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Clinical pharmacology of anti-angiogenic drugs in oncology

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ABSTRACT

Keywords:

Angiogenesis inhibitors
Neovascularization
Pharmacokinetics
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Monoclonal antibodies

Abnormal vasculature proliferation is one of the so-called hallmarks of cancer. Angiogenesis inhibitor therapies are one of the major breakthroughs in cancer treatment in the last two decades. Two types of anti-angiogenics have been approved: monoclonal antibodies and derivatives, which are injected and target the extracellular part of a receptor, and protein kinase inhibitors, which are orally taken small molecules targeting the intra-cellular Adenosine Triphosphate –pocket of different kinases. They have become an important part of some tumors' treatment, both in monotherapy or in combination. In this review, we discuss the key pharmacological concepts and the major pitfalls of anti-angiogenic prescriptions. We also review the pharmacokinetic and pharmacodynamics profile of all approved anti-angiogenic protein kinase inhibitors and the potential role of surrogate markers and of therapeutic drug monitoring.

1. Introduction

Due to their enlarged and tortuous vessels, Hippocrates compared the cross section of tumors to crab claws. This observation would explain the name “carcinoma” that he reportedly gave to this disease, which was later translated to the Latin word “cancer”. Judah Folkman (Folkman et al., 1971) first provided an explanation for this vasculature, isolating what he called tumor angiogenesis factor. Folkman later proposed the inhibition of this angiogenesis factor as a treatment. Tumor cells need oxygen and nutrients to grow, and passive diffusion only happens at scales of less than a millimeter. Therefore, angiogenesis is a key process for a macroscopic tumor, one of the so called hallmarks of cancer (Hanahan and Weinberg, 2000). In the last couple of decades, the development of drugs targeting angiogenesis through inhibition of vascular endothelial growth factors (VEGF) and their receptors (VEGFR), led to an important change in the oncology field. Although they are targeting the same pathway, two different categories of drugs were developed: monoclonal antibodies (MABs) and their derivatives, which are VEGF(R)-selective drugs administered intravenously and protein kinase inhibitors (PKIs), which are given orally (Figs. 1 and 2). PKIs are small molecules able to inhibit intracellular signal

transduction. Kinases have a phosphorylation activity that regulates survival and proliferation of cellular processes. PKIs inhibit a wide spectrum of kinases and are not specific to VEGF and/or its receptor (Fig. 3). They have a different spectrum of action and adverse effects depending on the kinases they inhibit. PKIs have a narrow therapeutic index. Hence, knowing basic pharmacological concepts, drug interactions and management of PKIs toxicity improves the quality of patient care. In this review, we discuss the pharmacological particularities of angiogenesis inhibitors, their indications, and their clinical management.

2. Clinical pharmacology

2.1. Pharmacological targets

2.1.1. VEGF/VEGFR pathway

VEGF/VEGFR pathway is one of the major pathways in angiogenesis. The VEGF family consists of five members: VEGF-A, B, C, D and Placental Growth Factor (Roskoski, 2017). VEGFR family consists of three members: VEGFR-1 (i.e, Fms Like Tyrosine kinase FLT-1, gene name *FLT1*) and VEGFR-2 (i.e, Kinase insert Domain Receptor KDR,

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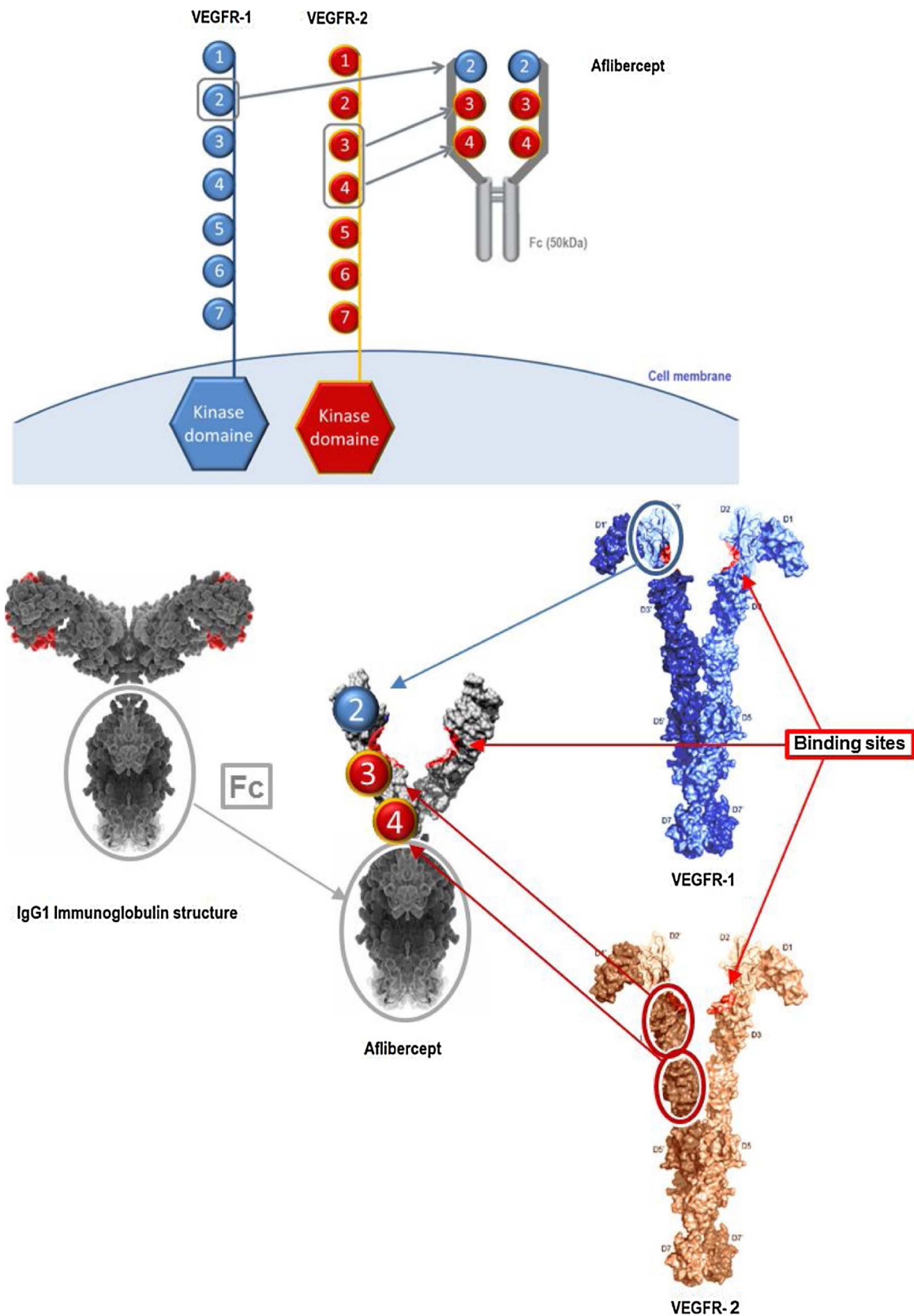


Fig. 1. Aflibercept structure. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.) Aflibercept is the product of the combination of Vascular Endothelial Growth Factor (VEGF) receptor-1 domain 2; of VEGF receptor-2 domain 3 and 4 and of the Fc part of an immunoglobulin. Aflibercept can bind with a high affinity to circulating VEGF-A, VEGF-B and PlGF which are both VEGFR-1 and VEGFR-2 ligands. Binding sites are shown in red. Abbreviations: Fc: crystallizable fragment; IgG: immunoglobulin type G; PlGF: Placental Growth Factor; VEGFR: vascular endothelial growth factor;

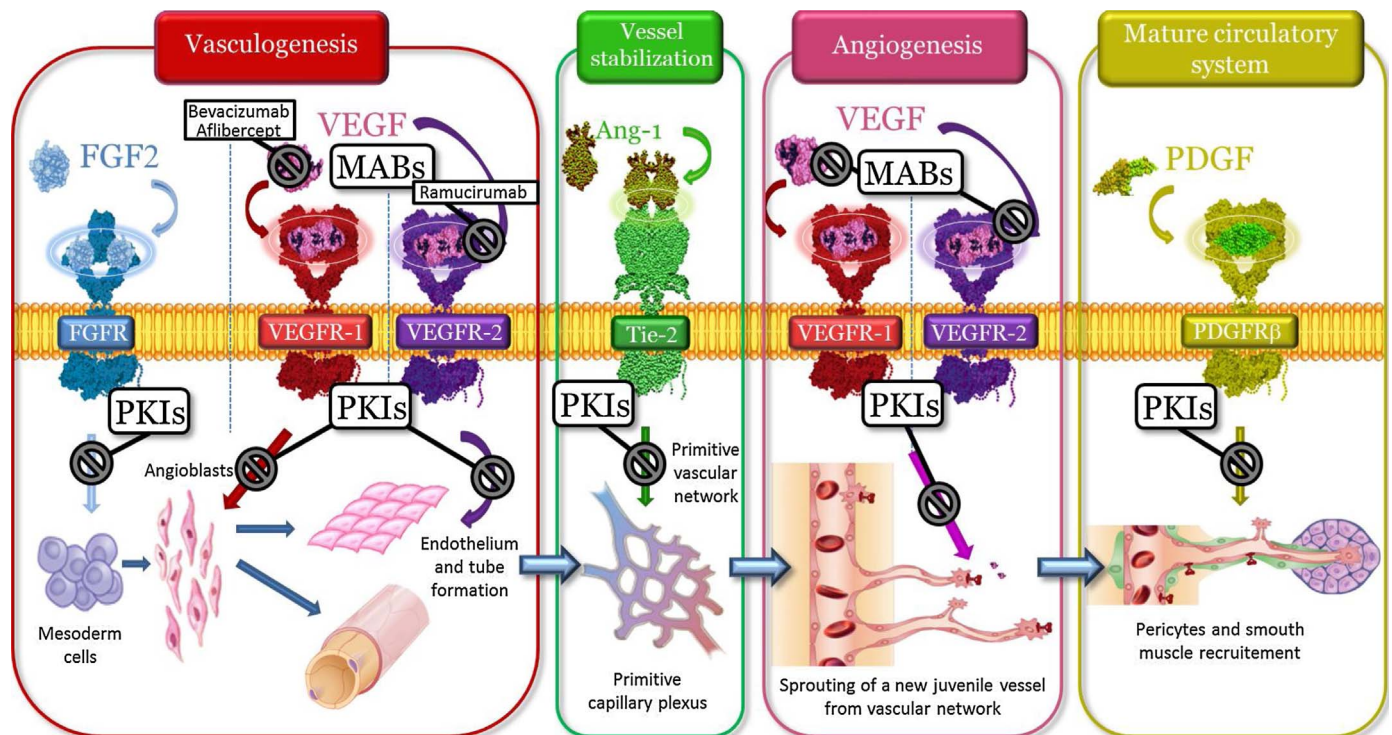


Fig. 2. Main tyrosine kinase receptors involved in tumor angiogenesis and vasculogenesis. Monoclonal antibodies (MABs) and derivatives directly target circulating Vascular Endothelial Growth Factor VEGF (bevacizumab and aflibercept) or the extracellular part of VEGF receptor-2 (ramucirumab) to prevent ligand receptor binding. Protein Kinase Inhibitors (PKIs) target the intra-cellular parts of the tyrosine kinase receptor, with an affinity depending on the PKI spectrum of kinase inhibition (Fig. 3).

Abbreviations: Ang-1: angiopoietin 1; FGF2: fibroblast growth factor 2; FGFR: fibroblast growth factor receptor; MAB: monoclonal antibodies (and derivatives for aflibercept); PDGF: platelet derived growth factor; PDGFRβ: platelet derived growth factor receptor; PKI: protein kinase inhibitor; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor;

gene name *KDR*) mainly involved in angiogenesis and vasculogenesis; VEGFR-3 (or Fms Like Tyrosine kinase FLT-4, gene name *FLT4*), mainly involved in lymphangiogenesis. VEGF-A, can either link to activate VEGFR-1, VEGFR-2 or neuropilin-1 (NRP1), the latter receptor also playing a role in both angiogenesis and vascular permeability (Shibuya, 2011). VEGF-A is a 45 kilo-Dalton (kDa) glycoprotein secreted by a large variety of human tumors. It is a mitogen protein, specific to endothelial cells, which is upregulated by hypoxia. It also triggers migration, differentiation, vascular permeability (Hicklin and Ellis, 2005) and mobilization of endothelial progenitor cells. VEGF receptors are transmembrane tyrosine kinase receptors: the ligand allows their dimerization that auto-phosphorylates and transduces the extracellular signal via either a mitogen activated protein (MAP) kinase or a phosphoinositide 3-kinase/mammalian target of rapamycin (PI3K/mTOR) pathway to promote the proliferation and the survival of vascular endothelial cells (Fig. 2).

There are different splicing variants of VEGF. These multiple isoforms do not bind VEGFR-1, VEGFR-2 or NRP1 with the same affinity (Abou-Fayçal et al., 2017). Splice variants are known as VEGFxxx, where xxx is the total number of amino acids in the mature protein, and differ by their amino-acid sequences. Therefore, they might play a different role. VEGF-A(165)b for instance, has the same amino-acid sequence as VEGF-A(165) except for the last 6 ones. It has been demonstrated that VEGF-A(165)b attenuates signaling potential through VEGF receptor 2 (Cébe Suarez et al., 2006). VEGF-A isoforms also have different epitopes, and bevacizumab might have a different binding affinity to different isoforms. This might affect bevacizumab's binding through competitive binding. For example, VEGF-A(165) and VEGF-A(165)b secretion produces a balance of antiangiogenic and proangiogenic actions in colorectal cancer (Varey et al., 2008). It regulates tumor growth rates and affects the sensitivity of tumors to bevacizumab by competitive binding. Of note, tumors might express different splicing

variants of VEGF (Vempati et al., 2014)

2.1.2. Extracellular targeting by monoclonal antibodies and immunoglobulin derivatives

MABs have a molecular weight of around 150 kDa and do not cross the cell membrane.

Bevacizumab is a recombinant humanized monoclonal antibody IgG1 targeting all isoforms of circulating VEGF-A.

Aflibercept was designed to have a broader spectrum of action than bevacizumab. It is a recombinant protein which is the fusion of both a VEGFR-1 and a VEGFR-2 extracellular domain portion to a crystallizable fragment (Fc) of immunoglobulin (Fig. 1). Aflibercept is, therefore, able to “trap” circulating ligands of VEGFR-1 and VEGFR-2, namely VEGF-A, VEGF-B and Placental Growth factor (Holash et al., 2002; Papadopoulos et al., 2012).

Ramucirumab is a human monoclonal antibody IgG1 designed to target VEGFR-2. It is an antagonist and prevents the binding of all the extra-cellular ligands of VEGFR-2 to their target, which is responsible for the majority of angiogenesis processes.

2.1.3. Intracellular targeting by PKIs

PKIs are much smaller lipophilic molecules able to diffuse through different membranes (Adrian et al., 2007). PKIs are a group of drugs that inhibit the transduction of a biological pathway by blocking the enzyme activity of a tyrosine or a serine/threonine kinase. Most of the PKIs are poorly selective and inhibit a wide spectrum of other protein kinases (Uitdehaag et al., 2012). Their spectrum of inhibition, characterized in vitro by their half maximal inhibitory concentration (IC50) or constant of inhibition K_i , is supposed to explain most of the differences in both activity and toxicity between PKIs (Davis et al., 2011). All approved anti-angiogenic (AA) PKIs target the VEGFR family, particularly VEGFR-1 and VEGFR-2. They also often inhibit members of the

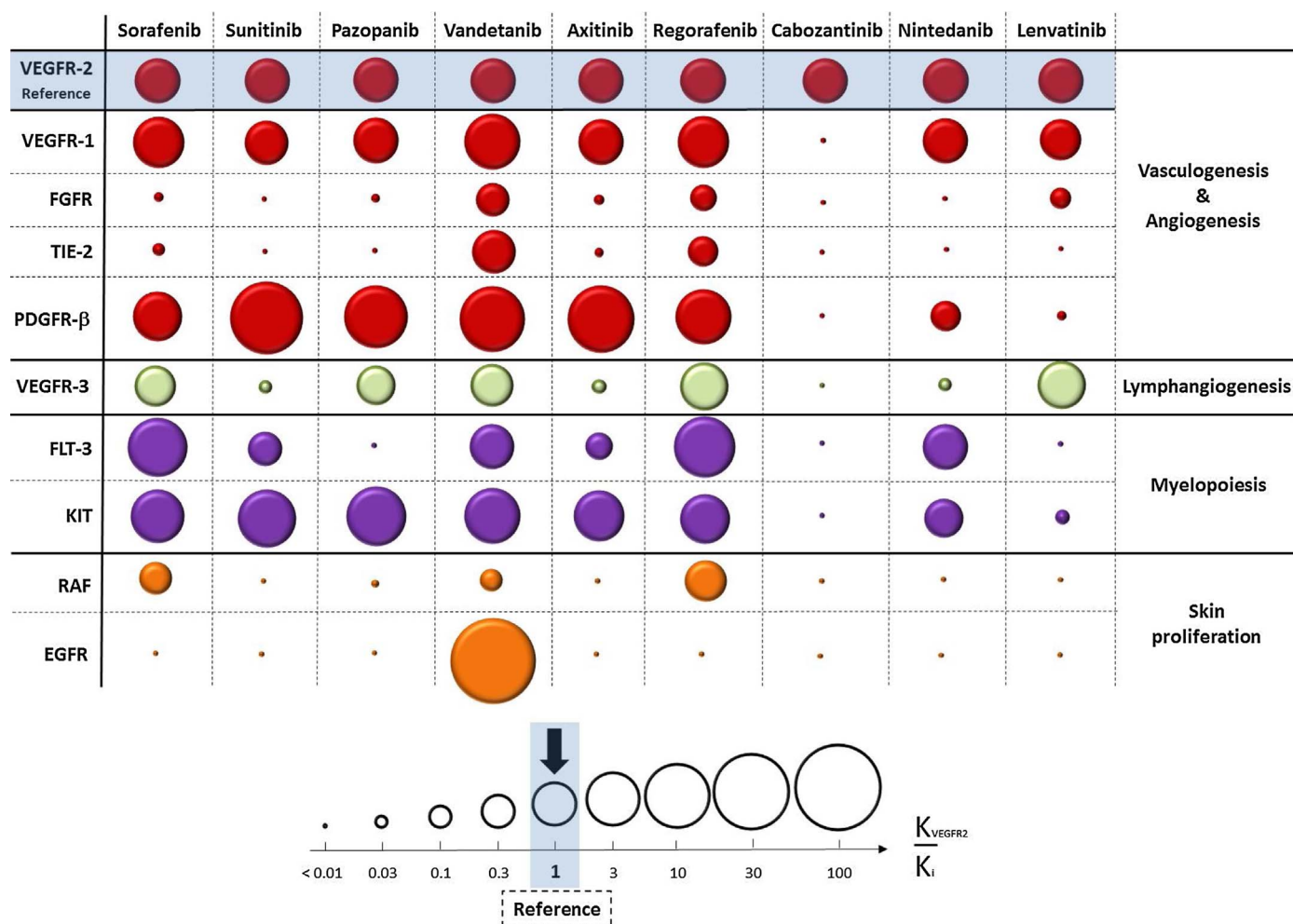


Fig. 3. Comparative spectrum of kinase inhibition for kinases of interest in angiogenesis and vasculogenesis and other physiological processes, for all approved antiangiogenic protein kinase inhibitors (PKIs). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Diagrammatic display of inhibition constant (K_i) ratios of different kinases by each anti-angiogenic protein kinase inhibitor, using Vascular Endothelial Growth Factor (VEGFR)-2 as a reference. For each molecule, the ratio is the K_i of VEGFR2 (which was used as a reference) divided by the K_i of each kinase receptor. On-target effects are represented in red. For each molecule, a bigger circle as compared to VEGFR2 represents a better in vitro inhibition of this kinase.

Abbreviations: EGFR: epidermal growth factor; FGFR: fibroblast growth factor receptor; FLT-3: Fms Like Tyrosine; K_i : constant of inhibition; KIT: tyrosine kinase KIT, also known as mast/stem cell growth factor receptor (SCFR); PDGFRβ: platelet derived growth factor receptor; RAF: rapidly accelerated Fibrosarcoma; VEGFR: vascular endothelial growth factor receptor;

Platelet Derived Growth Factor Receptor (PDGFR) family, like PDGFRβ (Davis et al., 2011). PDGF, the ligand of PDGFR, promotes the multiplication of mesenchymal cells, particularly fibroblasts and smooth muscle cells of vessels. Imatinib, which is a PDGFRβ inhibitor could also have an anti-vascular/anti-angiogenic property by targeting vascular pericytes within the smooth muscles (Rocha et al., 2007; Ruan et al., 2013). Similarly, Fibroblast Growth Factor (FGF) and its receptors (FGFRs) also modulate blood vessel growth (Presta et al., 2005) (Figs. 2 and 3).

AA PKIs may also have co-targets unrelated to angiogenesis inhibition. For instance, a difference of affinity for Epidermal Growth Factor Receptor (EGFR) kinases might explain a difference in the incidence of acneiform rashes among PKIs (Bunn and Franklin, 2002) (Figs. 3 and 4). Similarly, inhibitors of the serine/threonine Rapidly Accelerated Fibrosarcoma (B-RAF and C-RAF) induce more skin toxicity and hand-foot skin syndrome (Sibaud et al., 2013; Urban and Anadkat, 2013) than PKIs which does not.

Of note, some PKIs inhibiting these latter pathways with no relevant effect on VEGFR pathways, might also share AA properties. As an example, imatinib inhibits PDGFRβ and has been shown to have AA properties by targeting vascular pericytes (Rocha et al., 2007; Ruan et al., 2013).

2.1.4. Other mechanisms

Other mechanisms inhibiting angiogenesis should be mentioned. Metronomic chemotherapy, which consists in regularly giving a small amount of drug, particularly microtubule-targeting agents, also possesses anti-angiogenic properties at non-cytotoxic levels. This effect is mediated through direct effects on vascular endothelial cells proliferation (Biziota et al., 2017; Schwartz, 2009).

2.2. Pharmacokinetics in cancer

2.2.1. Antibodies and immunoglobulin derivatives intracellular targeting by PKIs

Pharmacokinetics (PK) of anti-cancer MABs differs from that of PKIs due to their high molecular weight. Their diffusion is slow, and they have a small volume of distribution. Like most therapeutic immunoglobulin G, they have a half-life of approximately 20 days, and they are administered intravenously (Table 1). Circulating phagocytic cells degrade them into amino acids and peptides via the reticuloendothelial system (Newsome and Ernstoff, 2008). Main PK characteristics of bevacizumab, aflibercept and ramucirumab are shown in Table 1 (Han et al., 2016; Thai et al., 2013; Ohtsu et al., 2011; Spratlin et al., 2010; Caulet et al., 2016).

	Sorafenib	Sunitinib	Pazopanib	Vandetanib	Axitinib	Regorafenib	Cabozantinib	Nintedanib	Lenvatinib
Hypertension	< 20%	20 - 50%	20 - 50%	20 - 50%	20 - 50%	20 - 50%	20 - 50%	< 20%	> 50%
Fatigue	< 15%	< 15%	< 15%	< 15%	15 - 30%	15 - 30%	< 15%	< 15%	> 30%
Nausea	< 10%	10 - 20%	10 - 20%	10 - 20%	10 - 20%	< 10%	> 20%	< 10%	> 20%
Diarrhea	20 - 40%	> 40%	> 40%	20 - 40%	20 - 40%	20 - 40%	> 40%	20 - 40%	> 40%
Stomatitis	< 15%	> 30%	< 15%	< 15%	< 15%	15 - 30%	15 - 30%	< 15%	> 30%
Rash	15 - 30%	< 15%	< 15%	> 30%	< 15%	15 - 30%	< 15%	< 15%	15 - 30%
Hand-foot skin reaction	> 40%	20 - 40%	< 20%	< 20%	< 20%	> 40%	20 - 40%	< 20%	< 20%
Hepatotoxicity	< 20%	20 - 40%	> 40%	> 40%	< 20%	< 20%	> 40%	20 - 40%	20 - 40%
Neutropenia	< 20%	> 40%	20 - 40%	< 20%	< 20%	< 20%	20 - 40%	< 20%	< 20%
Thrombopenia	< 20%	> 40%	20 - 40%	< 20%	< 20%	< 20%	20 - 40%	< 20%	< 20%

Fig. 4. Spectrum of main toxicities for anti-angiogenics protein kinase inhibitors. Absolute difference of percentage incidence of toxicity between the anti-angiogenic drugs arm and the placebo/control arm in main clinical trials.

A population PK model of bevacizumab using a bicompartamental model in 1792 patients with a wide variety of cancers (Han et al., 2016) showed a central volume of distribution (V1) of 2.88 L and a half-life of 19.6 days (normalized to 70-kg) (Table 1). Clearance and V1 increased with body weight and were higher in males. Other parameters influencing pharmacokinetics were albumin and plasma levels of alkaline phosphatase. Interestingly, bevacizumab PK vary among indications. For example, bevacizumab clearance is 50% higher in gastric cancer as compared to other cancers ($p < 0.0001$, Han et al., 2014). The AVA-GAST study, evaluating bevacizumab in addition to chemotherapy in gastric cancer versus chemotherapy alone, failed to significantly improve the primary endpoint of overall survival (Ohtsu et al., 2011) possibly due to higher clearance and lower plasma concentrations. Tumor burden also plays a role (Caulet et al., 2016), increasing bevacizumab's clearance.

2.2.2. Protein kinase inhibitors

2.2.2.1. Bioavailability. PKIs have different bioavailability, depending on their solubility, their acid constant (pKa), their passive permeability and their affinity with carrier-mediated transporters such as P-glycoprotein (P-gp) also called ATP-binding cassette sub-family B member 1 (ABCB1) or Breast Cancer Resistance Protein (BCRP) also known as ATP-binding cassette sub-family G member 2 (ABCG2), located in the intestinal wall. We summarize bioavailability data of AA PKIs in Table 2. Of note, bariatric surgery or gastric surgery can also be of great consequence on bioavailability (van Kinschot et al., 2015).

2.2.2.2. Volume of distribution. The volume of distribution is a virtual volume in which the drug is appears to be distributed. Depending on its lipophilic-hydrophilic balance, a drug diffuses more or less in different tissues. Patient's lean body mass and visceral fat influence the volume of distribution of the drug. Obese patients have a very different volume of distribution and PK than non-obese patients (Lemmens and Ingrande, 2013). No trial and only a few case reports have investigated on the role of obesity on PK of AA PKIs (Desar et al., 2009).

2.2.2.3. Drug metabolism and hepatic elimination. PKIs are mostly metabolized by the liver, through phase 1 (oxido-reduction reactions, mainly CYP3A4) and phase 2 reactions (glucosyl conjugation by UDP-glucuronosyltransferase like UGT1A1 for instance). Details concerning the metabolism of AA PKIs are provided in Table 2. Due to its frequent liver toxicity, cabozantinib dosage should be reduced in patients with Child-Pugh score A or B (Herbrink et al., 2015) and is contraindicated in patients with Child-Pugh score C. Dose adaptations for other PKIs are reported in Table 3.

2.2.2.4. Active metabolites. Sunitinib and regorafenib are PKIs which form active metabolites. Regorafenib has 2 active metabolites, M-2 and M-5. They have shown similar kinase inhibition profile as the parent drug in a preclinical model. Other approved AA PKIs do not form active metabolites.

2.2.2.5. Renal elimination. Except for vandetanib, most PKIs have a very limited renal clearance. Therefore, dose adaptation according to renal impairment is rarely required for most AA PKIs (Table 3). Vandetanib dose should be reduced to 200 mg once daily in patients with moderate renal insufficiency (creatinine clearance < 50 mL/min). Intriguingly, sunitinib and its main active metabolite SU12662 are not dialyzable but the mean plasma concentration of sunitinib is lower in patients with chronic hemodialysis as compared to patients with or without severe renal impairment: maximum concentration (C_{max}) and area under curve (AUC) have a hemodialyzed vs. normal ratio of 0.70 and 0.69 (90% confidence interval (CI) [54–90]) and [54–87], respectively (Josephs et al., 2011; Khosravan et al., 2010). Thus, Sunitinib is used at similar doses in patients with or without severe renal impairment or need for hemodialysis.

2.2.2.6. Sunitinib oral regimen. Most PKIs are administered orally and continuously. However, sunitinib was originally designed to be administered by sequences of 4 weeks ON (50 mg once a day) followed by two weeks OFF. Other schemes were tried (Escudier et al., 2009). In a randomized trial, the 37.5 mg continuous regimen

Table 1
Pharmacokinetic properties and clinical indications of monoclonal antibodies and derivatives.

Generic name	Bevacizumab	Aflibercept (Ziv-Aflibercept)	Ramucirumab
Target	Circulating VEGF A	Circulating VEGF A, VEGF B and PlGF	Tumoral VEGFR-2
Type of MAB	Humanized IgG1	MAB derivative : combination of VEGFR receptor and Fc region (Fig. 1)	Human IgG1
Volume of distribution (L)	2.88	~4	5.5
Terminal half-life (days)	19.6	5.5	15
Metabolism	Reticuloendothelial system	Likely reticuloendothelial system	Reticuloendothelial system
Dose adaptation if renal or hepatic impairment	No	No, NR for severe impairments	No
PK drug-drug interaction	NR	NR	NR
Colorectal cancer	Shorter half-life for gastric cancer 5 mg/kg every 2weeks Combined with bolus IFL	4mg/kg every 2 weeks with FOLFIRI after progression with FOLFOX	Clearance and half-life modified by tumor volume 8mg/kg every 2 weeks in combination with FOLFIRI after progression with FOLFOX and bevacizumab
	10 mg/kg every 2weeks Combined with FOLFOX4	-	-
	5 mg/kg every 2weeks or 7.5 mg/kg every 3weeks	-	-
Non-small cell lung cancer	Combined with FOLFIRI or FOLFOX for a 2nd line after 1st line with bevacizumab	-	-
	-	-	-
Gastric cancer	Non squamous non-small cell lung cancer : 15 mg/kg every 3 weeks in combination with carboplatin and paclitaxel for 1st line	-	10 mg/kg every 3 weeks in combination with docetaxel, for 2nd line after platinum based chemotherapy
Metastatic renal cell carcinoma	10 mg/kg IV every 2 weeks with interferon-alpha	-	8 mg/kg every 2 weeks monotherapy or in combination with weekly paclitaxel, for 2nd line
Metastatic or inoperable carcinoma of the cervix	15 mg/kg IV every 3 weeks with paclitaxel/cisplatin or paclitaxel/topotecan	-	-
Epithelial ovarian, fallopian tube, or primary peritoneal cancer	10 mg/kg IV every 2 weeks with paclitaxel, pegylated liposomal doxorubicin or weekly topotecan after no more than 2 chemotherapy regimen	-	-
	15 mg/kg IV every 3 weeks with topotecan given every 3 weeks after no more than 2 chemotherapy regimen	-	-
Platin resistant	15 mg/kg IV every 3 weeks in combination with carboplatin/paclitaxel for 6–8 cycles, and then as a single agent	-	-
Platin sensitive	15 mg/kg IV every 3 weeks in combination with carboplatin/gemcitabine for 6–10 cycles, and then as a single agent	-	-
Glioblastoma	10 mg/kg IV every 2 weeks	-	-

Abbreviations: DDI: drug-drug interaction; IFL: 5-Fluorouracil (5FU) and leucovorin (= folinic acid); IV: intravenous; Fc: fragment crystallizable region; FOLFIRI: 5FU, leucovorin and irinotecan; FOLFOX: 5FU, leucovorin and oxaliplatin; IV: intravenous; IgG: immunoglobulin; MAB: monoclonal antibody; NR: Not reported; PK: pharmacokinetics; PlGF: Placental growth factor; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor

Table 2
Pharmacokinetic properties of approved anti-angiogenic protein kinase inhibitors.

Generic name	Sorafenib	Sunitinib	Pazopanib	Vandetanib	Axitinib	Regorafenib	Cabozantinib	Nintedanib	Lenvatinib
Bioavailability (%) ¹ Volume of distribution (L)	43 ~200	NR ~2000	26 ~10	NR ~4000	52 ~200	69 NR	Unknown ~300	5 ~1000	90 ~100
Active metabolite	No	M-1: N-desethyl – sunitinib 41–86 and 93 for M-1	No	No	No	M-2: N-oxide, M-5: N-oxide, N-desmethyl	No	No	No
Terminal half-life (hours)	25–48	8 93 for M-1	31	216–247	2.5–6.1	14–58 and 14–32 for M-2 and 32–70 for M-5	55–100	12–14	28
Tmax (hours)	2	8	2–4	4–8	2–4	4	3–4	4	1–4
Excretion in feces in% (unchanged in%)	77 (50)	61 (Sunitinib 14, M1 25)	> 95 (NR)	64 (NR)	41 (12)	71 (47)	54 (NR)	93 (NR)	64 (NR)
Excretion in urines in%	19	16	4	36	23	19	27	< 1	25
Main Metabolism	CYP3A4, UGT1A9	CYP3A4	CYP3A4	CYP3A4, FMO-1/3	CYP3A4/5	CYP3A4, UGT1A9	CYP3A4, 2C8	Esterases	CYP3A and aldehyde oxidase
P-gp and BCRP substrate	Yes	Yes	Yes	Yes	Yes	Yes	No	P-gp only	Yes
Other transporters	OATP, MRP-2, MRP-3	OATP	OATP	OATP	OATP	OATP, MRP-2	MRP-2	NR	NR
CYP and transporters inhibited by the protein kinase inhibitor	P-gp	P-gp and BCRP	CYP3A4, CYP2D6, OCT2, MATE1, MATE2-K	OCT2, MATE1, MATE2-K	CYP3A5	P-gp and BCRP	P-gp, MATE	OATP1B1, IB3 and 2B1, OCT-2, and MRP-2	OAT(1–3), OCT(1–2), OATP1B1, BSEP
PK particularities	Non-linear PK, EHC ^a , long term decrease of steady state concentration	Highly non-linear bioavailability (14–39%) ^c , long term decrease of steady state concentration	Clinical relevance of renal clearance	Short half-life	Non-linear accumulation of active metabolites M-2 and M-5 with similar kinase inhibition profile, EHC	Good diffusion through blood brain barrier, different bioavailability for tablets and capsules	Very low bioavailability		

Abbreviations: BCRP: breast cancer resistant protein; BSEP: bile salt export pump; EHC: enterohepatic circulation; FMO: Flavin-containing Monooxygenases; MATE: multi-antimicrobial extrusion protein; MRP: multidrug resistance-associated protein; NR: not reported; OAT: Organic anion transporter; OATP: organic anion-transporting polypeptide; OCT: organic cation transporter; P-gp: P-glycoprotein; PK: pharmacokinetics.

¹ Herbrink et al. (2015).

^b Hilger et al. (2009).

^c Yu et al. (2017).

Table 3
Prescription guidelines for approved anti-angiogenic protein kinase inhibitors.

Generic name	Sorafenib	Sunitinib	Pazopanib	Vandetanib	Axitinib	Regorafenib	Cabozantinib	Nintedanib	Lenvatinib
Preclinical name	BAY 43-9006	SU11248	GW786034	ZD6474	AG-13736	BAY 73-4506	XL184	BIBF1120	E7080
Standard dose	400 mg BD	50 mg OD, 4w-ON/ 2w-OFF	800 mg OD	300 mg OD	5 mg BD	160 mg OD 3w-ON/ 1w-OFF	Cf. infra	200 mg BD	Cf. infra
Indication	Advanced Renal Cell Carcinoma	Any line	Any line	-	2nd line	-	2nd line 60 mg OD tablets	-	2nd line 18 mg OD with 5 mg everolimus OD
	Metastatic Colorectal Cancer	-	-	-	-	3rd line ^a	-	-	-
	Unresectable Hepatocellular Carcinoma	1st line	-	-	-	2nd line ^b , Child-Pugh A	-	-	-
	Iodine resistant Differentiated Thyroid Cancer	Any line	-	-	-	-	-	-	Any line
	Medullary Thyroid Cancer	-	-	Any line	-	-	Any line, 140 mg OD capsules	-	24 mg OD
	Gastro-Intestinal Stromal Tumor	-	2nd line (after imatinib)	-	-	3rd line (after imatinib/sunitib failure)	-	-	-
	Well-differentiated pancreatic neuroendocrine tumors	-	Any line, 37.5 mg OD continuously	-	-	-	-	-	-
	Advanced Soft-Tissue Sarcoma, (except adipocytic)	-	2nd line (after chemotherapy)	-	-	-	-	-	-
	Non-small cell lung cancer	-	-	-	-	-	-	2nd line ² with docetaxel 75 mg/m ² /3w	-
Administration fed or fasted	Fasted, avoid anti-acids	Fed or fasted	Fasted, avoid anti-acids	Fed or fasted	Fed or fasted	Fed with low fat meal, interaction with anti-acids unknown	Fasted	Fed, interaction with anti-acids unknown	Fed or fasted
Liver impairment	No adjustment	No adjustment	Reduced dose	Avoid	Reduced dose	No adjustment	Reduced dose	NR, avoid	No adjustment
Child-Pugh	NR	NR	Avoid	Avoid	NR	NR	Avoid	NR	Reduced dose
Renal impairment	No adjustment	No adjustment	No adjustment	Reduced dose (GFR < 50 _{ml/min})	No adjustment	No adjustment	NR for severe ^c	NR for severe ^c	Reduced dose for severe ^c
DDI	Avoid	Avoid	Avoid	Avoid	Avoid	Avoid	Avoid	Avoid	NCS
Strong CYP3A4 inducers	NCS	Avoid	Avoid	NCS	Avoid	Avoid	Avoid	Avoid	NCS
Strong CYP3A4 inhibitors	-	Green tea (decreased bioavailability of sunitinib), decreased effect of levothyroxine	Simvastatin (hepatotoxicity)	Digoxin (increased digoxin exposure), metformin (increased metformin exposure), decreased effect of levothyroxine	-	Rosuvastatin (rosuvastatin increased exposure)	-	-	-
Other DDI	-	-	-	-	-	-	-	-	-

Abbreviations: BCRP: breast cancer resistance protein; BD: bis in die (twice a day); CYP: cytochrome P450; DDI: drug-drug interaction; FDA: food and drug administration; GFR: Glomerular filtration rate (evaluated by creatinine clearance); NCS: not clinically significant; NR: not reported; OD: once daily; RAS: Rat Sarcoma; w: week; wt: wild type.

^a Previously treated with: fluoropyrimidin, irinotecan, oxaliplatin, bevacizumab and cetuximab (if RAS wt).

^b Not currently approved by FDA.

^c Severe renal impairment defined by GFR < 30 mL/min calculated with creatinine clearance.

had a trend to a worse time to progression when compared to 4/2 wk regimen (7.1 vs 9.9 months, $p = 0.09$, respectively) (Motzer et al., 2012). It was suggested that the intermittent dosing had a better activity, although it is counterintuitive that an AA drug would be more effective in an intermittent rather than in a continuous regimen. The RESTORE study (Lee et al., 2015a,b) also compared different dosing regimens for the treatment of clear cell renal cell carcinomas (CCRCC). Lee et al. compared a 2-week ON, 1 week OFF regimen, which tended to improve the rate of failure free survival at 6 months when compared to the 4/2 regimen (63% vs 44%, not clinically significant) and appeared to have a better safety profile.

2.3. Potential for drug interactions

2.3.1. Pharmacokinetic interactions

MABs and derivatives

Most monoclonal antibodies are not subject to drug–drug interactions (DDI) (Keizer et al., 2010). Mabs elimination is related to immune system (phagocytosis), and therefore immunosuppressive drugs can have a measurable effect on mabs PK (Keizer et al., 2010).

2.3.1.1. Gastric acidity. Anti-acid drugs modify gastric acidity. Some drugs like pazopanib are multiple acids with different pKa. Depending on their acid form, they are more or less ionized. Ionized forms have a better solubility in water and a very low passive diffusion through membrane barriers. Acidity is therefore critical for drug solubility and absorption. While on 40 mg esomeprazole daily, pazopanib AUC₀₋₂₄ and Cmax decreased by 40 and 42%, respectively (Tan et al., 2013). Therefore, pazopanib and anti-acids should not be used concomitantly (Table 3). Recommendations concerning AA PKIs intake fed or fasted and main interactions with drugs modifying gastric acidity are summarized in Table 3.

2.3.1.2. CYP interaction. Most PKIs are predominantly eliminated by the liver, mainly by cytochromes P-450 (CYP) pathways (Rowland et al., 2017). Table 3 summarizes known DDIs for each PKI and recommendations concerning dose adaptations in case of liver impairment. Association with CYP inhibitors or inducers (mainly CYP 3A4/5) should be avoided for most PKIs. Of note, main CYP3A4/5 inhibitors include azole antifungals (ketoconazole and itraconazole among others), ritonavir, macrolides (erythromycin and clarithromycin) and grapefruit juice. CYP3A4 inducers include antiretrovirals (efavirenz, nevirapin), barbiturates, carbamazepine, rifampin, glucocorticoids, and Saint-John's wort.

2.3.2. Pharmacodynamic interactions

Considering the increased risk of bleeding with all AA drugs, particularly in colorectal cancer and lung cancer (cf. § 1.5), a particular caution should be given to the association of anticoagulants or antiplatelets drugs.

The use of simvastatin concomitantly with pazopanib increases the risk of transaminase elevation (Xu et al., 2012). Other interactions (Table 3) have been described including the precipitation of sunitinib with concomitant green tea (Ge et al., 2011) with a decrease of Cmax and AUC of 50% ($p < 0.01$) when sunitinib is administered with green tea extracts compared to water in preclinical models. Another described interaction is the decreased effect of levothyroxine due to sunitinib and vandetanib (de Groot et al., 2006).

2.3.3. Pharmacogenetic interactions

Many findings about polymorphisms of CYP or drug transporters and their role in the elimination of PKIs have been reported. Some results were controversial (Erdem et al., 2012; Pander et al., 2010). Most studies did not show a clinically significant relevance for these polymorphisms. As an example, CYP3A4 variants change sunitinib and SU12662 clearance, but the effect is below inter-individual variability

(Diekstra et al., 2014). However, 421-AA genotype of adenosine triphosphate binding cassette subfamily G member 2 was associated with more sunitinib-related toxicity in a Korean population (Kim et al., 2013). In the E2100 study which assessed efficacy of bevacizumab combined with paclitaxel or placebo in metastatic breast cancer, Schneider et al., also demonstrated an influence of VEGF 2578-AA genotype on the outcome under bevacizumab. This genotype was associated with a better overall survival and a higher risk of hypertension (Schneider et al., 2008).

2.4. Different indications of angiogenesis inhibitors based on cancer types

All approved AA inhibit at least the VEGF/VEGFR-2 pathway. However, they do not share the same selectivity for other on-target (VEGFR1, VEGFR2 for example) or off-target kinases such as RAF (Fig. 3). Therefore, they do not have the same clinical efficacy on different cancer types (Table 3) or the same spectrum of side effects (Fig. 4).

2.4.1. Metastatic clear cell renal cell carcinoma

Most (90%) CCRCC have a mutation of the Von Hippel Lindau protein (pVHL), a tumor suppressor. In normal cells and under normoxic conditions, pVHL binds to the Hypoxia Inducible Factor (HIF) to promote its ubiquitination and degradation. The loss of pVHL function leads to a constant activation of HIF and an upregulation of VEGF among other pro-angiogenic factors (Frew and Moch, 2015). Although chemotherapy and radiotherapy are both inefficient, many drugs inhibiting the VEGF-VEGFR pathway improve the overall outcome in patients with metastatic CCRCC (mCCRCC).

Sorafenib was the first drug in the protein kinase inhibitor class to be approved for mCCRCC. It was first developed for its activity against RAF-1, but sorafenib also had a broad-spectrum tyrosine kinase inhibition including most receptors implicated in angiogenesis processes including VEGFR-2 (Fig. 2). Sorafenib improved progression-free survival (PFS) as compared to placebo (5.5 vs. 2.8 months, $p < 0.01$) (Escudier et al., 2007a).

Sunitinib is another VEGFR inhibitor and was approved for the same indication than sorafenib one month later. Sunitinib improved PFS, as compared to interferon alpha (11 vs. 5 months, $p < 0.001$) (Motzer et al., 2007). Although the populations of these phase 3 trials were not similar, sunitinib provided a higher response rate than sorafenib (31% vs. 10%, respectively). Of note, differences in the spectrum of kinase inhibition between these two drugs might explain the differences in both efficacy and safety (Figs. 3 and 4) (Stein and Flaherty, 2007).

Other AA PKIs were later developed for this indication. In a phase 2 open label study in mainly treatment naïve (69%) patients, pazopanib had an interesting activity with a PFS of 12 months and an overall response rate (ORR) of 35% (Hutson et al., 2010). In another randomized phase 3 trial, pazopanib was also non-inferior to sunitinib and showed a better safety profile and a better quality of life in first line (Motzer et al., 2013). Axitinib was developed to have a more specific activity against VEGFR family receptors, and less off-target side effects (Figs. 3 and 4). Rini et al. explored the possibility of drug titration for axitinib in a trial allowing axitinib increased dosage in case of good tolerance compared to no axitinib adaptation (Rini et al., 2013). The ORR was higher in the axitinib adaptation dose group (ORR = 54% vs. 34%, $p = 0.019$). The dose increase from 5 mg bid to 7 mg bid was allowed for patients with blood pressure $\leq 150/90$ mmHg on no more than two antihypertensive drugs and no other grade 3–4 treatment-related toxic effects. Axitinib also improved PFS, as compared to sorafenib as a second line therapy (6.7 vs. 4.7 months, $p < 0.0001$) (Rini et al., 2011).

Sorafenib, sunitinib pazopanib and axitinib have an activity against PDGF α and Stem Cell Factor Receptor, also known as c-KIT. Cabozantinib does not, and its spectrum of inhibition includes Mesenchymal-Epithelial Transition factor (c-MET), Rearranged during Transfection (RET) and AXL receptor tyrosine kinase in addition to

VEGFR. Recently, it was shown in the CABOSUN phase 2 trial that cabozantinib improved the PFS as compared to sunitinib in a first-line therapy (8.2 vs. 5.6 months, $p = 0.012$, respectively), with similar safety profile (Choueiri et al., 2017). Further investigations might be needed to make cabozantinib a standard in first line in mCCRCC treatment. Cabozantinib was also randomized against everolimus, an mTOR inhibitor, in a phase 3 trial in second line, with a significant improvement in the overall survival (21.4 months vs. 16.5, $p < 0.001$) (Choueiri et al., 2016).

Finally, lenvatinib, a PKI with a dual VEGFR and pan-FGFR activity (Fig. 3), in association with everolimus was also approved by the Food and Drug Agency (FDA) for the treatment of mCCRCC following one prior AA. The combination had an important activity but was more toxic than other PKIs in monotherapy (Fig. 4).

Among MABs, bevacizumab was evaluated in combination with interferon alpha-2a, which was the standard of care at that time (Escudier et al., 2007b). Despite a notable activity, this combination has been largely abandoned, due to the poor tolerance of interferon and the induced fatigue.

2.5. Choice of PKI for mCCRCC

In a recent meta-analysis, Rousseau et al. showed that the different AA PKIs (sunitinib, pazopanib, sorafenib, axitinib) and the association of bevacizumab plus interferon had similar efficacy on overall survival in first line when treating mCCRCC (Rousseau et al., 2016). This study supports the view that choice of AA PKI in this indication may be driven by its safety profile more than by its efficacy. Main toxicities with the different AA PKIs are summarized in Fig. 4. Briefly, sorafenib is associated with more hand-foot syndromes, and less nausea and anorexia. Sunitinib increases hematological toxicities (mainly neutropenia and thrombocytopenia) and anorexia. Pazopanib is associated with less fatigue and hand-foot skin reaction than sunitinib, but more liver toxicities (Motzer, 2016), and had a better quality of life score as compared to sunitinib, in the COMPARZ trial (Motzer et al., 2013). In the double-blind PISCES trial, Escudier et al. randomized patients in a cross-over scheme to receive either sunitinib or pazopanib (Escudier et al., 2014). The primary outcome was the patients' preference for the PKI administered: Pazopanib was preferred to sunitinib (70 vs. 22%, $p < 0.001$) with 8% of patients having no preference. Pazopanib also had better results as compared to sunitinib on measures evaluating fatigue, hand-foot skin reaction, and mouth/throat soreness.

Of note, the ability of cabozantinib to cross the blood-brain barrier as compared to other approved PKIs in mCCRCC raises the question of a potential increased beneficial effect in case of brain metastases (Abdelaziz and Vaishampayan, 2017). Clinical trials to evaluate such specific subpopulations need further evaluation. Finally, the approval of the immune checkpoint inhibitor nivolumab as second line in mCCRCC treatment also introduces complexity in the choice of the best sequence (Malouf et al., 2016).

2.5.1. Advanced hepatocellular carcinoma

Hepatocarcinoma (HCC) has two specific features. First, they are highly vascularized. As a consequence, they are hyperdense during the hepatic arterial phase on a multiphase perfusion CT-scan and then have an early wash-out. Second, most patients with HCC have underlying liver cirrhosis and many comorbidities.

In a randomized placebo controlled phase III trials, sorafenib, improved overall survival in patients with advanced HCC (Llovet et al., 2008) with a median overall survival which was increased from 7.9 months to 10.7 months compared to placebo ($p < 0.001$). Interestingly, the phase 1 trial of sorafenib concluded to the same maximum tolerated dose in patients treated for non-resectable HCC compared to other cancers, despite significant liver dysfunction in this population, with no PK difference between Child-Pugh A and Child-Pugh B patients (Abou-Alfa et al., 2006).

Regorafenib is active on many other pathways than VEGF/VEGFR2, namely: Tyrosine kinase with Immunoglobulin-like and EGF-like domains (TIE-2)/angiopoietin-1 (Ang1), PDGF/PDGFR, FGF/FGFR. In patients with advanced HCC previously treated with sorafenib Bruix et al. showed an increase of 3 months in overall survival (10.6 months vs 7.8 months, $p < 0.0001$) with regorafenib compared to placebo (Bruix et al., 2017).

2.5.2. Thyroid cancer

Like HCC and CCRCC, differentiated thyroid cancers (DTC) are also hyper vascularized. Lenvatinib, a PKI with a very large spectrum (Fig. 3), was particularly efficacious for the treatment of radioiodine-resistant DTC. In the SELECT phase 3 trial, the PFS was 18.3 months compared to 3.6 months in the placebo group (HR = 0.21, $p < 0.001$), with a response rate of 64.9% compared to 1.5% in the placebo group (Schlumberger et al., 2015). Sorafenib was assessed in a phase III and vandetanib was also assessed in a phase II, both compared to placebo in the same indication. Sorafenib was approved and vandetanib showed some activity. They both seemed less efficient than lenvatinib but they were also less toxic than lenvatinib, and the benefit of lenvatinib on overall survival has not been demonstrated yet. It should be noted that at the standard dose of 400 bid, more toxicities were observed with sorafenib in the DTC population than in the HCC and the RCC populations (Jean et al., 2016).

Medullary thyroid cancer (MTC) oncogenesis mostly happens through a sporadic or a congenital mutation of the RET oncogene. Vandetanib (Wells et al., 2012) and cabozantinib (Elisei et al., 2013) are two dual inhibitors of VEGFR and RET pathways, and they both proved to be effective in patients with advanced MTC.

2.5.3. Metastatic colorectal cancer

RAS-mutated metastatic colorectal cancer (mCRC), representing 50% of mCRC cases, are resistant to cetuximab and panitumumab, two MABs targeting EGFR. Bevacizumab, in contrast, is active in both RAS-mutated and RAS wild-type mCRC patients. A phase 2 study comparing Leucovorin and 5-Fluorouracil (LV5FU2 regimen) versus LV5FU2 plus bevacizumab, showed an increase of the PFS (5.5 vs. 10.2 months). However, the primary endpoint was overall survival which was not significantly improved (Kabbavar et al., 2003). A phase 3 trial comparing FOLFIRI (Folinic acid, 5-Fluorouracil, and Irinotecan) and FOLFIRI plus bevacizumab for mCRC, confirmed a higher PFS with the adjunction of bevacizumab, independently of the KRAS status (Hurwitz et al., 2004). In the FIRE-3 study, comparing FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab in mCRC harboring a KRAS mutation, there was no significant difference in the overall response rate (62% vs 58%, respectively, odds ratio (OR) = 1.18, $p = 0.18$) which was the primary endpoint. However, the cetuximab arm had a better median overall survival (28.7 months vs 25.0 months, $p = 0.017$) (Heinemann et al., 2014).

Aflibercept also proved to be useful, as a second line therapy and combined with FOLFIRI (Van Cutsem et al., 2012). But the modest improvement in the overall survival (13.5 vs. 12.0 months) was balanced with a significant increase in toxicities and cost (Wade et al., 2015). In addition, only 30.5% of the patients had previously received bevacizumab.

The RAISE trial compared FOLFIRI with Ramucirumab or FOLFIRI with a placebo, in patients who progressed after a prior therapy combining oxaliplatin, fluoropyrimidine, and bevacizumab, and found a benefit on overall survival (13.3 vs. 11.7 months, $p = 0.022$) which was the primary endpoint (Tabernero et al., 2015).

Regorafenib is the only PKI approved in the management of mCRC, after showing a benefit in the CORRECT study (Grothey et al., 2013). Interestingly, all patients were previously treated with bevacizumab. In comparison with the placebo, the increase of overall survival was modest, 6.4 months vs. 5.0 (hazard ratio = 0.77, $p = 0.0052$), but the population of the study was heavily pre-treated. To date, aflibercept,

ramucirumab and regorafenib are not standards of care because of their modest activity balanced with their significant toxicity and cost. However, patients often have no standard of care left at this stage of the disease, and these treatments significantly improved overall survival. They could therefore be considered as an option for patients with a good performance status and no limiting cardio-vascular comorbidities.

2.5.4. Sarcomas

Sunitinib and regorafenib are two inhibitors of c-KIT (Fig. 3), encoded by the *KIT* oncogene which is an important driver mutation in gastro-intestinal stromal tumors (GISTs). They were both approved, in second and third line of treatment respectively, in this indication (Demetri et al., 2006, 2013).

In the REGOSARC study (Mir et al., 2016) regorafenib had a promising activity in advanced soft-tissue sarcoma refractory to doxorubicin, particularly in the synovial sarcoma cohort (PFS: 5.6 months with regorafenib vs. 1.0 months with placebo, $p < 0.0001$), and the leiomyosarcoma cohort (PFS: 3.7 vs. 1.8 months, $p = 0.0045$). No activity was found in liposarcoma. For other soft-tissue sarcomas, PFS was 2.9 months versus 1.0 ($p = 0.0061$).

2.5.5. Glioblastomas

Bevacizumab has been approved by the FDA for the treatment of glioblastomas in monotherapy. Vredenburgh and others identified an unprecedented activity of bevacizumab in combination to irinotecan in recurrent glioblastoma, with a response rate of 57% (Vredenburgh et al., 2007). This “anti-glioma” activity was later confirmed with bevacizumab monotherapy (Kreisl et al., 2009), in a heavily pretreated glioblastoma population, although this study had no control group. However, it failed to improve the overall survival and the quality of life in combination to first line radiochemotherapy (Gilbert et al., 2014; Taphoorn et al., 2015). Its role in glioblastoma remains debated: no data has shown a benefit of bevacizumab on overall survival so far, despite an improvement in PFS, and bevacizumab has never been compared to placebo.

2.5.6. Other indications of anti-angiogenics in combination with cytotoxic chemotherapy

2.5.6.1. Rationale for combining AA and chemotherapy. Originally, AA were supposed to starve tumors, reversing the so-called “angiogenic switch” (Hanahan and Folkman, 1996). Most tumors have a very abnormal and heterogeneous vasculature, and some areas of the tumor are hypoxic and poorly perfused. Jain et al. suggested that AA could temporarily “normalize” this vasculature, therefore increasing the perfusion of the tumor and the benefit of a combination of AA with chemotherapy (Jain, 2005).

2.5.6.2. Combining AA MABs with chemotherapy. An important number of bevacizumab plus chemotherapy combinations demonstrated a significant increase of the PFS but no significant benefit on overall survival in various cancer types (Miles et al., 2010; Miller et al., 2007; Robert et al., 2011; Van Cutsem et al., 2009). Some indications of bevacizumab have been approved at 2.5 mg/kg per week (equivalent to 7.5 mg/kg every 3 weeks). Others have been approved at 5 mg/kg per week (15 mg/kg every 3 weeks).

Similarly to bevacizumab, ramucirumab was approved in second line for gastric or gastro-esophageal junction adenocarcinoma. It was also approved in second line in combination to docetaxel for non-small cell lung cancer (Tabernero et al., 2015).

2.5.6.3. Combination with PKIs. Many phase 3 trials in different cancer types failed to prove the efficiency of AA PKIs combined to cytotoxic chemotherapy and often showed a poorer safety profile (Bergh et al., 2012; Carrato et al., 2013; Crown et al., 2013; Flaherty et al., 2013; Gonçalves et al., 2012; Hauschild et al., 2009; Scagliotti et al., 2010). Nintedanib is the only exception: compared to placebo and combined to

docetaxel in previously treated lung adenocarcinoma. Nintedanib increased overall survival (10.9 months vs 7.9 months, $p = 0.007$) (Reck et al., 2014), with an important increase of the rate of diarrheas (Fig. 4). However, in this study, only 4% of the study population was previously treated with bevacizumab. Nintedanib was approved by the European Medicines Agency (EMA) in this setting, but not by the FDA.

2.6. Adverse effects of anti-angiogenics

2.6.1. Common to the angiogenesis inhibitor class

2.6.1.1. Hypertension. VEGF, through the receptor VEGFR-2, upregulates the endothelial nitric oxide synthase enzyme, responsible for the nitric oxide (NO) production. NO is a known vasodilator, and its inhibition results in hypertension. Moreover, microvascular endothelial cell rarefaction leads to a decrease in microvessel density (León-Mateos et al., 2015), and an increase in peripheral hydraulic resistance. Therefore, any drug targeting the VEGF-VEGFR pathway can induce hypertension. The kinetics of blood pressure rise is drug-dependent, but the increase in blood pressure generally occurs within the first days of treatment. Apparition of hypertension is dose-dependent and has been suggested as a surrogate of an effective inhibition of VEGF pathway (Zhu et al., 2007).

In a meta-analysis on 1032 patients developing hypertension under bevacizumab, 4 developed hypertensive encephalopathy, and 17 had uncontrolled hypertension that resulted in either bevacizumab discontinuation or hospitalization (Zhu et al., 2007). A pooled meta-analysis of 3745 patients treated for non-small cell lung cancer (NSCLC) with chemotherapy with or without bevacizumab found a higher risk of hypertension in the bevacizumab arm as compared to chemotherapy alone (8.2% vs 1.7%, grade 3–4 hypertension, $p < 0.001$, respectively) (Lai et al., 2016). The risk of hypertension with all AA is generally higher among the CCRCC population as compared to other cancers (Li et al., 2014). Vascular-selective calcium channel blockers such as amlodipine seem to control bevacizumab-induced hypertension in most cases (Mir et al., 2012a,b). Renin-Angiotensin-Aldosterone System inhibitors can also be used, although they might be less effective according to preclinical studies (de Jesus-Gonzalez et al., 2012; Lankhorst et al., 2014).

2.6.2. Proteinuria

Proteinuria is another common adverse event that needs to be monitored. When VEGF is inhibited, glomerular capsule podocytes lose their healthy fenestrated phenotype. Some preeclampsia-like syndromes associating hypertension, proteinuria, and edema have been reported with sorafenib and sunitinib (Patel et al., 2008). In the Lai et al. meta-analysis, 2.5% patients on bevacizumab plus chemotherapy had proteinuria compared to 0% with chemotherapy alone (Lai et al., 2016). The incidence of proteinuria is independent of the occurrence of hypertension. Izzedine et al. proposed an early referral to a nephrologist in case of pre-existing renal insufficiency or renal comorbidities. Urine dipstick analysis should be performed at each clinical work-up. When the dipstick is positive for proteinuria, quantitative measurement should be performed. A proteinuria > 1 g/L should be a limit to stop the treatment and lead to a nephrologist referral (Izzedine et al., 2010). It has been proposed to treat hyperproteinuria > 0.3 g/L associated with a hypertension $> 130/80$ mmHg with an Angiotensin-Converting Enzyme (ACE) or an Angiotensin II Receptor Antagonists (ARA II) (Izzedine et al., 2010). Inhibition of VEGF or VEGFR-2 can also result in glomerular endothelium damages characterized by swelling, development of microvascular injury and thrombotic microangiopathy (Eremina et al., 2008).

2.6.2.1. Hemorrhage and thrombo-embolic events. Hemorrhage is another class effect adverse event (Zhu et al., 2016). As compared to chemotherapy alone, the relative risk (RR) of bleeding on chemotherapy with bevacizumab is between 2–3 for most cancers,

depending on bevacizumab dosage. The risk of fatal bleeding is less than 1% in most cancer types, except for lung cancer (RR = 5.02, 95% CI: 1.52–16.66, absolute percentages not given) (Hapani et al., 2010).

Depending on the indication, bevacizumab does not have the same reported profile of toxicities. Lai et al., did not find a significant increase in the risk of venous or arterial thrombotic event or gastro-intestinal (GI) perforations in the NSCLC population (Lai et al., 2016), although the risk of GI perforations was tripled in metastatic colorectal cancer (2.2% versus 0.7%, OR = 3.21, 95% CI: 1.72–6.01) (Hurwitz et al., 2013) and in ovarian cancer (RR 2.76, 95%CI: 1.51–5.03) (Wu et al., 2017).

In a meta-analysis of different phase 2 and 3 trials, Hurwitz et al. concluded that there was no significant increase of thrombo-embolic events with bevacizumab compared to placebo (Hurwitz et al., 2011). In another meta-analysis, Nalluri et al. concluded differently, with a higher risk of thrombo-embolic events in the bevacizumab group compared to placebo, with no effect of the dose: low dose (2.5 mg/kg/week) RR = 1.31, $p = 0.007$ and high dose (5 mg/kg/week) RR = 1.31 $p = 0.04$ (Nalluri et al., 2008).

2.6.2.2. Cardiac toxicity. Inhibitors of the VEGF/VEGFR pathway can cause reversible or irreversible cardiac toxicity (Zamorano et al., 2016). In the BEATRICE trial, which assessed adjuvant bevacizumab in combination with chemotherapy in adjuvant setting for triple negative breast cancer, bevacizumab induced 2% of left ventricle dysfunction and 1% of heart failure (no event in the placebo plus chemotherapy group) (Cameron et al., 2013). The relative risk of congestive heart failure is increased with AA, although it is unclear whether the differential spectrum of kinase inhibited by AA plays a role or not (Qi et al., 2014a, 2014b). Similarly, a meta-analysis conducted on 10647 patients showed an increased incidence of all grades heart failures (HF) with AA PKIs as compared to control group not receiving such PKIs (RR = 2.69, 95% CI: 1.86–3.87) of (Ghatalia et al., 2015).

Patras de Campaigno et al. analyzed the proportion of HF in the WHO safety report database (VigiBase[®]) for different PKIs. They investigated the link between the proportion of HF incidence and their kinome profile (Patras de Campaigno et al., 2017). Level of inhibition of ABL1 and ABL2 protein kinase was significantly correlated to the proportion of HF. This could explain why sunitinib induces more HF than other AA PKIs.

2.6.2.3. Other toxicities. Posterior reversible encephalopathy syndrome (PRES) is another rare, but sometimes lethal, adverse effect of bevacizumab (Singer et al., 2015). This syndrome should be considered when dealing with unexpected encephalopathy symptoms, seizure, headache, visual abnormalities or acute hypertension. Case reports of PRES have also been reported with sorafenib, sunitinib, and pazopanib (Chelis et al., 2012; Cumurciuc et al., 2008; Hadj et al., 2012; Laruelle et al., 2016). A phase 2 trial evaluating aflibercept vs. placebo in association with cisplatin and pemetrexed in NSCLC was prematurely stopped due to an unexpected rate of PRES: 3 confirmed and 2 suspected cases among 42 randomized patients (Chen et al., 2014).

VEGF plays an important role in different steps of wound healing: phagocytosis, coagulation, chemotaxis, mitogenesis, and synthesis of collagen and other matrix components (Sharma and Marcus, 2013). As compared to chemotherapy alone, addition of AA delays wound healing and increases surgery complications. Scappaticci et al. evaluated that bevacizumab increased the risk of serious wound healing complication in colorectal cancer when the last bevacizumab injection was < 60 days (Scappaticci et al., 2005).

Osteonecrosis of the jaw is a serious side effect of bisphosphonate and denosumab. Concomitant use of AA might increase the risk of osteonecrosis (Christodoulou et al., 2009; Vrdoljak et al., 2013) although results are conflicting (Smidt-Hansen et al., 2013).

Fetal toxicity and teratogenicity are another toxicity of AA. A

chicken embryo model showed a similar effect of a wide panel of AA on embryos vasculature at relevant doses (Beedie et al., 2016).

2.6.3. Adverse effects specific to antibodies and derivatives

Like any monoclonal antibody, bevacizumab injection can be accompanied by $\approx 3\%$ of skin reactions during the infusion, of which 0.2% are severe and associated with features of anaphylaxis (Guan et al., 2015). Bevacizumab and ramucirumab adjunction to chemotherapy often have been reported to increase hematological toxicities such as febrile neutropenia (Rossari et al., 2012; von Minckwitz et al., 2012; Wilke et al., 2014). There is no obvious explanation to this toxicity.

2.6.4. Adverse effects specific to PKIs

Hepatotoxicity and transaminase increase are common adverse events for many PKIs, such as pazopanib or cabozantinib (Fig. 4). Patients having a transaminase increase with pazopanib that return to grade 1 (< 3 times the upper limit of normal) or less could be challenged again with a close monitoring of the liver function (Powles et al., 2015). Concomitant use of statins with pazopanib increases the risk of liver damage (Xu et al., 2012) and is contra-indicated.

PKIs frequently have gastro-intestinal toxicities such as nausea-vomiting or diarrhea (Strumberg et al., 2006) (Fig. 4). A possible role of pancreatic exocrine dysfunction was emphasized and it was proposed to supplement patients having a steatorrhea with pancreatic enzyme supplements (Mir et al., 2012a,b). Skin rash is very frequent with sorafenib, vandetanib, and regorafenib, compatible with the inhibition of the RAF and EGFR pathways (Fig. 3).

Hand-foot syndrome (HFS) is an important toxicity of PKIs which is often dose limiting. With regorafenib, 60% of patients have an HFS with 20% of grade 3 (McLellan et al., 2015), and there is a high variability between PKIs (Fig. 4) (Lipworth et al., 2009). Bevacizumab increases the risk of HFS when combined with capecitabine or docetaxel (Gopal et al., 2013). This adverse event seems to be linked with sudation (Lankheet et al., 2013) and is increased during summer, although the role of sweat excretion remains unclear.

Many PKIs can induce myelosuppression, with a different rate of neutropenia or thrombopenia. Sunitinib is the most myelosuppressive AA PKI (Fig. 4).

Destruction of tumor cells itself brings fatigue. However, PKIs have different impact on tiredness. This adverse event is sometimes related to anemia, which needs to be treated properly. An important drug-related fatigue might justify the change of a PKI in renal cancer. Patients using pazopanib have a better quality of life with less fatigue than those using sunitinib, with comparable outcomes (Motzer et al., 2014). Conversely, the association of lenvatinib with everolimus induces a lot of fatigue (73% all grade, Fig. 4).

Thyroid vasculature is very sensitive to inhibition of VEGF pathway (Kamba et al., 2006). As a result, hypothyroidism is a common side effect of all AA PKIs (Fallahi et al., 2014). The proportion of patients treated for a renal cancer with sunitinib who develop biological and clinical hypothyroidism is higher than 80% (Rini et al., 2007). Monthly monitoring of TSH and T4 is therefore recommended to initiate levothyroxine substitution as soon as needed (Wolter et al., 2008). Other endocrine dysfunction includes hypophosphatemia, present in 45% of patients treated with sorafenib for an RCC (Mir et al., 2012a,b). Sorafenib appears to induce steatorrhea due to pancreatic exocrine dysfunction which induces vitamin D malabsorption. Mir suggested that these patients could benefit both vitamin D supplementation and pancreatic enzyme replacement (Mir et al., 2012a,b).

PKIs can also increase QT interval. Vandetanib, in particular, prolongs QTc prolongation by a mean of 36 ms and the rate of QTc prolongation greater than 60 ms is 12–15%, with a risk of Torsade de Pointes arrhythmia (Salem et al., 2016; Zamorano et al., 2016). Therefore, this treatment needs a very close monitoring of electrocardiogram and electrolytes. A congenital long QT syndrome should be

eliminated before treatment initiation. Other PKIs have a milder effect on QTc lengthening but most of them prolong QTc beyond the 5 or even 10 ms cut-off, justifying close ECG monitoring and cardiologic monitoring (Zamorano et al., 2016).

3. Therapeutic drug monitoring

3.1. Pharmacokinetics

The relationship between exposure and toxicity or efficacy has been demonstrated for some AA PKIs (Bellesoeur et al., 2014; Houk et al., 2010; Pécuchet et al., 2012). Verheijen et al. showed that pazopanib exposure varied greatly in patients treated for mCCRCC or soft tissue sarcoma (Verheijen et al., 2016). They conducted a prospective trial in those populations, with a starting dose of 800 mg OD of pazopanib. Depending on the trough plasma concentration (C_{min}) of pazopanib and the toxicity of the drug, they allowed either a dose increase or a dose reduction. No patient with a trough concentration (C_{min}) < 20 mg/L had a decrease in tumor size, and 20 mg/L was therefore proposed as a lower plasma concentration threshold.

However, except for imatinib which has been extensively studied the interest of therapeutic drug monitoring (TDM) and target concentration intervention has been poorly investigated for the majority of PKIs in solid cancer. Many oncologists argue that TDM never proved to increase overall survival in a front line trial randomizing patients benefiting from TDM versus patients who did not. Although TDM might not be a convenient method for all patients, some patients have a high risk of inappropriate drug exposure. This includes patients who are obese, who have liver or renal impairment or who experience unexpected toxicity after treatment initiation.

3.2. Pharmacodynamics

Although a number of surrogate markers for anti-VEGF-Activity have been investigated, none have been clinically validated as a predictive factor of AA efficacy or toxicity (Jain et al., 2009; Longo and Gasparini, 2007).

3.2.1. Biological biomarkers

Circulating VEGF was originally identified as a marker of poor prognosis in various cancers (Poon et al., 2001). However, the baseline level of circulating VEGF-A, failed to prove its usefulness as a predictive biomarker in most AA studies (Dowlati et al., 2008; Murukesh et al., 2010). Other markers, e.g. circulating VEGFR-2 or VEGFR-3, decrease with AA PKIs therapy but have not been shown to be linked to prognosis (Jain et al., 2009).

3.2.2. Imaging biomarkers

The modification of vascular permeability and endothelial surface can be measured by Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI). Different permeability parameters such as the transfer constant (K_{trans}) could be measured with this technique, as described by Tofts. K_{trans} is the permeability surface area product per unit volume of tissue, which is calculated by pharmacokinetic modeling of gadolinium. Under flow-limited conditions K_{trans} equals the blood plasma flow per unit volume of tissue (Tofts, 1997; Tofts et al., 1999). K_{trans} measurement decreases with tumor vasculature density and a decrease has been described for various cancers with many different angiogenics (Cho et al., 2014; Kim et al., 2014; Li et al., 2015; Marinovich et al., 2012; Messiou et al., 2012; Stacchiotti et al., 2009). Dose-response relationship of this decrease has been shown with some anti-angiogenic investigational drugs (Morgan et al., 2003; Robinson et al., 2003). However, the measurement of K_{trans} by DCE-MRI after 4 weeks of sorafenib failed to predict an improvement in PFS (Hahn et al., 2008). DCE-MRI can also measure tissue homogeneity. The adiabatic approximation of tissue homogeneity, which is one parameter

described by Tofts pharmacokinetic model, could also be an interesting marker: it was predictive of the overall survival for patients treated by sorafenib for a HCC (S. H. Lee et al., 2015).

Dynamic Contrast-Enhanced Ultrasonography (DCE-US) is another method to measure tissue perfusion and can also detect reduction in tumor vascularization (Lassau et al., 2007). The mean transit time of the contrast product measured at day 7 after beginning of the treatment was significantly correlated to the freedom from progression in different tumor types treated with a combination of bevacizumab and chemotherapy (Lassau et al., 2016).

Because some PKIs might induce tumor necrosis without tumor shrinkage, some alternative response criteria other than RECIST 1.1 have been developed (Choi et al., 2007). Choi's criteria for example, adds the tumor density information to classify the tumor in either a response or a progression. For many cancers, alternative criteria have been proposed (Dudeck et al., 2011; Karakiewicz et al., 2016; Krajewski et al., 2011; Schmidt et al., 2013; Veldt et al., 2010). For patients with HCC treated by sorafenib (Ronot et al., 2014), Choi's and modified RECIST (mRECIST) criteria appear more appropriate than RECIST 1.1.

3.2.3. Clinical biomarkers

Specific on-target toxicity, such as hypertension, might be a surrogate of VEGF pathway inhibition. Several retrospective studies showed that patients having hypertension had better outcomes (Dahlberg et al., 2010; Rini et al., 2010). However, a meta-analysis by Hurwitz et al. confirmed these results in only one out of seven prospective studies, analyzing hypertension arising within 60 days of AA initiation (Hurwitz et al., 2013). These contrasting results could be explained by the kinetics of hypertension, its intensity, cutoff values or the variety of tumor types which were different between studies. Many other studies later confirmed the prognostic role of hypertension in patients with colorectal cancer and glioblastoma treated with AA as a predictive marker of overall survival (Khoja et al., 2014; Lombardi et al., 2013; Österlund et al., 2011).

The frequency of skin rash and diarrhea which are two sorafenib toxicities are also correlated with better outcomes in advanced solid tumors (Strumberg et al., 2006) and in HCC (Abdel-Rahman and Lamarca, 2017). Similar results were found for neutropenia and sunitinib in RCC (Donskov et al., 2015).

Axitinib is the only AA drug for which an increase in drug intakes is allowed, when no drug toxicity is observed. Axitinib up-titration was associated with increased efficacy in metastatic CCRCC compared to a placebo titration (Rini et al., 2013). Most trials assessing axitinib efficacy were using this dose-escalation strategy (Spano et al., 2008, 2012).

4. Perspectives

4.1. Different targetable pathways

Besides VEGF/VEGFR pathway, many other pathways contribute to angiogenesis, either initially, or as a resistance mechanism to VEGF/VEGFR inhibitors (Kerbel, 2008). Those alternative pathways may be new therapeutic targets.

Angiopoietin (ANG) is another family of protein growth factors. Similarly to the binding of VEGF-A to VEGFR-2, ANG1 and ANG2 bind to TIE2, a tyrosine kinase receptor of the endothelial cell membrane (Fig. 2). Trebananib is an example of peptibody that blocks binding of angiopoietin-1 and -2 to TIE2. It is currently under investigation in various cancers. It improves median PFS in ovarian cancer but failed to improve significantly overall survival with concomitant paclitaxel (Monk et al., 2016) or failed to improve PFS with concomitant pegylated liposomal doxorubicin (Marth et al., 2017). FGF/FGFR pathways are other promising angiogenesis targets (Porta et al., 2017; Ronca et al., 2015). Some PKIs already on the market have a FGFR inhibitor activity (cf. Fig. 3), and others are in development. Lucitanib or TAS-120, among others, have shown promising activity against FGFR

mutated breast cancer (Soria et al., 2014) or lung cancer and phase 2 trials are ongoing (NCT02053636, NCT02202746, NCT02109016).

Other currently studied pathways implicated in angiogenesis focus on Transforming Growth Factor- β , delta/Jagged-Notch and chemokines such as CXC chemokine receptor type 4 (CXCR4)/CXC motif chemokine 12 (CXCL12) signaling (Liang et al., 2007; Salem et al., 2012; Bruix et al., 2017; Kangsamaksin et al., 2015).

4.2. Mechanisms of resistance

Four main resistance mechanisms to AA drugs were proposed (Bergers and Hanahan, 2008): activation of alternative angiogenic pathways, recruitment of bone-marrow derived cells which promote angiogenesis, use of pericytes to support the tumor vasculature and finally the promotion of invasion and metastasis.

These resistances, could be reverted by ANG1/Tie2 inhibitors such as regorafenib in HCC (Bruix et al., 2017) or Notch pathway inhibitors, as a second line after currently approved AA (Kangsamaksin et al., 2015).

When PKIs are used to inhibit tumor kinases that are not directly involved in angiogenesis pathways, secondary mutation could also bring resistance to treatment. For example, secondary mutation D820Y, D820E, and N822K of the tyrosine kinase receptor cKIT in GIST confers secondary resistance to sunitinib (Guo et al., 2009).

Polymorphisms of VEGF rs2010963 (VEGF-A) and rs4604006 (VEGF-C) are associated with poorer prognosis in HCC treated by AA (Scartozzi et al., 2014). It could be hypothesized that a tumor could promote a secondary mutation to the VEGF secreted that could lead to treatment failure.

5. Conclusion

Angiogenesis has led to many treatment innovations in oncology and other drugs and combinations are about to come. The VEGF-A/VEGFR-2 pathway is central to every AA drug that has a significant AA activity. Toxicities of PKIs are strongly related to their spectrum of activity on the kinome. AA therapy used as maintenance seems more effective, particularly in combination with other targeted therapies. Therapeutic drug monitoring should be considered when patients have a high risk of change in its pharmacokinetics properties. Biological, imaging and clinical surrogates might be of some help, although their systemic use for guidance of prescription needs further evidence using rigorous methodology. However, many cancers remain resistant to current AA drugs, and require better understanding and possibly new class of drugs to be efficacious.

Conflicts of interest

The authors declare they have no conflict of interest.

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