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

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ABSTRACT

Purpose

We conducted a phase I and pharmacokinetic study of the epidermal growth factor receptor (EGFR) inhibitor erlotinib as a single agent and in combination with temozolomide in children with refractory solid tumors.

Patients and Methods

Erlotinib was administered orally once daily to cohorts of three to six children for a single 28-day course. Patients then received the combination of daily erlotinib and temozolomide daily for 5 days for all subsequent 28-day courses. An oral erlotinib solution was administered during the dose-finding phase and a tablet formulation was subsequently studied at the maximum-tolerated dose (MTD). Pharmacokinetic studies and ERBB-receptor expression and signaling studies were performed.

Results

Forty-six patients, median age 11.5 years, received erlotinib at doses of 35, 50, 65, 85, or 110 mg/m²/d. At 110 mg/m²/d, two of four patients had dose-limiting toxicity (DLT) consisting of rash and hyperbilirubinemia, whereas one of six patients developed dose-limiting rash at 85 mg/m²/d. The most frequent non-DLTs included diarrhea, rash, and hyperbilirubinemia. The combination of erlotinib and temozolomide was well tolerated. The median apparent erlotinib clearance was 3.1 L/h/m² and the median terminal half-life was 8.7 hours. One patient with a neurocytoma had stable disease for 19 months, two patients with neuroblastoma remained on study for 23 and 24 months, and one patient with myoepithelioma had a mixed response.

Conclusion

The recommended phase II dose of erlotinib in recurrent pediatric solid tumors is 85 mg/m²/d, either alone or in combination with temozolomide.

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INTRODUCTION

The epidermal growth factor receptor (EGFR, ERBB1) is a membrane-anchored protein tyrosine kinase that, when phosphorylated, activates a variety of downstream effector molecules regulating cell proliferation and differentiation. Aberrant cell signaling via the EGFR family has been implicated in the development or progression of several human cancers, including certain pediatric solid tumors.¹⁻⁴ Drugs that inhibit EGFR signaling may disrupt critical cellular functions⁵ and potentiate the effects of cytotoxic chemotherapy and radiation therapy.^{6,7} EGFR inhibition can be achieved either with monoclonal antibodies or with small-molecule inhibitors. Erlotinib, a highly potent oral inhibitor of the EGFR

tyrosine kinase⁸ with significant but lesser inhibitory activity against ERBB2,⁹ has been US Food and Drug Administration approved for adults with recurrent non-small-cell lung cancer (NSCLC) and advanced pancreatic cancer.

The addition of an EGFR pathway inhibitor to cytotoxic chemotherapy is a strategy being pursued for a number of adult malignancies.^{10,11} Preclinical xenograft models suggest that combining erlotinib with active chemotherapeutic agents leads to incremental improvements in outcome. Inhibition of tumor growth was significantly greater when erlotinib was combined with gemcitabine or cisplatin in NSCLC tumor models compared with erlotinib alone.¹² A phase III trial in patients with advanced pancreatic cancer

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showed a 23.5% improvement in survival when erlotinib was administered in combination with gemcitabine compared with gemcitabine alone.¹³

Temozolomide is an oral alkylating agent that has shown a broad spectrum of activity both in the preclinical¹⁴⁻¹⁶ and clinical settings^{17,18} in pediatric tumors. The combination of temozolomide and an EGFR inhibitor produced at least additive effects in human tumor xenograft models.¹⁹ We therefore performed a phase I trial and pharmacokinetic (PK) study of erlotinib administered orally for 28 consecutive days, followed by the combination of daily erlotinib and temozolomide administered daily for 5 days every 28 days in pediatric patients with recurrent or refractory solid tumors.

PATIENTS AND METHODS

Institutional review boards at participating institutions approved the study. Informed consent was obtained from patients aged ≥ 18 years or from parents/legal guardians of children aged less than 18 years, with child assent when appropriate, according to individual institutional policies.

Patients and Eligibility

Eligible patients were younger than 22 years with a recurrent or refractory CNS tumor, osteogenic sarcoma, rhabdomyosarcoma, soft tissue sarcoma, neuroblastoma, or germ cell tumor. Patients were required to have a Karnofsky or Lansky performance score of at least 50 for those older than or 10 years old and younger, respectively, and a life expectancy of more than 8 weeks. Adequate bone marrow (absolute neutrophil count $\geq 1000/\mu\text{L}$, platelet count $\geq 100,000/\mu\text{L}$, hemoglobin $\geq 8 \text{ gm/dL}$), renal (normal serum creatinine for age) and hepatic (total bilirubin $< 1.5 \times$ normal and ALT $< 2.5 \times$ upper limit of normal) function was required. Patients were required to have recovered from the acute toxic effects of all prior treatment and could not have received myelosuppressive chemotherapy within 2 weeks of study entry; palliative radiation within 2 weeks or radiation to more than 50% of the pelvis or craniospinal axis within 6 months; or biologic therapy or growth factors within 7 days or stem-cell transplantation within 3 months. Exclusion criteria included uncontrolled infection, pregnancy or lactation, any previous erlotinib exposure, concurrent administration of an enzyme-inducing anticonvulsant, use of a proton pump inhibitor within 5 days or H_2 blocker within 2 days of study entry, and use of a CYP3A4 inducer within 4 weeks or a CYP3A4 inhibitor within 1 week of study entry.

Study Design

Erlotinib was administered orally once daily in the morning, either at least 1 hour before or 2 hours after breakfast, without interruption. A course was defined as 28 consecutive days of drug administration. The erlotinib dose was escalated in cohorts of three to six patients. Because the bioavailability of the solution was undefined, 35 $\text{mg/m}^2/\text{d}$ was selected as the starting dose level with subsequent escalations to 50, 65, 85, and 110 $\text{mg/m}^2/\text{d}$. A minimum of three patients assessable for toxicity were treated at each dose level. If one of the first three patients treated at any dose level experienced dose-limiting toxicity (DLT) during the first course of treatment, up to three additional patients were treated at that dose level. The maximum-tolerated dose (MTD) was defined as the dose level immediately below that at which two or more patients in a cohort of up to six experienced DLT. Only course 1 (single-agent erlotinib) DLTs were used to guide dose escalation and define the MTD.

Toxicities were graded according to CTCAE v3.0 (<http://ctep.cancer.gov/forms/CTCAEv3.pdf>). DLTs were defined as any grade 3 or 4 thrombocytopenia or grade 4 neutropenia, any grade 2 nonhematologic toxicity that persisted for more than 7 days and was considered sufficiently severe to warrant treatment interruption, and any grade 3 or 4 nonhematologic toxicity attributable to erlotinib with the specific exceptions of weight loss, grade 3 nausea and vomiting which responded to antiemetics, grade 3 transaminases that return to grade 1 or better within 7 days of discontinuing erlotinib, or infection without neutropenia. Erlotinib treatment was interrupted if the

patient experienced a DLT and restarted at the next lowest dose level as long as the toxicity resolved to grade 1 or better within 7 days. If grade 3 nonhematologic toxicity (NHT) took longer than 7 days to resolve or recurred after one dose reduction, the patient was removed from protocol therapy. Patients with grade 2 NHT were allowed up to two dose reductions.

Erlotinib was continued after the first course as long as there was no irreversible toxicity. After course 1, temozolomide 180 $\text{mg/m}^2/\text{d}$ (and, if tolerated, escalating in subsequent courses to 200 $\text{mg/m}^2/\text{d}$) was administered concomitantly on days 1 through 5 of each 28-day erlotinib course. The definition of a hematologic DLT for courses 2 and later included grade 4 neutropenia or thrombocytopenia lasting more than 7 days or hematologic toxicity causing a delay of more than 7 days between courses. Response, assessed after course 1 and every other course thereafter, used Response Evaluation Criteria in Solid Tumors (RECIST) criteria²⁰ for patients with non-CNS tumors and criteria described by Gnekow et al²¹ for patients with CNS tumors.

The dose escalation component of the trial used an oral erlotinib solution because this initially was the only formulation that would allow for accurate pediatric body-surface area–based dosing. After the MTD of erlotinib in oral solution was determined, the tolerability and PK of tablet formulations of erlotinib (25, 100, and 150 mg) was studied at the MTD (Part B).

Drug Formulation and Administration

For the dose-escalation part of the study, the institutional pharmacy provided each patient with two sets of prefilled oral syringes: a single daily dose of erlotinib (10 mg/mL in 6% Captisol [CyDex, Lenexa, KS]) and a single dose of Ora-Sweet (Paddock Laboratories, Minneapolis, MN) at the same volume

Table 1. Characteristics of Eligible Patients (N = 46)

Characteristic	No.	%
Age, years		
Median	11.5	
Range	3-20	
Sex		
Male	30	65.2
Female	16	34.8
Race		
White	34	73.9
African American	5	10.9
Asian	3	6.5
American Indian or Alaska Native	1	2.2
Unknown	3	6.5
Ethnicity		
Hispanic or Latino	3	6.5
Non-Hispanic	41	89.1
Unknown	2	4.3
Diagnoses		
CNS tumors (n = 20)		
Brainstem glioma	5	
Medulloblastoma	6	
Supratentorial PNET	2	
Ependymoma	4	
Glioblastoma	1	
Neurocytoma	1	
Gliomatosis cerebri	1	
Non-CNS tumors (n = 26)		
Rhabdomyosarcoma	8	
Soft tissue sarcoma	5	
Neuroblastoma	5	
Osteosarcoma	6	
Germ cell	1	
Rhabdoid	1	

Abbreviation: PNET, primitive neuroectodermal tumor.

as the erlotinib. Syringes were refrigerated until just before administration, at which point parents were instructed to transfer the Ora-Sweet into a small medicine cup and add the erlotinib. The patient could either drink the solution directly from the cup or the contents could be drawn back up into a syringe and administered. For Part B of the study, the tablet dose was rounded either up or down to the nearest 25 mg.

Pharmacokinetic Studies

Erlotinib single dose PK, steady-state PK, and steady-state PK when administered concurrently with temozolomide were studied. Blood was obtained pretreatment and 0.5, 1, 2, 4, 6, 7, 10 to 12, 24, 26, 30, 48 and 50 hours after the first erlotinib dose. Patients who chose to participate in PK studies did not receive the course-1, day-2 dose; the day-3 dose was delayed until after PK sampling. Steady-state sampling was performed on day 10 of single-agent erlotinib and on day 5 of the combination phase. Blood samples were collected in sodium heparin, immediately refrigerated or stored on wet ice, centrifuged (≈ 15 minutes, $\approx 2,000 \times g$ at $\approx 4^\circ\text{C}$), and separated plasma stored at $\approx -20^\circ\text{C}$ until being shipped on dry ice to a central laboratory for analysis.

Plasma samples were analyzed for erlotinib and its *O*-demethylated active metabolite OSI-420 at MDS PharmaServices (St Laurent, Quebec) using validated liquid chromatography tandem mass spectrometry methods. Briefly, aliquots of the thawed samples were mixed with an internal standard and water and extracted into *t*-butyl methyl ether. The organic layer was evaporated to dryness under nitrogen and the residue reconstituted in mobile phase for analysis. Separation of analytes was by reverse-phase high-performance liquid chromatography followed by mass spectrometric single-reaction monitoring. The lower limit of quantitation was 1.1 and 1.0 ng/mL for erlotinib and OSI-420, respectively. This methodology does not separate OSI-420 from its positional isomer, OSI-413, but on the basis of data from a prior adult study, the latter is not detected in plasma.²²

Data were analyzed by noncompartmental methods with WINNonlin (Scientific Consultant, Apex, NC) Enterprise, Version 4.1 software (Pharsight Corporation, Mountain View, CA). The terminal rate constant λ_z was calculated using at least three quantifiable time points in each plasma profile obtained at approximately 24 hours following the dose or thereafter. Area under the concentration-time curve from baseline to infinity ($\text{AUC}_{0-\infty}$) was calculated after a single dose of erlotinib using the log linear trapezoidal method and extrapolated to infinite time: $\text{AUC extrapolated} = \text{plasma concentration of the last time period} (C_{\text{last}})/\lambda_z$.

Alpha-1 Acid Glycoprotein Determination

Erlotinib is approximately 95% bound to plasma proteins, with alpha-1 acid glycoprotein (AAGP) as the second most important binding protein following albumin. Plasma samples for the determination of AAGP were

therefore obtained before the first erlotinib dose of courses 1, 3, and 5 and analyzed by Clinical Reference Laboratory Inc (Lenexa, KS) using a validated turbidimetric assay (limit of quantitation = 0.1 g/L).

ERBB Receptor Expression and Signal Activity

Retrospectively collected fixed tumor samples were obtained from study patients and analyzed by immunohistochemistry (IHC) to determine the expression of total ERBB1 and ERBB2, active phosphorylated (p-)ERBB2^{Y1248}, pAKT1^{S473}, pERK1/2 and pS6^{S235/236}. To remove observer bias, IHC staining of tumors was scored blind to histologic diagnosis and treatment response using ImageJ software (<http://rsbweb.nih.gov/ij/>) analysis as described previously.²³ The IHC score provides a measure of the mean percentage of immunopositivity that is detected in each $\times 200$ field.

RESULTS

Forty-six patients, (median age, 11.5 years; range, 3 to 20 years) were enrolled onto the study from March 2004 to December 2005 (Table 1). Ten patients were not fully assessable for toxicity: three patients never started treatment and seven developed progressive disease before completion of the first course.

Toxicity

No DLTs were encountered at the first three dose levels (Table 2). Of the six patients treated at 85 mg/m²/d, one had a painful grade 2 rash lasting more than 7 days. Two of the four patients treated at 110 mg/m²/d experienced DLTs: one with a painful grade 2 rash and one with grade 3 direct hyperbilirubinemia. The MTD was therefore defined as 85 mg/m²/d. To study the PK and further assess the tolerability in children, an additional 17 assessable patients were enrolled and received the tablet formulation at a dose of 85 mg/m²/d. Two patients experienced a DLT: one had a painful grade 2 rash and one had grade 3 diarrhea. The profile of toxicities was similar between the oral solution and the tablets.

Table 3 lists the non-dose limiting NHTs observed for all patients during course 1 that were possibly attributed to erlotinib. In patients treated at the MTD with either formulation (n = 23), non-DLTs during course 1 included diarrhea in 13 (56%), 11 of whom experienced grade 1 diarrhea, rash in 10 (43%), and hyperbilirubinemia in six (26%). At the MTD, rash was more common in the

Table 2. DLTs During Treatment

Erlotinib Dose Level (mg/m ² /d)	No. of Patients Entered	No. of Patients Assessable	No. of Patients With DLT	DLT Type
First course*				
35	3	3	0	
50	3	3	0	
65	4	3	0	
85	8	6	1	Rash/desquamation
110	5	4	2	Rash/desquamation, hyperbilirubinemia
85 (tablet)	23	17	2	Rash/desquamation, diarrhea
Second course†				
35		3	0	
50		3	0	
65		2	0	
85		6	0	
110		3	0	
85 (tablet)		14	2	Platelets and neutrophils, mucositis/stomatitis

Abbreviation: DLT, dose-limiting toxicity.

*Single-agent erlotinib.

†Erlotinib + temozolomide.

Table 3. Non-Dose Limiting Nonhematologic Toxicities Related to Protocol Therapy and Observed in More Than 10% of Patients During Course 1 (n = 36)

Toxicity	No. of Patients		
	Grade 1	Grade 2	Grade 3
Fatigue	3	3	
Pruritus/itching		4	
Rash/desquamation	5	4	
Rash: acne/acneiform	4	2	
Anorexia	5	1	
Diarrhea	16	5	
Mucositis/stomatitis (clinical exam), oral cavity		4	
Nausea	6	1	
Vomiting	2	2	
ALT	4	3	
AST	7	2	1
Hyperbilirubinemia	3	4	
Hypokalemia	4		

older patients, with one in 10 patients younger than 12 versus nine of 13 patients 12 years of age or older developing grade 2 or worse rash (Fisher's exact $P = .0097$). Mild hematologic toxicity was observed, primarily in the heavily pretreated patients.

Table 2 lists the toxicities seen during course 2 with the combination of erlotinib and temozolomide. Hematologic toxicity, although commonly observed, was dose limiting in only one heavily pretreated patient who developed prolonged grade 4 neutropenia and thrombocytopenia. No cumulative toxicity was apparent in the three patients who remained on treatment for 19 to more than 24 months.

PK

The PK results for patients studied at steady-state, including both the oral solution and tablet formulation, are shown in Figure 1 and Table 4. Significant interpatient variability in erlotinib disposition was observed at all dose levels. There were no significant correlations between patient age and apparent drug clearance (Cl_{ss}/F) or dose-normalized maximum serum concentration (C_{max}), and no apparent effect of temozolomide on erlotinib drug disposition (Appendix Table A1, online only). The mean AAGP concentration obtained in 18 subjects was 1.03 g/L (standard deviation, 0.2 g/L). AAGP concentrations did not correlate with Cl_{ss}/F (Spearman $r = -0.27$; $P = .29$). A population PK model incorporating initial dose PK findings will be reported separately.

Compared with patients taking the tablet formulation, patients taking the solution achieved a higher C_{max} but had a shorter time to C_{max} , consistent with the expected dissolution of the tablet (Appendix Fig A1, online only). However, the dose normalized $AUC_{0-\infty}$ was not statistically different for the two formulations (Wilcoxon rank sum $P = .92$). The inpatient geometric mean ratio of OSI-420 $AUC_{0-\infty}$ to erlotinib $AUC_{0-\infty}$ was 0.082 (n = 18).

Antitumor Activity

Seventeen of 43 response-assessable patients had stable disease after the first course of single-agent erlotinib. One patient with metastatic myoepithelioma had a mixed response, with resolution of pulmonary nodules but progression of a pleural-based mass. One patient

Fig 1. Erlotinib plasma concentration-time curves at steady-state. Median values are shown. Monoexponential absorption – biexponential elimination equations were fit to the data using Kaleidgraph (Synergy Software, Reading, PA). (A) After administration of the liquid formulation. (B) Comparison of the liquid with the tablet formulation at the 85 mg/m²/d dose level.

with a medulloblastoma had progressive disease after the first course and a partial response after the first combination course, but came off study after the third course because of a dose-limiting rash. One patient with a neurocytoma had stable disease for 19 months. Two patients with neuroblastoma remained on study for 23 and 24 months; the longest-responding patient with neuroblastoma (bone marrow disease, positive [¹²⁵I]Metaiodobenzylguanidine scan) had a complete response to the combination therapy after developing progressive disease with single-agent erlotinib.

ERBB Receptor Expression and Signal Activity

Twenty-four samples of fixed tumor material were available from 20 patients, including three cases with consecutive (relapsed)

Table 4. Pharmacokinetic Parameters at Steady-State

Dose	Age (years)	T _{max} (hours)	C _{max} (μg/mL)	AUC _{0-τ} (μg · hr/mL)	CL _{ss} /F (L/h/m ²)	T _{1/2} (hours)
Solution						
35 mg/m ² /d (n = 3)						(n = 2)
Minimum	5.9	0.5	1.26	6.10	2.71	2.62
Median	8.8	0.5	1.32	9.51	4.22	8.05
Maximum	9.6	2.0	1.63	12.9	5.74	13.5
50 mg/m ² /d (n = 2)						(n = 1)
Minimum	10.9	0.5	1.84	18.5	2.08	8.67
Median	15.5	0.7	1.89	21.3	2.39	8.67
Maximum	20.1	1.0	1.94	24.1	2.70	8.67
65 mg/m ² /d (n = 2)						(n = 2)
Minimum	3.2	0.5	2.81	14.1	1.58	5.94
Median	3.6	0.5	3.93	27.6	3.09	6.65
Maximum	4.0	0.6	5.05	41.2	4.61	7.36
85 mg/m ² /d (n = 4)						(n = 4)
Minimum	5.8	0.5	2.19	18.3	3.04	3.58
Median	12.0	0.7	2.67	23.3	3.65	9.75
Maximum	20.1	1.0	3.30	27.9	4.64	10.3
Tablet						
85 mg/m ² /d (n = 12)						
Minimum	5.5	1.0	1.03	7.79	1.94	NA
Median	14.7	2.0	2.02	30.4	2.80	NA
Maximum	20.5	8.0	5.20	43.8	10.9	NA

Abbreviations: T_{max}, time to maximum serum concentration; C_{max}, maximum serum concentration; AUC_{0-τ}, area under the concentration-time curve over the dosing interval; CL_{ss}/F, apparent clearance at steady state; T_{1/2}, Terminal half-life from single-dose data (n); NA, not applicable because single-dose data not captured for the tablet formulation.

samples. Variable expression of the EGFR or ERBB2 receptors was detected in the great majority of tumor samples (Fig 2). The highest levels of EGFR and ERBB2 were observed in medulloblastoma and ependymoma, tumors that have been shown previously to express these receptors.⁴ Variable but significant levels of expression of phosphorylated cell signal intermediates were observed. Of particular note, we observed a highly-significant correlation between the expression levels of pERBB2^{Y1248} and pAKT^{S473} in tumor samples ($P < .0001$), suggesting that ERBB2 might promote activation of AKT in pediatric tumors, as has been shown in cells in culture.²⁴ Retrospective samples of tumors were available from four patients who demonstrated a response to the study protocol. Each of these tumor samples expressed EGFR and ERBB2 receptors and active signal intermediates, although expression levels were not significantly higher than those found in tumors obtained from nonresponding patients.

DISCUSSION

The MTD of erlotinib in children with solid tumors, 85 mg/m²/d, either alone or in combination with temozolomide, is similar to the adult MTD of 150 mg/d.²⁵ Overall, toxicities were also similar to those observed in adults, with painful rash being the most common DLT observed in children. Rash occurred more frequently in older children, although we could not identify a PK basis for this finding. A study in patients with NSCLC found significant overlap in the AUC between patients with and without rash.²⁶ Rash has also been suggested to be a surrogate for tumor response,²⁷ but in our phase I population, such a relationship could not be evaluated. Diarrhea, primarily grade 1, occurred in 60% of patients treated at the MTD. Diarrhea and rash usually developed after the first week and persisted

throughout therapy. Non-dose limiting hyperbilirubinemia was observed in 6 of 23 patients treated at the MTD.

The median apparent clearance of 3.1 L/h/m² in children is similar to the apparent clearance of 6.3 ± 6.1 L/h (approximately 3.6 ± 3.7 L/h/m²) in adult cancer patients.²⁵ The median terminal half-life of 8.7 hours in children after the first oral dose is similar to the half-life of 7 to 13 hours observed in healthy adult volunteers²⁸ but shorter than the more than 30-hours half-life observed in adult cancer patients.²⁶ This may be related in part to AAGP, the most important covariate for erlotinib clearance in adult patients with NSCLC.²⁶ The levels of AAGP in children was lower than in adult NSCLC patients treated with erlotinib (1.03 ± 0.2 v 1.43 ± 0.5 g/L) but within the range of what is seen in healthy adults (0.50 to 1.20 g/L).²⁹ Despite the difference in terminal half-life, the AUCs and C_{max} observed in children were consistent with those observed in adult cancer patients.

The combination of temozolomide and erlotinib was well tolerated, and the PK of erlotinib did not appear to be affected by concomitant administration of temozolomide. This differs from the conclusion of a study in adults with malignant gliomas³⁰ where a "modest interaction" was suggested. However, the adult study compared PK results between groups of patients; the current study compared effects within each patient.

The patient with metastatic myoepithelioma who experienced a mixed response had a tumor that expressed significant levels of EGFR and ERBB2. However, there were no differences between levels of EGFR expression in disease responding or not responding to the combination of erlotinib and temozolomide. Patients whose disease responded or who had prolonged stable disease with the combination included two patients with neuroblastoma and one each with a medulloblastoma and neurocytoma. The contribution of erlotinib to

Fig 2. Immunohistochemistry (IHC) expression scores of ERBB proteins and signal intermediates in 24 CNS-derived and other tumors. Samples from responding patients are indicated. Consecutive recurrent tumor samples from the same patients are shown together and numbered chronologically. NB, neuroblastoma; OST, osteosarcoma; RMS, rhabdomyosarcoma; STS, soft tissue sarcoma; EGFR, epidermal growth factor receptor; PR, partial response; SD, stable disease; MR, mixed response; p-, phosphorylated.

clinical activity, however, is not known because temozolomide has single-agent activity in these tumor types.^{17,18}

In conclusion, children appear to tolerate erlotinib similarly to adult patients, and drug disposition is similar between these populations. The combination of temozolomide and erlotinib is well tolerated and warrants further study.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).