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A Randomized Phase IIa Trial with Temsirolimus versus Sunitinib in Advanced Non-Clear Cell Renal Cell Carcinoma: An Intergroup Study of the CESAR Central European Society for Anticancer Drug Research-EWIV and the Interdisciplinary Working Group on Renal Cell Cancer (IAGN) of the German Cancer Society

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Keywords

Non-clear cell renal cell cancer · Sunitinib · Temsirolimus · Randomized trial · Phase II trial

Abstract

Background: Non-clear cell renal cell cancers (nccRCC) are rare entities, and the optimal therapy in metastatic disease has still to be defined. ***Methods:*** In this small prospectively randomized phase IIa multicenter trial, we investigated temsirolimus (TEM) versus sunitinib (SUN) as first-line therapy in patients with metastatic nccRCC. The patients were randomized 1:1 to either TEM in a dose of 25 mg i.v. once a week or SUN with 50 mg p.o. daily for 4 weeks on and 2 weeks off. Primary endpoint was progression-free survival (PFS). In total, 22 patients were included with predominantly papillary RCC (16/22) followed by chromophobe RCC and others. ***Results:*** The male to female ratio was 16:6. The tumor control rate (CR + PR + SD) was 58% for TEM and 90% for SUN-treated patients. There was also a trend for improved PFS with 9.3 versus 13.2 months (HR 1.64; 95% CI 0.65–4.18) in favor of SUN. There was no trend for overall survival. ***Conclusions:*** Despite this trial had to be terminated earlier due to low recruitment, the results match the other studies published so far with the mTOR inhibitor everolimus and SUN, which show a trend in favor of SUN for ORR and PFS.

Introduction

The therapeutic options in advanced renal cell carcinomas (RCC) have been improved dramatically in recent years. Various new agents as anti-angiogenic agents,

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tyrosine kinase inhibitors (TKIs), and immune checkpoint inhibitors (IOs) have been approved by the FDA and EMA. However, most clinical trials have been performed in clear cell (CC) RCC only or predominantly, which account for about 75% of all RCCs [1–3].

In contrast, data in advanced non-clear cell (ncc) RCCs are rather rare [1, 4, 5]. There are only a few studies focusing on nccRCC exclusively, showing only some limited data on the efficacy in response rates and survival of targeted agents as temsirolimus (TEM), everolimus, or sunitinib (SUN) or other TKIs in nccRCC [6–10]. Recommendations suggest to treat nccRCC in the same way as ccRCC due to missing corresponding trials [1, 3]. Uncertainties also exist in the proper treatment of sarcomatoid RCCs, which can be the dedifferentiated tumor form of nearly all histological subtypes of RCCs, but new data with combinations of immune-checkpoint inhibitors (IO/IO) or IOs with axitinib suggest an advantage [10–12].

Direct comparisons between the mammalian targets of rapamycin (mTOR) inhibitors everolimus and SUN have been studied in two small randomized trials showing a tendency towards SUN or no significant difference in efficacy, but still the numbers are rather small to draw final conclusions [6, 7]. Regarding the mTOR inhibitor TEM, the subgroup analysis of the "Advanced Renal Cell Carcinoma" (ARCC) study showed a comparable median OS (mOS) for ccRCC and nccRCC patients receiving TEM in comparison to interferon-α [13]. No data are available for the mTOR inhibitor TEM in comparison to SUN [14].

Additionally, nccRCC are heterogeneous entities, whereby the most frequent subtype of nccRCC with 10–15% is papillary RCC, followed by chromophobe RCC (5%), collecting duct carcinomas (1%), medullary carcinomas (1%), and MiT family translocation RCC (1%). Furthermore, new entities of nccRCC were described in the 2016 WHO classification [15] with still not defined frequency, clear cell papillary RCC, succinyldehydrogenase B-deficient RCC, hereditary leiomyomatosis, and RCC syndrome-associated RCC with fumarate hydratase deficiency.

In this small multicenter prospectively randomized phase IIa trial, TEM was compared to SUN in nccRCC.

Patients and Methods

This open-label randomized trial was performed in 9 centers of the Central European Society for Anticancer Drug Research-EWIV (CESAR) study group. It was an investigator-initiated trial. Eligible patients had histologically confirmed nccRCC, including sarcomatoid features, defined as >50% sarcomatoid component as assessed through pathological examination by a local site review. Mixed features were allowed if the nccRCC component was >50%. Additional eligibility criteria included a baseline Karnofsky performance status of 70 or higher, life expectancy of at least 3 months, and the presence of measurable metastatic disease as per RECIST 1.1 criteria. Patients had to have adequate bone marrow, kidney, and liver function and adequate laboratory parameters (baseline creatinine concentration ≤2 times the institutional upper limit of normal (ULN), as well as aspartate aminotransferase and alanine aminotransferase concentrations <2·5 times the ULN. The patients could not have received any prior systemic cancer treatment and should not have symptomatic brain metastases. Local irradiation and/or surgical procedures were not allowed within 4 weeks prior study inclusion. Additional exclusion criteria were severe cardiovascular disorders, poorly controlled hypertension, any cardiovascular event within 6 months of randomization or prolonged QTc time (>450 ms), abnormal pulmonary function (DCO <50%), poorly controlled diabetes mellitus, patients taking strong CYP3A inhibitors or inducers, active infections, or second malignancies as well as pregnant or nursing women.

Patients who met the eligibility criteria were randomly assigned 1:1 to receive either SUN 50 mg/day p.o. for 4 weeks, followed by 2 weeks rest each or 25 mg TEM as weekly infusions. Dose reductions were allowed according to the Summary of Product Characteristics (SmPc).

The primary endpoint was progression-free survival (PFS), secondary endpoints were objective response (ORR), time to progression, safety assessed according to CTCAE, PFS rate at 12 months, and overall survival. PFS was defined as time from randomization until disease progression. Tumor assessment was done in accordance with common guidelines every 3 months. The study was discontinued in case of tumor progression, intolerable adverse events, or pregnancy. The statistical analysis was done by the Assign Data Management and Biostatistics GmbH (Innsbruck, Austria).

Results

In total, 22 patients were eligible and randomized. Due to low recruitment over 2 years, the study was prematurely stopped. Twelve patients were randomized to arm A (TEM) and 10 patients to arm B (SUN). The median age was 60.8 years. A total of 59% of the patients had ECOG and 41% ECOG 1. Further, 86.5% of the patients had a metastatic disease, and 13.5% a locally advanced stage. The histological classification was done by the local pathologists. Sixteen patients (73%) had a papillary subtype, 2 patients a chromophobe, 1 patient a renal medullary and 3 patients an unclassified non-clear cell carcinoma (Table 1). The median treatment duration was slightly but not significantly lower in the TEM group. The reason for treatment stop was predominantly tumor progression or death (Table 1).

In the TEM arm, 2 of 12 patients achieved a partial remission (PR) and 5 of 12 patients a stable disease (SD) compared to 3 of 10 and 6 of 10 patients in the SUN arm, respectively (Table 2). The tumor control rate (CR + PR + SD) was 77.8% in the GEM arm and 90% in the SUN arm. The median PFS for TEM was inferior with 9.3 versus 13.2 months for SUN, but the difference was statistically not significant and the primary endpoint was not

Table 1. Patient characteristics

	Arm A: TEM (n = 12)	Arm B: SUN (n = 10)	Total (n = 22)
Median age, years (range)	59.5 (29–85)	65.5 (46–80)	60.8 (29–85)
Sex, m/f	8/4	8/2	16/6
ECOG, n (%)			
0	7	6	13 (59)
1	5	4	9 (41)
Tumor status, n (%)			
Locally advanced	3	0	3 (13.5)
Metastatic	9	7	16 (73)
Locally advanced/metastatic	0	3	3 (13.5)
Histological subtype, n (%)			
Papillary	8	8	16 (73)
Chromophobe	2	0	2 (9.0)
Renal medullary	1	0	1 (4.5)
Unclassified	1	2	3 (13.5)

Table 2. Treatment results

	Arm A: TEM (n = 12)	Arm B: SUN (n = 10)	Total (n = 22)
Response			
CR	0	0	0
PR	2	3	5
SD	5	6	11
PGR	2	1	3
NE	3	0	3
Median treatment duration, days (range)	121 (8–1,015)	144 (70–490)	126.5 (8–1,015)
Reason for treatment stop, n (%)			
Tumor progression	6	3	9 (41.0)
Adverse event	1	0	1 (4.5)
Death	1	1	2 (9.0)
Intolerable toxicity	0	1	1 (4.5)
Noncompliance	0	1	1 (4.5)
Other reasons	4	4	8 (36.5)

met (Fig. 1). There was no difference in mOS with 19.4 months TEM and 19.8 months for SUN (Fig. 2).

No dose modifications have been reported in the TEM arm, but 7 of 10 patients experienced at least one dose modification (reduction) during the treatment period in the SUN arm. Eleven of 12 patients had drug-related severe adverse events (SAE) in the TEM arm and all patients in the SUN arm (Table 3).

Discussion

Patients with metastatic nccRCC show a worse response to treatment with either VEGF- or mTOR-targeted therapies as well as a shorter overall survival (OS) compared to clear cell RCC (ccRCC) patients [1, 16].

Since nccRCC are excluded from most kidney cancer studies, their optimal treatment is yet not defined. Reports on mTOR inhibitors in RCC have proven a benefit for TEM compared to interferon-α (IFN) [9, 13]. The subgroup analysis of the ARCC study showed a comparable mOS for ccRCC and nccRCC patients receiving TEM, whereas nccRCC patients with IFN had a significantly shorter mOS and a lower ORR than nccRCC patients [13].

The subgroup analysis of the RAD001 Expanded Access Clinical Trial (REACT) demonstrated an ORR of 50.6% (1.3% PR and 49.3% SD) and a PFS of 2.8 months for everolimus [17]. Another trial reported a mOS of 14 months and a PFS of 5.2 months for patients receiving everolimus irrespective of pretreatment with VEGF-TKI. The benefit was especially high in chromophobe RCC

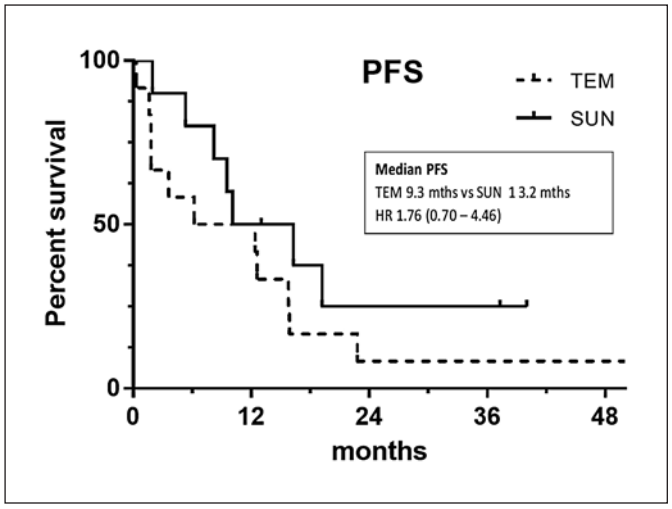

Fig. 1. Kaplan-Meier curves by treatment group for PFS.

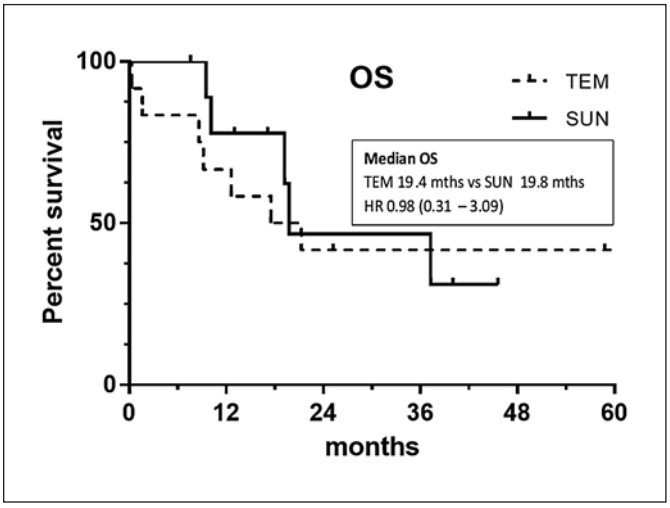

Fig. 2. Kaplan-Meier curves by treatment group for OS.

Table 3. Number of subjects experiencing at least one related serious event

Adverse event all/grade 3	TEM (n = 12)	SUN (n = 10)	Total (n = 22), n (%)
Cytopenia	0	3/2	3 (13.6)
Infections	2/2	0	2 (9.1)
Cardiac event (QTc)	0	2/1	2 (9.1)
Gastrointestinal	0	1/1	1 (4.5)
Nervous system	0	1/1	1 (4.5)
Renal	1/1	0	1 (4.5)
Respiratory	0	1/1	1 (4.5)

patients, documenting a PFS of 13.1 months compared to 3.4 months in other nccRCC subgroups (p = 0.084) [16]. The RAPTOR trial showed similar results concerning PFS for patients with papillary histology with a mOS of 21.4 months [18].

In this trial, we compared the mTOR inhibitor TEM with SUN. Unfortunately, the recruitment rate was low and the trial had to be ended prematurely. Despite this low patient number and the limitations of this trial, the findings suggest that patients with metastatic nccRCC may have a higher tumor control rate and longer PFS when treated with SUN compared with TEM.

Up to now, a few randomized studies evaluated the efficacy of SUN compared to everolimus in nccRCC patients (ASPEN, ESPN) [6, 7] showing a trend towards SUN regarding PFS and OS in a meta-analysis [4, 19]. Regarding different risk subgroups, ASPEN especially indicated a benefit for VEGF-TKI therapy in patients with good or intermediate risk according to MSKCC criteria (PFS 14 vs. 5.7 months in good risk and 6.5 vs. 4.9 months in intermediate risk patients) compared to everolimus. However high-risk patients according to MSKCC criteria showed a better PFS with everolimus (4.0 vs. 6.1 months, HR 0.3) [9]. Taken together, the three studies support a superiority of SUN to mTOR inhibitors as everolimus or TEM in nccRCC.

Recently, new combinations of immune checkpoint inhibitors (ipilimumab/nivolumab) or axitinib with an immune checkpoint inhibitor (axitinib + pembrolizumab; axitinib + avelumab) have been approved by the FDA and the European Commission for metastatic RCC independent from histological subtype, despite there are no sufficient data available in nccRCC. However, the significance of the immune checkpoint inhibitors in patients with metastatic nccRCC remains so far limited. Individual case reports and the subgroup analysis of the ipilimumab plus nivolumab and axitinib plus pembrolizumab pivotal studies show a promising response in nccRCC and especially those with sarcomatoid features [11, 20–22]. Initial data are also available for the combination of bevacizumab and atezolizumab [23]. The current ESMO guidelines therefore consider the IO/IO combination to be a good therapy option for sarcomatoid RCCs [24].

Despite this trial had to be terminated due to low recruitment and the numbers are small, the results match the other studies published so far with the mTOR inhibitor everolimus and SUN, which show a trend in favor of SUN. New options with IO/IO or TKI/IO combinations are of major interest. A recently initiated, multicenter, prospective, two-arm study of nivolumab in combination with ipilimumab compared to standard of care (e.g., SUN) aims to evaluate the efficacy and safety of this combination in nonccRCC (SUNNIFORECAST; NCT03075423).

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Statement of Ethics

The study was registered at www.clinicaltrials.gov (NCT00979966) and at EUDRACT 2009-010143-13 and was approved by the institutional ethical boards, and all patients provided written informed consent according to the EMA guideline for good clinical practice (ICH/GCP).

Disclosure Statement

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Author Contributions

L.B. concept and design, acquisition and interpretation of data, drafting of manuscript. V.G. concept and design acquisition of data, revision and approval of manuscript. L.M., M.-O.G., S.W., J.S., T.K., J.G., A.F., and T.G. acquisition of data, revision and approval of manuscript. A.H. pathology, revision and approval of manuscript.

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