S1314 Correlative analysis of ATM, RB1, ERCC2 and FANCC mutations and pathologic complete response after neoadjuvant chemotherapy (NAC) in patients with muscle invasive bladder cancer (MIBC)

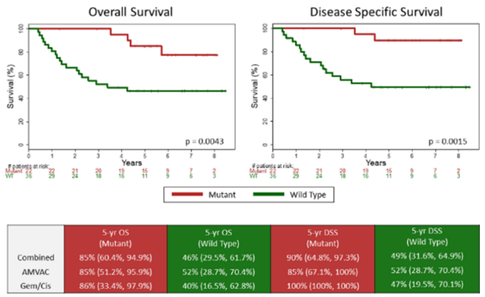
Elizabeth R. Plimack, Catherine Tangen, Melissa Plets, Rutika Kokate, Joanne Xiu, Chadi Nabhan, Eric A. Ross, Erin Grundy, Woonyoung Choi, Colin P.N. Dinney, I-Ling C. Lee, Scott Lucia, Thomas W. Flaig, David James McConkey

Fox Chase Cancer Center, Philadelphia, PA; Fred Hutchinson Cancer Research Center, Seattle, WA; SWOG Statistics and Data Management Center, Seattle, WA; Caris Life Sciences, Phoenix, AZ; Nationwide Children's Hospital, Columbus, OH; Johns Hopkins Greenberg Bladder Cancer Institute, Baltimore MD; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Colorado, Denver, CO; University of Colorado Cancer Center, Aurora, CO

Abstract 4581

BACKGROUND

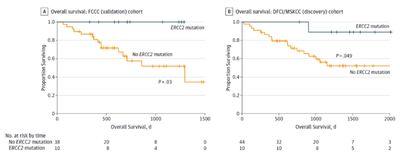
We previously reported that MIBC harboring mutations in one or more of ***ATM, RB1*** **or** ***FANCC*** is exquisitely responsive to platinum based NAC, resulting in a high rate of pathologic complete response (pT0) and excellent OS and DFS after surgery.



	5-yr OS (Mutant)	5-yr OS (Wild Type)	5-yr DSS (Mutant)	5-yr DSS (Wild Type)
Combined	85% (60.4%, 94.9%)	46% (29.5%, 61.7%)	90% (64.8%, 97.3%)	49% (31.6%, 64.9%)
AMVAC	85% (51.2%, 95.9%)	52% (28.7%, 70.4%)	85% (67.1%, 100%)	52% (28.7%, 70.4%)
Gem/Cis	86% (33.4%, 97.9%)	40% (16.5%, 62.8%)	100% (100%, 100%)	47% (19.5%, 70.1%)

Miron et al. European Urology 2019

Collaboration w DFCI/Broad validated another predictive marker: ***ERCC2***



ERCC2	n	Sensitivity for response	Specificity for response	PPV for response	NPV for response
Discovery: MSKCC DFCI	50	36%	100%	100%	61%
Validation: Philadelphia (DDGC+AMVAC)	48	80%	93%	80%	93%

Liu, et al. JAMA Onc 2016

HYPOTHESIS

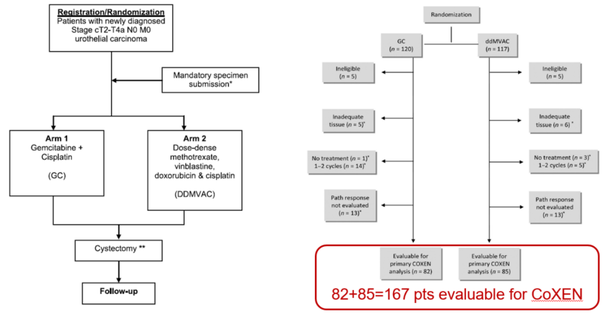
Alterations in ***ATM, RB1, FANCC*** **or** ***ERCC2*** will predict PT0 when applied to the cohorts in the S1314 trial.

SWOG 1314

SWOG S1314 (NCT02177695) was designed to validate the CoXEN classifier as a predictive biomarker in pts undergoing cystectomy after NAC.

Eligibility for S1314 included cT2-T4a N0 M0 MIBC, cisplatin eligible, with plan for cystectomy.

We repurposed banked DNA samples and prospective trial data from S1314 to further validate the ability of the 4 gene signature (any mutation in *ATM*, *RB1*, *FANCC*, *ERCC2)* to predict pT0.



Flaig et al. Clinical Cancer Research 2021

METHODS

Of 167 pts evaluable for the original CoXEN analysis adequate banked DNA was available for **105**.

Next-generation sequencing using the CARIS 592 Gene Panel (Caris Life Sciences, Phoenix, AZ) was pe

Pathogenic mutation or VUS of *ATM*, *RB1*, *FANCC* or *ERCC2* was noted as present or absent for each patient and correlated with pT0 using logistic regression, adjusting for clinical stage.

RESULTS

Patients with a mutation in *ATM*, *RB1*, or *ERCC2* have a statistically significantly higher odds (2-sided p=0.0006) of a pathologic complete response (pT0) at cystectomy after neoadjuvant chemotherapy with GC or DDMVAC compared to those who do not have any variant

Gene	Variant?	N (%) with pT0	Odds ratio (95% CI)*	2-sided p-value*
ATM	Yes	14/25 (56%)	4.23 (1.60, 11.2)	0.004
	No	20/80 (25%)		
ERCC2	Yes	12/18 (67%)	5.47 (1.80, 16.6)	0.003
	No	22/87 (25%)		
FANCC	Yes	0/4 (0%)	Too few variants	
	No	34/101 (34%)		
RB1	Yes	12/25 (48%)	2.31 (0.91, 5.86)	0.079
	No	22/80 (28%)		
Any Mutation	Yes	27/56 (48%)	5.36 (2.05, 14.02)	0.0006
	No	7/49 (14%)		

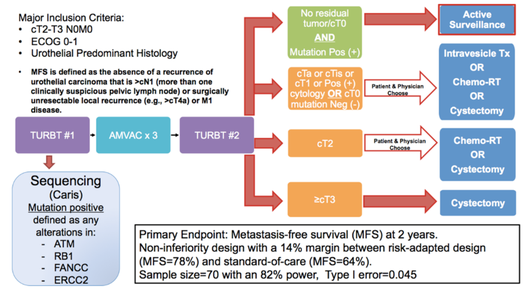
* adjusted for stratification factor T2 vs. T3-4a

No FANCC mutations were noted in this analysis and only one in RETAIN I, therefore due to low prevalence, *FANCC* was dropped from the RETAIN 2 signature.

ONGOING TRIALS

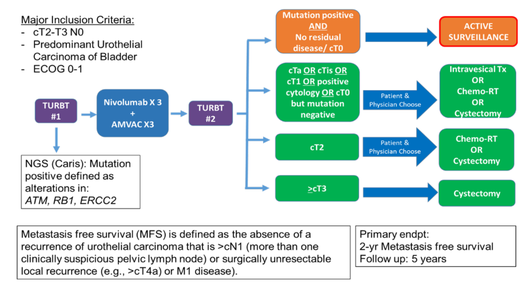
Can alterations in *ATM*, *RB1* or *ERCC2* [the RETAIN 2 signature] predict pT0 after NAC and allow patients to keep their native bladder with close surveillance?

RETAIN I: completed



PI Dan Geynisman: NCT02710734

RETAIN II: enrolling at FCCC and Jefferson



PI Pooja Ghatalia: NCT04506554

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