A phase I, pharmacokinetic and pharmacodynamic study of GSK2256098, a focal adhesion kinase inhibitor, in patients with advanced solid tumors


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Background: Focal adhesion kinase (FAK) is important in cancer growth, survival, invasion, and migration. The purpose of this study was to determine the maximum tolerated dose (MTD), safety, pharmacokinetics (PK), and pharmacodynamics (PD) of the FAK inhibitor, GSK2256098, in cancer patients.

Patients and methods: The dose of GSK2256098 was escalated, in cohorts of patients with advanced cancer, from 80 to 1500 mg, oral twice daily (BID), until the MTD was determined. Serial blood samples were obtained from all patients, and the PK was determined. Paired tumor biopsies were obtained in select patients, and the level of phospho-FAK (pFAK) was determined.

Results: Sixty-two patients (39 males, 23 females; median age 61 y.o., range 21–84) received GSK2256098. Dose-limiting toxicities of grade 2 proteinuria (1000 mg BID), grade 2 fatigue, nausea, vomiting (1250 mg BID), and grade 3 asthenia and grade 2 fatigue (1500 mg BID) were reported with the MTD identified as 1000 mg BID. The most frequent adverse events (AEs) were nausea (76%), diarrhea (65%), vomiting (58%), and decreased appetite (47%) with the majority of AEs being grades 1–2. The PK was generally dose proportional with a geometric mean elimination half-life range of 4–9 h. At the 750, 1000, and 1500 mg BID dose levels evaluated, the pFAK, Y397 autophosphorylation site, was reduced by 80% from baseline. Minor responses were observed in a patient with melanoma (−26%) and three patients with mesothelioma (−13%, −15%, and −17%). In the 29 patients with recurrent mesothelioma, the median progression-free survival was 12 weeks with 95% CI 9.1, 23.4 weeks (23.4 weeks merlin negative, n = 14; 11.4 weeks merlin positive, n = 9; 10.9 weeks merlin status unknown, n = 6).

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Conclusions: GSK2256098 has an acceptable safety profile, has evidence of target engagement at doses at or below the MTD, and has clinical activity in patients with mesothelioma, particularly those with merlin loss.

Key words: focal adhesion kinase, phase I, pharmacodynamics, mesothelioma, merlin, NF2

Introduction

Focal adhesion kinase (FAK, protein tyrosine kinase 2) is a non-receptor tyrosine kinase required for cancer cell growth, proliferation, survival, migration, angiogenesis, invasion, and mesenchymal transformation [1]. Recent data indicate that FAK may be important in the maintenance of cancer stem cells and in macrophage activation [1, 2]. Overexpression of FAK (gene or protein) has been reported in several cancers, including breast, colorectal, head and neck, endometrium, lung, ovarian, pancreas, prostate, stomach, thyroid, and other solid tumors [3, 4] and hematologic cancers [5, 6]. FAK expression increases as tumors become more advanced and is associated with poor survival in ovarian, glioma, and acute myelogenous leukemia [6–8].

GSK2256098 is a potent, ATP-competitive inhibitor of FAK kinase activity and is highly selective for FAK with an ~1000-fold selectivity over the nearest family member PYK2 [9]. Inhibition of FAK kinase activity has also been demonstrated in cells and in vivo, as determined by decreased levels of pFAK in a concentration-dependent manner [9]. In vitro cellular studies demonstrate that GSK2256098 inhibits cancer cell growth and induces apoptosis in cell selective and growth-dependent conditions [9]. GSK2256098 also inhibits cell migration, invasion [10], and angiogenesis [GSK internal data and 10]. As a single agent and in combination with other anticancer agents, GSK2256098 has demonstrated activity in in vivo models of ovarian cancer and glioblastoma [9, 11, 12].

The purpose of this first in cancer patient study was to determine the maximum tolerated dose (MTD), safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary clinical activity of GSK2256098 in patients with advanced solid tumors.

Patients and Methods

Patient Selection

Signed, written informed consent was obtained from all patients, and the study was approved by independent ethics committee. Patients, ≥ 18 years of age, with histologically confirmed, advanced solid tumors that were not responsive to standard therapy were eligible. For Part 1 of the study (see study design below), patients with advanced solid tumors reported in the medical literature to overexpress FAK were eligible. For Parts 2 and 3, patients with mesothelioma or cancers of the ovary, pancreas, head and neck, stomach, endometrium, non-small cell lung, and prostate were eligible. Other eligibility criteria included ECOG performance status of 0–1, adequate organ function (hematologic, hepatic, renal), and ability to swallow oral medications. Female patients of child-bearing potential were required to comply with protocol-defined contraceptive methods. Patients with symptomatic brain metastases requiring steroids or anticonvulsant therapy were not eligible to participate.

Study Design

This was a three-part Phase I study: Part 1 (Dose Escalation), Part 2 (Safety Expansion), and Part 3 (PD) (NCT01138033). Patients received GSK2256098, orally twice daily (BID), with a light meal (see supplementary material, available at Annals of Oncology online for details), until unacceptable toxicity, disease progression, or withdrawal of consent. For Part 1, Dose Escalation, a Modified Acceleration Titration design [13], was used permitting 100% dose increases in single-patient dose cohorts until a total of two patients in any cohort developed grade 2 toxicities within the first 21-day dosing period or one subject developed a DLT. At that point, a standard 3 + 3 design was used. The MTD was defined as the dose level where ≤ 1 of up to six patients had a dose-limiting toxicity (DLT) within the first 21 days. DLT was identified as NCI CTCAE v4.0 grade 3 or 4 nonhematologic toxicity (excluding nausea, vomiting, diarrhea without adequate supportive care), grade 4 neutropenia > 5 days, febrile neutropenia, grade 4 anemia/thrombocytopenia, toxicity that resulted in ≥ 7 days of drug interruption (continuous or not) in the first 21 days, or any toxicity ≥ grade 2 that in judgment of the study investigator was dose limiting.

Study Endpoints and Assessments

Adverse events (AEs) were assessed continuously throughout the study with CTCAE v4.0. Hematology, urinalysis, clinical chemistry, and electrocardiograms were assessed at baseline, on days 1, 8, 15, and 22, then every 3 weeks thereafter. Fasting lipid panels were performed at baseline and day 22, day 43 then every 6 weeks. Disease assessments were performed at baseline and every 6 weeks, and response was assessed using RECIST 1.1 [14]. In patients with malignant pleural mesothelioma, their scans were also reviewed independently using Modified RECIST for Mesothelioma [15].

Translational Research

Pharmacokinetics. Whole blood samples (2 ml) were collected during Parts 1–3 of the study, and specific details regarding PK studies are found in Supplementary materials, available at Annals of Oncology online.

Tumor biopsy collection and determination of pFAK levels. Tumor biopsies were mandatory for patients in Part 3 and optional for those in Parts 1 and 2. Paired tumor biopsies were collected prior to dosing on day 1 and on a day between days 8 and 15, 1–6 h after dosing. Details regarding the pFAK analysis methods are found in Supplementary materials, available at Annals of Oncology online.

evaluation of circulating tumor, endothelial, and endothelial progenitor cells. Details and references [16–18] regarding the evaluation of CTCs, CECs, and CEPs are found in Supplementary materials, available at Annals of Oncology online.

determination of merlin status. Paraffin-embedded, archival tumor samples were required for all patients. Merlin (the protein product of the gene neurofibromin 2 or NF2) status was determined by immunohistochemistry of formalin fixed paraffin-embedded archival samples collected from patients with mesothelioma (n = 29) and a patient with melanoma (n = 1). Details regarding the analysis of archival tumor samples for merlin expression are found in Supplementary materials, available at Annals of Oncology online.

Statistical Analysis

The primary focus was the determination of the MTD, the safety profile, to identify a range of biologically active doses, and to determine the PK and PD...
of GSK2256098 in patients with solid tumors. The analyses were primarily
descriptive or exploratory for toxicity, DLTs, and MTD. An exploratory anal-
ysis of progression-free survival (PFS) was conducted for the group of
patients with mesothelioma. PFS was defined as the time from the date of first
doctor of study drug to the date of first documented disease progression ac-
cording to radiological or clinical assessment, or to the date of death due to any
cause. For patients who did not progress or die, PFS was censored at the
date of last radiological disease assessment. Patients who discontinued the study
with no post treatment tumor assessment were censored at the date of first
doctor of study drug. Summaries of PFS and Kaplan–Meier curves were pro-
duced for all mesothelioma patients together and separately by merlin status.

results

Sixty-two patients were entered into the study and received at least one dose of GSK2256098. All patients had progressive dis-
ease of their tumor at study entry. Patient characteristics are pro-
vided in Table 1. Mesothelioma was the most common tumor
type (n = 29), and the rationale for enrollment of this tumor type
is found below in Results and Discussion sections. There were
26, 26, and 10 patients enrolled in Parts 1 (Dose Escalation), 2
(Safety Expansion), and 3 (PD) of the study, respectively.

determination of the MTD

A summary of the dose levels evaluated and DLTs during Part 1
are provided in Table 2. One DLT was observed at the 1000 mg
dose level, defined by reversible grade 2 proteinuria (elevation in
urine protein:creatinine ratio requiring a protocol-mandated
dose reduction). The cohort was expanded to six patients at 1000
mg BID and was well tolerated. Three patients were enrolled at
the 1500 mg BID dose level, and one had a DLT of grade 3 asthe-
nia. An additional two patients were enrolled, and one had grade
2 fatigue that was also considered dose limiting. Since the MTD
was exceeded, an intermediate dose cohort of 1250 mg BID was
enrolled with three patients. One patient had a DLT of grade 2
nausea, vomiting, and fatigue, and a further two were enrolled.

safety

A summary of AEs by dose, regardless of attribution, is provided
in Table 3. The majority of AEs were grades 1–2 in severity with
the four most frequent AEs being nausea, diarrhea, vomiting,
and decreased appetite. The most frequent grade 3 AEs were
hypertriglyceridemia, occurring in three patients (5%) and all at
1000 mg BID and hypokalemia occurring in three patients (5%),
one at 750 mg BID and two at 1000 mg BID. Two grade 4 AEs
were reported: one patient with elevated blood creatinine phos-
phokinase and one patient with a cerebrovascular accident.
Neither of these events was attributed to GSK2256098. Clinical
laboratory AEs ≥ 20% included proteinuria (26%), hyperbiliru-
binema (23%), and hypercholesterolemia (21%).

dose reductions and interruptions

Dose reductions due to AEs occurred in seven (11%) patients,
with nausea being the commonest reason (three patients, 5%).
At the MTD of 1000 mg BID (41 patients), there were six patients
(15%) with dose reductions due to AEs with nausea being the
most common reason (5%). Dose interruptions due to AEs
occurred in 17 patients (27%). The AEs leading to dose interrup-
tions included fatigue (6%), nausea (5%), vomiting (5%),
decreased appetite (3%), diarrhea (3%), pleural effusion (3%),
and pleuritic pain (3%). At the MTD of 1000 mg BID (41
patients), 15 patients (37%) had dose interruptions due to AEs
with fatigue, diarrhea, pleural effusion, and pleuritic pain (each
5%) being the most common reasons.

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Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients 62 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>61 (21–84)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Males/females</td>
<td>39/23 (63/37)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
</tr>
<tr>
<td>0/1</td>
<td>27/35 (44/56)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White (European ancestry)</td>
<td>54 (87)</td>
</tr>
<tr>
<td>Black (African ancestry)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Southeast Asian</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Arabic/North African</td>
<td>2 (3)</td>
</tr>
<tr>
<td>South Asian</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Mixed Race</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Median no. of prior therapies (range)</td>
<td>2 (1–8)</td>
</tr>
<tr>
<td>Tumor types</td>
<td></td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>29 (46)</td>
</tr>
<tr>
<td>Ovary</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Kidney</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Non-small-cell lung</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Othera</td>
<td>7 (11)</td>
</tr>
</tbody>
</table>

*Includes one each of angiosarcoma, bile duct cancer, bone cancer, bronchial cancer, hepatocellular carcinoma, cancer of the mouth, and cancer of the nasopharynx.

Table 2. Determination of the MTD

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose (mg BID)</th>
<th>N</th>
<th>DLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>160</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>300</td>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>600</td>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>1000</td>
<td>6*</td>
<td>Grade 2 proteinuria with dose interruption</td>
</tr>
<tr>
<td>6</td>
<td>1500</td>
<td>5</td>
<td>Grade 3 asthenia</td>
</tr>
<tr>
<td>7</td>
<td>1250</td>
<td>5</td>
<td>Grade 2 fatigue</td>
</tr>
</tbody>
</table>

*Three additional patients enrolled (nine total) following dose escalation, no additional DLTs occurred.
pharmacokinetic analyses

When administered with a light meal on day 1, GSK2256098 was rapidly absorbed (median $t_{\text{max}}$ 1.5–4 h). The geometric mean half-life ranged between 4.0 and 9.0 h. The $C_{\text{max}}$ and AUC, over the dose range of 80–1500 mg, were generally dose proportional after single and repeat dosing. A summary of the PKs of GSK2256098 on days 1 and 15 is provided in Table 4. The $C_{\text{max}}$ and AUC of GSK2256098 were lower after repeat dosing compared with day 1 values.

pharmacodynamic analyses

The percent decrease in Y397 pFAK/total FAK in paired pre- and on-treatment biopsy samples was determined from six patients at dose levels 750 mg BID, 1000 mg BID, and 1500 mg BID and was 80% or greater in five of six patients (Figure 1).

circulating cells

CTCs, CECs, and CEPs were collected and analyzed at one clinical research center (GR). CECs were not affected by GSK2256098 treatment. CTCs were very low before and following treatment, and no change was observed. However, a median decrease of 19% in CEPs from baseline values was noted.

merlin analysis

Tumor tissue from 23 patients (79%) with mesothelioma was available for merlin evaluation by IHC analysis. Samples were either not available or not evaluable for six patients. Tissue from 14 patients (48%) stained negative for merlin, indicating the putative loss of protein in these samples, and the tissue from nine...
patients stained positive. One melanoma subject tested was identified as merlin negative.

**clinical activity**

A best response of stable disease was achieved in 28 patients (45%). In patients with measurable disease, changes in tumor size from baseline by RECIST, duration on treatment, and patient tumor type are shown in Figure 2. A summary of minor responses or prolonged stable disease is provided in Table 5. One patient with nasopharyngeal cancer had a 31% decrease from baseline in his target lesions, but at the same scan date had a new lesion and was removed from the study due to progressive disease. In patients with malignant pleural mesothelioma, the overall median PFS (95% CI) was 12 weeks (9.1, 23.4). In patients with merlin-negative mesothelioma ($n = 14$), merlin positive ($n = 9$), or unknown ($n = 6$), the median PFS (95% CI) was 23.4 (6.0, 28.1), 11.4 (4.3, 22.6), and 10.9 (9.1, not determined) weeks, respectively.

**discussion**

The importance of FAK in multiple biological processes of cancer, including invasion and metastases means that targeting FAK is a rational treatment strategy. An earlier single-dose, dose-ranging, first time in human study evaluated the PKs, safety, and food effect in healthy volunteers (NCT00996671). The current study described here is the first in cancer patient and repeat-dose
study of GSK2256098, an oral selective inhibitor of FAK, in a patient population with advanced and metastatic cancers. In this study, the safety, PK, and clinical activity were evaluated over a dose range of 80–1500 mg BID, and tumor PD was performed at doses of 750, 1000, and 1500 mg BID. GSK2256098 had an acceptable safety profile at and below the MTD. Overall, the majority of AEs were grades 1–2 in severity. Gastrointestinal AEs were the most common AEs and were the major reason for dose reductions and interruptions. Reversible proteinuria, seen at doses of 750 mg BID and higher, was present in 26% of patients and was observed during preclinical studies at high doses in 28-day preclinical safety studies in rats and dogs (GSK internal data). Increases in total and direct bilirubin were observed. Increased total bilirubin was also seen in 28-day preclinical safety studies, although only total bilirubin was measured (GSK internal data). Increases in total bilirubin were also seen in 28-day preclinical safety studies in rats and dogs (GSK internal data). Increases in total and direct bilirubin were observed. Increased total bilirubin was also seen in 28-day preclinical safety studies, although only total bilirubin was measured (GSK internal data). In vitro, GSK2256098 is an inhibitor of UGT1A1 at concentrations achieved in this study. Elevated cholesterol and triglycerides was also seen in the current study and in preclinical animal safety studies. The mechanism for this increase is unclear.

At the MTD dose of 1000 mg BID, a reduction in \( C_{\text{max}} \) and AUC was observed on day 15 compared with day 1, while a comparison of the terminal elimination phases appeared similar (i.e. were parallel) between the two days. This finding suggests a change in bioavailability, perhaps due to changes in absorption with repeat dosing, rather than an alteration in systemic clearance. Autoinduction of key drug metabolizing enzymes in the gut, resulting in a reduction in \( C_{\text{max}} \) and AUC is one potential explanation for the reduction. Additional PK sampling and in vitro data are required to fully understand the mechanism of these changes.

Target engagement (reduced pFAK from baseline) was observed in multiple tumor types and was similar across the dose range of 750, 1000, and 1500 mg BID, the only doses at which biopsies were obtained. No correlation was observed between different measures of GSK2256098 systemic exposure and pFAK inhibition, possibly due to concentrations being in the range of maximal response on the dose–response curve for target engagement. Given that minor tumor responses were seen across the range of doses evaluated, including at the very first dose evaluated at 80 mg BID, it would be of interest to see whether target inhibition is occurring at lower doses. An ongoing clinical study of GSK2256098 is evaluating pFAK inhibition at lower GSK2256098 doses (FAK114746) in combination with trametinib. At doses of 250 mg and 500 mg BID of GSK2256098, pFAK is reduced by more than 80% and 60%, respectively [19].

During the conduct of the study, a patient with malignant pleural mesothelioma in the 300 mg BID cohort, with four prior regimens, was noted to have a 15% decrease in tumor size. Upon treatment with GSK2256098, this patient continued on therapy for 191 days. Analysis of the patient’s archival tumor sample indicated that the tumor was merlin negative. Merlin is a tumor suppressor frequently lost (40%–50%) in mesothelioma [20]. In mesothelioma cell lines, merlin-negative cells have increased invasiveness and FAK expression [21]. Auger et al. demonstrated that merlin-negative mesothelioma cell lines were >100× more sensitive than a merlin-positive cell line to GSK2256098 [9]. Shapiro et al. have also noted increased sensitivity of merlin-negative mesothelioma cells to a small molecule inhibitor of FAK [22]. Although merlin-negative mesothelioma cells have greater sensitivity to GSK2256098, antitumor activity is also seen in a merlin-positive mesothelioma cell line [9]. On the basis of the clinical and laboratory findings noted above, additional enrollment of patients with mesothelioma was encouraged. PFS in recurrent mesothelioma is poor with a recent phase 3 study of vorinostat versus placebo in recurrent mesothelioma, reporting a median 6-week PFS in the treatment and placebo groups [23]. In both merlin-negative and merlin-positive mesothelioma patients, the PFS for both groups was greater was noted in the vorinostat study, thus supporting the finding in the in vitro studies of GSK2256098 noted above [9] that activity is present in both merlin groups. The current study is unable to determine whether merlin negativity is a prognostic or predictive biomarker, and well-designed, prospective, clinical studies are needed to answer this question.

Merlin negativity may result in increased sensitivity of other tumor histologies to the FAK inhibitor GSK2256098. A patient with metastatic melanoma in the very first cohort (80 mg BID) was noted to have a minor response (26% decrease). This patient had progressed on two prior investigational small molecules and radiation therapy before receiving GSK2256098. The archival tumor from this patient was merlin negative. Additional laboratory and clinical studies, including evaluation of additional patient tumor specimens, are required to validate this hypothesis. Approximately 43% of meningioma has inactivated NF2 [24]. A recent study of GSK2256098 has been initiated in patients with recurrent meningioma that has mutant NF2 (NCT02523014)

Defactinib (VS-6063), a small molecule inhibitor of FAK and Pyk2, is in clinical development [25]. A phase 2, double-blind, placebo-controlled study of defactinib as maintenance therapy for mesothelioma following first-line treatment (COMMAND), with patients stratified based on merlin status, was stopped for futility due to an insufficient level of efficacy (www.verastem.com). Given that defactinib targets FAK and Pyk2 [25], while GSK2256098 is selective for FAK alone, it is unclear if this difference in target selectivity may result in different antitumor activity between the two compounds.

### Table 5. Response characteristics of selected patients

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Merlin status</th>
<th>Dose (mg BID)</th>
<th>Best response</th>
<th>% Decrease in tumor from baseline</th>
<th>Duration on study (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>Negative</td>
<td>80 SD</td>
<td>26</td>
<td>377</td>
<td></td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>Negative</td>
<td>300 SD</td>
<td>13</td>
<td>191</td>
<td></td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>Positive</td>
<td>1000 SD†</td>
<td>17</td>
<td>294</td>
<td></td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>Negative</td>
<td>1000 SD</td>
<td>15</td>
<td>169</td>
<td></td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>ND*</td>
<td>1000 SD</td>
<td>25</td>
<td>209</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>ND†β</td>
<td>1000 SD</td>
<td>6</td>
<td>452</td>
<td></td>
</tr>
</tbody>
</table>

*By independent review using modified RECIST for mesothelioma, this patient had an unconfirmed PR (34% decrease from baseline).

†Not determined.
A recent positive phase 3 trial of bevacizumab in mesothelioma supports the potential use of an FAK inhibitor since FAK signals through VEGF pathway, and VEGF/VEGFR act as an autocrine loop in mesothelioma [26], so the use of a FAK inhibitor may be rational.

This study provides preliminary evidence that GSK2256098 is active in patients with recurrent, mesothelioma with potentially enhanced clinical activity in merlin-negative mesothelioma. Future strategies could include preselecting patients for GSK2256098 by tumor merlin expression or using GSK2256098 in a treatment combination. Preliminary results from a phase Ib combination study of GSK2256098 and trametinib (MEK inhibitor) is ongoing and is being evaluated in multiple tumor types, including mesothelioma [19].

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disclosure
At the time of the clinical study, D. Gibson, V. Peddareddigari, S. Murray, N. Nebot, J. Mazumdar, L. Swartz, K.R. Auger, and R.A. Fleming were employees of GlaxoSmithKline. All remaining authors have declared no conflict of interest.

references