Title

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Journal

BJU International, 129(6)

ISSN

1464-4096

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Publication Date

2022-06-01

DOI

10.1111/bju.15587

Peer reviewed

Published in final edited form as:

BJU Int. 2022 June ; 129(6): 718–722. doi:10.1111/bju.15587.

Adjuvant therapy in patients with sarcomatoid RCC: Post hoc analysis from ECOG-ACRIN E2805

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Abstract

Objectives: To study the effects on adjuvant therapy in patients with sarcomatoid RCC enrolled in the randomized phase 3 clinical trial E2805.

Materials and Methods: The original trial (E2805) is a randomized, double-blinded phase 3 clinical trial comparing outcomes in 1,943 patients with RCC accrued between 2006 and 2010, and treated with up to 1 year of adjuvant placebo, sunitinib, or sorafenib. The current study analyses the cohort of patients with sRCC that participated in E2805.

Results: 171 patients (8.8%) had sarcomatoid features. 52 patients received sunitinib, 58 received sorafenib, and 61 received placebo. Most patients were pT3–4 (71.1%, 63.7%, 70.5%, respectively) and 17.3%, 19.0%, 27.9% had pathologically positive lymph nodes. 59.6%, 62.1%, and 62.3% of the patients were UCLA UISS very-high risk. Forty-nine percent of patients with

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Financial Disclosures: Jose A. Karam has served as consultant/advisory board member to Pfizer, EMD Serono, Novartis, Roche/Genentech and MD Anderson Cancer Center has received clinical trial research funding from Roche/Genentech, and Mirati.

Trial Registration: clinicaltrials.gov NCT00326898

subsequent development of metastatic disease recurred in the lung, followed by 30% in the lymph nodes, and 13% in the liver. There was a high local recurrence rate in the renal bed (16%, 29%, and 18%, respectively). Five-year DFS rates were 33.6%, 36.0%, and 27.8%, for sunitinib, sorafenib and placebo, respectively; [HR (95% CI) 0.74(0.45–1.20) for sunitinib versus placebo, and HR 0.82(0.53–1.28) for sorafenib versus placebo].

Conclusions: Adjuvant therapy with sunitinib or sorafenib did not show an improvement of DFS or OS in patients with RCC with sarcomatoid features.

Keywords

kidney cancer; adjuvant therapy; sarcomatoid

Introduction:

Sarcomatoid features are noted in 5–10% of patients with renal cell carcinoma (RCC) and can co-occur with any primary epithelioid histology. Even patients with clinically non-metastatic disease have poor survival outcomes after surgery with curative intent (1). Given the high risk of recurrence, this patient population is poised to benefit from adjuvant postoperative therapy. A recently reported clinical trial (E2805) (2) randomizing patients with RCC to adjuvant sunitinib, sorafenib, or placebo after nephrectomy did not show a difference in disease-free survival (DFS) or overall survival (OS). Given that E2805 enrolled patients with sarcomatoid features, we aimed to study the effects of adjuvant therapy in this subgroup of patients who are at very high risk of disease recurrence.

Methods:

E2805 was a randomized, double-blinded phase 3 trial, where patients with RCC were enrolled between 2006–2010, and received sunitinib, sorafenib, or placebo for up to 1 year (2). Patients with sarcomatoid features were extracted from this trial population. Descriptive statistics, Fisher’s exact test, Kaplan-Meier estimates and log-rank test were used.

Results:

Patients

Of the 1943 patients who participated in the trial, 171 patients (8.8%) had sarcomatoid features. 52 patients (34.6% female) received sunitinib, 58 (27.6% female) received sorafenib, and 61 (29.5% female) received placebo. Median (IQR) age was 56.0 (50.0 – 65.2) years, 56.0 (50.2 – 61.8) years, and 58.0 (51.0 – 63.0) years, respectively. Most patients had ECOG PS 0–1 (96.1%, 98.3%, and 98.4%, respectively), and anemia was common (28.8%, 36.2%, and 31.1%, respectively). These calculations were based on case report forms completed by the enrolling sites.

Outcomes

Patients generally underwent open surgery (67.3%, 53.4%, and 70.5%, with sunitinib, sorafenib, and placebo, respectively), predominantly by radical nephrectomy (92.3%, 96.6%, and 98.4%, respectively). The primary epithelioid histology was most commonly clear

cell (53.8%, 63.8%, 63.9%, respectively), or mixed (21.2%, 20.7%, 11.5%, respectively). Median (IQR) tumor size was 8.5 (6.8 – 11.5) cm, 10.0 (7.6 – 11.8) cm, 10.0 (8.0 – 11.6) cm, respectively. As expected, most patients were pT3–4 (71.1%, 63.7%, 70.5%, respectively) and 17.3%, 19.0%, 27.9% had pathologically positive lymph nodes. 59.6%, 62.1%, and 62.3% of the patients were UCLA UISS very-high risk. Further details of the study population are listed in Supplemental Table 1.

As expected, median DFS and OS were significantly worse in patients with sarcomatoid features (Non-sarcomatoid: 83.1 months, Sarcomatoid: 15.8 months; and Non-sarcomatoid: not reached, Sarcomatoid: 89.4 months, respectively; both $p<0.0001$). Patients with sarcomatoid features had a higher rate of subcutaneous/lymph node metastases compared to non-sarcomatoid (30% vs. 18%, respectively, $p=0.009$).

Exploratory analyses were performed in the sarcomatoid cohort. Data on percentage sarcomatoid features was available for only 96 (56%) patients with the median percentage 30%. The largest difference in both DFS and OS was seen when at 20% sarcomatoid cutoff, but these differences were not statistically significant ($p = 0.41$ and 0.19, respectively). There were no significant differences in DFS ($p = 0.74$) nor OS ($p = 0.14$) between patients with clear cell vs non-clear cell epithelioid histology. When dividing patients into groups by pre-surgery hemoglobin levels, the difference in DFS was not significant ($p = 0.11$). Patients with anemia had a median survival of 10.0 months compared with 21.6 months for patients with normal hemoglobin levels. There were no significant survival differences in DFS or OS when stratifying by post-surgery hemoglobin or by calcium at either time point.

Treatment Discontinuation

Among the 171 sarcomatoid patients, 72 (42%) completed treatment per protocol while 971 (54.9%) of non-sarcomatoid patients completed it ($p = 0.0008$). Fifty-six (32.7%) sarcomatoid patients were indicated to have discontinued treatment because of recurrence versus 152 (8.6%) of the non-sarcomatoid patients ($p < 0.0001$). The distribution of sarcomatoid patients was similar among those who started at the full dose versus the reduced dose.

We compared the discontinuation rate and grade≥3 toxicity between arms in this patient population and found it to be similar across arms to the primary study (2) (data not shown).

Recurrences

Forty-nine percent of patients with subsequent development of metastatic disease recurred in the lung (50%, 44% and 52% for sunitinib, sorafenib, and placebo, respectively), followed by 30% in the lymph nodes (44%, 21%, and 28%, respectively), and 13% in the liver (12%, 12%, and 15%, respectively). There was a high local recurrence rate in the renal bed (16%, 29%, and 18%, respectively). These recurrence rates and locations were similar to those reported retrospectively (1).

Efficacy

Five-year DFS rates were 33.6%, 36.0%, and 27.8%, for sunitinib, sorafenib and placebo, respectively; [HR (95% CI) 0.74 (0.45 – 1.20) for sunitinib versus placebo, and HR 0.82 (0.53 – 1.28) for sorafenib versus placebo], and 5-year OS rates were 51.8%, 55.9%, and 59.0%, respectively [HR 1.06 (0.62 – 1.82) for sunitinib versus placebo and HR 0.97 (0.57 – 1.64) for sorafenib versus placebo].

Patient characteristics based on central pathology review (total 138 with confirmed sarcomatoid features) from the primary study (2) were also examined. There was no difference in DFS or OS between the 3 arms when the analyses were repeated in this cohort (data not shown).

Discussion:

A recent study (1) investigating 77 patients with clinically N0M0 sarcomatoid RCC showed that even though these patients were clinically non-metastatic at presentation, they still had a 25% rate of occult positive nodes, as well as poor clinical outcomes, with a 2-year overall survival rate of 50%. Such results underscore the importance of finding an effective adjuvant therapy in this patient population.

In addition to E2805, 2 recent studies reported on adjuvant therapy with tyrosine kinase inhibitors in patients with RCC. Ravaud et al (3) randomized patients to sunitinib versus placebo and reported an improved DFS but not OS in patients who received sunitinib. Motzer et al (4) randomized patients to pazopanib versus placebo and did not note any difference in DFS or OS in patients receiving pazopanib. While these 2 reports did not specify how many patients with sarcomatoid features were included in the trials, the analysis of outcomes of patients with sarcomatoid features is potentially feasible, and of great importance. Such analysis will also be interesting to address in clinical trials that will report shortly (ATLAS; EVEREST; and SORCE). Of note, 2 ongoing clinical trials using immune checkpoint blockade have actively recruited patients with sarcomatoid features regardless of epithelioid histology (atezolizumab, IMmotion010; and pembrolizumab, KEYNOTE-564). These 2 trials are particularly interesting in the setting of sarcomatoid dedifferentiation as these tumors appear to be more sensitive to immune checkpoint blockade (5–7), and on the fact that they have higher/more frequent expression of PD-L1 compared to non-sarcomatoid tumors (5, 8). Limitations of the current study include its retrospective design, lack of information on percentage sarcomatoid elements, inclusion of multiple tumor histologies and absence of drug dosage information in this cohort.

Conclusions:

In this post-hoc subgroup analysis from E2805, adjuvant therapy with sunitinib or sorafenib did not show an improvement of DFS or OS in patients with RCC with sarcomatoid features. Subgroup analysis of other recently published adjuvant trials is warranted for this group at very high risk of recurrence and death from disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Support:

This study was coordinated by the ECOG-ACRIN Cancer Research Group (Peter J. O'Dwyer, MD and Mitchell D. Schnall, MD, PhD, Group Co-Chairs) and supported by the National Cancer Institute of the National Institutes of Health under the following award numbers: CA180820, CA180794, CA180821, CA180858, CA180888, CA180863, CCSRI704970. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. government.

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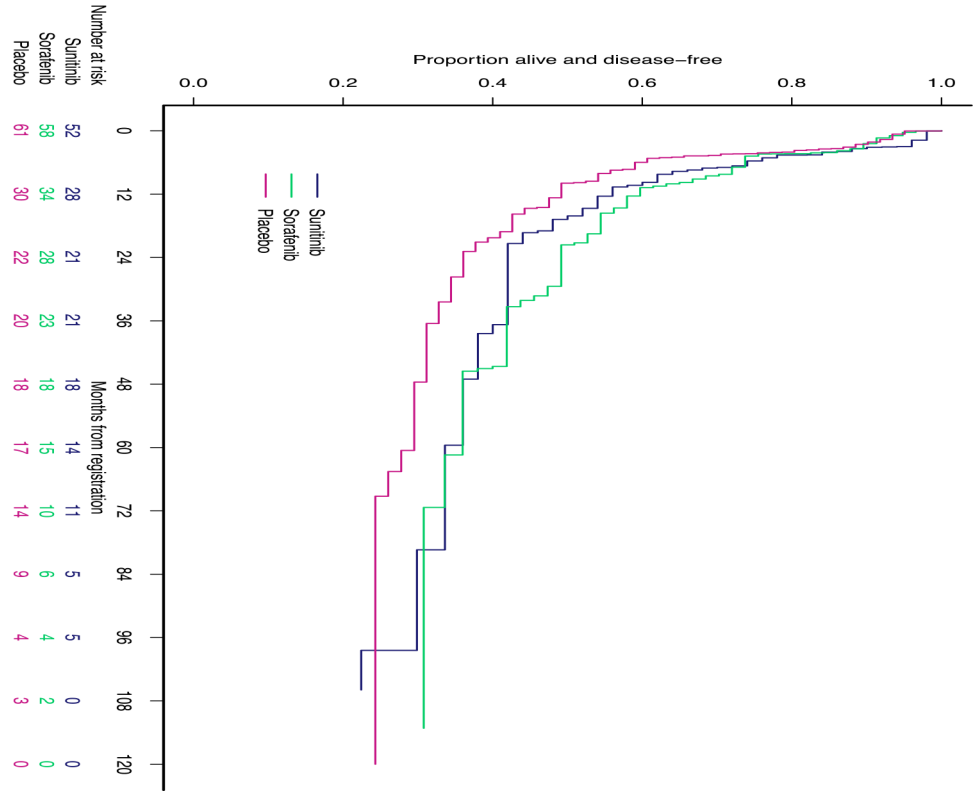

Figure 1.
Disease-free survival

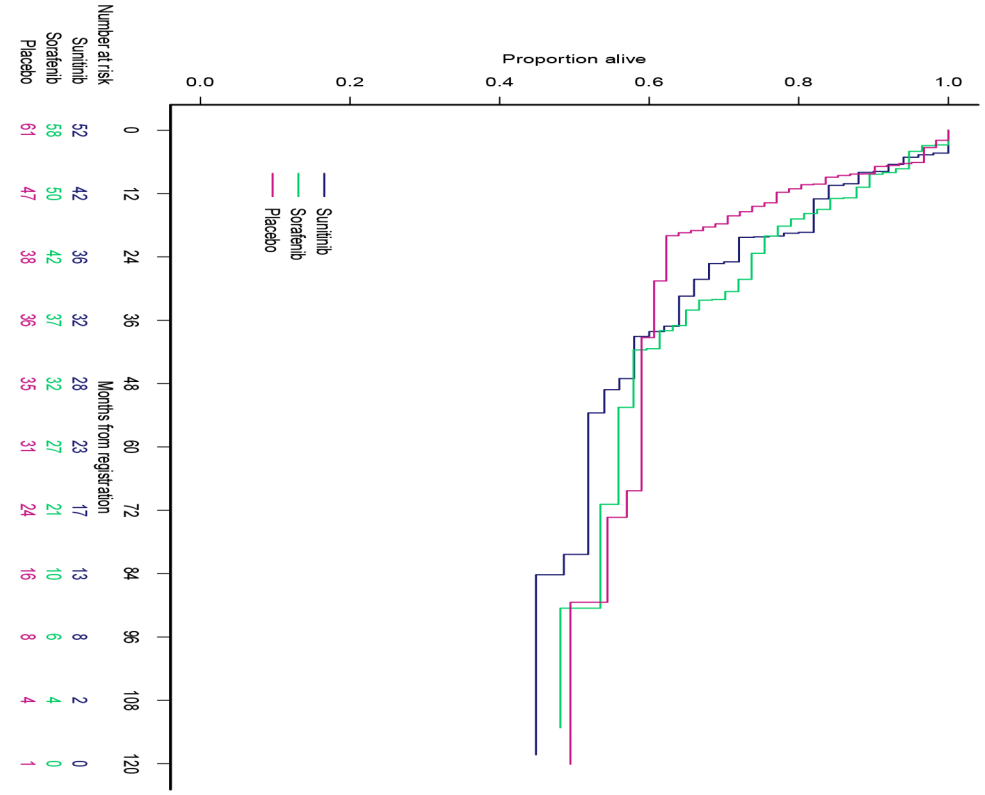

Figure 2.
Overall survival