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Children's Oncology Group's 2023 Blueprint for Research: Renal Tumors

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Abstract

Every year, approximately 600 infants, children and adolescents are diagnosed with renal cancer in the United States. In addition to Wilms tumor (WT) which accounts for about 80% of all pediatric renal cancers, clear cell sarcoma of the kidney, renal cell carcinoma, malignant rhabdoid tumor as well as more rare cancers (other sarcomas, rare carcinomas, lymphoma) and benign tumors can originate within the kidney. WT itself can be divided into favorable histology (FHWT), with a 5-year overall survival (OS) exceeding 90%,[1-4] and anaplastic histology, with 4-yr OS of 73.7%.[5,6] Outcomes for the other pediatric renal cancers include clear cell sarcoma (5-yr OS, 90%), malignant rhabdoid tumor (5-yr OS, 10% for stage 3 and 4), and renal cell carcinoma (4-yr OS, 84.8%).[7] Recent clinical trials have identified novel biological prognostic markers for FHWT, and a series of COG trials have demonstrated an improving outcomes with therapy modification, and opportunities for further care refinement.

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STATE OF THE DISEASE

Overview & Incidence

Cancers of the kidney account for approximately 7% of pediatric malignancies. The AREN03B2 Renal Classification and Biology Study, which captures the majority of pediatric and adolescent renal tumor cases in the United States and Canada, enrolled approximately 600 children and adolescents per year. Greater than 75% of pediatric renal tumors are favorable histology WT (FHWT), all other histologies, including anaplastic histology WT (AHWT), clear cell sarcoma of the kidney (CCSK), malignant rhabdoid tumor (MRT), renal sarcomas, lymphoma, and benign entities such as metanephric adenoma and others each represent < 5% of the spectrum of renal tumors affecting children. However, incidence varies significantly with age, with congenital mesoblastic nephroma (CMN) the most common tumor in children < 3 months of age, and renal cell carcinoma (RCC) the most common histology in children over age 15.[8,9]

Staging/Stratification

COG renal tumor staging relies on surgical-pathologic data. This is combined with tumor histology and biology to arrive at a risk-stratification that dictates study and treatment assignment. For WT, the evolution of risk stratification variables is demonstrated in Figure 1. Pediatric renal tumors using the COG system are classified as stage through IV based on the extent of disease. Stage V is a unique and specific (non-ordinal) stage that indicates bilateral disease.[9,10]

Certain histologic categories are considered high risk in the AREN03B2 risk assignment process, intended to risk classify patients for potential therapeutic trials, independent of stage, including focal or diffuse anaplastic WT, CCSK, MRT, and RCC. However, the risk ‘label’ can be misleading as stages I-III tumors including focal anaplastic WT, CCSK and RCC generally have favorable outcomes. Additional stratification of FHWT depends on age, histology, and biology, with age < 4 years and epithelial predominant histology suggested to represent lower-risk features of stage I tumors. Combined loss of heterozygosity (LOH) at 1p and 16q remain negative molecular risk factors that can be “overcome” with treatment intensification.[3] The next generation study of FHWT will expand the molecular risk-stratification to include data on LOH of 11p15 (stage I tumors) and gain of 1q.[11]

Current Outcome

The last generation of studies demonstrated improved survival for those with FHWT and standard biology regardless of stage. [1-7] However, improvements are needed for those with FHWT and adverse biology, anaplastic WT, MRT, and metastatic RCC. (Table 2) Alongside a focus on cure, careful attention is being paid to survivorship issues. This includes focus on cardiac toxicity, renal function, secondary malignancy, and fertility preservation.[12-16] An additional emerging area of focus is better understanding the impact of social determinants of health on outcomes for children with renal tumors. Current data indicate that children with WT who suffer from more social deprivation experience worse survival.[17] Comprehensive cancer care requires more than just chemotherapy, surgery, and

radiation. To achieve optimal survival for children with renal tumors, support of the whole child and their family is necessary.

Molecular Targets

The past decade has yielded significant gains in our understanding of pediatric renal tumors (particularly WT and MRT) due to advances in next-generation sequencing, functional genomics, small molecule and immune based discoveries. However, translating these targets to our patients remains limited given the small sample size. To overcome this, COG Renal Tumors Committee has increased its collaboration with the COG Developmental Therapeutics Committee and Pediatric Early Phase-Clinical Trial Network (PEP-CTN).

Wnt/β-catenin pathway has been long implicated in WT biology with recent sequencing studies identifying 15-20% of FHWT with WNT/β-catenin signaling pathway mutations.[18,19] Tegavivint, a small molecule that inhibits the interaction of TBL1 with β-catenin, is being investigated in children with relapsed FHWT (PEPN2011; NCT04851119).[20] HER2 (ERBB2) has been implicated in WT biology and trastuzumab was found to have activity in WT PDXs through the NCI Pediatric Preclinical Testing Consortium.[21] Other agents that have been identified include targeting ATM via the ATR inhibitor, elimusertib (PEPN2112; NCT05071209) and the XPO1 inhibitor selinexor in the targeting of WT and other renal tumors like MRT.[22] Given advances in immunotherapy in the past decade, investigation has developed with tumor-associated antigen-specific T-cell (TAA-T) targeting to WT1 (NCT02789228/NCT05238792) and GPC3 – (NCT04928677).[23,24]

Recently identified targets in MRT (and to a lesser degree, renal medullary carcinoma (RMC), which shares loss of the tumor suppressor, SMARCB1) have focused on inhibition of EZH2, a PRC2 complex member that opposes the SWI/SNF complex.[25,26] This has been investigated as part of the NCI-COG Pediatric MATCH trial Arm C (APEC1621C). Other targets include cell cycle inhibition, increasing TP53 through MDM2 inhibition, use of proteasome inhibitors or nuclear export inhibitors, and PDL1 inhibition.[27-29]

Molecular Prognostic factors

Several molecular prognostic factors in WT have been prospectively studied in WT (1p and 16q LOH)[3] and retrospectively studied (1q gain and 11p15). The role of 1q gain as an adverse prognostic factor has been validated in stage II-IV FHWT in retrospective studies.[4,11] In study AREN0532, there was an association of 11p15 alterations with relapse for stage I FHWT patients observed post-nephrectomy without chemotherapy. In the upcoming AREN2231 FHWT trial, these biomarkers will be incorporated into therapeutic risk stratification. For a patient who may be eligible for nephrectomy only, patients will be excluded if their tumor has any adverse biological features (LOH 11p15, or LOH 1p and 16q, or 1q gain). In other patients with stage I-IV FHWT, therapeutic strategies will hinge on 1q status in addition to LOH of 1p and/or 16q.

In AREN17B1-Q and AREN20B2-Q, feasibility of sequencing circulating tumor DNA (ctDNA) from patients enrolled on AREN0533 demonstrated that 1q gain, 1p and 16q deletions could be identified, suggesting that ctDNA may be a useful molecular biomarker.[30]

Studies AREN1721, AREN1921 and the upcoming AREN2231 collect samples at time of diagnosis, during therapy and follow-up off therapy for further study of ctDNA.

TP53 loss is a key driver in anaplastic WT. Although anaplasia is classified by histology alone, AREN1921 includes an exploratory aim to understand if TP53 alterations in the genome and proteome will correlate with histology and outcomes.[31]

MAJOR RECENT FINDINGS

AREN03B2:

Protocol AREN03B2 opened in 2006, and through 2022 has enrolled over 7000 patients. Real time central review of imaging, pathology, surgery was employed for all patients enrolled through the period of the first generation of COG renal tumor therapeutic studies, enabling timely enrollment of centrally classified patients onto appropriate therapeutic studies.[1-7] Since 2022, real time review has been limited to patients with institutionally suspected WT with anaplasia to support enrollment on AREN1921. The biology bank has accrued an unprecedented bank of biologic samples (including tumor, serum, urine and normal tissue/blood) from children with a wide diversity of renal tumors, providing in many instances largest known cohorts of rare renal tumors. The study has supported numerous biology studies and over 50 publications. The process of real time central review has been demonstrated to be both feasible and impactful.

AREN0532:

COG AREN 0532 examined a group of Very Low Risk FHWT patients, who were defined as Stage I, less than 2 years of age, with tumors < 550g and without a predisposition syndrome. These patients were candidates for treatment with nephrectomy only, and this approach showed a 4-year EFS of 89.7% and OS of 100%.[2i] This study also examined augmented therapy for stage I and II patients with LOH of 1p *and* 16q and treated them with DD-4A (and no radiation) and this cohort had a 4-year EFS of 87.3% vs 68.8% historical control.[3]

AREN0533:

COG AREN0533 also examined combined LOH in stage III and IV FHWT patients, who received augmented therapy with Regimen M (vincristine, dactinomycin, and doxorubicin alternating with cyclophosphamide and etoposide) and had a 90.2% 4-year EFS. This compared favorably to 61.3% EFS on NWTS-5.[3] Stage IV patients were stratified according to response of pulmonary metastases to six weeks of chemotherapy. Patients with a complete resolution of lung metastases at week 6 (RCR) had pulmonary radiation omitted from therapy and maintained a 4-year EFS of 79.5% (and OS of 96.1%). However importantly, a retrospective study of the impact of 1q gain in the group of RCR patients demonstrated a marked difference in outcome between patients with and without 1q gain, with 4 year EFS of 57% vs 86% ($p = 0.001$). Conversely patients with incomplete resolution of pulmonary metastases were treated with augmented therapy with Regimen M and pulmonary radiation and achieved a 4-year EFS of 88.5% (OS 95.4%).[4]

AREN0534:

Compared to unilateral FHWT, patients with bilateral WT (BWT) have historically suffered inferior EFS and OS, higher rates of renal failure, and prolonged courses of chemotherapy with associated late effects.[32-25] For patients with BWT on study AREN0534, 4-year EFS and OS were 82.1% (95% CI: 73.5%-90.8%) and 94.9% (95% CI: 90.1%-99.7%). 84% of patients underwent definitive surgical treatment in at least 1 kidney by 12 weeks. 39% were able to undergo bilateral nephron sparing surgery and 1 child was rendered anephric.[36] For children with genetically predisposed unilateral WT, neoadjuvant chemotherapy facilitated partial nephrectomy was feasible in 65%.[37] Thirty-four patients were enrolled, with 4-year EFS and OS rates of 94% (95% CI: 85.2%-100%) and 100%. For patients with diffuse hyperplastic perilobar nephroblastomatosis, the OS and renal salvage were excellent, and rates of anaplasia were low, but a 19-week course of EE4A was not fully effective in preventing WT development.[38]

AREN0321:

Study AREN0321 included children with ‘high risk’ renal tumors including anaplastic WT, non-CNS MRT, CCSK, and RCC. Results demonstrate the efficacy of vincristine/irinotecan in DAWT (79% response rate), improved survival for children with stage II-III DAWT treated with the addition of carboplatin and higher dose flank radiotherapy (stage 3), favorable outcomes for children with stage 1 FAWT and DAWT treated with regimen DD-4A and flank radiotherapy, safety of omission of radiotherapy for stage 1 CCSK (unpublished data), inadequate outcomes for stage 3/4 MRT (unpublished data), and favorable outcomes for completely resected RCC independent of lymph node status in the absence of adjuvant chemotherapy. The original regimen UH1 proved toxic prompting dose modifications (revised UH1).[5-7]

Biological findings—The NCI Therapeutically Applicable Research to Generate Effective Treatments (TARGET) program studied high-risk renal tumors from the COG renal tumor studies using genomics, methylation and transcriptomics. In WT, alterations identified included *WT1*, *CTNNB1*, *AMER1, SIX1/2, MLLT1, ARID1A* mutations; 1q copy number gain, 1p and 16q LOH; *MYCN* amplification; *LIN28B* and *MIRLET7A* loss; and germline mutations in *PALB2*, *CHEK2* and *TRIM28*.[39-42] AREN18B1-Q, the Molecular Profiling to Predict Response to Treatment (MP2PRT) effort as part of the NCI's Cancer Moonshot Initiative focused on genomic changes at relapse in FHWT – identifying roles of *SIX1*, genes in the *MYCN* pathway, *DIS3*, *TERT* and gain of 1q as being recurrent in relapse. [43]

Study AREN14B2-Q showed that WT could be further sub-divided into two groups based on methylation instability; [44] AREN12B1 demonstrated a potential role in macrophage recruitment with disease progression in FHWT; [45] and AREN12B4 and AREN16B1-Q identified prohibitin as a potential prognostic marker and target in chemotherapy-resistant WT. [46]

In MRT, TARGET and other studies identified the role of methylation in subgrouping patients, neural crest development and infiltration of cytotoxic T-cells, BRM silencing,

and a DNA transposase (PGBD5) that can disrupt SMARCB1 in MRT development.[47-50] AREN17B2-Q showed that patients with RMC harbor balanced translocations in *SMARCB1*,[51] *TCF21* hypermethylation was identified as a consistent alteration in CCSK in addition to the known ITDs within *BCOR* and fusion of *YWHAE* and *NUTM2B/E*.[52]

STRATEGIC APPROACH

Newly Diagnosed:

The first generation of COG AREN studies identified multiple clinical and biologic factors that significantly impact risk for adverse outcomes. To improve survival while reducing long term toxicities in a risk adapted manner, (Table 1) the COG studies have used an improved risk stratification model to reduce therapy for patients identified to have excellent EFS on standard therapy, while augmenting therapy for those identified to have a higher risk of relapse. Prognostic factors used in studies AREN0321, AREN0532, AREN0533, and AREN0534 for risk stratification included age, stage, histology, LOH of 1p and 16q, clinical response of lung metastasis at Week 6, post-chemotherapy stage and histology of patients with delayed nephrectomy (for bilateral tumors), and presence of extrapulmonary metastasis.[1-7]

Principles of front-line care continue to emphasize the role of upfront nephrectomy when feasible, risk adapted use of radiotherapy, and attempts at nephron sparing surgery after neoadjuvant chemotherapy in cases of Wilms tumor predisposed children or those with BWT. Integration of advancing supportive care now include consideration of fertility counseling, as well as cardioprotection for those receiving doxorubicin as part of care.

For patients with MRT, particularly with stage III and IV, and for those with stage 4 RCC, integration of novel therapies is indicated to attempt to improve cure, though the feasibility of prospective study of advanced pediatric RCC is limited by its rarity. Patients with stage 1-3 CCSK seem to have an excellent prognosis with current therapy, while stage 4 CCSK is seemingly too rare to formally study within a single cooperative group model.

Relapse WT:

The National Wilms Tumor Study 5 (NWTS5) demonstrated overall survival of relapsed WT ranging from 48% to 80% depending on original presenting features and treatment. Chemotherapies typically used at salvage include doxorubicin (for those that did not receive it front-line), cyclophosphamide, etoposide, carboplatin. [53,54] The approach to radiotherapy and surgery at relapse are not well standardized with regards to timing and dose, though remain important components of treatment.

The COG Renal Committee has advanced a risk-adapted approach to relapse FHWT in study AREN1921, based on number of chemotherapy agents used at front-line, defining standard, higher and high-risk relapse WT as those relapsing after 2-drug, 3-drug or > 3-drug therapy front-line. Efforts to optimize surveillance for relapse after front-line therapy,[55] as well as identify novel prognostic markers as well as targets for novel therapeutic development remain priorities going forward.[56]

KEY TRIALS TO BE PURSUED

Active studies:

AREN1721: The study of translocation renal cell carcinoma—The COG along with SWOG, ECOG and Alliance advanced study AREN1721 to define the activity of nivolumab PD1 immune checkpoint inhibitor with or without axitinib, an anti-VEGF-based tyrosine kinase inhibitor therapy in translocation renal cell carcinoma, building off of the COG phase 1 study of axitinib, ADVL1315.[57] Ultimately the trial closed in 2023 due to poor accrual (15 total; 12 from COG sites). Results are targeted for presentation in late 2023.

AREN1921: The study of stage II-IV DAWT and relapsed FHWT—The front-line study of treatment of DAWT and relapse treatment of FHWT are ongoing in study AREN1921, made of 4 strata. Stratum 1 includes stage II-III DAWT, Strata 2 stage IV DAWT, stratum 3 standard risk relapsed FHWT and stratum 4 higher and high risk relapsed FHWT. Strata 1-3 receive regimen UH3, a modification of regimen UH2 from study AREN0321, including vincristine/irinotecan, vincristine/doxorubicin/cyclophosphamide, and cyclophosphamide/carboplatin/etoposide cycles, adjusted to reduce toxicity through altered timing of radiotherapy to avoid concurrent radiosensitizing chemotherapy, and inclusion of dexrazoxane for cardioprotection. For patients on stratum 4 with relapsed higher or high risk FHWT, therapy includes cycles of ICE (ifosfamide/carboplatin/etoposide) and cyclo/topo (cyclophosphamide/topotecan). The trial includes important correlative aims looking at the role of gross total resection, biomarkers such as p53 and ctDNA (via serial blood sampling) and toxicity endpoints including novel markers of renal injury. As of May 2023, > 100 patients have enrolled to the various strata and the trial remains open.

Concept Approved:

AREN2231: The front-line study of FHWT—The COG Renal Tumor Committee has advanced a protocol concept for FHWT which will employ an expanded risk stratification to tailor therapy to study both augmentation and reduction of therapy. (Figure 1, Table 2) The refined risk stratification strategy will guide therapy assignment with overarching aims of: (1) *improved outcomes* within cohorts of FHWT patients with current long-term EFS rates at or below 80% and (2) *maintained outcomes despite therapy reduction* within cohorts of FHWT patients with current long-term EFS rates at or above 84%.

Risk stratification will build on factors previously employed in NWTS and COG AREN first generation trials, with inclusion of newly validated risk features (Table 1). Components of stratification and treatment assignment will include patient age, chromosome 1q gain status, LOH of 1p, 16q and 11p15, epithelial histology, pulmonary response to initial chemotherapy, post-chemotherapy stage and histology of patients with delayed nephrectomy, finding of positive LNs and presence of extrapulmonary metastatic disease.[1,2,11,58-63]

The study will continue to require real time central review to determine risk stratification and therapy assignment. Lymph node sampling will be required, as well as array testing for

segmental chromosomal aberrations. The trial plans to accrue 1200 patients and includes correlative biology and multidisciplinary exploratory aims.

The trial will employ 6 chemotherapy regimens: EE-4A (vincristine, actinomycin), DD-4A (vincristine, actinomycin, doxorubicin), Regimen M, (vincristine, actinomycin, doxorubicin, cyclophosphamide and etoposide), and regimen UH-3 (vincristine, doxorubicin, cyclophosphamide, etoposide, carboplatin and irinotecan), as well as two novel regimens, VIVA (vincristine, actinomycin, irinotecan) and MVI (vincristine, actinomycin, doxorubicin, cyclophosphamide, etoposide and irinotecan) which will be studied through randomization.

There will be an expansion (no limitation of tumor weight, and inclusion up to age 4) and refinement (new exclusions based on biology) of the cohort of patients treated with nephrectomy only.[2] The impact of omission of doxorubicin for stage III patients with favorable features will be studied.[64]

Trials In development:

Rhabdoid tumor (non-CNS): Survival for children with stage III and IV MRT arising in or outside of the kidney remains unacceptably poor, approximating 10%. (AREN0321, unpublished data) For such children, integration of novel therapy on a chemotherapy backbone is being considered, along with guidelines for timely surgery and radiotherapy. Pre-clinical and clinical data demonstrate that tazemetostat has single agent cytotoxic activity against MRT.[25,26,65,66] The current trial in development proposes to add tazemetostat, an oral biologic agent that selectively inhibits EZH2, onto a chemotherapy backbone that includes alternating cassettes of vincristine/doxorubicin/cyclophosphamide and ifosfamide/carboplatin/etoposide. Alternative biological agents are also under consideration.

Bilateral Wilms Tumor (BWT): In study AREN0534, while the overall survival for BWT patients exceeds 90%, the 4-year event free survival was 81% suggesting need for salvage therapies. In addition, the actual rate of bilateral renal sparing surgery (39%) fell below the expected goal (50%).[38] Subsequent efforts are underway to determine how to achieve improved EFS and nephron sparing surgical rates, focusing on both potential modifications of neoadjuvant chemotherapy. Further stratified post-nephrectomy chemotherapy based on tumor biology, as well as utilization and investigation of local control advancements will be integrated. The potential application of adult nephrometry scoring systems is being investigated and modeled with bilateral tumor imaging review and scoring for complexity. In addition, insight into individual surgeon decision making, and intraoperative adjuncts utilized including ultrasound and frozen section margin status will be investigated to determine impact on EFS. Integration of biomarkers impacting both volumetric response to chemotherapy as well as outcomes will be incorporated. Patterns and timing of relapse are being studied further to determine optimal therapy and surveillance strategies long-term for BWT.

Emphasis on Collaboration and Holistic Approach: The COG Renal Tumor Committee will continue to partner with other cooperative groups, both national and international, to advance the objective of improving care for all children, adolescents and

young adults impacted by renal cancer. To that end, discussions with the adult cooperative oncology groups is ongoing in consideration of next trials for adolecent and young adult renal cancers such as translocation RCC. Internationally, the COG RTC along with the SIOP RTSG formed the HARMONICA initiative in 2016. This is an international collaborative aimed at capitalizing on global expertise in pediatric renal tumors to help advance standards of care, identify areas for collaboration and future directions, and to enact multidisciplinary efforts to advance research priorities. Such efforts, recently culminating in the 'Pediatric Renal Tumors: a Harmonica Initiative' special issue in Pediatric Blood and Cancer, are ongoing.[67] The COG RTC also continues to advocate for the inclusion of study of all potential prognostic variables and/or insights that can advance improvement of outcomes for all children with renal tumors, inclusive of social determinants of health and biological outcome metrics. The historical successes in improving outcomes for children with renal tumors has relied on multidisciplinary collaboration and care, inclusivity of all potential stakeholders at all levels of research development and delivery, and scientific integrity, which remain the hallmarks of our pathway forward.

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Abbreviations:

AHWT	Anaplastic Histology Wilms Tumor
BWT	Bilateral Wilms Tumor
CCSK	Clear Cell Sarcoma of the Kidney
CMN	Congenital Mesoblastic Nephroma
COG	Children's Oncology Group
ctDNA	circulating tumor DNA
DAWT	Diffuse Anaplastic Wilms Tumor
FHWT	Favorable Histology Wilms Tumor
OS	Overall Survival
RCC	Renal Cell Carcinoma
RMS	Renal Medullary Carcinoma
RTK	Rhabdoid Tumor of the Kidney
WT	Wilms Tumor

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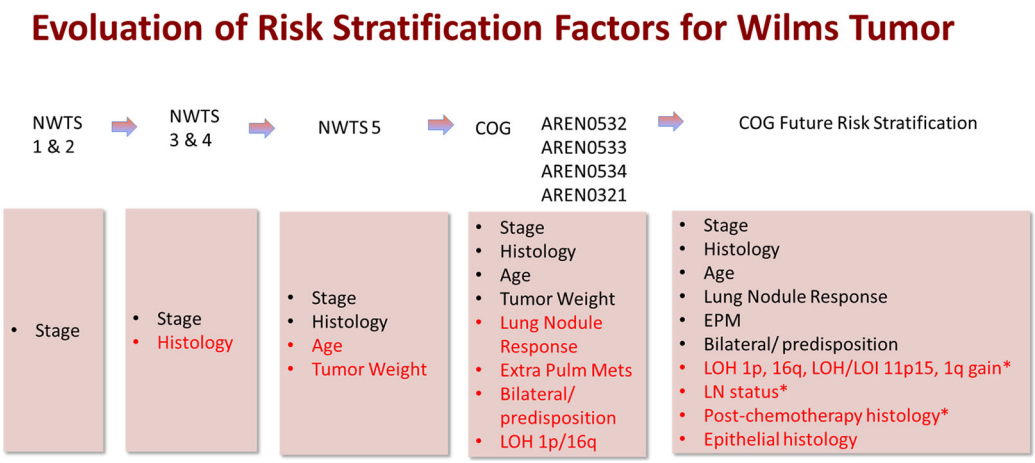

Figure 1:
Evoluation of risk stratification factors for Wilms tumor.

Table 1:

Approximate* Event Free Survival vs Potential for Late Effects

Event-Free Survival COG studies	**Potential for Late Effects**	
	Low	***Moderate to High***
Excellent (≥85%)	Stage I/II FHWT Stage I-III RCC	Stage III FHWT Stage I AHWT Stage I/II CCSK
Good (75-84%)		Stage IV FHWT Stage II/III AHWT Stage V WT Stage III CCSK Stage I/II RTK/MRT
Unsatisfactory (<75%)	Stage IV RCC	Stage IV AHWT Stage IV CCSK Stage III/IV RTK/MRT Relapsed FHWT

* These are generalizations as certain biological subgroups of the stage/diagnoses do not all fit within the defined box.

FHWT – favorable histology Wilms tumor, RCC – renal cell carcinoma, AHWT – anaplastic histology Wilms tumor, CCSK- clear cell sarcoma of the kidney, RTK – rhabdoid tumor of the kidney, MRT – malignant rhabdoid tumor

Table 2:

COG Risk Stratification for Next Generation of Therapeutic Studies

Patient age	Stage, Histology	Biology	Rapid Lung Nodule Response	Risk	Potential Therapeutic Trial
Any	I, Epithelial FH	N/A	N/A	Modified Very Low	AREN2231
< 4 years	I, FH	Standard	N/A	Modified Very Low	AREN2231
< 4 years	I, FH	Adverse	N/A	Low	AREN2231
≥ 4 years	I, FH	Any	N/A	Low	AREN2231
Any	II, FH	Standard	N/A	Low	AREN2231
Any	II, FH	Adverse	N/A	Standard	AREN2231
Any	III, FH	Standard	N/A	Standard	AREN2231
Any	III, FH	Adverse	N/A	Higher	AREN2231
Any	IV, FH	Standard	Yes	Standard	AREN2231
Any	IV, FH	Standard	No	Higher	AREN2231
Any	IV, FH	Adverse	Any	Higher	AREN2231
Any	V, FH, AH	Any	Any	Bilateral	Bilateral
Any	II-IV, DAWT	N/A	N/A	High	AREN1921
Any	III-IV, RTK/MRT	N/A	N/A	High	RTK/MRT
Any	FH, Relapsed disease	N/A	N/A	High	AREN1921

FH – favorable histology, AH – anaplastic histology, N/A – not applicable, DAWT – diffuse anaplastic Wilms tumor, RTK – rhabdoid tumor of the kidney, MRT – malignant rhabdoid tumor