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***Revision notes**

We thank the associate editor and reviewers for taking the time to review our manuscript and for their overall positive comments. Please find below our responses to the individual comments:

Associate Editor:

1) *Please add the interventions section at the abstract. Thanks.*

The 'Design, Setting and Participants' section of the abstract has been split to incorporate the interventions sections and now reads (lines 45-47):

'Design, Setting, and Participants: A retrospective analysis was conducted of a second-line phase II study in metastatic ccRCC (NCT00942877), evaluating 138 patients with 458 baseline lesions.

Intervention: The phase II trial assessed VEGF-targeted therapy ± Src inhibition.'

The words 'to validate these findings' have been removed from the abstract conclusion (line 61) to keep the word count below 300.

2) *The authors used definitions of radiological heterogeneity which were developed in patients with CRC liver mets and which were modified accordingly by the authors. Are the cut-offs used for 'homogeneous', 'low heterogeneous' and 'high heterogeneous' response arbitrary or is there evidence why these were chosen by the authors. Please briefly clarify to make it more understandable for our readers.*

The following has been added to the Patients and Methods section (lines 152-155):

'The cut-offs were determined using an optimal response model by van Kessel and colleagues. This involved modelling different cut-off values to identify which provided the highest discriminative capacity. Further details are provided in [6]. No further modelling was undertaken for the analysis presented in this paper.'

3) *Please add the number of patients at risk at each time point with KM-curves. Please also use 12-mo intervals to make it easier to see yearly changes.*

Figures 2 and 3 have been updated as suggested.

4) *Please briefly explain the development of the multivariate model. Which parameters from the univariate model were included? Which parameters were used for the univariate analyses?*

The Statistical Analysis section of Patients and Methods (lines 159-165) has been updated to clarify these points and now reads:

‘Uni- and multivariate analyses were undertaken using Cox regression to calculate Hazard Ratios (HR). The univariate parameters were chosen on the basis of being known prognostic variables from previous studies (gender, Eastern Cooperative Oncology Group [ECOG] performance status, Memorial Sloan Kettering Cancer Center [MSKCC] risk group, nephrectomy status) or because they may be confounding factors to radiological heterogeneity (number of target lesions, sum of lesion diameters) [2, 7, 8]. All univariate parameters were included in the multivariate analysis.’

Reviewer 1:

We thank the reviewer for their kind comments.

Reviewer 2:

We thank the reviewer for their kind comments.

Radiological response heterogeneity is of prognostic significance in metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted therapy

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ABSTRACT

Background: Response Evaluation Criteria in Solid Tumours (RECIST) is widely used to assess tumour response but is limited by not considering disease site or radiological heterogeneity.

Objective: To determine if radiological heterogeneity or disease site have prognostic significance in patients with metastatic clear cell renal cell carcinoma (ccRCC).

Design, Setting, and Participants: A retrospective analysis was conducted of a second-line phase II study in metastatic ccRCC (NCT00942877), evaluating 138 patients with 458 baseline lesions.

Intervention: The phase II trial assessed VEGF-targeted therapy ± Src inhibition.

Outcome Measurements and Statistical Analysis: Radiological heterogeneity at week 8 was assessed within individual patients with ≥2 lesions to predict overall survival (OS) using Kaplan-Meier method and Cox regression. We defined a high heterogeneous response as occurring when ≥1 lesion underwent a ≥10% reduction *and* ≥1 lesion underwent a ≥10% increase in size. Disease progression was defined by RECIST 1.1 criteria.

Results and Limitation: In patients with a complete/partial response or stable disease by RECIST 1.1 and ≥2 lesions at week 8, those with a high heterogeneous response had a shorter OS compared to those with a homogeneous response (hazard ratio [HR] 2.01 (95% confidence interval [CI]: 1.39-2.92; *P*<0.001). Response by disease site at week 8 did not affect OS. At disease progression, ≥1 new lesion was associated with worse survival compared to >20% increase in sum of target lesion diameters only (HR 2.12; 95% CI: 1.43-3.14; *P*<0.001). Limitations include retrospective study design.

Conclusions: Radiological heterogeneity and the development of new lesions may predict survival in metastatic ccRCC. Further prospective studies are required.

Patient summary: We looked at individual metastases in patients with kidney cancer and showed that a variable response to treatment and the appearance of new metastases may be associated with worse survival. Further studies are required to confirm these findings.

KEY WORDS

Heterogeneity; prognostic factor; radiological response; renal cell carcinoma; vascular endothelial growth factor.

INTRODUCTION

Inhibition of vascular endothelial growth factor (VEGF) signalling, usually by means of small-molecule tyrosine kinase inhibitors (TKIs), is the current mainstay of metastatic clear-cell renal cell carcinoma (ccRCC) therapy in both the first and second-line settings [1]. However, there is a wide variation in treatment responses by patients. Several prognostic scoring systems have been developed to identify poor and favourable risk patients [2, 3]. These are determined at baseline and are based around a combination of time to treatment, performance status and blood parameters [2, 3]. Response Evaluation Criteria in Solid Tumours (RECIST) response rates and disease progression have been used as surrogate markers of activity in clinical trials [4]. However, RECIST is limited as it overlooks details of dynamic changes by amalgamating total tumour burden into a single numerical entity. Confidence in RECIST as accurate surrogate marker of outcome is also questionable, partly due to variable responses within individual patients, also known as intra-patient heterogeneity. For these reasons, clinicians often continue treatment past disease progression. Therefore, more accurate tools for predicting outcome are required. We hypothesised that following individual lesion responses would better characterise clinical benefit. We therefore examined individual lesions in patients with metastatic ccRCC participating in a VEGF-targeted therapy clinical trial to address this.

PATIENTS AND METHODS

Study population

Prospectively collected data from the double-blind, randomised, phase II COSAK trial (ClinicalTrials.gov NCT00942877) were used in this retrospective *post hoc* analysis. One hundred and thirty-eight patients with metastatic ccRCC who had progressed after at least one line of VEGF targeted therapy were randomised to either cediranib (a VEGF TKI) alone (*N*=69) or in combination

with the Src inhibitor, saracatinib (*N*=69). Exclusion criteria included untreated brain metastases, uncontrolled hypertension and concurrent malignancies. The two arms were well-matched for patient characteristics. No significant difference was seen in progression-free survival (PFS) or overall survival (OS), published elsewhere [5]. The data from the two treatment arms were therefore combined for this analysis.

Imaging and image analysis

Computed tomography (CT) scans were undertaken every eight weeks using standard protocols and patient response assessed by RECIST 1.1 [4]. Staff were blinded to the outcome data, but no central review occurred. Baseline, week 8 and disease progression were the time points examined. Individual lesion responses (percentage change from baseline) for each patient were also determined at week 8. RECIST 1.1 criteria were used to categorise each lesion response.

Radiological heterogeneity

Radiological heterogeneity (RH) was assessed at week 8 in patients with ≥2 lesions using criteria developed by van Kessel and colleagues in patients with colorectal liver metastases (Suppl. Fig. 1, [6]). They used the terms 'homogeneous', 'mixed' and 'true mixed' response, but 'true' implies a validated comparison with a gold standard. We therefore have used the terms 'homogeneous', 'low heterogeneous' and 'high heterogeneous' response instead.

Briefly, the percentage change in each lesion was determined and the maximum difference calculated. A homogeneous response indicated that all the lesions for a patient had changed in the same direction with <30% difference between highest and lowest change. A low heterogeneous response indicated that all lesions changed in same direction, but that there was a ≥30% difference

between the highest and lowest. For the homogeneous and low heterogeneous response categories, small changes (-10% to +10%) could be re-assigned to count as a change in the same direction. A high heterogeneous response indicated that at least one lesion underwent a ≥10% reduction *and* at least one other lesion underwent a ≥10% increase. The cut-offs were determined using an optimal response model by van Kessel and colleagues. This involved modelling different cut-off values to identify which provided the highest discriminative capacity. Further details are provided in [6]. No further modelling was undertaken for the analysis presented in this paper.

Statistical analysis

The primary outcome for this study was OS. Kaplan-Meier method was used to assess OS and groups compared using the log-rank test. Uni- and multivariate analyses were undertaken using Cox regression to calculate Hazard Ratios (HR). The univariate parameters were chosen as known prognostic variables from previous studies (gender, Eastern Cooperative Oncology Group [ECOG] performance status, Memorial Sloan Kettering Cancer Center [MSKCC] risk group, nephrectomy status) or because they may be confounding factors to RH (number of target lesions, sum of lesion diameters) [2, 7, 8]. All univariate parameters were included in the multivariate analysis. Pearson's Chi-Square test was used to assess differences in RH between two groups. All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS, version 23). A *P* value of <0.05 was considered significant.

RESULTS

Patients

All 138 patients from the COSAK trial were evaluated (Table 1). Ninety-six percent of patients had received only one previous VEGF-targeted therapy whereas the remainder had received two. Median PFS and OS for the whole group were 4.1 months (95% confidence interval (CI): 3.1-5.1 months) and 12.0 months (95% CI: 8.5-15.6 months), respectively. No significant difference between the treatment arms was observed with regards to both baseline characteristics and treatment response (P>0.05). Therefore, the data for the two treatment arms were merged for this analysis.

Baseline site of disease

At baseline, 458 individual lesions from 138 patients were available for analysis. The median number of lesions per patient was 3 (range 1-5). A breakdown of the lesion sites was as follows: lymph nodes 138 (30%); lung 112 (24%); liver 42 (9%); bone 27 (6%); other 139 (30%). Twenty-seven patients had ≥ 1 liver metastasis (20%) and 18 (13%) had ≥ 1 bone metastasis. Two patients (1.4%) had both a liver and bone metastasis. The presence of a liver or bone metastasis was not predictive of PFS (HR 0.95; 95% CI: 0.66-1.38; P=0.80) or OS (HR 1.34; 95% CI: 0.91-1.97; P=0.14).

First follow-up CT scan (week 8)

The first follow-up CT scan occurred at week 8. One hundred and thirteen patients (82% of baseline) had week 8 data for analysis encompassing 369 of the baseline lesions (81%; lymph nodes 103 [28% of the 369], Lung 93 [25%], liver 30 [8%], bone 26 [7%], other 117 [32%]). Reasons for the reduced patient numbers at week 8 included death and drug toxicity.

Individual lesion responses at week 8

Assessment of the individual lesion responses at week 8 by RECIST criteria showed one complete response (0.3%), 49 partial responses (13%), 276 (75%) were classified as stable and 43 (12%) lesions progressed (Suppl. Table 1A). Lesion site responses of CR/PR (combined as only one lesion had a CR), SD or PD were not prognostic for OS (Suppl. Table 1B).

Overall patient responses at week 8

When overall patient responses were analysed by RECIST at week 8, no patients had a CR, 8 (7.1%) had a PR, 80 (70.8%) had SD and 25 (22.1%) had PD. As expected, PD at week 8 was associated with worse OS with a median of 3.9 months (95% CI: 1.0-6.8) compared to 12.1 months (95% CI: 9.7-14.5; HR 1.61; 95% CI: 1.07-2.43; P=0.02) for patients with a PR and 13.9 months (95% CI: 12.2-15.6; HR 3.21; 95% CI: 2.10-4.93; P<0.001) for patients with SD. No statistical difference was seen between the PR and SD groups (HR 0.82; 95% CI: 0.37-1.79; P=0.61).

Radiological heterogeneity at week 8

Given that no difference in outcome was seen between the RECIST-defined PR and SD groups at week 8, we examined whether OS in this subpopulation could be further characterised by RH. Of the 113 patients with individual lesion data available at week 8, 104 (75% of the initial 138 patients) had >1 lesion and therefore could be assessed for heterogeneity. Of these 104 patients, 81 (59% of the initial 138 patients), had PR (N=7) or SD (N=74) by RECIST at week 8 and were included in the heterogeneity analysis. The remaining 23 patients had PD by RECIST criteria and were not included.

Figure 1 demonstrates the frequency of different lesion responses by RECIST category for PR and SD patients combined. Radiological heterogeneity was commonly seen, with 34 patients (42%) having ≥2 RECIST categories amongst their lesion responses at week 8. However, heterogeneity by number

of RECIST categories (1 versus ≥2) was not associated with improved OS (HR 1.40; 95% CI: 0.84-2.32; *P*=0.19).

Radiological heterogeneity was assessed using criteria developed for colorectal liver metastases in the RECIST-defined PR and SD populations (Suppl. Fig. 1; [6]). Forty nine patients (60%) had a homogeneous response, 20 (25%) had a low heterogeneous response and 12 (15%) had a high heterogeneous response by RH criteria. For OS from week 8, the times were 16.9 months (Fig. 2; 95% CI: 11.1-22.7), 12.8 months (95% CI: 11.3-14.3) and 7.3 months (95% CI: 5.4-9.2) for the homogeneous, low heterogeneous and high heterogeneous response categories, respectively. Hazard ratios were: Homogeneous *vs* low heterogeneous 1.41 (95% CI: 0.78-2.55; *P*=0.26); Homogeneous *vs* high heterogeneous 2.01 (95% CI: 1.39-2.92; *P*<0.001); low heterogeneous *vs* high heterogeneous 2.58 (95% CI: 1.12-5.91; *P*=0.02).

We hypothesised that patients with smaller, more numerous lesions may demonstrate increased RH and therefore confound results. Of the 81 patients in the RH analysis, 28 (35%) had two target lesions and 53 (65%) had ≥3 lesions. The number of target lesions (2 *vs* ≥3) was not prognostic for OS (HR 0.66; 95% CI: 0.39-1.12; *P*=0.13). The median sum of target lesion diameters at week 8 was 92 mm (range 20-334). A sum below the median was associated with improved OS (HR 0.45; 95% CI: 0.27-0.74; *P*=0.002), but RH was not significantly different between the two groups (Suppl. Fig. 2; *P*=0.17). However, in a multivariate Cox regression including RH, sum of lesion diameters, number of lesions alongside the other variables, only RH, sum of lesion diameters and MSKCC score were independent prognostic factors for OS (Table 2).

Radiological heterogeneity was not prognostic for OS in patients with PD at week 8, although numbers were small (HR 0.76, 95% CI: 0.31-1.83; *P*=0.54; *N*=23).

New lesions at disease progression predict worse survival

One hundred and twenty one patients (88% of the initial 138) had data at disease progression. Of these, 64 (53%) had no new sites of disease and 57 (47%) had ≥1 new site. Lung was the commonest site of for a new lesion (23 patients, 41%) with liver and 'other' being the next commonest sites (16 patients each, 29%). This was followed by bone (13 patients, 21%), lymph node (8 patients, 14%) and brain (2 patients, 4%). The new site was unknown for one patient. Median survival was significantly shorter in patients with ≥1 new site of disease compared to none at disease progression (Fig. 3; 3.7 months [95% CI: 2.1-5.2] versus 9.9 months [95% CI: 7.5-12.2]; HR 2.12; 95% CI: 1.43-3.14; *P*<0.001). In patients with ≥1 new disease site, 32 patients (56%) had a <20% increase in the sum of lesion diameters at disease progression, 21% had ≥20% increase and 23% had missing data. No significant difference in survival was seen between the groups suggesting new sites rather than general progression in all sites was associated with poor outcome (HR 0.87; 95% CI: 0.42-1.79; *P*=0.66). The site of the new lesion was not predictive for survival (Suppl. Table 2).

DISCUSSION

This study examined radiological prognostic factors at baseline, first follow-up scan (week 8) and disease progression in metastatic ccRCC patients receiving second-line VEGF-targeted therapy.

Whilst patients with PD at first follow-up had a worse survival, no significant difference in survival was seen between patients with PR or SD when using RECIST 1.1 criteria. Therefore, alternative radiological prognostic markers were sought for these patients to predict prognosis and thus aid treatment decisions. Forty percent of patients with non-progressive disease at week 8 demonstrated RH, with increased RH associated with worse survival. Intratumoural and inter-metastasis heterogeneity has been shown to exist at a molecular level in RCC where clonal evolution is thought to play a role [9-11]. Similarly, RH has been shown to exist in metastatic ccRCC patients treated with first-line VEGF-targeted therapies at a similar frequency to that seen in this study and is

likely to represent different clones [12]. However, no outcome data were analysed. Radiological heterogeneity has also been shown in patients with colorectal liver metastases where increased RH was correlated to a worse OS [6]. We have described a method to assess RH that can be used in the clinic and, in our dataset, had prognostic significance for patients with metastatic ccRCC at their first follow-up scan thereby providing a potential alternative to RECIST for assessing treatment response. This may be beneficial to patients as ineffective treatments can be changed at an earlier timepoint. Radiological heterogeneity was found to be independent of potential confounders, number of target lesions and sum of lesion diameters, but further validation is required. Future studies may also look at the correlation between RH and tumour factors including Fuhrman grade and Von-Hippel-Lindau mutational status.

The development of ≥1 new lesion, rather than the growth of existing lesions, at disease progression was associated with a worse OS. This has previously been described for metastatic RCC patients treated with everolimus [13]. Similar effects have been shown in metastatic breast, colorectal and lung cancer [14, 15]. RECIST does not distinguish between the two types of disease progression, thereby reflecting a further limitation of its use. The development of new sites suggests increased clinical significance and may help decision making in terms of switching therapy.

Baseline site of disease was not a prognostic factor for OS in this study. In addition, treatment response at week 8 by disease site was not prognostic for survival. This is in contrast to previous studies which have shown that bone and liver metastases are adverse independent prognostic factors for OS in metastatic RCC [16-18]. This correlates with findings from patients treated with cytokines where liver and bone metastases have been included as adverse factors in a prognostic model [19]. It is unclear why bone and liver metastases were not prognostic in this study, although low *N* numbers may be one explanation.

There are several limitations of this study. This was a retrospective study that was not powered for the groups analysed and therefore requires validation before definitive conclusions can be reached,

ideally with prospective studies. The *N* numbers in this study were small, making it difficult to reject to the null hypothesis. Nonetheless, even with this restriction, we did manage to show significant results. Cediranib is not licensed for use in RCC, having not been developed further due largely to the competitive landscape in metastatic RCC. Its efficacy appears to be in line with other VEGF-targeted therapies tested in the ≥2nd line setting, but further work is required to see if the conclusions from this paper are applicable to other VEGF-targeted therapies in both the first- and second-line settings [5, 20].

CONCLUSIONS

In conclusion, we have shown that radiological heterogeneity may have prognostic value at the first follow-up scan and may help guide decisions about whether to change treatments. Similarly, the development of new lesions at disease progression is associated with a worse survival than solely an increase in the size of existing lesions. Further prospective validation is required to confirm these findings.

PATIENT SUMMARY

We looked at individual metastases in patients with kidney cancer and showed that a variable response to treatment and the appearance of new metastases may be associated with worse survival. Further studies are required to confirm these findings.

FUNDING AND SPONSORSHIP

This study was supported by Cancer Research UK and AstraZeneca. It was sponsored by the Common Services Agency (CSA; NHS National Services Scotland).

CONFLICT OF INTEREST STATEMENT

PEH has received honoraria from Merck Sharp & Dohme. JB has received honoraria from Amgen, Pfizer and Novartis. RJ has received research funding from AstraZeneca. CR has received sponsorship and honoraria from Pfizer, Novartis, Bristol-Meyers Squibb, Roche, GlaxoSmithKline, Viralytics, Janssen and the British Sarcoma Group. SC has received funding from GlaxoSmithKline and Pfizer for speaking. SJC has received sponsorship and honoraria from Novartis, Ipsen, Bristol-Myers Squibb, Roche and Merck, and research funding from AstraZeneca. KF has received honoraria from Roche, Pfizer and Novartis. TP has received honoraria for advisory boards from Novartis, Roche, Pfizer and Bristol-Myers Squibb and received a research grant from AstraZeneca. All remaining authors have declared no conflict of interest.

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TABLE LEGENDS

Table 1: Patients' characteristics at baseline. VEGF, vascular endothelial growth factor. MSKCC, Memorial Sloan Kettering Cancer Center.

Table 2: Multivariate Cox regression analysis of variables affecting overall survival at week 8. ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan Kettering Cancer Center.

FIGURE LEGENDS

Figure 1: Frequencies of individual lesion response categories by RECIST 1.1 at week 8 in patients with non-progressive disease. Individual lesion responses were assessed according to RECIST 1.1 criteria in patients who had an overall response of either PR or SD at week 8 (no CR by patient). Note, only one lesion had a CR and therefore was combined with the PR group. The types of RECIST category demonstrated by the lesions within a patient were assessed and the number of patient with those categories determined. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Figure 2: Radiological heterogeneity in patients with a partial response or stable disease at week 8 is associated with overall survival. In patients with a partial response or stable disease at week 8, radiological heterogeneity (homogeneous response, low heterogeneous response, high heterogeneous response) is prognostic for overall survival: 16.9 months (95% CI: 11.1-22.7), 12.8 months (95% CI: 11.3-14.3) and 7.3 months (95% CI: 5.4-9.2) for the homogeneous response, low heterogeneous response and high heterogeneous response categories, respectively. Hazard ratios were as follows: Homogeneous *vs* Low heterogeneous 1.41 (95% CI: 0.78-2.55; *P*=0.26);

Homogeneous *vs* High heterogeneous 2.01 (95% CI: 1.39-2.92; *P*<0.001); Low heterogeneous *vs* High heterogeneous 2.58 (95% CI: 1.12-5.91; *P*=0.02).

Figure 3: One or more new lesion at disease progression is associated with worse overall survival. %). Median survival was significantly shorter in patients with ≥1 new site of disease compared to none at disease progression (3.7 months [95% CI: 2.1-5.2] versus 9.9 months [95% CI: 7.5-12.2]; HR 2.12; 95% CI: 1.43-3.14; *P*<0.001).

SUPPLEMENTARY TABLE/FIGURE LEGENDS

Supplementary Table 1: Lesion response by site at first follow-up scan (week 8). Individual lesion responses were assessed by RECIST 1.1 criteria (A). Only one lesion had a CR at week 8 and was therefore combined with the PR category. Hazard ratios for overall survival (OS) were analysed by site and RECIST 1.1 response in individual lesions (B). None were predictive for OS (*P*>0.05). CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; N/A, not applicable due to low *N* numbers; ( ) indicate 95% confidence interval.

Supplementary Table 2: Site of new lesion at disease progression does not predict survival. Hazard ratios for the site of the new lesion at disease progression compared to all other sites. N/A, not applicable due to low *N* numbers.

Supplementary Figure 1: Methods used to assess radiological response heterogeneity. Radiological response heterogeneity was assessed at week 8 in patients with ≥2 lesions. The percentage change in each lesion was determined and the maximum difference calculated. A homogeneous response

453 indicated that all the lesions for a patient had changed in the same direction with <30% difference
454 between highest and lowest change. A low heterogeneous response indicated that all lesions
455 changed in same direction, but that there was a ≥30% difference between the highest and lowest.
456 For the homogeneous and low heterogeneous response categories, small changes (-10% to +10%)
457 could be re-assigned to count as a change in the same direction. A high heterogeneous response
458 indicated that at least one lesion underwent a ≤10% reduction *and* at least one other lesion
459 underwent a ≥10% increase [6].

460

461 **Supplementary Figure 2: Radiological heterogeneity by sum of lesion diameters in patients with PR**
462 **or SD at week 8.** Percentage of patients with a sum of lesion diameters below (blue bars) or above
463 the median size (orange bars) at week 8 which fall into the homogeneous, low heterogeneous or
464 high heterogeneous radiological response categories. The difference between the two groups was
465 not significant by Pearson's Chi-Square test (*P*=0.17).

466

Figure 1

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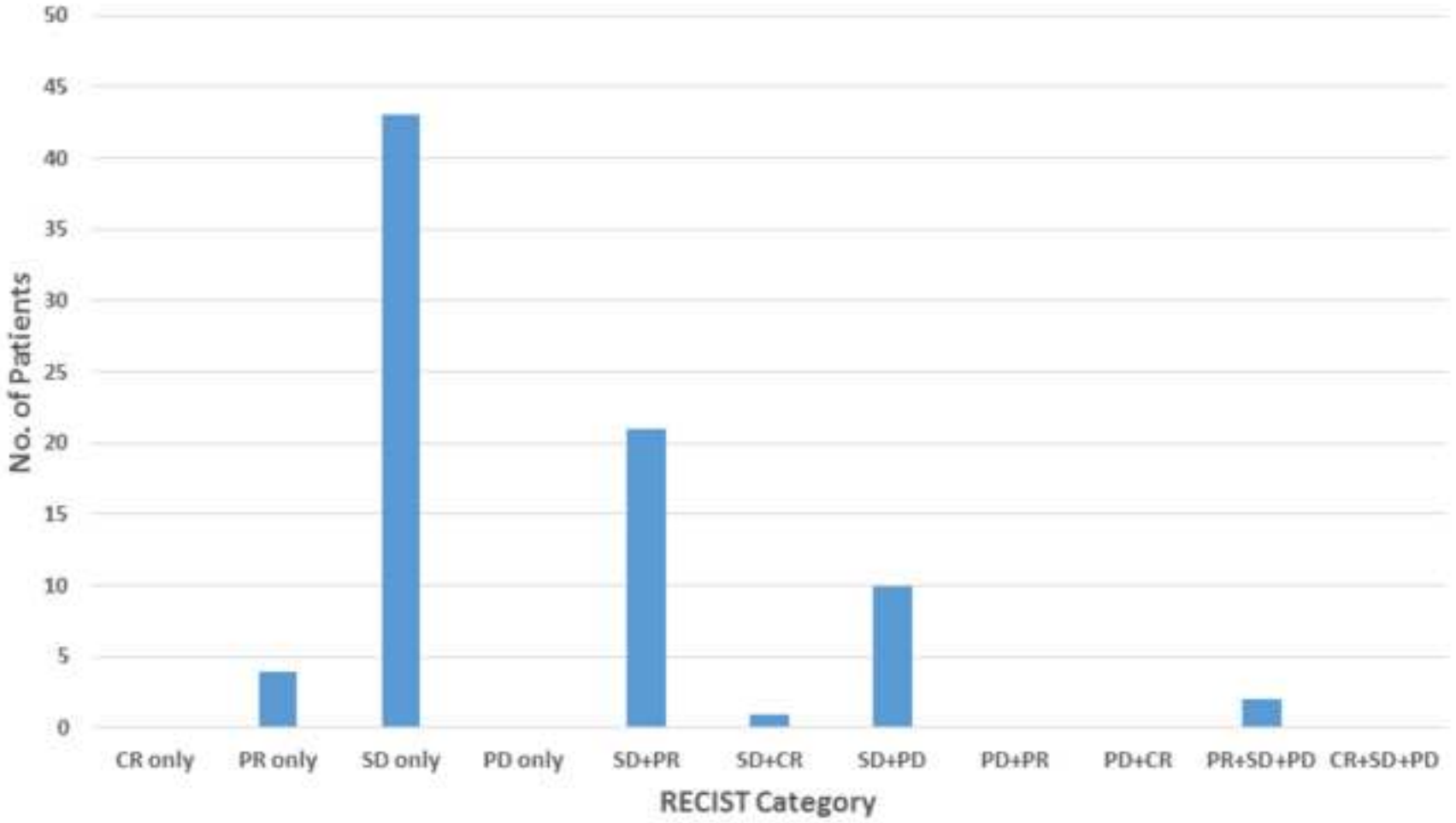

Figure 2

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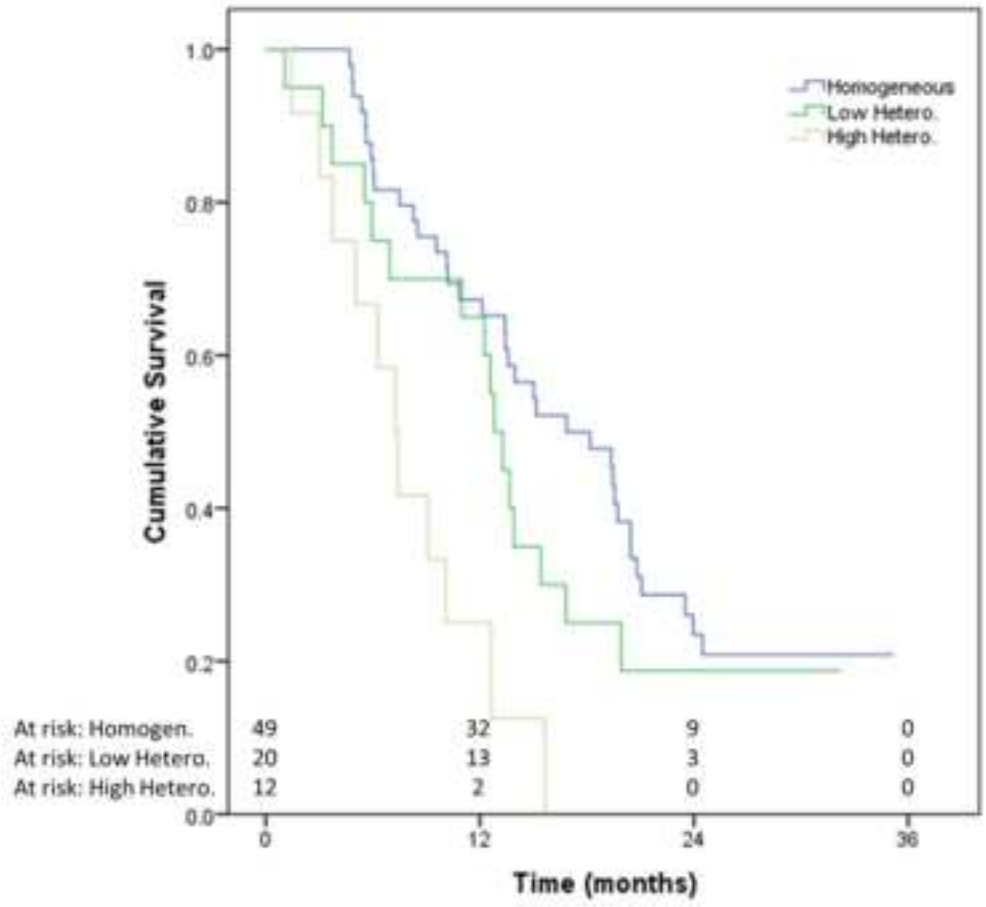

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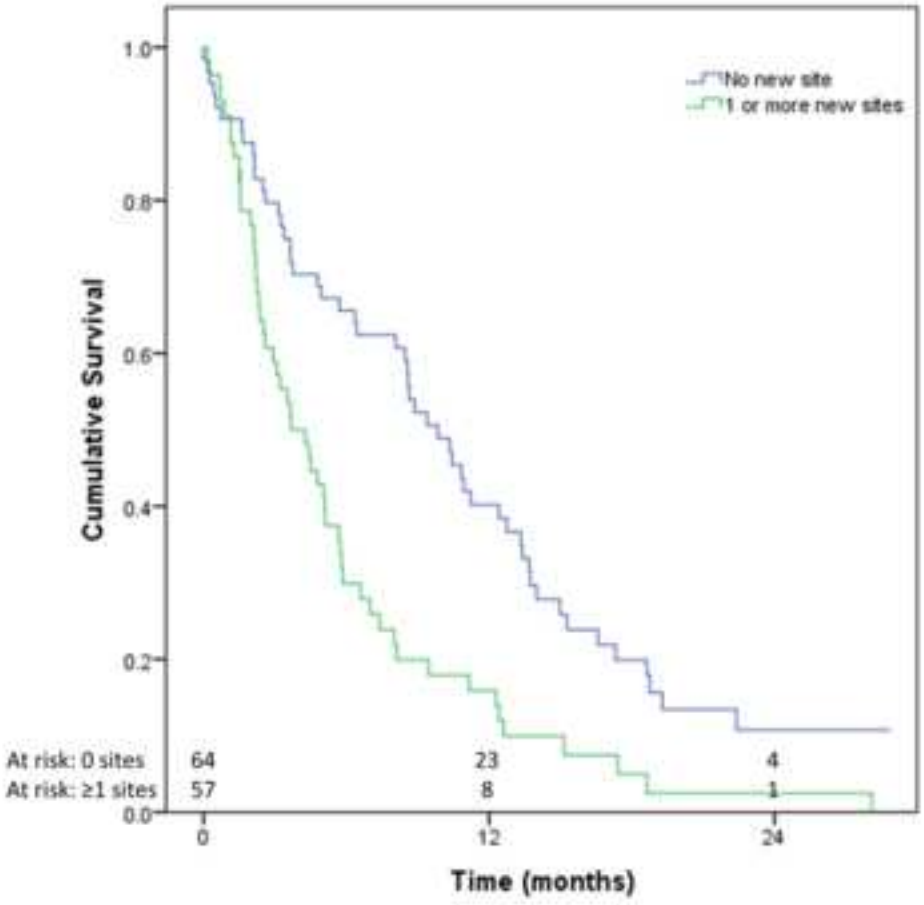

Table 1

Gender	Male	108 (78%)
Previous immune therapy	Yes	29 (21%)
Performance status	0	37 (27%)
	1	83 (60%)
	>1	18 (13%)
MSKCC risk group	Low	19 (14%)
	Intermediate	99 (72%)
	High	20 (14%)
Nephrectomy	Yes	111 (80%)
Site of disease (by patient)	Lymph nodes	65 (47%)
	Lung	92 (67%)
	Liver	13 (9%)
	Bone	20 (14%)
1st line VEGF-targeted therapy	Sunitinib	109 (81%)
	Pazopanib	17 (12%)
	Sorafenib	4 (3%)
	Bevacizumab	4 (3%)
Best response to 1st VEGF-targeted therapy	Complete response	2 (1%)
	Partial response	25 (18%)
	Stable disease	53 (38%)
	Progressive disease	49 (35%)

Table 2

Variable	Hazard ratio (95% CI)	*P* value
Number of target lesions	1.53 (0.75-3.12)	0.83
Prior nephrectomy	1.51 (0.74-3.08)	0.25
ECOG performance status	1.37 (0.81-2.32)	0.24
Gender	0.74 (0.40-1.36)	0.33
Radiological heterogeneity	**1.76 (1.22-2.54)**	**0.003**
Sum of lesion diameters	**0.51 (0.30-0.85)**	**0.01**
MSKCC score	**1.83 (1.03-3.23)**	**0.04**

Supplementary Figure 1

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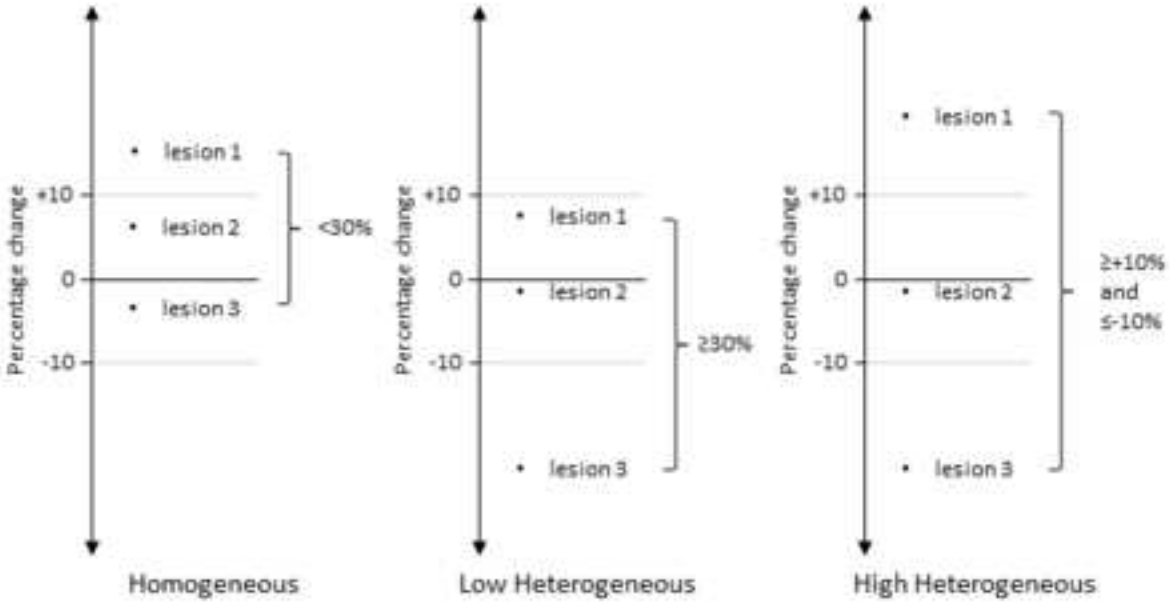

Supplementary Figure 2

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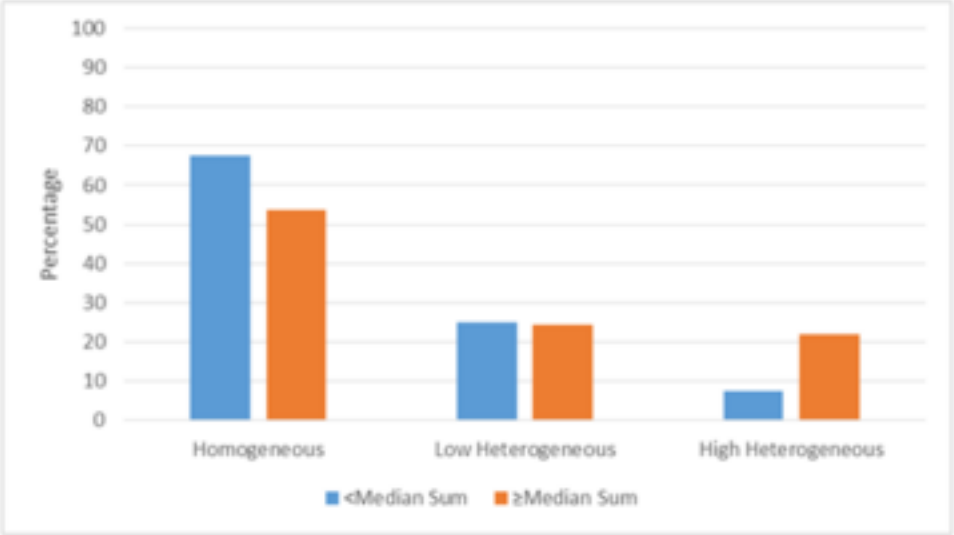

Supplementary Table 1

Site	Total No.	CR/PR	SD	PD
Total	369	50 (14%)	276 (75%)	43 (12%)
Lymph node	103 (28%)	17 (16%)	74 (72%)	12 (12%)
Lung	93 (25%)	15 (16%)	67 (72%)	11 (12%)
Liver	30 (8%)	0 (0%)	21 (70%)	9 (30%)
Bone	26 (7%)	1 (4%)	23 (88%)	2 (8%)
Other	117 (32%)	17 (14%)	91 (78%)	9 (8%)

A: Individual lesion responses by RECIST 1.1 criteria at week 8

Baseline site	CR/PR	SD	PD
Lymph node	1.23 (0.66-2.46)	1.11 (0.83-1.48)	1.10 (0.56-2.17)
Lung	0.72 (0.35-1.50)	0.90 (0.66-1.21)	0.78 (0.38-1.60)
Liver	N/A	1.14 (0.69-1.90)	1.22 (0.57-2.61)
Bone	N/A	1.17 (0.76-1.82)	N/A
Other	1.24 (0.64-2.40)	0.91 (0.69-1.19)	0.84 (0.37-1.91)

B: Hazard ratios for overall survival by lesion site at week 8

Supplementary Table 2

Site of new lesion	Hazard ratio (95% CI)	*P* value
Lung	1.65 (0.94-2.91)	0.08
Liver	1.33 (0.73-2.42)	0.35
Other	1.14 (0.61-2.11)	0.69
Bone	1.34 (0.70-2.58)	0.38
Lymph node	0.71 (0.32-1.58)	0.40
Brain	N/A	N/A

***Take Home Message**

Assessment by RECIST is widely used to assess treatment response in metastatic RCC patients, but is limited in scope. We show radiological heterogeneity within a patient is important. Progressive disease with ≥1 new disease sites is indicative of worse survival.

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