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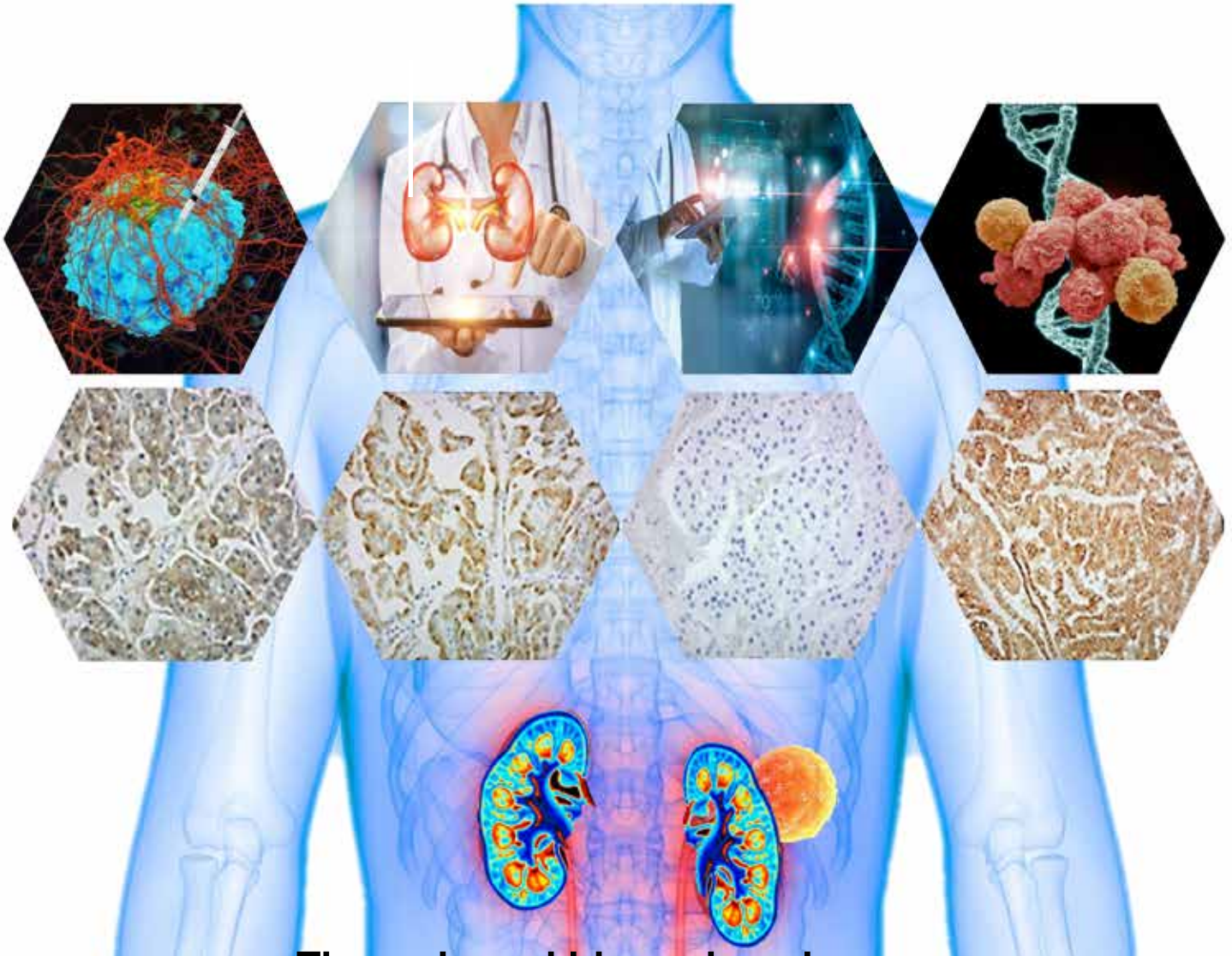

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An Educational Service for Medical Oncologists, Hematologist-Oncologists, and Urologists

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Novel Combination Therapies Shake Up the Spectrum of Renal Cancer Treatment

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In 2021, promising clinical outcomes from pivotal phase III CheckMate-9ER (NCT03141177) and CLEAR (NCT02811861) studies have secured the place for cabozantinib plus nivolumab as well as lenvatinib plus pembrolizumab respectively in the already crowded therapeutic landscape of renal cell carcinoma. New trials such as COSMIC-313 (NCT03937219) and the PDIGREE (NCT03793166) are currently evaluating different combinations of ipilimumab, nivolumab, and cabozantinib. The evolution of RCC therapies, demonstrates continuous improvement of new PD-1or PD-L1 inhibitor/TKI doublets as a shift away from monotherapies towards doublet therapy strategies. However, for those subpopulations of RCC that do not optimally benefit from checkpoint inhibitors or TKI therapies, the quest is still on to identify alternative class therapies. To this direction, recent findings from the phase 2 Study-004 trial (NCT03401788) demonstrated the encouraging clinical efficacy of the first-in-class agent belzutifan, a hypoxia-inducible factor inhibitor. An overall response rate of 49% was reported in patients with von Hippel-Lindau (VHL)–associated RCC that does not require immediate surgery. Following such strong performance, FDA on August 13th, 2021 approved belzutifan not only for VHL disease-related RCC but also for hemangioblastomas and pancreatic neuroendocrine tumors. Bezultifan's approval marks another significant step ahead for the management of RCCs based on their hypoxic pathway rather than their conventional TKI/IO mechanisms. Undoubtedly, such HIF-based therapies may now be positioned as the next breakthrough in cancer treatment following the success of checkpoint inhibitors. Currently, belzutifan in combination with cabozantinib was already investigated for synergistic potential in patients with advanced clear cell renal cell carcinoma (RCC). Similarly, a phase III trial (NCT04195750) evaluating MK-6482 vs everolimus in aRCC patients who progressed on IO plus a TKI is currently underway. The advent of such hypoxia-based novel therapies targeting the VHL pathway could revolutionize the treatment of renal cancer patients in the decades to come. However, in addition to improving the way IO-, TKI-, and HIF-based drugs are evaluated and used in clinical practice, equally challenging is the cross-trial comparison for these new agents. In the absence of comparative data, optimal treatment selection is frequently influenced by patient-specific factors or provider preference. We are just a few weeks away from the upcoming IKCS 2021 that can keep abreast of the latest advances in the care and treatment of people with kidney cancer. Following virtual conferences in the recent past, this year's symposium will be a hybrid event accommodating both in-person in Austin, Texas, and also online attendees virtually on November 5-6.

Currently, due to the lack of predictive biomarkers in the RCC paradigm, there is a major unmet need for the identification of novel biomarkers predictive of treatment response or resistance. In particular, initial treatment selection and identification of novel targets in patients with non-clear cell renal cell carcinomas have not been established. In this issue, Halabi et al demonstrated the negative prognostic value for Akt pathway activation and the positive prognostic value for c-kit expression in a prospective clinical trial of sunitinib vs. everolimus in patients with non-clear cell RCC. Authors also showed that c-MET expression is associated with a poor response to sunitinib or everolimus, while c-kit expression is associated with a better response to everolimus. However, no predictive biomarkers of treatment response were identified for clinical outcomes. In the expert perspective column, Dr. Ramaprasad Srinivasan, the principal investigator of Study-004, reflected on the journey of the belzutifan agent from clinical trials to clinical practice and also explored encouraging clinical outcomes and prospective aspects from the Study-004 trial. In another Q&A session, Dr. Nicholas Vogelzang provided his perspectives about currently ongoing studies in the evolving therapeutic landscape of RCC and also shared his insights on current challenges and prospective strategies in the management of mRCC. A review article which Dr. Thomas Hutson and I authored, outlines currently available treatment strategies, unprecedented changes, and also discusses challenges in the treatment landscape of RCC.

Tissue based biomarkers in non-clear cell RCC: Correlative analysis from the ASPEN clinical trial

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Biomarkers are needed in patients with non-clear cell renal cell carcinomas (NC-RCC), particularly papillary renal cell carcinoma, in order to inform on initial treatment selection and identify potentially novel targets for therapy. We enrolled 108 patients in ASPEN, an international randomized open-label phase 2 trial of patients with metastatic papillary, chromophobe, or unclassified NC-RCC treated with the mTOR inhibitor everolimus (n=57) or the vascular endothelial growth factor (VEGF) receptor inhibitor sunitinib (n=51), stratified by MSKCC risk and histology. The primary endpoint was overall survival (OS) and secondary efficacy endpoints for this exploratory biomarker analysis were radiographic progression-free survival (rPFS) defined by intention-to-treat using the RECIST 1.1 criteria and radiographic response rates. Tissue biomarkers (n=78) of mTOR pathway activation (phospho-S6 and -Akt, c-kit) and VEGF pathway activation (HIF-1α, c-MET) were prospectively explored in tumor tissue by immunohistochemistry prior to treatment and associated with clinical outcomes. We found that S6 activation was more common in poor-risk NC-RCC tumors and S6/Akt activation was associated with worse PFS and OS outcomes with both everolimus and sunitinib, while c-kit was commonly expressed in chromophobe tumors and associated with improved outcomes with both agents. C-MET was commonly expressed in papillary tumors and was associated with lower rates of radiographic response but did not predict PFS for either agent. In multivariable analysis, both pAkt and c-kit were statistically significant prognostic biomarkers of OS. No predictive biomarkers of treatment response were identified for clinical outcomes. Most biomarker subgroups had improved outcomes with sunitinib as compared to everolimus.

INTRODUCTION

Non-clear cell renal cell carcinoma (NC-RCC) comprises a genetically and histologically diverse set of cancers, including type 1 and 2 papillary renal cell carcinoma (RCC), chromophobe RCC, translocation carcinoma, as well as many other rare subtypes, some of which remain histologically unclassified[1,2]. NC-RCC accounts for about 25% of all cases of RCC. However, in the metastatic setting, the subtypes of NC-RCC that are most commonly found are type 2 papillary and unclassified NC-RCC given their more aggressive disease course[1].

We and others have recently reported on randomized prospective clinical trials comparing the vascular endothelial growth factor (VEGF) sunitinib with the mTOR inhibitor everolimus in patients with metastatic NC-RCC (ASPEN and ESPN)[3,4]. In these trials, sunitinib provided superior response rates and more durable control of disease; however, outcomes were heterogeneous based on histologic subtypes. For example, patients with papillary RCC and unclassified RCC, as well as those patients with good/intermediate risk disease had superior outcomes with sunitinib, while patients with chromophobe RCC and those with poor risk disease had superior outcomes with everolimus[3]. We recently reported differential outcomes based on differential plasma angiokine and immunokine levels in this setting, which were quite heterogeneously expressed according to disease risk and histology and over time during treatment resistance[5]. These data support the concept that these non-clear cell tumors should be regarded as distinct molecular and phenotypic entities with distinct treatment outcomes with molecularly targeted therapies, and has

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N (%)	Baseline Data (n=78)	No Baseline Data (n=30)	Total (N=108)
Treatment			
Sunitinib	36 (46.2)	15 (50.0)	51 (47.2)
Everolimus	42 (53.8)	15 (50.0)	57 (52.8)
Median Age (years, min - max)	63 [23 - 89]	59 [27 - 100]	63 [23 - 100]
Male Gender	53 (67.9)	28 (93.3)	81 (75.0)
Ethnicity			
Hispanic/Latino	2 (2.6)	0 (0)	2 (1.9)
Not Hispanic/Latino	75 (96.2)	29 (96.7)	104 (96.3)
Missing	1 (1.3)	1 (3.3)	2 (1.9)
Race			
White	69 (88.5)	25 (83.3)	94 (87.0)
Black	9 (11.5)	3 (10.0)	12 (11.1)
Other	0 (0.0)	2 (6.7)	2 (1.9)
Histologic Subtype			
Papillary Type I	3 (3.8)	3 (10.0)	6 (5.6)
Papillary Type II	21 (26.9)	5 (16.7)	26 (24.1)
Papillary Unspecified	18 (23.1)	11 (36.7)	29 (26.9)
Chromophobe	13 (16.7)	3 (10.0)	16 (14.8)
Poorly Differentiated	6 (7.7)	2 (6.7)	8 (7.4)
Mixed Papillary/Chromophobe	1 (1.3)	0 (0.0)	1 (0.9)
Other	16 (20.5)	6 (20.0)	22 (20.4)
Motzer Risk Score			
Good	23 (29.5)	6 (20.0)	29 (26.9)
Intermediate	44 (56.4)	20 (66.7)	64 (59.3)
Poor	11 (14.1)	4 (13.3)	15 (13.9)
Median Overall Survival (months, 95% CI)	22.2 (14.8 – 39.5)	13.1 (9.3 – NR)	18.2 (13.2 – 36.2)
Median Progression-free Survival (months, 95% CI)	6.0 (5.6 – 8.4)	6.4 (4.3 – 11.1)	6.0 (5.6 – 8.2)
Objective Response	11 (14.1)	3 (10.0)	14 (13.0)

Table 1 | Baseline characteristics of patients included in the present correlative IHC study as compared to those patients without available biomarker data. NR indicates the estimate was not reached.

been supported by retrospective studies suggesting a subset of patients with mTOR inhibitor sensitivity[6].

The identification of biomarkers predictive of treatment benefit is a major unmet need in the field of RCC therapy. In clear cell RCC, differential outcomes with immune checkpoint blockade have been observed in patients with tumors with sarcomatoid differentiation, those harboring particular immune subsets of T cell effector function, and perhaps certain complex genomic signatures [7,8]; however, these have not been established in non-clear cell RCC and are not commonly utilized to inform treatment selection. While histology (clear cell disease) is predictive of the benefits of high dose IL-2, and serum LDH may be predictive of the benefits of mTOR inhibition in poor risk RCC, there are no other clear predictors of treatment response or survival to specific therapies. An analysis of the RECORD-3 trial comparing sunitinib and everolimus identified several composite prognostic circulating biomarkers for progression-free survival with everolimus, but were unable to predict overall survival and the analyses were largely restricted to clear cell RCC[9]. In addition, a subset of papillary RCC patients have disease that is driven by activation of the c-MET oncogene, and may benefit from c-MET inhibitors10. Furthermore, recent data from the PAPMET randomized phase 2 trial suggests that dual VEGF/c-MET targeting with cabozantinib may provide a greater probability of durable disease control as compared to sunitinib in patients with advanced papillary RCC[11].

Given the heterogeneity of genomic alterations and phenotype as well as clinical outcomes of patients with metastatic non-clear cell RCC, we sought to characterize markers of specific pathway activation linked to molecularly targeted therapies. To accomplish this, we utilized tissue based protein biomarkers of mTOR and VEGF/MET pathway activation in patients with metastatic non-clear cell RCC as part of the international, randomized, prospective clinical trial comparing sunitinib and everolimus (ASPEN). We asked whether evidence of mTOR pathway activity or VEGF-HIF-1α/MET expression differed by histologic subtype and MSKCC risk group[12, 13], and whether clinical efficacy outcomes differed by baseline tissue pathway biomarker expression at the protein level. Based these previous studies, familial syndromes of mTOR pathway activation in chromophobe RCC14 and c-met pathway activation in hereditary and sporadic papillary RCC[15], and our own plasma biomarker analysis[5], our specific a priori hypotheses were that pS6 and pAKT high level expression will be associated with a greater radiographic progression free survival (rPFS) by RECIST 1.1 criteria with everolimus as compared to sunitinib as well as ORR and OS; c-KIT high level expression will be associated with chromophobe histology and a greater rPFS, ORR, and OS benefit with everolimus as compared to sunitinib; and finally that HIF-1α and c-MET will be associated with papillary RCC histology and will be associated with a greater rPFS, ORR, and OS benefit with sunitinib as compared to everolimus. We also suspected that high levels of pS6 and pAKT and cMET will be associated with poor outcomes overall including shorter rPFS, OS, and low ORR regardless of therapy.

We employed immunohistochemical studies of primary nephrectomy or metastatic biopsy specimens to examine the prognostic and predictive associations with progression-free and overall survival in this pre-specified prospective secondary analysis. Such findings could ideally permit the selection of patients for an mTOR or VEGF/MET treatment such as cabozantinib more optimally than histology or clinical risk score alone.

RESULTS

From September 23, 2010 through October 28, 2013, we accrued 109 subjects across three (3) countries and 17 participating sites. One subject did not receive the study drug and

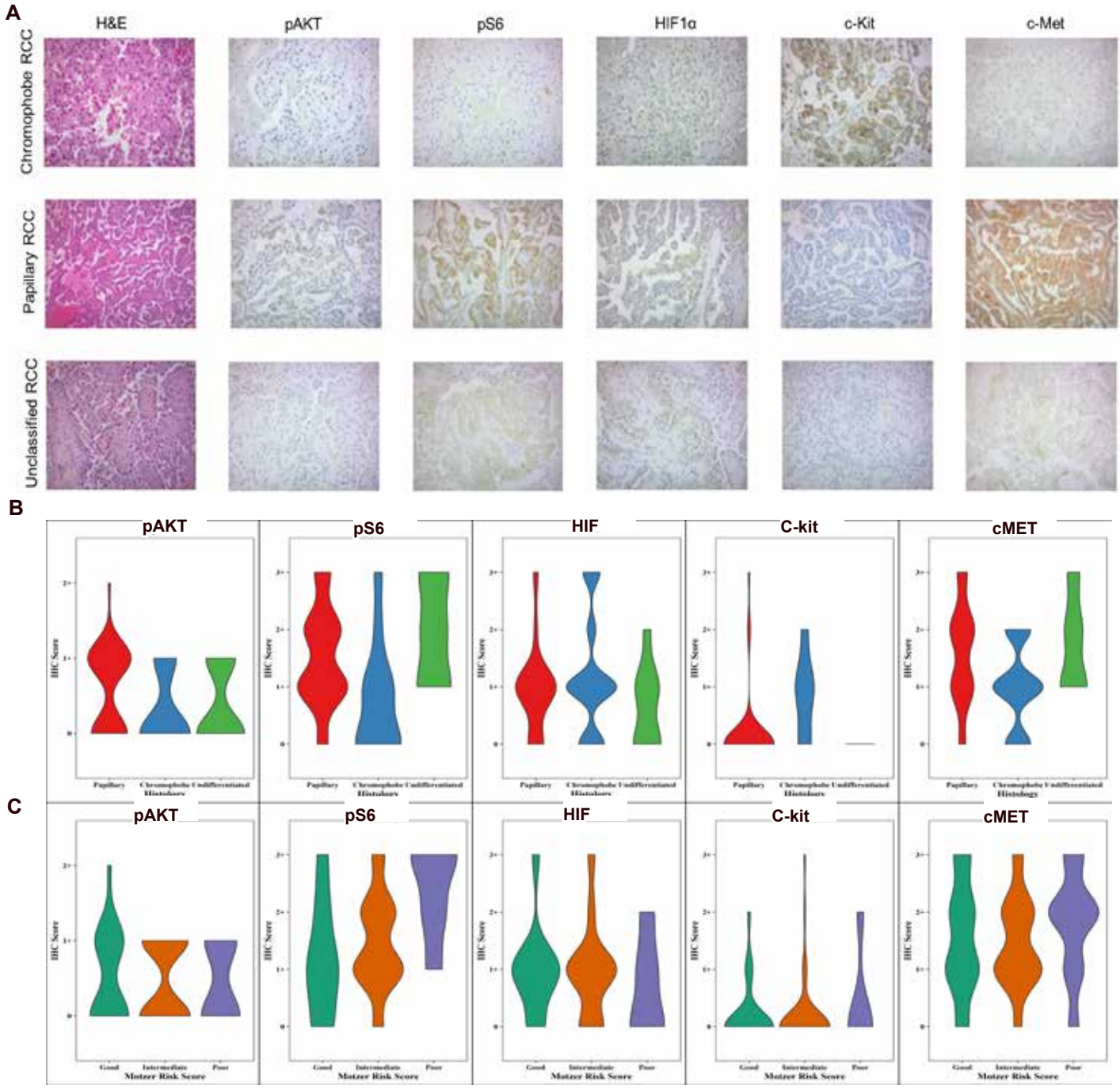

Figure 1: (A) Representative images of biomarker expression by immunohistochemistry from the ASPEN study according to histologic subtypes of papillary, chromophobe, and unclassified RCC. Note c-kit expression predominantly in chromophobe RCC, c-met expression in papillary RCC. **(B)** Distributions of tissue IHC biomarker expression levels according to histologic subtype categorized as papillary (red), chromophobe (blue), and undifferentiated (green). (**C**) Distributions of tissue IHC biomarker expression levels according to MSKCC risk groups coded as good (green), intermediate (orange), and poor (purple).

withdrew and was replaced, leaving 108 evaluable subjects who were then randomized to sunitinib (51 subjects) or everolimus (57 subjects). Biomarker data was available from 78 of 108 patients (72%), with over 90% of the cases derived from primary tumor tissue from nephrectomy or renal biopsy, including 36 patients treated with sunitinib and 38 patients treated with everolimus. Thirty patients (15 in each treatment group) had insufficient tissue available for IHC studies, and are excluded from this analysis (see CONSORT diagram, Supplementary Figure 1). The data lock for the final overall survival analysis was May 2016.

Patients in the biomarker evaluable population did not differ from those without evaluable biomarkers with the exception of more women (32% vs. 7%), more type 2 papillary (27% vs. 17%), and fewer intermediate MSKCC risk patients (56% vs. 67%) in the biomarker group, respectively (Table 1). The majority of evaluable patients (42/78, 54%) had metastatic papillary RCC with non-type 1 histology; only 3 patients had type 1 papillary RCC. The second most common histologic subtype was metastatic chromophobe RCC, which accounted for 17% of patients, followed by unclassified/poorly differentiated RCC, comprising 8% of patients.

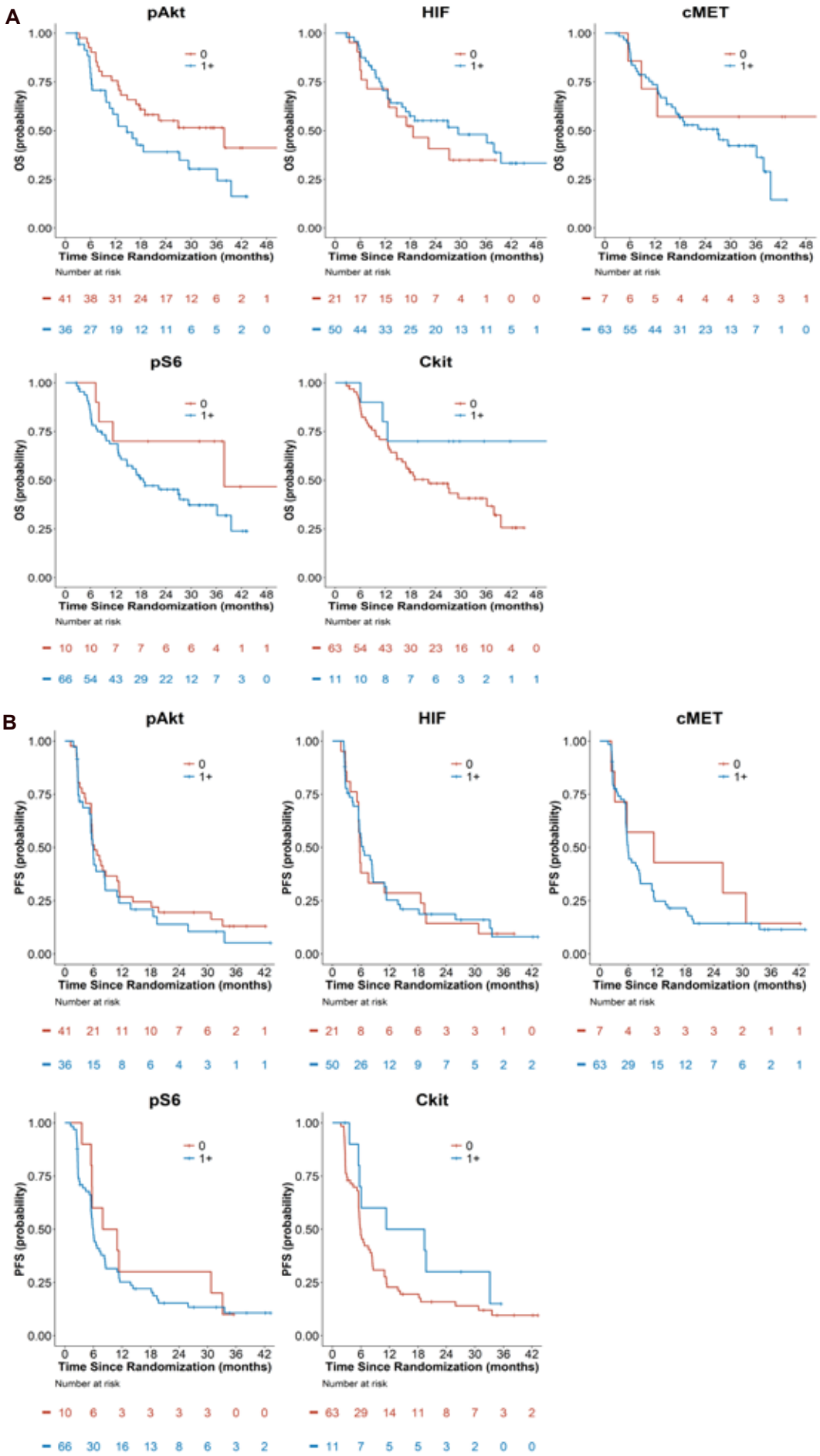

Figure 2: (A) Kaplan-Meier Overall Survival Curves by Tissue Biomakers (pAkt, pS6, HIF-1α, c-kit, and c-MET). **(B)**. Kaplan-Meier Progression-Free Survival Curves by Tissue Biomakers (pAkt, pS6, HIF-1α, c-kit, and c-MET).

Distribution of Tissue Protein Biomarkers

Lower protein expression scores were more common across all patients for p-Akt, HIF-1α, and c-kit with 1.3%, 12.8%, and 6.4% harboring at least 2+ expression by IHC. The distribution of IHC scores was fairly balanced for p-S6 and c-MET, with 44.8% and 43.6% of patients harboring at least 2+ expression by IHC (Supplementary Table 3). Representative IHC images of each biomarker across the 3 histologic subtypes are shown in Figure 1A.

Association of Tissue Protein Biomarkers with Histology and MSKCC Risk Group

Chromophobe patients had a greater percentage of 0 IHC values for p-Akt, p-S6, and c-MET, and as expected were more likely to have detectable (1+ or higher) c-kit expression than non-chromophobe RCC patients (62% vs. 5%) (Figure 1B, Supplementary Table 3). The distributions were fairly uniform within each group for p-S6 and c-MET. In papillary RCC, c-MET expression was absent in 9.3% of patients as compared to 23% of chromophobe and 0% of unclassified tumors. However, any expression and intense 3+ expression of c-MET was detected in 82%, 69%, and 86% in papillary, chromophobe, and unclassified tumors, respectively, while intense 3+ c-MET expression was detectable in 14%, 0%, and 18%, respectively, indicating the c-MET expression was not restricted to papillary subtypes.

Phospho-Akt, HIF-1α, and c-MET scoring distributions were similar across the three MSKCC risk groups. Patients with good MSKCC risk were more likely to have absent p-S6 (26%) as compared to patients with poor MSKCC risk (0%), and less likely to have intense p-S6 staining of at least 3+ (13% vs 55%). Patients with good MSKCC risk had lower scores

A

Biomarker	Median OS (months, 95% CI)		N	Univariate		Multivariable	
	0	1+		HR (95% CI)	P Value	HR* (95% CI)	FDR
pAkt	37.9 (17.7-NR)	14.7 (10.5-36.2)	77	1.8 (1.0-3.3)	0.055	2.2 (1.1-4.2)	0.056
pS6	37.9 (11.3-NR)	18.6 (13.2-39.5)	76	2.1 (0.8-6.0)	0.149	1.5 (0.4-5.0)	0.529
HIF-1α	18.6 (12.6-NR)	29.3 (16.0-NR)	71	0.8 (0.4-1.5)	0.410	0.8 (0.4-1.6)	0.529
c-kit	22.2 (14.8-39.5)	NR (12.5-NR)	74	0.4 (0.1-1.3)	0.131	0.1 (0.0-0.7)	0.056
c-MET	NR (8.7-NR)	26.9 (16.8-NR)	70	1.9 (0.6-6.5)	0.302	1.9 (0.5-7.2)	0.529

B

Biomarker	Median PFS (months, 95% CI)		N	Univariate		Multivariable	
	0	1+		HR (95% CI)	P Value	HR* (95% CI)	FDR
pAkt	6.1 (5.6-11.3)	5.9 (5.5-11.0)	77	1.2 (0.7-2.0)	0.431	1.3 (0.8-2.1)	0.851
pS6	9.5 (5.7-NR)	5.9 (5.5-8.4)	76	1.3 (0.7-2.7)	0.438	1.2 (0.5-2.9)	0.877
HIF-1α	5.7 (5.5-19.4)	6.5 (5.6-11.0)	71	1.0 (0.6-1.7)	0.927	1.1 (0.6-2.0)	0.877
c-kit	5.9 (5.5-8.4)	15.4 (5.7-NR)	74	0.6 (0.3-1.2)	0.155	0.4 (0.2-1.1)	0.333
c-MET	11.4 (3.2-NR)	5.9 (5.5-8.5)	70	1.4 (0.6-3.3)	0.447	1.1 (0.4-2.7)	0.899

Table 2: (A) Median overall survival (OS) by tissue biomarkers for all evaluable patients. Univariate and multivariable hazard ratios of OS for each biomarker. Cut-point of 1+ scoring. NR indicates the estimate was not reached. **Adjusting for treatment arm and stratification variables (histology and MSKCC risk groups)* (**B**) Median progression-free survival (PFS) by tissue biomarkers for all evaluable patients. Univariate and multivariable hazard ratios of PFS for each biomarker. Cut-point of 1+ scoring. NR indicates the estimate was not reached.

of p-S6 while relatively more poor risk patients had higher IHC scores for this biomarker (Figure 1, Supplementary Table 3). Thus, neither c-MET nor p-AKT staining distinguished risk groups, while downstream p-S6 was clearly associated with poor risk disease.

Associations of Tissue Biomarkers with Clinical Outcomes

There were 67 PFS events and 44 deaths in 78 patients with evaluable tissue biomarker data and as of the final data lock in May 2016, the median follow-up time in 34 alive patients was 29 months (range=2.6-55.7). Patients with 1+ pAkt tumor tissue staining had a shorter median OS (14.7 months) as compared with patients with absent p-Akt (37.9 months). However, none of the five tissue biomarkers were prognostic of OS in univariate analysis (Figure 2A and Table 2).

In multivariable analysis of OS, however, both p-Akt and c-kit were statistically significant prognostic biomarkers of OS after multiplicity adjustment and adjustment for histologic type and MSKCC risk. The multivariable hazard ratio (HR) for death for p-Akt was 2.2 (95% CI=1.1-4.2, FDR=0.056). On the other hand, detection of c-kit was associated with improved survival (HR=0.1;95% CI=0.0-0.7; FDR=0.056) irrespective of histology.

None of the tissue biomarkers were associated with PFS overall (Table 2B, Figure 2B). Additionally, when exploring a higher threshold cut-off for IHC positivity of 2-3+ expression, none of the biomarkers had statistically significant associations with OS or PFS in secondary analyses comparing biomarker expression 0-1 versus >2+ (Supplementary Tables 5A and 5B).

Predictive Associations with Clinical Outcomes

Finally, we examined each of the 5 pathway-based protein biomarkers for associations with outcomes of either sunitinib or everolimus and the predictive value of biomarker expression for superiority of one therapy over the other. None of the tissue biomarkers were predictive of treatment benefit for OS or PFS for sunitinib or everolimus (Tables 3A and 3B) regardless of the IHC scoring thresholds (Supplementary Tables 5A and 5B). Lastly, while none of the biomarkers were predictive of differential objective response (Tables 4B and Supplementary 7B), we did note that patients with c-MET expressing tumors had a lower objective response rate by RECIST 1.1 (11% ORR) as compared to patients with tumors lacking c-MET expression (43% ORR). In sunitinib treated patients, the ORR was 17% vs 50% in patients with c-MET expressing vs. non-expressing tumors, while in everolimus treated patients, the ORR was 6% vs. 33% respectively. The ORR for patients with high c-kit expression was 0% for sunitinib vs. 24% for patients with absent c-kit expression, as compared to the opposite result for everolimus, which had an ORR of 25% for patients with high c-kit expression as compared to 6% for patients that lacked c-kit expression.

DISCUSSION

The treatment of patients with metastatic non-clear cell RCC continues to evolve and improve. Based on the ASPEN and ESPN randomized trials, sunitinib was demonstrated to have more prolonged progression free and overall survival and higher objective response rates as compared to everolimus3,4 overall and particularly in favorable/intermediate risk and papillary/unclassified subtypes. However, everolimus had clear activity and and improved outcomes in patients with poor risk disease and chromophobe RCC variants, mirroring prior prospective data derived from the global phase 3 temsirolimus trial. Recently cabozanitinb was shown to have superior responses and PFS as compared to sunitinib in advanced papillary RCC (both type 1 and 2), suggesting that dual inhibition of c-MET and VEGF may provide more durable clinical benefits11. Here we sought to identify subgroups of patients

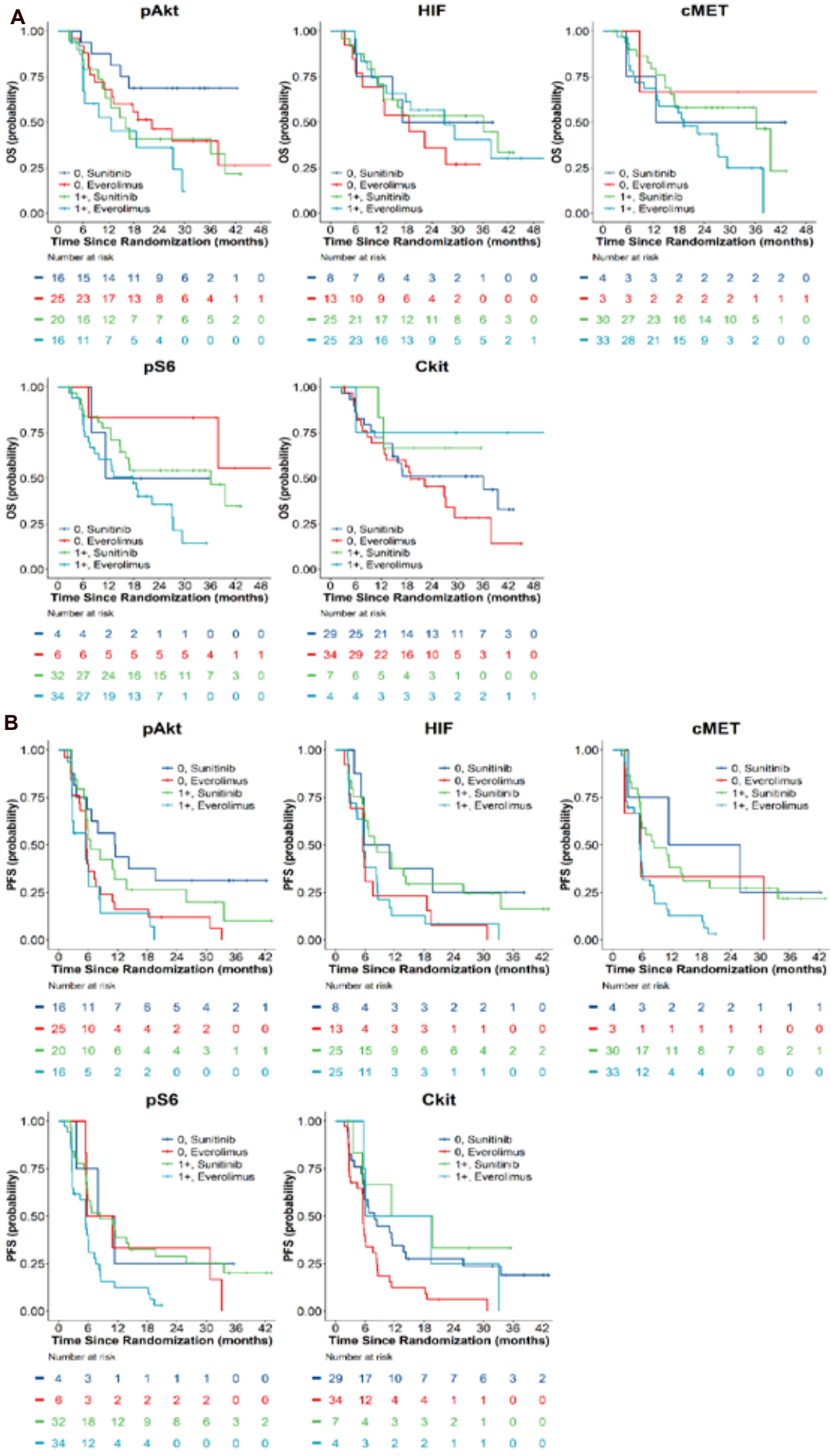

Figure 3: (A) Kaplan-Meier Overall Survival Curves by Treatment Assignment and Tissue Biomakers (pAkt, pS6, HIF-1α, c-kit, and c-MET). **(B)** Kaplan-Meier Progression-Free Survival Curves by Treatment Assignment and Tissue Biomakers (pAkt, pS6, HIF-1α, c-kit, and c-MET).

that may differentially respond to molecularly targeted therapies through the use of protein-based assays of potential driver pathways. While we found that activation of the mTOR pathway including low level Akt and S6 phosphorylation was associated with poor risk disease and worse survival, these biomarkers were not sufficiently predictive of clinical benefit for everolimus compared to sunitinib. While chromophobe patients with high c-kit expression had a numerically higher ORR with everolimus than sunitinib, this did not translate into longer PFS or OS potentially due to the relatively small sample size of this subgroup.

Recently, we identified specific subsets of non-clear cell RCC patients that have poor outcomes in the ASPEN trial based on levels of plasma angiokines associated with angiogenesis, metastasis, and immune evasion, particularly osteopontin (OPN), TIMP-1, thrombospondin-2, hepatocyte growth factor (HGF), and VCAM-116. These data suggest potential therapeutic targets associated with disease burden and treatment resistance. We could not directly assess most of these biologic features in tumor tissues, and thus cannot correlate tumor angiokine expression with plasma levels and clinical outcomes. However, when we could there was not a clear correlation with outcomes. For instance, we evaluated c-met, the receptor for hepatocyte growth factor, in tumors and found no correlation with c-met levels and clinical outcomes in non-clear cell as well as the subset of papillary RCC patients treated with sunitinib or everolimus, despite a prognostic association of high plasma HGF levels with poor overall survival5. Other assessments of pathway addiction such as c-met phosphorylation or amplification or splice variants, or mTOR pathway mutations[17, 18], should be further evaluated against specific targeted therapy outcomes in this

A

Biomarker	Median OS (months, 95% CI)				N	Univariate	Multivariable
	Sunitinib		Everolimus			P Value	FDR
	0	1+	0	1+			
pAkt	NR (16.8-NR)	16.0 (11.3-NR)	22.2 (12.7-NR)	12.6 (6.1-NR)	77	0.560	0.717
pS6	11.3 (8.0-NR)	36.2 (14.8-NR)	NR (37.9-NR)	17.7 (8.7-29.3)	76	0.101	0.717
HIF-1α	17.0 (14.7-NR)	36.2 (12.5-NR)	18.6 (7.6-NR)	26.9 (13.2-NR)	71	0.530	0.717
c-kit	36.2 (14.8-NR)	NR (12.5-NR)	19.0 (12.7-NR)	NR (6.1-NR)	74	0.473	0.717
c-MET	12.5 (5.5-NR)	36.2 (16.8-NR)	NR (8.7-NR)	19.0 (12.7-NR)	70	0.429	0.717

B

Biomarker	Median PFS (months, 95% CI)				N	Univariate	Multivariable
	Sunitinib		Everolimus			P Value	FDR
	0	1+	0	1+			
pAkt	11.4 (5.7-NR)	6.5 (5.6-NR)	5.7 (5.5- 8.6)	5.5 (2.8-18.6)	77	0.662	0.868
pS6	9.6 (3.5-NR)	8.4 (5.7-25.9)	8.3 (5.7-NR)	5.5 (3.0-7.3)	76	0.489	0.778
HIF-1α	8.4 (5.7-NR)	8.4 (5.9-33.6)	5.6 (3.0-NR)	5.7 (4.4-8.6)	71	0.735	0.869
c-kit	8.0 (5.8-14.3)	15.5 (5.5-NR)	5.5 (5.5-8.3)	12.7 (5.7-NR)	74	0.698	0.778
c-MET	18.6 (3.2-NR)	8.4 (5.8-19.7)	5.7 (2.4-NR)	5.6 (5.5-7.6)	70	0.957	0.778

Table 3: (A) Median overall survival (OS) by treatment group and tissue IHC biomarkers using a cut-point of 1+, including biomarker-treatment interaction p-values. NR indicates the estimate was not reached. (**B**) Median progression-free survival (PFS) by treatment group and tissue IHC biomarkers using a cut-point of 1+, including biomarker-treatment interaction p-values. NR indicates the estimate was not reached.

context.

Our analysis has several limitations. The first is the heterogeneous nature of our patient population, comprised of multiple tumor types with likely widely differing genotypes and biomarker expression profiles and differing clinical risk groups. This limits our power to determine predictive interactions for individual subgroups and therapies. The second is the current lack of genotyping data in this trial at the present time, which does not permit a more detailed molecular analysis of pathway mutations, amplifications, splice variants, or expression. We chose to focus our biomarker studies for the present analysis on protein and phosphoproteomic alterations given that the functional consequences of the known genomic alterations is frequently unknown, and we hypothesized that these pathway-based protein assays would be more functionally relevant to drug activity for therapies targeting the mTOR or VEGF pathways. Third is the lack of present information in this trial on the activity of other pathways, such as the NRF2/KEAP1, fumarate hydratase and other metabolic regulators, or epigenetic regulators. Further investigation into these and other key biologic processes including the immune landscape of these tumors may shed light into future therapeutic directions, including combination VEGF/c-MET and immune checkpoint blockade or novel approaches.

Our work has several strengths, including being the largest, prospective global trial conducted to date in this metastatic non-clear cell RCC population. We mandated tissue collection as part of eligibility, which ensured a robust program for biomarker study, and we utilized previously validated IHC assays with appropriate validated controls. Our pathologists were blinded to outcome, while our statisticians performed the clinical analysis while blinded to biomarker studies, ensuring a lack of bias in the data analysis plan. While the trial was open label for treatment, treatment was randomized and not selected based on any patient or tumor characteristics. IHC studies are relatively easy to conduct in clinical practice relative to complex genotyping assays, and thus this work could be readily applicable if successful. Finally, we conducted long term follow up to ensure an adequate number of events for the gold standard of overall survival as an endpoint.

In conclusion, we demonstrate the negative prognostic value for Akt pathway activation in non-clear cell RCC and the positive prognostic value for c-kit expression in a prospective clinical trial of sunitinib vs. everolimus. Additionally, we show that c-MET expression is associated with a poor response to sunitinib or everolimus, while c-kit expression is associated with a better response to everolimus. However, we were unable to show a predictive treatment-biomarker interaction using the 5 pathway-directed biomarkers in this study, and thus, overall sunitinib remained the superior therapy in the ASPEN trial.

MATERIALS & METHODS

Study design and patients

This was a prospective, open-label randomized United States Food and Drug Administration IND-exempt trial conducted across 17 participating global sites, including the United States, Canada, and the United Kingdom. Regulatory oversight in Canada and the UK was obtained for this trial. After meeting eligibility, randomized subjects were assigned 1:1 to either sunitinib malate or everolimus at approved doses until disease progression.

Patients were eligible if they had histologically confirmed advanced RCC with non-clear cell pathology after local site review by pathology, including unclassified subtypes. Mixtures of these non-clear cell variants were allowed provided they consisted predominantly (> 50%) of papillary, chromophobe or undifferentiated histology. Patients with minor clear cell components (<50%) were permitted provided the dominant histology and presumed primary histology was non-clear cell. Exclusion criteria for the study included active untreated CNS metastases, prior systemic therapy for RCC, and collecting duct or medullary histology. Full eligibility details are provided in the primary clinical manuscript[3].

This study was registered as an International Standard Randomised Controlled Trial with ClinicalTrials.gov number NCT01108445. All patients provided informed consent under an

A

Biomarker	0 N (%)	1+ N (%)	N	OR (95% CI)
pAkt	6 (14.6)	5 (13.9)	77	0.9 (0.2 – 3.4)
pS6	1 (10.0)	10 (15.2)	76	1.6 (0.3 – 31.3)
HIF-1α	3 (14.3)	7 (14.0)	71	1.0 (0.2 – 4.9)
c-kit	9 (14.3)	1 (9.1)	74	0.6 (0.0 – 3.8)
c-MET	3 (42.9)	7 (11.1)	70	0.2 (0.0 – 1.0)

B

Biomarker	Sunitinib			Everolimus		
	N	0 N (%)	1+ N (%)	N	0 N (%)	1+ N (%)
pAkt	36	3 (18.8)	4 (20.0)	41	3 (12.0)	1 (6.2)
pS6	36	0 (0.0)	7 (21.9)	40	1 (16.7)	3 (8.8)
HIF-1α	33	1 (12.5)	6 (24.0)	38	2 (15.4)	1 (4.0)
c-kit	36	7 (24.1)	0 (0.0)	38	2 (5.9)	1 (25.0)
c-MET	34	2 (50.0)	5 (16.7)	36	1 (33.3)	2 (6.1)

Table 4: (A) Objective response rate showing N (%) and odds ratio (95% CI) by IHC 0 vs. 1+ biomarker status. **(B)** Objective response rate by treatment assignment and IHC 0 vs. 1+ biomarker status.

institutional IRB-approved consent form. This was an investigator-initiated study, with the Duke Cancer Institute as lead coordinating center and biorepository. A contract research organization, inVentiv Health Clinical, oversaw the collection of data and safety monitoring on behalf of Duke globally.

Tissue Biomarker Studies

Primary nephrectomy or metastatic biopsy specimens were prospectively collected on all patients as part of the eligibility criteria for the ASPEN trial. Formalin-fixed paraffin embedded tissue was collected and underwent IHC studies for 5 biomarkers: phospho-S6 and phospho-Akt as measures of mTOR pathway activation; c-kit as a defining biomarker of chromophobe RCC which has been associated with mTOR pathway activation through folliculin mutations 14; c-MET total expression; and HIF-1α as a measure of VEGF pathway activation. The specific antibodies utilized and validated on control tissues, their concentration/dilution, and methods used are described in Supplementary Table 1. Investigators and statisticians were blinded to the results of these biomarker studies at the time of outcome analysis.

Outcomes

The primary endpoint of this tissue biomarker study was overall survival (OS), defined as the interval from date of random assignment until date of death or date of last follow-up. A key secondary outcome included radiographic progression-free survival (PFS), defined as the time from date of random assignment until date of disease progression (by RECIST 1.1 criteria), a new primary malignancy, or death, whichever occurred first. Other pre-specified efficacy secondary endpoints included radiographic response rates per RECIST 1.1, and clinical benefit response (CBR), defined as the composite sum of partial response, complete response, and prolonged stable disease for more than 6 months. Objective response rate (ORR) was defined as the sum of complete and partial response by RECIST 1.1.

Statistical analysis

The five tissue biomarkers (phospho-S6, phospho-Akt, c-kit, HIF-1α, and c-MET) include the IHC scores of 0, 1+, 2+, or 3+. Missing data from the 78 evaluable patients were excluded from the analyses and resulted from either an insufficient amount of tumor to categorize the sample, the sample being of an unacceptable quality, or a lack of tissue provided by the patient. All five tissue biomarkers were dichotomized and analyzed using two pre-specified cut-points in the statistical analysis plan. The primary analysis was based on 0 vs. 1+ whereas the secondary analysis was 0-1 vs. 2+, where the "1+" group included scores of 1+, 2+, and 3+, and the "2+" group included scores of 2+ and 3+. The proportional hazards model was utilized to determine the prognostic importance of the tissue biomarkers in predicting OS and PFS adjusting for the treatment arm and the stratification factors (histologic type and MSKCC risk groups). The association of each biomarker with OS and PFS was summarized with a hazard ratio (HR) and 95% confidence interval (CI) for this exploratory analysis, while p-values were adjusted for multiplicity using the false discovery rate (FDR) of 0.056, and we considered FDR<0.1 to be statistically significant. Additionally, the proportional hazards model was used to test for each of the tissue biomarker-treatment interaction terms in predicting OS and PFS. The Kaplan-Meier approach was used to estimate the OS and PFS distributions.

When assessing the association of the biomarkers with histologic subtype, we classified all papillary tumors, including types I and II, as "papillary." Chromophobe tumors were designated "chromophobe," and the remaining 30 patients fell into the "undifferentiated" category. Patients with an MSKCC risk score of 0 were classified as having "good" risk, while patients who had MSKCC risk scores of either 1 or 2 were assigned to the "intermediate" group, and those with a score of 3 or above were categorized as "poor."

Furthermore, logistic regression analysis was used to test for the prognostic importance of the tissue biomarkers in predicting objective response rate. Odds ratios (OR) and 95% confidence intervals (CI) summarized these findings. The final statistical analysis plan was approved by the Duke IRB on August 14, 2014. All analyses were performed using R version 3.5.3 and were adjusted for multiplicity using the false discovery rate (FDR) in determining whether any of tissue biomarkers were prognostic or predictive of OS or PFS.

SUPPLEMENTAL INFORMATION

Any supplementary information

including supplementary figures and supplementary tables, legends, respective materials and methods, conflicts of interest, other relevant data can be found online at:

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AUTHOR CONTRIBUTIONS

AJA: literature search, figures, study design, data analysis and interpretation, writing;
SH: data analysis and interpretation, study design, figures, writing;
QY, SZ, AC: data analysis and interpretation, figures, writing
TE, WMS, RJJ, JAG, UNV, JP, REH, JDH, CKK, TFL, IP, LMP, CWR, AP: data collection, analysis, and interpretation, writing;
WCF: data collection and analysis, writing;
DJG: literature search, figures, study design, data analysis and interpretation, writing.

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Bristol Myers Squibb™

Exploring beyond observation Checkmate 914 is exploring adjuvant IO regimen for RCC patients

Bristol Myers Squibb is currently conducting a clinical trial exploring immuno-oncology (IO) agents for early-stage, high-risk renal cell carcinoma (RCC): CheckMate 914.

CheckMate 914 is a randomized, Phase 3 clinical trial evaluating adjuvant nivolumab alone or in combination with ipilimumab in patients who underwent radical or partial nephrectomy and who are at high risk of relapse.

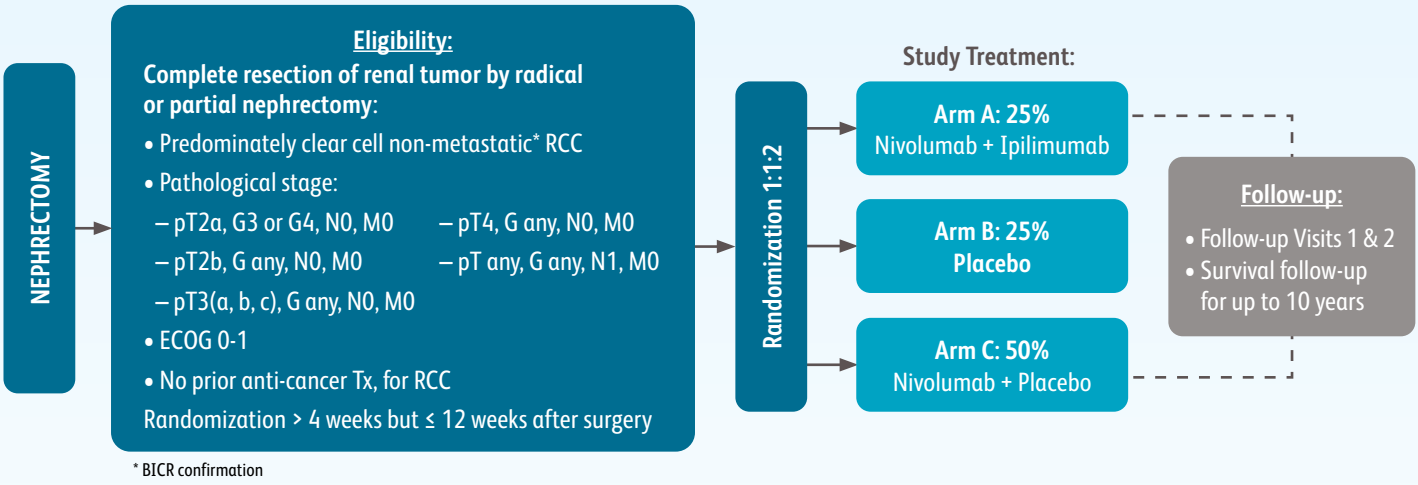
Timing is critical

Research post-surgery plans **before** surgery happens. For this clinical trial, randomization must occur between 4 and 12 weeks from the date of nephrectomy

Exploring beyond observation

This study seeks to investigate the role of an IO agent compared to the current standard of care (observation)

CHECKMATE 914 Study Design



* BICR confirmation

To find out if your patients are eligible for this trial, learn more at **BMSStudyConnect.com/KCJ**.

Reference: Data on file. Clinical protocol CA209-914. Princeton, NJ: Bristol-Myers Squibb Company, 2020.

RCC
CheckMate 914
CHECKpoint pathway and nivoluMAb clinical Trial Evaluation

STUDY CONNECT
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The Pathway of Belzutifan, from clinical trials to clinical practice: A conversation with Dr. Ramaprasad Srinivasan, MD, PhD

Urologic Oncology Branch, National Cancer Institute, NIH.

KCJ: What is the significance of belzutifan approval for VHL patients? Can you give us your perspective about the incredible journey that led us to development of first-in-class belzutifan ?

Dr. Srinivasan: In order to fully understand what this approval means to VHL patients, I think we should begin by reviewing VHL and how it is currently treated. VHL is an inherited disorder characterized by a predisposition to developing tumors in kidneys, pancreas, adrenal glands, CNS, eyes and the inner ear. Typically, patients are treated with surgery (or laser ablation, retinal hemangioblastomas), with the goal of either minimizing the risk of metastatic disease or preventing local complications from a growing tumor. For instance, in patients with clear cell carcinoma of the kidney (patients generally develop multiple, bilateral tumors), it has been shown that tumors less than 3 cm have little to no risk of metastatic spread, while the risk increased with increasing tumor size beyond this size; the surgical paradigm, therefore, was to operate on tumors that are 3 cm or more to minimize the risk of spread. The approach typically used today is nephron-sparing surgery. Since patients develop tumors throughout their life, most patients need to undergo multiple surgical procedures during their lifetime. Over the last 40 years or so, the major advancements in the treatment of VHL have largely been in the form of improved surgical approaches. Our center is one of the biggest referral centers for the VHL patients and we follow over a thousand patients with the condition. One of my goals, therefore, when I started as an oncologist treating patients with kidney cancer in the early 2000s was to find alternative treatment options for patients with VHL-associated tumors that might minimize the need for surgery or delay surgery.

The development and evaluation of belzutifan can be traced back to several scientific discoveries over the last 30-40 years. By studying patients/families with VHL starting in the 1980s, Drs. Linehan, Berton Zbar and colleagues were able to identify germline inactivating mutations in the VHL gene in affected members and show that this gene functioned as a classical tumor suppressor gene. Somatic mutations in VHL have since been identified in sporadic forms of clear cell RCC. It was subsequently shown that the VHL protein plays a key role in the cellular response to changes ambient oxygen by regulating the cellular levels of the alpha subunits of a group of transcription factors known as hypoxia inducible factors; with loss of VHL, there is overexpression of hypoxia inducible factors. Hypoxia inducible factors, in turn, upregulate a variety of proteins (including VEGF) that are believed to play a key role in VHL-dependent oncogenesis. Several lines of evidence have subsequently implicated HIF2 as the key player in this process. As you know, the 2019 Nobel Prize in Medicine and Physiology was awarded to Drs. William Kaelin, Gregg Semenza and Peter Ratcliffe for their work in understanding how cells adapt to changes in oxygen levels.

Understanding the biochemical consequences of VHL inactivation and how these changes lead to clear cell kidney cancer were critical drivers of the next step-trying to design and test pharmacologic inhibitors of these pathways. While HIF2 was a logical target for pharmacologic intervention, it was initially believed that HIF itself was 'undruggable'; therefore early efforts targeted downstream consequences of HIF overexpression, particularly the VEGF pathway. While several VEGFR inhibitors were found to be effective in sporadic clear cell RCC, their role in the management of VHL patients was limited. Phase 2 studies showed that although these agents had some activity against VHL-associated renal tumors there was little activity against other VHL-associated tumors. Moreover, the side effects associated with these agents were too much for VHL patients, who often preferred surgical intervention rather than dealing with the changes in quality of life associated with these agents. Then a big breakthrough was made by a group of scientists at UT Southwestern (led by Drs. Richard Bruick and Kevin Gardner) when they identified a particular binding pocket in HIF2 alpha that led to the design of small molecules that could bind in this pocket and prevent the interaction of the alpha subunit with its obligate heterodimeric partner, ARNT.PT 2385 was the first of these agent studied in the clinic , but was soon replaced by belzutifan (formerly PT2977 and MK-6482), which was more potent and had better pharmacologic characteristics. PT2977 quickly went through phase 1 evaluation, was shown to be well tolerated, and then evaluated in a phase 2 study that led to its approval for patients with VHL-associated tumors. As a result of this approval, we have, for the first time, a viable non-surgical treatment option for helping patients with certain types of VHL-associated tumors. Incidentally, this is also the first HIF2a inhibitor to be approved for any indication.

KCJ: That's a great summary. Before we delve into the results, can you please explain the trial design that studied the efficacy of the belzutifan in humans?

Dr. Srinivasan: For this open-label phase 2 study, eligible patients had to have VHL disease with at least one measurable renal tumor that did not require immediate surgery, no evidence of metastatic disease and should not have received any prior systemic anticancer therapy for VHL. The primary end point was the objective response rate in VHL-associated RCC as evaluated by independent central radiology review. Secondary outcomes included duration of response (DOR), time to response, progression-free survival (PFS), safety and tolerability as well as response rate in non-renal VHL associated tumors evaluated individually in each affected organ system.

KCJ: We are hearing a lot of clinical data from Study-004 trial. What are some key findings?

Dr. Srinivasan: As presented at the 2021 ASCO Annual meeting, almost half of all patients achieved an objective response in their renal tumors and an overwhelming majority had some reduction in their tumor size. Additionally, we also saw responses in other affected organ systems, including the pancreas, CNS and eyes. Importantly, the side effect profile was quite favorable, and severe side effects that led to drug discontinuation were uncommon. Anemia, an expected side effect based on the mechanism of action of the drug, was one of the most common side effects but was mild and easily managed in most patients.

KCJ: How would you compare study results from belzutifan Vs those agents that you may have used for treating patients with VHL-associated renal cell carcinoma?

Dr. Srinivasan: There have been no head- to head comparisons of belzutifan with other agents such as VEGFR inhibitors. However, as mentioned before, VEGFR inhibitors such as sunitinib and vandetanib appear to have limited activity against non-renal tumors and are also associated with patient tolerability concerns that we hope will not be an issue with belzutifan. My impression is that we will be seeing more consistent and more widespread reduction in tumor size across all organs in patients taking belzutifan, as compared to previously evaluated agents.

KCJ: Moving on from FDA approval based on phase 2 data involving 61 patients, you'll be seeing patients in a much broader context. How are you going to incorporate it into your real world scenario both in practice?

Dr. Srinivasan: I believe that belzutifan will play an important role in the management of certain VHL patients and should be used judiciously along with surgery as part of a multidisciplinary strategy. My hope is that if properly used, belzutifan will help reduce the number of surgical procedures patients will need to undergo. A lot of questions remain to be answered such as what is the best time to start the drug, how will patients tolerate in the long term and will resistance to the agent emerge? These are important questions that we will be able to answer in time. What is clear, however, is that the approval of belzutifan represents a significant addition to the VHL therapeutic landscape and will fundamentally alter the approach to these patients.

"I believe that belzutifan will play an important role in the management of certain VHL patients and should be used judiciously along with surgery as part of a multidisciplinary strategy."

KCJ: What are the key lessons from the Study 004 that you would like to see adopted and taken forward in phase 3 trials and further research stages?

Dr. Srinivasan: Given the relative rarity of VHL, it would be difficult to conduct a large, randomized study. The choice of a comparator in a randomized study would also pose a challenge since there isn't another agent with established activity in VHL. What we have learned, however, is that a small but well-designed study can effectively address important clinical questions that can serve as the basis for FDA approval, a paradigm that could be used in other rare diseases.

KCJ: Finally, can you sum up your expectations for the future in terms of how belzutifan in combination with TKIs/immunotherapies will continue to evolve?

Dr. Srinivasan: Currently, an ongoing phase 3 multicenter international study is studying metastatic clear cell RCC patients who have failed standard therapy; patients are being randomized to get either belzutifan or everolimus. There are also studies looking at belzutifan in combination with IO and/or TKIs in patients with advanced ccRCC. However, these studies are being done in patients with sporadic ccRCC, not in VHL patients. Combinations in VHL should be explored cautiously. We have learned from prior studies that some VEGFR TKIs are not well tolerated by VHL patients, which will limit our ability to use these agents as combination partners. IO based combinations may be considered, but it is important to keep in mind that when designing these studies, toxicity considerations and not just efficacy, are going to be key.

The Current and Evolving Therapeutic Paradigm in the Management of Metastatic Renal Cell Carcinoma

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There has been tremendous progress in the treatment landscape of advanced or metastatic RCC since the advent of efficacious targeted therapies, immunotherapies and combinatorial regimens, leading to rapid expansion of therapeutic armamentarium over the last two decades. New advances have offered considerable improvement in prognosis, treatment-related toxicities, quality of life, and survival for patients with mRCC. Despite such advantages, there is an unmet need for developing novel biomarkers predictive of treatment response, optimizing treatment selection, and also improving strategies to overcome therapeutic resistance in heterogenous RCC tumors. Herein, we outline currently available first- and later-lines treatment strategies, unprecedented changes, and also discuss challenges in the treatment landscape of RCC.

INTRODUCTION

Renal cell carcinoma (RCC) remains one of the top ten most frequently diagnosed neoplasms with an incidence of over 403,000 new cases and 175,000 deaths globally.[1] In the United States alone, about 73,750 new cases of kidney cancer were diagnosed, accounting for an estimated 14,830 deaths. In patients with RCC, about 30% of patients present with metastatic disease at the time of initial diagnosis typically requiring systemic therapy. Almost 30% of patients who are treated for localized RCC develop a recurrent disease during the follow-up and the 5-year survival rate remains 12% in patients with mRCC.[2] Given that RCC is chemo-resistant and radiation-resistant, and only a minority of patients with metastatic RCC surviving past 5 years, the treatment for the late-stage recurrent metastatic RCC remains highly challenging.

The precise treatment selection for patients with advanced or metastatic ccRCC has been guided by risk stratification models during the initial evaluation of patients. The Memorial Sloan Kettering Cancer Center (MSKCC) and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) are the most used nomograms and both frameworks have significant prognostic implications. Initially developed in the era of cytokine therapy, the MSKCC nomogram-based risk stratification has been updated for upfront decision-making in the current era of targeted therapies and immunotherapy. A modified version of the MSKCC nomogram was developed for decision-making in patients with previously treated RCC.[3] Per MSKCC guidelines, patients are categorized into risk groups based on five criteria: good-risk (0 risk factors), intermediate-risk (1–2), or poor-risk (≥ 3). The IMDC or Heng criteria wer developed in the era of targeted therapies and it overlaps with the MSKCC model. IMDC also classifies patients into three risk groups. Favorable risk (0 factors) with a median OS of 43.2 months, intermediate risk (1–2 factors) with a median OS of 22.5 months, and poor risk (3+ factors) with a median OS of 7.8 months. Despite the widespread utility of the IMDC model as a risk stratification tool for clinical trials involving VEGFR TKI and combination regimens, its applicability to IO therapies is rather limited. Although not widely used, other clinical practice guidelines have been issued by the National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology (ESMO), the European Organization for Research and Treatment of Cancer (EORTC), and the European Association of Urology (EAU).

FIRST-LINE THERAPIES

Given the large armamentarium of targeted therapies available alone or in combination, survival benefit is prolonged, and tolerability is enhanced for patients with metastatic clear cell renal cell carcinoma over almost two decades. And yet, physicians currently have to go through the difficult task of choosing the most optimal therapeutic regimen for first-line therapy. In the rapidly evolving therapeutic landscape of mRCC, this complexity is clear owing to enormous treatment options and access to new drugs arising from the latest clinical trials that lack real-world evidence. Especially, patient characteristics and survival outcomes in randomized trials may not accurately reflect a real-life clinical practice scenario. For the preferred treatment selection, IMDC risk stratification and PD-L1 biomarker status may provide some guidance. Treatment selection depends on several factors that include the patient's performance status, comorbidities, cancer subsets, and extent of disease burden as well as non-clinical factors namely, cost-effectiveness, and institutional availability, etc. Therefore, standardizing algorithms for optimized treatment sequencing remains a challenge. In recent years, the first-line treatment landscape has transitioned from recombinant cytokines to tyrosine kinase inhibitors (TKI), mammalian target of rapamycin (mTOR) inhibitors, and most recently, the immune checkpoint inhibitors (ICI).[3] In this review, we highlight some of the recent and ongoing trials of ICI, ICI/TKI combinations, and novel HIF-2α inhibitor agents that may potentially prolong survival benefits in patients with advanced and metastatic RCC.

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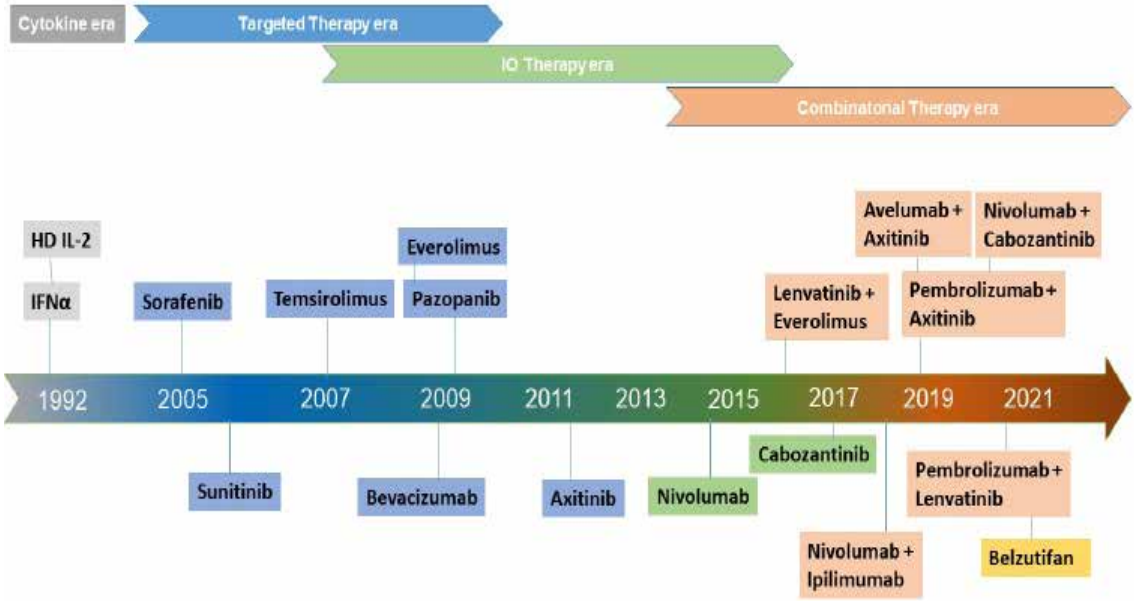

Figure 1. Advances in Evolving Landscape of First-line Systemic Therapies for Metastatic Renal Cell Carcinoma

First-line VEGF- Targeted Therapies

Before the advent of targeted therapies, cytokine-based traditional therapies i.e. interferon-alpha (IFN-α) or interleukin-2 had been the mainstay of the RCC landscape until 2005. These therapies provided only a modest survival in the majority of patients but also resulted in a substantial incidence of high-grade adverse events.[4, 5] With the improved understanding of implications of von Hippel–Lindau (VHL) gene mutations in angiogenic pathways, many VEGF-based TKIs were developed and eventually they evolved as defacto choice of first-line systemic therapy since 2005.[6] Currently approved VEGF-targeted therapies either selectively inhibit VEGF receptors (eg, sorafenib, sunitinib, pazopanib, axitinib), or target circulating VEGF ligands (eg, bevacizumab), and block tumor angiogenesis. Whereas agents like everolimus and temsirolimus agents exert cytotoxic effects by inhibiting mTORC1, blocking protein synthesis, and cell-cycle progression.

For more than a decade, sunitinib, an orally administered multitargeted TKIs remained as the standard-of-care and as the main comparator arm to clinical trials in first-line mRCC treatment. The survival benefit of sunitinib was evident in the pivotal randomized phase III trial in which sunitinib treatment resulted in improved PFS as compared with interferon in the first-line setting (11.0 vs. 5.0 months; p < 0.001).7 Although a higher OS in patients treated with sunitinib was observed compared with those treated with IFN-α (26.4 versus 21.8 months, respectively), it lacked statistical significance.[7] Based on the outcome, sunitinib was approved multinationally for the first- and second-line treatment of metastatic renal cell carcinoma (mRCC).

Here we will discuss results from important clinical trials involving VEGF targeting agents such as sorafenib, pazopanib, bevacizumab, and tivozanib as first-line therapy. A phase 3, randomized, double-blind, placebo-controlled study (TARGET) showed that treatment with sorafenib, a multikinase inhibitor results in improved progression-free survival (PFS) versus placebo in the second-line setting after cytokine therapy (5.5 vs. 2.8 months; P<0.01).[8] Sorafenib therapy improved progression-free survival (PFS) in patients with advanced clear-cell renal-cell carcinoma in whom previous therapy has failed. However, sorafenib treatment is associated with increased toxic effects; rare serious adverse events such as hypertension and cardiac ischemia were more common in patients receiving sorafenib than in those receiving placebo.[8] In other international, phase 3 study (COMPARZ), pazopanib and sunitinib therapy had comparable efficacy as compared with placebo or interferon. Pazopanib was non-inferior to sunitinib regarding PFS with similar OS between two arms. However, in terms of the patients perspective based on PISCES trial, more treatment-naive patients preferred pazopanib over sunitinib due to quality of life and safety.[9] In the randomized phase III study (VEG105192; NCT00334282), pazopanib demonstrated statistically and clinically meaningful improvement of PFS versus placebo (9.2 vs. 4.2 months; p<0.0001) in patients who had progressed after cytokines. Based on this data, the FDA approved both pazopanib and bevacizumab in combination with interferon in 2009. In a phase III AVOREN trial of bevacizumab, a monoclonal antibody directed against the VEGF receptor (VEGFR) plus interferon-α-2a (IFN α-2a) showed significant improvements in PFS (10.2 vs. 5.4 months, p = 0.0001) in contrast to treatment with interferon-α monotherapy in mRCC.[10] Median OS was 23.3 months with bevacizumab plus IFN and 21.3 months with IFN plus placebo. Although bevacizumab-IFN showed OS benefit, its use was limited by the toxicity of the regimen.[10] Overall, this AVOREN trial confirmed that bevacizumab plus IFN remains the first-line standard of care for patients with mRCC.

Similarly, a randomized controlled TIVO-1 trial has shown that tivozanib, a potent VEGFR-1, VEGFR-2, and VEGFR-3 inhibitor prolongs PFS (12.7 months) as compared with sorafenib (9.1 months) in the prespecified subpopulation of treatment-naive patients.[11] Similarly, cabozantinib is an oral TKI that targets multiple tyrosine kinases, including hepatocyte growth factor (cMet), VEGFRs, and AXL. In CABOSUN trial, cabozantinib therapy improved PFS (8.2 vs. 5.6 months) and ORR (46% vs. 18%) and reduced the rate of progression or death as compared to sunitinib in treatment-naïve patients with intermediate and poor IMDC risk group.[12] Currently, cabozantinib represents a suitable targeted first-line agent especially among patients who are not eligible to receive immunotherapy.

Front-Line mTOR Inhibitor Therapy

In parallel to the development of VEGF inhibitors, mTOR inhibitors were also evolved in the mRCC landscape. Temsirolimus, a potent mTOR inhibitor, was approved for the treatment of advanced RCC after the multicenter, phase 3 ARCC trial (NCT00065468). In this, treatment with temsirolimus has improved OS compared with interferon (10.9 vs. 7.3 months; p = .008) in treatment-naïve and poor risk mRCC patients. Temsirolimus monotherapy yielded longer OS (HR for death, 0.73; 95% CI, 0.58 to 0.92; P=0.008) and PFS (P<0.001) as compared to

Study RCT	Treatment arms	ORR		PFS		OS	
		ORR% (CR)	HR (95%CI)	Median, mo	HR (95%CI)	Median, mo	HR (95%CI)
Checkmate 214	Int/Poor risk NIVO/IPI (*N* = 425) SUN (*N* = 422)	42.1% (10.1) 26.3% (1.4)	*P* < 0.001	11.6 8.3	0.75 (0.62-0.90) (*P* = 0.015)	47 26.6	0.66 (0.55-0.80) (*P* < 0.0001)
	Favorable risk NIVO/IPI (*N* = 125) SUN (*N* = 124)	28.8% (12.8) 54.0% (5.6)	*P* < 0.0001	17.0 28.8	1.65 (1.16-2.35) (*P* = 0.0049)	NR NR	1.19 (0.77-1.85) (*P* =0.43)
	ITT NIVO/IPI (*N* = 550) SUN (*N* = 546)	39.1% (10.7) 32.6% (2.4)	*P* = 0.02	12.4 12.3	0.88 (0.75-1.04) (*P* = 0.126)	NR 38.4	0.72 (0.49-0.95) (*P* = 0.0002)
	Int/Poor (PD-L < 1) NIVO/IPI (*N* = 284) SUN (*N* = 278)	37% 28%	P = 0.03	11.0 10.4	1.00 (0.8-1.26)	NR NR	0.73 (0.56-0.96)
	Int/Poor (PD-L > 1) NIVO/IPI (*N* = 100) SUN (*N* = 114)	58% 22%	*P* < 0.001	22.8 5.9	0.46 (0.31-0.67)	NR NR	0.45 (0.29-0.71)
KEYNOTE 426	ITT AXI/PEMBRO (*N* = 432) SUN (*N* = 429)	60% (9) 40% (3)	*P* < 0.0001	15.4 11.1	0.71 (0.60-0.84) *P* < 0.0001	NR 35.7	0.68 (0.55-0.85) *P* = 0.0003
	Int/Poor risk AXI/PEMBRO (*N* = 294) SUN (*N* = 298)	55.8% (8) 35.2%	-	12.7 8.3	0.69 (0.56-0.84) *P* = 0.0002	NR 28.9	0.63 (0.50-0.81) *P* = 0.0001
	Favorable Risk AXI/PEMBRO (*N* = 138) SUN (*N* = 131)	69.6% (11) 50.4% (6)	-	20.8 18.0	0.79 (0.57-1.09) *P* = 0.078	NR NR	1.06 (0.6-1.86) *P* = 0.58
IMmotion 151	PD-L1+ ATEZO/BEV (*N* = 178) SUN (*N* = 184)	Inv 43% (9) 35% (4)	-	Inv 11.2 7.7	0.74 (0.57-096) *P* = 0.02	34.0 32.7	0.84 (0.62-1.15) *P* = 0.28
	PD-L1 + ATEZO/BEV (*N* = 178) SUN (*N* = 184)	IRC 36% (15) 33% (8)	-	IRC 8.9 7.2	0.93 (0.72-1.21)	-	-
	ITT ATEZO/BEV (*N* = 454) SUN (*N* = 461)	Inv 37% (5) 33% (2)	-	Inv 11.2 8.4	0.83 (0.70-0.97) *P* = 0.02	33.4 34.9	0.93 (0.76-1.14) *P* = 0.47
JAVELIN Renal 101	PD-L1 + AXI/AVEL (*N* = 270) SUN (*N* = 290)	BICR 55.9% (5.6) 27.2% (2.4)	OR = 3.389 (2.34-4.90)	BICR 13.8 7.0	0.62 (0.49-0.77) *P* < 0.0001	NR 28.6	0.83 (0.59-1.15) *P* = 0.13
	ITT AXI/AVEL (*N* = 442) SUN (*N* = 444)	BICR 52.5% (3.8) 27.3% (2.0)	OR = 2.99 (2.23-3.99)	BICR 13.8 8.4	0.69 (0.57-0.82) *P* < 0.0001	NR NR	0.80 (0.61-1.02) *P* = 0.039
CLEAR	ITT LENV/PEMBRO (*N* = 454)	71% (16)	*P* < 0.001	23.9	0.39 (0.32-0.49) P < 0.001	NR[b]	0.66 (0.49-0.88) *P* = 0.005
	LENV/EVERO (*N* = 461)	53% (10)	*P* < 0.001	14.7	0.65 (0.53-0.80) *P* < 0.001	NR[b]	1.15 (0.88-1.5) *P* = 0.30
Checkmate 9ER	ITT CABO/NIVO (*N* = 323) SUN (*N* = 328)	55.7% (8) 27.1% (5)	*P* < 0.0001	16.6 8.3	0.51 (0.41-0.64) *P* <0.0001	NR NR	0.60 (0.40-89) *P* = 0.001

Table 1. Summary of phase III front-line combination trials in Renal Cell Carcinoma. ***Abbreviations***: ATEZO: ATEZOlizumab; AVEL: AVELumab; AXI: AXItinib; BEV: BEVacizumab; CABO: CABOzantinib; CI: confidence interval; EVERO: EVEROlimus; HR: hazard ratio; IMDC: International Metastatic Renal Cell Carcinoma; int: intermediate; inv: investigator; IPI: IPIlimumab; IRC: independent review committee; ITT: intention to treat; LENV: LENVatinib; mo: month(s); NA: not applicable; NIVO: NIVOlumab; NR: not reached; ORR: objective response rate; OS: overall survival; PD-L1: programmed cell death ligand 1; PFS: progression free survival; Ph: phase; q3wk: every 3 weeks; qd: once daily; r: randomized; Sun: sunitinib; wk: week.

interferon alone.[13] However, the combination of interferon with temsirolimus also did not improve PFS or OS and only a modest improvement regarding PFS versus interferon (5.5 vs. 3.1 months) was observed.[13] Based on this, temsirolimus was approved by the FDA for the first-line treatment of advanced RCC in May 2007. A more pronounced survival advantage was observed only in patients with non-clear cell histology. However, the RECORD-3 trial subsequently showed everolimus was inferior to sunitinib across IMDC risk groups. Given such modest results and also due to its weekly intravenous injection limitation, temsirolimus is not a widely used therapy in front-line for patients and its utility has been relegated to second or later lines of therapy with mRCC who have poor risk prognostic features. Another mTOR inhibitor everolimus has been evaluated in ESPN study for the first-line setting in patients with metastatic nccRCC. In this, everolimus failed to yield a survival advantage as sunitinib had better mPFS than that of everolimus (6.1 months vs, 4.1 months, p=0.25).[14] Therefore, everolimus is not recommended in the first-line treatment for nccRCC.

ICI Based First-Line Therapies

Owing to their robust and clinically relevant survival benefits, immune checkpoint-inhibitor (ICI) proteins including anti-programmed death receptor 1 (PD-1), anti-programmed death receptor ligand 1 (PD-L1), and anti-cytotoxic T lymphocytes antigen-4 (CTLA-4) have been integrated into the therapeutic landscape as the first-line as well as second-line treatment for moderate to high-risk mRCC.[3] For instance, since the approval of the CTLA-4 antibody ipilimumab in patients with melanoma in 2011, the footprints of ICIs also expanded across the RCC landscape following studies of several PD-1/PD-L1 inhibitors including nivolumab, pembrolizumab, atezolizumab, durvalumab, and avelumab as well as the CTLA-4 inhibitor ipilimumab. Similarly, nivolumab a humanized IgG4 anti-PD-1, was the first

ICI in kidney cancer space approved by FDA in 2015. Such developments revolutionized the ICI-based immunotherapies in patients with refractory mRCC.

CheckMate 214 (NCT02231749) is the first trial in the RCC landscape to evaluate the CTLA-4 blocker (ipilimumab) and PD-1 inhibitor (nivolumab) combination in the IMDC intermediate or the high-risk population.[15] The results validated the proof of concept that PD-1 inhibitor plus CTLA-4 blocker combination can deliver synergistic benefit as compared to the anti-VEGF TKI sunitinib in the first-line metastatic RCC setting. Improved response rates (42%, 9% CR vs 27%, 1% CR; p<0.001), PFS (11.6 mo vs 8.4 mo, HR 0.82, p=0.03) and OS (NR vs 26.6 mo; HR 0.66; 95% CI 0.54–0.80; p<0.0001) were observed in combination arm as compared to sunitinib. In particular, the addition of ipilimumab to nivolumab resulted in significantly better overall survival and improved ORR as compared to sunitinib, secured a place in the first-line treatment algorithm.[15] In phase III, randomized keynote-426 trial, treatment with pembrolizumab plus axitinib resulted in significantly longer OS and PFS, as well as a higher ORR, than treatment with sunitinib among patients with previously untreated advanced renal-cell carcinoma.[16] Pembrolizumab plus axitinib therapy resulted in better OS (median not reached) as compared to therapy with sunitinib (35.7 months; HR 0.68, p=0.0003) and higher PFS (median 15.4 months vs 11.1 months, HR 0.69; p<0.0001). As compared to sunitinib arm, the combination arm also had better CR (9% versus 3%) and ORR (59.3% vs 35.7%, p<0·0001).[16] This study validated the benefit of pembrolizumab + axitinib combination therapy. Similarly, pembrolizumab monotherapy for treatment naïve patients has also demonstrated promising efficacy and acceptable tolerability in patients with accRCC in the KEYNOTE-427 (NCT02853344) trial.

HIF inhibitor based therapies

Belzutifan, a highly selective hypoxia-inducible factor inhibitor (HIF-2α), offers a novel approach, taking a different path than commonly used, to treat RCC. Most recently, the open-label study 004 (NCT03401788) has evaluated the efficacy of belzutifan in patients with VHL-associated RCC.[17] In patients with VHL-associated RCC (n=61), belzutifan resulted in an ORR of 49% (95% CI, 36%-62%); all responses were partial responses. Median DOR had not yet been reached (range, 2.8+ to 22.3+ months); among responders, 56% (n=17/30) were still responding after at least 12 months. Median TTR was eight months (range, 2.7-19 months). Based on these data, FDA approved belzutifan for adult patients with VHL disease who require therapy for RCC and other tumors.[17] Currently belzutifan was investigated in phase III trials as part of combination first-and second-line therapies for advanced clear cell renal cell carcinoma and also as monotherapy for previously treated patients.

Combinatorial Therapies: ICI Plus TKI

Tumor angiogenesis is largely driven by VEGF-mediated mechanisms in kidney cancers. Apart from exerting a proangiogenic effect, VEGFs also mediate immunosuppression in the tumor microenvironment. Interestingly, by promoting the accumulation of myeloid-derived suppressor cells and regulatory T cells and also by impeding the migration of T lymphocytes towards the tumor microenvironment, VEGFs potentially drive angiogenesis. Disruption of VEFG has been shown to facilitate promote cytotoxic T-cell infiltration into the tumor microenvironment and also decrease the activity of T-regulatory cells and myeloid-derived suppressor cells, thereby enhancing responsiveness to immunotherapy.[18] Such synergistic effectiveness of ICI agents in combination with either multi-kinase inhibitors or other monoclonal antibodies (CTLA4 and PD-1) have gained momentum and have been rapidly integrated into the first line treatment landscape.

There are several ongoing clinical studies based on doublet and triplet regimens for treatment-naïve metastatic or advanced ccRCC. In a phase II, randomized study (IMmotion150) by McDermott et al. investigated the combination of atezolizumab, an anti-PD-L1 antibody, with bevacizumab, an anti-VEGF agent as compared to sunitinib monotherapy in mRCC19. In ITT patient population, improved median PFS was noted with atezolizumab plus bevacizumab combination group (11.7 vs. 8.4 months).19 Besides, in PD-L1 positive patients, the combination arm had a PFS of 14.7 months versus 7.8 months with sunitinib. The ORR in PD-L1+ patients was 43% in the combination arm as compared to 35% in the sunitinib arm. The CR rate in the PD-L1+ patients was 9% in the combination arm as compared to 4% in the sunitinib arm.[19] In a phase III IMmotion 151 trial (NCT02420821), similar survival benefits were obtained. Similarly, CheckMate 016, a phase I, open-label, parallel-cohort, dose-escalation study investigated the efficacy and safety of nivolumab plus ipilimumab in combination, and nivolumab plus a TKI. ORR was 40.4% in both arms, with ongoing responses in 42.1% and 36.8% of patients in the N3I1 and N1I3 arms, respectively. This combination demonstrated manageable safety, notable antitumor activity, and durable responses with promising OS in patients with mRCC progressed after prior therapy. In another clinical trial (NCT03075423), a combination of pembrolizumab plus axitinib resulted in significantly longer OS and PFS, as well as a higher ORR, than treatment with sunitinib16. After a median follow-up of 12.8 months, the estimated percentage of patients who were alive at 12 months was 89.9% in the pembrolizumab–axitinib group and 78.3% in the sunitinib group. Median PFS was 15.1 months in the pembrolizumab–axitinib group and 11.1 months in the sunitinib group. The objective response rate was 59.3% in the pembrolizumab–axitinib group and 35.7% in the sunitinib group (P<0.001).[16]

Similarly, pembrolizumab was also being evaluated in the KEYNOTE 427 phase II trial. Similarly, durvalumab is being evaluated in combination with savolitinib, a highly selective MET tyrosine kinase inhibitor, in the CALYPSO phase II trial (NCT02819596). In another randomized phase III JAVELIN Renal 101 (NCT02684006) trial, Motzer et al investigated the combination of axitinib and avelumab in treatment-naive RCC patients with metastatic or advanced disease.[20] Avelumab plus axitinib arm had longer PFS and a significantly higher objective response rate than those who received sunitinib monotherapy. Results showed that mPFS in the combination arm was 13.8 months versus 8.4 months in sunitinib arm (HR, 0.69; p<0.001), and the ORR and CR rate were 55% and 4% in the combination arm versus 26% and 2% in the sunitinib arm respectively.20 The safety profile was comparable to the results of the JAVELIN Renal 101 trial. The subgroup analysis indicates that the benefit of pembrolizumab plus axitinib for OS, PFS, and ORR was observed in the entire population irrespective of IMDC prognostic group and PD-L1 tumor expression.

In CheckMate-9ER study, nivolumab plus cabozantinib combination had significant benefits over sunitinib in terms of PFS, OS in patients with treatment naïve aRCC. The mPFS was 16.6 months with nivolumab plus

cabozantinib and 8.3 months with sunitinib.[12] The probability of OS at 12 months was 85.7% with the combination arm and 75.6% with sunitinib. An OR occurred in 55.7% of patients in the combination arm versus 27.1% in sunitinib arm (P<0.001). Efficacy benefits with nivolumab plus cabozantinib were consistent across subgroups.[12] In another phase 3 trial, patients with aRCC and no previous systemic therapy were randomly assigned to receive lenvatinib plus pembrolizumab, lenvatinib plus everolimus, or sunitinib. Lenvatinib plus pembrolizumab therapy resulted in longer PFS (median, 23.9 vs. 9.2 months) and OS than with sunitinib. However similar benefits were not observed with lenvatinib plus everolimus as compared to sunitinib. This study demonstrated lenvatinib plus pembrolizumab therapy was associated with significantly longer PFS and OS as compared to sunitinib. In a non-randomized Phase Ib/II study, VEGF-TKI plus IO (tivozanib plus nivolumab) combination was assessed in patients previously treated with one oral TKI (NCT03136627). The ORR was 56%, with one patient achieving a complete response. The combination of tivozanib with nivolumab prolonged disease control (median PFS of 18.9 months) and also showed a tolerable AE profile in both treatment-naïve and previously treated metastatic RCC.[21]

In phase III CLEAR clinical trial, lenvatinib plus pembrolizumab treatment significantly improved PFS compared to sunitinib (HR: 39, median = 23.9 vs 9.2 months). This combination also improved the ORR compared to sunitinib (71.0% vs 36.1%) with an impressive complete response rate of 16.1% and OS was also significantly longer than sunitinib (HR = 0.66). Although lenvatinib plus everolimus, in the third arm, significantly improved PFS compared to sunitinib (median = 14.7 vs 9.2 months, HR = 0.65, 95% CI = 0.53–0.83), but overall survival benefit was inconclusive (HR = 1.15). Based on the promising data, this combination became the fifth immuno-oncology combination for the first-line treatment of metastatic RCC, in addition to nivolumab plus ipilimumab, pembrolizumab plus axitinib, avelumab plus axitinib, and nivolumab plus cabozantinib.

Although the combination of ICI and antiangiogenics has shown encouraging preliminary antitumor activity for advanced or mRCC, high incidence of toxicity along with less favorable tolerability profile may compromise the benefits in patients. For instance, in the phase I study CheckMate 016 (NCT01472081), the efficacy and safety of nivolumab in combination with antiangiogenic tyrosine kinase inhibitors or ipilimumab for the treatment of mRCC.[22] In this study, the addition of sunitinib or pazopanib to nivolumab resulted in a high incidence of high-grade toxicities, limiting its scope in future trials. Given the possibility that long-term cumulative adverse effects from antiangiogenic and ICI-combinations may accumulate over time and outweigh the benefits, such combinatorial therapies warrant close monitoring to avoid unprecedented risks.

VEGF-TKI plus mTOR inhibitors

Targeted therapies directed towards both VEGFR and mTOR pathways have long been considered a potential synergistic strategy in mRCC landscape. However, only a few combinations shown a successful synergy with the benefits that outranged the combined toxicities from the regimens involved. Lenvatinib, a novel potent multi-target TKI of VEGFR 1-3, PDGFR-β, RET, c-KIT, and FGFR 1–4, was approved in combination with everolimus for the treatment of advanced RCC following one prior antiangiogenic therapy. In a phase 2 trial (NCT01136733), 153 patients with mRCC previously treated with VEGF-TT were randomly allocated to receive either the combination of lenvatinib plus everolimus, single-agent lenvatinib, or single-agent everolimus. Lenvatinib plus everolimus significantly prolonged PFS compared with everolimus alone, but not compared with lenvatinib alone.[23] This trial demonstrated that lenvatinib plus everolimus and lenvatinib alone resulted in a progression-free survival benefit for patients with metastatic renal cell carcinoma who have progressed after one previous VEGF-targeted therapy.

VEGF inhibitor plus HIF inhibitor

The preliminary, interim results from a phase II trial has shown that belzutifan plus cabozantinib treatment resulted in 88% tumor shrinkage in target lesions and a disease control rate of 90% for patients with previously treated advanced clear cell RCC, according to preliminary results from cohort 2 in an ongoing phase II study. The PFS rate was 78% at 6 months and 65% at 12 months. Median progression-free survival was 16.8 months.

SECOND-LINE THERAPIES

Ideally, second-line therapies are designed to address the resistance mechanism obtained from first-line treatments and utilize different treatment modalities to gain better disease control in the second-line setting. For instance, for patients progressing despite first-line immunotherapy, TKI-based second-line therapy could deliver better outcome. If a patient has progressed on combination ICI/TKI treatment, the second-line regimen could include either a different TKI alone or in combination with an mTOR inhibitor. The different TKI is chosen based on their capacit still VEGF-TT
y to challenge escape pathways that led to treatment resistance to the prior TKI, via AKT, MET, AXL, and FGF signaling.[6] For patients progressing after first-line VEGF therapy, checkpoint inhibitors is not the only favorable therapy; TKI therapy can be also a viable option. Cabozantinib, an orally bioavailable TKI, inhibits VEGFRs, MET, and AXL targets implicated in the pathogenesis and progression of RCC. These favorable results in TKI-refractory disease support the hypothesis that the clinical activity of cabozantinib in RCC may result from combined inhibition of VEGFRs and additional targets, such as MET and AXL, that are not inhibited by other TKIs.[8,10 11] Another added advantage is that the number of prior therapies does not seem to affect the efficacy of cabozantinib or nivolumab.

Second-line post VEGFI therapy

The following studies explored survival benefits in patients who progressed VEGFR TKI therapies. The international randomized, open-label, phase III METEOR trial assessed the efficacy and safety of cabozantinib with the mTOR inhibitor everolimus in patients with advanced RCC following one or more VEGFR TKI therapy. Treatment with cabozantinib improved PFS, ORR, and OS versus everolimus in patients with aRCC. In cabozantinib arm, median OS was 21·4 months (95% CI 18·7-not estimable) as compared to 16·5 months in everolimus arm. Cabozantinib treatment also resulted in improved progression-free survival and objective response (17% with cabozantinib vs 3% with everolimus; p<0·0001). Cabozantinib treatment was also resulted in improved clinical outcomes in patients who had received both VEGFR TKI therapy and an immune checkpoint inhibitor. Cabozantinib may have added advantage over other therapies especially for patients with bone and brain metastasis subgroups that derived

increased benefit, that is, elderly, good and intermediate-risk patients. In the METEOR trial, cabozantinib therapy resulted in better median PFS of 7.4 months and 5.6 months as compared to 2.7 months and 1.9 months with everolimus in those with bone metastasis and bone and visceral disease, respectively. The rate of post-randomization skeletal-related events was lower (16%) with cabozantinib as compared to 34% events with everolimus. Taken together, these data strongly support the use of cabozantinib in mRCC patients with bone and brain metastasis.

The IO agent nivolumab can be given as a preferred second-line monotherapy option for patients who progressed on first-line anti-VEGF therapies. The CheckMate-025 (NCT01668784) trial has demonstrated that nivolumab delivers better PFS, overall response rate and overall survival, paving the way for the use of nivolumab as second-line therapy.[24] In a randomized open-label, phase III study, a total of 821 advanced ccRCC patients who had received previous treatment with one or two regimens of antiangiogenic therapy were randomly assigned either nivolumab or everolimus.[24] Results showed that ORR was greater with nivolumab than with everolimus (25% vs. 5%; p<0.001) and median PFS was better with nivolumab than with everolimus (4.6 months vs 4.4 months; p = 0.11).24 Results indicated that the nivolumab arm had 25.0 months median OS as compared to 19.6 months in the everolimus arm. Nivolumab's OS benefit was evident across prespecified MSKCC risk and PD-L1 subgroups. Taken together, these results especially obtained from METEOR and CheckMate 025 trials highlight the broad clinical utility of cabozantinib or nivolumab as a preferred second-line therapy for previously treated patients with advanced RCC in the post VEGFI setting.

In a randomized, open-label trial, patients who received at least two previous systemic treatments (including at least one previous treatment with VEGFR inhibitor) were randomly assigned to receive tivozanib or sorafenib.[25] Median PFS was significantly longer with tivozanib (5·6 months) than with sorafenib (3·9 months). This study showed that tivozanib as third-line or fourth-line therapy improved progression-free survival and was better tolerated compared with sorafenib in patients with metastatic renal cell carcinoma. In other randomized, phase 2, open-label, lenvatinib, everolimus, or their combination as a second-line treatment were assessed in patients with mRCC who had received treatment with a VEGF-targeted therapy. Lenvatinib plus everolimus significantly prolonged PFS compared with everolimus alone (median 14·6 months vs 5·5 months), but not compared with lenvatinib alone (7·4 months). Single-agent lenvatinib significantly prolonged PFS compared with everolimus alone. Lenvatinib plus everolimus and lenvatinib alone resulted in a PFS benefit for patients with mRCC who have progressed after one previous VEGF-targeted therapy.

Second-line post IO therapy

For those patients who progressed after initial ICI therapy, the second-line option would be VEGFR-TKI. Currently, preferred second line choice was the inhibitor of the mammalian target of rapamycin pathway (mTOR) everolimus in 53.3% of cases. Besides, alternative options including VEGFR-TKI options (cabozantinib) or mTOR combinations (lenvatinib plus everolimus) for a later rescue line are also considered. Similarly, RECORD-1 study shown demonstrated benefits from everolimus in patients who had received at least one prior treatment with sunitinib and/or sorafenib. The median PFS for everolimus was 4.0 vs 1.9 months with placebo. No OS impact was seen in the trial although the crossover rate was over 90%.[26] For those who receive either pazopanib or sunitinib in the first-line therapy, a mammalian target of rapamycin (mTOR) inhibitor and a TKI could be a possible choice of second-line therapy. Another interesting question will be the possibility of ICI rechallenge and elucidating the use of cytoreductive nephrectomy within the context of new immunotherapeutic interventions.

For patient progressed on first-line ICI/TKI combination, a second-line combination mTOR inhibitors/TKIs could be another option available. Although single-agent temsirolimus versus sorafenib yielded a lack of benefit after progression on a VEGF-TKI in the second-line setting[14], a randomized phase II Study 205 trial supported the use of lenvatinib plus everolimus vs lenvatinib alone vs everolimus alone in this setting.[15] A superior PFS was noted at 14.6 months vs 5.5 months with everolimus alone, but it lacked a statistically significant difference when compared with the lenvatinib arm (PFS, 7.4 months). The study results led to the first FDA-approved combination of a TKI and an mTOR inhibitor. However, high-grade toxicities that occurred in the combination arm warrant newer-generation multi-TKI/mTOR such as vorolanib to identify better-tolerated regimens.[16] Currently, a phase 1 trial involving vorolanib/everolimus combination in the second-line setting is underway.

Despite the robust profile of the anti-PD-1/anti-CTLA-4 dual checkpoint blockade, some mRCC patients do not respond well to the therapy and would have intermediate- and poor-risk IMDC factors. Given that the tumor is still VEGF-TT naïve in these subsets of patients, TKI approved for the first-line may have a role. For these patients, axitinib, cabozantinib, or the combination of lenvatinib + everolimus could be used as a second-line, depending on clinical and non-clinical factors. For patients who progressed after ICI therapy including ipilimumab/nivolumab, a phase 2 nonrandomized trial (n = 38) has shown that axitinib may provide clinical efficacy (PFS 9.2 mo, ORR 40%). Besides, small retrospective studies that shown median PFS of 8 months using TKI after dual checkpoint blockade, supported the use of cabozantinib compared with sunitinib in this specific population. In a retrospective analysis involving 86 patients who received cabozantinib after progression on ICI alone, ICI plus VEGFIs or other therapies. Cabozantinib arm had ORR of 36% with no complete response and 43% achieving stable disease; 21% had primary progressive disease. The median OS was 13.1 months with OS rate of 12 months.

For patients who progressed on prior PD-1/PD-L1 or ICI/TKI therapy may benefit from the combination of lenvatinib and pembrolizumab. The phase II KEYNOTE-146 trial has evaluated the benefit of lenvatinib plus pembrolizumab after up-front therapy with nivolumab/ipilimumab.[12,27] The 12-month rate of PFS was 45%, with a median value of 11.7 months, and the corresponding values for overall survival were 77% and not reached. The ORR was 55% for those given only PD-1 or PD-L1 inhibitors, and 59% and 47% for patients who had also received a VEGR inhibitor or nivolumab plus ipilimumab, respectively.[27] For patients who progressing after either first-line IL-2 or temsirolimus, the preferred second-line therapy could be pazopanib or sunitinib. However, the treatment choice remains unclear for patients previously treated with ICI. In this setting, the preferred treatment choice could be

VEGFR-TKI not previously used in combination with ICI therapy. For third-line therapy 63.5% of patients received TKI, primarily sorafenib and axitinib (23.5% each), whereas 36.5% of patients received everolimus. For fourth-line and beyond, sorafenib was used in 21.2% of patients as fourth-line therapy, and both sunitinib and everolimus were used equally as fifth-line therapy, in 23.8% of patients. A pivotal phase III CONTACT-03 study (NCT04338269) is currently underway in patients who received prior ICI as a first- or second-line treatment in RCC. For the patients who are ineligible to receive either nivolumab IO therapy or cabozantinib, axitinib is recognized as another appropriate second-line option according to the international guidelines and recommendations. Axitinib is recognized as another appropriate second-line option in this setting based on AXIS trial. In this, 23 patients with one prior therapy were randomized to axitinib or sorafenib, axitinib was established as the preferred second-line choice.[28] The median PFS for axitinib was 8.3 vs 5.7 months with sorafenib, although no statistical difference in OS was observed.

CONCLUDING REMARKS

Over the last decade, there has been tremendous progress in the treatment landscape of mRCC with new and efficacious monotherapies and combinatorial regimen, leading to an expansion of therapeutic armamentarium. With the continuous implementation of several first-line therapies (eg. cabozantinib, tivozanib, sunitinib or pazopanib, ipilimumab/nivolumab, pembrolizumab/axitinib, cabozantinib/nivolumab, axitinib/pembrolizumab, axitinib/avelumab, pembrolizumab/lenvatinib), the treatment landscape is rapidly shifting, paving the way for optimal management in subsequent lines of therapy. Conversely, the rapidness of emerging therapies with the advent of novel agents in the pipeline is adding further complexity to the already overwhelming mRCC landscape. The precise treatment selection remains a debated issue in the absence of head-to-head comparison among the randomized trials. This complexity reinforces the need for optimal therapeutic sequencing, patient selection, and the implication of prognostic risk models for both initial management and systemic therapy paradigms. The quest for optimizing sequence strategies that deliver robust survival, safety, while preserving the quality of life and the ability to tailor therapy to the individual patient remains. An equally important aspect to consider is that the identification of better biomarkers for response to ICIs and TKIs before individualizing therapies corresponding to tailored personalized treatments in mRCC paradigm. Future studies will explore another novel ICI/TKI, TKI, HIF-2a, and combinatorial therapies galvanized with personalized treatment approaches to deliver promising and meaningful therapeutic management in patients with advanced and metastatic RCC.

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Expert Perspectives: Q&A on Advances in Treatment Landscape of mRCC: Nicholas J. Vogelzang, MD, FASCO, FACP

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KCJ: Can you please provide your perspective about the currently evolving therapeutic landscape of metastatic renal cell carcinoma?

Dr. Vogelzang: The major phenomenon that we are all dealing in the kidney cancer space is the power of the immuno-oncology agents to effect complete responses. For the first-line therapy, physicians have f our FDA approved regimens to choose from: nivolumab/ipilimumab, pembrolizumab/axitinib, nivolumab/cabometyx, pembro/lenvantinib, and of course clinical trials. Nivolumab/ipilimumab combination has big advantages and performs dramatically well in eliminating the tumors in certain RCC patients. In some patients, complete response is attained fairly quickly within three months. Such complete responses are well documented both clinically and sometimes surgically by nephrectomy. Such highly impressive outcomes are driving a lot of physicians who are on the fence between nivolumab/ipilimumab versus pembrolizumab/axitinib to go with nivolumab and ipilimumab.

I am not denying that immunologic side effects can be daunting with the use of nivolumab/ipilimumab; certainly side effects could be severe or life threatening. But despite all, nivolumab/ipilimumab has an allure that is hard to match. The other combinations like pembro/axitinib, nivo/cabo and pembro/lenvantinib are competing, if you will, with nivolumab/ipilimumab for the first line space. The main draw back with the other 3 FDA approved regimens are the toxicities of their oral companion drugs (axitinib, cabometyx and lenvantinib). These drugs give chronic side effects over long periods of time eg. two to three years even with dose reductions.

"Now we have ten plus drugs, that's indeed an embarrassment of riches. As a matter of fact, we don't even quite know how best to sequence."

For good risk disease which is about 15% of subpopulation, a variety of approaches are used but generally Nivo/Ipi is not used. In this population, all three doublet regimens (including cabometyx) were superior to sunitinib. Since pembrolizumab/axitinib was the first regimen to show superiority to sunitinib in good risk patients and has been approved the longest, it is the most commonly used. Patients with very well differentiated clear cell subsets certainly need to be treated with tyrosine kinase inhibitors. Investigators Brian Rini and James Brugarolas have shown that this subset of tumors which can metastasize to the endocine organs (ie thyroid, pancreas, ovary etc) respond very poorly to immunological therapy, but respond well to TKIs. So we're beginning to get a flavor for the spectrum of disease. For the high grade sarcomatoid poor risk RCCs, almost everyone agrees should get nivolumab/ipilimumab. The good risk patients have more flexibility in treatment, patients can either go for TKI monotherapy or TKI/IO therapy. However, the large majority of kidney cancer patients fall into the intermediate group. Here, the debate is whether you give these people an IO/TKI doublet or nivolumab/ipilimumab.

Now, with highly effective regimens available, the role for nephrectomy may be increasing. With near complete responses in the lungs and/or other sites, a nephrectomy to remove residual disease makes clinical sense. With all disease removed or eliminated, therapy can realistically be discontinued. This has really been a fairly dramatic sea change compared to what we used to do with continuous sunitinib or pazopanib therapy, namely a rather long drawn out affair. The future is we can make the cancer go away fairly quickly with doublet therapy and surgical resection of all disease whenever feasible.

However, the question remains regarding which population will get the most from nivolumab/ipilimumab and the other doublet regimens? The way I read it is that the biomarkers for response are still to be determined. The best would be serum markers since tissue markers cannot be sequentially sampled.

Regarding therapeutic sequencing, the duration of response, degree of response and the type of toxicity from first line therapy determine which regimen is used in the 2nd line. There is also considerable debate about whether an IO agent should be continued into the 2nd /3rd line. For instance, if nivolumab/ipilumab was used as a 1st line therapy, should nivolumab/cabometyx combination or cabometyx monotherapy be given in the 2nd line? By the time patients get to 3rd or 4th line, IO agents have usually been dropped and patients revert to a sequence of TKI drugs; cabometyx, lenvantinib, axitinib, pazopanib, sorafenib etc. The role of nephrectomy still needs to be addressed if not done prior to systemic therapy. Overall, this whole field is still in flux with some new agents being introduced to the clinical practice, and some in the pipeline; IO and IO/TKI combinations, and HIF based targeting agents will require more studies and time to be validated and incorporated to the RCC treatment landscape.

KCJ: What are your expectations for evolving IO or TKI therapies under clinical trial pipeline getting integrated into the real world clinical practice?

Dr. Vogelzang: Currently, doublet therapies such as nivolumab/ipilimumab, pembrolizumab/axitinib, nivo/cabo and pembro/lenvantinib are getting incorporated in the mRCC landscape.

In addition, many other agents are currently being explored for their utility. For example, I've been working in a phase 1 trial involving macrogenics B7-H3 antibody which theoretically is able to be synergistic with pembrolizumab. Similarly other cytokines such as anti-IL8, anti-IL2 seem to be synergistic and are also being investigated in clinical research. First, they have to perform better as compared to standard regimens available in practice to prove that they have better efficacy and potentially less toxic. Remember, it took us almost 15 years to show that pembrolizumab/axitinib, nivo/cabo are better than sunitinib. So, my reaction to these new immunologic doublets is that they're going to have a big challenge. So I think we're not going to get the real world evidence for a while and they have to go through further clinical trials to assess their roles in clinical practice as compared to currently available standard regimens

KCJ: Recently, we come across favorable outcomes from belzutifan study which led to the FDA approval. What does the future hold for such therapies ?.

Dr. Vogelzang: Now that we have an RNA based approach to deliver HIF molecules, we can investigate it in patients who are in the third or the fourth line of treatment. If we see any glimmer of activity, we'll begin to compare it to those drugs that are in the second or third line. Overall, further clinical trials required us to assess the efficacy of HIF1/HIF2 inhibitor molecules against standard regimens such as cabometyx or lenvatinib at that level. But imagine doing the trial and HIF1/2 companies would then have to beat or at least be somewhat equivalent to axitinib. That's the path forward that I can see. That's going to take two or three years. Abstract: Close to 74,000 cases of renal cell carcinoma (RCC) are diagnosed each year in the United States. The past 2 decades have shown great developments in surgical techniques, targeted therapy and immunotherapy agents, and longer complete response rates. However, without a global cure, there is still room for further advancement in improving patient care in this space. To address some of the gaps restricting this progress, the Kidney Cancer Association brought together a group of 27 specialists across the areas of clinical care, research, industry, and advocacy at the inaugural "Think Tank: Coalition for a Cure" session. Topics addressed included screening, imaging, rarer RCC subtypes, combination drug therapy options, and patient response. This commentary summarizes the discussion of these topics and their respective clinical challenges, along with a proposal of projects for collaboration in overcoming those needs and making a greater impact on care for patients with RCC moving forward.

KCJ: What would you consider to be the greatest challenge for IO therapeutic regimens and how do you think we can overcome?

Dr. Vogelzang: The biggest challenge is to find out the reasons for immune resistance to IO agents. We already spent a lot of time investigating resistance to sunitinib like agents in the past. However, now sunitinib was supplanted by better drugs that came along. So, I think the balance of power, is not just about finding the resistance pathways to nivolumab/ipilimumab, but rather, finding the better third drug that will synergize with nivolumab/ipilimumab and bring that combo to a higher level. The best part is we already heading in that direction; nivolumab/ipilimumab versus nivolumab/ipilimumab/cabometyx trial is on the way.

KCJ: Moving on from the challenges we have now, what developments do you think are possible in the next five to 10 years ?

Dr. Vogelzang: I believe that, as I wrote in editorial many years ago when we had only three drugs for kidney cancer, we had an embarrassment of riches. Now we have 10 plus drugs, that's indeed an embarrassment of riches. As a matter of fact, we don't even quite know how best to sequence. Some of the newer things that I expect to happen will be EZH inhibitors and glutaminase inhibitors. But, there are other drugs are out there trying to find a home in renal cancer space. One of the other things that I'd like to see is developing therapies tailored for patients with renal dysfunction/real failure because they are not accounted for any clinical trial. So some savvy company may be able to figure out that that's an unmet medical need. For trials, I would imagine that that will be a niche that needs to be included. Likewise, we also need suitable therapies for rare subsets like non ccRCC subpopulation. There may be a carve out for some of these new drugs in non-clear cell RCC space.

KCJ: How do you think COVID-19 changes the treatment landscape in the future. What do you foresee ?

Dr. Vogelzang: There is an enormous investment in studying the immunologic underpinnings of cancers. They are currently directed towards vaccine development for COVID-19. I believe such vaccine development may have a large spin off for immunologic manipulation in kidney cancer patients. Given the hyper immune response in patients who are IO therapy, they may be already somewhat protected against COVID-19 infections. Right now, it sounds hypothetical. But I wouldn't be surprised if someone shows that renal cell carcinoma patients on pembrolizumab or nivolumab/ipilimumab have a lower rate of COVID infection rate than the general population. It could be an ancillary benefit to IO therapy. Even patients who were on nivolumab/ipilimumab or pembrolizumab in the distant past may be protected as well. So it's an interesting set of potentials that the COVID environment brings to us.

Immune-related AEs and Kidney Function Decline in Patients With RCCs Treated With ICIs

A recent retrospective study of patients with renal cell carcinoma (RCC) and urothelial carcinoma reveals that a higher likelihood of developing a sustained decline in renal function while receiving immune checkpoint inhibitor (ICI). This study findings were published by Seethapathy H et al in European Journal of Cancer. Authors foumd that over the course of ICI treatment, 25% of the cohort developed acute kidney injury and 16% developed a sustained decline in renal function while baseline CKD and prior full nephrectomy were not associated with an increased risk of AKI and sustained eGFR loss. Authors conclude that irAEs may be a novel risk factor for kidney function decline among patients receiving ICIs. Furthermore, patients who experienced non-renal immune-related adverse events were more likely to develop a sustained decline in renal function. The higher likelihood of a sustained decline in renal function in patients with mRCC and its association with immune-related adverse events warrant the strategies to minimize the impact and also the need for identification of patient subgroups at risk for renal function deterioration.

This was a retrospective study evaluating the association between ICI use and acute and chronic kidney dysfunction in patients with RCC and urothelial carcinomas. A total of 637 patients received at least one dose of an ICI between January 2012 and December 2018. Authors indicated that compared to patients with urothelial carcinoma, patients with RCC were more likely to develop irAEs and sustained eGFR loss but not AKI. This study also found that among patients surviving at least 1 year who developed irAEs were at a significantly higher risk for sustained eGFR loss. Authors noted further study is warranted to understand and mitigate the long-term impact of ICI-associated effects on chronic kidney function in RCC patients and others for whom ICI therapies are standard.

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A Global Study Reveals More Informational Resources Needed for Patients and Caretakers of Patients With Renal Cell Carcinoma

Patients and caretakers of patients with renal cell carcinoma (RCC) may lack adequate knowledge surrounding disease treatment, clinical trial enrollment, and the psychosocial impact of the cancer itself, according to the results from the global survey that were presented as a poster during ESMO Congress 2021.

The survey consisted of 35 questions focused on the diagnosis, management, and burden of RCC. It was distributed in 13 different languages to patients with kidney cancer and their caregivers between October 29, 2020, and January 5, 2021. The survey reached 2,012 (1,586 patients, 417 caregivers, 9 undisclosed) participants from 41 countries. "This survey results indicate opportunities to improve communication about diagnosis, psychosocial impacts, and clinical trials, as well as biopsies, physical exercise, and patient engagement," said Dr. Rachel H. Giles, chair of the International Kidney Cancer Coalition, and colleagues.

According to the survey, 42% of participants reported that the likelihood of surviving their cancer beyond 5 years was not explained, whereas 51% reported that they were involved as much as they wanted to be in developing their treatment plan. Fifty percent of younger-onset patients (< 46 years) did not know their tumor subtype and 56% experienced barriers to their treatment. Of the surveyed population, 74% took fewer than 3 months to obtain a correct diagnosis. Regarding clinical trials and perspectives on biopsies, 41% of respondents indicated that no one discussed cancer clinical trials with them, 46% had a biopsy and 3% said they were not willing to undergo an additional biopsy if asked.

For physical activity, survey results that 45% of respondents were insufficiently active and 55% said that they very often or always experienced a fear of recurrence.

REFERENCE: Giles RH, Maskens D, Martinez R, et al. Patient-Reported Experience of Diagnosis, Management, and Burden of Renal Cell Carcinomas: Results from a Global Patient Survey in 41 Countries. Presented at 2021 ESMO Congress; September 16-21, 2021; Virtual. Abstract 671P

Inhibition of HDL cholesterol receptor SCARB1 can kill or stop the proliferation of clear cell renal cell carcinoma

The researchers at the University of Pennsylvania have found that inhibiting the HDL cholesterol receptor SCARB1 can kill or stop the proliferation of clear cell renal cell carcinoma (ccRCC) cells highlighting the potential for a new way to treat the disease, according to findings published in Cancer Discovery.1,2 The scientists found the health of these specific cancer cells and tumors are dependent upon cholesterol and SCARB1 while also showing that medication that specifically targets the receptor could make it impossible for the cancer cells to survive and spread. "Previous studies demonstrated that SCARB1 and cholesterol were both part of the story of ccRCC, but our work here shows a causal role," lead study author M. Celeste Simon, PhD, Arthur H. Rubenstein, MBBCh, professor in the department of Cell and Developmental Biology, Perelman School of Medicine, and scientific director of the Abramson Family Cancer Research Institute, stated in press release. "My colleagues and I hope these investigations at the bench can translate to new and successful SCARB1 inhibitors and treatments for people facing this aggressive cancer."

According to the research team, additional studies now need to be conducted to examine the efficacy and safety of using SCARB1 inhibitors, such the investigational agent ITX-5061, in patients with ccRCC. "This study [also] suggests a causative relationship between obesity, BMI, and circulating HDL cholesterol and likelihood of developing ccRCC that can be further investigated," according to the press release.

REFERENCE: Riscal R, Bull CJ, Mesaros C, et al. Cholesterol auxotrophy as a targetable vulnerability in clear cell renal cell carcinoma [published online ahead of print July 8, 2021]. Cancer Discov. doi: 10.1158/2159-8290.CD-21-0211

4-gene expression signature Correlates with Outcomes in Metastatic Renal Cell Carcinoma Patients Treated with Everolimus

In a retrospective analysis of prospective trial data, a four-gene signature was determined to have prognostic value for using everolimus alone or with BNC105P. Overall, this represents the first transcriptomic signature that correlates with clinical benefit in mRCC patients treated with everolimus. Authors indicated if further validated, this signature could be useful in patient selection for mTOR inhibitors after VEGF TKIs or immune checkpoint inhibitors. Although the mTOR pathway has long been regarded as a promising therapeutic target in renal cell carcinoma, randomized clinical trials on mTOR inhibitors such as temsirolimus have shown modest activity in metastatic disease (mRCC). In their previous work, authors hypothesized that gene expression associated with everolimus benefit may provide the rationale to select appropriate patients. Their study showed similar outcomes in everolimus alone versus everolimus with a vascular disrupting agent (BNC105P) and no added benefit from BNC105P.

Samples from the everolimus arm of a phase III trial (CheckMate 025) were used for validation. Most patients (84%) had received one prior line of tyrosine kinase inhibitors (TKI). Using the Nanostring platform, authors shown that gene expression profiling of 82 samples for 517 genes enabled the identification of a 4-gene expression signature (ASXL1, DUSP6, ERCC2, and HSPA6) that was associated with clinical benefit in the entire discovery cohort (82 patients). Among 37 patients with high expression of this 4-gene signature, 81% displayed clinical benefit. This was validated in 130 patients from CheckMate 025 treated with everolimus.

REFERENCE: Gene Expression Signature Correlates with Outcomes in Metastatic Renal Cell Carcinoma Patients Treated with Everolimus Alone or with a Vascular Disrupting Agent Yang ES et al. Mol Cancer Ther 2021 Aug;20(8):1454-1461. doi: 10.1158/1535-7163.MCT-20-1091

Pancreatic metastasis (PM) has been associated with improved clinical outcomes in mRCC patients

Recent study demonstrated an increase in OS, PFS, and overall response rate (ORR) in mRCC patients with pancreatic metastasis (PM). This supports previous findings that certain metastases patterns within mRCC may predict prognosis, which could aid in therapy selection and clinical decision-making. Within the small cohort of PM patients (5%) extracted from our overall pool, there was a higher prevalence of patients that had IMDC favorable risk compared to patients without PM. This aligns with previous findings in several mRCC cohort analyses that demonstrated more indolent disease when PM is present.

Although pancreatic metastasis (PM) has been associated with improved clinical outcomes in mRCC patients, this has not been extensively studied in the context of systemic therapy.1,3,4 In patients with mRCC, patients with PM had significantly prolonged median OS (41.7 vs. 19.0 months) and progression-free survival (10.9 vs. 6.9 months) compared to patients without PM. These OS and progression-free survival (PFS) results were independent of the International mRCC Database Consortium (IMDC) risk group and other sites of metastasis. When categorized by IMDC risk group, OS was improved in the favorable and intermediate-risk group while PFS was improved only in the favorable risk group amongst patients with PM compared to without PM.8

Different therapy regimens should be considered when studying these improved outcomes. This study demonstrated improved PFS in patients with PM who received cytokine therapy and VEGF-targeted therapy compared to patients without PM. However, this finding was exclusive to first-line therapy, which could indicate the development of resistance to therapy with subsequent lines. Also, this study showed improved PFS with cytokine therapy in patients with PM. Considering that combination immunotherapy is now being administered as first-line therapy, it will be crucial to assess its unique effects on mRCC patients with PM.

Despite PM being rare in the context of RCC, their presence is associated improved clinical outcomes. However, further research must evaluate a more granular mechanism to understand the indolent disease behavior and integrate more recently emerging treatment regimens to comprehensively evaluate response to anti-VEGF therapy versus immunotherapy. The mechanism underlying these observations remains under investigation.

International Kidney Cancer Symposium 2021 will take place in Austin, Texas and virtually on November 5-6.

This year's IKCS2021 will be conducted both in-person format in Austin, Texas and virtual format on November 5-6. Dr. James P. "Jim" Allison, a trailblazing immunologist who won the 2018 Nobel Prize in Physiology or Medicine, will be the keynote speaker at the Kidney Cancer Association's 2021 (IKCS) in November in Austin, Texas. Allison, chair of Immunology and executive director of the Immunotherapy Platform at the University of Texas MD Anderson Cancer Center in Houston, Texas, was awarded the Nobel Prize for establishing that our immune systems can be stimulated to launch an effective attack against tumor cells. He helped develop the drug ipilimumab (Yerevoy®), which is proven to improve survival in many cancers including kidney, melanoma, lung, bladder and colorectal.

"We're thrilled to welcome Dr. Allison to IKCS 2021," said Dr. Christopher G. Wood, Chair of the KCA's Board of Directors and a surgeon and professor at MD Anderson Cancer Center. "Jim's discoveries over his career are foundational to how we treat kidney cancer today and how the field will advance in the future. It is fitting that we hear from him now as we're poised again on the verge of a whole new wave of possibilities for the kidney cancer community and I'm very excited he will be sharing his perspectives with us."

"After a year of holding virtual events, we're excited at the prospect of gathering safely once again to learn, share, and, perhaps most importantly, enjoy each other's company," said Gretchen E. Vaughan, KCA's President and CEO. KCA is working diligently to implement health- and safety-protocols based on the advice of health experts and the latest guidelines and local regulations to mitigate the risk of exposure to COVID-19 and to optimize health and safety conditions for attendees during the event.

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