IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Inventor(s): Joseph J. BUGGY, et al. Serial No.: 13/340,522 Filed: December 29, 2011 Title: USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)	Group Art Unit: 1627 Examiner: RAMACHANDRAN, UMAMAHESWARI Confirmation No.: 7251 Customer No.: 116469 Certificate of Electronic Filing I hereby certify that the attached Response to Final Office Action is being deposited by Electronic Filing on December 17, 2013, by using the EFS – Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450. By: /Lora Kim/ Lora Kim

M/S AFTER FINAL
Commissioner for Patents
P. O. Box 1450
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AMENDMENT AND RESPONSE TO FINAL OFFICE ACTION
MAILED NOVEMBER 1, 2013 AND REQUEST FOR AFTER FINAL CONSIDERATION

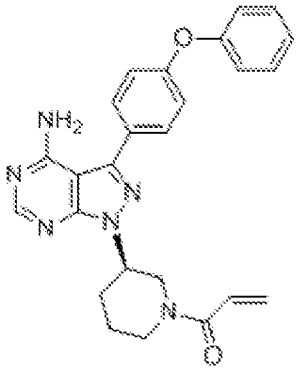
Dear Madam:

Applicants hereby submit a response to the Final Office Action mailed November 1, 2013. This Response is being filed within the three-month statutory period for reply. Therefore, this response is timely filed and no fee should be due. Consideration of the above-referenced application is respectfully requested in view of the following remarks. Consideration of this response under the After Final Consideration Pilot (AFCP) program respectfully is requested. In accordance with the requirements set forth by the USPTO, Form PTO/SB/434 is submitted herewith.

AMENDMENTS TO THE CLAIMS

LISTING OF THE CLAIMS:

131. (Currently Amended) A method for treating mantle cell lymphoma ~~a relapsed or refractory hematological malignancy~~ in an individual who has already received at least one prior therapy for mantle cell lymphoma comprising administering to the individual once per day between about 420 mg to about 840 mg of an oral dose of ~~a therapeutically effective amount of~~ an inhibitor of Bruton's tyrosine kinase (Btk) having the structure:



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132.-149. (Cancelled)

150. (New) The method of claim 131, wherein the once per day oral dose is about 560 mg.

REMARKS

Claims 131 and 150 are currently pending. Applicants have herein amended Claim 131 and added new Claim 150, which depends from Claim 131. Claims 132-149 are cancelled herein. Support for the claim amendments can be found throughout the specification and claims as originally filed, such as, for example paragraphs [0005], [00194] and [00195], and claims 62 and 65 as originally filed. No new matter has been added. Applicants reserve the right to pursue any withdrawn or cancelled subject matter, or no longer claimed or as-yet unclaimed subject matter, in this or a related application. Applicants respectfully request reconsideration of the claims as amended in view of the following arguments.

I. Examiner Interview

Applicants thank the Examiner for the telephone conference of December 2, 2013, during which the currently pending rejections and claims of the instant application were discussed. In view of this discussion, Applicants submit herein amendments to the claims and Response to the Final Office Action mailed November 1, 2013.

II. Rejection of the claims under 35 U.S.C. § 103

Claims 131, 132, 134-140, 144, 146-149 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Honigberg, et al. (US 2008/0076921, already of record) in view of PRNewswire (Dec 2009) and Pollyea et al. (Poster Abstracts, Dec. 3, 2009, 51st ASH Annual Meeting and Exposition) and further view of Hiddeman, et al. (Seminars in Oncology, 30, 1, 2, Feb 2003, p 16-20).

The rejection is moot with respect to claims 132, 134-140, 144, and 146-149, which are cancelled herein.

Applicants respectfully traverse the rejection with respect to claim 131.

A. Relevant Law

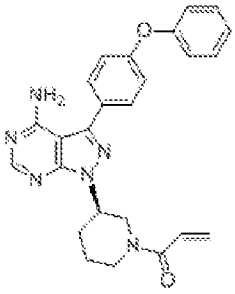
It is the burden of the Office to establish that the claimed subject matter is *prima facie* obvious. MPEP §§ 2141, 2142. To meet this burden, the Office must present prior art references that teach, suggest, or otherwise provide a reason for **all** the claim limitations. *In re Wilson*, 424 F.2d 1382, 1385 (CCPA 1970); MPEP § 2143.03. Moreover, the teaching to make the claimed combination and a reasonable expectation of success must both be found in the prior art and not based on the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

The Supreme Court instructs, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex, Inc.,* 550 U.S. 398, 418 (2007); *see also* MPEP § 2143.01. Rather, to establish a *prima facie* case of obviousness, basic criteria must be met. The prior art references or the combination of the prior art references with the knowledge of an ordinary artisan, must suggest all of the claim limitations. *See, e.g., Dann v. Johnston*, 425 U.S. 219, 230 (1976). Moreover, there must be some predictability allowing a reasonable expectation of success in making the combination. *See, e.g., PharmaStem Therapeutics, Inc. v. ViaCell, Inc*., 491 F.3d 1342, 1360 (Fed. Cir. 2007) (citing *KSR*, 550 U.S. at 416); MPEP § 2143.02. Importantly, "rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR*, 550 U.S. at 418 (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

B. Rejected Claims

Claim 1 recites:

> A method for treating mantle cell lymphoma in an individual who has already received at least one prior therapy for mantle cell lymphoma comprising administering to the individual once per day between about 420 mg to about 840 mg of an oral dose of an inhibitor of Bruton's tyrosine kinase (Btk) having the structure:



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Claim 150 depends from claim 1 and thus requires all limitations of the base claim. Claim 150 specifies that the Btk inhibitor is administered once per day oral dose is about 560 mg.

C. None of the cited references either alone or in combination teaches or suggests claimed method.

Applicants respectfully submit that none of the cited references either alone or in combination teaches or suggests every element of the method as claimed. Specifically, none of

the cited references either alone or in combination teaches or suggests a method for treating mantle cell lymphoma in an individual who has already received at least one prior therapy for mantle cell lymphoma comprising administering to the individual once per day between about 420 mg to about 840 mg of an oral dose of ibrutinib.

Relapsed or refractory MCL is a difficult disease to treat. In the attached article, Howard describes mantle cell lymphoma as "incurable with standard therapeutic techniques and also has an aggressive natural history that places it on par with the more aggressive forms of NHL" (Howard, O. "Mantle Cell Lymphoma," *Malignant Lymphomas* Ed. Grossbard, ML, London: BC Decker Inc 2002 135-151, 135). Howard also states that "mantle cell lymphoma is an insidious disease characterized by the aggressive natural history of the intermediate/high grade NHLs yet possessing the resistance to therapy of the low-grade NHLs (page 147). Thus, MCL has the worst properties of both the indolent and aggressive NHLs. The average survival rates of patients with MCL are low (see Table 9-1 of Howard). In addition, Howard states that "there is no clear evidence that standard dose chemotherapy regimens result in long-term DFS for patients with MCL."

In contrast to then existing therapies for relapsed/refractory MCL, treatment of relapsed/refractory MCL with ibrutinib resulted in an overall response rate of 68 percent with 21 percent of patients achieving a complete response and 47% achieving a partial response in a phase II trial (see attached *Science Daily* article entitled "Drug shows surprising efficacy as treatment for Chronic Leukemia, Mantle Cell Lymphoma, *Science Daily*, http://www.sciencedaily.com/releases/2013/06/130619195217; see also Byrd et al. *NEJM*, 2013 Aug 8;369(6):507-16). The estimated survival of the patients was high at 58% at 18 months. The response rate is considered remarkable given that that prior treatments for R/R MCL had only a 30% response rate. Such results are not taught or suggested by the cited art.

In view of these remarkable clinical results achieved, the FDA recently granted ibrutinib rare breakthrough status designation. Such designation requires preliminary clinical evidence that indicates that the drug may demonstrate substantial improvement over existing therapies. That ibrutinib demonstrates substantial improvement over existing therapies is not taught or suggested by the cited art. Such results are unexpected.

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