COG-AGCT1531: A Phase 3 Study of Active Surveillance for Low Risk and a Randomized Trial of Carboplatin vs. Cisplatin for Standard Risk Pediatric and Adult Patients with Germ Cell Tumors

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. Timing
Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than **five (5)** calendar days after the date of study enrollment.
___2. Newly diagnosed patients must be enrolled within 6 weeks (42 days) of diagnostic biopsy or surgery.
___3. For Low Risk patients, recommended imaging studies must be obtained within 8 weeks prior to enrollment (repeat the tumor imaging if clinically indicated). See Section 4.2.1 for Immature Teratoma imaging or Section 4.3.1 for Low Risk MGCT imaging
___4. For Standard Risk patients, recommended imaging studies must be obtained within 14 days prior to enrollment (repeat tumor imaging if clinically indicated). See Section 4.4.2 for Standard Risk 1 patients or 4.10.2 for Standard Risk 2 patients
___5. All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.
___6. The CIRB has determined that assent of children age 14 and older is a necessary condition for proceeding with the research.
___7. Retrospective Central Pathology Review
Central pathology review is always required and material should be submitted within three (3) weeks of enrollment. Tissue must be submitted for permanent sections and immunohistochemical analysis (see Section 14).
___8. **All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > 7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, if applicable, must be obtained within 8 weeks prior to enrollment for Low Risk patients, and within 14 days prior to enrollment for Standard Risk patients (repeat the tumor imaging if necessary).**
___9. Rapid Central Surgical Review
After enrollment on the low risk stratum, a central review will be performed by study surgeons and study chair **within 7 days of enrollment.** See Surgical Guidelines (Section 13) for detailed recommendations. The following must be submitted **within 72 hours of enrollment** via RAVE in order for central review to be completed within 7 days of enrollment:
- Surgical checklist,
- Operative note,
- Pathology report,
- Imaging report,
- Cytology report, if applicable, and
- Stage I Verification CRF.

If the review concludes that incomplete staging has occurred or that the patient has evidence of a higher stage, the treating physician may decide to transfer the patient to the standard-risk stratum if all eligibility requirements are met. Treatment randomization for those patients who will transfer to a standard-risk stratum will be accomplished by

completing the Late Randomization Callback in OPEN. **The callback must be completed prior to initiation of chemotherapy.**

___10. Note: Patients initially enrolled on the low risk stratum may be able to transfer to a standard risk stratum in certain circumstances (see Section 3.1.6, 4.2.2 and 4.3.2). Treatment randomization for these patients will be accomplished by completing the Late Randomization Callback in OPEN. **The callback must be completed prior to initiation of chemotherapy.**

___11. Age

- Low Risk Stratum (Stage I Ovarian Immature Teratoma and Stage I Malignant GCT (all sites))
  Patients must be < 50 years of age at enrollment.
- Standard Risk 1
  Patient must be < 11 years of age at enrollment.
- Standard Risk 2
  Patients must be ≥ 11 and < 25 years of age at enrollment.

___12. Diagnosis

Newly diagnosed patients must have histologic verification of a primary extracranial germ cell tumor in any of the categories outlined in the table below. Elevation of serum tumor markers without histologic confirmation is not sufficient for entry on the trial.
For COG, FIGO, AJCC and IGCCC staging criteria see Appendix II, Appendix III, Appendix IV and Appendix V, respectively.
NOTE: for low risk patients, materials for rapid surgical central review must be sent within 7 days of study enrollment. See Section 3.1.6.

___13. Performance Level

Patients must have a performance status corresponding to ECOG scores of 0, 1, 2 or 3. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age (see Appendix VI).

___14. Organ Function Requirements

Organ function requirements apply ONLY to patients who will receive chemotherapy (SR1 and SR2 patients).

- 3.2.4.1 Adequate renal function defined as:
  - Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m^2 or
  - A serum creatinine based on age/gender 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 (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

- Adequate liver function defined as:
  - Total bilirubin ≤ 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 (for the purpose of this study, the ULN for SGPT is 45 U/L).
- Adequate pulmonary function defined as:
  - No evidence of dyspnea at rest, no exercise intolerance, and a pulse oximetry > 94% if there is clinical indication for determination.
    Pulmonary Function Tests (PFTs) are not required.

___15. Eligibility Criteria to Participate in the Pilot Study of the AYA-Hears Instrument (PROs of Ototoxicity) – See Section 3.2.6

EXCLUSION CRITERIA:

___1. Patients with any diagnoses not listed in the table in Section 3.2.2 including:
- Stage I testicular cancer patients who have undergone primary RPLNC (retroperitoneal lymph node dissection),
- Pure dysgerminoma and pure seminoma,
- Pure mature teratoma,
- Pure immature teratoma COG Stage I, Grade I
- Pure immature teratoma COG Stage I, Grade 2, 3 with AFP ≥ 1000 ng/mL,
- Pure immature teratoma COG Stage II - IV or FIGO Stage IC to IV,
- Poor risk disease (age ≥ 11 years old and COG Stage IV ovarian, COG Stage III or IV EG, or IGCCC (see Appendix V) intermediate or poor risk testicular), or
- Primary CNS germ cell tumor.

___2. Patients must have had no prior systemic therapy.

___3. Patients must have had no prior radiation therapy with the exception of CNS irradiation of brain metastases. (This exception only applies to SR1 patients; any patients over age 11 with distant metastases to brain [Stage IV disease] would be considered poor risk and therefore not eligible for this trial.)

___4. Patients with significant respiratory compromise due to either abdominal tumor limiting diaphragmatic excursion or pulmonary metastases should not receive bleomycin and are ineligible for the trial.

___5. Pregnancy and Breast Feeding

These criteria apply ONLY to patients who will receive chemotherapy (SR1 and SR2 patients).
- 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.

___6. Concomitant Therapy
- Sodium Thiosulfate (STS) should not be administered to any patient on this trial.

REQUIRED OBSERVATIONS:

Low Risk Stage I Grade 2, 3 Ovarian Immature Teratoma

Required Observations at baseline

Required Studies to be Obtained
- History &physical exam with VS
- Performance status
- α-FP, β-HCG, LDH

Recommended Baseline Imaging to be Obtained
- Abdominal/Pelvic CT or MRI
- Chest CT
- CT or MRI of brain only if clinically indicated

Participation in Optional Banking Studies is strongly encouraged. See Section 15.0 and Appendix VIII for Optional Banking Specimen collection schedules.

Low Risk Stage I MGCT
Required and Optional Observations
Required Studies to be Obtained
- History & physical exam with VS
- Performance status
- α-FP, β-HCG, LDH

Recommended Baseline Imaging to be Obtained
- CT or MRI of primary site - Extragonadal
- Testicular ultrasound - Testes
- Abdominal/Pelvic CT or MRI – All patients
- Chest CT - All patients
- CT or MRI of brain - Only if clinically indicated

Participation in Optional Banking Studies is strongly encouraged. See Section 15.0 and Appendix VIII for Optional Banking Specimen collection schedules.

Required and Optional Observations - Standard Risk 1: Arm CEb – Cycle 1
- History, physical exam, Ht, Wt
- Performance status
- CT or MRI of brain, if clinically indicated
- Chest CT
- CT or MRI of abdomen/pelvis (all primary sites)
- Imaging of the primary site:
  - If primary site is testicular: Ultrasound of testes
  - If primary site is extragonadal: CT or MRI of primary site
  - If primary is ovarian: CT or MRI of abdomen/pelvis
- CBC, differential, platelets
- Electrolytes including Ca, PO_4, Mg^{++}
- BUN, creatinine
- AST, ALT, alkaline phosphatase, bilirubin
- Total serum protein/albumin
- Urinalysis
- α-FP, β-HCG, LDH (see Section 4.4.4)
- Audiogram/BAER (submit for rapid central review; see Appendix X)
- Pulmonary function tests
- Pregnancy test for all females of childbearing potential
- Discuss fertility preservation with both genders.
- Optional banking specimens (see Section 15.0 and Appendix VIII)*

* Only obtain in patients who have consented to participation in this component of the trial.

Required and Optional Observations– Standard Risk 1: Arm PEb – Cycle 1

- History, physical exam, Ht, Wt
- Performance status
- CT or MRI of brain, if clinically indicated
- Chest CT
- CT or MRI of abdomen/pelvis (all primary sites)
- Imaging of primary site:
  - If primary site is testicular: Ultrasound of testes
  - If primary site is extragonadal: CT or MRI of primary site
  - If primary is ovarian: CT or MRI of abdomen/pelvis
- CBC, differential, platelets
- Electrolytes including Ca, PO4, Mg++
- BUN, creatinine
- AST, ALT, alkaline phosphatase, bilirubin
- Total serum protein/albumin
- Urinalysis
- α-FP, β-HCG, LDH (see Section 4.7.4)
- Audiogram/BAER (submit for rapid central review, see Appendix X)
- Pulmonary function tests
- Pregnancy test for all females of childbearing potential
- Discuss fertility preservation with both genders.
- Optional banking specimens (see Section 15.0 and Appendix VIII)

* Only obtain in patients who have consented to participation in this component of the trial.

Required and Optional Observations – Standard Risk 2: Arm BEC – Cycle 1

- History, physical exam, Ht, Wt
- Performance status
- CT or MRI of brain, if clinically indicated
- Chest CT
- CT or MRI of abdomen/pelvis (all primary sites)
- Imaging of primary site:
  - If primary site is testicular: Ultrasound of testes
  - If primary site is extragonadal: CT or MRI of primary site
  - If primary is ovarian: CT or MRI of abdomen/pelvis
- CBC, differential, platelets
- Electrolytes including Ca, PO_4, Mg^{++}
- BUN, creatinine
- AST, ALT, alkaline phosphatase, bilirubin
- Total serum protein/albumin
- Urinalysis
- α-FP, β-HCG, LDH (see Section 4.10.4)
- Audiogram/BAER (submit for rapid central review, see Appendix X)
- Pulmonary function tests
- Pregnancy test for all females of childbearing potential
- Sperm banking for male patients prior to start of treatment (optional)
- Discuss fertility preservation with both genders.
- Optional banking specimens* (see Section 15.0 and Appendix VIII)
- PRO and QOL* (See Section 16.0)

* Only obtain in patients who have consented to participation in this component of the trial.

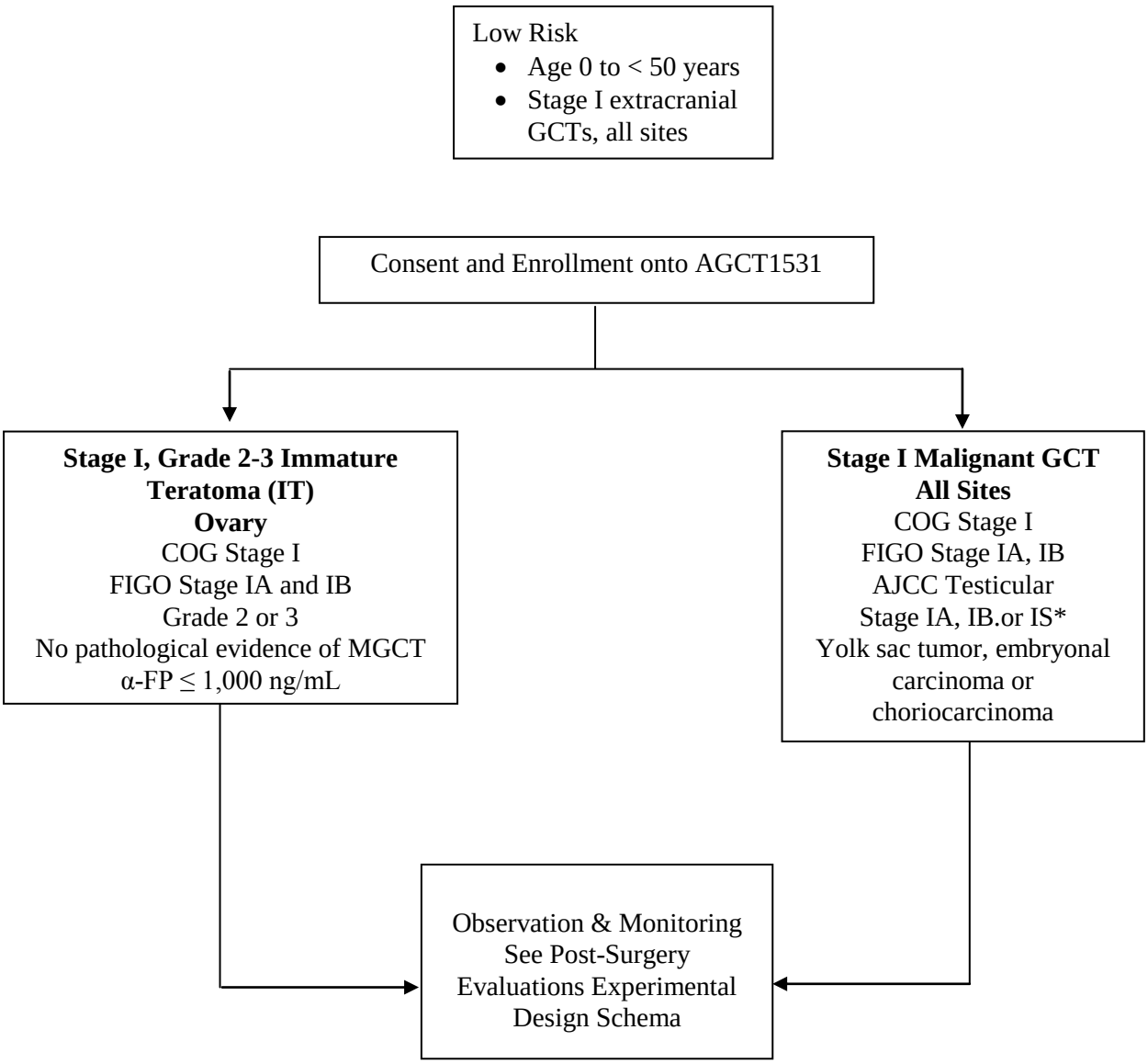
Required Observations and Optional– Standard Risk 2: Arm BEP – Cycle 1

- History, physical exam, Ht, Wt
- Performance status
- CT or MRI of brain, if clinically indicated
- Chest CT
- CT or MRI of abdomen/pelvis (all primary sites)
- Imaging of primary site:
  - If primary site is testicular: Ultrasound of testes
  - If primary site is extragonadal: CT or MRI of primary site
  - If primary is ovarian: CT or MRI of abdomen/pelvis
- CBC, differential, platelets
- Electrolytes including Ca, PO_4, Mg^{++}
- BUN, creatinine
- AST, ALT, alkaline phosphatase, bilirubin
- Total serum protein/albumin
- Urinalysis
- α-FP, β-HCG, LDH: Day 1, 8 and 15 (see Section 4.13.4)
- Audiogram/BAER (submit for rapid central review, see Appendix X)
- Pulmonary function tests
- Pregnancy test for all females of childbearing potential
- Sperm banking for male patients prior to start of treatment (optional)
- Discuss fertility preservation with both genders.
- Optional banking specimens* (see Section 15.0 and Appendix VIII)
- PRO and QOL* (See Section 16)

* Only obtain in patients who have consented to participation in this component of the trial.

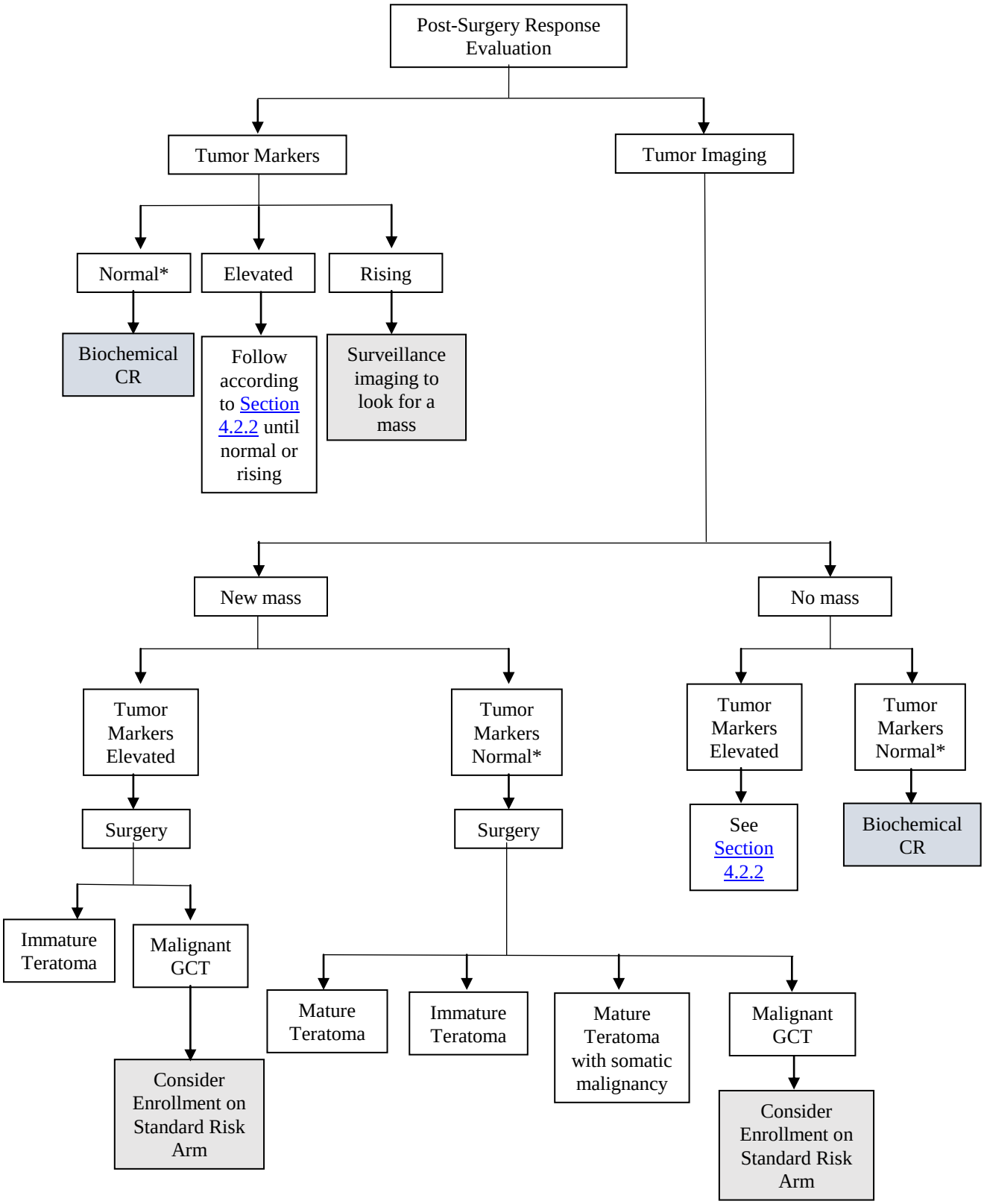
TREATMENT PLAN:

EXPERIMENTAL DESIGN SCHEMA: LOW RISK (LR)



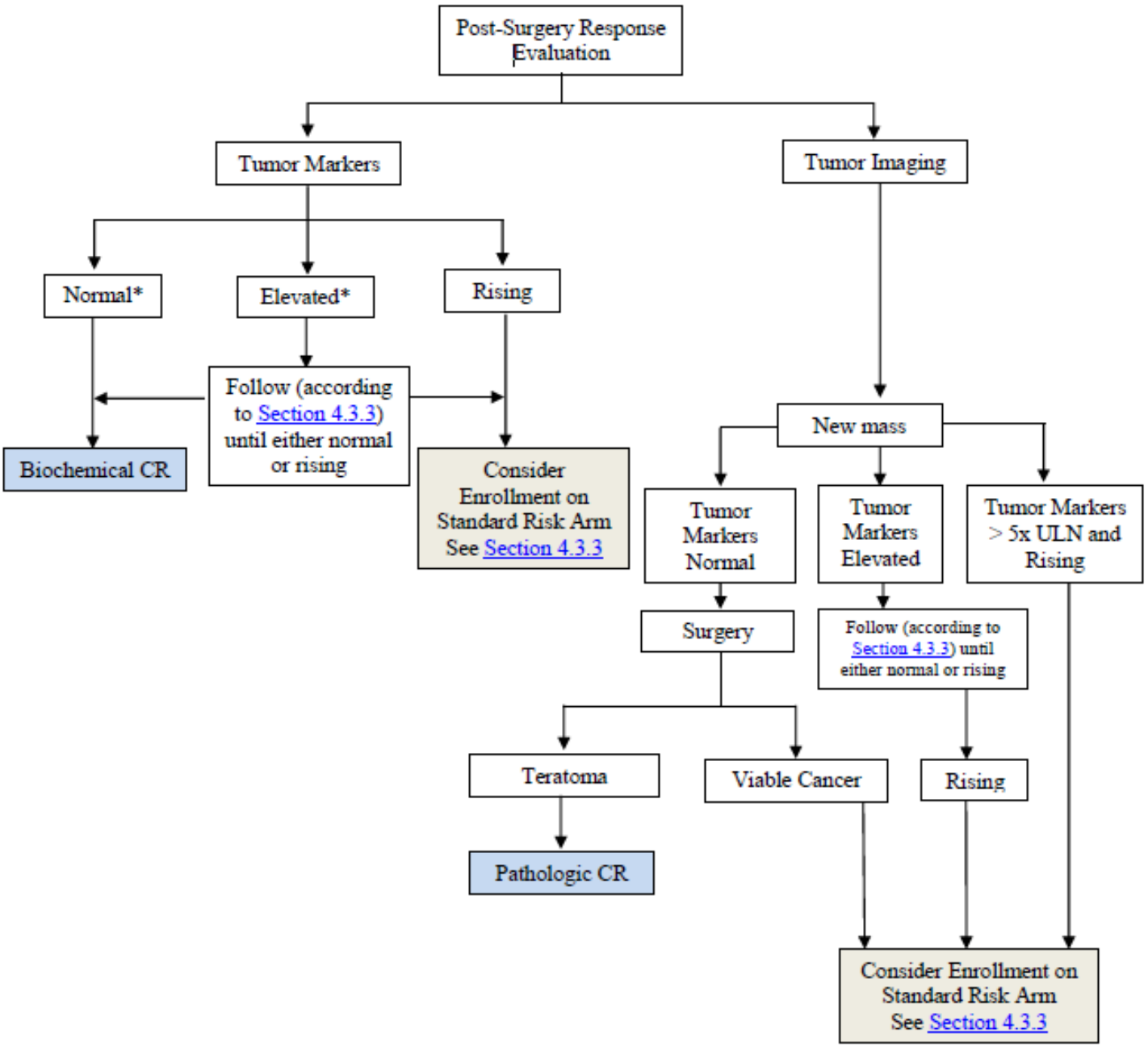
*Post-op tumor markers need to be lower (falling) compared to pre-op tumor markers.
Note: IGCCC criteria DO NOT apply to Low Risk/Stage I patients

EXPERIMENTAL DESIGN SCHEMA: POST-SURGERY EVALUATIONS FOR STAGE I GRADE 2, 3 OVARIAN IMMATURE TERATOMA



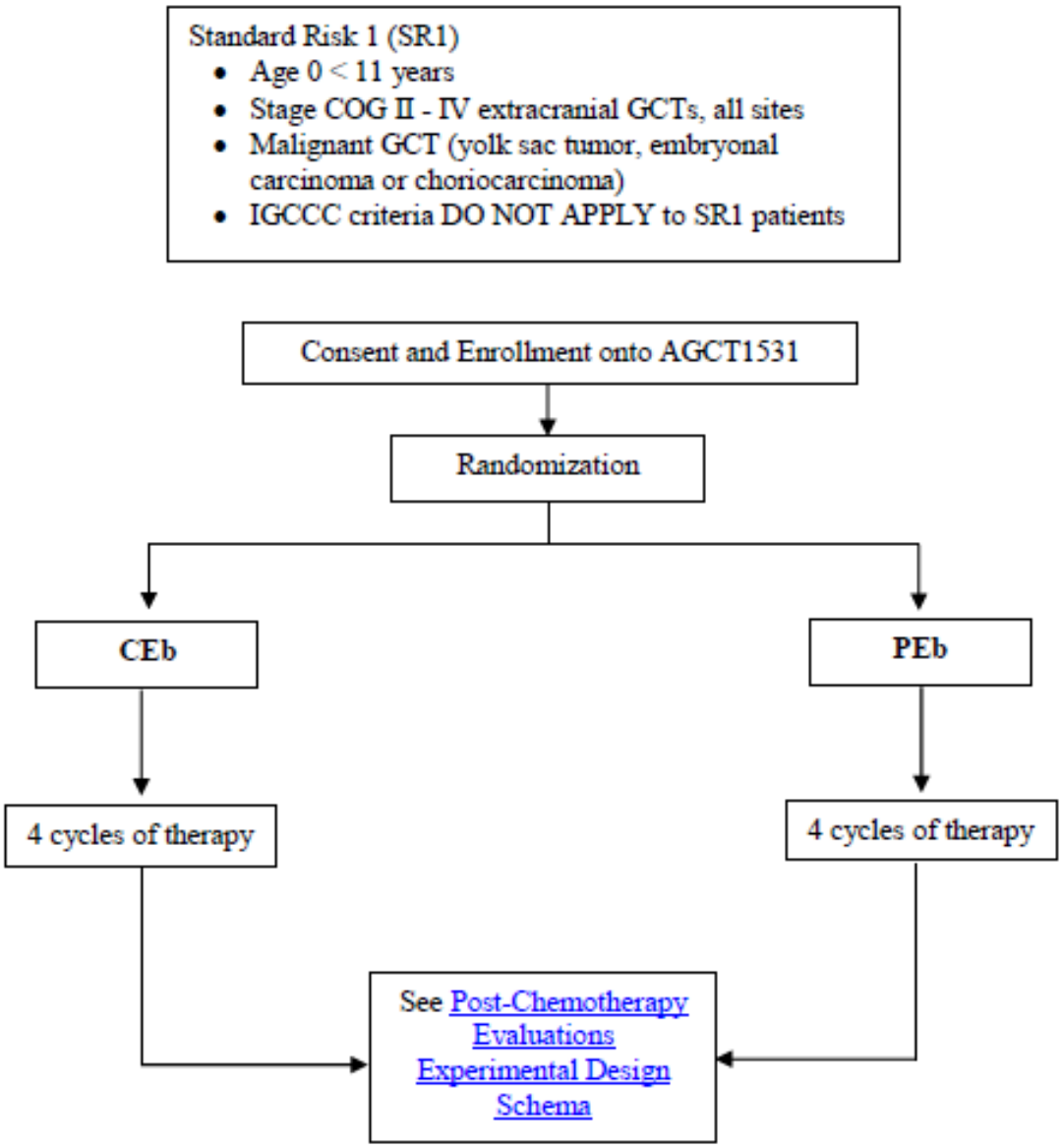
* Tumor markers are considered normal for this protocol if α-FP and β-HCG are less than 5 times the upper limit of institutional normal.

EXPERIMENTAL DESIGN SCHEMA: POST-SURGERY EVALUATIONS FOR STAGE I MALIGNANT GCT



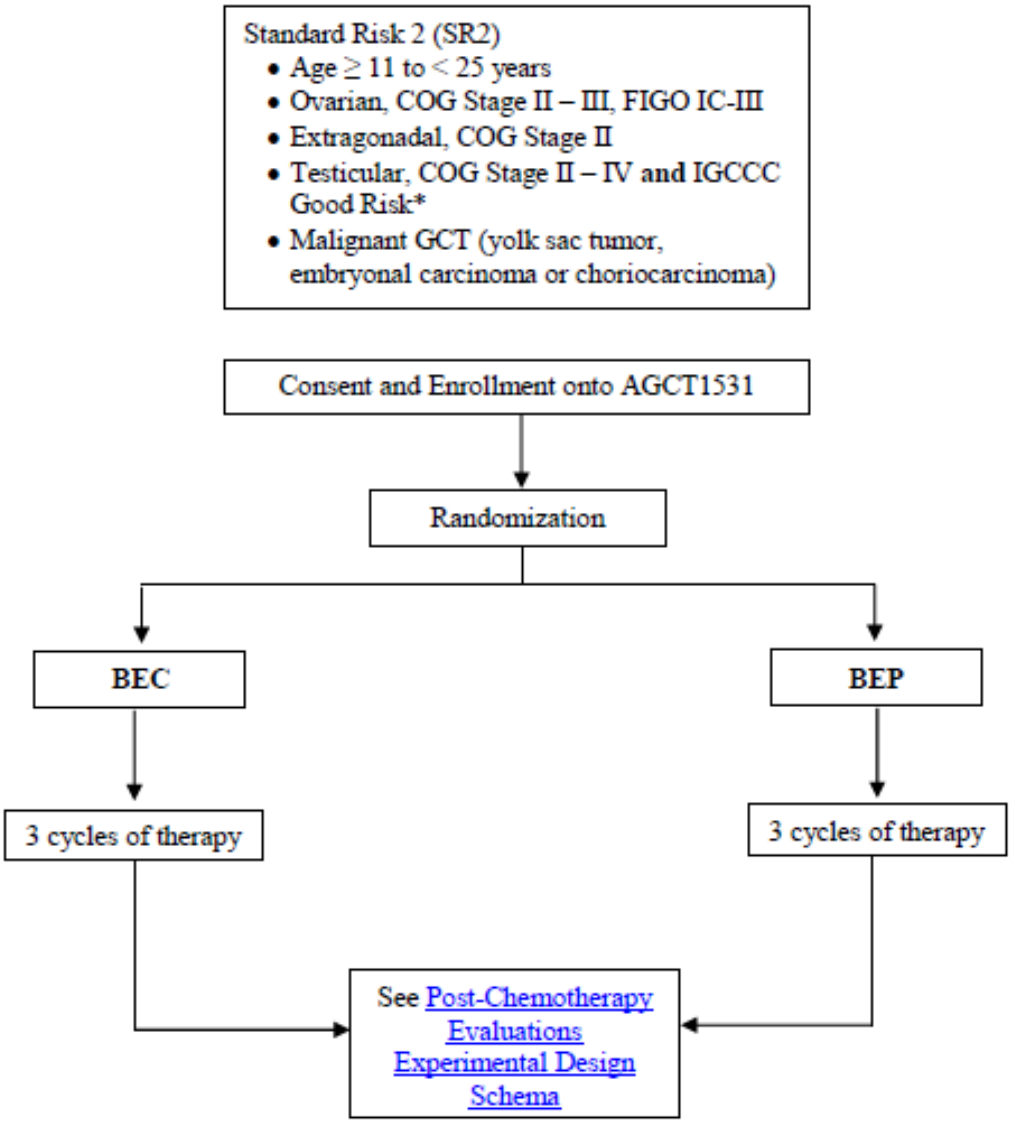
* Tumor markers are considered normal for this protocol if α-FP and β-HCG are less than 5 times the upper limit of institutional normal.

EXPERIMENTAL DESIGN SCHEMA: STANDARD RISK 1 (SR1)



C = CARBOplatin
P = CISplatin
E = Etoposide
b = Bleomycin

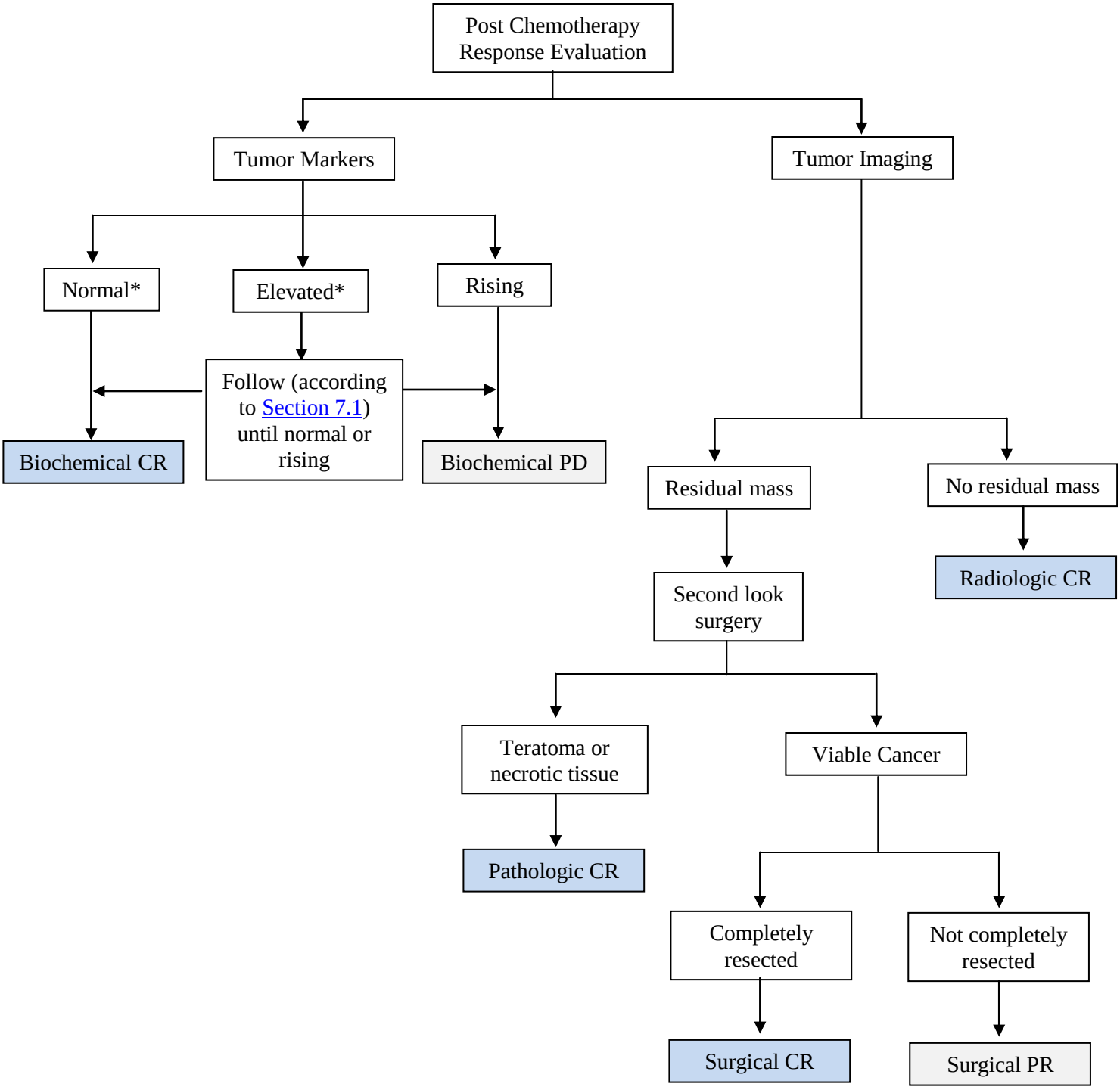
EXPERIMENTAL DESIGN SCHEMA: STANDARD RISK 2 (SR2)



B = Bleomycin
E = Etoposide
C = CARBOplatin
P = CISplatin

*IGCCC: Use **post-op** tumor marker levels to determine IGCCC risk category. IGCCC criteria apply ONLY to patients with a testicular primary tumor.

EXPERIMENTAL DESIGN SCHEMA: POST-CHEMOTHERAPY EVALUATIONS



* Tumor markers are considered normal for this protocol if α-FP and β-HCG are less than 5 times the upper limit of institutional normal.

TOXICITIES AND DOSAGE MODIFICATIONS:
See Section 5.0.

SPECIMEN REQUIREMENTS:
See Section 15.0 – Optional Banking Studies

Tissue (if not enrolled on APEC14B1)

- Snap frozen tumor tissue from primary and any metastatic site
- A block or 20 unstained slides cut sequentially from one representative block

Blood* - 5 mL in EDTA

Serum* - 5mL in a red top, spin and freeze

Plasma* - 10mL in EDTA, spin and freeze

Urine* - 10mL

*standard risk patients