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Novel therapy for pediatric and adolescent kidney cancer

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Abstract
Pediatric and adolescent renal tumors account for approximately 7% of all new cancer diagnoses in the USA each year. The prognosis and treatment are varied based on factors including the underlying histology and tumor stage, with survival rates ranging from greater than 90% in favorable histology Wilms tumor to almost universally fatal in other disease types, including those patients with advanced stage malignant rhabdoid tumor and renal medullary carcinoma. In recent years, our understanding of the underlying genetic drivers of the different types of pediatric kidney cancer has dramatically increased, opening the door to utilization of new targeted biologic agents alone or in combination with conventional chemotherapy to improve outcomes. Several ongoing clinical trials are investigating the use of a variety of targeted agents in pediatric patients with underlying genetic aberrations. In this manuscript, the underlying biology and early phase clinical trials relevant to pediatric renal cancers are reviewed.

Keywords Kidney cancer · Wilms tumor · Rhabdoid tumor · Pediatric · Novel therapy

1 Introduction

Pediatric and adolescent kidney cancer accounts for approximately 7% of all new cases of pediatric cancer in the USA and represents a diverse population of cancers, with the treatment and prognosis dependent upon the underlying histology of the tumor. Outcomes range from > 90% overall survival for some types of favorable histology Wilms tumor to < 25% for those patients with advanced rhabdoid tumor and renal medullary carcinoma. Outcomes with relapse are very poor for patients with anaplastic Wilms tumor, blastemal predominant Wilms tumor, renal cell carcinoma, and malignant rhabdoid tumor and remain suboptimal for patients with favorable histology Wilms tumor, indicating a need for novel therapies to improve outcomes. With the recent expansion of knowledge regarding the genetic basis of these tumors, more information is now available regarding the underlying genetic drivers of disease. Novel biologic therapies targeting such tumor drivers, once identified, will likely need to initially be paired with conventional chemotherapy agents to improve outcomes. This review will focus on biologic therapies and early phase clinical trials for pediatric renal cancer.

For this review, a literature search was performed using PubMed from 2000 to present time to investigate the current available knowledge regarding the genomic drivers of each of the following cancer types: favorable histology Wilms tumor, anaplastic histology Wilms tumor, malignant rhabdoid tumor, translocation renal cell carcinoma, renal medullary carcinoma, clear cell sarcoma of the kidney, and congenital mesoblastic nephroma. Additional information regarding current novel biologic agents in development was obtained through PubMed as well as from recent publications from the National Cancer Institute's (NCI) Pediatric Preclinical Testing Consortium (http://www.ncipptc.org/publications) and from the National Institutes of Health Clinical Trials database (https://clinicaltrials.gov/ct2/home).

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2 Targeting favorable histology Wilms tumor

Favorable histology Wilms tumor (FHWT) is the most common pediatric renal malignancy, accounting for approximately 75% of all new pediatric renal cancer cases per year [1]. Modern multimodality therapy has resulted in an overall cure rate of 90% for these patients [2–6]. Genetically, FHWTs are

most commonly characterized by mutations involving the following genes: *CTNNB1*, *DGCR8*, *DROSHA*, *MLLT1*, *MYCN*, *SIX1*, *SIX2*, *WT1*, and *FAM123B* [7]. It should be noted that FHWT is genetically heterogeneous, with none of these genes representing a driver mutation in more than 15% of patients. Loss of heterozygosity at 11p15 (for Stage 1 patients) and of chromosomes 1p and16q and chromosome 1q gain have been shown to impact treatment outcomes and are increasingly utilized for determining treatment intensity [2]. The overall survival for those patients with FHWT who experience relapse ranges from 40% to 80% and depends on the initial tumor stage and treatment [8–10]. This is a particularly urgent problem secondary to both the suboptimal survival of patients with relapsed FHWT and the highly significant anticipated burden of late effects for those with relapse who do survive [11–14]. Targeted therapies can offer novel treatment options for these patient populations.

Wilms tumor gene (WT1), which is mutated in ~6% of Wilms tumor (WT) patients, plays a role in the promotion of homologous recombination-mediated DNA damage repair through upregulation of genes such as XRCC1, RAD51D, and RAD54 [15]. Defects in DNA damage repair mechanisms are one of the hallmarks of cancer, causing genomic instability and favoring tumor progression. Inherited inactivating mutations in *breast cancer susceptibility genes 1 and 2* (*BRCA1* and *BRCA2*) are associated with cancer predisposition. In addition, mutations in *partner and localizer of BRCA2 (PALB2)*, which leads to loss of the WD40 domains in the C-terminus of the protein that block the ability of *PALB2* to associate with *BRCA2*, are associated with Fanconi anemia and non-*BRCA1/BRCA2* hereditary breast cancer [16, 17]. *PALB2* mutations have been documented in WTs [7, 17]. Therefore, targeting defects in DNA damage repair genes is a potential therapeutic avenue in WTs. Poly ADP-ribose polymerase (PARP) inhibitors are effective in the management of *BRCA*-mutant patients. The Pediatric Preclinical Testing Program (PPTP) investigated BMN 673, a potent PARP inhibitor that inhibits PARP catalytic activity and also traps PARP to DNA at sites of single-strand breaks, in a WT xenograft mouse model (KT-10, which has a truncating mutation in *PALB2*) [18]. The KT-10 xenograft showed a maintained complete response (CR) following treatment with BMN 673 and continued to show a high level of response even with a threefold reduction in dose, indicating that this xenograft is highly sensitive to PARP inhibition [18]. The Children's Oncology Group (COG) Pediatric Molecular Analysis for Therapy Choice (MATCH) clinical trial, which matches patients with targeted biologic agents on the basis of their underlying genomic changes, is currently conducting a Phase 2 subprotocol of the PARP inhibitor olaparib in patients with tumors harboring defects in DNA damage repair genes (NCT03233204).

M6620 is a novel inhibitor of the DNA repair enzyme ataxia telangiectasia and Rad3-related (ATR) that shows promise based on preclinical data in the treatment of patients with WT [19]. The effectiveness of typical chemotherapy agents that damage DNA is limited by repair of the DNA through the DNA damage response mechanism, which is mediated by two protein kinases, ataxia telangiectasia mutated (ATM) and ATR [20]. The combination of ATR inhibition with chemotherapy that induces DNA damage could result in increased therapeutic effectiveness [21–23]. M6620 is a potent and selective inhibitor of ATR that has entered clinical trials in adults with multiple different solid tumors, including those with head and neck squamous carcinoma, lung cancer, ovarian cancer, and cervical cancer; M6620 is being studied as a single agent and in combination with ionizing radiation and other chemotherapy agents that induce DNA damage (NCT02567422, NCT02487095, NCT03641547, NCT03517969, NCT02567409, NCT02595931, NCT02589522, and NCT02627443) [21, 23]. The PPTP has evaluated M6620 alone and in combination with cisplatin in WT mouse xenograft models (Table 1) [19]. Alone, M6620 single agent treatment resulted in no objective response, but the KT-5 FHWT model showed significantly superior event-free survival (EFS) with the combination of M6620 and cisplatin versus single agent cisplatin alone [19]. In fact, of all the solid tumor xenograft models tested during this project, the greatest enhancement of antitumor effect for the combination of M6620 and cisplatin was seen in the KT-5 FHWT model, where a complete response (CR) was achieved. Therefore, the combination of M6620 or other ATR inhibitors with DNA-damaging chemotherapy agents may be a potentially beneficial combination in FHWT patients. There are currently two clinical trials enrolling pediatric patients evaluating M6620 given alone (NCT03718091) and in combination with chemotherapy (NCT03641547) in solid tumors.

Targeting of the Wnt/β-catenin signaling pathway is another potentially attractive target for patients with WT as *CTNNB1* mutations are frequently encountered in this patient population. Wnt/β-catenin signaling plays a role in cellular proliferation, differentiation, and migration in multiple organ systems [24]. Wnt-activating *CTNNB1* mutations in WTs are

Table 1 Response to M6620 and cisplatin in Wilms' tumor mouse xenografts

Line	Tumor type	Treatment group	EFS activity	Response*
KT-5	FHWT	Cisplatin	Intermediate	PD2
KT-5	FHWT	M6620	Low	PD1
KT-5	FHWT	Combination	Intermediate	CR

**PD1* progressive disease with event-free survival (EFS) tumor/control ≤ 1.5, *PD2* progressive disease with EFS tumor/control > 1.5, *CR* complete response

likely to result in abnormal induction and/or continued progenitor proliferation in the developing nephron, resulting in tumor development [7]. Although promising biologically, agents targeting this pathway have been slow to develop secondary to treatment toxicity; no Wnt-β-catenin inhibitor is currently approved for human use. CWP232291 blocks proliferation of cancer cells via activation of caspases, targeting β-catenin for degradation, which results in inhibition of cell cycle and anti-apoptotic genes. A Phase 1 clinical trial of CWP232291 in adult patients with relapsed or refractory acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) is now complete (NCT01398462), with single agent efficacy observed in AML [25]. CWP232291 has also been studied in multiple myeloma (MM) alone (Phase 1A) and in combination with lenalidomide and dexamethasone (Phase 1B) (NCT02426723); CWP232291 showed single agent safety as well as early evidence of efficacy in MM patients [26]. PRI-724 is an inhibitor of the Wnt/β-catenin pathway that functions by inhibiting the interaction between the CREB-binding protein and β-catenin, downstream where both the canonical and noncanonical Wnt-β-catenin pathways function [27]. Several Phase 1 trials of PRI-724 in adults, alone or in combination with gemcitabine, have been completed (NCT01764477, NCT01606579). Currently, there are no pediatric investigational plans for PRI-724. Tegavivint is a novel β-catenin/transducing β-like protein 1 (TBL1) inhibitor that has shown antitumor activity in metastatic osteosarcoma both in vitro and in vivo using established human osteosarcoma cell lines [28]. Tegavivint is currently in a Phase 1 clinical trial for patients with proven primary or recurrent desmoid tumor that is unresectable and symptomatic or progressive (NCT03459469). Several other small molecule inhibitors of the Wnt/β-catenin pathway, functioning at various levels within the signaling cascade, such as Frizzled, GSK3, Axin, and Porcupine, are in preclinical or early clinical phases of development [27]. There are no current open pediatric clinical trials using Wnt/β-catenin inhibitors.

Mutations in microRNA (miRNA) processing genes occur in approximately 15% of WT patients [29]. Synthesis of mature miRNA requires normal function of *DGCR8*, *DROSHA*, *XPO5*, and *DICER1*. Given the multitude of cellular pathways miRNAs are known to affect, combined with their interactions and feedback loops, the range of effects associated with miRNA processing gene mutations is likely to be heterogenous and complex [29, 30]. miRNA processing gene mutations are associated with downregulation of all members of the miR-200 family, which are key regulators of the mesenchymal to epithelial transition. Targeting of miRNA processing is an intriguing treatment option for FHWTs. The COG Phase 1 study of selinexor, a XPO1 (which functions in miRNA biogenesis similar to XPO5) inhibitor, in recurrent and refractory pediatric solid tumors is currently accruing patients (NCT02323880). Research is ongoing to develop small molecule inhibitors targeting specific miRNAs and their production [31].

WTs are characterized by neural cell adhesion molecule (NCAM, CD56) expression, which plays a role in cell adhesion and signaling [32]. CD56 is not expressed on the majority of normal cells in the body, making it an intriguing therapeutic target [33]. IMGN901 (lorvotuzumab mertansine) is a CD56 monoclonal antibody conjugated to a cytotoxic maytansinoid, DM1. When IMGN901 binds to CD56 on tumor cells, the conjugate is internalized, and DM1 is released and subsequently disrupts microtubule assembly leading to G2/metaphase arrest and cell death (IMGN901 Investigator Brochure Version 13, May 2014). PPTP testing of IMGN901 showed antitumor activity in CD56-expressing pediatric cancer models; high CD56 expression was a marker of response, but not all mouse xenografts with high-level CD56 immunohistochemical staining responded to IMGN901, indicating a possible resistance mechanism [34]. The COG Phase 2 study of IMGN901 in children with relapsed or refractory WT and other CD56-expressing tumors has completed accrual (NCT02452554); no significant clinical activity was noted in the study. However, alternate approaches to CD56 targeting or alternative drug conjugates and/or payloads remain of interest and warrant further investigation.

In addition, other targets of potential interest in WT moving forward include apoptosis-directed agents. Apoptosis can be altered to favor cell survival within tumors; high expression of survivin, an inhibitor of apoptosis, and absence of caspase 8, a pro-apoptotic enzyme, independently correlate with poor outcomes in several tumor types [35–37]. Caspase 8 is activated by cytotoxic chemotherapeutic agents and endogenous ligands, including TRAIL and CD95 (Fas) ligand [38, 39]. Pediatric renal tumors express greater levels of both pro- and anti-apoptotic factors than the normal kidney, with survivin and Fas differentially expressed.[40] The survivin:fas ratio is prognostically relevant in WT outcome [40]. BCL2 also negatively regulates apoptosis [41]; WTs have been shown to express significant amounts of BCL2 [42]. Therefore, combination therapy with venetoclax, which targets BCL2, or other agents directed towards apoptosis are of interest in WT. Targeting of IGF2 also remains a focus area in WT research. Epigenetic alterations at 11p15 occur in 69% of WT patients [43–45]. Loss of imprinting of 11p15 has been shown to drive *IGF2* overexpression and oncogenic pathway activation [46]. Several different therapeutic agents that target either IGF2 or its receptor IGF1R are in development and are of interest for further study in WT patients [46]. Other areas of interest include methylation and epigenetic targeting agents; recurrent mutations in genes encoding proteins that mediate histone modifications have been reported in WT, including *MLLT1*, *BCOR*, *MAP3K4*, *BRD7*, and *HDAC4* [7].

3 Targeting anaplastic histology Wilms tumor

Approximately 5–10% of WTs demonstrate anaplastic histology, defined by the presence of polyploid atypical mitotic figures, a large nuclear size, and hyperchromasia [47, 48]. Anaplastic histology WT (AHWT) can be further classified as focal or diffusely anaplastic based on the geographic distribution of anaplasia. Patients with AHWT have an inferior EFS and overall survival (OS) compared to those with FHWT and require much more intensive therapy to achieve even these lesser outcomes [49]. AHWTs are characterized by alterations in the *TP53* gene, including both mutations and copy number alterations; TP53 loss plays a key role in the development of anaplasia in WTs [50]. AHWTs have also been shown to harbor the other genetic alterations common to FHWT [7]. Given that AHWTs contain many of the same genetic alterations noted in FHWTs, the agents discussed above are also promising for investigation in the AHWT cohort of patients. In addition, agents that impact the TP53 signaling pathway are logical to pursue. An attractive strategy involves the combination of targeted biologic agents with conventional chemotherapy, such as irinotecan-based regimens, as response has been shown to irinotecan previously [51].

WEE1 kinase plays a central role in the G2-M cell cycle checkpoint and is also required during S-phase. Cyclin-dependent kinase 1 (CDK1) activity is required for progression from G2 to the M phase. WEE1 maintains CDK1 in an inactive state through phosphorylation at tyrosine 15 [52]. WEE1 is activated in response to single-strand DNA breaks in a series of steps beginning with ATR activation, leading to CHK1 phosphorylation. CHK1 then phosphorylates and activates WEE1 leading to CDK1 phosphorylation and inactivation [53]. AZD1775 is a potent and selective ATP-competitive inhibitor of WEE1. Preclinical studies have shown the ability of AZD1775 to potentiate a range of cytotoxic agents, including topoisomerase I inhibitors, antimetabolites, and DNA cross-linking agents. Some studies have reported that the chemopotentiation is greatest when TP53 is defective [54–56]. The PPTP evaluated the ability of AZD1775 to potentiate the in vivo activity of irinotecan (Table 2). The combination of AZD1755 and irinotecan induced a partial response in KT13, a patient-derived AHWT line harboring a *TP53* mutation. The EFS was longer for the combination compared to single agent irinotecan [52]. AZD1775 is currently being tested in a Phase 1/2 study in combination with irinotecan in pediatric patients with relapsed or refractory solid tumors (NCT02095132).

Table 2 Response of AZD1775 and irinotecan in an AHWT mouse xenograft model

Line	Histology	Treatment	Response*
KT-13	AHWT	AZD1775	PD1
KT-13	AHWT	Irinotecan	PD2
KT-13	AHWT	AZD1775 + Irinotecan	PR

**PD1* progressive disease with time to event ≤ 200% the Kaplan-Meier median time to event in control group, *PD2* progressive disease when time to event is > 200% the Kaplan-Meier median time to event in control group, *PR* partial response

CHK1 inhibitors may also be of therapeutic interest in AHWT. Prexasertib (LYS2606360) is a potent ATP-competitive CHK1 inhibitor that exhibits single agent cytotoxicity through replication catastrophe [57]. It has also been shown to induce single-strand DNA breaks in multiple neuroblastoma-derived cell lines [58]. Prexasertib potentiates selected chemotherapy agents in some preclinical models of adult and childhood cancer. A COG Phase 1 clinical trial of prexasertib in pediatric patients with recurrent or refractory solid tumors (NCT02808650) is currently accruing patients.

In addition, given the genomic instability seen in *TP53*-mutated tumors and the advancement of immune checkpoint inhibitor therapy, targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) and programmed cell death protein 1 (PD-1) or its primary ligand PD-L1 in patients with AHWT may be of considerable therapeutic benefit. CTLA4 downregulates and deactivates T-cells leading to a diminished T-cell response, thereby decreasing overall response to tumor-associated antigens [59, 60]. Ipilimumab is a human monoclonal antibody specific for CTLA4 that has been FDA approved in multiple adult cancers, including melanoma, metastatic renal cell carcinoma, and colorectal cancer [59]. Immune tolerance is dependent on PD-1; when bound to PD-L1, PD-1 initiates signaling that blocks immune response by inhibiting T-cell receptor-mediated lymphocyte proliferation and cytokine secretion [61]. Nivolumab is a fully humanized monoclonal antibody that targets PD-1; it has been FDA approved for the treatment of metastatic melanoma, non-small cell lung cancer, renal cell carcinoma, hepatocellular carcinoma, and multiple other adult cancers [62]. PD-L1 expression has been documented in 14% (11/81) of patients with WT, with those with anaplastic histology being more likely to express PD-L1 (40% versus 9.8%, $p = 0.026$) [63]. WT has also been shown to be infiltrated by immune cells both before and after chemotherapy, indicating a potential for response to immune checkpoint inhibition [64]. An open COG Phase 1/2 clinical trial investigating the use of nivolumab with or without ipilimumab in pediatric patients with recurrent or refractory solid tumors is ongoing (NCT02304458).

4 Targeting malignant rhabdoid tumor

Malignant rhabdoid tumor (MRT) is one of the most aggressive and lethal malignancies in pediatric oncology. In contrast to WT, MRT of the kidney is characterized by the early onset

of local and distant metastases and resistance to chemotherapy. The survival rate for renal MRTs is only 20–25% for those with advanced stage disease. Intensification of chemotherapy has failed to significantly improve survival for patients with Stage 3 and 4 disease, emphasizing the importance of identification and implementation of novel biologic therapies for MRT [65]. MRTs are characterized genetically by biallelic, inactivating perturbations of the *SWI-/SNF*-related, matrix-associated, actin-dependent regulator of chromatin, subfamily B, member 1 (*SMARCB1*) gene [66]. *SMARCB1* is presumed to function as a classic tumor suppressor and is the primary gene responsible for MRT development [67]. The *SWI/SNF* complex acts in an adenosine triphosphate (ATP)-dependent manner to remodel chromatin, which regulates gene transcription and DNA repair. *SMACRB1* loss can promote cell cycle progression resulting from upregulation of targets of the p16INK4a-Rb-E2F pathway, primarily including cyclin D1 as well as several cyclin-dependent kinases [66]. Rb family loss has been shown to increase MRT tumorigenesis and progression, whereas ablation of *cyclin D1* abrogates MRT evolution in mouse models [68]. Similarly, tumor development in *SMARCB1*-deficient mice is greatly accelerated in the absence of functional p53 protein. These findings suggest a cooperative effect between *SMARCB1* and the *pRB*, *cyclin D1*, and *TP53* pathways. The loss of *SMARCB1* is postulated to result in a global failure of the repressive H3K27 trimethylation mark present on bivalently modified histones, mediated by the polycomb complex 2, resulting in widespread epigenetic modifications and leading to arrested development and abnormal proliferation [69]. Two members of the polycomb complex 2, *CBX6* and *EZH2*, are upregulated in MRT [69]. Aurora A kinase is also expressed in high levels in MRT and is repressible with *SMARCB1* reintroduction into rhabdoid tumor cells via transcriptional downregulation [70]. Bromodomain-containing protein 9 (BRD9) is also a subunit of the *SWI/SNF* complex that is involved in epigenetic mechanisms such as regulation of transcription, chromatin remodeling, and histone modification [71]. These findings suggest possible therapeutic targets for MRT.

EZH2 inhibitors have shown anti-rhabdoid tumor effects both in vitro and in vivo. Tazemetostat (EPZ-6438), a selective, orally bioavailable, small molecule inhibitor of the *EZH2* gene, induces apoptosis and differentiation specifically in SMARCB1-depleted MRT cells. Treatment of mice bearing MRT patient-derived xenografts with tazemetostat leads to dose-dependent regression of MRTs and prevention of regrowth after dosing cessation [72]. Additional preclinical investigations have demonstrated tazemetostat to have enhanced antitumor activity when administered in combination with chemotherapy regimens including vincristine, doxorubicin, and cyclophosphamide (Epizyme, Investigator Brochure, March 2016). In addition, the PPTP published results showing significant antitumor activity of tazemetostat in MRT mouse xenograft models (3/5 xenograft models), without demonstrable effect in the other histologies tested (0/22) [73]. Clinical activity of tazemetostat has been shown in subjects with genetically defined *SMARCB1*-altered tumors, including those with epithelioid sarcoma and MRT of the ovary. The current ongoing Phase 1 pediatric study EZH-102 (NCT02601937) is evaluating the administration of tazemetostat in pediatric patients with relapsed/refractory MRT and other *SMARCB1-/SMARCB4*-mutated tumors or synovial sarcoma; a recommended Phase 2 dose has been determined, and the protocol is currently enrolling expansion cohorts. A Phase 1/2 clinical trial is currently under development by the COG renal tumor committee combining tazemetostat with a chemotherapy backbone for up-front treatment of those patients with Stage 3 and 4 MRT.

Aurora A kinase (AURKA) is expressed at high levels in MRT. Alisertib is a selective AURKA inhibitor; the PPTP has shown objective responses to alisertib in tumors with decreased AURKA copy number [74]. A Phase 2 trial of alisertib in pediatric patients with recurrent or refractory solid tumors or leukemia enrolled 4 patients with rhabdoid tumor, with 3 having progressive disease (NCT01154816). Currently, a Phase 2 study of alisertib therapy for recurrent or progressive rhabdoid tumors is enrolling patients (NCT02114229).

Cyclin-dependent kinases (CDK) 4/6 activity are upregulated by the loss of *SMARCB1* in MRTs. Ribociclib (LEE011) is an orally bioavailable, specific inhibitor of CDK4/6 which has been shown to have in vitro activity in MRT cell lines. A Phase 1 study of ribociclib in pediatric patients with neuroblastoma, MRT, or other cyclin D-CDK4/6-INK4-retinoblastoma pathway-altered tumors showed prolonged stable disease that supports further testing of ribociclib in combination with other agents [75].

BRD9, which forms a subunit of the *SWI/SNF* complex, inhibition has been investigated [71]. Two specific chemical probes (I-BRD9 and BI-9564) that selectively target BRD9 were evaluated in 5 MRT cell lines alone and in combination with cytotoxic drugs. Single compound treatment with I-BRD9 and BI-9564 resulted in decreased cell proliferation and apoptosis. Combined treatment of doxorubicin or carboplatin with I-BRD9 resulted in additive to synergistic inhibitor effects on cell proliferation. Therefore, BRD9 is an attractive target for novel therapeutic investigation [71].

CHK1 is a serine-threonine kinase that plays a central role in pausing cell cycle progression in response to DNA damage and/or replicative stress. Activation of CHK1 in response to single-strand DNA breaks or stalled replication forks plays a central role in the G2-M and S-phase cell cycle checkpoints. Prexasertib (LYS2606360) is a potent ATP-competitive CHK1 inhibitor that exhibits single agent cytotoxicity through replication catastrophe [57]. The PPTP tested prexasertib in mice bearing a MRT xenograft and found it induced a maintained complete response (MCR) for approximately 4 weeks

after treatment was complete. In addition, the combination of prexasertib with irinotecan showed a significantly superior prolonged EFS in the MRT xenograft compared to irinotecan alone [76]. A COG Phase 1 clinical trial of prexasertib in pediatric patients with recurrent or refractory solid tumors is currently enrolling patients (NCT02808650).

Utilization of immune checkpoint inhibitors is another promising area of research for MRT patients. In a study of 16 cases of relapsed MRT, 9 cases showed high tumor-infiltrating lymphocytes with PD-1 staining ranging from 10 to 60%, correlating with PD-L1 staining [77]. In addition, it has been noted that both human MRT and a mouse MRT model are highly infiltrated by immune cells of both lymphoid and myeloid lineages, with T-cells expressing PD-1 and tumor cells expressing PD-L1. In these models, blockade of the PD-1/PD-L1 pathway impaired tumor growth [78]. An open COG Phase 1/2 clinical trial investigating the use of nivolumab with or without ipilimumab in pediatric patients with recurrent or refractory solid tumors and sarcomas is ongoing (NCT02304458).

5 Targeting translocation-positive renal cell carcinoma

Pediatric renal cell carcinoma (RCC) is rare, accounting for approximately 4% of new renal cancer cases [79], and is a distinctly different entity compared to the adult RCC population. The most common form of RCC in pediatric patients is translocation-positive RCC (tRCC), which is characterized by translocations involving Xp11.2, the TFE3 gene locus [79]. About 62.5% of tRCC patients present with Stage 3–4 disease. Overall survival for those with Stage 1–3 disease is generally favorable, but outcomes are very poor for those with Stage 4 or relapsed disease [80]. TFE3 is a member of the microphthalmia-TFE basic helix-loop-helix leucine zipper translocation factor subfamily; oncogenic TFE3 fusions result in upregulation of Met tyrosine kinase (MET*)* and activation of downstream signaling [81]. Therefore, MET inhibition is a potential therapeutic target for this disease. Tivantinib is a non-specific MET inhibitor that exhibited antitumor activity in a wide range of human tumor cell lines and xenograft models of human lung, prostate, colon, pancreas, and breast cancer [82]. A Phase 2 clinical trial of tivantinib in patients with microphthalmia transcription factor-associated tumors included 6 patients with tRCC, with limited short-term stable disease noted in 50% (NCT00557609) [83]. Newer-generation MET inhibitors such as tepotinib are of interest in tRCC. TFE3-mediated upregulation of MET leads to activation of downstream signaling and dysregulation of the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway, making this a potential therapeutic target in this patient population [84]. Responses to temsirolimus (mTOR inhibitor) have been observed in patients with tRCC [85, 86]. The COG Pediatric MATCH clinical trial is currently investigating LY3023414, a small molecule inhibitor of PI3K and mTOR, in a Phase 2 study in patients with activating mutations of the PI3K/mTOR pathway (NCT03213678).

Tyrosine kinase inhibitors targeting vascular endothelial growth factor receptor (VEGFR) are often utilized for the treatment of tRCC, with objective responses and dural complete remissions observed with sunitinib and sorafenib [86–89]. Axitinib is an inhibitor of VEGFRs 1–3 that is FDA approved for the treatment of advanced RCC and is of interest in patients with tRCC. Responses to axitinib have been reported in pediatric tRCC: in a retrospective analysis of 24 patients with RCC, the mean time to progression was the longest for patients treated with axitinib compared to other treatments [90]. A Phase 1 study of axitinib in children with recurrent or refractory solid tumors has completed accrual (NCT02164838), and a recommended Phase 2 dose of axitinib was determined [91]. Axitinib warrants further investigation in this patient population.

A correlation has been shown between TFE and PD-L1 expression in RCC tumors [92]. Recent reports have shown improved durable response rates with immune checkpoint inhibitor therapy for RCC [93]. New evidence suggests that a combination of VEGFR inhibition and immune check point inhibition may lead to improved outcomes; a recent Phase 1 trial combining avelumab (PD-L1 inhibitor) with axitinib (VEGFR inhibitor) [94] and a Phase 3 trial combining pembrolizumab (PD-1 antibody) with axitinib showed encouraging antitumor activity [95]. A current COG Phase 2 clinical trial, AREN1721, is investigating the combination of nivolumab (PD-L1 inhibitor) with axitinib (VEGFR inhibitor) versus nivolumab alone in patients with unresectable or metastatic tRCC (NCT03595124).

6 Targeting renal medullary carcinoma

Renal medullary carcinoma (RMC) is a rare, extremely aggressive malignancy that occurs most commonly in adolescents and young adults with sickle cell trait and other sickle hemoglobinopathies [96, 97]. Clinically, this disease is almost universally fatal once tumor has spread outside of the kidney [98, 99]. RMC is also characterized by *SMARCB1* inactivation [100]; it is postulated that these *SMARCB1* deletions and translocations can occur via dysregulation of DNA repair pathways due to regional ischemia induced by red blood cell sickling in the inner medulla [101]. The poor cure rates with standard chemotherapy regimens mean new therapies are needed to improve outcomes. Given the presence of *SMARCB1* alterations, many of the same therapies utilized for the management of MRT can be considered in patients with RMC. A Phase 1 clinic trial testing the EZH2 inhibitor tazemetostat in adult patients with INI1-negative tumors or

relapsed/refractory synovial sarcoma recently completed accrual; 14 patients with RMC were enrolled on this trial (NCT02601950). The current ongoing Phase 1 pediatric study EZH-102 (NCT02601937) is evaluating the administration of tazemetostat in pediatric patients with relapsed/refractory MRT and other *SMARCB1-/SMARCB4*-mutated tumors or synovial sarcoma; a recommended Phase 2 dose has been determined, and the protocol is currently enrolling expansion cohorts. In addition, the ongoing COG Pediatric MATCH contains a Phase 2 arm investigating the use of tazemetostat in patients with tumors harboring alterations in *EZH2*, *SMARCB1*, or *SMARCA4* (NCT03213665). SMACRB1 has also been shown to induce upregulation of protein anabolism which makes RMCs potentially susceptible to disruption by proteasome inhibitors such as bortezomib [102, 103]. A Phase 2 clinical trial evaluating the combination of the second-generation proteasome inhibitor ixazomib with the nucleoside analogue gemcitabine and the topoisomerase II inhibitor doxorubicin in patients with RMC is currently ongoing (NCT03587662) [103].

Utilization of immune checkpoint inhibitors is another promising area of research as a completed response has been reported in 1 of 3 patients with RMC [104, 105]. There are three open clinical trials currently looking at use of immune checkpoint inhibitors in RMC: (1) A Phase 2 trial of nivolumab plus ipilimumab in patients with renal medullary carcinoma (NCT03274258); (2) a Phase 2 trial of nivolumab and ipilimumab with the multi-tyrosine kinase inhibitor cabozantinib (NCT03866382); and (3) a Phase 1 study using nivolumab (PD-1 inhibitor) in combination with the multi-tyrosine kinase inhibitor cabozantinib with or without ipilimumab (CTLA4 inhibitor) (NCT02496208).

7 Targeting clear cell sarcoma of the kidney

Clear cell sarcoma of the kidney (CCSK) compromises 2–5% of primary kidney cancer in children [106]. Outcomes are very good with current treatment regimens for those with Stage 1 disease. A cure may be achieved in > 85% of patients with Stage 2 and 3 disease; however, aggressive front-line and often second-line therapy for relapse (especially in the CNS) are needed [107]. The majority of CCSKs (80–90%) have a somatic internal tandem duplication (ITD) in the X-linked *BCOR* affecting the 3' part of the exon 16 coding sequence [108–110]. DNA methylation profiling identified hypermethylation of the tumor suppressor *TCF21* [111]. Gene expression profiling shows strong upregulation of neural markers and members of the sonic hedgehog signaling pathway and the RACα AKT cell proliferation pathway [112]. In addition, a non-overlapping subgroup of CCSKs (5–10%) is characterized by the balanced t(10;17)(q22;p13) chromosomal translocation that results in an in-frame *YWHAE-NUTM2* fusion. Gene and protein expression studies in cells with the *YWHAE-NUTM2* fusion were indicative of dysregulated MAPK/PI3K-AKT signaling [113]. Given this known fusion in a subset of patients, inhibitors of the MAPK/PI3K-AKT signaling pathway can be considered as a targeted therapy option. Copanlisib is a PI3K inhibitor that is currently being evaluated in a COG Phase 1/2 clinical trial in pediatric patients with relapsed/refractory solid tumors (NCT03458728).

8 Targeting congenital mesoblastic nephroma

Congenital mesoblastic nephromas (CMN) are the most common renal tumors in the first 3 months of life and are generally benign. It is subclassified into classic, cellular, and mixed variants. Cellular CMN is associated with the potential for malignancy, is capable of recurrence following surgical resection, and has the potential for metastasis [114]. Cellular CMN is characterized by a *ETV6-NTRK* (t12;15) (p13;q25) fusion; within the cellular subgroup, patients having translocation-positive tumors have a significantly superior relapse-free survival [115] Larotrectinib is a highly selective inhibitor of TRKA, TRKB, and TRKC that is FDA approved for the treatment of adult and pediatric patients with *NTRK* gene fusions for metastatic disease, when surgical resection is likely to result in severe morbidity, or in the relapse setting. There are currently several open clinical trials investigating the use of larotrectinib in pediatric solid tumor patients harboring *NTRK* fusions (NCT03213704, NCT02637687, and NCT02576431).

9 Limitations

This review is not exhaustive given the continued rapid increase in genomic data that may identify new biologic targets. Therefore, readers should consider performing a current review of the literature should new therapeutic agents be required for the patients described within this review.

10 Challenges

The challenge regarding which agent to prioritize in the clinical translation of novel targeted therapies either alone or in combination therapy is not only prominent in renal cancers, typified by the rarity of these tumors, but also across other tumor types as molecular subtyping capabilities continue to expand. An excellent example is the number of agents potentially available that are rational considerations for management of MRT. It will be increasingly necessary to consider novel human clinical trial designs, but also to rely on robust preclinical data, including xenograft and organoid models, that will point us in the direction of the most promising agents. The

COG and other cooperative groups are exploring enhanced creation of these resources at a number of levels.

11 Future directions

Clinical trials focused on improving the outcomes of children and adolescents with higher-risk renal malignancies remain a priority of the pediatric oncology community. Advances in the evaluation of the underlying biological drivers of disease as well as continuing drug development provide promising new avenues for clinical trial development. Continued evaluation of new agents against renal tumor cell lines and patient-derived xenografts remains a powerful avenue of scientific development. A growing number of research labs are focusing on new tumor modules to investigate the underlying biology of renal cancer. For example, Ortiz et al. are investigating the use of urine proteomes obtained at diagnosis to identify urine tumor markers associated with Wilms tumor relapse [116]. Hong et al. have developed patient-derived RMC xenograft models, shown they are faithful to the patient through whole-genome sequencing, and have documented that RMC survival requires the loss of *SMARCB1* [117]. In addition, new tumor models for target identification and drug screening, such as patient-derived organoids, hold promise to more rapidly provide precision medicine options for patients [118, 119]. In addition, ongoing research by Dr. Elizabeth J. Perlman investigating the genetic changes associated with relapse and/or adaptive resistance in patients with FHWT funded through the Moonshot Initiative offers promise for further potential therapeutic targets in this patient population.

Advancement of targeted therapies, often administered in combination with a conventional chemotherapy backbone, is the focus of future clinical trials. Given the rarity of the diseases discussed here, international collaboration or disease agnostic/target-specific approaches will likely be required. The ongoing COG Pediatric MATCH clinical trial (NCT03155620), which matches patients with targeted biologic agents on the basis of their underlying genomic changes, and similar initiatives in Europe (INFORM2, NCT03838042 and MAPPYACTS, NCT02613962) are an important step towards a target-specific approach to the management of pediatric cancer; the results from these and similar trials will guide further precision medicine initiatives in the pediatric and adolescent population. Community advocacy through parent organizations remains a critical piece of the overall puzzle, providing the additional drive for moving these important endeavors forward.

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