AREN2231: Risk Adapted Treatment of Unilateral Favorable Histology Wilms Tumors (FHWT)

FAST FACTS
Eligibility Reviewed and Verified By
_____ MD/DO/RN/LPN/CRA Date _____
_____ MD/DO/RN/LPN/CRA Date _____
Consent Version Dated_____

PATIENT ELIGIBILITY:
Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical research record which will serve as the source document for verification at the time of audit.

___1. Required Enrollment on Project Every Child (APEC14B1)
Patients must be enrolled on APEC14B1, The Project: EveryChild: A Registry, Eligibility Screening, Biology, and Outcome Study and consent to Part A – Eligibility Screening prior to enrollment on AREN2231.

Adequate materials must be submitted to allow for the completion of mandatory central reviews that will occur under APEC14B1-REN. Please see the APEC14B1 Manual of Procedures for details of required material and submission timelines. It is strongly recommended that sites submit all required materials via APEC14B1- REN within 7 days post-biopsy or 7 days post-nephrectomy (biopsy/surgery date is considered Day 0)

Once enrolled on APEC14B1 and all the necessary review materials are submitted, central pathology, surgery, and imaging review results will be available for viewing by the institution. Upon completion of the appropriate reviews, for patients confirmed to have Stage I-IV Favorable Histology Wilms Tumor sites will be notified of the qualifying Initial Stratum Assignment for AREN2231.

___2. **CENTRAL QUALITY ASSURANCE REVIEW AND PRE-APPROVAL**: The treatment plans for all patients receiving Whole Lung IMRT, Liver IMRT, Liver proton, Flank proton and Whole abdominal proton irradiation must be sent to IROC Rhode Island for pre-approval prior to treating the patient. Plans for these patients should be submitted at least 5 business days prior to the start of radiation therapy to allow enough time for pre-review, contour or plan revision if required, prior to final approval. Rapid central review with approval or suggestions regarding image-guided interventions pertaining to protocol compliance (normal tissue contours, lung contours and dosimetric parameters etc.) will be forwarded to the participating institution within 3 business days once complete data required for this review is received. Treatment can only be delivered to patients after approval is obtained. **Please refer to Section 17.14 for details regarding submission requirements.** Submission of the radiation therapy treatment plan in digital format as DICOM RT is required. Submission of the digital files and reports via TRIAD is preferred. Instructions for TRIAD setup are provided in Section 17.14. See the IROC Rhode Island website (www.irocri.qarc.org) for digital data submission information.

___3. Timing
Study enrollment on AREN2231 must take place prior to beginning protocol therapy. **Patients who are started on protocol therapy prior to study enrollment will be considered ineligible**, except in situations where therapy is initiated on an emergent basis as noted in Section 3.1.6.

___4. Patients must begin protocol therapy on AREN2231 no later than fourteen (14) calendar days after initial diagnostic procedure, unless medically contraindicated or potentially eligible for the mVLR (Nephrectomy only) arm. Potential mVLR patients awaiting biomarker testing results to determine Final Stratum Assignment who are found to have adverse biology (and therefore not eligible for nephrectomy only arm) must begin protocol therapy no later than twenty-one (21) calendar days after initial diagnostic procedure.

All laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.

___5. Emergent Therapy

In the event that an investigator determines that emergent therapy is clinically indicated (e.g. significant symptoms from large tumor burden), therapy with VA as per Cycle 1 of Regimen DD-4A may be initiated before study enrollment. Treatment may begin before central review on APEC14B1 is completed if medically indicated. However, the following criteria must be met prior to the start of emergent therapy:

- Study consent for APEC14B1 and AREN2231 must be obtained.
- Must meet eligibility criteria for APEC14B1.
- Must meet all eligibility criteria for AREN2231, except for prior enrollment and central review on APEC14B1. Enrollment on APEC14B1, obtaining a qualifying Initial Stratum Assignment and subsequent enrollment on AREN2231 must all take place within seven (7) calendar days from beginning the emergent AREN2231 protocol therapy.

___6. Callback for Treatment Assignment/Randomization

Patients will receive an Initial Stratum Assignment on APEC14B1-REN prior to study entry, but may subsequently be assigned to a different treatment regimen following integration of biology and risk classification results**. For all patients, at least one callback is required to be completed prior to randomization and/or prior to any change in treatment or continuation of the same treatment (see table below for summary)**. When a callback is not correctly completed at a designated timepoint, and prior to initiation of the change in treatment, then the patient will be deemed inevaluable and be taken off protocol therapy.

The CIRB has determined that assent of children age 14 and older is a necessary condition for proceeding with the research.

Note: This trial has a protocol supplied wallet card that is required to be provided to the patient. See Appendix VII.

INCLUSION CRITERIA:

___1. Enrollment on APEC14B1

Patients must be enrolled on APEC14B1 and consent to Part A – Eligibility Screening prior to enrollment on AREN2231.

____2. Age

Patients must be <30 years old at enrollment

____3. Diagnosis

Patients with newly diagnosed Stage I-IV Favorable Histology Wilms Tumor confirmed by central review and with a qualifying Initial Stratum Assignment received on APEC14B1-REN.

Note: A reference document containing tables with detailed descriptions of each Initial, Interim, and Final Stratum Assignment applicable to AREN2231 is provided on the study page of the COG Member Website.

Timing of Initial Stratum Assignment

Patients must receive a qualifying Initial Stratum Assignment on APEC14B1-REN by Day 14 post-diagnostic procedure (nephrectomy or biopsy), where that procedure is Day 0.

Patients must enroll on AREN2231 by Day 14. See Section 3.1.5 for timing to begin protocol therapy.

Exceptions: If patient reaches Day 14 (post initial diagnostic nephrectomy or biopsy) without receiving an Initial Stratum Assignment on APEC14B1-REN, patient will not be eligible for enrollment on AREN2231 unless all required materials (reports and Case Report Forms and specimens) for an Initial Stratum Assignment arrived by Day 7, but an Initial Stratum Assignment was not completed by Day 14. In these circumstances, after obtaining appropriate protocol consent, the patient may proceed with treatment according to local institutional staging and enroll within 5 calendar days of notification of the central Initial Stratum Assignment being issued, only if the AREN2231 Initial Stratum Assignment is in agreement with any treatment already initiated. If the Initial Stratum Assignment is not in agreement with the local institution's assessment then the patient will be ineligible for AREN2231.

___4. Tumor Molecular Testing

All sites must have sent or plan to send diagnostic tumor sample for molecular testing through a CLIA-certified (or equivalent if outside of the US) laboratory that can detect Loss of Heterozygosity (LOH) of chromosome 1p AND 16q, and gain of chromosome 1q. Patients potentially eligible for mVLR must also have LOH of chromosome 11p15 included.

Note: Patients are eligible for enrollment prior to obtaining these molecular testing results, and it is strongly recommended that patients are enrolled before these results are available. However, molecular results must be returned and uploaded to APEC14B1-REN for integration into risk stratification by the required timepoints (specific timelines vary by treatment arm, see tables in Section 4.1). Patients who do not have molecular results available by the arm-specific timepoints may be taken off protocol therapy.

___5. Lymph Node Sampling

Patients who have an upfront nephrectomy must have at least one lymph node sampled and confirmed as a lymph node by central pathology review to be eligible.

Note: Lymph node sampling will also be required at delayed nephrectomy. Patients who do not have a lymph node sampled and confirmed as a lymph node by central pathology review at delayed nephrectomy will be taken off protocol therapy.

___6. Performance Level

Karnofsky performance status must be ≥ 50 for patients > 16 years of age and the Lansky performance status must be ≥ 50 for patients ≤ 16 years of age.

___7. Organ Function Requirements

- Adequate liver function defined as:
  - Serum total bilirubin ≤ 1.5 X ULN OR Direct bilirubin ≤ 3X ULN for subjects with total bilirubin levels > 1.5 ULN
  - Aspartate Aminotransferase (AST/SGOT) OR Alanine Transaminase (ALT/SGPT) ≤ 3X ULN OR ≤ 5 X ULN for patients with liver metastases.

- Adequate cardiac function defined as:
  - Shortening fraction of ≥ 27% by echocardiogram, or
  - Ejection fraction of ≥ 50%

  Note: This criteria only applies to patients centrally classified as Stage IV. Stage II and III patients subsequently assigned to a doxorubicin arm will be off protocol therapy if they do not meet this criteria at time of cardiac function assessment.

___8. HIV Status

Known HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

EXCLUSION CRITERA

___**1.** Patient with a diagnosis of Stage V Bilateral Wilms Tumor

___**2.** Patients who in the opinion of the investigator are not able to comply with the study procedures are not eligible.

___**3.** Patients with any uncontrolled, intercurrent illness including but not limited to symptomatic congestive heart failure.

___**4.** Patients with Stage I FHWT with a known or suspected Wilms Tumor predisposition syndrome or condition (contralateral nephrogenic rests and/or unilateral multicentric tumors) are excluded from treatment on the mVLR (Nephrectomy Only) arm.

Notes:

a) In the context of the renal tumor protocols, multicentric tumors and multifocal tumors are equivalent terms, and refer to the occurrence of two or more tumors arising within one kidney.

b) Exclusion 3.2.13 from the Nephrectomy Only arm applies to two groups of patients:
• Patients <4 years with Stage I FHWT other than epithelial subtype
AND
• Stage I patients of any age with Epithelial WT

c) For the purpose of exclusion from the Nephrectomy Only Arm, *known or suspected WT predisposition syndromes or conditions* are defined as follows:

WT Predisposition Syndromes:
Beckwith Wiedemann Spectrum, Denys Drash, Trisomy 18, Idiopathic Hemihypertrophy/Isolated Lateralized Overgrowth, WAGR, Simpson-GolabiBehmel, Bohring-Opitz, or other conditions considered by treating physician to predispose to WT.

WT Predisposing Conditions:
(1) a unilateral WT and (radiologic or pathologic) determination of contralateral nephrogenic rest(s)
AND/OR
(2) unilateral multicentric WT

___5. Patients treated with partial nephrectomy at initial diagnosis are excluded from mVLR (Nephrectomy Only) arm.

___6. Patients with lung metastases as the only metastatic site who already had complete resection of all radiologically evident lung nodules, and have at least one nodule confirmed pathologically as tumor.

Please note: Those with lung metastases as the only metastatic site who have complete resection of all radiologically evident lung nodules *after enrollment but prior to the lung imaging following Cycle 2 of DD-4A* will be inevaluable for lung assessment and subsequent stratum assignment and will, therefore, come Off Protocol Therapy.

___7. Patients with known Charcot-Marie-Tooth syndrome

___8. Prior Therapy or Concurrent Therapy

- Patients who have had prior tumor-directed chemotherapy or radiotherapy for the current diagnosis except for therapy delivered for an emergent issue, as medically indicted.
- Patients who will potentially require doxorubicin on this study and have previously received doxorubicin for another diagnosis
- Patients receiving concurrent chemotherapy for a different diagnosis.

Please see Section 4.1.8 for the concomitant therapy restrictions for patients during treatment.

___9. Pregnancy and Breastfeeding,

- Female patients who are pregnant since fetal toxicities and teratogenic effects have been noted for several of the study drugs. A pregnancy test is required for female patients of childbearing potential.
- Lactating females who plan to breastfeed their infants.
- Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation.

REQUIRED OBSERVATIONS:

1. Required Observations – Regimen EE-4A Cycles 1 – 3 (VCR/DACT)
   All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

   a. History
   b. Physical exam with vital signs, height and weight.
   c. Performance status – prior to start of Cycle 1 only
   d. CBC, differential and platelets.
   e. Electrolytes, BUN & Creatinine.
   f. Total bilirubin, AST, ALT. Direct bilirubin as clinically indicated.
   g. Urinalysis- prior to start of Cycle 1 only
   h. Tumor Imaging - prior to start of Cycle 1 only. Imaging required for enrollment on APEC14B1 does not need to be repeated prior to Cycle 1 of AREN2231. See Section 16.0 for complete details of the imaging relevant to each patient.
   i. Optional Biology Studies Specimens – This applies only to patients who received an upfront nephrectomy. Collect prior to Cycles 2 & 3. See Section 15.0 for complete details.
   j. Pregnancy Test – prior to Cycle 1 only

TREATMENT PLAN:

Overview of Treatment Plan

This Phase 3 study will use a new FHWT risk stratification strategy that will incorporate both previously employed and new clinical and molecular prognostic biomarkers across all disease stages. These will include patient age, chromosome 1q gain status, LOH of 1p, LOH of 16q, LOH of 11p15, clinical response after 2 initial cycles of 3-drug chemotherapy, post-chemotherapy stage and histology of patients with delayed nephrectomy, finding of positive LNs, presence of extrapulmonary metastatic disease (EPM) and epithelial histology.

Please note: Throughout this protocol, the term delayed nephrectomy is used to refer to delayed resection of primary tumor which encompasses nephrectomy, partial nephrectomy, and resection of an extrarenal primary tumor.

This study includes a cohort of patients treated with Nephrectomy only and 6 chemotherapy treatment regimens:

- **Regimen EE-4A** (vinCRIStine, DACTINomycin),
- **Regimen DD-4A** (incristine, DACTINomycin, DOXOrubicin),
- **Regimen VIVA** (vinCRIStine, DACTINomycin, irinotecan),
- **Regimen M** (vinCRIStine, DACTINomycin, DOXOrubicin, cyclophosphamide and etoposide),
- **Regimen MVI** (vinCRIStine, DACTINomycin, DOXOrubicin, cyclophosphamide, etoposide and irinotecan), and
- **Regimen UH-3** (vinCRIStine, DOXOrubicin, cyclophosphamide, etoposide, CARBOplatin and irinotecan).

All patients receiving chemotherapy (regardless of stratum assignment) will start with 1 cycle (3 weeks) of VA (vinCRIStine, DACTINomycin) chemotherapy.

The study will require real time central review via APEC14B1 to determine stratum assignment. Lymph node sampling will be required for all patients on this trial, as well as array testing of an expanded panel of segmental chromosomal aberrations.

Please note:

- Some patients will have changes in treatment based on information learned after enrollment. **For all patients, at least one callback is required to be completed prior to randomization and/or prior to any change in treatment or continuation of the same treatment**. Please refer to Section 3.1.7 for a table detailing when a callback is required.

- **Molecular results must be returned and uploaded to APEC14B1-REN for integration into risk stratification by the required timepoints** (specific timelines vary by treatment arm.
  Patients who do not have molecular results available by the arm-specific timepoints may be taken off protocol therapy.

Timing of radiation therapy (RT)
Timing of RT may differ from prior studies, as on this study all patients should receive radiation to all fields in need of radiation at the same time. The earliest radiation can occur for patients with delayed nephrectomy or lung metastases is with the start of Cycle 3. See Section 17.0 for complete RT details.

Timing of delayed resection of primary tumor
Sites are encouraged to time delayed nephrectomy as close to the completion of Cycle 2 chemotherapy as possible. Patients who undergo delayed nephrectomy prior to the start of Cycle 2 will be required to go Off Protocol Therapy (see Section 8.1)

TOXICITIES AND DOSAGE MODIFICATIONS: See Section 5.0

CENTRAL REVIEW REQUIREMENTS:

- See APEC14B1 MOP-Renal Tumors section IV for Rapid Imaging Review (IROC)
- Central Quality Assurance Review and Pre-Approval by IROC
  See Section 17 for details

SPECIMEN REQUIREMENTS:

See APEC14B1 MOP-Renal Tumors section II for Rapid Central Pathology Review

BIOLOGY REQUIREMENTS:

See section 15 for Optional Biology Studies

XI. APPENDIX I - TUMOR AND DISEASE STAGING FOR RENAL TUMORS

Staging for Wilms tumor, rhabdoid tumor of the kidney, clear cell sarcoma of the kidney

For extrarenal tumors, please see subsequent section below this table

Staging	Description
Local Stage I	Tumor limited to kidney, completely resected. The renal capsule is intact. The tumor was not ruptured or biopsied prior to removal. The vessels of the renal sinus are not involved. There is no evidence of tumor at or beyond the margins of resection.
Local Stage II	The tumor is completely resected and there is no evidence of criteria for local stage III (described below). The tumor extends beyond kidney, as is evidenced by any one of the following criteria: • There is regional extension of the tumor (i.e. penetration of the renal capsule, or extensive invasion of the soft tissue of the renal sinus, as discussed below). • Tumor within blood vessels within the nephrectomy specimen outside the renal parenchyma, including those of the renal sinus, renal vein and abdominal IVC, which are removed en bloc.
Local Stage **Ill**	Residual non-hematogenous tumor present following surgery, and confined to abdominopelvic region. Any one of the following may occur: • Lymph nodes within the abdomen or pelvis are involved by tumor. (Lymph node involvement in the thorax, or other extra-abdominal sites is a criterion for Stage IV), • The tumor has penetrated through the peritoneal surface, • Tumor implants are found on the peritoneal surface, • Non-hematogenous tumor deposits in the soft tissue of the abdomen or pelvis • Microscopic primary tumor remains postoperatively (e.g., tumor cells are found at the margin of surgical resection on microscopic examination), • Primary gross residual tumor remains • The tumor is not completely resectable because of local infiltration into vital structures, • Tumor spillage occurring intraoperatively (including any type of biopsy done on the renal primary or extra-renal primary tumor) • Pre-operative rupture detected at the time of surgery, • The tumor is treated with preoperative chemotherapy (with or without a biopsy regardless of type) before removal, • Tumor is removed in greater than one piece (e.g. tumor cells are found in a separately excised adrenal gland; a tumor thrombus within the renal vein is removed separately from the nephrectomy specimen). • Extension of the primary tumor within vena cava into thoracic vena cava and heart is considered Stage III, rather than Stage IV even though outside the abdomen. • NOTE: The clinical significance of positive abdominal cytology in the absence of other features of spillage or rupture has not been established and is not considered a criterion for local stage of 3 in this study.

Overall Stage IV	Presence ofhematogenous metastases, or lymph node metastases outside the abdominopelvic region are present. (The presence of tumor within the adrenal gland or via direct extension into adjacent organs is not interpreted as metastasis).
	Metastatic sites can include but are not limited to: • Lung(s) Extrapulmonary sites: • Liver • Bone • Brain • Pulmonary Emboli • Cytology-positive pleural effusion • Mediastinal, cervical or supraclavicular lymph nodes • Paraspinal/intraspinal * Patients with overall stage IV disease should also have determination of local (abdominal) stage)
Overall Stage V	Bilateral renal involvement by tumor is present at diagnosis. An attempt should be made to stage each side according to the above criteria on the basis of the extent of disease.

Note: Results of cytologic examination of ascites fluid, if performed, is not considered in tumor staging and has no therapeutic implications on current COG clinical trials.
***"Local" staging refers to staging of primary renal/abdominal tumor**
Extrarenal malignant rhabdoid tumor and Renal Cell Carcinoma staging see APEC14B1 MOP.

AREN2231 Stratum Assignment Tables

AREN2231 Initial Stratum Assignments (required for eligibility per protocol Section 3.2.3)

Stage	Stratum Name	Stratum Description
Stage I	Stage I Initial Nephrectomy Only	Stage I any age and epithelial predominant, OR Stage I age < 4 years and not epithelial predominant
	Stage I Initial EE4A	Stage I age 4+ years and non-epithelial type
Stage II	Stage II Initial EE4A	Initial treatment for all Stage II patients
Stage III	Stage III Initial DD4A Upfront Nephrectomy	Stage III patients with upfront nephrectomy
	Stage III Initial DD4A Delayed Nephrectomy	Stage III patients with upfront biopsy only and planned delayed nephrectomy after start of chemo
Stage IV	Stage IV Initial DD4A	Initial treatment for all Stage IV patients