

COG-AREN03B2: Renal Tumors Classification, Biology, and Banking Study

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. **AREN03B2 enrollment is mandatory prior to enrollment on therapeutic studies. Consult the relevant therapeutic study for renal tumors. Physicians are encouraged not to begin treatment until an initial risk assignment is made on AREN03B2.**

Patients with the first occurrence of any tumor of the kidney identified on CT scan or MRI are eligible for this study. Histologic diagnosis is not required prior to enrollment **but is required for all patients once on study.** Eligible tumors include (but are not limited to):

Nephroblastic Tumors	Nephroblastoma (Wilms Tumor) <ul style="list-style-type: none"> • Favorable histology • Anaplasia (Diffuse, Focal) Nephrogenic rests and Nephroblastomatosis Cystic Nephroma and Cystic Partially Differentiated Nephroblastoma Metanephric Tumors <ul style="list-style-type: none"> • Metanephric Adenoma • Metanephric Adenofibroma • Metanephric Stromal Tumor
Mesoblastic Nephroma	Cellular, Classic, Mixed
Clear Cell Sarcoma	
Rhabdoid Tumor	
Renal Epithelioid Tumors of Childhood	Papillary renal cell carcinoma Renal medullary carcinoma Renal tumors associated with Xp11.2 translocations Oncocytic renal neoplasms following neuroblastoma
Angiolipoma	
Ossifying renal tumor of infancy	

- ___2. Extrarenal tumors

Patients with the first occurrence of the following tumors are also eligible:

- Extrarenal nephroblastoma or extrarenal nephrogenic rests
- Malignant rhabdoid tumor occurring anywhere outside the Central Nervous System

- ___3. Required Specimens

Required specimens, reports, and copies of imaging studies must be available for submission or must become available during the required timeframe.

- ___4. For ALL patients (with exception of bilateral, bilaterally predisposed or unilateral tumor in solitary kidney planning to enroll without biopsy), the following submissions are required:
- A complete set of recut H & E slides. Tissue must be from diagnosis, prior to any chemotherapy or radiation.
 - Representative formalin-fixed paraffin-embedded tissue block or if a block is unavailable, 10 unstained slides from a representative block of tumor.
 - Institutional pathology report, transmittal form and pathology checklist.
 - Copies of images and institutional reports of CT and/or MRI abdomen and pelvis
 - Copies of images and institutional report of CT chest for all malignant tumors
 - Institutional surgical report(s)
 - For patients with clinical features and required imaging findings consistent with the eligibility for the bilateral study, AREN0534 (or successor study), confirmed by central review, biopsy is not required. However, if biopsy is done, tissue must be submitted as for other renal tumors, and initial risk assignment will require pathology and surgical rapid central reviews. Transmittal form and pathology checklist are also needed.
 - Patients with extrarenal Wilms tumor must have tumor tissue available for central review.
 - Patients with extra-CNS malignant rhabdoid tumor must have tumor tissue available for central review.
- ___5. Patients must be < 30 years old at the time of diagnosis.

Risk Assignment

All patients enrolling on AREN03B2 must have pathology specimens submitted for pathology central review, with the exception of patients with bilateral, bilaterally predisposed or unilateral tumor in a solitary kidney planning to enroll on AREN03B2 without biopsy or surgery. Tissue should be submitted for central pathology review from any initial diagnostic surgical procedure. Tissue samples are only required if a surgical procedure (biopsy from any tumor site or nephrectomy) was performed.

In order to allow adequate time for real-time central review and final risk assignment to be completed or amended in a timely manner, it is **STRONGLY RECOMMENDED** that pathology slides be submitted for central review by Day 7 after definitive nephrectomy (surgery is considered Day 0). To keep within the timing requirements, it is encouraged that slides be submitted for central review prior to a final institutional pathology report.

Initial Risk Assignment is issued after central review of imaging, pathology (for all patients with biopsy or surgery) and operative notes. Timing of submissions and required materials for all patients are outlined in [Section 3.1.4](#), and [Table 5.1](#). All patients who submitted required materials will receive an Initial Risk Assignment. Patients intending to enroll on a therapeutic study must meet the timing requirements of that therapeutic study to be eligible for enrollment on the therapeutic study. Investigators should refer to the appropriate therapeutic study eligibility section for details.

Data from enrollment on AREN03B2 will be used to determine eligibility for the COG renal therapeutic studies. Results of central pathology, imaging and surgical review will be made available to the institutional CRA and Oncologist, and together with the age, tumor weight, and consideration of underlying syndrome will be used to **CENTRALLY** assign the Initial Risk Group. We recommend shipping all central review materials to the BPC as soon as possible after surgery or biopsy to provide sufficient time for central review to be completed. **This Initial Risk is REQUIRED prior to enrollment on a therapeutic study.** In cases where it is medically necessary to begin therapy, treatment may be initiated up to seven days prior to enrollment on a therapeutic study. Informed consent for the appropriate therapeutic study must be obtained prior to initiating therapy. If the patient is started on a treatment which is inconsistent with their Initial Risk Assignment, **they will not be eligible for a therapeutic study.**

The following schema displays the prognostic factors that will be used to define eligibility requirements for COG therapeutic studies:

For Patients with Favorable Histology Wilms Tumor:

Patient Age	Tumor Weight	Stage	Initial Risk Group	Initial Therapeutic Study	LOH 1p/16q	Lung Metastases Response	Extra-Pulmonary Mets	Final Risk Group	Final Therapeutic Study
< 2 yrs	< 550 g	I [#]	Very Low	AREN0532 [^]	Any	N/A	N/A	Very Low	AREN0532 [^]
Any	≥ 550 g	I	Low	None	No	N/A	N/A	Low	None
≥ 2 yrs	Any	I	Low	None	No	N/A	N/A	Low	None
Any	Any	II	Low	None	No	N/A	N/A	Low	None
Any	≥ 550 g	I	Low	None	Yes	N/A	N/A	Standard	AREN0532 [^]
≥ 2 yrs	Any	I	Low	None	Yes	N/A	N/A	Standard	AREN0532 [^]
Any	Any	II	Low	None	Yes	N/A	N/A	Standard	AREN0532 [^]
Any	Any	III	Standard	AREN0532 [^]	No	N/A	N/A	Standard	AREN0532 ^{%^}
Any	Any	IV	Higher	AREN0533 [^]	No	Complete	No	Standard	AREN0533 [%]
Any	Any	III	Standard	AREN0532 [^]	Yes	N/A	N/A	Higher	AREN0533 [%]
Any	Any	IV	Higher	AREN0533 [^]	Yes	Any	Any	Higher	AREN0533 [%]
Any	Any	IV	Higher	AREN0533 [^]	Any	Partial	Any	Higher	AREN0533 [%]
Any	Any	IV	Higher	AREN0533 [^]	Any	Any	Yes	Higher	AREN0533 [%]
Any	Any	V*	Bilateral	AREN0534 [^]	Any	Any	Any	Bilateral	AREN0534

Lymph node biopsy is **required** to confirm Stage I disease in Very Low Risk patients, and **STRONGLY** encouraged for appropriate staging of **all** patients.

[^] Or successor study

% For patients enrolled on AREN0532 (or successor study) or AREN0533 (or successor study) who undergo delayed nephrectomy, a Subsequent Final Risk will be issued after rapid central review of subsequent pathology and surgical reports of the definitive delayed nephrectomy. Patients with an adjusted Subsequent Final Risk Assignment of High Risk Renal tumors will be potentially eligible for transfer to AREN0321 (or successor study).

*Please see the eligibility section in protocol AREN0534 (or successor study). Patients who will receive an initial risk of Bilateral include the following groups:

- a) Synchronous bilateral Wilms tumors^{**}; or
- b) 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
- c) Multicentric Wilms tumor (any age) (to be eligible, these patients must not undergo any nephrectomy at diagnosis); or
- d) Unilateral Wilms tumor with contralateral nephrogenic rest(s) (any size) in a child under one year, or with multiple contralateral rests (any size) independent of age (to be eligible, these patients must not undergo any nephrectomy at diagnosis); or
- e) Diffuse hyperplastic perilobar nephroblastomatosis (patients with unilateral DHPLNR must not have undergone nephrectomy of kidney with DHPLNR) defined by central radiological review; or
- f) Wilms tumor arising in a solitary kidney (please note, horseshoe kidney is NOT considered single kidney, and patients with metachronous Wilms tumor are not eligible).

Important Notes

A risk assignment of Bilateral does **NOT** imply assignment to a particular treatment arm on the protocol AREN0534 (or successor study). Please see AREN0534 (or successor study) for descriptions of the three treatment arms of that study. There are situations where a patient may be eligible for both protocol AREN0534 as well as one of the unilateral therapeutic protocols. The initial risk assignment will take into consideration the therapeutic intent of the institution communicated on the CRF.

Note that in some circumstances, upfront nephrectomy may make a patient ineligible for AREN0534 (or successor study). . Please see the eligibility section for AREN0534 (or successor study).

High Risk Renal Tumors: Patients with the following tumors (all stages) will receive an initial risk assignment of **High Risk** Renal Tumors, and will be potentially eligible for enrollment on AREN0321 (or successor study):

Anaplastic (focal or diffuse) Wilms tumor

Clear cell sarcoma of the kidney

Extra-CNS malignant rhabdoid tumor

Renal cell carcinoma All other patients with renal tumors (including all benign renal tumors) will receive an initial risk assignment of OTHER.

Therapeutic Study Eligibility

The following initial risk assignments make a patient potentially eligible for enrollment on the appropriate COG therapeutic study, if all other pertinent eligibility criteria are met:

Very Low (AREN0532 or successor study)

Standard (AREN0532 or successor study)

Favorable Wilms [higher risk] (AREN0533 or successor study)

High risk renal tumors (AREN0321 or successor study)

Bilateral (AREN0534 or successor study)

Patients with an Initial Risk Assignment of LOW will not be immediately eligible for a therapeutic study. Only initial LOW risk patients whose tumors are found to have combined LOH 1p and 16q – whose FINAL risk assignment is therefore STANDARD – will be potentially eligible for enrollment on the study AREN0532 (or successor study).

LOW risk patients may be treated at the investigator's discretion. A standard treatment regimen known as Regimen EE-4A, which was studied in National Wilms Tumor Studies 4 and 5 and is described in the Principles of Pediatric Oncology edited by Pizzo and Poplack, has resulted in excellent outcomes for this group of patients. As a reminder, to be potentially eligible for enrollment on study AREN0532 (or successor study), patients with an initial risk of LOW and found to have positive LOH are required to have started treatment with Regimen EE-4A within a 14 day time frame of initial surgery (surgery is Day 0).

Patients with Final Risk = LOW will remain on AREN03B2 and a follow-up every 6 months for three years, and then annually until five years have passed, will be required.

Final Risk Assignment

All patients receive an Initial Risk Assignment. For certain patient subgroups, LOH testing with or without central radiology review of pulmonary lesion response will result in a Final Risk Assignment. Final Risk Assignments will be communicated through email, and posted on eRDES. For the subgroup of patients enrolled in AREN0532 (or successor study) and AREN0533 (or successor study) that have a delayed nephrectomy (after chemotherapy), a Subsequent Final Risk Assignment will be issued after central pathology review of the nephrectomy specimen, and will be communicated through email and posted on eRDES.