# CLINICAL REVIEW

| | |
|---|---|
| Application Type | sNDA |
| Application Number(s) | 20896/32 |
| Priority or Standard | Priority |
| Submit Date(s) | June 10, 2013 |
| Received Date(s) | June 10, 2013 |
| PDUFA Goal Date | December 10, 2013 |
| Division / Office | DOP2/OHOP |
| Reviewer Name(s) | Martha Donoghue, MD<br>Suzanne Demko, PA-C (CDTL) |
| Review Completion Date | December 9, 2013 |
| Established Name | Capecitabine |
| Trade Name | Xeloda® |
| Therapeutic Class | Small molecule nucleoside metabolic inhibitor |
| Applicant | Hoffman-LaRoche,Inc./ Genentech, Inc. |
| Formulation(s) | Tablets |
| Dosing Regimen | Not applicable |
| Indication(s) | None |

# Table of Contents

# Table of Tables

# Table of Figures

# 1 Recommendations

I recommend that Pediatric Exclusivity be granted for Xeloda (capecitabine) and that the relevant information obtained from pediatric studies of capecitabine be incorporated into the Xeloda 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 (PWR).

The adverse event profile of capecitabine in the pediatric population studied appears to be similar to that of the adult population. However, the pediatric studies failed to demonstrate that capecitabine is effective in the treatment of pediatric patients with newly diagnosed non-disseminated intrinsic infiltrating brainstem glioma (IBSG). Therefore, use of capecitabine in this population is not recommended.

# 2 Introduction and Regulatory Background

## 2.1 Product Information

**Established Name:** Capecitabine

**Proprietary Name:** Xeloda®

**Applicant:** Hoffmann-LaRoche, Inc./Genentech, Inc.

**Pharmacological Class:** nucleoside metabolic inhibitor

**Mechanism of Action:** Enzymes convert capecitabine to 5-fluorouracil (5-FU) *in vivo*. Normal cells and tumor cells metabolize 5-FU to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cellular injury by two different mechanisms. First, FdUMP and the folate cofactor, $N^{5-10}$-methylenetetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from 2'-deoxyuridylate. Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA; therefore, a deficiency of this compound can inhibit cell division. Second, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein synthesis.

**Proposed Indication**: There is no proposed pediatric indication.

## 2.2 Rationale for Pediatric Studies of Capecitabine

The rationale for studying capecitabine in pediatric patients with newly diagnosed non-disseminated intrinsic infiltrating brainstem glioma (IBSG) relates to the mechanism of

action of capecitabine and the unmet medical need in this pediatric population. IBSG comprise approximately 15 to 20 percent of all central nervous system tumors occurring in pediatric patients[1]. The average age at diagnosis is five to nine years [2]. Approximately 80% of pediatric brainstem gliomas arise within the pons, and the majority of pontine tumors are IBSGs. Although thankfully rare, with only approximately 150 new pediatric diagnoses per year in the United States[3], these tumors are typically high grade, locally infiltrative, and incurable with standard therapy.

Current standard of care consists of radiation therapy and palliative management of symptoms. Patients are also typically treated with corticosteroids to ameliorate symptoms related to peri-tumoral edema. Surgery is generally not performed outside of the context of a clinical trial due its potential to lead to morbidities related to complications from surgery involving the brainstem. Radiation therapy, consisting of 54-59 Gy administered in 1.8 Gy fractions five times per week over six weeks, can result in dramatic tumor shrinkage; unfortunately, this tumor shrinkage is generally short-lived. The median survival of patients with intrinsic brainstem glioma is approximately 10 months and the two-year overall survival rate is less than 10 percent[4]. Although over twenty clinical trials have been conducted to investigate a variety of treatment regimens over the past two decades, the prognosis for patients with this disease remains dismal[5]. To date, no treatment, either administered prior to, concurrently with, or following radiation therapy, has been shown to increase survival in patients compared to administration of radiation therapy and palliative measures alone.

The rate-limiting and final step in the intratumoral conversion of capecitabine to 5-FU is performed by thymidine phosphorylase (TP). Cell culture and human xenograft models have shown that capecitabine activity correlates with the level of TP expression, and radiation has been shown to induce TP in glioblastoma xenografts. Additionally, capecitabine has shown activity as a radiosensitizer in metastatic brain lesions.

## 2.3 Summary of Presubmission Regulatory Activities

Capecitabine is approved for the following indications in adults:

- as a single agent for adjuvant treatment of Dukes' C colon cancer in patients who have undergone complete resection of the primary tumor when treatment with fluoropyrimidine therapy alone is preferred
- as a single agent for first-line treatment of metastatic colorectal carcinoma when treatment with fluoropyrimidine therapy alone is preferred
- in combination with docetaxel for the treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing chemotherapy
- as a single agent for the treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy

regimen or resistant to paclitaxel and for whom further anthracycline therapy is not indicated (e.g., patients who have received cumulative doses of 400 mg/m$^2$ of doxorubicin or doxorubicin equivalents).

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

**Table 1: Pediatric Regulatory History**

| Date | Action |
|---|---|
| 11/1/2004 | Proposed Pediatric Study Request (PPSR) submitted to IND 45,305 by Applicant |
| 3/16/2005 | Original PWR issued |
| 1/19/2007 | PWR Amendment # 1 issued |
| 5/7/2008 | PWR Amendment # 2 issued |
| 12/18/2009 | End of Phase 1 meeting to discuss results of Study 1 of the PWR (Protocol N018517/PBTC-02) and the design of Study 2 of the PWR (Protocol N021125/PBTC-030) |
| 7/1/11 | PWR Amendment # 3 issued. |
| 11/29/2011 | Type C meeting held to discuss the need for a bioavailability study to compare the pediatric formulation of capecitabine with the approved adult formulation. |
| 8/30/2012 | Type C meeting to discuss the requirements for a biowaiver. |
| 12/19/2012 | Pre-sNDA meeting to discuss the content and format of the supplemental NDA and adequacy of the information to support a pediatric exclusivity determination. |
| 2/7/2013 | FDA issued memo providing concurrence that a relative bioavailability study, not a dedicated bioequivalence study, should be conducted to compare the approved drug to the pediatric formulation if a biowaiver is not obtained. |

# 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 NO18517, NO21125, and Study BP27931. There were no disclosable financial interests evident.

# 4 Sources of Clinical Data

## 4.1 Tables of Clinical Trials

This submission contains the results of three clinical trials conducted in response to the PWR: two pediatric studies of a pediatric formulation of capecitabine in combination with radiation therapy conducted by the Pediatric Brain Tumor Consortium (PBTC) and sponsored by Genentech/Hoffman La Roche, and a relative bioavailability study in adult patients comparing the marketed capecitabine formulation to the pediatric formulation (Table 2). Pediatric development of capecitabine initially occurred under IND 45,305.

(b) (4)

**Table 2: Clinical Trials of Capecitabine Conducted in Response to the PWR**

| Study Number | Title | Design | Number of Patients |
|---|---|---|---|
| NO18517 | A phase I trial of capecitabine rapidly disintegrating tablets and concomitant radiation therapy in children with newly diagnosed brainstem gliomas and high grade gliomas | Multicenter dose-finding open label study.<br><br>Patients received capecitabine pediatric film-coated tablets at a dose of 500 mg/m$^2$, 650 mg/m$^2$, or 850 mg/m$^2$ orally twice daily plus standard radiotherapy for three 21-day cycles followed by a 2-week break. During the post-radiation phase, patients received capecitabine 1250 mg/m$^2$ twice daily for 14 consecutive days followed by a 7-day rest period for three cycles. | A total of 22 patients 3-21 years of age<br><br><u>capecitabine doses</u><br>500 mg/m$^2$ (n=4)<br>650 mg/m$^2$ (n=12)<br>850 mg/m$^2$ (n=6) |
| NO21125 | A phase II trial of capecitabine rapidly disintegrating tablets and concomitant radiation therapy in children with newly diagnosed brainstem gliomas | Multicenter, single arm, open label study.<br><br>Patients received capecitabine pediatric film-coated tablets at a dose of 650 mg/m$^2$ twice daily plus radiotherapy for three 21-day cycles followed by a 2-week break. During the post-radiation phase, patients received capecitabine 1250 mg/m$^2$ twice daily for 14 consecutive days followed by a 7-day rest period for three cycles | A total of 34 patients aged 3-17 years of age. |

| Study Number | Title | Design | Number of Patients |
|---|---|---|---|
| BP27931 | A randomized, open-label, single dose, two-way cross-over study to investigate the relative bioavailability of capecitabine in rapid disintegrating tablets (RDT) versus the commercial Xeloda® tablets following oral administrations in adult patients with solid tumors. | Randomized, open label single dose two-way cross-over study.<br><br>On 2 consecutive days, patients received a single oral dose of 2000 mg capecitabine pediatric film-coated tablets (8 X 250 mg) and a single oral dose of 2000 mg Xeloda film-coated tablets (4 X 500 mg) | 37 adult subjects enrolled; 31 adult subjects had evaluable pharmacokinetic data. |

The first clinical study of the pediatric formulation of capecitabine was Study NO18517, entitled "A Phase I Trial of Capecitabine Rapidly Disintegrating Tablets and Concomitant Radiation Therapy in Children with Newly Diagnosed Brainstem Gliomas and High Grade Gliomas." Based on results of Study NO18517, the maximum tolerated and recommended Phase 2 dose of capecitabine in pediatric patients with newly diagnosed brainstem and high grade gliomas was 650 mg/m$^2$ administered every 12 hours for a total of three 21-day cycles concurrently with radiation therapy followed by three additional cycles of capecitabine monotherapy (at a dose of 1250 mg/m$^2$ twice daily on Days 1-14 of a 21-day cycle) following completion of radiation therapy.

The second clinical study of the pediatric formulation of capecitabine was Study NO21125, entitled "A Phase II Trial of Capecitabine Rapidly Disintegrating Tablets and Concomitant Radiation Therapy in Children with Newly Diagnosed Brainstem Gliomas." This study enrolled 34 patients to receive capecitabine in conjunction with and following completion of radiation therapy at the recommended phase 2 dose. The primary efficacy endpoint of Study NO21125 was Progression-Free Survival (PFS), defined as the time from initiation of treatment to the earliest date of failure (disease progression, death from any cause, or second malignancy). Overall Survival (OS), defined as the time from initiation of treatment to death from any cause or the date the patient was last known to be alive, was a key secondary efficacy endpoint. All patients who received at least one dose of capecitabine were included in the primary analysis.

## 4.2 Review Strategy

The objectives of this review were two-fold: to determine if the Applicant fairly responded to the elements outlined in Amendment #4 of the PWR; and provide recommendations for incorporation of relevant pediatric information derived from the conduct of the studies outlined in the PWR into the Xeloda 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 capecitabine, the PWR, and relevant published literature were also reviewed.

## 4.3 Discussion of Individual Clinical Trials

Please see the November 4, 2013 clinical pharmacology review performed by Stacy Shord, Pharm.D. for a review of Study BP27931.

### 4.3.1 Study NO18517

Study Title
A phase I trial of capecitabine rapidly disintegrating tablets and concomitant radiation therapy in children with newly diagnosed brainstem gliomas and high grade gliomas.

Protocol Milestones
This clinical trial was conducted by nine U.S. investigators in the Pediatric Brain Tumor Consortium (PBTC) from May 24, 2007 through October 4, 2010.

Study Objectives
The primary objectives of this trial were to estimate the maximum tolerated dose (MTD) and evaluate the dose limiting toxicities of capecitabine administered concurrently with and following radiation therapy in children with newly diagnosed non-disseminated, intrinsic brainstem gliomas or newly diagnosed non-disseminated high-grade gliomas.

The secondary objectives of the trial are provided below:

- To evaluate the safety profile of capecitabine administered concomitantly with radiation therapy to pediatric patients
- To characterize the pharmacokinetics of capecitabine rapidly disintegrating tablets and its metabolites
- To explore the exposure-response relationship for measures of safety and effectiveness using pharmacokinetic and pharmacodynamics (PK/PD models)
- To make a preliminary assessment of the antitumor activity of capecitabine and radiation observed in children with newly diagnosed non-disseminated intrinsic brainstem gliomas (IBSG) and high grade gliomas (HGGs)
- To estimate distributions of progression-free survival and overall survival for patients with IBSG
- To characterize radiographic changes in newly diagnosed non-disseminated IBSG and HGGs treated with radiation and capecitabine using MRI, perfusion and diffusion imaging, and PET scans.

Study Design

Study NO18517 was an open label study consisting of two periods: an 11-week dose-finding treatment period during which capecitabine was administered concurrently with radiation, and a 9-week post-radiation treatment period during which capecitabine was administered as a single agent. During the 11-week dose-finding period, patients received oral capecitabine film-coated tablets [also called capecitabine rapidly disintegrating tablets (capecitabine RDT)] twice daily for 9 weeks beginning within 24 hours of the start of conventional or conformal volume-based external beam radiation therapy, followed by a 2-week break. It was estimated that the prescribed radiation therapy dose would be administered over approximately 6 weeks. During the post-radiation period, patients received 1250 mg/m$^2$ oral capecitabine twice daily on days 1-14 of a 21-day cycle for a total of nine weeks (Table 3, copied from protocol).

**Table 3: Capecitabine Dose Levels for Study NO18517**

| Dose finding Capecitabine Escalation Table | | |
|---|---|---|
| Dose Level | Dose bid (mg/m$^2$/dose) | Total Daily Dose (mg/m$^2$/day) |
| 0 | 375 | 750 |
| 1* | 500 | 1000 |
| 2 | 650 | 1300 |
| 3 | 850 | 1700 |
| Post RT Capecitabine Dose | | |
| 0 | 900 | 1800 |
| 1* | 1250 | 2500 |

* Starting dose

*Source: sNDA submission*

The dose-finding portion of the trial employed a traditional 3+3 dose escalation design. The starting dose, 500 mg/m$^2$ twice daily, corresponded to 80% of the maximum tolerated dose identified in adults (625 mg/m$^2$ twice daily). Cohorts of three to six patients were assigned to successive dose levels using the following rules.

- If none of the first three patients experienced a dose limiting toxicity (DLT), then the dose was escalated to the next dose level, which enrolled an additional three to six patients.
- If two or more patients experienced a DLT in a cohort, then de-escalation to the prior cohort occurred.
- If exactly one patient out of the first three patients in a cohort experienced a DLT at the current dose, then up to three additional patients were treated at this dose.
  - If none of these three additional patients experienced a DLT, then the dose was escalated to the next level.

- If one or more of these three patients experienced a DLT, then de-escalation to the previous dose occurred.

The Maximum Tolerated Dose (MTD) was identified as the maximum dose level in which six patients were treated without occurrence of more than one DLT.

Toxicities were graded using NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. The following adverse events, if considered at least possibly related to capecitabine and occurring during the dose-finding period, were considered DLT:

- Interruption of planned radiation for 5 consecutive days or 10 days total
- Any capecitabine-related adverse event that resulted in the need for dose reduction or permanent cessation of therapy
- Any Grade 4 non-hematologic toxicity
- Grade 3 non-hematologic toxicities, except for the following:
  - Grade 3 nausea and vomiting of < 5 days duration
  - Grade 3 transaminases that returned to baseline within 7 days of study drug interruption with a negative re-challenge
  - Grade 3 fever or infection of < 5 days duration
- Grade 2 non-hematologic toxicity that persisted for more than 7 days and required treatment interruption
- Any other capecitabine-related adverse event requiring interruption of study drug for > 7 days or recurred upon rechallenge.
- Grade 4 neutropenia or thrombocytopenia
- Grade 3 thrombocytopenia requiring platelet transfusion on more than 2 occasions.

Eligibility Criteria

In order to qualify for enrollment, patients had to meet all of the following inclusion criteria:

- Age: patients were ≥ 3 and ≤ 21 years of age at the time of study entry
- Diagnosis: patients must have been newly diagnosed with one of the following tumors
  - Non-disseminated intrinsic infiltrating brainstem glioma (histoplathologic diagnosis not required)
  - Non-disseminated, incompletely resected high-grade glioma confirmed by histopathology with evidence of residual measurable tumor on post-operative MRI or CT
    - Patients with anaplastic oligodendroglioma were excluded from enrollment
    - Patients must have been registered within 28 days of definitive surgery

- Performance level: Karnofsky Performance Scale or Lansky Performance Score of at least 50% assessed within two weeks prior to registration
- Prior/Concurrent therapy: Patients must not have received prior chemotherapy, radiation therapy, immunotherapy, or bone marrow transplant. Prior dexamethasone and surgery were permitted.
- Organ function requirements, documented by lab work obtained within two weeks prior to registration and one week prior to the start of therapy:
  - Absolute neutrophil Count (ANC) ≥ 1,000/µl
  - Platelet count ≥ 100,000/µl independent of transfusion
  - Hemoglobin ≥ 8 g/dL independent of transfusion
  - Creatinine clearance or radioisotope GFR ≥ 70 ml/min/1.73 $m^2$ or a serum creatinine within specified age-defined maximum levels
  - Bilirubin ≤ 1.5 X institutional upper limit of normal for age
  - SGPT (ALT) ≤ 5 X institutional upper limits of normal for age
- Patients of reproductive potential must have agreed to use an acceptable method of birth control, including abstinence, during study treatment
- Provision of informed consent.

Exclusion Criteria

- Prior receipt of any other anticancer or experimental therapy
- Uncontrolled infection
- Significant comorbid systemic disease
- Hypersensitivity to capecitabine or its components
- Dihydropyrimidine dehydrogenase (DPD) deficiency
- Requirement for warfarin, sorivudine or chemically related analogues
- Pregnancy or lactation.

Treatment Plan

Protocol treatment encompassed a 20 week period, including an 11-week dose-finding period and a 9 week post-radiation treatment period (Table 4, copied from the Applicant's submission)

**Table 4: Treatment Schedule for Protocol NO18517**

| | | Weeks | Protocol Therapy |
|---|---|---|---|
| Dose-Finding | Course 1 | Weeks 1 through 3 | Capecitabine + RT |
| | Course 2 | Weeks 4 through 6 | Capecitabine + RT |
| | Course 3 | Weeks 7 through 9 | Capecitabine ± RT* |
| | **Break** | Weeks 10 and 11 | None |
| Post Radiation Therapy | Course 4 | Weeks 12 and 13<br>Week 14 | Capecitabine<br>None |
| | Course 5 | Weeks 15 and 16<br>Week 17 | Capecitabine<br>None |
| | Course 6 | Weeks 18 and 19<br>Week 20 | Capecitabine<br>None |

*Patients who did not complete radiation as planned at the end of week 6 will continue to receive radiation during course 3 to complete the prescribed radiotherapy dose.

*Source: sNDA submission*

Patients received local irradiation using conventional or conformal, volume-based delivery techniques. Radiation was administered in 180 cGy fractions once daily, 5 days per week, to a total dose of 5580 cGy.

During the dose-finding period, patients received two doses of capecitabine RDT daily, approximately 12 hours apart. Dosing began within 24 hours of the start of radiation therapy and continued for 9 weeks. Tablets were swallowed intact with a full glass of water or dispersed in room temperature water. Following completion of the 9 week course of capecitabine, patients had a two week break prior to starting the post-radiation treatment period.

During the post-radiation treatment period, patients received up to 3 cycles of oral capecitabine twice daily, approximately 12 hours apart on Days 1-14 of a 21-day cycle.

Dose Modifications for Adverse Events

Capecitabine treatment was immediately suspended for a minimum of 5 days for any dose-limiting non-hematological or hematological toxicity. If the adverse event returned to baseline within 7 days of drug interruption, retreatment could be reinitiated at the next lower dose level. For patients who experienced DLTs during the dose-finding period who tolerated reinitiation of therapy at the next lower dose level, the post-XRT dose was

determined on an individual basis based upon the type of toxicity and the timing of the DLT. Patients who experienced recurrence of a DLT at the reduced dose were removed from study therapy.

Concomitant Therapies

Patients received corticosteroids as needed to control symptoms of edema and mass effect. Febrile neutropenia was managed according to local institutional guidelines. Prophylactic use of growth factors was not permitted during the DLT observation period, but therapeutic use in patients with complications from neutropenia was permitted with the approval of the study chair. Use of loperamide and antiemetics was permitted.

Protocol-Specified Discontinuation Criteria

Patients were discontinued from study therapy for any of the following conditions:

- unacceptable toxicity
- progressive disease
- medical or psychiatric illness rendering the patient incapable of further treatment
- completion of protocol-defined therapy
- pregnancy.

Patients were withdrawn from the study for any of the following reasons:

- determination that the patient was ineligible for the study
- withdrawal of consent
- death
- completion of the two year follow-up period from the initiation of therapy.

Study Schedule

Table 5, copied from the Applicant's submission, outlines the schedule of assessments for Study NO18517.

**Table 5: Schedule of Assessments for Study NO18517**

| | Prior to registration | Pre-Therapy | During Dose Finding (Weeks 1- 11) | Post Radiation Therapy | End of Tx |
|---|---|---|---|---|---|
| History | X | | | | |
| Physical exam / vitals | X | | Weekly | Day 1 each Course | X |
| Height/weight | | | Day 1 each Course | Day 1 each Course | X |
| Karnofsky/Lansky | X | | Day 1 each Course | Day 1 each Course | X |
| Neurologic exam | X | X | Day 1 each Course | Day 1 each Course | X |
| CBC w/ differential, platelets | X | X[A] | X[B] | Weekly | X |
| Electrolytes including Ca, Phos, Mg | X | X | X[C] | Day 1 each Course | X |
| Alkaline Phosphatase | | X | | | |
| BUN and Creatinine | X | X[A] | X[C] | Day 1 each Course | X |
| ALT, Total Bilirubin, Albumin | X | X[A] | X[C] | Day 1 each Course | X |
| β-HCG (for females of childbearing potential) | X | X[A] | | | |

| | Prior to registration | Pre-Therapy | During Dose Finding (Weeks 1- 11) | Post Radiation Therapy | End of Tx |
|---|---|---|---|---|---|
| PK studies[D] | | | X[D] | | |
| MRI brain | X | X[F] | week 11 | End of course 6 & Q 3 months | |
| PET-FDG | | X | week 11 | | |
| MRI spine | X[E] | | | | |
| Perfusion/diffusion MR, ECHO gradient MRI | | X | week 11 | | |

[A] Obtain these assessments prior to treatment to re-confirm eligibility if > 7 days have elapsed.

[B] Weekly during Dose Finding. Note: check CBC twice weekly if platelets < 75,000/mm$^3$ or ANC < 750/mm$^3$ until toxicity returns to grade 2 or less. Also see dose modification section.

[C] Weekly during Course 1 and Day 1 of Weeks 4, 7, and 10

[D] Blood for PK studies will be drawn as outlined in Section 8.1

[E] If clinically indicated. Note: Patients with disseminated disease are not eligible for study entry.

[F] Obtain MRI scan if 'prior to registration' scan is greater than two weeks prior to start therapy.

*Source: sNDA submission*

4.3.2 Study NO21125

Study Title
A phase II trial of capecitabine rapidly disintegrating tablets and concomitant radiation therapy in children with newly diagnosed brainstem gliomas

Protocol Milestones
This clinical trial was conducted across eight sites by the Pediatric Brain Tumor Consortium (PBTC). The first patient entered the study on May 23, 2007 and the last patient entered on May 23, 2011. The data cut-off date for the clinical study report was January 31, 2013.

Study Objectives
The primary objective of this trial was to estimate the distribution of progression-free survival (PFS) for patients with newly diagnosed diffuse IBSGs treated with the combination of capecitabine and radiation therapy compared to PBTC historical controls.

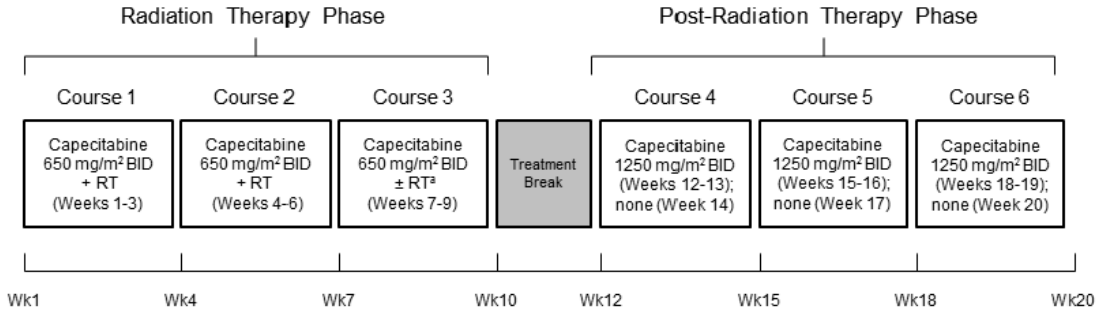
The main secondary objectives of the trial are listed below:

- To estimate the overall survival distribution and summarize the best tumor responses observed prior to treatment failure
- To further evaluate the safety profile of capecitabine administered concomitantly with radiation therapy to pediatric patients
- To further characterize the pharmacokinetics of capecitabine rapidly disintegrating tablets and its metabolites
- To explore the exposure-response relationship for measures of safety and effectiveness using pharmacokinetic and pharmacodynamic (PK/PD models).

Study Design

Study NO21125 was an open label single-arm study consisting of two periods: an 11-week period comprising 9 weeks of capecitabine administered at the maximum tolerated dose of 650 mg/m$^2$ orally twice daily concurrent with radiation therapy identified in Study NO18517, followed by a 2-week break and a 9-week post-radiation treatment period in which capecitabine was administered as a single agent (Figure 1, copied from the sNDA submission).

**Figure 1: Treatment Schema for Study N021125**




[a] Patients who did not complete radiation as planned at the end of Week 6 continued to receive radiation during Course 3 to complete the prescribed radiotherapy dose.

*Source: Clinical Study Report for Protocol NO21125*

The efficacy parameters of overall survival and progression-free survival were compared with historical controls derived from 140 similar patients who participated in five PBTC-run trials of radiation therapy in combination with other investigational products (phase 1 trial PBTC-006, phase 1 and 2 components of PBTC-007, and phase 1 and 2 components of PBTC-014).

A pre-specified interim analysis was performed for futility following the 21st PFS event. The 21st event occurred on February 7, 2011, and the analysis was completed and sent to the data safety monitoring board members for review on February 14, 2011. This analysis compared the PFS distributions for patients enrolled and treated on this trial with the historical PFS results. The threshold for stopping the trial for futility was not reached, so the study continued as planned.

Eligibility Criteria

In order to qualify for enrollment, patients had to meet all of the following inclusion criteria:

- Age: patients were ≥ 3 and < 18 years of age at the time of study entry
- Diagnosis: patients must have been newly diagnosed with non-disseminated intrinsic infiltrating brainstem glioma (histoplathologic diagnosis not required)
- Performance level: Karnofsky Performance Scale or Lansky Performance Score of at least 50% assessed within two weeks prior to registration
- Prior/Concurrent therapy: Patients must not have received prior chemotherapy, radiation therapy, immunotherapy, or bone marrow transplant. Prior dexamethasone and surgery were permitted.
- Organ function requirements, documented by lab work obtained within two weeks prior to registration and one week prior to the start of therapy:
    - Absolute neutrophil Count (ANC) ≥ 1,000/µl
    - Platelet count ≥ 100,000/µl independent of transfusion

- Hemoglobin ≥ 8 g/dL independent of transfusion
- Creatinine clearance or radioisotope GFR ≥ 70 ml/min/1.73 $m^2$ or a serum creatinine within specified age-defined maximum levels.
- Bilirubin ≤ 1.5 X institutional upper limit of normal for age
- SGPT (ALT) ≤ 5 X institutional upper limits of normal for age.

- Patients of reproductive potential must have agreed to use an acceptable method of birth control, including abstinence, during study treatment
- Provision of informed consent.

Exclusion Criteria

- Prior receipt of any other anticancer or experimental therapy
- Uncontrolled infection
- Significant comorbid systemic disease
- Hypersensitivity to capecitabine or its components
- Dihydropyrimidine dehydrogenase (DPD) deficiency
- Requirement for warfarin, sorivudine or chemically related analogues
- Pregnancy or lactation
- Inability to comply with study procedures.

Treatment Plan

Protocol treatment encompassed a 20 week period, including an 11-week radiation period and a 9 week post-radiation treatment period (Table 6, copied from submission).

**Table 6: Treatment Schedule for Study N021125**

| | | Weeks | Study Treatment |
|---|---|---|---|
| Radiation Phase | Course 1 | Weeks 1 through 3 | Capecitabine + RT |
| | Course 2 | Weeks 4 through 6 | Capecitabine + RT |
| | Course 3 | Week 7 through 9 | Capecitabine ± RT[a] |
| | **Break** | Weeks 10 and 11 | None |
| Post Radiation Phase | Course 4 | Weeks 12 and 13 | Capecitabine |
| | | Week 14 | None |
| | Course 5 | Weeks 15 and 16 | Capecitabine |
| | | Week 17 | None |
| | Course 6 | Weeks 18 and 19 | Capecitabine |
| | | Week 20 | None |

[a] Patients who did not complete radiation as planned at the end of week 6 continued to receive radiation during course 3 to complete the prescribed RT dose.

*Source: sNDA submission*

Patients received local irradiation using conformal, volume-based delivery techniques. Radiation was administered in 180 cGy fractions once daily, 5 days per week, to a total dose of 5580 cGy.

During the radiation therapy period, patients received two doses of capecitabine RDT daily, approximately 12 hours apart. Dosing began within 24 hours of the start of radiation therapy and continued for 9 weeks. Tablets were swallowed intact with a full glass of water or dispersed in room temperature water. Following completion of the 9 week course of capecitabine, patients had a two week break prior to starting the post-radiation treatment period.

Dosing for the entire radiation therapy period was based on the body surface area determined within one week prior to the initiation of radiation therapy. Patients initially received 650 mg/m$^2$ capecitabine twice daily, which corresponded to the MTD identified in Study NO18517 (Table 7, copied from the Applicant's submission). Patients requiring dose reduction due to toxicities received a decreased dose of 500 mg/m$^2$ twice daily.

**Table 7: Capecitabine Dose During Radiation Phase – 650 mg/m$^2$ BID**

| Body Surface Area ($m^2$) | | Morning Dose (mg) | Evening Dose (mg) | Total Daily Dose (mg) |
|---|---|---|---|---|
| Lower BSA | Higher BSA | | | |
| 0.30 | 0.35 | 250 | 175 | 425 |
| 0.36 | 0.43 | 250 | 250 | 500 |
| 0.44 | 0.52 | 375 | 250 | 625 |
| 0.53 | 0.62 | 375 | 375 | 750 |
| 0.63 | 0.72 | 500 | 375 | 875 |
| 0.73 | 0.81 | 500 | 500 | 1,000 |
| 0.82 | 0.91 | 625 | 500 | 1,125 |
| 0.92 | 1.00 | 625 | 625 | 1,250 |
| 1.01 | 1.10 | 750 | 625 | 1,375 |
| 1.11 | 1.20 | 750 | 750 | 1,500 |
| 1.21 | 1.29 | 875 | 750 | 1,625 |
| 1.30 | 1.39 | 875 | 875 | 1,750 |
| 1.40 | 1.49 | 1,000 | 875 | 1,875 |
| 1.50 | 1.58 | 1,000 | 1,000 | 2,000 |
| 1.59 | 1.68 | 1,125 | 1,000 | 2,125 |
| 1.69 | 1.77 | 1,125 | 1,125 | 2,250 |
| 1.78 | 1.87 | 1,250 | 1,125 | 2,375 |
| 1.88 | 2.00[a] | 1,250 | 1,250 | 2,500 |

[a] The dose for patients with a BSA >2.0 was capped at this dose.

*Source: Clinical Study Report for Study NO21125*

During the post-radiation treatment period, patients received up to 3 cycles of oral capecitabine twice daily, approximately 12 hours apart on Days 1-14 of a 21-day cycle. The dose administered was 1250 mg/m$^2$ twice daily. Patients requiring dose reduction due to toxicities received a decreased dose of 900 mg/m$^2$ twice daily.

Toxicity Monitoring

Toxicities were graded using NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. The following adverse events, if considered at least possibly related to capecitabine, were considered "unacceptable toxicities":

- Any Grade 4 non-hematologic toxicity
- Grade 3 non-hematologic toxicities, except for the following
    - Grade 3 nausea and vomiting of < 5 days duration
    - Grade 3 transaminases that returned to baseline or < Grade 1 within 10 days of study drug interruption with a negative re-challenge
    - Grade 3 fever or infection of < 5 days duration
    - Grade 3 electrolyte abnormalities that responded to supplementation
- Grade 2 non-hematologic toxicity that persisted for more than 10 days and required treatment interruption
- Grade 4 neutropenia or thrombocytopenia
- Grade 3 thrombocytopenia requiring platelet transfusion on more than 2 occasions within a 14 day period.

Dose Modifications for Adverse Events

Capecitabine treatment was immediately suspended for a minimum of 5 days for any unacceptable toxicity. If the adverse event returned to baseline or ≤ Grade 1 within 7 days of drug interruption, retreatment could be reinitiated at the lower dose level. For patients who required dose reduction during the radiation therapy period, the post-radiation therapy dose was also reduced. Patients who experienced recurrence of an unacceptable toxicity at the reduced dose were removed from study therapy.

Concomitant Therapies

Patients received corticosteroids as needed to control symptoms of edema and mass effect. Febrile neutropenia was managed according to local institutional guidelines. Prophylactic use of growth factors was not permitted but therapeutic use in patients with complications from neutropenia was permitted with the approval of the study chair. Use of pyridoxine for symptomatic or secondary prophylactic treatment of hand-foot skin reaction, vitamins, loperamide and antiemetics was permitted.

Protocol-Specified Discontinuation Criteria

Patients were discontinued from study therapy for upon occurrence of any of the following conditions:

- unacceptable toxicity requiring permanent discontinuation of therapy
- progressive disease
- medical or psychiatric illness rendering the patient incapable of further treatment
- completion of protocol-defined therapy
- withdrawal of consent for treatment
- pregnancy
- non-compliance with protocol guidelines.

Patients were withdrawn from the study for any of the following reasons:

- determination that the patient was ineligible for the study
- withdrawal of consent
- death
- completion of the three year follow-up period from the initiation of therapy.

Study Schedule

Table 8, copied from the Applicant's submission, outlines the schedule of assessments for Study NO21125.

**Table 8: Schedule of Assessments for Study NO21125**

| | Prior to Registration | Pre-Treatment | During Radiation Phase (Weeks 1-11) | Post-Radiation Treatment | End of Tx | Post Tx [i] |
|---|---|---|---|---|---|---|
| History | X | | | | | |
| Physical exam/vitals | X | | Day 1 ± 2 each Course | Day 1 ± 2 each Course | X | |
| Height/weight | | | Day 1 ± 2 each Course | Day 1 ± 2 each Course | X | |
| Karnofsky/Lansky | X | | | | | |
| Neurologic exam | X | X[a] | Day 1 ± 2 each Course | Day 1 ± 2 each Course | X | |
| CBC w/ differential, platelets | X | X[a] | Weekly[b] | Weekly[b] | X | |
| Electrolytes including Ca, Phos, Mg | X | X[a] | X[c] | Day 1 ± 2 each Course | X | |
| BUN and Creatinine | X | X[a] | X[c] | Day 1 ± 2 each Course | X | |
| ALAT, Total Bilirubin, Albumin | X | X[a] | X[c] | Day 1 ± 2 each Course | X | |
| β-HCG (for females of childbearing potential) | X | X[a] | | | | |
| PK studies[d] | | | X[d] | | | |
| MRI brain with DTI[j] | X | X[f,j] | Week 11[j] | End of course 6 | X | Q3 months[g] |
| MRI Spine | X[e] | | X[e] | X[e] | X[e] | X[e] |
| Patient Status | | | | | X | Q3 months[h] |

[a] Assessments obtained prior to treatment to re-confirm eligibility if > 7 days had elapsed.

[b] CBC checked twice weekly if platelets < 75,000/mm$^3$ or ANC < 750/mm$^3$ until toxicity returned to grade 2 or less.

[c] Weekly during Course 1 and Day 1 ± 2 of Weeks 4, 7, and 10.

[d] Blood for PK studies drawn as outlined in Section 3.7.1.

[e] If clinically indicated.

[f] MRI scan obtained if 'prior to registration' scan was recorded more than 2 weeks prior to start of treatment.

[g] MRI was obtained q3 mo until disease progression.

[h] Post initial progression, only survival status was required.

[i] Database was updated with patient status and MRI scans until patient is Off Study.

[j] Optional DTI was done only for pre-treatment and week 11 (or with off treatment MRI if occurred prior to week 11).

*Source: Clinical Study Report for Study NO21125.*

Tumor Response Criteria

The following criteria were used for assessment of objective response:

- Complete response (CR) was defined as complete disappearance on MRI of all enhancing tumor and mass effect while on a stable or decreasing dose of dexamethasone, accompanied by a stable or improving neurologic examination. Response must have been maintained for at least 12 weeks.
- Partial Response (PR) was defined as a ≥ 50% reduction in tumor size by bi-dimensional measurement while on a stable or decreasing dose of dexamethasone, accompanied by a stable or improving neurologic examination. Response must have been maintained for at least 12 weeks.
- Stable disease (SD) was defined as the presence of at least a stable neurologic exam while on a stable or decreased dose of dexamethasone, and magnetic resonance imaging results that did not meet the requirements for CR, PR, or progressive disease (PD). Disease status must have been maintained for a minimum of 12 weeks.
- Progressive disease (PD) was defined as the presence of progressive neurologic abnormalities or worsening neurologic status not explained by causes that were not related to tumor progression, a ≥25% increase in tumor bi-dimensional measurement compared with the previous scan, the appearance of a new lesion, or a requirement for increasing doses of dexamethasone to maintain stable neurologic status or imaging.

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

Table 9, adapted from the Applicant's submission, outlines the items contained in the PWR 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 reviewers concluded that the Applicant fulfilled the requirements of the PWR and recommended that pediatric exclusivity be awarded to the Applicant. The Pediatric Exclusivity Board provided concurrence with this recommendation on August 28, 2013. On September 6, 2013, DOP2 issued a letter notifying the Applicant that exclusivity was granted for pediatric studies of capecitabine conducted in response to the PWR, effective August 28, 2013, under section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a).

**Table 9: Summary of the Applicant's Response to the Pediatric Written Request**

| Written Request Items | Information Submitted/ Applicant's Response |
|---|---|
| Types of studies<br>• Open-label, phase 1-2 dose-finding, Pharmacokinetic (PK), safety, & efficacy study of capecitabine in combination with radiation in patients with primary brain stem tumors. | Studies conducted<br>• Phase I Study: CSR NO18517/PBTC-021, entitled "A Phase I Trial of Capecitabine Rapidly Disintegrating Tablets (RDT) and Concomitant Radiation Therapy in Children with Newly Diagnosed Brainstem Gliomas and High Grade Gliomas."<br>• Phase II Study: CSR NO21125/PBTC-030, entitled "A Phase II Trial of Capecitabine RDT and Concomitant Radiation Therapy in Children with Newly Diagnosed Brainstem Gliomas."<br>•The capecitabine pediatric film-coated tablet was initially referred to as a rapidly disintegrating tablet (RDT). After discussions with the Agency at a Type C meeting on November 29, 2011, the recommendation was to refer to the form as "capecitabine pediatric film-coated tablets". Therefore, the term RDT was replaced with capecitabine pediatric film-coated tablets. |
| Indication(s) to be studied:<br>• Children with newly-diagnosed non-disseminated intrinsic diffuse brain stem gliomas | Indication(s) studied:<br>• Studies were conducted in children with newly-diagnosed non-disseminated intrinsic diffuse brainstem gliomas (IBSGs).<br>• As outlined in the PWR study endpoints section, the phase I objectives were independent of type of glioma. Therefore, in the phase I study (NO18517) patients with newly diagnosed non-disseminated high-grade gliomas (HGGs) were also included. |

| Written Request Items | Information Submitted/ Applicant's Response |
|---|---|
| | • The intent-to-treat (ITT) population (safety and efficacy) consisted of 44 patients with IBSGs: 34 patients from Phase II Study NO21125 and 10 patients with IBSG from Phase I Study NO18517 treated at the MTD (650 mg/m$^2$/dose BID) and who met the same eligibility criteria as for the Phase II study. |
| <u>Age group and population in which study will be performed:</u><br>• In the Phase 1 portion of the study, when the Maximum Tolerated Dose has been reached or exceeded, an additional 3 or more patients will be treated at a dose level selected to provide further evidence of safety and anti-tumor activity. | <u>Age group and population in which the study was performed:</u><br>• Three capecitabine dose escalation cohorts were studied in Phase I study NO18517: 500 mg/m$^2$, 650 mg/m$^2$ and 850 mg/m$^2$. Four patients were enrolled in the 500 mg/m$^2$ cohort and DLT was not observed. In the 650 mg/m$^2$ cohort, one of the first three patients experienced DLT. An additional three patients were enrolled and DLT was not observed. The 850 mg/m$^2$ cohort exceeded the MTD with three of six enrolled patients developing DLT. The MTD was declared to be 650 mg/m$^2$ and an additional six patients were treated at this dose to provide further evidence of safety and anti-tumor activity. Two patients enrolled in the 650 mg/m$^2$ cohort did not receive trial treatment (during the dose escalation phase). The 22 patients treated in the Phase I Study were between the ages of ≥ 3yrs to ≤ 21 years of age. |
| • In the Phase 2 portion, patients under the age of 18 will be enrolled. Forty-four patients are required for the final | • The Phase II protocol for Study NO21125 was developed in close consultation with the FDA. The decision to move forward to Phase II was discussed and agreed with the FDA at an |

| Written Request Items | Information Submitted/ Applicant's Response |
|---|---|
| analysis of the phase 2 trial unless the trial is stopped for futility after 21 treatment failures have occurred. This total may include up to 10 patients from the phase 1 trial treated at the Maximum Tolerated Dose and who meet the same eligibility criteria for the phase 2 trial. The study protocol for the phase 2 study portion, addressing the issues outlined in this request, must be submitted to the Agency for review and agreement prior to study initiation. | End-of-Phase I (EOPI) meeting on December 18, 2009. The Agency indicated that an amendment to the Written Request #2 was needed to be consistent with the proposed protocol and that Roche/PBTC could proceed with the initiation of the Phase II trial (using the protocol v 1.0 included in the pre-meeting briefing package, Nov 10, 2009) while the protocol and the Written Request were amended and submitted to the Agency. The first Phase II study site was activated on January 29, 2010 and Roche's proposed changes to the Written Request Amendment 2 were submitted on April 15, 2010. The Written Request Amendment 3 was issued by the FDA on 1 July 2011.<br><br>The 34 children with IBSGs treated in the Phase II study NO21125 were between the ages of ≥ 3 to < 18 years and were distributed among the following age groups:<br>– ≥3 and <7 years: 18 patients<br>– ≥7 and <13 years: 10 patients<br>– ≥13 and < 18 years: 6 patients<br>The intent-to-treat (ITT) analysis population consisted of 44 patients: 34 patients from Phase II Study NO21125 and 10 patients with IBSG from Phase I Study NO18517 treated at the MTD (650 mg/m$^2$/dose BID) and who met the same eligibility criteria as for the Phase II Study. The ITT patients were between the ages of ≥ 3 to < 18 years and were distributed |

| Written Request Items | Information Submitted/ Applicant's Response |
|---|---|
| • The PK sub-study (which can be performed across phase 1 and phase 2) will include at least 9 patients in each of the following two age groups at time of enrollment: age under 6 years and age 7 years through 12 years. | among the following age groups:<br>– ≥ 3 and < 7 years of age: 21 patients<br>– ≥ 7 and < 13 years of age: 17 patients<br>– ≥ 13 and < 18 years of age: 6 patients<br><br>• The PK sub-study included samples from 25 patients (15 patients from Study NO21125 and 10 patients from Study NO18517). PK patients were distributed among the following age groups:<br>– < 6 years: 9 patients<br>– ≥6 and <7 years: 2 patients<br>– ≥7 and <13 years: 10 patients<br>– ≥13 years: 4 patients |
| <u>Study Endpoints</u><br>• The primary purpose of the phase 1 study will be to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) of capecitabine when administered concurrently with radiation therapy. Secondary objectives will include a description of the safety profile of the capecitabine-radiation therapy combination. As the phase 1 objectives would be | <u>Study endpoints used:</u><br>• The primary objectives of Phase I Study NO18517 are outlined below<br>– To estimate the MTD of capecitabine pediatric film-coated tablets administered concurrently with radiation therapy (RT) to children with newly diagnosed non-disseminated IBSGs or newly diagnosed non-disseminated high grade |

| Written Request Items | Information Submitted/ Applicant's Response |
|---|---|
| independent of type of glioma, patients with other types of malignant gliomas (e.g., high grade glioma) could be enrolled. | gliomas (HGGs).<br>– To describe the DLT(s) of capecitabine pediatric film-coated tablets administered concurrently with RT to children with newly diagnosed non-disseminated IBSGs or newly diagnosed non-disseminated HGGs.<br><br>Secondary objectives studied are outlined below:<br>– To describe the safety profile of oral capecitabine pediatric film-coated tablets administered concomitantly with RT.<br>– To characterize the PK of capecitabine and its metabolites as delivered by capecitabine pediatric film-coated tablets.<br>– To characterize the capecitabine exposure-response relationship, anti-tumor activity, radiographic changes, and estimate distributions of PFS and survival for IBSG patients. |
| • In the phase 2 portion of the study, the primary endpoint shall be progression-free-survival. Secondary endpoints will include response rate, overall survival, and one year survival. A comparative assessment with recent contemporary cooperative group historical controls will be performed. In addition, the study should provide a description of the safety endpoints of the addition of capecitabine to brain radiation in this setting. | • The primary objective of Phase II Study NO21125 is outlined below:<br>– To estimate the PFS distribution for newly diagnosed patients with diffuse IBSGs treated with the combination of capecitabine pediatric film-coated tablets and RT and compare the PFS distribution to Pediatric Brain Tumor Consortium (PBTC) historical controls. |

| Written Request Items | Information Submitted/ Applicant's Response |
|---|---|
| | Secondary Objectives studied are outlined below:<br>– To estimate the OS distribution (including an estimation for one year survival), and to summarize the best tumor responses observed prior to failure.<br>– To further characterize the safety profile of capecitabine pediatric film-coated tablets administered concomitantly with RT.<br>– To further characterize the PK of capecitabine and its metabolites as delivered by capecitabine pediatric film-coated tablets in this pediatric population.<br>For the primary efficacy analysis, the PFS rate of the ITT Population was compared with that of the PBTC historical control. The demographic data and baseline characteristics of the ITT Population were similar to those of the historical control. |
| • The PK sub-study will be achieved through secondary objectives of the phase 1 and phase 2 trials, i.e. an evaluation of the pharmacokinetics of capecitabine and its metabolites in pediatric age patients. Additionally, pharmacokinetic and pharmacodynamic (PK-PD) models will explore exposure-response relationships for measures of safety and effectiveness. | • The PK sub-study was achieved through secondary objectives of Study NO18517 and Study NO21125, as outlined below:<br>– To characterize the PK of capecitabine and its metabolites as delivered by capecitabine pediatric film-coated tablets in this pediatric population.<br>– To explore the exposure-response relationship for measures of safety and effectiveness PK/PD graphical analysis was performed. Exploratory graphical analysis of |

| Written Request Items | Information Submitted/ Applicant's Response |
|---|---|
| | the relationship of exposure for the two main metabolites 5'-DFUR and 5-FU with the efficacy and safety measures of interest were presented for patients diagnosed with IBSG who provided PK data. Safety measurements of interest were adverse events diarrhea, vomiting, and palmar-plantar erythrodysesthesia. Efficacy measurements of interest were PFS and tumor measurements. Due to the small sample size and the lack of clear relationship, this analysis was limited to the graphical exploration and PK/PD models were not developed for efficacy or safety. |
| <u>Drug information</u><br>• *Dosage form:* Age appropriate formulation (e.g., rapid-disintegrating flavored tablet).<br>• *Route of administration:* Oral<br>• *Regimen:* Oral capecitabine will be administered daily in two divided doses approximately 12 hours apart beginning within 24 hours of the start of radiation therapy.<br>• *Formulation*: Use an age-appropriate formulation in the studies described above. If the studies you conduct in response to this Written Request demonstrate this drug | <u>Drug information</u><br>• The following dosage form was used: Film-coated tablets, 125 mg and 175 mg. These tablets could be swallowed intact or dispersed in water prior to swallowing.<br>• Route of administration used: Oral<br>• Regimen: Pediatric patients were dosed by body surface area with 650 mg/m$^2$ capecitabine twice a day (BID) in combination with RT, and 1250 mg/m$^2$ capecitabine BID during the post-RT phase.<br>• Formulation used : Pediatric film-coated tablets.<br>Capecitabine pediatric tablets are a conventional immediate-release film-coated tablet, containing either 125 mg |

| Written Request Items | Information Submitted/ Applicant's Response |
|---|---|
| will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. | or 175 mg of capecitabine (250 mg and 350 mg film-coated tablets were also developed for clinical use). The pediatric film-coated tablets were designed to quickly disperse in water and the resulting suspension could be administered to pediatric patients unable to swallow tablets. Flavors were added to mask the bitter taste. |
| • Development of a commercially-marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval. | • Commercial marketing is not applicable because the Phase II study (NO21125/PBTC-030) did not meet its primary objective of improving PFS in children with newly-diagnosed IBSGs and therefore the indication for the XELODA pediatric formulation was not proposed. The Applicant does not plan to market the pediatric formulation for XELODA. |
| • If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from | • Not applicable |

| Written Request Items | Information Submitted/ Applicant's Response |
|---|---|
| commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents: detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information. | |
| • Bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age- appropriate formulation may be conducted in adults. If appropriate, a biowaiver strategy could be used to address the relative bioavailability study. | • The Applicant submitted a Study Report for Study BP27931, entitled "A Randomized, Open-label, Single Dose, Two-way Cross-Over Study to Investigate the Relative Bioavailability of Capecitabine in RDT Versus the Commercial Xeloda® Tablets Following Oral Administrations in Adult Patients with Solid Tumours" that was conducted to compare the bioavailability of capecitabine pediatric film-coated tablets with the commercial XELODA tablets in adult patients with colorectal or breast cancer. A total of 37 patients enrolled: and 36 patients completed the study.<br><br>Subjects with colorectal or breast cancer were enrolled prior to receiving their first XELODA treatment or prior to their next standard XELODA treatment cycle. Subjects were randomized to 1 of 2 cohorts:<br>– Cohort A: On Day 1 the subject received 2000 mg capecitabine pediatric film-coated tablets in the morning. |

| Written Request Items | Information Submitted/ Applicant's Response |
|---|---|
| | On Day 2 the subject received 2000 mg XELODA in the morning at the same time as on Day 1<br>– Cohort B: On Day 1 the subject received 2000 mg XELODA in the morning. On Day 2 the subject received 2000 mg capecitabine pediatric film-coated tablets in the morning at the same time as on Day 1.<br><br>The results of the relative bioavailability (RBA) study suggest that exposure to capecitabine and its metabolites is comparable following the administration of the marketed XELODA tablets and the pediatric film-coated tablets; the earlier $t_{max}$ does not appear to be clinically relevant.<br><br>*Reviewer Comment: For additional details regarding the results of this study, please refer to the FDA review performed by Stacy Shord, Pharm.D., of the Office of Clinical Pharmacology. Dr. Shord concurred with the Applicant's interpretation that the relative bioavailability of the marketed Xeloda tablets was comparable to that of the pediatric film-coated tablets.* |

| Written Request Items | Information Submitted/ Applicant's Response |
|---|---|
| Drug specific safety concerns<br>• The safety and efficacy of capecitabine, a potential radiation sensitizer, combined with radiation has not been evaluated in children with brainstem gliomas. Radiation therapy should be given in a typical manner, using conventional or conformal volume-based techniques at standard doses. Effects of radiation should be monitored closely.<br>• Safety evaluation must include clinical and neurologic examinations, evaluation of adverse events, and laboratory studies including CBCs, electrolytes, assessments of renal and hepatic function, and assessment of potential drug interactions with Dexamethasone and anti-seizure medications, if these medications are co-administered. Toxicities should be evaluated using Version 3.0 (or later) of the NCI Common Toxicity Criteria. | Drug specific safety concerns addressed<br>• The safety of combining capecitabine with radiation in children with brainstem gliomas was evaluated as outlined in the PWR. Study NO18517 was the first study to evaluate the safety and efficacy of capecitabine pediatric film-coated tablets in combination with RT in children with brainstem gliomas. RT was given in a typical manner, using conventional or conformal volume-based techniques at standard doses. The effects of radiation were closely monitored.<br>• Safety evaluations included routine clinical and neurological examinations, evaluation of symptomatic adverse events, and laboratory studies including complete blood counts (CBCs), electrolytes, and assessments of renal and hepatic function.<br>Descriptive analysis of potential drug interactions of XELODA in combination with dexamethasone and anti-seizure medications was provided in the sNDA. Toxicity was monitored and graded according to the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events version 3.0 (CTCAEv3.0) in NO18517 and version 4.0 (CTCAEv4.0) in NO21125. |

| Written Request Items | Information Submitted/ Applicant's Response |
|---|---|
| Statistical information, including power of study and statistical assessments<br>• Descriptive statistics should be used for reporting results. | Statistical information, including power of study and statistical assessments provided<br>• Descriptive statistics were used to report study results. |
| • A single interim analysis for futility will be performed when the 21st failure is observed (includes failures of phase 1 patients treated at the MTD and who meet the same eligibility criteria for phase 2). Using the sequential probability ratio procedure, the regimen of capecitabine and radiation therapy will be considered ineffective and the trial will be closed to accrual if the nominal p-value at the interim analysis is> 0.2745. With this sequential design, the overall type 1 error rate is 0.1004 and the statistical power is 0.8997. If the trial is halted, the maximum probability that the decision would have been different had the targeted goal of 44 patients been treated and followed for at least one year is 0.005 (0.5%). | • According to the statistical design of NO21125 (PBTC-030) one interim analysis (IA) of PFS for futility occurred when the 21st failure was observed (including failures of Phase I patients treated at the MTD and who met the same eligibility criteria for Phase II). If the nominal p-value of the comparison was greater (>) than 0.2745, then the trial was to be considered "futile" and accrual was to cease. The interim threshold for stopping the trial for futility was not reached and the Data Safety Monitoring Board recommended that the trial continue to enroll to reach the full cohort of 44 patients. |
| • Pharmacokinetic Substudy: A PK sub-study must examine capecitabine PK in children using accepted procedures and methods and will attempt to model important co-variates. | • Because limited PK data was available for the new pediatric formulation in the Phase I study, sample collection for PK was also performed in the Phase II study. Plasma samples were measured for the concentration of capecitabine and its metabolites using validated assays. The PK (time-concentration) profiles were plotted and associated PK parameters of capecitabine pediatric film-coated tablets and its metabolites were estimated individually on days 1 and 14 |

| Written Request Items | Information Submitted/ Applicant's Response |
|---|---|
| | (±7 days) of the RT treatment cycle. The following parameters were estimated using non-compartmental methods: $C_{max}$, $T_{max}$, $AUC_{6h}$ and $t_{1/2}$. These PK parameters were presented by listings and descriptive summary statistics including arithmetic means, geometric means, ranges, standard deviations and coefficients of variation. The parameters were estimated according to standard non-compartmental methods (NCA).<br><br>Using a previously developed population PK (PopPK) model developed for adults that supported bridging to the pediatric population, a Bayesian feedback analysis was used to describe the PK time course profile and obtain PK parameter estimates from the pooled pediatric PK data from the two (Phase I and Phase II) pediatric PK sub-studies. A comparison of the population and individual model predictions to the observations provided support for the premise that the model previously developed in adults accurately described the data in the pediatric population. |
| <u>Labeling that may result from the studies</u><br>• Any information to be included in labeling will depend on the results of the studies and discussions with FDA. | <u>Revised labeling submitted</u><br>• The Applicant submitted proposed labeling changes to update the Pediatric Use section of the Xeloda label to incorporate the results of Studies NO18517, NO21125, and BP27931. |
| <u>Format of reports to be submitted</u><br>• Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full | <u>Format of reports submitted</u><br>• The Applicant submitted full study reports not previously submitted to the Agency including full analysis, assessment, |

| Written Request Items | Information Submitted/ Applicant's Response |
|---|---|
| datasets (including individual patient data listings), analysis, assessment, and interpretation. Even if the study fails, we need full study reports with data to support study conclusions. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies 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, one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino. | and interpretation of the data. The reports included information on the representation of pediatric patients of ethnic and racial minorities according to the categories and designations in the FDA's Written Request. |
| • Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance. | • Per the December 19, 2012 Roche/FDA pre-NDA meeting agreement, the Applicant submitted the Periodic Safety Update Report, which was the most recent post-marketing adverse event report available at the time of the sNDA filing. |

| Written Request Items | Information Submitted/ Applicant's Response |
|---|---|
| • Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCMI99759.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format- Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm. | • The Applicant acknowledged the Agency's request for the data to be submitted electronically according to the SDTM standard, which was not required per the PWR. The Applicant stated that they did not have the necessary processes needed to accommodate CDISC and therefore provided the capecitabine pediatric studies datasets in their standard format, with each dataset provided as a SAS Transport (XPORT) file. |
| <u>Timeframe for submitting reports of the studies</u><br>• The study reports of the above studies must be submitted to the Agency on or before September 30, 2013. | <u>Timeframe for submitting reports of the studies</u><br>• The Applicant included the study reports in the sNDA, which was received by the Agency on June 10, 2013. |

*Source: Adapted from the Applicant's sNDA submission*

# 6 Review of Efficacy

*Efficacy Summary*

The data submitted with this application did not provide evidence of a treatment benefit from administration of capecitabine concurrently with and following standard radiation therapy to pediatric patients with newly diagnosed non-disseminated diffuse intrinsic brainstem gliomas (IBSGs).

The Pediatric Written Request (PWR) specified that "In the phase 2 portion of the study, the primary endpoint shall be progression-free survival….A comparative assessment with recent contemporary cooperative group historical controls will be performed." The PWR also specified that 44 patients were required for the final analysis of the phase 2 trial (Study NO21125), including up to 10 patients treated in the phase 1 trial (NO18517) with the maximum tolerated dose (MTD) of capecitabine who met the eligibility criteria for Study NO21125.

*Reviewer comment: Use of historical controls as a basis for comparison of a treatment effect can be fraught with problems due to potential differences in patient populations across studies and evolving standards of care and supportive measures that can change the natural history of the disease and render comparisons uninterpretable. However, because there has been negligible improvement in progression-free survival and overall survival in patients with IBSGs over the past few decades, using a historical comparator in this case seems reasonable.*

The control population serving as the comparator for the primary endpoint of one-year progression-free survival (PFS) rate and the secondary endpoint of one-year overall survival (OS) rate consisted of 140 similar pediatric patients who participated in five clinical trials of radiation therapy in combination with other investigational products conducted by the Pediatric Brain Tumor Consortium (phase 1 trial PBTC-006, phase 1 and 2 components of PBTC-007, and phase 1 and 2 components of PBTC-014).

Among the 44 patients with newly diagnosed IBSG enrolled in Study NO18517 and Study NO21125 who received capecitabine at the maximum tolerated dose of 650 mg/m$^2$ twice daily concurrently with radiation followed by 3 cycles at a dose of 1250 mg/m$^2$ twice daily post-radiation (the ITT population), there was no improvement in the one-year progression-free survival rate and one year overall survival rate compared to the control population. The data from Study N021125 failed to reject the null hypothesis for the primary endpoint of one-year PFS. There was a negative trend in the one-year PFS rate observed in patients treated with capecitabine; the one-year PFS rate was 0.08 (90% CI = 0.01, 0.14) for pediatric patients who received capecitabine in conjunction with standard radiation therapy, which was not statistically

superior to the historical control rate of 0.159. The Pediatric Brain Tumor Consortium, which holds the data for the historical control group, conducted a log-rank test on the two PFS distributions and reports that it numerically favored the control arm but the difference was not statistically significant (p=0.058). This log-rank test cannot be replicated by FDA because the control data were not submitted.

The one-year overall survival (OS) rate was 0.42 (90% CI = 0.29, 0.55), which is similar to the historical control rate of 0.46.

## 6.1 Methods

Clinical review was based primarily upon the clinical study report for Study NO21125, case report forms, and primary datasets submitted by the Applicant.

## 6.2 Baseline Demographic and Disease Characteristics

Demographic characteristics of the intent-to-treat (ITT) population used in the efficacy analysis of Study NO21125 are depicted in Table 10. Half of the patients were male and half were female. The majority of patients were White (73%), and the median age at enrollment was 7 years of age.

**Table 10: Summary of Patient Baseline Demographic Characteristics for Study NO21125**

| Demographic Characteristic | ITT Population N = 44 n (%) |
|---|---|
| Gender | |
| Male | 22 (50) |
| Female | 22 (50) |
| | |
| Race | |
| White | 32 (73) |
| Black or African American | 6 (14) |
| American Indian or Alaskan Native | 1 (2) |
| Asian | 1 (2) |
| Native Hawaiian or other Pacific Islander | 1 (2) |
| Unknown | 2 (5) |
| Other | 1 (2) |
| | |

| Demographic Characteristic | ITT Population N = 44 n (%) |
|---|---|
| Age (years) | |
| Mean (Standard deviation) | 7.5 (3.7) |
| Median (Min, Max) | 7 (3,16) |
| | |
| Age subgroup (years) | |
| ≥ 3 and < 7 | 21 (48) |
| ≥ 7 and < 13 | 17 (39) |
| ≥13 to <18 | 6 (14) |
| | |
| Weight (kg) | |
| mean (Standard deviation) | 34.7 (20.9) |
| Median (min, max) | 27.2 (14.2,97.2) |

All patients in the ITT population had newly diagnosed diffuse IBSG. A total of 4 of the 44 (9%) patients had undergone pre-treatment surgery.

## 6.3 Concomitant Medications

The most frequently used concomitant medication, corticosteroids, were administered to 39 of the 44 patients (89%) in the ITT analysis population. 5-HT3 antagonists were administered to 27 patients (61%) and histamine H2-receptor antagonists were administered to 19 patients (43%).

## 6.4 Patient Disposition

Patients enrolled at PBTC institutions from May 23 2007 through May 23 2011. As of January 31, 2013, three of the 44 patients in the ITT population remained alive and were still being followed (Table 11).

**Table 11: Summary of Reasons for Premature Withdrawal from Study NO21125**

| Reasons for Study Withdrawal | Capecitabine ITT Population N=44 n (%) |
|---|---|
| Death | 38 (86%) |
| Failure to return | 3 (7%) |

A total of 19 patients in the ITT population prematurely discontinued investigational treatment; ten (23%) patients discontinued due to disease progression and five (11%) patients discontinued treatment due to an adverse event (Table 12).

**Table 12: Summary of Reasons for Premature Capecitabine Discontinuation in Study NO21125**

| Reasons for Discontinuation of Study Therapy | Capecitabine ITT Population N=44 n (%) |
|---|---|
| Disease progression | 10 (23%) |
| Adverse event | 5 (11%) |
| Withdrawal of consent/ Lack of cooperation | 3 (7%) |
| Death | 1 (2%) |

## 6.5 Analysis of Primary Endpoints

The primary endpoint of this study was not met. Among the 44 patients with newly diagnosed IBSG who received capecitabine at the maximum tolerated dose of 650 mg/m$^2$ twice daily concurrently with radiation followed by 3 cycles at a dose of 1250 mg/m$^2$ post-radiation, there was no improvement in the one-year progression-free survival rate and the one year overall survival rate compared to the control population. The data from study N021125 failed to reject the null hypothesis for the primary endpoint of one-year PFS. There was a negative trend in the one-year PFS rate observed in patients treated with capecitabine; the one-year PFS rate was 0.08 (90% CI = 0.01, 0.14) for pediatric patients who received capecitabine in conjunction with standard radiation therapy, which was not statistically superior to the historical control rate of 0.159.

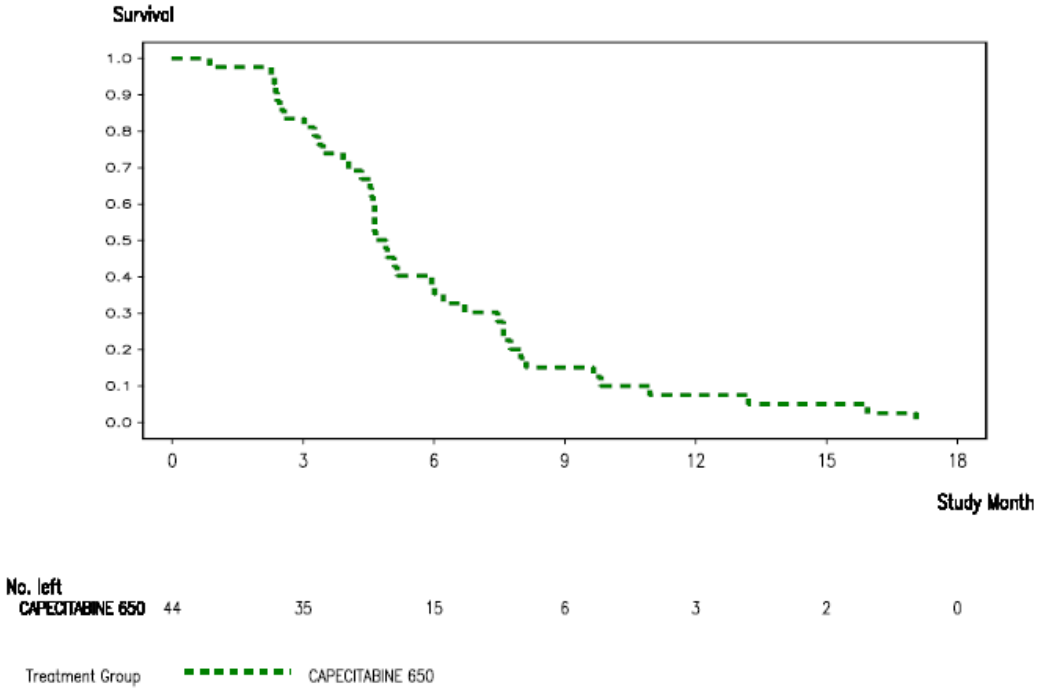
The Pediatric Brain Tumor Consortium, which holds the data for the historical control group, conducted a log-rank test on the two PFS distributions and reports that it numerically favored the control arm but the difference was not statistically significant

(p=0.058). This log-rank test cannot be replicated by FDA because the control data were not submitted.

*Reviewer note: The PWR did not require submission of the raw data from the control population analysis.*

The median time to a PFS event was 4.9 months. The Kaplan Meier curve for PFS in the ITT population, copied from the Applicant's submission, is depicted in Figure 2.

**Figure 2: Kaplan Meier Curve for PFS in Study NO21125**




*Source: Clinical Study Report for Study NO21125*

## 6.6 Other Endpoints

The one-year overall survival (OS) rate in the ITT population was 0.42 (90% CI = 0.29, 0.55), which is similar to the historical control rate of 0.46 provided by the Applicant. A total of 38 patients (86.4%) died, and the median time to death was 10.3 months (range 1.4 months to 22.5 months). At the time of data cut-off (January 31, 2013), three patients were lost to follow-up and three patients were known to be alive.

The Kaplan Meier curve for OS in the ITT population, copied from the Applicant's submission, is depicted in Figure 3.

**Figure 3: Kaplan Meier Curve for OS in Study NO21125**


*Source: Clinical Study Report for Study NO21125*

# 7 Review of Safety

*Safety Summary*

Clinical review of the safety of capecitabine in patients with newly diagnosed diffuse intrinsic brainstem gliomas (IBSGs) was based primarily upon the clinical study report for Study NO21125, case report forms, and primary datasets submitted by the Applicant. Care should be taken with interpretation of safety data derived from small, single arm trials, particularly in the context of a patient population with life-threatening brain tumors who typically require concomitant corticosteroid therapy and have neurological sequelae due to their underlying disease.

Overall, the adverse reaction profile of capecitabine was consistent with the known adverse reaction profile in adults, with the exception of laboratory abnormalities which occurred more commonly in pediatric patients. The most frequently reported laboratory abnormalities (per-patient incidence ≥40%) were increased ALT (75%), lymphocytopenia (73%), leukopenia (73%), hypokalemia (68%), thrombocytopenia

(57%), hypoalbuminemia (55%), neutropenia (50%), low hematocrit (50%), hypocalcemia (48%), hypophosphatemia (45%) and hyponatremia (45%).

## 7.1 Capecitabine Exposure

Table 13 provides a summary of capecitabine exposure for patients enrolled in Study NO21125. Of the 44 patients with IBSG who received the maximum tolerated dose of capecitabine, 26 patients (59%) completed six cycles of study treatment during the radiation therapy period. A total of 18 patients (41%) received five or fewer cycles. The median duration of study treatment was 133 days (range: 44 to 150).

**Table 13: Summary of Capecitabine Exposure**

| Exposure Parameter | Capecitabine Safety Population N=44 n (%) |
|---|---|
| Duration of study treatment (days) | |
| Mean (standard deviation) | 113 (32) |
| Median (min, max) | 133 (44, 150) |
| Number of cycles received | |
| 1 | 2 (5) |
| 2 | 1 (2) |
| 3 | 6 (14) |
| 4 | 5 (11) |
| 5 | 4 (9) |
| 6 | 26 (59) |
| Mean (standard deviation) | 5 (1.5) |
| Median (min, max) | 6 (1,6) |

In general, patients received the standard dose of radiation therapy. The mean cumulative radiation dose was 55.8 Gy (standard deviation: 0.27).

*Reviewer comment: Overall, the level of exposure to capecitabine was inadequate in comparison to the intended dose. It is likely that exposure was negatively impacted by the lack of efficacy of capecitabine, given that the median time to a PFS event was 4.9 months.*

## 7.2 Analysis of Adverse Events

### 7.2.1 Deaths

At the time of data analysis, 38 of 44 patients had died during the treatment or follow-up period. Deaths were attributed to disease progression, with the exception of one death due to a *Clostridium difficile* infection; in this case, capecitabine was cited as a possible contributing factor.

### 7.2.2 Nonfatal Serious Adverse Events

A total of 23 of 44 (52%) patients experienced at least one serious adverse event (SAE). The majority of SAEs (12/44, or 27%) belonged to the Nervous System Disorders MedDRA System Organ Class (SOC), and the most common SAE by preferred term was decreased neutrophil count (5/44, or 11% of patients).

Table 14 provides a listing by preferred term of serious adverse events that occurred in 2 or more patients.

**Table 14: Serious Adverse Events Occurring in ≥ 2 Patients in Study NO21125**

| Preferred Term | Capecitabine Safety Population N=44 n (%) |
|---|---|
| Decreased neutrophil count | 5 (11) |
| Central nervous system necrosis | 3 (7) |
| Hydrocephalus | 3 (7) |
| Convulsion | 2 (5) |
| Neurological symptom | 2 (5) |
| Disease Progression | 2 (5) |
| Pyrexia | 2 (5) |
| Decreased white blood cell count | 2 (5) |
| Diarrhea | 2 (5) |
| Dysphagia | 2 (5) |
| Dehydration | 2 (5) |

Review of case narratives revealed that many of the SAEs, particularly the neurological and infectious SAEs, were confounded by concomitant therapy (e.g., radiation therapy and corticosteroids) or the patient's underlying disease

7.2.3 Severe and Common Adverse Events

Toxicities were graded using NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

All patients treated with capecitabine in Study NO21125 experienced at least one adverse event. Adverse events were most frequently reported for the Investigations, Metabolism and Nutrition Disorders, and Gastrointestinal Disorders MedDRA SOCs (42/44 or 95% of patients each).

Table 15 lists the adverse events with a per-patient incidence of ≥20% overall, in addition to adverse events of ≥ Grade 3 severity that occurred in ≥ 5% of patients.

The most commonly reported (≥ 50% per-patient incidence) adverse events by preferred term were vomiting (80%), increased alanine aminotransferase (75%), decreased lymphocyte count (73%), decreased white blood cell count (61%), and decreased platelet count (57%).

The most common (≥10%) severe (≥ Grade 3 severity) adverse events were decreased lymphocyte count (50%), decreased white blood cell count (16%), decreased neutrophil count (16%), increased weight (14%), and lymphopenia (14%).

**Table 15: Summary of Common and Severe Adverse Events for Study NO21125**

| ***System Organ Class*** | ***Preferred Term*** | ***Capecitabine N=44*** | | | |
|---|---|---|---|---|---|
| | | ***All Grades*** | | ***Severe*** | |
| | | **n** | **%** | **n** | **%** |
| **Gastrointestinal Disorders** | Vomiting | 35 | 80% | 2 | 5% |
| | Nausea | 15 | 34% | 0 | 0% |
| | Constipation | 14 | 32% | 0 | 0% |
| | Diarrhea | 12 | 27% | 2 | 5% |
| | Abdominal Pain | 11 | 25% | 1 | 2% |
| **Investigations** | Alanine Aminotransferase Increased | 33 | 75% | 4 | 9% |
| | Lymphocyte Count Decreased | 32 | 73% | 22 | 50% |
| | White Blood Cell Count Decreased | 27 | 61% | 7 | 16% |
| | Platelet Count Decreased | 25 | 57% | 0 | 0% |

| System Organ Class | Preferred Term | Capecitabine N=44 | | | |
|---|---|---|---|---|---|
| | | All Grades | | Severe | |
| | | n | % | n | % |
| | Neutrophil Count Decreased | 15 | 34% | 7 | 16% |
| | Blood Bilirubin Increased | 14 | 32% | 0 | 0% |
| | Weight Increased | 11 | 25% | 6 | 14% |
| | Aspartate Aminotransferase Increased | 11 | 25% | 0 | 0% |
| | Neutrophil Count | 3 | 7% | 2 | 5% |
| **Metabolism And Nutrition Disorders** | Hypoalbuminemia | 21 | 48% | 1 | 2% |
| | Hypokalemia | 18 | 41% | 3 | 7% |
| | Hypocalcemia | 17 | 39% | 0 | 0% |
| | Hyponatremia | 16 | 36% | 2 | 5% |
| | Hyperglycemia | 16 | 36% | 1 | 2% |
| | Hypermagnesemia | 16 | 36% | 0 | 0% |
| | Hypophosphatemia | 14 | 32% | 1 | 2% |
| | Decreased Appetite | 11 | 25% | 0 | 0% |
| | Dehydration | 3 | 7% | 2 | 5% |
| **Nervous System Disorders** | Headache | 20 | 45% | 3 | 7% |
| | Ataxia | 9 | 20% | 1 | 2% |
| | Facial Nerve Disorder | 9 | 20% | 0 | 0% |
| | Convulsion | 3 | 7% | 2 | 5% |
| | Hydrocephalus | 3 | 7% | 3 | 7% |
| | Neurological Symptom | 2 | 5% | 2 | 5% |
| **General Disorders And Administration Site Conditions** | Fatigue | 18 | 41% | 1 | 2% |
| **Blood And Lymphatic System Disorders** | Anemia | 16 | 36% | 2 | 5% |
| | Lymphopenia | 9 | 20% | 6 | 14% |
| **Skin And Subcutaneous Tissue Disorders** | Palmar-Plantar Erythrodysaesthesia Syndrome | 16 | 36% | 0 | 0% |

| *System Organ Class* | *Preferred Term* | *Capecitabine N=44* | | | |
|---|---|---|---|---|---|
| | | *All Grades* | | *Severe* | |
| | | n | % | n | % |
| **Endocrine Disorders** | Cushingoid | 14 | 32% | 0 | 0% |
| **Musculoskeletal And Connective Tissue Disorders** | Muscular Weakness | 9 | 20% | 3 | 7% |
| **Cardiac Disorders** | Sinus Tachycardia | 3 | 7% | 2 | 5% |
| **Respiratory, Thoracic And Mediastinal Disorders** | Hypoxia | 3 | 7% | 3 | 7% |

# 8 Labeling Recommendations

I recommend that the following information be included in Section 8.4 (Pediatric Use) of the Xeloda package insert.

> The safety and effectiveness of XELODA in pediatric patients have not been established. No clinical benefit was demonstrated in two single arm trials in pediatric patients with newly diagnosed brainstem gliomas and high grade gliomas. In both trials, pediatric patients received an investigational pediatric formulation of capecitabine concomitantly with and following completion of radiation therapy (total dose of 5580 cGy in 20896180 cGy fractions). The relative bioavailability of the investigational formulation to XELODA was similar.
>
> The first trial was conducted in 22 pediatric patients (median age 8 years, range 5-17 years) with newly diagnosed non-disseminated intrinsic diffuse brainstem gliomas and high grade gliomas. In the dose-finding portion of the trial, patients received capecitabine with concomitant radiation therapy at doses ranging from 500 mg/m$^2$ to 850 mg/m$^2$ every 12 hours for up to 9 weeks. After a 2 week break, patients received 1250 mg/m$^2$ capecitabine every 12 hours on Days 1-14 of a 21-day cycle for up to 3 cycles. The maximum tolerated dose (MTD) of capecitabine administered concomitantly with radiation therapy was 650 mg/m$^2$ every 12 hours. The major dose limiting toxicities were palmar-plantar erythrodysesthesia and alanine aminotransferase (ALT) elevation.
>
> The second trial was conducted in 34 additional pediatric patients with newly diagnosed non-disseminated intrinsic diffuse brainstem gliomas (median age 7 years, range 3-16 years) and 10 pediatric patients who received the MTD of capecitabine in the dose-finding trial and met the eligibility criteria for this trial. All patients received 650 mg/m$^2$ capecitabine every 12 hours with concomitant radiation therapy for up to 9 weeks. After a 2 week break, patients received 1250 mg/m$^2$ capecitabine every 12 hours on Days 1-14 of a 21-day cycle for up to 3 cycles.
>
> There was no improvement in one-year progression-free survival rate and one-year overall survival rate in pediatric patients with newly diagnosed intrinsic brainstem gliomas who received capecitabine relative to a similar population of pediatric patients who participated in other clinical trials.

The adverse reaction profile of capecitabine was consistent with the known adverse reaction profile in adults, with the exception of laboratory abnormalities which occurred more commonly in pediatric patients. The most frequently reported laboratory abnormalities (per-patient incidence ≥40%) were increased ALT (75%), lymphocytopenia (73%), leukopenia (73%), hypokalemia (68%), thrombocytopenia (57%), hypoalbuminemia (55%), neutropenia (50%), low hematocrit (50%), hypocalcemia (48%), hypophosphatemia (45%) and hyponatremia (45%).

*Reviewer note: For leukopenia, hypokalemia, hypoalbuminemia, neutropenia, low hematocrit, hypocalcemia, hypophosphatemia, and hyponatremia, the per-patient incidence listed is based upon the laboratory dataset values because they were higher than the per-patient incidence derived from the adverse event datasets.*

# 9 References

1. Hargrave D, Bartels U, Bouffet E. Diffuse brainstem glioma in children: critical review of clinical trials. Lancet Oncol 2006;7:241-48.
2. David R, Bodensteiner J, Mandelbaum D, and Olson B. Clinical Pediatric Neurology. Third edition, Copyright 2009.
3. Smith MA, Freidlin B, Ries LA, Simon R. Trends in reported incidence of primary malignant brain tumors in children in the United States. J Natl Cancer Inst 1998;90:1269-77.
4. Frazier JL, Lee J, Thomale UW, Noggle JC, et al. Treatment of diffuse intrinsic brainstem gliomas: failed approaches and future strategies. J Neurosurg Pediatrics 2009;3(4):259-69.
5. Jansen MH, van Duurden DG, Vandertop WP, Kaspers GJL. Diffuse intrinsic pontine gliomas: A systematic update on clinical trials and biology. Cancer Treatment Reviews 2012; 38(1):27-35.

---

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

---

/s/

---

MARTHA B DONOGHUE
12/09/2013

SUZANNE G DEMKO
12/09/2013