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**Systemic treatments in MDM2 positive intimal sarcoma:  
a multicentre experience with anthracycline, gemcitabine and pazopanib within the  
World Sarcoma Network (WSN).**

**Running title:** Systemic treatments in intimal sarcoma

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### **Author contributions statement**

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*Acquisition, analysis or interpretation of data:* Anna Maria Frezza, Tarek Assi, Salvatore Lo Vullo, Eytan Ben-Amy, Armelle Dufresne, Kan Yonemori, Emi Noguchi, Brittany Siontis, Richard Ferraro; Pawel Teterycz, Florence Duffaud, Vinod Ravi, Bruno Vincenzi, Hans Gelderblom, Maria A. Pantaleo, Giacomo G. Baldi, Ingrid Desar, Alexander Fedenko, Robert G. Maki, Robin Jones, Robert S. Benjamin, Jean Yves Blay, Akira Kawai, Mrinal Gounder, Alessandro Gronchi, Axel Le Cesne, Olivier Mir, Anna M. Czarnecka, Scott Schuetze, Andrew J. Wagner, Julien Adam, Marta Barisella, Marta Sbaraglia, Jason L. Hornick, Alexandra Meurgey, Luigi Mariani, Paolo G. Casali, Katherine Thornton, Silvia Stacchiotti

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### **Precis for use in the Table of Contents**

Anthracycline-based regimens are a potentially effective medical option in intimal sarcoma. Of note, anthracyclines were used in patients with cardiac primary, with no significant cardiac toxicity. The value of gemcitabine and pazopanib was limited (though possibly exploitable as further-line therapy or in patients unfit for anthracyclines).

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**Abstract**  
**Background:** Intimal sarcoma (InS) is an exceedingly rare neoplasm with an unfavourable prognosis, for which new potentially active treatments are under development. This is to report on the activity of anthracycline-based regimens, gemcitabine-based regimens and pazopanib in patients with InS.

**Methods.** Seventeen sarcoma reference centres in Europe, US and Japan contributed data to this retrospective analysis. Patients with MDM2-positive InS 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 (OS) 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, 42 (64%) patients for advanced disease. 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 3.2 and 3.7 months, respectively,

**Conclusions:** This retrospective series shows 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.

**Key words.** Intimal sarcoma, systemic therapies, anthracycline, gemcitabine, pazopanib, MDM2.

## Introduction

Intimal sarcoma (InS) is an extremely rare, mesenchymal neoplasm originating from large blood vessels and from the heart, being one of the most common primary cardiac histologies<sup>1,2</sup>. Regarded as a high-grade tumour, it is marked by MDM2 nuclear overexpression, and amplification of the 12q12-15 region (containing CDK4 and MDM2)<sup>3</sup>. These molecular features suggest that this pathway might play a relevant role in tumour pathogenesis and that MDM2 inhibition might 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 8-13 months<sup>4,5</sup>.

Retrospective data on the activity of systemic therapies in InS are limited and no prospective studies have been conducted<sup>4,6-10</sup>. This lack of knowledge is increasingly important today, as new potentially active treatments are emerging.

This academic, international, collaborative effort, including 17 referral sarcoma centres in the EU, US and Japan, within the *World Sarcoma Network* initiative, aims to report on the activity of medical agents available for treatment of soft tissue sarcomas (STS), i.e. 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, treated with anthracycline-based regimens, gemcitabine-based regimens or pazopanib, between October 2001 and January 2018. Both patients with localized disease treated with curative intent and with advanced disease (locally advanced not eligible for complete surgical resection, or definitive RT, or metastatic) were included. A written informed consent to the treatment was obtained as required by local regulation. Approval by the Institutional Review Board of each participating institution was required.

## **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<sup>11</sup>.

## **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) by RECIST.

Recurrence-free survival (RFS), progression-free survival (PFS) and OS were estimated using the Kaplan-Meier method. Survival distributions were compared using the log-rank test. In patients receiving anthracycline-based regimens and 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 two-sided  $p < 0.05$  was considered statistically significant. Statistical analyses were carried out with SAS (version 9.4) and R software (version 3.5.2).

## **Results**

### *Patient population*

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

### *Treatment response and outcome*

Table 3 reports treatment details.

- Anthracycline-based regimens

Sixty-six patients were included, 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%) and as a further line in 1 (2%). Twenty (30%) patients received anthracyclines as 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.

Best RECIST response 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 (IQR: 9.1-35.7) and 50.8 (IQR: 33.8-N.E.) 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. Table 3 describes treatment details.

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 to 5 months in non-responding patients (P=0.02). Two patients are alive and disease free at more than 2 years (one patient metastatic to the lung had chemotherapy with complete response and exclusive radiation



therapy on the primary; one patient metastatic to the lung underwent lung metastasectomy, chemotherapy and exclusive radiation therapy on the primary).

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

- Gemcitabine-based regimens

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

Best RECIST response with gemcitabine-based regimens was 2 (8%) PR, 7 (28%) SD and 16 (64%) PD. 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

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

Best RECIST response with pazopanib 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 of adult patients affected by MDM2-positive InS treated with systemic therapy. Seventy-two patients (66, anthracycline-group; 26, gemcitabine-group; 12, pazopanib-group) were included. Anthracycline-based regimens showed a degree of activity towards the higher limits observed in STS (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 tumour even when localized. In this series, pulmonary artery was the most common primary site (56%), followed by heart (36%). Notably, 23/26 (88%) cardiac InS originated from the left atrium. Pathology review in sarcoma reference centres led to the exclusion of approximately 25% of the cases diagnosed in the community.

The previous data available are confined to case reports and small retrospective series, not always reporting MDM2 status, and suggest a poor activity of chemotherapy in InS, with few anecdotal responses observed<sup>4,6,8</sup>. In our series, including only confirmed MDM2-positive cases, InS showed sensitivity to anthracycline-based regimens, possibly greater than expected in other STS and to what has been reported previously by Van Dievel and Penel, who observed no responses over 5 InS patients each<sup>4,8,12</sup>. Given InS challenging sites of origin, tumor shrinkage may be crucial both in the localized and advanced stages, as it may facilitate local treatment (surgery and/or radiation therapy), control symptoms and improve patient's quality of life. Unfortunately, mPFS for advanced disease was only 7.7 months. This unfavourable prognosis is consistent with previous findings<sup>4,8,13</sup>.

Prognosis was also unsatisfactory in patients with localized disease, treated with anthracycline-based regimens plus an intended definitive local treatment, with a 14.6-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 following 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, though 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 vascular sarcoma potentially arising from the heart, a low rwORR (8%) and a limited m-PFS (3.2 months) were observed with gemcitabine-based chemotherapy<sup>14</sup>. Similarly, the activity of pazopanib, previously suggested by Kollar (2 RECIST PR/2 patients) and by Funatsu (1 PR /1 patient), was limited (rwORR: 8%, m-

PFS 3.7 months)<sup>6,7</sup>. Of note, if anthracyclines were mostly used upfront, gemcitabine and pazopanib were mainly used as further lines.

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 possibly exploitable as further-line therapy or in patients unfit for 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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**Table 1. Intimal sarcoma cases by institution.**

Institution	Cases (n)
IRCCS Fondazione Istituto Nazionale Tumori, Milano, Italy	12
Gustave Roussy Cancer Campus, Villejuif, France	9
Centre Léon Bérard & 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, USA	5
Maria Sklodowska-Curie Institute-Oncology Center, Warsaw, Poland	4
Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, USA	4
Università Campus Bio-Medico di Roma, Roma, Italy	3
La Timone University Hospital, Aix-Marseille Université (AMU), Marseille, France	3
The University of Texas MD Anderson Cancer Center, Houston, Texas	3
Leiden University Medical Center, Leiden, the 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, USA	1
Radboud University Medical Center, Nijmegen, the Netherlands	1
Nuovo Ospedale "S.Stefano", Prato, Italy	1
	TOT= 72

**Table 2. Population characteristics.**

	<b>Anthracycline-based regimens</b>	<b>Gemcitabine-based regimens</b>	<b>Pazopanib</b>
<b>Number of patients</b>	66*	26*	12*
<b>Median follow up (IQR)</b>	36.3 (16.6 – 58.4) months		
<b>MDM2 status</b>			
• IHC	67 (93%)		
• FISH/MPS	44 (61%)		

• <b>Both</b>	39 (54%)		
<b>Median age (range)</b>	45 (16-81)	42 (16-75)	51 (34-57)
<b>Gender (%)</b>			
• <b>M</b>	31 (47%)	12 (46%)	7 (58%)
• <b>F</b>	35 (53%)	14 (54%)	5 (42%)
<b>Stage at the time of treatment start (%)</b>			
• <b>Localized/locally advanced (curative intent)</b>	24 (36%)	2 (8%)**	0
• <b>Locally advanced/metastatic (palliative intent)</b>	42 (64%)	24 (92%)	12 (100%)
<b>Primary site</b>			
• <b>Pulmonary artery</b>	38 (58%)	16 (62%)	7(58%)
• <b>Heart</b>	22 (33%)	8 (31%)	3 (25%)
<b>Left atrium</b>	19 (86%) ***	7 (88%) ***	2 (67%) ***
• <b>Other sites</b>	6 (9%)	2 (7%)	2 (17%)

IQR: interquartile range; IHC: immunohistochemistry; FISH: fluorescence in situ hybridization; MPS: massive parallel sequencing.

\* 72 unique patients; 26 patients received more than one treatment

\*\* 1 patient was treated with surgery and adjuvant chemotherapy and died of disease; 1 patient was treated with neo-adjuvant chemotherapy and surgery and he it is currently disease free.

\*\*\* 26 cardiac InS – 23 (88%) left atrium; results are referred to the overall series (72 unique patients)

**Table 3. Treatment and outcome in patients treated with anthracycline-based regimens for localized disease.**

	All	Adjuvant CT	Neo-adjuvant CT
CT (%)	24	16 (67%)	8 (33%)
Surgery (%)	22 (92%)	16 (73%)	6 (27%)
• <i>Post-operative RT (%)</i>	5 (23%)		
Exclusive RT (%)	2 (8%)*	-	2 (100%)
Alive and disease free > 2 years	5		

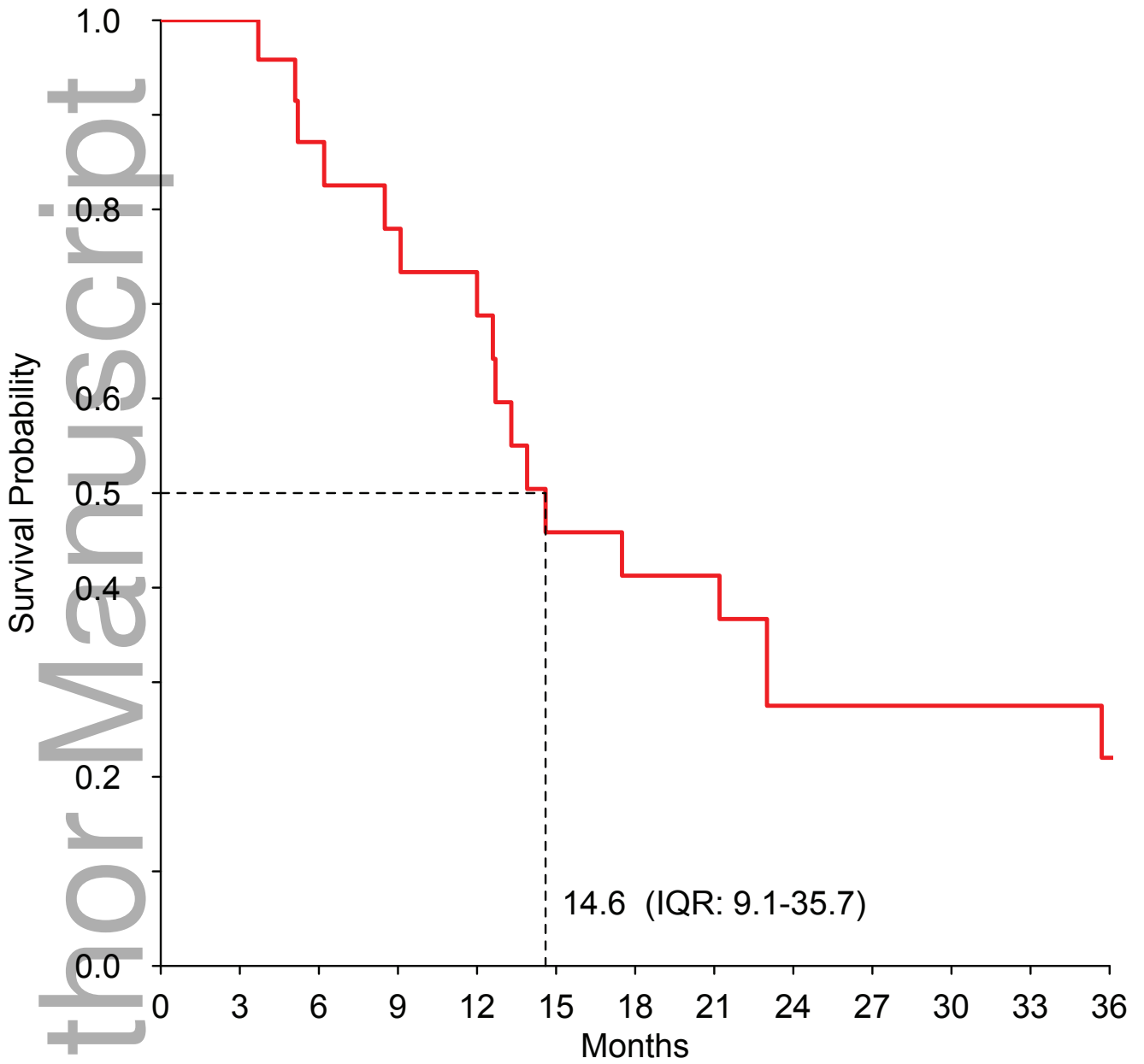
CT: chemotherapy; RT: radiation therapy

\* 1 patient was treated with proton therapy; 1 patient received 60 Gy (30 fractions) through volumetric modulated arc therapy.

**Figure 1. Intimal sarcoma patients treated with anthracycline-based regimens.** Kaplan-Meier curves for recurrence-free survival (A) and overall survival (B) in patients treated for localized disease with curative intent (n=24); progression-free survival (C) and overall survival (D) in patients treated for advanced disease with palliative intent (n=42).

A

RFS



No. pts at risk

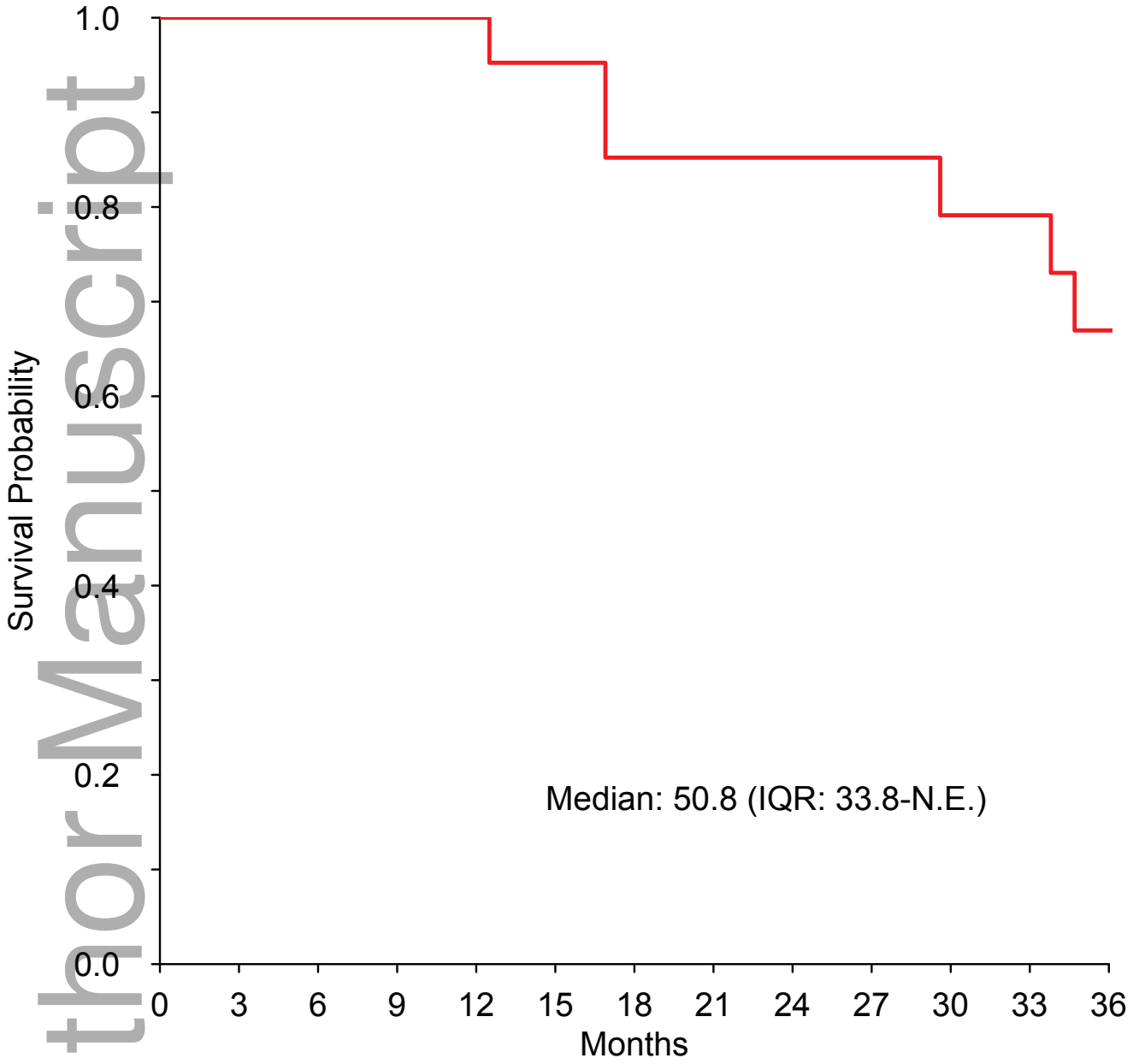
Overall 24 24 20 17 16 10 9 9 5 5 5 5 4

cncr\_32508\_f1a.eps



B

OS



No. pts at risk

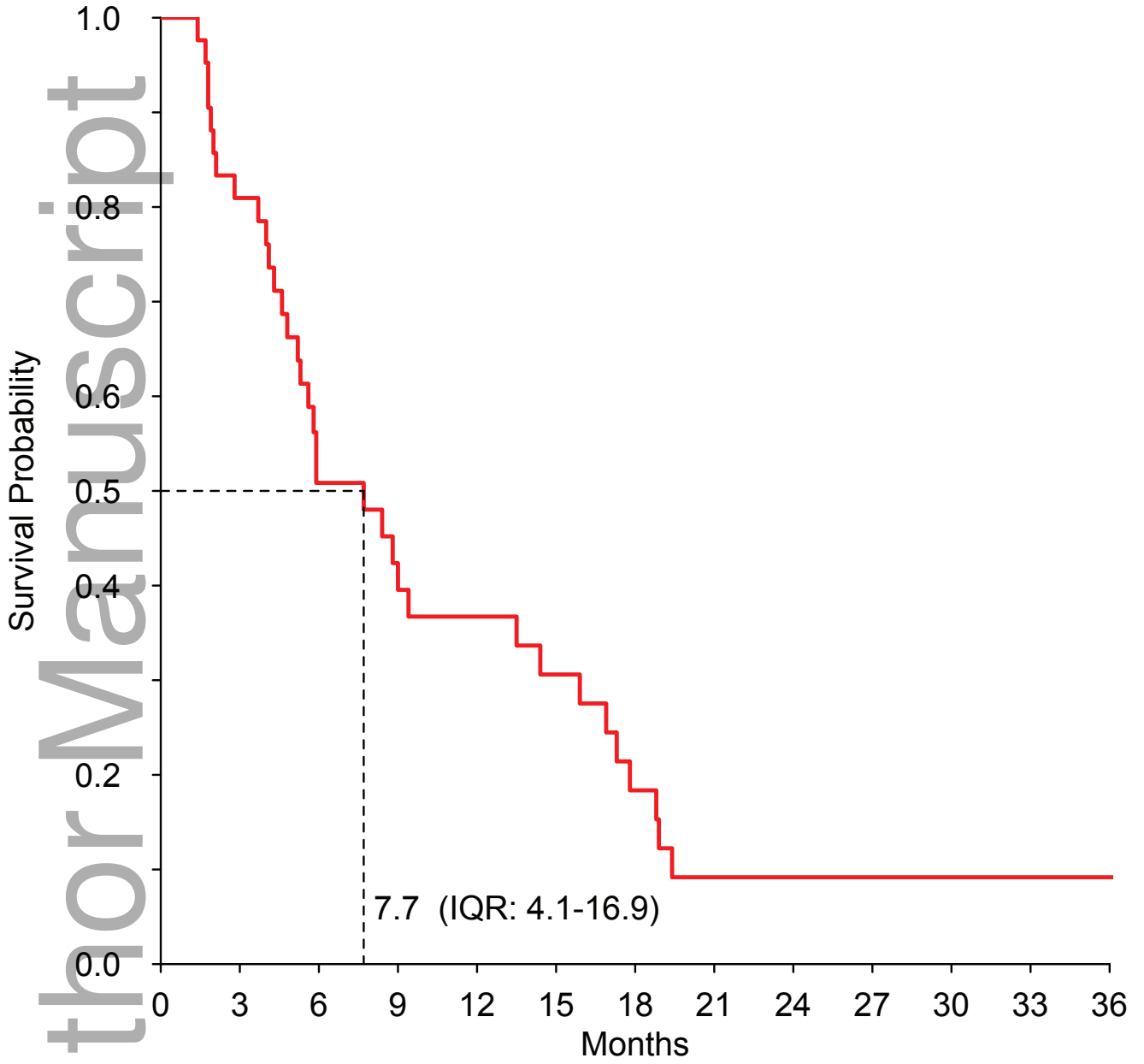
Overall

24 24 23 22 21 20 17 16 15 14 13 13 10

cncr\_32508\_f1b.eps

C

PFS



No. pts at risk

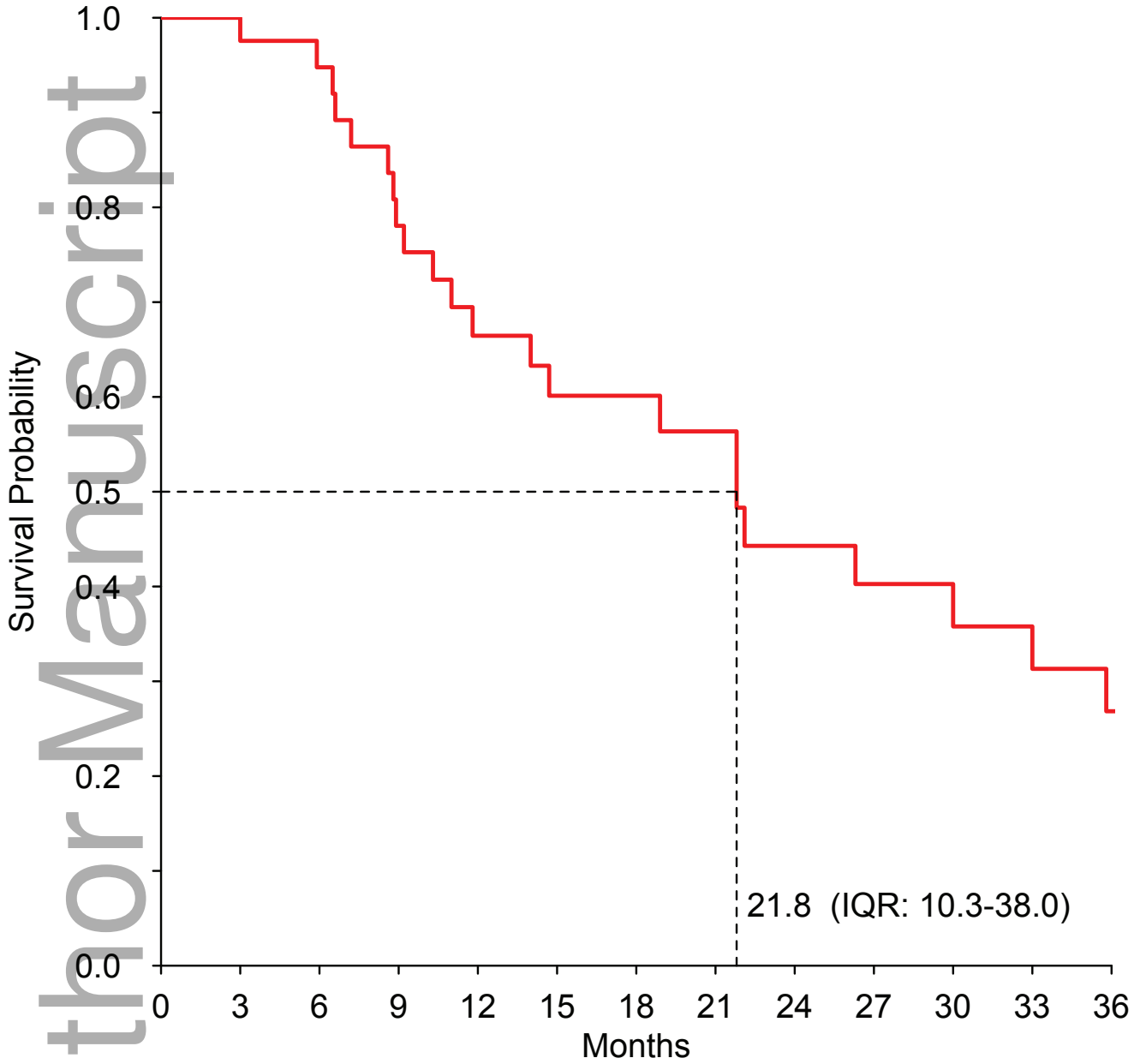
Overall

42 34 19 15 12 10 6 3 3 3 3 3 3

cncr\_32508\_f1c.eps

D

OS



No. pts at risk

Overall 42 41 34 28 22 19 16 14 11 10 9 8 6

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