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## **Biomarker-driven randomized phase II trial in frontline metastatic clear cell renal cell carcinoma: the BIONIKK study**

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**Keywords:** renal cell carcinoma, first-line treatment, randomized trial, biomarker, molecular group, nivolumab, nivolumab-ipilimumab, VEGFR-TKI

## **Abstract**

**Background:** We previously reported a 35-gene expression classifier (GEC) identifying four ccrc groups with different tumor microenvironments and sensitivities to sunitinib in metastatic clear cell renal cell carcinoma (mRCC): efficacy profiles may differ with nivolumab±ipilimumab.

**Methods:** In this multicentric non-comparative phase II trial, patients (age ≥18 years; Eastern Cooperative Oncology Group performance-status ≤2) with previously untreated mRCC were randomized using permuted blocks according to our GEC: IV nivolumab 3 mg/kg + IV ipilimumab 1 mg/kg every 3 weeks followed by nivolumab 240 mg every 2 weeks or IV nivolumab 240 mg every 2 weeks for ccrc1,4, and nivolumab-ipilimumab or oral sunitinib (50 mg/day for 4 weeks every 6 weeks) / pazopanib (800 mg daily) (VEGFR-TKI) for

ccrcc2,3. The primary endpoint was the objective response rate (ORR) by investigator assessment per RECIST 1.1, in the population who received  $\geq 1$  dose of study drug. Trial registered with ClinicalTrials.gov (NCT02960906) and closed to enrollment.

**Findings:** Between June 28<sup>th</sup>, 2017 and July 18<sup>th</sup>, 2019, of 202 patients randomized, 199 were treated. Median follow up was 18,0 months (IQR 17.6-18.4). In ccrcc1, ORR with nivolumab and nivolumab–ipilimumab were 29% (12/42) and 39% (16/41) (odds ratio 0,63 [95%CI 0,25-1,56]), respectively; in ccrcc4, ORR were 44% (7/16) and 50% (9/18) (odds ratio 0,78 [95%CI 0,20-3,01]). In ccrcc2, ORR with VEGFR-TKI and nivolumab-ipilimumab were 50% (18/36) and 51% (19/37) (odds ratio 0,95 [95%CI 0,38-2,37]), respectively. The most common treatment-related grade 3-4 adverse events were hepatic failure (2/58 [3%]) with nivolumab lipase increase (6/101 [6%]) with nivolumab-ipilimumab, and hypertension (6/40 [15%]) with VEGFR-TKI, respectively. Serious treatment- adverse events occurred in 22 [38%], 56 [55%] and 18 [45%] patients with nivolumab, nivolumab-ipilimumab and VEGFR-

TKI respectively. Three deaths were treatment-related: fulminant hepatitis with nivolumab–ipilimumab, heart failure and thrombotic microangiopathy with sunitinib.

**Interpretation:** We demonstrate the feasibility and positive impact of a prospective patient selection based on tumor molecular phenotype to choose the most effective treatment between nivolumab±ipilimumab and VEGFR-TKI in frontline mRCC.

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## **Introduction**

During the last 5 years, the arrival of immune-checkpoint inhibitors (ICI) has profoundly changed the front-line management of metastatic clear cell renal cell carcinoma (mRCC) patients<sup>1</sup>. After the approval of the nivolumab–ipilimumab (anti-PD-1-anti-CTLA-4) combination in patients with International Metastatic Database Consortium (IMDC) intermediate-poor risk tumors<sup>2</sup>, three other combinations have enriched the frontline landscape of mRCC treatment, pembrolizumab–axitinib<sup>3</sup>, nivolumab–cabozantinib<sup>4</sup>, and pembrolizumab–lenvatinib<sup>5</sup>. Despite these achievements, a majority of patients experience tumor progression within the first two years of treatment in the absence of predictive biomarker of efficacy available for their selection.

Our group described previously four biologically distinct RCC tumor groups (ccrcc1 to 4) based on transcriptomic data, associated with variable sensitivity to front-line sunitinib and related to distinct tumor microenvironment immune and angiogenic infiltration<sup>6,7</sup>. Tumors less responsive to sunitinib had either a pro-inflammatory and immune-high tumor microenvironment with a high expression of immunosuppressive checkpoints (ccrcc4) or, contrastingly, an immune-low tumor microenvironment (ccrcc1). Nearly half of most responsive tumors to sunitinib expressed an angiogenic-high and immune-high signature (ccrcc2)<sup>8</sup>. Finally, the smallest group with a good response to sunitinib had molecular and pathologic features closest to normal kidney tissue (ccrcc3). A minimal classifier of 35-genes was developed in order to identify these 4 groups<sup>6</sup>.

We hypothesized that that the immune high ccrcc4 tumors would be responsive to nivolumab-based therapy, either with or without ipilimumab because of the immune-enriched tumor microenvironment, and that the ccrcc1 tumors would respond better to nivolumab–ipilimumab than to nivolumab alone because of the need to recruit anti-tumor cytotoxic T cells. Furthermore, we hypothesized that both VEGFR-TKI (sunitinib or pazopanib) and

nivolumab–ipilimumab would have a high efficacy in ccrcc2 tumors due to their pro-angiogenic profile and an immune-high infiltrate observed in nearly half of these tumors. Regarding the low frequency ccrcc3 group, its non-specific biological features did not allow to formulate strong hypotheses on treatment efficacy. Thus, we decided to evaluate VEGFR-TKI versus nivolumab–ipilimumab in this group.

Based on these hypotheses, we designed the BIONIKK STUDY, a non-comparative biomarker-driven randomized phase II clinical trial evaluating treatment efficacy and tolerability in patients in mRCC.

## **Research in context**

### **Evidence before this study**

We searched PubMed on 29<sup>th</sup> November 2021, using the terms “renal cell carcinoma” AND “metastatic” AND “biomarker” for phase II or III clinical trials published with no restrictions on publication date or language. We mainly found post-hoc biomarker analyses from single arm phase II trials or more recently from randomized phase III trials. No biomarker-driven trial in metastatic renal cell carcinoma was ever published. Recent post-hoc analyses from randomized phase II/III trials strengthened the potent predictive role of treatment efficacy of tumor microenvironment-related gene expression signatures: an angiogenesis signature above the median expression (“high”) was associated with prolonged progression-free survival with sunitinib but not with atezolizumab or atezolizumab-bevacizumab whereas a T effector-high signature was associated with prolonged progression-free survival with atezolizumab-bevacizumab but not with sunitinib. Similarly, an immune-high signature (Javelin Renal 101) was associated with prolonged progression-free survival with avelumab-axitinib but not with sunitinib. Nevertheless, these gene-expression signatures have been established on whole cohorts in a post-hoc manner. Moreover, none of these signatures were able to predict better progression-free survival nor overall survival with nivolumab-ipilimumab. In 2015 we reported the ability of a 35-gene expression classifier to identify four distinct profiles of clear cell renal cell tumors (ccrcc1 to 4) and to predict sunitinib resistance in frontline metastatic RCC. We further detailed the distinctives tumor microenvironment of these four groups allowing us to generate research hypotheses supporting the BIONIKK trial.

### **Added value of this study**

To our knowledge this study is the first to show the feasibility of prospective patient and treatment selection based on tumor gene expression in metastatic renal cell carcinoma. By allocating treatment according to tumor molecular group, we enriched response rate to nivolumab, nivolumab-ipilimumab and VEGFR-TKI.

### **Implications of all the available evidence**

Our results confirm that the response to nivolumab alone or with ipilimumab and to VEGFR-TKI is different depending on the characteristics of the tumor and its microenvironment. The feasibility of prospectively selecting patients by their molecular group for treatment choice opens the way to larger biomarker-based trial designs.



## **Methods**

### ***Study design and participants***

BIONIKK was a French open-label, non-comparative randomized phase II trial including patients from 15 centers either university hospitals or expert anti-cancer centers. The trial protocol and subsequent amendments (**protocol appendix**) were approved by the French Health authorities and ethics committee. The trial was conducted in accordance with Good Clinical Practice guidelines. An independent data and safety monitoring committee assessed safety data after randomization of 100 patients.

Eligible patients were  $\geq 18$  years old, had newly diagnosed or recurrent stage IV RCC (according to the American Joint Commission on Cancer, seventh edition, classification), had an Eastern Cooperative Oncology Group performance-status  $\leq 2$ , had  $\geq 1$  measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, and had not received previous systemic therapy for metastatic disease. Other key inclusion criteria were availability of tumor tissue specimen (both frozen and formalin-fixed paraffin-embedded (FFPE) specimen), and adequate organ function according to local laboratory tests up to 14 days before randomization (including white blood cell count  $\geq 2000$  per  $\mu\text{L}$ , neutrophils  $\geq 1500$  per  $\mu\text{L}$ , hemoglobin  $> 9\text{g/dL}$ , platelets  $\geq 100\ 000$  per  $\mu\text{L}$ , creatinine clearance  $\geq 40\text{mL/min}$ ). A full list of inclusion criteria can be found in the appendix (**p3**).

Key exclusion criteria included any uncontrolled or symptomatic brain metastases, any history of autoimmune disease or any other condition requiring systemic corticosteroids  $> 10\text{ mg/day}$ , and any prior active malignancy within the previous 3 years. A full list of exclusion criteria can be found in the appendix (**p3-5**). All patients provided written informed consent.

### ***Randomization and masking***

Eligible patients were enrolled by investigators and randomly assigned (1:1) to receive either nivolumab (Bristol-Myers Squibb, New-York City, U.S.) or nivolumab-ipilimumab (Bristol-Myers Squibb, New-York City, U.S.) in the ccrcc1 and ccrcc4 group, and to receive nivolumab-ipilimumab or VEGFR-TKI (sunitinib [Pfizer, New York City, U.S.] or pazopanib [Novartis, Basel, Switzerland]) in the ccrcc2 and ccrcc3 group (study design in **appendix p12**). Initially, adaptive randomization was planned but based on anticipated drawbacks at late stage and recent experts' publications, we changed to a conventional randomization. In order not to impact the schedule of the study, no amendment to the protocol to the health authorities was made. We considered that a conventional randomization method would not change their evaluation, quite the opposite. Randomization was performed using blocks of different sizes to avoid any possible disclosure of the next allocated therapy (open-label trial). The allocation sequence method was implemented by the methodologist, and treatment assignment was performed automatically through the eCRF based on randomization list. Due to the open-label trial design, patients, investigators, and the study sponsor were not masked to the study treatment. Further details of the randomization procedure in appendix (**p5**).

### ***Procedures***

Molecular group determination was done before randomization as described in appendix (p5). Patients received either nivolumab 240 mg intravenously (IV) every 2 weeks or nivolumab 3 mg/kg IV plus ipilimumab 1 mg/kg IV every 3 weeks for 4 doses ( $\geq 3$  doses were mandatory to continue study treatment), followed by nivolumab 240 mg IV every two weeks, or a VEGFR-TKI (sunitinib 50 mg orally once daily for 4 weeks [6-week cycle] or pazopanib 800 mg once daily continuously according to Investigator's choice). Treatments were administered until the end of study set at 18 months, or until disease progression or death, unacceptable toxicity, or physician or patient decision. At the end of study, patients without criteria to discontinue treatment, were able to continue treatment outside the study protocol.

Dose reductions or dose escalations of nivolumab or ipilimumab were not permitted. Dose reductions of VEGFR-TKI were allowed in accordance with their respective summary of product characteristics. Nivolumab-ipilimumab administration should be delayed for any following drug-related adverse events: grade  $\geq 2$  non-skin, grade 3 skin or grade  $\geq 3$  laboratory abnormality. Dose delay for sunitinib or pazopanib was based on instructions in the approved product label and was considered for any severe or intolerable drug-related AEs. Further detailed of permitted dose reductions or interruptions are available in the protocol supplied in appendix.

Tumor response was assessed according to RECIST 1.1 guidelines per investigator assessment, with CT-scan or MRI of the chest, abdomen and pelvis, at baseline, at week 10, and every 12 weeks thereafter. Progressive disease was confirmed by a consecutive assessment 6 weeks later. Patients without subsequent confirmation of disease progression and clinically stable condition could continue treatment until confirmed progression.

Local laboratory tests including blood counts, ionogram, liver enzymes and calculated creatinine clearance (full tests listed **appendix p5-6**) were performed at baseline; on days 1, 14 and 28 in the first two cycles [6-weeks cycle]; on days 1, 14, and 28 in subsequent cycles for nivolumab±ipilimumab and on day 1 of each subsequent cycle for VEGFR-TKI; at study treatment discontinuation.

Adverse events were evaluated continuously during treatment until the end of study, according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Treatment-related adverse events were defined as any adverse event with a causal relationship to any study drug (nivolumab, ipilimumab, VEGFR-TKI). Serious adverse events were assessed throughout the treatment period until the end of study.

## **Outcomes**

The primary endpoint was the objective response rate (the proportion of patients with a confirmed complete response or confirmed partial response at the time of data cutoff), per molecular group and treatment arm. Secondary endpoints were the objective response rate at 22 weeks (defined as the proportion of patients with an objective response at the first post-baseline imaging evaluation [scheduled at week 22]), progression-free survival (defined as time from first study dose to first documentation of disease progression or death; or, if neither, date of last available tumor assessment), overall survival (defined as time from first study dose to death from any cause), duration of response (defined as the time from when the criteria for a partial response or complete response were met, to the date of confirmed disease progression or death), duration of treatment (defined as the time from first to the last study dose) and safety and tolerability.

### ***Statistical analyses***

The BIONIKK trial being non-comparative, a proper sample size calculation was not mandatory. Moreover, at the study design stage, the following uncertainties would have made a formal sample size calculation rather difficult: first, the effect size in the different molecular groups was completely unknown; second, immunotherapy's overall efficacy in the first line setting was still unavailable. And finally, few data were available to accurately estimate molecular group prevalence. Therefore, the target sample size was set at 200 patients, based on the anticipated number of eligible patients at the selected sites and accrual time.

Efficacy and safety were assessed in the analysis population, comprising all randomized patients who received  $\geq 1$  dose of investigational drug. Patients were assessable if they had a baseline and a post-baseline (at week 10, +/- 7days) imaging assessment. The response rate was calculated as the number of patients with at least one response upon RECIST1.1 during participation to the total number of patients. The Kaplan–Meier method provided estimates of progression-free survival, duration of response and overall survival. The log-rank test was

used to assess between-group differences for progression-free survival and overall survival. A Cox proportional-hazards model was used to assess the magnitude of the time-to-event endpoints.

While the main results were obtained using a frequentist framework, a hierarchical Bayesian model borrowing strength across molecular groups within each arm was used as a sensitivity analysis (appendix p5).

*Post-hoc* analyses assessed the median time to subsequent (second-line) therapy, defined as the time between randomization to the beginning of second-line therapy or death, time to response (defined as the time from first study dose to the date when the criteria for a partial response or complete response were met), time to events in responding patients, as well as the percentage change in sums of diameters of target lesions from baseline to nadir. *Post-hoc* exploratory analyses examined the ability of the 8 immune-related genes of the classifier known to discriminate ccrcc1 and 4<sup>6</sup>, to also identify responders in patients with ccrcc2 tumors. In order to further explore molecular groups in light of clinical and biological features, we also conducted *post-hoc* descriptive exploratory analyses of IMDC risk groups, sarcomatoid component and PDL-1 TC expression effects.

An interim analysis for toxicity was planned after randomization of 100 patients for review by the Data and Safety Monitoring Board.

Statistical analyses were performed using SAS v9.4 (Cary, USA) and R version 3.6.1. Posterior probabilities of hierarchical Bayesian model were obtained from OpenBUGS. The full statistical analysis plan is available in section 8.0 of the protocol (**protocol appendix**).

This study is registered with ClinicalTrials.Gov (NCT02960906) and with the EU Clinical Trials Register (EudraCT 2016-003099-28).

### ***Role of the funding source***

This study was funded by Bristol Myers Squibb (New-York, NY, USA) and ARTIC (Paris, France). Funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The authors had full access to all the raw data reported in the study. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

## Results

Between June 28<sup>th</sup>, 2017 and July 18<sup>th</sup>, 2019, 303 patients were screened across 16 French centers. Of those, 236 patients were subject to molecular group determination (**figure 1**) with a median turn-around time from tumor sample reception to molecular result of 8 days. Of those, 202 patients were randomized and 200 patients finally received allocated treatment (two patients had a serious adverse event before the first study dose, both allocated to nivolumab) (**figure 1**). Main reasons for exclusion before molecular grouping (67) and before randomization (34) are described in figure 1. Finally, one patient treated with nivolumab was later excluded from all analyses because the histological diagnosis was subsequently corrected to urothelial carcinoma. Consequently, 199 patients were eligible for the efficacy and safety endpoints (analysis population), 58 treated with nivolumab, 101 treated with nivolumab–ipilimumab and 40 treated with VEGFR-TKI (including 33 with sunitinib, and 7 with pazopanib). Molecular group, obtained from kidney primary lesions in 144 patients and from metastases in 55 patients, were distributed as follows: 83 ccrc1 (42%), 73 ccrc2 (37%), 34 ccrc4 (17%), and 9 ccrc3 (4%). Patient demographic and baseline characteristics are summarized in table 1. Despite the observed differences in the frequency of some patient characteristics, randomization to each ccrc subgroup ensured comparability. Given the limited number of ccrc3 patients (N=9), only the primary endpoint is reported in the dedicated table.

After a median duration of follow-up in the analysis population of 18.0 months (Interquartile range (IQR) 17.6-18.4), 59 patients continued receiving treatment; 40 patients had died, four were withdrawn from the study by investigator's decision and three had withdrawn consent (**figure 1**).

The primary endpoint - objective response rate by investigator assessment per RECIST 1.1 - was met in 19 (33%), of 58, 45 (45%) of 101, and 18 (45%) of 40 patients treated with nivolumab alone, nivolumab–ipilimumab, and VEGFR-TKI, respectively, including three

(5%), ten (10%), and one (2.5%) complete response. In the ccrcc1 cohort, objective response rates with nivolumab alone and nivolumab–ipilimumab were 29% (12 of 42 patients) and 39% (16 of 41 patients) (odds ratio 0,63 [95%CI 0,25-1,56]), respectively, while in the ccrcc4 cohort they were 44% (7 of 16 patients) and 50% (9 of 18 patients) (odds ratio 0,78 [95%CI 0,20-3,01]) (**table 2**). In the ccrcc2 cohort, objective response rates with VEGFR-TKI and nivolumab–ipilimumab were 50% (18 of 36 patients) and 51% (19 of 37 patients) (odds ratio 0,95 [95%CI 0,38-2,37]), respectively. Duration of responses was not achieved in any group except with VEGFR-TKI in the ccrcc2 group (Table 2). Objective response rate at 22 weeks is shown in supplemental table 1 (appendix p7).

After a median duration of follow-up for progression-free survival of 16.2 months (IQR 15.9-17.3), 128 patients had an event (7 died, 121 progressed), 40 (69%) of 58 with nivolumab, 67 (66%) of 101 with nivolumab–ipilimumab and 21 (53%) of 40 with VEGFR-TKI. Corresponding median progression-free survival were 5.3 months (95% CI 2.4–9.1) with nivolumab, 10.4 months (95% CI 7.7–13.8) with nivolumab–ipilimumab and 13.5 months (95% CI 7.8–NR) with VEGFR-TKI. Median progression-free survival with nivolumab and nivolumab–ipilimumab were 5.2 (95%CI 2.4-9.1) months and 7.7 (5.0-12.9) months (HR 1,27 [0,77-2,11]) in the ccrcc1 cohort (**figure 2 panel A**) and 7.8 months (95%CI 2.3-NR) and 13.0 months (95%CI 2.5-NR) (HR 1,23 [0,50-3,03]) in the ccrcc4 cohort, respectively (**figure 2 panel B**). In the ccrcc2 cohort, median progression-free survival with VEGFR-TKI and nivolumab–ipilimumab were 14.4 months (95%CI 10.6-NR) and 11.1 months (95%CI 7.7-23.2), respectively (HR 0.75 [95%CI 0.40-1.39]) (**figure 2, panel C**).

After a median follow-up of 18.0 months (IQR: 17.6-18.4) for overall survival, 40 (20%) of 199 patients had died, 17 (29%) of 58, 15 (15%) of 101, and 8 (20%) of 40 patients treated with nivolumab, nivolumab–ipilimumab, and VEGFR-TKI, respectively. The median survival was not reached in each treatment arm.



*Post-hoc* analyses of the best percentage changes in sums of diameters of target lesions from baseline to nadir is shown in supplemental figure 2 (**appendix p12**). In total, 33 (57%) of 58, 65 (64%) of 101, and 29 (72%) of 40 had any decrease in the sum of the target lesions with nivolumab, nivolumab-ipilimumab and VEGFR-TKI. *Post-hoc* analysis of time to events in responding patients is represented in supplemental figure 3 (**appendix p13**). Majority of objective responses were obtained at the first imaging assessment (week 10), particularly in the nivolumab alone arm (16 [84%] of 19 patients). *Post-hoc* analyses of the median time to response is shown in table 2.

Of the 140 patients who discontinued treatment, 114 (81%) received subsequent therapy, 36 (86%) of 42 after nivolumab, 58 (82%) of 71 after nivolumab–ipilimumab, and 20 (74%) of 27 after VEGFR-TKI. Corresponding median time to subsequent treatment (post-hoc analysis) were 11.0 months (95% CI 6.4–NR), 14.4 months (95% CI 13.1–23.2), and 15.0 months (95% CI 9.6–NR), respectively (**appendix p7**). Interestingly, 3 (30%) of 10 ccrc4 patients who progressed on nivolumab-ipilimumab did not start a second line of therapy compared with 1 (10%) of 10 patients on nivolumab in ccrc4, 3 (10%) of 29 and 3 (12%) of 25 patients on nivolumab-ipilimumab in ccrc1 and ccrc2, respectively.

Estimated ORs and HRs from hierarchical Bayesian models were similar to their frequentist counterparts (**appendix p7**). This sensitivity analysis only applied to ccrc1 and ccrc4 patients who shared the same treatments, ccrc3 sample size being too small to share information with ccrc2.

*Post-hoc* descriptive exploratory analyses of objective response rate and median progression-free survival according to IMDC risk groups are shown in supplemental table 4 (**appendix p7**). Nivolumab-ipilimumab provided comparable response rates and progression-free survival in the three risk groups. Of note, among the 16 IMDC favorable patients treated with VEGFR-TKI, the response rate of the 14 patients with a ccrc2 group reached 64%.

In other exploratory *post hoc* analyses, the presence of a sarcomatoid component and PD-L1 TC $\geq$ 1% favored objective response with nivolumab-ipilimumab but not with VEGFR-TKI (**appendix p8**).

In view of the high response rates with both nivolumab-ipilimumab and VEGFR-TKI in the ccrcc2 patients, we wondered whether it could be divided into two subgroups with different sensitivity to treatments. Thus, we explored in a *post-hoc* analysis the response rate according to an immune signature, measured by the expression of 8 immune-related genes from our classifier (used to separate groups 1 and 4, **appendix p6**). When applying these eight genes to ccrcc1 and 4 tumors, we discriminated these two groups as expected (up-regulated in ccrcc4 and down-regulated in ccrcc1) (**appendix p13**). When applied to the 67 ccrcc2 patients, we identified two groups (**appendix p14**), immune-low to intermediate (N=45), and immune-high (N=22) with distinct response rate, exclusively favoring VEGFR-TKI or nivolumab-ipilimumab (**appendix p8**).

Median durations of treatment were 7.4, 8.4 and 8.1 months for nivolumab, nivolumab–ipilimumab, and VEGFR-TKI, respectively. Overall, 54 (93%) of 58, 100 (99%) of 101 and 38 (95) of 40 patients had a treatment-related adverse event with nivolumab, nivolumab-ipilimumab and VEGFR-TKI, respectively (**table 3**). Among those, the most common treatment-related grade 3-4 adverse events were hepatic failure (2 [3%] of 58 patients), lipase increase (6 [6%] of 101 patients) and hypertension (6 [15%] of 40 patients), respectively (**table 3**). Treatment-related adverse events in each group are presented in appendix (**pp8-11**). Treatment-related serious adverse events of any grade occurred in 2 (3%) of 58 patients with nivolumab, 38 (38%) of 101 patients with nivolumab-ipilimumab, and 10 (25%) of 40 patients with VEGFR-TKI (**table 3**), of which the most common events were hypophysitis and Meniere's disease, adrenal insufficiency (N=5) and acute renal failure (N=3), respectively. Treatment-related adverse events of any grade that led to treatment

discontinuation were observed in 3 (5%) of 58 patients with nivolumab, 24 (24%) of 101 patients with nivolumab-ipilimumab, and 5 (13%) of 40 patients with VEGFR-TKI, of which the most common events were hypophysitis, diarrhea and rash (N=1), hepatic failure (N=6), and thrombotic micro-angiopathy (N=2), respectively. In the nivolumab-ipilimumab arm, of the 101 patients, 78 (77%) and 11 (6%) received 4 and 3 first co-administrations of nivolumab and ipilimumab, respectively. Treatment-related adverse events of any grade that led to dose reduction were observed in 12 (30%) of 40 patients with VEGFR-TKI (10 of 33 with sunitinib, 2 of 7 with pazopanib); dose reduction was not allowed with nivolumab±ipilimumab.

Of the 40 patients who died during the study, 30 were related to disease progression and 3 were related to study treatment: a fulminant hepatitis related to both nivolumab and ipilimumab, a heart failure and a thrombotic microangiopathy related to sunitinib (**table 3**).

## DISCUSSION

To our knowledge, BIONIKK is the first reported randomized trial in front-line mRCC with treatment allocation based on prospective molecular classification. We demonstrate the feasibility of such a strategy by being able to provide the molecular group of the tumors within 15 days. Our results suggest potential increase efficacy of nivolumab, nivolumab-ipilimumab and VEGFR-TKI in certain molecular groups compared with published prospective cohorts<sup>2,9</sup>, validating our initial assumptions. Indeed, in the deemed immune-desert ccrcc1 group<sup>6,7</sup>, response rate is increased and median progression-free survival is prolonged by nivolumab-ipilimumab compared with nivolumab alone; at the opposite in the deemed immune-infiltrated and inflammatory ccrcc4 group, the response rates were very high and close for both arms. In addition, in the ccrcc4 group, both nivolumab-based treatment arms provided an increased response rate and prolonged median progression-free survival compared with the ccrcc1 group or other prospective cohorts with unselected patients<sup>2,9</sup>. The lower efficacy of nivolumab-based treatments in ccrcc1, together with the previously reported low efficacy of sunitinib<sup>6</sup>, prompt us to explore new treatment options. In the deemed pro-angiogenic ccrcc2 group, both VEGFR-TKI and nivolumab-ipilimumab provided high response rate, but the median progression-free survival was prolonged with VEGFR-TKI. Finally, the frequency of the reputed normal-like ccrcc3 tumors was lower in our study than previously reported<sup>6</sup> and did not allow to draw any conclusion.

Altogether our results suggest that ccrcc4 patients might be the best candidates to receive nivolumab-ipilimumab. The efficacy results of the combination are of particular interest in this group because this group is associated with poor prognostic factors (sarcomatoid component, IMDC poor risk group, PD-L1 expression) and low efficacy of sunitinib<sup>8,6,10</sup>. Irrespective of ccrcc group, patients treated with nivolumab-ipilimumab and belonging to IMDC intermediate-poor risk group had comparable efficacy results compared to those of the

pivotal trial CheckMate 214 (response rate 42%, median progression-free survival 11.6 months)<sup>2</sup>. Thus, the increased response rate and prolonged progression-free survival in ccrcc4 seem to be truly related to molecular selection. Furthermore, the higher response rate of nivolumab-ipilimumab in the presence of a sarcomatoid component (in contrast to VEGFR-TKIs), present in three quarters of ccrcc4 patients, reinforces the relevance of this molecular group in predicting response to this immunotherapy combination. Tannir et al similarly found an enhanced response rate (and close to ours, 60.8%) with nivolumab-ipilimumab in the presence of sarcomatoid features in a *post-hoc* analysis of the CheckMate 214<sup>11</sup>. That said, we found, as others before<sup>2,3</sup>, that a substantial fraction of patients receiving nivolumab-ipilimumab had a progressive disease as a best response, including ccrcc4 patients. However, the large difference in duration between median time to subsequent therapy and median progression-free survival suggests that there is a definite clinical benefit for some patients to continue treatment beyond progression. Escudier et al reported that 13% of patients treated with nivolumab beyond progression had a subsequent  $\geq 30\%$  tumor burden reduction, including 14% of patients with progression at the first assessment<sup>12</sup>. We observed that one-third of ccrcc4 patients who progressed at first assessment on nivolumab-ipilimumab did not need to start second-line therapy during the entire follow-up period of the study (median 18 months). These findings highlight the fact that the high rate of early progression with nivolumab-ipilimumab does not systematically reflect primary resistance. Alternative endpoints such as time to subsequent therapy may provide additional information related to a true clinical benefit for these patients.

The results of nivolumab in the ccrcc4 group unveil the highest objective response rate ever reported in a prospective trial evaluating an anti-PD-1 agent alone<sup>13,9,14,15</sup>. In the four trials that reported the efficacy of nivolumab alone as first-line therapy, response rates ranged from 13% to 32%<sup>13,9,14,15</sup>. The response rate was close in our overall cohort of nivolumab-treated

patients (33%) but higher in ccrcc4 patients (44%). As reported before, the median progression-free survival was short<sup>16</sup>. However, it was longer in ccrcc4 than in ccrcc1 patients and most importantly, the median time to subsequent therapy was significantly higher than the median progression-free survival (exceeding 12 months in ccrcc4), again suggesting a significant a potential prolonged clinical benefit beyond progression. In an ancillary analysis of the CheckMate 009 trial evaluating nivolumab alone, the authors tried to classify tumors in ccrcc groups and observed a similar response rate (47%) in their ccrcc4 group<sup>17</sup>. The TITAN-RCC trial, which evaluated an ipilimumab boost in non-responding patients to nivolumab alone in metastatic renal cell carcinoma, showed a little but interesting increase in objective response rate, from 28% with nivolumab alone to 36% with ipilimumab boost in first-line<sup>9</sup>. This selection strategy based on early radiological response could be effectively combined with our selection of ccrcc4 tumors to offer nivolumab monotherapy as a treatment option in frail patients who would not be suitable for upfront combination with ipilimumab.

At the opposite, VEGFR-TKI alone or in combination would be the best option in ccrcc2 patients, particularly in IMDC favorable group or with an immune-low gene expression signature in accordance with previous data<sup>6,8</sup>. These results may be partly due to a high proportion of IMDC favorable-risk patients and a pro-angiogenic tumor microenvironment<sup>8,18</sup>. Indeed, we found that the ccrcc2 cohort was enriched in favorable-risk patients relative to the other groups. Additionally, independently of the ccrcc classification, response rate with VEGFR-TKI was higher in IMDC favorable than in intermediate-poor risk groups. Updated results of CheckMate 214 and KEYNOTE 426 reported comparable response rate (around 50%) with sunitinib in IMDC favorable-risk patients<sup>19,20</sup>. However, combining the ccrcc2 group and IMDC favorable risk, the response rate (64%) was higher than in either group suggesting an additional influence of molecular group on response to VEGFR-TKI. Our results support the positioning of a VEGFR-TKI alone as a valid option for patients in the

ccrcc2 group with favorable risk IMDC. Indeed, the new standard of care in IMDC favorable patients pembrolizumab-axitinib<sup>21,22</sup>, failed to show any progression-free or overall survival benefit in that group. Interestingly, the exploratory analysis of the subgroup of patients with an immune-low to intermediate signature within ccrcc2 tumors deserve to be further explored since it predicted mutually exclusive responses between VEGFR-TKI and nivolumab-ipilimumab.

Due to the limited number of expected patients, the BIONIKK study was mainly designed to generate hypothesis, and not to change practices. Thus, our results have certain limitations. First, BIONIKK was designed as a non-comparative trial, impeding any statistical comparison. Anticipating a possible low accrual rate in a rapidly evolving landscape of front-line treatment, we selected only highly experienced centers that routinely freeze freshly acquired tumor samples. Nevertheless, a randomized design was chosen in order to ensure that per arms-molecular groups hazard ratios would be unbiased and to be able to generate new hypotheses. Second, if the VEGFR-TKI plus anti-PD-1 combination is now a standard of care in frontline mRCC<sup>21</sup>, at the time of the trial's design such combination was not yet evaluated. Nevertheless, our results suggest that VEGFR-TKI-anti-PD-1 combination may provide its best efficacy in the ccrcc2 cohort since both immunotherapy and VEGFR-TKI led to good efficacy.

Finally, we think our results are reliable since our crcc groups reveal biological distinct entities linked to the main tumor microenvironment features which are angiogenesis (ccrcc2) and T effector/immune-infiltration (ccrcc4 / ccrcc1, immune-infiltrated/-desert). Based on multi-omic analyses of the IMmotion 151 randomized phase III trial, Motzer et al. similarly described 7 distinct RCC tumor subtypes with various responses to bevacizumab plus atezolizumab<sup>23</sup>. The BIONIKK study is the first, but important step, in tailoring treatment

based on tumor molecular phenotype in mRCC and provides several elements useful for further prospective larger biomarker-based randomized trials.



## Contributors

Conception and design: YAV, RE, WHF, CSF, SO.

Supervision: YAV, RE, SO, CSF.

Acquisition of data: YAV, MB, CC, DB, DP, DM, MGG, CT, BL, PBa, EC, GG, NH, MC, OH, PBe, AM, XC, ND, PP, JCB, AdIT, KB, TT, TW, GP.

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Analysis and interpretation of the data: RE, LP, YAV, WHF, CSF, SO

Drafting of the manuscript: YAV, RE

Critical revision of the manuscript: All authors

Technical or material support: LF, SC, CMS, VV, GL, MMo, MMe, AB, CTC, JZR.

Administrative management: EB, RE, LP

Obtaining funding: YAV, RE, SO, WHF, CSF

YAV, LP, RE and SO have accessed and verified the data.

All authors had full access to the data and control of the final approval and decision to submit the manuscript for publication.

## Declaration of interest

### **YV**

Research findings: BMS, Ipsen (all, institution); Consultancy fees: None; Advisory board/DSMB: BMS, Roche; Honoraria for lectures, presentations: BMS, MSD, Ipsen, Merck, Pfizer, Roche, Novartis, Janssen, Astellas, Viartis; Support for Travel/meeting: BMS, MSD, Pfizer, Ipsen, Roche.

### **RE**

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### **CC**

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### **MGG**

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**EC**

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**GG**

Research findings: None; Consultancy fees: None; Advisory board/DSMB: Bristol Myers Squibb, Janssen, Ipsen, Sanofi/Aventis, MSD Oncology, Pfizer, Bayer, AstraZeneca; Honoraria for lectures, presentations: Janssen Oncology, Ipsen, Bristol Myers Squibb, Amgen, Sanofi/Aventis, MSD Oncology, Astellas Pharma (all fees for institution); Support for Travel/meeting: Janssen Oncology, Bristol Myers Squibb, Astellas Pharma, Pfizer, Ipsen, Sanofi, AstraZeneca

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**MC**

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**AM**

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**XC**

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**ND**

Research findings: None; Consultancy fees: None; Advisory board/DSMB: None; Honoraria for lectures, presentations: None; Support for Travel/meeting: None

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Research findings: None; Consultancy fees: None; Advisory board/DSMB: None; Honoraria for lectures, presentations: None; Support for Travel/meeting: None

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Research findings: None; Consultancy fees: None; Advisory board/DSMB: None; Honoraria for lectures, presentations: None; Support for Travel/meeting: None

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**KB**

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**TT**

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**CMS**

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**VV**

Research findings: None; Consultancy fees: None; Advisory board/DSMB: None; Honoraria for lectures, presentations: None; Support for Travel/meeting: None

**GL**

Research findings: None; Consultancy fees: None; Advisory board/DSMB: None; Honoraria for lectures, presentations: None; Support for Travel/meeting: None

**MM**

Research findings: None; Consultancy fees: None; Advisory board/DSMB: None; Honoraria for lectures, presentations: None; Support for Travel/meeting: None

**MxM**

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**AB**

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**LP**

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**CTC**

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**JZR**

Research findings: None; Consultancy fees: None; Advisory board/DSMB: None; Honoraria for lectures, presentations: None; Support for Travel/meeting: None

**WHF**

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**CSF**

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### **Clinical trial information**

This study is registered with ClinicalTrials.Gov (NCT02960906) and with the EU Clinical Trials Register (EudraCT 2016-003099-28).

### **DATA SHARING STATEMENT**

Will individual participant data be available (including data dictionaries)?

Yes

What data in particular will be shared?

*Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices).*

What other documents will be available?

*Study Protocol, Statistical Analysis Plan, Informed Consent Form*

When will data be available (start and end dates)?

*Beginning 18 months and ending 36 months following article publication*

With whom?

*Upon proposal from investigators whose proposed use of the data has been approved by an independent review committee ("learned intermediary") identified for this purpose*

For what types of analyses?

*To achieve aims in the approved proposal*

By what mechanism will data be made available?

*Proposals should be directed to [yann.vano@aphp.fr](mailto:yann.vano@aphp.fr). To gain access, data requestors will need to sign a data access agreement.*

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## Figure legends and footnotes

### Figure 1, Trial profile

*Footnotes: ¶: Two patients had a serious adverse event before receiving the first administration of allocated treatment and were therefore excluded from the trial; one patient had an urothelial carcinoma instead of a clear cell renal cell carcinoma, which was confirmed after a second pathological review. \*At 18 months; \*\*analysis population: all randomized patients who received  $\geq 1$  dose of investigational drug; \*\*\* one patient developed a second locally advanced cancer requiring specific treatment.*

*TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor*

### Figure 2. Progression-free survival

Panel A. Kaplan-Meier analysis of progression free survival in ccrc1

The blue curve represents patients treated with nivolumab; the red curve represents patients treated with nivolumab-ipilimumab.

Panel B. Kaplan-Meier analysis of progression free survival in ccrc4

The blue curve represents patients treated with nivolumab; the red curve represents patients treated with nivolumab-ipilimumab.

Panel C. Kaplan-Meier analysis of progression free survival in ccrc2

The blue curve represents patients treated with VEGFR-TKI; the red curve represents patients treated with nivolumab-ipilimumab.

*Footnotes: TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor*

## Tables

**Table 1. Demographic and Clinical Characteristics at Baseline**

	ccrcc1		ccrcc4		ccrcc2		ccrcc3	
	Nivolumab (N=42)	Nivolumab- Ipilimumab (N=41)	Nivolumab (N=16)	Nivolumab- Ipilimumab (N=18)	VEGFR- TKI <sup>a</sup> (N=36)	Nivolumab- Ipilimumab (N=37)	VEGFR- TKI <sup>a</sup> (N=4)	Nivolumab- Ipilimumab (N=5)
<b>Age, years</b>	61 (52–68)	65 (54–73)	64 (56–66)	65 (56–72)	66 (56– 71)	65 (57–69)	64 (55– 68)	59 (49–63)
<b>Male</b>	26 (62)	34 (83)	13 (81)	14 (78)	25 (69)	33 (89)	1 (25)	2 (40)
<b>ECOG PS,</b>								
0	26 (62)	28 (68)	13 (81)	15 (83)	25 (69)	32 (87)	3 (75)	3 (60)
1	12 (29)	11 (27)	1 (6)	3 (17)	11 (31)	5 (14)	1 (25)	2 (40)
2	4 (10)	2 (5)	2 (13)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
<b>Prior nephrectomy</b>	28 (67)	30 (73)	11 (69)	14 (78)	27 (75)	29 (78)	3 (75)	2 (40)
<b>IMDC</b>								
Favorable	10 (24)	9 (22)	3 (19)	4 (22)	14 (39)	16 (43)	2 (50)	1 (20)
Intermediate	17 (41)	25 (61)	8 (50)	11 (61)	18 (50)	15 (41)	2 (50)	2 (40)
Poor	15 (36)	7 (17)	5 (31)	3 (17)	4 (11)	6 (16)	0 (0)	2 (40)
<b>No. of metastatic sites</b>								
1	22 (52)	20 (49)	7 (44)	7 (39)	17 (47)	21 (57)	1 (25)	1 (20)
≥2	20 (48)	21 (51)	9 (56)	11 (61)	19 (53)	16 (43)	3 (75)	4 (80)
<b>Metastasis sites</b>								
Lung	32 (76)	27 (66)	9 (56)	16 (89)	27 (75)	30 (81)	2 (50)	4 (80)
Lymph nodes	11 (26)	19 (46)	7 (44)	9 (50)	11 (31)	13 (35)	3 (75)	1 (20)
Liver	12 (29)	13 (32)	2 (13)	3 (17)	9 (25)	4 (11)	3 (75)	2 (40)
Bone	10 (24)	10 (24)	6 (38)	4 (22)	8 (22)	3 (8)	2 (50)	2 (40)
<b>Sarcomatoid</b>	12 (29)	12 (29)	5 (31)	13 (72)	7 (19)	2 (5)	2 (50)	0 (0)
<b>PD-L1, evaluable</b>	26 (62)	34 (83)	10 (56)	17 (94)	31 (86)	27 (73)	3 (75)	3 (60)
TC ≥1% <sup>b</sup>	6 (23)	4 (12)	2 (20)	3 (18)	0 (0)	4 (15)	2 (67)	0 (0)

Data are median (IQR) or n (%); ccrcc, clear-cell renal cell carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; MDC, International Metastatic RCC Database Consortium; IQR, interquartile range; PD-L1, programmed death-ligand 1; TC, tumor cells; TKI, tyrosine kinase inhibitor VEGFR, vascular endothelial growth factor receptor

<sup>a</sup>Of the 40 patients who received VEGFR-TKI, 33 received sunitinib and 7 received pazopanib

<sup>b</sup>Percentages are calculated in evaluable patients



**Table 2. Tumor responses**

	ccrcc1		ccrcc4		ccrcc2		ccrcc3	
	Nivolumab (N=42)	Nivolumab- Ipilimumab (N=41)	Nivolumab (N=16)	Nivolumab- Ipilimumab (N=18)	VEGFR- TKI <sup>a</sup> (N=36)	Nivolumab- Ipilimumab (N=37)	VEGFR- TKI <sup>a</sup> (N=4)	Nivolumab- Ipilimumab (N=5)
<b>Objective response rate</b>	29 (16-45)	39 (24-55)	44 (20-70)	50 (26-74)	50 (33-67)	51 (34-68)	0	20 (01-72)
Odds ratio (95% CI)	0.63 (0.25-1.56)	Reference	0.78 (0.20-3.01)	Reference	0.95 (0.38-2.37)	Reference	NE	Reference
<b>Best overall response<sup>b</sup></b>								
Complete response	2 (5)	2 (5)	1 (6)	2 (11)	1 (3)	6 (16)	0 (0)	0 (0)
Partial response	10 (24)	14 (34)	6 (38)	7 (39)	17 (47)	13 (35)	0 (0)	1 (20)
Stable disease	12 (29)	14 (34)	2 (13)	3 (17)	8 (22)	12 (32)	2 (50)	2 (40)
Progressive disease	17 (40)	11 (27)	6 (38)	6 (33)	6 (17)	5 (14)	2 (50)	1 (20)
Not evaluable	1 (2)	0 (0)	1 (6)	0 (0)	4 (11)	1 (3)	0 (0)	1 (20)
<b>Duration of response, months</b>	NR (6.0-NR)	NR (8.3-NR)	NR (NR-NR)	NR (11.6-NR)	14.7 (10.7-NR)	NR (11.8-NR)	NE	NR (NR-NR)
<b>Time to response, months</b>	2.4 (2.3-NR)	2.5 (2.2-5.3)	2.2 (2.2-NR)	4.5 (2.3-NR)	4.9 (2.8-16.5)	2.4 (2.3-5.0)	NE	NR (2.2-NR)

Data are n (%), % (95%CI), or median (95%CI); ccrcc, clear-cell renal cell carcinoma; CI, confidence interval; NE, not evaluable; NR, not reached; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

<sup>a</sup>Of the 40 patients who received VEGFR-TKI, 33 received sunitinib and 7 received pazopanib

<sup>b</sup>Percentages may not total 100 due to rounding

**Table 3. Summary of treatment-related adverse event**

	Nivolumab (N=58)				Ipilimumab-Nivolumab (N=101)				VEGFR-TKI <sup>a</sup> (N=40)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
All events	45 (76)	8 (14)	1 (2)	0	55 (54)	33 (33)	11 (11)	1 (1)	12 (30)	23 (58)	1 (3)	2 (5)
Serious events	1 (2)	0	1(2)	0	8 (8)	25 (25)	4 (4)	1 (1)	2 (5)	6 (15)	1 (3)	1 (3)
Events leading to treatment discontinuation	1 (2)	1 (2)	1 (2)	0	6 (6)	15 (15)	2 (2)	1 (1)	1 (3)	3 (8)	0	2 (5)
Events leading to dose reduction	NA <sup>b</sup>	NA <sup>b</sup>	NA <sup>b</sup>	NA <sup>b</sup>	NA <sup>b</sup>	NA <sup>b</sup>	NA <sup>b</sup>	NA <sup>b</sup>	4 (10)	8 (20)	0	0
Treatment-related adverse events‡												
Fatigue	29 (50)	1 (2)	0	0	53 (52)	2 (2)	1 (1)	0	26 (65)	0	1 (3)	0
Diarrhea	8 (14)	1 (2)	0	0	32 (32)	2 (2)	0	0	21 (53)	4 (10)	0	0
Nausea	6 (10)	0	0	0	17 (17)	0	0	0	14 (35)	0	0	0
Mucositis oral	3 (5)	0	0	0	12 (12)	0	0	0	17 (43)	0	0	0
Hypothyroidism	4 (7)	0	0	0	19 (19)	1 (1)	0	0	13 (33)	1 (3)	0	0
Pruritus	14 (24)	0	0	0	31 (31)	0	0	0	1 (3)	0	0	0
Anorexia	4 (7)	0	0	0	18 (18)	1 (1)	0	0	9 (23)	0	0	0
Dysgeusia	1 (2)	0	0	0	3 (3)	0	0	0	17 (43)	0	0	0
Skin and subcutaneous tissue disorders	9 (16)	0	0	0	11 (11)	0	0	0	7 (18)	1 (3)	0	0
Hyperthyroidism	8 (14)	0	0	0	14 (14)	2 (2)	0	0	3 (8)	0	0	0
Palmar-plantar erythrodysesthesia syndrome	0	0	0	0	2 (2)	0	0	0	13 (33)	3 (8)	0	0
Rash maculo-papular	10 (17)	1 (2)	0	0	14 (14)	1 (1)	1 (1)	0	1 (3)	1 (3)	0	0
Thrombotic thrombocytopenic purpura	0	0	0	0	0	0	0	0	0	1 (3)	0	0
Gastroesophageal reflux disease	0	0	0	0	0	0	0	0	0	1 (3)	0	0
Renal and urinary disorders	0	0	0	0	0	1 (1)	0	0	0	0	0	0
Proteinuria	0	0	0	0	0	0	0	0	0	1 (3)	0	0
Blood and lymphatic system disorders	0	0	0	0	0	1 (1)	0	0	0	1 (3)	0	1 (3)
Papulopustular rash	0	0	0	0	0	1 (1)	0	0	0	0	0	0

Pancreatitis	0	0	0	0	0	0	0	0	0	1 (3)	0	0
Anemia	0	0	0	0	0	1 (1)	0	0	0	1 (3)	0	0
Platelet count decreased	0	0	0	0	0	0	0	0	0	1 (3)	0	0
Fever	0	0	0	0	0	1 (1)	0	0	0	0	0	0
Rash acneiform	0	0	0	0	0	0	1 (1)	0	0	1 (3)	0	0
Bone marrow hypocellular	0	0	0	0	0	0	0	0	0	1 (3)	0	0
Skin infection	0	0	0	0	0	1 (1)	0	0	0	0	0	0
Hepatic failure	0	2 (3)	0	0	0	1 (1)	0	1 (1) <sup>b</sup>	0	1 (3)	0	0
Hepatobiliary disorders	0	0	0	0	0	5 (5)	1 (1)	0	0	0	0	0
Neutrophil count decreased	0	0	0	0	0	0	0	0	0	4 (10)	0	0
Endocrine disorders	0	0	1 (2)	0	0	2 (2)	0	0	0	0	0	0
Myocarditis	0	0	0	0	0	1 (1)	0	0	0	0	0	0
Musculoskeletal and connective tissue disorder - Other, specify	0	0	0	0	0	1 (1)	0	0	0	0	0	0
Aspartate aminotransferase increased	0	0	0	0	0	1 (1)	1 (1)	0	0	1 (3)	0	0
Lipase increased	0	2 (3)	0	0	0	2 (2)	4 (4)	0	0	1 (3)	0	0
Investigations	0	1 (2)	0	0	0	0	0	0	0	0	0	0
Allergic reaction	0	0	0	0	0	0	0	0	0	1 (3)	0	0
Infections and infestations	0	0	0	0	0	1 (1)	1 (1)	0	0	0	0	0
Immune system disorders	0	0	0	0	0	0	1 (1)	0	0	0	0	0
Dyspnea	0	0	0	0	0	2 (2)	0	0	0	1 (3)	0	0
Back pain	0	0	0	0	0	1 (1)	0	0	0	0	0	0
Epistaxis	0	0	0	0	0	0	0	0	0	1 (3)	0	0
Arthritis	0	0	0	0	0	3 (3)	0	0	0	0	0	0
Colitis	0	0	0	0	0	2 (2)	0	0	0	0	0	0
Hypoglycemia	0	0	0	0	0	2 (2)	0	0	0	0	0	0
Adrenal insufficiency	0	0	0	0	0	3 (3)	0	0	0	0	0	0
Febrile neutropenia	0	0	0	0	0	1 (1)	0	0	0	2 (5)	0	0
Pneumonitis	0	0	0	0	0	3 (3)	0	0	0	0	0	0
Blood bilirubin increased	0	0	0	0	0	0	0	0	0	1 (3)	0	0
GGT increased	0	0	0	0	0	1 (1)	0	0	0	0	0	0
Cardiac troponin I increased	0	0	0	0	0	1 (1)	0	0	0	0	0	0
Hypertension	0	0	0	0	0	0	0	0	0	6 (15)	0	0
Serum amylase increased	0	1 (2)	0	0	0	2 (2)	0	0	0	0	0	0
Hyperglycemia	0	1 (2)	0	0	0	2 (2)	0	0	0	0	0	0

Heart failure	0	0	0	0	0	0	0	0	0	0	0	1 (3)
Bronchial infection	0	0	0	0	0	1 (1)	0	0	0	1 (3)	0	0
Urticaria	0	1 (2)	0	0	0	0	0	0	0	0	0	0
Abdominal pain	0	0	0	0	0	0	0	0	0	1 (3)	0	0
Acute kidney injury	0	0	0	0	0	1 (1)	0	0	0	1 (3)	0	0
Alanine aminotransferase increased	0	0	0	0	0	3 (3)	0	0	0	1 (3)	0	0
Arthralgia	0	0	0	0	0	1 (1)	0	0	0	0	0	0
CPK increased	0	0	0	0	0	0	1 (1)	0	0	0	0	0
Hypercalcemia	0	0	0	0	0	1 (1)	0	0	0	0	0	0

Data are n (%); AEs, adverse events; NA, not applicable; TKI, tyrosine kinase inhibitor; TRAEs, treatment-related adverse events; VEGFR, vascular endothelial growth factor receptor.

‡Events occurring in ≥10% of patients or grade 3–5 events occurring in ≥1% of patients are shown.

<sup>a</sup>sunitinib: n=33; pazopanib: n=7.

<sup>b</sup>Dose reduction was not allowed with nivolumab and ipilimumab