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ORIGINAL ARTICLE

Prospective randomized phase-II trial of ipilimumab/nivolumab versus standard of care in non-clear cell renal cell cancer - results of the SUNNIFORECAST trial

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Background: Non-clear cell renal cell cancers (nccRCCs) are a heterogeneous group of more than 20 different entities, but are rarely included in large, randomized trials. Tyrosine kinase inhibitors with or without immune checkpoint inhibition are considered as a standard of care (SOC), but optimal treatment is not yet defined. We designed the first prospective randomized trial comparing ipilimumab/nivolumab to SOC.

Patients and methods: We randomized adult patients with previously untreated advanced or metastatic nccRCC 1:1 to nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for 4 doses followed by fixed dose nivolumab of 240 mg every 2 weeks or 480 mg every 4 weeks or to SOC. Patients were stratified by histology and by IMDC risk score. Central pathology review was mandatory. The primary endpoint was the overall survival (OS) rate at 12 months, secondary endpoints included median OS, response rate, progression-free survival (PFS), safety and quality of life.

Results: In total, 157 patients were assigned to receive ipilimumab/nivolumab, and 152 to SOC. The 12-month survival rate was 78% with ipilimumab/nivolumab [95% confidence interval (CI) 71-84%] compared to 68% with SOC (95% CI 60-75%, $P = 0.026$). Median OS was 33.2 months versus 25.2 months, $P = 0.163$ [HR 0.81 (0.61-1.099)]. PFS was similar in both arms [HR 0.99 (0.77-1.28)]. The ORR was 32.8% versus 19.3%. No major differences between papillary and non-papillary RCC subtypes were observed for any endpoint. Exploratory analysis showed a significant OS advantage [HR 0.56 (95% CI 0.37-0.86)] associated with a PD-L1 CPS score $\geq$1. Treatment discontinuation due to toxicity occurred in 27 patients (17%) with ipilimumab/nivolumab and 13 patients (9%) with SOC.

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Conclusions: Ipilimumab/nivolumab demonstrated a significantly longer OS at the 12-month milestone and an acceptable toxicity profile. Our results therefore underline a relevant clinical benefit of ipilimumab/nivolumab in previously untreated nccRCC entities compared to current SOC.

Key words: non-clear cell renal cell carcinoma, nccRCC, checkpoint inhibitors, tyrosine kinase inhibitors, nivolumab, ipilimumab

INTRODUCTION

New diagnoses of renal cell carcinoma (RCC) affected an estimated 390 000 patients globally in 2020.[1] Around 75% of RCC are histologically of the clear cell (cc) type, for which late-stage systemic treatment options have improved considerably especially by the advent of immunotherapies with immune checkpoint inhibitors (ICI) either alone or in combinations (nivolumab/ipilimumab immunotherapy and TKI-immunotherapy combinations[2]). The remaining RCCs are a heterogeneous group collectively termed as non-clear cell (ncc) RCC that comprise, according to the WHO classification of 2022, more than 20 histologically and molecularly defined entities. More common types of nccRCC are papillary and chromophobe RCC, while rarer types are often characterized by genetic rearrangements or deficiencies.[3]

Despite the transfer of improved systemic ccRCC treatments to the nccRCC setting, patients with nccRCC have a poorer prognosis.[4-7] Due to the heterogeneity and relative rarity of nccRCCs, these patients are included in large phase 3 RCC trials only as a small subgroup or even excluded. None of the targeted agents available for ccRCC were able to demonstrate a significant improvement in OS when compared to each other in ncc phase-2 studies, and immunotherapy combinations have mostly been tested in relatively small patient cohorts and single-arm settings.[7-9]

As a result, European marketing authorizations for RCC are subtype-agnostic, equally applying to cc and ncc histologies, despite the evidence bases for the two being fairly different. VEGF targeted therapy has until recently been the standard of care for NCCRCC based on small randomised trials. Recent single arm data on VEGF/PD-1 combination are impressive and are now considered at least as active and are widely used. Data for papillary renal cancer, which is the commonest subset has followed a similar pattern.[6,8-13] Current ESMO recommendations suggest cabozantinib for first-line treatment of papillary RCC, a tyrosine kinase inhibitor alone or in combination with an mTOR inhibitor or immunotherapy for chromophobe RCC, an immunotherapy combination for sarcomatoid RCC and platinum-based chemotherapy for collecting duct and medullary RCC.[6,8-11] By contrast, the NCCN recommends cabozantinib alone or in combination with immunotherapy for any nccRCC subtype, except for a tentative suggestion of platinum-based chemotherapy for collecting duct and medullary RCC.[12]

First results for combined ipilimumab/nivolumab in nccRCC cohorts have recently become available. The CheckMate 920 single-arm multicohort phase 3b/4 trial assessed treatment with four cycles of ipilimumab/nivolumab combination followed by nivolumab monotherapy in 52 patients with nccRCC.[14] The median OS was 21.2 months (95% CI 16.6-NA). The HCRN GU16260 trial enrolled 35 patients with nccRCC for treatment with nivolumab followed by salvage ipilimumab/nivolumab.[15] At median follow-up of 22.9 months, median OS had not been reached, but efficacy of the treatment approach was considered as limited. By comparison, the classic RCC treatment agent sunitinib provided a median OS of 16.2 months (95% CI 14.2-NA) in 33 nccRCC patients in the ESPN trial.[16] However, direct comparisons between immunotherapy strategies and targeted treatments in nccRCC are still missing. To close this gap, we are reporting here the first prospective randomized trial comparing an ipilimumab/nivolumab combination strategy to physician's choice standard-of-care, which was dominated by TKI.

METHODS

Patients

Eligible patients were at least 18 years old and had previously untreated advanced or metastatic nccRCC with at least 50% ncc component according to WHO classification.[3] Further key inclusion criteria were measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, a Karnofsky performance status of at least 70%, and availability of a recent or archival tumor tissue sample. Patients of all International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk scores[17] were allowed. Key exclusion criteria were current or recent use of systemic corticosteroids and other immunosuppressants and inadequate kidney or liver function. All patients provided written informed consent prior to initiation of study participation.

Trial procedures

This was a European, multicenter, prospectively randomized, open-label, investigator-initiated phase 2 trial (IIT) of ipilimumab plus nivolumab followed by nivolumab monotherapy versus standard of care (SOC). Randomization (ratio 1:1) was stratified by histology (papillary versus non-papillary nccRCC histology based on central pathology review; local pathology diagnosis was sufficient for inclusion if the central pathological result was not available within an acceptable timeframe) and IMDC prognostic score (0 versus 1-2 versus 3-6). The randomization was done by block randomization with 10 patients per block, created by defining an unstratified randomization list for each stratification factor level combination. The procedure of randomization then takes stratifcation data of the patient and

chooses the appropriate list. Within that list, the next free treatment arm is returned. IMDC prognostic score was determined by the presence of six risk factors: Karnofsky performance status below 80%, less than one year between diagnosis and systemic therapy, hemoglobin level below the lower limit of the normal range, corrected calcium level above the upper limit of normal, absolute neutrophil count above the upper limit of normal, and platelet count above the upper limit of normal.

Nivolumab was administered at a dose of 3 mg/kg of body weight, followed by ipilimumab at 1 mg/kg of body weight by intravenous infusion every three weeks for an induction phase of four treatment cycles. Nivolumab and ipilimumab were to be administered on the same day, with nivolumab given first. During a subsequent maintenance phase, nivolumab was administered at a fixed dose of 240 mg every two weeks, or at 480 mg every four weeks. Adverse events could be managed by dose delays. During combined treatment with ipilimumab and nivolumab, isolated delays or discontinuation of only one drug were not allowed. In case of ipilimumab-related toxicities, continuation with nivolumab monotherapy was possible. No dose reductions were allowed.

Standard of care (SOC) treatment was according to investigator's choice and any approved standard therapy was allowed. Independent of therapy, one cycle was considered as six weeks. Administration and management of toxic effects by dose delay and dose modifications was handled according to product label.

The trial was designed by the authors and sponsored by Goethe University, Frankfurt/Main, Germany. The trial was approved by the institutional review board or ethics committee at each site and was conducted according to Good Clinical Practice guidelines as defined by the International Council for Harmonization and to the Declaration of Helsinki. An independent data monitoring committee reviewed safety, efficacy and study conduct. The trial is registered as 2016-000706-1 (EudraCT) and NCT03075423 (clinicaltrials.gov).

Outcomes

The primary endpoint was the OS rate at the 12-month milestone. OS rates at 6 and at 18 months were secondary endpoints, as well as PFS, OS and objective response rate (ORR). The primary OS endpoint as a landmark analysis instead of logrank analysis was chosen due to the sparce OS date in nccRCC and based on the data of previous randomized trials showing a median OS in nccRCC of only about 12 months (e.g. ESPN trial[16]).

Tolerability, safety and quality of life (QoL) were further secondary endpoints. OS was defined as the time from randomization to death. PFS was defined as the time from randomization to first documented disease progression based on local radiology assessment according to RECIST 1.1 or iRECIST criteria, respectively, or death due to any cause. ORR was defined as the percentage of patients having a best response of complete (CR) or partial response (PR).

Tumor assessments were performed locally using computed tomography or magnetic resonance imaging of the chest, abdomen, pelvis, and all known sites of disease, starting at baseline and then every 12 weeks until disease progression or discontinuation of treatment, whichever occurred first. Follow-up for survival continued until death, withdrawal of consent or end of study, which was defined as 18 months after last-patient-in. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. In-person safety follow-up was conducted until 30 days after the last dose of study treatment. Quality of life was assessed by the FKSI-DRS questionnaire at baseline, after induction, and after 3, 12 and 18 months of treatment. Assessment of PD-L1 expression was done on tumor and immune cells using the Ventana antibody SP263 on a BenchMark ULTRA autostainer (Ventana Medical Systems, Inc) as described previously calculating the combined positive score CPS).[18]

Statistical analysis

The study was designed to provide 80% power to show superiority of the nivolumab-ipilimumab combination regimen over standard-of-care treatment for the primary endpoint of OS rate at 12 months. Based on the results for sunitinib in metastatic nccRCC in the phase 2 ESPN trial,[16] a 12-month survival rate of 65% was assumed for the SOC arm, while potential improvement through the experimental treatment approach to 80% was considered clinically significant. Based on these considerations, and on a one-sided Fisher's exact test for comparison of two independent proportions, a sample size of 122 patients per arm was calculated. In order to account for dropouts and censoring of 20%, sample size was increased to 153 patients per arm.

Demographic and baseline characteristics were analyzed descriptively for continuous parameters, the minimum, median and maximum values were reported, while for categorical variables, absolute and relative frequencies were presented. Statistical tests were applied in a descriptive manner (continuous variables: Wilcoxon rank sum test; categorical variables: χ^2-Test or Fisher's exact test if the requirements of the χ^2-Test were not met).

The confirmatory analysis of the primary endpoint, the 12-months OS rate, was conducted using a one-sided test at a significance level of 5% and was based on the ITT population. Secondary analyses of the primary endpoint were performed using Kaplan-Meier method and the logrank test. Hazard ratios (HR) and 95% CIs were calculated for the treatment comparison using the Cox proportional hazard in different prespecified subgroups, with results presented in a forest-plot. For sensitivity purposes, the analysis of the primary endpoint was also performed for the per protocol (PP) population.

The secondary endpoint PFS was evaluated in a similar manner to OS. ORR, adverse events and subsequent therapies were reported descriptively using absolute and relative frequencies. All statistical tests for secondary endpoints

Table 1. Demographic characteristics at baseline

	All ($N = 309$)	Ipilimumab/ nivolumab ($N = 157$)	Standard of care ($N = 152$)	*P* value
Age, years				0.69
Median (range)	62 (19-86)	61 (19-82)	64 (19-86)	
Sex, *n* (%)				0.83
Male	219 (71)	112 (71)	107 (70)	
Female	90 (29)	45 (29)	45 (30)	
Karnofsky score, *n* (%)				0.20
100	162 (52)	80 (51)	82 (54)	
90	76 (25)	34 (22)	42 (28)	
80	51 (17)	27 (17)	24 (16)	
70	16 (5)	12 (8)	4 (3)	
≤60	1 (0)	1 (1)	-	
Missing	3 (1)	3 (2)	-	
IMDC prognostic risk score, *n* (%)				0.87
Favorable: 0	74 (24)	39 (25)	35 (23)	
Intermediate: 1-2	160 (52)	79 (50)	81 (53)	
Poor: 3-6	75 (24)	39 (25)	36 (24)	
Prior therapies, *n* (%)				
Any surgery	237 (77)	124 (79)	113 (74)	0.33
Tumor nephrectomy (total or partial)	170 (55)	93 (59)	77 (51)	0.13
Any radiotherapy	29 (9)	14 (9)	15 (10)	0.77
Most common sites of target lesions, *n* (%)				
Lymph node	156 (51)	83 (53)	73 (48)	0.39
Lung	109 (35)	57 (36)	52 (34)	0.70
Kidney	102 (33)	51 (33)	51 (34)	0.84
Liver	66 (21)	26 (17)	40 (26)	0.04
Time since initial diagnosis, months				0.30
Median (range)	31 (1-1417)	34 (2-1417)	25 (1-1098)	
Histological subtypes for stratification, *n* (%)				0.61
Papillary RCC	190 (62)	99 (63)	91 (60)	
Non-papillary RCC	118 (38)	58 (37)	60 (40)	
Missing	1 (0)	0	1 (1)	
Histological subtypes according to extended reference pathology, *n* (%)	16 (5)			0.64
Papillary RCC	173 (56)	88 (56)	85 (56)	
Non-papilllary RCC	136 (44)	69 (44)	67 (44)	
Chromophobe renal cell carcinoma	59 (20)	27 (17)	32 (21)	
Collecting duct carcinoma	11 (4)	6 (4)	5 (3)	
Renal medullary carcinoma	5 (2)	1 (1)	4 (3)	
TFE3-rearranged and TFEB-altered RCC	16 (5)	11 (7)	5 (3)	
Succinate dehydrogenase-deficient renal cell carcinomas	2 (1)	1 (1)	1 (1)	
Mucinous tubular and spindle cell carcinoma	1 (0)	1 (1)	0	
Tubulocystic renal cell carcinoma	2 (1)	2 (1)	0	
Fumarate hydratase deficient	5 (2)	2 (1)	3 (2)	
Not otherwise specified	13 (4)	7 (5)	6 (4)	
Sarcomatoid and/ or rhabdoid	20 (7)	11 (7)	9 (6)	
SMARCA-4 deficient RCC	1 (0)	0	1 (1)	
Unclassifiable	1 (0)	0	1 (1)	
CPS, *n* (%)				
CPS < 1	129 (42)	71 (45)	58 (38)	0.35
CPS ≥ 1	149 (48)	73 (47)	76 (50)	
CPS < 10	210 (68)	107 (68)	103 (68)	0.51
CPS ≥ 10	68 (22)	37 (24)	31 (20)	
Missing	31 (10)	13 (8)	18 (12)	

CPS, combined positive score; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; RCC, renal cell carcinoma; SMARCA-4, SWI/SNF related BAF chromatin remodeling complex subunit ATPase 4; TFE-3, transcription factor binding to IGHM enhancer 3; TFEB, transcription factor EB.

were exploratory and were not adjusted for multiplicity. No imputation methods were applied for missing values.

Statistical analyses were performed using the statistical package SAS for Windows Version 9.4 (SAS Institute Inc, North Carolina).

RESULTS

Patient disposition, patient characteristics and analysis sets

Between 11/2017 and 2/2024, a total of 372 patients provided informed consent and were screened for study participation. Of these, 316 were found eligible and were enrolled at 31 European sites and 309 were randomly assigned to treatment: 157 participants to ipilimumab/nivolumab combination treatment followed by nivolumab monotherapy, and 152 participants to treatment according to standard-of-care (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2025.03.016). These randomized patients represent the intent-to-treat (ITT) population. Thereof, 299 patients received study treatment (156 in the ipilimumab/nivolumab arm and 143 in the SOC arm), and serve as patients set for safety reporting. One patient treated in the SOC arm was excluded from the PP population due to major protocol deviation, which therefore contains 156 participants in the ipilimumab/nivolumab arm and 142 participants in the SOC arm. The main reason for treatment discontinuation was disease progression (affecting 89 patients or 57% in the ipilimumab/nivolumab arm and 88 patients or 58% in the SOC arm). The median follow-up was 21.5 months (range 0.0-70.2 months). Patient characteristics were well balanced between the two treatment groups (Table 1). All histologies were reviewed by a central reference pathologist. Hereby, there were 9 patients in each arm were the local diagnosis has to be changed to papillary or non-papillary RCC, respectively.

Treatment exposure

In the ipilimumab/nivolumab treatment group, the median time under study treatment was 3.2 months (range 0-60

months). 155 patients received induction treatment with combined nivolumab and ipilimumab, and one patient received nivolumab monotherapy during induction. Of these 155 patients, 39 received up to two cycles, 28 received three cycles and 88 received all four cycles of combined induction treatment. Of these, 80 proceeded to the maintenance phase.

In the SOC arm, the median time under treatment was 5.0 months (range 0-60 months). Of the 143 patients treated in this arm, 112 (78%) received sunitinib, 10 (7%) cabozantinib, 15 (10%) axitinib in combination with a checkpoint inhibitor, 2 (1%) cabozantinib combined with nivolumab, and 4 (3%) received other treatments. In the standard-of-care arm, 753 cycles of study treatment were recorded. Of these, 175 cycles (23%), affecting 45 patients (32%) were subject to a modification of schedule. Dose modifications were recorded for 131 cycles (17%).

Efficacy outcomes

Ipilimumab plus nivolumab had a significant benefit over SOC treatment for the primary endpoint: In the ITT, the 12-month OS rate was 78% for patients in the ipilimumab/nivolumab arm (95% CI 71-84%) compared to 68% for patients who received SOC (95% CI 60-75%, $P = 0.026$). Similarly, secondary endpoints for OS tended towards a nominal benefit of ipilimumab/nivolumab treatment over SOC, including a difference in median OS by 8 months (33.2 months [95% CI 23.4-40.8 months] versus 25.2 months [95% CI 18.8-33.0 months], $P = 0.163$ [HR 0.81 (0.61-1.09)]) (Table 2 and Figure 1). Separate Kaplan-Meier analysis of subgroups according to the stratification factors histology (papillary versus non-papillary) and IMDC risk score (favorable versus intermediate versus poor) yielded better outcomes for ipilimumab/nivolumab combination treatment in most subgroups, but no statistically significant differences (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2025.03.016).

PFS was comparable between the two treatment groups: Median PFS was 5.4 months (95% CI: 3.2-7.8 months) with ipilimumab/nivolumab and 5.7 months (95% CI: 5.4-8.3 months) with SOC [HR 0.99 (0.77-1.28)] (Supplementary Figure S3A, available at https://doi.org/10.1016/j.annonc.2025.03.016). ORRs according to RECIST 1.1 criteria were 33% with ipilimumab/nivolumab, with 10 of 125 patients (8%) experiencing a CR and 31 patients (25%) a PR, and 20% with SOC, with CR seen in only 2 of 122 patients (2%) and PR in 22 patients (18%) (Table 3). Analysis of response by histology (papillary versus non-papillary nccRCC) gave results similar to the overall response profile. Responses were observed in all subentities of non-papillary RCC. The chromophobe RCC showed an ORR of 27% (7/26 patients) versus 10% (3/29) and the sarcomatoid/rhabdoid RCC an ORR of 70% (7/10 patients) versus 25% (1/4 patients) in favor of ipilimumab/nivolumab. In the small subgroup of collecting duct carcinoma, we observed a response rate of 40% (2/5 patients) versus 25% (1/4 patients).

Explorative subgroup analyses of OS resulted in a trend favoring ipilimumab/nivolumab combination treatment over SOC for most subgroups, but statistically significant differences were present for only few of them (Figure 2A). The papillary cohort had a median OS of 28.4 (18.4-40.9) versus 18.9 (14.4.-32.8) months in the SOC arm with a HR of 0.84 (0.59-1.21) and OS rate at 12 months of 74.6% (64.7%-82.0%) versus 64.1% (53.0%-73.3%). A comparison of ipilimumab/nivolumab versus TKI-only treated patients in the SOC arm ($n = 124$) (i.e. excluding combined therapies) demonstrated a very similar OS as the entire SOC ITT population [33.2 months (95% CI 23.4-40.8 months) versus 22.5 months (95% CI 17.6-30.0 months), $P = 0.093$]. Those 17 patients with a TKI/ICI combination in the SOC arm ($N = 17$; 5 favorable, 10 intermediate, 2 poor risk) had an ORR of 25%, an OS-rate at 12 months of 87.5% and median OS of 33.5 months [95% CI 19.4 months − not determinable].

As the most notable result of subgroup analysis, a CPS $\geq$ 1 was associated with an HR for OS of 0.56 (95% CI 0.37-0.86, $P = 0.008$) in favor of ipilimumab/nivolumab combination treatment (Figure 2A and C). Analysis for CPS $<$1, in turn, resulted in a nominal advantage for SOC ($P = 0.257$, Figure 2A and B). The same observation was made for PFS [Supplementary Figure S3B, available at https://doi.org/10.1016/j.annonc.2025.03.016, HR for CPS $\geq$ 1: 0.63 (95% CI 0.44-0.91), $P = 0.014$].

Exploratory analysis of the primary endpoint in the PP population produced very similar results to the ITT population: The OS rate at 12 months was 78% with ipilimumab/nivolumab (95% CI 71-84%) and 68% with SOC (95% CI 60-75%, $P = 0.029$). Results for 6- and 18-month milestone rates as well as median OS show the same high similarity between the ITT and the PP population (data not shown).

Table 2. Milestone rates and median overall survival for the ITT population. OS rates at 12 months are the primary endpoint of the study

	Ipilimumab/ nivolumab $N = 157$	Standard of Care $N = 152$	*P* value
OS rate at 12 months (95%CI)	**78%** (71%-84%)	**68%** (60%-75%)	**0.026**
OS rate at 6 months (95%CI)	91% (85%-95%)	85% (79%-90%)	0.064
OS rate at 18 months (95%CI)	67% (59%-73%)	60% (52%-68%)	0.124
Median OS, months (95%CI)	33.2 (23.4-40.8)	25.2 (18.8-33.0)	0.163

CI, confidence interval; ITT, intent-to-treat; OS, overall survival.

Safety outcomes

Adverse events of any grade occurred in 152 of 156 patients (97%) treated with ipilimumab/nivolumab and 141 of 143 patients (99%) treated with SOC. Treatment-related adverse events of any grade were reported for 135 patients (87%) in the ipilimumab/nivolumab group and for 137 patients (96%) in the standard group. Serious adverse events were

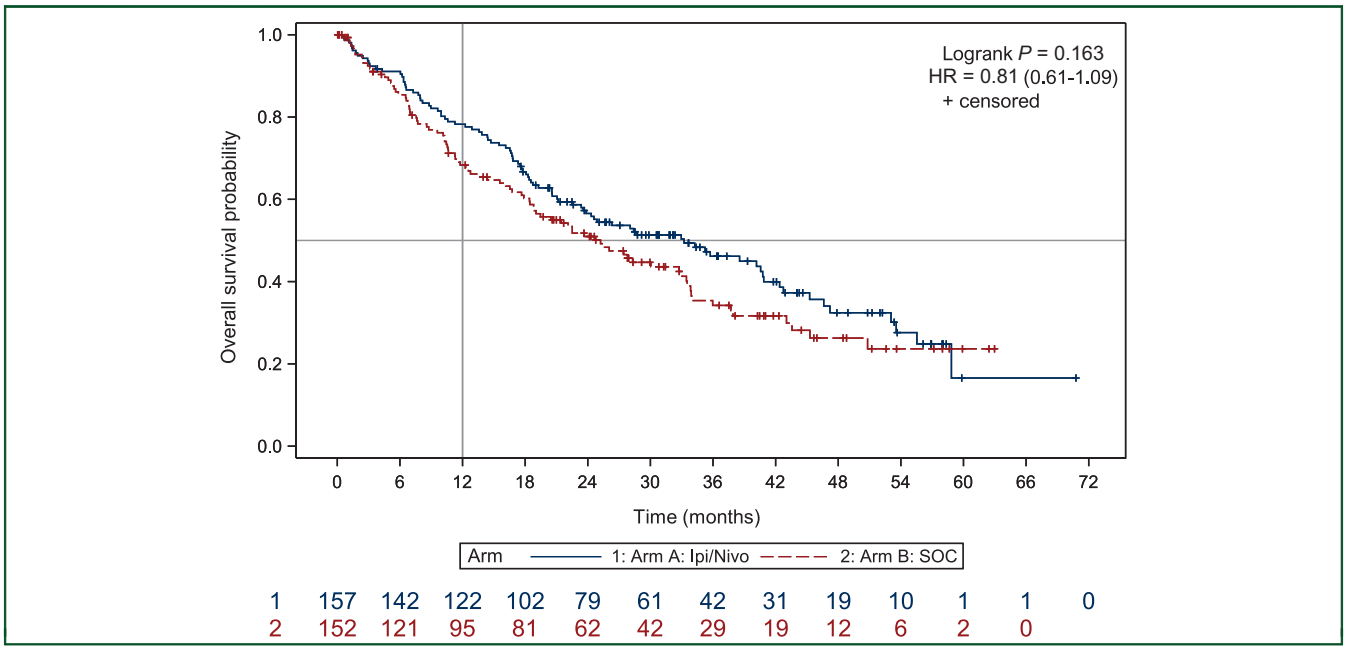

Figure 1. Kaplan-Meier analysis of overall survival in the ITT population. Vertical line marks the 12-month milestone (primary endpoint).
HR, hazard ratio; Ipi/Nivo, ipilimumab, nivolumab; SOC, standard of care.

reported for 75 patients (48%) and 55 patients (39%), respectively. Treatment discontinuation due to toxicity of study treatment occurred in 27 patients (17%) in the ipilimumab/nivolumab arm and in 13 patients (9%) in the standard arm. Eight adverse events with fatal outcomes were reported, 5 in the ipilimumab/nivolumab arm and 3 in the SOC arm. None of these were assessed as treatment related. Please refer to the Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.03.016.

Quality of life

In the ipilimumab/nivolumab arm, 87 of 157 patients (55%) provided answers to the FKSI-DRS questionnaire after 3 months of treatment, and 77 of 152 patients (51%) in the control arm. Response rates were lower at later time points. No significant differences in quality of life between the two treatment groups were detected (Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2025.03.016).

Subsequent therapies

The same proportion of patients received second line treatment after study participation: 100 patients (64%) from the ipilimumab/nivolumab group and 95 patients (66%) from the SOC group (Table 4). The second line treatments used most frequently in the ipilimumab/nivolumab group were cabozantinib (50 patients, 32%) and sunitinib (26 patients, 17%). Cabozantinib was also used frequently in second line for patients who received SOC study treatment (34 patients, 24%), but nivolumab was the most frequent second line treatment in the SOC arm (37 patients, 26%). In total, 43 patients (30%) from the SOC group received nivolumab in a subsequent line of therapy. Note that nivolumab was, to a limited extent, also given as subsequent treatment to ipilimumab/nivolumab study treatment (to 5 patients as second line and one patient as fourth line). If comparing arm A with those patients in the SOC arm without an subsequent ICI (93 patients), the median OS is 28.7 (22.6-40.8) months versus 17.9 (12.3-27.4) months ($P = 0.019$).

Table 3. Response according to RECIST v1.1 and ORR by study treatment and by histology strata. The analysis is restricted to 248 patients with a valid tumor response assessment during therapy

	All		Papillary nccRCC		Non-papillary nccRCC	
	Ipilimumab/ nivolumab ($N = 125$)	SOC ($N = 123$)	Ipilimumab/ nivolumab ($N = 72$)	SOC ($N = 77$)	Ipilimumab/ nivolumab ($N = 53$)	SOC ($N = 46$)
Objective response rate, *n* (%)	41 (33)	24 (20)	21 (29)	16 (21)	20 (38)	8 (17)
Best overall response, *n* (%)						
Complete response	10 (8)	2 (2)	7 (10)	2 (3)	3 (6)	0
Partial response	31 (25)	22 (18)	14 (20)	14 (18)	17 (32)	8 (17)
Stable disease	41 (33)	76 (62)	27 (38)	47 (61)	14 (26)	29 (63)
Progressive disease	43 (34)	23 (19)	24 (33)	14 (18)	19 (36)	9 (20)

nccRCC non-clear-cell renal cell carcinoma; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors; SOC, standard of care.

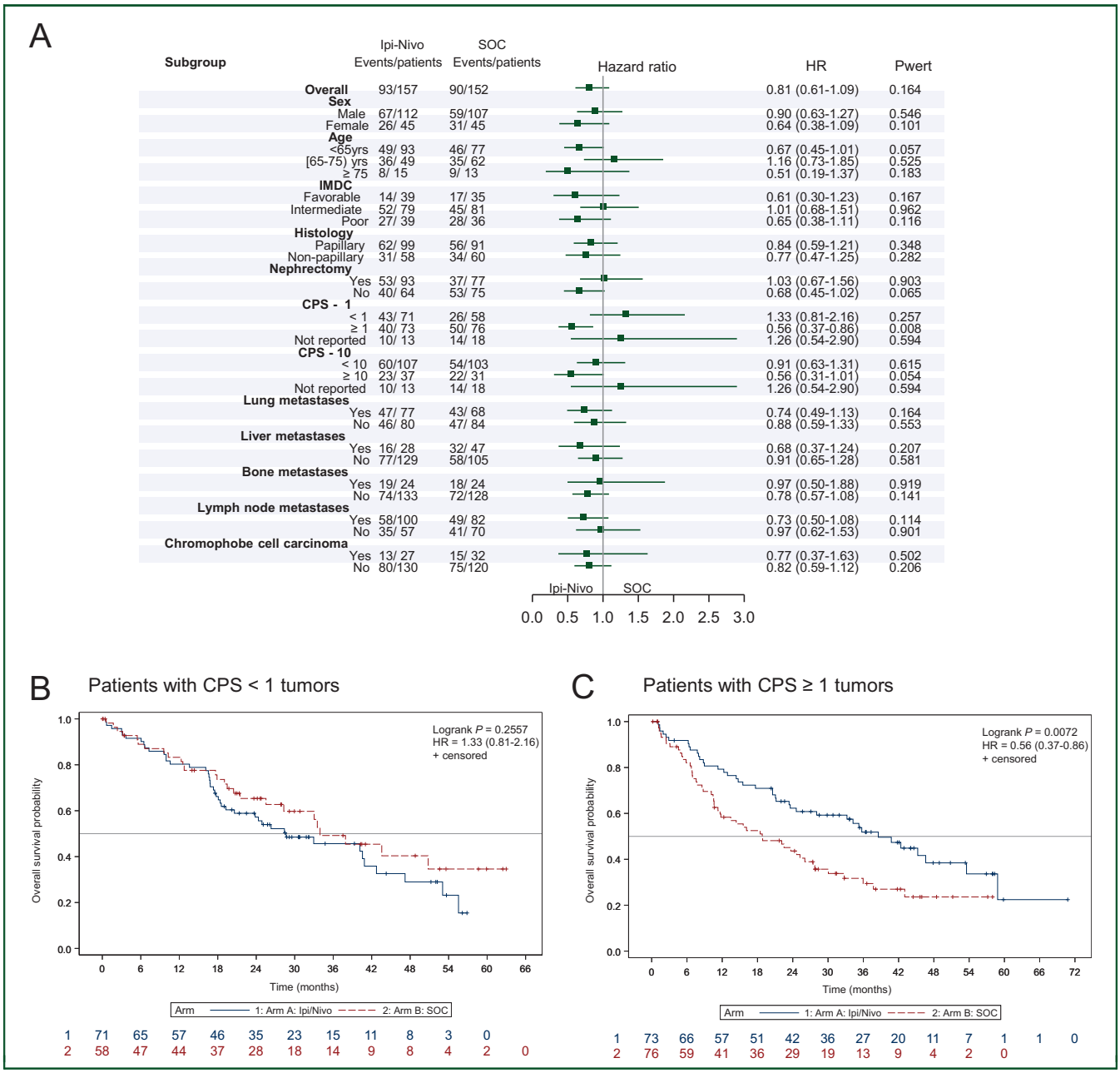

Figure 2. Subgroup analyses of overall survival in the ITT population.
CPS, combined positive score; HR, hazard ratio; IMDC, International Metastatic RCC Database Consortium; Ipi/Nivo, ipilimumab, nivolumab.

DISCUSSION

This prospective randomized IIT in treatment-naïve patients with advanced or metastatic nccRCC was conducted to evaluate a possible benefit of the combination of ipilimumab plus nivolumab compared to SOC. To our knowledge, this is the largest randomized trial so far in nccRCC. The local histological diagnoses were reviewed by a central pathology according to the WHO classification 2022.[3] The demographic data, risk factors according to IMDC and nccRCC entities (papillary and non-papillary) were well balanced between the two arms. About 62% (56% according to central review) were of papillary subtype, the most common entity in nccRCC. Within the non-papillary RCCs, chromophobe RCC was the largest entity, followed by 7% sarcomatoid or rhabdoid RCCs, 5% TFE3-rearranged and TFEB-altered RCC and more rare subtypes (Table 1). In 90% of the specimens the CPS score could be determined.

The primary endpoint, OS rate at 12 months, was met with 78% in the ipilimumab/nivolumab arm versus 68% in the SOC arm ($P = 0.026$). This is in a similar range as described by Tykodi et al. in a single arm trial with ipilimumab/nivolumab with 72.6%.[14] In our trial, the median OS was in favor of ipilimumab/nivolumab with 33.2 versus 25.2 months and a HR for death of 0.81 (95% CI 0.61-1.09). In the cohort of Tykodi et al., the median OS was only 21.2 months for the combination. In our trial, PFS was not

Table 4. Subsequent treatments by study treatment group and subsequent therapy line for the study's safety population. Percentages are based on study population

	All *N* = 299	Ipilimumab/nivolumab *N* = 156	Standard of care *N* = 143
	N (%)	*N* (%)	*N* (%)
2nd line			
Any	195 (65)	100 (64)	95 (66)
Nivolumab	42 (14)	5 (3)	37 (26)
Sunitinib	29 (10)	26 (17)	3 (2)
Pazopanib	2 (1)	2 (1)	0 (0)
Cabozantinib	84 (28)	50 (32)	34 (24)
Axitinib	12 (4)	9 (6)	3 (2)
Temsirolimus	2 (1)	0 (0)	2 (1)
Everolimus	2 (1)	1 (1)	1 (1)
Lenvatinib + everolimus	2 (1)	0 (0)	2 (1)
Other	20 (7)	7 (4)	13 (9)
3rd line			
Any	74 (25)	45 (29)	29 (20)
Nivolumab	7 (2)	0 (0)	7 (5)
Sunitinib	8 (3)	8 (5)	0 (0)
Pazopanib	1 (0)	1 (1)	0 (0)
Cabozantinib	27 (9)	16 (10)	11 (8)
Axitinib	9 (3)	6 (4)	3 (2)
Everolimus	3 (1)	1 (1)	2 (1)
Lenvatinib + everolimus	8 (3)	8 (5)	0 (0)
Other	11 (4)	5 (3)	6 (4)
4th line			
Any	36 (12)	17 (11)	19 (13)
Nivolumab	7 (2)	0 (0)	7 (5)
Sunitinib	3 (1)	3 (2)	0 (0)
Cabozantinib	7 (2)	4 (3)	3 (2)
Axitinib	3 (1)	2 (1)	1 (1)
Everolimus	3 (1)	2 (1)	1 (1)
Lenvatinib + everolimus	3 (1)	1 (1)	2 (1)
Other	10 (3)	5 (3)	5 (3)

different between the two arms and was 5.4 and 5.7 months, respectively, and therefore slightly higher than the 3.7 months reported by Tykodi et al.[14] Regarding the interpretation of the OS, the subsequent therapies have to be taken into account. About 65% of patients received a 2nd line therapy, 25% a 3rd line and even 12% a 4th line therapy. In the combination arm, most patients were treated with a TKI (predominantly cabozantinib or sunitinib), whereas in the SOC arm, more than 30% received a checkpoint inhibitor in subsequent therapy lines, which is known to prolong survival after TKI therapy and might have resulted in a better long-term outcome in the SOC arm than had been assumed.[19]

The best overall response (ORR) according to RECIST 1.1 was significantly higher in the combination arm with 33% (8% CR, 25% PR) compared to the SOC arm with 20% (CR 2%, PR 18%; $P = 0.001$). Again, this was somewhat higher than 19.6% ORR in the single arm trial by Tykodi et al.[14] and may be an explanation for the resulting longer median OS.[20] Looking at the stratification factor papillary versus non-papillary carcinoma, the difference in ORR between both arms was smaller for papillary (29% versus 21%) than for non-papillary RCC (38% versus 17%). Cabozantinib, a TKI considered more effective than sunitinib in papillary RCC due to its additional inhibitory effect on MET kinase, yielded a slightly lower ORR of 23% and shorter median OS of 19.9 months in papillary RCC in the study by Pal et al.[10] than our experimental treatment. However, with 44 patients treated with cabozantinib, the patient number was rather low. An indirect comparison with the retrospective cohort study by Martinez et al.[21] using cabozantinib in 112 nccRCC patients with about 59% papillary RCC is not useful, as only 20% were treated in 1st line. McDermott et al.[22] reported in a phase-II single arm trial with pembrolizumab in nccRCC an ORR of 26.7%, a 12-month OS rate of 73% and a median OS of 28.9 months, which is slightly below the results of the SUNNIFORECAST trial.

The high response rate with ipilimumab/nivolumab in RCC with sarcomatoid or rhabdoid features of about 70% is in accordance with the data from the Checkmate-214 trial in ccRCC[23] and data from other studies combining TKI/ICI, where ORR is in the range of 60%.[20,24,25] In collecting duct carcinomas, the optimal treatment remains uncertain; some prefer a chemotherapy or a TKI.[6,26] Procopio reported an ORR of 35% (8/23 patients) using cabozantinib; we found response rates of 40% with ICI and 20% with SOC in the 5 patients per arm with collecting duct carcinoma.

Regarding the outcome in the different risk groups, there was a tendency towards a better OS outcome with ipilimumab/nivolumab in poor risk patients compared to intermediate risk. Interestingly, patients without a tumor nephrectomy had a better OS than those with tumor resection in the ipilimumab/nivolumab arm. These data are in accordance with those of Albiges et al.,[27] who described similar results in a subgroup analysis of the Checkmate-214 trial in ccRCC for ipilimumab/nivolumab compared to sunitinib. It may be hypothesized that patients without nephrectomy are more of high risk, a group that is known to have more benefit from ipilimumab/nivolumab compared to TKI.

The expression of PD-L1 might be associated with a worse prognosis.[28] On the other hand, expression of PD-L1 and/or PD-1 in tumor specimens may play a role for the efficacy of ICI and might be an explanation, why ICI combinations are more effective in intermediate and poor risk patients.[29-31] In our study, exploratory analysis yielded a significantly better OS for patients with a CPS ≥ 1 with the ipilimumab/nivolumab combination than for those in the SOC arm [HR 0.56 (0.37-0.86); $P = 0.008$]. These data are somewhat in contrast to Chrabanska et al.,[31] however, who reported no differences in OS for PDL-1 positive or negative nccRCC, whereby in the latter study most patients had a local disease stage only and no therapy details were presented.

In the Checkmate-214 trial that compared ipilimumab/nivolumab versus sunitinib in ccRCC, the ORR was 39.5% versus 33.0%.[32] By comparison, the ORR was lower in our cohort with 32.8% versus 19.6%. Additionally, the median OS was even longer in the intermediate/poor risk group in ccRCC (median not reached versus 37.9 months) than in the entire cohort of the SUNNIFORECAST trial (33.2 versus 25.2 months). This is in accordance with data suggesting nccRCC to have a worse outcome than ccRCC in metastatic stage of disease.[6]

Taking the data together, this is the first prospective clinical trial comparing the combination of ipilimumab/nivolumab against SOC; the SOC being dominated by different TKIs. It shows a significant advantage in the OS rate at 12 months and a trend for prolongation of OS for the ICI combination. There were no major differences in terms of efficacy of the ICI combination compared to SOC between papillary and non-papillary RCC. Due to rather low numbers of rare non-papillary sub-entities, a possible superiority of ipilimumab/nivolumab versus SOC in OS rate or median OS could not be definitively elucidated, but responders could be observed in all of these entities. Some limitations may be the mixed therapies in the SOC arm, taking a landmark analysis as primary endpoint rather than logrank and some discrepancies between local and central pathological diagnosis. Whether a TKI/ICI combination has a similar efficacy has to be clarified by further randomized trials. Due to the rarity of different nccRCC entities, international cooperations will be essential.

In conclusion, the randomized SUNNIFORECAST trial underlines a potential clinical benefit of ipilimumab/nivolumab in nccRCC.

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