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Soft Tissue and Visceral Organ Sarcomas With *BCOR* Alterations

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Summary:

Sarcomas with *BCOR* alteration are a heterogenous group characterized by changes including internal tandem duplications (ITDs) and recurring fusions with *CCNB3*, *ZC3H7B*, and other rare partners. With widespread genomic testing, these alterations are now associated with histologies such as Ewing-like sarcoma (*BCOR*:: *CCNB3*), high-grade endometrial stromal sarcoma (*ZC3H7B*:: *BCOR*), and clear cell sarcoma of kidney (*BCOR*-ITD). *BCOR* altered sarcomas of soft tissues and organs were identified through PubMed using keywords "Sarcoma (AND) BCOR" from 2005 through October 2021. Summary statistics and outcome data were calculated using STATA v12.1. Forty-one publications described 190 patients with *BCOR* altered soft tissue or organ sarcomas. *BCOR*-ITD was most common, followed by *BCOR*::*CCNB3*, *ZC3H7B*:: *BCOR*. *BCOR*-ITD tumors occurred mainly in infants, *BCOR*:: *CCNB3* commonly occurred in adolescent young adults, and *ZC3H7B*::*BCOR* only in adults. The most common site for *BCOR*:: *CCNB3* fused tumors was extremity, *BCOR*-ITD kidney and *ZC3H7B*::*BCOR* uterus. Metastasis was rare in patients with *BCOR*::*CCNB3*. While most underwent resection and chemotherapy, few received radiation. Median follow-up of survivors was 24 months. Five year overall survival for patients with *BCOR*::*CCNB3* fusions was 68% (95% confidence interval [CI]: 46%−83%). Patients with *BCOR*-ITD and *ZC3H7B*::*BCOR* had worse prognoses with 5 years overall survival of 35% (95% CI: 15%−56%) and 41% (95% CI: 11%−71%), respectively, demonstrating need for collaborative efforts identifying optimal treatments to improve outcomes.

Keywords

BCOR; pediatric; soft tissue sarcoma

Sarcomas with *BCOR* alterations are a heterogenous group of tumors characterized by recurring genomic alterations involving the *BCOR* gene, which encodes an epigenetic regulator involved in diverse cellular processes including cell differentiation and histone regulation.[1,2] Recurring alterations in *BCOR* have been described in cancer, including

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internal tandem duplications (ITDs) in exon 15 in *BCOR*, and recurring fusions with *CCNB3*, *ZC3H7B*, and other rare fusion partners. With widespread use of genomic testing, recognition of these alterations is now associated with sarcoma diagnoses including undifferentiated round cell sarcoma (*BCOR::CCNB3*), clear cell sarcoma of the kidney (CCSK) (*BCOR*-ITD) and high-grade endometrial stromal sarcoma (HGESS) (*ZC3H7B::BCOR*).[3–5] Given the relatively recent identification of these recurring alterations and the heterogeneity in associated diagnoses, treatments have largely followed standards for the histologic diagnosis. For example, many *BCOR:: CCNB3* sarcomas have been classified as "Ewing-like" sarcoma and treated using Ewing sarcoma treatment protocols. However, there is lack of consensus regarding the appropriate classification and treatment for these patients.[6] While the majority of *BCOR* sarcomas arising from bone harbor *BCOR::CCNB3* fusions, the genomic landscape of *BCOR* altered sarcomas arising from soft tissues and organs is variable. We sought to summarize the available literature on the presentation, treatments, and survival of *BCOR* altered sarcomas occurring in soft tissues and viscera.

METHODS

A PubMed search was performed using the keywords "Sarcoma (AND) BCOR" from 2005 through October 2021. Publications that described clinical information regarding one or more of tumor location, size, treatment, and outcome were included. Papers that described pathologic findings only without clinical data were excluded. Demographic information including age, sex, tumor location, tumor size, presence of metastatic disease was collected, as well as treatment data related to surgical resection, chemotherapy and radiation therapy and outcome data including relapse, death, follow-up time, and survival time. *BCOR* altered sarcomas involving soft tissues and organs were included in the final analysis, excluding bone and brain primary tumors. Summary statistics and outcome data were calculated using STATA v12.1.

RESULTS

Forty-one publications met criteria for inclusion.[2,4,5,7–46] These publications described 190 patients with *BCOR* altered sarcomas arising from the soft tissues and organs (Table 1). *BCOR*-ITD was the most common alteration (43%), followed by *BCOR::CCNB3* (41%), *ZC3H7B::BCOR* fusion (11%), and other *BCOR* alterations (5%). The 10 patients with rare *BCOR* alterations are described in Table 2.[18,21,22] The median follow-up time for the survivors was 24 months.

BCOR-ITD

Tumors with *BCOR*-ITD were nearly equally split between males (54%) and females (46%) and occurred most frequently in infancy (median age 1.1 y). The most common tumor with *BCOR*-ITD was CCSK (42%), followed by primitive myxoid mesenchymal tumor of infancy (PMMTI) (31%), and undifferentiated round cell sarcoma (21%). While the majority of tumors occurred in young children, ~10% occurred in adults. These tumors included 5 HGESS, 2 undifferentiated sarcoma and 2 with unspecified sarcoma type.[7,18,35,44] Reports of *BCOR*-ITD harboring tumors of the kidney (all CCSK) did not report on treatment, metastatic sites, or outcome. Therefore, the remainder of the description of tumors harboring

BCOR-ITD were from tumors in extrarenal locations. A third of those reporting on metastatic status had metastatic disease at presentation. Sites of metastatic disease included lung, bone and liver. Treatment with chemotherapy (93%) and surgical resection (81%) was most common, with radiation therapy used in only 15%. Chemotherapy regimens were reported for 13 patients. Most received Ifosfamide, vincristine, actinomycin-D, sometimes combined with doxorubicin or etoposide (Table 3). Relapse was common (69%), and 55% of patients died of disease. Prognosis was poor in both localized and metastatic tumors (Fig. 1A). Patients who had surgical resection had improved outcomes compared with those with unresected disease ($P < 0.001$, Fig. 1B). Median follow-up time of the survivors was 33.5 months. Three-year overall survival (OS) was 48% (SE: 0.1, 95% confidence interval [CI]: 27%−67%) and the 5-year OS was 35% (SE: 0.11, 95% CI: 15%−56%) (Fig. 2).

BCOR::CCNB3

Soft tissue tumors harboring *BCOR::CCNB3* fusions were most common in males (82%) in the adolescent age range. These tumors represented a large variety of histologic categories with undifferentiated sarcomas and unspecified sarcomas making up 40% of these tumors. They were most often found in extremities (30%) or the pelvis/sacral region (20%), were more likely to be over 5 cm (86%), and were rarely metastatic (14%). Lung was most common site of metastases, with rare reports of pleural fluid and diaphragm involvement followed by liver and intra-abdominal sites. There were no reports of bone metastasis. Treatment was usually multimodal including surgical resection in 93%, chemotherapy in 75%, and radiation therapy in 61%. Specific chemotherapy regimens were only available for 17 of the 75 patients with *BCOR::CCNB3* fusions (Table 3). Chemotherapy regimens usually included combinations of vincristine, doxorubicin, ifosfamide, and etoposide, combinations often used for Ewing sarcoma treatment. Only 16 reports included information related to relapse, and 37% experienced relapse at time of publication. Of the 48 patients with available outcome information, 19% had died of disease, and 65% were alive with no evidence of disease, with a median follow-up time of survivors of 24 months. The 3-year OS was 78% (SE: 0.08, 95% CI: 56%−89%) and 5-year OS was 68% (SE: 0.09, 95% CI: 46%−83%) (Fig. 2). OS was significantly better for those with localized disease ($P = 0.02$) (Fig. 3). Notably, comparison of survival by *BCOR* alteration in tumors histologically classified as undifferentiated sarcoma demonstrates a significantly better survival for those with *BCOR::CCNB3* fusion compared with *BCOR*-ITD ($P = 0.02$).

ZC3H7B::BCOR

Most tumors with *ZC3H7B::BCOR* fusion were HGESS (81%), therefore these tumors most often occurred in females (90%), with a median age of 49.5 years. Other tumor sites included extremity, pelvis, and thorax. Metastatic disease occurred in 29% of patients, with bone, pancreatic and abdominal metastatic sites reported. Relapse was common (93%), with over 50% having died of disease at the time of presentation. All patients underwent surgical resection of their tumors, and close to 90% had chemotherapy, but only 37.5% received radiation therapy. Chemotherapy regimens were rarely reported (n = 4); 2 patients had hormonal therapies, 1 patient received gemcitabine with docetaxel, and 1 patient received vincristine, doxorubicin, and cyclophosphamide (Table 3). The median follow-up was 37

months. The 3-year OS was 78% (SE: 0.14, 95% CI: 36%−93%) and 5-year OS was 41% (SE: 0.17, 95% CI: 11%−71%) (Fig. 2).

DISCUSSION

BCOR altered sarcomas are a newly identified group of sarcomas with at least 3 distinct recurring alterations including *BCOR*-ITD, *BCOR::CCNB3* and *ZC3H7B::BCOR* fusions in addition a growing list of rarely reported fusion partners. When these tumors arise from soft tissues and visceral organs, their presentation varies greatly by *BCOR* alteration, with *BCOR*-ITD usually occurring in very young children, *BCOR::CCNB3* in teenagers and young adults, and *ZC3H7B::BCOR* occurring exclusively in adults, with the majority being uterine cancers in older women. Patients with *BCOR* altered tumors had overall poor prognosis, with *BCOR::CCNB3* fused tumors having the highest 5-year OS of 68%. Patients with *BCOR*-ITD or *ZC3H7B::BCOR* tumors had high relapse rates and low survival rates, with over 50% of patients in each group dying of their disease.

Importantly, outcomes of patients with *BCOR*-ITD of the kidney, which were all CCSK histologically, were not reported in the reviewed literature.[15,29,42] However, a prior study reporting on genomic findings in CCSK reported that of those with *BCOR*-ITD 14% experienced relapse and 10% died of disease.[47] Furthermore, since close to 90% of CCSK tumors harbor *BCOR*-ITD, results from the National Wilms Tumor Study-5, which enrolled CCSK can be used for comparison of outcome. This study enrolled patients with all stages of CCSK, treated with vincristine, doxorubicin, and cyclophosphamide, etoposide and radiation to the tumor bed. Patients with localized disease had favorable outcomes, with 5-year OS of 90% to 98% for those with stage 1 and 2 disease, and 89% for stage 3 disease. Patients with stage IV disease had poor outcomes with 5-year OS of only 36%.[48] In contrast, patients with extrarenal tumors harboring *BCOR*-ITD have poor survival regardless of localized or metastatic disease, as reported previously and consistent with our review.[33] Of the extrarenal *BCOR*-ITD harboring tumors, PMMTI was the most common histologic group, representing approximately one-third of *BCOR*-ITD tumors in our review, followed by undifferentiated sarcoma, representing 21% of *BCOR*-ITD tumors. PMMTI is a rare entity originally described in children as a fibroblastic-myofibroblastic tumor and later revealed to have similar expression profiling to CCSK, suggesting a common pathogenesis. While it is a distinct entity from URCS, similarities in myxoid components have led some to suggest it these entities may represent a morphologic spectrum.[33,49] This tumor is often chemotherapy unresponsive, and complete surgical resection is thought to offer the best chance for cure.[46,50] While cure in the absence of complete resection is rarely reported, response to doxorubicin containing chemotherapy and radiation therapy, similar to treatment for CCSK, is reported.[30]

Tumors harboring *BCOR::CCNB3* fusions are known to occur both in soft tissue and bone, with a slight predominance of bone sites reported in most studies.[5,8,12,20,39,43] Within the soft tissues, our study demonstrates that this tumor occurs throughout the body including uncommon locations in the kidneys, lungs, and abdomen. However, unlike the *BCOR*-ITD and *ZC3H73::BCOR* tumors, *BCOR::CCNB3* is not reported in uterine tumors.

Treatments for *BCOR* altered sarcomas have not been carefully described in the literature, demonstrating a need for collaborative efforts to determine the optimal treatment strategies for these patients. A recent meta-analysis by Kyriazoglou and Bagos[51] reviewed 57 cases of *BCOR* rearranged bone and soft tissue sarcoma comparing Ewing sarcoma treatment strategies to non-Ewing approaches and found no difference in outcomes. However, within soft tissue and organ sarcomas with *BCOR* alterations, there is a wide variety of clinical presentations including age of presentation, location, and histologic diagnosis, making a uniform treatment approach difficult. It remains unclear whether the histologic diagnosis or the *BCOR* alteration drives outcomes for each subtype.

This study is limited by its reliance on information available in the published literature. While we reviewed a large number of patients with relatively complete demographic data with respect to age, sex, and tumor location, data regarding treatments and outcomes were incomplete. Information related to specific chemotherapy regimens used were available for <20% of reported cases, making it impossible to draw conclusions on efficacy or superiority of particular regimens. Furthermore, our study conclusions are limited by potential publication biases. Given the paucity of comprehensive reporting on patients with BCOR altered sarcomas and the limitations of literature review, it is critically important that patients with rare tumors such as *BCOR* altered sarcomas enroll in multi-institution registries to capture comprehensive treatment and outcome data. Texas Children's Hospital's Rare Tumors Program has developed a registry for pediatric patients age 18 and under in North America with bone, soft tissue, and visceral organ *BCOR* mutated sarcomas (https://www.texaschildrens.org/research/area/cancer-and-blood-disorders/registries/north-american-bcor-mutated-sarcoma-registry). Given the rarity of these diseases, international collaboration between multi-institution registries will likely be required to best inform treatment strategies and lead to improvement in outcomes for these patients.

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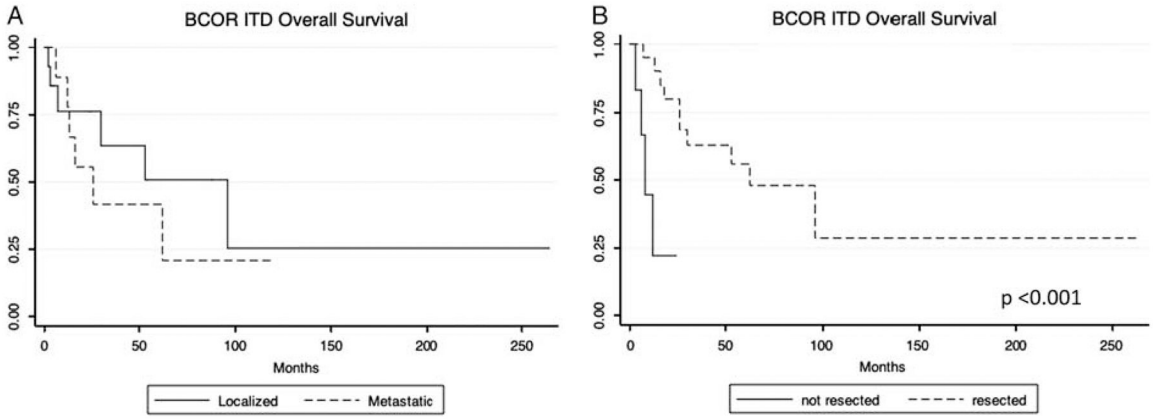

FIGURE 1.

A, Overall survival for patients with *BCOR*-ITD by localized versus metastatic disease. B, Overall survival for patients with *BCOR*-ITD by resection of tumor, $P < 0.001$. ITD indicates internal tandem duplication.

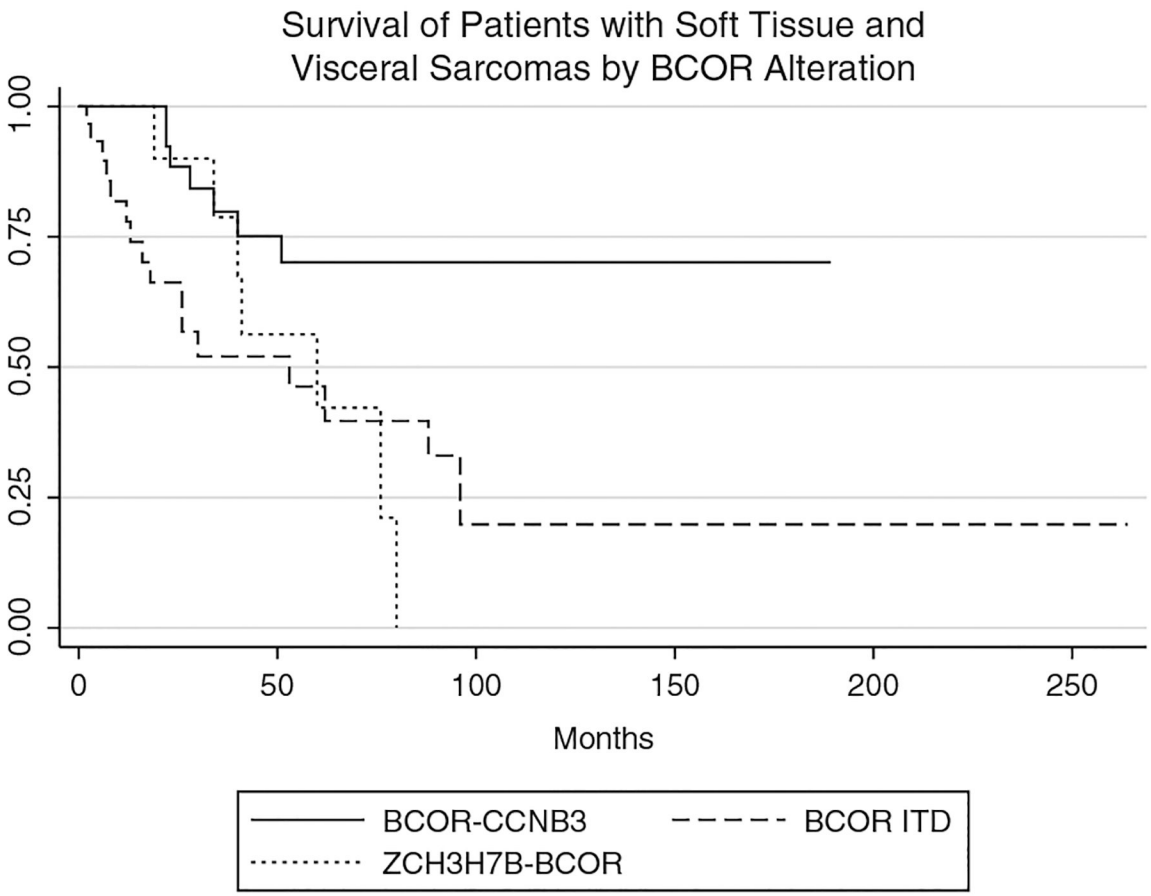

FIGURE 2.
Overall survival by *BCOR* alteration. ITD indicates internal tandem duplication.

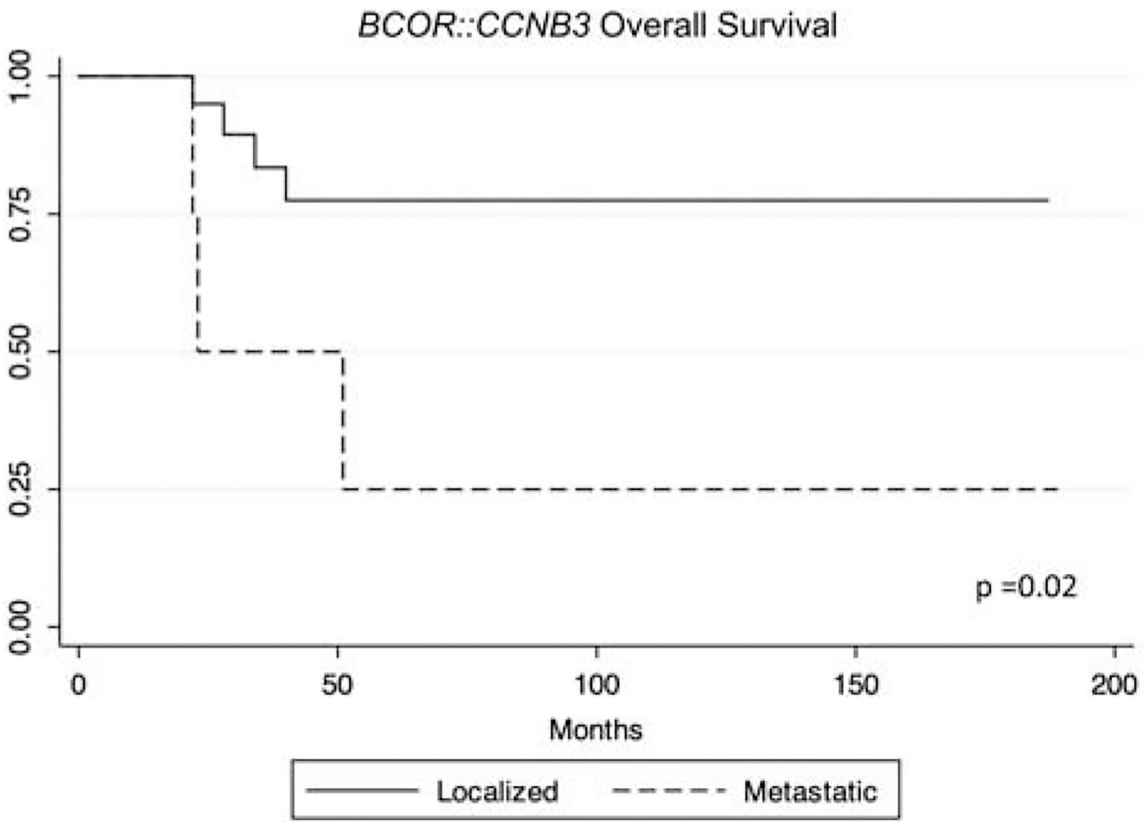

FIGURE 3.
Overall survival for patients with *BCOR::CCNB3* by localized versus metastatic disease.

TABLE 1.

Demographic and Tumor Characteristics

	***BCOR*-ITD, n (%)**	***BCOR*::*CCNB3* n (%)**	***ZC3H7B3*::*BCOR*, n (%)**
N = 190 (includes "other")	N = 82 (43)	N = 77 (41)	N = 21 (11)
Age (y) (median, range)	1.1 (0–71)	14 (1–47)	49.5 (36–71)
Sex	N = 82	N = 77	N = 21
Male	44 (54)	63 (82)	2 (10)
Female	38 (46)	14 (18)	19 (90)
Location	N = 82	N = 77	N = 18
Extremity	4 (5)	23 (30)	2 (9)
Pelvic/sacral	6 (7)	15 (20)	1 (5)
Thorax	8 (10)	9 (12)	1 (5)
Renal	30 (37)	10 (13)	—
Paraspinal	12 (15)	8 (10)	—
Head/neck	7 (9)	6 (8)	—
Lung	2 (2)	3 (4)	—
Abdomen	6 (7)	3 (4)	—
Uterus	7 (9)	—	17 (81)
Original histologic diagnosis	N = 72	N = 40	N = 21
Undifferentiated sarcoma	15 (21)	8 (20)	—
Sarcoma NOS	—	7 (17.5)	—
Synovial sarcoma	—	6 (15)	—
Small round cell sarcoma	—	5 (12.5)	2 (9)
Primary renal sarcoma	—	3 (7.5)	—
CCSK	30 (42)	3 (7.5)	—
Spindle cell sarcoma	—	2 (5)	—
MPNST	—	2 (5)	—
Ewing/PNET	—	2 (5)	—
Epithelioid fibrosarcoma	—	1 (2.5)	—
Fusiform sarcoma	—	1 (2.5)	—
PMMTI	22 (31)		—
HGESS	5 (7)	—	17 (81)
Desmoid tumor	—	—	1 (5)
Malignant ossifying fibromyxoid tumor	—	—	1 (5)
Size	N = 8	N = 37	N = 5
< 5 cm	4 (50)	5 (14)	1 (20)
> 5 cm	4 (40)	32 (86)	4 (80)
Metastatic	N = 32	N = 59	N = 7
No	23 (72)	51 (86)	5 (71)
Yes	9 (28)	8 (14)	2 (29)
Chemotherapy	N = 28	N = 32	N = 9
No	2 (7)	8 (25)	1 (11)

	***BCOR*-ITD, n (%)**	***BCOR*::*CCNB3* n (%)**	***ZC3H7B3*::*BCOR*, n (%)**
Yes	26 (93)	24 (75)	8 (89)
Surgical resection	N = 30	N = 41	N = 11
No	6 (19)	3 (7)	0
Yes	25 (81)	38 (93)	11 (100)
Radiation therapy	N = 26	N = 31	N = 8
No	22 (85)	12 (39)	5 (62.5)
Yes	4 (15)	19 (61)	3 (37.5)
Relapse	N = 26	N = 16	N = 14
No	8 (31)	10 (63)	1 (7)
Yes	18 (69)	6 (37)	13 (93)
Vital status	N = 30	N = 48	N = 13
DOD	17 (55)	9 (19)	7 (54)
DUC	1 (3)	1 (2)	0
AWD	5 (16)	5 (10)	4 (31)
Alive unknown status	0	2 (4)	0
NED	8 (26)	31 (65)	2 (15)

*Multiple sites of metastatic disease each captured (% does not = 100).

AWD indicates alive with disease; CCSK, clear cell sarcoma of the kidney; DOD, died of disease; DUC, died unrelated cause; HGESS, high-grade endometrial stromal sarcoma; MPNST, malignant peripheral nerve sheath tumor; NED, no evidence of disease; PMMTI, primitive myxoid mesenchymal tumor of infancy.

TABLE 2.

Other *BCOR* Alterations

***BCOR* Alteration**	**Age/Sex**	**Location**	**Metastatic**	**Treatment**	**Relapse (Time to Relapse)**	**Vital Status (Follow-up Time Months)**	**Reference**
BCOR::MAML3	44/Male	Abdomen	Yes	CT, RT	Yes (unknown)	DOD (19)	21
EPC1::BCOR	45/Female	Pelvic	Unknown	Unknown	Unknown	Unknown	22
CITTA-BCOR	48/Female	Sinonasal	No	RT	Yes	NED (32)	18
RGAG1::BCOR	54/Male	Extremity	No	Resection, RT	No	NED (84)	41
KMT2D::BCOR	10/Female	Pelvis	No	Resection, CT	Yes (2 y)	Unknown	5
BCOR only	15/Male	Extremity	Yes	Unknown	Unknown	Unknown	21
BCOR only	36/Male	Extremity	Yes	CT	Unknown	Unknown	21
BCOR only	70/Male	Lung	Yes	Resection only	Unknown	Unknown	21
BCOR only	76/Male	Extremity	Unknown	Unknown	Unknown	Unknown	40
BCOR only	10/Male	Extremity	No	CT	No	AWD (9)	43

BCOR only: no gene partner identified on flourescence in situ hybridization break-apart.

AWD indicates alive with disease; CT, computed tomography; DOD, died of disease; NED, no evidence of disease; RT, radiation therapy.

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TABLE 3.

Chemotherapy Regimens

Regimen	*BCOR*::*CCNB3*, N = 17	*BCOR*-ITD, N = 13	*ZC3H7B*::*BCOR*, N = 4
VIDE	2		
VIDE/VAI	3		
VDC/IE	6		
VDC/Carbo/E	3		
VAC	1	2	
DI	1	1 (with dacarbazine)	
I/CDDP	1		
IVADo ± IVE		4	
VAC/IE		1	
M/D/CDDP		1	
IVA		3	
I/Carbo/E		1	
VDC			1
Gemcitabine/Docetaxel			1
Hormone (megesterol, aromatase inhibitor)			2

A indicates actinomycin-D; C, cyclophosphamide; Carbo, carboplatin; CDDP, cisplatin; D, doxorubicin; E, etoposide; I, ifosfamide; M, methotrexate; V, vincristine; VDC, vincristine, doxorubicin, and cyclophosphamide.