Meeting minutes: SCLC Consortium WebEx
February 1st @ 1:00pm ET

Announcements/Updates

- March Meeting
  - Give headcount to Elizabeth Simon (simone@mskcc.org) ASAP
  - Hotel details TBD

Title: Tissue Microarray (TMA) Project

Afshin Dowlati and Gary Wildey of Case Western Reserve

- Small Cell Lung Carcinoma Database
  1. Retrospective (>6mo), dates back to 1998
  2. N=711 patient entries-updated twice a year
  3. Patient attributes: age, sex, race, smoking history, overall survival , PFS
  4. Clinical attributes: stage, tumor specimens (types and location), Rx-response
  5. Genomic attributes: targeted exome sequencing (FM
     - N=88 (as if 11/01/17)
- 40-50 limited small cell lung cancer patients (mostly female) that have survived 5 years
- 5 Provocative Questions
  1. Are there genetic subsets of SCLC?
  2. Are there genetic differences between primary and metastatic tumors?
  3. What determines initial chemo-sensitivity/resistance in SCLC? What molecular changes occur during acquired resistance in tumors?
  4. What is the relationship between "pure" SCLC and "combined" SCLC
  5. What distinguishes tumors of long-term survivors (>3 years) from those of more characteristic short-term (<1 year) survivors?
- Goal: Build TMAs that address questions
  - Build with primary vs. metastatic specimens from the same patients
  - Chemo response: build with chemo –naïve primary tumors
  - Resistance: build with sequential specimens: pre-treatment and at relapse
  - Build with "combined" SCLC tumors-separate specimens for each histology?
  - Build from various survival groups
  - Provide matching annotations from database
  - Cross-reference genomic alterations where available
- Currently Available TMAs
  - Initial TMA: mixture SCLC tissues (N=22) and cells (N=7), NSCLC tissues (N=12), normal tissues (N=4 lung)
  - New CLMA: cell lines only-29 SCLC, 15 NSCLC, 6 meso, 1 normal
  - Current build: primary chemo-refractory tumor specimens
  - Willing to construct any TMA of GEMM/PDX samples provided by consortium members (up to 100 cores/TMA)
- Establish cBioPortal database for CASE cohort
  - Targeted exome sequencing since fall 2013
  - N=88 (as of 11/1/17)
  - Have local instance running at CASE: working except for CNV
  - Test files (N=12) transferred to MSK for review/problem solving

- Ongoing SCLC research projects:
    - Role RB1 mutation status in chemo –sensitivity (submitted R21)
    - Role RUNX1T1 amplification in combined SCLC (DoD)
    - HEPACAM2 as a potential therapeutic target (DoD)
- Project 1: RB1 mutation status and chemo-response
    - Clinical correlation of extensive-stage small cell lung cancer genomics (Annals Oncol 2016)
    - Reciprocal expression of INSM1 and YAP1 defines subgroups in small cell lung cancer (Oncotarget 2017)
- Reciprocal expression of INSM1 and YAP1 defines subgroups in SCLC
    - CDK4/6 inhibitors are more active in YAP positive, INSM negative cell lines
    - Majority of SCLC tumors→mutant RB1 (non-functional) →chemo sensitive (apoptosis)→increased survival
    - Minority SCLC tumors→ Wt RB1 (functional)→Chemo-refractory (growth arrest)→decreased survival
    - **Goals**:
        - To determine whether RB1 mutation status and/or expression represents a biomarker of chemo-refractory drug response
        - To determine whether RB1 mutation status and/or expression predicts sensitivity to CDK4/6 inhibitors in SCLC models
- Project 2: RUNX1T1 amplification in SCLC:
    - RUNX1T1: RUNX1 translocation partner 1
        - ETO (eight twenty one)
        - MTG8 (myeloid translocation of gene 8)
    - Translocation between chromosome 8 and chromosome 21 (AML1) in acute myeloid leukemia (AML)
    - Interactions and functions: transcriptional co-repressor with HDACs (HDAC1 & HDAC3)
    - Initial Observation:
        - RUNX1T1 AMP rare in SCLC cohort (4/88 pts)
        - Two AMP found in the only two combined SCLC specimens of cohort, but NOT in matching NSCLC component
        - Patient specimen #1: 38 of 39 total mutations matched in SCLC/NSCLC tumors
        - Patient specimen #2: 7 of 20 total mutations matched in SCLC/NSCLC tumors
        - RUNX1T1 (8p22) did NOT co-amplify with MYC (8p24)
    - RUNX1T1 expression (mRNA level) in SCLC
        - neuroblastoma and SCLC express RUNX1T1 the most
        - neuroendocrine prostate cancer→RUNX1T1 amplification in 47%
    - Does RUNXT1 function in transformation from NSCLC to SCLC?
        - Overexpression of RUNX1T1 does NOT transform NSCLC to SCLC cells
    - What is RUNX1T1 function in SCLC: neuroendocrine features?
        - It's complicated!
- Expand Clinical Tissue Analysis
    - Compare SCLC component vs NSCLC component in more combined SCLC samples
    - Gene amplification: RNA scope
    - Protein expression: IHC
- Project 3: HEPACAM2 expression in SCLC
    - Initial gene clustering demonstrated expression in SCLC>>> NSCLC

    - CCLE demonstrated high and specific expression in SCLC
    - Higher level and more SCLC- specific expression compared with DLL3 expression
    - **Goals**:
        - Is HEPACAM2 expressed on cell surface in SCLC?
        - Can we target as a new antibody-drug conjugate, like ROVA-T?

Final Thoughts/Questions:

- Heterogeneity of different types of SCLC→same tumors differentiated along different pathways
    - While developing database, the path review often came back as combined small cell. There were very few publications on what the patient characteristics were for combined SCLC.
- Best markers in identifying NSCLC component of combined SCLC→ varies
    - Majority are poorly differentiated non small cell carcinomas that lack neuroendocrine markers completely
    - Few are adenocarcinomas with classic TTF1 positivity
    - Rare cases of squamous cell carcinoma
- With the right genetics, you can get neuroendocrine types of tumors from non-neuroendocrine cells of origin

Reminders:

- March Call canceled due to March Meeting
- Next Call: 4/5/18
    - Presenters: TBD