Original Article

Systemic Treatments in MDM2 Positive Intimal Sarcoma: A Multicentre Experience With Anthracycline, Gemcitabine, and Pazopanib Within the World Sarcoma Network

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BACKGROUND: Intimal sarcoma (InS) is an exceedingly rare neoplasm with an unfavorable prognosis, for which new potentially active treatments are under development. We report on the activity of anthracycline-based regimens, gemcitabine-based regimens, and pazopanib in patients with InS. **METHODS:** Seventeen sarcoma reference centers in Europe, the United States, and Japan contributed data to this retrospective analysis. Patients with MDM2-positive InS who were treated with anthracycline-based regimens, gemcitabine-based regimens, or pazopanib between October 2001 and January 2018 were selected. Local pathological review was performed to confirm diagnosis. Response was assessed by RECIST1.1. Recurrence-free survival (RFS), progression-free survival (PFS) and overall survival were computed by Kaplan-Meier method. **RESULTS:** Seventy-two patients were included (66 anthracycline-based regimens; 26 gemcitabine-based regimens; 12 pazopanib). In the anthracycline-based group, 24 (36%) patients were treated for localized disease, and 42 (64%) patients were treated for advanced disease. The real-world overall response rate (rwORR) was 38%. For patients with localized disease, the median RFS was 14.6 months. For patients with advanced disease, the median PFS was 7.7 months. No anthracycline-related cardiac toxicity was reported in patients with cardiac InS (n = 26). For gemcitabine and pazopanib, the rwORR was 8%, and the median PFS was 3.2 and 3.7 months, respectively. **CONCLUSION:** This retrospective series shows the activity of anthracycline-based regimens in InS. Of note, anthracyclines were used in patients with cardiac InS with no significant cardiac toxicity. The prognosis in patients with InS remains poor, and new active drugs and treatment strategies are needed. ***Cancer* 2020;126:98-104**. © *2019 American Cancer Society*.

KEYWORDS: anthracycline, gemcitabine, intimal sarcoma, MDM2, pazopanib, systemic therapies.

INTRODUCTION

Intimal sarcoma (InS) is an extremely rare, mesenchymal neoplasm originating from large blood vessels and the heart, and it is one of the most common primary cardiac histologies.[1,2] Regarded as a high-grade tumor, it is marked by MDM2 nuclear overexpression and amplification of the 12q12-15 region (containing CDK4 and MDM2).[3] These molecular features suggest that this pathway might play a relevant role in tumor pathogenesis and that MDM2 inhibition might

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represent a potential treatment strategy in this disease. The outcome for InS patients is poor, with a reported median overall survival (mOS) in the range of 8 to 13 months.[4,5] Retrospective data on the activity of systemic therapies in InS are limited, and no prospective studies have been conducted.[4,6-10] This lack of knowledge is increasingly important today, as new potentially active treatments are emerging.

This academic, multi-institutional retrospective study, which included 17 sarcoma reference centers in Europe, United States, and Japan within the World Sarcoma Network initiative, aims to report on the activity of medical agents available for treatment of soft tissue sarcomas (ie, anthracycline-based regimens, gemcitabine-based regimens, and pazopanib) in adult patients with InS.

PATIENTS AND METHODS

Patient Population

We sought data regarding adult patients with InS who were treated with anthracycline-based regimens, gemcitabine-based regimens, or pazopanib between October 2001 and January 2018. Patients with localized disease treated with curative intent and patients with advanced disease (ie, patients with locally advanced disease not eligible for complete surgical resection or definitive radiation therapy, or metastatic disease) were included. Written informed consent to the treatment was obtained as required by local regulation, and approval by the institutional review board of each participating institution was obtained.

Study Design and Data Collection

Data were extracted from clinical databases and confirmed through a review of patient records (Table 1 reports contributions). Only cases in which diagnosis of MDM2-positive InS was histologically reviewed and confirmed by a sarcoma pathologist at the respective institution were included. MDM2 status was determined by immunohistochemistry and/or molecular testing. Response was assessed by RECIST 1.1[11].

Statistical Analyses

Descriptive statistics and frequency tabulation were used to summarize patient and tumor characteristics. Real-world overall response rate (rwORR) was defined as the proportion of patients who achieved complete response (CR) or partial response (PR) according to RECIST.

Recurrence-free survival (RFS), progression-free survival (PFS), and overall survival (OS) were estimated using the Kaplan-Meier method. Survival distributions were compared using a log-rank test. In patients who were receiving anthracycline-based regimens and were being treated for localized disease with curative intent, RFS was calculated as the interval from primary treatment to the date of the first evidence of recurrence, death for any reason, or the last follow-up. PFS was calculated as the interval from the start of the medical treatment to the date of progressive disease (PD), death for any reason, or the last follow-up. OS was calculated as the interval from the start of treatment to the time of death for any reason or the last follow-up. A 2-sided P value of $<.05$ was considered statistically significant. Statistical analyses were performed with SAS (version 9.4) and R software (version 3.5.2).

TABLE 1. Intimal Sarcoma Cases by Institution

Institution	No. of Cases
IRCCS Fondazione Istituto Nazionale Tumori, Milano, Italy	12
Gustave Roussy Cancer Campus, Villejuif, France	9
Centre Léon Bérard and Université Claude Bernard Lyon I, Lyon, France	7
Dana-Farber Cancer Institute, Boston, Massachusetts	7
National Cancer Center Hospital, Tokyo, Japan	7
University of Michigan, Ann Arbor, Michigan	5
Maria Sklodowska-Curie Institute-Oncology Center, Warsaw, Poland	4
Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York	4
Università Campus Bio-Medico di Roma, Roma, Italy	3
La Timone University Hospital, Aix-Marseille Université, Marseille, France	3
The University of Texas MD Anderson Cancer Center, Houston, Texas	3
Leiden University Medical Center, Leiden, Netherlands	2
S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy	2
N. N. Blokhin Russian Cancer Research, Moscow, Russian Federation	1
Northwell Cancer Institute and Cold Spring Harbor Laboratory, New York	1
Radboud University Medical Center, Nijmegen, Netherlands	1
Nuovo Ospedale "S. Stefano," Prato, Italy	1
Total	72

RESULTS

Patient Population

Ninety-eight adult patients were identified retrospectively, and 72 were included after histological review (anthracycline group, n = 66; gemcitabine group, n = 26; pazopanib group, n = 12). Twenty-six patients received more than 1 treatment. The median follow-up was 36.3 months. Table 2 summarizes the population characteristics.

TABLE 2. Population Characteristics

	Anthracycline-Based Regimens	Gemcitabine-Based Regimens	Pazopanib
No. of patients[a]	66	26	12
Follow-up, mo, median (IQR)		36.3 (16.6-58.4)	
MDM2 status			
IHC		67 (93)	
FISH/MPS		44 (61)	
Both		39 (54)	
Age, y, median (range)	45 (16-81)	42 (16-75)	51 (34-57)
Sex, n (%)			
Male	31 (47)	12 (46)	7 (58)
Female	35 (53)	14 (54)	5 (42)
Stage at start of treatment, n (%)			
Localized/locally advanced (curative intent)	24 (36)	2 (8)[b]	0 (0)
Locally advanced/metastatic (palliative intent)	42 (64)	24 (92)	12 (100)
Primary tumor site, n (%)			
Pulmonary artery	38 (58)	16 (62)	7(58)
Heart	22 (33)	8 (31)	3 (25)
Left atrium[c]	19 (86)	7 (88)	2 (67)
Other	6 (9)	2 (7)	2 (17)

Abbreviations: FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; IQR, interquartile range; MPS, massive parallel sequencing.
[a]There were 72 unique patients; 26 patients received more than 1 treatment.
[b]One patient was treated with surgery and adjuvant chemotherapy and died of disease; 1 patient was treated with neo-adjuvant chemotherapy and surgery and is currently disease free.
[c]Of 26 cardiac InS, 23 (88%) were in the left atrium; the results are for the overall series (72 unique patients).

TABLE 3. Treatment and Outcome in Patients Treated With Anthracycline-Based Regimens for Localized Disease

	Total	Adjuvant Chemotherapy	Neo-adjuvant Chemotherapy
Chemotherapy, n (%)	24 (100)	16 (67)	8 (33)
Surgery, n (%)	22 (92)	16 (73)	6 (27)
Postoperative radiation therapy, n (%)	5 (23)	—	—
Exclusive radiation therapy, n (%)	2 (8)[a]	—	2 (100)
Alive and disease free >2 y		5	

[a]One patient was treated with proton therapy; 1 patient received 60 Gy (30 fractions) through volumetric modulated arc therapy.

Treatment Response and Outcome

The details regarding treatment response and outcome are provided in Table 3.

Anthracycline-based regimens

Of the 66 patients in the anthracycline group, 50 were evaluable for response. Sixteen patients underwent surgery before chemotherapy and therefore were not evaluable for response (however, they were included in the calculation of RFS). Anthracyclines were used as a first-line treatment in 59 (89%) patients, as a second-line treatment in 6 (9%) patients, and as a further line in 1 (2%) patient. Twenty (30%) patients received anthracyclines as a single agent, 39 (59%) as a combination with ifosfamide, and 7 (11%) as a combination with a different compound. Sixty-four patients (97%) completed the treatment at the time of the analysis: 15 (23%) for progressive disease, 9 (13%) for toxicity, 25 (38%) for having received a maximum cumulative dose, and 17 (26%) for other reasons.

The best RECIST response in the anthracycline group was 2 (4%) CR, 17 (34%) PR, 24 (48%) stable disease (SD), and 7 (14%) PD. The rwORR was 38%.

For patients with localized disease treated with curative intent (n = 24), the median RFS and mOS were 14.6 (interquartile range [IQR], 9.1-35.7) and 50.8 (IQR, 33.8-not evaluable) months, respectively. Five patients were alive and disease free at >2 years: 2 patients had chemotherapy and exclusive radiation therapy; 1 patient had chemotherapy, surgery, and radiation therapy; 2 patients had chemotherapy and surgery.

For patients with advanced disease (n = 42), the median PFS (mPFS) and mOS were 7.7 (IQR, 4.1-16.9) and 21.8 (IQR, 10.3-38) months, respectively. The median PFS in responding patients was 9 months, compared with 5 months in nonresponding patients ($P = .02$). Two patients are alive and disease free at more than 2 years (1 patient who was metastatic to the lung had chemotherapy with CR and exclusive radiation therapy on the

primary tumor; 1 patient who was metastatic to the lung underwent lung metastasectomy, chemotherapy, and exclusive radiation therapy on the primary tumor).

No cardiac toxicity was observed in patients with cardiac InS (n = 26). Figure 1 shows the Kaplan-Meier curves.

Gemcitabine-based regimens

Of the 26 patients in the gemcitabine group, 25 were evaluable for response (1 had surgery before chemotherapy). Gemcitabine-based regimens were used as a first-line treatment in 6 (23%) patients and as a second-line treatment in 20 (77%) patients. Seven (27%) patients received gemcitabine as a single agent, 16 (62%) as a combination with docetaxel, and 3 (11%) as a combination with a different compound. All patients completed treatment at the time of analysis: 20 (77%) for progressive disease, 2 (8%) for toxicity, and 4 (15%) for other reasons.

The best RECIST response in the gemcitabine group was 2 (8%) PR, 7 (28%) SD, and 16 (64%) PD. The rwORR was 8%. For patients with advanced disease (n = 24), the mPFS and mOS were 3.2 (IQR, 2.1-7.1) and 13.1 (IQR, 7.6-16.5) months, respectively.

Pazopanib

All 12 patients in the pazopanib group were evaluable for response. Pazopanib was used as a first-line treatment in 1 (8%) patient, as a second-line treatment in 3 (25%) patients, and as a further line in 8 (67%) patients. All patients completed treatment at the time of analysis: 11 (92%) for PD and 1 (8%) for toxicity.

The best RECIST response in the pazopanib group was 1 (8%) PR, 4 (34%) SD, and 7 (58%) PD. The rwORR was 8%. The mPFS and mOS were 3.7 (IQR, 2.6-4.6) and 12.1 (IQR, 4.1-18.9) months, respectively.

DISCUSSION

This academic, multi-institutional, international retrospective study collected the largest series currently available for adult patients affected by MDM2-positive InS who were treated with systemic therapy. Anthracycline-based regimens showed a degree of activity toward the higher limits observed in soft tissue sarcomas (rwORR, 38%; mPFS, 7.7 months), whereas gemcitabine and pazopanib had a limited antitumor effect (rwORR, 8%; mPFS, 3.2 and 3.7 months, respectively), though they were mainly used in advanced disease and further lines.

InS is extremely rare, mostly diagnosed in adult patients and often arising from critical anatomic sites, thus being an often life-threatening tumor even when localized. In this series, the pulmonary artery was the most common site of the primary tumor (56%), followed by the heart (36%). Notably, 23/26 (88%) cardiac InS originated in the left atrium. A pathology review in sarcoma reference centers led to the exclusion of approximately 25% of cases diagnosed in the community.

The previous data available are confined to case reports and small retrospective series, do not always report MDM2 status, and suggest a poor activity of chemotherapy in InS, with few anecdotal responses observed.[4,6,8] In our series, which included only confirmed MDM2-positive cases, InS showed sensitivity to anthracycline-based regimens, possibly greater than expected in other soft tissue sarcomas and to what has been reported previously by Van Dievel and Penel, who observed no responses over 5 InS patients each.[4,8,12] Given the challenging sites of origin, tumor shrinkage may be crucial both in localized and advanced stages, because it may facilitate local treatment (surgery and/or radiation therapy), control symptoms, and improve quality of life. Unfortunately, mPFS for advanced disease was only 7.7 months. This unfavorable prognosis is consistent with previous findings.[4,8,13] Prognosis was also unsatisfactory in patients with localized disease who were treated with anthracycline-based regimens plus an intended definitive local treatment, with a14.6-month mRFS. However, it is worth noting that around 25% of patients with localized disease are expected to be alive and disease free at >2 years. This suggests a possible role for (neo)adjuvant treatment in InS patients, although this series did not establish a comparison estimate of RFS for patients without chemotherapy, and a randomized study would be exceedingly difficult to accrue for this rare sarcoma subtype.

With a median follow-up of 36 months, no cardiac complications were observed after treatment with anthracyclines in this series. No data are available on long-term toxicity and, due to the retrospective nature of the study, asymptomatic cardiac toxicity could have been missed. However, although expected cardiac risk must be assessed individually, this observation in a significant number of patients may contribute to clinical decision making.

In contrast to angiosarcoma, another sarcoma potentially arising from the heart, a low rwORR (8%) and a limited mPFS (3.2 months) were observed with gemcitabine-based chemotherapy.[14] Similarly, the activity of pazopanib previously suggested by Kollar (2 RECIST PR/2 patients) and Funatsu (1 PR/1 patient) was limited (rwORR, 8%; mPFS, 3.7 months).[6,7] Of note, if

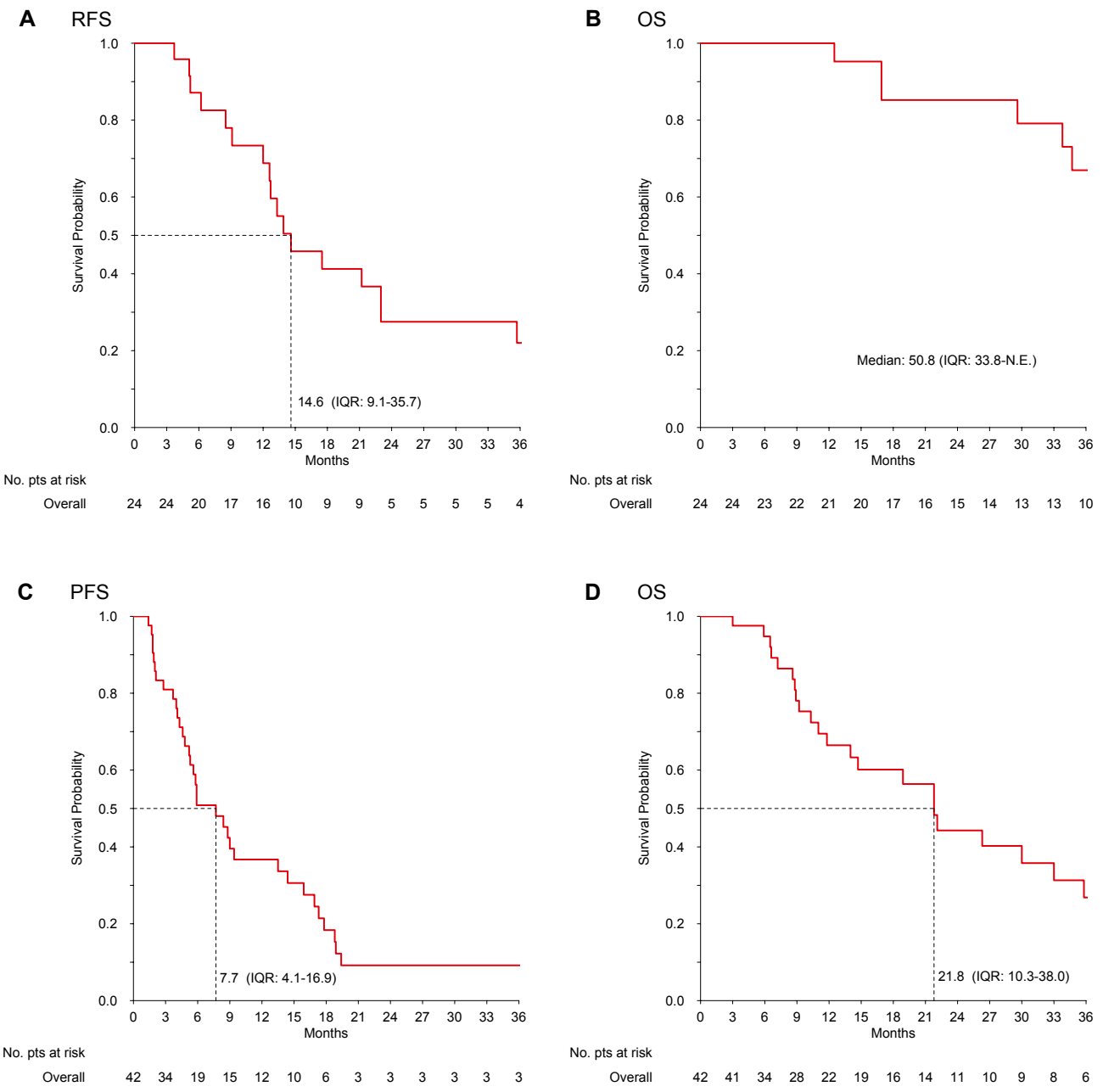

Figure 1. Intimal sarcoma patients treated with anthracycline-based regimens. Kaplan-Meier curves are shown for recurrence-free survival (A) and overall survival (B) in patients treated for localized disease with curative intent (n = 24) and for progression-free survival (C) and overall survival (D) in patients treated for advanced disease with palliative intent (n = 42). Abbreviations: IQR, interquartile range; N.E., not evaluable; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival.

anthracyclines were mostly used as an upfront treatment, gemcitabine and pazopanib were mainly used as a further line of treatment.

In conclusion, our results show that anthracycline-based regimens are a potentially effective medical option in InS. The value of gemcitabine and pazopanib was limited, though these agents could be used as further line therapy or in patients who are unfit to receive anthracyclines. The prognosis of InS patients remains poor, and new medical options are needed both in the localized and in the metastatic stages. MDM2 inhibitors are emerging as a promising venue in InS, requiring prospective studies. This series may be used as a benchmark for such future trials.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Anna Maria Frezza: Study concept and design; acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript; study supervision. **Tarek Assi:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Salvatore Lo Vullo:** Study concept and design; acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript; Statistical analysis; study supervision. **Eytan Ben-Ami:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Armelle Dufresne:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Kan Yonemori:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Emi Noguchi:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Brittany Siontis:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Richard Ferraro:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Pawel Teterycz:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Florence Duffaud:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Vinod Ravi:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Bruno Vincenzi:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Hans Gelderblom:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Maria A. Pantaleo:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Giacomo G. Baldi:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Ingrid Desar:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Alexander Fedenko:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Robert G. Maki:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Robin L. Jones:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Robert S. Benjamin:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Jean Yves Blay:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Akira Kawai:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Mrinal Gounder:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Alessandro Gronchi:** Study concept and design; acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript; study supervision. **Axel Le Cesne:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Olivier Mir:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Anna M. Czarnecka:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Scott Schuetze:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Andrew J. Wagner:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Julien Adam:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Marta Barisella:** Acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Marta Sbaraglia:** Acquisition, analysis, or interpretation of data; drafting of the manuscript;

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