Liquid biopsies in genitourinary cancers

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Learning objectives

- Describe tumor-informed and tumor-agnostic ”liquid biopsies”
- Contrast their current roles in renal, prostate, and urothelial cancers
- Explain what is meant by urothelial “field cancerization” and its implications for urine-based assays

What is a “liquid biopsy”?

- Any test that measures tumor properties in a body fluid
- Most effort has been invested in optimizing methods for measuring cell-free tumor DNA in plasma
- Other emerging examples include analyses of cerebral spinal fluid and urine

Approach

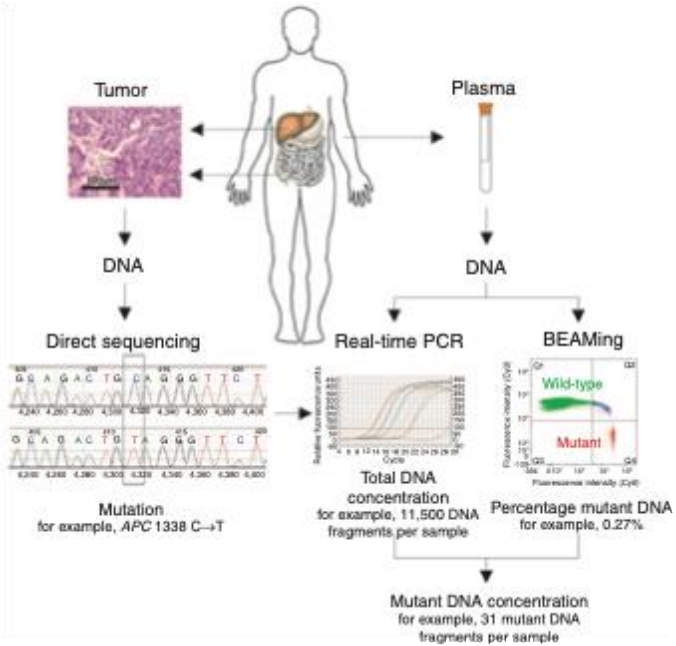
- Body fluids are usually collected into vessels that contain special preservatives
- Example: Streck tubes for collecting plasma
- DNA is then extracted from the fluid and sequenced using special platforms that are designed to dramatically reduce sequencing error rates

nature medicine

Circulating mutant DNA to assess tumor dynamics

Frank Diehl[1,5], Kerstin Schmidt[1,5], Michael A Choti[2], Katharine Romans[1], Steven Goodman[3], Meng Li[1], Katherine Thornton[1], Nishant Agrawal[1], Lori Sokoll[4], Steve A Szabo[1], Kenneth W Kinzler[1], Bert Vogelstein[1] & Luis A Diaz Jr[1]

"BEAMing"



Detection and quantification of rare mutations with massively parallel sequencing

Isaac Kinde, Jian Wu, Nick Papadopoulos, Kenneth W. Kinzler[1], and Bert Vogelstein[1]

The Ludwig Center for Cancer Genetics and Therapeutics and The Howard Hughes Medical Institute, Johns Hopkins Kimmel Cancer Center, Baltimore, MD 21231

Contributed by Bert Vogelstein, April 19, 2011 (sent for review March 21, 2011)

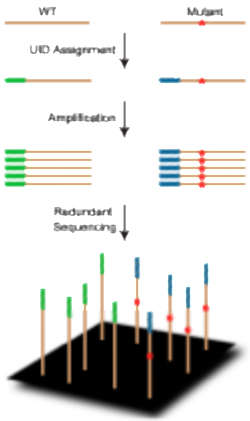


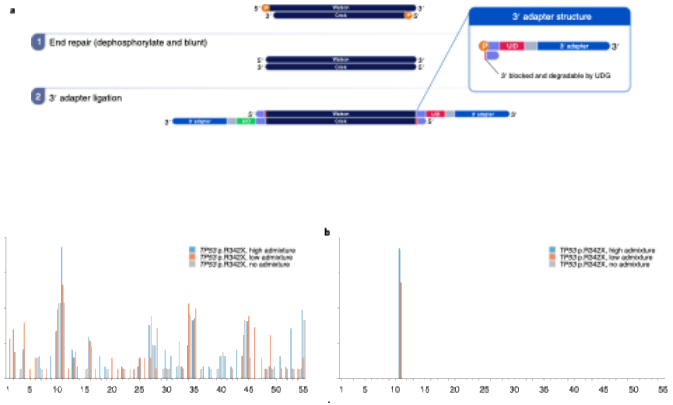
Fig. 1. Essential elements of Safe-SeqS. In the first step, each fragment to be analyzed is assigned a unique identification (UID) DNA sequence (green or blue bars). In the second step, the uniquely tagged fragments are amplified, producing UID families, each member of which has the same UID. A supermutant is defined as a UID family in which ≥95% of family members have the same mutation.

Safe-Sequencing System
"Safe-seqS" (2011)

LETTERS
https://doi.org/10.1038/s41587-021-00900-z
nature biotechnology

Detection of low-frequency DNA variants by targeted sequencing of the Watson and Crick strands

Joshua D. Cohen[1,2,3,4,5], Christopher Douville[1,2,3,4], Jonathan C. Dudley[1,2,3,4], Brian J. Mog[1,2,3,4,5], Maria Popoli[1,2,3,4], Janine Ptak[1,2,3,4], Lisa Dobbyn[1,2,3], Natalie Silliman[1,2,3,4], Joy Schaefer[1,2,3], Jeanne Tie[6,7,8,9], Peter Gibbs[6,8,9], Cristian Tomasetti[2,10], Nickolas Papadopoulos[1,2,3]✉, Kenneth W. Kinzler[1,2,3]✉ and Bert Vogelstein[1,2,3,4]✉



"SaferSeq-S" (2021)

Tumor-informed versus tumor-agnostic

- Tumor-informed assays use data obtained by sequencing tumor tissue to design custom assays – powerful tools for detection of minimal residual disease (MRD)
- Tumor-agnostic assays – panels of genes that are commonly mutated in cancers – useful in selection of targeted therapies
- *Need to filter out mutations due to clonal hematopoiesis (CH).*

Liquid biopsies in prostate, renal, and urothelial cancers

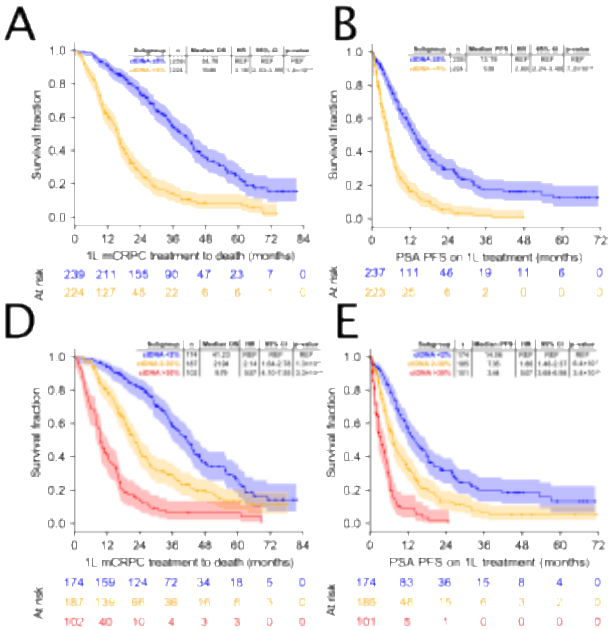
- Prostate cancer: PSA is already a powerful biomarker, and PSMA-PET is a sensitive tool for detection of metastasis; current role is for selection of patients for PARPi's
- Renal cancer: mutations are less prevalent; tests measuring methylated DNA may be more sensitive

nature communications

Article

https://doi.org/10.1038/s41467-024-45475-w

Prediction of plasma ctDNA fraction and prognostic implications of liquid biopsy in advanced prostate cancer



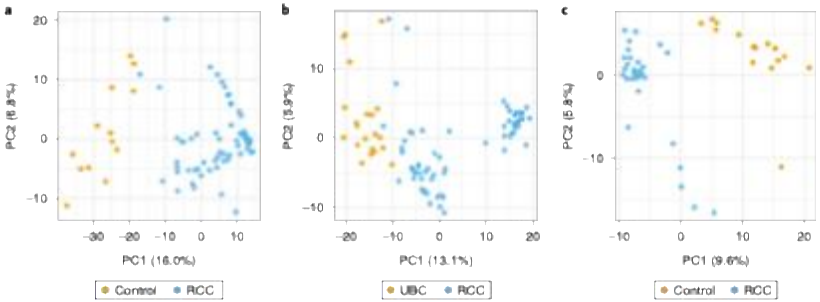
nature medicine

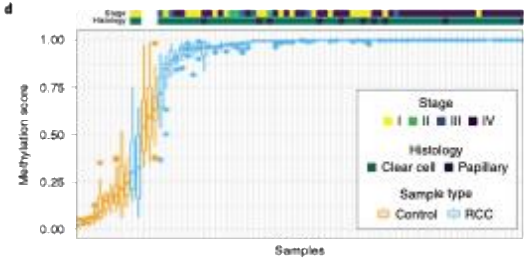
BRIEF COMMUNICATION

https://doi.org/10.1038/s41591-020-0933-1

Detection of renal cell carcinoma using plasma and urine cell-free DNA methylomes

Pier Vitale Nuzzo[1,2,3,16], Jacob E. Berchuck[1,2,16], Keegan Korthauer[4,5,16], Sandor Spisak[2,16], Amin H. Nassar[1,2], Sarah Abou Alaiwi[1,2], Ankur Chakravarthy[6], Shu Yi Shen[6], Ziad Bakouny[1], Francesco Boccardo[3,7], John Steinharter[1], Gabrielle Bouchard[1], Catherine R. Curran[1], Wenting Pan[1], Sylvan C. Baca[1,2,8], Ji-Heui Seo[1,2], Gwo-Shu Mary Lee[1,2], M. Dror Michaelson[9], Steven L. Chang[10], Sushrut S. Waikar[11,12], Guru Sonpavde[1], Rafael A. Irizarry[13,14], Mark Pomerantz[1,2], Daniel D. De Carvalho[6,15,17], Toni K. Choueiri[1,8,17 ✉] and Matthew L. Freedman[1,2,8,17 ✉]





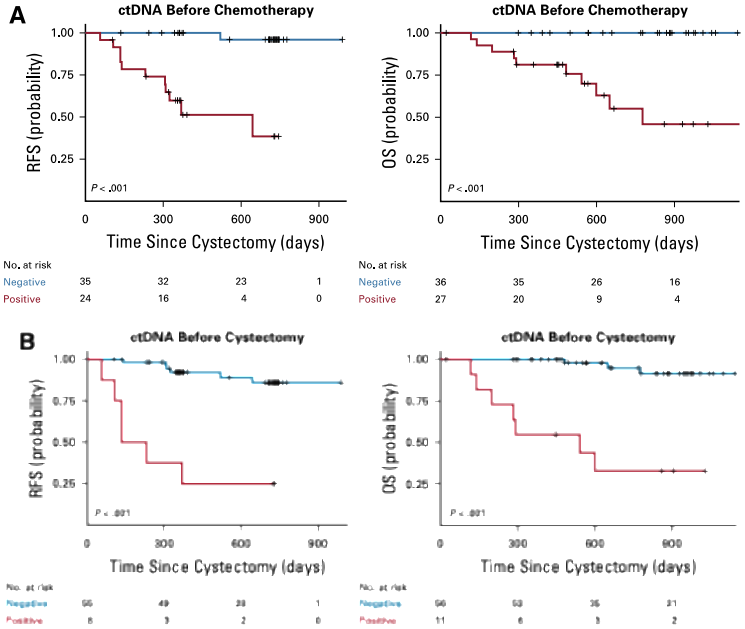
Liquid biopsies and urothelial cancer

- Plasma ctDNA: sensitive detection of subclinical metastatic disease, may inform the use of adjuvant therapy
- Urine tumor DNA (utDNA): sensitive detection of local disease burden, may inform the use of adjuvant therapies and bladder preservation

original report

Early Detection of Metastatic Relapse and Monitoring of Therapeutic Efficacy by Ultra-Deep Sequencing of Plasma Cell-Free DNA in Patients With Urothelial Bladder Carcinoma

Emil Christensen, PhD[1]; Karin Birkenkamp-Demtröder, PhD[1]; Himanshu Sethi, MPH[2]; Svetlana Shchegrova, PhD[2]; Raheleh Salari, PhD[2]; Iver Nordentoft, PhD[1]; Hsin-Ta Wu, PhD[2]; Michael Knudsen, PhD[1]; Philippe Lamy, PhD[1]; Sia Viborg Lindskrog, BS[1]; Ann Taber, MD[1]; Mustafa Balcioglu, PhD[2]; Søren Vang, PhD[1]; Zoe Assaf, PhD[2]; Shruti Sharma, PhD[2]; Antony S. Tin, PhD[2]; Ramya Srinivasan, MS[2]; Dina Hafez, PhD[2]; Thomas Reinert, PhD[1]; Samantha Navarro, BS[2]; Alexander Olson, BS[2]; Rosalyn Ram, PhD[2]; Scott Dashner, BS[2]; Matthew Rabinowitz, PhD[2]; Paul Billings, MD, PhD[2]; Styrmir Sigurjonsson, PhD[2]; Claus Lindbjerg Andersen, PhD[1]; Ryan Swenerton, PhD[2]; Alexey Aleshin, MD[2]; Bernhard Zimmermann, PhD[2]; Mads Agerbæk, MD[1]; Cheng-Ho Jimmy Lin, MD, PhD, MHS[2]; Jørgen Bjerggaard Jensen, MD, DMSc[1,3]; and Lars Dyrskjøt, PhD[1,3]



Article

ctDNA guiding adjuvant immunotherapy in urothelial carcinoma

https://doi.org/10.1038/s41586-021-03642-9

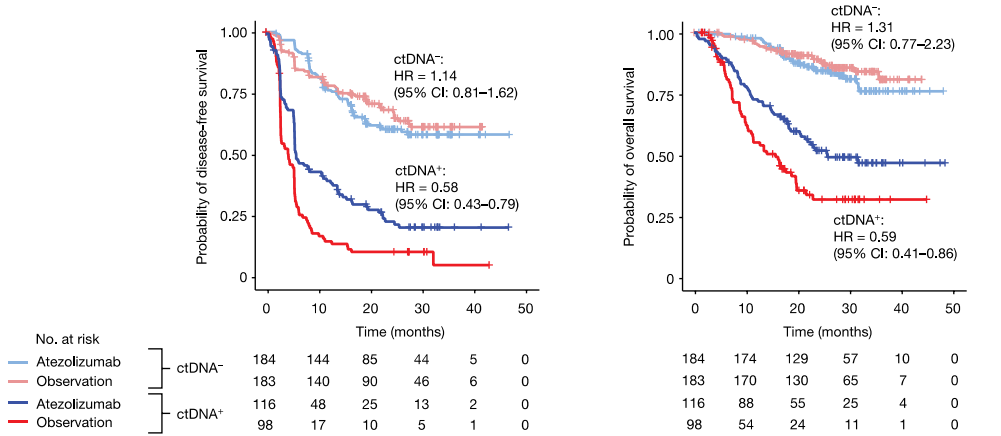
Received: 8 December 2020

Accepted: 13 May 2021

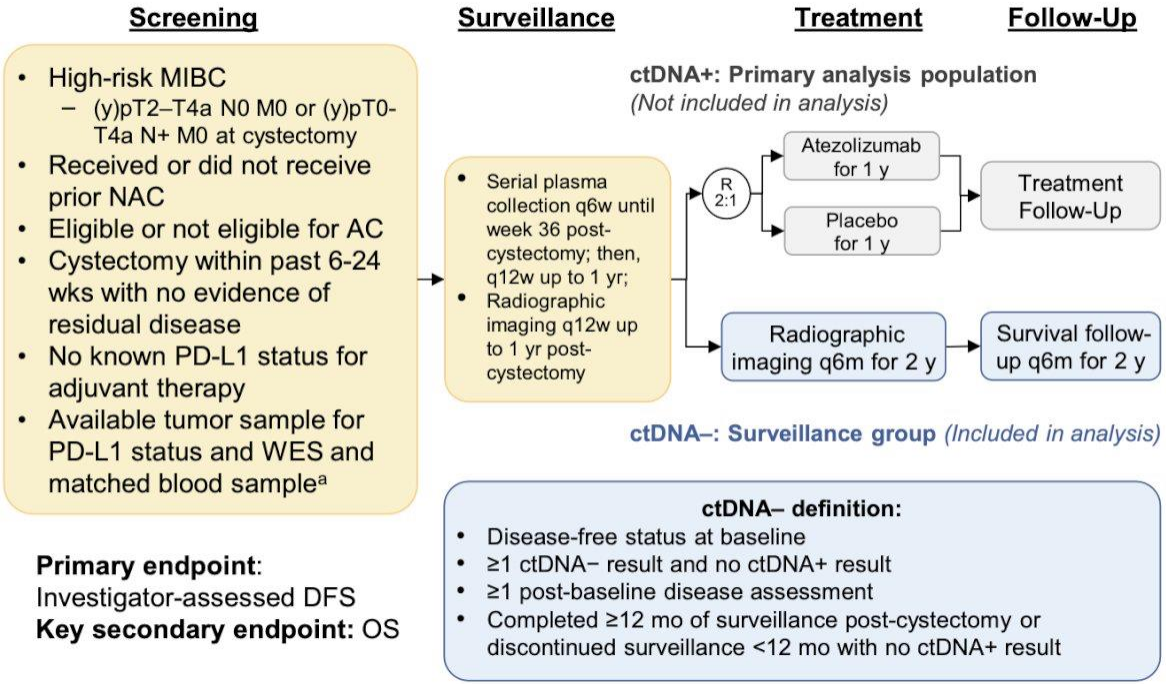
Published online: 16 June 2021

Check for updates

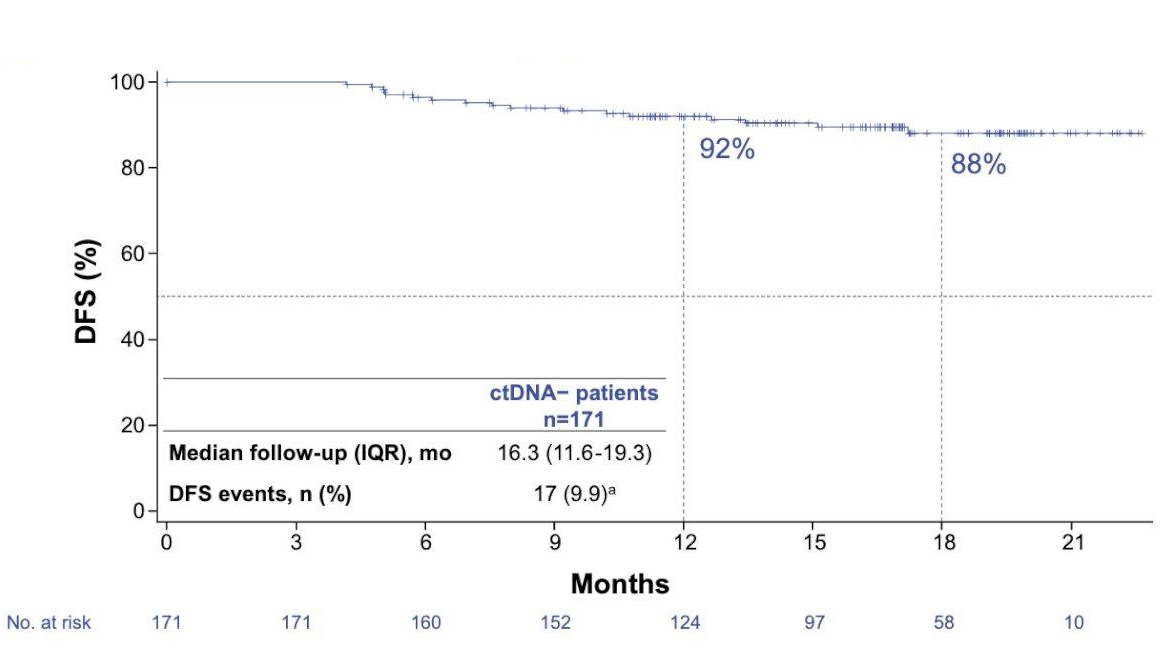
Thomas Powles[1,18]✉, Zoe June Assaf[2,18], Nicole Davarpanah[2], Romain Banchereau[2], Bernadett E. Szabados[3], Kobe C. Yuen[2], Petros Grivas[4,5,6], Maha Hussain[7], Stephane Oudard[8], Jürgen E. Gschwend[9], Peter Albers[10], Daniel Castellano[11], Hiroyuki Nishiyama[12], Siamak Daneshmand[13], Shruti Sharma[14], Bernhard G. Zimmermann[14], Himanshu Sethi[14], Alexey Aleshin[14], Maurizio Perdicchio[15], Jingbin Zhang[16], David S. Shames[2], Viraj Degaonkar[2], Xiaodong Shen[2], Corey Carter[2], Carlos Bais[2], Joaquim Bellmunt[17,19] & Sanjeev Mariathasan[2,19]✉



IMvigor011: using ctDNA to inform adjuvant therapy



Disease-free survival in ctDNA-negative patients



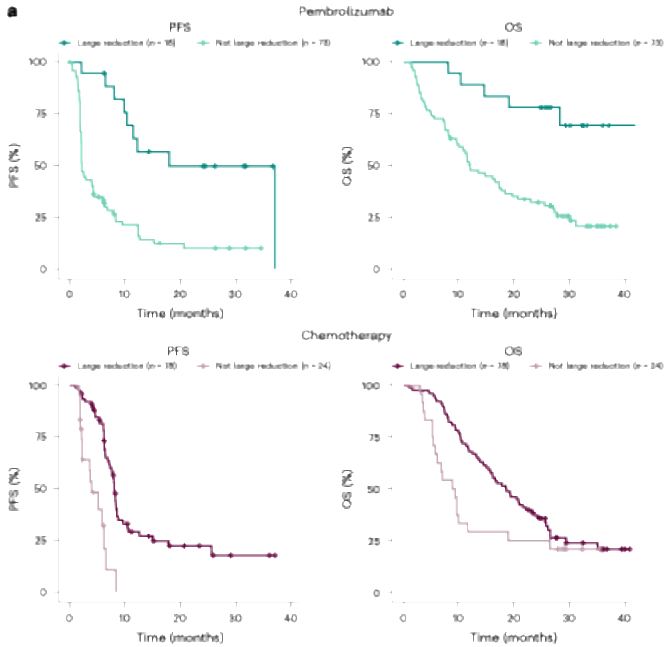
Deeper but less durable ctDNA responses with chemotherapy

nature medicine

Article

https://doi.org/10.1038/s41591-024-03091-7

Pembrolizumab for advanced urothelial carcinoma: exploratory ctDNA biomarker analyses of the KEYNOTE-361 phase 3 trial



Adjuvant therapy for high-risk NMIBC

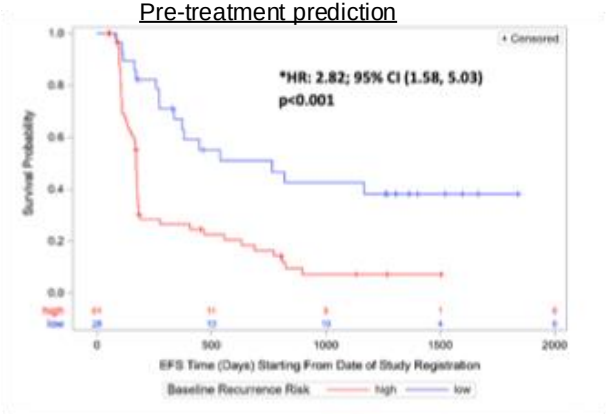
- Gemcitabine/docetaxel
- Immune checkpoint inhibitors
- IL-15 super agonist (N-803, Nogapendekin alfa inbakicept)
- Ad-IFNα gene therapy (nadofaragene firadenovec)
- Oncolytic adenovirus expressing GM-CSF (cretostimogene grenadenorepvec)

utDNA guiding use of adjuvant therapy for NMIBC

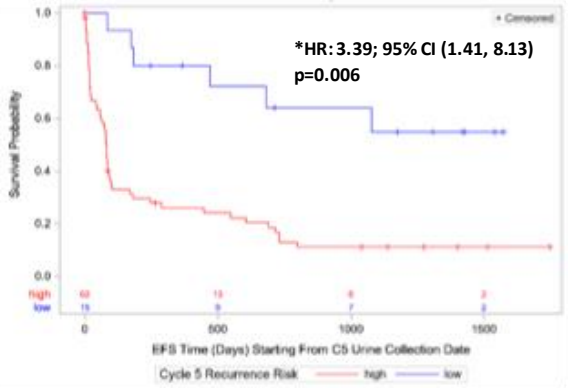
- Collaboration between SWOG and Convergent Genomics, Inc. (Trevor Levin)
- Have completed blinded analyses of longitudinal urine collections from two different Phase 2 clinical trials – S1605 (atezolizumab) and nadofaragene firadenovec
- Phase 3 trials of BCG (S1602) and nadofaragene firadenovec planned later this year

S1605: MRD is predictive of response and identifies molecular responders through longitudinal testing

Pre-treatment prediction



Post-treatment prognostic response



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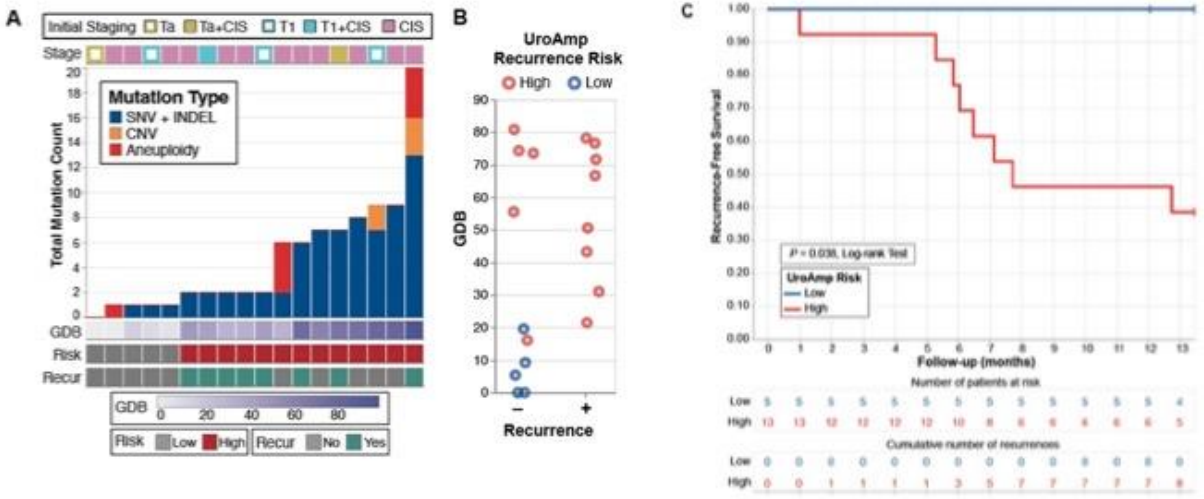
Nadofaragene firadenovec post-treatment GDB and RFS



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Conclusions

- MRD/GDB measurements in plasma and urine track subclinical micrometastatic and local responses
- Multiple platforms are being evaluated
- May be useful for escalation and de-escalation (bladder preservation)
- Combining them with other biomarkers