original report

# Safety and Efficacy of Nivolumab in Brain Metastases From Renal Cell Carcinoma: Results of the GETUG-AFU 26 NIVOREN Multicenter Phase II Study

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abstract

**PURPOSE** Nivolumab is standard of care for patients with metastatic clear cell renal cell carcinoma (ccRCC) after failure of antiangiogenic therapies, but its activity on brain metastases from ccRCC remains unknown, because these patients were excluded from pivotal studies. We aimed to assess the activity of nivolumab in this population.

**METHODS** The GETUG-AFU 26 NIVOREN phase II trial assessed the activity and safety of nivolumab in patients with metastatic ccRCC who failed vascular endothelial growth factor–directed therapies (ClinicalTrials.gov identifier: NCT03013335). Patients with asymptomatic brain metastases were prospectively identified and underwent dedicated brain evaluation. Two cohorts were constituted: cohort A comprised patients with previously untreated brain metastases, and cohort B comprised patients whose brain metastases underwent prior therapy. The primary end point was intracranial response rate in cohort A.

**RESULTS** Seventy-three patients with brain metastases were included: 39 in cohort A and 34 in cohort B. Intracranial response rate was 12% in cohort A; no objective response was reported in patients with brain lesions that were multiple or larger than 1 cm. Median intracranial progression-free survival was 2.7 months (95% CI, 2.3 to 4.6 months) in cohort A and 4.8 months (95% CI, 3.0 to 8.0 months) in cohort B, with adjusted hazard ratio of 2.04 (95% CI, 1.08 to 3.83). Overall survival rate at 12 months was 67% (95% CI, 49.6% to 79.1%) in cohort A and 59% (95% CI, 40.6% to 73.2%) in cohort B. Most patients in cohort A (72%) needed subsequent focal brain therapy. Nivolumab was well tolerated, with no unexpected toxicity.

**CONCLUSION** Nivolumab activity is limited in patients with untreated brain metastases from ccRCC. Brain imaging and focal therapy should be considered before immune checkpoint inhibitors in patients with metastatic ccRCC.

J Clin Oncol 37:2008-2016. 

ASSOCIATED CONTENT

See accompanying Editorial on page 1987

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on March 22, 2019 and published at jco.org on June 13, 2019: DOI https://doi.org/10.1200/JCO.18.02218

Clinical trial information: NCT03013335.

Bristol-Myers Squibb had no role in study design, data collection, analysis, and manuscript elaboration.

## INTRODUCTION

Brain metastases occur in approximately 10% of patients with metastatic clear cell renal cell carcinoma (ccRCC)[1-3] and are associated with dismal prognosis. In the era of targeted therapies and stereotactic radiation therapy, median overall survival (OS) rarely exceeded 12 months.[4] The only phase II trial prospectively evaluating intracranial response to sunitinib, standard of care for more than a decade in the first-line setting, did not report any response among 16 patients.[5]

Since then, the therapeutic landscape of ccRCC changed, with the dawn of immune checkpoint inhibitors. The anti-programmed cell death-1 (PD-1) nivolumab first demonstrated improved survival compared with everolimus in patients whose disease progressed after vascular endothelial growth factor (VEGFR)–targeted therapies.[6] However, the safety and activity of immune checkpoint inhibitors have not been reported in patients with metastatic ccRCC and brain metastases, because they have been excluded from pivotal trials.

We sought to assess the safety and efficacy of nivolumab in patients with ccRCC disseminated to the brain. The GETUG-AFU 26 NIVOREN phase II trial evaluated the safety and efficacy of nivolumab in

patients with metastatic ccRCC who experienced disease progression after VEGFR-directed therapies. Patients with asymptomatic brain metastases were prospectively identified and underwent dedicated brain evaluation within two non-randomly assigned cohorts: patients with brain metastases without previous focal brain therapy and patients with brain metastases who received previous focal treatment.

## METHODS

### Study Design and Patients

Adult patients with histology-proven stage IV ccRCC metastatic to the brain whose disease progressed after VEGFR-directed therapy were eligible. All patients had an Eastern Cooperative Oncology Group performance status of 2 or greater and at least one measurable brain lesion 5 mm or larger. Brain metastases should be asymptomatic and not require symptomatic treatments, including corticosteroids, surgery, or radiation therapy. Patients should not have received prior immune checkpoint inhibitors and should not have a history of autoimmune disease. The full list of inclusion and exclusion criteria is provided in the Appendix (online only).

Patients with measurable brain metastases that have not been focally treated by surgery or radiation therapy constituted cohort A, and patients whose measurable brain metastases were previously focally treated constituted cohort B. Of note, previous focal therapy by stereotactic radiation therapy or surgery was allowed in patients from cohort A provided untreated brain metastases were present at baseline. Patients should not have received any focal treatment or systemic corticosteroids within 2 weeks of cycle 1 day 1.

The study was conducted by UNICANCER, the French National Comprehensive Cancer Centers network. This study was approved by the human research ethics committee of UNICANCER and conducted in accordance with the International Conference on Harmonization and the Declaration of Helsinki.

### Procedures

All patients received intravenous nivolumab 3 mg/kg every 2 weeks until disease progression, unacceptable toxicity, death, consent withdrawal, or at the initiative of the investigator (Data Supplement). No dose reductions were allowed. Guidelines for dose delays and discontinuation are reported in the Appendix. Treatment beyond disease progression was allowed in a context of clinical benefit.

Assessment of intracranial response was performed every 12 to 15 weeks with modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 that allowed evaluation of target lesions 5 mm or larger,[7] using contrast-enhanced magnetic resonance imaging or computed tomography scan with millimetric slides. In the event of previous focal brain therapy for patients included in cohort A, only untreated brain metastases were considered target lesions. Intracranial response had to be confirmed at subsequent evaluation and no less than 4 weeks after first documented response. Brain imaging could be anticipated if clinically indicated.

Assessment of extracranial response was performed every 8 to 12 weeks during the first year, then every 12 to 15 weeks using RECIST 1.1, using computed tomography scans. Safety was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 at each consultation.

### Outcomes

The primary end point of this analysis was best intracranial response in cohort A, defined as the percentage of patients with confirmed intracranial partial or complete response. The secondary end points were extracranial response; intracranial, extracranial, and global progression-free survival (PFS); OS; CNS-specific end points including occurrence of any symptom related to brain metastases, corticoid use, or recourse to focal brain therapy; and treatment-related adverse events.

Intracranial and extracranial PFS were defined as the time between treatment initiation and date of first progression according to respective intracranial and extracranial assessments or death. Global PFS was calculated from treatment initiation to first intracranial or extracranial progression or death. For extracranial PFS, patients who were event free at the time of the analysis were censored at the time of the last tumor assessment. When considering intracranial end points, patients who were event free at the time of the analysis were censored to last tumor assessment or to date of focal brain therapy, whichever occurred first. OS was defined as the time between treatment initiation and death or date of final contact for patients alive.

### Statistical Analysis

The GETUG-AFU 26 NIVOREN trial was planned to enroll 735 patients, on the basis of a one-stage Fleming design to ensure a rate of grade 3 or 4 adverse events less than 24%, accepting a maximum toxicity increase of 5% in real-world patients treated with nivolumab for refractory metastatic ccRCCs,[6] with a one-sided 5% type I error and 95% power. We report here the results of the population with brain metastases present at inclusion. Planned analysis for the GETUG-AFU 26 NIVOREN Brain Metastases study was performed according to the dedicated end points mentioned previously.

Descriptive statistics were used to describe our population. Qualitative data are reported by frequency and proportion, quantitative data by median and range. Best objective response rate is reported using frequency and proportion, with assessment of the 95% CI. Median follow-up is calculated using the reverse Kaplan-Meier method and

presented associated with its 95% CI. PFS and OS were estimated using the Kaplan-Meier method and were described in terms of median or specific time point estimation in each subgroup, along with the associated two-sided 95% CI for the estimates. A multivariate cox regression model was used to estimate the hazard ratio and 95% CI for intracranial PFS between cohort A and B, adjusted for the following baseline characteristics: International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk groups, tumor grade, number of brain metastases, Eastern Cooperative Oncology Group performance status, and number of previous systemic therapies. Analyses were done in patients who received at least one dose of nivolumab. All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC).

## RESULTS

### Patients

In the GETUG-AFU 26 NIVOREN phase II trial, 729 patients were enrolled across 27 institutions between February 12, 2016 and July 27, 2017. Among these, 76 patients (10.4%) had brain metastases at baseline. Three patients did not receive nivolumab because of rapid alteration of their performance status. Overall, 39 patients in cohort A and 34 in cohort B were included in the final analysis (Fig 1).

Baseline characteristics of the patients were similar in both cohorts, including IMDC risk classification, tumor grade, and number of previous systemic therapies (Table 1). Patients usually had aggressive disease at diagnosis, with

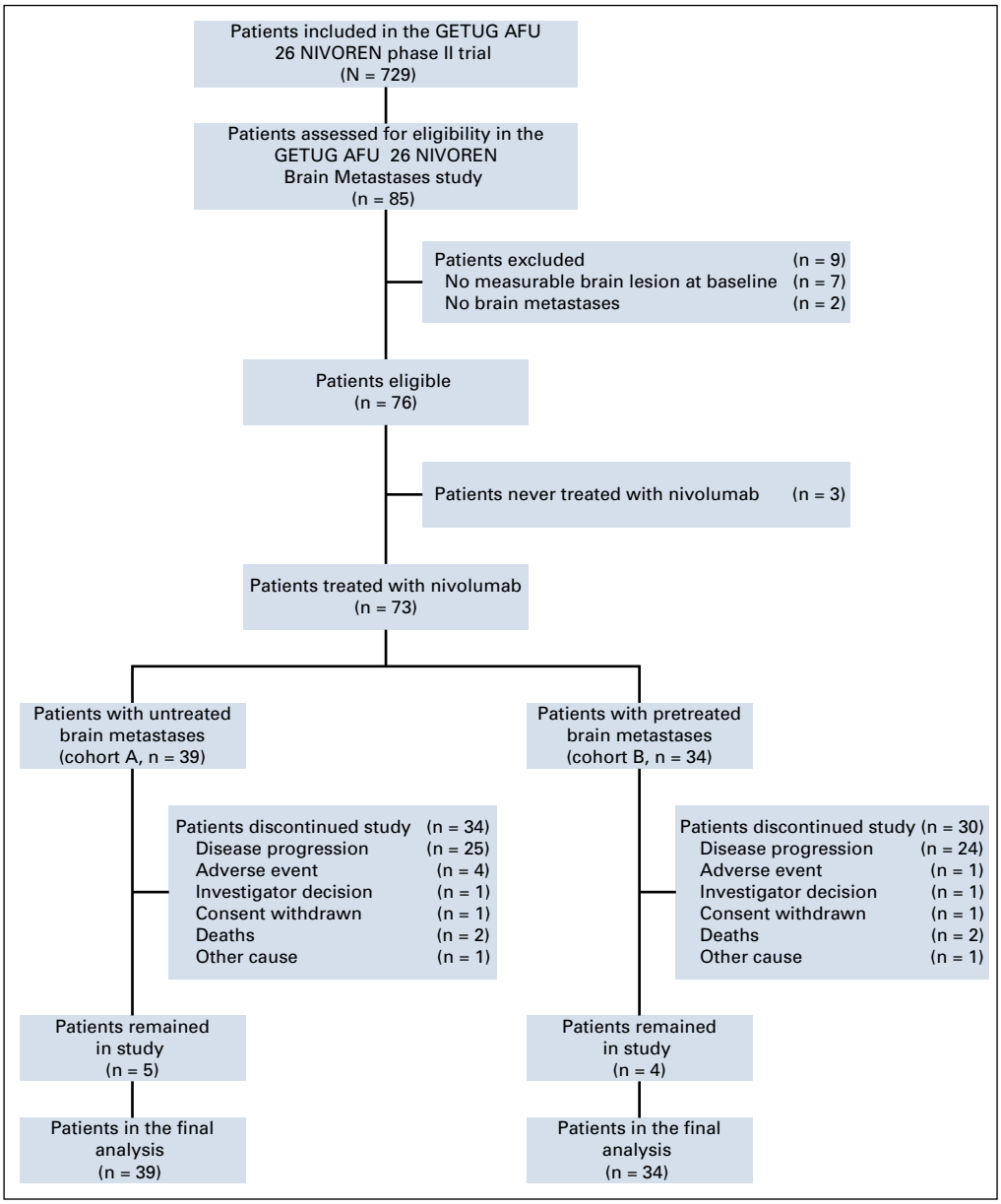


**FIG 1.** Study flowchart.

**TABLE 1.** Baseline Characteristics of the Patients

| Baseline Characteristic | Cohort A: Patients With Untreated Brain Metastases (n = 39) | Cohort B: Patients With Pretreated Brain Metastases (n = 34) |
|---|---|---|
| Sex | | |
| Men | 35 (90) | 29 (85) |
| Women | 4 (10) | 5 (15) |
| Median age, years (min; max) | 61 (39; 77) | 58 (33; 78) |
| ECOG performance status | | |
| 0 | 10 (27) | 3 (9) |
| 1 | 23 (62) | 24 (73) |
| 2 | 4 (11) | 6 (18) |
| IMDC risk groups* | | |
| Favorable | 9 (24) | 6 (18) |
| Intermediate | 16 (42) | 17 (50) |
| Poor | 13 (34) | 11 (32) |
| Tumor grade | | |
| ≤ 2 | 13 (36) | 7 (22) |
| 3-4 | 23 (64) | 25 (78) |
| No. of previous systemic therapies | | |
| 1 | 15 (39) | 17 (50) |
| 2 | 12 (31) | 9 (27) |
| ≥ 3 | 12 (31) | 8 (24) |
| No. of brain metastases | | |
| 1 | 26 (67) | 20 (59) |
| 2-3 | 9 (23) | 8 (24) |
| > 3 | 4 (10) | 6 (18) |
| Median sum of diameters of brain target lesions, mm (min; max) | 11 (5; 29) | 17 (5; 43) |
| Previous brain radiation therapy† | | |
| Stereotactic | 5 (13)† | 29 (85) |
| Whole brain | 0 (0) | 4 (12) |
| Stereotactic plus whole brain | 0 (0) | 1 (3) |

Data given as No. (%) unless otherwise noted.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IMDC, international metastatic renal cell carcinoma database.

*IMDC risk groups are segregated according to the presence of 0 (favorable), 1 or 2 (intermediate), or 3 (poor) of the following risk factors: Karnofsky performance status score of less than 80%, time from initial diagnosis to treatment of less than 1 year, hemoglobin level below the lower limit of the normal range, corrected serum calcium level above the upper limit of the normal range, absolute neutrophil count above the upper limit of the normal range, and platelet count above the upper limit of the normal range.

†Five patients from cohort A received stereotactic brain radiation therapy on nontarget lesions. All five patients presented with untreated target lesions at baseline.

64% and 78% of grade 3 or 4 tumors in cohort A and B, respectively. The respective proportion of patients in the good-, intermediate-, and poor-risk IMDC subgroups was 24%, 42%, and 34% in cohort A and 18%, 50%, and 32% in cohort B. Nivolumab was given in the third-line setting or later in 62% of patients from cohort A and 50% of patients from cohort B. Intracranial disease consisted of unique lesions for 67% of patients in cohort A and 59% in cohort B. The median sum of diameters of target lesions in the brain was 11 mm in cohort A and 17 mm in cohort B. Patients in cohort B had received mostly stereotactic radiation therapy (88%) as previous focal treatment. Five patients with untreated brain metastases at baseline had prior stereotactic radiation therapy for another brain lesion.

Median follow-up was 23.6 months (95% CI, 18.1 to 24.6 months) in cohort A and 20.2 months (95% CI, 16.3 to 22.9 months) in cohort B at data cutoff on September 17, 2018. Median duration of treatment was 4.9 months (range, 0.5 to 24.2 months) in cohort A and 4.5 months (range, 0.5 to

22.3 months) in cohort B. Nine patients were still receiving treatment at data cutoff, including five (12.8%) in cohort A and four (11.8%) in cohort B (Fig 1).

### Intracranial Response to Nivolumab in Patients With Untreated Brain Metastases

Intracranial response has been assessed in 34 patients in cohort A. Five patients could not be evaluated because of rapid clinical progression and death before first evaluation. Objective intracranial response was reported in four out of 34 patients (12%; Table 2; Fig 2A; Appendix Table A1, online only). Seventeen patients (50%) experienced intracranial progressive disease as best response, and 13 (38%) had stable intracranial disease at 8 weeks or later as best response. Noteworthy, all four patients who demonstrated intracranial response had a unique lesion with a longest diameter less than 10 mm at baseline (Appendix Fig A1, online only). These four patients exhibited confirmed complete response, with a median duration of response of 7.2 months (95% CI, 3.2 months to not estimable). Two of them had an ongoing intracranial response at the last evaluation, including one treated beyond brain progression who exhibited subsequent intracranial response (Fig 2B). Progressive intracranial disease as best response was reported in 73% of patients with multiple target lesions versus 39% of patients with unique lesions.

### Comparison of Intracranial and Extracranial Response in Patients With Untreated Brain Metastases

Extracranial response was observed in 21% of patients in cohort A (Table 2; Appendix Fig A2, online only). Six patients out of 34 (18%) with intracranial evaluation had discordant responses between brain and body assessments, including three who had extracranial response but intracranial stable or progressive disease (Appendix Fig A3, online only). However, all four patients who had intracranial response also had extracranial response (Appendix Table A2, online only).

### Intracranial PFS

At data cutoff, 30 of 39 patients (77%) experienced intracranial progression in cohort A including 14 of 30 (47%) with new brain metastases, compared with 26 of 34 (77%) in cohort B, including nine of 26 (35%) with new brain metastases. Median intracranial PFS was 2.7 months (95% CI, 2.3 to 4.6 months) in cohort A and 4.8 months (95% CI, 3.0 to 8.0) in cohort B (Fig 3A). The 6-month intracranial PFS rate was 23.8% (95% CI, 11.1% to 39.2%) and 49.4% (95% CI, 31.7% to 64.8%) in cohorts A and B, respectively. After adjustment for baseline characteristics, prior focal brain therapy (cohort B) decreased the risk of intracranial progression (hazard ratio, 0.49; 95% CI, 0.26 to 0.92; Appendix Table A3, online only).

### Extracranial PFS, Global PFS, OS

Median extracranial PFS was 2.8 months (95% CI, 2.2 to 4.6 months) in cohort A and 2.6 months (95% CI, 2.3 to 4.0 months) in cohort B (Fig 3B). Median global PFS was 2.4 months (95% CI, 2.0 to 4.2 months) in cohort A and 2.5 months (95% CI, 1.9 to 2.8 months) in cohort B. The 12-month OS rate was 66.7% (95% CI, 49.6% to 79.1%) and 58.8% (95% CI, 40.6% to 73.2%) in cohorts A and B, respectively (Fig 3C).

### CNS-Specific End Points

Occurrence of any symptom related to the brain metastases occurred in 19 of 39 patients (49%) in cohort A, and in 11 of 34 patients (32%) in cohort B (Appendix Table A4, online only). These symptoms were attributed to disease progression in the brain for 18 patients in cohort A (46%) and eight in cohort B (24%). Among patients who experienced symptoms unrelated to disease progression, one patient had brain hemorrhage in cohort A and two had edema attributed to radionecrosis after previous radiation therapy in cohort B. More than half of the patients (51%) in cohort A needed corticosteroids because of brain metastases, compared with 27% in cohort B. A total of 28 of 39 patients

**TABLE 2.** Activity of Nivolumab in Patients With Untreated Brain Metastases (Cohort A)

| | Cohort A: Patients With Untreated Brain Metastases (n = 39) | |
|---|---|---|
| **Activity** | **Intracranial** | **Extracranial** |
| Best response, No. (%) | | |
| Complete response | 4 (12) | 0 (0) |
| Partial response | 0 (0) | 7 (21) |
| Stable disease | 13 (38) | 10 (30) |
| Progressive disease | 17 (50) | 16 (49) |
| Missing | 5 | 6 |
| Overall response rate, % (95% CI) | 11.8 (3.3 to 27.5) | 21.2 (9.0 to 38.9) |
| Median PFS, months (95% CI) | 2.7 (2.3 to 4.6) | 2.8 (2.2 to 4.6) |
| 6-month PFS rate, % (95% CI) | 23.8 (11.1 to 39.2) | 27.8 (14.8 to 42.3) |
| 12-month overall survival rate (95% CI) | 66.7 (49.6 to 79.1) | |

Abbreviation: PFS, progression-free survival.

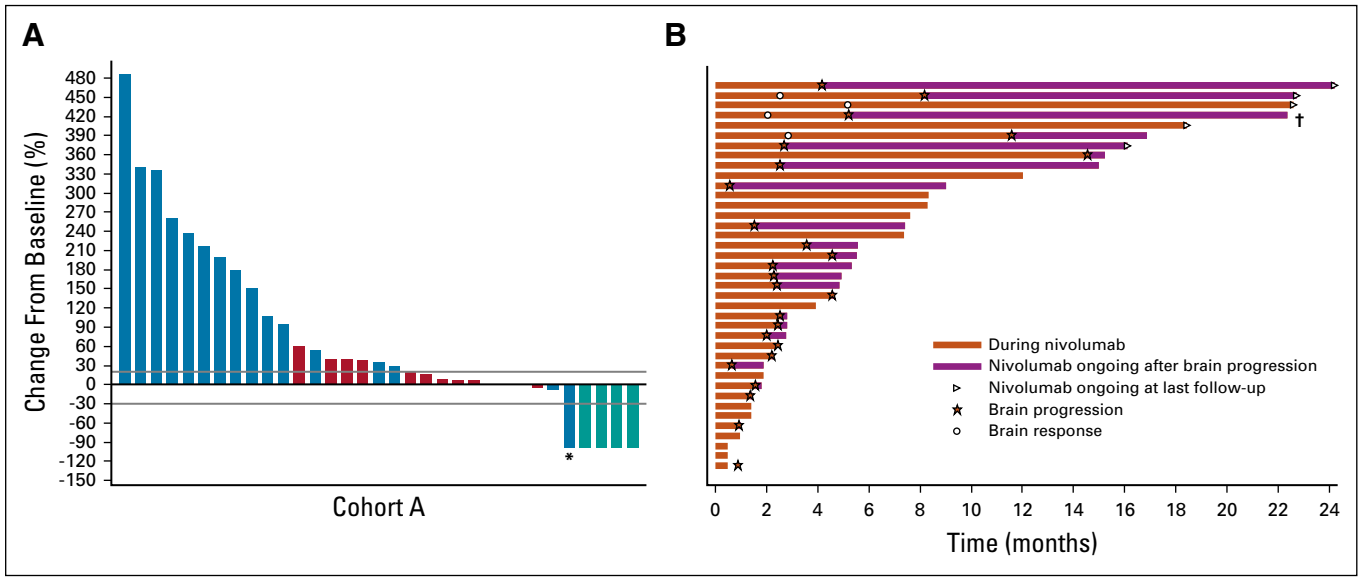


**FIG 2.** Assessment of intracranial response in patients with untreated brain metastases (cohort A, n = 34 patients evaluable for response). (A) Best intracranial response in cohort A according to modified Response Evaluation Criteria in Solid Tumors 1.1 evaluation. Blue indicates progressive disease, red stable disease, green complete or partial response. Each bar represents one patient. Horizontal lines indicate +20% and -30% change in target lesions size from baseline. (B) Duration of intracranial response in cohort A. Each bar represents one patient. (*) Occurrence of new brain lesion. (†) Treatment beyond intracranial progression with subsequent complete intracranial response (not shown).

(72%) in cohort A had subsequent local therapy to the brain (surgery or radiation therapy) compared with seven of 34 (21%) in cohort B (Appendix Table A4).

### Safety Analysis

The safety profile of nivolumab was acceptable and manageable in both cohorts (Appendix Table A5, online only). Nivolumab was permanently discontinued in one patient of the cohort A after treatment-related atrioventricular block. There was no other occurrence of treatment-related adverse event leading to treatment discontinuation.

Treatment-related adverse events of any grade occurring in 10% or more of patients from cohort A or B were asthenia in eight of 39 (21%) and eight of 34 (24%) patients and rash in four of 39 (10%) and three of 34 (9%) patients, respectively. Grade 3 or 4 treatment-related adverse events were reported in four of 39 (10%) patients in cohort A and five of 34 (15%) in cohort B. Grade 3 or 4 treatment-related adverse events in cohort A were asthenia in one of 39 (3%) patients, elevated liver function tests in one of 39 (3%), dyspnea in one of 39 (3%), and atrioventricular block in one of 39 (3%). Grade 3 or 4 treatment-related adverse events in cohort B were diarrhea in one of 34 (3%) patients, musculoskeletal pain in one of 34 (3%), psoriasis in one of 34 (3%), elevated creatinine in two of 34 (6%), and hypophosphatemia in one of 34 (3%). No toxic death was reported in either cohort.

## DISCUSSION

This study shows that nivolumab has limited intracranial activity in patients with untreated brain metastases from ccRCC, with only four (12%) out of 34 who experienced intracranial response. Moreover, only patients with limited intracranial tumor burden (< 10 mm) exhibited objective response in the brain. Patients who had received prior focal therapy had a significant decrease in the risk of intracranial progression compared with patients with untreated brain metastases, even though cohort B comprised numerically more patients with altered performance status, higher tumor grade, and higher number of brain metastases. We observed similar OS between the two cohorts, which may reflect the aggressive natural history of ccRCCs with intracranial evolution. Notably, the need for prior focal brain therapy in patients from cohort B could pinpoint that these patients harbored a more aggressive disease compared with patients in cohort A. Still, previous radiation therapy remained associated with improvement in multiple meaningful clinical outcomes, because these patients were less likely to experience symptoms related to their brain metastases, use corticosteroids, and undergo subsequent focal brain therapy.

To our knowledge, we report here the first study prospectively assessing the activity of immune checkpoint inhibitors in patients with brain metastases from ccRCC. In this setting, efficacy data of systemic therapies are lacking. Pivotal trials of immune checkpoint inhibitors excluded this population, and reports of intracranial response to angiogenesis inhibitors remain anecdotal.[8,9] Current recommendations do not include systematic brain imaging in patients with metastatic ccRCC, which may result in underevaluation of their true incidence. Failing to diagnose

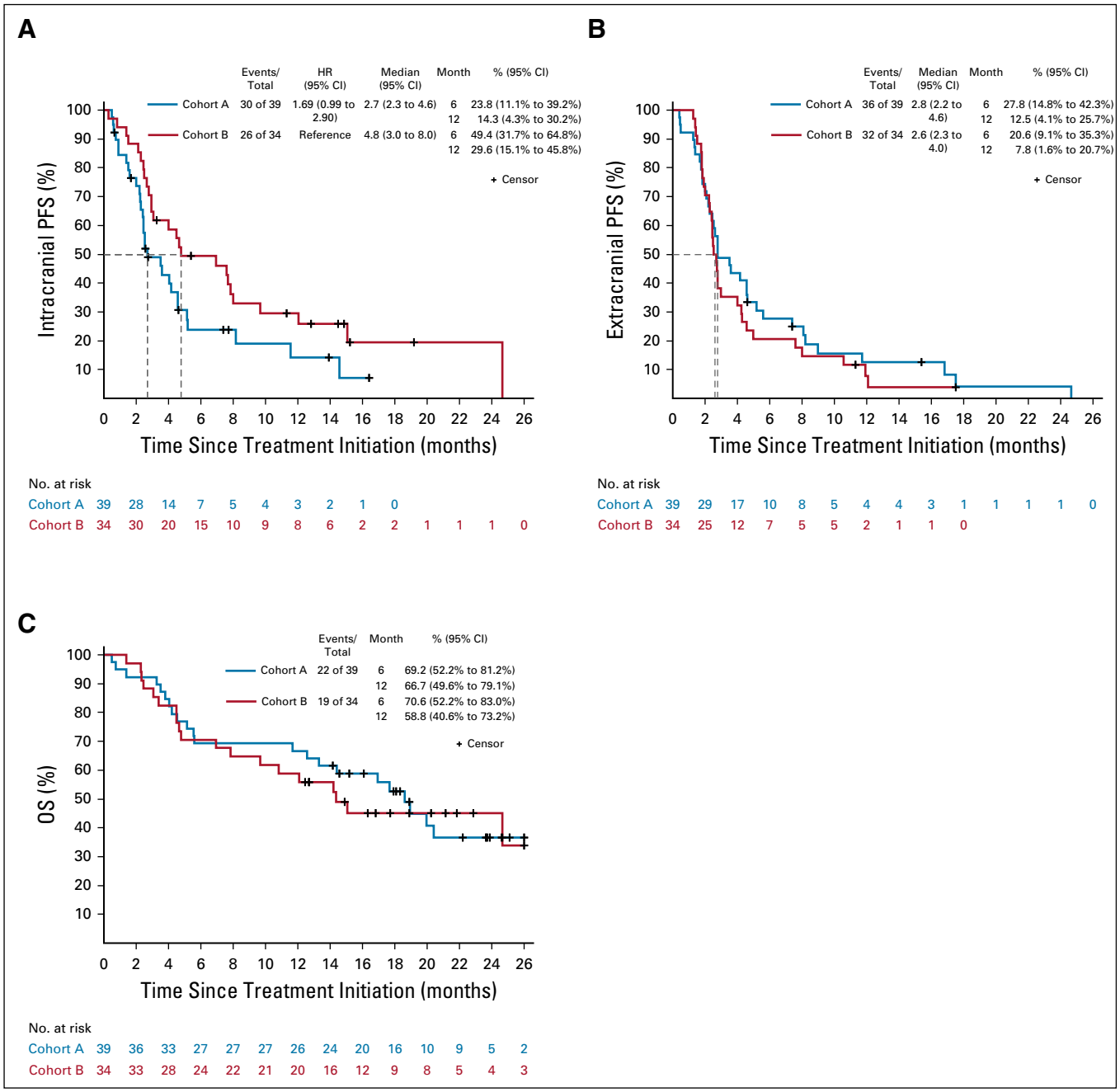


**FIG 3.** Progression-free survival (PFS) and overall survival (OS) in the study population. (A) Intracranial PFS in cohorts A (patients with untreated brain metastases) and B (patients with pretreated brain metastases). Patients who did not experience intracranial progression or death were censored at the date of last intracranial evaluation or at the date of focal brain therapy, including surgery or radiation therapy. (B) Extracranial PFS in cohorts A and B. (C) OS in cohorts A and B. HR, hazard ratio.

early intracranial metastases limits the opportunity for patients to benefit from stereotactic brain radiation therapy, which provides optimal control in the context of low intracranial tumor burden.[10] Our results suggest that systematic brain imaging in patients with metastatic ccRCC and consideration of focal brain therapy before systemic therapy can be a viable strategy. Such precautions might be particularly relevant when considering patients with multiple untreated brain metastases, of whom 73% experienced progressive disease as best response. Patients with symptomatic brain metastases, not included in our study, are likely to have a higher tumor burden and should be carefully managed.

Brain evaluation remains a critical issue in clinical trials. Here, intracranial response has been reported using modified RECIST 1.1,[7] allowing the evaluation of small target lesions, which would not have been captured using conventional RECIST 1.1. Standardized and dedicated

assessment of intracranial disease in solid tumors is thus a priority. Considering that median intracranial PFS in cohort A was shorter than the 12-week time point proposed for the first intracranial assessment, our study advocates for early brain imaging in this population, which might allow early detection of brain progression. Finally, the identification of patients with extracranial partial response but intracranial progressive disease pinpoints the importance of concomitant brain and body evaluation in patients with brain metastases from ccRCC.

The aggressiveness of ccRCC with brain metastases has been reported in multiple cohorts.[4,11] Here, the low intracranial response rate in patients with untreated brain metastases (12%) is numerically lower than the extracranial response rate (21%). It is also lower than the systemic response rates reported in the CheckMate 025 pivotal phase III trial (25%)[6] and in the overall population of the GETUG-AFU 26-NIVOREN trial (21%).[12] These peculiar outcomes might be explained in part by the biology of brain metastases. It has been notably reported that brain metastases from ccRCC frequently harbored distinct genomic alterations compared with extracranial lesions.[13] The emergence of aggressive tumor clones could also result from prior exposure to systemic therapies in our pretreated population. Although little is known about the immune contexture of ccRCC brain metastases, these lesions are reported to harbor frequent lymphocytic infiltration and programmed death-ligand 1 (PD-L1) expression,[14,15] which provide a strong rationale to evaluate checkpoint inhibitor combinations that are becoming standard of care in the first-line setting. Dual immune checkpoint inhibition with nivolumab plus ipilimumab, now approved up front in patients with intermediate and poor IMDC risk groups, may benefit patients with intracranial disease. Results of phase II trials in melanoma support this hypothesis, because the association of nivolumab plus ipilimumab provided high intracranial response rates (46% to 56%)[16,17] compared with PD-1 inhibition alone (20% to 22%).[16,18] Improved antitumor immunity in the brain may also be provided by combinations of antiangiogenics and immune checkpoint inhibitors.[19] This strategy may increase immune infiltration and deplete myeloid-derived suppressor cells, converting cold into hot tumors.[20] Because these combinations will soon emerge as a first-line standard, dedicated trials are needed to assess their impact on outcomes of patients with brain metastases.

In conclusion, our results suggest that single-agent nivolumab has limited activity in patients with untreated brain metastases from ccRCC and who experienced progression after VEGFR-directed therapy. These patients may benefit from systematic brain imaging and focal brain therapy before initiation of immune checkpoint inhibitors. These data highlight the need to pursue dedicated clinical trials in this population and advocate for the evaluation of combination strategies using systemic and focal brain therapies.


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B.E. and L.A. contributed equally to this work.


## PRIOR PRESENTATION

Presented in part at the European Society for Medical Oncology congress, Munich, Germany, October 19-23, 2018.

## SUPPORT

Supported by Bristol-Myers Squibb.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.18.02218.

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**Manuscript writing:** All authors

**Final approval of manuscript:** All authors

**Accountable for all aspects of the work:** All authors

ACKNOWLEDGMENT

We thank the patients and their families who participated in this study. We also thank UNICANCER research and development, data management, and biostatistics teams, including Lise Roca, Soazig Nenan, and Grégoire Colson. Ronan Flippot received funding from the ARC foundation. Translational research programs associated with the GETUG-AFU 26 NIVOREN trial are funded by the PRT-K research grant from the French National cancer Institute (INCa).

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Safety and Efficacy of Nivolumab in Brain Metastases From Renal Cell Carcinoma: Results of the GETUG-AFU 26 NIVOREN Multicenter Phase II Study**

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

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No other potential conflicts of interest were reported.

## APPENDIX Inclusion and Noninclusion Criteria for the GETUG-AFU 26 NIVOREN Study

***Inclusion criteria.***

1. Adult men and women 18 years or older.
2. Patients with a histologically confirmed renal cell carcinoma with a clear cell component.
3. Patients with metastatic (American Joint Committee on Cancer stage IV) renal cell carcinoma, with at least one measurable lesion by computed tomography scan or magnetic resonance imaging according to Response Evaluation Criteria in Solid Tumors 1.1 or with clinically apparent disease that can be reliably monitored by the investigator.
4. Patients having received at least one prior systemic antiangiogenic treatment, including but not limited to: sunitinib, sorafenib, pazopanib, axitinib, and bevacizumab, in the advanced or metastatic setting. Prior cytokine therapies (eg, interleukin-2, interferon alfa), vaccine therapy, or treatment with cytotoxics are allowed. Patients intolerant to prior systemic antiangiogenic treatment can also be eligible (except hypersensitivity to other monoclonal antibodies). A maximum of 25% of patients with more than two prior systemic treatments will be recruited per site.
5. Patients with Eastern Cooperative Oncology Group (ECOG) performance status less than or equal to 2.
6. Patients belonging to favorable, intermediate, or poor risk groups measured by the International Metastatic Renal Cell Carcinoma Database model.
7. Patients with brain metastases will be eligible if they are: asymptomatic, without edema, not receiving corticosteroids, not eligible for radiation therapy/surgery, and not receiving active treatments.
8. Patients who have experienced progression after radiation therapy. Palliative therapy, focal radiation therapy, and immunosuppressive doses of systemic corticosteroids, except replacement organotherapy (hydrocortisone and fludrocortisone), must be discontinued at least 2 weeks before the first nivolumab administration.
9. Potentially reproductive patients must agree to use an effective contraceptive method or practice adequate methods of birth control or practice complete abstinence while on treatment and for at least 31 weeks (approximately 7 months) for males and 23 weeks (approximately 5 months) for females after the last dose of study drug. Azoospermic males and women of childbearing potential who are continuously not heterosexually active are exempt from contraceptive requirements.
10. Women of childbearing potential must have a negative serum pregnancy test done within 24 hours before the first dosing.
11. Women who are breastfeeding should discontinue nursing before the first dose of study drug and until 6 months after the last dose.
12. Provision of signed and dated written informed consent before any study specific procedures, sampling, and analyses.
13. Patients with social insurance coverage.

***Noninclusion criteria.***

1. Patients with any active autoimmune disease or a history of known autoimmune disease (patients with type I diabetes mellitus, residual hypothyroidism as the result of an autoimmune condition requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are, however, eligible for this trial).
2. Patients with uncontrolled adrenal insufficiency.
3. Patients with known history of testing positive for HIV or known AIDS.
4. Patients with positive tests for hepatitis B virus surface antigen or hepatitis C virus RNA indicating active or chronic infection.
5. Patients having received prior therapy with anti–PD-1, anti–PD-L1, anti–PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) antibody (or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways).
6. Patients having received any nononcology vaccine therapy used for prevention of infectious diseases including seasonal (influenza) vaccinations within 4 weeks of the first dose of study drug
7. Patients receiving anticancer therapies must be discontinued at least 2 weeks before administration of study drug. Palliative therapy, focal radiation therapy, and immunosuppressive doses of systemic corticosteroids, except replacement organotherapy (hydrocortisone and fludrocortisone), must be discontinued at least 2 weeks before administration of study drug. All toxicities attributed to prior anticancer therapy other than alopecia must have resolved to grade 1 (National Cancer Institute Common Terminology Criteria for Adverse Events version 4) or baseline before administration of study drug.

8. Patients with prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.
9. Patients with altered hematopoietic or organ function, as indicated by the following criteria (assessed within 14 days before the first dosing):
   - WBC less than 2,000/$\mu$L
   - Polynuclear neutrophils less than $1.5 \times 10^9$/L
   - Platelets less than $100 \times 10^9$/L
   - Hemoglobin less than 8.0 g/dL
   - ALT/AST greater than 3.0 $\times$ upper limit of normal (ULN) in the absence of liver metastases or greater than 5 $\times$ ULN in the presence of liver metastases
   - Bilirubin greater than 1.5 $\times$ ULN (except Gilbert syndrome: less than 3.0 mg/dL)
   - Creatinine clearance 40 mL/min or less (measured or calculated by Cockroft and Gault formula) or serum creatinine greater than 2.0 $\times$ ULN
10. Patients with a history of hypersensitivity to other monoclonal antibodies or to the active or inactive excipients of study drug.
11. Known drug or alcohol abuse.
12. Known or underlying medical condition (eg, a condition associated with diarrhea or acute diverticulitis) that, in the investigator's opinion, would make the administration of study drug hazardous to the patient or obscure the interpretation of toxicity determination or adverse events.
13. History of uncontrolled seizures, CNS disorders, or psychiatric disability judged by the investigator to be clinically significant, precluding informed consent, or interfering with compliance of oral drug intake.
14. Unwillingness to give written informed consent, unwillingness to participate, or inability to comply with the protocol for the duration of the study.
15. Individuals deprived of liberty or placed under the authority of a tutor.
16. Treatment with any other investigational agent or participation in another clinical trial within 28 days before enrollment and during the treatment period.

### Treatment Adaptation and Termination

***Treatment adaptations.*** In all cases, tumor assessments for all patients should continue as per the study protocol, even if the administration of nivolumab is delayed.

Nivolumab administration should be interrupted in case of:

- Any grade 2 or higher nonskin, drug-related adverse event, with the following exceptions: grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment interruption.
- Any grade 3 skin, drug-related adverse event.
- Any grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, or total bilirubin:
  - Grade 3 lymphopenia or leukopenia does not require dose delay.
  - If a patient has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related grade 2 or greater toxicity.
  - If a patient has baseline AST, ALT, or total bilirubin within the grade 1 toxicity range, delay dosing for drug-related grade 3 or greater toxicity.
  - Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Dose modification of nivolumab during the course of study is not allowed.

***Criteria to resume treatment with nivolumab.*** Patients may resume treatment with nivolumab when the drug-related adverse event(s) resolve(s) to grade 1 or lower or baseline, with the following exceptions:

- Patients with baseline AST/ALT or total bilirubin in the grade 1 toxicity range who require dose delays for reasons other than a two-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of grade 2 AST/ALT OR total bilirubin.
- Patients with combined grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

If treatment is delayed more than 6 weeks, the patient must be permanently discontinued from study therapy, except as specified in treatment discontinuation criteria.

***Treatment termination.*** Nivolumab treatment should be permanently discontinued in case of:

- Any grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to grade 1 severity within the retreatment period OR requires systemic treatment.

- Any grade 3 nonskin, drug-related adverse event lasting more than 7 days, with the following exceptions:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
- Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
  - Grade 3 drug-related thrombocytopenia more than 7 days or associated with bleeding requires discontinuation.
  - Any drug-related liver function test abnormality that meets the following criteria requires discontinuation:

  a. AST or ALT greater than 5 × ULN

  b. Total bilirubin greater than 3 × ULN

  c. Concurrent AST or ALT greater than 3 × ULN and total bilirubin greater than 2 × ULN
- Any grade 4 drug-related adverse event or laboratory abnormality, except for the following events:
  - Grade 4 neutropenia 7 days or less does not require discontinuation.
  - Grade 4 lymphopenia or leukopenia does not require discontinuation.
  - Isolated grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset do not require discontinuation.
  - Isolated grade 4 amylase or lipase abnormalities those are not associated with symptoms or clinical manifestations of pancreatitis. The Sponsor Medical Monitor designee should be consulted for grade 4 amylase or lipase abnormalities.
- Any dosing interruption lasting more than 6 weeks with the following exceptions:
  - Dosing interruptions to manage drug-related adverse events, such as prolonged steroid tapers, are allowed. Before reinitiating treatment in a patient with a dosing interruption lasting longer than 6 weeks, the Sponsor Medical Monitor designee must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
  - Dosing interruptions longer than 6 weeks that occur for non–drug-related reasons may be allowed if approved by the Sponsor Medical Monitor designee. Before reinitiating treatment in a patient with a dosing interruption lasting longer than 6 weeks, the Sponsor Medical Monitor designee must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the patient with continued nivolumab dosing.

The investigator may also decide an early interruption of the treatment for any reason that would be beneficial for the patient, even in case of intercurrent disease.

At any stage of the treatment, the investigator must document in the Case Report Form and in the medical chart the reasons for a premature treatment stop as exhaustively as possible.

Except in case of consent withdrawal, patient follow-up will continue in compliance with the protocol, and follow-up data will be collected until the end of the trial.

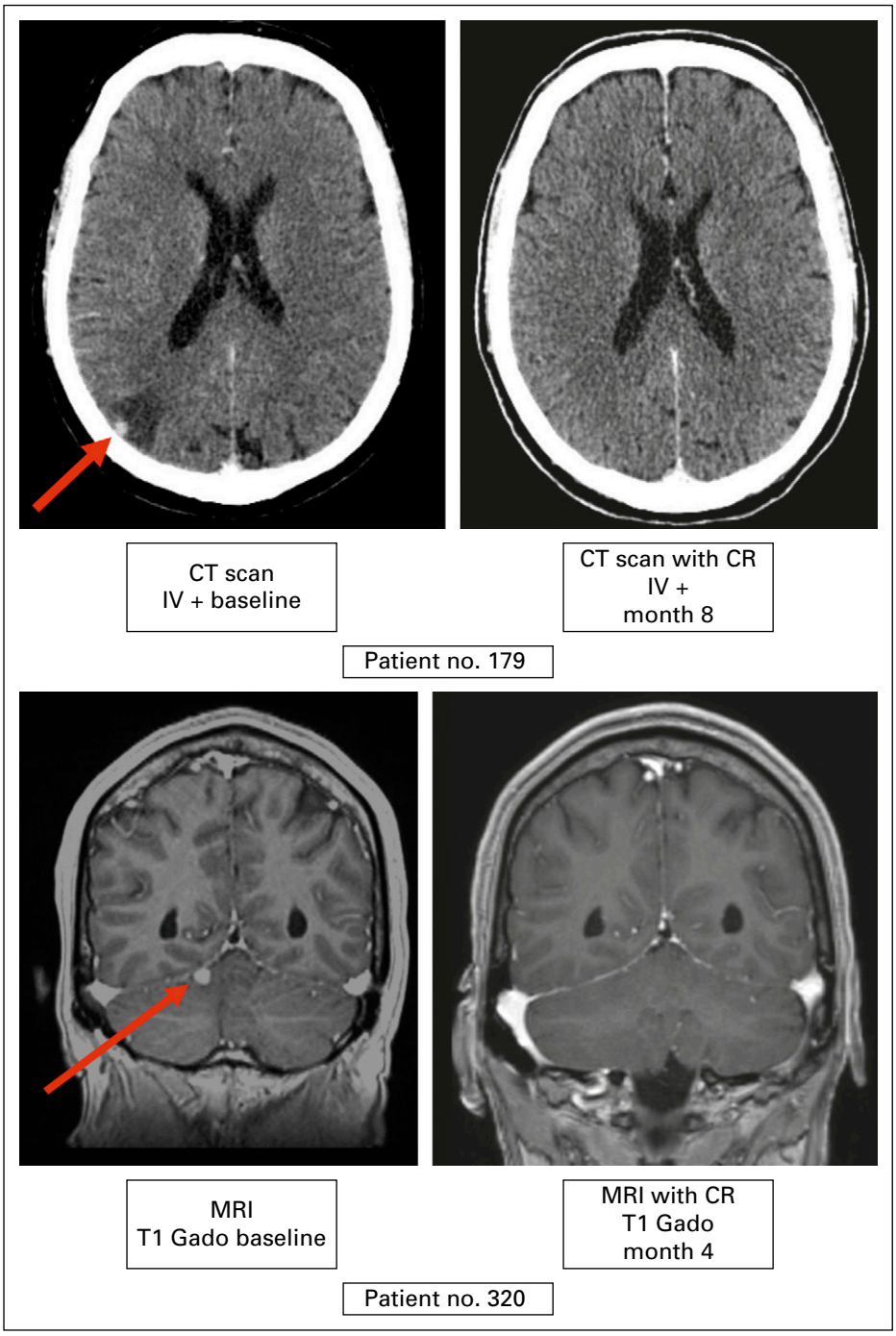


**FIG A1.** Brain assessments of patients who achieved completed intracranial response in cohort A (patients with untreated brain metastases). CR, complete intracranial response; CT, computed tomography; IV +, intravenous contrast-enhanced; MRI, magnetic resonance imaging; Gado, intravenous gadolinium-enhanced.

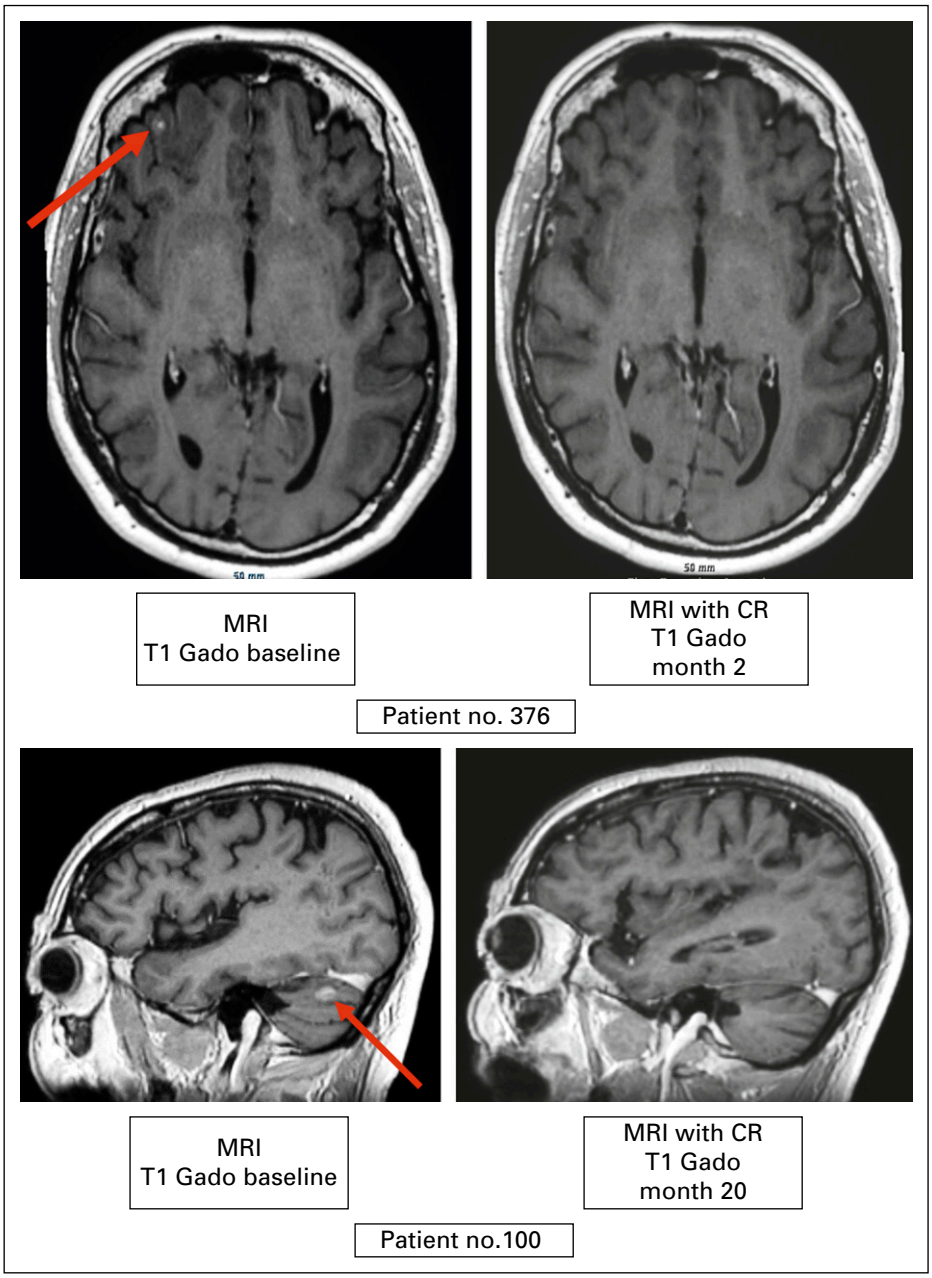


**FIG A1.** (Continued).

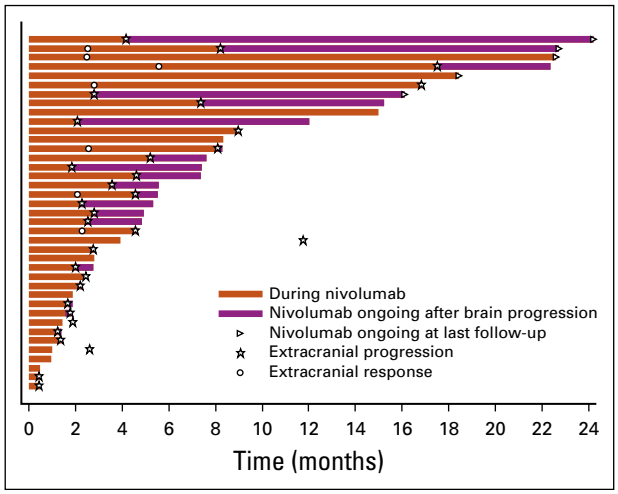


**FIG A2.** Duration of extracranial response in patients with untreated brain metastases (cohort A). Each horizontal bar represent one patient.

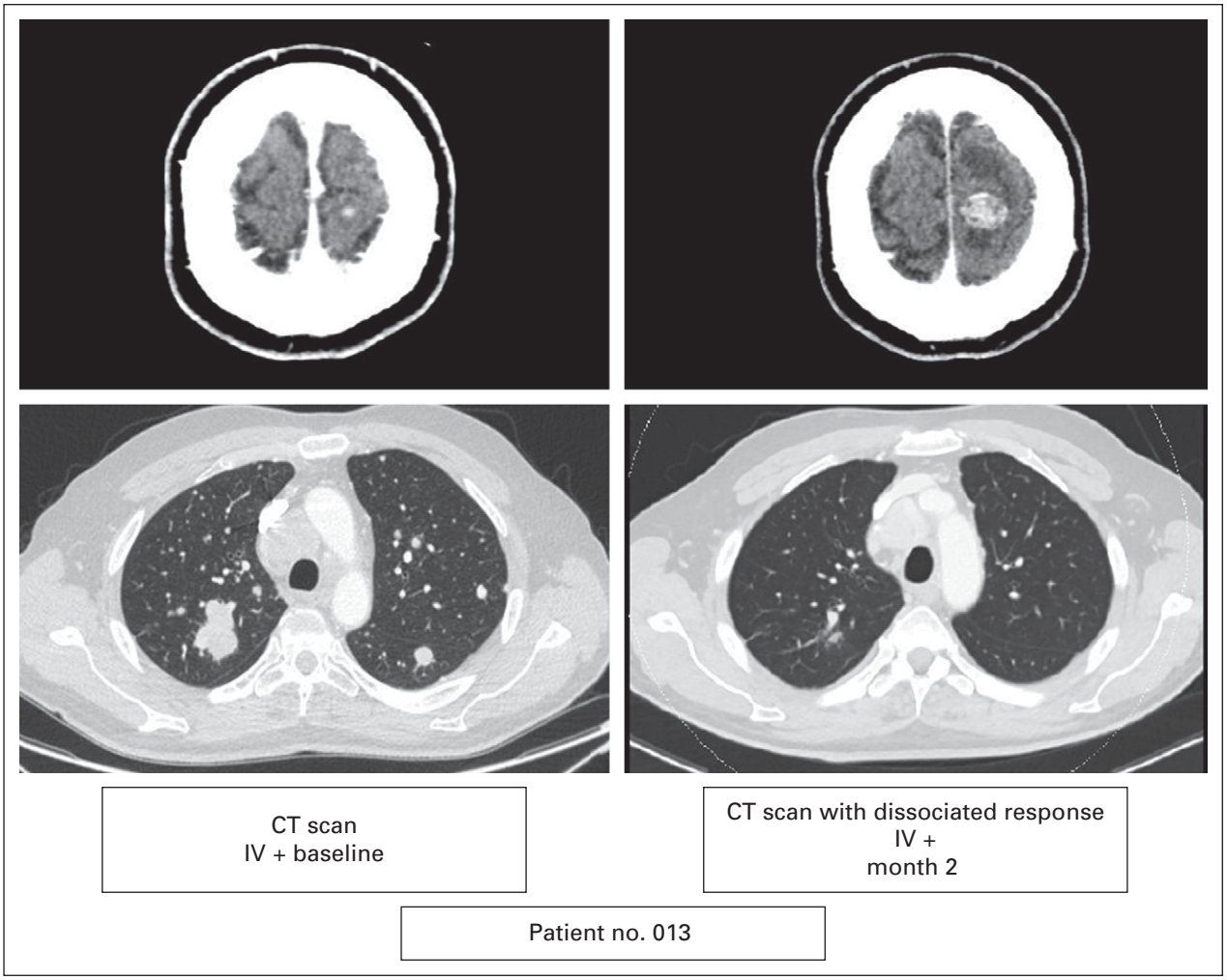


**FIG A3.** Discordant extracranial and intracranial response to nivolumab in a patient with untreated brain metastases from clear cell renal cell carcinoma. CT, computed tomography; IV +, intravenous contrast-enhanced.

**TABLE A1.** Intracranial Response in Patients With Untreated Brain Metastases (Cohort A) According to Baseline Characteristics

| | | | Brain Best Overall Response | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | CR | | SD | | PD | |
| Characteristic | No. | Missing Data | No. | % | No. | % | No. | % |
| ECOG PS | | | | | | | | |
| Missing data | | 1 | 0 | | 0 | | 1 | |
| 0-1 | 33 | 3 | 3 | 10 | 12 | 40 | 15 | 50 |
| 2-3 | 4 | 1 | 1 | 33 | 1 | 33 | 1 | 33 |
| No. of brain metastases | | | | | | | | |
| 1 | 26 | 3 | 4 | 17 | 10 | 43 | 9 | 39 |
| > 1 | 13 | 2 | 0 | 0 | 3 | 27 | 8 | 73 |
| Fuhrman grade | | | | | | | | |
| Missing data | | 0 | 2 | | 0 | | 1 | |
| I/II | 13 | 1 | 2 | 17 | 6 | 50 | 4 | 33 |
| III/IV | 23 | 4 | 0 | 0 | 7 | 37 | 12 | 63 |
| Previous lines of systemic therapy | | | | | | | | |
| 1-2 | 15 | 3 | 1 | 8 | 5 | 42 | 6 | 50 |
| ≥ 2 | 24 | 2 | 3 | 14 | 8 | 36 | 11 | 50 |
| IMDC risk groups | | | | | | | | |
| Missing data | | 0 | 0 | | 0 | | 1 | |
| Good or intermediate | 25 | 3 | 2 | 9 | 12 | 55 | 8 | 36 |
| Poor | 13 | 2 | 2 | 18 | 1 | 9 | 8 | 72 |
| Sum of the longest diameter of brain target lesions, mm | | | | | | | | |
| < 10 | 18 | 3 | 4 | 27 | 5 | 33 | 6 | 40 |
| ≥ 10 | 21 | 2 | 0 | 0 | 8 | 42 | 11 | 58 |

Abbreviations: CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; IMDC: International Metastatic Renal Cell Carcinoma Database; PD, progressive disease; PR, partial response; SD, stable disease.

**TABLE A2.** Intracranial and Extracranial Response in Patients With Untreated Brain Metastases (Cohort A)

| | Best Extracranial Overall Response | | | | |
|---|---|---|---|---|---|
| Best Intracranial Overall Response | Missing Data (n = 6) | CR (n = 0) | PR (n = 7) | SD (n = 10) | PD (n = 16) |
| Missing data | 3 | 0 | 0 | 0 | 2 |
| CR | 0 | 0 | 4 | 0 | 0 |
| PR | 0 | 0 | 0 | 0 | 0 |
| SD | 0 | 0 | 2 | 9 | 2 |
| PD | 3 | 0 | 1 | 1 | 12 |

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

**TABLE A3.** Multivariable Model for Intracranial Progression-Free Survival

| Variable | Event:No Event | HR | 95% CI | *P* |
|---|---|---|---|---|
| Prior focal brain therapy | | | | |
| Yes (cohort B) | 25:8 | | | |
| No (cohort A) | 24:7 | 2.036 | 1.081 to 3.833 | .0277 |
| ECOG PS | | | | |
| 0.1 | 41:15 | | | |
| 2.3 | 8:0 | 1.113 | 0.39 to 3.174 | .8413 |
| No. of brain lesions | | | | |
| 1 | 31:10 | | | |
| > 1 | 18:5 | 1.499 | 0.769 to 2.921 | .2341 |
| Fuhrman grade | | | | |
| I/II | 16:3 | | | |
| III/IV | 33:12 | 0.777 | 0.381 to 1.586 | .4884 |
| Previous systemic therapies ≥ 2 | | | | |
| No | 18:10 | | | |
| Yes | 31:5 | 1.025 | 0.527 to 1.991 | .9428 |
| IMDC risk groups | | | | |
| Good or intermediate | 31:14 | | | |
| Poor | 18:1 | 2.752 | 1.17 to 6.472 | .0203 |

NOTE. N = 64 after adjustment for available baseline characteristics.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database.

**TABLE A4.** CNS-Specific End Points

| End Points | Cohort A: Patients With Untreated Brain Metastases (n = 39) | Cohort B: Patients with Pretreated Brain Metastases (n = 34) |
|---|---|---|
| Symptoms associated with intracranial disease | | |
| Yes | 19 (49) | 11 (32) |
| No | 20 (51) | 23 (68) |
| Origin of symptoms associated with intracranial disease | | |
| Disease progression | 18 (95) | 8 (73) |
| Radionecrosis | 0 | 2 (18) |
| Brain hemorrhage | 1 (5) | 0 |
| Unknown | 0 | 1 (9) |
| Corticosteroid use | | |
| Yes | 20 (51) | 9 (27) |
| No | 19 (49) | 25 (73) |
| Brain focal therapy | | |
| Yes | 28 (72) | 7 (21) |
| No | 11 (28) | 27 (79) |
| Type of brain focal therapy | | |
| SRS | 14 (50) | 4 (57) |
| WBRT | 8 (25) | 2 (28.5) |
| WBRT plus SRS | 1 (3.5) | 0 |
| Surgery | 1 (3.5) | 1 (14) |
| Surgery plus SRS | 4 (12.5) | 0 |

NOTE. Data given as No. (%).

Abbreviations: SRS, stereotactic radiation therapy; WBRT, whole-brain radiation therapy.

**TABLE A5.** Safety of Nivolumab in the Study Population

| | Cohort A: Patients With Untreated Brain Metastases (n = 39) | | Cohort B: Patients With Pretreated Brain Metastases (n = 34) | |
|---|---|---|---|---|
| **Treatment-Related Adverse Events** | **All Grades** | **Grade 3 or 4** | **All Grades** | **Grade 3 or 4** |
| Any | 24 (62) | 4 (10) | 16 (47) | 5 (15) |
| GI | | | | |
| Diarrhea | 2 (5) | 0 | 3 (9) | 1 (3) |
| General | | | | |
| Asthenia | 8 (21) | 1 (3) | 8 (24) | 0 |
| Hepatic | | | | |
| Elevated ALT | 2 (5) | 1 (3) | 0 | 0 |
| Elevated GGT | 1 (3) | 1 (3) | 0 | 0 |
| Renal | | | | |
| Elevated creatinine | 1 (3) | 0 | 2 (6) | 2 (6) |
| Dermatologic | | | | |
| Xerosis | 2 (5) | 0 | 1 (3) | 0 |
| Pruritus | 2 (5) | 0 | 2 (6) | 0 |
| Rash | 4 (10) | 0 | 3 (9) | 0 |
| Psoriasis | 0 | 0 | 1 (3) | 1 (3) |
| Musculoskeletal | | | | |
| Musculoskeletal pain | 1 (3) | 0 | 1 (3) | 1 (3) |
| Metabolic | | | | |
| Hypophosphatemia | 1 (3) | 0 | 1 (3) | 1 (3) |
| Respiratory | | | | |
| Dyspnea | 1 (3) | 1 (3) | 1 (3) | 0 |
| Endocrine | | | | |
| Hypothyroidism | 2 (5) | 0 | 0 | 0 |
| Cardiac | | | | |
| Atrioventricular block | 1 (3) | 1 (3) | 0 | 0 |

NOTE. Data given as No. (%). Displayed treatment-related adverse events were grade 3 or 4 or reported in at least 5% of patients in either cohort.

Abbreviation: GGT, gamma-glutamyl transferase.