REVIEW

SMARCB1/INI1-deficient tumors of adulthood [version 1; peer review: 1 approved]

Nathaniel A. Parker ¹, Ammar Al-Obaidi ¹, Jeremy M. Deutsch²

¹University of Kansas School of Medicine, 1010 N Kansas St, Wichita, KS, 67214, USA

²Cancer Center of Kansas, 818 N. Emporia #403, Wichita, KS, 67214, USA

v1 First published: 30 Jun 2020, 9:662
<https://doi.org/10.12688/f1000research.24808.1>
 Latest published: 09 Dec 2020, 9:662
<https://doi.org/10.12688/f1000research.24808.2>

Abstract

The *SMARCB1/INI1* gene was first discovered in the mid-1990's, and since then it has been revealed that loss of function mutations in this gene result in aggressive rhabdoid tumors. Recently, the term "rhabdoid tumor" has become synonymous with decreased *SMARCB1/INI1* expression. When genetic aberrations in the *SMARCB1/INI1* gene occur, the result can cause reduced, complete loss, and mosaic expression. Although *SMARCB1/INI1*-deficient tumors are predominantly sarcomas, this is a diverse group of tumors with mixed phenotypes, which can often make the diagnosis challenging. Prognosis for these aggressive tumors is often poor. Moreover, refractory and relapsing progressive disease is common. As a result, accurate and timely diagnosis is imperative. Despite the *SMARCB1/INI1* gene itself and its implications in tumorigenesis being discovered over two decades ago, there is a paucity of rhabdoid tumor cases reported in the literature that detail *SMARCB1/INI1* expression. Much work remains if we hope to provide additional therapeutic strategies for patients with aggressive *SMARCB1/INI1*-deficient tumors.

Keywords

SMARCB1, INI1, loss of function mutation, rhabdoid, sarcoma

Open Peer Review

Approval Status

	1	2
version 2		
(revision)		
09 Dec 2020		view
version 1		
30 Jun 2020	view	
1. Conor Patrick Malone , Health Service Executive (Ireland), Dublin, Ireland 2. Abdulqadir Nashwan , Hamad Medical Corporation (HMC), Doha, Qatar		
Any reports and responses or comments on the article can be found at the end of the article.		

Corresponding author: Nathaniel A. Parker (neparker1031@gmail.com)

Author roles: Parker NA: Conceptualization, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; Al-Obaidi A: Writing – Review & Editing; Deutsch JM: Supervision

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2020 Parker NA *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Parker NA, Al-Obaidi A and Deutsch JM. *SMARCB1/INI1-deficient tumors of adulthood [version 1; peer review: 1 approved]* F1000Research 2020, 9:662 <https://doi.org/10.12688/f1000research.24808.1>

First published: 30 Jun 2020, 9:662 <https://doi.org/10.12688/f1000research.24808.1>

History of the *SMARCB1/INI1* Gene

SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (*SMARCB1*), also known as integrase interactor 1 (*INI1*), is a crucial component of a chromatin-remodeling protein complex. *SMARCB1/INI1* was first identified in yeast in the late 1980's¹. By 1994, its human homologue was isolated in fibroblast cells^{2,3}. Subsequent molecular investigations showed this nuclear protein complex enhances DNA transcription by interactions with HIV-1 integrase². Nuclear *SMARCB1/INI1* exists ubiquitously in all normal cells, and acts as a tumor suppressor gene⁴. It was revealed in the early 2000's by studies in mice that biallelic knockout of the *SMARCB1/INI1* gene resulted in early lethality⁵. Mice with heterozygous loss before birth, or who had later conditional single-allele knockout after birth, of *SMARCB1/INI1* developed aggressive rhabdoid tumors^{6–8}. Since its discovery, much work has revealed this chromatin-remodeling protein has crucial roles in

multiple signaling pathways that function to suppress tumorigenesis and tumor growth⁹. Although these pathways are highly complex, the development and use of targeted anti-cancer therapies has practically become ubiquitous for nearly all solid tumors. Thus, continued investigations are needed if we hope to provide additional therapeutic strategies for patients with aggressive *SMARCB1/INI1*-deficient tumors⁹.

Interestingly, the genetic signatures of *SMARCB1/INI1*-deficient tumors are far from monotonous. Three distinct patterns of abnormal *SMARCB1/INI1* gene expression have been identified – reduced, complete loss, and mosaic⁹.

Epidemiology, clinical, prognosis

Complete loss of *SMARCB1/INI1* expression has been linked to a number of pediatric and adult sarcomas (Table 1). Malignant rhabdoid tumor (MRT) and epithelioid sarcoma (ES)

Table 1. Epidemiologic, selected clinical, and prognostic data for *SMARCB1/INI1*-deficient tumors. STS, soft tissue sarcomas; MRT, malignant rhabdoid tumor; MPNST, malignant peripheral nerve sheath tumor; NF-1, neurofibromatosis type 1; NF-2; neurofibromatosis type 2, GI, gastrointestinal; NA, data not available.

		Epidemiology, Clinical	Survival
Reduced expression	Synovial sarcoma	5 – 10% of all STS; median age of 40 years; males ^{10,11}	5-year, 36–76% ¹¹
Complete loss	Malignant rhabdoid tumor	Typically < 3 years of age ¹¹ ; typically presents in intraabdominally in adult males ^{10,12}	MRT: 5-year, 15 – 20% ¹³ ; extrarenal rhabdoid tumor: 5-year, 35% ¹⁴
	Atypical teratoid/rhabdoid tumor	Typically < 3 years of age; 10% of CNS tumors in infants ¹²	20 months ^{15,16}
	Epithelioid sarcoma	< 1% of all STS; median age of 27 years, males ¹⁷	5-year, 68% (all ages) ¹⁸
	Renal medullary carcinoma	Third most common kidney cancer among children and young adults; median age of 28 years; males ^{19,20}	Overall survival less than 12 months ¹⁹
	Epithelioid malignant peripheral nerve sheath tumor	< 1% of all STS; < 5% of all MPNSTs; aggressive MPNST variant; unlike MPNST uncommonly associated with NF-1; median age > 40 years ^{21,22}	5-year, 34 – 43% ²²
	Myoepithelial carcinoma	About 70% occur in parotid gland; median age of 55 years ²³	5-year, 71% ²⁴
	Extraskelatal myxoid chondrosarcoma	< 3% of all STS; median age of 50 years; males ²⁵	5-year, 80 – 90% ²⁵
	Chordoma	Median age of 50 – 60 years in adults, males; median age of 10 – 12 years in children, females ^{26,27}	5-year, 70% ²⁸
	Pancreas undifferentiated rhabdoid carcinoma	Heterogeneous group of neoplasms; poorly characterized ²⁹	NA
	Sinonasal basaloid carcinoma	< 5% of all head/neck cancers; 0.5 cases per 100,000 population per year; males ³⁰	Median overall survival 17 months ³¹
	Rhabdoid carcinoma of the gastrointestinal tract	About 0.1% of all gastric cancers; < 50 cases reported in the upper and lower GI tract ^{32,33}	Overall survival six months ³³
Mosaic expression	Schwannomatosis	Third major form of neurofibromatosis; distinct from NF-1 and NF-2; median age of 40 years; 20% familial ³⁴	NA
	Gastrointestinal stromal tumor	5% of all STS, 80% of all mesenchymal GI tract tumors; median age of 60 years ^{35–37}	5-year, 83% ³⁸
	Ossifying fibromyxoid tumor	Only 300 cases reported worldwide; median age of 50 years; males ^{39,40}	NA

both result from biallelic deletions or mutations causing a complete loss of *SMARCB1/INI1* expression⁴¹. Commonly arising before the age of three years old, MRTs are considered one of the most aggressive childhood neoplasms associated with high mortality⁴¹. MRTs have been reported in adults^{42–49}. Based on MRT of adulthood being primarily reported anecdotally, estimated rates of incidence remain unclear. Data concerning the 5-year survival rate for MRT in adults is difficult to determine as well, as various percentages have been reported in literature^{13,14}. However, estimated average survival following MRT diagnosis has been reported to be six months¹⁰.

ES is now categorized into two subgroups: distal and proximal. Conventional or distal-type ES tends to be histologically similar squamous cells. Also, distal-type ES immunohistochemical (IHC) profiles can be diverse. Proximal-type ES is thought to be the more aggressive variant, and has an affinity for the proximal limbs of young adults. Microscopically, sheets of large rhabdoid tumor cells are predominantly observed⁵⁰. Based on more recent clinicopathologic and IHC data, many tumors that were previously diagnosed as a MRT are now classified as proximal ES⁵¹.

In addition to ES, atypical teratoid/rhabdoid tumor, renal medullary carcinoma, and pediatric chordoma are rare sarcomas that result from the complete loss of *SMARCB1/INI1* expression (Table 1). They predominantly occur in pediatric or young adult patients. Collectively, these neoplasms typically develop in the head/neck, CNS, thorax, kidneys, other visceral organs, retroperitoneum, trunk, and extremities^{12,17,19,26,52}. Exceedingly rare *SMARCB1/INI1*-deficient tumors that occur more commonly in adults include synovial sarcomas, epithelioid malignant peripheral nerve sheath tumor, myoepithelial carcinoma, extraskeletal myxoid chondrosarcoma, chordoma, schwannomatosis, gastrointestinal stromal tumors (GIST), and ossifying fibromyxoid tumor (Table 1). On light microscopy, these sarcomatous neoplasms exist on a morphological spectrum. Tissue specimens are often composed of epithelioid or rhabdoid cells⁵³. However, other morphologic patterns have been described⁵⁰. Thus, the diagnosis of *SMARCB1/INI1*-deficient tumors can be difficult based on their polyphenotypic variation⁴. *SMARCB1/INI1* immunostaining can be used to confirm the diagnosis of an epithelioid or rhabdoid sarcoma because loss of *SMARCB1/INI1* expression is rarely observed in other tumor types^{54,55}. Thus, in the absence of this genetic alteration, other malignant soft tissue tumors with epithelioid-like morphologies can be more confidently ruled out, such as melanoma, rhabdomyosarcoma, and undifferentiated carcinoma.

Aside from *SMARCB1/INI1*-deficient tumors sharing an aberration in the same gene, the relationship between these malignancies remains unclear. Following diagnosis in any age or organ, nearly all *SMARCB1/INI1*-deficient malignancies characteristically follow an aggressive clinical pattern and prognosis if often poor (Table 1). Survival rates are often reportedly low, but they may not be accurate given low rates of incidence, and considerations for newer treatments. Also, survival can be highly

dependent on surgical intervention and completeness of tumor resection, especially for chordomas. GIST are the most common sarcomas of the gastrointestinal (GI) tract. They commonly develop in the sixth decade of life and have no gender predominance³⁵. Following the diagnosis of a GIST, survival rates are highly variable and depend on specific biologic characteristics of the tumor, the type of treatment, and the risk of post-treatment recurrence³⁶.

Challenges in retrospective data collection for adult cases of *SMARCB1/INI1*-deficient tumors

Recently, the term “rhabdoid tumor” has become synonymous with tumors that harbor loss of function mutations in the *SMARCB1/INI1* gene⁵⁶. We reviewed the literature and found a paucity of cases reporting *SMARCB1/INI1* genetic aberrations in adult patients with sarcomas. A total of 450 cases of rare sarcomas were found to be described in single case reports, case series, or systematic reviews published between the years 2000 – 2020 (Table 2)^{57–92}. This number is likely far lower than the actual accounts of reported sarcoma cases in the literature. However, reports were excluded if it was apparent the case did not meet our inclusion criteria based on the publicly-available title or abstract information. Despite the *SMARCB1/INI1* gene being discovered in the mid-1990’s, the majority of previous reports were excluded for not mentioning the tumor’s *SMARCB1/INI1*-deficiency status. Also, tumor occurrence in the pediatric patient population accounted for multiple exclusions.

We located 25 cases of adult *SMARCB1/INI1*-deficient sarcomas that were described in 18 reports (Table 3)^{42,50,93–108}. Median age at the time of diagnosis was 36 years old. A male predominance was mildly observed (14 cases, 56%), which is consistent with other larger reviews. Presentation in the head and neck (e.g. brain, eye, nose, and scalp) occurred more frequently (6 cases, 24%). No descriptive data analysis was performed to determine if our observations were significant. The majority of reports were originally described as proximal epithelioid sarcoma, but overall these remained a morphologically diverse group of cases that also included rhabdoid and mixed phenotypes.

Treatment

Prior to, and still after, the discovery that *SMARCB1/INI1*-deficient tumors contribute to the large majority of soft tissue sarcomas, systemic cytotoxic agents have been used to treat this diverse group of neoplasms. Doxorubicin and ifosfamide have remained the mainstay of first-line treatment for advanced disease for the last few decades. Currently, the most widely used regimen for soft tissue sarcomas is termed AIM, which includes doxorubicin plus ifosfamide and mesna^{109–111}. Therapies such as these, and other cytotoxic agents, exhibit intermediate to improved anti-cancer activity, and prolong survival in metastatic soft tissue sarcoma (Table 4). However, refractory or progressive disease can occur. With the hopes of improving outcomes in patients who develop aggressive sarcomas, multiple new therapies are being introduced. Olaratumab, a monoclonal antibody that targets platelet-derived growth factor alpha and beta (PDGFRA/B), has been approved for first-line therapy in

Table 2. Excluded rare sarcomas in adults reported in single case reports, case series, or systematic reviews, 2000–2020. Exclusion criteria was as follows: 1.) individual patient age could not be confirmed; 2.) pediatric study population (less than 18 years of age); 3.) absence of documentation noting the loss of *SMARCB1/INI1* expression by immunohistochemistry or genetic studies; 4.) intact *SMARCB1/INI1* expression by immunohistochemistry or genetic studies; and 5.) non-sarcomatous histologic tumor type. PMID, PubMed Central © unique article identifier; GU, genitourinary; PNS, peripheral nervous system; GI, gastrointestinal.

Article	PMID	Cases, no.	Tumor site	Exclusion reason	Article	PMID	Cases, no.	Tumor site	Exclusion reason
Zhang <i>et al.</i> , 2019 ⁵⁷	31933781	1	scalp	3	Weisskopf <i>et al.</i> , 2006 ⁷⁵	16474944	1	spine	2,3
Kubota <i>et al.</i> , 2019 ⁵⁸	31034722	1	GU	2	Onol <i>et al.</i> , 2006 ⁷⁶	16343734	1	GU	3
Kolin <i>et al.</i> , 2018 ⁵⁹	29700418	5	GU	4	Zevallos-G. <i>et al.</i> , 2005 ⁷⁷	16082246	2	perineum	3
Kim <i>et al.</i> , 2018 ⁶⁰	30235775	1	brain	3	Masunaga <i>et al.</i> , 2004 ⁷⁸	15260853	1	lung	3
Strehl <i>et al.</i> , 2015 ⁶¹	25920939	25	GU	3	Chang <i>et al.</i> , 2004 ⁷⁹	14713833	1	GI	2
Santos <i>et al.</i> , 2013 ⁶²	23793215	1	pelvis	3	Altundag <i>et al.</i> , 2004 ⁸⁰	15579921	1	GU	3
Patrizi <i>et al.</i> , 2013 ⁶³	23886403	1	GU	3	Lee <i>et al.</i> , 2004 ⁸¹	14675288	1	pelvis	3
Zhao <i>et al.</i> , 2013 ⁴⁹	23761028	1	renal	3	Peng <i>et al.</i> , 2003 ⁴⁴	12946214	1	renal	3
Tocco <i>et al.</i> , 2012 ⁶⁴	23359842	1	scalp	3	Hanna <i>et al.</i> , 2002 ⁸²	12107573	8	multiple	3
Rizzo <i>et al.</i> , 2012 ⁶⁵	22614000	12	PNS	2	Etienne-M. <i>et al.</i> , 2002 ⁸³	12445750	12	multiple	3,5
Kuge <i>et al.</i> , 2012 ⁶⁶	22218708	1	brain	2	Moore <i>et al.</i> , 2002 ⁸⁴	11925150	1	GU	3
Hagström <i>et al.</i> , 2011 ⁶⁷	21420628	1	oral	3	Haidopoulos <i>et al.</i> , 2002 ⁸⁵	12440823	1	GU	3
Narendra <i>et al.</i> , 2010 ⁶⁸	20479553	1	GU	3	Tzilinis <i>et al.</i> , 2002 ⁸⁶	16093195	1	GU	3
Tholpady <i>et al.</i> , 2010 ⁶⁹	20881848	1	GU	2	Amrikachi <i>et al.</i> , 2002 ⁸⁷	12478486	4	GI	3
Chbani <i>et al.</i> , 2009 ⁵⁵	19141382	106	multiple	1	Hasegawa <i>et al.</i> , 2001 ⁸⁸	11454997	20	multiple	3
Hornick <i>et al.</i> , 2009 ⁷⁰	19033866	127	multiple	1	Kasamatsu <i>et al.</i> , 2001 ⁸⁹	11520372	1	GU	3
Kim <i>et al.</i> , 2008 ⁷¹	19471567	1	GU	3	Knapik <i>et al.</i> , 2001 ⁹⁰	11521235	1	GU	4
Rekhi <i>et al.</i> , 2008 ⁷²	18607629	40	multiple	3	Biegai <i>et al.</i> , 2000 ⁹¹	10738300	1	brain	2
Argenta <i>et al.</i> , 2007 ⁷³	17692365	1	GU	3	Spillane <i>et al.</i> , 2000 ⁹²	10791853	37	multiple	3
Bourdeaut <i>et al.</i> , 2007 ⁷⁴	17152049	26	multiple	2					

combination with doxorubicin due to improved progression and overall survival in sarcoma patients¹¹². The use of tyrosine kinase-inhibitors (TKIs) has transformed the treatment of advanced GIST. Imatinib, a TKI, as monotherapy is now approved for upfront treatment of metastatic GIST due to improved side effect profiles and outcomes in these patients^{113–115}. Given its mechanism of action, imatinib is also approved for first-line treatment of the fibrosarcomatous variant of dermatofibrosarcoma protuberans^{116,117}.

Additional TKIs have recently been introduced, with clinical trial data showing promise for their use in sarcomas. Sunitinib and regorafenib significantly improve overall survival in imatinib-resistant GIST patients¹¹⁸. Pazopanib, a TKI that targets angiogenesis by inhibiting vascular endothelial growth factor receptor, PDGFRA/B, and KIT, has been shown to improve progression free survival in certain histologic types of sarcoma. This led to its approval for advanced, refractory non-lipomatous sarcoma^{119,120}. Alveolar sarcomas appear to respond well to

Table 3. Included rare sarcomas reported in single case reports, case series, or systematic reviews, 2000–2020.

Inclusion criteria was as follows: ability to confirm an individual case patient was greater than 18 years of age; documentation of a loss of *SMARCB1/INI1* expression by immunohistochemistry or genetic studies; and confirmed sarcomatous histologic tumor type. “-” denotes complete, reduced, or mosaic loss of *SMARCB1/INI1* expression (exp.). M, male; F, female.

Article	PMID	Cases, no.	Age, Sex	Tumor site	SMARCB1/ INI1 exp.	Sarcoma morphology
Parker <i>et al.</i> , 2020 ⁴²	32467817	1	56 M	inguinal	-	epithelioid, rhabdoid
Ahmad <i>et al.</i> , 2019 ⁹³	31737506	1	27 M	pleura	-	epithelioid
Bodi <i>et al.</i> , 2018 ⁹⁴	29541486	1	22 F	brain	-	epithelioid, spindle-shaped
Gurwale <i>et al.</i> , 2017 ⁹⁵	-	1	18 F	scalp	-	epithelioid
Saha D <i>et al.</i> , 2016 ⁹⁶	27045049	1	41 M	lung	-	epithelioid
Rego <i>et al.</i> , 2015 ⁹⁷	25737787	1	34 F	vulva	-	epithelioid, spindle-shaped
Wetzel <i>et al.</i> , 2014 ⁹⁸	24997629	1	51 F	oral	-	rhabdoid
Agaimy <i>et al.</i> , 2014 ⁹⁹	24503755	1	66 M	stomach	-	rhabdoid
Madsen <i>et al.</i> , 2013 ¹⁰⁰	24457248	1	45 M	pleura	-	epithelioid
Frank <i>et al.</i> , 2013 ¹⁰¹	24308011	1	43 M	eye	-	epithelioid, spindle-shaped
		2	71 F	nasal	-	epithelioid
Kim <i>et al.</i> 2012 ¹⁰²	21724432	1	41 F	vulva	-	epithelioid
Mannan <i>et al.</i> , 2010 ¹⁰³	19757197	1	47 M	inguinal	-	epithelioid
Takei <i>et al.</i> , 2010 ¹⁰⁴	19911885	1	33 F	brain	-	rhabdoid
		2	79 M	cecum	-	rhabdoid
Raoux <i>et al.</i> , 2009 ¹⁰⁵	19342946	1	31 F	bone	-	epithelioid, spindle-shaped
Robbens <i>et al.</i> , 2006 ¹⁰⁶	16602014	1	19 M	vertebra	-	epithelioid
Sigauke <i>et al.</i> , 2006 ¹⁰⁷	16528370	1	26 M	wrist	-	epithelioid
		2	26 M	lymph	-	epithelioid
Perry <i>et al.</i> , 2005 ¹⁰⁸	15761491	1	29 M	soft tissue	-	spindle-shaped
Modena <i>et al.</i> , 2005 ⁵⁰	15899790	1	31 F	thigh	-	epithelioid
		2	47 F	perineum	-	rhabdoid
		3	30 M	spine	-	epithelioid
		4	36 M	spine	-	epithelioid, spindle-shaped
		5	66 F	inguinal	-	epithelioid, rhabdoid

anti-angiogenic sorafenib and cediranib^{121,122}. In phase II studies tivozanib, which mechanism of action mimics pazopanib, exhibits promising anti-cancer activity in metastatic or nonresectable soft tissue sarcomas¹²³.

Recently, much work studying the complex mechanisms involved in sarcoma tumorigenesis has revealed the potential for numerous new drug targets. Targeting mTOR by serine/threonine kinase inhibition has been widely studied. However, thus far either only equivocal or minor benefits have been shown with the administration of these agents¹²⁴. In contrast, phase II trial data is reassuring for the future use of palbociclib, a

cyclin-dependent kinase 4 and 6 inhibitor approved in breast cancer, for liposarcoma^{125,126}.

Preliminary data from pre-clinical and phase I/II trials is encouraging for small molecule inhibitors, such as with MDM2-antagonists, histone deacetylase inhibitors, and histone methylation inhibitors¹²⁴. A possible breakthrough in small molecular inhibition is represented by the recent discovery of histone-lysine N-methyltransferase EZH2 upregulation in SMARCB1/INI1-deficient tumors¹²⁷. Given the defining characteristic of SMARCB1/INI1 deficiency in the nearly all soft tissue sarcomas, tazemetostat has emerged as a highly intriguing compound for its direct

Table 4. Approved first-line treatments for sarcomas. ORR, overall response rate; PFS, progression free survival; OS, overall survival; STS, soft tissue sarcoma; GIST, gastrointestinal stromal tumor; D, doxorubicine; I, ifosfamide; P, palifosfamide; E, Evofosfamide; T, trabectedin; O, Olaratumab; G, gemcitabine; Doc, docetaxel; NA, data not available.

Tumor	Drugs	Schedules	ORR (%)	PFS (months)	OS (months)	Reference
STS	Doxorubicin	D + I	26	7.4	14.3	128
	Ifosfamide	D + P	28.3	6	15.9	129
	Evofosfamide	D + E	28.4	6.3	18.4	130
	Trabectedin	D + T	17	5.7	13.3	131
	Olaratumab	D + O	18.2	6.6	26.5	112
	Trabectedin	monotherapy	14.8	2.8	NA	132
	Aldoxorubicin	monotherapy	25	5.6	15.8	133
	Amrubicin	monotherapy	13	5.8	26	134
	Gemcitabine	G + Doc	58.6	5.6	14.7	135
	Docetaxel					
	Brostacillin	monotherapy	3.9	1.6	NA	136
GIST	Imatinib	monotherapy	68.1	18	55	113–115
Angiosarcoma	Paclitaxel	monotherapy	NA	4	8	137

inhibition of histone-lysine N-methyltransferase EZH2^{138,139}. Another new agent that hopes to improve outcomes for patients with these rare and aggressive SMARCB1/INI1-deficient rhabdoid sarcomas comes from the proteasome inhibitor drug class. Ixazomib selectively targets proteasomes involved in protein anabolism and cellular apoptosis, whose activity is directly enhanced by the transcription factor MYC in *SMARCB1/INI1*-deficient

states. Currently, ixazomib plus gemcitabine and doxorubicin is being studied in the phase II trial setting for renal medullary carcinoma^{140,141}.

Data availability Underlying data

No data are associated with this article.

References

- Abrams E, Neigeborn L, Carlson M: **Molecular analysis of SNF2 and SNF5, genes required for expression of glucose-repressible genes in *Saccharomyces cerevisiae*.** *Mol Cell Biol.* 1986; **6**(11): 3643–3651.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Kalpana GV, Marmon S, Wang W, *et al.*: **Binding and stimulation of HIV-1 integrase by a human homolog of yeast transcription factor SNF5.** *Science.* 1994; **266**(5193): 2002–2006.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Muchardt C, Sardet C, Bourachot B, *et al.*: **A human protein with homology to *Saccharomyces cerevisiae* SNF5 interacts with the potential helicase hbrm.** *Nucleic Acids Res.* 1995; **23**(7): 1127–1132.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Hollmann TJ, Hornick JL: **INI1-deficient tumors: diagnostic features and molecular genetics.** *Am J Surg Pathol.* 2011; **35**(10): e47–63.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Guidi CJ, Sands AT, Zambrowicz BP, *et al.*: **Disruption of In1 leads to peri-implantation lethality and tumorigenesis in mice.** *Mol Cell Biol.* 2001; **21**(10): 3598–3603.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Roberts CW, Orkin SH: **The SWI/SNF complex--chromatin and cancer.** *Nat Rev Cancer.* 2004; **4**(2): 133–142.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Roberts CW, Galusha SA, McMenamin ME, *et al.*: **Haploinsufficiency of Snf5 (integrator interactor 1) predisposes to malignant rhabdoid tumors in mice.** *Proc Natl Acad Sci U S A.* 2000; **97**(25): 13796–13800.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Roberts CW, Leroux MM, Fleming MD, *et al.*: **Highly penetrant, rapid tumorigenesis through conditional inversion of the tumor suppressor gene Snf5.** *Cancer Cell.* 2002; **2**(5): 415–425.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Kohashi K, Oda Y: **Oncogenic roles of SMARCB1/INI1 and its deficient tumors.** *Cancer Sci.* 2017; **108**(4): 547–552.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Ferrari A, Sultan I, Huang TT, *et al.*: **Soft tissue sarcoma across the age spectrum: a population-based study from the Surveillance Epidemiology and End Results database.** *Pediatr Blood Cancer.* 2011; **57**(6): 943–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Rare Soft Tissue Tumors: Synovial Sarcoma.** National Cancer Institute Web site. 2019.
[Reference Source](#)
- Shonka NA, Armstrong TS, Prabhu SS, *et al.*: **Atypical teratoid/rhabdoid tumors in adults: a case report and treatment-focused review.** *J Clin Med Res.* 2011; **3**(2): 85–92.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Doyle LA: **Malignant rhabdoid tumor: Pathology of Human Disease.** Academic press; 2014.
- Horazdovsky R, Manivel JC, Cheng EY: **Successful salvage and long-term**

- survival after recurrent malignant rhabdoid tumor. *Sarcoma*. 2007; 2007: 53549. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
15. Geller JL, Waltz AL: **Malignant Rhabdoid Tumor**. *Medscape*. 2018. [Reference Source](#)
 16. Chan V, Marro A, Findlay JM, *et al.*: **A Systematic Review of Atypical Teratoid Rhabdoid Tumor in Adults**. *Front Oncol*. 2018; 8: 567. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 17. Needs T, Fillman EP: **Cancer, Epithelioid Sarcoma**. *StatPearls*. Treasure Island (FL): StatPearls. 2020. [PubMed Abstract](#)
 18. Jawad MU, Extein J, Min ES, *et al.*: **Prognostic factors for survival in patients with epithelioid sarcoma: 441 cases from the SEER database**. *Clin Orthop Relat Res*. 2009; 467(11): 2939–48. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 19. Shetty A, Matrana MR: **Renal medullary carcinoma: a case report and brief review of the literature**. *Ochsner J*. 2014; 14(2): 270–5. [PubMed Abstract](#) | [Free Full Text](#)
 20. Msaouel P: **Renal Medullary Carcinoma**. *National organization for Rare Disorders*. 2019. [Reference Source](#)
 21. Du P, Zhu J, Zhang ZD, *et al.*: **Recurrent epithelioid malignant peripheral nerve sheath tumor with neurofibromatosis type 1: A case report and literature review**. *Oncol Lett*. 2019; 18(3): 3072–3080. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 22. Minagawa T, Shioya R, Sato C, *et al.*: **Advanced epithelioid malignant peripheral nerve sheath tumor showing complete response to combined surgery and chemotherapy: a case report**. *Case Rep Oncol Med*. 2011; 2011: 705345. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 23. **Salivary Gland Cancer Treatment: Myoepithelial carcinoma**. National Cancer Institute Web site. 2019. [Reference Source](#)
 24. Su YX, Roberts DB, Hanna EY, *et al.*: **Risk Factors and Prognosis for Myoepithelial Carcinoma of the Major Salivary Glands**. *Ann Surg Oncol*. 2015; 22(11): 3701–7. [PubMed Abstract](#) | [Publisher Full Text](#)
 25. Paoluzzi L, Ghesani M: **Extraskelatal myxoid chondrosarcoma with massive pulmonary metastases**. *Clin Sarcoma Res*. 2018; 8: 20. Published 2018 Dec 5. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 26. Beccaria K, Sainte-Rose C, Zerah M, *et al.*: **Paediatric Chordomas**. *Orphanet J Rare Dis*. 2015; 10: 116. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 27. **Rare Bone Tumors: Chordoma**. National Cancer Institute Web site. 2019. [Reference Source](#)
 28. Smoll NR, Gautschi OP, Radovanovic I, *et al.*: **Incidence and relative survival of chordomas: the standardized mortality ratio and the impact of chordomas on a population**. *Cancer*. 2013; 119(11): 2029–37. [PubMed Abstract](#) | [Publisher Full Text](#)
 29. Agaimy A, Haller F, Frohnaier J, *et al.*: **Pancreatic undifferentiated rhabdoid carcinoma: KRAS alterations and SMARCB1 expression status define two subtypes**. *Mod Pathol*. 2015; 28(2): 248–60. [PubMed Abstract](#) | [Publisher Full Text](#)
 30. Agaimy A, Koch M, Lell M, *et al.*: **SMARCB1(INI1)-deficient sinonasal basaloid carcinoma: a novel member of the expanding family of SMARCB1-deficient neoplasms**. *Am J Surg Pathol*. 2014; 38(9): 1274–81. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 31. Lee JS, Ko IJ, Jun SY, *et al.*: **Basaloid squamous cell carcinoma in nasal cavity**. *Clin Exp Otorhinolaryngol*. 2009; 2(4): 207–10. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 32. Öfkeli Ö, Bulut A, Yüsek YN, *et al.*: **Malignant rhabdoid tumour in the stomach**. *Ulus Cerrahi Derg*. 2013; 31(1): 55–7. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 33. Romera Barba E, Sánchez Pérez A, Duque Pérez C, *et al.*: **Malignant rhabdoid tumor of the colon: a case report**. *Cir Esp*. 2014; 92(9): 638–40. [PubMed Abstract](#) | [Publisher Full Text](#)
 34. Yohay K, Bergner A: **Schwannomatosis**. UpToDate. 2020. [Reference Source](#)
 35. Morgan J, Raut CP, Duensing A, *et al.*: **Epidemiology, classification, clinical presentation, prognostic features, and diagnostic work-up of gastrointestinal stromal tumors (GIST)**. UpToDate. 2019. [Reference Source](#)
 36. DeMatteo RP, Lewis JJ, Leung D, *et al.*: **Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival**. *Ann Surg*. 2000; 231(1): 51–58. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 37. Joensuu H, Fletcher C, Dimitrijevic S, *et al.*: **Management of malignant gastrointestinal stromal tumours**. *Lancet Oncol*. 2002; 3(11): 655–664. [PubMed Abstract](#) | [Publisher Full Text](#)
 38. Howlader N, Noone AM, Krapcho M, *et al.*: (eds). **SEER Cancer Statistics Review, 1975-2016**. National Cancer Institute, Bethesda, MD, based on November 2018 SEER data submission, posted to the SEER website, April. 2019. [Reference Source](#)
 39. Velasco IA, Zhang R, Li T, *et al.*: **Ossifying Fibromyxoid tumor of soft parts in head and neck: case report and literature review**. *Diagn Pathol*. 2018; 13(1): 21. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 40. Bakiratharajan D, Rekhi B: **Ossifying Fibromyxoid Tumor: An Update**. *Arch Pathol Lab Med*. 2016; 140(4): 371–375. [Publisher Full Text](#)
 41. Pawel BR: **SMARCB1-deficient Tumors of Childhood: A Practical Guide**. *Pediatr Dev Pathol*. 2018; 21(1): 6–28. [PubMed Abstract](#) | [Publisher Full Text](#)
 42. Parker NA, Al-Oubaidi A, Lalich D, *et al.*: **SMARCB1/INI1-Deficient Extrarenal Rhabdoid Tumor: A Case Report of a Rare and Aggressive Soft Tissue Sarcoma**. *Cureus*. 2020; 12(5): e8273. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 43. Poddaturi V, Campa-Thompson MM, Zhou XJ, *et al.*: **Malignant rhabdoid tumor of the kidney arising in an adult patient**. *Proc (Bayl Univ Med Cent)*. 2014; 27(3): 239–41. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 44. Peng HQ, Stanek AE, Teichberg S, *et al.*: **Malignant rhabdoid tumor of the kidney in an adult: a case report and review of the literature**. *Arch Pathol Lab Med*. 2003; 127(9): e371–e373. [PubMed Abstract](#) | [Publisher Full Text](#)
 45. Lowe W, Weiss RM, Todd MB, *et al.*: **Malignant rhabdoid tumor of the kidney in an adult**. *J Urol*. 1990; 143(1): 110–112. [PubMed Abstract](#) | [Publisher Full Text](#)
 46. Clausen HV, Horn T, Anagnostaki L, *et al.*: **Malignant rhabdoid tumour of the kidney in an adult: a case report with immunohistochemical and ultrastructural investigation**. *Scand J Urol Nephrol Suppl*. 1994; 157: 123–128. [PubMed Abstract](#)
 47. Ebbinghaus SW, Herrera G, Marshall ME: **Rhabdoid tumor of the kidney in an adult: review of the literature and report of a case responding to interleukin-2**. *Cancer Biother*. 1995; 10(3): 237–241. [PubMed Abstract](#) | [Publisher Full Text](#)
 48. Caballero JM, Collera P, Marti L, *et al.*: **[Malignant Rhabdoid Tumor of the Kidney in the Adult]**. *Actas Urol Esp*. 1996; 20(4): 377–379. [PubMed Abstract](#)
 49. Zhao G, Na R, Yang Y, *et al.*: **Pure malignant rhabdoid tumor of the left kidney in an adult: A case report and review of the literature**. *Oncol Lett*. 2013; 5(5): 1481–1484. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 50. Modena P, Lualdi E, Facchinetti F, *et al.*: **SMARCB1/INI1 tumor suppressor gene is frequently inactivated in epithelioid sarcomas**. *Cancer Res*. 2005; 65(10): 4012–9. [PubMed Abstract](#) | [Publisher Full Text](#)
 51. Margol AS, Judkins AR: **Pathology and diagnosis of SMARCB1-deficient tumors**. *Cancer Genet*. 2014; 207(9): 358–64. [PubMed Abstract](#) | [Publisher Full Text](#)
 52. Ng WK, Toe BP, Lau HY: **Malignant Rhabdoid Tumor of the Mediastinum: A Case Report and Literature Review**. *J Clin Imaging Sci*. 2019; 9: 7. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 53. Gupta RK, Batra VV, Das MC, *et al.*: **Malignant extra-renal rhabdoid tumor with unusual presentation: A report of two cases**. *J Cancer Res Ther*. 2015; 11(4): 963–6. [PubMed Abstract](#) | [Publisher Full Text](#)
 54. Hoot AC, Russo P, Judkins AR, *et al.*: **Immunohistochemical analysis of hSNF5/INI1 distinguishes renal and extra-renal malignant rhabdoid tumors from other pediatric soft tissue tumors**. *Am J Surg Pathol*. 2004; 28(11): 1485–91. [PubMed Abstract](#) | [Publisher Full Text](#)
 55. Chbani L, Guillou L, Terrier P, *et al.*: **Epithelioid sarcoma: a clinicopathologic and immunohistochemical analysis of 106 cases from the French sarcoma group**. *Am J Clin Pathol*. 2009; 131(2): 222–227. [PubMed Abstract](#) | [Publisher Full Text](#)
 56. Kohashi K, Tanaka Y, Kishimoto H, *et al.*: **Reclassification of rhabdoid tumor and pediatric undifferentiated/unclassified sarcoma with complete loss of SMARCB1/INI1 protein expression: three subtypes of rhabdoid tumor according to their histological features**. *Mod Pathol*. 2016; 29(10): 1232–1242. [Publisher Full Text](#)
 57. Zhang XW, Deng YJ, Zhou L, *et al.*: **Epithelioid sarcoma of the scalp: a case report and literature review**. *Int J Clin Exp Pathol*. 2019; 12(10): 3908–3914. [PubMed Abstract](#) | [Free Full Text](#)
 58. Kubota Y, Arakawa Y, Sekiguchi M, *et al.*: **A case of malignant rhabdoid tumor mimicking yolk sac tumor**. *Pediatr Blood Cancer*. 2019; 66(8): e27784. [PubMed Abstract](#) | [Publisher Full Text](#)
 59. Kolin DL, Dong F, Baltay M, *et al.*: **SMARCA4-deficient undifferentiated uterine sarcoma (malignant rhabdoid tumor of the uterus): a clinicopathologic entity distinct from undifferentiated carcinoma**. *Mod Pathol*. 2018; 31(9): 1442–1456. [PubMed Abstract](#) | [Publisher Full Text](#)
 60. Kim YS, Kwak HS, Chung GH, *et al.*: **Epithelioid sarcoma arising from the temporal space: A case report**. *Medicine (Baltimore)*. 2018; 97(38): e12529. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 61. Strehl JD, Wachter DL, Fiedler J, *et al.*: **Pattern of SMARCB1 (INI1) and SMARCA4 (BRG1) in poorly differentiated endometrioid adenocarcinoma of the uterus: analysis of a series with emphasis on a novel SMARCA4-deficient**

- dedifferentiated rhabdoid variant.** *Ann Diagn Pathol.* 2015; **19**(4): 198–202.
[PubMed Abstract](#) | [Publisher Full Text](#)
62. dos Santos LM, Nogueira L, Matsuo CY, *et al.*: **Proximal-type epithelioid sarcoma -- case report.** *An Bras Dermatol.* 2013; **88**(3): 444–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 63. Patrizi L, Corrado G, Saltari M, *et al.*: **Vulvar “proximal-type” epithelioid sarcoma: report of a case and review of the literature.** *Diagn Pathol.* 2013; **8**: 122.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 64. Tocco I, Bassetto F, Vindigni V: **Primary epithelioid sarcoma of the scalp complicated by humoral hypercalcemia of malignancy.** *Eplasty.* 2012; **12**: ic18.
[PubMed Abstract](#) | [Free Full Text](#)
 65. Rizzo D, Fréneaux P, Brisse H, *et al.*: **SMARCB1 deficiency in tumors from the peripheral nervous system: a link between schwannomas and rhabdoid tumors?** *Am J Surg Pathol.* 2012; **29**(3): 964–72.
[PubMed Abstract](#) | [Publisher Full Text](#)
 66. Kuge A, Sato S, Sakurada K, *et al.*: **Atypical teratoid rhabdoid tumor located in the pineal region following prophylactic irradiation for acute lymphoblastic leukemia.** *Brain Tumor Pathol.* 2012; **29**(3): 177–81.
[PubMed Abstract](#) | [Publisher Full Text](#)
 67. Hagström J, Mesimäki K, Apajalahti S, *et al.*: **A rare case of oral epithelioid sarcoma of the gingiva.** *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2011; **111**(4): e25–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 68. Narendra H, Ray S, Rao L, *et al.*: **Malignant extrarenal rhabdoid tumor of the vulva in an adult.** *J Cancer Res Ther.* 2010; **6**(1): 82–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
 69. Tholpady A, Loneragan CL, Wick MR: **Proximal-type epithelioid sarcoma of the vulva: relationship to malignant extrarenal rhabdoid tumor.** *Int J Gynecol Pathol.* 2010; **29**(6): 600–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
 70. Hornick JL, Dal Cin P, Fletcher CDM: **Loss of INI1 expression is characteristic of both conventional and proximal-type epithelioid sarcoma.** *Am J Surg Pathol.* 2009; **33**(4): 542–50.
[PubMed Abstract](#) | [Publisher Full Text](#)
 71. Kim JH, Choi YS, Lee TS: **A case of epithelioid sarcoma arising in the vulva.** *J Gynecol Oncol.* 2008; **19**(3): 202–204.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 72. Rekhi B, Gorad BD, Chinoy RF: **Clinicopathological features with outcomes of a series of conventional and proximal-type epithelioid sarcomas, diagnosed over a period of 10 years at a tertiary cancer hospital in India.** *Virchows Arch.* 2008; **453**(2): 141–153.
[PubMed Abstract](#) | [Publisher Full Text](#)
 73. Argenta PA, Thomas S, Chura JC: **Proximal-type epithelioid sarcoma vs. malignant rhabdoid tumor of the vulva: a case report, review of the literature, and an argument for consolidation.** *Gynecol Oncol.* 2007; **107**(1): 130–135.
[PubMed Abstract](#) | [Publisher Full Text](#)
 74. Bourdeau F, Fréneaux P, Thuille B, *et al.*: **hSNF5/INI1-deficient tumours and rhabdoid tumours are convergent but not fully overlapping entities.** *J Pathol.* 2007; **211**(3): 323–330.
[PubMed Abstract](#) | [Publisher Full Text](#)
 75. Weisskopf M, Munker R, Hermanns-Sachweh B, *et al.*: **Epithelioid sarcoma in the thoracic spine.** *Eur Spine J.* 2006; **15** Suppl 5(Suppl 5): 604–609.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 76. Onol FF, Tanidir Y, Kotiloğlu E, *et al.*: **Proximal type epithelioid sarcoma of the scrotum: a source of diagnostic confusion that needs immediate attention.** *Eur Urol.* 2006; **49**(2): 406–407.
[PubMed Abstract](#) | [Publisher Full Text](#)
 77. Zevallos-Giampietri EA, Barrionuevo C: **Proximal-type epithelioid sarcoma: report of two cases in the perineum: differential diagnosis and review of soft tissue tumors with epithelioid and/or rhabdoid features.** *Appl Immunohistochem Mol Morphol.* 2005; **13**(3): 221–230.
[PubMed Abstract](#) | [Publisher Full Text](#)
 78. Masunaga A, Ikeda K, Suzuki T, *et al.*: **Proximal-type epithelioid sarcoma in a 36-year-old man: closer immunoelectron-microscopic resemblance of the tumor cells to epithelial cells than to mesenchymal cells.** *Pathol Int.* 2004; **54**(8): 616–622.
[PubMed Abstract](#) | [Publisher Full Text](#)
 79. Chang JH, Dikranian AH, Johnston WH, *et al.*: **Malignant extrarenal rhabdoid tumor of the bladder: 9-year survival after chemotherapy and partial cystectomy.** *J Urol.* 2004; **171**(2 Pt 1): 820–821.
[PubMed Abstract](#) | [Publisher Full Text](#)
 80. Altundag K, Dikbas O, Oyan B, *et al.*: **Epithelioid sarcoma of vulva: a case report and review of the literature.** *Med Oncol.* 2004; **21**(4): 367–372.
[PubMed Abstract](#) | [Publisher Full Text](#)
 81. Lee MW, Jee KJ, Ro JY, *et al.*: **Proximal-type epithelioid sarcoma: case report and result of comparative genomic hybridization.** *J Cutan Pathol.* 2004; **31**(1): 67–71.
[PubMed Abstract](#) | [Publisher Full Text](#)
 82. Hanna SL, Kaste S, Jenkins JJ, *et al.*: **Epithelioid sarcoma: clinical, MR imaging and pathologic findings.** *Skeletal Radiol.* 2002; **31**(7): 400–412.
[PubMed Abstract](#) | [Publisher Full Text](#)
 83. Etienne-Mastroianni B, Falchero L, Chababreysse L, *et al.*: **Primary sarcomas of the lung: a clinicopathologic study of 12 cases.** *Lung Cancer.* 2002; **38**(3): 283–289.
[PubMed Abstract](#) | [Publisher Full Text](#)
 84. Moore RG, Steinhoff MM, Granai CO, *et al.*: **Vulvar epithelioid sarcoma in pregnancy.** *Gynecol Oncol.* 2002; **85**(1): 218–222.
[PubMed Abstract](#) | [Publisher Full Text](#)
 85. Haidopoulos D, Elsheikh A, Vlahos G, *et al.*: **Malignant rhabdoid tumor of the clitoris in an elderly patient: report of a case.** *Eur J Gynaecol Oncol.* 2002; **23**(5): 447–449.
[PubMed Abstract](#)
 86. Tzilinis A, Clarke LE, Affuso C, *et al.*: **Successful treatment of malignant rhabdoid tumor of the vulva in an older patient: a case report and review of the literature.** *Curr Surg.* 2002; **59**(6): 570–571.
[PubMed Abstract](#) | [Publisher Full Text](#)
 87. Amrikachi M, Ro JY, Ordóñez NG, *et al.*: **Adenocarcinomas of the gastrointestinal tract with prominent rhabdoid features.** *Ann Diagn Pathol.* 2002; **6**(6): 357–363.
[PubMed Abstract](#) | [Publisher Full Text](#)
 88. Hasegawa T, Matsuno Y, Shimoda T, *et al.*: **Proximal-type epithelioid sarcoma: a clinicopathologic study of 20 cases.** *Mod Pathol.* 2001; **14**(7): 655–663.
[PubMed Abstract](#) | [Publisher Full Text](#)
 89. Kasamatsu T, Hasegawa T, Tsuda H, *et al.*: **Primary epithelioid sarcoma of the vulva.** *Int J Gynecol Cancer.* 2001; **11**(4): 316–320.
[PubMed Abstract](#) | [Publisher Full Text](#)
 90. Knapik J, Yachnis AT, Ripley D, *et al.*: **Aggressive uterine sarcoma with rhabdoid features: diagnosis by peritoneal fluid cytology and absence of INI1 gene mutation.** *Hum Pathol.* 2001; **32**(8): 884–886.
[PubMed Abstract](#) | [Publisher Full Text](#)
 91. Biegel JA, Fogelgren B, Wainwright LM, *et al.*: **Germline INI1 mutation in a patient with a central nervous system atypical teratoid tumor and renal rhabdoid tumor.** *Genes Chromosomes Cancer.* 2000; **28**(1): 31–37.
[PubMed Abstract](#) | [Publisher Full Text](#)
 92. Spillane AJ, Thomas JM, Fisher C: **Epithelioid sarcoma: the clinicopathological complexities of this rare soft tissue sarcoma.** *Ann Surg Oncol.* 2000; **7**(3): 218–225.
[PubMed Abstract](#) | [Publisher Full Text](#)
 93. Ahmad Z, Stanazai Q, Wright S, *et al.*: **Primary pleural epithelioid sarcoma of the proximal type: a diagnostic and therapeutic challenge.** *Transl Lung Cancer Res.* 2019; **8**(5): 700–705.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 94. Bodi I, Giamouriadis A, Sibtain N, *et al.*: **Primary intracerebral INI1-deficient rhabdoid tumor with CD₃₄ immunopositivity in a young adult.** *Surg Neurol Int.* 2018; **9**: 45.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 95. Gurwale S, Gore C, Kaur S, *et al.*: **Primary epithelioid sarcoma of scalp.** *Asian J Oncol.* 2017; **3**: 71–73.
[Publisher Full Text](#)
 96. Saha D, Basu A, Maiti A, *et al.*: **Primary proximal epithelioid sarcoma of the lung successfully treated with pneumonectomy and adjuvant chemotherapy.** *BMJ Case Rep.* 2016; **2016**: bcr2015213966.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 97. Rego JL, Cintra GF, Netto AKJ, *et al.*: **Extremely rare case of vulvar myxoid epithelioid sarcoma.** *Case Rep Obstet Gynecol.* 2015; **2015**: 971217.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 98. Wetzel SL, Kerpel S, Reich RF, *et al.*: **Malignant rhabdoid tumor of the floor of mouth: first reported case in the oral cavity of an adult.** *Head Neck Pathol.* 2015; **9**(2): 269–272.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 99. Agaimy A, Rau TT, Hartmann A, *et al.*: **SMARCB1 (INI1)-negative rhabdoid carcinomas of the gastrointestinal tract: clinicopathologic and molecular study of a highly aggressive variant with literature review.** *Am J Surg Pathol.* 2014; **38**(7): 910–920.
[PubMed Abstract](#) | [Publisher Full Text](#)
 100. Madsen GA, Rasmussen TR, Bærentzen S: **A case of pleural epithelioid sarcoma of proximal type presenting as malignant pleural mesothelioma.** *J Thorac Oncol.* 2013; **8**(10): e89–e90.
[PubMed Abstract](#) | [Publisher Full Text](#)
 101. Frank R, Sadri N, Bhatti T, *et al.*: **Proximal-type Epithelioid Sarcoma of the Head and Neck (HN): A Study with Immunohistochemical and Molecular Analysis of SMARCB1.** *J Clin Exp Oncol.* 2013; **2**(2): 1000106.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 102. Kim HJ, Kim MH, Kwon J, *et al.*: **Proximal-type epithelioid sarcoma of the vulva with INI1 diagnostic utility.** *Ann Diagn Pathol.* 2012; **16**(5): 411–415.
[PubMed Abstract](#) | [Publisher Full Text](#)
 103. Mannan AA, Rifaat AA, Kahvic M, *et al.*: **Proximal-type epithelioid sarcoma in the groin presenting as a diagnostic dilemma.** *Pathol Oncol Res.* 2010; **16**(2): 181–188.
[PubMed Abstract](#) | [Publisher Full Text](#)
 104. Takei H, Adesina AM, Mehta V, *et al.*: **Atypical teratoid/rhabdoid tumor of the pineal region in an adult.** *J Neurosurg.* 2010; **113**(2): 374–379.
[PubMed Abstract](#) | [Publisher Full Text](#)
 105. Raoux D, Péoc'h M, Pedetour F, *et al.*: **Primary epithelioid sarcoma of bone: report of a unique case, with immunohistochemical and fluorescent in situ hybridization confirmation of INI1 deletion.** *Am J Surg Pathol.* 2009; **33**(6): 283–289.

- 954–958.
[PubMed Abstract](#) | [Publisher Full Text](#)
106. Robbins C, Vanwyck R, Wilms G, *et al.*: An extrarenal rhabdoid tumor of the cervical spine with bony involvement. *Skeletal Radiol.* 2007; 36(4): 341–345.
[PubMed Abstract](#) | [Publisher Full Text](#)
 107. Sigauke E, Rakheja D, Maddox DL, *et al.*: Absence of expression of *SMARCB1/INI1* in malignant rhabdoid tumors of the central nervous system, kidneys and soft tissue: an immunohistochemical study with implications for diagnosis. *Mod Pathol.* 2006; 19(5): 717–725.
[PubMed Abstract](#) | [Publisher Full Text](#)
 108. Perry A, Fuller CE, Judkins AR, *et al.*: *INI1* expression is retained in composite rhabdoid tumors, including rhabdoid meningiomas. *Mod Pathol.* 2005; 18(7): 951–958.
[PubMed Abstract](#) | [Publisher Full Text](#)
 109. Edmonson JH, Ryan LM, Blum RH, *et al.*: Randomized comparison of doxorubicin alone versus ifosfamide plus doxorubicin or mitomycin, doxorubicin, and cisplatin against advanced soft tissue sarcomas. *J Clin Oncol.* 1993; 11(7): 1269–75.
[PubMed Abstract](#) | [Publisher Full Text](#)
 110. Cesne A, Judson I, Crowther D, *et al.*: Randomized phase III study comparing conventional-dose doxorubicin plus ifosfamide versus high-dose doxorubicin plus ifosfamide plus recombinant human granulocyte-macrophage colony-stimulating factor in advanced soft tissue sarcomas: A trial of the European Organization for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group. *J Clin Oncol.* 2000; 18(14): 2676–84.
[PubMed Abstract](#) | [Publisher Full Text](#)
 111. Worden FP, Taylor JM, Biermann JS, *et al.*: Randomized phase II evaluation of 6 g/m² of ifosfamide plus doxorubicin and granulocyte colony-stimulating factor (G-CSF) compared with 12 g/m² of ifosfamide plus doxorubicin and G-CSF in the treatment of poor-prognosis soft tissue sarcoma. *J Clin Oncol.* 2005; 23(1): 105–12.
[PubMed Abstract](#) | [Publisher Full Text](#)
 112. Tap WD, Jones RL, Van Tine BA, *et al.*: Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. [published correction appears in *Lancet*. 2016 Jul 30; 388(10043):464]. *Lancet.* 2016; 388(10043): 488–497.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 113. van Oosterom AT, Judson I, Verweij J, *et al.*: Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. *Lancet.* 2001; 358(9291): 1421–1423.
[PubMed Abstract](#) | [Publisher Full Text](#)
 114. Demetri GD, von Mehren M, Blanke CD, *et al.*: Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med.* 2002; 347(7): 472–480.
[PubMed Abstract](#) | [Publisher Full Text](#)
 115. Blanke CD, Rankin C, Demetri GD, *et al.*: Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. *J Clin Oncol.* 2008; 26(4): 626–632.
[PubMed Abstract](#) | [Publisher Full Text](#)
 116. Rutkowski P, Van Glabbeke M, Rankin CJ, *et al.*: Imatinib mesylate in advanced dermatofibrosarcoma protuberans: pooled analysis of two phase II clinical trials. *J Clin Oncol.* 2010; 28(10): 1772–1779.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 117. Stacchiotti S, Pantaleo MA, Negri T, *et al.*: Efficacy and Biological Activity of Imatinib in Metastatic Dermatofibrosarcoma Protuberans (DFSP). *Clin Cancer Res.* 2016; 22(4): 837–846.
[PubMed Abstract](#) | [Publisher Full Text](#)
 118. Call JW, Wang Y, Montoya D, *et al.*: Survival in advanced GIST has improved over time and correlates with increased access to post-imatinib tyrosine kinase inhibitors: results from Life Raft Group Registry. [published correction appears in *Clin Sarcoma Res.* 2019 May 7;9:7]. *Clin Sarcoma Res.* 2019; 9: 4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 119. van der Graaf WTA, Blay JY, Chawla SP, *et al.*: Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet.* 2012; 379(9829): 1879–86.
[PubMed Abstract](#) | [Publisher Full Text](#)
 120. Sleijfer S, Ray-Coquard I, Papai Z, *et al.*: Pazopanib, a multitargeted angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). *J Clin Oncol.* 2009; 27(19): 3126–32.
[PubMed Abstract](#) | [Publisher Full Text](#)
 121. Ray-Coquard I, Italiano A, Bompas E, *et al.*: Sorafenib for Patients With Advanced Angiosarcoma: A Phase II Trial From the French Sarcoma Group (GSF/GETO). *Oncologist.* 2012; 17(2): 260–266.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 122. Kummur S, Allen D, Monks A, *et al.*: Cediranib for Metastatic Alveolar Soft Part Sarcoma. *J Clin Oncol.* 2013; 31(18): 2296–2302.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 123. Agulnik M, Costa RLB, Milhem M, *et al.*: A Phase II Study of Tivozanib in Patients With Metastatic and Nonresectable Soft-Tissue Sarcomas. *Ann Oncol.* 2017; 28(1): 121–127.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 124. Frezza AM, Stacchiotti S, Gronchi A: Systemic Treatment in Advanced Soft Tissue Sarcoma: What Is Standard, What Is New. *BMC Med.* 2017; 15(1): 109.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 125. Binh MB, Sastre-Garau X, Guillou L, *et al.*: MDM2 and CDK4 Immunostainings Are Useful Adjuncts in Diagnosing Well-Differentiated and Dedifferentiated Liposarcoma Subtypes: A Comparative Analysis of 559 Soft Tissue Neoplasms With Genetic Data. *Am J Surg Pathol.* 2005; 29(10): 1340–1347.
[PubMed Abstract](#) | [Publisher Full Text](#)
 126. Dickson MA, Tap WD, Keohan ML, *et al.*: Phase II trial of the CDK4 inhibitor PD0332991 in patients with advanced CDK4-amplified well-differentiated or dedifferentiated liposarcoma. *J Clin Oncol.* 2013; 31(16): 2024–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 127. Wilson BG, Wang X, Shen X, *et al.*: Epigenetic antagonism between polycomb and SWI/SNF complexes during oncogenic transformation. [published correction appears in *Cancer Cell*. 2011 Jan 18; 19(1): 153] *Cancer Cell.* 2010; 18(4): 316–28.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 128. Judson I, Verweij J, Gelderblom H, *et al.*: Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. *Lancet Oncol.* 2014; 15(4): 415–423.
[PubMed Abstract](#) | [Publisher Full Text](#)
 129. Ryan CW, Merimsky O, Agulnik M, *et al.*: PICASSO III: A Phase III, Placebo-Controlled Study of Doxorubicin With or Without Palifosfamide in Patients With Metastatic Soft Tissue Sarcoma. *J Clin Oncol.* 2016; 34(32): 3898–3905.
[PubMed Abstract](#) | [Publisher Full Text](#)
 130. Tap WD, Papai Z, Van Tine BA, *et al.*: Doxorubicin plus evofosfamide versus doxorubicin alone in locally advanced, unresectable or metastatic soft-tissue sarcoma (TH CR-406/SARC021): an international, multicentre, open-label, randomised phase 3 trial. *Lancet Oncol.* 2017; 18(8): 1089–1103, [published correction appears in *Lancet Oncol.* 2018 Feb; 19(2):e78].
[PubMed Abstract](#) | [Publisher Full Text](#)
 131. Martin-Broto J, Pousa AL, de Las Peñas R, *et al.*: Randomized Phase II Study of Trabectedin and Doxorubicin Compared With Doxorubicin Alone as First-Line Treatment in Patients With Advanced Soft Tissue Sarcomas: A Spanish Group for Research on Sarcoma Study. *J Clin Oncol.* 2016; 34(19): 2294–2302.
[PubMed Abstract](#) | [Publisher Full Text](#)
 132. Bui-Nguyen B, Butrynski JE, Penel N, *et al.*: A phase IIb multicentre study comparing the efficacy of trabectedin to doxorubicin in patients with advanced or metastatic untreated soft tissue sarcoma: the TRUSTS trial. *Eur J Cancer.* 2015; 51(10): 1312–1320.
[PubMed Abstract](#) | [Publisher Full Text](#)
 133. Chawla SP, Papai Z, Mukhametshina G, *et al.*: First-Line Aldoxorubicin vs Doxorubicin in Metastatic or Locally Advanced Unresectable Soft-Tissue Sarcoma: A Phase 2b Randomized Clinical Trial. *JAMA Oncol.* 2015; 1(9): 1272–1280.
[PubMed Abstract](#) | [Publisher Full Text](#)
 134. Gupta S, Gouw L, Wright J, *et al.*: Phase II study of amrubicin (SM-5887), a synthetic 9-aminoanthracycline, as first line treatment in patients with metastatic or unresectable soft tissue sarcoma: durable response in myxoid liposarcoma with TLS-CHOP translocation. *Invest New Drugs.* 2016; 34(2): 243–252.
[PubMed Abstract](#) | [Publisher Full Text](#)
 135. Seddon B, Strauss SJ, Whelan J, *et al.*: Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDis): a randomised controlled phase 3 trial. *Lancet Oncol.* 2017; 18(10): 1397–1410.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 136. Gelderblom H, Blay JY, Seddon BM, *et al.*: Brastallicin versus doxorubicin as first-line chemotherapy in patients with advanced or metastatic soft tissue sarcoma: an European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group randomised phase II and pharmacogenetic study. *Eur J Cancer.* 2014; 50(2): 388–96.
[PubMed Abstract](#) | [Publisher Full Text](#)
 137. Penel N, Bui BN, Bay JO, *et al.*: Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. *J Clin Oncol.* 2008; 26(32): 5269–74.
[PubMed Abstract](#) | [Publisher Full Text](#)
 138. Agulnik M, Tannir NM, Pressey JG, *et al.*: A phase II, multicenter study of the EZH2 inhibitor tazemetostat in adult subjects with INI1-negative tumors or relapsed/refractory synovial sarcoma. *J Clin Oncol.* 2016; 34(15_suppl): TPS11071–TPS11071. (suppl; abstr TPS11071).
[Publisher Full Text](#)
 139. Wilson BG, Wang X, Shen X, *et al.*: Epigenetic antagonism between polycomb and SWI/SNF complexes during oncogenic transformation. [published correction appears in *Cancer Cell*. 2011 Jan 18; 19(1): 153] *Cancer Cell.* 2010; 18(4): 316–28.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 140. Msaouel P, Carugo A, Genovese G: Targeting proteostasis and autophagy in SMARCB1-deficient malignancies: where next? *Oncotarget.* 2019; 10(40): 3979–3981.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 141. Msaouel P, Slack-Tidwell R, Genovese G, *et al.*: Phase II trial of ixazomib combined with gemcitabine and doxorubicin in patients with SMARCB1-deficient kidney malignancies. *J Clin Oncol.* 2019; 37(7_suppl): (suppl; abstr TPS678–TPS678).
[Publisher Full Text](#)

Open Peer Review

Current Peer Review Status:

Version 1

Reviewer Report 05 November 2020

<https://doi.org/10.5256/f1000research.27370.r74306>

© 2020 Malone C. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Conor Patrick Malone

Health Service Executive (Ireland), Dublin, Ireland

This article clearly and concisely reviews the role of *SMARCB1/INI1* in rhabdoid tumours, as well as summarising the literature and discussing management options. The structure is good, the language is accessible, and the references are appropriate and comprehensive.

I would suggest a short conclusion to recap the main points and to ensure that there are clear learning outcomes for readers of varying experience levels.

Below are minor grammar/punctuation corrections and suggestions:

"the result can cause reduced, complete loss, and mosaic expression." - this is not clear - I would suggest changing to "the result can cause reduced expression, complete loss of expression, and mosaic expression" ?

There should be no apostrophe in 1980's or 2000's, i.e. 1980s and 2000s are correct.

In Table 1 "typically presents **in** intraabdominally in adult males" the first "**in**" is an error.

"CNS" is used without expansion/explanation of the acronym.

"prognosis if often poor" - should read "**is** often poor".

In Tables 2 and 3 "criteria was as follows" should be "**were** as follows".

"A male predominance was mildly observed (14 cases, 56%), which is consistent with other larger reviews." - this wording is unclear - suggest "Consistent with other larger reviews, there was a slight male predominance (14 cases, 56%)."

"is termed AIM, which includes doxorubicin plus ifosfamide and mesna" - explain this more clearly so that the initialism (AIM) makes sense.

"KIT" is not an acronym/initialism but suggest "KIT proto-oncogene" so that it is clear what it is.

Explain what "mTOR" and "MDM2" and "EZH2" stand for.

"as a highly intriguing" - remove the word "highly".

Is the topic of the review discussed comprehensively in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Orbital rhabdomyosarcoma.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research