Gynecologic Cancer Steering Committee Clinical Trials Planning Meeting

Moving Forward in Cervical Cancer: Enhancing Susceptibility to DNA Repair Inhibition and Damage

NCI Shady Grove, Rockville MD, October 25-26, 2018

Co-Chairs: Don Dizon, M.D., Ritu Salani, M.D., and Anuja Jhingran, M.D.,
with Jean Lynn, M.P.H., R.N. & Elise C. Kohn, M.D.

Introduction

The Cervical Cancer Clinical Trials Planning Meeting was held October 25-26, 2018 at NCI-Shady Grove in Rockville, MD. Attendees included clinicians and researchers with experience in oncologic and gynecologic malignancies, statisticians, industry colleagues and patient advocates.

The meeting presentations were divided into the following scientific areas after which round table discussions on applying this knowledge to development of clinical trials occurred.:

- Molecular landscapes in cervical cancer
- DNA repair dysfunction and the tumor microenvironment
- DNA damage and repair inhibition in novel treatments

Background/Importance of Research Topic/Limitations

Advances in therapy for cervical cancer has remained mostly stagnant over the past decades, with low survival rates for advanced stage disease presentation or recurrent disease. Chemoradiation strategies and regimens including new drug combinations, recombinant erythropoietin, and hypoxic sensitization have shown little improvement over the current standard of care of cisplatin chemoradiation for women with locally advanced disease. The recent approval of chemotherapy with bevacizumab for newly diagnosed advanced stage disease, recurrent disease, or metastatic disease is the first approval for cervical cancer and leaves open the need to design effective and safe second line or better first line regimens.

Therapeutic challenges include tumor heterogeneity, target validation, high local and distant failure rates and late complications of chemoradiation. However, advances in patient selection and treatment including advances in radiation therapy techniques such as use of adaptive imaging and brachytherapy have decreased toxicity, yielding improved QOL and cancer control. The efficient application of effective trial design including use of available technology and genomic information are critical to improve outcomes.

Meeting Objectives

The goals of the meeting were to

- To identify novel treatment strategies by taking advantage of DNA damage repair (DDR) and cell cycle aberrations across drug classes for clinical development;
- To explore optimization of radiation therapy using DDR inhibitors in combination with other novel agents;
- To consolidate known and emerging data on candidate biomarker and targets to guide correlative studies into treatment trials;
- To design clinical trials addressing DDR opportunities, while expanding access to these clinical trials. Trial proposal breakout group one focused on primary and maintenance therapy to develop novel agent combinations incorporating radiation, while group two covered first and second line treatment in therapy settings.

Meeting Summary

State of the Standard of Care in Cervical Cancer

The first session addressed the current landscape and standards of care (SOC) in cervical cancer. The International Federation of Gynecology and Obstetrics (FIGO) recently updated their staging system to reflect current diagnostic methods, incorporating imaging results. The staging now classifies smaller tumors (stage IB1) amenable to less aggressive, fertility sparing therapy, as well as nodal involvement (stage IIIc) based on radiologic findings (designated with an R) and/or pathology results (designated, P).

Early stage disease is treated by surgery or chemoradiation depending upon stage. Cisplatin concurrent with external beam radiation and brachytherapy is endorsed internationally for locally advanced disease. Use of chemotherapy, such as cisplatin + paclitaxel, with bevacizumab (G0G 0240) was shown to have an overall survival benefit and is the FDA-approved SOC for first line combination chemotherapy use; recently, pembrolizumab has been approved for select PD-L1 positive patient populations based upon a single arm study response rate.

The wide use of cisplatin demands more non- platinum options for recurrence. Study evidence by the National Cancer Institute of Canada (NCIC), Gynecologic Oncology Group (GOG) and a meta-analysis of chemoradiation trials supports use of combined modality therapy noting the importance of dose, and treatment duration <8 weeks on outcome, with improvement seen in PFS, OS and reduction in regional and distant failure. However, how exposure to cisplatin in that setting may affect subsequent response is unclear. One approach has been to incorporate chemotherapy or neoadjuvant therapy in first treatment to try to improve cure rate up front. Current trials of chemoRT and systemic intensification include:

- OUTBACK- A Phase III trial of adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone. (closed to accrual)
- INTERLACE- A trial of chemotherapy before chemoradiation for cervical cancer (accruing)
- A Randomized Phase II trial of Radiation Therapy and Cisplatin Alone or in Combination with Intravenous Triapine in Women with Newly Diagnosed bulky Stage IB2, or Stage II, IIIB, or IVA Cancer of the Uterine Cervix or Stage II-IVA Vaginal Cancer (Protocol: NRG-GY006, accruing)
- CX5 SHAPE - A Randomized Phase III Trial Comparing Radical Hysterectomy and Pelvic Node Dissection vs Simple Hysterectomy and Pelvic Node Dissection in Patients with Low-Risk Early Stage Cervical Cancer. (accruing)

Molecular Landscapes in Cervical Cancer

Efforts in molecular tumor analysis and genomic profiling have led to a new era of precision oncology. Mutational analysis has yielded identification of small subsets of cervical cancer characterized by genomic events, such as the <4% of patients whose tumors have ERBB2/HER2 amplification. The TCGA cervical cancer project, the largest academic collection of cervical cancer molecular data to date, shows unexpected mutation rates within DNA repair genes. Potential targets were described by relative frequency, statistical significance, biological function and severity of disease.

Cervical cancer has been found to have mutations in some recognized targetable genes, such as PIK3CA and ERBB2, and rarely in BRCA 1 and BRCA 2, although the application of this to treatment is unknown. These genes may promote continued cell division, via the ATM and ATR pathway. Direct and indirect damage involving downstream biochemical effects impact many pathways suggesting the utility of targeting multiple pathways. Reactive oxygen species (ROS) have also been demonstrated and are known to promote radio-sensitization. Genomic biomarkers for radiation response include HPV status, genotype and gene signatures with additional targets to be addressed in the future.

Foundation Medicine has initiated comprehensive profiling of cervical cancer. They also assess microsatellite instability status and tumor mutational burden. TMB is considered one of several potential markers that may predict immunotherapy response. Foundation CORE has identified common mutations, pathways and gene interactions which can enhance diagnostics but are limited by a lack of clinical data on pretreatment effects. They confirm that this is generally a disease of low TMB.

DNA Repair Dysfunction and the Tumor Microenvironment in Cervical Cancer

DNA repair has been implicated as a target in cervical cancer first by the fact of cervical cancer's remarkable sensitivity to platinum agents and radiation. Newer data show that there are somatic mutations in many DDR genes, and HPV replication is dependent on activation of several DDR pathways. HPV uncouples DDR protein expression from the cell cycle and hijacks the DNA replication cellular machinery for HPV virus replication. Abrogation of the G1/S checkpoint by E6/E7 dysregulation of p53 and pRb contribute to the sensitivity of HPV+ cancers to RT. Repair inhibition administered with radiation therapy is a novel direction with data to support testing prospectively.

Tumor microenvironment and tissue hypoxia contribute to radiation sensitivity, as radiation can cause damage directly to DNA or indirectly via ROS. A shift to the glycolytic pathway occurs in cancers and targeting this event in combination with radiation is a new strategy with preclinical support. Change in radiation approaches incorporating dose, biology, volume-based therapy (EMBRACE), sensitizers, and tumor specific RT are emerging ideas.

Building on DNA Damage and Repair Inhibition in Novel Treatments

The NCI Cancer Therapeutics Evaluation Program (CTEP) has a broad portfolio with agents that may either contribute to radiation activity or be biologically active alone or in combination with other agents. The portfolio includes many agents active in the DDR pathway. In addition, the NCI Formulary contains agreements for access to agents not in the CTEP portfolio. Volume-based image guided adaptive brachytherapy (IGABT) is a novel technique being used to establish a correlation between dose, volume and local control, and from which to develop new hypotheses. Strategies to go beyond tumor size for response prediction and assessment of radiation effects include studies of serial tumor and blood biospecimens for endpoints such as HPV viral load, functional imaging response, and consideration of window of opportunity studies for pharmacodynamic and tissue clinical endpoint analysis. DDR inhibition, immune checkpoint antagonists, and PARP inhibitors are promising directions. Identifying and validating biomarkers is key to stratifying patients to personalize therapy and minimize toxicity.

Existing/Pending Industry Trials

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

Clinical Trial Brainstorming.

Breakout groups with the mission of brainstorming new clinical trial directions were organized, and met for months prior to the CTPM. CTPM Leaders had the participants break out into these Working Groups during the second half of the meeting tasked to hone prior ideas down to 2-3 potential clinical trial concepts to prioritize for development.

Breakout Group 1 Co-Chairs: Corinne Doll, M.D., Jennifer Scalici, M.D. and Julie Schwarz, M.D., Ph.D.
Breakout Group 2 Co-Chairs: Stephanie Lheureux, M.D., Ph.D. Tashanna Myers, M.D. and Anna Tinker, M.D.

Proposals prioritized for development:

Trial Proposal # 1: CB-839 added to chemoradiation (cisplatin + RT)

- Design: Phase II, single arm
- Details: Patients receive glutaminase inhibitor CB-839 (800 mg po twice daily) as lead-in with standard EBRT + cisplatin; IB2-IVA cervical cancer patients eligible for chemoradiation.
- Endpoints:
    - Primary – estimate the progression free survival and toxicity of CB-839 added to CRT for locally advanced cervical cancer.
    - Secondary – evaluation of response by MRI and FDG-PET imaging and estimation of overall survival. MRI will be performed at baseline, mid-treatment, and at 3 months after chemoradiation.
    - Exploratory
        - Changes in serum and tumor tissue glutathione levels as measured by mass spectroscopy.
        - Association of serum and tissue glutathione level changes with FDG-PET response.
        - Intratumoral cisplatin concentration will also be measured by mass spectrometry at the mid-treatment timepoint.
- Design will need to be re-discussed if GY006 yields positive results.

Trial Proposal # 2: ATRi followed by chemoradiation +/- re-dose prior to brachytherapy

- A Window of Opportunity design that calls for a molecular evaluation prior to chemoradiation.
- A low dose of the agent will be administered at early stages of chemoradiation.
- There will be an opportunity for the drug to be re-introduced at a low level following chemoradiation prior to brachytherapy.
- Phase I rolling platform pilot study.
- Correlatives include biopsies pre- and post- agent administration, apoptosis markers, and an evaluation of the tumor microenvironment.

Trial Proposal # 3: X4P-001 primary maintenance post chemoradiation GTAC arm

- Could enroll X4P-001 and bevacizumab, if available, as two independent arms.
- Randomization of patients after the initiation of chemoRT.
- Triapine study is not competing for a subset of the high risk locally advanced patients.
    - Node positive patients will not be eligible
- Endpoints
    - Primary – Progression free survival
    - Secondary – Overall survival; frequency and severity of adverse events; patient-reported outcome.

Trial Proposal # 4: First line GOG240 replacement with switch maintenance

- Agents to be determined.
- Bevacizumab maintenance will be the control arm per GOG240
- Endpoints
    - Primary –Progression free survival; patient-reported outcome
    - Secondary – ctDNA; QOL
- Retrospective ancillary analysis
    - At what point was chemotherapy stopped before bev maintenance was administered in patients who were on treatment longer than the median number of cycles?
    - A retrospective plan will help outline the hypothesis of the study.

Trial Proposal # 5: Post GOG240 population – ATRi+IO/prexasertib/prexasertib+IO

- Consider platform study modeled after GY012
- Endpoints
    - Primary – Overall response rate
- Retrospective ancillary analysis
    - Evaluation of platinum resistance in recurrent disease; focus on post CCRT.

- Prexasertib is in NCI formulary; currently not in CTEP portfolio

There was a consensus among the meeting attendees that there are many opportunities to use molecular knowledge to enhance therapy of cervical cancer, and that exploring treatment beyond cisplatin is a necessity. The patient advocates expressed that the presentation of specific trial proposals shows progress toward much needed advancement in the field. They confirmed a continued commitment to helping the NCI to connect with cervical cancer patients to improve study enrollment, provide key disease insight and accelerate new therapeutics.

Anticipated Actions

- Identification of the top feasible ideas suited to the NCTN mechanism to advance cervical cancer clinical trials;
- Consideration of how integral and integrated biomarkers can be applied;
- Publication of the proceedings.

(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.)

Cervical Cancer CTPM Planning Team

CTPM Core Planning Committee:

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Breakout Group Leaders:

Breakout Group 1: Corinne Doll, M.D., Julie Schwarz, M.D., Ph.D., and Jennifer Scalici, M.D. with Don Dizon, M.D.

Breakout Group 2: Stephanie Lheureux, M.D., Ph.D., Tashanna Myers, M.D., and Anna Tinker, M.D., with Ritu Salani, M.D. and Anuja Jhingran, M.D.

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