

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ INC.,
Petitioner,

v.

ACERTA PHARMA B.V.,
Patent Owner.

Case IPR2023-00478
Patent 10,272,083 B2

DECLARATION OF JOHN P. FRUEHAUF, M.D., Ph.D.

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LIST OF CITED EXHIBITS

No.	Description
1001	U.S. Patent No. 10,272,083 to Hamdy et al. (the “’083 patent”)
1004	Prosecution History of U.S. Patent No. 10,272,083 (Application No. 15/112,968)
1005	U.S. Patent No. 9,758,524 to Barf, et al. (“Barf”)
1006	PCT International Publication No. WO2013/010868 to Barf, et al. (“Barf-PCT”)
1007	U.S. Provisional Application No. 61/509,397 to Barf, et al. (“Barf Provisional”)
1008	Bruce D. Cheson, et al., <i>Advancements in the Treatment of B-Cell Malignancies</i> (International Conference on Malignant Lymphoma), CLINICAL ADVANCES IN HEMATOLOGY & ONCOLOGY, Vol. 11, Issue 9, Supplement 12 (Sept. 2013) (“Cheson”)
1009	Ranjana H. Advani, et al., <i>Bruton Tyrosine Kinase Inhibitor Ibrutinib (PCI-32765) Has Significant Activity in Patients With Relapsed/Refractory B-Cell Malignancies</i> , J. CLINICAL ONCOLOGY, 31(1):88-94 (Jan. 2013) (“Advani”)
1010	John C. Byrd, et al., <i>Acalabrutinib (ACP-196) in Relapsed Chronic Lymphomatic Leukemia</i> , N. ENGL. J. MED. 374(4):323-32 (Jan. 2016) (“Byrd”)
1011	U.S. Provisional Application No. 61/929,742
1012	U.S. Provisional Application No. 61/974,665
1013	U.S. Provisional Application No. 62/035,777
1014	Stefano A. Pileri, et al., <i>Mantle cell lymphoma</i> , HAEMATOLOGICA 94(11):1488-92 (2009) (“Pileri”)
1015	M. Dreyling, et al., <i>How to manage mantle cell lymphoma</i> , LEUKEMIA 28:2117-31 (2014) (“Dreyling”)
1016	IMBRUVICA™ (ibrutinib) Prescribing Information (2014)
1017	U.S. Food and Drug Administration Office of Clinical Pharmacology Review of IMBRUVICA™ (ibrutinib), Application No. NDA 205552 (Jan. 2014)
1018	Akintunde Akinleye, et al., <i>Ibrutinib and novel BTK inhibitors in clinical development</i> , J. OF HEMATOLOGY & ONCOLOGY 6:59 (2013) (“Akinleye”)

No.	Description
1019	Claire V. Hutchinson, et al., <i>Breaking good: the inexorable rise of BTK inhibitors in the treatment of chronic lymphocytic leukaemia</i> , BRITISH J. OF HAEMATOLOGY 166:12-22 (2014) (“Hutchinson”)
1020	Jennifer R. Brown, et al., <i>Phase I Study Of Single Agent CC-292, a Highly Selective Bruton’s Tyrosine Kinase (BTK) Inhibitor, In Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL)</i> , BLOOD 122(21):1630 (2013) (“Brown”)
1021	Daniel W. Pierce, et al., <i>Target Engagement, Pathway Inhibition, and Efficacy Of The Bruton’s Tyrosine Kinase (Btk) Inhibitor CC-292</i> , BLOOD 122(21):4169 (2013) (“Pierce”)
1022	Simon Rule, et al., <i>A Phase I Study Of The Oral Btk Inhibitor ONO-4059 In Patients With Relapsed/Refractory B-Cell Lymphoma</i> , BLOOD 122(21):4397 (2013) (“Rule”)
1023	Prosecution History of U.S. Patent No. 9,758,524
1024	U.S. Food and Drug Administration, <i>Good Review Practice: Clinical Review of Investigational New Drug Applications</i> (Dec. 2013) (“FDA 2013 Good Review Practice”)
1025	U.S. Patent No. 7,732,454 (“Verner”)
1026	International Conference on Harmonisation; Dose-Response Information to Support Drug Registration; Guideline; Availability, 59 Fed. Reg. 55,972 (Nov. 9, 1994)
1027	U.S. Food and Drug Administration, <i>Guidance for Industry - S9 Nonclinical Evaluation for Anticancer Pharmaceuticals</i> (March 2010) (“S9 Guidance”)
1028	U.S. Food and Drug Administration, <i>Guidance for Industry - Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers</i> (July 2005) (“MSSD Guidance”)
1029	Erica K. Evans, et al., <i>Inhibition of Btk with CC-292 Provides Early Pharmacodynamic Assessment of Activity in Mice and Humans</i> , J. PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS 346:219-228 (Aug. 2013) (“Evans”)
1030	Tjeerd Barf, et al., <i>Irreversible Protein Kinase Inhibitors: Balancing the Benefits and Risks</i> , J. MED. CHEM. 55:6243-62 (2012) (“Barf 2012”)

No.	Description
1031	Amit Mahipal, et al., <i>Risks and Benefits of Phase I Clinical Trial Participation</i> , CANCER CONTROL 21:193-99 (July 2014) (“Mahipal”)
1032	Sarah Brumskill, et al., <i>Conference Scene: Recent developments in the understanding and treatment of hematological malignancies</i> , INT’L J. HEMATOLOGIC ONCOLOGY, Vol. 2, No. 5, published online at https://doi.org/10.2217/ijh.13.52 (Oct. 8, 2013) (“Brumskill”)
1033	Toshio Yoshizawa, et al., <i>ONO-4059—a Potent and Selective Reversible Bruton’s Tyrosine Kinase (Btk) Inhibitor: Single Agent, Twice Daily (BD) Dosing and Dosing with Food Results in Sustained, High Trough Levels of ONO-4059, Translating into 100% Tumour Remission in a TMD-8 Xenograft Model</i> , BLOOD, 124(21):4502 (2014) (“Yoshizawa”)
1034	Plaintiffs’ Initial Infringement Contentions to Defendant Sandoz Inc., C.A. No. 22-154-GBW-SRF (Consolidated) (D. Del. Sept. 26, 2022)
1035	CALQUENCE [®] (acalabrutinib) Prescribing Information (2017)
1036	Jan de Jong, et al., <i>Effect of CYP3A perpetrators on ibrutinib exposure in healthy participants</i> , PHARMACOLOGY RESEARCH & PERSPECTIVES, Vol. 3, Issue 4 (2015) (“de Jong”)
1037	Dominique Levêque, <i>Evaluation of Fixed Dosing of New Anticancer Agents in Phase I Studies</i> , ANTICANCER RESEARCH 28:3075-78 (2008) (“Levêque”)
1038	ZYDELIG [®] (idelalisib) Prescribing Information (2014)
1039	TASIGNA [®] (nilotinib) Prescribing Information (2007)
1040	JAKAFI [™] (ruxolitinib) Prescribing Information (2011)
1041	LYNPARZA [™] (olaparib) Prescribing Information (2014)
1042	Betty Y. Chang, et al., <i>Egress of CD19⁺CD51⁺ cells into peripheral blood following treatment with the Bruton tyrosine kinase inhibitor ibrutinib in mantle cell lymphoma patients</i> , BLOOD 122(14):2142 (2013) (“Chang”)
1043	Yan Bao, et al., <i>Tyrosine Kinase Btk Is Required for NK Cell Activation</i> , J. Biological Chemistry 287(28):23769 (2012)

I, John P. Fruehauf, M.D., Ph.D., declare as follows:

I. INTRODUCTION

1. I have been retained by Sandoz Inc. (“Petitioner”) in connection with its request for *inter partes* review of U.S. Patent No. 10,272,083 (“the ’083 patent”). I understand that a copy of the ’083 patent has been marked EX1001. I have been asked to provide my expert opinions regarding the patentability of claims 8-12 and 9-20 of the ’083 patent (the “challenged claims”). I have personal knowledge of the facts stated in this declaration and, if called upon to testify in person, could and would competently testify thereto.

2. This declaration discusses my background and qualifications, the legal standards that I applied in my expert analysis, an overview of the ’083 patent from the perspective of a person of ordinary skill in the art as of the patent’s effective filing date (a “POSA”) of January 21, 2015, and my opinions regarding the patentability of the challenged claims as of that date.

3. My work in this proceeding is being charged to Petitioner at a standard rate of \$750 per hour. My compensation is in no way contingent on the substance of my opinions or the outcome of this proceeding.

4. I reserve the right to supplement or amend this declaration based on any new information that is relevant to my opinions.

5. In addition to my experience, education, and training, I have reviewed the materials listed in the List of Cited Exhibits above in connection with forming the opinions set forth in this declaration.

II. BACKGROUND AND QUALIFICATIONS

6. I am currently Professor of Clinical Medicine at the University of California, Irvine and Director of Clinical Pharmacology and Developmental Therapeutics at the University of California at Irvine's ("UC Irvine") Chao Family Comprehensive Cancer Center ("CFCCC").

7. I am involved in the direct oversight of multiple clinical trials at the CFCCC in the role of principal investigator. Several of the trials I have brought into our Cancer Center were phase I first-in-man studies, which means they were the first clinical study conducted in humans for a drug. Among other responsibilities, I work on the development and execution of clinical trials that incorporate translational endpoints, including phase I, II and III clinical trials. I also teach undergraduate students, graduate students, medical students, residents, and medical oncology fellows the principles of clinical trials in various courses.

8. Since starting to work as a medical oncologist faculty member in the Division of Hematology/Oncology, Department of Internal Medicine in 1993, I have participated in weekly UC Irvine cancer clinics in the outpatient setting as a clinician and instructor for medical oncology fellows. I have also rotated on an

annual basis as the in-patient Attending Physician overseeing the cancer patient service at the UC Irvine University Hospital. I have experience treating patients with mantle-cell lymphoma (“MCL”), among other types of cancers (including lymphomas and leukemias). I also have clinical experience using the Bruton’s Tyrosine Kinase (“BTK”) inhibitor ibrutinib (brand name: Imbruvica).

9. I obtained an M.D. from Rush University in 1985 and a Ph.D. in Pharmacology from Rush University. I received my undergraduate degree in Cellular and Organismal Biology, with a minor in Chemistry, from the University of California, Santa Barbara, in 1977.

10. I completed my Internal Medicine Residency at UC Irvine in 1987. I completed my Medical Oncology Fellowship in 1990 at the National Cancer Institute in Bethesda, Maryland, which was followed by a biotechnology fellowship at the same institution, which was completed in 1992.

11. I am a member of the American Association for Cancer Research, the American Society of Clinical Oncology, the Breast and Melanoma Committees of SWOG (a National Cancer Institute supported organization that conducts clinical trials in adult cancers), and the Medical Oncology Association of Southern California (“MOASC”).

12. I have published more than 91 peer reviewed articles, book chapters, and reviews in the field of oncology. I am an inventor on eight U.S. patents. I am

also a peer reviewer for the following journal publications: Gynecologic Oncology, Breast Cancer Research and Treatment, Clinical Cancer Research, Anti-Cancer Drugs. The Cancer Journal, European Journal of Cancer, Pharmacological Research, and Cancer.

13. A current copy of my curriculum vitae is attached as an Appendix to this declaration.

III. SUMMARY OF OPINIONS

14. The challenged claims of the '083 patent are generally directed to treating MCL by orally administering 100 mg twice daily of acalabrutinib, which is a previously known inhibitor of BTK. *E.g.*, EX1001, claim 8. As set forth more fully below, it is my opinion that the challenged claims are unpatentable under the following two grounds, which set forth the combinations of prior art references that would have rendered these claims obvious to a POSA. The full citations for these and other references cited in this Declaration are provided in the List of Cited Exhibits above. A POSA would have read the references listed below with the context provided by other background references discussed in this Declaration.

Ground	Claims	References
1	8-12, 19-20	Barf (EX1005), Cheson (EX1008)
2	8-12, 19-20	Barf-PCT (EX1006), Cheson (EX1008)

15. Under Ground 1, it is my opinion that all challenged claims would have been obvious to a POSA in view of teachings in Barf (EX1005) and Cheson (EX1008). *Infra* §XI.A. Barf is an issued patent with an effective filing date in 2011, whose sole independent claim recites a method of treating MCL by administering acalabrutinib. EX1005, 150:2-32. Barf's claim 12 narrows this method by reciting a dosing range for acalabrutinib that overlaps with the 100 mg dose claimed in the '083 patent. *Id.*, 151:14-16. As I explain in more detail below, I understand that this overlap triggers a presumption of obviousness. Moreover, other information that would have been available to a POSA in the prior art would have further guided a POSA toward the claimed 100 mg dose, which a POSA would have arrived at through routine experimentation by conducting a dose-finding study focused on maximizing BTK occupancy, which was successfully done for other BTK inhibitors in the prior art.

16. Administering the claimed dose twice daily would have been obvious over Cheson's teachings and a POSA's understanding based on other references in the prior art. For example, Cheson discloses the theory that "BTK inhibitors are being evaluated in a twice-daily schedule in an attempt to overcome the synthesis of new BTK molecules," and further discloses that twice-daily dosing "appeared to be more effective" than once-daily dosing in clinical trials. EX1008, 4, 10. As I explain in more detail below, Cheson's disclosures and the reported results of

studies on other BTK inhibitors would have made it obvious to attempt twice-daily dosing with a new BTK inhibitor like acalabrutinib. At a minimum, twice-daily dosing would have been obvious to try as one of two options that were used in the prior art for BTK inhibitors (once-daily dosing and twice-daily dosing).

17. Under Ground 2, I have been asked to assume in the alternative that Barf is not prior art. In that case, it remains my opinion that all challenged claims would have been obvious over Barf-PCT (EX1006) and Cheson. *Infra* §XI.B. I understand that Barf-PCT is the international application counterpart to Barf, which was published in 2013. EX1006, 1. Thus, Barf-PCT provides the same disclosures as Barf, including the structure of acalabrutinib, its use to treat MCL, and the overlapping dosing range. *See id.*, 35:16-36:2, 22:15-16, 20:24-25. Accordingly, even if Barf is ultimately found not be prior art, the challenged claims would still have been obvious over the disclosures of Barf-PCT in combination with Cheson and the knowledge and skill of a POSA.

18. I understand that during the prosecution of the '083 patent, the Examiner at the Patent Office reviewing the patent application repeatedly found the proposed claims obvious, allowing them only after the applicants alleged unexpected results. *Infra* §V.C. As I explain below, however, the results that the applicants alleged were neither probative nor unexpected. *Infra* §XI.C.1. Thus, in my opinion, the basis for allowing the claims of the '083 patent was incorrect.

IV. LEGAL STANDARDS USED IN MY ANALYSIS

19. I am not a patent attorney, nor have I independently researched patent law. Counsel for Petitioner have explained certain legal standards to me that I have relied upon in forming my opinions set forth in this Declaration. I set forth some of these legal standards below and set forth additional legal standards in my analysis in later sections of this Declaration where appropriate.

A. Effective filing date

20. I understand that an assessment of patentability must be undertaken from the perspective of a POSA as of the effective filing date of the challenged claims. I further understand that a POSA is presumed to have had access to all information relevant to the challenged claims that was publicly available as of the effective filing date. Such information is known as “prior art.”

21. I understand that the effective filing date of a patent claim is the earliest of (i) the actual filing date of the patent or the application for the patent containing the claimed invention; or (ii) the filing date of the earliest application for which the patent or application is entitled to claim priority. I understand that in order to claim priority to an earlier-filed patent application, that application must provide written-description support for the claimed invention.

22. I understand that a patent application provides sufficient written-description support for a claimed invention if the disclosure of the application

reasonably conveys to a POSA that the named inventors had possession of the claimed subject matter as of the application's filing date.

23. I provide my opinions regarding the '083 patent's effective filing date using these legal standards below in §VI.

B. Person of ordinary skill in the art

24. I understand that a POSA is a hypothetical person who is presumed to have known all the relevant prior art as of the effective filing date.

25. I understand that the factors that may be considered in determining the level of ordinary skill of a POSA include (i) the types of problems encountered in the art, (ii) prior art solutions to those problems, (iii) rapidity with which innovations are made, (iv) sophistication of the technology, and (v) educational level of active workers in the field. I understand that in a given case, every factor may not be present, and one or more factors may predominate.

26. I understand that a POSA is considered to be a person of ordinary creativity, not an automaton.

27. I provide my opinions regarding the level of ordinary skill for a POSA using these legal standards below in §VII.

C. Obviousness

28. I have been informed that a claim is unpatentable if the differences between the claimed invention and the prior art are such that the claimed invention

as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. For purposes of obviousness, I understand that a POSA may rely on multiple prior art references in combination.

29. I have been informed that the following four factors are considered when determining whether a patent claim would have been obvious to a POSA: (a) the level of ordinary skill in the art; (b) the scope and content of the prior art; (c) the differences between the prior art and the claim; and (d) any “secondary considerations” tending to prove nonobviousness. These secondary considerations, which are also called “objective indicia” or “objective evidence,” may include factors such as: (i) the invention’s satisfaction of a long-felt unmet need in the art; (ii) unexpected results of the invention; (iii) skepticism of the invention by experts; (iv) commercial success of an embodiment of the invention; and (vii) praise by others for the invention. I understand that there must be an adequate nexus or connection between the evidence that is the basis for an asserted secondary consideration and the scope of the invention claimed in the patent.

30. I understand that when every limitation of a claim is disclosed in the cited prior art references, the question of obviousness turns on whether a POSA would have been motivated to combine those teachings to derive the claimed subject matter with a reasonable expectation of success.

31. With respect to the reasonable expectation of success, I understand that obviousness does not require absolute predictability; only a reasonable expectation of success of achieving the claimed invention is necessary.

32. I have been informed that a claimed invention can be rendered obvious by combinations of teachings in the prior art even if there is no explicit teaching to combine them. Instead, any problem known in the field at the time of the alleged invention can provide a sufficient rationale to combine the elements of the prior art in the manner claimed in the patent.

33. In addition to the references that are cited in an asserted obviousness combination, I understand that background prior art references can legitimately serve to document the knowledge that a POSA would bring to bear in reading the prior art identified as producing obviousness.

34. I have been informed that examples of sufficient rationales for establishing obviousness include the following:

- combining prior art elements according to known methods to yield predictable results;
- substituting known elements for other known elements to obtain predictable results;
- using a known technique to improve similar devices, methods, or products in the same way;

- choosing from a finite number of identified, predictable solutions that would be obvious to try; and
- providing some teaching, suggestion, or motivation to modify the prior art reference or to combine teachings in prior art references to arrive at the claimed invention.

35. I understand that where there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations.

36. For purposes of this analysis, I understand that a prior art reference “teaches away” from a claimed invention if it criticizes, discredits, or otherwise discourages investigation into the invention claimed.

37. I understand that where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

38. I understand that an invention is obvious to try when there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions. I understand that in order for this analysis to apply, the number of solutions must be small or easily traversed in the context of

the relevant art. By contrast, I understand that an obvious-to-try analysis does not apply where it would only have been obvious (a) to vary all parameters or try every available option until one succeeds, where the prior art gave no indication of critical parameters and no direction as to which of many possibilities is likely to be successful; or (b) to explore a new technology or general approach in a seemingly promising field of experimentation, where the prior art gave only general guidance as to the particular form or method of achieving the claimed invention.

39. I provide my opinions regarding the obviousness of the challenged claims using these legal standards below in §XI. I also discuss additional legal standards in this Declaration where they are pertinent to my analysis.

V. THE '083 PATENT

A. Specification

40. I have reviewed and am familiar with the '083 patent, which is titled “Methods of treating chronic lymphocytic leukemia and small lymphocytic leukemia using a BTK inhibitor.” EX1001.

41. The specification of the '083 patent begins with a “Background of the Invention” section, which purports to describe the state of the art at the time the patent application was filed in January 2015. This section acknowledges that BTK is a “protein kinase expressed in B cells” whose physiological function “is well established” in the prior art. EX1001, 1:14-18. Citing the prior art, the

specification of the '083 patent admits that “[t]he reported role for BTK in the regulation of proliferation and apoptosis [i.e., death] of B cells indicates the potential for BTK inhibitors in the treatment of B cell lymphomas,” and “BTK inhibitors have thus been developed as potential therapies.” *Id.*, 1:28-32.

42. Like the title of the '083 patent, the specification largely focuses on methods for treating “B cell chronic lymphocytic leukemia (CLL)” (*id.*, 1:34) and “[s]mall lymphocytic leukemia (SLL)” (*id.*, 1:45). In particular, the specification of the '083 patent discloses treatments for these conditions by administering a compound of “Formula (II),” which is the name that the '083 patent uses for the compound that is known today as acalabrutinib. *E.g., id.*, 2:37-47.

43. The only recited clinical data in the '083 patent is from a study on patients with CLL. *See id.*, 7:24-61, Figs. 2-8. Notably, the '083 patent does not contain any *in vivo* or clinical data on treating MCL.

44. The specification of the '083 patent does not ascribe any particular significance to the doses used for treatment with acalabrutinib. Rather, the specification generally recognizes that “[t]he amounts of BTK inhibitors administered” may vary in “the discretion of the prescribing physician.” EX1001, 42:29-33. The '083 patent also states that “an effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day,” with a number of exemplary ranges listed that span anywhere from 1-500 mg. *Id.*, 42:33-34, 43:12-

38. As to dosing frequency, the patent states that dosing may occur as rarely as “once a month” or as often as “six times per day.” *Id.*, 42:50-62.

45. The only mention of dosing for MCL in the specification of the ’083 patent is in a list that includes 10 other conditions. *Id.*, 4:1-33. For these 11 conditions, the ’083 patent recites the administration of acalabrutinib “once daily at a dose selected from the group consisting of 100 mg, 175 mg, 250 mg, and 400 mg” or “twice daily at a dose of 100 mg.” *Id.*, 4:16-17, 4:33. No data, however, is provided for these dosing regimens to treat MCL.

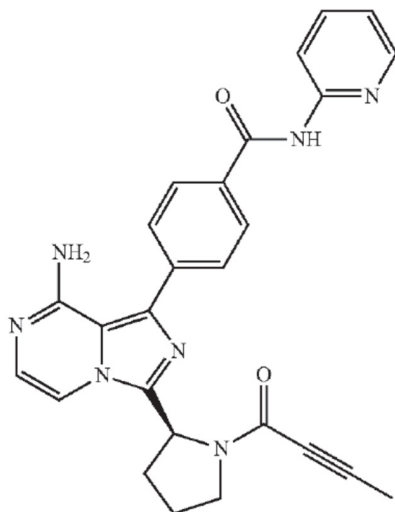
B. Claims

46. I understand that claims in a patent may be either independent or dependent. An independent claim is a standalone claim that contains all the limitations necessary to define an alleged invention, whereas a dependent claim refers to a claim previously set forth and adds additional limitations that further define the scope of that claim. Thus, a dependent claim incorporates by reference all the limitations of the claim to which it refers.

47. In this case, the ’083 patent has two independent claims: claim 1 and claim 8. Claim 1 and its dependent claims recite “treating chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL).” EX1001, 99:2-3. I have not been asked to offer, and this Declaration does not set forth, any opinions regarding the patentability of claim 1 or its dependent claims.

48. Claim 8 is the only independent claim of the '083 patent that I have been asked to address. Claim 8 is reproduced below and recites a method of treating MCL in a human by administering acalabrutinib:

8. A method of treating a mantle cell lymphoma (MCL) in a human subject suffering therefrom comprising the step of orally administering, to the human subject, a dose of 100 mg twice daily of a BTK inhibitor, wherein the BTK inhibitor is a compound of Formula (II):



or a pharmaceutically-acceptable salt, hydrate, or solvate thereof.

Id., 100:39-65.

49. In addition to claim 8, I have been asked to offer opinions regarding the patentability of claims 9-12 and 19-20, which are dependent claims that depend, directly or indirectly, from claim 8. These dependent claims exclude hydrates or solvates (claim 9), recite intended effects of certain treatment durations

(claim 10), limit MCL to certain morphologies (claim 11), add combination therapy with an anti-CD20 antibody (claim 12), require the free form of acalabrutinib (claim 19), or require a salt form (claim 20).

C. Prosecution history

50. I understand that the back-and-forth of submissions and responses between an applicant for a patent and the Patent Office is called the “prosecution history” (or sometimes “file history” or “file wrapper”) of a patent. I have reviewed the prosecution history of the ’083 patent, which is marked EX1004, and I have summarized my understanding of certain events below.

51. I understand that, when the application that ultimately issued as the ’083 patent was first filed, none of the claims as they were originally written were specific to treating MCL. *See* EX1004, 4-8. Like its issued version, claim 1 of the patent application recited a treatment for CLL/SLL. *Id.*, 4. The only other independent claim in the patent application (which was originally numbered claim 9) generally recited “[a] method of treating a hematological malignancy.” *Id.*, 5. This claim only mentioned MCL as one of 11 possible conditions in the following clause: “wherein the hematological malignancy is selected from the group consisting of non-Hodgkin’s lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), *mantle cell lymphoma (MCL)*, Hodgkin’s lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt’s lymphoma,

Waldenström’s macroglobulinemia (WM), Burkitt’s lymphoma, multiple myeloma, and myelofibrosis.” *Id.*, 6 (emphasis added). Thus, none of the claims in the original patent application were specific to treating MCL.

52. The Examiner initially rejected the proposed claims as obvious over the combination of two prior art references: U.S. Patent Application Publication No. 2013/0338172 (“Smyth ’172”) and Barf-PCT, which the Examiner called “Johannes” or “868.” EX1004, 908. The Examiner relied on Smyth ’172, which described an oral formulation of ibrutinib (another BTK inhibitor) because it “is similar to the compound of the instant claims and is used to treat similar disorders.” *Id.*, 909. The Examiner relied on Barf-PCT for the disclosure of acalabrutinib’s structure, stating (erroneously) that “[t]he compound of example 1 is identical to that of the instant claimed formula (II).” *Id.* In combining these references, the Examiner stated that “[i]t would have been obvious to include the compound of the 868 into the formulation of the 172 as the compound[s] have the same cores and treat the same conditions.” *Id.*

53. In response, the applicants amended both independent claims to recite “a human subject suffering” from the recited conditions, among other changes. *Id.*, 989, 991. For claim 9 (which I understand eventually issued as claim 8 when the claims were renumbered), the general term “hematological malignancy” was

narrowed to recite “mantle cell lymphoma (MCL).” *Id.*, 991. For both claims, the applicants added the dosing regimen, “100 mg twice daily.” *Id.*, 989-91.

54. In their remarks, the applicants revealed a reason for their newfound focus on MCL and this specific dosing regimen: On October 31, 2017, FDA approved acalabrutinib (CALQUENCE®) 100 mg twice daily to treat MCL. *Id.*, 994. Thus, the applicants stated that they were amending what was then claim 9 to specifically cover “the dosing regimen specified in the approved label for CALQUENCE®,” which was not previously claimed. *Id.*, 995.

55. In addressing the Examiner’s obviousness rejection, the applicants conceded that acalabrutinib is disclosed in Barf-PCT, but they correctly noted that this disclosure is in “Example 6,” not Example 1 as the Examiner mistakenly stated. *Id.*, 997. As for the Smyth ’172 reference regarding ibrutinib, the applicants did “not agree” that ibrutinib and acalabrutinib “have the same core or are similar compounds.” *Id.* Citing three structural differences, they argued that “[a]lthough the compounds have activity as BTK inhibitors, they are not structurally similar and, therefore, have distinct pharmacological properties.” *Id.*

56. The applicants further argued that even if ibrutinib and acalabrutinib were structurally similar, the dosing for ibrutinib in the prior art would not have led a POSA to the claimed dosing regimen for acalabrutinib. *Id.*, 998-1000. The applicants explained that ibrutinib (IMBRUVICA®) had been FDA-approved in the

prior art to treat MCL at a higher, once-daily dose of 560 mg. *Id.*, 998-99. Thus, the applicants argued that, under the Examiner’s theory that started from a patent application on ibrutinib, a POSA would not have expected success with a 100 mg twice-daily regimen in light of “the larger dose, once daily treatment for IMBRUVICA®.” *Id.*, 1000. According to the applicants, “[i]t was unexpected that acalabrutinib could be orally administered twice daily at a significantly lower dose (100 mg BID) than ibrutinib,” and a POSA “considering the ’172 application would not have expected the lower amount BID dosing of acalabrutinib to be sufficient to provide for full BTK occupancy....” *Id.*, 1002.

57. The applicants also cited certain clinical data on acalabrutinib that was not prior art but allegedly supported their view that the claimed methods of treatment provided unexpected improvements compared to the prior art. This data, however, only related to treating CLL patients. First, they cited Example 2 in the specification on treating CLL with *once*-daily acalabrutinib. *Id.*, 1000-01. Second, they cited a paper by Byrd (EX1010), which included the use of twice-daily dosing, but only in patients with “relapsed CLL.” EX1004, 1001.

58. The Examiner was unpersuaded and entered a final rejection, again citing the Smyth ’172 and Barf-PCT references along with a third reference, Evarts (U.S. Patent Application Publication No. 2014/0179673). *Id.*, 1034. The Examiner’s reliance on Barf-PCT was unchanged and included the same erroneous

citation to Example 1 (instead of Example 6) for acalabrutinib's structure. *Id.* Moreover, instead of citing Barf-PCT for acalabrutinib's dosage range (*see* EX1006, 20:24-25), the Examiner cited the Evarts reference as disclosing 100-150 mg doses for other BTK inhibitors (EX1004, 1035).

59. The applicants focused their response on alleged unexpected results. *Id.*, 1077-79. Because the Examiner continued to rely on Smyth '172 as a primary reference, they repeated that "[i]t was unexpected that acalabrutinib could be orally administered twice daily (BID) and at a significantly lower dose (100 mg BID)" than ibrutinib. *Id.*, 1077. They also provided a more detailed discussion of Byrd, which compared four once-daily cohorts (ranging 100-400 mg) to a single twice-daily cohort (100 mg) in CLL patients. *Id.*, 1078-79.

60. While acknowledging that "BTK target occupancy was complete (99 to 100%) four hours after dosing for all cohorts," the applicants pointed to a difference in the degree of BTK occupancy "immediately before administration of the next dose (at trough)." *Id.*, 1079. For once-daily cohorts, trough BTK occupancy "ranged from 87 to 95%," whereas the twice-daily cohort achieved "97% before dose administration on days 8 and 28." *Id.* The applicants argued that this difference in trough BTK occupancy was an "unexpected benefit." *Id.* Further, to contrast this result with ibrutinib, they quoted Byrd's statement that

“twice-daily dosing of ibrutinib ... may not be possible owing to the potential for drug accumulation given the ibrutinib half-life of 4 to 13 hours.” *Id.*, 1078.

61. This time, the Examiner was persuaded by the applicants’ arguments and allowed the claims to issue with the following Reasons for Allowance:

While other BTK inhibitor compounds, are known in the prior art, they differ [sic] chemically from [sic] the instant [sic] invention. Further the 100 mg, twice daily oral dosage in [sic] unexpectedly [sic] superior for BTK inhibition without increase [sic] toxicity. The closest [sic] chemical compound in the prior art is ibrutinib, but the half-life [sic] is such that a twice daily dosage would not be effective.

Id., 1382.

62. In my opinion, however, as shown below (§XI.C.1), the alleged results that led to allowance were neither unexpected nor probative, and the basis for allowance of the challenged claims was incorrect.

VI. EFFECTIVE FILING DATE

63. As I discussed above in the legal standards section, I understand that an evaluation of the patentability of a patent claim requires an understanding of the effective filing date to which the patent claim is entitled, which defines the scope of the prior art that would have been available to a POSA.

64. In my opinion, for the reasons explained below, the effective filing date of the challenged claims—i.e., the date as of which the prior art and knowledge and skill of a POSA must be assessed—is January 21, 2015.

65. I understand that the application that actually resulted in the '083 patent was filed on January 21, 2015. EX1001, 1(22). I understand that the '083 patent purports to claim priority to three provisional patent applications that were filed in 2014. *Id.*, 1(60). These are Provisional Application Nos. 61/929,742 (filed on January 21, 2014) (EX1011), 61/974,665 (filed on April 3, 2014) (EX1012), and 62/035,777 (filed on August 11, 2014) (EX1013). I have been asked to evaluate whether these provisional patent applications, which I have reviewed, provide written-description support for the claimed 100 mg twice-daily dosing regimen of acalabrutinib for treating MCL. In my opinion, they do not.

66. Provisional Application No. 61/974,665 (filed on April 3, 2014) and Provisional Application 62/035,777 (filed on August 11, 2014) both describe the treatment of lymphoma by administering a BTK inhibitor combined with a PI3K inhibitor. *See* EX1012; EX1013. Neither of these applications describes the twice-daily administration of 100 mg acalabrutinib to treat MCL, which is required by the challenged claims of the '083 patent. Thus, these provisional applications do not provide written-description support for the challenged claims.

67. Provisional Application No. 61/929,742 (January 21, 2014) is a phase I dose-escalation protocol for acalabrutinib in CLL patients. EX1011. It does not disclose a twice-daily dose of 100 mg acalabrutinib, let alone for treating MCL. On the contrary, it states that “ACP-196 [i.e., acalabrutinib] is intended to be administered orally once daily” in subjects with CLL/SLL. *Id.*, 32, 28.

68. Thus, none of the three provisional patent applications cited on the face of the '083 patent describes the treatment of MCL by administering 100 mg of acalabrutinib twice daily, as required by the challenged claims. Accordingly, it is my opinion that none of the cited provisional applications provides written-description support for the challenged claims and, as a result, the effective filing date of the '083 patent is its actual filing date, January 21, 2015.

69. Although I have used January 21, 2015, as the relevant date for evaluating the prior art and the level of ordinary skill for the '083 patent, my opinions would not materially change if the relevant date were January 21, 2014 (which is the filing date for the earliest-filed cited provisional application). This is because the grounds references that I have cited in my analysis—Barf, Cheson, and Barf-PCT—are all dated before January 21, 2014. Although I have cited certain background references that were published after January 21, 2014, and before January 21, 2015, these references are corroborative of my opinions and are not strictly necessary to my ultimate opinions of obviousness.

VII. LEVEL OF ORDINARY SKILL

70. Based on the relevant legal standard, my knowledge and expertise, and the prior art to the '083 patent, it is my opinion that a POSA as of the effective filing date would have been an oncologist with at least a medical degree (M.D.) and five years' clinical experience treating lymphomas/leukemias and/or researching treatments for them. In my opinion, this POSA would have had experience with designing, conducting, or participating in clinical trials on oncology drugs and would have been familiar with the state of the art regarding the clinical development and use of BTK inhibitors.

71. I meet this definition of a POSA today and met this definition at all times between January 21, 2015, and January 21, 2014.

VIII. CLAIM CONSTRUCTION

72. I understand that Petitioner is proposing the following claim constructions for the following claim terms. If Patent Owner proposes its own claim constructions, I reserve the right to address them.

- A. **“A method of treating a mantle cell lymphoma (MCL) in a human subject suffering therefrom comprising the step of orally administering, to the human subject” (claim 8)**

73. I understand that Petitioner has proposed that the preamble of claim 8 should be construed as limiting as to the intentional purpose for which the method must be performed, but without requiring any particular level of efficacy or result

of the intended treatment. I have been asked to assume that the preamble of claim 8 is, in fact, a limitation of the challenged claims.

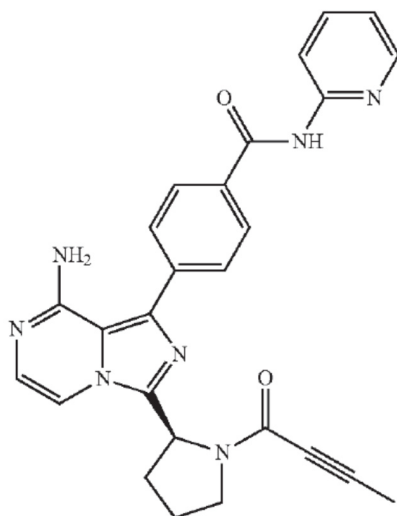
74. Beyond requiring the claimed method to be performed for the purpose (i.e., with intent) of treating MCL, however, I am not aware of any basis to import any efficacy requirement or result of the intended treatment into the claims.

Notably, as I mentioned above, the specification of the '083 does not provide any *in vivo* or clinical data showing that acalabrutinib is effective for treating MCL, let alone with the claimed dosing regimen. Thus, in my opinion, a POSA would not read the challenged claims as requiring any particular efficacy for the claimed method of treatment, but only the *intent* to treat MCL.

B. “a compound of Formula (II):...” (claims 8-9)

75. I understand that Petitioner has proposed construing the phrase “a compound of Formula (II)” that appears in claims 8 and 9 as acalabrutinib. I agree with this construction.

76. Claims 8 and 9 refer to “a compound of Formula (II)” with the structure:



EX1001, 100:43-62, 100:67-101:19.

77. During prosecution, the applicants represented that “[t]he compound of Formula (II) as specified in independent Claims 1 and 9 [which issued as claim 8] is ... acalabrutinib.” EX1004, 994. The applicants explained that now-claim 8 “specifies a method of treating mantle cell lymphoma (MCL) in a human subject by orally administering 100 mg of acalabrutinib twice daily to the subject...” *Id.*, 995. Thus, the compound of claims 8-9 is, in fact, acalabrutinib.

C. “wherein the Mantle Cell Lymphoma (MCL) increases monocytes and NK cells in peripheral blood after treatment with Formula (II) for a period selected from the group consisting of about 14 days, about 28 days, and about 56 days” (claim 10)

78. I understand that Petitioner has proposed construing the “wherein” clause in claim 10 of the ’083 patent as nonlimiting because it merely recites an inherent result. For purposes of my analysis, however, I have assumed that this

claim requires treating a patient for at least the recited durations of time. I address my opinions on the patentability of this claim below in §XI.

IX. TECHNICAL BACKGROUND

79. To understand the references cited in the grounds for obviousness, it is helpful to briefly review certain background information regarding MCL and BTK inhibitors that would have been well known to a POSA by January 2015.

80. MCL is a form of B-cell, non-Hodgkin's lymphoma ("NHL"), a cancer in which malignant cells form in the lymph system, including the lymph nodes. *See* EX1014 (Pileri), 1. B-cells are a type of white blood cell involved in the immune system. Other forms of B-cell NHL include CLL and SLL.

81. Traditionally, treatments for MCL centered on chemotherapy that is cytotoxic (i.e., that is toxic to cells). More recently, targeted anti-cancer agents have been introduced. *See* EX1008 (Cheson), 11-13. While MCL's prognosis has long been viewed as poor, by 2014, newer therapies meant that it was "no longer a hopeless disease," as therapies "dramatically improved." EX1015 (Dreyling), 1. Among the new "molecular targeted approaches" in the prior art were BTK inhibitors, which showed "durable single-agent efficacy in relapsed or refractory MCL" and "excellent tolerability." *Id.*, 10.

82. The first clinically developed BTK inhibitor was ibrutinib, which FDA approved for MCL under the brand name Imbruvica in 2013. EX1004, 998;

EX1016. As explained in Advani, which was published in 2013 and reports ibrutinib's phase I dose-finding trial: "Signaling from the B-cell antigen receptor (BCR) regulates multiple cellular processes, including proliferation, differentiation, apoptosis, and cell migration, and is essential for normal B-cell development and survival." EX1009, 7. Advani explains that "[t]he BCR pathway is implicated in the pathogenesis of several B-cell malignancies, including ... mantle-cell lymphoma." EX1009, 7. Advani also explains that BTK "is a signaling molecule positioned early within the BCR signaling cascade" and "is a uniquely attractive target for selective B-cell inhibition." *Id.*

83. Advani explains that ibrutinib is "a selective and irreversible small-molecule BTK inhibitor" with a half-maximal inhibitory concentration (IC₅₀) of 0.5 nM. *Id.* The IC₅₀ is the concentration required for 50% inhibition of the drug's maximum effect on BTK. A related concept is half-maximal *effective* concentration (EC₅₀), which for purposes of this proceeding is identical to IC₅₀ when referring to drugs whose effect is inhibition.

84. Advani reports that ibrutinib was tested at weight-based, daily doses in five cohorts of 1.25, 2.5, 5, 8.3, and 12.5 mg/kg. EX1009, 8. Advani discloses that "BTK occupancy >95% was observed in dose level cohorts II to V (2.5 to 12.5 mg/kg per day), and each of these cohorts had similar response rates, consistent with efficacy deriving from BTK inhibition." *Id.*, 12.

85. Although ibrutinib was later marketed with a 560 mg dose (EX1016), FDA recognized in its Clinical Pharmacology and Biopharmaceutics Reviews that Advani's "Phase 1 study suggested that maximum ORR [i.e., overall response rate] and maximum occupancy was achieved at doses of ≥ 2.5 mg/kg (≥ 175 mg for average weight of 70 kg)." EX1017, 5. Thus, FDA encouraged drugmakers to "consider exploring lower doses in future development programs." *Id.*, 5; *see also id.*, 10-12, 20, 55 (all endorsing lower doses of ibrutinib on this basis).

86. By January 2015, two other BTK inhibitors were in clinical use for cancer: CC-292 and ONO-4059. EX1018 (Akinleye), 3; EX1019 (Hutchinson), 4. Both had similar IC50s for BTK of < 0.5 nM and 2.2 nM, respectively. *Id.*

87. In the prior art, CC-292 was tested in clinical trials at daily doses of 750 and 1000 mg, including as divided doses of 375 and 500 mg twice daily, and the prior art suggested that twice-daily dosing "may show better nodal responses" than once-daily dosing. EX1019 (Hutchinson), 7; *see also* EX1020 (Brown), 3; EX1021 (Pierce), 2 (discussing benefits of twice-daily dosing).

88. ONO-4059 was being clinically tested in the prior art at lower doses, which ranged from 20-320 mg, and the prior art disclosed that clinical "responses have been seen at all dose levels." EX1019 (Hutchinson), 7; *see also* EX1022 (Rule), 2 (reporting clinical responses for ONO-4059 at 40, 80, 160 mg).

X. GROUNDS REFERENCES

A. Barf (EX1005)

89. I understand that Barf is prior art to the '083 patent because it is an issued patent that names another inventor and was effectively filed before the '083 patent's effective filing date. In particular, I understand that Barf claims priority to Provisional Application No. 61/509,397 (EX1007 ("Barf Provisional")), filed on July 19, 2011, which is before the '083 patent's effective filing date of January 21, 2015. EX1005, 1(60). I further understand that, for purposes of an obviousness analysis, a prior-art patent shall be considered to have been effectively filed, with respect to any subject matter described in the patent, as of the filing date of the earliest application that describes the subject matter.

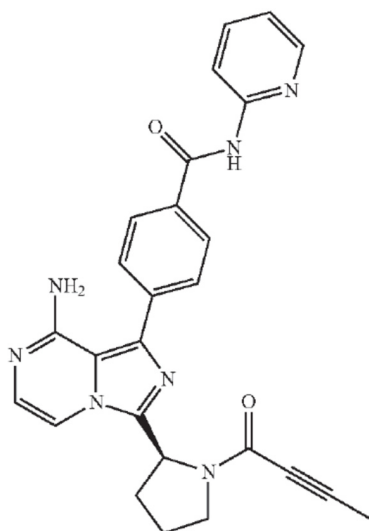
90. For purposes of determining whether the particular portions of Barf cited in my Declaration are properly cited as prior art to the challenged claims of the '083 patent, I have been asked to evaluate whether Barf Provisional (EX1007) describes the cited portions of Barf. In my opinion, every disclosure of Barf cited in this Declaration is supported by Barf Provisional. To confirm this, I have included citations to Barf Provisional (EX1007) when citing to Barf (EX1005), which shows that the same information is included in both documents.

91. As background, Barf explains that "[t]he reported role for Btk in the regulation of proliferation and apoptosis of B cells indicates there is potential for

Btk inhibitors in the treatment of B cell lymphomas.” EX1005, 2:3-6 (EX1007, 2:8-9). Barf describes a need for inhibitors that are selective for BTK because “an inhibitor that inhibits multiple or all kinases of the Src-family kinases simultaneously may cause serious adverse effects.” EX1005, 2:50-52 (EX1007, 2:38-39). To meet this need, Barf discloses “6-5 membered fused pyridine ring compounds,” “pharmaceutical compositions comprising these compounds and [] their use in therapy.” EX1005, 2:58-61 (EX1007, 3:4-5).

92. Barf has only one independent claim, which requires treating MCL in a human by administering an effective amount of acalabrutinib:

1. A method of treating Mantle Cell Lymphoma (MCL) in a human subject, the method comprising administering to the human subject a compound which is (S)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, having the structure:



or a pharmaceutically acceptable salt thereof, in an amount effective to treat the MCL in the human subject.

EX1005, 150:2-31. Claims 2 and 4 recite a pharmaceutical composition of acalabrutinib and its “oral administration.” *Id.*, 150:33-34, 150:39-41. Claim 12 narrows claim 1’s “amount effective to treat the MCL in the human subject” to the range, “0.0001-25 mg per kg body weight.” *Id.*, 151:14-16.

93. In my opinion, claims 1, 2, 4, and 12 of Barf are supported by Barf Provisional (filed in 2011) and are therefore prior art to the ’083 patent. Example 6 of Barf Provisional discloses the chemical name and structure in Barf’s claim 1 (i.e., acalabrutinib). EX1007, 37:8-11. Barf Provisional discloses that “[p]roliferative diseases that can be treated or prevented include ... mantle cell lymphoma (MCL).” *Id.*, 23:35-37. Barf Provisional discloses pharmaceutical compositions “[f]or oral administration.” *Id.*, 21:5-9. Barf Provisional discloses that “a dosage for humans preferably contains 0.0001-25 mg per kg body weight.” *Id.*, 21:37-38. Thus, in my opinion, Barf’s claims 1, 2, 4, and 12 are entitled to Barf Provisional’s filing date, July 19, 2011. I understand that this means that Barf’s claims 1, 2, 4, and 12, are prior art to the challenged claims of the ’083 patent and may be properly cited as such in my analysis.

94. As additional information, Barf's Table 1 reports the EC50 for BTK of Barf's covered compounds (which is also supported by and described in Barf Provisional as shown by the parenthetical citations to EX1007 below):

TABLE 1	
EC50 Btk activity values	
EC50	Example
≥ 1 μ M	91,
≥ 100 nM	52, 53, 54, 55, 68, 72, 74, 85, 86, 87, 88, 90, 92, 93, 94, 104
< 1 μ M	
≥ 10 nM	2, 4, 5, 7, 11, 24, 40, 41, 50, 51, 56, 57, 58, 59, 60, 69, 70, 71, 73, 80, 81, 82, 83,
< 100 nM	84, 89, 95, 96, 97, 98, 99, 103, 105, 106, 112, 113, 114, 119
< 10 nM	1, 3, 6, 8, 9, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 42, 43, 44, 45, 46, 47, 48, 49, 61, 62, 63, 64, 65, 66, 67, 75, 76, 77, 78, 79, 100, 101, 102, 107, 108, 109, 110, 111, 115, 116, 117, 118, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133

EX1005, col. 145 (EX1007, 97).

95. Example 6 (i.e., acalabrutinib) has the lowest EC50 of < 10 nM, which a POSA would understand means that it is among the most potent compounds disclosed in Barf. *Id.*; EX1005, 36:12-40 (EX1007, 37:8-11). Acalabrutinib (Example 6) also has a much higher EC50 (≥ 1 μ M) for other tested kinases (Lck, Src, FynT, and Lyn), which a POSA would understand confirms that it is highly selective for BTK. EX1005, cols. 146-49 (Tbls. 2-5) (EX1007, 98-101).

B. Barf-PCT (EX1006)

96. I understand that Barf-PCT is an international patent application publication from 2013, which makes it prior art to the '083 patent. EX1006, 1(43).

Like Barf, Barf-PCT claims priority to Barf Provisional. EX1006, 1(30). Thus, I understand that Barf and Barf-PCT share the same specification and written description; only their claims are different. EX1005; EX1006.

97. As in Barf, Example 6 of Barf-PCT discloses acalabrutinib. EX1006, 35:16-36:2. Barf-PCT discloses “[p]roliferative diseases that can be treated or prevented include ... mantle cell lymphoma (MCL).” *Id.*, 22:15-16. Barf-PCT discloses “oral administration.” *Id.*, 19:32-33. Barf-PCT discloses “a dosage for humans preferably contains 0.0001-25 mg per kg body weight.” *Id.*, 20:24-25. And Barf-PCT discloses the same EC50s for Example 6 (acalabrutinib), showing its high selectivity for BTK. *Id.*, 94-98 (Tbls. 1-5). Thus, Barf-PCT includes all the same relevant disclosures as Barf.

C. Cheson (EX1008)

98. I understand that Cheson is prior art to the '083 patent because it was published in 2013. EX1008, 1. Cheson is a supplement in the journal *Hematology & Oncology* featuring articles by several authors, including Bruce Cheson, John Gribben, and Susan O'Brien, who are highly regarded in the field on oncology and would have been well known to a POSA. I refer to the collection of articles as “Cheson,” even though I cite submissions by these different authors.

99. Cheson discloses that “[s]everal BTK inhibitors are being evaluated in clinical trials; the furthest in development is ibrutinib.” EX1008, 4. Although

“[i]brutinib is administered orally once daily,” Cheson notes that “[o]ther BTK inhibitors are being evaluated in a twice-daily schedule in an attempt to overcome the synthesis of new BTK molecules within those cells.” *Id.*

100. Specifically, Cheson discloses that “[t]he BTK inhibitor CC-292” has completed “[a] phase 1 dose-escalation study.” *Id.*, 10. Cheson states that “[a] twice-daily dosing schedule was evaluated to address the potential production of new BTK that could have occurred between daily doses,” and “twice-daily dosing appeared to be more effective, perhaps with more rapid responses.” *Id.* I discuss other noteworthy disclosures in Cheson in my analysis below.

XI. OPINIONS REGARDING OBVIOUSNESS

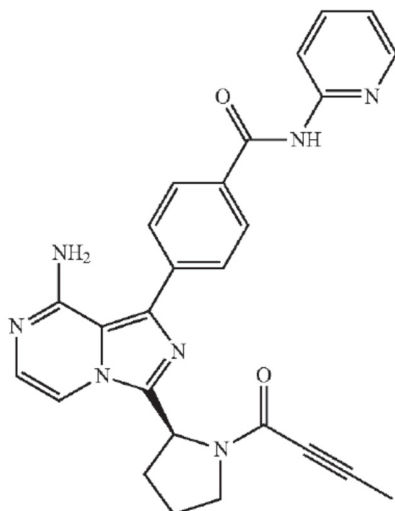
101. In my opinion, the challenged claims of the ’083 patent would have been obvious to a POSA under at least two grounds. In the first ground below, I explain how a POSA would have combined the teachings of Barf and Cheson to arrive at the challenged claims. In the second ground, I explain how a POSA would have similarly combined the teachings of Barf-PCT and Cheson. After discussing both grounds, I address the allegations of unexpected results raised in prosecution and in the specification, which in my opinion are incorrect.

A. Ground 1: Claims 8-12 and 19-20 would have been obvious over Barf and Cheson.

1. Claim 8

102. Claim 8 of the ’083 patent reads as follows:

8. A method of treating a mantle cell lymphoma (MCL) in a human subject suffering therefrom comprising the step of orally administering, to the human subject, a dose of 100 mg twice daily of a BTK inhibitor, wherein the BTK inhibitor is a compound of Formula (II):



or a pharmaceutically-acceptable salt, hydrate, or solvate thereof.

EX1001, 100:39-65.

103. In my opinion, claim 8 would have been obvious to a POSA in view of Barf and Cheson. As I explain below under headings (a) and (b), Barf expressly teaches all of claim 8's limitations except the dosing regimen of 100 mg twice daily. As I explain under heading (c), however, this claimed dosing regimen would have been obvious to a POSA in view of the combination of Barf and Cheson, as supported by the background knowledge and skill of a POSA.

a. “A method of treating a mantle cell lymphoma (MCL) in a human subject suffering therefrom comprising the step of”

104. As I explained above, I understand that the preamble of claim 8 is a limitation that must be disclosed in the prior art to render the claim obvious, but it does not require any particular level of efficacy in treating MCL. In my opinion, Barf discloses and renders this preamble obvious.

105. Barf’s claim 1, which is prior art for the reasons that I explained above, expressly recites “[a] method of treating Mantle Cell Lymphoma (MCL) in a human subject.” EX1005, 150:2-4; *supra* §X.A.

106. Thus, Barf discloses and renders obvious the preamble in claim 8 of the ’083 patent—i.e., “[a] method of treating a mantle cell lymphoma (MCL) in a human subject suffering therefrom...”

b. “orally administering, to the human subject, ... a BTK inhibitor, wherein the BTK inhibitor is a compound of Formula (II) ... or a pharmaceutically-acceptable salt, hydrate, or solvate thereof.”

107. Barf also discloses and renders obvious the next limitation of claim 8. I understand that because this clause requires acalabrutinib “*or* a pharmaceutically-acceptable salt, hydrate, or solvate thereof,” it is satisfied by either a disclosure of acalabrutinib or any of the other forms of that compound recited in the claim.

108. Barf’s claim 1 discloses that the recited method of treating MCL comprises “administering to the human subject a compound which is”

acalabrutinib (i.e., the same structure in claim 8 of the '083 patent) “or a pharmaceutically acceptable salt thereof.” EX1005, 150:4-30.

109. Barf’s claim 4 narrows claim 1 by requiring “oral administration.” EX1005, 150:39-41. Oral administration also would have been obvious to a POSA as the most convenient route of administration and was used exclusively for the only three BTK inhibitors in clinical use for oncology in the prior art—i.e., ibrutinib, CC-292, and ONO-4059. EX1009, 7; EX1020, 2; EX1022, 1.

110. Thus, Barf’s claims 1 and 4 disclose the limitation in claim 8 of the '083 patent that requires “orally administering, to the human subject, ... a BTK inhibitor, wherein the BTK inhibitor is a compound of Formula (II) ... or a pharmaceutically-acceptable salt, hydrate, or solvate thereof.”

111. Accordingly, Barf’s claims 1 and 4 meet every limitation in claim 8 of the '083 patent except “a dose of 100 mg twice daily.” I have illustrated this below by comparing these claims below and highlighting their equivalent limitations:

'083 patent claim 8	Barf claims 1, 4 (prior art)
<p>8. A method of treating a mantle cell lymphoma (MCL) in a human subject suffering therefrom comprising the step of orally administering, to the human subject, a dose of 100 mg twice daily of a BTK inhibitor, wherein the BTK inhibitor is a compound of Formula (II):</p> <div data-bbox="228 1115 581 1541"> </div> <p>or a pharmaceutically-acceptable salt, hydrate, or solvate thereof.</p>	<p>1. A method of treating Mantle Cell Lymphoma (MCL) in a human subject, the method comprising administering to the human subject a compound which is (S)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, having the structure:</p> <div data-bbox="842 732 1188 1188"> </div> <p>or a pharmaceutically acceptable salt thereof, in an amount effective to treat the MCL in the human subject.</p> <p>2. The method of claim 1, wherein the compound is present in a pharmaceutical composition.</p> <p>4. The method of claim 2, wherein the pharmaceutical composition is administered to the human subject by oral administration.</p>

c. “a dose of 100 mg twice daily”

112. In my opinion, the dosing regimen recited in claim 8 of the '083 patent—“a dose of 100 mg twice daily” of acalabrutinib—would have been obvious to a POSA in view of Barf and Cheson. Below, in section (i), I address the obviousness of administering a dose of 100 mg acalabrutinib. In section (ii), I address the obviousness of administering this dose twice a day.

i. A 100 mg dose would have been obvious.

113. In my opinion, the claimed 100 mg dose would have been obvious for two related, but independent, reasons. First, this dose falls within a range disclosed by Barf, and additional information in Barf and other prior art would have guided a POSA toward this claimed dose within Barf's range. Second, a POSA would have arrived at the claimed 100 mg dose through routine experimentation by conducting a dose-finding study focused on selecting the lowest dose that achieves maximal BTK occupancy. I discuss both these opinions in the subsections that follow.

(1) Barf discloses and claims a range that encompasses the claimed dose.

114. Barf's claim 12 depends from claim 1 of Barf and specifies that the “amount effective to treat the MCL” is “0.0001-25 mg per kg body weight.” EX1005, 150:30-31, 151:14-16. As I discussed above, I understand that claim 12 of Barf is prior art to the '083 patent because the dosing range that it recites is

described in Barf Provisional—i.e., the patent application to which Barf claims priority and that was filed in 2011. *See* EX1007, 21:37-38; *supra* §X.A.

115. The dosing range in Barf provides what are known as weight-based doses, which vary based on the weight of the patient. In my opinion, a POSA developing a drug like acalabrutinib for oral administration would have been motivated to convert this weight-based range to a range of fixed doses, which were widely preferred for oral drugs. Fixed dosing is far more convenient for patients and physicians. By simplifying administration of oral drugs, fixed dosing leads to less errors in following a dosing regimen. Moreover, with fixed doses, drugmakers can generally provide fewer pill sizes, which is also more efficient.

116. These and other benefits of fixed dosing for oral drugs were well recognized in the prior art and would have been well known to a POSA. For example, a review from 2008 by Levêque explains that “trials of agents given orally were mainly conducted with a fixed dose,” which “is far more convenient than that adjusted to body size” and can “reduce medication errors.” EX1037 (Levêque), 2. Indeed, almost all oral chemotherapies are administered as fixed doses. Moreover, Levêque posits that “it has never been proven that dosing of anticancer drugs according to ... body weight leads to improvement of therapeutic outcomes in adult patients when compared to fixed dosing.” *Id.*, 3. Levêque

explains that this is especially true for “targeted therapies” like Tyrosine Kinase inhibitors, which are all “administered at a fixed dose.” *Id.*

117. Indeed, a POSA would have known that while ibrutinib was initially tested using weight-bases doses (as reported in Advani (EX1009, 7)), FDA approved ibrutinib at a fixed dose (EX1016). The second-generation BTK inhibitors that were being clinically tested in the prior art, CC-292 and ONO-4059, were also being tested as oral agents at fixed doses, not weight-based doses. *See* EX1019 (Hutchinson), 7 (CC-292 tested at fixed doses of 1000 mg once daily, 375 mg twice daily, and 500 mg twice daily; ONO-4059 tested at fixed doses of 20-320 mg). Thus, a POSA practicing the dosage range in Barf would have started by converting the weight-based doses to a range of fixed doses.

118. For converting weight-based doses, a standard assumption in the prior art (and today) is an average human weight of 70 kg. For example, in FDA’s Clinical Pharmacology and Biopharmaceutics Reviews for ibrutinib, which are dated 2013 and 2014, FDA used an average weight of 70 kg to convert the weight-based doses in Advani to fixed doses. EX1017, 5, 20. Based on this standard assumption of 70 kg, Barf’s dosing range translates to a fixed dose of 0.007-1750 mg, which includes the ’083 patent’s claimed dose of 100 mg (as well as the daily dose of 200 mg when administered twice daily). This remains true if other common weight conversions are used, such as 60 kg (0.006-1500 mg) or 80 kg

(0.008-2000 mg). Thus, no matter which weight is used for an average human (e.g., 60 kg, 70 kg, or 80 kg), a POSA would have recognized that both a 100 mg single dose and 200 mg total daily dose falls within the dosing range that is disclosed for acalabrutinib in claim 12 of Barf.

119. I have been informed by counsel for Petitioner that when there is a range disclosed in the prior art, and the claimed invention is a value that falls within that range, there is a presumption of obviousness. Under this presumption, the burden of production falls upon the patentee to come forward with evidence of teaching away, unexpected results, or other pertinent objective indicia indicating that the claimed value would not have been obvious.

120. Here, I am not aware of any teaching away from the claimed 100 mg dose (or 200 mg daily), any unexpected results of this dosing regimen, or any other pertinent objective indicia of nonobviousness. Although the applicants alleged unexpected results during prosecution of the '083 patent, in my opinion the alleged results were neither probative nor unexpected, as explained below in §XI.C.1. To the extent that Patent Owner or its expert(s) attempt to assert any teaching away or objective indicia of nonobviousness, I reserve the right to respond. Absent such evidence, however, I understand that the overlap between Barf's dosing range and the claimed dose is sufficient to render the claimed dose obvious.

121. Although I understand that the presumption of obviousness is sufficient to render the claimed dose obvious, additional information about other BTK inhibitors in the prior art would have narrowed the range of possibilities in Barf and steered a POSA toward a 100 mg dose. I note that FDA’s 2013 Good Review Practice for Clinical Review of Investigational New Drug Applications provides that “[c]omparisons of an investigational drug’s potency and activity with that of other well-characterized drugs of the same class may also be useful in determining the starting dose.” EX1024, 14. Thus, a POSA would have turned to the available clinical data in the prior art on other BTK inhibitors to help determine the starting dose for a new BTK inhibitor such as acalabrutinib.

122. In this case, by January 2015, a POSA would have known that three irreversible BTK inhibitors had been clinically tested for treating cancers: ibrutinib, CC-292, and ONO-4059. *See* EX1019 (Hutchinson), 2, 4, Tbl. 1; EX1018 (Akinleye), 3, Tbl. 1. As shown below, the prior art reported the following EC50s for BTK inhibition for each of these compounds and the following dosing ranges that produced clinical responses:

Compound	EC50 (BTK)	Effective dosing range
Ibrutinib	0.5 nM	Maximal BTK occupancy and responses seen at doses from 2.5-12.5 mg/kg (175-875 mg for 70 kg). EX1009 (Advani), 9-12.

CC-292	<0.5 nM	Responses seen at 750-1000 mg once-daily and 375-500 mg twice-daily. EX1019 (Hutchinson), 7.
ONO-4059	2.2 nM	Responses seen at 20-320 mg. <i>Id.</i>

123. As shown above, the only three BTK inhibitors that had been clinically tested for leukemia/lymphoma in the prior art were successfully used at doses ranging from 20-1000 mg, which falls within Barf's broader range for acalabrutinib. Moreover, a POSA would have known that these compounds have the same biological target (BTK) and an inhibitory potency within the range reported for acalabrutinib in Barf (<10 nM). EX1005, 36:12-40 (EX1007, 37:8-11). Thus, in my opinion, a POSA testing acalabrutinib based on Barf's dosing range would have started by investigating doses within this narrowed dosing range of 20-1000 mg that was clinically used in the prior art, which encompasses the claimed 100 mg single dose as well as a 200 mg total daily dose.

124. This narrowed range is consistent with Barf's own teachings, which would have funneled a POSA away from both the highest and lowest ends of Barf's broader range and toward the effective dosing range of 20-1000 mg that had been used successfully with other known BTK inhibitors. First, Barf teaches that acalabrutinib (Example 6) is among the most potent compounds disclosed in Barf for inhibiting BTK, with a relatively low EC50 of <10 nM. EX1005, 36:12-40

(EX1007, 37:8-11). By contrast, multiple other compounds in Barf had much higher EC50s, below 100 nM or 1 μ M. EX1005, col. 145 (Tbl. 1) (EX1007, 97); EX1005, 36:12-40 (EX1007, 37:8-11). Thus, a POSA would have assumed that the highest end of Barf's range was intended for less potent compounds with higher EC50s. This would have led a POSA to deprioritize this highest end of Barf's range (e.g., >1000 mg) when testing acalabrutinib.

125. Second, Barf teaches that, “[i]n general[,] parenteral [i.e., non-oral] administration requires lower dosages than other methods of administration which are more dependent upon absorption.” EX1005, 17:60-63 (EX1007, 21:36-37). A POSA would have understood that some amount of drug may be lost (i.e., not absorbed) when administered orally, thus requiring higher doses than intravenous administration, which delivers the drug directly into the bloodstream. This is very common for orally administered drugs and is the main reason why doses for intravenous administration tend to be significantly lower than oral doses. Based on this guidance in Barf, which would have been well known to a POSA, the POSA would have assumed that the lowest end of Barf's range (e.g., <20 mg) was intended for intravenous or other parenteral administration. Thus, the guidance in Barf itself is consistent with the 20-1000 mg range reported in the prior art for other BTK inhibitors (i.e., ibrutinib, CC-292, and ONO-4059).

126. In short, Barf's guidance and the reported data on other BTK inhibitors in the prior art would have led a POSA to investigate doses ranging from 20-1000 mg, which fell within Barf's disclosed range and triggers a presumption of obviousness. Thus, absent any probative secondary considerations (of which I am not aware), the claimed 100 mg dose would have been obvious.

(2) A POSA practicing Barf would have arrived at a 100 mg dose by conducting a routine dose-finding study.

127. As an independent basis for concluding that the claimed dose would have been obvious, it is also my opinion that a POSA practicing Barf's method of treating MCL with acalabrutinib would have arrived at the claimed dose through routine experimentation by conducting a dose-finding study based on FDA guidance. Indeed, as I explain below, guidance by FDA and other sources in the prior art would have provided a roadmap for a POSA to determine optimal doses of a new BTK inhibitor like acalabrutinib.

128. As an initial matter, dose-finding studies have long been routine in the pharmaceutical industry, and BTK inhibitors are no exception. For example, a patent issued in 2010 to Verner and assigned to Pharmacyclics (the maker of ibrutinib), which is titled "Inhibitors of Bruton's Tyrosine Kinase," acknowledges that "therapeutically effective amounts [of a BTK inhibitor] may be determined by routine experimentation, including but not limited to a dose escalation clinical

trial.” EX1025 (Verner), 24:41-43. Thus, the prior art expressly teaches that “routine experimentation” in the form of “a dose escalation clinical trial” could reliably be used to determine suitable doses of BTK inhibitors.

129. Since at least 1994, FDA has issued guidelines to the drug industry for designing dose-response trials, which FDA has advised “help identify an appropriate starting dose.” EX1026, 1. FDA has advised that such trials “should be an integral component of drug development” and “can usually be accomplished with no loss of time and minimal extra effort” when compared to the time and effort that may be lost in later clinical trials when an adequate range of dosing options has not been studied at the outset of development. *Id.*, 2.

130. FDA’s 2013 Good Review Practice similarly recognizes that “[m]ost phase 1 clinical trials are characterized by progressive dose escalation with sponsors collecting safety information on each dose experience.” EX1024 (FDA Good Review Practice), 20. For safety reasons, following FDA’s guidance, a POSA would have followed the standard procedure of selecting “a low starting dose” and practiced “cautious dose escalation.” *Id.*, 21.

131. In particular, applying standard FDA guidelines, a POSA would have calculated a safe starting dose for a new drug like acalabrutinib by using preclinical toxicology studies and animal-to-human conversion tables. For example, in March 2010, FDA issued its “S9 Nonclinical Evaluation for Anticancer Pharmaceuticals,”

whose purpose “is to provide information to assist in the design of an appropriate program of nonclinical studies for the development of anticancer pharmaceuticals.”

EX1027, 4. As explained in this guidance, “nonclinical studies can facilitate dose selection, schedule, and escalation during Phase 1 studies.” *Id.*, 7.

132. Another key FDA guidance in the prior art is “Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers,” which was published in July 2005 and is referred to as the “MSSD” Guidance. EX1028. The MSSD Guidance outlines procedures “for deriving the maximum recommended starting dose (MRSD) for first-in-human clinical trials,” including “calculations used to generate the MRSD from animal data.” EX1028, 4.

133. A POSA would have turned to these standard guidelines to design and conduct preclinical toxicology studies on acalabrutinib, which a POSA would have used to derive first-in-human doses for a phase I clinical trial.

134. Once a suitable starting dose was determined through routine animal studies, a POSA would have conducted a phase I dose-escalation trial, in which the starting dose is gradually titrated upwards in humans. For a targeted therapy such as a BTK inhibitor, it would have been routine and obvious to seek the optimal biological dose. Specifically, a POSA would have been motivated to titrate up to the lowest dose of acalabrutinib that provides maximal BTK occupancy. This was

obvious based on Cheson, which teaches that, for a BTK inhibitor, “use of a dose that attains full occupancy appears to be important for obtaining maximal antitumor activity.” EX1008, 7. This guidance in Cheson was corroborated by the design of clinical trials for other BTK inhibitors in the prior art. As discussed below, a POSA would have known that BTK occupancy was used to evaluate doses in clinical trials for both ibrutinib and CC-292. EX1009, 12; EX1029, 1.

135. For example, in Advani (the phase I clinical trial for ibrutinib), the investigators utilized a “probe for BTK measuring active-site occupancy” during the trial, which “allows for dose escalation based ... on an optimal biologic dose, where target binding could be demonstrated.” EX1009 (Advani), 12. Similarly, BTK occupancy took a central role in determining doses for CC-292, as reported by Evans in 2013 (EX1029). Evans reports that the investigators for CC-292 at Celgene used a probe for measuring BTK occupancy in finding the optimal biological dose. EX1029, 3-4. Evans explains that “measurement of Btk occupancy can serve as a robust surrogate measurement of Btk kinase inhibition that correlates with inhibition of BCR signaling and its functional consequences,” and “there was a strong correlation between the concentration of CC-292 required for Btk occupancy, inhibition of BCR signaling, and consequent functions such as B cell proliferation.” *Id.*, 4-6. Evans concludes that “[t]he rapid identification of doses providing Btk target engagement provides an advantage in the design of

subsequent human clinical trials and supports Phase 2 dose selection to incorporate safety, tolerability, and on-target activity.” *Id.*, 8. Moreover, “direct quantification of Btk engagement in these trials will reduce uncertainty about the dose required for target inhibition and enable selection of the optimal pharmacological dose and dosing schedule.” *Id.* Further, Evans explains that this biological focus on BTK occupancy “has provided new opportunity for rapid and rational dose selections that will ultimately maximize patient benefit in clinical testing.” *Id.*, 9.

136. Thus, based on (i) Cheson’s teaching that the “use of a dose that attains full occupancy appears to be important for obtaining maximal antitumor activity” (EX1008, 7); and (ii) the corroborative experience in the prior art with both first- and second-generation BTK inhibitors (ibrutinib and CC-292), a POSA would have been motivated to select the lowest non-toxic dose of acalabrutinib that achieves maximal BTK occupancy for clinical development.

137. In contrast, a POSA would not have simply escalated the dose of acalabrutinib up to the maximum tolerated dose (“MTD”). Although this was the more traditional approach for cytotoxic (i.e., cell-killing) chemotherapy, it has effectively been superseded by seeking the optimal biological dose. As explained in Barf 2012, when testing traditional chemotherapies, “patients are treated with increasing doses of the drug until dose limiting toxicity is observed.” EX1030 (Barf 2012), 14. This is known as the MTD. *See, e.g.*, EX1031 (Mahipal), 2. By

2014, however, the industry had shifted away from exclusively seeking the MTD, particularly with “targeted agents” (such as BTK inhibitors), for which Mahipal recognized that “the biologically effective dose is now frequently used rather than the MTD.” *Id.* Specifically, for BTK inhibitors, Barf 2012 confirms that “a modest excess of exposure with respect to the dose where full target occupancy is observed should be more than sufficient.” EX1030 (Barf 2012), 14. Moreover, Barf 2012 indicates that, “[c]learly, one should be able to design and synthesize suitable probes for diagnosis and target occupancy purposes with modest efforts.” *Id.* Thus, Barf 2012 and Mahipal confirm that evaluating BTK occupancy in a dose-finding trial would have been obvious and routine to a POSA.

138. As additional corroboration for my opinion, FDA specifically endorsed the approach of basing a clinical dose on maximal BTK occupancy in the prior art. In the Clinical Pharmacology and Biopharmaceutics Reviews for ibrutinib, dated in 2013 and 2014, FDA’s reviewers remarked that the lowest dose of ibrutinib with “maximum BTK occupancy and maximum response” is “likely [to] be efficacious.” EX1017, 10. Although ibrutinib was ultimately marketed at a higher dose, FDA encouraged “exploring lower doses in future development programs.” *Id.*, 5; *see also id.*, 11-12, 20, 55 (all encouraging lower doses for the same reason). That is consistent with FDA’s longstanding recognition in its 1994 dose-response guidance that “drugs have often been initially marketed at what

were later recognized as excessive doses.” EX1026, 2. Thus, while ibrutinib was marketed at a higher dose than was necessary to achieve full BTK occupancy, it would have been obvious to use the lowest dose that achieved such occupancy for a new BTK inhibitor such as acalabrutinib.

139. There were many well-recognized reasons in the prior art for a POSA to favor lower doses that were equally efficacious as higher doses. For example, a POSA would generally expect lower doses to provide reduced side effects, lower risk of drug-drug interactions, reduced costs, and pills that are easier to swallow for the patient and easier to formulate for the drugmaker.

140. In my opinion, the obvious and FDA-endorsed approach of selecting the lowest dose that provides maximal BTK occupancy would have led a POSA directly to the 100 mg dose of acalabrutinib that is claimed in the '083 patent. I note that in the actual dose-finding study for acalabrutinib, reported in Byrd, “BTK occupancy was complete (99 to 100%)” at the starting dose of 100 mg. EX1010 (Byrd), 5. Moreover, the phase I protocol for acalabrutinib, which is reported in Provisional Application No. 61/929,742, admits that the starting dose of 100 mg used in Byrd was determined by following FDA’s published guidelines in the prior art and conducting “[s]tandard” preclinical studies:

The starting ACP-196 dose of 100 mg was selected based on Food and Drug Administration (FDA) Guidances: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult

Healthy Volunteers (MSSD), and Nonclinical Evaluation for Anticancer Pharmaceuticals (ICH S9) (FDA 2005 and 2010).

Standard GLP 28-day nonclinical systemic toxicity studies in rats and dogs were conducted in support of this trial.... [In rats], the 100 mg/kg/day was selected to conservatively represent the HNSTD [highest non-severely toxic dose]. Following the S9 guidance and using conversion factors from the MSSD guidance, the conversion factor for mg/kg to mg/m² for rodents is 6, which converts to 600 mg/m² in rats. The starting human dose for oncology would be one-tenth the HNSTD, 60 mg/m², or approximately 100 mg for a 60-kg subject with a body surface area of 1.6 m².

EX1011, 28 (emphasis added).

141. To be clear, I understand that acalabrutinib's phase-I trial protocol and results are not prior art, and I have not used them to determine what would have been obvious to a POSA. I understand, however, that post-filing evidence can be used to confirm that routine experimentation would have led a POSA to the claimed dose. Here, it is my opinion that a POSA would have used the S9 and MSSD guidelines published by FDA in the prior art to conduct standard preclinical studies and to derive a starting dose for acalabrutinib based on those standard guidelines. *See* EX1027; EX1028. Byrd and the protocol for acalabrutinib's phase I trial simply confirm that if a POSA had taken this obvious path based on the teachings of the prior art, the POSA would have been led directly to the claimed 100 mg dose, and routine testing for BTK occupancy during a phase I trial would

have confirmed that this 100 mg dose was optimal. Accordingly, because the claimed dose for acalabrutinib was, in fact, determined through routine experimentation, it would have been obvious to a POSA.

142. To the extent that Patent Owner or its expert(s) argue that a POSA would have escalated the dose of acalabrutinib all the way up to its MTD, I disagree for the reasons stated above. Even if this were true, however, the claimed 100 mg dose would *still* be obvious as the starting dose for a phase I clinical trial, as determined by standard preclinical procedures and conversions using the S9 and MSSD guidelines from FDA. Since claim 8 of the '083 patent only requires administering the claimed dose of acalabrutinib to at least one “human subject,” I understand that the act of conducting a phase I clinical trial would be sufficient to practice the claimed method of treatment. Thus, merely by conducting a dose-escalation study that *includes* the 100 mg starting dose, a POSA would be practicing the claimed dose in at least one “human subject,” which is all the claimed method requires. Because it was at least obvious to *include* the 100 mg dose in a phase I clinical trial (even if a POSA had continued escalating up to a higher dose), the claimed dose would have been obvious to a POSA.

ii. Twice-daily dosing would have been obvious.

143. In my opinion, the claimed twice-daily dosing frequency also would have been obvious. Indeed, one of the first considerations for a POSA conducting

a dose-finding study would have been the frequency of dosing. As relevant to this issue, Barf teaches that doses within its disclosed range “may be presented as one dose or multiple subdoses administered at appropriate intervals throughout the day.” EX1005, 17:63-66 (EX1007, 21:38-39). Thus, Barf’s guidance for dosing acalabrutinib encompasses twice-daily administration.

144. More specifically, twice-daily dosing of a BTK inhibitor is expressly disclosed in Cheson, which teaches both (i) a theory for using twice-daily dosing based on the resynthesis of BTK throughout the day; and (ii) the fact that clinical studies had reported superior responses with twice-daily dosing compared to once-daily dosing. On the first issue, Cheson states that “BTK inhibitors are being evaluated in a twice-daily schedule in an attempt to overcome the synthesis of new BTK molecules within those cells.” EX1008, 4. On the second issue, Cheson states that, for CC-292, “[a] twice-daily dosing schedule was evaluated to address the potential production of new BTK that could have occurred between daily doses,” and this strategy had already seen promising results: “In early follow-up, twice-daily dosing appeared to be more effective, perhaps with more rapid responses,” while remaining “well tolerated.” *Id.*, 10. Thus, based on Cheson (as corroborated by other information discussed below), a POSA practicing Barf would have been motivated to administer acalabrutinib twice daily.

145. Corroborating Cheson's statements, the same rationales and results had been reported in other publications in the prior art, which confirmed that CC-292 was being tested twice daily, in part to counteract the potential for BTK's resynthesis during the day. For example, Brumskill stated: "The half-life of CC-292 is 2 h and BTK resynthesis occurs after 12 h, therefore b.i.d. dosing maintains BTK inhibition." EX1032 (Brumskill), 3. Moreover, the prior art reported that twice-daily dosing produced promising results. For example, Brown reported phase I results for CC-292 and showed that patients dosed "BID showed continued lymph node size reduction over time." EX1020 (Brown), 3. In a follow-up analysis, Pierce found that these results were superior in patients who received twice-daily dosing, noting that "residual free Btk levels were lower with the BID schedule, offering a rationale for an early trend towards more rapid nodal responses, lymphocytosis, and partial responses." EX1021 (Pierce), 2. This was also expressly reported in Hutchinson, which noted that "[d]ata with AVL-292/CC-292 ... twice daily dosing suggests improved nodal responses." EX1019 (Hutchinson), 4. Thus, the prior art suggested that twice-daily dosing for CC-292 was producing superior clinical responses to once-daily dosing, and also offered a theory for these superior responses based on the resynthesis of BTK.

146. The prior art reported that ONO-4059 had also been tested twice-daily preclinically to prolong BTK inhibition. EX1033. Yoshizawa "hypothesized that

the efficacy of ONO-4059 could be further enhanced by increasing the drug trough concentration”—i.e., the drug’s blood levels before the next dose is administered—using twice-daily dosing. *Id.*, 1. Based on the reported preclinical results, Yoshizawa concluded that “a more frequent dosing regimen such as BD [twice-daily] may be a more effective treatment” than once-daily dosing that “warrants further investigation in the clinical setting.” *Id.*, 2.

147. Accordingly, twice-daily dosing was expressly suggested in the prior art for both of the second-generation BTK inhibitors that were in clinical development for cancers (i.e., both CC-292 and ONO-4059).

148. In my opinion, these results would have motivated a POSA to include a twice-daily administration cohort in a dose-finding study for acalabrutinib, both to ensure inhibition of BTK synthesized during the day and to test whether superior BTK occupancy and responses could be obtained. Because both of the second-generation BTK inhibitors being tested for cancers at the time—CC-292 and ONO-4059—showed promising results with twice-daily dosing, a POSA would have viewed any dose-finding study for acalabrutinib limited to once-daily administration as incomplete for failing to include a regimen that could result in more continuous BTK inhibition. Thus, in my opinion, a POSA would have included a twice-daily cohort in a dose-finding study for acalabrutinib.

149. Investigating twice-daily administration for a new targeted oncology drug like acalabrutinib would have been routine and uncontroversial to a POSA as of January 2015. Notably, many targeted oncology therapies that were FDA-approved in the prior art were dosed twice daily, as shown by their FDA-approved labeling—for example, idelalisb (EX1038), nilotinib (EX1039), ruxolitinib (EX1040), and olaparib (EX1041).

150. Moreover, FDA’s 1994 dose-response guidance teaches that drugmakers should consider “a comparison of [a] long dose interval regimen with the same dose in a more divided regimen, looking, where this is feasible, for persistence of desired effect throughout the dose interval and for adverse effects associated with blood level peaks.” EX1026, 2. Likewise, FDA’s 2013 Good Review Practice guidance teaches that “less frequent dosing than is indicated by the pharmacokinetics of the drug can lead to diminished drug efficacy near the end of the dosing interval.” EX1024, 26.

151. These guidelines would have been consistent with a POSA’s understanding that administering a given amount of drug as a single daily dose results in higher peak plasma levels and lower trough levels than the same amount divided into two doses, which provides more consistent plasma drug concentration. Having more consistent plasma drug concentration through twice-daily dosing avoids both excessive peak concentrations (likely to cause adverse effects) and

sub-optimal trough concentrations (insufficient for therapeutic benefit). A POSA would have been motivated to investigate twice-daily dosing to avoid this possibility, especially if acalabrutinib turned out to have a short half-life, which was seen with CC-292 and would be routinely determined as one of the first steps in drug development. *See* EX1032 (Brumskill), 3 (“The half-life of CC-292 is 2 h and BTK resynthesis occurs after 12 h, therefore b.i.d. dosing maintains BTK inhibition.”); EX1024 (FDA Good Review Practice), 26.

152. Relatedly, twice-daily dosing would have been obvious to account for potential rapid metabolizers of the drug, for whom blood levels would become depleted more quickly after initial administration. Given the interpatient variability seen with many drugs, a POSA would have viewed investigating twice-daily dosing in addition to once-daily dosing as logical and obvious.

153. At a minimum, twice-daily dosing would have been obvious to try. I understand that an invention is obvious to try when there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions. In this case, the problem to solve was the frequency of dosing for a new BTK inhibitor, and the number of identified, predictable solutions was very small: dosing would either be once a day or twice a day.

154. Notably, the only three irreversible BTK inhibitors with clinical data reported for lymphoma/leukemia in the prior art (ibrutinib, CC-292, ONO-4059)

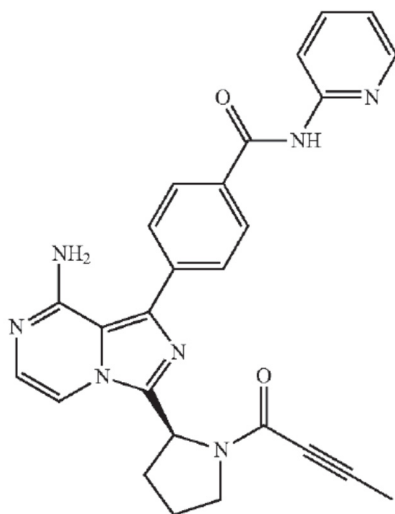
were dosed only once or twice daily. Ibrutinib—developed first and without the benefit of promising data on CC-292 and ONO-4059—was tested once-daily. EX1009 (Advani), 7. As discussed above, CC-292 was tested once and twice daily, and twice daily provided better results. EX1008 (Cheson), 10; EX1021 (Pierce), 2; EX1019 (Hutchinson), 7. ONO-4059 was tested once-daily, but a preclinical study on twice-daily dosing suggested “further investigation in the clinical setting.” EX1033 (Yoshizawa), 2. Moreover, FDA discouraged more frequent administration (e.g., three time a day) due to compliance concerns: The 2013 Good Review Practice stated that “[d]osing more often than twice per day appears to lead to poorer patient compliance and is unattractive to patients.” EX1024, 26. Thus, there were only two reasonable options: once and twice daily, which is a finite number of identified, predictable solutions. Out of these limited options (just two), twice-daily dosing was obvious to try.

155. Accordingly, it is my opinion that a POSA would have arrived at the claimed dosing regimen of 100 mg acalabrutinib twice daily by following the guidance in the prior art, rendering claim 8 as a whole obvious to a POSA over the combined teachings of Barf and Cheson.

2. Claim 9

156. Claim 9 depends from claim 8 and reads:

9. The method of claim 8, wherein the BTK inhibitor is a compound of Formula (II):



or a pharmaceutically acceptable salt thereof.

157. The only difference between claim 8 and claim 9 is that claim 8 limits the BTK inhibitor to acalabrutinib “or a pharmaceutically acceptable salt thereof,” which narrows the scope of claim 8 by omitting hydrates and solvates of acalabrutinib as possible compounds (which are included in claim 8).

158. Claim 9 would have been obvious to a POSA for the same reasons that I discussed above for claim 8. Barf discloses and claims acalabrutinib and its pharmaceutically acceptable salt. EX1005, 150:2-31 (EX1007, 37:8-11). All of my opinions above for claim 8 apply to acalabrutinib, which is also within the scope of claim 9. Thus, for the same reasons as claim 8, it is my opinion that claim 9 would have been obvious to a POSA over Barf and Cheson.

3. Claim 10

159. Claim 10 depends from claim 9 and reads: “10. The method of claim 9, wherein the Mantle Cell Lymphoma (MCL) increases monocytes and NK cells in peripheral blood after treatment with Formula (II) for a period selected from the group consisting of about 14 days, about 28 days, and about 56 days.”

160. As I noted above, I understand that Petitioner has proposed that the “wherein” clause in claim 9 should be construed as lacking any patentable weight because it merely recites an intended result and not any new treatment steps.

161. To the extent that claim 10 is construed as requiring the administration of acalabrutinib for the durations recited in the claim, it is my opinion that this would have been obvious to a POSA in view of Cheson, which teaches that the BTK inhibitor ibrutinib was clinically administered for at least “26 months” in a clinical trial, encompassing all recited durations. EX1008, 9; *see also id.*, 10 (reciting 24 months’ administration in Fig. 6), 14 (reciting 24 months’ administration in Fig. 8 and noting that the “response rate appeared to improve ... beyond 12 months”). Similarly, it was reported in the prior art that CC-292 had been clinically tested in 28-day cycles. EX1020 (Brown), 2.

162. Moreover, MCL is considered incurable, so in my opinion a POSA would have continued administering a BTK inhibitor indefinitely, and certainly for at least or longer than 14 days. *See* EX1014 (Pileri), 2 (noting that MCL is

considered incurable). Indefinite administration of a BTK inhibitor was standard practice in the prior art for ibrutinib, and a POSA would have done the same with acalabrutinib as a second-generation BTK inhibitor.

163. As for the claimed outcome of acalabrutinib's administration—i.e., an increase in monocytes and NK cells in peripheral blood—I understand that an inherent result does not distinguish the prior art. For example, I have been informed that an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting outcome.

164. In this case, I understand that Patent Owner has asserted that claim 10 is infringed simply by administering acalabrutinib for 26.6 months, as stated in Patent Owner's infringement contentions in parallel litigation. EX1034, 4. To show that the claimed result inherently occurs, Patent Owner's contentions rely on data in the '083 patent purporting to show that administering acalabrutinib results in an increase in monocytes and NK cells in peripheral blood. *See id.* (citing EX1001, 4:34-52, 67:64-68:41). Patent Owner did not cite any testing results purporting to show that Petitioner's (i.e., Sandoz's) generic product achieves these results. Thus, I understand that under Patent Owner's infringement theory, the claimed increase in monocytes and NK cells is an inherent result—one that allegedly always occurs when acalabrutinib is administered with the claimed dosing regimen for at least 14 days. Because it would have been obvious to

administer acalabrutinib for the recited durations (i.e., for at least 14 days and longer), claim 10 is obvious regardless of the expected outcome.

165. To the extent that claim 10 is construed to require the result of increasing monocytes and NK cells in peripheral blood after treatment with acalabrutinib, in my opinion this result would have been reasonably expected by a POSA based on the prior art. A POSA would have known that inhibiting BTK (among other kinases) causes cancer cells to detach from bone marrow and enter the peripheral blood. *See* EX1042 (Chang), 1 (“MCL cells are mobilized into the peripheral blood of patients treated with the BTK inhibitor ibrutinib”). Further, a POSA would have known that, once in the peripheral blood, the cancer cells undergo anoikis, i.e. programmed cell death, as they are no longer “well protected and nurtured by the stromal and accessory cells” in the bone marrow. *Id.*, 10.

166. A POSA would have reasonably expected that other cells that signal through the BTK pathway would likewise detach from the bone marrow and enter the peripheral blood, resulting in a transient increase of these cells peripherally. *See id.*, 2 (“many MCL patients had rapid increases of CD5+ B lymphocytes in the peripheral blood (PB) following ibrutinib treatment”). A POSA would have known that both monocytes and NK cells signal through the BTK pathway, and thus a POSA would have reasonably expected that treatment with acalabrutinib—a BTK inhibitor—would cause a transient increase in monocyte and NK cell levels

in the peripheral blood. *See* EX1043 (Bao), 1 (“Btk is required for activation of NK cells” and “is also involved in the regulation of Toll-like receptor-triggered innate response of macrophages”¹); EX1005 (Barf), 1:39–44 (explaining BTK is “expressed in B cells and myeloid cells” and there is also “a function for Btk as a downstream target in Toll like receptor signaling”); *accord* EX1007, 1:23–25.

167. In summary, (1) a POSA would have been motivated to administer acalabrutinib for at least about 14 days, if not longer; and (2) a POSA would have reasonably expected the result of such treatment to increase monocytes and NK cells in peripheral blood. Accordingly, it is my opinion that claim 10 of the ’083 patent would have been obvious to a POSA in view of Barf and Cheson.

4. Claim 11

168. Claim 11 recites: “The method of claim 9, wherein the MCL is selected from the group consisting of mantle zone MCL, nodular MCL, diffuse MCL, and blastoid MCL.”

169. In my opinion, claim 11 would have been obvious to a POSA for the same reasons as claims 8-9. Claim 11 merely lists particular morphologies of MCL. A POSA would have known that the first three recited morphologies are

¹ Bao refers to macrophages, which a POSA would have understood are activated monocytes, i.e., monocytes in tissue.

correlated with disease progression—with mantle-zone MCL progressing to nodular and then diffuse MCL. This was explained by Pileri in 2009:

In the lymph node, spleen and Waldayer's ring, neoplastic cells give rise to a mantle-fashion, nodular or – more frequently – diffuse growth pattern. Notably, repeated biopsies demonstrate that such patterns correspond to disease progression. In fact, in the early phases the tumor substitutes the mantle-zone; then, it invades reactive GC producing a nodular pattern; finally, the nodules merge together causing diffuse effacement of the organ's structure.

EX1014 (Pileri), 2. In contrast, the blastoid MCL morphology is described in Pileri as an aggressive variant of MCL. *Id.* (“Blastoid MCL is clinically aggressive, as is the pleomorphic form, which is characterized by a cell population that is highly variable in size and shape, with frequent mitotic figures and a proportion of rather large elements showing oval to irregular nuclear contours, pale cytoplasm and at times prominent nucleoli.”).

170. Regardless of the recited morphology, a POSA would have administered acalabrutinib to treat all these subtypes of MCL, which involve the same BCR signaling pathway. Barf's claims 1, 4, and 12, which I discussed above, are not limited to any MCL subtype, and a POSA would read them as including the treatment of any of these types of MCL morphologies. Thus, a POSA would have understood that Barf covers the treatment of MCL with acalabrutinib for the same MCL morphologies recited in claim 11 of the '083 patent.

171. Moreover, in parallel litigation, I understand that Patent Owner has asserted in its infringement contentions that the marketing of generic acalabrutinib would infringe claim 11 of the '083 patent (*see* EX1034, 4-5), even though the FDA-approved labeling for acalabrutinib (Calquence) does not mention any subtypes or morphologies of MCL and instead relates generally to treating patients with “mantle cell lymphoma (MCL) who have received at least one prior therapy” (EX1035, 1). Thus, under Patent Owner’s infringement theory that the treatment of MCL broadly includes the treatment of the recited subtypes, claim 11 of the '083 patent would have been obvious to a POSA over Barf, which similarly claims treating MCL generally. *See* EX1005, 150:2-3.

172. Accordingly, it is my opinion that claim 11 of the '083 patent would have been obvious to a POSA in view of Barf and Cheson.

5. Claim 12

173. Claim 12 recites: “The method of claim 9, further comprising the step of administering a therapeutically effective dose of an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, velutuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof.”

174. In my opinion, this additional limitation would have been obvious to a POSA in view of Cheson, which teaches the combination therapy of a BTK

inhibitor with rituximab. In particular, Cheson explains: “The addition of other agents such as rituximab or bendamustine to ibrutinib has been shown to reduce the duration of lymphocytosis.” EX1008, 4. Cheson reports initial results of a clinical trial combining ibrutinib and rituximab, which “appeared to reduce the lymphocytosis ... compared with ibrutinib alone” and “was well tolerated.” *Id.*, 9. Moreover, Barf also notes that anti-CD20 agents were used to treat B-cell disorders (EX1005, 1:66-2:2 (EX1007, 2:5-7)), and Barf covers the combination of acalabrutinib with other drugs (EX1005, 17:10-11 (EX1007, 21:3-4)).

175. Thus, in my opinion, a POSA would have been motivated to administer a BTK inhibitor like acalabrutinib together with rituximab to reduce lymphocytosis. Accordingly, claim 12 of the '083 patent would have been obvious to a POSA in view of Barf and Cheson.

6. Claim 19

176. Claim 19 recites: “The method of claim 9, wherein the free form of the compound of Formula (II) is administered to the human subject.” In other words, this claim requires acalabrutinib’s “free form.”

177. In my opinion, claim 19 of the '083 patent would have been obvious for the same reasons that I discussed above for claims 8-9.

178. Notably, Barf’s claim 1 covers treating MCL by administering acalabrutinib “*or* a pharmaceutically acceptable salt,” indicating that the claim

covers the free base. EX1005, 150:2-31 (emphasis added). Moreover, Barf teaches that its compounds “can be in the form of a free base.” EX1005, 26:40-42 (EX1007, 28:16-17). Thus, Barf discloses the free form of acalabrutinib.

179. Accordingly, claim 19 of the '083 patent would have been obvious to a POSA in view of Barf and Cheson.

7. Claim 20

180. Claim 20 recites: “The method of claim 9, wherein the pharmaceutically acceptable salt of the compound of Formula (II) is administered to the human subject.” In other words, claim 20 requires a “pharmaceutically acceptable salt of” acalabrutinib.

181. In my opinion, claim 20 of the '083 patent would have been obvious to a POSA for the same reasons that I discussed above for claims 8-9. Again, Barf's claim 1 covers acalabrutinib “or a pharmaceutically acceptable salt thereof.” EX1005, 150:2-31. Furthermore, Barf expressly describes salt forms of its covered compounds. *Id.*, 26:40-51 (EX1007, 28:16-22) (describing salt forms). Thus, Barf teaches a pharmaceutically acceptable salt form of acalabrutinib.

182. Accordingly, claim 20 of the '083 patent would have been obvious to a POSA in view of Barf and Cheson.

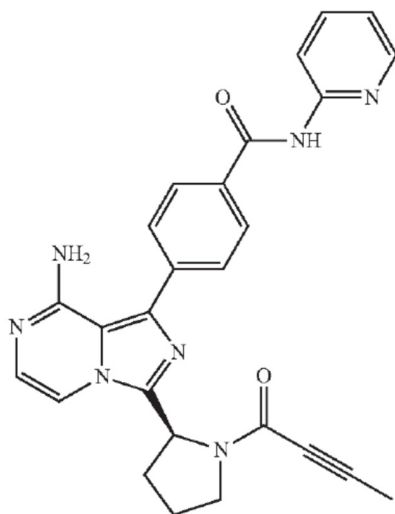
B. Ground 2: Claims 8-12 and 19-20 would have been obvious over Barf-PCT and Cheson.

183. I have also been asked to consider whether the challenged claims would have been obvious to a POSA if Barf were found not to be prior art. In my opinion, the claims would still have been obvious to a POSA for substantially the same reasons as in Ground 1, but in view of Barf-PCT and Cheson, with Barf-PCT replacing Barf as the primary reference. This is because Barf-PCT includes materially the same specification as Barf. Below, I explain the basis for my opinions of obviousness under Ground 2, incorporating the same discussions of background art and understandings of a POSA from Ground 1 above.

1. Claim 8

184. Again, claim 8 of the '083 patent reads as follows:

8. A method of treating a mantle cell lymphoma (MCL) in a human subject suffering therefrom comprising the step of orally administering, to the human subject, a dose of 100 mg twice daily of a BTK inhibitor, wherein the BTK inhibitor is a compound of Formula (II):



or a pharmaceutically-acceptable salt, hydrate, or solvate thereof.

EX1001, 100:39-65.

185. In my opinion, claim 8 would have been obvious to a POSA in view of Barf-PCT and Cheson. As I explain below under headings (a) and (b), Barf-PCT expressly teaches all of claim 8's limitations except the dosing regimen of 100 mg twice daily. As explained under heading (c), however, this claimed regimen would have been obvious to a POSA over the combination of Barf-PCT and Cheson, as supported by the background knowledge and skill of a POSA.

a. “A method of treating a mantle cell lymphoma (MCL) in a human subject suffering therefrom comprising the step of”

186. Similar to claim 1 of Barf that I addressed in Ground 1, Barf-PCT teaches that, by administering the compounds that it discloses, “[p]roliferative diseases that can be treated or prevented include ... mantle cell lymphoma

(MCL),” among other conditions. EX1006, 22:15-16. In addition, Barf-PCT provides that such compounds may be administered to humans. *Id.*, 20:24-25 (discussing “a dosage for humans”).

187. Thus, Barf-PCT expressly teaches a method of treating MCL in a human subject suffering therefrom and, accordingly, discloses the preamble of claim 8 of the ’083 patent.

b. “orally administering, to the human subject, ... a BTK inhibitor, wherein the BTK inhibitor is a compound of Formula (II) ... or a pharmaceutically-acceptable salt, hydrate, or solvate thereof.”

188. Barf-PCT also discloses the next clause of claim 8 of the ’083 patent. Barf-PCT teaches that its compounds may be formulated “[f]or oral administration.” EX1006, 19:32-33. There is no dispute that Barf-PCT discloses acalabrutinib (i.e., the “compound of Formula (II)” recited in claim 8 of the ’083 patent). Indeed, during prosecution of the ’083 patent, the applicants admitted that Barf-PCT teaches acalabrutinib in Example 6. *See id.*, 35:16-36:2; EX1004, 997. Thus, Barf-PCT teaches orally administering, to the human subject, the BTK inhibitor acalabrutinib (i.e., the compound of Formula (II)).

189. Moreover, in my opinion, a POSA would have been motivated to select acalabrutinib among the compounds disclosed in Barf-PCT as a suitable compound for treating MCL. A POSA would have understood that Barf-PCT teaches a preference for BTK inhibitors that are selective for BTK because,

according to Barf-PCT, “an inhibitor that inhibits multiple or all kinases of the Src-family kinases simultaneously may cause serious adverse effects.” EX1006, 2:32-33. The data in Barf-PCT shows that acalabrutinib (Example 6) meets the goal of providing selective BTK inhibition. Specifically, Barf-PCT teaches that acalabrutinib (Example 6) has an EC50 <10 nM for BTK, which is the lowest EC50 reported for BTK. *Id.*, 94 (Tbl. 1). At the same time, Barf-PCT shows that acalabrutinib has very low affinity for the other kinases that were tested, with a much higher EC50 $\geq 1 \mu\text{M}$. *Id.*, 95-98 (Tbls. 2-5). Thus, based on the data in Barf-PCT, a POSA would have understood that acalabrutinib (Example 6) was a suitable compound that met the goal of Barf-PCT to provide a compound that was selective for BTK and not other kinases.

190. Accordingly, a POSA would have found it obvious based on Barf to administer acalabrutinib to a human subject to treat MCL.

c. “a dose of 100 mg twice daily”

191. In my opinion, the claimed dosing regimen of “a dose of 100 mg twice daily” would have been obvious to a POSA for the same reasons that I discussed in Ground 1, which I incorporate by reference. *Supra* §XI.A.1.c.

192. For Barf-PCT’s covered compounds, which include acalabrutinib (Example 6), Barf-PCT teaches that “a dosage for humans preferably contains 0.0001-25 mg per kg body weight.” EX1006, 20:24-25. This is the same range

that is recited in claim 1 of Barf that I addressed in Ground 1. Thus, this range renders the claimed 100 mg dose obvious for the same reasons that I discussed above in Ground 1. Again, when converted to fixed doses (which would have been obvious to a POSA), this range includes the claimed 100 mg dose (and the 200 mg total daily dose when given twice a day), which triggers a presumption of obviousness. Thus, for the same reasons that I explained above, Barf-PCT's dosing range renders the claimed dose obvious. *Supra* §XI.A.1.c.i.(1).

193. Moreover, for the same reasons that I discussed in Ground 1, a POSA would have narrowed this range by focusing on the known 20-1000 mg range of doses that were effective for three other BTK inhibitors. *Supra* §XI.A.1.c.i.(1). Barf-PCT's guidance is also consistent with this narrowed range for the same reasons discussed for Barf. First, Barf-PCT shows that acalabrutinib is among the most potent compounds with the lowest EC50 for BTK, so a POSA would have deprioritized the highest end of Barf-PCT's range (i.e., >1000 mg), which a POSA would have recognized was intended for less potent compounds. EX1006, 94 (Tbl. 1).

194. Second, Barf-PCT teaches that "parenteral administration requires lower dosages than other methods of administration," so a POSA would have deprioritized the lowest end of Barf-PCT's range (i.e., <20 mg), which a POSA would have recognized was intended for non-oral routes of administration.

EX1006, 20:23-24. Thus, Barf-PCT's disclosures would have led a POSA toward the 20-1000 mg range of doses that had been used effectively in the prior art for other BTK inhibitors in clinical studies for cancers.

195. Relatedly, for all the reasons that I discussed above in Ground 1, a POSA would have (i) conducted routine preclinical studies to determine a starting dose in humans; and (ii) conducted a routine dose-finding study to select the lowest dose of acalabrutinib that achieves maximal BTK occupancy, which would have led a POSA directly to the claimed 100 mg dose. *Supra* § XI.A.1.c.i.(2).

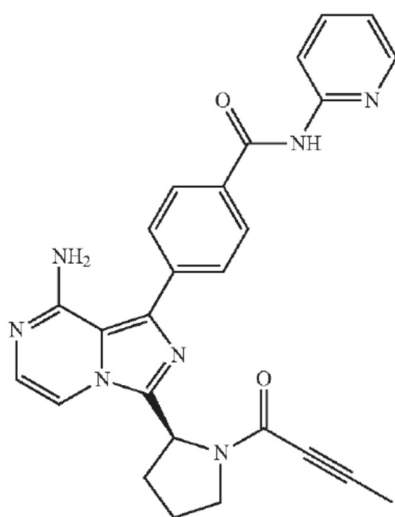
196. Administering this dose twice daily would have been obvious for the same reasons that I discussed in Ground 1. *Supra* § XI.A.1.c.ii. In particular, like Barf, Barf-PCT teaches the use of “multiple subdoses administered at appropriate intervals throughout the day” (EX1006, 20:25-26), and Cheson teaches that “BTK inhibitors are being evaluated in a twice-daily schedule in an attempt to overcome the synthesis of new BTK molecules within those cells,” which “appeared to be more effective” than once-daily dosing (EX1008, 4, 10). Other prior art corroborated Cheson's teaching that twice-daily dosing had achieved superior results for BTK inhibitors. *See* EX1021 (Pierce), 2; EX1019 (Hutchinson). At a minimum, for the reasons that I discussed in Ground 1, twice-daily dosing would have been at least obvious to try in designing a phase I clinical trial, given that the only identified options were once-daily and twice-daily dosing.

197. Thus, it is my opinion that claim 8 of the '083 patent would have been obvious to a POSA in view of Barf-PCT and Cheson.

2. Claim 9

198. Claim 9 depends from claim 8 and reads:

9. The method of claim 8, wherein the BTK inhibitor is a compound of Formula (II):



or a pharmaceutically acceptable salt thereof.

199. The only difference between claim 8 and claim 9 is that claim 8 limits the BTK inhibitor to acalabrutinib “or a pharmaceutically acceptable salt thereof,” which narrows the scope of claim 8 by omitting hydrates and solvates of acalabrutinib as possible compounds (which are included in claim 8).

200. Claim 9 would have been obvious to a POSA for the same reasons that I discussed above for claim 8, as well as the same reasons that I discussed in Ground 1 for claim 9. Barf-PCT discloses acalabrutinib and its pharmaceutically

acceptable salt. EX1006, 35:16-36:2, 17:15-18:5. All of my opinions above for claim 8 apply to acalabrutinib, which is also within the scope of claim 9. Thus, for the same reasons as claim 8, it is my opinion that claim 9 would have been obvious to a POSA over Barf-PCT and Cheson.

3. Claim 10

201. Claim 10 depends from claim 9 and reads: “10. The method of claim 9, wherein the Mantle Cell Lymphoma (MCL) increases monocytes and NK cells in peripheral blood after treatment with Formula (II) for a period selected from the group consisting of about 14 days, about 28 days, and about 56 days.”

202. As I noted above, I understand that Petitioner has proposed that the “wherein” clause in claim 9 should be construed as lacking any patentable weight because it merely recites an intended result and not any new treatment steps.

203. To the extent that claim 10 is construed as requiring the administration of acalabrutinib for the durations recited in the claim, it is my opinion that this would have been obvious to a POSA in view of Cheson for the same reasons that I discussed in Ground 1. *Supra* §XI.A.3. Again, Cheson teaches that the BTK inhibitor ibrutinib was clinically administered “26 months,” encompassing all recited durations. EX1008, 9; *see also id.*, 10 (24 months in Fig. 6), 14 (24 months in Fig. 8; “response rate appeared to improve ... beyond 12 months”). Similarly, it was reported in the prior art that CC-292 had been

clinically tested in 28-day cycles. EX1020 (Brown), 2. Moreover, as discussed in Ground 1, MCL is considered incurable, so in my opinion a POSA would have continued administering a BTK inhibitor indefinitely, and certainly for at least or longer than 14 days. *See* EX1014 (Pileri), 2.

204. As for the claimed outcome of acalabrutinib's administration—i.e., an increase in monocytes and NK cells in peripheral blood—I understand that an inherent result does not distinguish the prior art, and an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting outcome. In this case, the recited result is an inherent result for the reasons I discussed in Ground 1. *Supra* §XI.A.3.

205. To the extent that claim 10 is construed to require the result of increasing monocytes and NK cells in peripheral blood after treatment with acalabrutinib, this result would have been reasonably expected to a POSA, again for the same reasons that I discussed above in Ground 1. *Supra* § XI.A.3.

206. As discussed, a POSA would have known that inhibiting BTK (among other kinases) causes cancer cells to detach from bone marrow and enter the peripheral blood. *See* EX1042 (Chang), at 1 (“MCL cells are mobilized into the peripheral blood of patients treated with the BTK inhibitor ibrutinib”). Further, a POSA would have known that, once in the peripheral blood, the cancer cells

undergo anoikis, i.e. programmed cell death, as they are no longer “well protected and nurtured by the stromal and accessory cells” in the bone marrow. *Id.*, 10.

207. A POSA would have reasonably expected that other cells that signal through the BTK pathway would likewise detach from the bone marrow and enter the peripheral blood, resulting in a transient increase of these cells peripherally. *See id.*, 2 (“many MCL patients had rapid increases of CD5+ B lymphocytes in the peripheral blood (PB) following ibrutinib treatment”). A POSA would have known that both monocytes and NK cells signal through the BTK pathway, and thus a POSA would have reasonably expected that treatment with acalabrutinib—a BTK inhibitor—would cause a transient increase in monocyte and NK cell levels in the peripheral blood. *See* EX1043 (Bao), 1 (“Btk is required for activation of NK cells” and “is also involved in the regulation of Toll-like receptor-triggered innate response of macrophages”); EX1006 (Barf-PCT), 1:21–24 (explaining BTK is “expressed in B cells and myeloid cells” and there is also “a function for Btk as a downstream target in Toll like receptor signaling”).

208. Thus, it is my opinion that claim 10 of the ’083 patent would have been obvious to a POSA over Barf-PCT and Cheson.

4. Claim 11

209. Claim 11 recites: “The method of claim 9, wherein the MCL is selected from the group consisting of mantle zone MCL, nodular MCL, diffuse MCL, and blastoid MCL.”

210. In my opinion, claim 11 would have been obvious to a POSA for the same reasons as claims 8-9, and for the same reasons that I discussed above in Ground 1. *Supra* § XI.A.4. Claim 11 merely lists particular morphologies of MCL. A POSA would have known that the first three recited morphologies are correlated with disease progression (with mantle-zone MCL progressing to nodular MCL and then diffuse MCL), whereas blastoid MCL is an aggressive variant. EX1014 (Pileri), 2. A POSA would have administered acalabrutinib to treat all these subtypes, which involve the same BCR signaling pathway. *See id.*

211. Based on Barf-PCT’s teaching that acalabrutinib inhibits BTK and treats MCL, a POSA would have administered acalabrutinib to treat all these recited morphologies. EX1006, 22:15-16. Indeed, Barf-PCT’s disclosure of treating MCL does not distinguish between any morphologies. *Id.*

212. Thus, it is my opinion that claim 11 of the ’083 patent would have been obvious to a POSA over Barf-PCT and Cheson.

5. Claim 12

213. Claim 12 recites: “The method of claim 9, further comprising the step of administering a therapeutically effective dose of an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, velutuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof.”

214. In my opinion, this additional limitation would have been obvious to a POSA in view of Cheson for the same reasons that I discussed above in Ground 1. *Supra* § XI.A.5. Again, Cheson teaches the combination therapy of a BTK inhibitor with rituximab: “The addition of other agents such as rituximab or bendamustine to ibrutinib has been shown to reduce the duration of lymphocytosis.” EX1008, 4. Cheson reports initial results of a clinical trial combining ibrutinib and rituximab, which “appeared to reduce the lymphocytosis ... compared with ibrutinib alone” and “was well tolerated.” *Id.*, 9.

215. Moreover, Barf-PCT notes that anti-CD20 agents treat B-cell disorders (EX1006, 2:1-3) and covers combinations with other drugs (*id.*, 19:29).

216. Thus, in my opinion, a POSA would have been motivated to administer a BTK inhibitor like acalabrutinib together with rituximab to reduce lymphocytosis. Accordingly, claim 12 of the '083 patent would have been obvious to a POSA in view of Barf-PCT and Cheson.

6. Claim 19

217. Claim 19 recites: “The method of claim 9, wherein the free form of the compound of Formula (II) is administered to the human subject.” In other words, this claim requires acalabrutinib’s “free form.”

218. In my opinion, claim 19 of the ’083 patent would have been obvious for the same reasons that I discussed above for claims 8-9, and for the same reasons I discussed for claim 19 in Ground 1. *Supra* § XI.A.6.

219. Barf-PCT expressly teaches that its covered compounds, which include acalabrutinib (Example 6), “can be in the form of a free base.” EX1006, 26:31-32. Thus, Barf-PCT teaches the free form of acalabrutinib.

220. Accordingly, claim 19 of the ’083 patent would have been obvious to a POSA in view of Barf-PCT and Cheson.

7. Claim 20

221. Claim 20 recites: “The method of claim 9, wherein the pharmaceutically acceptable salt of the compound of Formula (II) is administered to the human subject.” In other words, claim 20 requires a “pharmaceutically acceptable salt of” acalabrutinib.

222. In my opinion, claim 20 of the ’083 patent would have been obvious to a POSA for the same reasons that I discussed above for claims 8-9, and for claim 20 in Ground 1. *Supra* § XI.A.7.

223. Barf-PCT provides that its covered compounds, which include acalabrutinib (Example 6), may be “in the form of a pharmaceutically acceptable salt” and further lists exemplary salts. EX1006, 26:31-37. Thus, Barf-PCT teaches a pharmaceutically acceptable salt form of acalabrutinib.

224. Accordingly, claim 20 of the '083 patent would have been obvious to a POSA in view of Barf-PCT and Cheson.

C. There are no probative secondary considerations.

225. I am not aware of any probative secondary considerations (also called “objective indicia”) of nonobviousness that would weigh against finding the challenged claims of the '083 patent obvious. I reserve the right to rebut any alleged considerations that Patent Owner or its expert(s) may assert.

226. Nevertheless, below, I have preliminary addressed the alleged unexpected results that were raised during prosecution and in the specification.

1. The results submitted during prosecution fail to demonstrate probative unexpected results.

227. As I discussed above in summarizing the prosecution of the '083 patent (§V.C), I understand that the applicants for the '083 patent argued that (1) it was unexpected that acalabrutinib could be dosed at a “significantly lower dose” than ibrutinib and achieve full BTK occupancy; and (2) it was unexpected that twice-daily dosing would sustain BTK occupancy longer than once-daily dosing.

See EX1004, 1002, 1077, 1079. In my opinion, these alleged results were neither probative nor unexpected. I address each alleged result below.

a. A daily dose of 200 mg acalabrutinib (100 mg BID) does not produce probative unexpected results.

228. During prosecution, as detailed above (§V.C), I understand that the Examiner's primary obviousness reference (Smyth '172) related to ibrutinib, which the Examiner deemed "similar" to acalabrutinib because both compounds "have the same cores." EX1004, 909, 1034. The Examiner appeared to assume that a POSA would have started with a method of treatment using ibrutinib and then substituted the known structure of acalabrutinib for ibrutinib. *Id.* In response, the applicants for the '083 patent did "not agree" that ibrutinib is structurally similar to acalabrutinib (*id.*, 997), but they alternatively argued that a POSA starting from ibrutinib would not have used the claimed dose of 100 mg twice daily because ibrutinib was marketed at a higher, once-daily dose of 560 mg (*id.*, 998-99).

229. In this context, where ibrutinib was considered the starting point for an obviousness analysis, the applicants argued that "[i]t was unexpected that acalabrutinib could be orally administered twice daily at a significantly lower dose (100 mg BID) than ibrutinib and provide continuous and improved BTK target occupancy (greater than 95% over a period of 24 hours) relative to ibrutinib." *Id.*, 1002. According to the applicants, a POSA "considering the [ibrutinib] '172 application would not have expected the lower amount BID dosing of acalabrutinib

to be sufficient to provide for full BTK occupancy by acalabrutinib.” *Id.*; *see also id.*, 1077. In my opinion, the alleged result of “full BTK occupancy” at a daily dose of 200 mg (100 mg BID) acalabrutinib is not a probative unexpected result, for the following two reasons.

230. First, I have been informed that, to properly evaluate whether a superior property was *unexpected*, a patentee must provide evidence of what properties *were* expected. During prosecution of the ’083 patent, however, the applicants provided no evidence that a POSA would assume acalabrutinib requires the same dose as ibrutinib to achieve the same BTK occupancy. On the contrary, as I noted above, the applicants *denied* that a POSA would equate acalabrutinib and ibrutinib. EX1004, 997-98, 1077. Nor did the applicants provide any evidence of what doses a POSA *would* expect were required for acalabrutinib to achieve full BTK occupancy. Thus, there is no basis to conclude that the BTK occupancy with the claimed dose of acalabrutinib was “unexpected.”

231. Notably, in arguing that this result was unexpected, the applicants relied on ibrutinib’s marketed dose to rebut the Examiner’s obviousness theory, which relied on an ibrutinib reference as a starting point. *Id.*, 909, 1034. By contrast, my obviousness analysis in both Grounds 1 and 2 starts from a dosing range for *acalabrutinib* disclosed in Barf and Barf-PCT, which does not depend on any structural similarity with ibrutinib. Any reliance on ibrutinib is in the context

of practicing Barf's range in view of data on other BTK inhibitors, including CC-292 and ONO-4059. *Supra* §XI.A.1.c.i.(1). That is, unlike the Examiner, I am not simply assuming that acalabrutinib would be administered at the same dose as ibrutinib. Because the applicants' arguments about ibrutinib were specific to rebutting the Examiner's theory and relied on a comparison that the applicants themselves rejected, they are irrelevant to my analysis and fail to show that a POSA would expect acalabrutinib to require ibrutinib's higher, FDA-approved dose.

232. Second, even assuming that a POSA would have expected acalabrutinib to require the same dose as ibrutinib to achieve the same BTK occupancy, it was not unexpected that a 200 mg daily dose would achieve greater-than-95% BTK occupancy. Indeed, the equivalent result was reported for ibrutinib. In particular, Advani discloses that a dose of 2.5 mg/kg ibrutinib achieved "BTK occupancy >95%." EX1009, 12. For the common assumption of a 70 kg average weight, this equates to 175 mg, and for a North American average of 80 kg, equates to 200 mg. Thus, the fact that acalabrutinib achieves the same BTK occupancy (>95%) at substantially the same daily dose (175-200 mg/day) as ibrutinib is neither superior to ibrutinib nor unexpected because the same result had already been achieved with ibrutinib.

233. In my opinion, given the maximal BTK occupancy that was reported with ibrutinib at doses as low as 175-200 mg/day in Advani, it is immaterial that ibrutinib was later marketed at a higher dose. Again, FDA's 1994 dose-response guidance recognizes that "drugs have often been initially marketed at what were later recognized as excessive doses." EX1026, 2. FDA reached that same conclusion for ibrutinib. In its Clinical Pharmacology and Biopharmaceutics Reviews, dated in 2013 and 2014 (EX1017), FDA repeatedly recommended lower doses for ibrutinib for this very reason, citing Advani:

- "[T]he proposed dose is 2.4-fold higher than the lowest dose that resulted in maximum BTK occupancy and maximum clinical response. Dose-response relationship for ORR and BTK occupancy from Phase 1 study suggested that maximum ORR and maximum occupancy was achieved at doses of ≥ 2.5 mg/kg (≥ 175 mg for average weight of 70 kg).... *The sponsor should thus consider exploring lower doses in future development programs.*" EX1017, 5.
- "[A] lower dose would likely be efficacious.... Evaluate lower doses of ibrutinib in future clinical development as *data from the Phase 1 trial showed that maximum BTK occupancy and maximum response were achieved at doses of ≥ 2.5 mg/kg.*" *Id.*, 10; see also *id.*, 11-12.
- "In the phase 1 dose escalation trial, full and sustained ($> 90\%$ at 24 hours) occupancy of the BTK active site was reached at ibrutinib doses ≥ 2.5 mg/kg/day (≥ 175 mg/day for average weight of 70 kg). *Therefore, doses lower than the selected doses are expected to have*

sustained occupancy of the BTK active site in vivo....” Id., 20; see also id., 55.

(Emphases added.)

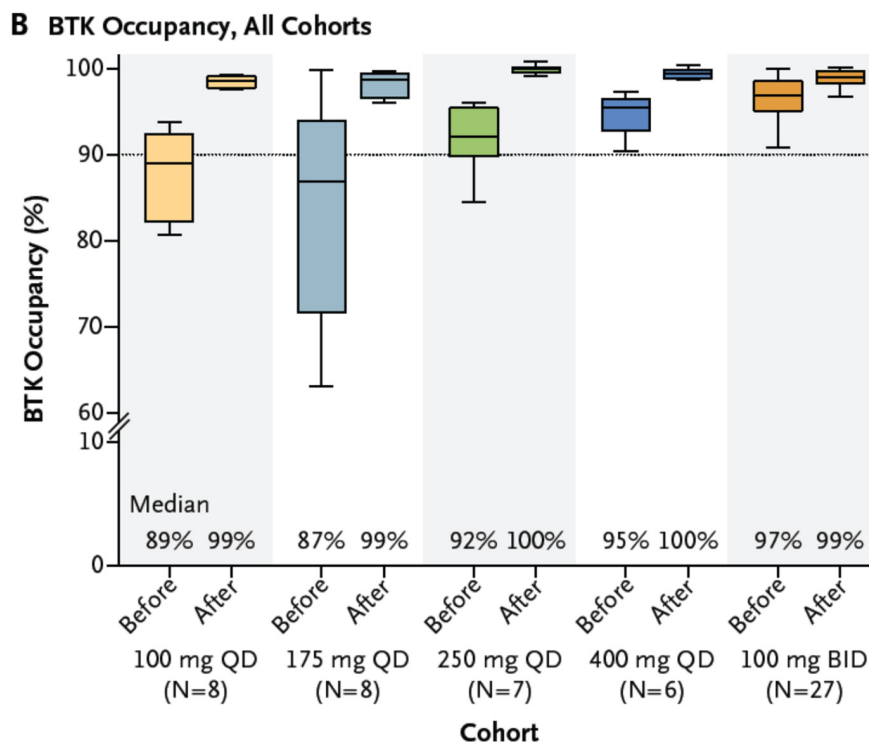
234. Moreover, lower doses were expressly contemplated in ibrutinib’s approved labeling. As of 2014, the ibrutinib label recommended up to two reductions by 140 mg (for a total 280 mg reduction) for toxicity-related adverse events and instructed physicians to “[r]educe IMBRUVICA dose to 140 mg if a moderate CYP3A inhibitor must be used.” EX1016, 2-3. Thus, notwithstanding the 560 mg default, doses as low as 140 mg were also FDA-approved. *Id.*

235. In short, given that the claims of the ’083 patent do not require FDA-approved doses, it is my opinion that the lower and equally effective doses of ibrutinib in Advani should have been used in any assertion of unexpected results as a more relevant comparator. In my opinion, when those lower ibrutinib doses—which achieved maximum BTK occupancy—are used as the comparator, it becomes clear that the BTK occupancy obtained with the claimed daily dose of acalabrutinib is not a probative unexpected result.

b. Acalabrutinib’s twice-daily dosing does not produce probative unexpected results.

236. The applicants also argued that twice-daily dosing produces unexpected results, but I disagree that these results were probative or unexpected.

237. As I discussed above (§V.C), the applicants relied on Byrd, which compared four *once-daily* cohorts (ranging 100-400 mg) to a single *twice-daily* cohort (100 mg) in CLL patients. EX1004, 1078-79. The applicants cited the following box plot in Byrd showing the BTK occupancy in each cohort:



EX1010, 6; EX1004, 1079. The applicants acknowledged that “BTK target occupancy was complete (99 to 100%) four hours after dosing for all cohorts” (labeled “After” above), reflecting no difference between once- and twice-daily dosing. EX1004, 1079. I agree. The applicants nevertheless highlighted two points from Byrd in support of alleged unexpected results.

238. First, the applicants contended that the degree of BTK occupancy “immediately before administration of the next dose (at trough)” (labeled “Before”

above) differed between once-daily and twice-daily groups because (i) the median BTK occupancy ranged from 87-95% for once-daily cohorts, whereas (ii) the median BTK occupancy was 97% for the twice-daily cohort. EX1004, 1079. Second, given the Examiner's focus on ibrutinib, the applicants quoted Byrd's statement that "twice-daily dosing of ibrutinib ... may not be possible owing to the potential for drug accumulation." *Id.*, 1078. The Examiner relied on both of these arguments in the Notice of Allowance for the '083 patent (*id.*, 1382), but they fail to show probative unexpected results for multiple reasons.

239. First, in my opinion, it was not unexpected that twice-daily dosing would provide more continuous BTK occupancy than once-daily dosing. Indeed, as I discussed above in Ground 1, that is one of the reasons why a POSA would have been motivated to use, or at least try, twice-daily dosing. *Supra* §XI.A.1.c.ii. Again, a POSA would have known that CC-292 and ONO-4059 had been administered twice daily for this reason, so a similar improvement in BTK occupancy with acalabrutinib was not unexpected. *See, e.g.*, EX1032 (Brumskill), 3 ("The half-life of CC-292 is 2 h and BTK resynthesis occurs after 12 h, therefore b.i.d. dosing maintains BTK inhibition."); EX1033 (Yoshizawa), 1-2 ("We hypothesized that the efficacy of ONO-4059 could be further enhanced by increasing the drug trough concentration," suggesting "a more frequent dosing regimen such as BD may be a more effective treatment"); EX1008 (Cheson), 4

(“Other BTK inhibitors are being evaluated in a twice-daily schedule in an attempt to overcome the synthesis of new BTK molecules....”).

240. Second, I have been informed that unexpected results that are probative of nonobviousness are those that are different in kind and not merely in degree from the results of the prior art. In my opinion, at most, the difference in BTK occupancy between Byrd’s once- and twice-daily cohorts is a difference in the *degree* of the same effect, not a difference in the *kind* of effect that was observed. As reported in Byrd and summarized by the applicants, the BTK occupancy at trough for once-daily dosing ranged 87-95% compared to 97% for twice-daily. EX1004, 1079; EX1010, 6. That is clearly a difference in degree, especially since the disparity between the highest-occupancy once-daily cohort (95%) and the twice-daily cohort (97%) was only 2%.

241. Third, I have been informed that in order to properly evaluate whether a superior property was unexpected, it is first necessary to understand what properties were expected. In my opinion, the applicants’ assertion of unexpected results fails because they did not establish what a POSA *would* have expected for the twice-daily dosing of acalabrutinib. Because the applicants were focused on rebutting the Examiner’s obviousness theory based on ibrutinib, they highlighted Byrd’s statement that “twice-daily dosing of ibrutinib ... may not be possible owing to the potential for drug accumulation given the ibrutinib half-life of 4 to 13

hours.” EX1004, 1078. But the applicants never showed that a POSA would have expected acalabrutinib’s half-life or accumulation to be the same as ibrutinib’s. On the contrary, they denied that a POSA would have expected acalabrutinib to share ibrutinib’s properties. EX1004, 997-98, 1077. Nor did the applicants cite any evidence suggesting that a POSA would have believed that acalabrutinib could *not* be dosed twice daily, or that twice-daily dosing would not have improved BTK occupancy. With no evidence of a contrary expectation, there is no basis to conclude that the results were “unexpected.”

242. Fourth, the applicants cited no probative evidence that a POSA would have expected ibrutinib’s half-life to preclude twice-daily dosing. Although the applicants cited Byrd’s speculation that twice-daily dosing for ibrutinib “may not be possible owing to the potential for drug accumulation” (EX1010, 9), Byrd was published no earlier than *December* 2015 (*id.*, 1), and thus I understand Byrd is not prior art to the ’083 patent. Moreover, contrary to Byrd’s statement, Advani (which *is* prior art) reports that ibrutinib has a “[m]ean apparent terminal half-life [that] ranged from 4 to 8 hours,” with “*no evidence of accumulation* of ibrutinib exposure after repeated daily oral dosing.” EX1009, 9 (emphasis added).

243. I note that Byrd cites another paper by de Jong that reports a range for terminal mean half-life of 4-13 hours (EX1010, 9, 10 n.32), which is somewhat broader than the range reported in Advani. But de Jong states that the article was

received in May 2015 and thus is not prior art to the '083 patent either. EX1036,

1. Moreover, Byrd fails to mention de Jong's statement that there was "minimum drug accumulation after repeated dosing" with ibrutinib. *Id.*, 2. Thus, the applicants did not provide any contemporaneous evidence that a POSA would have expected ibrutinib could not be dosed twice daily. As a result, the Examiner's statement that ibrutinib's half-life "is such that a twice daily dosage would not be effective" (EX1004, 1382) is neither relevant nor supported.

244. Accordingly, in my opinion, the applicants failed to show that twice-daily dosing produces any probative unexpected results.

2. The results in the specification fail to demonstrate probative unexpected results.

245. The specification of the '083 patent also includes alleged results comparing acalabrutinib to ibrutinib. EX1001, Figs. 1-25. As I discuss below, the specification characterizes certain of these results as "unexpected" or "surprising." My understanding, however, is that the applicants for the '083 patent did not rely on these findings during prosecution. Moreover, most of the alleged results that are deemed "unexpected" or "surprising" appear to be preclinical tests using cell cultures and animal models with small drug concentrations. *See* EX1001, 71:1-5, 70:17-21 (alleging "surprising" lack of platelet-aggregation inhibition in mouse model using human platelets pretreated with 0.1-1.0 μ M drug concentrations); *id.*, 71:22-42 (alleging "unexpected" cytotoxicity benefit in NK cells of CLL patients

treated with 0.1-1.0 μ M drug concentrations); *id.*, 75:7-76:8 (alleging “surprising” lack of inhibition in cells).

246. I have been informed that where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention. Moreover, I understand that a nexus between a secondary consideration and the claims is necessary for that secondary consideration to be probative of nonobviousness.

247. Here, in my opinion, none of the preclinical tests reported in the specification of the '083 patent have a nexus to the challenged claims. Most glaringly, none of these preclinical tests involved treating MCL in a human with 100 mg acalabrutinib twice daily, as required by all challenged claims. At most, these tests relate to alleged unexpected results of the acalabrutinib compound itself, which is not novel because it was disclosed in Barf and Barf-PCT. Notably, for one of the asserted unexpected results, the '083 patent itself admits that “[c]linical investigation is needed to determine the impact of this finding on patients ... for the unexpected property.” EX1001, 74:39-42.

248. The only *clinical* evidence in the '083 patent that is deemed unexpected or surprising is a comparison of a *CLL* study on acalabrutinib with previously reported results from a different trial on ibrutinib. *See id.*, 67:1-15, 67:48-49, 68:25-26. However, this evidence also lacks a nexus to the challenged

claims because it does not relate to treating MCL; the patent states that the results were only “observed in CLL patients.” *Id.*, 67:10.

249. Moreover, I have been informed that when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art. Here, treatment with ibrutinib is not the closest prior art. Rather, Barf’s treatment with *acalabrutinib* is the closest prior art. Thus, any unexpected result would need to compare the claimed therapy with the therapy that was previously disclosed in Barf. The specification of the ’083 patent fails to make this comparison in asserting unexpected results.

250. Even if ibrutinib were the relevant comparator, the alleged unexpected results would be discounted by a POSA as flawed. The specification does not cite any head-to-head trial comparing *acalabrutinib* and ibrutinib; the applicants simply compared results from different trials. A POSA would have viewed this as an improper comparison because the trials’ different conditions were not controlled or accounted for. Thus, a POSA would disregard this comparison.

251. Regardless, the specification lacks any evidence of what a POSA *would* have expected, let alone any evidence that the results with *acalabrutinib* were *unexpected*. At most, the specification states that some of the results were “attributable to the high BTK selectivity” of *acalabrutinib*. EX1001, 67:52. Yet, *acalabrutinib*’s selectivity for BTK was known in the prior art. Again, both Barf

and Barf-PCT show acalabrutinib (Example 6) is highly selective for BTK and not other kinases. EX1005, col. 145-49 (Tbls. 1-5) (EX1007, 97-101); EX1006, 94-98. Moreover, Barf and Barf-PCT express a preference for BTK selectivity, warning that “an inhibitor that inhibits multiple or all kinases of the Src-family kinases simultaneously may cause serious adverse effects.” EX1005, 2:50-52 (EX1007, 2:38-39); EX1006, 2:32-33. Thus, in my opinion, the ’083 patent does not show that any benefits of acalabrutinib’s selectivity were unexpected.

XII. CONCLUSION

252. In sum, for the reasons I have discussed above, it is my opinion that claims 8-12 and 19-20 of the ’083 patent are unpatentable because they would have been obvious to a POSA as of the patent’s effective filing date.

253. I understand that this declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also understand that I may be subject to cross-examination concerning this declaration, and I will appear for cross-examination, if required of me, during the time allotted for cross-examination.

254. I hereby declare that all of the statements made herein are true of my own knowledge and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge

that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Date: February 3, 2023



John P. Fruehauf, M.D., Ph.D.

APPENDIX

CURRICULUM VITAE

John Paul Fruehauf, M.D., Ph.D.

Work Address Division of Hematology/Oncology
UCI Medical Center, Building 56, Room 247
101 The City Drive
Orange, CA 92868
714-456-5153
714-456-2242 (FAX)
email: jfruehau@uci.edu

Home Address 1902 Park Skyline Road
North Tustin, CA 92705

Education and Training

1973–1977 **University of California, Santa Barbara**
B.A.: Cellular and Organismal Biology
B.A.: Psychology

1978–1985 **Rush University** M.D., Ph.D.: Pharmacology

1985–1987 **University of California, Irvine**
Internal Medicine Residency

1987–1992 **National Cancer Institute**, Bethesda, MD
Clinical Oncology Program Medical Staff Fellow
Research Officers Group, Commissioned Corps, PHS
Biotechnology Fellow

Professional Positions

1993–2000 Assistant Clinical Professor, U.C. Irvine
2003–2013 Associate Professor of Clinical Medicine,
Biological Chemistry, Pharmaceutical Sciences
and Biomedical Engineering

July 2014-present Professor of Clinical Medicine,
Biological Chemistry, Pharmaceutical Sciences
and Biomedical Engineering

2004-present Director, Clinical Pharmacology and Developmental Therapeutics
Chao Family Comprehensive Cancer Research Center
University of California, Irvine

Work Experience

Oncotech, Inc.

1992-1998	Vice President and Medical Director
1998-2002	Senior Vice President and Medical Director
2002-2004	Chief Scientific Officer

Licensure	Year
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California CA G58826	1986
Maryland D006157	1987

Certifications

American Board of Internal Medicine, Medical Oncology #124351, Recertified 2011

Memberships and Societies

American Association for Cancer Research	1988–Present
American Society of Clinical Oncology	1996–Present
SWOG, Melanoma Committee	1998–Present

Awards and Honors

Consumers Research Council of America Award for Top Oncologist	2007
OCMA Physician of Excellence	2010, 2014, 2016
U.S. News Top Doctor	2011
Teacher of the Year UCI Oncology Fellows	2011

Research Experience

1993-present UC Irvine

My group has focused on mechanisms of drug action and resistance with the goal of developing predictive tests that improve therapeutic outcomes for cancer patients. Active areas in my laboratory at UC Irvine include the role of glutathione and redox mechanisms in drug resistance, development of vascular endothelial cell models to predict response to antiangiogenesis agents, and the examination of differential gene expression that can distinguish between drug resistant and drug sensitive tumors. More recently we have focused on translating our bench work to the bedside through the development of clinical trials that include correlative laboratory studies.

Discovery of agents that inhibit formation of tumor blood vessels continues to be an active area of therapeutic development. Insights into the immunomodulatory activity of antiangiogenesis agents has led to their effective combination with check point inhibitors (UCI 16-63). However, resistance to antiangiogenesis agents as a deterrent to the success of this approach has been overlooked. In order to define the role of angiogenesis in tumor progression, and to develop models that might predict treatment response, my group developed an angiogenesis index based on mutant p53, the angiogenesis suppressor thrombospondin-1 (TSP1), and intratumor

microvessel counts (US Patent # 5,840,507). We applied this marker set to ovarian cancer patients receiving bevacizumab on a GOG clinical trial, finding that TSP1 expression was significantly associated with durability of response to Avastin (Gynecol Oncol 119:484-90, 2010).

Our group has also explored the relationship between tumor class, drug response and differential gene and protein expression (Clinical Cancer Res 5 (Suppl), #476, 1999). One significant deficiency in current molecular approaches to cancer genomics is specimen purity. The complex mixture of cells within a tumor makes it difficult to delineate which mRNA species are cancer cell specific. We therefore developed flow-cytometry methods to selectively separate malignant cells and tumor derived vascular endothelial cells (VEC) from their stromal background tissue. Transcript levels were determined for the purified cancer cell and VEC cell populations using Affymetrix U133 A and B gene arrays containing 30,000 distinct genes and EST's. Differential gene expression patterns that classify endothelial cells into drug resistance categories have been identified (Proc Am Assoc Cancer Res 43: #4502, 2002; Breast Cancer Res and Treat 76: #562, 2002; Proc Am Assoc Cancer Res 2003, #3998 (Minisymposium Podium Presentation).

My current position as Director of Clinical Pharmacology and Developmental Therapeutics in the Chao Family Comprehensive Cancer Center at UC Irvine allows me to take a translational approach to predictive oncology and to apply bioprofiling to patients on clinical trials. The tremendous complexity of aberrant pathways in cancer has been a major deterrent in the development of targeted therapeutics. With the advent of gene arrays and advanced mass spectrometry methods, this complexity may finally be captured. The capability to bioprofile the unique proteogenomic characteristics of an individual patient's tumor is at hand. Co-development of proteogenomic "theragnostic" tests in conjunction with clinical trials of targeted agents are helping to define patient subsets most likely to benefit, while excluding patients with inappropriate biomarker profiles from potentially toxic treatment. The convergence of biotechnology, molecular biology and clinical pharmacology with bioinformatics should enable a rational approach to target cancer related pathways and improve outcomes for patients with cancer.

Research Background

- | | |
|-----------|--|
| 1987-1993 | National Cancer Institute, NIH, Clin Pharm Branch
Examined the mechanisms of cross resistance between chemotherapy and tumor necrosis factor in breast cancer and prostate cancer cell lines. |
| 1978-1985 | Rush University, Department of Pharmacology
Determined a novel mechanism of action of BCNU to inhibit DNA synthesis via glutathione depletion in conjunction with inhibition of glutathione recycling. (PhD Thesis) |
| 1975-1977 | University of California, Santa Barbara, Dpt. Of Chemistry
Worked on the isolation of the red blood cell glucose transporter using 3-deoxy-3-fluoro-glucose. |

Active Research Grant and Contract Support

Current Peer Reviewed Awards

Fruehauf JP

01/31/19–01/31/24 NIH/NCI P30, CA-62203-14
UCI Cancer Center Support Grant. Center Grant to support UCI Cancer Center.
Role: Chair, Data Safety Monitoring Board

Company Sponsored Laboratory Research Awards

1/18-3/14/23 Astellas
Topotecan Reversal of Enzalutamide Resistance in 22Rv1 Cells via Blockade of AR-V7
Nuclear Translocation
Role: PI
\$172,154.00

Recently Completed Peer Reviewed Support

01/01/11–12/31/16 NIH/NCI R21, CA156032-02
Novel biologic markers of treatment resistance in locally advanced cervical carcinoma.
Role: CO-PI
\$150,000 (T)

6/13-5/18 NIH/NCI RO1
PAK Kinases Regulate Melanoma Chemoresistance and Metastasis
Role: Co-I (PI Anand Ganesan)
\$1,210,649 (T)

6/13-5/18 NIH/NCI RO1
PAK Kinases Regulate Melanoma Chemoresistance and Metastasis
Role: Co-I (PI Anand Ganesan)
\$1,210,649 (T)

Current Clinical Trials Funding

Industry Sponsored Trial/ UCI-18-64 : RPL-001-16 An Open-Label, Multicenter, Phase 1/2 Study of RP1 as a Single Agent and in Combination with PD1 Blockade in Patients with Solid Tumors.
PI 7/15/21-

Industry Sponsored Trial/ UCI-20-57: A Phase 3, Randomized, Open-label Study to Compare Adjuvant Immunotherapy of Bempegaldesleukin Combined with Nivolumab Versus Nivolumab After Complete Resection of Melanoma in Patients at High Risk for Recurrence (PIVOT-12).
PI \$593,944 (T) 11/01/2020 - 10/31/2023

Industry Sponsored Trial/ UCI-19-140: A Randomized Phase II, Open-label, Active-controlled, Multicenter Study Investigating the Efficacy and Safety of UV1 Vaccination in Combination with Nivolumab and Ipilimumab as First-line Treatment of Patients with Unresectable or Metastatic Melanoma (UV1-202).
PI \$338,316 (T) 09/01/2020 - 08/31/2023

Industry Sponsored Trial/ UCI-20-116: A RANDOMIZED, CONTROLLED, OPEN-LABEL, PHASE 2 STUDY OF CEMIPIMAB AS A SINGLE AGENT AND IN COMBINATION WITH RP1 IN PATIENTS WITH ADVANCED CUTANEOUS SQUAMOUS CELL CARCINOMA.
PI \$493,338 (T) 11/01/2020 - 10/31/2023

Industry Sponsored Trial/ UCI-19-15 A Phase 2, Open-Label, Randomized, Multicenter Trial of Encorafenib + Binimetinib Evaluating a Standard-dose and a High-dose Regimen in Patients With BRAFV600-Mutant Melanoma Brain Metastasis
PI \$299,658 (T) 11/5/19-10/21/22

Industry Sponsored Trial/ UCI-17-73: A Sequential 2-arm, Open-label Phase 1 Study to Evaluate the Effects of Encorafenib in Combination with Binimetinib on the Pharmacokinetics of Losartan, Midazolam, Caffeine, Omeprazole, and Dextromethorphan Administered in a Cocktail Approach and on the Pharmacokinetics of Rosuvastatin in Patients with BRAF V600-mutant Unresectable or Metastatic Melanoma or Other Advanced Solid Tumors.
PI \$171,895.00 (T) 1/24/18 – 10/21/22

Industry Sponsored Trial/ UCI-16-102: A PHASE III, OPEN-LABEL, MULTICENTER, TWO-ARM, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF COBIMETINIB PLUS ATEZOLIZUMAB VERSUS PEMBROLIZUMAB IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED BRAFV600 WILD-TYPE MELANOMA
PI \$378,399.00 (T). 11/15/17 - 11/14/20

Industry Sponsored Trial/ UCI 17-09: A randomized, double-blind, placebo-controlled, phase III study comparing the combination of PDR001, dabrafenib and trametinib versus placebo, dabrafenib and trametinib in previously untreated patients with unresectable or metastatic BRAF V600 mutant melanoma
PI \$507,335.00 (T). 08/01/17 - 07/31/20

Industry Sponsored Trial / UCI-16-92: A Phase III, Double-Blinded, Randomized, Placebo-Controlled Study of Atezolizumab Plus Cobimetinib and Vemurafenib versus Placebo plus Cobimetinib and Vemurafenib in Previously Untreated BRAFV600 Mutation-Positive Patients with Unresectable Locally Advanced or Metastatic Melanoma
PI \$689,151.00 (T). 2/15/17 - 5/30/22

Industry Sponsored Trial / UCI 16-63
Phase III Randomized, Open-label Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Axitinib versus Sunitinib Monotherapy as a First-line Treatment for Locally Advanced or Metastatic Renal Cell Carcinoma (mRCC) (KEYNOTE-426)
PI \$292,747.00 (T). 1/17/17- 07/5/20

Industry Sponsored Trial / UCI 15-12
A Phase III, Open-Label, Randomized Study of MPDL3280A (Anti-PD-L1 Antibody) in Combination with Bevacizumab versus Sunitinib in Patients with Untreated Advanced Renal Cell Carcinoma
PI \$5,268,204 (T). 09/24/15 - 09/23/20

Industry Sponsored Trial / UCI 14-82: PHASE III, RANDOMIZED, DOUBLE-BLIND, MULTICENTER TRIAL OF AUTOLOGOUS DENDRITIC CELLS LOADED WITH IRRADIATED AUTOLOGOUS TUMOR CELLS IN GM-CSF (DC-TC) VS. AUTOLOGOUS PERIPHERAL BLOOD MONONUCLEAR CELLS IN GM-CSF (MC) FOR THE TREATMENT OF PATIENTS WITH METASTATIC MELANOMA
PI \$216,091.00 (T). 06/25/15 - 06/24/20

Industry Sponsored Trial / UCI 13-36: A Phase III randomized, 3-arm, open label, multicenter study of LGX818 plus MEK162 and LGX818 monotherapy compared with vemurafenib in patients with unresectable or metastatic BRAF V600 mutant melanoma
PI \$225,878.00 (T). 6/24/13 - 3/1/20

UCI 14-48: A Phase 2, Multicenter, Randomized, Open-label Trial Assessing the Efficacy and Safety of Talimogene Laherparepvec Neoadjuvant Treatment Plus Surgery versus Surgery Alone for Resectable, Stage IIIB to IVM1a Melanoma
PI: \$133,069.00 (T). 08/21/15 - 08/20/20

Investigator Initiated Research Contracts

HDII Clinical Trial UCI 09-53 Novartis
A Phase II, Single-Arm Study of Pazopanib and Paclitaxel as First-Line Treatment for Subjects with Unresectable Stage III and Stage IV Melanoma.
PI \$560,730.00 (T) 6/24/10-12/31/20

HDII Clinical Trial UCI 10-55 Pfizer
Ph 2 Study of Anti-Angiogenesis Agent AG-013736 in Patients with Stage III Malignant Melanoma
PI \$469,970 12/15/11-5/11/20

Prior Completed Research Grant Support

1976	National Science Foundation Summer Research Award UCSB, Department of Chemistry
1980, 1981, 1982	March of Dimes Summer Research Fellowship Award Rush University Department of Pharmacology
1980	National Institutes of Health, COSTEP Program Laboratory of Immunodiagnosis, NCI, Dr. Ronald Herberman,
1981–1982	Pharmaceutical Manufacturers Association Foundation Medical Student Research Fellowship: Pharmacology-Clinical Pharmacology, Rush University
1994	NCI, NIH SBIR Grant, R43 CA60219-01, Development of a Therapeutic TNF-Degradation Product (\$75,000) PI
1994	NCI, NIH SBIR Grant, R43 CA61372-01, Development of an MDR-1 Resistance Reversal Assay (\$75,000) PI
2000	California Cancer Research Program, CRC Cycle-II Angiogenesis as predictor of metastatic risk (\$50,000) PI

Fruehauf JP

2001-2002	NCI, NIH R43 CA83551 A New High Throughput Assay for Human MDR1 Substrates (\$75,000) PI
2000–2001	NCI, NIH R21 Investigation of Angiogenic Function by MRI. Co-Investigator
2000-2003	NCI, NIH P20 CA-86182 Pre-Center Dvpmnt Grant, In Vivo Cellular and Molecular Imaging Centers Co-investigator
2001-2003	CA Breast Cancer Research Program 6JB-0029 Selective Thrombosis of Vessels for Anti-Angiogenic Therapy of Breast Cancer Co-Investigator
2002–2003	NCI, NIH R43 HL70490-01 Genomics Screening for Antiangiogenesis Drugs (\$75,000) PI
2001-2003	DOD DAMD 17-01-0178 Breast Cancer Research Program Anti-angiogenic Therapeutic Indicators in Breast Cancer Co-Investigator
2001–2007	NCI, NIH RO1 Prediction of Metastatic Disease in Early Breast Cancer PI, Sub-Contract
2008–2010	NCI, NIH R21 Lycopene & Docetaxel in Prostate Cancer: An IGF-I Receptor Targeting Approach Co-Investigator

Completed Clinical Translational Research Activities

2010–2013	Clinical Trial UCI 09-34 (GSK) A Double-Blind Randomized Placebo-Controlled Ph III Study to Assess Efficacy of recMAGE-A3+AS15 ASCI as Adjuvant Therapy in Patients with MAGE-A3 Positive Resected Stage III Melanoma PI
2009–2013	Clinical Trial UC 09-28 (GSK) Open, Single-Arm Study to Assess the Clinical Activity of recMAGE-A3 + AS15 in Patients With Unresectable, MAGE-A3 Positive Metastatic Cutaneous Melanoma PI
2008-2011	Translational Study (GSK) Oral Topotecan, Utilization of a Metronomic Dosing Schedule to Treat Recurrent Ovarian Cancer

Fruehauf JP

(\$24,000) PI

2008–2012 Clinical Trial UCI 07-55 (Wyeth)
Randomized Trial of Temsirolimus and Sorafenib as Second-Line Therapy in Advanced Renal Cell Carcinoma Who Have Failed First-Line Sunitinib Therapy.
(\$169,460) PI

2007-2009 Clinical Trial UCI 07-11 (Genentech)
Ph II Bevacizumab with Carboplatin & Paclitaxel in Metastatic Melanoma
(\$414,655) PI

2006-2008 Preclinical correlates ATN39758 and ATN224 (Attenuon)
Redox related antimelanoma activity of ATN224
(\$22,875) PI

2006-2009 Clinical Trial UCI 06-39 (Attenuon)
UCI 06-39: A randomized phase II trial of ATN-224 in combination with temozolomide or temozolomide followed by ATN-224 in systemic-treatment naive patients with advanced melanoma.
(\$107,467) PI

2006-2007 Clinical Trial UCI 04-48 (Cell Genesys)
A Phase III Randomized, Open-Label Study of CG1940 and CG8711 Versus Docetaxel and Prednisone in Patients with Metastatic Hormone-Refractory prostate Cancer who are Chemotherapy-Naive
(\$145,850) PI

2006-2008 Clinical Trial UCI 05-47 (GSK)
UCI 05-47 A Phase II Study of GW786034 Using a Randomized Discontinuation Design in Subjects with Locally Recurrent or Metastatic Clear-Cell Renal Cell Carcinoma
(\$69,335) PI

2006-2009 HDII Clinical Trial UCI 04-35 (Sanofi-Aventis)
Phase II Oxaliplatin with Gemcitabine for Stage IV Bladder Cancer
(\$227,925) PI

2006-2008 Preclinical Study OX-06-005 (Sanofi)
OX-06-005: "Defects in DNA adduct repair predict bladder cancer response to oxaliplatin"
(\$86,330) PI

2005–2010 HDII Clinical Trial UCI 02-23 (Berlex/Bayer)
Docetaxel plus Vinorelbine with Sargramostim for Stage IV Melanoma
(\$209,258) PI

2005-2007 Clinical Trial UCI 05-19 (Attenuon)
A Dose Ranging Phase II Open Label Study of ATN161 in Advanced Renal Cell Cancer
(\$246,491) PI

2004-2007 Clinical Trial UCI 04-34 (Pfizer)
Phase II Antiangiogenesis Study of AG 013736 for Stage IV Melanoma
(\$136,209) PI

Fruehauf JP

1999–2007 HDII Clinical Trial, UCI 99-25R (GSK)
Topotecan plus cisplatin followed by paclitaxel consolidation for the treatment of stage III and IV epithelial ovarian cancer and primary peritoneal cancer with in vitro correlates of response (\$72,813) PI

Editorial Activities

World Journal of Clinical Oncology Editorial Board Member

Ad Hoc Reviewer

Gynecologic Oncology
Breast Cancer Research and Treatment
Clinical Cancer Research
Anti-Cancer Drugs
The Cancer Journal
European Journal of Cancer
Pharmacological Research
Cancer

Study Sections

6/94 NCI, NIH: Ad Hoc Contracts Technical Review Group for Phase I Studies
3/03 NCI, NIH: ZES RAM-C-C3, Special Emphasis Panel for the Review of Development Of Microarray Profiles for Microbial Toxicity
4/03 NCI, NIH: ZRG SSS-1 12B, Diagnosis and Treatment of Cancer
6/07 NCI, NIH Cancer Center Renewal Site Visit Team, NYU
6/99 HHS Medicare Negotiated Rulemaking Taskforce: Author of Medicare Tumor Marker Coverage Policy for CA125

University Service

1996–2010 Member, UC Irvine Translational Seed Grants Committee
1999–2002 UC Irvine Institutional Biosafety Committee
1999–2004 Chair, Clinical Trials Protocol Review and Monitoring Committee
2003 Chair, Search Committee, UCI Department of Radiology
2005–2008 Member, UC Irvine Allied Health Committee
2006–2007 UC Wide Scientific Advisory Committee for Pharmacology
2008–2022 Vice Chair, UC Irvine Institutional Review Board B
2020 -Present Chair, UC Irvine Institutional Review Board WB
2010–Present Chair, Cancer Center Data Safety and Monitoring Board
2017-Present Chair, UC Irvine Institutional Review Board WB

Supervision of Graduate Students

Co-Chair, PhD Defense Committee: John Sinek, Biomedical Engineering 2005
Co-Chair, PhD Committee: Hermann Frieboes, Biomedical Engineering 2005

Primary PhD Advisor:

2004-2009 Valerie Trapp, PhD awarded Biomedical Engineering,
2007-2012 Basmina Parmakhtiar, PhD awarded Biological Chemistry
2010-2012 Maliheh Movassat, Biological Chemistry

Post Doctoral Trainees/Fellows Mentoring

2005-2007 Ernest Han, Fellow Gyn/Onc

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Fruehauf JP

2007-2008 Leslie Randall-Whitis, Fellow Gyn/Onc
2008-2009 Dana Chase, Fellow Gyn/Onc
2012-2013 Shlomid Ein-Gal, Fellow, Heme/Onc
2013-2014 GK Ford, Fellow, Gyn/Onc
2014-2016 Teresa Longoria, Fellow Gyn/Onc
2015-2016 Sarmen Sarkissian, Fellow Heme/Onc
2016-2017 Monica El-Masry, Fellow Heme/Onc

Masters Students Mentoring:

2005–2006: Miranda King, Biotechnology
2006–2007: Peter Foss, Biotechnology

Undergraduate Research Supervision

Bio 199 Instructor: 4-5 students per quarter 2004–Present

Teaching Experience

2007 to Present: Pharmaceutical Sciences M172 Course Director, Fall Quarter

Patents (Citations)

Treatment of Tumor Cells with TNF Degradation Products.
US Patent No 5,543,139, Aug 6, 1996
Methods for Cancer Prognosis and Diagnosis: Angiogenesis Index.
US Patent No 5,840,507. April 11, 1997
Radiation Resistance Assays for Predicting Treatment Response and Clinical Outcome.
US Patent No 6,008,007. Dec 28, 1999 (44)
(Co-Inventor: Dr. R. Parker)
Methods for Cancer Prognosis and Diagnosis
US Patent No 6,303,324. Nov 24, 1998 (19)
Radiation Resistance Assays for Predicting Treatment Response and Clinical Outcome.
US Patent No 6,261,795. July 17, 2001 (20)
(Co-Inventor: Dr. R. Parker)
Methods and Reagents for Preparing and Using Immunological Agents Specific for
P-glycoprotein.
US Patent No 6,365,357. April 2, 2002
(Co-inventor: Dr. E. Mechetner)
Methods for In Vitro Genotyping of Drug-Sensitive and Drug-Resistant Subsets of Primary
Tumors.
US Patent No 6,511,806. January 28, 2003 (19)
Methods for cancer prognosis and diagnosis relating to tumor vascular endothelial cells.
US patent No 6,998,234. February 14, 2006 (7)

Google Scholar: Citations 6541: h-Index 42

Peer Reviewed Publications (# Citations)

1. **Fruehauf JP**, Bonnard GD, Herberman RB. The effect of lentinan on production of interleukin-1 by human monocytes. Immunopharmacology 5:65-74, 1982. (118)
2. **Fruehauf JP**, Myers CE, Sinha BK. Synergistic activity of suramin with tumor necrosis factor and doxorubicin on prostate cancer cell lines. J Natl Cancer Inst 82:1206-1209, 1990. (70)

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3. **Fruehauf JP**, Mimnaugh E, Sinha BK. Doxorubicin-induced cross-resistance to tumor necrosis factor (TNF) related to differential TNF processing. *J Immunotherapy* 10:165-173, 1991. (15)
4. Mimnaugh EG, Fairchild CR, **Fruehauf JP**, Sinha BK. Biochemical and pharmacological characterization of MCF-7 drug-sensitive and AdrR multidrug-resistant human breast tumor xenografts in athymic nude mice. *Biochemical Pharm* 42:391-402, 1991. (48)
5. **Fruehauf JP**, Sinha BKS. Selective formation of tumor necrosis factor alpha (TNF) degradation products contributes to TNF mediated cytotoxicity. *Oncology Res* 4:91-101, 1992. (11)
6. Santin AD, Hiserodt JC, **Fruehauf J**, DiSaia PJ, Pecorelli S, Granger G. Effects of irradiation on the expression of surface antigens in human ovarian cancer. *Gynecol Oncol* 60:468-474, 1996. (37)
7. Santin AD, Rose GS, Hiserodt JC, **Fruehauf J**, Eck LM, Garcia RI, Schranz V, DiSaia PJ, Pecorelli S, Granger GA. Effects of tumor necrosis factor-alfa plus interferon-gamma combined with high dose gamma irradiation on the expression of major histocompatibility complex molecules and intercellular adhesion molecule-1 in human ovarian cancers. *Intl J Cancer* 65:688-694, 1996. (4)
8. Santin AD, Hermonat PL, Hiserodt JC, Fruehauf J, *et al*. Differential Transforming Growth Factor- β secretion in adenocarcinoma and squamous cell carcinoma of the uterine cervix. *Gyn Onc* 64:476-480, 1997. (29)
9. **Fruehauf JP**, Zonis S, Al-Bassam M, Kyshtoobayeva A, Dasgupta C, Milovanovic T, Parker RJ, Buzaid AC. Selective and synergistic activity of L-S,R-buthionine sulfoximine on malignant melanoma is accompanied by decreased expression of glutathione-S-transferase. *Pigment Cell Res* 10:236-249, 1997. (21)
10. Mechetner E, Kyshtoobayeva A, Zonis S, Kim H, Stroup R, Garcia R, Parker RJ, **Fruehauf JP**. Levels of multidrug resistance (MDR1) P-glycoprotein expression by human breast cancer correlates with in vitro resistance to taxol and doxorubicin. *Clinical Cancer Res* 4:389-398, 1998. (340)
11. Grant SW, Kyshtoobayeva AS, Jakowatz J, **Fruehauf JP**. Mutant p53 correlates with reduced expression of thrombospondin-1, increased angiogenesis, and metastatic progression in melanoma. *Cancer Det Prev* 22(3): 185-195, 1998. (96)
12. Coppola D, Lu L, **Fruehauf JP**, Kyshtoobayeva A, Karl RC, Nicosia SV, Yeatman TJ. Analysis of p53, p21 WAF1, and TGF-beta 1 in human ductal adenocarcinoma of the pancreas: TGF-beta1 protein expression predicts longer survival. *Am J Clin Pathol* 110:16-23, 1998. (73)
13. **Fruehauf JP**, Zonis, S., Al-Bassam, M., Kyshtoobayeva, A., Dasgupta, G., Milovanovic, T., Parker, R., Buzaid, A.C. Melanin content and down regulation of glutathione-S-transferase contribute to the action of L-buthionine-S-sulfoximine on human melanoma. *Chemico-Biological Interactions*. 111-112: 277-305, 1998. (31)
14. Haber M, Bordow SB, Gilbert J, Madafiglio J, Kavallaris M, , Marshall GM, Mechetner EB, **Fruehauf JP**, Tee L, Cohn SL, Salwen H, Schmidt ML, Norris MD. Altered expression of the MYCN oncogene modulates MRP gene expression and response to cytotoxic drugs in neuroblastoma cells. *Oncogene*, 18:2777-2782, 1999. (83)

15. Moore MM, Tewari KT, Rose S, **Fruehauf JP**, DiSaia PJ. Long-term consequences following conservative management of epithelial ovarian cancer in an infertile patient. *Gynecol Oncol* 73: 452-454, 1999. (19)
16. Tewari K, Kyshtoobayeva AS, Mehta RS, Yu I-R, Burger RA, DiSaia PJ, **Fruehauf JP**. Biomarker conservation in primary and metastatic epithelial ovarian carcinoma. *Gynecol. Oncol.* 78:130-136, 2000. (56)
17. Mehta R, Kyshtoobayeva A, Kurosaki T, Small EJ, Kim H, Stroup R, McClaren C, Li K-T, **Fruehauf JP**. Independent association of angiogenesis index with outcome in prostate cancer. *Clinical Cancer Res* 7:81-88, 2001. (121)
18. Mehta RS, Bornstein R, Yu IR, Parker RJ, McLaren CE, Nguyen KP, Li K-T, **Fruehauf JP**. Breast cancer survival and *in vitro* tumor response in the Extreme Drug Resistance Assay. *Breast Cancer Research and Treatment* 66:225-237, 2001. (65)
19. Reavy-Cantwell JF, Haroun RI, Zahurak M, Clatterbuck RE, Parker RJ, Mehta R, **Fruehauf JP**, Brem H. The prognostic value of tumor markers in patients with glioblastomas multiforme: analysis of 32 patients and review of the literature. *J Neuro-Onc* 55:195-204, 2001. (101)
20. Ellis RJ, Fabian CJ, Kimler BF, Tawfik O, Mayo MS, Decelis CR, Jewell WR, Connor C, Modrell C, Praeger M, McGinness M, Mehta R, **Fruehauf JP**. Factors associated with success of the extreme drug resistance assay in primary breast cancer specimens. *Breast Cancer Res Treat* 71:95-102, 2002. (11)
21. Haroun RI, Clatterbuck RE, Gibbons MC, Burger PC, Parker R, **Fruehauf JP**, Brem H. Extreme drug resistance in primary brain tumors: in vitro analysis of 64 resection specimens. *J Neuro-Onc* 58:115-123, 2002. (23)
22. Holloway RW, Mehta RS, Finkler NJ, Li K-T, McLaren CE, Parker RJ, **Fruehauf JP**. Association between in vitro platinum resistance in the EDR assay and clinical outcomes for ovarian cancer patients. *Gynecol Oncol* 87:8-16, 2002. (107)
23. Monk BJ, Burger RA, Parker R, Radney EH, Redpath L, **Fruehauf JP**. Development of an *in vitro* chemo-radiation response assay for cervical carcinoma. *Gynecol Oncol* 87:193-199, 2002. (13)
24. Su M-Y, Yu H, Chiou J-Y, Wang J, **Fruehauf JP**, Nalcioglu O, Mehta RS, Baick CH. Measurement of volumetric and vascular changes with dynamic contrast enhanced MRI for cancer therapy monitoring. *Technology in Cancer Research and Treatment*, 1(6): 479-488, 2002. (15)
25. Park SW, Lomri N, Simeoni LA, **Fruehauf JP**, Mechetner E. Analysis of p-glycoprotein-mediated membrane transport in human peripheral blood lymphocytes using the UIC2 shift assay. *Cytometry* 53A:67-78, 2003. (58)
26. Sommers KR, Kong KM, Bui DT, **Fruehauf JP**, Holcombe RF. Stevens-Johnson syndrome/toxic epidermal necrolysis in a patient receiving concurrent radiation and gemcitabine. *Anti-Cancer Drugs* 14:659-662, 2003. (34)
27. Su M-Y, Cheung Y-C, **Fruehauf JP**, Yu H, Mechetner E, Kyshtoobayeva A, Chen S-C, Hsueh S, McLaren CE, Nalcioglu O, Wan Y-L. Correlation of dynamic contrast enhancement MRI parameters with microvessel density and VEGF for assessment of angiogenesis in breast cancer. *JMRI* 18:467-477, 2003. (200)
28. del Carmen MG, Smith Sehdev AE, Nickles Fader A, Zahurak ML, Richardson M, **Fruehauf JP**, Montz FJ, Bristow RE. Endometriosis-associated ovarian carcinoma: Differential

- expression of vascular endothelial growth factor and estrogen/progesterone receptors. *Cancer* 98:1658-1663, 2003. (51)
29. Cloven N, Kyshtoobayeva A, Burger RA, Yu I-R, **Fruehauf JP**. In vitro chemoresistance and biomarker profiles are unique for histologic subtypes of epithelial ovarian cancer. *Gyn Oncol* 92: 160-166, 2004. (84)
 30. Parker RJ, **Fruehauf JP**, Mehta R, Filka E, Cloughesy T. A prospective blinded study of the predictive value of extreme drug resistance assays in patients receiving CPT-11 for recurrent glioma. *J Neuro-Oncology*, 66:365-375, 2004. (19)
 31. Gossett DR, Alo P, Bristow RE, Galati M, Kyshtoobayeva A, **Fruehauf J**, Montz FJ. Inability of immunohistochemistry to predict clinical outcomes of endometrial cancer patients. *Int J Gynecol Cancer* 14:145-151, 2004. (6)
 32. Fabian CJ, Kimler BF, Anderson J, Tawfik OW, Mayo MS, Burak Jr WE, O'Shaughnessy JA, Albain KS, Hyams DM, Budd GT, Ganz PA, Sauter ER, Beenken SW, Grizzle WE, **Fruehauf JP**, Arneson DW, Bacus JW, Lagios MD, Johnson KA, Browne D. Breast cancer chemoprevention phase I evaluation of biomarker modulation by arzoxifene, a third generation selective estrogen receptor modulator. *Clin Cancer Res* 10:5403-5417, 2004. (66)
 33. **Fruehauf JP**, Kong K, Jakowatz JG. Phase II clinical trial evaluating docetaxel and vinorelbine plus GM-CSF in malignant melanoma. *Oncology* 19 (suppl 2):19-22, 2005. (14)
 34. Goodhart MJ, Ritchie JM, Rose SL, **Fruehauf JP**, De Young BR, Buller RE. The relationship of molecular markers of P53 function and angiogenesis to prognosis of stage I epithelial ovarian cancer. *Clin Cancer Res* 11:3733-3742, 2005. (87)
 35. Tewari KS, Mehta RS, Burger RA, Yu I-R, Kyshtoobayeva AS, Monk BJ, Manetta A, Berman ML, DiSaia PJ, **Fruehauf JP**. Conservation of in vitro drug resistance patterns in epithelial ovarian carcinoma. *Gynecol Oncol* 98:360-368, 2005. (29)
 36. Tewari D, Monk BJ, Al-Ghazi MS, Parker R, Heck JD, Burger RA, **Fruehauf JP**. Gene expression profiling of *in vitro* radiation resistance in cervical carcinoma: a feasibility study. *Gynecol Oncol* 99:84-91, 2005. (31)
 37. **Fruehauf JP**, Brem H, Brem S, Sloan A, Barger G, Huang W, Parker R. In vitro drug response and molecular markers associated with drug resistance in malignant gliomas. *Clin Can Res* 12:4523-32, 2006. (86)
 38. Prabhu S, Saadat D, Zhang M, Halbur L, **Fruehauf JP**, Ong ST. A novel mechanism for Bcr-Abl action: Bcr-Abl-mediated induction of the eIF4F translation initiation complex and mRNA translation. *Oncogene* 26:1188-200, 2007. (58)
 39. Nishimoto KP, Newkirk D, Hou S, **Fruehauf J**, Nelson EL. Fluorescence activated cell sorting (FACS) using RNAlater to minimize RNA degradation and perturbation of mRNA expression from cells involved in initial host microbe interactions. *J Microbiol Methods*. 70(1):205-8, 2007. (16)
 40. Einspahr JG, Thomas TL, Saboda K, Nickolof BJ, Wameke J, Curiel-Lewandrowski C, Ranger-Moore J, Duckett L, Bangert J, **Fruehauf JP**, Alberts DS. Expression of Vascular Endothelial Growth Factor in early cutaneous melanocytic lesion progression. *Cancer*: 110:2519-27, 2007. (64)
 41. Mathews MS, Linskey ME, Hasso AN, **Fruehauf JP**. The effect of bevacizumab (Avastin) on neuroimaging of brain metastases. *Surg Neurol*. 70(6):649-53, 2008. (41)

42. Zhang M, Fu W, Prabhu S, Moore JC, Ko J, Kim JW, Druker BJ, Trapp V, **Fruehauf J**, Gram H, Fan HY, Ong ST. Inhibition of polysome assembly enhances imatinib activity against chronic myelogenous leukemia, and overcomes imatinib resistance. *Mol Cell Biol* 28:6496-509, 2008. (67)
43. Finley DS, Narula N, Valera VA, Merino MJ, **Fruehauf J**, Wu ML, Linehan WM, Clayman RV. Immunohistochemical basis for adjuvant anti-angiogenic targeted therapy for renal carcinoid: Initial case report. *Urol Oncol* 2008 Dec 24. [Epub ahead of print; paper publication 29:85-89, 2011 (9)]
44. Frieboes HB, Edgerton ME, **Fruehauf JP**, Rose FRAJ, Worrall LK, Gatenby RA, Ferrari M, Cristini V. Prediction of drug response in breast cancer using integrative experimental/computational modeling. *Cancer Res* 69(10):4484-92, 2009. (141)
45. Trapp V, Lee K, Doñate F, Mazar AP, **Fruehauf, JP**. Redox-related antimelanoma activity of ATN-224. *Melanoma Research* 19(6):350-360, 2009. (7)
46. Randall LM, Monk BJ, Darcy KM, Tian C, Burger RA, Liao S-Y, Peters WA, Stock RJ, **Fruehauf JP**. Markers of angiogenesis in high-risk, early-stage cervical cancer: A Gynecologic Oncology Group study. *Gynecologic Oncology*, 112(3):583-9, 2009. (113)
47. Liao SY, Darcy KM, Randall LM, Tian C, Monk BJ, Burger RA, **Fruehauf JP**, Peters WA, Stock RJ, Stanbridge EJ. Prognostic relevance of carbonic anhydrase-IX in high-risk, early-stage cervical cancer: A Gynecologic Oncology Group study. *Gynecol Oncol*. 116(3):452-8, 2010. (64)
48. Tran Cao HS, Bouvet M, Kaushal S, Keleman A, Romney E, Kim G, **Fruehauf J**, Imagawa DK, Hoffman RM, Katz MH. Metronomic gemcitabine in combination with sunitinib inhibits multisite metastasis and increases survival in an orthotopic model of pancreatic cancer. *Mol Cancer Ther* 9:2068-78, 2010. (51)
49. Trapp V, Parmakhtiar B, Papazian V, Willmott L, **Fruehauf JP**. Anti-angiogenic effects of resveratrol mediated by decreased VEGF and increased TSP1 expression in melanoma-endothelial cell co-culture. *Angiogenesis* 13:305-15, 2010. (110)
50. Han ES, Burger RA, Darcy KM, Sill MW, Randall LM, Chase D, Parmakhtiar B, Monk BJ, Greer BE, DeGeest K **Fruehauf JP**. Predictive and prognostic angiogenic markers in a Gynecologic Oncology Group Phase II Trial of Bevacizumab in recurrent and persistent ovarian or peritoneal cancer. *Gynecol Oncol* 119(3):484-90, 2010. (62)
51. Randall LM, Monk BJ, Moon J, Parker R, Al-Ghazi M, Wilczynski S, **Fruehauf JP**, Markman M, Burger RA. Prospective evaluation of an in vitro radiation resistance assay in locally advanced cancer of the uterine cervix: a Southwest Oncology Group Study. *Gynecol Oncol* 119:417-21, 2010. (10)
52. Tang Y, Parmakhtiar B, Simoneau AR, Xie J, **Fruehauf J**, Lilly M, Zi X. Lycopene enhances docetaxel's effect in castration-resistant prostate cancer associated with insulin-like growth factor I receptor levels. *Neoplasia*. 13:108-19, 2011. (101)
53. Rini BI, Schiller JH, **Fruehauf JP**, Cohen EEW, Tarazi JC, Rosbrook B, Bair AH, Ricart AD, Olszanski AJ, Letrent KJ, Kim S, Rixe O. Diastolic blood pressure as a biomarker of axitinib efficacy in solid tumors. *Clin Cancer Res* 17:3841-9, 2011. (194)
54. Eroglu Z, Kong KM, Jakowatz JG, Samlowski W, **Fruehauf JP**. Phase II clinical trial evaluating docetaxel, vinorelbine and GM-CSF in stage IV melanoma. *Cancer Chemother Pharmacol*. 68:1081-7, 2011. (14)

55. **Fruehauf JP**, Lutzky J, McDermott DF, Brown CK, Meric J-B, Rosbrook B, Shalinsky DR, Liao KF, Niethammer AG, Kim S, Rixe O. Multicenter, phase II study of axitinib, a selective second-generation inhibitor of vascular endothelial growth factor receptors 1, 2, and 3, in patients with metastatic melanoma. *Clin Cancer Research*. 17:7462-7469, 2011. (105)
56. Kim KB, Sosman JA, **Fruehauf JP**, Linette GP, Markovic SN, McDermott DF, Weber JS, Nguyen H, Cheverton P, Chen D, Peterson AC, Carson WE 3rd, O'Day SJ. BEAM: A Randomized Phase II Study Evaluating the Activity of Bevacizumab in Combination with Carboplatin Plus Paclitaxel in Patients with Previously Untreated Advanced Melanoma. *J Clin Oncol*. 30:34-41, 2012. (175)
57. Chase DM, Sill MW, Monk BJ, Chambers MD, Darcy KM, Han ES, Buening BJ, Sorosky JL, **Fruehauf JP**, Burger RA. Changes in Tumor Blood Flow as Measured by Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI) May Predict Activity of Single Agent Bevacizumab in Recurrent Epithelial Ovarian (EOC) and Primary Peritoneal Cancer (PPC) Patients: An exploratory analysis of a Gynecologic Oncology Group Phase II study. *Gynecol Oncol* 126:375-80, 2012. (20)
58. van der Graaf WT, Blay JY, Chawla SP, Kim DW, Bui-Nguyen B, Casali PG, Schöffski P, Aglietta M, Staddon AP, Beppu Y, Le Cesne A, Gelderblom H, Judson IR, Araki N, Ouali M, Marreaud S, Hodge R, Dewji MR, Coens C, Demetri GD, Fletcher CD, Dei Tos AP, Hohenberger P; EORTC Soft Tissue and Bone Sarcoma Group; **PALETTE study group**. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomized, double-blind, placebo-controlled phase 3 trial. *Lancet* 379:1879-86, 2012. (1323)
59. Lindner DJ, Wu Y, Haney R, Jacobs BS, **Fruehauf JP**, Tuthill R, Borden EC. Thrombospondin-1 expression in melanoma is blocked by methylation and targeted reversal by 5-Aza-deoxycytidine suppresses angiogenesis. *Matrix Biol*. 32:123-132, 2013. (49)
60. Eroglu Z, **Fruehauf JP**. A phase II study of gemcitabine and oxaliplatin in advanced transitional cell carcinoma of the bladder. *Cancer Chemother Pharm* 72: 263-267, 2013. (10)
61. Tortorici MA, Cohen EE, Pithavala YK, Garrett M, Ruiz-Garcia A, Kim S, **Fruehauf JP**. Pharmacokinetics of single-agent axitinib across multiple solid tumor types. *Cancer Chemother Pharmacol*. 74(6):1279-89, 2014. (7)
62. Saad F, Fizazi K, Jinga V, Efsthathiou E, Fong PC, Hart LL, Jones R, McDermott R, Wirth M, Suzuki K, MacLean DB, Wang L, Akaza H, Nelson J, Scher HI, Dreicer R, Webb IJ, de Wit R; **ELM-PC 4 investigators**. Orteronel plus prednisone in patients with chemotherapy-naïve metastatic castration-resistant prostate cancer (ELM-PC 4): a double-blind, multicenter, phase 3, randomized, placebo-controlled trial. *Lancet Oncol* 16:338-48, 2015. (68)
63. **Fruehauf JP**, El-Masry M, Osann K, Parmakhtiar B, Yamamoto M, Jakowatz JG. Phase II study of pazopanib in combination with paclitaxel in patients with metastatic melanoma. *Cancer Chemother Pharmacol* 82:353–360, 2018. (8)
64. Liao MC, Kim J-H, **Fruehauf JP**. Potentiation of ATRA activity in HL-60 cells by targeting methylation enzymes. *J Pharmacol Pharmaceut Pharmacovig* 3:009, 2019.
65. Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, Pouliot F, Alekseev B, Soulières D, Melichar B, Vynnychenko I, Kryzhanivska A, Bondarenko I, Azevedo SJ, Borchiellini D, Szczylik C, Markus M, McDermott RS, Bedke J, Tartas S, Chang YH, Tamada S, Shou Q, Perini

- RF, Chen M, Atkins MB, Powles T; **KEYNOTE-426 Investigators**. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med*. 380:1116-1127, 2019. (493)
66. Schmidinger M, Bamias A, Procopio G, Hawkins R, Sanchez AR, Vázquez S, Srihari N, Kalofonos H, Bono P, Pisal CB, Hirschberg Y, Dezzani L, Ahmad Q, Jonasch E; PRINCIPAL Study Group. Prospective Observational Study of Pazopanib in Patients with Advanced Renal Cell Carcinoma (**PRINCIPAL Study**). *Oncologist* 24:491-4907, 2019. (24)
67. Parmakhtiar B, Burger RA, Kim J-H, **Fruehauf JP**. HIF inactivation of p53 in ovarian cancer can be reversed by topotecan restoring cisplatin and paclitaxel sensitivity. *Molecular Cancer Res*. 17:1675-1686, 2019. (32)
68. Liao MC, Kim J-H, **Fruehauf JP**. Potentiation of ATRA activity in HL-60 cells by targeting methylation enzymes. *J Pharmacol Pharmaceut Pharmacovig* 3: 009, 2019. (3)
69. Liao MC, Fruehauf PA, Zheng Z-H, **Fruehauf JP**. Development of Synthetic Cell Differentiation Agent Formulations for the Prevention and Therapy of Cancer via Targeting of Cancer Stem Cells. *Cancer Stud Ther J* 4(1): 1–15, 2019. (4)
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Selected Invited Lectures (1999-2016)

International Gynecologic Cancer Society Meeting, Nervi Cathedral, The Vatican, Rome, Italy, 8/99.

“Association between breast cancer survival and in vitro drug response in the EDR assay.”

University of Wisconsin Comprehensive Cancer Center Grand Rounds, 8/9/99.

“In Vitro drug response assays in drug development and treatment selection.”

Duke University Department of Gynecologic Oncology Tumor Board, 12/6/99.

“Use of prognostic and predictive factors in ovarian cancer management.”

Louisiana State University Dept. of Medicine Grand Rounds, 12/7/99.

“Angiogenesis and in vitro drug response testing as guides in cancer patient management.”

University of North Carolina Dept. of Obstetrics and Gynecology Grand Rounds, 12/8/99.

“In vitro testing in treatment selection for gynecologic cancers.”

Smi Phrama Conf.: Commercial Issues in Oncology Drug Development

London, England, 9/10/01

“Molecular correlates of proteogenomics in the identification of new diagnostic and therapeutic targets.”

1st Symposium of the International Society for Chemosensitivity Testing in Oncology –

ISCO-1, Homburg, Germany, 9/14/01

“Maximizing chemoresistance testing data for the clinician.”

Cancer Care Ontario Conference, Ontario, Canada, 11/12/01

New Technologies: Applications to Cancer research, Diagnosis and Treatment

“Extreme drug resistance (EDR) assays, DNA microarray analysis and flow cytometric assessment of drug induced apoptotic potential from freshly resected human tumor samples.”

UT MD Anderson Cancer Center’s 43rd Annual Clinical Conference

Drug Discovery and Clinical Evaluation in the 21st Century. Houston, TX, 1/16/02

Fruehauf JP

“Clonogenic Assays.”

**Yale University Medical School Department of Pathology
Grand Rounds, New Haven, CT 2/7/02**

“Molecular Determinants of Drug Action and Approaches to Rational Treatment”

Society of Gynecologic Oncology Sunrise Session, Miami, FLA 3/18/02

“Use of In Vitro Drug Response Assays in Clinical Practice”

Baltimore Oncology Club, Baltimore, MD 1/16/03

“Prognostic and Predictive Testing to Guide Therapy of Cancer Patients”

Worldwide Oncoimaging Conference, Athens, 9/4/05

“Advances in imaging from the oncologist’s perspective”

International Immunologic Emerging Therapies Summit, Phoenix AZ, 10/8/05

“Metastatic Melanoma: A Docitaxel Plus Navelbine Combination
with Sargramostim Support”

Korean Society of Gynecological Oncology and Colposcopy, Gyeongju, Korea, 4/21/06

“Utility of In vitro drug response assays”

**University of Utah Cancer Center Grand Rounds, Salt Lake City, Utah
9/12/07**

“Current approach to the treatment of melanoma”

**Northwest Melanoma Symposium: Science to Survivorship,
Fred Hutchinson Cancer Research Center, Seattle, WA
11/ 2/07**

“Advances in the therapy of Melanoma”

Oncology Congress, San Francisco CA, 9/28/08

“Advanced Melanoma Treatment Update”

ASCO Plenary Melanoma Session 6/2/2008

Axitinib (AG-013736) in patients with metastatic melanoma: A phase II study.

Pacific Dermatology Society Annual Meeting. Huntington Beach, CA, 8/23/12

“Updates on Treatment of Advanced Melanoma”

Medical Oncology Association of Orange County, Irvine CA 7/16/15

“Melanoma it the Spotlight on ASCO”

Medical Oncology Association of Orange County, Huntington Beach CA 7/16/16

“Melanoma it the Spotlight on ASCO”

Medical Oncology Association of Orange County, Huntington Beach CA 8/11/18; 8/17/19

“ASCO update on Melanoma”