

## COG-AREN0321: Treatment of High Risk Renal Tumors

### FAST FACTS

#### 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. Enrollment on the AREN03B2 Renal Tumor Biology and Classification Study is required **prior to** enrollment on AREN0321. 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 AREN0321 until initial risk assignment occurs.
- \_\_\_2. Study enrollment must take place within seven (7) calendar days of beginning protocol therapy. 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.
- \_\_\_3. Protocol therapy must begin by Day 14 after the original surgery or 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.  
Patients with renal cell carcinoma may enroll on AREN0321 within 42 days of diagnostic surgery because there is no adjuvant therapy associated with this study. Patients with metastatic or unresectable renal cell carcinoma who are treated with adjuvant therapy according to the local physician's choice must enroll on AREN0321 within 7 days of beginning treatment.
- \_\_\_4. Patients must be < 30 years old at the time of initial diagnosis.
- \_\_\_5. Patients with newly diagnosed disease of one of the following histological types (Stages I-IV) are eligible for this study:
  - Focal Anaplastic Wilms Tumor
  - Diffuse Anaplastic Wilms Tumor
  - Clear Cell Sarcoma of Kidney
  - Malignant Rhabdoid Tumor (Renal or extra renal, excluding CNS tumors)
  - Renal Cell Carcinoma (clear cell, papillary, renal medullary, oncocytoid, sarcomatoid, chromophobe, translocation, collecting duct, carcinoma associated with neuroblastoma, renal cell carcinoma unclassified)
 Enrollment on AREN03B2 is required **prior to** enrollment on AREN0321. Patients with Stage V (bilateral) high-risk renal tumors will be treated on a separate study.
- \_\_\_6. Specimens/materials per Section 5.1 of AREN03B2 (see AREN0321 Section 15.0) should be submitted for central review **by Day 7**.  
Timing considerations:
  - Patients must begin protocol therapy on AREN0321 by Day 14 after surgery or biopsy, unless medically contraindicated. It is suggested that samples and studies be submitted by Day 7 to allow adequate time for central review to be completed.
  - Patients may begin protocol therapy before central review is completed if medically indicated (*e.g.*, significant symptoms from large tumor burden). However, enrollment on AREN0321 must occur within 7 days after beginning treatment or by Day 14 after surgery or biopsy, whichever comes first. If treatment begins before central review is completed, samples and studies must be submitted immediately to allow central review to be completed.
- \_\_\_7. 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.
- \_\_\_8. Patients must not have received systemic chemotherapy or radiation therapy prior to treatment on this study UNLESS they were enrolled on the AREN0532 or AREN0533 studies and received prenephrectomy chemotherapy for what was originally presumed to be favorable histology Wilms tumor. Additionally, patients with pediatric RCC who previously received chemotherapy for another type of malignancy (not the RCC) or non-malignant condition may enroll on the study.

- \_\_\_9. Organ Function Requirements (for all patients receiving chemotherapy on this protocol):
- Patients must have adequate liver function defined as:
    - Total bilirubin  $\leq 1.5$  x upper limit of normal (ULN) for age, and
    - SGOT (AST) or SGPT (ALT)  $< 2.5$  x upper limit of normal (ULN) for age.
  - Patients must have adequate cardiac function defined as:
    - Shortening fraction of  $\geq 27\%$  by echocardiogram, or
    - Ejection fraction of  $\geq 50\%$  by radionuclide angiogram.
- \_\_\_10. Female patients of childbearing age must have a negative pregnancy test.
- \_\_\_11. Female patients who are lactating must agree to stop breast-feeding.
- \_\_\_12. Sexually active patients of childbearing potential must agree to use effective contraception.

**REQUIRED OBSERVATIONS:**

**Required Clinical, Laboratory and Disease Evaluations**

STUDIES TO BE OBTAINED:

- History
- Physical Exam (Ht, Wt, BSA, VS)
- Performance Status
- CBC, differential, platelets
- Urinalysis
- Electrolytes including Ca<sup>++</sup>, PO<sub>4</sub>, Mg<sup>++</sup>
- Creatinine, SGPT, bilirubin
- Total protein/albumin
- Serum or urine pregnancy test <sup>3</sup>
- CT or MRI of the abdomen and pelvis
- CT chest
- Bone Scan <sup>1</sup>
- PET scan (optional)
- MRI brain <sup>1</sup>
- Echocardiogram/EKG <sup>2</sup>
- For confirmed malignant rhabdoid tumor cases only, Parental blood sample (Requested\*)

Pre-Operative Imaging Studies of the Primary Tumor are Sufficient; Post-Operative Studies need not be Obtained.

<sup>1</sup> For CCSK, malignant rhabdoid tumor, and renal cell carcinoma only

<sup>2</sup> Not necessary for renal cell carcinoma

<sup>3</sup> For females of childbearing potential

\* See Section 16.4 for instructions.

**TREATMENT PLAN:  
Overview of Treatment Plan**

Four treatment regimens, or surgery only, will be applied according to tumor histology, stage, and response to treatment.

| <b>Histology</b>               | <b>Stage</b>                          | <b>Regimen</b>                 |
|--------------------------------|---------------------------------------|--------------------------------|
| Focal Anaplastic Wilms Tumor   | I-III                                 | DD-4A (Section 4.5)            |
| Focal Anaplastic Wilms Tumor   | IV                                    | Revised UH-1 (Section 4.1)     |
| Diffuse Anaplastic Wilms Tumor | I                                     | DD-4A (Section 4.5)            |
| Diffuse Anaplastic Wilms Tumor | II-III and IV (no measurable disease) | Revised UH-1 (Section 4.1)     |
| Diffuse Anaplastic Wilms Tumor | IV (measurable disease)               | VCR/IRIN window*( Section 4.2) |
| Diffuse Anaplastic Wilms Tumor | IV (PR or CR after VCR/IRIN window)   | Revised UH-2 (Section 4.3)     |
| Clear Cell Sarcoma of Kidney   | I-III                                 | Regimen I (Section 4.4)        |
| Clear Cell Sarcoma of Kidney   | IV                                    | Revised UH-1 (Section 4.1)     |
| Malignant Rhabdoid Tumor       | I-IV                                  | Revised UH-1 (Section 4.1)     |
| Renal Cell Carcinoma           | I-IV, gross total resection           | Surgery only                   |
| Renal Cell Carcinoma           | III-IV, incomplete resection          | Physician choice               |

**\*Window Therapy**

Measurable disease is defined as the presence of at least one lesion that can be measured in 3-dimensions with the longest diameter (which may be in the cranio-caudal dimension) at least 1 cm on CT or MRI.

Patients whose tumors could potentially cause life-threatening complications with tumor progression, such as tumors with intracranial or intraspinal extension, or tumors that could compress the airway, are not eligible for window therapy.

Patients who are eligible for window therapy and who are unwilling to receive window therapy may be enrolled on study and will receive therapy on the revised UH-1 regimen.

Most patients will have had surgical resection before beginning chemotherapy, as outlined in the AREN03B2 Renal Tumor Biology and Classification Study. Patients with initially unresectable or incompletely resected tumors will receive chemotherapy and undergo imaging reevaluation after 4 cycles (approximately 12 weeks). If the tumor is deemed resectable at Week 13, surgery will be performed. Guidelines for delayed surgical resection and resection of metastases are discussed in Section 14. 1.1.

Some patients will have received pre-operative chemotherapy on AREN0532 or AREN0533 for what was presumed to be favorable histology Wilms tumor. Such patients will receive Revised Regimen UH-1 in its entirety starting from Week 1, except that the Week 28 DOXOrubicin dose should be withheld to maintain a cumulative DOXOrubicin dose  $\leq$  225 mg/m<sup>2</sup>. Patients who receive prior chemotherapy are not eligible for the Phase II vinCRISTine/irinotecan window arm.

Protocol therapy must begin by Day 14 after the original surgery or 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.

Concomitant Medications Restrictions

Concomitant use of aprepitant (Emend) is not allowed. Strong inhibitors of cytochrome P450 3A4 are known to alter vinCRISTine metabolism, leading to increased vinCRISTine neurotoxicity. Strong stimulators of cytochrome P450 3A4 alter irinotecan metabolism (leading to lower systemic exposure and reduced efficacy of irinotecan). Strong inhibitors or stimulators of cytochrome P450 3A4, including voriconazole, itraconazole, ketoconazole, rifampin, phenytoin, phenobarbital, carbamazepine, and St. John's wort, should all be avoided or used with great caution.

**TOXICITIES AND DOSAGE MODIFICATIONS:**

See Section 5.0.

**SPECIMEN REQUIREMENTS:**

Pathology guidelines and specimen requirements for primary tumor resections are described in the AREN03B2 Renal Tumors Classification and Banking Protocol. In addition to submitting primary tumor material, institutions are encouraged to submit samples of metastatic and post-chemotherapy tumor samples as part of the AREN03B2 study.