

Gynecologic Cancer Steering Committee
Designing Targeted Trials for Targeted Endometrial Cancer Populations Using Targeted Agents
January 7-8, 2016
Co-Chairs: Gini Fleming, M.D., Helen MacKay, M.D., David Mutch, M.D.

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.*

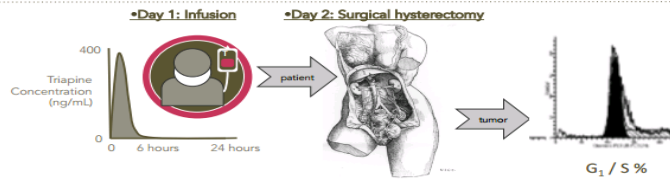
○ Phase 0-2 Group

Phase 0 pharmacodynamic trial of

TRIAPINE (NSC# 663249)

in uterine corpus serous adenocarcinoma

Schema



Day 1: Intravenous triapine infused at fixed dose of 25 mg m⁻². CTCAE v. 4 toxicities monitored.
 Day 2: Surgical hysterectomy with bilateral salpingo-oophorectomy and lymphadenectomy performed.
 Day 2 pharmacodynamic assay: Snap-frozen tumor (x4, 0.5cm-3) stored for H&E tumor confirmation, and then 2C versus 4C DNA content determination by flow cytometry.
 Duration of treatment: One (1) cycle
 Duration of study: Two (2) days
 Duration of follow-up: History & physical examination at baseline, Day 1, Day 2, and at post-surgical discharge.
 Complete blood counts with differential and serum chemistries are drawn at baseline, Day 1, and Day 2. Patients are followed until 6-week post-surgical follow-up history and physical examination.

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

Pineda/Matei/Fleming

Hypothesis and objectives:

- Measure change in cell proliferation induced by 2 wk tx with AI+CDK4/6i combination vs. AI
- Identify potential markers of response to the combination

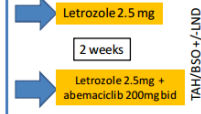
Eligibility:

- Endometrial cancer
- Candidate for TAH/BSO
- ER+/PR+
- Endometrioid histology

Endometrial biopsy

FFPE tumor material
 -IHC: ER, PR, Ki67, pRB, cyclin D1, p16, pAkt, PTEN, b-catenin
 -DNA: MSI, PI3K mutation, CTTN8 mutation

1:1 randomization



TAH/BSO +/- LND

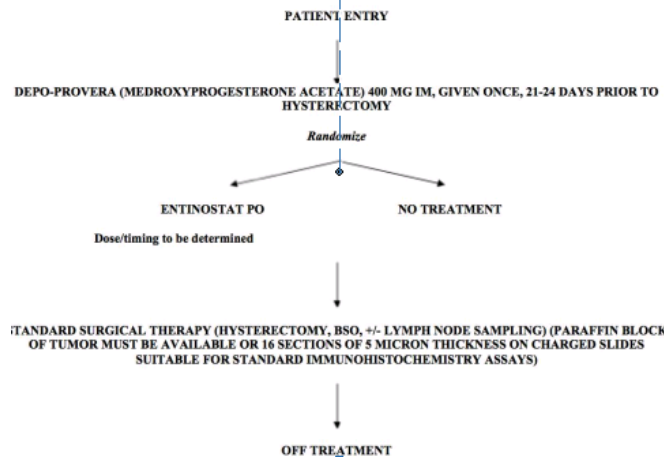
Endometrial tumor
 FFPE tumor material
 IHC: ER, PR, Ki67, pRB, cyclin D1, p16, pAkt, PTEN, b-catenin

Anticipated outcomes:

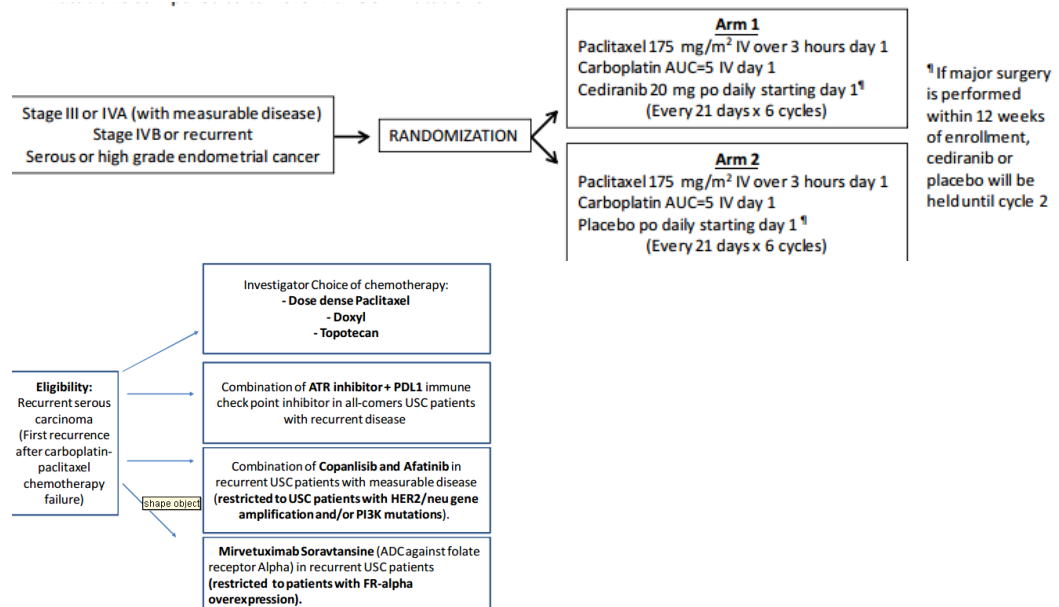
- δ Ki67 AI+CDK1 > AI
- Identify biomarkers correlated with δ Ki67

- Magnitude of δ Ki67 may support future RPh. 2 trial
- Markers for selecting patients for future RPh 2 trial

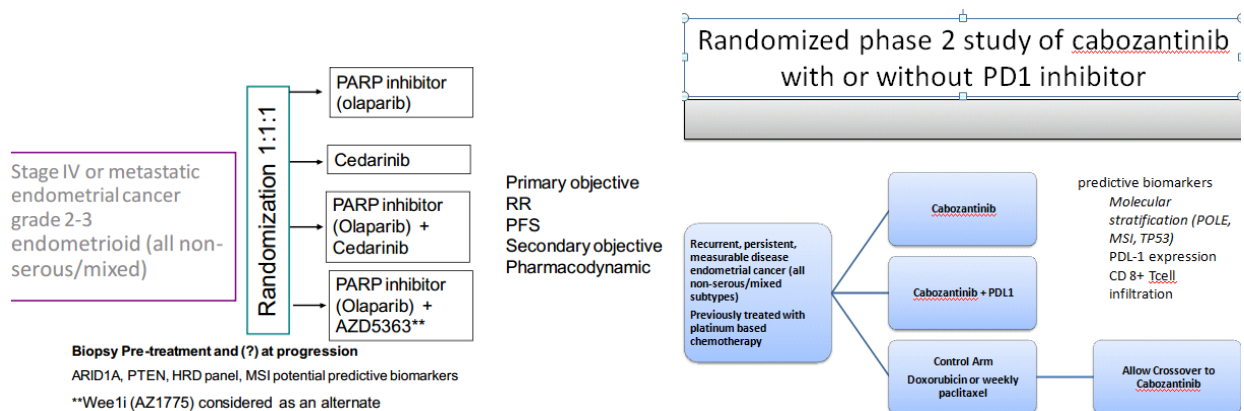
DIAGNOSIS OF PRIMARY ENDOMETRIOID ADENOCARCINOMA OF THE UTERINE CORPUS BY D&C OR BIOPSY (PARAFFIN BLOCK MUST BE AVAILABLE OR 16 UNSTAINED SECTIONS OF 5 MICRON THICKNESS ON CHARGED SLIDES SUITABLE FOR STANDARD IMMUNOHISTOCHEMISTRY ASSAYS)



○ Uterine Papillary Serous Carcinoma Group



○ Randomized Phase II Group



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:

- o Standardization of MSI definition and assays
- o Functional assay requirements for ARID1a, POLE mutation analysis?
- o 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.

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- *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.*