IJBPAS, December, 2023, 12(12): 5390-5417

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

TAILORED THERAPY BASED ON MOLECULAR CHARECTERISTICS OF OVARIAN CANCER

GVN KIRANMAYI*, S VIGNESHKUMAR, S KARTHIKA, N HARIKRISHNAN, AND S NANDHA KUMAR

Faculty of Pharmacy, Dr. M. G. R. Educational and Research Institute, Deemed to be University, Chennai - 95, Tamil Nadu, India

***Corresponding Author: Dr. G.V.N.Kiranmayi: E Mail: kiranmayi54@gmail.com**

Received 19th Oct. 2022; Revised 16th Nov. 2022; Accepted 23rd March 2023; Available online 1st Dec. 2023

https://doi.org/10.31032/IJBPAS/2023/12.12.7581

ABSTRACT

Ovarian cancer remains the most lethal gynaecological cancer in the world. The common cytoreductive surgery, accompanied by platinum-based cancer treatment, has still been used to treat ovarian cancer. Despite the fact that the major group of cases are initially platinum-sensitive, they will over time gain platinum resistance, and platinum-resistant cases have a low response to second-line chemotherapy. In addition, at the molecular level, ovarian cancer is thought to be a complex and heterogeneous disease. A more efficient and less harmful therapy strategy for ovary cancer is molecular targeted treatment. Presently, anti-vegf monoclonal antibodies and parp (poly-adp-ribose polymerase) inhibitors are the two main types of approved and most efficient targeted drugs for ovaria cancer.Potential therapeutic targets include the ras/raf/mer pathway, the pi3k/akt pathway, folate receptor alpha, and immune checkpoints. In this article, relevant clinical trials examining the efficacy and safety of potential targets in ovarian cancer, the major difficulties in targeted therapy, and suggested potential solutions to enhance the therapeutic effects were discussed. Due to advancements in next-generation sequencing technology and molecular biology techniques, we are now able to identify more targetable molecular alterations in a larger group of patients with ovarian cancer. The goal of personalised therapy will be closer to being attained, and the outcome for patients with ovarian cancer will be improved by focusing on these molecular characteristics.

INTRODUCTION AND EPIDEMOLOGY

Ovarian cancer (OC) is the most deadly gynaecological cancer across the evolving globe, with about 21,000 scenarios identified and about 14,000 no. of fatalities every year just in United States alone **[1]**. Most of the ovarian cancers diagnosed, originate from epithelium and most frequently detected when they are already in advanced stage. The choice of appropriate treatment for epithelial ovarian cancer involves platinum-taxane combination chemotherapy and maximal cytoreductive surgical resection **[2]**.

Numerous clinical outcomes produce a remarkable effect on chance of survival of the patient or successful treatment in those with ovarian cancer. In OC patients, survival which is progression free (PFS) and survival overall (OS) are independently affected by patient age ondetection, disease level, FIGO stage and the occurrence of peritoneal fluid excess **[3-5]**.

Inadequate debulking operation, resulting in macroscopic residual illness directly impacts patients survival **[6]**.

Histological classifications have historically been used to categorise epithelial OC, and there are currently five primary subtypes:

- Clear cell (CC),
- endometrioid,
- Low grade serous (LGS),
- Mucinous OC, and
- High grade serous (HGS) **[7]**

In contrast to endometrioid and clear cell Ovarian Cancer, as they deal with the layer of endometrium, HGS OC mostly develops in the distal region of the fallopian tubes, it is now acceptedthat the categories emerge from unique origins [8-16]. From adenofibroma or serous cystadenoma to borderline tumour of serous, then ultimately to low grade serous, it is believed that LGS OC develops gradually **[17]**. These histological subtypes have unique genomic and transcriptome molecular environments **[18-20]**.

Lately, it is gradually understood that the five categories of Ovarian canceract asdifferent disease groups and in clinical and research structure, more classification and organisation is required to distinctly diagnose the molecular pathogenesis and treat with more specification **[7, 21]**. The various levels of chemo sensitivity shown by these subtypes support the claim that they are distinct diseases. In the first-line scenario, HGS ovarian cancer is frequently platinum sensitive, whereas mucinous, Low grade serous, and clear cell ovarian cancer resist platinum extremely **[22-24]**.

Despite having a propensity to show therapeutic resistance, LGS OC has a better clinical prognosis than HGS **[23]**. When

compared to HGS, clear cell and endometrioid ovarian cancer also have typically better outcomes clinically, which is probably because the diagnosis mostly happensto be doneat early disease stage **[22, 26-30]**. However, the great clinical variation observed in OC cannot be entirely attributed to the histological subtype. Indeed, differential therapeutic sensitivity, PFS, and OS are observed in patients having high grade serous ovarian cancer who are picked for cancer level, strongly suggesting a a difference in genetics clinically, within the subtypes classified according to histogical characters **[31]**.

In order to find a base for molecular characteristics for different outcomes clinically and to find ways for targeted therapy and narrowing the treatment methods, high grade serous molecular characters are extensively categorised, so that subtypes can be classified according to the found out characters of genetic and transcriptomic information.Inheritable pathogenic mutations in the DNA of germ cells, frequently in genes such as BRCA1 or BRCA2 (responsible for almost 75% of disease hereditically for), are linked to about one-fifth of cases of OC **[32, 33]**.

The following section discusses the clinical and molecular effects of these abnormalities. Commonly prevalent hereditary ovarian cancer is BRCA-associated illness, however other DNA repair-related gene abnormalities have also been found. These genes include BARD1, RAD51, CHEK2, BRIP1 and PALB2 which, like BRCA1 and BRCA2, are involved in double-stranded DNA repair **[33-36]**.

The most prominent cancers to which Lynch syndrome predisposes people are cancers occurring in bowel and endometrium, and in these cases they also are prone to risk of ovarian cancer. Lynch syndrome is spurred on by hereditary modifications in genes that are entangled in mismatch DNA repair (MMR); single stranded **[37, 38]**. MLH1, MSH6, PMS2 and MSH2 are the most frequently impacted genes in this syndrome, and Lynch syndrome patients make up 10%–15% of hereditary OC **[39]**. Most of the remaining hereditary OC cases that have been reported (around 3%) are due to Li-Fraumeni syndrome, which is brought on by an inherited TP53 mutation **[33]**.

Recently, a variety of multi-omics data, including as investigations of the transcriptome, genome, and epigenome are accessible which allows the characterisation of molecular processes basically the onset and development of cancer. During the outbreak and growth of cancer, a variety of molecular pathways may have an impact on gene expression, changing the expression of genes crucial to carcinogenesis. More specifically, CNAs,

epigenetic events including DNA methylation alterations, germline and somatic factors, and CNAs all have an impact on gene expression **[40, 41]**. In light of this, integrated multi-omics analysis may one day enable the discovery of more reliable biomarkers for customised clinical decision-making **[42]**.

On accounting the epidemiology, statistical data proves that ovarian cancer results in 1,52,000 fatalities and 239,000 new victims per year **[43]**. The maximum statistics of OC (11.4 per 100,000) is found in Central and Eastern Europe. However the incidence rate in China is relatively low (4.1 per 100,000), this country's enormous inhabitants resulted in an approximately 52,100 new occurrences and 22,500 deaths associated with them in the year 2015 [44]. During the same year, it is anticipated that there will be 14,180 associated deaths and 21,290 cases in the USA **[45]**.

One in 75 women can get OC in their lifetime, and one in 1004 may pass away from the condition. The disease often manifests at an early stage, when only 29% of patients survive five years. When the 5-year survival rate is 92%, just 15% of individuals have localised tumours (stage 1). Surprisingly, the global 5-year relative survival rate has increased just very marginally (2%–4%) since 1995 and often falls between 30% and 40% **[46]**.

HETEROGENECITY IN OC

Epithelial OC has a wide range of tumour heterogeneity (e.g., heterogeneity between patients that includes cancers with the exact same histological subtype. Furthermore, these kinds of research have shown that inter- and intratumoral heterogeneity occur in each patients individually, a feature that was previously seen in various tumour forms **[47]**. The concept of spatial intertumoral heterogeneity is illustrated by synchronous ovarian tumours with unique molecular profiles that are spatially separated (e.g., lesions that are metastatic and primary). Another form of spatial heterogeneity is intratumoral heterogeneity, which develops mostly when subclonal tumour progression occurs **[48-50]**.

Additionally, type I ovarian cancer tumours showed significant regional variability **[39, 40]**. When it comes to heterogeneity temporally, some studies of HGS OC demonstrates that the majority of exact (cloned) traits are present in primary tumour as subclonal populace, like in metastatic or recurrent disease **[51-53]**, although one study revealed proof for evolution in growing tumour **[54]**. It is important to note in this context that while still in development, tests for hierarchizing tumour, DNA without cells taken through bloodstream is capable to identify the OC during it is in its early stage, and gives genomic data simultaneouslyin numerous tumour foci, then also unfolds the

progession of changes happening in tumour genetic modifications that happens after surgeryor following therapy, thus getting around numerous restrictions given in method of direct sampling.

In addition to sequencing the DNA, epithelial OC's molecular characterization atlevel of mRNA expression has the capacity to recognise and quantify particular copiesmanifestedinside the tumour sampleat a particular duration and to exhibit a better knowledge of tumour growth and maturation on a fine-grained microscopic level of molecules. In the past ten years, investigations on gene expression profiling have concentrated on determining how epithelial OC and healthy ovarian layers express their genes differently utilising RNA microarray analysis. These researches have shown that there are various unique categories at molecular level of high-grade OC (including differentiated, immunoreactive, mesenchymal and proliferative) that are associated with the results clinically **[55–57]**. When tumours in different anatomic regions (such as the each sides of the ovaries and uterus or bladder's peritoneal metastases) in separate patients who haven't undergone chemotherapy were examined, a similar sort of experiment was employed to see if more than one molecular subtype could be discovered **[58]**. While the majority of tumour subtypes exhibited little variation among anatomic regions, primary tumours belonging to the proliferative subtype had significant heterogeneity. However, findings from a related investigation showed that HGSOCsamples frequently revealed numerous characteristics categorisation **[59, 60]**.

This work aimed to identify particular messenger Ribonucleic acidisotopes. It also is categorised like predominantly or highly expressed in OCyet not within healthy layers of tissues, and the findings showed ETV4 expression was often present in the tumours.

FGFRL1, RAB11FIP4, LSR, FOXM1, CD9 and although, the authors noted as additional research was necessary previous to therapeutic implications of these findings are clarified **[61, 62]**.

CHEMORESISTANT EPITHELIAL OVARIAN CANCER CLASSIFICATION BY MOLECULAR METHODS

Selective forces (like chemotherapy) that cause alterations to ovarian epithelial tumours' genomic architecture can result in genomic heterogeneity. Recently, a study incorporating the genome-wide analysis of tissue samples of people with chemoresistant HGS OC was published. The detection of structural anomalies that could not take place inside of the sections of the genome that code, is advantageous

including whole DNA decoding over methods that merely sequence exons alone. Additionally, sequencing the entire genome provides a more precise and direct evaluation of both nucleotide sequence modifications and the exome portion of the genome itself. Particularly this research noteworthy for reasons like the following two: first, it is the pioneer to fully characterise the frequent kind of OC's genomewhose prognosis is not good and few effective treatments, and second, it offers more comprehensive understanding of the genetic differences of HGS OC that has been selectively influenced by one or more types of treatment interventions.. This study's findings revealed that inactivating gene breaks in the supressors of the cancer growth RB1, NF1, RAD51B, and PTEN are associated with developed resistance to chemotherapy, also that resistant illness is frequently linked to amplification of CCNE1 on a comparatively high frequency.

Furthermore, chemo resistant recurrent disease showed the same low incidence of point mutations as prior genotyping studies of HGS OC. Among the participants of this study were reversions in germline BRCA1 were discovered using matched sequencing of germline DNA samples or through BRCA2 mutations or tolerance, where there is a decline of BRCA1 promoter hypermethylation. ABCB1 gene, which produces the protein 1 with medication resistance, is also involved (MDR1) was increased in 8% of cases due to promoter fusion and translocation events. The findings of this research, along with several other recent works. As a result of the selective pressure of chemotherapy, research using next-generation/high throughput method of sequencing to analyse genetic alterations in HGS OC over period reveal that both selection of subclones existing in the main tumour as well as those with persistentHGS OC may develop acquired chemoresistance after acquiring a small number of additional genetic mutations **[63-65]**.

IMPLICATIONS OF EPITHELIAL OVARIAN CANCER'S MOLECULAR CHARECTERISTERIZATION FOR THE CHOICE OF TARGETED THERAPY

To make individualised treatment selection easier, a categorization system at molecular level for epithelial OC is being created to represent the pathophysiology of the illness. The majority of people with epithelial OC are presently prescribed platinum-based therapy as their primary systemic therapy, although the histopathological subtype or other clinical categorization is only sporadically used in the present treatment regimen for treating this cancer **[66]**. Further to that, these treatment suggestions are frequently

supported by scant evidence of efficacy, especially in the case of type I ovarian cancers The application of the dichotomous categorization concept (i.e., types I and II), that is primarily depending on the genetic categorization of OCs, has given a promising pathogenetic justification for the basic chemoresistance closely identified with type I tumours, which are believed to be more molecularly stable than type II OC cancerous tumors **[67, 68]**.

Despite this, HGS OC, which is classified to type II genomically reactive tumour, often returns after an initial chemotherapeutic response **[69-71]**. As was mentioned above, next-generation/high throughput sequencing technology was recently utilised to identify some molecular alterations linked to this type of chemoresistance **[72]**.

Furthermore, there isn't an established treatment protocol for treating epithelial OC that has or develops resistance regarding chemotherapy given based on platinum. Although ovarian cancer patients desperately require molecularly-targeted therapies, these kinds of therapeutic strategies require understanding of more than one genetic alterations which affects the operation of a small amount of biological transmission routes.The decision to use targeted therapy depends on the assumption that such genetic changes are "implementable" in the notion that they have useful treatment effects through specific dosage regimens and therapies in parts of OC patients.The precise molecular classification of cancers in epithelium by next-generation/high throughput sequencing has produced a large amount of extremely complicated biological markers, but only a tiny percentage of this data is expected to be translated into specialized therapeutic interventions in the coming years **[73]**.

Additionally, the selection pressure from the medicationmightmake a difference in the amount of subclonal populace, which would eventually result in treatment resistance. Therefore, a more logical approach to treating recurrent or chemoresistant ovarian cancer may involve progressively changing the target drugs combination whichhas been decided in accordance to the tumor's dynamic chemical alterations. Such plan is based on molecular discoveries made during successive biomarker evaluations carried out at tumour progression. Therapy targeted against targets that have been shown, to minimally be influenced by cellular proliferation and to happen extra frequently inside those cancer tissues, as determined by longitudinal genomic analyses of ovarian tumor tissues, may be another potential treatment strategy **[74, 75]**. Currently, only two targeted agents are

approved by the USFDA and EMA for treating OC. These are the antiangiogenic drug bevacizumab, and polyadenosine diphosphate (ADP)-ribose polymerase (PARP) inhibitor olaparib, each of these is authorised for use in chemotherapy-treated individuals with advanced illness. EMA has also approved bevacizumab to treat OC as the first-line treatment **[76, 77]**. Additionally, trabectedin, a DNA replication and transcription inhibitor, inducer of DNA double-strand fractures and deficit of mismatch repair, is marketed in Europe **[78]**.

MOLECULAR TARGET FOR THERAPY IN OVARIAN CANCER

The available methods only be effective in specific patient subsets, numerous potential therapies that focus on specific molecular modifications are now actively researched for to treat OC. However, this list is not meant to be comprehensive, the targeted medicines linked to the molecular targets described in the following subsection show the range of therapy approaches being researched in advanced OC. Identification of unique genetic abnormalities for subgroups classified histologically and stages has been attempted as a use of tailored therapies in healthcare with purpose (table II) **[79-81]**. In fact, p53 and BRCA mutation are more solely seen in HGS OC, whereas triggering mutations of k-ras and b-raf usually occur in LGS OC and mucinous cancer. As a result of downregulating gene mutation in PTEN and amplifying gene mutation in PIK3CA (the 110-alpha catalytic subunit of PI3K), HGS OC often show PIK3CA enhancement, which may indicate some correlation of engaged stimulated signalling pathways among subgroups and stages. Most endometrioid and CC cancers exhibit phosphatidylinositol 3-kinase (PI3K) pathway mutation **[82]**.

Perhaps a more beneficial strategy in the era of targeted therapy would be to use a molecular classification of OC, in relation to directing the use of targeted therapies, the division of tissues into accelerating the genomic and proteome processes be even more beneficial than conventional subgroups. As a matter of fact, cutting-edge technologies can take into account a number of extremely active signalling pathways within the specific cancerous condition to explain its underlying carcinogenetic factor to develop, enabling the estimation of a possible response to a particular targeted therapy RPPA, a proteome technique, identifies potential carcinogenic proteins with antibodies of high-quality **[83]**. Analysis of more than 300, Four protein expression profiles have been proposed by EOCs including mitogen-activated kinase signaling, stromal- and protein kinase [MAPK] and PI3K hormonal signatures that point to potential

Bevacizumab, a MAPK/PI3K pathway inhibitor, is useful and anti-estrogen treatments and anti-estrogen treatments **[84]**.

The following techniques are available for ovarian cancer molecular targeting **[130]**.

1.KinaseSignalling Pathways	2.Stromal Targets	3.Hormonal Signatures	4.Polyadenoribose Polymerase Inhibitors	5.Apoptosis and Cell Cycle Regulation
1.1Upstream Targeting: Receptors and Ligands 1.1.1 Receptor Tyrosine Kinases: Epidermal Growth Factor Receptor, c-kit and Insulin Growth Factor Receptor-1 1.1.2 Lysophosphatidic Acid 1.1.3 Endothelin-1 1.2 Downstream Targeting: Signalling Pathways 1.2.1 Ras/Raf/MAPK/MEK 1.2.2 PI3K/PTEN/AKT/mTOR Pathway 1.2.3 MEKK3/IKK/Nuclear Factor jb 1.2.4 Interleukin-6/JAK/JAK2/STAT3 1.2.5 Src 1.2.6 Notch-3	2.1 Angiogenesis Inhibition: Vascular Endothelial Growth Factor and PlateletDerived Growth Factor Receptor Blockade 2.2 Adhesion Molecule Inhibition: CD44, Mucin 16, Integrins 2,3Matrix Metalloproteinase Inhibitors	3.1Estrogen-areceptors (ER)	4.1 BRCA 1 and BRCA2 mutations	5.1 p53 5.2 Cell Surface and Cytoplasmic Regulators of Apoptosis 5.3 Aurora A Kinase 5.4 Telomerase and Kinesin Spindle Protein

BRCA½ MUTATIONS

Although defective homologous recombination in Gene regulation has been linked with changes in the BRCA1 or BRCA2 tumour suppressor genes as well, it is believed that PARP suppression is particularly effective in those with OCwho have these molecular changes. It has been demonstrated that PARP suppression causes a buildup of DNA strand breaks. Synthetic lethality, or more particularly, cell death brought on by a combination of defects in two or more genes, involves the use of Protease inhibitors in patients with cancers lacking reprogramming. There is indication that mixing a platinum drug, which similarly degrades DNA and prevents it from being repaired, with a PARP inhibitor may have even higher synergistic effects **[85, 86]**.

Olaparib was given regulatory clearance for treating advanced OC on the basis of the findings of a non-randomized phase II study comprising 298 patients with solid tumours also genetic BRCA1 or BRCA2 alterations, including 193 individuals with recurrent OC **[87, 88]**. The median PFS were seven months and median OS were 16.6 months, for the class of patients with OC the majority of whom underwent intensive preparation of chemotherapy **[89]**. Three new PARP blockers Niraparib, Veliparib, and Rucaparib are being studied for treating people with OC. Lately, the phase III ENGOT-OV16/NOVA was launched **[90, 91]**.

Cases with platinum-sensitive malignancy who had priorly received treatment for recurrent OC with more than two platinum-based therapies were segmented

dependingon whether or not they had a germline BRCA1/2 genetic defect, and they were either given niraparib maintenance therapy or a placebo **[92]**. The fact that the sample of patients who don't have a hereditary BRCA1/2 genetic variation also had a substantial advantage with niraparib compared to placebo was even more astounding (average PFS 9.3 vs. 3.9 months; hazard ratios = 0.38; 95% confidence interval (CI), 0.17 to 0.41; p 0.001).This was true even though patientswho have somatic BRCA1/2 genetic variations or various defects in recombination homologously benefited more from niraparib-associated PFS in this latter group, highlighting the potential use of biological markers apart from BRCA1/2 in the selection of individuals for PARP inhibitor therapy. Patients who have germline BRCA1/2 genetic variations or mutationsunderwent a significant PFS advantage. Although 20% of the patients who lacked any of these indicators benefited long-term on niraparib. Niraparib was generally well tolerated despite grade 3/4 problems in hematology that were reported by 20% - 33% of individuals taking the drug.

It's also crucial to highlight the outcomes of a just recently published interpretive assessment of patients who took part in the phase III OVA-301 research examining the application of pegylated liposomal doxorubicin combining with or combining without trabectedin in patients who have recurrent epithelial OC. The class of patients who have germline BRCA1 genetic variations in the trabectedin arm in this research had a substantially greater response rate, PFS and OS than this class of patients who only received drug therapy. Contrarily, in the subset of patients with BRCA1 alterations there wasn't a difference in OS among chemotherapy + trabectedin and just chemotherapy **[93]**. A phase III clinical trial is currently ongoing to assessthis hypothesis prospectively **[94]**.

TP53 MUTATIONS

The tumour suppressor p53 controls a multitude of signallingroutes implicated in cell cycle arrest, programmed cell death, and its ageing to govern how cells respond to stresses such as oxygen deprivation, oncogene activation, and DNA fragmentation **[95]**. Due to the exceptionally high proportion of TP53 gene alterations found in HGS carcinoma, its genetic change represents a highly promising potential therapeutic target. Patients with refractory solid tumours treated with the Wee1 G2 checkpoint kinase inhibitor AZD1775 as a single drug, including one with ovarian cancer carrying the BRCA1/2 mutations, showed partial responses in a recent phase I trial **[96]**.

In several randomised phase II clinical studies involving patients with TP53-affected epithelial OC, this combination of AZD1775 and chemotherapy showed some positive anti-tumor effects **[97, 98]**. This tactic is supported depending on roles played by p53 in the G1 DNA damage checkpoints and Wee1 in G2 DNA damage checkpoints **[102]**. When combined with chemotherapy, AZD1775 may be more lethal to tumour cells with defective G1 checkpoint function **[99]**. Another unique approach to battling TP53 mutations is to inhibit Hsp 90, which was discovered to establish a stable group with p53 mutant and prevent the degeneration of the protein **[100, 101]**. A twopart, multimodal, phase 1/2 clinical study testing the inhibitor of HSP 90 ganetesib is now recruiting patients with HG epithelial/HG endometrioid/ heterogeneous platinum-resistant epithelial OC, fallopian tube cancer or primary peritoneal tumor **[102]**.

PI3K/AKT/MAMMALIAN TARGET OF RAPAMYCIN (MTOR) PATHWAY

Type I and type II cancers have been shown to contain mutations connected to genes encoding for parts of the PI3K/Akt/mTOR signalling system (for example, PIK3CA and PTEN), a key survival pathway. This pathway's constitutive signalling may be stopped by treatments that target particular elements of it **[103]**. For instance, temsirolimus, a singledrugmTOR blocker, has demonstrated limited efficacy in treating epithelial OC **[104-106]**. However, genetic markers that are persistent across malignancies and indicate responsiveness to mammalian target of inhibitors of rapamycin (mTOR) pathway are still developing **[107, 108]**.

An inhibitor of mammalian target of rapamycin (mTOR) may also be more efficient when taken in combination with chemotherapy or another particular treatment to restrict the mTOR pathway due to the intricacy of the mTOR system, enabling its activation via a number of

route elements. For the treatment of ovarian cancer, several other methods of combination therapy employing this class of medications are being investigated, including everolimus or letrozole and everolimus plus bevacizumab **[109, 110]**.

Additionally, PI3K and Akt inhibitors, which are being evaluated in clinical settings in treating OC, will may be able to block this pathway in better manner **[104, 105]**. These drugs work by inhibiting the activity of the enzymes that upregulate mTOR inhibitors. Reportsin phase I trial using the inhibitor of Aktperifosine in conjunction with docetaxel in individuals having platinum- and taxane-resistant as well as refractory epithelial OC, for instance, showed signs of clinical benefit with a good safety profile **[106]**. Recently, a patient with OC with the BRCA1 mutation and a patient with OC with the BRCA1/2 wild-type, both responded in phase I research examining the pairing of an inhibitor of Akt, AZD5363, and the PARP blocker, olaparib, as a possible method for adapting to changes to PARP inhibitory activity **[111]**.

RAS/RAF/MEK/ERKSIGNALLING PATHWAY

Due to the relatively frequent occurrence of KRAS and BRAF genetic changes in numerous of these tumours, approaches to blocking the RAS/RAF/MEK/ERK signalling routes were not thoroughly investigated in epithelial ovarian cancer. However, they could be extremely crucial for treating type I lesions. 52 individuals with persistent low-grade ovarian serous tumour participated in an phase II study done open label, using the blocker of MEK - selumetinib, and the findings showed that more than 80% of subjects either had stable disease (65%) or an objective recovery (15.4%). Selumetinib was also well tolerated by this group of individuals. However, the findings of an exploratory study showed that the BRAF and KRAS mutation history of tumourswere not correspondingto reaction withselumetinib **[112]**.

A recently planned interim review of the results from the phase III MILO research of the inhibitor of MEK, binimetinib, in patients with LGS OC did not reveal a potentialvariation in PFS, particularly when differentiated with pharmacotherapy **[113, 114]**, despite the fact that a tumour genetic variation in a RAS/RAF/MEK/ERK signalling pathway component which failed to meet the inclusion requirement for part of the data collection. A phase II/III randomised study that compared trametinib, or some other MEK inhibitor, with conventional treatment is planned to identify tumour mutation history and correlate it to therapeutic response in females with recurrent or advancing LGS carcinoma **[115]**.

TYROSINE KINASE PATHWAYS: HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2

The significance of more and more evidence points to the significance of human epidermal growth receptor 2 activity in epithelial OC. Clinical studies using a single drug, trastuzumab, and pertuzumab, have revealed moderate rates of objective response in individuals with advanced, resistant ovarian cancer. Adding pertuzumab with carboplatin/paclitaxel in a randomizedstudy of phase II on patients who have platinum-sensitive carcinoma who had relapsed did not change the median PFS **[116-119]**. However, evidence gained from trial of phase II suggests that combining pertuzumab with gemcitabine may be useful in treating patients who have platinum-resistant malignancy **[120]**.

In this regard, it is notable that HGS OC has relatively infrequent ERBB2 amplification or mutation. Additionally, the higher prevalence of ERBB2 amplification shown in certain investigations of clear-cell and mucin-filled ovarian tumours suggests that anti-HER2 targeted chemotherapy may be more efficacious in these populations.

MICRO RNAs PATHWAY

The development of tumours may be inhibited or accelerated by post transcriptional gene regulators known as microRNAs (miRNAs), which are short small RNAs which doesn't code. Because of variations in miRNA expression among malignant and healthy tissue, miRNAs have been established to play a role in the carcinogenesis of several malignancies, including OC. To identify potential mRNA targets for miRNAs, one research looked at connections seen between activity of certain miRNAs and mRNAs in tumours. The TCGA's RNA microarray expression results were used in the study **[121]**.

MiRNA-based signatures or networks specific to epithelial ovarian tumours with a poor prognosis may be employed as diagnostic biomarkers in both the early and late phases of the disease. Additionally, serum and plasma from ovarian cancer patients had persistent, circulating, cell-free miRNAs that were very similar to the miRNA patterns of tumours **[122]**. Additionally, significant variations in circulating miRNA profiles were discovered between ovarian cancer patients and healthy subjects, suggesting that circulating miRNAs may serve as indicators of disease prognosis and early detection **[123]**. Last but not least, despite the lack of research trials investigating the role of miRNAs in ovarian cancer, the substitution or restriction of particular miRNAs has been suggested as a kind of therapy **[124]**.

IMMUNOLOGICAL PATHWAYS

High potential of inhibiting immuno checkpoints in the microenvironment of

tumours can reduce immune reactions, allowing cancerous cells to evade immune system invasion and fostering uncontrolled cell proliferation **[125, 126]**.

An antibody, Nivolumab, that stops predetermined cell death-1 (PD-1), an immunological checkpoint, was evaluated for safety and efficacy in a phase II study on patients diagnosed with OC that is platinum-resistant **[127]**. 40% and 10% of patients, respectively, reported adverse effects related to the medication that were graded three or four and substantial. 15% of patients demonstrated an objective response, the median OS was 20 months, and the disease control rate was 45%. 80 percent of the patients who participated in the study's tumour samples had high levels of the receptor-ligand 1 (PD-L1), which, when linked to PD-1, prevents activation of T cells **[128]**.

Alternative immune-based therapies for treating OC include vaccine, cytokine, and treatment of adoptive T-cell, which involves the transfer of lymphocytes. As further details about the group of genes implicated in the cellular regulation of immune activity become available, next-generation/high throughput sequencing is anticipated to become more significant in choosing the patients with OC for immune system-focused chemotherapy **[129]**.

CONCLUSION

Our understanding of molecular characteristics and our capabilities to logically target important pathways in particular EOCs will be improved by a systems approach using complete data generated by TCGA. It has been simpler to develop a more standardised strategy to identifying these tumours because to the molecular identification of several subgroups of ovarian epithelial carcinoma, considering findings from more latest researches employing next generation throughput sequencing technologies. This approach is predicted to be crucial in identifying evolutionary history involved in the pathophysiology of malignancy in ovarian epithelial malignancy when combined with several tumour samples collected at diverse points in time and location. Bevacizumab is an advantageousstep one in the clinical use of specific medications for OC, but the therapeutic effects of medications aiming the varioushighly potential pathways, likeinhibitors of PI3K and PARP, are less clear. The investigation on their therapeutic impact is ongoing, and the findings are highly anticipated. Major unmet needs include the lack of an efficient treatment for patients who have advanced epithelial OC are tolerant and refractory to chemotherapy done platinum-based and the low efficacy of the majority of single-agent

targeted treatments studied thus far. Although major improvements have recently been performed in understanding the molecular roots of epithelial OC, the therapeutic risks of this knowledge are still being fully grasped. The utilization of next-generation by using sequencing technology, for instance, is opening up new possibilities, such as techniques to identify the genetic characteristics causing medication resistance so that it enables individualized treatment choice and administration that will prevent the emergence of such resistance.However; it is evident that overcoming illness resistance to therapy will call for a variety of strategies. Finally, a strict search strategy that is restricted to cancers that express the required targets and molecular markers of response to the tested drug, along with improved trial designs, most probably will improve the advancement of important progressions clinically in Epithelial OC and potentially help womens who are affected by this terrible disease.

REFERENCES

[1] Farley J, Brady WE, Vathipadiekal V, Lankes HA, Coleman R, Morgan MA, *et al*. Selumetinib in women with recurrent low- grade serous carcinoma of the ovary or peritoneum: an open-label, single-arm, phase 2 study. Lancet Oncol. 2013; 14: 134-40.

[2] Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, *et al*. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005; 353: 1659-72.

[3] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015; 65: 5-29.

[4] Ledermann JA, Raja FA, Fotopoulou C, Gonzalez-Martin A, Colombo N, Sessa C, *et al*. Newly diagnosed and relapsed epithelial ovarian carcinoma: Esmo clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013 Oct;24 Suppl 6:vi24-32.

[5] Chan JK, Urban R, Cheung MK, Osann K, Husain A, Teng NN, *et al*. Ovarian cancer in younger vs older women: a population-based analysis. Br J Cancer. 2006; 95: 1314-20.

[6] Cancer RO. Survival and treatment differences by age. Cancer. 1993; 71: 524-9.

[7] Chan JK, Tian C, Monk BJ, Herzog T, Kapp DS, Bell J, *et al*. Prognostic factors for high-risk early-stage epithelial ovarian cancer: a Gynecologic Oncology Group study. Cancer. 2008; 112: 2202-10.

[8] du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory

analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). Cancer. 2009; 115: 1234-44.

[9] Prat J. Ovarian carcinomas: five distinct diseases with different origins, genetic alterations, and clinicopathological features. Virchows Arch. 2012; 460: 237-49.

[10] Kindelberger DW, Lee Y, Miron A, Hirsch MS, Feltmate C, Medeiros F, *et al*. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: Evidence for a causal relationship. Am J SurgPathol. 2007; 31:161-9.

[11] Marquez RT, Baggerly KA, Patterson AP, Liu J, Broaddus R, Frumovitz M, *et al*. Patterns of gene expression in different histotypes of epithelial ovarian cancer correlate with those in normal fallopian tube, endometrium, and colon. Clin Cancer Res. 2005; 11: 6116-26.

[12] Lee Y, Miron A, Drapkin R, Nucci MR, Medeiros F, Saleemuddin A, *et al*. A candidate precursor to serous carcinoma that originates in the distal fallopian tube. J Pathol. 2007; 211: 26-35.

[13] Kurman RJ, Shih IeM. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. Am J SurgPathol. 2010; 34: 433-43.

[14] Piek JM, Van Diest PJ, Zweemer RP, Jansen JA, Menko FH, Gille JJ, *et al*. Dysplastic changes in prophylactically removed Fallopian tubes of women predisposed to developing ovarian cancer. J Pathol. 2001; 195: 451-6.

[15] Falconer H, Yin L, Grönberg H, Altman D. Ovarian cancer risk after salpingectomy: a nationwide population-based study. J Natl Cancer Inst. 2015; 107. pii: dju410.

[16] Kuhn E, Kurman RJ, Vang R, Sehdev AS, Han GM, Soslow R, *et al*. TP53 mutations in serous tubal intraepithelial carcinoma and concurrent pelvic high-grade serous carcinoma-evidence supporting the clonal relationship of the two lesions. J Pathol. 2012; 226: 421-6.

[17] Perets R, Wyant GA, Muto KW, Bijron JG, Poole BB, Chin KT, *et al*. Transformation of the fallopian tube secretory epithelium leads to High-Grade serous ovarian cancer in Brca;Tp53;Pten models. Cancer Cell. 2013; 24: 751-65.

[18] Somigliana E, Vigano' P, Parazzini F, Stoppelli S, Giambattista E, Vercellini P. Association between endometriosis and cancer: a

comprehensive review and a critical analysis of clinical and epidemiological evidence. Gynecol Oncol. 2006; 101: 331-41.

[19] Vang R, Shih IeM, Kurman RJ. Ovarian low-grade and high-grade serous carcinoma: pathogenesis, clinicopathologic and molecular biologic features, and diagnostic problems. Adv AnatPathol. 2009; 16: 267-82.

[20] Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature. 2011; 474: 609-15.

[21] Tothill RW, Tinker AV, George J, Brown R, Fox SB, Lade S, *et al*. Novel molecular subtypes of serous and endometrioid ovarian cancer linked to clinical outcome. Clin Cancer Res. 2008; 14: 5198-208.

[22] Zorn KK, Bonome T, Gangi L, Chandramouli GV, Awtrey CS, Gardner GJ, *et al*. Gene expression profiles of serous, endometrioid, and clear cell subtypes of ovarian and endometrial cancer. Clin Cancer Res. 2005; 11: 6422-30.

[23] Vaughan S, Coward JI, Bast RC, Berchuck A, Berek JS, Brenton JD, *et al*. Rethinking ovarian cancer: recommendations for improving outcomes. Nat Rev Cancer. 2011; 11: 719-25.

[24] Sugiyama T, Kamura T, Kigawa J, Terakawa N, Kikuchi Y, Kita T, *et al*. Clinical characteristics of clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy. Cancer. 2000; 88: 2584-9.

[25] Schmeler KM, Sun CC, Bodurka DC, Deavers MT, Malpica A, Coleman RL, *et al*. Neoadjuvant chemotherapy for low-grade serous carcinoma of the ovary or peritoneum. Gynecol Oncol. 2008; 108: 510-4.

[26] Hess V, A'hern R, Nasiri N, King DM, Blake PR, Barton DP, *et al*. Mucinous epithelial ovarian cancer: a separate entity requiring specific treatment. J Clin Oncol. 2004; 22: 1040-4.

[27] Gershenson DM, Sun CC, Lu KH, Coleman RL, Sood AK, Malpica A, *et al*. Clinical behavior of stage II-IV low-grade serous carcinoma of the ovary. Obstet Gynecol. 2006; 108: 361-8.

[28] Gilks CB, Ionescu DN, Kalloger SE, Koebel M, Irving J, Clarke B, *et al*. Tumor cell type can be reproducibly diagnosed and is of Independent prognostic significance in patients with maximally debulked ovarian carcinoma. Hum Pathol. 2008; 39: 1239-51.

[29] Aysal A, Karnezis A, Medhi I, Grenert JP, Zaloudek CJ, Rabban JT. Ovarian endometrioid

adenocarcinoma: incidence and clinical significance of the morphologic and immunohistochemical markers of mismatch repair protein defects and tumor microsatellite instability. Am J SurgPathol. 2012; 36: 163-72.

[30] Storey DJ, Rush R, Stewart M, Rye TA, Williams AR, Smyth JF. Endometrioid epithelial ovarian cancer - 20 years of prospectively collected data from a single center. Cancer. 2008; 112: 2211-20.

[31] Takano M, Kikuchi Y, Yaegashi N, Kuzuya K, Ueki M, Tsuda H, *et al*. Clear cell carcinoma of the ovary: a retrospective multicentre experience of 254 patients with complete surgical staging. Br J Cancer. 2006; 94: 1369-74.

[32] Miyamoto M, Takano M, Goto T, Kato M, Sasaki N, Tsuda H, *et al*. Clear cell histology as a poor prognostic factor for advanced epithelial ovarian cancer: a single institutional case series through central pathologic review. J Gynecol Oncol. 2013; 24: 37-43.

[33] Cannistra SA. Cancer of the ovary. N Engl J Med. 2004; 351: 2519- 29.

[34] King MC, Marks JH, Mandell JB, New York Breast Canc Study Grp. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. 2003; 302: 643-6.

[35] Walsh T, Casadei S, Lee MK, Pennil CC, Nord AS, Thornton AM,*et al*. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc Natl Acad Sci U S A. 2011; 108: 18032-7.

[36] Loveday C, Turnbull C, Ramsay E, Hughes D, Ruark E, Frankum JR, *et al*. Germline mutations in RAD51D confer susceptibility to ovarian cancer. Nat Genet. 2011; 43: 879-82.

[37] Casadei S, Norquist BM, Walsh T, Stray S, Mandell JB, Lee MK, *et al*. Contribution of inherited mutations in the BRCA2-interacting protein PALB2 to familial breast cancer. Cancer Res. 2011; 71: 2222-9.

[38] Meindl A, Hellebrand H, Wiek C, Erven V, Wappenschmidt B, Niederacher D, *et al*. Germline mutations in breast and ovarian cancer pedigrees establish RAD51C as a human cancer susceptibility gene. Nat Genet. 2010; 42: 410-4.

[39] Watson P, Riley B. The tumor spectrum in the lynch syndrome. Fam Cancer. 2005; 4: 245-8.

[40] Santarius, T., Shipley, J., Brewer, D., Stratton, M. R. & Cooper, C. S. A census of amplified and overexpressed human cancer genes. *Nature reviews. Cancer* **10**, 59–64,

https://doi.org/10.1038/nrc2771 (2010).

[41] Blattler, A. & Farnham, P. J. Cross-talk between site-specific transcription factors and DNA methylation states. *J BiolChem***288**, 34287–34294, https://doi.org/10.1074/jbc.R113.512517 (2013).

[42] Olivier, M., Asmis, R., Hawkins, G. A., Howard, T. D. & Cox, L. A. The Need for Multi-Omics Biomarker Signatures in Precision Medicine. *Int J Mol Sci* **20**, https://doi.org/10.3390/ijms20194781 (2019).

[43] Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, *et al*. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer, 2013[2016-09-09]. http://globocan.iarc.fr.

[44] Chen WQ, Zheng RS, Baade PD, Zhang SW, Zeng HM, Bray F, *et al*. Cancer statistics in China, 2015. CA Cancer J Clin. 2016; 66: 115–32.

[45] American Cancer Society. Cancer Facts & Figures 2015. Atlanta: American Cancer Society, 2015.

[46] Howlader N, Noone AM, Krapcho M, *et al*. SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesa, MD, http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER website, April 2016.

[47] Catenacci, D.V. Next-generation clinical trials: Novel strategies to address the challenge of tumor molecular heterogeneity. Mol. Oncol. **2015**, 9, 967–996.

[48] Bashashati, A.; Ha, G.; Tone, A.; Ding, J.; Prentice, L.M.; Roth, A.; Rosner, J.; Shumansky, K.; Kalloger, S.; Senz, J.; *et al*. Distinct evolutionary trajectories of primary high-grade serous ovarian cancers revealed through spatial mutational profiling. J. Pathol. 2013, 231, 21–34

[49] Castellarin, M.; Milne, K.; Zeng, T.; Tse, K.; Mayo, M.; Zhao, Y.; Webb, J.R.; Watson, P.H.; Nelson, B.H.; Holt, R.A. Clonal evolution of high-grade serous ovarian carcinoma from primary to recurrent disease. J. Pathol. 2013, 229, 515–524.

[50] Cowin, P.A.; George, J.; Fereday, S.; Loehrer, E.; van Loo, P.; Cullinane, C.; Etemadmoghadam, D.; Ftouni, S.; Galletta, L.; Anglesio, M.S.; *et al*. LRP1B deletion in high-grade serous ovarian cancers is associated with acquired chemotherapy resistance to liposomal doxorubicin. Cancer Res. 2012, 72, 4060–4073.

[51] Paracchini, L.; Mannarino, L.; Craparotta, I.; Romualdi, C.;

Fruscio, R.; Grassi, T.; Fotia, V.; Caratti, G.;Perego, P.; Calura, E.; *et al*. Regional and temporal heterogeneity of epithelial ovarian cancer tumor biopsies:Implications for therapeutic strategies. Oncotarget 2016

[52] Castellarin, M.; Milne, K.; Zeng, T.; Tse, K.; Mayo, M.; Zhao, Y.; Webb, J.R.; Watson, P.H.; Nelson, B.H.; Holt, R.A. Clonal evolution of high-grade serous ovarian carcinoma from primary to recurrent disease. J. Pathol. 2013, 229, 515–524.

[53] Lee,J.Y.;Yoon,J.K.;Kim,B.;Kim,S.; Kim,M.A.;Lim,H.;Bang,D.;Song,Y. S.Tumorevolutionandintratumor heterogeneity of an epithelial ovarian cancer investigated using next-generation sequencing. BMCCancer 2015, 15, 85

[54] Schwarz, R.F.; Ng, C.K.; Cooke, S.L.; Newman, S.; Temple, J.; Piskorz, A.M.; Gale, D.; Sayal, K.; Murtaza, M.; Baldwin, P.J.; *et al*. Spatial and temporal heterogeneity in high-grade serous ovarian cancer: A phylogenetic analysis. PLoS Med. 2015, 12, e1001789

[55] Tothill, R.W.; Tinker, A.V.; George, J.; Brown, R.; Fox, S.B.; Lade, S.; Johnson, D.S.; Trivett, M.K.; Etemadmoghadam, D.; Locandro, B.; *et al*. Novel molecular subtypes of serous and endometrioid ovarian cancer linked to clinical outcome. Clin. Cancer Res. 2008, 14, 5198–5208.

[56] Konecny,G.E.;Wang,C.;Hamidi,H.; Winterhoff,B.;Kalli,K.R.;Dering,J.; Ginther,C.;Chen,H.W.;Dowdy,S.; Cliby, W.; *et al*. Prognostic and therapeutic relevance of molecular subtypes in high-grade serous ovarian cancer. J. Natl. Cancer Inst. 2014, 106, dju249.

[57] Tothill, R.W.; Tinker, A.V.; George, J.; Brown, R.; Fox, S.B.; Lade, S.; Johnson, D.S.; Trivett, M.K.; Etemadmoghadam, D.; Locandro, B.; *et al*. Novel molecular subtypes of serous and endometrioid ovarian cancer linked to clinical outcome. Clin. Cancer Res. 2008, 14, 5198–5208.

[58] Leong, H.S.; Galletta, L.; Etemadmoghadam, D.; George, J.; Australian Ovarian Cancer Study; Kobel, M.;Ramus, S.J.; Bowtell, D. Efficient molecular subtype classification of high-grade serous ovarian cancer.J. Pathol. 2015, 236, 272–277

[59] Verhaak, R.G.; Tamayo, P.; Yang, J.Y.; Hubbard, D.; Zhang, H.; Creighton, C.J.; Fereday, S.; Lawrence, M.;Carter, S.L.; Mermel, C.H.; *et al*. Prognostically relevant gene signatures of high-grade serous ovariancarcinoma. J. Clin. Investig. 2013, 123, 517–525.

[60] Barrett, C.L.; DeBoever, C.; Jepsen, K.; Saenz, C.C.; Carson, D.A.; Frazer, K.A. Systematic transcriptomeanalysis reveals tumor-specific isoforms for ovarian cancer diagnosis and therapy. Proc. Natl. Acad. Sci. USA2015, 112, 3050–3057.

[61] Bowtell DD. The genesis and evolution of high-grade serous ovarian cancer. Nat Rev Cancer. Epub 2010 Oct 14.

[62] Ahmed AA, Etemadmoghadam D, Temple J, *et al*. Driver mutations in TP53 are ubiquitous in high grade serous carcinoma of the ovary. J Pathol 2010; 221: 49-56.

[63] Patch, A.M.; Christie, E.L.; Etemadmoghadam, D.; Garsed, D.W.; George, J.; Fereday, S.; Nones, K.; Cowin, P.;Alsop, K.; Bailey, P.J.; *et al*. Whole-genome characterization of chemoresistant ovarian cancer. Nature **2015**,521, 489–494

[64] Lambrechts, S.; Smeets, D.; Moisse, M.; Braicu, E.I.; Vanderstichele, A.; Zhao, H.; van Nieuwenhuysen, E.;Berns, E.; Sehouli, J.; Zeillinger, R.; *et al*. Genetic heterogeneity after first-line chemotherapy in high-gradeserous ovarian cancer. Eur. J. Cancer **2016**, 53, 51–64.

[65] Kuo KT, Mao TS, Jones S, *et al*. Frequent activating mutations of PIK3CA in ovarian clear cell carcinoma. Am J Pathol 2009 May; 174 (5): 1597-601

[66] National Comprehensive Cancer Network (NCCN). Ovarian Cancer Guidelines V1 2016. Available online:https://www.nccn.org/ (accessed on 1 July 2016).

[67] Ross, J.S.; Ali, S.M.; Wang, K.; Palmer, G.; Yelensky, R.; Lipson, D.; Miller, V.A.; Zajchowski, D.;Shawver, L.K.; Stephens, P.J. Comprehensive genomic profiling of epithelial ovarian cancer by next generationsequencing-based diagnostic assay reveals new routes to targeted therapies. Gynecol. Oncol. **2013**, 130,554–559

[68] Kurman, R.J.; Shih Ie, M. The dualistic model of ovarian carcinogenesis: Revisited, revised, and expanded.Am. J. Pathol. **2016**, 186, 733–747

[69] Castellarin, M.; Milne, K.; Zeng, T.; Tse, K.; Mayo, M.; Zhao, Y.; Webb, J.R.; Watson, P.H.; Nelson, B.H.;Holt, R.A. Clonal evolution of high-grade serous ovarian carcinoma from primary to recurrent disease.J. Pathol. **2013**, 229, 515–524.

[70] Schwarz, R.F.; Ng, C.K.; Cooke, S.L.; Newman, S.; Temple, J.; Piskorz, A.M.; Gale, D.; Sayal, K.; Murtaza, M.;Baldwin, P.J.; *et al*. Spatial and temporal heterogeneity in high-grade serous ovarian cancer:

A phylogeneticanalysis. PLoS Med. **2015**, 12, e1001789.

[71] Lambrechts, S.; Smeets, D.; Moisse, M.; Braicu, E.I.; Vanderstichele, A.; Zhao, H.; van Nieuwenhuysen, E.;Berns, E.; Sehouli, J.; Zeillinger, R.; *et al*. Genetic heterogeneity after first-line chemotherapy in high-gradeserous ovarian cancer. Eur. J. Cancer **2016**, 53, 51–64.

[72] Kuhn, E.; Kurman, R.J.; Vang, R.; Sehdev, A.S.; Han, G.; Soslow, R.; Wang, T.L.; Shih Ie, M. TP53 mutations in serous tubal intraepithelial carcinoma and concurrent pelvic high-grade serous carcinoma–evidence supporting the clonal relationship of the two lesions. J. Pathol. 2012, 226, 421–426.

[73] Blagden, S.P. Harnessing Pandemonium: The clinical implications of tumor heterogeneity in ovarian cancer.Front. Oncol. **2015**, 5, 149.

[74] Bhang, H.E.; Ruddy, D.A.; Krishnamurthy Radhakrishna, V.; Caushi, J.X.; Zhao, R.; Hims, M.M.; Singh, A.P.;Kao, I.; Rakiec, D.; Shaw, P.; *et al*. Studying clonal dynamics in response to cancer therapy usinghigh-complexity barcoding. Nat. Med. **2015**, 21, 440–448

[75] Zeppernick, F.; Meinhold-Heerlein, I.; Shih Ie, M. Precursors of ovarian cancer in the fallopian tube: Serous tubal intraepithelial carcinoma–an update. J. Obstet. Gynaecol. Res. 2015, 41, 6–11.for the treatment of patients with advanced ovarian cancer [78].

[76] Avastin (bevacizumab). [package insert]. Genentech, Inc.: South San Francisco, CA, 2014. Availableonline: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125085s0169lbl.pdf (accessed on12 December 2016).

[77] Lynparza (olaparib). [package insert]. AztraZeneca Pharmaceuticals: Wilmington, DE, 2014. Available online:http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206162lbl.pdf (accessed on 12 December2016).

[78] European Medicines Agency. Available online: http://www.ema.europa.eu/ema/ (accessed on21 November 2016).

[79] Hennessy BT, Mills GB. Ovarian cancer: homeobox genes,autocrine/paracrine growth, and kinase signaling. Int JBiochem Cell Biol 2006; 38: 1450-6

[80] Shih IM, Kurman RJ. Ovarian tumorigenesis: a proposedmodel based on morphological and molecular geneticanalysis. Am J Pathol 2004; 164: 1511-8

[81] Ahmed AA, Etemadmoghadam D, Temple J, *et al*. Drivermutations in TP53 are ubiquitous in high grade serouscarcinoma of the ovary. J Pathol 2010; 221: 49-56

[82] Madore J, Ren F, Filali-Mouhim A, *et al*. Characterizationof the molecular differences between ovarian endometrioidand ovarian serous carcinoma. J Pathol 2010;220: 392-400

[83] Sheehan KM, Calvert VS, Kay EW, *et al*. Use of reversephase protein microarrays and reference standard developmentfor molecular network analysis of metastaticovarian carcinoma. Mol Cell Proteomics 2005; 4: 346-55.

[84] Tothill RW, Tinker AV, George J, *et al*. Novel molecularsubtypes of serous and endometrioid ovarian cancerlinked to clinical outcome. Clin Cancer Res 2008; 14:

[85] .Lee, J.M.; Ledermann, J.A.; Kohn, E.C. PARP Inhibitors for BRCA1/2 mutation-associated and BRCA-likemalignancies. Ann. Oncol. **2014**, 25, 32–40.

[86] Oza, A.M.; Cibula, D.; Benzaquen, A.O.; Poole, C.; Mathijssen, R.H.; Sonke, G.S.; Colombo, N.; Spacek, J.;Vuylsteke, P.; Hirte, H.; *et al*. Olaparib combined with chemotherapy for recurrent platinum-sensitiveovarian cancer: A randomised phase 2 trial. Lancet Oncol. **2015**, 16, 87–97.

[87] Domchek, S.M.; Aghajanian, C.; Shapira-Frommer, R.; Schmutzler, R.K.; Audeh, M.W.; Friedlander, M.;Balmana, J.; Mitchell, G.; Fried, G.; Stemmer, S.M.; *et al*. Efficacy and safety of olaparib monotherapy ingermline BRCA1/2 mutation carriers with advanced ovarian cancer and three or more lines of prior therapy.Gynecol. Oncol. **2016**, 140, 199–203.

[88] Kaufman, B.; Shapira-Frommer, R.; Schmutzler, R.K.; Audeh, M.W.; Friedlander, M.; Balmana, J.; Mitchell, G.;Fried, G.; Stemmer, S.M.; Hubert, A.; *et al*. Olaparib monotherapy in patients with advanced cancer and agermline BRCA1/2 mutation. J. Clin. Oncol. **2015**, 33, 244–250.]

[89] Coleman, R.L.; Sill, M.W.; Bell-McGuinn, K.; Aghajanian, C.; Gray, H.J.; Tewari, K.S.; Rubin, S.C.;Rutherford, T.J.; Chan, J.K.; Chen, A.; *et al*. A phase II evaluation of the potent, highly selective PARP inhibitorveliparib in the treatment of persistent or recurrent epithelial ovarian, fallopian tube, or primary peritonealcancer in patients who carry a germline BRCA1 or BRCA2 mutation-An NRG Oncology/GynecologicOncology

Group study. Gynecol. Oncol. **2015**, 137, 386–391 .

[90] Liu, J.F.; Matulonis, U.A. What is the place of PARP inhibitors in ovarian cancer treatment? Curr. Oncol. Rep.**2016**, 18, 29.

[91] Mirza, M.R.; Monk, B.J.; Herrstedt, J.; Oza, A.M.; Mahner, S.; Redondo, A.; Fabbro, M.; Ledermann, J.A.;Lorusso, D.; Vergote, I.; *et al*. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer.N. Engl. J. Med. **2016**, 375, 2154–2164.

[92] Hennessy BT, Timms KM, Carey MS, *et al*. Somatic mutations in BRCA1 and BRCA2 could expand the number of patients that benefit from poly (ADP rirbose) polymerase inhibitors in ovariancancer. J Clin Oncol 2010; 28: 3570-6

[93] Monk, B.J.; Ghatage, P.; Parekh, T.; Henitz, E.; Knoblauch, R.; Matos-Pita, A.S.; Nieto, A.; Park, Y.C.;Cheng, P.S.; Li, W.; *et al*. Effect of BRCA1 and XPG mutations on treatment response to trabectedin andpegylated liposomal doxorubicin in patients with advanced ovarian cancer: Exploratory analysis of thephase 3 OVA-301 study. Ann. Oncol. **2015**, 26, 914–920.

[94] ClinicalTrials.gov. NCT01846611. A Study Comparing the Combination of Trabectedin (YONDELIS) andDOXIL/CAELYX With DOXIL/CAELYX for the Treatment of Advanced-Relapsed Epithelial Ovarian,Primary Peritoneal, or Fallopian Tube Cancer. Available online: https://clinicaltrials.gov/ct2/show/NCT01846611 (accessed on 3 August 2016).

[95] Duffy, M.J.; Synnott, N.C.; McGowan, P.M.; Crown, J.; O'Connor, D.; Gallagher, W.M. p53 as a target for thetreatment of cancer. Cancer Treat. Rev. **2014**, 40, 1153–1160

[96] Do, K.; Wilsker, D.; Ji, J.; Zlott, J.; Freshwater, T.; Kinders, R.J.; Collins, J.; Chen, A.P.; Doroshow, J.H.;Kummar, S. Phase I study of single-agent AZD1775 (MK-1775), a Wee1 kinase inhibitor, in patients withrefractory solid tumors. J. Clin. Oncol. **2015**, 33, 3409–3415.

[97] Leijen, S.; van Geel, R.; Sonke, G.S.; de Jong, D.; Rosenberg, E.H.; Marchetti, S.; Pluim, D.;vanWerkhoven, E.D.; Rose, S.; Lee, M.A.; *et al*. Phase II study of Wee1 inhibitor AZD1775 plus carboplatinin patients with p53 mutated ovarian cancer refractory or resistant (<3 months) to standard

first-line therapy.J. Clin. Oncol. **2015**, 33, 2507.

[98] Oza, A.M.; Weberpals, J.I.; Provencher, D.M.; Grischke, E.-M.; Hall, M.; Uyar, D.; Estevez-Diz, M.D.;Marmé, F.; Kuzmin, A.; Rosenberg, P.; *et al*. An international, biomarker-directed, randomized, phase IItrial of AZD1775 plus paclitaxel and carboplatin (P/C) for the treatment of women with platinum-sensitiveTP53-mutant ovarian cancer. J. Clin. Oncol. **2015**, 33, 5506.

[99] Leijen, S.; Beijnen, J.H.; Schellens, J.H. Abrogation of the G2 checkpoint by inhibition of Wee-1 kinase resultsin sensitization of p53-deficient tumor cells to DNA-damaging agents. Curr. Clin. Pharmacol. **2010**, 5, 86–91.

[100] Li, D.; Marchenko, N.D.; Moll, U.M. SAHA shows preferential cytotoxicity in mutant p53 cancer cells bydestabilizing mutant p53 through inhibition of the HDAC6-Hsp90 chaperone axis. Cell Death Differ. **2011**, 18,1904–1913.

[101] Li, D.; Marchenko, N.D.; Schulz, R.; Fischer, V.; Velasco-Hernandez, T.; Talos, F.; Moll, U.M. Functionalinactivation of endogenous MDM2 and CHIP by HSP90 causes aberrant stabilization of mutant p53 inhuman cancer cells. Mol. Cancer Res. **2011**, 9, 577–588.

[102] Mueller, S.; Haas-Kogan, D.A. WEE1 kinase as a target for cancer therapy. J. Clin. Oncol. **2015**, 33, 3485–3487.

[103] Cheaib, B.; Auguste, A.; Leary, A. The PI3K/Akt/mTOR pathway in ovarian cancer: Therapeutic opportunities and challenges. Chin. J. Cancer 2015, 34, 4–16

[104] Behbakht, K.; Sill, M.W.; Darcy, K.M.; Rubin, S.C.; Mannel, R.S.; Waggoner, S.; Schilder, R.J.; Cai, K.Q.; Godwin,A.K.;Alpaugh,R.K.PhaseIItrialofthemTORinhibitor,temsirolimusandevaluationofcirculating tumor cells and tumor biomarkers in persistent and recurrent epithelial ovarian and primary peritoneal malignancies: A Gynecologic Oncology Group study. Gynecol. Oncol. 2011, 123, 19–26. [CrossRef] [PubMed]

[105] Emons, G.; Kurzeder, C.; Schmalfeldt, B.; Neuser, P.; de Gregorio, N.; Pfisterer, J.; Park-Simon, T.W.; Mahner, S.; Schroder, W.; Luck, H.J.; *et al*. Temsirolimus in women with platinum-refractory/resistant ovarian cancer or advanced/recurrent endometrial carcinoma. A phase II study of the AGO-study group (AGO-GYN8).

Gynecol. Oncol. 2016, 140, 450–456. [CrossRef] [PubMed]

[106] Husseinzadeh, N.; Husseinzadeh, H.D. mTOR inhibitors and their clinical application in cervical, endometrial and ovarian cancers: A critical review. Gynecol. Oncol. 2014, 133, 375–381. [CrossRef] [PubMed]

[107] Kwiatkowski, D.J.; Choueiri, T.K.; Fay, A.P.; Rini, B.I.; Thorner, A.R.; de Velasco, G.; Tyburczy, M.E.; Hamieh, L.; Albiges, L.; Agarwal, N.; *et al*. Mutations in TSC1, TSC2, and MTOR are associated with response to rapalogs in patients with metastatic renal cell carcinoma. Clin. Cancer Res. 2016, 22, 2445–2452.

[108] Lim, S.M.; Park, H.S.; Kim, S.; Kim, S.; Ali, S.M.; Greenbowe, J.R.; Yang, I.S.; Kwon, N.J.; Lee, J.L.; Ryu, M.H.; *et al*. Next-generation sequencing reveals somatic mutations that confer exceptional response to everolimus. Oncotarget 2016, 7, 10547–10556. [PubMed]

[109] ClinicalTrials.gov. NCT01031381. Study of RAD001 and Bevacizumab in Recurrent Ovarian, Peritoneal, and Fallopian Tube Cancer (RADBEV).

[110] ClinicalTrials.gov. NCT02188550. Single Arm Trial with Combination of Everolimus and Letrozole in Treatment of Platinum Resistant Relapse or Refractory or Persistant Ovarian Cancer. Endometrial Cancer.

[111] Michalarea, V.; Lorente, D.; Lopez, J. Accelerated phase I trial of 2 schedules of the combination of the PARP inhibitor olaparib and AKT inhibitor AZD5363 using a novel intrapatient dose escalation design in advanced cancer patients. In Proceedings of the American Association for Cancer Research Annual Meeting, Philadelphia, PA, USA, 18–22 April 2015. Abstract Number 8529

[112] Farley,J.;Brady,W.E.;Vathipadiekal, V.;Lankes,H.A.;Coleman,R.;Morga n,M.A.;Mannel,R.;Yamada,S.D.; Mutch, D.; Rodgers, W.H.; *et al*. Selumetinib in women with recurrent low-grade serous carcinoma of the ovary or peritoneum: An open-label, single-arm, phase 2 study. Lancet Oncol. 2013, 14, 134–140.

[113] ClinicalTrials.gov. NCT01849874. AStudyof MEK162vs. Physician's ChoiceChemotherapyinPatientswith Low-Grade Serous Ovarian, Fallopian Tube or Peritoneal Cancer. Available online: https://clinicaltrials. gov/ct2/show/NCT01849874 (accessed on 27 October 2016).

[114] MEK Inhibitor Misses Mark in Phase III Ovarian Cancer Study. Available online: http://www.onclive.com/ web-exclusives/mek-inhibitor-misses-mark-in-phase-iii-ovarian-cancer-study (accessed on 29 July 2016).

[115] ClinicalTrials.gov. NCT02101788. Trametinib in Treating Patients with Recurrent or Progressive Low-Grade Ovarian Cancer or Peritoneal Cavity Cancer. Available online: https://clinicaltrials.gov/ct2/show/ NCT02101788 (accessed on 29 July 2016).

[116] Bookman, M.A.; Darcy, K.M.; Clarke-Pearson, D.; Boothby, R.A.; Horowitz, I.R. Evaluation of monoclonal humanized anti-HER2 antibody, trastuzumab, in patients with recurrent or refractory ovarian or primary peritoneal carcinoma with overexpression of HER2: A phase II trial of the Gynecologic Oncology Group. J. Clin. Oncol. 2003, 21, 283–290..

[117] Langdon, S.P.; Faratian, D.; Nagumo, Y.; Mullen, P.; Harrison, D.J. Pertuzumab for the treatment of ovarian cancer. Expert Opin. Biol. Ther. 2010, 10, 1113–1120.

[118] Garcia, A.A.; Sill, M.W.; Lankes, H.A.; Godwin, A.K.; Mannel, R.S.; Armstrong, D.K.; Carolla, R.L.; Liepman, M.K.; Spirtos, N.M.; Fischer, E.G.; *et al*. A phase II evaluation of lapatinib in the treatment of persistent or recurrent epithelial ovarian or primary peritoneal carcinoma: A gynecologic oncology group study. Gynecol. Oncol. 2012, 124, 569–574.

[119] Kaye, S.B.; Poole, C.J.; Danska-Bidzinska, A.; Gianni, L.; del Conte, G.; Gorbunova, V.; Novikova, E.; Strauss, A.; Moczko, M.; McNally, V.A.; *et al*. A randomized phase II study evaluating the combination of carboplatin-based chemotherapy with pertuzumab versus carboplatin-based therapy alone in patients with relapsed, platinum-sensitive ovarian cancer. Ann. Oncol. 2013, 24, 145–152.

[120] Makhija, S.; Amler, L.C.; Glenn, D.; Ueland, F.R.; Gold, M.A.; Dizon, D.S.; Paton, V.; Lin, C.Y.; Januario, T.; Ng,K.;etal. Clinicalactivityofgemcitabinepluspertuzumabinplatinum-resistantovariancancer,fallopian tube cancer, or primary peritoneal cancer. J. Clin. Oncol. 2010, 28, 1215–1223

[121] Miles, G.D.; Seiler, M.; Rodriguez, L.; Rajagopal, G.; Bhanot, G. Identifying microRNA/mRNA dysregulations in ovarian cancer. BMC Res. Notes 2012, 5, 164.

[122] Nakamura, K.; Sawada, K.; Yoshimura, A.; Kinose, Y.; Nakatsuka, E.; Kimura, T. Clinical relevance of circulating cell-free microRNAs in ovarian cancer. Mol. Cancer 2016, 15, 48

[123] Traver, S.; Assou, S.; Scalici, E.; Haouzi, D.; Al-Edani, T.; Belloc, S.; Hamamah, S. Cell-free nucleic acids as non-invasive biomarkers of gynecologic cancers, ovarian, endometrial and obstetric disorders and fetal aneuploidy. Hum. Reprod. Update 2014, 20, 905–923.

[124] Traver, S.; Assou, S.; Scalici, E.; Haouzi, D.; Al-Edani, T.; Belloc, S.; Hamamah, S. Cell-free nucleic acids as non-invasive biomarkers of gynecologic cancers, ovarian, endometrial and obstetric disorders and fetal aneuploidy. Hum. Reprod. Update 2014, 20, 905–923.

[125] Hamanishi, J.; Mandai, M.; Konishi, I. Immune checkpoint inhibition in ovarian cancer. Int. Immunol. 2016, 28, 339–348.

[126] Mittica, G.; Genta, S.; Aglietta, M.; Valabrega, G. Immune checkpoint inhibitors: a new opportunity in the treatment of ovarian cancer? Int. J. Mol. Sci. 2016, 17, 1169.

[127] Hamanishi, J.; Mandai, M.; Ikeda, T.; Minami, M.; Kawaguchi, A.; Murayama, T.; Kanai, M.; Mori, Y.; Matsumoto, S.; Chikuma, S.; *et al*. Safety and antitumor activity of anti-PD-1 antibody, nivolumab, in patients with platinum-resistant ovarian cancer. J. Clin. Oncol. 2015, 33, 4015–4022.

[128] Spencer, K.R.; Wang, J.; Silk, A.W.; Ganesan, S.; Kaufman, H.L.; Mehnert, J.M. Biomarkers for immunotherapy: Current developments and challenges. Am. Soc. Clin. Oncol. Educ. Book 2016, 35, 493–503.

[129] ClinicalTrials.gov. NCT02718417. A Randomized, Open-LABEL., Multicenter, Phase 3 Study to Evaluate the Efficacy and Safety of Avelumab (msb0010718c) in Combination with and/or Following Chemotherapy in Patients with Previously Untreated Epithelial Ovarian Cancer, J Javelin Ovarian 100. Available online: https://clinicaltrials.gov/ct2/show/NCT02718417 (accessed on 9 September 2016).

[130] Coukos, G.; Tanyi, J.; Kandalaft, L.E. Opportunities in immunotherapy of ovarian cancer. Ann. Oncol. 2016, 27, 11–15