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Research Paper

Chemoresistance and targeted therapies in ovarian and endometrial cancers

Kevin Brasseur[1], Nicolas Gévry[2] and Eric Asselin[1]

[1] Research Group in Cellular Signaling, Department of Medical Biology, Canada Research Chair in Molecular Gyneco-Oncology, Université du Québec à Trois-Rivières, Trois-Rivières, Québec, Canada

[2] Département de Biologie, Faculté des Sciences, Université de Sherbrooke, Boulevard de l'Université, Sherbrooke, QC, Canada

Correspondence to: *Eric Asselin*, ***email***: *eric.asselin@uqtr.ca*

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ABSTRACT

Gynecological cancers are known for being very aggressive at their advanced stages. Indeed, the survival rate of both ovarian and endometrial cancers is very low when diagnosed lately and the success rate of current chemotherapy regimens is not very efficient. One of the main reasons for this low success rate is the acquired chemoresistance of these cancers during their progression. The mechanisms responsible for this acquired chemoresistance are numerous, including efflux pumps, repair mechanisms, survival pathways (PI3K/AKT, MAPK, EGFR, mTOR, estrogen signaling) and tumor suppressors (P53 and Par-4). To overcome these resistances, a new type of therapy has emerged named targeted therapy. The principle of targeted therapy is simple, taking advantage of changes acquired in malignant cancer cells (receptors, proteins, mechanisms) by using compounds specifically targeting these, thus limiting their action on healthy cells. Targeted therapies are emerging and many clinical trials targeting these pathways, frequently involved in chemoresistance, have been tested on gynecological cancers. Despite some targets being less efficient than expected as mono-therapies, the combination of compounds seems to be the promising avenue. For instance, we demonstrate using ChIP-seq analysis that estrogen downregulate tumor suppressor Par-4 in hormone-dependent cells by directly binding to its DNA regulatory elements and inhibiting estrogen signaling could reinstate Par-4 apoptosis-inducing abilities. This review will focus on the chemoresistance mechanisms and the clinical trials of targeted therapies associated with these, specifically for endometrial and ovarian cancers.

INTRODUCTION

Gynecological cancers are pathologies developing in the women's reproductive organs, mainly located in the uterus and ovaries. Overall, these cancers accounts for more than 10% of cancer deaths and new cases among women, each year in North America and Europe [1-6].

Ovarian cancer is hard to diagnose because of the almost total lack of symptoms during the early development stages of the tumor. Considering that more than 75% of the cases are detected at an advanced stage, ovarian cancer has a high mortality rate being the gynecological cancer with the lowest average 5-year survival rate (46%) (Figure 1A) [1-7]. An important fact to consider about ovarian cancer, as well as its low survival rate, is the current treatments low efficiency; current treatments become ineffective after a few cycles of administration, with a risk of recurrence estimated at 80-85% [4, 8].

Uterine cancer is the most frequent gynecological cancer and is frequently diagnosed early leading to a better outcome for the patient [1-5, 9]. Most of the cancers occurring in the uterus begin in the endometrium (> 95%) and this subtype is called endometrial cancer [5]. Considering this fact, endometrial cancer will be mainly discussed here. Although the prognosis of endometrial cancer is good, more than 25% of patients are diagnosed at an advanced stage (Stage > 1) with an invasive primary tumor and subsequently accompanied by metastases [10]. One considerable hurdle for these patients diagnosed with

an advanced/recurrent cancer, even though they are treated with aggressive therapies, is that the survival rate is very low (< 20%) (Figure 1B) [5].

In the last decades, treatments for gynecological cancers have not much advanced beyond the platinum-based chemotherapy when compared with many other types of cancer; nor has the patient survival and cure rates increased much (Figure 1) [5, 6, 11, 12]. Reasons for the low survival outcome of gynecological cancers diagnosed lately/recurrent are the resistance to chemotherapy acquired by cancer cells and the non-selectivity of current treatments. This problematic lead to highly damageable side effects for the patients, thus limiting the use of drugs and how they are administered. Because of the inefficacy of the current chemotherapeutic regimens, more research and improvement of the current treatments are required to overcome this challenge.

In this manuscript, we will review the current treatments, their limitations against gynecological cancers and the molecular pathways responsible for the acquired chemoresistance thus leading to the current use of targeted therapies in clinical trials to increase the efficiency of treatments, which prevents recurrent cancers and increases survival of women suffering from these types of cancers.

CURRENT TREATMENTS

Current treatments for both ovarian and endometrial cancers are known for being very similar. Initially, surgery is conducted in order to remove the vast majority of the tumor localized in its corresponding organ. Concerning advanced cancers, the remaining mass following the initial surgery is a good prognostic for survival. If needed, further treatments need to be administered to completely eliminate the tumor left and its distant metastases depending on the stage of the cancer [5, 13-15].

Radiation and hormone therapies are two potential methods of elimination of the remaining cancer cells, which can be used in both types of gynecological cancers. These two types of treatment are rarely used for ovarian

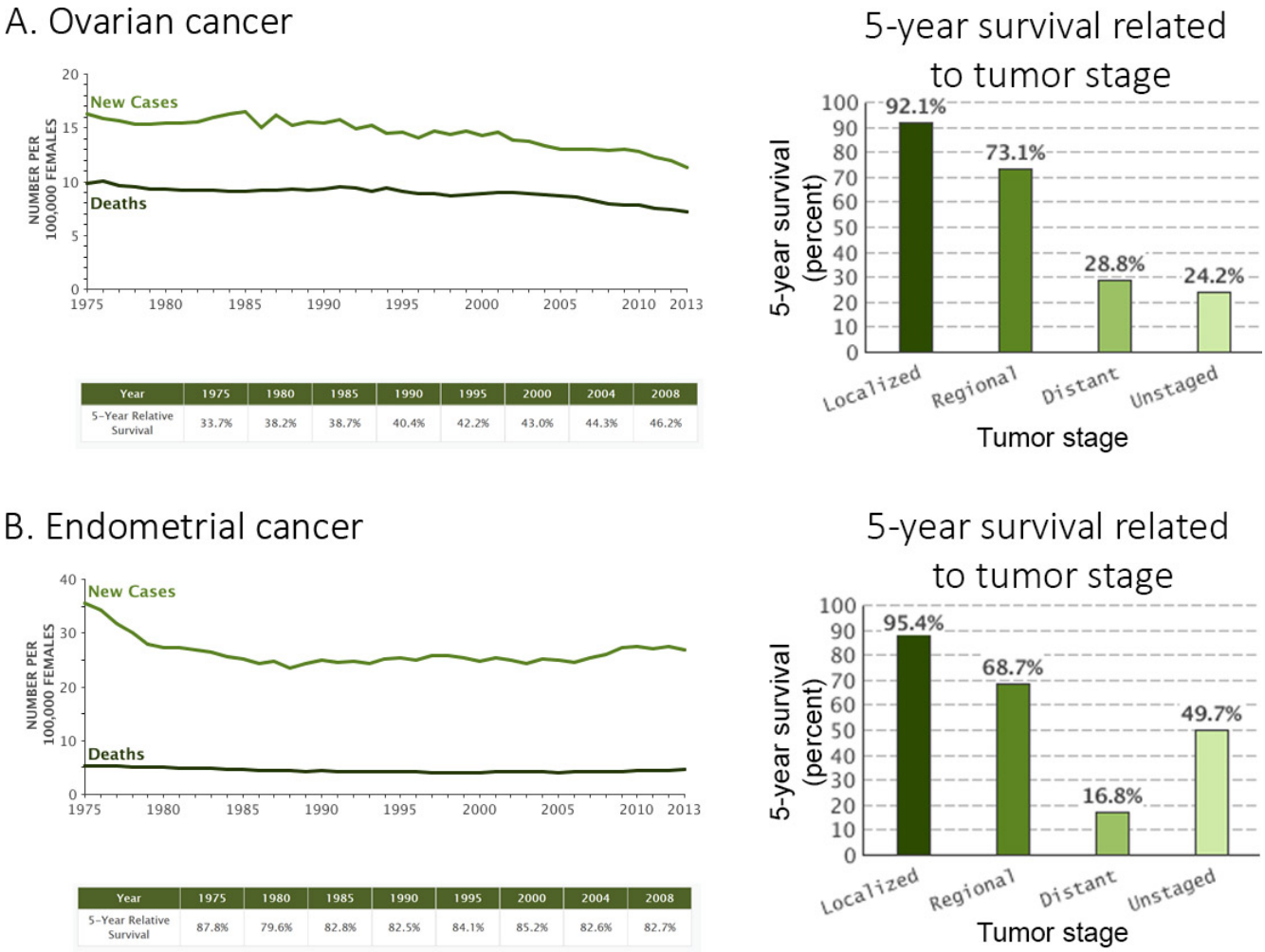

Figure 1: Ovarian and endometrial cancers statistics. A. Ovarian and **B.** endometrial cancers statistics for new cases, deaths and 5-year survival). Data for new cases and deaths are represented by the number per 100 000 females (1975 to 2013), the 5-year survival rate (%) is available for all diagnosed patients (1975-2008) in a table or specifically sorted by tumor stage (2006-2012) in a histogram. The tumor stage is a factor related the chemoresistance. Data were obtained from seer.cancer.gov.

Table 1: Chemoresistance mechanisms in ovarian and endometrial cancers

Mechanism	Tissue	Resistance	Comments	Reference
Efflux pumps				
↑ P-glycoprotein	Ovary and endometrium	Taxanes and doxorubicin		[34-37]
↑ ATP7A/ATP7B	Ovary and endometrium	Platinum		[38-42]
DNA Repair mechanisms				
↑ NER	Ovary	Platinum		[48-53]
↓ MMR	Ovary and endometrium	Platinum		[56-61, 64, 65]
↓ BRCA1	Ovary	Taxane	provides sensitivity to platinum compounds	[80-85]
↓ BRCA2	Ovary	-	provides sensitivity to platinum compounds	[85, 86]
Signaling pathways				
↑ PI3K	Ovary	Platinum		[94, 95]
↑ AKT	Ovary and endometrium	Platinum, taxanes and doxorubicin		[95-105, 120, 150]
↓ PTEN	Ovary and endometrium	Platinum		[91, 94, 106-110]
↑ XIAP	Ovary and endometrium	Platinum, taxanes and doxorubicin	XIAP induces chemoresistance against cisplatin (endometrial and ovarian), taxane (ovarian) and doxorubicin (endometrial)	[97, 100, 113-118]
↓ JNK	Ovary	Platinum		[105, 125]
↓ p-38	Ovary	Platinum		[105, 125, 126]
↑ ERK1/2	Ovary	Platinum		[127]
↑ EGFR	Ovary	Taxanes		[141]
↑ ErbB2	Ovary and endometrium	Platinum and taxanes		[137-140, 142]
↑ GRP78	Endometrium	Platinum and taxanes	Estrogen-regulated	[149]
↑ ASK1	Endometrium	Taxane	Estrogen-regulated	[150]
↑ ERα	Breast	Platinum, taxanes and doxorubicin		[151]
↓/mut P53	Ovary and endometrium	Platinum, taxanes and radiation	Resistance to radiation have been observed in ovarian cancer only	[99, 101, 102, 118-120, 157-167]
↑ BCL-2	Ovary and endometrium	Platinum		[168, 169]
↓ PAR-4	Ovary	Taxane		[179]

The table summarizes the mechanisms of chemoresistance observed in ovarian and endometrial cancers. The different column indicates the mechanism and its regulation, the tissues concerned, the drug resistance, additional comments as well as the bibliographical references.

and endometrial cancers when compared with breast tumors.

Concerning radiation, this method is rarely used as a treatment for ovarian cancer, considering their frequently late diagnosis, but is instead used as an option for recurrent cases, patients with high-risk of surgical mortality or those who cannot tolerate chemotherapeutic compounds. In the case of endometrial cancer, radiation is more frequently used considering the early diagnosis of the tumor; however, it is not as much used for advanced stages cancers [5, 14, 15].

Concerning hormonal therapies, a majority still expresses the estrogen receptors (mainly ERα) and progesterone receptor and those requiring hormones for growth can be classified as hormone dependent. Interestingly, hormone therapy has been used mainly to treat breast cancers and their effects are well known, but are sometimes prescribed in gynecological cancers despite the variability of their response rates [16, 17]. Not unlike breast cancer, mostly in the late stages, gynecological cancers can have mutations/inactivation leading to a loss of the expression of these hormone receptors or not responding to hormonal signals, becoming hormone-independent, thus making hormonal therapies ineffective [16, 18-21]. The different treatment administered for hormone therapy in gynecological cancers still expressing the ER consists of progestin, Luteinizing hormone-releasing hormone (LHRH) agonists and aromatase inhibitors [5, 14-17, 22-24]. The response rate of these types of treatment is moderate and they are mainly used for endometrial cancers expressing the ER. Notably, the success rate of hormonal therapy in gynecological cancers needs to be further investigated considering that many factors (receptor status, cancer stage, chemoresistance status, heterogeneity of the patients and drugs combination) can influence the efficiency of these treatments and were not always considered when used as a treatment in past studies [16, 17].

Lastly, the most frequently used method to eliminate the remaining gynecological cancer cells, widespread in the patient, is the chemotherapy approach. The principle of this method is to use anti-cancer drugs which generally target cells undergoing rapid division, a characteristic of cancer cells. The different chemotherapeutic drugs used for gynecological cancer consist mainly of platinum compounds (cisplatin or carboplatin), taxanes (paclitaxel or docetaxel) and doxorubicin [5, 10, 25]. Platinum compound mechanism consists of damaging DNA by forming platinum-DNA adducts leading to the inhibition of DNA replication and leading cells to apoptosis [26]. Taxanes mechanism is different and instead target microtubule polymerization, inhibiting mitosis and thus inducing apoptosis [27, 28]. Doxorubicin is an anthracycline compound which intercalate DNA, inhibits topoisomerase-II by stabilizing its complex and generate free radicals leading to cell death [29]. Some other chemotherapeutics drugs can also be helpful and used in gynecological cancers including cyclophosphamide (an alkylating agent), gemcitabine (a nucleoside analog), topotecan (a topoisomerase-I inhibitor) or vinorelbine (an inhibitor of mitosis through interaction with tubulin). These agents are mostly used in combination and the platinum-paclitaxel and platinum-doxorubicin combos have been designated as first-line treatment for gynecological cancers [5, 10, 30]. The response rate of these combinations is very good, being around 70% for ovarian cancer and 45% for endometrial cancer [5, 30]. However, a very frequent occurrence in gynecological cancers is that most of the patients relapse and the arising tumor becomes resistant to chemotherapeutic compounds, leading to a low survival rate [31, 32]. Overall, chemotherapy is a very efficient initial treatment but the recurrence of gynecological cancers and their acquisition of chemoresistance is a huge hurdle to overcome.

CHEMORESISTANCE IN GYNECOLOGICAL CANCERS

Chemoresistance is presumably responsible for causing treatment failure and mortality for more than 90% of patients with cancer of advanced stage [13, 33]. This major hurdle, having an impact on patient survival, can be acquired *via* diverse modifications including the increase of efflux pumps to reject drugs and a decrease in cell division limiting the effect of chemotherapeutic compounds targeting mitosis arrest. At the molecular level, genes can be modified to influence the efficiency of repair proteins and diverse survival pathways while decreasing the level of different tumor suppressor. The following will discuss about the literature of known mechanisms of chemoresistance exclusively in gynecological cancers. A better understanding of these mechanisms will allow more efficient therapies to be administered to patients in the clinic.

Efflux pumps

Overexpression of the multidrug-resistance gene MDR1 is associated with acquisition of chemoresistance, particularly against paclitaxel. This acquisition is explained by the increased level of the efflux pump P-glycoprotein (Pgp), thus eliminating more efficiently the presence of chemotherapeutic drugs in both endometrial and ovarian cancers [34-37]. Resistance to platinum compounds has also been related to increased levels of copper pumps [38-42]; indeed, it has been demonstrated that cisplatin-resistant ovarian cancer cell lines have acquired, in part, their resistance *via* an increased protein level of copper-transporting ATPases (ATP7A and ATP7B) [38, 42, 43]. In a patient-derived gene expression profile, ATP7B has also been associated as a chemoresistance

marker in ovarian carcinomas treated with cisplatin [39]. Concerning endometrial cancer, copper-transporter ATP7B overexpression in endometrial carcinoma is also related to cisplatin resistance and indicate an unfavorable outcome for patients [40].

DNA repair mechanisms

For a long time, mechanisms of DNA repair have been associated with chemoresistance in ovarian cancers [44-47].

Nucleotide excision repair process (NER)

One known mechanism responsible for the repair of platinum DNA adducts in ovarian cancer is the nucleotide excision repair process (NER) [48-51]. NER is a multi-step process implicating various proteins to remove and replace a sequence of nucleotides on a DNA strand. Enhanced NER is associated with increased resistance in ovarian cancer. The protein ERCC1, forming an endonuclease complex with XPF and involved in the 5' incision of DNA adducts, has been reported to be correlated in the degree of sensitivity to platinum compounds in ovarian cancers [48-52]. XPF and XPG proteins, involved in NER process, are also reported to have an impact on platinum sensitivity of ovarian cancers [53]. On the contrary, very little association have been drawn between endometrial cancer and NER.

Mismatch repair (MMR)

Another repair mechanism, mismatch repair (MMR), is also known to be associated with chemoresistance mechanisms of ovarian cancers. The principle of MMR is to recognize a mismatched or unmatched DNA base, repair and reassemble DNA correctly [54]. When platinum compounds are administered, the MMR process is unable to complete repairs of mismatched DNA, thus leading to apoptosis [55]. It is suggested that a MMR deficiency in ovarian cancers, mainly due to the loss of the MLH1 gene, allows the cells to continue proliferating, even in presence of cisplatin or carboplatin, thus enabling chemoresistance through the failure to enter apoptosis following exposure to chemotherapy [56-61]. Conversely, other studies seems to report that there is no significant association between MMR deficiency and resistance to platinum compounds [62, 63]. They suggest that the limited quantity of samples studied and the presence of other potential resistance mechanisms could explain the absence of a significant association with MMR and platinum resistance. Very little has been studied concerning chemoresistance and MMR deficiency in endometrial cancers. Few studies report the acquisition of chemoresistance associated with MMR *via* the use of HEC59 endometrial cancer cell line [60, 64, 65]. Interestingly, endometrial cancer frequently has MMR deficiency associated with microsatellite instability which could have an impact on the efficiency of platinum compounds [66-69].

Homologous recombination (BRCA1/2 genes)

BRCA1 and BRCA2 are a known genes involved in an error-free repair mechanism *via* homologous recombination for double strand DNA breaks [70]. These genes are well known for increasing risks of breast as well as ovarian cancers when mutated and transmitted through by heredity [71-75]. Interestingly, mutations on BRCA1 and BRCA2 genes have also been associated with an increased risk of endometrial cancer, but this relation was observed more frequently in association with tamoxifen-treated women's [76-78]. Downregulation of BRCA1 is frequent (> 72%) in high-grade ovarian cancers [79, 80]. It was also observed with BRCA genes that they are involved in response to various chemotherapeutic drugs and consequently associated to chemoresistance [80]. Downregulation of BRCA1 in ovarian cancer provides sensitivity to platinum compounds while providing resistance to taxane drugs [80-85]. BRCA2 has also been associated with sensitivity to platinum compounds when mutated/downregulated in ovarian cancer [85, 86].

Survival pathways

Survival pathways play a major role in mechanisms of chemoresistance of gynecological cancers.

PI3K/AKT pathway

The PI3K/AKT survival pathway is one major signaling cascade, which is frequently mutated/hyperactivated at different levels in both ovarian and endometrial cancers [12, 87-91]. Using TCGA datasets, it is possible to observe that major components of the PI3K/AKT pathway present a high frequency of alteration in gynecological cancers (> 40% in ovaries; > 90% in the uterus) (Figure 2A) [92, 93]. These alterations of the PI3K pathway are involved in the tumorigenesis of gynecological tumors but also their chemoresistance profile. PI3K is a kinase located on the cellular membrane, stimulated by growth hormones and responsible for phosphorylating PIP2 to PIP3. Once phosphorylated, PIP3 can activate downstream targets of the PI3K pathway such as AKT and PDK1 kinases, thus activating various downstream targets involved in protein synthesis and cell growth. PI3K and its subunits (mainly PIK3CA) are known for being highly mutated and responsible for increasing chemoresistance in ovarian cancer [94, 95]. Downstream of PI3K, AKT isoforms (AKT1-2-3) have been reported to also increase the chemoresistance against platinum drugs, taxane and doxorubicin, in both ovarian and endometrial cancers [95-104]. It has been demonstrated that only AKT1 and AKT2 isoforms are responsible for the acquisition of resistance against cisplatin and paclitaxel while all three isoforms of AKT increase doxorubicin resistance in endometrial cancer cells [98]. Concerning

ovarian cancer, it has been demonstrated that AKT2 expression increase resistance to cisplatin [105]. PTEN is a tumor suppressor lipid phosphatase acting negatively on the PI3K pathway *via* its ability to dephosphorylate PIP3 to PIP2, thus controlling the activity of PI3K downstream targets. A very interesting fact concerning PTEN is the high percentage of alterations observed in endometrial cancers (> 65%), which is astonishing when compared to other cancers types (Figure 2B) [92]. Observations have been made concerning this protein, PTEN, and chemoresistance status of gynecological cancers. Indeed, downregulation/inactivity of PTEN (frequently mutated in the endometrium) leads to an increase of resistance against platinum compounds [91, 94, 106-110]. XIAP, an inhibitor of apoptosis, is involved in PI3K/AKT pathway to protect cells by acting as a promoter of AKT activity *via* its interaction with PTEN as an E3 ubiquitin ligase, thus regulating negatively PTEN protein level and its cytosolic/nuclear localization [100, 111, 112]. XIAP is also involved in the chemoresistance against cisplatin (endometrial and

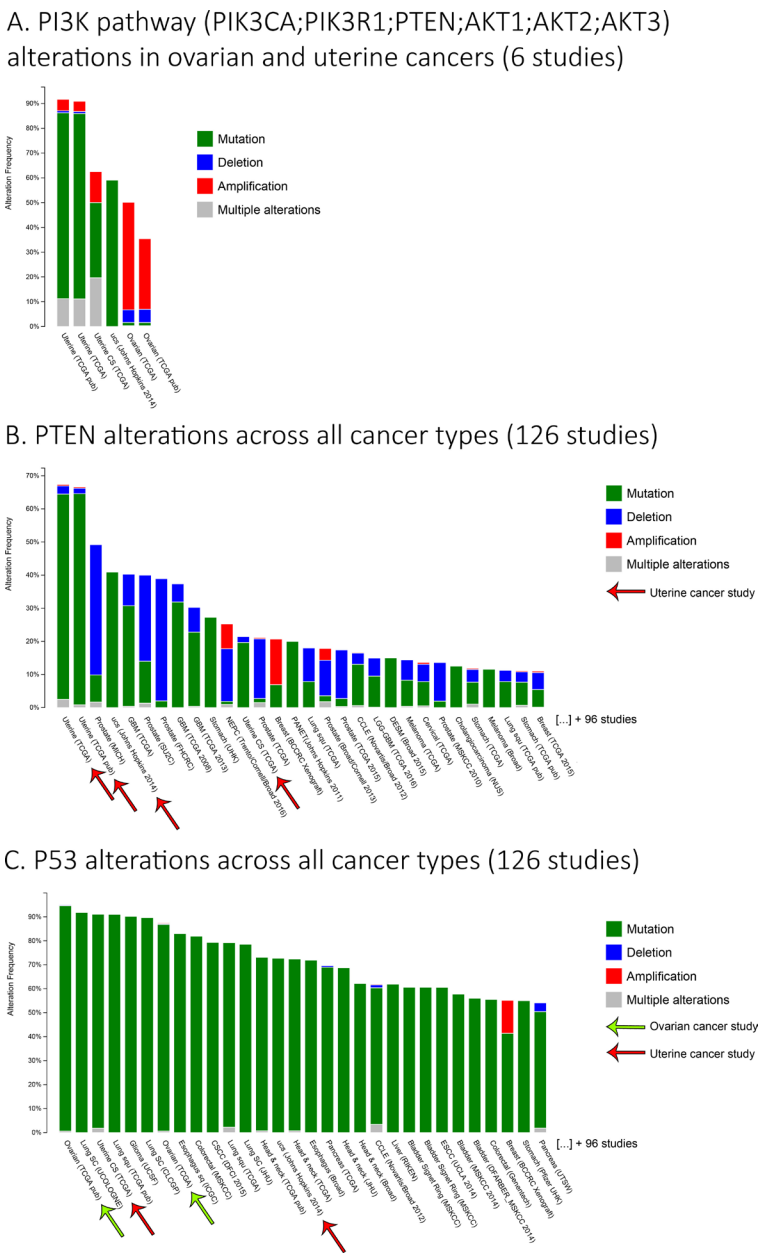

Figure 2: Ovarian and uterine cancers major alterations. A. A histogram representing the frequency of alterations for genes from the PI3K pathway (PIK3CA, PIK3R1, PTEN, AKT1-2-3), specifically in ovarian and uterine cancers from 6 studies. **B.-C.** The histograms representing the frequency of alterations for **B.** PTEN or **C.** P53 in various cancer types from 126 studies. Only the first 30 studies are shown to first simplify the figure, but also to indicate the importance of these alterations in ovarian and uterine cancers. The studies shown in the histograms were sorted from those with the highest to the lowest frequency of alterations for the associated genes. Data were obtained using www.cbioportal.org database.

ovarian), taxane (ovarian) and doxorubicin (endometrial) for both cancers [97, 100, 113-118]. P53 is another well-known tumor suppressor involved in the development of resistance observed in relation to the PI3K/AKT pathway in gynecological cancers. Indeed, it has been demonstrated that P53 inhibits PI3K activity, and consequently AKT, by binding on one of PIK3CA gene promoters thus inhibiting its transcription in ovarian cancer [119]. AKT can also, inversely, inhibit P53 activation through MDM2 and thus inhibit mitochondrial P53-dependent apoptosis [101, 102, 120]. Wild-type P53 is involved in the chemoresistance attributed to PI3K/AKT and XIAP in ovarian cancer. To overcome this resistance *via* the inhibition of PI3K pathway components, the presence of wild-type P53 is required for an optimal sensitization of the cancer cells [99, 101, 102, 118, 120].

MAPK pathway

Another survival pathway to consider in gynecological cancers is the MAPK pathway. MAPK pathway consists of cascades of protein kinases, which can be activated by various stimuli including growth factors or genotoxic stress. Following stimulation, MAPK play a major role for cell growth, survival and/or apoptosis. An important aspect of the MAPK pathway is the fact that upstream of one cascade lies the RAS oncogene, frequently deregulated in various cancers including those affecting gynecological tissues [121]. The activation of the MAPK pathway is divided in various cascades, the main ones being the ERK1/ERK2, JNK/SAPK and p-38 MAPK [121, 122]. RAS activates RAF, subsequently leading to the ERK1/ERK2 cascade, which is stimulated mainly by mitogenic factors and is associated to cell division and survival. Chemotherapeutic compounds can also stimulate and increase ERK1/ERK2 phosphorylation allowing them to play a role of balance in apoptosis and cell survival [123, 124]. JNK and p-38 MAPK cascades are stimulated differently, *via* genotoxic stress including chemotherapeutics compounds, and play roles in cell growth arrest, inflammation and apoptosis [122, 123]. In ovarian cancer, decreased MAPK activity by the JNK and p-38 cascades has been associated with platinum-resistant cancer models [125, 126]. On the contrary, ERK1/ERK2 are associated to survival and cell growth and their inhibition by the protein MKP3 sensitized ovarian cancer cells to cisplatin [127]. MAPK and PI3K pathways are interconnected and can influence each other [128]. In fact, the chemoresistance associated with AKT2 in ovarian cancer is related to the inability of cisplatin to activate JNK and p-38 to induce apoptosis. Indeed, AKT2 is responsible for inhibiting ASK1 and its downstream targets including JNK and p-38 [105]. Concerning endometrial cancer, MAPK and chemoresistance, not much has been studied so far but we can hypothesize that the effect observed would be similar to those reported in ovarian cancer models.

HER family

Another family of oncogenes to consider in gynecological cancers is the epidermal growth factor receptors EGFR (HER-1) and ErbB2 (HER-2), which are known for being cell-surface receptors tyrosine kinases being structurally similar. Indeed, EGFR and ErbB2 are known for being overexpressed in advanced stages of both ovarian and endometrial cancers and being markers of poor prognosis [129-136]. Both EGFR and ErbB2 receptors can activate various signaling pathways, including both the PI3K and MAPK (*via* RAS-RAF oncogenes) which provide survival signaling, cell growth to tumors and contribute to the overall acquisition of chemoresistance in gynecological cancers. Interestingly, it has been demonstrated that EGFR and ErbB2 overexpression, in association with the activation of PI3K and MAPK signaling pathways, increase resistance to cisplatin and paclitaxel in gynecological cancers [137-142]. It is worth noting that the effect of EGFR and ErbB2 on chemoresistance and prognosis is controversial in the literature. Some studies indicate no association with these oncogenes, but it is overall still worth considering for cancer research.

Estrogen receptors

An important characteristic unique to gynecological cancers is the high presence of estrogen and its corresponding receptors (ERα/β), thus promoting cell proliferation and tumorigenesis [143]. Estrogen binds to its receptor, dimerize, allowing its translocation from the cytoplasm to the nucleus, then bind on ERE (DNA Estrogen Response Element) and act as a transcription factor [144, 145]. Estrogen can also act in a non-genomic manner by binding with estrogen receptors, located on the plasma membrane, which then interact with other receptors such as IGF-1R and ErbB2 [146, 147]. Estrogen can also directly bind on a G-coupled protein, the GPR30 receptor, independently of the estrogen receptors [147]. These non-genomic interactions of estrogen induce activity for both the PI3K and MAPK pathways, pathways involved in the chemoresistance of gynecological cancer [146, 147]. It appears important to note that estrogen is strongly associated with chemoresistance mechanisms in both endometrial and ovarian cancers [148-150]. It has been demonstrated in endometrial cancer cells that estrogen can positively activate GRP78, thus preventing apoptosis and providing chemoresistance to both paclitaxel and cisplatin [149]. Another study demonstrated that estrogen can provide chemoresistance to paclitaxel treatment in ovarian cancer cells *via* the phosphorylation of AKT-ASK1 complex [150]. The use of hormonal therapy is much more prevalent in the context of breast cancer; consequently, more data is available with this model. Results show that higher levels of ERα in breast cancer are correlated with a chemoresistance status against cisplatin, paclitaxel and doxorubicin [151].

Tumor suppressors

Up to now, survival pathways were discussed in relation to chemoresistance of gynecological cancers, however, tumor suppressors also play an important role in these mechanisms.

P53

A largely studied tumor suppressor in all cancers is P53. Briefly, P53 is a tumor suppressor protein who has various roles of protection against cancer including DNA repair, cell growth arrest and apoptosis which gave this protein the nickname ‘’guardian of the genome’’. P53 a tetramer tightly regulated by MDM2 and can be stabilized/activated upon diverse stimuli including oncogene activation, DNA damage, starvation or hypoxia. P53 can act as a transcription factor and is involved in the regulation of many genes from different mechanisms to keep the cell in good condition [152, 153]. Nonetheless, P53 is highly mutated in gynecological cancers (> 90% in ovaries and 25-85% in the endometrium) being an important factor for tumorigenesis and cancer initiation (Figure 2C) [92, 152, 154]. Also noteworthy, ovarian and endometrial cancers frequently overexpress P53, WT or mutant [154-156]. Considering the importance of P53 apoptosis pathway, it appears clear that this protein is involved in gynecological cancers response to chemotherapy. As previously stated, P53 is involved in the chemoresistance associated to the PI3K pathway alteration in gynecological cancers [99, 101, 102, 118-120]. Epithelial-mesenchymal transition (EMT), a process of tumor invasion and metastasis, is related to the inhibition of P53-dependent apoptosis mechanisms and involved in the resistance of ovarian cancer to paclitaxel and radiation [157]. P53 alterations are also associated, *via* many different mechanisms, to the resistance of platinum compounds in ovarian [158-165] and in endometrial cancers [166, 167]. P53 inactivation is associated with an increase of the mitochondrial BCL-2, an anti-apoptotic protein, and it has been demonstrated that upregulation of BCL-2 was responsible for the acquired chemoresistance to platinum compounds in gynecological cancers [168, 169]. Overall, P53 is easily the most widely studied tumor suppressor in gynecological malignancies and its importance in these types of cancer is irrefutable.

Prostate apoptosis response-4 (Par-4)

Finally, an interesting tumor suppressor for therapies, and also related to chemoresistance, has recently taken interest in the scientific community and is named Prostate apoptosis response 4 (Par-4). Par-4 is a very interesting protein because of its unique ability to induce apoptosis in a cancer-selective manner [170, 171]. Indeed, this unique mechanism of selectivity has been demonstrated in various models and also seemed to be involved in chemoresistance (including Tamoxifen, taxane and platinum agents) and tumorigenesis mechanisms [172-176]. As previously described, gynecological tissues are known for being hormone-dependent and, interestingly, it has been demonstrated that estrogen can downregulate Par-4 and thus could be involved in chemoresistance-associated mechanisms [177, 178]. A study demonstrated that Par-4 increase the apoptotic response to paclitaxel treatment in ovarian cancer cells [179]. Our laboratory recently published a manuscript indicating that the cleaved form of Par-4 was highly reduced/absent in chemoresistant gynecological cancers indicating a potential venue for this protein to overcome this hurdle. This inhibition was post-translational and regulated by the PI3K and MAPK pathways, previously described as being involved in chemoresistance mechanisms [178]. Except these studies, the role of Par-4 on chemoresistance in gynecological cancer has received very little attention. We do believe that further studies of this promising tumor suppressor would be a very interesting avenue for gynecological cancer therapeutics.

A table summarizing the chemoresistance mechanisms discussed is available (Table 1).

TARGETED THERAPIES TO OVERCOME CHEMORESISTANCE

Considering current therapies are not sufficient to overcome advanced gynecological cancers, new therapies are still being researched by the scientific community. Targeted therapy is a new approach of treatment that uses compounds which aim, in a specific manner, the cancer cells by attacking its oncogenic mechanisms. These mechanisms are also often linked with their chemoresistance status, so targeting these could sensitize cancer cells to standard chemotherapy. This section will discuss of the current targets and their associated drugs currently under study, specifically in gynecological cancers. A figure summarizing the previous mechanisms/pathways involved in chemoresistance as well as the molecules targeting these is available to ease the reading (Figure 3). A table is also available to summarize the different clinical trials discussed in this section (Supplementary Table 1).

Targeting efflux pumps

The p-Glycoprotein, involved in chemoresistance mechanisms, is a target of interest in cancers and some drugs have been tested under clinical trials, specifically on gynecological tissues. First- (verapamil; cyclosporine) and second-generation (PSC833; VX-710) have been developed but the results in clinical trials were disappointing considering their low potency, the low specificity and the increase of toxicity when combined with other chemotherapeutic drugs such as paclitaxel in

ovarian cancer patients [180-182].

Tariquidar (XR9576) is a third-generation Pgp inhibitor, showing increased specificity and potency to inhibit the drug efflux mediated by Pgp. In contrast to second-generation Pgp inhibitors, Tariquidar, combined with docetaxel, showed minimal toxicity, less systemic pharmacokinetic interaction and was well tolerated by patients (including ovarian and cervical cancers) [183]. Interestingly, both *in vitro* and *in vivo* experiments indicated that Tariquidar can completely reverse the resistance of ovarian cancer cells against doxorubicin and paclitaxel [184]. *Ex vivo* experiments using ovarian tumors biopsies also demonstrated that combination of Tariquidar with either doxorubicin or paclitaxel increased

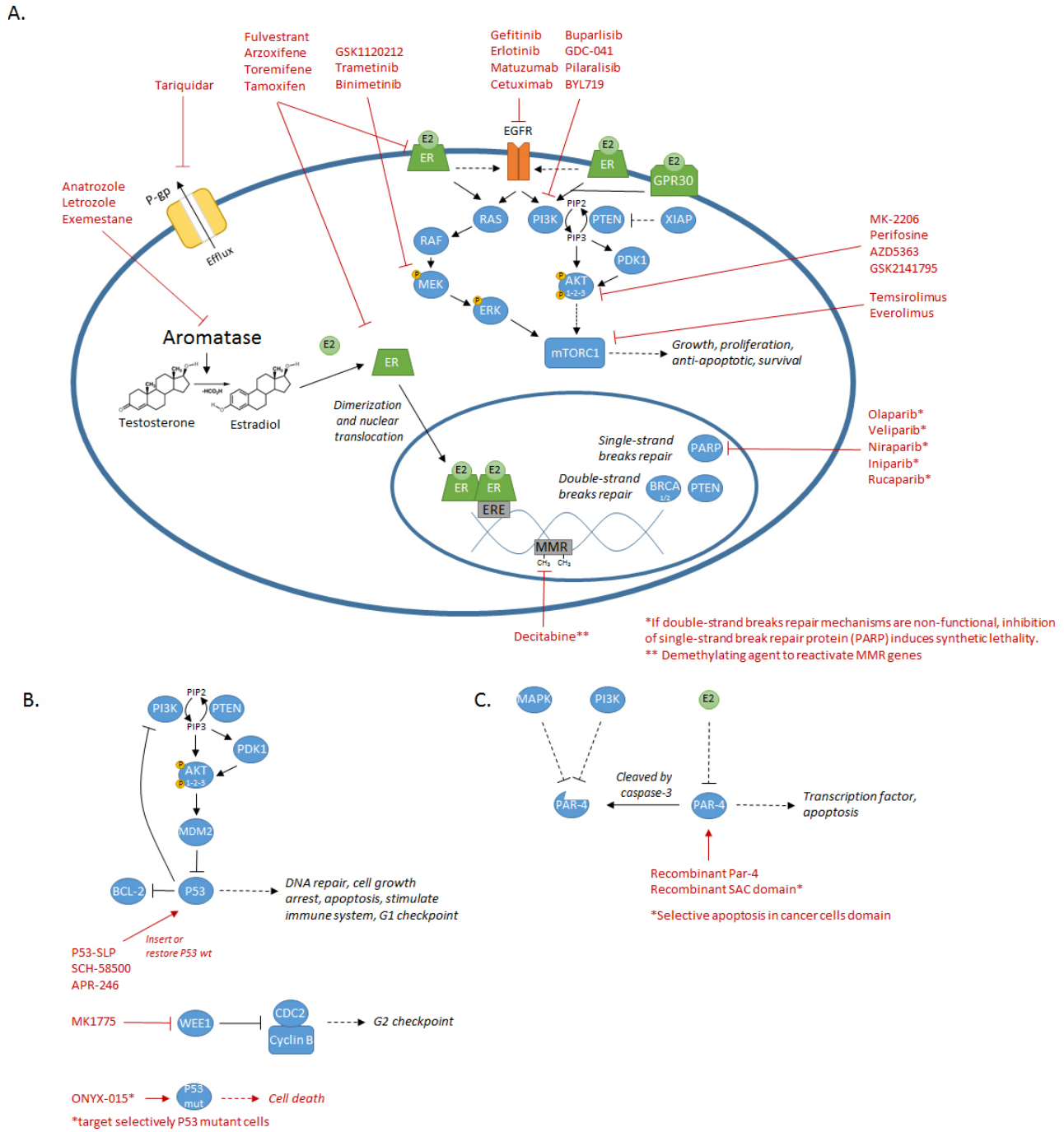

Figure 3: Summary of the diverse mechanisms/pathways involved in chemoresistance and their associated targeted treatments. A. Schematic representing most of the mechanisms/pathways (P-gp, MMR, PARP, aromatase, ER, EGFR, PI3K/AKT, MAPK, mTOR) discussed and their associated therapeutics molecules. **B.** Schematic of the P53 mechanisms discussed and the diverse targeted therapies previously tested on ovarian and endometrial cancers. **C.** Schematic of the Par-4 mechanisms and the targeted therapy approach suggested using recombinant proteins (Par-4 or SAC domain only) on cancer cells.

the efficiency of these standards chemotherapeutic treatments by decreasing the chemoresistance status [185]. Further studies in clinical trials are needed to determine if the effect observed on chemoresistance and increase of efficiency is reproducible the toxicity of the compound on various types of cancer.

Targeting repair mechanisms

PARP inhibitors

As previously introduced, BRCA mutations are frequent and involved in the chemoresistance mechanisms of gynecological cancers. One idea of therapy that has been developed involves the protein poly-ADP ribose polymerase (PARP), responsible for DNA repair of single strand break. The principle of this therapy is to inhibit PARP and thus reduce the ability of the cell to repair single strand breaks; these accumulated breaks will eventually lead to double strand breaks during cell DNA replication. Normal cells will be able to repair these double strand breaks, in part through homologous recombination repair, however, BRCA-1/2 deficient cancer cells will not and thus will undergo chromosomal instability and apoptosis. This is because the BRCA-1/2 genes, when mutated, induces a defect in homologous recombination, and pairing this with PARP inhibition allow synthetic lethality of cancer cells [186]. BRCA-1/2 deficiency is not required when using PARP inhibitors but they will be a lot more efficient with patients bearing this mutation. Some inhibitors of PARP previously used in clinical trials for gynecological cancers are the following: Olaparib, Veliparib, Niraparib, Iniparib and Rucaparib.

Olaparib has been widely studied in ovarian cancer disease. Indeed, many phase II trials have demonstrated an important improvement, using this PARP inhibitor as monotherapy, on the progression-free survival (PFS) and good response rate for women with advanced ovarian cancer [187-190]. The first study tested Olaparib on 33 patients with advanced and recurrent ovarian cancer and 11 of these had an objective response rate (the sum of partial responses (PR) and complete responses (CR); ORR) [187]. The second study was large scale with 265 platinum-sensitive relapsed patients randomized in 2 groups (Olaparib *versus* placebo). The results obtained were significant with a median progression-free survival of 8.4 months *versus* 4.8 months for the Olaparib-treated *versus* placebo-treated patients respectively. Regardless of the BRCA status, patients treated with Olaparib had a decreased risk of progression on the long term [188]. Another trial tested Olaparib in 63 patients with advanced ovarian carcinoma. The findings were very interesting: 7 of the 17 (41%) patients with BCRA1/2 mutations had an ORR to Olaparib while 11 of the 46 (24%) patient without mutations also had an ORR [189]. These results demonstrated that PARP inhibition can also be efficient in absence of BRCA mutations and that other proteins might be involved in the homologous recombination of cancer cells. A phase II trial also tested Olaparib in 193 women with advanced platinum-resistant ovarian cancer and 60 obtained an ORR (31%) demonstrating again a clinical benefit similar to previous trials with chemoresistant patients [190]. Further studies tested Olaparib in combination with chemotherapy in ovarian cancers. A phase I/Ib study tested Olaparib in combination with carboplatin on 37 women with ovarian cancer and BRCA mutations. Their findings were 1 CR and 15 PR, but also found out that FOXO3a expression, a transcription factor negatively regulated by AKT and involved in the regulation of genes in favor of apoptosis, may be predictive of the response to the treatment [191, 192]. Another phase II trial tested Olaparib in combination with both paclitaxel and carboplatin in 162 women with recurrent and platinum-sensitive ovarian cancer. The progression-free survival was significantly improved in the combination group (12.2 months) *versus* the chemotherapy alone (9.6 months). Very interestingly, only 41 of 107 measurable patients had BRCA mutations, demonstrating again, a clinical benefit of PARP inhibitors on patients without BRCA mutations [193]. A phase II trial tested Olaparib in combination with cediranib, an anti-angiogenic agent, in 90 patients with recurrent platinum-sensitive ovarian cancer. Women treated with Olaparib alone had a median progressive-free survival of 9 months while those who received the combination had median of 17.7 months [194]. The combination of these drugs (Olaparib and cediranib) improved the survival of patients greatly and studies further testing this combination are currently going on.

The other clinical PARP inhibitors also underwent a limited number of clinical trials in ovarian cancer. Veliparib was tested in a phase II trial as a single agent in ovarian cancer patients with BRCA mutations either platinum-sensitive (20 patients) or platinum-resistant (30 patients). The ORR of all patients was of 26% (2 CR and 11 PR) and when compared with their platinum-sensitivity, the ORR was of 20% for the resistant group *versus* 35% for the sensitive group [195]. A second study also tested Veliparib in combination with cyclophosphamide, an alkylating agent, in a study group of 72 women with BRCA mutated ovarian cancer. No significant results were obtained from these experiments and the addition of Veliparib did not improve the response rate nor the PFS [196]. Another PARP inhibitor selective for PARP-1 and PARP-2, Niraparib, went under a phase I study (42 ovarian/peritoneal cancer patients) and the preliminaries antitumor results were 8 PR and 2 SD among the 20 BRCA mutations carrier patients while being 5 PR and 3 SD among the 22 WT BRCA patients. Platinum sensitivity of patients was also considered when analyzing the response rate. No significant difference was observed in the CBR from BRCA mutation carrier (50% for sensitive and 50%

for resistant), however, CBR was twice lower in BRCA WT platinum-resistant patients (67% for sensitive *versus* 32% for resistant) [197]. Iniparib, an additional PARP inhibitor, had a very promising phase II trial involving 17 platinum-sensitive patients with recurrent ovarian cancer and was used in combination with carboplatin and gemcitabine, a nucleoside analog. The ORR of patients treated with carboplatin and gemcitabine alone is normally around 47% but adding Iniparib to the combination significantly increased the ORR to 71%. Additionally, the ORR did not seem to be associated with the BRCA status of the patients [198]. Iniparib, combined with paclitaxel and carboplatin, have also been tested in a group of 17 women with advanced or recurrent uterine carcinosarcoma (displaying histological features from both endometrium and the outer layer of the uterus). The results obtained were limited considering that only 4 patients responded to the treatment [199]. Still, PARP1 overexpression is present in uterine carcinomas and studies with PARP inhibitors should not be neglected because of the failure of Iniparib in those latter studies.

Finally, Rucaparib is another PARP1/2 inhibitor undergoing clinical studies in ovarian cancer. Rucaparib have been initially tested in a pre-clinical study with 39 ovarian cancer cell lines characterized for BCRA1/2, PTEN and their chemosensitivity to platinum compounds. Responses to platinum chemotherapy was associated with Rucaparib responses and combining the PARP inhibitor with topotecan, carboplatin, doxorubicin, paclitaxel or gemcitabine provided additive or synergistic effects resulting in increased apoptosis [200]. Phase I trial has been done using Rucaparib and 29 patients with advanced solid tumors including ovarian/peritoneal cancer (7 patients). Preliminary results were very interesting with 2 PR and 10 SD among the various doses of Rucaparib tested. The most interesting part of this trial is the efficiency observed in ovarian/peritoneal cancer patients, which account for half of the response rates obtained and a CBR of 86% (1 PR and 5 SD) [201]. A phase II trial has also been done testing Rucaparib in women with BRCA mutated advanced breast and ovarian cancer. 22 of the 27 patients tested for oral Rucaparib were ovarian cancer patients but the ORR with the different doses administered was only 15%. However, 12 of the 13 patients who received continuously Rucaparib achieved either CR, PR or SD for more than 12 weeks [202].

Even if BRCA mutations can also occur in endometrial cancers, they are sporadic and not much have been tested concerning these mutations through the use of PARP inhibitors. An aspect of endometrial cancers is their high mutation rates of PTEN (Figure 2B), which also has a phosphatase-independent role in genomic stability and homologous recombination [203]. Considering the repair role of PTEN for double strand break, Olaparib have been tested in endometrial cancers with this protein of interest (PTEN). Preclinical studies have been performed in endometrial cancer cells and one of these demonstrated, using 16 cell lines, that the PARP inhibitor Olaparib was efficient but not necessarily associated with the PTEN status of the cell line [204]. Another pre-clinical trial, however, demonstrated both *in vitro* and *in vivo* that Olaparib was efficient and the effect was related to the PTEN status of endometrial cancer cells [205]. A clinical case has also been done with Olaparib and a 58-year-old woman with metastatic and recurrent endometrial cancer. After treatment with the PARP inhibitor Olaparib, a significant reduction of brain metastases was observed as well as improvement of tumor-associated symptoms. This clinical case report, after a biopsy, also mention the absence of BRCA mutations but a loss of PTEN instead, thus indicating that PTEN status should be considered for administration of PARP inhibitors against gynecological cancers [206]. Considering these preliminary results, endometrial and PARP inhibitors should be further studied.

An important aspect of PARP inhibitors is their low toxicity for patients, a very desirable effect for cancer treatment and possible combination with other chemotherapeutic compounds. In addition, the platinum sensitivity of the patients was a good marker of efficiency when using different PARP inhibitors. Finally, patient who did not have BRCA mutations also had a clinical benefit, indicating that other biomarkers should be studied for PARP inhibitors efficiency, such as the protein PTEN which also has a role in genomic stability and homologous recombination. Further trials are thus required for measuring the efficiency of PARP inhibitors, which currently look like a very promising therapy to use in the context of advanced gynecological cancers.

Nucleotide excision repair (NER)

Nucleotide excision repair (NER) is also involved in the chemoresistance of gynecological cancer and therapies targeting this mechanism are also emerging. ERCC1 is a potential target involved in this repair mechanism and involved in platinum resistance. However no enzymatic activity related to this protein (ERCC1) is known, making it hard to target. Though, novel small molecules have been developed targeting the XPA-ERCC1 complex and thus reestablishing platinum sensitivity [207].

Mismatch repair (MMR)

Mismatch repair deficiency is known for being involved in cancer development as well as chemoresistance, and some research is currently going on to target this mechanism and provoke synthetic lethality, as previously discussed with PARP inhibitors and BRCA genes. The principle of synthetic lethality is based on the loss of two genes (one from the inhibitor and one from mutation) from the same pathway leading to cancer cell death while normal cells only lose one of these (from the inhibitor) and still survive. Potential targets have been identified to be targeted along with MMR deficiency: dihydrofolate reductase (DHFR), DNA polymerase β

(POLβ), DNA polymerase γ (POLγ) and PTEN-induced putative kinase 1 (PINK1), all causing accumulation of oxidative DNA damage when inhibited and combined with MMR deficiency (MSH1-2-6) [208-210]. However, synthetic lethality has not yet been tested in patients with advanced ovarian tumors [211]. Hypermethylation of hMLH1 gene is in part responsible for the MMR deficiency observed in ovarian cancer. Using Decitabine, a demethylating agent, on chemoeresistant/MLH1 silenced ovarian cancer xenografts, an improvement of sensitivity to cisplatin, carboplatin, temozolomide (an alkylating agent), and epirubicin (an anthracycline drug) was observed. Additionally, Decitabine also permitted a re-expression of MLH1 in these ovarian cancer xenografts [212]. Phase I trial has been done with Decitabine combined with carboplatin on 10 patients with recurrent platinum-resistant ovarian cancers. Results were 1 CR and 3 SD for more than 6 months. Noteworthy, HOXA11 and BRCA1 cancer associated genes were demethylated after treatment [213]. The same group is pursuing in a phase II trial with 17 patients with recurrent platinum-resistant ovarian cancer. They found out that Decitabine, followed by carboplatin treatment, allowed efficient demethylation of RASSF1A, HOXA10, HOXA11 and MLH1, which correlated with the progression-free survival of the patients (median of 10.2 months). The response rate obtained was of 35% and half of the patients were free of progression after 6 months [214]. The use of demethylating agent should be considered as a possible treatment to overcome chemoresistance in gynecological cancers presenting MMR deficiency and hypermethylation of genes.

Targeting PI3K/AKT and MAPK

Considering the PI3K/AKT pathway is one of the main pathways involved in tumorigenesis and being highly mutated in gynecological cancers, many drugs have been developed to target various proteins of this pathway and to increase the efficiency of anti-cancer treatment, partly *via* the loss of chemoresistance. First generation PI3K inhibitors, such as Wortmannin and LY294002, were developed and mainly used in promising pre-clinical studies to better understand this pathway and their implication in therapies against gynecological cancer cells. One of these pre-clinical studies demonstrated *in vivo*, using athymic mice bearing ovarian cancer cells, that administration of Wortmannin efficiently sensitized the cancer cells to cisplatin treatment [215]. Yet, because of their poor pharmacokinetics properties, a second generation of inhibitors have been developed being more selective and sometime isoform specific. Among these second-generation PI3K inhibitors, Buparlisib (BKM-120), GDC-0941 and Pilaralisib (XL-147) are pan-class I PI3K inhibitors, which have been tested in few trials for gynecological cancers.

PI3K inhibitors

A previous study involving Buparlisib, in combination with Olaparib (PARP inhibitor), administered *in vivo* in mice with BRCA-1 mutations demonstrated an important synergy, which leads to a phase I trial with 34 women bearing high-grade serous ovarian cancer or triple-negative breast cancer [216, 217]. Among the patients, 26 were known for having BRCA mutations, a biomarker of efficiency for PARP inhibitors. All dose combinations allowed the observation of clinical benefits among the patients being promising for further trials [217]. GDC-041 has been tested in two phases I trial in patients with advanced solid tumors [218, 219]. The first trial was tested with 49 patients and minimal clinical results were observed with only two patients with a PR; one of these was an endocervical tumor with mutations on PIK3CA. CA125 responses were also observed in three patients with ovarian cancer including one with known high PIK3CA gene copy number [218]. The second phase I trial with GDC-0941 had similar results. Among the 42 patients tested, clinical activity was observed only on two patients, including one with a PTEN negative ovarian cancer [219]. Pilaralisib has been used in a phase II study in 67 patients with advanced or recurrent endometrial carcinoma. The ORR was minimal and only two patients had CR and two other patients had PR. No association was made between the molecular alterations of the PI3K pathway (three of these patients had wild-type PTEN with PIK3R1 mutations, one had PTEN mutation) and the clinical activity observed [220]. BYL719 is a PI3KCA isoform specific inhibitor that has been tested in a phase I trial in 36 patients with diverse tumors with PIK3CA mutations. Results were 7 PR (including one from cervical, one from endometrium and one from the ovary) [221].

As introduced, PI3K inhibitors had a considerable success rate in preclinical studies, however, the clinical studies of PI3K inhibitors presented in gynecological cancer were not as successful. The PI3K network is vastly complex and ramified, including feedback loops, alternates signaling cascades and crosstalk, all plausibly explaining the observed ineffectiveness. Inhibition of the PI3K pathway is known for also activating the MAPK pathway *via* crosstalk and dual inhibition with MAPK inhibitors could be considerable. The opposite is also true: inhibiting the MAPK upregulates PI3K/AKT activity [178, 222, 223]. The PI3K inhibitor Buparlisib have been tested in combination with the MEK inhibitor Trametinib in a phase Ib trial with 113 patients with advanced solid tumors, including ovarian cancer. Results among the 21 patients with ovarian cancer were 1 CR, 5 PR and 10 SD for an ORR of 29%. Remarkably, Buparlisib was efficient almost exclusively in ovarian cancer, the exception being a PR observed in a KRAS mutated non-small cell lung Cancer patient. Also noteworthy was the fact that 19 ovarian cancer patients were KRAS mutated demonstrating an efficient way to overcome this aggressive mutation [224].

The PIK3CA isoform inhibitor, BYL719, has been tested in combination with the MEK inhibitor Binimetinib in 58 patients with advanced tumors and mutated with *RAS* or *BRAF.* Four patients with ovarian cancer had KRAS mutation and 3 of these had a PR with the combined treatment. A patient with endometrial cancer and a KRAS mutation also had a PR. Overall, among all patients, 5 had PR and 18 had SD indicating an interesting efficiency for advanced tumors, especially gynecological cancers [225]. This combination is of particular interest for patients with KRAS mutations considering this mutation is often associated with an absence of response when using PI3K/AKT/mTOR inhibitor alone in gynecological cancers [226].

The use of dual-inhibiting PI3K and mTOR is also considered because of the intricate relationship between these complexes. Considering this fact, NVP-BEZ235 has been developed as a molecule capable of inhibiting both PI3K and mTOR. Preclinical studies have been performed in both gynecological cancers using this new inhibitor. One of these demonstrated, *via* 18 ovarian cancer cell lines (cisplatin sensitive and resistant models), sensitization to cisplatin and a correlation of the effect observed with those bearing PI3K-activations mutations or PTEN deletions. They also used a transgenic murine model of ovarian cancer (LSL-*K-ras*$^{G12D/+}$*Pten*$^{loxP/loxP}$) treated with NVP-BEZ235 and observed a longer median of survival as well as apoptotic activity [227]. Another study made similar experiments, but this time using 13 endometrial cancer cell lines (possessing at least one alteration of *PTEN, PIK3CA* or *KRAS) and xenografts in nude mice in vivo. NVP-BEZ235 was efficient to eliminate cancer cells both in vitro and in vivo. Interestingly, cancer cells with PTEN mutations but without KRAS alterations demonstrated a higher sensitivity to NVP-BEZ235 than those with KRAS alterations. Considering these observations, they added a MAPK inhibitor,* PD98059 or U0126, and successfully sensitized the *K-RAS* mutants to NVP-BEZ235, again demonstrating the implication of MAPK in the efficiency of PI3K inhibitors [228].

AKT inhibitors

AKT is a downstream target of PI3K and an important kinase involved in many mechanisms. Considering PI3K is a kinase central to a large network, which entails all the previously stated problematic; targeting AKT, downstream of PI3K, is thus an interesting avenue. AKT specific inhibitors have been developed (MK-2206, Perifosine, AZD5363 and GSK2141795) and pre-clinical trials looked promising [229-235]. Following these, few trials have been done in gynecological cancer patients. MK-2206, an allosteric inhibitor of AKT, has been tested in a phase II trial in 36 women with recurrent endometrial cancer. PIK3CA status was checked on patients; 9 were mutated and 27 were wild-type. Each group only had one patient with a PR, indicating a limited activity of this AKT inhibitor administered as a single agent and independently of the PIK3CA status in endometrial cancer patients [236]. Phase I trial tested Perifosine, another AKT inhibitor, combined with docetaxel in 21 taxane-resistant ovarian cancer patients. One patient (PTEN mutant) had a PR, another patient (PIK3CA mutant) had a SD and two other patients (no PI3K mutations) also had a SD. Noteworthy, patients with KRAS mutations had a rapid progression indicating again a relation with this protein as an indicator of inefficiency for PI3K/AKT inhibitors. Again, the efficiency of this AKT inhibitor was limited and no direct correlation with mutations of the PI3K pathway was made [237]. AZD5363, a novel and potent AKT inhibitor, have been through a phase I trial with 92 patients bearing advanced tumors. Among these patients, only 2 obtained a PR (one endometrioid cancer of the ovary and one cervical cancer with either PIK3CA or AKT1 mutation) and one got a SD (endometrioid cancer of the ovary with PIK3CA mutations) [238]. The results obtained showed that efficiency was, again, minimal. GSK2141795, another AKT inhibitor, have been tested in a phase I trial in 12 patients with recurrent platinum-resistant ovarian cancer. 8 of the 12 patients had a SD while the 4 left had a progressive disease [239]. Another phase I trial tested GSK2141795, but with a large group of 66 patients with advanced tumors. Among these, 12 were endometrial cancer patients and only 2 had a SD (PIK3CA mutant and/or PTEN loss) [240]. Similarly to PI3K inhibitors, GSK2141795 has been tested in combination with GSK1120212, a MEK1/2 inhibitor, in 13 patients with diverse tumors. 3 of the 13 patients had weak tumor regression (2 patients with ovarian cancer and 1 with endometrial cancer). The results were limited here. The study was a dose-escalating trials, which could have an impact on the efficiency observed [241]. Overall, AKT inhibitors clinical activity was also limited when tested on human patients with gynecological cancers in clinical trials.

To better estimate the expected results following chemotherapy regimens and increase the low response rate previously observed when using PI3K/AKT/mTOR inhibitors, biomarkers are a very interesting option. A study including 140 patients (breast, cervical, endometrial, and ovarian cancers) from phase I program treated with PI3K/AKT/mTOR inhibitors, measured different potential biomarkers (PIK3CA, KRAS, NRAS, and BRAF) to see if a correlation was possible with the response rate of patients. PIK3CA mutations were detected in 25 patients and their response rate to PI3K/AKT/mTOR inhibitors was significantly higher (30%) when compared with patients without the mutation (10%) [242]. The PI3K network is large and additional combinations of inhibitors would be necessary to overcome the inefficiency observed. As suggested by previous studies, KRAS mutations seemed to be a good indicator of resistance to PI3K inhibitors

and combination with MAPK inhibitors seemed to be one of the attractive avenues to overcome absence of response. Another interesting avenue could be the use of PARP inhibitors. PI3K inhibition has been associated with the loss of homologous recombination and the addition of a PARP inhibitor could provide synthetic lethality selectively to cancer cells [243]. Indeed, as previously stated, PTEN has a role in homologous recombination and its status is considerable for using PARP inhibitors [203]. All things considered, to overcome the limited benefit of PI3K/AKT/mTOR inhibitors, a better understanding of the patient's mutation status combined with another inhibitor to prevent resistance to treatment would be an appealing avenue to increase the success rate of this targeted therapy.

Targeting mTor

Mammalian target of rapamycin (mTOR) is the catalytic subunit of two distinct complexes, mTORC1 and mTORC2. Both complexes associate with different proteins, thus regulating different substrates and play crucially important roles in protein synthesis, growth and survival. Interestingly, mTORC1 is sensitive to rapamycin while mTORC2 is not. It should be noted that mTOR lies downstream of the PI3K-AKT signaling cascade, a pathway frequently mutated in gynecological cancers and of paramount importance in the control of cell fate [244]. As such, it is a prime target for drug targeting and requires, in our opinion, further investigations.

Temsirolimus, a water-soluble derivative of rapamycin, is a specific mTOR inhibitor which blocks protein synthesis related to survival and tumor growth of cancer cells. Temsirolimus only target mTOR activity in the mTORC1 complex. A phase II trial was done with temsirolimus on 54 patients with recurrent ovarian cancer. Results obtained were modest with 9 patients having a PR [245]. Another study tested temsirolimus on 5 chemoresistant patients with clear cell carcinoma of the ovary. Of the 5 patients, 1 had a PR and another 1 had a stable disease (SD) [246]. Temsirolimus have been tested in combination with bevacizumab, an anti-angiogenesis compound under trial, enrolled with 31 women with recurrent ovarian cancer (17 chemosensitives *versus* 14 chemoresistants). Of the 25 patients evaluable, 3 obtained a PR and 9 had a SD. Interestingly, the 3 PR were from the platinum-resistant group, a desirable effect on advanced and recurrent cancer therapy [247]. Overall, temsirolimus showed only a modest activity on chemoresistant women with ovarian cancer. Concerning endometrial cancer, clinical studies have also been performed. A phase II trial tested temsirolimus alone or in combination with hormonal therapies (a progestin and tamoxifen) on patients with advanced/recurrent endometrial cancer. This study was focused on the fact that the mTOR pathway could be involved in the resistance to hormonal therapy

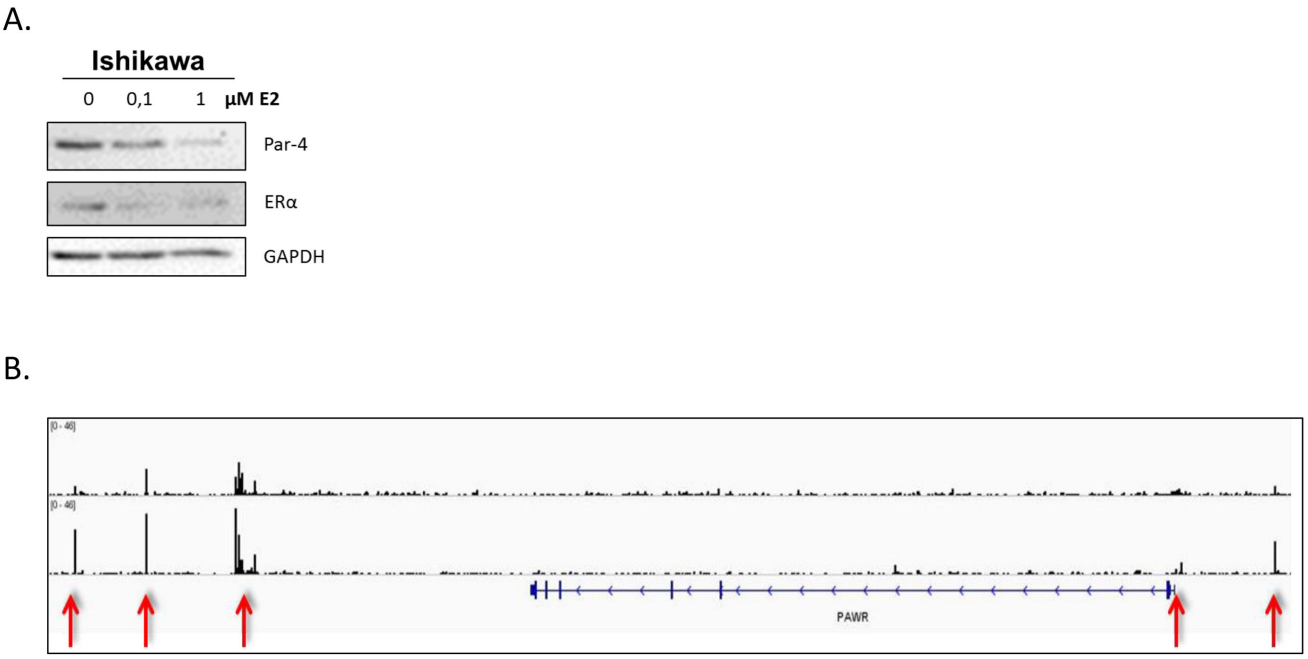

Figure 4 : Estrogen implication in Par-4 regulation. A. Ishikawa cancer cells were treated with either 0,1µM or 1µM estradiol (E2) for 4h. The levels of Par-4 and ERα were determined in treated cells using western blot analysis. GAPDH was used as a loading control. Results shown are representative of three independent experiments. **B.** ChIP-seq tracks showing ERα binding location on PAWR gene (Par-4) in control cells (top lane) and E2 treated cells (bottom lane) for 30 minutes. Genomic locations were obtained using the integrated genomic viewer (IGV 2.0). Red arrows indicate a novel ERα binding enrichment profile in the proximal region of Par-4 gene that can potentially be involved in negative regulation of the gene. Geo accession number: GSE23893.

in endometrial cancers. Temsirolimus alone was tested with 50 patients divided in two groups, 29 with prior chemotherapy and 21 without prior chemotherapy. The response rate was similar between these two groups with an ORR of 22% (24% ORR prior chemotherapy; 19% ORR without prior chemotherapy). This study also concluded that combining megestrol acetate (a steroidal progestin), tamoxifen and temsirolimus did not improve the treatment efficiency and was associated with an increased toxicity [248]. Another phase II trial tested temsirolimus alone in 54 recurrent and metastatic endometrial cancer patients. This study also considered if the patient had previously received chemotherapy, which were distributed in two distinct groups. Of the 29 chemo-naive patients, 4 had a PR and 20 a SD. From the 25 chemo-treated patients, 1 had a PR and 12 a SD. The single agent activity was higher in chemo-naive patients and demonstrated a beneficial effect to arrest cancer progression in both groups. They also checked if PTEN status, related to the regulation of mTOR pathway, was associated with the response rate of temsirolimus and found no association. Therefore, they concluded temsirolimus response was PTEN-independent [249]. Two other phase II trials tested temsirolimus in combination with bevacizumab, an angiogenesis inhibitor, in recurrent endometrial cancers patients. One study had 26 patients and obtained 5 PR and 12 were progression free at 6 months [250]. The second study had 49 patients and obtained 1 CR, 11 PR and 23 were progression free at 6 months [251]. Overall, these studies demonstrated a certain efficiency against recurrent endometrial cancer but also a considerable toxicity when combining both these compounds.

Everolimus (RAD-001) is another mTOR inhibitor with a mechanism similar to rapamycin and selective to mTORC1. A pre-clinical study has been done using 58 transgenic mice with bilateral ovarian serous adenocarcinomas developed accompanied by ascites and peritoneal dissemination. Treating these mice with everolimus alone reduced tumor burden by 84% and ascites and peritoneal dissemination were detected in only 21% of the treated mice *versus* 74% in the placebo-treated animals [252]. They also tested everolimus alone and in combination with cisplatin against ovarian cancer both *in vitro* and *in vivo*. Using ovarian cancer cell lines, they found out that everolimus was efficient for inhibiting cell proliferation and when combined with cisplatin, enhanced apoptosis. They also observed similar findings *in vivo* using xenografts models (inhibition of tumor growth, decrease of ascites and increased treatment efficiency when combined with cisplatin). Noteworthy, everolimus was efficient only in cells with high AKT/mTOR activity [253]. These pre-clinical findings were promising for the treatment of ovarian cancers. In endometrial cancer, phase II trials have been done using everolimus. One of these, tested everolimus in patients with recurrent endometrial cancer that have previously received chemotherapy. After treatment, 6 of the 28 patients had a SD, thus a clinical benefit rate of 22% (CBR; sum of CR, PR and SD) [254]. They also performed another phase II trial testing everolimus in combination with letrozole, an aromatase inhibitor, with 35 patients with advanced endometrial cancer. Using hormonal therapy in combination with everolimus increased the CBR, as well as the addition of CR and PR to the results, to 40% indicating a high benefit, considerable for therapy [255]. Another phase II trial tested everolimus alone in 44 patients with advanced endometrial cancer (2/3 previously received chemotherapy). After 3 months, 36% had a non-progressive disease and after 6 months, 4 patients had a PR [256].

Considering the high level of PTEN mutations in endometrial cancer, many trials tested mTOR inhibitors in this tissue. Results obtained were overall interesting but the combination of an mTOR inhibitor with another drug/compound such as an aromatase inhibitor provided very interesting results and will be necessary for optimal therapies. It is also worth noting that these two compounds inhibiting mTOR (temsirolimus and everolimus) tested in clinics only inhibit the mTORC1 complex. The mTORC2 complex is involved in the phosphorylation of the AKT protein at S473 leading to a full activation of this important kinase from the PI3K/AKT pathway, playing an important role in survival and proliferation [257, 258]. Another important fact concerning mTORC2 complex is that it can also subsequently activate the MAPK survival pathway [258]. An alternative pathway, insensitive to classical mTORC1 inhibition, is thus present and requires further attention to increase the efficiency of treatments.

Targeting EGFR

Considering the high level of mutation/overexpression of EGFR in gynecological cancers, some therapeutics compounds targeting this family of oncogene have been tested in gynecological cancers.

Low molecular weight tyrosine kinase inhibitors Gefitinib (ZD-1839) and Erlotinib (OSI-774) have been developed to inhibit EGFR activity and prevent tumor growth. Gefitinib alone was administered in a phase II trial in 26 women with advanced endometrial cancer and the results obtained were four patients with a PFS of more than 6 months, one had a CR and 7 had a SD [259]. In ovarian cancer, phase II trials also tested gefitinib as a single agent. The results indicated that the inhibitor was able to decrease EGFR and p-EGFR protein levels but had minimal clinical benefits observed when using the agent alone [260, 261]. A phase II study decided to assess Gefitinib effectiveness in combination with tamoxifen with 56 women with ovarian cancer resistant to platinum and taxane therapies. The results were not conclusive because of the inefficacy of the treatment against the resistant cancers; no additional side effects were observed when combining tamoxifen with Gefitinib [262]. A phase

II trial assessed the efficacy of Gefitinib in combination with paclitaxel and carboplatin for both platinum-sensitive and platinum-resistant ovarian, tubal or peritoneal adenocarcinoma patients (total of 68 patients). The results obtained were interesting considering the ORR of 19.2% and 61.9% and the CBR was of 69.2% and 81.0% for resistant and sensitive groups respectively [263]. Phase I/II trial combined Gefitinib with oxaliplatin and vinorelbine (an inhibitor of microtubule assembly) in 33 women with advanced ovarian cancer were divided between platinum-sensitive and resistant groups. The ORR was of 23.8% (3 CR and 2 PR) and 90% (4 CR and 5 PR) in the resistant and sensitive groups respectively [264]. These results show that Gefitinib present high effectiveness only when combined with chemotherapeutic compounds, particularly in chemosensitive cancers.

A phase II trial tested Erlotinib, as a single agent, in 32 women affected by advanced endometrial cancer and the results obtained were 4 PR and 15 SD [265]. Another phase II trial tested Erlotinib as a single agent, but this time in 34 women attained with advanced ovarian cancer. The results were 2 PR and 14 SD, similar to the results observed with endometrial cancers [266]. A phase IB trial tested Erlotinib combined with both carboplatin and docetaxel in 23 women with chemo-naive ovarian cancer. Results obtained were 5 CR and 7 PR giving an ORR of 52% [267]. A phase II study combined Erlotinib with carboplatin for 50 women with advanced ovarian cancer. Results were an ORR 7% (1 PR) for the resistant group *versus* 57% (14 PR) for the sensitive group [268]. Again, this indicates a good clinical efficiency when combined with chemotherapy but most particularly for chemosensitive patients.

Monoclonal antibodies against EGFR have also been developed, Cetuximab (IMC-C225; Erbitux) and matuzumab (EMD-72000). A phase II trial tested matuzumab, as a single agent, in ovarian cancer for 37 patients who previously received platinum treatment and became chemoresistant, demonstrated that the treatment was well tolerated but only led to 7 SD indicating that the clinical activity was limited [269]. Similar results were observed in a phase II trial of cetuximab as monotherapy in ovarian cancer patients with recurrent diseases [270]. Cetuximab combined with carboplatin and paclitaxel have been tested in another phase II trial for 40 women as an initial therapy for advanced ovarian cancer. The therapy was well tolerated, however, the results obtained were not beneficial (no increase of the progression-free survival (PFS) of the patients) [271]. Another phase II trial tested cetuximab combined with carboplatin in 28 patients with platinum sensitive ovarian cancers. Following treatments, 9 patients had an ORR and 8 SD indicating a certain clinical activity of the monoclonal antibody while not being optimal for therapy [272]. The effect of cetuximab seems to be reproducible in endometrial cancer and a pre-clinical study demonstrated that the monoclonal antibody was able to inhibit cell growth and invasion in endometrial Hec-1a cells *in vitro* while being able to inhibit tumor growth, lymph nodes and lung metastasis *in vivo* [273].

Interestingly, these trials demonstrated that inhibiting EGFR in gynecological cancers is well tolerated but the efficiency is low when used alone, thus necessitating a combination with another chemotherapeutic drug. The combination of EGFR inhibitors with another drug was effective in chemosensitive patients while being less effective in chemoresistant patients.

Targeting the estrogen signaling pathway

Two types of treatments have been developed to target the estrogen signaling pathway, aromatase inhibitors and estrogen receptor antagonists.

Aromatase inhibitors

Anastrozole is a potent non-steroidal aromatase inhibitor that had one phase II trial in 23 recurrent endometrial cancer patients. The results were minimal with only 2 PR and 2 SD [274]. A phase II trial was performed using Anastrazole as a single agent in 53 asymptomatic recurrent/persistent ovarian (43), peritoneal (7) and fallopian tube (3) cancer patients. Results were 1 patient with a PR and 68% of these with a SD (42% > 90 days; 15% > 180 days; 7% > 270 days; 4% > 360 days) [275]. The same research group also performed a phase II trial using both Anastrozole and EGFR inhibitor Gefitinib in 35 patients with asymptomatic recurrent/persistent ovarian (30), peritoneal (4) and fallopian tube (1) cancers. 23 patients were evaluable and results were 1 CR and 14 SD, thus having only modest activity [276].

Letrozole is another aromatase inhibitor under study. In a group of 28 patients with recurrent endometrial cancer, but never treated with chemotherapy previously, letrozole was studied as a single agent in a phase II trial. Results obtained were 1 CR, 2 PR and 11 SD indicating a modest antitumoral activity. Interestingly, different markers including the hormone receptors were screened but were not correlated with response to letrozole [277]. Another phase II study tested letrozole in combination with the clinical mTor inhibitor everolimus in 35 women with advanced recurrent endometrial cancer. The results were very interesting with 11 CR, 2 PR and 1 SD [255]. Their previous study using everolimus alone had a CBR of 21% and only SD [254]. The addition of letrozole increased the CBR to 40%, as well as the addition of CR and PR, indicating a benefit when adding this aromatase inhibitor [255]. Letrozole was also tested in 50 ovarian cancer patients in a phase II trial. No CR or PR was attained with tumors and only 10 patients had a SD. Noteworthy, they observed a correlation between the response to letrozole and high estrogen receptor level [278]. Another phase II study tested letrozole in 21 women with recurrent ovarian cancer. Following treatment, the results were 1 CR, 2 PR

and 4 SD, again indicating a modest antitumoral activity. No association was found between hormone receptors and response to letrozole [279]. Another study preselected 33 patients with ovarian cancer, all with the presence of estrogen receptors, and tested letrozole in a phase II trial. Results obtained were 3 PR and 14 SD, indicating that a pre-selection of patients can increase the efficiency of letrozole a little to arrest the progression of the cancer [280]. Finally, a phase II trial tested letrozole, but this time with 31 patients with ovarian cancer both resistant to platinum and taxane therapies. Notably, all patients were positive for estrogen receptors, however, none had a CR, one had a PR and 7 had a SD. These results indicate that chemoresistance has an impact on aromatase inhibitors, especially letrozole here, and their efficiency to stabilize tumor progression [281].

Exemestane is a novel aromatase inhibitor and one trial tested this compound in refractory ovarian cancer patients who previously received platinum and taxane therapies. No CR or PR was obtained with the 24 patients, however, 8 had a SD > 14 weeks [282]. Noteworthy, exemestane had an important effect on the tumor progression as previously observed with other aromatase inhibitors.

Estrogen receptor antagonists

Fulvestrant (Faslodex), is a novel estrogen receptor (ER) antagonist providing increased proteasomal degradation of its target. A phase II trial tested this compound in advanced endometrial cancer with 31 patients (estrogen receptor positive) and 22 patients (estrogen receptor negative). No patients demonstrated a CR or PR in the absence of estrogen receptor while 1 CR and 4 PR was observed in patients expressing the estrogen receptor. The disease was stable in 4 patients in the ER-negative group *versus* 9 in the ER-positive one. Fulvestrant antitumoral activity was absent without the presence of ER and minimal when the target (ER) was present; however the antagonist was efficient for stabilizing tumor growth [283]. Concerning ovarian cancer, a phase II was performed using fulvestrant in 26 women with advanced disease. The results obtained were similar to the ones obtained with endometrial cancer, 1 CR, 1 PR and 9 SD indicating a weak antitumoral activity with great stabilization of tumor growth [284]. The same research group measured the estrogen receptor protein level with tissue microarray (TMA) and correlated the expression measured, positively, with the clinical benefit previously observed [285]. Overall, Fulvestrant is also efficient for stabilizing tumor growth but modest for decreasing tumor size when administered alone.

Arzoxifene is another estrogen receptor antagonist tested for both the mammary and uterine tissues. An interesting aspect of arzoxifene is the lack of uterotrophic effect, a considerable feature for its use in endometrial cancers as compared to tamoxifen. Indeed, phase II trials have been done in patients with advanced or recurrent endometrial cancers and the results were promising. Two of these trials were done with 100 patients from two multi-institutional studies and results obtained were a low toxicity with an ORR of 25% and 31 % respectively [286]. Another trial specifically selected 29 patients with advanced endometrial cancer expressing ER and/or progesterone receptor and not previously treated with chemotherapy. Results obtained were a low toxicity, 1 CR and 8 PR (ORR = 31%) with a median duration of response greater than 13 months [287].

Toremifene is an antiestrogen that had a study using ovarian cancer cell lines *in vitro* and patients with ovarian and uterine cancers *in vivo*. Results *in vitro* demonstrated that toremifene was able to increase significantly the efficiency of doxorubicin on ovarian cancer cell lines; some were initially resistant to doxorubicin. On the 8 patients tested, 3 had PR, 3 had SD but 2 also had a tumor progression [288]. This study is thus promising for the further clinical trials tested with gynecological cancers.

The minimal effect observed in these diverse trials can be partly due to the non-selectivity of patients considering the frequent loss of estrogen receptors in recurrent gynecological cancers. However, the antitumoral effect of these agents seemed minimal but they were able to efficiently stabilize the disease. A combination of a compound from this family targeting the estrogen signaling pathway with a chemotherapeutic drug could increase the efficiency of the treatment. A combination with two targeted pathways could also be an interesting avenue. This was demonstrated in the promising study combining Letrozole with an mTOR inhibitor, which provided astonishing results [289]. Our laboratory previously studied a new chemotherapeutic compound called VP-128, which contained both a steroid portion (E2) and a toxic portion (platinum). Preclinical studies shown that this combination targeting the estrogen receptor was promising and efficient in ovarian cancer. Both *in vitro* and *in vivo* studies demonstrated a significant antitumoral effect against selected tumors expressing the estrogen receptor alpha. The effect was only modest in tumors without the estrogen receptor, similarly to the clinical results observed in trials [290]. Considering these observations, we suggest that screening patients before using therapeutic compounds targeting the estrogen signaling pathway seems to be of paramount importance to insure the combination therapy potency against endometrial and ovarian cancers.

Targeting P53

Another important tumor suppressor involved in chemoresistance mechanisms to consider is P53. Many therapeutic avenues have been studied concerning P53. Another aspect to consider is the high amount of gynecological cancers overexpressing P53, making

this protein an interesting target for therapy [154-156]. However, because of its multiple mechanisms and mutations, high levels of effectiveness are hard to achieve. In gynecological cancers, few trials have been made to test the efficiency of P53 targeting, a protein highly altered in these cancers (Figure 2C).

Gene therapy has been tested with the P53 gene *via* diverse techniques to re-express the functional P53 protein and regain its functions to eliminate tumor cells. P53-SLP is a synthetic peptide-vaccine containing a peptide derived from the middle portion of the P53 protein. The goal of this vaccine is to stimulate the immune system, a known function of P53, to mount a cytotoxic response against tumor cells overexpressing P53. This vaccine (P53-SLP) was tested in a phase II trial with 20 patients with ovarian cancer. Results obtained were 2 SD and 18 patients had a progression of the tumor. Beside the weak clinical benefit, they confirmed that the vaccine was well tolerated and stimulated T-cell responses in patients which was the primary objective of this vaccine [291]. P53-SLP was also tested in a phase II trial with 10 patients with recurrent ovarian cancer, pre-treated with low-dose cyclophosphamide to improve the immunogenicity of the vaccine. They observed a higher number of IFN-γ-producing T cells when compared to their previous study testing P53-SLP alone. However, the clinical results were again minimal with 2 SD and 8 progressive disease [292]. They also tested P53-SLP on 20 patients with advanced ovarian cancer, which also had a secondary chemotherapy following vaccine treatment. The administration of P53-SLP before chemotherapy allowed 2 SD only. Following analyses indicated that the administration of P53-SLP did not enhance the efficiency of chemotherapy treatments, thus was not able to overcome the chemoresistance of advanced ovarian cancer patients [293]. SCH-58500 is another therapy consisting of a genetically engineered adenovirus, unable to replicate and containing the wild-type gene P53. Phase I/II trial have been performed using SCH-58500 combined with platinum-based therapy with 24 patients diagnosed with recurrent ovarian cancer. Results obtained were satisfying considering the success to efficiently re-express P53 in tumors and a decrease higher than 50% CA125 (8/16 of the evaluable patients), an ovarian tumor marker, observed when combining both SCH-58500 with platinum compounds [294]. On the long term, they also observed that patients who only received a single dose of SCH-58500 had a median survival of 5 months *versus* 13 months for those who received multiple doses of SCH-58500 [295]. Overall, the trial of SCH-58500 in combination with platinum compounds tested on recurrent ovarian cancers was promising and more successful than the use of peptides-based approach.

Another promising compound, ONYX-015, is an oncolytic adenovirus that replicates selectively in cancer cells with malfunctioning P53, followed by lysis to eliminate tumors. Indeed, the replication and cytopathogenicity of this adenovirus is blocked by WT-P53 and thus only replicate in mutant P53 tumors [296]. If P53 is responsible for the chemoresistance of cancer cells, these would be eliminated leaving sensitive cells only to be treated with standard chemotherapy. Phase I trial tested ONYX-015 as monotherapy on patients with recurrent ovarian cancer but observed no clinical effect when used alone [297]. No more trials of ONYX-015 have been performed in gynecological cancer but the compound is still promising and has been tested in combination with chemotherapy in other tissues (head, neck and gastrointestinal with metastases) giving excellent results with complete responses and being responsive against chemoresistant patients [298, 299].

MK-1775 is a small molecule inhibitor targeting WEE1, a kinase responsible for inactivating CDC2/Cyclin B complex, involved in the G2 checkpoint for DNA damage. Most cell type presenting mutant-P53 lack the G1 checkpoint for DNA damage. Thus, inactivating the second checkpoint (G2) with a WEE1 inhibitor can sensitize to chemotherapeutic treatments in gynecological cancers [300]. Some trials have been performed using this new inhibitor in combination with chemotherapy in ovarian cancer. Phase I trial combining MK-1775 with carboplatin and paclitaxel with 14 patients sensitive to platinum therapy obtained 11 PR and 3 SD; 7 of these were evaluable by CA125 with 3 CR and 4 PR [301]. A similar trial has been done in a phase II trial with MK-1775 combined with carboplatin and paclitaxel and was tested on 121 women with platinum sensitive ovarian cancer (59 received carboplatin/paclitaxel + MK-1775 while 62 only received carboplatin/paclitaxel). Progression-free survival was greater with the addition of MK-1775 when compared with carboplatin/paclitaxel only group. The overall response rate was of 81% for the group who received the combination of carboplatin/paclitaxel including MK-1775 *versus* an ORR of 74% for patients who received only carboplatin/paclitaxel, indicating an increase of efficiency for treatment *via* the inhibition of WEE1 [302]. Another phase II study tested MK-1775 in combination with carboplatin on 22 patients with recurrent and platinum resistant ovarian cancer. Following treatments, 6 patients had a PR and 9 had a SD. The progression-free survival median was 11 months. Considering that patients were platinum-resistant, results were still interesting [303]. A similar phase II study is currently undergoing and testing MK-1775 in combination with gemcitabine also in recurrent and platinum-resistant ovarian cancer patients [304]. MK-1775 is relatively new and seems promising for the treatment of P53-mutated ovarian cancers. Trials in endometrial cancers could also be of interest considering the high alteration rate of P53 in this tissue.

APR-246 is a small molecule with the ability to restore mutant P53 to its wild-type conformation, allowing the activation apoptotic mechanisms to eliminate cancer

cells. Preclinical studies have demonstrated a high synergetic effect of the molecule in combination with platinum compounds in ovarian cancer models both *in vitro* and *in vivo*. These studies also demonstrated that the addition of APR-246 in combination with standard chemotherapy was able to sensitize ovarian cancer cells and overcome chemoresistance to cisplatin and doxorubicin [305, 306]. A Phase I/II trial is currently undergoing in 160 ovarian cancer patients treated with APR-246 combined with carboplatin and doxorubicin and preliminary results still show positive and similar effects to those observed in pre-clinical trials [307]. In general, P53 targeted therapy is still actively studied and impressive with the diversity of bioengineered compounds targeting this protein. The number of clinical trials studying therapies targeting P53 is limited in gynecological cancers but look promising.

Targeting Par-4

Par-4 is a promising candidate for future clinical trials because of its unique ability to induce apoptosis only and selectively in cancer cells. Using tumor suppressors is an alternative for cancer treatment *via* the use of recombinant proteins or gene therapy to express the gene as previously done with P53. Concerning Par-4, very little experimental data is available concerning therapeutic applications. However, a few *in vivo* experiments are convincing for future clinical studies and development of treatments. A study has demonstrated that the delivery of Par-4 plasmid *via* nanoliposomes to tumors in nude mice increased the efficiency of Fluorouracil, a thymidylate synthase inhibitor, in cancer [308]. Considering that Par-4 can activate apoptotic mechanisms *via* paracrine signaling, recombinant Par-4 has been studied. The effects observed using a recombinant variant of either Par-4 or its SAC (Selective for Apoptosis in Cancer cells) domain was successful in inducing apoptosis in cancer cells *in vitro* [309]. Another team produced recombinant SAC domain of Par-4 derived from plants, in the optic of large-scale production, which also kept its pro-apoptotic capabilities [310]. Considering the SAC domain is sufficient for apoptosis and selective for cancer cells, future compounds or treatments could be designed based on its structure for targeted therapy.

Another option to consider concerning Par-4 targeted therapy is to combine with hormonal therapy. In prostate cancer, a study showed that Par-4 was efficient for inducing apoptosis only in hormone-independent cancer cells, indicating a role for hormone and Par-4 negative regulation [170, 311]. A study, involving 126 patients treated with neoadjuvant chemotherapy, assessed the expression of different genes to observe correlations between these and the outcome of the treatment. Results obtained were very interesting. Par-4 mRNA was upregulated following chemotherapy and Par-4 had a significant impact on prognostic, dependent of the ER status. Indeed, Par-4 level was predictive of a good outcome in ER- patients and the opposite was observed in ER+ patients indicating an important role for hormones and Par-4 [312]. As introduced, few studies demonstrated that estrogen can downregulate Par-4 [177, 178]. To further explore this mechanism of regulation, we used Gene Expression Omnibus (GEO) database and found a study (GSE23893) in uterine cancer tissues showing that ERα binds near Par-4 promoter in its proximal region indicating a potential link with estrogen regulation (Figure 4B). Considering the negative regulation observed with estrogen, we did a chromatin immunoprecipitation assay and found out that ERα binds near Par-4 promoter in its proximal region indicating a potential link with estrogen regulation (Figure 4B). Considering that the ovaries and endometrium are continuously under the influence of hormones and that estrogen exerts such a strong influence on Par-4 transcription, we are allowed to hypothesize that estrogen might play a role in the regulation of Par-4 expression. It is also possible that estrogen regulates Par-4 activity and localization, either through genomic or non-genomic mechanisms, further controlling Par-4 dynamics; estrogen could thus act as a potent carcinogenic agent as well as an inducer of chemoresistance depending on the situation. Combining hormonal therapy with Par-4 is thus a considerable option to acquire an optimal efficiency to induce apoptosis and reduce estrogen-driven growth stimulation. These preliminary findings concerning the estrogen regulation of Par-4 combined with its unique ability to selectively induce apoptosis in cancer cells only are very interesting and should be considered for future studies.

FUTURE DIRECTIONS OF TARGETED THERAPIES

In light of the previous and current clinical trials reported in this review, our initial and primary observation is the modest amount of scrutiny endometrial cancer has been the subject of. Indeed, very few clinical studies have focused on endometrial cancer, probably because of its high survival rate in the case of early diagnosis. However, as introduced, endometrial cancer is very aggressive at advanced stage and the success rate of current therapies is very low. It is our opinion that, based on that fact, more investigations is required to develop novel therapies to improve the prognostic of women afflicted with recurrent endometrial cancer.

The idea of targeted-therapy is to eliminate gynecological cancer cells more selectively and turning-off their chemoresistance mechanisms. However, up to now, no cancer trials have been able to have the desired ‘’perfect’’ response rate *via* targeted therapy. Neither mono targeted-therapy nor combination with current chemotherapy regimen is sufficient to enhance greatly

the survival of patients. As already observed under trials, combination of diverse targeted-therapies is an interesting avenue to overcome the resistance/absence of response seen with mono targeted-therapy. Indeed, many of the pathways and mechanisms discussed can have crosstalk with other pathways, feedback loop regulations in their large network or simply alternative regulation not inhibited by the compounds. For example, MAPK inhibition combined with PI3K inhibition increase significantly the efficiency of these compounds against gynecological cancers. Considering this fact, the most promising trials were those combining two targets such as Everolimus (targeting mTORC1) combined with Letrozole (targeting aromatase) or Buparlisib/BYL719 (compounds targeting PI3K) combined with Trametinib/binimetinib (compounds targeting MEK) [224, 225, 255].

Another avenue to consider for increasing the efficiency of targeted therapies would be to find specific biomarkers correlating with the response to treatment. Indeed, many of these new compounds have not yet, found efficient biomarkers to estimate the success of the treatment, which can also explain the modest clinical activity observed in many of these trials. Using biomarkers would lead to personalized medicine with a large pre-screening of the patients and the diverse mutations located in their tumors, which can be costly for phases II and III trials. This pre-screening, however, would allow to better identify the right combination of targeting compounds and obtain an optimal success rate of treatment.

The heterogeneity between and within tumors also plays a large role in the response rate of targeted treatments and chemoresistance mechanisms. Genomic instability is an important factor related to the heterogeneity of the tumor and, as stated in this review, repair mechanisms are involved in this instability as well as the PI3K network, which is vastly mutated in gynecological cancers [313]. This heterogeneity is reflected on the recurrence of gynecological cancers at advanced stages where only sensitive cells are dying to leave a resistant population, which will eventually come back. Heterogeneity of the tumors is also related to cancer stem cells (CSC). CSC are a small population of the tumor which have the capacities to initiate tumor, self-renew and differentiate to make the bulk of the tumor. They also have the ability to metastasize, an event occurring in advanced stages of cancer. One characteristic of these CSC is that they also play a role in the resurgence of the tumor following chemotherapy, indicating that they also resist chemotherapeutic treatments which is likely associated with a poor prognosis [314, 315]. The presence of chemoresistant and tumorigenic CSC has already been observed in ovarian cancer, however, these are still difficult to identify and target [316-319]. Noteworthy, one of these mechanisms of resistance is also related to AKT, a protein implicated in the PI3K network which is highly mutated in ovarian and endometrial cancers [320]. The biology of CSC is unique and their mechanisms of resistance are diverse. Many trials targeting CSC are currently under study. Considering their important role in tumor, this particular type of cell should be considered when targeting tumors to prevent recurrence and improve success rate.

Overall, considering that heterogeneity is a major hurdle for chemotherapy, targeting multiple pathways/proteins would be useful to overcome a maximum of cancer cells, including stem cells, during treatment. A better understanding of patients' parameters will be profitable for the use of targeted-therapies.

Other elements to consider for efficient targeted-therapy against chemoresistant cancer cells are the fact that not only the modifications occurring inside the cells contribute to the chemoresistance. This manuscript mainly focus on this aspect, however, tumor cell micro-environment and the pharmacokinetic of compounds also play important roles on the acquisition of chemoresistance and should be considered for future therapies [13]. Concerning microenvironment, hypoxia is known for being related to radioresistance and chemoresistance of cancer [321, 322]. Hypoxic cancer cells, frequently located in the center of the solid tumor, have fewer blood vessels and consequently are less exposed to cancer drugs. Hypoxia is also involved in a slower proliferation rate, which affect current chemotherapy targeting cells with rapid division [322]. This microenvironment factor is thus a negative key player for the success of cancer therapies. Noteworthy, cancer stem cells also take advantage of the tumor microenvironment [314]. The immune system also interacts with the microenvironment of tumors as well as the extracellular matrix and signaling molecules from the environment. These microenvironment factors are considered in clinic and therapies targeting angiogenesis, hypoxia, immune system or tyrosine kinase receptors are currently under study [323]. A combination of treatment including these could be positive for the success rate of cancer treatment with other targeted-therapies.

Cancer is a complex disease and still requires research and investigations to better understand it. Current results indicate that mono-targeted therapies are not enough to overcome tumor progression and its resistance to various treatments. However, therapies and molecules are improving and the advance in technology allows a more precise diagnosis of the patients. A better understanding of tumor genetics will allow the administration of an efficient personalized medicine in gynecological cancers.

Abbreviations

CR: Complete response

PR: Partial response (at least 30% reduction of the tumor)

SD: Stable disease (between 30% reduction and

25% increase of the tumor)

PFS: Progression Free Survival
ORR: Objective response rate (CR+PR)
CBR: Clinical benefit rate (CR+PR+SD)
ER: Estrogen receptor
LHRH: Luteinizing hormone-releasing hormone
NER: Nucleotide excision repair
MMR: Mismatch repair
ERE: Estrogen response element
EMT: Epithelial-mesenchymal transition
Pgp: p-Glycoprotein
PARP: Poly-ADP ribose polymerase
DHFR: Dihydrofolate reductase
POLβ: DNA polymerase β
POLγ: DNA polymerase γ
PINK1: PTEN-induced putative kinase 1
TMA: Tissue microarray
E2: Estradiol
CSC: Cancer stem cell

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CONFLICTS OF INTEREST

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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