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State of the Biomarker Science in Ovarian Cancer: A National Cancer Institute Clinical Trials Planning Meeting Report

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abstract

PURPOSE Despite therapeutic advances in the treatment of ovarian cancer (OC), 5-year survival remains low, and patients eventually die from recurrent, chemotherapy-resistant disease. The National Cancer Gynecologic Cancer Steering Committee identified the integration of scientifically defined subgroups as a top strategic priority in clinical trial planning.

METHODS A group of experts was convened to review the scientific literature in OC to identify validated predictive biomarkers that could inform patient selection and treatment stratification. Here, we report on these findings and their potential for use in future clinical trial design on the basis of hierarchal evidence grading.

RESULTS The biomarkers were classified on the basis of mechanistic targeting, including DNA repair and replication stress, immunotherapy and tumor microenvironment, oncogenic signaling, and angiogenesis. Currently, *BRCA* mutations and homologous recombination deficiency to predict poly (ADP-ribose) polymerase inhibitor response are supported in OC by the highest level of evidence. Additional biomarkers of response to agents targeting the pathways above have been identified but require prospective validation.

CONCLUSION Although a number of biomarkers of response to various agents in OC have been described in the literature, high-level evidence for the majority is lacking. This report highlights the unmet need for identification and validation of predictive biomarkers to guide therapy and future trial design in OC.

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INTRODUCTION

Ovarian cancer (OC) is the eighth most commonly occurring cancer in women and the 18th most commonly occurring cancer worldwide.[1] In the United States, there were an estimated 21,410 new cases diagnosed and 13,770 deaths from OC in 2021. Initial treatment requires expert multidisciplinary care, which typically involves primary debulking surgery or neoadjuvant chemotherapy (NACT).[2] Despite therapeutic advances, the 5-year relative survival in the United States remains low (49.1%), and patients eventually die from recurrent, chemotherapy-resistant disease.[3]

The US National Cancer Institute (NCI) Gynecologic Cancer Steering Committee (GCSC) identified targeting scientifically defined OC subgroups to advance precision therapy as a top strategic priority in clinical trial planning. On the basis of this input, the NCI convened an OC Clinical Trials Planning Meeting (OCCTPM) in February 2021. The objectives of the OCCTPM were to review the molecular and immunologic landscape in OC, to develop trials on the basis of validated biomarkers, and to design novel combination therapies to overcome drug resistance. Before the meeting, a group of experts were assembled to cull the scientific literature for data on validated discriminants to inform treatment-focused groups and to identify validated markers for patient selection and treatment stratification. Reports were generated on several key areas including antiangiogenic therapy, DNA damage repair, hormone-related pathways, immunotherapy, gene signatures, epigenetics, and oncogenic signaling. We summarize the key findings from these individual reports below and identify potential candidate approaches for clinical trial planning and design on the basis of hierarchal evidence grading.

METHODS

Predictive biomarkers differentially segregate expected benefit from a defined therapy and measure the likelihood of better or worse outcomes in response to a specific biomarker-targeted intervention. Predictive biomarkers are differentiated from prognostic biomarkers by the requirement for a statistically significant treatment outcome by biomarker interaction.[4,5] This difference can be shown using *ERBB2/HER2* amplification as an example of both a prognostic and

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CONTEXT

Key Objective

To evaluate the predictive value of existing and emerging biomarkers in ovarian cancer (OC) for use in future clinical trial design on the basis of hierarchical evidence grading.

Knowledge Generated

Multiple potential biomarkers have been identified, but few have been found to be predictive on the basis of high-level evidence showing treatment/outcome interaction. Currently, *BRCA* mutations and homologous recombination deficiency to predict poly (ADP-ribose) polymerase inhibitor response are supported in OC by the highest level of evidence. Mismatch repair deficiency and high tumor mutation burden are predictive of response to pembrolizumab irrespective of cancer type and may be relevant to rare OCs exhibiting these alterations. Additional biomarkers of response to agents targeting DNA repair and replication stress, immune response, oncogenic signaling, and angiogenesis have been identified but require prospective validation.

Relevance

This report highlights the unmet need for identification and validation of predictive biomarkers to guide therapy and future trial design in OC.

predictive biomarker. *HER2*-amplified cancers have a worse overall prognosis compared with nonamplified cancers.[6] Additionally, *HER2*-amplified cancers show increased responsiveness to *HER2*-targeted agents.[7] Validated tests allowing the selection of patients with predictive biomarkers are known as companion diagnostics. These are defined by the US Food and Drug Administration (FDA) as medical devices that provide essential information for the safe and effective use of a corresponding drug or biological product.[8]

Biomarkers are further categorized depending on their use in clinical trial design and hypothesis testing. Integral biomarkers are inherent to study design and are used to determine trial eligibility or stratification or can be used as primary end points. Integrated biomarkers are incorporated prospectively into trials for hypothesis testing, often for prospective validation of their treatment interactive effect to allow promotion to use as integral biomarkers. Finally, exploratory biomarker testing can be planned for hypothesis generation leading eventually to implementation as integrated elements and then for integral use. Considerations for appropriate use of biomarkers in clinical trial design include a number of variables including assay performance characteristics, ease of implementation, costs, and strength of available evidence to support their use.

Several standardized guidelines for reporting the strength of evidence supporting the use of a given biomarker have been proposed. ASCO Tumor Markers Guidelines Committee recommended five Levels of Evidence (LOEs) to determine the clinical utility of a tumor marker.[9] Initially published in 1996, this LOE scale has been widely used and includes domains involving patients, specimens, assays, and statistical analyses. More recently, the LOE scale was revised by Simon and al. to provide more precise definitions for the types of studies that might be used to analyze the clinical utility of a given prognostic or predictive biomarker.[10] Level I evidence consists of a prospective trial designed to address the tumor marker in question or a prospective trial not designed to address the tumor marker but accompanied by one or more validation studies with consistent results. The consistent results from these validation studies must be equally compelling and performed using the same assay or similar assays that clearly identified the same marker.[7] Use of the estrogen receptor (ER) to predict endocrine therapy benefit in breast cancer is an example of a biomarker with supported by level 1 evidence, including both prospectively designed trials and multiple validation studies.[11] Level II evidence includes prospective trials not designed to address the tumor marker without confirmatory validation studies or with supportive evidence from two or more prospective observational studies. Level III/IV evidence includes singular prospective observational and retrospective studies correlating the biomarker with an outcome. It is important to note that the LOE for a particular biomarker is specific to the tumor type, drug, and clinical setting in which it has been validated. These criteria, qualified by correlation to treatment outcome, have been used for the grading of LOE in this summary report.

RESULTS

Data supporting biomarkers with level I and II evidence (Table 1) and select biomarkers of unclear predictive value (level III/IV; Table 2) and those not found to be predictive of clinical benefit (Table 3) are discussed below. The biomarkers have been categorized on the basis of cancer-associated pathways targeted by specific drugs.

DNA REPAIR AND REPLICATION STRESS

Homologous recombination repair (HRR) is a pathway responsible for repair of double-stranded DNA breaks. High-grade serous OC (HGSOC) is characterized by chromosomal instability due to impaired HRR pathways,

TABLE 1. Predictive Biomarkers With Supporting Level 1-2 Evidence for Use in Selection or Stratification in Clinical Trials for Epithelial Ovarian Cancer

Biomarker	Response to	Assigned Level of Evidence	Setting/Comments	References
DNA damage repair				
Germline/somatic *BRCA1/2* mutations	PARPi	I	Maintenance in primary and recurrent setting and monotherapy in recurrent setting	12-19
HRD	PARPi in combination with bevacizumab	I	Frontline maintenance setting	14
Tumor *BRCA1/2* reversion mutations	PARPI in combination with cediranib	II	Post-PARPi progression, associated with nonresponse	20
RAD51C/D mutations	PARPi	II	Monotherapy in recurrent setting	18,21
BRCA1 methylation	PARPi monotherapy		Monotherapy in recurrent setting	22
CCNE1 amplification	Adavosertib plus carboplatin or adavosertib plus carbo/taxol Adavosertib plus gemcitabine Praxaserib	II	Platinum-sensitive recurrent setting Platinum-resistant or refractory setting Recurrrent, BRCA wild-type	23-26
Immunotherapy				
Mismatch repair deficiency	PD-1/PD-L1 inhibitors	I	Positive association with response across cancer types	27
TMB	PD-1/PD-L1 inhibitors	I	Positive association with response across cancer types	28
Oncogenic signaling				
KRAS/NRAS/HRAS mutations (LGSOC)	Binimetinib (MEKi) and binimetinib plus paclitaxel	II	Platinum-resistant setting	29,30

Abbreviations: HRD, homologous recombination deficiency; LGSOC, low grade serous ovarian cancer; PARP, poly (ADP-ribose) polymerase; PARPi, poly (ADP-ribose) polymerase inhibitor; PD-1, programmed death receptor 1; PD-L1, program death receptor ligand-1; TMB, tumor mutational burden.

TABLE 2. Promising Biomarkers With Unclear Predictive Value (level of evidence 3-4) in Epithelial Ovarian Cancer

Biomarker	Response to	Setting/Comments	References
		Clinical evidence	
IFNγ signature	PD-1/PD-L1 inhibitors combined with PARP inhibitors	Positive association with response but used archived samples in a post hoc study not designed to address tumor marker. No validation studies	31,32
Mesenchymal and proliferative gene signature	Bevacizumab	Positive association with response but used archived samples in a post hoc study not designed to address tumor marker. No validation studies	33
ER and PrR receptors	Letrozole; anastrazole; fulvestrant; anastrazole combinations; letrozole combinations	Studies using ER as integral marker or positive association with response but used archived samples in a post hoc study not designed to address tumor marker	34-41
PI3K/AKT/PTEN pathway	Pictilisib; alpilisib; buparlisib	Early-phase, exploratory studies	42-45
IL-6	Bevacizumab	Positive association with response but used archived samples in a post hoc study not designed to address tumor marker. No validation studies	46
OPN	Bevacizumab	Positive association with response but used archived samples in a post hoc study not designed to address tumor marker. No validation studies	46
KELIM	Veliparib	Positive association with response but a post hoc study not designed to address biomarker. No validation studies	47
		Preclinical evidence only	
MYC amplification	THZ1 (CDK7 inhibitor)	Preclinical data	48
GLS	GLS inhibitor	Preclinical data	49
SWI/SNF (*ARID1A/SMARCA4*)	ATR inhibitors; HMT or HDAC inhibitors	Preclinical data	50-55

Abbreviations: ER, estrogen receptor; GLS, glutaminase; HDAC, histone deacetylase; IFN, interferon; IL-6, interleukin-6; KELIM, elimination rate constant K; OPN, osteopontin; PARP, poly (ADP-ribose) polymerase; PD-1, programmed death receptor 1; PD-L1, program death receptor ligand-1; PrR, progesterone receptor; PTEN, phosphatase and tensin homolog; SWI/SNF, SWItch/sucrose non-fermentable.

TABLE 3. Biomarkers Not Ready for Use in Epithelial Ovarian Cancer

Biomarker	Response to	Comments	References
		Not found to be useful	
PD-L1 expression	PD-1i/PD-L1i and PD-1i plus CTLA-4i	Not predictive of outcomes in most studies	42,56,57
ATM loss	Berzosertib (ATRi) monotherapy; BAY1895344 monotherapy	One CR with berzosertib All objective responses to BAY1895344 monotherapy observed in patients with tumors with *ATM* loss and/or *ATM* mutation	58,59
HER2 IHC	Seribantumab (ERBB inhibitor)	Increased treatment benefit with bivariable biomarker of detectable *HRG* mRNA and HER2 low	60
CHEK2 mutation	PARPi	Not associated with clinical benefit	18,61
TP53 mutation	Adavosertib plus carboplatin/taxol	Not associated with clinical benefit	23
CDK12 mutation	PARPi	Not associated with clinical benefit	18

Abbreviations: CR, complete response; HER2, human epidermal growth factor receptor 2; HRG, heregulin; IHC, immunohistochemistry; PARP, poly (ADP-ribose) polymerase; PARPi, poly (ADP-ribose) polymerase inhibitor; PD-1, programmed death receptor 1; PD-L1, program death receptor ligand-1.

known as HR deficiency (HRD). This results in the inability of a cell to perform HRR, thus requiring the use of alternative, less reliable repair pathways.[62] These generate patterns of chromosomal alterations referred to as genomic scars, which are permanent even in the event of HRR restoration.[63-65] HRD in cancer cells has many underlying causes, of which the most prevalent in OC are somatic and germline mutations in *BRCA1* or *BRCA2* (*BRCAm*).[66]

BRCA Mutations

The presence of germline or somatic *BRCAm* has consistently correlated with benefit from poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi) in multiple studies, including maintenance after platinum response in both the primary[12-14] and recurrent[15-17] settings, and for treatment of recurrent disease.[18,19] Many randomized clinical trials used *BRCAm* as criteria for eligibility or prospective stratification, including SOLO1 and SOLO2 (olaparib maintenance for frontline [ClinicalTrials.gov identifier: NCT01844986] and platinum-senstive [ClinicalTrials.gov identifier: NCT01874353] BRCAm OC), PRIMA (frontline niraparib maintenance; ClinicalTrials.gov identifier: NCT02655016), PAOLA-1 (frontline olaparib maintenance alone or with bevacizumab; ClinicalTrials.gov identifier: NCT02477644) NOVA (platinum-sensitive recurrent niraparib maintenance; ClinicalTrials.gov identifier: NCT01847274), and ARIEL4 (recurrent, platinum-resistant or partially platinum-sensitive; ClinicalTrials.gov identifier: NCT02855944). Trials including non-*BRCAm* cancers prospectively stratified on the basis of *BRCAm* status and preplanned a hierarchical statistical design to evaluate benefit across stratifications although they did not examine a treatment outcome by biomarker interaction. All demonstrated the greatest magnitude of benefit in patients with BRCAm cancers.

HRD Clinical Assays

Current HRD assays measure mutational profiles or genomic scars, which are a historical mark of previous HRD and do not provide dynamic measurements of real-time HRR function. Use of HRD as a predictive biomarker is complicated by this caveat. Multiple prospective randomized clinical trials have demonstrated statistically significant differential benefit of PARPi in patients with HRD cancers compared with those without HRD, athough none have formally tested the biomarker interaction.[12,15,16] However, there is heterogeneity in the assays used to define HRD across clinical trials.

The Myriad Genetics myChoice CDx incorporates BRCA mutation sequencing with a genomic instability score that is a composite of three different measures of genomic instability: loss of heterozygosity (LOH), telomeric allelic imbalance and large-scale state transitions which have been shown to be associated with HRD and response to platinum agents.[63,65,67,68] HRD is defined by this assay as BRCAm or BRCA wildtype with genomic instability score cutoff $\geq$ 42. The PRIMA and NOVA studies used the Myriad Genetics myChoice Cdx HRD for stratification of patients. Both *BRCAm* and the larger HRD population, which included *BRCAm*, had greater benefit than biomarker-negative cases.[12,15] The Myriad Genetics myChoice HRD Plus assay was used in the PAOLA-1 trial to stratify between HRD and non-HRD or HR-proficient cancers ($\geq$ 42 = HRD).[14] Analysis of the PAOLA-1 results again showed greater benefit to olaparib for patients with *BRCAm* and HRD biomarker-positive cancers compared with biomarker-negative cancers when given in combination with bevacizumab compared with bevacizumab alone. Greater magnitude of benefit from treatment with niraparib in platinum-sensitive recurrent HRD OC was also shown in the Quadra study using the MyChoice assay.[19] On the basis of these studies, Myriad Genetics myChoice CDx assay has been approved by the FDA as a companion diagnostic for therapy with olaparib in combination with bevacizumab in frontline maintenance and for single-agent niraparib therapy in the recurrent settting.

The Foundation Medicine NGS LOH assay (≥ 16% = LOH-high = HRD) was used for prospective patient stratification in ARIEL-3 (ClinicalTrials.gov identifier: NCT01968213). This assay measures the percentage of genomic LOH. Patients who had LOH high tumors had a greater magnitude of clinical benefit from rucaparib than those who did not.[16] In ARIEL-2 (ClinicalTrials.gov identifier: NCT01891344), a higher magnitude of benefit was observed in patients with HRD tumors (≥ 14% = LOH-high) compared with the LOH low subgroup (0.62, $P = .011$).[18]

BRCA Reversion Mutations

Secondary somatic reversion mutations in *BRCA1/2* restore an open reading frame and create a functional protein and, by restoring HRR, generate resistance to PARPi and platinum.[69-73] The impact of reversion mutations on rucaparib response/resistance was examined in ARIEL2, a prospective phase II trial of rucaparib in recurrent HGSOC.[18,74] In a retrospective analysis, cell-free DNA was sequenced from serial plasma samples collected from patients with *BRCA*m carcinomas receiving rucaparib in ARIEL2. *BRCA* reversion mutations were identified in 18% (2 of 11) of platinum-refractory and 13% (5 of 38) of platinum-resistant patients in pretreatment blood collected, compared with 2% (1 of 48) of patients with platinum-sensitive cancers ($P = .049$). Patients without *BRCA* reversion mutations detected in pretreatment cell-free DNA had significantly longer rucaparib progression-free survival (PFS) than those with reversion mutations (median, 9.0 *v* 1.8 months; hazard ratio, 0.12; $P < .0001$).

RAD51C and RAD51D Mutations and RAD51C Promoter Methylation

Additional genes and proteins are involved in the HRR pathway, including the RAD51 family. The impact of *RAD51C and RAD51D* mutations on response to rucaparib was also assessed in ARIEL2.[18,75] Rucaparib was shown to be active in ovarian carcinoma with *RAD51C* or *RAD51D* mutations, with five partial responses (PsR) among seven evaluable patients with *RAD51C/D* mutations treated with rucaparib. The results from multivariable analysis also identified *RAD51C/D* mutation as a significant prognosticator of objective response rate (odds ratio [OR], 20.658; 95% CI, 1.865 to 228.889; $P = .0136$).[75] However, because this was a single-arm trial, prognostic versus predictive characteristics of biomarkers cannot be separated. The role of *RAD51C/D* in PARPi sensitivity/resistance is also supported by the finding of *RAD51C/D* secondary somatic mutations that restore the open reading frame (ie, reversion mutations) in some OCs with acquired PARPi resistance.[21] In a study of 12 patients with *RAD51C* promoter-methylated HGSOC supplemented with patient-derived xenograft models, methylation of *RAD51C* promoter has been also demonstrated to be associated with sensitivity to platinum and PARPi while loss of methylation even in a single gene copy was sufficient to confer PARP inhibitor resistance.[76] Given the lack of prospective testing and validation studies, evidence for *RAD51C* mutation and promoter methylation status as biomarkers is considered level 3, but the data nevertheless highlight a strong rationale for inclusion of these biomarkers into prospective studies.

Homozygous BRCA1 Methylation

Methylation of the *BRCA1* promoter can lead to functional *BRCA1* loss if present in both alleles or there is methylation of one allele combined with a LOH event resulting in loss of the other allele. A correlation of loss of *BRCA1* function due to homozygous *BRCA1* promoter methylation with response to rucaparib was demonstrated in ARIEL2.[18,22,75] Testing was retrospectively performed on the pretreatment biopsy and was adjusted for *BRCA1* copy number and LOH to determine zygosity. The homozygous *BRCA1* methylation cancer subgroup had a median PFS of 14.5 months (95% CI, 4.8 to 18.3, n = 6) which was comparable with the *BRCAm* subgroup (12.8 months; 95% CI, 9.0 to 14.7, n = 40) and longer than *BRCAwt*, non–BRCA1-methylated cases (5.5 months, 95% CI, 5.0 to 6.2; $P = .062$, log-rank test, n = 143). Objective response rate was significantly better in the methylated subgroup compared with *BRCAwt* patients with non–*BRCA1*-methylated tumors ($P = .0014$, Fisher exact test), with five of six patients with homozygous *BRCA1* methylation achieving a partial response. A sixth patient had a 33% reduction in target lesions not confirmed by subsequent imaging. In paired samples and in patient derived xenograft models, methylation was frequently lost in pretreatment biopsies compared with earlier samples and appears to be another mechanism of acquired PARPi resistance.[22]

CCNE1 Amplification

CCNE1 amplification is identified as a dynamic event enriched in patients with platinum-resistant OC.[77] Tumors with CCNE1 amplification were found to have a prolonged response to the WEE1 inhibitor adavosertib in combination with chemotherapy (carboplatin alone or with paclitaxel) in platinum-sensitive *TP53*-mutant OC.[23] *CCNE1* amplification in platinum-resistant or -refractory OC was correlated with better response rate in the combination arm in a study of gemcitabine with adavosertib or placebo (Fisher exact test $P = .013$); this did not translate to improved PFS or overall survival (OS; $P > .10$).[24] Twelve of 19 (63%) patients with recurrent *BRCAwt* disease and high *CCNE1* copy number and/or mRNA expression measured on pretreatment core biopsy samples had PFS ≥ 6 months when treated with single-agent CHK1/2 inhibitor prexasertib.[25] Additionally, when Cyclin E1 and E2 are bound, this activates CDK2 (cyclin-dependent kinase 2) and drives G1/S progression of the cell cycle. Overexpression of CDK2 is associated with abnormal regulation of the cell cycle. Tumors with *CCNE1* amplification have been associated with preclinical response

to CDK2 inhibitors which are currently under development.[78,79] In summary, *CCNE1* amplification is emerging as a potential biomarker of response to adavosertib, prexasertib, and CDK2 inhibitors, and prospective vadlidation trials are needed to further support these findings.

IMMUNOTHERAPY AND TUMOR MICROENVIRONMENT

The majority of clinical trials using immune checkpoint blockade in OC have been disappointing to date. Mismatch repair (MMR) deficiency and/or high tumor mutational burden (TMB) are the only level 1 evidence biomarkers with a strong correlation to response to anti–programmed death receptor 1 (PD-1) inhibition in solid tumors.[27,28] However, MMR is a rare event in OC, occurring in $< 5\%$ overall and most common in low-grade endometrioid or clear cell type OC.[80]TMB over 10 mutations/megabase DNA is considered TMB high,[81] and this is a rare event in OC.[31,32,82] The median TMB in high-grade serous OC is 3.6 mutations/Mb, and the mean TMB is 5.3 mutations/Mb.

Expression of program death receptor ligand-1 (PD-L1) has been demonstrated to enrich for responders to immune checkpoint blockade across a number of cancer types. PD-L1 expression in OC at any cutoff has not shown response to anti–PD-1/PD-L1 inhibition; the lack of activity of this intervention makes measure of value of PD-L1 as a biomarker fraught.[42,56,57] Similar to PD-L1 expression, studies of genomic biomarkers to date have failed to identify predictors of response to immunotherapy in OC.

A study by Färkkilä et al identified potential predictors of response to niraparib and pembrolizumab that may be worthy of further prospective exploration. In this study, which retrospectively analyzed specimens from 62 women enrolled in the TOPACIO trial for platinum-resistant OC (ClinicalTrials.gov identifier: NCT02657889), mutational signature 3, reflecting defective homologous recombination DNA repair, and positive interferon gamma gene expression signature, as a surrogate of exhausted CD8+ T cells in the tumor microenvironment, were found to be associated with an improved outcome[31] (Table 2). However, this was not a randomized trial, so these findings could be due to a lack of a comparator arm.

ONCOGENIC SIGNALING

Several oncogenic pathways have been explored for therapeutic targeting across a number of OC histologic subtypes. Post hoc analysis of the negative trial MILO/ENGOT-ov11 (ClinicalTrials.gov identifier: NCT01849874) tested binimetinib versus physician's choice chemotherapy (PCC) in recurrent or persistent low-grade serous carcinoma. This trial found that patients with low-grade serous OCs bearing *KRAS* mutations had better response to binimetinib, a small-molecule inhibitor of MEK1/2.[29] This study included 303 patients of whom 215 had tumor testing data available. The frequency of *KRAS* mutation was evenly distributed between the two groups, 32%-34%, and was significantly associated with objective response to treatment with binimetinib (OR, 3.4; 95% CI, 1.53 to 7.66; unadjusted $P = .003$) but not with PCC (OR, 2.13; 95% CI, 0.67 to 6.81; $P = .2$). The positive GOG-0281 trial of trametinib versus PCC (which included hormonal therapy options) had molecular data for 134 of 260 randomly assigned patients for a preplanned analysis.[83] A treatment by *KRAS/NRAS/BRAF* mutation interaction analysis adjusted for multiple comparisons trended to predictive significance for response rate ($P = .11$) and was negative for PFS.

There are additional biomarkers that are promising but unclear in terms of predicting response to treatment of specific agents. Mutations in phosphatidylinositol-3-kinase (PI3K) pathway have been evaluated in the setting of PI3K inhibitor therapy and have not been identified as critical factors for predicting response. Mutations in *PIK3CA* and phosphatase and tensin homolog (*PTEN*) were found to be associated with response in patients with advanced stage solid tumors in a phase I trial of pictilisib/GDC-0941(ClinicalTrials.gov identifier: NCT00876122). Three of 60 participants had OC, one of whom had stable disease for 4 months.[43] Combination studies of olaparib with PI3K inhibitors such as alpelisib or buparlisib have also been explored. There was no relationship between presence of alteration and response to treatment combinations although PI3K alterations were detected in 33%-44% of tumors.[43-45,84] Additional oncogenic signaling pathways may be of future clinical significance for treatment response, but currently, these are only based on preclinical models. For example, in preclinical studies, c-*MYC* amplification has shown to be a potential predictor of response to bromodomain and extraterminal inhibitors[85] or to olaparib and palbociclib.[86] Emerging evidence also indicates that mutations in members of SWI/SNF chromatin remodeling complex such as *ARID1A* and *SMARCA4* may sensitize the tumors to epigenetic therapies such as histone deacetylase inhibitors and EZH2 inhibitors.[50-55] A trial of EZH2 inhibitor tazemetostat in *ARID1A*-mutated ovarian clear cell carcinoma (NRG-GY014) has recently completed accrual (ClinicalTrials.gov identifier: NCT03348631).

ER and progesterone receptors (PrRs) have been studied in the context of response to aromatase inhibitors and ER antagonists such as letrozole, anastrozole, and fulvestrant.[34-41] Several studies in heavily pretreated women with elevated ER-alpha tumor expression demonstrated evidence of disease stabilization compared with patients with tumors with lower ER-alpha expression. Most patients progressed within 6 months. There is limited evidence to date that ER and PrR are functionally active on different OC types, which may explain in part the limited benefit observed for these agents.

ANGIOGENESIS

Several analytes have been examined for relationship to outcome with antiangiogenic agents. To date, none of

these have had locked down values validated to show a treatment-by-biomarker effect. Examples include the mesenchymal and proliferative gene expression signature, and plasma interleukin-6 (IL-6), and osteopontin. The mesenchymal and proliferative gene signatures in high-grade serous OC have been shown to be associated with inferior survival. Evaluation of these signatures within the context of phase III ICON7 clinical trial (ClinicalTrials.gov identifier: NCT00483782) evaluating a combination of bevacizumab and carboplatin/paclitaxel chemotherapy in newly diagnosed OCs demonstrated improved outcomes with bevacizumab in the mesenchymal and proliferative signature subgroup.[33] However, these data were derived from a post hoc analysis of ICON7 data and have not been prospectively validated in other studies. Circulating IL-6 concentration is an additional promising biomarker, identified as part of the angiome analysis of seven putative biomarkers (IL-6, Ang-2, osteopontin, stromal cell-derived factor-1, VEGF-D, IL-6 receptor [IL-6R], and GP130). This cassette was analyzed retrospectively in plasma of patients enrolled in GOG 218, double-blind, placebo-controlled, phase III trial in newly diagnosed stage III or stage IV epithelial OC comparing chemotherapy with/without bevacizumab incorporated with/without bevacizumab maintenance.[46,87] The data were dichotomized at the median. Patients with high IL-6 levels had a longer PFS and OS when treated with bevacizumab compared with placebo. Osteopontin was found to be a negative prognostic marker for both PFS and OS in this angiome analysis. Validation requires, ideally, a prospective analysis using a locked down cutoff for IL-6.

CANCER ANTIGEN-125 ELIMINATION RATE CONSTANT K

The modeled cancer antigen-125 (CA-125) Elimination rate constant K (KELIM), determined on the basis of CA-125 clearance during the first 100 days of chemotherapy initiation, is a validated early marker of tumor chemosensitivity and prognosis.[88,89] Evaluation of KELIM as a predictor of response to maintenance PARP inhibitor response was also performed in an exploratory analysis of the phase III VELIA/GOG-3005 study, which evaluated veliparib vs. placebo administered concurrently with chemotherapy followed by veliparib vs. placebo maintenance (ClinicalTrials.gov identifier: NCT02470585).[47] Overall, high KELIM values appeared to enrich for patients with improved benefit from veliparib. However, it remains difficult to separate the predictive from prognostic value of KELIM, particularly since PARPi are only approved in the maintenance setting. Evaluation of KELIM as a predictive factor of future benefit from PARPi maintenance in other completed trials could be of value.

DISCUSSION

Although multiple biomarkers have been evaluated in the OC therapeutic landscape, few have been shown to be predictive on the basis of high-level evidence showing treatment/outcome interaction. Currently, use of *BRCA* mutations and HRD to predict for response to PARPi is supported by the highest LOE in OC. MMR deficiency and TMB have been shown to be predictors of response to pembrolizumab across several tumor types thus demonstrating Level 1 evidence. These biomarkers have limited applicability to OC, as very few OCs exhibit MMR deficiency or high TMB. Additional biomarkers involved in DNA damage repair (*BRCA1/2* reversion mutations, *RAD51C/D* mutations, biallelic *BRCA 1* methylation, *CCNE1* amplification) and oncogenic signaling (*KRAS*, *NRAS*, and *HRAS* mutations) are supported by Level 2 evidence and require validation testing. Although additional biomarkers such as interferon gamma signature and mesenchymal or proliferative gene signatures, PI3K/AKT/PTEN pathway mutations, and IL-6 are promising as predictors of response to some agents, further supporting evidence is needed to establish their predictive ability in OC.

Given the increasing recognition that incorporation of integrated and exploratory biomarkers into trials is essential to understand the predictors and mechanisms of response, the majority of NRG-sponsored trials now include collection of archival tissue and pretreatment and on-treatment blood. In addition, incorporation of novel agents into the neoadjuvant setting provides an opportunity to sample both pretreatment and on-treatment tissue which will enable better understanding on the impact of novel agents on cancer cells and the tumor microenvironment. A recently completed trial, NRG-GY007 (ClinicalTrials.gov identifier: NCT02713386), collected tumors and blood at baseline and post-NACT with paclitaxel and carboplatin with/without ruxolitinib. These tumors and blood specimens are currently undergoing analysis. A recently activated trial, NRG-GY027 (ClinicalTrials.gov identifier: NCT05276973), incorporates ipatasertib (AKT-inhibitor) with NACT. In an effort to identify biomarkers for response, tumors collected at baseline/pre-NACT will undergo whole-exome sequencing to evaluate for *PTEN*, *PIK3CA*, *PIK3R1*, *AKT1*, *TP53*, *KRAS*, *NF1*, *TSC1/TSC2*, and tumors collected post-NACT will be evaluated for changes in downstream pathway expression for pGSK3β, p-PRAS40, p4EB1, pERK, and p-AKT. Additional exploratory biomarkers such as immune cell population differences in blood using mass cytometry between responders and nonresponders have also been proposed.

The LOE scale used here also has limitations. Mainly, it is unclear how to grade LOE for biomarkers without supporting evidence in OC but with established and consistent predictive value or validation studies performed in multiple tumor types. One such example is TMB, which consistently predicts response to PD-1 inhibitors; the poor outcome to PD-1 and PD-L1 inhibitors is as anticipated given the low TMB of OC. Available LOE scales do not address whether biomarker data are reliable if dependent solely on evidence from other disease types to inform use as an integral biomarker in OC. It is also questionable whether validation studies performed in other tumor types can be considered

as a LOE for OC. For the purpose of this review, we have considered these where multiple, consistent studies are available to supplement evidence in OC.

This review highlights the need for correlative science as a key component of every clinical trial in OC. Furthermore, biomarker discovery and validation are imperative not only in OC but within specific histologic subtypes. Future trial design should allow for biomarker discovery through correlative studies and validation through prospective use of integrated biomarkers.

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