Biomarker studies in S1314: The CoXEN Trial

David J. McConkey, PhD, Chair

Translational Medicine

SWOG GU Committee

Disclosures

- Grant support: Astra-Zeneca, Janssen, Rainier Pharmaceuticals
- Honoraria: Janssen, Rainier, H3 Biomedicine

NON FDA Approved use of drugs or products referenced in this presentation – None.

David J. McConkey, PhD

Background

- Cisplatin-based combination neoadjuvant chemotherapy is the standard of care in eligible patient with muscle-invasive, localized disease
  - Both Gemcitabine + Cisplatin (GC) and dose-dense MVAC (dd-MVAC: Methotrexate, Vinblastine, Doxorubicin + Cisplatin) are acceptable regimens
- The use of this therapy, despite category 1 support, remains suboptimal
- There are no predictive biomarkers in use for cytotoxic chemotherapy in this setting

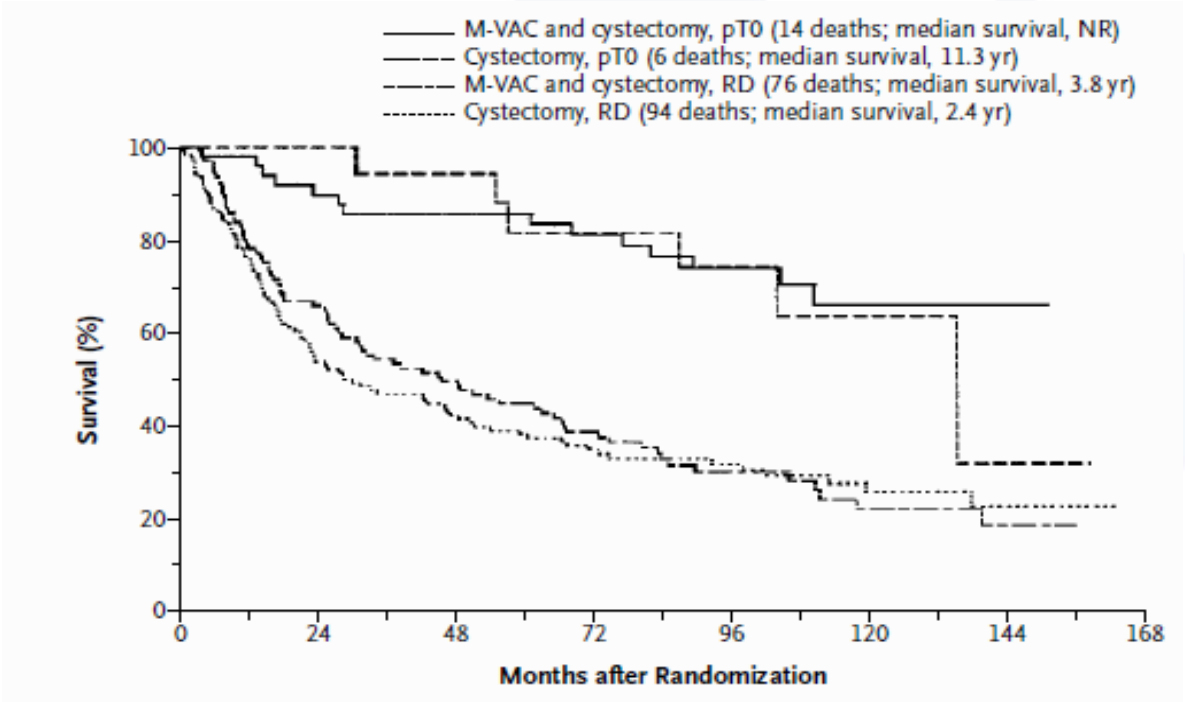
Downstaging as a surrogate for survival

- Radical cystectomy – removes primary tumor and lymph nodes (extent: S1011)
- Downstaging to <pT2 (i.e., no muscle-invasive disease) is associated with excellent outcomes
- In this setting, chemosensitivity of the primary tumor is considered a surrogate for the sensitivity of sub-clinical metastatic disease
- *However, the correlation is not perfect (i.e., disconnect with ctDNA, Dyrskjot, JCO 2019)*

Neoadjuvant chemotherapy in bladder cancer

SWOG 8710:

- Rate of pT0 was 38% with chemotherapy and 15% without
- 8 year survival
  - pT0 ~75%
  - > pT0 ~30%



N Engl J Med 2003; 349:859-866

NCI WORKSHOP

NOVEL NEOADJUVANT THERAPY FOR BLADDER CANCER

AGENDA

MONDAY, SEPTEMBER 19TH FROM 8:00 AM – 6:45 PM ET
TUESDAY, SEPTEMBER 20TH FROM 7:30 AM – 1:15 PM ET

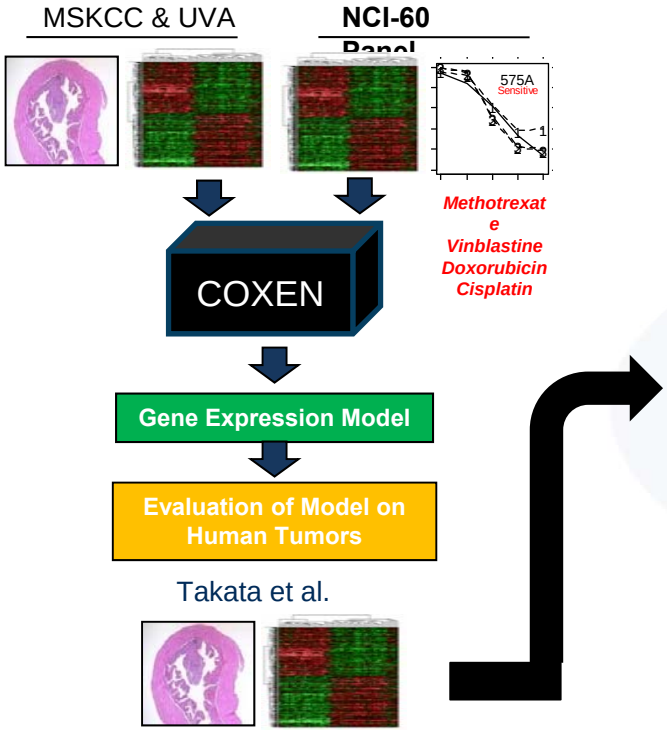
GAITHERSBURG MARRIOTT WASHINGTONIAN CENTER
9751 WASHINGTONIAN BLVD
GAITHERSBURG, MD

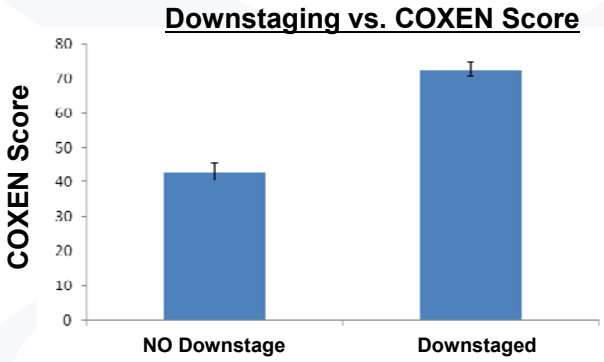
ROOM: SALONS EFG (FOR MAIN SESSION)

Session 1: Candidate biomarkers (McConkey and Theodorescu)

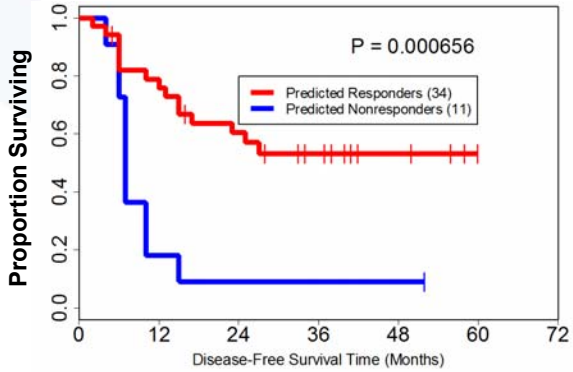
S1314 TM was the product of the meeting.

The CoXEN algorithm



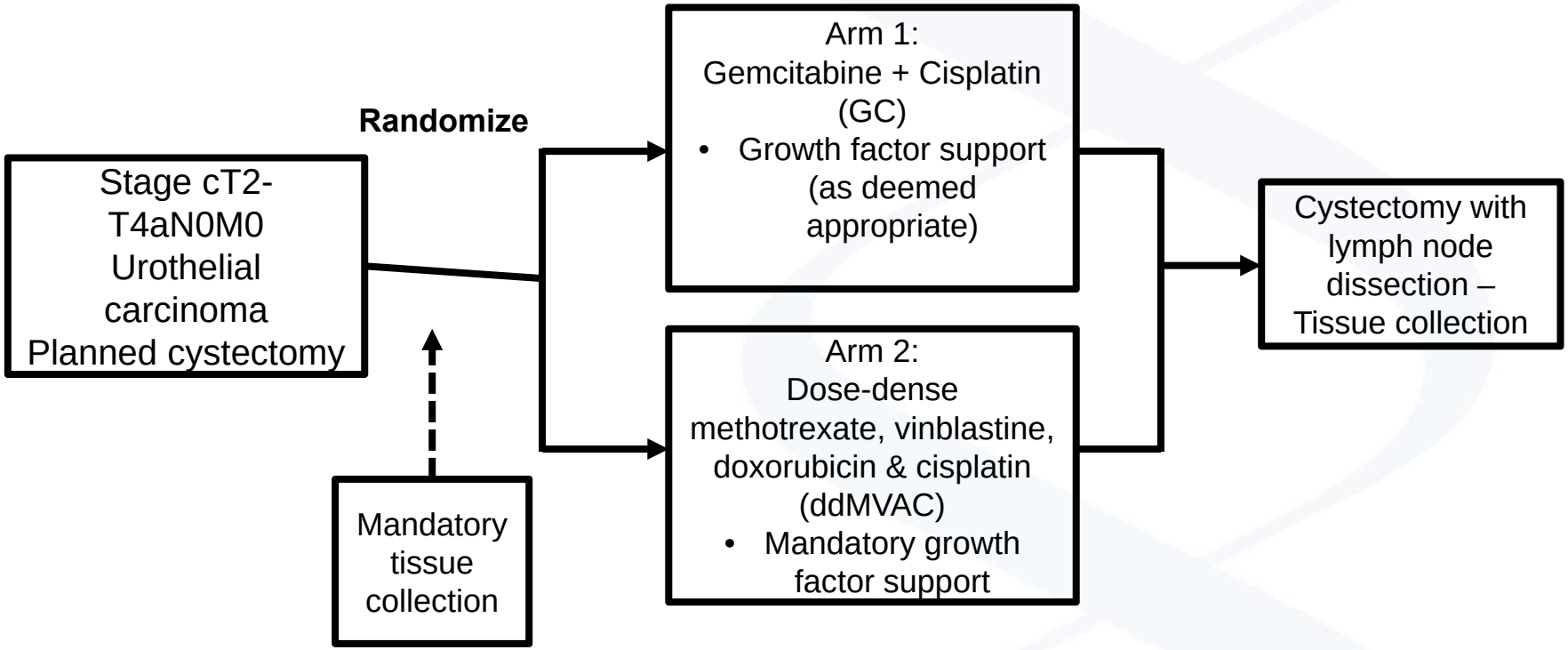


***Downstaging defined as* ≤pT1 or ≤T1 after two courses of MVAC**



Ref: Clin Can Res 2005;11(7): 2625
Tx: Neoadjuvant MVAC (N=45) + surgery or XRT
Outcome: Downstaging, Overall survival

Trial schema



Integrated translational medicine

- CoXEN (Theodorescu, Flaig): ***primary objective***
- miRNA-based molecular subtypes (Dinney, Choi, McConkey)
- Molecular subtypes (Lerner, Choi, others)
- DDR mutations (Rosenberg, Iyer, Plimack)
- SNPs associated with drug metabolism (O'Donnell)

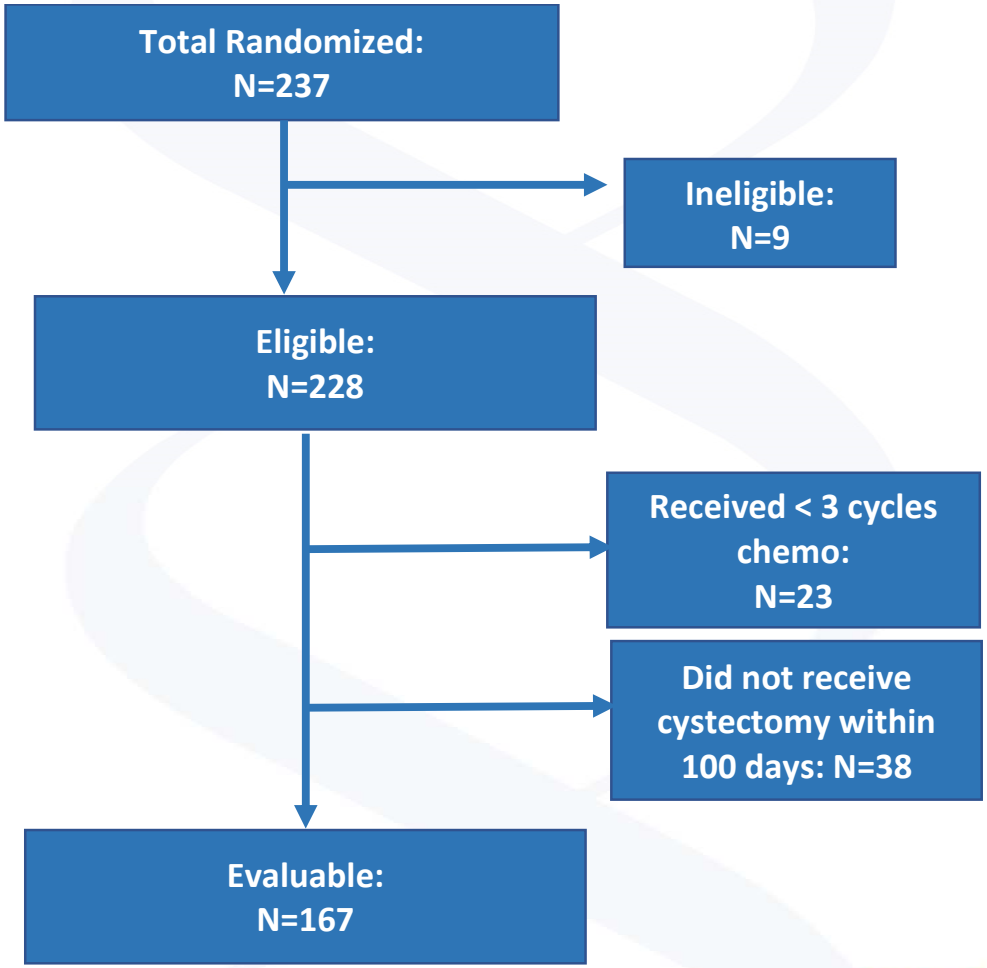
BISQFP funding

- RNA isolation and Affymetrix gene expression profiling (Flaig, Theodorescu)
- RNA and DNA isolation and Nanostring miRNA expression profiling (Dinney, Choi and McConkey)
- Blood germline and tumor MSK IMPACT panel exome sequencing (Rosenberg)

Tissue collection and processing

- Collected 20 unstained slides per patient
- 10x went to ALMAC for RNA isolation and Affymetrix gene expression profiling (HU133 chips)
- 5x went to MDACC for RNA and DNA extraction and miRNA profiling (NanoString)
- *5x remain in the SWOG tissue bank (Nationwide)*

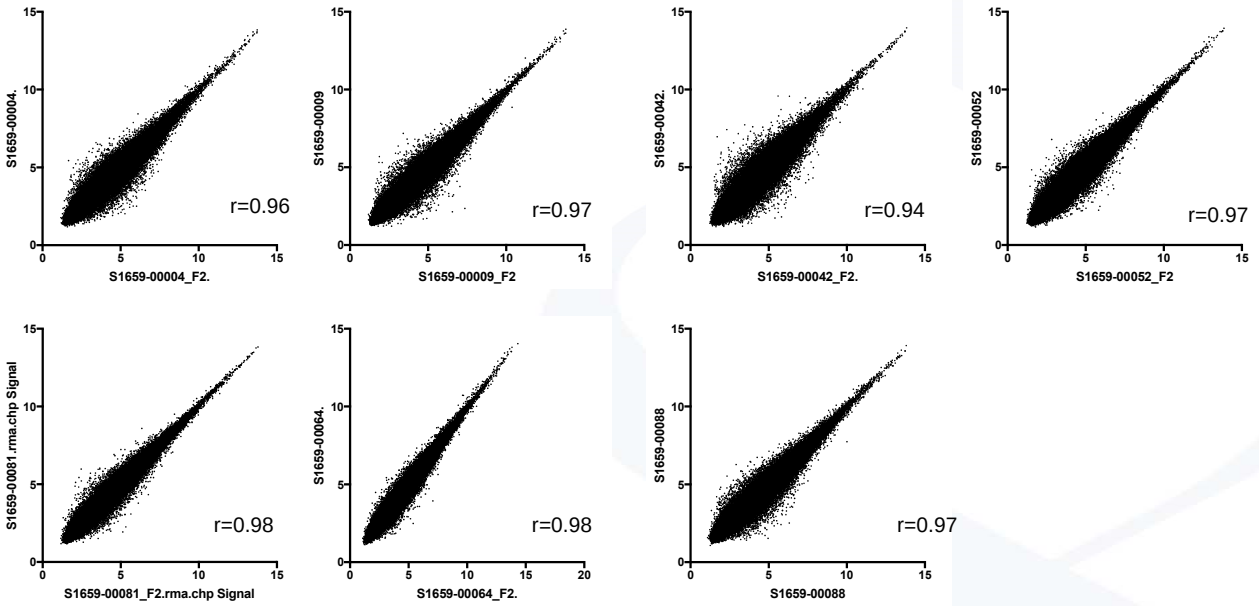
CONSORT Diagram

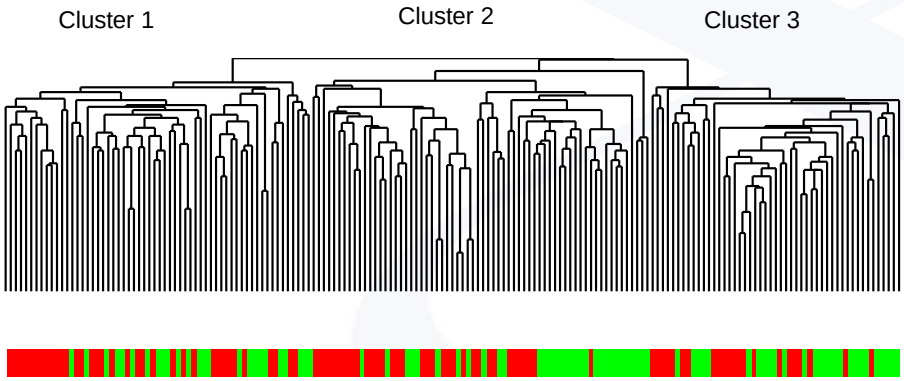


Pathologic response by treatment arm in evaluable subjects

N=167	GC (N=82)	ddMVAC (N=85)
Chemotherapy Response		
CR (pT0)	28 (35%)	27 (32%)
PR (downstaged to ≤T1)	12 (15%)	20 (24%)
CR + PR	*40 (50%)*	*47 (56%)*
Non-responders	42 (50%)	38 (44%)

Correlation of repeat samples between Batch 1 and 2





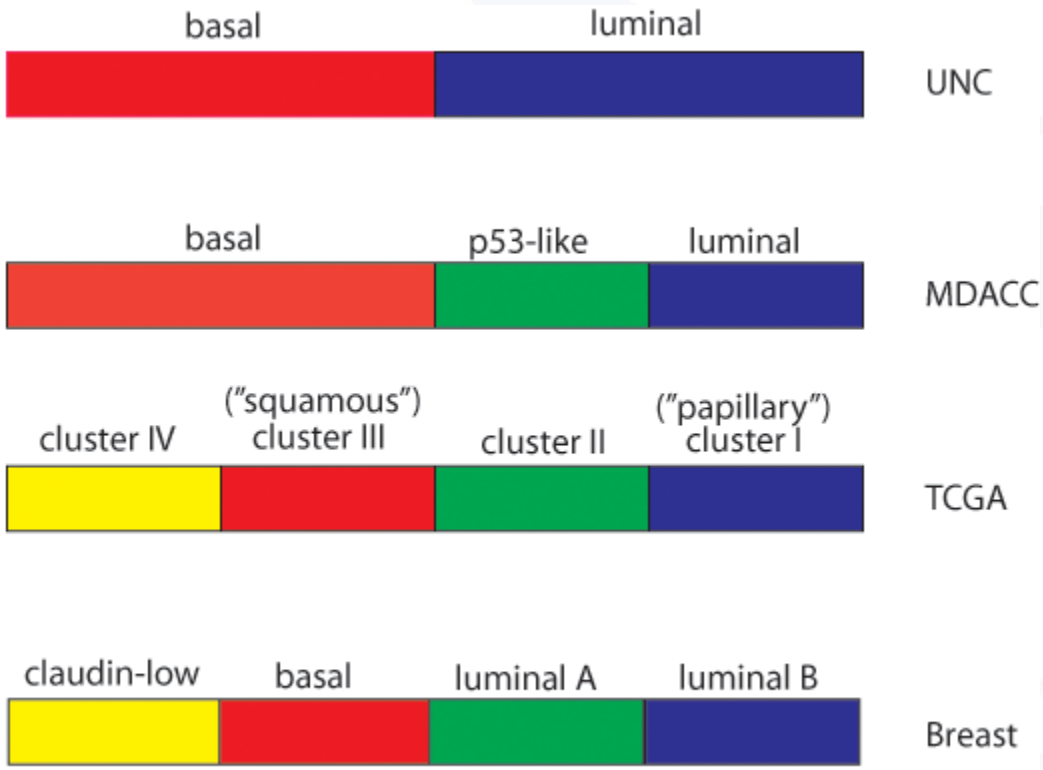
Red :Batch 2
Green: Batch 1

S1314: Primary Analysis

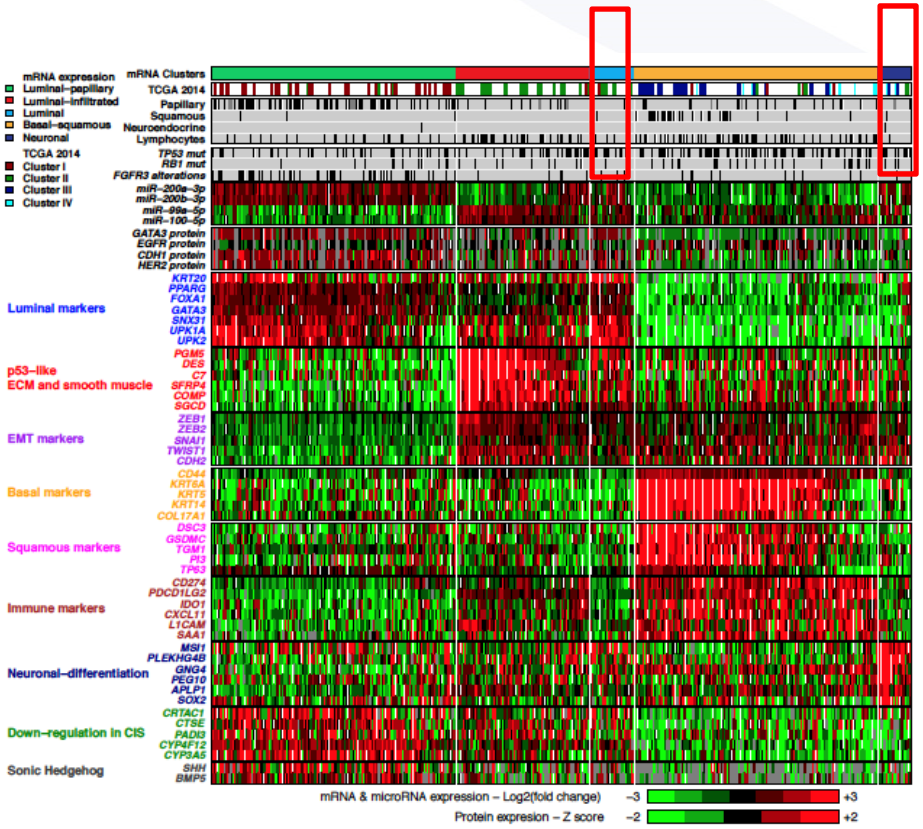
Coxen Score	Outcome	Arm	Number	Odds Ratio**	95% CI**	P-value**
GC*	**pT0**	**GC**	**82**	**2.63**	**(0.82, 8.36)**	**0.10**
GC*	≤pT1	GC	82	1.75	(0.60, 5.34)	0.30
ddMVAC*	pT0	ddMVAC	85	1.12	(0.42,2.95)	0.82
ddMVAC*	≤pT1	ddMVAC	85	0.92	(0.37, 2.27)	0.86
GC*	**≤pT1**	**Both**	**167**	**2.33**	**(1.11, 4.89)**	**0.02**
ddMVAC*	≤pT1	Both	167	0.90	(0.46, 1.75)	0.76
Moderate Spearman correlation between GC and MVAC Coxen scores: 0.39						

**** favorable based on prespecified algorithm and dichotomous cut point***

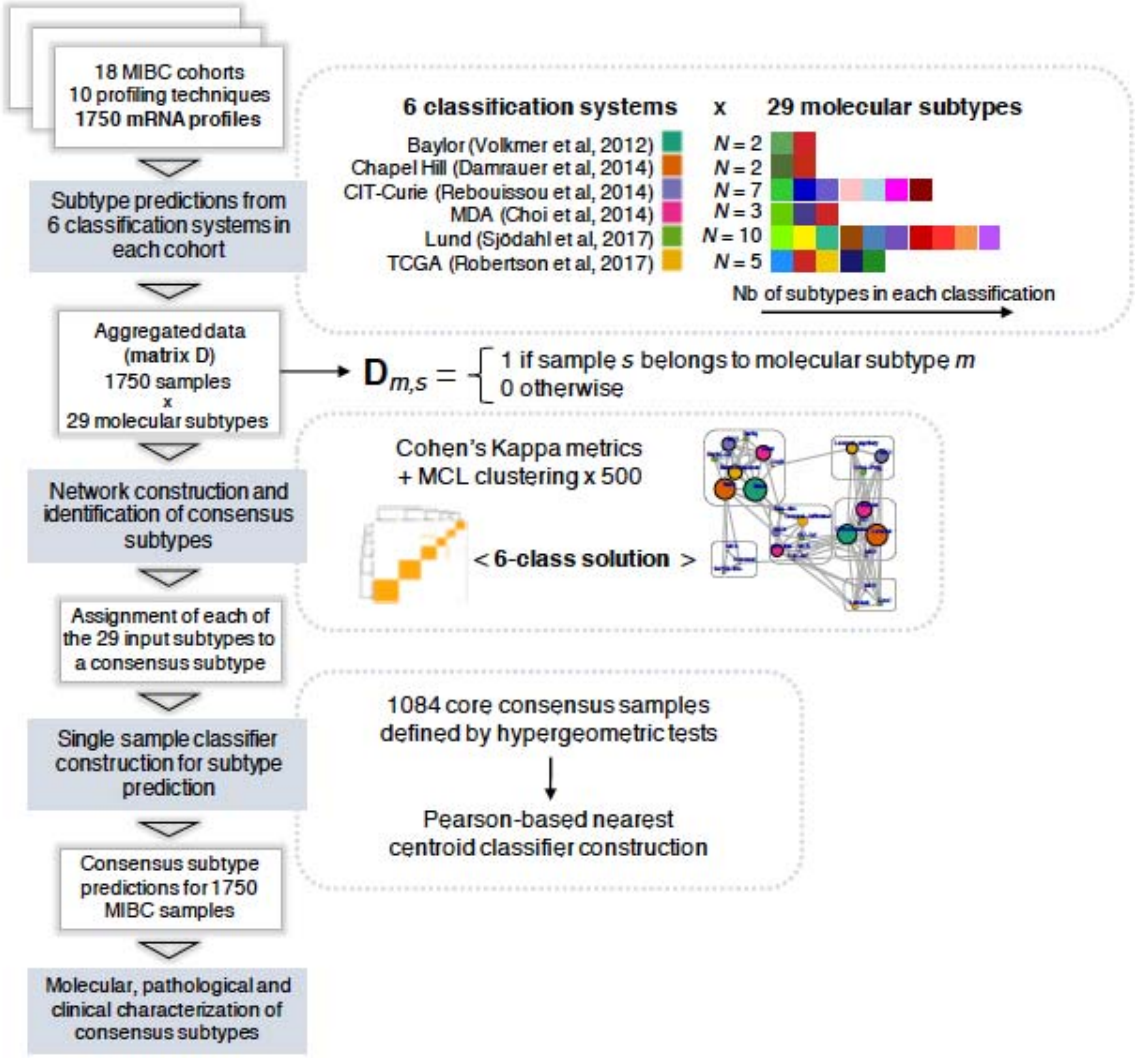
***** adjusted for two stratification factors – clinical stage at baseline (T2 vs T3, T4a), PS (0 vs 1)***

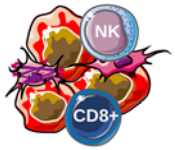

basal
luminal
UNC
basal
p53-like
luminal
MDACC
cluster IV
("squamous")
cluster III
cluster II
("papillary")
cluster I
TCGA
claudin-low
basal
luminal A
luminal B
Breast

TCGA final analyses: k = 5



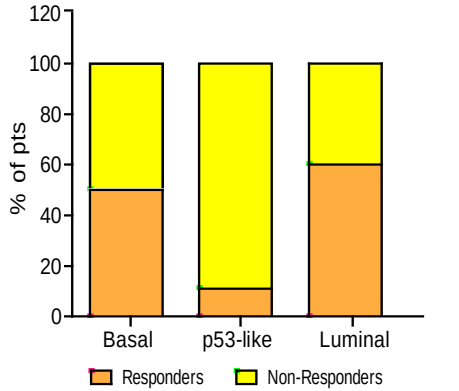
Cell, 2017

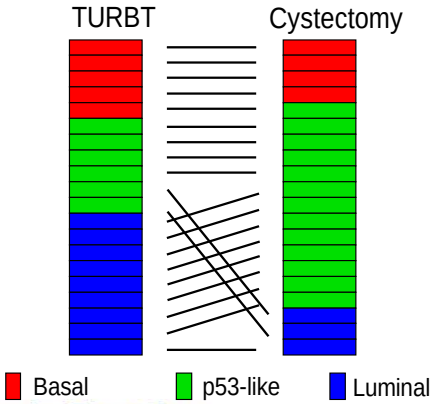

18 MIBC cohorts
10 profiling techniques
1750 mRNA profiles
Subtype predictions from 6 classification systems in each cohort
Aggregated data (matrix D)
1750 samples
x
29 molecular subtypes
Network construction and identification of consensus subtypes
Assignment of each of the 29 input subtypes to a consensus subtype
Single sample classifier construction for subtype prediction
Consensus subtype predictions for 1750 MIBC samples
Molecular, pathological and clinical characterization of consensus subtypes
6 classification systems x 29 molecular subtypes
Baylor (Volkmer et al, 2012) N = 2
Chapel Hill (Damrauer et al, 2014) N = 2
CIT-Curie (Rebouissou et al, 2014) N = 7
MDA (Choi et al, 2014) N = 3
Lund (Sjödahl et al, 2017) N = 10
TCGA (Robertson et al, 2017) N = 5
Nb of subtypes in each classification
$D_{m,s}$ = 1 if sample s belongs to molecular subtype m; 0 otherwise
Cohen's Kappa metrics
+ MCL clustering x 500
< 6-class solution >
1084 core consensus samples defined by hypergeometric tests
Pearson-based nearest centroid classifier construction

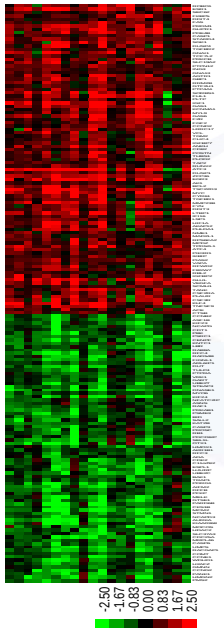
% of MIBC	24%	8%	15%	15%	35%	3%
Class Name	**Luminal Papillary (LumP)**	**Luminal Non-Specified (LumNS)**	**Luminal Unstable (LumU)**	**Stroma-rich**	**Basal/Squamous (Ba/Sq)**	**Neuroendocrine-like (NE-like)**
						
Differentiation	**Urothelial / Luminal**				**Basal**	**Neuroendocrine**
Oncogenic mechanisms	FGFR3 + PPARG + CDKN2A -	PPARG +	PPARG + E2F3 +, ERBB2 + Genomic instability Cell cycle +		EGFR +	TP53 -, RB1 -, Cell cycle +
Mutations	*FGFR3* (40%), *KDM6A* (38%)	*ELF3* (35%)	*TP53* (76%), *ERCC2* (22%) TMB +, APOBEC +		*TP53* (61%), *RB1* (25%)	*TP53* (94%) *RB1* (39%)*
Stromal infiltrate		Fibroblasts		Smooth muscle Fibroblasts Myofibroblasts	Fibroblasts Myofibroblasts	
Immune infiltrate				B cells	CD8 T cells NK cells	
Histology	Papillary morphology (59%)	Micropapillary variant (36%)			Squamous differentiation (42%)	Neuroendocrine differentiation (72%)
Clinical	T2 stage +	Older patients + (80+)			Women + T3/T4 stage +	
Median overall survival (years)	4	1.8	2.9	3.8	1.2	1

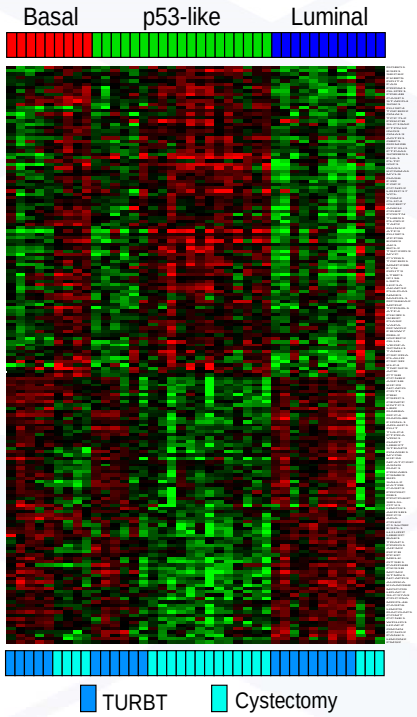
* 94% of these tumors present either RB1 mutation or deletion

Relationship between subtype membership and NAC response

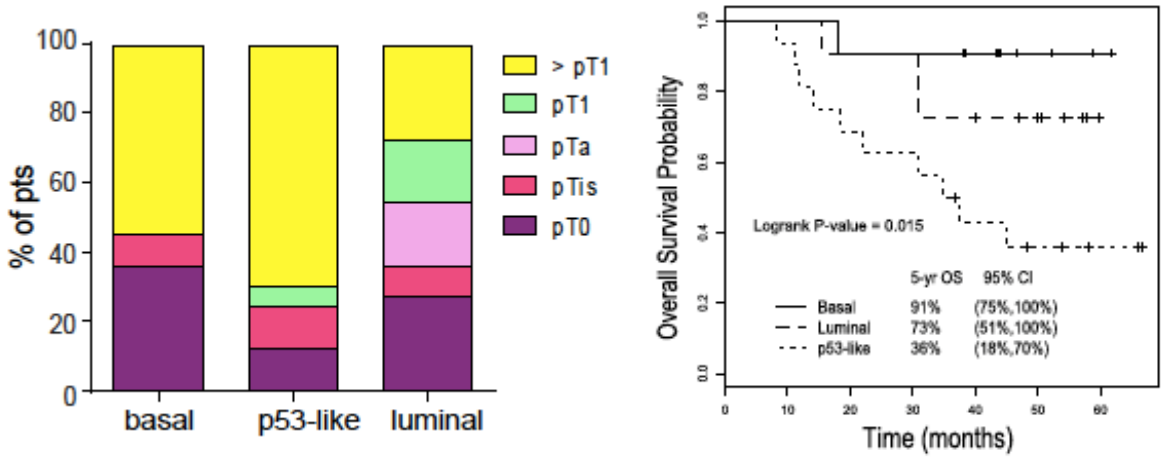






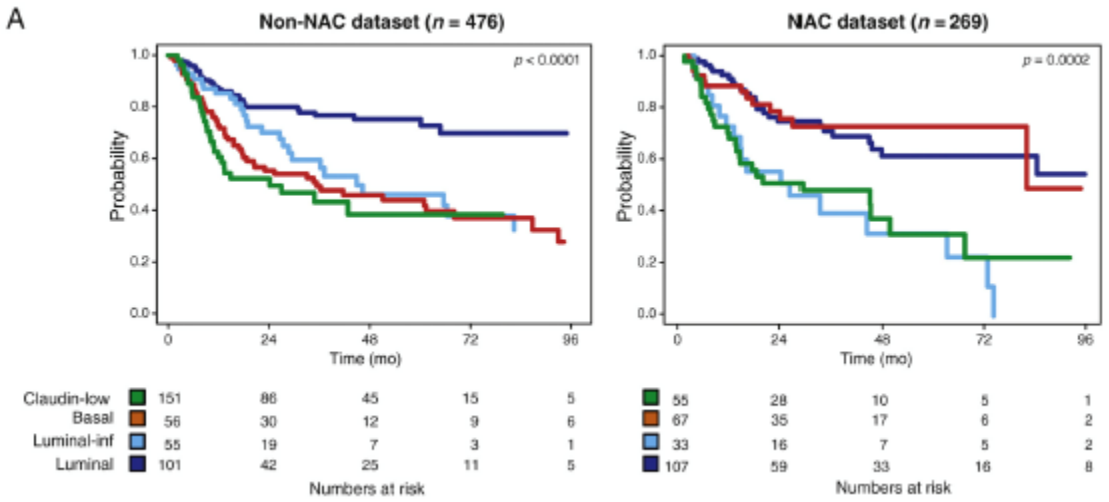


Molecular subtypes: prognostic for survival



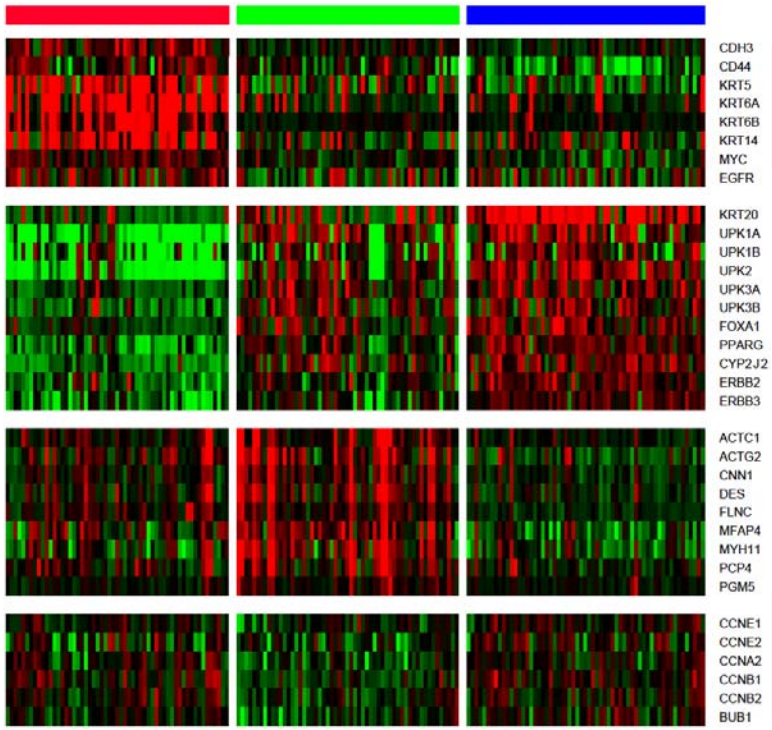
Siefker-Radtke, Eur Urol 2016

Basal tumors and NAC benefit



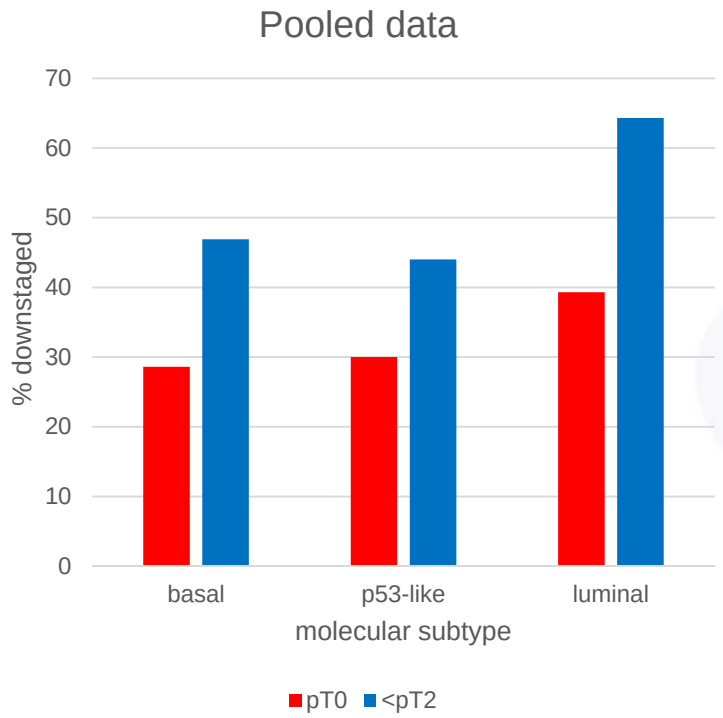
Seiler et al, Eur Urol 2017

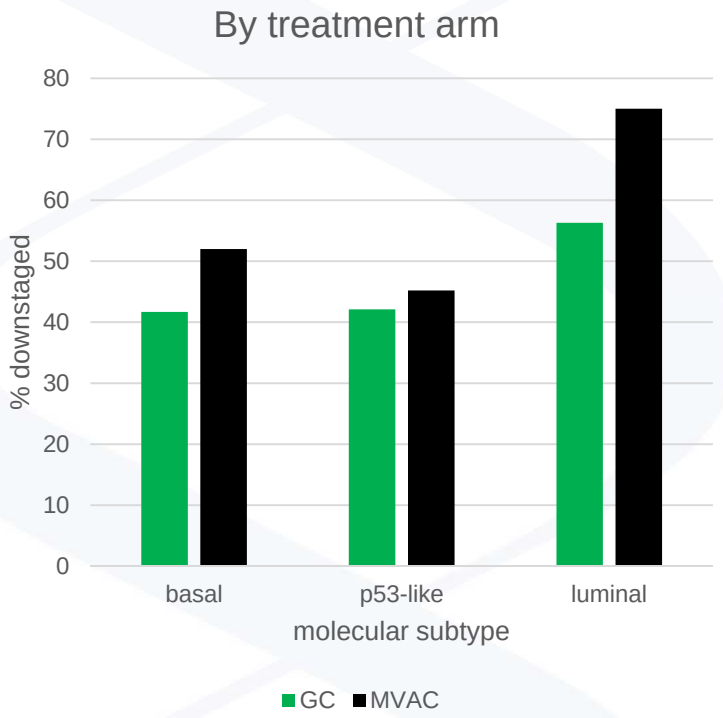
MD Anderson subtypes in S1314



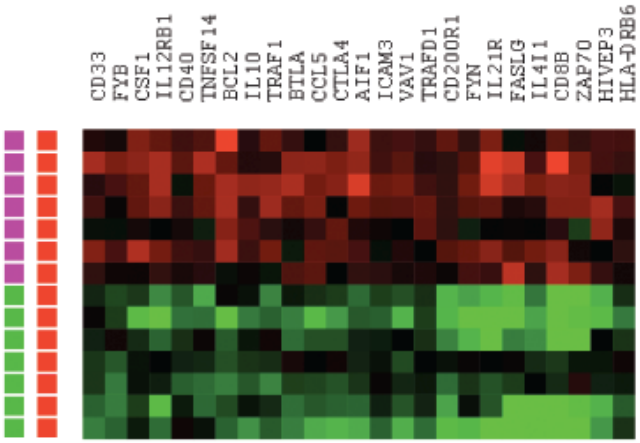
oneNN subtype assignments

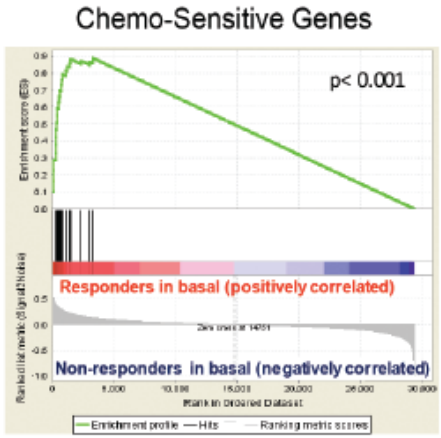
Relationship with downstaging





MVAC-sensitive basal tumors were infiltrated with lymphocytes





Future plans

- Train a CoXEN classifier on cisplatin alone, and reapply to the S1314 dataset
- Apply the other molecular subtyping algorithms to the Affy dataset and correlate with downstaging
- Use the leftover RNA at MDACC to perform RNAseq (Theodorescu)
- *Correlate molecular subtype membership with survival (18-24 months from now)*
- *ctDNA?*

RESEARCH ARTICLE

Somatic *ERCC2* Mutations Correlate with Cisplatin Sensitivity in Muscle-Invasive Urothelial Carcinoma

Eliezer M. Van Allen[1,2], Kent W. Mouw[3,4], Philip Kim[5], Gopa Iyer[6,7], Nikhil Wagle[1,2], Hikmat Al-Ahmadie[6,8], Cong Zhu[2], Irina Ostrovnaya[9], Gregory V. Kryukov[2], Kevin W. O'Connor[3], John Sfakianos[5], Ilana Garcia-Grossman[7], Jaegil Kim[2], Elizabeth A. Guancial[10], Richard Bambury[7], Samira Bahl[2], Namrata Gupta[2], Deborah Farlow[2], Angela Qu[1], Sabina Signoretti[11], Justine A. Barletta[11], Victor Reuter[6,8], Jesse Boehm[2], Michael Lawrence[2], Gad Getz[2,12], Philip Kantoff[1], Bernard H. Bochner[5,6], Toni K. Choueiri[1], Dean F. Bajorin[6,7], David B. Solit[6,7,13], Stacey Gabriel[1], Alan D'Andrea[3,4], Levi A. Garraway[1,2], and Jonathan E. Rosenberg[6,7]

EUROPEAN UROLOGY 68 (2015) 959–967

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Bladder Cancer

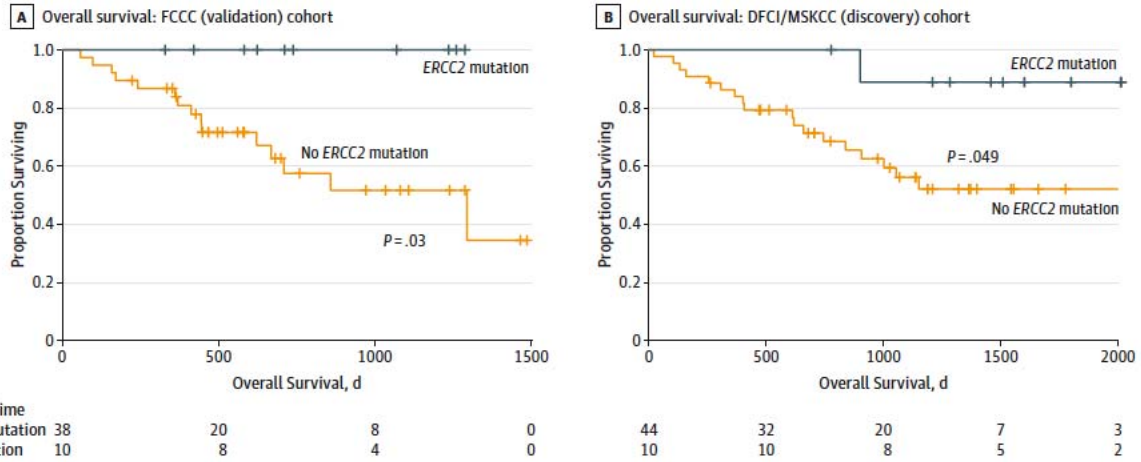
Editorial by Cyrill A. Rentsch, Frank Stenner, Christian Ruiz and Lukas Bubendorf on pp. 968–969 of this issue

Defects in DNA Repair Genes Predict Response to Neoadjuvant Cisplatin-based Chemotherapy in Muscle-invasive Bladder Cancer

Elizabeth R. Plimack[a,], Roland L. Dunbrack[a], Timothy A. Brennan[b], Mark D. Andrake[a], Yan Zhou[a], Ilya G. Serebriiskii[a], Michael Slifker[a], Katherine Alpaugh[a], Essel Dulaimi[a], Norma Palma[b], Jean Hoffman-Censits[c], Marijo Bilusic[a], Yu-Ning Wong[a], Alexander Kutikov[a], Rosalia Viterbo[a], Richard E. Greenberg[a], David Y.T. Chen[a], Costas D. Lallas[c], Edouard J. Trabulsi[c], Roman Yelensky[b], David J. McConkey[d], Vincent A. Miller[b], Erica A. Golemis[a], Eric A. Ross[a]*

[a] *Fox Chase Cancer Center, Philadelphia, PA, USA;* [b] *Foundation Medicine Inc., Cambridge, MA, USA;* [c] *Thomas Jefferson University Hospital, Philadelphia, PA, USA;* [d] *MD Anderson Cancer Center, Houston, TX, USA*

Figure. Overall Survival With and Without Somatic *ERCC2* Mutations

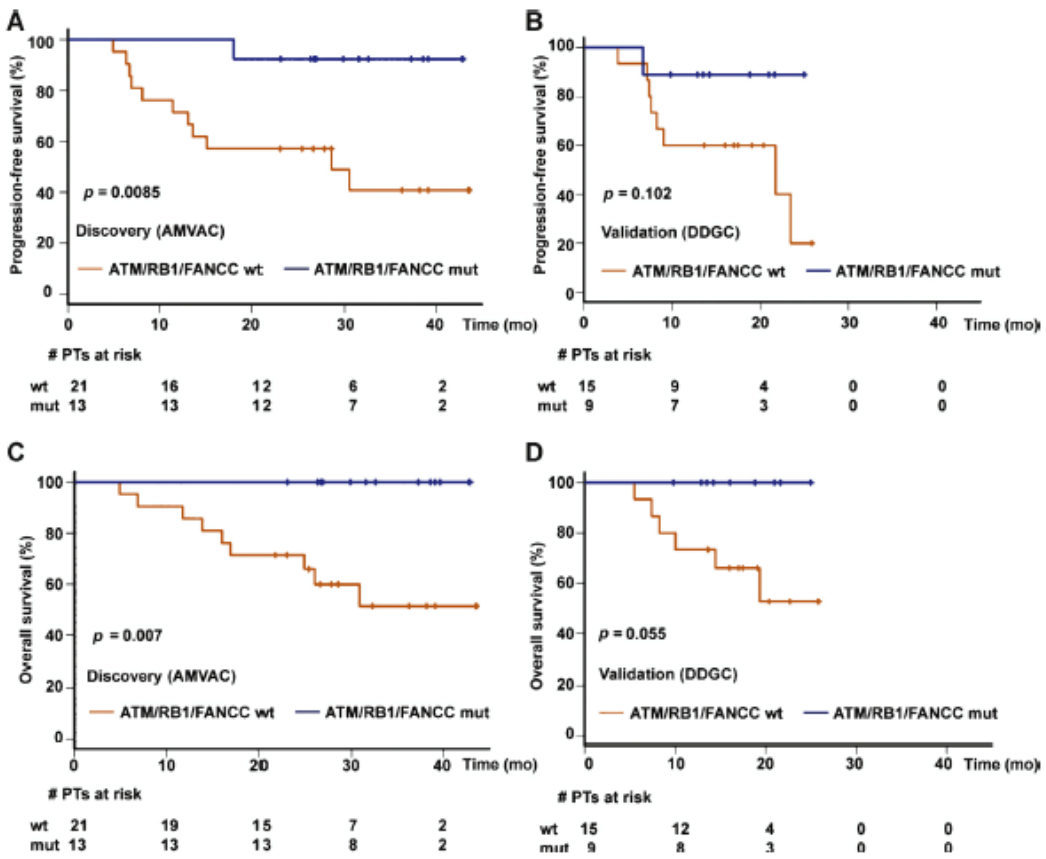


No. at risk by time

No *ERCC2* mutation	38	20	8	0	44	32	20	7	3
ERCC2 mutation	10	8	4	0	10	10	8	5	2

A, Overall survival with and without somatic *ERCC2* mutations in the current (Fox Chase Cancer Center [FCCC]) validation cohort. Kaplan-Meier analysis of overall survival by the presence or absence of a somatic *ERCC2* mutation. There is a statistically significant difference in survival (log-rank test; $P = .03$).
B, Overall survival with and without somatic *ERCC2* mutations in a previously reported[1] (Dana Farber Cancer Institute and Memorial Sloan Kettering Cancer Center [DFCI/MSKCC] combined) discovery cohort. Kaplan-Meier analysis of overall survival by the presence or absence of a somatic *ERCC2* mutation. There is a statistically significant difference in survival, log-rank test ($P = .049$).

David Liu, MD, MPH, MS
Elizabeth R. Plimack, MD, MS
Jean Hoffman-Censits, MD
Levi A. Garraway, MD, PhD
Joaquim Bellmunt, MD, PhD
Eliezer Van Allen, MD
Jonathan E. Rosenberg, MD


A
Progression-free survival (%)
100
80
60
40
20
0
p = 0.0085
Discovery (AMVAC)
ATM/RB1/FANCC wt
ATM/RB1/FANCC mut
0
10
20
30
40
Time (mo)
PTs at risk
wt 21 16 12 6 2
mut 13 13 12 7 2
B
Progression-free survival (%)
p = 0.102
Validation (DDGC)
ATM/RB1/FANCC wt
ATM/RB1/FANCC mut
Time (mo)
PTs at risk
wt 15 9 4 0 0
mut 9 7 3 0 0
C
Overall survival (%)
p = 0.007
Discovery (AMVAC)
ATM/RB1/FANCC wt
ATM/RB1/FANCC mut
Time (mo)
PTs at risk
wt 21 19 15 7 2
mut 13 13 13 8 2
D
Overall survival (%)
p = 0.055
Validation (DDGC)
ATM/RB1/FANCC wt
ATM/RB1/FANCC mut
Time (mo)
PTs at risk
wt 15 12 4 0 0

Ongoing studies

- Amendment to allow panel DNA exome sequencing (MSK IMPACT and Caris) was approved
- BISQFP funding is in place for MSK IMPACT
- DNA from MDACC will be sent to MSK
- Germline DNA will be isolated at MSKCC and shared with Peter O'Donnell
- Correlate ctDNA and CTCs with path responses and outcomes (Goldkorn, R01)

For the future

- Public Affy and Illumina RNAseq datasets
- Residual ALMAC RNA
- 5x unstained slides
- Urine
- Post-treatment tumors

The SWOG S1314 team

Tom Flaig (Colorado)
Cathy Tangen (FHCRC)
Melissa Plets (FHCRC)
Dan Theodorescu (Cedars-Sinai)
Dan Gustafson (Colorado State)
Scott Lucia (Colorado)
Seth Lerner (Baylor)
Amir Goldkorn (USC)
Colin Dinney (MDACC)

Woonyoung Choi (JHMI)
I-Ling Lee (MDACC)
Megan Fong (JHMI)
Sia Daneshmand (USC)
Aijai Alva (Michigan)
Matt Milowski (UNC)
Gary MacVicar (Illinois CancerCare)
Bruno Bastos (Baptist Health)
Ian Thompson (San Antonio)