



## ***Abigail Alliance for Better Access to Developmental Drugs***

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October 15, 2010

Ms. Margaret O. Hamburg, Commissioner  
Food and Drug Administration  
10903 New Hampshire Ave  
Silver Spring, MD 20993-0002

RE: Development Program, Clinical Trials Science, Approval Standards for Targeted Cancer Drugs and the Ethics of the Clinical Testing Program for Investigational New Drug PLX-4032 (RG7204)  
(Minor footnote reference and typographical errors corrected – resubmitted 11-3-10)

Dear Ms. Hamburg:

The Abigail Alliance for Better Access to Developmental Drugs is closely following the development, clinical research and regulatory track of the breakthrough investigational new drug PLX4032 (RG7204) presently being co-developed by Plexxikon, Inc. and Roche for the treatment of metastatic melanoma (Stage IIIC or Stage IV). Based on compelling results from Phase I clinical testing, PLX4032 has been shown to provide clinical benefit to more than 80 percent of patients with this terminal disease whose tumor cells exhibit the V600E mutation of the BRAF kinase gene. Reportedly, the tumor tissue of 40 to 60 percent of patients with metastatic melanoma exhibit the mutation. Results of Phase I clinical testing indicate that the mutation can be detected with a high degree of reliability, and that existing testing procedures can be applied to identify patients with the mutation that are highly likely to derive clinical benefit from treatment with PLX4032.

The Abigail Alliance believes that the development program and approval track for this drug raises serious questions regarding the FDA's regulatory policies for development of new cancer therapeutics, the ethics of one of the ongoing clinical trials being conducted by the sponsors, and FDA's policies that preclude the availability of new, breakthrough investigational cancer treatments to patients. The Abigail Alliance is raising the following specific concerns for your consideration:

- 1. Despite an enormous unmet need in the treatment of metastatic melanoma (more than 8,600 US deaths per year<sup>1</sup>), PLX4032 is unavailable to nearly all patients who would likely benefit, and is likely to remain unavailable until sometime in mid to late 2011, or very possibly later, given the time required for the sponsor to develop an application and for the FDA to review it, under the current development program.**
- 2. Clinical results already reported confirm that PLX4032 is a significant advance in the treatment of metastatic melanoma; however, information available to the public regarding the clinical testing track for this drug suggests that FDA has failed to recognize in a manner meaningful to cancer patients and the public health, the compelling medical utility of this drug.**
- 3. The design of the clinical trials, and in particular the design of the Phase III randomized BRIM3 trial, strongly suggests that the FDA has failed to properly consider the scientific and clinical facts applicable to this investigational drug, and instead imposed a formulaic set of clinical testing and approval**

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<sup>1</sup> Estimated New Cancer Cases and Deaths by Sex for All Sites, US, 2010\*, American Cancer Society, 2010

**endpoints on the development program that will ultimately yield little, if any, useful scientific or medical information.**

- 4. The design of the BRIM3 clinical trial raises serious questions regarding the FDA's consideration and review of the ethics of conducting a randomized controlled trial designed to compare overall survival for patients treated either with dacarbazine or PLX4032.**

## **Background**

Metastatic melanoma is a terminal disease. Median survival is less than one year and treatment options are severely limited. The only drug approved by the FDA for treatment of metastatic melanoma is dacarbazine. Dacarbazine was approved for the indication in May 1975.

According to the National Cancer Institute (NCI), only 10 to 20 percent of patients experience a response to treatment with dacarbazine, and the duration of response is generally limited to 3 to 6 months<sup>2</sup>. Other reports and summaries place the duration of responses for most patients treated with dacarbazine at only 1 to 2 months.

In March 1999, at an Oncologic Drugs Advisory Committee (ODAC) meeting<sup>3</sup> convened to consider approval of temozolomide for treatment of metastatic melanoma, Dr. Robert Temple of the FDA stated that the registration trial, which compared temozolomide to dacarbazine in a randomized study was flawed because dacarbazine, although approved by the FDA, had never been shown to provide clinical benefit as measured by FDA's standards then in effect. The sponsor was seeking approval based on temozolomide being equivalent to dacarbazine in clinical effect. One committee member described the prior approval of dacarbazine as having been an error, and discussions by the committee indicated general agreement that dacarbazine was a minimally effective drug for treatment of metastatic melanoma and perhaps little more than a toxic placebo. The committee voted ten to one against approval of temozolomide based primarily on the lack of demonstrated efficacy for the comparator drug, dacarbazine. Temozolomide was not approved for the treatment of metastatic melanoma.

Testing of dacarbazine in combination with other approved drugs has not demonstrated significantly improved response rates or response duration, and dacarbazine has never been shown to extend survival. In summary, outcomes for patients diagnosed with metastatic melanoma are dismal, and have remained essentially unchanged since the approval of dacarbazine 35 years ago. Few patients respond to dacarbazine, and most patients succumb to their disease within a year from receiving a diagnosis of advanced metastatic disease .

In early June 2009, Plexxikon announced the preliminary results of a Phase I clinical trial testing PLX4032 in patients with metastatic melanoma and several other types of solid tumor cancers. The results were simultaneously presented at the ASCO annual conference on June 1, 2009<sup>4</sup>. The trial included patients with and without the target mutation, and patients for whom the mutation status was unknown. In patients with the target mutation, 13 of 16 patients experienced responses in the form of tumor size reduction (9 partial responses of > 30 percent and 4 lesser responses of 10 - 30 percent) with an interim median progression-free survival of at least six months, and disease control lasting up to 14 months. No treatment response was observed in patients without the mutation and progression free survival for those patients was less than 2 months.

PLX4032 was well tolerated with the primary side effects being rash and photosensitivity. A possible link to increased occurrence of cutaneous squamous cell carcinoma in chronically treated patients was noted, and a risk management plan was implemented for baseline evaluation and monitoring of patients on study. Plexxikon also announced that, in collaboration with Roche, a companion diagnostic is in development.

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<sup>2</sup> National Cancer Institute Webpage as of October 16, 2010  
<http://www.cancer.gov/cancertopics/pdq/treatment/melanoma/HealthProfessional/page9Reference> and link to NCI MM webpage

<sup>3</sup> FDA Oncologic Drugs Advisory Committee Meeting Transcript, 61<sup>st</sup> Meeting, March 23, 1999, Bethesda, MD

<sup>4</sup> Flaherty et al, Abstract No. 9000, Phase I Study of PLX4032: Proof of Concept for V600E BRAF Mutation as a Therapeutic Target in Human Cancer, ASCO 2009 Annual Meeting

In September 2009, the results of the Phase I trial were updated in a presentation at the Joint ECCO 15 – 34<sup>th</sup> ESMO Multidisciplinary Congress in Berlin, Germany<sup>5</sup>. Fifty-five patients were enrolled in the dose escalation phase of the trial. A maximum tolerated dose (MTD) of 960 mg bid was established. Of sixteen melanoma patients with an activating BRAF mutation treated at a dose of 240 mg bid or more, 11 had a partial response. Thirty additional patients with melanoma and the activating mutation were treated at the MTD of 960 mg bid and 22 were evaluable at the time of the presentation. Fourteen of those patients had partial responses, with 6 others experiencing tumor regression less than that required for classification as a partial response. Tumor reduction occurred at multiple metastatic sites (subcutaneous, liver, lung, GI tract and bone), and the responses were associated with resolution of disease-related symptoms.

On February 22 through 24, 2010, the New York Times published a series of in depth articles by reporter Amy Harmon describing the early development of PLX4032, including certain case history details for some of the metastatic melanoma patients who were treated in the Phase I trial<sup>6</sup>. Some of the patients were experiencing rapid, dramatic disease regression with associated dramatic improvements in their quality of life, and the high percentage of patients responding – all with the BRAF mutation – was holding steady. The clinical information made public in the articles was consistent with the published trial data, and also consistent with a quality of life benefit associated with the disease regression conferred by treatment with PLX4032.

The scope of the article included information indicating that successful treatment of the disease with accompanying resolution of symptoms (effectively restoring the ability of patients to live near normal lives) extended the benefit of treatment to family members and friends. Although this extension of effect on quality of life to persons close to the patients is non-quantifiable by conventional clinical research methods, it is an obvious benefit of the successful treatment of disease symptoms and considered enormously important by the families and friends of patients with serious and life-threatening diseases.

On August 26, 2010, updated results of the Phase I trial were published in the New England Journal of Medicine (NEJM)<sup>7</sup>, along with an editorial commenting on the emergence of PLX4302 as “the poster child” of personalized medicine<sup>8</sup>.

In the article presenting the updated results, it was reported that a total of 55 patients were enrolled in a multi-center dose-escalation Phase 1 trial for PLX4032. Forty nine of the 55 patients had metastatic melanoma. Of the forty nine patients with metastatic melanoma, a total of 16 were confirmed to carry the V600E mutation and also received a dose of 240 mg BID or more. After determination of the recommended dose, an extension study adding 32 metastatic melanoma patients with the V600E mutation was initiated. The extension patients were administered PLX4032 at the recommended dose of 960 mg bid.

Ten of the original sixteen patients with the V600E mutation who were treated at doses of 240 mg BID or more in the dose escalation study experienced partial responses defined as a decrease in tumor size (sum of target lesions) of at least 30 percent, and one had a complete response. The total response rate was 69%, and responses were seen at all sites of disease. Duration ranged from 2 to 18 months with 4 patients still responding at cut off. Treatment at higher doses appeared to correlate with higher response rates.

None of the five metastatic melanoma patients enrolled in the study that did not carry the V600E mutation and were treated at doses of 240 mg BID or higher experienced tumor regression, and 4 of the five progressed within two months of beginning treatment

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<sup>5</sup> Chapman et al, Abstract 6BA, Early efficacy signal demonstrated in advanced melanoma in a phase I trial of the oncogenic BRAF-selective inhibitor PLX4032, Joint ECCO 15 - 34TH ESMO Multidisciplinary Congress, Berlin, September 20 – 24, 2009

<sup>6</sup> Amy Harmon, New York Times Three Part Series: September 22, 2010, A Roller-Coaster Chase for a Cure; September 23, After Long Fight, Drug Gives Sudden Reprieve; September 24, A Drug Trial Cycle: Recovery, Relapse, Reinvention

<sup>7</sup> Flaherty, et al, Inhibition of Mutated, Activated BRAF in Metastatic Melanoma, NEJM, August 26, 2010, Vol. 363, No.9; p.809-819

<sup>8</sup> Smalley, K.S.M. and Sondak, V.K., Melanoma — An Unlikely Poster Child for Personalized Cancer Therapy. NEJM, Editorial, August 26, 2010, Vol. 363, No. 9: p. 876-878

A total of 26 of the 32 metastatic melanoma patients (all carrying the V600E mutation) treated at the recommended dose of 960 mg BID in the extension study experienced a partial or complete response (24 partial; 2 complete), for a response rate of 81 percent. Sixteen of the 32 patients remained in the study (meaning they remained progression-free). Estimated median survival is more than seven months, and median overall survival has not been reached. In three patients with symptomatic disease, improvement was observed within 1 to 2 weeks.

Side effects included rash, fatigue, arthralgia and potentially, an increased incidence of a usually non-metastatic form of squamous cell carcinoma. Dose reductions were sometimes needed to alleviate side effects.

The final sentence of the article, and the only mention of the randomized trial comparing PLX4032 to dacarbazine in a clinical trial designed to measure overall survival is reproduced below:

“We do not yet know whether treatment with PLX4032 will improve overall survival; an ongoing phase 3 trial (ClinicalTrials.gov number, NCT01006980) is addressing that question.”

The reason for this passing reference to the Phase III trial might be Dr. Keith Flaherty’s (the principal author of the NEJM update article) strongly stated opinion in a fourth article by Amy Harmon published in the New York Times on September 20, 2010<sup>9</sup> that the Phase III trial is unnecessary.

In an accompanying editorial published in the same volume of the NEJM (see reference 8) titled “Melanoma – An Unlikely Poster Child for Personalized Cancer Therapy” the authors advanced the following introductory conclusion:

“In this issue of the journal, Flaherty and coworkers provide clinical proof that mutations in the gene encoding the serine – threonine protein kinase B-RAF (BRAF) are bona fide therapeutic targets in melanoma. A remarkable 81% of patients whose melanomas had an activating mutation in BRAF had a response to treatment with the new BRAF kinase inhibitor PLX4032 in a multi-center, phase 1, dose-escalation trial.”

The authors also conclude:

“These results represent a major breakthrough and provide proof of the principle that the treatment of metastatic melanoma can be individualized for a substantial percentage of patients.”

In the last paragraph of the editorial the authors note:

“Nonetheless, the data provided by Flaherty and colleagues represent a major advance in the treatment of metastatic melanoma.”

The September New York Times article by Amy Harmon (see reference 9) presented a compelling factual account of the outcomes experienced by two cousins, both diagnosed with advanced melanoma and both carrying the BRAF mutation. One got PLX4032 in a small Phase II trial, responded and was alive and still on treatment at the time of article publication. The other cousin entered the BRIM3 randomized trial, was randomized to dacarbazine, quickly progressed, was denied crossover to PLX4032 consistent with the trial rules, denied access to the drug by any other means, and died from his disease. Some oncologists opined in the article that the randomized trial was necessary; however, other oncologists, including leaders in the subspecialty of melanoma, were firmly convinced based on the Phase I results that PLX4032 represents a major advance against melanoma. Dr. Keith Flaherty of Massachusetts General Hospital and an investigator for the Phase I trial stated:

“I know all that I need to know based on the results we already have. My use of this drug is not going to be informed by testing it against a drug we all hate and would rather never give a dose of again in our lives.”

On September 19, 2010, the New York Times published a letter to the editor responding to the article with the header “Re “When Testing a Drug Means Withholding It” (“Target: Cancer” series, front page, Sept. 19).”<sup>10</sup>

<sup>9</sup> Amy Harmon, New York Times, September 18, 2010, New Drugs Stir Debate on Rules of Clinical Trials

<sup>10</sup> New York Times, Letter to the Editor, Andrew Eisenberger, September 19, 2010

The letter was submitted by Dr. Andrew Eisenberger, an assistant professor of clinical medicine, Division of Oncology/Hematology, Columbia University Medical Center. Dr. Eisenberger stated:

“When we see robust treatment responses in refractory cancers, like PLX4032’s effects in melanoma, oncologists, the Food and Drug Administration and the pharmaceutical industry need to be creative and find ways to distribute the medication without use of a randomized controlled trial.”

### **Ongoing Clinical Trials**

The following information is posted on the NCI’s [clinicaltrials.gov](http://clinicaltrials.gov) website, and is accurate as of the date of submittal of this letter.

The Phase I clinical trial including the extension cohort (discussed above), is ongoing, but closed to enrollment.

A Phase I study testing treatment with PLX4032 in combination with five CYP450 substrates (caffeine, warfarin + vitamin K, omeprazole, dextromethorphan, and midazolam) is listed as ongoing with a target enrollment of 6 previously-treated patients with the V600E mutation, and is closed to patient enrollment. The trial is listed as having started in November 2009. A target completion date is not provided.

A Phase II single-arm trial for previously treated metastatic melanoma patients with the V600E mutation study is listed as having started in October 2009 with a target enrollment of 132 patients. The trial is closed to enrollment with a target completion date of September 2010.

A Phase I pharmacokinetic and metabolism study of PLX4032 (with radiolabeling) is underway and enrolling for previously treated or previously untreated metastatic melanoma patients with the V600E mutation. The target enrollment is 6 patients. This trial is listed as having started in July 2010 with a target completion date of October 2010.

A Phase I pharmacokinetic/pharmacodynamic trial for previously treated metastatic melanoma patients is underway and enrolling patients. The trial started in May 2010 with a target enrollment of 55 patients. Patients will be randomized to receive one of four doses for the first 15 days, then the recommended dose of 960 mg BID beginning on day 22. The estimated completion date is October 2012.

A Phase III open-label trial for previously untreated, V600E positive metastatic melanoma patients, the BRIM3 trial, is underway and enrolling. The trial is designed to measure (as the primary endpoint) the difference in overall survival between patients randomized to receive either dacarbazine or PLX4032. The target enrollment is 680 patients. The trial was initiated in January 2010 with an estimated completion date of March 2014. The listing on [clinicaltrials.gov](http://clinicaltrials.gov) does not describe the ratio for randomization; however, Plexxikon has announced that the randomization ratio is one to one,<sup>11</sup> meaning that approximately 340 patients will be treated with PLX4032 and 340 with dacarbazine when the trial is fully enrolled.

Based on the information available on the [clinicaltrials.gov](http://clinicaltrials.gov) webpage (summarized above), a total of approximately 407 qualifying patients may receive PLX4032 in currently enrolling clinical trials for V600E mutation positive metastatic melanoma. The largest of the trials (the BRIM3 randomized trial) is open only to previously untreated patients; leaving a total of approximately 67 spaces in ongoing, still enrolling clinical trials for the indication in which PLX4032 has already been shown to be highly beneficial. Given that the largest of those trials began in May, and that physician and patient awareness of these trials is high, it can be safely assumed that the actual number of metastatic melanoma patients who will still succeed in gaining access to PLX4032 within a clinical trial is substantially smaller than 67. Further, enrollment in a clinical trial will be precluded for many patients who might well benefit from PLX4032 by the inclusion and exclusion criteria that apply to eligibility for the still enrolling trials.

In summary, the ongoing and still enrolling clinical trials will provide access to PLX4032 for only a tiny fraction of the thousands of patients likely to benefit in the form of disease regression, resolution of disease related

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<sup>11</sup> Press Release, Plexxikon Announces First Patient Dosed in Phase 3 Trial of PLX4032 (RG7204) for Metastatic Melanoma, Berkeley, CA, January 8, 2010

symptoms, associated improvement in quality of life, and almost certainly for some - longer survival, over the next 18 months to two years.

## Discussion and Recommendations

Our concerns are restated below, each followed by a discussion and recommendations.

- 1. Despite an enormous unmet need in the treatment of metastatic melanoma (more than 8,600 US deaths per year), PLX4032 is unavailable to nearly all patients who would likely benefit, and is likely to remain unavailable until sometime in mid to late 2011, or very possibly later, given the time required for the sponsor to develop an application and for the FDA to review it, under the current development program.**

### *Discussion*

The current plan for development of PLX4032 is consistent with policies stringently advanced by the OODP since March 2003 when Drs. Richard Pazdur and Robert Temple of the FDA announced a new set of policies for development and approval of cancer drugs at an ODAC meeting<sup>12</sup>. The meeting was ostensibly convened to discuss sponsor compliance with Phase IV (post-approval) clinical trials for oncology drugs that had received Accelerated Approval; however, as the meeting unfolded it became clear that the purpose of the meeting was to communicate a set of new policies that would generally neutralize the Congressional intent of the Accelerated Approval pathway (which was clearly *acceleration*).

Dr. Pazdur explained that, due to the difficulty of enrolling RCTs (generally speaking of trials like the BRIM3 trial) in a post-approval setting, FDA would henceforth require that the randomized trials be started, enrolled and run to at least an interim analysis point before Accelerated Approval would be considered by the FDA. Going forward no material distinction would be made between drugs that showed little or no evidence of safety and effectiveness, and drugs that showed compelling evidence of safety and effectiveness, in Phase I and Phase II trials.

The Abigail Alliance attended the meeting and attempted to object as the new policy announcements were being made by FDA staff. The ODAC chair refused the Abigail Alliance an opportunity to comment. Soon thereafter, the Abigail Alliance designated the major policy shift announced by Drs. Pazdur and Temple as the "Decelerated Approval Initiative." The Abigail Alliance delivered a presentation documenting the initiation of the Decelerated Approval Initiative and its deleterious effects at an ODAC meeting held on November 8, 2005. A prepared text version of the presentation is available on the Abigail Alliance website.<sup>13</sup>

The benefit of hindsight now affords a clear view of the effect of the Decelerated Approval Initiative, which was at its core a Phase IV trial enforcement initiative. The enforcement solution imposed by Dr. Pazdur was and continues to be elimination of randomized, post-approval, Phase IV clinical trials by simply refusing to grant Accelerated Approvals until the trials are started, enrolled and run to an interim analysis point as pre-approval, Phase III trials.

As a consequence, the approval and availability of most new safe and effective cancer drugs since 2003 have been delayed by 1.5 to 2 years (or more) to allow for conduct of pre-approval Phase III trials, effectively eliminating the Congressional intent of the Accelerated Approval pathway. The clear intent of Congress was to deliver new treatments to patients with serious and life-threatening diseases more quickly based on an effect on a surrogate endpoint likely to predict clinical benefit. This text was intended to facilitate early approvals and availability of new cancer drugs to patients sooner than would be afforded by waiting until the requirements for regular approval (demonstration of clinical benefit based on established [by FDA] endpoints) were met. Congress intended that drugs meeting the standards for Accelerated Approval would timely receive that approval. Congress also empowered FDA to require post-approval trials to meet the requirements for regular approval, but did not establish this requirement as mandatory for issuance of Accelerated Approval, in the following text:

(b) APPROVAL OF APPLICATION FOR A FAST TRACK PRODUCT.—

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<sup>12</sup> FDA Oncologic Drugs Advisory Committee Meeting Transcript, 74<sup>st</sup> Meeting, March 12-13, 2003, Bethesda, MD

<sup>13</sup> [http://www.abigail-alliance.org/docs/Nov\\_8\\_ODAC\\_STEVE\\_Presentation\\_Text\\_1\\_.pdf](http://www.abigail-alliance.org/docs/Nov_8_ODAC_STEVE_Presentation_Text_1_.pdf)

(1) IN GENERAL.—The Secretary may approve an application for approval of a fast track product under section 505(c) or section 351 of the Public Health Service Act upon a determination that the product has an effect on a clinical endpoint or on a surrogate endpoint that is reasonably likely to predict clinical benefit.

(2) LIMITATION.—Approval of a fast track product under this subsection *may* be subject to the requirements—

(A) that the sponsor conduct *appropriate* post-approval studies to validate the surrogate endpoint or otherwise confirm the effect on the clinical endpoint; [emphasis added]

The italicized and bolded word “*may*” clearly grants FDA the flexibility to either require, or not require, post-approval studies to validate the results of earlier trials. The use of the term “*appropriate*” in reference to post-approval studies is self-explanatory, and must be taken to mean that FDA should require only meaningful, and presumably ethical (since an unethical trial would clearly be inappropriate), trials. The FDA, and specifically the OODP have incorrectly applied these directions as meaning that the FDA “will” in almost every case require post-approval studies, and that “appropriate” will mean in almost every case, at least one successful RCT trial designed to measure a traditional statistically-based endpoint, whether or not the trial is ethical or will produce a relevant or meaningful result, and without regard to the effect of the trial on patients or the public health. FDA’s OODP has further distorted the intent of Congress by deciding unilaterally that, because enrolling and completing ethically-challenged RCTs in a post-approval setting is difficult, FDA will require that they be run to at least an interim analysis point prior to approval.

The effect is obvious. PLX4032 is a drug that undeniably meets the statutory requirements for Accelerated Approval in compelling fashion, but Accelerated Approval is effectively unavailable to the sponsor and the patients who would benefit from proper implementation of the law. Accelerated Approval as intended by Congress has been eliminated as an effective approval pathway for cancer drugs by the OODP. The severe curtailment of Accelerated Approval is a direct consequence of unilateral policy changes made by Dr. Richard Pazdur beginning in March 2003 and continuing through the present. His policies have been supported and/or tolerated by his superiors during that time frame.

Criticisms and calls for relief received from directly affected patients and their advocates outside the agency have been ignored and/or aggressively rejected by the agency. The consequences of Dr. Pazdur’s policies were not unknown to the FDA, nor can the agency credibly argue that they are unintended. Dr. Pazdur acknowledged in his comments in March 2003 that the policies would slow down the delivery of progress to patients, and we at the Abigail Alliance, and others, have repeatedly communicated the highly adverse effects the policies would, and in fact have, imposed on patients on multiple occasions, including in correspondence directed to, and meetings with, FDA commissioners and appropriate deputy commissioners, associate commissioners, center directors, office directors, review division directors, and numerous involved staff working within these various agency levels.

The result of the Decelerated Approval Initiative has been a rigidly enforced regulatory policy with a tenuous, at best, link to the intent of Congress when it established the Accelerated Approval pathway. Congress clearly intended that highly-promising new drugs for serious and life-threatening disease would be eligible for Accelerated Approval. Imposition of these policies for all drugs intended to treat a terminal form of cancer where the population is large enough, and the unmet need dire enough, to support enrollment and conduct of a randomized, usually double-blind and often placebo-only controlled RCT, has created a regulatory environment in which submittal of applications for Accelerated Approval based on compelling Phase I and Phase II data have been strongly discouraged, with the effect that they are considered prohibited by sponsors. They also have rendered initiation of Treatment INDs (the mechanism FDA claims mitigates the need for new approval and progress delivery policies for serious and life-threatening diseases) effectively impracticable for sponsors.

In the case of PLX4032, the New York Times (see reference 9) reported that Roche admitted the drug cannot be made available outside trials because of the ongoing Phase III trial. From the article:

“...several oncologists urged Roche to seek accelerated approval from the F.D.A. The agency allows a manufacturer to sell a drug based on early promise so long as it proceeds with the traditional controlled trial comparing it with the standard treatment. But with patients already begging doctors for the drug, it seemed unlikely that anyone would join a trial with only a 50-50 chance of getting PLX4032 once it was already on the market.”

“Unless the trial was conducted before approval, it seemed, there would be no chance to get definitive data on its effectiveness.”

The article also reported that Roche thought pursuing Accelerated Approval would reduce the size of the population ultimately approved to receive the drug, meaning that had they sought Accelerated Approval for PLX4032 in the population treated in the Phase I trial (patients who had already failed at least one prior treatment), they might have been unable to enroll a trial the FDA would require for approval of the drug in first line treatment, after the drug was approved and available to physicians and patients. (It should be noted that the FDA’s Office of Oncology Drug Product leadership - Drs. Pazdur and Keegan - have commented in ODAC meetings that such a trial must be run, even if ethically and practicably impossible, and/or medically inappropriate, to gain regular approval and in some cases for the drug to remain on the market if it had previously received only Accelerated Approval.)

To clarify, under the current policies of the OODP, the FDA would require an RCT large enough to demonstrate that PLX4032 conferred a statistically significant survival benefit over that conferred by dacarbazine producing a p-value of less than 0.05 (meaning less than a 5 percent chance that the difference in survival is due to chance). Based on the company’s comments in the September 2010, New York Times article, it is entirely reasonable to conclude that the company decided they had to run the trial before applying for approval. The balance of the information available for the drug strongly supports a conclusion that the development program is not based on a rational or reasonable doubt regarding the superiority of PLX4032 to dacarbazine for V600E mutation positive patients, nor is it based on a broad lack of physician consensus on whether PLX4032 is safe and effective. It is instead evidence of the inflexibility of FDA policies regarding Accelerated Approvals for cancer drugs, even in cases where delaying such an approval in pursuit of the policy results directly in the premature deaths of thousands.

In this case, Roche and Plexxikon (the sponsors for PLX4032) must be assumed to have considered the well-documented record of the OODP’s aggressive enforcement campaign against sponsors who fail to complete Phase IV randomized trials, which they also insist be designed and conducted in the same unethical and physician/patient off-putting manner as the BRIM3 trial. Consequently, Roche, Plexxikon and terminal cancer patients were boxed in by the continuing enforcement of Dr Richard Pazdur’s rigidly applied policies, termed by the Abigail Alliance, his Decelerated Approval Initiative.

### ***Recommendations***

The Abigail Alliance urges the FDA to immediately suspend the OODP policy of requiring and/or strongly encouraging the sponsors to start, enroll and run to an interim analysis point an RCT as a pre-condition for Accelerated Approval, and to begin immediately considering and communicating to the sponsor an openness to consider and accept alternate Phase IV trial designs for obtaining regular approval in the post-approval setting for both the refractory and other treatment settings (including first-line) for metastatic melanoma. We further strongly urge the FDA to encourage the sponsor(s) to prepare and submit an application for Accelerated Approval in pre-treated patients immediately based on the Phase I and extension cohort data (which in effect and design is actually a Phase I/II trial) and begin negotiations with the sponsors, appropriate clinical researchers and patient advocates on how to further develop PLX4032 without the ethical, progress-delivery preventing characteristics of the ongoing BRIM3 trial.

Pursuing this approach will require halting the BRIM3 trial, conducting an expedited analysis of the data as it currently stands, and allowing all patients in the dacarbazine arm to cross over to PLX4032. For patients responding to dacarbazine, cross over should be allowed upon progression. Patients not responding to dacarbazine, or that have stopped responding, whether still on study or not, should be offered PLX4032. Responses and duration of response observed in cross over patients should be monitored and considered as supplemental evidence of effectiveness. FDA should immediately develop methods for evaluating the significance of responses seen in cross

over patients, and begin a dialogue regarding application of data from cross over patients to approval decisions and product labeling.

In broader application, the Abigail Alliance urges the FDA to immediately begin a review of OODP policies regarding Accelerated Approval, Phase IV trial enforcement, and cancer drug approval standards, including timely (meaning as soon as possible) implementation of a transparent and public dialogue regarding how best to recapture the intent of Congress regarding Accelerated Approval (which was *acceleration*), how to apply flexibility to development programs and approval standards when the emerging data regarding a new therapeutic warrant that flexibility, and how to institute new policies that better fit the rapidly evolving science of cancer drug development, with the central goal of benefiting cancer patients, both present and future. In considering these concepts, FDA should not weigh the well being and interests of future cancer patients more heavily than that of patients fighting cancer now.

This effort should begin immediately in consultation with the sponsors of PLX4032, clinical researchers and the patient community, and be applied in real time to the ongoing development program for PLX4032 in a manner that accelerates the development and New Drug Application (NDA) process for this drug, with a goal of receiving an application for approval, and acting on that application by the end of 2010. The data supporting Accelerated Approval for PLX4032 already exists and has been submitted to the FDA in support of Investigational New Drug (IND) packages supporting requests for approval of now ongoing trials; consequently, this is an achievable schedule.

Dr. Hamburg, you have frequently spoken since your appointment on the pressing need for better regulatory science. The arrival of PLX4032 presents a signal opportunity to begin applying new, better approaches to the regulation of highly promising cancer drugs. This opportunity should not be missed. The fact that FDA's recently released Regulatory Science Report includes no specific initiatives, collaborations or action items intended to address this severe deficiency in the agency's performance for new cancer drugs *in real time* (meaning – starting now), is evidence that the FDA remains directionless and without a schedule of any kind to begin applying better regulatory science to its regulation of cancer drug development and approval. The FDA will not move forward without real action items supported by schedules to implement them, with the expectation that those action items will translate quickly into improved regulation *in real time*.

- 2. Clinical results already reported confirm that PLX4032 is a significant advance in the treatment of metastatic melanoma; however, information available to the public regarding the clinical testing track for this drug suggests that FDA has failed to recognize in a manner meaningful to cancer patients and the public health, the compelling medical utility of this drug.**

### *Discussion*

This concern is self-explanatory. Would people suffering from metastatic melanoma today, or at any time before PLX4032 is approved by the FDA, be better served by our regulatory system if they could get it in the interim, or if they could not. The answer is obvious and self-validating. They would be better served if PLX4032 was available to them. The arrival of PLX4032 is a direct test of FDA's commitment to its mission of protecting and promoting the public health. Withholding PLX4032 is harmful to the thousands of patients currently being denied access, violating the protection requirement of FDA's mission. Denial of access also clearly violates the promotion requirement of the agency's mission.

### *Recommendations*

FDA should immediately encourage the sponsor to apply for and begin a broadly inclusive Treatment IND for PLX4032. Approval of the Treatment IND should be forthcoming as quickly as possible, the process should be transparent, and involved Institutional Review Boards should be contacted and assisted by the FDA to expedite their review and approval of the program. The availability of the drug should be as geographically broad as possible. Further, FDA should dedicate necessary personnel to work with the sponsor on manufacturing, controls, distribution and supply to expedite availability of the drug to as many qualifying metastatic melanoma patients interested in getting the drug through their qualified physicians, as possible. Single-Patient INDs also should be considered for patients who don't qualify for the Treatment IND when supplying PLX4032 to those patients is medically reasonable, recognizing that given the dismal prognosis associated with a diagnosis of advanced metastatic

melanoma, considerable deference should be given to opinions of patients and their physicians regarding the acceptability of the known risk/benefit profile of this drug.

Charging should be allowed if requested by the sponsor; however, if an expedited application and review process is pursued by FDA and the sponsor, charging for provision of the drug in an access program may well be considered unnecessary by the sponsor(s).

PLX4032 is a small molecule drug; consequently, rapid ramp up of production is likely possible if the sponsor and FDA work diligently to make it happen.

We understand that the sponsors must agree to submit the necessary applications, manufacture sufficient quantities of the drug, provide access to the drug and do other things that the agency has no direct power to compel; however, a response from the FDA that directs the blame at the sponsor for not having already proposed some or all these things to the agency would be deliberately disingenuous. It is exceedingly clear in this case that the PLX4032 development program, the BRIM3 trial design, the ethical challenges raised by the trial, and the decision by the sponsor not to ask for Accelerated Approval for the refractory patient population are the direct and unavoidable result of clearly communicated, inflexible and rigidly enforced OODP policies for cancer drug development and approval. For the sake of unequivocal clarity regarding what we mean here – this mess is of FDA's making.

Finally, PLX4032 further illustrates the need for an expedited, restricted approval authority that allows compellingly effective, breakthrough drugs for serious and life-threatening diseases to be delivered to patients who cannot wait more quickly than is presently allowed by the Accelerated Approval and regular approval mechanisms, or is practicable for sponsors through the FDA's largely unworkable investigational drug access mechanisms. FDA should begin working with the patient community and interested members of Congress to craft legislation that will accomplish creation of a new, rapid approval mechanism for drugs like PLX4032.

**3. The design of the clinical trials, and in particular the design of the Phase III randomized BRIM3 trial, strongly suggests that the FDA has failed to properly consider the scientific and clinical facts applicable to this investigational drug, and instead imposed a formulaic set of clinical testing and approval endpoints on the development program that will ultimately yield little, if any, useful scientific or medical information.**

*Discussion*

The hypothesis being tested in the BRIM3 trial (that PLX4032 will provide for an overall survival advantage compared to dacarbazine) is a scientifically and medically meaningless hypothesis. Dacarbazine is a toxic and at best, barely effective drug. PLX4032 has already demonstrated a median progression-free survival advantage in an identifiable population of patients that is roughly equal to median overall survival results reported for dacarbazine, and dacarbazine in combination with other drugs. The very low response rate and duration associated with dacarbazine has been tested and confirmed in multiple trials performed over a period of more than 35 years. The response rate for PLX4032 is 4 to 5 times greater and the median duration of response is two to three times the duration of response afforded by dacarbazine. PLX4032 is a better drug, and in fact so much better than dacarbazine, that the outcome of the ongoing BRIM3 trial will have no utility in medical practice.

In any case, if dacarbazine provides any clinical benefit at all as a first line drug, it fails to cure anyone, leaving an enormous unmet need for a safe and effective second line treatment option.

The relevant hypotheses for PLX4032 are related to the molecular response to treatment occurring in each patient's cancer cells that cause their disease to stop responding to the drug. As explained by some of the researchers involved in development for this drug (and others now weighing in), the hypotheses needing further testing can only be addressed through clinical research that provides PLX4032 to patients in combination with other targeted drugs, administered in combination with real time biopsies during treatment and at the time of changes in response, to support tracking of genetic and epigenetic responses to treatment. These trials will not produce the same kinds of simplistic statistical results that flow from RCTs. Rather they will yield "first principal" scientific information regarding the mechanisms of the disease that will, in turn, allow informed, directed decisions to be made regarding next steps for patients already in the trials, and for new patients enrolled into the trials.

Outcomes for identifiable subsets of patients identified through this directed testing will further refine our understanding of the molecular basis of disease mechanisms, why some patients respond, why some don't, and for those who do, why they stop responding. These findings will guide (in real time) new directions for the trials, and new ideas for drug development. Instead of blinding the data to preclude bias (a purely statistical requirement), data will be reviewed and analyzed as it emerges, and used in real time to learn and adjust to the new knowledge it provides, including how to personalize treatments to the appropriate subsets of patients, and eventually to individuals.

Randomized controlled trials are not well suited for this kind of scientific clinical testing, and in fact, by design are incompatible with it. The Phase I PLX4032 program already includes some of these scientific characteristics and going forward, clinical research for PLX4032 and many other targeted drugs should be based primarily on "first principal" scientific hypotheses pursued in adaptive trials aimed at answering cause and effect questions, not the crude, population-based statistical questions sometimes very narrowly answered by RCTs. This will require a new approach to regulation, a new culture of change-acceptance and pursuit at FDA, strong direction from the commissioner's office, and in all likelihood changes in some key supervisory personnel in the drugs and biologics centers (CBER and CDER) and the review divisions where agency performance, as in this case with PLX4032, has been considerably less than optimal.

### ***Recommendations***

This is an opportunity to jumpstart FDA's development of new regulatory science to accommodate and facilitate the obvious potential PLX4032 represents for applying better science to drug development and accelerating the application of personalized medicine – the right drug(s) to the right patient at the right time. FDA should begin immediately to work with the sponsor(s), clinical researchers and patients to develop more scientifically driven (as opposed to statistically-driven) adaptive clinical trial designs for this drug. It is another opportunity that should not be missed, and it is another area where the agency is likely to need considerable help from scientists outside the agency.

The ODAC, given its membership of oncologists and statisticians with a demonstrated bias toward retaining the models for clinical research favored by the current leadership of OODP, may not be the best forum for obtaining the new ideas FDA needs. It is not surprising that the views of ODAC members reflect the views of the Director of OODP, given that the director effectively selects all voting members of the committee, both permanent and temporary.

#### **4. The design of the BRIM3 clinical trial raises serious questions regarding the FDA's consideration and review of the ethics of conducting a randomized controlled trial designed to compare overall survival for patients treated either with dacarbazine or PLX4032.**

The BRIM3 trial fails to satisfy any of the requirements for ethical research established by human clinical research codes. Consider the following:

- The answer to the question being asked in the BRIM3 trial - PLX4032 provides a survival advantage compared to dacarbazine in the first line treatment setting - is almost certainly a true hypothesis. It is also entirely irrelevant for refractory patients at this time.
- The basis of the concept of clinical equipoise is also not satisfied. Many oncologists, including those who have worked with the drug, others who have not, and even some who conditionally support the BRIM3 trial for various reasons, acknowledge that the drug is a major advance in the treatment of metastatic melanoma. It would be exceedingly difficult to identify even a small number of oncologists who would not prescribe this drug to refractory V600E positive metastatic melanoma patients, if it were available to them. This results in a circular and false logic being relied on to judge the BRIM3 trial ethical. The virtually guaranteed acceptance and use of PLX4032 by oncologists if it were available, which on its face obliterates the primary basis for the existence of clinical equipoise, is also the reason the sponsor (and although unacknowledged – the OODP by long-standing policy) is using to claim that the drug can't be made available, else the (unethical) BRIM3 trial would be too difficult to enroll.

- While dacarbazine is the only drug approved for treatment of metastatic melanoma, it has never been shown to provide clinical benefit, as defined by FDA, and may well be a toxic placebo. If this is true, then some might argue that use of a placebo as a control would be more ethical with respect to toxicity for patients, but the number of physicians who would argue that we don't know PLX4032 is more effective than nothing, would be nonexistent; thus such a trial would also be unethical.
- The BRIM3 trial is unethical on its face, and it is by no means a rare example of the human clinical research being conducted to meet the OODP's rigidly enforced and increasingly obsolete and unethical approval standards. The BRIM3 trial is correctly being viewed by many, including many oncologists, as morally reprehensible. It is the result of ethical creep, largely encouraged and enforced by FDA's drug development and approval policies for cancer drugs over the last decade.
- Among FDA's most important responsibilities is ensuring that human clinical research is meaningful and ethical. In this case, FDA has utterly failed to exercise that responsibility. FDA reviewed and approved the BRIM3 trial design, almost certainly participated in its design through discussions with the sponsor regarding the development program for PLX4032, and played a powerfully influential role both directly and indirectly in the sponsor's development of a strategy to gain approvals for PLX4032.
- The fact that this trial was approved by FDA as an ethical trial begs the following very important questions: How does FDA, and specifically OODP evaluate the ethics of the INDs it receives proposing clinical trials? Are the reviewers trained to conduct reviews of the ethics of proposed clinical trials? What standards do they use? How are conflicts between OODP policies for trial designs and approval standards and the ethical challenges posed by a trial like BRIM3 considered, discussed and resolved as a formal part of the review process? If the BRIM3 trial is not unethical, what would be considered unethical by the FDA? Who in OODP has responsibility for making those determinations and for making final decisions on ethics?

### ***Recommendations***

Based on the ethical deficiencies of the BRIM3 trial alone, the trial should be immediately stopped and patients in the control arm allowed to cross over in accordance with recommendations presented in the recommendations for Concern No. 1, presented above.

You, as Commissioner should immediately begin a transparent, comprehensive and expedited review regarding how the FDA's review divisions consider and rule on the ethics of clinical research proposed by sponsors, or required/encouraged by the FDA. The review should also include consideration of how ethics is considered when developing drug development and approval policies, guidance, and proposed rules. The review process should result in clear and transparent statements of FDA policy on the ethics of human clinical research, a formal review and appeal process for interested parties outside the FDA to challenge the policies or the application of those policies, and an annual formal review to make sure FDA's policies regarding the ethics of human clinical research are keeping up with the advancing science of drug discovery, and the associated changes in proposed trial designs that will surely flow from those advances.

### **Closing Comments**

The Abigail Alliance believes that the arrival of PLX4032 represents an important test for the FDA in its role as a regulatory and public health agency. If FDA fails to take immediate and effective action with respect to the items described in this letter, it will demonstrate a continuing inability to do its job competently, ethically and effectively in today's environment of rapidly advancing knowledge regarding the biology and treatment of disease. To put it bluntly, if PLX4032 doesn't get FDA moving, what will?

FDA also must address these items without further slowing the delivery of medical progress to patients with serious and life-threatening diseases. In fact, this example clearly illustrates how enforcement of rigid, ill-fitting agency policies is slowing the delivery of medical progress to patients, with devastating effect. Each action FDA decides to take should include consideration and implementation of measures intended to speed up the process of progress delivery.

FDA has the statutory authority, flexibility and responsibility to respond to emergencies. Major advances against terminal diseases create very real "emergencies of progress" for those suffering from those diseases. FDA

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has long demonstrated an inability, and perhaps more importantly, a strong cultural unwillingness to respond to these kinds of emergencies. That not only should change, it must change if FDA is to achieve its missions of protecting and promoting the public health.

Today, FDA is the reason the progress represented by PLX4032 is stalled, and to deny that obvious fact is to deny the effect of bad policies rigidly enforced over many years that resulted in the deeply flawed, formulaic and outdated drug development and approval program now in place for PLX4032. FDA's usual response to these types of criticisms consists of carefully worded brief statements designed to deflect blame toward the sponsors. That strategy is likely to backfire in this case because many would see it for what it is – a deepening of the agency's failures and a continued commitment to resist change. As more of these compellingly effective cancer drugs follow, and more articles describing the failures of the FDA to deliver progress to patients appear in major media reports, the significance of this moment will become apparent.

We hope the FDA will consider the concerns presented in this letter in good faith and open a dialogue with the Abigail Alliance and others, including individual patients, who are directing well deserved criticism toward the FDA.

We can find real hope in the fact that after decades of intensive effort, we have crossed a scientific threshold that is going to support unprecedented progress against many diseases. It is only a matter of time, but the question remains – how much time; and that will depend in significant part on how fast the FDA can catch up and remake itself into a modern, responsive agency that values and pursues change. At present, the FDA continues to fall further behind the science, as it stands virtually still in its application of 50 year old clinical research and approval concepts. The FDA also remains a largely unresponsive agency with respect to those it most directly affects, patients.

We believe that PLX4032 represents an opportunity to get started, and we hope the FDA agrees. In judging how quickly the agency should be moving, consider the schedules faced by the hundreds of metastatic melanoma patients who need PLX4032 right now. For many of them, if they are to benefit from even the beginnings of the process of change, the first of those changes must happen within at most, a few weeks.

Sincerely,

Abigail Alliance for Better Access to Developmental Drugs

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