DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

(b) (4)

WRITTEN REQUEST – AMENDMENT # 1

Bristol-Myers Squibb
Attention: Ralu Vlad, Pharm.D.
Director, Global Regulatory, Safety and Biometrics, U.S. Oncology
Route 206 & Province Line Road
Room D1 264
Princeton, NJ 08543

Dear Dr. Vlad:

Please refer to your correspondence dated March 10, 2015, requesting changes to FDA's September 11, 2014, Written Request for pediatric studies for "nivolumab."

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on September 11, 2014, remain the same. (Text added is underlined. Text deleted is strikethrough.)

Study 1, Part C:

> This portion of Study 1 will include a dose-escalating safety evaluation of nivolumab and ipilimumab at dose levels of 1mg/kg nivolumab in combination with 1 mg/kg ipilimumab (dose level 1) and with 3mg/kg nivolumab and ipilimumab at 1mg/kg (dose level 2). Once the optimal dose of ~~ipilimumab~~ nivolumab in combination with ~~nivolumab~~ ipilimumab is determined, the cohort regimen will be: nivolumab 1mg/kg or 3mg/kg combined with ~~either~~ipilimumab 1 mg/kg ~~or 3mg/kg~~ every 3 weeks for 4 doses followed by nivolumab 3mg/kg every 2 weeks until progression. For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated September 11, 2014, as amended by this letter must be submitted to the Agency on or before Q2, 2018, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

If FDA has not determined whether nivolumab is eligible for reference product exclusivity under section 351(k)(7) of the PHS Act, you may submit a request for reference product exclusivity with supporting data and information to the Agency. Note that neither the issuance of this Written Request amendment, nor any request for exclusivity made by you, confers or otherwise implies that you are eligible for reference product exclusivity under section 351(k)(7) of the PHS Act.

Submit reports of the studies as a supplement to an approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission to the Office of New Drugs, Immediate Office, Therapeutic Biologics and Biosimilars Team, 10903 New Hampshire Ave, Building 22, Mail Stop 6411, Silver Spring, MD 20993. If you wish to fax it, the fax number is 301-796-9855.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, call Meredith Libeg, Senior Regulatory Project Manager, at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Gregory Reaman, M.D.
Associate Director for Oncology Sciences
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE: Attachment 1 - Clean Copy of Written Request as Amendment 1

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

/s/

GREGORY H REAMAN
04/01/2016