COG-APEC1621SC:
NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) Screening Protocol

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. **Procedures for Eligibility to Screening Protocol**
Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial must only be done after obtaining written informed consent. This can be accomplished through the study-specific protocol. Documentation of the informed consent will be maintained in the patient's research chart. Studies or procedures that were performed for clinical indications (not exclusively to determine eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

___2. **Genetic Screening Procedures for Eligibility to Subprotocols**
Tumor and blood samples will be obtained from patients who enroll in the study. The results of the evaluation of the tumor specimens will determine if the patient's tumor has an actionable Mutation of Interest (aMOI) for which a MATCH treatment subprotocol is available.

- A tumor sample for screening is obtained from enrolled patients (see Section 5.2, Biopsy Methods, for additional information).
- A blood sample is obtained for germline testing.
- Tumor and blood samples are submitted to the COG Biopathology Center (BPC) at Nationwide Children's Hospital in Columbus, Ohio for pre-analytic processing, including DNA and RNA extraction, and quality control.
- FFPE specimens for immunohistochemistry (IHC) testing will be forwarded from the Biopathology Center to the MDACC clinical laboratory.
- The nucleic acid analytes (DNA/RNA) will be forwarded from the Biopathology Center to one of the CLIA-certified laboratories in the MATCH study-specific network for molecular profiling (MDACC, the NCI Molecular Characterization Laboratory (Frederick, MD) and Dartmouth) to assess for the presence of specific, pre-defined actionable mutations, amplifications or translocations of interest (aMOIs).
- The laboratories will report whether or not an aMOI for patient assignment to one of the clinical trial subprotocols has been detected to the NCI informatics pipeline (MATCHbox).
- The automated rules engine in MATCHbox will generate a list of potential treatment assignments (TA) and the highest priority TA will be determined.
- The highest priority TA (or notification if no match was available) will be sent to the COG Operations Office. This will then be made available to the registering site via CTSU OPEN/Medidata Rave, with an email sent as notification of available TA (or if no match was available) approximately 14 days after receipt of the patient's tumor sample at the BPC. **The BPC does not provide testing results: any inquiries about treatment assignments or results should be directed to the COG study chair and COG research coordinator.**
- Patient is assessed for subprotocol eligibility and patient/family consents to treatment with the indicated agent in the trial subprotocol.
- If the patient is ineligible for the highest priority TA, the treatment assignment process is repeated, in order of priority, until either all TAs are exhausted or the patient is confirmed eligible and is registered to a treatment subprotocol.
- In cases where insufficient tumor is obtained for biomarker analysis, the enrolling site will be notified by the BPC and given the option of providing an additional tumor sample for screening.
- When each new treatment subprotocol is added, the informatics process will review previous test results for subjects who have been enrolled on the screening protocol within the past two years and report if there is a new treatment assignments (i.e. if there are any patients with a mutation that is an aMOI for the new subprotocol).

___3. **Eligibility Checklist**
Before the patient can be enrolled, the responsible institutional investigator must sign and date the completed eligibility checklist documenting that the patient meets the criteria in Section 4.1 for study enrollment. A signed copy of the checklist will be uploaded into RAVE immediately following enrollment.
NOTE: For enrollment onto the APEC1621SC screening protocol, patients do not need to meet all criteria described in Section 4.2 for subprotocol eligibility. However, patients will need to meet all criteria prior to enrollment on any assigned treatment subprotocol. Investigators are encouraged to consider these criteria when determining appropriateness and timing of enrollment onto the screening protocol.

___4. **Institutional Pathology Report**
Immediately following enrollment, the institutional pathology report from the tumor specimen to be submitted for sequencing must be uploaded into RAVE. The report must include the associated study number and COG patient registration and accession numbers. Personal identifiers, including the patient's name and initials must be removed from the institutional pathology report prior to submission. The surgical pathology ID (SPID) from the report will be used by the BPC to link the report to the tumor specimen.

___5. **Study Enrollment**
Patients may be enrolled on the APEC1621SC screening protocol if they meet the eligibility criteria in Section 4.1. Patients who give informed consent for the protocol in order to eligibility assessments are not considered enrolled and should not be enrolled until the eligibility assessments are completed and they are determined to meet all eligibility criteria.

___6. **Patients must be enrolled onto a therapeutic subprotocol within 8 weeks (56 days) of treatment assignment.**
Subprotocol therapy must start no later than 7 calendar days after the date of enrollment to the subprotocol.
Note: Drug orders should be placed with CTEP with consideration for timing of processing and shipping to ensure receipt of drug supply prior to start of protocol therapy onto a subprotocol. No starter supplies will be provided and agents can be ordered only after the patient is registered to a subprotocol.

___7. **Reassignment Request (if unable to enroll within 8 week timeframe):**
The treating team may email PedsMATCHOps@childrensoncologygroup.org and the APEC1621SC study co-chairs (dwparson@txch.org seibelnl@mail.nih.gov) with a request for a single treatment re-assignment for any patient who was previously matched to a therapeutic subprotocol arm, but were unable to enroll during the original specified reservations window. The request can be made within a year of the 'Pediatric MATCH-Reservation expiration date' stipulated in the original treatment assignment email when the patient was assigned. The treatment re-assignment request is subject to slot availability on the therapeutic subprotocol at the time of the request.

Eligibility Criteria for Enrollment onto APEC1621SC

___8. **Age:** Patients must be ≥ 12 months and ≤ 21 years of age at the time of study enrollment.

___9. **Diagnosis:** Patients with recurrent or refractory solid tumors, including non-Hodgkin lymphomas, histiocytoses (e.g. LCH, JXG, histiocytic sarcoma), and CNS tumors are eligible. Patients must have had histologic verification of malignancy at original diagnosis or relapse except in patients with intrinsic brain stem tumors, optic pathway gliomas, or patients with pineal tumors and elevations of CSF or serum tumor markers including alpha-fetoprotein or beta-HCG. In cases where patient enrolls prior to histologic confirmation of recurrent disease, patient is ineligible and should be withdrawn from study if histology fails to confirm recurrence. **Please Note: Patients with Hodgkin lymphoma and plexiform neurofibroma are not eligible.**

___10. **Tumor Sample Availability:** Patients must have an FFPE tumor sample available for MATCH study testing from a biopsy or surgery that was performed at any point after initial tumor recurrence/progression, or be planned to have a procedure to obtain such a sample that is considered to be of potential benefit by the treating clinicians including but not limited to the procedures listed in Section 5.2 below. A tumor sample from a clinically performed diagnostic (pre-treatment) biopsy will be acceptable for enrollment onto Pediatric MATCH only for children with high-grade gliomas of the brainstem (diffuse intrinsic pontine gliomas) or thalamus.
Please note: **Samples that have been decalcified using standardly utilized acid-based decalcification methods are not generally suitable for MATCH study testing; the nucleic acids will have been degraded in the decalcification process.**

___11. **Performance Status:** Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50 for patients ≤ 16 years of age).
Note: Neurologic deficits in patients with CNS tumors must have been stable for at least 7 days prior to study enrollment. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

___12. **Disease Status: Patients must have radiographically measurable disease** (Refer to Section 12). **Measurable disease based on imaging obtained less than or equal to 56 days prior to enrollment.** Patients with neuroblastoma who do not have measurable disease but have MIBG+ evaluable disease are eligible. Measurable disease in patients

with CNS involvement is defined as tumor that is measurable in two perpendicular diameters on MRI and visible on more than one slice.
Note: The following do not qualify as measurable disease:
- malignant fluid collections (e.g., ascites, pleural effusions)
- bone marrow infiltration except that detected by MIBG scan for neuroblastoma
- lesions only detected by nuclear medicine studies (e.g., bone, gallium or PET scans) except as noted for neuroblastoma
- elevated tumor markers in plasma or CSF
- previously radiated lesions that have not demonstrated clear progression post radiation
- leptomeningeal lesions that do not meet the measurement requirements for RECIST 1.1.

General Inclusion Criteria for Subprotocols

NOTE: patient does not need to meet all subprotocol criteria at time of enrollment onto the APEC1621SC screening protocol, but will need to meet all criteria prior to enrollment on any assigned treatment subprotocol. Patients must be enrolled onto a subprotocol within 8 weeks (56 days) of treatment assignment.

___13. **Performance Status:** (See Section 4.1.4)

___14. **Disease Status: At the time of treatment with subprotocol specified therapy, the patients must have radiographically measurable disease.** (See Section 12). Patients with neuroblastoma who do not have measurable disease but have MIBG+ evaluable are eligible. Measurable disease in patients with CNS involvement is defined as tumor that is measurable in two perpendicular diameters on MRI and visible on more than one slice.
Note: The following do not qualify as measurable disease:
- malignant fluid collections (e.g., ascites, pleural effusions)
- bone marrow infiltration except that detected by MIBG scan for neuroblastoma
- lesions only detected by nuclear medicine studies (e.g., bone, gallium or PET scans) except as noted for neuroblastoma
- elevated tumor markers in plasma or CSF
- previously radiated lesions that have not demonstrated clear progression post radiation
- leptomeningeal lesions that do not meet the measurement requirements for RECIST 1.1.

___15. **Prior Therapy:** At the time of enrollment onto a subprotocol, the following general criteria for initiation of therapy will be required:
Patients must have fully recovered from the acute toxic effects of all prior anticancer therapy and must meet the following minimum duration from prior anticancer directed therapy prior to enrollment to the subprotocol. If after the required timeframe, the numerical eligibility criteria are met, e.g. blood count criteria, the patient is considered to have recovered adequately.
- Cytotoxic chemotherapy or other anticancer agents known to be myelosuppressive.
  See https://www.cogmembers.org/site/disc/devtherapeutics/default.aspx for commercial and Phase 1 investigational agent classifications. For agents not listed, the duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator prior to enrollment.≥ 21 days after the last dose of cytotoxic or myelosuppressive chemotherapy (42 days ifprior nitrosourea).
- Anticancer agents not known to be myelosuppressive (e.g. not associated with reduced platelet or ANC counts): ≥ 7 days after the last dose of agent.
  See https://www.cogmembers.org/site/disc/devtherapeutics/default.aspx for commercial and Phase 1 investigational agent classifications. For agents not listed, the duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator prior to enrollment.
- Antibodies: ≥ 21 days must have elapsed from infusion of last dose of antibody, and toxicity related to prior antibody therapy must be recovered to Grade ≤ 1.
- **Corticosteroids:** If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid.
- **Hematopoietic growth factors:** ≥ 14 days after the last dose of a long-acting growth factor (e.g. Neulasta) or 7 days for short-acting growth factor. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator.
- **Interleukins, Interferons and Cytokines (other than Hematopoietic Growth Factors)**: ≥ 21 days after the completion of interleukins, interferon or cytokines (other than Hematopoietic Growth Factors)
- **Stem cell Infusions (with or without TBI):**

  - Allogeneic (non-autologous) bone marrow or stem cell transplant, or any stem cell infusion including DLI or boost infusion: ≥ 84 days after infusion and no evidence of GVHD.
  - Autologous stem cell infusion including boost infusion: ≥ 42 days.
- **Cellular Therapy:** ≥ 42 days after the completion of any type of cellular therapy (e.g. modified T cells, NK cells, dendritic cells, etc.)
- **XRT/External Beam Irradiation including Protons:** ≥ 14 days after local XRT; ≥ 150 days after TBI, craniospinal XRT or if radiation to ≥ 50% of the pelvis; ≥ 42 days if other substantial BM radiation. Note: Radiation may not be delivered to "measurable disease" tumor site(s) being used to follow response to subprotocol treatment.
- **Radiopharmaceutical therapy** (e.g., radiolabeled antibody, 131I-MIBG): ≥ 42 days after systemically administered radiopharmaceutical therapy.

___16. **Organ Function Requirements**

- Adequate Bone Marrow Function Defined as:
  - For patients with solid tumors without known bone marrow involvement:
    - Peripheral absolute neutrophil count (ANC) ≥ 1000/mm^3
    - Platelet count ≥ 100,000/mm^3 (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment)
  - Patients with known bone marrow metastatic disease will be eligible for study provided they meet the blood counts in 4.2.4.1.a (may receive transfusions provided they are not known to be refractory to red cell or platelet transfusions). These patients will not be evaluable for hematologic toxicity.
- Adequate Renal Function Defined as:
  - Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m^2 or
  - A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
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:
  - Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age
  - SGPT (ALT) ≤ 135 U/L. (For the purpose of this study, the ULN for SGPT is 45 U/L.)

___17. Patients must be able to swallow intact capsules/tablets, unless otherwise specified in the subprotocol to which they are assigned.

___18. Agent specific limitations on prior therapy will be included with specific treatment subprotocols.

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

General Exclusion Criteria for Subprotocols

___1. Pregnancy or Breast-Feeding

Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies, or because there is currently no available information regarding human fetal or teratogenic toxicities. Pregnancy tests must be obtained in females who are post-menarcheal. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method.

REQUIRED OBSERVATIONS:

See eligibility above

TREATMENT PLAN:

Per the identified sub protocol

TOXICITIES AND DOSAGE MODIFICATIONS:

Per the identified sub protocol

SPECIMEN REQUIREMENTS:

MATCH panel testing: Blood sample (EDTA)

MATCH panel testing: Tumor sample, FFPE block. Tumor tissue area should be at least the size of a dime in order to be sufficient for testing. Also see section 5

Blood sample (Streck tube) for ctDNA research

If available, Diagnostic (pre-relapse) tumor sample for additional genomics research

Note: This trial has a protocol supplied wallet card that is required to be provided to the patient.

BIOLOGY REQUIREMENTS:

As stated in the eligibility section