(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
04 June 2020 (04.06.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/112761 A1

(51) International Patent Classification:
A61P 35/02 (2006.01) *A61K 31/519* (2006.01)

(21) International Application Number:
PCT/US2019/063234

(22) International Filing Date:
26 November 2019 (26.11.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/773,678 30 November 2018 (30.11.2018) US

(71) Applicant: **JANSSEN BIOTECH, INC.** [US/US]; 800/850 Ridgeview Drive, Horsham, PA 19044 (US).

(72) Inventor: **BALASUBRAMANIAN, Sriram**; 800/850 Ridgeview Drive, Horsham, PA 19044 (US).

(74) Agent: **GROTH, Felicity E.** et al.; Baker & Hostetler LLP, 2929 Arch Street, Cira Centre, 12th Floor, Philadelphia, PA 19104-2891 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

(54) **Title:** METHODS OF TREATING FOLLICULAR LYMPHOMA

(57) **Abstract:** Provided herein are methods of treating follicular lymphoma (FL) and gene mutations that can be used to predict a subject's nonresponsiveness to treatment of follicular lymphoma with ibrutinib.

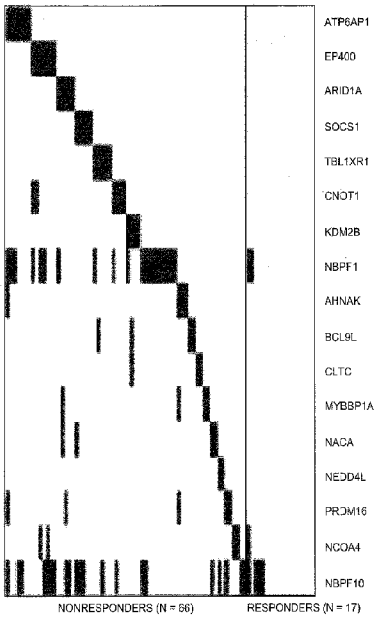

FIG. 3

WO 2020/112761 A1

METHODS OF TREATING FOLLICULAR LYMPHOMA

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/773,678, filed November 30, 2018, the disclosure of which is hereby incorporated by reference in its entirety.

TECHNICAL FIELD

[0002] Provided herein are methods of treating follicular lymphoma (FL) and gene mutations that can be used to predict a subject's nonresponsiveness to treatment of follicular lymphoma with ibrutinib.

BACKGROUND

[0003] The genetic landscape of follicular lymphoma is complex. In addition to the hallmark t(14;18) translocation resulting in BCL2 overexpression, molecular genetic studies have also identified recurrent somatic mutations in a number of genes. Such mutations may reduce a subject's responsiveness to therapy.

SUMMARY

[0004] Provided herein are methods of treating follicular lymphoma (FL) in a subject, the methods comprising administering to the subject a therapeutically effective amount of ibrutinib to thereby treat the FL, wherein the subject does not have one or more mutations as defined in Table 2 in one or more genes selected from *AHNAK*, *ARID1A*, *ATP6AP1*, *BCL9L*, *CLTC*, *CNOT1*, *EP400*, *KDM2B*, *MYBBP1A*, *NACA*, *NBPF1*, NBPF10, *NCOA4*, *NEDD4L*, *PRDM16*, *SOCS1*, and *TBL1XR1*.

[0005] Also provided are methods of predicting a likelihood of nonresponsiveness to ibrutinib in a subject having follicular lymphoma, the method comprising analyzing a sample from the subject for one or more of the mutations as defined in Table 2 in one or more genes selected from *AHNAK*, *ARID1A*, *ATP6AP1*, *BCL9L*, *CLTC*, *CNOT1*, *EP400*, *KDM2B*, *MYBBP1A*, *NACA*, *NBPF1*, *NBPF10*, *NCOA4*, *NEDD4L*, *PRDM16*, *SOCS1*, and *TBL1XR1*, wherein one or more of the mutations in the one or more genes is indicative of nonresponsiveness to ibrutinib.

BRIEF DESCRIPTION OF THE DRAWINGS

[0006] The summary, as well as the following detailed description, is further understood when read in conjunction with the appended drawings. For the purpose of illustrating the disclosed methods, there are shown in the drawings exemplary embodiments of the methods; however, the methods are not limited to the specific embodiments disclosed. In the drawings:

[0007] **FIG. 1** illustrates the number of mutated genes in the DAWN study patients with responder data (N = 83).

[0008] **FIG. 2** illustrates a heatmap of genes mutated in > 10% of samples (75 genes) from the DAWN study.

[0009] **FIG. 3** illustrates a heatmap of ranked nonresponder gene mutations from the DAWN study.

[0010] **FIG. 4** illustrates the mean ORR of predicted responders based on cross-validation studies.

[0011] **FIG. 5** is an exemplary plot of somatic mutations in the *ATP6AP1* gene in DAWN patients.

[0012] **FIG. 6** is an exemplary plot of somatic mutations in the *EP400* gene in DAWN patients.

[0013] **FIG. 7** is an exemplary plot of somatic mutations in the *ARID1A* gene in DAWN patients.

[0014] **FIG. 8** is an exemplary plot of somatic mutations in the *SOCS1* gene in DAWN patients.

[0015] **FIG. 9** is an exemplary plot of somatic mutations in the *TBL1XR1* gene in DAWN patients.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0016] The disclosed methods may be understood more readily by reference to the following detailed description taken in connection with the accompanying figures, which form a part of this disclosure. It is to be understood that the disclosed methods are not limited to the specific methods described and/or shown herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of the claimed methods.

[0017] Unless specifically stated otherwise, any description as to a possible mechanism or mode of action or reason for improvement is meant to be illustrative only, and the disclosed methods are not to be constrained by the correctness or incorrectness of any such suggested mechanism or mode of action or reason for improvement.

[0018] Where a range of numerical values is recited or established herein, the range includes the endpoints thereof and all the individual integers and fractions within the range, and also includes each of the narrower ranges therein formed by all the various possible combinations of those endpoints and internal integers and fractions to form subgroups of the larger group of values within the stated range to the same extent as if each of those narrower ranges was explicitly recited. It is not intended that the scope of the methods be limited to the specific values recited when defining a range. All ranges are inclusive and combinable.

[0019] When values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment. Reference to a particular numerical value includes at least that particular value, unless the context clearly dictates otherwise.

[0020] It is to be appreciated that certain features of the disclosed methods which are, for clarity, described herein in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the disclosed methods that are, for brevity, described in the context of a single embodiment, may also be provided separately or in any subcombination.

[0021] As used herein, the singular forms "a," "an," and "the" include the plural.

[0022] Various terms relating to aspects of the description are used throughout the specification and claims. Such terms are to be given their ordinary meaning in the art unless otherwise indicated. Other specifically defined terms are to be construed in a manner consistent with the definitions provided herein.

[0023] The term "about" when used in reference to numerical ranges, cutoffs, or specific values is used to indicate that the recited values may vary by up to as much as 10% from the listed value. Thus, the term "about" is used to encompass variations of ± 10% or less, variations of ± 5% or less, variations of ± 1% or less, variations of ± 0.5% or less, or variations of ± 0.1% or less from the specified value.

[0024] The term "comprising" is intended to include examples encompassed by the terms "consisting essentially of" and "consisting of"; similarly, the term "consisting essentially of" is intended to include examples encompassed by the term "consisting of."

[0025] Ibrutinib, a first-in-class, oral, covalent inhibitor of Bruton's tyrosine kinase (BTK), approved for several B-cell malignancies in the United States and other countries, disrupts signaling pathways essential for the adhesion, proliferation, homing, and survival of malignant B cells.

[0026] "Treat," "treatment," and like terms include reducing the severity and/or frequency of symptoms, eliminating symptoms and/or the underlying cause of the symptoms, reducing the frequency or likelihood of symptoms and/or their underlying cause, and improving or remediating damage caused, directly or indirectly, by the follicular lymphoma. Treatment includes complete response and partial response to the administered agent (ibrutinib). Treatment also includes prolonging survival as compared to the expected survival of a subject not receiving treatment.

[0027] As used herein, the phrase "therapeutically effective amount" refers to an amount of the ibrutinib, as described herein, effective to achieve a particular biological or therapeutic result such as, but not limited to, biological or therapeutic results disclosed, described, or exemplified herein. The therapeutically effective amount may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the composition to cause a desired response in a subject. Exemplary indicators of a therapeutically effective amount include, for example, improved well-being of the patient, reduction of a tumor burden, arrested or slowed growth of the follicular lymphoma, and/or absence of metastasis of follicular lymphoma cells to other locations in the body.

[0028] The term "subject" as used herein is intended to mean humans. "Subject" and "patient" are used interchangeably herein.

[0029] The following abbreviations are used herein: Bruton's tyrosine kinase (BTK); relapsed or refractory (R/R); overall response rate (ORR); overall survival (OS); follicular lymphoma (FL); complete response (CR); and partial response (PR).

Methods of treating follicular lymphoma and uses

[0030] Provided herein are methods of treating follicular lymphoma (FL) in a subject, the methods comprising:

administering to the subject a therapeutically effective amount of ibrutinib to thereby treat the FL, wherein the subject does not have one or more mutations as defined in Table 2 in one or more genes selected from *AHNAK*, *ARID1A*, *ATP6AP1*, *BCL9L*, *CLTC*, *CNOT1*, *EP400*, *KDM2B*, *MYBBP1A*, *NACA*, *NBPF1*, *NBPF10*, *NCOA4*, *NEDD4L*, *PRDM16*, *SOCS1*, and *TBL1XR1*.

[0031] The mutations provided in Table 2 in one or more of *AHNAK*, *ARID1A*, *ATP6AP1*, *BCL9L*, *CLTC*, *CNOT1*, *EP400*, *KDM2B*, *MYBBP1A*, *NACA*, *NBPF1*, NBPF10, *NCOA4*, *NEDD4L*, *PRDM16*, *SOCS1*, and *TBL1XR1* are associated with nonresponsiveness to ibrutinib treatment, as disclosed herein. Thus, the methods comprise administering to the subject a therapeutically effective amount of ibrutinib to thereby treat the FL, wherein the subject does not have one or more mutations as defined in Table 2 in one or more genes selected from *AHNAK*, *ARID1A*, *ATP6AP1*, *BCL9L*, *CLTC*, *CNOT1*, *EP400*, *KDM2B*, *MYBBP1A*, *NACA*, *NBPF1*, *NBPF10*, *NCOA4*, *NEDD4L*, *PRDM16*, *SOCS1*, and *TBL1XR1*. The methods can be performed on subjects not having one or more mutations as defined in Table 2 in 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or all 17 of *AHNAK*, *ARID1A*, *ATP6AP1*, *BCL9L*, *CLTC*, *CNOT1*, *EP400*, *KDM2B*, *MYBBP1A*, *NACA*, *NBPF1*, *NBPF10*, *NCOA4*, *NEDD4L*, *PRDM16*, *SOCS1*, and *TBL1XR1* as provided in Table 2 and various combinations thereof.

[0032] Also disclosed are methods of treating follicular lymphoma (FL) in a subject, the methods comprising:

to a subject having FL and not having one or more mutations as defined in Table 2 in one or more genes selected from *AHNAK*, *ARID1A*, *ATP6AP1*, *BCL9L*, *CLTC*, *CNOT1*, *EP400*, *KDM2B*, *MYBBP1A*, *NACA*, *NBPF1*, *NBPF10*, *NCOA4*, *NEDD4L*, *PRDM16*, *SOCS1*, and *TBL1XR1*

administering a therapeutically effective amount of ibrutinib to thereby treat the FL.

[0033] Also provided are methods of treating follicular lymphoma (FL) in a subject not having one or more mutations as defined in Table 2 in one or more genes selected from *AHNAK*, *ARID1A*, *ATP6AP1*, *BCL9L*, *CLTC*, *CNOT1*, *EP400*, *KDM2B*, *MYBBP1A*, *NACA*, *NBPF1*, *NBPF10*, *NCOA4*, *NEDD4L*, *PRDM16*, *SOCS1*, and *TBL1XR1*, the methods comprising administering to the subject a therapeutically effective amount of ibrutinib to thereby treat the FL.

[0034] The therapeutically effective amount of ibrutinib can comprise from about 420 mg to about 840 mg. For example, the therapeutically effective amount of ibrutinib can comprise about 420 mg, 440 mg, 460 mg, 480 mg, 500 mg, 520 mg, 540 mg, 560 mg, 580 mg, 600 mg, 620 mg, 640 mg, 660 mg, 680 mg, 700 mg, 720 mg, 740 mg, 760 mg, 780 mg, 800 mg, 820 mg, or 840 mg. In some embodiments, the therapeutically effective amount of ibrutinib is 560 mg.

[0035] In some embodiments, the FL is relapsed/refractory (R/R) FL.

[0036] Suitable subjects for treatment include those who, prior to the administering:

- had a diagnosis of grade 1, 2, or 3a nontransformed FL;
- had been treated with ≥ 2 prior lines of therapy;
- was R/R to a last prior line of therapy with an anti-CD20 monoclonal antibody-containing chemoimmunotherapy regimen; or
- any combination thereof.

[0037] In some embodiments, the subject can have a partial response. In some embodiments, the subject can have a complete response.

[0038] Further provided is the use of ibrutinib in the manufacture of a medicament for the treatment of follicular lymphoma (FL) in a subject not having one or more mutations as defined in Table 2 in one or more genes selected from *AHNAK*, *ARID1A*, *ATP6AP1*, *BCL9L*, *CLTC*, *CNOT1*, *EP400*, *KDM2B*, *MYBBP1A*, *NACA*, *NBPF1*, *NBPF10*, *NCOA4*, *NEDD4L*, *PRDM16*, *SOCS1*, and *TBL1XR1*.

[0039] Also provided is ibrutinib for use in the treatment of follicular lymphoma (FL) in a subject not having one or more mutations as defined in Table 2 in one or more genes selected from *AHNAK*, *ARID1A*, *ATP6AP1*, *BCL9L*, *CLTC*, *CNOT1*, *EP400*, *KDM2B*, *MYBBP1A*, *NACA*, *NBPF1*, *NBPF10*, *NCOA4*, *NEDD4L*, *PRDM16*, *SOCS1*, and *TBL1XR1*.

Methods of predicting a likelihood of nonresponsiveness to ibrutinib in a subject having follicular lymphoma

[0040] Provided are methods of predicting a likelihood of nonresponsiveness to ibrutinib in a subject having follicular lymphoma, the methods comprising:

analyzing a sample from the subject for one or more mutations as defined in Table 2 in one or more genes selected from *AHNAK*, *ARID1A*, *ATP6AP1*, *BCL9L*, *CLTC*, *CNOT1*, *EP400*, *KDM2B*, *MYBBP1A*, *NACA*, *NBPF1*, *NBPF10*, *NCOA4*, *NEDD4L*, *PRDM16*, *SOCS1*, and *TBL1XR1*, wherein a mutation in the one or more genes is indicative of nonresponsiveness to ibrutinib.

[0041] The mutations provided in Table 2 in one or more of *AHNAK*, *ARID1A*, *ATP6AP1*, *BCL9L*, *CLTC*, *CNOT1*, *EP400*, *KDM2B*, *MYBBP1A*, *NACA*, *NBPF1*, *NBPF10*, *NCOA4*, *NEDD4L*, *PRDM16*, *SOCS1*, and *TBL1XR1* are indicative of nonresponsiveness to ibrutinib treatment, as disclosed herein. A mutation in 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or all 17 of *AHNAK*, *ARID1A*, *ATP6AP1*, *BCL9L*, *CLTC*, *CNOT1*, *EP400*, *KDM2B*, *MYBBP1A*, *NACA*, *NBPF1*, *NBPF10*, *NCOA4*, *NEDD4L*, *PRDM16*, *SOCS1*, and *TBL1XR1* as provided in Table 2 and various combinations thereof can be indicative of nonresponsiveness to ibrutinib treatment.

[0042] In some embodiments, the methods comprise analyzing a sample from the subject for one or more mutations as defined in Table 2 in one or more genes selected from *AHNAK*, *ARID1A*, *ATP6AP1*, *BCL9L*, *CLTC*, *CNOT1*, *EP400*, *KDM2B*, *MYBBP1A*, *NACA*, *NBPF1*, *NBPF10*, *NCOA4*, *NEDD4L*, *PRDM16*, *SOCS1*, and *TBL1XR1*, wherein a lack of the one or more mutations in the one or more genes is indicative of responsiveness to the ibrutinib.

[0043] In some embodiments, methods of predicting a likelihood of nonresponsiveness to ibrutinib in a subject having follicular lymphoma is combined with a subsequent treatment of the follicular lymphoma. Thus, provided are methods of treating follicular lymphoma (FL) in a subject, the methods comprising:

analyzing a sample from the subject for one or more mutations as defined in Table 2 in one or more genes selected from *AHNAK*, *ARID1A*, *ATP6AP1*, *BCL9L*, *CLTC*, *CNOT1*, *EP400*, *KDM2B*, *MYBBP1A*, *NACA*, *NBPF1*, *NBPF10*, *NCOA4*, *NEDD4L*, *PRDM16*, *SOCS1*, and *TBL1XR1*, wherein the one or more mutations in the one or more genes is indicative of nonresponsiveness to ibrutinib

and administering a therapeutically effective amount of ibrutinib to thereby treat the FL if the subject does not have the one or more mutations in the one or more genes.

[0044] Suitable samples from the subject include any biological sample that contains the gene of interest including, but not limited to, whole blood samples and tumor biopsy samples.

EXAMPLES

[0045] The following examples are provided to further describe some of the embodiments disclosed herein. The examples are intended to illustrate, not to limit, the disclosed embodiments.

Identification Of A Genetic Signature Enriching For Response To Ibrutinib In Relapsed/Refractory Follicular Lymphoma (FL)

[0046] The DAWN study (NCT01779791) evaluated the efficacy and safety of ibrutinib monotherapy in patients with relapsed/refractory (R/R) follicular lymphoma (FL). The overall response rate (ORR) for ibrutinib was 20.9% (95% confidence interval [CI], 13.7-29.7), not meeting the primary end point. However, responders experienced a long duration of response (median 19.4 months). A genetic investigation was performed on

samples from the DAWN study to determine whether somatic mutations could be used to identify FL patients who will respond, or not respond, to ibrutinib.

Study Design and Patients

[0047] Detailed methodology for the DAWN trial is published in Gopal AK, *et al.* J Clin Oncol. 2018;36:2405-2412. Briefly, DAWN was a multicenter, single-arm, phase 2 study of ibrutinib (560 mg once daily) in patients aged ≥ 18 years with a diagnosis of grade 1, 2, or 3a nontransformed FL who had been treated with ≥ 2 prior lines of therapy, and were R/R to their last prior line of therapy with an anti-CD20 monoclonal antibody-containing chemoimmunotherapy regimen. The primary end point was overall response rate (ORR = complete response [CR] + partial response [PR]), assessed by an independent review committee using the International Working Group Revised Response Criteria for Malignant Lymphoma.

[0048] Whole exome sequencing was performed on 88 formalin-fixed, paraffin-embedded tumor samples (LabCorp, Burlington, NC) from responders or nonresponders following ibrutinib treatment. Multiple filters were applied to rule out potential germline variants, and a custom panel of 1216 genes known to be involved in cancer was used for further analysis. Variants enriched in responders or nonresponders were identified using Fisher's exact test. Variants were marked as "deleterious" based on meta-analytic support vector machine (metaSVM) annotations in the database for nonsynonymous single nucleotide polymorphisms functional predictions (dbNSFP). Classifiers were built with variable numbers of genes ranked with a greedy algorithm that selected genes that would, at each iteration, allow the removal of the greatest number of nonresponders from the patient pool, while severely penalizing the removal of responders. Classification results were first assessed with 10-fold cross-validation within the DAWN dataset, subsequently (*See* Bartlett NL, *et al. Blood.* 2018;131:182-190).

Sample Collection and Processing

[0049] Whole blood samples and tumor biopsy samples were collected and whole blood and plasma fractions were used for gene analysis.

[0050] Exome data were generated from FFPE samples of 88 subjects with FL, each from a different subject. Eighty-three of these subjects were indicated as either "responder" (CR + PR) or "nonresponder" (SD + PD) after ibrutinib treatment.

Exome Sequencing

[0051] Whole-exome data was generated using Nimblegen kits and sequencing libraries were made using KAPA construction kits. Sequencing was performed using the Illumina HiSeq2500 platform with a goal of 100× coverage for each sample.

Variant Calling/Annotation

[0052] A total of 88 FFPE FL samples had full exome sequencing performed and were analyzed first by LabCorp. Results of LabCorp analyses were examined by generating a variant allele frequency (VAF) histogram to qualitatively assess (a) the degree to which somatic vs. germline variants were present in the data and (b) whether low VAF variants were properly represented in the set of calls. Since large peaks were seen near VAF = 0.5 and VAF = 1.0, it was inferred that a large proportion of the variants were likely to be heterozygous or homozygous germline variants; as very few variants were seen at the low end of the VAF histogram, it was determined that a procedure should be used to specifically enrich for the low VAF variants.

[0053] To correct for the potential issues seen in the LabCorp data, an in-house exome analysis pipeline was run on DNAnexus using raw FASTQ sequence data files. Quality was assessed using FastQC 1.0.0, sequences were aligned to the hs37d5 genome build using the BWA-MEM algorithm in BWA Software Package 0.5.9, alignments were recalibrated with the GATK 3.5 Exome Pipeline, and variants were annotated with MuTect 1.1.7, SnpEff 4.2 (using the GRCh37.75 database), and GEMINI 0.20.0 (modified by using non-TCGA gnomAD and ExAC references). Non-synonymous coding variants (defined in R as is_coding="1" & impact!="synonymous_variant") were filtered to reduce the likelihood of incorporating sequencing artifacts and germline variants into the association analysis. Variants were marked as (a) “deleterious” based on MetaSVM annotations in dbNSFP and/or (b) “Personalis gene” variants based on whether they were in genes found in the Personalis Cancer Panel used in the Bartlett CTEP study.

[0054] A major goal of this exome sequencing evaluation was to identify responders/nonresponders from somatic mutations. To accomplish this, analyses were run with only “Personalis genes” and tested in the Bartlett CTEP dataset (a dataset generated using the Personalis ACE ExtendedCancer Panel on FL data). In both the more restricted (“Personalis genes”) and the full whole-exome datasets, statistical analyses were run on all likely somatic variants as well as only those gene variants inferred to be deleterious. Multiple classifiers using variable gene numbers were developed with nonresponder gene ranking

based on a greedy algorithm (with a misclassification penalty) and responder/nonresponder binning using gene mutation status. Classification results were first assessed with 10-fold cross-validation within the dataset; subsequently, a subset of classifiers was assessed based on the overall ibrutinib response rate of the predicted responder group in the Bartlett CTEP FL subject study

Summary of Variants

[0055] Exome data were generated from the paraffin-embedded tumor samples from 88 patients. 974,686 total nonsynonymous variants were identified. After filtering out potential errors and likely germline mutations, the number of variants was reduced to 13,554. Response data were available on 83 patients, comprising 17 responders and 66 nonresponders.

[0056] The final VAF histogram for filtered variants showed a significant reduction in the peaks at 0.5 and 1.0 seen in the original set of variants return by LabCorp, indicating a much higher ratio of somatic to germline variants. VAF values for EZH2-Y646 and STAT6-D419, known somatic FL-associated mutations, fell below 0.4, indicating that it would be reasonable to exclude variants not below this threshold if they were in dbSNP, but not in COSMIC. The variants in the dbSNP non-COSMIC set largely fell in the zones near 0.5 and 1.0, indicating that many of them are likely germline mutations. As a check of the final distribution of the filtered variants, the VAF distribution of the COSMIC ("known somatic") variants found within the dataset was examined and found to have a similar distribution (note, however, that there are known contaminating variants in COSMIC that are likely to be nearly exclusively germline, accounting for the small peak around 0.5). The number of mutated genes in each sample varied from under 100 to over 500, and variance was greater across non-responder NR subjects, likely due to a larger sample size.

[0057] The overall pattern of variant frequencies identified from the whole exome sequencing is provided in FIG. 2. There were 75 genes with putative mutations in > 10% of the patients, including many of those previously implicated in FL (e.g., *CREBBP*, *BCL2*, and *KMT2D*). The left panel of FIG. 2 shows the percentage of individuals with a mutation in each gene, while the right panel shows the distribution of mutations in those genes in the 83 patients for which responder data were available.

[0058] Due to the greater number of samples from nonresponders versus responders, univariate analysis yielded mostly variants significantly enriched in ibrutinib responders but in very low numbers, e.g., *FANCA*, *HISTH1B*, *ANXA6*, and *PARP10* (Table

1). Interestingly, 2 patients with variants in *BTG1*, which is a tumor suppressor, also responded to ibrutinib. Few nonresponder genes were identified in univariate analysis, including *NBPF1*, *ATP6AP1*, *EP400*, and *CNOT1* (mutations in these genes may activate pathways that bypass BTK, including the mTOR and JAK/STAT pathways).

Table 1. Univariate analysis of gene variants in responders versus nonresponders*

Gene	Responder (N = 17) n (%)	Nonresponder (N = 66) n (%)	Odds Ratio (95% CI)	*p* Value
FANCA	3 (17.6)	0 (0.0)	Inf (1.721-Inf)	0.007
HIST1H1B	5 (29.4)	3 (4.5)	8.417 (1.426-61.654)	0.008
ANXA6	2 (11.8)	0 (0.0)	Inf (0.750-Inf)	0.04
BTG1	2 (11.8)	0 (0.0)	Inf (0.750-Inf)	0.04
DIAPH1	2 (11.8)	0 (0.0)	Inf (0.750-Inf)	0.04
PARP10	2 (11.8)	0 (0.0)	Inf (0.750-Inf)	0.04
PBRM1	2 (11.8)	0 (0.0)	Inf (0.750-Inf)	0.04
PRDM1	2 (11.8)	0 (0.0)	Inf (0.750-Inf)	0.04
RAD50	2 (11.8)	0 (0.0)	Inf (0.750-Inf)	0.04
RECQL4	2 (11.8)	0 (0.0)	Inf (0.750-Inf)	0.04

Inf = infinite
*Results are shown only for genes with p values < 0.2.

Cross-Validation Analysis

[0059] Because the genes that defined responders were few, genes mutated in more nonresponder patients were targeted for classifier development. A panel of genes were selected and ranked by choosing the gene that allowed inference of the most additional nonresponders in each iteration until all nonresponders were covered. From the selected panel, 17 classifier models were developed including variants in *ATP6AP1*, *EP400*, *ARID1A*, *SOCS1*, *TBL1XR1*, *CNOT1*, and *KDM2B* (FIG. 3).

[0060] The mean ORR of predicted responders shown by the solid line ("mean ORR of predicted responders") in FIG. 4 is based on 10-fold cross-validation for 17 different responder/nonresponder classification models, showing an increase in predicted ORR as more genes were added. Each model was defined by the number of genes used to build it, with genes being added in order of decreasing new information content, as shown in FIG. 3. The dotted line in FIG. 4 ("ORR") represents the ORR of the entire patient cohort regardless of classification.

Genes of Interest in Nonresponders

[0061] The mutation status of the top 5 ranked genes (*ATP6AP1*, *EP400*, *ARID1A*, *SOCS1*, and *TBL1XR1*) was most informative in predicting a lack of response. Mutations in these genes were found exclusively in nonresponders and are described below.

[0062] *ATP6AP1* - The majority of the mutations seen in the *ATP6AP1* gene were found in the ATP-synthase S1 region (FIG. 5).

[0063] *EP400* - 7 nonresponder patients had somatic mutations in the *EP400* gene, and 5 of these patients had mutations marked as "deleterious" by metaSVM (FIG. 6). *EP400* encodes a histone acetylase complex component.

[0064] *ARID1A* - 5 mutations in putative tumor suppressor *ARID1A* occurred in the DAWN dataset and 2 of these caused the formation of premature stop codons (FIG. 7).

[0065] *SOCS1* - The majority of the 6 *SOCS1* mutations observed in the DAWN study were predicted as deleterious by metaSVM and are in the SH2 domain (FIG. 8).

[0066] *TBL1XR1* - 4 of the 5 putative somatic mutations in the *TBLXR1* gene were predicted as deleterious by metaSVM; the remaining variant represents the gain of a premature stop codon (FIG.9).

[0067] *CARD11* - *CARD11* contained 8 variants found in 6 patients. Each of the *CARD11* variants were identified individually, even though *CARD11* was not a top ranked gene in this analysis. A total of 4 variants from 2 patients were left after the filtering applied here (T117P, D230N, C351S, and S352P), and could be deleterious, though they were not identified as deleterious by metaSVM. Of the variants filtered out, 1 had a variant allele frequency (VAF) of < 0.05 (VAF = 0.04672897), 1 was in the non-Catalogue Of Somatic Mutations In Cancer (COSMIC) dbSNP group that was subjected to the VAF < 0.4 filter (VAF = 0.49371981), and the others were marked in dbSNP as "germline only," suggesting that much of the trend in *CARD11* is due to germline variants.

Somatic mutations

[0068] Somatic mutations identified in the responders and nonresponders are provided in Table 2.

Table 2. Somatic mutations identified in DAWN FL patients

Gene	Transcript	Allele	Codon change	AA change
AHNAK	ENST00000378024	A/T	gTt/gAt	V3640D

Gene	Transcript	Allele	Codon change	AA change
AHNAK	ENST00000378024	T/C	aAg/aGg	K2180R
AHNAK	ENST00000378024	C/T	Ggg/Agg	G799R
AHNAK	ENST00000378024	G/C	Caa/Gaa	Q3796E
AHNAK	ENST00000378024	T/C	gAt/gGt	D4045G
ANXA6	ENST00000354546	C/T	atG/atA	M582I
ANXA6	ENST00000354546	T/A	aaA/aaT	K374N
ARID1A	ENST00000324856	C/T	Cga/Tga	R693*
ARID1A	ENST00000324856	T/C	cTc/cCc	L2056P
ARID1A	ENST00000324856	G/A	Ggc/Agc	G1375S
ARID1A	ENST00000324856	A/G	Aat/Gat	N1997D
ARID1A	ENST00000324856	C/A	taC/taA	Y229*
ATP6AP1	ENST00000369762	T/C	aTg/aCg	M342T
ATP6AP1	ENST00000369762	T/A	gTc/gAc	V374D
ATP6AP1	ENST00000369762	T/C	cTg/cCg	L82P
ATP6AP1	ENST00000369762	C/G	aCa/aGa	T222R
ATP6AP1	ENST00000369762	G/A	Gcc/Acc	A415T
ATP6AP1	ENST00000369762	G/A	Ggg/Agg	G363R
ATP6AP1	ENST00000369762	G/A	Ggg/Agg	G363R
BCL9L	ENST00000334801	T/G	Aat/Cat	N627H
BCL9L	ENST00000334801	T/G	Aat/Cat	N627H
BCL9L	ENST00000334801	T/G	Aat/Cat	N627H
BCL9L	ENST00000334801	T/G	Aat/Cat	N627H
BTG1	ENST00000256015	G/C	Cga/Gga	R35G
BTG1	ENST00000256015	C/T	Gaa/Aaa	E50K
CLTC	ENST00000269122	C/A	aCc/aAc	T109N
CLTC	ENST00000269122	G/C	Gca/Cca	A81P
CLTC	ENST00000269122	G/A	Gca/Aca	A68T
CNOT1	ENST00000317147	T/C	Aca/Gca	T818A
CNOT1	ENST00000317147	T/A	gAt/gTt	D2179V
CNOT1	ENST00000317147	C/T	gGc/gAc	G404D
CNOT1	ENST00000317147	C/T	gGa/gAa	G690E
CNOT1	ENST00000317147	G/A	cCa/cTa	P1628L
CNOT1	ENST00000317147	G/A	aCt/aTt	T927I
DIAPH1	ENST00000253811	G/A	Ctc/Ttc	L977F
DIAPH1	ENST00000253811	C/A	Gtt/Ttt	V762F
EP400	ENST00000333577	C/T	Cgg/Tgg	R1437W
EP400	ENST00000333577	A/C	Atg/Ctg	M546L
EP400	ENST00000333577	C/T	gCg/gTg	A707V
EP400	ENST00000333577	C/T	Cag/Tag	Q28*
EP400	ENST00000333577	C/T	tCg/tTg	S49L
EP400	ENST00000333577	A/G	cAt/cGt	H1322R

Gene	Transcript	Allele	Codon change	AA change
EP400	ENST00000333577	G/A	aGg/aAg	R1958K
EP400	ENST00000333577	C/T	cCg/cTg	P48L
FANCA	ENST00000389301	G/A	Cgc/Tgc	R1011C
FANCA	ENST00000389301	C/A	agG/agT	R1349S
FANCA	ENST00000389301	A/G	cTg/cCg	L379P
HIST1H1B	ENST00000331442	C/T	gGc/gAc	G106D
HIST1H1B	ENST00000331442	C/T	gGc/gAc	G73D
HIST1H1B	ENST00000331442	C/T	Gct/Act	A215T
HIST1H1B	ENST00000331442	C/G	ttG/ttC	L90F
HIST1H1B	ENST00000331442	C/T	Gct/Act	A215T
HIST1H1B	ENST00000331442	G/T	agC/agA	S89R
HIST1H1B	ENST00000331442	C/G	Gct/Cct	A50P
HIST1H1B	ENST00000331442	C/G	Gct/Cct	A131P
HIST1H1B	ENST00000331442	C/G	aGc/aCc	S89T
HIST1H1B	ENST00000331442	C/T	gGc/gAc	G106D
KDM2B	ENST00000377071	C/T	Gat/Aat	D122N
KDM2B	ENST00000377071	C/T	Gcc/Acc	A818T
KDM2B	ENST00000377071	G/A	Cgg/Tgg	R1025W
KDM2B	ENST00000377071	T/A	Aca/Tca	T602S
MYBBP1A	ENST00000381556	G/C	Ctg/Gtg	L1323V
MYBBP1A	ENST00000381556	G/A	Cgt/Tgt	R885C
MYBBP1A	ENST00000381556	G/C	cCg/cGg	P500R
MYBBP1A	ENST00000381556	C/A	Gac/Tac	D749Y
NACA	ENST00000454682	A/G	Tcc/Ccc	S1190P
NACA	ENST00000454682	A/G	Tcc/Ccc	S1190P
NACA	ENST00000454682	C/G	aGc/aCc	S394T
NACA	ENST00000454682	A/G	Tcc/Ccc	S1190P
NBPF1	ENST00000430580	C/A	gGt/gTt	G916V
NBPF1	ENST00000430580	G/A	cCg/cTg	P675L
NBPF1	ENST00000430580	T/A	cAg/cTg	Q1132L
NBPF1	ENST00000430580	T/A	cAg/cTg	Q1132L
NBPF1	ENST00000430580	T/A	aAg/aTg	K623M
NBPF1	ENST00000430580	T/C	Agc/Ggc	S853G
NBPF1	ENST00000430580	C/G	caG/caC	Q650H
NBPF1	ENST00000430580	C/T	tGc/tAc	C663Y
NBPF1	ENST00000430580	A/G	Tgt/Cgt	C251R
NBPF1	ENST00000430580	T/A	Agg/Tgg	R364W
NBPF1	ENST00000430580	T/C	gAa/gGa	E1011G
NBPF1	ENST00000430580	G/T	gaC/gaA	D905E
NBPF1	ENST00000430580	T/A	gAt/gTt	D896V
NBPF1	ENST00000430580	C/T	Gag/Aag	E448K

Gene	Transcript	Allele	Codon change	AA change
NBPF1	ENST00000430580	C/T	Ggc/Agc	G6S
NBPF1	ENST00000430580	T/G	Aag/Cag	K59Q
NBPF1	ENST00000430580	T/A	aAg/aTg	K623M
NBPF1	ENST00000430580	T/A	cAg/cTg	Q1132L
NBPF1	ENST00000430580	C/G	caG/caC	Q650H
NBPF1	ENST00000430580	C/A	Gtt/Ttt	V174F
NBPF1	ENST00000430580	C/A	Gtg/Ttg	V1100L
NBPF1	ENST00000430580	G/A	tCt/tTt	S611F
NBPF1	ENST00000430580	C/T	Gaa/Aaa	E439K
NBPF1	ENST00000430580	T/A	aAg/aTg	K623M
NBPF1	ENST00000430580	G/C	Cct/Gct	P1070A
NBPF1	ENST00000430580	C/T	Ggc/Agc	G1062S
NBPF1	ENST00000430580	C/G	caG/caC	Q650H
NBPF1	ENST00000430580	C/G	caG/caC	Q650H
NBPF1	ENST00000430580	T/A	aAg/aTg	K623M
NBPF1	ENST00000430580	C/T	atG/atA	M1133I
NBPF1	ENST00000430580	T/A	aAg/aTg	K623M
NBPF1	ENST00000430580	T/A	Agg/Tgg	R364W
NBPF1	ENST00000430580	C/G	caG/caC	Q650H
NBPF10	ENST00000342960	G/C	aaG/aaC	K56N
NBPF10	ENST00000342960	C/T	Ccc/Tcc	P1180S
NBPF10	ENST00000342960	C/T	Ctc/Ttc	L92F
NBPF10	ENST00000342960	A/G	gAg/gGg	E1171G
NBPF10	ENST00000342960	G/T	Ggg/Tgg	G387W
NBPF10	ENST00000342960	C/T	Ctc/Ttc	L92F
NBPF10	ENST00000342960	C/A	tgC/tgA	C1179*
NBPF10	ENST00000342960	A/T	cAg/cTg	Q3488L
NBPF10	ENST00000342960	A/G	gAc/gGc	D65G
NBPF10	ENST00000342960	C/T	Ctc/Ttc	L92F
NBPF10	ENST00000342960	C/T	Ctc/Ttc	L92F
NBPF10	ENST00000342960	C/T	Ctc/Ttc	L92F
NBPF10	ENST00000342960	C/T	Ctc/Ttc	L92F
NBPF10	ENST00000342960	C/T	Ctc/Ttc	L92F
NBPF10	ENST00000342960	C/T	Ctc/Ttc	L92F
NBPF10	ENST00000342960	C/A	aaC/aaA	N308K
NBPF10	ENST00000342960	C/T	Cga/Tga	R104*
NBPF10	ENST00000342960	C/T	Ctc/Ttc	L92F
NBPF10	ENST00000342960	C/T	Cga/Tga	R375*
NBPF10	ENST00000342960	A/T	gaA/gaT	E3455D
NBPF10	ENST00000342960	C/T	Ctc/Ttc	L92F
NBPF10	ENST00000342960	C/T	Ctc/Ttc	L92F

Gene	Transcript	Allele	Codon change	AA change
NBPF10	ENST00000342960	G/A	cGc/cAc	R25H
NBPF10	ENST00000342960	G/T	Gcc/Tcc	A48S
NBPF10	ENST00000342960	G/C	caG/caC	Q142H
NBPF10	ENST00000342960	C/T	Ctc/Ttc	L92F
NBPF10	ENST00000342960	C/T	Ctc/Ttc	L92F
NCOA4	ENST00000452682	A/C	gaA/gaC	E54D
NCOA4	ENST00000431200	G/A	Gca/Aca	A7T
NCOA4	ENST00000431200	G/A	Gca/Aca	A7T
NCOA4	ENST00000431200	T/G	cTa/cGa	L9R
NCOA4	ENST00000452682	G/A	cGg/cAg	R52Q
NCOA4	ENST00000431200	G/A	Gca/Aca	A7T
NEDD4L	ENST00000400345	G/A	Gag/Aag	E271K
NEDD4L	ENST00000400345	C/T	Cag/Tag	Q305*
PARP10	ENST00000525773	C/T	Gac/Aac	D260N
PARP10	ENST00000525773	C/T	Gag/Aag	E1017K
PBRM1	ENST00000296302	G/T	cCt/cAt	P1343H
PBRM1	ENST00000296302	G/T	gaC/gaA	D159E
PRDM1	ENST00000369096	T/C	aTt/aCt	I329T
PRDM1	ENST00000369096	G/A	Gtg/Atg	V250M
PRDM16	ENST00000270722	C/T	Ccc/Tcc	P112S
PRDM16	ENST00000270722	G/A	Gtg/Atg	V48M
PRDM16	ENST00000270722	C/A	cCa/cAa	P50Q
PRDM16	ENST00000270722	C/T	aCc/aTc	T609I
PRDM16	ENST00000270722	A/G	Aat/Gat	N161D
RAD50	ENST00000434288	C/A	taC/taA	Y109*
RAD50	ENST00000265335	A/G	aAa/aGa	K398R
RAD50	ENST00000265335	C/T	Cga/Tga	R365*
RECQL4	ENST00000428558	C/A	cGg/cTg	R755L
RECQL4	ENST00000428558	C/T	Gga/Aga	G892R
SOCS1	ENST00000332029	G/T	agC/agA	S125R
SOCS1	ENST00000332029	T/C	gAc/gGc	D105G
SOCS1	ENST00000332029	A/T	Tga/Aga	212R**
SOCS1	ENST00000332029	G/C	Ctg/Gtg	L74V
SOCS1	ENST00000332029	C/T	Gga/Aga	G122R
SOCS1	ENST00000332029	G/C	Ctg/Gtg	L150V
TBL1XR1	ENST00000430069	G/A	Caa/Taa	Q442*
TBL1XR1	ENST00000430069	A/C	gTc/gGc	V228G
TBL1XR1	ENST00000430069	G/A	tCt/tTt	S461F
TBL1XR1	ENST00000430069	C/T	gGa/gAa	G285E
TBL1XR1	ENST00000430069	C/T	gGa/gAa	G285E
TBL1XR1	ENST00000430069	A/T	gTa/gAa	V466E

* Stop codon gained; ** Stop codon lost.

Conclusions

[0069] Mutational analysis of genes in patients from the phase 2 DAWN trial yielded insights into the mechanism of ibrutinib response and resistance in R/R FL.

[0070] Those skilled in the art will appreciate that numerous changes and modifications can be made to the preferred embodiments of the invention and that such changes and modifications can be made without departing from the spirit of the invention. It is, therefore, intended that the appended claims cover all such equivalent variations as fall within the true spirit and scope of the invention.

[0071] The disclosures of each patent, patent application, and publication cited or described in this document are hereby incorporated herein by reference, in its entirety.

EMBODIMENTS

[0072] The following list of embodiments is intended to complement, rather than displace or supersede, the previous descriptions.

Embodiment 1. Use of ibrutinib in the manufacture of a medicament for the treatment of follicular lymphoma (FL) in a subject not having one or more mutations as defined in Table 2 in one or more genes selected from *AHNAK*, *ARID1A*, *ATP6AP1*, *BCL9L*, *CLTC*, *CNOT1*, *EP400*, *KDM2B*, *MYBBP1A*, *NACA*, *NBPF1*, *NBPF10*, *NCOA4*, *NEDD4L*, *PRDM16*, *SOCS1*, and *TBL1XR1*.

Embodiment 2. Ibrutinib for use in the treatment of follicular lymphoma (FL) in a subject not having one or more mutations as defined in Table 2 in one or more genes selected from *AHNAK*, *ARID1A*, *ATP6AP1*, *BCL9L*, *CLTC*, *CNOT1*, *EP400*, *KDM2B*, *MYBBP1A*, *NACA*, *NBPF1*, *NBPF10*, *NCOA4*, *NEDD4L*, *PRDM16*, *SOCS1*, and *TBL1XR1*.

Embodiment 3. A method of treating follicular lymphoma (FL) in a subject, the method comprising administering to the subject a therapeutically effective amount of ibrutinib to thereby treat the FL, wherein the subject does not have one or more mutations as defined in Table 2 in one or more genes selected from *AHNAK*, *ARID1A*, *ATP6AP1*, *BCL9L*, *CLTC*, *CNOT1*, *EP400*, *KDM2B*, *MYBBP1A*, *NACA*, *NBPF1*, *NBPF10*, *NCOA4*, *NEDD4L*, *PRDM16*, *SOCS1*, and *TBL1XR1*.

Embodiment 4. A method of treating follicular lymphoma (FL) in a subject not having one or more mutations as defined in Table 2 in one or more genes selected from *AHNAK*, *ARID1A*, *ATP6AP1*, *BCL9L*, *CLTC*, *CNOT1*, *EP400*, *KDM2B*, *MYBBP1A*, *NACA*, *NBPF1*, *NBPF10*, *NCOA4*, *NEDD4L*, *PRDM16*, *SOCS1*, and *TBL1XR1*, the method comprising administering to the subject a therapeutically effective amount of ibrutinib to thereby treat the FL.

Embodiment 5. The use or method of any one of embodiments 2-4, wherein the therapeutically effective amount of ibrutinib comprises from about 420 mg to about 840 mg.

Embodiment 6. The use or method of embodiment 5, wherein the therapeutically effective amount of ibrutinib comprises 560 mg.

Embodiment 7. The use or method of any one of the previous embodiments, wherein the FL is relapsed/refractory (R/R) FL.

Embodiment 8. The use or method of any one of the previous embodiments, wherein, prior to the administering, the subject had a diagnosis of grade 1, 2, or 3a nontransformed FL.

Embodiment 9. The use or method of embodiment 8, wherein, prior to the administering, the subject had been treated with ≥ 2 prior lines of therapy.

Embodiment 10. The use or method of embodiment 9, wherein, prior to the administering, the subject was R/R to a last prior line of therapy with an anti-CD20 monoclonal antibody-containing chemoimmunotherapy regimen.

Embodiment 11. The use or method of any one of the previous embodiments, wherein the subject has a partial response or a complete response.

Embodiment 12. A method of predicting a likelihood of nonresponsiveness to ibrutinib in a subject having follicular lymphoma, the method comprising analyzing a sample from the subject for one or more mutations as defined in Table 2 in one or more genes selected from *AHNAK*, *ARID1A*, *ATP6AP1*, *BCL9L*, *CLTC*, *CNOT1*, *EP400*, *KDM2B*, *MYBBP1A*, *NACA*, *NBPF1*, *NBPF10*, *NCOA4*, *NEDD4L*, *PRDM16*, *SOCS1*, and *TBL1XR1*, wherein the one or more mutations in the one or more genes is indicative of nonresponsiveness to ibrutinib.

Embodiment 13. The method of embodiment 12, further comprising administering a therapeutically effective amount of ibrutinib to thereby treat the FL if the subject does not have the one or more mutations in the one or more genes.

WHAT IS CLAIMED:

1. Use of ibrutinib in the manufacture of a medicament for the treatment of follicular lymphoma (FL) in a subject not having one or more mutations as defined in Table 2 in one or more genes selected from *AHNAK*, *ARID1A*, *ATP6AP1*, *BCL9L*, *CLTC*, *CNOT1*, *EP400*, *KDM2B*, *MYBBP1A*, *NACA*, *NBPF1*, *NBPF10*, *NCOA4*, *NEDD4L*, *PRDM16*, *SOCS1*, and *TBL1XR1*.

2. Ibrutinib for use in the treatment of follicular lymphoma (FL) in a subject not having one or more mutations as defined in Table 2 in one or more genes selected from *AHNAK*, *ARID1A*, *ATP6AP1*, *BCL9L*, *CLTC*, *CNOT1*, *EP400*, *KDM2B*, *MYBBP1A*, *NACA*, *NBPF1*, *NBPF10*, *NCOA4*, *NEDD4L*, *PRDM16*, *SOCS1*, and *TBL1XR1*.

3. A method of treating follicular lymphoma (FL) in a subject, the method comprising:

administering to the subject a therapeutically effective amount of ibrutinib to thereby treat the FL, wherein the subject does not have one or more mutations as defined in Table 2 in one or more genes selected from *AHNAK*, *ARID1A*, *ATP6AP1*, *BCL9L*, *CLTC*, *CNOT1*, *EP400*, *KDM2B*, *MYBBP1A*, *NACA*, *NBPF1*, *NBPF10*, *NCOA4*, *NEDD4L*, *PRDM16*, *SOCS1*, and *TBL1XR1*.

4. A method of treating follicular lymphoma (FL) in a subject not having one or more mutations as defined in Table 2 in one or more genes selected from *AHNAK*, *ARID1A*, *ATP6AP1*, *BCL9L*, *CLTC*, *CNOT1*, *EP400*, *KDM2B*, *MYBBP1A*, *NACA*, *NBPF1*, *NBPF10*, *NCOA4*, *NEDD4L*, *PRDM16*, *SOCS1*, and *TBL1XR1*, the method comprising:

administering to the subject a therapeutically effective amount of ibrutinib to thereby treat the FL.

5. The use or method of any one of claims 2-4, wherein the therapeutically effective amount of ibrutinib comprises from about 420 mg to about 840 mg.

6. The use or method of claim 5, wherein the therapeutically effective amount of ibrutinib comprises 560 mg.

7. The use or method of any one of the previous claims, wherein the FL is relapsed/refractory (R/R) FL.

8. The use or method of any one of the previous claims, wherein, prior to the administering, the subject had a diagnosis of grade 1, 2, or 3a nontransformed FL.

9. The use or method of claim 8, wherein, prior to the administering, the subject had been treated with ≥ 2 prior lines of therapy.

10. The use or method of claim 9, wherein, prior to the administering, the subject was R/R to a last prior line of therapy with an anti-CD20 monoclonal antibody-containing chemoimmunotherapy regimen.

11. The use or method of any one of the previous claims, wherein the subject has a partial response or a complete response.

12. A method of predicting a likelihood of nonresponsiveness to ibrutinib in a subject having follicular lymphoma, the method comprising:

analyzing a sample from the subject for one or more mutations as defined in Table 2 in one or more genes selected from *AHNAK*, *ARID1A*, *ATP6AP1*, *BCL9L*, *CLTC*, *CNOT1*, *EP400*, *KDM2B*, *MYBBP1A*, *NACA*, *NBPF1*, *NBPF10*, *NCOA4*, *NEDD4L*, *PRDM16*, *SOCS1*, and *TBL1XR1*, wherein the one or more mutations in the one or more genes is indicative of nonresponsiveness to ibrutinib.

13. The method of claim 12, further comprising administering a therapeutically effective amount of ibrutinib to thereby treat the FL if the subject does not have the one or more mutations in the one or more genes.

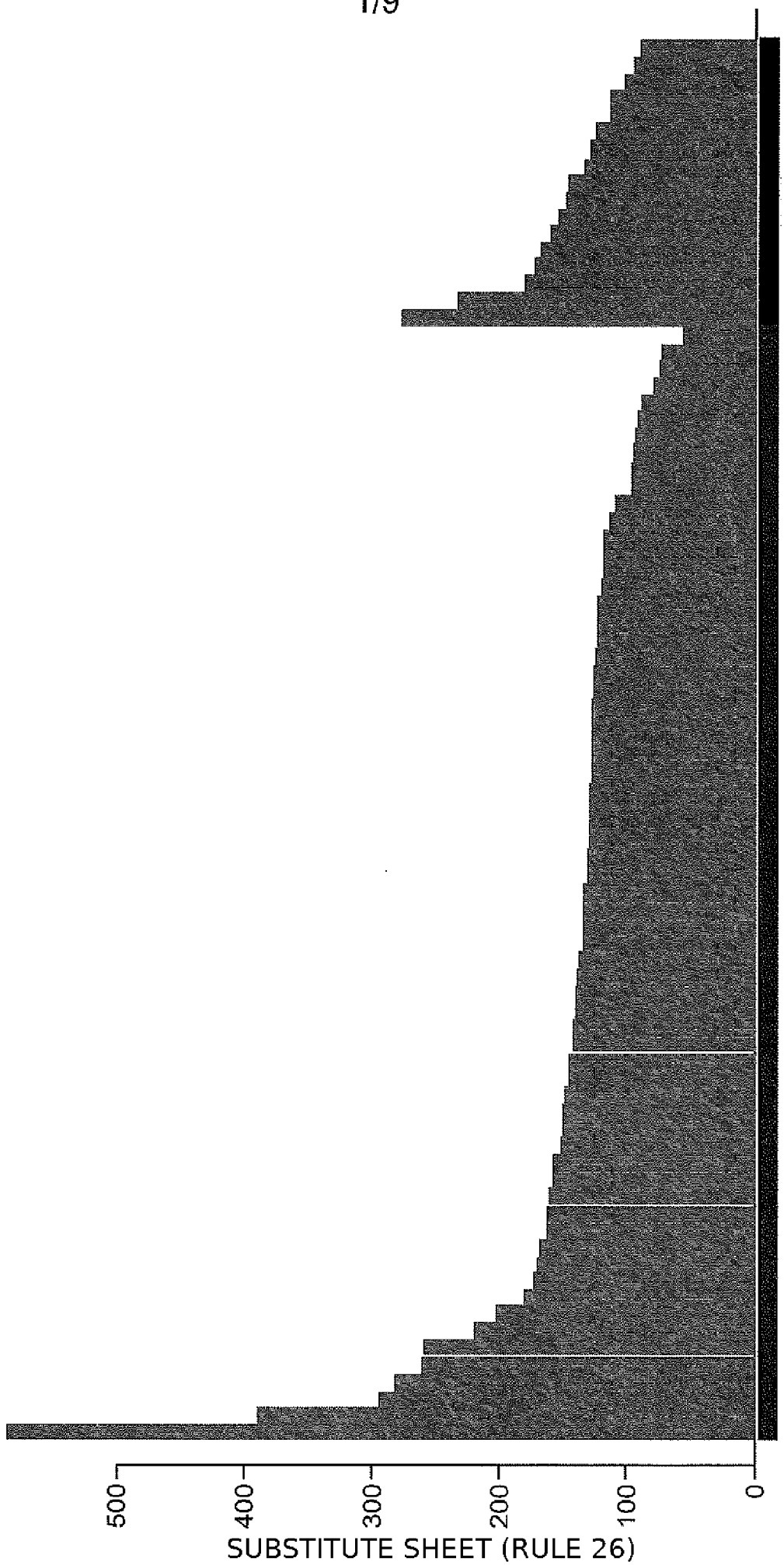

FIG. 1

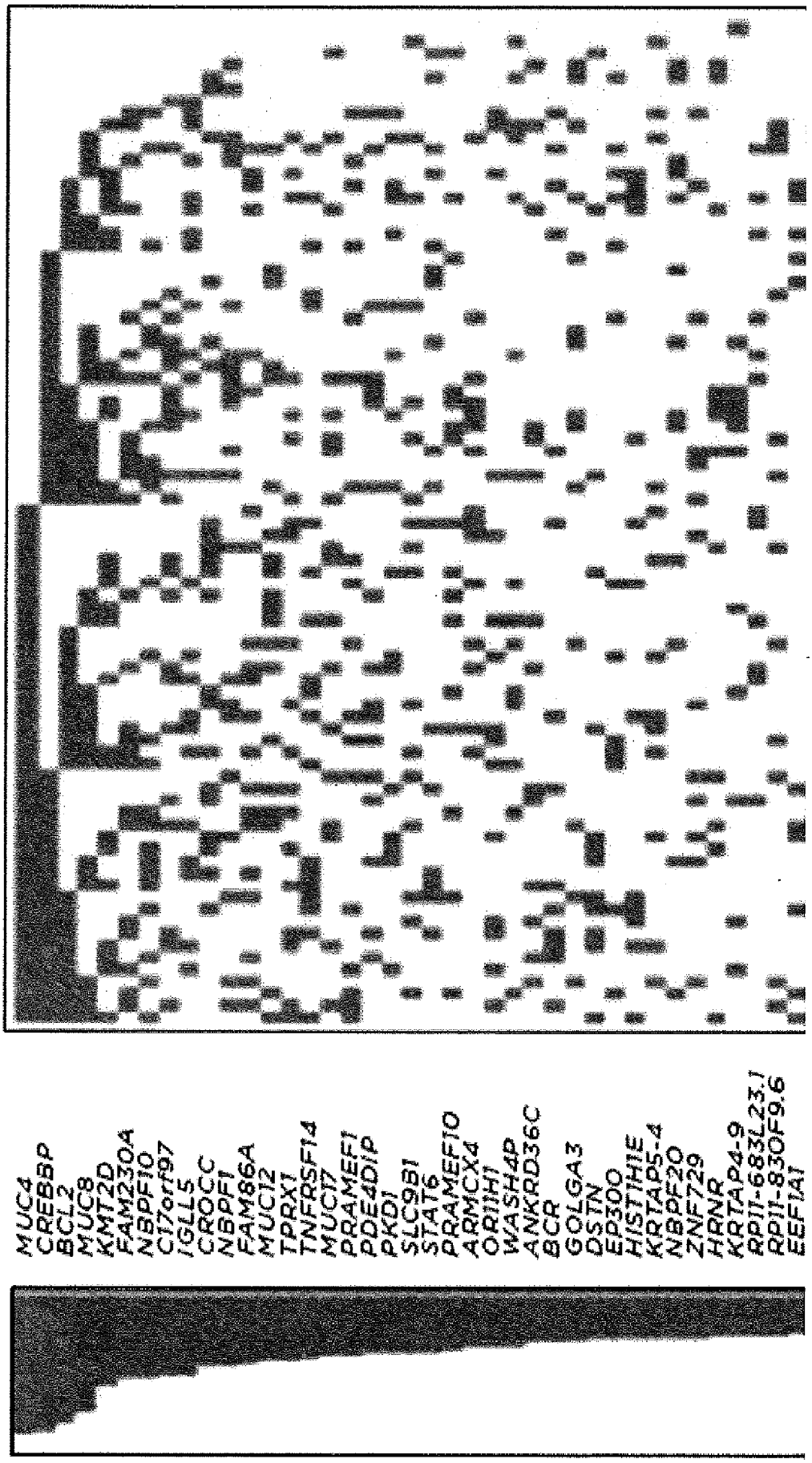
MUC4
CREBBP
BCL2
MUC8
KMT2D
FAM230A
NBPF10
C17orf97
IGLL5
CROCC
NBPF1
FAM86A
MUC12
TPRX1
TNFRSF14
MUC17
PRAMEF1
PDE4DIP
PKD1
SLC9B1
STAT6
PRAMEF10
ARMCX4
ORI1H1
WASH4P
ANKRD36C
BCR
GOLGA3
OSTN
EP300
HIST1H1E
KRTAP5-4
NBPF20
ZNF729
HRNR
KRTAP4-9
RP11-683L23.1
RP11-830F9.6
EEF1A1

FIG. 2

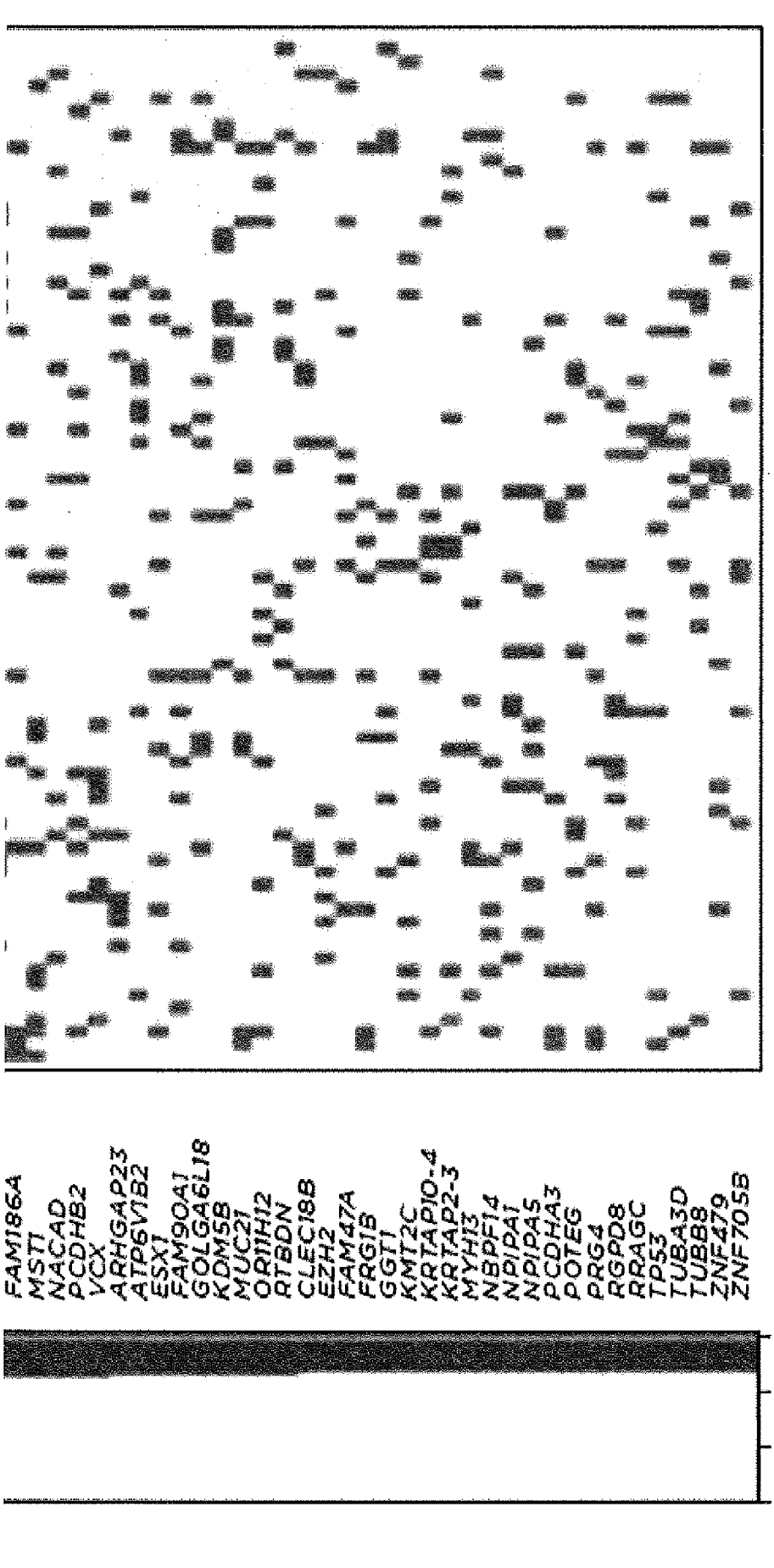
FAM186A
MST1
NACAD
PCDHB2
VCX
ARHGAP23
ATP6V1B2
ESX1
FAM90A1
GOLGA6L18
KDM5B
MUC21
ORIIH12
RTBDN
CLEC18B
EZH2
FAM47A
FRG1B
GGT1
KMT2C
KRTAP10-4
KRTAP2-3
MYH13
NBPF14
NPIPA1
NPIPA5
PCDHA3
POTEG
PRG4
RGPD8
RRAGC
TP53
TUBA3D
TUBB8
ZNF479
ZNF705B
60 40 20 0
Individuals (%)
Individuals (N = 83)

FIG. 2 cont.

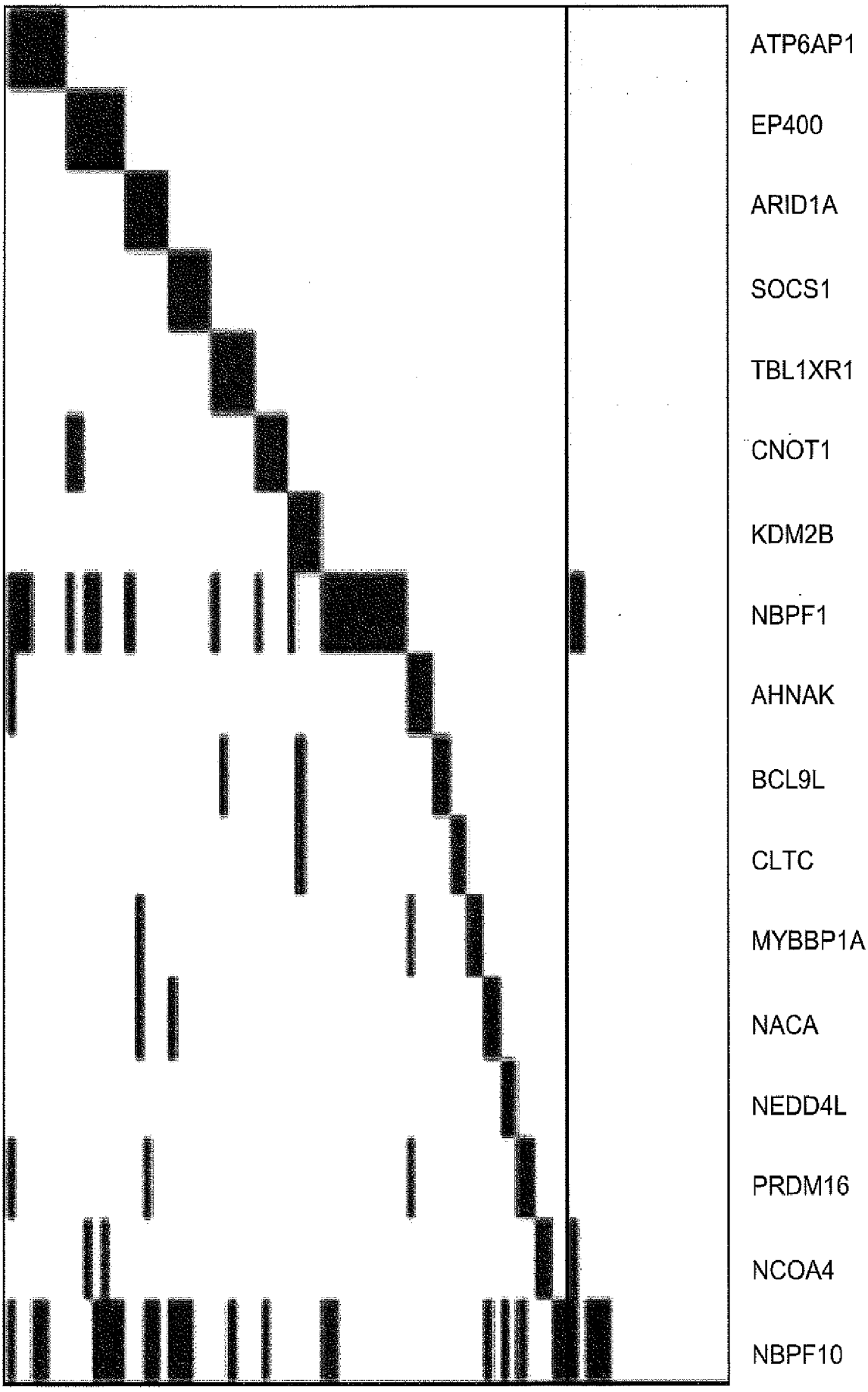
ATP6AP1
EP400
ARID1A
SOCS1
TBL1XR1
CNOT1
KDM2B
NBPF1
AHNAK
BCL9L
CLTC
MYBBP1A
NACA
NEDD4L
PRDM16
NCOA4
NBPF10
NONRESPONDERS (N = 66)
RESPONDERS (N = 17)

FIG. 3

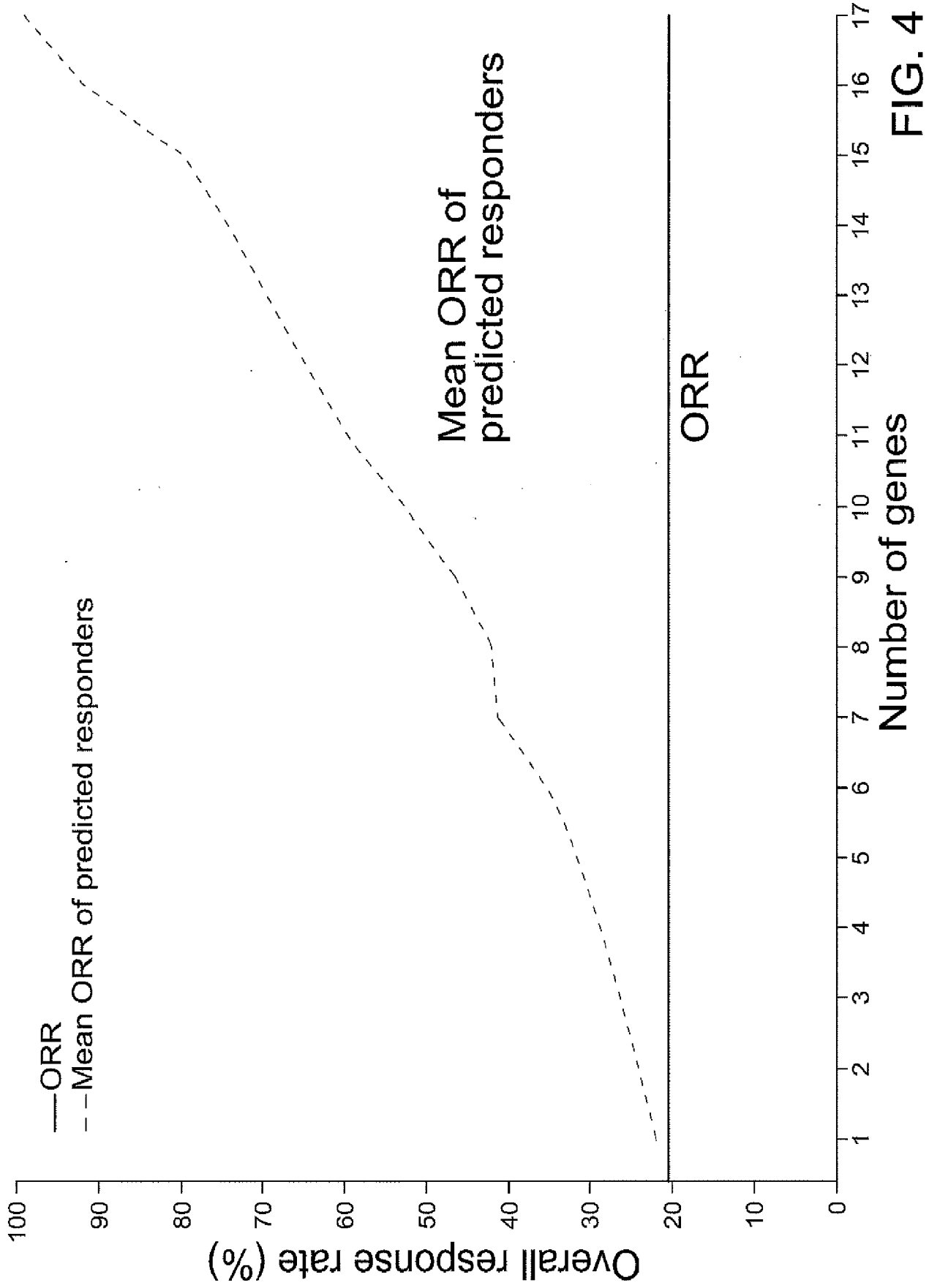
Overall response rate (%)
100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
Number of genes
ORR
Mean ORR of predicted responders
Mean ORR of predicted responders
ORR

FIG. 4

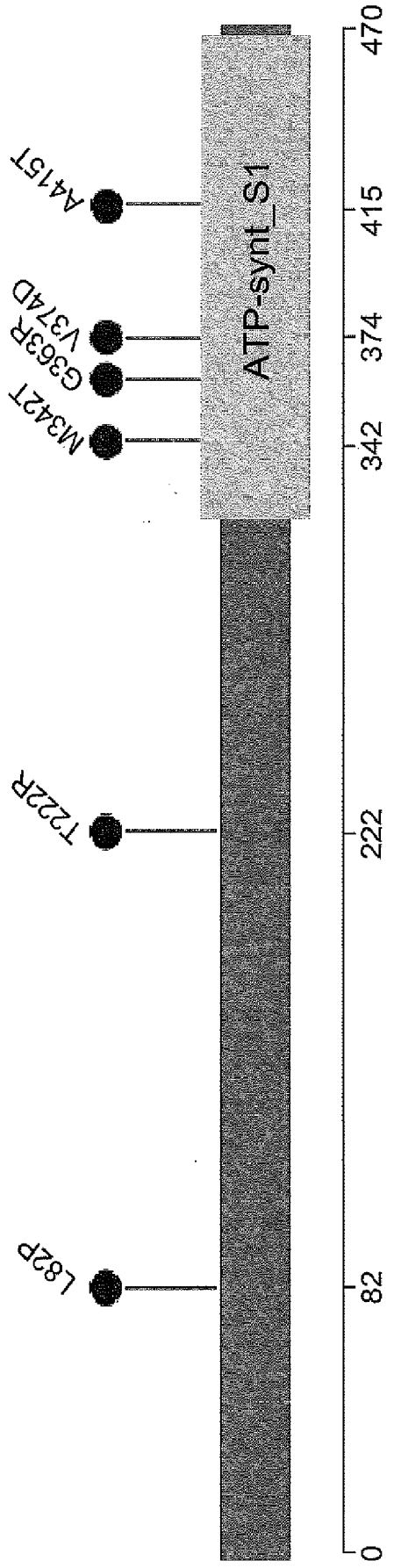
470
415
374
342
222
82
0
ATP-synt_S1
A415T
V374D
G363R
M342T
T222R
L82P

FIG. 5

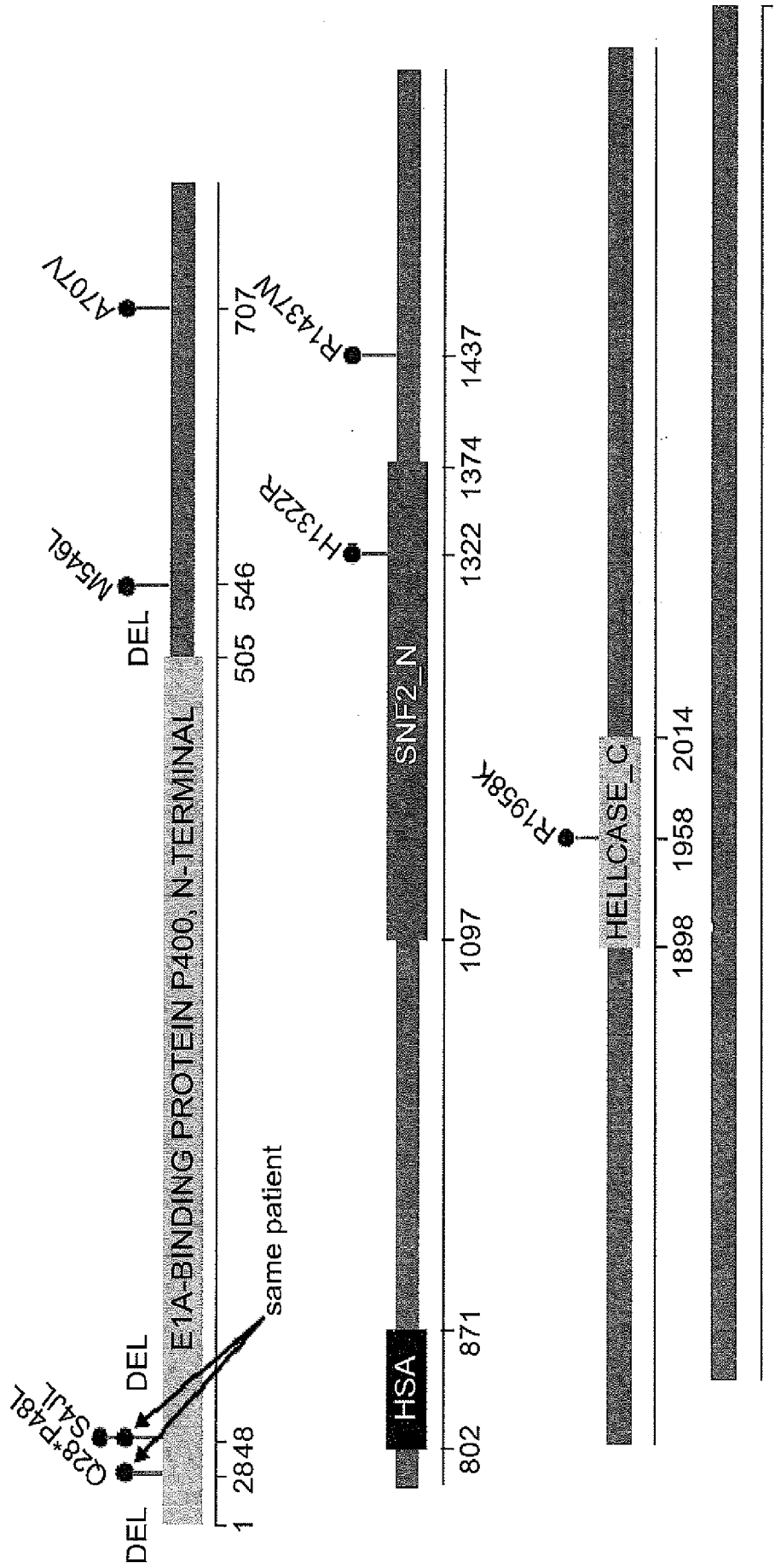
A70TV
M546L
DEL
Q28*P48L
S4JL
DEL
DEL
E1A-BINDING PROTEIN P400, N-TERMINAL
same patient
HSA
SNF2_N
HELICASE_C
R1437W
H1322R
R1958K
1
2848
505
546
707
802
871
1097
1322
1374
1437
1898
1958
2014

FIG. 6

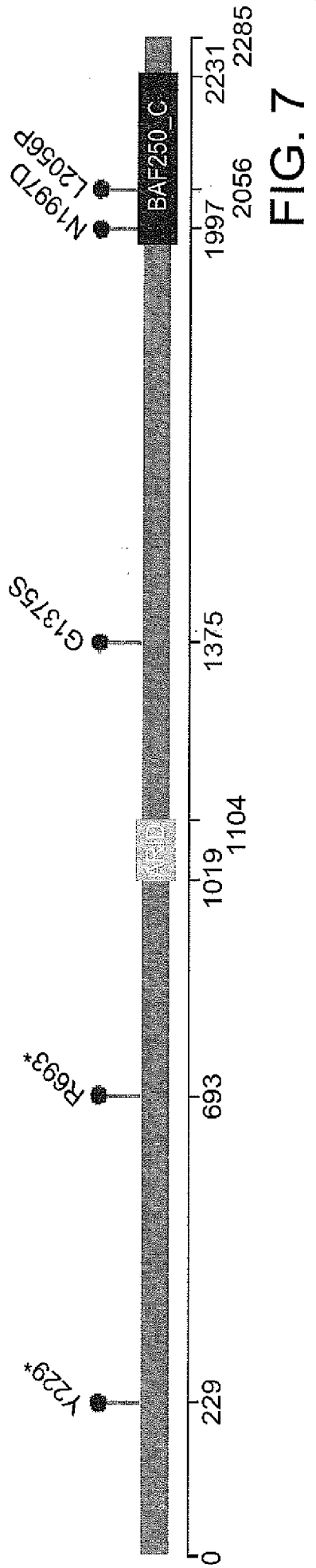
BAF250_C
ARID
0
229
693
1019
1104
1375
1997
2056
2231
2285
Y229*
R693*
G1375S
N1997D
L2056P

FIG. 7

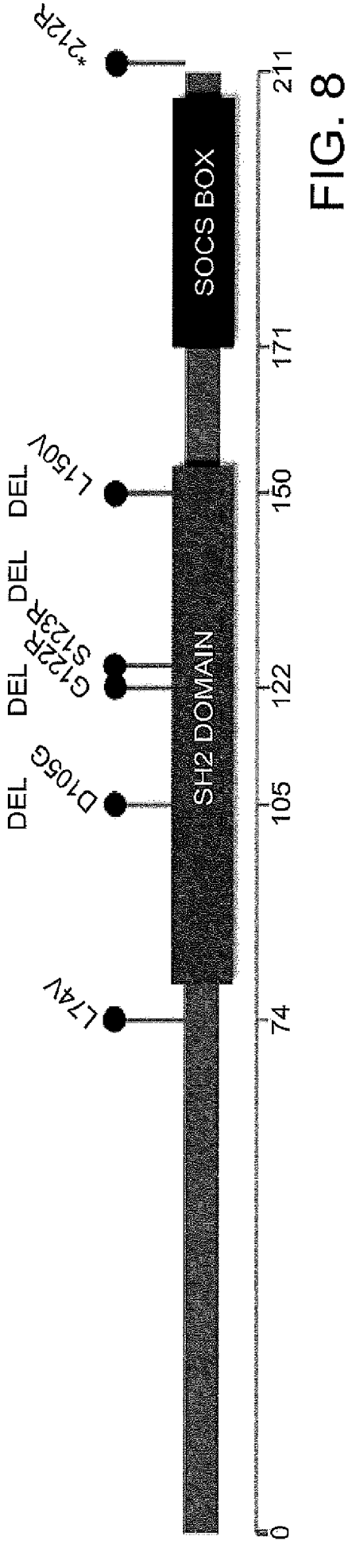
SOCS BOX
SH2 DOMAIN
0
74
105
122
150
171
211
L74V
D105G
DEL
G122R-S125R
DEL
L150V
DEL
*212R

FIG. 8

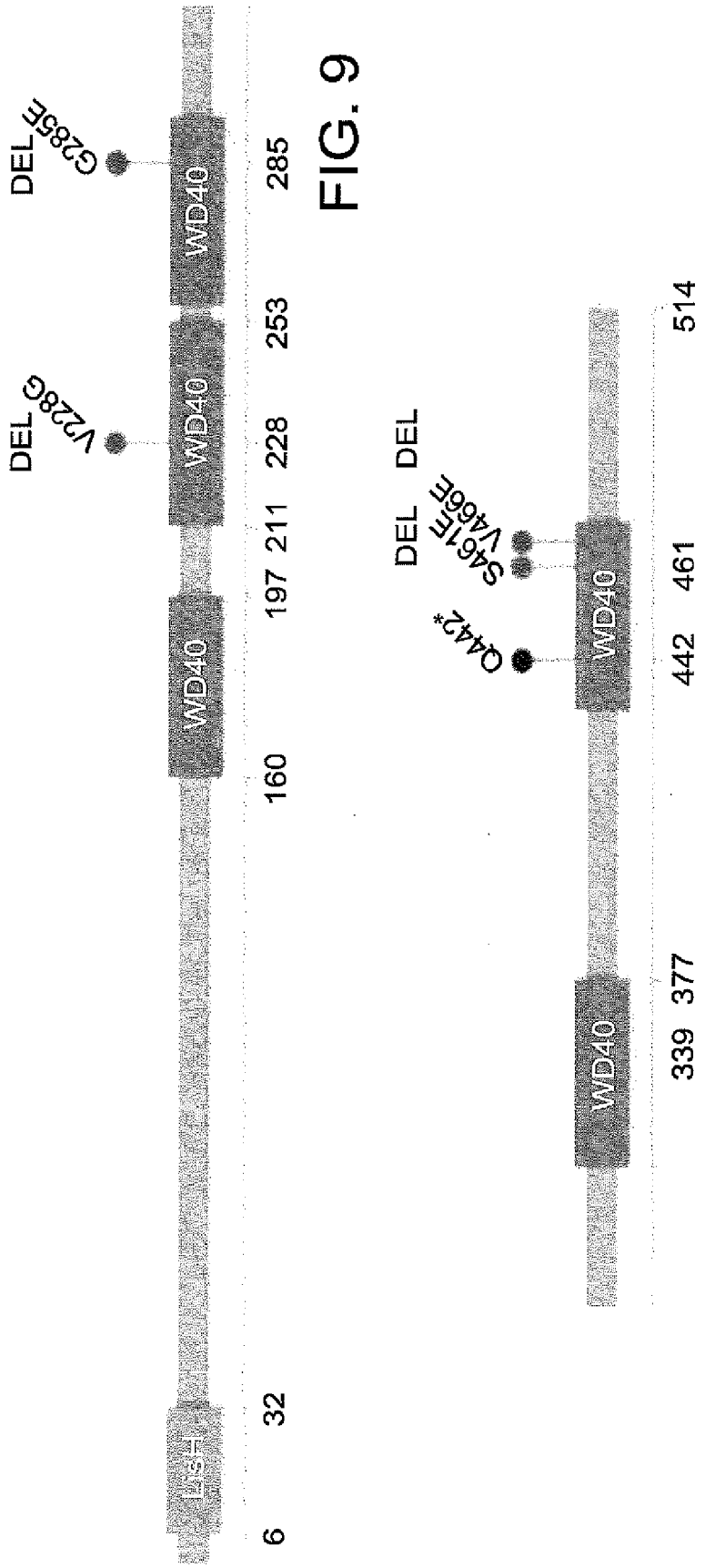

FIG. 9

FIG. 9 cont.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/063234

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P35/02 A61K31/519
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017/087947 A2 (PHARMACYCLICS LLC [US]; WANG ZHENGYUANG [US]) 26 May 2017 (2017-05-26) *cf. abstract, section [0039] at pages 13-20, section [0049] at page 24, claim 17*	1-13
X	US 2016/032404 A1 (SCHWEIGHOFER KARL [US] ET AL) 4 February 2016 (2016-02-04) *cf. abstract, section [0004] at page 1, claims 1, 2, 8 and 9*	1-13

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 January 2020	11/02/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Stoltner, Anton

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2019/063234

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2017087947 A2	26-05-2017	NONE	
US 2016032404 A1	04-02-2016	AU 2015296010 A1	02-02-2017
		BR 112017001677 A2	17-07-2018
		CA 2955744 A1	04-02-2016
		CN 106714804 A	24-05-2017
		EP 3185870 A1	05-07-2017
		JP 2017523188 A	17-08-2017
		KR 20170042614 A	19-04-2017
		RU 2017106794 A	03-09-2018
		SG 11201700774U A	27-02-2017
		US 2016032404 A1	04-02-2016
		WO 2016019341 A1	04-02-2016