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Uterine cancer, mutational phenotype, and the era of immune checkpoint blockade

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Keywords

Uterine cancer; mutational phenotype; the era of immune checkpoint blockade

1. Uterine cancer: advances despite under-funding of research

Endometrial cancer represents the fourth most common malignancy in the United States and sixth leading cause of cancer-related death in women. In 2016, there will be a projected 60,050 cases and over 10,470 deaths from this disease.[1] Annually, uterine cancer research receives between $39–57 million from the National Institutes of Health (NIH), based on data from fiscal years 2012 through 2015.[2] This is in contrast to breast cancer, which will account for only four times as many estimated deaths this year (40,450)[1] but will have attracted more than 10 times as much research funding from NIH (between $674–800 million per year) during the same period.[2]

Nevertheless, pivotal advances in the molecular characterization of uterine cancer have been made in the last half a decade. In 2013, the Cancer Genome Atlas Research Network recognized four distinct categories of endometrial cancer after rigorous integrated genomic and proteomic inquiries. A total of 373 samples were analyzed, including 307 endometrioid, 66 serous and 13 mixed tumors. Whole exome sequencing of the available tumor-normal pairs revealed four distinct categories of endometrial cancer:

1. an ultramutated group containing as many as 232×10^{-6} mutations/Mb in conjunction with alteration in DNA polymerase epsilon (POLE) (n = 17)
2. a hypermutated group with 18×10^{-6} mutations/Mb and microsatellite instability (n = 65)
3. copy number low (endometrioid) tumors with 2.9×10^{-6} mutations/Mb (n = 90)

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Declaration of Interests

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4. copy number low (serous) tumors with a low mutation rate of 2.3×10^{-6} mutations/Mb but somatic copy number alterations such as *MYC*, *ErbB2*, and *CCNE1* amplification (n = 60).[3]

Soon after this publication, a subset of tumors with exceptional somatic mutational patterns was also demonstrated within matched tumor-normal pairs restricted to uterine serous histology using whole-exome sequencing.[4]

2. Neoantigen load confers a favorable prognosis and predicts response to immune checkpoint inhibition

Abscopal effects, the induction of an often dramatic but relatively rare tumor response distant from the site of radiation, were initially described as early as 1953[5] and may be attributable to immune activation due to enhanced neoantigen burden as a result of radiotherapy. Tumor immunogenicity is also inherently enhanced by the mutational diversity that occurs in the absence of functional POLE proofreading or mismatch repair mechanisms resulting in microsatellite instability (MSI) due to either germline (Lynch syndrome) or somatic (Lynch-like) alterations in mismatch repair genes (*MSH2, MSH6, MLH1, PMS2*) or somatic silencing of the *MLH1* promoter.

Accordingly, hypermutated tumors generally display favorable survival outcome. This has been demonstrated in gastric cancers,[6] colorectal carcinoma,[7] and gynecologic malignancies, though there is heterogeneity among data. In a series of 57 patients with uterine serous carcinoma, 8.7% (n=5) demonstrated a hypermutated phenotype.[4][8] A marked survival advantage was apparent relative to tumors that lacked hypermutation, despite stage III disease in 40% of these patients. The phenomenon has been also described in *BRCA 1/2*-deficient high-grade serous ovarian cancers (n=54) compared to matched homologous recombination proficient counterparts (n=122) (p=0.012).[9] Mutational variation also predicts response to immune checkpoint inhibitors. This was first noted among 41 consecutive patients (78% colorectal, 10% biliary, 5% endometrial, 5% small bowel, and 2% gastric carcinoma) treated with the checkpoint inhibitor pembrolizumab at 10 mg/kg every 14 days over a median follow-up of 36 weeks: median overall survival was 5 months in mismatch repair proficient tumors but not reached in mismatch repair deficient tumors.[10]

In 2015, Howitt and colleagues suggested PD-1 targeted immunotherapy might be particularly effective for POLE and MSI endometrial cancers.[11] In a study of 63 endometrial cancers, neoantigen load as well as CD3+ and CD8+ tumor-associated lymphocytes were greater in POLE-mutated and MSI tumors relative to microsatellite-stable tumors. Furthermore, PD-L1 expression was more common in the intraepithelial tumors of POLE and MSI tumors (39% versus 13%, p=0.02). Consistent with these initial findings, administration of the anti-PD1 agent nivolumab at 3 mg/kg every 14 days has recently been shown to induce with minimal side effects partial responses by RECIST criteria in recurrent heavily pre-treated ultramutated and hypermutated endometrial cancers, even in the setting of minimal expression of PD-L1 within tumor.[12]

3. Beyond rational drug design: responsible drug diffusion

Checkpoint inhibition is not cheap. Anti-PD1 therapies nivolumab and pembrolizumab cost approximately $28 and $104 per mg. Estimates of per-patient cost during the progression-free interval for pembrolizumab and nivolomab are as high as $145,000 and $64,000, respectively, and would total $3.8 billion annually based on World Health Organization estimates of disease for melanoma.[13]

While it is tempting to rapidly apply immunotherapy to countless other tumor types given the excitement generated by the experience in melanoma, the scientific community must simultaneously work towards identification of predictive markers for response.

In 2013, a study of whole-exome and whole-genome sequencing of 3,083 tumor-normal pairs revealed that median somatic mutational frequency may vary by more than 1000-fold across cancer types.[14] Mutational heterogeneity is dominated by melanoma followed by lung carcinomas, while pediatric tumors such as rhabdoid and Ewing's sarcoma, thyroid cancers, and acute myelogenous leukemia offer a relatively bland landscape. Gynecologic malignancies, such as ovarian and cervical, as well as colorectal carcinomas appear to be intermediate in mutational burden. Interestingly, regardless of median mutational frequency by tissue of origin, inter-individual mutational burden within each group varied by 3 orders of magnitude, indicating that the rational diffusion of immunotherapies must be refined beyond discrimination by histology alone. Herein, ultramutated or hypermutated status may outperform traditional protein targets as biomarkers for immunotherapy response.

As endometrial cancers rank among the most frequent to harbor microsatellite instability (22–33%) relative to colorectal (20%), cervical (8%), esophageal (7%), and breast cancers (0%–2%),[15] immunotherapy with checkpoint inhibition has the potential to represent one of the most promising advances in the treatment of endometrial cancer in recent years. PD-1 and PD-L1 expression in primary, recurrent, and metastatic endometrial cancers is 67–100% in some series.[16] PD-1 expression by immunohistochemistry staining was found to be highest in carcinosarcoma and endometrioid histologies (80%), followed by clear cell, serous, and stromal sarcoma (64–60%), and variable in leiomyosarcoma (47%).[10]

Preliminary results from the endometrial carcinoma cohort (n=24) of KEYNOTE-028 study (NCT02054806)[17] were presented at the 2016 annual meeting of the American Society for Clinical Oncology. All patients had failed prior systemic therapy and had excellent performance status. PD-L1 expression was only required in ≥ 1% of tumor or stroma cells by immunohistochemistry. Pembrolizumab was administered at 10 mg/kg every 2 weeks for up to 24 months or until confirmed progression. At a median follow-up of 69.9 weeks (range, 5.4–84.4), confirmed overall response rate was 13.0%; median duration of response was not yet reached (range: 40.3–65.1 weeks). Three patients achieved stable disease (13%; 95% CI, 2.8–33.6; median duration, 24.6 wk [range, 13.1–24.6]). Six-month progression-free and overall survival rates were 19.0% and 68.8%, respectively. The drug was well-tolerated; three patients experienced grade 3 adverse events, including back pain/asthenia (n=1, resolved), diarrhea (n=1, resolved), and asthenia/anemia/hyperglycemia/hyponatremia (n=1, unresolved). There were no treatment-related deaths or discontinuation of therapy due

to side effects. Pembrolizumab for advanced endometrial cancer has now progressed to phase 2 (KEYNOTE-158, NCT02628067).

To date, immunotherapeutic approaches outside of checkpoint inhibition in endometrial cancer have been limited and often disappointing.[18] Some of the earliest studies employed vaccination. A trial of recombinant vaccinia-NY-ESO-1 and recombinant fowlpox-NY-ESO-1 constructs in patients with advanced cancers included one patient with endometrial cancer, who had progressive disease on therapy.[19] In another study, a patient with uterine carcinosarcoma received HLA-A2402-restricted modified 9-mer WT1 peptide emulsified with Montanide ISA51 adjuvant, but also progressed on therapy.[20] In a separate inquiry, two endometrial cancer patients were treated in a phase I study of a novel peptide combination vaccine consisting of two B-cell epitopes derived from the HER2 extracellular domain; one patient has a partial durable (4 years) response.[21] Other studies have exploited dendritic cells (DCs). In a report of 4 patients with uterine serous carcinoma treated with autologous DCs loaded with WT1 mRNA, 75% demonstrated immune activation, 50% experienced a decrease in serum CA-125, but 0% exhibited a radiologic response.[22][23] Peripheral blood T cells stimulated with tumor lysate-pulsed autologous DCs have been used in patients with metastatic endometrial[24] and uterine serous carcinomas.[25] Cytotoxic T-lymphocytes were generated but did not correlate with tumor response. Intraperitoneal adoptive transfer of lymphokine-activated killer cells with IL-2 has also been tested in a phase I trial that enrolled one endometrial cancer patient with abdominal metastases.[26] Significant toxicities were incurred in multiple patients, without any clinical benefit in the one patient with endometrial cancer.

Presently, a basic search of www.clinicaltrials.gov for “immunotherapy” or “pembolizumab” trials will yield at least 8 recruiting for uterine cancer (Table 1), 7 for cervical cancer, ≥31 for ovarian, and over 76 for breast cancer. Across all disease sites, the current dominance of anti-PD-1 therapy is apparent. Given that the Institute of Medicine has long recommended that research effort be comparable to societal burden of disease,[27] it seems that the era of immunotherapy is thus a time ripe for uterine cancer to achieve a zenith.

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Reference annotations

* Of interest

** Of considerable interest

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TABLE 1

Immune check point blockade trials in women's cancers[28]

DISEASE SITE	SEARCH TERMS	TRIAL NUMBER & COUNTRY	PHASE	TRIAL NAME	PREMISE OF IMMUNE INTERVENTION	TOTAL * ** *** ****
UTERINE	"uterine cancer" OR "endometrial cancer" AND "immunotherapy" OR "pembrolizumab"	NCT02630823 (United States)	0	MK-3475 Immunotherapy in Endometrial Carcinoma	anti-PD-1	≥ **8**
		NCT02728830 (United States)	0	A Study of Pembrolizumab on the Tumoral Immunoprofile of Gynecologic Cancers*	anti-PD-1	
		NCT02646748 (United States)	I	Pembrolizumab Combined With INCB039110 and/or Pembrolizumab Combined With INCB050465 in Advanced Solid Tumors	anti-PD1 in combination with anti-JAK	
		NCT02393248 (United States)	I/II	Open-Label, Dose-Escalation Study of INCB054828 in Subjects With Advanced Malignancies	anti-fibroblast growth factor receptor in combination with anti-PD-1 therapy or cytotoxic chemotherapy	
		NCT02501096 (United States)	I/II	Phase 1b/2 Trial of Lenvatinib (E7080) Plus Pembrolizumab in Subjects With Selected Solid Tumors	tyrosine kinase with anti-PD-1	
		NCT02628067 (United States, Australia, Canada, Brazil, Denmark, France, Germany, Israel, Italy, Japan, Mexico, Netherlands, Philippines, Russia, South Africa, Spain, Taiwan, United Kingdom)	II	Study of Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-3475-158/ KEYNOTE-158)	anti-PD-1	
		NCT02899793 (United States)	II	Pembrolizumab in Ultramutated and Hypermutated Endometrial Cancer	anit-PD-1	
		NCT01174121 (United States)	II	Immunotherapy Using Tumor Infiltrating Lymphocytes for Patients With Metastatic Cancer**	IL-2, anti-PD-1, *ex vivo* stimulated TILs	
CERVICAL	"cervical cancer" AND "immunotherapy" OR "pembrolizumab"	NCT02858310 (United States)	I	E7 TCR T Cells With or Without PD-1 Blockade for Human Papillomavirus-Associated Cancers***	T cells genetically engineered with a TCR targeting HPV-16 E7 protein, anti-PD1	≥ **7**
		NCT02554812 (United States, Canada, Australia, France, Japan, Netherlands)	I	A Study Of Avelumab In Combination With Other Cancer Immunotherapies In Advanced Malignancies (JAVELIN Medley)	anti-PD1 (IgG1)	

DISEASE SITE	SEARCH TERMS	TRIAL NUMBER & COUNTRY	PHASE	TRIAL NAME	PREMISE OF IMMUNE INTERVENTION	TOTAL * ** *** ****
		NCT02096614 (Japan)	I	Investigator Initiated Phase 1 Study of TBI-1201	MAGE-A4-specific TCR gene transduced T lymphocytes	
		NCT02457650 (China)	I	T Cell Receptor-transduced T Cells Targeting NY-ESO-1 for Treatment of Patients With NY-ESO-1- Expressing Malignancies	anti-NY-ESO-1 TCR transduced T cells	
		NCT02849340 (China)	I/II	Combination of Cryosurgey and NK Immunotherapy for Recurrent Cervical Cancer	infusion of 8–10 billion NK cells	
		NCT02128126 (Netherlands)	I/II	Study of the Therapeutic Vaccine (ISA101/ISA101b) to Treat Advanced or Recurrent Cervical Cancer	peggylated IFNα, vaccination against HPV proteins	
		NCT02635360 (United States)	II	Pembrolizumab and Chemoradiation Treatment for Advanced Cervical Cancer	anti-PD-1	
OVARIAN	"ovarian cancer" AND "immunotherapy" OR "pembrolizumab"	NCT02785250 (United States, Canada)	I	Study of DPX-Survivac Vaccine Therapy and Epacadostat in Patients With Recurrent Ovarian Cancer	survivin protein-based vaccine, activation of immune response through inhibition of indoleamine 2,3-dioxygenase (IDO1)	**≥31**
		NCT02475213(United States)	I	Safety Study of Enoblituzumab (MGA271) in Combination With Pembrolizumab in Refractory Cancer	anti-CTLA-4 with anti-PD-1	
		NCT02606305 (United States, Belgium, Canada, Spain)	I	Study of IMGN853 in Comb. With Bevacizumab, Carboplatin, PLD or Pembrolizumab in Adults With Folate Receptor + Ovarian, Primary Peritoneal, Fallopian Tube, or Endometrial Cancer****	anti-folate receptor α in combination with anti-PD1 therapy	
		NCT02759588 (United States)	I	GL-ONC1 Oncolytic Immunotherapy in Patients With Recurrent Ovarian Cancer	oncolytic attenuated vaccinia virus (Lister strain)	
		NCT02327468 (United States)	I	Inovio TRT-001: Telomerase DNA Immunotherapy	IL-12 immune activator with intradermal vaccination of the hTERT-encoding DNA vaccine	
		NCT02140996 (Singapore)	I	Safety Study of Human MUC-1 (Mucin-1) Adenoviral Vector Vaccine for Immunotherapy of Epithelial Cancers (MUC-1)	activation of dendritic cells and promotion of antigen specific B cells or antigen specific CD8 effector T cells to suppress the growth of tumor cells that express MUC-1	

DISEASE SITE	SEARCH TERMS	TRIAL NUMBER & COUNTRY	PHASE	TRIAL NAME	PREMISE OF IMMUNE INTERVENTION	TOTAL * ** *** ****
		NCT02009449 (United States)	I	A Phase 1 Study of AM0010 in Patients With Advanced Solid Tumors	pegylated IL-10	
		NCT02096614 (Japan)	I	Investigator Initiated Phase 1 Study of TBI-1201	MAGE-A4-specific TCR gene transduced T lymphocytes	
		NCT02366546 (Japan)	I	Investigator Initiated Phase 1 Study of TBI-1301	NY-ESO-1-specific TCR gene transduced T lymphocytes	
		NCT02457650 (China)	I	T Cell Receptor-transduced T Cells Targeting NY-ESO-1 for Treatment of Patients With NY-ESO-1- Expressing Malignancies	anti-NY ESO-1 TCR-transduced T cells	
		NCT02856425 (France)	I	Trial Of Pembrolizumab And Nintedanib	IgG4 anti-PD-1 blocking monoclonal antibody	
		NCT02122861 (United States)	I	Phase 1 Study of Intradermal LV305 in Patients With Locally Advanced, Relapsed or Metastatic Cancer Expressing NY-ESO-1	Stimulation of dendritic cells against NY-ESO-1 antigen	
		NCT02298959 (United States, Canada)	I	Pembrolizumab and Ziv-aflibercept in Treating Patients With Advanced Solid Tumors	anti-PD-1 and anti-vascular endothelial growth factor	
		NCT02346955 (United States, Israel)	I	Study of CM-24 (MK-6018) Alone and In Combination With Pembrolizumab (MK-3475) in Participants With Selected Advanced or Recurrent Malignancies (MK-6018-001)	anti-PR-1 and anti-CEACAM	
		NCT02419495 (United States)	I	Phase IB of Selinexor in Combination With Standard Chemotherapy in Patients With Advanced Malignancies	anti-PD-1 with small molecule inhibitor of CRM1 (chromosome region maintenance 1 protein, exportin 1 or XPO1	
		NCT02849353 (China)	I/II	Combination of Cryosurgey and NK Immunotherapy for Recurrent Ovarian Cancer	argon beam ablation ±infusion of 8~10 billion NK cells	
		NCT02178722 (United States)	I/II	A Phase 1/2 Study Exploring the Safety, Tolerability, and Efficacy of Pembrolizumab (MK-3475) in Combination With Epacadostat (INCB024360) in Subjects With Selected Cancers (INCB 24360-202/ MK-3475-037/KEYNOTE-037/ ECHO-202)	anti-PD-1 with inhibition of indoleamine 2,3-dioxygenase (IDO1)	

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		NCT01583686 (United States)	I/II	CAR T Cell Receptor Immunotherapy Targeting Mesothelin for Patients With Metastatic Cancer	anti-mesothelin chimeric antigen receptor with IL-2	
		NCT02571725 (United States)	I/II	Olaparib and Tremelimumab in BRCA-deficient Ovarian Cancer	PARP-inhibition, checkpoint (CTLA-4) blockade	
		NCT02575807 (United States)	I/II	Safety and Efficacy of CRS-207 With Epacadostat in Platinum Resistant Ovarian, Fallopian, or Peritoneal Cancer (SEASCAPE)	live-attenuated, double-deleted (LADD) Listeria monocytogenes expressing immunogenic mesothelin, activation of immune response through inhibition of indoleamine 2,3-dioxygenase (IDO1)	
		NCT02331251 (United States)	I/II	Study of Pembrolizumab Plus Chemotherapy in Patients With Advanced Cancer (PembroPlus)	anti-PD-1 with cytotoxic chemotherapy	
		NCT02657889 (United States)	I/II	Study of Niraparib in Combination With Pembrolizumab (MK-3475) in Patients With Triple-negative Breast Cancer or Ovarian Cancer (TOPACIO)	anti-PD-1 with PARP inhibition	
		NCT02520154 (United States)	II	Pembrolizumab in Combination With Chemotherapy in Frontline Ovarian Cancer	anti-PD-1 with cytotoxic chemotherapy	
		NCT02608684 (United States)	II	A Study of Pembrolizumab With Standard Treatment in Patients With Recurrent Platinum-resistant Ovarian Cancer (PemCiGem)	anti-PD-1 with cytotoxic chemotherapy	
		NCT02900560 (United States)	II	Study of Pembrolizumab With or Without CC-486 in Patients With Platinum-resistant Ovarian Cancer	anti-PD-1 with epigenetic modifier and DNA methyltransferase inhibitor	
		NCT02440425 (United States)	II	Dose Dense Paclitaxel With Pembrolizumab (MK-3475) in Platinum Resistant Ovarian Cancer	anti-PD1 with cytotoxic chemotherapy	
		NCT01556841 (United Kingdom)	II	The Activity of TroVax® Versus Placebo in Relapsed Asymptomatic Ovarian Cancer	vaccinia virus Ankara against surface protein 5T4	
		NCT02853318 (United States)	II	Pembrolizumab, Bevacizumab, and Cyclophosphamide in Treating Patients With Recurrent Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	anti-vascular endothelial growth factor, anti-PD-1, cytotoxic chemotherapy	
		NCT01174121 (United States)	II	Immunotherapy Using Tumor Infiltrating Lymphocytes for Patients	IL-2, anti-PD-1, ex vivo stimulated TILs	

DISEASE SITE	SEARCH TERMS	TRIAL NUMBER & COUNTRY	PHASE	TRIAL NAME	PREMISE OF IMMUNE INTERVENTION	TOTAL * ** *** ****
				With Metastatic Cancer (also open to endometrial cancers)		
		NCT02132988 (Taiwan)	II	Trial of Active Immunotherapy With Globo H-KLH (OPT-822/821) in Women Who Have Non-Progressive Ovarian Cancer	vaccination with tumor antigen fused to carrier protein in adjuvant OBI-821	
		NCT02346747 (United States)	II/III	Phase II/III Trial of Maintenance Vigil™ for High Risk Stage III/IV Ovarian Cancer (VITAL)	bi-shRNA:furin and GMCSF augmented autologous tumor cell therapy	
BREAST	“breast cancer” AND “immunotherapy” OR “pembrolizumab”					≥**76**

TIL = tumor infiltrating lymphocytes, PD1 = programmed death protein-1, participant in immune checkpoint blockade, IL-2 = interleukin-2 (stimulates natural killer cells, lymphokine-activated killer cells, T cells including tumor-infiltrating lymphocytes), NK = natural killer (cytotoxic lymphocyte of the innate immune system), IFNα = interferon-α (stimulates natural killer cells), TCR = T cell receptor (responsible for antigen recognition); GM-CSF = granulocyte macrophage colony-stimulating factor; shRNA = short hairpin (interfering) RNA,

*
also open to ovarian, cervical, vulva or vaginal cancers if microsatellite unstable

**
also open to ovarian cancer

***
also open to vulvar or vaginal cancers

****
also open to endometrial cancers

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