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REVIEW – CLINICAL ONCOLOGY

Preclinical rationale and clinical efficacy of antiangiogenic therapy and immune checkpoint blockade combination therapy in urogenital tumors

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Abstract

Purpose In recent years, immune checkpoint blockade (ICB) therapies have shown good clinical responses in various solid cancers. However, a major challenge in the process of ICB treatment is when tumors do not have enough infiltrating T cells. Antiangiogenic drugs targeting vascular endothelial growth factor (VEGF) and its receptors have been approved for the treatment of various malignant solid tumors alone or in combination with other therapies. Our review mainly discusses the preclinical rationale and clinical efficacy of antiangiogenic and ICB combination therapy in urogenital tumors.

Methods We reviewed relevant literature on preclinical research and clinical trial results regarding antiangiogenic and ICB combination therapy in urogenital tumors from PubMed. In addition, we searched ongoing clinical trials on ClinicalTrials.gov to collect information related to this specific topic.

Results Antiangiogenesis therapy could enhance T cell recruitment and increase T cell infiltration into the tumor microenvironment by blocking VEGF–VEGF receptor 2 binding and downstream signaling pathways to normalize tumor blood vessels. The combination of ICB and antiangiogenesis therapy could improve antitumor activity according to subsequent preclinical experiments and several phase I/II/III clinical trials on urogenital tumors.

Conclusion Combined therapy has shown some antitumor efficacy in several urogenital tumors, such as metastatic renal cell carcinoma, metastatic urothelial and genitourinary tumors, endometrial carcinoma, ovarian cancer, and fallopian tube cancer. Combination therapy is a promising strategy that can be used to improve the therapeutic efficacy, and the identification of precise biomarkers of this combined therapy is the direction of future studies.

Keywords PD-1 · PD-L1 · VEGF · T cell infiltration · Tumor blood vessel · Urogenital tumor

Introduction

In recent years, immune checkpoint blockade (ICB) therapies have shown durable clinical responses in various solid cancers since first used in the treatment of melanoma (Nowak 2013; Phan et al. 2003). Since Dr. Judah Folkman first proposed the concept that malignant tumors need pathological angiogenesis to support growth (Folkman et al. 1971), angiogenesis now has been recognized as one of the essential processes for tumors to proliferate and a feature of malignant tumors (Hanahan and Weinberg 2000). Pharmacological studies of antiangiogenesis are endlessly emerging. Since 2004, at least ten anti-vascular endothelial growth factor (VEGF) or anti-vascular endothelial growth factor receptor (VEGFR) drugs have been approved for the treatment of multiple malignant tumors (Jain 2014).

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Renal cell carcinoma (RCC) is a kind of hypervascularized tumor. Previous studies have proven that a mutation in or inactivation of the von Hippel–Lindau (VHL) tumor suppressor gene is related to the development and progression of clear cell RCC, the most major histologic subtype of RCC (Cancer Genome Atlas Research 2013; Gnarra et al. 1994; Latif et al. 1993). Mutations in the VHL gene have a certain influence on the upregulation of VEGF and the expression of other angiogenesis-related factors (Linehan et al. 2007). Based on this mechanism, VEGF-targeted agents such as sunitinib and pazopanib are considered first-line treatments for metastatic RCC (Escudier et al. 2016; Ljungberg et al. 2015). Nivolumab combined with ipilimumab therapy is recommended as a first-line treatment option for patients with International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate- or poor-risk advanced RCC (Checkmate 214) (Escudier et al. 2016). Pembrolizumab, a programmed cell death protein 1 (PD-1) inhibitor, is approved for patients with metastatic urothelial cancer as a second-line treatment [objective response rate (ORR) 21%] (Bellmunt et al. 2017) and for patients with cisplatin-ineligible advanced urothelial cancer as a first-line treatment (ORR 29%) (Vuky 2018). It has been demonstrated that lenvatinib can reverse the immunosuppressive environment and improve resistance to immune checkpoint blockade. Antiangiogenesis agents are also active in gynecologic cancers. Cediranib (a kind of VEGFR1-3 tyrosine kinase inhibitor) and bevacizumab (a VEGF antibody) improve the progression-free survival (PFS) of ovarian cancer patients in both front-line and recurrent settings (Garcia and Singh 2013; Ivy et al. 2016). High programmed cell death ligand 1 (PD-L1) expression is related to a poor prognosis in patients with ovarian cancer, and PD-L1 expression is inversely proportional to the number of intratumoral CD8+ T cells (Hamanishi et al. 2007). However, recent phase I/II clinical trials have suggested that PD-1/PD-L1 inhibitors have limited efficacy as a monotherapy in recurrent ovarian cancer and the need for a rational treatment combination (Bourla and Zamarin 2016).

The concept of combined immune checkpoint blockade (ICB) and antiangiogenesis therapy was confirmed by preliminary results from several phase I/II clinical trials (Hodi et al. 2014; Motzer et al. 2019; Xu et al. 2019), and multiple phase III clinical trials in different solid tumors are ongoing. Our review mainly discusses the preclinical rationale and clinical efficacy of antiangiogenic and ICB combination therapy in urogenital tumors, including metastatic RCC, metastatic urothelial and genitourinary tumors and gynecologic cancers.

Immune checkpoint blockade

Immune checkpoint blockade (ICB) includes three major antibody types: cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody, PD-1 antibody and PD-L1 antibody (Lipson and Drake 2011; Long et al. 2017; Topalian et al. 2012; Wang et al. 2017).

Antibodies targeting CTLA-4 are thought to reverse immune suppression by strengthening tumor antigen recognition and the antitumor immunity of CD8+ T cells (Grosso and Jure-Kunkel 2013). In 2010, the Food and Drug Administration (FDA) approved ipilimumab, the first immune checkpoint inhibitor for patients with melanoma (Hodi et al. 2010). At present, five PD-1/PD-L1 antibodies (anti-PD-1: nivolumab and pembrolizumab; anti-PD-L1: atezolizumab, durvalumab and avelumab) have been approved by the FDA for different tumor types (Ribas and Wolchok 2018; Wei et al. 2018).

Unlike many antibodies that target tumor cells directly, immune checkpoint inhibitors target receptors or their ligands on immunocytes to enhance endogenous antitumor activity. Concerning this point, there is a major challenge in immunotherapy if when tumors do not have enough infiltrating T cells.

Antiangiogenic therapy

To date, over 40 molecules are thought to be related to tumor angiogenesis, but VEGF is overexpressed in most solid tumors, and its receptor (VEGFR) has been thoroughly studied and determined to play a critical role in the process of tumor angiogenesis (Ferrara 2002; Ferrara et al. 2003; Jayson et al. 2016).

Three main types of antiangiogenic drugs at present targeting VEGF and its receptor have been approved for the treatment of various malignant solid tumors alone or in combination with other therapies: anti-VEGF agents, VEGFR monoclonal antibodies and VEGFR tyrosine kinase inhibitors (TKIs) (Jain 2014). Bevacizumab was the first VEGF monoclonal antibody designed and developed by Dr. Napoleone Ferrara to block VEGF-A (Ferrara et al. 2005; Ferrara and Kerbel 2005). The VEGFR monoclonal antibody, which is mainly referred to as ramucirumab, targets VEGFR-2 and has been proven to prolong patient survival in several solid tumors (Fuchs et al. 2014; Garon et al. 2014; Wilke et al. 2014). Multiple VEGFR-TKIs, including lenvatinib, sorafenib, cabozantinib, apatinib, pazopanib, sunitinib, axitinib, nintedanib and vandetanib, block nutrients and the oxygen supply of tumors by inhibiting VEGFR and its downstream targets. Increased overall

survival (OS) or PFS have been observed in multiple phase III clinical trials on various solid tumors (Bible et al. 2010; Brose et al. 2014; Bruix et al. 2017; Cheng et al. 2009; Choueiri et al. 2015; Demetri et al. 2013; Elisei et al. 2013; George et al. 2012; Grothey et al. 2013; Kurzrock et al. 2011; Motzer et al. 2014, 2015b; Rini et al. 2011; Wells et al. 2012).

Preclinical rationale for combined immune checkpoint blockade and antiangiogenic therapy

Anti-CTLA-4 enhances T cell activation (Fig. 1)

Naïve T cells become activated when they recognize the major histocompatibility complex (MHC)–antigen complex displayed on antigen-presenting cells (APCs) under the stimulation of inflammatory cytokines and through the participation of costimulatory molecules (CD28 and CD80/CD86) (Gaud et al. 2018; Golstein and Griffiths 2018). CD28 is expressed on T cells, and its ligands CD80 (B7-1) and CD86 (B7-2) are expressed on the surface of APCs (Freeman et al. 1993; Hathcock et al. 1993). CD28 binding to B7 offers a costimulatory signal for T cell activation

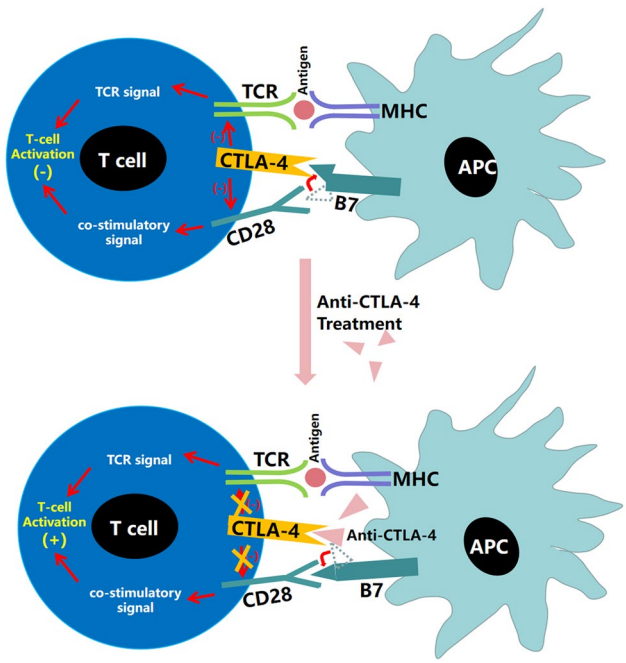

Fig. 1 Anti-CTLA-4 agents enhance T cell activation. CTLA-4 has a higher affinity for B7 than CD28. On the one hand, CTLA-4/B7 ligation reduces CD28/B7 ligation and then suppresses T cell activation. On the other hand, the interaction between CTLA-4 and B7 inhibits the stimulatory signals produced by TCR/MHC and CD28/B7 binding. Antibodies targeting CTLA-4 deplete CTLA-4 from the tumor microenvironment and thereby enhance T cell activation

(Azuma et al. 1993; Linsley et al. 1990, 1991). Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) is expressed on T cells to prevent their overactivation by binding to B7 family members (Linsley et al. 1994; van der Merwe et al. 1997; Walunas et al. 1994; Wei et al. 2018). At the moment of T cell receptor (TCR) signal triggering, the expression of CTLA-4 becomes upregulated and peaks at 2–3 days (Brunner et al. 1999; Walunas et al. 1994). In addition, CTLA-4 is rapidly transported to the immunologic synapse from intracellular vesicles (Egen and Allison 2002). Because CTLA-4 has a higher affinity for B7 than CD28, CTLA-4/B7 ligation reduces CD28/B7 ligation and then suppresses T cell activation (Chambers et al. 2001; Collins et al. 2002; Egen et al. 2002). In addition, the interaction between CTLA-4 and B7 can inhibit the stimulatory signals produced by TCR/MHC and CD28/B7 binding (Fallarino et al. 1998; Masteller et al. 2000). Thus, CTLA-4 attenuates the CD28 downstream signal, which is mediated by phosphatidylinositol-3 kinase (PI3K) and Akt (Kane et al. 2001; Pages et al. 1994). Other mechanisms that modulate T cell activation include the suppressive function of CTLA-4 expressed on Tregs and the restrictive function of CTLA-4 that reduces the available B7 ligands via the transendocytosis of B7 ligands (Fallarino et al. 2009; Qureshi et al. 2011; Read et al. 2006). A certain number of CTLA-4-expressing T cells in tumors results in the inhibition of MHC–antigen complex recognition and a reduction in T cell activation, proliferation and infiltration. Antibodies targeting CTLA-4 can deplete CTLA-4 from the tumor microenvironment by their Fc effector functions, thereby enhancing T cell activation (Arce Vargas et al. 2018). However, enhancing T cell activation with CTLA-4 blockade in tumors may also arouse autoimmune responses.

Antiangiogenesis therapy enhances T cell recruitment by normalizing tumor blood vessels (Fig. 2)

The uncontrolled proliferation of malignant cancer cells results in hypoxia. In clear cell RCC, the most major histologic subtype of RCC, a mutation in or inactivation of the von Hippel–Lindau (VHL) tumor suppressor gene can also induce hypoxia (Cancer Genome Atlas Research 2013; Gnarra et al. 1994; Latif et al. 1993). Then, a transcription factor, hypoxia-inducible factor (HIF)-1, triggers the upregulation of multiple proangiogenic genes (Liao and Johnson 2007). Subsequently, tumors secrete several proangiogenetic factors, such as VEGF. Its receptor, VEGFR2, contains three domains: a ligand-binding domain, a transmembrane domain and a tyrosine kinase domain (Kendrew et al. 2011). The binding of VEGF and VEGFR2 triggers multiple intracellular pathways to regulate the sprouting, proliferation and migration of endothelial cells and vascular permeability (Claesson-Welsh and Welsh 2013; Ye 2016).

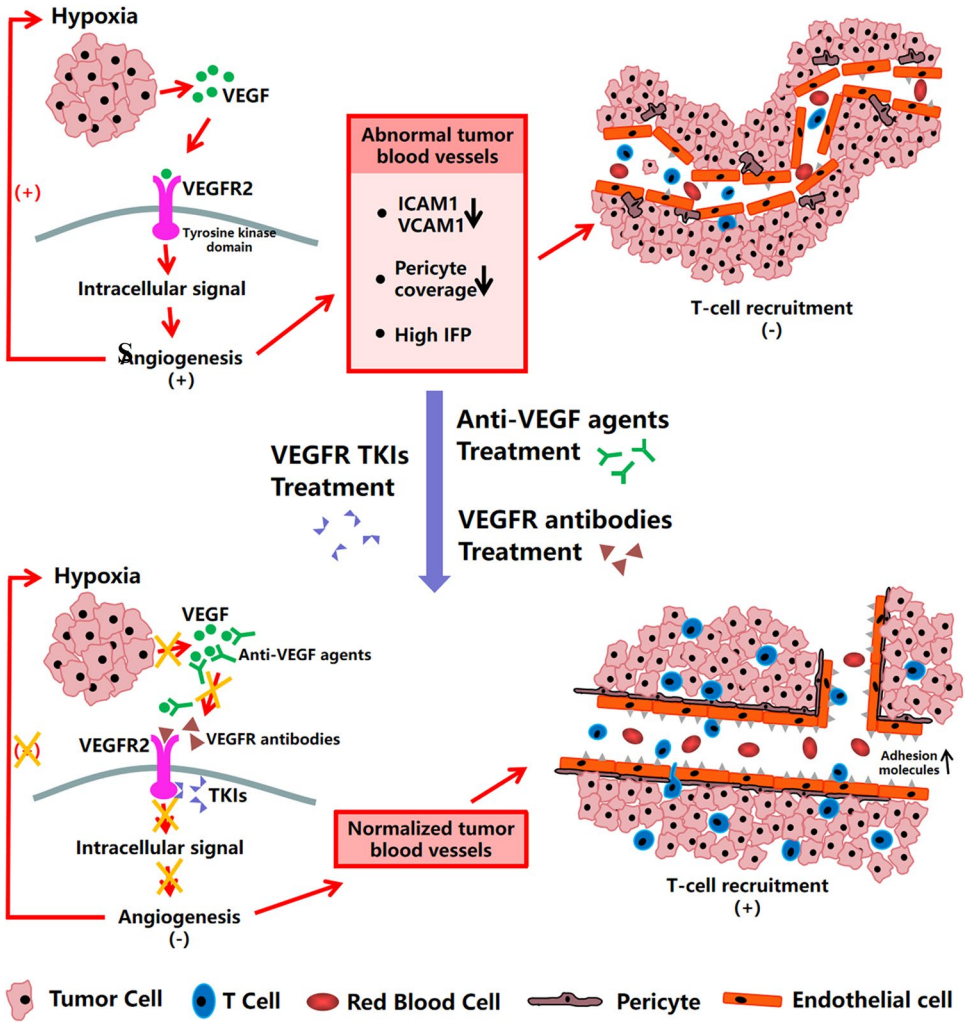

Fig. 2 Antiangiogenesis therapy enhances T cell recruitment by normalizing tumor blood vessels. Hypoxia caused by the uncontrolled proliferation of malignant cancer cells triggers the excessive expression of VEGF. Then, the binding of VEGF and VEGFR2 triggers abnormal angiogenesis: downregulated expression of the integrin ligands intercellular adhesion molecule 1 (ICAM1) and vascular cell adhesion protein 1 (VCAM1), loose pericyte coverage, disrupted endothelial cell junctions and high interstitial fluid pressure (IFP). A suitable dosage of anti-VEGF agents, VEGFR2 antibodies and VEGFR-TKIs can restore angiogenic signals, resulting in normalized tumor blood vessels and enhanced T cell recruitment

Before immune cells infiltrate into the tumor microenvironment and kill tumor cells, they must undergo the processes of entering tumor blood vessels through the blood circulation, adhering to the endothelium and transmigrating across the vessel wall (Chen and Mellman 2013). However, due to the excessive expression of angiogenic molecules such as VEGF, tumor blood vessels often exhibit abnormal structures and functions (De Bock et al. 2011). On the one hand, VEGF reduces T cell recruitment by downregulating the expression of adhesion molecules, such as the integrin ligands intercellular adhesion molecule 1 (ICAM1) and vascular cell adhesion protein 1 (VCAM1) (Hendry et al. 2016; Jain et al. 1996; Melder et al. 1996). On the other hand, nascent tumor vessels are often leaky due to loose pericyte coverage and disrupted endothelial cell junctions (Bergers and Benjamin 2003). This results in high interstitial fluid pressure (IFP) and then reduces T cell infiltration into the tumor microenvironment and limits drug delivery (Jain et al. 2014; Teng et al. 2015). High IFP can compress or even collapse vessels, resulting in limited oxygen and nutrient supplies and aggravating hypoxia (Jain et al. 2014).

In addition to reducing T cell recruitment, inhibitory molecules such as Fas ligand (FasL) expressed on endothelial cells, called the tumor endothelial barrier, can selectively kill effector CD8 T cells instead of Treg cells (Lanitis et al. 2015; Motz et al. 2014).

In addition, a preclinical study conducted by Meder et al. (2018) suggested that VEGF could stimulate the upregulated expression of PD-1 on T cells. Voron et al. (2015) found that the activated signaling pathway of VEGFR2–PLCγ–calcineurin–NFAT was the intrinsic upregulating mechanism of PD-1. Hypoxia also leads to inhibition of the antitumor immune response by upregulating PD-L1, interleukin-6 (IL-6) and interleukin-10 (IL-10) (Ramjiawan et al. 2017).

A suitable dosage of anti-VEGF agents can restore angiogenic signals, resulting in normalized tumor blood vessels with tight pericyte coverage, decreased permeability and increased tumor perfusion (Tolaney et al. 2015). VEGFR2 antibodies can increase the pericyte recruitment of tumor

blood vessels by activating Ang-1/Tie2 signaling (Winkler et al. 2004). Moreover, studies have proven that antiangiogenic agents can reverse immunosuppression by decreasing immunosuppressive cells such as myeloid-derived suppressor cells and regulatory T cells (Tartour et al. 2011). Anti-VEGFR agents are capable of inducing tumor cells to activate immune checkpoints (Topalian et al. 2015; Vanneman and Dranoff 2012).

Thus, anti-PD-1 therapy combined with anti-VEGF agents could achieve dramatic synergistic antitumor efficacy based on preclinical theories.

Anti-PD-1/PD-L1 enhances the antitumor activity of T cells (Fig. 3)

PD-1 is an extracellular surface checkpoint molecule expressed on immunocytes such as B cells, monocytes/macrophages, dendritic cells, natural killer T cells, and CD4+ and CD8+ T cells (Chen et al. 2016; Francisco et al. 2010). It can suppress the excessive immune response and prevent autoimmunity (Freeman et al. 2000). Its ligand (PD-L1) is mostly overexpressed on tumor cells to suppress the tumor lysis function of cytotoxic CD8+ T cells (Blank et al. 2005). PD-L2 is also a ligand overexpressed on tumor cells for PD-1, and it inhibits T cell activation (Latchman et al. 2001). It has been reported that the expression of PD-L1 on tumor cells and tumor-infiltrating immune cells is associated with a poor prognosis and suppresses antitumor immunity in metastatic RCC (Choueiri et al. 2014; Herbst et al. 2014; Motzer et al. 2015a; Thompson et al. 2004, 2006, 2007).

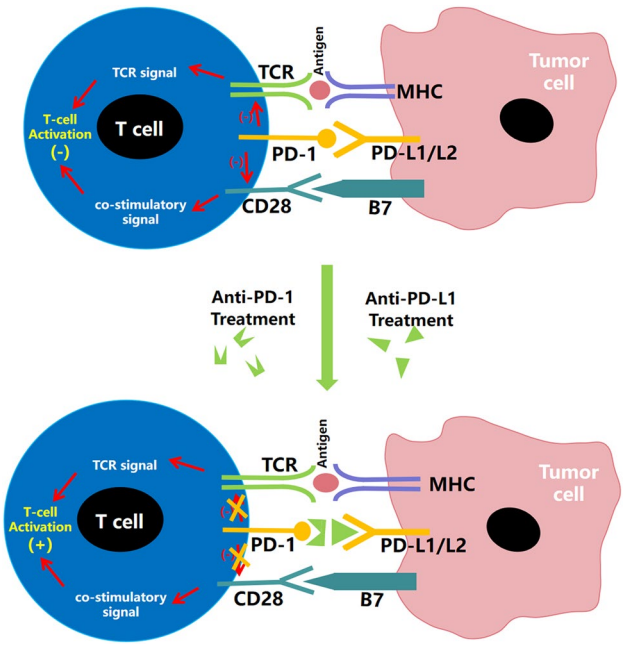

Fig. 3 Anti-PD-1/PD-L1 agents enhance the antitumor activity of T cells. PD-1/PD-L1 or PD-1/PD-L2 ligation inhibits T cell activation and the TCR signal. Antibodies targeting PD-1 or PD-L1 can block the PD-1/PD-L1 pathway to reactivate tumor antigen recognition as well as the proliferation, infiltration, and activation of cytotoxic CD8+ T cells

It is believed that PD-1 is induced at the late stage of T cell activation. Then, PD-1/PD-L1 or PD-1/PD-L2 ligation will weaken the TCR signal by recruiting the tyrosine phosphatase SHP2 (Chemnitz et al. 2004; Freeman et al. 2000). However, recent studies have indicated that PD-1 induces the preferential dephosphorylation of CD28 instead of the TCR through the recruitment of SHP2 to attenuate T cell activation (Hui et al. 2017). In addition, PD-L1 expression on macrophages may evict T cells from the tumor microenvironment (Kortlever et al. 2017). Antibodies targeting PD-1 or PD-L1 can block the PD-1/PD-L1 pathway to reactivate tumor antigen recognition as well as the proliferation, infiltration, and activation of cytotoxic CD8+ T cells (Balar and Weber 2017; Dolan and Gupta 2014; Francisco et al. 2009).

Immune checkpoint blockade and antiangiogenesis therapy establish a positive reinforcing feedback loop

Recently, some studies have provided a novel understanding of tumor vessel normalization and the antitumor effects of immune checkpoint blockade (Huang et al. 2018). Tian et al. studied the mutual regulation between immunostimulatory reprogramming and tumor vessel normalization. Their bioinformatic analyses suggested that immunostimulation pathways are related to gene expression features of vessel normalization (Tian et al. 2017). The animal model experiments revealed that increased vessel normalization could be found in the setting of CD4+ T cell activation by immune checkpoint blockade (Tian et al. 2017).

Due to hypoxia and acidosis, the activity of effector T cells is always suppressed, and the tumor microenvironment is often immunosuppressive (Barsoum et al. 2014; Gabrilovich et al. 2012). As discussed above, a suitable dosage of antiangiogenesis therapy normalizes tumor blood vessels and alleviates hypoxia by increasing tumor perfusion, which reverses immunosuppression to increase the activation and infiltration of effector T cells in the tumor microenvironment. Additionally, immune checkpoint blockade therapies enhance T cell activation and the antitumor activity of T cells, which further increases tumor vessel normalization. Then, further vessel normalization leads to the further activation and infiltration of effector T cells in the tumor microenvironment. Thus, a positive reinforcing feedback loop is established between immune checkpoint blockade and antiangiogenesis therapy.

Clinical data and results

Metastatic renal cell carcinoma (mRCC)

The IMmotion150 study (NCT01984242) was a multicenter, randomized, open-label phase II study that evaluated the efficacy, safety and tolerability of atezolizumab with or without bevacizumab versus sunitinib in participants with untreated mRCC (McDermott et al. 2018). A stratified analysis in the intent-to-treat (ITT) population ($N=305$) showed a median PFS of 11.7 months [hazard ratio (HR) 1.00; 95% CI 0.69–1.45 versus sunitinib], 8.4 months and 6.1 months (HR 1.19; 95% CI 0.82–1.71 versus sunitinib) in patients treated with atezolizumab combined with bevacizumab, sunitinib monotherapy and atezolizumab monotherapy, respectively, and the ORRs were 32% [7% achieved a complete response (CR), 25% achieved a partial response (PR)], 25% (11% achieved CR, and 14% achieved PR) and 29% (5% achieved CR, and 24% achieved PR), respectively. In the population with PD-L1 expression ≥ 1% on immune cells (PD-L1+), the median PFS was 14.7 months with atezolizumab combined with bevacizumab, 7.8 months with sunitinib monotherapy (HR 0.64; 95% CI 0.38–1.08) and 5.5 months with atezolizumab monotherapy (HR 1.03; 95% CI 0.63–1.67 versus sunitinib). The ORRs were 46% (12% achieved CR, and 34% achieved PR), 28% (15% achieved CR, and 13% achieved PR), and 27% (7% achieved CR, and 20% achieved PR), respectively. Regarding its safety, the toxicity of atezolizumab combined with bevacizumab therapy can be managed. Additionally, biomarker analyses of the IMmotion150 study suggested that the tumor mutation burden (TMB) and tumor neoantigen burden (TNB) were not related to PFS. Patients with a high T-effector score and high PD-L1 immune cell expression may have PFS benefit from atezolizumab and bevacizumab combination therapy. The IMmotion151 phase 3 study of this combination (NCT02420821) also had preliminary results (A Study of Atezolizumab in Combination With Bevacizumab Versus Sunitinib in Participants With Untreated Advanced Renal Cell Carcinoma (RCC) (IMmotion151) 2019). PFS in the PD-L1 ≥ 1% population was 11.2 months in the atezolizumab combined with bevacizumab group and 7.5 months in the sunitinib group. The ORRs were 36.6% and 33.3%, respectively. OS data were not available.

Overall, the IMmotion150 and IMmotion151 studies showed the encouraging efficacy of atezolizumab combined with bevacizumab therapy in patients with untreated mRCC. A high T-effector score and high PD-L1 expression on immune cells might serve as biomarkers for selecting appropriate patients.

Based on the promising antitumor activity and safety of axitinib plus pembrolizumab combination treatment in patients with untreated advanced RCC in the phase Ib trial (NCT02133742) (Atkins et al. 2018), the open-label, phase III trial KEYNOTE-426 (NCT02853331) was launched (Rini et al. 2019). Among the 861 patients enrolled, 432 received 200 mg pembrolizumab intravenously once every 3 weeks plus 5 mg axitinib orally twice daily and 429 patients received 50 mg sunitinib orally once daily for 4 weeks of each 6-week cycle. The median PFS was 15.1 months in the combination group and 11.1 months in the sunitinib group (HR for disease progression or death, 0.69, $P<0.001$). The ORR in the combination group was 23.6% higher than that in the sunitinib group (59.3% versus 35.7%, respectively, $P<0.001$). Longer PFS and OS rates were observed in all subgroups of the combination group [e.g., IMDC risk category (favorable, intermediate or poor), PD-L1 expression (< 1% or ≥ 1%) and number of organs with metastases (1 or ≥ 2 organs)]. According to the safety assessment, 62.9% of patients in the combination group and 58.1% of patients in the sunitinib group had events of grade 3 or higher treatment-related adverse events. In the combination group, the first three common treatment-related adverse events were diarrhea, hypertension and hypothyroidism. Thus, in the latest National Comprehensive Cancer Network (NCCN) guidelines of Kidney Cancer (version 4.2019), axitinib combined with pembrolizumab therapy is recommended as a first-line treatment option for patients with advanced RCC regardless of their IMDC risk category (NCCN Clinical Practice Guidelines in Oncology-Kidney Cancer (Version 4.2019) 2019).

The JAVELIN Renal 100 study was a phase Ib study that reached a 58% ORR by combining avelumab and axitinib in treatment-naïve patients with advanced RCC (Choueiri et al. 2018). Then, a phase III trial (JAVELIN Renal 101, NCT02684006) compared the efficacy of avelumab and axitinib combination therapy with sunitinib monotherapy (Motzer et al. 2019). The median PFS was 13.8 months in the avelumab plus axitinib group and 8.4 months in the sunitinib group (HR, 0.69; $P<0.001$), and the ORRs were 51.4% and 25.7%, respectively. We found that the combination treatment group had significantly improved PFS and that the ORR was onefold higher than that in the control group. Of note, the median PFS (13.8 months versus 7.2 months, HR 0.61; $P<0.001$) and ORR (55.2% versus 25.5%) in the PD-L1-positive subgroup were similar to those in the overall population. Thus, this therapy is not related to PD-L1 expression in patients and has been granted the US FDA breakthrough therapy designation.

However, the results of the phase I CheckMate 016 study (NCT01472081) of the combination of sunitinib or pazopanib with nivolumab showed high frequencies of high-grade toxicities (Amin et al. 2018). Although the response and OS benefit were notable, these two combination

regimens need dosage adjustments in future phase II/III studies.

In addition to the clinical trials mentioned above, there are many other ongoing studies on immune checkpoint inhibitors plus antiangiogenic drug combination therapies, such as the combination of lenvatinib with pembrolizumab (NCT02501096, NCT02811861), in patients with advanced RCC (Table 1).

Based on the published clinical trial data described above, combined immunotherapy will play an important role in the treatment of advanced RCC, and optimization will be the focus of future research. IMDC risk stratification, PD-L1 expression and adverse drug reactions are the main selection factors. According to the literature, high PD-L1 expression is closely related to the poor prognosis of RCC (Thompson et al. 2004, 2006).

Metastatic urothelial and genitourinary tumors

At the ESMO 2017 Congress, Nadal et al. (2017) presented the encouraging final results of a phase I study of cabozantinib plus nivolumab in patients with refractory metastatic urothelial and genitourinary tumors (Abstract #846O, NCT02496208). Forth-two patients were enrolled between July 2015 and April 2017. The combined therapy of cabozantinib and nivolumab was well tolerated. The ORR was 35% (3 achieved CR, and 11 achieved PR). The median PFS was 5.5 months, and the median OS was not determined.

A multicohort, phase Ia/b trial (NCT02443324) demonstrated the antitumor activity of ramucirumab and pembrolizumab combination therapy in patients with advanced urothelial transitional cell carcinoma who failed platinum-based therapy (Petrylak et al. 2017). As of July 23, 2016, 24 patients received 10 mg/kg ramucirumab and 200 mg pembrolizumab once every 3 weeks. There have been no treatment-related grade 4 or 5 events. Two (8%) patients with PD-L1 (+) achieved PR, while ten (42%) patients achieved SD. The median PFS was 1.87 months.

The 33rd Annual Meeting and Pre-Conference Programs of the sitc 2018 reported the subgroup results of the phase Ib/II trial Study111/KEYNOTE-146 (NCT02501096, abstract #11201/poster #P393) for metastatic urothelial cancer treated with pembrolizumab plus lenvatinib (33rd Annual Meeting and Pre-Conference Programs of the Society for Immunotherapy of Cancer (SITC 2018) 2018). As of March 1, 2018, 20 patients were enrolled. Of all 20 patients, 9 (45%) patients were PD-L1 (+), 5 (25%) patients were PD-L1 (−), and 6 (30%) patients were not tested. The ORR was 25% [including 1 (5%) patient who achieved CR and 4 patients who achieved PR]. The median PFS was 5.5 months. Ten patients experienced grade 3–4 treatment-related adverse events.

Based on current study results, antiangiogenic and immune checkpoint blockade combination therapy may be used for the treatment of advanced urothelial cancer, but whether PD-L1 can serve as a biomarker deserves further investigation.

Ongoing clinical trials with regard to metastatic urothelial and genitourinary tumors are shown in Table 2.

Gynecologic cancers

Study 111/KEYNOTE 146 was a phase Ib/II study that evaluated the safety and effectiveness of pembrolizumab combined with lenvatinib in patients with select solid tumors (NCT02501096) (Makker 2018). As of August 1, 2017, 54 patients were enrolled in the subgroup with metastatic endometrial carcinoma. Three (6%) patients were classified as microsatellite instability high (MSI-H), 43 (80%) patients were classified as having proficient mismatch repair (pMMR/non-MSI-H), and 8 (15%) patients were not tested. The ORR was 36.7%, the ORR at week 24 was 50% (95% CI 32.4–67.6), and the median PFS was 10.1 months. Of note, in patients with pMMR (non-MSI-H), the ORR at week 24 was also 50.0% (95% CI 29.9–70.1). In patients with MSI-H, one achieved PR, one achieved SD and one achieved PD. Hypertension (59%), fatigue (50%) and diarrhea (44%) were the three most common treatment-related adverse events.

Therefore, this study suggests that pembrolizumab combined with lenvatinib is effective for patients with metastatic endometrial carcinoma regardless of their MSI/MMR status. On July 31, 2018, the US FDA granted breakthrough therapy designation to pembrolizumab plus lenvatinib for patients with metastatic endometrial carcinoma. The phase III trial is ongoing (Study 309/KEYNOTE-775, NCT03517449).

In addition, a phase I study (NCT02484404) evaluated the safety and clinical efficacy of durvalumab combined with olaparib or cediranib in recurrent women's cancers (Lee et al. 2017). There were 12 patients in the durvalumab plus olaparib group (10 with ovarian cancer and 2 with triple-negative breast cancer) and 14 patients in the durvalumab plus cediranib group (9 with ovarian cancer, 3 with uterine cancer and 2 with cervical squamous cell cancer). The ORR of the durvalumab plus olaparib group was 17%, and the DCR was 83% (2 achieved PR, and 8 achieved SD), while the ORR in the durvalumab plus cediranib group was 50%, and the DCR was 75% (6 achieved PR, 8 achieved SD, and 2 stopped due to drug toxicity). Most treatment-related adverse events were manageable, but the cardiovascular adverse events associated with the cediranib combination need our attention. The same study found that patients with PD-L1 (3+) tumor-infiltrating lymphocytes (TILs) had a better response and longer response duration compared with other patients. However, in either treatment subgroup, no statistical

Table 1 Clinical trials investigating antiangiogenic therapy in combination with immune checkpoint inhibitors in patients with mRCC

Trial (phase + NCT number + line)	Category	Specific dosage and usage (arm of combination therapy)	Patient population	Key results	Treatment-related adverse events
Phase I, NCT01633970, 1st line	Anti-PD-L1 + anti-VEGF	20 mg/kg atezolizumab and 15 mg/kg bevacizumab intravenously every 3 weeks	Untreated unresectable locally advanced or mRCC	ORR: 40%	–
Phase II, NCT01984242, 1st line (IMmotion150)	Anti-PD-L1 + anti-VEGF	1200 mg atezolizumab and 15 mg/kg bevacizumab intravenously every 3 weeks	Untreated unresectable locally advanced or mRCC	ITT ORR: 32% PD-L1 + ORR: 46%	All grades: fatigue (59.4%), arthralgia (37.6%), hypertension (36.6%), proteinuria (35.6%), diarrhea (33.7%)
Phase III, NCT02420821, 1st line (IMmotion151)	Anti-PD-L1 + anti-VEGF	1200 mg atezolizumab and 15 mg/kg bevacizumab intravenously every 3 weeks	Untreated unresectable locally advanced or mRCC	ITT ORR: 36.6% PD-L1 + ORR: 43%	–
Phase I, NCT02133742	Anti-PD-1 + VEGFR-TKI	5 mg Axitinib orally twice daily and 200 mg pembrolizumab intravenously every 3 weeks	Untreated advanced RCC with primary tumor resected and at least one measureable lesion	ORR: 73%	≥ Grade 3: hypertension (23%), diarrhea (10%), fatigue (10%), increased alanine aminotransferase concentration (8%)
Phase III, NCT02853331 (KEYNOTE-426)	Anti-PD-1 + VEGFR-TKI	5 mg axitinib orally twice daily and 200 mg pembrolizumab intravenously every 3 weeks	Untreated advanced clear cell RCC	ORR: 59.3% mPFS: 15.1 months	≥ Grade 3: hypertension (21.2%), alanine aminotransferase increased (12.1%), diarrhea (7.2%), aspartate aminotransferase increased (6.8%), palmar-plantar erythrodysesthesia (5.1%)
Phase Ib, NCT02493751, 1st line (JAVELIN Renal 100)	Anti-PD-L1 + VEGFR-TKI	5 mg axitinib orally twice daily for 7 days, followed by combination therapy with 10 mg/kg avelumab intravenously every 2 weeks and 5 mg axitinib orally twice daily	Primary untreated advanced RCC	ORR: 58%	≥ Grade 3: hypertension (29%), amylase increased (8%), lipase increased (8%), palmar-plantar erythrodysesthesia syndrome (7%), ALT increased (7%)
Phase III, NCT02684006, 1st line (JAVELIN Renal 101)	Anti-PD-L1 + VEGFR-TKI	10 mg/kg avelumab intravenously every 2 weeks plus 5 mg axitinib orally twice daily	Primary untreated clear-cell advanced RCC	ITT ORR: 51.4% PD-L1 + ORR: 55.2% ITT mPFS: 13.8 months PD-L1 + mPFS: 13.8 months	≥ Grade 3: hypertension (24.4%), palmar-plantar erythrodysesthesia syndrome (5.8%), diarrhea (5.1%), alanine aminotransferase increased (4.8%), fatigue (3.0%), aspartate aminotransferase increased (2.8%)
Phase I, NCT01472081, 1st line (CheckMate 016 Arm N + S)	Anti-PD-1 + VEGFR-TKI	2 mg/kg nivolumab intravenously every 3 weeks plus 50 mg sunitinib once daily for 4 weeks	Untreated advanced or metastatic RCC	ORR: 55% mPFS: 12.7 months	≥ Grade 3: hypertension (18.2%), increased ALT (18.2%), increased AST (9.1%), diarrhea (9.1%), and fatigue (9.1%)

Table 1 (continued)

Trial (phase + NCT number + line)	Category	Specific dosage and usage (arm of combination therapy)	Patient population	Key results	Treatment-related adverse events
Phase I, NCT01472081, ≥ 1st line (CheckMate 016 Arm N + P)	Anti-PD-1 + VEGFR-TKI	2 mg/kg nivolumab intravenously every 3 weeks plus 800 mg pazopanib once daily for 4 weeks	Advanced or metastatic RCC with ≥ 1 prior systemic therapy	ORR: 45% mPFS: 7.2 months mOS: 27.9 months	≥ Grade 3: hypertension (10.0%), increased ALT (20.0%), increased AST (20.0%), diarrhea (20.0%), and fatigue (15.0%)
Phase I, NCT00372853, ≥ 1st line	Anti-CTLA-4 + VEGFR-TKI	6 mg/kg, 10 mg/kg, or 15 mg/kg tremelimumab intravenously every 12 weeks and 50 mg sunitinib orally once daily for 4 weeks	Metastatic RCC with ≥ 1 prior systemic therapy	–	–
Phase Ib/II, NCT02348008, ≥ 1st line	Anti-PD-1 + anti-VEGF	10 mg/kg or 15 mg/kg bevacizumab and 200 mg pembrolizumab intravenously every 3 weeks	Metastatic clear cell RCC with ≥ 1 prior systemic therapy	–	–
Phase Ib/II, NCT02501096, ≥ 1st line	Anti-PD-1 + VEGFR-TKI	Tolerated dose lenvatinib orally once daily and 200 mg pembrolizumab intravenously every 3 weeks	RCC with ≥ 1 prior anti-PD-1/PD-L1 monoclonal antibody monotherapy or combination therapy	ORR: 63.3%	–
Phase III, NCT02811861, 1st line (CLEAR)	Anti-PD-1 + VEGFR-TKI	20 mg lenvatinib orally once daily and 200 mg pembrolizumab intravenously every 3 weeks	Untreated advanced RCC	–	–
Phase III, NCT03141177, (CheckMate 9ER)	Anti-PD-1 + VEGFR-TKI	Nivolumab and cabozantinib (specified dose on specified day)	Previously untreated advanced or metastatic RCC	–	–
Phase I/II, NCT02014636, 1st line (KEYNOTE-018)	Anti-PD-1 + VEGFR-TKI	Dose range of 400–800 mg pazopanib orally and dose range of pembrolizumab 1–10 mg/kg intravenously	Untreated advanced RCC	–	–

mRCC metastatic renal cell carcinoma, *PD-L1* programmed cell death ligand 1, *PD-1* programmed cell death protein 1, *VEGFR-TKI* vascular endothelial growth factor receptor tyrosine kinase inhibitor, *ORR* objective response rate, *ITT* intent-to-treat population, *mPFS* median progression-free survival, *mOS* median overall survival

Table 2 Clinical trials investigating antiangiogenic therapy in combination with immune checkpoint inhibitors in patients with metastatic urothelial, genitourinary tumor, endometrial carcinoma and ovarian, fallopian tube cancer

Trial (phase + NCT number + line)	Category	Specific dosage and usage (arm of combination therapy)	Patient population	Key results	Treatment-related adverse event
Phase I, NCT02496208, > 1st line	Anti-PD-1 + VEGFR-TKI	40 mg or 60 mg cabozantinib orally daily and 1 mg/kg or 3 mg/kg nivolumab intravenously every 2 weeks	Patients with refractory metastatic urothelial and genitourinary tumors	ORR: 35% mPFS: 5.5 months	≥ Grade 3: hypophosphatemia (21%), neutropenia (21%), fatigue (12%), elevated lipase (12%); diarrhea (8%), hypertension (8%)
Phase Ia/b, NCT02443324, > 1st line	Anti-PD-1 + anti-VEGFR	10 mg/kg ramucirumab and 200 mg pembrolizumab on Day 1 every 3 weeks	Patients with advanced urothelial transitional cell carcinoma who failed in platinum-based therapy	2 patients PR 10 patients SD mPFS: 1.87 months	All grades: fatigue (21%), nausea (17%), pyrexia (13%), elevated alanine aminotransferase (13%) and elevated aspartate aminotransferase (13%)
Phase Ib/II, NCT02501096, ≥ 1st line (Study111, KEYNOTE-146)	Anti-PD-1 + VEGFR-TKI	20 mg lenvatinib orally once daily and 200 mg pembrolizumab intravenously every 3 weeks	Metastatic urothelial carcinoma (previously untreated or received up to two treatments)	ORR: 25% mPFS: 5.5 months	All grades: proteinuria (45%), diarrhea (40%), fatigue (30%), hypertension (30%), and hypothyroidism (30%)
			Metastatic endometrial carcinoma who failed in previously therapy	ORR: 36.7% mPFS: 10.1 months	All grades: hypertension (59%), fatigue (50%), diarrhea (44%), hypothyroidism (35%), and stomatitis (33%)
Phase I, NCT02484404, ≥ 1st line	Anti-PD-L1 + VEGFR-TKI	1500 mg durvalumab every 4 weeks with 20 mg cediranib 5 days on and 2 days off	Advanced or recurrent solid tumors	ORR: 50% DCR: 75%	All grades: hypertension (87.5%), diarrhea (87.5%), fatigue (75%), lymphopenia (75%), Thrombocytopenia (75%)
Phase III, NCT03038100, 1st line (IMagyn050)	Anti-PD-L1 + Anti-VEGF	175 mg/m^2 paclitaxel, 6 mg/mL*min carboplatin, 1200 mg atezolizumab intravenously every 3 weeks for 6 cycles, and 15 mg/kg bevacizumab intravenously starting with Cycle 2 for a total of 5 cycles	Newly Diagnosed Stage III or Stage IV Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	–	–
Phase III, NCT03353831, > 1st line	Anti-PD-L1 + Anti-VEGF	80 mg/m^2 paclitaxel d1, 8, 14, 22 or 40 mg/m^2 pegylated liposomal doxorubicin every 4 weeks, 10 mg/kg bevacizumab and 840 mg Atezolizumab every 2 weeks	Recurrent ovarian-, fallopian tube, or primary peritoneal cancer with 1st or 2nd relapse within 6 months after platinum-based chemotherapy or 3rd relapse	–	–
PhaseII/III, NCT02839707, > 1st line	Anti-PD-L1 + Anti-VEGF	Pegylated liposomal doxorubicin hydrochloride IV on day 1 plus bevacizumab and atezolizumab IV every 2 weeks	Recurrent ovarian, fallopian tube, or primary peritoneal cancer	–	–

Table 2 (continued)

Trial (phase + NCT number + line)	Category	Specific dosage and usage (arm of combination therapy)	Patient population	Key results	Treatment-related adverse event
Phase III, NCT02891824, > 1st line (ATALANTE)	Anti-PD-L1 + Anti-VEGF	1200 mg atezolizumab for 6 cycles every 3 weeks or 800 mg for 6 cycles every 4 weeks during treatment with platinum-based chemotherapy and 15 mg/kg bevacizumab, followed by 1200 mg atezolizumab every 3 weeks until progression	Epithelial ovarian cancer (including patients with primary peritoneal and/or fallopian tube adenocarcinoma) who have platinum-sensitive relapse (platinum-free interval > 6 months)	–	–
Phase II, NCT02659384, > 1st line	Anti-PD-L1 + Anti-VEGF	Atezolizumab + bevacizumab + acetylsalicylic acid	Advanced recurrent platinum-resistant ovarian cancer	–	–
Phase II, NCT03363867, 1st line (BEACON)	Anti-PD-L1 + Anti-VEGF	840 mg atezolizumab and 5 mg/kg bevacizumab intravenously every 2 weeks plus 60 mg cobimetinib daily for 3 weeks of each 28 days cycle	Female patients with high-grade serous ovarian carcinoma	–	–

PD-L1 programmed cell death ligand 1, *PD-1* programmed cell death protein 1, *VEGFR-TKI* vascular endothelial growth factor receptor tyrosine kinase inhibitor, *ORR* objective response rate, *mPFS* median progression-free survival, *DCR* disease control rate, *PR* partial response, *SD* stable disease

association was observed between clinical activity and the presence of PD-L1 (+) TILs, the degree of TILs, or the PD-L1 expression status. Thus, this study suggests that the response to the combination therapy is not related to the status of PD-L1 expression. Phase II studies are ongoing.

Thus, regardless of the MSI/MMR and PD-L1 expression statuses, patients with metastatic endometrial carcinoma or ovarian or fallopian tube cancer can obtain clinical benefits from ICB combined with antiangiogenesis therapy. Ongoing clinical trials with regard to gynecologic cancers are shown in Table 2.

Adverse events and drug administration in clinical trials

Regarding safety assessments, in general, the toxicity of antiangiogenic and immune checkpoint blockade combined therapy can be managed. Adverse events vary due to differences in specific drugs; however, hypertension, diarrhea, fatigue, increased alanine aminotransferase levels and increased aspartate aminotransferase levels are the most common treatment-related adverse events in combined therapy. Tables 1 and 2 show the most common treatment-related adverse events in each clinical trial mentioned above.

Some preclinical studies have suggested that a high dose of antiangiogenesis agents may excessively prune tumor blood vessels, which leads to decreased perfusion and hypoxia and then increased tumor invasion and metastasis (Bergers and Hanahan 2008; Casanovas et al. 2005; Jain 2013; Ramjiawan et al. 2017). It should be noted that the dose of antiangiogenesis agents used in preclinical studies is higher than that used in clinical trials (Jain 2013). To date, no phase III randomized clinical trial has directly compared the effect difference between a high dose and a low dose of antiangiogenesis agents on efficacy or toxicity. Based on the clinical trials listed above, combination therapy is safe and effective. However, there is no denying that the major challenge of combination therapy is the optimization of the dose of antiangiogenesis agents administered. To avoid excessive vessel pruning, during combined therapy, technology measuring interstitial fluid pressure, imaging technologies quantifying the vessel diameter, vessel density, vessel tortuosity, and vascular permeability and perfusion magnetic resonance imaging are needed (Griffon-Etienne et al. 1999; Jain 2001).

Concerning drug administration, the specific dosage and usage of each drug in each clinical trial are listed in Tables 1 and 2. As discussed in the section "Preclinical rationale for combined immune checkpoint blockade and antiangiogenic therapy", immune checkpoint blockade and antiangiogenesis therapy establish a positive reinforcing feedback loop. Thus, there is no strict limit on which drug can be used first in the combined therapy.

Conclusions and future prospects

Here, we reviewed the mainstream understanding of the interactional mechanisms of antiangiogenic therapy and immune checkpoint blockade in solid tumors. A suitable dosage of antiangiogenesis therapy increases T cell infiltration in tumors by normalizing tumor blood vessels to enhance the antitumor effect of immune checkpoint blockade. In turn, immune checkpoint blockade therapies further increase tumor vessel normalization by activating T cells. We have largely focused on the clinical efficacy, safety and potential biomarkers from the latest clinical trials. Combined therapy has shown some antitumor efficacy in urogenital tumors such as mRCC, metastatic urothelial and genitourinary tumors, endometrial carcinoma and ovarian and fallopian tube cancers.

In addition, the exploration of effective prediction biomarkers in these clinical trials suggests that high PD-L1 expression might be a biomarker for selecting appropriate patients with mRCC. However, concerning gynecologic cancers, patients could obtain clinical benefits from ICB combined with antiangiogenesis therapy regardless of their MSI/MMR and PD-L1 expression statuses. In metastatic urothelial and genitourinary tumors, whether PD-L1 is a biomarker deserves further investigation.

Overall, in urogenital tumors, the combination therapy of antiangiogenic drugs and immune checkpoint blockade is a promising strategy that can be used to improve the therapeutic efficacy. However, along with our increased understanding of combined therapy, there are some problems that need to be discussed and resolved. For example, there are no clinical data on the direct relationship between the dose of antiangiogenesis agents administered and the efficacy of combined therapy, differences between vascular normalization mediated by antiangiogenic therapy and immunotherapy-induced vascular normalization, or precise biomarkers for combined therapy. All of these issues are the direction of future studies and require further characterization and validation.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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