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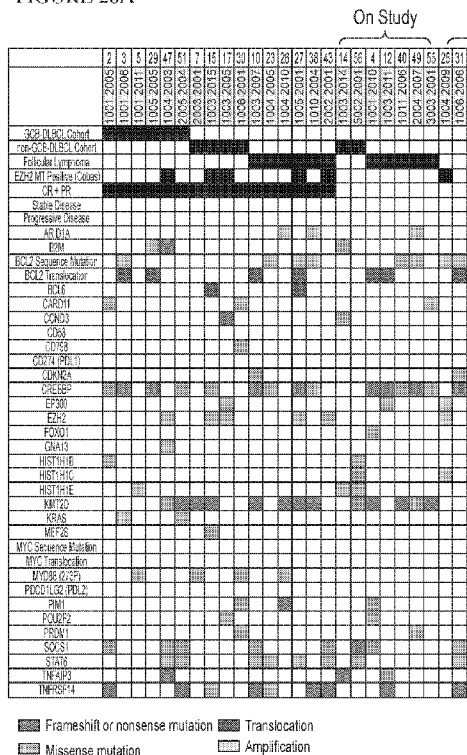
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[Continued on next page]

(54) Title: INHIBITORS OF EZH2 AND METHODS OF USE THEREOF

FIGURE 20A



(57) Abstract: The disclosure provides a method of treating cancer in a
subject in need thereof including administering to the subject a therapeut-
ically-effective amount of an enhancer of a zeste homolog 2 (EZH2) in-
hibitor. In certain embodiments of this method, the subject has one or
more mutations in one or more sequences encoding a gene listed in
Tables 1-9, Tables 17-19, and/or Figures 19-22.



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INHIBITORS OF EZH2 AND METHODS OF USE THEREOF

RELATED APPLICATIONS

[01] This application claims priority to, and the benefit of, U.S. Provisional Application Nos. 62/264,169, filed December 7, 2015, and 62/409,320 filed October 17, 2016, the contents of each of which are incorporated herein by reference in their entireties.

BACKGROUND

[02] There is a long-felt yet unmet need for effective treatments for certain cancers caused by genetic alterations that result in EZH2-dependent oncogenesis.

SUMMARY

[03] In some aspects, the disclosure provides a method of treating cancer comprising administering a therapeutically effective amount of an inhibitor of Enhancer to Zeste Homolog 2 (EZH2) to a subject in need thereof, wherein the subject has at least one mutation in one or more sequences encoding a gene or gene product listed in Tables 1-9, Tables 17-19, and/or Figures 19-22.

[04] In some aspects, the disclosure provides an inhibitor of Enhancer to Zeste Homolog 2 (EZH2) for use in treating cancer, wherein the inhibitor is for administration in a therapeutically effective amount of to a subject in need thereof, and wherein the subject has at least one mutation in one or more sequences encoding a gene or gene product listed in Tables 1-9, Tables 17-19, and/or Figures 19-22.

[05] In some aspects, the disclosure provides a method, which comprises selecting a subject having cancer for treatment with an EZH2 inhibitor based on the presence of at least one mutation associated with a positive response (e.g., a positive mutation) to such treatment in the subject and/or based on the absence of at least one mutation associated with no response or with a negative response (e.g., a negative mutation) to such treatment in the subject.

[06] The disclosure also provides a method, comprising selecting a subject having cancer for treatment with an EZH2 inhibitor based on the presence of a mutation profile in the subject that matches a mutation profile of a patient exhibiting a complete or partial response or stable disease in any of Figures 19-22.

[07] The disclosure further provides a method of treating cancer comprising administering a therapeutically effective amount of an inhibitor of Enhancer to Zeste Homolog 2 (EZH2) to a subject; wherein the subject has a mutation in a sequence encoding a human histone acetyltransferase (HAT), wherein the mutation decreases a function of the HAT.

[08] The methods and EZH2 inhibitors for use disclosed herein may have one or more of the following features.

[09] In some embodiments, the subject has at least one mutation in one or more sequences encoding: MYD88 (e.g., GenBank Accession No. NM_001172567.1, NM_002468.4, NM_001172568.1, NM_001172569.1, and NM_001172566.1), STAT6A (e.g., GenBank Accession No. NM_001178078.1, NM_003153.4, NM_001178079.1, NM_001178080.1, or NM_001178081.1), SOCS1 (e.g., GenBank Accession No. NM_003745.1), MYC (e.g., GenBank Accession No. NM_002467.4), HIST1H1E (e.g., GenBank Accession No. NM_005321.2), ABL1 (e.g., GenBank Accession No. NM_005157), ACVR1 (e.g., GenBank Accession No. NM_001105.4), AKT1 (e.g., GenBank Accession No. NM_001014431.1), AKT2 (e.g., GenBank Accession No. NM_001243027.2), ALK (e.g., GenBank Accession No. NM_004304.4), APC (e.g., GenBank Accession No. NM_000038.5), AR (e.g., GenBank Accession No. NM_000044.3), ARID1A (e.g., GenBank Accession No. NM_006015.4), ARID1B (e.g., GenBank Accession No. NM_020732.3), ASXL1 (e.g., GenBank Accession No. NM_015338.5), ATM (e.g., GenBank Accession No. NM_000051.3), ATRX (e.g., GenBank Accession No. NM_000489.4), AURKA (e.g., GenBank Accession No. NM_003600.3), AXIN2 (e.g., GenBank Accession No. NM_004655.3), BAP1 (e.g., GenBank Accession No. NM_004656.3), BCL2 (e.g., GenBank Accession No. NM_000633.2), BCR (e.g., GenBank Accession No. X02596.1), BLM (e.g., GenBank Accession No. NM_000057.3), BMPR1A (e.g., GenBank Accession No. NM_004329.2), BRAF (e.g., GenBank Accession No. NM_004333.4), BRCA1 (e.g., GenBank Accession No. NM_007294.3), BRCA2 (e.g., GenBank Accession No. NM_000059.3), BRIP1 (e.g., GenBank Accession No. NM_032043.21), BTK (e.g., GenBank Accession No. NM_001287344.1), BUB1B (e.g., GenBank Accession No. NM_001211.5), CALR (e.g., GenBank Accession No. NM_004343.3), CBL (e.g., GenBank Accession No. NM_005188.3), CCND1 (e.g., GenBank Accession No. NM_053056.2), CCNE1 (e.g., GenBank Accession No. NM_001322262.1), CDC73 (e.g., GenBank Accession No. NM_024529.4), CDH1 (Accession No. NM_001317186.1), CDK4 (e.g., GenBank Accession

No. NM_000075.3), CDK6 (e.g., GenBank Accession No. NM_001145306.1), CDKN1B (e.g., GenBank Accession No. NM_004064.4), CDKN2A (e.g., GenBank Accession No. NM_001195132.1), CDKN2B (e.g., GenBank Accession No. NM_078487.2), CDKN2C (e.g., GenBank Accession No. NM_078626.2), CEBPA (e.g., GenBank Accession No. NM_001285829.1), CHEK2 (e.g., GenBank Accession No. NM_145862.2), CIC (e.g., GenBank Accession No. NM_015125.4), CREBBP (e.g., GenBank Accession No. NM_001079846.1), CSF1R (e.g., GenBank Accession No. NM_001288705.2), CTNNB1 (e.g., GenBank Accession No. NM_001098209.1), CYLD (e.g., GenBank Accession No. NM_001042355.1), DAXX (Accession No. NM_001141969.1), DDB2 (e.g., GenBank Accession No. NM_001300734.1), DDR2 (e.g., GenBank Accession No. NM_001014796.1), DICER1 (e.g., GenBank Accession No. NM_001291628.1), DNMT3A (e.g., GenBank Accession No. NM_001320893.1), EGFR (e.g., GenBank Accession No. NM_001346900.1), EP300 (e.g., GenBank Accession No. NM_001429.3), ERBB2 (e.g., GenBank Accession No. NM_001289936.1), ERBB3 (e.g., GenBank Accession No. NM_001982.3), ERBB4 (e.g., GenBank Accession No. NM_005235.2), ERCC1 (e.g., GenBank Accession No. NM_001166049.1), ERCC2 (e.g., GenBank Accession No. NM_001130867.1), ERCC3 (e.g., GenBank Accession No. NM_001303418.1), ERCC4 (Accession No. NM_005236.2), ERCC5 (e.g., GenBank Accession No. NM_000123.3), ESR1 (e.g., GenBank Accession No. NM_001291241.1), ETV1 (e.g., GenBank Accession No. NM_001163147.1), ETV5 (Accession No. NM_004454.2), EWSR1 (e.g., GenBank Accession No. NM_001163287.1), EXT1 (e.g., GenBank Accession No. NM_000127.2), EXT2 (Accession No. NM_001178083.1), FANCA (e.g., GenBank Accession No. NM_001286167.1), FANCB (Accession No. NM_001324162.1), FANCC (e.g., GenBank Accession No. NM_001243744.1), FANCD2 (e.g., GenBank Accession No. NM_001319984.1), FANCE (e.g., GenBank Accession No. NM_021922.2), FANCF (e.g., GenBank Accession No. NM_022725.3), FANCG (e.g., GenBank Accession No. NM_004629.1), FANCI (e.g., GenBank Accession No. NM_018193.2), FANCL (Accession No. NM_001114636.1), FANCM (e.g., GenBank Accession No. NM_001308133.1), FBXW7 (e.g., GenBank Accession No. NM_018315.4), FGFR1 (Accession No.) NM_001174065.1, FGFR2 (e.g., GenBank Accession No. NM_000141.4), FGFR3 (e.g., GenBank Accession No. NM_001163213.1), FGFR4 (e.g., GenBank Accession No. NM_213647.2), FH (e.g., GenBank Accession No. NM_000143.3), FLCN (e.g., GenBank Accession No.

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GenBank Accession No. NM_000546.5), TSC1 (e.g., GenBank Accession No. NM_001162427.1), TSC2 (e.g., GenBank Accession No. NM_001318832.1), TSHR (e.g., GenBank Accession No. NM_000369.2), VHL (e.g., GenBank Accession No. NM_000551.3), WAS (e.g., GenBank Accession No. NM_000377.2), WRN (e.g., GenBank Accession No. NM_000553.4), WT1 (e.g., GenBank Accession No. NM_000378.4), XPA (e.g., GenBank Accession No. NM_000380.3), XPC (e.g., GenBank Accession No. NM_004628.4), and/or XRCC1 (e.g., GenBank Accession No. NM_006297.2). It will be understood that the sequences provided above and elsewhere herein are exemplary, and serve to illustrate sequences suitable for some embodiments of the present disclosure. It will also be understood that, in some embodiments, the sequence encoding the gene product referred to herein is a genomic DNA sequence. The skilled artisan will be aware of additional suitable sequences beyond the exemplary, non-limiting RNA sequences provided above, for each gene or gene product (e.g., transcript, mRNA, or protein) referred to herein, or will be able to ascertain such suitable sequences without more than routine effort based on the present disclosure and the knowledge in the art.

[010] In some embodiments, the subject has at least one mutation in one or more sequences encoding: ABL1, ACVR1, AKT1, AKT2, ALK, APC, AR, ARID1A, ARID1B, ASXL1, ATM, ATRX, AURKA, AXIN2, BAP1, BCL2, BCR, BLM, BMPR1A, BRAF, BRCA1, BRCA2, BRIP1, BTK, BUB1B, CALR, CBL, CCND1, CCNE1, CDC73, CDH1, CDK4, CDK6, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CEBPA, CHEK2, CIC, CREBBP, CSF1R, CTNNB1, CYLD, DAXX, DDB2, DDR2, DICER1, DNMT3A, EGFR, EP300, ERBB2, ERBB3, ERBB4, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, ESR1, ETV1, ETV5, EWSR1, EXT1, EXT2, EZH2, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FBXW7, FGFR1, FGFR2, FGFR3, FGFR4, FH, FLCN, FLT3, FLT4, FOXL2, GATA1, GATA2, GNA11, GNAQ, GNAS, GPC3, H3F3A, H3F3B, HNF1A, HRAS, IDH1, IDH2, IGF1R, IGF2R, IKZF1, JAK1, JAK2, JAK3, KDR, KIT, KRAS, MAML1, MAP2K1, MAP2K4, MDM2, MDM4, MED12, MEN1, MET, MLH1, MLL, MPL, MSH2, MSH6, MTOR, MUTYH, MYC, MYCL1, MYCN, MYD88, NBN, NCOA3, NF1, NF2, NKX2-1, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NPM1, NRAS, NTRK1, PALB2, PAX5, PBRM1, PDGFRA, PHOX2B, PIK3CA, PIK3R1, PMS1, PMS2, POLD1, POLE, POLH, POT1, PRKAR1A, PRSS1, PTCH1, PTEN, PTPN11, RAD51C, RAF1, RB1, RECQL4, RET, RNF43, ROS1, RUNX1, SBDS, SDHAF2, SDHB,

SDHC, SDHD, SF3B1, SMAD2, SMAD3, SMAD4, SMARCB1, SMO, SRC, STAG2, STK11, SUFU, TERT, TET2, TGFB2, TNFAIP3, TOP1, TP53, TSC1, TSC2, TSHR, VHL, WAS, WRN, WT1, XPA, XPC, and/or XRCC1.

[011] In some embodiments, the subject has at least one mutation in one or more sequences encoding: ARID1A, ATM, B2M, BCL2, BCL6, BCL7A, BRAF, BTG1, CARD11, CCND3, CD58, CD79B, CDKN2A, CREBBP, EP300, EZH2, FOXO1, GNA13, HIST1H1B, HIST1H1C, HIST1H1E, IKZF3, IRF4, ITPKB, KDM6A, KIT, KMT2D, KRAS, MEF2B, MYC, MYD88, NOTCH1, NOTCH2, NRAS, PIK3CA, PIM1, POU2F2, PRDM1, PTEN, PTPN1, PTPN11, PTPN6, PTPRD, RB1, S1PR2, SGK1, SMARCB1, SOCS1, STAT6, TBL1XR1, TNFAIP3, TNFRSF14, TP53, and/or XPO1.

[012] In some embodiments, the subject has at least one mutation in one or more sequences encoding: AKT1, ALK, ARID1A, ATM, B2M, BCL2, BCL6, BCL7A, BTG2, CARD11, CCND3, CD79B, CDKN2A, CREBBP, EP300, EZH2, FBXW7, FOXO1, HLA-C, HRAS, IKZF3, IRF4, KDM6A, KRAS, MEF2B, MYD88, NOTCH1, NPM1, NRAS, PIK3CA, PIM1, PRDM1, PTEN, RB1, RBBP4, SMARCB1, SUZ12, TNFRSF14, and/or TP53.

[013] In some embodiments, the subject has at least one mutation in one or more sequences encoding: ALK, EWSR1, ROS1, BCL2, MLL, TMPRSS2, BCR, MYC, FGFR3, BRAF, NTRK1, TACC3, DNAB1, PDGFRA, EGFR, PDGFRB, ETV1, PRKACA, ETV4, RAF1, ETV5, RARA, ETV6, and/or RET.

[014] In some embodiments, the subject has at least one mutation in one or more sequences encoding: ALK (Intron 19), BCL2 (MBR breakpoint region), BCL2 (MCR breakpoint region), BCL6, CD274, CIITA, MYC (entire Gene + 40kbp upstream), and/or PDCD1LG2.

[015] In some embodiments, the subject has at least one mutation in one or more sequences encoding: BCL2, CD274 (PDL1), FOXP1, JAK2, KDM4C, PDCD1LG2 (PDL2), and/or REL.

[016] In some embodiments, the subject has at least one mutation in one or more sequences encoding: ARID1A, ATM, B2M, BCL2, BCL6, BCL7A, BRAF, CARD11, CCND3, CD274 (PDL1), CD58, CD79B, CDKN2A, CIITA, CREBBP, EZH2 (non-Y646), EZH2 (Y646), EP300, FOXO1, FOXP1, GNA13, HIST1H1B, HIST1H1C, HIST1H1E, IRF4, IKZF3, JAK2, KDM4C, KDM6A, KIT, KMT2D, KRAS, MEF2B, MYC, MYD88, NOTCH1, NOTCH2, NRAS, PDCD1LG2 (PDL2), PIK3CA, PIM1, POU2F2, PRDM1, PTEN, PTPN11, PTPN6, PTPRD, REL, SOCS1, STAT6, TNFAIP3, TNFRSF14, and/or TP53.

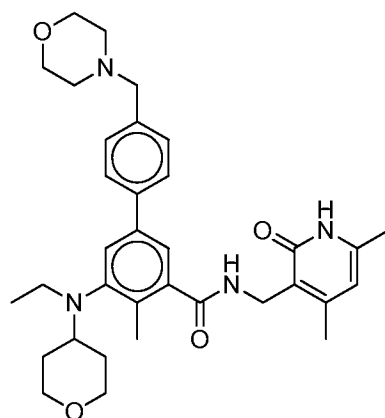
[017] In some embodiments, the subject has at least one mutation in one or more sequences encoding: ARID1A, B2M, BCL2, BCL6, CARD11, CCND3, CD274 (PDL1), CD58, CD79B, CDKN2A, CREBBP, EZH2, EP300, FOXO1, GNA13, HIST1H1B, HIST1H1C, HIST1H1E, KMT2D, KRAS, MEF2B, MYC, MYD88 (273P), PDCD1LG2 (PDL2), PIM1, POU2F2, PRDM1, SOCS1, STAT6, TNFAIP3, and/or TNFRSF14.

[018] In some embodiments, the at least one mutation decreases the function of a protein encoded by the mutated sequence as compared to the function of the protein encoded by the wild-type sequence. In some embodiments, the at least one mutation is a loss-of-function mutation.

[019] In some embodiments, the method further comprises detecting the at least one mutation in the subject.

[020] In some embodiments, the detecting comprises subjecting a sample obtained from the subject to a sequence analysis assay.

[021] In some embodiments, the inhibitor of EZH2 is



(tazemetostat),

or a pharmaceutically-acceptable salt thereof.

[022] In some embodiments, the inhibitor of EZH2 is administered orally.

[023] In some embodiments, the inhibitor of EZH2 is formulated as a tablet.

[024] In some embodiments, the therapeutically effective amount of the inhibitor of EZH2 is between 100 mg and 3200 mg per day. -In some embodiments, the therapeutically effective amount of the inhibitor of EZH2 is 100 mg, 200 mg, 400 mg, 600 mg, 800 mg, 1000 mg, 1200 mg, 1400 mg, 1600 mg or 3200 mg per day. In some embodiments, the therapeutically effective amount is 1600 mg per day. In some embodiments, the therapeutically effective amount of the inhibitor of is administered at 800 mg twice per day (BID).

[025] In some embodiments, the at least one mutation decreases a level of acetylation of a lysine (K) on histone (3) compared to a level of acetylation of the same lysine by a wild type HAT.

[026] In some embodiments, the lysine (K) on histone (3) is at position 27 (H3K27).

[027] In some embodiments, the at least one mutation occurs in a sequence of an EP300 gene or in a sequence encoding histone acetyltransferase p300.

[028] In some embodiments, the at least one mutation results in a substitution of serine (S) for phenylalanine (F) at position 1289 of histone acetyltransferase p300.

[029] In some embodiments, the mutation may occur in a sequence of an EP300 gene or protein encoding Histone acetyltransferase p300. The mutation may occur in a sequence of the EP300 gene or protein encoding p300 is a substitution of tyrosine (Y) for aspartic acid (D) at position 1467 (for example, as numbered in SEQ ID NO: 20). The mutation may occur in a sequence of the EP300 gene or protein encoding p300 is a substitution of serine (S) for phenylalanine (F) at position 1289 (for example, as numbered in SEQ ID NO: 20).

[030] In some embodiments, the at least one mutation occurs in a sequence of a CREB binding protein gene or in a sequence encoding CREBB. In some embodiments, the at least one mutation results in a substitution of phosphate (P) for threonine (T) at position 1494 of CREBBP (for example, as numbered in SEQ ID NO: 24). In some embodiments, the at least one mutation results in a substitution of arginine (R) for Leucine (L) at position 1446 of CREBBP (for example, as numbered in SEQ ID NO: 24). In some embodiments, the at least one mutation results in a substitution of Leucine (L) for phosphate (P) at position 1499 of CREBBP (for example, as numbered in SEQ ID NO: 24).

[031] In some embodiments, the subject expresses a wild type EZH2 protein and does not express a mutant EZH2 protein.

[032] In some embodiments, the subject expresses a mutant EZH2 protein. In some embodiments, the mutant EZH2 protein comprises a substitution of any amino acid other than tyrosine (Y) for tyrosine (Y) at position 641 of SEQ ID NO: 1. In some embodiments, the mutant EZH2 protein comprises a substitution of any amino acid other than alanine (A) for alanine (A) at position 682 of SEQ ID NO: 1. In some embodiments, the mutant EZH2 protein comprises a substitution of any amino acid other than alanine (A) for alanine (A) at position 692 of SEQ ID NO: 1.

[033] In some embodiments, the at least one mutation comprises a MYD88, STAT6A, and/or a SOCS1 mutation.

[034] In some embodiments, the subject does not have a MYC and/or a HIST1H1E mutation.

[035] In some embodiments, the subject (a) has a MYD88, STAT6A, and/or a SOCS1 mutation, and (b) does not have a MYC and/or a HIST1H1E mutation.

[036] In some embodiments, the subject has a mutation in a sequence encoding a human histone acetyltransferase (HAT).

[037] In some embodiments, the subject is a human subject. In some embodiments, the subject has cancer.

[038] In some embodiments, the cancer is B-cell lymphoma. In some embodiments, the B-cell lymphoma is an activated B-cell (ABC) type. In some embodiments, the B-cell lymphoma is a germinal B-cell (GBC) type.

[039] In some embodiments, the cancer is follicular lymphoma.

[040] In some embodiments, the at least one mutation associated with a positive response comprise (a) an EZH2 mutation; (b) a histone acetyl transferase (HAT) mutation; (c) a STAT6 mutation; (d) a MYD88 mutation; and/or (e) a SOCS1 mutation.

[041] In some embodiments, the at least one mutation associated with no response or with a negative response comprise (a) a MYC mutation; and/or (b) a HIST1H1E mutation.

[042] In some embodiments, the method comprises detecting the at least one mutation associated with a positive response and/or the at least one mutation associated with no response or a negative response in a sample obtained from the subject.

[043] In some embodiments, the method comprises selecting the subject for treatment with the EZH2 inhibitor based on the subject (a) having at least one of a MYD88 mutation, a STAT6A mutation, and a SOCS1 mutation, and (b) not having at least one of a MYC mutation and/or a HIST1H1E mutation.

[044] In some embodiments, the at least one mutation consists of a single mutation. In some embodiments, the at least one mutation comprises 2 mutations or more. In some embodiments, the at least one mutation comprises 3 mutations or more. In some embodiments, the at least one mutation comprises 4 mutations or more. In some embodiments, the at least one mutation comprises 5 mutations or more.

[045] In some embodiments, the at least one mutation comprises 2 mutations, 3 mutations, 4 mutations, 5 mutations, 6 mutations, 7 mutations, 8 mutations, 9 mutations, 10 mutations, 11 mutations, 12 mutations, 13 mutations, 14 mutations, 15 mutations, 16 mutations, 17 mutations, 18 mutations, 19 mutations, or 20 mutations.

[046] In some embodiments, the at least one mutation comprises at least one positive mutation (e.g., with or without a negative mutation). In some embodiments, the at least one mutation comprises at least one negative mutation (e.g., with or without a positive mutation). In some embodiments, the at least one mutation comprises both positive and negative mutations. The term “positive mutation”, as used herein, refers to a mutation that sensitizes a subject, a cancer, or malignant cell or population of cells, to EZH2 treatment, or, in some embodiments, that renders a subject, cancer, or malignant cell or population of cells, more sensitive to EZH2 treatment. The term “negative mutation”, as used herein, refers to a mutation that desensitizes a subject, a cancer, or malignant cell or population of cells, to EZH2 treatment, or, in some embodiments, that renders a subject, cancer, or malignant cell or population of cells, less sensitive to EZH2 treatment. In some embodiments, the disclosure provides a method of identifying molecular variants in tumor samples harvested from NHL patients treated with a compound of the disclosure. In some embodiments, the disclosure provides a method of identifying molecular variants in cell free circulating tumor DNA (ctDNA) harvested from NHL patients treated with a compound of the disclosure.

[047] In some embodiments, the molecular variants identified therein may correlate with clinical response, minimal residual disease or emergence of resistance.

[048] The summary above is meant to illustrate, in a non-limiting manner, some of the embodiments, advantages, features, and uses of the technology disclosed herein. Other embodiments, advantages, features, and uses of the technology disclosed herein will be apparent from the Detailed Description, the Drawings, the Examples, and the Claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[049] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[050] The above and further features will be more clearly appreciated from the following detailed description when taken in conjunction with the accompanying drawings.

[051] Figure 1 is a schematic diagram showing EZH2 catalyzed chromatin remodeling. EZH2 is the catalytic subunit of the multi-protein PRC2 (polycomb repressive complex 2). PRC2 is the only human protein methyltransferase that can methylate H3K27. Catalyzes mono-, di- and tri-methylation of H3K27. H3K27me3 is a transcriptionally repressive histone mark. H3K27 is the only significant substrate for PRC2. Aberrant trimethylation of H3K27 is oncogenic in a broad spectrum of human cancers, such as B-cell NHL.

[052] Figure 2 is a schematic diagram depicting how tazemetostat drives apoptosis or differentiation in lymphoma cells independently of EZH2 mutation status.

[053] Figure 3 is a schematic diagram showing tazemetostat (EPZ-6438) as a potent and highly selective EZH2 inhibitor.

[054] Figure 4 is a waterfall plot of best response in NHL from the trial described in Table 10.

[055] Figure 5 is a graph depicting the objective response in NHL from the intended treatment population at RP2D from the trial described in Table 10.

[056] Figure 6 is a series of photographs and a schematic diagram showing the response in EZH2-mutated DLBCL from the trial described in Table 10.

[057] Figure 7 a series of photographs, table, and a chart showing tazemetostat dose selection.

[058] Figure 8 is a graph depicting somatic mutations detected using a 39 gene next generation sequencing (NGS) panel, demonstrating that somatic mutations in histone acetyltransferases may co-segregate with response to tazemetostat.

[059] Figure 9 is a graph depicting somatic mutations detected using a 39 gene NGS panel.

[060] Figure 10 is a graph showing the details of baseline tumor mutation profiling.

[061] Figure 11 is a graph illustrating the duration of therapy and tumor response in a phase 1 clinical trial (all NHL patients, N=21).

[062] Figure 12 is a scheme illustrating the detection of mutations in cell-free DNA through suppressing NGS errors.

[063] Figure 13 is a pair of graphs showing variant allelic frequencies for a set of 20 validation cases at varying levels of tumor cell line contribution relative to their genomic location, observed in the NHL specific plasma select panel of the disclosure. The individual graphs show the results for the sequence mutation analyses a) pre- and b) post correction.

The figure illustrates that the NGS background suppression enables detection of variant alleles down to 0.1% in ctDNA.

[064] Figure 14 is a graph showing the results of digital karyotyping and personalized analysis of rearranged ends (PARE) to identify structural alterations at varying levels of tumor DNA concentrations. ALK translocations were detected in a cell-free DNA validation test set down to a tumor purity of 0.1 %.

[065] Figures 15A-D is a series of graphs showing the relative distribution of mutations in the Phase 2 NHL trial with variant allele frequencies of >2% in archive tumors. The bar graphs plot the frequency of appearance of each of the individual gene mutations observed in: (A) all samples, (B) GCB DLCL cohorts, (C) Non-GCB DLCL cohorts, and (D) Follicular Lymphoma cohorts.

[066] Figures 16A-D is a series of graphs showing the relative distribution of mutations in the Phase 2 NHL trial with variant allele frequencies of >0.1% in ctDNA. The bar graphs plot the frequency of appearance of each of the individual gene mutations observed in: (A) all samples, (B) GCB DLCL cohorts, (C) Non-GCB DLCL cohorts, and (D) Follicular Lymphoma cohorts.

[067] Figure 17 is a graph illustrating the duration of therapy and tumor response in phase 2 patients. ctDNA samples were taken at various assessment time points for 16 patients for further ctDNA NGS analysis to monitor for clonal switching, minimum residual disease and emergence of resistance.

[068] Figure 18 is a combination of graphs illustrating mutations of STAT6 observed in the 62 gene NGS panel. The panel covers exons 9-14 (DNA binding domain) of STAT6. Panel (a) is a scheme of the STAT6 protein domain structure. The approximate location of somatic mutations identified in STAT6 in follicular lymphoma is indicated. Panel (b) shows a homology model of the STAT6-DNA complex. STAT6 residues undergoing mutation are close to the DNA binding interface and are displayed in ball-and-stick diagrams (*see, e.g.,* Yildiz et al. *Blood* 2015; **125**: 668-679, the content of which is incorporated herein by reference in its entirety). Panel (c) is an enrichment plot of the KEGG_JAK_STAT_signaling_pathway.

[069] Figure 19 is a table summarizing the molecular variants observed in archive tumor in samples from phase 1 patients. Observed molecular variants were frameshift or nonsense mutations, missense mutations, translocations and amplifications. If multiple mutations were

found in the same sample only the most damaging alteration are shown. Trends later identified in phase 2 samples also appear in the phase 1 NHL samples (e.g., EZH2, STAT6 and MYC).

[070] Figure 20 is a table summarizing the molecular variants observed in archive tumor tissue from phase 2 Patients. Observed molecular variants were frameshift or nonsense mutations, missense mutations, translocations and amplifications. Variants of interest included, inter alia, EZH2, MYD88 (273P) and MYC. EZH2 mutations were observed in 9 patients, wherein 7 displayed a variant allele frequency of $> 10\%$; 2 had variant allele frequencies of $\leq 10\%$ (10042008, 8%; 10032004, 10%; best response: 4 PR, 3 SD and 2 PD). MYD88 (273P) mutations were observed in 6 patients (best response: 3 CR, 1PR, 1 PD and 1 unknown response); STAT6 mutations were observed in 13 patients (best response: 1 CR, 5 PR, 4 SD and 3 PD). MYC mutations were observed in 7 patients (best response: 5 PD and 2 unknown responses). 2 MYC translocations were associated with lack of response.

[071] Figure 21 is a table summarizing the molecular variants with variant allele frequencies of 0.1% observed in ctDNA in phase 2 patients. Observed molecular variants were frameshift or nonsense mutations, missense mutations, translocations and amplifications. Variants of interest included, inter alia, EZH2, MYD88 (273P) and MYC. EZH2 mutations were observed in 11 patients (best response: 5 PR, 2 SD, 3 PD and 1 unknown response). MYD88 (273P) mutations were observed in 6 patients (best response: 2 CR, 1PR, 1 SD and 2 PD); STAT6 mutations were observed in 14 patients (best response: 5 PR, 6 SD and 3 PD). MYC mutations were observed in 18 patients (best response: 2 PR, 3SD, 9 PD and 4 unknown responses). 5 MYC translocations were associated with lack of response.

[072] Figure 22 is a table summarizing the molecular variants with variant allele frequencies of 1% observed in ctDNA in phase 2 patients. Observed molecular variants were frameshift or nonsense mutations, missense mutations, translocations and amplifications. Variants of interest included, inter alia, EZH2, MYD88 (273P) and MYC. EZH2 mutations were observed in 8 patients (best response: 4 PR, 1 SD and 3 PD). MYD88 (273P) mutations were observed in 5 patients (best response: 2 CR, 1PR, and 2 PD); STAT6 mutations were observed in 10 patients (best response: 4 PR, 4 SD and 2 PD). MYC mutations were observed in 5 patients (best response: 3 PD and 2 unknown responses). 5 MYC translocations were associated with lack of response.

[073] Figure 23 is a structure model of partial EZH2 protein based on the A chain of nuclear receptor binding SET domain protein 1 (NSD1). This model corresponds to amino acid residues 533-732 of EZH2 sequence of SEQ ID NO: 1.

DETAILED DESCRIPTION

[074] Tazemetostat demonstrates clinical activity as a monotherapy in patients with relapsed or refractory DLBCL (both GCB and non-GCB), follicular lymphoma (FL) and marginal zone lymphomas (MZL). Objective responses in tumors with either wild-type or mutation in EZH2 are durable as patients are ongoing at 7+ to 21+ months. Safety profile as monotherapy continues to be acceptable and favorable for combination development. Recommended phase II dose (RP2D) of 800 mg BID supported by safety, efficacy, PK and PD.

[075] Baseline somatic mutation profiling revealed associations between objective response to tazemetostat and genetic alterations, e.g., mutations in genomic sequences encoding MYD88, STAT6A, SOCS1, MYC, HIST1H1E, and histone acetyltransferases, such as, for example CREBBP and EP300.

EZH2

[076] EZH2 is a histone methyltransferase that is the catalytic subunit of the PRC2 complex which catalyzes the mono- through tri-methylation of lysine 27 on histone H3 (H3-K27).

[077] Point mutations of the EZH2 gene at a single amino acid residue (e.g., Tyr641, herein referred to as Y641) of EZH2 have been reported to be linked to subsets of human B-cell lymphoma. Morin et al. (2010) *Nat Genet* 42(2):181-5. In particular, Morin et al. reported that somatic mutations of tyrosine 641 (Y641F, Y641H, Y641N, and Y641S) of EZH2 were associated with follicular lymphoma (FL) and the germinal center B cell-like (GCB) subtype of diffuse large B-cell lymphoma (DLBCL). The mutant allele is always found associated with a wild-type allele (heterozygous) in disease cells, and the mutations were reported to ablate the enzymatic activity of the PRC2 complex for methylating an unmodified peptide substrate.

[078] The mutant EZH2 refers to a mutant EZH2 polypeptide or a nucleic acid sequence encoding a mutant EZH2 polypeptide. Preferably the mutant EZH2 comprises one or more

mutations in its substrate pocket domain as defined in SEQ ID NO: 6. For example, the mutation may be a substitution, a point mutation, a nonsense mutation, a missense mutation, a deletion, or an insertion. Exemplary substitution amino acid mutation includes a substitution at amino acid position 677, 687, 674, 685, or 641 of SEQ ID NO: 1, such as, but is not limited to a substitution of glycine (G) for the wild type residue alanine (A) at amino acid position 677 of SEQ ID NO: 1 (A677G); a substitution of valine (V) for the wild type residue alanine (A) at amino acid position 687 of SEQ ID NO: 1 (A687V); a substitution of methionine (M) for the wild type residue valine (V) at amino acid position 674 of SEQ ID NO: 1 (V674M); a substitution of histidine (H) for the wild type residue arginine (R) at amino acid position 685 of SEQ ID NO: 1 (R685H); a substitution of cysteine (C) for the wild type residue arginine (R) at amino acid position 685 of SEQ ID NO: 1 (R685C); a substitution of phenylalanine (F) for the wild type residue tyrosine (Y) at amino acid position 641 of SEQ ID NO: 1 (Y641F); a substitution of histidine (H) for the wild type residue tyrosine (Y) at amino acid position 641 of SEQ ID NO: 1 (Y641H); a substitution of asparagine (N) for the wild type residue tyrosine (Y) at amino acid position 641 of SEQ ID NO: 1 (Y641N); a substitution of serine (S) for the wild type residue tyrosine (Y) at amino acid position 641 of SEQ ID NO: 1 (Y641S); or a substitution of cysteine (C) for the wild type residue tyrosine (Y) at amino acid position 641 of SEQ ID NO: 1 (Y641C).

[079] The mutation may also include a substitution of serine (S) for the wild type residue asparagine (N) at amino acid position 322 of SEQ ID NO: 3 (N322S), a substitution of glutamine (Q) for the wild type residue arginine (R) at amino acid position 288 of SEQ ID NO: 3 (R288Q), a substitution of isoleucine (I) for the wild type residue threonine (T) at amino acid position 573 of SEQ ID NO: 3 (T573I), a substitution of glutamic acid (E) for the wild type residue aspartic acid (D) at amino acid position 664 of SEQ ID NO: 3 (D664E), a substitution of glutamine (Q) for the wild type residue arginine (R) at amino acid position 458 of SEQ ID NO: 5 (R458Q), a substitution of lysine (K) for the wild type residue glutamic acid (E) at amino acid position 249 of SEQ ID NO: 3 (E249K), a substitution of cysteine (C) for the wild type residue arginine (R) at amino acid position 684 of SEQ ID NO: 3 (R684C), a substitution of histidine (H) for the wild type residue arginine (R) at amino acid position 628 of SEQ ID NO: 21 (R628H), a substitution of histidine (H) for the wild type residue glutamine (Q) at amino acid position 501 of SEQ ID NO: 5 (Q501H), a substitution of asparagine (N) for the wild type residue aspartic acid (D) at amino acid

position 192 of SEQ ID NO: 3 (D192N), a substitution of valine (V) for the wild type residue aspartic acid (D) at amino acid position 664 of SEQ ID NO: 3 (D664V), a substitution of leucine (L) for the wild type residue valine (V) at amino acid position 704 of SEQ ID NO: 3 (V704L), a substitution of serine (S) for the wild type residue proline (P) at amino acid position 132 of SEQ ID NO: 3 (P132S), a substitution of lysine (K) for the wild type residue glutamic acid (E) at amino acid position 669 of SEQ ID NO: 21 (E669K), a substitution of threonine (T) for the wild type residue alanine (A) at amino acid position 255 of SEQ ID NO: 3 (A255T), a substitution of valine (V) for the wild type residue glutamic acid (E) at amino acid position 726 of SEQ ID NO: 3 (E726V), a substitution of tyrosine (Y) for the wild type residue cysteine (C) at amino acid position 571 of SEQ ID NO: 3 (C571Y), a substitution of cysteine (C) for the wild type residue phenylalanine (F) at amino acid position 145 of SEQ ID NO: 3 (F145C), a substitution of threonine (T) for the wild type residue asparagine (N) at amino acid position 693 of SEQ ID NO: 3 (N693T), a substitution of serine (S) for the wild type residue phenylalanine (F) at amino acid position 145 of SEQ ID NO: 3 (F145S), a substitution of histidine (H) for the wild type residue glutamine (Q) at amino acid position 109 of SEQ ID NO: 21 (Q109H), a substitution of cysteine (C) for the wild type residue phenylalanine (F) at amino acid position 622 of SEQ ID NO: 21 (F622C), a substitution of arginine (R) for the wild type residue glycine (G) at amino acid position 135 of SEQ ID NO: 3 (G135R), a substitution of glutamine (Q) for the wild type residue arginine (R) at amino acid position 168 of SEQ ID NO: 5 (R168Q), a substitution of arginine (R) for the wild type residue glycine (G) at amino acid position 159 of SEQ ID NO: 3 (G159R), a substitution of cysteine (C) for the wild type residue arginine (R) at amino acid position 310 of SEQ ID NO: 5 (R310C), a substitution of histidine (H) for the wild type residue arginine (R) at amino acid position 561 of SEQ ID NO: 3 (R561H), a substitution of histidine (H) for the wild type residue arginine (R) at amino acid position 634 of SEQ ID NO: 21 (R634H), a substitution of arginine (R) for the wild type residue glycine (G) at amino acid position 660 of SEQ ID NO: 3 (G660R), a substitution of cysteine (C) for the wild type residue tyrosine (Y) at amino acid position 181 of SEQ ID NO: 3 (Y181C), a substitution of arginine (R) for the wild type residue histidine (H) at amino acid position 297 of SEQ ID NO: 3 (H297R), a substitution of serine (S) for the wild type residue cysteine (C) at amino acid position 612 of SEQ ID NO: 21 (C612S), a substitution of tyrosine (Y) for the wild type residue histidine (H) at amino acid position 694 of SEQ ID NO: 3 (H694Y), a substitution of alanine (A) for

the wild type residue aspartic acid (D) at amino acid position 664 of SEQ ID NO: 3 (D664A), a substitution of threonine (T) for the wild type residue isoleucine (I) at amino acid position 150 of SEQ ID NO: 3 (I150T), a substitution of arginine (R) for the wild type residue isoleucine (I) at amino acid position 264 of SEQ ID NO: 3 (I264R), a substitution of leucine (L) for the wild type residue proline (P) at amino acid position 636 of SEQ ID NO: 3 (P636L), a substitution of threonine (T) for the wild type residue isoleucine (I) at amino acid position 713 of SEQ ID NO: 3 (I713T), a substitution of proline (P) for the wild type residue glutamine (Q) at amino acid position 501 of SEQ ID NO: 5 (Q501P), a substitution of glutamine (Q) for the wild type residue lysine (K) at amino acid position 243 of SEQ ID NO: 3 (K243Q), a substitution of aspartic acid (D) for the wild type residue glutamic acid (E) at amino acid position 130 of SEQ ID NO: 5 (E130D), a substitution of glycine (G) for the wild type residue arginine (R) at amino acid position 509 of SEQ ID NO: 3 (R509G), a substitution of histidine (H) for the wild type residue arginine (R) at amino acid position 566 of SEQ ID NO: 3 (R566H), a substitution of histidine (H) for the wild type residue aspartic acid (D) at amino acid position 677 of SEQ ID NO: 3 (D677H), a substitution of asparagine (N) for the wild type residue lysine (K) at amino acid position 466 of SEQ ID NO: 5 (K466N), a substitution of histidine (H) for the wild type residue arginine (R) at amino acid position 78 of SEQ ID NO: 3 (R78H), a substitution of methionine (M) for the wild type residue lysine (K) at amino acid position 1 of SEQ ID NO: 6 (K6M), a substitution of leucine (L) for the wild type residue serine (S) at amino acid position 538 of SEQ ID NO: 3 (S538L), a substitution of glutamine (Q) for the wild type residue leucine (L) at amino acid position 149 of SEQ ID NO: 3 (L149Q), a substitution of valine (V) for the wild type residue leucine (L) at amino acid position 252 of SEQ ID NO: 3 (L252V), a substitution of valine (V) for the wild type residue leucine (L) at amino acid position 674 of SEQ ID NO: 3 (L674V), a substitution of valine (V) for the wild type residue alanine (A) at amino acid position 656 of SEQ ID NO: 3 (A656V), a substitution of aspartic acid (D) for the wild type residue alanine (A) at amino acid position 731 of SEQ ID NO: 3 (Y731D), a substitution of threonine (T) for the wild type residue alanine (A) at amino acid position 345 of SEQ ID NO: 3 (A345T), a substitution of aspartic acid (D) for the wild type residue alanine (A) at amino acid position 244 of SEQ ID NO: 3 (Y244D), a substitution of tryptophan (W) for the wild type residue cysteine (C) at amino acid position 576 of SEQ ID NO: 3 (C576W), a substitution of lysine (K) for the wild type residue asparagine (N) at amino acid position 640

of SEQ ID NO: 3 (N640K), a substitution of lysine (K) for the wild type residue asparagine (N) at amino acid position 675 of SEQ ID NO: 3 (N675K), a substitution of tyrosine (Y) for the wild type residue aspartic acid (D) at amino acid position 579 of SEQ ID NO: 21 (D579Y), a substitution of isoleucine (I) for the wild type residue asparagine (N) at amino acid position 693 of SEQ ID NO: 3 (N693I), and a substitution of lysine (K) for the wild type residue asparagine (N) at amino acid position 693 of SEQ ID NO: 3 (N693K).

[080] The mutation may be a frameshift at amino acid position 730, 391, 461, 441, 235, 254, 564, 662, 715, 405, 685, 64, 73, 656, 718, 374, 592, 505, 730, or 363 of SEQ ID NO: 3, 5 or 21 or the corresponding nucleotide position of the nucleic acid sequence encoding SEQ ID NO: 3, 5, or 21. The mutation of the EZH2 may also be an insertion of a glutamic acid (E) between amino acid positions 148 and 149 of SEQ ID NO: 3, 5 or 21. Another example of EZH2 mutation is a deletion of glutamic acid (E) and leucine (L) at amino acid positions 148 and 149 of SEQ ID NO: 3, 5 or 21. The mutant EZH2 may further comprise a nonsense mutation at amino acid position 733, 25, 317, 62, 553, 328, 58, 207, 123, 63, 137, or 60 of SEQ ID NO: 3, 5 or 21.

[081] Human EZH2 nucleic acids and polypeptides have previously been described. See, e.g., Chen et al. (1996) *Genomics* 38:30-7 [746 amino acids]; Swiss-Prot Accession No. Q15910 [746 amino acids]; GenBank Accession Nos. NM_004456 and NP_004447 (isoform a [751 amino acids]); and GenBank Accession Nos. NM_152998 and NP_694543 (isoform b [707 amino acids]), each of which is incorporated herein by reference in its entirety.

Amino acid sequence of human EZH2 (Swiss-Prot Accession No. Q15910) (SEQ ID NO: 1)
MGQTGKKSEKGPVCRKRVKSEYMRLRQLKRFRRADDEVKSMFSSNRQKILERTTEILNQEW KQRRIQPVHILTSVSSLRGTRECSVTSDLDFPTQVIPLKTLNAVASVPIMYSWSPLQONF MVEDETVLHNI PYMGDEVLDQDGT FIEELIKNYDGKVGHDRECGFINDEIFVELVNALGQ YNDDDDDDGDDPEEREKQKDLLEDHRDDKESRPPRKFP SDKI FEAISSMFPDKGTAEEL KEKYKELTEQQLP GALPPECTPNIDGPNAKSVQREQSLHSFHTLFCRRCFKYDCFLHPFH ATPNTYKRKNTETALDNKPCGPQCYQHLEGAKEFAAALTAERIKTPPKRPGGRRRGRLPN NSSRPSTPTINVLESKDTDS DREAGTETGGENNDKEEEEKKDETSSSSEANSRCQTPIKM KPNIEPPENVEWSGAEASMFRLVIGTYDNFCAIARLIGTKTCRQVYEFVKESSIIAPA PAEDVDTPPRKKRKHLWAAHCRKIQLKKDGSSNHVYNYQPCDHP RQPCDSSCPCVIAQ NFCEKFCQCSSECQNRFP GCRCKAQCN TKQPCYLA VRECDPDLCLTCGAADHWDSKNVS CKNC SIQRGSKKHL LAPS DVAGWGI FIKDPVQKNEFI SEYCGEII SQDEADRRGKVYDK YMC SFLFNLNDFVVDATRKGNKIRFANH SVNPNCYAKVMMVNGDHRIGIFAKRAIQTGE ELFFDYRYSQADALKYVGIEREMEIP

mRNA sequence of human EZH2, transcript variant 1 (GenBank Accession No. NM_004456) (SEQ ID NO: 2)
ggcggcgcttgattgggctgggggggccaataaaaagcgatggcgattgggctgccgcgt ttggcgctcggctccggtcgcgctccgacacccggtgggactcagaaggcagtgagccccg gcggcgcgccggcgcgcgcgggggcgacgcgcgggaacaacgcgagtcggcgcgcggg acgaagaataatcatggggccagactgggaagaaatctgagaagggaccagtttggtggcg

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gaagcgtgtaaaatcagagtacatgcgactgagacagctcaagagggttcagacgagctga
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gaaatttccttctgataaaatttttgaagccatttcctcaatgtttccagataaggggcac
agcagaagaactaaaggaaaaatataaagaactcaccgaacagcagctcccaggcgact
tcctcctgaatgtaccccccaacatagatggaccaaagtctaaatctgttcagagagagca
aagcttacactcctttcatagcctttctgtaggcgatgttttaaatatgactgcttcct
acatcgtaagtgcgaattattcttttcatgcaacacccaacacttataagcggagaagcac
agaaacagctctagacaacaaaccttgtggaccacagtgttaccagcatttggagggagc
aaaggagtgtgtgctgtctcaccgctgagcggataaagacccccacaaaacgtccagg
aggccgcagaaaggagcggcttcccaataacagtagcaggcccagcacccccaccattaa
tgtgctggaatcaaaggatacagacagtgataggggaagcagggactgaaacgggggggaga
gaacaatgataaagaagaagaagagaagaagaatgaaacttcgagctcctctgaagcaaa
ttctcggtgtcaaacaccaataaagatgaagccaaatattgaacctcctgagaatgtgga
tggtgagtggtgtgctgaagcctcaatgttttagagtccctcattggcacttactatgacaattt
ctgtgccattgtcaggttaattgggaccaaacatgtagacaggtgtatgagtttagagt
caaagaatctagcatcatagctccagctcccgtgaggatgtggatactcctccaaggaa
aaagaagaggaaacaccggttgtgggctgcacactgcagaaagatacagctgaaaaagga
cggctcctctaaccatgtttacaactatcaaccctgtgatcatccacggcagccttgtga
cagttcgtgccccttgtgtgatagcacaaaatttttgtgaaaagttttgtcaatgtagttc
agagtgtcaaaaccgctttccgggatgccgtgcaaagcacagtgcacaccaagcagtg
cccgtgtacctggctgtccgagagtgtgacctgacctctgtcttacttgtggagccgc
tgaccattgggacagtaaaaatgtgtcctgcaagaactgcagatctcagcggggtccaa
aaagcatctattgctggcaccatctgacgtggcaggtgggggatttttatcaaatgacc
tgtgcagaaaaatgaattcatctcagaatactgtggagagattatttctcaaatgaagc
tgacagaagagggaaagtgtatgataaatacatgtgcagctttctgttcaacttgaaaca
tgattttgtggtggatgcaacccgcaagggtacaaaattcgttttgcaaatcattcgggt
aaatccaaactgctatgcaaaagttagatggttaacgggtgatcacaggataggtatttt
tgccaagagagccatccagactggcgaagagctgttttttgattacagatacagccaggc
tgatgccctgaagtatgtcggcatcgaaagagaaatggaaatcccttgacatctgtacc
tcctccccctcctctgaaacagctgccttagcttcaggaaacctcgagtactgtgggcaa
tttagaaaaagaacatgcagtttgaaattctgaatttgcaaaagtactgtaagaataattt
atagtaattgatttttaaaaatcaactttttattgccttctcaccagctgcaagtggtttg
taccagtgaatttttgcaataatgcagtatggtacatttttcaactttgaataaagaata
cttgaacttgccttgttgaatc

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Full amino acid of EZH2, isoform a (GenBank Accession No. NP_004447) (SEQ ID NO: 3)

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MGQTGKKSEKGPVCRKRVKSEYMRLRQLKRFRRADDEVKSMFSSNRQKI LERTEILNQEW
KQRRIQPVHILTSVSSLRGTRECSVTSDLDFPTQVI PLKTLNAVASVPIMYSWSPLQQNF
MVEDETVLHNI PYMGDEVLDQDGT FIEELIKNYDGKVHGDRECGFINDEI FVELVNALGQ
YNDDDDDDDGDDPEEREKQKQDLEDHRDDKESRPPRKFP SDKI FEAISSMFPDKGTAEEL
KEYKELTEQQLP GALPPECTPNIDGPNAKSVQREQSLHSFHTLFCRRCFKYDCFLHRKC
NYSFHATPNTYKRKNTETALDNKPCGPQCYQHLEGAKEFAAALTAERIKTPPKRPGGRRR
GRLPNNSSRPSTPTINVLESKD TSDREAGTETGGENNDKEEEEKDETSSSSEANSRCQ
TPIKMKPNIEPPENVEWSGAEASMFVRLIGTYDNFCAIARLIGTKTCRQVYEFVKES
IIAPAPAEDVTPPRKKRKRHLWAAHCRKIQLKKGSSNHVYNYQPCDHP RQPCDSSCP
CVIAQNFCEKFCQSSSECQNRFP GCRCKAQCN TKQCPCYLAVRECDPDLCLTCGAADHWD
SKNVSCKNCSIQRGSKKHL LAPS DVAGWGI FIKDPVQKNEFI SEYCGEII SQDEADRRG
KVYDKYMCSFLN LND FVVDATRKGNKIRFANH SVNPNCYAKVMVNGDHRI GI FAKRA
IQTGEELFFDYRYSQADALKYVGIEREMEIP

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mRNA sequence of human EZH2, transcript variant 2 (GenBank Accession No. NM_152998) (SEQ ID NO: 4)

ggcgccgcttgattgggctgggggggccaataaaagcgatggcgattgggctgccgcgt
 ttggcgctcgggtccggctcgctccgacacccgggtgggactcagaaggcagtgagccccg
 gcggcgccgcgccggcgcgcgggggcgacgcggggaacaacgcgagtcggcgcgccggg
 acgaagaataatcatgggcccagactgggaagaaatctgagaagggaccagtttggtggcg
 gaagcgtgtaaaatcagagtacatgcgactgagacagctcaagagggttcagacgagctga
 tgaagtaaagagtattgttttagttccaatcgtcagaaaattttgaaagaacggaaatcct
 aaaccaagaatggaaacagcgaaggatacagcctgtgcacatcctgacttctgtgagctc
 attgcgcgggactaggagggtggaagatgaaactgttttacataacattccttatatggg
 agatgaagtttttagatcaggatgggtactttcattgaagaactaataaaaaattatgatgg
 gaaagtacacggggatagagaatgtgggtttataaatgatgaaatttttgtggagtgggt
 gaatgcccttggtcaatataatgatgatgacgatgatgatgatggagacgatcctgaaga
 aagagaagaaaagcagaaagatctggaggatcacccgagatgataaagaaagccgccacc
 tcggaaatttccttctgataaaaattttgaagccatttcctcaatgtttccagataaaggg
 cacagcagaagaactaaaggaaaaatataaagaactcacccgaacagcagctcccaggcgc
 acttcctcctgaatgtaccctcccaacatagatggaccaaagtctaactctgttcagagaga
 gcaaagccttacactcctttcatacgccttttctgtaggcgatgttttaaatatgactgctt
 cctacatccttttcatgcaacacccaacacttataagcggaagaacacagaaacagctct
 agacaacaaaccttgtggaccacagtggtaccagcatttggaggaggagcaaaggagtgtgc
 tgctgctctcaccgctgagcggataaagaccccaaaaacgtccaggaggccgcagaag
 aggacggcttccaataacagtagcaggccagcaccaccaccattaatgtgctggaatc
 aaaggatacagacagtgataggggaagcagggactgaaacggggggagagaacaatgataa
 agaagaagaagagaagaaagatgaaacttcgagctcctctgaagcaaattctcggtgtca
 aacaccaataaaagatgaagccaaatattgaacctcctgagaatgtggagtggagtgggtgc
 tgaagcctcaatgttttagagtcctcattggcacttactatgacaatttctgtgccattgc
 taggttaatttgggaccaaacaatgtagacaggtgtatgagtttagagtcaaagaatctag
 catcatagctccagctcccgctgaggatgtggatactcctccaaggaaaaagaaggaa
 acaccgggttgtgggctgcacactgcagaaagatacagctgaaaaaggacggctcctctaa
 ccatgtttacaactatcaaccctgtgatcatccacggcagccttgtgacagttcgtgcc
 ttgtgtgatagcacaataatttttgtgaaaagttttgtcaatgtagttcagagtgtcaaaa
 ccgctttccgggatgccgctgcaaagcacagtgcacaccaagcagtgcccggtgctacct
 ggctgtccgagagtgtgacctgacctctgtcttacttgtggagccgctgaccattggga
 cagtaaaaatgtgtcctgcaagaactgcagtattcagcggggctccaaaaagcatctatt
 gctggcaccatctgacgtggcaggctggggatttttatcaaatcctgtgcagaaaaa
 tgaattcatctcagaatactgtggagagattatttctcaagatgaagctgacagaagg
 gaaagtgtatgataatacatgtgcagctttctgttcaactgaacaatgattttgtgggt
 ggatgcaaccggcaagggttaacaaaattcgttttgcaaatcattcggtaaatccaaactg
 ctatgcaaaagttagatgggttaacgggtgatcacaggataggatatttttgcaagagagc
 catccagactggcgaagagctgttttttgattacagatacagccaggctgatgccctgaa
 gtatgtcggcatcgaaagagaaatgaaatcccttgacatctgctacctcctccccctc
 ctctgaaacagctgccttagcttcaggaacctcgagtactgtgggcaatttagaaaaaga
 acatgcagtttgaaattctgaatttgcaagtactgtaagaataatttatagtaagtgt
 ttaaaaatcaactttttattgccttctcaccagctgcaaagtgtttgtaccagtgaatt
 tttgcaataatgcagtatggtacatttttcaactttgaataaagaatacttgaaattgtc
 cttgttgaatc

Full amino acid of EZH2, isoform b (GenBank Accession No. NP_694543) (SEQ ID NO: 5)

MGQTGKKSEKGPVCWRKRVKSEYMRLRQLKRFRRADDEVKSMFSSNRQKIL
 ERTEILNQEWKQRRIQPVHILTSVSSLRGTREVEDETVLHNI PYMGDEVL
 DQDGT FIEELIKNYDGKVHGDRECGFINDEIFVELVNALGQYND DDDDD
 GDDPEEREKQKDL EHRDDKESRPPRKFP SDKIFEAISSMFDPKGTAEE
 LKEYKELTEQQLPGALPPECTPNIDGPNKSVQREQSLHSFHTLFCRRC
 FKYDCFLHPFHATPNTYKRKNTETALDNKPCGPQCYQHLEGAKEFAAALT
 AERIKTPPKRPGGRRRLPNNSSRPSTPTINVLESKDTSDREAGTETG
 GENNDKEEEEKDETS SSSSEANSRCQTP IKMKPNIEPPENVEWSGA EASM
 FRVLIGTYDDNFCAIARLIGTKTCRQVYEFVKESSIIAPAPAEDVDTPP

RKKKRKHLWAAHCRKIQLKKDGSSNHVYNYQPCDHPQPCDSSSCPCVIA
QNFCEKFCQCSSECQNRFPGCRCKAQCNTKQCPCYLAVRECDPDLCLTCG
AADHWDSKNVSKNCISIQRGSKHLLAPSDVAGWGI FIKDPVQKNEFIS
EYCGEIIISQDEADRRGKVYDKYMCSFLFNLNDFVVDATRKGNKIRFANH
SVNPNCYAKVMMVNGDHRIGIFAKRAIQTGEELFFDYRYSQADALKYVGI
EREMEIP

Full amino acid of EZH2, isoform e (GenBank Accession No. NP_001190178.1) (SEQ ID NO: 21)

MGQTGKKSEKGPVCWRKRVKSEYMRLRQLKFRRADEVKSMFSSNRQKILERTELNQEWKQRRIQPVHI
LTSCSVTSDLDFPTQVIPLKTLNAVASVPIMYSWSPLQQNFMEDETVLHNI PYMGDEVLDQDGT FIEEL
IKNYDGKVHGDRECGFINDEIFVELVNALGQYND DDDDDGDDPEEREKQKDL EDRDDKESRPPRKFP
SDKIFEAISSMFPDGTAEELKEKYKELTEQQLPGALPPECTPNIDGPNKSVQREQLSHSFHTLFCRRRC
FKYDCFLHPFHATPNTYKRKNTETALDNKPCGPQCYQHLEGAKEFAAALTAERIKTPPKRPGRRRGRRLP
NNSSRPSTPTINVLESKDTSDREAGTETGGENNDKEEEEKKDETSSSEANSRCQTPIKMKPNIEPPEN
VEWSGAEASMFVRLIGTYDNFCAIARLIGTKTCRQVYEFVRKESSIIAPAPAEDVDTPPRKKRKHRLW
AAHCRKIQLKKGQNRFPGCRCKAQCNTKQCPCYLAVRECDPDLCLTCGAADHWDSKNVSKNCISIQRGSK
KHL L L L L A P S D V A G W G I F I K D P V Q K N E F I S E Y C G E I I S Q D E A D R R G K V Y D K Y M C S F L F N L N D F V V D A T R K G
NKIRFANHSVNPNCYAKVMMVNGDHRIGIFAKRAIQTGEELFFDYRYSQADALKYVGIEREMEIP

Homo sapiens enhancer of zeste homolog 2 (Drosophila) (EZH2), transcript variant 5, mRNA (GenBank Accession No. NM_001203249.1) (SEQ ID NO: 22)

GACGACGTTTCGCGGCGGGGAACCTCGGAGTAGCTTCGCCTCTGACGTTTCCCCACGACGCACCCCGAAATC
CCCCTGAGCTCCGGCGGTTCGCGGGCTGCCCTCGCCGCTGGTCTGGCTTTATGCTAAGTTTGAGGGAAGA
GTCGAGCTGCTCTGCTCTCTATTGATTGTGTTCTGGAGGGCGTCCTGTTGAATCCCACCTTCATTGTGT
ACATCCCCCTTCCGTTCCCCCAAAAATCTGTGCCACAGGGTTACTTTTTGAAAGCGGGAGGAATCGAGAA
GCACGATCTTTTGGAAAACCTTGGTGAACGCCATAAATCATGGGCCAGACTGGGAAGAAATCTGAGAAG
GGACAGTTTGTGGCGGAAGCGTGTAAATCAGAGTACATGCGACTGAGACAGCTCAAGAGGTTTCAGAC
GAGCTGATGAAGTAAAGAGTATGTTTAGTTCCAATCGTCAGAAAATTTTGGAAAGAACGGAAATCTTAAA
CCAAGAATGGAAACAGCGAAGGATACAGCCTGTGCACATCCTGACTTCTGTTCGGTGACCAAGTACCTG
GATTTTCCAACACAAGTCATCCCATTAAGACTCTGAATGCAGTTGCTTCAGTACCCATAATGTATTCTT
GGTCTCCCTACAGCAGAATTTTATGGTGGAGATGAAACTGTTTTACATAACATTCCCTTATATGGGAGA
TGAAGTTTATAGTACAGGATGGTACTTTTATTGAAGAACTAATAAAAAATTATGATGGGAAAGTACACGGG
GATAGAGAATGTGGGTTTATAAATGATGAAATTTTGTGGAGTTGGTGAATGCCCTTGGTCAATATAATG
ATGATGACGATGATGATGATGGAGACGATCCTGAAGAAAGAGAAGAAAAGCAGAAAGATCTGGAGGATCA
CCGAGATGATAAAGAAAGCCGCCACCTCGGAAATTTCTTCTGATAAAATTTTGAAGCCATTTCTCA
ATGTTTCCAGATAAGGGCACAGCAGAAGAACTAAAGGAAAAATATAAGAACTACCCGAACAGCAGCTCC
CAGGCGCACTTCTCTGAATGTACCCCAACATAGATGGACCAAATGCTAAATCTGTTTCAGAGAGAGCA
AAGCTTACACTCCTTTTATACGCTTTTCTGTAGGCGATGTTTTAAATATGACTGCTTCCTACATCCTTTT
CATGCAACACCCAACTTATAAGCGGAAGAACACAGAAACAGCTCTAGACAAACAACTTGTGGACCAC
AGTGTACACGATTTGGAGGGAGCAAAGGAGTTTGTCTGCTGCTCTCACCCTGAGCGGATAAAGACCCC
ACCAAAACGTCCAGGAGGCCGAGAGAGGACGGCTTCCCAATAACAGTAGCAGGCCCAGCACCCCCACC
ATTAATGTGCTGGAATCAAAGGATACAGACAGTATAGAGGAAGCAGGGACTGAAACGGGGGGAGAGAACA
ATGATAAAGAAGAAGAAGAGAAGAAAGATGAAACTTCGAGCTCCTCTGAAGCAAATTCGCGTGTCAAAC
ACCAATAAAGATGAAGCCAAATATTGAACCTCCTGAGAATGTGGAGTGGAGTGGTGTGAAGCCTCAATG
TTTAGAGTCTCATTGGCACTTACTATGACAATTTCTGTGCCATTGCTAGGTTAATTGGGACCAAAACAT
GTAGACAGGTGTATGAGTTTAGAGTCAAAGAATCTAGCATCATAGCTCCAGCTCCCGCTGAGGATGTGGA
TACTCCTCCAAGGAAAAAGAAGAGGAAACACCGGTTGTGGGCTGCACACTGCAGAAAGATACAGCTGAAA
AAGGTCAAAACCGCTTTCCGGGATGCCGCTGCAAAGCACAGTGCAACACCAAGCAGTGCCCGTGCTACC
TGGCTGTCCGAGAGTGTGACCCTGACCTCTGTCTTACTTGTGGAGCCGCTGACCATTTGGGACAGTAAAA
TGTGTCTGCAAGAACTGCAGTATTCAGCGGGCTCCTTCTTCTGAGGACCATCTATTGCTGGCACCATTGACGTG
GCAGGCTGGGGGATTTTATCAAAGATCCTGTGCGAGAAAATGAATTCATCTCAGAATACTGTGGAGAGA
TTATTTCTCAAGATGAAGCTGACAGAAGAGGGAAGTGTATGATAAATACATGTGCAGCTTTCTGTTCAA
CTTGAACAATGATTTTGTGGTGGATGCAACCCGCAAGGGTAACAAAATTCGTTTTGCAAAATCATTGGTA
AATCCAACTGCTATGCAAAAGTTATGATGGTTAACGGTGATCACAGGATAGGTATTTTGGCAAGAGAG
CCATCCAGACTGGCGAAGAGCTGTTTTTGTATACAGATACAGCCAGGCTGATGCCCTGAAGTATGTGCG
CATCGAAAGAGAAATGGAATCCCTTGACATCTGCTACCTCCTCCCCCTCCTCTGAAACAGCTGCCTTA

GCTTCAGGAACCTCGAGTACTGTGGGCAATTTAGAAAAAGAACATGCAGTTTGAAATTCTGAATTTGCAA
 AGTACTGTAAGAATAATTTATAGTAATGAGTTTAAAAATCAACTTTTTATTGCCTTCTCACCAGCTGCAA
 AGTGTGTTGTACCAGTGAATTTTTGCAATAATGCAGTATGGTACATTTTCAACTTTGAATAAAGAATAC
 TTGAACCTGTCCTTGTGAATC

[082] A structure model of partial EZH2 protein based on the A chain of nuclear receptor binding SET domain protein 1 (NSD1) is provided in Figure 23. This model corresponds to amino acid residues 533-732 of EZH2 sequence of SEQ ID NO: 1.

[083] The corresponding amino acid sequence of this structure model is provided below. The residues in the substrate pocket domain are underlined. The residues in the SET domain are shown italic.

SCPCVIAQNFCEKFCQCSSECQNRFPGCRCKAQCNTKQCPCYLAVRECDPDLCLTCG
 AADHWDSKNVSCKNCSIQRGSKKHLLLAPSDVAGWGFIKDPVQKNEFISEY⁶⁴¹CGEIIIS
QDEADRRGKVYDKYMCSFLNLNNDFY⁶⁷⁴VD⁶⁷⁷TRKGNKIR⁶⁸⁵EA⁶⁸⁷NHSVNPNCYAKV
MMVNGDHRGIFAKRAIQTGEELFFDYRYSQAD (SEQ ID NO: 6)

[084] The catalytic site of EZH2 is believed to reside in a conserved domain of the protein known as the SET domain. The amino acid sequence of the SET domain of EZH2 is provided by the following partial sequence spanning amino acid residues 613-726 of Swiss-Prot Accession No. Q15910 (SEQ ID NO: 1):

HLLLAPSDVAGWGIFIKDPVQKNEFISEYCGEIIISQDEADRRGKVYDKYMCSFLNLNNDFY
 VDATRKGNKIRFANHSVNPNCYAKVMMVNGDHRIGIFAKRAIQTGEELFFDY (SEQ ID NO: 7).

[085] The tyrosine (Y) residue shown underlined in SEQ ID NO: 7 is Tyr641 (Y641) in Swiss-Prot Accession No. Q15910 (SEQ ID NO: 1).

[086] The SET domain of GenBank Accession No. NP_004447 (SEQ ID NO: 3) spans amino acid residues 618-731 and is identical to SEQ ID NO:6. The tyrosine residue corresponding to Y641 in Swiss-Prot Accession No. Q15910 shown underlined in SEQ ID NO: 7 is Tyr646 (Y646) in GenBank Accession No. NP_004447 (SEQ ID NO: 3).

[087] The SET domain of GenBank Accession No. NP_694543 (SEQ ID NO: 5) spans amino acid residues 574-687 and is identical to SEQ ID NO: 7. The tyrosine residue corresponding to Y641 in Swiss-Prot Accession No. Q15910 shown underlined in SEQ ID NO: 7 is Tyr602 (Y602) in GenBank Accession No. NP_694543 (SEQ ID NO: 5).

[088] The nucleotide sequence encoding the SET domain of GenBank Accession No. NP_004447 is

catctattgctggcaccatctgacgtggcaggctgggggatttttatcaaagatcctgtgca
 gaaaaatgaattcatctcagaataactgtggagagattatttctcaagatgaagctgacagaa

gagggaaagtgtatgataaatacatgtgcagcttttctgttcaacttgaacaatgattttgtg
 gtggatgcaaccgcgaagggttaacaaaattcgttttgcaaatacttcggtaaatccaaactg
 ctatgcaaaagtattatgatgggttaacgggtgatcacaggataggtatttttgccaagagagcca
 tccagactggcgaagagctgttttttgattac (SEQ ID NO: 8),

where the codon encoding Y641 is shown underlined.

[089] For purposes of this application, amino acid residue Y641 of human EZH2 is to be understood to refer to the tyrosine residue that is or corresponds to Y641 in Swiss-Prot Accession No. Q15910.

Full amino acid sequence of Y641 mutant EZH2 (SEQ ID NO: 9)

MGQTGKKSEKGPVCRKRVKSEYMRLRQLKRFRRADDEVKSMFSSNRQKILERTEILNQEW
 KQRIQPVHILTSVSSLRGTRECSVTSDDLDFPTQVIPLKTLNAVASVPIMYSWSPLQONF
 MVEDETVLHNI PYMGDEVLDQDGT FIEELIKNYDGKVHGDRECGFINDEIFVELVNALGQ
 YNDDDDDDDDGDDPEEREKQKDLEDHRDDKESRPPRKFP SDKI FEAISSMFPDKGTAEEL
 KEKYKELTEQQLPGALPPECTPNIDGPNAKSVQREQSLHSFHTLFCRRCFKYDCFLHPFH
 ATPNTYKRKNTETALDNKPCGPQCYQHLEGAKEFAAALTAERIKTPPKRPGRRRGRLPN
 NSSRPSTPTINVLESKDTSDREAGTETGGENNDKEEEEKKDETSSSSEANSRCQTPIKM
 KPNIEPPENVEWSGAEASMFVLI GTYYDNFCAIARLIGTKTCRQVYEFVKESSIIAPA
 PAEDVDTPPRKKKRKHLWAAHCRKIQLKKGSSNHVYNYQPCDHPRQPCDSSCPCVIAQ
 NFCEKFCQCSSECQNRFP GCRCKAQCNTKQPCYLAVRECDPDLCLTCGAADHWDSKNVS
 CKNC SIQRGSKKHL LAPS DVAGWGI FIKDPVQKNEFTISEXCGEII SQDEADRRGKVYDK
 YMC SFLENLNDFVVDATRKGNKIRFANHSVNPNCYAKVMMVNGDHRIGIFAKRAIQTGE
 ELFFDYRYSQADALKYVGIEREMEIP

Wherein x can be any amino acid residue other than tyrosine (Y)

[090] A Y641 mutant of human EZH2, and, equivalently, a Y641 mutant of EZH2, is to be understood to refer to a human EZH2 in which the amino acid residue corresponding to Y641 of wild-type human EZH2 is substituted by an amino acid residue other than tyrosine.

[091] In one embodiment the amino acid sequence of a Y641 mutant of EZH2 differs from the amino acid sequence of wild-type human EZH2 only by substitution of a single amino acid residue corresponding to Y641 of wild-type human EZH2 by an amino acid residue other than tyrosine.

[092] In one embodiment the amino acid sequence of a Y641 mutant of EZH2 differs from the amino acid sequence of wild-type human EZH2 only by substitution of phenylalanine (F) for the single amino acid residue corresponding to Y641 of wild-type human EZH2. The Y641 mutant of EZH2 according to this embodiment is referred to herein as a Y641F mutant or, equivalently, Y641F.

Y641F (SEQ ID NO: 10)

MGQTGKKSEKGPVCRKRVKSEYMRLRQLKRFRRADDEVKSMFSSNRQKILERTEILNQEW
 KQRIQPVHILTSVSSLRGTRECSVTSDDLDFPTQVIPLKTLNAVASVPIMYSWSPLQONF
 MVEDETVLHNI PYMGDEVLDQDGT FIEELIKNYDGKVHGDRECGFINDEIFVELVNALGQ
 YNDDDDDDDDGDDPEEREKQKDLEDHRDDKESRPPRKFP SDKI FEAISSMFPDKGTAEEL

KEKYKELTEQQLPGALPPECTPNIDGPNAKSVQREQSLHSFHTLFCRRCFKYDCFLHPPH
 ATPNTYKRKNTETALDNKPCGPGQCYQHLEGAKEFAAALTAERIKTTPKRPGGRRRGRLPN
 NSSRPSTPTINVLESKDTSDREAGTETGGENNDKEEEEKKDETSSSSEANSRCQTPIKM
 KPNIEPPENVEWSGAEASMFVLIIGTYYDNFCAIARLIGTKTCRQVYEFVRKESSIIAPA
 PAEDVDTPPRKKKRKHRLWAAHCRKIQLKKDGSSNHVYNYQPCDHPRQPCDSSCPCVIAQ
 NFCEKFCQCSSECQNRFPGCRCKAQCNKQPCPYLAVRECDPDLCLTCGAADHWDSKNVS
 CKNCISIQRGSKKHLALLAPSDVAGWGI FIKDPVQKNEFISEFCGEIISQDEADRRGKVYDK
 YMCSEFLNLLNDFVVDATRKGNKIRFANHSVNPNCYAKVMMVNGDHRIGIFAKRAIQTGE
 ELFFDYRYSQADALKYVGIEREMEIP

[093] In one embodiment the amino acid sequence of a Y641 mutant of EZH2 differs from the amino acid sequence of wild-type human EZH2 only by substitution of histidine (H) for the single amino acid residue corresponding to Y641 of wild-type human EZH2. The Y641 mutant of EZH2 according to this embodiment is referred to herein as a Y641H mutant or, equivalently, Y641H.

Y641H (SEQ ID NO: 11)

MGQTGKKSEKGPVCWRKRVKSEYMRLRQLKRFRRADEVKSMFSSNRQKILERTEILNQEW
 KQRRIQPVHILTSVSSLRGTRRECSVTSDDLDFPTQVIPLKTLNAVASVPIMYSWSPLQQNF
 MVEDETVLHNI PYMGDEVLDQDGT FIEELIKNYDGKVHGDRECGFINDEIFVELVNALGQ
 YNDDDDDDDDGDDPEEREKQKQDLEDHRDDKESRPPRKFPSPDKI FEAISSMFPDKGTAEEL
 KEKYKELTEQQLPGALPPECTPNIDGPNAKSVQREQSLHSFHTLFCRRCFKYDCFLHPPH
 ATPNTYKRKNTETALDNKPCGPGQCYQHLEGAKEFAAALTAERIKTTPKRPGGRRRGRLPN
 NSSRPSTPTINVLESKDTSDREAGTETGGENNDKEEEEKKDETSSSSEANSRCQTPIKM
 KPNIEPPENVEWSGAEASMFVLIIGTYYDNFCAIARLIGTKTCRQVYEFVRKESSIIAPA
 PAEDVDTPPRKKKRKHRLWAAHCRKIQLKKDGSSNHVYNYQPCDHPRQPCDSSCPCVIAQ
 NFCEKFCQCSSECQNRFPGCRCKAQCNKQPCPYLAVRECDPDLCLTCGAADHWDSKNVS
 CKNCISIQRGSKKHLALLAPSDVAGWGI FIKDPVQKNEFISEHCGEIISQDEADRRGKVYDK
 YMCSEFLNLLNDFVVDATRKGNKIRFANHSVNPNCYAKVMMVNGDHRIGIFAKRAIQTGE
 ELFFDYRYSQADALKYVGIEREMEIP

[094] In one embodiment the amino acid sequence of a Y641 mutant of EZH2 differs from the amino acid sequence of wild-type human EZH2 only by substitution of asparagine (N) for the single amino acid residue corresponding to Y641 of wild-type human EZH2. The Y641 mutant of EZH2 according to this embodiment is referred to herein as a Y641N mutant or, equivalently, Y641N.

Y641N (SEQ ID NO: 12)

MGQTGKKSEKGPVCWRKRVKSEYMRLRQLKRFRRADEVKSMFSSNRQKILERTEILNQEW
 KQRRIQPVHILTSVSSLRGTRRECSVTSDDLDFPTQVIPLKTLNAVASVPIMYSWSPLQQNF
 MVEDETVLHNI PYMGDEVLDQDGT FIEELIKNYDGKVHGDRECGFINDEIFVELVNALGQ
 YNDDDDDDDDGDDPEEREKQKQDLEDHRDDKESRPPRKFPSPDKI FEAISSMFPDKGTAEEL
 KEKYKELTEQQLPGALPPECTPNIDGPNAKSVQREQSLHSFHTLFCRRCFKYDCFLHPPH
 ATPNTYKRKNTETALDNKPCGPGQCYQHLEGAKEFAAALTAERIKTTPKRPGGRRRGRLPN
 NSSRPSTPTINVLESKDTSDREAGTETGGENNDKEEEEKKDETSSSSEANSRCQTPIKM
 KPNIEPPENVEWSGAEASMFVLIIGTYYDNFCAIARLIGTKTCRQVYEFVRKESSIIAPA
 PAEDVDTPPRKKKRKHRLWAAHCRKIQLKKDGSSNHVYNYQPCDHPRQPCDSSCPCVIAQ
 NFCEKFCQCSSECQNRFPGCRCKAQCNKQPCPYLAVRECDPDLCLTCGAADHWDSKNVS
 CKNCISIQRGSKKHLALLAPSDVAGWGI FIKDPVQKNEFISENCGEIISQDEADRRGKVYDK

YMCSFLFNLNDFVVDATRKGNKIRFANHSVNPNCYAKVMMVNGDHRIGIFAKRAIQTGE ELFFDYRYSQADALKYVGIEREMEIP

[095] In one embodiment the amino acid sequence of a Y641 mutant of EZH2 differs from the amino acid sequence of wild-type human EZH2 only by substitution of serine (S) for the single amino acid residue corresponding to Y641 of wild-type human EZH2. The Y641 mutant of EZH2 according to this embodiment is referred to herein as a Y641S mutant or, equivalently, Y641S.

Y641S (SEQ ID NO: 13)

MGQTGKKSEKGPVCRKRVKSEYMRLRQLKRFRADEVKSMFSSNRQKILERTEILNQEW KQRRIQPVHILTSVSSLRGTRRECSVTSDDLDFPTQVIPLKTLNAVASVPIMYSWSPLQQNF MVEDETVLHNI PYMGDEVLDQDGT FIEELIKNYDGKVHGDRECGFINDEIFVELVNALGQ YNDDDDDDDDGDDPEEREKQKQDLEDHRDDKESRPPRKFP SDKI FEAISMFDPKGTAEEEL KEKYKELTEQQLP GALPPECTPNIDGPNKSVQREQSLHSFHTLFCRRCFKYDCFLHPPFH ATPNTYKRKNTETALDNKPCGPQCYQHLEGAKEFAAALTAERI KTPPKRPGRRRRGRLPN NSSRPSTPTINVLESKDTSDREAGTETGGENNDKEEEEKKDETSSSSSEANSRCQTPIKM KPNIEPPENVEWSGAEASMFVRLIGTYDDNFCAIARLIGTKTCRQVYEFVRKESSIIAPA PAEDVDTPPRKKKRKHLWAAHCRKIQLKKDGSSNHVYNYQPCDHPRQPCDSSCPCVIAQ NFCEKFCQCSSECQNRFP GCRCKAQCN TKQPCYLAVRECDPDLCLTCGAADHWDSKNVS CKNC SIQRGSKKHL LAPS DVAGWGI FIKDPVQKNEFISECCGEIISQDEADRRGKVYDK YMCSFLFNLNDFVVDATRKGNKIRFANHSVNPNCYAKVMMVNGDHRIGIFAKRAIQTGE ELFFDYRYSQADALKYVGIEREMEIP

[096] In one embodiment the amino acid sequence of a Y641 mutant of EZH2 differs from the amino acid sequence of wild-type human EZH2 only by substitution of cysteine (C) for the single amino acid residue corresponding to Y641 of wild-type human EZH2. The Y641 mutant of EZH2 according to this embodiment is referred to herein as a Y641C mutant or, equivalently, Y641C.

Y641C (SEQ ID NO: 14)

MGQTGKKSEKGPVCRKRVKSEYMRLRQLKRFRADEVKSMFSSNRQKILERTEILNQEW KQRRIQPVHILTSVSSLRGTRRECSVTSDDLDFPTQVIPLKTLNAVASVPIMYSWSPLQQNF MVEDETVLHNI PYMGDEVLDQDGT FIEELIKNYDGKVHGDRECGFINDEIFVELVNALGQ YNDDDDDDDDGDDPEEREKQKQDLEDHRDDKESRPPRKFP SDKI FEAISMFDPKGTAEEEL KEKYKELTEQQLP GALPPECTPNIDGPNKSVQREQSLHSFHTLFCRRCFKYDCFLHPPFH ATPNTYKRKNTETALDNKPCGPQCYQHLEGAKEFAAALTAERI KTPPKRPGRRRRGRLPN NSSRPSTPTINVLESKDTSDREAGTETGGENNDKEEEEKKDETSSSSSEANSRCQTPIKM KPNIEPPENVEWSGAEASMFVRLIGTYDDNFCAIARLIGTKTCRQVYEFVRKESSIIAPA PAEDVDTPPRKKKRKHLWAAHCRKIQLKKDGSSNHVYNYQPCDHPRQPCDSSCPCVIAQ NFCEKFCQCSSECQNRFP GCRCKAQCN TKQPCYLAVRECDPDLCLTCGAADHWDSKNVS CKNC SIQRGSKKHL LAPS DVAGWGI FIKDPVQKNEFISECCGEIISQDEADRRGKVYDK YMCSFLFNLNDFVVDATRKGNKIRFANHSVNPNCYAKVMMVNGDHRIGIFAKRAIQTGE ELFFDYRYSQADALKYVGIEREMEIP

[097] In one embodiment the amino acid sequence of a A677 mutant of EZH2 differs from the amino acid sequence of wild-type human EZH2 only by substitution of a non-alanine

corresponding to R685 of wild-type human EZH2. The R685 mutant of EZH2 according to this embodiment is referred to herein as an R685 mutant and preferably an R685C mutant or an R685H mutant or, equivalently, R685H or R685C.

A685 (SEQ ID NO: 17)

MGQTGKKSEKGPVCWRKRVKSEYMRLRQLKRFRRRADEVKSMFSSNRQKILERTEILNQEW
KQRRIQPVHILTSVSSLRGTRECSVTSDLDFPTQVIPLKTLNAVASVPIMYSWSPLQONF
MVEDETVLHNI PYMGDEVLDQDGT FIEELIKNYDGKVHGDRECGFINDEIFVELVNALGQ
YNDDDDDDDDGDDPEEREKQKQDLEDHRDDKESRPPRKFPSPDKI FEAISSMFPDKGTAEEL
KEKYKELTEQQQLPGALPPECTPNIDGPNKSVQREQSLHSFHTLFCRRCFKYDCFLHPPFH
ATPNTYKRKNTETALDNKPCGPGQCYQHLEGAKEFAAALTAERI KTPPKRPGGRRRGRLPN
NSSRPSTPTINVLESKDTSDREAGTETGGENNDKEEEEKKDETSSSSEANSRCQTPIKM
KPNIEPPENVWGSAGAEASMFVRLIGTYDNFCAIARLIGTKTCRQVYEFVRKESSIIAPA
PAEDVDTPPRKKKRKHRLWAAHCRKIQLKKDGSSNHVYNYQPCDHPRQPCDSSCPCVIAQ
NFCEKFCQCSSECNRFPGCRCKAQCN TKQPCYLA VRECDPDLCLTCGAADHWDSKNVS
CKNC SIQRGSKKHL L LAPS DVAGWGI FIKDPVQKNEFISEYCGEIIISQDEADRRGKVYDK
YMC SFLFNLNDFVVDATRKGNKIXFANH SVNPNCYAKVMMVNGDHRIGIFAKRAIQTGE
ELFFDYRYSQADALKYVGIEREMEIP

Wherein X is preferably a cysteine (C) or a histidine (H).

[0100] In one embodiment the amino acid sequence of a mutant of EZH2 differs from the amino acid sequence of wild-type human EZH2 in one or more amino acid residues in its substrate pocket domain as defined in SEQ ID NO: 6. The mutant of EZH2 according to this embodiment is referred to herein as an EZH2 mutant.

Mutant EZH2 comprising one or more mutations in the substrate pocket domain (SEQ ID NO: 18)

MGQTGKKSEKGPVCWRKRVKSEYMRLRQLKRFRRRADEVKSMFSSNRQKILERTEILNQEW
KQRRIQPVHILTSVSSLRGTRECSVTSDLDFPTQVIPLKTLNAVASVPIMYSWSPLQONF
MVEDETVLHNI PYMGDEVLDQDGT FIEELIKNYDGKVHGDRECGFINDEIFVELVNALGQ
YNDDDDDDDDGDDPEEREKQKQDLEDHRDDKESRPPRKFPSPDKI FEAISSMFPDKGTAEEL
KEKYKELTEQQQLPGALPPECTPNIDGPNKSVQREQSLHSFHTLFCRRCFKYDCFLHPPFH
ATPNTYKRKNTETALDNKPCGPGQCYQHLEGAKEFAAALTAERI KTPPKRPGGRRRGRLPN
NSSRPSTPTINVLESKDTSDREAGTETGGENNDKEEEEKKDETSSSSEANSRCQTPIKM
KPNIEPPENVWGSAGAEASMFVRLIGTYDNFCAIARLIGTKTCRQVYEFVRKESSIIAPA
PAEDVDTPPRKKKRKHRLWAAHCRKIQLKKDGSSNHVYNYQPCDHPRQPCDSSCPCVIAQ
NFCEKFCQCSSECNRFPGCRCKAQCN TKQPCYLA VRECDPDLCLTCGAADHWDSKNVS
CKNC SIQRGSKKHL L LAPS DVAGWGI FIKDPVQKNEFISEXCGEIIISQDEADRRGKVYDK
YMXXXLXNLNDFXXDXTRKGNKXXXXH SVNPNCYAKVMMVNGDHRXGIFAKRAIQTGE
ELFXDXRYSXADALKYVGIEREMEIP

Wherein X can be any amino acid except the corresponding wild type residue.

Histone Acetyltransferases

[0101] Histone acetyltransferase (HAT) enzymes of the disclosure activate gene transcription by transferring an acetyl group from acetyl CoA to form ε-N-acetyllysine, which serves to modify histones and increase transcription by, for example, generating or exposing binding sites for protein-protein interaction domains.

[0102] HAT enzymes of the disclosure include, but are not limited to, those enzymes of the p300/CBP family.

[0103] In certain embodiments, a mutation of the disclosure may occur in a sequence encoding the p300 HAT, including the nucleotide sequence of the EP300 gene, encoding p300 (below, corresponding to GenBank Accession No. NM_001429.3, defined as Homo sapiens E1A binding protein p300 (EP300), mRNA; and identified as SEQ ID NO: 19).

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1  GCCGAGGAGG AAGAGGTTGA TGGCGGCGGC GGAGCTCCGA GAGACCTCGG CTGGGCAGGG
61  GCCGGCCGTG GCGGGCCGGG GACTGCGCCT CTAGAGCCGC GAGTTCTCGG GAATTCGCCG
121 CAGCGGACGC GCTCGGCGAA TTTGTGCTCT TGTGCCCTCC TCCGGGCTTG GGCCAGGCC
181 CGGCCCTCG CACTTGCCCT TACCTTTTCT ATCGAGTCCG CATCCCTCTC CAGCCACTGC
241 GACCCGCGCA AGAGAAAAG GAACTTCCCC CACCCCTCG GGTGCCGTG GAGCCCCCA
301 GCCCACCCCT GGGTGC GGCG CGGGGACCCC GGGCCGAAGA AGAGATTTC TGAGGATTCT
361 GGTTTTCCTC GCTTGTATCT CCGAAAGAAT TAAAAATGGC CGAGAATGTG GTGGAACCGG
421 GGCCGCTTC AGCCAAGCGG CCTAACTCT CATCTCCGGC CCTCTCGGCG TCCGCCAGCG
481 ATGGCACAGA TTTTGGCTCT CTATTTGACT TGGAGCACGA CTTACCAGAT GAATTAATCA
541 ACTCTACAGA ATTGGGACTA ACCAATGGTG GTGATATTAA TCAGCTTCAG ACAAGTCTTG
601 GCATGGTACA AGATGCAGCT TCTAAACATA AACAGCTGTC AGAATTGCTG CGATCTGGTA
661 GTTCCCTTAA CCTCAATATG GGAGTTGGTG GCCCAGGTCA AGTCATGGCC AGCCAGGCC
721 AACAGAGCAG TCCTGGATTA GGTTCGATAA ATAGCATGGT CAAAAGCCCA ATGACACAGG
781 CAGGCTTGAC TTCTCCCAAC ATGGGGATGG GCACTAGTGG ACCAAATCAG GGTCTTACGC
841 AGTCACAGG TATGATGAAC AGTCCAGTAA ATCAGCCTGC CATGGGAATG AACACAGGGA
901 TGAATGCGGG CATGAATCCT GGAATGTTGG CTGCAGGCAA TGGACAAGGG ATAATGCCTA
961 ATCAAGTCAT GAACGGTTCA ATTGGAGCAG GCCGAGGGCG ACAGAATATG CAGTACCCAA
1021 ACCAGGCAT GGAAGTGCT GGCACTTAC TGA CTGAGCC TCTTCAGCAG GGCTCTCCCC
1081 AGATGGGAGG ACAAACAGGA TTGAGAGGCC CCCAGCCTCT TAAGATGGGA ATGATGAACA
1141 ACCCAATCC TTATGGTTCA CCATATACTC AGAATCCTGG ACAGCAGATT GGAGCCAGTG
1201 GCCTTGGTCT CCAGATTGAG AAAAAACTG TACTATCAAA TAAGTATCT CCATTTGCTA
1261 TGGACAAAAA GGCAGTTTCT GGTGGAGGAA TGCCCAACAT GGGTCAACAG CCAGCCCCGC
1321 AGGTCCAGCA GCCAGGCCTG GTGACTCCAG TTGCCCAAGG GATGGGTTCT GGAGCACATA
1381 CAGCTGATCC AGAGAAGCGC AAGCTCATCC AGCAGCAGCT TGTTCTCCTT TTGCATGCTC
1441 ACAAGTGCCA GCGCCGGGAA CAGGCCAATG GGGAAGTGAG GCAGTGCAAC CTTCCCCACT
1501 GTCGCACAAAT GAAGAATGTC CTAAACCACA TGACACACTG CCAGTCAGGC AAGTCTTGCC
1561 AAGTGGCACA CTGTGCATCT TCTCGACAAA TCATTTTACA CTGGAAGAAT TGTACAAGAC
1621 ATGATTGTCC TGTGTGTCTC CCCCTCAAAA ATGCTGGTGA TAAGAGAAAT CAACAGCCAA
1681 TTTTGACTGG AGCACCCGTT GGACTTGGA ATCCTAGCTC TCTAGGGGTG GGTCAACAGT
1741 CTGCCCCCAA CCTAAGCACT GTTAGTCAGA TTGATCCCAG CTCCATAGAA AGAGCCTATG
1801 CAGCTCTTGG ACTACCCTAT CAAGTAAATC AGATGCCGAC ACAACCCAG GTGCAAGCAA
1861 AGAACCAGCA GAATCAGCAG CCTGGGCAGT CTCCCCAAGG CATGCGGCC ATGAGCAACA
1921 TGAGTGCTAG TCCTATGGGA GTAAATGGAG GTGTAGGAGT TCAAACGCCG AGTCTTCTTT
1981 CTGACTCAAT GTTGCAATCA GCCATAAATT CTCAAACCC AATGATGAGT GAAATGCCA
2041 GTGTGCCCTC CCTGGGTCCT ATGCCAACAG CAGCTCAACC ATCCACTACT GGAATTCGGA
2101 AACAGTGGCA CGAAGATATT ACTCAGGATC TTCGAAATCA TCTTGTTTAC AAACCTGTC
2161 AAGCCATATT TCCTACGCCG GATCCTGCTG CTTTAAAAGA CAGACGGATG GAAAACCTAG
2221 TTGCATATGC TCGGAAAGTT GAAGGGGACA TGTATGAATC TGCAAACAAT CGAGCGGAAT
2281 ACTACCACCT TCTAGCTGAG AAAATCTATA AGATCCAGAA AGAACTAGAA GAAAAACGAA
2341 GGACCAGACT ACAGAAGCAG AACATGCTAC CAAATGCTGC AGGCATGGTT CCAGTTTCCA
2401 TGAATCCAGG GCCTAACATG GGACAGCCGC AACCAGGAAT GACTTCTAAT GGCCCTCTAC
2461 CTGACCCAAAG TATGATCCGT GGCAGTGTGC CAAACCAGAT GATGCCTCGA ATAACCTCAC
2521 AATCTGGTTT GAATCAATTT GGCCAGATGA GCATGGCCCA GCCCCCTATT GTACCCCGG
2581 AAACCCCTCC TCTTCAGCAC CATGGACAGT TGGCTCAACC TGGAGCTCTC AACCCGCCTA
2641 TGGGCTATGG CCCTCGTATG CAACAGCCTT CCAACAGGG CCAGTTCTCT CACTCAGCTC
2701 AGTTCCCATC ACAGGGAATG AATGTAACAA ATATCCCTTT GGCTCCGTCC AGCGGTCAAG
2761 CTCCAGTGTC TCAAGCACAA ATGTCTAGTT CTTCTGCCC GGTGAAGTCT CCTATAATGC
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 3061 CAACAACACA ACTTCCCCAA CAAGTGCAGC CTTCACTTCC TGCTGCACCT TCTGCTGACC
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 3181 CACCGCTGCT TCCTCCGCAG CCTGCAACTC CACTTTCCCA GCCAGCTGTA AGCATTGAAG
 3241 GACAGGTATC AAATCCTCCA TCTACTAGTA GCACAGAAGT GAATTCTCAG GCCATTGCTG
 3301 AGAAGCAGCC TTCCAGGAA GTGAAGATGG AGGCCAAAAT GGAAGTGGAT CAACCAGAAC
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 3541 TCAAACCAGA AGAACTACGA CAGGCCTGA TGCCAACCTT GGAGGCACCT TACCGTCAGG
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 4681 GTTACACAAC AGGGCATATT TGGGCATGTC CACCAAGTGA GGGAGATGAT TATATCTTCC
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 5461 ATGACTTGTTG TATCACCTGC TATAACACTA AAAACCATGA CCACAAAATG GAGAACTAG
 5521 GCCTTGCGCTT AGATGATGAG AGCAACAACC AGCAGGCTGC AGCCACCCAG AGCCCAGGCG
 5581 ATTCTCGCCG CCTGAGTATC CAGCGCTGCA TCCAGTCTCT GGTCCATGCT TGCCAGTGTC
 5641 GGAATGCCAA TTGCTCACTG CCATCCTGCC AGAAGATGAA GCGGGTTGTG CAGCATACCA
 5701 AGGGTTGCAA ACGGAAAACC AATGGCGGGT GCCCATCTG CAAGCAGCTC ATTGCCCTCT
 5761 GCTGCTACCA TGCCAAGCAC TGCCAGGAGA ACAAATGCCC GGTGCCGTTT TGCCTAAACA
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 5881 GCAGGAGGAT GGCCAGCATG CAGCGGACTG GTGTGGTTGG GCAGCAACAG GGCCTCCCTT
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 6001 CCCAGCCCAC TTCTCAGCCT CAGCCTACCC CTCCCAATAG CATGCCACCC TACTTGCCCA
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 6301 CACCTCCCAT GACCAGAGGT CCCAGTGGGC ATTTGGAGCC AGGGATGGGA CCGACAGGGA
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6421 GGATGCCAAG GCCAGCCATG ATGTCAGTGG CCCAGCATGG TCAACCTTTG AACATGGCTC
6481 CACAACCAGG ATTGGGCCAG GTAGGTATCA GCCCACCTCA ACCAGGCACT GTGTCTCAAC
6541 AAGCCTTACA AAACCTTTTG CGGACTCTCA GGTCTCCAG CTCTCCCTG CAGCAGCAAC
6601 AGGTGCTTAG TATCCTTCAC GCCAACCCCC AGCTGTTGGC TGCATTCATC AAGCAGCGGG
6661 CTGCCAAGTA TGCCAACTCT AATCCACAAC CCATCCCTGG GCAGCCTGGC ATGCCCCAGG
6721 GGCAGCCAGG GCTACAGCCA CCTACCATGC CAGGTCAGCA GGGGGTCCAC TCCAATCCAG
6781 CCATGCAGAA CATGAATCCA ATGCAGGCGG GCGTTCAGAG GGCTGGCCTG CCCCAGCAGC
6841 AACCACAGCA GCAACTCCAG CCACCCATGG GAGGGATGAG CCCCAGGCT CAGCAGATGA
6901 ACATGAACCA CAACACCATG CCTTCACAAT TCCGAGACAT CTTGAGACGA CAGCAAATGA
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7261 CCCAGTCCCC ACACCTACAA GGCCAGCAGA TCCCTAATTC TCTCTCAAT CAAGTGCCT
7321 CTCCCAGCC TGTCCTTCT CCACGGCCAC AGTCCCAGCC CCCCCTCC AGTCTTCCC
7381 CAAGGATGCA GCCTCAGCCT TCTCCACACC ACGTTTCCCC ACAGACAAGT TCCCACATC
7441 CTGGACTGGT AGCTGCCCAG GCCAACCCCA TGGAACAAGG GCATTTTGCC AGCCCGGACC
7501 AGAATTCAAT GCTTCTCAG CTTGCTAGCA ATCCAGGCAT GGCAAACCTC CATGGTGCAA
7561 GCGCCACGGA CCTGGGACTC AGCACCGATA ACTCAGACTT GAATTCAAAC CTCTCACAGA
7621 GTACACTAGA CATACTAG AGACACCTTG TAGTATTTTG GGAGCAAAA AATTATTTTC
7681 TCTTAACAAG ACTTTTTGTA CTGAAAACAA TTTTTTGAA TCTTTCGTAG CCTAAAAGAC
7741 AATTTTCCTT GGAACACATA AGAACTGTGC AGTAGCCGTT TGTGGTTTAA AGCAAACATG
7801 CAAGATGAAC CTGAGGGATG ATAGAATACA AAGAATATAT TTTTGTATG GCTGGTTACC
7861 ACCAGCCTTT CTTCCTCTT GTGTGTGTGG TTCAAGTGTG CACTGGGAGG AGGCTGAGGC
7921 CTGTGAAGCC AAACAATATG CTCTGCCTT GCACCTCCAA TAGGTTTTAT TATTTTTTTT
7981 AAATTAATGA ACATATGTAA TATTAATAGT TATTATTTAC TGGTGCAGAT GGTGACATT
8041 TTTCCCTATT TTCCTCACTT TATGGAAGAG TTAAACATT TCTAAACCAG AGGACAAAAG
8101 GGGTTAATGT TACTTTAAAA TTACATTCTA TATATATATA AATATATATA AATATATATT
8161 AAAATACCAG TTTTTTTTCT CTGGGTGCAA AGATGTTTCAT TCTTTTAAAA AATGTTTTAA
8221 AAAAAAAAAA AACTGCCTTT CTTCCTCTCA AGTCAACTTT TGTGCTCCAG AAAATTTTCT
8281 ATTCTGTAAG TCTGAGCGTA AAACCTCAAG TATTAAAATA ATTTGTACAT GTAGAGAGAA
8341 AATGACTTT TTCAAAAATA TACAGGGGCA GCTGCCAAAT TGATGTATTA TATATTGTGG
8401 TTTCTGTTTC TTGAAAGAAT TTTTTCGTT ATTTTACAT CTAACAAAGT AAAAAATTA
8461 AAAAGAGGGT AAGAAACGAT TCCGGTGGGA TGATTTTAAC ATGCAAAATG TCCCTGGGGG
8521 TTTCTCTTT GCTTGCTTTC TTCTCCTTA CCCTACCCCC CACTCACACA CACACACACA
8581 CACACACACA CACACACACA CACACACTTT CTATAAACT TGAAAATAGC AAAAACCTC
8641 AACTGTTGTA AATCATGCAA TTAAAGTTGA TTACTTATAA ATATGAACCT TGGATCACTG
8701 TATAGACTGT TAAATTTGAT TTCTTATTAC CTATTGTTAA ATAACTGTG TGAGACAGAC
8761 A

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[0104] In certain embodiments, a mutation of the disclosure may occur in a sequence encoding the p300 HAT, including the amino acid sequence of the p300 protein (below, corresponding to GenBank Accession No. NP_001420.2, defined as Homo sapiens E1A-binding protein, 300kD; E1A-associated protein p300; p300 HAT; and identified as SEQ ID NO: 20).

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1 MAENVVEPGP PSAKRPKLSS PALSASASDG TDFGSLFDLE HDLPDELINS TELGLTNGGD
61 INQLQTSLSGM VQDAASKHKQ LSELLRSGSS PNLNMGVGGP GQVMASQAQQ SSPGLGLINS
121 MVKSPMTQAG LTSPNMGMGT SGPNQGPTQS TGMMNSPVNQ PAMGMNTGMN AGMNPGLMLAA
181 GNGQGIMPNQ VMNGSIGAGR GRQNMQYPNP GMGSAGNLLT EPLQQGSPQM GGQTGLRGPQ
241 PLKMGMNNP NPYGSPYTQN PGQQIGASGL GLQIQTKTVL SNNLSPFAMD KKA VPGGGMP
301 NMGQQPAPQV QQPGLVTPVA QMGSGAHTA DPEKRKLIQQ QLVLLHHAHK CQRREQANGE
361 VRQCNLPHCR TMKNVLNHLT HCQSGKSCQV AHCASSRQII SHWKNCTRHD CPVCLPLKNA
421 GDKRNQQPIL TGAPVGLGNP SSLGVGQQA PNLSTVSQID PSSIERAYAA LGLPYQVNM
481 PTQPQVQAKN QQNQPGQSP QGMRPMSNMS ASPMGVNGGV GVQTPSLLSD SMLHSAINSQ

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541 NPMMSENASV PSLGPMPTAA QPSTTGIRKQ WHEDITQDLR NHLVHKLQVA IFPTPDPAAL
601 KDRRMENLVA YARKVEGDMY ESANNRAEYY HLLAEKIYKI QKELEEKRRT RLQKQNMMLPN
661 AAGMPVPSMN PGPNGMQPQP GMTSNGPLPD PSMIRGSVPN QMMPRITPQS GLNQFGQMSM
721 AQPPIVPRQT PPLQHHGQLA QPGALNPMPG YGPRMQQPSN QGQFLPQTQF PSQGMNVNTNI
781 PLAPSSGQAP VSQAQMSSSS CPVNSPIMPP GSQGSIHCP QLPQPALHQN SPSPVPSRTP
841 TPHTTPPSIG AQOPPATTIP APVPTPPAMP PGPQSQUALHP PPRQTPTPPT TQLPQQVQPS
901 LPAAPSADQP QQQPRSQQST AASVPTPTAP LLPPQPATPL SQPAVSIEGQ VSNPPSTSST
961 EVNSQAIAEK QPSQEVKMEA KMEVDQPEPA DTQPEDISES KVEDCKMEST ETEERSTELK
1021 TEIKEEDQP STSATQSSPA PGQSKKIKF PEELRQALMP TLEALYRQDP ESLPFRQVPD
1081 PQLLGIPDYF DIVKSPMDLS TIKRKLDTGQ YQEPWQYVDD IWLMFNNAWL YNRKTSRVYK
1141 YCSKLSEVFE QEIDPVMQSL GYCCGRKLEF SPQTLCCYK QLCITIPRDAT YYSYQNRHYF
1201 CEKCFNEIQG ESVSLGDDPS QPQTITINKEQ FSKRKNDTLD PELFVECTEC GRKMHQICVL
1261 HHEIWPAGF VCDGCLKKS RTRKENKFS KRLPSTRLGT FLENRVNDFL RRQNHPESGE
1321 VTVRVVHASD KTVEVKPGMK ARFVDSGEMA ESFPYRTKAL FAFEEIDGVD LCFFGMHVQE
1381 YGSDCPPPNQ RRVYISYLD VHFVRPKCLR TAVYHEILIG YLEYVKKLGY TTGHIWACPP
1441 SEGDDYIFHC HPPDQKIPKP KRLQEWYKKM LDKAVSERIV HDYKDFKQA TEDRLTSAKE
1501 LPYFEGDFWP NVLEESIKEL EQEEERKRE ENTSNESTDV TKGDSKNAKK KNNKTSKNK
1561 SLSRGNKKK PGMPNVNDL SQKLYATMEK HKEVFFVIRL IAGPAANSLP PIVDPDPLIP
1621 CDLMDGRDAF LTLARDKHLE FSSLRRAQWS TMCMLVELHT QSQDRFVYTC NECKHHVETR
1681 WHCTVCEDYD LCITCYNTKN HDHKMEKLG GLDDSENNOQ AAATQSPGDS RRLSIQRCIQ
1741 SLVHACQCRN ANCSLPSCQK MKRVVQHTKG CKRKTNGGCP ICKQLIALCC YHAKHCENK
1801 CPVPFCLNIK QKLRQQQLQH RLQQAQMLRR RMASMQRTGV VGQQQGLPSP TPATPTTPTG
1861 QQTPTPTPTQ PTSQPQPTPP NSMPPYLPRT QAAGPVSQ GK AAGQVTPPTP PQTAPPLPG
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2041 LKPGTVSQQA LQNLRLTLRS PSSPLQQQV LSILHANPQL LAAFIKQRAA KYANSNPQPI
2101 PGQPGMPQGG PGLQPPTMPG QQGVSHPNPM QNMNPMQAGV QRAGLPQQQP QQQLQPPMGG
2161 MSPQAQMMNM NHNTMPSQFR DILRRQMMQ QQQQQGAGPG IGPGMANHNQ FQQPQGVGYP
2221 PQQQORMQHH MQQMQQGNMG QIGQLPQALG AEAGASLQAY QQRLLQQQM SPVQPNMPS
2281 QQHMLPNQAA SPHLQGGQIP NSLSNQVRS PVPSPRPQS QPPHSSPSR MQPQSPHHV
2341 SPQTSPPHPG LVAAQANPME QGHFASPDQN SMLSQLASNP GMANLHGASA TDLGLSTDNS
2401 DLNSNLSQST LDIH

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[0105] In certain embodiments, a mutation of the disclosure may occur in a sequence encoding the CREB Binding Protein (CREBBP) HAT, including the nucleotide sequence encoding CREBBP (below, corresponding to GenBank Accession No. NM_004380, defined as Homo sapiens CREB binding protein (CREBBP), transcript variant 1, mRNA; and identified as SEQ ID NO: 23).

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1 CTGCGGGGCG CTGTTGCTGT GGCTGAGATT TGGCCGCCGC CTCCCCACC CGGCCTGCGC
61 CCTCCCTCTC CCTCGGCGCC CGCCGCCCG CTGCGGCCC GCGCTCGCTC CTCTCCCTCG
121 CAGCCGGCAG GGGCCCCGAC CCCCCTCCGG GCCCTCGCCG GCGCGGCCGC CCGTGCCCGG
181 GGCTGTTTTC GCGAGCAGGT GAAAATGGCT GAGAACTTGC TGGACGGACC GCCCAACCCC
241 AAAAGAGCCA AACTCAGCTC GCCCGGTTTC TCGGCGAATG ACAGCACAGA TTTTGGATCA
301 TTGTTTGAAT TGGAAAATGA TCTTCTGAT GAGCTGATAC CCAATGGAGG AGAATTAGGC
361 CTTTTAAACA GTGGGAACCT TGTCCAGAT GCTGCTTCCA AACATAAACA ACTGTCGGAG
421 CTTCTACGAG GAGGCAGCGG CTCTAGTATC AACCAGGAA TAGGAAATGT GAGCGCCAGC
481 AGCCCCGTGC AGCAGGGCCT GGTGGCCAG GCTCAAGGGC AGCCGAACAG TGCTAACATG
541 GCCAGCCTCA GTGCCATGGG CAAGAGCCCT CTGAGCCAGG GAGATTCTTC AGCCCCCAGC
601 CTGCCTAAAC AGGCAGCCAG CACCTCTGGG CCCACCCCG CTGCCTCCCA AGCACTGAAT
661 CCGCAAGCAC AAAAGCAAGT GGGCTGGCG ACTAGCAGCC CTGCCACGTC ACAGACTGGA
721 CCTGGTATCT GCATGAATGC TAACTTTAAC CAGACCCACC CAGGCCTCCT CAATAGTAAC
781 TCTGGCCATA GCTTAATTAA TCAGGCTTCA CAAGGGCAGG CGCAAGTCAT GAATGGATCT
841 CTTGGGGCTG CTGGCAGAGG AAGGGAGCT GGAATGCCGT ACCCTACTCC AGCCTGCAG
901 GGCCTGCTCGA GCAGCGTCTG GGCTGAGACC CTAACGCAGG TTTCCCCGCA AATGACTGGT
961 CACGCGGGAC TGAACACCGC ACAGGCAGGA GGCATGGCCA AGATGGGAAT AACTGGGAAC

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1261 CTGATACAGC AGCAGCTGGT TCTACTGCTT CATGCTCATA AGTGTCTAGAG ACGAGAGCAA
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1681 ATGAACCAGC CCCAGACGCA GCTGCAGCCT CAGGTTCCCTG GCCAGCAACC AGCACAGCCT
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 7981 TAATGTATCC CGATAACTTT GTGATGTTTC GGGAAGATTT TTTTCTATAG TGAACCTCTG
 8041 GGGCGTCTCC CAGTATTACC CTGGATGATA GGAATTGACT CCGGCGTGCA CACACGTACA

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8101 CACCCACACA CATCTATCTA TACATAATGG CTGAAGCCAA ACTTGTCTTG CAGATGTAGA
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8221 TTAGACCATG CTAATGTTAC TAGAGAAGAA GCCTTCTTTT CTTTCTTCTA TGTGAAACTT
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8821 GGGCGACTGA GGTGGGCGGC TCACGCTTGG CCCCACACAT TCGAGGCTCA AGGTGATTG
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10141 AAACCTGAAA TGTGATGGTG TTTATAATAA AAGATGGTAA AACTACTTGG ATTCAA

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[0106] In certain embodiments, a mutation of the disclosure may occur in a sequence encoding the CREB Binding Protein (CREBBP) HAT, including the amino acid sequence encoding CREBBP (below, corresponding to GenBank Accession No. NP_004371, defined as Homo sapiens CREB-binding protein isoform a; and identified as SEQ ID NO: 24).

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1 MAENLLDGPP NPKRAKLSSP GFSANDSTDF GSLFDLENDL PDELIPNGGE LGLLNSGNLV
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241 ETLTQVSPQM TGHAGLNTAQ AGGMAKMGIT GNTSPFGQPF SQAGGQPMGA TGVNPQLASK
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1921 FPSVARTQPP TTVSTGKPTS QVPAPPPPAQ PPPAAVEAAR QIEREAQQQQ HLYRVNINNS
1981 MPPGRGTGMT PGSQMAPVSL NVPRPNQVSG PVMPSMPPGQ WQQAPLPQQQ PMPGLPRPVI
2041 SMQAQAAVAG PRMPSPVQPPR SISPSALQDL LRTLKSPSSP QQQQQVNLIL KSNPQLMAAF
2101 IKQRTAKYVA NQPGMQPQPG LQSQPGMQPQ PGMHQQPSLQ NLNAMQAGVP RGPVPQQQA
2161 MGGLNPQGQA LNIMNPGHNP NMASMNPPYR EMLRRQLLQQ QQQQQQQQQQ QQQQQQGSAG
2221 MAGGMAGHGQ FQQPQGGPGY PPAMQQQORM QQHLPLQGS MGQMAAQMGQ LGQMGPGLG
2281 ADSTPNIQQA LQQRILOQQQ MKQQIGSPGQ PNPMSPPQHM LSGQPQASHL PGQQIATSLS
2341 NQVRSPAPVQ SPRPQSQPPH SSPSPRIQPO PSPHHVSPQT GSPHPGLAVT MASSIDQGHL
2401 GNPEQSAML P QLNTPSRSAL SSELSLVGDT TGD TLEKFVE GL

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[0107] In certain embodiments, a mutation of the disclosure may occur in a sequence encoding the CREB Binding Protein (CREBBP) HAT, including the nucleotide sequence encoding CREBBP (below, corresponding to GenBank Accession No. NM_001079846, defined as Homo sapiens CREB binding protein (CREBBP), transcript variant 2, mRNA; and identified as SEQ ID NO: 25).

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1 CTGCGGGGCG CTGTTGCTGT GGCTGAGATT TGGCCGCCGC CTCCCCACC CGGCCTGCGC
61 CCTCCCTCTC CCTCGGCGCC CGCCCGCCCG CTCGCGGCCG GCGCTCGCTC CTCTCCCTCG
121 CAGCCGGCAG GGGCCCCGAC CCCCCTCCGG GCCCTCGCCG GCCCGGCCGC CCGTGCCCCG
181 GGCTGTTTTT GCGAGCAGGT GAAAATGGCT GAGAACTTGC TGGACGGACC GCCCAACCCC
241 AAAAGAGCCA AACTCAGCTC GCCCGGTTTC TCGGCGAATG ACAGCACAGA TTTTGGATCA
301 TTGTTTGACT TGGAAAATGA TCTTCTGAT GAGCTGATAC CCAATGGAGG AGAATTAGGC
361 CTTTTAAACA GTGGGAACCT TGTTCCAGAT GCTGCTTCCA AACATAAACA ACTGTGCGAG
421 CTTCTACGAG GAGGCAGCGG CTCTAGTATC AACCAGGAA TAGGAAATGT GAGCGCCAGC
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541 GCCAGCCTCA GTGCCATGGG CAAGAGCCCT CTGAGCCAGG GAGATTCTTC AGCCCCCAGC
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661 CCGCAAGCAC AAAAGCAAGT GGGGCTGGCG ACTAGCAGCC CTGCCACGTC ACAGACTGGA
721 CCTGGTATCT GCATGAATGC TAACTTTAAC CAGACCCACC CAGGCCTCCT CAATAGTAAC
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901 GGCCTCTCGA GCAGCGTGCT GGCTGAGACC CTAACGCAGG TTTCCCCGCA AATGACTGGT
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1201 GGAATTGTAC CCACACAAGC AATTGCAACA GGCCCCACTG CAGATCCTGA AAAACGCAAA
1261 CTGATACAGC AGCAGCTGGT TCTACTGCTT CATGCTCATA AGTGTCAGAG ACGAGAGCAA

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1321 GCAAACGGAG AGGTTCGGGC CTGCTCGCTC CCGCATTGTC GAACCATGAA AAACGTTTTG
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 2761 CCTGTGTCGT CTTCCGGGCA GACTCCCACC CCGACTCCTG GCTCAGTGCC CAGTGCTACC
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 7681 GGGAGGGGGG TTTTGTTTTG ATTCTTTTTG TCGTCATTGC TGGTGACTCA TGCCTTTTTT
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8401 ACATTGTATT TGGACTATGC ATGTGTTTTT TCCCCATTGT ATATAAAGTA CCGCTTAAAA
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10081 AAA

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[0108] In certain embodiments, a mutation of the disclosure may occur in a sequence encoding the CREB Binding Protein (CREBBP) HAT, including the amino acid sequence encoding CREBBP (below, corresponding to GenBank Accession No. NP_001073315.1, defined as Homo sapiens CREB-binding protein isoform b; and identified as SEQ ID NO: 26).

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Next Generation Sequencing

[0109] The compounds of the disclosure are inhibitors of the histone methyltransferase EZH2 for use in the treatment of patients with non-Hodgkin lymphoma (NHL), and in patients with certain genetically defined solid tumors. Activating EZH2 mutations present in NHL patients has been implicated to predict response to EZH2 inhibition (Knutson et al., Nat. Chem. Biol. 2012; **8**: 890-896, the content of which is incorporated herein by reference in its entirety). Furthermore, a phase 1 clinical trial of tazemetostat demonstrated clinical responses in both EZH2 mutant and wild type patients (ClinicalTrials.gov identifier: NCT01897571). However, the impact of somatic mutations other than EZH2 on likelihood of response to tazemetostat in NHL patients is currently unknown. In some aspects, the present disclosure provides a multi-gene NHL targeted next generation sequencing (NGS) panel (e.g., a 39-gene panel or a 62-gene panel, or a panel combining a plurality of genes or gene products referred to herein) capable of analyzing samples from malignant cells, tissues, or body fluids, e.g., archive tissue or cell-free circulating tumor DNA (ctDNA) isolated from plasma. In some aspects, the NGS panel is capable of identifying molecular variants, including specific somatic sequence mutations (single base and insertion/deletion, e.g., EZH2), amplifications (e.g., BCL2) and translocations (e.g., BCL2 and MYC) in the tumor and ctDNA samples down to variant allele frequencies of 2% and 0.1% for archive and ctDNA respectively. For example, molecular variants associated with positive (e.g., EZH2, STAT6, MYD88, and SOCS1 mutations) and negative (e.g., MYC and HIST1H1E mutations) clinical responses to tazemetostat treatment were identified. Furthermore, sequencing of phase 1 NHL patients utilizing a 62 gene NHL NGS panel revealed a complex genetic landscape with epigenetic modifiers CREBBP and KMT2D representing the most frequently mutated genes in this sample set. Further aspects of the disclosure provide for an

NGS panel with the ability to determine molecular profiles using ctDNA that enables patient characterization where archive tumor tissue or DNA is absent or limiting. Additionally, profiling ctDNA enables longitudinal monitoring of a patient's mutation burden without the need for tumor biopsies.

[0110] Without wishing to be bound by theory, mutations identified by the NGS panel disclosed herein, may be used for patient stratification. Accordingly, in some embodiments, the disclosure provides a method of selecting a patient for cancer treatment if the patient has one or more mutations disclosed herein. In some embodiments, the patient selected for the cancer treatment has two or more (e.g., two, three, four, five, six, seven, eight, or more) mutations disclosed herein.

[0111] In some embodiments, a method is provided in which a subject having cancer is selected for treatment with an EZH2 inhibitor, e.g., an EZH2 inhibitor disclosed herein, based on the presence of one or more mutations associated with a positive response to such treatment in the subject, e.g., as determined by ctDNA analysis. In some embodiments, a mutation (or a combination of two or more mutations) associated with a positive response is a mutation (or a combination of mutations) that is present only in patients who responded with complete or partial response or, in some embodiments, with stable disease in any of the studies presented herein, e.g., those summarized in Figures 19-22. In some embodiments, a mutation (or a combination of two or more mutations) associated with a positive response is a mutation (or a combination of mutations) that is not randomly distributed within the patient population examined, but is overrepresented in those patients who responded with a complete or partial response or, in some embodiments, stable disease, in any of the studies presented herein, e.g., those summarized in Figures 19-22. In some embodiments, a mutation (or combination of mutations) associated with a positive response is a mutation (or combination of mutations) that is overrepresented in the responding (CR, PR, or, in some embodiments, SD) patient population at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, or at least 10-fold, as compared to the patient population that did not respond or responded with progressive disease (PD).

[0112] In some embodiments, a method is provided in which a subject having cancer is selected for treatment with an EZH2 inhibitor, e.g., an EZH2 inhibitor disclosed herein, based on the absence of one or more mutations associated with a negative response to such treatment in the subject, e.g., as determined by ctDNA analysis. In some embodiments, a

mutation (or a combination of two or more mutations) associated with a negative response is a mutation (or a combination of mutations) that is present only in patients who did not respond or responded with progressive disease (PD) in any of the studies presented herein, e.g., those summarized in Figures 19-22. In some embodiments, a mutation (or a combination of two or more mutations) associated with a negative response is a mutation (or a combination of mutations) that is not randomly distributed within the patient population examined, but is overrepresented in those patients who did not respond or responded with progressive disease in any of the studies presented herein, e.g., those summarized in Figures 19-22. In some embodiments, a mutation (or combination of mutations) associated with a negative response is a mutation (or combination of mutations) that is overrepresented in the non-responding or progressive disease (PD) patient population at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, or at least 10-fold, as compared to the patient population that responded with CR, PR, or, in some embodiments, SD.

[0113] In some embodiments, a subject having cancer is selected for treatment with an EZH2 inhibitor, e.g., an EZH2 inhibitor disclosed herein, based on the presence of two or more (e.g., two, three, four, five, six, seven, eight, or more) mutations in the subject that match the mutations observed in a profile of a patient who exhibited a complete or partial response in any of the studies described herein (e.g., those summarized in Figures 19-22). In some embodiments, a subject having cancer is selected for treatment with an EZH2 inhibitor, e.g., an EZH2 inhibitor disclosed herein, based on the presence of a mutation profile (e.g., of two or more (e.g., two, three, four, five, six, seven, eight, or more)) mutations in the subject that match the mutation profile of a patient who exhibited a complete or partial response in any of the studies described herein (e.g., those summarized in Figures 19-22). Typically, a mutation in a gene or gene product (e.g., in a transcript, mRNA, or protein) is detected by comparing a given sequence with a reference sequence, e.g., a human reference genome sequence (e.g., human reference genome hg19), and identifying a mismatch in the sequence at hand as compared to the reference sequence.

[0114] In some embodiments, a subject having cancer is selected for treatment with an EZH2 inhibitor, e.g., an EZH2 inhibitor disclosed herein, based on the presence of two or more (e.g., two, three, four, five, six, seven, eight, or more) mutations in the subject that match the mutations observed in a profile of a patient who exhibited stable disease in any of the studies described herein (e.g., those summarized in Figures 19-22). In some embodiments, a subject

having cancer is selected for treatment with an EZH2 inhibitor, e.g., an EZH2 inhibitor disclosed herein, based on the presence of a mutation profile (e.g., two or more (e.g., two, three, four, five, six, seven, eight, or more)) mutations in the subject that match the mutation profile of a patient who exhibited stable disease in any of the studies described herein (e.g., those summarized in Figures 19-22).

[0115] In some embodiments, methods of treating cancer is provided that comprises administering a therapeutically effective amount of an inhibitor of EZH2 to a subject in need thereof, wherein the subject has at least one mutation in one or more sequences encoding a gene or a gene product (e.g., a transcript, mRNA, or protein) listed in Tables 1-9, Tables 17-19, and/or Figures 19-22. In some embodiments, the subject has at least one mutation in one or more sequences encoding: MYD88, STAT6A, SOCS1, MYC, HIST1H1E, ABL1, ACVR1, AKT1, AKT2, ALK, APC, AR, ARID1A, ARID1B, ASXL1, ATM, ATRX, AURKA, AXIN2, BAP1, BCL2, BCR, BLM, BMPR1A, BRAF, BRCA1, BRCA2, BRIP1, BTK, BUB1B, CALR, CBL, CCND1, CCNE1, CDC73, CDH1, CDK4, CDK6, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CEBPA, CHEK2, CIC, CREBBP, CSF1R, CTNNB1, CYLD, DAXX, DDB2, DDR2, DICER1, DNMT3A, EGFR, EP300, ERBB2, ERBB3, ERBB4, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, ESR1, ETV1, ETV5, EWSR1, EXT1, EXT2, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FBXW7, FGFR1, FGFR2, FGFR3, FGFR4, FH, FLCN, FLT3, FLT4, FOXL2, GATA1, GATA2, GNA11, GNAQ, GNAS, GPC3, H3F3A, H3F3B, HNF1A, HRAS, IDH1, IDH2, IGF1R, IGF2R, IKZF1, JAK1, JAK2, JAK3, KDR, KIT, KRAS, MAML1, MAP2K1, MAP2K4, MDM2, MDM4, MED12, MEN1, MET, MLH1, MLL, MPL, MSH2, MSH6, MTOR, MUTYH, MYCL1, MYCN, NBN, NCOA3, NF1, NF2, NKX2-1, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NPM1, NRAS, NTRK1, PALB2, PAX5, PBRM1, PDGFRA, PHOX2B, PIK3CA, PIK3R1, PMS1, PMS2, POLD1, POLE, POLH, POT1, PRKAR1A, PRSS1, PTCH1, PTEN, PTPN11, RAD51C, RAF1, RB1, RECQL4, RET, RNF43, ROS1, RUNX1, SBDS, SDHAF2, SDHB, SDHC, SDHD, SF3B1, SMAD2, SMAD3, SMAD4, SMARCB1, SMO, SRC, STAG2, STK11, SUFU, TERT, TET2, TGFB2, TNFAIP3, TOP1, TP53, TSC1, TSC2, TSHR, VHL, WAS, WRN, WT1, XPA, XPC, and/or XRCC1. In some embodiments, the subject has at least one mutation in one or more sequences encoding ABL1, ACVR1, AKT1, AKT2, ALK, APC, AR, ARID1A, ARID1B, ASXL1, ATM, ATRX, AURKA, AXIN2, BAP1, BCL2, BCR, BLM, BMPR1A,

BRAF, BRCA1, BRCA2, BRIP1, BTK, BUB1B, CALR, CBL, CCND1, CCNE1, CDC73, CDH1, CDK4, CDK6, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CEBPA, CHEK2, CIC, CREBBP, CSF1R, CTNNB1, CYLD, DAXX, DDB2, DDR2, DICER1, DNMT3A, EGFR, EP300, ERBB2, ERBB3, ERBB4, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, ESR1, ETV1, ETV5, EWSR1, EXT1, EXT2, EZH2, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FBXW7, FGFR1, FGFR2, FGFR3, FGFR4, FH, FLCN, FLT3, FLT4, FOXL2, GATA1, GATA2, GNA11, GNAQ, GNAS, GPC3, H3F3A, H3F3B, HNF1A, HRAS, IDH1, IDH2, IGF1R, IGF2R, IKZF1, JAK1, JAK2, JAK3, KDR, KIT, KRAS, MAML1, MAP2K1, MAP2K4, MDM2, MDM4, MED12, MEN1, MET, MLH1, MLL, MPL, MSH2, MSH6, MTOR, MUTYH, MYCL1, MYCN, NBN, NCOA3, NF1, NF2, NKX2-1, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NPM1, NRAS, NTRK1, PALB2, PAX5, PBRM1, PDGFRA, PHOX2B, PIK3CA, PIK3R1, PMS1, PMS2, POLD1, POLE, POLH, POT1, PRKAR1A, PRSS1, PTCH1, PTEN, PTPN11, RAD51C, RAF1, RB1, RECQL4, RET, RNF43, ROS1, RUNX1, SBDS, SDHAF2, SDHB, SDHC, SDHD, SF3B1, SMAD2, SMAD3, SMAD4, SMARCB1, SMO, SRC, STAG2, STK11, SUFU, TERT, TET2, TGFB2, TNFAIP3, TOP1, TP53, TSC1, TSC2, TSHR, VHL, WAS, WRN, WT1, XPA, XPC, and/or XRCC1. In some embodiments, the subject has at least one mutation in one or more sequences encoding ARID1A, ATM, B2M, BCL2, BCL6, BCL7A, BRAF, BTG1, CARD11, CCND3, CD58, CD79B, CDKN2A, CREBBP, EP300, EZH2, FOXO1, GNA13, HIST1H1B, HIST1H1C, HIST1H1E, IKZF3, IRF4, ITPKB, KDM6A, KIT, KMT2D, KRAS, MEF2B, MYC, MYD88, NOTCH1, NOTCH2, NRAS, PIK3CA, PIM1, POU2F2, PRDM1, PTEN, PTPN1, PTPN11, PTPN6, PTPRD, RB1, S1PR2, SGK1, SMARCB1, SOCS1, STAT6, TBL1XR1, TNFAIP3, TNFRSF14, TP53, XPO1. In some embodiments, the subject has at least one mutation in one or more sequences encoding AKT1, ALK, ARID1A, ATM, B2M, BCL2, BCL6, BCL7A, BTG2, CARD11, CCND3, CD79B, CDKN2A, CREBBP, EP300, EZH2, FBXW7, FOXO1, HLA-C, HRAS, IKZF3, IRF4, KDM6A, KRAS, MEF2B, MYD88, NOTCH1, NPM1, NRAS, PIK3CA, PIM1, PRDM1, PTEN, RB1, RBBP4, SMARCB1, SUZ12, TNFRSF14, and/or TP53. In some embodiments, the subject has at least one mutation in one or more sequences encoding ALK, EWSR1, ROS1, BCL2, MLL, TMPRSS2, BCR, MYC, FGFR3, BRAF, NTRK1, TACC3, DNAJB1, PDGFRA, EGFR, PDGFRB, ETV1, PRKACA, ETV4, RAF1, ETV5, RARA, ETV6, RET. In some embodiments, the subject has at least one mutation in one or more

sequences encoding ALK (Intron 19), BCL2 (MBR breakpoint region), BCL2 (MCR breakpoint region), BCL6, CD274, CIITA, MYC (entire Gene + 40kbp upstream), and/or PDCD1LG2. In some embodiments, the subject has at least one mutation in one or more sequences encoding BCL2, CD274 (PDL1), FOXP1, JAK2, KDM4C, PDCD1LG2 (PDL2), and/or REL. In some embodiments, the subject has at least one mutation in one or more sequences encoding ARID1A, ATM, B2M, BCL2, BCL6, BCL7A, BRAF, CARD11, CCND3, CD274 (PDL1), CD58, CD79B, CDKN2A, CIITA, CREBBP, EZH2 (non-Y646), EZH2 (Y646), EP300, FOXO1, FOXP1, GNA13, HIST1H1B, HIST1H1C, HIST1H1E, IRF4, IZKF3, JAK2, KDM4C, KDM6A, KIT, KMT2D, KRAS, MEF2B, MYC, MYD88, NOTCH1, NOTCH2, NRAS, PDCD1LG2 (PDL2), PIK3CA, PIM1, POU2F2, PRDM1, PTEN, PTPN11, PTPN6, PTPRD, REL, SOCS1, STAT6, TNFAIP3, TNFRSF14, and/or TP53. In some embodiments, the subject has at least one mutation in one or more sequences encoding ARID1A, B2M, BCL2, BCL6, CARD11, CCND3, CD274 (PDL1), CD58, CD79B, CDKN2A, CREBBP, EZH2, EP300, FOXO1, GNA13, HIST1H1B, HIST1H1C, HIST1H1E, KMT2D, KRAS, MEF2B, MYC, MYD88 (273P), PDCD1LG2 (PDL2), PIM1, POU2F2, PRDM1, SOCS1, STAT6, TNFAIP3, and/or TNFRSF14. In some embodiments, the subject has at least one mutation in in one or more sequences encoding: EZH2, MYD88, STAT6A, SOCS1, MYC, and/or HIST1H1E,

[0116] In some embodiments, the subject has at least one mutation that decreases or abolishes the function of a gene product (e.g., a transcript, mRNA, or protein) encoded by the mutated sequence as compared to the function of the respective gene product encoded by the wild-type sequence. Such mutations are also sometimes referred to as loss-of-function mutations. Many loss-of-function mutations for the genes and gene products referred to herein that are suitable for some embodiments of this disclosure will be known to the skilled artisan. For example, in some exemplary embodiments, the subject has a loss-of-function mutation in SOCS1. In some embodiments, the subject has at least one mutation that increases the function of a gene product (e.g., a transcript, mRNA, or protein) encoded by the mutated sequence as compared to the function of the respective gene product encoded by the wild-type sequence. Such mutations are also sometimes referred to as gain-of-function mutations or activating mutations. Many gain-of-function mutations for the genes and gene products referred to herein that are suitable for some embodiments of this disclosure will be known to the skilled artisan. For example, in some embodiments, the subject has a gain-of-

function mutation in a sequence encoding EZH2, MYD88, STAT6, or MYC. In some embodiments, the subject has at least one loss-of-function and at least one gain-of function mutation. For example, in some embodiments, the subject has at least one gain-of-function mutation in a sequence encoding EZH2 or STAT6, and at least one loss-of-function mutation in a sequence encoding SOCS1. In some embodiments, the subject does not have a specific mutation, e.g., a gain-of-function in a sequence encoding MYC or a loss-of-function mutation in SOCS1.

[0117] In some embodiments, the subject expresses a mutant EZH2 protein. In some embodiments, the mutant EZH2 protein comprises a substitution of any amino acid other than tyrosine (Y) for tyrosine (Y) at position 641 of SEQ ID NO: 1, a substitution of any amino acid other than alanine (A) for alanine (A) at position 682 of SEQ ID NO: 1, and/or a substitution of any amino acid other than alanine (A) for alanine (A) at position 692 of SEQ ID NO: 1. In some embodiments, the subject expresses at least one mutant MYD88, STAT6, and/or a SOCS1 protein, either in addition to the mutant EZH2 protein or in the absence of a mutant EZH2 protein. In some embodiments, the subject does not express a mutant MYC and/or a mutant HIST1H1E protein. In some embodiments, the mutant EZH2 protein, the mutant MYD88 protein, the mutant STAT6 protein, and/or the mutant MYC protein exhibits an increase in activity as compared to the respective wild-type protein. In some embodiments, the mutant SOCS1 protein exhibits a decreased activity as compared to the respective wild-type SOCS1 protein.

[0118] In some embodiments, the methods provided herein further comprise detecting the at least one mutation in the subject. Such detecting may, in some embodiments, comprise subjecting a sample obtained from the subject to a suitable sequence analysis assay, e.g., to a next generation sequencing assay. Suitable sequencing assays are provided herein or otherwise known to those of skill in the art, and the disclosure is not limited in this respect.

[0119] Some aspects of this disclosure provide methods comprising selecting a subject having cancer for treatment with an EZH2 inhibitor based on the presence of at least one mutation associated with a positive response to such treatment in the subject and/or based on the absence of at least one mutation associated with no response or with a negative response to such treatment in the subject. In some embodiments, the at least one mutation associated with a positive response comprises (a) an EZH2 mutation (e.g., a gain-of-function EZH2 mutation); (b) a histone acetyl transferase (HAT) mutation; (c) a STAT6 mutation (e.g., a

gain-of-function STAT6 mutation); (d) a MYD88 mutation (e.g., a gain-of-function MYD88 mutation); and/or (e) a SOCS1 mutation (e.g., a loss-of-function SOCS1 mutation). In some embodiments, the at least one mutation associated with no response or with a negative response comprises (a) a MYC mutation (e.g., a gain-of-function MYC mutation); and/or (b) a HIST1H1E mutation. In some embodiments, the method comprises detecting the at least one mutation associated with a positive response and/or the at least one mutation associated with no response or a negative response in a sample obtained from the subject by subjecting the sample to a suitable sequence analysis assay. In some embodiments, the method comprises selecting the subject for treatment with the EZH2 inhibitor based on the subject (a) having at least one of a MYD88 mutation, a STAT6A mutation, and a SOCS1 mutation, and/or (b) not having at least one of a MYC mutation and/or a HIST1H1E mutation. In some embodiments, the method comprises selecting the subject for treatment with the EZH2 inhibitor based on the subject (a) having at least one of a MYD88 mutation, a STAT6A mutation, and a SOCS1 mutation, and (b) not having a MYC mutation and a HIST1H1E mutation.

[0120] Some aspects of this disclosure provide methods for selecting a subject having cancer for treatment with an EZH2 inhibitor based on the presence of a mutation profile in the subject that matches a mutation profile (e.g., at least 2, at least 3, at least 4, or at least 5, or more mutations, or, in some embodiments, all mutations), of a patient exhibiting a complete or partial response or stable disease as described in any of Figures 19-22.

Definitions

[0121] According to the methods of the disclosure, a “normal” cell may be used as a basis of comparison for one or more characteristics of a cancer cell, including the presence of one or more mutations in a histone acetyltransferase that result in a decreased activity of the enzyme. For example, the one or more mutations in a histone acetyltransferase may result in a decreased acetylation activity or efficacy of the enzyme, and, consequently, a reduced or decreased level of acetylation of at least one lysine on Histone 3 (H3). In certain embodiments, the one or more mutations in a histone acetyltransferase may result in a decreased acetylation activity or efficacy of the enzyme, and, consequently, a reduced or decreased level of acetylation of lysine 27 on Histone 3 (H3) (H3K27). As used herein, a “normal cell” is a cell that cannot be classified as part of a “cell proliferative disorder”. A

normal cell lacks unregulated or abnormal growth, or both, that can lead to the development of an unwanted condition or disease. Preferably, a normal cell expresses a comparable amount of EZH2 as a cancer cell. Preferably a normal cell contains a wild type sequence for all histone acetyltransferases, expresses a histone acetyltransferase transcript without mutations, and expresses a histone acetyltransferase protein without mutations that retains all functions a normal activity levels.

[0122] As used herein, “contacting a cell” refers to a condition in which a compound or other composition of matter is in direct contact with a cell, or is close enough to induce a desired biological effect in a cell.

[0123] As used herein, “treating” or “treat” describes the management and care of a subject for the purpose of combating a disease, condition, or disorder and includes the administration of an EZH2 inhibitor of the disclosure, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, to alleviate the symptoms or complications of cancer or to eliminate the cancer.

[0124] As used herein, the term "alleviate" is meant to describe a process by which the severity of a sign or symptom of cancer is decreased. Importantly, a sign or symptom can be alleviated without being eliminated. In a preferred embodiment, the administration of pharmaceutical compositions of the disclosure leads to the elimination of a sign or symptom, however, elimination is not required. Effective dosages are expected to decrease the severity of a sign or symptom. For instance, a sign or symptom of a disorder such as cancer, which can occur in multiple locations, is alleviated if the severity of the cancer is decreased within at least one of multiple locations.

[0125] As used herein, the term "severity" is meant to describe the potential of cancer to transform from a precancerous, or benign, state into a malignant state. Alternatively, or in addition, severity is meant to describe a cancer stage, for example, according to the TNM system (accepted by the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC)) or by other art-recognized methods. Cancer stage refers to the extent or severity of the cancer, based on factors such as the location of the primary tumor, tumor size, number of tumors, and lymph node involvement (spread of cancer into lymph nodes). Alternatively, or in addition, severity is meant to describe the tumor grade by art-recognized methods (see, National Cancer Institute, www.cancer.gov). Tumor grade is a system used to classify cancer cells in terms of how abnormal they look under a microscope

and how quickly the tumor is likely to grow and spread. Many factors are considered when determining tumor grade, including the structure and growth pattern of the cells. The specific factors used to determine tumor grade vary with each type of cancer. Severity also describes a histologic grade, also called differentiation, which refers to how much the tumor cells resemble normal cells of the same tissue type (see, National Cancer Institute, www.cancer.gov). Furthermore, severity describes a nuclear grade, which refers to the size and shape of the nucleus in tumor cells and the percentage of tumor cells that are dividing (see, National Cancer Institute, www.cancer.gov).

[0126] In another aspect of the disclosure, severity describes the degree to which a tumor has secreted growth factors, degraded the extracellular matrix, become vascularized, lost adhesion to juxtaposed tissues, or metastasized. Moreover, severity describes the number of locations to which a primary tumor has metastasized. Finally, severity includes the difficulty of treating tumors of varying types and locations. For example, inoperable tumors, those cancers which have greater access to multiple body systems (hematological and immunological tumors), and those which are the most resistant to traditional treatments are considered most severe. In these situations, prolonging the life expectancy of the subject and/or reducing pain, decreasing the proportion of cancerous cells or restricting cells to one system, and improving cancer stage/tumor grade/histological grade/nuclear grade are considered alleviating a sign or symptom of the cancer.

[0127] As used herein the term "symptom" is defined as an indication of disease, illness, injury, or that something is not right in the body. Symptoms are felt or noticed by the individual experiencing the symptom, but may not easily be noticed by others. Others are defined as non-health-care professionals.

[0128] As used herein the term "sign" is also defined as an indication that something is not right in the body. But signs are defined as things that can be seen by a doctor, nurse, or other health care professional.

[0129] Cancer is a group of diseases that may cause almost any sign or symptom. The signs and symptoms will depend on where the cancer is, the size of the cancer, and how much it affects the nearby organs or structures. If a cancer spreads (metastasizes), then symptoms may appear in different parts of the body.

[0130] As a cancer grows, it begins to push on nearby organs, blood vessels, and nerves. This pressure creates some of the signs and symptoms of cancer. Cancers may form in places where it does not cause any symptoms until the cancer has grown quite large.

[0131] Cancer may also cause symptoms such as fever, fatigue, or weight loss. This may be because cancer cells use up much of the body's energy supply or release substances that change the body's metabolism. Or the cancer may cause the immune system to react in ways that produce these symptoms. While the signs and symptoms listed above are the more common ones seen with cancer, there are many others that are less common and are not listed here. However, all art-recognized signs and symptoms of cancer are contemplated and encompassed by the disclosure.

[0132] Treating cancer may result in a reduction in size of a tumor. A reduction in size of a tumor may also be referred to as "tumor regression". Preferably, after treatment according to the methods of the disclosure, tumor size is reduced by 5% or greater relative to its size prior to treatment; more preferably, tumor size is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75% or greater. Size of a tumor may be measured by any reproducible means of measurement. The size of a tumor may be measured as a diameter of the tumor.

[0133] Treating cancer may result in a reduction in tumor volume. Preferably, after treatment according to the methods of the disclosure, tumor volume is reduced by 5% or greater relative to its size prior to treatment; more preferably, tumor volume is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75% or greater. Tumor volume may be measured by any reproducible means of measurement.

[0134] Treating cancer may result in a decrease in number of tumors. Preferably, after treatment, tumor number is reduced by 5% or greater relative to number prior to treatment; more preferably, tumor number is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75%. Number of tumors may be measured by any reproducible

means of measurement. The number of tumors may be measured by counting tumors visible to the naked eye or at a specified magnification. Preferably, the specified magnification is 2x, 3x, 4x, 5x, 10x, or 50x.

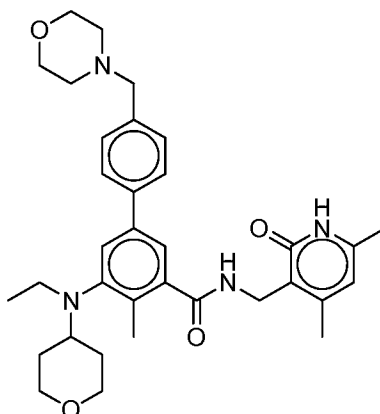
[0135] Treating cancer may result in a decrease in number of metastatic lesions in other tissues or organs distant from the primary tumor site. Preferably, after treatment according to the methods of the disclosure, the number of metastatic lesions is reduced by 5% or greater relative to number prior to treatment; more preferably, the number of metastatic lesions is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75%. The number of metastatic lesions may be measured by any reproducible means of measurement. The number of metastatic lesions may be measured by counting metastatic lesions visible to the naked eye or at a specified magnification. Preferably, the specified magnification is 2x, 3x, 4x, 5x, 10x, or 50x.

[0136] An effective amount of an EZH2 inhibitor of the disclosure, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, is not significantly cytotoxic to normal cells. For example, a therapeutically effective amount of an EZH2 inhibitor of the disclosure is not significantly cytotoxic to normal cells if administration of the EZH2 inhibitor of the disclosure in a therapeutically effective amount does not induce cell death in greater than 10% of normal cells. A therapeutically effective amount of an EZH2 inhibitor of the disclosure does not significantly affect the viability of normal cells if administration of the compound in a therapeutically effective amount does not induce cell death in greater than 10% of normal cells.

[0137] Contacting a cell with an EZH2 inhibitor of the disclosure, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, can inhibit EZH2 activity selectively in cancer cells. Administering to a subject in need thereof an EZH2 inhibitor of the disclosure, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, can inhibit EZH2 activity selectively in cancer cells.

EZH2 Inhibitors

[0138] EZH2 inhibitors of the disclosure comprise tazemetostat (EPZ-6438):



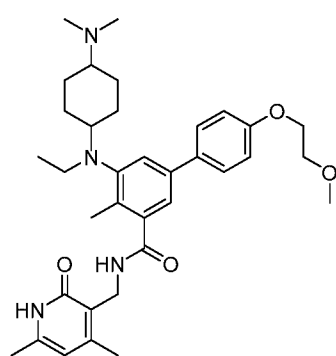
or a pharmaceutically acceptable salt thereof.

[0139] Tazemetostat is also described in US Patent Nos. 8,410,088, 8,765,732, and 9,090,562 (the contents of which are each incorporated herein in their entireties).

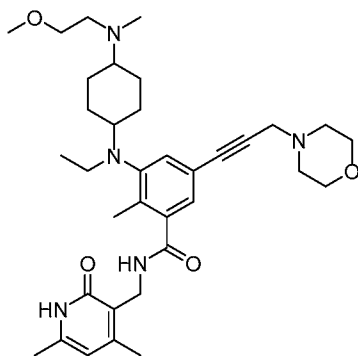
[0140] Tazemetostat or a pharmaceutically acceptable salt thereof, as described herein, is potent in targeting both WT and mutant EZH2. Tazemetostat is orally bioavailable and has high selectivity to EZH2 compared with other histone methyltransferases (i.e., >20,000 fold selectivity by K_i). Importantly, tazemetostat has targeted methyl mark inhibition that results in the killing of genetically defined cancer cells *in vitro*. Animal models have also shown sustained *in vivo* efficacy following inhibition of the target methyl mark. Clinical trial results described herein also demonstrate the safety and efficacy of tazemetostat.

[0141] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof is administered to the subject at a dose of approximately 100 mg to approximately 3200 mg daily, such as about 100 mg BID to about 1600 mg BID (e.g., 100 mg BID, 200 mg BID, 400 mg BID, 800 mg BID, or 1600 mg BID), for treating a NHL. On one embodiment the dose is 800 mg BID.

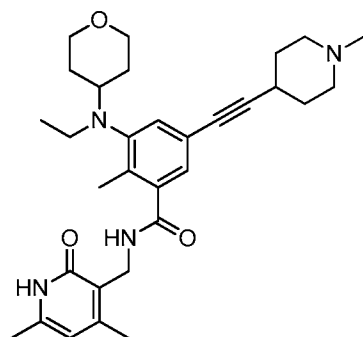
[0142] EZH2 inhibitors of the disclosure may comprise, consist essentially of or consist of:



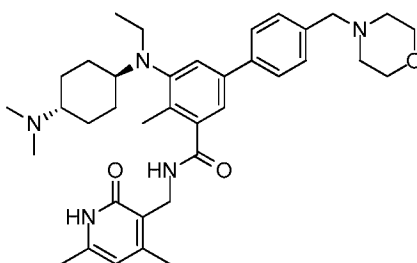
(A),



(B) or



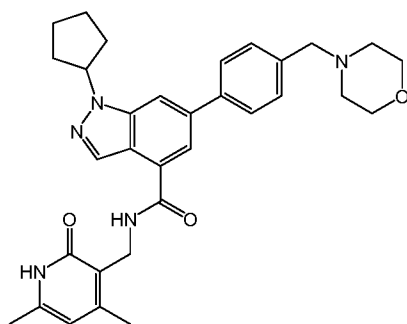
(C) or



(D), or stereoisomers

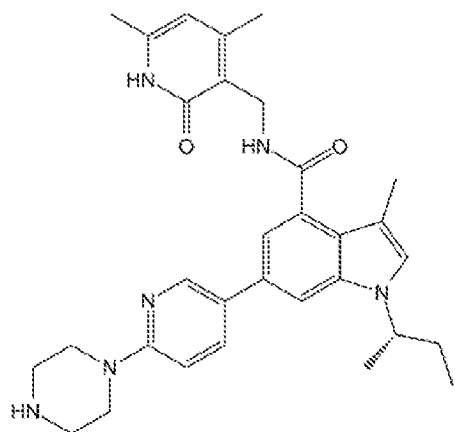
thereof or pharmaceutically acceptable salts and solvates thereof.

[0143] EZH2 inhibitors of the disclosure may comprise, consist essentially of or consist of Compound E:



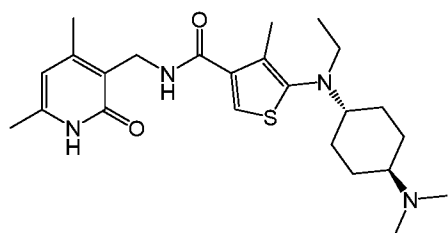
(E) or pharmaceutically acceptable salts thereof.

[0144] EZH2 inhibitors of the disclosure may comprise, consist essentially of or consist of GSK-126, having the following formula:



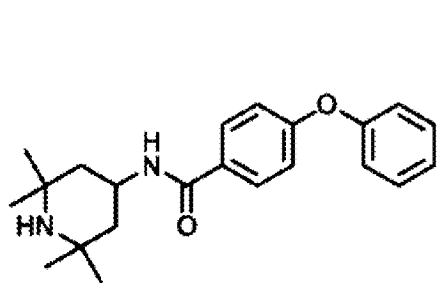
, stereoisomers thereof, or pharmaceutically acceptable salts or solvates thereof.

[0145] EZH2 inhibitors of the disclosure may comprise, consist essentially of or consist of Compound F:

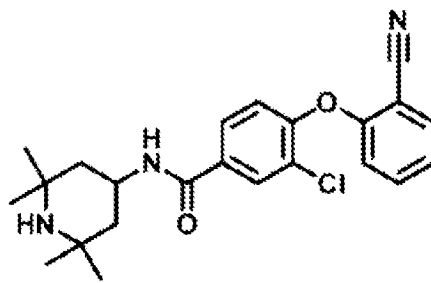


(F), or stereoisomers thereof or pharmaceutically acceptable salts and solvates thereof.

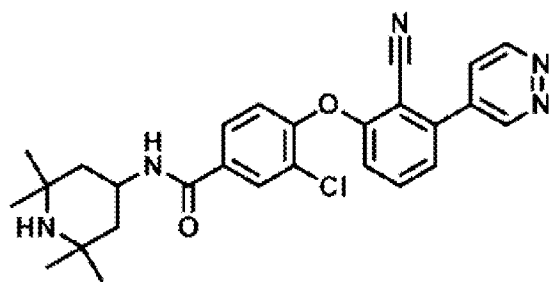
[0146] EZH2 inhibitors of the disclosure may comprise, consist essentially of or consist of any one of Compounds Ga-Gc:



(Ga),



(Gb),



(Gc), or a stereoisomer, pharmaceutically

acceptable salt or solvate thereof.

[0147] EZH2 inhibitors of the disclosure may comprise, consist essentially of or consist of CPI-1205 or GSK343.

[0148] Additional suitable EZH2 inhibitors will be apparent to those skilled in the art. In some embodiments of the strategies, treatment modalities, methods, combinations, and compositions provided herein, the EZH2 inhibitor is an EZH2 inhibitor described in US 8,536,179 (describing GSK-126 among other compounds and corresponding to WO 2011/140324), the entire contents of each of which are incorporated herein by reference.

[0149] In some embodiments of the strategies, treatment modalities, methods, combinations, and compositions provided herein, the EZH2 inhibitor is an EZH2 inhibitor described in PCT/US2014/015706, published as WO 2014/124418, in PCT/US2013/025639, published as WO 2013/120104, and in US 14/839,273, published as US 2015/0368229, the entire contents of each of which are incorporated herein by reference.

[0150] In some embodiments, the compound disclosed herein is the compound itself, i.e., the free base or “naked” molecule. In some embodiments, the compound is a salt thereof, e.g., a mono-HCl or tri-HCl salt, mono-HBr or tri-HBr salt of the naked molecule.

[0151] Compounds disclosed herein that contain nitrogens can be converted to N-oxides by treatment with an oxidizing agent (e.g., 3-chloroperoxybenzoic acid (*m*CPBA) and/or hydrogen peroxides) to afford other compounds suitable for any methods disclosed herein. Thus, all shown and claimed nitrogen-containing compounds are considered, when allowed by valency and structure, to include both the compound as shown and its N-oxide derivative (which can be designated as N $\square$ O or N⁺-O⁻). Furthermore, in other instances, the nitrogens in the compounds disclosed herein can be converted to N-hydroxy or N-alkoxy compounds. For example, N-hydroxy compounds can be prepared by oxidation of the parent amine by an oxidizing agent such as *m*-CPBA. All shown and claimed nitrogen-containing compounds are also considered, when allowed by valency and structure, to cover both the compound as shown and its N-hydroxy (i.e., N-OH) and N-alkoxy (i.e., N-OR, wherein R is substituted or unsubstituted C₁-C₆ alkyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, 3-14-membered carbocycle or 3-14-membered heterocycle) derivatives.

[0152] “Isomerism” means compounds that have identical molecular formulae but differ in the sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers.” Stereoisomers that are not mirror images of one another are termed “diastereoisomers,” and

stereoisomers that are non-superimposable mirror images of each other are termed “enantiomers” or sometimes optical isomers. A mixture containing equal amounts of individual enantiomeric forms of opposite chirality is termed a “racemic mixture.”

[0153] A carbon atom bonded to four nonidentical substituents is termed a “chiral center.”

[0154] “Chiral isomer” means a compound with at least one chiral center. Compounds with more than one chiral center may exist either as an individual diastereomer or as a mixture of diastereomers, termed “diastereomeric mixture.” When one chiral center is present, a stereoisomer may be characterized by the absolute configuration (R or S) of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. The substituents attached to the chiral center under consideration are ranked in accordance with the *Sequence Rule* of Cahn, Ingold and Prelog. (Cahn *et al.*, *Angew. Chem. Inter. Edit.* 1966, 5, 385; errata 511; Cahn *et al.*, *Angew. Chem.* 1966, 78, 413; Cahn and Ingold, *J. Chem. Soc.* 1951 (London), 612; Cahn *et al.*, *Experientia* 1956, 12, 81; Cahn, *J. Chem. Educ.* 1964, 41, 116).

[0155] “Geometric isomer” means the diastereomers that owe their existence to hindered rotation about double bonds or a cycloalkyl linker (e.g., 1, 3-cyclobutyl). These configurations are differentiated in their names by the prefixes cis and trans, or Z and E, which indicate that the groups are on the same or opposite side of the double bond in the molecule according to the Cahn-Ingold-Prelog rules.

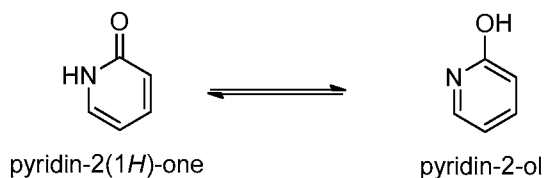
[0156] It is to be understood that the compounds disclosed herein may be depicted as different chiral isomers or geometric isomers. It should also be understood that when compounds have chiral isomeric or geometric isomeric forms, all isomeric forms are intended to be included in the scope of the disclosure, and the naming of the compounds does not exclude any isomeric forms.

[0157] Furthermore, the structures and other compounds discussed in this disclosure include all atropic isomers thereof. “Atropic isomers” are a type of stereoisomer in which the atoms of two isomers are arranged differently in space. Atropic isomers owe their existence to a restricted rotation caused by hindrance of rotation of large groups about a central bond. Such atropic isomers typically exist as a mixture, however as a result of recent advances in chromatography techniques; it has been possible to separate mixtures of two atropic isomers in select cases.

[0158] “Tautomer” is one of two or more structural isomers that exist in equilibrium and is readily converted from one isomeric form to another. This conversion results in the formal migration of a hydrogen atom accompanied by a switch of adjacent conjugated double bonds. Tautomers exist as a mixture of a tautomeric set in solution. In solutions where tautomerization is possible, a chemical equilibrium of the tautomers will be reached. The exact ratio of the tautomers depends on several factors, including temperature, solvent and pH. The concept of tautomers that are interconvertible by tautomerization is called tautomerism.

[0159] Of the various types of tautomerism that are possible, two are commonly observed. In keto-enol tautomerism a simultaneous shift of electrons and a hydrogen atom occurs. Ring-chain tautomerism arises as a result of the aldehyde group (-CHO) in a sugar chain molecule reacting with one of the hydroxy groups (-OH) in the same molecule to give it a cyclic (ring-shaped) form as exhibited by glucose.

[0160] Common tautomeric pairs are: ketone-enol, amide-nitrile, lactam-lactim, amide-imidic acid tautomerism in heterocyclic rings (*e.g.*, in nucleobases such as guanine, thymine and cytosine), imine-enamine and enamine-enamine. An example of keto-enol equilibria is between pyridin-2(1H)-ones and the corresponding pyridin-2-ols, as shown below.



[0161] It is to be understood that the compounds disclosed herein may be depicted as different tautomers. It should also be understood that when compounds have tautomeric forms, all tautomeric forms are intended to be included in the scope of the disclosure, and the naming of the compounds does not exclude any tautomer form.

[0162] The compounds disclosed herein include the compounds themselves, as well as their salts and their solvates, if applicable. A salt, for example, can be formed between an anion and a positively charged group (*e.g.*, amino) on an aryl- or heteroaryl-substituted benzene compound. Suitable anions include chloride, bromide, iodide, sulfate, bisulfate, sulfamate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, glutamate, glucuronate, glutarate, malate, maleate, succinate, fumarate, tartrate, tosylate, salicylate, lactate, naphthalenesulfonate, and acetate (*e.g.*, trifluoroacetate). The term

“pharmaceutically acceptable anion” refers to an anion suitable for forming a pharmaceutically acceptable salt. Likewise, a salt can also be formed between a cation and a negatively charged group (e.g., carboxylate) on an aryl- or heteroaryl-substituted benzene compound. Suitable cations include sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion. The aryl- or heteroaryl-substituted benzene compounds also include those salts containing quaternary nitrogen atoms. In the salt form, it is understood that the ratio of the compound to the cation or anion of the salt can be 1:1, or any ration other than 1:1, e.g., 3:1, 2:1, 1:2, or 1:3.

[0163] Additionally, the compounds disclosed herein, for example, the salts of the compounds, can exist in either hydrated or unhydrated (the anhydrous) form or as solvates with other solvent molecules. Nonlimiting examples of hydrates include monohydrates, dihydrates, etc. Nonlimiting examples of solvates include ethanol solvates, acetone solvates, etc.

[0164] “Solvate” means solvent addition forms that contain either stoichiometric or non-stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate; and if the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one molecule of the substance in which the water retains its molecular state as H₂O.

[0165] As used herein, the term “analog” refers to a chemical compound that is structurally similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group, or the replacement of one functional group by another functional group). Thus, an analog is a compound that is similar or comparable in function and appearance, but not in structure or origin to the reference compound.

[0166] As defined herein, the term “derivative” refers to compounds that have a common core structure, and are substituted with various groups as described herein. For example, all of the compounds represented by Formula (I) are aryl- or heteroaryl-substituted benzene compounds, and have Formula (I) as a common core.

[0167] The term “bioisostere” refers to a compound resulting from the exchange of an atom or of a group of atoms with another, broadly similar, atom or group of atoms. The objective of a bioisosteric replacement is to create a new compound with similar biological

properties to the parent compound. The bioisosteric replacement may be physicochemically or topologically based. Examples of carboxylic acid bioisosteres include, but are not limited to, acyl sulfonimides, tetrazoles, sulfonates and phosphonates. See, *e.g.*, Patani and LaVoie, *Chem. Rev.* 96, 3147-3176, 1996.

[0168] The present disclosure is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include C-13 and C-14.

Pharmaceutical Formulations

[0169] The present disclosure also provides pharmaceutical compositions comprising at least one EZH2 inhibitor described herein in combination with at least one pharmaceutically acceptable excipient or carrier.

[0170] A “pharmaceutical composition” is a formulation containing the EZH2 inhibitors of the present disclosure in a form suitable for administration to a subject. In some embodiments, the pharmaceutical composition is in bulk or in unit dosage form. The unit dosage form is any of a variety of forms, including, for example, a capsule, an IV bag, a tablet, a single pump on an aerosol inhaler or a vial. The quantity of active ingredient (*e.g.*, a formulation of the disclosed compound or salt, hydrate, solvate or isomer thereof) in a unit dose of composition is an effective amount and is varied according to the particular treatment involved. One skilled in the art will appreciate that it is sometimes necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration. A variety of routes are contemplated, including oral, pulmonary, rectal, parenteral, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal, inhalational, buccal, sublingual, intrapleural, intrathecal, intranasal, and the like. Dosage forms for the topical or transdermal administration of a compound of this disclosure include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. In some embodiments, the active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers or propellants that are required.

[0171] As used herein, the phrase “pharmaceutically acceptable” refers to those compounds, materials, compositions, carriers, and/or dosage forms which are, within the

scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0172] “Pharmaceutically acceptable excipient” means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A “pharmaceutically acceptable excipient” as used in the disclosure includes both one and more than one such excipient.

[0173] A pharmaceutical composition of the disclosure is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), and transmucosal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0174] A compound or pharmaceutical composition of the disclosure can be administered to a subject in many of the well-known methods currently used for chemotherapeutic treatment. For example, for treatment of cancers, a compound of the disclosure may be injected directly into tumors, injected into the blood stream or body cavities or taken orally or applied through the skin with patches. The dose chosen should be sufficient to constitute effective treatment but not as high as to cause unacceptable side effects. The state of the disease condition (*e.g.*, cancer, precancer, and the like) and the health of the patient should preferably be closely monitored during and for a reasonable period after treatment.

[0175] The term “therapeutically effective amount”, as used herein, refers to an amount of an EZH2 inhibitor, composition, or pharmaceutical composition thereof effective to treat, ameliorate, or prevent an identified disease or condition, or to exhibit a detectable

therapeutic or inhibitory effect. The effect can be detected by any assay method known in the art. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Therapeutically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician. In a preferred aspect, the disease or condition to be treated is cancer, including but not limited to, B cell lymphoma, including activated B-cell (ABC) and germinal B-cell (GBC) subtypes.

[0176] For any EZH2 inhibitor of the disclosure, the therapeutically effective amount can be estimated initially either in cell culture assays, *e.g.*, of neoplastic cells, or in animal models, usually rats, mice, rabbits, dogs, or pigs. The animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

Therapeutic/prophylactic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, ED₅₀ (the dose therapeutically effective in 50% of the population) and LD₅₀ (the dose lethal to 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, and it can be expressed as the ratio, LD₅₀/ED₅₀. Pharmaceutical compositions that exhibit large therapeutic indices are preferred. The dosage may vary within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

[0177] Dosage and administration are adjusted to provide sufficient levels of the active agent(s) or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

[0178] The pharmaceutical compositions containing an EZH2 inhibitor of the present disclosure may be manufactured in a manner that is generally known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers

comprising excipients and/or auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Of course, the appropriate formulation is dependent upon the route of administration chosen.

[0179] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0180] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0181] Oral compositions generally include an inert diluent or an edible pharmaceutically acceptable carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0182] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser, which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

[0183] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[0184] The active compounds (*e.g.*, EZH2 inhibitors of the disclosure) can be prepared with pharmaceutically acceptable carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as

pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[0185] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the disclosure are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved.

[0186] In therapeutic applications, the dosages of the pharmaceutical compositions used in accordance with the disclosure vary depending on the agent, the age, weight, and clinical condition of the recipient patient, and the experience and judgment of the clinician or practitioner administering the therapy, among other factors affecting the selected dosage. Generally, the dose should be sufficient to result in slowing, and preferably regressing, the growth of the tumors and also preferably causing complete regression of the cancer. An effective amount of a pharmaceutical agent is that which provides an objectively identifiable improvement as noted by the clinician or other qualified observer. For example, regression of a tumor in a patient may be measured with reference to the diameter of a tumor. Decrease in the diameter of a tumor indicates regression. Regression is also indicated by failure of tumors to reoccur after treatment has stopped. As used herein, the term “dosage effective manner” refers to amount of an active compound to produce the desired biological effect in a subject or cell.

[0187] The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[0188] The compounds of the present disclosure are capable of further forming salts. All of these forms are also contemplated within the scope of the claimed disclosure.

[0189] As used herein, “pharmaceutically acceptable salts” refer to derivatives of the compounds of the present disclosure wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically

acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, 1,2-ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, toluene sulfonic, and the commonly occurring amine acids, *e.g.*, glycine, alanine, phenylalanine, arginine, etc.

[0190] Other examples of pharmaceutically acceptable salts include hexanoic acid, cyclopentane propionic acid, pyruvic acid, malonic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo-[2.2.2]-oct-2-ene-1-carboxylic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, muconic acid, and the like. The present disclosure also encompasses salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

[0191] It should be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same salt.

[0192] The EZH2 inhibitors of the present disclosure can also be prepared as esters, for example, pharmaceutically acceptable esters. For example, a carboxylic acid function group in a compound can be converted to its corresponding ester, *e.g.*, a methyl, ethyl or other ester. Also, an alcohol group in a compound can be converted to its corresponding ester, *e.g.*, an acetate, propionate or other ester.

[0193] The EZH2 inhibitors of the present disclosure can also be prepared as prodrugs, for example, pharmaceutically acceptable prodrugs. The terms “pro-drug” and “prodrug” are used interchangeably herein and refer to any compound which releases an active parent drug

in vivo. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (*e.g.*, solubility, bioavailability, manufacturing, etc.), the compounds of the present disclosure can be delivered in prodrug form. Thus, the present disclosure is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. “Prodrugs” are intended to include any covalently bonded carriers that release an active parent drug of the present disclosure *in vivo* when such prodrug is administered to a subject. Prodrugs in the present disclosure are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present disclosure wherein a hydroxy, amino, sulfhydryl, carboxy or carbonyl group is bonded to any group that may be cleaved *in vivo* to form a free hydroxyl, free amino, free sulfhydryl, free carboxy or free carbonyl group, respectively.

[0194] Examples of prodrugs include, but are not limited to, esters (*e.g.*, acetate, dialkylaminoacetates, formates, phosphates, sulfates and benzoate derivatives) and carbamates (*e.g.*, N,N-dimethylaminocarbonyl) of hydroxy functional groups, esters (*e.g.*, ethyl esters, morpholinoethanol esters) of carboxyl functional groups, N-acyl derivatives (*e.g.*, N-acetyl) N-Mannich bases, Schiff bases and enaminones of amino functional groups, oximes, acetals, ketals and enol esters of ketone and aldehyde functional groups in compounds of the disclosure, and the like, See Bundegaard, H., *Design of Prodrugs*, p1-92, Elsevier, New York-Oxford (1985).

[0195] The EZH2 inhibitors, or pharmaceutically acceptable salts, esters or prodrugs thereof, are administered orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperitoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally and parenterally. In some embodiments, the compound is administered orally. One skilled in the art will recognize the advantages of certain routes of administration.

[0196] The dosage regimen utilizing the compounds is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

[0197] The dosage regimen can be daily administration (*e.g.*, every 24 hours) of a compound of the present disclosure. The dosage regimen can be daily administration for consecutive days, for example, at least two, at least three, at least four, at least five, at least six or at least seven consecutive days. Dosing can be more than one time daily, for example, twice, three times or four times daily (per a 24 hour period). The dosing regimen can be a daily administration followed by at least one day, at least two days, at least three days, at least four days, at least five days, or at least six days, without administration.

[0198] Techniques for formulation and administration of the disclosed compounds of the disclosure can be found in *Remington: the Science and Practice of Pharmacy*, 19th edition, Mack Publishing Co., Easton, PA (1995). In some embodiments, the compounds described herein, and the pharmaceutically acceptable salts thereof, are used in pharmaceutical preparations in combination with a pharmaceutically acceptable carrier or diluent. Suitable pharmaceutically acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The compounds will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described herein.

[0199] Methods of the disclosure for treating cancer including treating a B cell lymphoma, including the activated B-cell (ABC) and germinal B-cell (GBC) subtypes. In preferred embodiments, methods of the disclosure are used to treat a subject having a B cell lymphoma. In certain embodiments, the B cell lymphoma cell and/or the subject are characterized as having one or more mutations in a sequence that encodes a histone acetyltransferase (HAT). B cell lymphoma cells may contain a mutation in a gene that encodes a HAT, a corresponding HAT transcript (or cDNA copy thereof), or a HAT protein that decreases/inhibits an activity of a HAT protein. In preferred embodiments, the mutation in a gene that encodes a HAT, a corresponding HAT transcript (or cDNA copy thereof), or a HAT protein that decreases/inhibits an activity of a HAT protein, decreases or inhibits an acetylation activity or efficacy of the enzyme, resulting in a decreased level of acetylation of one or more lysines of histone 3 (H3) (*e.g.*, H3K27). The presence of the HAT mutation resulting in a decreased level of acetylation of one or more lysines of histone 3 (H3) (*e.g.*, H3K27) in a cell renders that cell sensitive to oncogenic transformation and treatment with an EZH2 inhibitor.

[0200] Methods of the disclosure may be used to treat a subject who has one or more mutations in a HAT that decrease/inhibit the ability of the HAT to acetylate one or more

lysines of histone 3 (H3) (e.g., H3K27) or who has one or more cells with one or more mutations in a HAT that decrease/inhibit the ability of the HAT to acetylate one or more lysines of histone 3 (H3) (e.g., H3K27). HAT expression and/or HAT function may be evaluated by fluorescent and non-fluorescent immunohistochemistry (IHC) methods, including well known to one of ordinary skill in the art. In a certain embodiment the method comprises: (a) obtaining a biological sample from the subject; (b) contacting the biological sample or a portion thereof with an antibody that specifically binds HAT; and (c) detecting an amount of the antibody that is bound to HAT. Alternatively, or in addition, HAT expression and/or HAT function may be evaluated by a method comprising: (a) obtaining a biological sample from the subject; (b) sequencing at least one DNA sequence encoding a HAT protein from the biological sample or a portion thereof; and (c) determining if the at least one DNA sequence encoding a HAT protein contains a mutation affecting the expression and/or function of the HAT protein. HAT expression or a function of HAT may be evaluated by detecting an amount of the antibody that is bound to HAT and by sequencing at least one DNA sequence encoding a HAT protein, optionally, using the same biological sample from the subject.

[0201] All percentages and ratios used herein, unless otherwise indicated, are by weight.

[0202] Other features and advantages of the present disclosure are apparent from the different examples. The provided examples illustrate different components and methodology useful in practicing the present disclosure. The examples do not limit the claimed disclosure. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present disclosure.

EXAMPLES

[0203] In order that the invention disclosed herein may be more efficiently understood, examples are provided below. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting the disclosure in any manner.

Example 1: Identification of one or more mutant histone acetyltransferase from 39

Gene Panel

[0204] Analysis of somatic sequence mutations (including single base and insertion/deletions) for 39 genes (Table 1 below) was performed on DNA from archival tumor tissue isolated and embedded in paraffin blocks prior to the treatment with EZH2 inhibitor Tazemetostat. DNA was extracted from up to four 10-micron slides sectioned from a formalin fixed paraffin embedded tumor sample. Samples were macrodissected if tumor content was determined to be less than 80% by a trained pathologist. Amplicon based library prep using custom Ampli-Seq primers (ThermoFisher) was performed using 10 ng of DNA as input. Quantitation of the library was completed using emulsion PCR and then sequenced using the Ion Torrent Personal Genome Machine (ThermoFisher) to an average depth of 500X. Base calling, mapping and mutation calling was performed by Torrent Suite 3.6.2 or later and Variant caller plug-in 3.6.63335 or later. Mutation calls were reported only for mutations with greater than 500X coverage and supported by at least 10% allelic frequency.

[0205] **Table 1:** Custom 39 gene sequencing panel.

Gene	# of Amplicons	Gene	# of Amplicons
AKT1	2	IKZF3	1
ALK	2	IRF4	1
ARID1A	6	MDM2	3
ATM	17	KRAS	3
B2M	1	MEF2B	3
BCL2	1	MYD88	3
BCL6	1	NOTCH1	3
BCL7A	1	NPM1	1
BTG2	1	NRAS	3
CARD11	3	PIK3CA	11
CCND3	1	PIM1	2
CD79B	1	PRDM1	2
CDKN2A	2	PTEN	9
CREBBP	1	RB1	7
EP300	1	RBBP4	1
EZH2*	33	SMARCB1	5
FBXW7	5	SUZ12	1
FOXO1	1	TNFRSF14	1
HLA-C	1	TP53	11
HRAS	2		

*EZH2 & KDM6A covered the entire Coding Region

Example 2: Identification of one or more mutant histone acetyltransferase from 62 Gene Panel from Non-Hodgkin's Lymphoma (NHL) Tissue

[0206] A panel of 62 NHL specific and 203 well-characterized cancer genes was designed to selectively analyze regions of the genome previously identified as somatically altered (Tables 2 through 6). The panel was designed to capture somatic sequence mutations (single base and small insertions/deletions), amplifications, translocations, and microsatellite instability (MSI). DNA was extracted from up to five, 5-micron slides sectioned from a formalin fixed paraffin embedded tumor sample that was prepared prior to the start of Tazemetostat treatment. Targeted genomic capture was performed using 100 ng of input DNA and then sequenced to an average depth of 1500-fold using the Illumina HiSeq2500 platform with 100 bp paired-end reads. Bioinformatics was performed by aligning the filtered data to the hg19 reference genome allowing for the identification of tumor specific sequence alterations (single base and small insertion/deletion alterations). Further analysis for identification of copy number alterations and translocations was performed using digital karyotyping and PARE analyses respectively. The validation of the panel was completed through the analyses of cell line specimens with an experimental tumor purity of 20-100% using 50-100ng of DNA yielded sensitivity and specificity of 100% for detection of 358 previously characterized sequence mutations and structural variants.

[0207] **Table 2:** Custom Lymphoma CancerSelect™ Sequence Mutation Gene List (in addition to the CancerSelect-R™ 203 Gene Panel).

Gene Name	Sequence Region(s) Included	Gene Name	Sequence Region(s) Included
PRDM1	Full Coding Sequence	KIT	Specific Exon(s)
EZH2	Full Coding Sequence	KRAS	Specific Exon(s)
KDM6A	Full Coding Sequence	MEF2B	Specific Exon(s)
KMT2D	Full Coding Sequence	MYC	Specific Exon(s)
ARID1A	Specific Exon(s)	MYD88	Specific Exon(s)
ATM	Specific Exon(s)	NOTCH1	Specific Exon(s)
B2M	Specific Exon(s)	NOTCH2	Specific Exon(s)
BCL2	Specific Exon(s)	NRAS	Specific Exon(s)
BCL6	Specific Exon(s)	PIK3CA	Specific Exon(s)
BCL7A	Specific Exon(s)	PIM1	Specific Exon(s)
BRAF	Specific Exon(s)	POU2F2	Specific Exon(s)
BTG1	Specific Exon(s)	PTEN	Specific Exon(s)
CARD11	Specific Exon(s)	PTPN1	Specific Exon(s)
CCND3	Specific Exon(s)	PTPN11	Specific Exon(s)
CD58	Specific Exon(s)	PTPN6	Specific Exon(s)
CD79B	Specific Exon(s)	PTPRD	Specific Exon(s)
CDKN2A	Specific Exon(s)	RB1	Specific Exon(s)
CREBBP	Specific Exon(s)	S1PR2	Specific Exon(s)
EP300	Specific Exon(s)	SGK1	Specific Exon(s)
FOXO1	Specific Exon(s)	SMARCB1	Specific Exon(s)

GNA13	Specific Exon(s)	SOCS1	Specific Exon(s)
HIST1H1B	Specific Exon(s)	STAT6	Specific Exon(s)
HIST1H1C	Specific Exon(s)	TBL1XR1	Specific Exon(s)
HIST1H1E	Specific Exon(s)	TNFAIP3	Specific Exon(s)
IKZF3	Specific Exon(s)	TNFRSF14	Specific Exon(s)
IRF4	Specific Exon(s)	TP53	Specific Exon(s)
ITPKB	Specific Exon(s)	XPD1	Specific Exon(s)

*Specific exons were chosen based on those regions which were mutated recurrently in COSMIC

[0208] **Table 3:** Custom Lymphoma CancerSelect™ Translocation Analyses Gene List (in addition to the CancerSelect-R™ 203 Gene Panel).

Gene Name	Sequence Region(s) Included	Gene Name	Sequence Region(s) Included
ALK	ALK_NM_004304_Intron19	CIITA	Entire Gene
BCL2	BCL2_MCR_Breakpoint_Region	MYC	Entire Gene + 40kbp upstream
BCL2	BCL2_MBR_Breakpoint_Region	CD274 (PDL1)	Entire Gene
BCL6	Entire Gene	PDCD1LG2 (PDL2)	Entire Gene

[0209] **Table 4:** Custom Lymphoma CancerSelect™ Amplification Analyses Gene List (in addition to the CancerSelect-R™ 203 Gene Panel).

Gene Name	Gene Name
BCL2	JAK2
CD274 (PDL1)	KDM4C
FOXP1	PDCD1LG2 (PDL2)
	REL

[0210] **Table 5:** CancerSelect-R™ 203 Gene Panel (Sequence and copy number* analyses for the full coding sequence of 195 well-characterized cancer genes).

Gene Name	Gene Name	Gene Name	Gene Name	Gene Name
ABL1*	CBL*	ERBB3*	FGFR2*	KDR*
ACVR1	CCND1*	ERBB4*	FGFR3*	KIT*
AKT1*	CCNE1*	ERCC1	FGFR4*	KRAS*
AKT2*	CDC73	ERCC2	FH	MAML1*
ALK*	CDH1	ERCC3	FLCN	MAP2K1*
APC	CDK4*	ERCC4	FLT3*	MAP2K4
AR*	CDK6*	ERCC5	FLT4	MDM2*
ARID1A	CDKN1B	ESR1	FOXL2*	MDM4*
ARID1B	CDKN2A	ETV1	GATA1	MED12*
ASXL1	CDKN2B	ETV5	GATA2*	MEN1
ATM	CDKN2C	EWSR1	GNA11*	MET*
ATRX	CEBPA	EXT1	GNAQ*	MLH1
AURKA	CHEK2	EXT2	GNAS*	MLL*
AXIN2	CIC	EZH2*	GPC3	MPL*
BAP1	CREBBP	FANCA	H3F3A*	MSH2
BCL2*	CSF1R*	FANCB	H3F3B	MSH6
BCR	CTNNB1*	FANCC	HNF1A	MTOR
BLM	CYLD	FANCD2	HRAS*	MUTYH
BMPR1A	DAXX	FANCE	IDH1*	MYC*
BRAF*	DDB2	FANCF	IDH2*	MYCL1*
BRCA1	DDR2	FANCG	IGF1R*	MYCN*
BRCA2	DICER1	FANCI	IGF2R*	MYD88*
BRIP1	DNMT3A*	FANCL	IKZF1	NBN
BTK	EGFR*	FANCM	JAK1*	NCOA3*
BUB1B	EP300	FBXW7	JAK2*	NF1
CALR	ERBB2*	FGFR1	JAK3*	NF2
NKX2-1*	PIK3CA*	RAD51C	SF3B1*	TNFAIP3
NOTCH1*	PIK3R1	RAF1	SMAD2	TOP1
NOTCH2*	PMS1	RB1	SMAD3	TP53
NOTCH3*	PMS2	RECQL4	SMAD4	TSC1
NOTCH4*	POLD1	RET*	SMARCB1	TSC2
NPM1	POLE	RNF43	SMO*	TSHR*
NRAS*	POLH	ROS1	SRC	VHL
NTRK1	POT1	RUNX1*	STAG2	WAS
PALB2	PRKAR1A	SBDS	STK11	WRN
PAX5*	PRSS1	SDHAF2	SUFU	WT1
PBRM1	PTCH1	SDHB	TERT	XPA
PDGFRA*	PTEN	SDHC	TET2	XPC
PHOX2B	PTPN11*	SDHD	TGFBR2	XRCC1

[0211] Table 6: CancerSelect-R™ 203 Gene Panel (Rearrangement analyses for selected regions of 24 well-characterized genes.

Gene Name	Gene Name	Gene Name
ALK	EWSR1	ROS1
BCL2	MLL	TMPRSS2
BCR	MYC	FGFR3
BRAF	NTRK1	TACC3
DNAJB1	PDGFRA	
EGFR	PDGFRB	
ETV1	PRKACA	
ETV4	RAF1	
ETV5	RARA	
ETV6	RET	

Example 3: Non-Hodgkin's Lymphoma Circulating DNA Panel

[0212] A panel of 62 NHL specific genes was designed to selectively analyze regions of the genome previously identified as somatically altered (Table 7) with high specificity down to an allelic frequency of 0.1%. The panel was designed to capture somatic sequence mutations (single base and small insertions/deletions), amplifications, translocations, and microsatellite instability (MSI). DNA was extracted from plasma derived from up to 20 mLs of peripheral blood. Blood was collected prior to treatment and at defined time points during the course of Tazemetostat treatment. Targeted genomic capture was performed using 150 ng of input DNA and then sequenced using the Illumina HiSeq2500 platform with 100 bp paired-end reads. The average depth of sequencing coverage was approximately 20,000-fold for sequence mutations and 5,000-fold for structural alterations. Bioinformatic analyses were accomplished by aligning the filtered data to the hg19 reference genome allowing for the identification of tumor specific sequence alterations (single base and small insertion/deletion alterations). Further analyses for identification of copy number alterations and translocations was performed by digital karyotyping and PARE analyses respectively. The validation of the panel was completed using analyses of fragmented cell line and plasma derived DNA with an experimental tumor purity of 0.10%-25.0% using 9-167 ng of DNA yielded a sensitivity of 100% for detection of over 100 genetic variants.

[0213] Table 7: Custom Lymphoma CancerSelect™ Sequence Mutation Gene List.

Gene Name	Sequence Region(s) Included	Gene Name	Sequence Region(s) Included
PRDM1	Full Coding Sequence	KIT	Specific Exon(s)
EZH2	Full Coding Sequence	KRAS	Specific Exon(s)
KDM6A	Full Coding Sequence	MEF2B	Specific Exon(s)
KMT2D	Full Coding Sequence	MYC	Specific Exon(s)
ARID1A	Specific Exon(s)	MYD88	Specific Exon(s)
ATM	Specific Exon(s)	NOTCH1	Specific Exon(s)
B2M	Specific Exon(s)	NOTCH2	Specific Exon(s)
BCL2	Specific Exon(s)	NRAS	Specific Exon(s)
BCL6	Specific Exon(s)	PIK3CA	Specific Exon(s)
BCL7A	Specific Exon(s)	PIM1	Specific Exon(s)
BRAF	Specific Exon(s)	POU2F2	Specific Exon(s)
BTG1	Specific Exon(s)	PTEN	Specific Exon(s)
CARD11	Specific Exon(s)	PTPN1	Specific Exon(s)
CCND3	Specific Exon(s)	PTPN11	Specific Exon(s)
CD58	Specific Exon(s)	PTPN6	Specific Exon(s)
CD79B	Specific Exon(s)	PTPRD	Specific Exon(s)
CDKN2A	Specific Exon(s)	RB1	Specific Exon(s)
CREBBP	Specific Exon(s)	S1PR2	Specific Exon(s)
EP300	Specific Exon(s)	SGK1	Specific Exon(s)
FOXO1	Specific Exon(s)	SMARCB1	Specific Exon(s)
GNA13	Specific Exon(s)	SOC51	Specific Exon(s)
HIST1H1B	Specific Exon(s)	STAT6	Specific Exon(s)
HIST1H1C	Specific Exon(s)	TBL1XR1	Specific Exon(s)
HIST1H1E	Specific Exon(s)	TNFAIP3	Specific Exon(s)
IKZF3	Specific Exon(s)	TNFRSF14	Specific Exon(s)
IRF4	Specific Exon(s)	TP53	Specific Exon(s)
ITPKB	Specific Exon(s)	XPO1	Specific Exon(s)

*Specific exons were chosen based on those regions which were mutated recurrently in COSMIC

[0214] Table 8: Custom Lymphoma CancerSelect™ Translocation Analyses Gene List.

Gene Name	Sequence Region(s) Included	Gene Name	Sequence Region(s) Included
ALK	ALK_NM_004304_Intron19	CIITA	Entire Gene
BCL2	BCL2_MCR_Breakpoint_Region	MYC	Entire Gene + 40kbp upstream
BCL2	BCL2_MBR_Breakpoint_Region	CD274 (PDL1)	Entire Gene
BCL6	Entire Gene	PDCD1LG2 (PDL2)	Entire Gene

[0215] Table 9: Custom Lymphoma CancerSelect™ Amplification Analyses Gene List.

Gene Name	Gene Name
BCL2	JAK2
CD274 (PDL1)	KDM4C
FOXP1	PDCD1LG2 (PDL2)
	REL

[0216] Table 10 describes a Phase 1 clinical trial design (sponsor protocol no.: E7438-G000-001, ClinicalTrials.gov identifier: NCT01897571). The study population included subjects with relapsed or refractory solid tumors or B-cell lymphoma. Subjects received a 3+3 dose escalation in expansion cohorts receiving 800 mg BID and 1600 mg BID, respectively, or a cohort for ascertaining the effect of food on dosing at 400 mg BID. The primary endpoint was a determination of recommended phase II dose (RP2D)/ maximum tolerated dose (MTD). Secondary endpoints included safety, pharmacokinetics (PK), pharmacodynamics (PD) and tumor response, assessed every 8 wks.

Table 10

Dose (mg BID)	Patients (n=58)	Solid tumors (n=37)**	B-cell NHL (n=21)	* 2 formulations
100*	6	5	1	
200	3	1	2	
400	3	2	1	
800	14	6	8	
1600	12	8	4	
Food Effect	13	8	5	
Drug-Drug	7	7	0	

[0217] Table 11 provides patient tumor type data from the trial described in Table 10.

Table 11

Relapsed or refractory NHL		n=21
Diffuse Large B cell Lymphoma (DLBCL)*	GCB	5
	Non GCB	6
	undetermined	3
Follicular lymphoma (FL)*		6
Marginal Zone lymphoma (MZL)		1
Relapsed or refractory solid tumors		n=37
INI1-deficient or negative	Malignant rhabdoid tumor	5
	Epithelioid sarcoma	3
	Synovial sarcoma	4
SMARCA4-negative tumors		3
Other solid tumors		22

* 2/17 NHL patients tested to date are EZH2 mutant by cobas® test (Roche Molecular Systems, Inc.)

[0218] Table 12 summarizes solid tumor patient demographics from the trial described in Table 10.

Table 12

Characteristic		n=21 (%)
Median age, years [range]		63 [24-84]
Sex (M / F)		15/6
# of prior therapeutic systemic regimens	1	2 (10)
	2	1 (5)
	3	8 (38)
	4	3 (14)
	≥5	7 (33)
Prior autologous hematopoietic cell transplant		8 (38)
Prior radiotherapy		17 (57)

[0219] Table 13 describes a safety profile in NHL (non-Hodgkin's lymphoma) and solid tumor patients (n=51)

Table 13

	All Events		All Treatment-Related	
	All Grades *	Grade ≥3	All Grades	Grade ≥3 **
Anorexia	23	0	13	0
Decreased appetite	9	1	4	0
Thrombocytopenia	8	2	7	1
Nausea	8	0	8	0
Constipation	7	0	2	0
Diarrhea	6	0	4	0
Vomiting	6	0	5	0
Anemia	5	0	3	0
Dry skin	5	0	4	0
Dysgeusia	5	0	3	0
Dyspnea	5	0	0	0
Muscle spasms	5	0	3	0
Abdominal pain	4	1	1	0
Hypophosphatemia	4	0	1	0
Anxiety	3	0	1	0
Depression	3	2	1	0
Hypertension	3	1	2	1
Insomnia	3	0	0	0
Neutropenia	3	1	3	1
Night sweats	3	0	3	0
Peripheral edema	3	0	2	0
Hepatocellular injury	2	1	1	1

* All AEs with frequency >5% regardless of attribution shown

** All grade ≥3 treatment-related events shown

[0220] Table 14 describes a panel of biomarkers for tumor somatic profiling the 39 gene NGS of the disclosure (Example 1). Somatic mutations were determined in archived tumor tissue from 13 Phase 1 patients. Somatic mutations were identified when 1) variant allele frequency was greater than or equal to 10%, 2) sequence coverage was greater than or equal to 1000, and 3) the variant was not identified in dbSNP.

Table 14

	# of genes assessed	DNA Sequencing Modality	Average Coverage
Panel 1	39	- 37 genes specific exons only - All coding exons = EZH2, KDM6A	1000x

Example 4: Detection of Mutation in ct-DNA through suppressing NGS errors

[0221] Archive and cell-free tumor DNA collected from relapsed refractory NHL patients phase I and II trials, were tested in the NGS panel as described in Examples 1 and 2. The content of the panel included molecular variants occurring in NHL at $\geq 5\%$ frequency. (Tables 15 and 17-19, Figures 19-22). Redundant sequencing and molecular barcoding was found to suppress NGS error rates such as to enable the identification of mutations in archive tumor DNA down to 2% allelic frequency. Through correction of the background error by molecular bar coding the NHL specific plasma select panel was able to accurately detect mutations down to 0.1% allelic frequency (Figure 13). Translocations of ALK were detected in a cell-free DNA validation test set with samples from the phase I patients at a tumor purity of as low as 0.1% (Figure 14). Sequencing of phase I NHL patients utilizing the 62 gene NHL NGS panel was completed for 10 archive tumor samples and 15 ctDNA samples (Table 15, Figure 19). In addition, microsatellite instability was monitored through the analysis of 5 distinct markers (BAT-25, BAT-26, MONO-27, NR-21 and NR-24), leading to one patient in the phase I trial being identified as microsatellite unstable based on the five tested markers (Table 15 and Figure 19, columns A16 and C16). Sequencing and an initial analysis of samples from patients in a phase 2 trial was completed with 58 archive tumor and 72 ctDNA baseline patient samples, wherein 48 of the archive tumor patients and 68 of the ctDNA patients were sequenced with reported response data.

[0222] Table 15 summarizes the molecular variants observed in archive tumor in samples from phase I patients. Observed molecular variants were frameshift or nonsense mutations, missense mutations, translocations and amplifications. If multiple mutations were found in the same sample only the most damaging alteration are shown. Trends later identified in phase 2 samples also appear in the phase I NHL samples (e.g., EZH2, STAT6 and MYC).

Table 15

	Best Response = CR or PR											non-Responder < CR or PR										
	A5	C5	A8	C8	C9	A4	C4	C6	C2	A7	C7	A16	C16	A18	C18	C11	C15	C17	A10	C10	A14	C14
GCB-DLBCL																						
non-GCB-DLBCL																						
Follicular Lymphoma																						
ARID1A																						
ATM																						
B2M **																						
BCL2																						
BCL6																						
BCL7A																						
BRAF																						
CARD11 **																						
CCND3																						
CD58																						
CD79B																						
CD274 (PDL1)																						
CDKN2A																						
CIITA																						
CREBBP **																						
EP300 **																						
E2H2 (Y646) **																						
E2H2 (non-Y646) **																						
FOXO1 **																						
FOXP1																						
GNA13																						
HIST1H1B																						
HIST1H1C																						
HIST1H1E																						
IZKF3																						
IRF4																						
JAK2																						
KDM4C																						
KDM6A **																						
KIT																						
KMT2D																						
KRAS																						
MEF2B																						
MYC																						
MYD88																						
NOTCH1																						
NOTCH2																						
NRAS																						
PDCD1LG2 (PDL2)																						
PIK3CA																						
PIM1																						
POU2F2																						
PRDM1																						
PTEN																						
PTPN6																						
PTPN11																						
PTPRD																						
REL																						
SOCS1																						
STAT6																						
TNFAIP3																						
TNFRSF14 **																						
TP53																						

Frameshift or nonsense mutation

Translocation

Missense mutation

Amplification

** Molecular variants identified in the 39 gene NGS panel of Example 1.

[0223] Table 16 shows a comparison between a Cobas® test (Roche Molecular Systems, Inc.) and the 62 gene NGS Panel of the disclosure in the of detection of EZH2 hot spot mutations.

[0224] Table 17 summarizes the molecular variants observed in archive tumor in phase 2 Patients. Observed molecular variants were frameshift or nonsense mutations, missense mutations, translocations and amplifications. Variants of interest included, inter alia, EZH2, MYD88 (273P) and MYC. EZH2 mutations were observed in 9 patients, wherein 7 displayed a variant allele frequency of > 10%; 2 had variant allele frequencies of $\leq$ 10% (10042008, 8%; 10032004, 10%; best response: 4 PR, 3 SD and 2 PD). MYD88 (273P) mutations were observed in 6 patients (best response: 3 CR, 1PR, 1 PD and 1 unknown response); STAT6 mutations were observed in 13 patients (best response: 1 CR, 5 PR, 4 SD and 3 PD). MYC mutations were observed in 7 patients (best response: 5 PD and 2 unknown responses). 2 MYC translocations were associated with lack of response.

[0225] Table 18 summarizes the molecular variants with variant allele frequencies of 0.1% observed in ctDNA in phase 2 patients. Observed molecular variants were frameshift or nonsense mutations, missense mutations, translocations and amplifications. Variants of interest included, inter alia, EZH2, MYD88 (273P) and MYC. EZH2 mutations were observed in 11 patients (best response: 5 PR, 2 SD, 3 PD and 1 unknown response). MYD88 (273P) mutations were observed in 6 patients (best response: 2 CR, 1PR, 1 SD and 2 PD); STAT6 mutations were observed in 14 patients (best response: 5 PR, 6 SD and 3 PD). MYC mutations were observed in 18 patients (best response: 2 PR, 3SD, 9 PD and 4 unknown responses). 5 MYC translocations were associated with lack of response.

[0226] Table 19 summarizes the molecular variants with variant allele frequencies of 1% observed in ctDNA in phase 2 patients. Observed molecular variants were frameshift or nonsense mutations, missense mutations, translocations and amplifications. Variants of interest included, inter alia, EZH2, MYD88 (273P) and MYC. EZH2 mutations were observed in 8 patients (best response: 4 PR, 1 SD and 3 PD). MYD88 (273P) mutations were observed in 5 patients (best response: 2 CR, 1PR, and 2 PD); STAT6 mutations were observed in 10 patients (best response: 4 PR, 4 SD and 2 PD). MYC mutations were observed in 5 patients (best response: 3 PD and 2 unknown responses). 5 MYC translocations were associated with lack of response.

Table 16

Patient ID ²	Cohort Designation	Cell of Origin (Nanostring)	EZH2 Cobas® Result	Tumor Content for Cobas® Assay	Archive Tumor NGS Result (vaf)	cdDNA NGS Result (vaf)	Clonal or Subclonal mutation ¹
1003-2004	GCB-DLBCL EZH2 MT	GCB DLBCL	Y646F	100%	EZH2 Y646F (10%)	EZH2 Y646F (1.3%)	Subclonal
1003-2015	Non-GCB DLBCL	GCB DLBCL	Y646X	20%	EZH2 Y646H (19%)	EZH2 Y646H (12.7%)	Clonal
1003-2019	GCB-DLBCL EZH2 MT	GCB DLBCL	Y646F	100%	EZH2 Y646F (38%)	EZH2 Y646F (8.94%)	Clonal
1004-2004	FL EZH2 mutant	N/A	Y646N	100%	Not sequenced (failed library)	EZH2 Y646N (34.9%)	Unknown
1004-2008	FL EZH2 mutant	N/A	Y646F	100%	EZH2 Y646F (8%)	Not detected	Subclonal
1004-2009	GCB-DLBCL EZH2 MT	Not performed	A682G	95%	EZH2 A682G (34%)	EZH2 A682G (0.9%)	Clonal
1004-2011	GCB-DLBCL EZH2 MT	GCB DLBCL	WT	100%	Low DNA Yield	Not detected	Unknown
1005-2001	FL EZH2 mutant	N/A	Y646N	90%	EZH2 Y646N (22%)	Low DNA yield	Clonal
1007-2002	GCB-DLBCL EZH2 MT	GCB DLBCL	Y646N	70%	Not sequenced (failed library)	EZH2 Y646F (0.36%)	Unknown
1008-2003	GCB-DLBCL EZH2 MT	Not performed	Y646N	70%	Not sequenced (failed library)	EZH2 Y646N (3.18%)	Unknown
2002-2001	FL EZH2 mutant	N/A	Y646X	100%	EZH2 Y646S (22%)	EZH2 Y646S (6.6%)	Clonal
2002-2010	GCB-DLBCL EZH2 WT	GCB DLBCL	WT	100%	Not detected	EZH2 Y646C (0.33%)	Unknown
2004-2003	GCB-DLBCL EZH2 MT	GCB DLBCL	Y646X	Unknown	EZH2 Y646H (25%)	EZH2 Y646H (28%)	Unknown
2004-2004	GCB-DLBCL EZH2 MT	GCB DLBCL	Y646N	20%	Not sequenced (failed library)	EZH2 Y646N (39.2%)	Unknown

¹ Patients determined to have EZH2 mutant tumor DNA copies $\geq 20\%$ were considered clonal² All EZH2 mutant patients enrolled before May 1st 2016 are represented in this table.

Table 17

[illegible]

Gameplay or narrative mutation

1012 *Journal of Management Education*

Transcription

Appendix

Table 18

	On Study	Off Study	Off Study
10032005			
50022004			
10042001			
10012012			
90022003			
20042005			
20022010			
10012002			
20022002			
20022003			
20022004			
20022005			
20022006			
20022007			
20022008			
20022009			
20022010			
20022011			
20022012			
20022013			
20022014			
20022015			
20022016			
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20022019			
20022020			
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20022419			

Table 19

	On Study										Off Study									
	10012002	20022010	20042005	30022003	10012012	10042001	50022004	10032005												
GCB-DLCL Cohort																				
non-GCB-DLCL Cohort																				
Follicular Lymphoma																				
EBV MT Positive (Cohort)																				
CR + PR																				
Stable Disease																				
Progressive Disease																				
ARID1A																				
B2M																				
BC12 Sequence Mutation																				
BC12 Translocation																				
BC16																				
CARD11																				
CND3																				
COS8																				
CD79B																				
CD274 (PD-L1)																				
CDKN2A																				
CREBBP																				
EP300																				
EPH4 (Y664, A682)																				
EPH4 non hot spot																				
FOSD1																				
FOP1																				
GNAL3																				
HST1HB																				
HST1HC																				
HST1HE																				
IMT7D																				
IRAS																				
MEF2B																				
MYC Sequence Mutation																				
MYC Translocation																				
MYD88 (L279P)																				
PDOLG2 (PD-L2)																				
PIM1																				
POU2F2																				
PRDM1																				
PTPRD																				
SIX3																				
STAT6																				
TNFRSF3																				
TNFRSF14																				
transient or nonsense mutation																				
Missense mutation																				
Translocation																				
Amplification																				

[0227] Table 20 summarizes specific variants of STAT6, and their variant allele frequencies, observed in patients of different patient cohorts (DLBCL GCB EZH2 wild type, FL EZH2 wild type, FL EZH2 mutant and DLBCL non-GCB).

Table 20

Sample ID	Variant	vaf	Response	Cohort
10012004	419D>G	42%	Progressive Disease	DLBCL GCB EZH2 Wild-type
10032007	419D>G	36%	Partial Response	FL EZH2 Wild-type
10042005	419D>G	19%	Partial Response	FL EZH2 Wild-type
10052001	419D>G	24%	Partial Response	FL EZH2 Mutant
10062002	419D>G	29%	Stable Disease	DLBCL GCB EZH2 Wild-type
20012001	286Q>R	24%	Stable Disease	DLBCL GCB EZH2 Wild-type
20012003	417N>S	27%	Stable Disease	DLBCL GCB EZH2 Wild-type
20022001	377E>K	33%	Partial Response	FL EZH2 Mutant
20022008	371C>R	35%	Progressive Disease	FL EZH2 Wild-type
20042003	419D>A	39%	Partial Response	DLBCL GCB EZH2 Mutant
20052004	419D>A	30%	Complete Response	DLBCL GCB EZH2 Wild-type
30022001	419D>H	42%	Progressive Disease	DLBCL GCB EZH2 Wild-type
50022001	419D>Y	39%	Stable Disease	DLBCL non-GCB

[0228] All publications and patent documents cited herein are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference. Citation of publications and patent documents is not intended as an admission that any is pertinent prior art, nor does it constitute any admission as to the contents or date of the same. The invention having now been described by way of written description, those of skill in the art will recognize that the invention can be practiced in a variety of embodiments and that the foregoing description and examples below are for purposes of illustration and not limitation of the claims that follow. Where names of cell lines or genes are used, abbreviations and names conform to the nomenclature of the American Type Culture Collection (ATCC) or the National Center for Biotechnology Information (NCBI), unless otherwise noted or evident from the context.

[0229] The invention can be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

What is claimed is:

1. A method of treating cancer comprising administering a therapeutically effective amount of an inhibitor of Enhancer to Zeste Homolog 2 (EZH2) to a subject in need thereof, wherein the subject has at least one mutation in one or more sequences encoding a gene or gene product listed in Tables 1-9, Tables 17-19, and/or Figures 19-22.

2. The method of 1, wherein the subject has at least one mutation in one or more sequences encoding:

MYD88, STAT6A, SOCS1, MYC, HIST1H1E, ABL1, ACVR1, AKT1, AKT2, ALK, APC, AR, ARID1A, ARID1B, ASXL1, ATM, ATRX, AURKA, AXIN2, BAP1, BCL2, BCR, BLM, BMPR1A, BRAF, BRCA1, BRCA2, BRIP1, BTK, BUB1B, CALR, CBL, CCND1, CCNE1, CDC73, CDH1, CDK4, CDK6, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CEBPA, CHEK2, CIC, CREBBP, CSF1R, CTNNB1, CYLD, DAXX, DDB2, DDR2, DICER1, DNMT3A, EGFR, EP300, ERBB2, ERBB3, ERBB4, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, ESR1, ETV1, ETV5, EWSR1, EXT1, EXT2, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FBXW7, FGFR1, FGFR2, FGFR3, FGFR4, FH, FLCN, FLT3, FLT4, FOXL2, GATA1, GATA2, GNA11, GNAQ, GNAS, GPC3, H3F3A, H3F3B, HNF1A, HRAS, IDH1, IDH2, IGF1R, IGF2R, IKZF1, JAK1, JAK2, JAK3, KDR, KIT, KRAS, MAML1, MAP2K1, MAP2K4, MDM2, MDM4, MED12, MEN1, MET, MLH1, MLL, MPL, MSH2, MSH6, MTOR, MUTYH, MYCL1, MYCN, NBN, NCOA3, NF1, NF2, NKX2-1, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NPM1, NRAS, NTRK1, PALB2, PAX5, PBRM1, PDGFRA, PHOX2B, PIK3CA, PIK3R1, PMS1, PMS2, POLD1, POLE, POLH, POT1, PRKAR1A, PRSS1, PTCH1, PTEN, PTPN11, RAD51C, RAF1, RB1, RECQL4, RET, RNF43, ROS1, RUNX1, SBDS, SDHAF2, SDHB, SDHC, SDHD, SF3B1, SMAD2, SMAD3, SMAD4, SMARCB1, SMO, SRC, STAG2, STK11, SUFU, TERT, TET2, TGFB2, TNFAIP3, TOP1, TP53, TSC1, TSC2, TSHR, VHL, WAS, WRN, WT1, XPA, XPC, and/or XRCC1.

3. The method of claim 1, wherein the subject has at least one mutation in one or more sequences encoding:

ABL1, ACVR1, AKT1, AKT2, ALK, APC, AR, ARID1A, ARID1B, ASXL1, ATM, ATRX, AURKA, AXIN2, BAP1, BCL2, BCR, BLM, BMPR1A, BRAF, BRCA1, BRCA2, BRIP1, BTK, BUB1B, CALR, CBL, CCND1, CCNE1, CDC73, CDH1, CDK4, CDK6, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CEBPA, CHEK2, CIC, CREBBP, CSF1R, CTNNB1, CYLD, DAXX, DDB2, DDR2, DICER1, DNMT3A, EGFR, EP300, ERBB2, ERBB3, ERBB4, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, ESR1, ETV1, ETV5, EWSR1, EXT1, EXT2, EZH2, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FBXW7, FGFR1, FGFR2, FGFR3, FGFR4, FH, FLCN, FLT3, FLT4, FOXL2, GATA1, GATA2, GNA11, GNAQ, GNAS, GPC3, H3F3A, H3F3B, HNF1A, HRAS, IDH1, IDH2, IGF1R, IGF2R, IKZF1, JAK1, JAK2, JAK3, KDR, KIT, KRAS, MAML1, MAP2K1, MAP2K4, MDM2, MDM4, MED12, MEN1, MET, MLH1, MLL, MPL, MSH2, MSH6, MTOR, MUTYH, MYCL1, MYCN, NBN, NCOA3, NF1, NF2, NKX2-1, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NPM1, NRAS, NTRK1, PALB2, PAX5, PBRM1, PDGFRA, PHOX2B, PIK3CA, PIK3R1, PMS1, PMS2, POLD1, POLE, POLH, POT1, PRKAR1A, PRSS1, PTCH1, PTEN, PTPN11, RAD51C, RAF1, RB1, RECQL4, RET, RNF43, ROS1, RUNX1, SBDS, SDHAF2, SDHB, SDHC, SDHD, SF3B1, SMAD2, SMAD3, SMAD4, SMARCB1, SMO, SRC, STAG2, STK11, SUFU, TERT, TET2, TGFB2, TNFAIP3, TOP1, TP53, TSC1, TSC2, TSHR, VHL, WAS, WRN, WT1, XPA, XPC, and/or XRCC1.

4. The method of any one of claims 1-3, wherein the subject has at least one mutation in one or more sequences encoding:

ARID1A, ATM, B2M, BCL2, BCL6, BCL7A, BRAF, BTG1, CARD11, CCND3, CD58, CD79B, CDKN2A, CREBBP, EP300, EZH2, FOXO1, GNA13, HIST1H1B, HIST1H1C, HIST1H1E, IKZF3, IRF4, ITPKB, KDM6A, KIT, KMT2D, KRAS, MEF2B, MYC, MYD88, NOTCH1, NOTCH2, NRAS, PIK3CA, PIM1, POU2F2, PRDM1, PTEN, PTPN1, PTPN11, PTPN6, PTPRD, RB1, S1PR2, SGK1, SMARCB1, SOCS1, STAT6, TBL1XR1, TNFAIP3, TNFRSF14, TP53, and/or XPO1.

5. The method of any one of claims 1-4, wherein the subject has at least one mutation in one or more sequences encoding:

AKT1, ALK, ARID1A, ATM, B2M, BCL2, BCL6, BCL7A, BTG2, CARD11, CCND3, CD79B, CDKN2A, CREBBP, EP300, EZH2, FBXW7, FOXO1, HLA-C, HRAS, IKZF3, IRF4, KDM6A, KRAS, MEF2B, MYD88, NOTCH1, NPM1, NRAS, PIK3CA, PIM1, PRDM1, PTEN, RB1, RBBP4, SMARCB1, SUZ12, TNFRSF14, and/or TP53.

6. The method of any one of claims 1-5, wherein the subject has at least one mutation in one or more sequences encoding:

ALK, EWSR1, ROS1, BCL2, MLL, Tmprss2, BCR, MYC, FGFR3, BRAF, NTRK1, TACC3, DNAB1, PDGFRA, EGFR, PDGFRB, ETV1, PRKACA, ETV4, RAF1, ETV5, RARA, ETV6, and/or RET.

7. The method of any one of claims 1-6, wherein the subject has at least one mutation in one or more sequences encoding:

ALK (Intron 19), BCL2 (MBR breakpoint region), BCL2 (MCR breakpoint region), BCL6, CD274, CIITA, MYC (entire Gene + 40kbp upstream), and/or PDCD1LG2.

8. The method of any one of claims 1-7, wherein the subject has at least one mutation in one or more sequences encoding:

BCL2, CD274 (PDL1), FOXP1, JAK2, KDM4C, PDCD1LG2 (PDL2), and/or REL.

9. The method of any one of claims 1-8, wherein the subject has at least one mutation in one or more sequences encoding:

ARID1A, ATM, B2M, BCL2, BCL6, BCL7A, BRAF, CARD11, CCND3, CD274 (PDL1), CD58, CD79B, CDKN2A, CIITA, CREBBP, EZH2 (non-Y646), EZH2 (Y646), EP300, FOXO1, FOXP1, GNA13, HIST1H1B, HIST1H1C, HIST1H1E, IRF4, IKZF3, JAK2, KDM4C, KDM6A, KIT, KMT2D, KRAS, MEF2B, MYC, MYD88, NOTCH1, NOTCH2, NRAS, PDCD1LG2 (PDL2), PIK3CA, PIM1, POU2F2, PRDM1, PTEN, PTPN11, PTPN6, PTPRD, REL, SOCS1, STAT6, TNFAIP3, TNFRSF14, and/or TP53.

10. The method of any one of claims 1-9, wherein the subject has at least one mutation in one or more sequences encoding:

ARID1A, B2M, BCL2, BCL6, CARD11, CCND3, CD274 (PDL1), CD58, CD79B, CDKN2A, CREBBP, EZH2, EP300, FOXO1, GNA13, HIST1H1B, HIST1H1C, HIST1H1E, KMT2D, KRAS, MEF2B, MYC, MYD88 (273P), PDCD1LG2 (PDL2), PIM1, POU2F2, PRDM1, SOCS1, STAT6, TNFAIP3, and/or TNFRSF14.

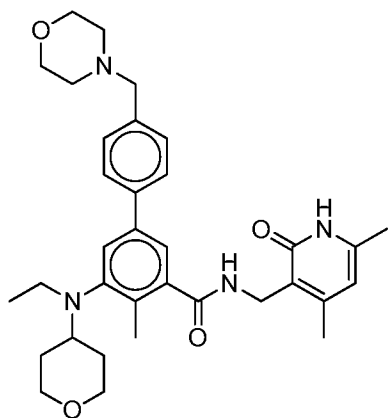
11. The method of any one of claims 1-10, wherein the at least one mutation decreases the function of a protein encoded by the mutated sequence as compared to the function of the protein encoded by the wild-type sequence.

12. The method of any one of claims 1-10, wherein the at least one mutation is a loss-of-function mutation.

13. The method of any one of claims 1-12, wherein the method further comprises detecting the at least one mutation in the subject.

14. The method of claim 13, wherein the detecting comprises subjecting a sample obtained from the subject to a sequence analysis assay.

15. The method of any one of claims 1-14, wherein the inhibitor of EZH2 is



(tazemetostat),

or a pharmaceutically-acceptable salt thereof.

16. The method of any one of claims 1-15, wherein the inhibitor of EZH2 is administered orally.

17. The method of claim 16, wherein the inhibitor of EZH2 is formulated as a tablet.
18. The method of any one of claims 1-17, wherein the therapeutically effective amount of the inhibitor of EZH2 is between 100 mg and 3200 mg per day.
19. The method of claim 18, wherein the therapeutically effective amount of the inhibitor of EZH2 is 100 mg, 200 mg, 400 mg, 600 mg, 800 mg, 1000 mg, 1200 mg, 1400 mg, 1600 mg or 3200 mg per day.
20. The method of claim 19, wherein the therapeutically effective amount is 1600 mg per day.
21. The method of any one of claims 1-20, wherein the therapeutically effective amount of the inhibitor of is administered at 800 mg twice per day (BID).
22. The method of any one of claims 1-21, wherein the at least one mutation decreases a level of acetylation of a lysine (K) on histone (3) compared to a level of acetylation of the same lysine by a wild type HAT.
23. The method of claim 22, wherein the lysine (K) on histone (3) is at position 27 (H3K27).
24. The method of any one of claims 1-23, wherein the at least one mutation occurs in a sequence of an EP300 gene or in a sequence encoding histone acetyltransferase p300.
25. The method of claim 24, wherein the at least one mutation results in a substitution of tyrosine (Y) for aspartic acid (D) at position 1467 of histone acetyltransferase p300.
26. The method of any one of claims 1-25, wherein the at least one mutation results in a substitution of serine (S) for phenylalanine (F) at position 1289 of histone acetyltransferase p300.

27. The method of any one of claims 1-26, wherein the at least one mutation occurs in a sequence of a CREB binding protein gene or in a sequence encoding CREBBP.
28. The method of claim 27, wherein the at least one mutation results in a substitution of phosphate (P) for threonine (T) at position 1494 of CREBBP.
29. The method of claim 27, wherein the at least one mutation results in a substitution of arginine (R) for Leucine (L) at position 1446 of CREBBP.
30. The method of claim 27, wherein the at least one mutation results in a substitution of Leucine (L) for phosphate (P) at position 1499 of CREBBP.
31. The method of any one of claims 1-30, wherein the subject expresses a wild type EZH2 protein and does not express a mutant EZH2 protein.
32. The method of any one of claims 1-30, wherein the subject expresses a mutant EZH2 protein.
33. The method of claim 32, wherein the mutant EZH2 protein comprises a substitution of any amino acid other than tyrosine (Y) for tyrosine (Y) at position 641 of SEQ ID NO: 1.
34. The method of claim 32 or 33, wherein the mutant EZH2 protein comprises a substitution of any amino acid other than alanine (A) for alanine (A) at position 682 of SEQ ID NO: 1.
35. The method of any one of claims 32-34, wherein the mutant EZH2 protein comprises a substitution of any amino acid other than alanine (A) for alanine (A) at position 692 of SEQ ID NO: 1.
36. The method of any one of claims 1-35, wherein the at least one mutation comprises a MYD88, STAT6A, and/or a SOCS1 mutation.

37. The method of any one of claims 1-36, wherein the subject does not have a MYC and/or a HIST1H1E mutation.
38. The method of any one of claims 1-37, wherein the subject (a) has a MYD88, STAT6A, and/or a SOCS1 mutation, and (b) does not have a MYC and/or a HIST1H1E mutation.
39. The method of any one of claims 1-38, wherein the subject has a mutation in a sequence encoding a human histone acetyltransferase (HAT).
40. The method of any one of claims 1-39, wherein the subject is a human subject.
41. The method of any one of claims 1-40, wherein the subject has cancer.
42. The method of claim 41, wherein the cancer is B-cell lymphoma.
43. The method of claim 42, wherein the B-cell lymphoma is an activated B-cell (ABC) type.
44. The method of claim 42, wherein the B-cell lymphoma is a germinal B-cell (GBC) type.
45. The method of claim 41, wherein the cancer is follicular lymphoma.
46. A method, comprising selecting a subject having cancer for treatment with an EZH2 inhibitor based on the presence of at least one mutation associated with a positive response to such treatment in the subject and/or based on the absence of at least one mutation associated with no response or with a negative response to such treatment in the subject.
47. The method of claim 46, wherein the at least one mutation associated with a positive response comprise
(a) an EZH2 mutation;

- (b) a histone acetyl transferase (HAT) mutation;
- (c) a STAT6 mutation;
- (d) a MYD88 mutation; and/or
- (e) a SOCS1 mutation.

48. The method of claim 46 or 47, wherein the at least one mutation associated with no response or with a negative response comprise

- (a) a MYC mutation; and/or
- (b) a HIST1H1E mutation.

49. The method of any one of claims 46-48, wherein the method comprises detecting the at least one mutation associated with a positive response and/or the at least one mutation associated with no response or a negative response in a sample obtained from the subject.

50. The method of any one of claims 46-49, wherein the method comprises selecting the subject for treatment with the EZH2 inhibitor based on the subject

- (a) having at least one of a MYD88 mutation, a STAT6A mutation, and a SOCS1 mutation, and
- (b) not having at least one of a MYC mutation and/or a HIST1H1E mutation.

51. The method of any one of claims 46-49, wherein the method comprises selecting the subject for treatment with the EZH2 inhibitor based on the subject

- (a) having at least one of a MYD88 mutation, a STAT6A mutation, and a SOCS1 mutation, and
- (b) not having a MYC mutation and a HIST1H1E mutation.

52. The method of any one of claims 1-51, wherein the at least one mutation consists of a single mutation.

53. The method of any one of claims 1-51, wherein the at least one mutation comprises 2 mutations or more.

54. The method of any one of claims 1-53, wherein the at least one mutation comprises 3 mutations or more.

55. The method of any one of claims 1-54, wherein the at least one mutation comprises 4 mutations or more.

56. A method, comprising selecting a subject having cancer for treatment with an EZH2 inhibitor based on the presence of a mutation profile in the subject that matches a mutation profile of a patient exhibiting a complete or partial response or stable disease in any of Figures 19-22.

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FIGURE 1

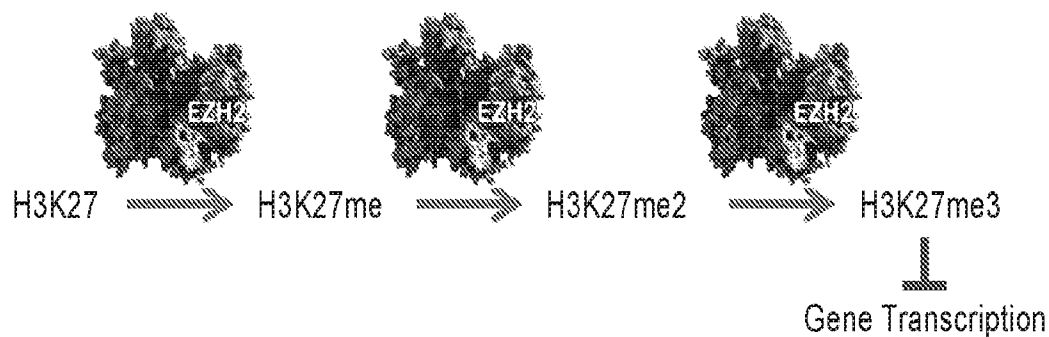


FIGURE 2

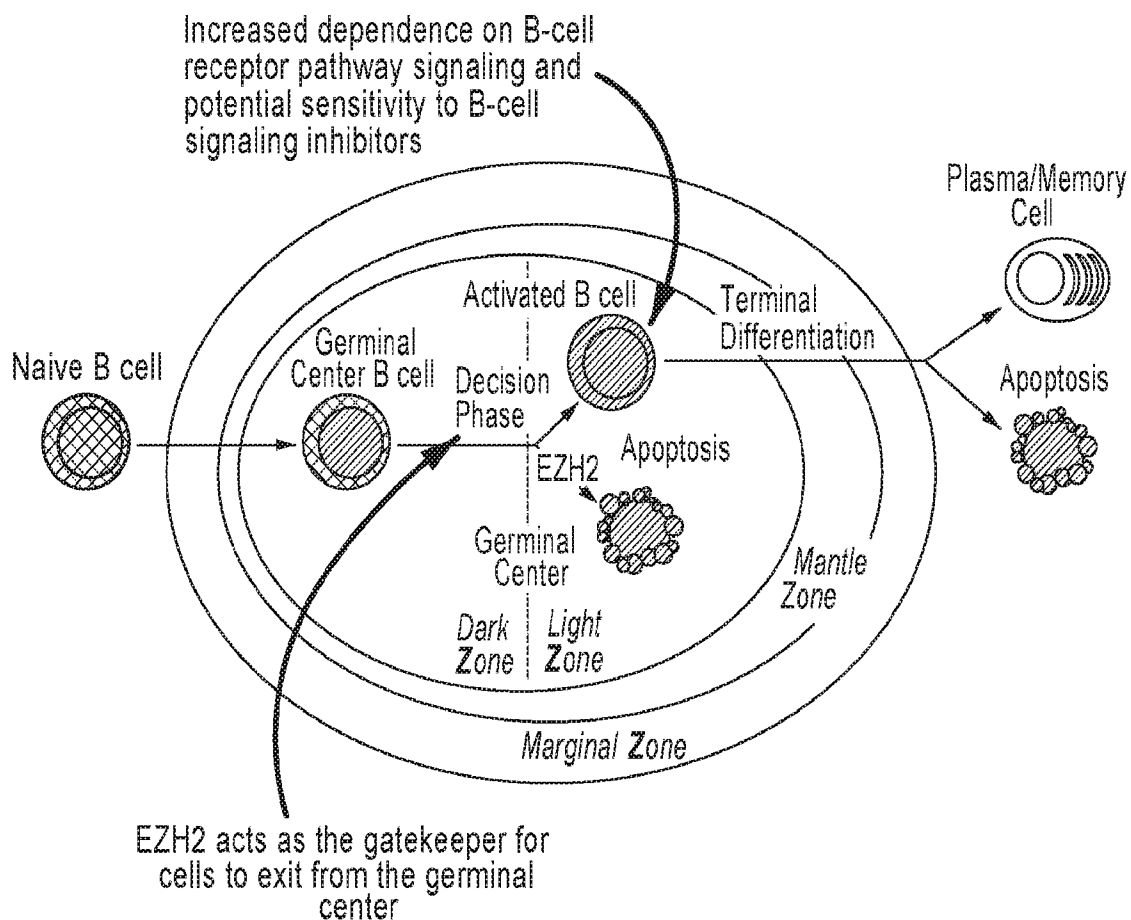
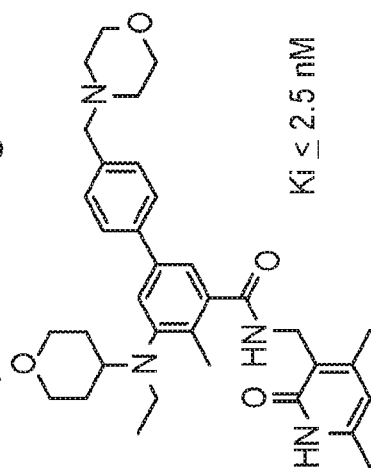
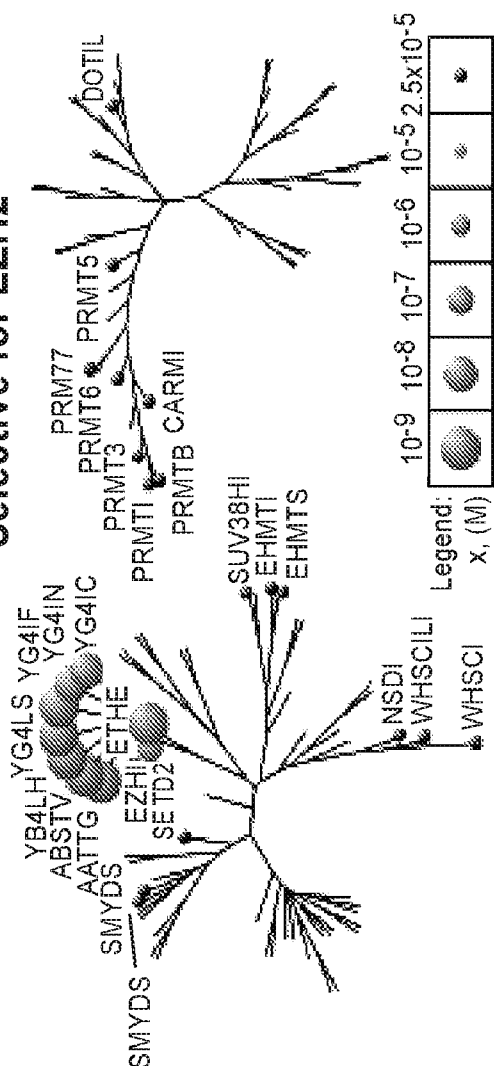


FIGURE 3

Novel Structure, Potent Target Inhibition



Selective for EZH2



Antitumor Activity in EZH2 Mutant and WT Xenograft Models of DLBCL

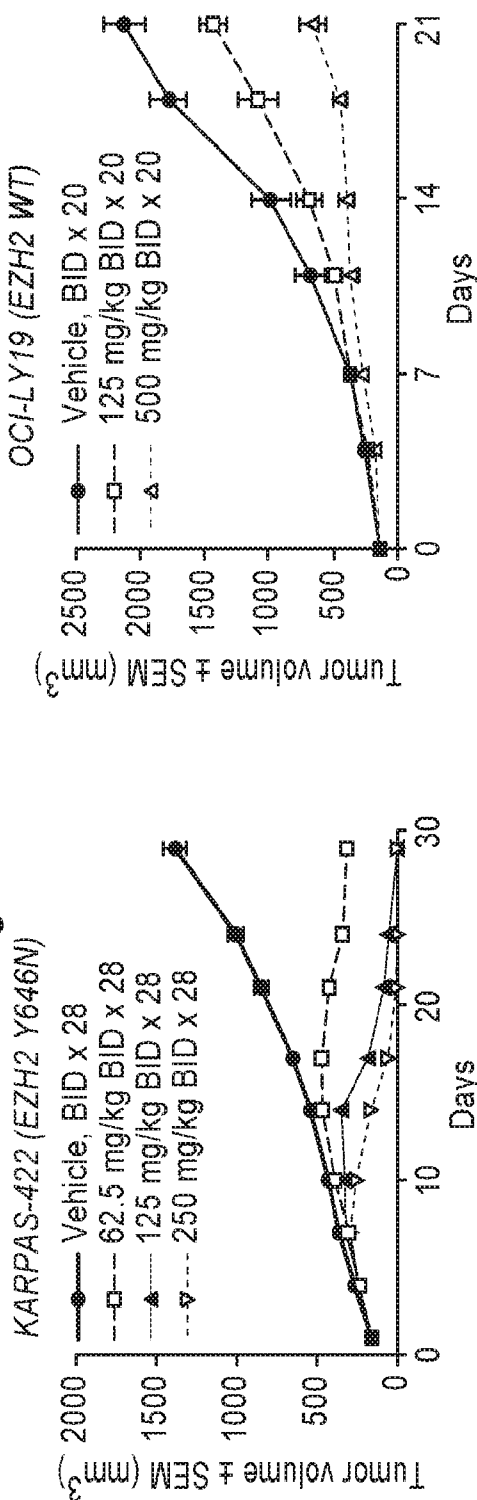


FIGURE 4

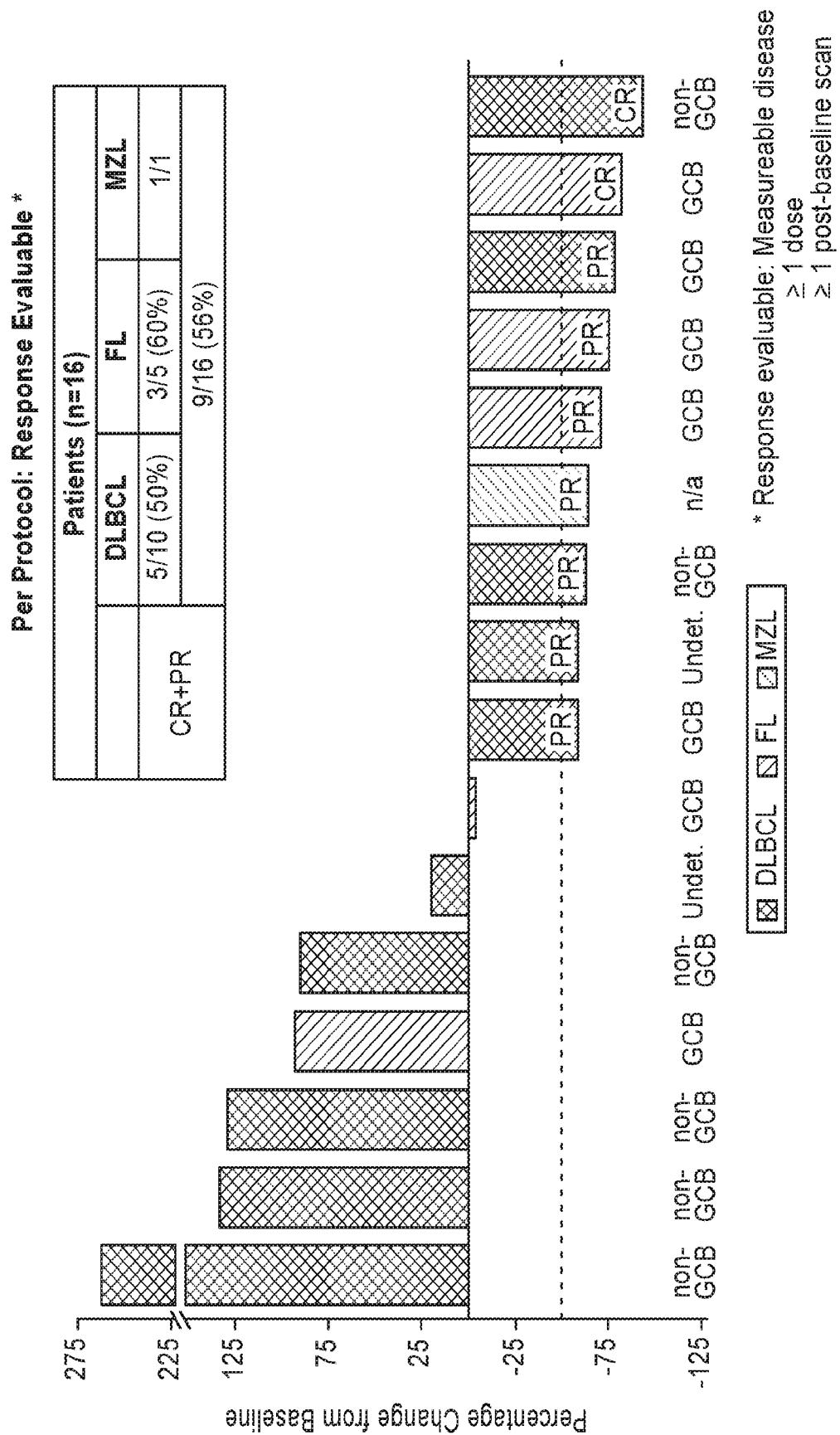


FIGURE 5

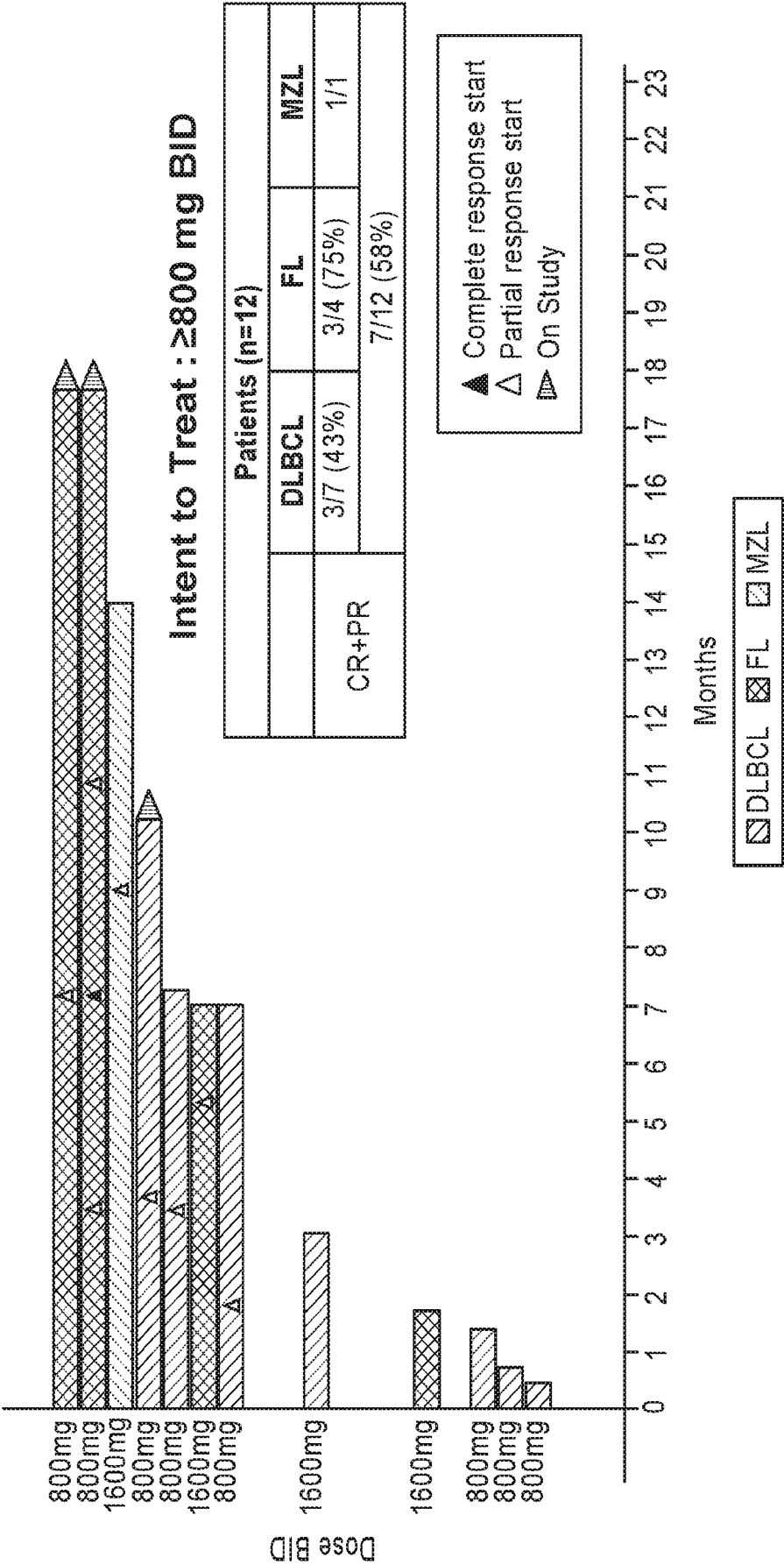


FIGURE 6

53 year old female (EZH2^{Y646H}) treated at RP2D (800 mg BID)

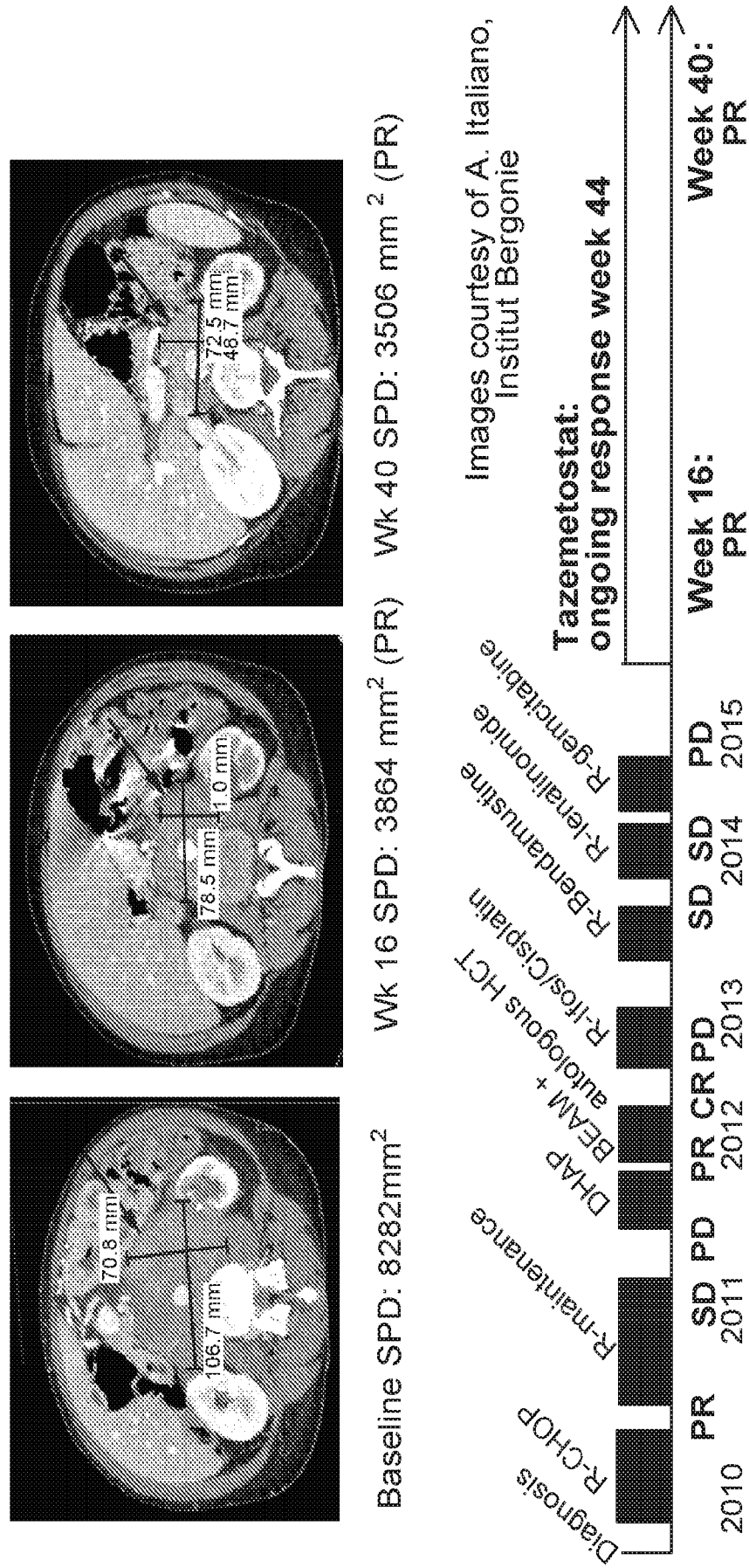


FIGURE 7

Dose BID	Efficacy	Safety	PK/PD
	Response in NHL (%)	Grade ≥3 TEAE *	H3K27me3 Inhibition Emax **
<800 mg	2/9 (22%)	7/24 (29%)	-
800 mg	5/8 (62%)	3/19 (16%)	80%
1600 mg	2/4 (50%)	4/12 (33%)	84%

* Treatment Emergent Adverse Events in all patients (n=55)

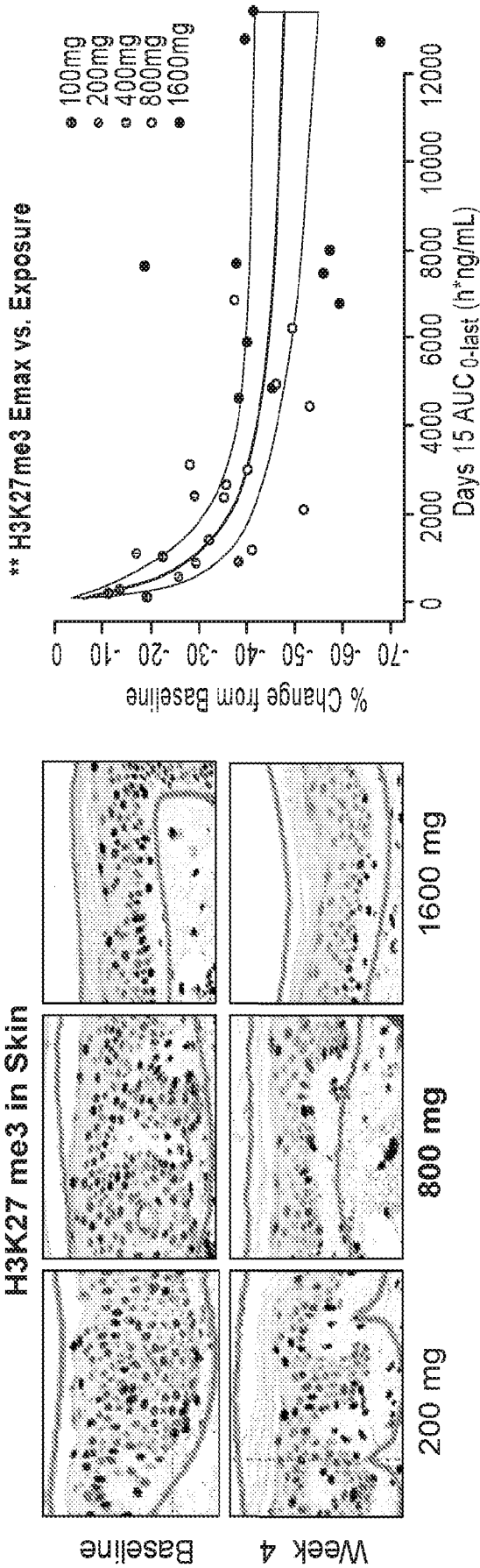
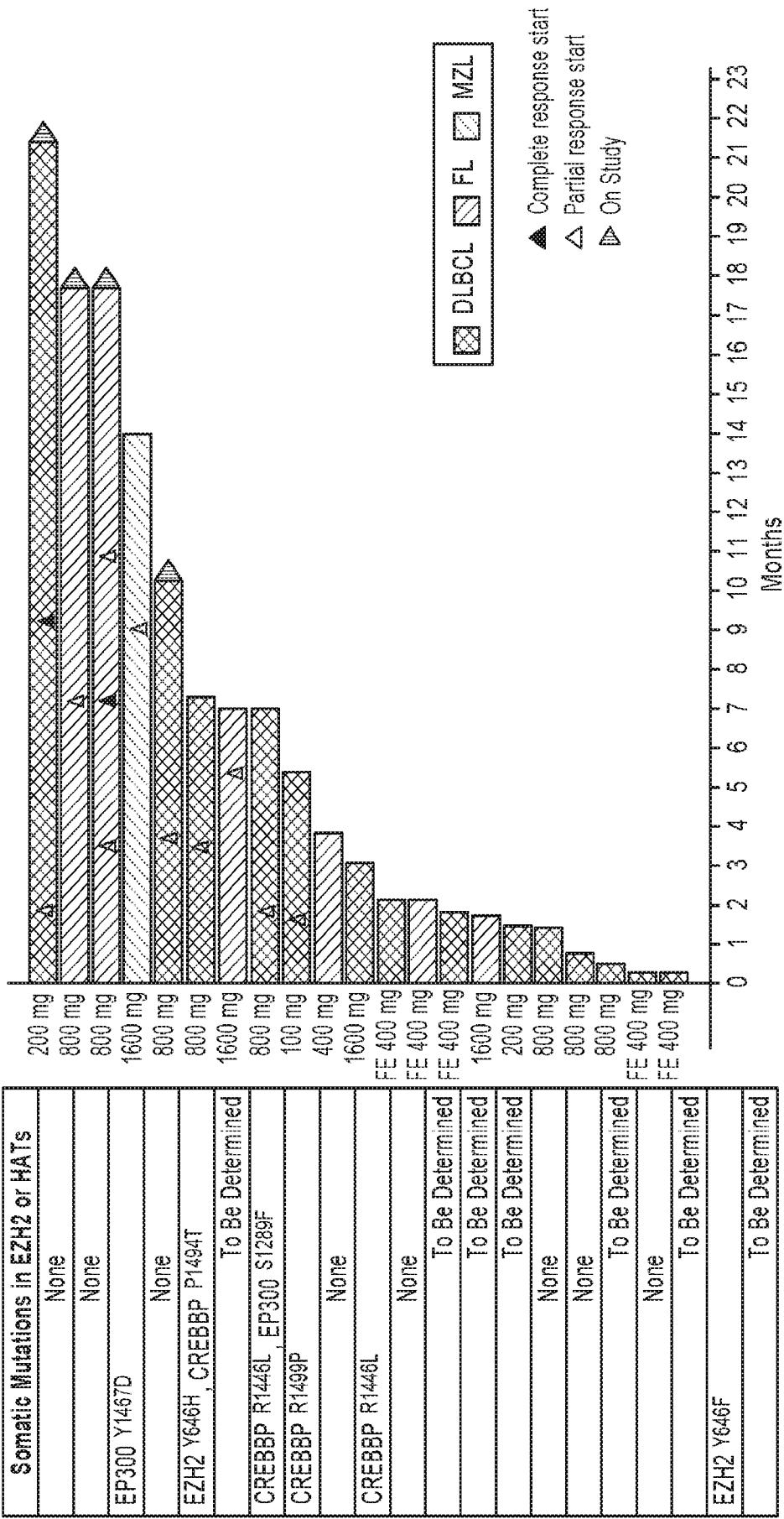
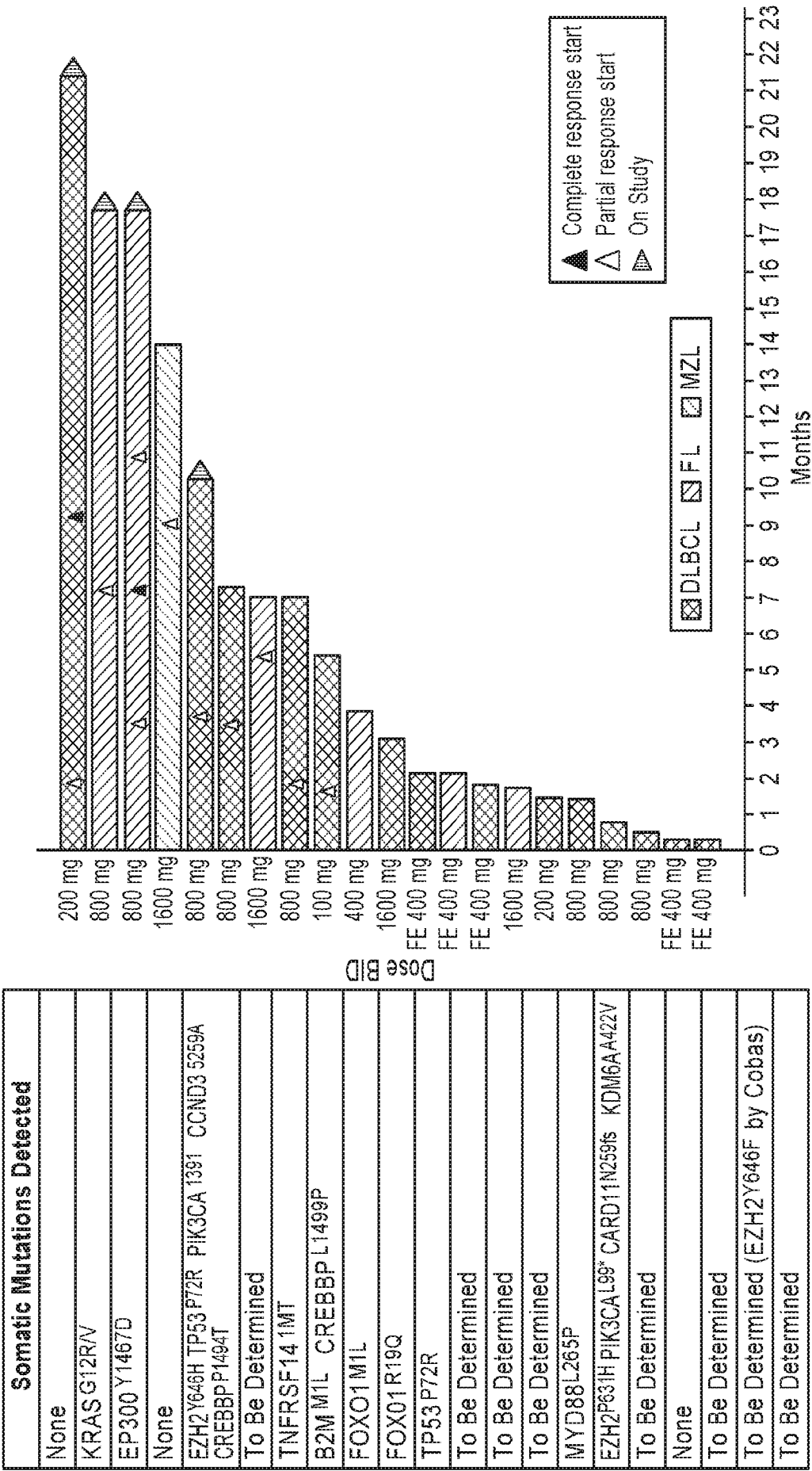


FIGURE 8



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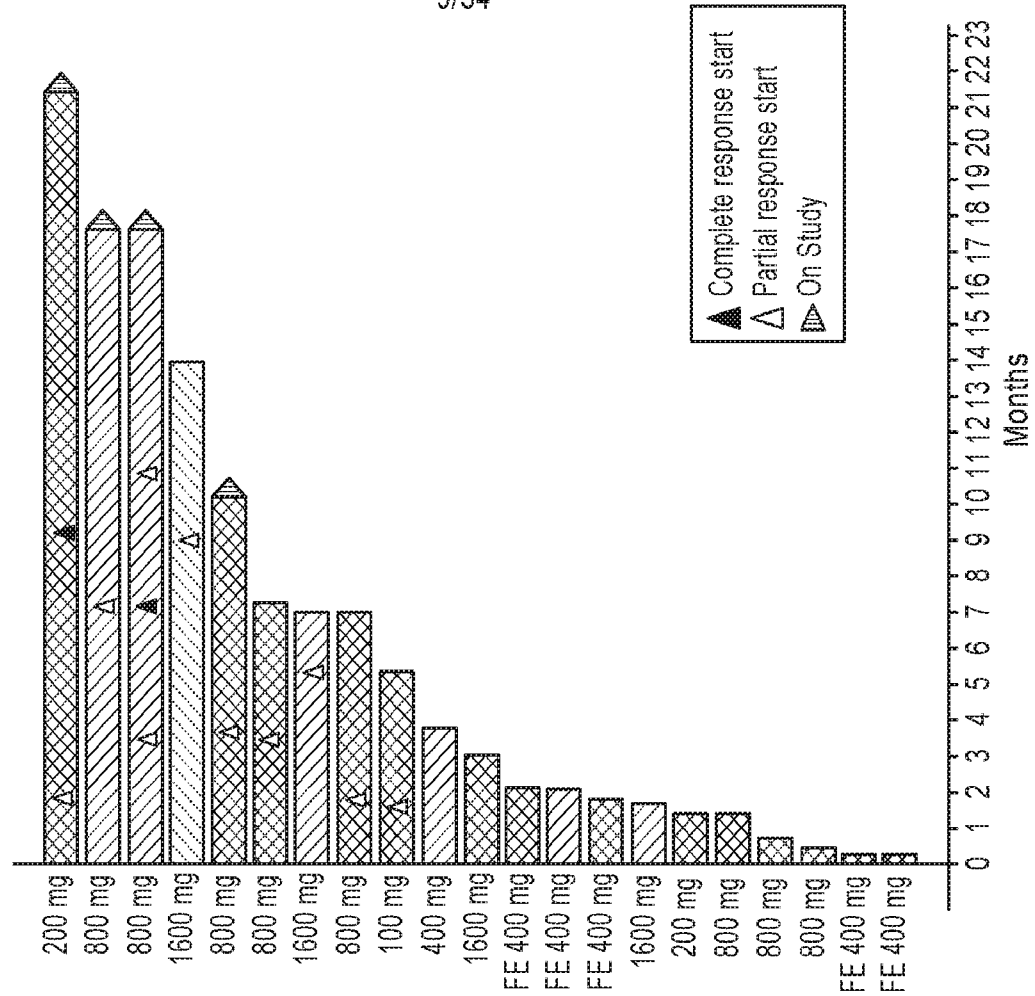
FIGURE 9



Somatic Mutations Detected
None
KRAS G12R/V
EP300 Y1467D
None
EZH2 Y646H TP53 P72R PIK3CA I391 CCND3 5259A CREBBP P1494T
To Be Determined
TNFRSF14 1MT
B2M M1L CREBBP L1499P
FOXO1 M1L
FOXO1 R19Q
TP53 P72R
To Be Determined
To Be Determined
To Be Determined
MYD88 L265P
EZH2 P631H PIK3CA L99* CARD11 N259fs KDM6A A422V
To Be Determined
None
To Be Determined
To Be Determined (EZH2 Y646F by Cobas)
To Be Determined

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FIGURE 10



Key Variants Detected >10% Allelic Frequency	
JAK2 and PDL2 amplification, SOCS1 (100T>S)	
KRAS (G12R/V)	
FGFR2 amplification, ARID1A (L298Pfs*103), ARID1B (445A>AP), EP300 (1467Y>D)	
GATA2 & FOXL2 amplification, AR (58Q>L)	
EZH2 Y646H, TP53 (P72R), PIK3CA (I391M), CREBBP (P1494T)	
To Be Determined	
AR (58Q>L), ARID1B (445A>AP), CREBBP (1446R>L), EP300 (1289S>F), MEK4 (13G>R), STAT6 (371C>R), TNFRSF14 (1M>T)	
MYCN & REL amplification, CREBBP (1489L>P), IGFR2 996L>F, STAT6 (372E>K), TNFAIP3 (N414Kfs*7), TP53 (248R>W)	
FOXO1 (M1L)	
AR (58Q>L), CREBBP (1446R>L), FGFR1 (487M>I), FGFR3 (513D>N), F OX01 (R19Q)	
TP53 (P72R)	
To Be Determined	
To Be Determined	
To Be Determined	
MYD88 (L265P)	
EZH2 (P631H), PIK3CA (L99*), CARD11 (N259fs), KDM6A (A422V)	
To Be Determined	
BCL2 & MYC translocations, BCL6 (377K>N), BCL6 (377K>X), MYC (72P>S)	
To Be Determined	
EZH2 Y646F	
To Be Determined	

FIGURE 11

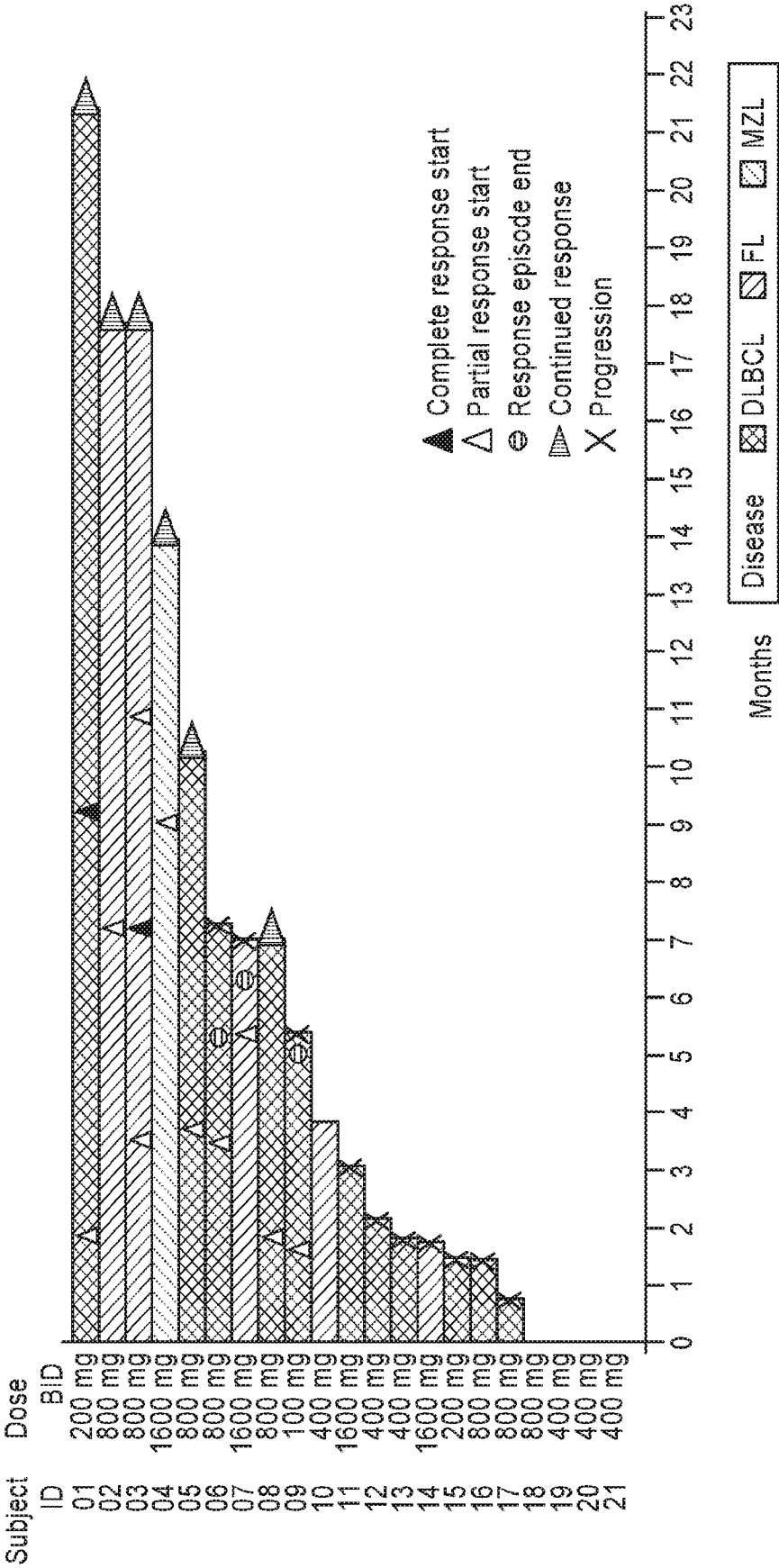
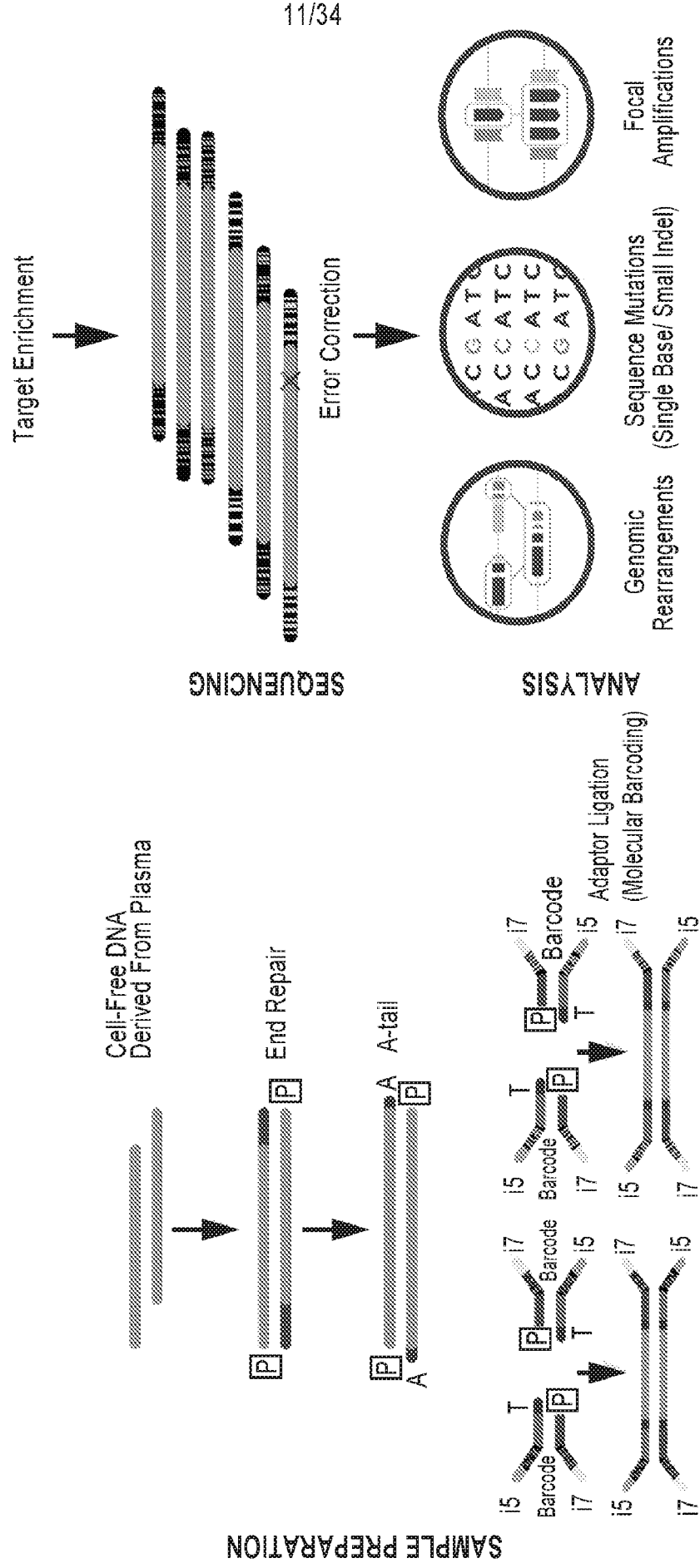


FIGURE 12



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FIGURE 13A

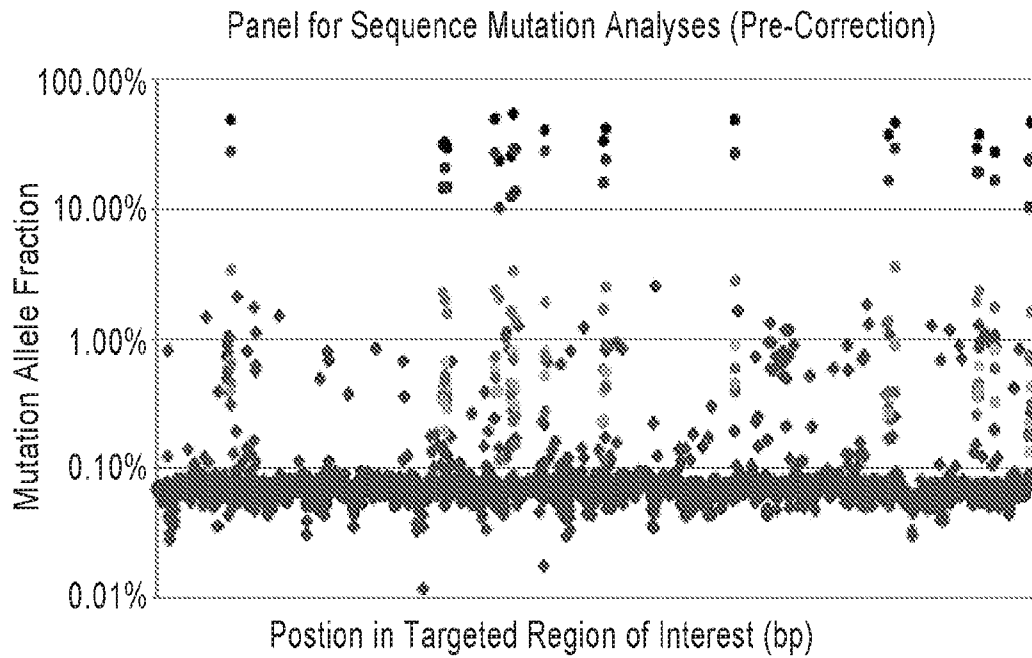


FIGURE 13B

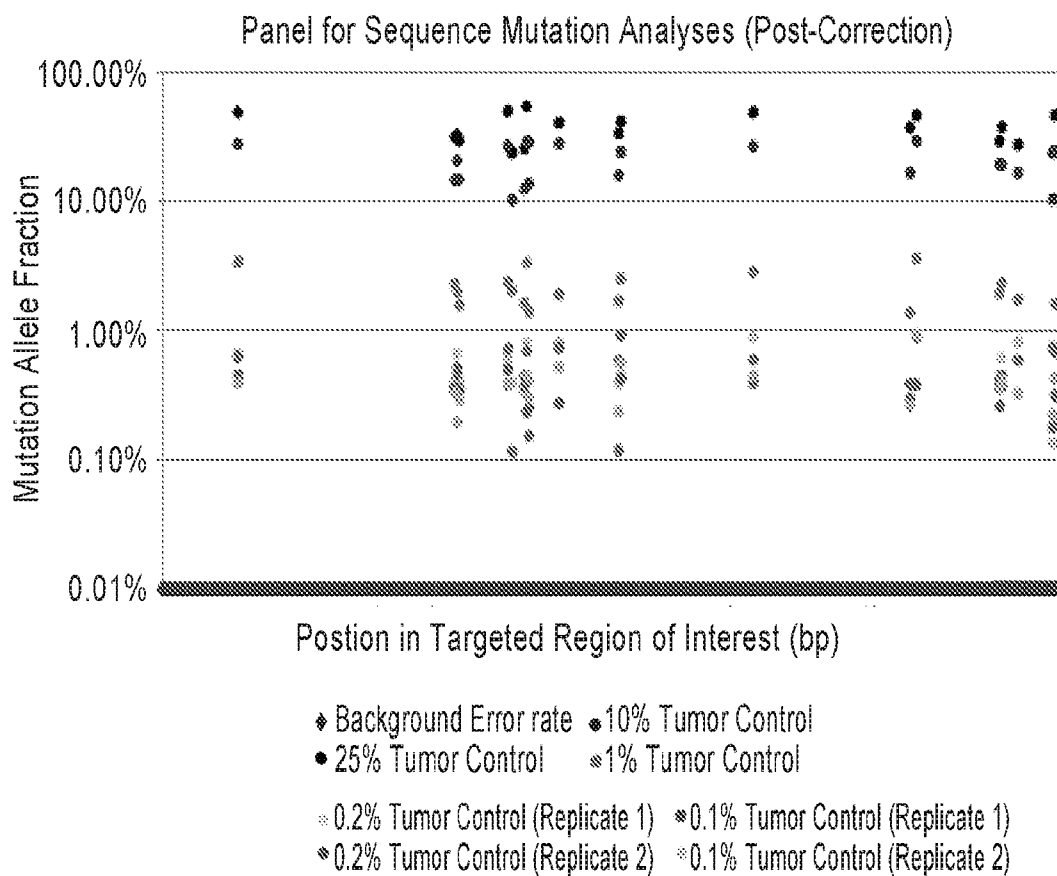
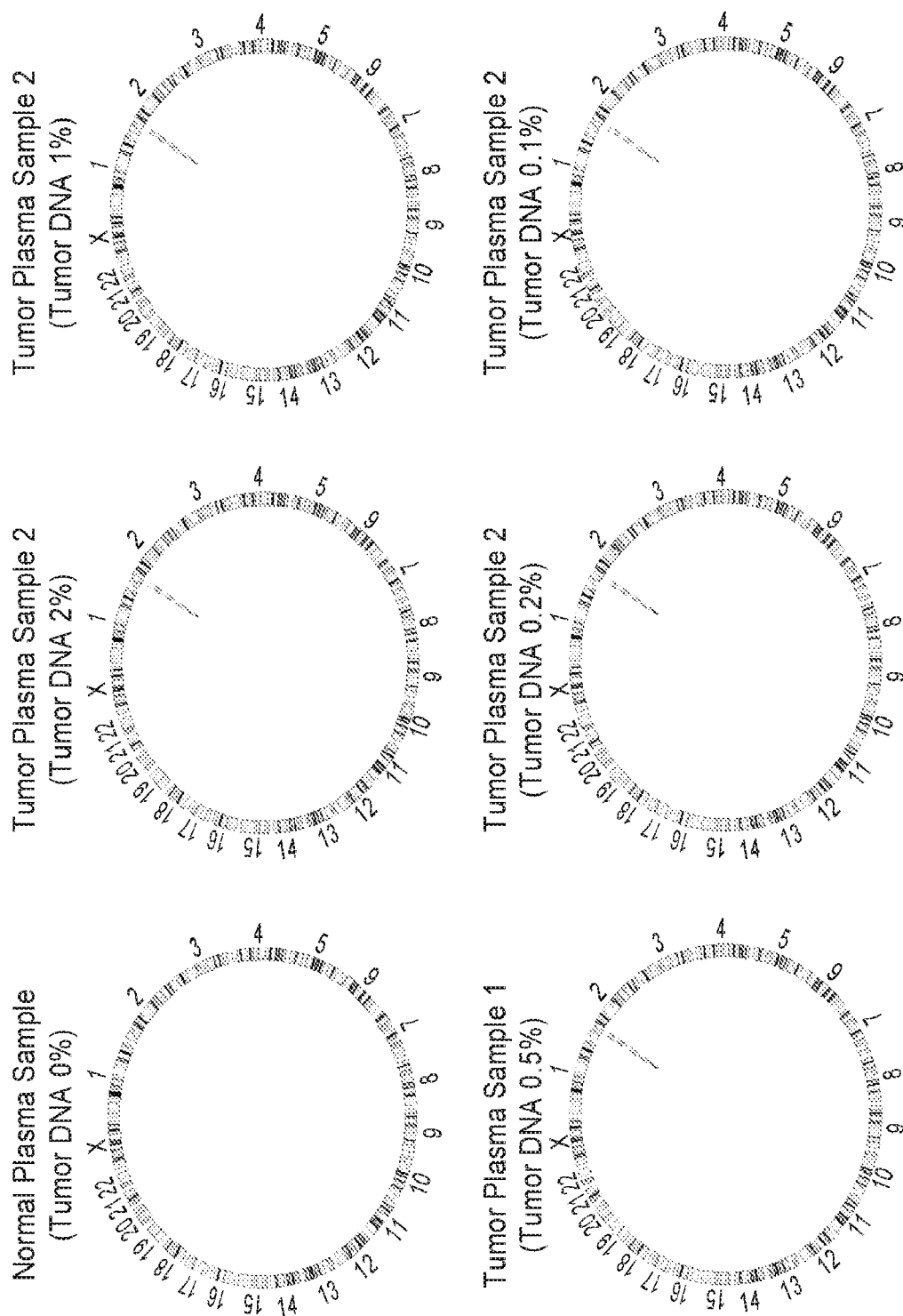
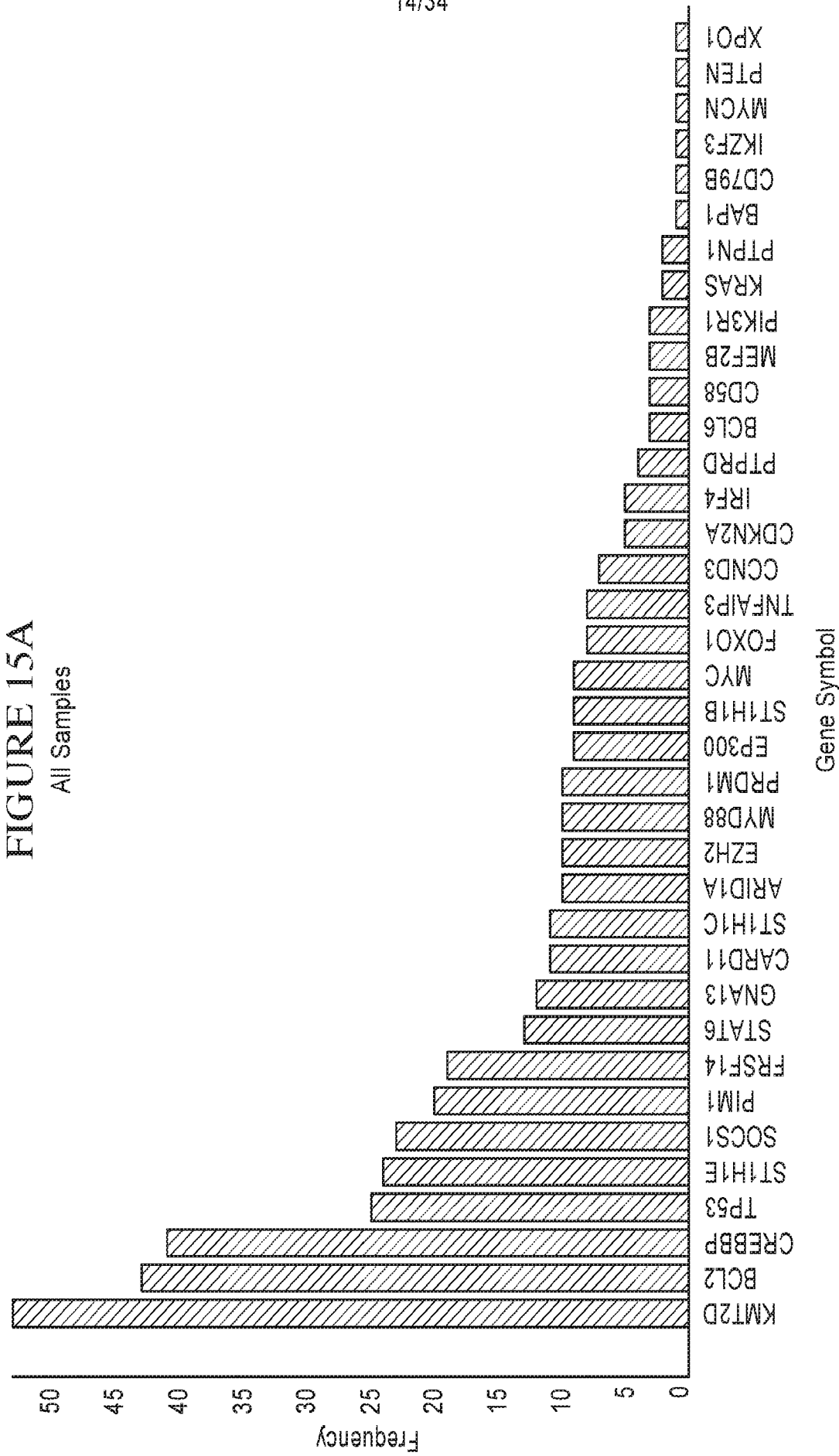


FIGURE 14





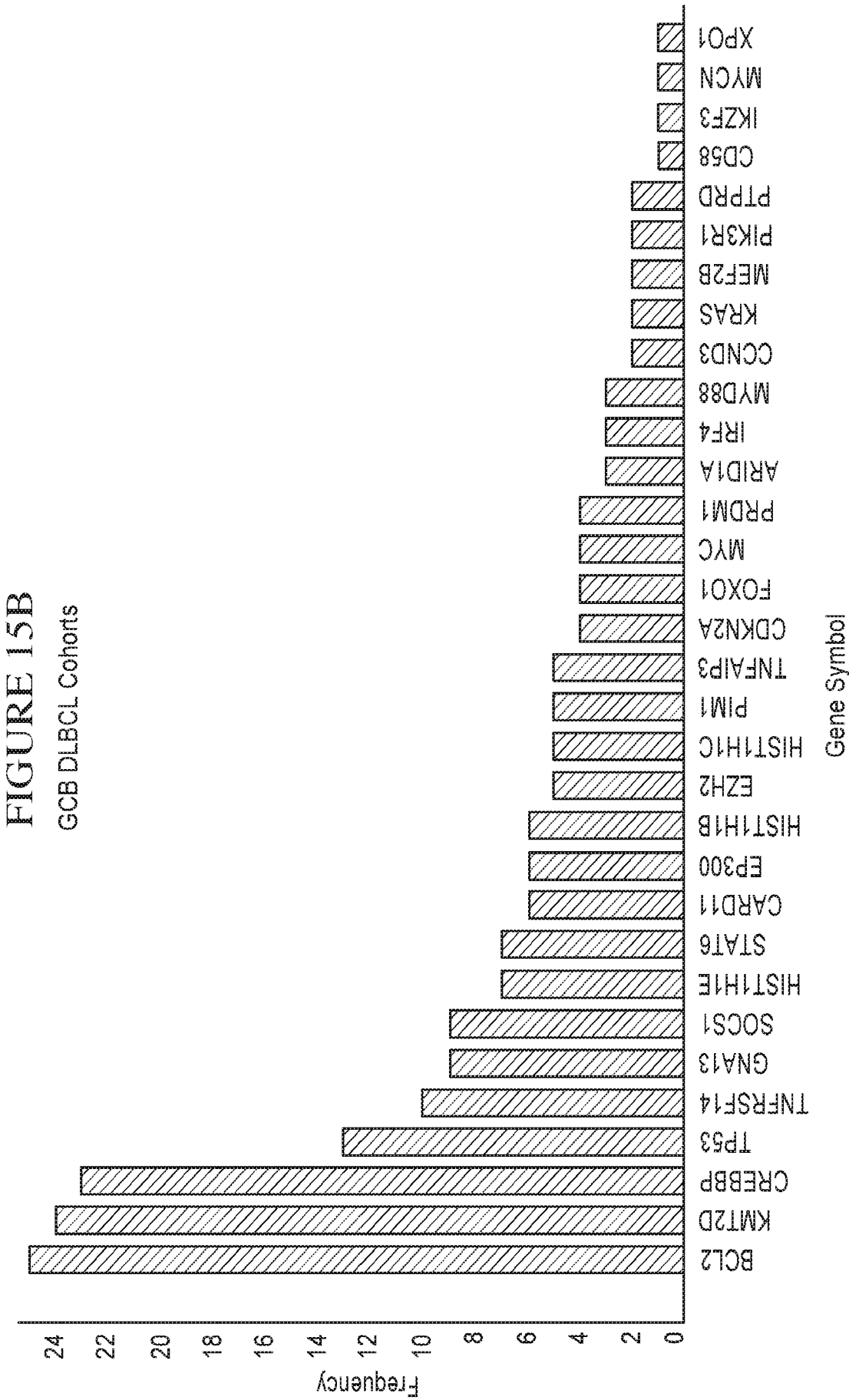


FIGURE 15C
Non-GCB DLBCL Cohort

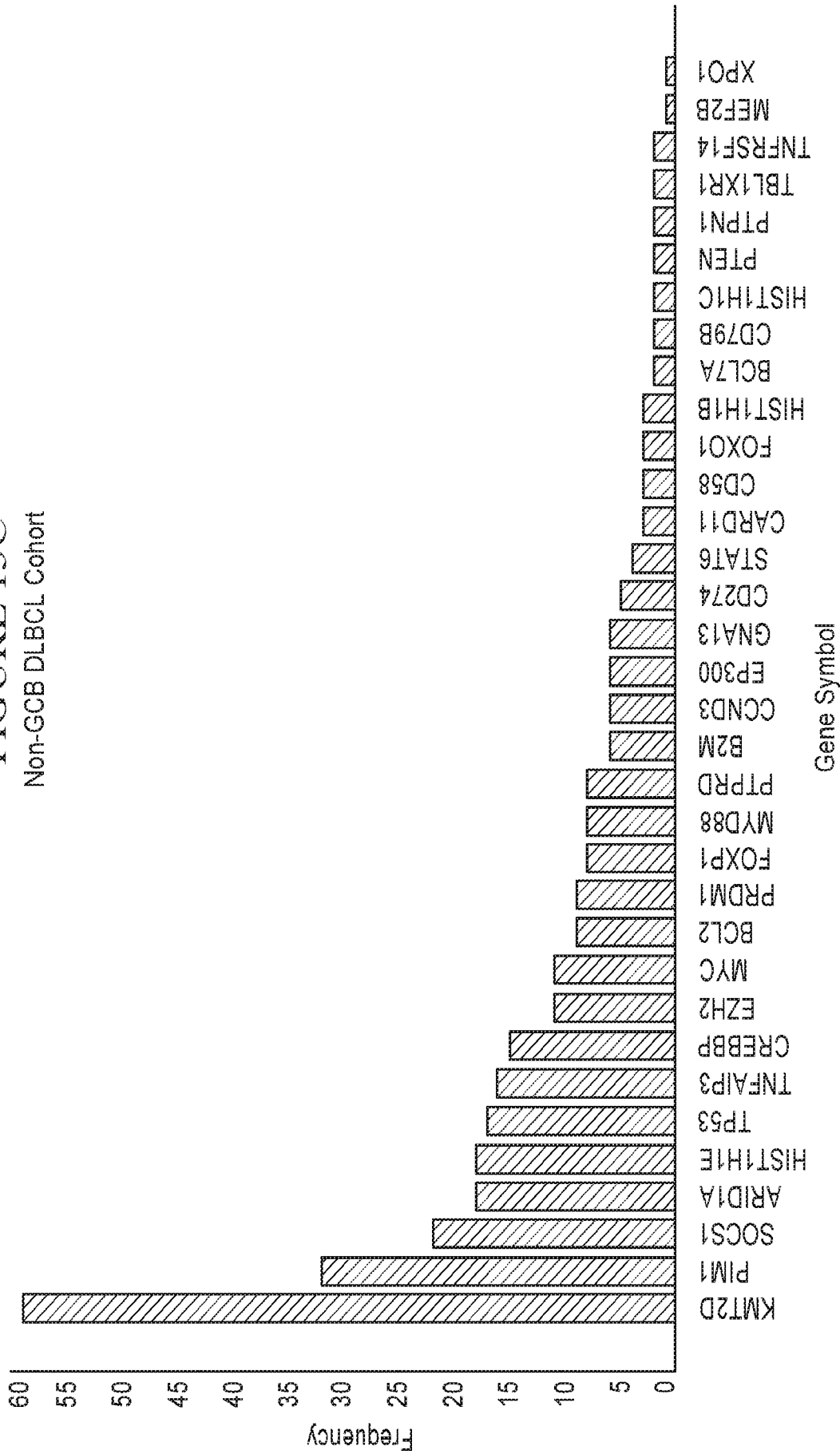


FIGURE 15D
Follicular Lymphoma - Cohorts

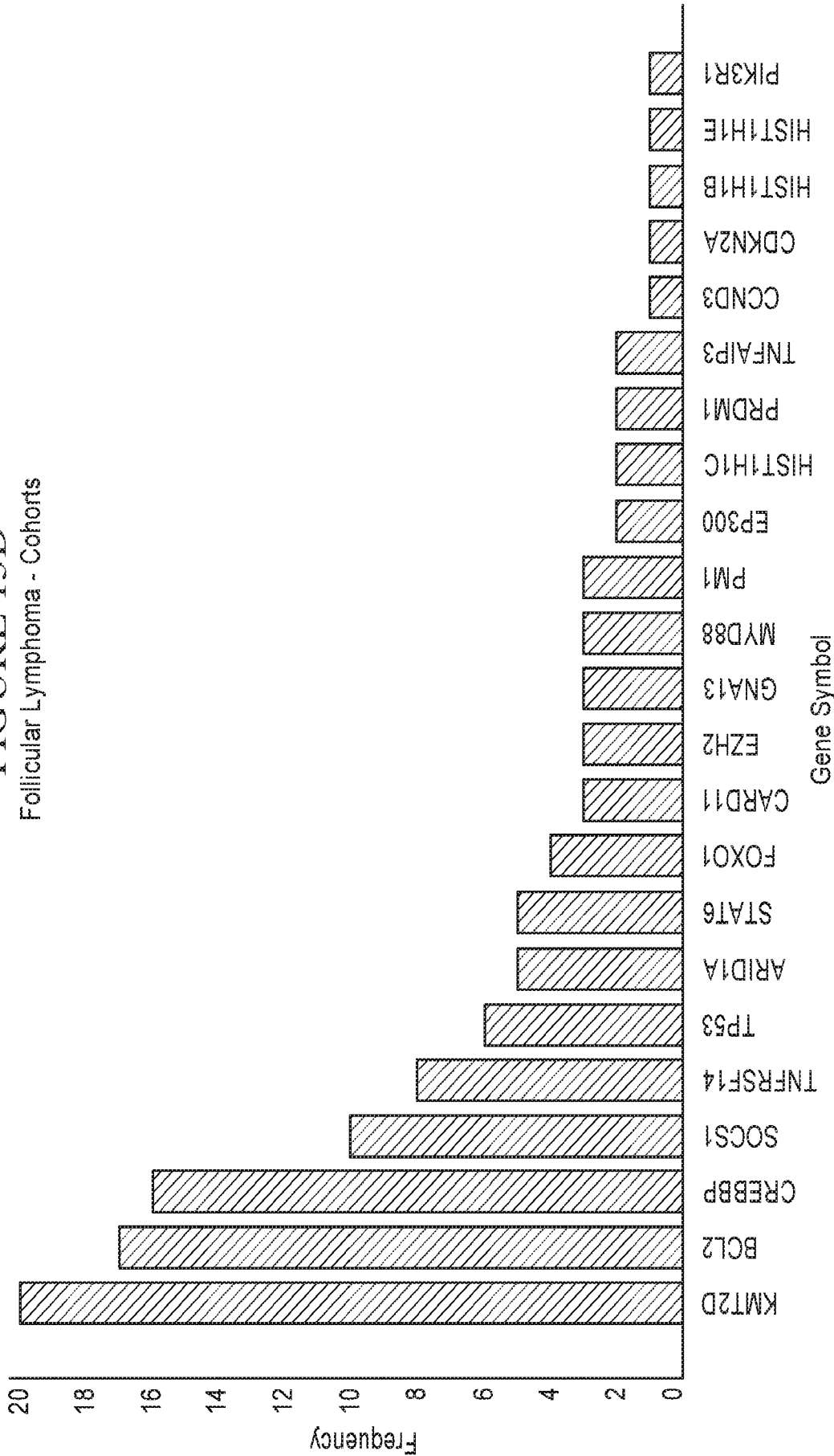
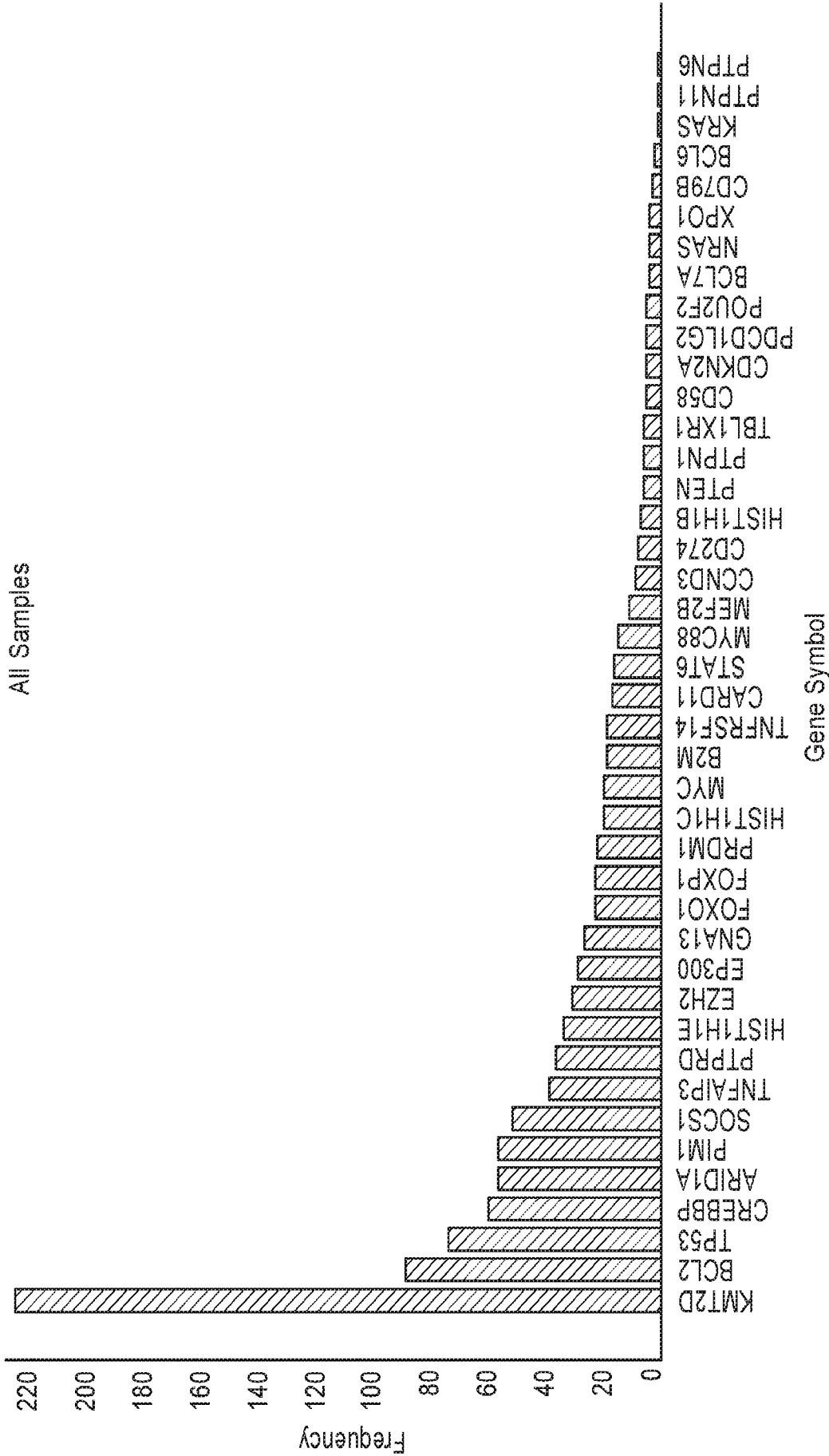


FIGURE 16A



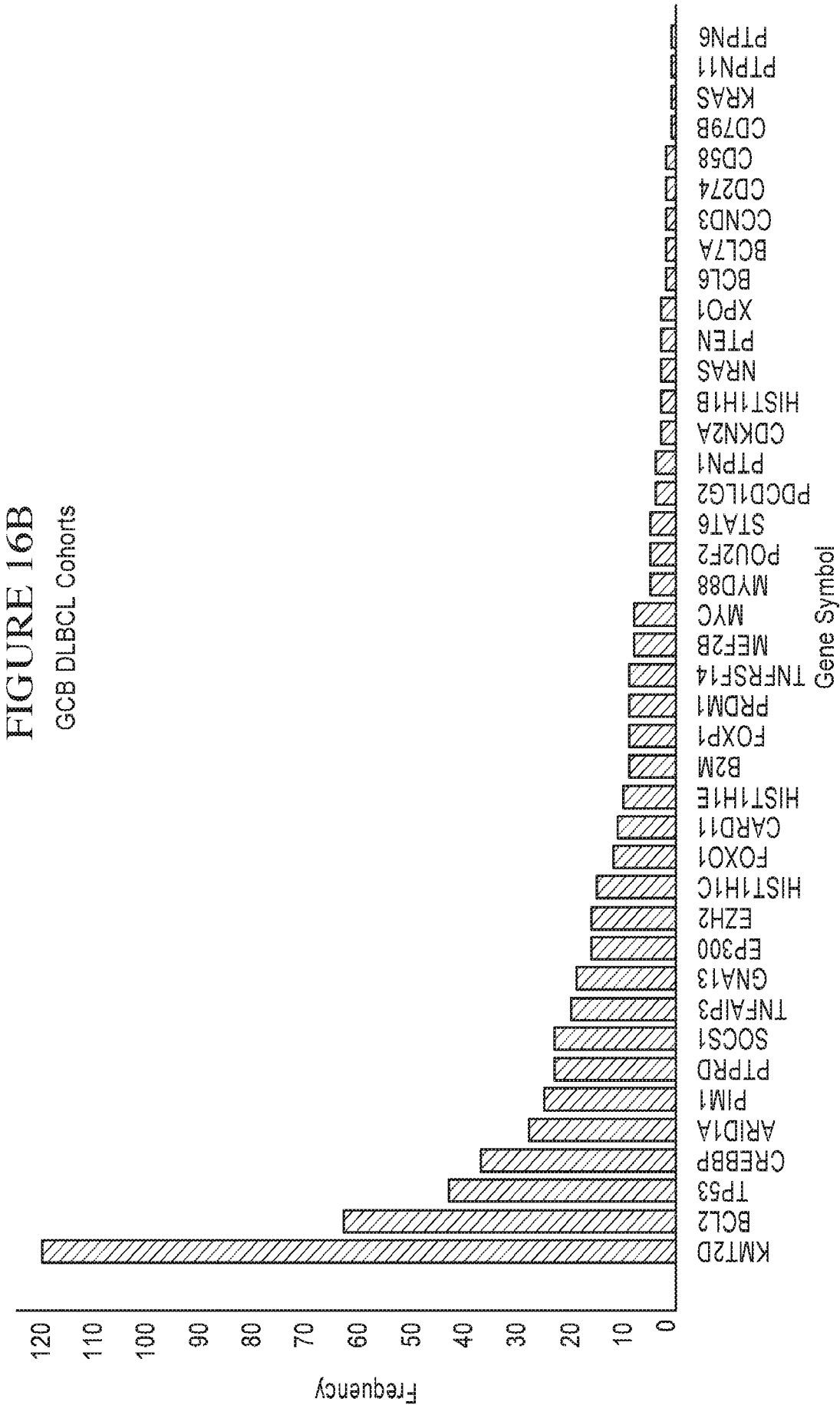


FIGURE 16C
Non-GCB DLBCL Cohort

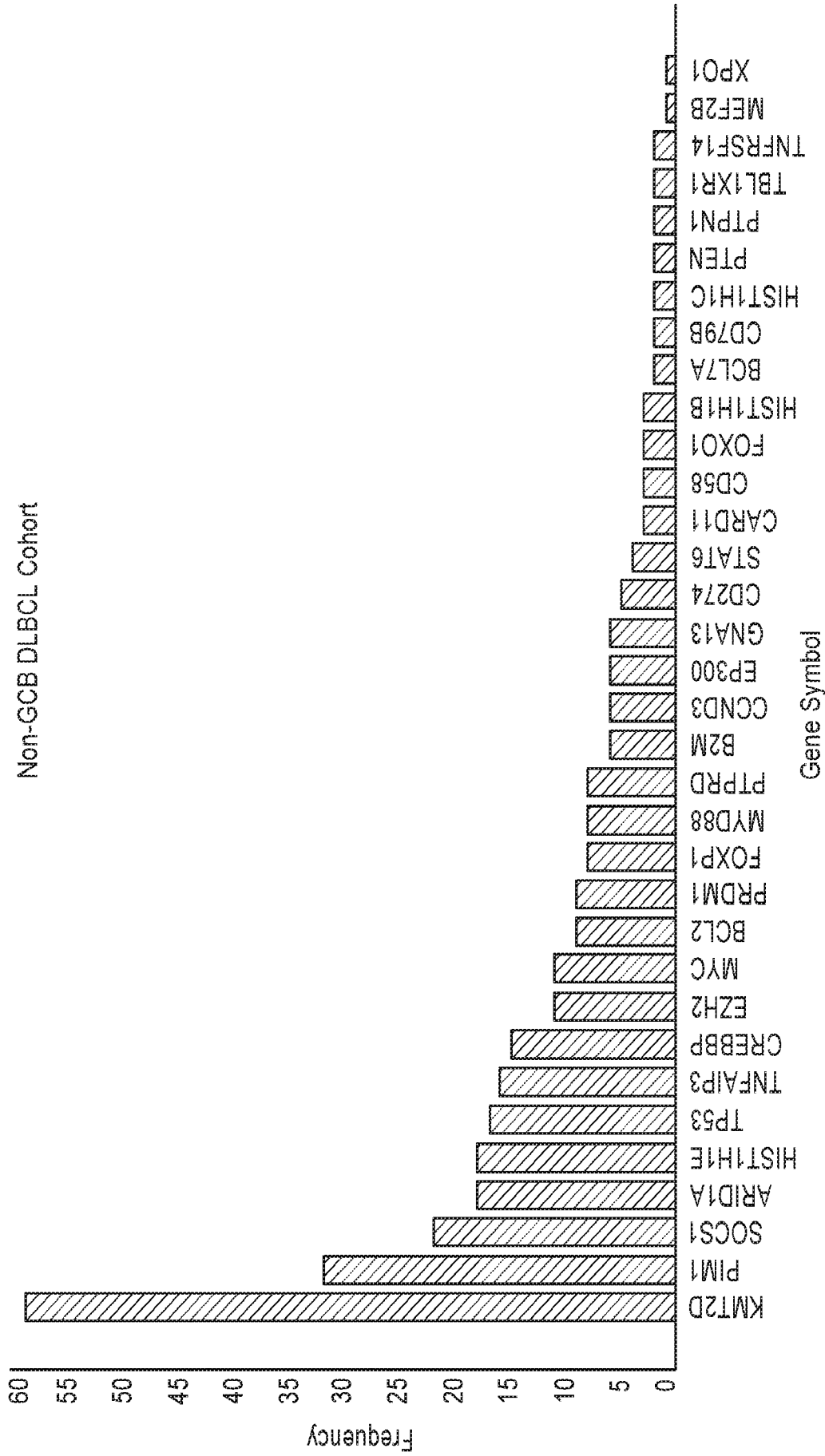


FIGURE 16D
Follicular Lymphoma - Cohorts

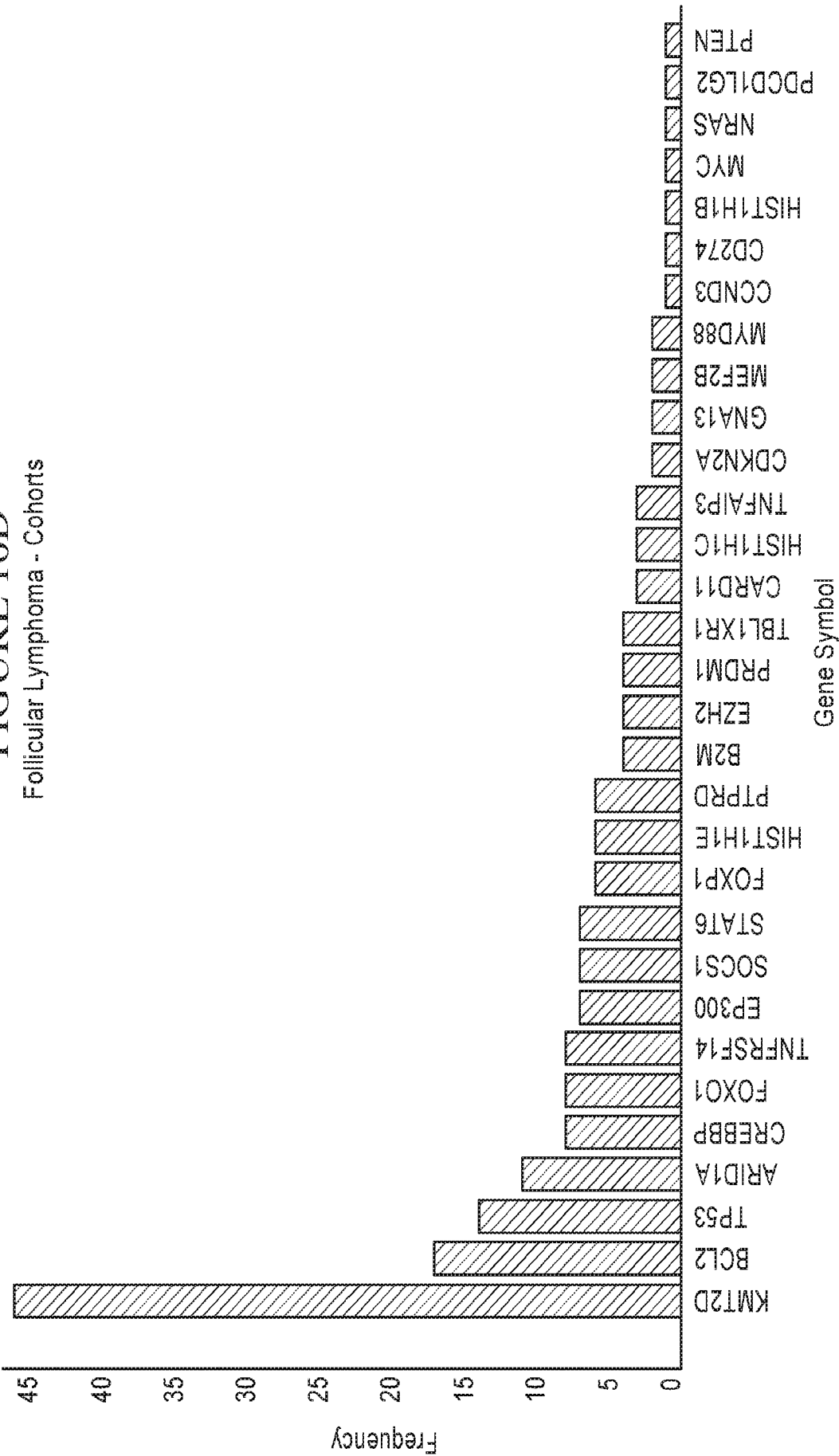
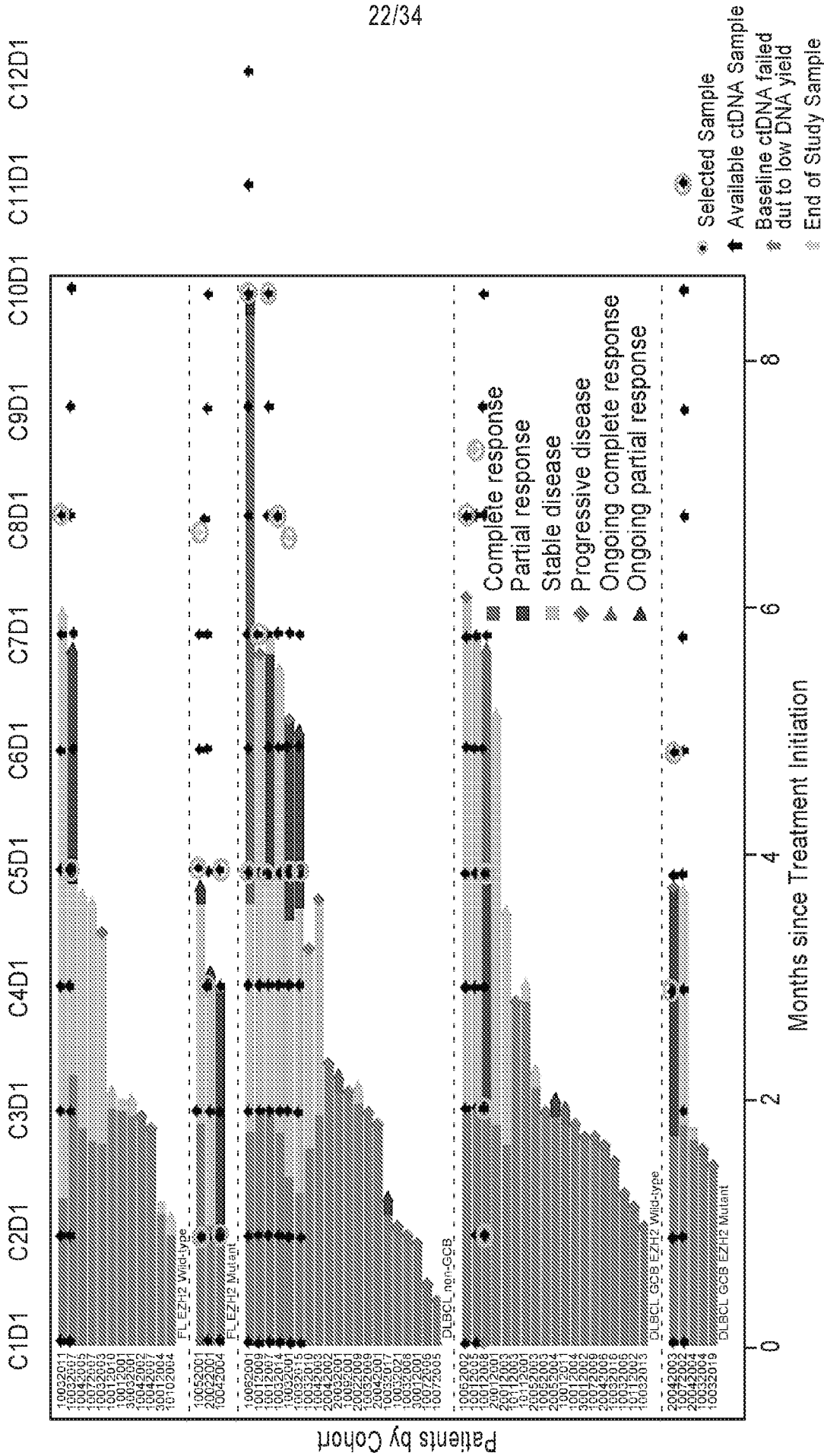
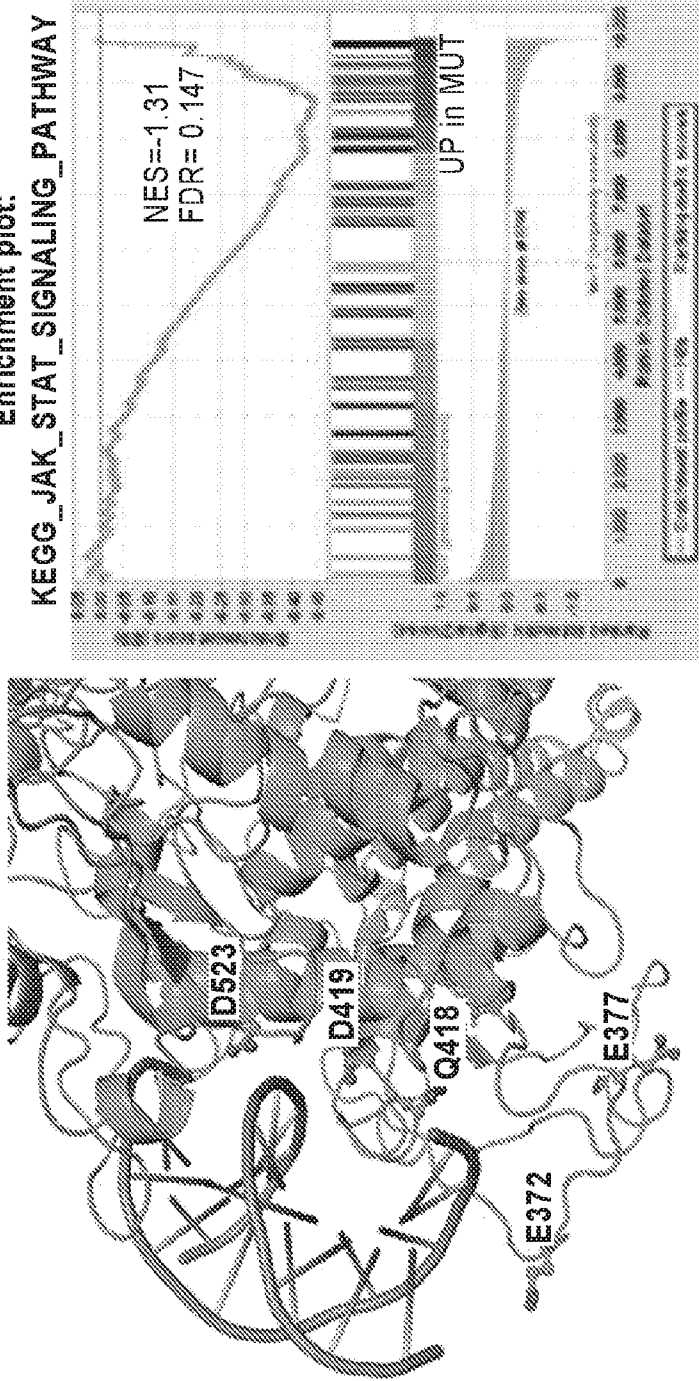
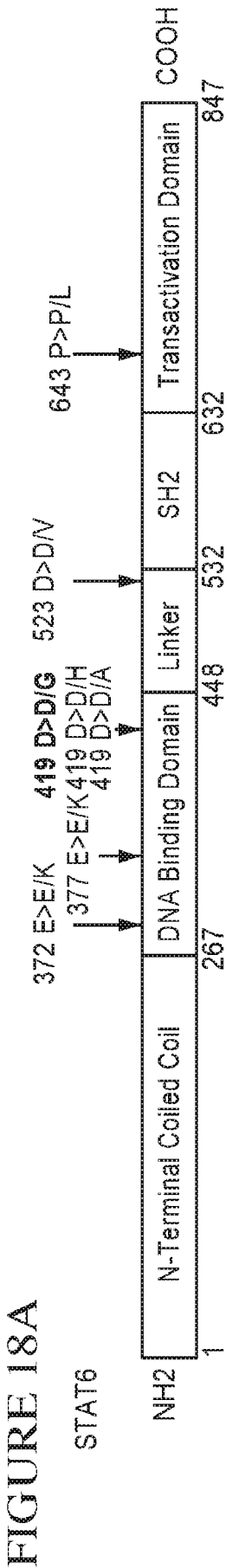


FIGURE 17



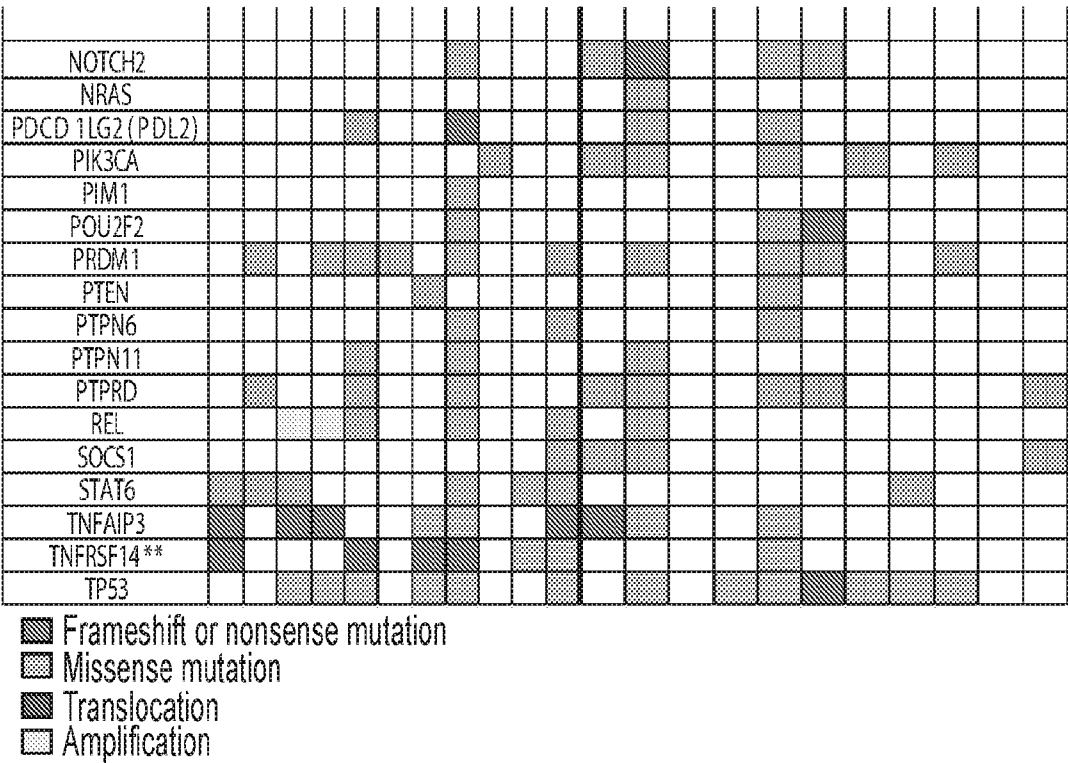


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FIGURE 19A

	Best Reponse = CR or PR											non-Responder <CR or PR											
	A5	C5	A8	C8	C9	A4	C4	C6	C2	A7	C7	A16	C16	A18	C18	C11	C15	C17	A10	C10	A14	C14	
GCB-DLBCL																							
non-GCB-DLBCL																							
Follicular Lymphoma																							
ARID1A																							
ATM																							
B2M **																							
BCL2																							
BCL6																							
BCL7A																							
BRAF																							
CARD11 **																							
CCND3																							
CD58																							
CD79B																							
CD274 (PDL1)																							
CDKN2A																							
CIITA																							
CREBBP **																							
EP300 **																							
E2H2 (Y646) **																							
E2H2 (non-Y646) **																							
FOXO1 **																							
FOXP1																							
GNA13																							
HIST1H1B																							
HIST1H1C																							
HIST1H1E																							
IKZF3																							
IRF4																							
JAK2																							
KDM4C																							
KDM6A **																							
KIT																							
KMT2D																							
KRAS																							
MEF2B																							
MYC																							
MYD88																							
NOTCH1																							

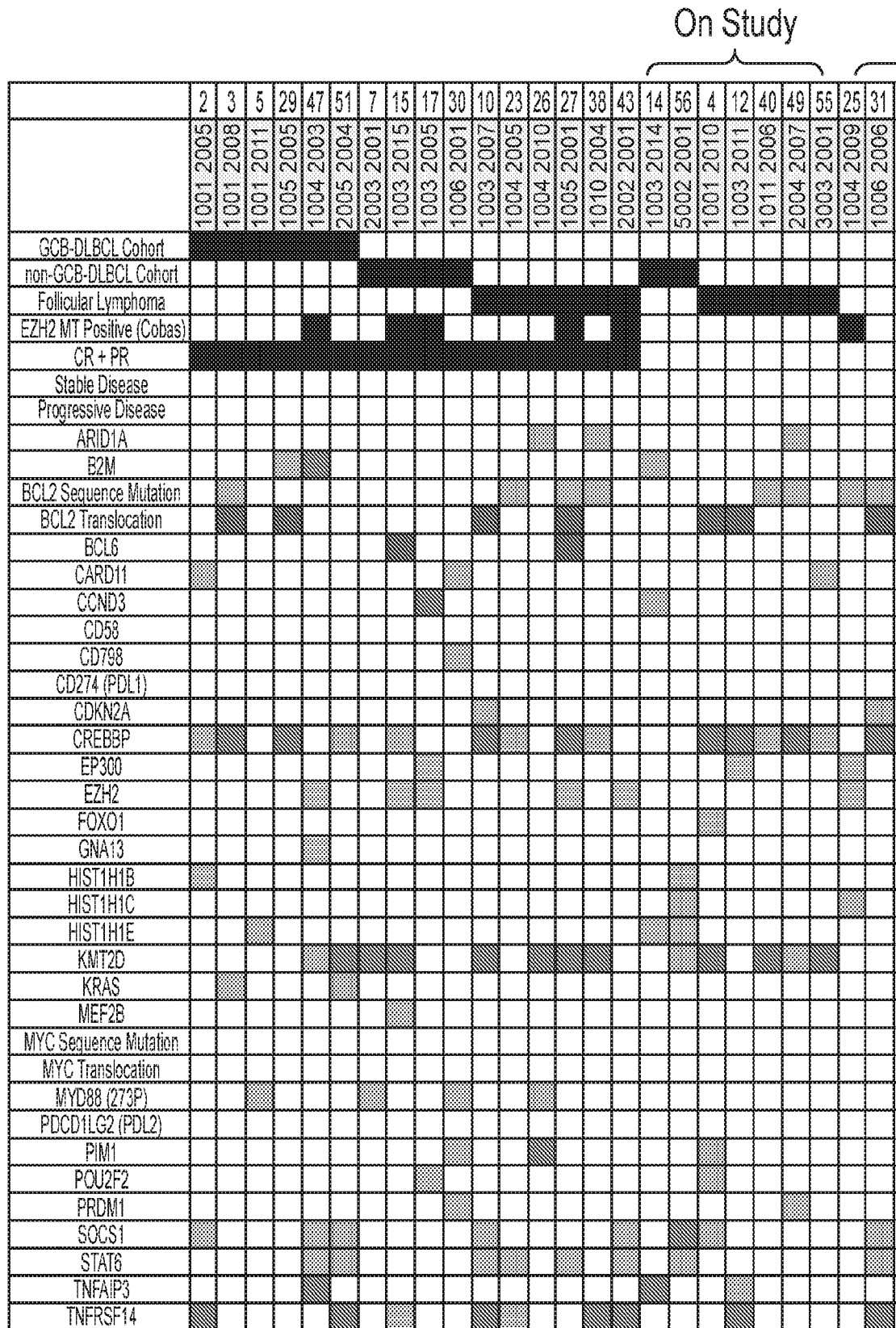
FIGURE 19B



** Molecular variants identified in the 39 gene NGS panel of Example 1

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FIGURE 20A



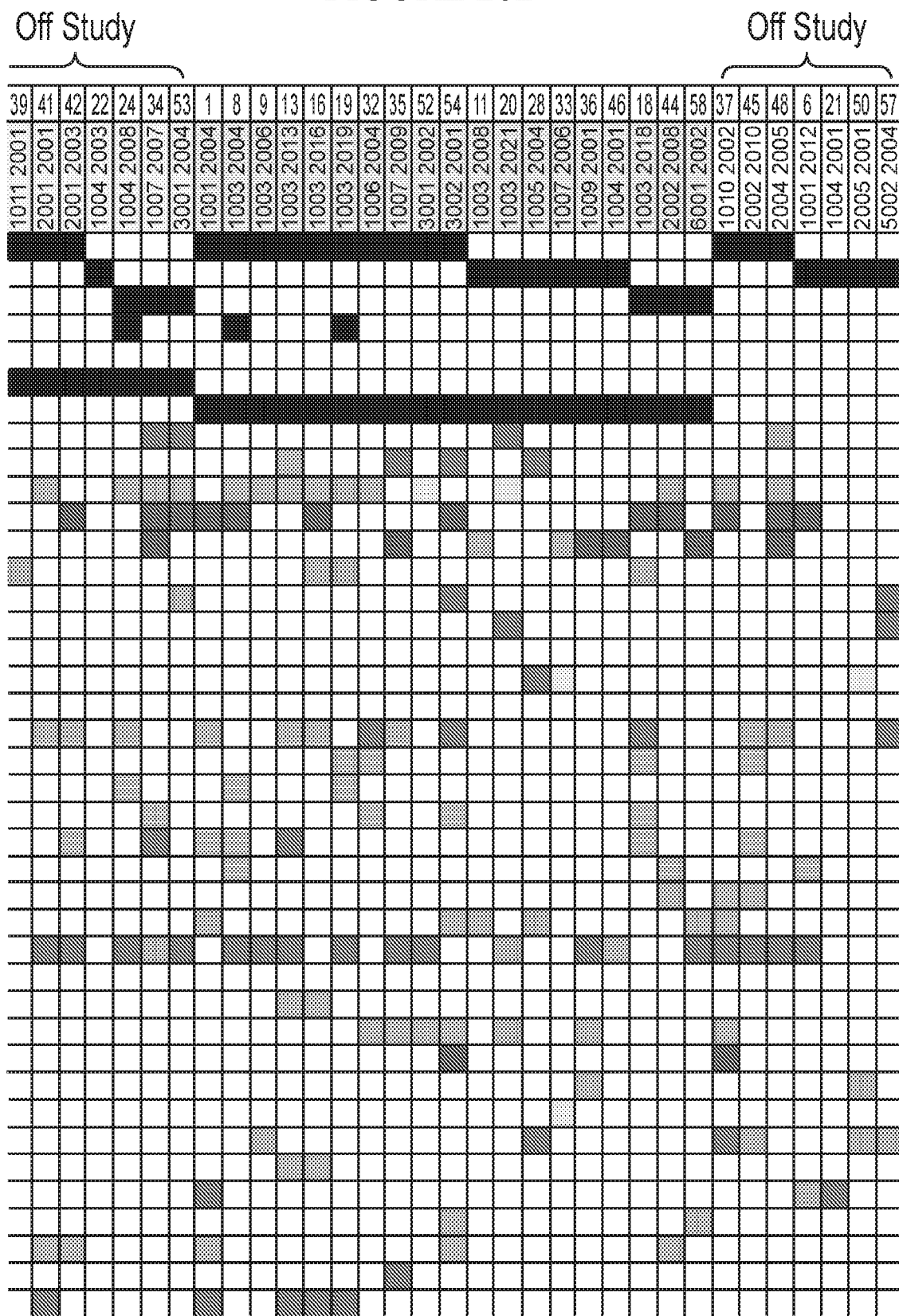
Frameshift or nonsense mutation
 Translocation

Missense mutation
 Amplification

SUBSTITUTE SHEET (RULE 26)

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FIGURE 20B

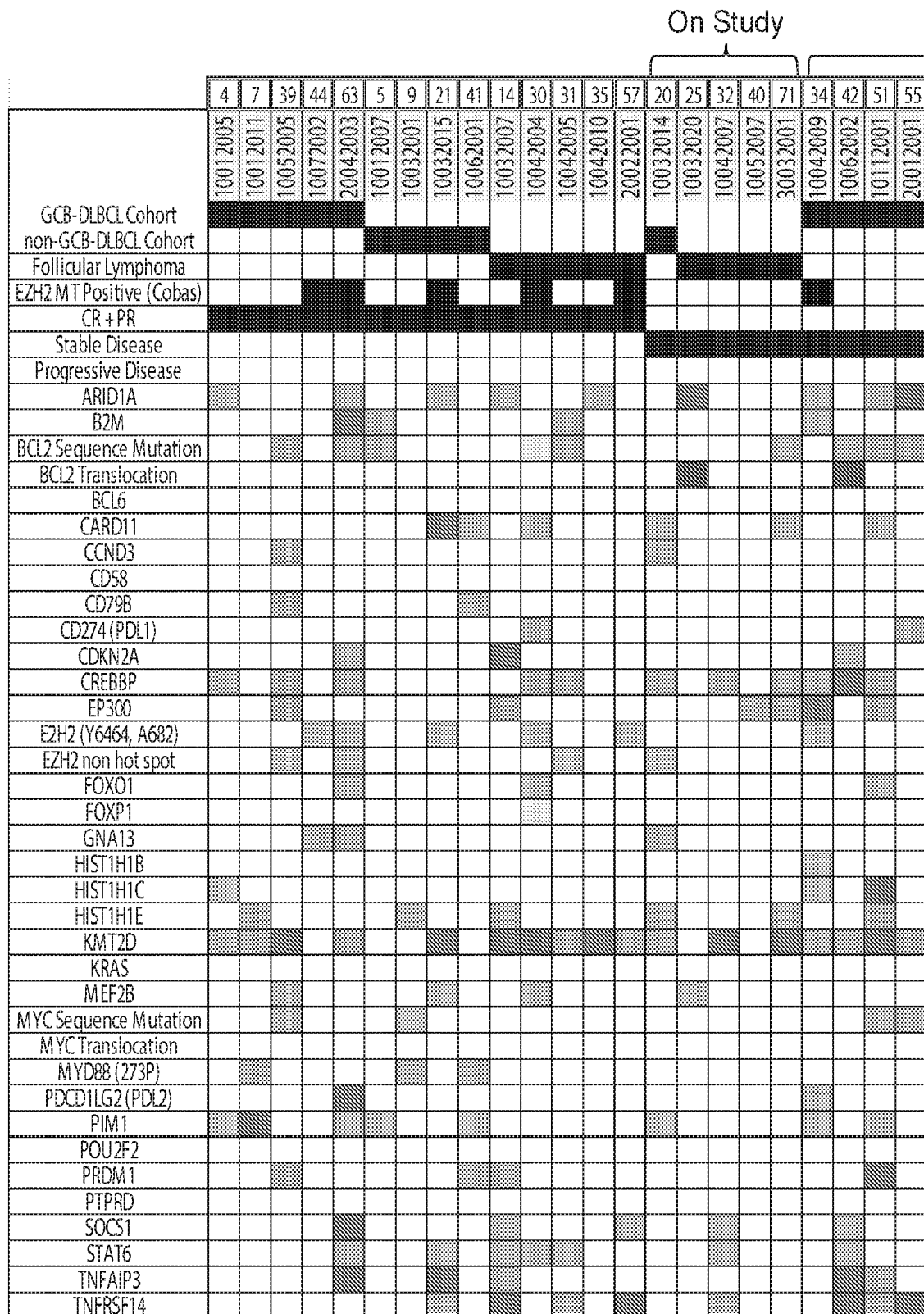


Frameshift or nonsense mutation Translocation
Missense mutation Amplification

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FIGURE 21A

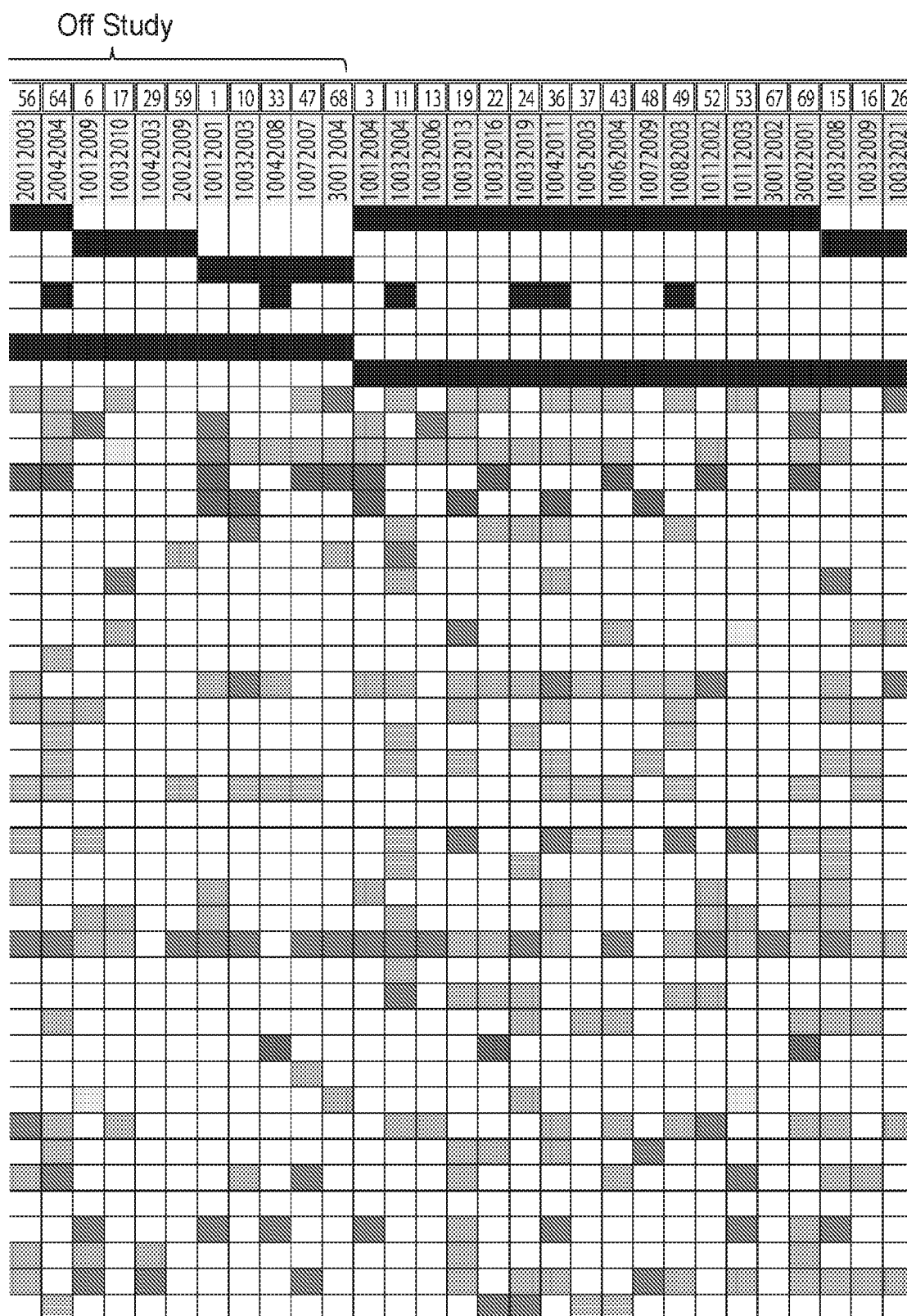


 Frameshift or nonsense mutation
  Translocation
 Missense mutation
  Amplification

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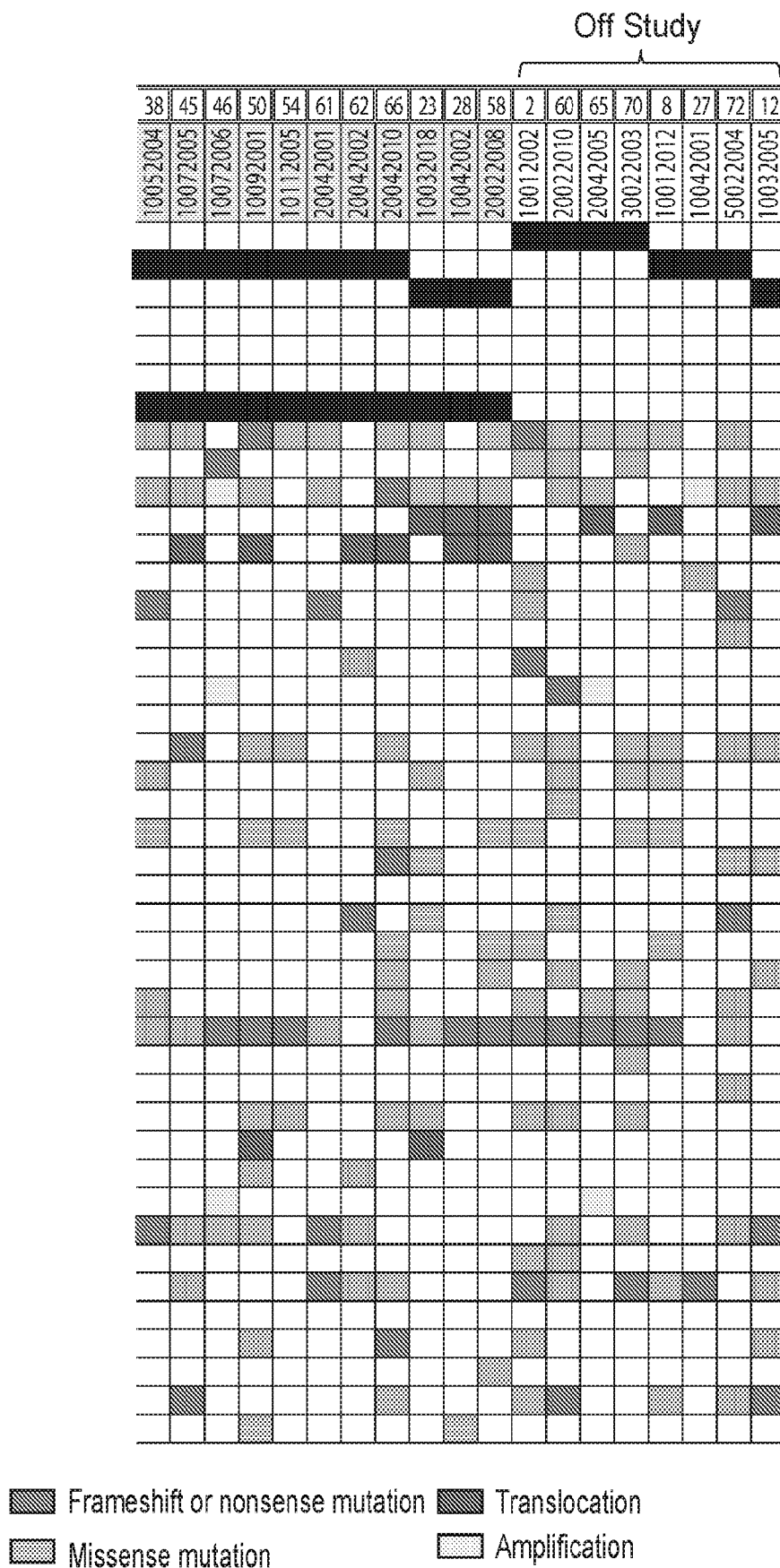
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FIGURE 21B



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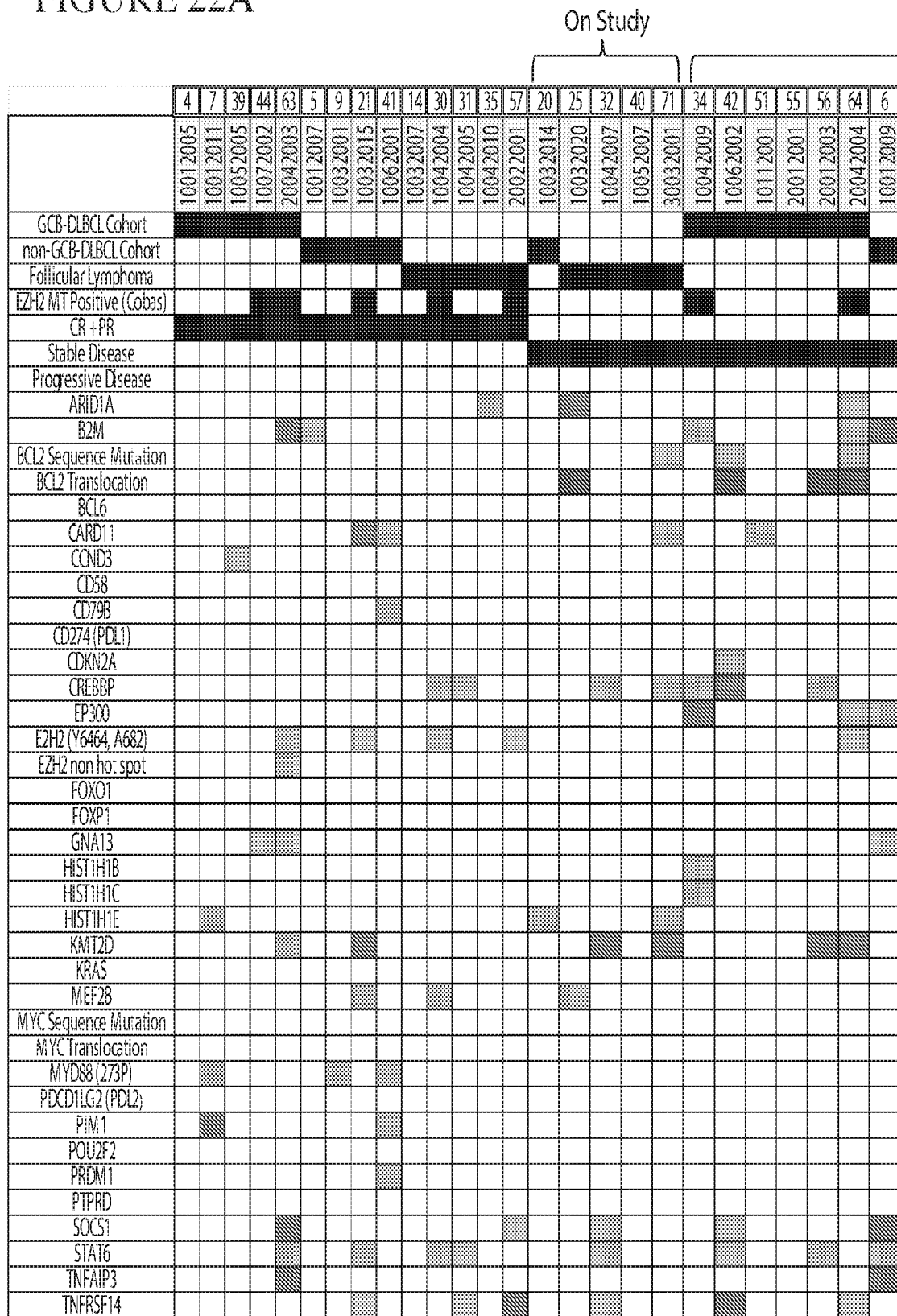
FIGURE 21C



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FIGURE 22A



 Frameshift or nonsense mutation
  Translocation

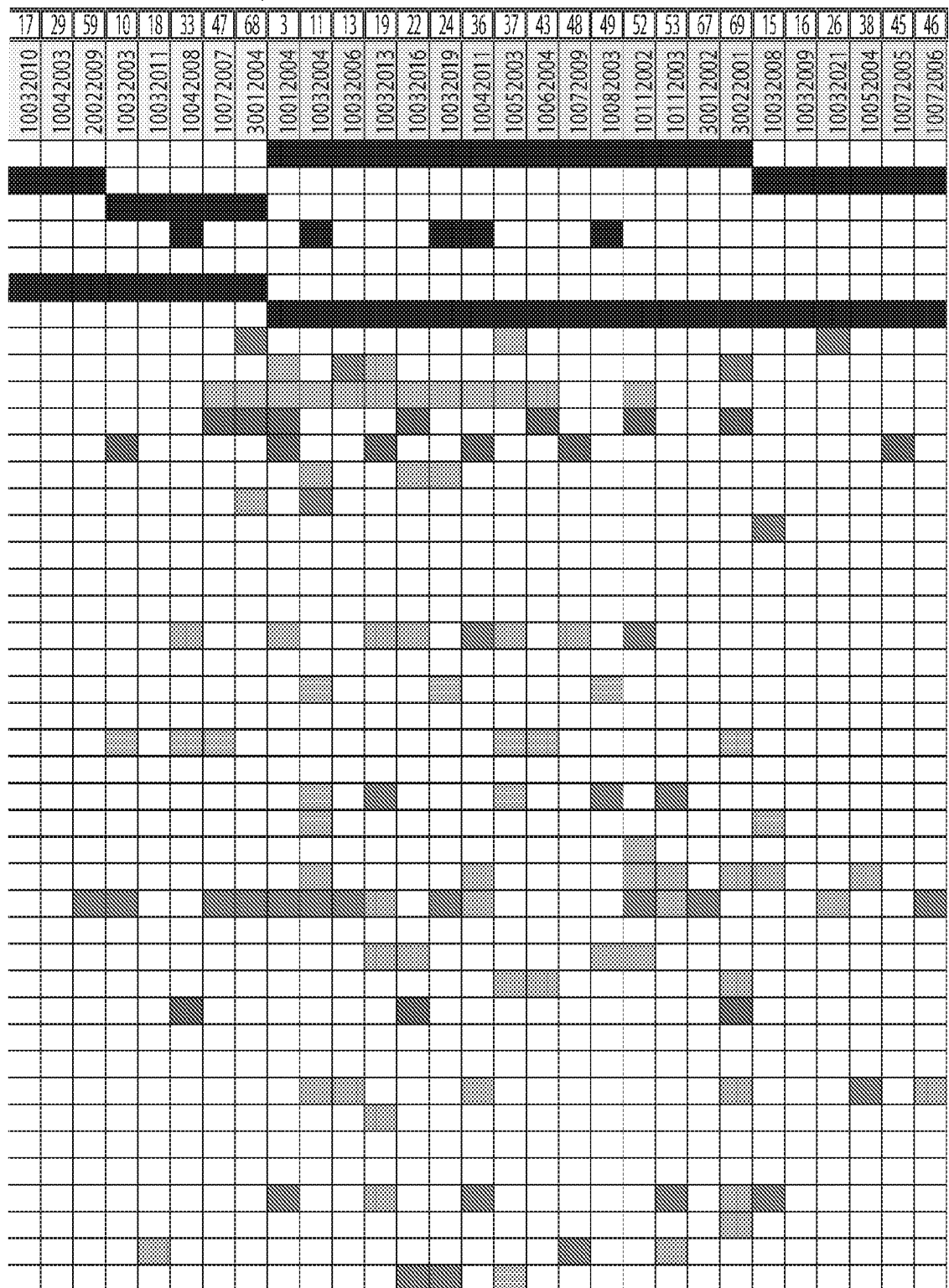
 Missense mutation
  Amplification

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FIGURE 22B

Off Study

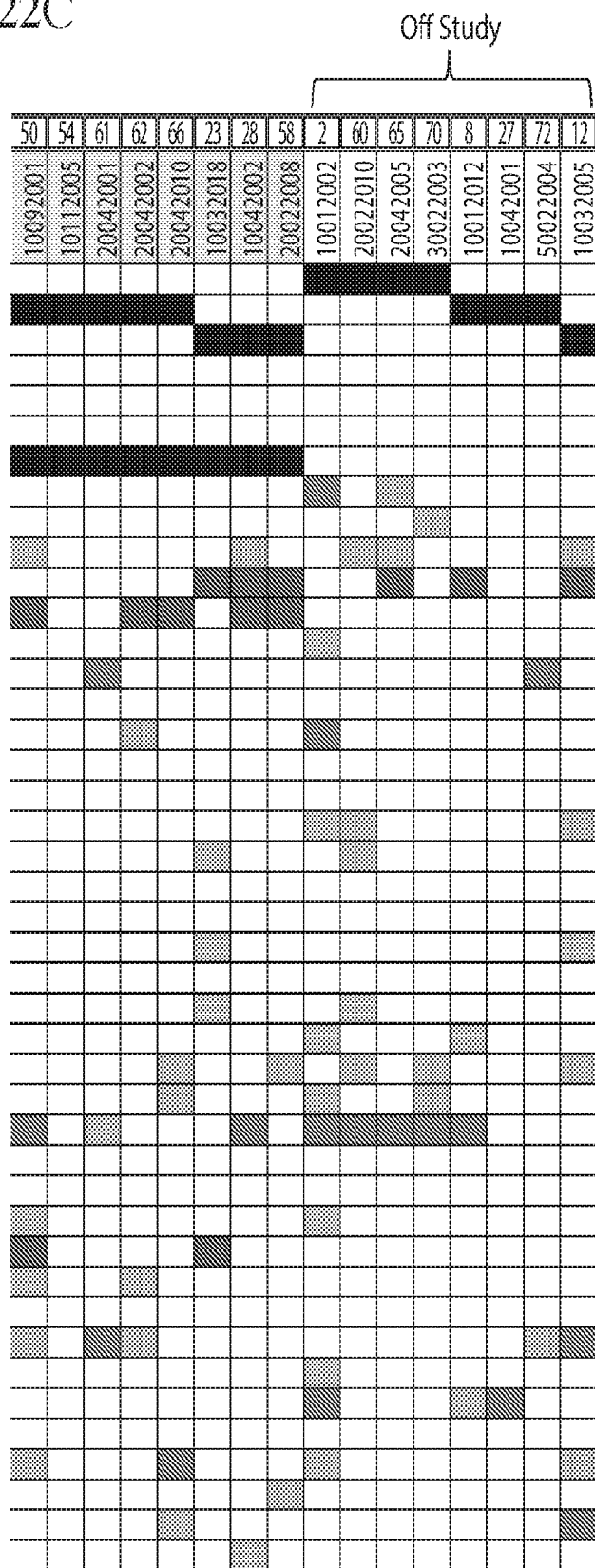


Frameshift or nonsense mutation Translocation
Missense mutation Amplification

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FIGURE 22C



Frameshift or nonsense mutation Translocation
Missense mutation Amplification

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FIGURE 23

