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Targeting angiosarcomas of the soft tissues: A challenging effort in a heterogeneous and rare disease

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ABSTRACT

Angiosarcomas are rare malignant tumors with a heterogeneous clinical presentation and generally poor prognosis. It has been difficult to establish consistent molecular characteristics and driver events in angiosarcoma development. Oncogenic and angiogenesis-related pathways have been investigated pre-clinically and clinically with varying results. A few promising responses to checkpoint inhibitors have been described, but immunological features require further elucidation. With this review we present an overview of the critical biological pathways and processes affected in angiosarcoma, and their potential role in novel, non-cytotoxic, systemic treatments.

1. Introduction

Angiosarcoma is a rare type of sarcoma, comprising about 1–2% of all sarcomas. Until this day, its underlying mechanisms remain mostly unclear, although angiosarcomas are thought to arise along the differentiation from mesenchymal stem cell to endothelial (progenitor) cell. The clinical classification of angiosarcomas is mostly based on etiology and/or tissue of origin. Primary angiosarcomas can be distinguished from secondary angiosarcomas which arise due to previous radiation therapy, chronic lymphedema or exposure to vinyl chloride. Median age at diagnosis is between 52 and 67 years (range 0.2–91) (Fayette et al., 2007; Buehler et al., 2014). The reported male to female ratio varies strongly, between 1:0.8 and 1:1.5 (Buehler et al., 2014; Abraham et al., 2007), which is partly due to the different subtypes described within the cohorts. Clinically, there appears to be a difference in clinical behavior based on location of the primary tumor. For instance, cutaneous angiosarcoma of the head and neck region occurs mainly in elderly men as a consequence of UV light exposition of the scalp (Patel et al., 2015), whereas angiosarcoma of the breast tends to present at a much younger age (median 35–54 years), almost exclusively in female patients and most often after radiotherapy of breast cancer (Yin et al., 2017).

In case of limited, local disease, treatment consists of resection, often combined with radiotherapy. Patients with locally advanced or metastatic disease are treated with systemic therapy, either paclitaxel or doxorubicin. In case of cutaneous angiosarcoma, a favorable response was seen with weekly paclitaxel compared to doxorubicin (Italiano et al., 2012a). Despite this treatment, overall survival after primary diagnosis remains poor, with a reported 5-year survival of 30–40% (Fayette et al., 2007; Fury et al., 2005), compared to 50–60% for soft tissue sarcomas in general (Mocellin et al., 2006). Once metastasized, the reported median overall survival is only 3–12 months (Fayette et al., 2007; Buehler et al., 2014; Abraham et al., 2007; Lahat et al., 2010). So far, patients with angiosarcoma have had limited benefit from the recent breakthroughs in oncology, such as targeted therapy and immunotherapy.

With this review, we aim to present an overview of the critical biological pathways and processes affected in angiosarcoma, and their potential role in novel, non-cytotoxic, systemic treatments.

2. Targets for treatment

2.1. Angiogenesis-related targets

Several components involved in the regulation of angiogenesis have been investigated in angiosarcoma, both on a genetic level as well as on a protein level.

2.1.1. VEGF-pathway

One of the most investigated pathways in angiosarcomas is the

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Table 1
Mutations found in angiosarcoma.

Gene	Type of mutation(s)	Pathway	N =	Type of AS	Ref
KDR	Hotspot exon 16 (codon 771; transmembrane domain); Exon 15 (codon 717 and 731, extracellular domain Ig-like C2 type 7); Exon 24 (codon 1065, kinase domain)	VEGFR2	8/113 (7%)	Primary AS (breast, lumbar spine), secondary AS (breast area)	(Huang et al., 2016)
	G681R mutation		1	Primary AS (cardiac)	(Zhrebker et al., 2017)
	Amplification		1	Primary AS (scalp)	(Ravi et al., 2016)
	Amplification		4/34 (11.8%)	Primary AS (head&neck + liver)	(Murali et al., 2015)
	Missense		2/34 (5.9%)	Primary AS and metastasis	
PLCG1	Exon 18 (p.R707Q, 8; p.R707L); exon 11 (p.S345F)	VEGFR2	11/116 (9.5%)	Primary (breast + visceral) and secondary AS (breast area)	(Huang et al., 2016)
	R707Q missense		1	Primary AS (liver)	(Prenen et al., 2015)
	R707Q missense		3/15 (20%)	Secondary AS (n = 1), unknown (n = 1)	(Behjati et al., 2014)
	R707Q missense		1/34 (2.9%)	Secondary AS (trunk)	(Murali et al., 2015)
PTPRB	Nonsense; Missense; Essential splice; Frameshift indel	VEGFR2, Angiopoietin	10/39 (25.6%)	Secondary AS	(Behjati et al., 2014)
	Nonsense; Frameshift		6/34 (17.6%)	Primary AS (head&neck, lower limb) and secondary AS (trunk)	(Murali et al., 2015)
FLT4	Amplification	VEGFR3	6/110 (5.5%)	Primary AS (scalp, n = 1), secondary AS (n = 5)	(Huang et al., 2016)
	Amplification		1	Primary AS (scalp)	(Ravi et al., 2016)
	Amplification		1/39 (2.6%)	Unknown	(Behjati et al., 2014)
	Amplification		3/17 (17.6%)	Secondary AS (breast area)	(Cornejo et al., 2015a)
	Amplification		2/34 (5.9%)	Secondary AS (trunk)	(Murali et al., 2015)
	Amplification		5/20 (25%)	Secondary AS	(Guo et al., 2011)
KRAS	Hotspot mutation (G12)	RAS/RAF/MEK/Erk, PI3K/ AKT/mTOR	1/34 (2.9%)	Secondary AS (trunk)	(Murali et al., 2015)
	Hotspot mutation (G12)		1/39 (2.6%)	Metastasis	(Behjati et al., 2014)
HRAS	Hotspot mutation (A59, Q61)	RAS/RAF/MEK/Erk, PI3K/ AKT/mTOR	4/34 (11.8%)	Primary AS (cheek) and secondary AS (trunk)	(Murali et al., 2015)
	Hotspot mutation (G13, Q61)		2/39 (5.5%)	Unknown	(Behjati et al., 2014)
NRAS	Hotspot mutation (Q61)	RAS/RAF/MEK/Erk, PI3K/ AKT/mTOR	2/34 (5.9%)	Primary AS (nose + liver)	(Murali et al., 2015)
	Hotspot mutation (G13, Q61)		2/39 (5.5%)	Primary AS (breast) and secondary AS (breast)	(Behjati et al., 2014)
BRAF	Amplification	RAS/RAF/MEK/Erk	4/34 (11.8%)	Primary AS (head&neck, mediastinum, lower limb)	(Murali et al., 2015)
	Hotspot mutation (V600)		1/34 (2.9%)	Primary AS (head&neck)	
MAPK1	Amplification	RAS/RAF/MEK/Erk	3/34 (8.8%)	Primary AS (head&neck)	(Murali et al., 2015)
	Hotspot mutation (E322)		1/34 (2.9%)	Metastasis	
NF1	Deletion	RAS/RAF/MEK/Erk	1/34 (2.9%)	Secondary AS (trunk)	(Murali et al., 2015)
	Insertion (frame shift)		1/39 (2.6%)	Primary AS (breast)	(Behjati et al., 2014)
PIK3CA	Point mutation (R108)	PI3K/AKT/mTOR	1/39 (2.6%)	Primary AS (lower limb)	(Behjati et al., 2014)
	Missense mutation exon 9		1/6 (16.7%)	Unknown	(Je et al., 2012)
	Truncating frame shift mutation exon 10		13/33 (39.4%)	Primary AS and secondary AS	(Italiano et al., 2012b)
CDKN2A	Deletion	p16(INK4A)	9/34 (26.5%)	Primary tumors AS (trunk, head&neck, liver) and metastasis	(Murali et al., 2015)
	Deletion		3/10 (30.0%)	Primary AS (cardiac)	(Leduc et al., 2017)
MYC	Amplification	MYC	1/34 (2.9%)	Primary AS (liver)	(Murali et al., 2015)
			7/34 (20.6%)	Secondary AS (trunk)	
	Amplification		5/69 (7.2%)	Primary AS	(Huang et al., 2016)
			32/35 (91.4%)	Secondary AS	
	Amplification		3/3 (100.0%)	Primary AS (adrenal)	(Cornejo et al., 2015b)
	Amplification		1/34 (2.9%)	Primary AS	(Behjati et al., 2014)
			11/34 (32.4%)	Secondary AS Unknown	
			3/34 (8.8%)		
	Amplification		20/20 (100.0%)	Secondary AS	(Guo et al., 2011)
			0/18 (0%)	Primary AS	
TP53	Exon 5 A138S mutation; Exon 7 R238Q mutation	p53	2/52 (4%)	Secondary AS (breast)	(Italiano et al., 2012b)
	c.375 + 1G > A truncating mutation; R273H missense mutation; 1.3 kb rearrangement.		3/15 (20%)	Secondary AS (2 breast, 1 tibia)	(Behjati et al., 2014)
	C > T alterations (71%)		12/34 (35%)	Unknown	(Murali et al., 2015)

(*continued on next page*)

Table 1 (*continued*)

Gene	Type of mutation(s)	Pathway	N =	Type of AS	Ref
CIC	CIC-LEUTX fusion; CIC rearrangement (unknown partner); CIC missense mutation	–	1/50 (2%)	Primary AS (thigh)	(Huang et al., 2016)
			2/50 (4%)	Primary AS (back, kidney)	
			6/98 (6%)	5 primary AS, 1 secondary AS (spleen)	
ROS1	CEP85L/ROS1 fusion	ROS1	1/34 (3%)	Primary AS	(Giacomini et al., 2013)

VEGF-pathway. VEGFR2/KDR (Vascular Endothelial Growth Factor Receptor 2 or Kinase Insert Domain Receptor) is the main VEGF receptor on normal endothelial cells. In about 10% of angiosarcomas mutations have been found in the VEGFR2 gene (Table 1) (Huang et al., 2016). FLT4 (Fms Related Tyrosine Kinase 4, or VEGFR3), becomes upregulated during physiological angiogenesis. Amplification of FLT4 has been demonstrated in 11–25% of secondary angiosarcomas and often co-occurs with MYC amplification (Huang et al., 2016; Guo et al., 2011). Interestingly, only one out of 73 primary angiosarcomas harbored an FLT4 amplification (1.4%) (Huang et al., 2016).

VEGFR1 and VEGFR2 interact with VEGF-A (a known promoter of angiogenesis) in both normal as well as in malignant endothelial cells. Immunohistochemical expression of VEGF-A, VEGRF1 and VEGFR2 was shown to be present in 65–95% of angiosarcoma cases (Itakura et al., 2008; Zietz et al., 1998). Low or absent VEGFR2 expression was associated with poor survival. However, given the discrepancy between the low prevalence of VEGFR mutations and positive immunochemical expression, it would be useful to directly compare mutational status and protein expression in order to gain insight in their actual correlation.

2.1.1.1. Bevacizumab. Bevacizumab is an anti-VEGF monoclonal antibody and has been tested in angiosarcoma both pre-clinically as well as in clinical studies. When applied as monotherapy in pre-clinical experiments, bevacizumab showed variable efficacy varying from no effect *in vitro* and *in vivo* (Young et al., 2014; Hoshina et al., 2013), to a strong reduction in cell growth *in vitro* (Tables 2 and 3) (Azzariti et al., 2014). *In vitro* combination of bevacizumab with paclitaxel in angiosarcoma showed an additive rather than synergistic effect (Table 4) (Young et al., 2014). In the first clinical study in angiosarcoma patients, single agent bevacizumab showed partial response (PR) in 9% (2/23) and stable disease (SD) in 48% (11/23) of patients at 6 weeks (Table 5) (Agulnik et al., 2013). Median progression free survival (PFS) and overall survival (OS) were 12.0 and 52.7 weeks, respectively. In a randomized angiosarcoma specific phase II trial with 50 patients, the combination of bevacizumab and paclitaxel did not show improvement compared to paclitaxel alone (Ray-Coquard et al., 2015). A second, non-randomized trial showed no significant difference of weekly paclitaxel *versus* paclitaxel every three weeks, both combined with bevacizumab (Bui et al., 2018). Median PFS was 5.4 months for weekly paclitaxel/bevacizumab and 3.4 months in the three weekly group, respectively. Combination of bevacizumab with gemcitabine and docetaxel was investigated in soft tissue sarcoma (STS) patients, where three out of five angiosarcoma patients included (60%) had a partial response (Dickson et al., 2015).

2.1.1.2. TKI's targeting VEGFR. Pazopanib is a multi-targeting TKI (tyrosine kinase inhibitor) approved for second and higher line treatment of STS patients, targeting PDGFR, VEGFR1, 2 and 3. A retrospective analysis of 40 angiosarcoma patients treated in the PALETTE study with pazopanib showed a response rate of 20% (PR 8/40 patients) (Kollar et al., 2017; van der Graaf et al., 2012). Median PFS was 3 months (95% CI 2.1–4.4) compared to 4.6 months in the total STS population (Young et al., 2014). In a phase IB/IIA clinical trial testing pazopanib in combination with anti-endoglin antibody TRC105 in soft tissue sarcoma patients, encouraging activity was seen in angiosarcoma patients with durable complete response (CR) in 2/5 angiosarcoma patients enrolled (Attia et al., 2016). A randomized phase III trial comparing single agent pazopanib with pazopanib and TRC105 in angiosarcoma patients is currently ongoing (NCT02979899). Endoglin (or CD105) is a transforming growth factor β (TGFβ) co-receptor which is required for angiogenesis and is considered to be important in preventing resistance against VEGF-inhibition. In angiosarcoma, endoglin expression was present on tumor cells in the vast majority of cases (Verbeke et al., 2013). No pre-clinical experiments targeting endoglin in angiosarcoma have been reported yet.

Table 2
In vitro experiments with targeted therapy.

Compound	Target(s)	Cell line	Result	Mechanism of action	Ref
Bevacizumab	VEGF	AS-M5, ISO-HAS	No effect on cell viability, differentiation or migration	Binds VEGF, inhibits binding of VEGF to VEGFR-1 and VEGFR-2	(Young et al., 2014)
		Patient derived (RTx induced AS of skin)	Strong reduction of proliferation		(Azzariti et al., 2014)
		HAMON	No effect on cell proliferation		(Hoshina et al., 2013)
Vandetanib	VEGFR2/ EGFR/RET	Patient derived (RTx induced AS of skin)	Strong reduction of proliferation	Inhibition of EGFR, VEGFR-2 and RET-pathways	(Azzariti et al., 2014)
Axitinib	VEGFR1/ VEGFR2/ VEGFR3	AS-M5, ISO-HAS	No effect on cell viability or migration. Reduction of tube formation in AS-M5, not in ISO-HAS.	Inhibition of VEGFR-1, VEGFR-2, VEGFR-3, PDGFRs.	(Young et al., 2014)
Sunitinib	VEGFR1/ VEGFR2/ VEGFR3, PDGFR, KIT, FLT3, CSF-1R, RET	HAMON	No inhibition of cell proliferation.	Inhibition of multiple tyrosine protein kinases including VEGFR-1, VEGFR-2 and VEGFR-3.	(Hoshina et al., 2013)
		SVR (murine AS)	Modest effect on cell survival (dose-dependent)		(Hasenstein et al., 2012)
CAS 948,557-43-5	Tie2 kinase	SVR (murine AS)	Modest effect on cell survival (dose-dependent)	Selective inhibition of Tie2 kinase.	(Hasenstein et al., 2012)
Vadimezan	Multi-kinase (VEGFR2)	AS-M5, ISO-HAS	Reduction of cell viability and tubule formation. No increase in apoptosis.	Reduction of tumor blood flow, induction of tumor apoptosis (exact mechanism unknown).	(Young et al., 2014)
SFRP2 monoclonal Ab	Secreted Frizzled Related Protein 2	SVR (murine AS)	Inhibition of tube formation and cell migration. No effect on cell number.	Inhibition of SFRP2, inhibition of NFATc3 activation and β-catenin.	(Fontenot et al., 2013)
Propranolol	Beta adrenergic receptor	SVR (murine AS), Emma, SB, Frog (canine AS)	Dose-dependent inhibition of cell proliferation, increased apoptosis.	Non-specific inhibition of beta-adrenergic receptor.	(Stiles et al., 2013)
Selumetinib	MEK	AS-M5, ISO-HAS	Significant reduction of AS-M5 cell viability, only minimal in ISO-HAS cells. Reduction of AS-M5 tubule formation.	Inhibition of MEK1/2.	(Young et al., 2014)
PD0325901	MEK	ISOS-1, ISO-HAS	Weak effect on cell proliferation.	Selective inhibition of MEK.	(Wada et al., 2015)
PLX4720	RAF	ISOS-1, ISO-HAS	No effect on cell proliferation.	Selective inhibition of BRAF.	(Wada et al., 2015)
Rapamycin	mTOR	AS-M5	Reduction of cell proliferation.	Inhibition of mTOR activation.	(Du et al., 2013)
LY294002	PI3K	ISOS-1, ISO-HAS	Growth inhibition of about 80%.	Specific inhibition of PI3K.	(Wada et al., 2015)
NVP-BEZ235 (Dactolisib)	PI3K/mTOR	ISOS-1, ISO-HAS	Growth inhibition of about 80%.	Inhibition of PI3K and mTOR.	(Wada et al., 2015)
Everolimus	mTOR	ISOS-1, ISO-HAS	Growth inhibition of about 50-60%.	Inhibition of mTOR. Reduction of VEGF by reduction of HIF-1α synthesis.	(Wada et al., 2015)
		AS-M5, ISO-HAS	Modest reduction of cell proliferation (20%).		(Young et al., 2014)
MK2206	Akt kinase	ISOS-1, ISO-HAS	No effect on cell growth.	Selective inhibition of pan-Akt.	(Wada et al., 2015)
OSU-03012 (AR-12)	PDK1	ISOS-1, ISO-HAS	Dose-dependent inhibition of cell growth; reduction of colony growth in ISOS-1.	Inhibition of PDK-1 (resulting in inhibition of PI3K/Akt pathway).	(Wada et al., 2015)
TRAM-34	KCa3.1	ISO-HAS	Dose-dependent decrease of cell-number, inhibition of cell invasion.	Selective blockade of potassium channel KCa 3.1 (target of miR-497-5p).	(Chen et al., 2016)
Ganetespib	HSP90	HAMON, ISO-HAS, MO-LAS, ISOS-1	Inhibition of cell proliferation, enhanced apoptosis (HAMON, ISO-HAS).	Binding to and inhibition of Hsp90.	(Yamada-Kanazawa et al., 2017)
YM155	Survivin	ISO-HAS	Dose-dependent suppression of cell growth.	Inhibition of survivin expression.	(Tsuneki et al., 2017)

Table 3
In vivo experiments with targeted therapy.

Compound	Target(s)	Xenograft	Result	Ref
Bevacizumab	VEGF	HAMON	No effect on tumor growth or survival duration.	(Hoshina et al., 2013)
Sunitinib	VEGFR1/ VEGFR2/ VEGFR3, PDGFR, KIT, FLT3, CSF-1R, RET	HAMON	No effect on tumor growth or survival duration.	(Hoshina et al., 2013)
		SVR (murine AS)	Reduction of tumor volume (44%, day 20)	(Hasenstein et al., 2012)
CAS 948,557-43-5	Tie2 kinase	SVR (murine AS)	Reduction of tumor volume (61%, day 20)	(Hasenstein et al., 2012)
Tacrolimus	Calcineurin	SVR (murine AS)	Reduction of tumor volume (46%, day 19)	(Courtwright et al., 2009)
SFRP2 monoclonal Ab	Secreted Frizzled Related Protein 2	SVR (murine AS)	Reduction of tumor volume (55-60%)	(Fontenot et al., 2013)
Propranolol	Beta adrenergic receptor	SVR (murine AS)	Reduction of tumor size and weight.	(Stiles et al., 2013)
TRAM-34	KCa3.1	ISO-HAS	Suppression of development of tumors, decreased tumor weight.	(Chen et al., 2016)

Sorafenib, a RAF kinase inhibitor also targeting VEGFR2 and 3, has been examined in a phase 2 study with STS patients (Maki et al., 2009). Out of 37 angiosarcoma patients included in the study, 5 had a partial response (RR 14%), and median PFS in the angiosarcoma cohort was 3.8 months. Based on these findings, an angiosarcoma-specific phase II trial was performed with 41 patients (Ray-Coquard et al., 2012). In this study the median PFS was only 1.8 months for superficial angiosarcoma, and 3.8 months for visceral angiosarcoma.

In vitro treatment of a secondary breast angiosarcoma patient-derived cell line with vandetanib, a TKI targeting VEGFR2, led to a strong reduction of proliferation (Azzariti et al., 2014). These results have not yet been confirmed *in vivo* or clinically. Axitinib (inhibiting VEGFR1, 2 and 3 activity) failed to induce cell death as monotherapy *in vitro,* but yielded an additive effect in combination with paclitaxel (Young et al., 2014). A multi strata phase 2 study with axitinib, including an arm with angiosarcoma patients, has been performed and results are awaited (NCT01140737). Sunitinib (a TKI targeting among others VEGFR1, 2 and 3) was tested both *in vitro* and *in vivo,* but didn't show a cytotoxic effect (Young et al., 2014; Hoshina et al., 2013). Only a few angiosarcoma patients treated with sunitinib have been reported (Yoo et al., 2009; Silva et al., 2015). A phase II clinical study is currently investigating the effects of regorafenib (targeting the VEGF-receptors among others), in angiosarcoma patients specifically (NCT02048722).

2.1.2. Angiopoietin-Tie pathway

The Angiopoietin-Tie pathway is another important signaling pathway regulating angiogenesis through its role in remodeling and maturation of blood vessels. Part of this pathway is the endothelium-specific tyrosine kinase receptor Tie2 kinase, interacting with Angiopoietin 1 and 2 (Ang1 and 2) ligands. This complex interaction can result in both pro-angiogenic as well as anti-angiogenic effects. Immunohistochemistry expression of Angiopoietin-Tie-pathway proteins was shown in a study of 51 angiosarcoma patients, with Ang1, Tie1 and Tie2 being expressed in the majority of cases (68–86%) and Ang2 in 42% (Buehler et al., 2013). By univariate analysis, Ang1 expression was correlated with improved survival. However, data regarding the correlation between genetic aberrations and immunohistochemical expression are lacking.

Pharmacological inhibition of Tie2 kinase with CAS 948557-43-5 was investigated in murine angiosarcoma cell lines, resulting in a dose dependant reduction of cell survival (Hasenstein et al., 2012). Combination with VEGF inhibitor sunitinib yielded a synergistic effect *in vitro* and showed a stronger reduction of tumor volume *in vivo* compared to both monotherapies. This synergism may be explained by Ang2 function switching from anti-angiogenic to pro-angiogenic in the presence of VEGF (Amo et al., 2004). Clinical trials with CAS 948557-43-5 have not yet been reported.

Trebananib, which targets the Angiopoietin-Tie interaction by sequestering Angiopoietin 1 and 2, was tested in 16 angiosarcoma patients in a phase II study (D' Angelo et al., 2015). The drug was well tolerated but unfortunately did not lead to confirmed responses, with median PFS of only 1.6 months (95% CI 1.41–1.74). Given the above mentioned *in vivo* synergy of CAS 948557-43-5 with sunitinib, combination of trebananib with other TKIs might be more promising than monotherapy.

Both angiopoietin and VEGFR2 signaling can be inhibited by PTPRB (Protein Tyrosine Phosphatase Receptor B), a negative regulator of angiogenesis. PTPRB mutations were found in 26% (10/39) of angiosarcomas (Behjati et al., 2014). All of these PTPRB mutated tumors were either known to be secondary angiosarcoma and/or had MYC amplification, a biomarker frequently, though not exclusively, associated with radiation-associated angiosarcoma. In addition, in 7 and 20% of angiosarcoma cases respectively, a mutation in PLCG1 (Phospholipase C Gamma 1, a known signal transducer for tyrosine kinases) was found (Huang et al., 2016; Behjati et al., 2014). Transfection of this mutation into normal endothelial cells led to apoptosis resistance and invasiveness *in vitro* (Kunze et al., 2014). Neither PTPRB nor PLCG1 can yet be directly inhibited.

2.1.3. Other targets – angiogenesis

Secreted frizzled related protein 2 (SFRP2) is a stimulator of angiogenesis. Positive immuno-histochemical staining of SFRP2 was found in 9/9 (100%) angiosarcoma samples (Courtwright et al., 2009). Further investigation of its function in angiosarcoma revealed that SFRP2 mediates angiogenesis through a calcineurin-dependent NFAT (Nuclear Factor of Activated T-cells) pathway. The drug tacrolimus interferes with this pathway through inhibition of calcineurin, thereby indirectly inhibiting SFRP2 effects. *In vivo* treatment of the murine SVR angiosarcoma tumor model with tacrolimus significantly reduced tumor growth with 46% (Courtwright et al., 2009). Treatment of murine angiosarcoma cells with a SFRP2 monoclonal antibody (mAb) inhibited endothelial cell tube formation and migration *in vitro*, without effect on proliferation (Fontenot et al., 2013). *In vivo,* treatment of angiosarcoma with SFRP2 mAb did result in about 55–60% growth inhibition. There are no clinical trials yet with SFRP2 targeting agents or tacrolimus, although this does appear to be an effective approach.

ROCK1 and 2 (Rho-Associated Kinases) are modulators of angiogenesis through regulation of cell shape and cytoskeleton in endothelial cells. Disruption of ROCK signaling has been reported to inhibit VEGF-mediated activation of endothelial cells (Bryan et al., 2010). Overexpression of ROCK1 was present in all angiosarcoma samples (n = 6), whereas ROCK2 was overexpressed in both benign and malignant vascular tumors (Amaya et al., 2017). ROCK1 and 2 knockdown in angiosarcoma cells led to reduced tumor weight *in vivo* (Amaya et al., 2017; Montalvo et al., 2013). ROCK2 knockdown displayed a stronger inhibitory effect on tumor growth than knockdown of ROCK1 in both studies. Rho-kinase inhibitors have been clinically tested, though not yet in solid tumors.

Angiogenesis can also be targeted through blockade of beta-adrenergic receptors by propranolol, which exerts its effect through vasoconstriction, decreased responsiveness to VEGF, and induction of apoptosis. In angiosarcoma, strong expression of three beta-adrenergic receptors was present in 21–48% of cases (Stiles et al., 2013). *In vitro* treatment of canine and mouse angiosarcoma cells with propranolol

Table 4
Combination therapy *in vitro/ in vivo*.

Compound 1	Compound 2	Model	*In vitro/in vivo*	Result	Ref
Axitinib	Paclitaxel	AS-M5, ISO-HAS	*In vitro*	Additive	(Young et al., 2014)
Bevacizumab	Paclitaxel	AS-M5, ISO-HAS	*In vitro*	Additive	(Young et al., 2014)
Sunitinib	CAS 948,557-43-5 (Tie2 kinase)	SVR (murine AS)	Both	Synergy (*in vitro*), stronger reduction of tumor volume (*in vivo*, 70% at day 20)	(Hasenstein et al., 2012)
Propranolol	Cisplatin	SVR (murine AS), Emma, SB, Frog (canine AS)	*In vitro*	Synergy (SVR, Emma, SB)	(Stiles et al., 2013)
	Busulfan	SVR (murine AS), Emma, SB, Frog (canine AS)	*In vitro*	Synergy (SVR, Emma, SB)	
	Vincristine	SVR (murine AS), Emma, SB, Frog (canine AS)	*In vitro*	Synergy (SVR, Emma, SB)	
Rapamycin	PD0325901 (MEKi)	VCT115 (canine AS)	*In vitro*	Synergy	(Andersen et al., 2015)
Temsirolimus	PD0325901 (MEKi)	VCT115 (canine AS)	*In vivo*	Reduced tumor growth compared to temsirolimus or PD0325901 alone.	(Andersen et al., 2015)
Everolimus	Doxorubicin	AS-M5, ISO-HAS	*In vitro*	Additive	(Young et al., 2014)
Ganetespib	Paclitaxel	HAMON, ISO-HAS	*In vitro*	Synergy (both cell lines).	(Yamada-Kanazawa et al., 2017)

Table 5
Clinical studies and retrospective angiosarcoma cohort analyses with targeted agents in angiosarcoma.

Drug	NCT/Phase	Target(s)	n (AS)	RR (%)	PFS (mo)	OS (mo)	Year of publication
Bevacizumab (Agulnik et al., 2013)	NCT unknown/ Phase II	VEGF	23	9	12.0 wks	52.7 wks	2013
Bevacizumab + paclitaxel vs paclitaxel (Ray-Coquard et al., 2015)	NCT01303497/ Phase II	VEGF	49	45.8 vs 28.0	6.6 vs 6.6	19.5 vs 15.9	2015
Bevacizumab + paclitaxel (Q3 vs weekly) (Nea, 2017)	NCT01055028/ Phase II	VEGF	16	37.5 vs 25.0	3.4 vs 5.4	11.1 vs > 13.6	2017
Bevacizumab + gemcitabine + docetaxel (Dickson et al., 2015)	NCT00887809/ Phase II	VEGF	5	60	–	–	2015
Pazopanib (Kollar et al., 2017)	NA (retrospective study)	VEGFR1, 2, 3, cKIT, PDGFRs	40	20	3	9.9	2017
Pazopanib + TRC105 (Attia et al., 2016)	NCT01975519/ Phase IB/ Phase IIA	VEGFR1, 2, 3, cKIT, PDGFRs, Endoglin	5	1 CR	–	–	2016
Sorafenib (Maki et al., 2009)	NCT00245102/ Phase II	VEGFR2, PDGFR, RAF	40	13.5	3.8	14.9	2009
Sorafenib (Ray-Coquard et al., 2012)	NCT00874874/ Phase II	VEGFR2, PDGFR, RAF	41	14.6	1.8 (skin AS), 3.8 (visceral AS)	12.0 (skin AS),9.0 (visceral AS)	2012
Trebananib (D' Angelo et al., 2015)	NCT01623869/ Phase II	Angiopoietin 1, 2	16	0 (25% diseasecontrol)	1.6	6.4	2015
Everolimus (Yoo et al., 2013)	NCT01830153/Phase II	mTOR	3	33	PFR at 16 wks 67%	–	2013
Nivolumab + ipilimumab (D'Angelo et al., 2018)	NCT02500797/ Phase II	PD-1 CTLA-4	42 3	33	Duration of response 6 wks		2018

AS = angiosarcoma, RR = Response Rate, PFS = Progression Free Survival, OS = Overall Survival, wks = weeks, mo = months, PFR = Progression Free Rate.

resulted in blockade of cell proliferation and induction of apoptosis. Its cytotoxic effects were selective for vascular tumor cells, and a synergistic effect was found when combined with cisplatin, busulfan and vincristine. *In vivo* treatment with single agent propranolol resulted in reduced angiosarcoma tumor growth. Analysis of propranolol treatment effects revealed upregulation of TEK expression, a gene encoding for Tie2 receptor (Stiles et al., 2013). Clinically, responses to combination treatment of propranolol with cyclophosphamide or paclitaxel have been described in three case reports (Banavali et al., 2015; Daguze et al., 2016; Chow et al., 2015). Immunostaining for beta adrenergic receptors was reported positive in two of the cases. Based on *in vitro* assessment of propranolol combinations which showed synergy with vinblastine, seven patients received treatment of propranolol with weekly vinblastine and methotrexate (Pasquier et al., 2016). Treatment was well tolerated and resulted in clinical responses in all patients, varying from partial response to complete clinical and metabolic response. It is unclear whether this effect is related to the propranolol, the metronomic schedule of the chemotherapy, or the combination.

The vascular disruptive agent vadimezan, which reduces tumor blood flow and induces tumor necrosis, significantly inhibited angiosarcoma cell growth *in vitro* (Hoshina et al., 2013). Its clinical effect seemed promising in non-angiosarcoma phase I and –II trials, but has not yet been confirmed in phase III trials and no angiosarcoma trials are initiated so far (Daei Farshchi Adli et al., 2017).

In conclusion, angiogenesis-related genes and proteins have been rather extensively studied as a therapeutic target in angiosarcoma. However, clinical success of angiogenesis-targeting agents is lacking so far. Whether angiogenesis-related markers in angiosarcoma indicate a substantial role in angiosarcoma pathogenesis or merely reflect the degree of tumor cell differentiation, requires further investigation.

2.2. Oncogenic pathways in angiosarcoma

2.2.1. RAS/RAF/MEK/Erk -pathway

The RAS/RAF/MEK/Erk pathway is known to play a critical role in survival of human cancer cells. Mutated genes can lead to induced or sustained activation of the pathway, such as mutations in signal transducers (RAS) or downstream kinases within the pathway (BRAF). Genetic alterations involving the RAS/RAF/MEK/Erk pathway have been reported in 13–53% of angiosarcoma cases (Murali et al., 2015; Behjati et al., 2014). However, specific assessment of the mutational status of NRAS and BRAF performed in another series of 52 angiosarcoma cases showed no mutations (Italiano et al., 2012b).

An attempt to inhibit the RAS/RAF/MEK/Erk-pathway with the MEK-inhibitor selumetinib yielded varying responses *in vitro*, inhibiting cell growth in the AS-M5 cell line but with only minimal effect in ISO-HAS cells (Young et al., 2014). Both a RAF-inhibitor (PLX4720) and a MEK inhibitor (PD0325901) were tested in different angiosarcoma cell lines (Wada et al., 2015). The RAF inhibitor did not induce cell death, and the MEK inhibitor only induced weak responses. Combination therapy of the MEK inhibitor with the mTOR (mammalian target of rapamycin) inhibitor rapamycin appeared to render canine angiosarcoma cells as sensitive for MEK inhibition as BRAF-positive melanomas (Andersen et al., 2015). *In vivo*, combined MEK and mTOR inhibition significantly reduced tumor growth. Treatment with mTOR or MEK inhibitor alone was less effective than the combination, possibly because resistance to MEK inhibition might develop *via* activation of the MAPK pathway upon mTOR inhibition (Carracedo et al., 2008).

2.2.2. PI3K/AKT/mTOR-pathway

Another oncogenic pathway of interest in angiosarcoma is the PI3K/AKT/mTOR-pathway, which is known to control cell survival, cell growth and cell cycle progression in both physiological conditions as well as in malignant cells. It can be activated through RAS mutation, loss of PTEN (phosphatase and tensin homolog) or increased expression of growth factor receptors such as Epidermal Growth Factor Receptor (Karar and Maity, 2011).

Both genetic alterations as well as (over)expression of downstream components of the PI3K/AKT/mTOR pathway indicate its involvement in angiosarcoma. Mutations of the PIK3CA gene (encoding PIK3) has been reported in 3–17% of angiosarcoma cases (Behjati et al., 2014; Je et al., 2012; Italiano et al., 2012b). Of note, the PIK3CA mutational status did not show correlation with the expression of downstream protein kinases pS6K and/or p-4eBP1 (Italiano et al., 2012b). Overexpression of pS6K and/or p-4eBP1 was observed in 42% of angiosarcoma cases. Two other downstream components, p-Akt and elF41, were present in 85% and 87% of cases respectively.

Several drugs targeting downstream molecules in the PI3K/AKT/mTOR pathway have been investigated (Wada et al., 2015). Treatment of angiosarcoma cell lines with a PI3K inhibitor (LY294002) and PI3K/mTOR inhibitor (NVP-BEZ235) yielded 80% growth reduction (Wada et al., 2015). Treatment with mTOR inhibitor rapamycin resulted in significant reduction of cell proliferation *in vitro* (Du et al., 2013), whereas a 50–60% growth reduction was seen upon treatment with mTOR inhibitor everolimus (Wada et al., 2015). Combination of everolimus with doxorubicin did not yield a synergistic effect (Young et al., 2014). The Akt kinase inhibitor MK2206 failed to suppress cell growth (Wada et al., 2015). However, targeting PDK1 (Pyruvate Dehydrogenase Kinase 1, a downstream signal of PI3K which activates 20 substrates) showed more promising results. PDK1 inhibitor OSU-03012 inhibited growth of both ISOS-1 and ISO-HAS cell lines in a dose-dependent manner (Wada et al., 2015). Also, silencing of PDK1 with siRNA reduced pS6 and p4E-BP1 protein expression.

mTOR Inhibition has not yet been tested in a specific angiosarcoma population. However, two out of three angiosarcoma patients included in a phase II trial of everolimus reached the primary endpoint of Progression Free Rate at 16 weeks (Yoo et al., 2013), compared to 27% in the overall group of bone and soft tissue sarcoma patients. In addition, partial response to everolimus 10 mg/day was reported in two other angiosarcoma patients, with PFS of 6 and 12 months, respectively (Zhang et al., 2017). Overall survival was 10 and 18 months and treatment was well tolerated.

2.2.3. p16(INK4A) pathway

Genetic alterations in the tumor suppressor gene CDKN2A (Cyclin Dependent Kinase Inhibitor 2A, also known as *Ink4a/Arf)* in angiosarcoma were first described in primary angiosarcoma of the liver (Tannapfel et al., 2001). The *Ink4a/Arf* locus encodes the cycle-regulatory proteins p14(ARF) and p16(INK4a). Loss of p16(INK4A) results in immortalization of cells and is often caused by hypermethylation of CDKN2A p16(INK4A) promoter, as was the case in 12/17 (71%) of liver angiosarcomas (Tannapfel et al., 2001). Inactivation of p16(INK4a) in endothelial cells specifically resulted in defects in motility, morphogenesis and cytoskeletal organization (Kan et al., 2012). Furthermore, a higher proliferation rate was seen. In 40% (9/23) of angiosarcoma cases of unknown origin, immunohistochemical p16 expression was absent, indicating that loss of expression had occurred (Knosel et al., 2014). Whereas in other types of STS loss of p16 was associated with poor overall survival, no significant difference in survival was noted for angiosarcoma patients. This might be explained by the relatively small numbers.

More recent genomic studies revealed loss of CDKN2A in 26% (9/34) of angiosarcoma cases of different origins (Murali et al., 2015). In addition, homozygous deletion of CDKN2A was found in 3 out of 10 cases of cardiac angiosarcoma which were analyzed by whole genome analysis (Leduc et al., 2017). In theory, as CDKN2A negatively regulates CDK4 and -6, angiosarcomas with CDKN2A loss might benefit from treatment with CDK4/6 inhibitors such as palbociclib.

2.3. Other genetic alterations

2.3.1. MYC

One of the most well-known genetic alterations in angiosarcoma is high level amplification of MYC, a proto-oncogene involved in regulation of cellular proliferation, differentiation and apoptosis. Amplification is predominantly seen in secondary angiosarcoma related to radiation therapy or chronic lymphedema, with reported prevalence of 54–100%, compared to 0–7% in primary angiosarcoma (Huang et al., 2016; Guo et al., 2011; Fraga-Guedes et al., 2015; Shon et al., 2014; Mentzel et al., 2012). Most studies report a much higher prevalence in radiotherapy-associated angiosarcoma of the breast compared to other localizations (90–100% vs 25% respectively), although only a very limited number of non-breast secondary angiosarcoma cases has been analyzed. Analysis of 23 cases of cutaneous angiosarcoma of UV-exposed skin showed amplification in 17% of cases by FISH (Shon et al., 2014). The prognostic value of MYC amplification is yet to be determined, though there is some evidence of a negative correlation with survival (Huang et al., 2016; Fraga-Guedes et al., 2015). However, in UV-related cutaneous angiosarcoma, presence of MYC amplification was not correlated with clinical outcome (Shon et al., 2014).

As yet, the exact role of MYC in pathogenesis of (secondary) angiosarcoma remains unclear. Its subsequent potential as a target for treatment is still under investigation but bromodomain (BET) inhibitors might be effective inhibitors of the c-MYC protein.

2.3.2. Fusion genes

Other genetic alterations found in angiosarcoma include two different fusion genes, CEP85L-ROS1 (Giacomini et al., 2013) and CIC-LEUTX (Huang et al., 2016). ROS1 kinase can be targeted with ROS1 kinase inhibitors, however this fusion was only detected in 1/34 (2.9%) of angiosarcoma cases and further experiments were not reported. CIC fusions are not yet targetable.

2.4. Other targets

In addition to the abovementioned pathways and genetic alterations studied in angiosarcoma, several other potential targets have been described.

2.4.1. HSP90

Heat shock protein 90 (HSP90) regulates various cancer-related proteins by stabilizing and activating proteins required for survival of malignant cells. In angiosarcoma cell lines and patient samples (n = 4), levels of HSP90 protein expression were increased compared to controls (Yamada-Kanazawa et al., 2017). The HSP90 inhibitor ganetespib induced apoptosis as monotherapy, and an additive to synergistic effect was seen upon combination with docetaxel and paclitaxel. Knockdown of HSP90 selectively suppressed several downstream targets of VEGF signaling in angiosarcoma cells, but did not exert a direct effect on VEGFR2.

2.4.2. CD30

Expression of CD30, a member of the TNF receptor superfamily, was present in 34% (31/91) of angiosarcoma cases (Alimchandani et al., 2014). CD30 antibody drug conjugates may therefore present a potential therapy for patients with strongly positive CD30 angiosarcoma. Brentuximab is a CD30 antibody drug conjugate, delivering the highly toxic anti-microtubule agent momomethyl auristatin E to CD30-positive cells. Only one case of brentuximab treatment of angiosarcoma has been described so far in a patient with CD30-positive secondary angiosarcoma of the breast, after failure of first line paclitaxel, showing a response after 2 cycles but progression after 4 cycles (Holm et al., 2016).

2.4.3. YAP

Yes-associated protein (YAP) is a downstream protein in the Hippo-pathway, which is involved in regeneration and cell proliferation. Upon inactivation of the Hippo-pathway, YAP moves to the nucleus and activates genes involved in cell proliferation and the suppression of apoptosis. It has been suggested that YAP-activation leads to increased expression of survivin in endothelial cells (Tsuneki and Madri, 2014). In angiosarcoma, survivin expression was found in 86% (73/85) of cases (Tsuneki et al., 2017). Expression of YAP was present in 85% (72/85), of which 90% showed nuclear staining, thus indicating the Hippo-pathway to be switched off. Presence of survivin or nuclear YAP expression did not significantly correlate with patient survival. The ISO-HAS angiosarcoma cell line showed survivin expression, and suppression of cell growth occurred after treatment with survivin inhibitor YM155. These findings suggest that activated YAP and/or survivin could be a target for therapy.

A proposed underlying mechanism of the abovementioned changes in survivin and nuclear YAP expression is found in genetic depletion of CD31 (Tsuneki and Madri, 2014). Further analysis indicated a small population of $CD31^{low}$ cells was present in the majority of angiosarcoma tumor samples (11/17; 65%) (Venkataramani et al., 2018). In addition, a population of $CD31^{low}$ cells of up to 60% was found in the AS-M5 cell line. These $CD31^{low}$ cells were highly proliferative, resistant to stress and more tumorigenic compared to $CD31^{high}$ cells. Interestingly, $CD31^{low}$ cells were also more resistant to doxorubicin. Upon treatment with pazopanib, which is known to also inhibit YAP, $CD31^{low}$ cells were resensitized to doxorubicin treatment.

2.4.4. ALT/DAXX

Alternative lengthening of telomeres (ALT) is a mechanism involved in a subset of cancers which maintain telomere lengths without detectable telomerase activity. The ALT phenotype has been frequently associated with loss of expression of ATRX (α-thalassemia/mental retardations syndrome X-linked) and DAXX (death domain-associated 6). Receptor expression of ATRX was absent in 6% (7/118) of angiosarcoma cases (Panse et al., 2019). Absence of ATRX in angiosarcomas was significantly associated with inferior Event Free Survival and localization of the primary tumor in the deep soft tissue. DAXX expression was retained in all cases examined. Of note, absence of ATRX was reported in 21% (16/77) of primary angiosarcomas in another study (Liau et al., 2015). A tumor with ALT-phenotype may be sensitive to ATR inhibitors, although conflicting results have been reported and the strategy of targeting ALT phenotype should be further investigated (Flynn et al., 2015; Deeg et al., 2016).

2.4.5. Notch

Notch signaling is involved in regulation of stem cells and progenitor cells, through control of gene transcription. Mutations in Notch1 have been found in angiosarcoma (Murali et al., 2015), and inhibition of Notch signaling has led to development of malignant vascular tumors in mice (Dill et al., 2012). Decreased Notch1 expression was found in 24% (29/123) of angiosarcoma cases and was associated with advanced disease and cutaneous site of origin (Panse et al., 2019). Notch2 expression was lost in 16% (16/103) of cases and was associated with worse disease specific survival and visceral site of origin. It is known that Notch can act both oncogenic as well as tumor suppressive depending on the cellular context (Nowell and Radtke, 2017). Based on the before mentioned results, Notch appears to have a tumor suppressive role in angiosarcoma. However, 1 out of 8 angiosarcoma patients included in a recent phase 1 trial with Notch-inhibitor LY3039478 had unconfirmed partial response (Mir et al., 2018). These conflicting data emphasize the need for further research into the exact role and targetability of Notch signaling in angiosarcoma subtypes.

2.5. Epigenetics

Besides attempts to target specific mutations and their downstream pathways, another emerging field in cancer treatment lies in epigenetics. This involves changes in gene activity without altering the DNA sequence, thus leading to modifications in transcription. Epigenetic mechanisms can be divided into four categories: DNA methylation, histone modification, ATP-dependent nucleosome remodeling, and microRNAs or other noncoding RNAs. So far, in angiosarcoma only microRNAs (miRNAs) have been described. MiRNAs are capable of inflicting post-transcriptional changes, thus controlling target gene expression by interfering in the RNA pathway. In angiosarcoma, downregulation of miR-497-5p was found (Chen et al., 2016). Further analysis showed reduced growth both *in vitro* and *in vivo* growth upon inhibition of miR-497-5p or its target gene KCa3.1. In addition, expression of miR-210 was markedly decreased in angiosarcoma cells, both *in vitro* and *in vivo* (Nakashima et al., 2017). Further analysis of two putative targets of miR-210, E2F3 and Ephrin A3, revealed upregulation of protein expression in angiosarcoma tumor cells. E2F3 is a transcription factor and involved in regulation of apoptotic response, cell proliferation and differentiation. Ephrin A3 is a member of the ephrin family, regulating vascular development. A significant reduction of angiosarcoma cells was seen upon E2F3 or Ephrin A3 knockdown, thus indicating a potential target for growth inhibition (Nakashima et al., 2017).

2.6. Immunotherapy

Immunotherapy has been a major breakthrough in the treatment of several types of cancer, such as melanoma and lung cancer. Immunotherapy can be divided into different main strategies, including cytokines (*e.g.* IL-2, IFN-α), cell-based therapies (vaccines, adoptive cell therapy) and immune checkpoint blockade (anti-CTLA-4, anti-PD-1, anti-PD-L1).

In the field of sarcoma, to date immunotherapy has not given major clinical breakthroughs, but interesting signals have been observed. In angiosarcoma specifically, only limited research has been published yet. One of the targets of immunotherapy is the tumor-infiltrating lymphocyte (TIL). A higher number of CD8(+) TILs was found to be associated with higher survival by immunohistochemical evaluation of 55 cutaneous angiosarcoma samples (Fujii et al., 2014). Moreover, presence of interferon-γ producing CD4(+) and CD8(+) peripheral blood mononuclear cells was significantly higher compared to healthy controls and melanoma patients. Further stimulation of already present CD8(+) cells might provide a new strategy for angiosarcoma treatment.

Based on the presence of CD8(+) TILs in cutaneous angiosarcomas, Programmed Death Ligand 1 (PD-L1) expression was examined in this subgroup and found present in 30–40% of cutaneous angiosarcoma cases (Honda et al., 2017; Shimizu et al., 2017). In one study, PD-L1 expression was found to be an independent prognostic marker for worse survival in stage 1 patients (Shimizu et al., 2017). In contrast, in another study a high infiltration of PD-1 positive lymphocytes into the tumor was significantly related to favorable survival in stage 1 cutaneous angiosarcoma patients by univariate and multivariate analysis (hazard ratio 0.38, $p = 0.021$, CI $0.16 - 0.86$) (Honda et al., 2017). In an additional study with 24 primary angiosarcomas, 66% of cases showed PD-L1 expression (Botti et al., 2017). Of interest, PD-L1 positivity was not only found in cases of cutaneous origin but also in soft tissue and breast angiosarcomas.

Hence, PD-L1 expression appears to be present in a subset of angiosarcomas, but the relationship between PD-1 and PD-L1-expression and susceptibility to anti-PD-1 treatment has yet to be established in general. So far, clinical data of immune checkpoint inhibitors in angiosarcoma are scarce. Combination of nivolumab (anti-PD-1 antibody) and ipilimumab (anti-CTLA4 antibody) in patients with advanced sarcoma yielded an objective response in one out of 3 angiosarcoma patients participating (D'Angelo et al., 2018). Details with regard to the tumor characteristics of this responsive patient have not yet been published. Pembrolizumab was investigated in combination with cyclophosphamide in a phase II trial for advanced sarcoma and GIST patients (Toulmonde et al., 2017). No specific results regarding angiosarcoma patients have been reported yet. Two cases of checkpoint inhibitors in angiosarcoma have been published, reporting angiosarcoma of the nose yielding a PR on pembrolizumab (Sindhu et al., 2017), and nivolumab treatment of a PD-L1 negative angiosarcoma of the scalp remarkably resulting in durable complete response (Hofer et al., 2018). Of note, all published responses to checkpoint inhibitors have been in cutaneous angiosarcoma. The combination of PD-L1 inhibitor avelumab and paclitaxel is currently under investigation in a phase 2 trial (NCT03512834). This study includes all clinical subtypes of locally advanced and metastatic angiosarcoma, independent of PD-L1 expression.

Based on promising results in synovial sarcoma patients with T-cell based immunotherapy directed against cancer testis antigen NY-ESO-1, expression was also investigated in angiosarcoma samples. NY-ESO-1 expression was demonstrated in 7/54 (13%) angiosarcoma samples (Lai et al., 2012; Iura et al., 2017). MAGEA4 is another cancer testis antigen and is known to be recognized by specific cytotoxic T lymphocytes as well. MAGEA4 expression was present in 41% (12/29) of angiosarcomas, with strong MAGEA4 expression in about 20% of cases (Iura et al., 2017). Application of NY-ESO-1 or MAGEA4 directed therapy has not yet been reported in angiosarcoma.

3. Future perspectives

The prognosis of angiosarcoma patients remains poor and improving their treatment opportunities is necessary. Due to the rarity and heterogeneity of angiosarcomas, attempts to improve its treatment have been limited. Although a bench to bedside approach is advocated as the ideal sequence of medical science, there are only a few clear examples of this sequence. Therefore, we suggest that future research should focus on both further understanding of known promising preclinical targets, as well as on acquiring knowledge based on clinical, genetic and immunological large datasets of angiosarcomas.

As for known promising targets, we here described the PI3K/AKT/mTOR pathway, SFRP2 and YAP/survivin as potentially interesting targets for further research. Furthermore, extended investigation of combination therapies such as Tie2 kinase and VEGF inhibition, or combined mTOR and MEK inhibition, could help to improve efficacy and overcome treatment resistance. The first promising signs with checkpoint inhibitors in cutaneous angiosarcomas also deserve further study. Next Generation Sequencing panel screening might help speed up our knowledge of drivers and could also help to identify targets for individualized treatment. Genetic aberrations should be validated by investigating their downstream functional components and new treatments should be tested pre-clinically. Furthermore, genomic and phenotypic data should be merged to understand the differences in biology and response to treatments in the different clinical angiosarcoma subtypes. This would improve and fasten the selection of the right patients for the right treatments.

Several promising initiatives have been set up to enable the collection of data of larger numbers of patients, such as the AACR GENIE project in which cancer genomic data of cancer patients are integrated with clinical outcome data (AACR Project GENIE, 2017). This database is freely accessible and contains about 1400 STS samples, including almost 100 angiosarcoma patients. Another revolutionary project is the Angiosarcoma Project (Dunphy et al., 2018), which also provides publicly available data. They involve angiosarcoma patients themselves to provide saliva, blood and tumor samples to perform whole exome sequencing. In addition, their clinical data are collected. By setting up international networks and freely accessible data collections, these

projects are extremely valuable and provide the opportunity to achieve the progress we desperately need in angiosarcoma.

Conflict of interest statement

We declare to have no conflict of interest.

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