COG-AREN1921: Treatment of Newly Diagnosed Diffuse Anaplastic Wilms Tumors (DAWT) and Relapsed 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. Enrollment onto AREN03B2

Patients with newly diagnosed Stages 2 - 4 diffuse anaplastic Wilms tumor (DAWT) must be enrolled on AREN03B2, and have received either an Initial Risk Assignment showing DAWT (if anaplasia first identified at diagnostic, pre-treatment nephrectomy or biopsy) or a Delayed Nephrectomy Classification showing DAWT (if anaplasia first noted at delayed nephrectomy) prior to enrollment on AREN1921.

Once enrolled on AREN03B2 and all the necessary review materials are submitted, central pathology, surgery, and imaging review results will be entered for viewing by the institution. Shortly thereafter, the Initial Risk Assignment or Delayed Nephrectomy Classification will be entered and made available to the institution.

For patients with relapsed favorable histology Wilms tumor (FHWT), prior enrollment on AREN03B2 is not required for enrollment on AREN1921.

___2. Emergent Therapy

- Diffuse Anaplastic Wilms Tumors

  Treatment should not begin until after the AREN03B2 central reviews are completed, an Initial Risk Assignment or Delayed Nephrectomy Classification showing that DAWT has been issued on AREN03B2, *and* AREN1921 study enrollment has occurred. However, in the event that an investigator determines that emergent therapy is clinically indicated (e.g. significant symptoms from large tumor burden), therapy as per AREN1921 may be initiated before study enrollment. However, the following criteria must be met prior to the start of emergent therapy:
  - Study consent for AREN03B2 and AREN1921 must be obtained.
  - Must meet eligibility criteria for AREN03B2, including required specimens and imaging.
  - Must meet eligibility criteria for AREN1921, except for Section 3.2.1 as Initial Risk Assignment or Delayed Nephrectomy Classification results may be pending from AREN03B2.

  Enrollment on AREN03B2, obtaining an Initial Risk Assignment or Delayed Nephrectomy Classification showing DAWT and subsequent enrollment on AREN1921 must all take place within **seven (7) calendar** days from beginning the emergent AREN1921 protocol therapy.

  In addition, DAWT patients may receive emergent radiation therapy, if clinically indicated, prior to study enrollment and remain eligible for the study. Clinical situations which emergent radiation therapy is indicated may include, but is not limited to, anatomic or mechanical compromise of critical organ function by tumor (e.g., respiratory distress/failure, abdominal compartment syndrome, urinary obstruction, etc.).

- Relapsed Favorable Histology Wilms Tumor
  Patients with relapsed favorable histology Wilms tumor who received emergency radiation to preserve organ function are eligible and are not required to washout with the criteria in Section 3.2.8.2.

___3. Rapid Central Pathological Review
Mandatory rapid central pathology review will be performed on AREN1921 for relapsed Favorable Histology Wilms Tumor patients to confirm appropriate histology (see Section 14.2).

To remain on study, central pathology review materials must be submitted within 6 weeks of enrollment (see Section 14.0 for complete details).

___4. Timing
Patients must be enrolled before treatment begins except in situations of emergent therapy and as specified below. The date protocol therapy is projected to start must be no later than **five (5)** calendar days after the date of study enrollment. **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 3.1.5. Please also note the timing and prior therapy requirements in Section 3.2.4 and 3.2.8.

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

___5. **Patient Eligibility Criteria**

Laboratory Studies
All laboratory studies to determine eligibility must be performed within 7 days prior to *enrollment* unless otherwise indicated.

The following laboratory studies must be repeated prior to the *start of protocol therapy* if > 7 days have elapsed from their most recent prior assessment: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. Laboratory tests need not be repeated if therapy starts within seven (7) days of their most recent prior assessment.

If the result of a laboratory study that is repeated at any time *post-enrollment* and prior to the *start of protocol therapy* is outside the limits for eligibility, then the evaluation must be rechecked within 48 hours prior to initiating protocol therapy. The results of the recheck must be within the limits for eligibility to proceed. If the result of the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy.

Clinical Studies
Clinical studies (eg, cardiac imaging, pulmonary function tests), if applicable, must be obtained within 21 days prior to *enrollment* and *start of protocol therapy* (repeat if necessary).

Disease/Staging Imaging
Disease/staging imaging studies must be obtained within 21 days prior to *enrollment* and *start of protocol therapy* (repeat if necessary). For patients with diffuse anaplasia, this applies regardless of whether a patient is enrolling and starting protocol therapy at Cycle 1 of UH3; or whether a patient is enrolling after a delayed diagnosis of anaplasia (after initial treatment for presumed favorable histology Wilms tumor) and starting protocol therapy at Cycle 3 of UH3.

___6. Enrollment on AREN03B2
Patients with newly diagnosed Stages 2 - 4 diffuse anaplastic Wilms tumor must be enrolled on AREN03B2 and have received an Initial Risk Assignment showing DAWT (if anaplasia first identified at diagnostic, pre-treatment nephrectomy or biopsy) or a Delayed Nephrectomy Classification showing DAWT (if anaplasia first noted at delayed nephrectomy) **prior to** enrollment on AREN1921.

___7. Prior enrollment on AREN03B2 is not an eligibility requirement for patients with relapsed favorable histology Wilms tumor.

___8. Age
Patients must be ≤ 30 years old at study enrollment.

___9. Diagnosis

Patients with the following diagnoses are eligible for this study:

- Newly diagnosed Stages 2 - 4 diffuse anaplastic Wilms tumor as confirmed by central review. Wilms tumor staging criteria can be found in Appendix III.
- Favorable histology Wilms tumor at first relapse. Relapsed FHWT patients must have previously achieved remission for their initial FHWT diagnosis to be eligible for this study. The relapse risk groups are defined as follows, regardless of radiation therapy:
    a. **Standard-Risk relapse:** Patients who received two chemotherapy agents for frontline therapy; primarily actinomycin D and vincristine.
    b. **High-Risk relapse:** Patients who received three chemotherapy agents for frontline therapy; primarily vincristine, actinomycin D and doxorubicin or vincristine, actinomycin D and irinotecan.
    c. **Very High-Risk relapse:** Patients who received four or more chemotherapy agents as part of initial therapy; primarily Regimen M or its variations.

___10. Patients with newly diagnosed DAWT must have had histologic verification of the malignancy. For relapsed FHWT patients, biopsy to prove recurrence is encouraged, but not required.
Note: for relapsed FHWT patients, an institutional pathology report confirming favorable histology Wilms tumor (from relapse, if available, or from original diagnosis) must be available for upload prior to initiation of protocol therapy. Please refer to Section 14.2.1 for further details.

___11. Timing

Patients with newly diagnosed Stages 2 – 4 diffuse anaplastic Wilms tumor must be enrolled on AREN1921 within 2 weeks of the tumor-directed surgery or biopsy procedure that first confirms a diagnosis of DAWT, whether at initial diagnostic procedure or delayed nephrectomy (such surgery/biopsy is Day 0). For patients who received prior therapy for presumed favorable histology Wilms tumor, later confirmed to have diffuse anaplastic Wilms tumor at subsequent review of the initial biopsy, please see Section 3.2.8.1.

___12. Lymph Node Sampling

Patients with newly diagnosed DAWT who undergo upfront nephrectomy must have at least 1 lymph node sampled prior to study enrollment per Section 13.2.4.

___13. Performance Level

___14. Patients must have a performance status corresponding to ECOG scores of 0, 1 or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age.
Refer to Performance Status Scales Scoring on the COG members website (Protocol Reference Material) and use appropriate score for study population.

___15. Life Expectancy

Patients must have a life expectancy of ≥ 8 weeks.

___16. Prior Therapy

- Diffuse Anaplastic Wilms Tumor
  Patients with diffuse anaplastic histology must have had no prior systemic therapy, except in the following situations:
  – Patients with diffuse anaplastic Wilms tumor who received no more than 12 weeks of pre-nephrectomy chemotherapy for what was originally presumed to be favorable histology Wilms tumor, subsequently confirmed to be diffuse anaplastic Wilms tumor at delayed nephrectomy.
  – Patients with diffuse anaplastic Wilms tumor who received no more than 12 weeks of pre-nephrectomy chemotherapy for what was originally presumed to be favorable histology Wilms tumor, subsequently confirmed to be diffuse anaplastic Wilms tumor at delayed nephrectomy
  – Treatment consisting of vincristine/doxorubicin/ cyclophosphamide initiated on an emergent basis and within allowed timing as described in Section 3.1.5.1.

  Note:
  Patients who received prior therapy for presumed favorable histology Wilms tumor, later identified to have diffuse anaplastic Wilms tumor as per above, must begin study treatment starting at Cycle 3 (Week 7) of Regimen UH-3. For treatment details specific to this group of patients, refer to Sections 4.1 and 4.3.1 for further details.

  Patients who received emergency radiation to preserve organ function are eligible as noted in Section 3.1.5.1.

Patients who received radiation as part of standard of care for presumed newly diagnosed favorable histology Wilms tumor, along with chemotherapy as noted above, prior to identification of diffuse anaplasia, are also eligible.

- Relapsed Favorable Histology Wilms Tumor
  Patients must not have received prior chemotherapy for their relapsed favorable histology Wilms tumor diagnosis.

___17. Relapsed Favorable Histology Wilms Tumor
Patients must not have received prior chemotherapy for their relapsed favorable histology Wilms tumor diagnosis.

In addition, patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.

a. Myelosuppressive chemotherapy: Must not have received within 2 weeks of entry onto this study.
b. Radiation therapy (RT): ≥ 2 wks must have elapsed for local palliative RT (small port); ≥ 6 months must have elapsed if prior craniospinal RT or if ≥ 50% radiation of pelvis; ≥ 6 wks must have elapsed if other substantial BM radiation. Patients with relapsed favorable histology Wilms tumor who received emergency radiation to preserve organ function are eligible and do not need to washout with the above criteria.

___18. Concomitant Medications Restrictions

a. Patients may not be receiving any other investigational agents (within 4 weeks prior to study enrollment).

Please see Section 4.1.2 for the concomitant therapy restrictions for patients during treatment.

___19. Organ Function Requirements
Adequate Bone Marrow Function Defined As:

- Peripheral absolute neutrophil count (ANC) ≥ 750/µL
- Platelet count ≥ 75,000/µL (transfusion independent)
- Hemoglobin ≥ 8.0 g/dL (may receive RBC transfusions)

___20. Adequate Renal Function:
Patients with high-risk or very high-risk relapsed FHWT (Section 3.2.3), who will be treated with Regimen ICE/Cyclo/Topo, must have renal function assessed by creatinine clearance or radioisotope GFR and meet the following requirement:

- Creatinine clearance or radioisotope GFR ≥ 60 mL/min/1.73 m^2 m

Patients diagnosed with Stage 2-4 DAWT or standard-risk relapsed FHWT (Section 3.2.3), who will be treated with Regimen UH-3, may either obtain a creatinine clearance, radioisotope GFR (meeting the above criteria of GFR ≥ 60 mL/min/1.73 m^2), or an adequate serum creatin2ine as per the following table:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating utilizing child length and stature data published by the CDC.

___21. Adequate Liver Function Defined As:

- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age or direct bilirubin ≤ ULN for patients whose total bilirubin > 1.5 x ULN, and
- SGOT (AST) or SGPT (ALT) < 2.5 x upper limit of normal (ULN) for age or ≤ 5x ULN for patients with liver metastases.

___22. Adequate Cardiac Function Defined As:
- Shortening fraction of ≥ 27% by echocardiogram, or
- Ejection fraction of ≥ 50% by radionuclide angiogram

___23. The CIRB has determined that assent of children age 14 and older is a necessary condition for proceeding with the research.

EXCLUSION CRITERIA:

___1. Patients with a history of bilateral Wilms tumor (synchronous or metachronous)

___2. Patients with any uncontrolled, intercurrent illness including, but not limited to, ongoing or active infection, or symptomatic congestive heart failure (defined as Grade 2 or higher heart failure per CTCAE version 5.0)

___3. Relapsed FHWT patients who did not receive frontline chemotherapy (e.g., very low risk FHWT initially observed without chemotherapy) or received only one chemotherapy agent for frontline therapy

___4. For patients with high-risk or very high-risk relapsed FHWT:
- Patients with Renal Tubular Acidosis (RTA) as evidenced by serum bicarbonate < 16 mmol/L and serum phosphate ≤ 2 mg/dL (or < 0.8 mmol/L) without supplementation

___5. For Stages 2-4 DAWT and standard-risk relapsed FHWT patients:
- Chronic inflammatory bowel disease and/or bowel obstruction
- Concomitant use of St. John's wort, which cannot be stopped prior to the start of trial treatment

___6. 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:

Required Observations - Regimen UH-3: Cycles 1, 5, 7, 10, and 13

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

a. Physical exam with vital signs, height and weight. – Prior to each cycle.
b. CBC with differential and platelets. - Weekly
c. Total and direct bilirubin, AST, ALT, total protein/albumin. – Prior to each cycle.
d. BUN, creatinine, and electrolytes, including calcium, magnesium, and phosphorus – Prior to each cycle.
e. Urinalysis – Prior to each cycle.
f. ECHO or MUGA – Prior to the start of Cycles 1, 7, and 13.
g. CT or MRI of abdomen and pelvis or abdominal ultrasound (See Section 16.2) – Prior to Cycles 1, 5, and 13.
h. CT chest or chest x-ray (See Section 16.2) – Obtain prior to Cycles 1, 5, and 13.
i. When metastases outside the chest, abdomen, or pelvis are clinically suspected by symptoms or signs, CT/MRI (for brain/soft tissue metastases) or Bone/PET scan (for bone metastases) of metastatic sites – Obtain prior to Cycle 1. If metastases in such loci are confirmed at baseline, similar repeat assessments should be obtained for the involved site(s) prior to Cycles 5 and 13.
j. Audiogram – may be obtained any time prior to or during Cycle 1 in the case of logistical constraints.
k. Pregnancy test. Female patients of childbearing potential require a negative pregnancy test prior to starting treatment. – required prior to Cycle 1 only.
l. Specimens for optional studies – Obtain prior to Cycle 1 only. See Section 15.2 and Appendix II for complete details.

Required Observations – Regimen ICE/Cyclo/Topo: Cycles 1, 2, 4, 5, 7, and 9

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

a. Physical exam with vital signs, height and weight. – Prior to each cycle.
b. CBC with differential and platelets. - Weekly
c. Total and direct bilirubin, AST, ALT, total protein/albumin – Prior to each cycle.
d. BUN, creatinine, and electrolytes, including calcium, magnesium, phosphorus, and bicarbonate – Prior to each cycle.
e. Urinalysis – Prior to each cycle.
f. ECHO – Prior to Cycle 1 only.
g. GFR or creatinine clearance – Prior to Cycles 1, 4, and 7, and whenever serum creatinine is > 1.5x ULN.
h. Audiogram – Prior to Cycle 1 only.
i. CT or MRI of abdomen and pelvis or abdominal ultrasound (See Section 16.2) – Obtain prior to Cycles 1, 4, and 7.
j. CT chest or chest x-ray (See Section 16.2) – Obtain prior to Cycles 1, 4, and 7.
k. When metastases outside the chest, abdomen, or pelvis are clinically suspected by symptoms or signs, CT/MRI of metastatic sites (for brain/soft tissue metastases) or Bone/PET scan (for bone metastases) of metastatic sites – Obtain prior to Cycle 1. If metastases in such loci are confirmed at baseline, similar repeat assessments should be obtained for the involved site(s) prior to Cycles 4 and 7. Sites may omit pre-Cycle 7 scans if definitive local control (radiation/surgery) has been provided to a particular metastatic site.
l. Pregnancy test. Female patients of childbearing potential require a negative pregnancy test prior to starting treatment. – required prior to Cycle 1 only.
m. Specimens for optional studies – See Section 15.2 and Appendix II for complete details.
    - Obtain specimens prior to Day 1 during Cycles 1, 2, 4, 5 and 9.
    - On Day 3 of Cycles 1, 5 and 9, obtain urine specimen 12-24 hours post-Day 3 ifosfamide infusion.

TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5.

SPECIMEN REQUIREMENTS:

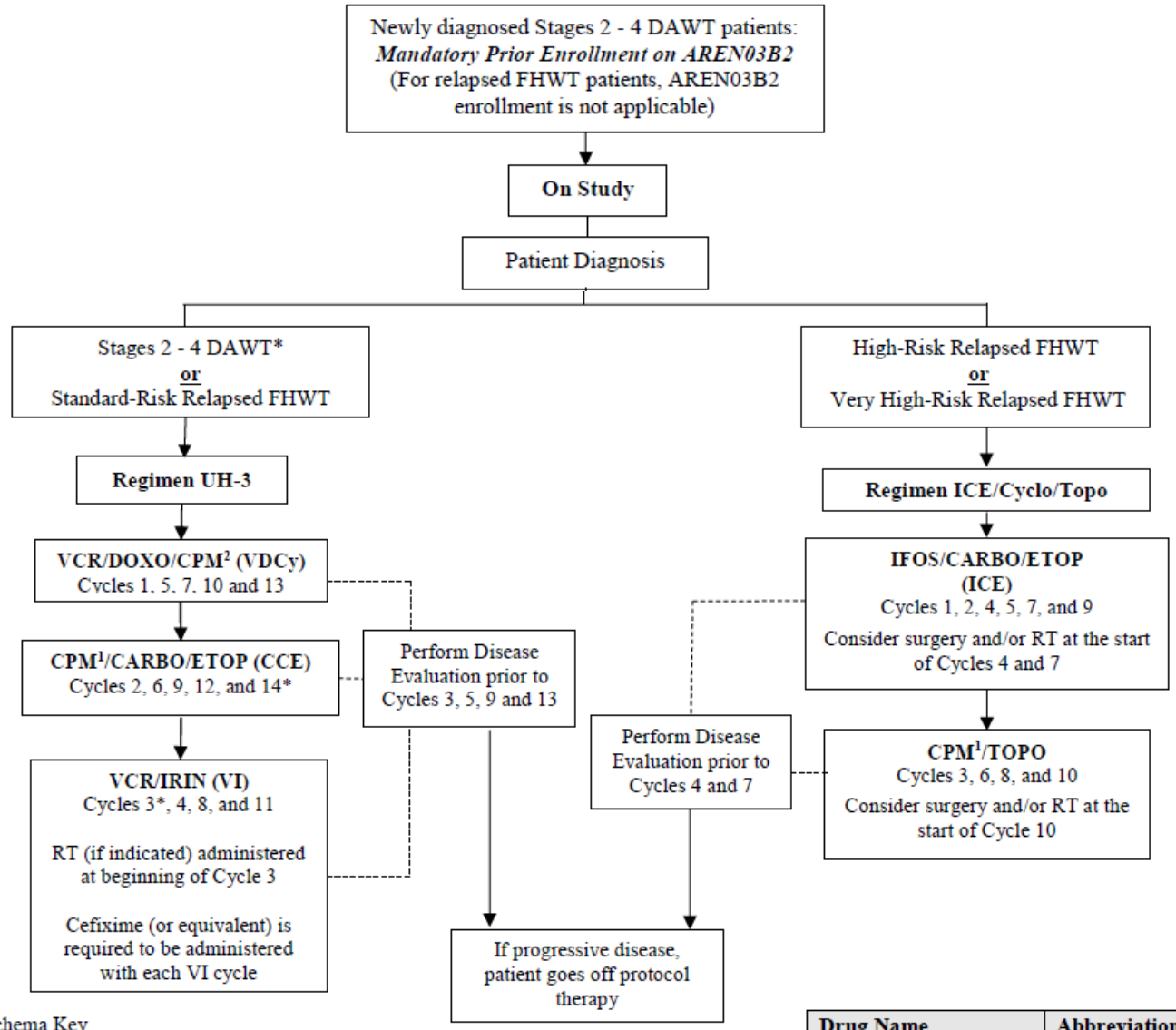
Per AREN03B2 for DAWT, for relapsed FHWT - See Section 14.2.

BIOLOGY REQUIREMENTS:

Optional labs – See Appendix II and Section 15.
Every effort should be made to obtain samples from all timepoints.

TREATMENT PLAN:

EXPERIMENTAL DESIGN SCHEMA



Schema Key

DAWT: Diffuse anaplastic Wilms tumor

FHWT: Favorable histology Wilms tumor

Standard-Risk relapsed FHWT: Patients who received two chemotherapy agents during initial therapy.

High-Risk relapsed FHWT: Patients who received three chemotherapy agents during initial therapy.

Very High-Risk relapsed FHWT: Patients who received four or more chemotherapy agents as part of initial therapy.

*** Patients who received prior therapy for presumed favorable histology Wilms tumor, subsequently confirmed to have Stages 2 – 4 DAWT, will begin study treatment starting at Cycle 3 of Regimen UH-3.** In addition, these patients will receive an extra cycle of CCE after the end of Cycle 14 to make up for the missed cycle of CCE (Cycle 2), but the missed VDCy cycle (Cycle 1) will not be made up. See Sections 3.2.8.1, 4.1, and 4.3.1 for further details.

Drug Name	Abbreviation
Carboplatin	CARBO
Cyclophosphamide (400 mg/m^2/dose)	CPM[1]
Cyclophosphamide (1200 mg/m^2/dose)	CPM[2]
Doxorubicin	DOXO
Etoposide	ETOP
Ifosfamide	IFOS
Irinotecan	IRIN
Topotecan	TOPO
Vincristine	VCR