Publisher: Taylor & Francis

Journal: *Expert Opinion on Drug Safety*

DOI: 10.1080/14740338.2017.1330410

Experience with Sunitinib in metastatic renal cell carcinoma (mRCC) patients: pooled analysis from 3 Spanish observational prospective studies.

Daniel Castellano[*,1], José Pablo Maroto[2], Enrique Espinosa[3], Enrique Grande[4], Victoria Bolos[5], Julia Linares[5], Emilio Esteban[6], Aranzazu Gonzalez del Alba[7], M.A Climent[8], JA Arranz[9], Mª José Méndez[10], Eva Fernadez Parra[11], Luis Antón-Aparicio[12], Cristina Bayona[13], Isabel Gallegos[14], Enrique Gallardo[15], Luz Samaniego[5] and J Garcia Donas[16]

Affiliations

[1] Hospital Universitario 12 de Octubre, Madrid, Spain

[2] Hospital de la Santa Creu i Sant Pau - Medical Oncology, Carrer Sant Quintí, 89 , Barcelona 08026, Spain

[3] H. Universitario La Paz, Madrid, Spain

[4] Ramón y Cajal University Hospital, Madrid, Spain

[5] Pfizer, Madrid, Spain

[6] General University Hospital of Asturias, Asturias, Spain

[7] H. Universitario Son Espases, Palma de Mallorca, Spain

[8] Instituto Valenciano de Oncología, Valencia, Spain

[9] H. General Universitario Gregorio Marañón, Madrid, Spain

[10] Hospital Univ. Reina Sofia - Medical oncology, Avda. Menéndez Pidal, s/n. , Córdoba 14004, Spain

[11] H. de Valme, Sevilla Spain

[12] Juan Canalejo University Hospital, La Coruña, Spain

ACCEPTED MANUSCRIPT

[13] H. General Yague, Burgos, Spain

[14] H. de Segovia, H. de Segovia, Spain

[15] Parc Taulí Hospital Universitari, Sabadell, Spain

[16] 17HM Hospitales, Centro Integral Oncológico HM Clara Campal, Madrid, Spain

***Corresponding author: e-mail: cdanicas@hotmail.com**

ACCEPTED MANUSCRIPT

Abstract

Background: A pivotal, randomized, phase III trial demonstrated a statistically significant superiority of sunitinib over interferon-α in metastatic renal cell carcinoma (mRCC) patients.

Objective: To evaluate the effectiveness and safety of sunitinib in patients with advanced or mRCC in routine clinical practice.

Methods: Retrospective pooled analysis of clinical data from three observational and prospective studies carried out between 2007 and 2011 in 33 Spanish hospitals. Tumor response, Progression-free survival (PFS) and overall survival (OS), and main sunitinib-related toxicities were registered.

Results. 224 patients were analyzed. Median PFS 10.6 months (95% CI: 9.02-12.25), median OS 21.9 months (95% CI: 17.2-26.6). Objective response rate (ORR) 43.8% (95% CI: 36.8-50.7). Median time to PR was 3.8 months (95% CI: 3.86-5.99) and to CR 8.2 months (95% CI: 4.75-9.77). The most common ≥ grade-3 AEs were asthenia/fatigue (18.7%), hand-foot syndrome (6.2%), hypertension (5.8%) and neutropenia (4.8%). Hand-foot syndrome, diarrhea and mucositis were confirmed as independent predictors for PFS and/or OS in a multivariate analysis ($p<0.05$)

Conclusions. Outcomes with sunitinib in daily clinical practice resemble those obtained in clinical trials. Long-term benefit with sunitinib is possible in advanced RCC patients but the appropriate management of toxicities is mandatory to enable patients to remain on treatment.

Key words: Effectiveness, routine clinical practice, safety, sunitinib

ACCEPTED MANUSCRIPT

Article highlights

- Observational studies in patients treated under common clinical conditions are needed in addition to clinical trials**.**
- Outcomes with sunitinib in daily clinical practice resemble those obtained in clinical trials**,** however new schemes of administration (2 wks on/ 1 wks off9 could be ameliorate the tolerance without change the clinical efficacy.

ACCEPTED MANUSCRIPT

1.-Introduction

Renal cell carcinoma is the most common cancer of the kidney[1]. Approximately one third of patients present at initial diagnosis with evidence of metastases [2], and local recurrence or distant metastasis develops up to 40% of the patients treated for localized tumors [1].

Targeted therapies have led to clinically meaningful advances in the treatment of patients with metastatic renal carcinoma (mRCC)[3].

Sunitinib malate (Sutent®, Pfizer), an oral multi-targeted receptor tyrosine kinase inhibitor (TKI), is a potent inhibitor of vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR) and other tyrosine kinase receptors[4, 5]. Sunitinib is a standard of care for first-line treatment of mRCC[6]. Motzer et al in a pivotal, randomized and phase III trial conducted in 750 treatment-naïve clear cell mRCC patients, demonstrated a statistically significant superiority of sunitinib over interferon-α in progression-free survival (PFS) (11 vs. 5 months; $p>0.001$) [7] and objective response rate (ORR) (47% vs. 12%; $p<0.001$)[8]. In addition, a greater overall survival (OS) trend (26.4 vs. 21.8 months; $p=0.051$)[8] was also observed.

Gore et al in an expanded access study with 4,543 locally advanced or mestastatic RCC patients on sunitinib treatment, including patients with ECOG ≥2 (15%), brain metastases (7%), and non-clear-cell histology (12%), reported a median PFS of 9.4 months and a safety profile consistent with the initial phase III trial mentioned above [9].

Observational studies in patients treated under common clinical conditions are needed in addition to clinical trials. Here, we carried out a pooled analysis of clinical data of patients from three observational and prospective studies aimed to identify biomarkers of response to sunitinb [10-13].

ACCEPTED MANUSCRIPT

The objective of the present retrospective analysis was to assess whether sunitinib efficacy and safety outcomes reported in the pivotal trial and in the expanded access study were also reproduced in our Spanish population of patients.

2.- Patients and Methods

We here describe a retrospective pooled analysis of data from 224 evaluable patients out of the 233 enrolled in three observational and prospective studies SUT-IIG-9 (N=49)[10], SUTREN-07 (N=94) [11, 12 13] and MAR-SUT-2008-01 (N=81) aimed at evaluating the predictive value in terms of efficacy of different biomarkers. The reasons for exclusion of 9 (3.9%) patients included screening failure 7 (77.8%), patient's death 1 (11.1%) and no available data 1 (11.1%). These studies were carried out between 2007 and 2011 in 33 Spanish hospitals.

Common eligibility criteria for all patients in these studies included ≥ 18 years of age, histologically confirmed RCC, and locally advanced or metastatic disease. Patients received sunitinib as first-line systemic treatment in a daily clinical practice setting, initiating treatment in most cases at a standard dose and schedule (50mg/d, 4 weeks on, 2 weeks off).

Written informed consent was obtained from all patients. In accordance with the Spanish regulations, all studies were approved by the Ethics Committee of all participating institutions, and were conducted in compliance with the principles contained in the Declaration of Helsinki for studies in humans.

Statistical analysis

PFS was defined as the time between the first day of treatment with sunitinib and the date of radiological progressive disease (PD), clear clinical evidence of PD or death. Patients who had not progressed at database closure were censored at final

ACCEPTED MANUSCRIPT

follow-up. OS was defined as the time between the first day of sunitinib treatment and the date of death from any cause. Patients who had not died at database closure were censored at final follow-up. ORR was defined as the proportion of patients with either a complete response (CR) or a partial response (PR) and disease control rate was defined as the proportion of patients with an ORR or a stable disease (SD). Tumor assessments according to Response Evaluation Criteria in Solid Tumors (RECIST)[14] were done in accordance with current local practice guidelines for patients with RCC.

Main sunitinib-related toxicities (mucositis, asthenia/fatigue, diarrhea, neutropenia, hypertension, hand-foot syndrome and hypothyroidsm) were registered. Adverse events (AEs) were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0 or version 4.0. Other toxicities were also recorded but severity was not graded. AEs leading to dose reductions and the date on which they occurred were registered. Sunitinib treatment schedule and dose, including median duration of therapy, and dose reductions were also recorded.

Memorial Sloan-Kettering Cancer Center (MSKCC)[15] criteria were used in this analysis considering the following variables as poor risk: Time from diagnosis to treatment less than 12 months, Karnofsky performance status (KPS) < 80% or Eastern Cooperative Oncology Group performance status (ECOG) ≥2, serum lactate dehydrogenase (LDH) more than 1.5-times the upper limit of normal (ULN), corrected serum calcium >10mg/dl and hemoglobin less than the lower limit of normal (LLN). Patients were grouped according to prognostic risk category on the basis of MSKCC[15] criteria: favorable (0 risk factors), intermediate (1 or 2 risk factors) and poor (≥ 3 risk factors).

2.1 Statistical analyses

ACCEPTED MANUSCRIPT

All data were presented using descriptive statistics. Quantitative and qualitative variables were analyzed using measurements of central tendency and dispersion (95% confidence interval [CI]). Qualitative variables were defined according to their absolute and relative frequencies. Quantitative variables were described with mean and standard deviation. Median PFS and OS were estimated using the Kaplan Meier method. Both univariate and multivariate Cox regression models were used to identify potential prognostic factors for PFS and OS. Each variable was investigated by univariate and thereafter, the variables with a significance of $p<0.05$ were used for multivariate analysis. Tests were two-tailed with a significance level of 5%. Data were analysed using SPSS statistical software v17.0.

3.- Results

Baseline demographic and clinical characteristics of the 224 patients analyzed are summarized in table 1. Patients from the three studies included in this analysis were predominantly men with a median age (range) at study inclusion of 64.1(32.5-87.3) years. Eighty one percent had a prior nephrectomy. The majority had clear cell histology (92.7%) or a clear cell component and presented favorable or intermediate prognostic risk according to MSKCC criteria (88.9%) when they started treatment. Ninety-three (42.3%) patients presented with metastatic disease at the time of diagnosis. Lung was the most common site of metastasis (70.3%) and 3.2% of the patients presented brain metastases (Table 1). The time interval from diagnosis to sunitinib was $\leq$ 1 year in 129 patients (58.1%).

3.1 Treatment administration

Median duration of treatment was 7.7 months (Interquartile range (IQR) Q1-Q3:3.7-13.0). Of the overall population, 89.3% started on a dose of 50 mg given once daily for 4 weeks, followed by 2 weeks without treatment (schedule 4/2), the standard

ACCEPTED MANUSCRIPT

dose and schedule for local advanced or mRCC; 4.5% and 4.9% of patients initiated treatment with a daily continuous dose of 37.5 mg and of 25 mg, respectively. One hundred and twenty two (55%) patients had at least one dose reduction during sunitinib treatment. Of these, 55% reduced dose only once and the remaining 45% at least twice. Eight (6.6%) patients reduced dose during the first cycle of treatment, 38 (31.1%) during the second cycle, and 96 (79%) during the third cycle or beyond. Toxicity was the main reason for dose reduction in 73.8% of patients.

One hundred and seventy-one (76%) patients had discontinued treatment at the time of the analysis; 116 (68%) due to progressive disease, 34 (20%) due to adverse events and 30 (18%) for other reasons There could be more than one reason for discontinuation for each patient.

3.2 Efficacy

Table 2 and Figure 1 show the median PFS and OS according to MSKCC criteria. At a median follow-up of 13.1 months (IQR: Q1-Q3: 7.0-22.2) the median PFS for all patients was 10.6 months (95% CI: 9.02-12.25). Patients with a favorable prognosis achieved the highest median PFS (18.0 months; $p<0.001$; Table 2 and Figure1).

At the time of the analysis 102 (46%) patients had died. Median OS was 21.9 (95% CI 17.2-26.6) months in the overall population. In patients with favorable-risk features the median OS had not been reached at the time of the analysis; median OS for intermediate and poor risk groups (MSKCC criteria) was 22.4 months (95% IC: 15.37-29.43) and 7.7 (4.58-10.82) respectively (Table 2, Figure 2)

Of the overall population, 208 (92.9%) patients were evaluable for tumor response; 5.3% had a CR and 38.5% a PR, yielding an ORR of 43.8% (95% CI: 36.8-50.7; Table 3). Eighty (38.5%) patients exhibited stable disease (SD), 80% of them for

ACCEPTED MANUSCRIPT

more than 6 months, resulting in a disease control rate (PR+CR+SD) of 82% (Table 3). Median time to PR was 3.8 months (95% CI: 3.86-5.99) and to CR 8.2 months (95% CI: 4.75-9.77). Median (Q1-Q3) duration of response (PR or CR) was 7.4 (4.1-16.2) months. The proportion of patients with progression as best response to treatment was higher in the poor prognosis patients compared with those with a favorable prognosis (23.8% vs. 15.4%). Similarly, in the poor prognosis group the proportion of patients who suffered from progression (80% vs. 50%) and died (80% vs. 21.4%) were also higher than in the favorable prognosis group. Patients with poor prognosis suffered from progression earlier than the other patients (median PFS of 5.9 ($CI_{95\%}$ 3.92-7.88) months in the poor prognosis group, 11.10 ($CI_{95\%}$ 9.47-12.72) months in the intermediate prognosis group, and 17.97 ($CI_{95\%}$ 2.09-33-85) months in the favorable prognosis group

3.3 Safety

Two hundred and sixteen (96.4%) patients experienced at least one treatment-related AE of any grade. Common treatment-related adverse events were mostly grade 1 or 2, and only few grade 3 or 4 toxicities were observed (Table 4). Among the seven AEs in which severity was graded, the most common all-grade AEs (≥40%) were asthenia/fatigue and mucositis (Table 4). The most frequent grade-3 AEs were asthenia/fatigue (18.3%), hand-foot syndrome (6.2%), hypertension (5.8%) and mucositis (4.5%; Table 4). Only three cases of grade 4 toxicity were reported (Table 4). Other frequently reported all-grade AEs suffered by more than 10% of the patients included skin and hair color changes (19.2%), anemia (18.3%), leucopenia (14.3%), thrombocytopenia (13.8%), anorexia (13.4%) and increased creatinine (12.1%).

ACCEPTED MANUSCRIPT

Treatment-related cardiac disorders were reported in 3 (1.3%) patients from the overall population. There were no treatment related deaths. PFS and OS were significantly higher for patients with sunitinib associated hypertension, hand-foot syndrome, neutropenia, diarrhea and mucositis (Table 5). The multivariate analysis identified 2 independent toxicities predictor for PFS and OS. Patients with hand-foot syndrome [(HR ($CI_{95\%}$) 0.619 (0.431-0.890)] or diarrhea [HR ($CI_{95\%}$) 0.483 (0.343-0.680)] have increased the likelihood for PFS. Similarly patients with hand-foot syndrome [HR ($CI_{95\%}$) 0.508 (0.313-0.824)] or mucositis [HR ($CI_{95\%}$) 0.654 (0.430-0.997)] have increased the likelihood for OS.

4. Discussion

This analysis assessed the effectiveness and safety of sunitinib in three prospective translational studies in clinical practice. In the present study, unlike the Pivotal trial[7, 8] (Table 1), patients with ECOG PS ≥ 2 (12%), brain metastases (3%) or non-clear-cell histologies (7%) were also included. In addition, the proportion of patients with poor performance status, with intermediate-poor prognosis and non clear cell component was also higher than in the Pivotal trial (ECOG PS 1: 63.1 % vs. 38%; ECOG PS ≥ 2: 11.6 % vs. 0%; MSKCC intermediate-poor prognosis: 93.8% vs. 62%; non clear cell component: 7% vs. 0%; Table 1). In spite of that, the efficacy data here presented, as in the expanded access trial of Sunitinib[9], seem to resemble those obtained in the pivotal trial, supporting the fact that clinical practice with sunitinib mirrors clinical trials (Table 2).

In this pooled analysis, the median PFS (10.6 months) appeared to be also similar to that obtained in the pivotal trial (11 months). In line with our findings, Gore et al in the expanded access study with 4,543 patients [ECOG ≥2 (15%), brain metastases (7%), non-clear-cell histology (12%)] reported a median PFS of 9.4 months[9]

ACCEPTED MANUSCRIPT

In the present pooled analysis, it should be noted the excellent long-term survival, particularly in the good-prognosis group. The rate of poor prognosis patients, non nephrectomized patients, patients with ECOG PS ≥ 2 and without clear cell component included in this analysis was higher than in the phase III pivotal trial (see Table 1) which could explain the lower median OS reported in this analysis vs. the pivotal trial. Poor prognosis patients had a bad outcome because although they are able to respond to treatment, they have a worse prognosis and they die earlier. In agreement with this, median OS reported in the expanded access trial, with an even higher rate of poor prognosis patients and patients with ECOG PS ≥ 2 and without clear cell component (see Table 1), was lower than in our analysis (18.7 months vs . 21.9 months). In addition this pooled analysis represents the first experience with sunitinib in our country. At the time of the study (2007-2011), the availability of second line options was still quite low. In fact, in some Spanish hospitals second line patients were directly derived to palliative options which could also explain the lower OS reported in this analysis vs, recent retrospective analysis in the real world setting[16]. Regrettably, non further lines of treatment were collected in these three observational studies which have led to this pooled analysis of clinical data and we are not able to provide bibliography that supports this hypothesis either. Taking into account these data, the Spanish Oncology Genitourinary Group (SOGUG) decided to carry out a retrospective translational trial to search for clinical and molecular factors predictors of Sunitinib associated long term response comparing long responders with early refractory patients[17]. This observational, retrospective study included 97 patients with metastatic ccRCC who achieved PFS ≥22 months, and 26 patients who showed progressive disease at first radiological evaluation. The proportion of patients with higher Fuhrman grade, metastasis at diagnosis, shorter

ACCEPTED MANUSCRIPT

time from primary to metastatic diagnosis, no nephrectomy and brain, lung and hepatic metastasis was significantly higher in the primary refractory patient cohort.

The safety profile seemed to be also comparable to the pivotal trial results. This assertion is supported by the observation that the overall incidence of most common related adverse events, dose reduction (55%) and discontinuations due to adverse events (19.9%) in this report were quite similar to those seen in the pivotal trial (50% and 18.6% respectively). For any grade of AEs, the present study found comparable rates with those of the pivotal trial for fatigue/asthenia (71.9% vs. 75%), stomatitis/mucositis (55.8% vs. 56%), hypertension (35.7% vs. 30%) and hand-foot syndrome (34.8% vs. 29%) and a lower rate of diarrhea (41.5% vs. 61%) and neutropenia (35.7% vs. 77%). Only hypothyroidism showed a higher rate greater compared with the pivotal trial [8] (24.1% vs. 14%).

Some retrospective analyses have suggested that sunitinib-associated AEs are related to an improvement in clinical outcomes and could be considered as efficacy biomarkers [18-21]. The fact that AEs seem to be linked to efficacy leads to the supposition that AEs identify patients with inherent pharmacokinetic and pharmacodynamic characteristics that predispose to clinical benefit and toxicity [22] . In the present study PFS and OS were significantly higher for patients suffering from sunitinib associated hypertension, hand-foot syndrome, neutropenia, diarrhea and mucositis.

To obtain the greatest clinical benefit with sunitinib is important an appropriate management of toxicities through dose adjustments and treatment interruptions[23] [22], [24]. .

Retrospective studies suggest that a change in schedule -not only in daily dose- can improve tolerability. Patients starting sunitinib with the recommended 50 mg/ day 4/2 schedule in case of toxicity may show and improvement in their safety profile with a 50 mg/day 2/1 schedule, [22, 23]. There are ongoing studies that prospectively explore this

ACCEPTED MANUSCRIPT

2/1 schedule (NCT02689167, NCT02398552, NCT01499121). This also leaves the possibility for other treatment schedules that may increase treatment tolerance based on these data.

Certain limitations should be taken into consideration in relation to this analysis. Firstly, tumor assessment was performed according to local standard care, so efficacy data may not have been recorded in a homogeneous way. Furthermore, safety assessment was not an aim of the three studies herein analyzed, so this was evaluated based mainly on the documentation of the seven AEs in which severity was graded.

Real world data are always required to confirm drug efficacy in a non-selected patient population. Recent data presented by Basappa et al, at ASCO GU 2017 from a Canadian database of first line mRCC patients suggests significant improvement in OS and Time to Treatment Failure (TTF) with the use of sunitinib under an individualized approach (treatment starting at standard dose/schedule with subsequent schedule alterations to keep dose intensity, SI) vs. sunitinib use as per product monograph (SS) and even vs. pazopanib use as per product monograph (PS). Median OS was improved in SI vs. SS (40.8 vs. 22.6 months, $p<0.001$) and SI vs. PS (40.8 vs. 20.3 m, $p<0.001$). TTF was better in SI vs. SS (16.6 vs. 5.4 m, $p<0.001$) and SI vs. PS (16.6 vs. 7.0 m, $p<0.001$)[25]. Our analysis represents first Spanish experience with sunitinib in daily clinical practice (data from patients treated between 2007 to 2011), prior to the use of an individualized approached to manage sunitinib associated toxicity. Efficacy outcomes in this real world setting resemble those obtained in the phase III pivotal trial with sunitinib where this individualized approach was not applied either. Further analysis is warranted to explore if this individualized approach with sunitinib can result like in the Canadian study not only in better tolerability but also in better outcome in our patient population.

5.- Conclusion

This analysis shows that sunitinib provides efficacy outcomes in daily clinical practice that resemble those obtained in clinical trials and new treatment schedules appear to be changing the way of managing this drug without loss of efficacy.

Funding

This study was funded by Pfizer. Medical writing support was provided by Esther Tapia, PhD, freelance and was funded by Pfizer

Declaration of interest

P. Maroto has advisory roles at Pfizer, Novartis, Bayer, Astellas and Janssen-Cilag and funding for research grants from Pfizer. M. A. Climent has advisory roles at Pfizer, Bristol and Novartis. A. González del Alba has received honoraria from Bayer, Astellas and GlaxoSmithKline and has advisory roles at Bayer, Astellas, GlaxoSmithKline and Sanofi. J. García-Donas is a member of the speakers' bureau for Pfizer. E. Grande has received honoraria for lectures and advisory board meetings and funding for research grants from Pfizer. E.Gallardo has received honoraria by lectures and/or advisory boards and travel expenses from Pfizer, Novartis and Bayer.M.V. Bolos and J. Linares are employees of Pfizer, S.L.U. The other authors declare that they have no conflicts of interest.

ACCEPTED MANUSCRIPT

References

Papers of special note have been highlighted as: * of interest ** of considerable interest

1. Cohen HT, McGovern FJ. Renal-cell carcinoma. N Engl J Med 2005;353(23):2477-2490.

2. Molina AM, Jia X, Feldman DR, Hsieh JJ, Ginsberg MS, Velasco S et al. Long-term response to sunitinib therapy for metastatic renal cell carcinoma. Clin Genitourin Cancer 2013;11(3):297-302.

3. Saylor PJ, Michaelson MD. New treatments for renal cell carcinoma: targeted therapies. J Natl Compr Canc Netw 2009;7(6):645-656.

4. O'Farrell AM, Abrams TJ, Yuen HA, Ngai TJ, Louie SG, Yee KW et al. SU11248 is a novel FLT3 tyrosine kinase inhibitor with potent activity in vitro and in vivo. Blood 2003;101(9):3597-3605.

5. Mendel DB, Laird AD, Xin X, Louie SG, Christensen JG, Li G et al. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. Clin Cancer Res 2003;9(1):327-337.

6. Escudier B, Porta C, Schmidinger M, Algaba F, Patard JJ, Khoo V et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25 Suppl 3:iii49-iii56.

Eupean Clinical Guidelines for the treatment of renal cell carcinoma. Sunitinib is recommended as a standard of care for the treatment of metastatic renal cell carcinoma in the first line setting

7. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356(2):115-124.

Sunitinib Phase III pivotal trial in first line metastatic renal cell carcinoma

8. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27(22):3584-3590.

Sunitinib Phase III pivotal trial in first line metastatic renal cell carcinoma: OS data

9. Gore ME, Szczylik C, Porta C, Bracarda S, Bjarnason GA, Oudard S et al. Final results from the large sunitinib global expanded-access trial in metastatic renal cell carcinoma. Br J Cancer 2015;113(1):12-19.

Global expanded-access trial of sunitinib in n metastatic renal cell carcinoma (N=4565). Available clinical data wiyth sunitininb in different patient subgroups (patients with brain metastasis (N=320), ECOG PS≥2 (N=582), non clear cell hystology (N=588), patients ≥65 yerars (N=1414)

10. Gamez-Pozo A, Anton-Aparicio LM, Bayona C, Borrega P, Gallegos Sancho MI, Garcia-Dominguez R et al. MicroRNA expression profiling of peripheral blood samples predicts resistance to first-line sunitinib in advanced renal cell carcinoma patients. Neoplasia 2012;14(12):1144-1152.

ACCEPTED MANUSCRIPT

Publication associated to one of the observational prospective studies which led to this pooled analysis of studies (SUT-IIG9)

11. Garcia-Donas J, Esteban E, Leandro-Garcia LJ, Castellano DE, del Alba AG, Climent MA et al. Single nucleotide polymorphism associations with response and toxic effects in patients with advanced renal-cell carcinoma treated with first-line sunitinib: a multicentre, observational, prospective study. Lancet Oncol 2011;12(12):1143-1150.

Publication associated to one of the observational prospective studies which led to this pooled analysis (SUTREN-07) 12. Garcia-Donas J, Leandro-Garcia LJ, Gonzalez Del AA, Morente M, Alemany I, Esteban E et al. Prospective study assessing hypoxia-related proteins as markers for the outcome of treatment with sunitinib in advanced clear-cell renal cell carcinoma. Ann Oncol 2013;24(9):2409-2414.

Publication associated to one of the observational prospective studies which led to this pooled analysis (SUTREN-07)

13. Prior C, Perez-Gracia JL, Garcia-Donas J, Rodriguez-Antona C, Guruceaga E, Esteban E et al. Identification of Tissue microRNAs Predictive of Sunitinib Activity in Patients with Metastatic Renal Cell Carcinoma. PLoS One 2014;9(1):e86263.

Publication associated to one of the observational prospective studies which led to this pooled analysis (SUTREN-07)

14. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92(3):205-216.

15. Motzer RJ, Bacik J, Murphy BA, Russo P, Mazumdar M. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol 2002;20(1):289-296.

16. Lalani A, Li H, Heng D, Wood L, Kalirai A, Bjarnason G et al. Real world outcomes of patients with metastatic renal cell carcinoma (mRCC) using first-line sunitinib or pazopanib: the Canadian experience. Annals of Oncology 2016; 27 (6):266-295.

17. Puente J, Lainez N, Méndez-Vidal MJ, Esteban E, Castellano D E, Basterretxea L et al. Comparison of stem cell signaling pathways in long-term responders (LR) versus primary refractory (PR) patients with metastatic clear-cell renal cell carcinoma (ccRCC) under sunitinib (SU) treatment (SULONG study). J Clin Oncol 32:5s, 2014 (suppl; abstr 4578) 2014.

ACCEPTED MANUSCRIPT

18. Schmidinger M, Vogl UM, Bojic M, Lamm W, Heinzl H, Haitel A et al. Hypothyroidism in patients with renal cell carcinoma: blessing or curse? Cancer 2011;117(3):534-544.

19. Rini BI, Cohen DP, Lu DR, Chen I, Hariharan S, Gore ME et al. Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib. J Natl Cancer Inst 2011;103(9):763-773. Retrospective data about hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib

20. Levy BI. Blood pressure as a potential biomarker of the efficacy angiogenesis inhibitor. Ann Oncol 2009;20(2):200-203.

21. Ravaud A, Sire M. Arterial hypertension and clinical benefit of sunitinib, sorafenib and bevacizumab in first and second-line treatment of metastatic renal cell cancer. Ann Oncol 2009;20(5):966-967.

22. Atkinson BJ, Kalra S, Wang X, Bathala T, Corn P, Tannir NM et al. Clinical outcomes for patients with metastatic renal cell carcinoma treated with alternative sunitinib schedules. J Urol 2014;191(3):611-618. Outcomes in patients with metastatic renal cell cancer treated with an individualized approach to manage sunitinib associated toxicity (retrospective real world data)

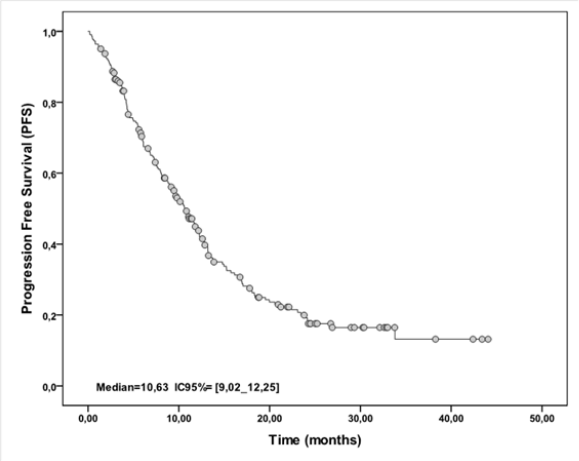
23. Bjarnason GA, Khalil B, Hudson JM, Williams R, Milot LM, Atri M et al. Outcomes in patients with metastatic renal cell cancer treated with individualized sunitinib therapy: Correlation with dynamic microbubble ultrasound data and review of the literature. Urol Oncol 2014;32(4):480-487. Outcomes in patients with metastatic renal cell cancer treated with an individualized approach to manage sunitinib associated toxicity (retrospective real world data)

24. Houk BE, Bello CL, Poland B, Rosen LS, Demetri GD, Motzer RJ. Relationship between exposure to sunitinib and efficacy and tolerability endpoints in patients with cancer: results of a pharmacokinetic/pharmacodynamic meta-analysis. Cancer Chemother Pharmacol 2010;66(2):357-371.

25. Basappa NS, Lalani A, Li H, Kalirai A, Wood L, Kollmannsber et al.. Individualized treatment with sunitinib versus standard dosing with sunitinib or pazopanib in patients with metastatic renal cell carcinoma (mRCC): Results from the Canadian Kidney Cancer information system (CKCis). J Clin Oncol 2017;35 (suppl 6S; abstract 468). Outcomes in patients with metastatic renal cell cancer treated with an individualized approach to manage sunitinib associated toxicity (retrospective real world data)

ACCEPTED MANUSCRIPT

Figure 1. Kaplan-Meier estimates. A), progression-free survival (PFS). B) PFS by MSKCC risk.



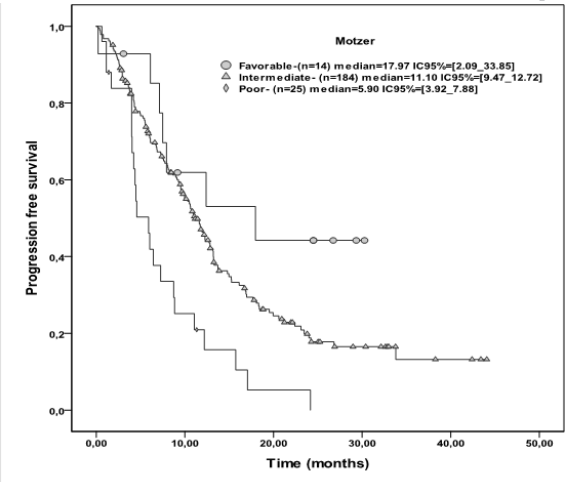
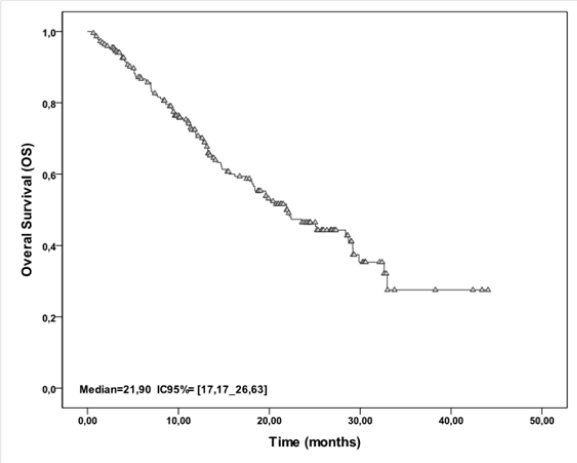


Figure 2. Kaplan-Meier estimates A) overall survival (OS). B) OS by MSKCC risk.



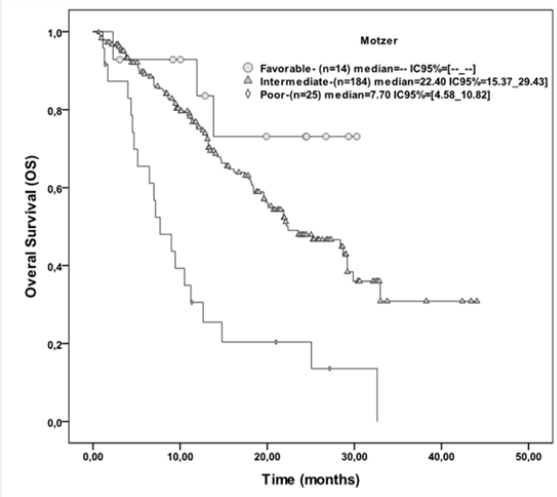


Table 1. Baseline demographic and clinical characteristics

	Pooled analysis N N (224)	Phase III trial* N (375)	Expanded-access trial[§] N (4543)
Median age (range), years	64.1 (32.5-87.3)	62 (27-87)	59.0 (19.0-89.0)
Male	119 (69.2)	267 (71)	3364 (74)
Clear cell component	205 (92.7)	375 (100)	4010 (88)
Prior nephrectomy	181 (80.8)	340 (91)	4044 (89)
ECOG PS			
0	54 (25.2)	231 (62)	1868 (41)
1	135 (63.1)	144 (38)	1949 (43)
≥ 2	25 (11.6)	0 (0)	634 (15)
MSKCC risk group			
Favorable (0 risk factors)	14 (6.3)	143 (38)	915 (20)
Intermediate (1-2 risk factors)	185 (82.6)	209 (56)	1495 (33)
Poor(≥ 3 risk factors)	25 (11.2)	23 (6)	1177 (26)
Number of metastatic sites			
0	2 (0.9)		
1	81 (36.2)	55 (15)	
2	84 (37.5)	106 (28)	
≥ 3	57 (25.4)	214 (57)	
Site of metastases			
Lung	156 (70.3)	292 (78)	3469 (76)
Lymph nodes	92 (41.4)	218 (58)	2333 (51)
Bone	55 (24.8)	112 (30)	1593 (35)
Liver	38 (17.1)	99 (26)	1236 (27)
Brain	7 (3.2)	0 (0)	338 (7)

Data are n (%). Missing data: age (12); sex (52); Histology (3); EGOG (10). EGOG PS: Eastern Cooperative Oncology Group performance status. MSKCC: Memorial Sloan-Kettering Cancer Center. Risk factors are low serum hemoglobin level, elevated corrected serum calcium level, elevated serum lactate dehydrogenase level, a poor performance status (ECOG ≥2 or Karnosfky <80%) and an interval of less than 1 year between diagnosis and systemic treatment. .

*Motzer RJ et al. N Engl J Med 2007;356(2):115-124; data from sunitinib arm (N=375)
[§] Gore et al. Br J Cancer 2015;113(1):12-19 ; [£] ≥2 metastatic sites

ACCEPTED MANUSCRIPT

Table 2. Median progression-free survival and overall survival

	Pooled analysis	Phase III trial*§	Expanded-access trial† 4543
	Median (95% CI)	**Median (95% CI)**	**Median (95% CI)**
Overall PFS, months	10.6 (9.0-12.2)	§11 (11-13)	9.4(8.8-10.0)
£PFS by MKSCC risk, months			
Favorable	17.9 (2.0-33.8)	14.9 (13.4-17.4)	15.0 (13.8-16.3
Intermediate	11.1 (9.4-12.7)	*10.7 (8.3-11.4)	10.6 (9.4-11.1)
Poor	5.9 (3.9-7.8)	*3.9 (2.5-13,5)	5.4 (5.1-5.7)
Overall OS, months	21.9 (17.7-26-6)	§26.4 (23.0-32.9)	18.7 (17.5-19.5)
£OS by MKSCC risk, months			
Favorable	-	-	56.5 (41.6-NA)
Intermediate	22.4 (15.3-29.4)	§20.7 (18.2-25.6)	20.0 (18.4-21.3)
Poor	7.7 (4.5-10.8)	§5.3 (4.2-10.0)	9.1 (8.4-9.7)

PFS: Progression-free survival. OS: Overall Survival. MSKCC: Memorial Sloan-Kettering Cancer Center
£p>0.001
*Motzer RJ et al. N Engl J Med 2007;356(2):115-124; §Motzer RJ et al. J Clin Oncol 2009;27(22):3584-3590; data from Sunitinib arm (N=375)
†Gore et al. Br J Cancer 2015;113(1):12-19

Table 3. Tumor response

	Pooled analysis	Phase III trial* N(375)	Expanded-access trial† N(3353)
Complete response	11 (5.3)	11 (3)	63 (1)
Partial response	80 (38.5)	165 (44)	597 (14)
Stable disease	80 (38.5)	150 (40)	1893 (45)
Progressive disease	37 (17.8)	26 (7)	800 (19)
Objective response rate (CR+PR)	91 (43.8)	176 (47)**	660 (16)
Disease control (PR+CR+SD)	171 (82)	326 (87)	-
Non evaluable	16 (7)	-	-

Data are number of patients (%); A total of 208 patients
*Motzer RJ et al. J Clin Oncol 2009;27(22):3584-3590; data from Sunitinib arm (N=375).
†Gore et al. Br J Cancer 2015;113(1):12-19
**ORR evaluated by investigator-assessment at a time when around 45% of the patients had died in the study. In the first interim analysis, at a less mature stage (when only 13% of sunitinib patients had died) ORR by investigator-assessment was 37% and by independent-central review was 31%

ACCEPTED MANUSCRIPT

Table 4. Most common treatment-related adverse events

Adverse Event	All grades	Grade 3	Grade 4
Asthenia and fatigue	161 (71.9)	41 (18.3)	1 (0.4)
Mucositis	125 (55.8)	11 (4.9)	1 (0.4)
Diarrhea	93 (41.5)	9 (4.0)	0
Neutropenia	80 (35.7)	10 (4.4)	1(0.4)
Hypertension	80 (35.7)	13 (5.8)	0
Hand-foot syndrome	78 (34.8)	14 (6.2)	0
Hypothyroidism	54 (24.1)	1 (0.4)	0

Data are number of patients (%). A total of 224 patients

Table 5. Median progression-free survival and overall survival based on adverse events

	PFS			OS		
	No	**Yes**	**p**	**No**	**Yes**	**p**
Asthenia and fatigue	N (62)	N (161)		N (62)	N (161)	
	11.6 (8.1-15.1)	10.5 (8.7-12.3)	0.094	20.1 (15.3-24.8)	22.2 (16.4-27.9)	0.998
Mucositis	N (98)	N (125)		N (98)	N (125)	
	9.2 (6.3-12.2)	11.5 (9.5 -13.7)	0.035	15.6 (9.8-21.3)	28.4 (20.9-35.8)	0.007
Diarrhea	N (130)	N (93)		N (130)	N (93)	
	8.7 (6.6-10.9)	15.2 (11.7-18.7)	<0.001	18.4 (12.7-24.0)	29.9 (19.3-40.5)	0.005
Neutropenia	N (143)	N (80)		N (143)	N (80)	
	9.9 (7.7-12.2)	11.8 (9.6-13.9)	0.048	17.3 (13.1-21.6)	-	<0.001
Hand-foot syndrome	N (145)	N (78)		N (145)	N (78)	
	8.6 (6.3-10.4)	13.7 (10.6-16.9)	<0.001	15.6 (10.5-20.6)	28.7 (-)	<0.001
Hypertension	N (143)	N (80)		N (143)	N (80)	
	9.6 (7.7-11.5)	12.1 (10.4-13.8)	0.031	17.3 (12.5-22.1)	29.2 (25.1-33.2)	<0.001
Hypothyroidsm	N (169)	N (54)		N (169)	N (54)	
	10.3 (8.5-12.1)	11.8 (7.6-15.9)	0.134	20.1 (15.4-24.8)	28.4 (20.7-36.1)	0.075

PFS progression free survival; OS Overall survival

Data are median PFS ($IC_{95\%}$) and median OS ($IC_{95\%}$), months

ACCEPTED MANUSCRIPT