Plasma KIM-1 Is Associated with Recurrence Risk after Nephrectomy for Localized Renal Cell Carcinoma: A Trial of the ECOG-ACRIN Research Group (E2805)

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ABSTRACT

Purpose: No circulating biomarkers are currently available to identify patients at highest risk of recurrence after nephrectomy for renal cell carcinoma (RCC). Kidney injury molecule-1 (KIM-1) is overexpressed in RCC and its ectodomain circulates in plasma. We investigated whether plasma KIM-1 is a prognostic biomarker in patients with localized RCC after nephrectomy.

Experimental Design: The ECOG-ACRIN E2805 (ASSURE) trial evaluated adjuvant sunitinib, sorafenib, or placebo in resected high-risk RCC. KIM-1 levels were measured from banked plasma at trial enrollment 4–12 weeks after nephrectomy. Lognormal accelerated failure time models were used to test for association between KIM-1 and disease-free survival (DFS) as well as overall survival (OS).

Results: Plasma from 418 patients was analyzed. Higher post-nephrectomy KIM-1 was associated with worse DFS across all study arms after adjustment for Fuhrman grade, T stage, N stage, and tumor histology [survival time ratio 0.56 for 75th vs. 25th percentile of KIM-1; 95% confidence interval (CI), 0.42–0.73; $P < 0.001$]. The association between KIM-1 and DFS was stronger among patients with pathologic nodal involvement ($P_{interaction} = 0.0086$). The addition of post-nephrectomy KIM-1 improved the concordance of clinical prognostic models [Stage, Size, Grade, and Necrosis (SSIGN) concordance 0.57 vs. 0.43, $P = 0.05$; UCLA International Staging System (UISS) concordance 0.60 vs. 0.40, $P = 0.0005$]. Higher post-nephrectomy KIM-1 was also associated with worse OS after multivariable adjustment (survival time ratio 0.71 for 75th vs. 25th percentile of KIM-1; 95% CI, 0.56–0.91; $P < 0.001$).

Conclusions: Post-nephrectomy plasma KIM-1 is associated with DFS and OS in RCC, and may be a biomarker for microscopic residual disease.

Introduction

In 2018, there were more than 400,000 new cases and 175,000 deaths attributed to renal cell carcinoma (RCC; ref. 1). Although some patients with localized disease are cured by surgical excision, 30% or more experience subsequent disease recurrence leading to poor long-term outcomes (2–6). Despite many recent advances in the treatment of metastatic RCC, the standard of care for high-risk localized disease after nephrectomy remains imaging surveillance alone. Although sunitinib has FDA regulatory approval status for adjuvant therapy, it is rarely used because of toxicity, lack of known survival benefit, and the inability to determine *a priori* which patients may benefit (2, 4, 7). These problems are compounded by the lack of a circulating biomarker for RCC. Such a biomarker, if available, could help to identify patients at high risk for recurrence after surgical excision, identify patients for adjuvant therapy, and assist in the early detection of recurrent disease.

Kidney injury molecule-1 (KIM-1) is a transmembrane glycoprotein expressed by injured renal proximal tubular cells and RCC cells (8, 9). The ectodomain of KIM-1 undergoes cleavage and can be detected in both urine and blood (10, 11). Urinary KIM-1 levels have been shown to decrease after nephrectomy in people with RCC that expresses KIM-1 (10). In addition, elevated KIM-1 levels have been identified in patients up to 5 years prior to a subsequent diagnosis of RCC, and are associated with higher risk of RCC mortality (12). These findings suggest that KIM-1 may be a marker for overall RCC tumor burden. In patients with resected RCC and no radiographic evidence of disease, KIM-1 could indicate the presence of occult tumor and therefore high risk for future recurrence. However, it is currently not known whether post-nephrectomy KIM-1 levels are associated with clinical outcomes.

We therefore performed a *post hoc* analysis of the ECOG-ACRIN E2805 (ASSURE) trial to determine whether post-nephrectomy plasma KIM-1 levels are associated with worse disease-free survival (DFS) among patients with high-risk localized RCC.

Materials and Methods

Patient population

ECOG-ACRIN E2805 (ASSURE) was a double-blinded, placebo-controlled phase III trial of 1,943 participants with completely resected, high-grade, pathologic stage T1b or higher RCC (2). Participants were randomized in a 1:1:1 manner to 54 weeks of treatment with adjuvant sunitinib, sorafenib, or placebo. The primary outcome was DFS, defined as time from randomization to either recurrence, development of a second primary cancer, or death from any cause. Because of an interim calculation of low conditional power for the

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

Disease recurrence after nephrectomy for localized renal cell carcinoma (RCC) is common, and the identification of a tumor marker could help risk stratify patients after nephrectomy, identify patients who may benefit from adjuvant treatment, and enhance surveillance. Kidney injury molecule-1 (KIM-1) is a transmembrane protein overexpressed in RCC and detectable in circulating plasma. We report that elevated post-nephrectomy KIM-1 is associated with worse progression-free survival and overall survival in banked plasma from a large randomized trial, particularly among patients with pathologic node involvement at time of nephrectomy. We also show that the inclusion of plasma KIM-1 into existing post-nephrectomy risk assessment models improves their concordance. If validated in further studies, KIM-1 is a potential circulating biomarker in RCC to identify patients who are at high risk of recurrence after nephrectomy.

primary endpoint, the Data Safety Monitoring Committee determined in 2014 that blinded follow-up should cease; analysis for the primary endpoint subsequently showed no difference in DFS between the study arms. Further data regarding the conduct and outcomes of the ECOG-ACRIN E2805 study have been previously reported in detail (2).

Banked plasma from ECOG-ACRIN E2805 was randomly selected and allocated by study statisticians for preplanned biomarker analyses. Plasma samples from 418 patients who had undergone total nephrectomy across all treatment arms were allocated for this KIM-1 study. Patient demographics including age, sex, race/ethnicity, pathologic information, and clinical outcomes were collected prospectively as per trial protocol. Patients who underwent partial nephrectomy (5.4% of the E2805 study cohort) were excluded from the analysis to minimize possible confounding due to KIM-1 release from injured postsurgical kidney epithelium.

All participants provided written informed consent prior to participation, and consent for exploratory biomarker analysis was embedded within the ECOG-ACRIN E2805 trial consent. Approval for the study was granted by the institutional review board at each participating study center. This study was conducted in accordance with the Declaration of Helsinki.

Specimen characteristics

As part of the ECOG-ACRIN E2805 study protocol, plasma was collected in sodium citrate at the pretreatment baseline (4–12 weeks after nephrectomy) and at cycle 2 day 1 (either 4 or 6 weeks after initiation of therapy). All plasma samples were processed centrally and stored at −80°C until the time of analysis.

KIM-1 measurement

Plasma KIM-1 levels were measured in duplicate using a microbead-based assay as described previously (11). This analysis was performed at the laboratory of Venkata Sabbisetti, and investigators were blinded to the identity of samples at the time of analysis. Each sample was diluted 10-fold in sample diluent buffer (0.1 mol/L HEPES, 0.1 mol/L NaCl, 0.1% Tween-20, and 1% BS; pH 7.4; filter sterilized). Thirty microliters (30 μL) of diluted sample, recombinant standards, and internal control urine samples were incubated with approximately 6,000 microbeads coupled with KIM-1 capture antibody for 1 hour (R&D Systems, catalog no. AF1750). Beads were then washed 3× with PBST and incubated with detection antibody for 45 minutes (R&D Systems, catalog no. BAF1750). Beads were washed 3× with PBS-Tween and incubated with Streptavidin-PE (Invitrogen) for 15 minutes. The signal from the fluorochrome was captured using Bio-Plex 200 system (Bio-Rad). Data were generated and interpreted using a five parametric logistic regression analysis. The lower limit of detection for KIM-1 was set at 9.1 pg/mL, and all values lower than this were considered undetectable.

Statistical analysis

Univariable analyses were performed to assess for associations between KIM-1 level and baseline participant characteristics. Univariable and multivariable lognormal accelerated failure time (AFT) models were used to assess the association between post-nephrectomy plasma KIM-1 and DFS (13). The AFT model was used to avoid making a proportional hazards assumption. The multivariable model was adjusted for sex, Eastern Cooperative Oncology Group performance status (ECOG PS), Fuhrman grade, tumor stage, nodal stage, histology, and the presence of sarcomatoid features. KIM-1 was fit as a restricted cubic spline with three knots and was stratified by nodal stage. An additional AFT multivariable model was used to assess the association between post-nephrectomy plasma KIM-1 level and overall survival (OS).

Results

We analyzed post-nephrectomy, baseline plasma KIM-1 levels from 418 patients randomly selected from among the 1,837 participants in the ASSURE trial who underwent total nephrectomy. Baseline characteristics of these 418 participants were similar to those of the overall ASSURE trial population and are shown in **Table 1**. The majority of patients had clear cell histology (79%). Eleven percent (11%) of the participants had sarcomatoid features; 19% had Fuhrman grade 4 disease. Forty-seven percent (47%) of patients were very-high risk as classified by the modified UCLA International Staging System (UISS) Criteria and pathologic grading (14, 15). Thirty-six percent (36%) were randomized to sunitinib, 31% were randomized to sorafenib, and 33% were randomized to placebo. There were no significant differences in baseline characteristics between our cohort and the overall ECOG-ACRIN E2805 study population who underwent total nephrectomy (2).

The distribution of post-nephrectomy KIM-1 values observed is shown in Supplementary Fig. S1. The median level of KIM-1 after nephrectomy and prior to the start of study treatment was 76.00 pg/mL [interquartile range (IQR), 40.55–219.75 pg/mL]. Because we observed a right skewed KIM-1 distribution with very high values seen in a minority of patients, the KIM-1 values were log transformed for univariable and multivariable analyses. We observed no significant associations between post-nephrectomy KIM-1 and sex, age, or ECOG PS. There were also no significant associations between KIM-1 and histologic subtype, sarcomatoid features, Fuhrman grade, T stage, or N stage, suggesting that post-nephrectomy KIM-1 is independent of known clinicopathologic predictors of recurrence (Supplementary Fig. S2).

To evaluate whether plasma KIM-1 levels correlate over time within a given patient, we compared post-nephrectomy KIM-1 levels with those at C2D1 of follow-up (Supplementary Fig. S3). This analysis showed an association between post-nephrectomy KIM-1 and C2D1 KIM-1 levels (Spearman $\rho = 0.633$).

Among 418 studied patients, we observed 199 DFS events and 128 deaths. Kaplan–Meier curves representing the rate of DFS and OS events per KIM-1 quartile are presented in **Fig. 1A** and **B**, respectively. A nonlinear relationship was seen where higher KIM-1 was associated

Table 1. Baseline characteristics.

	Number of patients (%) or median (IQR)
Total	418 (100)
Male sex	292 (70)
Race	
African American	21 (5)
Asian	10 (2)
Other/unknown	11 (3)
White	376 (90)
Ethnicity	
Hispanic	25 (6)
Non-Hispanic	367 (88)
Missing	26 (6)
Age	56 (49–64)
Histology	
Clear cell	329 (79)
Papillary	37 (9)
Chromophobe	22 (5)
Other	30 (7)
ECOG PS	
0	317 (76)
1	89 (21)
2	0 (0)
3	0 (0)
Missing	12 (3)
Surgical approach	
Open	236 (56)
Laparoscopic	182 (44)
Sarcomatoid features	
Absent	370 (89)
Present	47 (11)
Missing	1 (0)
Fuhrman grade	
1	7 (2)
2	123 (29)
3	204 (49)
4	79 (19)
Missing	5 (1)
T stage	
1	46 (11)
2	115 (28)
3	250 (60)
4	7 (2)
N stage	
0/X	386 (92)
1/2	32 (8)
UISS risk group	
Intermediate high	222 (53)
Very high	196 (47)
Treatment arm	
Sunitinib	150 (36)
Sorafenib	128 (31)
Placebo	140 (33)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; UISS, UCLA Integrated Staging System.

with worse DFS (logrank $P = 0.004$), and this effect appeared to be driven by DFS events within the first 2 years after nephrectomy. Similar associations were noted among subgroups of patients with and without lymph node involvement at time of nephrectomy (Supplementary Fig. S4). A univariable AFT model showed a survival time ratio of 0.65 for the 75th versus 25th percentile of baseline KIM-1 [95% confidence interval (CI), 0.39–1.06, Wald $P = 0.0004$].

To further understand the relationship between KIM-1 and disease recurrence in relation to known clinicopathologic variables, a multivariable AFT model was used to evaluate the association between baseline KIM-1 and DFS while adjusting for sex, PS, Fuhrman grade, nodal stage, tumor stage, presence of sarcomatoid features, and tumor histology (**Table 2A**). Higher post-nephrectomy baseline KIM-1 was associated with worse DFS in this multivariable model (survival time ratio 0.56 for 75th vs. 25th percentile of KIM-1; 95% CI, 0.42–0.73; $P < 0.001$). Of note, no significant interaction was seen between KIM-1 and assigned treatment arm on the risk of recurrence ($P = 0.53$), suggesting that KIM-1 is not a predictive biomarker for response to adjuvant therapy with sunitinib or sorafenib.

We assessed for interaction terms on the effect of baseline KIM-1 on DFS. The presence of nodal disease at time of nephrectomy was noted to be an effect modifier, with greater effect size of KIM-1 on DFS seen among patients with at least N1 nodal disease ($P_{\text{interaction}}$ 0.0086). A restricted cubic spline was used to illustrate the effect of nodal status on the relationship between baseline KIM-1 and recurrence risk (**Fig. 2**).

We evaluated whether subsequent changes in KIM-1 during follow-up provide additional prognostic information. We found that C2D1 KIM-1 was not independently predictive of recurrence risk after adjustment for baseline KIM-1 ($P = 0.67$). In addition, no difference was seen in the pattern of KIM-1 change between the placebo and treatment arms (Supplementary Fig. S3).

To provide clinically interpretable estimates for KIM-1 and recurrence risk, we calculated model-derived survival rates for patients both with and without nodal disease at time of nephrectomy, based on various percentiles of baseline KIM-1. Model-predicted survival curves for representative post-nephrectomy plasma KIM-1 levels are presented in Supplementary Fig. S5. For a representative male with PS 0, clear-cell histology, T3 tumor, no sarcomatoid features, Fuhrman grade 3 or less, and N1 or N2 disease at nephrectomy, the predicted DFS is 4.93 (2.74–8.85) times longer when post-nephrectomy KIM-1 is at the 10th percentile compared with the 90th percentile of KIM-1.

We evaluated whether KIM-1 adds to the prognostic value of previously published clinical models (14, 16, 17). When added as a spline term to either the Stage, Size, Grade, and Necrosis (SSIGN) score or the UISS score for disease recurrence after nephrectomy, baseline KIM-1 improved the predictive value of both models (likelihood ratio test $P = 0.078$ and $P = 0.0022$, respectively). In addition, when applied to the E2805 cohort, both the SSIGN and UISS models produced higher concordance when KIM-1 was included in the model (SSIGN concordance 0.57 vs. 0.43, $P = 0.052$; UISS concordance 0.60 vs. 0.40, $P = 0.0005$).

We evaluated the association between post-nephrectomy plasma KIM-1 and OS. Kaplan–Meier analysis showed a trend toward worse OS for patients with higher baseline KIM-1 (logrank $P = 0.056$; **Fig. 1B**). Higher post-nephrectomy baseline KIM-1 was associated with worse OS in a multivariable AFT model, after adjustment for age, sex, PS, Fuhrman grade, nodal stage, tumor stage, presence of sarcomatoid features, and tumor histology (survival time ratio 0.71 for 75th vs. 25th percentile of KIM-1; 95% CI, 0.56–0.91; $P < 0.001$; **Table 2B**; Supplementary Fig. S6).

A sensitivity analysis was performed with statistical imputation of KIM-1 levels that fell below the lower limit of detection. Similar associations between KIM-1 and DFS were seen when using the imputed low KIM-1 values (Supplementary Table S1).

Discussion

In this study, we demonstrate that higher post-nephrectomy plasma KIM-1 is associated with worse DFS among patients with high-risk

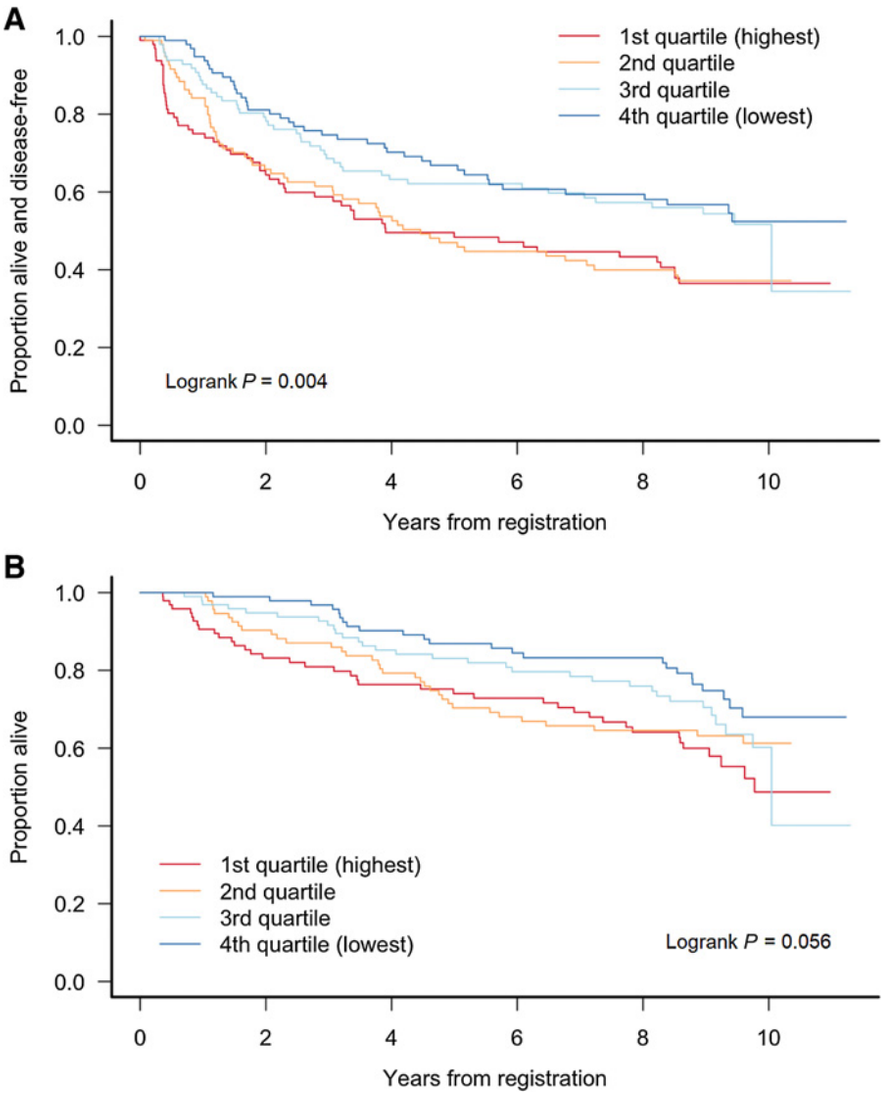

Figure 1.
Kaplan–Meier curves of clinical outcomes by baseline KIM-1. Patients are stratified by quartile of plasma KIM-1 measured at post-nephrectomy baseline. **A,** DFS stratified by baseline KIM-1 quartile. **B,** OS stratified by baseline KIM-1 quartile.

localized RCC. This association was strongest among patients with pathologic nodal disease at the time of nephrectomy.

To our knowledge, this is the largest study to date to evaluate the prognostic performance of a circulating tumor-derived biomarker in assessing post-nephrectomy risk of recurrence in RCC. Plasma KIM-1 is a minimally invasive biomarker that we show improves the risk stratification of patients with RCC after nephrectomy. Indeed, we found that the addition of post-nephrectomy plasma KIM-1 to both the UISS (14) and SSIGN (18) risk stratification scores significantly improved both models' discriminatory performance. Proposed circulating biomarkers for RCC have included circulating cytokines, tumor proteins including CA-IX, tumor cells, cell-free tumor DNA and RNA, and DNA methylation patterns (19–24). In a previous analysis of circulating cytokines in ECOG-ACRIN E2805, we demonstrated that cytokine levels are sensitive to host–drug interactions and that post-nephrectomy baseline CXCL10/IP-10 is associated with worse DFS (25). However, methodologic limitations have thus far limited the widespread clinical adoption of known circulating biomarkers. Some potential barriers have included low sensitivity (for instance with circulating tumor cells), fluctuations in response to host factors and antitumor therapy (seen with cytokine biomarkers), and high inter-patient variability and computational complexity (circulating tumor DNA, transcriptomic and methylation signatures). Compared with other circulating biomarkers, KIM-1 is a single protein overexpressed in the majority of patients with RCC, directly correlated with tumor burden, and easily measurable in banked plasma with a relatively straightforward antibody-based microbead assay with the potential for implementation at scale. The management of high-risk localized RCC continues to pose a clinical dilemma. Despite a multitude of completed phase III trials, no systemic adjuvant therapy for RCC has ever been shown to improve OS (2–5, 26). Sunitinib received FDA approval for adjuvant therapy after nephrectomy for high-risk RCC based on improved DFS seen in the S-TRAC randomized trial (4). However, there was no OS benefit and patients receiving sunitinib experienced substantial toxicity and reduction in health-related quality of life. All other adjuvant trials of VEGF inhibitors, including the ECOG-ACRIN

Table 2A. Multivariable model of KIM-1 and DFS.

		Survival time ratio	95% CI
KIM-1	75th percentile vs. 25th percentile[a]	0.56	(0.42–0.73)
N stage	N1/N2 vs. N0/NX	0.41	(0.21–0.80)
Fuhrman grade	4 vs. <4	0.34	(0.21–0.54)
Histology	Papillary vs. CC	1.24	(0.67–2.28)
	Chromophobe vs. CC	2.88	(1.09–7.58)
	Other vs. CC	0.58	(0.3–1.09)
ECOG performance status	1 vs. 0	0.61	(0.41–0.91)
T stage	1 vs. 3	2.01	(1.14–3.55)
	2 vs. 3	1.51	(1.01–2.26)
	4 vs. 3	1.79	(0.46–6.98)
Sarcomatoid features	Present vs. absent	0.76	(0.43–1.34)
Sex	Female vs. male	1.22	(0.84–1.78)

Note: A multivariable lognormal AFT model was used to assess the association between post-nephrectomy plasma KIM-1 and DFS or OS. In these models, lower survival time ratio represents shorter DFS relative to the covariate of interest. The reported KIM-1 survival time ratio compares the 75th percentile with the 25th percentile of KIM-1.

[a]The 25th percentile of KIM-1 was 40.55 pg/mL. The 75th percentile of KIM-1 was 219.8 pg/mL.

E2805 ASSURE trial, failed to show improvement in DFS or OS compared with placebo in resected RCC (2, 3, 5, 26).

In this study, KIM-1 was a prognostic but not predictive biomarker in setting of therapy with VEGFR tyrosine kinase inhibitors (TKI). There was no trend seen in the pattern of plasma KIM-1 change over time when comparing the placebo and treatment arms (Supplementary Fig. S3). This is consistent with prior preclinical studies suggesting that macroscopic tumors are limited by vascular supply whereas microscopic tumors are not, and therefore VEGFR TKIs may have limited activity in treating micrometastatic disease (27, 28).

It is therefore possible that KIM-1 may yet prove to be a predictive biomarker for adjuvant immune checkpoint inhibition.

Table 2B. Multivariable model of KIM-1 and OS.

		Survival time ratio	95% CI
KIM-1	75th percentile vs. 25th percentile[*]	0.71	(0.56–0.91)
N-stage	N1/N2 vs. N0/NX	0.65	(0.37–1.15)
Fuhrman grade	4 vs. <4	0.50	(0.33–0.75)
Histology	Papillary vs. CC	0.84	(0.50–1.41)
	Chromophobe vs. CC	4.15	(1.28–13.47)
	Other vs. CC	0.51	(0.30–0.87)
ECOG performance status	1 vs. 0	0.73	(0.51–1.03)
T stage	1 vs. 3	1.91	(1.13–3.24)
	2 vs. 3	1.14	(0.80–1.63)
	4 vs. 3	2.12	(0.56–8.08)
Sarcomatoid features	Present vs. absent	0.87	(0.54–1.41)
Age at enrollment	75th percentile vs. 25th percentile[a]	0.75	(0.61–0.93)
Sex	Female vs. male	1.21	(0.87–1.70)

[a]The 75th percentile of age was 64 years. The 25th percentile of age was 49.5 years.

Currently, there are several ongoing phase III trials evaluating adjuvant anti-PD-1/PD-L1 blockade alone or in combination with CTLA-4 blockade. These include PROSPER (NCT03055013), IMmotion 010 (NCT03024996), KEYNOTE 564 (NCT03142334), RAMPART (NCT03288532), and CheckMate 914 (NCT03138512; refs 29–33). Several of these adjuvant trials have completed enrollment and results are expected in the coming years. Although the vast majority of circulating KIM-1 in RCC is thought to derive from tumor cells, KIM-1 is also expressed in regulatory B cells and some T cells and appears to play a role in immune tolerance signaling (34, 35). It is not known whether circulating KIM-1 is immunologically active in the adjuvant setting, and whether plasma KIM-1 could help to select patients for adjuvant immune checkpoint blockade. We are planning preclinical and clinical studies using specimens from these ongoing adjuvant immune checkpoint trials to better elucidate these questions.

Strengths of this study include the use of the ECOG-ACRIN E2805 (ASSURE) cohort, which consists of highly annotated, prospectively collected clinical data and outcomes, in conjunction with patient plasma that was collected at prespecified time points across multiple institutions (2). These strengths have made the ECOG-ACRIN E2805 cohort uniquely valuable for the development of new clinical and laboratory prognostic biomarkers (25, 36, 37).

Our results are consistent with the prior literature describing KIM-1 in RCC. Urinary KIM-1 has been shown to decrease in patients with RCC following nephrectomy, consistent with the hypothesis that it is released directly from tumors (10). Similarly, KIM-1 has been previously shown to be higher in patients with RCC pre-diagnosis compared with healthy controls, and also associated with subsequent risk of death (12). While one prior study showed that urine and tissue KIM-1 levels were associated with T stage and tumor histology (38), we did not see such an association, likely because all patients in this study underwent complete macroscopic resection of disease and the primary tumor was no longer the main source of KIM-1. It is not clear why higher post-nephrectomy KIM-1 levels had a stronger effect on DFS among node-positive (N1 or N2) participants compared with node-negative (N0 or NX) participants. One possibility is that this simply reflects higher recurrence risk among node-positive patients, but it is also possible that patients who do experience disease recurrence despite no nodal disease at time of surgery have less well-differentiated RCC that is less likely to express KIM-1.

Our study has several limitations. Because of the schedule of plasma collection, we were unable to reassess KIM-1 levels at time of relapse among those participants whose cancer recurred. Such information could help to further characterize the utility of KIM-1 in surveillance after nephrectomy. We excluded patients who underwent partial nephrectomy because surgically injured nephrons are expected to release KIM-1 during healing, but patients with partial nephrectomy represented only a small proportion (5.4%) of the overall ASSURE study cohort (2, 11). In addition, in this study, we investigated a single biomarker and it is possible that comeasurement of additional investigational biomarkers could further improve prognostic performance.

Because KIM-1 is an established biomarker for kidney injury, impaired renal function may confound the relationship between KIM-1 and clinical outcomes. Eligibility criteria for ECOG-ACRIN E2805 required serum creatinine $\leq$ 2 times the normal limit or CrCl $\geq$ 30 mL/minute and our study therefore did not include patients with severe renal impairment (2). However, in a prior cohort of prediagnostic plasma samples from patients with RCC, we saw no

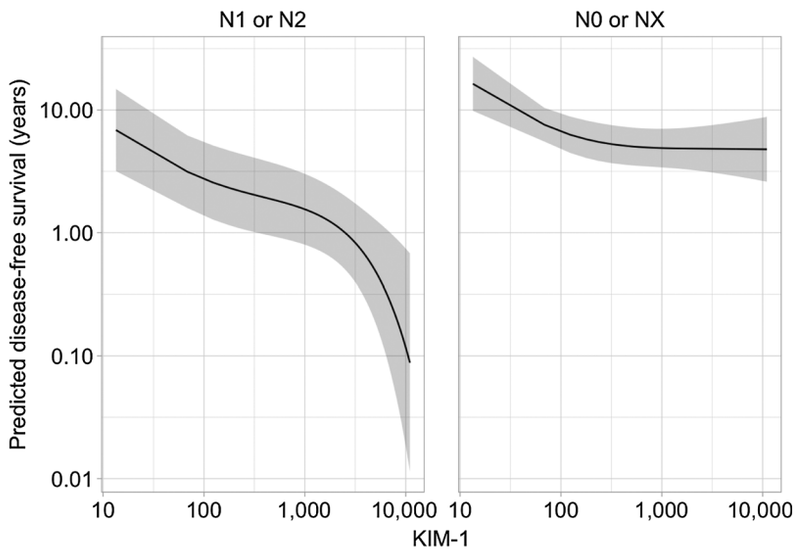

Figure 2.
Log DFS time in relation to KIM-1. A restricted cubic spline was used to model the relationship between DFS and baseline KIM-1, in patients with and without pathologic nodal involvement at time of nephrectomy.

correlation between plasma KIM-1 and plasma creatinine, and the addition of creatinine did not change the multivariable risk estimate for KIM-1 and new RCC (12). In patients with kidney cancer, the amount of KIM-1 shed by RCC into plasma likely predominates compared with the smaller amount shed via ongoing injury of normal kidney epithelium.

In this study, we did not have nephrectomy tumor tissue available to assess transcriptomic expression of KIM-1. However, previous investigators have assessed tissue expression of KIM-1 using 133 nephrectomy samples from patients who participated in the S-TRAC randomized trial of adjuvant sunitinib versus placebo (39). In data presented at the 2019 ESMO Congress, a nonsignificant trend was seen between KIM-1 expression above the median and favorable DFS (HR in sunitinib arm 0.50; 95% CI, 0.22–1.15; HR in placebo arm 0.48; 95% CI, 0.22–1.02; unadjusted $P = 0.06$). These data are consistent with our hypothesis that circulating KIM-1 likely reflects residual tumor burden rather than inherently unfavorable tumor biology.

Because our study was carried out using patients from a single randomized trial, we have planned further studies to validate these findings in additional cohorts, including independent adjuvant therapy trials. In addition, studies are warranted to investigate the role of KIM-1 in patients who underwent partial nephrectomy or ablative therapies, and in patients with chronic kidney disease. If validated, these studies could help to define appropriate cut-off levels for plasma KIM-1 for use in risk stratification and/or surveillance after nephrectomy.

Conclusions

Among patients at high risk for relapse for localized RCC, elevated plasma KIM-1 post-nephrectomy is associated with worse DFS and OS. Plasma KIM-1 may be a minimally invasive circulating biomarker for the detection of microscopic residual disease after nephrectomy.

Authors' Disclosures

K.T. Flaherty reports personal fees from Loxo Oncology, Clovis Oncology, Strata Oncology, Checkmate Pharmaceuticals, Vivid Biosciences, Kinnate Biopharma, Scorpion Therapeutics, X4 Pharmaceuticals, PIC Therapeutics, Shattuck Labs, Apricity, Oncoceutics, Fog Pharma, Tvardi, xCures, Monopteros, Vibliome, Sanofi, Amgen, Asana, Neon Therapeutics, Tolero, Lilly, Genentech, Bristol Myers Squibb, Merck, Takeda, Verastem, Boston Biomedical, Pierre Fabre, Debiopharm, and ALX Oncology, as well as grants and personal fees from Novartis and Sanofi during the conduct of the study. R.G. Uzzo reports other from Urogen, Genentech, Pfizer, Janssen, and Amgen outside the submitted work. V. Sabbisetti reports a patent 10712349 issued. No disclosures were reported by the other authors.

Disclaimer

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Authors' Contributions

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