Adjuvant Targeted Therapy Following Standard Adjuvant Therapy for Resected NSCLC: An Initial Report from ALCHEMIST (Alliance A151216)

Geoffrey R. Oxnard[1], Sumithra Mandrekar[2], Shauna Hillman[2], Angelina Tan[2], Ramaswamy Govindan[3]

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Background

- The Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST; NCT02194738) was launched in 2014 across the National Clinical Trials Network (NCTN) of the National Cancer Institute (NCI).
- This trial platform aims to enroll up to 8,300 patients with resected high-risk non-small cell lung cancer (NSCLC) to facilitate enrollment to adjuvant targeted therapy trials following completion of standard adjuvant therapy.
- On 5/1/2016, the study was expanded to include squamous NSCLC and PDL1 testing to facilitate enrollment to a new immunotherapy study.
- Additionally, ALCHEMIST aims to collect biospecimens for clinical and investigational genomics.

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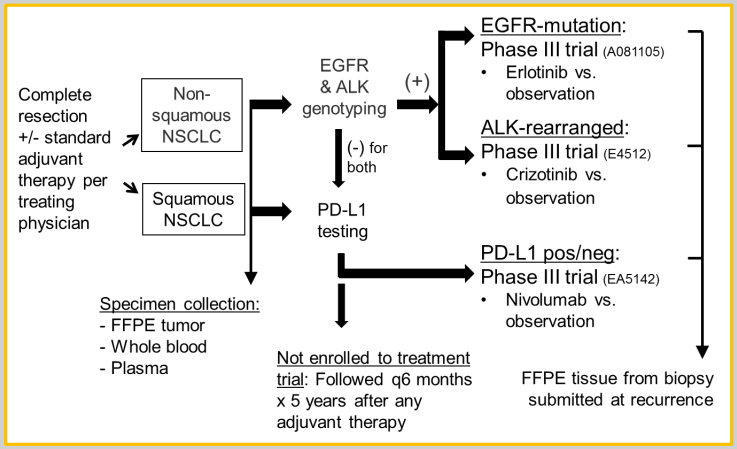
Methods and Study Design

- Eligible patients have completely resected NSCLC, any histologic subtype, stage IB (≥4cm) to IIIA by AJCC 7.
- Eligibility window extends 75-285 days post-op depending upon receipt of adjuvant chemotherapy and/or radiation.
- Molecular testing of EGFR, ALK, PDL1 is performed centrally (depending on the histology and testing results) and results are returned to sites within 7-21 business days.
- FFPE tissue, whole blood, and plasma are collected at enrollment for genomic analysis.
- Appropriate patients may then enroll to one of three therapeutic trials studying single agent adjuvant targeted therapy (erlotinib NCT02193282, crizotinib NCT02201992, or nivolumab NCT02595944) versus observation.



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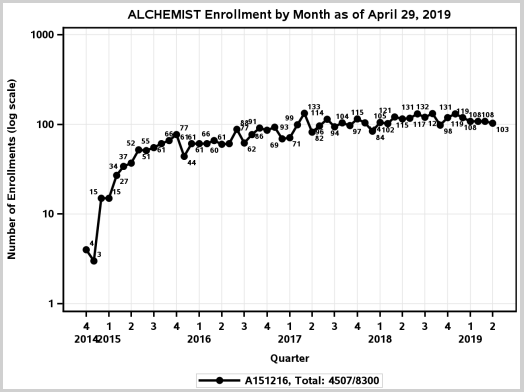
Enrollment Data

- This feasibility analysis was performed on patients enrolled as of April 29, 2019.
- 4,507 patients have been enrolled from 685 sites within the U.S.
- In the calendar year of 2018, median monthly enrollment to A151216 was 119 (range: 98-132).
- Central molecular testing was completed in 89.0%-92.7% of appropriate patients:
  - EGFR L858R/19del was detected in 560 of 3514 patients (15.9%).
  - ALK FISH was positive in 134 of 3,506 patients (3.8%).
  - PDL1 IHC was completed in 2,617 patients, and was >1% in 1,628 patients (62.2%).



- 3,304 patients were potentially eligible for the adjuvant treatment trials based upon molecular results and with sufficient post-surgical follow-up:
  - An additional 270 patients remained within the eligibility window for enrollment to treatment trial.
- 1,089 patients (33.0%) were enrolled to a treatment trial.
- Patients who enrolled were younger (p<0.01) and had higher N stage (p<0.01) than those not enrolled.

Variables *Median (Range)	Enrolled (N=1089)	Not Enrolled (N=1945)	P-value
Age, years*	66 (33 – 92)	68 (34 - 91)	<0.01
Gender: Female, Male	55%, 45%	53%, 47%	0.55
Tumor Size, cm*	3.7 (0-14)	4.0 (0.6-16.5)	<0.01
Pathologic T Stage:			0.34
T0, T1a, T1b	0%, 12%, 10%	0%, 10%, 9%	
T2a, T2b	41%, 15%	39%, 16%	
T3, T4	19%, 3%	23%, 3%	
Pathologic N Stage:			<0.01
N0, N1, N2	35%, 38%, 27%	41%, 38%, 22%	
Clinical M Stage:			0.51
M0, M1	100%, 0%	99.9%, 0.1%	

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ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

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Biospecimen Collection

- Adequate FFPE tissue and blood for advanced genomics was collected on 2859 of 4507 patients enrolled (63.4%):
  - Tumor sequencing is ongoing at the Genome Characterization Centers of the NCI's Center for Cancer Genomics, using multiple parallel sequencing platforms.
  - Following completion of the genomic analysis by study team, genomic data will be posted for public access.
- Plasma was collected at time of enrollment on 2006 patients enrolled since January 2017 (44.5% of all patients enrolled):
  - Plasma specimens can be used in the future for MRD studies, including analysis that are informed by tumor genomics or approaches that are agnostic to tumor sequencing results.

Specimen	Analysis Plan
FFPE slides for clinical genotyping	EGFR sequencing, ALK FISH, PDL1 IHC
FFPE block or scrolls for advanced genomics	Whole exome sequencing Whole genome sequencing RNA sequencing miRNA sequencing
Whole blood	Paired germline for tumor genomics
Plasma and paired cell pellet (two Streck tubes)	Save for future studies of minimal residual disease (MRD) detection
FFPE tissue from recurrence biopsy (if available)	Comparison to initial resection specimen

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Conclusions

- ALCHEMIST has achieved an enrollment of ~100 patients/month with resected high-risk NSCLC.
- This initial report demonstrates the feasibility of central molecular testing for enrollment to adjuvant targeted therapies.
- Only 36.3% of potentially eligible patients were enrolled to an adjuvant treatment trial with the primary reason being lack of interest in further adjuvant therapy.
- Enrollment continues toward the aim of using adjuvant targeted therapies to improve survival in high risk resected NSCLC.

Future Directions

- We are currently working to add additional treatment arms to replace those arms that complete enrollment.
- Tumor sequencing results offer a unique opportunity to rigorously assess the prognostic significance of a range of molecular features.
- We hope to use existing plasma to clinically validate MRD assays which could be prospectively studied in future NCTN studies.

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Acknowledgement

- We appreciate the time and energy committed by patients and investigators across the NCTN.
- We especially want to acknowledge these 10 top enrolling sites to A151216 (as of 4/29/2019):

Site	N
Moffitt Cancer Center	87
Saint Luke's University Hospital-Bethlehem Campus	60
Rhode Island Hospital	53
University of Pittsburgh Cancer Institute (UPCI)	50
Duke University Medical Center	48
University of Michigan Comprehensive Cancer Center	45
Dana-Farber/Harvard Cancer Center	44
Roswell Park Cancer Institute	43
Mayo Clinic	42
Memorial Sloan Kettering Cancer Center	41

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