The Genomics of Young Lung Cancer Study

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GYLC Study

Our study is the first to prospectively characterize the clinical characteristics and somatic genomic alterations of young lung cancer.

Our goals are to identify a genomically enriched subtype of lung cancer, facilitate delivery of targeted therapy and lay the groundwork for further studies of heritable and environmental lung cancer risk factors.

STATISTICS: Compared to the Lung Cancer Mutation Consortium (Johnson et al, JCO 2013) we believe we will show an increase in the prevalence of "targetable" genomic alterations (EGFR/ROS1/ALK/BRAF/HER2/MET) from 35% to 50%; and an improvement in the use of targeted therapy from 22% (Historic Data) to 40%.

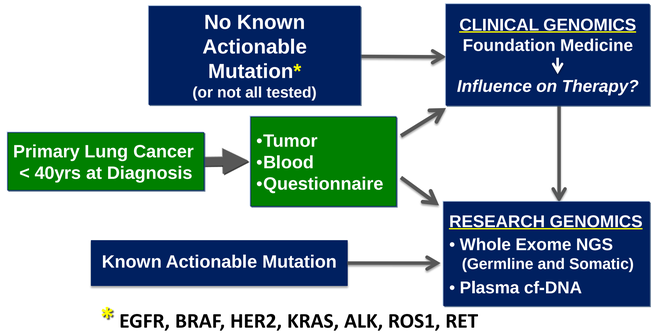
The trial is currently accruing (NCT02273336). First Patient entered July 2014.

https://www.openmednet.org/site/alcmi-goyl

Inclusion Criteria

- Age less than 40 at lung cancer diagnosis
- Pathologically confirmed bronchogenic lung carcinoma (SCLC or NSCLC) of any stage: at any treatment time point
- For patients with stage IV non-squamous NSCLC: *EGFR* and *ALK* genotyping performed by a CLIA certified laboratory is required prior to study enrollment
- Consent for participation must be given by a parent or legal guardian for individuals who are under 18 years

Study Schema

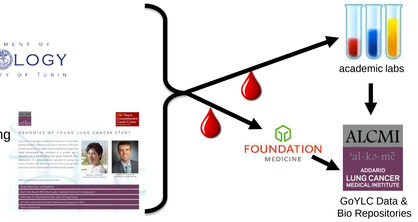


* EGFR, BRAF, HER2, KRAS, ALK, ROS1, RET

Implementing GoYLC

Option A:
Enrolling Sites: (traditional model)

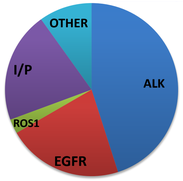
Option B:
Remote Participation:
- Online recruitment via Social Networking
- Online consenting
- Remote sample handling
- Remote clinical data collection
- Remote follow up



Preliminary Results

Results of the first 98 Subjects
- **Median Age at Diagnosis: 34 years; Range 16-39 Years**
- **45 Males (46%): 53 Females (54%)**
- **Histology: Adenocarcinoma n=85 (87%): Squamous n=9: Small Cell n=4**
- **Stage at Diagnosis: Stage 4 n=78 (79%); Stage 1-3 n=20 (21%)**

Subset: Stage 4 Adenocarcinoma n=71 (72%)

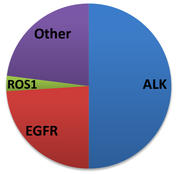


Driver Mutation Stage 4 AC (N) %	
ALK	(32) 45%
EGFR	(17) 24%
ROS1	(5) 7%
QNS/None	(5) 7 %
Other mutations	(12) 17%

→ 77%

→ HER2, RET, ATM, BRCA2, TP53, NF1

Males w/Stage 4 AdenoCA

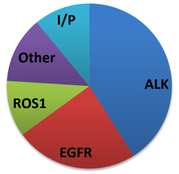


Driver Mutation ♂ N=34	
ALK	(17) 50%
EGFR	(8) 24%
ROS1	(1) 3%
Other Mutation	(8) 23%

26/34; 76% with ALK/EGFR/ROS1.

3 HER2, 1 ATM, 1 BRCA2, 1 RET, 1 NF1, 1 TP53

Females w/Stage 4 AdenoCA

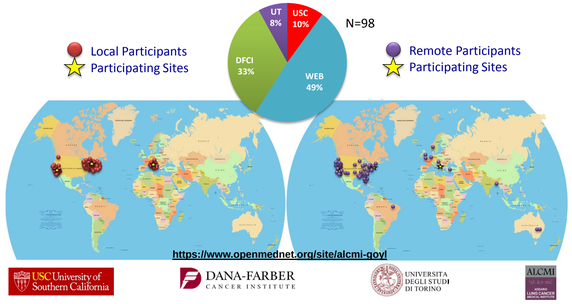


Driver Mutation ♀ N=37	
ALK	(15) 41%
EGFR	(9) 24%
ROS1	(4) 11%
QNS/P	(5) 13%
Other Mutation	(4) 11%

28/33; 85% of Females with genomic testing (ALK/EGFR/ROS1) +

2 RET, 2 TP53

Bringing Research to the Patient



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Preliminary Results

- For 71 pts with stage 4 adenocarcinoma: High prevalence of EGFR, ALK, ROS1 mutations observed at study entry (77%).
- 9 subjects (8M and 1F) with stage 4 adenocarcinoma wild type for EGFR and ALK had tissue sent for further on study clinical genomics with Foundation Medicine. (see table)
- Our participants have been part of 2 peer reviewed papers describing the novel, actionable EGFR Kinase Domain Duplication and EGFR-RAD51 Fusion[1, 2].

Clinical Genomics (gender)	Influence on Rx
EGFR-RAD51 fusion[1] (1M)	Response to Erlotinib
EGFR-Kinase Domain Duplication[2] exon 18-25 (1M)	Response to Afatinib
EML4-ALK (1M)	Currently on maintenance pemetrexed
HER2 (L869R) mutation (1M)	1M Response to Afatinib
HER2 (V659E) mutation (1M)	1M currently on Pemetrexed/Carboplatin
ATM K2811fs*46 mutation (1M)	responding to PDL-1 inhibition (PARP inhibitor planned at PD)
CCDC6-RET Fusion (1F)	1F currently on Pemetrexed/Carboplatin
KIF5B-RET Fusion (1M)	1M on Cabozantinib
NF1 R2258* mutation (1M)	currently on Pemetrexed/Carboplatin

[1] Gallant, Lovly, et al. EGFR Kinase Domain Duplication Is a Novel Oncogenic Driver in Lung Cancer That Is Clinically Responsive to Afatinib. Cancer Discovery. Aug 2015

[2] Konduri, Gallant, et al. EGFR Fusions as Novel Therapeutic Targets in Lung Cancer. Cancer Discovery. Apr 2016

Conclusions

- We hypothesized that young adults with lung cancer might be a special population enriched for driver mutations. Thus far we have exceeded our statistical expectations with the majority of participants having stage 4 adenocarcinoma, of which 76% of males and 85% of females have ALK, EGFR or ROS1 mutations.
- A website allowing for virtual consenting and social networking to share trial information is a novel, feasible way to conduct research across continents. Thus far 49% of participants have consented remotely.
- Though numbers are small, analysis of exposures show interesting findings including: ROS1 fusion pts are never smokers, without exposure to secondhand smoke; and compared to those with EGFR and ALK mutations, had a higher proportion of family history of lung cancer (60% vs. 25%).
- We plan to continue accrual for another year and would appreciate more international participants. https://www.openmednet.org/site/alcmi-goyl
- We plan a larger follow up study "Epidemiology of Young Lung Cancer" building upon our unique web-based, patient engaged, trial design. Partnering with Epidemiologists from USC, OSU and the Cancer Prevention Institute of CA; we will recruit 500 cases and 2000 controls and use the internet to "go viral" with our questionnaire.

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