Arizona Oncology Clinical Trials and Research

Disease Type	Protocol
Carcinoma of the Cervix (KN 826).	Have persistent, recurrent, or metastatic squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix which has not been treated with systemic chemotherapy and is not amendable to curative treatment (such as with surgery and/or radiation). Note: Prior chemotherapy utilized as a radiosensitizing agent and completed at least 2 weeks prior to randomization of all radiation-related toxicities is allowed. NCT03635567
Cervical Adenocarcinoma or Squamous Carcinoma (CALLA)	Female, Aged at least 18 years. Documented evidence of cervical adenocarcinoma or squamous carcinoma FIGO Stage IB2-IIB Node positive or IIIA-IVA any node. No prior chemotherapy or radiotherapy for cervical cancer. WHO/ ECOG performance status of 0-1. At least 1 lesion, not previously irradiated, that qualifies as a RECIST 1.1 Target Lesion at baseline. NCT03830866
Cervical Cancer (Empower Cervix-1)	Recurrent, persistent, and/or metastatic cervical cancer, for which there is not a curative-intent option (surgery or radiation therapy with or without chemotherapy). Tumor progression or recurrence within 6 months of last dose of platinum therapy that was used to treat metastatic, persistent or recurrent cervical cancer. Candidates to receive REGN2810 (Cemiplimab) and chemotherapy per the label of the combination. Acceptable histologies are squamous carcinoma, adenocarcinoma, and adenosquamous carcinoma. Sarcomas and neuro-endocrine carcinomas are not eligible histologies. NCT03257267
Cervical Cancer (RaPiDs)	This is a randomized, blinded, non-comparative, two-arm Phase 2 clinical trial to assess the efficacy and safety of AGEN2034 (anti PD-1) administered with placebo (Treatment Arm 1 - monotherapy) or with AGEN1884 (anti CTLA4) (Treatment Arm 2 - combination therapy) for treatment of patients with advanced cervical cancer who relapsed or progressed after receiving first-line platinum-based chemotherapy. Patients will receive AGEN2034 with placebo as a monotherapy or with AGEN1884 as combination therapy for a maximum of 24 months or until confirmed progression, unacceptable toxicity, or any criterion for stopping the study drug or withdrawal from the trial occurs. NCT03981796
Endometrial Carcinoma (KN 775)	Histologically confirmed diagnosis of endometrial carcinoma. Documented evidence of advanced, recurrent or metastatic EC. Radiographic evidence of disease progression after 1 prior systemic, platinum-based chemotherapy regimen for recurrent, metastatic or primary unresectable disease. NCT03517449
Endometrioid, or clear cell Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (Moonstone).	Patient must be female ≥ 18 years of age, able to understand the study procedures, and subsequently agreed to participate in the study by providing written informed consent. Patients must have recurrent high-grade serous, endometrioid, or clear cell ovarian, fallopian tube, or primary peritoneal cancer. Patients must be considered resistant to the last administered platinum therapy. Patients must have completed at least 1 but no more than 3 prior lines of therapy for advanced or metastatic ovarian cancer. Patients will receive both Niraparib and TSR-042 (dosarlimab) to evaluate the efficacy and safety of the combination of both drugs. NCT03955471
Epithelial Ovarian, Fallopian Tube, or primary Peritoneal Cancer (ATHENA)	newly diagnosed, histologically confirmed, advanced (FIGO stage III-IV), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer. Completed cytoreductive surgery, including at least a bilateral salpingo-oophorectomy and partial omentectomy, either prior to chemotherapy (primary surgery) or following neoadjuvant chemotherapy (interval debulking). Received 4 to 8 cycles of first-line platinum-doublet treatment per standard clinical practice, including a minimum of 4 cycles of platinum/ taxane combination (a patient with best response of PR must have received >/=6 cycles. Bevacizumab is allowed during the chemotherapy phase, but not during maintenance). NCT03522246
Ovarian Cancer (FISRT)	Patients with a histologically confirmed diagnosis of high-grade non-mucinous epithelial ovarian cancer (serous, endometrial, clear cell, carcinosarcoma, and mixed pathologies) that is Stage III or IV according to the International Federation of Gynecology and Obstetrics or tumor, node and metastasis staging criteria lie, American Joint Committee on Cancer). All patients with Stage IV disease are eligible. This includes those with inoperable disease, those who undergo PDS (CC0 or macroscopic disease), or those for whom NACT is planned. NCT03602859
Ovarian Cancer (GOG 3018)	Histologically confirmed epithelial ovarian cancer and documented disease. Patients must have platinum-resistant disease. Patients must have disease that is measurable according to RECIST 1.1 & require chemotherapy treatment. NCT03398655
Ovarian, Fallopian tube, and Peritoneal cancer (AVB8500)	Age 18 years or older. Histologically confirmed and documented recurrent ovarian, fallopian tube, and peritoneal cancer. Platinum resistant disease, defined as progression within Must have available archived tumor tissue OR if archived tissue is not available, willing to provide a fresh tumor biopsy. NCT03639246

Please note: If you are unable to find a clinical trial that works for you, contact 888.972.CURE and ask for the Research Department.
Disclaimer: Studies may close promptly when target enrollment is met.

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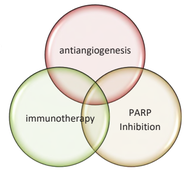
Arizona Oncology ■ 888.972.CURE ■ September 2019

GynOncology UPDATE

Immunotherapy in Gynecologic Cancers

by | DANA CHASE, MD



Over the last decade, we have had many new FDA-approved therapies for gynecologic cancers. Patients have more options and treatment-free intervals are improving. After many years of traditional chemotherapy agents, we are now in a new world of targeted therapies in gynecologic cancers. Within these cancers there are currently 3 distinct but potentially synergistic approaches with 1) immunotherapy, 2) PARP inhibitor therapy, and 3) anti-angiogenesis therapy. Immunotherapy has become a particularly interesting and impactful new treatment for many different cancer types. While we only have one immunotherapy drug FDA-approved for gynecologic cancers, many are currently being studied in clinical trials.

Immunotherapies act to 1) increase the tumor antigens presented to the immune system, 2) recruit immune fighting tumor cells, and 3) alter the tumors ability to avoid attack by the patient's own immune system. The anticancer cycle promoted by the immune system involves the process demonstrated in figure. Unfortunately, some tumor cells are able to escape this process and avoid being identified and killed by the immune system. These cells then become the predominant cell type within the tumor. In addition, some tumors lack infiltration of T cells or the T cells remain in the stroma and do not infiltrate the tumor itself. However, there are also messenger molecules and cytokines, in the tumor environment, that likely aid in immune suppression or tolerance. There are inhibitory molecules called immune checkpoints.

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WELCOME

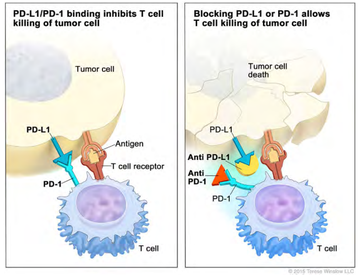
Welcome to Arizona Oncology's The Gyn Oncology Update newsletter. We are dedicated to educate and serve patients in our community. We hope you enjoy the educational content presented within. If you have any questions or feedback, please do not hesitate to contact us.

In This **ISSUE**

ARIZONA ONCOLOGY
The US Oncology Network

(cont'd) Immunotherapy in Gynecologic Cancers

CTLA-4 and PD-1 are 2 other inhibitory molecules that negatively affect the ability of the immune system, specifically T cells, to recognize the tumor cells as foreign. PD-L1 is the ligand for PD-1 and is expressed on antigen presenting cells, and tumor infiltrating lymphocytes. Tumors that are "noninflamed" lack the cytokine programmed death-ligand 1 (PD-L1).



For gynecologic cancers, we currently have 1 immunotherapy agent FDA-approved for treatment. This is pembrolizumab (Keytruda) which is approved for the treatment of recurrent endometrial cancer with at least 1 prior line of therapy that are mismatch repair protein deficient (dMMR) or microsatellite stability index-high (MSI-H). In all endometrial cancers, all tumors are routinely stained by the pathology lab for these proteins. A patient may qualify for this therapy with pembrolizumab if there is 1) lack of staining, 2) a genetic mutation identified in the tumor by profiling or in the patient with genetic testing, and/or 3) a PCR test is used to detect MSI status as high. Although not common, these types of abnormalities may be seen in other tumors such as ovarian, cervical, or vulvar cancers. In this group of patients, who have already had tumor progression or recurrence on prior chemotherapies, we see a 36% response rate and the majority of those patients with a response have a response for over 7 months. In this group of patients, we were very excited to have new options for therapy. Furthermore, current trials are examining combination therapies using immunotherapy medications in upfront and recurrent treatment.

Cervical cancer is a virally-driven cancer and thus likely to induce an immune system reaction. In fact, a high proportion of cervical cancers express PD-L1. In recurrent cervical cancer patients, the use of pembrolizumab (Keytruda) is indicated for tumors that demonstrate PD-L1 positivity, with a CPS scores over 1. The overall response rate of this therapy in previous studies was 17%. After progressing or recurring after platinum-based therapy, these women traditionally have very poor prognosis and limited options thus this was an exciting new option for eligible cervical cancer patients. Current research in cervical cancer is exploring combinations of immunotherapy with radiation to improve disease free intervals. In addition, trials have been designed to boost the immune response include infusions of tumor infiltrating lymphocytes (TILs) selected for HPV proteins along with IL-2. Preliminary data suggests that these strategies could improve outcomes for cervical cancer patients.
In ovarian cancer, single agent immunotherapy approaches for treatment have to yet prove themselves successful. However it has been shown that higher PD-L1 expression is associated with poorer prognosis in ovarian cancer. Because chemotherapy alone is though to be immunogenic there is the thought that combinations between chemotherapy and immunotherapy in ovarian cancer may be beneficial, especially in tumors low in PD-L1 expression. In addition, both anti-angiogenesis and PARP inhibitor therapy may prove to be effective in combination with immunotherapies. Currently many of these trials are either accruing patients or soon to be resulted.

The side effect profiles of immunotherapies in general include inflammatory conditions much like in autoimmune diseases such as gastritis, colitis, cystitis, arthritis, pneumonitis, thyroiditis, etc. Thankfully the prevalence of severe reactions is less than 10%. Many of these side effects can be managed carefully with holding therapy and/or steroid treatment with the assistance of consulting services on occasion. It is not thought that patient-reported quality of life is greatly affected by the addition of these therapies.

Congratulations!
Mike Janicek, MD has recently achieved an impressive milestone of performing over 2,500 da Vinci® Robotic System surgery cases, the most gynecologic robotic cases in Arizona. Arizona Oncology has the largest group of gynecologic oncologists in the Southwest and performs the most da Vinci® robotic minimally invasive cancer surgeries in Arizona.

Endometrial Hyperplasia

by | HEATHER DALTON, MD

Endometrial hyperplasia encompasses a diverse group of diagnoses, including both precancerous and benign entities. Hyperplasia is a proliferation of endometrial glands resulting in irregular size and shape. This is frequently seen in the setting of unopposed estrogen. Historically, many terms have been used for this, including atypical hyperplasia, carcinoma in situ, and adenomatous hyperplasia. There are currently 2 categories for describing endometrial hyperplasia: the 2014 World Health Organization system, which is more commonly used, and the Endometrial Intraepithelial Neoplasia system. The updated WHO endometrial hyperplasia classification system utilizes only 2 categories of hyperplasia: hyperplasia without atypia (non-neoplastic) and atypical hyperplasia (endometrial intraepithelial neoplasm).[1] The prior 1994 WHO criteria is often still cited in pathology reports and can be recognized by the familiar terms of simple hyperplasia without atypia, complex hyperplasia without atypia, simple atypical hyperplasia, and complex atypical hyperplasia. The new 2014 WHO classification system is designed to reduce confusion associated with numerous pathologic terms and also to reflect hyperplasia without atypia as a non-neoplastic process.

The Endometrial Intraepithelial Neoplasia (EIN) classification system was proposed in 2000, but has been adopted somewhat slowly.[2] A key component to the system is a computerized measure of stromal volume as a portion of total tissue volume resulting in a "D-score."

New WHO classification of endometrial hyperplasias (2014)

New Term	Synonym	Genetic Changes	Coexistent invasive endometrial carcinoma	Progression to invasive carcinoma
Hyperplasia without atypia	Non-atypical EM hyperplasias	Low level of somatic mutations	< 1 %	RR: 1.01-1.03
Atypical hyperplasia/endometrioid intraepithelial neoplasia	Atypical EM hyperplasias, EIN	Many of the genetic changes typical for endometrioid endometrial cancer are present	25-33 % 2 43% 1	RR: 14-45

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The EIN system defines 2 classes of endometrial hyperplasia: benign endometrial hyperplasia and endometrial intraepithelial neoplasia.[2] Benign endometrial hyperplasia includes that previously known as simple hyperplasia. Endometrial intraepithelial neoplasia is considered an endometrial precancer and includes some complex hyperplasias without atypia and essentially all complex hyperplasia with atypia. The risk of progression to endometrial carcinoma using either system has been found to be similar. Both the American College of Obstetricians and Gynecologists and the Society of Gynecologic Oncology have endorsed the EIN system is a superior method of classification.

Management of endometrial hyperplasia is largely determined by both the pathologic diagnosis as well as clinical risk factors including obesity, unopposed estrogen, PCOS, as well as desire for fertility and medical fitness. Options for simple hyperplasia without atypia/benign endometrial hyperplasia include progestin-only therapy, OCPs, or expectant management. Management is often dictated by pre-or postmenopausal status. While there are no definitive guidelines, some experts recommend 3 to 6 months of progestin therapy for premenopausal woman with this diagnosis. Options for progestin therapy include oral progestins, a levonorgestrel-releasing IUD, or oral contraceptives. In woman who resume normal menses following treatment, repeat biopsy is not required. Premenopausal women with complex hyperplasia without atypia are typically recommended to undergo a repeat endometrial biopsy every 3 to 6 months for 1 to 2 years. Premenopausal women who do not have resumption of normal menses should continue to receive some form of progestin indefinitely. Postmenopausal women with complex hyperplasia without atypia are typically treated with progestin therapy alone with repeat biopsies every 3 to 6 months for up to 1 year. Hysterectomy is often recommended after one year if normal endometrium is not achieved. It may also be considered in the setting of risk factors for endometrial cancer or contraindications to progestin therapy. Expectant management is also an option.

Atypical hyperplasia/EIN is considered a precursor to endometrial cancer. Hysterectomy is the definitive choice for most women with this diagnosis; however, progestin therapy is a reasonable option for those patients desiring to preserve fertility or medically unfit for surgery. There is approximately 15 to 30% risk of progression to endometrial carcinoma.[3-4] Hysterectomy is typically recommended to be performed with ovarian preservation, as the risk of ovarian involvement even with invasive cancer diagnosed on final pathology is low, approximate 5%.[5] Supracervical hysterectomy is not recommended in this setting due to the possibility of endometrial glands persisting cervix. For those who are not surgical candidates or are wishing to preserve fertility, progestin therapy is very effective, most commonly in form of the levonorgestrel-releasing IUD. Meta-analyses have demonstrated rates of regression to normal endometrium approaching 90%.[6] The levonorgestrel-releasing IUD offers superior response rates compared to oral progestin therapy.[6-7] In premenopausal women being managed this way, endometrial sampling is usually repeated every 3 to 6 months for up to 1 year. If atypical hyperplasia persists at 6 to 12 months, progestogen therapy may be increased and oral progestins may be used in combination with the levonorgestrel-releasing IUD. If no resolution after 1 year, hysterectomy should be considered. In postmenopausal woman, endometrial sampling may be repeated every 6 months for 1 to 2 years. If regression cannot be achieved, management should be tailored to the patient's overall medical picture and fitness for surgery.

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