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ORIGINAL RESEARCH ARTICLE

Cabozantinib After a Previous Immune Checkpoint Inhibitor in Metastatic Renal Cell Carcinoma: A Retrospective Multi-Institutional Analysis

Roberto Iacovelli[1] · Chiara Ciccarese[1,2] · Gaetano Facchini[3] · Michele Milella[4] · Federica Urbano[5] · Umberto Basso[6] · Ugo De Giorgi[7] · Roberto Sabbatini[8] · Daniele Santini[9] · Rossana Berardi[10] · Matteo Santoni[11] · Sergio Bracarda[12] · Francesco Massari[13] · Cristina Masini[14] · Michele De Tursi[15] · Riccardo Ricotta[16] · Sebastiano Buti[17] · Fable Zustovich[18] · Pierangela Sepe[19] · Sabrina Rossetti[3] · Marco Maruzzo[6] · Enrico Cortesi[5] · Giampaolo Tortora[1,2] · Giuseppe Procopio[19]

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Abstract

Background Angiogenesis has been recognized as the most important factor for tumor invasion, proliferation, and progression in metastatic renal cell carcinoma (mRCC). However, few clinical data are available regarding the efficacy of cabozantinib following immunotherapy.

Objective To describe the outcome of cabozantinib in patients previously treated with immunotherapy.

Patients and methods Patients with mRCC who received cabozantinib immediately after nivolumab were included. The primary endpoint was to assess the outcome in terms of efficacy and activity.

Results Eighty-four mRCC patients met the criteria to be included in the final analysis. After a median follow-up of 9.4 months, median overall survival was 17.3 months. According to the IMDC criteria, the rates of patients alive at 12 months in the good, intermediate, and poor prognostic groups were 100%, 74%, and 33%, respectively ($p < 0.001$). The median progression-free survival (PFS) was 11.5 months (95% CI 8.3–14.7); no difference was found based on duration of previous first-line therapy or nivolumab PFS. The overall response rate was 52%, stable disease was found as the best response in 25.3% and progressive disease in 22.7% of patients. Among the 35 patients with progressive disease on nivolumab, 26 (74.3%) patients showed complete/partial response or stable disease with cabozantinib as best response after nivolumab. The major limitations of this study are the retrospective nature and the short follow-up.

Conclusions Cabozantinib was shown to be effective and active in patients previously receiving immune checkpoint inhibitors. Therefore, cabozantinib can be considered a valid therapeutic option for previously treated mRCC patients, irrespective of the type and duration of prior therapies.

1 Introduction

Angiogenesis has been recognized as the most important factor for tumor invasion, proliferation, and progression in renal cell carcinoma (RCC). The last 10 years have been characterized by the development of some therapeutic drugs able to inhibit the vascular endothelial growth factor (VEGF) or its receptors (VEGFR), leading to an improvement of progression-free survival (PFS) and overall survival (OS). Despite these results, the majority of patients progress and die of their disease. The mechanisms of acquired resistance to single-agent VEGF inhibitors remain largely unknown. Several cellular pathways involving transmembrane receptors such as fibroblast growth factor receptor (FGFR), hepatocyte growth factor receptor (MET), and AXL have been related to the development of resistance to anti-VEGFR inhibitors in preclinical RCC models [1].

Cabozantinib is a small molecule receptor tyrosine kinase inhibitor (TKI) that binds to and inhibits MET, VEGFR-1, 2, and 3, mast/stem cell growth factor (KIT), FMS-like tyrosine kinase 3 (FLT-3), TEK tyrosine kinase, endothelial (TIE-2), tropomyosin-related kinase B (TRKB), and AXL. This may

Giampaolo Tortora and Giuseppe Procopio share the co-last authorship.

✉ Roberto Iacovelli
Roberto.iacovelli@policlinicogemelli.it

Extended author information available on the last page of the article

Key Points

Limited data are available about the efficacy of cabozantinib after immunotherapy in metastatic renal cell carcinoma.

In this study, cabozantinib resulted in a median progression-free survival of more than 11 months.

Early use of cabozantinib was associated with a better outcome.

result in an inhibition of both tumor growth and angiogenesis, and eventually to tumor regression.

The phase III METEOR trial compared cabozantinib with everolimus in patients with metastatic RCC (mRCC), progressing after prior antiangiogenic therapies (70% of patients had one prior anti-VEGFR TKI, and 30% had two or more prior anti-VEGFR TKIs). Treatment with cabozantinib prolonged OS (21.4 vs. 16.5 months; hazard ratio (HR) 0.66; $p=0.00026$), delayed disease progression (HR for PFS of 0.51; $p<0.0001$), and improved the overall response rate (ORR; 17% vs. 3%; $p<0.0001$) [2].

At the same time, the use of immune checkpoint inhibitors has been included in the clinical armamentarium—both in patients who progressed on a previous anti-VEGFR TKI and in previously untreated patients—and is becoming a new standard therapy because of significant OS improvement [3–6]. Despite some preliminary reports that suggested that VEGFR TKIs retain clinical activity after immunotherapy [7, 8], no large amounts of clinical data are available regarding the efficacy of cabozantinib following immune checkpoint inhibitors. Therefore, the aim of our study was to evaluate the efficacy of cabozantinib in mRCC patients previously treated with nivolumab.

2 Patients and Methods

2.1 Patients

In this analysis, we included consecutive patients with mRCC who received cabozantinib immediately after nivolumab at 18 cancer centers or tertiary hospitals in Italy. Only patients with complete baseline characteristics such as histology and prognostic factors at the of therapy line initiation were included in the final analysis.

The baseline characteristics required for inclusion in the analysis were: age; ECOG performance status; disease extant; biochemical values for corrected calcium, hemoglobin, neutrophils, and platelet counts; previous type and length of therapy received before cabozantinib. The prognostic group at baseline as well as before each therapy line was evaluated for each patient using the IMDC criteria [9].

The primary endpoint was to assess the outcome of cabozantinib after nivolumab in terms of efficacy, PFS, OS, and objective response rate (ORR).

Subgroup analyses were performed to assess the impact of baseline characteristics such as the IMDC prognostic factors at baseline, PFS of the first-line therapy as well as of nivolumab (≤ 6 months vs. >6 months), and the line of cabozantinib administration ("early"—third line, vs. "late"—fourth to subsequent lines). The study (i.e., RenAll) was approved by the Internal Review Board of the Azienda Ospedaliera Integrata of Verona.

2.2 Statistics

Baseline values were expressed as median values. Baseline was defined as the start date of cabozantinib treatment. PFS was evaluated from the beginning of cabozantinib treatment to disease progression or death. Patients were assessed for progression every 12 weeks using RECIST (v. 1.0) criteria according to mandatory national guidelines required by the Agenzia Italiana del Farmaco (AIFA).

OS was evaluated from the start of cabozantinib to death or last follow-up. All survivals were estimated using the Kaplan–Meier method and compared across groups using the log-rank test. A Chi-square or t-test was used to compare groups as appropriate. Cox proportional hazards models were applied to explore patient characteristics. Predictors of PFS and OS in univariate- and multivariable-adjusted analysis were evaluated using a stepwise selection approach with a type I error of 0.05 for model entry and 0.10 for elimination. Additional elimination was applied to identify significant variables. All the variables were considered to be significant if $p<0.05$. The PASW software (Predictive Analytics SoftWare; v 21; IBM SPSS) was used for the analysis.

3 Results

3.1 Study population

A total of 84 RCC patients met the criteria to be included in the final analysis. Thirty-nine out of 84 (46.4%) patients received cabozantinib as third-line treatment after second-line nivolumab (i.e., early cabozantinib); the remaining 45 patients were treated with cabozantinib after nivolumab in the fourth to sixth lines of therapy (i.e., late cabozantinib). According to the IMDC criteria, 15.5% of patients were in the good prognosis risk group, 60.7% in the intermediate, and 23.8% in the poor prognosis risk group. Most patients started cabozantinib at 60 mg, while 27 (32.1%) patients

started at 40 mg. During cabozantinib treatment, 50% of patients reduced the starting dose. Baseline characteristics of the included patients are reported in Table 1.

All patients received VEGFR TKIs as first-line therapy. The median PFS of the first line was 13.9 months (95% CI 10.2–17.6). Nivolumab was administered as second-line therapy in 39 (46.4%) patients, and in subsequent lines in the remaining 45 (53.6%) patients. The median PFS of nivolumab was 5.0 months (95% CI 3.4–6.6), and the median duration of treatment was 5.9 months. When the baseline characteristics of the patients were compared based on the therapy line of cabozantinib (early vs. late), patients who received cabozantinib earlier received more pazopanib more frequently than sunitinib and had nephrectomy less frequently (Table 1).

3.2 Overall Survival

After a median follow-up of 9.4 months, 25 of the 84 patients had died, and 35 patients had progressed to cabozantinib.

Table 1 Patients' characteristics at the beginning of cabozantinib

Characteristic	Patients $N=84$ (%)	Early Cabo $N=39$	Late Cabo $N=45$	χ^2 p-value
Median age (year)	65.5	66.1	65.3	0.67[§]
Male	71.4%	79.5%	64.4%	0.13
Nephrectomy	86.9%	76.9%	95.6%	0.012
First-line therapy				
Sunitinib	71.4%	64.1%	77.8%	0.037
Pazopanib	25.0%	35.9%	15.6%	
Other	3.6%	0	6.7%	
Number of previous lines				
2	46.4%	NA	NA	
≥3	53.6%			
Number of metastatic sites				
1–2	28.6%	28.2%	28.9%	0.99
3	25.0%	25.6%	24.4%	
>3	46.4%	46.2%	46.7%	
Metastatic site				
Lung	85.7%	87.2%	84.4%	0.72
Lymph node	71.4%	69.2%	73.3%	0.68
Bone	40.5%	41.0%	40.0%	0.92
Liver	39.3%	35.9%	42.2%	0.55
Pancreas	22.6%	20.5%	24.4%	0.67
Brain	15.5%	17.9%	13.3%	0.56
IMDC risk class				
Good	15.5	23.1%	8.9%	0.19
Intermediate	60.7	53.8%	66.7%	
Poor	23.8	23.1%	24.4%	
PFS at first line				
Median value (months)	13.9	13.8	14.0	0.71*
PFS of nivolumab				
≥6 months	46.4%	38.5%	53.3%	0.17
Initial dose of cabozantinib				
60 mg	67.9%	79.5%	57.8%	0.034
40 mg	32.1%	20.5%	42.2%	

IMDC International mRCC Database Consortium classification, *N* number, *NA* not applicable, *PFS* progression-free survival, *mRCC* metastatic renal cell carcinoma

[§] t-test

*Log-rank test

Table 2 Multivariable analysis for overall and progression-free survival

Variable	Overall survival			Progression-free survival		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Nephrectomy (Y/N)	0.88	0.18–4.24	0.88	0.78	0.25–2.46	0.67
Type of 1st line	0.96	0.47–1.95	0.91	1.06	0.58–1.95	0.84
Cabozantinib (E/L)	0.31	0.11–0.92	0.035*	0.50	0.22–1.11	0.089
Dose of cabozantinib (60/40)	0.73	0.31–1.77	0.49	0.66	0.31–1.44	0.30

CI confidence interval, *E* early, *L* late, *Y* yes, *N* no

*Statistically significant

The median OS was 17.3 months. According to the IMDC criteria, the rate of patients alive at 12 months was 100% for the good prognosis risk group, 74% for the intermediate group, and 33% for the poor prognosis group ($p < 0.001$) (Fig. 1a).

Comparing patients treated with early versus late cabozantinib, the median OS rates were not reached versus 14.7 months, respectively ($p = 0.027$), while the 1-year survival rates were 85% and 57%, respectively. Moreover, we evaluated the outcome of cabozantinib taking into account the median PFS of the first line of treatment. The OS rate at 12 months was 68% for the subgroup of patients who had PFS of the first line that was less than or equal to the median value, and 70% for the subgroup with a median PFS of the first line that was longer than the median value ($p = 0.64$). Further, no statistically significant difference was found on analysis of the type of first-line therapy, the 18-month OS rate was 53% for first-line sunitinib, 62% for first-line pazopanib, and 60% for other options ($p = 0.76$). Furthermore, we analyzed the effect of the duration of PFS with previous nivolumab (> 6 months vs. ≤ 6 months) on the median OS, which was 52% and 48%, respectively ($p = 0.16$). No differences were found based on initial dose of cabozantinib ($p = 0.82$).

Considering the differences in patients' baseline characteristics, the outcome between early versus late cabozantinib use was evaluated in a multivariable analysis suggesting that patients who received early cabozantinib had longer OS (adjusted HR 0.32; 95% CI 0.11–0.92; $p = 0.034$) (Table 2 and Fig. 2).

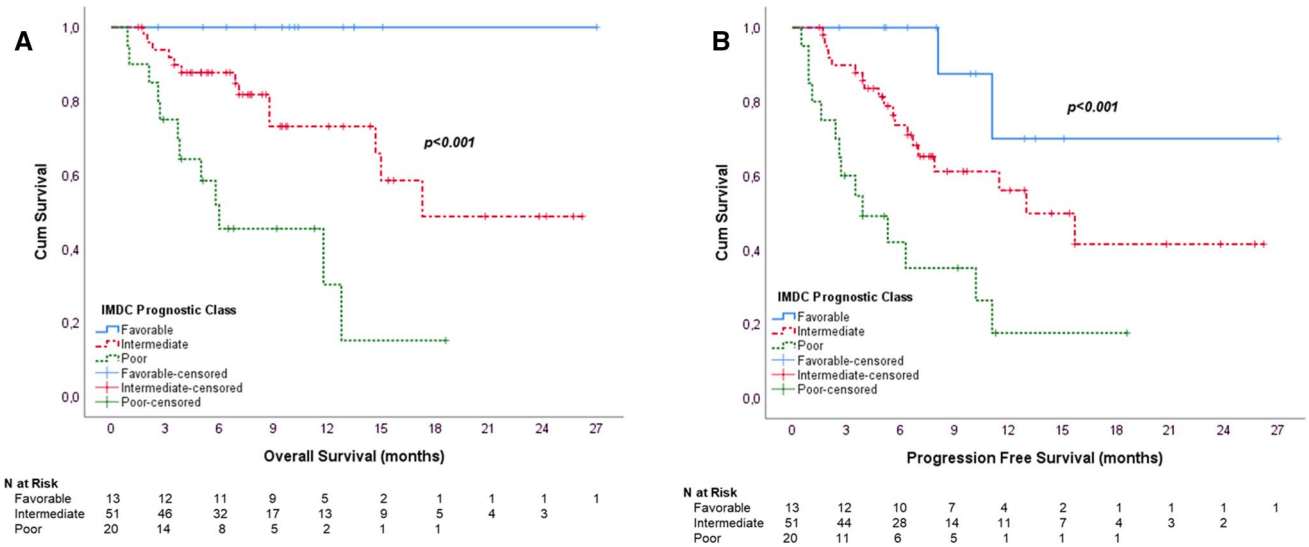

Fig. 1 Overall survival (**a**) and progression-free survival (**b**) in patients who received cabozantinib after nivolumab

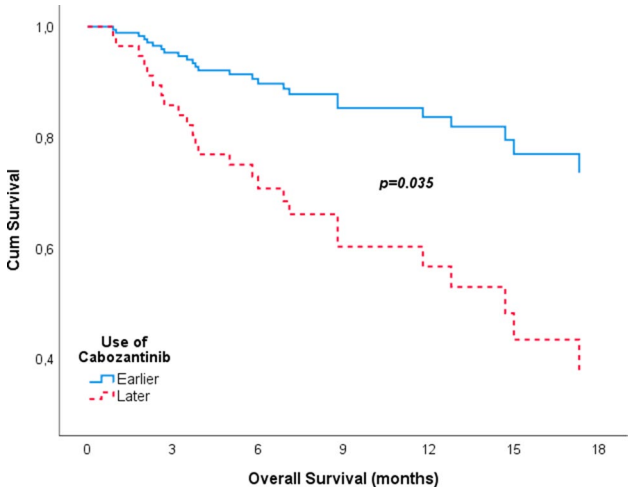

Fig. 2 Overall survival for early versus late use of cabozantinib after immunotherapy adjusted for significant variables at baseline (i.e., nephrectomy, type of first line, initial dose of cabozantinib)

3.3 Progression-Free Survival

The median PFS was 11.5 months (95% CI 8.3–14.7); according to the IMDC criteria, the rate of patients without progression at 6 months was 100% in the good prognosis risk group, 74% in the intermediate group, and 42% in the poor prognosis group ($p < 0.001$) (Fig. 1b).

Comparing patients treated with early versus late cabozantinib, the median PFS were not reached versus 11.1 months, respectively ($p = 0.13$), and the 6-month PFS rates were 78% and 64%, respectively. No significant difference in PFS was found when the analysis was performed based on the median PFS of the first-line of treatment (11.1 vs. 15.7 months; $p = 0.45$) or based on type of first-line therapy used; the 6-month PFS rate was 72% for first-line sunitinib, 67% for first-line pazopanib, and 67% for other options ($p = 0.76$). The duration of PFS with previous nivolumab has no effect on cabozantinib, the 6-month PFS rate was 68% in patients with previous PFS ≤ 6 months and 74% in those with PFS greater than 6 months ($p = 0.28$). No differences were found based on the initial dose of cabozantinib ($p = 0.53$).

Table 3 Cross-response to nivolumab and cabozantinib

Response to cabozantinib	Response to nivolumab			Total
	CR/PR	SD	PD	
CR/PR	9	1	2	12
SD	14	7	6	27
PD	15	11	9	35
Total	38	19	17	

Considering the differences among the baseline characteristics of patients, the outcome between early versus late use of cabozantinib was evaluated in a multivariable analysis suggesting that patients receiving early cabozantinib had longer PFS (adjusted HR 0.51; 95% CI 0.23–1.11; $p = 0.088$) (Table 2).

3.4 Objective Response Rate

Among the 75 patients treated with cabozantinib who were evaluable for the objective responses, the ORR was 52%. Stable disease was the best response achieved in 19 (25.3%) patients, and progressive disease in 17 (22.7%) patients. Seventy-four patients were evaluable for the objective responses to both nivolumab and cabozantinib therapy (Table 3). Among the 35 patients with progressive disease on nivolumab, 26 (74.3%) patients achieved complete/partial response or stable disease with cabozantinib as best response after nivolumab.

4 Discussion

Recently, immune checkpoint inhibitors targeting PD-1/PD-L1 have revolutionized the treatment landscape of mRCC, showing durable responses and improved OS in first line (in combination) and in previously treated (nivolumab monotherapy) patients [3–6]. Subsequent therapies after failure of immunotherapy are likely to become de facto those VEGFR TKIs with well-established efficacy in mRCC. Among them, cabozantinib represents the only targeted agent demonstrating OS benefit in pre-treated mRCC patients [2]. Therefore, understanding cabozantinib activity after immune checkpoint inhibitor treatments is a clinically relevant topic. In the METEOR trial, the vast majority of patients treated with cabozantinib were immunotherapy naïve, while only 5% ($n = 18$) of patients had received prior immune checkpoint inhibitor therapy. For the latter subgroup, cabozantinib was associated with improved PFS (HR 0.22; 95% CI 0.07–0.65), OS (HR 0.56; 95% CI 0.21–1.52), and ORR (22% vs. 0%) compared with everolimus [10]. Small retrospective studies further support cabozantinib activity after progression on PD-1/PD-L1 checkpoint inhibitors, showing ORR ranging from 33 to 42% [11–13].

To the best of our knowledge, this current study represents the biggest specific report of outcomes with cabozantinib after nivolumab failure for mRCC patients reporting the median PFS of cabozantinib in patients who have progressed on PD-1 checkpoint inhibitors. Interestingly, a median PFS of more than 11 months in heavily pre-treated patients (almost 50% received cabozantinib in the fourth or subsequent lines of therapy) supports the persistent efficacy of this drug even after immunotherapy. A limitation of our

analysis is the selection of patients with a better prognosis, who reached at least the third line of therapy, and these results require a prospective validation. Of note, the efficacy of cabozantinib in terms of PFS was maintained regardless of the therapy line ("early" vs. "late" cabozantinib) even if early use seems to suggest a longer survival.

The activity of cabozantinib post-nivolumab observed in our study reinforces the potential role of cabozantinib in this setting. The disease control rate demonstrated in our cohort exceeded 77%. Moreover, the possibility in the vast majority of cases (74.3%) of obtaining a response with cabozantinib in patients refractory to nivolumab highlights the lack of cross-resistance between these two treatment strategies. Preclinical data support the clinical activity of cabozantinib after prior anti-PD-1/PD-L1 therapy due to the inhibition of immunosuppressive and pro-angiogenic cytokines and transcription factors promoting epithelial-mesenchymal transition, which are over-expressed in tumors resistant to PD-1/PD-L1 inhibitors [14, 15]. Another possible hypothesis to explain this finding is the fact that PD-1 blockade may actually affect the efficacy of subsequent therapies, regardless of the PFS of the immunotherapy itself. This is in line with the demonstration of an OS benefit without a PFS prolongation with nivolumab [3]. The completely different treatment mechanism of immunotherapy compared to anti-angiogenetic targeted agents might explain this discrepancy. Thus, we found that the OS of cabozantinib did not differ based on the duration of both the first-line treatment and that of nivolumab. Therefore, selecting cabozantinib treatment should not be influenced by the efficacy of prior therapies. However, the availability of drugs able to significantly prolong OS (such as cabozantinib and nivolumab) requires their early use in the therapeutic algorithm of mRCC patients, as demonstrated by a significant longer median OS ($p = 0.027$) of patients treated with early cabozantinib (as third line after nivolumab in second line) compared to those who received this molecule later, as observed in our study. In our study, toxicity of cabozantinib was comparable to results published in the scientific literature, with side effects leading to a dose reduction in 50% of cases (compared to 60% of the METEOR trial).

The retrospective nature of our study, together with a relatively short follow-up period, and the lack of patients treated with the inverse sequence (cabozantinib-nivolumab) represent major limitations. Furthermore, an independent review committee should have evaluated response rate and PFS as expected in a retrospective study; however, included centers have great experience in RCC management. The issue of the optimal sequence for mRCC treatment, taking into account the approval of several immunotherapy combinations as first-line regimens, is yet to be defined and requires prospective studies.

In conclusion, cabozantinib, a standard of care for second-line treatment of mRCC after VEGFR TKI therapy, also demonstrated improved clinical outcomes in patients who received an immune checkpoint inhibitor, and trials in this setting (e.g. NCT04338269, NCT03428217) are ongoing. Therefore, cabozantinib could be considered a valid therapeutic option for previously treated mRCC patients, irrespective of the type and duration of prior therapies.

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Data availability Availability of data and materialavailable after request to the corresponding authors.

Compliance with Ethical Standards

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Conflict of interest R. Iacovelli served as consultant for Ipsen; Pfizer; Novartis; BMS, MSD, Janssen. G. Procopio served as consultant for Bayer, BMS, Ipsen, Janssen, MSD, Novartis, Pfizer. Conflict of interest/Competing interests: Roberto Iacovelli served as consultant for Ipsen; Pfizer; Novartis; BMS, MSD, Janssen. Giuseppe Procopio served as consultant for Bayer, BMS, Ipsen, Janssen, MSD, Novartis, Pfizer. Chiara Ciccarese, Gaetano Facchini, Michele Milella, Federica Urbano, Umberto Basso, Ugo De Giorgi, Roberto Sabbatini, Daniele Santini, Rossana Berardi, Matteo Santoni, Sergio Bracarda, Francesco Massari, Cristina Masini, Michele De Tursi, Riccardo Ricotta, Sebastiano Buti, Fable Zustovich, Pierangela Sepe, Sabrina Rossetti, Marco Maruzzo, Enrico Cortesi, and Giampaolo Tortora declare that they have no conflicts of interest that might be relevant to the contents of this article.

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Affiliations

Roberto Iacovelli[1] · Chiara Ciccarese[1,2] · Gaetano Facchini[3] · Michele Milella[4] · Federica Urbano[5] · Umberto Basso[6] · Ugo De Giorgi[7] · Roberto Sabbatini[8] · Daniele Santini[9] · Rossana Berardi[10] · Matteo Santoni[11] · Sergio Bracarda[12] · Francesco Massari[13] · Cristina Masini[14] · Michele De Tursi[15] · Riccardo Ricotta[16] · Sebastiano Buti[17] · Fable Zustovich[18] · Pierangela Sepe[19] · Sabrina Rossetti[3] · Marco Maruzzo[6] · Enrico Cortesi[5] · Giampaolo Tortora[1,2] · Giuseppe Procopio[19]

1 Oncologia Medica, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Largo Agostino Gemelli 8, 00158 Rome, Italy

2 Oncologia Medica, Facoltà di Medicina e Chirurgia, Università Cattolica del Sacro Cuore, Rome, Italy

3 Departmental Unit of Clinical and Experimental Uro-Andrologic Oncology, Istituto Nazionale Tumori, IRCCS, Fondazione G. Pascale, Naples, Italy

4 Oncologia Medica, Azienda Ospedaliera Universitaria Integrata (AOUI), Verona, Italy

5 Oncology Unit, Department of Radiology, Oncology and Human Pathology, Sapienza University of Rome, Rome, Italy

6 Medical Oncology Unit 1, Department of Oncology, Istituto Oncologico Veneto IOV IRCCS, Padua, Italy

7 Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy

8 Department of Oncology, Hematology and Respiratory Diseases, University of Modena and Reggio Emilia, Modena, Italy

9 Oncologia Medica, Campus Bio-Medico University of Rome, Rome, Italy

10 Clinica Oncologica, Università Politecnica delle Marche, Azienda Ospedaliero-Universitaria Ospedali Riuniti Umberto I, Ancona, Italy

11 Oncologia Medica, Ospedale di Macerata, Via Santa Lucia 2, 62100 Macerata, Italy

12 S.C. Medical Oncology, Azienda Ospedaliera S. Maria, Terni, Italy

13 Dipartimento di Oncologia Medica, Ospedale Sant'Orsola-Malpighi, Bologna, Italy

14 Medical Oncology Unit, AUSL-IRCCS di Reggio Emilia, Reggio Emilia, Italy

15 Dipartimento di Scienze Orali e Mediche, Sezione di Oncologia, Università G. D'Annunzio, Chieti, Italy

16 Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, Milan, Italy

17 Unità Operativa di Oncologia Medica, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy

18 Oncologia Medica, San Martino Hospital, Belluno, Italy

19 Genitourinary Cancer Unit, Dipartimento di Oncologia Medica, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy