COXEN FOR PREOPERATIVE BLADDER CANCER CHEMOTHERAPY
- IN DEVELOPMENT

Slide support from Dan Theodorescu
Bladder Cancer: 2013

• **In need of transformative change**

• Kidney cancer:
  – 7 newly approved drugs, more on the way
  – Thoughtful post-operative trials underway

• Prostate cancer – many recent approvals
  – Sipuleucel-T, Cabazitaxel, Abiraterone, Enzalutamide, Radium 223

• Bladder cancer
  – Advanced: No improvement in therapy effectiveness in decades
  – Muscle-invasive, localized: Pre-operative chemotherapy
Neoadjuvant chemotherapy in bladder cancer

SWOG 8710:
• Rate of no residual cancer (pT0) at time of surgery was 38% with chemotherapy and 15% without
• 8 year survival with pT0 ~75% vs. ~30% if > pT0

• Despite this, current community use of pre-operative chemotherapy in bladder cancer is low (< 10%)
  – One concern, losing the window of curability by giving chemotherapy in insensitive patient, needlessly delaying surgery
Rationale

- COXEN is a genetic (gene expression model - GEM) approach to predict individual patient’s likelihood of responding to a specific chemotherapy.
- It has been applied to bladder, breast, ovarian, lung, etc. cancers successfully.
  - Largely been tested on prospectively gathered data, but COXEN analysis was retrospective.
- Feasibility of using COXEN from a standard gene expression platform on bladder biopsy samples in Cooperative group setting has not been tested prospecively.
**COXEN**

**Use in Predictive Biomarkers**

[Diagram showing the process of COXEN including NCI-60 Cell Line Panel, IC50 for Classic Chemotherapeutic or Targeted Compounds, Bladder Cancer patient samples, Gene Expression Model (GEM) for each Test Compound, GEM Score Evaluation on Bladder Cancer patient tissues or cells, COXEN Score for each patient for specific drug, and Personalized Therapy.]

- NCI-60 Cell Line Panel
- IC50 for Classic Chemotherapeutic or Targeted Compounds
- Bladder Cancer patient samples
- Gene Expression Model (GEM) for each Test Compound
- GEM Score Evaluation on Bladder Cancer patient tissues or cells
- COXEN Score for each patient for specific drug
- Personalized Therapy
COXEN prediction of treatment outcome in patients treated with neoadjuvant MVAC

Downstaging defined as ≤pT1 or ≤T1 after two courses of MVAC

Ref: Clin Can Res 2005;11(7): 2625
Tx: Neoadjuvant MVAC (N=45) + surgery or XRT
Outcome: Downstaging, Overall survival
Primary study objective: To characterize the relationship of MVAC-and GC-specific COXEN scores in terms no residual cancer (pT0) in patients treated with pre-operative chemotherapy. This will be done in several ways:

- To assess whether either chemotherapy-specific Coxen score is associated with tumor response (pT0 = no residual cancer found at surgery)
- To evaluate the correlation between the 2 different chemotherapy Coxen scores – how different are they?
  - Are we predicting general good prognosis unrelated to treatment or are we predicting a response to a specific chemotherapy?
SWOG COXEN-directed neoadjuvant chemotherapy trial

**Selection Criteria SWOG 8710**
(T2-T4a N0M0, cisplatin eligible, excluding non-bulky T2 disease)

**Primary outcome:** Assess COXEN’s ability to predict response to chemotherapy, as assessed by pT0 rate

**Biomarker validation and Biomarker discovery**

**Tumor Sample TURBT**

- Randomize to chemo
- Gem-Cis 21 day X 4
dose-dense MVAC X4 cycles

**Collection**
Tissue, blood, urine

**Molecular Analysis**
Gene expression
Sequencing
microRNA
SNP, others

**Discovery**

**Cystectomy Pathology**

**Collection**
Tissue (>P0), blood, urine

**Molecular Analysis**
Gene expression
Sequencing
microRNA
SNP, others
Translational resources

- Planned establishment of a pre-operative tissue/sample source for future investigations
- Many tissue will be collected to maximize impact:
  - mRNA and microRNA profiling
  - Potentially tissue microarray
  - DNA collection
  - Urine collection/storage
Potential translational aims

• In addition to the COXEN analysis, other predictive tests of chemotherapy response will be assessed:
  – microRNA expression profile
  – Oncogenomic analysis
  – Stem cell analysis
  – Cisplatin pharmacogenomics/SNP analysis