ALCHEMIST

Adjuvant Lung Cancer Enrichment Marker Identification And Sequencing Trials
What is ALCHEMIST?

ALCHEMIST is 3 integrated trials testing targeted therapy in early stage lung cancer:

- **A151216**: Screening trial for EGFR and ALK
- **A081105**: Treatment trial for the EGFR+ patients
- **E4512**: Treatment trial for the ALK+ patients
ALCHEMIST Objectives

- Central genotyping of lung cancers for EGFR mutations and ALK rearrangements to assist in accrual to A081105 and E4512
- To obtain clinically annotated tumor tissue and DNA from blood, as well as epi and follow-up data, for genomic analyses at the NCI CCG.
ALCHEMIST Background

- ALCHEMIST will evaluate molecularly targeted therapy in early stage NSCLC with non-squamous histologies
- Molecularly targeted therapy has improved outcomes within these histologies in advanced NSCLC
  - Erlotinib (target: EGFR activating mutation)
  - Crizotinib (target: EML4-ALK)
- Patients treated with TKIs eventually develop resistance
25 Years of Therapeutic Research in Lung Cancer

- 5-year survival for all non-small cell lung cancer patients has increased by 4% over 25 years
- Adjuvant therapy improves overall survival
- Novel therapeutics are desperately needed

Courtesy of Dr. Ravi Salgia
Non-Small Cell Lung Cancer

Incidence of major histologic types*

- 30% Squamous cell carcinoma
- 40% Adenocarcinoma
- 15% Large-cell carcinoma
- 16% Small-cell carcinoma

* Numbers do not sum to 100% because of differences in diagnostic criteria.


Courtesy of Dr. Ravi Salgia
Non-Small Cell Lung Cancer

Stages at presentation


Courtesy of Dr. Ravi Salgia
# NSCLC: Treatment and Outcome by Stage

<table>
<thead>
<tr>
<th>Pathologic Stage</th>
<th>Treatment</th>
<th>5-Year Survival, %*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Surgery/Chemo</td>
<td>60-70</td>
</tr>
<tr>
<td>II</td>
<td>Surgery/Chemo</td>
<td>30-50</td>
</tr>
<tr>
<td>IIIA</td>
<td>Surgery/Multimodality Regimen</td>
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<td>Chemotherapy/Radiation</td>
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<tr>
<td>IV</td>
<td>Chemotherapy</td>
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</table>

*Overall 5-year survival is 14%.


Courtesy of Dr. Ravi Salgia
Biomarker analyses from a phase III, randomized, open-label, first-line study of gefitinib vs carboplatin/paclitaxel in clinically selected patients with advanced non-small cell lung cancer in Asia (IPASS)

Masahiro Fukuoka,¹ Yi-Long Wu,² Sumitra Thongprasert,³ Chih-Hsin Yang,⁴ Da-Tong Chu,⁵ Nagahiro Saijo,⁶ Claire Watkins,⁷ Emma Duffield,⁷ Alison Armour,⁷ Tony Mok⁸

¹Kinki University School of Medicine, Osaka, Japan; ²Guangdong General Hospital, Guangzhou, China; ³Maharaj Nakorn Chiang Mai Hospital, Chiang Mai, Thailand; ⁴National Taiwan University Hospital, Taipei, Taiwan; ⁵Chinese Academy of Medical Sciences, Beijing, China; ⁶Chinese Cancer Centre Hospital East, Chiba, Japan; ⁷AstraZeneca, Macclesfield, United Kingdom; ⁸The Chinese University of Hong Kong, Hong Kong, China
Study design

Conducted in China, Japan, Thailand, Taiwan, Indonesia, Malaysia, Philippines, Hong Kong and Singapore

Randomization period: March 2006 – October 2007

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

1:1 randomization

Gefitinib (250 mg / day)

Carboplatin (AUC 5 or 6) / paclitaxel (200 mg / m²) 3 weekly

End points

Primary
- Progression-free survival (non-inferiority)

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

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

*Never smokers, <100 cigarettes in lifetime; ex-light smokers, stopped ≥15 years ago and smoked ≤10 pack years;
*limited to a maximum of 6 cycles. Carboplatin/paclitaxel was offered to gefitinib patients upon progression
WHO, World Health Organization; PS, performance status; AUC, area under the curve; EGFR, epidermal growth factor receptor

Mok et al 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
- No. events gefitinib, 97 (73.5%)
- No. events CIP, 111 (86.0%)
- Median PFS G, 9.5 months
- Median PFS CIP, 6.3 months

**EGFR mutation negative**
- **Gefitinib** (n=91)
  - Carboplatin/paclitaxel (n=85)
  - HR (95% CI) = 2.86 (2.06, 3.98) p<0.0001
- No. events gefitinib, 88 (96.7%)
- No. events CIP, 70 (82.4%)
- Median PFS G, 1.5 months
- Median PFS CIP, 5.5 months

**Patients at risk**
- CIP: 129, 103, 37, 7, 2, 1, 0
- Gefitinib: 91, 21, 4, 2, 1, 0, 0
- CIP: 85, 58, 14, 1, 0, 0, 0

**Treatment by EGFR mutation status interaction test, p<0.0001**

Cox analysis with covariates; HR <1 implies a lower risk of progression on gefitinib; ITT population

Mok et al 2008
Summary

- EGFR mutation status
  - In mutation positive patients, PFS was significantly longer with gefitinib than with carboplatin/paclitaxel
  - In EGFR mutation negative patients, PFS was significantly shorter with gefitinib than with carboplatin/paclitaxel

- EGFR-gene-copy number
  - A possibly related trend in PFS was observed. Post hoc explorations suggest this effect was driven by the overlap of high EGFR-gene-copy number with a positive EGFR mutation status

- EGFR protein expression
  - This was found to be less of a differentiator between the two treatment arms in terms of PFS

- ORR results were consistent with PFS results
A Randomized Double Blind Phase 3 Trial of Adjuvant Erlotinib vs. Placebo Following Complete Tumor Resection with or without Adjuvant Chemotherapy in Patients with Stage IB–IIIA EGFR Positive (IHC/FISH) Non–Small Cell Lung Cancer: RADIANT Results

for the RADIANT Investigators
**RADIANT Trial Design**

- **Tumor samples**
  - EGFR IHC+ and/or EGFR FISH+

- **Stage IB-III A NSCLC**
  - Complete surgical resection

- **No adjuvant chemotherapy**
  - Up to 4 cycles of platinum-based doublet
  - ≤90 d
  - ≤180 d

- **Randomization stratified by:**
  - histology, stage, prior adjuvant chemo, **EGFR FISH** status, smoking status, country
  - (N=973)

- **(n=623)** Erlotinib 150mg/day
  - 2:1
  - 2-yr treatment period

- **(n=350)** Placebo

- **Radiology assessment:** every 3 months on treatment and yearly during long-term follow up

- **Primary endpoint:** DFS
- **Secondary endpoints:** Overall survival (OS); DFS and OS in patients with del19/L858R (EGFR M+)
Disease-free Survival KM Plot

- **Placebo** (156 events)
  - Median: 48.2 months

- **Erlotinib** (254 events)
  - Median: 50.5 months

**Log-rank test:** $p=0.3235$

**HR:** 0.90 (95% CI: 0.741, 1.104)

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**Number at Risk**

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Presented By Karen Kelly at 2014 ASCO Annual Meeting
Disease-free Survival: **EGFR M+**

![Graph showing disease-free survival probability over time for Erlotinib and Placebo groups.](image)

- **Placebo**
  - 32 events
  - Median: 28.5 months

- **Erlotinib**
  - 39 events
  - Median: 46.4 months

**Log-rank test:** p=0.0391 (not statistically significant due to hierarchical testing)

**HR:** 0.61 (95% CI: 0.384, 0.981)

**Number at Risk**

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Presented by: Dr. Karen Kelly

Presented At: 2014 ASCO Annual Meeting
2007: **EML4-ALK** Rearrangements described as transforming event in NSCLC

Identification of the transforming **EML4-ALK** fusion gene in non-small-cell lung cancer

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


*Courtesy of Dr. Ravi Salgia*
ALK Pathway

Inamura K et al. J Thorac Oncol 2008;3:13–17
Figure based on: Chiarle R et al. Nat Rev Cancer 2008;8(1):11–23

*Subcellular localization of the ALK fusion gene, while likely to occur in the cytoplasm, is not confirmed.\(^1,2\)
Tumor Responses to Crizotinib | Patients w/ALK-positive NSCLC

Maximum change in tumor size (%)

- Progressive disease
- Stable disease
- Confirmed partial response
- Confirmed complete response


Courtesy of Dr. Ravi Salgia
Treatment with crizotinib resulted in impressive clinical activity in patients with ALK-positive advanced NSCLC:
- ORR: 57%
- DCR at 8 weeks: 87%
- PFS probability at 6 months: 72%
- 77% of patients with ALK-positive NSCLC remain on crizotinib treatment

Crizotinib was well tolerated:
The most frequent adverse events were mild and moderate gastrointestinal events and mild visual disturbances.
Crizotinib — ALK inhibition

- Phase 3 trial of crizotinib as 2nd-line therapy in patients who had disease progression while receiving a platinum-based regimen
- Randomized pts to crizotinib vs chemotherapy with pemetrexed or docetaxel
- Primary endpoint PFS

Crizotinib — ALK inhibition

**A** Overall Change from Baseline in Symptoms and Global QOL

- Reduction in Symptom Score
- Mean Change from Baseline
- P<0.001 for all comparisons
- Crizotinib vs Chemotherapy

**B** Time to Deterioration with Respect to a Composite Lung-Cancer-Symptom End Point

- Hazard ratio, 0.54 (95% CI, 0.40–0.71)
- P<0.001

ALCHEMIST Support

- Agents are being supplied:
  - A081105: Erlotinib by Astellas
  - E4512: Crizotinib by Pfizer
- Testing for ALK and EGFR is funded by the NCI and will be performed by Response Genetics
- Advanced genomic analysis will be done by the NCI Center for Cancer Genomics
Eligibility Criteria

- Resectable NSCLC, Stage IB (≥4cm), II or IIIA
- PS 0-1, Age ≥8 years
- No patients with neoadjuvant therapy
- Patients with local genotyping are eligible, regardless of local results
- Registration timeframes: If no adjuvant therapy within 75 days after surgery, if adjuvant chemo within 165 days after surgery, if chemo and RT 225 days after surgery
**ALCHEMIST | Molecular Tests Used**

- EGFR gene mutation
- Sequencing a certain part of the gene (the pieces defined as exons 18-21)
- ALK gene rearrangement
- The FDA approved Vysis ALK break-apart probe.
- Response Genetics, Inc. (Los Angeles) commercial CLIA-certified laboratory
- Results within 14 business days
- The costs of these molecular tests for ALCHEMIST are being covered by the NCI
<table>
<thead>
<tr>
<th>Trial Category</th>
<th>ALCHEMIST Screening Trial A151216</th>
<th>ALCHEMIST ALK Treatment Trial E4512 (± crizotinib)</th>
<th>ALCHEMIST EGFR Treatment Trial A081105 (± erlotinib)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Registry/Intervention with biopsy at recurrence</td>
<td>ALK rearrangement</td>
<td>EGFR mutation</td>
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<tr>
<td>Prevalence of Target</td>
<td>~5%</td>
<td>~10%</td>
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<tr>
<td>Total Sample Size</td>
<td>6000 – 8000</td>
<td>378 (5% ineligible)</td>
<td>430 (5% ineligible)</td>
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<td>Primary Endpoint</td>
<td>Correlative endpoints &amp; epidemiology</td>
<td>Overall survival</td>
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<tr>
<td>Power</td>
<td>80%</td>
<td>85%</td>
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<tr>
<td>One-sided $\alpha$</td>
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<tr>
<td>Hazard Ratio</td>
<td>0.67</td>
<td>0.67</td>
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ALCHEMIST FAQs

Q1: Is ALCHEMIST one trial or three separate trials?
The ALCHEMIST study is made up of three separate protocols: ALCHEMIST-screening (A151216), ALCHEMIST-EGFR (A081105), and ALCHEMIST-ALK (E4512).

Q2: Do I need to have all 3 trials open before I accrue patients?
Yes, all the trials (A151216, A081105 and E4512) need to be IRB approved before patients are accrued to any of them. Sites will not be able to use the OPEN system to register patients to ALCHEMIST-screening until all 3 trials have been IRB approved.
Q3: Can I just register patients to ALCHEMIST-screening (A151216) and not consider the treatment trials, or is the intent to register patients to the screening study in order to then put the eligible patients on the treatment trials?

The intent of ALCHEMIST-screening is to screen patients for the treatment trials. Therefore, all patients registered to the screening study and found to be eligible for the treatment trials should be registered to the treatment trials.
Q4: I have a patient where we did local testing and the patient is negative for both ALK and EGFR. Is this patient eligible?

Yes, patients are now eligible to be enrolled regardless of any local genotyping results as this was in Update #1 of ALCHEMIST-screening, issued on 3/15/15. These patients will still have tumor submitted for analysis to Response Genetics. If positive for EGFR or ALK on the screening study, they then would be potentially eligible for the treatment trials.
ALCHEMIST FAQs

Q5: Is there a timeframe I need to follow to register post-op patients to this trial?
Yes, the timeline for ALCHEMIST-screening is intended to allow sufficient time for genotyping so that patients will remain potentially eligible for the treatment trials. Patients that do not receive adjuvant therapy need to be registered the screening study up to 75 days following surgery, those patients that are receiving adjuvant therapy are to be registered up to 165 days after surgery, and those patients receiving both adjuvant chemotherapy and radiation therapy are to be registered up to 225 days following surgery.
ALCHEMIST FAQs

**Q6**: Can patients be receiving adjuvant therapy while being registered to ALCHEMIST?

Yes, patients can be receiving adjuvant therapy while being registered to ALCHEMIST-screening.
ALCHEMIST FAQs

Q7: I don’t understand the pre-registration and registration steps?

The pre-registration step was developed to allow flexibility so that patients can be consented to ALCHEMIST-screening either prior to surgery or after surgery. All patients must pre-register first. Those that have already undergone surgery will then immediately proceed to registration to the study. However, pre-operative patients will first need to complete surgery to allow a final eligibility review prior to registering to the screening study.
ALCHEMIST FAQs

Q8: When do I send in the tissue to Response Genetics? When do I collect and send in the blood?  
Tissue is sent to Response Genetics for genotyping after the patient is registered. Blood can be collected at any point following pre-registration up until 30 days after registration. Once collected the blood is to be shipped to the NCI BCR within 1 week of collection.

Q9: If my patient is locally EGFR or ALK positive, do I need to send in a block?  
Yes, patients who are locally positive for EGFR or ALK still need to send in tissue and blood. The tissue is used for confirmation of the genotype, and the tissue and blood are both used for further genomic studies.
ALCHEMIST FAQs

Q10: If my patient is locally EGFR or ALK positive, do I need to wait for results on ALCHEMIST-screening before enrolling the patient onto one of the treatment trials?

No, you do not need to wait for the results. Patients who are locally positive for EGFR or ALK can register to one of the treatment trials immediately after registering for ALCHEMIST-screening, without waiting for genotyping results from Response Genetics.
ALCHEMIST FAQs

Q11: Are there shipping kits available for the block and blood collection?
No, there are no shipping kits available for those submissions. The instructions about how to ship the materials are in the protocol.

Q12: I have a patient with adenosquamous carcinoma. Is she eligible?
Yes, she is eligible. The eligibility for ALCHEMIST-screening has been updated with Update #1 to specifically allow patients with adenosquamous carcinoma, as this is a subtype of lung adenocarcinoma.
Q13: I have a patient with a second primary lung cancer. Would they be eligible?

No, a second primary lung cancer is considered a concurrent malignancy therefore such a patient would not be eligible for ALCHEMIST.