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. **As of Amendment #4: Screening approach for Stage 2 of Pediatric MATCH (for patients enrolled starting 2022):**
A clinical tumor molecular profiling report from a CAP/CLIA-approved laboratory will be submitted for patients who enroll in the study. The treating COG site will indicate which molecular alteration in the submitted report they believe to be actionable and the open Pediatric MATCH study arm for which the patient is thought to be eligible.

NOTE: patients should only be enrolled in APEC1621SC if the treating clinician/site believes that the tumor molecular profiling report submitted for review contains an actionable mutation for an open Pediatric MATCH treatment subprotocol.

The results of the evaluation of this report by the Pediatric MATCH Molecular Review Committee (MRC) will determine if the patient's tumor has an actionable Mutation of Interest (aMOI) for which a MATCH treatment subprotocol is available. The levels of evidence used to define mutation actionability will remain as defined from the start of the study (Appendix III). The MRC will be composed of oncologists and molecular pathologists with specific expertise in interpretation of genomic testing results, including the screening protocol COG study chair, vice chair, and pathologists.

- The MRC 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 to the treating institution as notification of available TA (or if no match was available) within one week after submission of the patient's tumor molecular testing report.
- 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.

___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**

- *As of Amendment #4:* Pathology report submission procedure for Stage 2 of Pediatric MATCH (for patients enrolled starting 2022):
  Immediately following enrollment, the institutional pathology report for the same tumor specimen analyzed in the submitted molecular profiling report (section 3.3) must be uploaded into RAVE using the same procedures as described for Stage 1 (section 3.6.1).

___5. ***As of Amendment #4:*** **Institutional Tumor Molecular Profiling Report (Stage 2 of Pediatric MATCH only)**
Immediately following enrollment, the clinical tumor molecular profiling report which will be used to evaluate the tumor specimen treatment assignment 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 molecular report prior to submission.

If a patient enrolled on APEC1621SC has clinical molecular tumor profiling performed on a sample obtained at a later date (i.e. not the tumor report initially reviewed for Pediatric MATCH) this report can be submitted for review by the Molecular Review Committee as described above. An institutional pathology report must also be submitted as described in Section 3.6 above that corresponds to the same sample as the new molecular profiling report.

At the time of APEC1621SC enrollment, the treating COG site must indicate which molecular alteration in the submitted report they believe to be actionable and the open Pediatric MATCH study arm for which the patient is thought to be eligible. This will be indicated in the CRFs in Medidata Rave.

Examples of report types that cannot be submitted for review and cannot be used to determine eligibility for Pediatric MATCH treatment subprotocols include:

- Immunohistochemistry (IHC) reports
- Cytogenetics reports
- Fluorescence in situ hybridization (FISH) reports

Any questions about whether a specific report is acceptable or mutation is actionable can be referred to the COG study chair and vice chair (Drs. Parsons and Janeway) who will consult with the Molecular Review Committee (MRC) as required.

___6. **Study Enrollment Instructions for Subprotocols**
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.
Patients must be enrolled onto a therapeutic subprotocol within 2 weeks (14 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.

- Reassignment Request (if unable to enroll within 2 week timeframe):
  The treating team may email PedsMATCHOps@childrensoncologygroup.org and the APEC1621SC study co-chairs (dwparson@texaschildrens.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

___7. Age**:** Patients must be ≥ 12 months and ≤ 21 years of age at the time of study enrollment.

___8. 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.**

___9. Tumor molecular profiling report availability requirement for Stage 2 of Pediatric MATCH (patients enrolled starting 2022):
In Stage 2 of the study, no tumor samples will be submitted for centralized clinical tumor profiling. Instead, a tumor molecular profiling report from a CAP/CLIA-approved testing laboratory must be submitted for review by the Molecular Review Committee (MRC) as described in Section 3.8.
This molecular profiling must have been performed on a tumor sample that was obtained at any point after initial tumor recurrence/progression and must be accompanied by a pathology report for the same tumor specimen as specified in Section 3.7. A molecular profiling report for a diagnostic (pre-treatment) tumor sample will be acceptable for enrollment onto Pediatric MATCH only for children with high-grade gliomas of the brainstem (diffuse intrinsic pontine gliomas) or thalamus. In the event that molecular profiling reports are available from multiple timepoints, the most recent report should be prioritized for study submission.

___10. **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.

___11. 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 any lesion that is at minimum 10 mm in one dimension on standard MRI or CT.
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.

___12. Performance Status: (See Section 4.1.4)

___13. Disease Status: **A 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 any lesion that is at minimum 10 mm in one dimension on standard MRI or CT.

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.

___14. **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.

___15. **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 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.)

___16. Patients must be able to swallow intact capsules/tablets, unless otherwise specified in the subprotocol to which they are assigned.

___17. 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.

___2. Concomitant Medications
- Corticosteroids: At the time of consent and enrollment to regimen specific subprotocols, patients receiving corticosteroids who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment to the subprotocol will not be eligible. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid.
- Investigational Drugs: Patients must meet criteria for prior therapy (Section 4.2.3) at the time of consent and enrollment to a subprotocol. Other investigational agents may not be administered to patients while they are receiving study drug as part of a subprotocol (See Section 8).
- Anticancer Agents: Patients must meet criteria for prior therapy (Section 4.2.3) at the time of consent and enrollment to a subprotocol. Other investigational agents may not be administered to patients while they are receiving study drug as part of a subprotocol (See Section 8).
- Anti-GVHD agents post-transplant: Patients who are receiving cyclosporine, tacrolimus or other agents to prevent graft-versus-host disease post bone marrow transplant are not eligible.

___3. Infection: Patients who have an uncontrolled infection are not eligible.

___4. Patients who have had a prior solid organ transplant are not eligible.

___5. Additional agent specific criteria will be included with specific treatment subprotocols.

REQUIRED OBSERVATIONS:
See eligibility above

TREATMENT PLAN:
Per the identified sub protocol

TOXICITIES AND DOSAGE MODIFICATIONS:
Per the identified sub protocol

SPECIMEN REQUIREMENTS:
Blood sample (K2EDTA tube) for genomics research, if available.
Relapse tumor sample for genomics research, if available.
Blood sample (Streck tube) for ctDNA research, if available.
If available, Diagnostic (pre-relapse) tumor sample for additional genomics research
As of Amendment #4: **Stage 2 of Pediatric MATCH (patients enrolled starting 1/01/22):** Starting in Stage 2 of Pediatric MATCH, no tumor samples are being submitted for central clinical testing as part of the study and no biopsy-related complications will be reported or tracked.

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