
<td>Gemcitabine/Carboplatin ± Iniparib (SAR240550) in 1L Squamous NSCLC</td>
<td>PARP inhibitor</td>
<td>OS</td>
<td>2Q2010</td>
<td>2Q2013/7</td>
<td>NCT01082549</td>
</tr>
</tbody>
</table>

**Click on the table above to view the ongoing trial information on clinicaltrials.gov**
Non-Small Cell Lung Cancer

Squamous

SOC BY REGION:

- Paclitaxel + Carboplatin
- Gemcitabine + Cisplatin
- Vinorelbine + Cisplatin
- Cisplatin-Based Combination

APPROVED AGENTS:

- 1995: Vinorelbine (+ cis)
- 1998: Gemcitabine (+ cis)
- 1999: Paclitaxel (+ cis)
- 2003: Docetaxel (+ cis)
- 1996: Docetaxel
- 1999: Paclitaxel, Gemcitabine, Vinorelbine
- 2004: TS-1

KEY TRIALS (NON-PIVOTAL):

- ECOG-1594: Four Platinum-Based Regimens; Same Outcome (2002)
- EORTC-08975: Platinum vs. Non-Platinum-Based Doublets; Same OS
- FACS: Regulatory Authorities Required Study to Compare Four Platinum-Based Regimens (2007)
Establishing Cisplatin-Based Combinations as SOC in 1L NSCLC:

- Cisplatin, in combination with vinca alkaloid vindesin, had been recognized as an active regimen for NSCLC since the 1980’s (Elliot. Eur J Cancer Clin Oncol. 1984)
- European phase III trial in advanced NSCLC comparing the novel, semi-synthetic vinca alkaloid vinorelbine to cisplatin-based doublets with either vinorelbine or vindesine
- Trial supported both European and US approval of vinorelbine in combination with cisplatin as a standard chemotherapy regimen for chemo-naïve NSCLC patients
Establishing Cisplatin-Based Combinations as SOC in 1L NSCLC:

**Eligibility Criteria**
- Diagnosis of stage III or IV NSCLC
- ≤75 years of age
- WHO PS of 0, 1 or 2
- Inoperable disease
- No prior chemotherapy

**Primary Endpoint**
- OS

**Accrual Window**
- June 1989 – May 1991

**Dosing & Schedule**
- **Vinorelbine**
  - 30 mg/m²
  - Weekly
- **Cisplatin**
  - 120 mg/m²
  - D1, d29; then q6w
- **Vindesine**
  - 3 mg/m²
  - Weekly

Le Chevalier et al., JCO. 1994; 12: p360
Click here to see more information on the patient population
Establishing Cisplatin-Based Combinations as SOC in 1L NSCLC:
Establishing Cisplatin-Based Combinations as SOC in 1L NSCLC:

Combination of vinorelbine and cisplatin significantly improved OS compared to either vinorelbine alone or vindesine plus cisplatin.
Establishing Cisplatin-Based Combinations as SOC in 1L NSCLC:

**Impact**, **Design**, **Efficacy**, **Toxicity**

**OVERALL RESPONSE RATE**

Combination of vinorelbine and cisplatin significantly improved ORR compared to either vinorelbine alone or vindesine plus cisplatin.
Establishing Cisplatin-Based Combinations as SOC in 1L NSCLC:

<table>
<thead>
<tr>
<th>Gr. 3/4 AEs</th>
<th>Cisplatin/ Vindesine</th>
<th>Cisplatin/ Vinorelbine</th>
<th>Vinorelbine</th>
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<tr>
<td><strong>Hematologic</strong></td>
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<tr>
<td>Neutropenia</td>
<td>48%</td>
<td>79%</td>
<td>53%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3%</td>
<td>3%</td>
<td>0.0%</td>
</tr>
<tr>
<td><strong>Non-Hematologic</strong></td>
<td></td>
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<tr>
<td>Neurologic</td>
<td>17%</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>59%</td>
<td>58%</td>
<td>12%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7%</td>
<td>11%</td>
<td>4%</td>
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</table>

Vinorelbine significantly increased the incidence of gr. 3/4 neutropenia compared to vindesine; however, gr. 3/4 neurotoxicity was reduced with vinorelbine.
### TRAILS

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<th>2L</th>
<th>3L</th>
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<td>Shepherd. JCO. <strong>2000</strong>; 18: p2095</td>
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<td>US (TAX320): Vinorelbine or Ifosfamide vs. Docetaxel</td>
<td>Fossella. JCO. <strong>2000</strong>; 18: p2354</td>
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<td>JPN/EU (IDEAL): Single Agent Gefitinib</td>
<td>Fukuoka. JCO. <strong>2003</strong>; 21: p2237</td>
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<td></td>
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<td></td>
<td>Global: Docetaxel vs. Pemetrexed</td>
<td>Hanna. JCO. <strong>2004</strong>; 22: p1589</td>
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<td></td>
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<td></td>
<td>Canada (BR.21): Best Supportive Care vs. Erlotinib</td>
<td>Shepherd. NEJM. <strong>2005</strong>; 353: p123</td>
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</tbody>
</table>

**PIVOTAL TRIALS**

- US/EU (TAX317): Best Supportive Care vs. Docetaxel
- US (TAX320): Vinorelbine or Ifosfamide vs. Docetaxel
- JPN/EU (IDEAL): Single Agent Gefitinib
- Global: Docetaxel vs. Pemetrexed
- Canada (BR.21): Best Supportive Care vs. Erlotinib

**KEY TRIALS**

- Shepherd. JCO. **2000**; 18: p2095
- Fossella. JCO. **2000**; 18: p2354
- Fukuoka. JCO. **2003**; 21: p2237
- Hanna. JCO. **2004**; 22: p1589
- Shepherd. NEJM. **2005**; 353: p123

**ONGOING TRIALS**
Non-Small Cell Lung Cancer
Non-Squamous

1L Maintenance 2L 3L

KEY TRIALS
JPN/EU (IDEAL): Single Agent Gefitinib
Global: Docetaxel vs. Pemetrexed
Canada (BR.21): Best Supportive Care vs. Erlotinib

PIVOTAL TRIALS
KEY COOP GROUP TRIALS
KEY TRIALS
ONGOING TRIALS

Fukuoka. JCO. 2003; 21: p2237
Hanna. JCO. 2004; 22: p1589
Shepherd. NEJM. 2005; 353: p123
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<th>Start Date</th>
<th>Estimated Completion Date</th>
<th>ID Number</th>
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<tbody>
<tr>
<td>MetMab (Roche)</td>
<td>137</td>
<td>MetMab in Combination with Erlotinib in Advanced NSCLC</td>
<td>c-Met mAb</td>
<td>PFS</td>
<td>1Q2009</td>
<td>4Q2011</td>
<td>NCT00854308</td>
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<td>Bayer (Mission)</td>
<td>703</td>
<td>Sorafenib vs. Placebo in Pretreated, Advances, Nonsquamous NSCLC</td>
<td>VEGFR, PDGFR, Raf TKI</td>
<td>OS</td>
<td>2Q2009</td>
<td>4Q2011</td>
<td>NCT00863746</td>
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<td>BI (Lume-Lung 1)</td>
<td>1300</td>
<td>BIBF 1120/Docetaxel vs. Placebo/Docetaxel in Pretreated, Advanced NSCLC</td>
<td>VEGFR, PDGFR, FGFR TKI</td>
<td>PFS</td>
<td>4Q2008</td>
<td>4Q2012</td>
<td>NCT00805194</td>
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<td>NCIC (BR.26)</td>
<td>720</td>
<td>PF-00299804 vs. Placebo in Advanced Refractory NSCLC</td>
<td>Her1 (EGFR)</td>
<td>OS</td>
<td>3Q2009</td>
<td>4Q2012</td>
<td>NCT01000025</td>
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<td>SYNTA</td>
<td>240</td>
<td>Ganetepib (STA-9090) + Docetaxel vs., Docetaxel in Pretreated Advanced NSCLC</td>
<td>Hsp 90 inhibitor</td>
<td>PFS (OS in subset)</td>
<td>2Q2011</td>
<td>1Q2013</td>
<td>NCT01348126</td>
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<td>Pfizer (Archer 1009)</td>
<td>800</td>
<td>PF-00299804 vs. Erlotinib in Pretreated, Advanced NSCLC</td>
<td>Her1 (EGFR)</td>
<td>PFS</td>
<td>2Q2011</td>
<td>1Q2013</td>
<td>NCT01360554</td>
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<td>BI (Lume-Lung 2)</td>
<td>1302</td>
<td>BIBF 1120/Pemetrexed vs. Placebo/Pemetrexed in Pretreated, Advanced, Nonsquamous NSCLC</td>
<td>VEGFR, PDGFR, FGFR TKI</td>
<td>PFS</td>
<td>4Q2008</td>
<td>2Q2013</td>
<td>NCT00806819</td>
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<td>Daiichi Sankyo Inc. (Marquee)</td>
<td>988</td>
<td>Erlotinib ±Tivantinib (ARQ 197) in Pretreated, Advanced, Nonsquamous NSCLC</td>
<td>C-Met TKI</td>
<td>OS</td>
<td>4Q2010</td>
<td>3Q2013</td>
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<td>Lilly</td>
<td>1242</td>
<td>Docetaxel/Ramucirumab vs. Docetaxel/Placebo in Pretreated Advanced NSCLC</td>
<td>VEGFR-2 mAb</td>
<td>OS</td>
<td>4Q2010</td>
<td>2Q2014</td>
<td>NCT01168973</td>
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<td>Overview</td>
<td>Stage</td>
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<td>Biology</td>
<td>Standard of Care by Line of Treatment</td>
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<tr>
<td>Non-Small Cell Lung Cancer Non-Squamous</td>
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</tbody>
</table>

**2L+ SOC BY REGION:**

- **Single Agent CT or Erlotinib**
  - US (TAX317): Docetaxel (Shepherd. JCO. 2000)
  - JPN/EU (IDEAL): Gefitinib (Fukuoka. JCO. 2003)
  - US (TAX320): Docetaxel (Fossella. JCO. 2000)
  - Global: Pemetrexed (Hanna. JCO. 2004)
  - 2000
  - 2003

- **Single Agent CT or Erlotinib**
  - US (BR.21): Erlotinib (Shepherd. NEJM. 2005)
  - 2004

- **EGFR TKI**
  - 2005

**APPROVED AGENTS:**

- **1999:** Docetaxel
- **2004:** Erlotinib
- **2004:** Pemetrexed

- **1999:** Docetaxel
- **2004:** Pemetrexed
- **2005:** Erlotinib

- **1996:** Docetaxel
- **1999:** Paclitaxel, Gemcitabine, Vinorelbine
- **2002:** Gefitinib
- **2004:** TS-1
- **2007:** Erlotinib
- **2009:** Pemetrexed

**KEY TRIALS (NON-PIVOTAL):**

- US (TAX320): Docetaxel (Fossella. JCO. 2000)
- EU/US (TAX317): Docetaxel (Shepherd. JCO. 2000)
- JPN/EU (IDEAL): Gefitinib (Fukuoka. JCO. 2003)
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- Global: Pemetrexed (Hanna. JCO. 2004)