Bay Area Team Against Resistance

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Unleashing the full potential of molecular medicine

- **Targeted therapy** is effective:
  - Almost all tumors develop resistance:
    - Subtypes
    - Targeted therapy
    - New targeted therapy
    - Resistance
• 1 in 15 Americans will be diagnosed with lung cancer

• 65% of lung cancer diagnoses are in non-smokers

• Lung cancer kills more people than the next 3 deadliest cancers combined
  • Lung cancer kills 3X as many men as prostate cancer
  • Lung cancer 2X as many women as breast cancer

• Only $1,680 is spent on federal research per life lost from lung cancer; $25,118 is spent in breast cancer; $12,644 in prostate cancer
Paradigm-defining molecular landscape of lung adenocarcinoma
Precision oncology: promise & challenge

Intrinsic resistance can promote an incomplete drug impact. Multiple mechanisms can operate within tumor cell subpopulations within a generally sensitive tumor, leading to residual disease. The presence and etiology of residual disease can be the result of therapy-induced changes in the tumor cells that enable adaptive survival and/or drug-tolerance. Residual disease may be linked to the incomplete response to therapy but also mutant PI3K (PI3K*).

Principles of residual disease.

The goal of therapies targeting residual disease will be to achieve chronic disease management, whereas in others it will be to cure disease. In principle, three primary types of residual disease exist in individual tumors, and intertumoral heterogeneity, in which different clonal populations of cells within a metastatic tumor may harbor the relevant target of a particular drug, whereas others may exist in individual tumors, and intertumoral heterogeneity, in which multiple different tumor cell clones with distinct mutational profiles state and manifests as both intratumoral heterogeneity, in which different clonal populations of cells within a metastatic tumor may exist in individual tumors, and intertumoral heterogeneity, in which different clonal populations of cells within a metastatic tumor may.

Intrinsic resistance.

Tumor genetic heterogeneity is present in the treatment-naive tumor cell subpopulation and manifests as both intratumoral heterogeneity, in which different clonal populations of cells within a metastatic tumor may.

**Incomplete response**

(residual disease)

**Progressive disease**

Stable disease

Partial response

Complete response

Bivona and Doebele 2016
Systematic study of human specimens

Diagnosis

EGFR TKI
ALK TKI

I/O

Residual Disease
(maximal RECIST response)

acquired resistance

Relapse

Lung Cancer Residual Disease Biopsy Program

cfDNA Collection (2 week interval)

Core and liquid biopsy

Novel Tumor Models

Organoid/ PDX models

Core and liquid biopsy

Tumor Characterization

Bulk RNAseq
Exome Seq

Single Cell RNAseq/tumor associated TILs
Kinome Proteomics

Molecular Modeling/ Heterogeneity Analysis

Exome Seq Bulk RNAseq cfDNA Seq

Candidate screening using drugs and CRISPR

Follow up validation

New Combination Therapies

Candidate Targets

NFκB (EGFR TKI)
Aurora Kinase (EGFR TKI)
MAPK (ALK TKI)
KDM5A (Both)
Bay Area Team Against Resistance - U54 Project (BATAR-UP)

**Organoid and PDX Development**
- Kuo (organoid)
- Bivona (PDX)

**Tumor Characterization**
- Bivona
- Shokat
- Weissman

**Lung Cancer Residual Disease Core Biopsies**
- Blakeley
- Wakelee
- Padda

**Follow Up/Mechanistic Studies**
- Project 1 - TKI resistance
  - Bivona
  - Bandyopadhyay
- Project 2 - anti-PD1
  - Levy
  - Kuo

**Data Integration and Modeling**
- Bandyopadhyay
- Collisson

**Drug and CRISPR Screening**
- Bivona
- Bandyopadhyay
- Weissman

**Advisory Board**
- Ashworth
- McCormick
- Fong
- Shannon
- Mackall

**Administration**
- Bivona
- Kuo
- Project Manager

**Other DRSCs**
- CTEP
Bay Area Team Against Resistance

Systematic Collection of Lung Cancer On-Treatment Core Biopsies

**Project 1**
Tyrosine Kinase Inhibitor Resistance
- EGFR TKI
- ALK TKI

Leads: Bivona, Bandyopadhyay

**Project 2**
Immunotherapy Resistance
- anti PD-1 (pembrolizumab, nivolumab)

Leads: Kuo, Levy

Molecular profiling
Single cell analysis
Organoid development
PDX models
Computational modeling
Small molecule/CRISPR screens

UCSF + Stanford
Characterizing and targeting the tumor ecosystem

Monotherapy
Targeted-therapy naive

Tumor biopsy
Liquid biopsy

EGFR TKI: erlotinib
Residual tumor fraction

Polytherapy

EGFR TKI + MEK1 inhibitor

EGFR TKI JAK1/2 inhibitor ± anti-PD1

EGFR\textsuperscript{L858R/BRAF\textsuperscript{V600E}}
EGFR\textsuperscript{L858R}
EGFR\textsuperscript{L858R, T790M}
EGFR\textsuperscript{L858R/STAT3}
EGFR\textsuperscript{L858R/MET}
EGFR\textsuperscript{L858R/AXL}
EGFR\textsuperscript{L858R/JARID1A}
CD8 T cell

Thank you!

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