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RESEARCH

Central and Eastern European Experience with Sunitinib in Metastatic Renal Cell Carcinoma: A Sub-analysis of the Global Expanded-Access Trial

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Abstract A global, open-label, expanded-access trial (EAT) provided sunitinib treatment on a compassionate-use basis to patients with metastatic renal cell carcinoma (mRCC) between 2005 and 2011. This retrospective analysis examines outcomes in patients from Central and East European (CEE) countries participating in the global EAT. Sunitinib (starting dose 50 mg orally once daily, with dose reduction for toxicity) was administered in repeated 6-week cycles (4 weeks on and 2 weeks off) until occurrence of disease progression or unacceptable toxicity. Tumor assessments were guided by Response Evaluation Criteria in Solid Tumors (RECIST) criteria but were performed according to local standards of care. In total, 401 CEE patients received sunitinib (median treatment duration 9.6 months), of whom 378 were evaluable for tumor response. The most frequent grade ≥3 toxicities were fatigue (7.5 %), hypertension (7.0 %), thrombocytopenia (6.5 %), diarrhea (4.2 %), nausea and hand-foot syndrome (both 3.7 %) and neutropenia (3.0 %). Median overall survival was 30.7 months (95 % CI 23.3, months). Overall survival tended to be longer in cytokine-naïve than cytokine-experienced patients (median 60.8 vs. 27.5 months; $P=$ 0.1324). Among patients with evaluable tumors, 4.0 % achieved a complete and 14.6 % a partial response [objective response rate (ORR) 18.5 % (95 % CI 14.7, 22.8 %)]. Median progression-free survival was 11.6 months (95 % CI 10.3, 12.8 months). Sunitinib demonstrates safety and effectiveness in real-world mRCC patients in CEE countries. Expanded-access program patients showed a lower tumor response rate but similar survival outcomes to patients in the pivotal Phase III clinical trial of sunitinib in mRCC.

Keywords Renal cell carcinoma · Metastatic · Sunitinib · Expanded-access

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Introduction

Sunitinib, an orally active, small-molecule inhibitor that targets multiple receptor tyrosine kinases involved in tumor growth and angiogenesis, including vascular endothelial growth factor receptor (VEGFR)-1, -2- and -3, platelet-derived growth factor receptor (PDGFR)-α and -β, stem cell growth factor receptor (c-KIT), fms-like tyrosine kinase 3 (FLT3), colony-stimulating factor 1 receptor (CSF-1R), and glial cell line-derived neurotrophic factor receptor (RET) [1]. Sunitinib was approved in Europe in 2006 for the treatment of metastatic renal cell carcinoma (RCC) and has since become a

reference standard of care for first-line treatment of favorable- or intermediate-risk metastatic RCC and as a second-line option in poor-risk disease [2, 3]. The drug's efficacy was demonstrated in a large international randomized Phase III registration trial that compared sunitinib with interferon-α in treatment-naïve patients with metastatic RCC (n=750) [4, 5]. Sunitinib demonstrated superiority over interferon-α in terms of progression-free survival (PFS) (median 11 vs. 5 months; $P<0.001$), overall survival (OS) (median 26.4 vs. 21.8 months; $P=0.05$) and objective response rate (47 vs. 12 %; $P<0.001$) [4, 5].

Community-based patients with advanced RCC typically present with more diverse demographic and disease characteristics than the patients selected for inclusion in clinical trials. Expanded-access programs generally apply less stringent entry criteria than clinical trials, and allow patients who have no access to, or who are ineligible for clinical trials, the opportunity to receive a new drug therapy prior to its approval. The findings from expanded-access programs complement those of regular clinical trials by providing insight into real-world treatment patterns, safety and effectiveness in a broad spectrum of community-based cancer patients, including those with poor prognosis.

A global, open-label, expanded-access trial was initiated at sites in North, Central and South America, Europe, Asia-Pacific, Australia and Africa in 2005 to provide sunitinib on a compassionate-use basis to patients with metastatic RCC in countries where regulatory approval had not yet been granted [6]. Final results based on extended patient follow-up over the period 2005–2011 confirmed the safety and effectiveness of sunitinib in community-based metastatic RCC patients across 52 countries with different practice patterns [7]. The drug's toxicity profile in this real-world population was consistent with that demonstrated in the pivotal Phase III trial [4, 5]. Median PFS and OS were 9.4 months and 18.7 months, respectively, and the objective response rate was 16 % [7].

This retrospective analysis of the sunitinib global expanded-access trial data examines treatment outcomes among study participants in Central and Eastern Europe, a region with some of the highest rates of RCC in the world [8], as well as historically inferior oncological outcomes and limited second- and third-line treatment options compared with other parts of Europe [9–11].

Patients and Methods

Patient Selection and Study Treatment

Patient Selection

Patient eligibility criteria for inclusion in the global expanded-access trial were minimized to achieve a diverse study population. Patients were required to be ≥18 years of age, to have histologically confirmed metastatic RCC (any histological subtype), adequate organ function, and no major comorbidities, and to have recovered from any prior treatment toxicities. Study entry was permitted regardless of Eastern Cooperative Oncology Group (ECOG) performance status and treatment status (treatment-naïve or -experienced), and patients with asymptomatic brain metastases were also eligible for study entry. Patients were excluded if they had received prior sunitinib treatment.

Study approval was obtained from the institutional review board or independent ethics committees at each participating centre. All patients provided their written informed consent. The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines. The study was supported by Pfizer Inc. and registered with the ClinicalTrials.gov registry (NCT00130897).

For the Central and East European (CEE) sub-analysis, patients with metastatic RCC who received sunitinib treatment at study sites in Bulgaria, Croatia, the Czech Republic, Hungary, Romania, the Russian Federation, Serbia, Slovakia and Slovenia were selected from the global expanded-access trial population.

Study Treatment

Patients received oral sunitinib at an initial dose of 50 mg once daily (reduced to 37.5, 25 or, in some cases, 12.5 mg once daily in the event of toxicity) in repeated 6-week cycles of 4 weeks on followed by two weeks off treatment, until disease progression, unacceptable toxicity or consent withdrawal. Palliative radiotherapy (other than to target lesions) was permitted at the discretion of the treating physician; in such cases, sunitinib treatment was briefly interrupted for each session of radiotherapy.

Study Assessments

Safety assessments (physical examination and clinical laboratory tests) were performed at screening and on Days 1, 14 and 28 of treatment cycle 1, and on Days 1 and 28 of each subsequent cycle. Adverse events were graded for severity according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 and were assessed for relationship to sunitinib treatment. Patients who discontinued sunitinib therapy because of an adverse event were followed-up until resolution or stabilization of symptoms.

Tumor assessments were guided by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, but were not scheduled in the study protocol. These were performed in accordance with the local standard pattern of care at each participating site, and there was no coordinated (central)

review of CT scans. Outcomes of interest were objective response rate (complete+partial responses), PFS (time from start of sunitinib treatment to disease progression or death from any cause) and OS (time from start of sunitinib treatment to death from any cause, with censoring at last follow-up for surviving patients).

Statistical Analysis

Safety and efficacy analyses were conducted in the intent-to-treat (ITT) population, comprising all patients who received at least one dose of sunitinib. Subjects with non-RECIST tumor measurements or other data integrity issues were excluded from those efficacy analyses based on tumor response. Median PFS and OS were estimated using the Kaplan-Meier method. Intergroup comparisons of survival functions were conducted for different prognostic factors [prior cytokine therapy, and Memorial Sloan-Kettering Cancer Center (MSKCC) risk category] using the log-rank test at a two-sided significance level of 0.05. Hazard ratios and corresponding 95 % two-sided confidence intervals (CIs) for the intergroup comparisons were calculated from Cox proportional hazard models considering the different prognostic factors. Objective response rates and corresponding 95 % two-sided CIs were calculated using standard methods based on binomial distribution. All *P*-values are considered exploratory.

Results

Patient Population

In total, 4543 patients in the global expanded-access trial received one or more doses of sunitinib (ITT population), of whom 401 patients (8.8 %) were from the identified CEE countries, including Bulgaria (n=18), Croatia (n=71), Czech Republic (n=50), Hungary (n=59), Romania (n=52), the Russian Federation (n=58), Serbia (n=31), Slovakia (n=41) and Slovenia (n=21).

The CEE patient population had a generally favorable prognosis, with 85 % of patients having an ECOG performance status of 0 (35.4 %) or 1 (49.9 %), and 87 % of patients being classified at intermediate (45.9 %) or favorable (40.6 %) risk according to the MSKCC risk criteria. The great majority of patients (93 %) had clear-cell histology and had undergone prior nephrectomy; almost two-thirds of patients had received prior systemic cytokine therapy, but few (3 %) had received anti-angiogenic therapy (Table 1). At screening, the main sites of metastasis were the lungs (71.1 % of patients), bone (31.2 %) and liver (20.2 %); approximately 50 % of patients showed lymph node involvement.

Treatment Exposure

The CEE sub-population received a median of 7 (range 1–57) cycles of sunitinib treatment, amounting to a median duration of treatment of 9.6 months (95 % CI 8.1, 11.1 months) (Table 2). The median duration of patient follow-up (from commencement of sunitinib therapy until censorship for survival or death) was 15.5 (range 0.2–75.0) months. Following initiation of sunitinib treatment (starting dose 50 mg once daily), dose reduction was required in 159 (39.6 %) patients; dose was decreased to 37.5 mg (32.2 % of patients), 25 mg (7.2 %) or 12.5 mg (0.2 %). The study was discontinued by 388 (96.8 %) patients, with the most common reasons for discontinuation being lack of treatment efficacy (43.1 %),

Table 1 Patient demographics and baseline clinical characteristics

Characteristic	Intent-to-treat population (n=401)
Median age, years (range) (19 79)	58.0
Age ≥65 years, *n* (%)	89 (22.2 %)
Male/Female, *n* (%)	298/103 (74.3/25.7 %)
ECOG Performance status,*n* (%)	
0	142 (35.4 %)
1	200 (49.9 %)
2	48 (11.9 %)
3 4	4 (1.0 %)
Missing data	7 (1.7 %)
Histology, *n* (%)	
Clear cell	373 (93.0 %)
Non-clear cell	28 (7.0 %)
Total number of metastatic sites, *n* (%)	
0	4 (1.0 %)
1	111 (27.7 %)
2	133 (33.2 %)
3	73 (18.2 %)
>3	80 (20.0 %)
Prior cancer surgery, *n* (%)	
Prior nephrectomy	374 (93.0 %)
Prior radiotherapy	123 (30.7 %)
Prior systemic therapy	
Chemotherapy	155 (38.7 %)
Anti-angiogenic	12 (3.0 %)
Immunotherapy	247 (61.6 %)
Modified MSKCC risk group, *n* (%)	
Favorable	163 (40.6 %)
Intermediate	184 (45.9 %)
Poor	37 (9.2 %)
Missing	17 (4.2 %)

ECOG=Eastern cooperative oncology group; MSKCC=Memorial sloan-kettering cancer center

Table 2 Treatment and disposition of the patient population

Characteristic	Intent-to-treat population (n=401)
Sunitinib therapy	
Median number of treatment cycles (range)	7 (1 57)
Dose reduction, n (%)	159 (39.6 %)
Discontinuation, n (%)	388 (96.8 %)
Primary reason for discontinuation, n (%)	
Lack of efficacy	173 (43.1 %)
Death	60 (15.0 %)
Adverse events	46 (11.5 %)
Consent withdrawn	40 (10.0 %)
Lost to follow-up	17 (4.2 %)
Other (e.g., sponsor decision)	52 (12.9 %)

death (15.0 %), poor treatment tolerability (11.5 %) and withdrawal of consent (10.0 %).

Safety

The most frequently reported treatment-related adverse events in the ITT population (n=401) were diarrhea (31.9 %), nausea (30.9 %), fatigue (29.4 %), stomatitis (27.7 %), decreased appetite (23.7 %) and hypertension (23.2 %), which were predominantly of low-grade severity. The most common grade≥3 adverse events were fatigue (7.5 %), hypertension (7.0 %), thrombocytopenia (6.5 %), diarrhea (4.2 %), nausea (3.7 %), hand-foot syndrome (3.7 %) and neutropenia (3.0 %). Treatment-related adverse events occurring in≥5 % of the CEE patient population are listed in Table 3.

Table 3 Safety profile of sunitinib: treatment-related adverse events occurring in ≥5 % of patients

Adverse event	Intent-to-treat population (n=401) n (%)	
	All grades	Grade ≥3
Diarrhea	128 (31.9 %)	17 (4.2 %)
Nausea	124 (30.9 %)	15 (3.7 %)
Fatigue	118 (29.4 %)	30 (7.5 %)
Stomatitis	111 (27.7 %)	9 (2.2 %)
Decreased appetite	95 (23.7 %)	8 (2.0 %)
Hypertension	93 (23.2 %)	28 (7.0 %)
Dysgeusia	76 (19.0 %)	1 (0.2 %)
Vomiting	71 (17.7 %)	10 (2.5 %)
Thrombocytopenia	63 (15.7 %)	26 (6.5 %)
Dyspepsia	63 (15.7 %)	0
Hand-foot syndrome	62 (15.5 %)	15 (3.7 %)
Rash	58 (14.5 %)	6 (1.5 %)
Anemia	56 (14.0 %)	10 (2.5 %)
Leukopenia	53 (13.2 %)	8 (2.0 %)
Asthenia	53 (13.2 %)	11 (2.7 %)
Dermatitis	51 (12.7 %)	11 (2.7 %)
Yellow skin	42 (10.5 %)	1 (0.2 %)
Neutropenia	38 (9.5 %)	12 (3.0 %)
Hair colour changes	35 (8.7 %)	2 (0.5 %)
Epistaxis	34 (8.5 %)	0
Skin discoloration	29 (7.2 %)	0
Mucosal inflammation	27 (6.7 %)	2 (0.5 %)
Skin exfoliation	27 (6.7 %)	0
Extremity pain	23 (5.7 %)	2 (0.5 %)
Headache	22 (5.5 %)	1 (0.2 %)
Glossitis	21 (5.2 %)	1 (0.2 %)
Blood creatinine increased	21 (5.2 %)	0

Efficacy

In total, 378 patients were evaluable for tumor response, of whom 15 (4.0 %) achieved a complete response and 55 (14.6 %) a partial response, translating into an objective response rate of 18.5 % (95 % CI 14.7, 22.8 %). In total, 204 patients (54.0 %) exhibited stable disease, including 12 patients (3.2 %) who had stabilization for <3 months and 192 patients (50.8 %) for ≥3 months, and 41 patients (10.8 %) showed disease progression (Table 4).

Median PFS in the population evaluable for tumor response (n=378) was 11.6 months (95 % CI 10.3, 12.8 months) (Fig. 1a). PFS was longer in cytokine-naïve patients (n=161) (median 12.2 months, 95 % CI 9.3, 16.5 months) than in cytokine-experienced patients (n=217) (median 11.0 months, 95 % CI 8.8, 12.6 months). Intergroup comparison indicated a significant inferiority in PFS for cytokine-experienced compared with cytokine-naïve patients (hazard ratio 1.376, 95 % CI 1.065, 1.779; P=0.0141).

Median overall survival in the ITT population (n=401) was 30.7 months (95 % CI 23.3, – months) (Fig. 1b). Overall survival was a function of MSKCC risk, and was of longer duration in patients with good prognosis (median overall survival was not reached) than in those with intermediate prognosis (median 23.1 months, 95 % CI 18.9, 33.8 months) or poor prognosis (median 6.4 months, 95 % CI 3.9, 8.0 months) (Fig. 2). Overall survival tended to be shorter in cytokine-experienced patients (median 27.5 months, 95 % CI 20.9, 36.6 months) than in cytokine-naïve patients (median 60.8 months, 95 % CI 26.3, – months), although the difference did not reach statistical significance (hazard ratio 1.276, 95 % CI 0.928, 1.754; P=0.1324) (Fig. 3).

Table 4 Efficacy of sunitinib therapy in the intent-to-treat population

Outcome	Intent-to-treat population (n=401)
Survival	
Median OS, months	30.7
95 % CI	(23.3,)
Median PFS[†], months	11.6
95 % CI	(10.3, 12.8)
Antitumor response[a]	
Objective response, (CR+PR), n (%)	70 (18.5 %)
[95 % CI]	[14.7 %, 22.8 %]
Complete response, n (%)	15 (4.0 %)
Partial response, n (%)	55 (14.6 %)
Stable disease ≥3 months, n (%)	192 (50.8 %)
Stable disease <3 months, n (%)	12 (3.2 %)
Progressive disease, n (%)	41 (10.8 %)
Not assessed/evaluable	16 (4.3 %)
Missing data	47 (12.4 %)

CI=Confidence interval, CR=Complete response, OS=Overall survival, PFS=Progression-free survival, PR=Partial response

[a] PFS and anti-tumor response were assessed in 378 evaluable patients

Discussion

The results of this retrospective analysis of the global expanded-access trial dataset testify to the safety and effectiveness of sunitinib in real-world patients receiving treatment for metastatic RCC in Central and Eastern Europe. Survival outcomes in the CEE sub-population closely mirrored those of the overall (global) patient population of the expanded-access trial [7], and in several respects compared favorably with those obtained in the pivotal Phase III randomized clinical trial of sunitinib in metastatic RCC [4, 5]. Thus, while the sunitinib treatment arm in the clinical trial showed median PFS and overall survival durations of 11.0 and 26.4 months, respectively [4, 5], the real-world CEE population had median PFS and overall survival times of 11.6 and 30.7 months. However, the objective tumor response rate in the real-world CEE population (18.5 %) was considerably lower than that reported in the sunitinib treatment arm of the clinical trial (47 %) [4, 5]. This discrepancy is likely due to the fact that, in contrast to the clinical trial protocol, tumor assessments in the expanded-access study were performed on an irregular basis, and in a non-standardized manner across the participating study centers. As a result, estimates of tumor response obtained in the expanded-access study are subject to greater

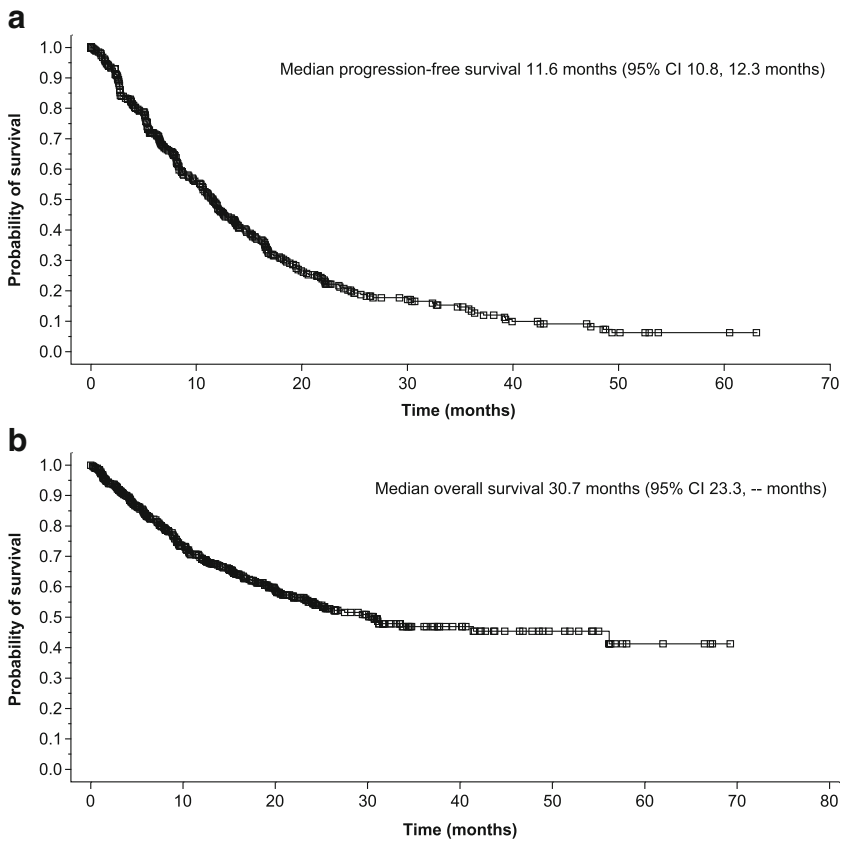

Fig. 1 Kaplan-Meier estimate of (**a**) progression-free survival in the tumor-evaluable population receiving sunitinib (n=378), and (**b**) overall survival in the intent-to-treat population receiving sunitinib (n=401)

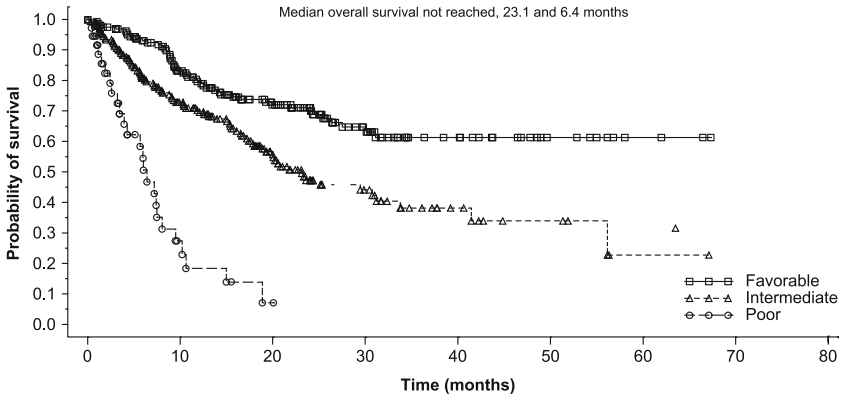

Fig. 2 Kaplan-Meier estimates of overall survival by MSKCC risk group (intent-to-treat population). Inter-cohort comparison of favorable versus intermediate/poor risk: hazard ratio (favourable=1, intermediate/poor =0)=0.428, 95 % CI=0.305, 0.600; $P<0.0001$. Inter-cohort comparison of poor versus intermediate/favorable risk: hazard ratio (poor=1, intermediate/favorable=0)=5.288, 95 % CI=3.385, 8.263; $P<0.0001$

variation and greater potential inaccuracy than is the case in the controlled clinical trial setting. Moreover, the overall prognosis of patients in an expanded-access program is likely to be inferior to that of patients enrolled into a Phase III clinical trial.

The duration of sunitinib treatment in the CEE population was somewhat shorter than in the Phase III trial population (median 9.6 vs. 11.0 months) - presumably because the expanded-access trial was initiated at a time (2005) when experience in the use of anti-angiogenic therapy was limited and the investigators received no formal guidance on the preferred length of treatment. Nevertheless, comparison of outcomes between the two populations is justified by their generally similar demographic and clinical features: the sunitinib treatment arm in the pivotal Phase III study, although treatment-naïve and restricted to patients with an ECOG performance status of 0-1 (and consequently having a better prognosis), resembled the CEE population in terms of age, gender balance, prior nephrectomy, sites of metastasis and MSKCC risk profile.

Despite the clinical diversity of patients in the CEE population, the toxicity profile of sunitinib in this group [predominantly diarrhea (31.9 %), nausea (30.9 %), fatigue (29.4 %), stomatitis (27.7 %), decreased appetite (23.7 %) and hypertension (23.2 %)] was broadly consistent with that in the more homogenous clinical trial population, for whom the most frequently reported treatment-related adverse events were diarrhea (61 %), fatigue (54 %), nausea (52 %), dysgeusia (46 %) and anorexia (34 %). Similarly, the pattern of grade ≥3 adverse events was compatible between the CEE population [most commonly fatigue (7.5 %), hypertension (7.0 %), thrombocytopenia (6.5 %), diarrhea (4.2 %), nausea (3.7 %), hand-foot syndrome (3.7 %) and neutropenia (3.0 %)] and the clinical trial population [most commonly hypertension (12 %), fatigue (11 %), diarrhea (9 %), hand-foot syndrome (9 %), asthenia (7 %), nausea (5 %) and vomiting (4 %)]. The generally lower incidence of adverse events in the CEE population may be due to the nature of expanded-access programmes, with their primary purpose being to provide treatment to broad patient populations. Despite observance of the standardized safety monitoring and reporting requirements specified in the study protocol, adverse events may have been under-reported.

Information to date on real-world (i.e., non-clinical trial) treatment patterns and clinical outcomes with sunitinib in advanced and metastatic RCC has come largely from retrospective observational studies typically involving small patient samples; these have included studies conducted in Spain

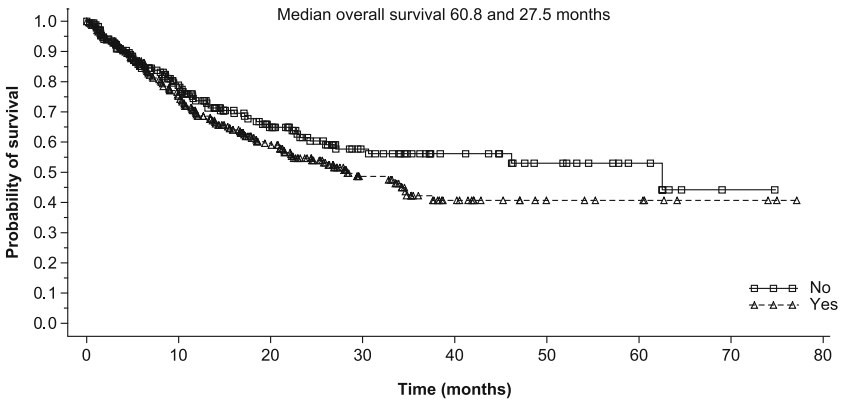

Fig. 3 Kaplan-Meier estimates of overall survival by prior cytokine exposure (intent-to-treat population). Inter-cohort comparison of prior cytokine versus no prior cytokine: hazard ratio (Yes=1, No =0)=1.276, 95 % CI 0.928, 1.754; $P=0.1324$

[12], Italy [13], the United Kingdom [14], the United States [15–18] and South Korea [19]. Findings from such studies have consistently indicated significant rates of treatment modification, including dose reduction, treatment interruption and treatment discontinuation, often as the result of adverse events associated with sunitinib therapy [12–20]. The global expanded-access trial and the present CEE subanalysis supplement these retrospective observational studies by providing extended prospective follow-up data for large, ethnically and clinically diverse populations of metastatic RCC patients receiving sunitinib therapy within different healthcare systems. Among the CEE study population, approximately 40 % of patients required reduction in sunitinib dose from the starting level of 50 mg (typically to 37.5 mg), while poor treatment tolerability was responsible for 11.5 % of patients discontinuing sunitinib therapy.

Central and Eastern Europe have some of the highest rates of RCC in the world, with the Czech Republic reporting prevalences of kidney cancer of ~20 per 100,000 in men and ~10 per 100,000 in women [8]. Possible contributory factors include high levels of industrial pollution, occupational exposure to chemical carcinogens, employment in the agricultural sector, high tobacco use, obesity and low dietary intake of fruit and vegetables [21–23]. Cancer outcomes in Central and Eastern Europe have historically been inferior to those in Western Europe [9–11], and the continent is still divided by differences in cancer mortality. While overall cancer deaths have been steadily decreasing in Western Europe since the 1990s, the cancer mortality rate in Central and Eastern Europe has continued to increase [24, 25], and is predicted to reach 201 per 100,000 (men) and 106 per 100,000 (women) by 2015 [26]. Several factors may play a part in the geographical variation of cancer incidence and mortality, including differences in prevalence of underlying risk factors (including local and regional environmental factors), differences in host susceptibility, and/or regional variations in cancer detection and prevention campaigns, reporting, classification systems and, importantly, available treatment options [27]. The relative contributions that these factors make to the overall picture is not known, but differences in cancer care may account for a substantial proportion of the higher cancer mortality rates seen in some countries. The findings of the present study suggest that, with access to appropriate therapeutic options, clinical prospects for patients with metastatic RCC patients in Central and Eastern Europe are as good as those in Western Europe and North America.

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References

1. Mena AC, Pulido EG, Guillén-Ponce C. Understanding the molecular-based mechanism of action of the tyrosine kinase inhibitor: sunitinib. Anti-Cancer Drugs 21 Suppl. 1: S3-S11. doi: 10.1097/01.cad.0000361534.44052.c5
2. Escudier B, Eisen T, Porta C, Patard JJ, Khoo V, Algaba F, Mulders P, Kataja V (2012) Renal cell carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 23(7):vii65–vii71. doi:10.1093/annonc/mds227
3. Patard JJ, Pignot G, Escudier B, Eisen T, Bex A, Sternberg C, Rini B, Roigas J, Choueiri T, Bukowski R, Motzer R, Kirkali Z, Mulders P, Bellmunt J (2011) ICUD-EAU International consultation on kidney cancer 2010: treatment of metastatic disease. Eur Urol 60(4):684–690. doi:10.1016/j.eururo.2011.06.017
4. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, Oudard S, Negrier S, Szczylik C, Kim ST, Chen I, Bycott PW, Baum CM, Figlin RA (2007) Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 356(2):115–124. doi: 10.1056/NEJMoa065044
5. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, Negrier S, Szczylik C, Pili R, Bjarnason GA, Garcia-del-Muro X, Sosman JA, Solska E, Wilding G, Thompson JA, Kim ST, Chen I, Huang X, Figlin RA (2009) Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 27(22):3584–3590. doi: 10.1200/JCO.2008.20.1293
6. Gore ME, Szczylik C, Porta C, Bracarda S, Bjarnason GA, Oudard S, Hariharan S, Lee SH, Haanen J, Castellano D, Vrdoljak E, Schoffski P, Mainwaring P, Nieto A, Yuan J, Bukowski R (2009) Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. Lancet Oncol 10(8):757–763. doi:10.1016/S1470-2045(09)70162-7
7. Gore ME, Porta C, Bracarda S, Bjarnason GA, Oudard S, Lee S, Crino L, Kim TM, Fly K, Szczylik C (2012) Sunitinib global expanded-access trial in metastatic renal cell carcinoma (mRCC): final results. Ann Oncol 23(9):271, Abstract 820P
8. Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, Boyle P (2007). In: Cancer Incidence in Five Continents Vol. IX, vol Scientific Publication No. 160. IARC, Lyon, France
9. Levi F, Lucchini F, Negri E, Boyle P, La Vecchia C (2004) Cancer mortality in Europe, 1995-1999, and an overview of trends since 1960. Int J Cancer 110(2):155–169. doi:10.1002/ijc.20097
10. Levi F, Lucchini F, Negri E, Zatonski W, Boyle P, La Vecchia C (2004) Trends in cancer mortality in the European Union and accession countries, 1980-2000. Ann Oncol 15(9):1425–1431. doi:10.1093/annonc/mdh346
11. Berrino F, De Angelis R, Sant M, Rosso S, Bielska-Lasota M, Coebergh JW, Santaquilani M (2007) Survival for eight major cancers and all cancers combined for European adults diagnosed in

1995-99: results of the EUROCARE-4 study. Lancet Oncol 8(9): 773–783. doi:10.1016/S1470-2045(07)70245-0
12. Castellano D, Duh MS, Korves C, Suthoff ED, Neary M, Hernández Pastor LJ, Bellmunt J (2013) Safety and treatment patterns of angiogenesis inhibitors in patients with advanced renal cell carcinoma in Spain. Expert Opin Drug Saf 12(4):455–463. doi:10.1517/14740338.2013.781581
13. Porta C, Paglino C, Imarisio I, Canipari C, Chen K, Neary M, Duh MS (2011) Safety and treatment patterns of multikinase inhibitors in patients with metastatic renal cell carcinoma at a tertiary oncology center in Italy. BMC Cancer 11:105. doi:10.1186/1471-2407-11-105
14. Ansari J, Fatima A, Fernando K, Collins S, James ND, Porfiri E (2010) Sunitinib in patients with metastatic renal cell carcinoma: Birmingham experience. Oncol Rep 24(2):507–510
15. Hess G, Borker R, Fonseca E (2013) Treatment patterns: targeted therapies indicated for first-line management of metastatic renal cell carcinoma in a real-world setting. Clin Genitourin Cancer 11(2):161–167. doi:10.1016/j.clgc.2012.10.003
16. Filson CP, Redman BG, Dunn RL, Miller DC (2011) Initial patterns of care with oral targeted therapies for patients with renal cell carcinoma. Urology 77(4):825–830. doi:10.1016/j.urology.2010.11.003
17. Choueiri TK, Duh MS, Clement J, Brick AJ, Rogers MJ, Kwabi C, Shah K, Percy AG, Antras L, Jayawant SS, Chen K, Wang ST, Luka A, Neary MP, McDermott D, Oh WK (2010) Angiogenesis inhibitor therapies for metastatic renal cell carcinoma: effectiveness, safety and treatment patterns in clinical practice-based on medical chart review. BJU Int 105(9):1247–1254. doi:10.1111/j.1464-410X.2009.08972.x
18. Feinberg BA, Jolly P, Wang ST, Fortner B, Scott J, Gilmore J, Neary MP, Duh MS (2012) Safety and treatment patterns of angiogenesis inhibitors in patients with metastatic renal cell carcinoma: evidence from US community oncology clinics. Med Oncol 29(2):786–794. doi:10.1007/s12032-011-9922-z
19. Hong MH, Kim HS, Kim C, Ahn JR, Chon HJ, Shin SJ, Ahn JB, Chung HC, Rha SY (2009) Treatment outcomes of sunitinib treatment in advanced renal cell carcinoma patients: a single cancer center experience in Korea. Cancer Res Treat 41(2):67–72. doi:10.4143/crt.2009.41.2.67
20. Schmidinger M, Larkin J, Ravaud A (2012) Experience with sunitinib in the treatment of metastatic renal cell carcinoma. Ther Adv Urol 4(5):253–265. doi:10.1177/1756287212454933
21. Heck JE, Charbotel B, Moore LE, Karami S, Zaridze DG, Matveev V, Janout V, Kollarova H, Foretova L, Bencko V, Szeszenia-Dabrowska N, Lissowska J, Mates D, Ferro G, Chow WH, Rothman N, Stewart P, Brennan P, Boffetta P (2010) Occupation and renal cell cancer in central and Eastern Europe. Occup Environ Med 67(1):47–53. doi:10.1136/oem.2009.046250
22. Moore LE, Hung R, Karami S, Boffetta P, Berndt S, Hsu CC, Zaridze D, Janout V, Kollarova H, Bencko V, Navratilova M, Szeszenia-Dabrowska N, Mates D, Mukeria A, Holcatova I, Yeager M, Chanock S, Garcia-Closas M, Rothman N, Chow WH, Brennan P (2008) Folate metabolism genes, vegetable intake and renal cancer risk in central Europe. Int J Cancer 122(8):1710–1715. doi:10.1002/ijc.23318
23. Fabiánová E, Szeszenia-Dabrowska N, Kjaerheim K, Boffetta P (1999) Occupational cancer in central European countries. Environ Health Perspect 107(Suppl 2):279–282
24. Döbrossy L (2002) Cancer mortality in central-eastern Europe: facts behind the figures. Lancet Oncol 3(6):374–381
25. Antunes JL, Toporcov TN, de Andrade FP (2003) Trends and patterns of cancer mortality in European countries. Eur J Cancer Prev 12(5):367–372. doi:10.1097/01.cej.0000090182.08740.97
26. Zatonski W, Didkowska J (2008) Closing the gap: cancer in Central and Eastern Europe (CEE). Eur J Cancer 44(10):1425–1437. doi:10.1016/j.ejca.2008.02.014
27. Vrdoljak E, Wojtukiewicz MZ, Pienkowski T, Bodoky G, Berzinec P, Finek J, Todorovic V, Borojevic N, Croitoru A (2011) Cancer epidemiology in Central, South and Eastern European countries. Croat Med J 52(4):478–487. doi:10.3325/cmj.2011.52.478