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A Study of Pazopanib Safety and Efficacy in Patients With Advanced Clear Cell Renal Cell Carcinoma and ECOG Performance Status 2 (Pazo2): An Open label, Multicentre, Single Arm, Phase II Trial

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Abstract

Patients with advanced kidney cancer and who are unwell are often deemed unsuitable for treatment. Pazo2 was a trial recruiting 75 patients; 70.8% patients did not develop "intolerable" side effects, with 56.9% still alive and cancer-free 6-months after starting pazopanib. Therefore, pazopanib could be a treatment option for patients who cannot receive or tolerate immune checkpoint inhibitors.

Aim: Patients with advanced renal cell carcinoma and poor performance status (PS≥2) are often deemed unsuitable for treatment. The Pazo2 trial aimed to assess tolerability and efficacy of pazopanib as first-line treatment in renal cancer patients with ECOG PS2. **Methods:** Pazo2 was a prospective, single arm, open label, multicentre, phase II trial, conducted in 26 UK centres. Eligible patients were aged ≥18 years, with advanced or metastatic renal cancer and a clear cell component (aRCC), measurable disease as per RECIST Criteria 1.1, and ECOG PS2. Co-primary outcomes, assessed at 6-months after patients entered the trial, were tolerability, defined as the proportion of patients who did not develop "intolerable" adverse events, and efficacy, defined as the proportion of all patients who were progression-free and alive. **Results:** Between February 21, 2013 and August 12, 2016, 75 patients were registered. Median age was 68.6 years (IQR 64.6-76.0), 100% ECOG PS2, 62.7% 'poor risk' (International Metastatic Renal-Cell Carcinoma Database Consortium). Of the 65 evaluable patients, 70.8% (95% CI: 58.8, 80.4) did not develop "intolerable" adverse events and 56.9% (95% CI: 44.8, 68.2) were still alive and progression-free 6 months after starting pazopanib. Twenty-seven patients developed serious adverse events deemed to be related to pazopanib. **Conclusion:** These data suggests that pazopanib is tolerated and effective in aRCC patients with PS2 and represents a treatment option for patients who cannot receive or tolerate immune checkpoint inhibitors.

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Keywords: Advanced clear cell renal cell carcinoma, Pazopanib, Clinical trial, Poor performance status

Introduction

Treatment of advanced or metastatic renal cell carcinomas (aRCC) has improved during the past decade. However, management of patients with poor performance status (ECOG PS≥2) remains suboptimal. These patients have a poor prognosis and are often excluded from treatment because it is felt that they are unable

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to derive significant benefit from it and/or because of their perceived inability to withstand treatment-related side effects. As a result, there is no accepted standard of care, and no clear guidelines of how best to treat patients with poor PS.

Trials of first-line treatments for aRCC have shown significant improvements of progression-free survival rates (PFS) and overall survival rates (OS). These studies included trials of tyrosine kinase inhibitors (TKIs) targeting vascular endothelial growth factor receptors (VEGFRs)[1-4] and, more recently, trials of either 2 immune checkpoint inhibitors (ICI) or a combination of 1 ICI with a TKI.[5-9] However, within the majority of these trials, aRCC patients with ECOG PS≥2 or Karnofsky PS < 70% were not eligible; and only 1 permitted patients with ECOG PS 0-2[3]. Therefore, limited data exist regarding the tolerability and efficacy of treatments for aRCC patients with poor PS.

Pazopanib is a TKI targeting VEGFR -1, -2 and -3, as well as other signalling pathways involved in tumour growth.[10] A large phase III trial in aRCC patients with PS 0-1 showed that pazopanib was not inferior, in terms of PFS, to sunitinib, a VEGFR targeting TKI, which at that time represented the standard of care for aRCC.[11] In addition, the same trial demonstrated that pazopanib was better tolerated than sunitinib with better health-related quality of life (QoL) scores.

Between 13 and 29% of all aRCC patients present with poor PS.[12,13] Therefore, the Pazo2 trial was designed to address this knowledge gap and establish a better standard of care for these patients. The aim of Pazo2 was to assess tolerability and efficacy of pazopanib as first-line treatment in aRCC patients with ECOG PS2.

Methods

Trial design and patients

This single arm, open label phase II clinical trial took place in 26 UK hospitals centres. Ethical approval was obtained from East Midlands – Nottingham 2 Research Ethics Committee (11/EM/0450) on February 24, 2012. Clinical trial authorisation was obtained from the UK's competent authority, the Medicines and Healthcare Products Regulatory Authority. An independent Data Monitoring Committee (DMC) operated in accordance with a trial specific charter based on the template created by the Damocles Group[14], providing independent trial oversight.

Eligible patients were aged ≥18 years, with aRCC with a clear cell component, measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST) Criteria v1.1,[15] and a life expectancy of ≥12 weeks. Patients were ECOG PS2,[16] had received no prior systemic therapy for aRCC, and had adequate organ function.

Patients were ineligible if they had major surgery or trauma < 4 weeks or received radiotherapy < 2 weeks prior to starting treatment. Patients were also excluded if they had non-healing wounds, fractures, or ulcers, or a history of brain metastases or active seizure disorders, uncontrolled hypertension, prolonged QT interval or a significant cardiac event within past 6-months or cerebrovascular accident in the past 12 months or were on medications with known strong Cytochrome P450 Family 3 Subfamily A Member 4 inhibition.

Pregnant and breast-feeding women were excluded. Those with reproductive potential were required to use effective contraception. All patients gave written informed consent.

At the time of Pazo2, ECOG was the standard assessment criteria accepted in the UK; we have subsequently assumed that ECOG PS2 was equivalent to Karnofsky PS < 70, ≥60.[17]

Procedures

800mg pazopanib was taken once daily PO until disease progression, death, unacceptable toxicity, or withdrawal of consent for any reason. Patients also received best supportive therapy according to institutional guidelines. The study drug was provided free of charge, first by GlaxoSmithKline and then Novartis.

Two dose reductions were permitted in a stepwise fashion to 600mg and 400mg. If a side effect did not recur or worsen, the dose could be increased, in a stepwise fashion. Dose interruptions of up to 21 days were permitted.

Patients attended follow-up visits, where data was collected, at weeks 2, 4, 6 and 8, and then 3-monthly for a minimum of 24-months or until death. Assessments for tumour response were carried out at weeks 6 and 12, and then 8-weekly within the first year; from week 52 onwards, CT scans were 12-weekly. To reflect clinical practice, local review and reporting of disease was conducted without central blinded review.

Outcomes

Co-primary outcomes were tolerability and efficacy. Tolerability assessed as the proportion of patients who did not develop "intolerable" AEs within 6-months from trial entry. AEs deemed as "intolerable" satisfied all the following definitions:

- A Grade 3 or 4 AE according to National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) version 4.0;[18]
- Rated as being possibly, probably, or definitely related to pazopanib by the investigator, and;
- Rated as a serious (S)AE, or resulting in discontinuation of pazopanib for greater than 21 days.

The onset date of SAEs or the first day treatment was stopped were used as the dates of intolerable events. Patients who died prior to completing 6 months of treatment without having an event were counted as tolerable.

Efficacy was assessed as the proportion of patients alive and progression-free at 6 months. Progression was assessed via local review and defined as per RECIST Criteria v1.1[15] with a window of ± 21 days deemed acceptable for the 6-month scan.

Key secondary outcome measures included: Progression-free survival, defined as the number of days from registration until radiological disease progression or death from any cause. Patients alive and progression-free were censored at the date last known to be progression-free; overall survival, defined as the number of days from registration until death from any cause. Patients alive at the end of the trial were censored at the date last known to be alive; objective response rate (ORR), defined as proportion of patients achieving complete or partial response by RECIST v1.1; clinical benefit rate, defined as proportion of patients achieving complete

response, partial response or stable disease by RECIST v1.1; treatment safety included the collection of Grade ≥3 AEs according to NCI-CTCAE v4.03[18] from consent until 30 days after administration of last treatment; drug dose administered, defined as the incidence of dose reductions, interruptions, escalations and discontinuations, and; dose intensity, defined as the total dose prescribed as a proportion of the planned protocol dose during tolerability assessment and overall.

Statistical analysis

The Bryant and Day's 2-Stage Design was used to obtain a joint evaluation of the co-primary outcomes of tolerability and efficacy[19] with 5% α and 85% power. Tolerability rate within 6-months was assumed to be 60% with an undesirable tolerability of 40%. One interim analysis was planned and required treatment to be tolerable in at least 12 out of 26 patients and 8 out of 26 patients to be alive and progression-free to proceed. As published by Gore *et al.*,[12] efficacy (based on 6-month PFS) was assumed to be 44%. We set an undesirable 6-month PFS of < 25%. The DMC identified no issues regarding data quality or patient safety in the initial 26 patients recruited.

Final analysis included only patients who were assessable for both tolerability and efficacy and required treatment to be tolerable in at least 34 patients, and 23 patients to be alive and progression-free (in total across both stages) to conclude pazopanib was tolerable and effective, and warrants further investigation. A drop-out rate of 10% was permitted resulting in a total of 75 patients recruited.

Sensitivity analysis of tolerability, included all available tolerability data regardless of whether efficacy data was available, and a worst-case scenario, which classified all unknown data as intolerable. Sensitivity analysis of efficacy, included all available efficacy data regardless of whether tolerability data was available, and a worst-case scenario, whereby patients were classified as efficacy failures if a CT scan was not performed, and includes those who withdrew prior to completing 6-months treatment.

PFS and OS were calculated using the Kaplan Meier method. Response rate and clinical benefit rate were calculated by dividing the numbers of responders by the total number of patients recruited. Duration of response is reported descriptively due to limited patient number.

The primary outcome measures were analysed using only those patients who were evaluable, after which the sensitivity analyses were performed. All other data, including secondary outcomes, were analysed using all registered patients.

As a *post-hoc* analysis, patients were categorised according to the International Metastatic Renal-Cell Carcinoma Database Consortium (IMDC)'s prognostic model.[20]

Analyses were performed using Stata v16.1.

The final date of database lock was 10-Sep-2020.

Results

Between February 21, 2013 and August 12, 2016, 243 patients were screened, 75 of whom were registered (Figure 1). Ten patients were excluded from the primary outcome analysis; 6 patients did not have a 6-month scan performed, no target lesions were identified at baseline in 2 patients, and 2 patients withdrew prior to the 6-month time point (Figure 1). Baseline characteristics of all registered patients are described in Table 1. Median age of patients was 68.6 years (range 48.2-87.4) and 54 (72.0%) were male. All patients were ECOG PS2 and 47 (62.7%) classified as IMDC poor-risk. Thirty-eight patients (50.6%) had undergone previous nephrectomy. All patients had metastatic disease.

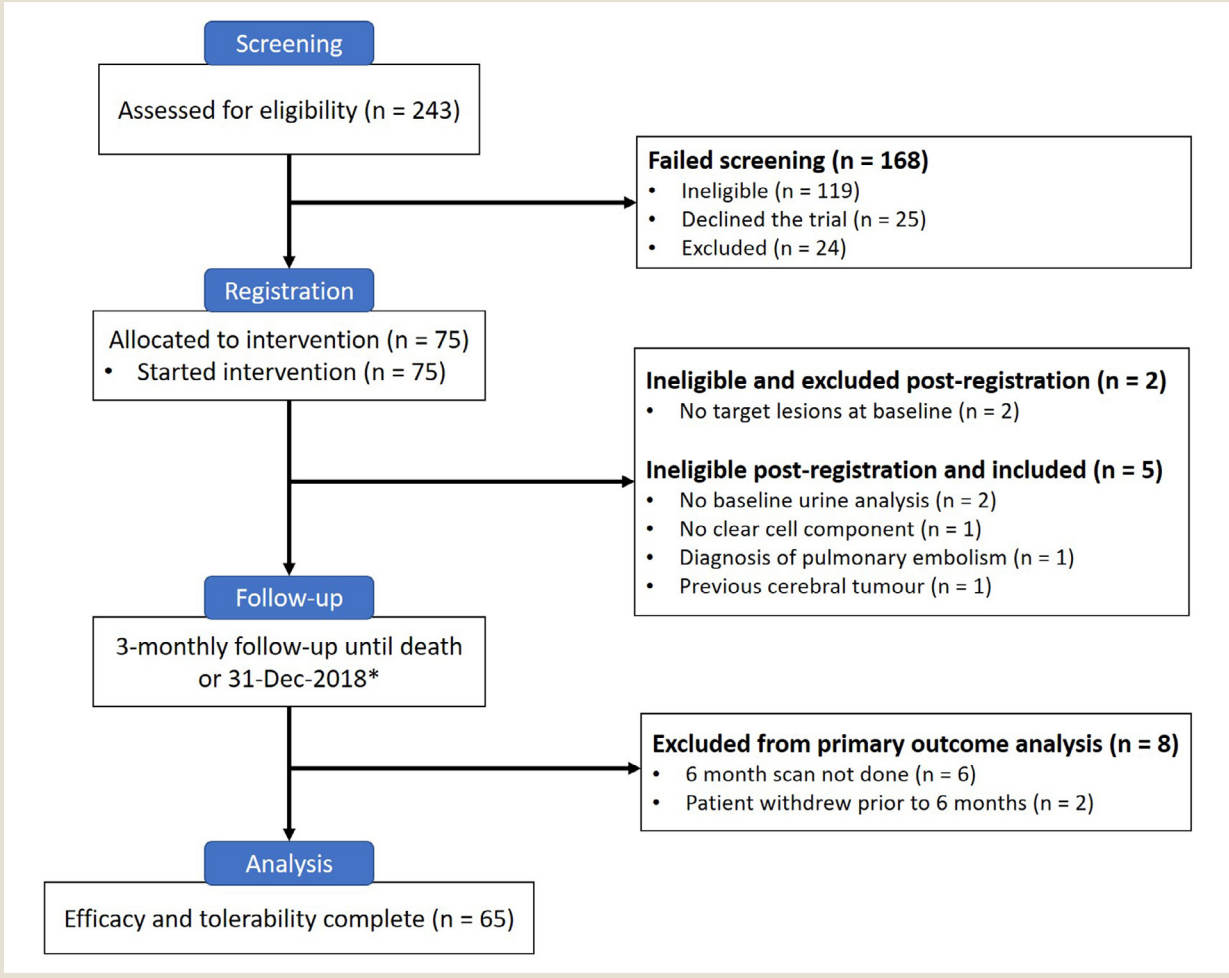
Table 1 Patient Characteristics of All Registered Patients.

Patient characteristics		N = 75 n (%)
Age (y)		
	Median	68.6
	Range	48.2 - 87.4
Sex		
	Male	54 (72.0)
	Female	21 (28.0)
ECOG Performance Status		
	2	75 (100.0)
IMDC Prognostic Indicator		
	Intermediate	28 (37.3)
	Poor	47 (62.7)
Previous Nephrectomy		
	No	37 (49.3)
	Yes	38 (50.7)
Histopathology		
Clear cell component		
	No	1 (1.3)
	Yes	74 (98.7)
Sarcomatoid component		
	No	66 (88.0)
	Yes	8 (10.7)
	Unknown	1 (1.3)
Number of Metastatic Sites		
	1	36 (48.0)
	2	19 (25.3)
	3	18 (24.0)
	4	2 (2.7)
Subsequent Second-Line Therapy During Trial		
	Tyrosine kinase inhibitor	16 (21.3)
	mTOR inhibitor	4 (5.3)
	Tyrosine kinase and mTOR inhibitors	1 (1.3)
	None	54 (72.0)

Abbreviation: mTOR = mammalian target of rapamycin.

Median pazopanib treatment duration was 5.6 months (interquartile range (IQR) 7.8-14.5; range 0.0-41.9) (Figure 2). There were 406 dose modifications reported; 21 (28.0%) patients had at least 1 dose reduction, and 48 (64.0%) had at least 1 dose interruption (dose reduced to 0) followed by dose escalation(s) (Supplemental Appendix 2). Not all dose reductions, interruptions, or discontinuations were due to toxicity, but also included progression, clinician's choice, patient's choice and/or a combination of these. The most common reason for permanent discontinuation

Figure 1 Pazo2 trial profile. Consort diagram showing all patients approached for trial entry through to those included in final analysis of the primary outcome. Registered patients were excluded from the final analysis at 2 points in the pathway. Firstly, those found to be ineligible following registration due to not having measurable disease and those who did not have outcome data at the 6-month timepoint either due to missed scans or patient withdrawals. * This date allowed a minimum follow-up period of two years from the last patient recruited. Note: All adverse event, trial treatment data, and secondary outcomes are reported for all 75 registered patients.



of pazopanib was progression alone (24 of 75 patients). Forty-six patients discontinued treatment due to progression with or without other reasons, while 38 patients stopped treatment for toxicity with or without other reasons (Supplemental Appendix 2).

Of the 65 evaluable patients included in the primary outcome analyses, 46 were found to tolerate treatment (70.8% [95% CI: 58.8, 80.4]) and 37 were found to be alive and progression-free at 6-months (56.9% [95% CI: 44.8, 68.2]; Table 2).

Median PFS was 9.0 months (95% CI: 6.8, 12.7) with median OS amongst of 19.4 months (95% CI: 13.2, 24.7). Response rate/ORR, clinical benefit rate, and dose intensity are presented in Table 2.

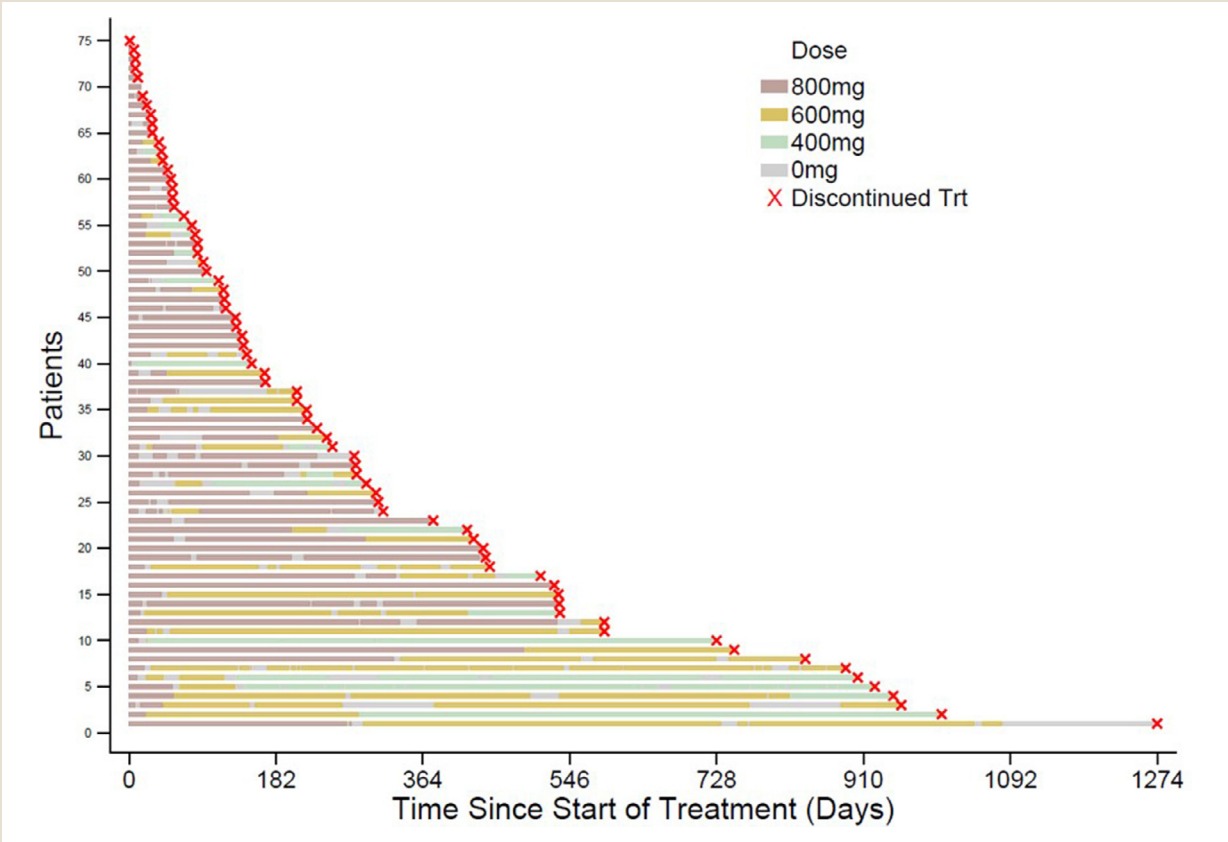
Post-hoc analysis demonstrated that the median PFS of IMDC intermediate-risk patients was 14.7 months (95% CI: 9.9, 25.7) compared to 6.3 months (95% CI: 4.3, 8.7) for those classified as poor-risk (Figure 3A). Median OS of intermediate-risk patients was 35.3 months (95% CI: 21.8, not reached) compared to 13.0 months (95% CI: 6.8, 19.4) for poor-risk patients (Figure 3B).

The initial protocol mandated collection of all AEs to monitor safety. After confirmation of an appropriate safety profile, and considering the additional burden this placed on- sites, the DMC advised that the collection of Grade $\leq$2 AEs could be halted.

There incidence of Grades $\geq$3 treatment-related AEs and those where the relatedness was unknown that occurred more than once are shown in Table 3. Out of 205 occurrences, the most common events were hypertension (72 [35.1%]), and fatigue (27 [13.2%]).

There were 77 SAEs, reported by 49 patients. Only 27 (35.1%) were deemed related to trial treatment; 22 resolved without sequelae, 4 resolved with sequelae, and 1 had a fatal outcome. The most common serious adverse reaction was vomiting, which occurred 3 times in 3 separate patients.

Figure 2 Pazopanib doses delivered in all registered patients. Per patient trial dosing ordered by treatment duration. Each patient is represented by a horizontal bar, day 0 is the day that patient started trial medication. The bar is coloured depending on the dose being taken at that point showing dose reductions, interruptions, and escalations for each patient. The red X denotes the point at which the patient permanently discontinued trial treatment.



Discussion

The Pazo2 trial assessed efficacy and tolerability of pazopanib as first-line treatment in aRCC patients with ECOG PS2. Both primary outcomes were met, suggesting that pazopanib could represent a treatment option for this group of patients.

We acknowledge that Pazo2 reports longer median OS and PFS than demonstrated in the TemPa[21] and FLIPPER[22] trials in which safety and efficacy of pazopanib were studied in IMDC intermediate and poor-risk patients. Potential reasons for this discrepancy include the small size of our trial and/or use of the ECOG PS assessment which, although evaluated by local recruiting clinicians, still requires significant patient's input. Another contributing factor could be the small size and weaker power of previous studies.

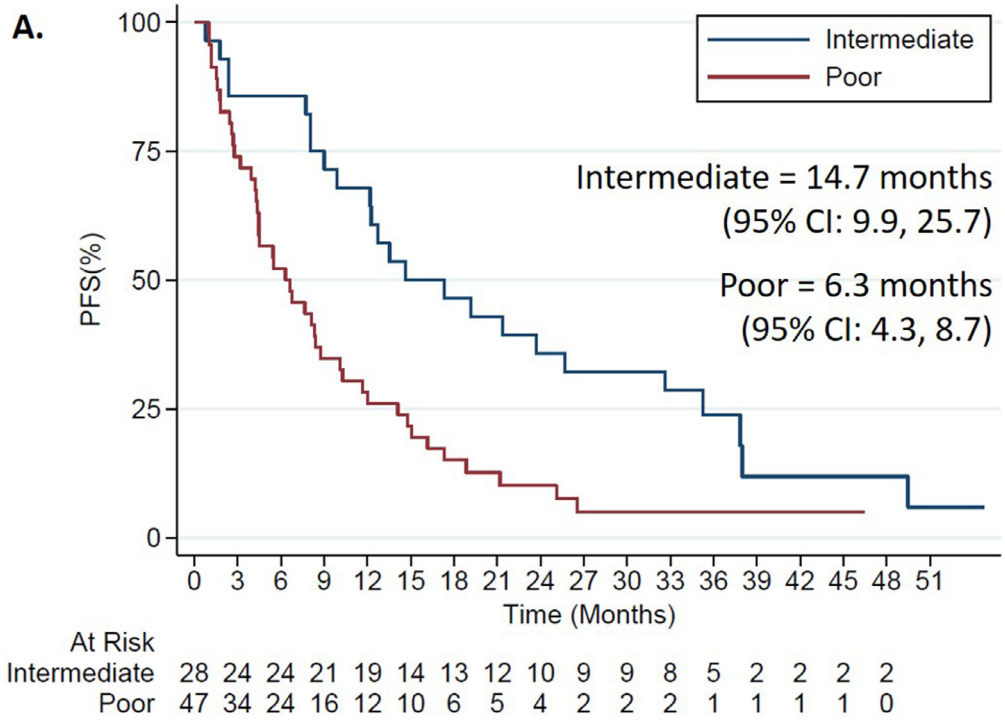
Blinded, central review of progression outcomes was not used during the Pazo2 trial. Rather, we made the conscience decision to use a risk-adapted, pragmatic approach so as to reflect standard clinical practice. We note, however, that RECIST v1.1 was used as per current standard of care and all data to evaluate response was collected, cleaned, and reviewed to confirm each assessment.

Several clinical trials have demonstrated that immunotherapeutic agents and immunotherapy-based combination strategies have improved outcomes and represent the standard first-line treatment for aRCC patients.[23] Although these trials included patients with IDMC intermediate and poor-risk, patients with PS2 were usually excluded.[5-9] It is also worth mentioning that the majority of patients enrolled in these trials had a good PS (Karnofsky 90-100). Patients with aRCC, with PS≥2 were permitted in a randomised phase II study of 2 TKIs; however, these patients represent only 12.7% of the intention-to-treat population making it difficult to assess the impact of treatment in this poor PS subgroup.[3]

Patient's performance status represents 1 of the IDMC criteria, however, the exclusion of patients with PS≥2 from most trials suggests that these patients are deemed to be unfit for treatment or for trial entry regardless of their IMDC classification. As mentioned above, the efficacy and tolerability of immunotherapy-based combinations in aRCC patients with PS2 has not yet been assessed. Such lack of data is not reflected in the licensed indication, but funding for these treatments is not available from the UK National Health Service for aRCC patients with PS≥2.

Although the Pazo2 trial met its safety outcome, a significant number of AEs were observed during the trial. Similarly, immunotherapy-based combinations were often associated with AEs

Figure 3 IMDC-based progression-free survival and overall survival time of all registered patients. (A). Kaplan Meier curves showing median PFS amongst intermediate and poor risk patients. Sixty-seven patients progressed radiologically or died, and 8 patients remained alive and progression-free. Two patients who withdrew consent were censored; one patient less than 1-month after registration and 1 at 17-months post-registration. The remaining 6 patients were followed up for between 33- and 54-months post-registration. (B). Kaplan Meier curves showing median OS amongst intermediate and poor risk patients. Fifty-eight patients have died. Three patients who withdrew consent were censored; one patient less than 1-month after registration, 1 at 14-months post-registration, and 1 at 17-months post-registration. The remaining 14 patients were followed up for between 33- and 58-months post-registration.NR, not reached.



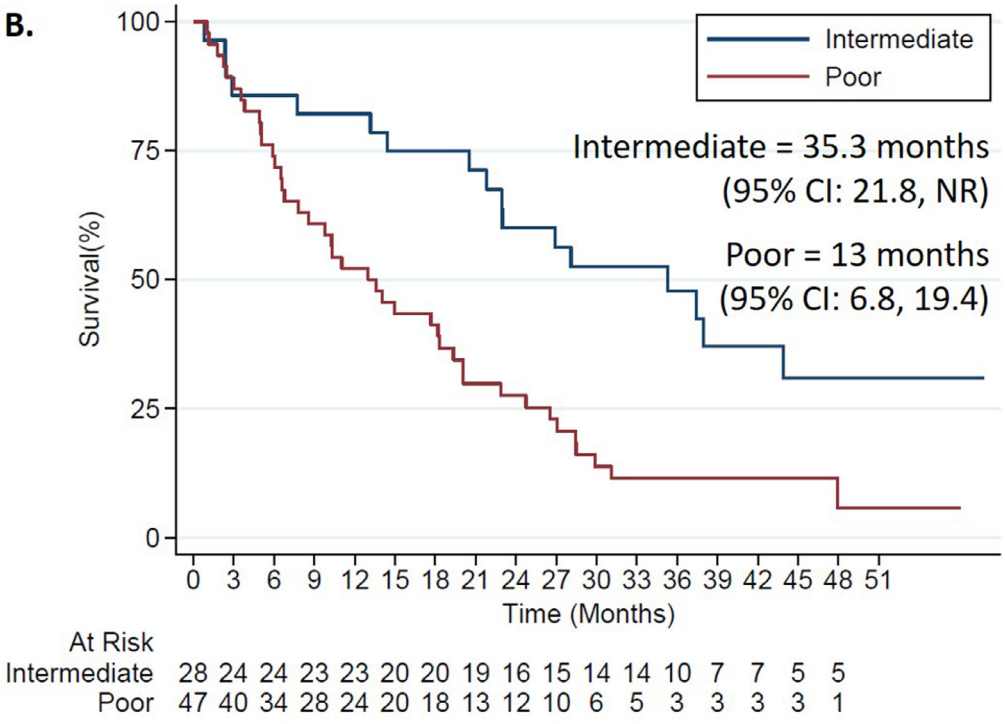


Table 2 Primary and Secondary Outcomes of the Pazo2 Trial.

Outcomes	Number of Patients Achieving Outcome	Proportion	95% CI
Primary Outcomes			
Tolerability[a]	46/65	0.708	0.588, 0.804
Sensitivity analysis[b]	49/73	0.671	0.557, 0.768
Worst-case scenario[c]	49/75	0.653	0.541, 0.751
Efficacy[a]	37/65	0.569	0.448, 0.682
Sensitivity analysis[d]	37/65	0.569	0.448, 0.682
Worst-case scenario[e]	37/73	0.507	0.395, 0.618
Secondary Outcomes[f]			
Progression-free survival			
6-mo (%)	-	65	53, 75
Median overall (mo)[g]	-	9.0	6.8, 12.7
Overall survival	58/75		
6-mo (%)	-	78	67, 86
Median overall (mo)[g]	-	19.4	13.2, 24.7
Response rate/ORR	22/75	0.29	0.20, 0.40
Clinical benefit rate	62/75	0.83	0.73, 0.90
	N	Median (IQR)	Range
Dose intensity (%)			
6-mo	75	91.8 (72.2, 100.0)	37.7, 100.0
Overall	75	87.4 (66.5, 100.0)	41.8, 100.0

[a] Analysed in all 65 evaluable patients.
[b] Sensitivity analysis includes all available tolerability data regardless of whether efficacy data are available; 73 patients in total.
[c] The worst-case scenario classifies all unknown data as intolerable; 75 patients in total.
[d] Sensitivity analysis includes all available efficacy data regardless of whether tolerability data are available; 65 patients in total.
[e] The worst-case scenario classifies patients as efficacy failures if a CT scan was not performed, and includes those who withdrew prior to completing 6-months treatment; 73 patients in total.
[f] Analysed in all 75 registered patients.
[g] Based on Kaplan Meier estimations.CI, confidence intervals; IQR, interquartile range; ORR, overall response rate.

(Grade ≥3), in particular AEs were seen in > 70% of the patients treated with combinations of immunotherapy and TKIs.[7]

Until new data are available, the results of the Pazo2 trial appear to support the use of pazopanib in aRCC patients with PS2. Pazopanib could also represent a treatment option for patients who are frail or elderly and deemed unsuitable for immunotherapy because of a perceived short life expectancy or their reduced capacity to withstand severe side effects.[24,25] Flexible dosing and acceptable safety profile allows pazopanib treatment to continue in these vulnerable patients as clinically required. In our study, we report that 21/75 patients (28.0%) were able to receive subsequent second-line therapy within the timeframe of the trial, suggestive of the broader benefit of pazopanib. Pazopanib could also represent a viable option when hospital visits must be minimised. This can either be due to patient-driven choice or, as seen during the COVID-19 pandemic, when many centres issued guidance to convert intravenous-based treatments to oral/subcutaneous regimens where possible.[26]

In summary, results from the Pazo2 trial suggest to offer pazopanib to untreated aRCC patients with PS2. Patients with aRCC who are deemed unsuitable for immunotherapy-based combinations could also be considered for treatment with this drug.

Clinical Practice Points

- Treatment of advanced or metastatic renal cell carcinomas (aRCC) with poor performance status (ECOG performance status [PS]>2) remains suboptimal. Between 13 and 29% of all aRCC patients present with poor PS and, in the majority of previously published trials of first-line treatments, ECOG PS≥2 or Karnofsky PS < 70% were not eligible. Therefore, limited data exist regarding the tolerability and efficacy of treatments for aRCC patients with poor PS. The Pazo2 trial was designed to address this knowledge gap and establish a better standard of care for these patients.
- The aim of Pazo2 was to assess tolerability and efficacy of pazopanib as first-line treatment in aRCC patients with ECOG PS2. Both primary outcomes of Pazo2 were met, suggesting that pazopanib could represent a treatment option for this group of patients.
- The results of the Pazo2 trial support the use of pazopanib in aRCC patients with PS2. Pazopanib could also represent a treatment option for patients who are frail or elderly and deemed unsuitable for immunotherapy because of a perceived short life expectancy or their reduced capacity to withstand severe side effects. Flexible dosing and acceptable safety profile allows pazopanib treatment to continue in these vulnerable patients as clinically required. In addition, pazopanib could also represent a viable option when hospital visits must be minimised. This can either be due to patient-driven choice or, as seen during the COVID-19 pandemic, when many centres issued guidance to convert intravenous-based treatments to oral/subcutaneous regimens where possible.

Table 3 Treatment-related or Unknown Related grade ≥3 Adverse Events Occurring More Than Once in all Registered Patients.

Category	Toxicity	Number Patients Affected	Number of AE Occurrences		
			Related	Unknown Related	Total
Blood and lymphatic system disorders	Anaemia	1	1	2	3
Gastrointestinal disorders	Abdominal pain	4	0	4	4
	Diarrhea	2	4	0	4
	Mucositis oral	2	2	0	2
	Nausea	3	2	1	3
	Vomiting	3	2	1	3
General disorders and administration site conditions	Fatigue	19	25	2	27
	Pain	2	0	2	2
Infections and infestations	Lung infection	2	0	2	2
	Urinary tract infection	3	0	3	3
Investigations	Alanine aminotransferase increased	7	4	4	8
	Alkaline phosphatase increased	1	2	0	2
	Aspartate aminotransferase increased	2	1	1	2
	Blood bilirubin increased	2	0	2	2
	GGT increased	3	3	1	4
	INR increased	2	4	0	4
	Other investigations	3	11	1	12
Metabolism and nutrition disorders	Anorexia	1	2	0	2
	Hypertriglyceridemia	3	9	0	9
	Hyponatremia	3	3	1	4
Musculoskeletal and connective tissue disorders	Back pain	2	0	2	2
	Bone pain	6	1	6	7
	Muscle weakness lower limb	4	0	4	4
Nervous system disorders	Paraesthesia	2	1	1	2
Renal and urinary disorders	Chronic kidney disease	1	3	0	3
	Proteinuria	3	6	0	6
Respiratory, thoracic and mediastinal disorders	Dyspnoea	5	0	7	7
Vascular disorders	Hypertension	21	71	1	72
Total			157	48	205

Data Sharing Statement

Participant data and the associated supporting documentation will be available within 6 months after the publication of this manuscript. Details of our data request process is available on the CRCTU web site. Only scientifically sound proposals from appropriately qualified research groups will be considered for data sharing. The decision to release data will be made by the CRCTU Director's Committee, who will consider the scientific validity of the request, the qualifications and resources of the research group, the views of the Chief Investigator and the trial steering committee, consent arrangements, the practicality of anonymising the requested data and contractual obligations. A data sharing agreement will cover the terms and conditions of the release of trial data and will include publication requirements, authorship and acknowledgments and obligations for the responsible use of data. An anonymised encrypted dataset will be transferred directly using a secure method and in accordance with the University of Birmingham's IT guidance on encryption of data sets.

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Disclosure

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2022.06.012.

CRediT authorship contribution statement

Anjali Zarkar: Investigation, Writing – original draft, Writing – review & editing. **Sarah Pirrie:** Data curation, Formal analysis, Methodology, Validation, Writing – original draft, Writing – review & editing. **Clive Stubbs:** Project administration, Writing – original draft, Writing – review & editing. **Anne-Marie Hodgkins:** Project administration, Writing – review & editing. **David Farrugia:** Investigation, Writing – review & editing. **Kathryn Fife:** Investigation, Writing – review & editing. **Carey MacDonald-Smith:** Investigation, Writing – review & editing. **Naveen Vasudev:** Investigation, Writing – review & editing. **Emilio Porfiri:** Conceptualization, Funding acquisition, Investigation, Supervision, Writing – original draft, Writing – review & editing.

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