of potential CAM use and more actively discuss the topic. More research is needed to gain knowledge about possible anticancer effects of CAM and their interactions with conventional therapies.

EARLY PHASE CLINICAL TRIALS

EPCT-01. PHASE I STUDY OF DAY101 (TAK580) IN CHILDREN AND YOUNG ADULTS WITH RADIOGRAPHICALLY RECURRENT OR PROGRESSIVE LOW-GRADE GLIOMA (LGG)

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BACKGROUND: We report a phase I study examining pharmacokinetics, safety and recommended dosage of the type 2 RAF inhibitor DAY101 in children/young adults with radiographically recurrent/progressive LGGs harboring MAPK pathway alterations. METHODS: Applying a 3 + 3 design, patients < 18 years of age with radiographically recurrent/progressive LGG received oral DAY101 weekly for 4-week cycles up to a maximum of 2 years, if deriving clinical benefit. The starting DAY101 dosage was 280 mg/m^2. Dose limiting toxicities were determined after one cycle. RESULTS: We treated nine eligible patients at 280, 350, and 420 mg/m^2. Eight patients had KIAA1549:BRAF fusions. One patient with NF1 did not have a biopsy. There were no DLTs. Weekly administration of DAY101 in children resulted in dose-proportional increases in C_{max} and AUC similar to that described in adults. A 2.2-fold mg/kg exposure difference was observed with respect to weight-based dosing and suggested a correlation to best radiographic RANO responses of 2 complete responses, 2 partial responses, 3 stable disease, and 2 progressive disease (independently-reviewed). Median time to response was 10.5 weeks (range: 8–32 weeks). CONCLUSION: The phase 1A data provide initial pharmacokinetic parameters to describe oral weekly dosing of DAY101 in pediatric patients with radiographically recurrent/progressive LGG. Plasma exposures of DAY101 achieved in adults can be reached in pediatric patients. Oral weekly DAY101 is well-tolerated and possesses anti-tumor activity. The amended protocol will explore additional dose levels and the potential for differential dosing to achieve similar responses across a variety of BSAs.

EPCT-02. PBTC-051: FIRST IN PEDIATRICS PHASE 1 STUDY OF CD40 AGONISTIC MONOCLONAL ANTIBODY APX005M IN PEDIATRIC SUBJECTS WITH RECURRENT/REFRACTORY BRAIN TUMORS

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BACKGROUND: CD40 is a co-stimulatory molecule expressed on antigen presenting cells (APCs). APX005M is a CD40 agonist monoclonal antibody which stimulates innate and adaptive anti-tumor immunity through activation of APCs, macrophages, and antigen-specific CD8$^+$T-cells. Pediatric Brain Tumor Consortium study PBTC-051 is the first investigation of APX005M in pediatric patients and is evaluating the safety, recommended phase 2 dose (RP2D), pharmacokinetics, and preliminary efficacy of APX005M in children with central nervous system (CNS) tumors. RESULTS: Accrual of patients with recurrent/refractory primary malignant CNS tumors (stratum 1) began in March 2018. 16 patients (2 ineligible) have enrolled on this stratum; 14 were treated. Dose escalation through 3 planned dose levels of APX005M was completed without excessive or unanticipated toxicities. The highest dose level (0.6 mg/kg q3 weeks) is the presumptive RP2D, and an expansion cohort is currently enrolling at this dose. 2 patients at dose level 3 have received >12 cycles of therapy. Grade 3 or higher adverse events at least possibly attributable to APX005M include 11 lymphopenia, 5 neutropenia, 5 leukopenia, 3 ALT elevations, 1 AST elevation, 1 thrombocytopenia, and 1 hypoalbuminemia. PK data will be available March 2020. Stratum 2 is now enrolling patients with post-radiation/pre-progression DIPG beginning at dose level 2, with 1 patient currently enrolled. CONCLUSION: The CD40 agonistic antibody APX005M has demonstrated preliminary safety in pediatric patients with recurrent/refractory primary malignant CNS tumors and has a likely RP2D of 0.6 mg/kg q3 weeks in this population. Preliminary efficacy data are pending.

EPCT-03. A PHASE I TRIAL OF 2-HYDROXYOLEIC ACID IN PEDIATRIC PATIENTS WITH ADVANCED CENTRAL NERVOUS SYSTEM TUMORS

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2-hydroxyoleic acid (2-OHOA) is the first potential anti-cancer drug to act by modification of cell membrane lipid content. The agent is a derivative of oleic acid, a naturally occurring component of olive oil. Through its unique mechanism of activating sphingomyelin synthase 1, 2-OHOA targets the membrane lipid composition of cancer cells. These lipid changes alter membrane-dependent signaling cascades, such as the Ras/MAPK pathway, that promote tumor cell proliferation. A comprehensive pre-clinical program has characterized the safety and effects of 2-OHOA across a host of animal models. A European phase I/IIa trial of 2-OHOA in adult patients has shown initial promising results with five refractory high-grade glioma patients demonstrating objective clinical benefit by RANO criteria for six or more months. The drug has been very well-tolerated in adult patients with minimal toxicity. This phase I study is the first pediatric investigation of 2-OHOA and focuses on the treatment of relapsed/refractory pediatric central nervous system (CNS) tumors. The trial consists of a dose-escalation phase in up to 18 patients using a standard "3 + 3" design, followed by an expanded safety cohort of up to 10 patients treated at the maximum tolerated dose to confirm the recommended phase II dose. Due to the promising clinical results in adult neuro-oncology patients and the widespread involvement of the Ras/MAPK pathway and other membrane-dependent signaling cascades in the development of pediatric malignancies, we hypothesize that 2-OHOA may be a safe and effective treatment for pediatric patients with several types of advanced CNS tumors.

EPCT-05. A PHASE I TRIAL OF THE CDK 4/6 INHIBITOR PALBOCICLIB IN PEDIATRIC PATIENTS WITH PROGRESSIVE OR REFRACTORY CNS TUMORS: A PEDIATRIC BRAIN TUMOR CONSORTIUM (PBTC) STUDY

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PBTC-042 was a phase I trial of palbociclib to determine the maximum tolerated dose (MTD) and describe toxicities in children. Palbociclib is an oral, selective cyclin dependent kinase 4/6 inhibitor. METHODS: A rolling-6 design was utilized. Eligible patients were children ≥4 and ≤21 years-old with a progressive/refractory CNS tumor with intact retinoblastoma protein, measurable disease, and ability to swallow capsules. Pharmacokinetic studies were performed during the first course. Here, we report on the heavily pretreated stratum, which included patients who received >4 prior treatment regimens (either chemotherapy or biologic agent), and/or craniospinal irradiation, and/or myeloablative chemotherapy plus stem cell rescue. Palbociclib was initiated at 50 mg/m^2/day for 21 consecutive days of a 28-day course. This was one dosage level below the MTD for the less heavily pretreated stratum (75 mg/m^2). RESULTS: Fourteen eligible patients were enrolled (median age 12.8 years; male 79%). Eleven patients (79%) had either ependymoma or medulloblastoma. Four eligible and evaluable patients were enrolled at 50 mg/m^2 with no DLTs. This prompted a dosage increase to 75 mg/m^2. Ten eligible subjects were enrolled and 7 were evaluable for DLT assessment. One of 7 evaluable patients experienced a DLT (grade 3 thrombocytopenia). This established 75 mg/m^2 as the MTD for more heavily pretreated patients. Mean ± SD palbociclib apparent oral clearance was 34.6 ± 18.4 L/h/m2. CONCLUSION: The MTD for palbociclib on a 3 week on/1 week off schedule in children with brain tumors is 75 mg/m^2 and does not appear to be influenced by the degree of prior therapy.