Review Article

Therapeutic implications for ovarian cancer emerging from the Tumor Cancer Genome Atlas

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Abstract: With increasing insights into the molecular landscape of ovarian cancer, subtypes are emerging that might require differential targeted therapies. While the combination of a platinum and a taxane remains the standard of care, newer therapies, specifically targeted to molecular anomalies, are rapidly being tested in various cancers. A major effort to better understand ovarian cancer occurred through the Cancer Atlas Project. The Catalogue of Somatic Mutations in Cancer (COSMIC) is a database that collates mutation data and associated information extracted from the primary literature. The information from the Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC), which systematically analyzed hundreds of ovarian cancer, are included in COSMIC, sometimes with discordant results. In this manuscript, the published data (mainly from TCGA) on somatic high grade papillary serous ovarian cancer (HGSOC) mutations has been used as the basis to propose a more granular approach to ovarian cancer treatment, already a reality for tumors such as lung and breast cancers. *TP53* mutations are the most common molecular anomaly in HGSOC, and lead to genomic instability, perhaps through the FOXM1 node. Normalizing P53 has been a therapeutic challenge, and is being extensively studied. BRCAness is found an about 50% of HGSOC and can be targeted with poly (ADP-ribose) polymerase (PARP) inhibitors, such as olaparib, recently approved for ovarian cancer treatment. Other less common mutations have been found (*MECOM*, *MAP15*, *CCNE1*). Common mutations in other cancer (PI3K pathway, ERK kinase pathway, and EGFR family) are uncommon in ovarian cancer.

Keywords: High grade papillary serous ovarian cancer (HGSOC); somatic mutations; targeted therapies; Cancer Genome Atlas

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Introduction

Today, all epithelial ovarian cancers (EOC) are treated with the same approach which involves a debulking surgery and chemotherapy with a carboplatin doublet, usually paclitaxel, for six cycles. These cycles of chemotherapy can be administered in a neoadjuvant, sandwiched, or adjuvant fashion. The outcome is the same and depends on the quality of the debulking and the responsiveness to platinum. Despite an 80% response rate, less than 20% of women will be cured, and most will eventually recur. Patients with recurrent disease are usually incurable. Five year survival for stage III ovarian cancer, the stage at which EOC is commonly diagnosed, is between 35% and 45%. The current combined surgical-chemotherapy approach has reached a plateau of efficacy. Cells protect themselves from environmental and physiological pressures through complex adaptation strategies including cell cycle checkpoints, DNA damage response pathways, programmed cell death (1) and other mechanisms. When imbalance between DNA damage/repair and activation/inactivation occur in these processes, through carcinogenesis or other intrinsic or extrinsic anomalies, cells might become cancerous. These complex adaptation pathways are being discovered through constant molecular

biology discoveries, although our comprehension remains limited. The TCGA data helps make further inroads in our understanding of the biology of high grade papillary serous ovarian cancer (HGSOC).

In the last decade, an effort to better understand the biology of ovarian cancer led to its inclusion in The Cancer Genome Atlas (TCGA) project (2). The analysis included 489 high grade ovarian papillary cystadenocarcinomas or papillary serous ovarian cancers (HGSOC) of individual patients. The TCGA project produced the following results:

(I) It confirmed that mutations affecting p53 expression are present in most HGSOC (96%). The *TP53* gene encodes a tumor suppressor protein. The p53 protein is the guardian of the genome of normal cells. It acts by arresting growth, holding the cell cycle at the G1/S regulation checkpoint on DNA damage recognition, activating DNA repair proteins when DNA has sustained damaged, and initiating apoptosis when DNA damage is beyond repair;

(II) The gene expression patterns of HGSOC could be classified in signatures that correlate with poor or better survival;

(III) Similarly, four distinct subtypes of ovarian cancer could be determined through examination of RNA transcription and DNA methylation patterns;

(IV) Mutations of *BRCA1* and *BRCA2* genes were found in 20% of cases and methylation-mediated loss of expression in 11%;

(V) Genes expressed in various targetable pathways were matched with existing Food and Drug Administration (FDA) approved or experimental therapeutic agents.

This review will attempt to associate the TCGA discoveries and other genomic analyses of ovarian cancer with potential treatment approaches for HGSOC. *Table 1* describes therapeutic targets that have been identified, and selected ones will be further described in ensuing sections (for more details consult: http://cancergenome.nih.gov/newsevents/newsannouncements/ovarianpaper and https://icgc.org/).

TP53, the guardian of cellular homeostasis

The *TP53* tumor suppressor gene which encodes p53 has long been recognized as a critical regulator of cell proliferation and as a frequent target for mutation in cancer (59). The TCGA project identified *TP53* mutations in 96% of ovarian cancers (2). The p53 protein binds to DNA and to a rich network of proteins that are involved in response to DNA damage and other cellular stresses, DNA repair, and cell growth (60). Many of the proteins that either interact with p53 or are part of p53-regulated pathways have been related to ovarian cancer and are discussed below as potential therapeutic targets (e.g., BRCA1, BRCA2, the FoxM1 network).

The most intensely studied function of the p53 protein is as a transcriptional activator. The p53 protein consists of an N-terminal trans-activating domain, a central DNA binding region, and a C-terminal oligomerization domain. In non-stressed conditions, the p53 protein is associated with the MDM2 and MDM4 proteins, which promote the ubiquitination and rapid degradation of p53 (61). A tightly regulated negative feedback loop controls p53 levels, which are typically low. In response to DNA damage and other cellular stressors, these regulatory proteins are inhibited by a variety of upstream proteins, and p53 is released. The p53 protein tetramers bind to DNA and activate the transcription of a large network of genes involved with DNA repair, cellular growth arrest, and apoptosis. The p53 protein acts as a cell cycle checkpoint regulator because it becomes active in cells that exhibit damaged DNA. The p53-mediated induction of several cell cycle regulating genes such as *p21* prevents cells from entering G1 or continuing past the G2/M cell cycle checkpoint. There is clear evidence that p53 is also involved in regulating expression of genes that promote apoptosis through both intrinsic (*Fas*) and extrinsic pathways (*Bax*). Because of these checkpoint and apoptotic functions, the *TP53* gene has been labeled the "guardian of genome". If there is loss of p53 function due to mutation, deletion, or down-regulation, then cells proceed though the cell cycle despite DNA damage and are prone to further mutations, including potentially oncogenic changes (60).

In addition to its established role as a tumor suppressor through its regulation of gene transcription, several transcription-independent p53 functions have emerged in recent years. These functions include regulation of microRNA networks, effects on mitochondrial survival proteins, and possibly direct involvement of p53 in DNA repair pathways (60,62). Although the network of p53 interactions is very complex, the variety of protein targets with diverse mechanisms within these pathways could provide attractive targets for interventions that bypass specific mutational defects in p53 function.

Table 1 Potential therapeutic targets

Potential target	Biological dysfunction	Function-gain/loss	Pathway(s)	Frequency of alteration*	Drugs	References
Most frequent						
TP53	Mutation	Loss	Major tumor suppressor gene	>90%	Gene therapy and vaccine trials	(3-8)
FOXM1	Inactivated by wild type p53; overexpressed when p53 mutated, leading to transcriptional activation of spindle cell protein regulators and chromosome passage protein complex (CPC):	Gain	Transcription factor network	87%		(1,9)
	AURB	Activated	Mitosis	N/A	Aurora kinase inhibitors	(10,11)
	CCNB1	Activated	Mitosis	N/A	None	
	BIRC5	Activated	Mitosis	N/A	Survivin inhibitors	(12)
	CDC25	Activated	Mitosis	N/A	Checkpoint abrogator	(13)
	PLK1	Activated	Mitosis	N/A	Polo kinase inhibitors	(14-17)
BRCA	Mutation, epigenetic silencing, phenotypic modification	Loss	Homologous repair	BRCAness 50%	Olaparib, veliparib	(18-21)
Possible targetable less frequent proteins/pathways						
MECOM	Amplification	Gain	Complex transcription factor with multiple functions. Interactions with acetylation	28.0%	HDAC inhibitors?	(22)
MAPK15	Amplification	Gain	Autophagy? Interference with steroidal receptors?	27.4%	Very little is known	(23-25)
CCNE1	Amplification	Gain	Mitosis	22.7%	CDK4/6 inhibtors	(26-30)
CDK2	Amplification	Gain	Mitosis	3.9%	CDK4/6 inhibitors	(26-30)
TERT	Amplification	Gain	Telomerase	9.2%	Vaccine techniques, oligonucleotide decoy	
NOS3	Amplification	Gain	Reactive oxides	5.9%	Arginine modulation	(31)
RHEB	Amplification	Gain	PI3K pathway	6.3%	mTOR inhibitors	(32)
RICTOR	Amplification	Gain	PI3K pathway	5.7%	mTOR inhibitors	(32)
AKT3	Amplification	Gain	PI3K pathway	5.1%	AKT inhibitors	(32)
RPTOR	Amplification	Gain	PI3K pathway	3.9%	mTOR inhibitors	(32)
AKT1	Amplification	Gain	PI3K pathway	3.7%	AKT inhibitors	(32)
POLB	Amplification	Gain	DNA repair	5.7%	None	
MSTN	Amplification	Gain	TGF beta family	5.1%	No known inhibitors	(33)

Table 1 *(continued)*

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Potential target	Biological dysfunction	Function-gain/loss	Pathway(s)	Frequency of alteration*	Drugs	References
ERBB3	Amplification	Gain	Driver mutation	4.5%	EGFR inhibitors-monoclonal antibodies	(34,35)
ERBB2	Amplification	Gain	Driver mutation	3.1%	EGFR inhibitors-monoclonal antibodies and tyrosine kinase inhibitors	(36-41)
IGF1R	Amplification	Gain	Cell signaling	3.7%	Monoclonal antibody (not tested in HGSOC)	
VEGFA	Amplification	Gain	Angiogenesis	3.5%	Direct inhibition: bevacizumab & aflibercept; indirect inhibition: tyrosine kinase inhibitors of VEGFR	(42-45)
HSP90AB1	Amplification	Gain	Apoptosis	3.1%	Tanespimycin & geldanamycin	(46-49)
EPCAM	Amplification	Gain	Cell migration	2.7%	Monoclonal antibody	(50-52)
KRAS	Mutations (G12D), amplification	Gain	PI3K + RAF/MEK/ERK pathways	<1% & 11%	PI3K & MEK inhibitors	(53)
Low frequency in HGSOC with available targeted therapies						
BRAF	Mutation (N581S)	Gain	RAF/MEK/ERK pathway	<1% (rare)	BRAF & MEK inhibitors	(54)
NRAS	Mutation (Q61R)	Gain	Control of intracellular signaling networks	<1%	PI3K & MEK inhibitors	(55)
PIK3CA	Mutations (E545K and H1047R)	Gain	PI3K pathway	<1%	PI3K, AKT & mTOR inhibitors	(56,57)
PTEN	Deletion	Loss	PI3K pathway	<1%	PI3K & MEK inhibitors	(32)
No known targetable drugs						
RB1	Mutation	Loss	Major tumor suppressor gene, cyclin/CDK activation	<1%	Low incidence	(26)
NF1	Mutation	Loss	Major tumor suppressor gene Ras pathway?	<1%	Low incidence	(58)
CSMD3	Mutation			<1%	Low incidence	
CDK12	Mutation	Loss	RNA splicing regulation	<1%	Low incidence	
STAT1	Amplification	Gain	Signal transduction	3.7%	None	
STAT4	Amplification	Gain	Signal transduction	3.7%	None	
TTN	Mutation	N/A	Chromosome interaction?	Mathematically predicted	None	
FAT3	Mutation	Unknown biological relevance		Matching normal fallopian tube tissue		
GABRA6	Mutation	Unknown biological relevance		Matching normal fallopian tube tissue		

*, amplification or deletion percents are from supplemental information table S5.3 from ref. (2).

The analysis of *TP53* mutations in databases from cancer cell lines, animal models of cancer and the TCGA human cancer database has yielded many insights into *TP53* biology that complement experimental studies. Early on, *TP53* was found to be the most commonly somatically mutated tumor suppressor gene in human cancers (59). The database of somatic *TP53* mutations found in tumors now exceeds 45,000 entries (63). Additionally, inherited germ line *TP53* mutations were found to be responsible for Li-Fraumeni syndrome, a cancer predisposition syndrome characterized by a number of early onset cancers, most notably breast and sarcomas, but not HGSOC germline ovarian cancer type (64). These specific differences in cancer types allude to the complex biology of *TP53*, where various mutations affect the host in different ways.

Most *TP53* alterations are missense point mutations, but nonsense point mutations, frameshift alterations, and large deletions also occur. *TP53* point mutations cluster in the central DNA binding domain. The two main molecular mechanisms that abrogate wild type p53 activity are modification of the folded conformation of the DNA binding domain or direct alteration of amino acids that contact DNA (59). The result is that p53 protein oligomers fail to bind DNA and cannot exert their growth inhibitory effects. Many of these mutations are "dominant negative", such that the presence of the mutation suppresses the activity of residual wild type p53. Some mutations gain growth stimulatory or "oncogenic" properties, thought to be due to an inhibition of mutant p53 on the homologous p53 family members p73 and p63, thereby reducing their transcriptional activity (60,65).

Several strategies have attempted to exploit the p53 pathways in targeted therapeutics. Small molecule screens have produced compounds that bind to either full-length p53 or the core DNA-binding domain of mutant p53 to restore its normal activity. In another approach, molecules that inhibit the protein-protein interaction of p53 with MDM2 have been developed that show clear anti-tumor activity in preclinical animal models. Also, molecules and drug combinations have been tested that selectively kill tumor cells by activating mutant or wild-type p53. Recombinant adenovirus-based gene therapy and anti-p53 vaccines are another method that have been attempted to achieve tumor regression through the p53 pathway (60). The new insights gained from the TCGA project will provide new strategies to more accurately target proteins associated with specific p53 defects in ovarian cancer that can be identified during diagnostic testing.

Genetic & epigenetic profiles and therapies

Efforts associated with TCGA have greatly expanded our knowledge of the genetic and epigenetic (specifically, DNA methylation) landscape of HGSOC (2).

Epigenetic studies of HGSOC

Analysis of epigenetic silencing, through correlation of patterns of DNA methylation and reduced gene expression, also revealed four distinct subtypes (2). Unlike the gene expression subtypes, these epigenetic clusters did show significant correlation with survival and other metrics (age, functional BRCA inactivation). Unlike the expression subtypes, the epigenetic clusters were only modestly 'stable', insofar as that application of their signatures to independent datasets did not always fully or faithfully recapitulate the subtypes. Finally, a similar clustering analysis was performed on the expression of micro-RNAs (miRNAs), small (~22 nucleotides) non-coding RNA molecules that function in RNA silencing and other aspects of post-transcriptional regulation of gene expression, and generated three distinct subtypes. Interestingly, two of the miRNA clusters overlapped significantly with two of the mRNA gene expression subtypes, while one of these miRNA subtypes was associated with significantly longer survival than the other two. These clustering analyses not only provide an unexpected level of stratification and cohesion within the spectrum of HGSOCs, but also provide an enduring resource that can be mined to significant scientific and potentially, clinical effects.

In addition to the analysis of expression of coding RNAs, utilization of miRNA profiles may prove imminently useful as a screening tool. An increasing number of cancer-associated miRNAs ('oncomirs') have been implicated in every step of pathogenesis, from initiation to metastasis to drug resistance. Recently, miR-152 and miR-185 have been found to be down-regulated in platinum-resistant HGSOC (66-68) and up-regulating them promotes platinum sensitivity (68). Conversely, other miRNAs (e.g., miR-93, miR-182, miR-199, miR-214) appear to promote or to be specifically up-regulated in resistant disease [myriad references, searchable at the miRCancer or OncomiRDB database (69,70)].

The molecular mechanisms and pathways connecting miRNAs to metastatic potential and drug resistance are, at best, quite complex and, at worst, wholly unknown. Nonetheless, the strong correlations between some miRNAs and clinical outcomes stand well-poised to be

developed into a useful screening target for informing treatment decisions during management of HGSOC. Of particular interest, here, is the recent demonstration that some oncomirs—miR-152 and miR-185—can suppress DNA methyltransferase-1 (DNMT1) and promote DNA hypomethylation (68), thus directly linking genetic and epigenetic regulatory mechanisms. This latter report's demonstrates a causal relationship between miRNA and regulation of DNMT1. Platinum sensitivity is restored by epigenetic modulators (e.g., DNMT1 inhibitors) (71). A number of HGSOC trials utilizing agents that block DNA hypermethylation are in progress—with varying levels of success (*Table 2*). With further refinement, genetic subtyping of HGSOC may be used to stratify patients into groups most likely to benefit from regimens that include epigenetic modifying agents that are either FDA approved [e.g., azacitidine (72,73) and decitabine (74,75)] or under active development [e.g., zebularine (76) and others (77)]. Of particular recent interest here is the possible synergy between epigenetic modifier therapy and vaccination against ovarian cancer antigens. The cancer-testis/cancer-germline antigen NY-ESO-1 is a vaccine target regulated by DNA methylation, Inhibition of DNMT by decitabine augments NY-ESO-1 vaccine therapy, with increased NY-ESO-1 serum antibodies and T cell responses observed in the majority of patients. Antibody spreading to additional tumor antigens was also observed (78).

Expression patterns in HGSOC

The largest and most recent effort selected approximately 1,500 intrinsically variable genes (out of nearly 12,000 genes available across three commercial expression analysis platforms) (2). After characterizing their distinct transcriptional profiles, they identified four mRNA expression 'clusters' or subtypes of HGSOC: differentiated, immunoreactive, mesenchymal, and proliferative. Impressively, the gene expression signatures used to generate these subtypes were applied to a non-overlapping, publicly available repository of *HGSOC* gene expression and generated highly comparable clusters, validating the signatures and the four subtype classifications. While OS was not significantly different between the subtypes, further analysis generated an expression signature of 193 genes that predicted OS: 85 associated with good survival and 108 correlated with poor survival. This survival signature was similarly validated with independent datasets.

A reasonable goal is the further scrutiny, development, and refinement of TCGA data to establish a 'PAM50'-type paradigm for ovarian cancer. The *PAM50* gene signature (79) uses the level of expression of 50 genes in breast cancer biopsies or resections to classify a tumor as one of four intrinsic subtypes (luminal A, luminal B, HER2-enriched, or basal-like), a classification proven to have significant value in both treated and untreated patients for both prognosis and individualized likelihood of disease recurrence (80-82). This is a realistic and attainable goal for TCGA HGSOC data that can be used to begin to personalize treatment options based on genetic and epigenetic landscapes and perhaps increase OS.

Unlike the breast cancer PAM50 signatures, however, the four identified subtypes of HGSOC do not reveal any immediately useful or distinct therapeutic targets—at least not yet. So far, the subtyping has not revealed any novel or pervasive 'smoking gun' targets in HGSOC that are assailable by currently-available antineoplastics—i.e., no single, causally-dysregulated receptor tyrosine kinase, topoisomerase, or other enzymatic activity presents as an overt Achilles heel to be used for increased clinical outcomes. However, while there is no immediate therapeutic revolution in the TCGA HGSOC analysis, the identified subtypes are still well-poised to pay immediate, intermediate, and long-term dividends. In the near future, patient screening and assignment to one of these disease subtypes could prove useful in helping predict overall prognosis, which in turn may facilitate decision-making for both physician and patient. With more development and validation, the subtyping of HGSOC patients may inform chemotherapeutic choices (e.g., dosing and/or scheduling of platinum therapy; inclusion on trials using epigenetic regulators such as azacytidine and zebularine). Finally, with a considerable amount of additional, focused study of their underlying molecular and cellular biology, HGSOC subtypes may facilitate the identification of discrete molecular etiologic targets that will allow development of rationally-designed and/or disease-specific therapeutics for ovarian cancer.

Clinical implications of *BRCA1* and *BRCA2* status

Several recent studies have used models from previous research powered by the TCGA to reveal important connections between *BRCA* mutations in sporadic ovarian cancer and the impact on patient survival and treatment strategy. The breast cancer 1, early onset (*BRCA1*) gene locus on chromosome 17 was first linked to inherited susceptibility of early-onset breast cancer in 1990 (83).

Table 2 Drugs in clinical trials for ovarian cancer or in phase 1

Drugs	Pathway	NCT*
MEK162	MEK inhibitor	NCT01363232, NCT01449058, NCT01885195
Pimasertib	MEK inhibitor	NCT01936363
Dabrafenib	MEK inhibitor	NCT01902173
GSK1120212	MEK inhibitor	NCT01155453
BKM120	Pan-PI3K inhibitor	NCT01155453, NCT01068483, NCT01833169, NCT01623349, NCT01363232
GDC 0941 (pictilisib)	Pan-PI3K inhibitor	NCT00876109
SAR245409 and SAR245408	Pan-PI3K inhibitor	NCT01936363, NCT00756847
BYL719	PI3K α-isoform specific inhibitor	NCT01708161, NCT01449058
MLN1117	PI3K α-isoform specific inhibitor	NCT01449370
GSK2636771	PI3K β-isoform specific inhibitor	NCT01458067
AZD5363	AKT1 and PIK3CA	NCT01226316
GSK2141795	AKT inhibitor	NCT01902173
GDC0068	AKT inhibitor	NCT01090960
MK2206 [2206]	AKT inhibitor	NCT00670488
Temsirolimus, ridaforolimus, everolimus	mTORC1 inhibitors	About 12 studies
GDC0980	Dual PI3K/mTOR inhibitor	NCT00854152
BEZ235	Dual PI3K/mTOR inhibitor	NCT01343498
XL765	Dual PI3K/mTOR inhibitor	NCT00485719
AZD8055	Dual mTORC1 and mTORC2 inhibitor	NCT00731263
MLN0128	Dual mTORC1 and mTORC2 inhibitor	NCT01058707
OSI027	Dual mTORC1 and mTORC2 inhibitor	NCT00698243
Olaparib	PARP inhibitor	NCT01623349, over 15 other studies
Veliparib	PARP inhibitor	About 15 studies
AZD1775	For p53 mutated tumors: Wee1 G2 checkpoint kinase inhibitor	NCT02272790, NCT02101775, and others
Various gene therapies	p53	About 5 trials
APR-246	p53: PRIMA-1 (p53 re-activation and induction of massive apoptosis)	NCT02098343
GSK1070916A	Aurora kinase B/C inhibitor	NCT01118611
AMG 900	Pan Aurora kinase inhibitor	NCT00858377
Terameprocol (EM-1421)	Survivin and cyclin-dependent kinase-1 (Cdc2) inhibitor	NCT00664586
BI 2536	Polo-like-kinase 1 inhibitor	NCT00710710
NMS-1286937	Polo-like-kinase 1 inhibitor	NCT01014429
BI 6727 (volasertib)	Polo-like-kinase 1 inhibitor	NCT01145885, NCT01121406
TAK-960	Polo-like-kinase 1 inhibitor	NCT01179399
Vemurafenib	BRAF V600E inhibitor	NCT01524978
U3-1287 (AMG 888)	Erb3 monoclonal antibody	NCT00730470
Neratinib	Pan ERB tyrosine kinase inhibitor	NCT01953926
PD0332991 (palbociclib)	Cyclin dependent kinases 4 and 6 inhibitor (in patients with recurrent ovarian cancer demonstrating rb-proficiency and low p16 expression)	NCT01536743
LEE011(ribociclib)	For patients with CDK4 amplification or mutation, CDK6 amplification or mutation, cyclin D1 (CCND1) amplification, cyclin D3 (CCND3) amplification, or p16 (CDKN2A) mutation	NCT02187783, NCT01237236
LY2835219 (abemaciclib)	CDK4/6 inhibitor	NCT01394016

*, available online: https://clinicaltrials.gov/.

A second familial breast cancer gene (*BRCA2*) was later found on chromosome 13 (84). The relationship between familial risks for breast cancer with that of ovarian cancer led to studies showing that hereditary ovarian cancer is also associated with *BRCA1/2* mutations (85). The strongest risk factors for ovarian cancer is a family history of the disease, and mutations in either *BRCA1* or *BRCA2* are found in the majority of patients with hereditary ovarian cancer (86).

The proteins encoded by *BRCA1* and *BRCA2* are both important in the cell response to DNA damage, but they have distinct functions. BRCA1 has diverse roles in several DNA repair pathways including homologous recombination and cell cycle checkpoint regulation where it primarily acts as a scaffold protein. BRCA2 is a DNA-binding protein that functions through its direct interaction with the homologous recombinase RAD51 (87). Both proteins are tumor suppressors, and mutations that result in functional loss of either protein increase genomic instability or a hypermutator phenotype, the so-called "BRCAness" (88). Because of their similar impact on homologous recombination, they are often referred to interchangeably, however the difference in their biology is clear and has only recently become appreciated after analysis of large datasets. While the mutation rate for either *BRCA1* or *BRCA2* in the general population is approximately 1 in 500, 10% of women diagnosed with EOC have germline *BRCA1* or *BRCA2* mutations (89). The TGCA ovarian cancer project evaluated the impact of *BRCA1/2* genes and homologous recombination by evaluating mRNA expression, miRNA expression, promoter methylation, and DNA copy number in nearly 500 HGSOC. The results revealed that 20% of HGSOC have germline (17%) or somatic (3%) mutations in *BRCA1/2*, and an additional 11% have lost *BRCA1* expression through DNA hypermethylation. Perhaps more significant with respect to clinical impact was the pathway analysis that indicated at least one genetic or epigenetic defect in genes associated with homologous recombination in half of the cancers (2).

An association between *BRCA1/2* mutations and improved survival in ovarian cancer has been shown consistently in small-scale studies, reviewed by Liu *et al*. (90). Because of the rareness of individual non-germline *BRCA1/2* mutations in ovarian cancer, these studies were unable to differentiate the individual impacts of *BRCA1* and *BRCA2* until data from large scale studies such as TCGA were available for analysis. The TCGA group reported that a univariate analysis of *BRCA1/2* mutation status showed improved OS, however no improvement was observed in cases where *BRCA1* was epigenetically silenced (2). A focused follow-up study using the TCGA data found that only mutation in *BRCA2* was significantly correlated with improved survival. This study also demonstrated that cases harboring *BRCA2*, but not *BRCA1* mutations had more genomic instability, higher primary chemotherapy sensitivity, and longer platinum-free duration (91). A separate study combining TCGA data with 20 additional studies concluded that *BRCA1* mutations may also confer a survival advantage, but that this advantage is dependent on the site of mutation within *BRCA1* (92). Together these data found that *BRCA2* carriers exhibit a 52% 5-year OS compared with 44% for *BRCA1* carriers and 36% for non-carriers. With respect to clinical implications, these data suggest that *BRCA2* status may represent a phenotype of genomic instability that would predict better response to chemotherapy.

The progress in understanding *BRCA* gene profiles and their phenotypic outcome has an important impact on choosing a therapeutic strategy. The combination of platinum and taxane has been the standard of care for treatment of advanced ovarian cancer ever since a landmark randomized study showed improved patient survival over cisplatin-cyclophosphamide (93). Mutations in *BRCA1/2* correlate with hypersensitivity to platinum agents which likely accounts for the better overall prognosis for those ovarian and breast cancer patients with germline or somatic *BRCA1/2* mutations.

The recognition that 50% of high grade serous ovarian cancers have either *BRCA1/2* mutations or other related defects in homologous recombination led to clinical trials with poly (ADP-ribose) polymerase (PARP) inhibitors. PARP inhibitors block base excision repair, which promotes apoptosis in cells that lack effective homologous recombination due to synthetic lethality. Early trials using the PARP inhibitor, olaparib, were successful in cases with germline *BRCA1/2* mutations in ovarian, but not breast cancer (18). In December 2014, olaparib (94-96) and a companion diagnostic test, BRACAnalysis CDx (that detect the presence of mutations in the BRCA genes in blood samples from patients with ovarian cancer) were approved for women with advanced ovarian cancer associated with defective *BRCA* genes. The activity of olaparib was examined in 137 patients with ovarian cancer and mutated *BRCA* gene. Thirty-four percent of patients had a complete or partial response (PR), lasting for an average of 7.9 months. Side effects include nausea, fatigue, vomiting, diarrhea, dysgeusia, dyspepsia, headache, nasopharyngitis, cough, arthralgia, myalgia, back pain, dermatitis,

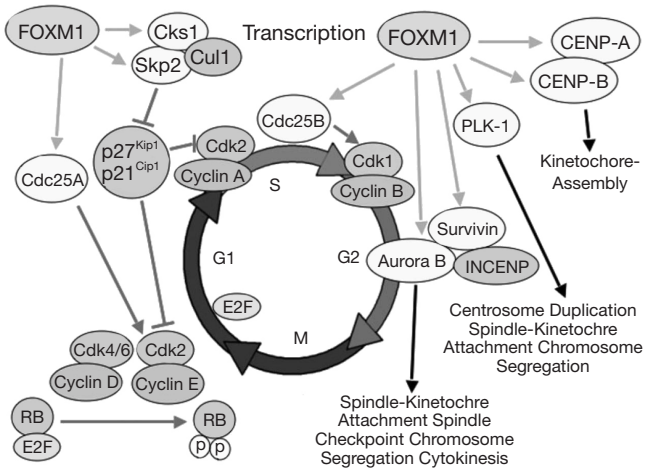

Figure 1 FOXM1 (available online: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1316960/figure/f10/). Reproduced with permission from (99).

pancytopenia, and abdominal pain. Potential serious side effects included myelodysplastic syndrome and acute myeloid leukemia, and lung inflammation. More recent and ongoing studies have shown additional effectiveness of PARP inhibitors in non-germline *BRCA1/2*-related and sporadic high-grade serous ovarian cancers (19,20). The differences in biology of BRCA1 and BRCA2, as well as the large-scale studies showing increased chemotherapeutic response in tumors with *BRCA2* mutation over *BRCA1* infer that *BRCA2* status will be a better predictor of clinical outcome in patients treated with PARP inhibitors (21).

Dysregulation of pathways as opportunities for targeted therapies

TCGA has enlighten the role of DNA mutations in the ovarian cancer landscape. The following pathways have been found to have potentially actionable mutations in the TCGA analysis, and are proposed in decreasing order of potential importance, prioritized based on the p53 and BRCA discussions. The perspective from the literature is also included to help understand the utility of pathway targeting.

Forkhead box protein M1 (FoxM1) network

The stability of the ovarian epithelial cell genome is centrally regulated by p53, as described above. Once p53 becomes dysregulated, a cascade of events leads to multiple alterations that usually coalesce into BRCA dysfunction, also described above. Forkhead box M1 (FOXM1) is a central pivot of stability in nuclear divisions, and was found to be upregulated in p53 mutated HGSOC. FOXM1 is a transcription factor, member of the forkhead family, and it induces the expression of genes involved in the execution of mitosis. FoxM1 is regulated by p53 (97), and perhaps also regulates p53 to maintain homeostasis of mitosis (98).

Through siRNA experiments, FOXM1 expression levels positively correlate with its transcriptional targets, Cdc25B and Aurora B kinase, and negatively with p27, an indirect target of FOXM1 (via suppression of Skp2) (*Figure 1*) (100). The TCGA analysis found an upregulation of Aurora kinase B expression (101). Others have also described overexpression of Aurora kinase A (102). Both Aurora kinases cooperate in the mitosis process through association with microtubules during chromosome movement and segregation in a cell cycle dependent manner. Aurora kinase B localizes to specialized microtubules called K-fibers, near kinetochores, and Aurora kinase A (MIM 603072) localizes to centrosomes (103,104). Expression of Aurora A reaches a maximum at the G2-M cell cycle transition, whereas Aurora B protein is most active during mitosis. Aurora B and C (Aurora C is mainly expressed in testes) are chromosomal passenger proteins and complex with three other proteins; survivin, borealin, and INCENP. The complex is required for proper mechanism of action (105). Additionally, topoisomerase II has been implicated in the regulation of Aurora B localization and enzymatic activity (106).

Only Aurora kinase A inhibitors have been studied in ovarian cancer patients. Unfortunately, there was no selection for overexpression (107). In a single-arm phase II study of 31 patients with platinum-resistant EOC treated with alisertib (MLN8237), an Aurora A kinase inhibitor, 10% of patients achieved a PR and 20% of patients achieved stable disease (SD) lasting for longer than 3 months. Alisertib (MLN8237) was administered orally twice daily at a dose of 50 mg for 7 days in 21-day cycles. Grade 3 drug-related adverse events (AEs) included neutropenia (42%) with 6% febrile neutropenia, stomatitis (19%), and thrombocytopenia (19%). One Aurora B/C kinase inhibitor, GSK1070916A, has been tested in patients with solid tumors and the only responding patient had ovarian cancer (108). Other pan-Aurora kinase inhibitors are in clinical trials. AMG 900 is such a compound where an ovarian cancer patient had the best response (*Table 2*) (109). However, the observed activity remains low and aligned with common chemotherapy agents. Future trials might

benefit from increased selection to match patient target with the correct inhibitor.

CDC25 phosphatase activates cyclin-dependent kinase (CDK) complexes by dephosphorylation. In humans, there are three CDC25s labeled A (110), B and C. CDC25 B together with polo-like kinase 1 (PLK1) helps in regulating the resumption of cell cycle progression after DNA damage-dependent checkpoint arrest in G2. PLK1 regulates relocation of CDC25B from the cytoplasm to the nucleus, leading to CDC25B-induced mitotic entry (111). Thus, inhibitors of PLK1 indirectly can block the overexpression of CDC25B seen in ovarian cancer. The PLK1 inhibitor, volasertib, has been studied in patients with platinum resistant ovarian cancer in a phase 2 randomized study comparing it to best standard chemotherapy. Overall responses were similar to the best chemotherapy with a PR rate of 13% and a SD rate of 44%. AEs were manageable and six patients treated with volasertib remained progression-free after 1 year on treatment compared to no patients on standard chemotherapy (112).

MDS1 and EVI1 complex locus protein EVI1 (MECOM)

The protein encoded by *MECOM* is a transcriptional regulator and oncoprotein that may be involved in hematopoiesis, apoptosis, development, cell differentiation, and proliferation. The encoded protein can interact with CTBP1, SMAD3, CREBBP, KAT2B, MAPK8, and MAPK9. This gene can undergo translocation with the *AML1* gene, resulting in overexpression of this gene and the onset of leukemia. Several transcript variants encoding a few different isoforms have been found for this gene. Diseases associated with *MECOM* include 3q21q26 syndrome (a subtype of leukemia and a somatic myelodysplastic syndrome). The gene ontology (GO) annotations related to this gene include protein homodimerization activity and sequence-specific DNA binding transcription factor activity. *MECOM* also interacts with both classes (class I and class II) of histone deacetylases (HDAC), which abrogate the assembly of MECOM in nuclear speckles. Inhibitors of HDAC could lead to acetylation of this complex transcription factor to induce its proper function (113). Inhibitors of HDAC have not been systematically studied in ovarian cancer. Possibly reflecting effects from epigenetic modulation of this transcription factor is the study of azacytidine and erlotinib that showed activity in patients with platinum resistant ovarian cancer (114). The HDAC inhibitor vorinostat has also been studied but lacked activity (115).

Cyclins and CDK

Progression through the cell cycle involves coordinated activation of CDK proteins that bind to their partner cyclins. Kinases (CDK4, CDK6, CDK2, and CDC2) are successively expressed, along with their partner cyclins (cyclins D, E, A, and B) as cells go through mitosis. Cyclins function as regulators of CDK kinases. Different cyclins exhibit distinct expression and degradation patterns which contribute to the temporal coordination of each mitotic event.

Cyclin E1 (CCNE1) and CDK2 have been found amplified in the TCGA analysis of ovarian cancer and other studies (116,117). CCNE1 is specifically expressed during the G1/S phase transition. CCNE1 forms a complex with and functions as a regulatory subunit of CDK2, whose activity is required for cell cycle G1/S transition. Overexpression of CCNE1 results in chromosome instability, and might contribute to tumorigenesis. CCNE1 is also involved in phosphorylation of NPAT protein (nuclear protein mapped to the ATM locus), which participates in cell-cycle regulated histone gene expression and plays a critical role in promoting cell-cycle progression in the absence of pRB (26). New inhibitors of CDK are being tested in clinical trials. Currently, only CDK4/6 has been clinically targeted, including palbociclib, LEE011 (ribociclib), abemaciclib, milciclib (118), SNS-032, TG02 (119), and seliciclib (27). Minimal information is available for ovarian cancer (*Table 2*) (28).

Telomerase reverse transcriptase (TERT)

Telomerase is a ribonucleoprotein polymerase that maintains telomere ends by addition of the telomere repeat TTAGGG. The enzyme consists of a protein component with reverse transcriptase activity, encoded by *TERT*, and an RNA component which serves as a template for the telomere repeat. Telomerase repression in adult somatic cells results in progressive shortening of telomeres, called "erosion of telomeric sequences", which leads to cellular senescence. Cancers have been known to overexpress telomerase to avoid senescence through various mechanisms (locus variants, promoter activity) (120,121). Alternative splicing encoding different isoforms might regulate telomerase activity. Telomerase activity is regulated by a number of factors including telomerase complex-associated proteins, chaperones and polypeptide modifiers.

There are few studies of telomerase inhibitors. Imetelstat

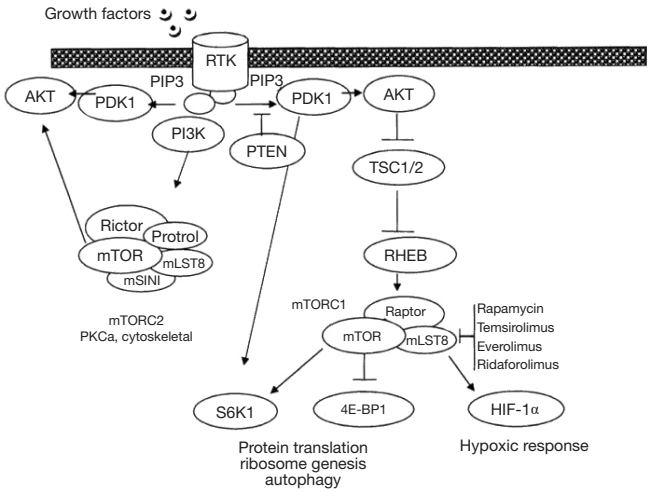

Figure 2 PI3K pathway (available online: http://www.mdpi.com/2072-6694/5/2/418/htm#fig_body_display_cancers-05-00418-f001). Reproduced with permission from (127).

is a covalently-lipidated 13-mer thiophosphoramidate oligonucleotide that acts as a potent specific inhibitor of telomerase. It binds with high affinity to the template region of the RNA component of human telomerase (hTERC) and is a competitive inhibitor of telomerase enzymatic activity (122). Telomerase-specific $CD4^+$ and $CD8^+$ T cell responses can be induced upon vaccination with hTERT-transfected dendritic cells and vaccination with telomerase derived peptide, GV1001, induces T cell responses in patients with solid tumors (123). Neither of these approaches have been studied in ovarian cancer.

Nitric oxide synthase 3 (NOS3)

The free radical nitric oxide is involved in ovarian carcinogenesis by reacting to carcinogenics, modulating apoptosis and possibly by promoting growth, invasion, and metastasis (124). Of all studied polymorphisms, only one mutant allele of intron 4 (27-bp repeat in intron 4) was associated with advanced tumor stage and positive lymph node involvement. This protein is so ubiquitous that the implication of NOS3 amplification is not clear in ovarian cancer. Additionally, platinums regulate the NOS isoforms in ovarian cancer. Endogenous NOS3/NOS1 activity in platinum-resistant ovarian cancer cells produces low-level NO that protects against apoptosis. However, NOS2 contributes to platinum-induced apoptosis. These three NOS isoforms are regulated differentially by platinum agents in resistant and sensitive ovarian cancer cells. Inhibition of all NOS isoforms in platinum-resistant cells dramatically increases apoptosis (125). The inhibition of NOS can be accomplished by arginine depletion or by N^{ω}-amino-L-arginine (LNAA) a NOS3 inhibitor. The only human studies of arginine inhibition were done with intradermal microdialysis to study vasodilation. Another approach, which was tested in hepatocellular carcinoma, involved the use of arginase. In this study, pegylated recombinant human arginase (Peg-rhAgr1) was well tolerated. A weekly dose of 1,600 U/kg induced arginine depletion and prolonged progression free survival was noted for patients achieving arginine depletion (126).

PI3K pathway

As shown in *Table 1*, many proteins are involved in the PI3K pathway (*Figure 2*). Many drugs are being tested to block one or more kinase domain of various molecules. PI3K/AKT/mTOR pathway inhibitors fall into four main categories; mTORc1 and/or mTORC2 inhibitors, PI3K inhibitors, dual mTOR/PI3K inhibitors, and AKT inhibitors. Most studies are dose or schedule finding, enrolling patients with various cancers. The evidence for activity in patients with ovarian cancer has been minimal. The pan-PI3Kinase inhibitors, especially pictilisib, have demonstrated some activity against ovarian cancer (128). Further trials should select the population with the molecular anomalies that could be targeted by this class of agents, however, the number of patients with somatic mutations within their ovarian cancer is <2%. Specific trials in a selected population would not be feasible, and these patients are better enrolled in basket trials matching patients with a rare mutation, regardless of tumor histology, to a drug expected to work through the mutated pathway.

DNA *polymerase B* (*POLB*)

The protein encoded by this gene is a DNA polymerase involved in base excision and repair. The encoded protein, acting as a monomer, is normally found in the cytoplasm, but translocates to the nucleus upon DNA damage. There are several transcript variants of this gene. Pol β is crucial for the maintenance of genomic stability (129). Pol β transcription and protein levels are increased in many cancers, including ovarian cancer. Overexpression of Pol β results in aneuploidy. *POLB* has also been called the "platinum resistance gene" because

low expression results in increased susceptibility to platinum (130). Purified Pol β incorporates the nucleotide analogues 2'-3' deoxycytidine (ddC)-triphosphate and 3'-azido-3'-deoxythymidine (AZT)-triphosphate into DNA, causing chain termination (131). There is no known drug targeting Pol β in cancer therapy.

Myostatin (MSTN)

MSTN is a secreted growth factor expressed in skeletal muscle and adipose tissue that negatively regulates skeletal muscle mass. Null MSTN mice have increase in muscle mass, reduction in fat mass, and resistance to diet-induced and genetic obesity. MSTN propeptide (MPRO) and follistatin are experimental inhibitors of MSTN which are being studied for muscle regeneration. There is very little understanding of the relation of MSTN and ovarian cancer. Interestingly, follistatin was first isolated from the ovary and is known to suppress follicle-stimulating hormone (132). One gene transfer study of follistatin is open for muscular dystrophy (NCT01519349).

Epidermal growth factor receptors (EGFR)

The human EGFR2/neu (HER2/neu) is overexpressed in about 11% of patients with high grade HGSOC (36,37). A phase 2 clinical trial of the monoclonal anti-HER2 antibody, trastuzumab, in patients overexpressing HER2 by immunohistochemistry (IHC) proved to be very difficult to implement, requiring screening of over 800 women to diagnose less than 100 with overexpression. Of these, less than half were eligible for the trial. Trastuzumab resulted in minimal therapeutic benefit with a 7% remission rate. One of the three responding patients was a long term survivor. When the fluorescence in situ hybridization (FISH) test was added to select patients by HER2 amplification, the number of eligible patients decreased to 6%; however, the sensitivity to trastuzumab increased with a 40% response rate (84). Trials of unselected patients testing pertuzumab, another monoclonal antibody, or the dual EGFR/HER2 inhibitor, lapatinib, have been negative (39-41,133). However, targeting patients with specifically HER2 over-expression and/or HER3 down-regulation might be worthwhile (134). Neratinib and afatinib are newer multi-tyrosine kinase inhibitors with EGFR inhibitory activity. Today, with improved molecular techniques, the search for less common molecular endpoints might become a necessity to deliver optimal care. Inhibition of other members of this family (erb1, erb3, and erb4) is under clinical investigation, such as MM-121 (SAR256212), a fully human monoclonal antibody that targets the HER3 receptor (NCT01447706).

Signal transducer and activator of transcription (STAT) pathway

While there is some investigation of STAT3 in ovarian cancer (99), much less is known about the STAT1 and STAT4 overexpression noted by the TCGA analysis. STAT1 has been linked to platinum resistance. STAT proteins function downstream of JAKs and MAPKs, which induce the dimerization of STAT proteins, thereby allowing the translocation of STAT proteins into the nucleus (135). Jak inhibitors have only been studied *in vitro* in ovarian cancer models (136). STAT1 is best known for its pro-apoptotic role in response to interferons, but STAT1 has also been reported to have a pro-survival role in some cancers (137). STAT1 might be regulated by HDACs which remove an acetyl group on STAT1, which leads to cancer cell survival and resistance to platinum as was noted earlier under MECOM.

Insulin-like growth factor 1 receptor (IGF1R)

IGF1R is a member of the receptor tyrosine kinase family. Upon activation by its ligands (IGF-I or IGF-II), IGF1R phosphorylates tyrosine residues on two major substrates, insulin receptor substrate 1 (IRS-1) and SH2 domain-containing oncogenic protein (Shc), which signal through the RAS/RAF and the phosphatidylinositol 3'-kinase (PI3K)/AKT pathways (138). Without IGF1R, cells cannot transform, as shown in IGF1R knockout mice which are resistant to transformation by various viral and cellular oncogenes (139). Ganitumab (AMG 479), a human monoclonal antibody against IGF1R, has shown preclinical activity in ovarian cancer cell lines that did not have a mutated PI3K or RAS/RAF pathway (140). The drug is in clinical trials but not in ovarian cancer. The phase 1 study showed activity in the Ewing family of sarcomas.

Vascular endothelial growth factor A (VEGFA)

The VGF/VGFR pathway has been studied intensively in ovarian cancer (141). The only drug that has recently received FDA approval is bevacizumab for patients with platinum resistant ovarian cancer (42). In first and second line treatment, where bevacizumab was studied in multiple

randomized studies, there was no improvement in survival despite an improvement in progression free survival (142-144). Additionally, many tyrosine kinase inhibitors of VEGFR have been studied But similarly, most studies have not shown an OS benefit: trebananib (145), sunitinib (146), nintedanib (147), sorafenib (148), and pazopanib (149). Cediranib might be effective in patients with platinum sensitive recurrent ovarian cancer, but the full report has not been published (150).

The most benefit of anti-angiogenic drugs seems to be for patients with platinum resistant ovarian cancer, and the addition of an antiangiogenic agent comes at the expense of increased toxicity (43).

Heat shock protein 90kda alpha (cytosolic), class B member 1 (HSP90AB1)

The molecular chaperones, Hsp90 and Hsp70, are involved in the folding and maturation of key regulatory proteins, such as transcription factors, kinases, and others that are involved in cancer progression (151). Client oncoproteins include EGFR, Her2/neu, Akt, c-RAF, IGFR, and others. The chaperones interact with these regulatory proteins to help conformation, transportation and degradation through ubiquitination. Chaperones (named by their molecular weight) ensure the maintenance of a functional proteome under normal and stress conditions (152).

The only targetable chaperone thus far has been Hsp90. The Hsp90 inhibitor, geldanamycin, proved to be ineffective in cancer. Tanespimycin has been tested in ovarian cancer in patients receiving concurrent gemcitabine with limited activity (46). While changes are observed among client proteins with Hsp90 inhibition, this inhibition has also resulted in a prolonged increase in Hsp70, which can lead to resistance to Hsp90 inhibition (153). Inhibitors of Hsp70 have been notoriously difficult to design (127).

Epithelial cellular adhesion molecule (EpCAM)

EpCAM is a transmembrane glycoprotein mediating Ca^{2+}-independent homotypic cell-cell adhesion exclusively in epithelial cells. EpCAM may upregulate c-myc and cyclins A & E and play a role in tumorigenesis and metastasis. Immunotherapeutic trials have been completed in patients with ovarian cancer. Catumaxomab, a monoclonal antibody against CD3 and EpCAM, has been tested for the treatment of refractory ascites (50) and improves quality of life. It is approved in Europe for refractory ascites, but not in the US.

TITIN (TNN)

When the TGCA analysis searched for driver mutations, 518 genes were ranked from highest probability to lowest. For example, *BRAF* and serine/threonine kinase 11 (*STK11)* were ranked second and sixteenth. *TTN* ranked number one with 63 non-synonymous and 13 synonymous mutations. Half of the non-synonymous mutations in *TTN* are likely to be passenger mutations. *TTN* has been involved with muscle contractility. It is the largest polypeptide encoded by the human genome. *TTN* is expressed in many cell types and interferes with chromosomal structure and elasticity that could be compatible with a role in oncogenesis (154). The role of *TTN* as a cancer gene is currently a mathematically based prediction, and will require direct biological evaluation (155).

RAS/RAF/MEK pathway

This pathway has been extensively studied in cancer and is currently being therapeutically targeted with great success. Mutations in proteins that activate this pathway are labeled driver mutations. The most famous one in melanoma is the *BRAF* V600E. *BRAF* and *RAS* mutations seem mutually exclusive. The BRAF inhibitors, vemurafenib and dabrafenib, and the MEK inhibitor, trametinib are approved for the treatment of melanoma. Many other tyrosine kinases inhibitors are under clinical trials. This pathway has not been found to be activated in most high grade HGSOC, contrarily to the low grade HGSOC where *RAS* or *BRAF* mutations are detected (156). Patients with NF1 mutations might have an activation of the MAPK pathway (118). Again, the recommendation is to enroll the rare patients with one such mutation in basket trials, matching mutated proteins to specific tyrosine kinases.

Conclusions

The in-depth analysis done by the TCGA Atlas project on HGSOC has revealed known and previously unknown targets that are usually normal cellular processes gone 'berserk' by changes in the ballet of protein interactions. These changes are due to various mechanisms, ranging from DNA mutations, mitotic machinery, dysregulation of signaling pathways, and epigenetic modifications that prevent homeostasis in the affected cells. These dysregulations involve mainly DNA repair (in about 50% of ovarian cancers) or transcription alterations of critical

proteins. Interestingly, no specific protein disruption that is known to affect the immune recognition of ovarian cancer by T cells and other killer immune cells has been identified. Despite some effectiveness of antiangiogenic therapy, very few HGSOC cases are intrinsically driven by alterations of the basic angiogenic protein machinery. The data from the TCGA has been integrated with other extensive ovarian cancer molecular studies in the hopes of leading to improved understanding of ovarian cancer biology. Much remains to be investigated and further research must probe the interactome that pushes normal cells to descend into the trap of immortality.

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Footnote

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