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GYNECOLOGIC CANCERS (J BROWN AND RW NAUMANN, SECTION EDITORS)

Integrating Precision Medicine into the Contemporary Management of Gynecologic Cancers

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Abstract

Purpose of Review The treatment of patients with advanced gynecologic malignancies remains challenging. Advancements in genomics have led to recognition and development of individualized therapeutic targets. This article reviews the current trends in precision medicine for treatment of gynecologic cancers.

Recent Findings With the identification of the molecular aberrations inherent to gynecologic malignancies, we have discovered targetable mutations. Specific to ovarian, endometrial and cervical cancers, potential therapeutic targets that have been identified and shown to have benefit include: hormonal therapies, anti-angiogenic agents, poly-ADP-ribose polymerase inhibitors (PARPi), and immunotherapy.

Summary The adoption of targeted therapeutics for the treatment of gynecologic cancers has been gradual, but we have started to see the rapid employment of novel targeted agents into clinical trial development, leading to new treatment approvals. However, there are challenges to the universal precision medicine implementation, and future studies need to identify, discover, and validate robust biomarkers with strong prognostic/predictive capabilities.

Keywords Precision medicine · Personalized medicine · Gynecologic cancers · Ovarian cancer · Endometrial cancer · Cervical cancer

Introduction

The journey to incorporate precision therapeutics into the clinical armamentarium to optimize outcomes in gynecologic cancers has been challenging, yet recent regulatory approvals have witnessed multiple agents that leverage the precision medicine platform. In fact, virtually, all new gynecologic therapeutic approvals in the past decade have been based upon targeted molecular alterations and pathways aberrant in cancer.

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While targeted strategies have been standard for over a decade in high-incidence cancers like lung, breast, and colon cancer, the statistical challenges of stratifying smaller case volumes have limited the development of tailored treatments in gynecologic malignancies. Incorporation of the significant advances in molecular biology, translational genetics, pharmaco-kinetics, pharmaco-dynamics, and bioinformatics has facilitated rapid development of therapeutics based upon specific molecular alterations or gene products that are upregulated in cancers. Not only can precision medicine deliver the right drug to the right person at the right time and right dose/schedule, but this field can predict and ameliorate toxicities a priori by understanding the molecular underpinnings of drug metabolism.

One of the first forays into precision medicine in gynecologic cancers was the recognition of distinct survival outcomes for epithelial ovarian cancers based on histologic subtypes, which translated into prognostic markers for survival. These findings were then correlated with distinct molecular aberrations that have served as potential therapeutic targets that have been incorporated into clinical trials, whereby potentially predictive molecular markers are interrogated for

efficacy outcomes. Subsequently, distinct endometrial cancer types were identified based on their associated genetic aberrations, and the oncogenic potential of human papilloma virus was recognized in cancers of the lower female genital tract. These changes further expanded precision medicine targets.

Challenges continue with incorporation of precision strategies in gynecologic malignancies such as effectively targeting driver mutations, overcoming pathway redundancies, and developing effective companion diagnostics; nonetheless, the promise of more active therapies that avoid the cost and toxicity of ineffective agents is a goal well worth pursuing. Furthermore, the basic science and translational knowledge bases continue to expand exponentially coupled with availability of genetic sequencing of not only DNA but RNA and the proteome, thus making the promise of precision medicine, including gene and cell-based therapies, ever more attainable in gynecologic malignancies. Table 1 summarizes the recent progress of precision medicine in gynecologic cancers by disease site.

Molecular Profiling

Molecular profiling is a genomic and molecular analysis of tumor expression for diagnostic, therapeutic, or prognostic purposes. It is performed by using distinct technologies such as immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), reverse transcription polymerase chain reaction (RT-PCR), next gene sequencing (NGS), and circulating tumor cells (CTCs), each of which is utilized in different capacities within gynecologic malignancies (Fig. 1a-e).

Immunohistochemistry (IHC)

Utilizing the antibody-antigen relationship, IHC aids in establishing malignant classification of a tumor or identifying the primary site of origin. Microscopic analysis of tissue sections with histochemical stains such as hematoxylin and eosin (H&E) provides information about the tissue origin, grade, and stage. However, lesions can have inconclusive morphology, pleomorphism or lack of differentiation that present diagnostic challenges. IHC utilizes antibodies to identify the presence or pattern of specific tissue antigens to establish the diagnosis. The desired antibody is marked with a fluorescent tag that is visualized with a microscopic analysis. [1, 2] Additionally, IHC provides information about proliferation rates, tumor grade, and tumor type. Classification through IHC has been found to be indicative of clinical treatment and treatment response. For example, IHC plays a key role in the diagnosis of Lynch syndrome [3]. Microsatellite instability (MSI) is genetic instability as a consequence of impaired DNA mismatch repair (MMR), ultimately leading to hypermutation. Evaluable loci for MSI are 4 mutations of MMR (MLH1, MSH2, MSH6, PMS2) or the EPCAM gene (3-end deletions). Though DNA analysis for mismatch repair deficiency (MMRd) is the definitive test, it is not cost effective for screening. Therefore, if tumor testing reveals the presence of the four MMR gene proteins, Lynch syndrome is typically excluded. IHC will not differentiate between loss of MLH1 due to mutation or due to promoter methylation, whereas isolated loss of MSH2 or MSH6 is virtually diagnostic of Lynch syndrome.

Fluorescence In Situ *Hybridization*

Fluorescence in situ hybridization (FISH) can detect specific DNA sequences on a chromosome by utilizing short sequences of single-stranded DNA with a fluorescent probe to identify complementary DNA within a cell. While its use is limited relative to other techniques, FISH is frequently used for detection of HER-2/neu gene amplification in breast cancer and endometrial cancer. [4] Additionally, FISH is useful for identification of aneuploidy, such as for hydatidiform moles or for genetic abnormalities in ovarian cancer[5].

Reverse Transcription Polymerase Chain Reaction

Reverse transcription polymerase chain reaction (RT-PCR) combines the reverse transcription of RNA into DNA with the amplification of a specific DNA using PCR to analyze gene expression. While IHC is used to screen tumors for Lynch syndrome, when there is a loss of MLH1, RT-PCR can be used to determine if downregulation of MLH1 is due to mutation or promotor methylation. [6]Microsatellites are multiple tandem repeats of nucleotides that are susceptible to instability, and MSI is evaluated using RT-PCR-based analysis of BAT25, BAT26, D5S346, D2S123 and D17S250, BAT40, and TGF-βR2 [7]. Microsatellites in tumor are compared to normal tissue with a shift in ≥ 3 markers defined as MSI-high [6].

Next-generation sequencing

By sequencing small fragments of DNA in parallel simultaneously using next-generation sequencing (NGS), the entire human genome can be sequenced in less than a day. Significantly decreasing time and cost, NGS represents the forefront of tumor analysis and has allowed for significant advances in the molecular profiling of tumors through the identification of previously unrecognized genomic alterations, expanding the potential for targeted therapy. NGS is

Table 1 Overview of precision medicine in gynecologic cancers by disease site

Table	Histology	Molecular Alteration	Function	Routine Testing	Anticancer Agent	Indications	Clinical Trial Examples (ongoing trials designated by NCT)
Ovarian Cancer	High grade serous	BRCA 1/2 HRD (BRIP1, RAD51C/D, BARD1, CHEK2, PALB2, and ATM)	Homologous recombination DNA repair	DNA sequencing	PARPi (olaparib, niraparib, rucaparib)	Olaparib: 1st-line maintenance (monotherapy or +bevacizumab) if BRCA; PS recurrence if HRD or BRCA; 4th-line if BRCA Niraparib: 1st-line maintenance; PS recurrence; 4th-line if HRD Rucaparib: PS recurrence; 3rd-line if BRCA	SOLO-1: Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer (NCT01844986); PAOLA-1: Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer (NCT02477644); SOLO-2: Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial (NCT01874353); QUADRA: Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial (NCT02354586) PRIMA: Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer (NCT02655016); NOVA: Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer (NCT01847274) ARIEL-2: Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial (NCT01891344); ARIEL-3: Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial (NCT01968213)
		MSI-H or dMMR	DNA mismatch repair gene	IHC, DNA sequencing, PCR	Immunotherapy (pembrolizumab)	MSI-H or dMMR solid tumors	Study of Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-3475-158/KEYNOTE-158) (NCT02628067)
		ERBB2 or HER 2/neu	Phosphorylates signaling molecules that play roles involving cell growth, division, movement, transport and survival	IHC, FISH	Monoclonal antibody that targets HER2/neu (trastuzumab), HER-2/neu peptide vaccine	Stage IV HER 2/neu positive breast or OC receiving trastuzumab Recurrent (2nd or 3rd line) HER 2/neu positive OC	Vaccine Therapy in Treating Patients With Stage IV HLA-A2 and HER2 Positive Breast or Ovarian Cancer Receiving Trastuzumab (NCT00194714) HER2 Overexpression/Amplification and Trastuzumab Treatment in Advanced Ovarian Cancer: A GINECO Phase II Study
		TP53	Encodes instructions for KRAS protein, involved in signaling for cell growth, function, differentiation	DNA sequencing, multiplex ligation-dependant probe assay	Gene therapy (adenoviral p53), monoclonal antibody, MDM2/4 antagonists	Recurrent, advanced, persistent OC	Phase I Trial of Intraperitoneal Adenoviral p53 Gene Therapy in Patients With Advanced Recurrent or Persistent Ovarian Cancer (NCT00003450)
		PIK3CA	Signal transduction molecules that regulate proliferation and apoptosis	DNA sequencing	mTOR inhibitors (temsirolimus, everolimus)	Recurrent or peristent OC (2nd, 3rd or 4th line) Advanced solid tumors refractory to standard treatment	Phase II trial of the mTOR inhibitor, temsirolimus and evaluation of circulating tumor cells and tumor biomarkers in persistent and recurrent epithelial ovarian and primary peritoneal malignancies: a Gynecologic Oncology Group study (NCT04931342) A Phase I Study of Bevacizumab, Everolimus, and Panitumumab in Advanced Solid Tumors (NCT00586443)
		KRAS	Part of the RAS/MAPK pathway, involved in cell proliferation, migration, differentiation, apoptosis	DNA sequencing	Monoclonal antibody that targets KRAS (adagrasib); anti-interleukin (IL)-6 monoclonal antibody (siltuximab)	Recurrent, advanced solid tumors	KRYSTAL-1: Activity and Safety of Adagrasib (MRTX849) in Patients with Colorectal Cancer (CRC) and Other Solid Tumors Harboring a KRAS G12C Mutation (NCT03785249) A Safety, Efficacy and Pharmacokinetic Study of Siltuximab (CNTO 328) in Participants With Solid Tumors (completed, not published) (NCT00841191)
		ER/PR	Encodes instructions for K-RAS protein, involved in signaling for cell growth, function, differentiation	IHC	Endocrine therapy (tamoxifen, raloxifene, medroxyprogesterone acetate or megestrol acetate)	Paclitaxel-refractory OC Recurrent, platinum resistant OC	Phase I Trial of Paclitaxel Plus Megestrol Acetate in Patients with Paclitaxel-refractory Ovarian Cancer Chemotherapy vs tamoxifen in platinum-resistant ovarian cancer: a phase III, randomised, multicentre trial (Ovaresist)
	Low grade serous	BRAF	Encodes for gene involved in cell division, proliferation, and differentiation	IHC, PCR, DNA sequencing	BRAF inhibitors (trametinib, vemurafenib, dabrafenib, and encorafenib)	Recurrent or progressive low grade serous ovarian cancer	Trametinib in Treating Patients With Recurrent or Progressive Low-Grade Ovarian Cancer or Peritoneal Cavity Cancer (NCT02101788)
		KRAS	Protein coding gene that encodes EGF-R of tyrosine kinase	DNA sequencing	Monoclonal antibody that targets KRAS (adagrasib); anti-interleukin (IL)-6 monoclonal antibody (siltuximab), PIK3CA inhibitor (serabelisib)	Recurrent, advanced solid tumors	KRYSTAL-1: Activity and Safety of Adagrasib (MRTX849) in Patients with Colorectal Cancer (CRC) and Other Solid Tumors Harboring a KRAS G12C Mutation (NCT03785249) A Safety, Efficacy and Pharmacokinetic Study of Siltuximab (CNTO 328) in Participants With Solid Tumors (NCT00841191)
		NRAS	Part of SNF/SWI, which is required for transcriptional activation of genes normally repressed by chromatin	Multiplex PCR	ERK 1/2 - Kinase inhibitor (ulixertinib)	Advanced solid tumors with mutations in the MAPK pathway	Expanded Access to Ulixertinib (BVD-523) in Patients With Advanced MAPK Pathway-Altered Malignancies (NCT04488003)

Table 1 (continued)

		ERBB2 or HER 2/neu	Phosphorylates certain signaling molecules that play roles involving cell growth, division, movement, transport and survival	IHC, FISH	Monoclonal antibody that targets HER2/neu (trastuzumab)	Not currently being investigated	
	Endometrioid	ARID1A	Tumor suppressor gene, plays a role in cell apoptosis	DNA sequencing	EZH2 inhibitor, ATr inhibitor (AZD6738), PARPi, immunotherapy	Recurrent gynecologic malignancies with ARID1A mutation	ATARI: ATr Inhibitor in combination with Olaparib in gynaecological cancers With ARId1A loss or no loss (NCT04065269)
		PIK3CA	DNA mismatch repair gene	DNA sequencing	mTOR inhibitors (temsirolimus, everolimus), PI3K inhibitor (copanlisib), PIK3CA inhibitor (taselisib, serabelisib), AKT inhibitor (ipatasertib, MK-2206)	Advanced solid tumors refractory to standard treatment Advanced, refractory solid tumors with a PIK3CA mutation	A Phase I Study of Bevacizumab, Everolimus, and Panitumumab in Advanced Solid Tumors (NCT00586443) Targeted Therapy Directed by Genetic Testing in Treating Patients With Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma (The MATCH Screening Trial) (NCT02465060)
		PTEN	Regulates proliferation and induction of apoptosis, DNA repair	DNA sequencing	mTOR inhibitors (temsirolimus, everolimus), PI3K inhibitor (copanlisib)	PTEN loss for advanced, refractory solid tumors	Targeted Therapy Directed by Genetic Testing in Treating Patients With Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma (The MATCH Screening Trial) (NCT02465060)
	Clear cell	MSI-H or dMMR	Part of SNF/SWI, which is required for transcriptional activation of genes normally repressed by chromatin	IHC, DNA sequencing, PCR	Immunotherapy (pembrolizumab)	MSI-H or dMMR solid tumors	Study of Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-3475-158/KEYNOTE-158) (NCT02628067)
		TP53	Phosphorylates certain signaling molecules that play roles involving cell growth, division, movement, transport and survival	DNA sequencing, multiplex ligation-dependant probe assay	Gene therapy, monoclonal antibody, MDM2/4 antagonists	Not currently being investigated	
		ARID1A	Tumor suppressor gene, plays a role in cell apoptosis	DNA sequencing	EZH2 inhibitor, ATr inhibitor (AZD6738), PARPi, immunotherapy	Recurrent gynecologic malignancies with ARID1A mutation	ATARI: ATr Inhibitor in combination with Olaparib in gynaecological cancers With ARId1A loss or no loss (NCT04065269)
		PIK3CA	General protein kinase capable of phophorylating several known proteins, over expression leads to being an oncogene	PCR	mTOR inhibitors (temsirolimus, everolimus), PI3K inhibitor (copanlisib), PIK3CA inhibitor (taselisib)	Advanced, refractory solid tumors with a PIK3CA mutation	Targeted Therapy Directed by Genetic Testing in Treating Patients With Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma (The MATCH Screening Trial) (NCT02465060)
		PTEN	Encodes instructions for K-RAS protein, involved in signaling for cell growth, function, differentiation	DNA sequencing	mTOR inhibitors (temsirolimus, everolimus), PI3K inhibitor (copanlisib)	PTEN loss for advanced, refractory solid tumors	Targeted Therapy Directed by Genetic Testing in Treating Patients With Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma (The MATCH Screening Trial) (NCT02465060)
	Mucinous	AKT2	Protein coding gene that encodes EGF-R of tyrosine kinase	DNA sequencing, PCR	AKT inhibitor (capivasertib, AZD5363)	Advanced, refractory solid tumors with AKT mutation	Targeted Therapy Directed by Genetic Testing in Treating Patients With Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma (The MATCH Screening Trial) (NCT02465060) AZD5363 in Patients With Advanced Solid Tumors Harboring AKT Mutations (NCT03310541)
		KRAS	Tumor suppressor gene, plays a role in cell apoptosis	DNA sequencing	Monoclonal antibody that targets KRAS (adagrasib); anti-interleukin (IL)-6 monoclonal antibody (siltuximab), PIK3CA inhibitor (serabelisib)	Recurrent, advanced solid tumors	KRYSTAL-1: Activity and Safety of Adagrasib (MRTX849) in Patients with Colorectal Cancer (CRC) and Other Solid Tumors Harboring a KRAS G12C Mutation (NCT03785249) A Safety, Efficacy and Pharmacokinetic Study of Siltuximab (CNTO 328) in Participants With Solid Tumors (NCT00841191)
		ERBB2 or HER 2/neu	Phosphorylates certain signaling molecules that play roles involving cell growth, division, movement, transport and survival	IHC, FISH	Monoclonal antibody that targets HER2/neu (trastuzumab)	Stage IV HER 2/neu positive breast or OC receiving trastuzumab Recurrent (2nd or 3rd line) HER 2/neu positive OC	Vaccine Therapy in Treating Patients With Stage IV HLA-A2 and HER2 Positive Breast or Ovarian Cancer Receiving Trastuzumab (NCT00194714) HER2 Overexpression/Amplification and Trastuzumab Treatment in Advanced Ovarian Cancer: A GINECO Phase II Study
Endometrial Cancer	Type I (Endometrioid Adenocarcinoma)	PTEN	Cell to cell adhesion	DNA sequencing	mTOR inhibitors (temsirolimus, everolimus), PI3K inhibitor (copanlisib), AKT inhibitor (AZD5363)	Advanced or metastatic solid cancers bearing either AKT1 / PIK3CA or PTEN mutation Advanced, recurrent endometrial cancer with PTEN or PIK3CA mutation	Safety, Tolerability & Potential Anti-cancer Activity of Increasing Doses of AZD5363 in Different Treatment Schedules (NCT01226316) Pilot Phase II Study of the PI3K Inhibitor Copanlisib in Combination With a Ketogenic Diet in the Treatment of Patients With Relapsed or Refractory Follicular Lymphoma or Endometrial Cancer (NCT04750941)
		PIK3CA	Encodes instructions for K-RAS protein, involved in signaling for cell growth, function, differentiation	PCR	mTOR inhibitors (temsirolimus, everolimus), PI3K inhibitor (copanlisib), PIK3CA inhibitor (taselisib, serabelisib), AKT inhibitor (ipatasertib, MK-2206)	Recurrent or advanced endometrial cancer with PIK3CA mutation Persistent or recurrent endometrial cancer with PIK3CA mutation	Phase II, 2-stage, 2-arm, PIK3CA mutation stratified trial of MK-2206 in recurrent endometrial cancer (NCT01307631) Copanlisib in Treating Patients With Persistent or Recurrent Endometrial Cancer (NCT02728258)

Table 1 (continued)

						Advanced, metastatic endometrial cancer with PIK3CA mutation Advanced solid tumors that have PI3Ka and KRAS mutations Persistent/recurrent endometrial cancer with no specific mutations, PIK3CA/AKT1/PTEN mutations, or loss of heterozygosity	Study of CYH33 in Combination With Olaparib an Oral PARP Inhibitor in Patients With Advanced Solid Tumors (NCT04586335) A Phase 1b/2 Study of Serabelisib in Combination With Canagliflozin in Patients With Advanced Solid Tumors With PIK3CA or KRAS Mutations (NCT04073680) A Phase IB/II Multi-Cohort Study of Targeted Agents With Atezolizumab for Patients With Recurrent or Persistent Endometrial Cancer (NCT04486352)
		Beta-catenin	Part of SNF/SWI, which is required for transcriptional activation of genes normally repressed by chromatin	IHC, DNA sequencing, PCR		Not currently being investigated	
		KRAS	DNA mismatch repair gene	DNA sequencing	Monoclonal antibody that targets KRAS (adagrasib); anti-interleukin (IL)-6 monoclonal antibody (siltuximab), PIK3CA inhibitor (serabelisib)	Advanced solid tumors that have PI3Ka and KRAS mutations	A Phase 1b/2 Study of Serabelisib in Combination With Canagliflozin in Patients With Advanced Solid Tumors With PIK3CA or KRAS Mutations (NCT04073680)
		ARID1A	Regulates proliferation and induction of apoptosis, DNA repair	DNA sequencing	EZH2 inhibitor, ATr inhibitor (AZD6738), PARPi, immunotherapy	Recurrent gynecologic malignancies with ARID1A mutation	ATARI: ATr Inhibitor in combination with Olaparib in gynaecological cancers With ARId1A loss or no loss (NCT04065269)
		MSI-H or dMMR	Protein coding gene that encodes EGF-R of tyrosine kinase	IHC, DNA sequencing, PCR	Immunotherapy (pembrolizumab, avelumab) Avelumab and Axitinib or Talazoparib	MSI-H or dMMR solid tumors MSI-H or Pole mutated recurrent or persistent endometrial cancer	Study of Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-3475-158/KEYNOTE-158) (NCT02628067) Avelumab in Patients With MSS, MSI-H and POLE-mutated Recurrent or Persistent Endometrial Cancer and of Avelumab/Talazoparib and Avelumab/Axitinib in Patients With MSS Recurrent or Persistent Endometrial Cancer (NCT02912572)
	Type 2 (High Grade Serous, Clear Cell,	TP53	Tumor suppressor gene, regulates cell cycle	DNA sequencing, multiplex ligation-dependant probe assay	Gene Therapy (adenoviral p53), monoclonal anibody, MDM2/4 antagonists, Wee1 inhibitor (adavosetib	Recurrent or persistent uterine serous carcinoma or uterine carcinosarcoma	AZD1775 in Women With Recurrent or Persistent Uterine Serous Carcinoma or Uterine Carcinosarcoma (NCT03668340)
	Mucinous)	ERBB2 or HER 2/neu	Cell to cell adhesion	IHC, FISH	Monoclonal antibody that targets HER2/neu (trastuzumab, SYD985, ZW25)	Locally advanced, unresectable, or metastatic disease with HER2 mutation Advanced or recurrent uterine serous carcinoma with HER2/neu overexpression Advanced or recurrent uterine serous carcinoma with HER2/neu overexpression HER2-overexpressed endometrial cancer or carcinosarcoma	A Phase 2 Study of T-DXd in Patients With Selected HER2 Expressing Tumors (DPT02) (NCT04482309) Randomized Phase II Trial of Carboplatin-Paclitaxel Versus Carboplatin-Paclitaxel-Trastuzumab in Uterine Serous Carcinomas That Overexpress Human Epidermal Growth Factor Receptor 2/neu (NCT01367002) SYD985 in Patients With HER2-expressing Recurrent, Advanced or Metastatic Endometrial Carcinoma (NCT04205630) A Phase 2 Trial of ZW25 in HER2 Overexpressed Advanced Endometrial Cancers and Carcinosarcomas (ZW25-IST-2) (NCT04513665)
		p16	Regulates proliferation and induction of apoptosis, DNA repair	IHC, FISH	CDK4/6 inhibitors (Palbociclib, Ribociclib, Abemaciclib)	Not currently being investigated	
		E-cadherin	Tumor suppressor gene, critical for the formation and maintenance of adherent junctions in areas of epithelial cell-cell contact	IHC	Monoclonal antibodies, N-cadherin antagonist (ADH-1)	Not currently being investigated	
	Leiomyos arcoma	TP53	Tumor suppressor gene, regulates cell cycle	DNA sequencing, multiplex ligation-dependant probe assay	Gene therapy (adenoviral p53), monoclonal antibody, MDM2/4 antagonists	Not currently being investigated	
		RB1	Regulates cell cycles and encodes a protein that stabilizes heterochromatin to maintain the overall chromatin structure.	DNA sequencing	CDK4/6 inhibitors (Palbociclib, Ribociclib, Abemaciclib)	Not currently being investigated	
		ATRX	Involved in regulation of interphase and chromosomal segregation during mitosis. Mutations	IHC, DNA sequencing	Wee1 kinase inhibitor (adavosertib)	Not currently being investigated	

Table 1 (continued)

			cause diverse changes in DNA methylation.				
		MED12	Mediator complex subunit 12 plays a role as part of a large complex protein assembly that regulates transcription initiation	DNA sequencing		Not currently being investigated	
		CDKN2A	Regulates CDK4 and stabilitizes p53, thereby regulating G1 progression in the cell cycle	DNA sequencing	CDK4/6 inhibitors (Palbociclib, Ribociclib, Abemaciclib)	Not currently being investigated	
	High Grade Endometrial Stromal Sarcoma	ZRSR2	An essential splicing factor associated with U2, which is required for the recognition of splice sites	DNA sequencing	Splicing factor inhibitor (H3B-8800)	Not currently being investigated	
		CDKN2A	Regulates CDK4 and stabilitizes p53, thereby regulating G1 progression in the cell cycle	DNA sequencing	CDK4/6 inhibitors (Palbociclib, Ribociclib, Abemaciclib)	Not currently being investigated	
		YWHAE	By binding to phosphoserine-containing proteins it mediates signal transduction in processes including such as cell division and regulation of insulin sensitivity	IHC		Not currently being investigated	
		PTEN	Phosphorylates certain signaling molecules that play roles involving cell growth, division, movement, transport and survival	DNA sequencing	mTOR inhibitors (temsirolimus, everolimus), PI3K inhibitor (copanlisib)	Not currently being investigated	
		PBRM1	Acts through its signalling pathway to halt the cell cycle at the G1 stage. Increased TGF-β causes also effects immunosuppresion and angiogenesis	DNA sequencing		Not currently being investigated	
Cervical Cancer	HPV-related	PIK3CA	Upregulation of PD-L1/2 allows cancers to evade the immune system by reducing both the proliferation of antigen specific T-cells and the apoptosis of regulatory T cells	PCR	mTOR inhibitors (temsirolimus, everolimus), PI3K inhibitor (copanlisib), PIK3CA inhibitor (taselisib, serabelisib), AKT inhibitor (ipatasertib, MK-2206)	Advanced solid tumors with PI3Ka and KRAS mutations	A Phase 1b/2 Study of Serabelisib in Combination With Canagliflozin in Patients With Advanced Solid Tumors With PIK3CA or KRAS Mutations (NCT04246489)
		TGF-β	Encodes instructions for K-RAS protein, involved in signaling for cell growth, function, differentiation	DNA sequencing	PD-L1/TGF-β trap (bintrafusp alfa, M7824)	Locally advanced or metastatic HPV associated cancer Advanced, unresectable and/or metastatic cervical cancer with disease progression during or after the prior platinum-containing chemotherapy	Phase I/II Trial of HPV Vaccine PRGN-2009 Alone or in Combination With Anti-PD-L1/TGF-Beta Trap (M7824) in Subjects With HPV Positive Cancers (NCT04432597) A Phase II, Multicenter, Open Label Study of Bintrafusp Alfa (M7824) Monotherapy in Participants With Advanced, Unresectable Cervical Cancer With Disease Progression During or After Platinum-Containing Chemotherapy (NCT04246489)
		PDL-1/2	Part of SNF/SWI, which plays a role in transcriptional activation of genes normally repressed by chromatin, repair DNA damage, DNA replication and cell growth	IHC	Immunotherapy (pembrolizumab)	Persistent, recurrent, or metastatic cervical cancer Locally advanced cervical cancer	Efficacy and Safety Study of First-line Treatment With Pembrolizumab (MK-3475) Plus Chemotherapy Versus Placebo Plus Chemotherapy in Women With Persistent, Recurrent, or Metastatic Cervical Cancer (MK-3475-826/KEYNOTE-826) (NCT03635567) Study of Chemoradiotherapy With or Without Pembrolizumab (MK-3475) For The Treatment of Locally Advanced Cervical Cancer (MK-3475-A18/KEYNOTE-A18/ENGOT-cx11/GOG-3047) (NCT04221945)
		KRAS	Tumor suppressor gene, plays a role in cell apoptosis	DNA sequencing	Monoclonal antibody that targets KRAS (adagrasib); anti-interleukin (IL)-6 monoclonal antibody (siltuximab), PIK3CA inhibitor (serabelisib)	Advanced solid tumors that have PI3Ka and KRAS mutations	A Phase 1b/2 Study of Serabelisib in Combination With Canagliflozin in Patients With Advanced Solid Tumors With PIK3CA or KRAS Mutations (NCT04073680)
		ARID1A	Tumor suppressor gene, regulates cell cycle	DNA sequencing	ATR Inhibitors (AZD6738)	Recurrent gynecologic malignancies with ARID1A mutation	ATARI: ATr Inhibitor in combination with Olaparib in gynaecological cancers With ARId1A loss or no loss (NCT04065269)
		PTEN	Phosphorylates certain signaling molecules that play roles involving cell growth,	DNA sequencing	mTOR inhibitors (temsirolimus, everolimus), PI3K inhibitor (copanlisib)	PTEN loss for advanced, refractory solid tumors	Targeted Therapy Directed by Genetic Testing in Treating Patients With Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma (The MATCH Screening Trial) (NCT02465060)

Table 1 (continued)

			division, movement, transport and survival				
		p16	Regulates proliferation and induction of apoptosis, DNA repair	IHC	P16_37-63 peptide vaccine	p16 positive gynecologic cancers, squamous cell carcinoma of the cervix HPV-induced cancers	Avelumab With Valproic Acid in Virus-associated Cancer (LATENT) (NCT03357757) Cisplatin-based Chemotherapy Combined With P16_37-63 Peptide Vaccination in Patients With HPV-positive Cancers (VICORYX-2) (NCT02526316)
		TP53	Encodes instructions for KRAS protein, involved in signaling for cell growth, function, differentiation	DNA sequencing, multiplex ligation-dependent probe assay	Gene Therapy (adenoviral p53), monoclonal anibody, MDM2/4 antagonists, Wee1 inhibitor (adavosetib)	Not currently being investigated; pre-clinical trials only	

most often utilized for identification of high-risk inherited genes in gynecologic malignancies. However, through the identification of germline and somatic mutations, NGS allows for novel tumor classification, mechanisms of treatment resistance, and identification of new therapeutic strategies.

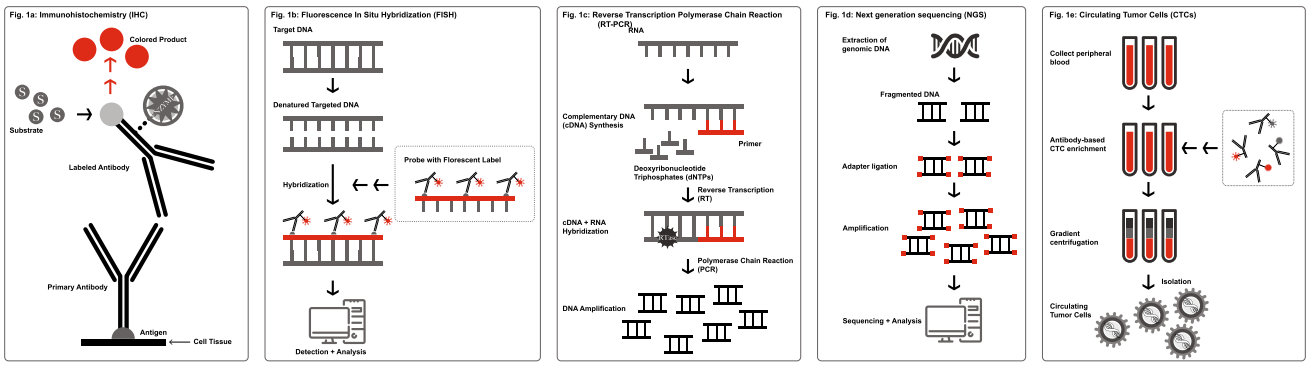

Fig. 1 Molecular profiling.

The Cancer Genome Atlas (TGCA) project evaluated 489 high-grade serous ovarian carcinomas (HGSOC) and identified 168 silenced genes throughout promoter methylation, 9 genes with significant recurrent mutations, and 113 copy number mutations [8••]. For example, mutations in the TP53 gene were nearly ubiquitous in HGSOC and among those that do not have a TP53 mutation, p53 dysfunction is elicited through MDM2 or MDM4 copy number gain [9]. The whole exome sequencing has demonstrated patterns associated with platinum resistance such as inactivation of tumor suppressor genes RB1, NF1, RAD51B, PTEN, and CCNE1 [10]. Other important mutations such as BRCA1, BRCA2, CSMD3, CDK12, FAT3, and GABRA6 were also discovered via NGS [11]. Because of the impact on prognosis and treatment decisions that high-risk inherited genes can have, it is recommended that every patient with an epithelial ovarian cancer undergo hereditary susceptibility testing. Now FDA approved and commercially available, NGS allows for the rapid testing of multiple high-risk alterations for these patients. Additionally, because of the rapidity of testing, we now have the ability to perform whole transcriptome and exome sequencing.

Circulating tumor cells

Detection of circulating tumor cells (CTCs), often referred to as a liquid biopsy, is an emerging technology transitioning from the laboratory to clinical trials. This technology allows for the detection of scarce tumor cells, thought to have been shed from the primary tumor within billions of peripheral blood cells. Thus far, they have shown a promise for diagnostic and prognostic assessments, and for monitoring treatment response. For cervical cancer, detection of CTCs of viral oncogenes of HPV can be utilized. CTCs have been associated with advanced disease in ovarian cancer, likely reflecting higher tumor burden and the ability to shed higher number of CTCs into circulation [12, 13]. Though CTCs may be predictive of outcome in ovarian cancer, a lack of standardization of methods and large prospective studies have limited the implementation into clinical practice, but current trials will likely broaden the role of CTCs for early detection of primary cancers and recurrences.

Molecular Alterations of Gynecologic Malignancies

Ovarian cancers have varied histopathology and malignant potential, making molecular alterations in these cancers equally as varied. BRCA 1/2, inherited genetic mutations, are attributed to 10–15% of ovarian cancers [14]. The study of BRCA 1/2 revealed that other germline mutations could be responsible for ovarian cancer and the concept of homologous recombination deficiency (HRD) emerged [15]. Other molecular alterations in the HR repair pathway are BRIP1, RAD51C/D, BARD1, CHEK2, PALB2, and ATM. Lynch syndrome also known as hereditary nonpolyposis colon cancer (HNPCC) is the second most common cause of heredity epithelial ovarian cancer (EOC). MMR alterations have been documented in 10-15% of ovarian cancers, most commonly the endometrioid subtype, and may play a role in predictors of response to checkpoint therapies [16].

EOC historically was divided into type I and type II based upon histology and genetic alterations. As the most common subtype of ovarian cancer, 96% high grade serous ovarian cancers have a TP53 mutation. Endometrioid and clear cell adenocarcinomas have been associated with endometriosis and possess frequent mutations of PTEN and PIK3CA. Endometriosis-driven cancers have also been linked to ARID1A mutations, with over 50% of clear cell carcinomas demonstrating this mutation [17].

Sex cord-stromal tumors include granulosa cell tumors, thecomas, fibromas, Sertoli-Leydig tumors, and gynandroblastomas. The most common alterations in granulosa cell tumors include AKT1 followed by the nuclear receptor, rev-erbAα, and FOXL2 [18]. Hereditary syndromes also associated with these tumors include Peutz-Jeghers syndrome, Ollier disease and Maffucci syndrome, and DICER1 syndrome. These syndromes are associated with alterations in STK11/LKB1, isocitrate dehydrogenase (IDH) 1 and 2 genes, and DICER1 genes, respectively [19]. A rare, aggressive ovarian cancer that occurs in young women, small-cell carcinoma, hypercalcemic type (SCCOHT) confers a poor prognosis. It characteristically has a loss of function in the SMARCA4 gene, a protein that regulates transcription of genes through chromatin remodeling. SCCOHT typically harbors a high frequency of these mutations but unfortunately, there is no directed therapy as of yet [20, 21].

Uterine malignancies include endometrial carcinomas, which arise from the endometrial lining, and uterine sarcomas, which arise from mesenchymal elements. For type I, the primary causality is unopposed estrogen stimulation with almost 80% arising from loss of PTEN expression. [22] Other commonly mutated genes in type I include FGFR2, ARID1A, CTNNB1, PIK3CA, PIK3R1, and KRAS. TCGA consortium data has defined four prognostic subgroups of endometrial cancer (prognostically best to worst): POLE, MSI hypermutated, copy number low, and copy number high. This study reported frequent mutations in the PI3K/AKT pathway. [23••] Hormone receptors also play a prognostic role for endometrial cancer, most often for endometrioid types, and loss of estrogen and progesterone receptors demonstrates poor prognosis with increased risk of lymph node metastasis and reduced disease specific survival [24] Contrarily, type II endometrial cancers are comprised of clear cell or serous histologies. Almost 90% of serous adenocarcinomas are secondary to TP53 mutations as well as associated high Ki-67 scores, p16 inactivation, and CDH1 and HER2/neu amplification. TCGA consortium studied molecular alterations of type II carcinomas, which revealed ERBB2 amplification in 27% of tumors and PIK3CA mutations in 42%. Less common uterine malignancies include uterine sarcomas. Leiomyosarcomas are commonly correlated with alterations in TP53, RB1, ATRX, MED12, and CDKN2A whereas endometrial stromal sarcomas are more commonly affected by mutations of ZRSR2, CDKN2A, YWHAE, PTEN, and PBRM1 [8••, 25, 26].

Carcinogenesis of cervical cancer is associated with the human papilloma virus (HPV), specifically the E6 (TP53) and E7 (retinoblastoma) oncoproteins, often promoted by alterations in PI3K/MAPK pathways [27]. Disruption in TGF-beta signaling is associated with development of cervical cancer. TGF-beta signaling is associated with normal cervical remodeling, but inactivation of these genes' receptors leads to increased circulating TGF-beta, correlated with cervical cancer tumorigenesis. [28] Frequently overexpressed in cervical cancer, a common component targeted for treatment of cervical cancer is the programmed cell death-1 and programmed cell death ligand-1 (PD-1/PD-L1). [29] The higher number of expression of these ligands has been associated with poorer survival outcomes for cervical cancer. Nevertheless, newer immune checkpoint therapies are attempting to overcome the immune tolerance associated with cervical cancer development [30].

While HPV is associated with most cervical cancers, other mutations have been identified. TCGA has identified mutations in PTEN, K-RAS, and ARID1A as being more frequently associated with these HPV-negative subtypes of cervical cancer. [31•] Uncommon types of cervical cancer include neuroendocrine tumors (2%), which have alterations in these tumors involving the MAPK, PI3K/AKT/mTOR, and TP53/BRCA pathways and are potential targets for therapy [32].

Similar to cervical cancer, vulvar and vaginal cancers are primarily HPV driven and have been known to be associated with TP53 mutations. In more recent studies, hypermethylation has been examined as factors leading to carcinogenesis,

most commonly in vulvar cancers involving hypermethylation of RASSF2A, MGMT, and TSP1. [33] Recent studies have also examined the genetic profiles of melanomas involving the vagina and vulva. The most common genetic alterations associated with vaginal and vulvar melanomas included BRAF, KIT, and PD-L/PD-L1 with NRAS mutations being rarer and more commonly involved in cutaneous melanomas [34].

While we can identify a multitude of mutations with current testing techniques, not all of the mutations are necessarily targetable at this time.

Currently Approved Targeted Therapies for Gynecologic Malignancies

With the molecular data collected from the TCGA on ovarian, endometrial, and cervical cancer, the understanding of the molecular complexity of gynecologic malignancies was realized, thereby spurring novel therapeutic developments. Unfortunately, the pace to adopt precision medicine in gynecologic malignancies has not been as rapid as in other disease sites, secondary to the heterogeneity and inherent molecular intricacies of these cancers coupled with relatively fewer patients. Nonetheless, recent efforts have produced multiple approved targeted therapies for gynecologic malignancies.

Hormonal Therapy

Although not traditionally thought of as a targeted therapy, hormonal treatments are some of the earliest and most widely utilized molecularly targeted therapies. Several gynecological cancers, such as ovarian and endometrial carcinomas, as well as some gynecological sarcomas express estrogen and/or progesterone receptors. The most common gynecologic malignancy, type I endometrial cancer, results from excess estrogen exposure and thus hormonal treatment is an option in the setting of fertility-sparing, metastatic/recurrent disease, or non-surgical management scenarios. Progesterone therapy can be utilized orally or via an intrauterine device. The two most commonly used oral progestins in this setting are medroxyprogesterone acetate and megestrol acetate. [35–37] Other hormonal treatments include aromatase inhibitors (AI), luteinizing hormone agonists, or selective estrogen receptor modulators (SERMs). Baker et al. showed a complete response in 50% patients with hyperplasia or low-grade endometrial cancer in those unable to undergo surgical resection. [38] A rare type of endometrial cancer, low-grade endometrial stromal sarcoma (LG-ESS), has a high expression of progesterone/estrogen receptors and has an equally high-response rate to endocrine therapy. Most commonly used endocrine therapies for LG-ESS are progestins, and they are recommended post-surgery for all patients with stage II to stage IV disease, as well as those with metastatic/recurrent disease [39–41].

For HGSOC, hormonal therapy is occasionally used in patients who have exhausted chemotherapy agents. Estrogen receptor positivity in ovarian cancer ranges from 43 to 81%, but response rates to SERMs and AIs are 10–15% in this difficult-to-treat population. [42] In breast cancer, hormonal status, especially ER positive, has proven to be highly predictive of proportional response, for which we have extrapolated the use to HGSOC with positive ER/PR with variable benefit further elucidating the heterogeneity of ovarian cancer. Thus far, there have been limited studies utilizing hormone receptor status to determine efficacy of hormone therapy for HGSOC. Though ineffective as a single agent, multiple studies are investigating combinations with other therapies. Conversely, low-grade serous ovarian cancers often exhibit estrogen and/or progesterone receptor positivity, thus substituting endocrine therapy for chemotherapy is under investigation for stage II-IVB disease after primary surgery. In 2017, Fader et al. showed a progression free survival (PFS) of 79% and overall survival (OS) of 92.6% at 2 years in this population (median PFS and OS had yet to be reported). [43] Phase III trial, NRG-GY-019 (NCT04095364), is underway comparing chemotherapy followed by letrozole versus letrozole monotherapy in those with stage II-IVB low-grade serous ovarian cancer following primary surgery.

Anti-angiogenics

Angiogenesis is critical to tumor growth and metastases; thus, anti-angiogenic therapy has established a role in virtually all gynecologic malignancies. Vascular endothelial growth factor (VEGF) is upregulated by tumor cells thereby promoting cell proliferation, migration, survival, and vascular permeability. [44] Monoclonal antibody against VEGF, bevacizumab, received its first approval for the treatment of platinum-resistant recurrent ovarian cancer in 2014 following the phase III AURELIA trial that showed an increase in progression-free survival (PFS) and overall response rate (ORR), but a non-significant difference in overall survival (OS). [45•] Subsequently, it then received approvals for treatment of platinum-sensitive recurrent ovarian cancer in 2016 (GOG-0213 and OCEANS), in combination with chemotherapy and as first-line ovarian maintenance in 2018 (GOG-0218), and in combination with poly-ADP-ribose polymerase inhibitors (PARPi), olaparib, in 2019 for first-line ovarian treatment/maintenance (PAOLA-1). [46•, 47•, 48•, 49•] Bevacizumab received FDA approval for use in cervical cancer in 2014 for the treatment of metastatic or recurrent cervical cancer (GOG-0240), added to the standard chemotherapy doublet. It showed an increased response rate

of 50% and added a survival benefit of 3.7 months in a population of patients with limited treatment options. [50••] For endometrial cancer, currently bevacizumab is not approved for use but is often used off-label for treatment refractory disease as it has shown to confer some benefit as single-agent and in combination with chemotherapy. [51–53] The anti-angiogenic that does have approval for use in endometrial cancer is lenvatinib, a tyrosine kinase inhibitor that inhibits VEGFR1, VEGFR2, and VEGFR3. It is currently approved for use in combination with immunotherapy, pembrolizumab, for recurrent endometrial cancer that are MSS, thus not MSI-H/MMRd [54••].

Poly-ADP-ribose polymerase inhibitors

PARPi, responsible for the repair of single strand DNA breaks, are a key component of the DNA repair process where multiple pathways are critical. With PARPi, single-strand DNA breaks are not repaired, which results in double strand breaks that are dependent on the double-stranded repair mechanisms, such as homologous recombination (HR) in part governed by BRCA1/2 genes. Deficiencies in HR impairs normal DNA damage repair, resulting in a loss of specific chromosomal regions. Current assays determine if tumor cells are HR-deficient (HRD) by two mechanisms, evaluating for specific mutations (BRCA1/2, PALB2, ATM, CHECK1/2, RAD51) or calculating a score based on the phenotypic effects of HRD on the genome of the tumor (i.e., loss of heterozygosity or LOH). If tumor cells are HR deficient (HRD), cell death ensues; a concept termed synthetic lethality where two non-lethal events are lethal when present in combination (i.e., BRCA1/2 mutation (BRCAmut) + PARPi). Consequently, HRD cells, with BRCA1/2mut, are sensitive to PARPi because they are unable to repair the unrepaired DNA breaks. [55] This observation fostered clinical trials for PARPi in BRCA-deficient and HRD tumors. Nearly 50% of HGSOC demonstrate HRD, resulting in nine FDA approvals for the use of PARPi in ovarian cancer. [56] Olaparib, the first FDA-approved PARPi, has four indications—as a frontline maintenance therapy for BRCA1/2-mutated patients (SOLO-1), as frontline maintenance therapy in combination with bevacizumab for those with HRD (PAOLA-1), as maintenance therapy for platinum-sensitive recurrent ovarian cancer (SOLO-2), and as a treatment for BRCA1/2-mutated patients who have received 3 prior lines of treatment (Study 42). [49•, 57••, 58•, 59•] Niraparib currently has three indications—as frontline maintenance therapy regardless of biomarker status (PRIMA), as maintenance therapy for platinum sensitive recurrent ovarian cancer (NOVA), and as treatment for fourth-line and beyond for HRD population (QUADRA). [60•, 61•, 62] Rucaparib, the third PARPi, utilized in the treatment of ovarian cancer currently has two indications—as maintenance therapy for platinum-sensitive recurrent ovarian cancer (ARIEL-3) and as treatment for BRCA1/2-mutated patient who have had 2 prior lines of chemotherapy (Study 10/ARIEL-2 part 1). [63•, 64, 65] There are currently studies underway investigating PARPi in endometrial and cervical cancer.

Immunotherapy

As a critical regulator of cancer, the immune system has the capacity to inhibit tumor development, growth, and metastasis, but immune evasion and escape has long been the hallmark of oncogenesis. Immunotherapy re-engages the immune system to recognize markers of malignant transformation in order to eradicate malignant cells. [66] The biologic rationale for the incorporation of immunotherapy as treatment for gynecologic malignancies has been postulated to be beneficial for several reasons: presence of tumor-infiltrating lymphocytes in ovarian cancer correlating with outcomes, high mutational burden associated with HPV-related cancers, and the abundance of neoantigens in MSI endometrial cancers rendering them immunogenic. [67] For endometrial cancer, immunotherapy, pembrolizumab, has been approved for use as a single agent for those with MSI-H disease and as a combination regimen with lenvatinib for those who are MMR proficient. [54••] Importantly, approval for single-agent pembrolizumab based on KEYNOTE-158, arose as the first tissue agnostic FDA approval. Its approval was irrespective of tumor site origin and was based on the genetic alteration of the tumor (MSI-H/MMRd status), paving the way for future tissue agnostic approvals. Additionally, as of April 2021, immunotherapy dorstarlimab was granted accelerated approval for the treatment of dMMR advanced or recurrent endometrial cancer for those who have progressed or recurred following treatment with a platinum. This approval was based on the GARNET trial (NCT02715284) with an ORR of 42% and 93.3% of patient having a duration of response (DOR) > 6 months, with median DOR having not been reached at the time of approval. [68•] Pembrolizumab was also approved for use as a monotherapy for advanced cervical cancer with disease progression during or after chemotherapy for patients who have tumor that express PD-L1 with a CPS ≥ 1, also based on KEYNOTE-158. [69] In October of 2021, pembrolizumab was approved for use in combination with chemotherapy with or without bevacizumab, for the first-line treatment of metastatic cervical cancer, or for persistent or recurrent cervical cancer for those with tumors that express PD-L1 with a CPS ≥ 1, based on KEYNOTE-826 (NCT03635567). [70••] Promising cervical targeted therapy, tisotumab vedotin (antibody–drug-conjugate targeting tissue factor), received accelerated FDA approval in September 2021 for the treatment of recurrent or metastatic cervical cancer after treatment with or progression chemotherapy based on the innovaTV 204

trial (NCT03438396). [71••] Other novel targeted therapies for cervical cancer being investigated include nivolumab and ipilimumab (PD-1 and CTLA-4 inhibitors), bintrafusp-alpha (targets TGF-*B* and PDL-1), and tumor-infiltrating lymphocyte therapy with adoptive cell transfer among others [72–76].

Though there is evidence of obvious benefit of immunotherapy with endometrial cancer and cervical cancer illuminated by recent positive trials resulting in an unprecedented, multitude of FDA approvals, thus far, immunotherapy trials for treatment of front-line and recurrent ovarian cancer have been disappointing. [77–79] Further translational science progress is needed to understand how to convert these ovarian relatively immunogenically cold tumors to hot tumors.

Biomarker-Driven Approach in Clinical Practice and Recent Clinical Trials

With the onset of identifiable biomarkers, there was then a shift to initiating their use into clinical practice and clinical trial design. Herzog et al. examined the impact of molecular profiling in patients with advanced ovarian cancer in a retrospective review, utilizing a large commercial registry that concluded that patients who received treatment based on their molecular profiling demonstrated a 9-month OS benefit versus those who had not. [80] At the University of Oklahoma, they implemented a multi-disciplinary Precision Medicine Tumor Board, maintaining a database for each patient in order to prospectively follow individual treatment courses and the outcomes in order to prioritize engagement in early phase clinical trials. [81] The ProfiLER programme, a multi-center, multi-disease site, prospective trial in France, performed molecular profile of tumors from patients in with advanced, recurrent cancer to identify molecular-based treatments. Of those with gynecologic malignancies, 42% were found to have actionable mutations, yet only 13% received recommended molecular-based treatment; however, for those who did, 46% of them derived clinical benefit. [82] Several single institution studies retrospectively reviewed the implications of molecular profiling in clinical practice and found that even though 72–76% had actionable mutations, only 14–35% based treatment on molecular results. [83, 84] Others have investigated the utility of ctDNA for gynecologic malignancies and found 75% had an identified mutation, and of the 31% of patients that were matched to therapy by ctDNA, OS was improved (*HR*: 0.34, $P = 0.007$). [85] CTCs have been used in cervical cancer as a biomarker associated with poor disease-free survival in patients with locally advanced cervical cancer. [86] Additionally, GOG-0240, a phase III trial for patients with advanced or recurrent cervical cancer, demonstrated that significant declines in CTCs were associated with lower risk of death *HR* 0.87 (95% *CI* 0.79–0.95) whereas higher pretreatment CTCs correlated with improved PFS (*HR* 0.59) in the bevacizumab cohort [87].

PORTEC-3, a trial investigating the benefit of combined adjuvant chemotherapy and radiation, versus radiation alone for high-risk endometrial cancer, modified molecular classifications of four subgroup system derived from TCGA data. They grouped tumors as p53-abnormal (p53abn), *POLE*-ultramutated (*POLE*mut), mismatch repair-deficient (MMRd), and no specific molecular profile (NSMP). p53abn had poor outcomes in contrast to the *POLE*mut persistent to excellent outcomes, while MMRd and NSMP exhibited intermediate outcomes. With the clinical endpoint of recurrence free survival (RFS), the p53abn had significant benefit to chemoradiation rather than radiation alone. Molecular profiling was successful in 97% of the tumors [88].

With the rapidly evolving landscape of biomarkers amid the recent studies showing their clinical importance, almost all recent clinical trials include therapies that target their matched biomarker. It is thought that the mutational burden of TP53 is related to the efficacy of wee1 inhibition. Additionally, pre-clinical data suggested that the addition of a wee1inhibitor plus gemcitabine worked synergistically to overcome platinum resistance. Phase II study of wee1 inhibitor, adavosertib plus gemcitabine exhibited a significant benefit in PFS and OS over chemotherapy alone in heavily pretreated patients with platinum-resistant or platinum refractory HGSOC [89]. Low-grade serous ovarian cancers often are impacted along their mitogen-activated protein kinase/extra-cellular signal-regulated kinase (MEK) signaling pathway. GOG-0281 (NCT02101788), a phase II/III, compared MEK inhibitor, trametinib, to chemotherapy for patients with recurrent low-grade serous ovarian cancer. PFS improved by 5.8 months (*HR*:0.48; $P < 0.001$). [90] With incorporation of a predictive biomarker for response found in other disease sites, BRAF V600 mutation has the potential for improved responses. [91] For advanced or recurrent high-grade serous uterine cancer, Fader et al. demonstrated that trastuzumab in combination with chemotherapy improved PFS by 4.6 months (HR 0.44) in HER2/neu overexpressors. [92•] Uterine serous carcinomas, with a 95% rate of TP53 mutations, have also displayed a benefit to wee 1 inhibition. In a phase 2 study, single arm study, oral Wee1-inhibitor, adavosertib was used with patients with recurrent uterone serous carcinoma. Objective response rate was 29.4% (95% CI; 15.1-47.5%) and PFS rate at 6 months was 58.7% (95% CI; 39.5-73.7%) (NCT03668340) [93]. For cervical cancer, current clinical trial development has focused on disrupting the immune tolerance inherent to HPV, specifically targeting HPV E6 and E7 oncoproteins.

With the advent of precision medicine, clinical trial platform design has evolved with numerous basket and umbrella

trials to investigate the actions of targeted therapies on their paired molecular aberrations. Simply put, basket trials investigate a shared molecular alteration across multiple cancer types; whereas, an umbrella trial enrolls patients of the same cancer type but with differing molecular alterations. Two of the largest platform trials are the National Cancer Institute-Molecular Profiling-based Assignment of Cancer Therapy (NCI-MPACT NCT01827384) and the National Cancer Institute-Molecular Profiling-based Assignment of Cancer Therapy (NCI-MATCH NCT02465060), tumor-agnostic trials focused on genetic alterations rather than cancer origin. The NCI-MPACT trial was a large randomized, basket trial comparing response rates for patients with an actionable mutation (DNA repair, PI3K, or RAS/RAF/MEK) when treated with an agent targeting the specific pathway versus not. The NCI-MPACT trial established the molecular profiling assay that was later utilized in the NCI-MATCH trial. [94•] The NCI-MATCH included patients with a solid tumor, myeloma, or lymphoma who had progressed on standard therapy. As an umbrella-basket hybrid trial design, it had 30 parallel, single-arm, phase II trials that enrolled patients onto mutation-specific treatment trial arms. Of the 5540 patients screened, 38% were found to have an actionable mutation, yet variable across disease type. Interestingly, rare cancers were found to have an increased rate of actionable mutations and thus higher match rates to targeted treatment. [95••] These trials prompted further large, multicenter, tumor-agnostic trials that are currently ongoing, such as the Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study (NCT04589845), a phase II global trial evaluating the safety and efficacy of targeted agents and immunotherapy as single agents or in combination on solid tumors that harbor actionable mutations or have a high tumor mutational burden. [96•] The Targeted Agent and Profiling Utilization Registry (TAPUR) Study (NCT02693535) the first study sponsored by the American Society of Clinical Oncology (ASCO) also investigates the safety and efficacy of targeted agents on their paired mutations, but by utilizing providers' choice commercial genomic testing matched with targeted agents that have FDA approval. [97•] These platform trials demonstrate the feasibility of implementing NGS technology to accomplish a large, national trial, including common and rare tumor types, inferring important implications for our rare, difficult to treat gynecologic malignancies.

Conclusions and Future Directions

Multiple molecular alterations coupled with the subsequent rapid advancement of anti-cancer therapeutics have changed the landscape for treatment of gynecologic malignancies. These molecular aberrations were found to serve as actionable mutations, prognostic indicators, and predictive biomarkers that foreshadow efficacy and tolerability. Challenges for the universal use of precision medicine remain and include spatial and temporal tumor heterogeneity, identification of true driver mutations, and financial costs and toxicity of these agents especially in combination. Although slow to adopt due to the rarity of gynecologic malignancies; precision strategies continue to proliferate. PARPi and anti-angiogenics for ovarian cancer treatment have been true clinical success stories and further promise is seen in endometrial and cervical cancers with immune-oncologics and other precision compounds. Continued progress in sequencing with whole exome, where all protein-coding regions of genes in a genome are sequenced, and now transcriptome analysis with big data interrogation with artificial intelligence as well as cDNA and cell-free DNA analysis, will continue to revolutionize oncologic therapeutics.

Innovative adaptive clinical trial designs are required to keep pace with these translational science discoveries that likely will predicate smaller, nimbler, biomarker driven, and validating trials to fuel the next round of breakthrough therapeutics for women afflicted with gynecologic malignancies.

Declarations

Conflict of Interest JE Wolford, E Ferrigini, and D Margul have no conflicts of interests to disclose. TJ Herzog has served on scientific advisory boards for Johnson & Johnson, Clovis, AstraZeneca, GlaxoSmithKline, Roche Genentech, Caris, Abbvie, Aravive, Merck, and Eisai outside of this article.

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•• Of major importance

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