MANAGEMENT OF ADVANCED NSCLC

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CUSTOMIZING THERAPEUTIC STRATEGIES TO OPTIMIZE OUTCOMES IN THE MANAGEMENT OF ADVANCED NSCLC

1. Discuss efficacy and safety data for current and emerging targeted agents and chemotherapy regimens in the treatment of advanced NSCLC
2. Integrate findings from histopathology and mutation analyses into safe and effective treatment strategies for advanced NSCLC
3. Analyze ASCO and NCCN's latest guidelines on the treatment of advanced NSCLC
4. Examine the rationale for treatment with EGFR TKIs as initial therapy and review the current status of second-generation EGFR TKIs in the management of EGFR-mutant NSCLC
5. Identify patient factors that can be used to guide treatment selection and determine a patient's ability to tolerate therapy for advanced NSCLC
**Background**

- Lung cancer is the most common cause of cancer death in the US and worldwide.
- Around 200,000 Americans die every year of lung cancer.
- 1 in 7 smokers will die of lung cancer.
- The 5 year survival: 15%
**Lung Cancer Subtypes**

- **Non-Small Cell Lung Cancer (NSCLC)** ~85%
- **Small Cell Lung Cancer (SCLC)** ~15%
- **Squamous Cell Carcinoma** 25%-30%
- **Adenocarcinoma** 35%-40%
- **Large Cell Carcinoma** 10%-15%


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**SMALL CELL LUNG CANCER TREATMENT**

- Rare patients are surgical candidates
- Cisplatin and Etoposide is standard therapy
- For limited stage disease, combine with radiation
- Follow with prophylactic whole brain radiotherapy in limited stage patients with complete response
STAGE I-II NSCLC

- Surgery
- Radiation is becoming an option (when patients can’t tolerate surgery)

ADJUVANT THERAPY

Disease-free Survival

Overall Survival

HR = 0.86 [0.74-0.99]  p<0.03

Summary

4.1% absolute benefit from 40.4% to 44.5% at 5 years for overall survival  p<0.03

* 5.1% absolute benefit from 34.3% to 39.4% at 5 years for disease-free survival (p<0.003)
* No treatment interaction identified
* Lethal toxicity 0.8%
ADVANCED NSCLC. STAGE III

- Mediastinal LN involvement
- Supraclavicular or scalene LN
- Primary tumor invades local structures (heart, spine, great vessels, etc)

ADVANCED NSCLC. STAGE IV

M1a  Pleural or pericardial effusion
      Tumor with pleural nodules
      Nodule in the contralateral lung

M1b  Cancer spread outside of the chest
Chemotherapy vs. Supportive Care

ECOG 1594: Platinum-Based Combination Chemotherapies – Survival

**Median survival (mo)**

- Carboplatin + paclitaxel: 7.9 mo, *P*=NS
- Cisplatin + gemcitabine: 8.1 mo, *P*=NS
- Cisplatin +/docetaxel: 7.4 mo, *P*=NS
- Carboplatin + paclitaxel: 8.1 mo, *P*=NS

NS = not significant

TREATMENT PARADIGMS AFTER 2004

- Determination of histology at diagnosis is mandatory.
- There are differences in survival between platinum based doublets.
- Three drugs may be better than two, in specific populations.
- Platinum-based chemo are still the standard of care (except for subpopulations of patients with “driving mutations” in EGFR and ALK)
- Maintenance therapy is a novel strategy and an option.

“JMDB” Randomized Phase III Trial of Cisplatin/Gemcitabine vs. Cisplatin/Alimta

- First-line Adv. NSCLC (N = 1725) Excluding pts with: wt loss >10% body wt uncontrolled pleural effusions
- Cisplatin 75 mg/m² IV day 1 Gemcitabine 1250 mg/m² IV d1, 8 Every 21 days x 6 cycles with B12 and folate acid supplementation
- Cisplatin 75 mg/m² IV day 1 Pemetrexed 500 mg/m² IV d1 Every 21 days x 6 cycles with B12 and folate acid supplementation

- Primary endpoint: Overall Survival
- Pre-specified/planned analysis of results by tumor histology

Scagliotti, J Thoracic Oncology 2007
**NSCLC CHEMO APPROACHES BY HISTOLOGY**

**Non squamous**

First-line
- Platinum + pemetrexed
- Carboplatin/paclitaxel/bevacizumab
- Carbo/pem/bev?

Second-line
- Taxane or Pem
- Erlotinib

Others
- Gemcitabine or vinorelbine

**Squamous**

First-line
- Platinum + gemcitabine or taxane
- Cisplatin/vinorelbine/cetuximab

Second-line
- Taxane or gem
- Erlotinib

Others
- Vinorelbine

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**Outcomes of Different NSCLC Subtypes on Alternate Chemo Regimens**

**Non-Squamous NSCLC**

- Median; 95% CI
  - CP: 11.8; 10.4, 13.2
  - CG: 10.4; 8.6, 11.2

- CP vs CG Adjusted HR; 95% CI
  - 0.81; 0.70, 0.94

**Squamous NSCLC**

- Median; 95% CI
  - CP: 9.4; 8.4, 10.2
  - CG: 10.4; 9.5, 12.1

- CP vs CG Adjusted HR; 95% CI
  - 1.23; 1.00, 1.51

*P* = 0.03

*P* = 0.05

Scagliotti, J Clin Oncol 2008
Chemotherapy + Targeted Agents

Targeted Therapies

- Targeting Vascular Endothelial Growth Factor (VEGF)
  - Monoclonal antibody against VEGF-A
- Targeting Epidermal Growth Factor Receptor (EGFR)
  - Monoclonal antibody against EGFR
  - Tyrosine kinase inhibitors
- Targeting Anaplastic Lymphoma Kinase (ALK)
  - Crizotinib
ANGIOGENESIS

VEGF Production
Blood Vessel Growth
Tumor Growth

PHASE III TRIAL IN NON-SQUAMOUS NSCLC: ECOG 4599 (N=855)

Eligibility
- No previous chemotherapy
- Non-squamous cell
- No hx of hemoptysis
- No CNS metastases

CP
- Paclitaxel 200 mg/m²
- Carboplatin AUC 6 (Q3 weeks) x 6 cycles
- No crossover to bevacizumab

CPB
- CP x 6 cycles
- Bevacizumab (15 mg/kg) (Q3 weeks to DP)

Stratification Variables:
- RT vs. no RT
- Stage IIIB or IV vs. recurrent
- Wt loss <5 % vs. > 5%
- Measurable vs. non-measurable

Sandler, et al. NEJM 355:2542-2550, 2006
**Overall Survival**

- PCB (305 events/417 cases)
- PC (344 events/433 cases)
- HR = 0.80
- P = 0.003

Medians: 10.3, 12.3 months

2-year survival 23 vs. 15%

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**Cetuximab (Erbitux)**

- EGFR monoclonal antibody, IgG1.
- Exclusive for EGFR and its heterodimers.
- Prevents ligand binding to EGFR. Stimulates receptor internalization.
- Blocks receptor dimerization, tyrosine kinase phosphorylation, and signal transduction.
- IgG1-induced Antibody-dependent Cellular Cytotoxicity (ADCC)
Randomized Phase III of Cis/Vinorelbine +/- Cetuximab in 1st Line (FLEX)

First-Line treatment for patients with EGFR-expressing advanced NSCLC

**Stratification**
- Study Patients (N=1100)
- Stage III B or IV NSCLC
- + EGFR by IHC

**Primary End Point**
- Overall Survival

**Secondary End Points**
- Progression-Free Survival
- Response Rate
- Disease Control Rate
- QOL
- Safety

Cisplatin + Vinorelbine

Cisplatin + Vinorelbine + Cetuximab

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FLEX TRIAL: EFFICACY

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Survival benefit seen across major subgroups: PS, smoking status, histology, sex, age, stage.

### Clinical Trials with Gefitinib in Advanced NSCLC

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### Irreversible EGFR Inhibitors

- Afatinib, approved 2013
- Dacomitinib
- Neratinib
Identification of the transforming 
**EML4-ALK** fusion gene in non-small-cell 
lung cancer

Manabu Soda\(^1\), Young Lim Choi\(^1\), Masaehiro Enomoto\(^2\), Shuji Takada\(^1\), Yoshihiro Yamashita\(^1\), Shunpei Ishikawa\(^3\), Shin-ichi Fujii\(^4\), Hideki Watanabe\(^5\), Kentaro Kurashina\(^1\), Hisashi Hakunaka\(^6\), Masashi Baso\(^7\), Steuf Ohno\(^8\), Yuichi Ishikawa\(^9\), Hironori Aburatani\(^10\), Toshio Niki\(^1\), Yasunori Sotora\(^1\), Yukihiko Sugiyama\(^1\) & Hiroyuki Mano\(^12\)

**EML4-ALK FUSION**

**EML4-ALK** frequency: 
~4% (64/1709) 
Primarily lung adenocarcinoma
ALK INHIBITOR: CRIZOTINIB

Chemotherapy vs. Targeted Agent For 1st Line Therapy
**IPASS STUDY**

Gefitinib vs. Carbo/Taxol in First Line Therapy in Asian Patients

**Randomization**
- Advanced NSCLC
  - No prior therapy
  - Never or light ex-smokers
  - N+ 1217

**Primary Endpoint**
- PFS

**Secondary:**
- ORR
- OS
- QOL
- Safety
- Disease-related symptoms

**Randomization**
- Carbo-Taxol IV
  - Every 3 weeks
- Iressa 250 mg/day

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**IPASS: Progression-free survival in EGFR-mutation + vs - patients**

**EGFR mutation-positive**
- Gefitinib (n=122)
- Carboplatin/Paclitaxel (n=129)
  - HR (95% CI) = 0.46 (0.36, 0.56)
  - p < 0.0001
- No. events gefitinib, 97 (73.8%)
- No. events CP, 111 (86.0%)

**EGFR mutation-negative**
- Gefitinib (n=9)
- Carboplatin/Paclitaxel (n=66)
  - HR (95% CI) = 2.85 (2.06, 3.88)
  - p < 0.0001
- No. events gefitinib, 88 (86.7%)
- No. events CP, 70 (82.4%)

**At risk**
- Gefitinib: 132
- Carboplatin/Paclitaxel: 132

**Treatment by subgroup interaction test, p < 0.0001**

**Incidence of EGFR mutation: 261/437 = 59.7%**

Mok et al 2008
TARGETED THERAPIES

- Driving mutations
- Immunotherapy

ONCOGENE ADDICTION

Some cancers may be driven by a single mutation, without which the cancer cells dies.
Incidence of Single Driver Mutations

Mutation found in 54% (280/516) of tumors completely tested (CI 50-59%)

TYROSINE KINASES AND TKI'S

Diagram showing how growth factor inhibitor stops the signal to divide the cell.
DOWNSTREAM PATHWAYS

CLINICAL RESPONSES AND RESISTANCE

Clinical Example of a Patient with Acquired Resistance to Erlotinib

Axial computed tomography studies of the chest in a patient with metastatic EGFR mutant lung adenocarcinoma before (day 0) and during erlotinib treatment (4 mo and 25 mo), demonstrating initial response and subsequent disease progression. Reprinted with permission, Paz et al 2005.23
MOLECULAR BASIS OF RESISTANCE

- KRAS mutation
- ROS1 fusion: sensitive to crizotinib
- RET fusion
- PI3K/mTOR pathway
- MET (MetMab)

TARGETS UNDER DEVELOPMENT
IMMUNOTHERAPY

Activated T-Cell
with some of the major secretory factors

IMMUNE CHECKPOINT INHIBITION

T-cell receptor recognizes tumour cell
Antibodies block inhibitory signal to PD-1
A separate therapy uses antibodies that bind PD-1L on the tumour cell
PD1 INHIBITOR IN NSCLC

Response of Metastatic NSCLC (BMS-936558, 10mg/kg)

- Initial progression in pulmonary lesions of a NSCLC patient with non-squamous histology was followed by regression
- Dx ’04. EGFR mutation +. Rx Gem/carbo, erlotinib, erlotinib + LBH589 (trial for T790 mutation), and lastly pemetrexed

PD1 AND CTLA4 CO-INHIBITION
**NCCN GUIDELINES**

**METASTATIC DISEASE**

- Established histologic subtype* with adequate tissue for molecular testing (consider reanalysis if appropriate)
- Smoking cessation counseling
- Integrate palliative care**

**EGFR MUTATION POSITIVE**

- Consider EGFR mutation and ALK testing especially in never smokers or small biopsy specimen, or selected histology**
- Sensitizing EGFR mutation and ALK negative or unknown**
- Sensitizing EGFR mutation and ALK positive

**SECOND-LINE THERAPY**

- Consider local therapy and continue erlotinib** or afatinib

**PROGRESSION**

- Symptomatic
- Asymptomatic

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*See Priorities of Care: Pancreatic, Colorectal, Gastroesophageal, Peritoneal, & Renal (NECI-94)
**See EGFR Mutations in Non-Small Cell Lung Cancer (NECI-101)

**See Priorities of Care: Pancreatic, Colorectal, Gastroesophageal, Peritoneal, & Renal (NECI-94)

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**See Priorities of Care: Pancreatic, Colorectal, Gastroesophageal, Peritoneal, & Renal (NECI-94)
SQUAMOUS HISTOLOGY

FIRST-LINE THERAPY

- Doublet chemotherapy\(^{1,2}\) (category 1)
  - Cisplatin/5-fluorouracil
- PS 0-1
- Progression
- Tumor response evaluation
- Response or stable disease
- I-4 (cicles test)
- Tumor response evaluation

SECOND-LINE THERAPY\(^{3,4}\)

- If not already given:
  - Docetaxel\(^{5}\)
  - Erbitux\(^{6}\)

THIRD-LINE THERAPY

THIRD-LINE THERAPY

- If not already given:
  - Docetaxel\(^{7,8,9}\)
  - Pembrolizumab\(^{10}\)
  - Erbitux\(^{6}\)

- PS 3-4
- Progression
- Tumor response evaluation

- Response or stable disease
- Continuation maintenance\(^{11,12}\)

- PS 3-4
- Progression
- Tumor response evaluation

- Response or stable disease
- Continuation maintenance\(^{11,12}\)

- PS 3-4
- Progression
- Tumor response evaluation

- Response or stable disease
- Continuation maintenance\(^{11,12}\)

Best supportive care
See NCCN Guidelines for Palliative Care

\(^{1}\) See Systemic Therapy for Advanced or Metastatic Disease (NCCN).
\(^{2}\) In areas of the world where pembrolizumab is available, it may be used in place of erbitux.

\(^{3}\) See Systemic Therapy for Advanced or Metastatic Disease (NCCN).

\(^{4}\) See Systemic Therapy for Advanced or Metastatic Disease (NCCN).
It's a new world for lung cancer therapy.  
The future is now.

THANK YOU!  
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