Examples of ECOG-ACRIN research initiatives

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Novembre 25 2022
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Disclosures

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Broad scope

- Biomarker Sciences Program
- Developmental Therapeutics Committee
- Imaging Committee
- Laboratory Science and Pathology Committee
- Therapeutic Studies Program
- Cancer Control and Outcomes Program

Developmental Therapeutics Committee

Chair

Keith T. Flaherty, MD

Massachusetts General Hospital Cancer Center

Biography

Genomics Subcommittee

Chair

Kristen Spencer, DO, MPH

New York University/NYU Langone Perlmutter Cancer Center

Biography

Compare and Contrast

	ComboMATCH	ECOG-ACRIN	PrECOG
Drug/agent	NCI-CRADA	NCI-CRADA Partner	Partner
Combinations	Targeted therapy	Any	Any
Preclinical support	So good we don't need a study	Convince us	Convince us
Correlates	NCI	NCI Partner	Partner
Flexibility	Battleship	Cruiser	Jet ski
Timelines (Concept submission to study activation)	NCI Operational Efficiency Working Group -depending on Phase of study 13 months-18 months	NCI Operational Efficiency Working Group -depending on Phase of study 13 months-18 months	~ 4-6 months (protocol/contract finalization to study activation)

Advantages of Collaborating

- The talent!
  - Key opinion leaders across several fields
  - Experience in studies of all phases, types
  - Mentoring from senior investigators built in
  - Advising on portfolio development throughout trial conception
- The centers
  - Well equipped to conduct studies of all phases & modalities
- Ability to conduct studies of any phase
- Rarer tumor types and/or indications (e.g. peri-operative space)

Common Questions

- Are registration studies possible?
  - Yes through ECOG-ACRIN & PrECOG
  - Not planned through ComboMATCH
- Is international participation possible?
  - Not through ComboMATCH
  - Yes through ECOG-ACRIN/PrECOG if company is committed to drug supply & distribution
    - ECOG-ACRIN/PrECOG several international members

About ComboMATCH

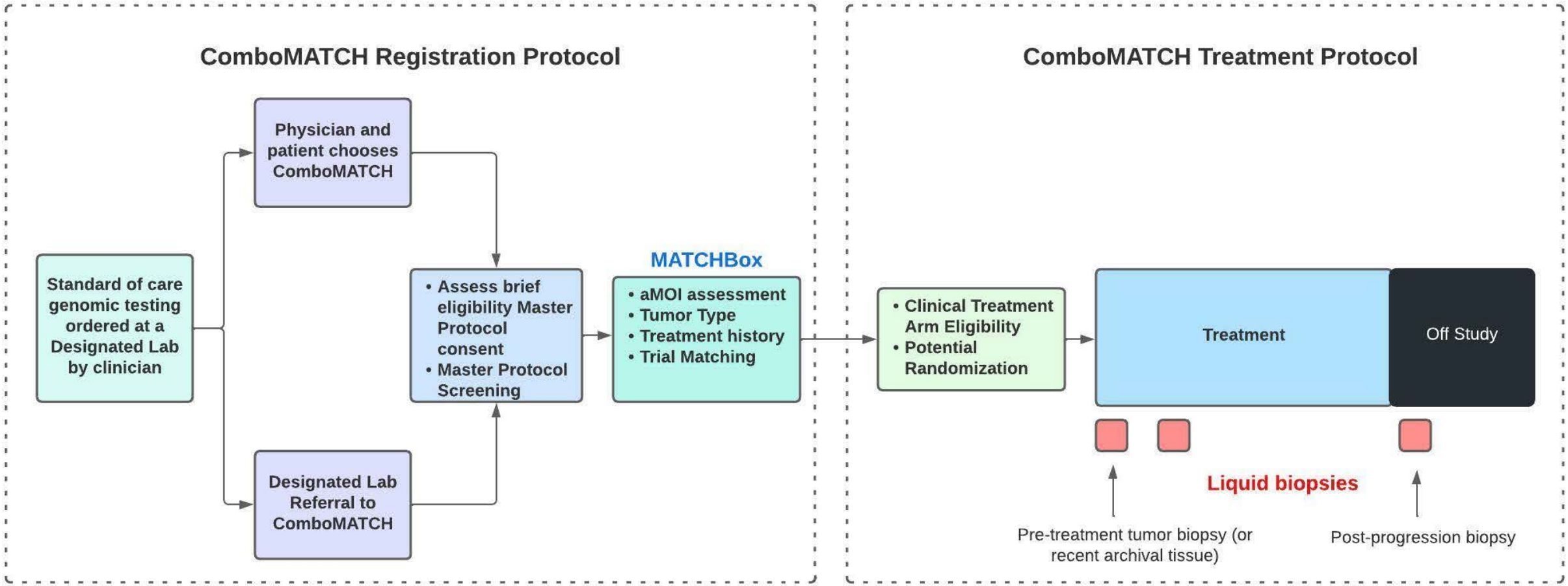
- Successor to the *NCI-MATCH* trial
- Hypothesizes genomically-driven, evidence-based addition of a targeted agent to another anticancer therapy will produce greater clinical benefit than treatment without the added targeted agent
  - Most tumors don't have only one genomic 'driver'
  - Many genes proposed as 'drivers', only a few successfully targeted by single-agent therapies
  - Responses limited by concurrent and/or emergent alterations, and not durable due to resistance
  - Variable responses to targeted therapies based on adaptive responses in tumors

Requirements for ComboMATCH Studies

- *In vivo* evidence of synergistic antitumor activity of drug combination in at least 2 genomically relevant pre-clinical models (PDX, cell line derived xenografts)
- *In vivo* antitumor activity of the combination must be analogous to clinical benefit, e.g. not merely a statistically significant slowing of growth rate
- Clinical evidence of tolerability of the combination; otherwise, a phase I study will be required
- Potentially eligible patients will be identified by SoC genomic sequencing at qualified network labs (academic and commercial); not paid for by NCI
- Each patient will have an on-study biopsy for WES and RNAseq provided centrally by NCI; biopsy material and cfDNA may also be used for study-specific objectives
- Each study may have several cohorts, one should be histology agnostic
- Statistical design of each cohort and each study will be developed in collaboration between NCI, NCTN groups and study teams

Courtesy of Jim Ford

ComboMATCH Design



Courtesy of Jim Ford

ComboMATCH First Wave Treatment Trials

First Wave: Fall 2022

Trial Number	EA191-A2	EAY191-A3	EAY191-A6	EAY191-E4	EAY191-E5	EAY191-N2	EAY191-N4	EAY191-S3
Study Agents	Olaparib & Alpelisib (PIK3CAi)	Palbociclib & Binimetinib (MEKi)	Binimetinib & FOLFOX	Nilotinib & Paclitaxel	Sorotasib & Panitumumab	Binimetinib & Fulvestrant	Olaparib & Selumetinib (NF1 TKI)	Ipatasertib & Paclitaxel (AKTi)
Molecular eligibility	DDR-altered breast	mRAS/unselected	mRAS/RAF	none	KRAS G12C	ER+ mNF1	RAS pathway mutation NF1 loss Breast/Gyn	PIK3CA/AKT/ PTEN

Courtesy of Jim Ford

A few examples of potential targets

- HER2
- HER3
- TROP2
- EZH1/2
- DS-7300 (B7-H3 DXd-ADC)
- CDH6 ADC
- GARP

- ROS1/TRK
- MET (+ SARC & CSF1R activity)
- RET
- ALK
- Claudin

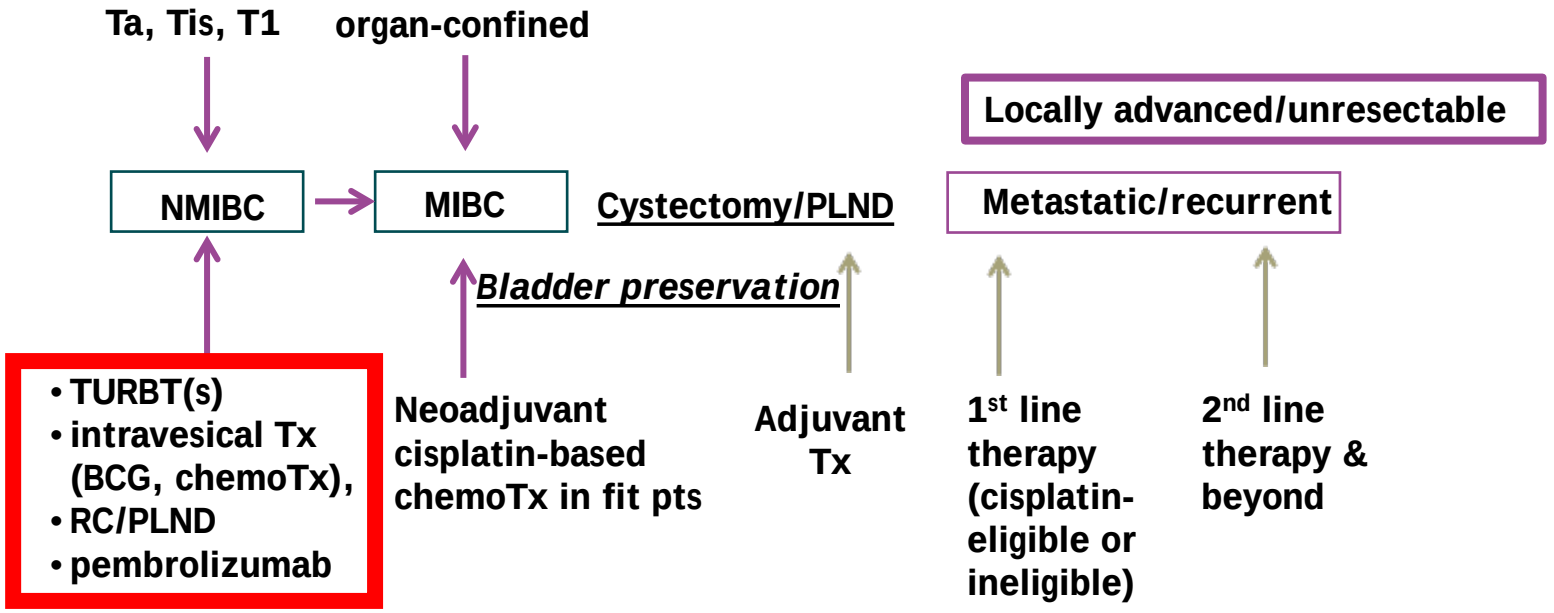
- TROP2
- TIGIT
- CD47, CD73, CD137
- Adenosine receptors A2a/A2b
- FLT3R
- MCL1
- SIRPa
- TREM 1 & 2
- CCR8
- HIF2a

Bladder Cancer Subcommittee Update

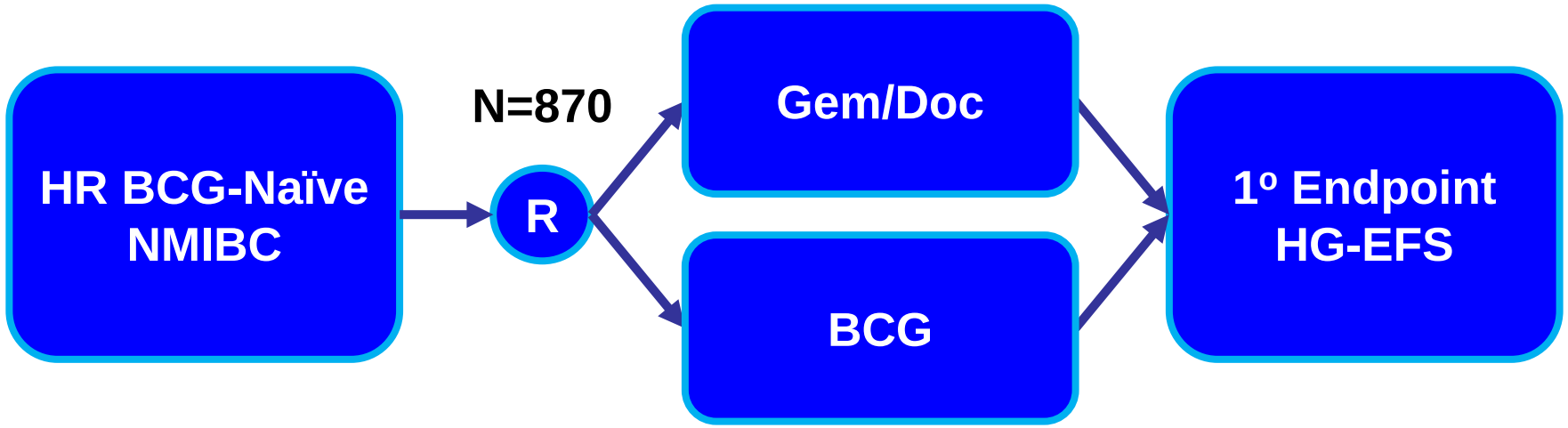
Noah M. Hahn MD

Johns Hopkins University

Disease / treatment settings

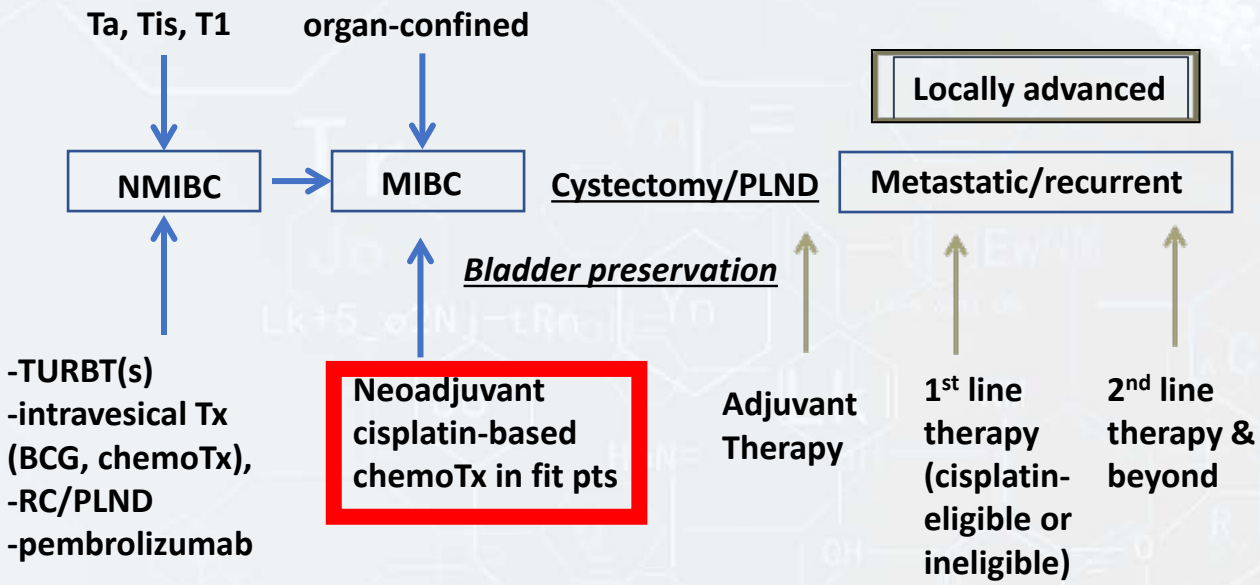


EA8212 BRIDGE
PI: Max Kates



- Stratification
  - Ta/T1 vs CIS vs Ta/T1 + CIS
- Noninferiority Design
  - Margin 1.25 (Gem/Doc vs SOC)
  - 2-yr HGEFS 58% vs 65%
  - 85% power

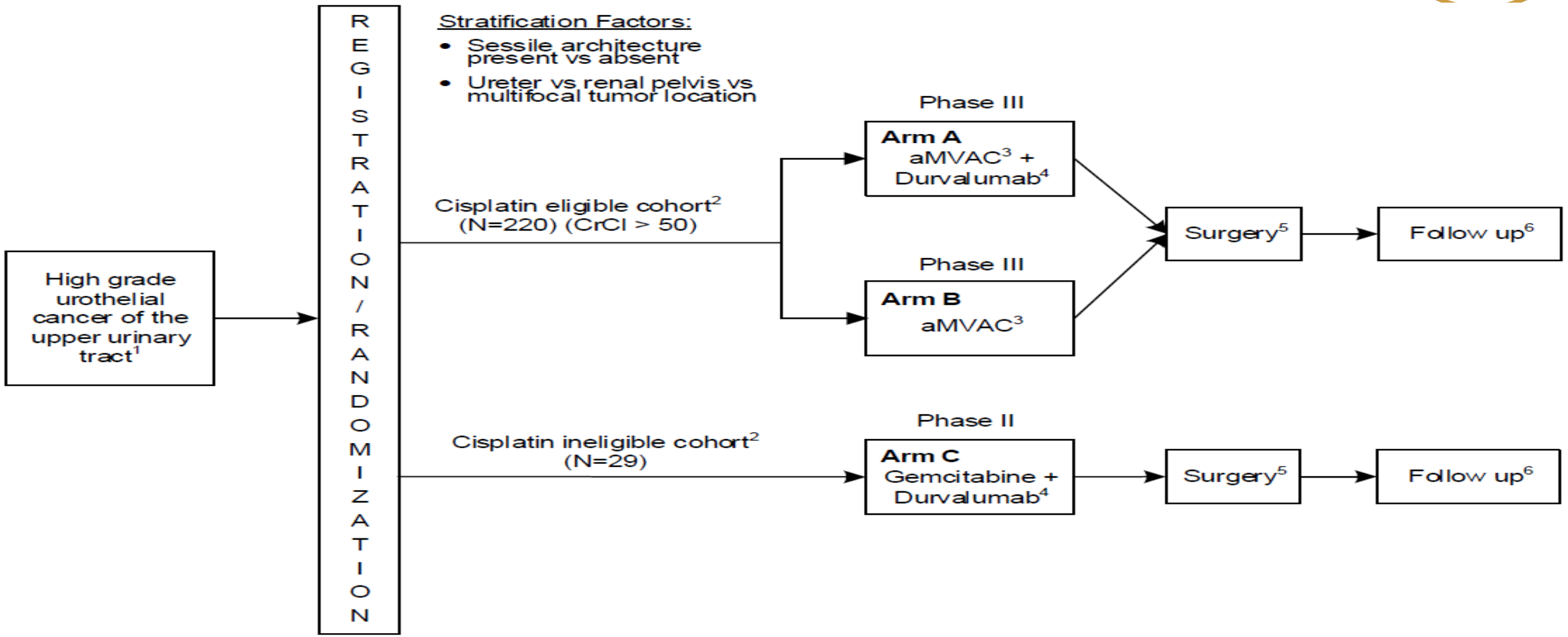
Disease / treatment settings



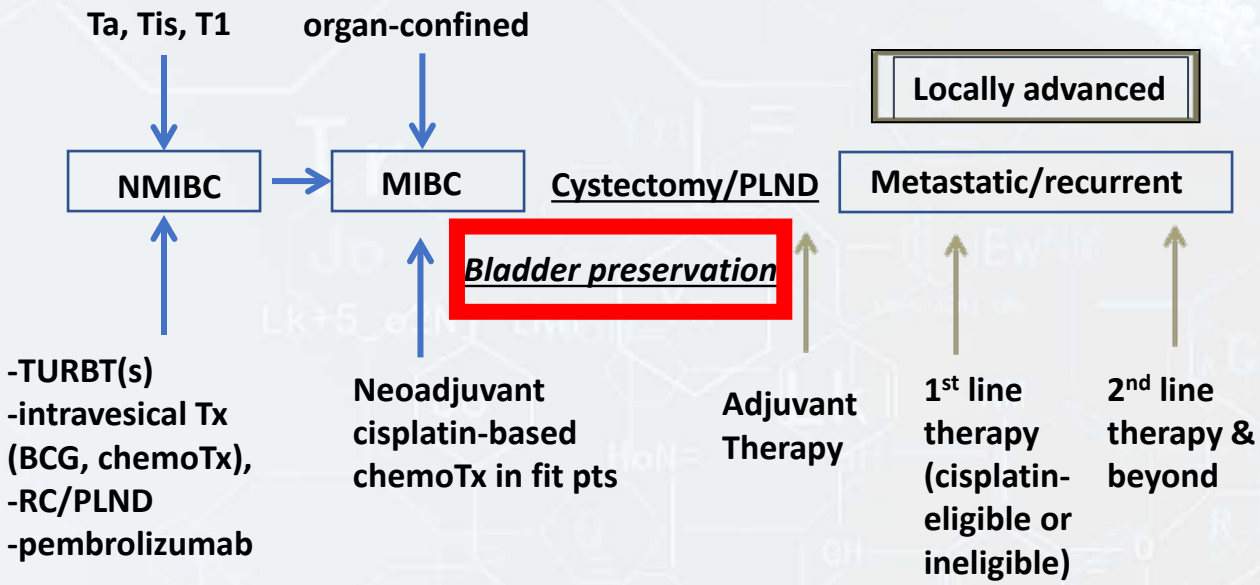
EA8192 Neo aMVAC +/- Durvalumab UTUC

Chair: Jeannie Hoffman-Censits

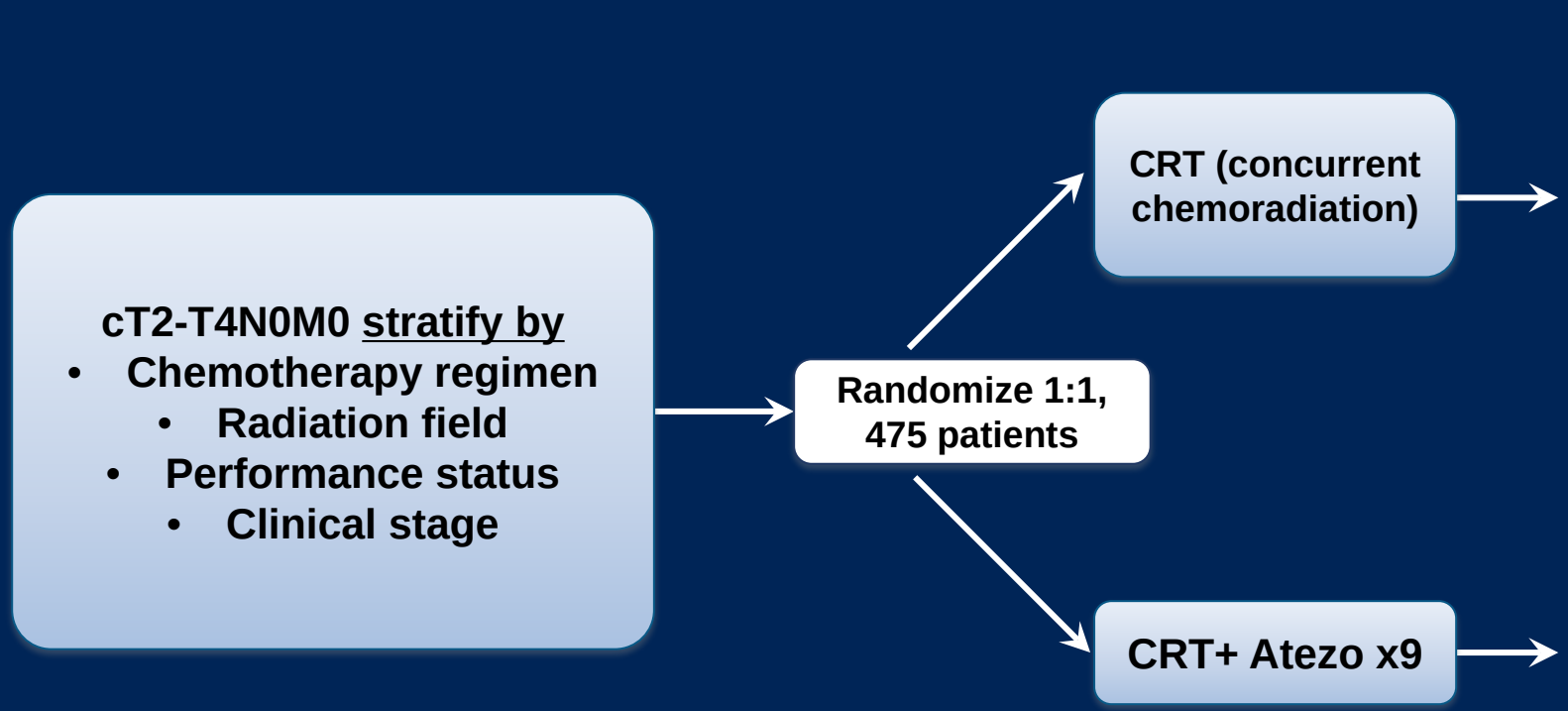
Co-Chairs: Petros Grivas, Vitaly Margulis



Disease / treatment settings



SWOG/NRG 1806: Phase III Trial of Concurrent Chemoradiation With or Without Atezolizumab for Localized Muscle Invasive Bladder Cancer



Primary endpoint
BIEFS*

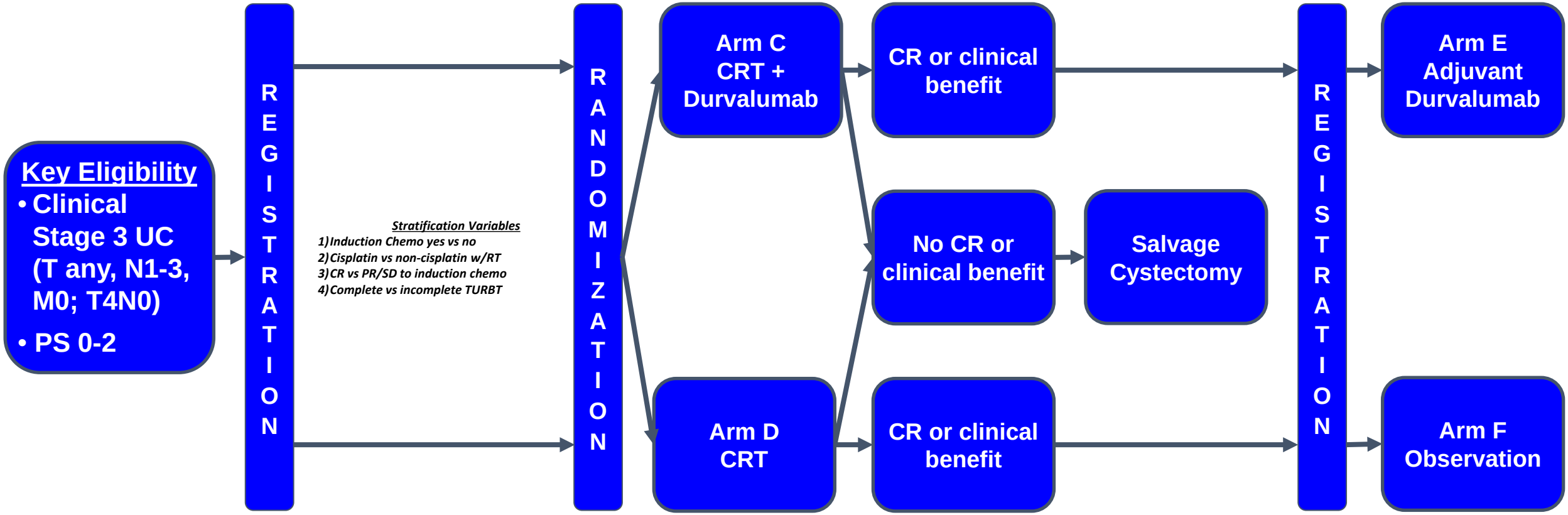
Secondary end point
- OS at 5 years
- Clinical response at 5 mths
- DSS
- MFS
- Toxicity at 1& 2 years
- NMIBC recurrence
- Cystectomy rate
- Global QoL

TM endpoints
- MRE 11
- DDR alterations
- Immune-related biomarkers

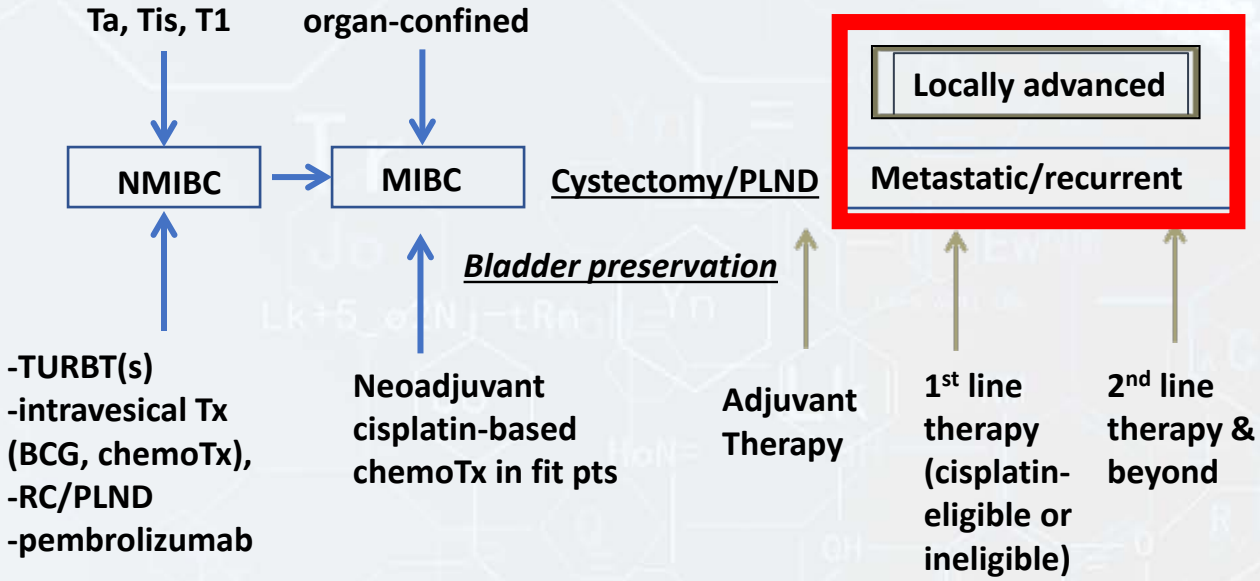
*BIEFS (bladder intact event free survival): muscle invasive recurrence in bladder, regional pelvic soft tissue or LN recurrence, distant mets, bladder cancer or toxicity related death or cystectomy

EA8185 INSPIRE
PI: Monika Joshi

N = 102



Disease / treatment settings



MAIN-CAV: Phase III randomized trial of maintenance cabozantinib and avelumab versus avelumab after first-line platinum-based chemotherapy in patients with metastatic urothelial cancer (mUC) (Alliance A032001)

Shilpa Gupta, Karla V. Ballman, Matt D. Galsky, Michael J. Morris, Ronald C. Chen, Timothy A. Chan, Laurent Dercle, Yujia Wen, Srikala S. Sridhar, Aihua Edward Yen, Petros Grivas, Alan Tan, Shiva Baghaie, Jonathan E. Rosenberg

Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, OH; Weill Cornell Medicine, New York, NY; The Tisch Cancer Institute, Mount Sinai, New York, NY; Memorial Sloan Kettering Cancer Center, New York, NY; University of Kansas, Kansas City, KS; Memorial Sloan Kettering Cancer Center, New York, NY; Department of Radiology, Columbia University Medical Center, New York-Presbyterian Hospital, New York, NY; Univ of Chicago, Chicago, IL; Cancer Clinical Research Unit, Princess Margaret Cancer Centre, Toronto, ON; Baylor Coll of Medcn, Houston, TX; University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA; Premier Onc Hem Assoc, Chicago, IL; Alliance for Clinical Trials in Oncology, Chicago, IL

Background/Rationale

- First-line (1L) platinum-based chemotherapy followed by maintenance avelumab (Av) is the current preferred standard of care in patients (pts) with mUC who do not progress after platinum-based chemotherapy.
- There is an unmet need to further improve outcomes in 1L maintenance setting
- Cabozantinib (CABO) is an oral inhibitor of MET, VEGFR and TAM family receptors involved in tumor growth, angiogenesis and immune cell regulation and has shown efficacy in mUC in combination with PD-1/PD-1L1 inhibitors.
- We hypothesize that CABO-Av combination will be synergistic in pts with mUC with an acceptable safety profile and will improve upon the benefit seen with Av maintenance in mUC.

Study Design

Phase III randomized, multicenter trial ; 654 will be randomized 1:1 within 3-10 weeks (wk) after last dose of chemotherapy to receive Av 800 mg IV every 2 wk or combination of Av and CABO 40 mg orally daily for up to 2 yrs.

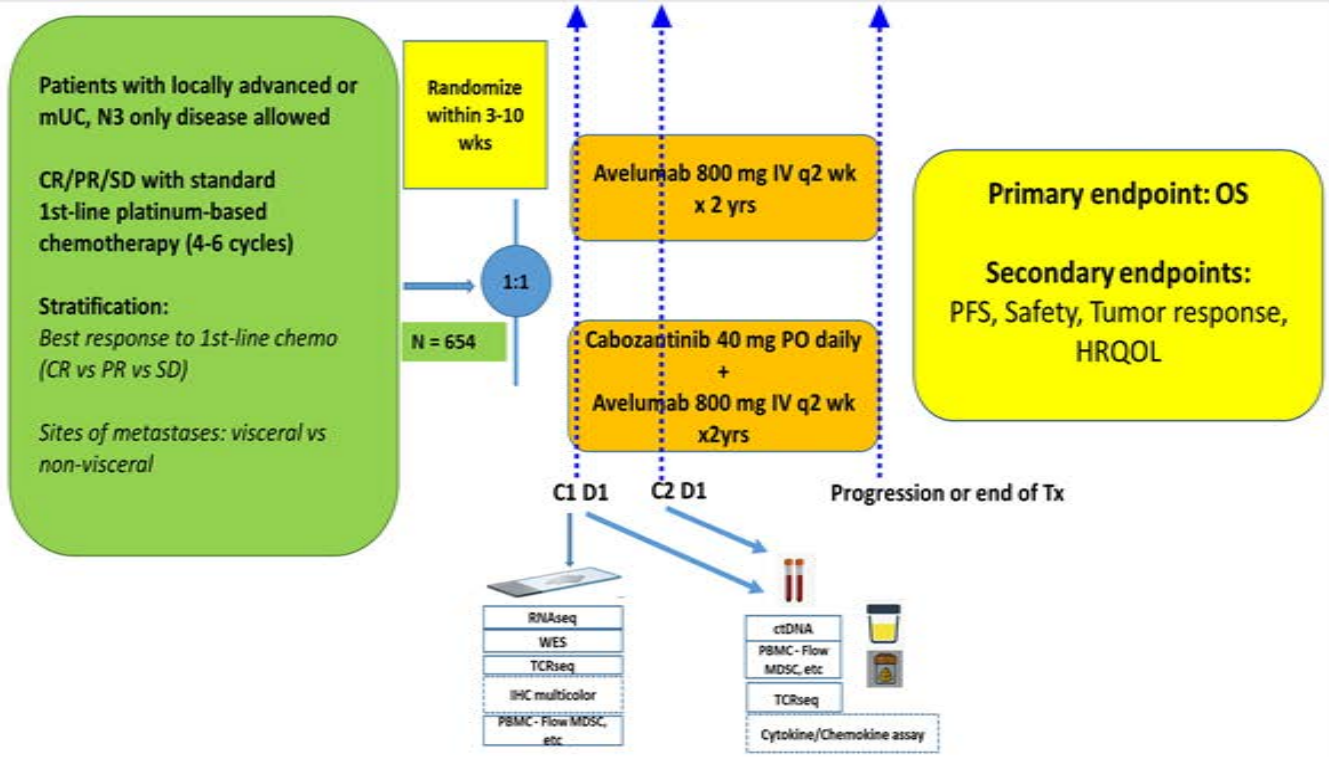
Key Eligibility criteria

- Locally advanced/mUC pts (including N3 only disease) who do not progress after 4-6 cycles of any platinum-based chemotherapy (gem-cis, gem-carbo, MVAC or ddMVAC)
- ECOG PS 0-1, adequate organ function, creatinine clearance >/= 30 ml/min
- Prior chemotherapy allowed if > 12 mo prior to study entry, no prior use of immunotherapy (exception of BCG)
- No active central nervous system metastases, no major surgery within 4 wks, no uncontrolled hypertension or cardiovascular disorders, no contraindication to immunotherapy

Endpoints

- The primary endpoint is overall survival (OS)
- Secondary endpoints include progression-free survival (PFS), safety, tolerability, and activity of CABO-Av compared to Av alone based on RECIST 1.1 and iRECIST criteria and PD-L1 status of pts' tumors.
- Quality of life (QOL) will be assessed using EQ-5D-5L, PROMIS-Fatigue 4a, EORTC QLQ-C30, EORTC QLQ-BLM30 between pts on CABO-avelumab vs avelumab alone.
- Correlatives to study biomarkers of response and resistance to avelumab using tissue, blood, ctDNA, stool and urine.
- Imaging studies will test correlation of radiomic signatures with OS, adverse events and QOL

Study Schema



Importance of this study:
This is the first trial investigating whether intensification of avelumab maintenance with adding cabozantinib can improve survival in mUC compared to avelumab alone.

Study Chair: Shilpa Gupta, M.D.
Email: Guptas5@ccf.org
@shilpaonc

CT.gov: NCT05092958, Open to accrual

Support: U10CA180821, U10CA180882, U24CA196171,U10CA180863 (CCTG); Clinical trial information:

In Development Open to Accrual Closed to Accrual

Current NCI Group Studies

Non-muscle Invasive		Muscle Invasive		Metastatic		
BCG-naïve	EA8212 BRIDGE BCG vs Gem/Doce (0/870)	Bladder-sparing	SN1806 CRT +/- Atezo (332/475) EAN8185 INSPIRE CRT +/- Durva (8/102)	1L Cisplatin Eligible	None	A031901 Continuous IO vs Stop IO (3/1038)
BCG-relapse	None	Neoadjuvant Upper Tract	EA8192 ddMVAC +/- Durva Gem + Durva (8/249)	1L Cisplatin Ineligible	A032002 Atezo + SBRT vs Atezo (0/144)	
BCG-unresponsive	A031803 Pembro + Gem (78/161)	Neoadjuvant Bladder	A031701 Cis/Gem NAC (DDR+) (143/271) S1600 SIMmune (152/200) S2011 Carbo + Gem + Avelumab vs no peri-op therapy (1/196)	Post-platinum Checkpoint Naive	None	
				Post-platinum Maintenance	A032001 MAIN-CAV Maintenance Cabo + Avel vs Avel (4/654)	
				Variant Histology	A031702 Cabo + Nivo + Ipi Rare Tumors (164/224)	
		Adjuvant Bladder	Nivo +/- Relatlimab ctDNA+ (0/856)	Post-Checkpoint	S1937 Eribulin +/- Gem (14/465)	

In Development Open to Accrual Closed to Accrual

Current NCI Group Studies

Non-muscle Invasive		Muscle Invasive		Metastatic		
BCG-naïve	• Intermediate Risk • 2L BCG-unresponsive	Bladder-sparing	SN1806 CRT +/- Atezo (269/475) EAN8185 INSPIRE CRT +/- Durva (6/102)	1L Cisplatin Eligible	None	A031901 Continuous IO vs Stop IO (0/1038)
BCG-relapse		Neoadjuvant Upper Tract	EA8192 ddMVAC +/- Durva / Gem + Durva (5/249)	1L Cisplatin Ineligible	A032002 Atezo + SBRT vs Atezo (0/144)	
BCG-unresponsive		Neoadjuvant Bladder	• Bladder-sparing MIBC • Neoadjuvant Cisplatin-eligible MIBC • **UTUC Peri-procedure Bladder Intravesical Gem** (0/196)	Post-platinum Checkpoint Naive	• ?1L mUC w/EV + Pembro as SOC? • **Post-EV 2L/3L Sacituzumab +/- IO** • Variant Histology • Genomically-targeted subgroups	
				Post-platinum Maintenance	Avel vs Avel (0/654)	
				Variant Histology	A031702 Cabo + Nivo + Ipi Rare Tumors (158/224)	
		Adjuvant Bladder	A032103 Nivo +/- Relatlimab ctDNA+ patients (0/856)	Post-Checkpoint	S1937 Eribulin +/- Gem (6/465)	

Cancer screening using ctDNA

- **Population: age range & risk factors, e.g. obesity, smoking, germline mutations (enrichment)**

-patients with prior treated localized cancer, e.g. > 5 years ago with low recurrence rate?

- **Testing strategy: “reveal/conceal” (test both groups but blind result) vs test only the intervention group**

- **Design: One large heterogeneous population vs smaller “cassettes” of tumor types with specific sub-studies**

-Example: SOC screening (e.g. colorectal, breast, lung, prostate, cervical) +/- ctDNA

- **Assay: single assay across the study/ies vs different assays depending on preliminary data per tumor type**

- **Endpoint: cancer-specific mortality vs overall mortality vs stage-adjusted projected mortality vs other**

- **Centralized operations via NCI & NCTN; specific roles/assignments of the several co-operative groups?**

- **Relationship with industry & existing studies; opportunity for collaborations vs separate approach?**

- **Funding, time, labs, providers across academic & community practices, compliance, healthcare disparities**

…a few last thoughts…

- **NCTN has a unique opportunity to lead the landscape for optimal incorporation of ctDNA in several innovating and practice-informing clinical trials designs:**

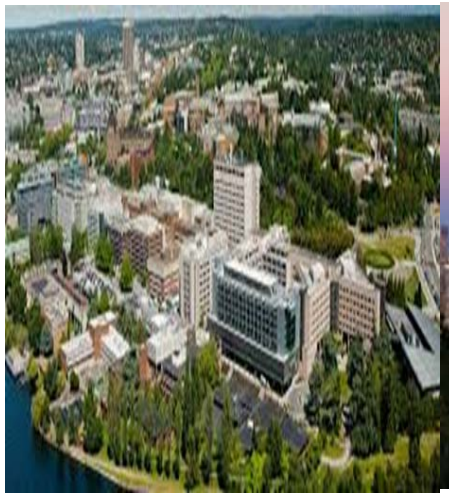
-screening/early detection
-therapy response / detection of MRD (serial biomarker for detection, clearance, reemergence)
-resistance mechanisms (particular genomic alterations with functional impact)
-concordance with tumor tissue; prognostic and/or predictive value

- **Number of patients across academic & community practices; expertise across spectrum of specialties**
- **Collaboration with industry can be synergistic & customized to particular questions per tumor type**
- **Opportunities for database/registry, biobanking in a harmonized/standardized manner across NCTN**
- **Working groups/Think Tank with specific & timely deliverables → scientific retreat / workshop with NCI**
- **Funding & time considerations: building infrastructure, adaptation, flexibility, learning from experience**

Patient and families!

- Collaborators, sponsors, institutions, foundations, colleagues, research, admin & clinical staff: Teams!

@PGrivasMDPhD





ECOG-ACRIN
cancer research group