European Journal of Medicinal Chemistry 142 (2017) 87–94

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Review article

Angiogenesis and cancer stem cells: New perspectives on therapy of ovarian cancer

Anna Markowska [a], Stefan Sajdak [b], Janina Markowska [c], Adam Huczyński [d, *]

[a] Department of Perinatology and Women's Diseases, Karol Marcinkowski Medical University in Poznan, Poland
[b] Department of Gynecological Surgery, Karol Marcinkowski Medical University in Poznan, Poland
[c] Department of Oncology, Karol Marcinkowski Medical University in Poznan, Poland
[d] Faculty of Chemistry, Adam Mickiewicz University, Poznan, Poland

ARTICLE INFO

Article history:
Received 9 April 2017
Received in revised form
14 June 2017
Accepted 16 June 2017
Available online 20 June 2017

Keywords:
Ovarian cancer
Cancer stem cells
Anti-angiogenic therapy
Metformin
Salinomycin

ABSTRACT

Failure in ovarian cancer therapy, following cytoreduction and chemotherapy, is related to the presence of cancer stem cells - a small subpopulation of cells resistant to chemotherapy and irradiation - in the tumour which may cause cancer relapse and manifestation of metastases. Therapies targeted at Cancer Stem Cells (CSCs), such as those employing metformin (a drug used in the treatment of diabetes type II) and salinomycin, an antibiotic isolated from *Streptococcus albus* bacteria, seem promising. Anti-angiogenic therapy with bevacizumab was found to be effective in all phases of ovarian cancer treatment. The presence of CSCs has been associated with angiogenesis. Several CSC biomarkers correlate with the markers of angiogenesis and some signalling pathways, *e.g.* Notch, and are used by both CSCs and by pro-angiogenic factors.

Contents

1. Introduction

Numerous studies indicate that standard treatment with cytostatic drugs linked to anti-angiogenic therapy targeted at cancer stem cells (CSCs) may be effective in the treatment of many malignant tumours, including ovarian cancer. Ovarian cancer is the leading cause of death from among all gynaecological malignant tumours. About 70% of such tumours are diagnosed at advanced clinical stages, the majority reach full remission following cytoreduction and chemotherapy. Nevertheless, in 75–85% of ovarian cancer cases relapses, linked to resistance to the applied therapy and an unfavourable course of the disease, develop within 2 years. 5-year survival is achieved by less than 30% of ovarian cancer patients [1–4]. Identification of molecular mechanisms involved in cancer growth, invasion and metastases has resulted in the introduction of promising targeted therapies. These include anti-angiogenic treatment involving the administration of VEGFR inhibitors like monoclonal antibody Bevacizumab (Avastin) and other agents such as Cediranib, Pazopanib, Nintedanib (Fig. 1), application of PARP enzyme inhibitors in *BRCA1/2* mutations carriers Olaparib

* Corresponding author.
E-mail address: adhucz@amu.edu.pl (A. Huczyński).

http://dx.doi.org/10.1016/j.ejmech.2017.06.030
0223-5234/

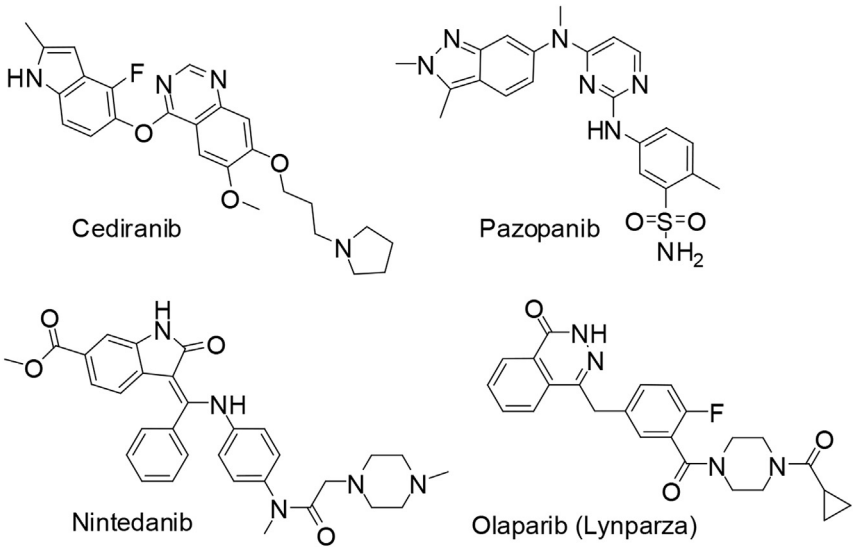

Fig. 1. Chemical structure of cediranib, pazopanib, nintedanib and olaparib.

(Lynparza) (Fig. 1) and attempts to use specific antibodies to block key immunological points PD-1/PD-L1 like Nivolumab (Opdivo) and Pembrolizumab (Keytruda) [5–8].

Recent studies have revealed that the principal cause of cancer relapse and metastases involves cancer stem cells (CSCs), potentially linked to cancer progression through several mechanisms, including the promotion of angiogenesis [9–11].

2. Cancer stem cells (CSCs)

CSCs constitute a small cell subpopulation in the tumour, comprising less than 2–5% of the tumour mass and are resistant to standard treatment with chemotherapy and radiotherapy. In ovarian cancer, the term ovarian cancer initiating cells (OCICs) is also applied. CSCs were isolated for the first time from serous ovarian carcinoma in 2005, in India [12–16].

Resistance to treatment with cytostatic drugs and irradiation reflects the unique properties of CSCs, mainly self-renewal, asymmetric cell division, existence as dormant cells (persisting in the G1 or G0 cell-cycle phase), their ability to differentiate, to repair DNA, to express various genes and their ability to take advantage of certain signalling pathways (including Wnt, Notch and Sonic hedgehog (Shh)) [12,13,17–21].

Studies continue into the identification and isolation of CSC biomarkers. Table 1 shows selected CSC markers found to be typical of ovarian cancer.

Signalling pathways are engaged in the self-renewal of CSCs. According to numerous studies the following are of key importance: Notch, Wnt/βcatenin and Sonic Hedgehog. The activation of Wnt/βcatenin is highly significant in chemoresistance to cisplatin and paclitaxel [12,16,20,21,29].

Studies on CSCs indicate their heterogeneity: according to Tomao et al. [20] and Zeng et al. [26], a specific portrait of CSCs for each type of ovarian cancer as well as also for primary and relapsing cancers may exist, complicating targeted therapy. Attempts to treat ovarian cancer through the eradication of CSCs using metformin, salinomycin, *Clostridium perfringens* enterotoxin (CPE) continue [30–34].

Metformin (Fig.2), an oral biguanide used worldwide in the treatment of type 2 diabetes, has gained significant attention as an anti-cancer drug. Taking into account extensive reports of its *in vitro* and *in vivo* anti-tumour activity, many clinical trials have recently been presented in literature [35,36]. A study by Dilokthornsakul et al. [32] indicated that metformin significantly decreased the incidence of ovarian cancer in type 2 diabetic patients. Thus, metformin has the potential to positively influence prevention and survival of patients with diabetes type 2. A lot of *in vitro* studies support the efficacy of metformin in cancer therapy and prevention. It has been proved that metformin inhibits proliferation and also metastasis and angiogenesis in ovarian tumors *in vivo*. Moreover, metformin treatment increases AMPK activation in the tumor. AMPK inhibits the activity of mTOR in the phosphoinositide 3-kinase/Akt/mTOR signal transduction pathway, which stimulates cellular proliferation. AMPK is also known to inhibit cell cycle progression via the activation of tumor protein p53 [37]. Additional mechanisms of metformin that do not involve AMPK have been also reported. Metformin inhibits cell cycle progression by decreasing the cyclin D1 expression [38] or by

Table 1
Characteristics of selected CSC markers in ovarian cancer.

Cancer Stem Cell Markers	Characteristics	References
CD44+ CD117+(c-kit)	linked to chemoresistance to cisplatin, carboplatin and fluorouracil; it may reflect a high expression of genes resistant to cytostatic drugs in the cells (ABCB1/MDR1) responsible for the ejection of the drug from the cell	[12,17,22–24]
CD133+(promin 1) ALDH1A1	participate in resistance to platine and taxanes	[25–28]
Oct-4 (POU5F1) NANOG BMI1 Nestin	active in self-renewal of CSCs, linked to resistance to cytostatic drugs	[24,26]

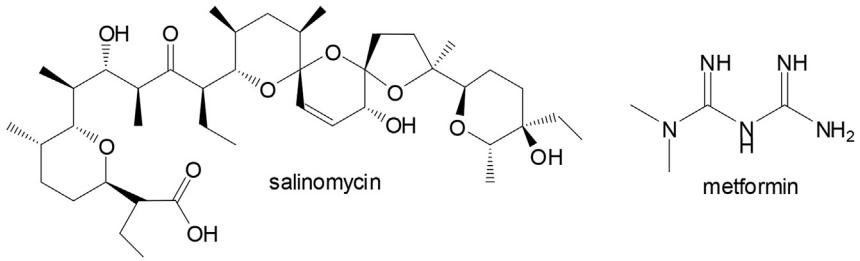

Fig. 2. Chemical structure of salinomycin and metformin.

inhibition of telomerase activity [39]. Gotlieb et al. have reported that metformin is able to inhibit tumor growth and induces apoptosis in OVCAR-3 and OVCAR-4 cells in a dose-dependent manner *in vitro* and that metformin in combination with cisplatin enhanced this pharmacological effect [40].

Although metformin seems to be promising as a cancer chemopreventive or therapeutic drug, the principal issue is whether metformin is also effective in cancer clinical trials for nondiabetics (Table 2) [41].

One of the most important properties of metformin relates to its ability to restrict the growth and proliferation of ovarian cancer stem cells *in vitro* and *in vivo*. The data obtained by Shank et al. demonstrated that metformin can specifically hinder the growth of ovarian CSC. These results provide a rationale for using metformin to treat ovarian cancer patients [42].

Currently, well-conducted controlled clinical trials to confirm the effects of metformin on ovarian cancer survival and ovarian cancer prevention are ongoing. (Table 2).

A new and one of the most potential drug candidates which has prospects of use in anti-CSC therapy is Salinomycin (Fig. 2) - a polyether ionophore isolated from *Streptomyces albus*. Salinomycin has become a subject of international interest since 2009, when Gupta et al. [43] declared that this ionophore is about 100-fold more effective against breast cancer stem cells (CSCs) than paclitaxel, a commonly applied breast cancer chemotherapeutic drug. Gupta et al. have performed tests on about 16 000 biologically active substances, of which only 32 were destroying CSCs studied and the most effective proved to be salinomycin. The use of salinomycin in mice resulted in inhibiting mammary tumour growth *in vivo* and inducing increased epithelial differentiation of tumour cells. Furthermore, salinomycin treatment resulted in the loss of expression of breast CSC genes, previously identified by analyses of breast tissues isolated directly from patients [43].

Major efforts have been undertaken to explain the biological mechanism of the anti-CSC activity of salinomycin. It may prove to be a new therapeutic tool in the treatment of cancer [31]. Since the discovery of unusual anti-tumour activity salinomycin, this compound along with its derivatives have been studied *in vivo* and *in vitro* against different human cancer cells. Salinomycin has shown strong activity against the proliferation of various cancer cells, including those that display multi-drug resistance (MDR), and cancer stem cells (CSCs) [44,45]. Salinomycin has been found to inhibit breast CSC-induced tumoursphere formation, overcome adenosine triphosphate-binding cassette (ABC) transporter-mediated multidrug resistance and apoptosis resistance in human acute myeloid leukaemia stem cells, and target CSCs of hepatocellular carcinoma and brain, pancreatic, lung, and prostate cancer Additionally, the application of salinomycin has been proved to enhance the anti-cancer effect of radio- and chemotherapy. Salinomycin exhibits also significant anti-CSC activity, alone or in combination with cytostatic drugs or tumour targeted drugs, as recently shown *in vitro* and in human xenograft mice [44,45]. Up to now, major efforts have been devoted to elucidate the biological mechanisms of anti-tumour activity of salinomycin and it is expected that the results may provide new therapeutic strategies based on biological modulation of salinomycin activity [46]. Combinatorial treatment of salinomycin and other anticancer drugs such as doxorubicin, gemcitabine, cisplatin, paclitaxel, lapatinib sensitized tumor cells reduced salinomycin toxicity, increased apoptosis and revealed strong synergism [45].

Since then, very extensive research works have been undertaken to explain the extremely effective anti-tumour properties of salinomycin and up to now more than 100 publications describing the remarkable anti-tumour properties of salinomycin have been published [check review articles 44–45].

It has been also proved that salinomycin affects the cell cycle progression in ovarian OVCAR-8 and OV2008 cancer cell lines as well as two MDR ovarian NCI/ADR-RES and DXR cancer cell lines, which are derived from parental cells. OVCAR-8 cells are sensitive to several anti-cancer drugs, but NCI/ADR-RES and DXR exhibit resistance to several drugs [47]. What is interesting, the tests performed on different ovarian cancer cell lines clearly proved that salinomycin causes cell growth inhibition as well as apoptosis in all three cell lines tested *via* downregulation or inactivation of cell cycle-associated oncogenes, such as Stat3, cyclin D1 and Skp2 [48]. Also salinomycin induces the process of apoptosis in cisplatin-resistant colorectal and cisplatin-resistant ovarian cancer cells. This happens by accumulation of ROS as well as inhibition of cell signalling molecules, such as Akt or NF-kB [48]. Furthermore, growth inhibitory effects of salinomycin in the ovarian A2780, A2780-cp, C13, OV2008, OVCAR3 and SKOV3 cancer cell lines, which are associated with the p38 MAPK activation, have been

Table 2
Selected ongoing and currently recruiting participants for clinical trials in all phases of ovarian cancer treatment based on metformin treatment.

Title of clinical trials	ClinicalTrials.gov Identifier:
Study of metformin with carboplatin/paclitaxel chemotherapy in patients with advanced ovarian cancer	NCT02312661
Study of paclitaxel, carboplatin and oral metformin in the treatment of advanced stage ovarian carcinoma	NCT02437812
Evaluation of metformin, targeting cancer stem cells for prevention of relapse in gynaecological patients	NCT01579812
Metformin hydrochloride and combination chemotherapy in treating patients with stage iii-iv ovarian, fallopian tube, or primary peritoneal cancer	NCT02122185

observed in the *in vivo* tests [49] (Table 3).

In recent studies the effect of salinomycin on ovarian cancer stem cells (OCSCs), both alone and in combination with paclitaxel have been evaluated (see Table 3) [50].

All of the above mentioned activities of salinomycin suggest that salinomycin is a new potential drug for effective ovarian cancer treatment approach that can target cancer stem cells. Just three years after the discovery of unusually high anticancer activity of salinomycin, in 2012, salinomycin was approved for testing on humans. The tests were made on a small group of patients with invasive carcinoma of the head, neck, breast and ovary in the screening studies [46]. Patients were administered 200–250 μg/kg of salinomycin intravenously every second day for three weeks. Two cases have been described in literature in details. In both cases the administration of salinomycin resulted in inhibition of disease progress over an extended period of time. Acute side effects were rare and the serious long-term adverse side effects were not observed [46].

The antiproliferative activity of different salinomycin derivatives [51–54] such as, esters, amides, C20-acylated analogs as well as conjugates of salinomycin with other biologically active compounds (*e.g.* conjugate with anticancer drug floxuridine) have been evaluated recently against several cancer lines including MDR phenotype of cancer cells It is worth noting that many derivatives of salinomycin showed less toxicity and stronger anticancer activity against doxorubicin-resistant colon cancer subline LoVo/DX than unmodified salinomycin or exhibited improved activity against CSCs across several assays even at nanomolar concentrations. Thus, the chemical modification of salinomycin structure can also be a very effective way to obtain its new interesting derivatives [51–54].

Clostridium perfringens enterotoxin (CPE) involves Claudins 3 and 4, tight junction proteins in action leading to apoptosis of $CD44^{+}$, which is resistant to paclitaxel and carboplatin [34].

Recent results have also indicated a relationship between CSCs and angiogenesis [9–11].

3. Angiogenesis

Angiogenesis is a multi-stage process of key significance in tumour growth and metastases. Angiogenesis is controlled by several factors: endothelial cells, blood platelets, macrophages/lymphocytes, fibroblasts. The best recognised proangiogenic factor involves the VEGF (vascular endothelial factor) family, composed of five members: VDEGF A to VEGF E, PLGF1 and 2 (platelet factor). VEGF binds to VGFR1 and VEGFR2 receptors, promoting angiogenesis. The binding of all VEGF isoforms to receptors can be blocked by IgG class Bevacizumab - a monoclonal humanized antibody. Bevacizumab (Avastin) has been the best evaluated molecular targeted therapy in the treatment of advanced and recurrent ovarian cancer with proven clinical efficacy (Table 4) [55]. Bevacizumab blocks the development of new blood vessels in the tumour, destroys existing blood vessels and reduces intratumoral pressure, increasing the penetration of cytostatic drugs to the tumour [56–58]. Some trials of Bevacizumab in women with ovarian cancer have shown tumour responses and delayed disease progression. Bevacizumab is applied in all phases of ovarian cancer treatment: in first line therapy, as well as in relapses of platin-sensitive and platin-resistant tumours (Table 4).

Angiogenesis inhibitors of another target point are also used. For example Trebananib - an angiogenic protein, which is a non-VEGF-dependent angiogenesis pathway inhibitor acting through binding to the angiopoietins 1 and 2, to the Tie2 receptor, and thereby inhibiting angiogenesis, provided a clinically meaningful prolongation in progression-free survival. This non-VEGF anti-angiogenesis option for women with recurrent epithelial ovarian cancer has been investigated in combination with additional agents such as paclitaxel [59].

Another targeting anti-angiogenesis agent is also Pazopanib directed at VEGF, PDGF and c-Kit and Cediranib, targeted against VEGFR1-3 [57,58,60,61]. As regards the application of bevacizumab, the results of the GOG 218 trial involving bevacizumab with carboplatin/paclitaxel, and in particular the ICON 7 trial, concerning high-risk group patients with advanced ovarian cancer, modest progression-free survival (PFS) was recorded [62]. In 2013, Rauh-Hain et al. [63] presented a comparative analysis of relapse sites in 292 patients with advanced ovarian cancer (Grade III and IV) treated with bevacizumab or exclusively with cytostatic drugs. The relapses following the treatment with bevacizumab were located

Table 3
Anti-tumour activity of salinomycin against ovarian cancer cells [44,50].

Cancer line	Effect against cancer cells
Ovarian cancer OVCAR-8, OV2008	The viability of OVCAR-8 cell line is reduced to about 53% and 45% after 72 h treatment of 4 μM as well as 8 μM of salinomycin, respectively. IC_{50} of salinomycin on OV2008 cell line for 24, 48 and 72 h treatment is 7.44, 4.78 and 3.20 μM, respectively.
Ovarian epithelial cancer A2780	Salinomycin induces a moderate pro-apoptotic effect on A2780 cells, particularly evident at days 2–3 of culture and at salinomycin dosages of 1–5 μM.
Ovarian epithelial cancer cells (OCC) and ovarian cancer stem cells (OCCs) CD44+, CD117+	CSCs were obtained from the ascitic fluid of patients with epithelial ovarian cancer by using an immune magnetic-activated cell sorting system. OCSCs were treated with paclitaxel (PTX) and salinomycin either singly or in combination. Treatment with salinomycin alone reduced the stemness marker expression and spheroid-forming ability of OCSCs. Treatment with PTX alone did not decrease the viability of OCSCs. Treatment with a combination of salinomycin decreased the viability of OCSCs and promoted cell apoptosis. The enhancement of combination treatment was achieved through the apoptosis. Inhibition of growth of OCCs and OCSCs by PTX (20 nM) combined with salinomycin (0.5 μM) was 58% and 59%, respectively. These findings suggest that salinomycin and PTX could have a synergistic effect for treating ovarian cancer and holds promise as an ovarian cancer treatment approach that can target OCSCs.
Ovarian cancer A2780 DXR NCI/ADR-RES	The viability of DXR and NCI/ADR-RES cell lines is reduced to about 50% after 72 h treatment of 4 μM of salinomycin. The treatment of 8 μM of salinomycin causes reduction of viability of DXR and NCI/ADR-RES cell lines to about 43% and 37%, respectively. On the other hand, the cisplatin-resistant A2780 cell growth is decreased by about 55% in 5 μM of salinomycin.
Ovarian cancer *In vivo* activity against cancer cells tested on mice	Animal experiments were performed on 6-week-old female mice. The two experimental groups were administered salinomycin (5 mg/kg) and 5% ethanol (vehicle), respectively, through intraperitoneal injection every other day for three weeks. The size of the tumour was measured every two days. Compared with the vehicle-treated controls, a significant reduction in the tumour volume was observed in the salinomycin-treated mice. At the end of the test, the tumour volume of salinomycin-treated and the control groups, in the C13 tumour model, was 84.2 ± 30.8 as well as 252.5 ± 63.4 mm^3, respectively.

Table 4
Selected ongoing and currently recruiting participants in clinical trials in all phases of ovarian cancer treatment based on discussed anti-angiogenesis agents.

Compounds	Title of clinical trials	ClinicalTrials.gov Identifier:
Bevacizumab	First line ovarian cancer treatment - cohort study	NCT01832415
	Bevacizumab plus gemcitabine, docetaxel, melphalan, and carboplatin in ovarian cancer patients	NCT00583622
	Bevacizumab and carboplatin for patients with ovarian cancer	NCT00744718
	Bevacizumab and carboplatin for patients with ovarian cancer	NCT00744718
	A study of the addition of avastin (bevacizumab) to carboplatin and paclitaxel therapy in patients with ovarian cancer	NCT01239732
	A study of bevacizumab in ovarian cancer or primary peritoneal cancer where doxil or topotecan therapy has failed	NCT00097019
	Study of bevacizumab/doxil in treatment of platinum-resistant/refractory ovarian cancer	NCT00945139
	Pilot study of taxol, carboplatin, and bevacizumab in advanced stage ovarian carcinoma patients	NCT00127920
Cediranib	A study of cediranib and olaparib at the time ovarian cancer worsens on olaparib	NCT02340611
	Efficacy and safety study of cediranib in combination with olaparib in patients with recurrent platinum-resistant ovarian cancer	NCT02889900
	A study of cediranib and olaparib at disease worsening in ovarian cancer	NCT02681237
	Olaparib ± cediranib or chemotherapy in patients with brca mutated platinum-resistant ovarian cancer	NCT03117933
	Cediranib maleate and olaparib or standard chemotherapy in treating patients with recurrent platinum-resistant or -refractoryovarian, fallopian tube, or primary peritoneal cancer	NCT02502266
Pazopanib	Pazopanib and weekly topotecan in patients recurrent ovarian cancer	NCT01600573
	Phase I/II study of pazopanib and cyclophosphamide in patients with platinum-resistant recurrent ovarian cancer	NCT01238770
	Phase Ib and phase II trial of pazopanib ± fosbretabulin in advanced recurrent ovarian cancer	NCT02055690
	Paclitaxel/pazopanib for platinum resistant/refractory ovarian cancer	NCT02383251
	Clinical trial investigating pazopanib in patients with platinum-resistant advanced ovarian cancer	NCT01262014
	Pazopanib hydrochloride, paclitaxel, and carboplatin in treating patients with refractory or resistant ovarian epithelial cancer, fallopian tube cancer, or peritoneal cancer	NCT01402271
Trebananib	Study of AMG 386 in combination with paclitaxel and carboplatin in subjects with ovarian cancer	NCT01253681
AMG 386	Trinova-1: a study of AMG 386 or placebo, in combination with weekly paclitaxel chemotherapy, as treatment for ovarian cancer, primary peritoneal cancer and fallopian tube cancer	NCT01204749
	A phase 1b study of AMG 386 in combination with either pegylated liposomal doxorubicin or topotecan in subjects with advanced recurrent epithelial ovarian cancer	NCT00770536
	A randomized, double-blind, placebo controlled, phase 2 trial of paclitaxel in combination with AMG 386 in subjects with advanced recurrent epithelial ovarian or primary peritoneal cancer	NCT00479817

significantly more frequently in the pleura and in the lungs and in distant locations, while the relapses following treatment with cytostatic drugs alone were more common in the liver.

According to Robinson et al. [64], from among 233 women carrying grade III disease with relapses, the extraperitoneal metastases (skin, brain, pleura/lung) were detected more frequently in patients primarily treated with intraperitoneal chemotherapy and then with bevacizumab. The scheme of relapses following bevacizumab proved to be more distinct than that in the relapses after treatment with cytostatic drugs alone. Robinson et al. [64] speculated that combinations of intraperitoneal therapy with bevacizumab initiate complex immune alterations in the peritoneal cavity which reduce its properties as the site of cancer relapse. Thus, there is a selection of extraperitoneal sites of relapse, particularly the sites well supplied with blood, such as skin and the central nervous system. .

Bottsford-Miller et al. [62] have reviewed the results of anti-angiogenic agent application. When used to target VEGF, the results of ovarian cancer treatment improved but the cancer cells also manifested resistance to the applied therapy by taking advantage of alternative proangiogenic pathways (*e.g.* Ang1 and Ang2), thus bypassing the effects of anti-angiogenic therapy.

As it has been demonstrated that relapses and metastases of cancer may be dependent on the activity of CSCs, the link between CSCs and angiogenesis seems a promising development in the search for new treatment approaches.

4. CSCs and angiogenesis

The relation between CSCs and angiogenesis has been the focus of numerous studies. Conley et al. [65] and Chau and Figg [66] have advanced a hypothesis that inhibitors of angiogenesis induce hypoxia, which increases tumour growth rate and metastases due to an increase in the CSC population through the activation of the Akt/β catenin pathway. Eyler and Rich [11] have found that CSCs produce higher levels of VEGF in normal or hypoxic conditions than the non-CSC population in the tumour. The increased levels of VEGF lead to the augmented migration of endothelial cells and to the formation of new “pipe” type blood vessels. The administration of bevacizumab *in vivo* inhibited vascular growth and haemorrhages from xenografts stemming from CSCs. CSCs and angiogenesis can have a mutual influence and anti-angiogenic therapy may induce HIF-1α leading to the production of VEGF and an increase in the CSC population. According to Heddleston et al., HIF-1α participates in CSC proliferation and self-renewal [67].

Bao et al. [68] have found that if stem cell-like glioma cells (SCLGC) are supplemented with CSCs carrying the CD133 + marker, the tumour develops a dense vascular supply. VEGF estimated in the CD133 + plus SCLGC complex manifested a ten-fold higher expression and the addition of bevacizumab reduced tumour growth. A similar phenomenon probably develops in cancers of other organs.

According to the review of Zhao et al. [10] the Notch pathway used by CSCs operates in CSCs self-renewal and angiogenesis. Tang et al. [69] have demonstrated that CSCs can differentiate into functional endothelial cells due to the activation of NF- $_{\kappa}$B and the STAT3 signalling pathway promotes angiogenesis of the tumour. Numerous CSC biomarkers show a correlation with angiogenesis markers (VEGF, Ang1 and Ang 2, Tie, VEGF-C, PL-EGF). Furthermore, CSCs were found to manifest expression of VEGFR, which results in their nesting in significant metastatic sites, termed “vascular niches”. VEGFR1+ additionally expresses VLA-4 (termed α4 and β1 integrin), whose ligand fibronectin - promotes the adherence of circulating tumour cells forming a niche of potential properties which are indispensable to the survival of CSCs, i.e. for self-renewal and differentiation and additionally provide a potential site for

cancer metastasis. The application of antibodies to VEGF1 can destroy the vascular niche, partially preventing metastases [6,65,66,68–70]. According to Xiang et al. [71], inflammatory cytokines, components of vascular niches *e.g.* IL-17, can influence self-renewal of CSCs and metastases of cancer [70]. The vascular niche is a complex structure composed of CSCs and the microenvironment as shown in Fig. 3 [72,73].

Cells in the "vascular niche" have been demonstrated to exhibit expression of SDF-1 cytokine, which attracts CXCR4 phenotype tumour cells (Fig. 3), and may again initiate metastasis [20,24].

Moreover, a recent study has demonstrated that combinatorial treatment of mammospheres with trastuzumab (anti- HER2 monoclonal antibody) and salinomycin efficiently targets HER2-positive cancer cells and CSCs [74]. Overexpression of HER2 in human tumour cells is closely associated with increased expression of vascular endothelial growth factor (VEGF) and angiogenesis [75]. Thus, salinomycin can also help to block vascularization (angiogenesis) for productive cancer growth and metastasis.

Very interesting and strong evidence that salinomycin inhibits tumour angiogenesis has been given in a recent publication written by Tao Li and co-workers [76]. In this study salinomycin has been shown to be able to directly act on both tumour endothelial cells and tumour cells and inhibit various aspects of angiogenesis including endothelial cell proliferation, migration and capillary structure formation *in vitro* at relatively low concentrations. Sal significantly inhibited neovascularization *in vivo* in a dose-dependent manner. Detailed evaluation of salinomycin properties has shown that this compound affects the multiple facets of vascular endothelial angiogenic signalling through VEGFR2, *via* prohibiting the binding of ATP at its binding pocket of VEGFR2. The results suggested the possibility that salinomycin exerts its anti-angiogenic effect preferentially *via* VEGFR2 signalling pathway. This interesting paper has also shown that salinomycin suppresses tumour growth and angiogenesis in a human gastric cancer xenograft mouse model. The authors concluded that all performed studies indicate that salinomycin is distinct from the presently used

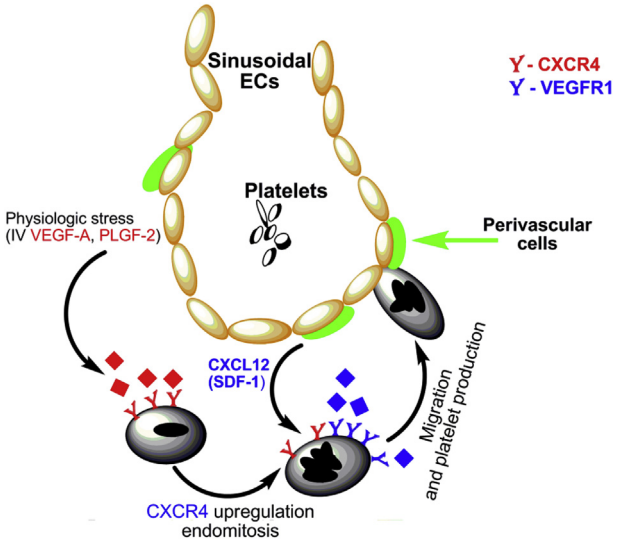

Fig. 3. Vascular niche. Vascular endothelial growth factor (VEGF), one of the major angiogenic factors, promotes the formation of leaky tumour vasculatures that are the hallmarks of tumour progression. CXCR4 induced the expression of VEGF and induced Akt phosphorylation, which resulted in upregulation of VEGF at both mRNA and protein levels. The balance between pro-angiogenic VEGF-A and angio-inhibitory factors (angiostatin, endostatin and tumstatin) shifts to favour the pro-angiogenic way. Targeting VEGF and CXCR4 could provide a potential new anti-angiogenic therapy to suppress the formation of both primary and metastatic tumours.

angiogenesis inhibitors; especially those used in the clinic, and can become a promising anticancer drug candidate [76].

5. Conclusion

Ovarian cancer remains a clinical challenge and there is a need to optimise the currently available treatment and to urgently develop new therapeutic strategies. Several clinical trial data provide strong support for the suggestion that antiangiogenic agents as well as anti CSCs agents have the potential to play a major therapeutic role in this difficult malignancy.

Anti-angiogenetic agents are going to be an alternative to standard chemotherapy in metastatic ovarian cancer patients. The main targets of clinically approved anti-angiogenic drugs are vascular endothelial growth factor VEGFR receptors (exemplary agent is Bevacizumab) but also a non-VEGF-dependent angiogenesis pathway is possible (exemplary agent is Trebananib). These compounds have recently been recognized as useful candidates for clinical studies. They have been found to significantly improve both progression-free and overall survival in different types of cancers.

On the other hand metformin – the first-line drug used for the treatment of type 2 diabetes - is suitable for rapid clinical application in ovarian cancer treatment because it selectively and simultaneously targets CSCs and has relatively high safety and low cost.

It has been proved that the natural compound salinomycin is able to selectively kill CSCs and sensitize tumour cells at a very low concentration over a broad range of CSCs, including ovarian cancer stem cells. Salinomycin sensitized also tumour cells to many currently used anticancer drugs by inhibiting many MDR genes. All of these biological properties of salinomycin make this compound a promising anticancer drug.

Results of the hitherto clinical studies on the combination of anti-angiogenetic agents with anti-CSCs agents together with chemotherapy are very encouraging, even though preliminary. Numerous studies have indicated that traditional treatment with cytostatic drugs or irradiation combined with anti-angiogenic therapy and therapy targeted at CSCs may provide a reasonable and promising option of treatment. We propose here that further clinical studies of anti-angiogenetic agents and anti-CSCs agents in ovarian cancer therapy should start in near future and need to be conducted for evaluating the safety and effectiveness of these promising anticancer drugs.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.ejmech.2017.06.030. These data include MOL files and InChiKeys of the most important compounds described in this article.

References

[1] F. Modugno, R.P. Edwards, Ovarian cancer: prevention, detection, and treatment of the disease and its recurrence. Molecular mechanisms and personalized medicine meeting report, Int. J. Gynecol. Cancer 22 (8) (2012) S45–S57.
[2] C. Gourley, J. Farle, D.M. Provencher, S. Pignata, L. Mileshkin, P. Harter, J. Maenpaa, J.W. Kim, E. Pujaide-Lauraine, R.M. Glasspool, I. Ray-Coquard, D. Gershenson, Gynecologic Cancer InterGroup (GCIG) consensus review for ovarian and primary peritoneal low-grade serous carcinomas, Int. J. Gynecol. Cancer. 24 (2014) S9–S13.
[3] K. Abubaker, A. Latifi, R. Luwor R, S. Nazaretian, H. Zhu, M.A. Quinn, E.W. Thompson, J.K. Findlay, N. Ahmed, Short-term single treatment of chemotherapy results in the enrichment of ovarian cancer stem cell-like cells leading to an increased tumor burden, Mol. Cancer. 12 (2013) 24.
[4] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2016, CA Cancer J. Clin. 66 (1) (2016) 7–30.
[5] J. Lopez, S. Banerjee, S.B. Kaye, New developments in the treatment of ovarian

cancer - future perspectives, Ann. Oncol. 24 (2013) 69–76.
[6] C. Calabrese, H. Poppleton, M. Kocak, T.L. Hogg, C. Fuller, B. Hamner, E.Y. Oh, M.W. Gaber, D. Finklestein, M. Allen, A. Frank, I.T. Bayazitov, S.S. Zakharenko, A. Gajjar, A. Davidoff, R.J. Gilbertson, A perivascular niche for brain tumor stem cells, Cancer Cell 11 (1) (2007) 69–82.
[7] J. McLachlan, A. George, S. Banerjee, The current status of PARP inhibitors in ovarian cancer, Tumori 102 (5) (2016) 433–440.
[8] A. Markowska, S. Sajdak, J. Lubin, J. Markowska, The role of PD-1-a programmed cell death receptor 1-and its ligands in ovarian cancer immunotherapy, Curr. Gynecol. Oncol. 14 (2) (2016) 117–120.
[9] C. Folkins, Y. Shaked, S. Man, T. Tang, C.R. Lee, Z. Zhu, R.M. Hoffman, R.S. Kerbel, Glioma tumor stem-like cells promote tumor angiogenesis and vasculogenesis via vascular endothelial growth factor and stromal-derived factor 1, Cancer Res. 69 (18) (2009) 7243–7251.
[10] Y. Zhao Y, Q. Bao Q, A. Renner, Pr Camaj, M. Eichhorn, I. Ischenko, M. Angele, A. Kleespies, K.W. Jauch, C. Bruns, Cancer stem cells and angiogenesis, Int. J. Dev. Biol. 55 (2011) 477–482.
[11] C.E. Eyler, J.N. Rich, Survival of the Fittest: cancer stem cells in therapeutic resistance and angiogenesis, J. Clin. Oncol. 26 (17) (2008) 2839–2845.
[12] J. Chen, J. Wang, Y. Zhang, D. Chen, C. Yang, C. Kai, X. Wang, F. Shi, J. Dou, Observation of ovarian cancer stem cell behaviour and investigation of potential mechanisms of drug resistance in three-dimensional cell culture, J. Biosci. Bioeng. 118 (2) (2014) 214–222.
[13] M.M. Shah, C.N. Landen, Ovarian cancer stem cells: are they real and why are they important ? Gynecol. Oncol. 132 (2) (2014) 483–489.
[14] J.N. Rich, Cancer stem cells in radiation resistance, Cancer Res. 67 (19) (2007) 8980–8984.
[15] P. Giménez-Bonafé, A. Tortosa, R. Pérez-Tomás, Overcoming drug resistance by enhancing apoptosis of tumor cells, Curr. Cancer Drug Targets. 9 (3) (2009) 320–340.
[16] S.A. Bapat, Human ovarian cancer stem cells, Reproduction 140 (1) (2010) 33–41.
[17] G. Shukla, A.K.R. Srivastava, P. Khare, R. Patidar, R. Saxena, Therapeutic potential, future perspective and challenges of cancer stem cells in translational oncology: a critical review, Curr. Stem. Cell Res. 12 (3) (2017) 207–224.
[18] L.Y. Bourguignon, K. Peyrollier, W. Xia, E. Gilad, Hyaluronan-CD44 interaction activates stem cell marker Nanog, Stat-3-mediated MDR1 gene expression, and ankyrin-regulated multidrug efflux in breast and ovarian tumor cells, J. Biol. Chem. 283 (2008) 1735–1751.
[19] N. Zhou, X. Wu, B. Yang, X. Yang, D. Zhang, G. Qing, Stem cell characteristics of dormant cells and cisplatin-induced effects on the stemness of epithelial ovarian cancer cells, Mol. Med. Rep. 10 (5) (2014) 2495–2504.
[20] F. Tomao, A. Papa, L. Rossi, M. Strudel, P. Vici, G. Lo Russo, S. Tomao, Emerging role of cancer stem cells in the biology and treatment of ovarian cancer: basic knowledge and therapeutic possibilities for an innovative approach, J. Exper. Clin. Cancer Res. 32 (2013) 48.
[21] C. Massard, E. Deutsch, J.C. Soria, Tumour stem cell-targeted treatment: elimination or differentiation, Ann. Oncol. 17 (11) (2006) 1620–1624.
[22] F. Casagrande, E. Cocco, S. Bellone, C.E. Richter, M. Bellone, P. Todeschini, E. Siegel, J. Varughese, D. Arin-Silasi, M. Azodi, T.J. Rutherford, S. Pecorelli, P.E. Schwartz, A.D. Santin, Eradication of chemotherapy-resistant CD44+ human ovarian cancer stem cells in mice by intraperitoneal administration of Clostridium perfringens enterotoxin, Cancer 117 (24) (2011) 5519–5528.
[23] T. Kolonisch, E. Wiechec E, S. Hombach-Klonisch, S.R. Ande, S. Wessleborg, K. Shulze-Osthoff, M. Los, Cancer stem cell markers in common cancers - therapeutic implications, Trends Mol. Med. 14 (10) (2008) 450–460.
[24] L. Luo, J. Zeng, B. Liang, Z. Zhao, L. Sun, D. Cao, J. Yang, K. Shen, Ovarian Cancer Cells with the Cd117 phenotype are highly tumorigenic and are related to chemotherapy outcome, Exp. Mol. Pathol. 91 (2011) 596–602.
[25] V. Craveiro, Y. Yang-Hartwich, J.C. Holmberg, W.D. Joo, N.J. Sumi, J. Pizzonia, B. Griffin, S.K. Gill, D.A. Silasi, M. Azodi, T. Rutherford, A.B. Alvero, G. Mor, Phenotypic modifications in ovarian cancer stem cells following Paclitaxel treatment, Cancer Med. 2 (6) (2013) 751–762.
[26] J. Zeng, J. Ruan, L. Luo, J. Shi, Q. Cui, J. Yang, K. Shen, Molecular portraits of heterogeneity related to cancer stem cells in human ovarian cancer, Int. J. Gynecol. Cancer. 24 (1) (2014) 29–35.
[27] J. Liao, F. Qian F, N. Tchabo, P. Mhawech-Fauceglia, A. Beck, Z. Qian, X. Wang, W.J. Huss, S.B. Lele, C.D. Morrison, K. Odunsi, Ovarian cancer spheroid cells with stem cell-like properties contribute to tumor generation, metastasis and chemotherapy resistance through hypoxia-resistant metabolism, PLoS One 9 (1) (2014) e84941.
[28] I.A. Silva, S. Bai, K. McLean, K. Yang, K. Griffith, D. Thomas, C. Ginestier, C. Johnston, A. Kueck, R.K. Reynolds, M.S. Wicha, R.J. Buchanovich, Aldehyde dehydrogenase in combination with CD133 defines angiogenic ovarian cancer stem cells that portend poor patient survival, Cancer Res. 71 (11) (2011) 3991–4001.
[29] M.F. Clarke, J.E. Dick, P.B. Dirks PB, C.J. Eaves, C.H. Jamieson, D.L. Jones, J. Visader, I.L. Weissman, G.M. Wahl, Cancer stem cells-perspectives on current status and future directions: AACR Workshop on cancer stem cells, Cancer Res. 66 (19) (2006) 9339–9344.
[30] B. Zhang, X. Wang, F. Cai, W. Chen, U. Loesch, X.Y. Zhong, Antitumor properties of salinomycin on cisplatin-resistant human ovarian cancer cells in vitro and in vivo: involvement of p38 MAPK activation, Oncol. Rep. 29 (4) (2013) 1371–1378.
[31] C. Naujokat, R. Steinhart, Salinomycin as a drug for targeting, J. Biomed. Biotechnol. 2012 (2012) 950658.
[32] P. Dilokthornsakul, N. Chaiyakunapruk, W. Termrungruanglert, The effects of metformin on ovarian cancer: a systematic review, Int. J. Gynecol. Cancer. 23 (9) (2013) 1544–1551.
[33] S. Kumar, A. Meuter, P. Thapa, C. Langstraat, S. Giri, J. Chien, R. Rattan, W. Cliby, V. Shridhar, Metformin intake is associated with better survival in ovarian cancer: a case control study, Cancer 119 (3) (2013) 555–562.
[34] Y. Hashimoto, K. Yagi, M. Kondoh, Roles of the first-generation claudin binder, Clostridium perfringens enterotoxin, in the diagnosis and claudin-targeted treatment of epithelium-derived cancers, Pflugers Arch. 469 (1) (2017) 45–53.
[35] H. Irie, K. Banno, M. Yanokura, M. Iida, M. Adachi, K. Nakamura, K. Umene, Y. Nogami, K. Masuda, Y. Kabayashi, E. Tominage, D. Aoki, Metformin: a candidate for treatment of gynecological tumours based on drug repositioning, Oncol. Lett. 11 (2) (2016) 1287–1293.
[36] H. Noto H, A. Goto, T. Tsujimoto, M. Noda, Cancer risk in diabetic patients treated with metformin: a systematic review and meta-analysis, PloS One 7 (3) (2012) e 33411.
[37] R. Rattan, R.P. Graham, J.L. Maguire, S. Giri, V.Shridhar, metformin suppresses ovarian cancer growth and metastasis with enhancement of cisplatin cytotoxicity *in vivo*, Neoplasia 13 (5) (2011) 483–491.
[38] B.I. Sahra, K. Laurent, A. Loubat, S. Giorgetti-Peraldi, P. Colosetti, P. Auberger, J.F. Tanti, Y. Le Marchand-Brustel, F. Bost, The antidiabetic drug metformin exerts an antitumoral effect *in vitro* and *in vivo* through a decrease of cyclin D1 level, Oncogene 27 (2008) 3576–3586.
[39] L.A. Cantrell, C. Zhou, A. Mendivil, K.M. Malloy, P.A. Gehrig, V.L. Bae-Jump, Metformin is a potent inhibitor of endometrial cancer cell proliferation - implications for a novel treatment strategy, Gynecol. Oncol. 116 (2010) 92–98.
[40] W.H. Gotlieb, J. Saumet, M.C. Beauchamp, J. Gu, S. Lau, M.N. Pollak, I. Bruchim, *In vitro* metformin anti-neoplastic activity in epithelial ovarian cancer, Gynecol. Oncol. 110 (2008) 246–250.
[41] N. Provinciali, M. Lazzeroni, M. Cazzaniga, F. Gorlero, B.K. Dunn, A. DeCensi, Metformin: risk-benefit profile with a focus on cancer, Expert Opin, Drug Saf. 14 (10) (2015) 1573–1585.
[42] J.J. Shank, K. Yang, J. Ghannam, L. Cabrera, C.J. Johnston, R.K. Reynolds, R.J. Buckanovich, Metformin targets ovarian cancer stem cells in vitro and in vivo, Gynec. Oncol. 127 (2) (2012) 390–397.
[43] P.B. Gupta, T. Onder, G. Jiang, K. Tao, C. Kuperwasser, R.A. Weinberg, E.S. Lander, Identification of selective inhibitors of cancer stem cells by high-throughput screening, Cell 138 (4) (2009) 645–659.
[44] M. Antoszczak, A. Huczyński, Anticancer activity of polyether ionophore-salinomycin, Anticancer. Agents Med. Chem. 15 (5) (2015) 575–591.
[45] J. Dewangan, S. Srivastava, S.K. Rath, Salinomycin: a new paradigm in cancer therapy, Tumor Biol. 39 (3) (2017) 1–12.
[46] C. Naujokat, S. Laufer, Targeting cancer stem cells with defined compounds and drugs, J. Cancer Res. Updat. 2 (2013) 36–67.
[47] B. Zhang, X. Wang, F. Cai, W. Chen, U. Loesch, J. Bitzer, X.Y. Zhong, Effects of salinomycin on human ovarian cancer cell line OV2008 are associated with modulating p38 MAPK, Tumour Biol. 33 (6) (2012) 1855–1862.
[48] B. Parajuli, H.-G. Lee, S.-H. Kwon, S.-D. Cha, S.-J. Shin, G.-H. Lee, I. Bae, C.-H. Cho, Salinomycin inhibits Akt/NF-κB and induces apoptosis in cisplatin resistant ovarian cancer cells, Cancer Epidemiol. 37 (4) (2013) 512–517.
[49] B. Zhang, X. Wang, F. Cai, W. Chen, U. Loesch, X.Y. Zhong, Antitumor properties of salinomycin on cisplatin-resistant human ovarian cancer cells in vitro and in vivo: involvement of p38 MAPK activation, Oncol. Rep. 29 (4) (2013) 1371–1378.
[50] H.G. Lee, S.J. Shin, H.W. Chung, S.H. Kwon, S.D. Cha, J.E. Lee, C.H. Cho, Salinomycin reduces stemness and induces apoptosis on human ovarian cancer stem cell, J. Gynecol. Oncol. 28 (2) (2017) e14.
[51] X. Huang, B. Borgström, S. Kempengren, L. Persson, C. Hegardt, D. Strand, Breast cancer stem cell selectivity of synthetic nanomolar-active salinomycin analogs, BMC Cancer 16 (2016) 145.
[52] A. Huczyński, M. Antoszczak, N. Kleczewska, M. Lewandowska, E. Maj, J. Stefańska, J. Wietrzyk, J. Janczak, L. Celewicz, Synthesis and biological activity of salinomycin conjugates with floxuridine, Eur. J. Med. Chem. 93 (2015) 33–41.
[53] M. Antoszczak, K. Popiel, J. Stefańska, J. Wietrzyk, E. Maj, J. Janczak, G. Michalska, B. Brzezinski, A. Huczyński, Synthesis, cytotoxicity and antibacterial activity of new esters of polyether antibiotic – salinomycin, Eur. J. Med. Chem. 76 (2014) 435–444.
[54] T.T. Mai, A. Hamaï, A. Hienzsch, T. Cañeque, S. Müller, J. Wicinski, O. Cabaud, C. Leroy, A. David, V. Acevedo, A. Ryo, C. Ginestier, D. Birnbaum, E. Charafe-Jauffret, P. Codogno, M. Mehrpour, R. Rodriguez, Salinomycin kills cancer stem cells by sequestering iron in lysosomes, Nat. Chem. (2017), http://dx.doi.org/10.1038/nchem.2778.
[55] F. Tomao, A. Papa, L. Rossi, D. Caruso, P.B. Panici, M. Venezia, S. Tomao, Current status of bevacizumab in advanced ovarian cancer, OncoTargets Ther. 6 (2013) 889–899.
[56] R. Burger, Overview of anti-angiogenic agents in development for ovarian cancer, Gynecol. Oncol. 121 (1) (2011) 230–238.
[57] A. Reinthaller, Antiangiogenic therapies in ovarian cancer, Memo 9 (3) (2016) 139–143.
[58] B.J. Monk, L.E. Minion, R.L. Coleman, Antiangiogenic agents in ovarian cancer: past, present, and future, Ann. Oncol. 27 (suppl_1) (2016) i33–i39.
[59] B.J. Monk, Anti-angiopoietin therapy with trebananib for recurrent ovarian

cancer (TRINOVA-1): a randomised, multicentre, double-blind, placebo-controlled phase 3 trial, Lancet Oncol. 15 (8) (2014) 799–808.
[60] C. Dinkic, M. Eichbaum, M. Schmidt, E.M. Grischke, G. Gebauer, H.C. Fricke, F. Lenz, M. Wallwiener, F. Marme, A. Schneeweiss, C. Sohn, J. Rom, Pazopanib (GW786034) and cyclophosphamide in patients with platinum-resistant, recurrent, pre-treated ovarian cancer - results of the PACOVAR-trial, Gynecol. Oncol. (2017), http://dx.doi.org/10.1016/j.ygyno.2017.05.013.
[61] J.M. Lee, A. Cimino-Mathews, C.J. Peer, A. Zimmer, S. Lipkowitz, C.M. Annunziata, L. Cao, M.I. Harrell, E.M. Swisher, N. Houston, D.A. Botesteanu, J.M. Taube, E. Thompson, A. Ogurtsova, H. Xu, J. Nguyen, T.W. Ho, W.D. Figg, E.C. Kohn, Safety and clinical activity of the programmed death-ligand 1 inhibitor durvalumab in combination with poly (ADP-Ribose) polymerase inhibitor olaparib or vascular endothelial growth factor receptor 1-3 inhibitor cediranib in Women's cancers: a dose-escalation, phase I study, J. Clin. Oncol. (2017), http://dx.doi.org/10.1200/JCO.2016.72.1340.
[62] J.N. Bottsford-Miller, R.L. Coleman, A.K. Sood, Resistance and escape from antiangiogenesis therapy: clinical implications and future strategies, J. Clin. Oncol. 30 (32) (2012) 4026–4034.
[63] J.A. Rauh-Hain, S.H. Guseh, K.M. Esselen, W.B. Growdon, J.O. Schorge, N.S. Horowitz, C.N. Krasner, M.G. del Carmen, M.J. Birrer, D.S. Dizon, Patterns of recurrence in patients treated with Bevacizumab in the primary treatment of advanced epithelial ovarian cancer, Int. J. Gynecol. Cancer 23 (7) (2013) 1219–1225.
[64] W.R. Robinson, J. Beyer, S. Griffin, P. Kanjanavaikoon, Extraperitoneal metastases from recurrent ovarian cancer, Int. J. Gynecol. Cancer 22 (1) (2012) 43–46.
[65] S.J. Conley, E. Gheordunescu, P. Kakarala, Antiangiogenic agents increase breast cancer stem cells via the generation of tumor hypoxia, Proc. Natl. Acad. Sci. U. S. A. 109 (8) (2012) 2784–2789.
[66] C.H. Chau, W.D. Figg, Angiogenesis inhibitors increase tumor stem cells, Cancer Biol. Ther. 13 (8) (2012) 586–587.
[67] J.M. Heddleston, Z. Li, J.D. Lathia, Hypoxia inducible factors in cancer stem cells, Br. J. Cancer 102 (2010) 189–195.
[68] S.D. Bao, Q. Wu, S. Sathornsumetee, Hao, Z. Li, A.B. Hjelmeland, Q. Shi, R.E. McLendon, D.D. Bigner, J.N. Rich, Stem cell-like glioma cells promote tumor angiogenesis through vascular endothelial growth factor, Cancer Res. 66 (16) (2006) 7843–7848.
[69] S. Tang, T. Xiang, S. Huang, J. Zhou, Z. Wang, R. Xie, H. Long, B. Zhu, Ovarian cancer stem-like cells differentiate into endothelial cells and participate in tumour angiogenesis through autocrine CCL5 signalling, Cancer Lett. 376 (1) (2016) 137–147.
[70] R.N. Kaplan, R.D. Riba, S. Zacharoulis, A.H. Bramley, L. Vincent, C. Costa, D.D. MacDonald, D.K. Jin, K. Shido, S.A. Kerns, Z. Zhu, D. Hicklin, Y. Wu, J.L. Port, N. Altorki, E.R. Port, D. Ruggero, S.V. Shmelkov, K.K. Jensen, S. Rafii, D. Lyden, VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche, Nature 438 (7069) (2005) 820–827.
[71] T. Xiang, H. Long, L. He, X. Han, K. Lin, Z. Liang, W. Zhuo, R. Xie, B. Zhu, Interleukin 17 produced by tumor microenvironment promotes self-renewal of CD133+ cancer stem-like cells in ovarian cancer, Oncogene 34 (2) (2015) 165–176.
[72] N. Takakura, Formation and regulation of the cancer stem cell niche, Cancer Sci. 103 (7) (2012) 1177–1181.
[73] A. Carnero A, M. Lleonart, The hypoxic microenvironment: a determinant of cancer stem cell evolution, Bioessays 38 (Suppl 1) (2016) S65–S74.
[74] P.S. Oak, F. Kopp, C. Thakur, J.W. Ellwart, U.R. Rapp, A. Ullrich, E. Wagner, P. Knyazev, A. Roidl, Combinatorial treatment of mammospheres with trastuzumab and salinomycin efficiently targets HER2-positive cancer cells and cancer stem cells, Int. J. Cancer 131 (12) (2012) 2808–2819.
[75] R.S. Alameddine, Z.K. Otrock, A. Awada, A. Shamseddine, Crosstalk between HER2 signaling and angiogenesis in breast cancer: molecular basis, clinical applications and challenges, Curr. Opin. Oncol. 25 (2013) 313–324.
[76] T. Li, X. Liu, Q. Shen, W. Yang, Z. Huo, Q. Liu, H. Jiao, J. Chen, Salinomycin exerts anti-angiogenic and anti-t umorigenic activities by inhibiting vascular-endothelial growth factor receptor 2-mediated angiogenesis, Oncotarget 7 (18) (2016) 26580–26592.