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Kidney Cancer

Real-life Use of Cabozantinib in Front-line therapy for Metastatic Renal Cell Carcinoma: The CabFRONT Study (Meet-URO 24)

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Abstract

Background and objective: Cabozantinib remains the cornerstone for treatment of patients metastatic renal cell carcinoma (mRCC), whether pretreated with an immune-oncology (IO) agent and/or tyrosine kinase inhibitor, or treatment-naïve but ineligible for IO-based combinations.
Methods: CabFRONT (Meet-URO 24) was a retrospective, observational, multicentre study of a real-life population of treatment-naïve patients with intermediate-risk or poor-risk mRCC treated with cabozantinib.
Key findings and limitations: A total of 211 treatment- naïve patients with intermediate- or poor-risk mRCC according to the International Metastatic RCC Database Consortium criteria were included. At median follow-up of 50.4 mo (interquartile range 46.9–53.2), median progression-free survival (PFS) was 9.1 mo (interquartile range 7.4–10.4) and median overall survival (OS) was 19.8 mo (95% confidence interval [CI] 14.1–27.0). A reduced dose was not associated with significant differences in median OS (hazard ratio [HR] 1.08, 95% CI 0.77–1.52; $p = 0.7$) or PFS (HR 1.25, 95% CI 0.91–1.70; $p = 0.16$). A modified schedule because of toxicities

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was also not associated with significant differences in survival or progression (HR for death 0.56, 95% CI 0.25–1.28; p = 0.16; HR for progression or death 0.88, 95% CI 0.48–1.64; p= 0.7). The objective response rate according to Response Evaluation Criteria in Solid Tumours version 1.1 was 39%. The most common grade 3 adverse events were mucositis (9%), fatigue (9%), and diarrhoea (8.5%).

Conclusions and clinical implications: Front-line cabozantinib was effective and safe in an unselected real-life population of patients with intermediate-risk or poor-risk mRCC. Cabozantinib could be a choice for patients who cannot receive IO-based combinations or a speculative option for individuals with "early progression" on adjuvant IO.

Patient summary: We looked at outcomes for patients with metastatic kidney cancer treated with an inhibitor called cabozantinib in a large European population. We found that cabozantinib is active and safe, and that changes in the dose or treatment schedule because of side effects do not affect outcomes. Cabozantinib could be an option for patients who cannot receive immunotherapy for metastatic disease.

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1. Introduction

Renal cell carcinoma (RCC) is ranked 14th for cancer incidence, and clear-cell RCC is the most common histology [1]. The therapeutic scenario for metastatic RCC (mRCC) is continuously evolving, with progressive improvements in survival and quality of life for patients. For many decades, tyrosine kinase inhibitor (TKI) monotherapy was the treatment of choice for mRCC [2]. Immune-oncology (IO) agents, alone or in combination, then led to improvements in outcomes and became the new standard of care [3–7]. More recently, adjuvant pembrolizumab has demonstrated improvements in overall survival (OS) for patients with intermediate-high-risk and high-risk resected RCC, prompting interest in IO use in early RCC settings [8]. The role of immunotherapy in mRCC is changing, as IO rechallenge has not been effective for patients progressing on immunotherapy. Consequently, the treatment algorithm for mRCC is evolving, prompting a reconsideration of TKI monotherapy for patients progressing on adjuvant IO.

Cabozantinib is an oral TKI with multiple targets, including MET, VEGFR, AXL, RET, ROS1, and KIT, and is approved for treatment of mRCC [9]. Cabozantinib is effective in patients progressing on IO and VEGFR TKI therapy [10] and patients pretreated with IO-based combinations [11].

The pivotal randomised phase 2 CABOSUN trial demonstrated that cabozantinib monotherapy was effective and safe as first-line treatment in intermediate-risk or poor-risk mRCC [12,13]. Cabozantinib monotherapy can thus be considered as an option in patients who cannot receive an IO-based combination. Furthermore, cabozantinib is still the preferred first-line regimen for non–clear-cell RCC, particularly for papillary RCC [14].

Nevertheless, data on the effectiveness of first-line cabozantinib for mRCC outside the clinical trial setting are limited. It is therefore of particular interest to collect data on cabozantinib use as first-line therapy for mRCC under real-world conditions, even considering the possible role of TKI monotherapy in patients with early recurrence after adjuvant IO, as recently proposed [15].

2. Patients and methods

2.1. Study design and patients

CabFRONT is an Italian multicentre retrospective study in a real-life population of treatment-naïve patients with intermediate-risk or poor-risk mRCC treated with cabozantinib in clinical practice.

Data for patients who received cabozantinib between September 2019 and October 2024 were collected from Italian oncology referral centres belonging to the Italian Network for Research in Urologic Oncology (Meet-URO) Network and coordinated by Fondazione IRCCS Istituto Nazionale Tumori di Milano. Only deidentified data were shared with the coordinating centre. Eligibility criteria included patients with mRCC who started cabozantinib as first-line therapy in clinical practice. The study was approved by the ethics committee and institutional review board of Fondazione IRCCS Istituto Nazionale Tumori di Milano and was conducted in accordance with the relevant guidelines and regulations. Each participating centre obtained regulatory approval according to their institutional guidelines. Patients alive at the time of data collection and/or analysis signed informed consent for the use of their personal data for research purposes.

2.2. Assessments

We collected baseline demographic information, including patient sex and age, Eastern Cooperative Oncology Group performance status (ECOG PS), date of initial diagnosis, histology, date of metastatic disease diagnosis, medical history including nephrectomy and metastatic sites, and concomitant medications. We also evaluated cabozantinib administration parameters such as the starting dose, dose modifications, temporary interruptions and permanent

discontinuations, reasons for and outcomes of dose modifications and/or interruptions and/or discontinuation, hospitalisation rates for toxicity, and safety. Adverse events (AEs) were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

2.3. Statistical analysis and outcomes

Results for continuous variables are presented as the mean and standard deviation or the median and interquartile range (IQR). Results for categorical variables are reported as the frequency and percentage, with percentages expressed in relation to the total population unless otherwise specified. A χ^2 test of independence was performed to examine the relationship between dose reduction and baseline patient characteristics.

The primary endpoints of the study were progression-free survival (PFS) and the objective response rate according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Secondary endpoints were OS and safety.

OS was defined as the time from initiation of therapy to the date of death. PFS was defined as the time from treatment initiation to radiographic disease progression or death from any cause, whichever occurred first. Patients without progression or death at the time of the last follow-up were considered as censored, and OS and PFS were calculated up to the last recorded visit.

Kaplan-Meier survival curves were generated to visualise survival distributions for OS and PFS. These curves provide a nonparametric estimate of the survival function and allow assessment of the proportion of patients surviving over time. Follow-up time was computed from the date of therapy initiation.

Univariable Cox proportional-hazards models were fitted to the variables to assess their impact on OS and PFS. For each clinical variable, the hazard ratio (HR) and corresponding 95% confidence interval (CI) and the p value from a Wald test are reported.

Multivariable models were developed by applying stepwise regression to identify the most significant clinical variables associated with patient survival. During stepwise selection, variables are iteratively added or removed according to their statistical significance, as measured by the likelihood ratio test, with a threshold of $p < 0.05$ for inclusion in the model and a threshold of 0.1 for exclusion. The goal was to retain only the variables that contributed meaningfully to model accuracy, while avoiding multicollinearity and overfitting. The clinical variables identified are then implemented to fit a multivariable Cox proportional-hazards model. Models were adjusted for age and gender because of their potential confounding effects on patient survival.

All statistical analyses were performed using R version 3.6.3 (R Foundation for Statistical Analysis, Vienna, Austria).

3. Results

At data cutoff (October 2024), 211 patients were considered eligible for the analysis. Patient characteristics are reported in Table 1. Of the 211 patients, 173 (82%) had a clear-cell component, 29 (14%) had a sarcomatoid component, and 73 (35%) had not undergone nephrectomy. A total of 126 patients (60%) had metastasis at diagnosis: 44 (21%) had liver metastasis, 72 (34%) had bone metastasis, and 34 (16%) had brain metastasis at baseline.

All patients received cabozantinib as first-line treatment. The starting dose was 60 mg in 160/211 patients (76%) and 40 mg in 51/211 (24%). At least one dose reduction was applied for 100/211 patients (47%), and 131/211 (62%) patients had a dose and/or schedule modification because

Table 1 – Patient characteristics at baseline (n = 211)

Parameter	Result
Median age, yr (interquartile range)	65 (59–71)
Sex, *n* (%)	
Female	55 (26)
Male	156 (74)
ECOG performance score, *n* (%)	
0	99 (47)
1	72 (34)
2	40 (19)
IMDC risk group, *n* (%)	
Intermediate risk	142 (67)
Poor risk	69 (33)
IMDC risk factors, *n* (%)	
Time from diagnosis to treatment <12 mo	172 (81)
Karnofsky performance status <80%	55 (26)
Calcaemia >ULN	22 (10)
Haemoglobin <LLN	111 (53)
Neutrophil count >ULN	22 (10)
Platelet count >ULN	30 (14)
Histology, *n* (%)	
Clear cell	173 (82)
Papillary	20 (9.5)
Chromophobe	6 (2.8)
Not otherwise specified	12 (5.7)
Sarcomatoid features, *n* (%)	
Yes	29 (14)
No	182 (86)
Previous nephrectomy, *n* (%)	
Yes	138 (65)
No	73 (35)
Metastasis at diagnosis, *n* (%)	
Yes	126 (60)
No	85 (40)
Sites of metastasis, *n* (%)	
Bone	72 (34)
Brain	34 (16)
Liver	44 (21)
Lung	139 (66)
Lymph nodes	115 (54)
Glandular	24 (11)
Peritoneal	17 (8)
Initial dose, *n* (%)	
40 mg	51 (24)
60 mg	160 (76)
Dose reduction, *n* (%)	
Yes	117 (55)
No	94 (45)
Platelet/lymphocyte ratio, *n* (%)	
<150	72 (34)
>150	113 (54)
<200	107 (51)
>200	78 (37)
Data missing	26 (12)
Neutrophil/lymphocyte ratio, *n* (%)	
<3.2	96 (46)
>3.2	89 (42)
Data missing	26 (12)

ECOG = Eastern Cooperative Oncology Group; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ULN = upper limit of normal; LLN = lower limit of normal.

of AEs. A modified schedule consisted of cabozantinib administration on 5 or 6 d/wk.

At median follow-up of 50.4 mo (IQR 46.9–53.2), median PFS was 9.1 mo (IQR 7.4–10.4; Fig. 1) and median OS was 19.8 mo (95% CI 14.1–27.0; Fig. 2). There were 186 progression events and 150 deaths.

Univariable Cox regression analysis revealed that in comparison to 40 mg, a starting dose of 60 mg was significantly associated with better PFS (HR for progression or death 0.52, 95% CI 0.38–0.73; $p < 0.001$) and OS (HR for death 0.50, 95% CI 0.35–0.71; $p< 0.001$). The results are presented in Supplementary Table 1.

Multivariable Cox regression revealed that ECOG PS 2, poor risk according to the International Metastatic RCC Database Consortium (IMDC) scheme, sarcomatoid features, neutrophilia, and brain metastasis were associated with higher risk of death and shorter OS. ECOG PS 2, sarcomatoid features, neutrophilia, and brain metastasis were strongly associated with shorter PFS. As expected, previous nephrectomy was positively associated with both PFS and OS (Supplementary Tables 2 and 3).

Survival analysis for patients who received a reduced dose of cabozantinib during their treatment course versus patients who did not showed no significant difference in OS (HR 1.08, 95% CI 0.77–1.52; $p = 0.7$) or PFS (HR 1.25, 95% CI 0.91–1.70; $p = 0.16$).

Similarly, survival analysis for patients whose treatment schedule was modified versus patients whose schedule was not showed no significant differences in OS (HR for death 0.56, 95% CI 0.25–1.28; $p = 0.16$) or PFS (HR for progression or death 0.88, 95% CI 0.48–1.64; $p = 0.7$).

Consequently, survival analysis stratified by dose reduction and/or schedule modification revealed no differences in OS (HR for death 0.95, 95% CI 0.67–1.34; $p = 0.8$) or PFS (HR for progression or death 1.19, 95% CI 0.87–1.64; $p = 0.3$).

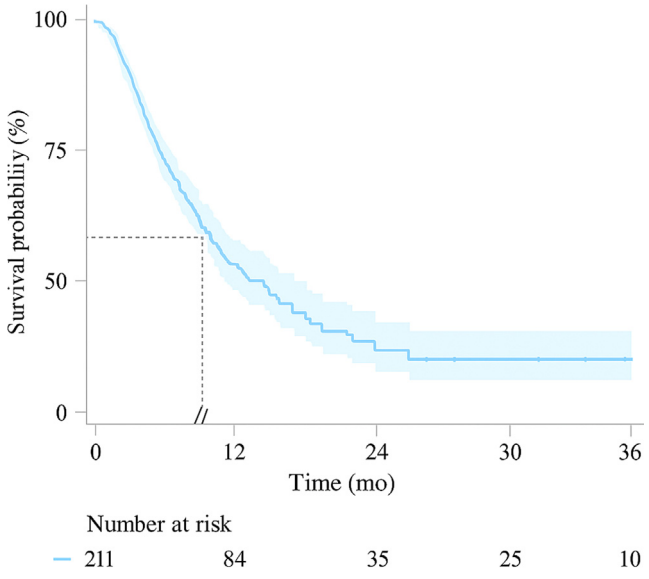

Fig. 1 – Results for progression-free survival (PFS). At median follow-up of 50.4 mo (interquartile range 46.9–53.2), median PFS was 9.1 mo (interquartile range 7.4–10.4). The number of progression events was 186.

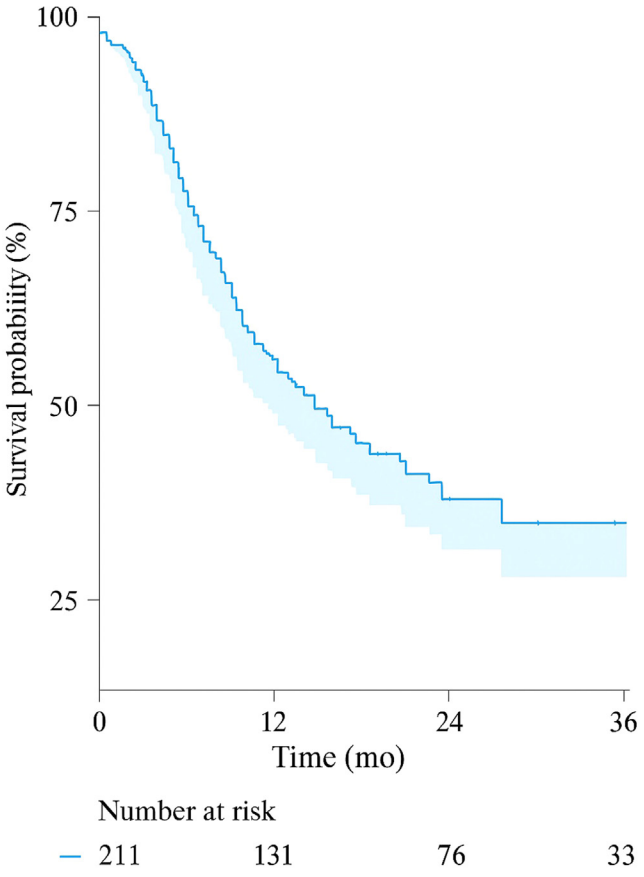

Fig. 2 – Results for overall survival (OS). At median follow-up of 50.4 mo (interquartile range 46.9–53.2), median OS was 19.8 mo (95% confidence interval 14.1–27.0). The number of deaths was 150.

Baseline characteristics of the groups with and without a dose reduction are reported in Supplementary Table 4. χ^2 tests revealed a significant association between dose reduction and previous nephrectomy ($p = 0.013$), ECOG PS ($p = 0.04$), and IMDC risk group ($p = 0.014$). Specifically, patients with ECOG PS 2 were more likely to maintain the full cabozantinib dose, as were patients with poor-risk disease and those who had not undergone nephrectomy.

The percentage of patients evaluable for radiological response according to RECIST version 1.1 was 98% (206/211). The objective response rate was 39% and the disease control rate was 77%. The best response to cabozantinib was a complete response in 3.4% of patients (seven of 206), a partial response in 36% (74/206), and stable disease in 38% (78/206; Table 2).

Table 2 – Investigator-assessed tumour responses for the 206 patients evaluable according to Response Evaluation Criteria in Solid Tumours v.1.1

Parameter	Patients, *n* (%)
Objective response	81 (39)
Disease control	159 (77)
Best overall response	
Complete response	7 (3.4)
Partial response	74 (36)
Stable disease	78 (38)
Progressive disease	47 (23)

After progression on cabozantinib, 82 patients received nivolumab, eight received cabozantinib beyond progression, five received TKI monotherapy (sunitinib), and 88 received best supportive care, while 28 patients were still on treatment at the time of the analysis.

3.1. Safety

The AEs reported are summarised in Table 3. Of the 211 patients, 191 (91%) reported at least one grade 1–2 AE. The most common were fatigue (114 patients, 54%), mucositis (103 patients, 49%), hand-foot syndrome (96 patients, 46%), diarrhoea (83 patients, 39%), hypertension (68 patients, 32%), and hypothyroidism (60 patients, 28%).

Grade ≥3 AEs occurred in 69/211 patients (33%). The most common were mucositis (9.0%), asthenia (9.0%), diarrhoea (8.5%), and hand-foot syndrome (8.0%). Permanent treatment discontinuation because of grade 3 AEs was observed in seven of 211 patients (3.3%), primarily for diarrhoea, asthenia, and mucositis. At least 131/211 patients (62%) required a dose reduction and 86 (41%) required a transitory interruption for toxicity management.

4. Discussion

Despite the advent of IO agents, VEGFR TKI therapy can still be considered the backbone of mRCC treatment, in combination with IO agents as first-line treatment and alone in subsequent lines, with evidence of excellent responses and beyond-progression treatment for selected patients [15–18].

Cabozantinib is an inhibitor of multiple tyrosine kinases—including VEGFR2, MET, and AXL—implicated in tumour growth and angiogenesis, pathologic bone remodelling, drug resistance, and metastatic progression of cancer [9,19,20].

Cabozantinib can be considered a standard of care in IO-pretreated mRCC and is also an alternative in IMDC intermediate- and poor-risk disease for patients who cannot receive first-line PD-1-targeted therapy [11,14]. Cabozantinib can also be considered as a primary option in metastatic non–clear-cell RCC subtypes such as collecting duct carcinoma, as reported in the BONSAI trial [21], and papillary RCC [22,23].

Table 3 – Adverse events among the 211 patients

Event	Patients, *n* (%)	
	Grade 1–2	Grade 3
Any event	191 (91)	69 (33)
Fatigue	114 (54)	19 (9)
Mucositis	103 (49)	18 (9)
Diarrhoea	83 (39)	18 (8.5)
Hand-foot syndrome	96 (46)	16 (8)
Hypertension	68 (32)	6 (3)
Hypothyroidism	60 (28)	4 (2)
AST/ALT increase	2 (1.0)	3 (2)
Anaemia	1 (0.5)	4 (2)
Proteinuria	1 (0.5)	1 (0.5)
Rash	0	1 (0.5)
Weight loss	0	1 (0.5)

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

The CABOSUN trial demonstrated that cabozantinib is superior to sunitinib in treatment-naïve patients with intermediate-risk or poor-risk mRCC. However, the CABOSUN results are for a small, selected population enrolled in a clinical trial, even though patients with unfavourable features such as bone metastasis, a high number of metastatic sites, and the primary tumour in situ were well represented [12,13].

Our study included an unselected cohort of 211 patients with mRCC with intermediate or poor IMDC risk who received cabozantinib as first-line treatment in a real-world setting. Patient characteristics reveal a well-represented population with poor prognostic features such as the primary tumour in situ (34.6%), synchronous metastatic disease (59.7%), and sarcomatoid features (13.7%). The cohort included patients with metastatic sites associated with poor outcomes, such as liver (20.9%) and bone metastases (34.1%), or under-represented in clinical trials, such as peritoneal metastasis (8.1%) and brain metastasis (16.1%) [24,25]. The latter are commonly excluded from clinical trials and considered to have dismal prognosis, with data on the efficacy of drugs in this population only derived from real-world evidence [26].

Cabozantinib is currently considered a preferred option for mRCC with brain metastases on the basis of efficacy data available for this population [15,26]. Our study provides more data on cabozantinib in patients with brain metastases, as the incidence of brain metastases in our cohort (16.1%) was higher than in previous reports [25,27]. This may be attributed in part to routine brain computed tomography scans at baseline, which could lead to greater detection; conversely, it could be partly due to selection bias, as patients with brain involvement are more likely to be treated with cabozantinib.

Our study demonstrates that in a real-world setting, cabozantinib is active and safe in patients with intermediate-risk or poor-risk mRCC, with strong results for the disease control rate, which is relevant in patients with symptomatic disease because of a high tumour burden.

Interestingly, we report for the first time that a dose reduction and/or schedule modification did not impact cabozantinib efficacy: there were no differences in median PFS or OS between the groups with and without a reduced or modified dose and/or schedule. However, within the limits of the univariable analysis, a starting dose of 60 mg seemed to be associated with better PFS (HR for progression or death 0.52, 95% CI 0.38–0.73; $p < 0.001$) and OS (HR for death 0.50, 95% CI 0.35–0.71; $p < 0.002$) in comparison to 40 mg (Supplementary Table 1). These results are similar to findings from the RAINBOW trial regarding the sunitinib schedule, and would be an interesting issue for further research [28].

Our results are highly relevant in the ever-evolving treatment landscape for RCC in both adjuvant and first-line settings. Results for pembrolizumab from the KN564 trial showed for the first time that adjuvant therapy in genitourinary cancer improved survival for patients. These results had relevant implications for several fields. However, although pembrolizumab improved disease-free survival

and OS, almost 30% of patients will experience disease progression and there are few data on outcomes for patients treated after progression on IO therapy [8,29]. It is worth noting that early IO use would preclude the use of IO-based combinations in the metastatic setting, as IO rechallenge did not improve OS, even if in a different setting. Thus, the choice of first-line treatment in patients progressing during or after adjuvant IO is an emerging issue and there are no randomised controlled trials in this setting. Pivotal trials of IO-based combinations enrolled IO-naïve patients, and trials enrolling patients pretreated with IOs for metastatic disease, such as CONTACT-03 and TI-NIVO, failed to demonstrate that IO addition to VEGF-targeted therapy (VEGF-TT) in mRCC provided a benefit over VEGF-TT alone [30,31]. El Zarif et al [32] reported that VEGFR TKIs are active in IO-pretreated patients, and real-world data for patients progressing after adjuvant IO revealed that a VEGFR TKI was the preferred first-line treatment in these patients (40%). Moreover, early recurrences are more commonly observed in the bones, and patients with favourable-risk disease at recurrence appear to benefit more from VEGF-TT than from IO combinations.

Thus, according to novel algorithms, monotherapy with a TKI such as cabozantinib could be an option in patients with intermediate-risk or poor-risk mRCC who experience early progression on adjuvant IO, even those with bone metastasis, according to promising results for cabozantinib in groups with bone disease. It is important to point out that further trials will be crucial for assessing the best treatment after progression on adjuvant immunotherapy, as our study cohort comprised immunotherapy-naïve patients.

Limitations of our study include retrospective collection of data and the lack of availability of IO combinations during the first 2 yr of the study period, with consequent selection bias. Furthermore, we acknowledge that the use of stepwise selection methods in multivariable modelling may result in overfitting and unstable variable selection, which may limit the generalisability of our findings.

5. Conclusion

In conclusion, CabFRONT provides valuable information on the effectiveness and safety of cabozantinib in a real-life setting across the full spectrum of patients treated in routine practice, including subpopulations that are often overlooked in randomised clinical trials.

In the ever-evolving treatment landscape for mRCC, even though IO-based combinations are the primary option for first-line treatment in IO-naïve patients, cabozantinib may still have a role in patients not eligible for IO. We also speculate that cabozantinib could be an option for patients with mRCC who experience early progression on adjuvant IO.

Author contributions: Marco Stellato had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data: Lalli, Stellato, Verzoni, Procopio.
Drafting of the manuscript: Stellato, Zanardi, Maiorano, Cossu Rocca, Verzoni.
Critical revision of the manuscript for important intellectual content: Stellato, Verzoni, Procopio.
Statistical analysis: Stellato, Lalli.
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Appendix A. Supplementary data

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