Real-World Data on the Use of Nivolumab Monotherapy in the Treatment of Advanced Renal Cell Carcinoma after Prior Therapy: Interim Results from the Noninterventional NORA Study

Marc-Oliver Grimm a,*, Viktor Grünwald b, Harald Müller-Huesmann c, Philipp Ivanyi d, Martin Schostak e, Eyck von der Heyde f, Wolfgang Schulter-Seemann g, Hanjo Belz h, Martin Bögemann i, Meng Wang j, Martin Herber k, Jens Bedke l, for the NORA Study Group

a Department of Urology, Jena University Hospital, Jena, Germany; b Medical Oncology and Urology Clinics, West-German Cancer Center Essen, Essen University Hospital, Essen, Germany; c Department of Internal Medicine, Hematology and Oncology, Brüderkrankenhaus St. Josef, Paderborn, Germany; d Clinic for Hematology, Hemostaseology, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany; e Department of Urology, Urooncology, Robot-Assisted and Focal Therapy, Magdeburg University Hospital, Magdeburg, Germany; f Gemeinschaftspraxis für Strahlentherapie und Radioonkologie, Onkologische Praxis am Raschplatz, Hannover, Germany; g Department of Urology, Freiburg University Hospital, Freiburg, Germany; h Zeisigwaldkliniken Bethanien, Chemnitz, Germany; i Department of Urology, Münster University Hospital, Münster, Germany; j Bristol-Myers Squibb UK, Uxbridge, UK; k Bristol-Myers Squibb Germany, Munich, Germany; l Department of Urology, Eberhard Karls University, Tübingen, Germany

Article info

Article history:
Accepted November 26, 2021
Associate Editor: Christian Gratzke

Keywords:
Advanced renal cell carcinoma
Nivolumab
Real-world data
Effectiveness
Safety

Abstract

Background: Nivolumab monotherapy is approved for the treatment of advanced renal cell carcinoma (aRCC) after prior therapy on the basis of results from CheckMate 025.

Objective: The NORA (NivOlumab in Renal cell Arcinoma) noninterventional study (NIS) aims to capture real-world data to complement the pivotal CheckMate 025 clinical trial.

Design, setting, and participants: NORA is a prospective, multicenter NIS in Germany. Consenting patients with aRCC of any subtype who started nivolumab after previous therapy were eligible.

Outcome measurements and statistical analysis: The primary objective was to estimate overall survival (OS) in the overall population and relevant subgroups. Secondary objectives included progression-free survival (PFS), the objective response rate (ORR), the duration of response (DOR), safety, and patient-reported outcomes (PROs). Baseline characteristics were summarized using descriptive statistics. OS and PFS were estimated via the Kaplan-Meier-method.

Results and limitations: A total of 228 patients with aRCC were eligible. The median age was 70 yr, 71% were male, 14% had favorable, 58% had intermediate, and 15% had poor International Metastatic RCC Database Consortium risk (12% missing information). The median follow-up was 37 mo. In the overall population, median OS was 24 mo (95% confidence interval [CI] 19–28) and median PFS was 5.3 mo (95% CI 3.9–6.7). The ORR was 20% and the median DOR was 28 mo (95% CI 16–not estimable). No new safety signals emerged (46% and 15% of patients had treatment-related adverse events of all grades and grade 3–4, respectively; there was 1 treatment-related death due to liver failure). PROs did not reveal detriments during the study duration. Limitations include the lack...
of central pathology review and no standardization for imaging evaluation and toxicity assessment.

Conclusions: Effectiveness and safety in this real-world population were in line with the pivotal clinical trial and support the use of nivolumab after prior systemic therapy in a broad aRCC population.

Patient summary: Nivolumab is an antibody treatment approved for patients with advanced kidney cancer who have already received systemic therapy. Its approval was based on results from a clinical trial. Our study demonstrates its effectiveness and safety in “real-world” patients.

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1. Introduction

The European Medicines Agency approved the immune checkpoint inhibitor (ICI) nivolumab in 2016 as the first antibody targeting PD-1 for the treatment of advanced renal cell carcinoma (aRCC) after prior therapy [1]. The decision was based on results from the pivotal phase III CheckMate 025 (CM025) randomized clinical trial (RCT) that enrolled patients with aRCC in the second to fourth line [2]. Long-term follow-up demonstrates a continuous benefit with nivolumab in comparison to everolimus, a prior second-line standard therapy. Nivolumab showed a significant improvement in overall survival (OS; 26 vs 20 mo; hazard ratio [HR] 0.73, 95% confidence interval [CI] 0.62–0.85), a significantly higher objective response rate (ORR; 23% vs 4%), and a better toxicity profile. Progression-free survival (PFS) also favored nivolumab (HR 0.84, 95% CI 0.72–0.99; p = 0.0331) [3]. According to European and German guidelines on RCC, nivolumab monotherapy is a standard of care (SOC) in second-line therapy after progression on treatment with a VEGFR tyrosine kinase inhibitor (TKI) [4–6].

However, the conditions in RCTs only partially reflect routine clinical practice, in which nivolumab is applied without strict selection criteria [1,7]. For CM025, only patients with predominant clear-cell (cc) tumor histology, Karnofsky performance score (KPS) ≥70, and a maximum of three previous lines of systemic treatment (one or two antiangiogenic therapies) were included [2]. In CM025, prior treatment with an mTOR inhibitor was prohibited, as well as any history of or current metastases of the central nervous system.

Real-world data may complement data obtained from RCTs and may demonstrate effectiveness in a broader population that includes patient subgroups that were poorly studied so far (eg, elderly patients and patients with non-clear cell [ncc] histology or KPS <70) and can thus provide support for therapeutic decisions. Moreover, assessment of safety data in the post-approval setting is of paramount importance.

The present noninterventional study (NIS) NORA (Nivolumab in Renal cell aRcInoma) was designed to capture the early period after market authorization approval for nivolumab. The study aim was to describe the outcomes, patient characteristics, safety, and treatment patterns among adults with aRCC starting a second-line or later systemic treatment with nivolumab overall and by subgroups of interest.

2. Patients and methods

NORA (NCT02940639) is a prospective, observational, multicenter NIS in Germany (54 active study sites for the second-line and further cohort) supported by the Arbeitsgemeinschaft Urologische Onkologie study group (AN 47/17). It collects real-world data on effectiveness, safety, and patient-reported outcomes (PROs) from aRCC patients starting systemic nivolumab monotherapy after prior therapy according to the German marketing authorization. Patients were enrolled from October 2016 to December 2018. Results are reported from the fourth interim analysis (cutoff date December 31, 2020) with minimum follow-up of 24 mo (median follow-up 37 mo).

The trial was approved by all relevant ethics committees and regulatory authorities and was conducted in compliance with the International Society for Pharmacoepidemiology guidelines for good pharmacoepidemiology practice and the Declaration of Helsinki [8]. Before entering the study, all patients signed to indicate their informed consent.

2.1. Inclusion and exclusion criteria

Eligible patients were adults aged ≥18 yr who were diagnosed with histologically and cytologically confirmed aRCC with cc or ncc histology according to local pathology reports and who started nivolumab treatment after prior therapy (at least the 2nd line). Patients were excluded if they had a second cancer within the previous 5 yr (except for prostate cancer on active surveillance), had previously received nivolumab and/or ipilimumab, or were currently included in an interventional clinical study.

2.2. Objectives

The primary objective was OS estimation in the overall population and by relevant subgroup. Secondary objectives included estimation of progression-free survival (PFS), best overall response (BOR), the objective response rate (ORR) and disease control rate (DCR), and the duration of response (DOR) in the overall population and in relevant subgroups. Progression was assessed by the investigator on the basis of clinical or, if available, imaging evaluations according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1).

The incidence, severity, and management of adverse events (AEs) and treatment-related AEs (trAEs) were evaluated and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Event (CTCAE v4.0) grading system. PROs were assessed at baseline, in week 6, and at months 3, 6, 9, 12, 18, 24, 36, 48, and 60 using the Functional Assessment of Cancer Therapy–Kidney Symptom Index-19 (FKSI-19) and European Quality of Life 5 Dimensions 3 Level (EQ-5D-3L) questionnaires.

Please cite this article as: Marc-Oliver Grimm, V. Grünwald, H. Müller-Huesmann et al., Real-World Data on the Use of Nivolumab Monotherapy in the Treatment of Advanced Renal Cell Carcinoma after Prior Therapy: Interim Results from the Noninterventional NORA Study, Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.11.006
2.3. Statistical analysis

All patients fulfilling the study entry criteria were included in the data set for analyses. As NORA is of descriptive character, no formal hypotheses were tested and no comparative analyses assessing the effectiveness of other treatments were undertaken. Instead, patient and clinical characteristics were summarized using descriptive statistics to provide context for the observations for patients treated with nivolumab in real life. The statistical analysis was performed using SAS v9.4 (SAS Institute, Cary, NC, USA).

OS and PFS were estimated using the Kaplan-Meier method. The median and two-sided 95% CIs were calculated. The index date (day 0) corresponds to the day of the first dose of nivolumab treatment. Patients were censored at the last record or assessment for those lost to follow-up, or the date of enrollment into a clinical trial. ORR, DCR, and BOR are reported as rates. Subgroup analyses were conducted in a complete case manner.

3. Results

In total, 228 patients were eligible and enrolled in NORA and their data for effectiveness and safety were analyzed. The baseline patient characteristics are summarized in Table 1. The median age was 70 yr (range 44–86) and 71% of the patients were male. Of the patients, 77% had a documented KPS ≥70, the majority (58%) had intermediate International Metastatic RCC Database Consortium (IMDC) risk (14% favorable, 15% poor, 12% missing information; assessed according to [9,10]), and 86% had undergone prior nephrectomy. The predominant histology was ccRCC in 81%

We coded trAEs by severity grade, with results reported using descriptive statistics. PROs were assessed as the mean change from baseline in week 6 and at months 3, 6, 9, 12, 18, 24, and 36.
of the patients; nccRCC histologies included papillary type 1 (4.8%), papillary type 2 (5.7%), chromophobe (1.8%), and others (4.4%). A sarcomatoid fraction was noted in 4.4% of the patients. The most common metastases were in the lung (4.8%), papillary type 2 (5.7%), chromophobe (1.8%), and others (4.4%). A sarcomatoid fraction was noted in 4.4% of the patients. The most common metastases were in the lung (4.8%), papillary type 2 (5.7%), chromophobe (1.8%), and others (4.4%).

### Treatment characteristics

Nivolumab treatment characteristics are shown in Table 2. For 56% of the patients more than 12 mo had passed between their primary diagnosis and the start of the first systemic treatment. At the first nivolumab dose, the median time since initial RCC diagnosis was 31 mo (range 1.6–363). Treatment discontinuation due to a trAE was considered by the investigator to be nivolumab-related in only 4.8% of the patients with brain metastases. The most frequent prior second-line therapies were pazopanib, axitinib (31% each of 51 patients receiving nivolumab as ≥3rd line), and everolimus (20%). Treatments in prior third and later lines were more diverse.

In NORA, the median treatment duration was 6.9 mo (95% CI 6.0–8.5). At the data cutoff point, 196 patients had discontinued nivolumab treatment. The main reasons for discontinuation were disease progression (52%), death (18%), non-trAEs (8.3%), and trAEs (4.4%).

### 3.2. Real-world effectiveness

Median OS for the overall population was 24.3 mo (95% CI 19–28) with OS rates of 65% (95% CI 59–71%) at 1 yr, 51% (95% CI 44–58%) at 2 yr, and 37% (95% CI 28–45%) at 3 yr (Fig. 1A). Median PFS was 5.3 mo (95% CI 3.9–6.7; Fig. 2A).

The ORR was 20% in the overall population; three patients (1.3%) experienced a complete response. Another 26% of patients achieved stable disease, which corresponds to a DCR of 46%; 33% had progressive disease as their best response (Table 3). At data cutoff, the estimated median DOR was 28 mo (95% CI 16–not estimable; from 17 responders with a documented progressive disease date and without censoring; Fig. 3).

Subgroup analyses revealed lower median OS and ORR in the nccRCC group compared to ccRCC (median OS 13 mo [95% CI 5.3–26] vs 24 mo [95% CI 21–34]; ORR 16% vs 22%; Fig. 1B and Table 3). Furthermore, ORR was lower for later lines of treatment (2nd line 23% vs ≥3rd line 12%). However, the median duration of nivolumab treatment and the respective Kaplan-Meier plots were similar irrespective of the treatment line (data not shown). Of 11 patients with brain metastases, three had a partial response, one experienced stable disease, and five had progressive disease as their BOR (data missing for 2 patients). Further subgroup analyses for OS revealed that median OS was not reached (NR) for patients with favorable IMDC risk and was 24 mo for the intermediate group and 12 mo for the poor risk group (Fig. 1C), and was longer for higher KPS, at 26 mo for KPS ≥70 and 6.1 mo for KPS <70 (Supplementary Fig. 1A). OS did not differ by patient age or the presence of bone metastases (Supplementary Fig. 1B,C). PFS subgroup analyses revealed similar trends (Fig. 2B, Supplementary Fig. 2A–D).

### 3.3. Safety outcomes

A total of 301 trAEs (any grade) were reported by 105 patients (46%) in the overall cohort (Table 4). The most frequent trAE was diarrhea (9.2%), followed by fatigue (6.6%), malignant neoplasm progression (6.1%), pruritus (5.7%), and rash (4.4%). Thirty-four patients (15%) had at least one grade 3–4 trAE, with malignant neoplasm progression (3.1%) and diarrhea (1.8%) being the most common. One grade 5 trAE occurred (liver failure). Of the 301 trAEs, 11% were managed with treatment interruption. Treatment was discontinued for another 12% of trAEs of any cause; however, treatment discontinuation due to a trAE was considered by the investigator to be nivolumab-related in only 4.4% of the patients.
3.4. Quality of life

The number of evaluable baseline questionnaires completed by the 228 NORA patients was 201 for the EQ-5D Visual Analog Scale (VAS) and 213 for FKSI-19. Up to 18 mo, more than half of the overall population were eligible for PRO assessments. The proportion of EQ-5D VAS and FKSI-19 questionnaires completed by patients with ongoing treatment was 66% and 77% at 6 wk, 57% and 62% at 6 mo, and 48% and 53% at 12 mo, respectively. PRO results are

Fig. 1 – Overall survival (OS) in (A) the overall population, (B) tumor histology subgroups, and (C) IMDC risk groups (favorable, intermediate, poor). CI = confidence interval; RCC = renal cell carcinoma; cc = clear cell; ncc = non-clear cell; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; NR = not reached.
Table 3 – Antitumor activity: best overall response to nivolumab monotherapy after at least one prior treatment line for the overall NORA population and by histology subgroup in comparison to the CheckMate 025 cohort a

| Parameter                  | NORA trial Overall (n = 228) | NORA trial ccRCC (n = 184) | NORA trial nccRCC (n = 38) | CheckMate 025 (n = 410) [23] |
|---------------------------|------------------------------|----------------------------|---------------------------|------------------------------|
| Objective response rate (%)| 20                           | 22                         | 16                        | 26                           |
| Disease control rate (%)   | 46                           | 47                         | 39                        | 60                           |
| Best overall response, n (%)|                             |                            |                           |                              |
| Complete response          | 3 (1.3)                      | 2 (1.1)                    | 1 (2.6)                   | 4 (1)                        |
| Partial response           | 43 (19)                      | 38 (21)                    | 5 (13)                    | 102 (25)                     |
| Stable disease             | 60 (26)                      | 47 (26)                    | 9 (24)                    | 137 (33)                     |
| Progressive disease        | 75 (33)                      | 60 (33)                    | 14 (37)                   | 143 (35)                     |
| Missing                    | 47 (21)                      | 37 (20)                    | 9 (24)                    | 24 (6)                       |

ccRCC = clear-cell renal cell carcinoma; ncc = non–clear-cell renal cell carcinoma.

a According to Response Evaluation Criteria in Solid Tumors (response assessed at site level according to clinical practice).

Fig. 2 – Progression-free survival (PFS) in (A) the overall population and (B) tumor histology subgroups. CI = confidence interval; RCC = renal cell carcinoma; cc = clear cell; ncc = non–clear cell.
reported for time points up to 36 mo (Fig. 4), but were only interpreted up to 12 mo because of the low number of patients with ongoing treatment and the small proportion of questionnaires completed at later time points. EQ-5D VAS revealed no change in quality of life (QoL) during the first year of nivolumab treatment. RCC-specific PROs reported with FKSI-19 also remained stable during the first year of nivolumab treatment.

4. Discussion

NORA recorded real-world data for nivolumab monotherapy in aRCC. In comparison to the pivotal CM025 study [2], NORA patients were older (median age 70 vs 62 yr), had lower KPS (14% with KPS ≤70 vs 5.9% in CM025) and more patients had metastases of the bone (32% in NORA vs 19% in CM025). Of all patients, 4.8% had brain metastases and 17% had ncc histology, which were both excluded from CM025. In addition, 8.3% of patients had received three or more prior tumor therapies in NORA, while in CM025 a maximum of two prior antiangiogenic therapies were allowed. The distribution of IMDC risk categories also differed, with fewer patients having poor risk disease in the NORA population (15% vs 23% in CM025; information missing for 12% in NORA). In total, only 46% of the patients in NORA would have been eligible for CM025, the majority because of ncc histology, poor performance status, and prior treatments (data not shown).

Nonetheless, our study suggests that the effectiveness of nivolumab under real-world conditions is comparable to that in the pivotal RCT, supporting similar data from a real-world study by the Italian Nivolumab Renal Cell Cancer Early Access Programme (IEAP) group. The IEAP population was comparable to the NORA cohort, with more patients with favorable IMDC risk (20% favorable, 29% intermediate, and 11% poor risk), fewer patients with nccRCC (6.7%), and more patients with brain metastases (8.2%) [11]. Median OS was consistent between NORA (24 mo, 95% CI 19–NR) and CM025 (25 mo, 95% CI 22–NR); the 1-yr and 2-yr survival rates were 65% (95% CI 59–71%) and 51% (95% CI 44–58%) in NORA, compared to 76% and 52% for CM025, respectively (minimum follow-up 26 mo) [2,12]. The IEAP study reported a similar 1-yr survival rate of 63% (median follow-up 12 mo) [11]. Median PFS was similar across NORA, CM025, and IEAP (5.3 vs 4.2 vs 4.5 mo). The numerical difference in the 24-mo PFS landmark favors NORA (21% vs 14% in CM025) [13]. The differences in imaging assessments and evaluation of progression may contribute to these outcomes. ORR varied numerically among the studies, but remained comparable (NORA 20%, CM025 26%, IEAP 23%). Complete response rates were similar across the studies (NORA 1.3%, CM025 1.0%, IEAP 0.8%) [2,11].
Table 4 – Treatment-related adverse events among patients treated with nivolumab monotherapy for advanced renal cell carcinoma after at least one prior treatment line: reported for all grades (if incidence \(\geq 1\%\)) and grade 3–4 (all events), \(n=228^a\)

| Patients, n (%) | Grade 3–4 |
|----------------|-----------|
| Number of treatment-related adverse events | 301 | 49 |
| Patients with at least one treatment-related adverse event | 105 (46) | 34 (15) |
| Blood and lymphatic system disorders | | |
| Anemia | 3 (1.3) | 1 (0.4) |
| Hemolysis | 1 (0.4) | 1 (0.4) |
| Cardiac disorders | | |
| Arrhythmia | 1 (0.4) | 1 (0.4) |
| Endocrine disorders | | |
| Hyperthyroidism | 6 (2.6) | 0 (0.0) |
| Hypothyroidism | 3 (1.3) | 0 (0.0) |
| Gastrointestinal disorders | | |
| Diarrhea | 21 (9.2) | 4 (1.8) |
| Nausea | 7 (3.1) | 0 (0.0) |
| Constipation | 4 (1.8) | 0 (0.0) |
| Abdominal pain | 3 (1.3) | 0 (0.0) |
| Colitis | 3 (1.3) | 2 (0.9) |
| Stomatitis | 3 (1.3) | 0 (0.0) |
| Vomiting | 3 (1.3) | 0 (0.0) |
| General disorders and administration site conditions | | |
| Fatigue | 15 (6.6) | 1 (0.4) |
| Pyrexia | 8 (3.5) | 0 (0.0) |
| General physical health deterioration | 3 (1.3) | 3 (1.3) |
| Peripheral edema | 3 (1.3) | 1 (0.4) |
| Mucosal inflammation | 3 (1.3) | 0 (0.0) |
| Hepatobiliary disorders | | |
| Autoimmune hepatitis | 2 (0.9) | 1 (0.4) |
| Liver disorder | 2 (0.9) | 1 (0.4) |
| Immune system disorders | | |
| Hypersensitivity | 1 (0.4) | 1 (0.4) |
| Infections and infestations | | |
| Clostridium difficile colitis | 1 (0.4) | 1 (0.4) |
| Gastroenteritis | 1 (0.4) | 1 (0.4) |
| Laboratory abnormalities | | |
| Blood creatinine increased | 3 (1.3) | 0 (0.0) |
| Blood lactate dehydrogenase increased | 1 (0.4) | 1 (0.4) |
| Blood potassium increased | 1 (0.4) | 1 (0.4) |
| C-reactive protein increased | 1 (0.4) | 1 (0.4) |
| Gamma-glutamyltransferase increased | 1 (0.4) | 1 (0.4) |
| General physical condition abnormal | 1 (0.4) | 1 (0.4) |
| Metabolism and nutrition disorders | | |
| Decreased appetite | 6 (2.6) | 0 (0.0) |
| Hyperkalemia | 2 (0.9) | 1 (0.4) |
| Dehydration | 1 (0.4) | 1 (0.4) |
| Musculoskeletal and connective tissue disorders | | |
| Arthralgia | 3 (1.3) | 0 (0.0) |
| Bone pain | 1 (0.4) | 1 (0.4) |
| Benign, malignant, and unspecified neoplasms (including cysts and polyps) | | |
| Malignant neoplasm progression | 14 (6.1) | 7 (3.1) |
| Nervous system disorders | | |
| Dysgeusia | 4 (1.8) | 0 (0.0) |
| Disturbance in attention | 1 (0.4) | 1 (0.4) |
| Renal and urinary disorders | | |
| Acute kidney injury | 3 (1.3) | 2 (0.9) |
| Chronic kidney disease | 1 (0.4) | 1 (0.4) |
| Respiratory, thoracic and mediastinal disorders | | |
| Dyspnea | 6 (2.6) | 1 (0.4) |
| Pneumonitis | 5 (2.2) | 2 (0.9) |
| Cough | 3 (1.3) | 0 (0.0) |
| Pleural effusion | 1 (0.4) | 1 (0.4) |
| Skin and subcutaneous tissue disorders | | |
| Pruritus | 13 (5.7) | 0 (0.0) |
| Rash | 10 (4.4) | 0 (0.0) |
| Psoriasis | 4 (1.8) | 1 (0.4) |
| Alopecia | 3 (1.3) | 0 (0.0) |
| Palmar-plantar erythrodysthesia syndrome | 3 (1.3) | 0 (0.0) |
| Lichenoid keratosis | 1 (0.4) | 1 (0.4) |
| Vascular disorders | | |
| Hypertension | 1 (0.4) | 1 (0.4) |

* One treatment-related death occurred (liver failure). Patients could experience several treatment-related adverse events.
Since the NORA real-world population features less favorable characteristics, it is not surprising that the results differ compared to the pivotal CM025 RCT. One such feature is the presence of ncc histology, associated with worse prognosis in comparison to cc histology [14] and accounting for 17% of NORA patients, while nccRCC was excluded from CM025. Although the results are numerically lower than outcomes for ccRCC patients, nivolumab treatment was effective in nccRCC patients, as shown by median OS, median PFS, and ORR data. Of the NORA nccRCC population, 11% had chromophobe tumor histology, which probably contributed to the lower effectiveness of nivolumab in this subpopulation in comparison to the ccRCC group and the entire cohort. This assumption is based on observations for pembrolizumab, another PD-1 ICI: in the first-line setting, an ORR of 26% was observed for the overall nccRCC population, but only 9.5% of patients with chromophobe RCC responded [15]. Our data are also consistent with recently published results from a phase 3b/4 safety study on nivolumab monotherapy (CheckMate 374) that suggest somewhat inferior outcomes for nccRCC in comparison to ccRCC [16,17]. However, since other available treatments such as VEGFR TKIs are also less effective in nccRCC, nivolumab remains an effective and well-tolerated treatment option [18].

NORA patients with poor performance status (KPS <70, excluded from CM025) had notably worse OS outcomes compared to those with KPS ≥70. However, the number of patients with KPS <70 was low. Brain metastases, accounting for 4.8% of NORA patients and excluded from CM025, are also considered unfavorable and have been associated with lower ICI antitumor activity [19].

A noteworthy proportion of patients in NORA were aged ≥75 yr (38% vs 8% in CM025) [2]. In our study, OS and PFS did not differ by patient age, demonstrating that elderly patients also benefit from nivolumab. This extends and sup-

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**Fig. 4 – Quality of life. Mean change in score from baseline for (A) the European Quality of Life 5 Dimensions (EQ-5D) Visual Analog Scale (VAS) and (B) the Functional Assessment of Cancer Therapy–Kidney Symptom Index-19 (FKSI-19) questionnaires. CI = confidence interval; M = month; Wk = week.**

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ports a subgroup analysis for CM025 that revealed that patient groups aged <65 yr and >65 years benefit similarly from nivolumab in comparison to everolimus [20]. In addition, ORR, DCR, and estimated OS curves in the IEAP study were similar for elderly patients and the overall population [21].

Interestingly, the presence of bone metastases in NORA had hardly any influence on OS outcomes, again in line with the IEAP data [11]. This finding is of particular interest, as cabozantinib, an alternative to nivolumab in the pretreated aRCC setting, has been suggested as a treatment option for these patients [22].

An association was found between OS and IMDC risk, an accepted prognostic factor in aRCC [9]. As expected, favorable risk was associated with the highest survival probabilities, consistent with results from CM025 and IEAP data [11,20].

The proportion of patients with trAEs was much lower in NORA than in CM025 (all grades, 46% vs 79%; grade 3–4, 15% vs 19%) [2]. Differences in the reporting system for a real-world NIS compared to the strict intervals for interrogation and reporting in RCTs are likely to be the cause of this discrepancy. However, no new safety signals emerged and, similar to CM025, only 11% of trAEs in NORA led to permanent discontinuation of nivolumab (CM025: 8%) [2]. Overall, our data support the low toxicity of nivolumab in a broad real-world population.

In line with the safety profile observed, at least during the first 12 months with nivolumab, QoL is maintained. Long-term analysis of PROs in NORA is hampered by the limited number of questionnaires completed. However, our data are consistent with PROs from CM025 demonstrating stable or even improved QoL up to 3 yr after treatment initiation [3]. This constitutes an important aspect of disease management, especially considering the sometimes long treatment duration.

Our study has some limitations, mainly related to data capture. The lack of central pathology review, unstructured imaging modalities, and the limited utilization of RECIST evaluations in the real-world setting are key limitations. Nonetheless, our data suggest that nivolumab has a robust treatment effect and favorable tolerability profile.

5. Conclusions

The real-life setting of the NORA study demonstrates the effectiveness, safety, and tolerability of nivolumab monotherapy in a broad aRCC patient population after one or more prior systemic therapies. The outcomes are generally consistent with those reported in the pivotal phase 3 CM025 trial. NORA extends the evidence of effectiveness for nivolumab to subpopulations excluded from CM025.

Author contributions: Marc-Oliver Grimm had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Grimm, Grünwald, Bedke.

Acquisition of data: Grimm, Grünwald, Müller-Huesmann, Ivanvy, Schostak, von der Heyde, Schultze-Seemann, Belz, Bögemann, Bedke.

Analysis and interpretation of data: Grimm, Grünwald, Bedke.

Drafting of the manuscript: Grimm, Grünwald, Bedke, Herber.

Critical revision of the manuscript for important intellectual content: Grimm, Grünwald, Müller-Huesmann, Ivanvy, Schostak, von der Heyde, Schultze-Seemann, Belz, Bögemann, Bedke, Herber, Wang.

Statistical analysis: Wang.

Obtaining funding: Bristol-Myers Squibb.

Administrative, technical, or material support: Herber.

Supervision: Grimm, Grünwald, Bedke.

Other: None.

Financial disclosures: Marc-Oliver Grimm certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Marc-Oliver Grimm reports grants and personal fees from Bristol-Myers Squibb and personal fees from Pfizer, Bayer Healthcare, Astellas, Hexal, AstraZeneca, MSD, Ipsen, Merck Serono, EUSA Pharma, Eisai Roche, and Takeda outside the submitted work. Viktor Grimm reports grants, personal fees, and nonfinancial support from AstraZeneca, Bristol-Myers Squibb, Ipsen, and Pfizer, and personal fees from MSD, Merck Serono, EUSA Pharma, Novartis, and Eisai during the conduct of the study; and grants and nonfinancial support from AstraZeneca, grants, personal fees, and nonfinancial support from Bristol-Myers Squibb, personal fees and nonfinancial support from Bayer, grants and personal fees from MSD, grants from Novartis, and personal fees from Roche, Janssen-Cilag, PharmaMar, and Nanobiotix outside the submitted work. Harald Müller-Huesmann reports honoraria from a consulting/advisory role for, and research funding from Roche, Bristol-Myers Squibb, and Boehringer-Ingelheim; honoraria from a consulting/advisory role for, and travel and accommodation expenses from AstraZeneca; a consulting/advisory role for MSD; consulting/advisory role for and travel and accommodation expenses from Janssen; and research funding from Eisai, all outside the submitted work. Philipp Ivanvy reports personal fees from Bristol-Myers Squibb, Ipsen, MSD, Pfizer, and Merck outside the submitted work. Martin Schostak reports grants and personal fees from Bristol-Myers Squibb during the conduct of the study. Martin Bögemann reports personal fees from Bristol-Myers Squibb, Merck, Ipsen, Eisai, Novartis, Exelixis, and EUSA Pharma during the conduct of the study; and personal fees from Janssen, Bayer, ABX, Astellas, PharmTrace AstraZeneca, and Amgen outside the submitted work. Jens Bedke reports grants from Bristol-Myers Squibb during the conduct of the study; and personal fees from AstraZeneca and EUSA Pharma, grants from Novartis and Nektar, and grants and personal fees from Astellas, Bristol-Myers Squibb, Eisai, Ipsen, MSD, Merck Darmstadt, Roche, and Pfizer outside the submitted work. Eyck von der Heyde, Wolfgang Schultze-Seemann, Hanjo Belz, Meng Wang, and Martin Herber have nothing to disclose.

Funding/Support and role of the sponsor: This study was funded by Bristol-Myers Squibb. The sponsor played a role in the design and conduct of the study and in data collection, management, and analysis.

Acknowledgments: We thank all the participating patients and their families for making this study possible, as well as the clinical study teams that contributed to the study. We also thank the CONSORT Markets Team (Bristol-Myers Squibb, Uxbridge, UK) for compiling the biometric reports and Christine Kleemann (Bristol-Myers Squibb, Medical Capabilities, Germany) and Max Endelev (Bristol-Myers Squibb, Medical Department, Germany) for publication support. Medical writing and manuscript development were carried out by Katharina Leucht (University of Jena, Germany) and were funded by Bristol-Myers Squibb.
Data sharing statement: The Bristol-Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euf.2021.11.006.

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