Lung Cancer Treatments 2017

Edward S. Kim, MD, FACP
Chair, Solid Tumor Oncology and Investigational Therapeutics
Donald S. Kim Distinguished Chair for Cancer Research
Medical Director, Clinical Trials Office
Levine Cancer Institute, Carolinas HealthCare System
Charlotte, North Carolina
Organizations

Carolinas HealthCare System
Levine Cancer Institute

LUNG CANCER INITIATIVE
of North Carolina
A NETWORK OF HOPE AND ACTION
Levine Cancer Institute
Carolinas HealthCare System

- 20 regional sites across NC, SC
- 15,000 new cancer cases
- 2\textsuperscript{nd} building construction (eta late 2018)
- Dedicated Phase I Unit (expansion to regional site)
- Bone Marrow Transplant Unit
- Biostatistics Department
- Biospecimen Repository
- Patient Navigation
- Oncology-centric Palliative Care
- Integrative Medicine
- Senior Oncology
- Weekly Molecular Tumor Board
- Mobile CT Lung screening unit

Derek Raghavan, MD
President, Levine Cancer Institute
NSCLC: A Major Public Health Problem

• Estimated 1.6 million deaths each year worldwide from lung cancer

• In 2015:
  • Estimated 221,200 new cases of lung cancer expected to be diagnosed in US
  • 158,000 Americans expected to die from lung cancer

• Leading cause of cancer-related deaths in US men and women
  • More deaths from lung cancer than breast, prostate, colon, liver, melanoma, and kidney cancers combined

• Need for better thought out, patient-driven studies

The Changing and *Challenging* Landscape of Oncology

- New drugs being approved
- Several new drugs for same indications
  - Bladder cancer (Immunotherapy)
  - Lung cancer (EGFR TKIs, Immunotherapy)
  - Head and neck cancer (Immunotherapy)
- Same drugs in disease type in different stage or line of therapy
  - Lung (EGFR TKIs, ALK TKIs, Immunotherapy)
- Biomarkers for some and not others (PD-L1, level of expression, Mutational Burden, MSI, MMR)
- Different biomarkers in same family (EGFR: Del19, L858R, T790M)
The Changing and Challenging Landscape of Oncology

- 71 Anti-Cancer Drugs approved by the FDA from 2002-2014 for Metastatic and/or Advanced and/or Refractory Solid Tumors for top ten pharma companies
  - Median PFS improvement was only 2.5 months
  - Median OS improvement was only 2.1 months
- Cancer treatment is ineffective in 75% of patient population

2Precision Medicine Coalition 4th Edition 2014
**Renaissance in the Field of Lung Cancer**

- Molecular biomarkers determine treatment
  - We are finally like breast cancer
- Immunotherapy is the new cornerstone
  - Melanoma was the front-runner but lung cancer has brought it into the mainstream
- Diagnostic comprehensive gene panels
- Plasma/Serum diagnostic tests
  - Are we getting closer to PSA, CA-125?
- New clinical trials in early stage disease
- Screening and detection
The Beginning: Lung Cancer Milestones

• 2000  Doublets all we got
• 2000  Docetaxel 2\textsuperscript{nd} line
• 2002  Gefitinib data reported
• 2004  Adjuvant cisplatin-based chemotherapy
• 2004  EGFR Mutations described
• 2005  Gefitinib wild-type data reported
• 2005  Pemetrexed, Erlotinib
• 2005  Bevacizumab approved E4599
• 2009-2013  EGFR mutations incorporated into clinical testing
• 2011  ALK inhibitor approved
• 2013  Afatinib approved
• 2015  T790M
• 2015  Nivolumab
• 2016  Pembrolizumab first line, Atezolizumab
• 2017  Brigatinib; BRAF v600E (Trametinib, Dabrafenib)
Lung Cancer Treatment 2000: ECOG 1594 Comparison of 4 First-Line Doublet Regimens in Advanced NSCLC

- Nonsquamous and squamous histologies
- No differences
- Efficacy not so encouraging
- Easy for providers to “take home a message”
- “Treat with any doublet you would like”

**E4599: Bevacizumab with Chemotherapy in NSCLC Overall Survival**

Median survival: 12.5 vs 10.2 months
HR = 0.77 (95% CI: .65, .93), \( P = 0.007 \)

1-yr Survival: 52% vs 44%
2-yr Survival: 22% vs 17%

Treatment group
- Carboplatin and paclitaxel
- Carboplatin and paclitaxel + bevacizumab

Sandler et al. *NEJM* 2006
**Erlotinib: NCIC BR.21 Trial**

2:1 randomization to the experimental arm

- **NSCLC** Failed 1 or 2 Prior Therapies (N=700)

- **Erlotinib 150 mg/d PO + best supportive care** vs **Placebo 150 mg/d PO + best supportive care**

- Survival + QOL

- 90% power to detect a 33% survival benefit, $\alpha=0.05$

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Not Targeted Therapy 2005: BR.21- Overall Survival

42.5% improvement in median survival

<table>
<thead>
<tr>
<th>Survival distribution function</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
</tr>
<tr>
<td>0.75</td>
</tr>
<tr>
<td>0.50</td>
</tr>
<tr>
<td>0.25</td>
</tr>
<tr>
<td>0.00</td>
</tr>
</tbody>
</table>

Survival time (months)

0 5 10 15 20 25 30

*HR and P-value adjusted for stratification factors at randomization plus HER1/EGFR status.

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• 2015  Nivolumab
• 2016  Pembrolizumab first line, Atezolizumab
• 2017  Brigatinib; BRAF v600E (Trametinib, Dabrafenib)
NSCLC Drug Approvals/Indications: 2015 - Present

- Alectinib
- Necitumumab
- Nivolumab
- Osimertinib
- Gefitinib
- Ramucirumab
- Atezolizumab
- Ceritinib
- Brigatinib

- Pembrolizumab
  - PD-L1 + (1st, 2nd line)
  - MSI-H or dMMR solid tumors
  - NSCLC (Carboplatin + Pemetrexed)
- Crizotinib (ROS1)
- Dabrafenib, Trametinib
The Changing Landscape of Lung Cancer: 2005

80 of 100 patients eligible for chemotherapy

Only 15-20% of tumors had a partial response
The Changing Landscape of Lung Cancer: 2017

Molecular subsets: EGFR Mutations
The Changing Landscape of Lung Cancer: 2017
Molecular subsets: ALK
The Changing Landscape of Lung Cancer: 2017

Molecular subsets: ROS1
The Changing Landscape of Lung Cancer: 2017

Molecular subsets: PD-L1
The Changing Landscape of Lung Cancer: 2017

Molecular subsets: BRAFv600E
The Changing Landscape of Lung Cancer: 2017

Molecular subsets: 50% of patients candidates for targeted therapy
Lung Cancer Histology

- Squamous Cell: 25-30%
- Adenocarcinoma: 40%
- SCLC: 13%
- NOS: 1-15%
- Large Cell: 10-15%
National Lung Screening Trial

August, 2002 – September, 2004
53,454 participants at Risk for Lung Cancer

Smoked >1 pack per day of cigarettes for 30 years
Age 55-74

Primary Endpoint:
Mortality Due to Lung Cancer

Low-dose spiral CT

Randomize

Year 1 Year 2 Year 3

Chest X-Ray

NLST Research Team, Radiology 2011 258(1)
Screening for Lung Cancer

National Lung Screening Trial Research Team *NEJM.* 368:1980, 2013
American College of Physicians, ASCO, USPSTF Recommendations

• The USPSTF recommends annual screening for lung cancer with low-dose computed tomography in adults ages 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. *Grade B Recommendation*

• The Centers for Medicare & Medicaid Services (CMS) issued a national coverage determination (NCD) for Medicare coverage of screening for lung cancer with low dose computed tomography (LDCT) if certain eligibility requirements are met, effective February 5, 2015.

  • [www.uspreventiveservicestaskforce.org/uspstf/uspslung.html](http://www.uspreventiveservicestaskforce.org/uspstf/uspslung.html)

  • [www.cms.gov/Medicare/Medicare-General/Information/MedicareApprovedFacilities/Lung-Cancer-Screening-Registries.html](http://www.cms.gov/Medicare/Medicare-General/Information/MedicareApprovedFacilities/Lung-Cancer-Screening-Registries.html)
Levine Cancer Institute Launches Nation's First Mobile Lung CT Unit to Improve Care for Region's Underserved and Rural Patients

Carolinas HealthCare System's Levine Cancer Institute, in partnership with Bristol-Myers Squibb Foundation, Samsung and Frazer, designed and created the nation's first mobile lung unit with a computed tomography scanner.

NEWS PROVIDED BY
Carolinas HealthCare System
Mar 22, 2017, 09:00 ET

CHARLOTTE, N.C., March 22, 2017 /PRNewswire/ -- Levine Cancer Institute, in partnership with the Bristol-Myers Squibb Foundation, Samsung and Frazer, designed and created the nation's first mobile lung computed tomography (CT) unit designed to bring diagnostic services to underserved and rural populations across the Carolinas. The team will work to expand lung cancer education and treatment interventions through collaboration with medical staff.
The Era of Precision Medicine

• Genomic sequencing has revolutionized our understanding of the cancer genome
• Deeper understanding of the cancer genome enabled significant advances in the development of targeted therapies
• Molecular profiling of tumor tissue biopsies has enabled targeted therapies to be directed to patients most likely to benefit
• Optimizing the utilization of targeted therapies requires effective serial monitoring of treatment response and emergence of resistance

BRAF V600E: Vemurafinib
ALK rearrangement: Crizotinib, Ceritinib, Alectinib
EGFR Del 19; L858R: TKIs e.g. Erlotinib, Gefitinib
EGFR T790M: Osimertinib
Lung Cancer Mutation Consortium: Incidence of Driver Mutations


PD-L1 and others now overlapping
Evaluation for Patients with Lung Cancer

- Confirmed biopsy (histology)
- Staging from head to toe
  - intrathoracic, extrathoracic, brain, bones
- Physical Assessment
- Biomarker Assessment
  - EGFR mutation
  - ALK
  - ROS 1
  - PD-L1

“Molecular assessment is an essential element for the evaluation of patients with lung cancer”
EGFR Mutations: Big Change in Lung Cancer Treatment

- EGFR is a cell surface protein that dimerizes to activate a tyrosine kinase
- Activating mutations in EGFR yield constitutive activation, resulting in downstream cell proliferation, angiogenesis, and potential metastasis

EGFR Mutations

• Found in 15-18% of adenocarcinoma patients and 50% of never-smoking adenocarcinoma patients

• Characteristics that enhance chances are low or never-smokers, adenocarcinomas, Asians

• Predominantly located in EGFR exons 18-21
  • 90% of EGFR mutations are either exon 19 deletions or exon 21 point mutations (L858R)

• All EGFR mutations are not the same
  • Del 19 and L858R are most associated with response
  • Exon 20 insertions and T790M are most associated with resistance
## Treatment-Naïve \( \text{EGFR}^{\text{MUT}} \) Patients

### EGFR TKIs vs Chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>N</th>
<th>Median PFS, months</th>
<th>Median OS, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maemondo</td>
<td>Gefitinib vs Carboplatin/Paclitaxel</td>
<td>230</td>
<td>10.8 vs 5.4</td>
<td>30.5 vs 23.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>((P &lt; 0.001))</td>
<td>((P = 0.31))</td>
</tr>
<tr>
<td>Mitsudomi</td>
<td>Gefitinib vs Cisplatin/Docetaxel</td>
<td>177</td>
<td>9.2 vs 6.3</td>
<td>36 vs 39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>((P &lt; 0.0001))</td>
<td>((\text{HR: 1.19}))</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>Erlotinib vs Carboplatin/Gemcitabine</td>
<td>165</td>
<td>13.1 vs 4.6</td>
<td>HR: 1.065</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>((P &lt; 0.0001))</td>
<td>((P = 0.65))</td>
</tr>
<tr>
<td>EURTAC</td>
<td>Erlotinib vs plat-based Chemotherapy</td>
<td>174</td>
<td>9.7 vs 5.2</td>
<td>19.3 vs 19.5</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>((P &lt; 0.0001))</td>
<td>((P = 0.87))</td>
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<tr>
<td>LUX-Lung 3</td>
<td>Afatinib vs CDDP/Pemetrexed</td>
<td>307*</td>
<td>13.6 vs 6.9</td>
<td>31.6 vs 28.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>((P &lt; 0.0001))</td>
<td>((P = 0.1090))</td>
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<tr>
<td>LUX-Lung 6</td>
<td>Afatinib vs Cisplatin/Gemcitabine</td>
<td>324*</td>
<td>11.0 vs 5.6</td>
<td>23.6 vs 23.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>((P &lt; 0.0001))</td>
<td>((P = 0.1756))</td>
</tr>
</tbody>
</table>

*Common mutations only.*

EGFR Mutations: TKI vs Chemotherapy

- NSCLC with sensitive EGFR mutations
- Stage IIIb/IV
- No prior chemo.
- PS 0-1
- Age 20-75 y.o

R Balanced: Institution
Sex Stage

Gefitinib n = 160

Primary endpoint
- PFS
2ndary endpoints
- OS
- Response
- Side-effects
- QOL

CBDCA + TXL n = 160

- The sample size was calculated to be 320 in total (alpha = 5%, power = 80%) to confirm the superiority of Arm A (hazard ratio = 0.69).
- An interim analysis to investigate PFS was planned 4 months after 200 pts were entered.

Maemondo M NEJM 362:2380, 2010
EGFR Mutations: TKI vs Chemotherapy

Hazard Ratio 0.30; P<0.001
Median 10.8 months for gefitinib
Median 5.4 months for chemo

Maemondo M *NEJM* 362:2380, 2010
First-Line EGFR TKI Demonstrates Efficacy in EGFR Mutation-Positive NSCLC

Patient With Del19 EGFR Mutation

December 2000

December 2002
Afatinib OS in Del 19 Subgroup: 
Type of mutation matters

LUX-Lung 3

<table>
<thead>
<tr>
<th></th>
<th>Afatinib</th>
<th>Pem/Cis</th>
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<tbody>
<tr>
<td>Median, months</td>
<td>33.3</td>
<td>21.1</td>
</tr>
<tr>
<td>HR (95%CI), p-value</td>
<td>0.54 (0.36–0.79), $p=0.0015$</td>
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</table>

LUX-Lung 6

<table>
<thead>
<tr>
<th></th>
<th>Afatinib</th>
<th>Gem/Cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, months</td>
<td>31.4</td>
<td>18.4</td>
</tr>
<tr>
<td>HR (95%CI), p-value</td>
<td>0.64 (0.44–0.94), $p=0.0229$</td>
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</table>

Afatinib OS in L858R Subgroup

**L858R/LUX-Lung 3**

<table>
<thead>
<tr>
<th></th>
<th>Afatinib (n=91)</th>
<th>Cis/Pem (n=47)</th>
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</thead>
<tbody>
<tr>
<td>Median, months</td>
<td>27.6</td>
<td>40.3</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.30 (0.80–2.11)</td>
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<tr>
<td><em>P</em> value</td>
<td></td>
<td><em>P=0.2919</em></td>
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</table>

**L858R/LUX-Lung 6**

<table>
<thead>
<tr>
<th></th>
<th>Afatinib (n=92)</th>
<th>Cis/Gem (n=46)</th>
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</thead>
<tbody>
<tr>
<td>Median, months</td>
<td>19.6</td>
<td>24.3</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.22 (0.81–1.83)</td>
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</tr>
<tr>
<td><em>P</em> value</td>
<td></td>
<td><em>P=0.3432</em></td>
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</table>

No. of patients:

<table>
<thead>
<tr>
<th></th>
<th>Afatinib</th>
<th>Cis/Pem</th>
<th>Cis/Gem</th>
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</thead>
<tbody>
<tr>
<td>Afatinib</td>
<td>91</td>
<td>47</td>
<td>9292</td>
</tr>
<tr>
<td>Cis/Pem</td>
<td>89</td>
<td>43</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>83</td>
<td>42</td>
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<td>0</td>
<td>1</td>
<td>0</td>
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</tbody>
</table>

Mechanisms of Resistance to EGFR TKI

![Pie chart showing the frequency of observed drug resistance mechanisms.]

Fig. 1 The frequency of observed drug resistance mechanisms.

**Novel Mechanisms**

- **T790M** Mutation – 49%
- **MET** amplification – 5%
- **PI3KCA** Mutation - 5%
- EMT Changes – 5%
- SCLC Features – 14%
- Unknown – 30%

T790M Blocks Erlotinib Binding and Leads to Resistance to First-Generation Inhibitors

## Third Generation EGFR TKIs

<table>
<thead>
<tr>
<th>“3rd” Generation</th>
<th>N</th>
<th>RR* T790M-</th>
<th>RR T790M+</th>
<th>PFS</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rociletinib (CO-1686)</td>
<td>256</td>
<td>37%</td>
<td>53%</td>
<td>~ 8.0 mo</td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Osimertinib (AZD9291)</td>
<td>253</td>
<td>21%</td>
<td>61%</td>
<td>~ 8.2 mo</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>HM61713 (800 mg)</td>
<td>62</td>
<td>12% (300 mg)</td>
<td>55%</td>
<td>NR</td>
<td>Dyspnea/rash</td>
</tr>
<tr>
<td>EGF816X*</td>
<td>53</td>
<td>–</td>
<td>60%</td>
<td>NR</td>
<td>Rash</td>
</tr>
<tr>
<td>ASP8273*</td>
<td>47</td>
<td>~ 33%</td>
<td>61%</td>
<td>NR</td>
<td>Hyponatremia/diarrhea</td>
</tr>
</tbody>
</table>

*Multiple other agents earlier in development

* T790M– subgroups are very small.

RR, response rate; PFS, progression-free survival.

Osimertinib (AZD9291) in Patients With Acquired Resistance to EGFR TKI and *EGFR* T790M

Response Rate = 61%

Osimertinib vs. Pemetrexed Platinum in T790M Positive EGFR mutant NSCLC

- Non-Squamous NSCLC
- EGFR+ NSCLC with Progression on EGFR-TKI
- Central confirmation of T790M variant
- ECOG 0 or 1

RANDOMIZE

1. Pemetrexed 500 mg/m2 Cis/Carbo q 3 Wks
2. Osimertinib 80 mg Day

Mok et al. *NEJM* 2017; 376:629
Osimertinib vs. Pemetrexed Platinum in T790M Positive EGFR mutant NSCLC

Mok et al. *NEJM* 2017; 376:629
CNS response to osimertinib in patients with T790M-positive advanced NSCLC: data from a randomized Phase III trial (AURA3)

Tony Mok¹, Myung-Ju Ahn², Ji-Youn Han³, Jin-Hyoung Kang⁴, Nobuyuki Katakami⁵, Hye Ryun Kim⁶, Rachel Hodge⁷, Dana Ghiorghiù⁷, Mireille Cantarini⁸*, Yi-Long Wu⁹, Vassiliki A Papadimitrakopoulou¹⁰, Marina Chiara Garassino¹¹

¹State Key Laboratory in Oncology in South China, Sir YK Pao Centre for Cancer, Department of Clinical Oncology, Chinese University of Hong Kong, Hong Kong; ²Samsung Medical Centre, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; ³Center for Lung Cancer, National Cancer Center, Goyang, Republic of Korea; ⁴Catholic University Seoul St Mary’s Hospital, Seoul, Republic of Korea; ⁵Institute of Biomedical Research and Innovation, Kobe, Japan; ⁶Department of Internal Medicine, Division of Medical Oncology, Yonsei University College of Medicine, Seoul, Republic of Korea; ⁷AstraZeneca, Cambridge, UK; ⁸AstraZeneca, Macclesfield, UK; ⁹Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China; ¹⁰Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; ¹¹Thoracic Oncology Unit, Medical Oncology Department Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

*Former employee of AstraZeneca

Presented By Maria Garrassino at 2017 ASCO Annual Meeting
Tumor response in CNS – evaluable for response set

**Osimertinib 80 mg**

![Chart showing percentage change from baseline in target lesions for Osimertinib 80 mg.]

- **Best response:** Complete response, Partial response, Stable disease, Progressive disease, Not evaluable
- **Median baseline CNS target lesions size:** 16.3 mm (range 10–60 mm)
- **Median best percentage change from baseline in CNS target lesions size:** -43% (range -100% to +20%)

**Chemotherapy**

![Chart showing percentage change from baseline in target lesions for chemotherapy.]

- **Best response:** Complete response, Partial response, Stable disease, Progressive disease, Not evaluable
- **Median baseline CNS target lesions size:** 16.2 mm (range 11–56 mm)
- **Median best percentage change from baseline in CNS target lesions size:** -16% (range -100% to +20%)

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Population: CNS evaluable for response set; patients with ≥1 measurable CNS metastases on baseline brain scan by BICR

Data cutoff: April 15, 2016. 11 patient was not evaluable due to no evaluable follow-up assessments. 

*Best % change in CNS target lesion for 3 patients with stable disease could not be imputed as the patients did not meet any of the three imputation criteria, 2 patients were not evaluable due to death (n=1) and study withdrawal due to progressive disease (n=1)."
FLAURA: Phase III, Double-Blind, Randomized Study of TAGRISSO as 1L Therapy\(^{1,2}\)

**Patients**
- Biopsy-confirmed, \(^a\) EGFRm NSCLC
- Treatment-naïve for advanced NSCLC

**Key inclusion criteria:**
- Age ≥18 years
- Locally advanced or metastatic NSCLC
- No prior therapy for advanced disease
- Patients must have EGFR -TKI-sensitizing mutation (ex19del or L858R)
- Mandatory tumor sample of sufficient quantity to allow central analysis of EGFR mutation status
- CNS efficacy analysis is planned

**TAGRISSO** (80 mg orally once daily)

**Erlotinib** 150 mg once daily\(^b\)
- OR
**Gefitinib** 250 mg once daily\(^b\)

**Primary endpoint:**
- PFS

**Secondary endpoints:**
- ORR
- PFS in T790M(+/−) patients
- OS
- PROs

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Tagrisso significantly improves progression-free survival in the Phase III FLAURA trial for lung cancer

Published 27 July 2017

Tagrisso met the primary endpoint, demonstrating a statistically significant and clinically-meaningful progression-free survival benefit in 1st-line EGFRm non-small cell lung cancer compared to current standard-of-care treatment.
Acquired EGFR C797S mutation mediates resistance to AZD9291 in non–small cell lung cancer harboring EGFR T790M

Kenneth S Thress1, Cloud P Paweletz2,3, Enriqueta Felip4,5, Byoung Chul Cho2, Danid Stetson1, Brian Dougherty1, Zhongwu Lai1, Aleksandra Markovets1, Ana Vivancos4, Yanan Kuang2, Dalia Erkan2, Sarah E Matthews2, Mireille Cantarini7, J Carl Barrett1, Pasi A Jänne2,3 & Geoffrey R Oxnard2

Here we studied cell-free plasma DNA (cfDNA) collected from subjects with advanced lung cancer whose tumors had developed resistance to the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) AZD9291. We first performed next-generation sequencing of cfDNA from seven subjects and detected an acquired EGFR C797S mutation in study, AZD9291 induced durable responses in EGFR-mutant lung cancer patients with acquired resistance to other EGFR TKIs, with preliminary progression-free survival estimates of ~10 months in T790M+ patients6.

To identify potential mechanisms of resistance to AZD9291 before the availability of resistance biopsy specimens, we studied cfDNA collected during the phase 1 AURA study. We first performed next-generation sequencing (NGS) on cfDNA from seven subjects whose disease progressed and from whom paired pretreatment and post-disease progression plasma specimens were available. cfDNA was isolated from plasma and all exons of a 20-gene panel were PCR-amplified and analyzed using an Illumina HiSeq.

One subject (Subject 1) was a 33-year-old female whose cancer had progressed on multiple prior lines of chemotherapies and EGFR TKIs; resistance biopsy was T790M+. After 6 weeks of AZD9291 treatment, scans demonstrated a partial response (Supplementary Fig. 1); however, she developed systemic progression after 23 weeks of AZD9291. NGS of plasma collected from this subject at time of systemic progression revealed a new C797S mutation in exon 20 of EGFR in addition to the exon 19 deletion and T790M mutations that were
Summary: Acquired Resistance to EGFR TKIs

- First-line EGFR TKIs should be continued at least until initiation of next line of therapy … and beyond progressive disease in “smoldering progression”

- Local therapy should be considered in patients with isolated metastases or oligometastases … with continuation of the original EGFR TKI

- The T790M mutation is responsible for ~60% of all acquired resistance to frontline EGFR TKIs

- Osimertinib FDA approved after EGFR-TKI
  - Recent data positive in 1st line treatment in EGFR mutations
Identification of the transforming
**EML4–ALK** fusion gene in non-small-cell lung cancer

Manabu Soda\(^1,2\), Young Lim Choi\(^1\), Munehiro Enomoto\(^1,2\), Shuji Takada\(^1\), Yoshihiro Yamashita\(^1\), Shunpei Ishikawa\(^5\), Shin-ichiro Fujiwara\(^1\), Hideki Watanabe\(^1\), Kentaro Kurashina\(^1\), Hisashi Hatanaka\(^1\), Masashi Bando\(^2\), Shoji Ohno\(^2\), Yuichi Ishikawa\(^6\), Hiroyuki Aburatani\(^8,7\), Toshiro Niki\(^3\), Yasunori Sohara\(^4\), Yukihiro Sugiyama\(^2\) & Hiroyuki Mano\(^1,7\)

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

\(\text{Soda et al. Nature 2007}\)
43yo Male Never Smoker with Stage IV NSCLC (+) for EML4-ALK

Pre-Treatment

After 1 cycle PF-02341066
Tumor Responses to Crizotinib for Patients with ALK-positive NSCLC

Response Rate Crizotinib vs. Chemotherapy

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

- **Crizotinib (n=173) vs. Chemotherapy (n=174)**
- **Crizotinib (n=172) vs. Pemetrexed (n=99) vs. Docetaxel (n=72)**

*RECIST v1.1; ITT population; as-treated population*
Ceritinib in Crizotinib-Naïve, ALK+ NSCLC

*Patients with measurable disease at baseline and at least 1 post baseline assessment without unknown response for target lesion or overall response

Felip et al., ESMO 2014
There Are Multiple Secondary Resistance Mutations


\(^{a}\)F1174V.
About One-Third of Resistant Tumors Harbor ALK Resistance Mutations or Amplification


*Approximate frequencies.
# ALK Inhibitor Therapy in ALK-Rearranged NSCLC

<table>
<thead>
<tr>
<th>Drug/Study</th>
<th>N</th>
<th>Dose</th>
<th>Outcomes</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| • Alectinib in crizotinib-resistant NSCLC (AF-002JG)  
• Phase I/II dose-escalation | 47  | Phase I: 300-900 mg bid  
Phase II: 600 mg bid (recommended) | • ORR 59.5%  
• Median PFS not yet reached  
• Activity against brain mets in 2/4 pts | • Fatigue  
• Myalgia  
• Peripheral edema |
| • Alectinib crizotinib naïve NSCLC (AF-001JP)  
• Phase II | 46  | 300 mg bid | • ORR 93.5%  
• 2 yr PFS 76%  
• 2 yr OS 79% | • Increased AST  
• Dysgeusia  
• Increased ALT |
| • Brigatinib in advanced malignancies  
• Post-hoc analysis | 137 | 90 mg/day,  
90 mg/day → 180 mg/day, or 180 mg/day  
Of 137, 79 pts ALK+ and 71 prior crizotinib tx | • ORR  
– 79% 90 mg  
– 81% 90 → 180 mg  
– 68% 180 mg  
• Median PFS  
– 12.9 mo 90 mg  
– 11.1 mo 180 mg  
– Not reached in 90 → 180 | • Nausea  
• Diarrhea  
• Fatigue |

bid, twice daily; ORR, overall response rate; PFS, progression-free survival; pts, patients; mets, metastases; tx, treatment; mo, months.
Alectinib vs crizotinib in treatment-naïve advanced ALK+ NSCLC: primary results of the global phase III ALEX study (LBA9008)

Alice Shaw¹, Solange Peters², Tony Mok³, Shirish M. Gadgeel⁴, Jin Seok Ahn⁵, Sai-Hong Ignatius Ou⁶, Maurice Perol⁷, Rafał Dziadziuszko⁸, Dong-Wan Kim⁹, Rafael Rosell¹⁰, Ali Zeaiter¹¹, Ting Liu¹¹, Sophie Golding¹¹, Bogdana Balas¹¹, Johannes Noe¹¹, Peter N. Morcos¹², and D. Ross Camidge¹³ on behalf of the ALEX investigators

1. Massachusetts General Hospital, Boston, MA, USA; 2. Lausanne University Hospital, Switzerland; 3. Chinese University of Hong Kong, Hong Kong; 4. Karmanos Cancer Institute/Wayne State University, Detroit, MI, USA; 5. Sungkyunkwan University School of Medicine, Seoul, South Korea; 6. Chao Family Comprehensive Cancer Center, University of California, Irvine School of Medicine, Orange, CA, USA; 7. Department of Medical Oncology, Léon Bérard Cancer Center, Lyon, France; 8. Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk, Poland; 9. Seoul National University Hospital, Seoul, South Korea; 10. Catalan Institute of Oncology, Barcelona, Spain; 11. F. Hoffmann-La Roche Ltd, Basel, Switzerland; 12. Roche Innovation Center, New York, USA; 13. University of Colorado, Denver, CO, USA
Primary endpoint: PFS, investigator-assessed

- **Progression-free Survival (%)**
  - **Crizotinib** (N=151)
  - **Alectinib** (N=152)

- **Patients with events, n (%)**
  - Crizotinib: 102 (68)
  - Alectinib: 62 (41)

- **Median PFS, months**
  - Crizotinib: NR
  - Alectinib: 11.1 (95% CI: 9.1–13.1)

- **HR**
  - Crizotinib: 0.47 (95% CI: 0.34–0.65)
  - Alectinib: NR

- **P-value (log-rank test)**
  - Crizotinib: P<0.0001

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**No. at Risk**

- **Crizotinib**: 151, 132, 104, 84, 65, 46, 35, 16, 5
- **Alectinib**: 152, 135, 113, 109, 97, 81, 67, 35, 15, 3

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*Presented By Alice Shaw at 2017 ASCO Annual Meeting*
PFS by baseline CNS metastases status*

Patients with CNS metastases at baseline

- Alectinib (N=64)
  - Progression-free Survival: 7.4 months (6.6–9.6)
- Crizotinib (N=58)

Patients without CNS metastases at baseline

- Alectinib (N=88)
  - Progression-free Survival: 14.8 months (10.8–20.3)
- Crizotinib (N=93)

HR 0.40
(95% CI 0.25–0.64)

HR 0.51
(95% CI 0.33–0.80)

*Investigator assessment
Secondary endpoint: OS

Patients with events, n (%)
Crizotinib (N=151) 40 (27) 35 (23)
Alectinib (N=152)

Median OS, months (95% CI)
Crizotinib NR (NR) NR (NR)
Alectinib

HR
Crizotinib 0.76
Alectinib (95% CI) (0.48–1.20)
P-value (log-rank test) P=0.24

No. at Risk
Crizotinib 151 141 127 115 103 95 73 33 13 1
Alectinib 152 142 131 127 119 107 87 51 24 5
Leptomeningeal carcinomatosis responded to alectinib

Pre-alectinib

6 weeks on alectinib

Pre-alectinib CSF cytology

Ou, S et al., WCLC 2013
ROS1+ NSCLC treated with Crizotinib

A Best Response

- Advanced NSCLC
- ROS1 Rearrangement
- PS 0-2
- Measureable Disease

Shaw et al. NEJM 2014 371:1963
BRAF V600E: Dabrafenib and Trametinib

36 of 57 (63%) had a Complete or Partial Response
Median Progression-Free Survival 9.7 Months

June 2017 FDA granted approval to dabrafenib and trametinib for Pts with metastatic NSCLC with BRAF V600E mutation

Planchard et al. Lancet Oncol 2016 Jul;17(7):984
The efficacy of larotrectinib (LOXO-101), a selective tropomyosin receptor kinase (TRK) inhibitor, in adult and pediatric TRK fusion cancers

Hyman DM, 1 Laetsch TW, 2 Kummar S, 3 DuBois SG, 4 Farago AF, 5 Pappo AS, 6 Demetri GD, 7 El-Deiry WS, 8 Lassen UN, 9 Dowlati A, 10 Brose MS, 11 Boni V, 12 Turpin B, 13 Nagasubramanian R, 14 Cruickshank S, 15 Cox MC, 15 Ku NC, 15 Hawkins DS, 16 Hong DS, 17 Drilon AE 1

1Memorial Sloan Kettering Cancer Center, New York, NY; 2University of Texas Southwestern, Dallas, TX; 3Stanford University School of Medicine, Palo Alto, CA; 4Dana-Farber Cancer Institute/Boston Children’s Cancer and Blood Disorders Center, Boston, MA; 5Massachusetts General Hospital, Boston, MA; 6St. Jude Children's Research Hospital, Memphis, TN; 7Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA; 8Fox Chase Cancer Center, Philadelphia, PA; 9Rigshospitalet, Copenhagen, Denmark; 10UH Cleveland Medical Center, Cleveland, OH; 11Department of Otorhinolaryngology: Head and Neck Surgery, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; 12START Madrid CIOCC, Hospital HM Universitario Sanchinarro, Madrid, Spain; 13Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 14Nemour’s Children's Hospital, Orlando, FL; 15Loxo Oncology, Inc., San Francisco, CA; 16Seattle Children’s Hospital, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA; 17The University of Texas MD Anderson Cancer Center, Houston, TX
Efficacy regardless of tumor type

*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; #Pathologic CR

Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.
SQSTM1-NTRK1 lung cancer patient

Baseline

Cycle 4

45F NSCLC & paraneoplastic hypertrophic osteoarthropathy

Prior therapy: platinum/pemetrexed

Larotrectinib ongoing in month 8, resolution of paraneoplastic symptoms

Presented at: ASCO Annual Meeting '17 | #ASCO17
Hyman, LBA2501

Courtesy of S. Kummar, Stanford University

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Carolinas Healthcare System
Entrectinib (RXDX-101)

**Most potent, orally available pan-TRK inhibitor in clinical development**

<table>
<thead>
<tr>
<th>Target</th>
<th>TrkA</th>
<th>TrkB</th>
<th>TrkC</th>
<th>ROS1</th>
<th>ALK</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC50* (nM)</td>
<td>1.7</td>
<td>0.1</td>
<td>0.1</td>
<td>0.2</td>
<td>1.6</td>
</tr>
</tbody>
</table>

- Most potent pan-Trk-inhibitor in clinical development; active against most known Trk-resistant mutants
- 30x more potent against ROS1 than crizotinib; high potency against ALK
- Designed to cross blood brain barrier (BBB) and to address primary brain tumors and secondary CNS metastases
- Demonstrates inhibition of its RTK targets and downstream effectors in the PLCγ, MAPK and PI3K/AKT pathways
- Entrectinib-mediated inhibition of oncogenic fusion proteins results in rapid tumor response in preclinical models and in selected patient populations

* Biochemical kinase assay
46M with \textit{SQSTM1-NTRK1} NSCLC

Ongoing response at 15.1 months

Baseline

Day 26: - 47\% response

Day 317: - 79\% response

15-20 CNS mets

CR

CR

Images courtesy of A. Shaw, MD, PhD and A. Farago, MD, PhD (MGH)
STARTRK-2
Entrectinib Global Phase 2 Basket Study

Studies of Tumor Alterations Responsive to Targeting Receptor Kinases

STARTRK-2: Open-Label, Multicenter, Global Basket Study of Entrectinib

Patients with Solid Tumors

Molecular Testing [NGS] for NTRK1/2/3, ROS1, or ALK Gene Rearrangements

Basket Assignments by Gene Rearrangement

- NTRK1/2/3 (Trki-naïve)
- ROS1 (ROS1i-naïve)
- ALK (ALKi-naïve)

Possible Chemotherapy per MD
Modernizing Eligibility Criteria for Molecularly Driven Trials


ABSTRACT

As more clinical trials of molecularly targeted agents evolve, the number of eligibility criteria seems to be increasing. The importance and utility of eligibility criteria must be considered in the context of the fundamental goal of a clinical trial: to understand the risks and benefits of a treatment in the intended-use patient population. Although eligibility criteria are necessary to define the population under study and conduct trials safely, excessive requirements may severely restrict the population available for study, and often, this population is not reflective of the general population for which the drug would be prescribed. The American Society of Clinical Oncology Cancer Research Committee, which comprises academic faculty, industry representatives, and patient advocates, evaluated this issue. Evaluation results were mixed. Most physicians agreed that excessive eligibility criteria slow study enrollment rates and prolong the duration of enrollment; however, this hypothesis was difficult to validate with the data examined. We propose the organization of a public workshop, with input from regulatory bodies and key stakeholders, with the goal of developing an algorithmic approach to deconstructing eligibility criteria for individual study protocols, which may help guide future...
<table>
<thead>
<tr>
<th>Category</th>
<th>Question for Consideration</th>
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<tbody>
<tr>
<td><strong>Relationship to scientific objective</strong></td>
<td>Does the eligibility criterion support the scientific hypothesis?</td>
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<td>Could the scientific goal be achieved without including this particular eligibility criterion?</td>
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<tr>
<td><strong>Generalizability</strong></td>
<td>Will the results of the study be applicable to a patient not enrolled on the study?</td>
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<td>Are the eligibility criteria too restrictive for practical clinical use?</td>
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<tr>
<td><strong>Patient safety and drug toxicity</strong></td>
<td>Is patient safety being adequately protected and does this eligibility criterion contribute to this?</td>
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<td></td>
<td>Are potential drug toxicities and mechanism of action being accounted for and does limiting or including this criterion support or hinder the scientific goal?</td>
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<tr>
<td><strong>Continual review on a regular basis</strong></td>
<td>At what point should eligibility criteria be re-justified during protocol development and during enrollment?</td>
</tr>
<tr>
<td></td>
<td>Should a trial close due to poor accrual or be allowed to reduce/relax eligibility criteria as a first step?</td>
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Importance to Cancer Moonshot

Strategic Goal 3—Accelerate Bringing New Therapies to Patients: Plans for Year 2 & Beyond

1. Modernize eligibility criteria for clinical trials

“In coordination with the American Society of Clinical Oncology, Friends of Cancer Research, and other stakeholders, FDA will evaluate clinical trial entrance criteria that may unnecessarily restrict clinical trial access—such as brain metastases, HIV status, organ dysfunction, and age restrictions (e.g., pediatrics)—to better assess when restrictions are warranted for specific clinical trials to protect patient safety. … Moving forward, FDA will work with sponsors to improve the use of science-based, clinically relevant eligibility criteria to allow greater patient access to clinical trials while maintaining patient safety.”
ASCO-Friends Project Overview

• Prioritized assessment of four eligibility criteria
  – Brain Metastases; Minimum Age; HIV/AIDS; & Organ Dysfunction, Prior Malignancies, and Comorbidities

• Formed multi-stakeholder working groups
  – Patient advocates
  – Clinical investigators
  – FDA medical reviewers
  – Drug and biotech manufacturers
  – NCI
  – Biostatisticians
  – Pharmacologists
ASCOr-Friends Project Leadership

**ASCOr**
Edward S. Kim, MD, FACP
Richard L. Schilsky, MD, FACP, FASCO
Suanna Bruinooge, MPH
Caroline Schenkel, MSc

**FDA**
Richard Pazdur, MD
Gwynn Ison, MD
Julia Beaver, MD
Tatiana Prowell, MD
Raji Sridhara, PhD

**Working Group Chairs**
Stuart Lichtman, MD (MSKCC)
Nancy Lin, MD (Harvard & RANO Group)
Thomas Uldrick, MD (NCI)
Lia Gore, MD (Univ. of CO)

**Friends of Cancer Research**
Ellen Sigal, PhD
Jeff Allen, PhD
Samantha Roberts, PhD
Marina Kozak, PhD

**Planning Committee**
Eric Rubin, MD (Merck)
Nancy Roach (Fight Colorectal Cancer)
Elizabeth Garret-Mayer (Medical Univ. of SC)
ASCO-Friends Project Overview

• 6 manuscripts submitted for publication to JCO
  – Accepted July 2017
• Implementation of current recommendations
  – Templates
• Next eligibility criteria in discussion
The Targeted Agent and Profiling Utilization Registry (TAPUR) Study

- Pragmatic phase 2 study with FDA-approved, targeted agents
- Incorporates general and drug-specific eligibility criteria
- Prior Malignancy:
  - No exclusion or time limit for patients with prior malignancies
- HIV+
  - General Criteria – included except where clinician decides to exclude
  - Drug-specific – pembrolizumab and olaparib exclude
- Performance Status (PS):
  - General eligibility: 0-2 per general eligibility
  - Drug-specific: pembrolizumab or regorafenib must have PS 0-1
TAPUR Study Eligibility Criteria (cont’d)

• Brain Metastases – eligible, so long as the patient is:
  – Not progressive and not on treatment
  – Has not experienced a seizure or had a clinically significant change in neurological status within the 3 months
  – Off steroids for at least one month prior to enrollment.

• Patients must have acceptable organ function as defined below:
  – AST (SGOT) and ALT(SGPT) < \(2.5 \times \text{institutional ULN}\) (or < \(5 \times \text{ULN}\) in patients with known hepatic metastases)
  – Serum creatinine ≤ \(1.5 \times \text{ULN}\) or calculated or measured creatinine clearance ≥ \(50 \text{ mL/min/1.73 m}^2\)

• Pediatric Population:
  – Current TAPUR study eligibility criteria requires ≥ 18 years
  – Plans to lower minimum age to 12 years where pediatric dose defined
Levine Cancer Institute first site to register 100th patient for TAPUR

LCI-Cleveland (0)
LCI-Rutherford (0)
LCI-Lincolnton (1)
LCI-South Tryon (7)
LCI-Pineville (2)
LCI-AnMed (0)
LCI-Rock Hill (0)
LCI-Carolina Lakes (0)

LCI-Main (34)
LCI-University (4)
LCI-Mallard Creek (1)
LCI-NorthEast (9)
LCI-Stanly (2)
LCI-Southpark (5)
LCI-Matthews (0)
LCI-Union (5)
LCI-Ballantyne (6)

LCI-RSFS (pending)

LCI-Whiteville (0)
The Fight Against Lung Cancer
“Why we fight the BATTLE!”

- 52 yr woman
- Stage 4 lung cancer
- Brain mets
- April 2002
Thank you for your attention!