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

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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.

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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

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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

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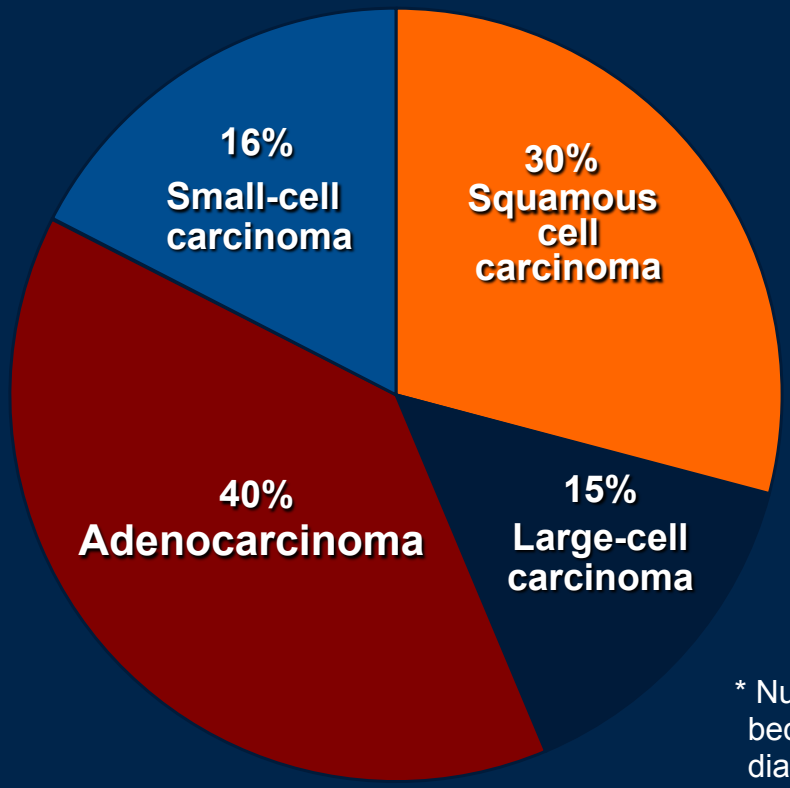
Non-Small Cell Lung Cancer

Incidence of major histologic types*



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

Ginsberg RJ, et al. *Cancer: Principles and Practices of Oncology*. 5th ed. 1997;858-911.

Courtesy of Dr. Ravi Salgia

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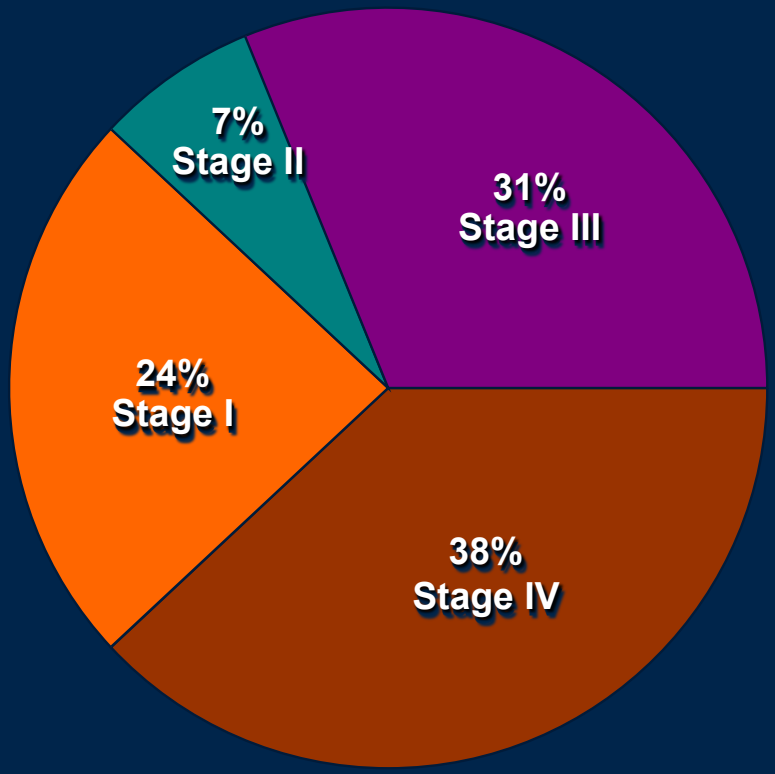
Non-Small Cell Lung Cancer

Stages at presentation



Fry WA, et al. *Cancer.* 1996;77:1949-1995.

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NSCLC: Treatment and Outcome by Stage

Pathologic Stage	Treatment	5-Year Survival, %*
I	Surgery/Chemo	60-70
II	Surgery/Chemo	30-50
IIIA	Surgery/ Multimodality Regimen	10-30
IIIB	Chemotherapy/ Radiation	5
IV	Chemotherapy	<1

*Overall 5-year survival is 14%.

1. Mountain CF. *Semin Surg Oncol*. 2000;18:106-115.
2. National Cancer Institute. *SEER Cancer Statistics Review 1973-1999*.

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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 Mok[8]

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

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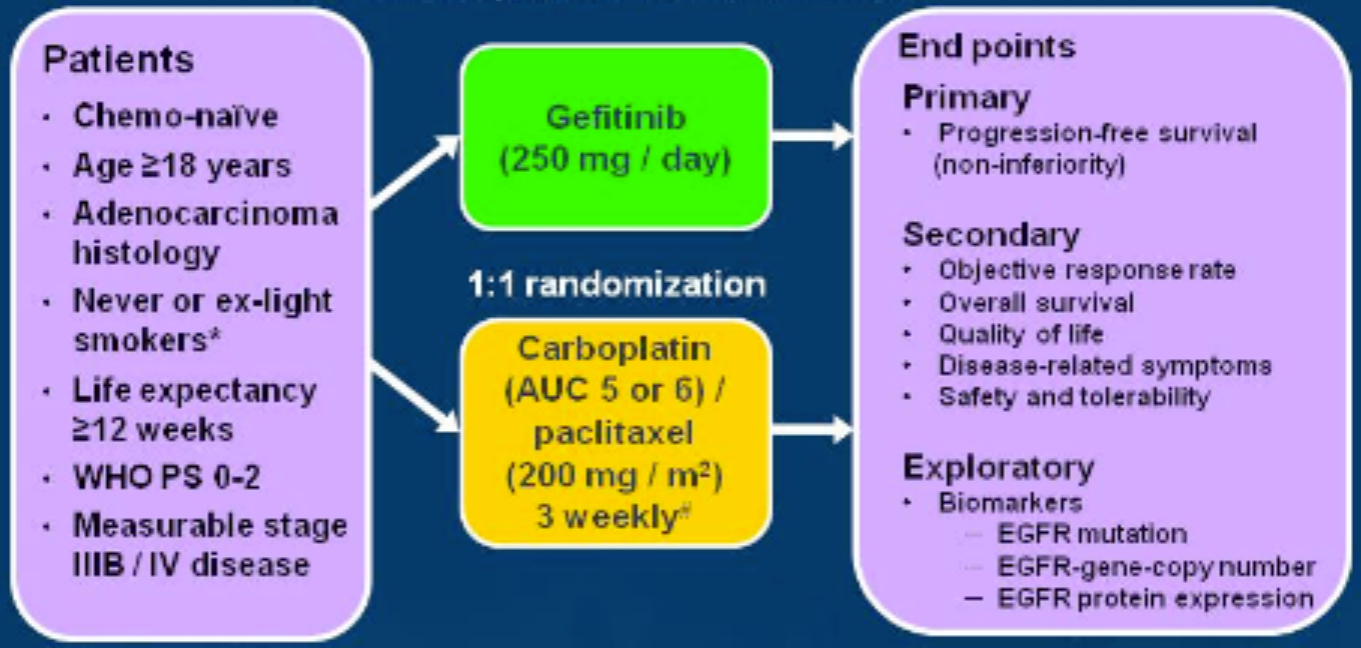
Study design

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

Randomization period: March 2006 – October 2007



*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

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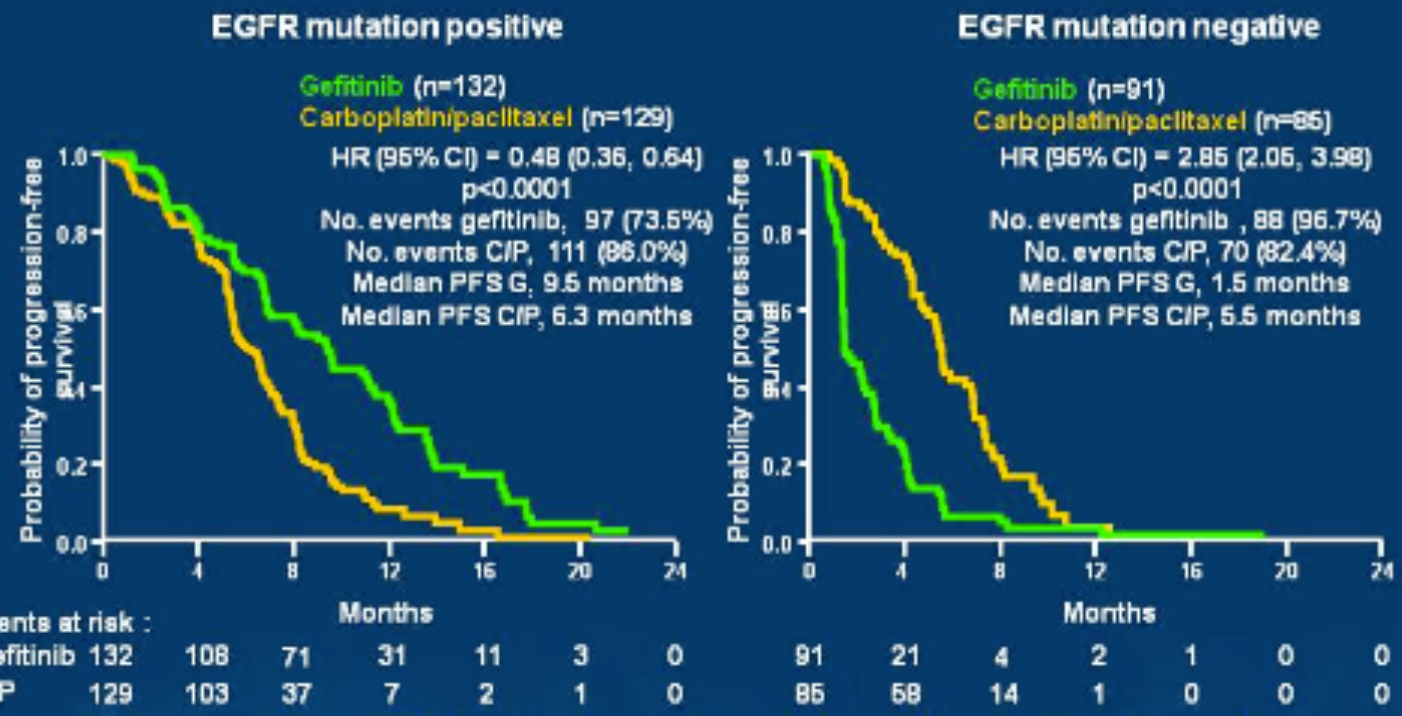
Mok et al 2008

Progression-free survival in EGFR mutation positive and negative patients



Patients at risk :							
Gefitinib	132	108	71	31	11	3	0
C/P	129	103	37	7	2	1	0

91	21	4	2	1	0	0
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

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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

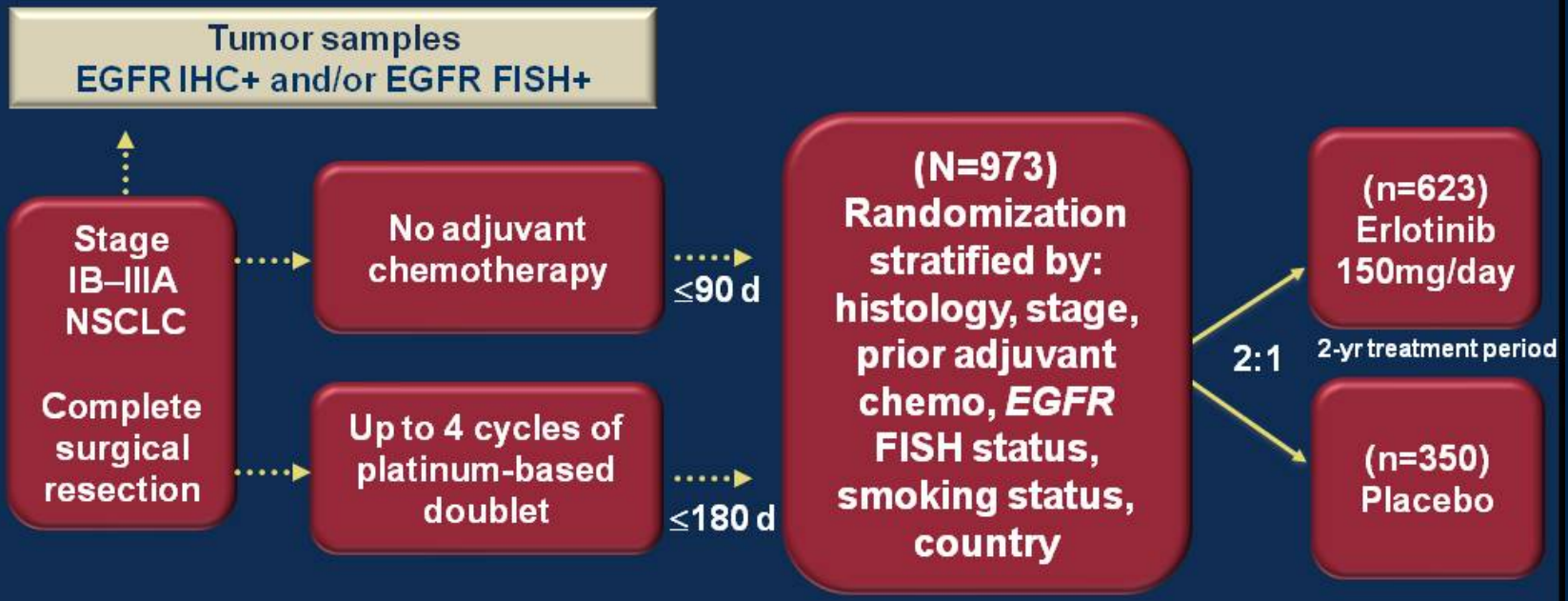
A Randomized Double Blind Phase 3 Trial of Adjuvant Erlotinib vs. Placebo Following Complete Tumor Resection with or without Adjuvant Chemotherapy in Patients with Stage IB–IIIA EGFR Positive (IHC/FISH) Non–Small Cell Lung Cancer: RADIANT Results

Kelly K, Altorki NK, Eberhardt WEE, O'Brien MER, Spigel DR, Crinò L, Tsai CM, Kim JH, Cho EK, Szczesna A, Burghuber OC, Hoffman PC, Keshavjee SH, Orlov SV, Serwatowski P, Wang J, Foley MA, Horan JD, Park J, Shepherd FA

for the RADIANT Investigators

Presented By Karen Kelly at 2014 ASCO Annual Meeting

RADIANT Trial Design

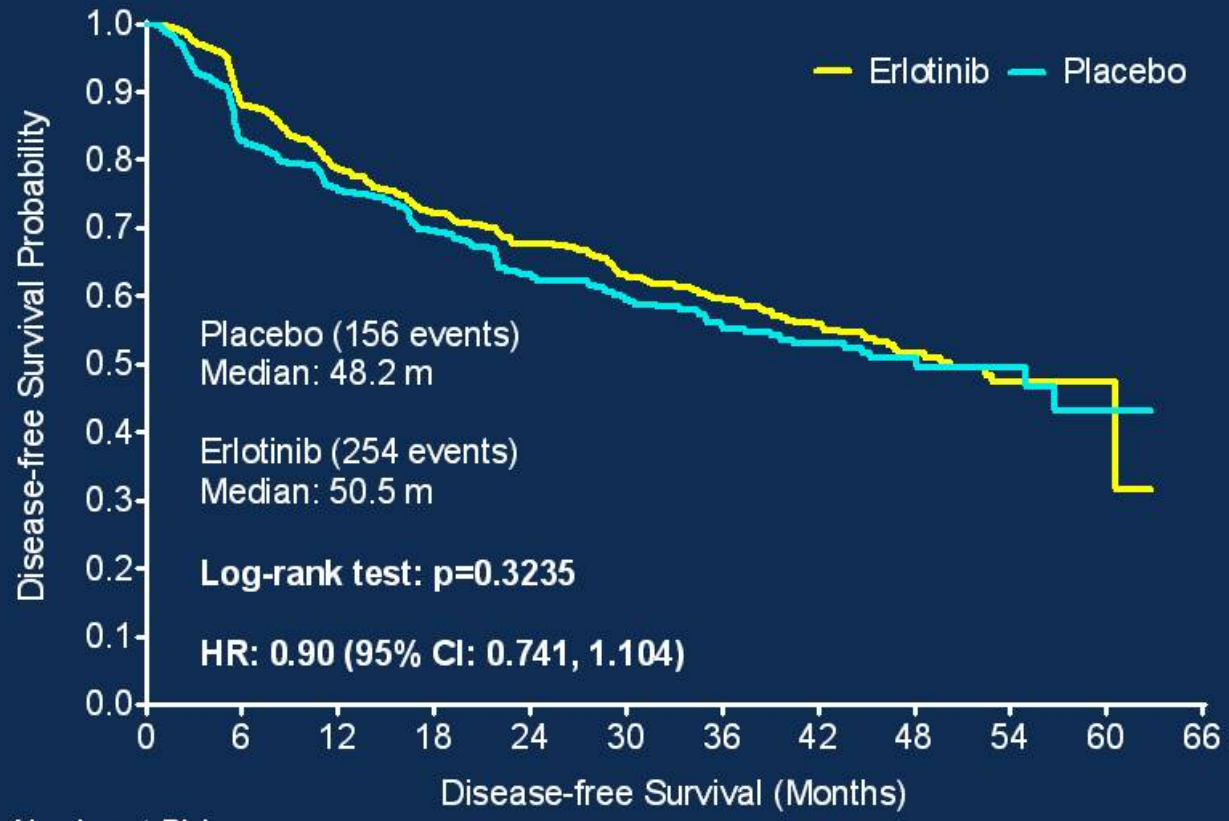


- **Radiology assessment:** every 3 months on treatment and yearly during long-term follow up

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

Presented By Karen Kelly at 2014 ASCO Annual Meeting

Disease-free Survival KM Plot



Number at Risk

Placebo	350	280	255	231	198	174	124	83	43	22	1	0
Erlotinib	623	514	451	411	368	320	223	154	82	40	8	0

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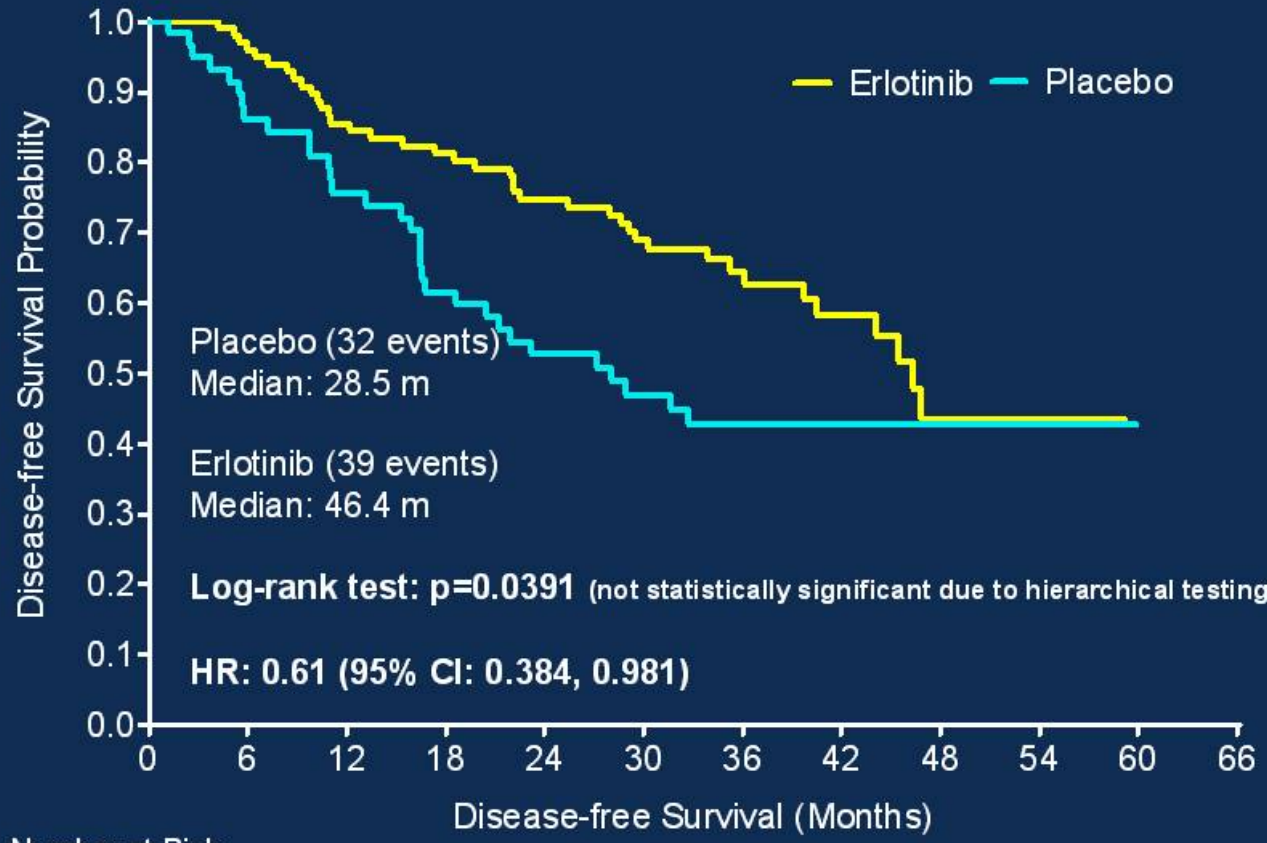
Disease-free Survival: *EGFR* M+



Number at Risk

Placebo	59	49	43	35	30	23	15	12	10	5	0	0
Erlotinib	102	94	80	76	68	56	35	22	10	3	0	0

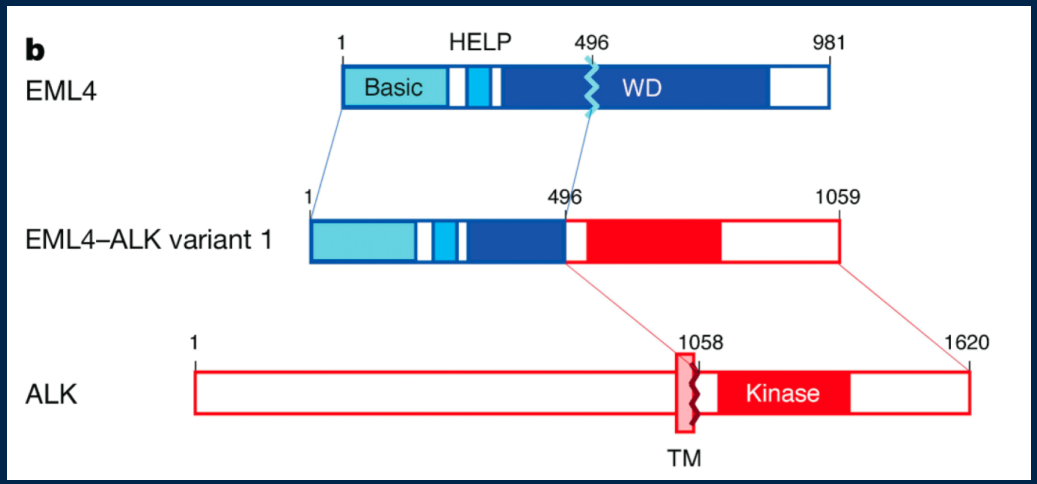
PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Karen Kelly 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[1,2], 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[5,7], Toshiro Niki[3], Yasunori Sohara[4], Yukihiko Sugiyama[2] & Hiroyuki Mano[1,7]



Soda et al., Nature 448: 561-566, 2007

Courtesy of Dr. Ravi Salgia

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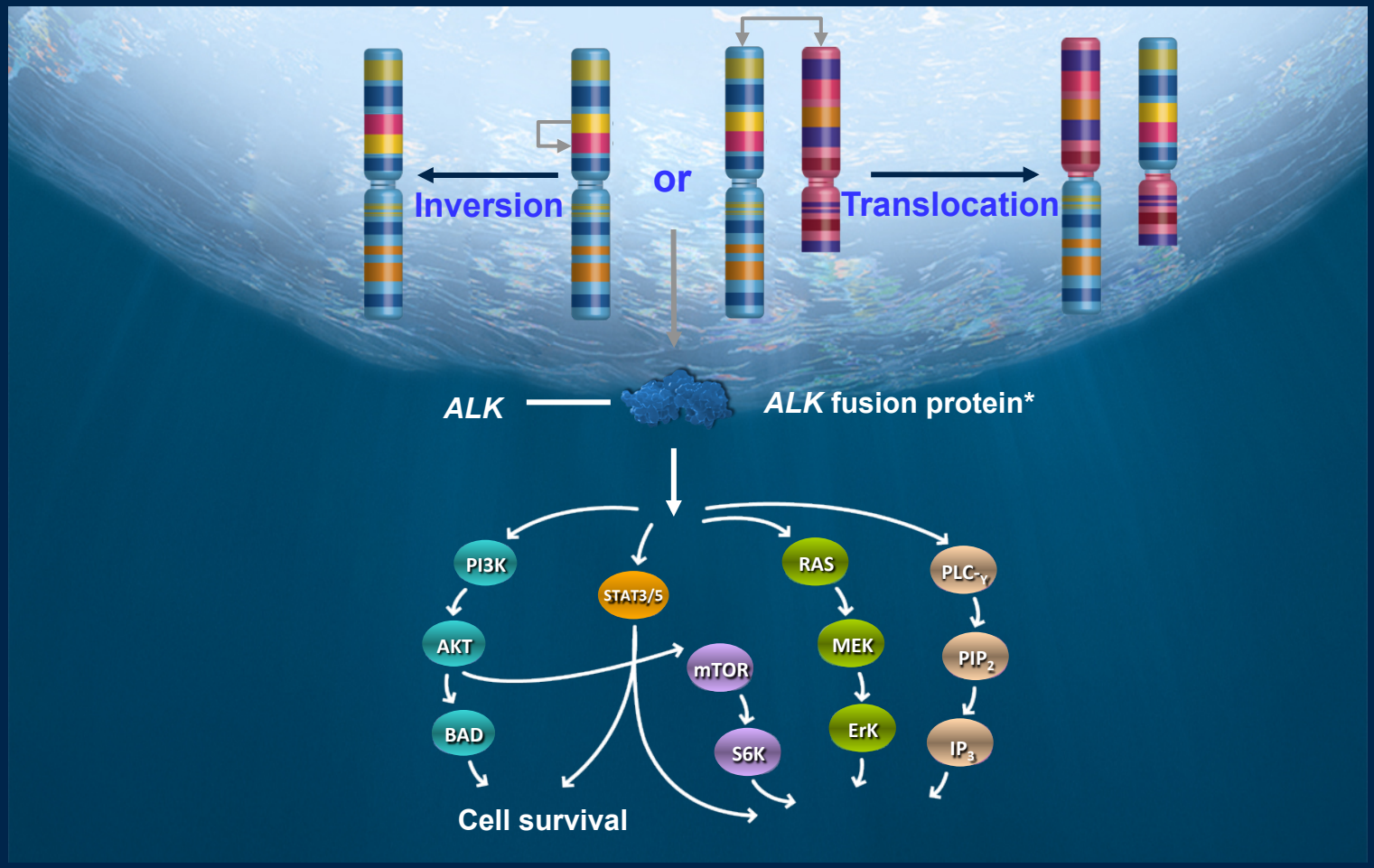
ALK Pathway



*Subcellular localization of the ALK fusion gene, while likely to occur in the cytoplasm, is not confirmed.[1,2]

1. Inamura K et al. J Thorac Oncol 2008;3:13–17
2. Soda M et al. Proc Natl Acad Sci U S A 2008;105:19893–19897
Figure based on: Chiarle R et al. Nat Rev Cancer 2008;8(1):11–23
Mossé YP et al. Clin Cancer Res 2009;15(18):5609–5614; and Data on file. Pfizer Inc.

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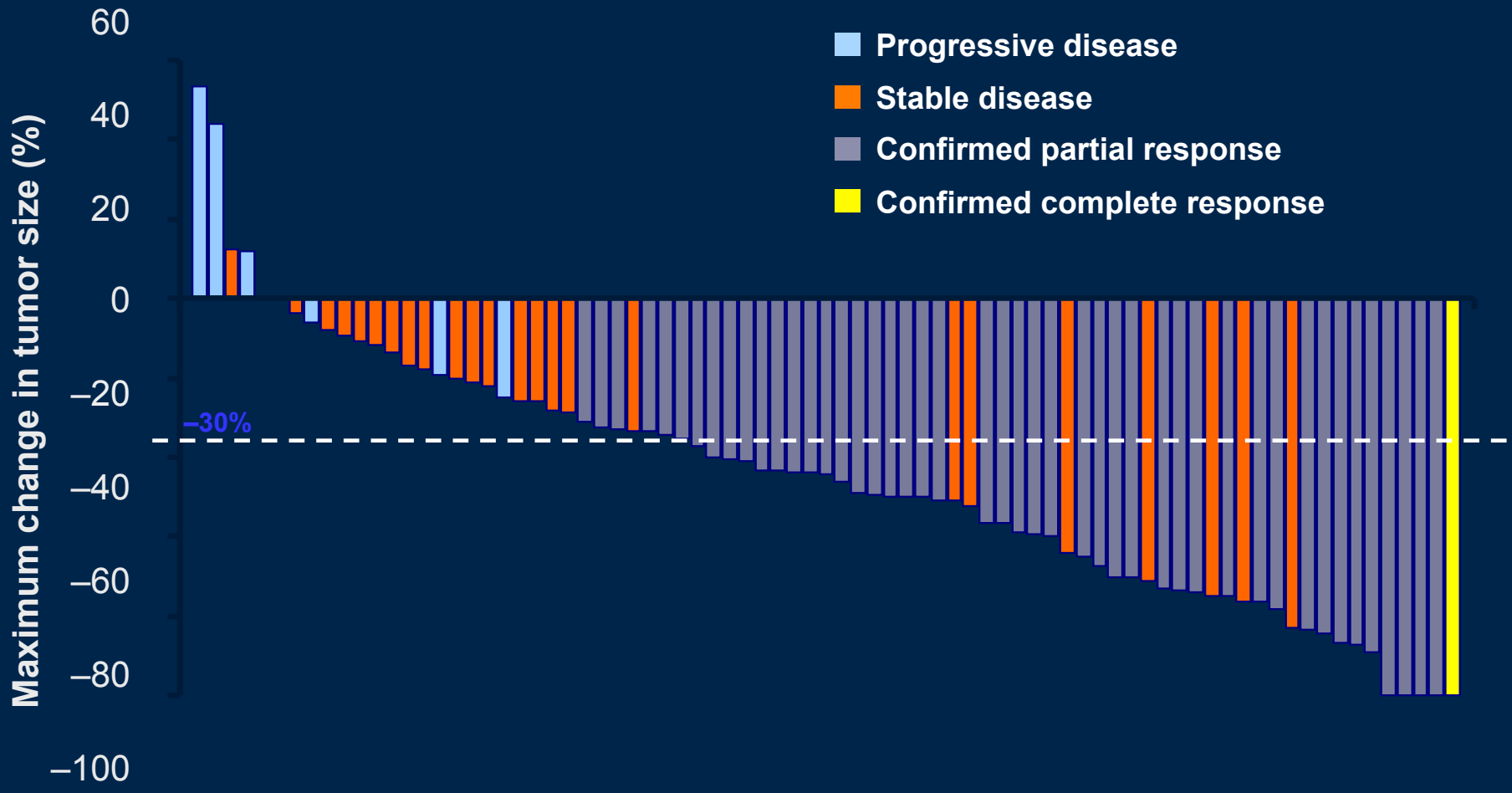
Tumor Responses to Crizotinib | Patients w/ALK-positive NSCLC



Kwak, Salgia, et al, ASCO & NEJM, 2010

Courtesy of Dr. Ravi Salgia

Crizotinib — ALK inhibition

- 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

Courtesy of Dr. Ravi Salgia

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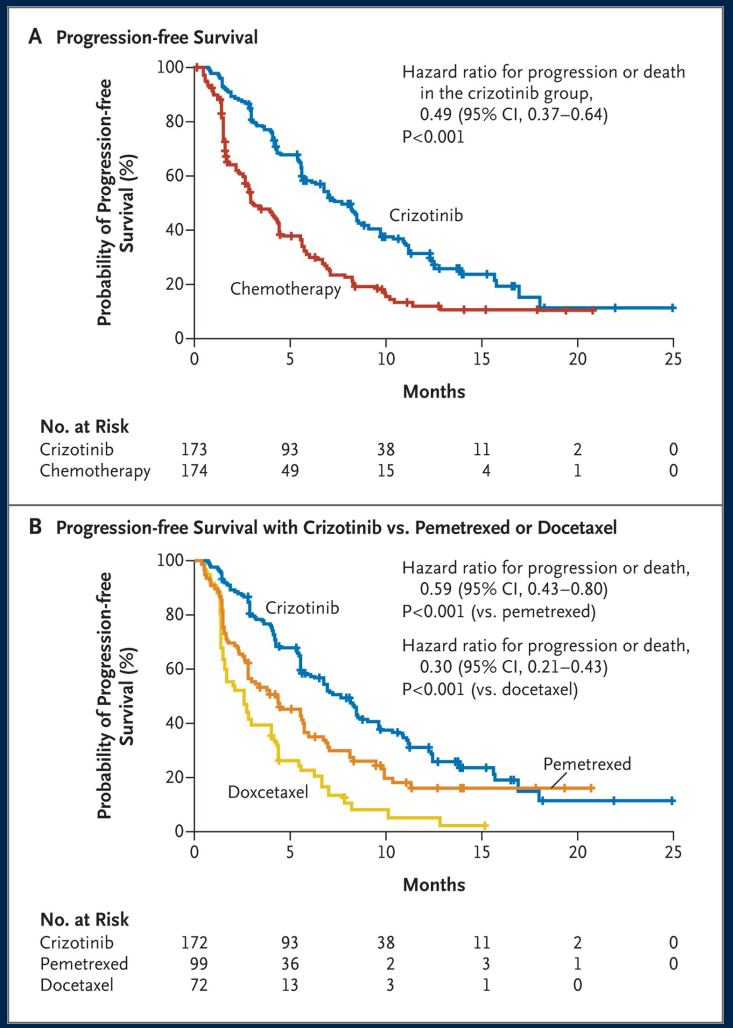
Crizotinib — ALK inhibition

- 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



Shaw AT et al. N Engl J Med 2013;368:2385-2394.

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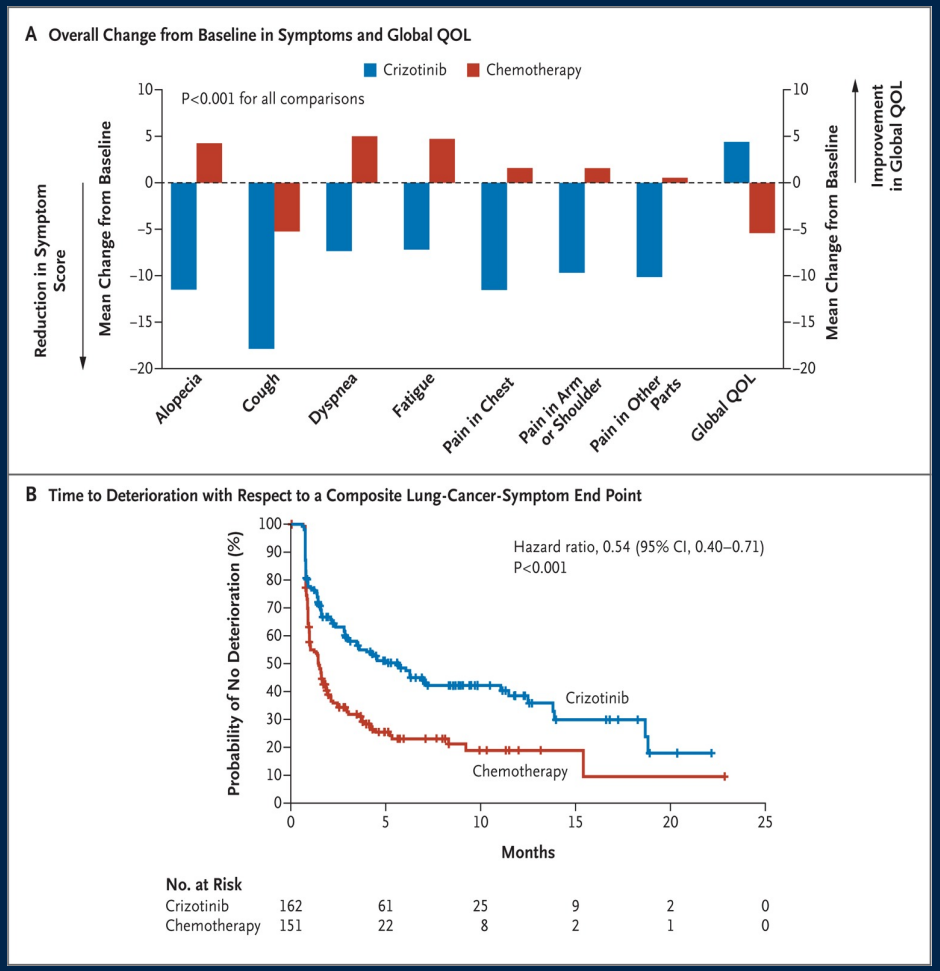
The NEW ENGLAND JOURNAL of MEDICINE

Crizotinib — ALK inhibition



Shaw AT et al. N Engl J Med 2013;368:2385-2394.

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The NEW ENGLAND JOURNAL of MEDICINE

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

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ALCHEMIST A151216

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

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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

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ALCHEMIST | Statistical Design Elements

Trial Category	ALCHEMIST Screening Trial A151216	ALCHEMIST ALK Treatment Trial E4512 (± crizotinib)	ALCHEMIST EGFR Treatment Trial A081105 (± erlotinib)
Target	Registry/Intervention with biopsy at recurrence	ALK rearrangement	EGFR mutation
Prevalence of Target		~5%	~10%
Total Sample Size	6000 – 8000	378 (5% ineligible)	430 (5% ineligible)
Primary Endpoint	Correlative endpoints & epidemiology	Overall survival	Overall survival
Power		80%	85%
One-sided α		0.05	0.05
Hazard Ratio		0.67	0.67

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.

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ALCHEMIST FAQs

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.

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ALCHEMIST FAQs

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.

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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.

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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.

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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.

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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.

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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.

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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.

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ALCHEMIST FAQs

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.

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