National Cancer Institute

Clinical Trials Planning Meeting on 'Defining the next generation of clinical trials with combination therapies in non-muscle invasive bladder cancer'

Virtual Event, December 8-9, 2022

Co-Chairs: Peter Black, M.D., Andrea Apolo, M.D., Brian Baumann, M.D. and Matthew Milowsky, M.D.

Introduction and Background

The National Cancer Institute organized a virtual Clinical Trials Planning Meeting (CTPM) on 'Defining the next generation of clinical trials with combination therapies in non-muscle invasive bladder cancer' in an effort by the Bladder Cancer Task Force of the NCI Genitourinary Cancers Steering Committee. This CTPM occurred on December 8-9, 2022, and was chaired by Drs. Peter Black, Andrea Apolo, Brian Baumann and Matthew Milowsky. The purpose of this meeting was to accelerate further advances in clinical trials for patients with high-risk non-muscle invasive bladder cancer (NMIBC). The meeting focused on the evaluation of strategies incorporating intravesical therapy, systemic therapy, trimodal therapy (incorporating radiation therapy), and combination therapies toward a goal of improving bladder preservation rates and survival outcomes for patients with high risk including BCG-unresponsive NMIBC.

The goal of the CTPM was to improve bladder preserving therapy with intravesical, systemic and radiation-based approaches in patients with high risk and treatment-refractory NMIBC. The objectives of this effort were to (i) establish consensus on key components of trial design; (ii) explore the feasibility of a multi-arm adaptive randomized clinical trial (RCT); (iii) develop two clinical trial concepts focused on bladder preservation for patients with high risk NMIBC for implementation through the NCTN Groups, and (iv) plan biomarker integration into NMIBC clinical trials.

Potential deliverables of this CTPM include determination of a multidisciplinary expert consensus on optimal strategies for next-generation clinical trial designs in NMIBC, prioritization of combination therapies for NMIBC, determination of feasibility of adaptive multi-arm RCT in NMIBC, identification of biomarkers to incorporate into trials (with the aim of validating candidate predictive biomarkers for each treatment arm) and recommendations for tissue handling for the most robust and impactful downstream analyses in these trials. Streamlining the design of the 2 clinical trial concepts proposed in the context of this CTPM for potential implementation within the NCTN Groups was among key deliverables of this enterprise.

Summary of Discussions Leading to Action Plans for Addressing the Scientific and Clinical Challenges

Clinicians, statisticians, pathologists, and scientists convened in this CTPM, focused their effort on enhancing our knowledge of the scientific and clinical fields involved in the management of NMIBC, designing most effective clinical trials and ensuring that the best available science is applied to the design of biomarker studies and methods of specimen collection in the context of these trials. The CTPM included 3 working groups who joined their expertise to address scientific and clinical challenges in the

NMIBC clinical trials field. Two working groups focused on the above 2 clinical trial concepts respectively, and a third one on the biomarker studies ancillary to the trials.

The working group on concept 1 ‘A multi-arm RCT testing multiple combination therapies in BCG-unresponsive NMIBC’ further discussed the design and feasibility of a multi-arm, adaptive, randomized controlled combination therapy trial that would prioritize a patient-centric approach to assessing the burden of treatment in NMIBC. The group agreed that while an adaptive trial would be ideal, a more straightforward design would be more feasible for this concept. The Phase II/III trial would enroll patients with BCG-unresponsive carcinoma in situ (CIS) into one of four trial arms. Possible treatment arms include a combination of BCG and the IL-15 superagonist N-803; a combination of BCG, N-803, and immuno-oncology (IO) agents; gemcitabine and docetaxel (Gem/Doce); or a combination of cabazitaxel, gemcitabine, and cisplatin. At 6 months, the investigators would conduct futility and event-free survival analyses to drop the two lowest-performing arms before proceeding to a Phase III trial. As this concept will be refined, the investigators will identify detailed criteria for a trial arm’s success or elimination.

The focus of clinical trial concept 2 ‘A multi-arm RCT testing trimodal therapy versus alternative therapies in high risk T1 bladder cancer’ further assessed in a separate working group, whether pembrolizumab or a similar IO agent improves oncologic outcomes when added to chemoradiation therapy and whether a combination of pembrolizumab and a novel intravesical chemotherapy delivery system, TAR-200, can achieve outcomes superior to those with chemoradiation. The study would enroll patients with either recurrent T1 high-grade urothelial carcinoma following initial transurethral resection of bladder tumor (TURBT) and intravesical therapy or de novo T1 with very-high-risk features who otherwise would be treated with cystectomy off trial. Eligibility criteria would include prior maximally complete TURBT and being eligible for radiation treatment, chemotherapy, and IO therapy. The randomized phase II design would enroll patients into one of three arms including concurrent chemotherapy and radiotherapy (RT); concurrent chemotherapy, RT and IO therapy; or TAR-200 and IO therapy. The hypothesis is that both combinations—chemoradiation plus IO therapy and TAR-200 plus IO therapy —will demonstrate improved 3-year bladder-intact survival over chemoradiation alone. The group further discussed some modifications regarding inclusion criteria, treatment arms, feasibility and whether a two-arm trial would be able to achieve the goals if a three-arm trial proved infeasible.

The working group on biomarkers focused on exploring strategies and methods to facilitate the design of standard processes for tissue, blood and urine collection, and on recommendations for maximizing the impact of biomarker studies. The group concentrated their efforts to identify areas of consensus on methods of handling, storage and banking of biospecimens from all potentially relevant sources for future studies including, omics, ctDNA and utDNA analyses, artificial intelligence/deep learning studies and the banking of imaging data for radiomic studies.

A number of substantive and collaborative ideas were generated as direct outcomes of this CTPM while the two trial concepts will be returned to the NCTN groups for further development and maturation as the process of organizing the next steps of this endeavor is underway.

This Executive Summary presents the consensus arising from the CTPM. These action plans are not meant to address all clinical contexts, but rather represent priorities for publicly funded clinical research.

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Agenda

Thursday December 8, 2022

All times EST

10:00	**NCI Welcome**	**Abdul Tawab Amiri**
10:05	**Welcome & Overview of Objectives for CTPM**	**Co-Chairs**
10:15	Clinical Trial Challenges in NMIBC	
10:15	Defining NMIBC disease states (focus also on unmet needs of each)	Ashish Kamat
10:25	Patient perspectives: Unmet needs in NMIBC care	Robert Lipman
10:35	Financial toxicity: implications of treatment intensification for patients with NMIBC	Angie Smith
10:45	Defining a role for trimodal therapy in T1 bladder cancer	Sophia Kamran
10:55	Pathology considerations for determining endpoints in NMIBC trials	Francesca Khani
11:05	Regulatory considerations in NMIBC trials	Chana Weinstock
11:15	Clinical trial endpoints in NMIBC	Seth Lerner
11:30	Discussion	
12:10	NMIBC clinical trial concepts and design considerations	
12:10	Introduction of Concept 1: Background and Objectives	Scott Delacroix

12:20	Introduction of Concept 2: Background and Objectives	Brian Baumann
12:30	Applying innovative trial designs to NMIBC (include: adaptive trial designs, multi-arm randomized controlled trial, etc.)	Noah Hahn
12:45	Statistical considerations	Emma Hall
13:00	Roundtable: Feasibility of novel trial designs within NCTN infrastructure (include NCI perspective)	
13:20	**Break**	
13:50	**Introduction to Working Groups**	**Co-Chairs**
13:55	**Break-Out Session: Parallel Working Groups**	
	Clinical Trial Concept 1	Delacroix et al
	Clinical trial Concept 2	Baumann et al
	Incorporation of biomarkers into NMIBC clinical trials	McConkey et al
15:55	**Day #1 Wrap-up**	**Co-Chairs**
16:00	**Adjourn**	

Friday December 9, 2022

10:00	**Introduction to Day #2**	**Co-Chairs**
10:05	Biomarkers	David McConkey
10:05	Plasma ctDNA in NMIBC	Alex Wyatt
10:15	Urine ctDNA in NMIBC	Trevor Levin
10:25	Tissue markers in NMIBC	Eugene Pietzak
10:35	Immune microenvironment in NMIBC	William Kim

10:45	Optimizing the quality of transurethral resection of bladder tumor	Joseph Liao
10:55	Setting priorities of biomarker integration in NMIBC clinical trials	Josh Meeks
11:05	Statistical considerations of integrating biomarkers into clinical trials	James Proudfoot
11:15	Discussion	
11:50	**Working Group Reports**	
11:50	Clinical Trial Concept 1	Delacroix et al
12:50	**Break**	
13:20	**Working Group Reports**	
13:20	Clinical Trial Concept 2	Baumann et al
14:20	Biomarker Integration	McConkey et al
15:20	**Trial Design Discussion & Consensus**	**Co-Chairs**
15:45	**Summary and Next Steps**	**Co-Chairs**
16:00	**Adjourn**	

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Meeting Participants

Philip	Abbosh	Fox Chase Cancer Center
Ahmed	Aboumohamed	Albert Einstein College of Medicine
Sundeep	Agrawal	US Food & Drug Administration
Hikmat	Al Ahmadie	Memorial Sloan Kettering Cancer Center
Andrea	Apolo	National Cancer Institute
Leslie	Ballas	Cedars Sinai
Rouf	Banday	CCR, National Cancer Institute
Rick	Bangs	SWOG Cancer Research Network
Ali	Bashashati	University of British Columbia
Brian	Baumann	Washington University in St. Louis
Ambaw	Bellete	Lion Healthcare Strategies
Joaquim	Bellmunt	Department of Medical Oncology, Dana-Farber Cancer Institute
Peter	Black	University of British Columbia
Bernard	Bochner	Memorial Sloan Kettering Cancer Center
Michelle	Brockman	Genentech US Medical Affairs Team
Kenneth	Brothers	NIH Bladder Cancer Task Force
Elaine	Chang	US Food & Drug Administration
Aadel	Chaudhuri	Washington University School of Medicine
Jane	Chen	Medical Devise
Stephanie	Chisolm	Bladder Cancer Advocacy Network
Rod Carlo	Columbres	CCR, National Cancer Institute
Alberto	Contreras-Sanz	University of British Columbia/Vancouver Prostate Centre
Stephanie	Cooper-Greenberg	Johns Hopkins Greenberg Bladder Cancer Institute
Theresa	Crane	
Fabio	Cury	McGill University Health Centre
Jeffrey	Damrauer	University of North Carolina at Chapel Hill
Sia	Daneshmand	USC Keck School of Medicine
Nicole	Davarpanah	Genentech
David	DeGraff	Pennsylvania State University College of Medicine
Scott	Delacroix	LSU New Orleans/ Gulf South NCORP
Lisa	Delmastro	AstraZeneca
Neil	Desai	University of Texas Southwestern
James	Dignam	University of Chicago/ NRG Oncology
Jason	Efstathiou	Massachusetts General Hospital
Adam	Feldman	Massachusetts General Hospital
Thomas	Flaig	University of Colorado Anschutz Medical Campus
Jared	Foster	National Cancer Institute
Matt	Galsky	Icahn School of Medicine at Mount Sinai
Guilherme	Godoy	Baylor College of Medicine
Erik	Goluboff	Genentech
John	Gore	University of Washington
Domenic	Grignano	Bladder Cancer Advocacy Network
Petros	Grivas	University of Washington, Fred Hutchinson Cancer Center
Susan	Groshen	USC Keck School of Medicine (retired)
Erin	Grundy	Nationwide Children's Hospital
Shilpa	Gupta	Cleveland Clinic Foundation
Noah	Hahn	Johns Hopkins University
Susan	Halabi	Duke University

Emma	Hall	The Institute of Cancer Research
Donna	Hansel	University of Texas MD Anderson Cancer Center
Comron	Hassanzadeh	University of Texas MD Anderson Cancer Center
Stefanie	Hayoz	Swiss Group for Clinical Cancer Research (SAKK)
Stephan	Hois	AstraZeneca
Amir	Horowitz	Icahn School of Medicine at Mount Sinai
Maggie	House	National Cancer Institute
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Shidong	Jia	Predicine, Inc.
Edward	Kadel	Genentech
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Sophia	Kamran	Massachusetts General Hospital
Ekta	Kapadia	Merck & Co
Wed	Kassouf	McGill University Health Center
Max	Kates	Johns Hopkins University
Mairah	Khan	Northwestern university
Francesca	Khani	Weill Cornell Medicine
William	Kim	University of North Carolina at Chapel Hill
Sung Han	Kim	Baylor College of Medicine
Zachary	Kornberg	Stanford University
Seth	Lerner	Baylor College of Medicine
Trevor	Levin	Convergent Genomics
Roger	Li	H Lee Moffitt Cancer Center
YANYANG	LI	Northwestern University
Joseph	Liao	Stanford University
Robert	Lipman	Bladder Cancer Advocacy Network
Khyati	Meghani	Northwestern University
Kathy	Mach	Stanford University
William	Maguire	US Food & Drug Administration
Bhupinder	Mann	National Cancer Institute
David	McConkey	Johns Hopkins School of Medicine
James	McKiernan	Columbia University
Joshua	Meeks	Northwestern University
Matthew	Milowsky	University of North Carolina Lineberger Comprehensive Cancer Center
David	Miyamoto	Massachusetts General Hospital
Kent	Mouw	Dana-Farber Cancer Institute
Neema	Navai	University of Texas MD Anderson Cancer Center
Giordan	Nicola	Fidia Farmaceutici S.p.A.
Michael	O'Donnell	University of Iowa Hospitals & Clinics - Urology Clinic
Sun Min	Oh	AstraZeneca pharmaceutical
Eugene	Pietzak	Memorial Sloan Kettering Cancer Center
Elizabeth	Plimack	Fox Chase Cancer Center
Kamal	Pohar	Ohio State University
Sarah	Psutka	University of Washington
Pramod	Pujari	Serum Institute of India Pvt Ltd
Sandip	Reddy	ImmunityBio
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Cyrill	Rentsch	University of Basel
Lori	Roscoe	University of South Florida
Tracy	Rose	University of North Carolina
Jonathan	Rosenberg	Memorial Sloan Kettering Cancer Center
Karen	Sachse	Bladder Cancer Advocacy Network
Kristen	Scarpato	Vanderbilt University Medical Center
Matthew	Schipper	University of Michigan
Mark	Schoenberg	Montefiore Medical Center and The Albert Einstein College of Medicine

Kristen	Scholz	UroGen
Connie	Secor	Patient
Roland	Seiler	Spitalzentrum Biel
Lennie	Sender	ImmunityBio
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Eugene	Shkolyar	Stanford University
Arlene	Siefker Radtke	University of Texas MD Anderson Cancer Center
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Angela	Smith	University of North Carolina
David	Solit	Memorial Sloan Kettering Cancer Center
Guru	Sonpavde	AdventHealth Cancer Institute
Patrick	Soon-Shiong	ImmunityBio
Srikala	Sridhar	Princess Margaret Cancer Center
Mark	Stein	Columbia Irving Medical Center
Gary	Steinberg	New York University Langone Health
Chen	Suen	National Cancer Institute
Debasish	Sundi	Ohio State University
Richard	Sylvester	EAU Guidelines Office
Cathy	Tangen	SWOG Stat Center Fred Hutch Cancer Center
Connie	Tat	Genentech
Tilman	Todenhoefer	Studienpraxis Urologie
Antoun	Toubaji	NIH/NCI lab of pathology
Daniel	Vaena	West Cancer Center and Research Institute
Eliezer	Van Allen	Dana-Farber Cancer Institute
Alexander	Wei	Columbia University Irving Medical Center
Chana	Weinstock	US Food & Drug Administration
Sara	Wobker	University of North Carolina Chapel Hill
Michael	Wu	Fred Hutchinson Cancer Center
Alex	Wyatt	University of British Columbia
James	Yu	Columbia University Irving Medical Center