VITAS: Atezolizumab in Combination With Chemotherapy for Pediatric Relapsed/Refractory Solid Tumors

Status: RECRUITING

Eligibility Criteria

Sex: ALL
Age: 6 months to 30 years old
Healthy Volunteers: This study is NOT accepting healthy volunteers
Inclusion Criteria:

1. Signed informed consent
2. Relapsed or refractory solid tumor after at least one prior course of therapy.

    1. Hodgkin lymphoma or non-Hodgkin lymphoma are not permitted.
    2. Patients with CNS malignancy or asymptomatic CNS metastases may be enrolled, provided all of the following criteria are met.

* No metastatic or primary disease affecting the brainstem, midbrain, pons, or cerebellum, or within 10 mm of optic nerve
* No history of leptomeningeal disease
* No history of intracranial or spinal cord hemorrhage
* No evidence of progression of neurologic deficit, in the investigator's judgment, within 7 days prior to initiation of study medications.

1. Must have histologically confirmed rhabdomyosarcoma (RMS) for RMS efficacy cohort.

    1. Age ≥ 6 months and ≤ 30 years
    2. Lansky Performance Status (patients < 16 years old) or Karnofsky Performance Status (patients ≥ 16 years old) ≥ 50
    3. Ability to comply with the study protocol, in the investigator's judgment
    4. For RMS efficacy cohort, disease must be measurable as defined by RECIST v1.1.
2. For the feasibility cohort, disease must be evaluable, but patients enrolled in the feasibility cohort will be prospectively assessed for measurable disease, RMS patients will also be included in the RMS efficacy cohort.

3. Previously irradiated lesions can be considered as measurable disease only if progressive disease has been unequivocally documented at that site since radiation.

    1. Availability of a tumor specimen suitable for determination of PD-L1 status, either from initial diagnosis or from a recurrence.
4. For PD-L1 staining to be performed at the central site, a formalin-fixed paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least 15 slides containing unstained, freshly cut, serial sections must be available along with an associated pathology report prior to study enrollment.

5. Patients for whom the required number of slides are not available may still be eligible to enroll on study with PI approval

    1. For the RMS efficacy cohort, it will be required that at least 8 of 17 patients have PD-L1(+) tumor. PD-L1 status will be determined at time of enrollment for all patients. When the maximum allowable number of PD-L1(-) patients has been enrolled and treated on study, PD-L1 positivity will be required for all further enrolled patients.
6. Staining will be performed in the central site CAP/CLIA-certified laboratory using the 22c3 antibody for immunohistochemical analysis

7. PD-L1(+) status will be defined as staining on ≥1% of tumor cells or ≥1% of stroma.

8. For the feasibility cohort, PD-L1 positivity is not required but will be performed centrally in all cases for exploratory biomarker studies.

    1. Adequate organ and marrow function as defined by the following laboratory values obtained within 21 days prior to initiation of study medication.
9. For patients without known bone marrow involvement:

* Absolute neutrophil count ≥ 1.0 x 10\^9 / L (1000/µL) without granulocyte colony-stimulating factor support (≥14 days after the last dose of a long-acting gro wth factor such as pegfilgrastim, or 7 days after short-acting growth factor)
* Platelet count ≥ 75 x 10\^9 / L (75,000/µL) without transfusion in the last 7 days

1. Patients with known bone marrow metastatic disease will be eligible for the study if they meet the following criteria:

* Patients with documented liver metastases: AST and ALT ≤ 5 x ULN
* Patients with documented liver or bone metastases: ALP ≤ 5 x ULN
* Absolute neutrophil count (ANC) ≥ 750/mm\^3
* Platelet count ≥ 50,000/mm\^3 (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 4 of 6 patients in the feasibility cohort must be evaluable for hematologic toxicity. If dose -limiting hematologic toxicity is observed, all subsequent patients enrolled must be evaluable for hematologic toxicity.

1. Total bilirubin ≤1.5 x upper limit of normal (ULN) for age (Patients with known Gilbert disease: serum bilirubin ≤ 3 x ULN)
2. AST (SGOT) and ALT (SPGT) ≤ 2.5 x ULN for age
3. Serum albumin ≥ 25 g/L (2.5 g/dL)
4. Creatinine ≤ 1.5 x ULN for age or creatinine clearance (or radioisotope glomerular filtration rate) ≥ 70 mL/min/1.73 m2
5. Left ventricular ejection fraction ≥ 50% or shortening fraction ≥ 30%

6. Hemoglobin ≥ 90 g/L (9 g/dL)
7. Patients may be transfused to meet this criterion.
8. For patients not receiving therapeutic anticoagulation: INR or aPTT ≤ 1.5 x ULN
9. For patients receiving therapeutic anticoagulation: stable anticoagulant regimen

    1. Negative HIV and hepatitis B surface antigen (HBsAg) tests at screening
    2. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating eggs, as defined below:
    3. Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 5 months after the final doses of atezolizumab, vincristine, and temozolomide. Women must refrain from donating eggs during this same period.
    4. A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus), regardless of sexual orientation or marital status.
    5. Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
    6. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
    7. For men who are not surgically sterile: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:
    8. With a female partner of childbearing potential who is not pregnant, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of less 1% per year during the treatment period and for 5 months after the final doses of atezolizumab, irinotecan, and temozolomide. Men must refrain from donating sperm during this same period.
    9. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception

Exclusion Criteria:

1. Pregnancy or breast-feeding:

    1. Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 5 months after the final dose of study treatment
    2. Women of childbearing potential must have a negative serum pregnancy test result within 21 days prior to initiation of study treatment.
2. Medical conditions that are excluded:

    1. Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Guillain-Barré syndrome, multiple sclerosis, or Kawasaki syndrome with the following exceptions:

* Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.
* Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.
* Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met at study initiation: (1) Rash must cover less 10% of body surface area, (2) Disease is well con trolled at baseline and requires only low-potency topical corticosteroids, (3) No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 mont hs

1. Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL or corrected serum calcium > ULN)
2. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

* Patients with indwelling catheters (e.g., PleurX®) are allowed.

1. Uncontrolled tumor-related pain

* Patients requiring pain medication must be on a stable regimen at study entry for at least 2 weeks. Intermittent use of as-needed medication is allowed during this period.

1. Clinically significant gastrointestinal disorder that may interfere with absorption of orally administered drugs (at the discretion of the treating physician)
2. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan

* History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

1. Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina
2. History of severe asthma or uncontrolled asthma
3. Dyspnea at rest or requirement for supplemental oxygen
4. Uncontrolled seizures. Patients taking a stable dose of anticonvulsants (for 2 weeks) are permitted, as long as they are not strong inducers or inhibitors of CYP3A4.
5. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications in the opinion of the treating investigator

    1. Washout periods from prior therapies:

1. Washout periods from prior therapies:
6. Myelosuppressive chemotherapy or radiotherapy within 21 days prior to starting study treatment.

* Subjects must have recovered from all acute prior treatment-related toxicities to grade 1 or baseline (excluding alopecia and clinically stable toxicities requiring ongoing medical management, such as hypothyroidism).

1. Non-myelosuppressive cancer therapy, such as kinase inhibitors, within 7 days prior to study treatment.
2. Treatment with monoclonal antibodies with long half-lives, within 3 half-lives prior to study treatment.
3. Treatment with targeted cellular therapies within 28 days prior to starting study treatment.
4. Major surgical procedure, other than for diagnosis, within 30 days prior to initiation of study treatment, or anticipation of the need for a major surgical procedure during the first four cycles of the study.

* Biopsy tissue collection or placement of a vascular access device is permitted if the site has healed prior to initiation of study medications.
* For patients with CNS disease, no neurosurgical resection, brain biopsy, or stereotactic/whole-brain radiation within 30 days prior to Cycle 1, Day 1

1. Treatment with a live, attenuated vaccine within 30 days prior to initiation of study treatment, or anticipation of the need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
2. Treatment with investigational therapy within 21 days prior to initiation of study treatment or concurrent participation with another investigational agent
3. Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment
4. Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF-agents) within 2 weeks prior to initiation of study treatment, or anticipation of the need for systemic immunosuppressive medication during study treatment, with the following exceptions:

* Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after Principal Investigator confirmation has been obtained.
* Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
* Patients with CNS disease can be receiving concurrent treatment with corticosteroids with approval from the Principal Investigator. Patients must be receiving a stable or decreasing dose for ≥ 5 days prior to the baseline MRI scan and at the time of drug initiation. The Principal Investigator should be informed when steroid doses are increased because of declining patient status.

1. Use of strong CYP3A4 inhibitors or inducers or strong UGT1A1 inhibitors within 12 days of Cycle 1, Day 1.
2. Treatment with high-dose chemotherapy and hematopoietic stem-cell rescue within 3 months prior to initiation of study drug
3. Treatment with herbal cancer therapy within 1 week prior to initiation of study medications.
4. Treatment with a long-acting hematopoietic growth factor (such as pegfilgrastim) within 2 weeks prior to initiation of study medications, or a short-acting hematopoietic growth factor (such as G-CSF) within 1 week prior to initiation of study medications.

    1. Prior treatments:
5. Prior allogeneic stem cell or solid organ transplantation
6. Prior treatment with CD137 agonists or immune checkpoint blockade therapies to include all anti-PD-1, and anti-PD-L1 therapeutic antibodies
7. Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2] within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment
8. Subjects must not have previously progressed while receiving regimens that include irinotecan or temozolomide. Patients who have received irinotecan or temozolomide and did not progress while on these medications are eligible.

    1. Known ongoing or untreated infection, including, but not limited to bacteremia, active tuberculosis, or severe pneumonia
9. Active tuberculosis
10. Current treatment with anti-viral therapy for HBV
11. Active hepatitis C
12. Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study

    1. Known allergy or hypersensitivity to any component of the study medications
13. History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
14. Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation

Conditions & Interventions

Interventions:
DRUG: Atezolizumab, DRUG: Vincristine, DRUG: Irinotecan, DRUG: Temozolomide
Conditions:
Solid Tumor, Rhabdomyosarcoma
Keywords:
Relapsed solid tumor, Refractory solid tumor, Rhabdomyosarcoma

More Information

Description:
This trial is a multi-center, non-randomized, open-label Phase I/II study evaluating the feasibility and efficacy of vincristine, irinotecan, temozolomide, and atezolizumab in children with relapsed/refractory solid tumors.

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Principal Investigator:
Principal Investigator ID:
Phase: PHASE1
IRB Number:
System ID: NCT04796012
