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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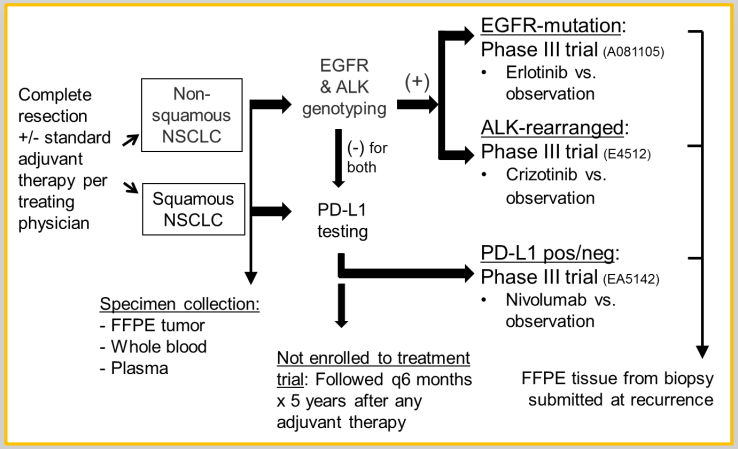
Methods and Study Design

- 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.
  Note: *The nivolumab NCT02595944 trial is now closed to enrollment.*



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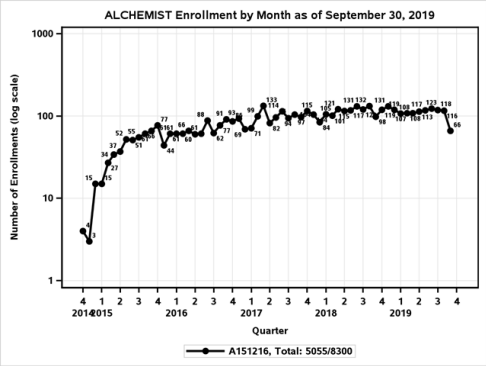
Enrollment Data

- This feasibility analysis was performed on patients enrolled as of September 30, 2019.
- 5,055 patients have been enrolled from 713 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 ~97% of appropriate patients:
  - EGFR L858R/19del was detected in 649 of 4108 patients (15.8%).
  - ALK FISH was positive in 156 of 4,092 patients (3.8%).
  - PDL1 IHC was completed in 3,244 patients, and was >1% in 2,007 patients (61.9%).



- 4,038 patients were potentially eligible for the adjuvant treatment trials based upon molecular results and with sufficient post-surgical follow-up:
  - An additional 433 patients remained within the eligibility window for enrollment to treatment trial.
- 1,330 patients (32.9%) 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=1330)	Not Enrolled (N=2275)	P-value
Age, years*	66 (33 – 92)	68 (31 - 91)	<0.01
Gender: Female, Male	55%, 45%	53%, 47%	0.35
Tumor Size, cm*	3.7 (0-14)	4.0 (0.4-16.5)	<0.01
Pathologic T Stage:			0.10
T0, T1a, T1b	0%, 11%, 10%	0%, 10%, 9%	
T2a, T2b	41%, 15%	39%, 16%	
T3, T4	20%, 3%	23%, 2%	
Pathologic N Stage:			<0.01
N0, N1, N2	34%, 40%, 26%	40%, 39%, 21%	
Clinical M Stage:			0.28
M0, M1	100%, 0%	99.9%, 0.1%	

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Biospecimen Collection

- Adequate FFPE tissue and blood for advanced genomics was collected on 3152 of 5055 patients enrolled (62.4%):
  - 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 2392 patients enrolled since January 2017 (47.3% 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 35.2% 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.
- The Nivolumab trial (EA5142) closed to accrual on October 1, 2019, the Pembrolizumab trial (A081801) will be replacing this trial and is targeted for activation first quarter of 2020.

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 9/30/2019):

Site	N
Moffitt Cancer Center	96
Saint Luke's University Hospital-Bethlehem Campus	65
University of Pittsburgh Cancer Institute (UPCI)	59
Rhode Island Hospital	57
Duke University Medical Center	51
University of Michigan Comprehensive Cancer Center	50
Dana-Farber/Harvard Cancer Center	49
Mayo Clinic	48
Roswell Park Cancer Institute	45
Vanderbilt University/Ingram Cancer Center	44

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