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Original Research

Efficacy and safety of nivolumab in bone metastases from renal cell carcinoma: Results of the GETUG-AFU26-NIVOREN multicentre phase II study

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Bone-targeting agent;
Immune checkpoint inhibitors;
Survival analyses;
Denosumab

Abstract ***Introduction:*** Bone metastases (BM) in renal cell carcinoma (RCC) are associated with a poor prognosis based on retrospective studies evaluating antiangiogenic agents. Few data are available regarding immune checkpoint inhibitors (ICI) in patients with bone metastatic RCC. NIVOREN is a multicentre prospective study in which patients were treated with nivolumab after the failure of antiangiogenic agents. We aim to assess the impact of BM on prognosis, and the efficacy and safety of nivolumab in patients enrolled in the NIVOREN trial.

Materials and methods: All patients with BM at inclusion were included in our study. The primary endpoint was overall survival (OS). Secondary endpoints were progression-free survival (PFS), objective response rate (ORR), safety, and skeletal-related events (SRE).

Results: Among 720 patients treated with nivolumab, 194 presented BM at inclusion. The median follow-up was 23.9 months. Median OS was 17.9 months in patients with BM versus 26.1 months in patients without BM ($p = 0.0023$). The difference was not statistically significant after adjustment ($p = 0.0707$). The median PFS was shorter in patients with BM even after adjustment (2.8 versus 4.6 months, $p = 0.0045$), as well as the ORR (14.8% versus 23.3%). SRE occurred for 36% of patients with BM. A post-hoc analysis evaluating the impact of bone-targeting agents (BTA) on SRE incidence showed a significant benefit of BTA on the incidence of SRE (OR = 0.367, CI95% [0.151–0.895]).

Conclusion: Nivolumab is associated with shorter PFS, and lower ORR in RCC patients with BM. Our study suggests that BTA in association with immunotherapy decreases the incidence of SRE.

1. Introduction

Bone metastases (BM) concern one-third of patients with metastatic clear cell renal cell carcinoma (ccRCCm) and are associated with shorter progression-free survival (PFS), overall survival (OS), and a higher morbidity [1–4]. However, those data were based on studies conducted before the approval of immune checkpoint inhibitors (ICI), which have revolutionised the prognosis of patients treated for a ccRCCm in recent years.

Nivolumab, an anti-programmed cell death 1,improved the OS in the CheckMate 025 study the compared to everolimus in second-line therapy after failure of one previous antiangiogenic tyrosine kinase inhibitors (TKI) [5]. Moreover, there is limited data available on the efficacy and safety with ICI in patients with BM (BM+). The subgroup analysis of CheckMate 025 study showed no benefit from nivolumab in terms of OS for patients BM+ [6].

Skeletal-related events (SRE) are defined by the occurrence of a pathological fracture, spinal cord compression, the need for bone surgery, or antalgic bone radiotherapy. SRE are a common complication of BM that occur in 70–85% of patients BM+ and are responsible of a quality of life deterioration and significant additional costs [7–9]. Few studies have focused on the use of bone-targeting agents (BTA) in patients with BM+ clear cell RCC (ccRCC). BTA demonstrated survival benefits and reduced SRE in several types of cancer [10–12]. In ccRCCm, available data concerning the use of BTA are based on retrospective studies conducted with antiangiogenic TKI and reported an increased risk of adverse event (AE), particularly osteonecrosis of the jaw (ONJ), without any benefit on OS [13,14]. However, the efficacy and safety profile of BTA in mRCC patients treated with immunotherapy remains unknown.

GETUG-AFU26-NIVOREN (NIVOREN) [15] is a large phase II French multicentre prospective study in which patients were treated with nivolumab after the failure of one or more antiangiogenic TKIs. The aim was to confirm the safety and efficacy of nivolumab in a 'real-life' population. In a post-hoc analysis, we aim to evaluate the impact of BM on prognosis, as well as the efficacy and safety of nivolumab in patients BM + included in NIVOREN.

2. Materials and methods

2.1. Patients.

All inclusion and exclusion criteria of the NIVOREN study are described in supplementary appendix 1.

All patients with BM at inclusion were included in the analyses. The diagnosis of BM was made on the baseline CT scan, and the BM were classified as target or non-target lesions according to RECIST criteria v1.1.

2.2. Treatment and evaluation

Patients received nivolumab (3 mg/kg every 2 weeks) until disease progression, unacceptable toxicity, death, or withdrawal consent. BM management (radiotherapy, surgery, interventional radiology (IR) procedures, etc.) was allowed according to routine practice. CT scan or MRI (thoracic, abdominal, and pelvic) were performed at baseline, every 8–12 weeks during the first year of treatment, and then every 12–15 weeks until disease progression or discontinuation. The radiological response was prospectively assessed according to RECIST version 1.1 criteria. Nivolumab could be continued if radiological progression is in case of clinical benefit. The safety profile of nivolumab was prospectively assessed using CTCAE version 4.0.

2.3. Endpoints

The primary endpoint was the OS of patients BM+. The secondary endpoints were as follows: PFS, objective response rate (ORR), safety, and SRE in patients BM+. The ORR was calculated based on RECIST criteria v1.1, using all site lesions. Hypercalcemia and IR procedures on bone were not considered as SRE but were collected.

2.4. Data collection

Clinical and biological patients' characteristics at inclusion were prospectively collected according to NIVOREN protocol, including SRE (defined by the occurrence of a pathological fracture, spinal cord compression, the need for bone surgery, or antalgic bone radiotherapy), IR procedures on bone, and hypercalcemia after inclusion. Only data on BM were collected retrospectively and included: bone disease characteristics before and at inclusion and in case of progression, SRE and IR on bone before enrolment in NIVOREN trial, bone pain.

2.5. Regulatory approvals

Our study was conducted in conformity with the Declaration of Helsinki. It was authorised by the competent national authority (Agence Nationale de Sécurité du Médicament et des Produits de Santé) and approved by a research ethics committee (**N°EudraCT:** 2015-004117-24). Because we performed a post-hoc analysis, the consent of patients that were still alive was required.

2.6. Statistical analysis

Patient characteristics were described as a number (percentage) for binary or categorical variables, and as median (interquartile range, IQR) or range (minimum–maximum) for continuous variables. All analyses were performed using SAS software version 9.4. OS was defined as the time in months between the date of initiation of treatment and the date of death or last news. Patients alive at the date of last news were censored. PFS was defined as the time (months) between the date of initiation of treatment and the date of the first event (progression or death from any cause).

Patients alive without an event were censored at the date of last news. The median follow-up time was estimated by the inverse Kaplan–Meier method, taking a 95% confidence interval (95%CI). Survival curves were estimated by the Kaplan–Meier method and were compared between the groups BM+ and without BM (BM-) using the LogRank test. The comparison of baseline characteristics, toxicity, and ORR observed with nivolumab was performed using the Chi-2 test. A post-hoc analysis was performed to assess the impact of BTA on the incidence of SRE using a logistic regression test. In the multivariate analysis, the risk of SRE was adjusted for sex, ECOG-PS at inclusion, and a history of SRE before inclusion. The alpha risk value in our analyses was equal to 5%.

3. Results

3.1. Patients' characteristics

Between 12 February 2016 and 27 July 2017, 729 patients from 27 centres in France were included in the NIVOREN study, and 720 received at least one dose of nivolumab. One hundred ninety-four patients (27% of the total population) had BM at inclusion in the NIVOREN study, and additional data collection specific to BM was performed for 171 patients (Fig. 1). Patients BM+ were more frequently associated with a poor International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognosis (31% versus 23%) than favourable prognosis (12% vs. 20%) ($p = 0.017$) and had more often an ECOG-PS > 1 ($p = 0.001$). Other baseline patient characteristics were similar (Table 1).

The characteristics of the bone lesions before and at inclusion are summarised in Table 2. BM were known at the metastatic diagnosis for 54% of patients. One-third of patients BM+ (64%, n = 109/171) experienced one or more SRE before inclusion: antalgic bone radiotherapy (n = 94, 55%), bone surgery (n = 44, 26%), pathological bone fracture (n = 27, 16%), and spinal cord compression (n = 10, 6%). In addition, 25 patients (15%) among patients BM + underwent a bone IR procedure before inclusion.

At inclusion, BM sites were spine (n = 101, 59%), pelvis (n = 88, 52%), rib (n = 53, 31%), long bone (n = 47, 28%), or another bone site (n = 31, 18%). Only 26% of patients (n = 42) had a single BM of whom two patients had no extraosseous metastases. Bone pain concerned 56% (n = 96/171) of patients BM + at inclusion. Only 25% of patients (n = 42/171) were treated with a BTA at baseline.

3.2. Efficacy

At the date of analyses (January 2019, 15th), 10.6% of patients were still receiving nivolumab: 15 (7.7%) patients BM+ and 60 (11.6%) patients BM-. The median duration of treatment was 4.6 months (0.5–31.3) and

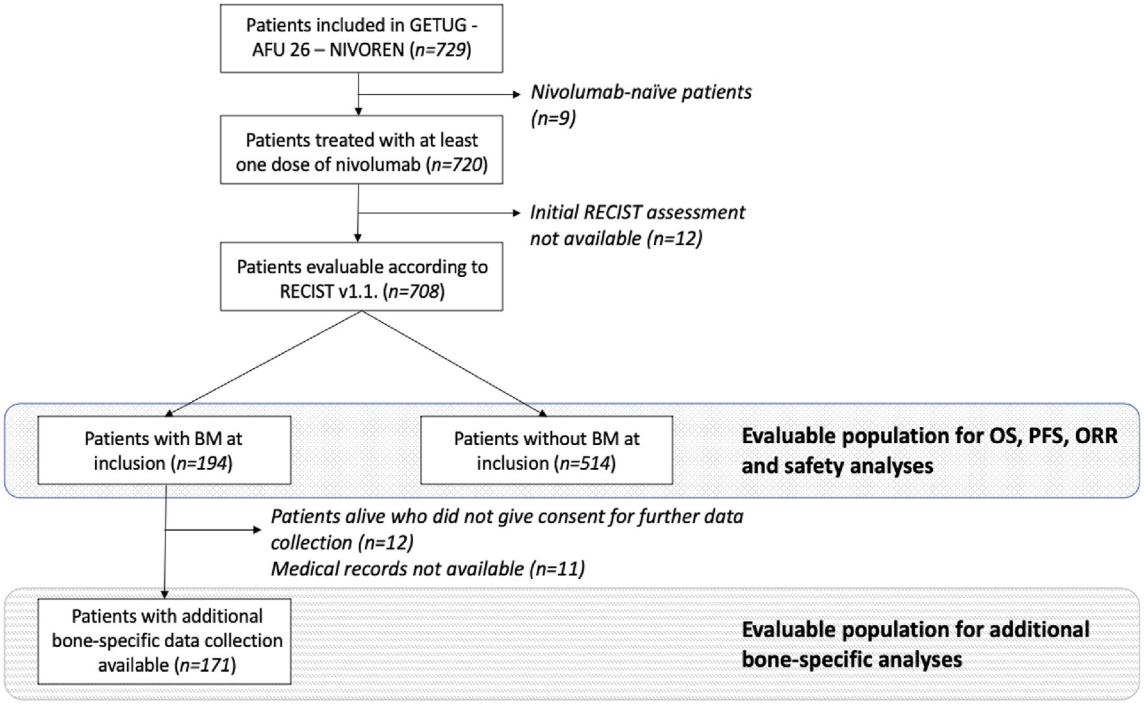

Fig. 1. Flowchart. Abbreviations: OS: overall survival; PFS: progression-free survival; ORR: objective response rate; RECIST: response evaluation criteria in solid tumours; BM: bone metastases.

Table 1
Baseline characteristics of the patients.

Variable	Patients without BM (BM-) N = 514	Patients with BM (BM+) N = 194
Median age, years (min; max)	64 (22; 90)	64 (33; 86)
Sex ratio, N (%)		
Female	110 (21%)	50 (26%)
Male	404 (79%)	144 (74%)
ECOG-PS, N (%)		
≤1	432 (89%)	140 (76%)
>1	55 (11%)	45 (24%)
IMDC score, N (%)		
Favourable	104 (20%)	24 (12%)
Intermediate	289 (56%)	110 (57%)
Poor	119 (23%)	60 (31%)
Number of previous lines		
1	262 (51%)	92 (47%)
2	143 (28%)	50 (26%)
3	63 (12%)	33 (17%)
≥4	46 (9%)	19 (10%)
Previous systemic treatments (all lines)		
Sunitinib	425 (83%)	165 (85%)
Axitinib	133 (26%)	60 (31%)
Pazopanib	122 (24%)	52 (27%)
Everolimus	101 (20%)	50 (26%)
Sorafenib	34 (7%)	11 (6%)
Bevacizumab	29 (6%)	10 (5%)
Cytokines (IFN, IL2)	21 (4%)	3 (2%)
Temsirolimus	15 (3%)	4 (2%)
Cabozantinib	3 (0.5%)	1 (0; 5%)
Other	20 (4%)	8 (4%)
History of nephrectomy	436 (85%)	163 (84%)
History of radiotherapy	143 (28%)	126 (65%)

Abbreviations: BM: bone metastases; IMDC: International Metastatic Renal Cell Carcinoma Database; ECOG-PS: Eastern Cooperative Oncology Group - Performance Status; min: minimum; max: maximum; IFN: interferon; IL2: interleukin 2.

Table 2
Characteristics of bone metastases at inclusion.

Variables	Patients, N (%) (n = 171)
Synchronous BM with the metastatic diagnosis	90 (54%)
BM sites at metastatic diagnosis	
Spine	43 (48%)
Pelvic bone	45 (50%)
Long bone	16 (18%)
Rib	16 (18%)
Other	11 (12%)
BM sites at inclusion in NIVOREN	
Spine	101 (61%)
Pelvic bone	88 (53%)
Long bone	47 (28%)
Rib	53 (32%)
Other	31 (19%)
Number of BM at inclusion in NIVOREN	
Single	42 (25%)
Multiple	121 (71%)
Bone pain at inclusion	
Yes	96 (60%)
No	65 (40%)
History of SRE	109 (67%)
History of interventional radiology procedures on bone	25 (17%)
Use of a bone-targeting agent at inclusion	
No	120 (74%)
Yes	42 (26%)
BTA used, N (%) (n = 42)	
Denosumab	31 (74%)
Bisphosphonates	11 (26%)

Abbreviation: BM: bone metastasis; SRE: skeletal-related event; BTA: bone-targeting agent.

5.6 months (0.5–32.7) in patients BM+ and BM-, respectively.

Regarding OS, 344/708 patients died. The median follow-up time calculated by the reverse Kaplan–Meier method was 23.9 months (95% CI [23.3–24.7]). OS was 17.9 months (95% CI [14.4–24.6]) and 26.1 months (95% CI [23.0–30.3]) in patients BM+ and BM-, respectively (hazard ratio, HR = 1.42 95% CI [1.13–1.79]; $p = 0.0023$) (Fig. 2). In a multivariate Cox model available for 706 patients (adjusted on gender, age, IMDC prognostic score, and number of prior lines), OS difference between patients BM+ and BM-was not statistically different (HR = 1.24 CI95% [0.98–1.56]; p = 0.0707) (Table 3).

Regarding PFS, 592/708 patients experienced an event « death » or « progression ». PFS were 2.8 months (95% CI [2.6–3.0]) and 4.6 months (95% CI [3.1–5.1]) for patients BM+ and BM-, respectively (HR = 1.39, 95% CI [1.16–1.66], $p = 0.0003$) (Fig. 2). In a multivariate Cox model of 706 patients (adjusted on gender, age, IMDC prognostic score, and number of prior lines), the existence BM at inclusion remained a factor significantly associated with a shorter PFS (HR = 1.30, 95% CI [1.08–1.56]; $p = 0.0045$) (Table 3). O6RR was significantly lower in patients BM+ (14.8%) than BM- (23.3%) ($p = 0.014$). One patient BM+ (0.5%) experienced a complete response versus eight patients BM- (1.6%) (Table 4). Radiological bone progression on nivolumab was observed in 67.5% of patients (n = 104/171). Sites of bone progression were the spine for 63% of patients, pelvis for 47% of patients, and peripheral skeleton for 20.5% of patients. Half of the patients (n = 50/104) had a dissociated response, i.e. the radiological bone progression occurred while the extraosseous disease was controlled (SD) or in response (PR).

A decrease in bone pain with nivolumab was observed in 15.5% of patients BM+, whereas 53% of patients BM + reported worsening of pain with nivolumab.

3.3. Safety

Nivolumab exposure duration was 4.6 months (0.5–31.3) and 5.6 months (0.5–32.7) in patients BM+ and BM-, respectively. The toxicity profile did not show unexpected toxicity and was similar between the two groups (Table 5). Nivolumab had to be discontinued because of toxicity in 54 (10.5%) patients BM- and in 10

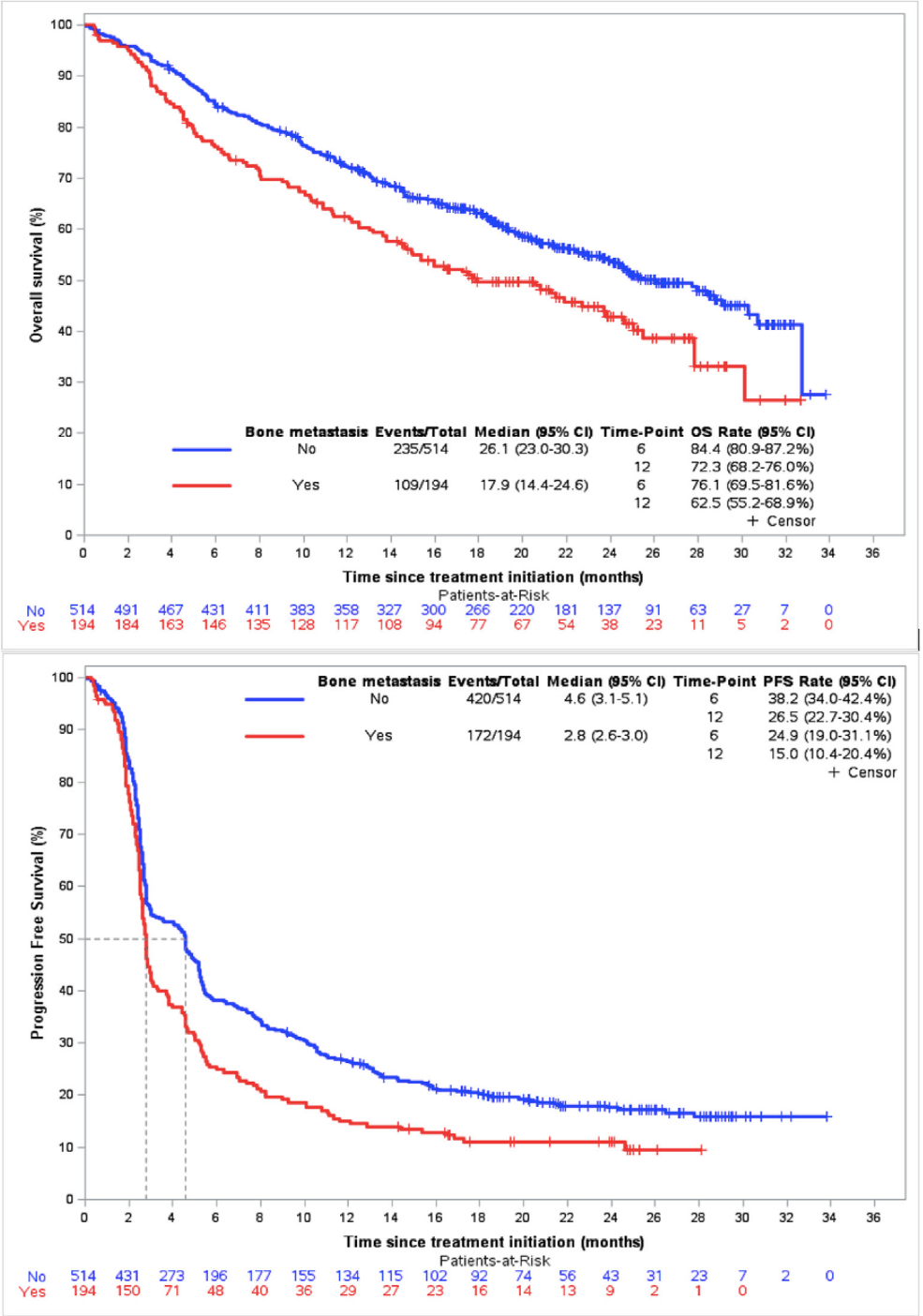

Fig. 2. Overall survival and progression-free survival.

(5.2%) patients BM+. Two patients BM- died from nivolumab-related AE versus no patients BM+.

3.4. Bone-related events

Bone-related events (SRE and IR) during nivolumab treatment period were collected retrospectively for 171 patients BM+. During the treatment period, 59/171 patients (36%) had one or more SRE: antalgic bone radiotherapy (n = 41, 24.0%), symptomatic bone fracture (n = 23, 14%), spinal cord compression (n = 18, 11%), and bone surgery (n = 19, 11%). Two-thirds (62%, n = 37/59) of patients who experienced SRE on nivolumab had a history of prior SRE before inclusion. In addition, 17 patients (10%) also underwent IR on bone (cryotherapy n = 6, vertebroplasty n = 7, tumour embolisation n = 5, radiofrequency n = 1; one patient had been treated with radiofrequency followed by

Table 3
Multivariate Cox model of overall survival and progression-free survival according to bone metastases (n = 706).

Multivariate Cox model of OS Variable	Events/N	Hazard ratio (95% CI)	P-value
Bone metastase			0.0707
No	234/512	1	
Yes	109/194	1.24 (0.98-1.56)	
Gender			0.4497
Male	268/547	1	
Female	75/159	0.91 (0.70-1.17)	
Age, yo			0.0014
<70	231/504	1	
>/ = 70	112/202	1.45 (1.16-1.82)	
IMDC			<0.0001
Good	36/128	1	
Intermediate	186/399	1.98 (1.38-2.83)	
Poor	121/179	4.15 (2.84-6.05)	
Number of previous lines >2			0.7175
No	255/545	1	
Yes	88/161	1.05 (0.82-1.34)	
Multivariate Cox model of PFS Variable	Events/N	Hazard ratio (95% CI)	P-value
Bone metastase			0.0045
No	419/512	1	
Yes	172/194	1.30 (1.08-1.56)	
Gender			0.1445
Male	451/547	1	
Female	140/159	1.15 (0.95-1.39)	
Age, yo			0.8540
<70	422/504	1	
>/ = 70	169/202	0.98 (0.82-1.18)	
IMDC			0.0008
Good	100/128	1	
Intermediate	333/399	1.28 (1.02-1.60)	
Poor	158/179	1.63 (1.26-2.10)	
Number of previous lines >2			0.6163
No	446/545	1	
Yes	145/161	1.05 (0.87-1.27)	

Abbreviations: OS: overall survival; PFS: progression-free survival; yo: years old; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium.

Table 4
Objective response rate and best response (all sites).

	Bone metastases at inclusion		Patients n = 708	Test (Chi-2)
	No n = 514	Yes n = 194		
Objective response rate (686[a])	116/497 (23.3%) [19.7%; 27.3%]	28/189 (14.8%) [10.1%; 20.7%]	144/686 (21%) [18.0%; 24.2%]	$p = 0.014$
Best response				
Missing data[b]	13	3	16	
No evaluable[b]	4	2	6	
Complete response	8 (1.5%)	1 (0.5%)	9 (1.5%)	
Partial response	108 (22%)	27 (14.5%)	135 (19.5%)	
Stability	157 (31.5%)	57 (30%)	214 (31%)	
Progression	224 (45%)	104 (55%)	328 (48%)	

[a] Number of patients for whom objective response rate calculation is possible.
[b] Deaths related to cancer or disease progression and occurring before the first tumour assessment (two months) are classified as no objective response and progression for best response. Deaths without reason for death are classified as NE (not evaluable). Patients with clinical progression occurring before the first tumour assessment are classified as no objective response and progression for best response.

Table 5
Common nivolumab-related adverse events of any grade.

	Bone metastases at inclusion		Patients n = 708
	No (n = 518)	Yes (n = 194)	
Anaemia	13 (2.5%)	10 (5.2%)	23 (3.2%)
Lymphopenia	6 (1.2%)	6 (3.1%)	12 (1.7%)
Hypothyroidism	19 (3.7%)	6 (3.1%)	25 (3.5%)
Dry eye syndrome	7 (1.4%)	1 (0.5%)	8 (1.1%)
Abdominal pain	7 (1.4%)	3 (1.5%)	10 (1.4%)
Diarrhoea	61 (11.9%)	12 (6.2%)	73 (10.3%)
Constipation	14 (2.7%)	9 (4.6%)	23 (3.2%)
Nausea	26 (5.1%)	9 (4.6%)	35 (4.9%)
Vomiting	14 (2.7%)	2 (1.0%)	16 (2.3%)
Fatigue	134 (26.1%)	47 (24.2%)	181 (25.6%)
Skin dryness	30 (5.8%)	3 (1.5%)	33 (4.7%)
Pruritus	48 (9.3%)	12 (6.2%)	60 (8.5%)
Skin rash	38 (7.4%)	4 (2.1%)	42 (5.9%)
Cytolysis	8 (1.6%)	3 (1.5%)	11 (1.6%)
Loss of appetite	26 (5.1%)	9 (4.6%)	35 (4.9%)
Arthralgia	39 (7.6%)	10 (5.2%)	49 (6.9%)
Myalgia	23 (4.5%)	7 (3.6%)	30 (4.2%)
Dyspnoea	18 (3.5%)	6 (3.1%)	24 (3.4%)

vertebroplasty and another patient had been treated with cryotherapy followed by vertebroplasty). Characteristics at inclusion were similar in both groups of patients with and without SRE, except for the gender (p = 0.027) and ECOG-PS (p = 0.039) (Table 6). Bone events (SRE or IR procedure on bone, n = 75 patients) were related to bone tumour progression in 71% of cases (n = 53 patients). Early bone events (<15 days after nivolumab initiation) were not considered in this study to be related to bone tumour progression under nivolumab and involved 22 (13%) patients BM+. The development of hypercalcemia was reported in 25/171 patients (16%).

3.5. Bone-targeting agent

BTA were used at baseline for 25% of patients (n = 42/171) and introduced during nivolumab treatment for 11% of patients (n = 17/171). An additional analysis was performed to investigate the impact of the use of BTA at baseline on SRE occurrence in patients BM+. Data about SRE incidence during nivolumab period was missing for eight patients. In a multivariate model adjusted for gender, ECOG-PS, and history of SRE before inclusion, patients receiving a BTA at inclusion had a 64% reduction in the risk of having SRE with nivolumab compared with patients who were not treated with BTA at inclusion (OR = 0.367, p-value = 0.028) (Table 6). No ONJ or hypocalcaemia was observed in patients treated with BTA in association with nivolumab.

4. Discussion

To our knowledge, this is the largest prospective study evaluating efficacy and safety of nivolumab in patient with ccCCRm BM+. In our study, BM had a negative prognostic value: OS tended to be shorter (17.9 vs. 26.1 months, NS), and PFS was statistically shorter (2.8 vs. 4.6 months, p = 0.045). One hypothesis to explain the absence of statistically different in terms of OS is the short follow-up. However, these results are consistent with previous studies evaluating antiangiogenic agents [16–18]. Santoni *et al.* compared in a retrospective study nivolumab and cabozantinib in second line after antiangiogenic TKI and found no benefit of nivolumab regarding OS for the group of patients BM+. Regarding efficacy, our results suggest that nivolumab might be less effective in patients BM+. Indeed, the ORR was statistically lower (14.8% vs 23.3%; p = 0.014), and half of the patients with painful BM experienced worsening of pain under nivolumab. The safety profile of nivolumab was comparable between patients BM+ and BM-.

Our study is the first to assess SRE and the use of BTA in patients with ccCCRm BM + treated with ICI. The rate of SRE during nivolumab period was frequent (36%). In METEOR study, the rate of SRE with

Table 6
Logistic regression modelling of the probability of having a symptomatic bone event.

	Univariate model (N = 163)			Multivariate model (N = 146)		
	Without SRE/with SRE	OR IC95%	*p*-value	Without SRE/with SRE	OR IC95%	*p*-value
Use of bone-targeting agent at inclusion						
No	68/47	1		63/45	1	
Yes	32/10	0.452 [0.203; 1.008]	0.0522	29/9	0.367 [0.151; 0.895]	0.0276
Gender						
Male	85/39	1		74/37	1	
Female	19/20	2.294 [1.102; 4.777]	0.0265	18/17	2.124 [0.945; 4.774]	0.0684
ECOG-PS						
0/1	66/48	1		62/45	1	
2/3	32/10	0.43 [0.193; 0.958]	0.0389	30/9	0.375 [0.157; 0.896]	0.0273
SRE before inclusion						
No	32/20	1		29/18	1	
Yes	69/37	0.858 [0.432; 1.705]	0.662	63/36	1.062 [0.494; 2.28]	0.878

SRE: skeletal-related events; OR: odds ratio; IC95%: 95% confidence interval; ECOG-PS: Eastern Cooperative Oncology Group - Performance Status.

cabozantinib was only 23% [19]. However, all patients enrolled received cabozantinib as second line, whereas half of the patients had more than two treatment lines before enrolment in NIVOREN. In our study, only 25% of patients BM + received BTA, but this low rate is found in previous studies [20]. Indeed, the benefit of BTA in ccCCRm is debated. In a post-hoc analysis of pooled studies involving 285 patients, Mckay *et al.* found no benefit of BTA on OS, PFS, or SRE rate reduction and reported an increased rate of ONJ with concomitant administration of anti-angiogenic agents [14,20]. We observed, in our study, a benefit from using BTA on the incidence of SRE, without increasing the rate of ONJ or hypocalcaemia. Our findings may be explained by the predominant use of denosumab in our study, which showed its superiority compared to zoledronic acid in other tumour locations [21]. Three-quarters of the patients treated with BTA, in our study, had denosumab compared to none in the study of McKay. Furthermore, patients receiving BTA in the previous study were mostly treated with antiangiogenic agents. The combination of antiangiogenic agents probably increases the observed toxicity of bisphosphonate and especially of ONJ [13,14]. Based on our results, we believe that BTA should be used in patients with ccCCRm treated with immunotherapy. However, prospective studies are needed to confirm our findings, especially regarding the use of denosumab in ccRCCm BM + treated with ICI.

The main strength of our study is the quality of our data, mainly collected prospectively in a large multicentric phase 2 study. The additional collection was done for descriptive data of BM and therefore did not bias our survival statistical analyses. Regarding BTA, missing data may have reduced the statistical power of the analysis on their impact on the SRE rate. Our population was representative of the target population (27% of patients with BM) [6,7,19] and included all-comers patients. These results are easily applicable to the real-life patient population.

Limitations of our study are the absence of centralised review and the use of RECIST v1.1 criteria for radiological assessment, which are not adapted to evaluate tumour response with ICI [22] or for bone evaluation. Indeed, bone lesions are rarely target lesions [23,24]. Although we provide a detailed description of patients BM + treated with ICI, further prospective studies are needed to provide more information on the management strategy for these patients and on the evaluation of focal treatments that concerned many patients in our study.

5. Conclusion

Our study confirms that patients BM + treated with nivolumab in the second or subsequent line after antiangiogenic therapy for ccCCRm have a poorer prognosis, with a statistically shorter PFS and lower ORR. The association of BTA with ICI may decrease the incidence of SRE without increasing the risk of ONJ.

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Cécile Dalban: formal analysis, software, writing - review & editing.
Christine Chevreau: data curation, writing - review & editing.
Gwenaelle Gravis: data curation, writing - review & editing.
Sylvie Negrier: data curation, writing - review & editing.
Brigitte Laguerre: data curation, writing - review & editing.
Marine Gross-Goupil: data curation, writing - review & editing.
Sylvain Ladoire: data curation, writing - review & editing.
Delphine Borchiellini: data curation, writing - review & editing.
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Stephane Oudard: writing - review & editing, supervision.
Florence Tantot: supervision, methodology.
Bernard Escudier: writing - review & editing.
Sylvie Chabaud: formal analysis, software writing - review & editing.
Laurence Albiges*: conceptualisation, methodology, writing - review & editing, supervision, investigation, writing - review & editing.

1Constance Thibault* (corresponding author): conceptualisation, methodology, writing - review & editing, supervision, investigation, writing - review & editing.
*Laurence Albiges and Constance Thibault contributed equally.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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