Introduction/ Meeting Description

The Gynecologic Cancer Steering Committee’s Clinical Trials Planning Meeting “Designing Targeted Trials for Targeted Endometrial Cancer Populations Using Targeted Agents” was held at the NCI in Rockville, MD on January 7-8, 2016.

The purposes of the meeting were to focus on:

- Consolidation of current molecular uterine cancer knowledge and optimization of molecular subgrouping;
- Dissection of molecular subgroups for actionable molecular and/or clinicopathologic findings;
- Identification and selection of agents for actionable molecular targets within the molecular subgroups as appropriate for phase II and later phase III evaluation;
- Consideration of novel and alternative trial designs to examine, validate, and advance molecular diagnostic grouping;
- Identification of new translational and clinical directions for study across the spectrum of NCI and non-NCI funding mechanisms, including SPOREs, P01s, R01s, Cooperative Groups, CCR, TCGA, phase I and phase II consortia, as well as with the broad range of worldwide academic endometrial cancer researcher.

The goals of this meeting were the:

- Development and validation of diagnostic strategies for molecular subtypes of uterine carcinomas, including biomarkers that are need for critical pathways, biomarkers that are in development but need clinical grade validation, and biomarkers that are CLIA approved and ready for use in clinical trials that can be conducted through the NCTN network.
- Develop a research agenda to include phase 0 to phase III evaluation of agents that target molecularly defined pathways, alone or in combination with
standard chemotherapy in uterine carcinoma and for translational directions to further advance knowledge of -omics characterization of endometrial cancers.

- Publication(s) of findings in a peer-reviewed journal.

Invited attendees included gynecologic oncologists, medical oncologists, radiation oncologists, translational researchers, pathologists, statisticians, industry partners with agents focusing on endometrial cancer and patient advocates.

**Background/Importance of Research Topic/Disease/Limitations**

The molecular revolution has yielded remarkable advances in many cancers where driver mutations and actionable pathway activation has been identified. There has been a 50% increase in endometrial cancer incidence, with a nearly 300% increase in deaths over the period from 1987 to 2008. This is in part due to increased frequency of high grade endometrial cancer subtypes with more frequently recurrent, and thus non-curable disease. No new agents have been approved for treatment of endometrial cancer over this same two decade period, leaving progress in treatment of this disease a major unmet need for the women of the United States.

The GCSC polled its membership in 2014 to identify directions for trials in endometrial cancer, and the top priority was integration of molecular and/or histologic stratification into endometrial cancer management with 50% of the votes cast as 1st or 2nd priority, and an overall top score of 80%. The GCSC tasked the UTF to develop a CTPM plan to couple advances in molecular characterization with clinicopathologic parameters to direct new clinical trials in endometrial cancer.

New molecular knowledge from NCI-sponsored endeavors such as the TCGA, SPOREs, and NCTN-associated translational research has yielded a minimum critical mass of information to allow dissection of endometrial cancers into at least four molecular and potentially actionable groups:

- High copy number (serous-like), poor prognosis: p53 mutation, DNA damage repair pathways, PI3K hi, KRAS mutated, chemo-sensitive, ~30% HER2 overexpression
Low copy number (endometrioid), intermediate prognosis: hormone receptor positive, alterations in Pi3K, PTEN, and mTOR

Microsatellite instability, hypermutated, intermediate prognosis: loss of PTEN, PI3K mutated, MSIhi

Polymerase ε (POLE) over-expressors, ultramutated, excellent prognosis: Question remains if and when is there a need for treatment.

These subsets have different molecular signatures and appear to have different behaviors. Therefore, the task of how to design trials to focus therapies to the molecular vulnerabilities of these entities was the challenge facing this CTPM. Directions to address included consideration of creative trial designs using agents designed to disrupt uterine cancer pathways demonstrated to be common and activated, selection of agents, patient selection biomarkers, and optimal combinatorial strategies.

Consensus & Recommendations

The CTPM Leaders had the participants break out into 4 Working Groups:

- Gene and Pathway Group
- Phase 0-2 Group
- Uterine Papillary Serous Carcinoma Group
- Randomized Phase II Group

The Gene and Pathway group identified potential pathways and targets. Their review and interpretation of the literature and therapeutic opportunities was provided to each of the breakout groups for their consideration. Each breakout group developed 3-5 potential concepts that were discussed at the face-to-face meeting and then prioritized for development.
Phase 0-2 Group

Phase 0 pharmacodynamic trial of TRIAPINE (NSC# 663249) in uterine corpus serous adenocarcinoma

- Day 1: Infusion
- Day 2: Surgical hysterectomy

Day 1: Intravenous triapine infused at fixed dose of 25 mg/m². CTCAE v. 4.0 criteria monitored.
Day 1: Surgical interventions with vaginal endometrial hysterectomy and lymphadenectomy performed.
Day 2: Confirmation of H&E tumor confirmation and then GC versus GC DNA content determination by flow cytometry.

Duration of treatment: One (1) cycle
Duration of study: Two (2) weeks

Phase 0 trial testing AI+/- CDK 4,6 Inhibitor: Schema

Hypothesis and objectives:
- Measure change in cell proliferation induced by 1 agent with AI+/-CDK4/6 combination vs. AI
- Identify potential markers of response to the combination

Eligibility:
- Endometrial cancer
- Candidate for hysterectomy
- Younger than 70 years
- Endometrial histology

Endometrial biopsy
FFPE tumor material
- IHC: ER, PR, Ki67, pRB, cyclin D1, p16, p53, PTEN, b-catenin
- DNA: MSI, PIK3CA mutation

Endometrial tumor
FFPE tumor material
- IHC: ER, PR, Ki67, pRB, cyclin D1, p16, p53, PTEN, b-catenin

Anticipated outcomes:
- Expression of 5Ki67 may support future AI-CDK4/6 trials
- Markers for selecting patients for future AI-CDK4/6 trials

Diagnosis of Primary Endometrioid Adenocarcinoma of the Uterine Corpus by D&C or Biopsy (Paraffin Block Must be Available) or 16 Sections of 3 Micron Thickness on Charged Slides Suitable for Standard Immunohistochemistry Assays

Patient entry

Depo-Provera (Medroxyprogesterone Acetate): 400 mg IM, given once, 11-24 days prior to hysterectomy

Entinostat PO
No treatment

Decision to be determined

(Standard surgical therapy: Hysterectomy, BSO, +/- lymph node sampling) (Paraffin block of tumor must be available or 16 unstained sections of 3 micron thickness on charged slides suitable for standard immunohistochemistry assays)

Off treatment
- **Uterine Papillary Serous Carcinoma Group**

Stage III or IVa (with measurable disease)
Stage IVb or recurrent
Serous or high grade endometrial cancer

Randomization

Eligibility:
Recurrent serous carcinoma
(First recurrence after carboplatin-
paclitaxel chemotherapy failure)

Investigator Choice of chemotherapy:
- Dense dense Paclitaxel
- Docetaxel
- Topotecan

Combination of ATR inhibitor + PD1 immune
check point inhibitor in all comers USG patients
with recurrent disease

Combination of Capcitabine and Atarimid in
recurrent USG patients with measurable disease
(restricted to USG patients with HER2/new gene
amplification and/or PIK3CA mutations)

Mirvetuximab Soravtamide (ADC against folate
receptor Alpha in recurrent USG patients
(restricted to patients with FR-alpha
overexpression).

- **Randomized Phase II Group**

Randomized phase 2 study of cabozantinib
with or without PD1 inhibitor

**Anticipated Action(s)**

Two publications from the meeting are now planned, which will be developed with the planning team. The first is focusing on the genetic targets and pathways, and the second, the meeting clinical outcomes.

Questions going forward for the field:

- Standardization of MSI definition and assays
- Functional assay requirements for ARID1a, POLE mutation analysis?
- How to address intratumoral heterogeneity, especially when types are mixed
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.

References


Planning Team members:

- Michael Birrer, M.D., Ph.D.
- Linda Duska, M.D.
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- David Gershenson, M.D.
- Randall Gibb, M.D.
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- Charles Kunos, M.D.
- Douglas Levine, M.D.
- Amit Oza, M.D.
- Sarah Temkin, M.D.

Breakout Group Leaders:

- Gene and Pathway: Douglas Levine, M.D., Helen MacKay, M.D.
- Phase 0-2: Linda Duska, M.D., Gini Fleming, M.D.,
- Uterine Papillary Serous: Michael Birrer, M.D., Ph.D., Alessandro Santin, M.D. Ph.D.
- Randomized Phase II: Amit Oza, M.D., Matthew Powell, M.D.