Review Article: Genitourinary Cancer

A narrative review of precision medicine in metastatic renal cell carcinoma

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Background and Objective: In recent years, many drugs have been developed for the treatment of metastatic renal cell carcinoma (mRCC). However, there is no consensus on which drugs are currently the best to treat for patients with mRCC. Herein we discuss the optimal treatment modality for these patients by reviewing gene-based personalized medicines.

Methods: A literature search was performed using PubMed, with keywords, such as mRCC, gene expression, precision medicine, gut microbiome, and antibiotics. In addition, we collected evidence from the reference articles.

Key Content and Findings: The standard first-line combination therapies [immune-oncology (IO) drugs + tyrosine kinase inhibitors or dual IO drugs] for patients with mRCC showed excellent clinical outcomes. Polybromo 1 (PBRM1), BRCA1-associated protein 1 (BAP1) and repertoire analysis of T-cell receptors, are potential prognostic biomarkers for mRCC. Dynamic contrast-enhanced magnetic resonance imaging has been used to determine the therapeutic effect of vascular endothelial cell growth factor receptor for patients with mRCC. Recently, the use of antibiotics is also related to the therapeutic effects of IO therapy on urological cancer.

Conclusions: These will be the development of a comprehensive therapy for mRCC in the near future. Moreover, various tumor markers and genetic abnormalities must be combined to take best advantage of precision medicine. Especially, the gut microbiome appears to be an importance factor to treatment of cancer.

Keywords: Metastatic renal cell carcinoma (mRCC); gene expression; precision medicine; gut microbiome; antibiotics

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Introduction

Background

In 2020, new cases of renal cell carcinoma (RCC) were diagnosed about 430,000 patients all over the world (1). Clinically, surgery is the first choice for RCC without metastasis. In addition, approximately 30% of new RCC cases are metastatic RCC (mRCC), and these patients mainly receives systematic therapy (2). Conventionally, treatment of mRCC consists of interferon-alpha (IFNα)

therapy (3,4), which leads to poor therapeutic outcomes.

Rationale and knowledge gap

However, with the development of tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin (mTOR), outcomes for mRCC have improved dramatically; with these drugs, there have been significant improvements in overall survival (OS) (5-7). The prognosis for mRCC is generally based on the International mRCC Database Consortium (IMDC). In the TKIs era, 2-year OS was 81.6% (favourable risk), 48.7% (intermediate risk), 23.4% (poor risk) (8). Since then, several TKIs have been developed to improve treatment outcomes for mRCC, with an increasing number of treatment options, including first-, second-, and third-line treatments (9,10).

Objective

Immune checkpoints suppress the antitumor immune response; antibody drugs against anti-programmed cell death 1 (PD-1), programmed cell death-ligand 1 (PD-L1), or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) were developed, and their efficacy was confirmed by randomized controlled trials (RCTs). CheckMate 025 compared nivolumab, a PD-1 antibody drug, to everolimus in patients with mRCC. This study included 821 patients with advanced renal cancer. Nivolumab showed significant reduction of mRCC tumor size and prolonged OS (11). Since then, immune-oncology (IO) treatments have changed the treatment of cancer. The treatment options for mRCC have increased with the advent of various IO drugs. For these reasons, the most widely used first-line treatment of mRCC is dual IO drugs or a combination of IO-TKIs. However, it has been difficult to decide which drug is the best choice with regard to therapeutic effects, adverse events (AEs), and immune-related adverse events (irAEs).

The difference between our narrative and other reviews discussed we reported not only untreated clear cell mRCC but also untreated non-clear cell mRCC (12,13). In addition, we discuss the optimal treatment modality for patients with mRCC based on the currently under developed drugs, using analysis of polybromo 1 (*PBRM1*), BRCA1-associated protein 1 (*BAP1*), plasma cell-free DNAs (cfDNA), repertoire analysis of T-cell receptors (TCR), the gut microbiome and so on. Especially, we discuss gut microbiome as a various potential to treatment of mRCC because it associated with cancer immune response. We present this article in accordance with the Narrative Review reporting checklist (available at https://amj.amegroups.com/article/view/10.21037/amj-22-83/rc).

Methods

A literature search was performed on PubMed for articles published from January 1998 to December 2022, focusing on articles relevant to mRCC and first-line mRCC therapy using IO drugs. The keywords, “mRCC”, “gene expression”, “precision medicine”, “gut microbiome”, and “antibiotics” from clinical studies were used (*Table 1*).

First-line mRCC therapy using dual IO drugs or IO-TKIs drugs

Several guide lines for mRCC patients recommend combination IO therapies or IO-TKIs therapies as a first-line treatment. RCTs have shown that these combination therapies improve OS and progression-free survival (PFS). We summarized the pivotal the trials of mRCC studies regarding outcomes, AEs, and irAEs (14-25) (*Table 2*).

PD-L1 expressed on the surface of cancer cells allows them to escape immune cells. Nivolumab promotes immune cells to attack cancer cells by suppressing PD-1 (26). Nivolumab is the first anti-PD-1 antibody to be indicated for mRCC from CheckMate 025 results (11). CTLA-4 is up-regulated shortly after T-cell activation and initiates negative regulatory signaling on T-cells during ligation with B7 costimulatory molecules expressed by antigen-presenting cells (27). Ipilimumab is a monoclonal antibody targeting CTLA-4 that blocks inhibitory signals to cytotoxic T-lymphocytes. CheckMate 214, comparing nivolumab + ipilimumab versus sunitinib, showed OS improvement for intermediate/poor (I/P)-risk untreated clear cell mRCC with nivolumab + ipilimumab (18,19). This study showed no significant differences in OS between the favorable risk groups. However, these combination therapies show a durable effect of I/P-risk untreated clear cell mRCC by inducing cancer immunity. In these groups, nivolumab + ipilimumab had significant benefits over sunitinib with respect to PFS [hazard ratio (HR) =0.68; 95% confidence interval (CI): 0.58–0.81] and OS (HR =0.73; 95% CI: 0.61–0.87). An objective response occurred in 41.9% of patients treated with nivolumab + ipilimumab and 26.8% of patients treated with sunitinib. In the pathological analysis of CheckMate 214, nivolumab + ipilimumab is also effective with sarcomatoid mRCC in first-line treatment (PFS:

Table 1 The search strategy summary

Items	Specification
Date of search	2022.12.31
Databases and other sources searched	PubMed
Search terms	"metastatic renal cell carcinoma" [MeSH]
	"gene expression" [MeSH]
	"precision medicine" [MeSH]
	"gut microbiome" [MeSH]
	"antibiotics" [MeSH]
Timeframe	January 1998 to December 2022
Inclusion and exclusion criteria	Inclusion: original papers and reviews in English about themes such as renal cell carcinoma, gene expression, precision medicine, gut microbiome and antibiotics
	Exclusion: articles which we considered with low reliability
Selection process	It was conducted by K Sugiomo, K Fujita and other co-authors

HR =0.54; 95% CI: 0.33–0.86 and OS: HR =0.45; 95% CI: 0.30–0.70) (28). In other study, CheckMate 920 study showed these combination therapies is safety and efficacy in patients with non-clear cell mRCC (29). The results showed median PFS was 3.7 (95% CI: 2.7–4.6) months, median OS was 21.2 (95% CI: 16.6–estimable) months.

Axitinib is a potent, and highly selective inhibitor of vascular endothelial cell growth factor receptor-1, -2, -3 (VEGFR-1, -2, and -3). Excessive production VEGFR suppresses immune cell function. The tumor microenvironment consists of tumor cells, blood vessels, and extracellular matrix. The tumor microenvironment affects the efficacy of IO drugs, and the combination of axitinib with IO drugs is considered to improve the microenvironment favoring IO drugs (30,31). Comparing the effects of pembrolizumab, PD-1 inhibitor, + axitinib or sunitinib on first-line mRCC therapies, combination therapy has superior clinical outcomes.

Cabozantinib, which has been used to treat mRCC and hepatocellular carcinoma (22,32). Cabozantinib is a multikinase inhibitor that targets receptor tyrosine kinases, including VEGFR-2, the hepatocyte growth factor receptor (MET), and the growth arrest-specific 6 (GAS6) receptor (AXL) (33,34). Nivolumab + cabozantinib had significant benefits over sunitinib with respect to PFS (HR =0.51; 95% CI: 0.41–0.64) and OS (HR =0.60; 95% CI: 0.40–0.89) with previously untreated mRCC (20). An objective response occurred in 55.7% of patients treated with nivolumab + cabozantinib and 27.1% of patients treated with sunitinib. In addition, subgroup analysis showed that combination therapy of nivolumab + cabozantinib was highly effective in cases with bone metastasis, and showed superior response rates to sunitinib. Moreover, combination therapy led to improved quality of life compared to sunitinib monotherapy. In other pathological analysis, cabozantinib + nivolumab showed promising efficacy in the patients with papillary, unclassified, translocation-associated RCC and chromophobe RCC in a phase II trial (35).

Lenvatinib is a multi-kinase inhibitor that, inhibits VEGFRs and fibroblast growth factor receptors (FGFR). Moreover, by inhibiting tyrosine kinase receptors such as rearranged during transfection (RET) and FGFR in cancer cells, lenvatinib suppresses signal transduction in cancer growth (36). Another study using mouse and RCC cell lines showed that lenvatinib + anti-PD-1 antibody strengthened the antitumor activity (37). Lenvatinib blocked FGFR signaling in cancer cells, and restored the expression of interferon-gamma (IFNγ) target molecules that were suppressed by FGFR signaling. These mechanisms provide strong anti-tumor activity by combination therapy with lenvatinib and PD-1 inhibitors. Activation of the IFNγ/Janus kinase (JAK)/signal transducers and activator of transcription (STAT) pathway increases the expression of PD-L1 and chemokines to suppress cancer immunology. Therefore, this combination therapy helps tumor cells to avoid the host immune system (34). In a CLEAR trial comparing pembrolizumab + lenvatinib or sunitinib to advanced RCC, pembrolizumab + lenvatinib was associated

Table 2 First-line mRCC therapy using dual IO drugs or IO-TKIs drugs

Variables	Regimen												
	JAVELIN Renal 101 (14,15)		KEYNOTE-426 (16,17)		Check Mate 214 (18-21)		Check Mate 9ER (22)		CLEAR (23)			IMmotion151 (24,25)	
	Ave + Axi	Sun	Pem + Axi	Sun	Nivo + Ipi	Sun	Nivo + Cabo	Sun	Pem + Len	Len + Eve	Sun	Atz + Bev	Sun
N	442	444	432	429	425	422	323	328	355	357	357	454	461
Median age [range] (years)	62 [29–83]	61 [27–88]	62 [30–89]	61 [26–90]	62 [26–85]	61 [21–85]	62 [29–90]	61 [28–86]	64 [34–88]	62 [32–86]	61 [29–82]	62 [24–88]	60 [18–84]
Sex (male/female), n (%)	316 (71.5)/126 (28.5)	344 (77.5)/100 (22.5)	308 (71.3)/124 (28.7)	320 (74.6)/109 (25.4)	314 (73.9)/111 (26.1)	301 (71.3)/121 (28.7)	249 (77.1)/74 (22.9)	232 (70.7)/96 (29.3)	255 (71.8)/100 (28.2)	266 (74.5)/91 (25.5)	275 (77.0)/82 (23.0)	317 (70.0)/137 (30.0)	352 (76.4)/109 (23.6)
IMDC risk, %													
Favorable	21.3	21.6	31.9	30.5	–	–	22.9	22.0	31.0	31.9	34.7	–	–
Intermediate	61.3	62.20	55.1	57.3	79.0	79.0	58.2	57.3	59.2	54.6	53.8	–	–
Poor	16.3	16.0	13.0	12.1	21.0	21.0	18.9	20.7	9.3	11.8	10.4	–	–
Not reported	1.1	0.2	–	–	–	–	–	–	0.6	1.7	1.1	–	–
PD-L1 expression ≥1%, n (%)	270 (61.1)	290 (65.3)	243 (59.3)	254 (61.7)	100 (26)	114 (29)	83 (25.7)	83 (25.3)	107 (30.1)	116 (32.5)	119 (33.3)	178 (39.2)	184 (40.0)
Median follow-up (months)	13.0		30.6		67.7		18.1		27.0			–	
OS (months)													
Median (95% CI)	NR (30.0–NE)	NR (27.4–NE)	NR	35.7	47.0 (35.5–57.4)	26.6 (22.1–35.5)	NR	NR (22.6–NE)	NR (33.6–NE)	NR	NR	36.1 (31.5–42.3)	35.3 (28.6-42.1)
HR (95% CI); P value	0.80 (0.616–1.027); 0.0392		0.68 (0.55–0.85); 0.0003		0.68 (0.58–0.81); <0.0001		0.60 (98.89% CI: 0.40–0.89); 0.001		Pem + Len *vs.* Sun: 0.66 (0.49–0.88); 0.005 Len + Eve *vs.* Sun: 1.15 (0.88–1.50); 0.30			0.91 (0.76–1.08); 0.27	
PFS (months)													
Median (95% CI)	13.3 (11.1–15.3)	8.0 (6.7–9.8)	15.4	11.1	11.6 (8.4–16.5)	8.3 (7.0–10.4)	16.6 (12.5–24.9)	8.3 (7.0–9.7)	23.9 (20.8–27.7)	14.7 (11.1–16.7)	9.2 (6.0–11.0)	–	–
HR (95% CI); P value	0.69 (0.574–0.825); <0.0001		0.71 (0.60–0.84); <0.0001		0.73 (0.61–0.87); 0.0004		0.51 (0.41–0.64); <0.001		Pem + Len vs. Sun: 0.39 (0.32–0.49); <0.001 Len + Eve *vs.* Sun: 0.65 (0.53–0.80); <0.001			–	
ORR (95% CI), %	52.5 (47.7–57.2)	27.3 (23.2–31.6)	60.4	39.6	41.9	26.8	55.7 (50.1–61.2)	27.1 (22.4–32.3)	71.0 (66.3–75.7)	53.5 (48.3–58.7)	36.1 (31.2–41.1)	–	–
DCR, %	80.8	70.9	83.3	72.8	72.7	71.1	87.9	69.2	90.1	87.1	74.2	–	–
Best overall response, n (%)													
Complete response	17 (3.8)	9 (2.0)	38 (8.8)	13 (3.0)	44 (10.4)	6 (1.4)	26 (8.0)	15 (4.6)	57 (16.1)	35 (9.8)	15 (4.2)	–	–
Partial response	215 (48.6)	112 (25.2)	222 (51.4)	158 (36.8)	134 (31.5)	107 (25.4)	154 (47.7)	74 (22.6)	195 (54.9)	156 (43.7)	114 (31.9)	–	–
Stable disease	125 (28.3)	194 (43.7)	100 (23.1)	150 (35.0)	131 (30.8)	187 (44.3)	104 (32.2)	138 (42.1)	68 (19.2)	120 (33.6)	136 (38.1)	–	–
Progressive disease	55 (12.4)	86 (19.4)	49 (11.3)	74 (17.2)	82 (19.3)	71 (16.8)	18 (5.6)	45 (13.7)	19 (5.4)	26 (7.3)	50 (14.0)	–	–
Unknown	30 (6.8)	43 (9.7)	23 (5.3)	34 (7.9)	34 (8.0)	51 (12.1)	21 (6.5)	56 (17.1)	16 (4.5)	20 (5.6)	42 (11.8)	–	–
Toxicities, % (all grades)	99.5	97.3	96.3	97.6	94.0	97.4	99.7	99.1	99.7	99.7	98.5	98.0	98.9
Events, %	G3,4: 71.2	G3,4: 71.5	G3–5: 67.8	G3–5: 63.8	G3,4: 47.9	G3,4: 64.1	G3,4: 75.3	G3,4: 70.6	G3,4: 82.4	G3,4: 83.1	G3,4: 71.8	G3,4: 45.5	–

Atz, atezolizumab; Ave, avelumab; Axi, axitinib; Bev, bevacizumab; Cabo, cabozantinib; CI, confidence interval; DCR, disease control rate; Eve, everolimus; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IO, immune-oncology; Ipi, ipilimumab; Len, lenvatinib; mRCC, metastatic renal cell carcinoma; NE, could not be estimated; Nivo, nivolumab; NR, not reached; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death-ligand 1; Pem, pembrolizumab; PFS, progression-free survival; Sun, sunitinib; TKIs, tyrosine kinase inhibitors.

with significantly longer PFS (HR =0.39; 95% CI: 0.32–0.49) and OS (HR =0.66; 95% CI: 0.49–0.88) than sunitinib alone. However, this combination therapy resulted in grade 3 or higher AEs (e.g., hypertension or diarrhea) in at least 10% of patients (23). These combination therapies are very effective for the IMDC poor risk group in the subgroup analysis of PFS because it is useful with large tumor volume patients. From these results, there also hoped to be effective for mRCC in many various pathological types.

PD-L1 is expressed on RCC cells, and inhibits the activation of cytotoxic T cells that can recognize and attack cancer cells (38). Avelumab inhibits PD-1/PD-L1 compound formation and promotes the immune response (14,39). In a JAVELIN Renal 101 clinical trial comparing avelumab + axitinib or sunitinib for patients with mRCC first-line treatment, avelumab + axitinib was associated with a significantly longer PFS than sunitinib (HR =0.69; 95% CI: 0.574–0.825). It has been suggested that almost half of patients do not benefit from this regimen because of its efficacy and the resulting toxicity. Therefore, the identification of factors associated with treatment efficacy remains a problem.

Atezolizumab, a PD-L1 inhibitor, has pharmacological effects similar to those of avelumab (37). Bevacizumab is a monoclonal antibody for VEGF-A. It suppresses angiogenesis, tumor growth, and metastasis (40). In an IMmotion151 trial, atezolizumab + bevacizumab or sunitinib was compared as first-line treatment for treatment-naïve patients with mRCC. Combination therapy showed as improvement in PFS, but no improvement in OS (HR =0.91; 95% CI: 0.76–1.08) in patients with previously untreated mRCC (24,25).

The type of AEs differs depending on the drug combination used. Including TKIs regimens of any grade resulted in hypertension in approximately 50% of patients, hypothyroidism in about 25–45%, and fatigue in about 30%. Diarrhea should be noted when using avelumab + axitinib, nivolumab + cabozantinib, and pembrolizumab + lenvatinib because the rate of grade ≥3 AE was ≥7% in these first-line treatment options.

All combination therapies showed excellent outcomes. For these reasons, therapeutic efficacy for mRCC has dramatically improved (41). The combination therapy of nivolumab + ipilimumab or pembrolizumab + lenvatinib may be the good option for IMDC poor risk group; however, these trials did not directly compare each therapy for the first-line treatment of mRCC. Therefore, combination therapies should be chosen based on treatment efficacy, patient risk profile, and tolerance to each treatment.

Recently, many DNA-based biomarkers such as tumor mutational burden (TMB), tumor indel burden (TIB), human leukocyte antigen (HLA) have been associated with response to immune checkpoint inhibitors (ICI). Biomarker analysis of CheckMate 214 showed that low TIB was associated with PFS, but not OS (42). In the future, biomarker analysis helped to provide an insight into which mRCC patients would benefit from these combination therapies.

Precision medicine based on T-cell related gene expression, *PBRM1*, and *BAP1*

The development of next-generation sequencing has enabled us to understand the details of gene expression and mutations.

PBMR1 and *BAP1* are tumor suppressor genes located on the short arm of chromosome 3. Recent studies showed that *PBMR1* and *BAP1* mutations are involved in chromatin regulation (43,44), and that these mutated genes are responsible for the pathogenesis of RCC. The predictive roles of these mutated genes have been reported. Mutational biomarkers reported, the study using targeted sequencing of 341 cancer genes was performed on tumor samples from 258 patients with mRCC. For the first-line treatment of mRCC, everolimus and sunitinib showed good efficacy rates in patients with *PBRM1* mutations, but not in patients with *BAP1* mutations (45). *BAP1* gene mutations and the expression of intrinsic endogenous retroviruses (ERVs) are related to each other. ERVs are involved in the immune induction of cancer. ERV expression is associated with local immune checkpoint activation (ICA) and the response to immune checkpoint blockade (ICB) (46). For these reasons, IO is effective when ERV expression exists in clear cell RCC.

Analysis of *PBRM1* and *BAP1* gene mutations could help in selecting treatment options for patients with mRCC.

cfDNAs are degraded DNA fragments (50–200 bp) released into the blood plasma from tumor cells as well as normal cells. cfDNA could be a surrogate marker for multiple cancers, and can be used for diagnosis, prognosis, and monitoring because of tumor specific alterations in cfDNA (47).

Analysis of plasma cfDNA is less invasive than that of needle biopsy specimens. Mutated *PBRM1* and *BAP1* could be detected by the analysis of plasma cfDNA (48-50), which could lead to precision medicine.

Comprehensive molecular characterization

Omic-based medicine integrates comprehensive molecular information to improve precision medicine. Motzer *et al.* reported integrated multi-omics analyses, leading to the identification of robust molecular subtypes in 823 tumors from patients with advanced RCC, including 134 tumors with sarcomatoid features (51). This trial compared atezolizumab + bevacizumab with sunitinib as the first-line treatment for patients with mRCC (24). Unsupervised transcriptomic analysis revealed seven molecular subsets with angiogenesis, immunity, cell-cycle, metabolism, and stromal programs. Angiogenesis-enriched patients demonstrated superior prognosis in both the atezolizumab + bevacizumab and sunitinib groups because of the presence of an angiogenesis inhibitor. Atezolizumab + bevacizumab showed clinical benefits in patients with high T-effectors and/or cell-cycle transcription. These findings can be applied to stratify patients based on molecular subsets, improve the clinical outcomes of mRCC by selecting checkpoint blockade or antiangiogenic therapy alone, and lead to personalized therapies for mRCC.

Radiogenomic

The therapeutic effects of VEGFR for patients with mRCC was determined using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). DCE-MRI is a multiparametric MRI, that can evaluate the permeability of blood vessels in tumor microenvironments (52). The pharmacodynamic effects of VEGFR TKIs were evaluated by assessing changes in contrast-enhancement parameters of metastatic liver lesions using DCE-MRI in patients with colon cancer. DCE-MRI parameters are correlated with pharmacological responses, and DCE-MRI can monitor vascular changes (53). Another prospective study included 49 patients with clear cell RCC who underwent DCE-MRI prior to nephrectomy. The surgical specimens were sectioned to match the MRI acquisition planes. RNA data from tumor sampling were correlated with the percent enhancement on DCE-MRI. DCE-MRI findings suggested the method can be used to determine associated gene expression of angiogenesis, IO cells, and the response of metastatic lesions. DCE-MRI can predict the response of patients to VEGFR-TKI therapy. Hence, DCE-MRI has the highest potential among comprehensive imaging-based approaches (54).

Repertoire analysis of TCR

TCR analysis is a potential biomarker for treatment outcomes of immune ICI. To recognize a large variety of antigens, humans have a huge diversity of TCR repertoires through somatic recombination of TCR chains. Advances in next-generation sequencing technologies, coupled with powerful novel bioinformatics tools, allow quantitative and reproducible characterization of TCR repertoires in tumor and blood samples from an increasing number of patients with a variety of solid cancers. The analysis of TCR repertoires can be used to detect malignant lymphoma and, leukemia cells, and to evaluate the efficacy of ICIs (55).

Analysis of the TCR repertoire in peripheral blood samples predicts the efficacy of PD-1 monotherapy (nivolumab). Patients with a decreased diversity index (DI) of TCR repertoires one month after treatment have a better prognosis compared to patients with increased DI (56). The TCR repertoire and level of PD-1 expression in peripheral blood have the potential to provide predictive biomarkers for the therapeutic efficacy of ICIs due to the response to anti-PD-1 monotherapy after treatment initiation in patients with mRCC. TCR repertoire analysis could be a useful tool for determining the treatment efficiency of IO therapies.

Gut microbiome

Recently, it has been proven that the gut microbiome is involved in the pathogenesis of inflammatory bowel disease, obesity, diabetes, cancer, autism, atherosclerosis, etc. (57-60). The gut microbiome is also associated with immune regulations (61). The gut microbiome was affected by diet, residential area, and race (62,63).

The influence of antibiotics in patients with advanced non-small cell lung cancer (NSCLC), RCC, and urothelial carcinoma who received IO drugs was recently reported. Antibiotics can significantly alter the gut microbiome. A total of 249 patients were analyzed; 69 patients were prescribed antibiotics from two months prior up to one month after the first administration of IO. PFS and OS were significantly shorter in the antibiotic treated group than in the treated group (64).

In another study, the gut microbiomes of 69 patients with mRCC who underwent nivolumab treatment were analyzed. Therapeutic effects were examined based on the presence or absence of a recent history of antibiotic administration. Among the 69 patients, 11 (16%) received antibiotics, and

Table 3 Relationship of therapeutic effect between presence or absence gut microbiota and IO therapy

Cancer	Endpoint	Patients (N)	Clinical outcome	Reference
NSCLC	OS	140	Median OS: non-ATBs 15.3 mo *vs.* ATBs 8.3 mo, P=0.001	(64)
RCC	PS	67	Median OS: non-ATBs 7.4 mo *vs.* ATBs 4.3 mo, P=0.012	(64)
mRCC	ORR	69	Non-ATBs 52% *vs.* ATBs 18%	(65)
mRCC	PFS, OS	72	Non-ATBs *vs.* ATBs: PFS, P=0.272; OS, P=0.270	(66)

ATBs, antibiotics; IO, immune-oncology; mRCC, metastatic renal cell carcinoma; mo, month; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma.

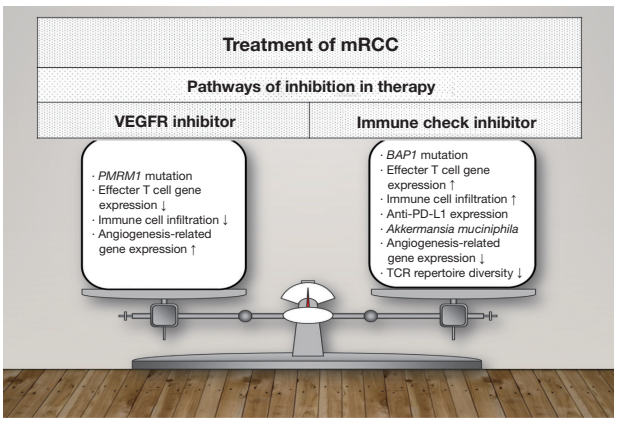

Figure 1 Relationship of therapeutic effect between VEGFR and immune check inhibitor. BAP1, BRCA1-associated protein 1; mRCC, metastatic renal cell carcinoma; PD-L1, programmed cell death-ligand 1; PMRM1, polybromo 1; TCR, T-cell receptors; VEGFR, vascular endothelial cell growth factor receptor.

58 (84%) did not. The group that received antibiotics had a lower objective response rate than the non-antibiotic group. *Akkermansia muciniphila* and *Bacteroides salyersiae* are prevalent in the feces of the responder group (65). We summarized the three studies for the gut microbiome in urological cancer (*Table 3*). The effect of antibiotic use was also studied in patients with mRCC who received nivolumab + ipilimumab. There were no significant differences between patients with a history of antibiotic use within 3 months compared to patients without a history of antibiotic use in terms of PFS and OS. However, the patients without a history of antibiotic use had a longer OS compared with patients with a history [median OS: non-antibiotics: not reached (NR) (95% CI: 18.7 to NR) months *vs.* antibiotics: NR (95% CI: 16.4 to NR) months, P=0.270] (66). Gut microbiota directly affects the immune cells in the gut, or the metabolites from gut microbiota, that can enter the systemic circulation and affect immune cells.

The relationship between microbiota and the therapeutic effects of IO drugs is summarized in *Table 2*. As these studies had a small number of cases, it is necessary to increase the number of cases to prove their credibility. Analysis of the gut microbiome might be a promising method for predicting treatment efficacy in patients with mRCC.

The limitation of our narrative review is no consensus on the optimal treatment for such patients because there are no phase III clinical studies based on biomarkers for mRCC treatment. In the near future, we believe that these biomarkers will lead to precision medicine in the treatment of mRCC by being analyzed carefully and strategically.

Conclusions

The standard first-line therapies for patients with mRCC are combination IO therapies or IO-TKIs drugs. *PBRM1*, *BAP1*, DCE-MRI, and TCR repertoire are potential biomarkers for therapeutic efficacy in patients with mRCC. Furthermore, the presence or absence of a history of antibiotics use was related to the prognosis of patients with mRCC undergoing IO therapy (*Figure 1*).

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://amj.amegroups.com/article/view/10.21037/amj-22-83/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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