

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. Patients on the Low Risk arms must be enrolled within 6 weeks (42 days) of diagnostic biopsy or surgery.
- ___ 3. Patients on the Standard Risk arms must be enrolled within 6 weeks (42 days) of diagnostic biopsy or surgery with the following exceptions:
 - A patient who initially has Stage I disease, not enrolled on AGCT1531, and was under surveillance post-surgery off study. This patient may be enrolled on one of the Standard Risk arms at recurrence if all relevant eligibility criteria **and** criteria in [Section 4.3.3](#) are met.
 - A patient who initially had a mature/immature teratoma, not enrolled on AGCT1531, and was under surveillance post-surgery off study. If this patient recurs with a malignant germ cell tumor per the criteria in [Section 4.2.2](#), the patient may be enrolled on one of the Standard Risk arms at recurrence if all relevant eligibility criteria are met.
- ___ 4. For Low Risk patients, recommended imaging studies should be obtained within 8 weeks prior to enrollment (repeat the tumor imaging if clinically indicated). See [Section 4.2.1](#) for Immature Teratoma imaging, [Section 4.3.1](#) for Low Risk Non-Seminoma MGCT imaging, or [Section 4.4.1](#) for Low Risk Seminoma MGCT imaging.
- ___ 5. For Standard Risk patients, recommended imaging studies should be obtained within 14 days prior to enrollment (repeat tumor imaging if clinically indicated). See [Section 4.5.2](#) for Standard Risk 1 patients or [4.11.2](#) for Standard Risk 2 patients.
- ___ 6. 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.
- ___ 7. The CIRB has determined that assent of children age 14 and older is a necessary condition for proceeding with the research.
- ___ 8. 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](#)).
- ___ 9. **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. The recommended 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 (clinical judgement should be used to determine if repeating the tumor imaging is necessary).**
- ___ 10. Low Risk/Stage 1 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.**

- ___ 11. 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.**
- ___ 12. Age
- There is no age limit for the Low Risk Stratum (Stage I Ovarian Immature Teratoma and Stage I Non-Seminoma or Seminoma Malignant GCT (all sites))
 - 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.
- ___ 13. Diagnosis
- Patients enrolling on one of the Low Risk arms must be newly diagnosed with a Stage I germ cell tumor. For the Standard Risk arms, patients must be newly diagnosed with metastatic germ cell tumor (Stage II or higher). Histologic confirmation of a primary extracranial germ cell tumor in any of the categories outlined in the table below is required of all patients at enrollment except for those who were initially diagnosed with Stage I non-seminoma malignant GCT and later recur during observation post surgery off study (see [Section 3.1.4](#)). For these patients, if elevated tumor markers rise to > 5x ULN on at least 2 measurements taken at least 1 week apart, a diagnostic biopsy is not required for enrollment. Please refer to [Section 4.2.2](#) (for immature teratoma) and [Section 4.3.3](#) (for non-seminomatous malignant GCT) for complete details.
- For COG, FIGO, AJCC and IGCC 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](#).**

Diagnosis	Site	Stage	Grade	Histology	Tumor Markers	Age (years)
Low Risk Stage I Immature Teratoma (IT)	Ovarian	COG Stage I FIGO Stage IA and IB	2 or 3	Pure immature teratoma (may contain microscopic foci of yolk sac tumor) Mixed immature and mature teratoma (no pathological evidence of MGCT)	α -FP \leq 1,000 ng/mL β -HCG institutional normal	All ages
Non-Seminoma MGCT	Ovarian, Testicular, or Extragenadal	COG Stage I FIGO Stage IA and IB AJCC Testicular Stage IA IB, and IS		Must contain at least one of the following: <ul style="list-style-type: none"> yolk sac tumor (see notes), embryonal carcinoma, or choriocarcinoma (pure or mixed) 	N/A	All ages
Low Risk Stage I Seminoma-MGCT	Testicular	COG Stage I AJCC Testicular Stage IA IB, and IS		May contain <ul style="list-style-type: none"> immature/mature teratoma May NOT contain <ul style="list-style-type: none"> yolk sac tumor, embryonal carcinoma, or choriocarcinoma 	N/A	All ages
Standard Risk 1 (SR1)	Ovarian, Testicular, or Extragenadal	COG Stage II – IV FIGO Stage IC, FIGO Stages II – IV (IGCCC criteria DO NOT apply)		Must contain at least one of the following: <ul style="list-style-type: none"> yolk sac tumor (see notes), embryonal carcinoma, or choriocarcinoma 	N/A	< 11
Standard Risk 2 (SR2)	Ovarian	COG Stage II and III FIGO Stage IC, II and III		Must contain at least one of the following: <ul style="list-style-type: none"> yolk sac tumor (see notes), embryonal carcinoma, or choriocarcinoma 	N/A	\geq 11 and < 25
	Testicular	COG Stage II - IV AJCC Stage II, III and IGCCC Good Risk (See Appendix V)		Must contain at least one of the following: <ul style="list-style-type: none"> yolk sac tumor (see notes), embryonal carcinoma, or choriocarcinoma 	Must be IGCCC Good Risk. Post op: α -FP < 1,000 ng/mL β -HCG < 5,000 mIU/mL and LDH < 3.0 x normal	
	Extragenadal	COG Stage II		Must contain at least one of the following: <ul style="list-style-type: none"> yolk sac tumor (see notes), embryonal carcinoma, or choriocarcinoma 	N/A	

Notes:

- **IGCCC criteria only apply to SR2 patients with a testicular primary tumor.**
- **Use post-op tumor marker levels to determine IGCCC risk group.**
- **Stage 1 seminoma patients are not eligible for the Standard Risk arms of the study.**
- **For the Low Risk Stage I Non-Seminoma MGCT and the Standard Risk arms,** components of yolk sac tumor, embryonal carcinoma, or choriocarcinoma can be mixed with other forms of GCT, such as seminoma or mature or immature teratoma. If yolk sac tumor is the only malignant component present, then it must be deemed by the pathologist to be greater than a “microscopic component” of yolk sac tumor.

14. 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 \leq 16 years of age (see [Appendix VI](#)).

15. 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 \geq 70 mL/min/1.73 m² 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 Hematological Function defined as:
 - Peripheral absolute neutrophil count (ANC) $\geq 1,000/\text{mm}^3$, and
 - Platelet count $\geq 100,000/\text{mm}^3$

- ___ 16. Patients enrolling on the standard risk arms must be medically fit to receive protocol treatment and with no contraindications to protocol treatment.
- ___ 17. Eligibility Criteria to Participate in the Pilot Study of the AYA-Hears Instrument (PROs of Ototoxicity) – See Section 3.2.7

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
 - Pure mature teratoma,
 - Pure immature teratoma COG Stage I, Grade I
 - Pure immature teratoma COG Stage I, Grade 2, 3 with AFP \geq 1000 ng/mL,
 - Pure immature teratoma COG Stage II - IV or FIGO Stage IC to IV,
 - Poor risk disease (age \geq 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.
 - Germ cell tumor with somatic malignant transformation
 - Spermatocytic seminoma
- ___ 2. Patients must have had no prior systemic therapy for the current cancer diagnosis.
- ___ 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, pre-existing co-morbid respiratory disease that contraindicate the use of bleomycin, are ineligible for the standard risk arms of 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

- Performance status
- α -FP, β -HCG, LDH
- Serum (see Section 15.1) Testes only

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.

Low Risk Stage I Seminoma Testicular MGCT

Observations– Low Risk Stage I Seminoma Testicular MGCT, All Ages

All required baseline studies must be performed within 7 days prior to the date of enrollment unless otherwise indicated below.

Imaging performed up to 8 weeks prior to the date of enrollment does not need to be repeated.

Note: The imaging modes and schedules listed here are not intended to replace institutional guidelines and are recommendations, not requirements.

Collection of serum specimens for banking for future research is **REQUIRED** for seminoma patients enrolled on this trial. See [Section 15.0](#) and [Appendix VIII](#) for the Required and Optional Specimen Banking collection schedules.

Required Studies and Specimens to be Obtained

- Performance status
- α -FP, β -HCG, LDH ¹
- Serum (see [Section 15.1](#)) ²

Recommended Baseline and Relapse Imaging to be Obtained

- CT or MRI of primary site
- Testicular ultrasound
- Abdominal/Pelvic CT or MRI
- Chest CT
- CT or MRI of brain (Only if clinically indicated)

Optional Banking Studies (see [Section 15.2](#) for complete details)

- Tumor Tissue (At diagnostic surgery)

¹ If available, please document all tumor markers recorded prior to enrollment in RAVE.

² Serum specimens should ideally be drawn as specified within +/- 14 days of the requested timepoint.

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, PO₄, 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) may be obtained within 8 weeks prior to the start of therapy
- 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) may be obtained within 8 weeks prior to the start of therapy
- 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, PO₄, 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) may be obtained within 8 weeks prior to the start of therapy
- 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.

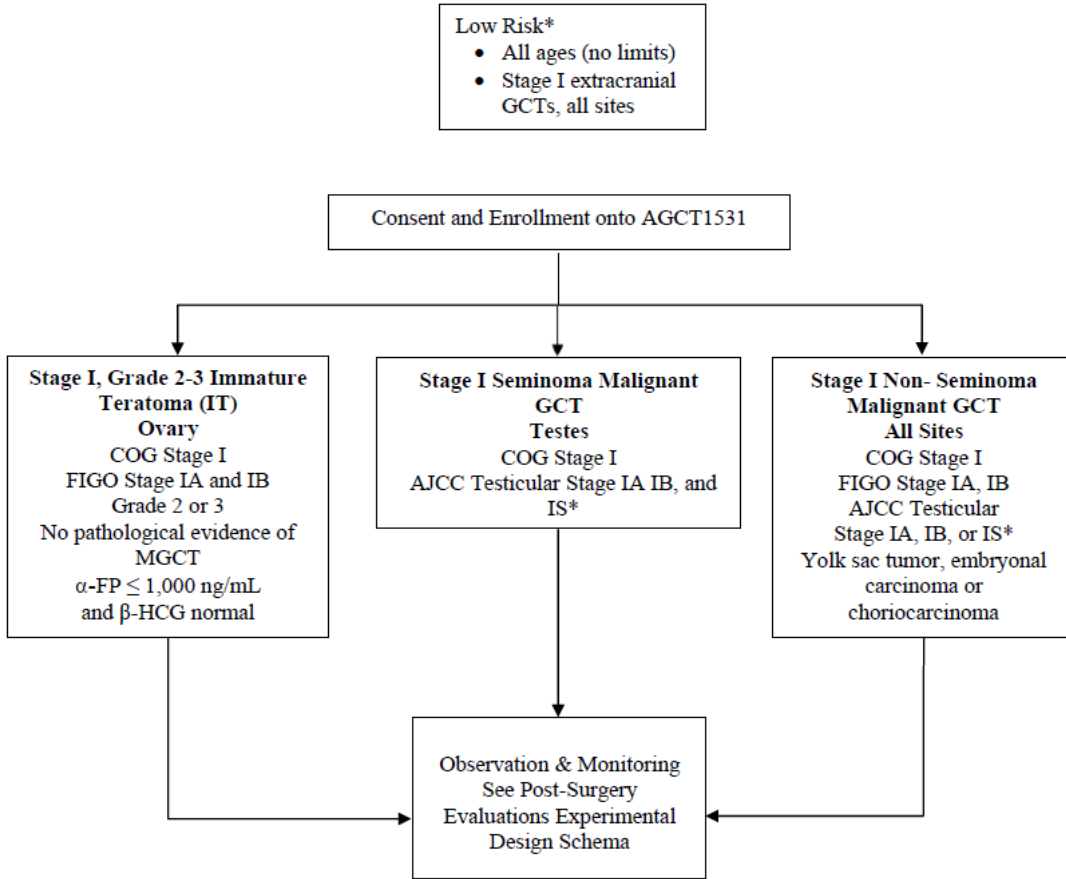
Required Observations and Optional– Standard Risk 2: Arm BEP – Cycle 1

- 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, PO₄, 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) may be obtained within 8 weeks prior to the start of therapy
- 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.

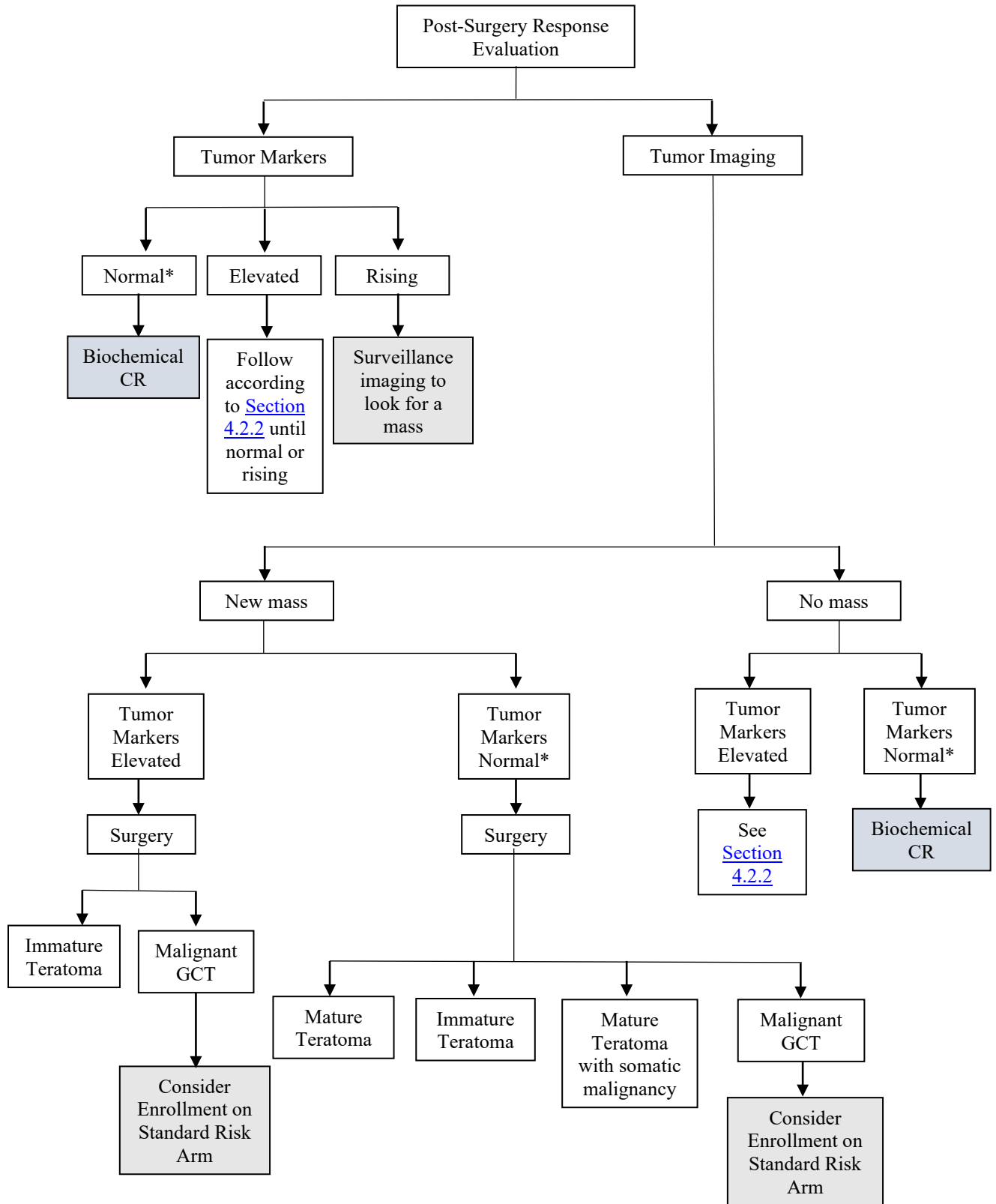
TREATMENT PLAN:

EXPERIMENTAL DESIGN SCHEMA: LOW RISK (LR)



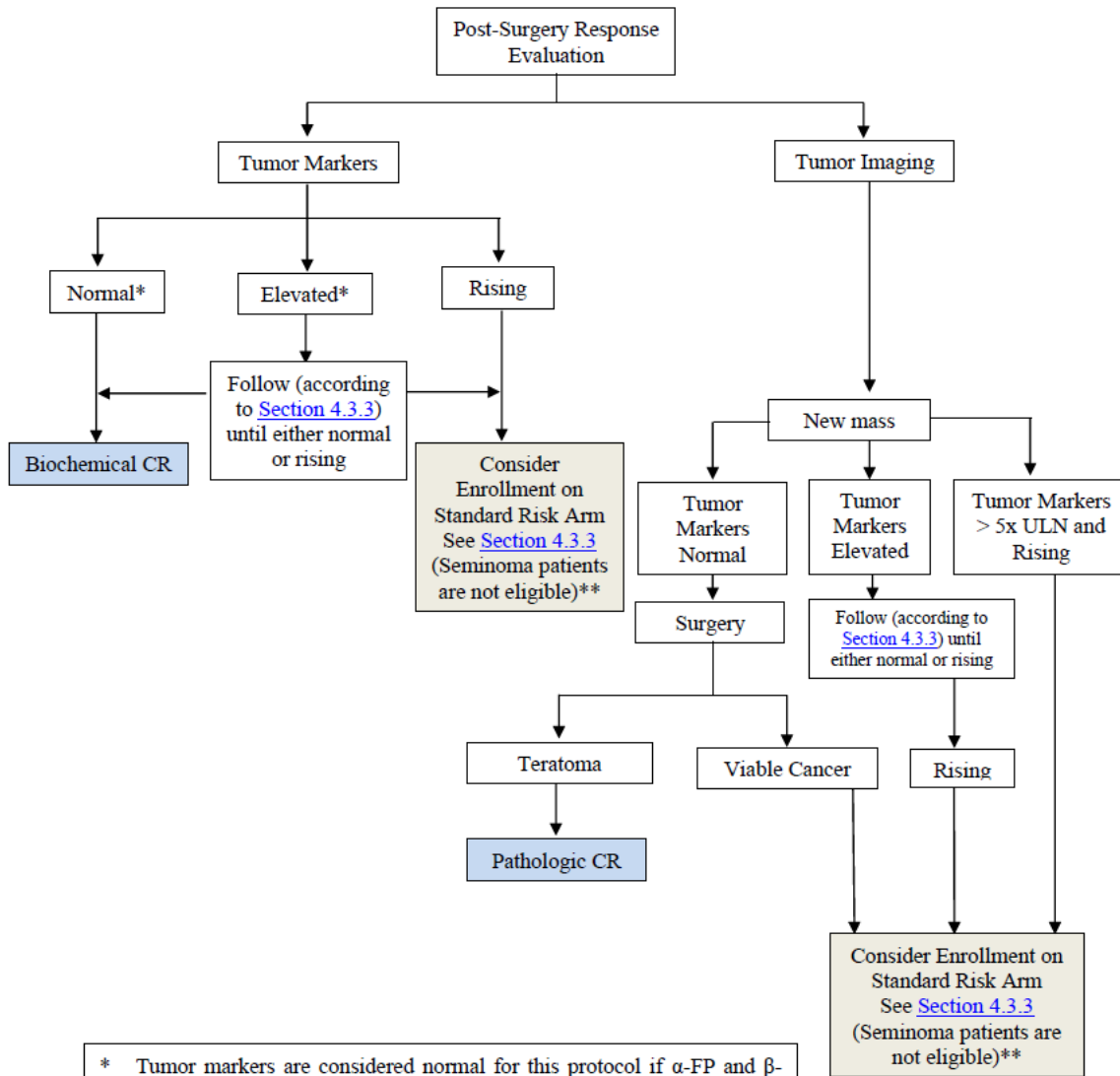
*Post-op tumor markers need to be lower (falling) compared to pre-op tumor markers.
Note: IGCCC criteria DO NOT apply to Low Risk/Stage I patients

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



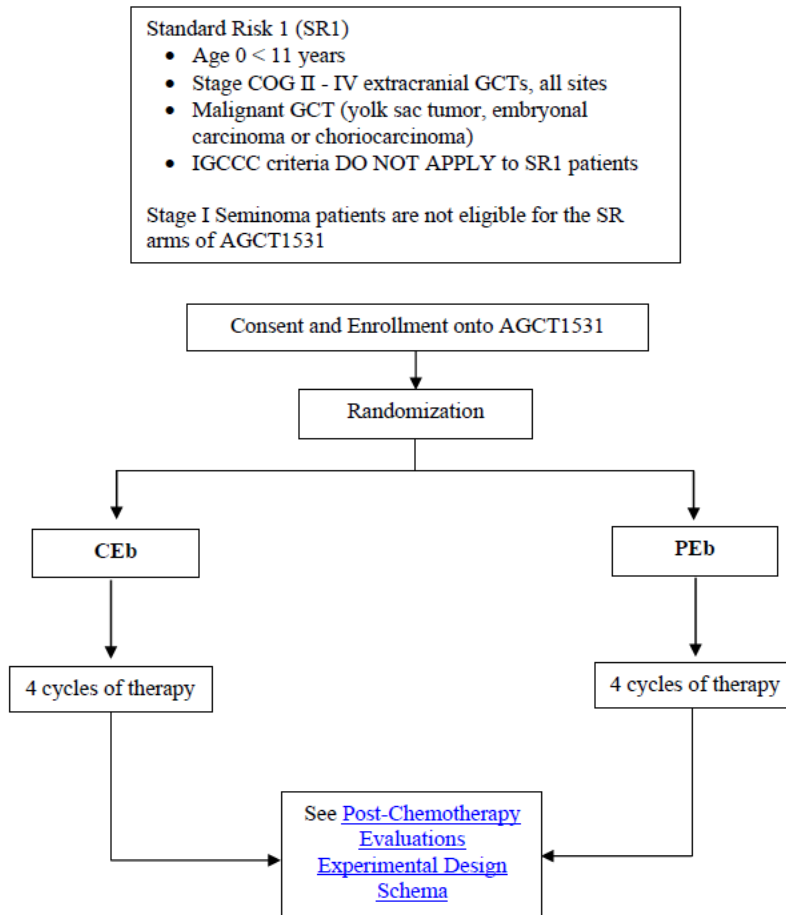
* Tumor markers are considered normal for this protocol if α -FP and β -HCG are less than 5 times the upper limit of institutional normal.

EXPERIMENTAL DESIGN SCHEMA: POST-SURGERY EVALUATIONS FOR STAGE I MALIGNANT GCT (SEMINOMA AND NON-SEMINOMA)



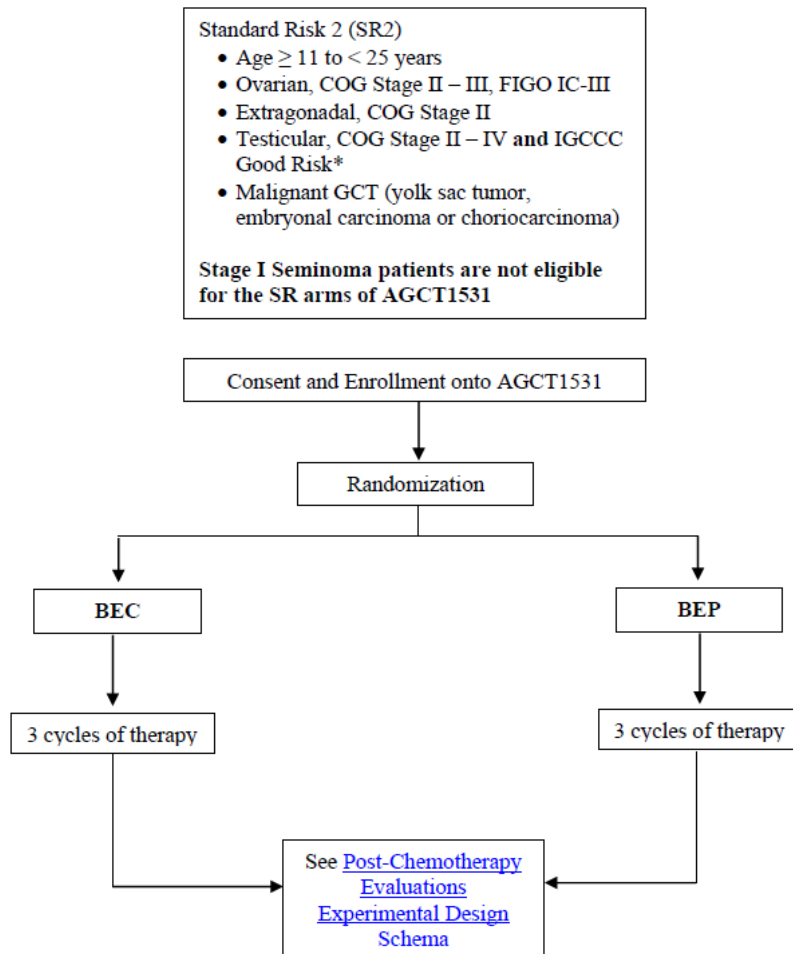
* Tumor markers are considered normal for this protocol if α -FP and β -HCG are less than 5 times the upper limit of institutional normal.
 ** If there is evidence of recurrence, seminoma patients are not eligible for the SR arms and should be treated at the discretion of the treating physician.

EXPERIMENTAL DESIGN SCHEMA: STANDARD RISK 1 (SR1)



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

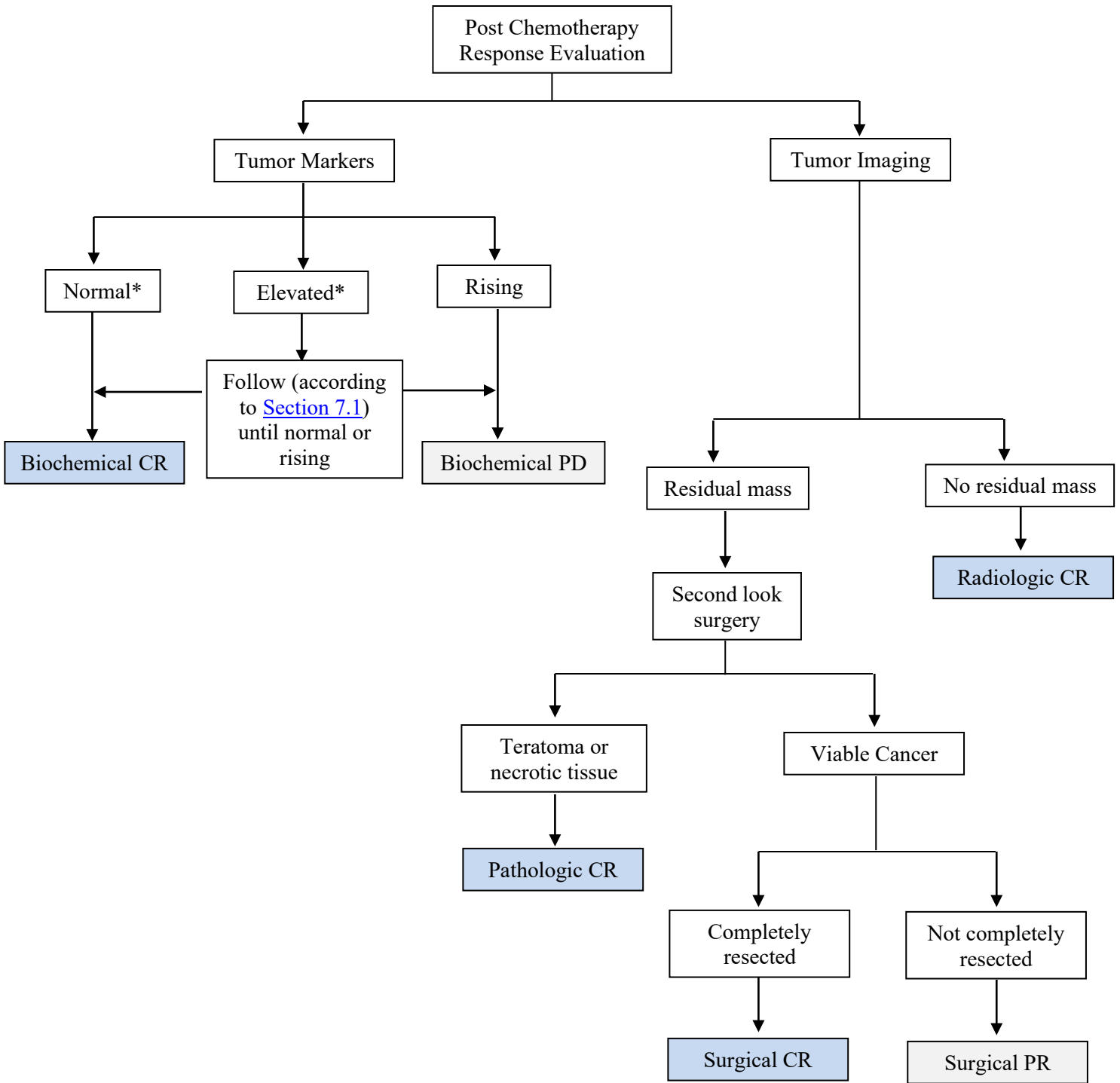
EXPERIMENTAL DESIGN SCHEMA: STANDARD RISK 2 (SR2)



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 – Required and 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

Required Serum Specimens

Blood collection: 5 mL of blood in a red top tube should be collected and processed into serum at baseline and as indicated in Section 15.1

- Allow to clot at room temperature for up to 60 minutes, spin at 1500g for 15 minutes at room temperature. Split serum into 2 cryovials per time point.
- Label and ship per guidelines in 15.1