PEPN2112 - A Phase 1/2 Study of BAY 1895344 (elimusertib, IND#152153, NSC#810486) in Pediatric Patients with Relapsed or Refractory Solid Tumors

Status: Recruiting

Eligibility Criteria

Sex: All
Age: 12 Months to 30 Years old
This study is NOT accepting healthy volunteers

Inclusion Criteria:

• Part A: Patients between >= 12 months and < 18 years of age

• Part B:

• Patients between >= 12 months and =< 30 years of age for the phase 2 expansion cohorts for both EWS and PAX3-FOXO1 ARMS.

• Patients between >= 12 months and =< 21 years of age for the phase 2 DDR expansion cohort

• The Phase 2 cohorts will initially open concurrently with the Phase 1 portion but will only enroll patients at least 18 years of age. Patients < 18 years of age will be included in the Phase 2 cohorts only after the RP2D/MTD has been estimated in the Phase 1 portion

• All patients for both Parts A and B must have a minimum body surface area (BSA) >= 0.74 m^2

• All patients for both Parts A and B must have the ability to swallow BAY 1895344 (elimusertib) tablets intact

• Patients with recurrent or refractory solid tumors. Patients must have had histologic verification of malignancy at original diagnosis or relapse

• Part A: Any (non-CNS primary) solid tumor diagnosis including lymphoma which meets one of the following criteria:

• Any Ewing Sarcoma (histological confirmation alone is adequate) or any EWS-fusion positive solid tumor (i.e. including related Ewing's family of tumors with EWS fusions such as EWS-WT1, EWS-ATF1, etc.)

• Alveolar rhabdomyosarcoma (ARMS) with the PAX3-FOXO1 fusion. This does not include PAX7-FOXO1 or other variant fusion ARMS. Please note that a FISH showing FOXO1 breakapart is NOT sufficient for eligibility onto this cohort since it cannot distinguish between FOXO1 partners

• Any (non-CNS primary) solid tumor including lymphoma with inactivating alterations of any of the DNA Damage Repair (DDR) genes: ATM, ATRX, BRCA1, BRCA2, CDK12, CHEK1, CHEK2, FANCA, MSH2, MRE11, PALB2, PARP1, POLD1, RAD51, or XRCC2

• Part B: Any (non-CNS primary) solid tumor diagnosis including lymphoma which meets one of the following criteria:

• B1, EWS Cohort:

• Any Ewing Sarcoma (histological confirmation alone is adequate) or any EWS-fusion positive solid tumor (i.e. including related Ewing's family of tumors with EWS fusions such as EWS-WT1, EWS-ATF1, etc.)

• B2, PAX3-FOXO1 ARMS Cohort:

• Alveolar rhabdomyosarcoma (ARMS) with the PAX3-FOXO1 fusion. This does not include PAX7-FOXO1 or other variant fusion ARMS. Please note that a FISH showing FOXO1 breakapart is NOT sufficient for eligibility onto this cohort since it cannot distinguish between FOXO1 partners

• B3, DDR Non-statistical Cohort:

• Any (non-CNS primary) solid tumor including lymphoma with inactivating alterations of any of the DNA Damage Repair (DDR) genes: ATM, ATRX, BRCA1, BRCA2, CDK12, CHEK1, CHEK2, FANCA, MSH2, MRE11, PALB2, PARP1, POLD1, RAD51, or XRCC2

• All the genes on the DDR panel are annotated with OncoKB, a precision oncology knowledge base which is publicly available here: https://www.oncokb.org/. Alterations which are categorized either 'Oncogenic' or 'Likely Oncogenic' would be considered sufficient for eligibility on either the phase 1 or phase 2 portions of this study. Alterations which are not annotated in OncoKB will need to be reviewed with locally qualified experts in molecular pathology, such as via an established molecular tumor board, in order to determine the likely oncogenicity AND will require approval by the study chair, Dr. Michael Ortiz. If such experts are not available at any institution, the study chair will review

• In cases where multiple mutations are present or multiple samples are available, either at different locations or different points in time, the presence of a single qualifying genomic alteration in any of those samples will is considered sufficient for eligibility on the phase 2 portions of this study

• Qualifying aberrations must be detected in either DNA or ribonucleic acid (RNA) in any tumor tissue sample (i.e. detection of a variant on circulating tumor DNA/RNA is not sufficient to qualify) using a somatic (and/or germline) mutational testing approach with either a targeted panel or whole exome/genome sequencing in the context of a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory setting. Any CLIA certified laboratory is acceptable to use

• Part A: Patients must have either measurable or evaluable disease

• Part B (1, 2, 3): Patients must have measurable disease

• Patients with a prior history of CNS metastases may enroll on study provided there is no current evidence of active disease at the time of enrollment

• Patient's current disease state must be one for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life

• Patients must have a performance status corresponding to Eastern Cooperative Oncology Group (ECOG) scores of 0, 1 or 2. Use Karnofsky >= 50% for patients > 16 years of age and Lansky >= 50% for patients =< 16 years of age. Note that neurologic deficits in patients with tumors previously metastatic to the CNS (or other non-oncologic reasons) 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

• Patients must have fully recovered from the acute toxic effects of all prior anti-cancer therapy and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. 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 anti-cancer agents known to be myelosuppressive: >= 21 days after the last dose of myelosuppressive chemotherapy (42 days if prior nitrosourea)

• Anti-cancer agents not known to be myelosuppressive (e.g., not associated with reduced platelet or absolute neutrophil count [ANC] counts): >= 7 days after the last dose of agent

• 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., pegfilgrastim) 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

• 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 total-body irradiation [TBI]):

• Allogeneic (non-autologous) bone marrow or stem cell transplant, or any stem cell infusion including donor lymphocyte infusions (DLI) or boost infusion: >= 84 days after infusion and no evidence of graft versus host disease (GVHD)

• Autologous stem cell infusion including boost infusion: >= 30 days

• Cellular therapy: >= 42 days after the completion of any type of cellular therapy (e.g., modified T cells, natural killer [NK] cells, dendritic cells, etc.)

• Radiation therapy (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 bone marrow (BM) radiation

• Radiopharmaceutical therapy (e.g., radiolabeled antibody, 131I MIBG): >= 42 days after systemically administered radiopharmaceutical therapy

• Study specific prior therapy: Patients must not have received prior exposure to BAY 1895344 (elimusertib) or any other specific ATR inhibitors including berzosertib (M6620, VX-970),

ceralasertib (AZD6738), M4344 (VX-803), M1774, and RP-3500. Treatment with other DNA damage repair inhibitors which do not specifically inhibit ATR (e.g. PARP inhibitors, WEE1 inhibitors, CHEK1 inhibitors, etc.) does not exclude them from eligibility on this study

• For patients with solid tumors without known bone marrow involvement

• Peripheral absolute neutrophil count (ANC) >= 1000/uL

• For patients with solid tumors without known bone marrow involvement

• Platelet count >= 100,000/uL (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment)

• For patients with solid tumors without known bone marrow involvement

• Hemoglobin >= 8.0 g/dL at baseline (may receive red blood cell [RBC] transfusions)

• Patients with known or possible bone marrow metastatic disease will be eligible for study provided they meet the blood counts in above inclusion criteria (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. At least 5 of every cohort of 6 patients must be evaluable for hematologic toxicity for the dose-escalation part of the study. If dose-limiting hematologic toxicity is observed, all subsequent patients enrolled must be evaluable for hematologic toxicity

• Serum creatinine clearance or radioisotope glomerular filtration rate (GFR) >= 70 mL/min/1.73 m^2 or a creatinine based on age/gender as follows:

• Age: 1 to < 2 years; Maximum serum creatinine (mg/dL): 0.6 (male); 0.6 (female)

• Age: 2 to < 6 years; Maximum serum creatinine (mg/dL): 0.8 (male); 0.8 (female)

• Age: 6 to < 10 years; Maximum serum creatinine (mg/dL): 1 (male); 1 (female)

• Age: 10 to < 13 years; Maximum serum creatinine (mg/dL): 1.2 (male); 1.2 (female)

• Age: 13 to < 16 years; Maximum serum creatinine (mg/dL): 1.5 (male); 1.4 (female)

• Age: >= 16 years; Maximum serum creatinine (mg/dL): 1.7 (male); 1.4 (female)

• Bilirubin (sum of conjugated + unconjugated or total) =< 1.5 x upper limit of normal (ULN) for age

• Serum glutamate pyruvate transaminase (SGPT) (alanine aminotransferase [ALT]) =< 135 U/L. For the purpose of this study, the ULN for SGPT is 45 U/L

• Patients with seizure disorder may be enrolled if on anticonvulsants and well controlled as evidenced by no increase in seizure frequency in the prior 7 days. For patients a history of seizure but not on anticonvulsants, no seizure in the past 3 months

• Nervous system disorders (Common Terminology Criteria for Adverse Events [CTCAE] version [v]5) resulting from prior therapy must be =< grade 2, with the exception of decreased tendon reflex (DTR). Any grade of DTR is eligible

---

Exclusion Criteria:

• 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 yet no available information regarding human fetal or teratogenic toxicities. Pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to use two effective methods of birth control, including a medically accepted barrier or contraceptive method (e.g., male or female condom) for the duration of the study and for 3 months + 2 days for males and 6 months + 2 days for females after receiving the last dose of BAY 1895344 (elimusertib) on the study. Abstinence is an acceptable method of birth control. Female patients must not breastfeed during treatment and until 4 months after last study drug administration

• Corticosteroids: Patients receiving corticosteroids who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment are not eligible. If used to modify immune adverse events related to prior therapy, >= 14 days must have elapsed since last dose of corticosteroid

• Patients who are currently receiving another investigational drug are not eligible

• Patients who are currently receiving other anti-cancer agents are not eligible

• Patients who are receiving cyclosporine, tacrolimus or other agents to prevent graft-versus-host disease post bone marrow transplant are not eligible for this trial

• Patients who are currently receiving drugs that are strong inducers or inhibitors of CYP3A4 are not eligible. Strong inducers or inhibitors of CYP3A4 should be avoided from 14 days prior to enrollment to the end of the study. Drugs that are considered sensitive or narrow therapeutic range CYP3A4 substrates should be avoided for the duration of protocol therapy

• Dedicated CNS imaging is not required but patients with current active CNS metastasis whether symptomatic or discovered incidentally without clinical symptoms, will be excluded from study participation

• Patients who have an uncontrolled infection are not eligible

• Patients who have received a prior solid organ transplantation are not eligible

• Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible

Conditions & Interventions

Interventions:
Drug: Elimusertib
Conditions:
Recurrent Alveolar Rhabdomyosarcoma, Recurrent Ewing Sarcoma, Recurrent Lymphoma, Recurrent Malignant Solid Neoplasm, Refractory Alveolar Rhabdomyosarcoma, Refractory Ewing Sarcoma, Refractory Lymphoma, Refractory Malignant Solid Neoplasm

More Information

Description: This phase I/II trial tests the safety, best dose, and whether BAY 1895344 (elimusertib) monotherapy works in treating patients (â‰¥ 12 months and â‰¤ 30 years) with solid tumors that have come back (relapsed) or does not respond to treatment (refractory). Elimusertib may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth.
Contact(s): Allison Fullenkamp - fulle631@umn.edu
Principal Investigator: Emily Greengard
Phase: Phase 1/Phase 2
IRB Number: STUDY00014678
System ID: NCT05071209
