

**COG-AREN0534: Treatment for Patients with Bilateral, Multicentric,  
or Bilaterally-Predisposed Unilateral Wilms Tumor**

**FAST FACTS**

**Eligibility Reviewed and Verified By**

MD/DO Date \_\_\_\_\_

RN 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. Patient must be <30 years old at time of diagnosis.
- \_\_\_2. Patient MUST be previously enrolled on AREN03B2 and confirmed to be eligible for AREN0534
- \_\_\_3. The patient must have one of the following conditions to be eligible for AREN0534:
  - Synchronous bilateral Wilms tumors\*; or
  - Unilateral Wilms tumor *and* aniridia, Beckwith-Wiedemann Syndrome, idiopathic hemihypertrophy, Simpson-Golabi-Behmel-Syndrome, Denys-Drash Syndrome or other associated genitourinary anomalies (to be eligible, these patients must not undergo any nephrectomy at diagnosis); or
  - Multicentric Wilms tumor (any age) (to be eligible, these patients must not undergo any nephrectomy at diagnosis); or
  - Unilateral Wilms tumor with contralateral nephrogenic rest(s) (any size) in a child under one year of age (to be eligible, these patients must not undergo any nephrectomy at diagnosis); or
  - Diffuse hyperplastic perilobar nephroblastomatosis (unilateral or bilateral) defined by central radiological review; or
  - Wilms tumor arising in a solitary kidney (patients with metachronous Wilms tumor are not eligible).

\* It is often difficult to distinguish Wilms tumors from nephrogenic rests based on imaging studies and percutaneous biopsies. The AREN0534 study uses the guideline that Wilms tumor with a single lesion 1 cm or greater in the contralateral kidney or multiple lesions (of any size) in the contralateral kidney should be treated on the synchronous bilateral Wilms tumor stratum. Patients with an isolated lesion less than 1 cm in the contralateral kidney should be treated on the appropriate study for unilateral Wilms tumor OR on the unilateral Wilms tumor/contralateral nephrogenic rest stratum of this study if they have not undergone nephrectomy and are under one year of age.

Loss of heterozygosity (LOH) results—which are used in the unilateral Wilms tumor studies—are **not a requirement** for enrollment on AREN0534. Blood samples can be submitted but will not be used to direct AREN0534 therapy

- \_\_\_4. The Karnofsky performance status must be  $\geq 50$  for patients > 16 years of age and the Lansky performance status must be  $\geq 50$  for patients  $\leq 16$  years of age.
- \_\_\_5. Patients must not have received systemic chemotherapy or radiation therapy prior to treatment on this study.

Patients with unilateral Wilms tumor *and* aniridia, Beckwith-Wiedemann Syndrome, idiopathic hemihypertrophy, Simpson-Golabi-Behmel-Syndrome, Denys-Drash Syndrome or other associated genitourinary anomalies; or multicentric or unilateral Wilms tumor with contralateral nephrogenic rest(s) (any size) in a child under 1 year of age **who undergo a nephrectomy at diagnosis are not eligible for this study (see Section 3.3.2.b above) and should be directed to a unilateral Wilms tumor study.**

- \_\_\_6. Organ function requirements
  - Adequate liver function defined as:
    - Total bilirubin  $\leq 1.5$  X the upper limit of normal (ULN) for age and
    - AST or ALT  $< 2.5$  X upper limit of normal for age.
  - Adequate cardiac function defined as:
    - Shortening fraction of  $\geq 27\%$  by echocardiogram, or
    - Ejection fraction of  $\geq 50\%$  by radionuclide angiogram.

(Cardiac function does not need to be assessed in patients who will not receive doxorubicin as part of their initial therapy on this study [*i.e.*, patients who start on Regimen EE-4A].)

- \_\_\_7. Female patients of childbearing age must have a negative pregnancy test.  
 \_\_\_8. Female patients who are lactating must agree to stop breastfeeding.  
 \_\_\_9. Sexually active patients of childbearing potential must agree to use effective contraception.  
 \_\_\_10. All patients and/or their parent or legal guardian must sign a written informed consent.  
 \_\_\_11. All institutional, FDA, and NCI requirements for human studies must be met.

#### REQUIRED OBSERVATIONS:

- History and physical exam at baseline and per regimen guidelines.
- Labs: CBC with differential, CMP, UA, at baseline and per regimen guidelines
- Chest x-ray\*
- CT chest
- Abdominal CT or MRI AND abdominal Doppler US.
- ECHO and EKG for all regimens except EE-4A at baseline and per regimen guidelines
- Radionuclide renal scan (such as DMSA or MAG-3) prior to renal sparing surgery to assess differential renal function (for all regimens)

\*Not required if a CT chest is obtained

#### TREATMENT PLAN:

Patients will receive two cycles of initial chemotherapy over 6 weeks. The following table applies regardless of stage, unless otherwise noted:

<b>BILATERAL WILMS TUMOR (OR WILMS TUMOR IN A SOLITARY KIDNEY)</b>		
	<b>INITIAL REGIMEN</b>	
Imaging only (no histology)	VAD (Section 4.4)	
Imaging and biopsy - Reveal favorable histology	VAD (Section 4.4)	
Imaging and biopsy - Reveal diffuse anaplastic Wilms tumor	Revised UH-1 (Section 4.6)	
Total or partial nephrectomy at diagnosis Treatment based on the highest assigned risk for either kidney	Therapy appropriate for stage and histology (see Appendix III)	
<b>UNILATERAL WILMS TUMOR (WITH HIGH RISK FOR METACHRONOUS WILMS TUMOR [E.G., PREDISPOSITION SYNDROME, CONTRALATERAL NR IN CHILD LESS THAN 1 YEAR, OR MULTICENTRIC TUMORS])</b>		
	<b>INITIAL IMAGING</b>	<b>INITIAL REGIMEN</b>
Imaging only (no histology)	Localized disease by imaging/no biopsy performed	EE-4A (Section 4.2)
Imaging only (no histology)	Evidence of distant metastatic disease by imaging	VAD (Section 4.4)
Imaging and biopsy - Reveal favorable histology	All patients*	
Imaging and biopsy - Reveal anaplastic Wilms tumor	All patients*	Revised UH-1 (Section 4.6)
<b>DHPLN</b>		
	<b>INITIAL REGIMEN</b>	
Imaging only	EE-4A (Section 4.2)	

\* Biopsy renders the local Stage to be III; distant metastasis is Stage IV. Please remember that a biopsy makes the patient Stage III for chemotherapy but patient will NOT require radiation therapy unless they meet other criteria for Stage III designation, such as positive lymph nodes. Additionally, patients with anaplastic histology receive radiation therapy.

**TOXICITIES AND DOSAGE MODIFICATIONS:**

See Section 5.0 for dose modifications due to toxicities.

**SPECIMEN REQUIREMENTS:**

Specimens/materials per Section 5.1 of AREN03B2 **must** be submitted for central review by **day 7**. For enrollment on AREN0534, unless a biopsy was done, the submission requirements at enrollment on AREN03B2 refer to imaging studies. Tissue samples are required only if a surgical procedure (biopsy or nephrectomy) was performed at the time of enrollment on AREN03B2.

**TIMING CONSIDERATIONS:**

1. Enrollment on the AREN03B2 Renal Tumor Biology and Classification Study is required **prior to** enrollment on AREN0534. Physicians are encouraged not to begin treatment until the central radiology review (and surgery and pathology reviews, when applicable) is completed and an initial risk assignment is made on the AREN03B2 study. However, treatment may begin before central review on AREN03B2 is completed if medically indicated (*e.g.*, significant symptoms from large tumor burden).
2. Study enrollment must take place within seven (7) calendar days after beginning protocol therapy unless condition (a) or (b) stipulated below occurs. If enrollment takes place before starting therapy, the date protocol therapy is projected to start must be no later than seven (7) calendar days after enrollment or by Day 14 following the initial CT/MRI, whichever occurs first. If surgery is performed up-front, therapy must start no later than Day 14 after surgery.
3. **Initial biopsy or nephrectomy is not required for patients in this protocol**, which is different from all other COG therapeutic renal tumor studies. While there are system checks for patients enrolling on AREN0534 with imaging alone, if you are considering enrolling your patient on this study, it is recommended that you contact the AREN0534 Study Chair or Research Coordinator to help ensure that your patient's case gets reviewed and properly assigned in a timely manner. All patients must begin chemotherapy by Day 14 following surgery or diagnosis by initial CT/MRI, unless medically contraindicated. Patients may not enroll on AREN0534 until central review is completed and initial risk assignment occurs. If all the required materials were submitted for central review by Day 7 but initial risk assignment has not occurred by Day 12 or within 5 days of starting treatment (whichever occurs first), please notify the AREN03B2 Study Chair and Research Coordinator to discuss the status of the risk assignment. If patient reaches Day 14 or Day 7 of starting treatment without initial risk assignment, patient will not be eligible for enrollment unless: (a) central pathology required further diagnostic tests, (b) materials and specimens arrived by Day 7 and central review did not occur by Day 14. In these circumstances, the patient may proceed with treatment according to local risk assessment (after obtaining appropriate protocol consent) and enroll within 3 working days of notification of central risk assignment, if the central risk assignment is in agreement with the local institution's assessment.