Executive Summary

National Cancer Institute Gynecologic Cancer Steering Committee

Clinical Trials Planning Meeting: Refining the Approach to Endometrial Cancer in the Immunotherapy Era

Virtual Event, January 8–9, 2024

Co-Chairs: Susana M. Campos, M.D., M.P.H.; Linda R. Duska, M.D.; and Akila N. Viswanathan, M.D., M.P.H., M.Sc.

Introduction/Meeting Description

The National Cancer Institute Gynecologic Cancer Steering Committee (GCSC) convened a Clinical Trials Planning Meeting (CTPM) on approaches to endometrial cancer (EC) treatment in the immunotherapy era on January 8–9, 2024. Experts from across the EC research community discussed the state of the science and proposed clinical trials to optimize treatment under new immune checkpoint inhibitor (ICI) treatment paradigms.

Background

Uterine cancer, of which the vast majority are endometrial cancers (EC), is the most common and second deadliest of the gynecologic cancers in the US, with 65,950 new cases and 12,500 deaths expected in 2022[1]. Unlike other solid tumors, the incidence of uterine cancer has been increasing[2] and is projected to surpass ovarian and colorectal cancer as a leading cause of cancer death among women by 2040.[3] US uterine cancer incidence increased 1% per year from 2003 to 2015, with the sharpest increases in Asian, Hispanic, and Black individuals.[2] Furthermore, uterine cancer mortality increased by 1.8% per year from 2010-2017, and 2.7% per year for non-endometrioid histologic subtypes, with substantial disparities in mortality rates in Black patients.[4]

The designation of endometrial cancers has evolved over the last decade with advancing molecular and histologic data. We now recognize four major types of endometrial cancer, with different clinical behavior, treatment susceptibilities, outcomes, and population distributions.[5, 6] Mismatch repair deficiency, associated with microsatellite instability (dMMR/MSI), in approximately 25-35% of cases, portends a greater sensitivity to immune checkpoint therapy (ICI), a somewhat worse prognosis, and is predominantly found in individuals with endometrioid endometrial cancer. In contrast, cases with TP53 mutation, approximately 30% of endometrial cancers, tend to be serous in histology, aggressive, microsatellite stable, poorly responsive to single agent ICI, but susceptible to chemotherapy, and are disproportionately common in Black patients.[7]

Studies are ongoing to examine the role of ICI in front line treatment and recurrent EC. The increasing use of ICI in the second line, and the ongoing move into front line for some types of endometrial cancer, leaves a critical unmet need to understand the best time in the life cycle of EC into which to bring ICI, for whom it should be used, and how

to optimize its use. Some subsets of people with EC may require combination therapy to obtain best benefit, while others may benefit from ICI alone. There are limited data currently available to guide management strategies for recurrent or persistent EC after ICI. A better understanding of why and how ICI works will allow planning for reapplication of this category of agents, that can be addressed in an evidence-based fashion. Finally, increasing opportunities for specimen collection is critical to analyze mechanisms of sensitivity and resistance and to translate that knowledge into novel treatment strategies in the immunotherapy era.

Meeting Objectives

- Identify characteristics that are associated with magnitude of benefit from ICI through analysis of preclinical and translational literature.
- Develop treatment strategies for patient subgroups based on molecular and clinical characteristics.
- Examine ICI sequencing and timing across the EC lifecycle.
- Explore combinations with which to optimize initial exposure and/or with which to reengage the immune system for second benefit from ICI.
- Promote clinical trial designs to enhance access to the broadest population of EC patients.

Meeting Outcomes and Deliverables

- Review of the ICI literature with a focus on biomarkers and clinical variables that may identify discriminants to guide EC trial design and patient selection.
- Development of phase 2–3 clinical trials to lead to improvement in outcome for ICI-naïve and previously ICI-treated patients with EC.
- Exploration of clinical trial designs to enhance access for the broadest population of EC patients.
- Identification of potential areas for correlative analysis to advance our knowledge of patient benefit discriminants.
- Publication of workshop recommendations and trial outcomes.

Meeting Summary

Investigators gave presentations on a variety of topics, including the evolution of molecularly-directed therapy in EC, generalized treatment criteria for EC with mismatch repair deficiency (dMMR), differences between hypermethylation and dMMR by mutation, the interplay between tumor-intrinsic and extrinsic factors that influence ICI response, the importance of combining radiation therapy (RT) with ICI, and approaches that may “warm up” cold tumors to increase susceptibility to ICI therapy. Other topics included endpoint selection, incorporation of biomarkers, lumping versus splitting patient cohorts to optimize outcomes, and the importance of inclusion and diversity in the study

of new agents and treatment combinations. Overarching themes included opportunities in the EC landscape, informing new clinical trial directions, and precision medicine.

Keynote presentations focused on how tumor mutations translate to increased immune responses, augmenting tissue-resident memory T cells in EC, and overcoming T cell exhaustion, as well as how RT primes the immune response, enhancing the efficacy of ICI, particularly when few large fraction sizes are utilized.

Highlights from one keynote presentation included the following:

- Higher tumor mutational burden (TMB) increases the likelihood that mutation-associated neoantigens will arise.
- Available biomarkers (e.g., tumor infiltrating lymphocyte signature, interferon-gamma signature, PD-L1, TMB) represent areas of ongoing research.
- A pilot study performed with 10 patients with dMMR EC who received neoadjuvant ICI then went to hysterectomy, yielded a response rate of 37.5%; molecular and immunological assessments were done.[8]
- Questions remain about which combinations, duration, route of administration, and sequence of ICI, chemotherapy, and RT will be most effective in EC.

Another keynote presentation focused on challenges and opportunities for combining RT and ICI for the treatment of EC.

Highlights included the following:

- Barriers to clinical translation include the complex, highly individual nature of a patient's baseline immune fitness, the need to deconvolute the immune effects of RT in irradiated cancer patients (e.g., alteration of microbiome in rectal cancer, durability of effect), and unanswered questions about optimal dose/fractionation, optimal sequencing of ICI and RT. Preclinical data presented provided strong rationale for nonconcurrent RT therapy and ICI with RT preceding ICI for optimal response.
- Mechanisms and diversity of immune response, evasion, and tolerance of irradiated cancers remain poorly understood, and varies between patients, warranting more RT-specific research.
- Application of RT as an immunogenic tool requires modification of standard practices (e.g., excluding draining nodes from combined RT and ICI approaches).

Consensus and Recommendations

The following ideas for clinical trial concepts were developed by working groups prior to the CTPM, refined during the meeting, and prioritized for further development.

- *Adjuvant study of different hormonal combinations in patients with NSMP tumors*
    - Advanced, completely resected, no specific molecular profile (NSMP) estrogen receptor (ER)-positive EC
    - Phase 2/3, non-inferiority design
    - Experimental arm 1: aromatase inhibitor + CDK4/6 inhibitor
    - Experimental arm 2: aromatase inhibitor + mTOR inhibitor
    - Control: carboplatin + paclitaxel
- *Optimizing ICI after ICI combinations*
    - Post-ICI, recurrent EC
    - Phase 2
    - Arm 1: lenvatinib + pembrolizumab
    - Arm 2: bevacizumab + atezolizumab
    - Arm 3 (control): physician's choice of chemotherapy (paclitaxel, doxorubicin)
- *Pharmacodynamic assessment of endocrine priming to enhance immune response*
    - Window-of-opportunity in newly diagnosed NSMP EC
    - Arm 1: aromatase inhibitor
    - Arm 2: aromatase inhibitor followed by ICI
    - Arm 3: aromatase inhibitor + CDK4/6 inhibitor
    - Arm 4: aromatase inhibitor + CDK4/6 inhibitor followed by ICI
    - Primary endpoint is pharmacodynamic immune measurement
    - It may be possible to expand this study to also include a separate dMMR randomization between single agent ICI versus chemo, using the same pharmacodynamic immune measure primary endpoint.
- Discussions continued around designs to test timing of RT and ICI in follow up to the preclinical data described in the second keynote presentation.
    - SBRT + ICI in inoperable endometrial cancer was proposed for further consideration.

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

Anticipated Actions

- A manuscript will be prepared for documentation of meeting outcomes and recommendations.
- A review manuscript of characteristics that are associated with magnitude of benefit from ICI is under development.

References

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3. Rahib L, Wehner MR, Matrisian LM, Nead KT. Estimated Projection of US Cancer Incidence and Death to 2040. *JAMA Netw Open*. Apr 1 2021;4(4):e214708. doi:10.1001/jamanetworkopen.2021.4708
4. Clarke MA, Devesa SS, Hammer A, Wentzensen N. Racial and Ethnic Differences in Hysterectomy-Corrected Uterine Corpus Cancer Mortality by Stage and Histologic Subtype. *JAMA Oncol*. Jun 1 2022;8(6):895-903. doi:10.1001/jamaoncol.2022.0009
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6. Kommoss S, McConechy MK, Kommoss F, et al. Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series. *Ann Oncol*. May 1 2018;29(5):1180-1188. doi:10.1093/annonc/mdy058
7. Guttery DS, Blighe K, Polymeros K, Symonds RP, Macip S, Moss EL. Racial differences in endometrial cancer molecular portraits in The Cancer Genome Atlas. *Oncotarget*. Mar 30 2018;9(24):17093-17103. doi:10.18632/oncotarget.24907
8. De Bruyn M, Eerkens AL, Brummel K, et al. Neoadjuvant immune checkpoint blockade in mismatch repair deficient endometrial cancer. *Annals of Oncology*. Oct 2023;34:S508-S509. doi:10.1016/j.annonc.2023.09.1921

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Agenda

Monday, January 8, 2024

All times EST	**Agenda items**
10:00 a.m.	Welcome and Call to Order *Wolf Lindwasser and Elise Kohn*
10:05 a.m.	Webex 101 *NCI IT Support Team*
10:10 a.m.	Meeting Goals and Objectives *CTPM Co-Chairs: Susana Campos, Linda Duska, and Akila Viswanathan*
10:20 a.m.	All MMRd Are Created Equal (“Debate” Point) *Jose Conejo-Garcia*
10:35 a.m.	PD-1 Immunotherapy in MSI-H Endometrial Cancer: Mutation Isn’t Everything (“Debate” Counterpoint) *Alessandro Santin*
10:50 a.m.	Keynote: IO after IO, PD1+ v TMBhi v MMRd/ Neoadjuvant CPI/What’s Next *Hans Nijman*
11:35 a.m.	Dialing It Up (It’s Getting Hot in Here) *Casey Cosgrove*
11:50 a.m.	Q&A/Open Discussion *Moderators: Sarah Adams and Casey Cosgrove*
12:20 p.m.	Lunch
1:10 p.m.	Keynote: Immunotherapy/Radiation Therapy: Science and Treatment *Silvia Formenti*
1:55 p.m.	The Evolution of Immunotherapy in EC – Sequence and Science *Ramez Eskander*
2:15 p.m.	Immunotherapy and Targeted Agents (e.g., Other IO, Targeted Agents) *Helen MacKay*
2:35 p.m.	Q&A/Open Discussion *Moderators: Susana Campos and Kathy Han*
3:05 p.m.	Break
3:15 p.m.	New Paths to Success *Masha Kocherginsky*

3:35 p.m.	Endometrial Cancer in the Era of Precision Medicine: Lumping and Splitting to Optimize Outcomes *Lainie Martin*
3:55 p.m.	What Is Your Ruler? (Success/Primary Endpoints/Surrogates) *Dmitriy Zamarin*
4:15 p.m.	Q&A/Open Discussion *Moderators: Jessica McAlpine and Akila Viswanathan*
4:45 p.m.	Break
5:00 p.m.	Working Group 2 Proposed Trials *Co-Chairs: Kathy Han and Lainie Martin*
5:15 p.m.	Working Group 3 Proposed Trials *Co-Chairs: Linda Duska and Matthew Harkenrider*
5:30 p.m.	Working Group 4 Proposed Trials *Co-Chairs: Susana Campos and Katherine Fuh*

Tuesday, January 9, 2024
Closed Meeting

All times EST	Agenda items
10:00 a.m.	GCIG Endometrial Cancer Consensus Conference on Clinical Trials *Linda Duska and Elise Kohn*
10:10 a.m.	Breakouts for Final WG Recommendations *Moderators: WG Co-Chairs*
11:10 a.m.	Rapid Presentation of Final Group Recommendations *WG Co-Chairs*
11:25 a.m.	Open Discussion and Prioritization of Trial Ideas *Moderators: CTPM Co-Chairs*
12:25 p.m.	Closing Remarks *CTPM Co-Chairs and Elise Kohn*
12:30 p.m.	Adjourn
12:30 p.m.	Concept Prioritization and Publication Plan Discussion *Elise Kohn*

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Meeting Participants

First name	Last Name	Institution
Sarah	Adams	University of New Mexico
Carol	Aghajanian	Memorial Sloan Kettering Cancer Center
Abdul-Tawab	Amiri	National Cancer Institute
Deborah	Armstrong	Johns Hopkins University
Floor	Backes	Ohio State University
Victoria	Bae-Jump	University of North Carolina at Chapel Hill
Joyce	Barlin	Women's Cancer Care Associates
Susana	Campos	Dana-Farber Cancer Institute
Junzo	Chino	Duke University
Jose	Conejo-Garcia	Duke Cancer Institute
Bradley	Corr	University of Colorado, Denver
Casey	Cosgrove	Ohio State University
Kristina	Creek	The Emmes Company, LLC
Paul	DiSilvestro	Woman & Infants Hospital
Ellen	Dolinar	Patient Advocate
Linda	Duska	University of Virginia
Britt	Erickson	University of Minnesota
Ramez	Eskander	UC San Diego Health
Silvia	Formenti	Weill Cornell Medicine
Katherine	Fuh	University of California, San Francisco
David	Gaffney	University of Utah
Stephanie	Gaillard	Johns Hopkins University
Kari	Hacker	New York University School of Medicine
Kathy	Han	University of Toronto
Kara	Hannah	Lumina Corps
Matt	Harkenrider	Loyola University Medical Center
Jane	Hettinger	National Cancer Institute
Vanessa	Hill	Project Nana, Inc.
Gloria	Huang	Yale University
Amelia	Jernigan	LSU Healthcare Network
Anuja	Jhingran	University of Texas MD Anderson Cancer Center
Mitchell	Kamrava	Cedars-Sinai Medical Center
Ann	Klopp	University of Texas MD Anderson Cancer Center
Masha	Kocherginsky	Northwestern University Feinberg School of Medicine
Elise	Kohn	National Cancer Institute
Eric	Leung	Odette Cancer Centre
Stephanie	Lheureux	Odette Cancer Centre
Ken	Lin	Albert Einstein College of Medicine
Wolf	Lindwasser	National Cancer Institute
Helen	MacKay	Odette Cancer Centre
Stephanie	Markovina	Washington University
Lainie	Martin	Hospital of the University of Pennsylvania

First name	Last Name	Institution
Jessica	McAlpine	University of British Columbia
Mehrdad	Mohseni	National Cancer Institute
Adrienne	Moore	Endometrial Cancer Action Network for African-Americans
David	Mutch	Washington University
Hans	Nijman	University of Groningen
Krista	Pfaendler	West Virginia University
Matthew	Powell	Washington University
Sheila	Prindiville	National Cancer Institute
Kara	Romano	University of Virginia
Goli	Samimi	National Cancer Institute
Angeles	Secord	Duke University
Kathy	Sedgwick	Lumina Corps
Ramy	Serour	National Cancer Institute
Michael	Toboni	UAB Medicine
Akila	Viswanathan	Johns Hopkins University
Stephen	Welch	London Health Sciences Centre
Dmitriy	Zamarin	Icahn School of Medicine at Mount Sinai