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# Phase 2 trial of linifanib (ABT-869) in patients with advanced renal cell cancer after sunitinib failure

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ABSTRACT

*Purpose:* This study assessed the efficacy and safety of linifanib in patients with advanced renal cell carcinoma (RCC) who were previously treated with sunitinib.

*Materials and methods:* This open-label, multicentre, phase 2 trial of oral linifanib 0.25 mg/kg/day enrolled patients who had prior nephrectomy and adequate organ function. The primary end-point was objective response rate (ORR) per response evaluation criteria in solid tumors (RECIST) by central imaging. Secondary end-points were progression-free survival (PFS), overall survival (OS) and time to progression (TTP). Safety was also assessed.

*Results:* Fifty-three patients, median age 61 years (range 40–80) were enrolled (August 2007 to October 2008) across 12 North-American centres. Median number of prior therapies was 2 (range 1–4); 43 patients (81%) had clear-cell histology. ORR was 13.2%, median PFS was 5.4 months (95% Confidence Interval (CI): 3.6, 6.0) and TTP was the same; median OS was 14.5 months (95% CI: 10.8, 24.1). The most common treatment-related adverse events (AEs) were diarrhoea (74%), fatigue (74%) and hypertension (66%), and the most common treatment-related Grade 3/4 AE was hypertension (40%).

*Conclusions:* Linifanib demonstrated clinically meaningful activity in patients with advanced RCC after sunitinib failure. At 0.25 mg/kg/day, significant dose modifications were required. An alternative, fixed-dosing strategy is being evaluated in other trials.



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## 1. Introduction

The most common kidney cancer in adults is renal cell cancer (RCC).[1] Approximately 85% of RCC tumors have clear-cell histology, characterised by over-expression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF).[2,3] As VEGF and PDGF tyrosine kinases mediate tumor progression via multiple mechanisms, their simultaneous inhibition by linifanib may result in greater antitumor activity.[4–6] Nearly one-third of patients with RCC have metastatic disease at initial diagnosis and approximately one-fourth of patients with localised disease develop metastases following nephrectomy.[1,3,7] Cytokine-based therapy has been associated with low response rates and significant treatment-related toxicities.[2,3]

Treatments approved in the United States for patients with untreated, advanced RCC, based on improved progression-free survival (PFS), include the multi-targeted tyrosine-kinase inhibitors (TKIs) sunitinib and pazopanib, the dual TKI and serine/threonine kinase inhibitor, sorafenib,[8–10] the regimen of bevacizumab with interferon alpha[11] and the selective inhibitor of mammalian target of rapamycin (mTOR), temsirolimus.[12,13] Optimal treatment regimens for advanced RCC following failure of first-line TKI therapy have been under evaluation. Trials evaluating inhibitors of vascular endothelial growth factor receptor (VEGFR) and different cellular pathways such as mTOR[14–17] show that patients with post-therapy progressive disease (PD) may respond to another TKI with different target specificities and/or pharmacologic properties. The mTOR inhibitor everolimus is approved for advanced RCC following sunitinib or sorafenib failure.[18] A phase 3 trial of temsirolimus[19] versus sorafenib as second-line therapy in advanced RCC is ongoing. In a recent phase 3 trial, axitinib showed superiority to sorafenib in terms of PFS.[20,21]

Linifanib (ABT-869) is a novel, adenosine triphosphate competitive inhibitor, selective for all VEGFR and platelet-derived growth factor receptor (PDGFR) tyrosine kinases with minimal activity against unrelated receptor tyrosine kinases, cytosolic tyrosine kinases and serine/threonine kinases.[22] A phase 1 study in patients with refractory solid malignancies provided evidence of the safety and activity of single-agent linifanib.[23] Dose-limiting toxicities of hypertension and proteinuria were seen at 0.30 mg/kg; therefore, the recommended phase 2 dose was 0.25 mg/kg once daily with continuous dosing.[23] This current phase 2 study[24] assessed the efficacy and safety of linifanib in patients with advanced RCC after sunitinib failure.

## 2. Materials and methods

### 2.1. Patients

Patients were adults with advanced RCC, prior nephrectomy, $\geqslant 1$ unidimensionally measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST),[25] who had disease progression within 100 days pre-screening following at least two cycles (12 weeks) of sunitinib therapy. Sunitinib failure was defined as treatment discontinuation due to disease progression. Additional eligibility criteria included Eastern Cooperative Oncology Group Performance Score (ECOG PS) 0–1, life expectancy of at least 4 months, and adequate bone marrow, renal and hepatic function. Exclusion criteria included anti-cancer therapy or major surgery within 21 days before linifanib administration and prior treatment with a TKI other than sunitinib or sorafenib (prior bevacizumab was permitted). All patients gave written informed consent.

### 2.2. Study design and treatment

This single-arm, open-label, multicentre phase 2 trial assessed the efficacy and safety of linifanib 0.25 mg/kg, administered once daily, fasting, at bedtime until disease progression or intolerable toxicity. Treatment was discontinued if patients required radiotherapy, surgery or alternate anti-neoplastic agents due to tumor progression. Independent ethics committees and/or institutional review boards of participating institutions approved the protocol. The study was conducted in accordance with the Declaration of Helsinki and all applicable regulations and guidelines governing clinical study conduct.

### 2.3. Assessments

Within 21 days before the first linifanib dose, a physical examination, assessment of ECOG PS, a pregnancy test for female patients of childbearing potential and laboratory tests were conducted. Baseline radiographic tumor assessments included CT scans of the chest and abdomen and optional dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). Optional fluorodeoxyglucose positron emission tomography (FDG-PET) scans were performed at three selected study sites with PET-scanning capabilities.

Clinical disease progression was assessed at each visit. Radiographic tumor assessments were performed using RECIST[25] every 8 weeks and at the final visit. Assessments were implemented by a central imaging centre, and the readers were not blinded to study and sequence. Post-baseline DCE-MRI scans at Day 15 assessed changes in vascular permeability and endothelial surface area ($K^{trans}$).[26] Post-baseline FDG-PET scans at the end of the first 8 weeks, with CT attenuation when available, evaluated tumor metabolic activity as assessed by standard uptake value (SUV).[27]

The primary efficacy end-point was objective response rate (ORR), defined as the percentage of all dosed patients with confirmed CR or PR based on RECIST[25] by central imaging centre. Complete response or PR required confirmation at two assessments at least 28 days apart. Secondary efficacy end-points included PFS, overall survival (OS) and time to progression (TTP). A subgroup analysis evaluated PFS and OS by Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic risk groups based on corrected serum calcium, haemoglobin and Karnofsky performance status.[28]

Safety evaluations included physical examinations, laboratory tests, and assessment of ECOG PS and adverse events (AEs).

### 2.4. Pharmacokinetics

Blood samples were collected on Days 8, 15, 29, 50 and 77, and analysed for plasma concentration of linifanib using liquid

chromatography and tandem mass spectrometry. A non-linear mixed-effect population modelling approach with NONMEM® software described the disposition of linifanib and identified significant covariates.

### 2.5. Statistical analysis

A sample size of 44 patients was required to test the null hypothesis that the response rate to linifanib was ⩽5% compared with the alternate hypothesis that ORR was ⩾15%, with 80% power and a 1-sided type 1 error rate of 0.10. A target enrollment of approximately 50 patients accounted for potential dropouts.

The primary efficacy end-point was calculated for all dosed patients with at least one measurable lesion at baseline. The proportion of patients with a confirmed complete response (CR) or partial response (PR) was estimated based on tumor assessment by the central imaging centre using RECIST[25] and the exact binomial distribution was used to construct a 95% Confidence Interval (CI) for the estimated ORR. Secondary efficacy end-points were analysed for all dosed patients. Statistical significance for all analyses was determined by a two-sided $p$-value ⩽0.05. Time to event end-points were analysed using the Kaplan–Meier method,[29] with median times and two-sided 95% CIs presented.

Death occurring within 56 days of the last tumor assessment was counted as an event in the PFS analysis. When progression was not observed, death was counted as an event if it occurred within one scan interval (56 days).

Patients with at least one dose of linifanib were included in all safety analyses. Safety evaluations included study-drug exposure, AEs, serious AEs, deaths, laboratory findings and vital signs. Adverse events were summarised according to MedDRA. The number and percent of patients experiencing an AE were summarised by NCI-CTCAE v3[30] toxicity grade, relationship to study drug, association with study drug discontinuation and severity. Survival information was collected at 4–6-month intervals after the last study visit and for 2 years after patients were removed from the study.

## 3. Results

### 3.1. Patient characteristics

Fifty-three patients, median age 61 years, were enrolled from August 2007 to October 2008 from 12 North American sites. Most patients had clear-cell histology and ECOG PS 1 (Table 1). The median initial daily dose was 20.0 mg (range, 12.5–25.0). The response rate to prior sunitinib treatment was 13.2%. Thirty-three patients (62%) received systemic therapy with a cytokine, bevacizumab, sorafenib and/or temsirolimus in addition to sunitinib. Seventeen patients (32%) had received two prior lines of therapy, and 10 patients (19%) had received >2 (Table 1). One patient continued on linifanib. The dose intensity of linifanib was 63.8%.

### 3.2. Efficacy

All patients were included in the efficacy analysis. Seven patients had confirmed radiographic PRs according to image assessment by central imaging for an ORR of 13.2% (95% CI: 5.5, 25.3) (Table 2, Fig. 1), six of which occurred with linifanib as second-line therapy, and one with linifanib as third-line therapy. The responders' median time on study was 12.9 months (range: 5.0–26.6 months). Two of 10 patients with

**Table 1 – Patient and disease characteristics.**

| Baseline characteristics | All patients, N = 53 |
|---|---|
| Median age, yrs (range) | 61 (40–80) |
| Male, *n* (%) | 42 (79) |
| ECOG PS, *n* (%) | |
| 0 | 19 (36) |
| 1 | 34 (64) |
| Histology, *n* (%) | |
| Clear cell | 43 (81) |
| Non-clear cell | 10 (19) |
| Number of prior systemic therapies, *n* (%) | |
| 1 | 26 (49) |
| 2 | 17 (32) |
| >2 | 10 (19) |
| Type of prior systemic therapies,[a] *n* (%) | |
| Cytokine[b] | 12 (23) |
| Sorafenib | 10 (19) |
| Temsirolimus[c] | 2 (4) |
| Bevacizumab | 9 (17) |
| Response rate to prior sunitinib (%) | 13.2 |

*Abbreviations:* ECOG PS, Eastern Cooperative Oncology Group Performance Status.

[a] All patients had received prior sunitinib therapy: 28 in first-line, 15 in second-line, 8 in third-line, 2 in fourth-line. Other prior therapies included erlotinib ($n$ = 4), gemcitabine ($n$ = 2), vaccine ($n$ = 2), zoledronic acid ($n$ = 1), ABT-510 ($n$ = 1), atrasentan ($n$ = 1). Two patients received sunitinib retreatment as a separate line of therapy. Two patients received another line of treatment after sunitinib, but prior to linifanib; both had progressed on prior sunitinib within 100 days of the linifanib study per protocol.

[b] Includes IL-2 ($n$ = 8), INFα ($n$ = 3), IL-2 plus INFα ($n$ = 1).

[c] One patient received temsirolimus in combination with bevacizumab.

**Table 2 – Efficacy results.**

| End-points | All patients, N = 53 | |
|---|---|---|
| | Central imaging | Site assessment |
| *Primary* | | |
| ORR[a], % [95% CI] | 13.2 [5.5, 25.3] | 22.6 [12.3, 36.2] |
| *Secondary* | | |
| PFS[b] median months [95% CI] | 5.4 [3.6, 6.0] | 5.8 [3.9, 7.3] |
| Number of events (%) | 43 (81.1) | 46 (86.8) |
| OS, median months [95% CI] | 14.5 [10.8, 24.1] | |
| Number of events (%) | 33 (62.3) | |

*Abbreviations:* ORR, objective response rate; PFS, progression-free survival; TTP, time to progression; OS, overall survival.

[a] All responses were confirmed at two visits >4 weeks apart.

[b] TTP was the same as PFS.

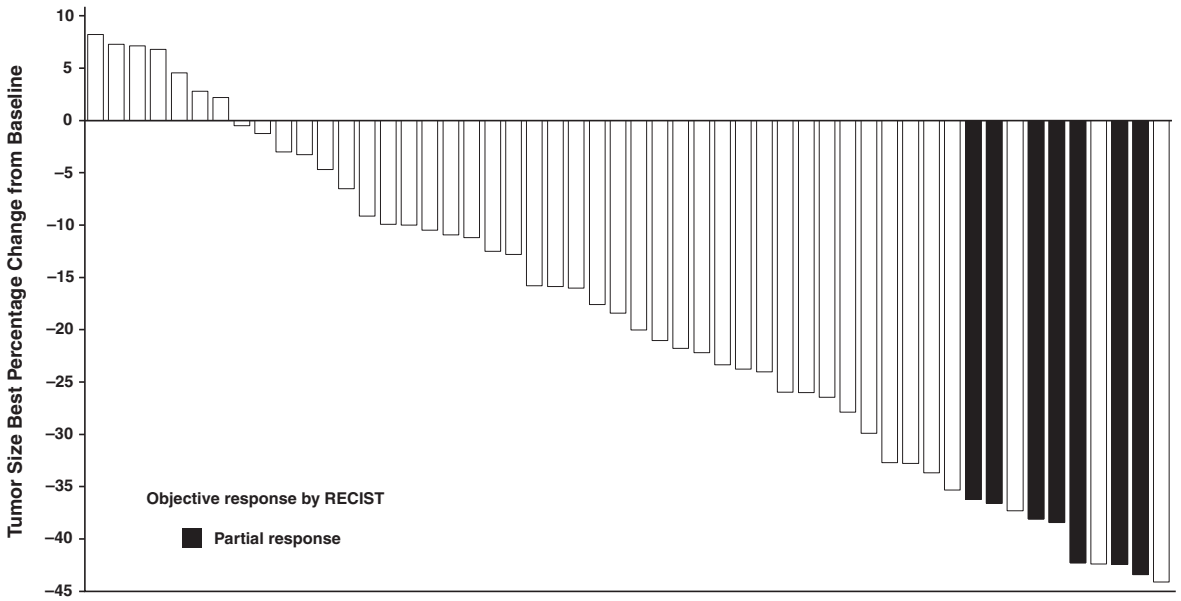


**Fig. 1 – Best percentage change from baseline in tumor size in evaluable patients treated with linifanib. Pre- and post-treatment target lesions were assessed by central imaging using RECIST.**

non-clear cell histology achieved a PR. One of the seven responders had responded to prior sunitinib therapy. The median PFS was 5.4 months (95% CI: 3.6, 6.0 months) (Table 2, Fig. 2A) and median TTP was the same; median OS was 14.5 months (95% CI: 10.8, 24.1) (Fig. 2B). Patients who had received one prior systemic therapy had similar PFS and OS, compared with those who had received more than one (PFS hazard ratio 0.80 [0.44, 1.49], $p = 0.49$; OS hazard ratio 1.28 [0.64, 2.54], $p = 0.49$). Overall, 12 of 17 patients (71%) with pre- and post-treatment DCE-MRI scans had at least a 40% reduction in $K^{trans}$, consistent with an antiangiogenic effect from linifanib. Three of 10 patients (30%) who underwent FDG-PET at baseline and at Week 8 had at least a 25% reduction in maximum SUV. Although exploratory, the FDG-PET results indicate decreased metabolic tumor activity in a subset of patients.

Data for 53 patients were available for analysis of PFS and OS according to MSKCC risk factors[28] (Fig. 3). For the nine patients in the favourable-risk group, median PFS was 7.5 months, and median OS was not reached. For the 44 patients in the intermediate/poor-risk group, median PFS was 4.0 months, and median OS was 13.3 months. Of the seven confirmed PRs per central imaging, two (22.2%) occurred in the favourable-risk group, and five (11.4%) in the intermediate/poor-risk group.

### 3.3. *Safety*

Forty-one patients discontinued therapy due to PD (clinical, radiographic or AE related to PD), eight discontinued due to AEs not related to PD, two due to withdrawal of consent and one due to surgery. The most common treatment-related AEs are shown in Table 3. Non-haematological AEs Grade 3/4 included hypertension (39.6%), fatigue (24.5%), diarrhoea (20.8%) and hand-foot syndrome (22.6%) (Table 3). Most haematological AEs were mild to moderate. The only haematological AEs occurring in $\geqslant$5% of patients were anaemia (20.8%), lymphopaenia (7.5%) and leukopaenia (5.7%). Three patients experienced Grade 3/4 haematological AEs, two (3.8%) with lymphopaenia, and one (1.9%) with neutropenia (Table 3).

Most patients had dose interruptions (84.9%) or dose reductions (66.0%) due to AEs. Dose interruption for hypertension and proteinuria were mandated by protocol. The most common AEs leading to dose interruption were diarrhoea (30.2%), hand-foot syndrome (26.4%), fatigue (20.8%), proteinuria (18.9%), hypertension (15.1%), nausea (13.2%), and vomiting (13.2%), and these were reversible. Adverse events not related to PD leading to discontinuation included fatigue, abdominal pain, nausea, vomiting, decreased appetite, decreased weight, haemoptysis and myocardial infarction. The myocardial infarction occurred in a patient with multiple cardiac risk factors, who had a prior myocardial infarction treated with angioplasty and stenting. There were two events of deep venous thrombosis; one was Grade 3, possibly related to linifanib. There were no deaths due to treatment-related AEs.

### 3.4. *Pharmacokinetics*

Pharmacokinetic data were available for 42 patients and are described by a 1-compartment model[31] with first-order absorption and elimination. Influence of covariates on pharmacokinetic parameters was assessed by following a forward addition and backward elimination method.[32] Only the most significant relationships between covariates and pharmacokinetic parameters were included in the final model. The model containing gender as a covariate on both apparent clearance and volume of distribution, and body weight as a covariate on apparent volume of distribution became the final

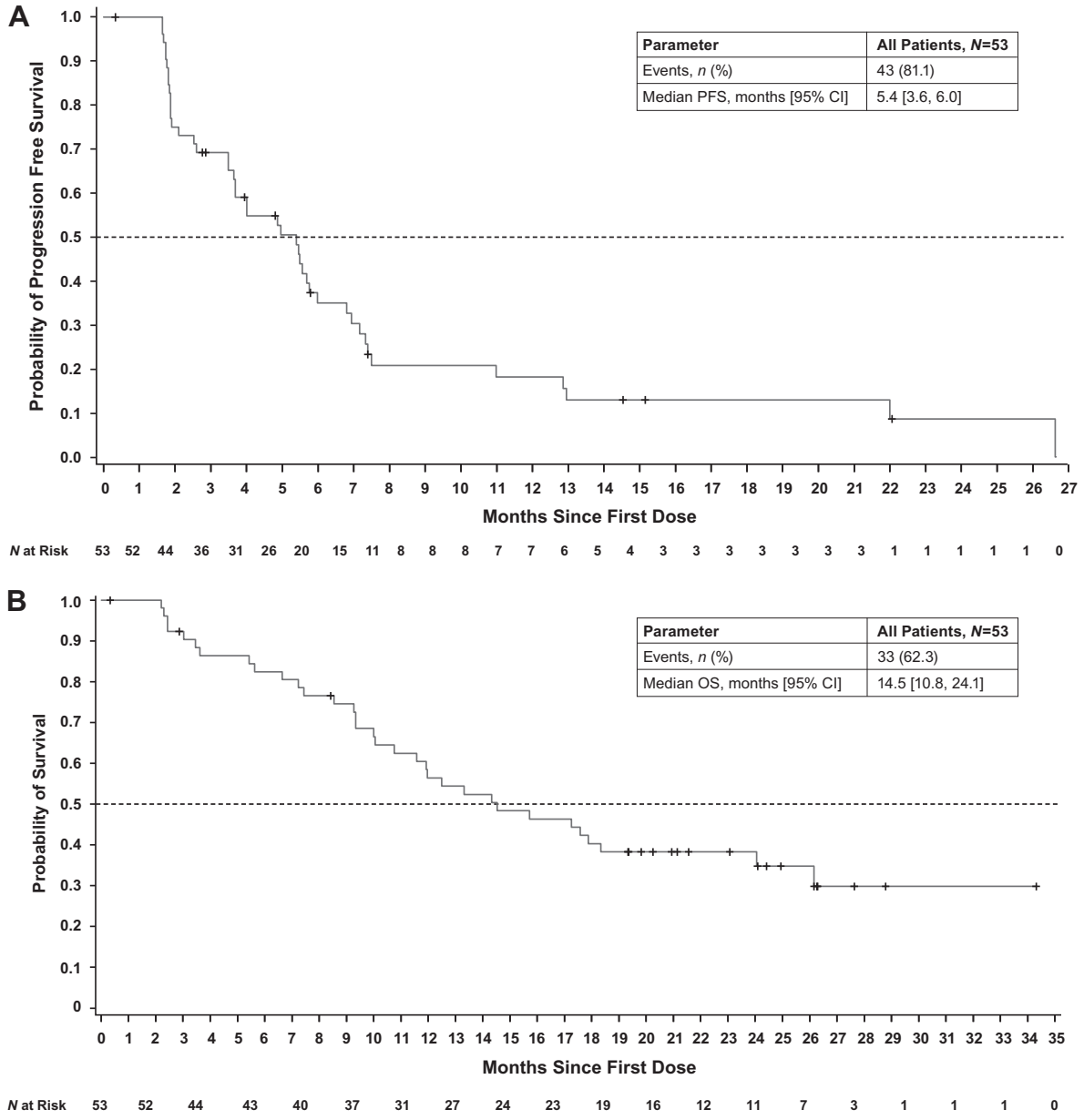


**Fig. 2 – Kaplan–Meier curves of progression-free survival and overall survival in patients treated with linifanib. (A) Progression-free survival (PFS) plot. (B) Overall survival (OS) plot.**

population pharmacokinetics model for this dataset. Creatinine clearance was not a significant covariate on apparent clearance or volume of distribution. Body weight was not a significant covariate on apparent clearance. The average apparent clearance value was 3.9 L/h and the terminal half-life was 21.6 h ($N = 42$) based on the parameter estimates from the final model.

## 4. Discussion

A number of targeted agents have demonstrated activity in advanced RCC. Sunitinib is considered a standard of care for initial therapy of patients with favourable- and intermediate-prognosis advanced clear-cell RCC, based on demonstrated superiority compared with IFNα in this patient population.[9,33] Temsirolimus is the standard of care for patients with poor-prognosis advanced RCC.[12,13] Optimal therapeutic regimens for patients with RCC who develop PD during sunitinib or temsirolimus therapy are being defined. In a randomised phase 3 trial in patients with clear-cell RCC with prior TKI therapy who developed PD with sunitinib, sorafenib or both,[18,34] everolimus demonstrated improved PFS (median 4.9 months) and 2% ORR, compared to median PFS 1.9 months and 0% ORR with placebo. Additionally, in phase 2 trials, sorafenib demonstrated occasional activity in patients with PD during first-line sunitinib therapy,[16] and axitinib showed activity in sorafenib-refractory patients, including a subset who had also received sunitinib.[17] In a phase 3 trial of axitinib

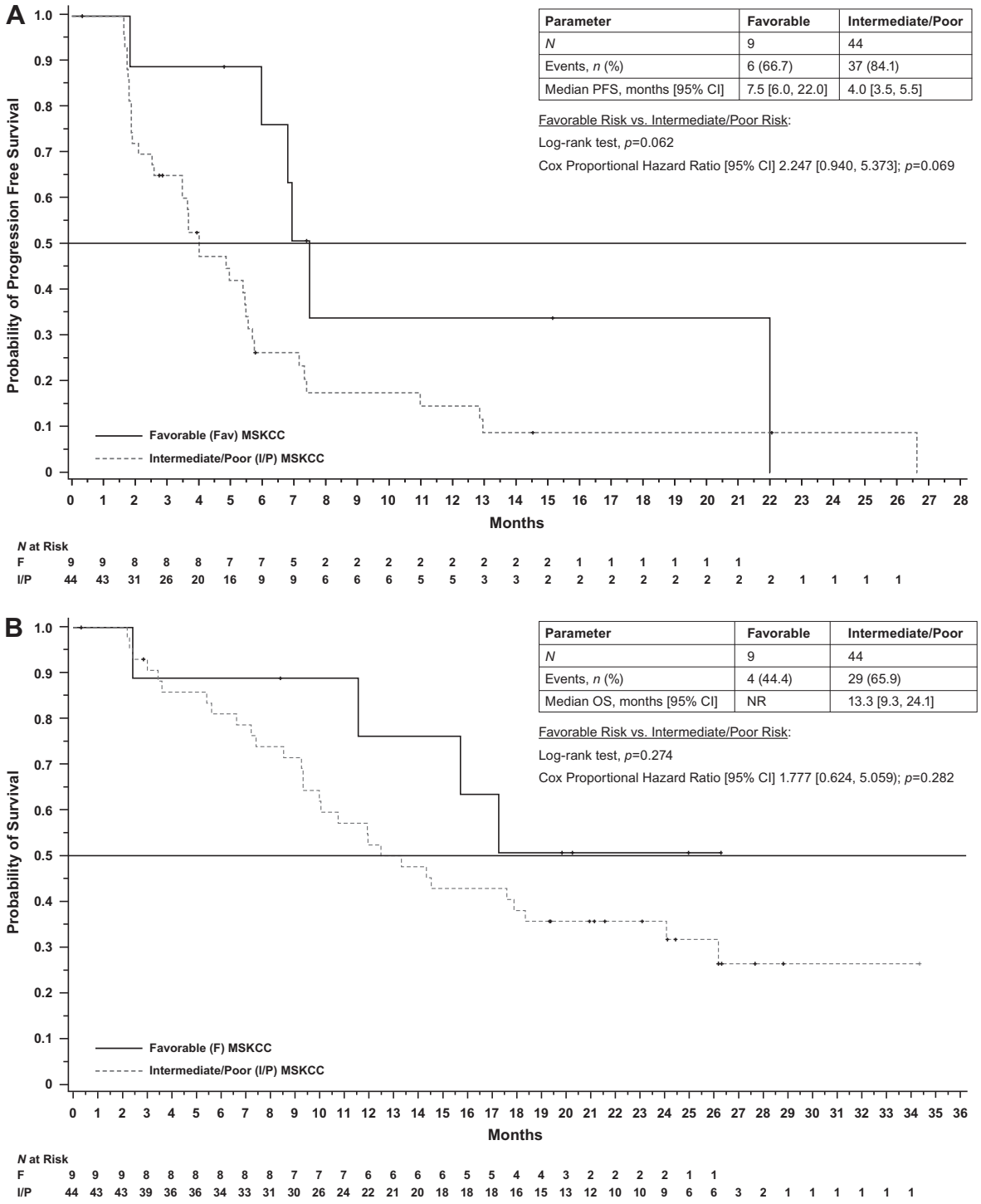


**Fig. 3 – Progression-free survival and overall survival by MSKCC risk groups. (A) Progression-free survival (PFS) plot. (B) Overall survival (OS) plot. *Abbreviations:* MSKCC, Memorial Sloan-Kettering Cancer Center.**

versus sorafenib as second-line therapy for RCC, PFS for patients with prior sunitinib favored axitinib (4.8 versus 3.4 months, $p = 0.0107$).[21] In this trial, we examined the antitumor activity of the novel agent linifanib, with greater selectivity towards VEGFR and PDGFR, in patients with advanced RCC who experienced disease progression during sunitinib therapy exclusively within 100 days from enrollment. Single-agent linifanib demonstrated clinically relevant activity (ORR 13.2%, median PFS 5.4 months per central imaging, median OS 14.5 months). Investigator assessments of PFS (median 5.8 months) and ORR (22.6%) were generally consistent with the central imaging assessments reported above. Although

**Table 3 – Adverse events.**

| Adverse events | Grade 1 or 2, *n* (%) N = 53 | Grade 3 or 4, *n* (%) N = 53 |
|---|---|---|
| *Treatment-related*[a] | | |
| Diarrhoea | 28 (52.8) | 11 (20.8) |
| Nausea | 27 (50.9) | 3 (5.7) |
| Fatigue | 26 (49.1) | 13 (24.5) |
| Weight loss | 23 (43.4) | 1 (1.9) |
| Decreased appetite | 20 (37.7) | 3 (5.7) |
| Proteinuria | 17 (32.1) | 3 (5.7) |
| Vomiting | 17 (32.1) | 3 (5.7) |
| Hypertension | 14 (26.4) | 21 (39.6) |
| Rash | 14 (26.4) | 0 |
| Hypothyroidism | 13 (24.5) | 0 |
| Mucosal inflammation | 12 (22.6) | 0 |
| Hand-foot syndrome[b] | 11 (20.7) | 12 (22.6) |
| *Haematologic*[c] | | |
| Anaemia | 11 (20.8) | 0 |
| Leukopaenia | 3 (5.7) | 0 |
| Lymphopaenia | 2 (3.8) | 2 (3.8) |
| Thrombocytopenia | 2 (3.8) | 0 |
| Polycythaemia | 1 (1.9) | 0 |
| Neutropenia | 0 | 1 (1.9) |
| *Serum chemistry*[c] | | |
| AST increased | 9 (17.0) | 1 (1.9) |
| ALT increased | 8 (15.1) | 1 (1.9) |
| Creatinine increased | 6 (11.3) | 0 |
| Alkaline phosphatase increased | 5 (9.4) | 1 (1.9) |
| Bilirubin increased | 4 (7.5) | 1 (1.9) |
| Phosphorus decreased | 4 (7.5) | 1 (1.9) |
| Uric acid increased | 4 (7.5) | 2 (3.8) |
| Carbon dioxide decreased | 3 (5.7) | 0 |
| Cholesterol increased | 2 (3.8) | 0 |
| Glucose increased | 2 (3.8) | 0 |
| Magnesium decreased | 2 (3.8) | 0 |

*Abbreviations:* ALT, alanine transaminase; AST, aspartate transaminase; WBC, white blood cell.

[a] By >20% of patients with treatment-related Grade 1 or 2. There were no deaths due to treatment-related AEs.

[b] Coded as palmar-plantar erythrodysesthesia.

[c] Regardless of relationship to linifanib. Serum chemistry AEs by ⩾2 patients with Grade 1 or 2.

this was a small, uncontrolled single-arm study in a highly refractory population (median prior therapies of 2, range 1–4), results indicate at least the same order of activity as reported for the everolimus phase 3 study mentioned above, the axitinib versus sorafenib phase 3 trial,[20,21] and with a similar phase 2 study evaluating sorafenib activity in patients with disease progression during sunitinib treatment (ORR 9.6%, median TTP 16 weeks per investigator assessments and median OS 32 weeks).[16]

The main limitation of this study was the rate of non-haematological AEs at the studied dose. Grade 3/4 AEs including hypertension, fatigue, hand-foot syndrome and diarrhoea occurred at a higher rate than with sunitinib or sorafenib.[14,16] Proteinuria, which has not been routinely reported with other in-class agents, may be mechanism-based.[35] Administration at 0.25 mg/kg daily (maximum 25 mg) was associated with high rates of dose interruptions and dose reductions with a median (range) dose intensity of 63.8% (37.2, 100), which was suboptimal. Further linifanib studies are evaluating an alternative, fixed-dosing strategy: 17.5 mg as monotherapy, and 7.5 or 12.5 mg in combination with chemotherapy. Additionally, analyses of correlative linifanib biomarkers are ongoing, including alternative imaging, which may be predictive of improved patient outcome or permit improved AE management and/or dose optimisation.

The extent of renal impairment, measured by creatinine clearance, was not a significant covariate in the population pharmacokinetics model, indicating that dose adjustment for renal dysfunction is not needed for linifanib. The terminal half-life of approximately 1 day in this study is similar to the half-life from other linifanib studies. However, increased toxicity seen in this study compared with the phase 1 results at the same dose level may indicate that these patients with advanced RCC are more susceptible to AEs than other patient populations.

Linifanib may be differentiated from other multi-targeted receptor TKIs in a number of respects. Linifanib simultaneously demonstrates potent inhibition, greater selectivity towards VEGFR and PDGFR kinases, and may result in fewer off-target effects than other angiogenesis inhibitors.[22]

Consistent with this hypothesis, we observed a lower rate of haematological AEs (neutropenia, thrombocytopenia) of all grades and Grade 3/4 than observed in a phase 2 sorafenib trial in patients with RCC whose disease progressed on sunitinib.[16] These results support further evaluation of this inhibitor as a single agent or in combination with other agents. Ongoing studies are evaluating the efficacy of single-agent linifanib in other malignancies including a phase 3 trial versus sorafenib in unresectable or metastatic hepatocellular carcinoma.[36]

## 5. Conclusions

The results observed in this study suggest that further evaluation of linifanib in patients with advanced RCC is warranted. Future trials would need to investigate alternative approaches. These may include an alternative fixed-dose regimen and biomarker assessment at baseline to identify a subset of patients who may experience improved outcome[37] as compared to a defined standard of care.

## Trial registration

ClinicalTrials.gov number, NCT00486538.

## Support

Abbott Laboratories, IL, USA provided linifanib for this study.

## Conflict of interest statement

N.M.T. has had a consultant/advisory role for Abbott, Novartis, Genentech, Seattle Genetics and Aveo Pharmaceuticals, Inc., and has conducted research funded by Abbott, Pfizer, Novartis, Lilly, Amgen and Seattle Genetics. M.S.E. has had a consultant/advisory role for Abbott, owns stock in Abbott and conducted research funded by Abbott. D.J.P. conducted research funded by Abbott, and attended a Genentech advisory board. L.J.A. received research funding from Abbott. D.C. has had a consultant/advisory role for Genentech Inc., T.K.C. has had a consultant/advisory role for Abbott. A.C., R.P., J.Q., J.L.R. and D.M.C. are employees of Abbott and own Abbott stock. N.G. and J.C. are former employees of Abbott and own Abbott stock; N.G. is currently employed at Millennium: The Takeda Oncology Company, Cambridge, MA, and J.C. is currently employed at Astellas Pharma Global Development, Inc., Deerfield, IL. F.A.S. is an employee of Genentech, Inc., South San Francisco, CA, and owns stock in Roche. M.D.M. has had a consultant/advisory role for Abbott and Pfizer, and received honoraria from Wyeth. The other authors have no conflict of interest.

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