Gynecologic Cancer Steering Committee Clinical Trials Planning Meeting

Defining and Targeting Molecular Pathways to Direct Personalized Value-added Treatments for Patients with Epithelial Ovarian Cancer

National Cancer Institute, Rockville MD, February 25-26, 2021

Co-Chairs: Gottfried Konecny, M.D., Carolyn Muller, M.D., and Shannon Westin, M.D., M.P.H
with Jean Lynn, M.P.H., R.N. & Elise C. Kohn, M.D.

Introduction

The Gynecologic Cancer Steering Committee (GCSC) received a proposal for a Clinical Trials Planning Meeting (CTPM) to identify and prioritize novel and existing therapeutics and combinations to target scientifically defined ovarian cancer subgroups, in an effort to advance precision therapy of epithelial ovarian cancer. The proposal was endorsed by the GCSC in February 2019 and was approved for funding by the NCI Clinical and Translational Research Operations Committee in April 2019. The Core Planning Team began meeting in January 2020 to set the agenda, identify speakers and set the stage for breakout brainstorming groups that began meeting bi-weekly in July 2020 and continued right up to the week before the meeting.

There were three breakout groups:

- Group 1 – Molecular/Mutational Landscape- their focus was to cull the scientific literature for data on validated discriminants to direct and inform treatment focused groups;
- Group 2 – Focused on trial designs based on molecular selection using validated markers that would inform patient selection and treatment stratification;
- Group 3 – Focused on novel combination therapies to overcome drug resistance in pretreated patients.

The meeting was held virtually on February 25-26, 2021. Invited attendees included medical oncologists, radiation oncologists, gynecologic oncologists, immunologists, translational researchers, statisticians, patient advocates and industry partners with agents and/or interest focusing on epithelial ovarian cancer.

Background/Importance of Research Topic/Limitations

- In 2021, the American Cancer Society estimates the incidence of ovarian cancer in the United States to be 21,410 women and approximately 13,770 women will die from ovarian cancer.(www.acs.org)
- Epithelial ovarian cancer generally presents at an advanced stage and is the most common cause of gynecological cancer death.
- The majority of ovarian cancer patients recur due to drug resistance and succumb to their disease
- Epithelial ovarian cancer is composed of distinct histological subtypes with unique genomic characteristics, which is anticipated to improve the precision and effectiveness of therapy, allowing discovery of predictors of response such as mutations in breast cancer susceptibility genes *BRCA1* and *BRCA2*, and homologous recombination (HR) deficiency (HRD) for DNA damage response pathway inhibitors or resistance (cyclin E1).
- Treatment requires expert multidisciplinary care to include surgery and adjuvant therapy. https://pubmed.ncbi.nlm.nih.gov/30910306

Meeting Objectives

The objectives of the meeting were to

- To define current and emerging molecular and clinical classifications of epithelial ovarian cancer subgroups and subsequent implications for trial design and eligibility;
- To design clinical trials that will explore new hypotheses needed to drive targeted treatment approaches in epithelial ovarian cancer;
- To incorporate novel trial designs and clinical endpoints that promote integral patient selection in a personalized medicine approach.

Meeting Summary

Keynote Address: *Learning from Failure: Next Steps for Patients with Recurrent, Persistent, and Resistant Disease & Approaches to Trial Design in the Heterogeneous Landscape of Prior Drug Exposure- Dr. Amit Oza.* Highlights include:

- Covered four decades of treatment for ovarian cancer to include surgery, chemotherapy (platinum and taxanes) antiangiogenic therapy, parp inhibitors (PARPi) and potentially immunotherapy;
- Importance of evidence-based standard of care and where to use the different treatment modalities e.g., 1st line, second line alone and in combination;
- Importance of looking at ovarian cancer types (high grade serous, mucinous, low grade, clear cell, endometrioid) as treatment will vary on the type;

- How to plan for treatment and integrate newer combinations of agents;
- Review the evolution of resistance by obtaining molecular data at different points in treatment phase as drugs can alter the tumor microenvironment;
- Focus on quality of life and patients living longer.

Molecular Landscape of Ovarian Cancer – Biomarkers & Pathways

Overview of the landscape included:

- What is a fit-for-purpose biomarker?
- Status of validated DNA damage repair biomarkers
- Exploration of MEK and PI3K/AKT inhibition
- Synthetic lethality pathways & biomarkers of opportunity
- Status of biomarkers for immune checkpoint blockade
- Is angiogenesis a targetable pathway?
- Other potential biomarkers/targets (ATR/Wee1; Neddylation; GAS6/AXL; MYC/GLS; XPO1)

Therapeutic Landscape of Ovarian Cancer – Clinical Opportunities

Presenters provided an overview of the therapeutic landscape with respect to novel combinatorial strategies to target synergy and potentiation, and adaptive and resistant response. Key highlights included:

- The need to use combinations of drugs to target synergy and potentiation;
- Acknowledgment of the clinical challenge in combining drugs at effective doses without unacceptable side effects e.g., MEK inhibitor and AKT inhibitor;
- Critical to understand underlying biology of the individual tumor as it's the driver of molecular events;
- Need to understand compensatory mechanisms as a result of blocking complex networks involving crosstalk and feedback loops;
- Need for longitudinal molecular monitoring alongside treatment efficacy, to enable the early identification of resistant clones;
- Pre-emptively target resistance with new drugs combinations prior to the onset of progression;
- Newer technologies (shRNA and CRISPR, phosphoproteomics) provide opportunities to identify synthetic lethal drug combinations and understand compensatory signaling mechanisms;
- Trial design evolution: dosing schedules (intermittent, sequential) adaptive designs, importance of randomized trials;

- Combine novel agents early in drug development, rather than delaying until approval of one or both drugs;
- The need for novel agents that target adaptive behavior and acquired resistance;
- HR deficient cells adapt via upregulation of POLθ and MMEJ, which can be targeted by novobiocin;
- PARPi harm HR-deficient cells by a variety of mechanisms. Acquired resistance is heterogeneous although restoration of HR and stabilization of replication forks are major mechanisms;
- Multiple strategies for reversing restored HR; relative selectivity for tumor cells must be considered;
- ATR-CHK1 inhibition reverses restored HR and destabilizes replication forks;
- Many HGSOCs have evidence of replication stress;
- Replication stress can be exacerbated to the threshold for lethality by gemcitabine and ATR or CHK1 inhibition, either alone or in combination, depending on the baseline levels of endogenous replication stress;
- WEE1 stabilization is a critical consequence of ATR-CHK1 activation and relieves replication stress and promotes survival;
- WEE1 inhibition may reverse resistance to ATR or CHK1 inhibition.

Existing/Pending Industry Trials

Industry partners provided updates on their portfolios and current and future oncology clinical trials, several with application to ovarian cancer. Presentations focused on use of inhibitors and combination therapies. New public/industry partnerships are anticipated.

Conclusion

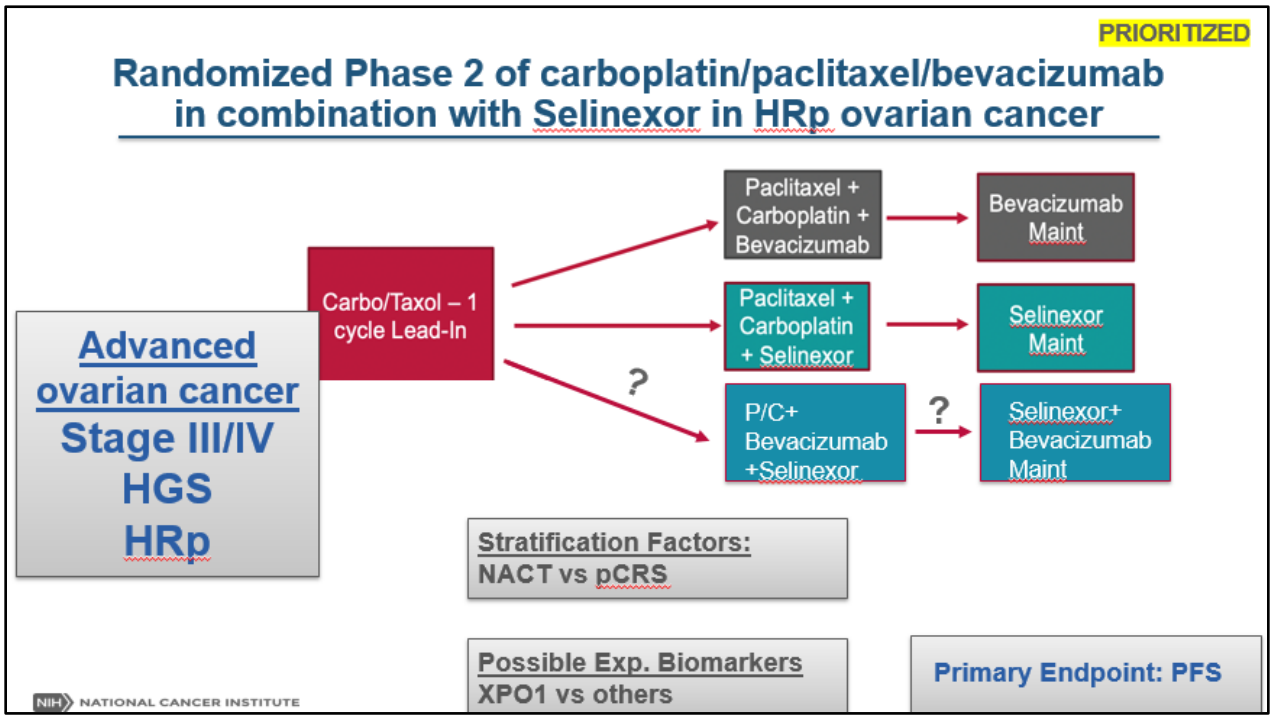
There was a consensus among the meeting attendees that there are many opportunities to use and advance molecular knowledge to optimize treatment of epithelial ovarian cancer. Considering the heterogeneous molecular landscape of this disease, shifting the treatment paradigm toward personalized approaches is a necessity. The patient advocates expressed that the presentation of the trial proposals herein shows progress toward much needed advancement in the field.

Clinical Trial Brainstorming & Development

There was a total of 4 clinical trial concept ideas that were prioritized by the Executive Committee for further development in the areas of HR proficient (HRp) disease, biomarker-directed neoadjuvant treatment, primary platinum resistant disease, and ovarian clear cell

carcinoma. There was also a robust discussion on how to best pursue primary platinum refractory patients and patients who have acquired PARPi resistance, with trial ideas for consideration under development.

Proposals prioritized for development:



PRIORITIZED

Toward strategy for HR-proficient ovarian cancer: Phase 1 trial of novel agents with biomarker discovery

Recurrent ovarian cancer HRd or HRp Unlimited priors

- Olaparib + AVB-500
- Olaparib + telaglenastat
- Olaparib + selinexor

- **Primary Endpoint: Safety/RP2D**
- **BOIN design vs 3+3**
- **Expansion phase for signal assess**

Use this trial to feed into future HRp or PARP/Platinum Resistant Trials.

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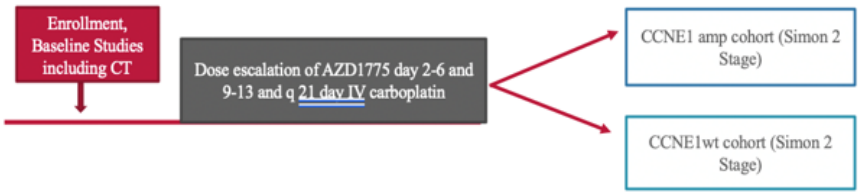
PRIORITIZED

A phase 2 study of AZD1775 + carboplatin in 2 cohorts of women with primary platinum resistant ovarian cancer selected by +/- CCNE1 amplification



Primary platinum resistant ovarian cancer

Daily dosing based on recent data presented from ETCTN 9350 (Naquash et al.) Identifying the RPh2 monotherapy dose of 300mg day 1-5 and day 8-12.

- **Primary Endpoint: Safety and RR**
- **N: ~ 40 in each arm**

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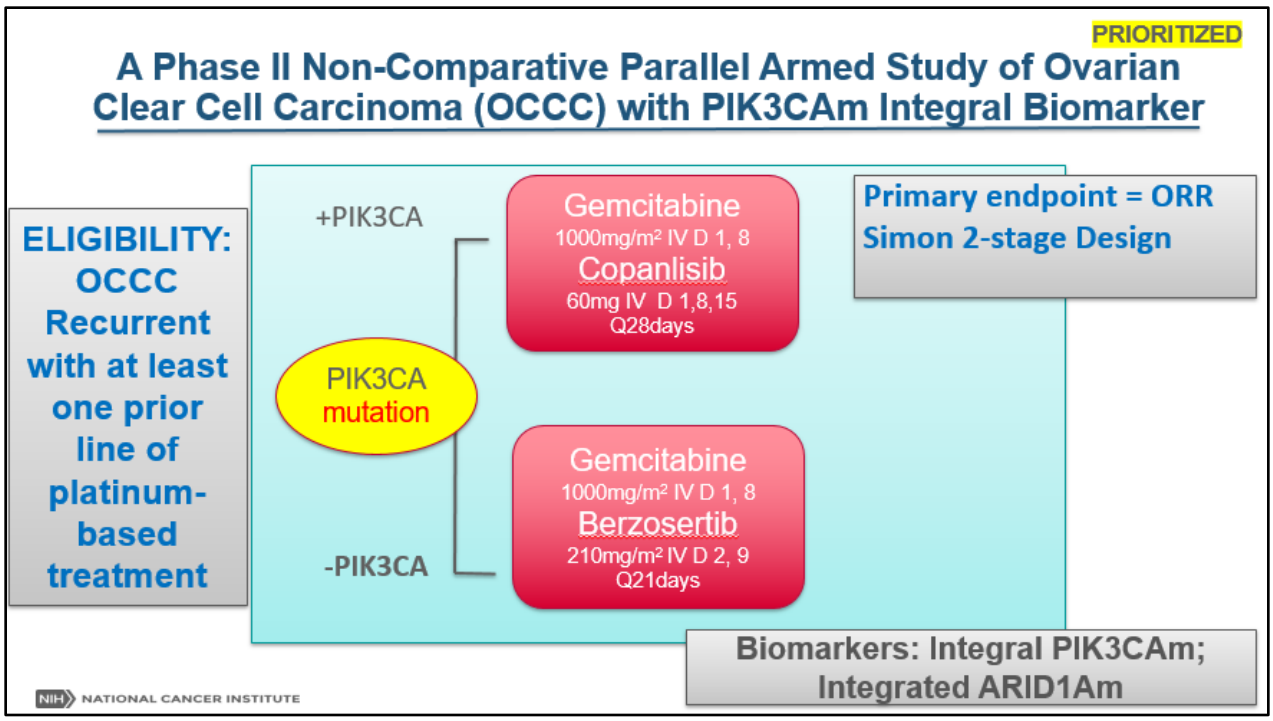

Anticipated Actions

- NRG and CCTG will prioritize which concept(s) to move forward;
- Publication of the outcome of the meeting that will include mentored junior investigators.

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.

Meeting Participants

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