CLINICAL REVIEW

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Reviewer Name(s)	Amy Barone, MD Suzanne Demko, PA-C (TL)
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Established Name	erlotinib
(Proposed) Trade Name	Tarceva
Therapeutic Class	EGFR inhibitor
Applicant	OSI Pharmaceuticals, LLC
Formulation(s)	Tablet
Dosing Regimen	Not applicable
Indication(s)	None
Intended Population(s)	None

Template Version: March 6, 2009

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1 Recommendations

I recommend that Pediatric Exclusivity be granted for Tarceva (erlotinib) and that relevant information obtained from pediatric studies of erlotinib be incorporated into the Tarceva package insert. This recommendation is based on the review finding that the Application Holder fairly responded to all of the elements in the Pediatric Written Request (WR).

The adverse event profile of erlotinib in the pediatric population studied appears to be similar to that of the adult population. However, the pediatric studies failed to demonstrate that erlotinib is effective in the treatment of pediatric patients with recurrent or refractory ependymoma. Therefore, use of erlotinib in this population is not recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Established name: Erlotinib
Proprietary Name: Tarceva®
Applicant: OSI Pharmaceuticals, Inc.
Pharmacological Class: Epidermal growth factor receptor (EGFR) inhibitor
Mechanism of Action: Tarceva acts through direct and reversible inhibition of the human epidermal growth factor receptor 1/epidermal growth factor receptor (HER1/EGFR)
Proposed Indication: There is no proposed pediatric indication.

2.2 Rationale for Pediatric Studies of Erlotinib

There are few options available for the treatment of recurrent ependymomas in pediatric patients and the role of both chemotherapy and EGFR inhibitors remains unclear. Ependymomas have been shown to over-express EGFR and EGFR-positivity is associated with poorer prognosis in this patient population. Mendrzyk reported over expression (>5% of cells) of EGFR in 96 of 163 (59%) intracranial ependymoma (mixed child and adult population)[1]. High-level amplification of EGFR by FISH was associated with adverse outcome ($p = 0.002$) and in a multivariate analysis was the only statistically significant variable for poor prognosis in the subset of Grade II ependymoma. In an evaluation of immunohistochemical markers (tenascin, vascular endothelial growth factor, epidermal growth factor, and p53 protein) for prognosis in 112 patients with ependymoma, Korshunov reported that tumors from 48 (43%) patients stained for EGFR[2]. High-grade tumors were more likely to be EGFR positive (61%) compared with 25% of low-grade ependymomas. The patients with low-grade tumors that were EGFR-positive had a significantly shorter progression free survival. In addition, ERBB2 (HER 2, a member of the EGFR family) protein expression has been detected in over 75% of childhood ependymoma studied. Thus, targeting this pathway in pediatric ependymoma with an EGFR inhibitor is a rational approach in recurrent ependymoma.

Erlotinib has been studied in three phase 1 pediatric studies and the apparent clearance of erlotinib was similar to that seen in an adult cancer patient population. The Jakacki et al. study characterized the dose of erlotinib in a recurrent/refractory pediatric patient population, including patients with CNS tumors[3]. In that study, the recommended phase 2 dose was determined to be 85 mg/m2 and was demonstrated to result in similar erlotinib exposure in patients <16 yrs of age to that observed in adult NSCLC patients at the approved dose of 150 mg. The safety profile of erlotinib in pediatric patients who were administered a dose of 85 mg/m^2 was similar to the safety profile observed in adult cancer patients.

2.3 Summary of Pre-submission Regulatory Activity

Erlotinib is approved for the following indications in adults:

- as single agent for non-small cell lung cancer (NSCLC), metastatic, first-line therapy in patients with EGFR exon 19 or exon 21 (L858R) substitution mutations
- as single agent for refractory NSCLC
- as single agent for maintenance therapy in NSCLC
- in combination with gemcitabine for pancreatic cancer

Table 1 provides a brief summary of the regulatory history of the pediatric development of erlotinib.

Table 1: Pediatric Regulatory History

Date	Action
11/27/2000	Written request (WR) issued for evaluation in pediatric brain tumors (a dose-finding and pharmacokinetic (PK) study and an efficacy study in pediatric patients with refractory tumors expressing receptors for EGF). OSI began collaboration with COG for ADVL0214. Study began in 2004 and used an IV formulation administered orally and then tablets later in the study. Deadline of 12/31/05 for submitting results
1/2007	FDA info request for update on pediatric development plan.
7/11/2007	Meeting with FDA to discuss ADVL0214 and the Broniscer study in pediatric glioma[4]. FDA advised an additional study in a defined tumor type and stated that a new WR would need to be issued if OSI were to seek pediatric exclusivity.
3/2009	Meeting with FDA to discuss the design of a clinical study in recurrent ependymoma comparing single agent erlotinib to oral etoposide. FDA found indication and overall design acceptable but recommended primary endpoint of response rate, 20 patients per arm, uniform administration of drug (either crushed OR whole tablets). FDA agreed to (b) (4) Discussed need to

	submit a new PPSR for the phase 2 study. There was agreement that 20 patients per arm sample size would not be powered to compare response rate but that any safety and efficacy data from the etoposide arm could be valuable.
5/1/2009	Proposed Pediatric Study Request (PPSR) submitted with revised phase 2 protocol with a provision for an interim analysis and early stopping for lack of efficacy. The age range was increased to 21 years.
10/8/2009	FDA provided comments and asked for justification for the phase 2 dose of 85 mg/m^2/day and requested more information on the phase 1 studies to be included in the PPSR. Sponsor submits revised PPSR 11/18/2009.
2/09/2010	FDA provides comments and asks for summaries of phase 1 studies, further dose justification, PK sampling schedule, details of the planned interim and final analysis and stopping criteria, and PK info for each age group. Sponsor submits requested information and draft WR on 3/10/2010.
5/7/2010	FDA issues WR for a PK study (3-21 yo) in pediatric cancer patients and a phase 2 study (1-21 yo) in recurrent ependymoma - at least 40 patients (20 in the erlotinib arm and 20 in the etoposide arm) with primary endpoint of objective response rate (ORR) assessed by investigator and secondary endpoint of duration of response, progression free survival (PFS) and overall survival (OS).
5/21/2012	DMC meeting was held to review the first interim analysis. The DMC acknowledged that the termination criteria were met, they believed that there was not enough data to establish futility and that there were no safety issues that necessitated termination of enrollment in the study.
8/15/2012	DMC reviewed second interim analysis: All 11 patients in the erlotinib group had progressive disease (PD). In the oral etoposide treatment group the following responses were observed (n=1 each): a confirmed partial response (PR), a confirmed minimal response (MR), a confirmed MR and unconfirmed PR, and an unconfirmed MR.
9/18/2012	Teleconference cancelled due to FDA agreement that futility criteria on the trial were met.
2/26/2014	PAS submitted including clinical study reports, datasets and proposed labeling.
10/27/201	Sponsor submitted an amended supplement to fulfill the PK/PD and popPK portions of the WR.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission contained the debarment certificate, sufficient datasets and relevant case report forms. The quality and integrity of the submission were adequate to permit a comprehensive review.

3.2 Compliance with Good Clinical Practices

According to the ethics sections of the submission, the submitted studies were conducted in compliance with all applicable laws and regulations, and in accordance with GCP guidelines and the Declaration of Helsinki.

3.3 Financial Disclosures

This submission contained the required financial disclosure information for clinical investigators who participated in Studies OSI-774-205 and OSI-774-206. There were no disclosable financial interests evident.

4 Significant Efficacy/Safety Issues Related to Clinical Pharmacology

The expectations of the WR were met from a clinical pharmacology perspective. Please see review by Dr. Ruby Leong for full detail on the issues related to clinical pharmacology.

5 Sources of Clinical Data

This supplemental application contains the results of a single clinical trial (a pediatric study of single-agent oral erlotinib compared to oral etoposide in pediatric patients with recurrent or refractory ependymoma) and a pharmokinetic analysis conducted in response to the WR. The study was conducted by OSI Pharmaceuticals. An additional study that was not conducted in response to the WR is included in this application. This study, entitled "Open-label Phase 2 Study of Single-agent Erlotinib for Patients with Pediatric Ependymoma previously Treated with Oral Etoposide in Protocol OSI-774-205" was included in this submission to provide the safety data for four additional pediatric patients.

5.1 Tables of Studies/Clinical Trials

Table 2: Clinical Trials of Erlotinib Conducted in Response to the WR

Study Number	Title	Design	Number of Patients
OSI-774-205	A Randomized, Phase 2 Study of Single-agent Erlotinib versus Oral Etoposide in Patients with Recurrent or Refractory Pediatric Ependymoma	International, multi-center, open-label study Patients were randomized 1:1 to receive either single agent oral erlotinib (85 mg/m2 daily, continuously for a 28	Anticipated 20 patients per arm. The study was stopped after a planned interim analysis due to futility criteria being met. 25 patients were randomized

		day cycle) or oral etoposide (50 mg/m2 daily for 21 days followed by 7 days of rest)	Erlotinib arm (n=13) Etoposide arm (n=12)
OSI-774-206*	Open-label Phase 2 Study of Single-agent Erlotinib for Patients with Pediatric Ependymoma previously Treated with Oral Etoposide in Protocol OSI-774-205	Patients registered to Study OSI-774-206 no more than 21 days from the last dose of oral etoposide in Study OSI-774-205. Enrolled patients received single-agent erlotinib (85 mg/m2 daily for a 28 day cycle).	Planned: 20 Actual enrollment: 4

* NOTE: Study OSI-774-206 was not conducted in response to the WR, however, the four patients enrolled are included in this submission for safety reporting purposes.

5.2 Review Strategy

The objectives of this review were two-fold: to determine if the Applicant fairly responded to the elements outlined in Amendment 1 of the WR and to provide recommendations for incorporation of relevant pediatric information derived from the conduct of the studies outlined in the WR into the Tarceva package insert. To accomplish these objectives, data from the clinical trials submitted with this supplement were comprehensively reviewed. Documentation from previous interactions with FDA regarding the pediatric development plan for erlotinib, the WR, and relevant published literature were also reviewed.

5.3 Discussion of Individual Clinical Trials

Note: the following descriptions of trials OSI-774-206 and OSI-774-206 are adapted from the trial protocol.

5.3.1 OSI-774-205

Study Title
A Randomized, Phase 2 Study of Single-agent Erlotinib versus Oral Etoposide in Patients with Recurrent or Refractory Pediatric Ependymoma

Study Milestones
This clinical trial was conducted by OSI Pharmaceuticals at 13 sites in the United States, Canada and United Kingdom from September 27, 2010 to November 26, 2012.

Study Objectives

The primary objective of this study was to determine the objective response rate (ORR) of single-agent erlotinib versus oral etoposide in patients with recurrent pediatric ependymoma.

The secondary objectives of this study were to:

- determine duration of response, minor response rate (MRR), disease control rate (DCR), progression-free survival (PFS), rate of prolonged stable disease (SD), duration of SD and overall survival (OS) of erlotinib versus oral etoposide
- describe the safety profile of erlotinib and oral etoposide in this patient population
- evaluate pharmacokinetics of erlotinib based on sparse sampling at steady state
- explore the prognostic and predictive value of epidermal growth factor receptor (EGFR)-related biomarkers, genes and other relevant biomarkers that may be associated with clinical outcomes

Study Design

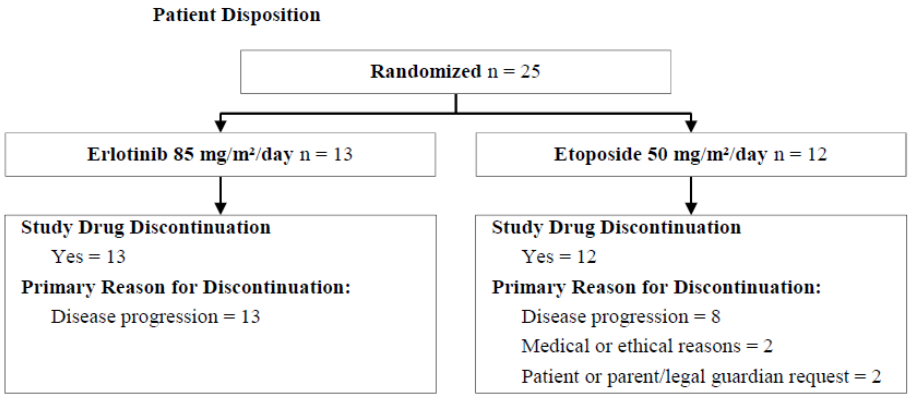
Methodology**:** This was an international, multi-center, randomized, open-label, phase 2 study of single-agent erlotinib versus oral etoposide in patients with recurrent pediatric ependymoma. A total of 40 patients were planned to be randomized 1:1 (20 patients per treatment arm) to receive either single-agent oral erlotinib at 85 mg/m2 per day continuously or oral etoposide at 50 mg/m2 per day for 21 days followed by a 7-day rest. Patients were to receive study drug until one of the following occurred: progression, death, patient request, investigator decision to discontinue study drug or intolerable toxicity.

The study was designed to include an interim analysis for futility in order to minimize patient exposure to treatment that was unlikely to provide benefit. There were to be up to 2 interim analyses: the first was to have occurred when the first 10 patients in the erlotinib arm had at least one scheduled radiological assessment or assessment showing progressive disease (PD) and the second was to have occurred when the first 10 patients in the erlotinib arm had at least two scheduled radiological assessments or assessment showing PD.

A Data Monitoring Committee (DMC) was used to evaluate safety on a periodic basis during the trial and to review the results of interim efficacy and safety analyses.

Number of Patients (Planned, Enrolled and Analyzed): The planned number of patients was 40 patients. Per DMC recommendation and FDA's agreement, the enrollment of patients was permanently closed due to futility criteria being met. Twenty-five patients were randomized and analyzed in the study: 13 patients in the erlotinib arm and 12 patients in the etoposide arm. The disposition of subjects in each treatment group is presented below.

Figure 1: Patient Disposition (adapted from sponsor submitted Study Synopsis)



Inclusion criteria

- Patients must have recurrent or refractory ependymoma or subependymoma and be ≥1 year to ≤ 21 years of age at the time of randomization/study entry;
- Performance status: Lansky ≥ 50% for patients ≤10 years of age or Karnofsky ≥ 50% for patients > 10 years of age;
- Measurable disease, defined as 1 measurable lesion that can be accurately measured in 2 planes. Measurable disease cannot include any lesion that has received radiation therapy within 12 weeks;
- Must have recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy before randomization/study entry;
- Serum creatinine based on age OR Creatinine Clearance/GF ≥70 mL/min/m2 6.
- Total bilirubin ≤ 1.5 x upper limit of normal for age, SGPT (ALT) ≤3 x ULN;
- Absolute neutrophil count > 1000/µL; platelet count > 100,000/µL (unsupported); and hemoglobin > 8 gm/dL (may receive PRBC transfusions);
- Patients must be neurologically stable for at least 7 days before randomization/study entry;
- If receiving corticosteroids, patients must be on a stable or decreasing dose for at least 7 days before randomization/study entry; and
- Patients – both males and females – with reproductive potential must agree to practice effective contraceptive measures for the duration of study drug therapy and for at least 90 days after completion of study drug therapy.

Exclusion criteria

- Must not have previously received an EGFR-targeted therapy (eg, erlotinib, gefitinib, lapatinib, cetuximab, etc);
- Must not have previously received oral etoposide;

- Must not have received craniospinal radiotherapy within 24 weeks before randomization/study entry or involved field radiotherapy to the target lesion (and/or lesion designated as "measurable" for protocol purposes) within 12 weeks before randomization/study entry; focal radiation to areas of symptomatic metastatic disease must not be given within 14 days before randomization/study entry;
- Must not have received myelosuppressive chemotherapy within 21 days before randomization/study entry (6 weeks if prior nitrosourea);
- Must not have received growth factors within 7 days before randomization/study entry;
- Must not participate in another investigational drug trial while on study;
- Must not have received a biologic agent within 7 days or a monoclonal antibody within 28 days before randomization/study entry (treatment with glucocorticoids are allowed);
- Must not be taking strong/moderate CYP3A4 or CYP1A2 inhibitors/inducers within 14 days before randomization/study entry
- Must not be taking proton pump inhibitors within 14 days before randomization/study entry;
- Must agree not to smoke during treatment;
- Pregnant or breast-feeding females.

Duration of Treatment

Patients were to be administered study drug until one of the following occurred: progression, death, patient request or investigator decision to discontinue study drug or intolerable toxicity.

Study drug was discontinued for the following reasons:

- Disease progression
- Adverse event
  - Resulting in death
  - Requiring withdrawal from study
  - Failure to recover from hematologic and/or nonhematologcial toxicity despite a dosing interruption of up to 21 days
- Medical or ethical reasons, including noncompliance, following discussion between the investigator and OSI
- Patient or parent/legal guardian request (excluding adverse events)

Concomitant Therapies

Prophylactic treatment for skin toxicity was encouraged by use of alcohol-free, emollient cream to moisturize dry areas of the body twice daily while taking erlotinib. Antidiarrheal and anti-emetic medications were allowed as needed. Concomitant treatment with warfarin or Coumadin-derived anticoagulants was permitted provided there would be increased vigilance with INR

monitoring. Patients with dry eyes were advised to use an ocular lubricant; patients were encouraged to discuss continuation of wearing contact lenses with their providers.

The use of CYP34a or CYP1A inhibitors/inducers and proton pump inhibitors was prohibited for patients randomized to the erlotinib arm. Those randomized to the etoposide arm were not prohibited from using CYP34a or CYP1A inhibitors/inducers or proton pump inhibitors. Palliative radiotherapy and the use of cytotoxic, hormonal therapy, biological or immune modifiers was prohibited for all patients enrolled on the trial.

Dose Reductions for Adverse Events

In the event of a toxicity that is not tolerated due to symptoms, or interference with normal daily activities (regardless of severity), or that is not controlled by optimal supportive care, the daily dose of erlotinib will be decreased to 65 mg/m2/day. If significant toxicity is still apparent, the dose may be reduced a second time to 50 mg/m2/day. No more than 2 dose reductions are allowed. The smallest erlotinib tablet strength is 25 mg. Because erlotinib can only be administered as a whole, crushed tablet, if a patient is being dosed at 25 mg and experiences a toxicity requiring a dose reduction, the patient will be discontinued from study treatment. Patients who require a dose reduction must be evaluated at least weekly until the toxicity stabilizes or improves. No dose re-escalations are allowed. Once determined to be stable, patients can resume evaluations according to the protocol-specified visit schedule. Any patient who fails to tolerate treatment with 50 mg/m2/day will be discontinued from erlotinib therapy and enter the post-treatment period of the study.

Criteria for Evaluation

Response and progression were evaluated using the International Society of Pediatric Oncology Brain Tumor Subcommittee for the Reporting of Trials criteria with slight modification. Response was assessed by magnetic resonance imaging scan every 8 weeks (every 2 cycles). The investigator assessed the best response (complete response [CR], partial response [PR], minor response [MR], SD, PD, not evaluable) patients achieved during the study. The best responses were used to calculate the efficacy variables and response rates. The primary efficacy variable was ORR, defined as the proportion of patients with a best overall response of CR or PR based on central nervous system (CNS)-specific evaluation criteria. The secondary efficacy variables included duration of response (days of CR/PR), MRR (CR/PR/MR), DCR (CR/PR/MR/SD [8 week minimum duration of SD]), PFS (days), rate of prolonged SD (CR/PR/MR/SD [16 week minimum duration of SD]), duration of SD (days of CR/PR/MR/SD [8 week minimum duration of SD]), OS (days) and an optional EGFR-related biomarker analysis. Patients were to receive study drug until 1 of the following occurred: progression, death, patient request, investigator decision to discontinue study drug or intolerable toxicity. Post-treatment assessments were to be performed $\leq$ 30 days after the last dose of study drug; and long-term follow-up was performed every 3 months for up to 12 months (or until study termination, whichever occurred first).

Pharmacokinetic parameters that were to be determined included, but were not limited to, steady state AUC_{tau},C_{max}, t_{max} and apparent body clearance (CL/F).

The safety and tolerability of the test drug was assessed using treatment-emergent adverse events (TEAEs) (frequency, severity, seriousness and relationship to study drug regimen), vital signs (systolic and diastolic blood pressure, pulse rate and temperature), clinical laboratory analyses (hematology and biochemistry) and physical examinations.

Statistical Methods

The following populations were defined for the analyses:

- Full Analysis Set (FAS): all randomized patients. This definition was consistent with intent-to-treat population as defined in the protocol.
- Efficacy Evaluable Set (EES): all patients in the FAS who also met the following criteria: received at least 1 cycle of study therapy and had a baseline tumor assessment as well as at least 1 post-baseline tumor assessment.
- Safety Analysis Set (SAF): all randomized subjects who received at least 1 dose of study drug.
- Pharmacokinetics Analysis Set (PKAS): patients treated with erlotinib for whom sufficient analyte concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter.

For continuous variables, descriptive statistics include the number of patients (n), mean, standard deviation, median, minimum and maximum. In addition, the coefficient of variation was calculated for continuous pharmacokinetic parameters, and the geometric mean was calculated for the pharmacokinetic parameter steady state AUC_{tau}. All confidence intervals are presented with 2-sided 95% confidence level unless otherwise stated. Frequencies and percentages are displayed for categorical data.

For the purpose of safety assessments in this study, events recorded during the pre-treatment period were classified as baseline signs and symptoms. A TEAE was defined as an adverse event observed after starting administration of the study drug. If a patient experienced an event both prior to and after starting administration of the study drug, the event was considered a TEAE only if it worsened in severity (i.e., it was reported with a new start date) after starting administration of the study drug. TEAEs observed or spontaneously reported from the first dosing of study drug to 30 days after the last dosing of study drug were summarized.

Study Schedule

Copied form Protocol OSI 774-205

Table 3: Schedule of Assessments for Study OSI-774-205

Baseline, During Treatment, Post-treatment, and Long-term Follow-up Assessments

Required Procedure/Investigations	Baseline	During Treatment[1]			Post-treatment	Long-term Follow-up[2]
	Before Study Treatment	Study Visit[3] Day 1	Weekly	Unscheduled Visits	End of Study Visit	Once Every 3 Months for up to 12 months
Informed Consent	X					
Medical History, Prior Therapy and Smoking History (if applicable)[4]	X					
NE, PE, Weight, Height, BSA, and PS[4]	X	X		X	X	
Vital Signs[4]	X	X		X	X	
Hematology[5]	X	X	X[5]	X	X	
Biochemistry[6]	X	X		X	X	
PK and Urine Cotinine[7]			X[7]			
Tumor Tissue Sample(s) Acquisition (optional)	X					
Radiology[8]	X	Every second cycle (8 weeks)				
Drug Dispensing/ Compliance Check[9]		X		X	X	
Serum Pregnancy Test[10]	X	If indicated			X	
Signs, Symptoms, and Toxicities[11]	X	Record on an ongoing basis			X	X
Concomitant Medications	X	Record on an ongoing basis			X	
Disease and Survival Status[12]						X
CSF[13]	If indicated					

1. For visit scheduling purposes, a month is defined as 4 weeks (28 days). Therefore, patients should be scheduled to return to the clinic **before** they run out of study drug. A window of up to ± 48 hours may be used in performing relevant tests.
2. Data collection during Long-term Follow-up will be limited to disease status, additional anti-cancer therapy, long-term survival, and new or ongoing study drug-related AEs.
3. Patients who require a dose reduction must be evaluated at least weekly until the toxicity stabilizes or improves. Once determined to be stable, patients can resume evaluations according to the protocol-specified visit schedule.
4. ≤ 14 days before randomization/study entry.
5. Hematology: WBC, hematocrit, hemoglobin, platelets, and differential. Baseline hematology assessment to be done ≤ 14 days before randomization/study entry. Etoposide patients **only** will need hematology performed weekly while on treatment. To be collected at unscheduled visits only if indicated.
6. Biochemistry: Sodium, potassium, BUN/Urea, creatinine, total bilirubin, calcium, total protein, AST, ALT, albumin, phosphate, magnesium, chloride, and bicarbonate. Baseline biochemistry assessment to be done ≤ 14 days before randomization/study entry. To be collected at unscheduled visits only if indicated.
7. PK only collected from erlotinib patients during Cycle 1 on Day 14 ± 2 (see **Section 9.1**). Urine for analysis of cotinine to be collected from erlotinib patients on the PK sampling day only.
8. Radiological evaluations include: MRI scans of brain and spine to evaluate for relapse/residual disease. At Baseline, the MRI scan of the brain and spine are to be done ≤ 14 days before randomization/study entry. During the treatment period, MRI evaluations should be performed every 2 cycles (8 weeks). Spine MRI only needs to be repeated if positive at baseline. Other radiological evaluations should be performed only if clinically indicated. Radiological evaluations to be repeated more often if clinically indicated to assess patient for relapse. During Long-term Follow-up, radiological evaluations should be done every 3 months for up to 12 months. If possible, the same method should be employed and assessed by the same institution on each occasion.
9. The date the patient takes the first dose of study drug will be considered Day 1 of this study. Patients should be scheduled to return to the clinic **before** they run out of study drug. At each visit, patients must return all unused study drug dispensed at the previous visit. Compliance will be assessed during patient visits. Study drug remaining in the returned bottle(s) must be counted and recorded. Data regarding missed and/or modified doses will be recorded in the CRF.
10. To be done ≤ 14 days before randomization/study entry for females of childbearing potential only. Repeat while on study (through post-treatment) only if clinically indicated.
11. Signs, symptoms, and toxicities will be assessed at Baseline before start of study drug and will be graded according to the NCI CTCAE, v 4.0. The Baseline evaluation should document residual toxicity from previous therapy and any current signs and symptoms. If patients are experiencing any skin reactions, they should be advised to see the study physician as soon as possible for assessment and appropriate treatment.
12. During Long-term Follow-up, new or ongoing study drug-related toxicities and disease and survival status should be evaluated at least every 3 months.
13. If indicated for disease evaluation based on investigator assessment.

5.3.2 OSI-774-206

Study Title

Open-label, Phase 2 Study of Single-agent Erlotinib for Patients with Pediatric Ependymoma Previously Treated with Oral Etoposide in Protocol OSI-774-205

Study Milestones
This clinical trial was conducted by OSI Pharmaceuticals at 13 sites in the United States, Canada and United Kingdom from September 27, 2010 to November 26, 2012.

Study Objectives
The primary objective of this study was to assess the safety profile of single-agent erlotinib in patient with recurrent or refractory pediatric ependymoma who were previously treated with oral etoposide in Protocol OSI-774-205.

The secondary objectives of this study were to evaluate:

- best disease response as determined by the investigator per institutional standards; and
- the median treatment duration for patients receiving erlotinib in this clinical setting

Study Design

Methodology: This was an international, multi-center, open-label, single-agent study of erlotinib in patients with recurrent pediatric ependymoma who were previously treated with oral etoposide in Protocol OSI-774-205. A total of 20 patients were planned to be enrolled to receiver single-agent oral erlotinib at 85 mg/m2 per day continuously Patients were to receive study drug until one of the following occurred: progression, death, patient request, investigator decision to discontinue study drug or intolerable toxicity.

A Data Monitoring Committee (DMC) was used to evaluate safety on a periodic basis during the trial and to review the results of interim efficacy and safety analyses.

Number of Patients (Planned, Enrolled and Analyzed): The planned number of patients was 20 patients. Per DMC recommendation and FDA's agreement, the enrollment of patients on Protocol OSI-774-205 was permanently closed due to futility criteria being met. Four patients enrolled on Protocol OSI-774-206 prior to the closure of Protocol OSI-774-205.

Inclusion criteria

- Patients must have enrolled in Protocol OSI-774-205, been randomized to oral etoposide and either progressed (according to study criteria) while on study or discontinued due to unacceptable toxicity related to etoposide;
- Performance status: Lansky $\geq$ 50% for patients $\leq$10 years of age or Karnofsky $\geq$ 50% for patients > 10 years of age;
- Must have recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy before randomization/study entry;
- Serum creatinine based on age OR Creatinine Clearance/GF $\geq$70 mL/min/m2 6.
- Total bilirubin $\leq$ 1.5 x upper limit of normal for age, SGPT (ALT) $\leq$3 x ULN;

- Patients must be neurologically stable for at least 7 days before randomization/study entry;
- Patients – both males and females – with reproductive potential must agree to practice effective contraceptive measures for the duration of study drug therapy and for at least 90 days after completion of study drug therapy.
- Patients must be able to take erlotinib orally.

Exclusion criteria

- Must not be taking strong/moderate CYP3A4 or CYP1A2 inhibitors/inducers within 14 days before randomization/study entry
- Must not have received any other chemotherapy or immunotherapy to treat ependymoma after discontinuation from Protocol OSI-774-205.
- Must not be taking proton pump inhibitors within 14 days before randomization/study entry;
- Participating in another investigational drug trial while on study; and/or
- Pregnant or breast-feeding females.

Duration of Treatment

Patients were to be administered study drug until one of the following occurred: progression, death, patient request or investigator decision to discontinue study drug, or intolerable toxicity.

Study drug was discontinued for the following reasons:

- Disease progression
- Adverse event
    - Resulting in death
    - Requiring withdrawal from study
    - Failure to recover toxicity despite a dosing interruption of up to 21 days
    - Inability to dose reduce
    - Continued and unacceptable toxicity associated with erlotinib despite 2 dose reductions
- Medical or ethical reasons, including noncompliance, following discussion between the investigator and OSI
- Patient or parent/legal guardian request (excluding adverse events)

Concomitant Therapies

Prophylactic treatment for skin toxicity was encouraged by use of alcohol-free, emollient cream to moisturize dry areas of the body twice daily while taking erlotinib. Antidiarrheal and anti-emetic medications were allowed as needed. Concomitant treatment with warfarin or Coumadin-derived anticoagulants was permitted proved increased vigilance with INR monitoring. Patients with dry eyes were advised to use an ocular lubricant; the patient was encouraged to discuss continuation of wearing contact lenses with provider.

The use of CYP34a or CYP1A inhibitors/inducers and proton pump inhibitors was prohibited. The use of cytotoxic, hormonal therapy, biological or immune modifiers was prohibited for all patients enrolled on the trial. Palliative radiotherapy may be allowed on a case-by-case basis after discussion with the investigator and the sponsor's medical monitor.

Dose Reductions for Adverse Events

In the event of a toxicity that is not tolerated due to symptoms, or interference with normal daily activities (regardless of severity), or that is not controlled by optimal supportive care, the daily dose of erlotinib will be decreased to 65 mg/m2/day. If significant toxicity is still apparent, the dose may be reduced a second time to 50 mg/m2/day. No more than 2 dose reductions are allowed. The smallest erlotinib tablet strength is 25 mg. Because erlotinib can only be administered as a whole, crushed tablet, if a patient is being dosed at 25 mg and experiences a toxicity requiring a dose reduction, the patient will need discontinued from study treatment. Patients who require a dose reduction must be evaluated at least weekly until the toxicity stabilizes or improves. No dose re-escalations are allowed. Once determined to be stable, patients can resume evaluations according to the protocol-specified visit schedule. Any patient who fails to tolerate treatment with 50 mg/m2/day will be discontinued from erlotinib therapy and enter the post-treatment period of the study.

Criteria for Evaluation

While assessment of disease during treatment on this study should occur as determined by the investigator and per institutional standards, information on disease assessment will not be captured as part of the CRF during the on-study treatment period. However, at the end of study treatment, a best disease response determination will be derived from an integrated clinical assessment by the study investigator as per institutional standards. This will include radiographic assessments deemed appropriate by the investigator in the normal care of the patient. A determination of best disease response at the end of study treatment (CR, PR, MR or SD) will only be made if 1) any disease-related neurologic symptoms are stable or improving over the interval of the radiographic assessment and 2) corticosteroid dosing for the control of tumor-related signs/symptoms is stable or decreasing. If the investigator deems that a radiographic assessment is not needed, then evidence of clinical improvement may be used to determine best response provided that corticosteroid dosing for tumor-related signs/symptoms is stable or decreasing.

The safety and tolerability of the test drug was assessed using treatment-emergent adverse events (TEAEs) (frequency, severity, seriousness and relationship to study drug regimen), vital signs (systolic and diastolic blood pressure, pulse rate and temperature), clinical laboratory analyses (hematology and biochemistry) and physical examinations.

Statistical Methods

All patients who received at least one dose of study drug were considered evaluable for all safety measures. The safety evaluation was based mainly on adverse events, laboratory tests, and physical exam. Descriptive statistics were used to summarize safety data.

Study Schedule
Copied form Protocol OSI-774-206

Table 4: Schedule of Assessments for Study OSI-774-206

Investigations			Timing[a]
Physical Examination and Other Evaluations	• PE • Height	• Weight • BSA	≤ 7 days before Day 1 of each cycle, at unscheduled visits, and at the last study visit
Vital Signs	• Pulse • BP • Temperature		≤ 7 days before Day 1 of each cycle, at unscheduled visits, and at the last study visit
Biochemistry	• Sodium • Potassium • BUN/Urea • Creatinine • Total bilirubin • Calcium • Total protein	• AST • ALT • Albumin • Phosphate • Magnesium • Chloride • Bicarbonate	On Day 1 of each cycle and at the last study visit. To be collected at unscheduled visits only if indicated
Hematology	• WBC • Hematocrit • Hemoglobin	• Platelets • Differential	
Other Investigations	Pregnancy test[b]		If indicated
	Concomitant medications		Record on an ongoing basis
Signs, Symptoms, and Toxicities[c]	Evaluated on an ongoing basis throughout the study and at the last study visit		
Disease Assessment[d]	Best disease response		On Day 1 of each cycle and at the last study visit. To be collected at unscheduled visits only if indicated

[a] A window of up to ± 48 hours may be used in performing relevant tests.
[b] For females of childbearing potential only. Repeat while on study only if clinically indicated.
[c] Signs, symptoms, and toxicities will be assessed and graded according to the NCI CTCAE, v 4.0. If patients are experiencing any skin reactions, they should be advised to see the study physician as soon as possible for assessment and appropriate treatment.
[d] Best disease response determination at the end of study treatment will be derived from an integrated clinical assessment by the study investigator per institutional standards (see **Section 7.3.2**).

5 Evaluation of the Applicant's Fulfillment of the Requirements of the Pediatric Written Request

Table 5, adapted from the Applicant's submission, outlines the items contained in the WR and the information and responses submitted by the Applicant with this sNDA. After conducting a thorough interdisciplinary review of the data submitted, the clinical, clinical pharmacology, and

statistical reviewer concluded that the Applicant fulfilled the requirements for the WR and recommended that pediatric exclusivity be awarded to the Applicant. The Pediatric Exclusivity Board provided concurrence with this recommendation and exclusivity was granted for pediatric studies of erlotinib conducted in response to the WR, effective March 18, 2015, under section 505A of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355a).

Table 5: Summary of the Applicant's Response to the Pediatric Written Request

Written Request Items	Information Submitted/Sponsor's Response
Types of studies/Study Design: 1. Phase 2 Study (OSI-774-205, PETEY): An open-label, multi-center, randomized trial evaluating the safety, efficacy and pharmacokinetics of erlotinib and etoposide utilizing a 1:1 randomization scheme. 2. Pharmacokinetic (PK) Studies: Studies and/or analyses, including pharmacokinetics that defines age appropriate dosing in pediatric patients. Pharmacokinetic samples must be collected through approaches such as rich sampling or optimal sparse sampling in patients. Such data must then be appropriately analyzed using methods such as nonlinear mixed effects modeling or noncompartmental analysis. Available Phase 1 data and the data from the Phase 2 trial must be combined to develop pharmacokinetic and pharmacodynamic (PK-PD) models to explore exposure-response relationships for measures of safety and effectiveness.	**Types of studies:** 1. OSI-774-205: An open-label, multi-center, randomized trial evaluating the safety, efficacy and pharmacokinetics of erlotinib and etoposide utilizing a 1:1 randomization scheme. 2. Pharmacokinetic (PK) Studies: Data from the following four erlotinib pediatric studies were used to adequately address the PK and pharmacodynamic (PD) components of erlotinib: • OSI-774-205 (PETEY) conducted by Astellas Pharma Global Development. Sparse sampling (4 samples around a dose) for PK was collected at steady-state on day 14. • 3 investigator-sponsored studies - Geoerger, 2011: open label, 3+3 dose-escalation (dose levels 75, 100, 125 and 150 mg/m^2 daily) trial in pediatric patients with refractory/recurrent malignant brain tumors. Intensive PK sampling was collected at various steady-state time points during the first 6 cycles of therapy. - Jakacki, 2008: open label, 3+3 dose escalation of erlotinib (dose levels 35, 60, 85, and 110 mg/m^2 daily) in combination with temozolomide in children younger than 22 years with recurrent or refractory central nervous system tumor, osteogenic sarcoma, rhabdomyosarcoma, soft tissue sarcoma, neuroblastoma, or germ cell tumor. Intensive PK sampling was collected after the first dose and at steady-state on day 10). - Broniscer, 2009: open label, 3+3 dose escalation of erlotinib (dose levels 70, 90, 120, 160 and 200 mg/m^2 daily) in combination with radiation therapy in patients

	(age 3 to 25 years) with newly diagnosed high-grade glioma. Intensive PK sampling was collected after the first dose and at steady-state on day 8. • Available data from these studies were used to explore exposure-response relationships for safety. Given that responses were not observed in patients treated with erlotinib in Study OSI-774-205, the planned exposure-response analysis for activity/efficacy was not conducted.
3. Study 2 (OSI-774-206): Single-arm study of single-agent erlotinib in patients with recurrent or refractory pediatric ependymoma who were previously treated with oral etoposide on PETEY 774-205 (companion study for Study 1).	**3. Study 2 (OSI-774-206): Single-arm study of single-agent erlotinib in patients with recurrent or refractory pediatric ependymoma who were previously treated with oral etoposide on PETEY 774-205 (companion study for Study 1).**
Indication(s) to be studied: 1. OSI-774-205: pediatric patients with recurrent ependymoma. 2. PK Studies: pediatric patients with cancer. 3. OSI-774-206: Not specified in WR	**Indication(s) studied:** 1. OSI-774-205: pediatric patients with recurrent ependymoma. 2. PK Studies: - OSI-774-205: pediatric patients with recurrent ependymoma - Geoerger, 2011: pediatric patients with recurrent/refractory malignant brain tumors - Jakacki, 2008: pediatric patients with recurrent or refractory centeral nervous system tumor, osteogenic sarcoma, rhabdomyosarcoma, soft tissue sarcoma, neuroblastoma, or germ cell tumor first with oral solution and later tablet formulation. - Broniscer, 2009: pediatric patients with newly diagnosed high-grade glioma. 3. OSI-774-206: pediatric patients with recurrent ependymoma.

<table>
<tr><td></td><td></td></tr>
<tr><td>Written Request Items</td><td>Information Submitted/ Sponsor's response</td></tr>
<tr><td>Age group and population in which study will be performed:

1. OSI-774-205: Patients ≥1 year to ≤ 21 years of age at randomization

2. PK Studies: Patients 3 to 21 years of age.

3. OSI-774-206: Not specified in WR</td><td>Age group and population in which study was performed:

1. OSI-774-205: This study enrolled patients aged 1 to 21 years, distributed among the following age groups: 1-6 years (n=7), 7-11 years (n=5), 12-16 years (n=8), and 17-21 years (n=5).

<table><tr><th>Parameter</th><th>Erlotinib 85 mg/m²/day (n = 13)</th><th>Etoposide 50 mg/m²/day (n = 12)</th><th>Total (n = 25)</th></tr><tr><td>Age (Years)</td><td></td><td></td><td></td></tr><tr><td>Mean (SD)</td><td>12.8 (5.87)</td><td>9.2 (4.99)</td><td>11.1 (5.67)</td></tr><tr><td>Median</td><td>14</td><td>8.5</td><td>12</td></tr><tr><td>Min - Max</td><td>3 - 20</td><td>2 - 18</td><td>2 - 20</td></tr></table>*Table adapted from Sponsor submitted Study Synopsis

2. PK Studies:
- OSI-774-205: Patients 3 to 21 years of age.
- Geoerger, 2011: 1 to 21 years
- Jakacki, 2008: pediatric patients younger than 22 years of age
- Broniscer, 2009: pediatric patients age 3 to 25 years

3. OSI-774-206: Patients ≥1 year to ≤ 21 years of age at randomization who were enrolled on OSI-774-205</td></tr>
<tr><td>Number of patients to be studied or power of study to be achieved:

1. OSI-774-205: at least 40 (at least 20 per erlotinib arm; at least 20 per etoposide arm)</td><td>Number of patients studied or power achieved:

1. OSI-774-205: Enrollment in this study was permanently closed due to the futility criteria being met at the second interim analysis as recommended by the Data Monitoring Committee and agreed to by FDA. Disease progression was the reason for study drug</td></tr>
</table>

<table>
<tr><td></td><td>discontinuation in all (13/13) patients in the erlotinib arm and in 66.7% (8/12) patients in the etoposide arm. The majority of patients in both arms were male, not Hispanic Latino, white between 2 and 20 years of age.

<table>
<tr><th>Parameter</th><th>Erlotinib
85 mg/m²/day
(n = 13)</th><th>Etoposide
50 mg/m²/day
(n = 12)</th><th>Total
(n = 25)</th></tr>
<tr><td>Sex, n (%)</td><td></td><td></td><td></td></tr>
<tr><td>Male</td><td>10 (76.9%)</td><td>9 (75.0%)</td><td>19 (76.0%)</td></tr>
<tr><td>Female</td><td>3 (23.1%)</td><td>3 (25.0%)</td><td>6 (24.0%)</td></tr>
<tr><td>Ethnicity, n (%)</td><td></td><td></td><td></td></tr>
<tr><td>Hispanic/Latino</td><td>1 (7.7%)</td><td>2 (16.7%)</td><td>3 (12.0%)</td></tr>
<tr><td>Not Hispanic/Latino</td><td>12 (92.3%)</td><td>10 (83.3%)</td><td>22 (88.0%)</td></tr>
</table>
*Table adapted from Sponsor submitted Study Synopsis</td></tr>
<tr><td>2. PK Studies: The number of patients entered must be sufficient to achieve Phase 1 objectives.</td><td>2. PK Studies: A total of 105 patients were included in the PK analysis.
- OSI-774-205: see above (13 patients received erlotinib)
- Geoerger, 2011: 51 patients enrolled (50 received treatment)
- Jakacki, 2008: 46 patients received treatment (mean age 11.5 years) . Of the 46 patients, 30 were male, 16 female; 34 were white, 5 African American, 3 Asian, 1 American Indian or Alaska Native and 3 unknown; 3 Hispanic or Latino, 41 non-Hispanic, 2 unknown.
- Broniscer, 2009: 23 patients received treatment (mean age 10.7 years, range 3.7-22.5 years).</td></tr>
<tr><td>3. OSI-774-206: not specified in WR</td><td>3. OSI-774-206: Up to 20 patients were expected to enroll. The study closed after the OSI-774-205 close due to futility. Four patients enrolled on this trial</td></tr>
<tr><td>Written Request Items</td><td>Information Submitted/ Sponsor’s response</td></tr>
<tr><td>Entry criteria:</td><td>Entry criteria used:</td></tr>
</table>

Not specified in the WR	**OSI-774-205:** **(adapted from Sponsor submitted Study Synopsis)** • Patients eligible to participate were patients 1 to 21 years of age with recurrent or refractory ependymoma or subependymoma. • Patients must have recovered from the acute toxic effects of all prior chemotherapy, immunotherapy or radiotherapy and must have had measurable disease, defined as 1 measurable lesion that could be accurately measured in 2 dimensions. • Patients must have also been neurologically stable and if on corticosteroids, be on a stable or decreasing dose for at least 7 days before randomization/study entry. • Their performance status must have been ≥ 50% on the Lansky or Karnofsky scale (depending on age). • Serum creatinine or creatinine clearance/glomerular filtration rate, total bilirubin and alanine aminotransferase must have all been below protocol-specified limits. • Absolute neutrophil count, platelet count and hemoglobin must have all been above protocol-specified limits. • Patients (both males and females) with reproductive potential must have agreed to practice effective contraceptive measures for the duration of study drug therapy and for at least 90 days after completion of study drug therapy. • The informed consent statement was to be signed by all patients or their parent/legal guardian or legal representative.
Clinical endpoints: 1. OSI-774-205: a. Primary: Objective response rate (ORR) as assessed by investigator	**Clinical endpoints used:** 1. OSI-774-205: a. The primary objective of this study was to determine the objective response rate (ORR) of single-agent erlotinib versus oral etoposide in patients with recurrent pediatric ependymoma.

b. Secondary: Duration of response, progression-free survival (PFS), and overall survival (OS)	b. The secondary objectives of this study were to: • determine duration of response, minor response rate (MRR), disease control rate (DCR), progression-free survival (PFS), rate of prolonged stable disease (SD), duration of SD and overall survival (OS) of erlotinib versus oral etoposide. • describe the safety profile of erlotinib and oral etoposide in this patient population. • explore the prognostic and predictive value of epidermal growth factor receptor (EGFR)-related biomarkers, genes and other relevant biomarkers that may be associated with clinical outcomes.
2. PK Studies: Determine the maximum tolerated dose (MTD), dose-limiting and other toxicities in pediatric patients with cancer	2. PK Studies: - OSI-774-205: evaluate PK of erlotinib based on sparse sampling at steady-state. - Geoerger, 2011: to estimate the MTD of erlotinib and determine the PK of erlotinib and its metabolite (OSI-420). - Jakacki, 2008: to estimate the MTD of erlotinib in oral solution and once determined, to study the tolerability and PK of tablet formulations. - Broniscer, 2009: to estimate the MTD of erlotinib administered during and after radiotherapy and to describe the PK of erlotinib and its metabolite OSI-420.
3. OSI-774-206: not specified in WR	3. OSI-774-206: not specified in WR a. The primary objective of this study was to: - Assess the safety profile of single-agent erlotinib in

	patients with recurrent or refractory pediatric ependymoma who were previously treated with oral etoposide in Protocol OSI-774-205. b. The secondary objectives of this study were to evaluate: - Best overall response at the end of treatment with erlotinib as determined by the investigator per institutional standards; and - Median treatment duration for patients receiving erlotinib in this clinical setting.
Timing of assessments: if appropriate *Not applicable*	**Timing of assessments:** *Not applicable*
Written Request Items	**Information Submitted/ Sponsor's response**
Drug specific safety concerns: In clinical trials with adults, rash (dermatosis), diarrhea, nausea, fatigue, stomatitis, vomiting, and headache were the most frequently observed undesirable effects following exposure to single-agent erlotinib.	**Drug specific safety concerns evaluated:** 1. OSI-774-205: Safety evaluations included routine clinical examinations, evaluation of symptomatic adverse events, and laboratory studies including complete blood counts (CBCs), electrolytes, assessments of renal and hepatic function, and pregnancy. For skin reactions, patients were advised to see the study physician as soon as possible for assessment. Toxicity was monitored and graded according to the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events version 4.0 (CTCAEv4.0). 2. PK Studies: similar to OSI-774-205, see above 3. OSI-774-206: same as OSI-774-205, see above
Drug information: **Dosage Form:** OSI-774-205/206: Tablets crushed in apple sauce. PK Studies: Oral solution, whole tablets and/or crushed tablets.	**Drug information:** **Dosage Form:** OSI-774-205/206: Tablets crushed in apple sauce. PK Studies: Oral solution, whole tablets and/or crushed tablets.

Route of Administration: Oral **Regimen:** OSI-774-205/206: 85 mg/m2/day continuously PK Studies: 35-160 mg/m2/day continuously	**Route of Administration:** Oral **Regimen:** OSI-774-205/206: 85 mg/m2/day continuously PK Studies: 35-160 mg/m2/day continuously
Statistical information (statistical analyses of the data to be performed): 1. OSI-774-205: All randomized patients will be included in the efficacy analysis. Following the intent-to-treat principle, patients will be analyzed according to the treatment to which they were assigned at randomization. The ORR along with exact 95% confidence intervals will be calculated for each treatment arm. In addition, the ORR between the 2 treatment arms will be compared using Fisher's exact test. Assuming ORR is between 10% and 40% for single-agent erlotinib, the power for the final analysis of ORR using Fisher's exact test (alpha = 0.05, two-sided) is no more than 12% with the current sample size (20 patients per arm). With 20 patients in each arm, the chance to observe at least 1 responder in each arm will be 64%, 88%, 96%, and 99% if the true response rate in each arm is 5%, 10%, 15%, and 20%, respectively. If the response rate is at least 15% in each arm, the chance of not observing any responder in each arm is less than 5%.	**Statistical information (statistical analyses of the data to be performed):** 1. OSI-774-205: • Descriptive statistics were used to report study results. • According to the statistical design of OSI-774-205, the first of two planned interim analyses was conducted when the first 10 patients in the erlotinib arm had a least 1 scheduled radiological assessment or assessment showing progressive disease (PD). Based on this analysis, the study was permanently closed due to futility criteria being met.

The study has been designed to consider stopping early at an interim analysis due to lack of efficacy, minimizing additional patient exposure to treatment that is unlikely to provide benefit. There will be two interim analyses: the first will occur when the first 10 patients in the erlotinib arm have had at least 1 scheduled radiological assessment and the second will occur when the first 10 patients in the erlotinib arm have had at least 2 scheduled radiological assessments. The criteria for lack of efficacy have been strictly defined. The lack of efficacy for the first interim analysis is defined as follows: • ≥ 7 of the 10 patients in the erlotinib arm have PD; and • No response [complete response (CR) or partial response (PR)] or minor response in the erlotinib arm; and • ≥ 1 response (CR, PR) in the etoposide arm. The lack of efficacy for the second interim analysis is defined as following: • All 10 patients in the erlotinib arm have progressive disease (PD); and • ≥ 1 response (CR, PR) in the etoposide arm. Time to event variables (PFS or OS) will be analyzed by constructing Kaplan-Meier curves for each treatment arm. Median time to event and 95% confidence intervals will be estimated from the Kaplan-Meier curve. The treatment effect of erlotinib relative to etoposide will be analyzed using log-rank test. The corresponding hazard ratio of the treatment effect along with 95% confidence intervals will be calculated using a Cox proportional hazard model.	

2. PK Studies: • Descriptive statistics • The pharmacokinetic studies must be prospectively powered to target a 95% confidence interval within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution for erlotinib in each of the age groups (1-6, 7-16 years old). 3. OSI-774-206: not specified in WR	2. PK Studies • Descriptive Statistics • The population PK analysis showed that the 95% CI for the geometric mean estimates of CL/F and V_d/F in each age group fell within the predefined range of 60% and 140%, which suggests sufficient power to define these parameters for the age groups of 1 to 6 years and 7 to 16 years. 3. OSI-774-205: Descriptive statistics only
Written Request Items	**Information Submitted/ Sponsor's response**
Labeling that may result from the studies: You must submit proposed pediatric labeling to incorporate the findings of the study. Under section 505A(j) of the Act, regardless of whether the study demonstrate that erlotinib is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study. Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study.	**Labeling that may result from the studies:** *The sponsor proposes the following labeling changes to Section 8.4 Pediatric Use:* **Current label:** The safety and effectiveness of TARCEVA in pediatric patients have not been established. **Sponsor Proposed label:** (b) (4) (b) (4)

	(b) (4) **New Label (agreed upon by Sponsor and FDA):** The safety and effectiveness of TARCEVA in pediatric patients have not been established. In an open-label, multi-center trial, 25 pediatric patients (median age 14 years, range 3-20 years) with recurrent or refractory ependymoma were randomized (1:1) to TARCEVA or etoposide. Thirteen patients received TARCEVA at a dose of 85 mg/m^2/day orally until disease progression, death, patient request or investigator decision to discontinue study drug or intolerable toxicity. Four patients randomized to etoposide also received TARCEVA following disease progression. The trial was terminated prematurely for lack of efficacy; there were no objective responses observed in these 17 TARCEVA-treated patients. No new adverse events were identified in the pediatric population. Based on the population pharmacokinetics analysis conducted in 105 pediatric patients (2 to 21 years old) with cancer, the geometric mean estimates of CL/F/BSA (apparent clearance normalized to body surface area) were comparable across the three age groups: 2-6 years (n=29), 7-16 years (n=59), and 17-21 years (n=17).
Format of reports to be submitted: You must submit full study report (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the report must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to	**Format of reports submitted:** Full study reports not previously submitted to the Agency including full analysis, assessment, and interpretation of the data were submitted. The reports included information on the representation of pediatric patients of ethnic and racial minorities according to the categories and designations in the WR. A population PK and PK/PD report was also submitted.

use other categories, you should obtain agency agreement. Under section 505A(d)(2)(B) of the Act, when you submit the study report, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. These postmarketing adverse event reports should be submitted as narrative and tabular reports.	
Timeframe for submitting reports of the studies: Original WR: Report of the above study must be submitted to the Agency on or before June 30, 2104. Amendment #1 submitted on June 12, 2014 to request extending the due date for final study reports from June 30, 2014 to December 31, 2014. Rationale: there was a delay in the receipt of PK/PD datasets from the three phase 1 investigator-sponsored studies leading to a delay in completing the population PK/PD analysis. The request for extension was granted by FDA on June 23, 2014.	**Timeframe for submitting reports of the studies:** The clinical study reports, associated data sets and proposed labeling changes were submitted on February 26, 2014. The population PK and PK/PD report and datasets were submitted on October 27, 2014.

6 Review of Efficacy

Efficacy Summary

The data submitted with this application did not provide evidence of a treatment benefit from administration of erlotinib to pediatric patients with relapsed/recurrent ependymoma.

The trial submitted in response to the WR was closed due to the futility criteria being met at the planned second interim analysis. This is a randomized controlled trial of erlotinib verses etoposide, randomized 1:1. A total of 25 patients enrolled on the trial, 13 in the erlotinib arm and 12 in the etoposide arm. In FAS, the best response was achieved by patients in the erlotinib arm was stable disease (SD) and no patients in the erlotinib arm achieved a complete response (CR) or partial response (PR). In the etoposide arm, 16.7% (2/12) of patients achieved PR, which resulted in an ORR 16.7%. The SD seen in 2 patients in the erlotinib arm was sustained for less than 16 weeks (78 and 80 days). The median PFS was 52 days for the erlotinib arm and 65 days for the etoposide arm. PFS evens occurred in all of the erlotinib-treated patients and 9 of the 12 etoposide treated patients. The three etoposide-treated patients without a PFS event were treated for a range of 248 to 679 days. The PFS hazard ratio of erlotinib versus etoposide was 2.88 (95% CI: 1.12 to 7.39). Median OS was not reached in the erlotinib arm and was 261 days in the etoposide arm. The OS hazard ratio of erlotinib versus etoposide was 0.54 (95% CI: 0.14 to 2.18). Given the small sample size and large variability in both arms, conclusions regarding the OS and PFS cannot be made.

6.1 Methods

Clinical review was based primarily upon the clinical study report for study OSI-774-205, case report forms, and primary datasets submitted by the Applicant.

6.2 Demographics

Demographic characteristics of the intent-to-treat (ITT) population used in the efficacy analysis of Study OSI-774-205 are depicted in Table 6 below.

Table 6: Summary of Patient Baseline Demographic Characteristics for Study OSI-774-205 (adapted from Sponsor submitted Study Synopsis, verified by clinical reviewer)

Parameter	Erlotinib 85 mg/m²/day (n = 13)	Etoposide 50 mg/m²/day (n = 12)	Total (n = 25)
Sex, n (%)			
Male	10 (76.9%)	9 (75.0%)	19 (76.0%)
Female	3 (23.1%)	3 (25.0%)	6 (24.0%)
Ethnicity, n (%)			
Hispanic/Latino	1 (7.7%)	2 (16.7%)	3 (12.0%)
Not Hispanic/Latino	12 (92.3%)	10 (83.3%)	22 (88.0%)
Race†, n (%)			
Asian - Indian Subcontinent	0	1 (8.3%)	1 (4.0%)
Asian - Southeast Asia	0	1 (8.3%)	1 (4.0%)
Black	1 (7.7%)	1 (8.3%)	2 (8.0%)
Other	1 (7.7%)	0	1 (4.0%)
White	11 (84.6%)	9 (75.0%)	20 (80.0%)
Age Group (Years), n (%)			
1 - 6	3 (23.1%)	4 (33.3%)	7 (28.0%)
7 - 11	2 (15.4%)	3 (25.0%)	5 (20.0%)
12 - 16	4 (30.8%)	4 (33.3%)	8 (32.0%)
17 - 21	4 (30.8%)	1 (8.3%)	5 (20.0%)
Age (Years)			
Mean (SD)	12.8 (5.87)	9.2 (4.99)	11.1 (5.67)
Median	14	8.5	12
Min - Max	3 - 20	2 - 18	2 - 20
Weight (kg)			
Mean (SD)	56.9 (31.33)	37.6 (18.76)	47.6 (27.36)
Median	62.2	44.3	44.7
Min - Max	15.9 - 121.4	13.5 - 62.6	13.5 - 121.4
Height (cm)			
Mean (SD)	148.7 (28.23)	135.6 (31.7)	142.4 (30.06)
Median	165	129.6	147.4
Min - Max	101 - 182.8	90 - 177.4	90 - 182.8
BSA (m^2)			
Mean (SD)	1.51 (0.556)	1.17 (0.439)	1.35 (0.521)
Median	1.72	1.26	1.32
Min - Max	0.67 - 2.42	0.58 - 1.7	0.58 - 2.42
Performance Scale - Lansky			
All Lansky	5 (38.5%)	7 (58.3%)	12 (48.0%)
100	3 (23.1%)	2 (16.7%)	5 (20.0%)
90	2 (15.4%)	4 (33.3%)	6 (24.0%)
80	0	0	0
70	0	1 (8.3%)	1 (4.0%)
< 70	0	0	0
Performance Scale - Karnofsky			
All Karnofsky	8 (61.5%)	5 (41.7%)	13 (52.0%)
100	6 (46.2%)	4 (33.3%)	10 (40.0%)
90	1 (7.7%)	0	1 (4.0%)
80	1 (7.7%)	1 (8.3%)	2 (8.0%)
70	0	0	0
< 70	0	0	0

Table 7 Summary of Patient Baseline Demographic Characteristics for Study OSI-774-206 (adapted from Sponsor submitted Study Synopsis, verified by clinical reviewer)

Age (Years)	Sex	Race	Weight (kg)	Height (cm)	BSA (m^2)
13	M	Asian-Indian Subcontinent	53.0	159.7	1.50
5	M	White	18.9	106.7	0.75
7	F	White	16.0	110.0	0.70
14	M	White	58.9	178.1	1.70

6.3 Concomitant Medications

The most frequently used concomitant medications, corticosteroids, were administered to 25 patients of 25 patients (100%) in the ITT analysis populations and to two patients on study OSI-774-206. Ondansetron was administered to 17 patients (68%) and H2-receptor antagonists were administered to 11 patients (44%) in study OSI-774-205; patients in study OSI-774-206 had a similar incidence of medication use.

6.4 Patient Disposition

Patients enrolled in 13 institutions in the United States, Canada, and United Kingdom from September 27, 2010 through November 26, 2012. Reasons for discontinuation of treatment for patients in the erlotinib arm include disease progression (13 of 13 patients). Reasons for discontinuation for treatment in the etoposide arm include disease progression (n=8), patient/parent/legal guardian request (n=2, one was unable to swallow pills [last dose on study day 4] and one went on an extended vacation out of the country [last dose on study day 248]), medical or ethical reasons including non-compliance (n=2, one completed 24 cycles and one completed 12 cycles).

6.5 Analysis of Primary Endpoint(s)

The primary endpoint of this study, to determine the objective response rate (ORR) of single-agent erlotinib versus oral etoposide in patients with recurrent ependymoma, was not met. Enrollment in the study was permanently close due to the futility criteria being met at the second planned interim analysis.

Response and progression were evaluated using the International Society of Pediatric Oncology Brain Tumor Subcommittee for the Reporting of Trials criteria with slight modification. Response was assessed by magnetic resonance imaging scan every 8 weeks (every 2 cycles). The investigator assessed the best response (complete response [CR], partial response [PR], minor response [MR], SD, PD, not evaluable) patients achieved during the study. The best responses were used to calculate the efficacy variables and response rates. The primary efficacy variable was ORR, defined as the proportion of patients with a best overall response of CR or PR based on central nervous system (CNS)-specific evaluation criteria.

In FAS, the best response was achieved by patients in the erlotinib arm was SD and no patients in the erlotinib arm achieved a CR or PR. In the etoposide arm, 16.7% (2/12) of patients achieved PR, which resulted in an OR 16.7%. The SD seen in 2 patients in the erlotinib arm was sustained for less than 16 weeks (78 and 80 days).

Table 8: Objective Response Rate (CR+PR) by Investigator Assessment, FAS and EES (adapted from Sponsor submitted Study Synopsis, verified by clinical reviewer)

Analysis Set	Erlotinib 85 mg/m²/day	Etoposide 50 mg/m²/day	Fisher's Exact P value
FAS	**n = 13**	**n = 12**	--
n (%) (95% CI)‡	0 (0%, 24.7%)	2 (16.7%) (2.1%, 48.4%)	0.2200
EES	**n = 11**	**n = 11**	--
n (%) (95% CI)‡	0 (0%, 28.5%)	2 (18.2%) (2.3%, 51.8%)	0.4762

--: not applicable; CR: complete response; EES: Efficacy Evaluable Set; FAS: Full Analysis Set; PR: partial response

† Includes only confirmed responses.

‡ 95% CI for response rate was calculated using the Clopper-Pearson method.

6.6 Analysis of Secondary Endpoints(s)

In the FAS group, the median PFS was 52 days for the erlotinib arm and 65 days for the etoposide arm. PFS events occurred in all of the erlotinib-treated patients and 9 of the 12 etoposide treated patients. The three etoposide-treated patients without a PFS event were treated for a range of 248 to 679 days. The PFS hazard ratio of erlotinib versus etoposide was 2.88 (95% CI: 1.12 to 7.39). Median OS was not reached in the erlotinib arm and ass 261 days in the etoposide arm. The OS hazard ratio of erlotinib viruses etoposide was 0.54 (95% CI: 0.14 to 2.18).

Table 9: Summary of Time to Event Endpoints, FAS and EES (adapted from Sponsor submitted Study Synopsis, verified by clinical reviewer)

Endpoint	Erlotinib 85 mg/m²/day	Etoposide 50 mg/m²/day	Log-rank P value
FAS	**n = 13**	**n = 12**	--
Progression-free Survival (Days)			
Number of Events (%)	13 (100%)	9 (75.0%)	0.0205
Median (95% CI)†	52 (29.0, 62.0)	65 (23.0, --)	
HR (95% CI) Relative to Etoposide	2.88 (1.12, 7.39)	--	
Overall Survival (Days)			
Number of Events (%)	3 (23.1%)	6 (50.0%)	0.3820
Median (95% CI)†	-- (114.0, --)	261 (154.0, --)	
HR (95% CI) Relative to Etoposide	0.54 (0.14, 2.18)	--	
Duration of Response (CR + PR) (Days)			
n (%)‡	0	2 (16.7%)	--
Median (95% CI)	--	--	
Duration of Stable Disease (CR + PR + MR + SD) (Days)			
n (%)§	2 (15.4%)	5 (41.7%)	0.0082
Median (95% CI)	79 (78, 80)	-- (117, --)	
EES	**n = 11**	**n = 11**	--
Progression-free Survival (Days)			
Number of Events (%)	11 (100%)	8 (72.7%)	0.0190
Median (95% CI)†	56 (34.0, 63.0)	66 (52.0, --)	
HR (95% CI) Relative to Etoposide	3.14 (1.13, 8.67)	--	
Overall Survival (Days)			
Number of Events (%)	2 (18.2%)	5 (45.5%)	0.2974
Median (95% CI)†	-- (114.0, --)	-- (157.0, --)	
HR (95% CI) Relative to Etoposide	0.43 (0.08, 2.21)	--	
Duration of Response (CR + PR) (Days)			
n (%)‡	0	2 (18.2%)	--
Median (95% CI)	--	--	
Duration of Stable Disease (CR + PR + MR + SD) (Days)			
n (%)§	2 (18.2%)	5 (45.5%)	0.0082
Median (95% CI)	79 (78, 80)	-- (117, --)	

--: not applicable; CR: complete response; EES: Efficacy Evaluable Set; FAS: Full Analysis Set; MR: minor response; PR: partial response; SD: stable disease

† Calculated using Kaplan-Meier estimates.

‡ n is the number of patients whose best overall response was CR or PR.

§ n is the number of patients whose best overall response was CR, PR, MR or SD.

In study OSI-774-206, the best response was stable disease in two patients, one who had a complete resection immediately prior to entering the trial. Two patients had disease progression as a best response. Again, the small sample size precludes any meaningful conclusion regarding the efficacy of erlotinib in pediatric patients with recurrent or refractory ependymoma or subependymoma following treatment with oral etoposide.

6.7 Other Endpoints

An analysis of biomarkers was not conducted in this study. Please see the clinical pharmacology review performed by Ruby Leong, Pharm.D. for a review of the pharmacokinetic endpoints.

7 Review of Safety

7.1 Safety Summary

Overall, the adverse reaction profile of erlotinib is consistent with the known adverse reaction profile in adults.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Clinical review of the safety of erlotinib in pediatric patients was based primarily on the clinical study report for OSI-774-205, case report forms and primary datasets submitted by the Applicant. Care should be taken with interpretation of safety data derived from small trials, particularly in the context of a patient population with life-threatening brain tumors who typically require concomitant corticosteroid therapy

7.1.2 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Overall, the adverse reaction profile in Study OSI-774-205 and OSI-774-206 of erlotinib is consistent with the known adverse reaction profile in adults and the literature.

7.2 Analysis of Adverse Events

7.2.1 Deaths

Three and six patients died in the erlotinib and etoposide arms, respectively, during the prescribed follow-up time, of which one occurred during the study or within 30 days of the last dose of treatment. This patient was an (b) (4) in the erlotinib arm who died (b) (4) days after the last dose of study drug due to disease progression. Given the small number of deaths and small sample size, the variability in OS in both arms is quite large. Consequently, conclusions regarding OS cannot be drawn. One death occurred on study OSI-774-206 within 30 days of the last daily dose of erlotinib. The patient had an MRI that showed interval compression of disease with compression of the brainstem on Day (b) (4) the patient was withdrawn from the trial and died on Day (b) (4)

7.2.2 Treatment Emergent Adverse Events

The most frequently reported treatment-emergent adverse events (TEAEs) in patients in the erlotinib arm were vomiting (46.2%) and diarrhea (46.2%). The most frequent TEAEs in the

etoposide arm were vomiting (66.7%), headache (66.7%), and fatigue (66.7%). Consistent with known safety profile of erlotinib, more patients in the erlotinib arm experienced TEAEs in the SOC of Skin and Subcutaneous Disorders compared to etoposide (84.6% vs. 58.3% respectively).

Table 10: Treatment Emergent Adverse Events in ≥3 patients (adapted from Sponsor submitted Study Synopsis, verified by clinical reviewer)

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MedDRA (v13.0) System Organ Class Preferred Term	Erlotinib 85 mg/m²/day (n = 13)	Etoposide 50 mg/m²/day (n = 12)	Total (n = 25)
Any TEAE	**13 (100.0%)**	**11 (91.7%)**	**24 (96.0%)**
Gastrointestinal Disorders			
Diarrhoea	6 (46.2%)	5 (41.7%)	11 (44.0%)
Vomiting	6 (46.2%)	8 (66.7%)	14 (56.0%)
Constipation	3 (23.1%)	6 (50.0%)	9 (36.0%)
Nausea	3 (23.1%)	5 (41.7%)	8 (32.0%)
Abdominal pain	2 (15.4%)	4 (33.3%)	6 (24.0%)
Stomatitis	2 (15.4%)	1 (8.3%)	3 (12.0%)
Gastritis	1 (7.7%)	2 (16.7%)	3 (12.0%)
Skin and Subcutaneous Tissue Disorders			
Rash	4 (30.8%)	1 (8.3%)	5 (20.0%)
Dermatitis acneiform	3 (23.1%)	0	3 (12.0%)
Pruritus	3 (23.1%)	0	3 (12.0%)
Dry skin	1 (7.7%)	2 (16.7%)	3 (12.0%)
Rash macular	1 (7.7%)	2 (16.7%)	3 (12.0%)
Alopecia	0	4 (33.3%)	4 (16.0%)
Nervous System Disorders			
Headache	5 (38.5%)	8 (66.7%)	13 (52.0%)
Nystagmus	3 (23.1%)	2 (16.7%)	5 (20.0%)
Convulsion	2 (15.4%)	1 (8.3%)	3 (12.0%)
General Disorders and Administration Site Conditions			
Fatigue	3 (23.1%)	8 (66.7%)	11 (44.0%)
Oedema peripheral	2 (15.4%)	1 (8.3%)	3 (12.0%)
Pyrexia	2 (15.4%)	4 (33.3%)	6 (24.0%)
Musculoskeletal and Connective Tissue Disorders			
Muscular weakness	3 (23.1%)	2 (16.7%)	5 (20.0%)
Pain in extremity	1 (7.7%)	4 (33.3%)	5 (20.0%)
Investigations			
Weight decreased	3 (23.1%)	2 (16.7%)	5 (20.0%)
Infections and Infestations			
Upper respiratory tract infection	0	3 (25.0%)	3 (12.0%)
Respiratory, Thoracic and Mediastinal Disorders			
Cough	2 (15.4%)	4 (33.3%)	6 (24.0%)
Dyspnoea	1 (7.7%)	2 (16.7%)	3 (12.0%)
Nasal congestion	1 (7.7%)	3 (25.0%)	4 (16.0%)
Epistaxis	0	3 (25.0%)	3 (12.0%)
Metabolism and Nutrition Disorders			
Decreased appetite	2 (15.4%)	2 (16.7%)	4 (16.0%)
Blood and Lymphatic System Disorders			
Anaemia	1 (7.7%)	2 (16.7%)	3 (12.0%)
Psychiatric Disorders			
Insomnia	0	3 (25.0%)	3 (12.0%)

All enrolled patients who received at least 1 dose of study drug (Safety Analysis Set).

A TEAE was defined as an adverse event observed after starting administration of the study drug to 30 days after the last dosing of study drug.

TEAE: treatment-emergent adverse event

TEAEs that occurred in study OSI-774-206 in two or more patients (all ≤ Grade 2) included fatigue (n=3), headache (n=3), cough (n=2), and oropharyngeal pain (n=2).

7.2.3 Dropouts and/or Discontinuations

No patients experienced a TEAE that lead to permanent discontinuation of study drug in either study. Seven patients on study OSI-774-205 experienced a TEAE that lead to study interruption (2 patients on erlotinib arm, 5 patients on etoposide arm) and three patients experienced TEAs that lead to study drug interruption and reduction (1 patient on erlotinib arm, 2 patients on etoposide arm).

7.2.4 Significant Adverse Events

Serious adverse events were reported for 46.2% of erlotinib patients and 41.7% for etoposide patients. Those most common SOC reported was Nervous System Disorders with convulsion being the most common within that SOC. All SAEs from the SOC of Nervous System Disorder were considered not related to study drug by investigator, as these events were expected in the population of pediatric patients with ependymoma.

Table 11: Incidence of SAEs, Safety Analysis Set (adapted from Sponsor submitted Study Synopsis, verified by clinical reviewer)

MedDRA (v13.0) System Organ Class Preferred Term	Erlotinib 85 mg/m²/day (n = 13)	Etoposide 50 mg/m²/day (n = 12)	Total (n = 25)
Any SAE	**6 (46.2%)**	**5 (41.7%)**	**11 (44.0%)**
Nervous System Disorders			
Convulsion	2 (15.4%)	1 (8.3%)	3 (12.0%)
Hydrocephalus	2 (15.4%)	0	2 (8.0%)
Grand mal convulsion	1 (7.7%)	0	1 (4.0%)
Headache	0	2 (16.7%)	2 (8.0%)
Hemiparesis	0	1 (8.3%)	1 (4.0%)
Loss of consciousness	0	1 (8.3%)	1 (4.0%)
Gastrointestinal Disorders			
Gastritis haemorrhagic	1 (7.7%)	0	1 (4.0%)
Lower gastrointestinal haemorrhage	1 (7.7%)	0	1 (4.0%)
Diarrhoea	0	1 (8.3%)	1 (4.0%)
General Disorders and Administration Site Conditions			
Pyrexia	1 (7.7%)	0	1 (4.0%)
Infections and Infestations			
Viral upper respiratory tract infection	1 (7.7%)	0	1 (4.0%)
Lung infection	0	1 (8.3%)	1 (4.0%)
Metabolism and Nutrition Disorders			
Dehydration	1 (7.7%)	0	1 (4.0%)
Hypokalaemia	0	1 (8.3%)	1 (4.0%)
Hypophosphataemia	0	1 (8.3%)	1 (4.0%)
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)			
Malignant neoplasm progression	1 (7.7%)	0	1 (4.0%)
Psychiatric Disorders			
Confusional state	1 (7.7%)	0	1 (4.0%)
Investigations			
Weight decreased	0	1 (8.3%)	1 (4.0%)
Renal and Urinary Disorders			
Pollakiuria	0	1 (8.3%)	1 (4.0%)
Urinary hesitation	0	1 (8.3%)	1 (4.0%)

All enrolled patients who received at least 1 dose of study drug (Safety Analysis Set).

Serious adverse events that occurred in study OSI-774-206 in two or more patients included fatigue (n=3), pyrexia (n=2), decreased appetited (n=2), convulsion (n=2), headache (n=3), cough (n=2), and oropharyngeal pain (n=2).

8 Labeling Recommendations

After negotiations with the applicant, the following language was agreed upon to include in Section 8.4 (Pediatric Use) of the Tarceva package insert:

The safety and effectiveness of TARCEVA in pediatric patients have not been established.

In an open-label, multi-center trial, 25 pediatric patients (median age 14 years, range 3-20 years) with recurrent or refractory ependymoma were randomized (1:1) to TARCEVA or etoposide. Thirteen patients received TARCEVA at a dose of 85 mg/m^2/day orally until disease progression, death, patient request or investigator decision to discontinue study drug or intolerable toxicity. Four patients randomized to etoposide also received TARCEVA following disease progression. The trial was terminated prematurely for lack of efficacy; there were no objective responses observed in these 17 TARCEVA-treated patients.

No new adverse events were identified in the pediatric population.

Based on the population pharmacokinetics analysis conducted in 105 pediatric patients (2 to 21 years old) with cancer, the geometric mean estimates of CL/F/BSA (apparent clearance normalized to body surface area) were comparable across the three age groups: 2-6 years (n=29), 7-16 years (n=59), and 17-21 years (n=17).

9 References

1. Mendrzyk, F., et al., *Identification of Gains on 1q and Epidermal Growth Factor Receptor Overexpression as Independent Prognostic Markers in Intracranial Ependymoma.* Clinical Cancer Research, 2006. **12**(7): p. 2070-2079.
2. Korshunov, A., A. Golanov, and V. Timirgaz, *Immunohistochemical Markers for Prognosis of Ependymal Neoplasms.* Journal of Neuro-Oncology, 2002. **58**(3): p. 255-270.
3. Jakacki, R.I., et al., *Pediatric Phase I and Pharmacokinetic Study of Erlotinib Followed by the Combination of Erlotinib and Temozolomide: A Children's Oncology Group Phase I Consortium Study.* Journal of Clinical Oncology, 2008. **26**(30): p. 4921-4927.
4. Broniscer, A., et al., *Phase I and Pharmacokinetic Studies of Erlotinib Administered Concurrently with Radiotherapy for Children, Adolescents, and Young Adults with High-Grade Glioma.* Clinical Cancer Research, 2009. **15**(2): p. 701-707.

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