

COG-AREN0532: Treatment for Very Low and Standard Risk Favorable Histology Wilms Tumor

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. Timing

- Enrollment on AREN03B2 and Initial Risk Assignment
 - Enrollment on AREN03B2 is required **prior to** enrollment on AREN0532. Investigators are strongly encouraged to review the radiological, surgical and pathological specimen criteria for enrollment on AREN03B2 prior to nephrectomy, as an inadequate approach will not allow enrollment on AREN03B2, and thus AREN0532. Adequate lymph node sampling must occur for very low risk patients.
 - Patients will be assigned through AREN03B2 to a stratum based on an “initial risk” classification determined by clinical, radiological, surgical and pathological characteristics. Treatment will be initiated based on this “initial risk” classification.
- Timing of Enrollment and Starting Protocol Therapy
 - All low and standard risk patients must begin chemotherapy within 14 days of nephrectomy or renal biopsy (surgery/biopsy is Day 0), unless medically contraindicated. If the specimens were submitted for central review by Day 7 and there is no return of central pathology review by Day 14, the patient may proceed with treatment according to local risk assessment and enroll once the central review is available. Physicians are encouraged not to begin treatment until the central radiology, surgery, and pathology reviews are 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), but patients may not enroll on AREN0532 until initial risk assignment occurs. Consent for study enrollment must be obtained before any AREN0532 protocol chemotherapy is given.
 - > Initial Standard Risk

Patients initially assigned as standard risk patients may enroll on AREN0532 and start therapy before obtaining the LOH results. Study enrollment must take place within seven (7) calendar days after beginning protocol therapy for patients with initial standard risk disease. Seven calendar days do not include the start date. 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 surgery, whichever occurs first.
 - > Initial Low Risk

Patients initially assigned as low risk patients may **not** enroll on AREN0532 before obtaining the LOH results. Final risk assignment – and thus, eligibility for AREN0532 – for this arm may potentially be affected by the results of the LOH testing. These results are expected to be obtained within 3 weeks of tumor submission. Patients with initial risk assignment of Low Risk disease will be followed on AREN03B2. Standard treatment is Regimen EE-4A, which must be started by Day 14 following nephrectomy (unless medically contraindicated) for the patient to be eligible for AREN0532. Low risk patients found to have LOH 1p and 16q (and who have had treatment with EE-4A) will receive a final risk assignment indicating upgrading to Standard Risk and eligibility for AREN0532 Stratum 5. Study enrollment must take place within seven (7) calendar days after beginning AREN0532 protocol-prescribed DD-4A therapy on Stratum 5. Seven calendar days do not include the start date. These patients must enter by Week 4 of the DD-4A regimen.
 - > Very Low Risk

Patients initially assigned as very low risk patients may enroll on AREN0532 before obtaining the LOH results. The LOH results will not impact the assigned stratum for very low risk patients. Patients who are eligible for the very low risk arm (Stage I, tumor weight < 550 g, age < 2 years) may enroll up to 30 days following nephrectomy.
 - If enrollment takes place before starting therapy, the date protocol therapy is projected to start is open since there are unforeseen medical complications that may delay a patient's actual start of protocol therapy. However, if the start of protocol therapy is more than seven days after enrollment, the medical indication for the delay must be documented in the patient's medical/research record.

- Timing of Radiation Therapy Scheduling
 - Patients with a renal mass should be scheduled for simulation and radiation therapy at diagnosis. Radiation therapy can then be canceled if not required by "initial risk" assignment provided by central review on AREN03B2.
- ___2. Patients must be less than 30 years of age at the time of diagnosis.
- ___3. Patients must have previously enrolled on AREN0B32 and be found to have newly diagnosed Stage I-III favorable histology Wilms tumor, confirmed by central pathology, surgical and radiology review.
- ___4. The 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.
- ___5. No prior tumor-directed chemotherapy or radiotherapy is acceptable, except if previously treated with EE-4A and enrolling from AREN03B2 with Stage I or II Favorable Histology Wilms tumor found to have LOH 1p and 16q, or for those treated for emergent issues, as medically indicated.
- ___6. Organ Function Requirements:
 - Patients must have adequate liver function defined as:
 - Total (direct) bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
 - SGOT (AST) and SGPT (ALT) < 2.5 x upper limit of normal (ULN) for age.
 - For patients assigned to Standard risk stratum (DD-4A): Adequate cardiac function defined as:
 - Shortening fraction of $\geq 27\%$ by echocardiogram, or
 - Ejection fraction of $\geq 50\%$ by radionuclide angiogram.
- ___7. Other
 - Female patients of childbearing potential must have a negative pregnancy test.
 - Female patients who are lactating must agree to stop breast-feeding.
 - Sexually active patients of childbearing potential must agree to use effective contraception.

INDUCTION STRATIFICATION FACTORS:

Note: Patients will be assigned through AREN03B2 to a stratum based on an “initial risk” classification determined by clinical, radiological, surgical and pathological characteristics. Stage I favorable histology patients with tumor ≥ 550 g or ≥ 2 years of age, and Stage II favorable histology patients may not enroll on AREN0532 before obtaining a final risk classification indicating that the patient is eligible for Stratum 5 based on the results of the LOH testing. Patients assigned as very low or standard risk favorable histology should enroll on AREN0532 and start treatment before obtaining the LOH results. Treatment for very low risk patients will not be modified based on LOH results. For patients with very low risk tumors (Stage I favorable histology < 550 g and age < 2 years), lymph node sampling must occur. Treatment will be initiated based on this “initial risk” classification. By three weeks, a “final risk” classification will be assigned based on LOH findings and this “final risk” stratification will be used for assigning continuing treatment. Investigators will be notified of this final stratification.

- a. Patients will be eligible for the very low risk arm (surgery and observation only) if they have Stage I, Favorable Histology Wilms tumor, are < 2 yrs of age, and have a tumor weight < 550 g. They also must have had adequate submission of regional lymph nodes demonstrating histologically nodes negative for tumor and confirmation of absence of pulmonary metastases on CT scan of chest by central radiology review.
- b. Patients will be eligible for the standard risk arm (DD-4A) with no radiotherapy, if they have Loss of Heterozygosity for 1p **and** 16q, AND are either Stage I, Favorable Histology, Wilms tumor (age ≥ 2 years or tumor weight of ≥ 550 g), **or** Stage II, Favorable Histology, Wilms tumor with of any weight of tumor or patient age.
- c. Patients will be eligible for the standard risk arm (DD-4A) with radiotherapy, if they have no Loss of Heterozygosity for 1p **and** 16q and have Stage III, Favorable Histology Wilms tumor. Note: Patients found to have combined LOH at 1p **and** 16q will be taken off AREN0532 protocol therapy and eligible to enroll on AREN0533.

Patients with synchronous bilateral Wilms tumors (Stage V) and some patients predisposed to develop bilateral Wilms tumors are **not** eligible for the very low risk observation arm of AREN0532 and should be directed to AREN0534. **Predisposition syndromes excluded from the observation arm of AREN0532 include unilateral Wilms tumor and any of the following: aniridia, Beckwith-Wiedemann syndrome, Simpson-Golabi-Behmel syndrome, Denys-Drash syndrome or other associated genito-urinary anomalies, multicentric Wilms tumor or unilateral WT with contralateral nephrogenic rest(s) in a child under one year of age or diffuse hyperplastic perilobar nephroblastomatosis. Isolated hemihypertrophy patients are allowed, except for those associated with known 11p15 uniparental disomy. All other lower risk predisposition syndromes are allowed.**

REQUIRED OBSERVATIONS:

Required Observations for Patients on Regimen DD-4A (baseline to tumor progression or relapse)

- History
- Physical Exam (Ht, Wt, BSA, VS)
- Performance Status
- CBC, differential, platelets ¹
- Electrolytes
- Creatinine, SGOT, SGPT, Bilirubin ¹
- Total protein/albumin
- Urinalysis
- Pregnancy test ²
- Abdominal US ³
- Chest Xray
- CT chest ⁴
- CT or MRI abdomen/pelvis
- Echo and ECG

Baseline investigations collected to satisfy enrollment on AREN03B2 do not need to be repeated for AREN0532.

¹ Recommend weekly during treatment

² For females of child bearing potential

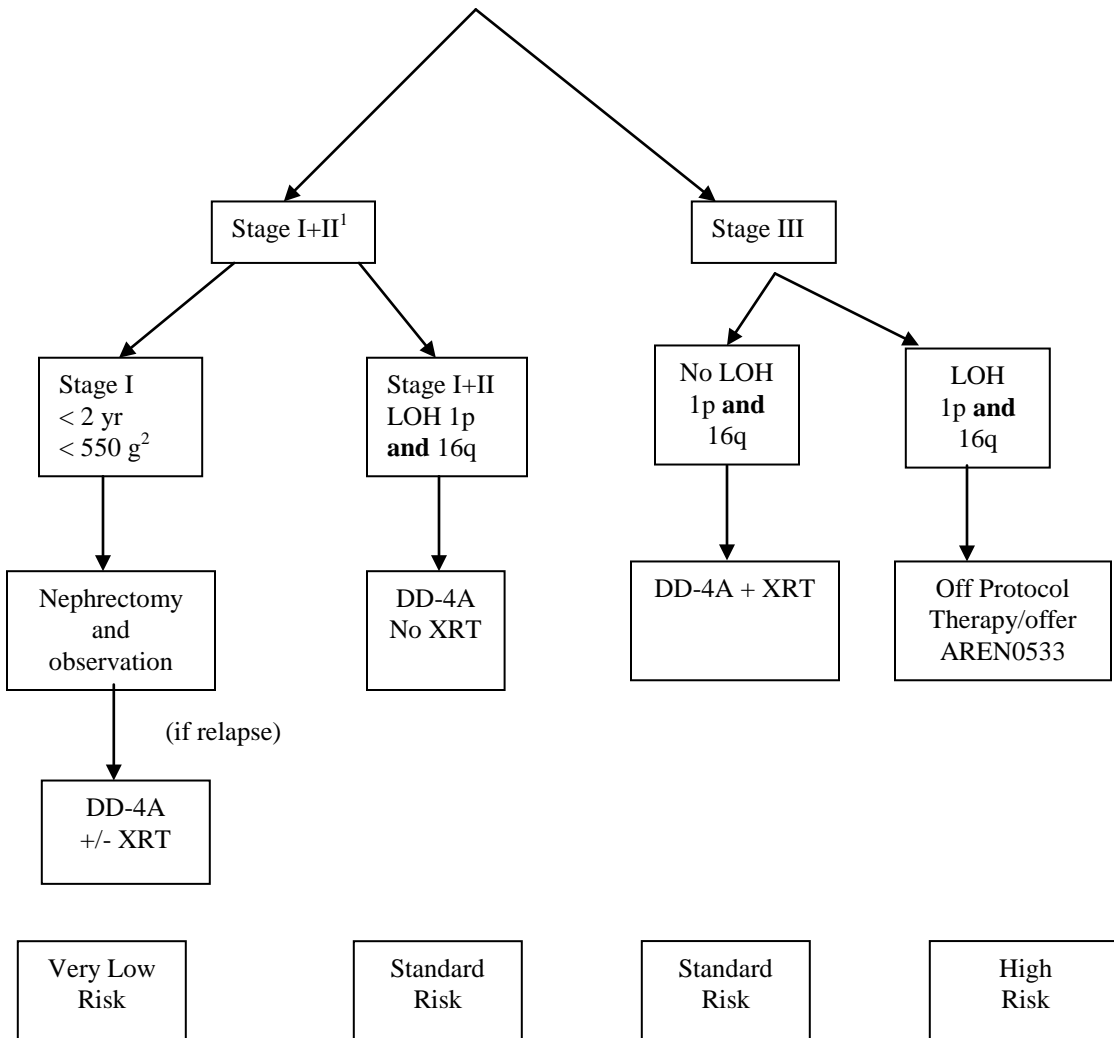
³ Abd US and Doppler recommended but not required at baseline to exclude IVC tumor thrombus

⁴ Required only for patients with pulmonary relapse from the Very Low risk arm (observation only)

Note: Symptomatic patients should have appropriate studies (e.g. Bone scan, MRI head) as clinically indicated.

TREATMENT PLAN:

Wilms Tumor-Favorable Histology (central review pathology)
Unilateral



Notes:

1. Stage I and II patients without combined LOH 1p and 16q will be followed on AREN03B2.
2. Must have had lymph node sampling at the time of nephrectomy to be eligible for this arm.

TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5.0.

SPECIMEN REQUIREMENTS:

Per AREN03B2, enrollment on AREN03B2 is required prior to enrollment on AREN0532.

QARC REQUIREMENTS:

See Section 16.1.10