

# Therapeutic Molecular Biomarkers in Gynecological Cancers

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Molecular profiling helps define the phenotype of a cell and is designed to aid in early cancer detection, risk assessment, and targeted therapies.<sup>1</sup> Profiles should be measurable across populations, useful for detection of cancer at an early stage, or assist in identification of high-risk individuals. As technology has developed, so has our ability to explore tumor biology down to the level of gene expression.

Endometrial cancer is the most common gynecologic malignancy in developed countries and the second most common in developing countries. Patients typically present with symptoms such as postmenopausal bleeding, which allows for detection at an earlier stage. Ovarian cancer is less common but carries a poorer prognosis given its typical late stage of diagnosis. This section will discuss developments in the treatment of endometrial and ovarian cancer at a molecular level. Considerable breakthroughs have been made in the area of poly ADP-ribose polymerase (PARP) inhibitors in BRCA mutated ovarian, fallopian tube, and primary peritoneal cancers. Epithelial cellular adhesion molecule (EpCAM) overexpression has been a target for the treatment of malignant ascites in ovarian cancer. There has been utility in targeting hormone receptors in the setting of recurrent endometrial cancer while the role of human epidermal growth factor 2 (HER2) and mTOR inhibitors shows promise but remains investigational.

## POLY ADP-RIBOSE POLYMERASE (PARP) INHIBITORS

PARPs are a constitutive factor of the DNA damage surveillance network developed to cope with numerous environmental and endogenous toxic agents.<sup>2</sup> In particular, the roles of PARP 1 and 2 in the base excision DNA repair pathway have been elucidated. Inhibition of the PARP enzyme leads to persistence of spontaneously occurring single-strand breaks and subsequent formation of double-strand breaks.<sup>3</sup> PARP inhibitors were found to have anti-cancer activity both in vitro and in vivo in germline BRCA mutated cancer.<sup>4</sup> BRCA1 and BRCA2 mutations act on the cellular level as tumor suppressor genes involved in double-stranded DNA (dsDNA) break repair.<sup>5</sup> Using the concept of synthetic lethality, which is defined as the situation when mutation in either of two genes individually has no effect but combining the mutations leads to death, the use of a PARP inhibitor in patients with an existing BRCA mutation should disable the back-up repair mechanism thus leading to cell death.<sup>6</sup> The

implication is that targeting one of these genes in a cancer where the other is defective should be selectively lethal to the tumor cells but not toxic to the normal cells.<sup>7</sup> In December 2014, olaparib (Lynparza™) became the first PARP inhibitor approved by the FDA in the treatment of advanced ovarian cancer in patients with a known BRCA mutation who have received three or more prior lines of therapy.<sup>8</sup> Approval is contingent upon the demonstration of positive results in two ongoing phase III clinical trials with olaparib limited to patients with BRCA mutations. Other PARP inhibitors such as veliparib have shown promising results in a phase II Gynecology Oncology Group (GOG) trial of patients with persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer with a BRCA 1 or 2 mutation.<sup>9</sup> Niraparib and rucaparib are in ongoing clinical trials.

## EpCAM

EpCAM is abundantly expressed on human cancers and EpCAM overexpression has been associated with a poor prognosis in patients with ovarian, breast, prostate and gallbladder carcinoma, both functioning as an oncogene and suppressing CD4+ T-cell-dependent immune responses.<sup>10</sup> Tumor cells in malignant ovarian cancer-associated ascites have been shown to express EpCAM in 70–100% of cases, while the mesothelial cells lining the peritoneal cavity lack expression.<sup>11</sup> Catumaxomab is a trifunctional monoclonal antibody with two different antigen-binding sites and a functional Fc domain: one binds to epithelial tumor cells via EpCAM and the other to T cells via CD3.<sup>12</sup> Catumaxomab was evaluated as part of a phase I/II dose-escalating study for intraperitoneal application in patients with ovarian cancer who had EpCAM-positive tumor cells.<sup>13</sup> Treatment with catumaxomab resulted in significant and sustained reduction of ascites.<sup>12</sup> In April 2009, the European Union approved catumaxomab for the intraperitoneal treatment of malignant ascites in patients with EpCAM positive carcinomas where standard therapy was not feasible. It has not been FDA approved in the United States but is in clinical trials.

## HORMONE RECEPTORS

The presence of progesterone receptors has been found to correlate with low-grade histology and overall more favorable outcomes.<sup>14</sup> Receptor expression can be lost in either the

primary tumor or in metastatic disease; its loss is associated with disease progression and decreased patient survival.<sup>15</sup> Progestins have been employed to exploit the presence of progesterone receptors, however they paradoxically down regulate receptors when given continuously. The addition of tamoxifen to counter the progestin induced down regulation has shown clinical benefit. Megesterol acetate (megace) and tamoxifen for the treatment of metastatic endometrial cancer is based on a Gynecologic Oncology Group (GOG) study where patients alternated three-week courses of megace and tamoxifen with an overall response rate of 27%, a median progression-free survival of 2.7 months and median overall survival of 14 months.<sup>16</sup> This is a viable treatment option in patients who are not eligible for secondary cytoreduction or multidrug cytotoxic chemotherapy, which has demonstrated a response rate from 33–57%.<sup>17,18</sup> Endocrine therapy has shown some, albeit limited, clinical utility in the treatment of relapsed epithelial ovarian, fallopian tube, and primary peritoneal cancers. Studies using tamoxifen, thalidomide, and letrozole have shown improvements in progression free survival (PFS) and overall survival (OS).<sup>19,20</sup>

## HER2

Although currently investigational, the role of human epidermal growth factor 2 (HER2) was shown to be a potential target in women with uterine serous carcinomas that overexpress HER2. A small GOG trial of 34 women with advanced or recurrent endometrial cancer showed no responses but 12 patients with overexpression of HER2 had stable disease.<sup>21</sup> A clinical trial evaluating the role of trastuzumab in combination with chemotherapy in uterine serous papillary carcinoma is ongoing.

Single agent lapatanib in one trial of patients with endometrial cancer showed that 3 out of 30 patients were progression free after 6 months, 1 patient had a partial response, and 7 had stable disease.<sup>22</sup> Although these appear to be modest results, treatment options in the platinum resistant setting are needed. These women have a poor prognosis. The limited data suggest that the most likely response to second line treatment is stable disease at best and overall survival is usually less than a year.<sup>23</sup>

## mTOR INHIBITORS

Overactivation of the PI3K/AKT/mTOR pathway, a signaling pathway that plays an important role in cellular growth and survival, has been implicated in endometrial cancer pathogenesis.<sup>24</sup> In a phase II study of previously treated recurrent or metastatic endometrial carcinoma patients, 25mg of IV temsirolimus showed a response rate of seven percent, however, 44 percent had stable disease, with a median duration of 5.1 to 9.7 months.<sup>25</sup> These results have been promising enough to proceed with a clinical trial. GOG 86-P incorporates temsirolimus into one of three treatment arms for

women with advanced, recurrent, or metastatic endometrial cancer not previously treated with chemotherapy. Results are anticipated in the near future.

## CONCLUSION

Biomarkers for gynecological cancers, especially ovarian cancer, are the subject of multiple ongoing and planned clinical trials. Targeted therapies for these biomarkers are in rapid development and are hoped to improve the prognosis of women with gynecological malignancies by providing improvement in outcomes and treatment tolerability.

## References

1. Negm R, Verma M, et al. The promise of biomarkers in cancer screening and detection. *Trends in Molecular Medicine*. 2002;8:288-293.
2. Shall S, de Murcia G. Poly(ADP-ribose) polymerase-1: what have we learned from the deficient mouse model?. *Mutat Res*. 2000;460(1):1-15.
3. Liu J, Panagiotis A., et al. PARP inhibitors in ovarian cancer: Current status and future promise. *Gynecol Oncol*. 2014; 133:362-369.
4. Farmer H, McCabe N, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature*. 2005; 434: 917–921.
5. Stratton MR, Rahman N. The emerging landscape of breast cancer susceptibility. *Nat Genet*. 2008; 40: 17-22.
6. Dobzhansky T: Genetics of natural populations: Xiii. Recombination and variability in populations of *Drosophila Pseudoobscura*. *Genetics*. 31:269-290,1946
7. Ashworth, A. A Synthetic Lethal Therapeutic Approach: Poly(ADP) Ribose Polymerase Inhibitors for the Treatment of Cancers Deficient in DNA Double-Strand Break Repair. *JCO*. 2008; 26:3785-3790.
8. Kaufman B, Shapira-Frommer R, et al. Olaparib Monotherapy in Patients with Advanced Cancer and a Germline BRCA1/2 Mutation. *J Clin Oncol*. 2015; 33(3):244-50.
9. Coleman RL, Sill MW, et al. A phase II evaluation of the potent, highly selective PARP inhibitor veliparib in the treatment of persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who carry a germline BRCA1 or BRCA2 mutation - An NRG Oncology/Gynecologic Oncology Group study. *Gynecol Oncol*. 2015; pii: S0090-8258(15)00759-3.
10. Eskander RN, Tewari KS. Epithelial cell-adhesion molecule-directed trifunctional antibody immunotherapy for symptom management of advanced ovarian cancer. *Clinical Pharmacology : Advances and Applications*. 2013;5(Suppl 1):55-61.
11. Heiss MM, Murawa P, et al. The trifunctional antibody catumaxomab for the treatment of malignant ascites due to epithelial cancer: results of a prospective randomized phase II/III trial. *Int J Cancer*. 2010;127(9):2209–2221.
12. Ruf P, Gires O, et al. Characterisation of the new EpCAM-specific antibody HO-3: implications for trifunctional antibody immunotherapy of cancer. *Br J Cancer*.2007;97:315-21.
13. Burges A, Wimberger P, et al. Effective relief of malignant ascites in patients with advanced ovarian cancer by a trifunctional anti-EpCAM x anti-CD3 antibody: a phase I/II study. *Clin Cancer Res*. 2007; 13(13):3899-3905.
14. Creasman WT. Prognostic significance of hormone receptors in endometrial cancer. *Cancer* 1993; 71 (suppl): 1467-1470.
15. Singh M, Zaino RJ, et al. Relationship of estrogen and progesterone receptors to clinical outcome in metastatic endometrial

- carcinoma: a Gynecologic Oncology Group Study. *Gynecol Oncol.* 2007; 106: 325-333.
16. Fiorica JV, Brunetto VL, et al. Phase II trial of alternating courses of megestrol acetate and tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2004; 92(1):10-14.
  17. Fleming GF, Filiaci VL, Bentley RC, et al. Phase III randomized trial of doxorubicin + cisplatin versus doxorubicin + 24-h paclitaxel + filgrastim in endometrial carcinoma: a Gynecologic Oncology Group study. *Ann Oncol.* 2004;15(8):1173-1178
  18. Fleming GF, Brunetto VL, Cella D, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol.* 2004;22(11):2159-2166
  19. Hurteau JA, Brady MF, et al. Randomized phase III trial of tamoxifen versus thalidomide in women with biochemical-recurrent-only epithelial ovarian, fallopian tube or primary peritoneal carcinoma after a complete response to first-line platinum/taxane chemotherapy with an evaluation of serum vascular endothelial growth factor (VEGF): A Gynecologic Oncology Group Study. *Gynecol Oncol.* 2010; 119:444
  20. Smyth JF, Gourley C, et al. Antiestrogen therapy is active in selected ovarian cancer cases: the use of letrozole in estrogen receptor-positive patients. *Clin Cancer Res.* 2007; 13:3617.
  21. Fleming GF, Sill MW, Darcy KM, et al. Phase II trial of trastuzumab in women with advanced or recurrent, HER2-positive endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2010; 116:15.
  22. Leslie KK, Sill MW, et al. Lapatinib and potential prognostic value of EGFR mutations in a Gynecologic Oncology Group phase II trial of persistent or recurrent endometrial cancer. *Gynecol Oncol.* 2012; 127:345.
  23. Ueda Y, Miyake T, et al. Second-line chemotherapy for advanced or recurrent endometrial carcinoma previously treated with paclitaxel and carboplatin, with or without epirubicin. *Cancer Chemother Pharmacol.* 2011 Apr;67(4):829-35.
  24. Slomovitz BM, Coleman RL. The PI3K/AKT/mTOR pathway as a therapeutic target in endometrial cancer. *Clin Cancer Res.* 2012; 18(21):5856-64
  25. Westin SN, Broaddus RR. Personalized therapy in endometrial cancer: Challenges and opportunities. *Cancer Biol Ther.* 2012;13(1):1-13.

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