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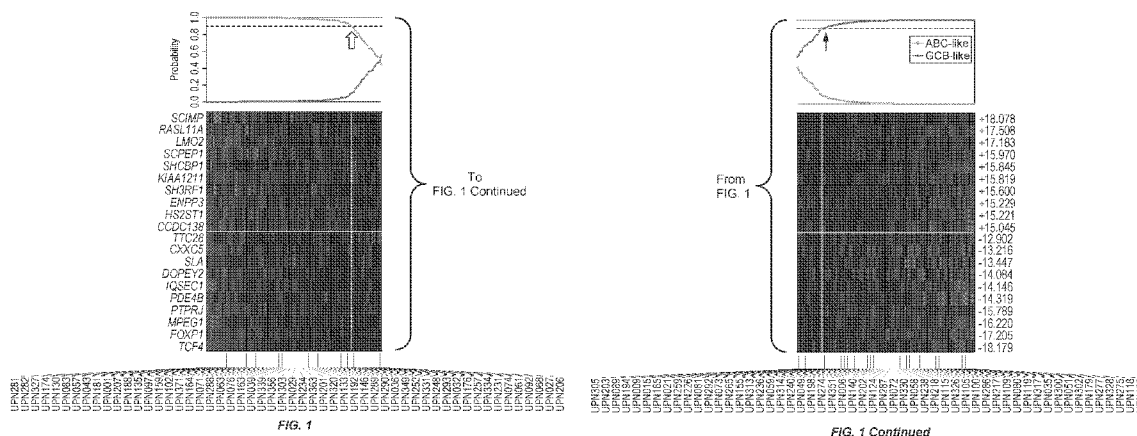
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(54) Title: BIOMARKERS AND METHODS OF TREATMENT OF FOLLICULAR LYMPHOMA



(57) Abstract: Provided herein are methods and kits of using certain biomarkers in identifying subtypes of follicular lymphoma, selectively treating the subtypes of follicular lymphoma (FL), and identifying a subject who is likely to be responsive and predicting the responsiveness of a subject to a FL treatment.

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BIOMARKERS AND METHODS OF TREATMENT OF FOLLICULAR LYMPHOMA**CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims priority to United States Provisional Application No. 63/507,966 filed June 13, 2023, the content of which is incorporated by reference in its entirety herein.

1. FIELD

[0002] Provided herein are methods and kits of using certain biomarkers in identifying subtypes of follicular lymphoma, selectively treating the subtypes of follicular lymphoma (FL), and identifying a subject who is likely to be responsive and predicting the responsiveness of a subject to a FL treatment.

2. BACKGROUND

[0003] Although follicular lymphoma (FL) is considered as an indolent lymphoma, about 20% of patients experience adverse outcomes, especially those presenting early relapse (Gupta et al., *Am J Blood Res.* 2022 Aug 15;12(4):105-124). This heterogeneity in the prognosis of FL patients is only partly addressed by indices used in daily practice and based on classic clinic-biological parameters, like the FL-International Prognostic Index (FLIPI), FLIPI-2 or PRIMA-PI (Rodriguez-Sevilla et al., *Evaluation of four prognostic indices in follicular lymphoma treated in first line with immunochemotherapy*, *Blood Adv.* 2022 Oct 19). So far, efforts to identify prognostic factors from the biology of FL tumors cannot be accurately translated in daily practice.

[0004] The prognostic relevance of the tumor microenvironment (TME) has long been inferred by gene expression signatures (GES) and immunohistochemical (IHC) studies; however, there is no consensus on a preferred GES or IHC study. (Dave et al., *N Engl J Med.*, 2004 Nov. 18; 351(21): 2159-2169; Xerri et al., *Hum. Pathol.* 2017 June; 64:128-136; Bolen 2017 et al., *Blood Adv.* 2017 Sept. 27; 1(22):1884-1890; Araujo-Ayala et al., *Hematol. Oncol.* 2021 June: Suppl 1:83-87; Tobin et al., 2019 Dec. 1; 37(34):3300-3309). In fact, the prognostic value of TME markers appears to be dependent on the treatment regimens and may have been modified by the widespread use of immuno-chemotherapy (Bolen et al., 2021 May 13; 137(19):2704-2707, Xerri et al., 2017 June; 64:128-136).

[0005] The molecular risk prediction models based on genomic alterations and GES have been developed, including the m7-Follicular Lymphoma International Prognostic Index (m7-FLIPI) (Pastore et al., *Lancet Oncol.* 2015 Sept; 16(9):1111-1122), and a predictor based on the

expression of 23 genes (Huet et al., Erratum in: *Lancet Oncol.* 2018 Jun; 19(6):e283). The latter model was somewhat related to a putative “cell of origin” (COO), especially a GES named ICA13, which was reminiscent of the dark zone of germinal centers and associated with poor prognosis. Similarly, another study showed that the GES of FL tumors with high FOXP1 expression was enriched in both dark zone-related and activated B-cell (ABC) gene sets (Mottock et al., *Blood* 2018 Jan 11; 131(2):226-235). Some interconnectivity between these models was suggested by shared regulated expression networks (Silva et al., *Haematologica* 2019 Jun; 104(6):e252-255). However, the results of these models are inconsistent and their biological relevance and impact on treatment decisions in individual FL patients are still unclear.

[0006] The COO defined by gene profiling has enabled a molecular classification of diffuse large B-cell lymphoma (DLBCL) between prognostically favorable germinal center (GC) and unfavorable ABC subtypes (Schmitz et al., *N Engl J Med.*, 2018 Apr 12; 378(15):1396-1407, Wienand et al., *Hematol Oncol.* 2021 Jun; 39 suppl 1:24-30, Wright et al. *Cancer Cell* 2020 Apr 13;37(4):551-568). However, a similar subcategorization has long been considered as irrelevant to FL. Bulk FL tumors were generally thought to resemble normal GC light zone B cells, given the observed similarities in their gene expression profiles (Victora et al. *Blood* 2012 Sep 13; 120(11):2240-2248). Nonetheless, a pioneering epigenetic analysis provided some clues toward a putative COO subtyping of FL tumors, namely between “GCB centrocyte-like” and “in vitro–activated plasmablast-like” subtypes (Koues et al. *Immunity* 2015 Jan 20; 42(1):186-198).

[0007] This appeared consistent with the observation of a minor subset of BCL2-unrearranged FL tumors showing enrichment in ABC–like signatures (Leich et al., *Blood* 2009 Jul 23; 114(4):826-834) or displaying microRNA profiles associated with a “late” GC B-cell phenotype with increased IRF4/MUM1 expression (Leich et al., *Blood* 2011 Nov 17; 118(20):5550-5558). It is also supported by the recent observation of discrete steps of plasmablastic differentiation starting from a subset of light zone GC B cells and of a distinct subpopulation composed of memory B cell precursors within the GC (Holmes et al. *J Exp Med* 2020 Oct 5; 217(10):e20200483). Furthermore, a recent meta-analysis study suggested that a COO-based FL classification might have prognostic significance, with an ABC-like signature correlated with poor survival (Tsukamoto et al., *Blood Adv.* 2022 Mar 22; 6(6):1932-1936).

[0008] There remains a significant need for effective methods for classifying subtypes of FL and for predicting sensitivity to treatments.

3. SUMMARY OF THE INVENTION

[0009] In one aspect, provided herein is a method for identifying a subject as having an Activated/Memory B-cell like (ABC/MEM-like) follicular lymphoma (FL), comprising: (a) determining the gene expression level of at least one biomarker in a sample from the subject, wherein the biomarker is selected from the group consisting of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1; (b) determining a composite score based on the gene expression level of the at least one biomarker; and (c) identifying the subject as having ABC/MEM-like FL based on the composite score.

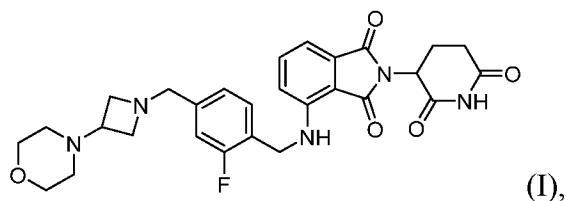
[0010] In certain embodiments, the method further comprises administering to the subject identified as having ABC/MEM-like FL a treatment of ABC/MEM-like FL comprising a therapeutically effective amount of an immunomodulatory drug (IMiD[®]) and/or a cereblon E3 ligase modulating compound.

[0011] In another aspect, provided herein is a method of selectively treating a subject having FL, comprising: (a) determining the gene expression level of at least one biomarker in a sample of the subject, wherein the biomarker is selected from the group consisting of: TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1; (b) determining a composite score based on the gene expression level of the at least one biomarker; (c) identifying the subject as having ABC/MEM-like FL based on the composite score; and (d) administering to the subject identified as having ABC/MEM-like FL a treatment of ABC/MEM-like FL comprising a therapeutically effective amount of an IMiD[®] and/or a cereblon E3 ligase modulating compound.

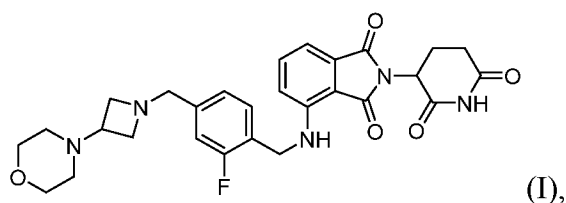
[0012] In another aspect, provided herein is a method of identifying a subject who is likely to be responsive to a treatment of ABC/MEM-like FL or predicting the responsiveness of a subject to a treatment of ABC/MEM-like FL, comprising: (a) determining the gene expression level of at least one biomarker in a sample of the subject, wherein the biomarker is selected from the group consisting of: TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1; (b) determining a composite score based on the gene expression level of the at least one biomarker; (c) identifying or predicting the subject as being likely to be responsive to the treatment of ABC/MEM-like FL based on the composite score, wherein the treatment of ABC/MEM-like FL comprises a therapeutically effective amount of an IMiD[®] and/or a cereblon E3 ligase modulating compound. In certain embodiments, the method further

comprises administering the treatment of ABC/MEM-like FL to the subject likely to be responsive to the treatment of ABC/MEM-like FL.

[0013] In certain embodiments, the IMiD[®] is selected from the group consisting of lenalidomide, pomalidomide, and thalidomide, and enantiomers, mixture of enantiomers, tautomers, isotopologs, and pharmaceutically acceptable salts thereof. In certain embodiments, the cereblon E3 ligase modulating compound is selected from the group consisting of iberdomide and a compound of Formula (I)



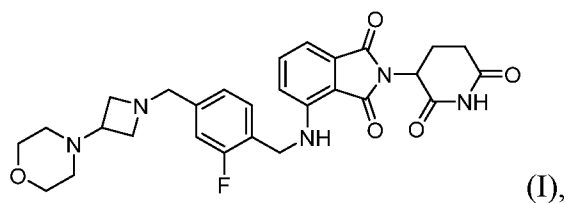
and enantiomers, mixture of enantiomers, tautomers, isotopologs, and pharmaceutically acceptable salts thereof. In certain embodiments, the IMiD[®] and/or cereblon E3 ligase modulating compound is selected from the group consisting of lenalidomide, pomalidomide, thalidomide, iberdomide, and a compound of Formula (I)



and enantiomers, mixture of enantiomers, tautomers, isotopologs, and pharmaceutically acceptable salts thereof.

[0014] In certain embodiments, the treatment of ABC/MEM-like FL further comprises a therapeutically effective amount of an anti-CD20 antibody. In certain embodiments, the anti-CD20 antibody is selected from the group consisting of rituximab, obinutuzumab, ocrelizumab, and combinations thereof.

[0015] In certain embodiments, the treatment of ABC/MEM-like FL comprises therapeutically effective amounts of rituximab and lenalidomide, or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof. In certain embodiments, the treatment of ABC/MEM-like FL comprises therapeutically effective amounts of rituximab and a compound of Formula (I)



or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

[0016] In certain embodiments, the treatment of ABC/MEM-like FL improves overall survival, PFS, and/or FFS of the subject having ACB/MEM-like FL.

[0017] In certain embodiments, the composite score is determined based on the gene expression levels of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1. In certain embodiments, the composite score is determined based on the sum of weighted gene expression levels of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1. In certain embodiments, the composite score is determined based on the following formula: $(-12.90235 \times \text{the gene expression level of TTC28}) + (-17.20497 \times \text{the gene expression level of FOXP1}) + (-14.08426 \times \text{the gene expression level of DOPEY2}) + (-14.14635 \times \text{the gene expression level of IQSEC1}) + (-15.78924 \times \text{the gene expression level of PTPRJ}) + (-13.44714 \times \text{the gene expression level of SLA}) + (-13.21572 \times \text{the gene expression level of CXXC5}) + (-14.31872 \times \text{the gene expression level of PDE4B}) + (-18.17919 \times \text{the gene expression level of TCF4}) + (-16.21973 \times \text{the gene expression level of MPEG1}) + (15.81861 \times \text{the gene expression level of KIAA1211}) + (15.97033 \times \text{the gene expression level of SCPEP1}) + (17.50829 \times \text{the gene expression level of RASL11A}) + (17.18333 \times \text{the gene expression level of LMO2}) + (15.22055 \times \text{the gene expression level of HS2ST1}) + (15.22908 \times \text{the gene expression level of ENPP3}) + (15.60008 \times \text{the gene expression level of SH3RF1}) + (18.07827 \times \text{the gene expression level of SCIMP}) + (15.04494 \times \text{the gene expression level of CCDC138}) + (15.84456 \times \text{the gene expression level of SHCBP1})$.

[0018] In certain embodiments, the subject is identified as having ABC/MEM-like FL or is identified or predicted as being likely to be responsive to the treatment of ABC/MEM-like FL if the composite score is lower than a predetermined value, optionally the predetermined value is zero. In certain embodiments, the subject is identified as having ABC/MEM-like FL or is identified or predicted as being likely to be responsive to the treatment of ABC/MEM-like FL if the composite score is lower than a reference score. In certain embodiments, the reference score is derived from a healthy subject or a population of healthy subjects and is calculated the same way as the composite score.

[0019] In another aspect, provided herein is a method of identifying a subject as having a Germinal Center B-Cell like (GCB-like) follicular lymphoma (FL), comprising: (a) determining the gene expression level of at least one biomarker in a sample from the subject, wherein the

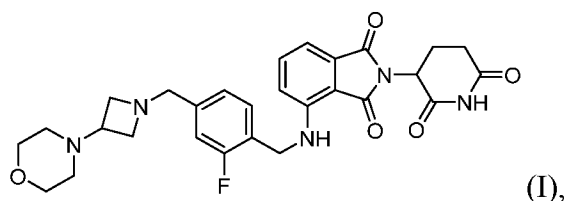
biomarker is selected from the group consisting of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1; (b) determining a composite score based on the gene expression level of the at least one biomarker; and (c) identifying the subject as having the GCB-like FL based on the composite score. In certain embodiments, the method further comprises administering to the subject identified as having GCB-like FL a treatment of GCB-like FL.

[0020] In another aspect, provided herein is a method of selectively treating a subject having FL, comprising: (a) determining the gene expression level of at least one biomarker in a sample of the subject, wherein the biomarker is selected from the group consisting of: TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1; (b) determining a composite score based on the gene expression level of the at least one biomarker; (c) identifying the subject as having GCB-like FL based on the composite score; and (d) administering to the subject identified as having GCB-like FL a therapeutically effective amount of a GCB-like FL treatment.

[0021] In another aspect, provided herein is a method of identifying a subject who is likely to be responsive to a treatment of GCB-like FL or predicting the responsiveness of a subject to a treatment of GCB-like FL, comprising: (a) determining the gene expression level of at least one biomarker in a sample of the subject, wherein the biomarker is selected from the group consisting of: TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1; (b) determining a composite score based on the gene expression level of the at least one biomarker; and (c) identifying or predicting the subject as being likely to be responsive to the treatment of GCB-like FL based on the composite score. In certain embodiments, the method further comprises administering the treatment of GCB-like FL to the subject likely to be responsive to the treatment of GCB-like FL.

[0022] In certain embodiments, the treatment of GCB-like FL comprises a therapeutically effective amount of an IMiD[®], a cereblon E3 ligase modulating compound, an anti-CD20 antibody, a chemotherapeutic agent, or a combination thereof. In certain embodiments, the treatment of GCB-like FL comprises a therapeutically effective amount of a cereblon E3 ligase modulating compound, an anti-CD20 antibody, a chemotherapeutic agent, or a combination thereof.

[0023] In certain embodiments, the IMiD[®] and/or cereblon E3 ligase modulating compound is selected from the group consisting of lenalidomide, pomalidomide, thalidomide, iberdomide, and a compound of Formula (I)



and enantiomers, mixture of enantiomers, tautomers, isotopologs, and pharmaceutically acceptable salts thereof.

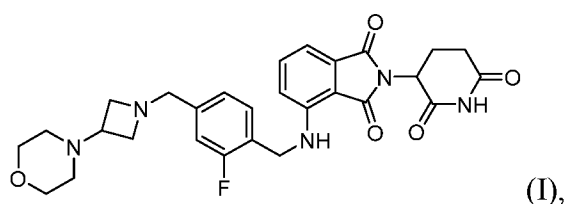
[0024] In certain embodiments, the anti-CD20 antibody is selected from the group consisting of rituximab, obinutuzumab, ocrelizumab, and combinations thereof.

[0025] In certain embodiments, the chemotherapeutic agent is selected from the group consisting of cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and combinations thereof.

[0026] In certain embodiments, the treatment of GCB-like FL comprises the therapeutically effective amounts of the anti-CD20 antibody and the chemotherapeutic agent. In certain embodiments, the treatment of GCB-like FL comprises the therapeutically effective amounts of rituximab, cyclophosphamide, doxorubicin hydrochloride, and vincristine sulfate. In certain embodiments, the treatment of GCB-like FL comprises the therapeutically effective amounts of rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone

[0027] In certain embodiments, the treatment of GCB-like FL comprises the therapeutically effective amounts of the IMiD[®] and the anti-CD20 antibody. In certain embodiments, the treatment of GCB-like FL comprises the therapeutically effective amounts of rituximab and lenalidomide, or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

[0028] In certain embodiments, the treatment of GCB-like FL comprises the therapeutically effective amounts of rituximab and a compound of Formula (I)



or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

[0029] In certain embodiments, the composite score is determined based on the gene expression levels of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1. In certain embodiments, the composite score is determined based on the sum of weighted gene expression levels of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1. In certain embodiments, the composite score is determined based on the following formula: $(-12.90235 \times \text{the gene expression level of TTC28}) + (-17.20497 \times \text{the gene expression level of FOXP1}) + (-14.08426 \times \text{the gene expression level of DOPEY2}) + (-14.14635 \times \text{the gene expression level of IQSEC1}) + (-15.78924 \times \text{the gene expression level of PTPRJ}) + (-13.44714 \times \text{the gene expression level of SLA}) + (-13.21572 \times \text{the gene expression level of CXXC5}) + (-14.31872 \times \text{the gene expression level of PDE4B}) + (-18.17919 \times \text{the gene expression level of TCF4}) + (-16.21973 \times \text{the gene expression level of MPEG1}) + (15.81861 \times \text{the gene expression level of KIAA1211}) + (15.97033 \times \text{the gene expression level of SCPEP1}) + (17.50829 \times \text{the gene expression level of RASL11A}) + (17.18333 \times \text{the gene expression level of LMO2}) + (15.22055 \times \text{the gene expression level of HS2ST1}) + (15.22908 \times \text{the gene expression level of ENPP3}) + (15.60008 \times \text{the gene expression level of SH3RF1}) + (18.07827 \times \text{the gene expression level of SCIMP}) + (15.04494 \times \text{the gene expression level of CCDC138}) + (15.84456 \times \text{the gene expression level of SHCBP1})$.

[0030] In certain embodiments, the subject is identified as having GCB-like FL or is identified or predicted as being likely to be responsive to the treatment of GCB-like FL if the composite score is higher than a predetermined value, optionally the predetermined value is zero. In certain embodiments, the subject is identified as having GCB-like FL or is identified or predicted as being likely to be responsive to the treatment of GCB-like FL if the composite score is higher than a reference score. In certain embodiments, the reference score is derived from a healthy subject or a population of healthy subjects and is calculated the same way as the composite score.

[0031] In certain embodiments, the gene expression level of the at least one biomarker is mRNA level. In certain embodiments, the gene expression level is measured by RNA sequencing. In certain embodiments, the gene expression level is measured by PCR-based quantification methods.

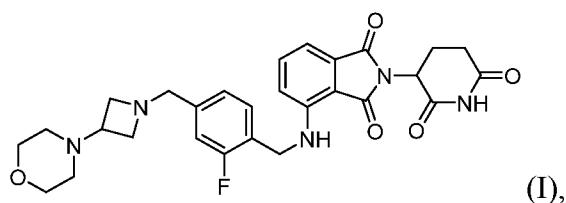
[0032] In another aspect, provided herein is a method of identifying a subject as having an ABC/MEM-like FL, comprising: (a) determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and (b) identifying the subject as having the ABC/MEM-like FL

based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1. In certain embodiments, the method further comprises administering to the subject identified as having ABC/MEM-like FL a therapeutically effective amount of an immunomodulatory drug (IMiD[®]) and/or a cereblon E3 ligase modulating compound.

[0033] In another aspect, provided herein is a method of selectively treating a subject having FL, comprising: (a) determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1; (b) identifying the subject as having ABC/MEM-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and (c) administering to the subject identified as having ABC/MEM-like FL a therapeutically effective amount of an IMiD[®] and/or a cereblon E3 ligase modulating compound.

[0034] In another aspect, provided herein is a method of identifying a subject who is likely to be responsive to a treatment of ABC/MEM-like FL or predicting the responsiveness of a subject to a treatment of ABC/MEM-like FL, comprising: (a) determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and (b) identifying or predicting the subject as being likely to be responsive to the treatment of ABC/MEM-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1, wherein the treatment of ABC/MEM-like FL comprises an IMiD[®] and/or a cereblon E3 ligase modulating compound. In certain embodiments, the method further comprises administering the treatment of ABC/MEM-like FL to the subject likely to be responsive to the treatment of ABC/MEM-like FL.

[0035] In certain embodiments, the IMiD[®] and/or cereblon E3 ligase modulating compound is selected from the group consisting of lenalidomide, pomalidomide, thalidomide, iberdomide, and a compound of Formula (I)

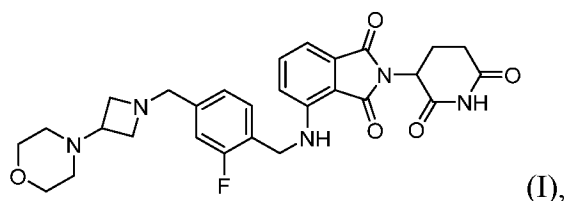


and enantiomers, mixture of enantiomers, tautomers, isotopologs, and pharmaceutically acceptable salts thereof.

[0036] In certain embodiments, the treatment of ABC/MEM-like FL further comprises a therapeutically effective amount of an anti-CD20 antibody. In certain embodiments, the anti-CD20 antibody is selected from the group consisting of rituximab, obinutuzumab, ocrelizumab, and combinations thereof.

[0037] In certain embodiments, the treatment of ABC/MEM-like FL comprises therapeutically effective amounts of rituximab and lenalidomide, or an enantiomer, mixture of enantiomers,

tautomer, isotopolog, or pharmaceutically acceptable salt thereof. In certain embodiments, the treatment of ABC/MEM-like FL comprises therapeutically effective amounts of rituximab and a compound of Formula (I)



or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

[0038] In certain embodiments, the treatment of ABC/MEM-like FL improves overall survival, PFS, and/or FFS of the subject having ABC/MEM-like FL.

[0039] In certain embodiments, the protein expression levels of FOXP1, LMO2, CD22, and MUM1 are protein levels. In certain embodiments, the protein levels are measured using immunohistochemistry (IHC). In certain embodiments, the protein levels are measured using other antibody-based imaging and quantification methods such as Multiplexed Ion Beam Imaging (MIBI) and Imaging Mass Cytometry (IMC).

[0040] In certain embodiments, the subject is identified as having ABC/MEM-like FL or is identified or predicted as being likely to be responsive to the treatment of ABC/MEM-like FL if (i) the protein expression level of FOXP1 is strong or moderate and the protein expression level of LMO2 is weak or negative; (ii) the protein expression level of FOXP1 is close to the protein expression level of LMO2 (equally strong, moderate, or weak) or otherwise noninformative, and the protein expression level of CD22 is weak; or (iii) the protein expression level of FOXP1 is close to that of LMO2 (equally strong, moderate, or weak) or otherwise noninformative, and the protein expression level of CD22 is moderate or otherwise noninformative and the percentage of MUM1 positive cells in the sample is greater than about 15%.

[0041] In certain embodiments, the subject is identified as having ABC/MEM-like FL or is identified or predicted as being likely to be responsive to the treatment of ABC/MEM-like FL if (i) the percentage of FOXP1 positive cells in the sample is more than about 50% and the percentage of LMO2 positive cells in the sample is less than about 50%, and the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is about 20% or more; (ii) if the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is less than about 20%, and the percentage of CD22 positive cells in the sample is less than about 20%; or (iii) if the difference between the percentage of FOXP1 positive cells in the sample and

the percentage of LMO2 positive cells in the sample is less than about 20%, and the percentage of CD22 positive cells in the sample is between about 20% and about 80%, and the percentage of MUM1 positive cells in the sample is greater than about 15%.

[0042] In another aspect, provided herein is a method of identifying a subject as having a GCB-like FL, comprising: (a) determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and (b) identifying the subject as having the GCB-like FL based on the protein expression levels of FOXP1, LMO2,, CD22, and MUM1.

[0043] In certain embodiments, the method further comprises administering to the subject identified as having GCB-like FL a treatment of GCB-like FL.

[0044] In another aspect, provided herein is a method of selectively treating a subject having FL, comprising: (a) determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1; (b) identifying the subject as having GCB-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and (c) administering to the subject identified as having GCB-like FL a therapeutically effective amount of GCB-like FL treatment.

[0045] In another aspect, provided herein is a method of identifying a subject who is likely to be responsive to a treatment of GCB-like FL or predicting the responsiveness of a subject to a treatment of GCB-like FL, comprising: (a) determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and (b) identifying or predicting the subject as being likely to be responsive to the treatment of GCB-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and optionally (c) administering the treatment of GCB-like FL to the subject likely to be responsive to the treatment of GCB-like FL.

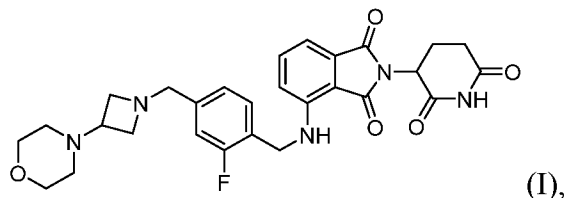
[0046] In another aspect, provided herein is a method of identifying a subject who is likely to be responsive to a treatment of GCB-like FL or predicting the responsiveness of a subject to a treatment of GCB-like FL, if: (i) the protein expression level of LMO2 is strong or moderate and the protein expression level of FOXP1 is weak or negative; (ii) the protein expression level of LMO2 is close to that of FOXP1 (equally strong, moderate, or weak) or otherwise noninformative, and the protein expression level of CD22 is strong; or (iii) the protein expression level of LMO2 is close to that of FOXP1 (equally strong, moderate, or weak) or otherwise noninformative, and the protein expression level of CD22 is moderate or otherwise noninformative, and the percentage of MUM1 positive cells in the sample is less than about 10%.

[0047] In certain embodiments, the subject is identified as having GCB-like FL or is identified or predicted as being likely to be responsive to the treatment of GCB-like FL if (i) the percentage of LMO2 positive cells in the sample is more than about 50% and the percentage of

FOXP1 positive cells in the sample is less than about 50%, and the difference between the percentage of LMO2 positive cells in the sample and the percentage of FOXP1 positive cells in the sample is about 20% or more, (ii) if the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is less than about 20%, and the percentage of CD22 cells in the sample is greater than about 80%; or (iii) if the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is less than about 20%, the percentage of CD22 positive cells in the sample is between about 20% and about 80%, and the percentage of MUM1 positive cells in the sample is less than about 10%.

[0048] In certain embodiments, the treatment of GCB-like FL comprises a therapeutically effective amount of an IMiD[®], a cereblon E3 ligase modulating compound, an anti-CD20 antibody, a chemotherapeutic agent, or a combination thereof. In certain embodiments, the treatment of GCB-like FL comprises a therapeutically effective amount of a cereblon E3 ligase modulating compound, an anti-CD20 antibody, a chemotherapeutic agent, or a combination thereof.

[0049] In certain embodiments, the IMiD[®] and/or cereblon E3 ligase modulating compound is selected from the group consisting of lenalidomide, pomalidomide, thalidomide, iberdomide, and a compound of Formula (I)



and enantiomers, mixture of enantiomers, tautomers, isotopologs, and pharmaceutically acceptable salts thereof.

[0050] In certain embodiments, the anti-CD20 antibody is selected from the group consisting of rituximab, obinutuzumab, ocrelizumab, and combinations thereof.

[0051] In certain embodiments, the chemotherapeutic agent is selected from the group consisting of cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and combinations thereof.

[0052] In certain embodiments, the treatment of GCB-like FL comprises the therapeutically effective amounts of the anti-CD20 antibody and the chemotherapeutic agent.

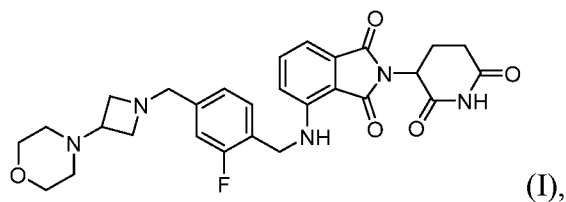
[0053] In certain embodiments, the treatment of GCB-like FL comprises the therapeutically effective amounts of rituximab, cyclophosphamide, doxorubicin hydrochloride, and vincristine sulfate. In certain embodiments, the treatment of GCB-like FL comprises the therapeutically

effective amounts of rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone.

[0054] In certain embodiments, the treatment of GCB-like FL comprises the therapeutically effective amounts of the IMiD[®] and the anti-CD20 antibody. In certain embodiments, the treatment of GCB-like FL comprises the therapeutically effective amounts of the cereblon E3 ligase modulating compound and the anti-CD20 antibody.

[0055] In certain embodiments, the treatment of GCB-like FL comprises the therapeutically effective amounts of rituximab and lenalidomide, or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

[0056] In certain embodiments, the treatment of GCB-like FL comprises the therapeutically effective amounts of rituximab and a compound of Formula (I)



or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

[0057] In certain embodiments, the protein expression levels of FOXP1, LMO2, CD22, and MUM1 are protein levels.

[0058] In certain embodiments, the protein levels are measured using immunohistochemistry (IHC). In certain embodiments, the protein levels are measured using other antibody-based imaging and quantification methods such as Multiplexed Ion Beam Imaging (MIBI) and Imaging Mass Cytometry (IMC).

[0059] In certain embodiments, the sample is a tumor biopsy.

[0060] In another aspect, provided herein is a kit for performing the methods disclosed herein, wherein the kit comprises an agent for determining (i) the gene expression level of at least one biomarker selected from the group consisting of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1 or (ii) the protein expression levels of FOXP1, LMO2, CD22, and MUM1.

[0061] In certain embodiments, the kit further comprises a tool for obtaining the sample. In certain embodiments, the kit further comprises an instruction on interpreting the determined expression level.

4. BRIEF DESCRIPTION OF THE DRAWINGS

[0062] **FIG. 1** depicts a heat map of a 20 gene based Linear Predictor Score (LPS20) which classifies patients by either Activated/Memory B-cell like (ABC/MEM-like) (as indicated by thick arrow) FL or Germinal Center B-Cell like (GCB-like FL) (as indicated by thin arrow).

[0063] **FIG. 2A** depicts a progression free survival (PFS) curve of ABC/MEM-like patients (as indicated by thick arrow) and GCB-like patients (as indicated by thin arrow) treated with rituximab plus chemotherapy drugs (R-chemo), such as cyclophosphamide, doxorubicin, and hydrochloride (R-CHOP). **FIG. 2B** depicts a PFS curve of ABC-MEM-like patients (as indicated by thick arrow) and GCB-like patients (as indicated by thin arrow) treated with a combination of lenalidomide plus rituximab (R2, also disclosed as R+R herein).

[0064] **FIG. 3A** depicts a PFS curve of ABC/MEM-like patients (as indicated by thick arrow) and GCB-like patients (as indicated by thin arrow) in the PRIMA FL cohort who have been treated with R-chemo. **FIG. 3B** depicts a FFS curve of ABC/MEM-like patients (as indicated by thick arrow) and GCB-like patients (as indicated by thin arrow) in the BCCA FL cohort who have been treated with R-chemo.

[0065] **FIG. 4** depicts a mutation profile in ABC/MEM-like patients compared to GCB-like patients.

[0066] **FIG. 5** depicts a diagram of the algorithm used to subtype formalin-fixed, paraffin-embedded (FFPE) FL biopsies.

[0067] **FIG. 6A** depicts immunohistochemistry (IHC) of FOXP1 and LMO2 on whole sections of FFPE biopsy samples that were classified as ABC/MEM-like FL (FOXP1 strong staining and LMO2 weak staining). **FIG. 6B** depicts immunohistochemistry (IHC) of FOXP1 and LMO2 on whole sections of FFPE biopsy samples that were classified as GCB-like FL (FOXP1 weak staining and LMO2 strong staining).

[0068] **FIGS. 7A** depicts immunohistochemistry (IHC) of FOXP1, LMO2, CD22, and MUM1 on whole sections of FFPE biopsy samples that were classified as GCB-like FL (FOXP1 weak staining, LMO2 strong staining, CD22 strong staining, and MUM1 weak staining). **FIG. 7B** depicts immunohistochemistry (IHC) FOXP1, LMO2, CD22, and MUM1 on whole sections of FFPE biopsy samples that were classified as ABC/MEM-like FL (FOXP1 moderate staining, LMO2 moderate staining, CD22 weak staining, and MUM1 stained between 10% and 15% of the cells).

[0069] **FIG. 8** depicts immunohistochemistry (IHC) of FOXP1, LMO2, CD22, and MUM1 on whole sections of FFPE biopsy samples.

5. DETAILED DESCRIPTION OF THE INVENTION

[0070] Provided herein are methods of using certain biomarkers in identifying subtypes of follicular lymphoma, selectively treating the subtypes of follicular lymphoma, and identifying a subject who is likely to be responsive and predicting the responsiveness of a subject to a FL treatment. It is based, in part, on the discoveries that the expression levels (*e.g.*, mRNA levels, protein levels) of certain biomarkers were associated with subtypes of follicular lymphoma (*e.g.*, ACE/MEM-like follicular lymphoma and GCB-like follicular lymphoma), and that ACE/MEM-like follicular lymphoma patients were high-risk subgroup with inferior outcome when treated with R-chemo (rituximab plus chemotherapy) but not with R² (lenalidomide plus rituximab).

5.1 Definitions

[0071] As used herein, and unless otherwise specified, the terms “treat,” “treating,” and “treatment” refer to an action that occurs while a patient is suffering from the specified cancer (*e.g.*, a specific type of follicular lymphoma, *e.g.*, ACE/MEM-like follicular lymphoma, GCB-like follicular lymphoma), which reduces the severity of the cancer or retards or slows the progression of the cancer.

[0072] As used herein, the terms “compound” and “treatment compound” are used interchangeably, and include the compound of formula (I) or a tautomer, isotopolog, or pharmaceutically acceptable salt thereof. It is to be understood that the compounds provided herein may contain chiral centers. Such chiral centers may be of either the (*R*) or (*S*) configuration, or may be a mixture thereof. It is to be understood that the chiral centers of the compounds provided herein may undergo epimerization *in vivo*. As such, one of skill in the art will recognize that administration of a compound in its (*R*) form is equivalent, for compounds that undergo epimerization *in vivo*, to administration of the compound in its (*S*) form. Optically active (+) and (−), (*R*)- and (*S*)-, or (*D*)- and (*L*)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, such as chromatography on a chiral stationary phase. In the description herein, if there is any discrepancy between a chemical name and chemical structure, the structure controls.

[0073] The term “sensitivity” or “sensitive” when made in reference to a cancer treatment is a relative term which refers to the degree of effectiveness of the cancer treatment in lessening or decreasing the progress of a tumor or the cancer being treated. For example, the term “increased sensitivity” when used in reference to treatment of a cell or tumor in connection with a compound refers to an increase of, at least about 5%, or more, in the effectiveness of the cancer treatment.

[0074] As used herein, and unless otherwise specified, the term “therapeutically effective amount” of a cancer treatment (*e.g.*, an immunomodulatory drug (IMiD[®])) is an amount sufficient to provide a therapeutic benefit in the treatment or management of a cancer, or to delay or minimize one or more symptoms associated with the presence of the cancer. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment or management of the cancer. The term “therapeutically effective amount” can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of cancer, or enhances the therapeutic efficacy of another therapeutic agent. The term also refers to the amount of a compound that is sufficient to elicit the biological or medical response of a biological molecule (*e.g.*, a protein, enzyme, RNA, or DNA), cell, tissue, system, animal, or human, which is being sought by a researcher, veterinarian, medical doctor, or clinician.

[0075] The term “responsiveness” or “responsive” when used in reference to a cancer treatment (*e.g.*, an IMiD[®]) refers to the degree of effectiveness of the treatment in lessening or decreasing the symptoms of a cancer, *e.g.*, follicular lymphoma, being treated. For example, the term “increased responsiveness” when used in reference to a treatment of a cell or a subject refers to an increase in the effectiveness in lessening or decreasing the symptoms of the disease compared to a reference treatment (*e.g.*, of the same cell or subject, or of a different cell or subject) when measured using any methods known in the art. In certain embodiments, the increase in the effectiveness is at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, or at least about 50%.

[0076] As used herein, the terms “effective subject response,” “effective patient response,” and “effective patient tumor response” refer to any increase in the therapeutic benefit to the patient. An “effective patient tumor response” can be, for example, about 5%, about 10%, about 25%, about 50%, or about 100% decrease in the rate of progress of the tumor. An “effective patient tumor response” can be, for example, about 5%, about 10%, about 25%, about 50%, or about 100% decrease in the physical symptoms of a cancer. An “effective patient tumor response” can also be, for example, about 5%, about 10%, about 25%, about 50%, about 100%, about 200%, or more increase in the response of the patient, as measured by any suitable means, such as gene expression, cell counts, assay results, tumor size, etc.

[0077] An improvement in the cancer (*e.g.*, follicular lymphoma or a subtype thereof) or cancer-related disease can be characterized as a complete or partial response. “Complete response” refers to an absence of clinically detectable disease with normalization of any previously abnormal radiographic studies, bone marrow, and cerebrospinal fluid (CSF) or abnormal

monoclonal protein measurements. “Partial response” refers to at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, or about 90% decrease in all measurable tumor burden (*i.e.*, the number of malignant cells present in the subject, or the measured bulk of tumor masses or the quantity of abnormal monoclonal protein) in the absence of new lesions. The term “treatment” contemplates both a complete and a partial response.

[0078] The term “likelihood” generally refers to an increase in the probability of an event. The term “likelihood” when used in reference to the effectiveness of a patient tumor response generally contemplates an increased probability that the rate of tumor progress or tumor cell growth will decrease. The term “likelihood” when used in reference to the effectiveness of a patient tumor response can also generally mean the increase of indicators, such as mRNA or protein expression, that may evidence an increase in the progress in treating the tumor.

[0079] The term “predict” generally means to determine or tell in advance. When used to “predict” the effectiveness of a cancer treatment (*e.g.*, an IMiD[®]), for example, the term “predict” can mean that the likelihood of the outcome of the cancer treatment can be determined at the outset, before the treatment has begun, or before the treatment period has progressed substantially.

[0080] A “biological marker” or “biomarker” is a substance whose detection indicates a particular biological state, such as, for example, the presence of a type of cancer. In certain embodiments, biomarkers can be determined individually. In other embodiments, several biomarkers can be measured simultaneously.

[0081] As used herein, the term “source” when used in reference to a reference sample refers to the origin of a sample. For example, a sample that is taken from blood would have a reference sample that is also taken from blood. Similarly, a sample that is taken from bone marrow would have a reference sample that is also taken from the bone marrow.

[0082] The term “expressed” or “expression” as used herein refers to the transcription from a gene to give an RNA nucleic acid molecule at least complementary in part to a region of one of the two nucleic acid strands of the gene. The term “expressed” or “expression” as used herein also refers to the translation from the RNA molecule to give a protein, a polypeptide, or a portion thereof. A “biological marker” or “biomarker” is a substance whose detection indicates a particular biological state, such as, for example, the presence of a type of cancer. In certain embodiments, biomarkers can be determined individually. In other embodiments, several biomarkers can be measured simultaneously.

[0083] The terms “polypeptide” and “protein,” as used interchangeably herein, refer to a polymer of three or more amino acids in a serial array, linked through peptide bonds. The term

“polypeptide” includes proteins, protein fragments, protein analogues, oligopeptides, and the like. The term “polypeptide” as used herein can also refer to a peptide. The amino acids making up the polypeptide may be naturally derived, or may be synthetic. The polypeptide can be purified from a biological sample. The polypeptide, protein, or peptide also encompasses modified polypeptides, proteins, and peptides, *e.g.*, glycopolypeptides, glycoproteins, or glycopeptides; or lipopolypeptides, lipoproteins, or lipopeptides.

[0084] In certain embodiments, a “biomarker” indicates a change in the level of mRNA expression that may correlate with the risk or progression of a disease, or with the susceptibility of the disease to a given treatment. In certain embodiments, the biomarker is a nucleic acid, such as mRNA or cDNA.

[0085] In additional embodiments, a “biomarker” indicates a change in the level of polypeptide or protein expression that may correlate with the risk or progression of a disease, or patient's susceptibility to treatment. In certain embodiments, the biomarker can be a polypeptide or protein, or a fragment thereof. The relative level of specific proteins can be determined by methods known in the art. For example, antibody-based methods, such as an immunoblot, immunohistochemistry, enzyme-linked immunosorbent assay (ELISA), or other methods can be used.

[0086] The term “level” refers to the amount, accumulation, or rate of a molecule. A level can be represented, for example, by the amount or the rate of synthesis of a messenger RNA (mRNA) encoded by a gene, the amount or the rate of synthesis of a polypeptide or protein encoded by a gene, or the amount or the rate of synthesis of a biological molecule accumulated in a cell or biological fluid. The term “level” refers to an absolute amount of a molecule in a sample or a relative amount of the molecule, determined under steady-state or non-steady-state conditions.

[0087] The terms “determining,” “measuring,” “evaluating,” “assessing,” and “assaying” as used herein generally refer to any form of measurement, and include determining whether an element is present or not. These terms include quantitative and/or qualitative determinations. Assessing may be relative or absolute.

[0088] As used herein and unless otherwise indicated, the term “pharmaceutically acceptable salt” encompasses non-toxic acid and base addition salts of the compound to which the term refers. Acceptable non-toxic acid addition salts include those derived from organic and inorganic acids known in the art, which include, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulphonic acid, acetic acid, tartaric acid, lactic acid, succinic acid, citric acid, malic acid, maleic acid, sorbic acid, aconitic acid, salicylic acid,

phthalic acid, embolic acid, enanthic acid, and the like. Compounds that are acidic in nature are capable of forming salts with various pharmaceutically acceptable bases. The bases that can be used to prepare pharmaceutically acceptable base addition salts of such acidic compounds are those that form non-toxic base addition salts, *i.e.*, salts containing pharmacologically acceptable cations such as, but not limited to, alkali metal or alkaline earth metal salts (calcium, magnesium, sodium, or potassium salts in particular). Suitable organic bases include, but are not limited to, N,N-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), lysine, and procaine.

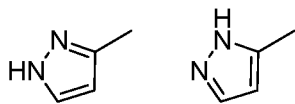
[0089] As used herein, and unless otherwise indicated, the term “solvate” means a compound provided herein or a salt thereof that further includes a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. Where the solvent is water, the solvate is a hydrate.

[0090] As used herein, and unless otherwise specified, the term “stereoisomer” encompasses all enantiomerically/stereomerically pure and enantiomerically/stereomerically enriched compounds of this invention.

[0091] As used herein, and unless otherwise indicated, the term “stereoisomer” or “stereoisomerically pure” means one stereoisomer of a compound that is substantially free of other stereoisomers of that compound. For example, a stereoisomerically pure compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereoisomerically pure compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereoisomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, or greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound. The compounds can have chiral centers and can occur as racemates, individual enantiomers or diastereomers, and mixtures thereof. All such isomeric forms are included within the embodiments provided herein, including mixtures thereof.

[0092] As used herein, the term “tautomer” refers to isomeric forms of a compound that are in equilibrium with each other. The concentrations of the isomeric forms will depend on the environment the compound is found in and may be different depending upon, for example, whether the compound is a solid or is in an organic or aqueous solution. For example, in

aqueous solution, pyrazoles may exhibit the following isomeric forms, which are referred to as tautomers of each other:



[0093] Unless specifically stated otherwise, where a compound may assume alternative tautomeric, regioisomeric and/or stereoisomeric forms, all alternative isomers are intended to be encompassed within the scope of the claimed subject matter. For example, where a compound can have one of two tautomeric forms, it is intended that both tautomers be encompassed herein. Thus, the compounds provided herein may be enantiomerically pure, or be stereoisomeric or diastereomeric mixtures. As used herein and unless otherwise indicated, the term “enantiomerically pure” means a stereomerically pure composition of a compound having one chiral center.

[0094] The use of stereoisomerically pure forms of such compounds, as well as the use of mixtures of those forms, are encompassed by the embodiments provided herein. For example, mixtures comprising equal or unequal amounts of the enantiomers of a particular compound may be used in methods and compositions provided herein. These isomers may be asymmetrically synthesized or resolved using standard techniques such as chiral columns or chiral resolving agents. See, e.g., Jacques, J., *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley-Interscience, New York, 1981); Wilen, S. H., *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, E. L., *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); Wilen, S. H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972); Todd, M., *Separation Of Enantiomers : Synthetic Methods* (Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2014); Toda, F., *Enantiomer Separation: Fundamentals and Practical Methods* (Springer Science & Business Media, 2007); Subramanian, G. *Chiral Separation Techniques: A Practical Approach* (John Wiley & Sons, 2008); Ahuja, S., *Chiral Separation Methods for Pharmaceutical and Biotechnological Products* (John Wiley & Sons, 2011).

[0095] As used herein, an “isotopolog” or “isotopologue” refers to an isotopically enriched compound. The term “isotopically enriched” refers to an atom or compound having an isotopic composition other than the natural isotopic composition of that atom or compound.

Radiolabeled and isotopically enriched compounds are useful as therapeutic agents, e.g., a hematological cancer and inflammation therapeutic agents, research reagents, e.g., binding assay reagents, and diagnostic agents, e.g., *in vivo* imaging agents. All isotopic variations of the compounds as described herein whether radioactive or not, are intended to be encompassed

within the scope of the embodiments provided herein. Exemplary isotopologs include deuterium, carbon-13, or nitrogen-15 enriched compounds. For example, an isotopolog can be a deuterium enriched compound, such as Compound 1, 2, or 3, where the deuteration occurs on the chiral center.

[0096] The term “about” or “approximately” means an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In certain embodiments, the term “about” or “approximately” means within 1, 2, 3, or 4 standard deviations. In certain embodiments, the term “about” or “approximately” means within 50%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.05% of a given value or range.

[0097] The use of the word “a” or “an” when used in conjunction with the term “comprising” in the claims and/or the specification can mean “one,” but it is also consistent with the meaning of “one or more,” “at least one,” and “one or more than one.”

[0098] As used herein, unless otherwise specified or indicated from context, the term “pre-treatment” as used in accordance with the methods described herein refers to prior to administration of a treatment.

[0099] As used herein, the terms “patient” and “subject” refer to an animal, such as a mammal. In certain embodiments, the patient or subject is a human. In other embodiments, the patient or subject is a non-human animal, such as a dog, cat, farm animal (*e.g.*, horse, pig, or donkey), chimpanzee, or monkey. In specific embodiments, the patient or subject is a human with follicular lymphoma (*e.g.*, ABC/MEM-like FL) in need of treatment.

5.2 Methods of Identifying and Treating Subtypes of Follicular Lymphoma

[00100] The present disclosure provides methods of using the expression levels (*e.g.*, mRNA levels or protein levels) of certain biomarkers in identifying a subject as having a subtype of follicular lymphoma (FL), selectively treating a subtype of FL, and identifying a subject who is likely to be responsive and predicting the responsiveness of a subject to a FL treatment. In certain embodiments, the subtype of FL is Activated/Memory B-cell like (ABC/MEM-like) FL. In certain embodiments, the subtype of FL is Germinal Center B-Cell like (GCB-like) FL.

[00101] In one aspect, provided herein is a method of identifying a subject as having an ABC/MEM-like FL, comprising: (a) determining the gene expression level of at least one biomarker in a sample from the subject; (b) determining a composite score based on the gene expression level of the at least one biomarker; and (c) identifying the subject as having ABC/MEM-like FL based on the composite score. In certain embodiments, the method further

comprises treating the subject with an ABC/MEM-like FL treatment (*e.g.*, an ABC/MEM-like FL treatment as disclosed in Section 5.3).

[00102] In another aspect, provided herein is a method of selectively treating a subject having FL, comprising: (a) determining the gene expression level of at least one biomarker in a sample from the subject; (b) determining a composite score based on the gene expression level of the at least one biomarker; (c) identifying the subject as having ABC/MEM-like FL based on the composite score; and (d) administering to the subject identified as having ABC/MEM-like FL an ABC/MEM-like FL treatment (*e.g.*, an ABC/MEM-like FL treatment as disclosed in Section 5.3).

[00103] In another aspect, provided herein is a method identifying a subject who is likely to be responsive to a treatment of ABC/MEM-like FL or predicting the responsiveness of a subject to a treatment of ABC/MEM-like FL, comprising (a) determining the gene expression level of at least one biomarker in a sample of the subject, (b) determining a composite score based on the gene expression level of the at least one biomarker; (c) identifying or predicting the subject as being likely to be responsive to the treatment of ABC/MEM-like FL based on the composite score. In certain embodiments, the method further comprises administering the treatment of ABC/MEM-like FL to the subject likely to be responsive to the treatment of ABC/MEM-like FL.

[00104] In certain embodiments, the ABC/MEM-like treatment disclosed herein comprises a therapeutically effective amount of an immunomodulatory drug (IMiD[®]). In certain embodiments, the ABC/MEM-like treatment disclosed herein comprises a therapeutically effective amount of a cereblon E3 ligase modulating compound. In certain embodiments, the ABC/MEM-like treatment further comprises a therapeutically effective amount of an anti-CD20 antibody. In certain embodiments, the ABC/MEM-like treatment comprises a combination of therapeutically effective amounts of the IMiD[®] and/or the cereblon E3 ligase modulating compounds, and the anti-CD20 antibody. Further description of the ABC/MEM-like treatment discloses herein is provided in Section 5.3.

[00105] In another aspect, provided herein is a method of identifying a subject as having a GCB-like FL, comprising: (a) determining the gene expression level of at least one biomarker in a sample from the subject; (b) determining a composite score based on the gene expression level of the at least one biomarker; and (c) identifying the subject as having GCB-like FL based on the composite score. In certain embodiments, the method further comprises treating the subject with a GCB-like FL treatment (*e.g.*, a GCB-like FL treatment as disclosed in Section 5.3).

[00106] In another aspect, provided herein is a method of selectively treating a subject having FL, comprising: (a) determining the gene expression level of at least one biomarker in a sample; (b) determining a composite score based on the gene expression level of the at least one biomarker; (c) identifying the subject as having GCB-like FL based on the composite score; and (d) administering to the subject identified as having GCB-like FL a GCB-like FL treatment (*e.g.*, a GCB-like FL treatment as disclosed in Section 5.3).

[00107] In another aspect, provided herein is a method identifying a subject who is likely to be responsive to a treatment of GCB-like FL or predicting the responsiveness of a subject to a treatment of GCB-like FL, comprising (a) determining the gene expression level of at least one biomarker in a sample of the subject, (b) determining a composite score based on the gene expression level of the at least one biomarker; (c) identifying or predicting the subject as being likely to be responsive to the treatment of GCB-like FL based on the composite score. In certain embodiments, the method further comprises administering the treatment of GCB-like FL to the subject likely to be responsive to the treatment of GCB-like FL.

[00108] In certain embodiments, the GCB-like treatment disclosed herein comprises a therapeutically effective amount of an immunomodulatory drug (IMiD[®]), an anti-CD20 antibody, a chemotherapeutic agent, or a combination thereof. In certain embodiments, the GCB-like treatment comprises a combination of therapeutically effective amounts of an IMiD[®] and an anti-CD20 antibody. In certain embodiments, the GCB-like treatment disclosed herein comprises a therapeutically effective amount of a cereblon E3 ligase modulating compound, an anti-CD20 antibody, a chemotherapeutic agent, or a combination thereof. In certain embodiments, the GCB-like treatment comprises a combination of therapeutically effective amounts of a cereblon E3 ligase modulating compound and an anti-CD20 antibody. In certain embodiments, the GCB-like treatment comprises a combination of therapeutically effective amounts of an anti-CD20 antibody and at least one chemotherapeutic agent. In certain embodiments, the GCB-like treatment comprises a combination of therapeutically effective amounts of an anti-CD20 antibody and two or more (*e.g.*, two, three, four, five) chemotherapeutic agents. In certain embodiments, the GCB-like treatment disclosed herein further comprises a steroid hormone. In certain embodiments, the GCB-like treatment comprises a combination of therapeutically effective amounts of an anti-CD20 antibody, at least one chemotherapeutic agent, and a steroid hormone. In certain embodiments, the GCB-like treatment comprises a combination of therapeutically effective amounts of an anti-CD20 antibody, and two or more (*e.g.*, two, three, four, five) chemotherapeutic agents, and a steroid

hormone. Further description of the GCB-like treatment disclosed herein is provided in Section 5.3.

[00109] In certain embodiments, the methods disclosed herein further comprises obtaining the sample from the subject.

[00110] In certain embodiments, the biomarker is selected from the group consisting of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1.

[00111] In certain embodiments, the subject is a subject having FL or suspected of having FL. In certain embodiments, the subject is a human subject.

[00112] In certain embodiments, the sample is a peripheral blood sample. In certain embodiments, the sample is a tissue sample. In certain embodiments, the sample is a tumor biopsy. In certain embodiments, the sample disclosed herein comprises FL cells. More detailed description of the sample (*e.g.*, biological sample) is provided in Section 5.5 below.

[00113] In certain embodiments, the composite score is a gene signature comprising a set of genes found to be increased or decreased in a subject with one subtype of FL (*e.g.*, ABC/MEM-like FL) compared to a subject with another subtype of FL (*e.g.*, GCB-like FL). In certain embodiments, the composite score indicates a subject having ABC/MEM-like FL. In certain embodiments, the composite score indicates a subject having GCB-like FL.

[00114] In certain embodiments, the composite score is determined based on the gene expression level of one or more biomarkers selected from the group consisting of: TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1.

[00115] In certain embodiments, the composite score is determined based on the gene expression level of one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, or twenty biomarkers selected from the group consisting of: TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1.

[00116] In certain embodiments, the composite score is calculated as the weighted sum of the gene expression level of one or more biomarkers selected from the group consisting of: TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1.

[00117] In certain embodiments, the composite score is calculated as follows: (gene expression level of TTC28 × weight of TTC28) + (gene expression level of FOXP1 × weight of FOXP1) +

(gene expression level of DOPEY2 $\times$ weight of DOPEY2) + (gene expression level of IQSEC1 $\times$ weight of IQSEC1) + (gene expression level of PTPRJ $\times$ weight of PTPRJ) + (gene expression level of SLA $\times$ weight of SLA) + (gene expression level of CXXC5 $\times$ weight of CXXC5) + (gene expression level of PDE4B $\times$ weight of PDE4B) + (gene expression level of TCF4 $\times$ weight of TCF4) + (gene expression level of MPEG1 $\times$ weight of MPEG1) + (gene expression level of KIAA1211 $\times$ weight of KIAA1211) + (gene expression level of SCPEP1 $\times$ weight of SCPEP1) + (gene expression level of RASL11A $\times$ weight of RASL11A) + (gene expression level of LMO2 $\times$ weight of LMO2) + (gene expression level of HS2ST1 $\times$ weight of HS2ST1) + (gene expression level of ENPP3 $\times$ weight of ENPP3) + (gene expression level of SH3RF1 $\times$ weight of SH3RF1) + (gene expression level of SCIMP $\times$ weight of SCIMP) + (gene expression level of CCDC138 $\times$ weight of CCDC138) + (gene expression level of SHCBP1 $\times$ weight of SHCBP1).

[00118] In certain embodiments, the composite score is calculated as follows: (gene expression level of TTC28 $\times$ weight of TTC28) + (gene expression level of FOXP1 $\times$ weight of FOXP1) + (gene expression level of DOPEY2 $\times$ weight of DOPEY2) + (gene expression level of IQSEC1 $\times$ weight of IQSEC1) + (gene expression level of PTPRJ $\times$ weight of PTPRJ) + (gene expression level of SLA $\times$ weight of SLA) + (gene expression level of CXXC5 $\times$ weight of CXXC5) + (gene expression level of PDE4B $\times$ weight of PDE4B) + (gene expression level of TCF4 $\times$ weight of TCF4) + (gene expression level of MPEG1 $\times$ weight of MPEG1).

[00119] In certain embodiments, the composite score is calculated as follows: (gene expression level of KIAA1211 $\times$ weight of KIAA1211) + (gene expression level of SCPEP1 $\times$ weight of SCPEP1) + (gene expression level of RASL11A $\times$ weight of RASL11A) + (gene expression level of LMO2 $\times$ weight of LMO2) + (gene expression level of HS2ST1 $\times$ weight of HS2ST1) + (gene expression level of ENPP3 $\times$ weight of ENPP3) + (gene expression level of SH3RF1 $\times$ weight of SH3RF1) + (gene expression level of SCIMP $\times$ weight of SCIMP) + (gene expression level of CCDC138 $\times$ weight of CCDC138) + (gene expression level of SHCBP1 $\times$ weight of SHCBP1).

[00120] In certain embodiments, the weighted value for the gene expression level of one or more or all biomarkers selected from the group consisting of: TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, and MPEG1 is less than zero. In certain embodiments, the weighted value for the gene expression level of one or more or all biomarkers selected from the group consisting of: TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, and MPEG1 is between about -20 and about -10. In certain embodiments, the weighted value for the gene expression level of one or more or all biomarkers

selected from the group consisting of: TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, and MPEG1 is between about -19 and about -12, between about -19 and about -13, between about -18 and about -12, or between about -18 and about -13.

[00121] In certain embodiments, the weighted value for the gene expression level of one or more or all biomarkers selected from the group consisting of: KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1 is more than zero. In certain embodiments, the weighted value for the gene expression level of one or more or all biomarkers selected from the group consisting of: KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1 is between about 10 and about 20. In certain embodiments, the weighted value for the gene expression level of one or more or all biomarkers selected from the group consisting of: KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1 is between about 15 and about 19 or between about 15 and about 18.

[00122] In certain embodiments, the composite score is calculated as follows: (gene expression level of TTC28 $\times$ -12.90235) + (gene expression level of FOXP1 $\times$ -17.20497) + (gene expression level of DOPEY2 $\times$ -14.08426) + (gene expression level of IQSEC1 $\times$ -14.14635) + (gene expression level of PTPRJ $\times$ -15.78924) + (gene expression level of SLA $\times$ -13.44714) + (gene expression level of CXXC5 $\times$ -13.21572) + (gene expression level of PDE4B $\times$ -14.31872) + (gene expression level of TCF4 $\times$ -18.17919) + (gene expression level of MPEG1 $\times$ -16.21973) + (gene expression level of KIAA1211 $\times$ 15.81861) + (gene expression level of SCPEP1 $\times$ 15.97033) + (gene expression level of RASL11A $\times$ 17.50829) + (gene expression level of LMO2 $\times$ 17.18333) + (gene expression level of HS2ST1 $\times$ 15.22055) + (gene expression level of ENPP3 $\times$ 15.22908) + (gene expression level of SH3RF1 $\times$ 15.60008) + (gene expression level of SCIMP $\times$ 18.07827) + (gene expression level of CCDC138 $\times$ 15.04494) + (gene expression level of SHCBP1 $\times$ 15.84456).

[00123] In certain embodiments, the composite score is calculated as follows: (gene expression level of TTC28 $\times$ -12.9) + (gene expression level of FOXP1 $\times$ -17.2) + (gene expression level of DOPEY2 $\times$ -14.1) + (gene expression level of IQSEC1 $\times$ -14.1) + (gene expression level of PTPRJ $\times$ -15.8) + (gene expression level of SLA $\times$ -13.4) + (gene expression level of CXXC5 $\times$ -13.2) + (gene expression level of PDE4B $\times$ -14.3) + (gene expression level of TCF4 $\times$ -18.2) + (gene expression level of MPEG1 $\times$ -16.2) + (gene expression level of KIAA1211 $\times$ 15.8) + (gene expression level of SCPEP1 $\times$ 16.0) + (gene expression level of RASL11A $\times$ 17.5) + (gene expression level of LMO2 $\times$ 17.2) + (gene expression level of HS2ST1 $\times$ 15.2) + (gene expression level of ENPP3 $\times$ 15.2) + (gene expression level of SH3RF1 $\times$ 15.6) + (gene

expression level of SCIMP $\times$ 18.1) + (gene expression level of CCDC138 $\times$ 15.0) + (gene expression level of SHCBP1 $\times$ 15.8).

[00124] In certain embodiments, the composite score is calculated as follows: (gene expression level of TTC28 $\times$ -12.90235) + (gene expression level of FOXP1 $\times$ -17.20497) + (gene expression level of DOPEY2 $\times$ -14.08426) + (gene expression level of IQSEC1 $\times$ -14.14635) + (gene expression level of PTPRJ $\times$ -15.78924) + (gene expression level of SLA $\times$ -13.44714) + (gene expression level of CXXC5 $\times$ -13.21572) + (gene expression level of PDE4B $\times$ -14.31872) + (gene expression level of TCF4 $\times$ -18.17919) + (gene expression level of MPEG1 $\times$ -16.21973). In certain embodiments, the composite score is calculated as follows: (gene expression level of KIAA1211 $\times$ 15.81861) + (gene expression level of SCPEP1 $\times$ 15.97033) + (gene expression level of RASL11A $\times$ 17.50829) + (gene expression level of LMO2 $\times$ 17.18333) + (gene expression level of HS2ST1 $\times$ 15.22055) + (gene expression level of ENPP3 $\times$ 15.22908) + (gene expression level of SH3RF1 $\times$ 15.60008) + (gene expression level of SCIMP $\times$ 18.07827) + (gene expression level of CCDC138 $\times$ 15.04494) + (gene expression level of SHCBP1 $\times$ 15.84456).

[00125] In certain embodiments, the composite score is calculated as follows: (gene expression level of TTC28 $\times$ -12.9) + (gene expression level of FOXP1 $\times$ -17.2) + (gene expression level of DOPEY2 $\times$ -14.1) + (gene expression level of IQSEC1 $\times$ -14.1) + (gene expression level of PTPRJ $\times$ -15.8) + (gene expression level of SLA $\times$ -13.4) + (gene expression level of CXXC5 $\times$ -13.2) + (gene expression level of PDE4B $\times$ -14.3) + (gene expression level of TCF4 $\times$ -18.2) + (gene expression level of MPEG1 $\times$ -16.2). In certain embodiments, the composite score is calculated as follows: (gene expression level of KIAA1211 $\times$ 15.8) + (gene expression level of SCPEP1 $\times$ 16.0) + (gene expression level of RASL11A $\times$ 17.5) + (gene expression level of LMO2 $\times$ 17.2) + (gene expression level of HS2ST1 $\times$ 15.2) + (gene expression level of ENPP3 $\times$ 15.2) + (gene expression level of SH3RF1 $\times$ 15.6) + (gene expression level of SCIMP $\times$ 18.1) + (gene expression level of CCDC138 $\times$ 15.0) + (gene expression level of SHCBP1 $\times$ 15.8).

[00126] In certain embodiments, a subject is identified as having ABC/MEM-like FL or is identified or predicted as being likely to be responsive to the treatment of ABC/MEM-like FL if the composite score is lower than a predetermined value. In certain embodiments, a subject is identified as having GCB-like FL or is identified or predicted as being likely to be responsive to the treatment of GCB-like FL if the composite score is higher than a predetermined value. In certain embodiments, the predetermined value is zero or about zero.

[00127] In certain embodiments, a subject is identified as having ABC/MEM-like FL or is identified or predicted as being likely to be responsive to the treatment of ABC/MEM-like FL if

the composite score is lower than a reference score. In certain embodiments, a subject is identified as having GCB-like FL or is identified or predicted as being likely to be responsive to the treatment of GCB-like FL if the composite score is higher than a reference score. In certain embodiments, the reference score is derived from a healthy subject or a population of healthy subjects. In certain embodiments, the reference score is calculated the same way as the composite score. In certain embodiments, the reference score is zero or about zero.

[00128] In another aspect, provided herein is a method of identifying a subject as having an ABC/MEM-like FL, comprising: (a) determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1 in a sample from the subject; and (b) identifying the subject as having ABC/MEM-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1. In certain embodiments, the method further comprises treating the subject with an ABC/MEM-like FL treatment (*e.g.*, an ABC/MEM-like FL treatment as disclosed in Section 5.3).

[00129] In another aspect, provided herein is a method of selectively treating a subject having FL, comprising: (a) determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1 in a sample of the subject; (b) identifying the subject as having ABC/MEM-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and (c) administering to the subject identified as having ABC/MEM-like FL an ABC/MEM-like FL treatment (*e.g.*, an ABC/MEM-like FL treatment as disclosed in Section 5.3).

[00130] In another aspect, provided herein is a method identifying a subject who is likely to be responsive to a treatment of ABC/MEM-like FL (*e.g.*, an ABC/MEM-like FL treatment as disclosed in section 5.3) or predicting the responsiveness of a subject to a treatment of ABC/MEM-like FL, comprising (a) determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1 in a sample of the subject; and (b) identifying or predicting the subject as being likely to be responsive to the treatment of ABC/MEM-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1. In certain embodiments, the method further comprises administering the treatment of ABC/MEM-like FL to the subject likely to be responsive to the treatment of ABC/MEM-like FL.

[00131] In certain embodiments, the ABC/MEM-like treatment disclosed herein comprises a therapeutically effective amount of an immunomodulatory drug (IMiD®). In certain embodiments, the ABC/MEM-like treatment disclosed herein comprises a therapeutically effective amount of a cereblon E3 ligase modulating compound. In certain embodiments, the ABC/MEM-like treatment further comprises a therapeutically effective amount of an anti-CD20 antibody. In certain embodiments, the ABC/MEM-like treatment comprises a combination of

therapeutically effective amounts of the IMiD[®] and/or cereblon E3 ligase modulating compound, and anti-CD20 antibody. Further description of the ABC/MEM-like treatment disclosed herein is provided in Section 5.3.

[00132] In another aspect, provided herein is a method of identifying a subject as having a GCB-like FL, comprising: (a) determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1 in a sample from the subject; and (b) identifying the subject as having GCB-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1. In certain embodiments, the method further comprises treating the subject with a GCB-like FL treatment (*e.g.*, a GCB-like FL treatment as disclosed in Section 5.3).

[00133] In another aspect, provided herein is a method of selectively treating a subject having FL, comprising: (a) determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1 in a sample; (b) identifying the subject as having GCB-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and (c) administering to the subject identified as having GCB-like FL a GCB-like FL treatment (*e.g.*, a GCB-like FL treatment as disclosed in Section 5.3).

[00134] In another aspect, provided herein is a method identifying a subject who is likely to be responsive to a treatment of GCB-like FL (*e.g.*, a GCB-like FL treatment as disclosed in section 5.3) or predicting the responsiveness of a subject to a treatment of GCB-like FL, comprising (a) determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1 in a sample of the subject; and (b) identifying or predicting the subject as being likely to be responsive to the treatment of GCB-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1. In certain embodiments, the method further comprises administering the treatment of GCB-like FL to the subject likely to be responsive to the treatment of GCB-like FL.

[00135] In certain embodiments, the GCB-like treatment disclosed herein comprises a therapeutically effective amount of an immunomodulatory drug (IMiD[®]), an anti-CD20 antibody, a chemotherapeutic agent, or a combination thereof. In certain embodiments, the GCB-like treatment comprises a combination of therapeutically effective amounts of an IMiD[®] and an anti-CD20 antibody. In certain embodiments, the GCB-like treatment disclosed herein comprises a therapeutically effective amount of a cereblon E3 ligase modulating compound, an anti-CD20 antibody, a chemotherapeutic agent, or a combination thereof. In certain embodiments, the GCB-like treatment comprises a combination of therapeutically effective amounts of a cereblon E3 ligase modulating compound and an anti-CD20 antibody. In certain embodiments, the GCB-like treatment comprises a combination of therapeutically effective amounts of an anti-CD20 antibody and at least one chemotherapeutic agent. In certain

embodiments, the GCB-like treatment comprises a combination of therapeutically effective amounts of an anti-CD20 antibody and two or more (*e.g.*, two, three, four, five) chemotherapeutic agents. In certain embodiments, the GCB-like treatment disclosed herein further comprises a steroid hormone. In certain embodiments, the GCB-like treatment comprises a combination of therapeutically effective amounts of an anti-CD20 antibody, at least one chemotherapeutic agent, and a steroid hormone. In certain embodiments, the GCB-like treatment comprises a combination of therapeutically effective amounts of an anti-CD20 antibody, and two or more (*e.g.*, two, three, four, five) chemotherapeutic agents, and a steroid hormone.

[00136] In certain embodiments, the methods disclosed herein further comprises obtaining the sample from the subject.

[00137] In certain embodiments, the expression levels of FOXP1, LMO2, CD22, and MUM1 are the protein levels of FOXP1, LMO2, CD22, and MUM1. In certain embodiments, the protein levels of FOXP1, LMO2, CD22, and MUM1 are measured using immunohistochemistry (IHC). In some embodiments, the protein levels of FOXP1, LMO2, CD22, and MUM1 are measured using Multiplexed Ion Beam Imaging (MIBI). In some embodiments, the protein levels of FOXP1, LMO2, CD22, and MUM1 are measuring using Imaging Mass Cytometry (IMC). Additional methods for measuring protein levels of FOXP1, LMO2, and MUM1 are disclosed in Section 5.6.

[00138] In certain embodiments, the expression level of a protein is determined based on whether a cell is positive or negative for the protein. In certain embodiments, the expression level of FOXP1, LMO2, CD22, and MUM1 is determined based on whether a cell is positive or negative for FOXP1, LMO2, CD22, and MUM1. In certain embodiments, a cell is positive for FOXP1, LMO2, CD22, or MUM1 if there is strong or moderate staining of the respective protein in the cell. In certain embodiments, a cell is negative for FOXP1, LMO2, CD22, or MUM1 if there is weak or no staining of the respective protein in the cell.

[00139] In certain embodiments, the subject is identified as having ABC/MEM-like FL or is identified or predicted as being likely to be responsive to the treatment of ABC/MEM-like FL if the protein expression level of FOXP1 is strong or moderate and the protein expression level of LMO2 is weak or negative. In certain embodiments, the subject is identified as having ABC/MEM-like FL or is identified or predicted as being likely to be responsive to the treatment of ABC/MEM-like FL if the protein expression level of FOXP1 is significantly different from the protein expression level of LMO2, where the percentage of FOXP1 positive cells in the sample is more than about 50% and the percentage of LMO2 positive cells in the sample is less

than about 50%, and the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is about 20% or more. In certain embodiments, the subject is identified as having ABC/MEM-like FL or is identified or predicted as being likely to be responsive to the treatment of ABC/MEM-like FL if the protein expression level of FOXP1 is close to the protein expression level of LMO2 (equally strong, moderate, or weak) or otherwise noninformative, and the protein expression level of CD22 is weak. In certain embodiments, the subject is identified as having ABC/MEM-like FL if the protein expression level of FOXP1 is close to that of the protein expression level of LMO2 (equally strong, moderate or weak) or otherwise noninformative, and the protein expression level of CD22 is moderate or otherwise noninformative and the percentage of MUM1 positive cells in the sample is greater than about 15%. In certain embodiments, the protein expression level of CD22 is weak if the percentage of CD22 positive cells in the sample is less than about 20%. In certain embodiments, the protein expression level of CD22 is moderate or otherwise noninformative if the percentage of CD22 positive cells in the sample is between about 20% and about 80%. In certain embodiments, the protein expression level of FOXP1 is close to that of the protein expression level of LMO2 (equally strong, moderate or weak) or otherwise noninformative if the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is less than about 20%.

[00140] In certain embodiments, the subject is identified as having ABC/MEM-like FL or is identified or predicted as being likely to be responsive to the treatment of ABC/MEM-like FL if (i) the percentage of FOXP1 positive cells in the sample is more than about 50% and the percentage of LMO2 positive cells in the sample is less than about 50%, and the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is about 20% or more; (ii) if the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is less than about 20%, and the percentage of CD22 positive cells in the sample is less than about 20%; or (iii) if the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is less than about 20%, and the percentage of CD22 positive cells in the sample is between about 20% and about 80%, and the percentage of MUM1 positive cells in the sample is greater than about 15%.

[00141] In certain embodiments, the subject is identified as having GCB-like FL or is identified or predicted as being likely to be responsive to the treatment of GCB-like FL if the protein expression level of FOXP1 is weak or negative and the protein expression level of LMO2 is strong or moderate. In certain embodiments, the subject is identified as having GCB-like FL or

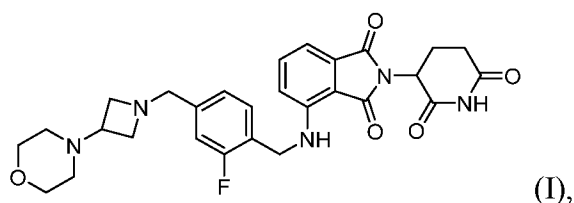
is identified or predicted as being likely to be responsive to the treatment of GCB-like FL if the protein expression level of FOXP1 is significantly different from the protein expression level of LMO2, where the percentage of FOXP1 positive cells in the sample is less than about 50% and the percentage of LMO2 positive cells in the sample is more than about 50%, and difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is about 20% or more. In certain embodiments, the subject is identified as having GCB-like FL or is identified or predicted as being likely to be responsive to the treatment of GCB-like FL if the protein expression level of LMO2 is close to that of the protein expression level of FOXP1 (equally strong, moderate, or weak) or otherwise noninformative, and the protein expression level of CD22 is strong. In certain embodiments, the subject is identified as having GCB-like FL or is identified or predicted as being likely to be responsive to the treatment of GCB-like FL if the protein expression level of LMO2 is close to that of FOXP1 (equally strong, moderate, or weak) or otherwise noninformative, and the protein expression level of CD22 is moderate or otherwise noninformative, and the percentage of MUM1 positive cells in the sample is less than about 10%. In certain embodiments, the protein expression level of LMO2 is close to that of the protein expression level of FOXP1 (equally strong, moderate, or weak) or otherwise noninformative if the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is less than about 20%. In certain embodiments, the protein expression level of CD22 is strong if the percentage of CD22 positive cells in the sample is greater than about 80%. In certain embodiments, the protein expression level of CD22 is moderate or otherwise noninformative if the percentage of CD22 positive cells in the sample is between about 20% and about 80%.

[00142] In certain embodiments, the subject is identified as having GCB-like FL or is identified or predicted as being likely to be responsive to the treatment of GCB-like FL if (i) the percentage of LMO2 positive cells in the sample is more than about 50% and the percentage of FOXP1 positive cells in the sample is less than about 50%, and the difference between the percentage of LMO2 positive cells in the sample and the percentage of FOXP1 positive cells in the sample is about 20% or more, (ii) if the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is less than about 20%, and the percentage of CD22 cells in the sample is greater than about 80%; or (iii) if the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is less than about 20%, the percentage of CD22 positive cells in the sample is between about 20% and about 80%, and the percentage of MUM1 positive cells in the sample is less than about 10%.

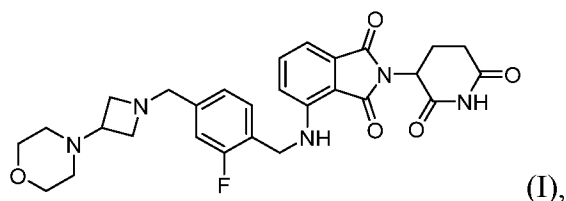
[00143] In certain embodiments, strong, moderate, weak, or negative protein level is determined by staining intensity measured by immunohistochemistry methods. One skilled in the art would understand how to determine strong, moderate, weak, and negative protein levels using methods known in the art (*e.g.*, H-score, Allred-score, and Immunoreactive score).

5.3 ABC/MEM-like FL Treatments and GCB-like FL Treatments

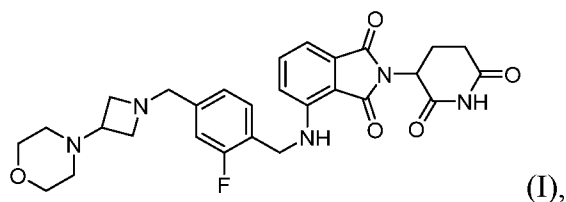
[00144] In certain embodiments, the ABC/MEM-like treatment disclosed herein comprises a therapeutically effective amount of an immunomodulatory drug (IMiD[®]). In certain embodiments, the ABC/MEM-like treatment disclosed herein comprises a therapeutically effective amount of a cereblon E3 ligase modulating compound. In certain embodiments, the ABC/MEM-like treatment further comprises a therapeutically effective amount of an anti-CD20 antibody. In certain embodiments, the ABC/MEM-like treatment comprises a combination of therapeutically effective amounts of the IMiD[®] and/or the cereblon E3 ligase modulating compound, and the anti-CD20 antibody. In certain embodiments, the IMiD[®] and/or cereblon E3 ligase modulating compound is selected from the group consisting of lenalidomide, pomalidomide, thalidomide, iberdomide, and a compound of formula (I)



and enantiomers, mixture of enantiomers, tautomers, isotopologs, and pharmaceutically acceptable salts thereof. In certain embodiments, the IMiD[®] is selected from the group consisting of lenalidomide, pomalidomide, and thalidomide, and enantiomers, mixture of enantiomers, tautomers, isotopologs, and pharmaceutically acceptable salts thereof. In certain embodiments, the cereblon E3 ligase modulating compound is selected from the group consisting of iberdomide and a compound of Formula (I)



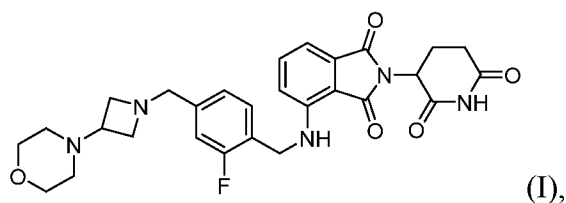
and enantiomers, mixture of enantiomers, tautomers, isotopologs, and pharmaceutically acceptable salts thereof. In certain embodiments, the cereblon E3 ligase modulating compound is selected from the group consisting of lenalidomide, pomalidomide, thalidomide, iberdomide, and a compound of Formula (I)



and enantiomers, mixture of enantiomers, tautomers, isotopologs, and pharmaceutically acceptable salts thereof.

[00145] In certain embodiments, the ABC/MEM-like treatment disclosed herein comprises therapeutically effective amounts of rituximab and lenalidomide, or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

[00146] In certain embodiments, the ABC/MEM-like treatment disclosed herein comprises therapeutically effective amounts of rituximab and a compound of Formula (I)

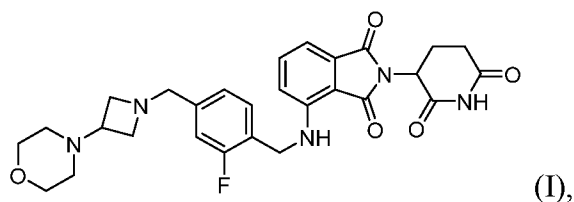


or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

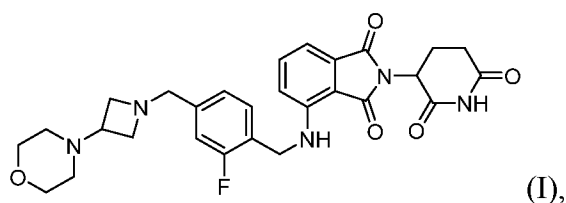
[00147] In certain embodiments, the GCB-like treatment disclosed herein comprises a therapeutically effective amount of an IMiD[®], a cereblon E3 ligase modulating compound, an anti-CD20 antibody, a chemotherapeutic agent, or a combination thereof. In certain embodiments, the GCB-like treatment comprises a combination of the IMiD[®] and an anti-CD20 antibody. In certain embodiments, the GCB-like treatment comprises a combination of the cereblon E3 ligase modulating compound and an anti-CD20 antibody. In certain embodiments, the GCB-like treatment comprises a combination of the anti-CD20 antibody and chemotherapeutic agent. In certain embodiments, the GCB-like treatment comprises a combination of the anti-CD20 antibody and two or more chemotherapeutic agents (*e.g.*, two, three, four, five or more chemotherapeutic agents). In certain embodiments, the GCB-like treatment comprises a combination of the anti-CD20 antibody and three chemotherapeutic agents. In certain embodiments, the GCB-like treatment disclosed herein further comprises a steroid hormone. In certain embodiments, the GCB-like treatment comprises a combination of therapeutically effective amounts of an anti-CD20 antibody, at least one chemotherapeutic agent, and a steroid hormone. In certain embodiments, the GCB-like treatment comprises a combination of therapeutically effective amounts of an anti-CD20 antibody, and two or more chemotherapeutic agents (*e.g.*, two, three, four, five or more chemotherapeutic agents)

chemotherapeutic agents, and a steroid hormone. In certain embodiments, the GCB-like treatment comprises a combination of the anti-CD20 antibody, three chemotherapeutic agents, and a steroid hormone.

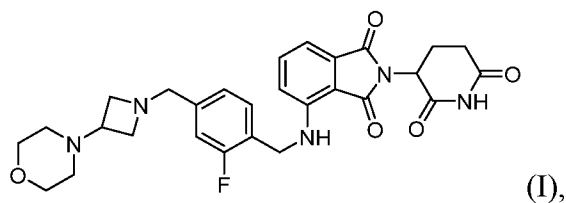
[00148] In certain embodiments, the GCB-like treatment disclosed herein comprises therapeutically effective amounts of rituximab and lenalidomide, or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof. In certain embodiments, the GCB-like treatment comprises a combination of the cereblon E3 ligase modulating compound and rituximab. In certain embodiments, the IMiD[®] and/or cereblon E3 ligase modulating compound disclosed herein is selected from the group consisting of lenalidomide, pomalidomide, thalidomide, iberdomide, and a compound of formula (I)



or enantiomers, mixture of enantiomers, tautomers, isotopologs, and pharmaceutically acceptable salts thereof. In certain embodiments, the IMiD[®] is selected from the group consisting of lenalidomide, pomalidomide, and thalidomide, and enantiomers, mixture of enantiomers, tautomers, isotopologs, and pharmaceutically acceptable salts thereof. In certain embodiments, the cereblon E3 ligase modulating compound is selected from the group consisting of iberdomide and a compound of Formula (I)

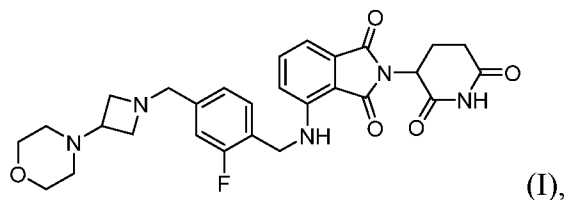


and enantiomers, mixture of enantiomers, tautomers, isotopologs, and pharmaceutically acceptable salts thereof. In certain embodiments, the cereblon E3 ligase modulating compound is selected from the group consisting of lenalidomide, pomalidomide, thalidomide, iberdomide, and a compound of Formula (I)



and enantiomers, mixture of enantiomers, tautomers, isotopologs, and pharmaceutically acceptable salts thereof.

[00149] In certain embodiments, the GCB-like treatment disclosed herein comprises therapeutically effective amounts of rituximab and a compound of Formula (I)



or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

[00150] In certain embodiments, the GCB-like treatment disclosed herein comprises therapeutically effective amounts of rituximab, cyclophosphamide, doxorubicin hydrochloride, and vincristine sulfate.

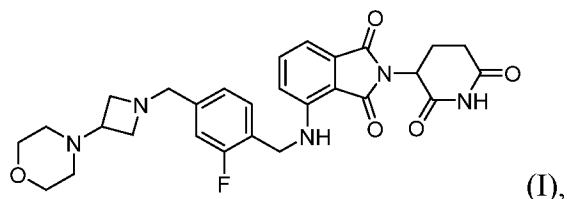
[00151] In certain embodiments, the GCB-like treatment comprises a combination of an anti-CD20 antibody, a chemotherapeutic agent, and a steroid hormone. In certain embodiments, the steroid hormone is prednisone. In certain embodiments, the GCB-like treatment disclosed herein comprises therapeutically effective amounts of rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone

[00152] Therapeutic agents in a combination therapy can be administered at the same time or as a separate course of treatment. As used herein, the term “in combination” does not restrict the order in which therapies (*e.g.*, prophylactic and/or therapeutic agents) are administered to a patient with a disease or disorder. Administration of a second treatment provided herein, to a patient can occur simultaneously or sequentially by the same or different routes of administration. The suitability of a particular route of administration employed for a particular active agent will depend on the active agent itself (*e.g.*, whether it can be administered orally without decomposing prior to entering the blood stream).

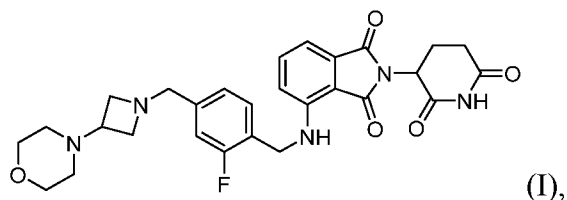
[00153] In certain embodiments, IMiD[®]s disclosed herein comprise a group of compounds that can be useful to treat several types of human diseases, including certain cancers. As used herein and unless otherwise indicated, the term “immunomodulatory compound” can encompass cereblon (CRBN) modulators. In certain embodiments, a CRBN modulator is an agent that can modulate at least one of CRBN’s biological activities directly or indirectly. In certain embodiments, a CRBN modulator is an agent that can physically bind to CRBN. In other embodiments, a CRBN modulator does not directly bind to CRBN, but can otherwise exert an effect via a CRBN mediated pathway. CRBN, a component of the DDB1-CUL4a-Roc1 ubiquitin ligase complex, has been identified as a target of certain immunomodulatory compounds, *e.g.*, thalidomide, lenalidomide, and pomalidomide. It is believed that the

interactions of CRBN with certain immunomodulatory compounds mediate their anti-proliferative effects in multiple myeloma (MM) cells (Lopez-Girona *et al.*, *Leukemia* 2012; Zhu *et al.*, *Blood* 2011, 118, Abstract 127). CRBN is encoded by a 25 kb gene on chromosome 6, consisting of 11 exons and 10 introns. Thus, alternative splicing process can potentially generate multiple functional proteins as well as variants of a protein from a single gene having different structural organization and functional activity. Truncated proteins that have lost interaction domains or critical functional amino acid residues may create non-functional or aberrant CRBN proteins that may interfere with the functions of the full-length CRBN protein and reduce or alter the therapeutic activity of a treatment compound that exerts its activity *via* its interactions with the full-length CRBN protein. At least two isoforms of the protein cereblon (CRBN) exist, which are 442 and 441 amino acids long, respectively, and CRBN is conserved from plant to human. In humans, the CRBN gene has been identified as a candidate gene of an autosomal recessive nonsyndromic mental retardation (ARNSMR). *See* Higgins, J.J. *et al.*, *Neurology*, 2004, 63:1927-1931. CRBN was initially characterized as an RGS-containing novel protein that interacted with a calcium-activated potassium channel protein (SLO1) in the rat brain, and was later shown to interact with a voltage-gated chloride channel (CIC-2) in the retina with AMPK1 and DDB1. *See* Jo, S. *et al.*, *J. Neurochem*, 2005, 94:1212-1224; Hohberger B. *et al.*, *FEBS Lett*, 2009, 583:633-637; Angers S. *et al.*, *Nature*, 2006, 443:590-593. DDB1 was originally identified as a nucleotide excision repair protein that associates with damaged DNA binding protein 2 (DDB2). Its defective activity causes the repair defect in the patients with xeroderma pigmentosum complementation group E (XPE). DDB1 also appears to function as a component of numerous distinct DCX (DDB1-CUL4-X-box) E3 ubiquitin-protein ligase complexes which mediate the ubiquitination and subsequent proteasomal degradation of target proteins. CRBN has also been identified as a target for the development of therapeutic agents for diseases of the cerebral cortex. *See* WO 2010/137547 A1. In certain embodiments, binding to CRBN or one or more substrates of CRBN is required for the beneficial effects of certain treatment compounds provided herein. In certain embodiments, the compound provided herein to treat CFS can induce CRBN to undergo conformational changes. In certain embodiments, the use of a treatment compound provided herein leads to a distinct conformational change or other alteration in the properties of the CRBN surface, and a resulting distinct phenotypic response. **[00154]** In certain embodiments, compounds disclosed herein are cereblon E3 ligase modulating compounds. In certain embodiments, a cereblon E3 ligase modulating compound is an agent that can modulate at least one of cereblon E3 ligase's biological activities directly or indirectly. In certain embodiments, the cereblon E3 ligase modulating compound is an IMiD®. In certain

embodiments, the IMiD[®] is selected from the group consisting of lenalidomide, pomalidomide, and thalidomide, and enantiomers, mixture of enantiomers, tautomers, isotopologs, and pharmaceutically acceptable salts thereof. In certain embodiments, the cereblon E3 ligase modulating compound is selected from the group consisting of iberdomide and a compound of Formula (I)



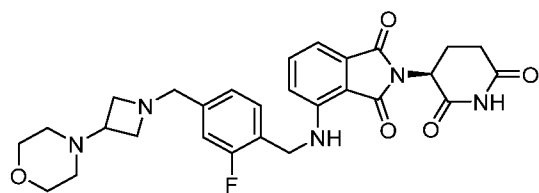
and enantiomers, mixture of enantiomers, tautomers, isotopologs, and pharmaceutically acceptable salts thereof. In certain embodiments, the cereblon E3 ligase modulating compound is selected from the group consisting of lenalidomide, pomalidomide, thalidomide, iberdomide, and a compound of Formula (I)



and enantiomers, mixture of enantiomers, tautomers, isotopologs, and pharmaceutically acceptable salts thereof.

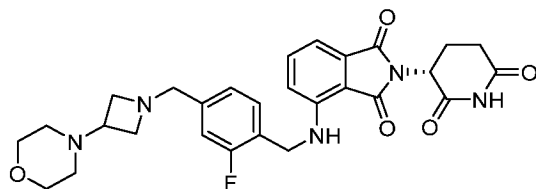
[00155] In certain embodiments, the cereblon E3 ligase modulating compound is iberdomide (Lopez-Girona *et al.*, *Leukemia* volume 26, pages 2326–2335 (2012); Bjorklund *et al.*, *Leukemia*. 2020; 34(4): 1197–1201), or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

[00156] In certain embodiments, the cereblon E3 ligase modulating compound is (S)-2-(2,6-dioxopiperidin-3-yl)-4-((2-fluoro-4-((3-morpholinoazetidin-1-yl)methyl)benzyl)amino)isoindoline-1,3-dione (Compound 1):



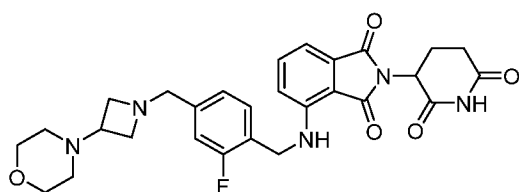
or a tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

[00157] In certain embodiments, the cereblon E3 ligase modulating compound is (R)-2-(2,6-dioxopiperidin-3-yl)-4-((2-fluoro-4-((3-morpholinoazetidin-1-yl)methyl)benzyl)amino)isoindoline-1,3-dione (Compound 2):



or a tautomer, isotopolog or pharmaceutically acceptable salt thereof.

[00158] In certain embodiments, the cereblon E3 ligase modulating compound comprises a mixture of (S)-2-(2,6-dioxopiperidin-3-yl)-4-((2-fluoro-4-((3-morpholinoazetidin-1-yl)methyl)benzyl)amino)isoindoline-1,3-dione, and (R)-2-(2,6-dioxopiperidin-3-yl)-4-((2-fluoro-4-((3-morpholinoazetidin-1-yl)methyl)benzyl)amino)isoindoline-1,3-dione (Compound 3):



or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

[00159] In certain embodiments, the cereblon E3 ligase modulating compound or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer or racemic mixtures thereof, such as any of the compounds described in this section, can be administered to a subject orally, topically or parenterally in the conventional form of preparations, such as capsules, microcapsules, tablets, granules, powder, troches, pills, suppositories, injections, suspensions, syrups, patches, creams, lotions, ointments, gels, sprays, solutions and emulsions. Suitable formulations can be prepared by methods commonly employed using conventional, organic or inorganic additives, such as an excipient (*e.g.*, sucrose, starch, mannitol, sorbitol, lactose, glucose, cellulose, talc, calcium phosphate or calcium carbonate), a binder (*e.g.*, cellulose, methylcellulose, hydroxymethylcellulose, polypropylpyrrolidone, polyvinylpyrrolidone, gelatin, gum arabic, polyethyleneglycol, sucrose or starch), a disintegrator (*e.g.*, starch, carboxymethylcellulose, hydroxypropylstarch, low substituted hydroxypropylcellulose, sodium bicarbonate, calcium phosphate or calcium citrate), a lubricant (*e.g.*, magnesium stearate, light anhydrous silicic acid, talc or sodium lauryl sulfate), a flavoring agent (*e.g.*, citric acid, menthol, glycine or orange powder), a preservative (*e.g.*, sodium benzoate, sodium bisulfite, methylparaben or propylparaben), a stabilizer (*e.g.*, citric acid, sodium citrate or acetic acid), a suspending agent (*e.g.*, methylcellulose, polyvinyl pyrrolidone or aluminum stearate), a dispersing agent (*e.g.*, hydroxypropylmethylcellulose), a diluent (*e.g.*, water), and base wax (*e.g.*, cocoa butter, white petrolatum or polyethylene glycol). The effective amount of the

compounds in the pharmaceutical composition may be at a level that will exercise the desired effect; about 0.001 mg/kg of a subject's body weight to about 1 mg/kg of a subject's body weight in unit dosage for both oral and parenteral administration.

[00160] In certain embodiments, the cereblon E3 ligase modulating compound or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer or racemic mixtures thereof can be prepared by methods known to one of skill in the art, for example, according to the procedure described in U.S. Patent No. 8,518,972 B2, or U.S. Application No. 16/390,815, which are each incorporated herein by reference in their entirety.

[00161] In certain embodiments, the chemical properties, features, and structures are all described in U.S. Application No. 17/075,594, which is incorporated herein by reference in its entirety.

[00162] In certain embodiments, one or more additional cereblon E3 ligase modulating compounds can be used in combination with the administration of a treatment described herein to treat a subject with FL. In certain embodiments, the one or more additional cereblon E3 ligase modulating compounds can be administered prior to, concurrently with, or subsequent to the administration of a treatment described herein. Administration of a cancer treatment, such as an antibody or chemotherapy, and a cereblon E3 ligase modulating compound to a patient can occur simultaneously or sequentially by the same or different routes of administration. The suitability of a particular route of administration employed for a particular cereblon E3 ligase modulating compound will depend on the cereblon E3 ligase modulating compound itself (*e.g.*, whether it can be administered orally without decomposing prior to entering the blood stream) and the condition of lymphoma (*e.g.*, FL) being treated. Routes of administration for cereblon E3 ligase modulating compounds are known to those of ordinary skill in the art. See, *e.g.*, Physicians' Desk Reference.

[00163] In certain embodiments, a subject having ABC/MEM-like FL is administered an IMiD[®] and/or a cereblon E3 ligase modulating compound. In certain embodiments, a subject having ABC/MEM-like FL is administered an IMiD[®] and/or a cereblon E3 ligase modulating compound selected from the group consisting of thalidomide, lenalidomide, pomalidomide, iberdomide, and the compound of formula (I) or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof. In certain embodiments, the IMiD and/or cereblon E3 ligase modulating compound administered to a subject having ABC/MEM-like FL improves the overall survival, progression free survival (PFS), and/or failure-free survival (FFS) of the subject having ABC/MEM-like FL.

[00164] As used herein, progression-free survival (PFS) refers to the time from the date of treatment to the first of either disease progression, relapse or death from any cause. As used herein, failure-free survival (FFS) refers to absence of secondary therapy for FL, non-relapse mortality, and recurrent or progressive malignancy during treatment.

[00165] In certain embodiments, a subject having GCB-like FL is administered an IMiD[®] and/or a cereblon E3 ligase modulating compound. In certain embodiments, a subject having GCB-like FL is administered an IMiD[®] and/or a cereblon E3 ligase modulating compound comprising modulator selected from the group consisting of thalidomide, lenalidomide, pomalidomide, iberdomide, and the compound of formula (I), or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

[00166] Any suitable anti-CD20 antibodies can be used with the presently disclosed methods. In certain embodiments, the ABC/MEM-like treatment comprises an anti-CD20 antibody. In certain embodiments, the ABC/MEM-like treatment comprises an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, and ocrelizumab. In certain embodiments, the GCB-like treatment comprises an anti-CD20 antibody. In certain embodiments, the GCB-like treatment comprises an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, and ocrelizumab.

[00167] Any suitable chemotherapeutic agents can be used with the present disclosure.

[00168] In certain embodiments, the chemotherapeutic agent is selected from the group consisting of cyclophosphamide, doxorubicin, vincristine, bendamustine, doxorubicin, etoposide, methotrexate, cytarabine, vincristine, ifosfamide, melphalan, oxaliplatin, dexamethasone, or a stereoisomer, mixture of stereoisomers, tautomer, isotopolog, prodrug, or pharmaceutically acceptable salt thereof.

5.5 Biological Samples

[00169] In certain embodiments, the various methods provided herein use samples (*e.g.*, biological samples) from FL patients. The patient can be male or female, and can be an adult, child or infant. Samples can be analyzed at a time during an active phase of FL, or when FL is inactive. In one embodiment, a sample is obtained from a patient prior, concurrently with and/or subsequent to administration of a drug described herein. In a specific embodiment, a sample is obtained from a patient prior to administration of a drug described herein. In certain embodiments, more than one sample from a patient can be obtained.

[00170] In certain embodiments, the biological sample is a tissue biopsy. In certain embodiments, the biological sample is a tumor biopsy. In certain embodiments, the biological

sample is a lymph node biopsy. In certain embodiments, the biological sample is a biopsy of an affected lymph node (*e.g.*, a lymph node comprising tumor cells). In certain embodiments, the biological sample is an excisional or core needle biopsy of affected lymph node. In certain embodiments, the tissue biopsy (*e.g.*, biopsy of an affected lymph node) is preserved as a FFPE slide. In certain embodiments, the FFPE slide can be used to (i) extract RNA for gene expression classification; (ii) immunofluorescence histochemistry (IF) staining or similar imaging-based platform such as MIBI and IMC for protein-based classification.

[00171] In certain embodiments, the sample used in the methods provided herein comprises body fluids from a subject. Non-limiting examples of body fluids include blood (*e.g.*, peripheral whole blood, peripheral blood), blood plasma, amniotic fluid, aqueous humor, bile, cerumen, cowper's fluid, pre-ejaculatory fluid, chyle, chyme, female ejaculate, interstitial fluid, lymph, menses, breast milk, mucus, pleural fluid, pus, saliva, sebum, semen, serum, sweat, tears, urine, vaginal lubrication, vomit, water, feces, internal body fluids, including cerebrospinal fluid surrounding the brain and the spinal cord, synovial fluid surrounding bone joints, intracellular fluid is the fluid inside cells, and vitreous humour the fluids in the eyeball. In certain embodiments, the sample is a blood sample. The blood sample can be obtained using conventional techniques as described in, *e.g.*, Innis *et al*, editors, PCR Protocols (Academic Press, 1990). White blood cells can be separated from blood samples using convention techniques or commercially available kits, *e.g.*, RosetteSep kit (Stein Cell Technologies, Vancouver, Canada). Sub-populations of white blood cells, *e.g.*, mononuclear cells, B cells, T cells, monocytes, granulocytes or lymphocytes, can be further isolated using conventional techniques, *e.g.*, magnetically activated cell sorting (MACS) (Miltenyi Biotec, Auburn, California) or fluorescently activated cell sorting (FACS) (Becton Dickinson, San Jose, California).

[00172] In certain embodiments, the blood sample is from about 0.1 mL to about 10.0 mL, from about 0.2 mL to about 7 mL, from about 0.3 mL to about 5 mL, from about 0.4 mL to about 3.5 mL, or from about 0.5 mL to about 3 mL. In another embodiment, the blood sample is about 0.3 mL, 0.4 mL, 0.5 mL, 0.6 mL, 0.7 mL, 0.8 mL, 0.9 mL, 1.0 mL, 1.5 mL, 2.0 mL, 2.5 mL, 3.0 mL, 3.5 mL, 4.0 mL, 4.5 mL, 5.0 mL, 6.0 mL, 7.0 mL, 8.0 mL, 9.0 mL, or 10.0 mL.

[00173] In certain embodiments, the sample used in the present methods comprises a biopsy (*e.g.*, a tumor biopsy). The biopsy can be from any organ or tissue, for example, skin, liver, lung, heart, colon, kidney, bone marrow, teeth, lymph node, hair, spleen, brain, breast, or other organs. In a specific embodiment, the sample used in the methods described herein comprises a tumor biopsy. Any biopsy technique known by those skilled in the art can be used for isolating

a sample from a subject, for instance, open biopsy, close biopsy, core biopsy, incisional biopsy, excisional biopsy, or fine needle aspiration biopsy.

[00174] In certain embodiments, the sample used in the methods provided herein is obtained from the subject prior to the patient receiving a treatment for FL. In another embodiment, the sample is obtained from the patient during the subject receiving a treatment for FL. In another embodiment, the sample is obtained from the patient after the patient received a treatment for FL. In various embodiments, the treatment comprises administering a compound described herein (*e.g.*, a compound of Formula (I) to the subject.

[00175] In certain embodiments, the sample used in the methods provided herein comprises a plurality of cells. Such cells can include any type of cells, *e.g.*, stem cells, blood cells (*e.g.*, peripheral blood mononuclear cells), lymphocytes, B cells, T cells, monocytes, granulocytes, immune cells, or tumor or cancer cells. The tumor or cancer cells or a tumor tissue, such as a tumor biopsy or a tumor explants. T cells (T lymphocytes) include, for example, helper T cells (effector T cells or Th cells), cytotoxic T cells (CTLs), memory T cells, and regulatory T cells. In one embodiment, the cells used in the methods provided herein are CD3⁺ T cells, *e.g.*, as detected by flow cytometry. The number of T cells used in the methods can range from a single cell to about 10⁹ cells. B cells (B lymphocytes) include, for example, plasma B cells, dendritic cells, memory B cells, B1 cells, B2 cells, marginal-zone B cells, and follicular B cells. B cells can express immunoglobulins (antibodies, B cell receptor

[00176] In certain embodiments, specific cell populations can be obtained using a combination of commercially available antibodies (*e.g.*, Quest Diagnostic (San Juan Capistrano, Calif.); Dako (Denmark)).

[00177] In certain embodiments, the sample used in the methods provided herein is from a diseased tissue from a FL patient. In certain embodiments, the number of cells used in the methods provided herein can range from a single cell to about 10⁹ cells. In certain embodiments, the number of cells used in the methods provided herein is about 1 × 10⁴ cells, 5 × 10⁴ cells, 1 × 10⁵ cells, 5 × 10⁵ cells, 1 × 10⁶ cells, 5 × 10⁶ cells, 1 × 10⁷ cells, 5 × 10⁷ cells, 1 × 10⁸ cells, or 5 × 10⁸ cells.

[00178] In certain embodiments, the number and type of cells collected from a subject can be monitored, for example, by measuring changes in morphology and cell surface markers using standard cell detection techniques such as flow cytometry, cell sorting, immunocytochemistry (*e.g.*, staining with tissue specific or cell-marker specific antibodies) fluorescence activated cell sorting (FACS), magnetic activated cell sorting (MACS), by examination of the morphology of cells using light or confocal microscopy, and/or by measuring changes in gene expression using

techniques well known in the art, such as PCR and gene expression profiling. These techniques can be used, too, to identify cells that are positive for one or more particular markers.

Fluorescence activated cell sorting (FACS) is a well-known method for separating particles, including cells, based on the fluorescent properties of the particles (Kamarch, 1987, *Methods Enzymol*, 151:150-165). Laser excitation of fluorescent moieties in the individual particles results in a small electrical charge allowing electromagnetic separation of positive and negative particles from a mixture. In one embodiment, cell surface marker-specific antibodies or ligands are labeled with distinct fluorescent labels. Cells are processed through the cell sorter, allowing separation of cells based on their ability to bind to the antibodies used. FACS sorted particles may be directly deposited into individual wells of 96-well or 384-well plates to facilitate separation and cloning.

[00179] In certain embodiments, subsets of cells are used in methods provided herein. Methods to sort and isolate specific populations of cells are well-known in the art and can be based on cell size, morphology, or intracellular or extracellular markers. Such methods include, but are not limited to, flow cytometry, flow sorting, FACS, bead-based separation such as magnetic cell sorting, size-based separation (*e.g.*, a sieve, an array of obstacles, or a filter), sorting in a microfluidics device, antibody-based separation, sedimentation, affinity adsorption, affinity extraction, density gradient centrifugation, laser capture microdissection, *etc.*

5.6 Methods for Detecting Expression Levels

[00180] In certain embodiments, the gene expression levels of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, or SHCBP1 are determined by measuring the mRNA levels of these genes. Several methods of detecting or quantitating mRNA levels are known in the art. Exemplary methods include but are not limited to northern blots, ribonuclease protection assays, PCR-based methods, and the like. The mRNA sequence can be used to prepare a probe that is at least partially complementary. The probe can then be used to detect the mRNA sequence in a sample, using any suitable assay, such as PCR-based methods, Northern blotting, a dipstick assay, and the like.

[00181] In certain embodiments, a nucleic acid assay for testing for immunomodulatory activity in a biological sample can be prepared. An assay typically contains a solid support and at least one nucleic acid contacting the support, where the nucleic acid corresponds to at least a portion of an mRNA of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP,

CCDC138, or SHCBP1. The assay can also have a means for detecting the altered expression of the mRNA in the sample.

[00182] In certain embodiments, the assay method can be varied depending on the type of mRNA information desired. Exemplary methods include but are not limited to Northern blots and PCR-based methods (*e.g.*, RT-qPCR). Methods such as RT-qPCR can also accurately quantitate the amount of the mRNA in a sample.

[00183] In certain embodiments, any suitable assay platform can be used to determine the presence of the mRNA in a sample. For example, an assay may be in the form of a dipstick, a membrane, a chip, a disk, a test strip, a filter, a microsphere, a slide, a multiwell plate, or an optical fiber. An assay system may have a solid support on which a nucleic acid corresponding to the mRNA is attached. The solid support may comprise, for example, a plastic, silicon, a metal, a resin, glass, a membrane, a particle, a precipitate, a gel, a polymer, a sheet, a sphere, a polysaccharide, a capillary, a film a plate, or a slide. The assay components can be prepared and packaged together as a kit for detecting an mRNA.

[00184] In certain embodiments, the nucleic acid can be labeled, if desired, to make a population of labeled mRNAs. In general, a sample can be labeled using methods that are well known in the art (*e.g.*, using DNA ligase, terminal transferase, or by labeling the RNA backbone, etc.; *see, e.g.*, Ausubel, *et al.*, *Short Protocols in Molecular Biology*, 3rd ed., Wiley & Sons 1995 and Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, Third Edition, 2001 Cold Spring Harbor, N.Y.). In certain embodiments, the sample is labeled with fluorescent label. Exemplary fluorescent dyes include but are not limited to xanthene dyes, fluorescein dyes, rhodamine dyes, fluorescein isothiocyanate (FITC), 6 carboxyfluorescein (FAM), 6 carboxy-2',4',7',4,7-hexachlorofluorescein (HEX), 6 carboxy 4', 5' dichloro 2', 7' dimethoxyfluorescein (JOE or J), N,N,N',N' tetramethyl 6 carboxyrhodamine (TAMRA or T), 6 carboxy × rhodamine (ROX or R), 5 carboxyrhodamine 6G (R6G5 or G5), 6 carboxyrhodamine 6G (R6G6 or G6), and rhodamine 110; cyanine dyes, *e.g.*, Cy3, Cy5 and Cy7 dyes; Alexa dyes, *e.g.*, Alexa-fluor-555; coumarin, Diethylaminocoumarin, umbelliferone; 45enzamide dyes, *e.g.*, Hoechst 33258; phenanthridine dyes, *e.g.*, Texas Red; ethidium dyes; acridine dyes; carbazole dyes; phenoxazine dyes; porphyrin dyes; polymethine dyes, BODIPY dyes, quinoline dyes, Pyrene, Fluorescein Chlorotriazinyl, R110, Eosin, JOE, R6G, Tetramethylrhodamine, Lissamine, ROX, Naphthofluorescein, and the like.

[00185] In certain embodiments, a typical mRNA assay method can contain the steps of 1) obtaining surface-bound subject probes; 2) hybridization of a population of mRNAs to the surface-bound probes under conditions sufficient to provide for specific binding (3) post-

hybridization washes to remove nucleic acids not bound in the hybridization; and (4) detection of the hybridized mRNAs. The reagents used in each of these steps and their conditions for use may vary depending on the particular application.

[00186] In certain embodiments, hybridization can be carried out under suitable hybridization conditions, which may vary in stringency as desired. Typical conditions are sufficient to produce probe/target complexes on a solid surface between complementary binding members, i.e., between surface-bound subject probes and complementary mRNAs in a sample. In certain embodiments, stringent hybridization conditions may be employed.

[00187] In certain embodiments, hybridization is typically performed under stringent hybridization conditions. Standard hybridization techniques (*e.g.*, under conditions sufficient to provide for specific binding of target mRNAs in the sample to the probes) are described in Kallioniemi *et al.*, *Science* 258:818-821 (1992) and WO 93/18186. Several guides to general techniques are available, *e.g.*, Tijssen, *Hybridization with Nucleic Acid Probes*, Parts I and II (Elsevier, Amsterdam 1993). For descriptions of techniques suitable for *in situ* hybridizations, see Gall *et al. Meth. Enzymol.*, 21:470-480 (1981); and Angerer *et al.* in *Genetic Engineering: Principles and Methods* (Setlow and Hollaender, Eds.) Vol 7, pgs 43-65 (Plenum Press, New York 1985). Selection of appropriate conditions, including temperature, salt concentration, polynucleotide concentration, hybridization time, stringency of washing conditions, and the like will depend on experimental design, including source of sample, identity of capture agents, degree of complementarity expected, etc., and may be determined as a matter of routine experimentation for those of ordinary skill in the art.

[00188] In certain embodiments, those of ordinary skill in the art will readily recognize that alternative but comparable hybridization and wash conditions can be utilized to provide conditions of similar stringency.

[00189] In certain embodiments, after the mRNA hybridization procedure, the surface bound polynucleotides are typically washed to remove unbound nucleic acids. Washing may be performed using any convenient washing protocol, where the washing conditions are typically stringent, as described above. The hybridization of the target mRNAs to the probes is then detected using standard techniques.

[00190] In certain embodiments, other methods, such as PCR-based methods, can also be used to follow the expression of the genes of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, or SHCBP1. Examples of PCR methods can be found in the literature. Examples of PCR assays can be found in U.S. Patent No. 6,927,024, which is

incorporated by reference herein in its entirety. Examples of RT-PCR methods can be found in U.S. Patent No. 7,122,799, which is incorporated by reference herein in its entirety. A method of fluorescent in situ PCR is described in U.S. Patent No. 7,186,507, which is incorporated by reference herein in its entirety.

[00191] In certain embodiments, Real-Time Reverse Transcription-PCR (RT-qPCR) can be used for both the detection and quantification of RNA targets (Bustin, *et al.*, 2005, *Clin. Sci.*, 109:365-379). Quantitative results obtained by RT-qPCR are generally more informative than qualitative data. Thus, in certain embodiments, RT-qPCR-based assays can be useful to measure mRNA levels during cell-based assays. The RT-qPCR method is also useful to monitor patient therapy. Examples of RT-qPCR-based methods can be found, for example, in U.S. Patent No. 7,101,663, which is incorporated by reference herein in its entirety.

[00192] In certain embodiments, in contrast to regular reverse transcriptase-PCR and analysis by agarose gels, real-time PCR gives quantitative results. An additional advantage of real-time PCR is the relative ease and convenience of use. Instruments for real-time PCR, such as the Applied Biosystems 7500, are available commercially, as are the reagents, such as TaqMan Sequence Detection chemistry. For example, TaqMan[®] Gene Expression Assays can be used, following the manufacturer's instructions. These kits are pre-formulated gene expression assays for rapid, reliable detection and quantification of human, mouse and rat mRNA transcripts. An exemplary PCR program, for example, is 50°C for 2 minutes, 95°C for 10 minutes, 40 cycles of 95°C for 15 seconds, then 60°C for 1 minute.

[00193] In certain embodiments, to determine the cycle number at which the fluorescence signal associated with a particular amplicon accumulation crosses the threshold (referred to as the CT), the data can be analyzed, for example, using a 7500 Real-Time PCR System Sequence Detection software v1.3 using the comparative CT relative quantification calculation method. Using this method, the output is expressed as a fold-change of expression levels. In certain embodiments, the threshold level can be selected to be automatically determined by the software. In certain embodiments, the threshold level is set to be above the baseline but sufficiently low to be within the exponential growth region of an amplification curve.

[00194] In certain embodiments, techniques known to one skilled in the art may be used to measure the amount of an RNA transcript(s). In certain embodiments, the amount of one, two, three, four, five or more RNA transcripts is measured using deep sequencing, such as ILLUMINA[®] RNASeq, ILLUMINA[®] next generation sequencing (NGS), ION TORRENT[™] RNA next generation sequencing, 454[™] pyrosequencing, or Sequencing by Oligo Ligation Detection (SOLID[™]). In other embodiments, the amount of multiple RNA transcripts is

measured using a microarray and/or gene chip. In certain embodiments, the amount of one, two, three or more RNA transcripts is determined by RT-PCR. In other embodiments, the amount of one, two, three or more RNA transcripts is measured by RT-qPCR. Techniques for conducting these assays are known to one skilled in the art. In yet other embodiments, NanoString (*e.g.*, nCounter® miRNA Expression Assays provided by NanoString® Technologies) is used for analyzing RNA transcripts.

[00195] In certain embodiments, the protein expression levels of FOXP1, LMO2, and MUM1 are determined by measuring the protein levels of FOXP1, LMO2, and MUM1. Several protein detection and quantitation methods can be used to measure the level of proteins. Any suitable protein quantitation method can be used. In certain embodiments, antibody-based methods are used. Exemplary methods that can be used include but are not limited to immunoblotting (western blot), enzyme-linked immunosorbent assay (ELISA), immunohistochemistry, flow cytometry, cytometric bead array, mass spectroscopy, Multiplexed Ion Beam Imaging (MIBI) Imaging Mass Cytometry (IMC), and the like. Several types of ELISA are commonly used, including direct ELISA, indirect ELISA, and sandwich ELISA.

[00196] In certain embodiments, the protein level is determined by immunohistochemistry (IHC). IHC refers to a lab test that uses antibodies to test for certain antigens (markers) in a sample of tissue, and is a process of detecting antigens (*e.g.*, proteins) in cells of a tissue section by exploiting the principle of antibodies binding specifically to antigens in biological tissues. The antibodies are usually linked to an enzyme or a fluorescent dye. Typically, when the antibodies bind to the antigen in the tissue sample, the enzyme or dye is activated, and the antigen can then be seen under a microscope. IHC can be used to help diagnose diseases, such as cancer. It may also be used to help tell the difference between different types of cancer. IHC can be used to image discrete components in tissues by using appropriately-labeled antibodies to bind specifically to their target antigens *in situ*. IHC makes it possible to visualize and document the high-resolution distribution and localization of specific cellular components within cells and within their proper histological context. While there are multiple approaches and permutations in IHC methodology, all of the steps involved can be generally separated into two groups: sample preparation and sample staining. In certain embodiments, IHC is based on the immunostaining of thin sections of tissues attached to individual glass slides. Multiple small sections can be arranged on a single slide for comparative analysis, a format referred to as a tissue microarray. In other embodiments, IHC is performed by using high-throughput sample preparation and staining.

[00197] In certain embodiments, samples can be viewed by either light or fluorescence microscopy. In certain embodiments, antigen detection in tissue can be performed using an antibody conjugated to an enzyme (horseradish peroxidase) and utilized a colorimetric substrate that could be detected by light microscopy.

[00198] In certain embodiments, the sample (*e.g.*, a tissue from the patient) has been snap frozen in liquid nitrogen, isopentane or dry ice. In other embodiments, the sample (*e.g.*, a tissue from the patient) has been fixed in formaldehyde and embedded in paraffin wax (FFPE). In both of the above-mentioned methods, the tissue or sections of the tissue can be mounted on slides prior to staining. In yet other embodiments, the IHC-free-floating technique may be used, where the entire IHC procedure is performed in liquid to increase antibody binding and penetration and slide mounting only takes place upon experimental completion. IHC-free-floating appears to be most popular in neuroscience research. When analysis of the tissue by electron microscopy is desired, the tissue can be embedded in acrylate resins such as glycol methacrylate (GMA), a technique referred to as IHC-resin.

[00199] In certain embodiments, IHC can be performed using the method described in the Examples section below.

5.7 Kits

[00200] In another aspect, provided herein is a kit for performing a method provided herein. In certain embodiments, provided herein is a kit comprising an agent for determining the expression levels (*e.g.*, mRNA levels or protein levels) of certain biomarkers for identifying a subject as having a subtype of follicular lymphoma (FL), selectively treating a subtype of FL, and identifying a subject who is likely to be responsive and predicting the responsiveness of a subject to a FL treatment. In certain embodiments, the subtype of FL is Activated/Memory B-cell like (ABC/MEM-like) FL. In certain embodiments, the subtype of FL is Germinal Center B-Cell like (GCB-like) FL. In certain embodiments, the kit comprises an instruction for identifying a subject as having a subtype of FL, selectively treating a subtype of FL, and/or identifying a subject who is likely to be responsive and predicting the responsiveness of a subject to a FL treatment.

[00201] In certain embodiments, provided herein is a kit for identifying a subject as having an ABC/MEM-like FL, comprising an agent for determining the gene expression level of at least one biomarker in a sample from the subject. In certain embodiments, the kit further comprises instructions for determining a composite score based on the gene expression level of the at least one biomarker; and identifying the subject as having ABC/MEM-like FL based on the

composite score. In certain embodiments, the kit further comprises instructions for administering a treatment of ABC/MEM-like FL to the subject identified as having ABC/MEM-like FL. In certain embodiments, the kit further comprises a tool for obtaining a sample from a subject.

[00202] In certain embodiments, provided herein is a kit for selectively treating a subject having FL, comprising an agent for determining the gene expression level of at least one biomarker in a sample. In certain embodiments, the kit further comprises instructions for determining a composite score based on the gene expression level of the at least one biomarker; identifying the subject as having ABC/MEM-like FL based on the composite score; and administering to the subject identified as having ABC/MEM-like FL an ABC/MEM-like FL treatment (*e.g.*, an ABC/MEM-like FL treatment as disclosed in Section 5.3). In certain embodiments, the kit further comprises a tool for obtaining a sample from a subject.

[00203] In certain embodiments, provided herein is a kit for identifying a subject who is likely to be responsive to a treatment of ABC/MEM-like FL or predicting the responsiveness of a subject to a treatment of ABC/MEM-like FL, comprising an agent for determining the gene expression level of at least one biomarker in a sample of the subject. In certain embodiments, the kit further comprises instructions for determining a composite score based on the gene expression level of the at least one biomarker; and identifying or predicting the subject as being likely to be responsive to the treatment of ABC/MEM-like FL based on the composite score. In certain embodiments, the kit further comprises instructions for administering the treatment of ABC/MEM-like FL to the subject likely to be responsive to the treatment of ABC/MEM-like FL. In certain embodiments, the kit further comprises a tool for obtaining a sample from a subject.

[00204] In certain embodiments, provided herein is a kit for identifying a subject as having a GCB-like FL, comprising an agent for determining the gene expression level of at least one biomarker in a sample from the subject. In certain embodiments, the kit further comprises determining a composite score based on the gene expression level of the at least one biomarker; and identifying the subject as having GCB-like FL based on the composite score. In certain embodiments, the kit further comprises instructions for administering a treatment of GCB-like FL to the subject identified as having GCB-like FL. In certain embodiments, the kit further comprises a tool for obtaining a sample from a subject.

[00205] In certain embodiments, provided herein is a kit for selectively treating a subject having FL, comprising an agent for determining the gene expression level of at least one biomarker in a sample. In certain embodiments, the kit further comprises determining a composite score based

on the gene expression level of the at least one biomarker; identifying the subject as having GCB-like FL based on the composite score; and administering to the subject identified as having GCB-like FL a GCB-like FL treatment (*e.g.*, a GCB-like FL treatment as disclosed in Section 5.3). In certain embodiments, the kit further comprises a tool for obtaining a sample from a subject.

[00206] In certain embodiments, provided herein is a kit for identifying a subject who is likely to be responsive to a treatment of GCB-like FL or predicting the responsiveness of a subject to a treatment of GCB-like FL, comprising an agent for determining the gene expression level of at least one biomarker in a sample of the subject. In certain embodiments, the kit further comprises determining a composite score based on the gene expression level of the at least one biomarker; (c) identifying or predicting the subject as being likely to be responsive to the treatment of GCB-like FL based on the composite score. In certain embodiments, the kit further comprises instructions for administering the treatment of GCB-like FL to the subject likely to be responsive to the treatment of GCB-like FL. In certain embodiments, the kit further comprises a tool for obtaining a sample from a subject.

[00207] In certain embodiments of the various kits provided herein, the biomarker is selected from the group consisting of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1.

[00208] In certain embodiments, the sample is a peripheral blood sample. In certain embodiments, the sample is a tissue sample. In certain embodiments, the sample is a tumor biopsy. In certain embodiments, the sample disclosed herein comprises FL cells. More detailed description of the sample (*e.g.*, biological sample) is provided in Section 5.5 below.

[00209] In certain embodiments of the various kits provided herein, the kits comprise instructions for determining the composite score based on the gene expression level of at least one biomarker. In certain embodiments, the kits comprise agents for determining the gene expression level of one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, or twenty biomarkers selected from the group consisting of: TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1.

[00210] In certain embodiments of the various kits provided herein, the kits comprise instructions for calculating the composite score as disclosed in Section 5.2

[00211] In another aspect, provided herein is a kit for identifying a subject as having an ABC/MEM-like FL, comprising agents for determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1 in a sample from the subject. In certain embodiments, the kit further comprises instructions for identifying the subject as having ABC/MEM-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1. In certain embodiments, the kit further comprises instructions for administering a treatment of ABC/MEM-like FL to the subject identified as having ABC/MEM-like FL. In certain embodiments, the kit further comprises a tool for obtaining a sample from a subject.

[00212] In certain embodiments, provided herein is a kit for selectively treating a subject having FL, comprising an agent for determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1 in a sample. In certain embodiments, the kit further comprises instructions for identifying the subject as having ABC/MEM-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and administering to the subject identified as having ABC/MEM-like FL an ABC/MEM-like FL treatment (*e.g.*, an ABC/MEM-like FL treatment as disclosed in Section 5.3). In certain embodiments, the kit further comprises a tool for obtaining a sample from a subject.

[00213] In certain embodiments, provided herein is a kit for identifying a subject who is likely to be responsive to a treatment of ABC/MEM-like FL (*e.g.*, an ABC/MEM-like FL treatment as disclosed in section 5.3) or predicting the responsiveness of a subject to a treatment of ABC/MEM-like FL, comprising an agent for determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1 in a sample of the subject. In certain embodiments, the kit further comprises instructions for identifying or predicting the subject as being likely to be responsive to the treatment of ABC/MEM-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1. In certain embodiments, the kit further comprises instructions for administering the ABC/MEM-like FL treatment to the subject likely to be responsive to a treatment of ABC/MEM-like FL. In certain embodiments, the kit further comprises a tool for obtaining a sample from a subject.

[00214] In certain embodiments, provided herein is a kit for identifying a subject as having a GCB-like FL, comprising an agent for determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1 in a sample from the subject. In certain embodiments, the kit further comprises instructions for identifying the subject as having GCB-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1. In certain embodiments, the kit further comprises instructions for administering a treatment of GCB-like FL to the subject identified as

having a GCB-like FL. In certain embodiments, the kit further comprises a tool for obtaining a sample from a subject.

[00215] In certain embodiments, provided herein is a kit for selectively treating a subject having FL, comprising an agent for determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1 in a sample. In certain embodiments, the kit further comprises instructions for identifying the subject as having GCB-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and administering to the subject identified as having GCB-like FL a GCB-like FL treatment (*e.g.*, a GCB-like FL treatment as disclosed in Section 5.3). In certain embodiments, the kit further comprises a tool for obtaining a sample from a subject.

[00216] In certain embodiments, provided herein is a kit for identifying a subject who is likely to be responsive to a treatment of GCB-like FL or predicting the responsiveness of a subject to a treatment of GCB-like FL, comprising an agent for determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1 in a sample of the subject. In certain embodiments, the kit further comprises instructions for identifying or predicting the subject as being likely to be responsive to the treatment of GCB-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1. In certain embodiments, the kit further comprises instructions for administering the GCB-like FL treatment to the subject identified as likely to be responsive to the treatment of GCB-like FL. In certain embodiments, the kit further comprises a tool for obtaining a sample from a subject.

[00217] In certain embodiments of the various kits provided herein, the ABC/MEM-like treatment disclosed herein comprises a therapeutically effective amount of an immunomodulatory drug (IMiD[®]). In certain embodiments of the various kits provided herein, the ABC/MEM-like treatment disclosed herein comprises a therapeutically effective amount of a cereblon E3 ligase modulating compound. In certain embodiments, the ABC/MEM-like treatment further comprises a therapeutically effective amount of an anti-CD20 antibody. In certain embodiments, the ABC/MEM-like treatment comprises a combination of therapeutically effective amounts of the IMiD[®] and anti-CD20 antibody. In certain embodiments, the ABC/MEM-like treatment comprises a combination of therapeutically effective amounts of the cereblon E3 ligase modulating compound and anti-CD20 antibody. Further description of the ABC/MEM-like treatment disclosed herein is provided in Section 5.3.

[00218] In certain embodiments, the GCB-like treatment disclosed herein comprises a therapeutically effective amount of an immunomodulatory drug (IMiD[®]), an anti-CD20 antibody, a chemotherapeutic agent, or a combination thereof. In certain embodiments, the GCB-like treatment comprises a combination of therapeutically effective amounts of an IMiD[®]

and an anti-CD20 antibody. In certain embodiments, the GCB-like treatment disclosed herein comprises a therapeutically effective amount of a cereblon E3 modulating compound, an anti-CD20 antibody, a chemotherapeutic agent, or a combination thereof. In certain embodiments, the GCB-like treatment comprises a combination of therapeutically effective amounts of a cereblon E3 modulating compound and an anti-CD20 antibody. In certain embodiments, the GCB-like treatment comprises a combination of therapeutically effective amounts of an anti-CD20 antibody and at least one chemotherapeutic agent. In certain embodiments, the GCB-like treatment comprises a combination of therapeutically effective amounts of an anti-CD20 antibody and two or more (*e.g.*, two, three, four, five) chemotherapeutic agents. In certain embodiments, the GCB-like treatment disclosed herein further comprises a steroid hormone. In certain embodiments, the GCB-like treatment comprises a combination of therapeutically effective amounts of an anti-CD20 antibody, at least one chemotherapeutic agent, and a steroid hormone. In certain embodiments, the GCB-like treatment comprises a combination of therapeutically effective amounts of an anti-CD20 antibody, and two or more chemotherapeutic agents (*e.g.*, two, three, four, five or more chemotherapeutic agents) chemotherapeutic agents, and a steroid hormone. In certain embodiments, the GCB-like treatment comprises a combination of the anti-CD20 antibody, three chemotherapeutic agents, and a steroid hormone. Further description of the GCB-like treatment disclosed herein is provided in Section 5.3.

[00219] In certain embodiments of the various kits provided herein, the kits further comprise an agent for measuring the protein level of the biomarker. In certain embodiments, the kits further comprise instructions for using the agent to measure the protein level of FOXP1, LMO2, CD22, and MUM1. In certain embodiments, the kits further comprise instructions for using the agent to measure the protein levels of FOXP1, LMO2, CD22, and MUM1 using immunohistochemistry (IHC).

[00220] In certain embodiments of the various kits provided herein, the kits provide instructions for identifying a subject as having ABC/MEM-like FL or identifying or predicting a subject as being likely to be responsive to the treatment of ABC/MEM-like FL if: (i) the protein expression level of FOXP1 is strong or moderate and the protein expression level of LMO2 is weak or negative; (ii) the protein expression level of FOXP1 is close to the protein expression level of LMO2 (equally strong, moderate, or weak) or otherwise noninformative, and the protein expression level of CD22 is weak; or (iii) the protein expression level of FOXP1 is close to that of LMO2 (equally strong, moderate, or weak) or otherwise noninformative, and the protein expression level of CD22 is moderate or otherwise noninformative, and the percentage of MUM1 positive cells in the sample is greater than about 15%.

[00221] In certain embodiments of the various kits provided herein, the kits provide instructions for identifying a subject as having ABC/MEM-like FL or identifying or predicting a subject as being likely to be responsive to the treatment of ABC/MEM-like FL if: (i) the percentage of FOXP1 positive cells in the sample is more than about 50% and the percentage of LMO2 positive cells in the sample is less than about 50%, and the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is about 20% or more; (ii) the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is less than about 20%, and the percentage of CD22 positive cells in the sample is less than about 20%; or (iii) the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is less than about 20%, and the percentage of CD22 positive cells in the sample is between about 20% and about 80%, and the percentage of MUM1 positive cells in the sample is greater than about 15%.

[00222] In certain embodiments of the various kits provided herein, the kits provide instructions for identifying a subject as having GCB-like FL or identifying or predicting a subject as being likely to be responsive to the treatment of GCB-like FL if: (i) the expression level of LMO2 is strong or moderate and the expression level of FOXP1 is weak or negative; (ii) the expression level of LMO2 is close to that of FOXP1 (equally strong, moderate, or weak) or otherwise noninformative, and the expression level of CD22 is strong; or (iii) the expression level of LMO2 is close to that of FOXP1 (equally strong, moderate, or weak) or otherwise noninformative, and the expression level of CD22 is moderate or otherwise noninformative, and the percentage of MUM1 positive cells in the sample is less than about 10%.

[00223] In certain embodiments of the various kits provided herein, the kits provide instructions for identifying a subject as having GCB-like FL or identifying or predicting a subject as being likely to be responsive to the treatment of GCB-like FL if: (i) the percentage of LMO2 positive cells in the sample is more than about 50% and the percentage of FOXP1 positive cells in the sample is less than about 50%, and the difference between the percentage of LMO2 positive cells in the sample and the percentage of FOXP1 positive cells in the sample is about 20% or more; (ii) the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is less than about 20%, and the percentage of CD22 cells in the sample is greater than about 80%; or (iii) the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is less than about 20%, the percentage of CD22 positive cells in the sample is

between about 20% and about 80%, and the percentage of MUM1 positive cells in the sample is less than about 10%.

[00224] In certain embodiments, a kit comprises a reagent or reagents necessary for carrying out an assay(s) described herein, in one or more other containers. In certain embodiments, the kit comprises a solid support, and a means for detecting the RNA or protein expression of at least one biomarker in a biological sample. Such a kit may employ, for example, a dipstick, a membrane, a chip, a disk, a test strip, a filter, a microsphere, a slide, a multiwell plate, or an optical fiber. The solid support of the kit can be, for example, a plastic, silicon, a metal, a resin, glass, a membrane, a particle, a precipitate, a gel, a polymer, a sheet, a sphere, a polysaccharide, a capillary, a film, a plate, or a slide.

[00225] In certain embodiments, the kit comprises, in one or more containers, components for conducting RT-PCR, RT-qPCR, deep sequencing, or a microarray such as NanoString assay. In certain embodiments, the kit comprises a solid support, nucleic acids contacting the support, where the nucleic acids are complementary to at least 10, 20, 50, 100, 200, 350, or more bases of mRNA, and a means for detecting the expression of the mRNA in a biological sample.

[00226] In certain embodiments, the kit comprises, in one or more containers, components for conducting assays that can determine one or more protein levels, such flow cytometry, ELISA, or IHC.

[00227] In certain embodiments, the kits may comprise materials and reagents required for measuring RNA or protein. In certain embodiments, such kits include microarrays, wherein the microarray is comprised of oligonucleotides and/or DNA and/or RNA fragments which hybridize to one or more of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEP1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1. In certain embodiments, such kits may include primers for PCR of either the RNA product or the cDNA copy of the RNA product of the genes or subset of genes, or both. In certain embodiments, such kits may include primers for PCR as well as probes for Quantitative PCR. In certain embodiments, such kits may include multiple primers and multiple probes wherein some of said probes have different fluorophores so as to permit multiplexing of multiple products of a gene product or multiple gene products. In certain embodiments, such kits may further include materials and reagents for creating cDNA from RNA. In certain embodiments, such kits may include antibodies specific for FOXP1, LMO2, CD22, and MUM1. Such kits may additionally comprise materials and reagents for isolating RNA and/or proteins from a biological sample. In addition, such kits may include materials and reagents for synthesizing cDNA from RNA isolated from a biological sample. In certain

embodiments, such kits may include, a computer program product embedded on computer readable media for predicting whether a patient is responsive to a compound as described herein. In certain embodiments, the kits may include a computer program product embedded on a computer readable media along with instructions.

[00228] In certain embodiments, antibody based kits can comprise, for example, (1) a first antibody (which may or may not be attached to a solid support) which binds to a peptide, polypeptide or protein of interest; and, optionally, (2) a second, different antibody which binds to either the peptide, polypeptide or protein, or the first antibody and is conjugated to a detectable label (*e.g.*, a fluorescent label, radioactive isotope or enzyme). The antibody-based kits may also comprise beads for conducting an immunoprecipitation. Each component of the antibody-based kits is generally in its own suitable container. Thus, these kits generally comprise distinct containers suitable for each antibody. Further, the antibody-based kits may comprise instructions for performing the assay and methods for interpreting and analyzing the data resulting from the performance of the assay. In a specific embodiment, the kits contain instructions for predicting whether a FL patient is a patient having the ABC/MEM-like subtype or GCB-like subtype of FL.

[00229] In certain embodiments of the methods and kits provided herein, solid phase supports are used for purifying proteins, labeling samples, or carrying out the solid phase assays. Examples of solid phases suitable for carrying out the methods disclosed herein include beads, particles, colloids, single surfaces, tubes, multi-well plates, microtiter plates, slides, membranes, gels, and electrodes. When the solid phase is a particulate material (*e.g.*, a bead), it is, in one embodiment, distributed in the wells of multi-well plates to allow for parallel processing of the solid phase supports.

[00230] From the foregoing, it will be appreciated that, although specific embodiments have been described herein for the purpose of illustration, various modifications may be made without deviating from the spirit and scope of what is provided herein. All of the references referred to above are incorporated herein by reference in their entireties.

6. EMBODIMENTS

[00231] The present disclosure includes the following non-limiting embodiments:

1. A method of identifying a subject as having an Activated/Memory B-cell like (ABC/MEM-like) follicular lymphoma (FL), comprising:
 - (a) determining the gene expression level of at least one biomarker in a sample from the subject, wherein the biomarker is selected from the group consisting of TTC28, FOXP1,

DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1;

(b) determining a composite score based on the gene expression level of the at least one biomarker; and

(c) identifying the subject as having ABC/MEM-like FL based on the composite score.

2. The method of embodiment 1, further comprising administering to the subject identified as having ABC/MEM-like FL a treatment of ABC/MEM-like FL comprising a therapeutically effective amount of an immunomodulatory drug (IMiD[®]) and/or a cereblon E3 ligase modulating compound.

3. A method of selectively treating a subject having FL, comprising:

(a) determining the gene expression level of at least one biomarker in a sample of the subject, wherein the biomarker is selected from the group consisting of: TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1;

(b) determining a composite score based on the gene expression level of the at least one biomarker;

(c) identifying the subject as having ABC/MEM-like FL based on the composite score; and

(d) administering to the subject identified as having ABC/MEM-like FL a treatment of ABC/MEM-like FL comprising a therapeutically effective amount of an IMiD[®] and/or a cereblon E3 ligase modulating compound.

4. A method of identifying a subject who is likely to be responsive to a treatment of ABC/MEM-like FL or predicting the responsiveness of a subject to a treatment of ABC/MEM-like FL, comprising:

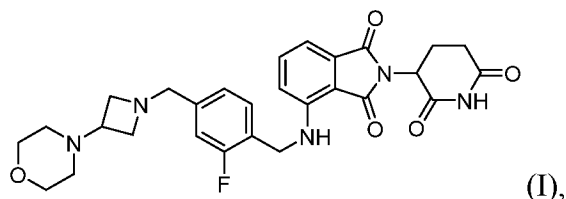
(a) determining the gene expression level of at least one biomarker in a sample of the subject, wherein the biomarker is selected from the group consisting of: TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1;

(b) determining a composite score based on the gene expression level of the at least one biomarker; and

(c) identifying or predicting the subject as being likely to be responsive to the treatment of ABC/MEM-like FL based on the composite score, and optionally (d) administering the treatment of ABC/MEM-like FL to the subject likely to be responsive to the treatment of ABC/MEM-like FL;

wherein the treatment of ABC/MEM-like FL comprises a therapeutically effective amount of an IMiD[®] and/or a cereblon E3 ligase modulating compound.

5. The method of any one of embodiments 2-4, wherein the IMiD[®] and/or cereblon E3 ligase modulating compound is selected from the group consisting of lenalidomide, pomalidomide, thalidomide, iberdomide, and a compound of Formula (I)



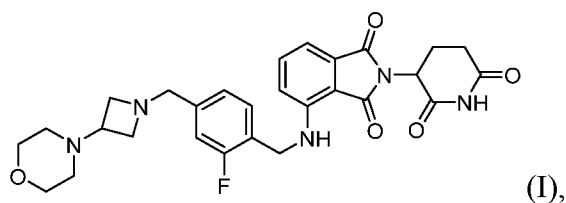
and enantiomers, mixture of enantiomers, tautomers, isotopologs, and pharmaceutically acceptable salts thereof.

6. The method of any one of embodiments 2-5, wherein the treatment of ABC/MEM-like FL further comprises a therapeutically effective amount of an anti-CD20 antibody.

7. The method of embodiment 6, wherein the anti-CD20 antibody is selected from the group consisting of rituximab, obinutuzumab, ocrelizumab, and combinations thereof.

8. The method of any one of embodiments 2-7, wherein the treatment of ABC/MEM-like FL comprises therapeutically effective amounts of rituximab and lenalidomide, or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

9. The method of any one of embodiments 2-7, wherein the treatment of ABC/MEM-like FL comprises therapeutically effective amounts of rituximab and a compound of Formula (I)



or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

10. The method of any one of embodiments 2-9, wherein the treatment of ABC/MEM-like FL improves overall survival, progression free survival (PFS), and/or failure free survival (FFS) of the subject having ABC/MEM-like FL.

11. The method of any one of embodiments 1-10, wherein the composite score is determined based on the gene expression levels of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1.

12. The method of embodiment 11, wherein the composite score is determined based on the sum of weighted gene expression levels of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1.

13. The method of embodiment 12, wherein the composite score is determined based on the following formula: $(-12.90235 \times \text{the gene expression level of TTC28}) + (-17.20497 \times \text{the gene expression level of FOXP1}) + (-14.08426 \times \text{the gene expression level of DOPEY2}) + (-14.14635 \times \text{the gene expression level of IQSEC1}) + (-15.78924 \times \text{the gene expression level of PTPRJ}) + (-13.44714) \times (\text{the gene expression level of SLA} + -13.21572) \times (\text{the gene expression level of CXXC5}) + (-14.31872 \times \text{the gene expression level of PDE4B}) + (-18.17919 \times \text{the gene expression level of TCF4}) + (-16.21973 \times \text{the gene expression level of MPEG1}) + (15.81861 \times \text{the gene expression level of KIAA1211}) + (15.97033 \times \text{the gene expression level of SCPEP1}) + (17.50829 \times \text{the gene expression level of RASL11A}) + (17.18333 \times \text{the gene expression level of LMO2}) + (15.22055 \times \text{the gene expression level of HS2ST1}) + (15.22908 \times \text{the gene expression level of ENPP3}) + (15.60008 \times \text{the gene expression level of SH3RF1}) + (18.07827 \times \text{the gene expression level of SCIMP}) + (15.04494 \times \text{the gene expression level of CCDC138}) + (15.84456 \times \text{the gene expression level of SHCBP1})$.

14. The method of any one of embodiments 1-13, wherein the subject is identified as having ABC/MEM-like FL or is identified or predicted as being likely to be responsive to the treatment of ABC/MEM-like FL if the composite score is lower than a predetermined value, optionally wherein the predetermined value is zero.

15. The method of any one of embodiments 1-13, wherein the subject is identified as having ABC/MEM-like FL or is identified or predicted as being likely to be responsive to the treatment of ABC/MEM-like FL if the composite score is lower than a reference score, optionally wherein the reference score is derived from a healthy subject or a population of healthy subjects and is calculated the same way as the composite score.

16. A method of identifying a subject as having a Germinal Center B-Cell like (GCB-like) follicular lymphoma (FL), comprising:

(a) determining the gene expression level of at least one biomarker in a sample from the subject, wherein the biomarker is selected from the group consisting of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1;

(b) determining a composite score based on the gene expression level of the at least on

biomarker; and

(c) identifying the subject as having the GCB-like FL based on the composite score.

17. The method of embodiment 15, further comprising administering to the subject identified as having GCB-like FL a treatment of GCB-like FL.

18. A method of selectively treating a subject having FL, comprising:

(a) determining the gene expression level of at least one biomarker in a sample of the subject, wherein the biomarker is selected from the group consisting of: TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1;

(b) determining a composite score based on the gene expression level of the at least one biomarker;

(c) identifying the subject as having GCB-like FL based on the composite score; and

(d) administering to the subject identified as having GCB-like FL a therapeutically effective amount of a GCB-like FL treatment.

19. A method of identifying a subject who is likely to be responsive to a treatment of GCB-like FL or predicting the responsiveness of a subject to a treatment of GCB-like FL, comprising:

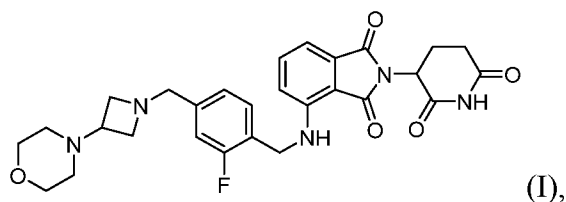
(a) determining the gene expression level of at least one biomarker in a sample of the subject, wherein the biomarker is selected from the group consisting of: TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1;

(b) determining a composite score based on the gene expression level of the at least one biomarker;

(c) identifying or predicting the subject as being likely to be responsive to the treatment of GCB-like FL based on the composite score, and optionally (d) administering the treatment of GCB-like FL to the subject likely to be responsive to the treatment of GCB-like FL.

20. The method of any one of embodiments 15-19, wherein the treatment of GCB-like FL comprises a therapeutically effective amount of an IMiD[®], a cereblon E3 ligase modulating compound, an anti-CD20 antibody, a chemotherapeutic agent, or a combination thereof.

21. The method of embodiment 20, wherein the IMiD[®] and/or cereblon E3 ligase modulating compound is selected from the group consisting of lenalidomide, pomalidomide, thalidomide, iberdomide, and a compound of Formula (I)



and enantiomers, mixture of enantiomers, tautomers, isotopologs, and pharmaceutically acceptable salts thereof.

22. The method of embodiment 20, wherein the anti-CD20 antibody is selected from the group consisting of rituximab, obinutuzumab, ocrelizumab, and combinations thereof.

23. The method of embodiment 20, wherein the chemotherapeutic agent is selected from the group consisting of cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and combinations thereof.

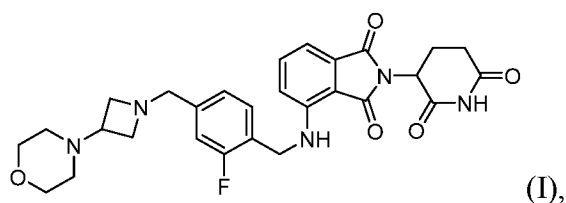
24. The method of any one of embodiments 15-20, wherein the treatment of GCB-like FL comprises the therapeutically effective amounts of the anti-CD20 antibody and the chemotherapeutic agent.

25. The method of embodiment 24, wherein the treatment of GCB-like FL comprises the therapeutically effective amounts of rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone.

26. The method of any one of embodiments 15-20, wherein the treatment of GCB-like FL comprises the therapeutically effective amounts of the IMiD® and/or cereblon E3 ligase modulating compound, and the anti-CD20 antibody.

27. The method of embodiment 26, wherein the treatment of GCB-like FL comprises the therapeutically effective amounts of rituximab and lenalidomide, or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

28. The method of embodiment 26, wherein the treatment of GCB-like FL comprises the therapeutically effective amounts of rituximab and a compound of Formula (I)



or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

29. The method of any one of embodiments 15-28, wherein the composite score is determined based on the gene expression levels of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ,

SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1.

30. The method of embodiment 29, wherein the composite score is determined based on the sum of weighted gene expression levels of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1.

31. The method of embodiment 30, wherein the composite score is determined based on the following formula: $(-12.90235 \times \text{the gene expression level of TTC28}) + (-17.20497 \times \text{the gene expression level of FOXP1}) + (-14.08426 \times \text{the gene expression level of DOPEY2}) + (-14.14635 \times \text{the gene expression level of IQSEC1}) + (-15.78924 \times \text{the gene expression level of PTPRJ}) + (-13.44714 \times \text{the gene expression level of SLA}) + (-13.21572 \times \text{the gene expression level of CXXC5}) + (-14.31872 \times \text{the gene expression level of PDE4B}) + (-18.17919 \times \text{the gene expression level of TCF4}) + (-16.21973 \times \text{the gene expression level of MPEG1}) + (15.81861 \times \text{the gene expression level of KIAA1211}) + (15.97033 \times \text{the gene expression level of SCPEP1}) + (17.50829 \times \text{the gene expression level of RASL11A}) + (17.18333 \times \text{the gene expression level of LMO2}) + (15.22055 \times \text{the gene expression level of HS2ST1}) + (15.22908 \times \text{the gene expression level of ENPP3}) + (15.60008 \times \text{the gene expression level of SH3RF1}) + (18.07827 \times \text{the gene expression level of SCIMP}) + (15.04494 \times \text{the gene expression level of CCDC138}) + (15.84456 \times \text{the gene expression level of SHCBP1})$.

32. The method of any one of embodiments 15-31, wherein the subject is identified as having GCB-like FL or is identified or predicted as being likely to be responsive to the treatment of GCB-like FL if the composite score is higher than a predetermined value, optionally wherein the predetermined value is zero.

33. The method of any one of embodiments 15-31, wherein the subject is identified as having GCB-like FL or is identified or predicted as being likely to be responsive to the treatment of GCB-like FL if the composite score is higher than a reference score, optionally wherein the reference score is derived from a healthy subject or a population of healthy subjects and is calculated the same way as the composite score.

34. The method of any one of embodiments 1-33, wherein the gene expression level of the at least one biomarker is mRNA level.

35. The method of embodiment 34, wherein the gene expression level is measured by RNA sequencing or PCR-based quantification methods.

36. A method of identifying a subject as having an ABC/MEM-like FL, comprising:
(a) determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and

(b) identifying the subject as having the ABC/MEM-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1.

37. The method of embodiment 36, further comprising administering to the subject identified as having ABC/MEM-like FL a therapeutically effective amount of an immunomodulatory drug (IMiD[®]) and/or a cereblon E3 ligase modulating compound.

38. A method of selectively treating a subject having FL, comprising:

(a) determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1;
 (b) identifying the subject as having ABC/MEM-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and

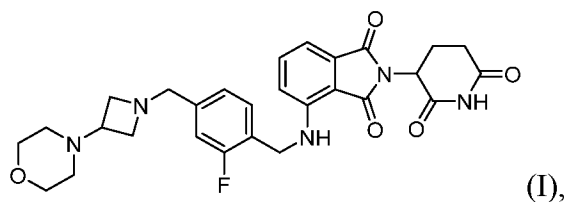
(c) administering to the subject identified as having ABC/MEM-like FL a therapeutically effective amount of an IMiD[®] and/or a cereblon E3 ligase modulating compound.

39. A method of identifying a subject who is likely to be responsive to a treatment of ABC/MEM-like FL or predicting the responsiveness of a subject to a treatment of ABC/MEM-like FL, comprising:

(a) determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and
 (b) identifying or predicting the subject as being likely to be responsive to the treatment of ABC/MEM-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and optionally (c) administering the treatment of ABC/MEM-like FL to the subject likely to be responsive to the treatment of ABC/MEM-like FL;

wherein the treatment of ABC/MEM-like FL comprises an IMiD[®] and/or a cereblon E3 ligase modulating compound.

40. The method of any one of embodiments 37-39, wherein the IMiD[®] and/or cereblon E3 ligase modulating compound is selected from the group consisting of lenalidomide, pomalidomide, thalidomide, iberdomide, and a compound of Formula (I)



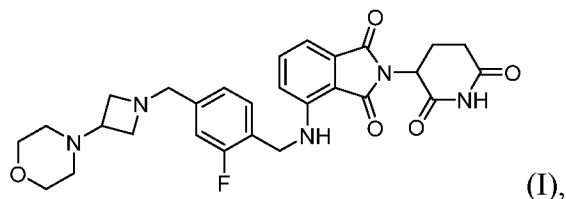
and enantiomers, mixture of enantiomers, tautomers, isotopologs, and pharmaceutically acceptable salts thereof.

41. The method any one of embodiments 37-40, wherein the treatment of ABC/MEM-like FL further comprises a therapeutically effective amount of an anti-CD20 antibody.

42. The method of embodiment 41, wherein the anti-CD20 antibody is selected from the group consisting of rituximab, obinutuzumab, ocrelizumab, and combinations thereof.

43. The method of any one of embodiments 37-42, wherein the treatment of ABC/MEM-like FL comprises therapeutically effective amounts of rituximab and lenalidomide, or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

44. The method of any one of embodiments 37-42, wherein the treatment of ABC/MEM-like FL comprises therapeutically effective amounts of rituximab and a compound of Formula (I)



or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

45. The method of any one of embodiments 37-44, wherein the treatment of ABC/MEM-like FL improves overall survival, PFS, and/or FFS of the subject having ABC/MEM-like FL.

46. The method of any one of embodiments 37-45, wherein the protein expression levels of FOXP1, LMO2, CD22, and MUM1 are protein levels.

47. The method of embodiment 46, wherein the protein levels are measured using immunohistochemistry (IHC), Multiplexed Ion Beam Imaging (MIBI), or Imaging Mass Cytometry (IMC).

48. The method of embodiment 47, wherein the subject is identified as having ABC/MEM-like FL or is identified or predicted as being likely to be responsive to the treatment of ABC/MEM-like FL if

(i) the protein expression level of FOXP1 is strong or moderate and the protein expression level of LMO2 is weak or negative;

(ii) the protein expression level of FOXP1 is close to the protein expression level of LMO2 (equally strong, moderate, or weak) or otherwise noninformative, and the protein expression level of CD22 is weak; or

(iii) the protein expression level of FOXP1 is close to that of LMO2 (equally strong, moderate, or weak) or otherwise noninformative, and the protein expression level of CD22 is moderate or otherwise noninformative, and the percentage of MUM1 positive cells in the sample is greater than about 15%.

49. The method of embodiment 47 or 48, wherein the subject is identified as having ABC/MEM-like FL or is identified or predicted as being likely to be responsive to the treatment of ABC/MEM-like FL if

(i) the percentage of FOXP1 positive cells in the sample is more than about 50% and the percentage of LMO2 positive cells in the sample is less than about 50%, and the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is about 20% or more;

(ii) if the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is less than about 20%, and the percentage of CD22 positive cells in the sample is less than about 20%; or

(iii) if the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is less than about 20%, and the percentage of CD22 positive cells in the sample is between about 20% and about 80%, and the percentage of MUM1 positive cells in the sample is greater than about 15%.

50. A method of identifying a subject as having a GCB-like FL, comprising:

- (a) determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and
- (b) identifying the subject as having the GCB-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1.

51. The method of embodiment 50, further comprising administering to the subject identified as having GCB-like FL a treatment of GCB-like FL.

52. A method of selectively treating a subject having FL, comprising:

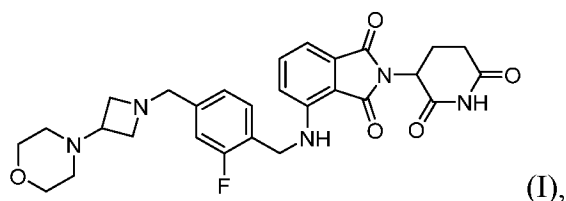
- (a) determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1;
- (b) identifying the subject as having GCB-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and
- (c) administering to the subject identified as having GCB-like FL a therapeutically effective amount of GCB-like FL treatment.

53. A method of identifying a subject who is likely to be responsive to a treatment of GCB-like FL or predicting the responsiveness of a subject to a treatment of GCB-like FL, comprising:

- (a) determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and
- (b) identifying or predicting the subject as being likely to be responsive to the treatment of GCB-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and optionally (c) administering the treatment of GCB-like FL to the subject likely to be responsive to the treatment of GCB-like FL.

54. The method of any one of embodiments 51-53, wherein the treatment of GCB-like FL comprises a therapeutically effective amount of an IMiD[®], a cereblon E3 ligase modulating compound, an anti-CD20 antibody, a chemotherapeutic agent, or a combination thereof.

55. The method of embodiment 54, wherein the IMiD[®] and/or cereblon E3 ligase modulating compound is selected from the group consisting of lenalidomide, pomalidomide, thalidomide, iberdomide, and a compound of Formula (I)



and enantiomers, mixture of enantiomers, tautomers, isotopologs, and pharmaceutically acceptable salts thereof.

56. The method of embodiment 54, wherein the anti-CD20 antibody is selected from the group consisting of rituximab, obinutuzumab, ocrelizumab, and combinations thereof.

57. The method of embodiment 54, wherein the chemotherapeutic agent is selected from the group consisting of cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and combinations thereof.

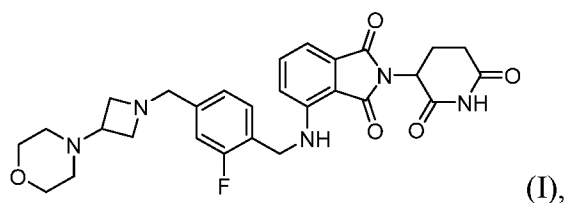
58. The method of any one of embodiments 51-54, wherein the treatment of GCB-like FL comprises the therapeutically effective amounts of the anti-CD20 antibody and the chemotherapeutic agent.

59. The method of embodiment 58, wherein the treatment of GCB-like FL comprises the therapeutically effective amounts of rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone.

60. The method of any one of embodiments 51-54, wherein the treatment of GCB-like FL comprises the therapeutically effective amounts of the IMiD[®] and/or cereblon E3 ligase modulating compound, and the anti-CD20 antibody.

61. The method of embodiment 59, wherein the treatment of GCB-like FL comprises the therapeutically effective amounts of rituximab and lenalidomide, or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

62. The method of embodiment 59, wherein the treatment of GCB-like FL comprises the therapeutically effective amounts of rituximab and a compound of Formula (I)



or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

63. The method of any one of embodiments 50-62, wherein the protein expression levels of FOXP1, LMO2, CD22, and MUM1 are protein levels.

64. The method of embodiment 63, wherein the protein levels are measured using immunohistochemistry (IHC), Multiplexed Ion Beam Imaging (MIBI), or Imaging Mass Cytometry (IMC).

65. The method of embodiment 64, wherein the subject is identified as having GCB-like FL or is identified or predicted as being likely to be responsive to the treatment of GCB-like FL if

(i) the protein expression level of LMO2 is strong or moderate and the protein expression level of FOXP1 is weak or negative;

(ii) the protein expression level of LMO2 is close to that of FOXP1 (equally strong, moderate, or weak) or otherwise noninformative, and the protein expression level of CD22 is strong; or

(iii) the protein expression level of LMO2 is close to that of FOXP1 (equally strong, moderate, or weak) or otherwise noninformative, and the protein expression level of CD22 is moderate or otherwise noninformative, and the percentage of MUM1 positive cells in the sample is less than about 10%.

66. The method of embodiment 64 or 65, wherein the subject is identified as having GCB-like FL or is identified or predicted as being likely to be responsive to the treatment of GCB-like FL if

(i) the percentage of LMO2 positive cells in the sample is more than about 50% and the percentage of FOXP1 positive cells in the sample is less than about 50%, and the difference between the percentage of LMO2 positive cells in the sample and the percentage of FOXP1 positive cells in the sample is about 20% or more;

(ii) if the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is less than about 20%, and the percentage of CD22 cells in the sample is greater than about 80%; or

(iii) if the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is less than about 20%, the percentage of CD22 positive cells in the sample is between about 20% and about 80%, and the percentage of MUM1 positive cells in the sample is less than about 10%.

67. The method of any one of embodiments 1-65, wherein the sample is a tumor biopsy.

68. A kit for performing the method of any one of embodiments 1-67, the kit comprising an agent for determining (i) the gene expression level of at least one biomarker selected from the group consisting of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4,

MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1 or (ii) the protein expression levels of FOXP1, LMO2, CD22, and MUM1.

69. The kit of embodiment 68, wherein the kit further comprises a tool for obtaining the sample.

70. The kit of embodiment 68 or 69, wherein the kit further comprises an instruction on interpreting the determined expression level.

7. EXAMPLES

[00232] The examples below are carried out using standard techniques, which are well known and routine to those of skill in the art, except where otherwise described in detail. The examples are intended to be merely illustrative.

7.1 Example 1: Identification of an Activated /Memory B-Cell Signature of Poor Outcome and Sensitivity to Lenalidomide in Follicular Lymphoma

MATERIAL AND METHODS

Patients and Samples

[00233] The RELEVANCE trial (ClinicalTrials.gov identifier: NCT01650701) showed that the combination of lenalidomide plus rituximab (R2) provided similar efficacy to rituximab plus chemotherapy (R-chemo) in patients with advanced-stage, previously untreated follicular lymphoma (FL) after 6 years of follow-up (Morschhauser et al., N Engl J Med 2018 Sep 6; 379(10):934-947, Morschhauser et al., J Clin Oncol 2022 Oct 1; 40(28):3239-3245). A total of 1030 patients were randomly assigned to receive one of the two regimens, followed by maintenance monotherapy with rituximab. Patient characteristics are detailed elsewhere (Morschhauser et al., N Engl J Med 2018 Sep 6; 379(10):934-947).

Pathological Reviewing and FISH Analysis

[00234] Formalin-fixed, paraffin-embedded (FFPE) biopsy specimens were obtained at the time of diagnosis before any treatment. Patients were included into the trial based on a histologically proven diagnosis of FL grade 1, 2, or 3A. Grade 3B FL was excluded. The pathological material was centrally reviewed by a panel of expert hematopathologists at the GELA pathology center (Paris, France) to confirm the diagnosis using appropriate staining and phenotyping. The pathology screening included FISH analysis using break-apart DNA probes for BCL2/18q21, BCL6/3q27 (probes Z-2192, and Z-2177; Zytovision, Germany); and MYC/8q24 (1N6320,

Abbott Laboratories, Chicago, IL). A dual Color Probe 1p36/1q25 (Z-2075, Zytovision, Germany) was also included.

RNA Sequencing Analysis

[00235] As a result of sample availability and technical limitations, FFPE samples from 324 patients with confirmed FL histology were available for DNA and mRNA extraction using a *Maxwell*® device according to the supplier instructions. Shavings from each FFPE block were obtained from areas of interest containing malignant follicles representative of the entire biopsy sample. The 324 informative patient set displayed slightly better survival compared to the whole Relevance cohort for both PFS and OS.

RNA Sequencing Preprocessing

[00236] RNA counts were quantified at the gene level using salmon based on the transcript definitions from Gencode version 24. The counts were normalized for library size using DESeq2 sizeFactor normalization and log2 transformed after adding a pseudo-count value of 1. Low expressed genes defined as genes expressed in less than about 10 samples at a minimum of 0.2 counts per million were discarded.

Independent Component Analysis Based Consensus Clustering

[00237] An approach was developed that is similar to Non-negative Matrix Factorization (NMF) consensus clustering but relying on Independent Component Analysis (ICA) instead of NMF for signal deconvolution. ICA was run in parallel mode using the R package fastICA to extract 50 components on the normalized matrix after gene wise standardization (to mean 0 and variance 1). Each ICA component can be seen as a metagene with each individual gene weighted by a coefficient that can be either positive or negative. The 50 ICA components were used to define 100 gene clusters, each component defining one cluster composed of all the genes with strongly negative (threshold ≤ -3) weights, and one composed of all the genes with strongly positive (threshold ≥ 3) weights. This process was repeated 100 times and a consensus matrix was computed to record for each pair of genes the proportion of ICA runs in which they belonged to a common cluster. Hierarchical clustering with ward.D2 agglomeration was performed using this consensus matrix as a similarity matrix, followed by cluster assignment using DynamicTreeCut (Langfelder et al. 2008). The resulting clusters were then scored in individual patients by computing the mean of the standardized expression of all genes within a cluster. Following this step, the resulting clusters were filtered based on the following criteria: 1) poorly concordant clusters grouping genes that were part of the same initial clusters in less than 50% (on average) of the ICA runs were discarded; 2) clusters containing few than 20 genes were

utilized; and 3) clusters who score variation was mainly driven by a few outlier samples with standard deviation of the cluster score greater than $1.5 * \text{median absolute deviation}$.

Linear Predictor Score Design

[00238] A linear Predictor Score classifier (LPS) was designed to classify samples into either an ABC/MEM-like subtype of FL or a GCB-like subtype of FL based on the top-most discriminant genes. A differential analysis was performed on an initial classification of samples defined by unsupervised hierarchical clustering (Euclidean distance, ward.D2) on the combined standardized expression of all genes from both signatures combined. Moderated t-statistics (Limma-like) were computed for each of the genes from both signatures for differentiating both clusters, and the top 10 protein coding genes were selected in both directions (20 genes). A Linear Predictor Score was then computed by using the t-statistics associated with the 20 genes as weights and multiplying by the individual standardized expression of the genes. This process was performed using the LPS package (v1.0.16) in the R computing environment, which computes the LPS20 score as the weighted sum of the 20 genes' expression values, and classifies cases with respect to the score threshold.

Statistical Analysis

[00239] Statistical analyses were performed using R. Survival analyses were performed using the coxph function from the survival analysis, and survival curves were drawn using the survminer R package. Two patients were excluded from the analyses because they received no treatment. Fisher exact test was used for frequency comparisons and gene set overrepresentation.

Gene Set Overrepresentation Analyses

[00240] Gene Sets were taken from MSigDB (Hallmarks, c2,c6 and c8 collections) and the LLMPP signatureDB. NCBI entrez gene IDs were used to match genes between the ICA consensus cluster signatures and the gene set collections. Overrepresentation was assessed using one sided Fisher exact test and p-values were adjusted using Benjamini-Hochberg correction to account for the number of gene sets tested.

Immunohistochemistry

[00241] To set up an immunoscore based on immunohistochemistry (IHC) detection of FOXP1/LMO2/CD22/ MUM1 (FLCM score), the correlations between RNAseq and IHC profiles were analyzed using IHC on either whole sections or tissue micro arrays (TMA) of FFPE biopsy samples. The same samples were used for either RNAseq or IHC analysis. For TMA construction, areas containing malignant follicles representative of the entire biopsy sample and lacking fibrotic portions were marked on the paraffin blocks during the pathological reviewing

of each case. Cylinders of 1-mm diameter from 3 different areas were then collected and included in TMA blocks. FOXP1 (clone D35D10, Cell Signaling Technologies, Ozyme) was used at a dilution of 1/200 (Envision Flex diluent, Agilent Technologies) after heat induced epitope retrieval during 20 minutes in ER2 buffer (pH9, Leica Biosystems). LMO2 (Ready-to-use, clone RBT-LMO2, BioSB, Diagnostics) was used after heat induced epitope retrieval during 30 minutes in ER1 buffer (pH6, Leica Biosystems). Both FOXP1 and LMO2 immunostainings were performed using a LEICA Bond polymer DAB refine detection kit on a Leica BOND RX automated slide stainer (Leica Biosystems). Slides were counterstained using Hematoxylin, dehydrated and mounted using xylene-based mounting (Sakura TissueTek, Sakura FineTek). MUM1 (Ready-to-use, clone EP190, Roche Diagnostics) was used after heat induced-epitope retrieval during 32 minutes in CC1 buffer (pH6, Roche Diagnostics) using a Benchmark Optiview DAB detection kit on a Benchmark ULTRA automated slide stainer (Roche Diagnostics). Slides were counterstained using Hematoxylin, dehydrated and mounted using xylene-based mounting (Sakura TissueTek, Sakura FineTek).

RESULTS

Gene Expression Profile Highlights a Cell-Of-Origin Subcategorization of FL Tumors in Germinal Center (GC)-like and Activated/Memory B-cell (ABC/MEM)-like Subgroups

[00242] To investigate the biological basis of transcriptome heterogeneity in FL tumors, an exploratory unsupervised analysis of the gene expression data was performed. Using a consensus clustering approach based on Independent Component Analysis (ICA), 46 gene clusters were extracted and functional enrichment was performed on the gene clusters which tested their association with clinical outcome.

[00243] Of the 46 identified gene expression signatures (GES), two GES displayed opposite and treatment-dependent associations with progression free survival (PFS). The first GES called CC17 (213 genes), strongly anti-correlated with the first GES was enriched for genes expressed in GCB-subtype DLBCLs (25% genes belonging to LLMP:GCBDLBCL-3 signature, FDR =9.35e-38, Supplementary Table 2) while the second GES called CC21 (179 genes) was enriched for genes expressed not only in ABC-subtype DLBCLs (17% of genes belonging to LLMP:ABCDLBCL-4 signature, FDR =2.5e-16) but also in normal memory B cells as shown by comparison with several published datasets (Stewart et al., Front Immunol. 2021 Mar 18; 12:602539, Attaf et al., Eur J Immunol. 2021 Nov; 51(11):2555-2567, Wang et al., Nat Commun. 2022 Nov 9; 13(1):6772) .

[00244] The CC17 and CC21 gene expression signatures were combined into a 20-gene based Linear Predictor Score (LPS20) which classified patients into either an ABC/MEM-like FL subtype (n=160) or a GCB-like FL subtype (n=164) (**FIG. 1**).

The ABC/MEM Signature is Predictive of Poor Outcome and Sensitivity to Lenalidomide in FL Patients

[00245] In the R-chemo arm, the 6-year PFS of ABC/MEM like patients (45% [35-59]) was significantly shorter than GCB-like patients (67% [59-80]) (HR= 2.13[1.30-3.51], p=0.003) (**FIG. 2A**). In the R2 arm, both the GCB-like subgroup and the ABC/MEM-like subgroup had comparable PFS (65% vs 62%; HR=1.04[0.61-1.77], p=0.9) (**FIG. 2B**). In a multivariate model including FLIPI, the association between subtype and outcome remained significant for R-chemo patients (adjusted HR=2.15[1.31-3.53], p=0.002) and the treatment dependence as well (interaction subtype*treatment p=0.041). A marked benefit of R2 compared to R-chemo was observed (HR =0.46[0.28-0.75], p=0.002) for ABC/MEM-like patients with FLIPI ≥2. In contrast, no benefit of R2 was observed for GC-like patients with FLIPI ≥2 (p=0.88). Among patients with FLIPI >2 treated by R-chemo, GC-like patients had a much better outcome than ABC/MEM-like patients (p=0.00034).

The Poor Prognostic Value of the ABC/MEM Signature can be Validated in Previously Reported R-chemo Treated FL Cohorts

[00246] The COO prognostic value was validated in two independent R-chemo treated FL cohorts from the LYSA (PRIMA, n=134) and BCCA (GSE119214, n=137). In PRIMA, the ABC/MEM-like subtype was associated with a shorter PFS (vs GCB-like) but only among FLIPI ≥2 patients (n=111, HR=1.72[1.01-2.93], p=0.044) (**FIG. 3A**). In the BCCA cohort, the classifier had to be adapted as only 17/20 genes were assayed in the publicly available dataset and the ABC/MEM-like subtype was associated with inferior FFS (HR=1.78[1.1-2.87], p=0.019) and overall survival (HR=2.13[1.18-3.82], p=0.012) (**FIG. 3B**).

Comparison of the ABC/MEM Signature With Previously Reported Prognostic GES

[00247] The value of the 23 gene score (GS23), that was previously developed in R-chemo treated patients from the PRIMA trial (Huet et al., Lancet Oncol. 2018 Apr; 19(4):549-561) was analyzed in the Relevance cohort. GS23 shared 2 genes with CC17 and 6 with CC21 signatures. As expected, the GS23 was associated with PFS in the R-chemo Relevance arm (p=0.013). In contrast, GS23 in the whole cohort of Relevance patients showed only a trend toward significance (p=0.058) and was not significant in the R2 arm (p=0.97).

[00248] The value of the recently described 33 genes signature (GS33) was assessed in Relevance patients. The GS33 gene signature shared 9/33 and 3/33 common genes with the CC17 gene signature (SYT17, PRPSAP2, SSBP2, HS2ST1, ENPP3, ZFAND4, MARCKSL1, ASB13, S1PR2) and the CC21 gene signature (NLRC5, SAMD9L, KIF13B), respectively. Since individual gene weights were not provided, a simple scoring based on the average of standardized gene expression with a +1 weight for ABC genes and -1 weight for GCB genes was used. This method showed that GS33 was not correlated with PFS in the Relevance cohort ($p=0.6$), nor in the R-chemo and R2 arms ($p=0.11$ and $p=0.39$, respectively).

GCB-like FL Cases Show a Mutation Profile Reminiscent of GC-DLBCLs, whereas ABC/MEM-like FL Cases are Enriched in Mutations of KMT2D and ATPases Genes

[00249] WES analysis was informative in cases including Y GCB-type cases and Z ABC-type FL cases. GC-subtype cFL cases exhibited a WES profile reminiscent of GC-DLBCLs, with high frequency of mutations targeting TNFSFR14, EZH2, STAT6, SOCS1, HVCN1, KLHL6 and GNAI2 (**FIG. 4**). In particular, when compared to the ABC/MEM-subtype, GC-like FLs showed over-representation of TNFSFR14, EZH2, SOCS1 and STAT6 mutations. In contrast, ABC/MEM FL cases displayed a higher number of mutations of KMT2D, ATP6V1B2, ATP6AP1 (**FIG. 4**).

The ABC/MEM-like FL Subtype Displays Higher Frequency of BCL6 Translocations

[00250] FISH analysis was informative for 342 cases (including 16 cases with only 1 or 2 informative FISH probes). Out of these 342 cases, the number of cases with informative RNAseq was 255, 256 and 253 for BCL2, BCL6 and MYC, respectively. BCL2 and BCL6 rearrangement were observed in 312 /342 cases (91%) and in 50/342 cases (14.5%); respectively. 1p36 deletion was present in 49 cases (14.5%), whereas MYC rearrangement was detected in 6 cases (1.75%) including 5 cases with MYC/BCL2 double hit. There was no correlation between GC and ABC/MEM subtypes and the presence of BCL2 break ($p=0.27$) nor MYC break ($p=0.18$) nor 1p36 deletions. In contrast, BCL6 breaks were more frequent in the ABC subtype (20% vs 9%, $p=0.037$).

An Algorithm Based on Routine Immunohistochemistry is Capable of Subtyping FFPE FL Biopsies

[00251] To allow for an easy subtyping of FL tumors in the routine practice, an immunoscore based on IHC detection of FOXP1, LMO2, CD22, and MUM1 (called the FLCM score) was developed. Three targets were selected due to their significant influence on either the ABC-like

(FOXP1 and MUM1) or the GCB-like signatures (LMO2). In fact, the corresponding genes are included in the top genes influencing either signature, especially FOXP1 and LMO2 (see **Table 1**). Another reason was the reliability of either immunodetection, as well as straightforward and unambiguous interpretation.

Table 1: Most discriminating genes influencing the GES based on t-statistic (LPS20)

ABC/MEM Signature	
Gene	t
TTC28	-12.90235
FOXP1	-17.20497
DOPEY2	-14.08426
IQSEC1	-14.14635
PTPRJ	-15.78924
SLA	-13.44714
CXXC5	-13.21572
PDE4B	-14.31872
TCF4	-18.17919
MPEG1	-16.21973
GCB Signature	
Gene	t
KIAA1211	15.81861
SCPEP1	15.97033
RASL11A	17.50829
LMO2	17.18333
HS2ST1	15.22055
ENPP3	15.22908
SH3RF1	15.60008
SCIMP	18.07827
CCDC138	15.04494
SHCBP1	15.84456

[00252] The most convenient interpretation used the algorithm in which FOXP1 and LMO2 are tested first (**FIG. 5**). In case of clear difference in the pattern of staining of the two antibodies in terms of intensity and percentage of positive cells, the sample was classified as ABC/MEM-like FL if there was strong staining for FOXP1 and weak staining for LMO2 (**FIG. 6A**). In contrast, if the sample contained weak staining for FOXP1 and strong staining for LMO2, the sample was classified as GCB-like FL (**FIG. 6B**). The samples can also be stained for CD22 and MUM1 to classify the sample as either ABC/MEM-like FL or GCB-like FL. For example, if the sample contained weak staining for FOXP1, strong staining for LMO2, strong staining for CD22, and weak staining for MUM1, the sample was classified as GCB-like FL (**FIG. 7A**). MUM1 can also be used when there is no clear difference between FOXP1 and LMO2 and weak staining for CD22. For example, if the sample contained moderate staining for both FOXP1 and LMO2, weak staining for CD22, and MUM1 stained positive in greater than about 15% of the cells, then

the sample was classified as ABC/MEM-like FL (**FIG. 7B**). Similarly, if the sample contained strong staining of FOXP1, LMO2, moderate staining of CD22 and MUM1 stained positive in less than about 10% of the cells, then the sample was classified as GCB-like FL (**FIG. 8**).

[00253] These results confirm that FL tumors can be subcategorized into cell of origin-based ABC/MEM-like or GCB-like subtypes, and this distinction has reliable prognostic significance as shown by its validation in two other cohorts of IC-treated patients using a reduced 20-gene panel predictor. Notably, a simple and reliable IHC algorithm was developed using 4 antibodies (FLCM score) which retains sufficient information to assess this subtyping using routine FFPE samples in future cohorts, and thus represents a promising theragnostic tool. The FLCM score identified ABC/MEM-like FL patients as a high-risk subgroup with inferior outcome when treated with R-chemo. However, when treated with the immunomodulatory regimen R2, ABC/MEM-like FL patients have a good prognosis compared to ABC/MEM-like FL patients treated with R-chemo.

WHAT IS CLAIMED IS

1. A method of identifying a subject as having an Activated/Memory B-cell like (ABC/MEM-like) follicular lymphoma (FL), comprising:
 - (a) determining the gene expression level of at least one biomarker in a sample from the subject, wherein the biomarker is selected from the group consisting of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1;
 - (b) determining a composite score based on the gene expression level of the at least one biomarker; and
 - (c) identifying the subject as having ABC/MEM-like FL based on the composite score.
2. The method of claim 1, further comprising administering to the subject identified as having ABC/MEM-like FL a treatment of ABC/MEM-like FL comprising a therapeutically effective amount of an immunomodulatory drug (IMiD[®]) and/or a cereblon E3 ligase modulating compound.
3. A method of selectively treating a subject having FL, comprising:
 - (a) determining the gene expression level of at least one biomarker in a sample of the subject, wherein the biomarker is selected from the group consisting of: TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1;
 - (b) determining a composite score based on the gene expression level of the at least one biomarker;
 - (c) identifying the subject as having ABC/MEM-like FL based on the composite score; and
 - (d) administering to the subject identified as having ABC/MEM-like FL a treatment of ABC/MEM-like FL comprising a therapeutically effective amount of an IMiD[®] and/or a cereblon E3 ligase modulating compound.
4. A method of identifying a subject who is likely to be responsive to a treatment of ABC/MEM-like FL or predicting the responsiveness of a subject to a treatment of ABC/MEM-like FL, comprising:
 - (a) determining the gene expression level of at least one biomarker in a sample of the subject, wherein the biomarker is selected from the group consisting of: TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1,

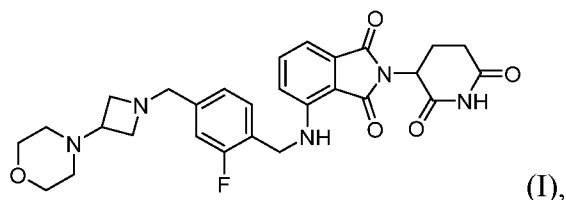
RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1;

(b) determining a composite score based on the gene expression level of the at least one biomarker; and

(c) identifying or predicting the subject as being likely to be responsive to the treatment of ABC/MEM-like FL based on the composite score, and optionally (d) administering the treatment of ABC/MEM-like FL to the subject likely to be responsive to the treatment of ABC/MEM-like FL;

wherein the treatment of ABC/MEM-like FL comprises a therapeutically effective amount of an IMiD[®] and/or a cereblon E3 ligase modulating compound.

5. The method of any one of claims 2-4, wherein the IMiD[®] and/or cereblon E3 ligase modulating compound is selected from the group consisting of lenalidomide, pomalidomide, thalidomide, iberdomide, and a compound of Formula (I)



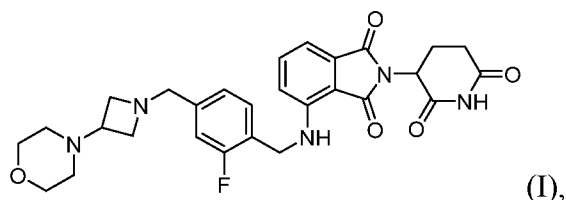
and enantiomers, mixture of enantiomers, tautomers, isotopologs, and pharmaceutically acceptable salts thereof.

6. The method of any one of claims 2-5, wherein the treatment of ABC/MEM-like FL further comprises a therapeutically effective amount of an anti-CD20 antibody.

7. The method of claim 6, wherein the anti-CD20 antibody is selected from the group consisting of rituximab, obinutuzumab, ocrelizumab, and combinations thereof.

8. The method of any one of claims 2-7, wherein the treatment of ABC/MEM-like FL comprises therapeutically effective amounts of rituximab and lenalidomide, or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

9. The method of any one of claims 2-7, wherein the treatment of ABC/MEM-like FL comprises therapeutically effective amounts of rituximab and a compound of Formula (I)



or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

10. The method of any one of claims 2-9, wherein the treatment of ABC/MEM-like FL improves overall survival, progression free survival (PFS), and/or failure free survival (FFS) of the subject having ACB/MEM-like FL.

11. The method of any one of claims 1-10, wherein the composite score is determined based on the gene expression levels of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1.

12. The method of claim 11, wherein the composite score is determined based on the sum of weighted gene expression levels of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1.

13. The method of claim 12, wherein the composite score is determined based on the following formula: $(-12.90235 \times \text{the gene expression level of TTC28}) + (-17.20497 \times \text{the gene expression level of FOXP1}) + (-14.08426 \times \text{the gene expression level of DOPEY2}) + (-14.14635 \times \text{the gene expression level of IQSEC1}) + (-15.78924 \times \text{the gene expression level of PTPRJ}) + (-13.44714 \times \text{the gene expression level of SLA}) + (-13.21572 \times \text{the gene expression level of CXXC5}) + (-14.31872 \times \text{the gene expression level of PDE4B}) + (-18.17919 \times \text{the gene expression level of TCF4}) + (-16.21973 \times \text{the gene expression level of MPEG1}) + (15.81861 \times \text{the gene expression level of KIAA1211}) + (15.97033 \times \text{the gene expression level of SCPEP1}) + (17.50829 \times \text{the gene expression level of RASL11A}) + (17.18333 \times \text{the gene expression level of LMO2}) + (15.22055 \times \text{the gene expression level of HS2ST1}) + (15.22908 \times \text{the gene expression level of ENPP3}) + (15.60008 \times \text{the gene expression level of SH3RF1}) + (18.07827 \times \text{the gene expression level of SCIMP}) + (15.04494 \times \text{the gene expression level of CCDC138}) + (15.84456 \times \text{the gene expression level of SHCBP1})$.

14. The method of any one of claims 1-13, wherein the subject is identified as having ABC/MEM-like FL or is identified or predicted as being likely to be responsive to the treatment of ABC/MEM-like FL if the composite score is lower than a predetermined value, optionally wherein the predetermined value is zero.

15. The method of any one of claims 1-13, wherein the subject is identified as having ABC/MEM-like FL or is identified or predicted as being likely to be responsive to the treatment of ABC/MEM-like FL if the composite score is lower than a reference score, optionally wherein the reference score is derived from a healthy subject or a population of healthy subjects and is calculated the same way as the composite score.

16. A method of identifying a subject as having a Germinal Center B-Cell like (GCB-like) follicular lymphoma (FL), comprising:

(a) determining the gene expression level of at least one biomarker in a sample from the subject, wherein the biomarker is selected from the group consisting of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1;

(b) determining a composite score based on the gene expression level of the at least on biomarker; and

(c) identifying the subject as having the GCB-like FL based on the composite score.

17. The method of claim 15, further comprising administering to the subject identified as having GCB-like FL a treatment of GCB-like FL.

18. A method of selectively treating a subject having FL, comprising:

(a) determining the gene expression level of at least one biomarker in a sample of the subject, wherein the biomarker is selected from the group consisting of: TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1;

(b) determining a composite score based on the gene expression level of the at least one biomarker;

(c) identifying the subject as having GCB-like FL based on the composite score; and

(d) administering to the subject identified as having GCB-like FL a therapeutically effective amount of a GCB-like FL treatment.

19. A method of identifying a subject who is likely to be responsive to a treatment of GCB-like FL or predicting the responsiveness of a subject to a treatment of GCB-like FL, comprising:

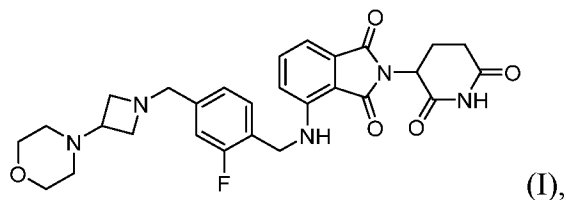
(a) determining the gene expression level of at least one biomarker in a sample of the subject, wherein the biomarker is selected from the group consisting of: TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1;

(b) determining a composite score based on the gene expression level of the at least one biomarker;

(c) identifying or predicting the subject as being likely to be responsive to the treatment of GCB-like FL based on the composite score, and optionally (d) administering the treatment of GCB-like FL to the subject likely to be responsive to the treatment of GCB-like FL.

20. The method of any one of claims 15-19, wherein the treatment of GCB-like FL comprises a therapeutically effective amount of an IMiD[®], a cereblon E3 ligase modulating compound, an anti-CD20 antibody, a chemotherapeutic agent, or a combination thereof.

21. The method of claim 20, wherein the IMiD[®] and/or cereblon E3 ligase modulating compound is selected from the group consisting of lenalidomide, pomalidomide, thalidomide, iberdomide, and a compound of Formula (I)



and enantiomers, mixture of enantiomers, tautomers, isotopologs, and pharmaceutically acceptable salts thereof.

22. The method of claim 20, wherein the anti-CD20 antibody is selected from the group consisting of rituximab, obinutuzumab, ocrelizumab, and combinations thereof.

23. The method of claim 20, wherein the chemotherapeutic agent is selected from the group consisting of cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and combinations thereof.

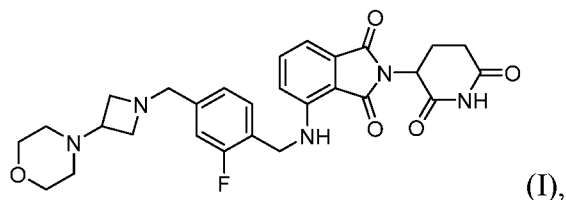
24. The method of any one of claims 15-20, wherein the treatment of GCB-like FL comprises the therapeutically effective amounts of the anti-CD20 antibody and the chemotherapeutic agent.

25. The method of claim 24, wherein the treatment of GCB-like FL comprises the therapeutically effective amounts of rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone.

26. The method of any one of claims 15-20, wherein the treatment of GCB-like FL comprises the therapeutically effective amounts of the IMiD® and/or cereblon E3 ligase modulating compound, and the anti-CD20 antibody.

27. The method of claim 26, wherein the treatment of GCB-like FL comprises the therapeutically effective amounts of rituximab and lenalidomide, or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

28. The method of claim 26, wherein the treatment of GCB-like FL comprises the therapeutically effective amounts of rituximab and a compound of Formula (I)



or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

29. The method of any one of claims 15-28, wherein the composite score is determined based on the gene expression levels of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1.

30. The method of claim 29, wherein the composite score is determined based on the sum of weighted gene expression levels of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1.

31. The method of claim 30, wherein the composite score is determined based on the following formula: $(-12.90235 \times \text{the gene expression level of TTC28}) + (-17.20497 \times \text{the gene expression level of FOXP1}) + (-14.08426 \times \text{the gene expression level of DOPEY2}) + (-14.14635 \times \text{the gene expression level of IQSEC1}) + (-15.78924 \times \text{the gene expression level of PTPRJ}) + (-13.44714 \times \text{the gene expression level of SLA}) + (-13.21572 \times \text{the gene expression level of CXXC5}) + (-14.31872 \times \text{the gene expression level of PDE4B}) + (-18.17919 \times \text{the gene expression level of TCF4}) + (-16.21973 \times \text{the gene expression level of MPEG1}) + (15.81861 \times \text{the gene expression level of KIAA1211}) + (15.97033 \times \text{the gene expression level of SCPEP1}) + (17.50829 \times \text{the gene expression level of RASL11A}) + (17.18333 \times \text{the gene expression level of LMO2}) + (17.18333 \times \text{the gene expression level of HS2ST1}) + (17.18333 \times \text{the gene expression level of ENPP3}) + (17.18333 \times \text{the gene expression level of SH3RF1}) + (17.18333 \times \text{the gene expression level of SCIMP}) + (17.18333 \times \text{the gene expression level of SHCBP1})$

LMO2) + (15.22055 × the gene expression level of HS2ST1) + (15.22908 × the gene expression level of ENPP3) + (15.60008 × the gene expression level of SH3RF1) + (18.07827 × the gene expression level of SCIMP) + (15.04494 × the gene expression level of CCDC138) + (15.84456 × the gene expression level of SHCBP1).

32. The method of any one of claims 15-31, wherein the subject is identified as having GCB-like FL or is identified or predicted as being likely to be responsive to the treatment of GCB-like FL if the composite score is higher than a predetermined value, optionally wherein the predetermined value is zero.

33. The method of any one of claims 15-31, wherein the subject is identified as having GCB-like FL or is identified or predicted as being likely to be responsive to the treatment of GCB-like FL if the composite score is higher than a reference score, optionally wherein the reference score is derived from a healthy subject or a population of healthy subjects and is calculated the same way as the composite score.

34. The method of any one of claims 1-33, wherein the gene expression level of the at least one biomarker is mRNA level.

35. The method of claim 34, wherein the gene expression level is measured by RNA sequencing or PCR-based quantification methods.

36. A method of identifying a subject as having an ABC/MEM-like FL, comprising:
(a) determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and
(b) identifying the subject as having the ABC/MEM-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1.

37. The method of claim 36, further comprising administering to the subject identified as having ABC/MEM-like FL a therapeutically effective amount of an immunomodulatory drug (IMiD[®]) and/or a cereblon E3 ligase modulating compound.

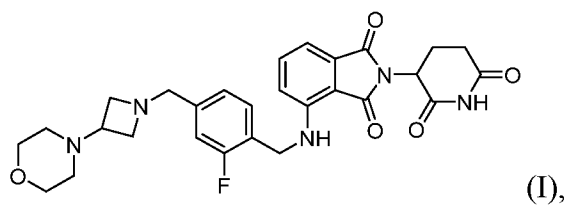
38. A method of selectively treating a subject having FL, comprising:
(a) determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1;
(b) identifying the subject as having ABC/MEM-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and
(c) administering to the subject identified as having ABC/MEM-like FL a therapeutically effective amount of an IMiD[®] and/or a cereblon E3 ligase modulating compound.

39. A method of identifying a subject who is likely to be responsive to a treatment of ABC/MEM-like FL or predicting the responsiveness of a subject to a treatment of ABC/MEM-like FL, comprising:

- (a) determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and
- (b) identifying or predicting the subject as being likely to be responsive to the treatment of ABC/MEM-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and optionally (c) administering the treatment of ABC/MEM-like FL to the subject likely to be responsive to the treatment of ABC/MEM-like FL;

wherein the treatment of ABC/MEM-like FL comprises an IMiD[®] and/or a cereblon E3 ligase modulating compound.

40. The method of any one of claims 37-39, wherein the IMiD[®] and/or cereblon E3 ligase modulating compound is selected from the group consisting of lenalidomide, pomalidomide, thalidomide, iberdomide, and a compound of Formula (I)



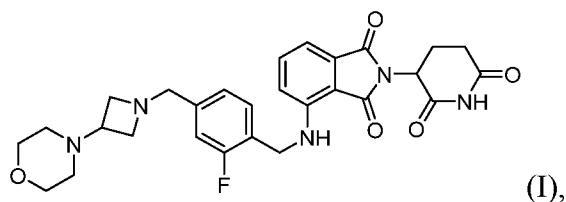
and enantiomers, mixture of enantiomers, tautomers, isotopologs, and pharmaceutically acceptable salts thereof.

41. The method any one of claims 37-40, wherein the treatment of ABC/MEM-like FL further comprises a therapeutically effective amount of an anti-CD20 antibody.

42. The method of claim 41, wherein the anti-CD20 antibody is selected from the group consisting of rituximab, obinutuzumab, ocrelizumab, and combinations thereof.

43. The method of any one of claims 37-42, wherein the treatment of ABC/MEM-like FL comprises therapeutically effective amounts of rituximab and lenalidomide, or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

44. The method of any one of claims 37-42, wherein the treatment of ABC/MEM-like FL comprises therapeutically effective amounts of rituximab and a compound of Formula (I)



or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

45. The method of any one of claims 37-44, wherein the treatment of ABC/MEM-like FL improves overall survival, PFS, and/or FFS of the subject having ACB/MEM-like FL.

46. The method of any one of claims 37-45, wherein the protein expression levels of FOXP1, LMO2, CD22, and MUM1 are protein levels.

47. The method of claim 46, wherein the protein levels are measured using immunohistochemistry (IHC), Multiplexed Ion Beam Imaging (MIBI), or Imaging Mass Cytometry (IMC).

48. The method of claim 47, wherein the subject is identified as having ABC/MEM-like FL or is identified or predicted as being likely to be responsive to the treatment of ABC/MEM-like FL if

(i) the protein expression level of FOXP1 is strong or moderate and the protein expression level of LMO2 is weak or negative;

(ii) the protein expression level of FOXP1 is close to the protein expression level of LMO2 (equally strong, moderate, or weak) or otherwise noninformative, and the protein expression level of CD22 is weak; or

(iii) the protein expression level of FOXP1 is close to that of LMO2 (equally strong, moderate, or weak) or otherwise noninformative, and the protein expression level of CD22 is moderate or otherwise noninformative, and the percentage of MUM1 positive cells in the sample is greater than about 15%.

49. The method of claim 47 or 48, wherein the subject is identified as having ABC/MEM-like FL or is identified or predicted as being likely to be responsive to the treatment of ABC/MEM-like FL if

(i) the percentage of FOXP1 positive cells in the sample is more than about 50% and the percentage of LMO2 positive cells in the sample is less than about 50%, and the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2

positive cells in the sample is about 20% or more;

(ii) if the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is less than about 20%, and the percentage of CD22 positive cells in the sample is less than about 20%; or

(iii) if the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is less than about 20%, and the percentage of CD22 positive cells in the sample is between about 20% and about 80%, and the percentage of MUM1 positive cells in the sample is greater than about 15%.

50. A method of identifying a subject as having a GCB-like FL, comprising:

- (a) determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and
- (b) identifying the subject as having the GCB-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1.

51. The method of claim 50, further comprising administering to the subject identified as having GCB-like FL a treatment of GCB-like FL.

52. A method of selectively treating a subject having FL, comprising:

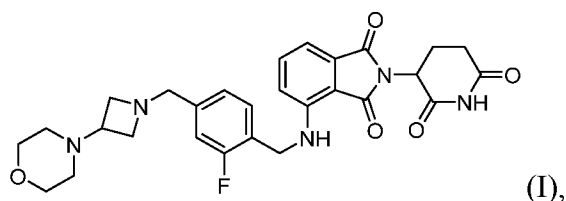
- (a) determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1;
- (b) identifying the subject as having GCB-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and
- (c) administering to the subject identified as having GCB-like FL a therapeutically effective amount of GCB-like FL treatment.

53. A method of identifying a subject who is likely to be responsive to a treatment of GCB-like FL or predicting the responsiveness of a subject to a treatment of GCB-like FL, comprising:

- (a) determining the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and
- (b) identifying or predicting the subject as being likely to be responsive to the treatment of GCB-like FL based on the protein expression levels of FOXP1, LMO2, CD22, and MUM1; and optionally (c) administering the treatment of GCB-like FL to the subject likely to be responsive to the treatment of GCB-like FL.

54. The method of any one of claims 51-53, wherein the treatment of GCB-like FL comprises a therapeutically effective amount of an IMiD[®], a cereblon E3 ligase modulating compound, an anti-CD20 antibody, a chemotherapeutic agent, or a combination thereof.

55. The method of claim 54, wherein the IMiD[®] and/or cereblon E3 ligase modulating compound is selected from the group consisting of lenalidomide, pomalidomide, thalidomide, iberdomide, and a compound of Formula (I)



and enantiomers, mixture of enantiomers, tautomers, isotopologs, and pharmaceutically acceptable salts thereof.

56. The method of claim 54, wherein the anti-CD20 antibody is selected from the group consisting of rituximab, obinutuzumab, ocrelizumab, and combinations thereof.

57. The method of claim 54, wherein the chemotherapeutic agent is selected from the group consisting of cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and combinations thereof.

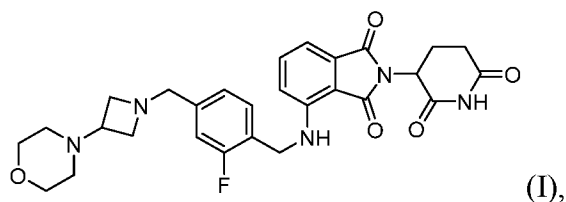
58. The method of any one of claims 51-54, wherein the treatment of GCB-like FL comprises the therapeutically effective amounts of the anti-CD20 antibody and the chemotherapeutic agent.

59. The method of claim 58, wherein the treatment of GCB-like FL comprises the therapeutically effective amounts of rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone.

60. The method of any one of claims 51-54, wherein the treatment of GCB-like FL comprises the therapeutically effective amounts of the IMiD[®] and/or cereblon E3 ligase modulating compound, and the anti-CD20 antibody.

61. The method of claim 59, wherein the treatment of GCB-like FL comprises the therapeutically effective amounts of rituximab and lenalidomide, or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

62. The method of claim 59, wherein the treatment of GCB-like FL comprises the therapeutically effective amounts of rituximab and a compound of Formula (I)



or an enantiomer, mixture of enantiomers, tautomer, isotopolog, or pharmaceutically acceptable salt thereof.

63. The method of any one of claims 50-62, wherein the protein expression levels of FOXP1, LMO2, CD22, and MUM1 are protein levels.

64. The method of claim 63, wherein the protein levels are measured using immunohistochemistry (IHC), Multiplexed Ion Beam Imaging (MIBI), or Imaging Mass Cytometry (IMC).

65. The method of claim 64, wherein the subject is identified as having GCB-like FL or is identified or predicted as being likely to be responsive to the treatment of GCB-like FL if

(i) the protein expression level of LMO2 is strong or moderate and the protein expression level of FOXP1 is weak or negative;

(ii) the protein expression level of LMO2 is close to that of FOXP1 (equally strong, moderate, or weak) or otherwise noninformative, and the protein expression level of CD22 is strong; or

(iii) the protein expression level of LMO2 is close to that of FOXP1 (equally strong, moderate, or weak) or otherwise noninformative, and the protein expression level of CD22 is moderate or otherwise noninformative, and the percentage of MUM1 positive cells in the sample is less than about 10%.

66. The method of claim 64 or 65, wherein the subject is identified as having GCB-like FL or is identified or predicted as being likely to be responsive to the treatment of GCB-like FL if

(i) the percentage of LMO2 positive cells in the sample is more than about 50% and the percentage of FOXP1 positive cells in the sample is less than about 50%, and the difference between the percentage of LMO2 positive cells in the sample and the percentage of FOXP1 positive cells in the sample is about 20% or more;

(ii) if the difference between the percentage of FOXP1 positive cells in the sample and the percentage of LMO2 positive cells in the sample is less than about 20%, and the percentage of CD22 cells in the sample is greater than about 80%; or

(iii) if the difference between the percentage of FOXP1 positive cells in the sample and

the percentage of LMO2 positive cells in the sample is less than about 20%, the percentage of CD22 positive cells in the sample is between about 20% and about 80%, and the percentage of MUM1 positive cells in the sample is less than about 10%.

67. The method of any one of claims 1-65, wherein the sample is a tumor biopsy.

68. A kit for performing the method of any one of claims 1-67, the kit comprising an agent for determining (i) the gene expression level of at least one biomarker selected from the group consisting of TTC28, FOXP1, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEG1, KIAA1211, SCPEP1, RASL11A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1 or (ii) the protein expression levels of FOXP1, LMO2, CD22, and MUM1.

69. The kit of claim 68, wherein the kit further comprises a tool for obtaining the sample.

70. The kit of claim 68 or 69, wherein the kit further comprises an instruction on interpreting the determined expression level.

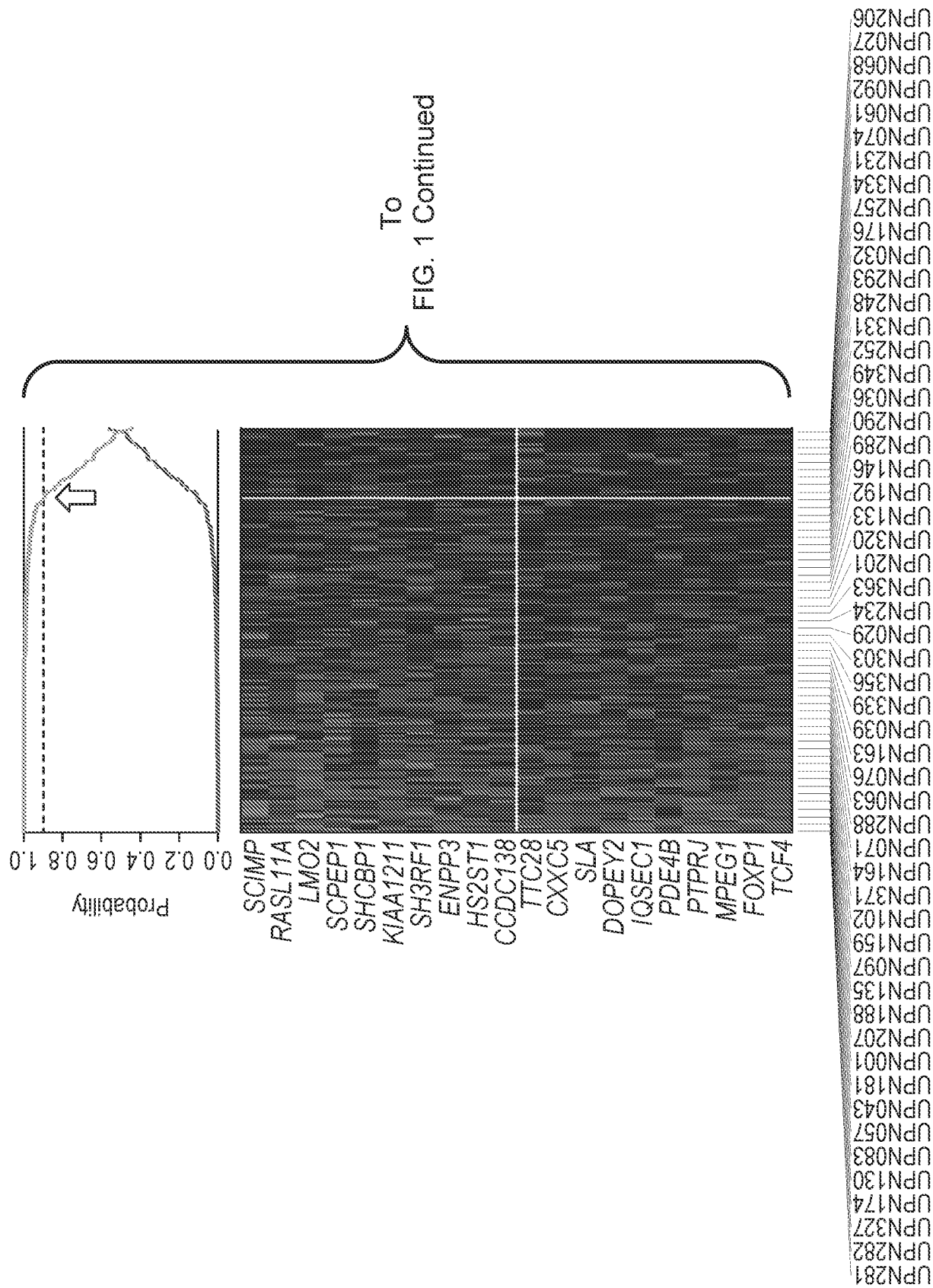


FIG. 1

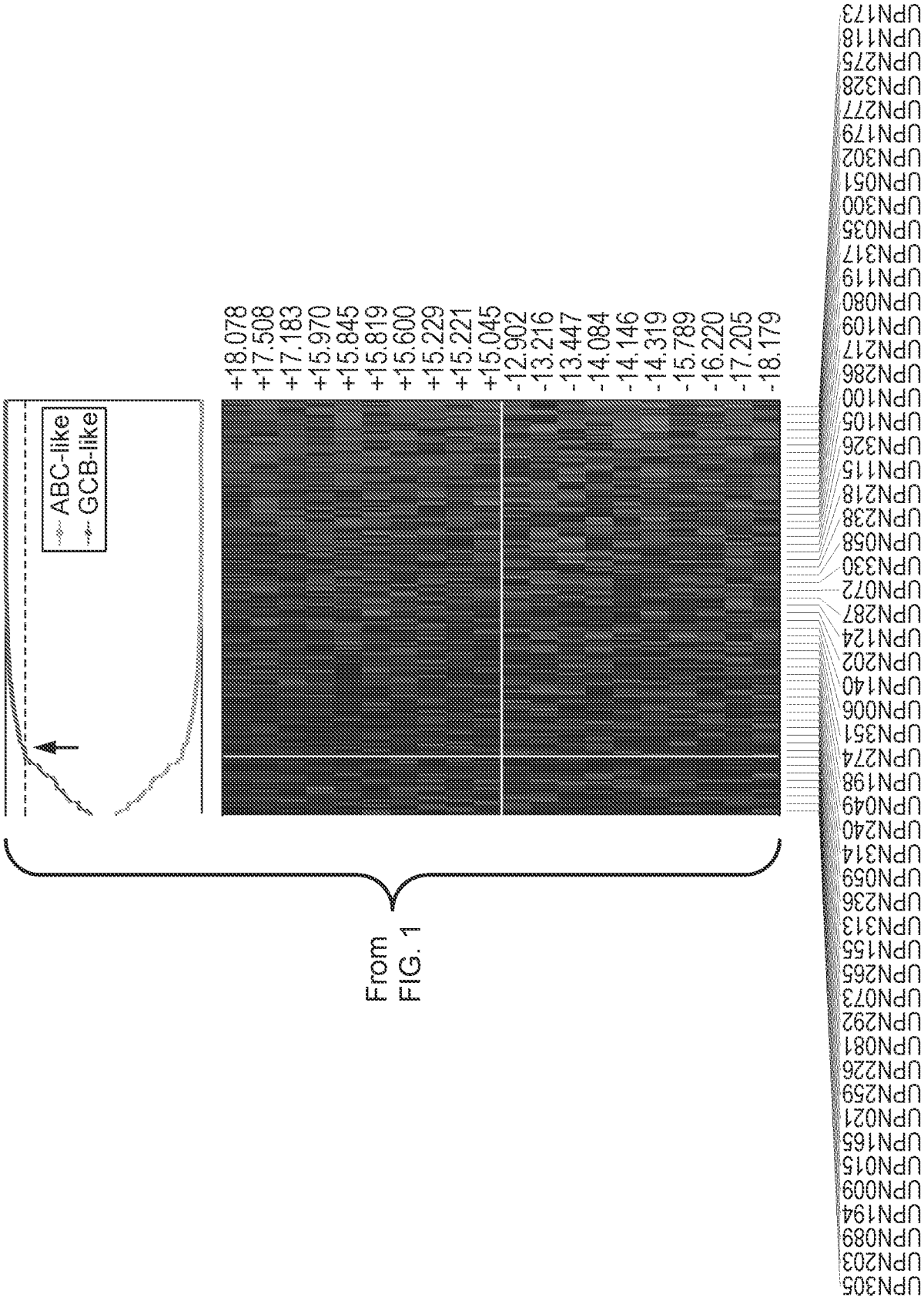
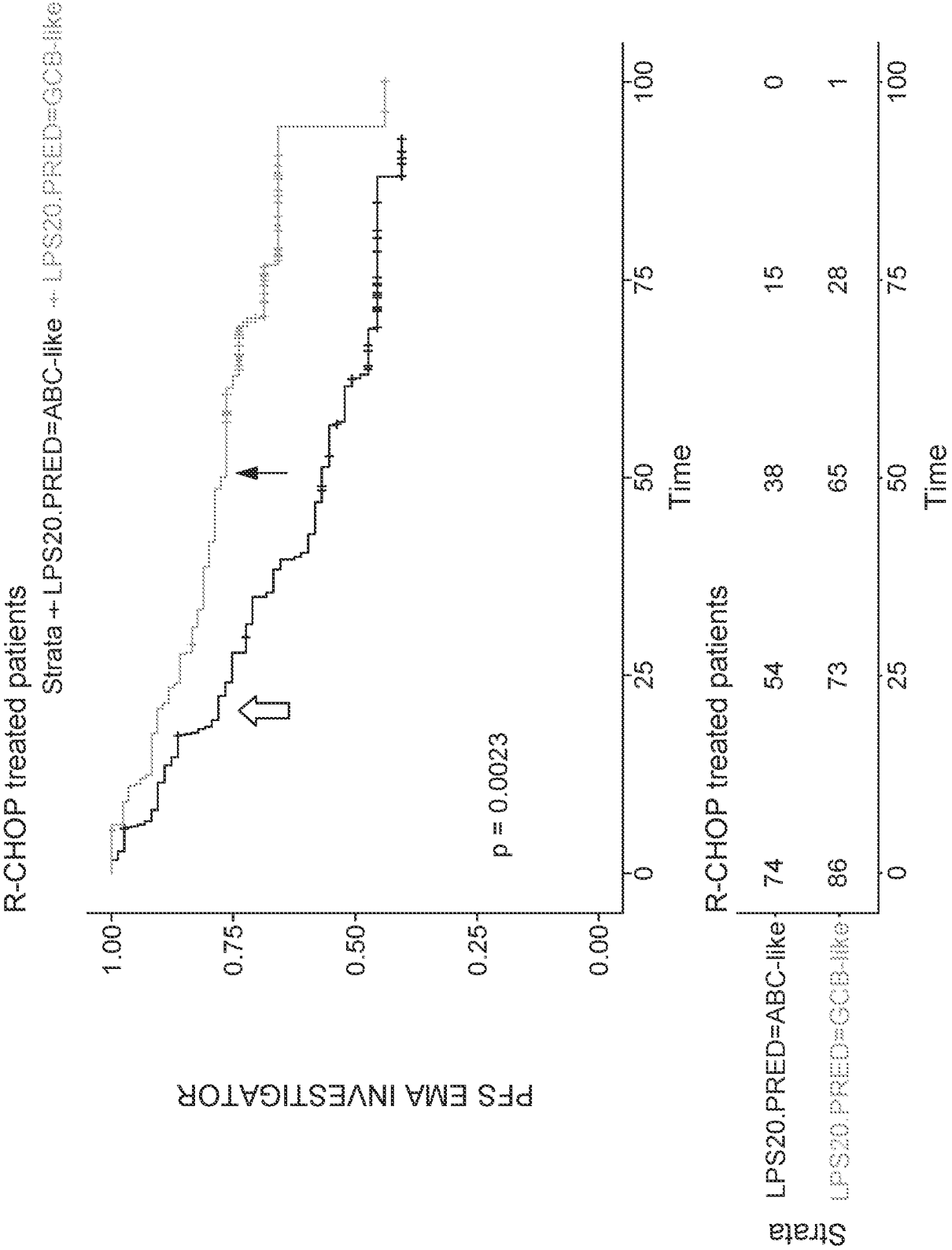
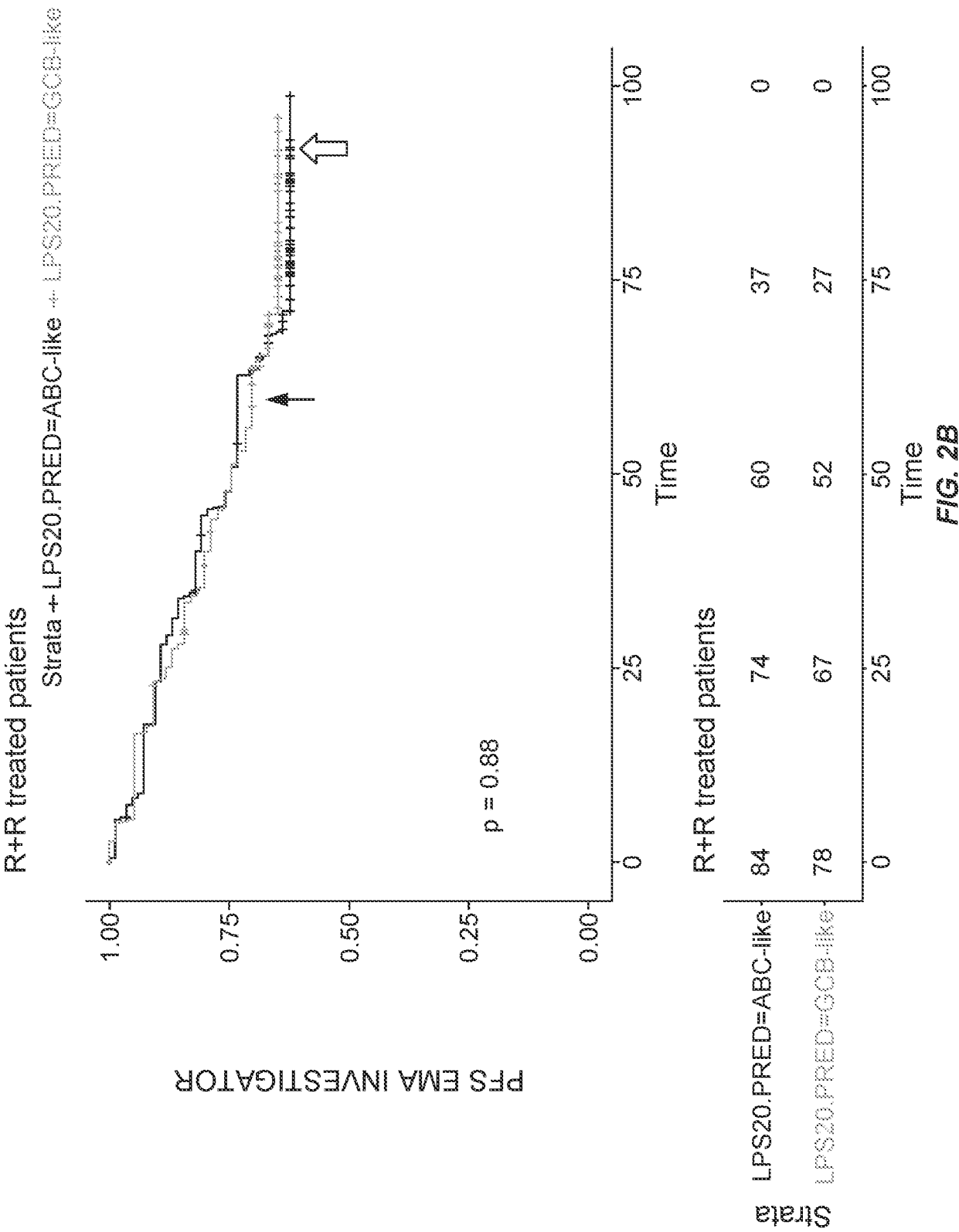
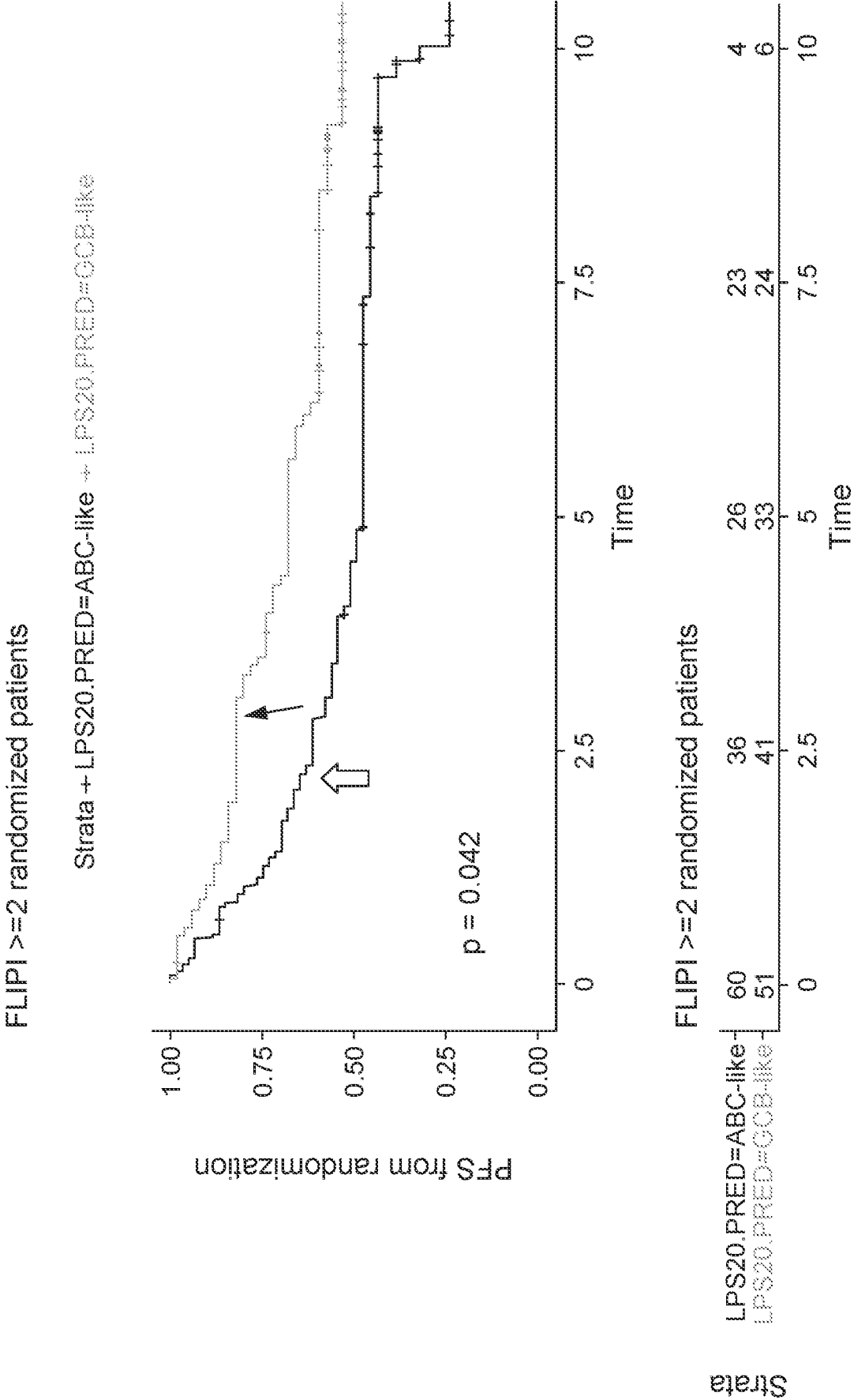


FIG. 1 Continued







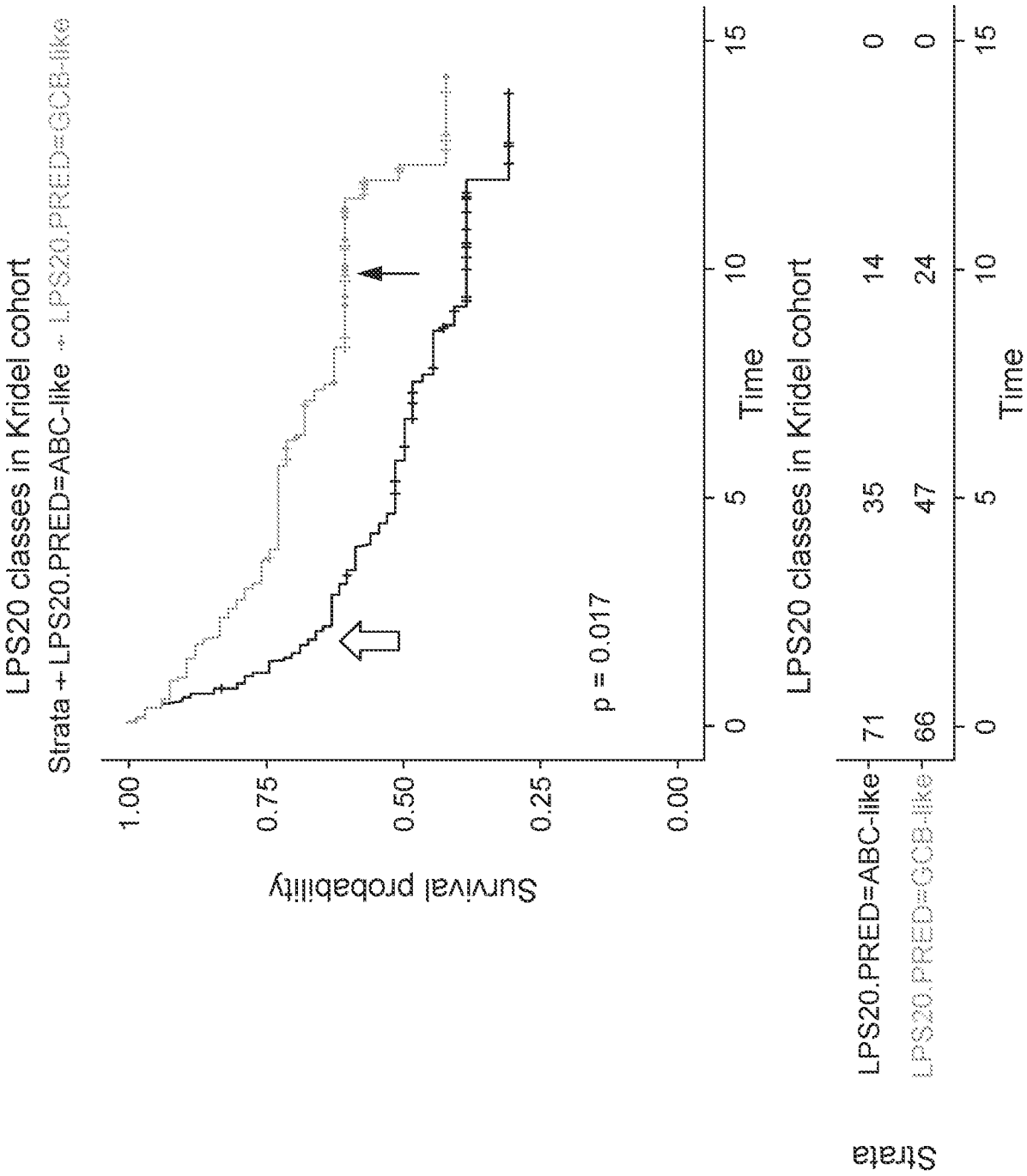
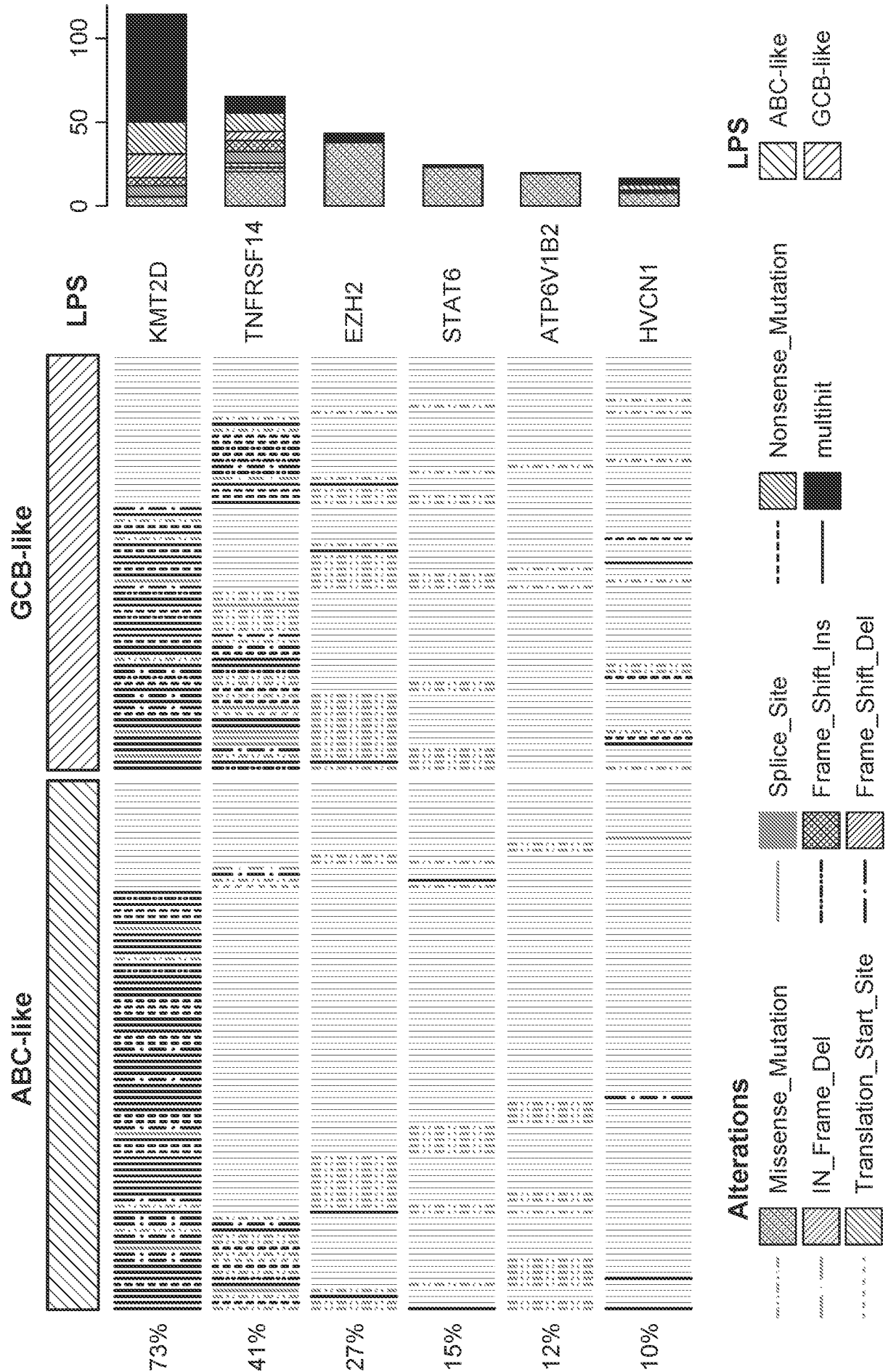


FIG. 3B



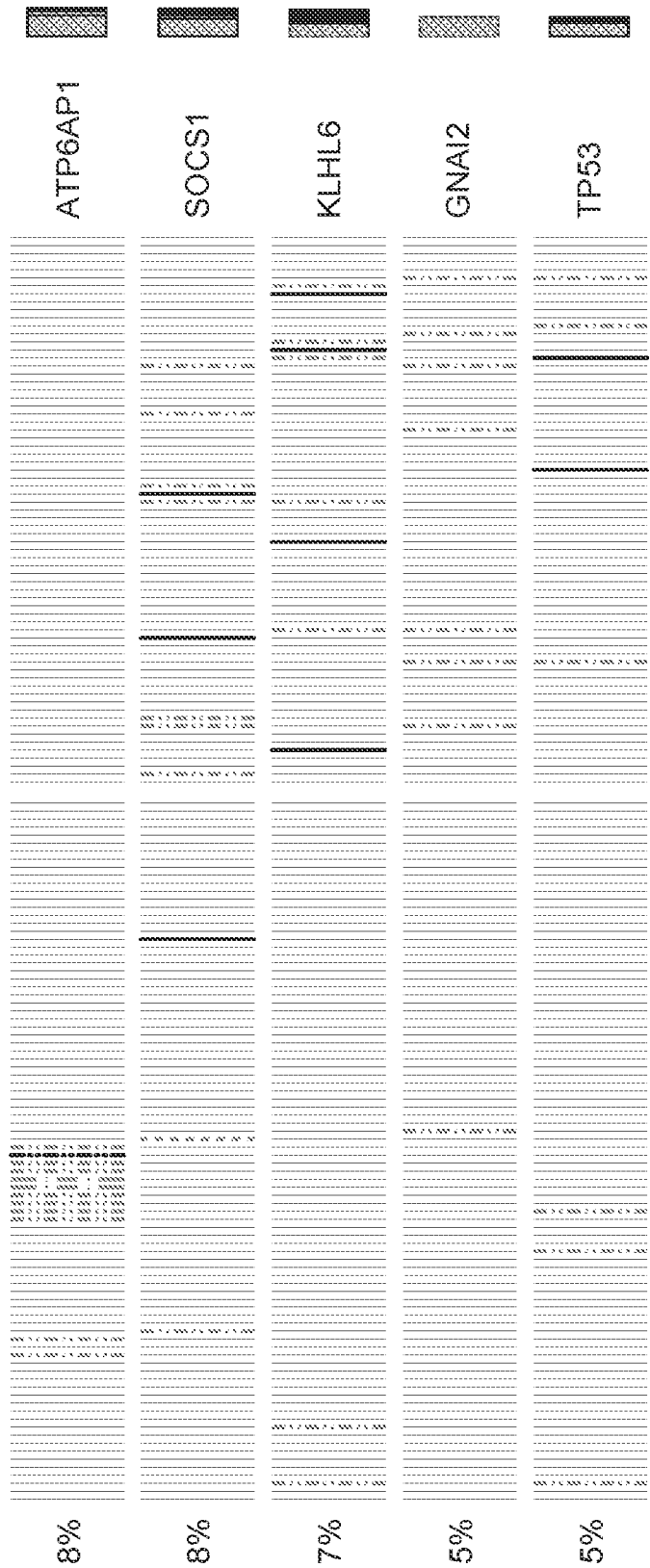


FIG. 4 Continued

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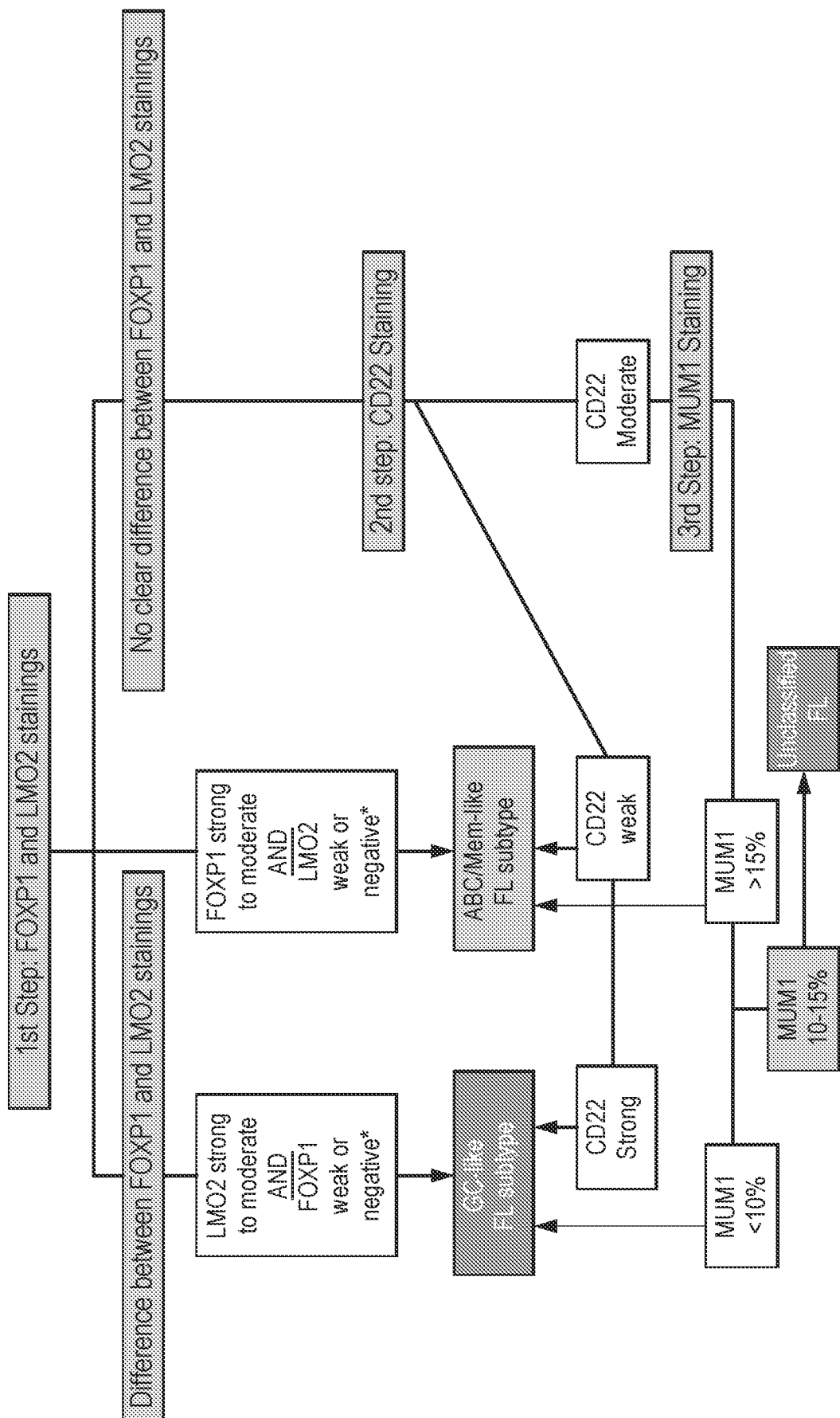
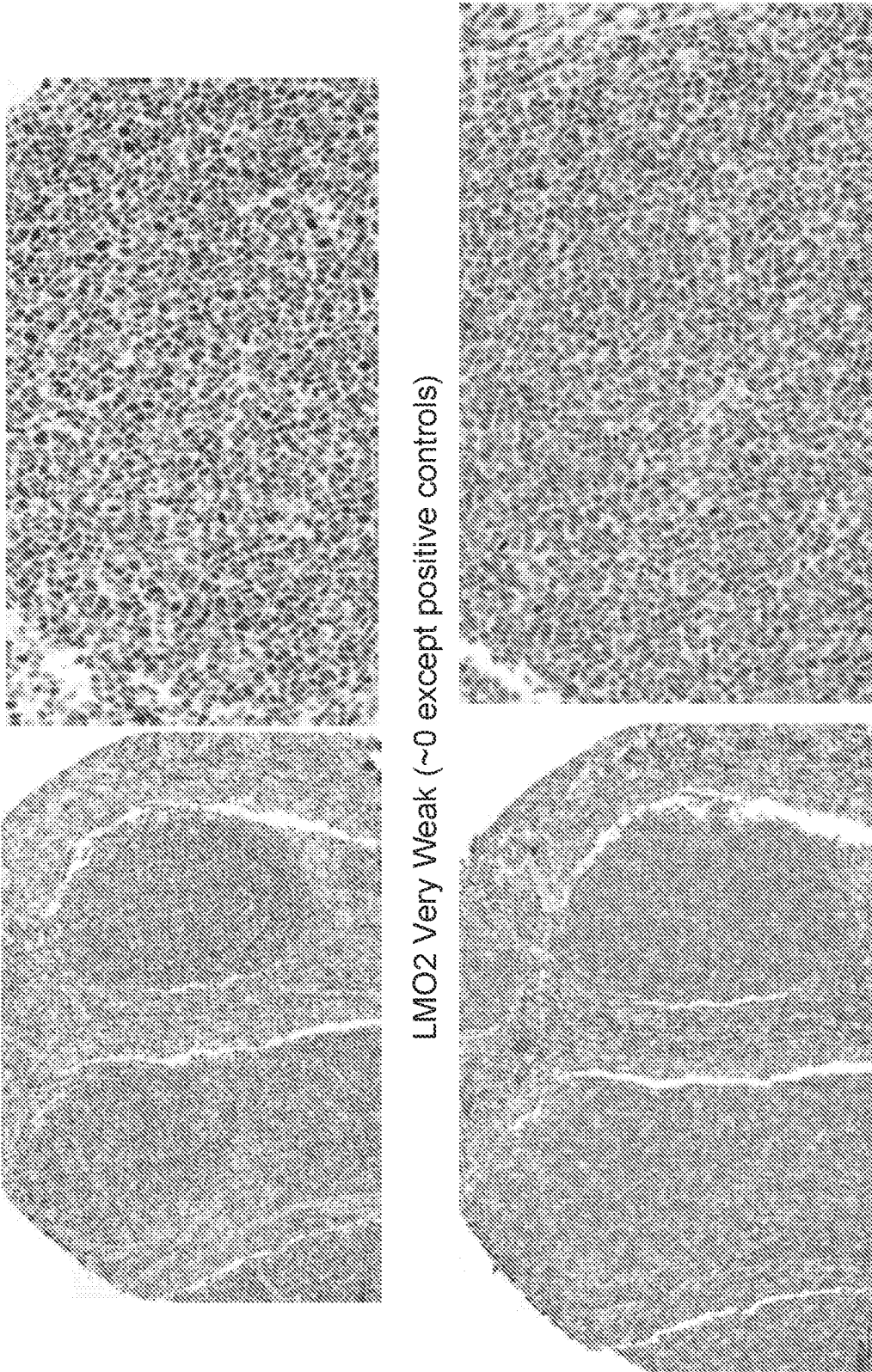


FIG. 5

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FOXP1 Super Strong (~100% of the cells with high intensity of staining)



LMO2 Very Weak (~0 except positive controls)

FIG. 6A

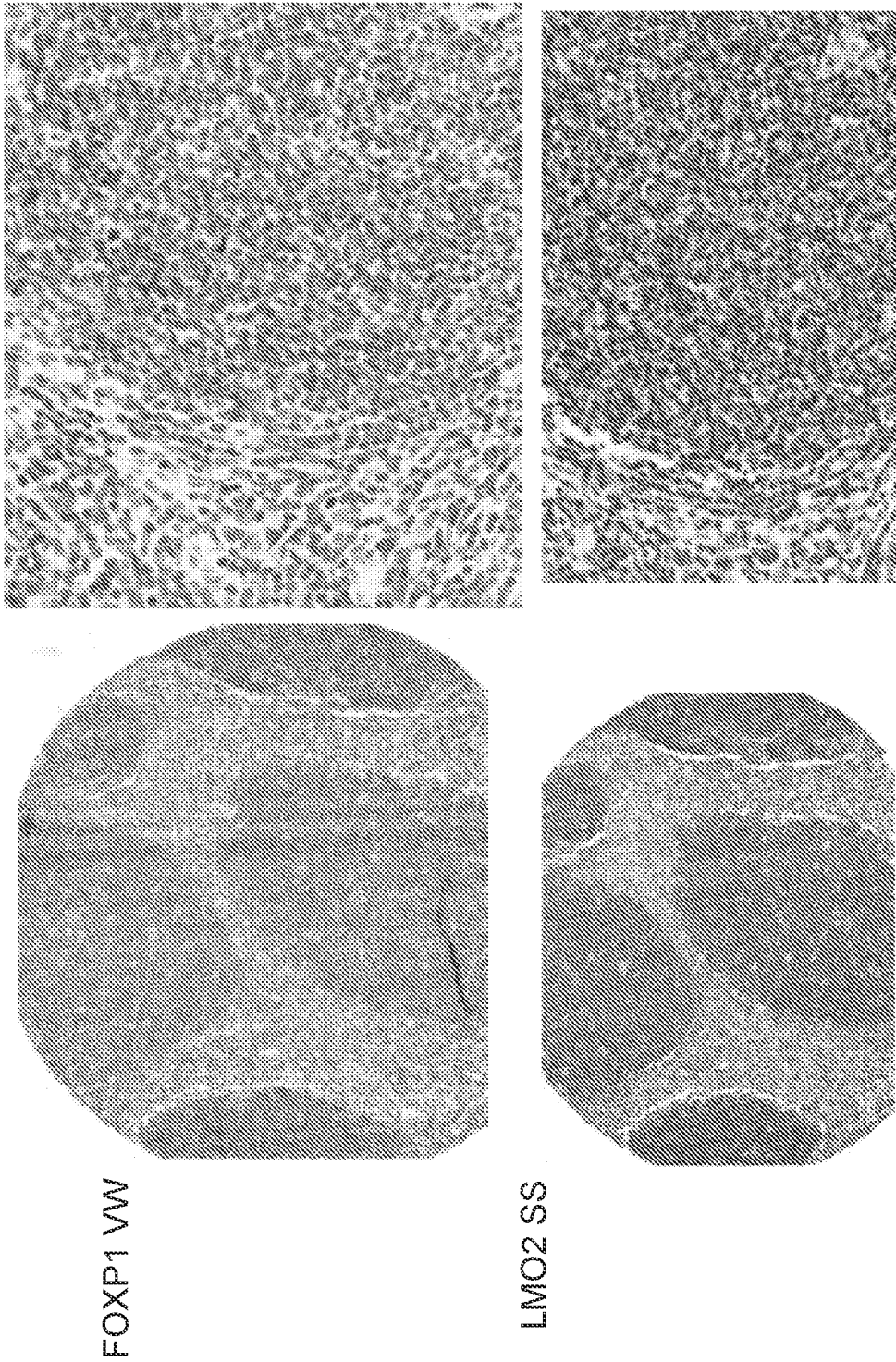


FIG. 6B

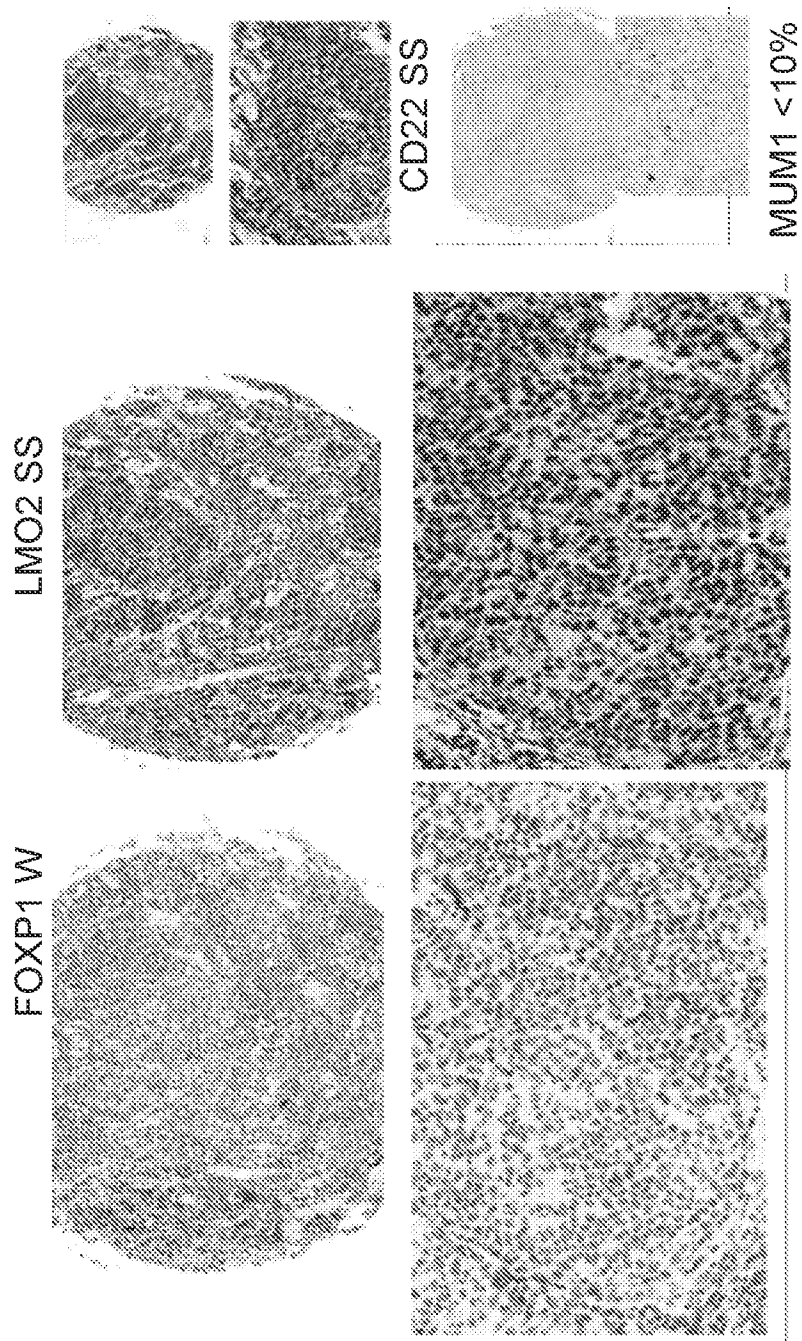


FIG. 7A

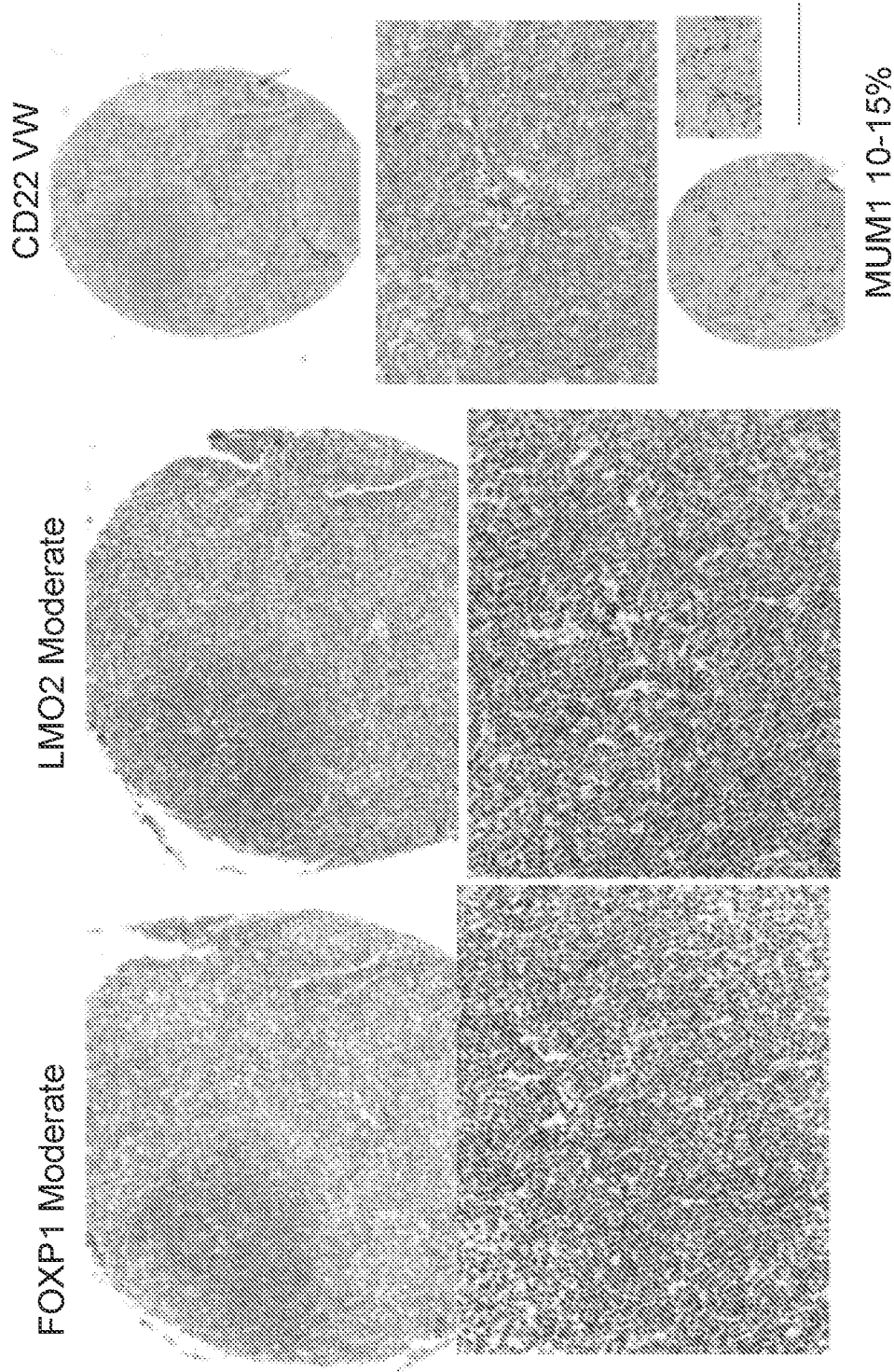


FIG. 7B

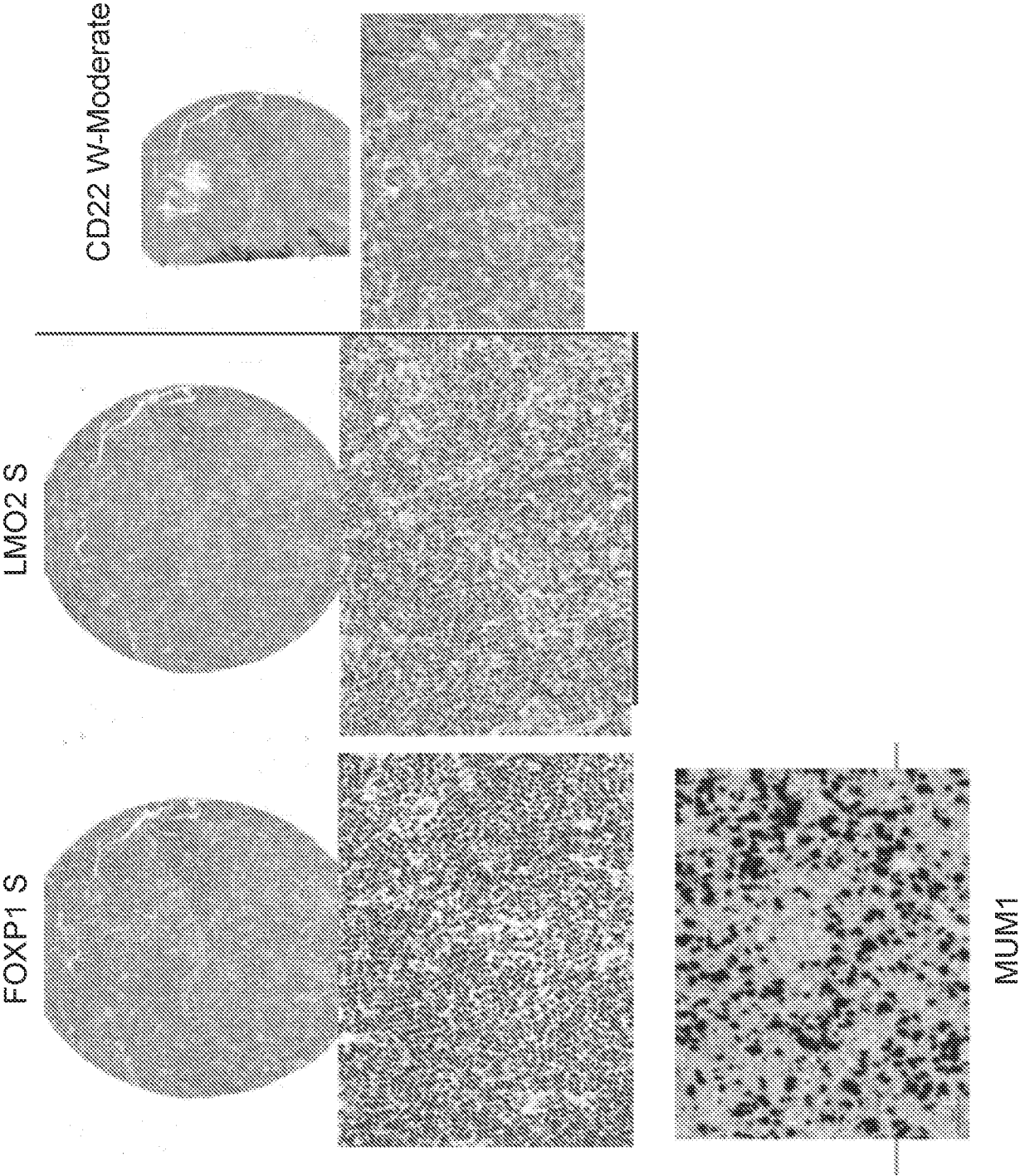


FIG. 8

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/033562

A. CLASSIFICATION OF SUBJECT MATTERIPC: **C07K 14/47** (2024.01); **A61P 35/00** (2024.01); **C12Q 1/6886** (2024.01)CPC: **C07K 14/47**; **A61P 35/00**; **C12Q 1/6886**; **C12Q 2600/106**; **C12Q 2600/112**

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

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

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2020/0118646 A1 (CELGENE CORPORATION) 16 April 2020 (16.04.2020) entire document	1-5, 16, 18, 19
A	US 2021/0071258 A1 (JUNO THERAPEUTICS INC.) 11 March 2021 (11.03.2021) entire document	1-5, 16, 18, 19
A	WO 2022/248573 A2 (CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES et al.) 01 December 2022 (01.12.2022) entire document	1-5, 16, 18, 19
A	US 2018/0223368 A1 (MEMORIAL SLOAN KETTETING CANCER CENTER et al.) 09 August 2018 (09.08.2018) entire document	1-5, 16, 18, 19
A	KRIDEL et al., Cell of origin of transformed follicular lymphoma, Blood, Vol. 126, No. 18, pp. 2118-2127, 25 August 2015 [retrieved 02 August 2024]. Retrieved from the Internet <URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4626253/ >. entire document	1-5, 16, 18, 19



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

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

“D” document cited by the applicant in the international application

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

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

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

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

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

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

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

“&” document member of the same patent family

Date of the actual completion of the international search

13 August 2024 (13.08.2024)

Date of mailing of the international search report

05 November 2024 (05.11.2024)

Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/033562

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: **6-15, 17, 20-35, 41-49, 58-70**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-5, 16, 18, and 19 are drawn to methods of identifying a subject as having an ABC/MEM-like FL, methods of selectively treating a subject having FL, methods of identifying a subject who is likely responsive to a treatment of ABC/MEM-like FL or predicting the responsiveness of a subject to a treatment of ABC/MEM-like FL, methods of identifying a subject as having GCB-like FL, and methods of identifying a subject who is likely to be responsive to a treatment of GCB-like FL or predicting the responsiveness of a subject to a treatment of GCB-like FL comprising determining gene expression level.

Group II: claims 36-40 and 50-57 are drawn to methods of identifying a subject as having an ABC/MEM-like FL, methods of selectively treating a subject having FL, methods of identifying a subject who is likely responsive to a treatment of ABC/MEM-like FL or predicting the responsiveness of a subject to a treatment of ABC/MEM-like FL, methods of identifying a subject as having GCB-like FL, and methods of identifying a subject who is likely to be responsive to a treatment of GCB-like FL or predicting the responsiveness of a subject to a treatment of GCB-like FL comprising determining protein expression level.

The first invention of Group I+ is restricted to a biomarker selected to be TTC28 and methods comprising the same. The first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Specifically, the first named invention was selected based on the first listed biomarker species presented in the claims (see claim 1). It is believed that claims 1-5, 16, 18, and 19 read on this first named invention and thus these claims will be searched without fee to the extent that they read on TTC28.

Applicant is invited to elect additional biomarkers to be searched in a specific combination by paying additional fee for each set of election. An exemplary election would be a biomarker selected to be FOXP1 and methods comprising the same. Additional biomarkers will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

The inventions listed in Groups I+ and II do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Group I+ formulas do not share a significant structural element responsible for determining gene expression level for a composite score requiring the selection of alternative biomarkers where “determining the gene expression level of at least one biomarker in a sample from the subject, wherein the biomarker is selected from the group consisting of TTC28, FOXPI, DOPEY2, IQSEC1, PTPRJ, SLA, CXXC5, PDE4B, TCF4, MPEGI, KIAA1211, SCPEP1, RASLI A, LMO2, HS2ST1, ENPP3, SH3RF1, SCIMP, CCDC138, and SHCBP1.”

The special technical features of Group I+, methods of identifying a subject as having an ABC/MEM-like FL, methods of selectively treating a subject having FL, methods of identifying a subject who is likely responsive to a treatment of ABC/MEM-like FL or predicting the responsiveness of a subject to a treatment of ABC/MEM-like FL, methods of identifying a subject as having GCB-like FL, and methods of identifying a subject who is likely to be responsive to a treatment of GCB-like FL or predicting the responsiveness of a subject to a treatment of GCB-like FL comprising determining gene expression level, are not present in Group II; the special technical features of Group II, methods of identifying a subject as having an ABC/MEM-like FL, methods of selectively treating a subject having FL, methods of identifying a subject who is likely responsive to a treatment of ABC/MEM-like FL or predicting the responsiveness of a subject to a treatment of ABC/MEM-like FL, methods of identifying a subject as having GCB-like FL, and methods of identifying a subject who is likely to be responsive to a treatment of GCB-like FL or predicting the responsiveness of a subject to a treatment of GCB-like FL comprising determining protein expression level, are not present in Group I+.

Additionally, even if Groups I+ and II were considered to share the technical features of a method of identifying a subject as having an Activated/Memory B-cell like (ABC/MEM-like) follicular lymphoma (FL), comprising: (a) determining the gene expression level of at least one biomarker in a sample from the subject; (b) determining a composite score based on the gene expression level of the at least one biomarker; and (c) identifying the subject as having ABC/MEM-like FL based on the composite score; a method of selectively treating a subject having FL, comprising: (a) determining the gene expression level of at least one biomarker in a sample of the subject; (b) determining a composite score based on the gene expression level of the at least one biomarker; (c) identifying the subject as having ABC/MEM-like FL based on the composite score; and (d) administering to the subject identified as having ABC/MEM-like FL a treatment of ABC/MEM-like FL comprising a therapeutically effective amount of an IMiD and/or a cereblon E3 ligase modulating compound; a method of identifying a subject who is likely to be responsive to a treatment of ABC/MEM-like FL or predicting the responsiveness of a subject to a treatment of ABC/MEM-like FL, comprising: (a) determining the gene expression level of at least one biomarker in a sample of the subject; (b) determining a composite score based on the gene expression level of the at least one biomarker; and (c) identifying or predicting the subject as being likely to be responsive to the treatment of ABC/MEM-like FL based on the composite score, and optionally (d) administering the treatment of ABC/MEM-like FL to the subject likely to be responsive to the treatment of ABC/MEM-like FL; wherein the treatment of ABC/MEM-like FL comprises a therapeutically effective amount of an IMiD and/or a cereblon E3 ligase modulating compound; a method of identifying a subject as having a Germinal Center B-Cell like (GCB-like) follicular lymphoma (FL), comprising: (a) determining the gene expression level of at least one biomarker in a sample from the subject; (b) determining a composite score based on the gene expression level of the at least one biomarker; and (c) identifying the subject as having the GCB-like FL based on the composite score; a method of selectively treating a subject having FL, comprising: (a) determining the gene expression level of at least one biomarker in a sample of the subject; (b) determining a composite score based on the gene expression level of the at least one biomarker; (c) identifying the subject as having GCB-like FL based on the composite score; and (d) administering to the subject identified as having GCB-like FL a therapeutically effective amount of a GCB-like FL treatment; and a method of identifying a subject who is likely to be responsive to a treatment of GCB-like FL or predicting the responsiveness of a subject to a treatment of GCB-like FL, comprising: (a) determining the gene expression level of at least one biomarker in a sample of the subject; (b) determining a composite score based on the gene expression level of the at least one biomarker; (c) identifying or predicting the subject as being likely to be responsive to the treatment of GCB-like FL based on the composite score, and optionally (d) administering the treatment of GCB-like FL to the subject likely to be responsive to the treatment of GCB-like FL. However, these shared technical features do not represent a contribution over the prior art.

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

US 2018/0223368 A1 to Memorial Sloan Kettering Cancer Center et al. (hereinafter, "Sloan") teaches a method of identifying a subject as having a follicular lymphoma (FL) (a method for diagnosing a follicular lymphoma in a subject; Para. [0006]), comprising: (a) determining the gene expression level of at least one biomarker in a sample from the subject (obtaining a biological sample and detecting the presence or absence of KMT2D alteration in the sample; Para. [0006]; the terms "KMT2D" alteration refers to a change in the expression level of KMT2D mRNA or protein; Para. [0032]); (b) determining a composite score based on the gene expression level of the at least one biomarker; and (c) identifying the subject as having FL based on the gene expression level (wherein the presence of said KMT2D alteration indicates a diagnosis of said follicular lymphoma; Para. [0006]); a method of selectively treating a subject having FL (the invention provides a method of determining a treatment outcome for treating a follicular lymphoma...methods for treating follicular lymphoma include a determination of KMT2D alteration and guiding therapy; Para. [0007]), comprising: (a) determining the gene expression level of at least one biomarker in a sample of the subject (obtaining a biological sample and detecting the presence or absence of KMT2D alteration in the sample; Para. [0007]; the terms "KMT2D" alteration refers to a change in the expression level of KMT2D mRNA or protein; Para. [0032]); (c) identifying the subject as having FL based on the gene expression level (wherein the presence of said KMT2D alteration indicates a diagnosis of said follicular lymphoma; Para. [0006]); and (d) administering to the subject identified as having FL a treatment of FL comprising a therapeutically effective amount of an IMiD and/or a cereblon E3 ligase modulating compound (the presence of said KMT2D alteration may not be effectively treated with anti-CD40 therapy; Para. [0007]; the step of detection can be performed prior to treatment by one or more therapies...for example immunotherapy; Para. [0061]); a method of identifying a subject who is likely to be responsive to a treatment of FL or predicting the responsiveness of a subject to a treatment of FL (the invention provides a method of determining a treatment outcome for treating a follicular lymphoma; Para. [0007]), comprising: (a) determining the gene expression level of at least one biomarker in a sample of the subject (obtaining a biological sample and detecting the presence or absence of KMT2D alteration in the sample; Para. [0007]; the terms "KMT2D" alteration refers to a change in the expression level of KMT2D mRNA or protein; Para. [0032]); and (c) identifying or predicting the subject as being likely to be responsive to the treatment of FL based on the gene expression level (the presence of said KMT2D alteration may not be effectively treated with anti-CD40 therapy; Para. [0007]), and optionally (d) administering the treatment of ABC/MEM-like FL to the subject likely to be responsive to the treatment of ABC/MEM-like FL (optional); wherein the treatment of FL comprises a therapeutically effective amount of an IMiD and/or a cereblon E3 ligase modulating compound (the step of detection can be performed prior to treatment by one or more therapies...for example immunotherapy; Para. [0061]).

WO 2022/248573 A2 to Centre Hospitalier Universitaire De Nantes et al. (hereinafter, "Nantes") teaches determining a composite score based on the gene expression level of the at least one biomarker (determining a composite score with the level of at least one biomarker; Para. [0014]); identifying the subject as having a disease based on the composite score (concluding that the subject is afflicted with subclinical kidney rejection when the composite score is substantially higher than the reference composite score; Para. [0014]); identifying or predicting the subject for treatment based on the composite score (concluding that the subject is afflicted with subclinical kidney rejection when the composite score is substantially higher than the reference composite score; Para. [0014]; treating the subject with an immunosuppressive therapy if or when the subject is diagnosed with subclinical rejection; Para. [0014]).

The publication entitled "Cell of origin of transformed follicular lymphoma" by Kridel et al. (hereinafter, "Kridel") teaches an Activated/Memory B-cell like (ABC/MEM-like) follicular lymphoma (FL) (activated B cell subtype) (we demonstrate that transformed follicular lymphoma...has a significant proportion of cases of the activated B-cell-like subtype; abstract); a Germinal Center B-Cell like (GCB-like) follicular lymphoma (FL) (we demonstrate that transformed follicular lymphoma is of the germinal-center B-cell-like subtype in the majority of cases; abstract).

The inventions listed in Groups I+ and II therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/033562

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: **1-5, 16, 18, 19**

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.