Lung Cancer Translational Science at Alliance

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Disclosures

- None related to this presentation
  - Consulting: AstraZeneca, Genentech/Roche
  - Royalties: Wolters-Kluwer (UpToDate)

Topics

- ALCHEMIST
- Alliance Respiratory studies with translational science
  - A081801, A082002, A082101
- Legacy studies
  - CALGB 150802, CALGB 140503

ALCHEMIST

Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials

- Five integrated trials testing targeted therapy and immunotherapy in early-stage NSCLC (stage II, IIIA-B (T3-4N2) per AJCC 8)
  - A151216: Screening trial: Eligible patients have their tumor tissue tested for molecular markers and submitted for investigational genomic analysis (study chair: Kozono)
  - Three randomized treatment trials closed to accrual:
    - A081105: Erlotinib for EGFR mutations
    - E4512: Crizotinib for ALK fusions
    - EA5142 ANVIL: Nivolumab for neither EGFR or ALK alterations
  - A081801 ACCIO: Concurrent versus sequential chemotherapy and pembrolizumab for neither EGFR or ALK alterations

ALCHEMIST accrual update

Trial #	Date activated, closed	Number of sites open	Number of patients enrolled	Trial Status
A151216	08/18/2014, 03/14/2025	-	7345[1] (pre-reg: 7450[2])	Closed
A081105	08/18/2014, 01/20/2021	-	390	Closed
E4512	08/18/2014, 05/10/2024	-	166	Closed
EA5142	05/06/2016, 10/01/2019	-	935	Closed
A081801	06/03/2020	675	752/1210	Accruing

Tissue adequacy for genomics

Specimen Type	Was the tissue adequate for shipping for WES?		
	No	Yes	Total*
Tissue Block	512 (10%)	4594 (90%)	5106
Tissue Scrolls	601 (30%)	1391 (70%)	1992

*209 patients with neither block nor scrolls submission; 38 patients with information pending

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

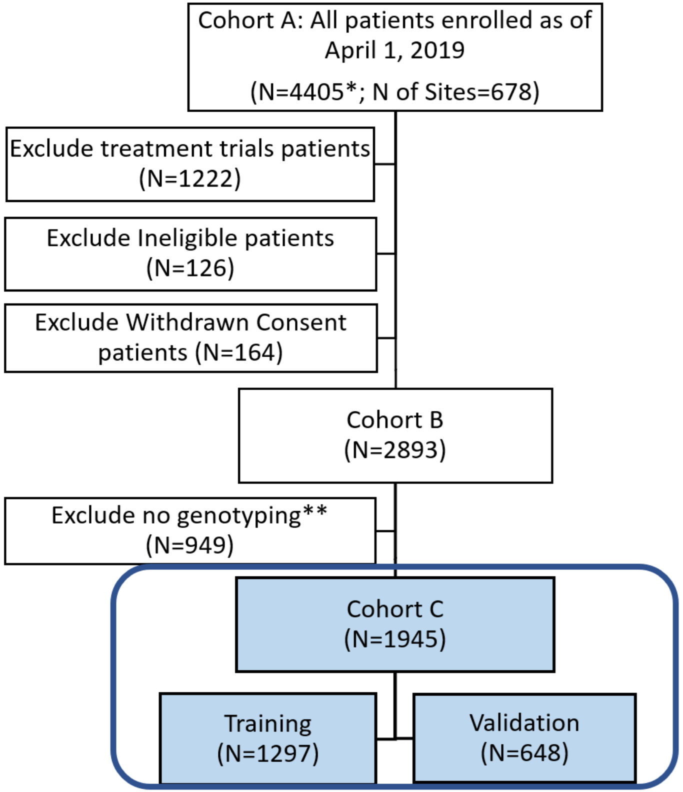
NCI National Clinical Trials Network
a National Cancer Institute program

NCI Community Oncology Research Program
A program of the National Cancer Institute of the National Institutes of Health

ALCHEMIST molecular testing

- Central testing on A151216
  - EGFR mutations by sequencing exons 18–21 (positive: exon 19 deletion or L858R)
  - ALK fusions by FISH using the Vysis break apart probe
  - PD-L1 tumor proportion score using the 22C3 antibody
- Due to subsequent FDA approvals of osimertinib (EGFR), alectinib (ALK), and atezolizumab (PD-L1), testing is now standard of care in resected NSCLC
- Ongoing PD-L1 central testing for patients enrolled on A081801
- When available, results of local testing are requested

ALCHEMIST genomics subset



- Patients enrolled as of 4/1/2019
- Boxes highlighted in blue represent the cohorts being used for genomic analyses
- 95.4% with full 5 years of follow-up
- Training and validation outcomes and updated clinical data shared with NCI Genomic Data Commons on 10/25/2024 (validation data to be released to the analysis working group once all training analyses are complete)

Analysis Working Group

- Led by NCI Center for Cancer Genomics (CCG)
- Genomic analyses performed by Genomic Data Analysis Network (GDAN)
- Alliance (Ann Oberg) is leading prognostic modeling efforts
- Primary manuscript ~end of 2025

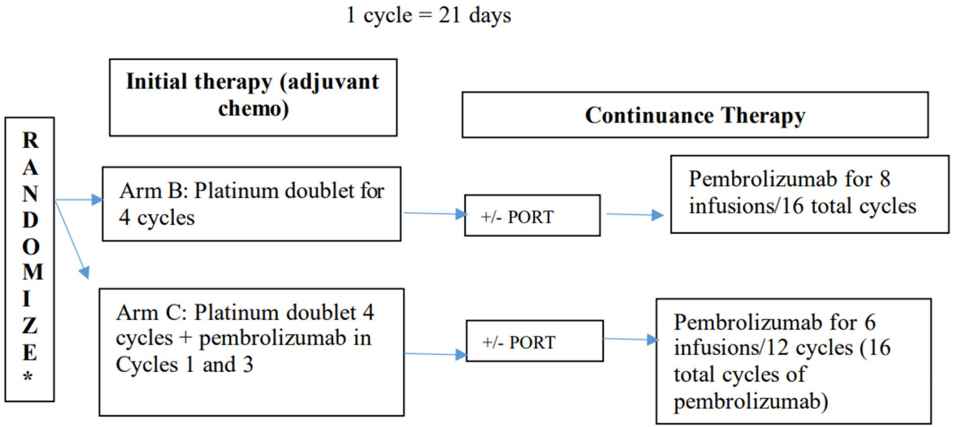
Genomic Analysis Plan

- Whole exome and genome sequencing at the Broad Institute
- Total RNA and miRNA sequencing at the University of North Carolina
- Paired germline sequencing
- Calculation of tumor mutational burden

ALLIANCE RESPIRATORY STUDIES WITH TRANSLATIONAL SCIENCE

A081801 ALCHEMIST CHEMO-IO (ACCIO)

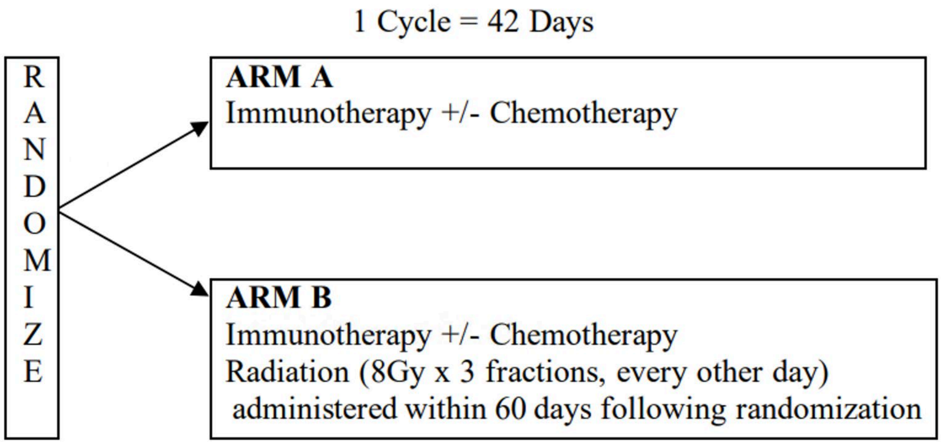
Integration of immunotherapy into adjuvant therapy for resected NSCLC (study chair: Sands)



- Biospecimens: FFPE tumor tissue, EDTA plasma/buffy coat (baseline), Streck tubes (baseline, end of chemo, q6mo × 3y, recurrence)
- Objectives: identify a cfDNA marker associated with risk of recurrence and improved DFS and OS with addition of pembrolizumab to standard adjuvant chemo

A082002 Phase II/III trial of modern IO-based systemic therapy w/wo radiotherapy for PD-L1-negative, advanced NSCLC

(study chair: Bestvina) (n=86/100)



- Biospecimens: FFPE tumor tissue, EDTA plasma/PBMCs (baseline, C3D1, C5D1, C7D1, C9D1, EOT)
- Objectives: evaluate changes in the peripheral immune microenvironment between the arms, e.g., flow cytometry immnophenotyping, TCR sequencing, cytokine assays

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A082101 Multimodality therapy with immunotherapy in Stage I-IIIA pleural mesothelioma (study chair: Mansfield) (n=6/26)

1 cycle = 6 weeks, treat for 2 cycles

Nivolumab 360mg by IV on days 1 and 22 of each 6 week cycle

Ipilimumab 1mg/kg by IV on day 1 of each 6 week cycle

→ STEP 2 REGISTRATION → Surgery

- Biospecimens: FFPE tumor tissue, EDTA plasma/buffy coat (baseline), Streck tubes (baseline, C2D1, EOT)
- Objectives: evaluate association between change in peripheral T cell clonality relative to baseline and treatment response, and between PD-L1 expression and treatment response

LEGACY STUDIES

CALGB 150802

- Participation in Lung Adjuvant Cisplatin Evaluation (LACE) Bio
- Pooled analyses including pivotal adjuvant chemo trials
  - CALGB 9633, JBR.10, IALT, and ANITA
- Seven manuscripts published since 2017
  - e.g., a LACE-Bio II analysis published as Kumar AP et al. *Clin Lung Cancer* 2023 Sep;24(6):528-40

LACE-Bio analysis by Kumar et al.

- 375 patients with stage II-III lung adenocarcinomas
- Divided into five subgroups
  - Lepidic, acinar/papillary, micropapillary/solid, mucinous, other
- Genes/biomarkers selected from LACE-Bio
  - Mucin, β-tubulin, p27, TILs, p53, *KRAS*, *EGFR*, ERCC1, Cyclin E, p16, FAS, FASL, BAX, BRCA1, PD-L1, and TMB

Kumar et al. results

- Micropapillary/solid was most commonly positive for various biomarkers
- PD-L1 negative/high TMB was associated with better OS and DFS relative to PD-L1 negative/low TMB
- High TMB predicted worse OS with adjuvant chemo (consider IO?)
- Marked TILs had better DFS with adjuvant chemo

CALGB 140503 secondary studies

- Phase 3 noninferiority trial of lobar vs. sublobar resection for ≤ 2 cm NSCLC (Altorki N, Wang X, Kozono D et al. *N Engl J Med*. 2023 Feb 9;388(6):489-98)
- Several completed, ongoing, and planned secondary analyses, including one to evaluate spread through air spaces (STAS) as a biomarker (A152429)

A152429 STAS study

- STAS is emerging as a histologic descriptor associated with worse recurrence-free and overall survival
- Desire to assess this in CALGB 140503, however H&E slides were not collected on this legacy study
- Plan: obtain digitized slide data from the nearly 400 patients enrolled at the top seven accruing sites

Concluding thoughts

- Alliance is championing inclusion of blood sample collection for biobanking as a minimum for future translational science
  - E.g., 2 × 10 ml EDTA tubes for frozen plasma and buffy coat at three timepoints
- Impactful secondary analyses of legacy trials are ongoing, although there can be challenges
  - Lesson learned: collect H&E slides or digitized images given wealth of emerging uses including AI/ML based approaches

Thank You