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Original Article

Cytoreductive nephrectomy and exposure to sunitinib – a *post hoc* analysis of the Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients With Metastatic Kidney Cancer (SURTIME) trial

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Abstract

Objective

To analyse if exposure to sunitinib in the Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients With Metastatic Kidney Cancer (SURTIME) trial, which investigated opposite sequences of cytoreductive nephrectomy (CN) and systemic therapy, is associated with the overall survival (OS) benefit observed in the deferred CN arm.

Patients and Methods

A *post hoc* analysis of SURTIME trial data. Variables analysed included number of patients receiving sunitinib, time from randomisation to start sunitinib, overall response rate by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1, and duration of drug exposure and dose in the intention-to-treat population of the immediate and deferred arm. Descriptive methods and 95% confidence-intervals (CI) were used.

Results

In the deferred arm, 97.7% (95% CI 89.3–99.6%; n = 48) received sunitinib vs 80% (95% CI 66.9–88.7%, n = 40) in the immediate arm. Following immediate CN, 19.6% progressed 4 weeks after CN and the median time to start sunitinib was 39.5 vs 4.5 days in the deferred arm. At week 16, 46.0% had progressed at metastatic sites in the immediate CN arm vs 32.7% in the deferred arm. Sunitinib dose reductions, escalations and interruptions were not statistically significantly different between arms. Among patients who received sunitinib in the immediate or deferred arm the median total sunitinib treatment duration was 172.5 vs 248 days. Reduction of target lesions was more profound in the deferred arm.

Conclusions

In comparison to the deferred CN approach, immediate CN impairs administration, onset, and duration of sunitinib. Starting with systemic therapy leads to early and more profound disease control and identification of progression prior to planned CN, which may have contributed to the observed OS benefit.

Keywords

cytoreductive nephrectomy, deferred, immediate, renal cell carcinoma, sunitinib, survival, #uroonc, #kcsm, #KidneyCancer

Introduction

Renal cell carcinoma (RCC) accounts for 3–5% of all adult tumours and is the seventh most common in men and eighth among women [1]. Despite nephrectomy with curative intent, 15–20% of patients are metastatic at the time of diagnosis and 20–40% are expected to develop postoperative metastases [2].

In the cytokine era, cytoreductive nephrectomy (CN) has become the standard treatment in selected patients on the basis of two prospective, randomised studies [3,4]. However, this standard has lately been re-challenged by the Cancer du Rein Metastatique Nephrectomie et Antiangiogéniques (CARMENA) trial [5] in which patients were randomised to receive either vascular endothelial growth factor receptor (VEGFR)-targeted therapy (TT) with sunitinib alone or the former standard of upfront CN followed by sunitinib. Ultimately, median overall survival (OS) with sunitinib alone was non-inferior to the upfront CN approach followed by sunitinib but deferred CN was an option in the sunitinib only arm and performed in 17% of the patients. The concept of deferred CN was investigated in the Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients with Metastatic Kidney Cancer (SURTIME) trial [6]. In which patients with metastatic RCC (mRCC) were randomised to sunitinib therapy first, followed by CN in the absence of progression vs immediate CN followed by sunitinib. The study results were mainly exploratory due to poor accrual, but suggested that with the deferred approach, patients were more likely to receive sunitinib and had better OS results. End-points were previously reported [6]. The hazard ratio (HR) of the secondary end-point OS favoured deferred CN (HR 0.57, 95% CI 0.34–0.95, $P = 0.032$) with a median OS of 32.4 vs only 15.0 months after immediate CN. The conclusion by the authors was that pre-treatment with sunitinib may identify patients with inherent resistance to systemic therapy before planned CN and avoid an unnecessary intervention [6]. In accordance with the recent studies [5-7], the European Association of Urology (EAU) RCC guidelines have responded to this paradigm change [8] and recommend systemic therapy for patients with primary mRCC and progressive metastatic disease with the option to consider deferred CN in those responding at metastatic sites. In the present study, we investigated in a *post hoc* analysis of SURTIME data if differences in the exposure to sunitinib in the study arms occurred that may be associated with the survival benefit observed after upfront systemic therapy followed by deferred CN compared to immediate CN followed by sunitinib in the postoperative setting.

Patients and Methods

The present study is a *post hoc* analysis of the SURTIME clinical trial [6]. SURTIME was designed as a randomised phase III trial comparing deferred to immediate CN in patients with clear-cell mRCC treated by sunitinib. The primary end-point was progression-free survival in the intention-to-treat population. Patients were recruited to the trial from July 2010 to March 2016, according to pre-defined eligibility criteria. Patients were randomised 1:1 at the European Organisation for the Research and Treatment of Cancer (EORTC) to immediate CN followed by sunitinib therapy vs treatment of sunitinib (three cycles) followed by CN and sunitinib. In case of systemic progressive disease in the deferred arm, nephrectomy was not recommended but left at the discretion of each investigator In both arms a per-protocol rest period of 4 weeks after CN was scheduled to allow for recovery from surgery. Sunitinib was started at 50 mg/day 4 weeks on/2 weeks off followed by dose reductions by increments of 12.5 mg in case of treatment-related adverse events and administered until disease progression or unmanageable toxicity. Dose interruptions were allowed. The study was approved by the Institutional Review Board at each centre included. All patients signed written informed consent forms, and all data were deidentified [6].

Outcomes

The primary aim of this *post hoc* analysis was to assess exposure to sunitinib defined by number of individuals treated with the study drug, the length of treatment period, and dose reductions and modifications. Duration of sunitinib exposure for patients in the immediate CN arm include the time from start sunitinib after a per-protocol recovery period of 4 weeks after CN until discontinuation. In the deferred arm the duration was assessed from sunitinib start until discontinuation taking into account the 4-week per-protocol interruption of sunitinib for surgery (i.e. sum of pre- and post-surgery treatment period). The secondary aim was to assess the treatment response in the sum of target lesions (including the primary tumour and distant metastatic sites) according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) in both arms over time.

Inclusion and Exclusion Criteria

The study included patients aged ≥18 years with histologically confirmed, previously untreated clear-cell mRCC with an asymptomatic resectable primary tumour, eligible to therapy with sunitinib. Further requirements included a WHO Performance Status of 0–1; measurable disease according to RECIST 1.1; life expectancy of >3 months; adequate bone marrow, liver, cardiac, and renal function. Exclusion criteria included clinical signs of CNS involvement; three or more surgical risk factors including serum albumin according to Common Terminology Criteria For Adverse Events (CTCAE), version 4.0 Grade ≥2, serum lactate dehydrogenase (LDH) of

≥1.5-times the upper limit of normal (ULN), liver metastases, symptomatic metastases, retroperitoneal or supradiaphragmatic lymph node involvement, and Stage cT3-T4 disease [6].

Analysis Methods

Reasons for dose reductions, modifications, and discontinuation (progression, toxicity) were collected and the sequence and duration of study treatment (sunitinib, CN, second-line therapies) were illustrated as swimmer plots. We used spider plots to illustrate the combined response of sunitinib and CN on the sum of the longest diameter of all target lesions (according to RECIST 1.1) including the primary tumour and metastatic sites in both pre-specified treatment groups over time. CIs are presented at the 95% confidence level.

Results

A total of 99 patients (80 men and 19 women; mean [SD] age, 60 [8.5] years) were randomised, 50 in the immediate CN arm and 49 in the deferred CN arm [1]. Patient characteristics are listed in Table 1.

In the deferred CN arm, 97.7% (95% CI 89.3–99.6%; n = 48) received sunitinib vs only 80% (95% CI 66.9–88.7%, n = 40) in the immediate CN arm (Table 2). In the deferred CN arm, 48 patients started on sunitinib at a median of 4.5 days after randomisation and had a total duration of sunitinib exposure of 248 days, corrected for the per-protocol 4-week recovery time for those patients following deferred CN. Postoperative sunitinib was continued in 29 of the 40 patients who underwent CN in the deferred arm, six of whom despite progression at metastatic sites. After immediate CN, 40 of 50 patients (80%) started on trial drug with a median time of 39.5 days after randomisation. This includes the per-protocol 4-week recovery period from CN at the end of which 19.6% had confirmed RECIST progression at a pre-planned interval CT scan to assess the progression rate after CN prior to start of systemic therapy. In addition, 25% started with sunitinib beyond the 4-week recovery period after surgery. The median

Table 1 Baseline characteristics.

Variable	Assigned to immediate nephrectomy (*N* = 50)	Assigned to deferred nephrectomy (*N* = 49)	All randomised patients (*N* = 99)
Age, years, median (range)	60 (39–78)	58 (43–74)	59 (39–78)
Gender, *n* (%)			
Male	41 (82.0)	39 (79.6)	80 (80.8)
Female	9 (18.0)	10 (204)	19 (19.2)
WHO performance status, *n* (%)			
0	36 (72.0)	31 (63.3)	67 (67.7)
1	14 (28.0)	18 (36.7)	32 (32.3)
Primary tumour size, mm			
Mean (SD)	93.1 (37.8)	96.8 (31.3)	95.0 (34.6)
Median (range)	91 (13–200)	96 (33–180)	94.5 (13–200)
Sum of all target lesions at entry, mm			
Mean (SD)	169.7 (71.9)	159.2 (46.7)	164.5 (60.5)
Median (range)	162 (48–419)	162 (45–244)	162 (45–419)
Number of surgical risk factors*, *n* (%)			
0	8 (16.0)	11 (22.4)	19 (19.2)
1	14 (28.0)	16 (32.7)	30 (30.3)
2	16 (32.0)	15 (30.6)	31 (31.3)
3	12 (24.0)	7 (14.3)	19 (19.2)
Clinical T stage†, *n* (%)			
T1	9 (18.0)	8 (16.3)	17 (17.2)
T2	15 (30.0)	23 (46.9)	38 (38.4)
T3	22 (44.0)	15 (30.6)	37 (37.4)
T4	4 (8.0)	3 (6.1)	7 (7.1)
Clinical N stage†, *n* (%)			
N0	17 (34.0)	20 (40.8)	37 (37.4)
N1	15 (30.0)	10 (20.4)	25 (25.3)
N2	10 (20.0)	8 (16.3)	18 (18.2)
Unknown	8 (16.0)	11 (22.5)	19 (19.1)
MSKCC risk score‡, *n* (%)			
Intermediate risk (1–2 factors)	43 (86.0)	44 (89.8)	87 (87.9)
Poor risk (3 factors)	7 (14.0)	5 (10.2)	12 (12.1)

**Surgical risk factors include serum albumin < 3 g/dL, serum LDH > 1.5 × ULN, liver metastases, symptoms at presentation due to metastases, retroperitoneal lymph node involvement, supra-diaphragmatic lymph node involvement, clinical stage T3 or T4. †Clinical T stage and clinical N stage according to TNM classification, seventh edition (2009). ‡Memorial Sloan-Kettering Cancer Center (MSKCC) score for mRCC include time from diagnosis to systemic treatment of < 1 year (replaced by the time between first diagnosis of mRCC and randomisation), haemoglobin < lower limit of normal (135 g/L for men, 120 g/L for women), calcium > 100 mg/dL (> 2.5 mmol/L), serum LDH > 1.5 × ULN, Karnofsky Performance Status < 80% (replaced by WHO performance status ≥2).*

total duration of sunitinib exposure in the immediate CN arm was 172.5 days.

Of those who received systemic therapy in the deferred and immediate arm, 41.7% (20/48) and 32.5% (13/40) had dose reductions, respectively, among other dose modifications (Table 3). Of the 20 patients in the deferred arm, 14 reduced to 37.5 mg, five to 25 mg and one to 12.5 mg. Similar rates were observed in the immediate arm as 11 of 13 reduced to 37.5 mg and two to 12.5 mg (Table 3).

At week 16, 46.0% (23/50) had progressed at metastatic sites in the immediate CN arm vs 32.7% (16/49) in the deferred arm. An overview of treatment received (surgery/sunitinib) and timing are given in Fig. 1. In both arms, the major reason for sunitinib discontinuation was disease progression (Fig. 1). In the deferred and immediate arm only two and four patients discontinued sunitinib after surgery because of adverse events, respectively.

Regarding target lesions, both arms had a comparable size of target lesions and primary tumours before therapy (Table 1). Reduction of all target lesions over time was more profound in the deferred arm (Fig. 2).

Table 2 Treatment duration (in days) of sunitinib for patients who started on study drug in both arms.

	Immediate (*N* = 50)	Deferred (*N* = 49)
Patients who started on sunitinib, *n*; % (95% CI)	40; 80 (66.9–88.7)	48; 97.7 (89.3–99.6)
Total duration of sunitinib exposure (before and after surgery, taking into account the interruption of sunitinib for surgery in the deferred arm, i.e. sum of pre- and post-surgery treatment period), days		
Median	172.5	248.0
Range	4.0–1744.0	17.0–1623.0
Time from randomisation to sunitinib start, days		
Median	39.5	4.5
Range	31.0–85.0	1.0–15.0
Interruption of sunitinib for surgery in the experimental arm, days		
Median	-	37.0
Range	-	22.0–75.0
N	-	30

Table 3 Dose modification sunitinib treatment.

Total sunitinib treatment – subset of patients who received sunitinib (pre- and/or post-operative treatment)		
Dose modifications (pre- and/or postoperative treatment)	**Immediate (*N* = 40)**	**Deferred (*N* = 48)**
Dose reduction		
Patients, *n* (%)	13 (32.5)	20 (41.7)
95% CI of %	(18.6–49.1)	(27.6–56.8)
Dose escalation		
Patients, *n* (%)	1 (2.5)	2 (4.2)
95% CI	(0.00–0.13)	(0.01–0.14)
Dose interruption		
Patients, *n* (%)	10 (25.0)	17 (35.4)
95% CI	(12.7–41.2)	(22.1–50.5)
Dose reduction – subset of patients with a dose reduction by 12.5 mg increments (pre- and/or postoperative treatment)		
Dose reduction (pre- and/or postoperative treatment)	**Immediate (*N* = 13)**	**Deferred (*N* = 20)**
Lowest dose level reached, *n* (%)		
37.5 mg/day	11 (84.6)	14 (70.0)
25 mg/day	2 (15.4)	5 (25.0)
12.5 mg/day	0 (0.0)	1 (5.0)

Discussion

In the present *post hoc* analysis, fewer patients received systemic therapy in the immediate CN arm, which was administered later and for a shorter time compared to the deferred approach. Moreover, the decrease in the sum of target lesions over time was more profound in the deferred CN arm. In the SURTIME clinical trial, deferred CN in patients with mRCC did not improve the rate of progression-free survival at 28 weeks. However, the deferred CN approach resulted in favourable OS, which was a secondary end-point [6]. These findings are supported by several retrospective studies including a high number of patients, which suggest that deferred CN is associated with improved OS compared to immediate CN [9,10]. In support of these findings, a recent retrospective study by Bhindi *et al.* [11] reported that sunitinib followed by deferred CN was associated with improved OS and time to sunitinib treatment failure. Also, patients who underwent deferred CN after upfront TT had improved OS at 3 and 6 months compared to those who received TT alone [7,10]. However, it needs to be acknowledged that these retrospective real-world data are limited by selection bias. Therefore, it is interesting that in the prospective CARMENA trial, in the sunitinib-alone arm, secondary nephrectomy was also associated with improved OS compared with no nephrectomy [5]. These results may support the role of deferred CN in some patients with mRCC, yet, the optimal timing and indication remains to be defined. In the present analysis, we found that the concept of immediate systemic therapy followed by deferred CN in the absence of disease progression is associated with earlier and longer TT treatment. Further, there is a more profound control of the disease, which may have contributed to the difference in OS between the two groups. Interestingly, it has been suggested that one of the major concerns regarding the immediate CN approach is the risk of not receiving subsequent systemic therapy in up to 30% of patients, mainly due to rapid disease progression or postoperative complications [12]. And indeed, in SURTIME,

Fig. 1 Overview of events immediate vs deferred arms; (**A**) immediate arm, (**B**) deferred arm.

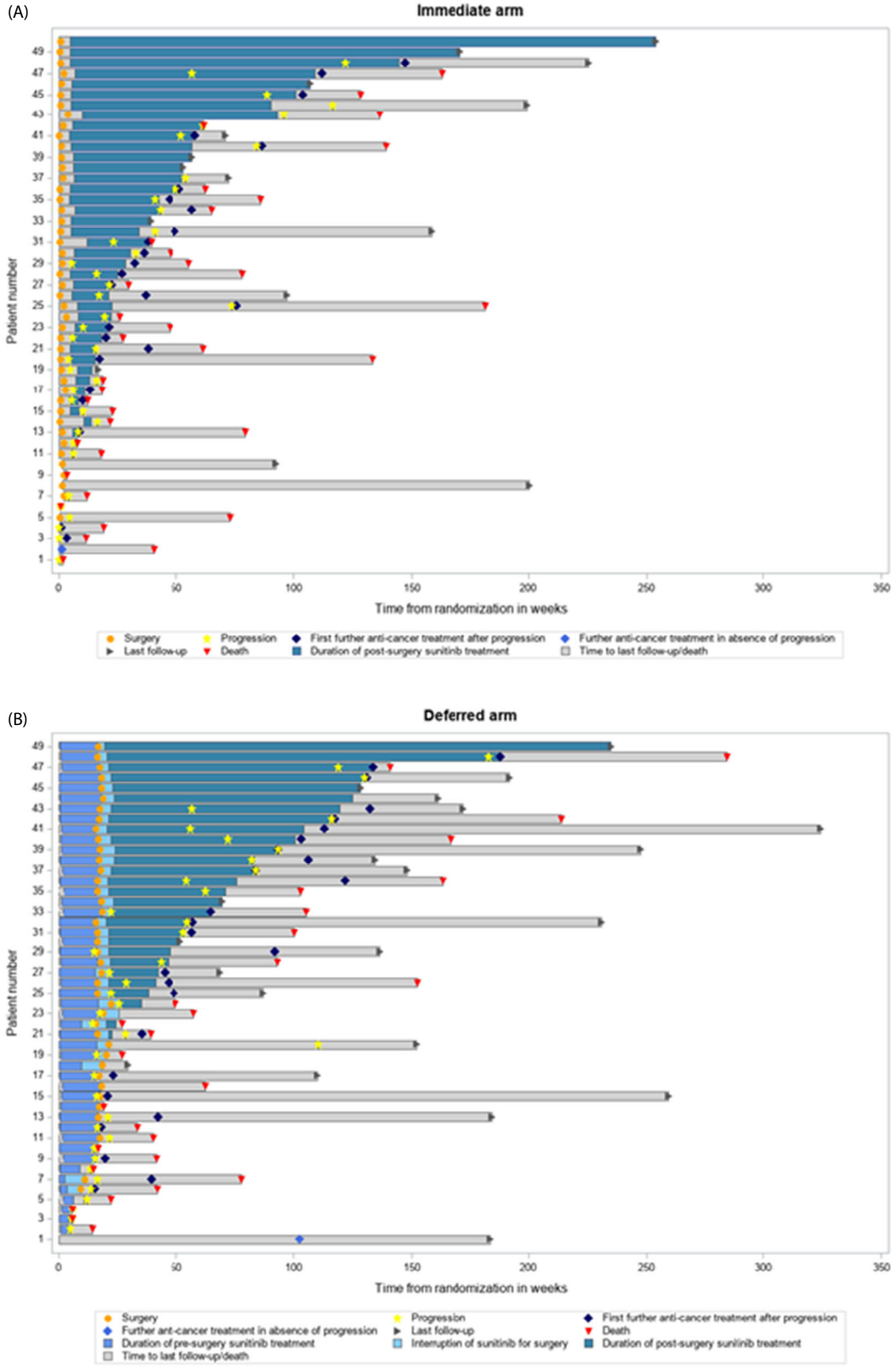
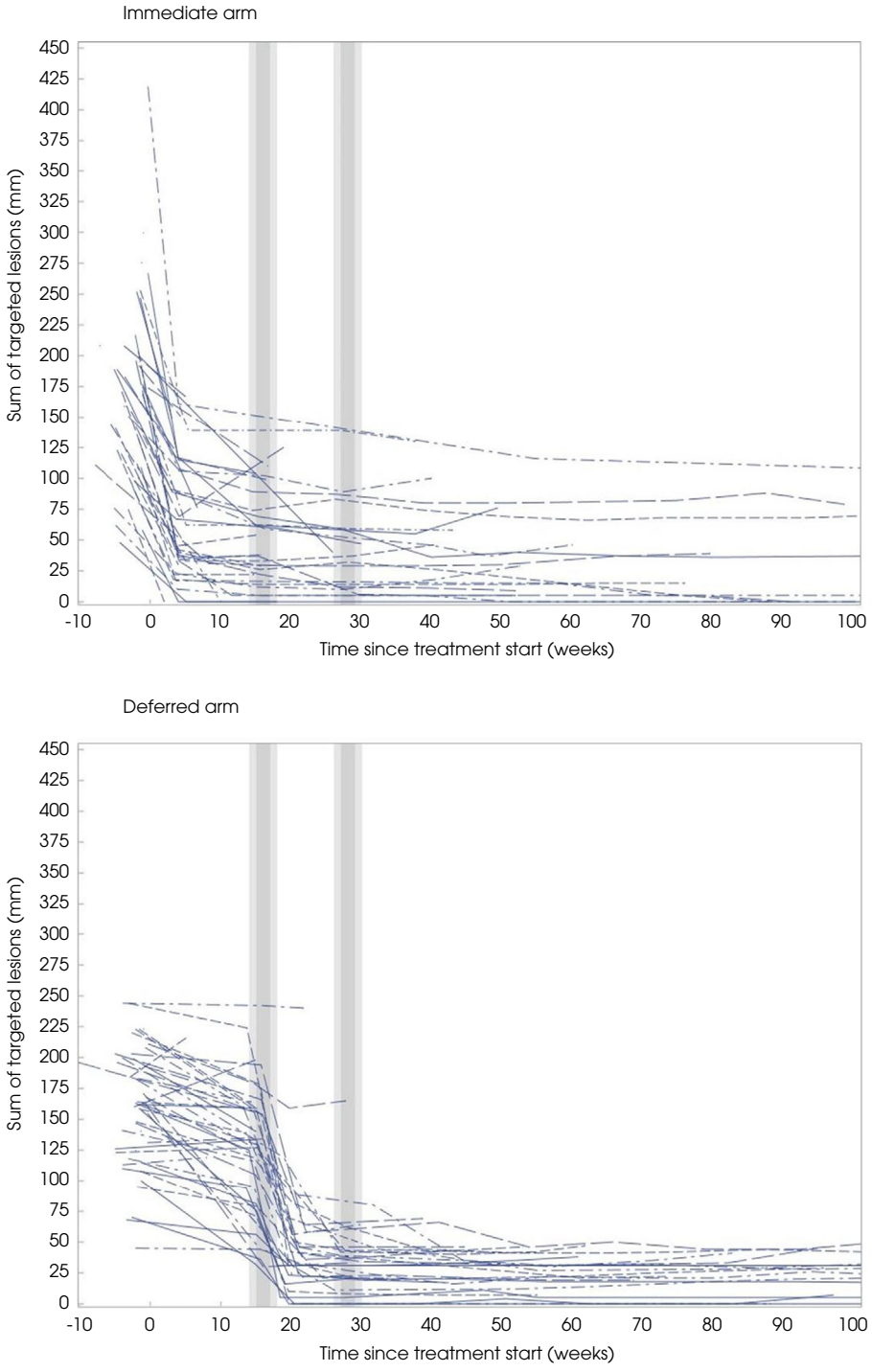


Fig. 2 Target lesions measurements immediate vs deferred arms; Time since treatment start (weeks); Negative numbers indicate baseline tumour burden assessment prior to start of treatment as was the case in this trial; Grey bars show progression status assessment at week 16 and 28 in accordance with trial methods.



after immediate CN fewer patients received systemic treatment and for a shorter period.

Immediate systemic therapy is now recommended for patients with poor performance status or high metastatic burden in association with intermediate and poor prognosis as no benefit has been shown for CN in this setting [5,13,14]. Also, immediate systemic therapy could serve as a litmus test to decide about subsequent CN [15,16]. Upfront systemic therapy

with VEGFR-TT potentially distinguishes between patients with an aggressive tumour biology who are unlikely to benefit from CN, and those with mainly angiogenesis-driven tumours who undergo deferred CN as a consequence of a favourable disease biology. As seen in the present *post hoc* analysis of SURTIME, these patients have better OS and are treated longer with the VEGFR-tyrosine kinase inhibitor, sunitinib. Meanwhile, sunitinib has been replaced by several immune checkpoint inhibitor (ICI) combined therapies including monoclonal antibodies directed against the programmed death receptor 1 (PD-1) or its ligand (PDL-1) in combination with either monoclonal antibodies against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) VEGFR inhibitors as standard of care in treatment-naive clear-cell RCC [17,18]. Nevertheless, control of the disease in patients who require systemic therapy by administering drug treatment first rather than surgery first may be a universal concept and a legacy from CARMENA and SURTIME. This is reflected in the fact that in all pivotal ICI combination phase III trials 16–30% of the included patients with mRCC had unresected primary tumours and were treated with acceptable safety and favourable outcome in exploratory subgroup analyses compared to sunitinib [19]. Complete pathological responses have been described in 10% of these patients [20,21] and increasingly patients with near complete response are offered deferred CN. This concept is currently not supported by prospective data but randomised controlled trials investigating deferred CN in the era of ICI combined therapy have started accrual (NCT03977571 and NCT04510597).

Strengths of our present study include the use of randomised trial data. Furthermore, availability of data on duration of treatment and response in target lesions allowed for more thorough comparison between groups. Limitations include accrual limitation as previously described [6], as well as the nature of a *post hoc* analysis of the data.

In conclusion, our present data support the use of upfront systemic therapy in patients with primary mRCC. This allows more patients to receive a longer duration of systemic therapy. Time on systemic therapy is associated with a greater reduction in tumour burden and prolonged OS. In comparison, immediate CN impairs early onset of systemic therapy with control of the disease in fewer patients.

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Conflicts of Interest

Prof Bex reported serving as a member of the medical steering committee of the International Kidney Cancer Coalition and the Kidney Cancer Association. Dr Blank reported receiving personal fees for advisory roles for BMS, MSD, Roche, GlaxoSmithKline, Eli Lilly and Company, Novartis, and Pfizer and grants from Novartis and BMS outside the submitted work. Dr Jewett reported receiving honoraria from Pfizer, Ipsen, Olympus, and Theralase Therapeutics. Dr Lattouf reported receiving honoraria from Janssen and Bayer for participation in advisory boards outside the submitted work. Dr Powles reported receiving grants from AstraZeneca and Roche and personal fees from AstraZeneca, Roche, Pfizer, Novartis, Merck & Co, and BMS outside the submitted work. Dr Tombal reported receiving grants from Amgen, Myovant, Astellas, Janssen, Bayer Sanofi, Ferring. No other disclosures were reported.

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Abbreviations: CN, cytoreductive nephrectomy; EAU, European Association of Urology; HR, hazard ratio; ICI, immune checkpoint inhibitor; LDH, lactate dehydrogenase; mRCC, metastatic RCC; OS, overall survival; RECIST, Response Evaluation Criteria In Solid Tumors; SURTIME, Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients With Metastatic Kidney Cancer; TT, targeted therapy; ULN, upper limit of normal; VEGFR, vascular endothelial growth factor receptor.