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Review

Non-cytotoxic systemic treatment in malignant peripheral nerve sheath tumors (MPNST): A systematic review from bench to bedside

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ABSTRACT

Background: Malignant peripheral nerve sheath tumors (MPNSTs) are aggressive soft tissue sarcomas. Once metastasized, prognosis is poor despite regular treatment with conventional cytotoxic drugs. This study reviews the preclinical and clinical results of non-cytotoxic systemic therapy in MPNST.

Methods: A systematic search was performed in PubMed and Embase databases according to the PRISMA guidelines. Search terms related to 'MPNST', 'targeted therapy', 'immunotherapy', and 'viral therapy' were used. Only *in vivo* studies and clinical trials were included. Clinicaltrials.gov was also searched for any ongoing trials including MPNST patients. Qualitative synthesis was performed on all studies stratifying per target: membrane, cytoplasmic, nuclear, immunotherapy and oncolytic viruses, and other. *In vivo* studies were assessed for treatment effect on tumor growth (low/intermediate/high), survival, and metastases. Clinical trials were assessed on response rate, progression-free survival, and overall survival.

Results: After full-text screening, 60 *in vivo* studies and 19 clinical trials were included. A total of 13 trials are ongoing and unpublished. The included trials displayed relatively poor response rates thus far, with patients achieving stable disease at best. Inhibiting cytoplasmic targets most commonly yielded high treatment effect, predominantly after mTOR inhibition. Oncolytic viruses and angiogenesis inhibition also demonstrate intermediate to high effect. Therapies including a combination of drugs were most effective in controlling tumor growth. Several ongoing trials investigate potentially promising pathways, while others have yet to be established.

Conclusion: Targeting the PI3K/Akt/mTOR pathway seems most promising in the treatment of MPNSTs. Oncolytic viruses and angiogenesis inhibition represent emerging therapies that require further study. Combinations of targeted therapies are most likely key to maximize treatment effect.

1. Introduction

Malignant peripheral nerve sheath tumors (MPNSTs) are rare, but aggressive soft tissue sarcomas (STS) with high rates of recurrence and metastasis (Carli et al., 2005; Stucky et al., 2012; Valentin et al., 2016). Almost half of all cases are related to neurofibromatosis type I (NF1), while others occur sporadically or after radiation exposure (Stucky et al., 2012; Zou et al., 2009). The *NF1* gene is commonly affected in MPNSTs causing the loss of neurofibromin, a Ras inhibiting enzyme (Basu et al., 1992). Ras activation results in the downstream activation of Ras pathways, leading to upregulation of mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) (Endo et al., 2013). However, loss of neurofibromin alone is not enough to cause an MPNST (Kluwe et al., 1999). Research over the last three decades has implicated multiple factors in the pathogenesis of MPNSTs, including loss of function in *TP53*, *CDKN2A*, *SUZ12*, and *PTEN* genes, as well as amplification of epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), and MET (Beert et al., 2011; De Raedt et al., 2014; Legius et al., 1994; Masliah-Planchon et al., 2013; Upadhyaya et al., 2012). Despite our increased understanding of the

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complex biology underlying MPNSTs, prognosis has remained poor, with 5-year survival rates ranging from 30 to 60% in patients who have undergone curative surgery of their tumor, and even lower rates in those with advanced and metastatic disease (Carli et al., 2005; Ducatman et al., 1986; Stucky et al., 2012; Valentin et al., 2016).

Surgery with wide negative margins remains the mainstay treatment for MPNST (Stucky et al., 2012; Valentin et al., 2016). Radiotherapy is commonly used either postoperatively or in a neoadjuvant setting as it improves local control, but does not affect overall survival (Bradford and Kim, 2015; Kahn et al., 2014; Stucky et al., 2012). In a study investigating neoadjuvant chemotherapy, histotype-guided treatment of four STS types, including MPNST (this cohort was treated with etoposide-ifosfamide), has not shown any benefit compared to standard anthracycline based chemotherapy (Gronchi et al., 2017). Therefore, there has thus far been no rationale for treating MPNST differently from other STS. Neoadjuvant chemotherapy could be considered for high-grade, large, and deep MPNST (Gronchi et al., 2017; Higham et al., 2017), and may allow initially inoperable patients to become operable (Carli et al., 2005; Kroep et al., 2011). However, over 10% of MPNST patients present with unresectable or metastatic disease (Carli et al., 2005; Valentin et al., 2016; Wong et al., 1998). Additionally, 40–60% of patients receiving treatment with curative intent will develop metastatic disease (Anghileri et al., 2006; Wong et al., 1998; Zehou et al., 2013).

For the whole group of STS, first line palliative chemotherapy consists of an anthracycline (doxorubicin or epirubicin) containing schedule. This might be combined doxorubicin and ifosfamide or doxorubicin monotherapy. Overall, a clinical response rate of approximately 21% has been reported for MPNST treated with combined doxorubicin and ifosfamide (Kroep et al., 2011). Adding ifosfamide to doxorubicin has improved progression-free survival (PFS), but not overall survival (OS), and comes at the cost of increased toxicity (Judson et al., 2014).

The high rates of advanced and metastatic disease and poor response to standard chemotherapy highlight the need for novel therapies in the treatment of MPNST. Targeted therapy and immunotherapy has brought new options to many other cancer types, but is not yet established in STS in general or MPNST specifically. Especially target specific, non-cytotoxic treatments are of interest as they may specifically target tumors and have limited systemic side-effects. As insights in the differences between STS subtypes are growing, more specific testing to allow for identification and subsequent personalization of treatment is necessary; however, given that MPNST represent a rare sarcoma subtype, such personalization has thus far been challenging. To better understand emerging treatment options, we pooled the available literature and performed a systematic review of non-cytotoxic systemic therapies in MPNST, aiming to guide future research efforts by identifying the most relevant targets and combinations.

2. Methods

2.1. Literature search

A systematic search was performed in both PubMed and Embase databases according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, in order to identify all potentially relevant articles published from 2000 to 2018. The search string was built with the help of a professional librarian using search terms related to 'MPNST' and non-cytotoxic treatments. The exact search syntaxes for PubMed and Embase are provided in Supplemental Table S1. Preclinical studies were included if they studied non-cytotoxic drugs on MPNSTs *in vivo*. Clinical studies were included if they presented results of non-cytotoxic systemic therapy specifically in MPNST patients. Articles were excluded if they were retrospective or single case studies, reviews, presented non-specific MPNST data, included data on cytotoxic drugs or drugs that were only tested *in vitro*, or did not provide data on tumor growth, survival, or metastases. Clinicaltrials.gov was also searched with synonyms of 'MPNST' to obtain all ongoing non-cytotoxic drug trials enrolling MPNST patients. Cross-referencing of included papers and registered trials was performed, which identified six additional papers. These studies did not include a synonym of MPNST in either their title or abstract. The initial review was carried out by two independent authors (EM, NL). Disagreements were solved through discussion, in which one additional senior author was involved (ID).

2.2. Data extraction and synthesis

Data extracted from preclinical studies included: animal model used, most effective treatment regimen studied, tissues investigated, and treatment effect on tumor growth, survival, and metastasis. The treatment effect on tumor growth was evaluated according to the mean relative tumor volume (RTV) comparing the latest mean volume measurement of the control group (C) to the mean volume of the treatment group (T) at that time point (Houghton et al., 2007; Plowman et al., 1999): T/C $\leq$15% represented high effect (black); T/C $\leq$45% but > 15% represented intermediate effect (dark gray); and T/C > 45% represented low effect (light gray, Table 1). Tumor growth was either assessed by tumor volume, weight, or area. Drugs were categorized as membrane targets, cytoplasmic targets, nuclear targets, immunotherapy and oncolytic viruses, or other targets.

Data extracted from clinical trials included: study design, number of patients, age of population, treatment regimen, and treatment effect on response rate, PFS, and OS. Study phase, country, intervention, anticipated accrual, and end date were extracted from registered unpublished trials.

Qualitative synthesis was performed summarizing data from preclinical and clinical studies according to target pathway, immunotherapy and oncolytic viruses, and a rest group.

3. Results

Following removal of duplicates, a total of 1938 articles and registered trials were identified in PubMed and Embase databases. Title/abstract screening resulted in selection of 203 potentially relevant articles, of which sixty-six were selected for qualitative synthesis after full-text screening (Fig. 1). A total of sixty preclinical *in vivo* studies were found that used numerous genetically engineered mouse models (GEMM), (non)-cultured NF1 and sporadic patient xenografts, allografts from GEMMs, and one zebrafish model (Table 1). Nineteen trials were identified, of which six have already been published (Table 2), and thirteen are ongoing (Table 3). Fig. 2 presents the most important target pathways identified in MPNSTs.

3.1. Membrane targets – in vivo

Eight studies investigated membrane targets *in vivo* (Table 1). Six used receptor tyrosine kinase (RTK) targeted treatments with intermediate to high effect on tumor growth (Ki et al., 2017; Lock et al., 2016; Mo et al., 2013; Ohishi et al., 2013; Torres et al., 2011; Wu et al., 2018). The addition of verteporfin (TAZ/YAP inhibitor) to sorafenib yielded intermediate effects on tumor growth in an allograft model, while monotherapy of either drugs had significantly worse effects (Wu et al., 2018). The chemokine receptor CXCR4 stimulates cell cycle progression through PI3K and β-catenin signalling. In one *in vivo* study, inhibition of CXCR4 showed intermediate effect on tumor growth and increased survival of mice (Mo et al., 2013). Two *in vivo* studies investigated the effect of estrogen receptor blockade; one found a low effect on tumor growth (Byer et al., 2011), and another showed that the addition of a calmodulin inhibitor enhanced the effect on tumor growth (Brosius et al., 2014).

Table 1
Preclinical *in vivo* studies.

Author, year	Model	Regimen	Pathway	Tissue	NF1[a]	Outcome		
						Growth[b]	Survival[c]	Metastasis[d]
Membrane targets								
Byer, 2011	OXM	Tamoxifen	ER	ST88-14	NF1		*NA*	*NA*
Torres, 2011	XM	Cabozantinib	Multikinase (incl. MET, VEGFR2)	STS26T	S		*NA*	
				MPNST724	S		*NA*	*NA*
Mo, 2013	AA, GEMM	AMD3100	CXCR4	sMPNST	*NA*		*NA*	*NA*
				NPcis	*NA*	*NA*		*NA*
Ohishi, 2013	XM	Imatinib	Multikinase (incl. c-Kit)	HS-Sch-2	S		*NA*	*NA*
				FMS-1	NF1		*NA*	*NA*
				NMS-2PC	NF1		*NA*	*NA*
Brosius, 2014	OXM	Tamoxifen + trifluoperazine	ER, calmodulin	ST88-14	NF1		*NA*	*NA*
				STS26T	S		*NA*	*NA*
Lock, 2016	GEMM	Cabozantinib + PD0325901	Multikinase (incl. MET, VEGFR2), MEK	NPcis	*NA*		*NA*	*NA*
Ki, 2017	ZFM	Sunitinib	Multikinase (incl. VEGFR)	*NF1a*$^{+/-}$; *NF1b*$^{-/-}$;*p53*$^{m/m}$	*NA*		*NA*	*NA*
Wu, 2018	AA	Sorafenib + verteporfin	Multikinase (incl. VEGFR), TAZ/YAP	*Lats1/2*$^{-/-}$	*NA*		*NA*	*NA*
Cytoplasmic targets								
Hirokawa, 2006	XM	Sichuan	PAK1	S462	NF1		*NA*	*NA*
Johannessen, 2008	GEMM	Sirolimus	mTOR	NPcis	*NA*		*NA*	*NA*
Johansson, 2008	XM	Sirolimus + erlotinib	mTOR, EGFR	STS26T	S		*NA*	*NA*
Demestre, 2009	XM	Bio 30 + CAPE	PAK1	S462	NF1		*NA*	
Lee, 2009	XM	OSU03012	PDK1	HMS-97	S		*NA*	*NA*
Qi, 2009	XM	Saposin C protein	Lysosomes	STS26T	S		*NA*	*NA*
Banerjee, 2010	XM	Cucurbaticin-1	STAT3	ST88-14	NF1		*NA*	*NA*
Bhola, 2010	XM	Sirolimus	mTOR	*NA*	NF1		*NA*	*NA*
De Raedt, 2011	GEMM	Sirolimus + IPI-504	mTOR, Hsp90	NPcis	*NA*			*NA*
Ghadimi, 2012	XM	Voxtalisib + chloroquine	PI3K, mTOR, autophagy	MPNST724	S		*NA*	*NA*
				STS26T	S		*NA*	
Dodd, 2013	GEMM	PD0325901	MEK	*NF1*$^{fl/fl}$; *Ink4a/Arf*$^{fl/fl}$	*NA*		*NA*	*NA*
Jessen, 2013	XM	PD0325901	MEK	S462TY	NF1			*NA*
Brundage, 2014	XM	Everolimus	mTOR	S462TY	NF1		*NA*	*NA*
De Raedt, 2014	GEMM	PD0325901 + JQ1	MEK, BET	NPcis; *SUZ12*$^{-/-}$	*NA*		*NA*	*NA*
				NPcis	*NA*		*NA*	*NA*
Malone, 2014	GEMM	Sirolimus + PD0325901	mTOR, MEK	NPcis	*NA*		*NA*	*NA*
Patwardhan, 2014	XM	Sirolimus + pexidartinib	mTOR, multikinase (incl. c-Kit)	MPNST	*NA*		*NA*	*NA*
Watson, 2014	GEMM	Everolimus + PD0325901	mTOR, MEK	*NF1*$^{fl/fl}$; *Pten*$^{fl/fl}$	*NA*	*NA*		*NA*
				Pten$^{fl/fl}$; *EGFR*	*NA*	*NA*		*NA*
Wu, 2014	XM	FLLL32	JAK2/STAT3	S462TY	NF1		*NA*	*NA*
Yamashita, 2014	XM	Everolimus + bortezomib	mTOR, proteasome	NF90.8	NF1		*NA*	*NA*
Castellsagué, 2015	OXM	Sirolimus/doxorubicin + sorafenib	mTOR, multikinase (incl. VEGFR)	NF1-001	NF1		*NA*	*NA*
				NF1-002	NF1		*NA*	*NA*
				SP-001	S		*NA*	*NA*
				SP-002	S		*NA*	*NA*
				S462	NF1		*NA*	*NA*
Slotkin, 2015	XM	Sapanisertib + sirolimus	mTOR	MPNST	*NA*		*NA*	*NA*
Kendall, 2016	XM	PD0325901	MEK	S462TY	NF1			*NA*
Sweeney, 2016	AA	PD0325901 + PTT	MEK	M2	*NA*			*NA*
Malone, 2017	GEMM	Sapanisertib + panobinostat	mTOR, HDAC	NPcis	*NA*		*NA*	*NA*
Semenova, 2017	XM	Frax1036 +/- PD0325901	PAK1, MEK	S462TY	NF1		*NA*	*NA*
				STS26T	S		*NA*	
Nuclear targets								
Hirokawa, 2005	XM	Depsipeptide	HDAC	S805	NF1		*NA*	*NA*
Lopez, 2011	XM	Abexinostat + chloroquine	HDAC, autophagy	MPNST642	NF1		*NA*	*NA*
				MPNST724	S		*NA*	*NA*
				STS26T	S		*NA*	
Patel, 2012	XM	Alisertib	AURKA	S462TY	NF1			*NA*
Mohan, 2013	XM	Alisertib	AURKA	NF1-MPNST	NF1		*NA*	*NA*
				SP-MPNST	S		*NA*	*NA*
Patel, 2014	AA	JQ1	BET	sMPNST	*NA*		*NA*	*NA*
Lopez, 2015	AA	PCI-48012	HDAC8	MPNST6IEPVI	*NA*		*NA*	*NA*
Nair, 2015	XM	TAK-960	PLK1	MPNST	*NA*		*NA*	*NA*
Perez, 2015	XM	Palbociclib	CDK4/6	S14	*NA*			*NA*
Zhang, 2015	XM	DZNep	EZH2	MPNST724	S		*NA*	*NA*
Kivlin, 2016	XM	Olaparib	PARP	STS26T	S			*NA*
				MPNST724	S		*NA*	*NA*
Nair, 2017	XM	Selinexor + carfilzomib	XPO1, proteasome	MPNST	*NA*		*NA*	*NA*
Payne, 2018	OXM	Alisertib	AURKA	STS26T	S	*NA*		*NA*
Immunotherapy and oncolytic viruses								
Liu, 2006	AA	G47Δ-PF4	oHSV	M2	*NA*			*NA*
Liu, 2006	AA	G47Δ-dnFGFR	oHSV	M2	*NA*		*NA*	*NA*
Mahller, 2007	XM	hrR3	oHSV	STS26T	S			*NA*
Mahller, 2008	XM	rQT3	oHSV	STS26T	S		*NA*	*NA*
				S462TY	NF1			*NA*
Maldonado, 2010	XM	oHSV-MDK-34.5	oHSV	STS26T	S			*NA*
Antoszczyk, 2014	OXM, AA	G47Δ-IL12/PF4	oHSV	S462	S			*NA*
				M2	*NA*			*NA*
				M3	*NA*			*NA*
Deyle, 2015	XM	MV-NIS	oMV	ST88-14	NF1			*NA*
				S462TY	NF1			*NA*
Currier, 2017	XM	HSV1716 + alisertib	oHSV, AURKA	S462TY	NF1			*NA*
Other								
Mashour, 2005	AA	DHA	Apoptosis	32-5-30	*NA*			*NA*
Ghadimi, 2012	XM	Sepantromium bromide	Survivin	MPNST724	S		*NA*	*NA*
				STS26T	S		*NA*	
Wang, 2012	XM	Triptolide	Apoptosis	STS26T	S		*NA*	*NA*
Demestre, 2013	XM	PEDF	Multi-antitumor	S462	NF1		*NA*	*NA*
Patel, 2015	XM	C75	FAS	STS26T	S		*NA*	*NA*
Zewdu, 2016	XM	Verticillin A	Apoptosis	MPNST724	S		*NA*	*NA*
Ikuta, 2017	XM	MU	Hyaluronan synthesis	sNF96.2	NF1		*NA*	*NA*
Semenova, 2017	XM	Nifedipine	Ca^{2+}-channel	S462TY	NF1		*NA*	*NA*

a: NF1 patient cells or sporadic patient cells, b: either volume, weight, or area, low activity (light gray), intermediate activity (dark gray), high activity (black), c: increased survival (black) d: less metastases (black).

Abbreviations: AA: auto- and/or allograft mouse model; AURKA: aurora kinase A; BET: bromo- and extra-terminal domain; CAPE: caffeic acid phenethyl ester; CDK: cyclin-dependent kinase; CXCR4: CXC-chemokine receptor 4; DHA: docosahexaenoic acid; DZNep: 3-deazaneplanocin A; EGFR: epidermal growth factor receptor; ER: estrogen receptor; EZH2: enhancer of zeste homolog 2; FAS: fatty acid synthase; GEMM: genetically modified mouse model; HDAC: histone deacetylase; Hsp90: heat shock protein 90; JAK2: Janus kinase 2; MEK: mitogen-activated protein kinase kinase; MPNST: malignant peripheral nerve sheath tumor; mTOR: mammalian target of rapamycin; MU: 4-methylumbelliferone; NA: not applicable/available; NF1: neurofibromatosis type 1; NPcis: mutation of NF1 and p53 gene on both alleles; oHSV: oncolytic herpes simplex virus; oMV: oncolytic measles virus; OXM: orthotopic xenograft mouse model; PARP: poly (ADP-ribose) polymerase; PEDF: pigment epithelium-derived factor; PDK1: phosphoinositide-dependent kinase-1; PDX: patient-derived xenograft; PI3K: phosphoinositide 3-kinase; PLK1: polo-like kinase 1; PTT: phototermal therapy; S: sporadic; STAT3: signal transducer and activator of transcription 3; XM: xenograft mouse model; XPO1: exportin 1; ZFM: genetically engineered zebrafish model.

3.2. Membrane targets – trials

Four published clinical trials investigating the effect of an RTK inhibitor, of which one (Albritton et al., 2006) specifically examined MPNST patients (Table 2), were identified. None of the trials found an appreciable clinical response in MPNST patients, with only 0–20% of the patients achieving stable disease (Albritton et al., 2006; Chugh et al., 2009; Maki et al., 2009; Schuetze et al., 2016). Four additional trials were still ongoing at the time this review was written, one of which will only include MPNST patients. This study will evaluate the efficacy of the multikinase inhibitor pexidartinib in combination with mTOR inhibitor sirolimus (NCT02584647, Table 3). Multiple other trials were identified that will enroll patients with soft tissue sarcomas (NCT02584309, NCT02180867) and CD56 expressing tumors (NCT02452554) targeting additional membrane targets. One of these trials will investigate the effect of doxorubicin and ifosfamide with the addition of pazopanib, currently the only registered RTK inhibitor for STS, in a neoadjuvant setting including patients with resectable soft tissue sarcomas (NCT02180867).

3.3. Cytoplasmic targets – in vivo

Cytoplasmic targets were investigated in 25 *in vivo* studies (Table 1). Most studies ($n = 22$) focused on a target within the MAPK or the PI3K/Akt/mTOR pathway. In those targeting the PI3K/Akt/mTOR pathway, a high effect on tumor growth (14/17 cell lines) and survival was observed (3/3 cell lines). Targeting mTOR in combination with membrane targets (Castellsagué et al., 2015; Johansson et al., 2008; Patwardhan et al., 2014), other cytoplasmic targets (De Raedt et al., 2011; Malone et al., 2014; Watson et al., 2014), or an epigenetic target (Malone et al.,

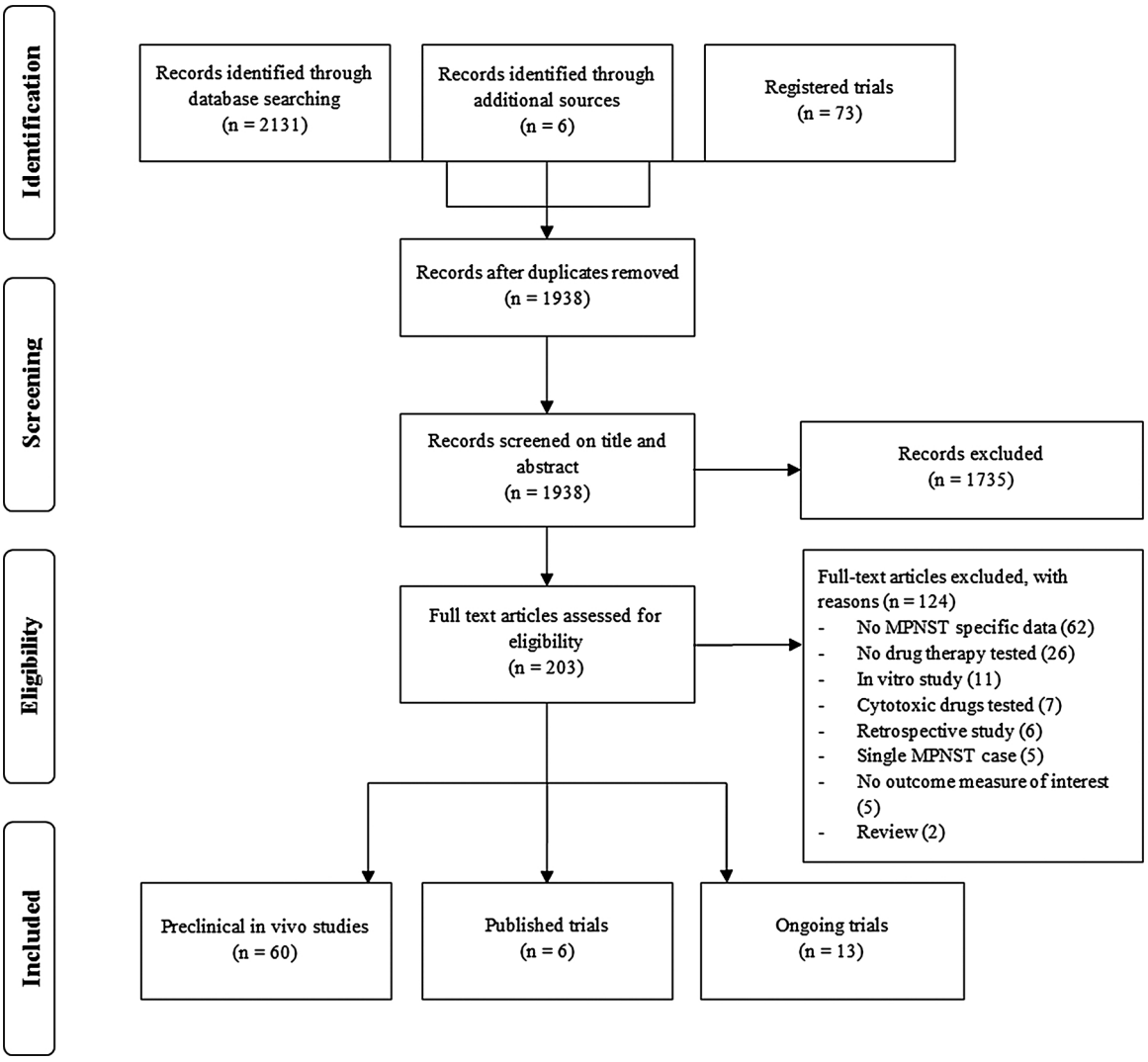

Fig. 1. Flowchart depicting study selection.

Table 2
Clinical trials.

Author, year	Study design	*N*	Age	Drug	Pathway	Outcome		
						RR	PFS	OS
Membrane targets								
Albritton et al. (2006)	Phase II unresectable or metastatic MPNST	20	≥18	Erlotinib	EGFR	1 SD, 19 PD	2 months	4 months
Chugh et al. (2009)	Phase II metastatic or recurrent sarcomas	5	≥10	Imatinib	Multikinase (incl. c-Kit)	1 SD, 4 PD	NA	NA
Maki et al. (2009)	Phase II metastatic or recurrent sarcomas	12	≥18	Sorafenib	Multikinase (incl. VEGFR)	3 SD, 9 PD	1.7 months	4.9 months
Schuetze et al. (2016)	Phase II high-grade, advanced sarcomas	14	≥13	Dasatinib	Multikinase (incl. BCR/ABL)	14 PD	2-month: 14% 4-month: 7%	NA
Cytoplasmic targets								
Widemann et al. (2016)	Phase II recurrent or metastatic MPNST	25	≥18	Everolimus + Bevacizumab	mTOR, VEGF	3 SD, 22 PD	NA	NA
Nuclear targets								
Dickson et al. (2016)	Phase II advanced or metastatic sarcomas	10	≥18	Alisertib	AURKA	No response (SD and PD)	13 weeks, 12-week: 60%	69 weeks

Abbreviations: AURKA: aurora kinase A; CI: confidence interval; CR: complete remission; EGFR: endothelial growth factor receptor; mTOR: mammalian target of rapamycin; N: total MPNST patients included; NA: not available; OS: overall survival; PD: progressive disease; PFS: progression free survival; RR: response rate; SD: stable disease; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor.

2017) showed high effect on tumor growth (8/8 cell lines) and survival (3/3 cell lines). One study found a higher effect of pexidartinib compared to imatinib as an addition to mTOR inhibition (Patwardhan et al., 2014). The addition of sorafenib (targets include VEGFR, PDGFR, and Raf) to an mTOR inhibitor showed the best effect on tumor size in NF1-mutated xenografts, while the addition of doxorubicin showed best effects in sporadic patient xenografts (Castellsagué et al., 2015). The addition of a proteasome inhibitor to mTOR inhibition was only effective if radiotherapy was administered as well (Yamashita et al., 2014). The addition of a mitogen-activated protein kinase (MEK) inhibitor to mTOR inhibition did not prolong survival in a murine model, but did decrease toxicity compared to single agent usage (Watson et al., 2014). MEK inhibition itself did not show high effects on tumor growth (Dodd et al., 2013; Jessen et al., 2013; Kendall et al., 2016; Sweeney et al., 2016); however in combination with other target inhibitors the effect on tumor growth improved (5/5 cell lines) (De Raedt et al., 2014; Lock et al., 2016; Semenova et al., 2017a,b). The addition of silmasertib, an epigenetic modulator of CK2, did not have a superior effect over MEK-inhibiting monotherapy (Kendall et al., 2016). PAK1 influences the MAPK pathway by activating MEK and ERK. In multiple studies, inhibition of PAK1 resulted in intermediate to high effects on tumor growth as a single drug (Demestre et al., 2009; Hirokawa et al., 2006; Semenova et al., 2017a,b). One study showed that the addition of a MEK inhibitor to a PAK1 inhibitor increased its effect in both NF1 and sporadic cell lines (Semenova et al., 2017a,b). Although EGFR inhibitors in MPNST have shown poor results in clinical studies,

Table 3
Current trials in advanced or metastatic MPNST.

NCT number	Country	Phase	Tumor type	*N*	Age	Drug	Pathway	Completion date
Membrane targets								
NCT02584647	US	I II	STS MPNST	49	≥18	Pexidartinib + sirolimus	Multikinase, mTOR	10-2021
NCT02452554	US	II	CD56 expressing tumors (MPNST)	114	1–30	Lorvotuzumab mertansine	CD56	03-2020
NCT02584309	US	II	STS (MPNST)	73	≥18	Doxorubicin + olaratumab	Anthracycline, PDGFRα	10-2023
NCT02180867	US	II/III*	STS (MPNST)	340	≥2	Doxorubicin + ifosfomide ± pazopanib	Multikinase, anthracycline, alkylans	12-2018
Cytoplasmic targets								
NCT03433183	US	II	MPNST	21	≥18	Vistusertib + selumetinib	mTOR, MEK	09-2021
NCT02008877	US	I/II	MPNST	20	≥16	Sirolimus + ganetespib	mTOR, Hsp90	07-2018
NCT02601209	US	I II	STS STS (MPNST)	137	≥18	Sapanisertib ± pazopanib	mTOR, multikinase	09-2020
Nuclear targets								
NCT02986919	US	II	MPNST	24	≥18	CPI-0610	BET	03-2020
NCT03009201	US	IB	STS (MPNST)	36	≥12	Ribociclib + doxorubicin	CDK4/6, anthracycline	12-2020
Immunotherapy and oncolytic virus								
NCT02691026	Norway	II	MPNST	18	≥18	Pembrolizumab	PD1	12-2025
NCT02834013	US	II	Rare tumors (MPNST)	707	≥18	Nivolumab + ipilimumab	PD1, CTLA4	08-2020
NCT02700230	US	I	MPNST	30	≥18	MV-NIS	oMV	06-2021
NCT00931931	US	I	Non-CNS solid tumors (MPNST)	18	7–30	HSV1716	oHSV	03-2018

Abbreviations: BET: bromo- and extra-terminal domain; CDK: cyclin-dependent kinase; CNS: central nervous system; Hsp90: heat shock protein 90; M: months; MEK: mitogen-activated protein kinase kinase; MPNST: malignant peripheral nerve sheath tumor; mTOR: mammalian target of rapamycin; N: accrual of patients; oHSV: oncolytic herpes simplex virus; oMV: oncolytic measles virus; PD1: programmed cell death protein 1; PDGFRα: platelet-derived growth factor receptor alpha; STS: soft tissue sarcoma; US: United States.

* Neoadjuvant in resectable disease.

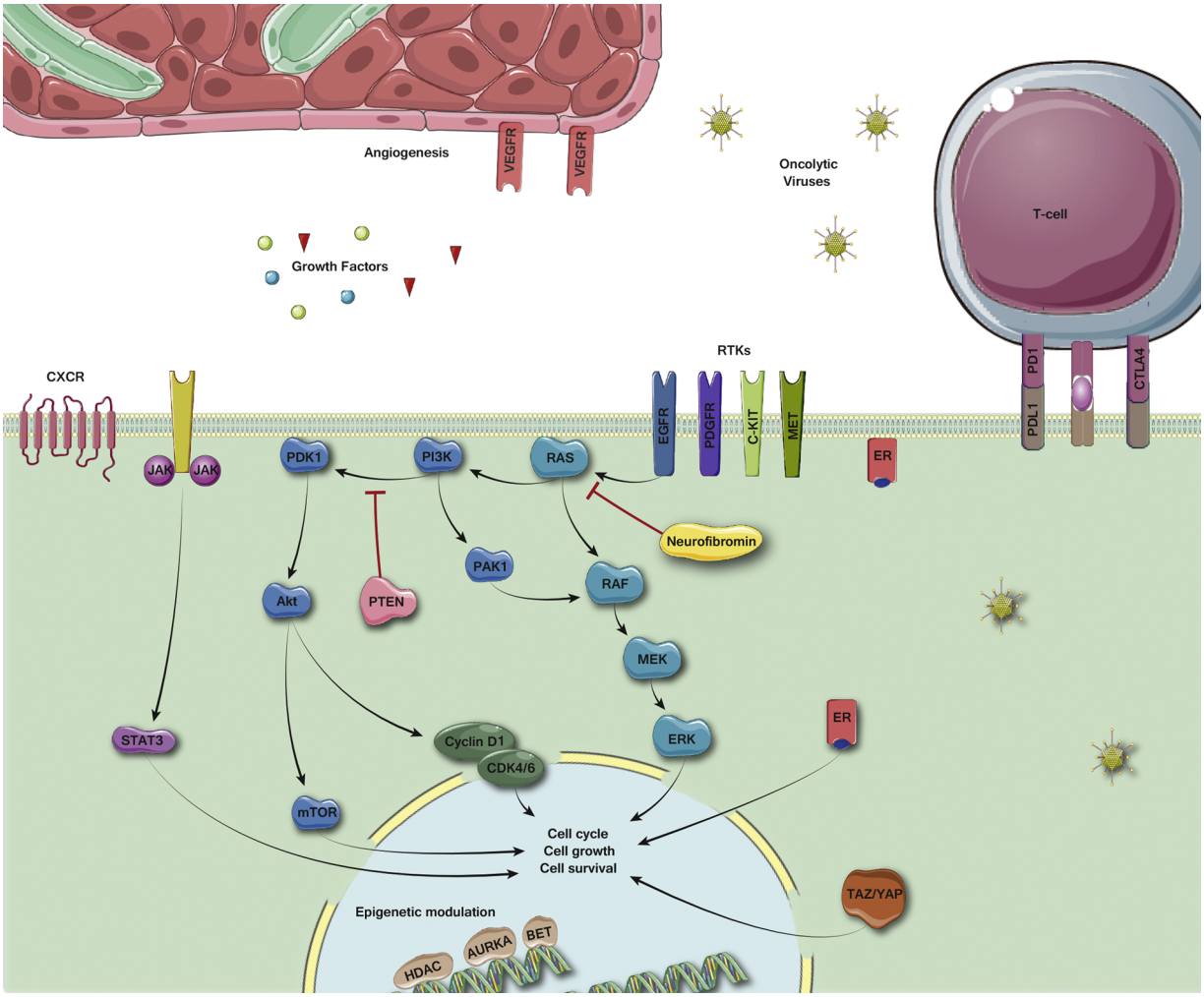

Fig. 2. Cellular pathways in MPNST. *Abbreviations*: AURKA: aurora kinase A; BET: bromo- and extra-terminal domain; CDK: cyclin-dependent kinase; CTLA4: cytotoxic T-lymphocyte associated protein 4; CXCR: CXC-chemokine receptor; EGFR: epidermal growth factor receptor; ER: estrogen receptor; ERK: extracellular signal-regulated kinases; HDAC: histone deacetylase; JAK: Janus kinase; MEK: mitogen-activated protein kinase kinase; mTOR: mammalian target of rapamycin; PD1: programmed cell death protein 1; PDGFR: platelet-derived growth factor receptor; PDK1: phosphoinositide-dependent kinase-1; PDL1: programmed death-ligand 1; PI3K: phosphoinositide 3-kinase; PTEN: phosphatase and tensin homolog; STAT3: signal transducer and activator of transcription 3; VEGFR: vascular endothelial growth factor receptor.

downstream inhibition of Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) showed intermediate to high effect *in vivo* (Banerjee et al., 2010; Wu et al., 2014).

3.4. Cytoplasmic targets – trials

One trial evaluating the effect of mTOR inhibition in combination with bevacizumab, a VEGF inhibitor, demonstrated stable disease in 3/25 patients (Widemann et al., 2016). A total of three trials that were ongoing at the time of this review were investigating the role of an mTOR inhibitor in combination with a MEK inhibitor (NCT03433183), pazopanib (NCT02601209), or heat shock protein 90 (Hsp90) inhibitor (NCT02008877, Table 3). The latter trial was completed, although its results were not yet published.

3.5. Nuclear targets – in vivo

The effect of nuclear target inhibitors was investigated in twelve studies, identifying this class of drugs to have intermediate to high effects on tumor growth (Table 1). Multiple studies found a high effect on survival (4/4 cell lines) or tumor growth (5/15 cell lines) via *in vivo* inhibition of several epigenetic pathways (Hirokawa et al., 2005; Kivlin et al., 2016; Lopez et al., 2015, 2011; Mohan et al., 2013; Nair and Schwartz, 2015; Patel et al., 2014, 2012; Payne et al., 2018). Aurora kinase A (AURKA) is one of these epigenetic regulators, which regulates centrosome maturation and chromosome separation. Alisertib, an AURKA inhibitor was found to have a higher effect on tumor growth and survival compared to a combination of doxorubicin and ifosfamide *in vivo* (Payne et al., 2018).

CDK4/6 and EZH2 act via influence on the cell cycle; *in vivo* studies showed that their inhibition has intermediate effect on tumor growth (Perez et al., 2015; Zhang et al., 2015).

XPO1 is the main nuclear export protein and transports proteins such as survivin. One *in vivo* study found intermediate effect of XPO1 inhibition combined with proteasome inhibitor carfilzomib (Nair et al., 2017).

3.6. Nuclear targets – trials

Although in a preclinical setting alisertib showed positive results, a trial that included ten MPNST patients found no tumor response (Table 2) (Dickson et al., 2016). Median PFS was thirteen weeks, with a median OS of sixty-nine weeks. A trial that was ongoing at time of publication was investigating the effect of a bromo- and extra-terminal

domain (BET) inhibitor in advanced or metastatic MPNST patients (NCT02986919, Table 3). An ongoing phase Ib trial enrolling patients with MPNSTs, among other soft tissue sarcomas, is investigating the effect of ribociclib, a CDK4/6 inhibitor, combined with doxorubicin (NCT03009201).

3.7. Immunotherapy and oncolytic viruses – in vivo

Next to tumor cell specific targeting, immunotherapy may also play a role in MPNST treatment. With an evolving role in other cancer types, no *in vivo* studies have thus far been published investigating immunotherapy regimens specifically in MPNST. Oncolytic viruses are thought to affect tumors in several ways, one of which involves the upregulation of the immune system. Eight studies investigated the effect of oncolytic viruses in MPNST *in vivo* (Table 1). Seven studies used an oncolytic herpes simplex virus (oHSV) with mostly intermediate to high effect (10/12 cell lines) on tumor growth (Antoszczyk et al., 2014; Currier et al., 2017; Liu et al., 2006a,b; Mahller et al., 2007, 2008; Maldonado et al., 2010). One study used an oncolytic measles virus (oMV) and showed high efficacy in one xenograft model, but low effect in another (Deyle et al., 2015). Almost all studies looked at survival and showed a statistically significant benefit for treatment with oncolytic viruses compared to a placebo control group. The addition of erlotinib, an EGFR inhibitor, did not significantly improve the efficacy compared to oHSV monotherapy *in vivo* (Mahller et al., 2007). However, additional AURKA inhibition was found to have a synergistic effect on both tumor growth and survival (Currier et al., 2017).

3.8. Immunotherapy and oncolytic viruses – trials

Two ongoing trials are investigating the role of PD1 checkpoint inhibitors (Table 3): one looks at PD1 inhibitors alone and includes MPNST patients only (NCT02691026), while the other study combines the PD1 inhibitor nivolumab with CTLA-4 inhibitor ipilimumab and includes patients with rare tumors, one of which is MPNST (NCT02834013).

No clinical trial has yet evaluated the effect of oncolytic viruses in MPNSTs. Two trials are registered of which one will use an oMV in MPNST patients only (NCT02700230) and the other, which is complete and whose results are pending, investigated the effect of an oHSV in non-central nervous system (CNS) solid tumors including MPNSTs (NCT00931931, Table 3).

3.9. Other targets – in vivo

Eight studies investigated other types of drugs, targeting different pathways including fatty acid synthase (FAS) (Patel et al., 2015), pigment epithelium-derived factor (PEDF) (Demestre et al., 2013), calcium channels (Semenova et al., 2017a,b), survivin (Ghadimi et al., 2012), hyaluronan synthesis (Ikuta et al., 2017), and other apoptosis-inducing pathways (Table 1) (Mashour et al., 2005; Wang et al., 2012; Zewdu et al., 2016). Most studies found an intermediate effect on tumor growth (6/9 cell lines), and only verticillin A and PEDF were found to have a high effect on tumor growth (Demestre et al., 2013; Zewdu et al., 2016). Docosahexaenoic acid (DHA) showed an intermediate effect on tumor growth, but increased survival significantly (Mashour et al., 2005). None of these drugs has yet been established in a trial setting that includes MPNST patients.

4. Discussion

MPNST still remains a highly aggressive sarcoma subtype with poor outcome despite regular cytotoxic treatment. Novel strategies to target metastatic MPNST and improve its outcomes, both in terms of survival as well as quality of life, are needed. In locally advanced disease, neoadjuvant treatment that can downsize the primary tumor and allow for subsequent surgical resection is also of value.

In this review, we sought to describe new approaches to treat advanced MPNST. Multiple membrane, cytoplasmic, and nuclear actors are potential targets in the therapy of MPNST, of which mTOR inhibition is most commonly investigated *in vivo* and has frequently resulted in high responses on tumor growth (81.3% of cell lines) and survival (100% of cell lines).

In vivo, RTK inhibitors that include VEGFR inhibition have also shown intermediate to high responses. However, monotherapy with an RTK inhibitor has not shown tumor regression clinically in MPNSTs except for a modest prolongation of median progression free survival in case of pazopanib treatment in all types STS (van der Graaf et al., 2012). Apart from two *in vivo* studies using cabozantinib, no other study has yet investigated the effect of MET inhibition, although it is a known contributor to malignancy in MPNSTs. RTK inhibitors targeting both the VEGF pathway as well as other pathways, or combinations with other treatment types might therefore be of interest.

Unfortunately, although MPNSTs are Ras-driven tumors, no drug has yet been found to successfully target Ras. Ras inhibitors are difficult to create due to a lack of well-defined druggable pockets and cavities on its surface (Simanshu et al., 2017). Targeting upregulated downstream targets of Ras is nevertheless possible. Besides upregulation of the PI3K/Akt/mTOR pathway, upregulation of the MAPK pathway in NF1 tumors has been described several times (Endo et al., 2013). In this review we described the potential of mTOR inhibitors, which might be increased by the current development of more specific inhibitors of elements of the mTOR pathway. Although single agent MEK inhibition has not resulted in tumor suppression (Dodd et al., 2013; Jessen et al., 2013; Kendall et al., 2016), combinations with mTOR inhibitors might prove potent in terms of anti-tumorigenic effects, but at the cost of increased toxicity (Lock et al., 2016; Malone et al., 2014). The, translationally controlled tumor protein (TCTP), a downstream effector of both the MAPK and mTOR, can be successfully inhibited leading to cell death in NF1-associated tumors (Kobayashi et al., 2014), and was found to increase mTOR activity when upregulated, indicating a positive feedback loop. *In vivo* studies on MPNST models are, however, still warranted. Other targets of interest identified in this review are PAK1 inhibitors (Demestre et al., 2009; Hirokawa et al., 2006; Semenova et al., 2017a,b), as well as PI3K inhibitors. ERK inhibitors are being developed as well, which may have less toxicity, but their effect on MPNST cells is still unknown (Nissan et al., 2013).

While checkpoint inhibitors are gaining interest in other types of tumors, they have yet to be extensively studied in STS. Two ongoing trials will hopefully elucidate the role of these types of drugs in MPNST (NCT02691026, NCT02834013). Oncolytic viruses are showing efficacy without severe toxicity in various cancers including MPNSTs (Chiocca and Rabkin, 2014; Lichty et al., 2014). Moreover, as demonstrated for other tumors, an additional pathway inhibitor may give a synergistic effect when combined with oncolytic viruses (Currier et al., 2017). Overall, while therapies with oncolytic viruses appear promising in MPNST, more *in vivo* studies are needed to better understand their role as well at the role for any treatment combinations.

The lack of progress in the treatment of MPNST is multi-factorial. First, adequate preclinical models representing both NF1-associated MPNSTs as well as sporadic MPNSTs are lacking. The causal mechanisms behind NF1-associated MPNST may differ from those in sporadic MPNST, resulting in different sensitivity for treatment. This is supported by the fact that in conventional chemotherapy, NF1 patients are known to have a lower response rate (Carli et al., 2005; Ferrari et al., 2011; Higham et al., 2017). However, only few *in vivo* studies show a difference in response on tumor growth between NF1 and sporadic patient-derived models, while others show no difference. Thus, clinical translation of these differences might be difficult and should ultimately be assessed in clinical trials. Second, the preclinical data have to be robust before performing a clinical trial. For example, Albritton et al. based their trial on evidence found from one *in vitro* study (Li et al.,

2002). It is reasonable to consider *in vitro* studies by themselves as weaker evidence compared to *in vivo* studies, and it is therefore unsurprising that such studies might not effectively translate to the clinical setting (Mak et al., 2014). Third, most studies include all types of STS since it is challenging to perform a trial in a disease as rare as MPNST. In this review, four out of the six identified studies were performed in all types of soft tissue sarcomas, for which preclinical evidence was not necessarily found in MPNSTs specifically. The investigators should however be applauded for their efforts in performing histotype subanalyses, although likely underpowered, as certain histological subtypes might well be more sensitive to a particular drug therapy than others. Finally, as suggested by the present review that is based on *in vivo* evidence, a combination of different drugs is likely to be more potent in MPNST patients compared to monotherapy. However, many of the published trials only investigated single targeted therapy.

Unfortunately, quantitative comparison between different studies investigating different treatments *in vivo* was not fully feasible. To date, no tool has been established that shows high reliability of translating preclinical outcomes into clinical evidence, limiting the ability to make direct comparisons between preclinical studies. Despite the challenges in drawing quantitative comparisons across studies, assessing treatment effect by stratifying outcomes into low, intermediate, and high effect has been successfully done previously (Houghton et al., 2007). Overall, despite these limitations, to our knowledge, the current article represents the largest review to date to pool the available literature on *in vivo* therapies for MPSNT. By assessing various animal models and treatment regimens through a descriptive systematic review, we aimed to facilitate treatment-related decisions in patients with MPNST (Hooijmans et al., 2018). For now, such animal studies serve as the cornerstone to the advancement of therapeutics for MPNST in humans and are therefore necessary to carefully review and assess prior to initiation of human trials (Mak et al., 2014). Identification of multiple potential MPNST drugs in this review underscore fundamental principles that will guide optimization of treatment regimens in the future. For example, novel therapies should focus on improving survival while simultaneously limiting toxicity and maintaining quality of life. The utility of ultimately discovering a systemic treatment specifically targeting MPNSTs may drastically alter the course of the MPNST management, allowing for preoperative tumor reduction and potentially minimizing the need for higher doses of radiation as well as more intensive surgeries.

5. Conclusion

Non-cytotoxic systemic treatments have not yet demonstrated clinical efficacy for MPNST, but most promising are approaches targeting the PI3K/Akt/mTOR and VEGFR pathways, as well as utilization of oncolytic viruses. A combination of therapies will most likely be key to maximizing treatment effects. With several clinical trials now, at least in part, recruiting MPNST patients, new insights into therapeutic options for MPNST will likely result.

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Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.critrevonc.2019.04.007.

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