ARAR2331: Prospective Treatment of Types I, II and III Pleuropulmonary Blastoma (PPB) A COG Groupwide Phase 3 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. Reservation Requirements Prior to obtaining informed consent and enrolling a patient, a reservation must be made following the steps in **Section 3.1.3.** Reservations may be obtained 24 hours a day through the Oncology Patient Enrollment Network (OPEN) system. Patients must be enrolled within 5 calendar days of making a reservation.

___2. Timing
Patients with locally determined Type I/Ir PPB or for whom there is uncertainty for Type I vs II PPB
Chemotherapy is not administered to patients with Type Ir PPB and is administered only to a subset of patients with Type I PPB. Enrollment and central pathology review must take place before starting chemotherapy. Central pathology review outcome is required for treatment assignment (See Section 14.3.1). Submission of tissue for central review must be projected to occur no later than 14 calendar days after enrollment.

___3. Patients with Type I PPB assigned to receive VAC/VA chemotherapy following Central Review must be projected to begin protocol therapy within 14 days after return of results or 60 days after resection, whichever is later. Patients determined to have Type II or III PPB on Central Review must be projected to begin protocol therapy within 7 days of return of results.

Patients with locally determined Type II/III PPB
Study enrollment must take place within five (5) calendar days of beginning protocol therapy. If enrollment takes place before starting therapy, the date protocol therapy is projected to start should generally be no later than five (5) calendar days after enrollment. However, for patients with type II or III PPB with completely resected disease, sites may choose to await the results of central pathology review before starting therapy. Submission of tissue for central pathology review must be no later than five (5) calendar days after enrollment (see Section 14.3.1). In patients for whom the site chose to wait for central path review, treatment must be projected to begin within 7 days of return of results if Type II or III PPB is confirmed.

PATIENTS MUST SIGN CONSENT BEFORE RECEIVING PROTOCOL THERAPY ON ARAR2331.

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

___4. In order for an institution to maintain COG membership requirements, every patient with a known or suspected neoplasm needs to be offered participation in *APEC14B1, THIS PROTOCOL IS FOR RESEARCH Project:EveryChild A Registry, Eligibility Screening, Biology and Outcome Study, and the*

NCI-sponsored Molecular Characterization Initiative (MCI) through the Childhood Cancer Data Initiative (CCDI). The MCI is open to newly diagnosed patients with rare tumors, including Types I, Ir, II and III PPB, and provides comprehensive molecular testing at diagnosis, including germline, with rapid return of results at no cost to patient/family or institution. Enrollment on APEC14B1 is highly encouraged.

Laboratory Studies: Clinical laboratory studies are only required for patients assigned to receive chemotherapy.

All laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Please note that laboratory studies are not required prior to enrollment for children with Type I or Ir PPB.

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), if applicable, must be obtained within 21 days prior to start of protocol therapy (repeat if necessary).

Disease/Staging Imaging
For Type II or III PPB patients, disease/staging imaging studies, must be obtained within 21 days prior to enrollment and start of protocol therapy (repeat if necessary).

For Type I or Ir PPB patients, post-operative imaging may occur before or after enrollment.

INCLUSION CRITERIA

___**1.** Age 21 years of age or younger.
___**2.** Diagnosis Newly Diagnosed PPB. Note that patients with known germline DICER1 variant or mosaicism with a large, solid unresectable thoracic mass with imaging features characteristic for Type II or III PPB are eligible without histologic confirmation of the diagnosis if a biopsy of the mass is not considered safe or feasible.
Individuals are eligible based on institutional diagnosis of Type I, Ir, II or III PPB diagnosed within 60 days prior to enrollment. Children with Type II or III PPB at risk for clinical decompensation may receive protocol therapy while awaiting rapid central pathology review. Children with Type I or Ir PPB will be assigned to chemotherapy vs. observation based on imaging and central pathology review diagnosis. Type I and Ir patients should not begin chemotherapy prior to return of central pathology results.

___3. Organ Function Requirements
There are no specific organ function requirements for patients with Type I or Ir PPB.
For patients with Type II or III PPB, the following criteria apply:

- Adequate renal function defined as:
  - A serum creatinine based on age/sex as follows:

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 GFR[13] utilizing child length and stature data published by the CDC.

OR - a 24 hour urine Creatinine clearance ≥ 60 mL/min/1.73 m2

OR - a GFR ≥ 60 mL/min/1.73 m2 . GFR must be performed using direct measurement with a nuclear blood sampling method OR direct small molecule clearance method (iothalamate or other molecule per institutional standard).

Note: Estimated GFR (eGFR) from serum creatinine, cystatin C or other estimates are not acceptable for determining eligibility.

- Adequate liver function defined as:
  - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
  - SGPT (ALT) ≤ 135 U/L*

** Note: For the purpose of this study, the ULN for SGPT (ALT) has been set to the value of 45 U/L*

- Adequate cardiac function defined as:
  - Shortening fraction of ≥ 27% by echocardiogram, or
  - Ejection fraction of ≥ 50% by radionuclide angiogram.

- HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible as long as they are NOT receiving antiretroviral agents that are strong inhibitors or inducers of CYP3A4. See Concomitant Therapy Restrictions Section 4.1.8.

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

EXCLUSION CRITERIA:

___1. Administration of prior PPB-directed chemotherapy is an exclusion criterion. Prior treatment for another malignancy is not an exclusion criterion.

___2. Patients with known Charcot-Marie-Tooth disease.

___3. 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:

Please note that laboratory studies are not required prior to enrollment for Children with TipeI or IrPPB

1. Required Observations - Regimen VAC1200/VA, Cycles 1-3 (VAC1200)
   All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

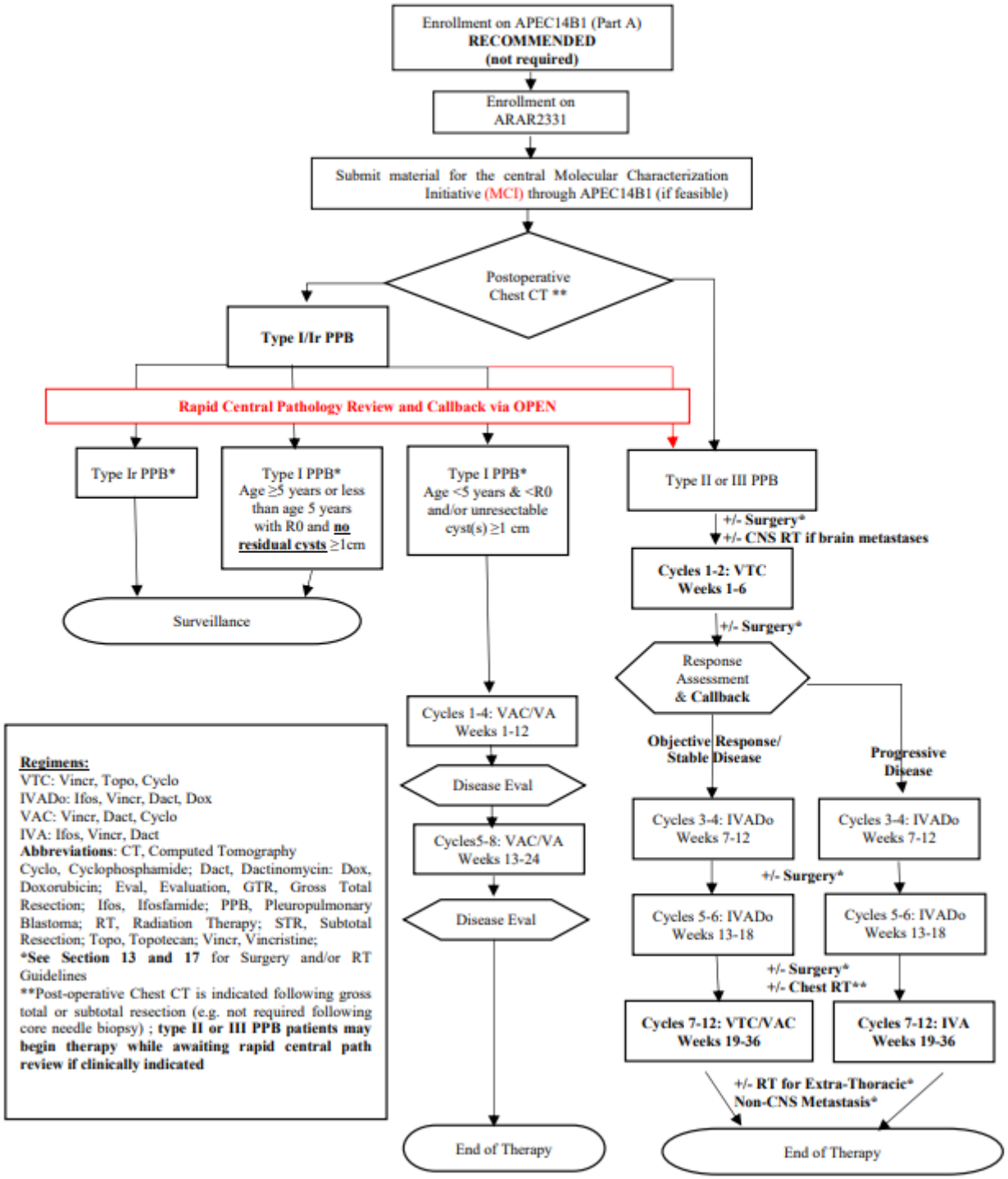
   a. Physical exam with vital signs, height and weight. Note: Height is required prior to each cycle.
   b. CBC, differential and platelets.
   c. Bilirubin, AST, ALT, albumin, creatinine
   d. Electrolytes, BUN, Ca++, PO4, Mg++
   e. Urinalysis
   f. GFR or Creatinine Clearance if clinically indicated
   g. Tumor Imaging (chest CT and abdominal ultrasound)
   h. ctDNA sample
   i. Pregnancy test. Female patients of childbearing potential require a negative pregnancy test prior to each cycle.
2. Required Observations - Regimen VAC1200/VA, Cycle 4 (VAC1200)
   All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

   a. Physical exam with vital signs, height and weight. Note: Height is required prior to each cycle. b. CBC, differential and platelets.
   c. Bilirubin, AST, ALT, albumin, creatinine
   d. Electrolytes, BUN, Ca++, PO4, Mg++
   e. Urinalysis
   f. Pregnancy test. Female patients of childbearing potential require a negative pregnancy test prior to each cycle.

TREATMENT PLAN:

This study will be open to any patient 21 years of age or younger with Type I, Ir, II or III PPB. Individuals are eligible based on institutional diagnosis of Type I, Ir, II or III PPB. Children with Type II or III PPB at risk for clinical decompensation may receive protocol therapy while awaiting rapid central pathology review. Children with Type I or Ir PPB will be assigned to chemotherapy vs. observation based on central pathology review diagnosis and imaging and should not begin chemotherapy prior to return of central pathology results.

Types II and III PPB: All individuals with Types II or III PPB will receive a window chemotherapy regimen consisting of 2 cycles of VinCRIStine, Topotecan and CycloPHOSphamide (VTC400) with response assessment at 6 weeks using RECIST criteria.



TOXICITIES AND DOSAGE MODIFICATIONS: See Section 5

SPECIMEN REQUIREMENTS:

If patient enrolled on APEC, see MOP section 11.

Please note that patients remain eligible for ARAR2331 regardless of availability of tissue for APEC14B1 MCL. See protocol section 15.

BIOLOGY REQUIREMENTS:

If patient enrolled on APEC, see MOP section 11.

Please note that patients remain eligible for ARAR2331 regardless of availability of tissue for APEC14B1 MCL. See protocol section 15.