TREATMENT OF RELAPSED FOLLICULAR LYMPHOMA

CROSS REFERENCE TO RELATED APPLICATIONS

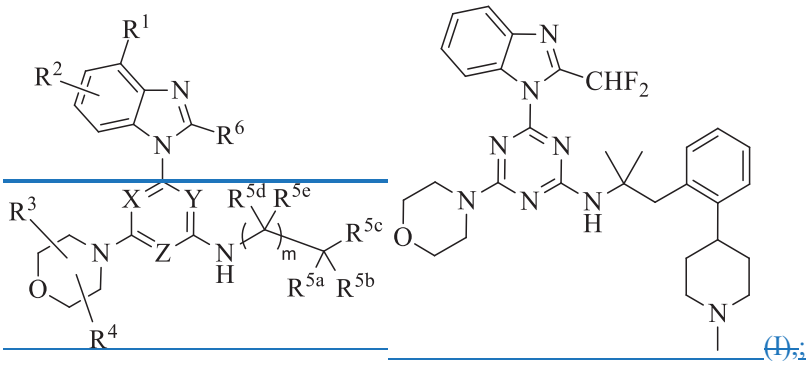
[0001] This application claims the benefit of U.S. Provisional Application No. 62/718,926, filed August 14, 2018 and U.S. Provisional Application No. 62/836,507, filed April 19, 2019; the disclosure of each of the prior applications is considered part of, and is incorporated by reference in, the disclosure of this application.

BACKGROUND OF THE DISCLOSURE

[0002] Follicular lymphoma (FL) is among the most common malignant lymphomas worldwide and remains incurable for most patients.

SUMMARY

[0002a] In one aspect, the present disclosure refers to a use of ~~a e~~Compound ~~of Formula (I)~~A35:



~~(I),~~;

~~or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers,~~ or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; ~~wherein:~~

~~X, Y, and Z are each independently N or CR^X, with the proviso that at least two of X, Y, and Z are nitrogen atoms; where R^X is hydrogen or C_{1-6} alkyl;~~

~~R^1 and R^2 are each independently (a) hydrogen, cyano, halo, or nitro;~~

~~(b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (c) $C(O)R^{1a}$, $C(O)OR^{1a}$, $C(O)NR^{1b}R^{1c}$, $C(NR^{1a})NR^{1b}R^{1c}$, OR^{1a}, $OC(O)R^{1a}$, $OC(O)OR^{1a}$, $OC(O)NR^{1b}R^{1c}$, $OC(=NR^{1a})NR^{1b}R^{1c}$, $OS(O)R^{1a}$, $OS(O)_2R^{1a}$, $OS(O)NR^{1b}R^{1c}$, $OS(O)_2NR^{1b}R^{1c}$, $NR^{1b}R^{1c}$, $NR^{1a}C(O)R^{1d}$, $NR^{1a}C(O)OR^{1d}$, $NR^{1a}C(O)NR^{1b}R^{1c}$, $NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $NR^{1a}S(O)R^{1d}$, $NR^{1a}S(O)_2R^{1d}$, $NR^{1a}S(O)NR^{1b}R^{1c}$, $NR^{1a}S(O)_2NR^{1b}R^{1c}$, SR^{1a}, $S(O)R^{1a}$, $S(O)_2R^{1a}$, $S(O)NR^{1b}R^{1c}$, or $S(O)_2NR^{1b}R^{1c}$; wherein each R^{1a}, R^{1b}, R^{1c}, and R^{1d} is independently (i) hydrogen;~~

~~(ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) R^{1b} and R^{1c} together with the N atom to which they are attached form heterocyclyl;~~

~~R^3 and R^4 are each independently hydrogen or C_{1-6} alkyl; or R^3 and R^4 are linked together to form a bond, C_{1-6} alkylene, C_{1-6} heteroalkylene, C_{2-6} alkenylene, or C_{2-6} heteroalkenylene;~~

R^{5a} is (a) hydrogen or halo; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (c) $C(O)R^{1a}$, $C(O)OR^{1a}$, $C(O)NR^{1b}R^{1c}$, $C(NR^{1a})NR^{1b}R^{1c}$, OR^{1a}, $OC(O)R^{1a}$, $OC(O)OR^{1a}$, $OC(O)NR^{1b}R^{1c}$, $OC(=NR^{1a})NR^{1b}R^{1c}$, $OS(O)R^{1a}$, $OS(O)_2R^{1a}$, $OS(O)NR^{1b}R^{1c}$, $OS(O)_2NR^{1b}R^{1c}$, $NR^{1b}R^{1c}$, $NR^{1a}C(O)R^{1d}$, $NR^{1a}C(O)OR^{1d}$, $NR^{1a}C(O)NR^{1b}R^{1c}$, $NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $NR^{1a}S(O)R^{1d}$, $NR^{1a}S(O)_2R^{1d}$, $NR^{1a}S(O)NR^{1b}R^{1c}$, $NR^{1a}S(O)_2NR^{1b}R^{1c}$, SR^{1a}, $S(O)R^{1a}$, $S(O)_2R^{1a}$, $S(O)NR^{1b}R^{1c}$, or $S(O)_2NR^{1b}R^{1c}$;

R^{5b} is (a) halo; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (c) $C(O)R^{1a}$, $C(O)OR^{1a}$, $C(O)NR^{1b}R^{1c}$, $C(NR^{1a})NR^{1b}R^{1c}$, OR^{1a}, $OC(O)R^{1a}$, $OC(O)OR^{1a}$, $OC(O)NR^{1b}R^{1c}$, $OC(=NR^{1a})NR^{1b}R^{1c}$, $OS(O)R^{1a}$, $OS(O)_2R^{1a}$, $OS(O)NR^{1b}R^{1c}$, $OS(O)_2NR^{1b}R^{1c}$, $NR^{1b}R^{1c}$, $NR^{1a}C(O)R^{1d}$, $NR^{1a}C(O)OR^{1d}$, $NR^{1a}C(O)NR^{1b}R^{1c}$, $NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $NR^{1a}S(O)R^{1d}$, $NR^{1a}S(O)_2R^{1d}$, $NR^{1a}S(O)NR^{1b}R^{1c}$, $NR^{1a}S(O)_2NR^{1b}R^{1c}$, SR^{1a}, $S(O)R^{1a}$, $S(O)_2R^{1a}$, $S(O)NR^{1b}R^{1c}$, or $S(O)_2NR^{1b}R^{1c}$;

R^{5c} is $(CR^{5f}R^{5g})_n$ $(C_{6-14}$ aryl) or $(CR^{5f}R^{5g})_n$ heteroaryl;

R^{5d} and R^{5e} are each independently (a) hydrogen or halo; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (c) $C(O)R^{1a}$, $C(O)OR^{1a}$, $C(O)NR^{1b}R^{1c}$, $C(NR^{1a})NR^{1b}R^{1c}$, OR^{1a}, $OC(O)R^{1a}$, $OC(O)OR^{1a}$, $OC(O)NR^{1b}R^{1c}$, $OC(=NR^{1a})NR^{1b}R^{1c}$, $OS(O)R^{1a}$, $OS(O)_2R^{1a}$, $OS(O)NR^{1b}R^{1c}$, $OS(O)_2NR^{1b}R^{1c}$, $NR^{1b}R^{1c}$, $NR^{1a}C(O)R^{1d}$, $NR^{1a}C(O)OR^{1d}$, $NR^{1a}C(O)NR^{1b}R^{1c}$, $NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $NR^{1a}S(O)R^{1d}$, $NR^{1a}S(O)_2R^{1d}$, $NR^{1a}S(O)NR^{1b}R^{1c}$, $NR^{1a}S(O)_2NR^{1b}R^{1c}$, SR^{1a}, $S(O)R^{1a}$, $S(O)_2R^{1a}$, $S(O)NR^{1b}R^{1c}$, or $S(O)_2NR^{1b}R^{1c}$;

R^{5f} and R^{5g} are each independently (a) hydrogen or halo; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (c) $C(O)R^{1a}$, $C(O)OR^{1a}$, $C(O)NR^{1b}R^{1c}$, $C(NR^{1a})NR^{1b}R^{1c}$, OR^{1a}, $OC(O)R^{1a}$, $OC(O)OR^{1a}$, $OC(O)NR^{1b}R^{1c}$, $OC(=NR^{1a})NR^{1b}R^{1c}$, $OS(O)R^{1a}$, $OS(O)_2R^{1a}$, $OS(O)NR^{1b}R^{1c}$, $OS(O)_2NR^{1b}R^{1c}$, $NR^{1b}R^{1c}$, $NR^{1a}C(O)R^{1d}$, $NR^{1a}C(O)OR^{1d}$, $NR^{1a}C(O)NR^{1b}R^{1c}$, $NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $NR^{1a}S(O)R^{1d}$, $NR^{1a}S(O)_2R^{1d}$, $NR^{1a}S(O)NR^{1b}R^{1c}$, $NR^{1a}S(O)_2NR^{1b}R^{1c}$, SR^{1a}, $S(O)R^{1a}$, $S(O)_2R^{1a}$, $S(O)NR^{1b}R^{1c}$; or $S(O)_2NR^{1b}R^{1c}$; or (d) when one occurrence of R^{5f} and one occurrence of R^{5g} are attached to the same carbon atom, the R^{5f} and R^{5g} together with the carbon atom to which they are attached form a C_{3-10} cycloalkyl or heterocyclyl;

R^6 is hydrogen, C_{1-6} alkyl, S-C_{1-6} alkyl, $S(O)$-C_{1-6} alkyl, or SO_2-C_{1-6} alkyl;

m is 0 or 1; and

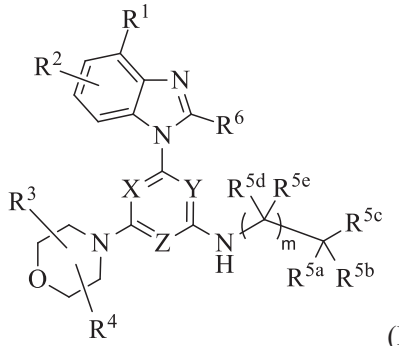
n is 0, 1, 2, 3, or 4;

wherein each alkyl, alkylene, heteroalkylene, alkenyl, alkenylene, heteroalkenylene, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl in R^1, R^2, R^3, R^4, R^6, R^X, R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, and R^{5g} is optionally substituted with one, two, three, or four substituents Q, wherein each substituent Q is independently selected from (a) oxo, cyano, halo, and nitro; (b) C_{1-6}

~~alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl, each of which is further optionally substituted with one, two, three, or four substituents Q^a; and (c) $C(O)R^a$, $C(O)OR^a$, $C(O)NR^bR^e$, $C(NR^a)NR^bR^e$, OR^a, $OC(O)R^a$, $OC(O)OR^a$, $OC(O)NR^bR^e$, $OC(=NR^a)NR^bR^e$, $OS(O)R^a$, $OS(O)_2R^a$, $OS(O)NR^bR^e$, $OS(O)_2NR^bR^e$, NR^bR^e, $NR^aC(O)R^d$, $NR^aC(O)OR^d$, $NR^aC(O)NR^bR^e$, $NR^aC(=NR^d)NR^bR^e$, $NR^aS(O)R^d$, $NR^aS(O)_2R^d$, $NR^aS(O)NR^bR^e$, $NR^aS(O)_2NR^bR^e$, SR^a, $S(O)R^a$, $S(O)_2R^a$, $S(O)NR^bR^e$, and $S(O)_2NR^bR^e$, wherein each R^a, R^b, R^e, and R^d is independently (i) hydrogen; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each of which is further optionally substituted with one, two, three, or four substituents Q^a; or (iii) R^b and R^e together with the N atom to which they are attached form heterocyclyl, which is further optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a; wherein each Q^a is independently selected from the group consisting of (a) oxo, cyano, halo, and nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl; and (c) $C(O)R^e$, $C(O)OR^e$, $C(O)NR^fR^g$, $C(NR^e)NR^fR^g$, OR^e, $OC(O)R^e$, $OC(O)OR^e$, $OC(O)NR^fR^g$, $OC(=NR^e)NR^fR^g$, $OS(O)R^e$, $OS(O)_2R^e$, $OS(O)NR^fR^g$, $OS(O)_2NR^fR^g$, NR^fR^g, $NR^eC(O)R^h$, $NR^eC(O)OR^h$, $NR^eC(O)NR^fR^g$, $NR^eC(=NR^h)NR^fR^g$, $NR^eS(O)R^h$, $NR^eS(O)_2R^h$, $NR^eS(O)NR^fR^g$, $NR^eS(O)_2NR^fR^g$, SR^e, $S(O)R^e$, $S(O)_2R^e$, $S(O)NR^fR^g$, and $S(O)_2NR^fR^g$; wherein each R^e, R^f, R^g, and R^h is independently (i) hydrogen; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) R^f and R^g together with the N atom to which they are attached form heterocyclyl;~~

in the manufacture of a medicament for the treatment of follicular lymphoma (FL), wherein the subject has progression of disease within 24 months of initiating treatment of FL with immunochemotherapy (POD24)~~ or the subject has relapsed/refractory FL~~.

[0003] Some examples provided herein describe a method of treating follicular lymphoma (FL), comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I):



(I),

or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or hydrate; wherein:

X, Y, and Z are each independently N or CR^X, with the proviso that at least two of X, Y, and Z are nitrogen atoms; where R^X is hydrogen or C_{1-6} alkyl;

R^1 and R^2 are each independently (a) hydrogen, cyano, halo, or nitro;

(b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (c) $–C(O)R^{1a}$, $–C(O)OR^{1a}$, $–C(O)NR^{1b}R^{1c}$, $–C(NR^{1a})NR^{1b}R^{1c}$, $–OR^{1a}$, $–OC(O)R^{1a}$, $–OC(O)OR^{1a}$, $–OC(O)NR^{1b}R^{1c}$, $–OC(=NR^{1a})NR^{1b}R^{1c}$, $–OS(O)R^{1a}$, $–OS(O)_2R^{1a}$, $–OS(O)NR^{1b}R^{1c}$, $–OS(O)_2NR^{1b}R^{1c}$, $–NR^{1b}R^{1c}$, $–NR^{1a}C(O)R^{1d}$, $–NR^{1a}C(O)OR^{1d}$, $–NR^{1a}C(O)NR^{1b}R^{1c}$, $–NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $–NR^{1a}S(O)R^{1d}$, $–NR^{1a}S(O)_2R^{1d}$, $–NR^{1a}S(O)NR^{1b}R^{1c}$, $–NR^{1a}S(O)_2NR^{1b}R^{1c}$, $–SR^{1a}$, $–S(O)R^{1a}$, $–S(O)_2R^{1a}$, $–S(O)NR^{1b}R^{1c}$, or $–S(O)_2NR^{1b}R^{1c}$; wherein each R^{1a}, R^{1b}, R^{1c}, and R^{1d} is independently (i) hydrogen;

(ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) R^{1b} and R^{1c} together with the N atom to which they are attached form heterocyclyl;

(i) the first two cycles comprise a continuous daily dosing schedule (CS), comprising administering to subject the compound of Formula (I), or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof once daily for 28 consecutive days in a 28-day cycle; and

(ii) the third and subsequent cycles comprise an intermittent dosing schedule (IS), comprising administering to subject the compound of Formula (I), or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof once daily for 7 consecutive days followed by 21 days without treatment in a 28-day cycle.

[0040] In some examples of the methods provided herein, T-cells are recovered and/or re-populated during the 21 days without treatment.

[0041] In some examples of the methods provided herein, regulatory T-cells (TREG) and/or effector T-cells are recovered and/or re-populated during the 21 days without treatment.

In some examples of the methods provided herein, the incidence of at least one toxicity is reduced.

[0042] In some examples of the methods provided herein, the at least one toxicity is enterocolitis, a cutaneous toxicity, liver toxicity, pulmonary toxicity, infection, or any combination thereof.

[0043] In some examples of the methods provided herein, the IS is continued until progression of disease.

[0044] In some examples of the methods provided herein, the subject has progression of disease within 24 months (POD24) of initiating treatment of FL with first-line immunochemotherapy. In some examples, the first-line immunochemotherapy comprises administering to the subject R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone), G-CHOP (~~Gazyza~~Gazyva, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone), RB (rituximab, bendamustine), R-CVP (rituximab, cyclophosphamide, vincristine sulfate, and prednisone), or similar regimens.

[0045] In some examples of the methods provided herein, an additional therapeutic agent is administered in combination with the compound of Formula (I), or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In some examples of the methods provided herein, the additional therapeutic agent is rituximab. In some examples of the methods provided herein, rituximab is administered at a dose of about 375 mg/m^2. In some examples of the methods provided herein, 8 doses of rituximab are administered to the subject over a period of about 6 months the subject is treated for a period of about 6 months.

[0046] In an example, provided herein is a composition, comprising:

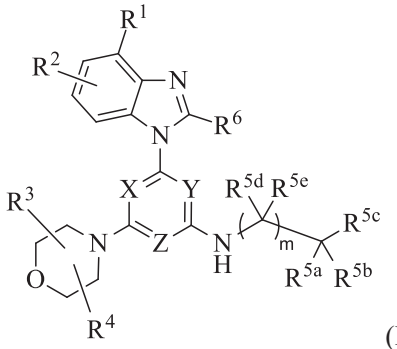
(i) a compound of Formula (I):

wherein each Q^a is independently selected from the group consisting of (a) oxo, cyano, halo, and nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl; and (c) $–C(O)R^e$, $–C(O)OR^e$, $–C(O)NR^fR^g$, $–C(NR^e)NR^fR^g$, $–OR^e$, $–OC(O)R^e$, $–OC(O)OR^e$, $–OC(O)NR^fR^g$, $–OC(=NR^e)NR^fR^g$, $–OS(O)R^e$, $–OS(O)_2R^e$, $–OS(O)NR^fR^g$, $–OS(O)_2NR^fR^g$, $–NR^fR^g$, $–NR^eC(O)R^h$, $–NR^eC(O)OR^h$, $–NR^eC(O)NR^fR^g$, $–NR^eC(=NR^h)NR^fR^g$, $–NR^eS(O)R^h$, $–NR^eS(O)_2R^h$, $–NR^eS(O)NR^fR^g$, $–NR^eS(O)_2NR^fR^g$, $–SR^e$, $–S(O)R^e$, $–S(O)_2R^e$, $–S(O)NR^fR^g$, and $–S(O)_2NR^fR^g$; wherein each R^e, R^f, R^g, and R^h is independently (i) hydrogen; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) R^f and R^g together with the N atom to which they are attached form heterocyclyl; and

(ii) rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone, ~~gazyza~~gazyva, fludarabine, mitoxantrone, mitoxantrone, or dexamethasone.

[0047] In another example, provided herein is a pharmaceutical composition, comprising:

(i) a compound of Formula (I):



(I),

or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or hydrate; wherein:

X, Y, and Z are each independently N or CR^X, with the proviso that at least two of X, Y, and Z are nitrogen atoms; where R^X is hydrogen or C_{1-6} alkyl;

R^1 and R^2 are each independently (a) hydrogen, cyano, halo, or nitro;

(b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (c) $–C(O)R^{1a}$, $–C(O)OR^{1a}$, $–C(O)NR^{1b}R^{1c}$, $–C(NR^{1a})NR^{1b}R^{1c}$, $–OR^{1a}$, $–OC(O)R^{1a}$, $–OC(O)OR^{1a}$, $–OC(O)NR^{1b}R^{1c}$, $–OC(=NR^{1a})NR^{1b}R^{1c}$, $–OS(O)R^{1a}$, $–OS(O)_2R^{1a}$, $–OS(O)NR^{1b}R^{1c}$, $–OS(O)_2NR^{1b}R^{1c}$, $–NR^{1b}R^{1c}$, $–NR^{1a}C(O)R^{1d}$, $–NR^{1a}C(O)OR^{1d}$, $–NR^{1a}C(O)NR^{1b}R^{1c}$, $–NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $–NR^{1a}S(O)R^{1d}$, $–NR^{1a}S(O)_2R^{1d}$, $–NR^{1a}S(O)NR^{1b}R^{1c}$, $–NR^{1a}S(O)_2NR^{1b}R^{1c}$, $–SR^{1a}$, $–S(O)R^{1a}$, $–S(O)_2R^{1a}$, $–S(O)NR^{1b}R^{1c}$, or $–S(O)_2NR^{1b}R^{1c}$; wherein each R^{1a}, R^{1b}, R^{1c}, and R^{1d} is independently (i) hydrogen;

(ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) R^{1b} and R^{1c} together with the N atom to which they are attached form heterocyclyl;

R^{5e}, R^{5f}, and R^{5g} is optionally substituted with one, two, three, or four substituents Q, wherein each substituent Q is independently selected from (a) oxo, cyano, halo, and nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl, each of which is further optionally substituted with one, two, three, or four substituents Q^a; and (c) $–C(O)R^a$, $–C(O)OR^a$,

$–C(O)NR^bR^c$, $–C(NR^a)NR^bR^c$, $–OR^a$, $–OC(O)R^a$, $–OC(O)OR^a$, $–OC(O)NR^bR^c$, $–OC(=NR^a)NR^bR^c$, $–OS(O)R^a$, $–OS(O)_2R^a$, $–OS(O)NR^bR^c$, $–OS(O)_2NR^bR^c$, $–NR^bR^c$, $–NR^aC(O)R^d$, $–NR^aC(O)OR^d$, $–NR^aC(O)NR^bR^c$, $–NR^aC(=NR^d)NR^bR^c$, $–NR^aS(O)R^d$, $–NR^aS(O)_2R^d$, $–NR^aS(O)NR^bR^c$, $–NR^aS(O)_2NR^bR^c$, $–SR^a$, $–S(O)R^a$, $–S(O)_2R^a$, $–S(O)NR^bR^c$, and $–S(O)_2NR^bR^c$, wherein each R^a, R^b, R^c, and R^d is independently (i) hydrogen; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each of which is further optionally substituted with one, two, three, or four substituents Q^a; or (iii) R^b and R^c together with the N atom to which they are attached form heterocyclyl, which is further optionally substituted with one, two, three, or four substituents Q^a;

wherein each Q^a is independently selected from the group consisting of (a) oxo, cyano, halo, and nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl; and (c) $–C(O)R^e$, $–C(O)OR^e$, $–C(O)NR^fR^g$, $–C(NR^e)NR^fR^g$, $–OR^e$, $–OC(O)R^e$, $–OC(O)OR^e$, $–OC(O)NR^fR^g$, $–OC(=NR^e)NR^fR^g$, $–OS(O)R^e$, $–OS(O)_2R^e$, $–OS(O)NR^fR^g$, $–OS(O)_2NR^fR^g$, $–NR^fR^g$, $–NR^eC(O)R^h$, $–NR^eC(O)OR^h$, $–NR^eC(O)NR^fR^g$, $–NR^eC(=NR^h)NR^fR^g$, $–NR^eS(O)R^h$, $–NR^eS(O)_2R^h$, $–NR^eS(O)NR^fR^g$, $–NR^eS(O)_2NR^fR^g$, $–SR^e$, $–S(O)R^e$, $–S(O)_2R^e$, $–S(O)NR^fR^g$, and $–S(O)_2NR^fR^g$; wherein each R^e, R^f, R^g, and R^h is independently (i) hydrogen; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) R^f and R^g together with the N atom to which they are attached form heterocyclyl;

(ii) rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone, ~~gazyza~~gazyva, fludarabine, mitoxantrone, mitoxantrone, or dexamethasone; and

(iii) at least one pharmaceutically acceptable excipient or pharmaceutically acceptable carrier.

INCORPORATION BY REFERENCE

[0048] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0049] **FIGS. 1A-1B**. Schematic representations of dosing schedules: **A** depicts the Continuous Schedule (CS); and **B** depicts the Intermittent Schedule (IS).

[0050] **FIG.2**. Graphical representation showing the best change from baseline of measurable lesions for treatment with Compound A35 alone or in combination with rituximab on a continuous dosing schedule (CS) or intermittent dosing schedule (IS) in follicular lymphoma patients (N = 49).

(~~Gazyza~~Gazyva, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone); or a combination thereof.

[0258] In some embodiments, the immunochemotherapy treatment the patient previously received is i) BR (bendamustine and rituximab); ii) RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone); iii) RCVP (rituximab, cyclophosphamide, vincristine sulfate, prednisone); iv) FCMR (fludarabine, cyclophosphamide, mitoxantrone and rituximab); v) fludarabine and rituximab; vi) RFND (rituximab, fludarabine, mitoxantrone, dexamethasone); or a combination thereof.

[0259] In some embodiments, the immunochemotherapy treatment the patient previously received is i) RB (rituximab and bendamustine) ; ii) RCHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone); iii) RCVP (rituximab, cyclophosphamide, vincristine sulfate, prednisone); iv) FCMR (fludarabine, cyclophosphamide, mitoxantrone and rituximab); v) fludarabine and rituximab; vi) RFND (rituximab, fludarabine, mitoxantrone, dexamethasone); or a combination thereof.

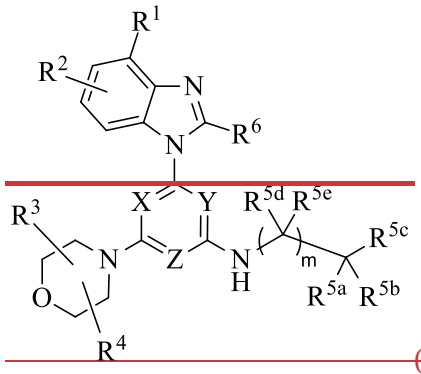
[0260] In some embodiments, the immunochemotherapy treatment the patient previously received is RB (rituximab and bendamustine). In some embodiments, the immunochemotherapy the patient previously received is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). In some embodiments, the immunochemotherapy treatment the patient previously received is RCVP (rituximab, cyclophosphamide, vincristine sulfate, prednisone). In some embodiments, the immunochemotherapy treatment the patient previously received is FCMR (fludarabine, cyclophosphamide, mitoxantrone and rituximab). In some embodiments, the immunochemotherapy treatment the patient previously received is fludarabine and rituximab. In some embodiments, the immunochemotherapy treatment the patient previously received is RFND (rituximab, fludarabine, mitoxantrone, dexamethasone). In some embodiments, the immunochemotherapy treatment the patient previously received is R-MCP (rituximab with mitoxantrone, chlorambucil, and prednisolone). In some embodiments, the immunochemotherapy treatment the patient previously received is R-FM (rituximab with fludarabine and mitoxantrone). In some embodiments, the immunochemotherapy treatment the patient previously received is G-CHOP (~~Gazyza~~gazyva, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone)

[0261] In some embodiments, the first-line immunochemotherapy treatment the patient previously received is RB (rituximab and bendamustine). In some embodiments, the first-line immunochemotherapy treatment the patient previously received is RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). In some embodiments, the first-line immunochemotherapy treatment the patient previously received is RCVP (rituximab, cyclophosphamide, vincristine sulfate, prednisone). In some embodiments, the first-line immunochemotherapy treatment the patient previously received is FCMR (fludarabine, cyclophosphamide, mitoxantrone and rituximab). In some embodiments, the first-line immunochemotherapy treatment the patient previously received is fludarabine and rituximab. In some embodiments, the first-line immunochemotherapy treatment the patient previously received is RFND (rituximab, fludarabine, mitoxantrone, dexamethasone). In some embodiments, the first-line immunochemotherapy treatment the patient previously received is R-MCP (rituximab with mitoxantrone,

CLAIMS

WHAT IS CLAIMED IS:

1. Use of a compound of Formula (I):



(I),

or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or hydrate; wherein:

X, Y, and Z are each independently N or CR^X, with the proviso that at least two of X, Y, and Z are nitrogen atoms; where R^X is hydrogen or C_{1-6} alkyl;

R^1 and R^2 are each independently (a) hydrogen, cyano, halo, or nitro;

(b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (c) $C(O)R^{1a}$, $C(O)OR^{1a}$, $C(O)NR^{1b}R^{1c}$, $C(NR^{1a})NR^{1b}R^{1c}$, OR^{1a}, $OC(O)R^{1a}$, $OC(O)OR^{1a}$, $OC(O)NR^{1b}R^{1c}$, $OC(=NR^{1a})NR^{1b}R^{1c}$, $OS(O)R^{1a}$, $OS(O)_2R^{1a}$, $OS(O)NR^{1b}R^{1c}$, $OS(O)_2NR^{1b}R^{1c}$, $NR^{1b}R^{1c}$, $NR^{1a}C(O)R^{1d}$, $NR^{1a}C(O)OR^{1d}$, $NR^{1a}C(O)NR^{1b}R^{1c}$, $NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $NR^{1a}S(O)R^{1d}$, $NR^{1a}S(O)_2R^{1d}$, $NR^{1a}S(O)NR^{1b}R^{1c}$, $NR^{1a}S(O)_2NR^{1b}R^{1c}$, SR^{1a}, $S(O)R^{1a}$, $S(O)_2R^{1a}$, $S(O)NR^{1b}R^{1c}$, or $S(O)_2NR^{1b}R^{1c}$; wherein each R^{1a}, R^{1b}, R^{1c}, and R^{1d} is independently (i) hydrogen;

(ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) R^{1b} and R^{1c} together with the N atom to which they are attached form heterocyclyl;

R^3 and R^4 are each independently hydrogen or C_{1-6} alkyl; or R^3 and R^4 are linked together to form a bond, C_{1-6} alkylene, C_{1-6} heteroalkylene, C_{2-6} alkenylene, or C_{2-6} heteroalkenylene;

R^{5a} is (a) hydrogen or halo; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (c) $C(O)R^{1a}$, $C(O)OR^{1a}$, $C(O)NR^{1b}R^{1c}$, $C(NR^{1a})NR^{1b}R^{1c}$, OR^{1a}, $OC(O)R^{1a}$, $OC(O)OR^{1a}$, $OC(O)NR^{1b}R^{1c}$, $OC(=NR^{1a})NR^{1b}R^{1c}$, $OS(O)R^{1a}$, $OS(O)_2R^{1a}$, $OS(O)NR^{1b}R^{1c}$, $OS(O)_2NR^{1b}R^{1c}$, $NR^{1b}R^{1c}$, $NR^{1a}C(O)R^{1d}$, $NR^{1a}C(O)OR^{1d}$, $NR^{1a}C(O)NR^{1b}R^{1c}$, $NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $NR^{1a}S(O)R^{1d}$, $NR^{1a}S(O)_2R^{1d}$, $NR^{1a}S(O)NR^{1b}R^{1c}$, $NR^{1a}S(O)_2NR^{1b}R^{1c}$, SR^{1a}, $S(O)R^{1a}$, $S(O)_2R^{1a}$, $S(O)NR^{1b}R^{1c}$, or $S(O)_2NR^{1b}R^{1c}$;

R^{5b} is (a) halo; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (c) $C(O)R^{1a}$, $C(O)OR^{1a}$, $C(O)NR^{1b}R^{1c}$, $C(NR^{1a})NR^{1b}R^{1c}$, OR^{1a}, $OC(O)R^{1a}$, $OC(O)OR^{1a}$, $OC(O)NR^{1b}R^{1c}$, $OC(=NR^{1a})NR^{1b}R^{1c}$, $OS(O)R^{1a}$, $OS(O)_2R^{1a}$, $OS(O)NR^{1b}R^{1c}$, $OS(O)_2NR^{1b}R^{1c}$, $NR^{1b}R^{1c}$,

~~$NR^{1a}C(O)R^{1d}$, $NR^{1a}C(O)OR^{1d}$, $NR^{1a}C(O)NR^{1b}R^{1c}$, $NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $NR^{1a}S(O)R^{1d}$, $NR^{1a}S(O)_2R^{1d}$, $NR^{1a}S(O)NR^{1b}R^{1c}$, $NR^{1a}S(O)_2NR^{1b}R^{1c}$, SR^{1a}, $S(O)R^{1a}$, $S(O)_2R^{1a}$, $S(O)NR^{1b}R^{1c}$, or $S(O)_2NR^{1b}R^{1c}$;~~

~~R^{5c} is $(CR^{5f}R^{5g})_n$-(C_{6-14} aryl) or $(CR^{5f}R^{5g})_n$-heteroaryl;~~

~~R^{5d} and R^{5e} are each independently (a) hydrogen or halo; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (c) $C(O)R^{1a}$, $C(O)OR^{1a}$, $C(O)NR^{1b}R^{1c}$, $C(NR^{1a})NR^{1b}R^{1c}$, OR^{1a}, $OC(O)R^{1a}$, $OC(O)OR^{1a}$, $OC(O)NR^{1b}R^{1c}$, $OC(=NR^{1a})NR^{1b}R^{1c}$, $OS(O)R^{1a}$, $OS(O)_2R^{1a}$, $OS(O)NR^{1b}R^{1c}$, $OS(O)_2NR^{1b}R^{1c}$, $NR^{1b}R^{1c}$, $NR^{1a}C(O)R^{1d}$, $NR^{1a}C(O)OR^{1d}$, $NR^{1a}C(O)NR^{1b}R^{1c}$, $NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $NR^{1a}S(O)R^{1d}$, $NR^{1a}S(O)_2R^{1d}$, $NR^{1a}S(O)NR^{1b}R^{1c}$, $NR^{1a}S(O)_2NR^{1b}R^{1c}$, SR^{1a}, $S(O)R^{1a}$, $S(O)_2R^{1a}$, $S(O)NR^{1b}R^{1c}$, or $S(O)_2NR^{1b}R^{1c}$;~~

~~R^{5f} and R^{5g} are each independently (a) hydrogen or halo; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (c) $C(O)R^{1a}$, $C(O)OR^{1a}$, $C(O)NR^{1b}R^{1c}$, $C(NR^{1a})NR^{1b}R^{1c}$, OR^{1a}, $OC(O)R^{1a}$, $OC(O)OR^{1a}$, $OC(O)NR^{1b}R^{1c}$, $OC(=NR^{1a})NR^{1b}R^{1c}$, $OS(O)R^{1a}$, $OS(O)_2R^{1a}$, $OS(O)NR^{1b}R^{1c}$, $OS(O)_2NR^{1b}R^{1c}$, $NR^{1b}R^{1c}$, $NR^{1a}C(O)R^{1d}$, $NR^{1a}C(O)OR^{1d}$, $NR^{1a}C(O)NR^{1b}R^{1c}$, $NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $NR^{1a}S(O)R^{1d}$, $NR^{1a}S(O)_2R^{1d}$, $NR^{1a}S(O)NR^{1b}R^{1c}$, $NR^{1a}S(O)_2NR^{1b}R^{1c}$, SR^{1a}, $S(O)R^{1a}$, $S(O)_2R^{1a}$, $S(O)NR^{1b}R^{1c}$; or $S(O)_2NR^{1b}R^{1c}$; or (d) when one occurrence of R^{5f} and one occurrence of R^{5g} are attached to the same carbon atom, the R^{5f} and R^{5g} together with the carbon atom to which they are attached form a C_{3-10} cycloalkyl or heterocyclyl;~~

~~R^6 is hydrogen, C_{1-6} alkyl, S-C_{1-6} alkyl, S(O)-C_{1-6} alkyl, or SO_2-C_{1-6} alkyl;~~

~~m is 0 or 1; and~~

~~n is 0, 1, 2, 3, or 4;~~

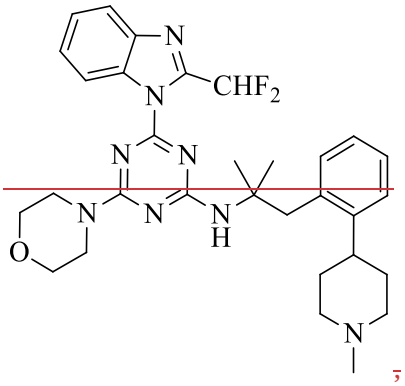
~~wherein each alkyl, alkylene, heteroalkylene, alkenyl, alkenylene, heteroalkenylene, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl in R^1, R^2, R^3, R^4, R^6, R^x, R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, and R^{5g} is optionally substituted with one, two, three, or four substituents Q, wherein each substituent Q is independently selected from (a) oxo, cyano, halo, and nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl, each of which is further optionally substituted with one, two, three, or four substituents Q^a; and (c) $C(O)R^a$, $C(O)OR^a$, $C(O)NR^bR^c$, $C(NR^a)NR^bR^c$, OR^a, $OC(O)R^a$, $OC(O)OR^a$, $OC(O)NR^bR^c$, $OC(=NR^a)NR^bR^c$, $OS(O)R^a$, $OS(O)_2R^a$, $OS(O)NR^bR^c$, $OS(O)_2NR^bR^c$, NR^bR^c, $NR^aC(O)R^d$, $NR^aC(O)OR^d$, $NR^aC(O)NR^bR^c$, $NR^aC(=NR^d)NR^bR^c$, $NR^aS(O)R^d$, $NR^aS(O)_2R^d$, $NR^aS(O)NR^bR^c$, $NR^aS(O)_2NR^bR^c$, SR^a, $S(O)R^a$, $S(O)_2R^a$, $S(O)NR^bR^c$, and $S(O)_2NR^bR^c$, wherein each R^a, R^b, R^c, and R^d is independently (i) hydrogen; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each of which is further optionally substituted with one, two, three, or four substituents Q^a; or (iii) R^b and R^c~~

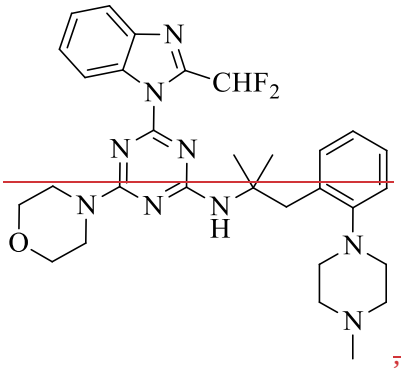
~~together with the N atom to which they are attached form heterocyclyl, which is further optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a;~~

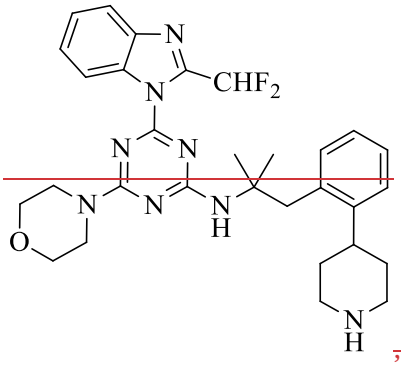
~~wherein each Q^a is independently selected from the group consisting of (a) oxo, cyano, halo, and nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl; and (c) $C(O)R^e$, $C(O)OR^e$, $C(O)NR^fR^g$, $C(NR^e)NR^fR^g$, OR^e, $OC(O)R^e$, $OC(O)OR^e$, $OC(O)NR^fR^g$, $OC(=NR^e)NR^fR^g$, $OS(O)R^e$, $OS(O)_2R^e$, $OS(O)NR^fR^g$, $OS(O)_2NR^fR^g$, NR^fR^g, $NR^eC(O)R^h$, $NR^eC(O)OR^h$, $NR^eC(O)NR^fR^g$, $NR^eC(=NR^h)NR^fR^g$, $NR^eS(O)R^h$, $NR^eS(O)_2R^h$, $NR^eS(O)NR^fR^g$, $NR^eS(O)_2NR^fR^g$, SR^e, $S(O)R^e$, $S(O)_2R^e$, $S(O)NR^fR^g$, and $S(O)_2NR^fR^g$; wherein each R^e, R^f, R^g, and R^h is independently (i) hydrogen; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) R^f and R^g together with the N atom to which they are attached form heterocyclyl;~~

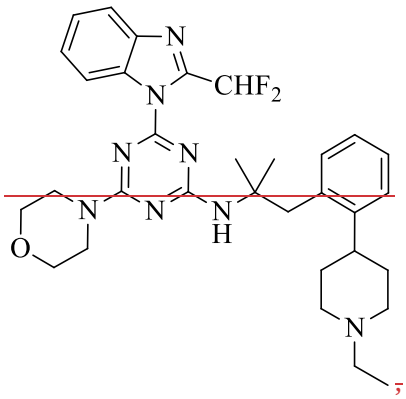
~~in the manufacture of a medicament for the treatment of follicular lymphoma (FL), wherein the subject has progression of disease within 24 months of initiating treatment of FL with immunochemotherapy (POD24) or the subject has relapsed/refractory FL.~~

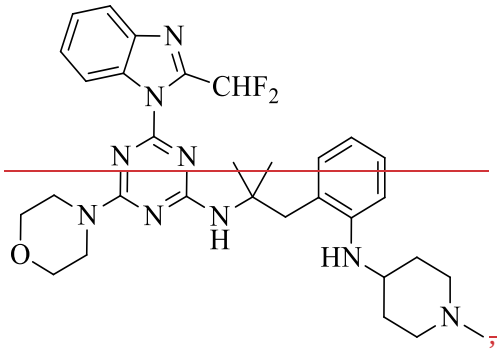
~~2. The use of claim 1, wherein the compound of Formula (I) is:~~



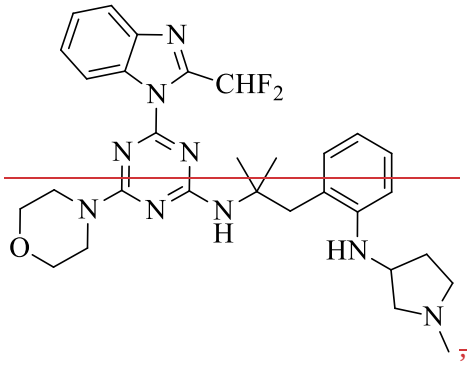




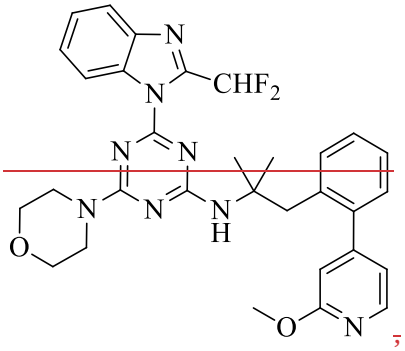




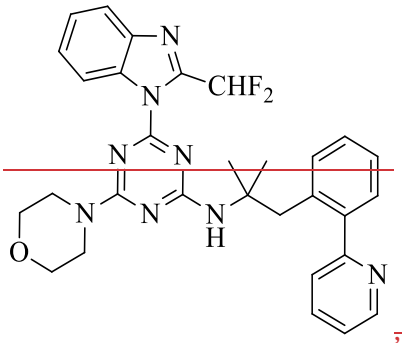
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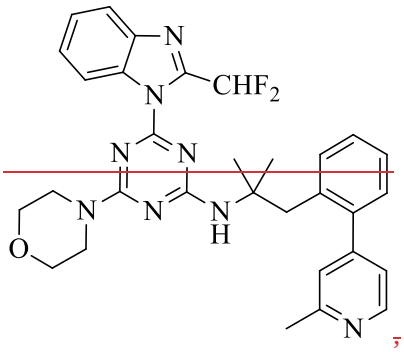
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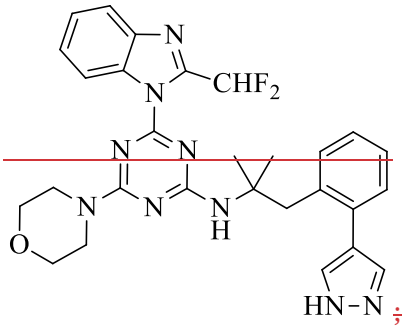


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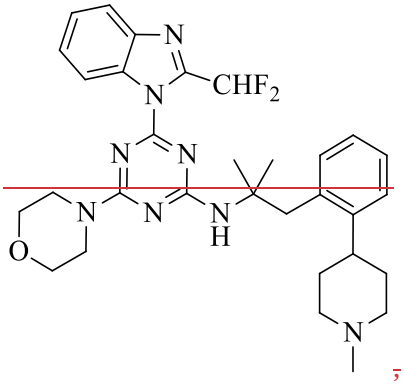
or



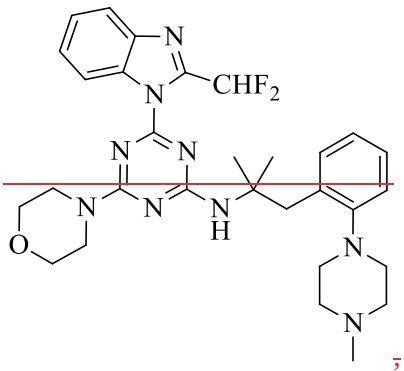
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or an isotopic variant thereof, or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

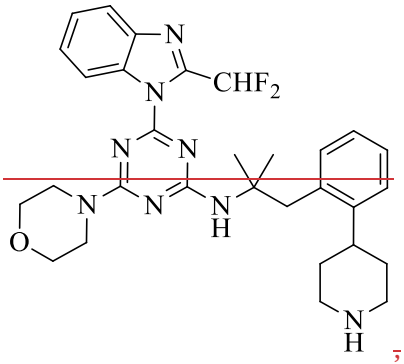
3. The use of claim 1 or 2, wherein the compound of Formula (I) is:



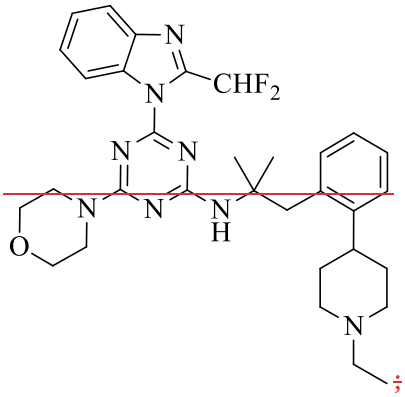
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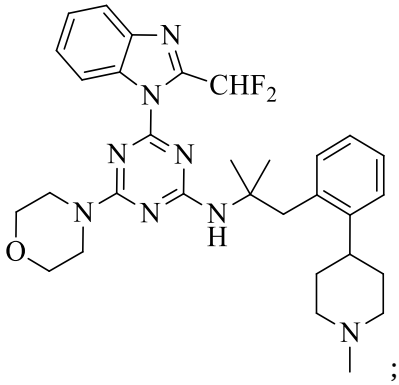
; or



;

or an isotopic variant thereof, or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

41. The use of any one of claims 1-3, wherein the compound of Formula (I) isUse of Compound A35:



;

or an isotopic variant thereof, or a pharmaceutically acceptable salt, solvate, or hydrate thereof; in the manufacture of a medicament for the treatment of follicular lymphoma (FL), wherein the subject has progression of disease within 24 months of initiating treatment of FL with immunochemotherapy (POD24).

52. The use of any one of claims 1-4 claim 1, wherein about 30 mg, about 45 mg, about 60 mg, or about 120 mg, or about 180 mg of Compound A35 a compound of Formula (I), or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof, is to be administered to the subject.

63. The use of any one of claims 1-5 claim 1 or 2, wherein about 60 mg/day of Compound A35 the compound of Formula (I), or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof, is to be administered to the subject.

74. The use of any one of claims 1-61-3, wherein the subject has progression of disease within 24 months of initiating treatment of FL with first-line immunochemotherapy, and the immunochemotherapy comprises that a combination of chemotherapy and immunotherapy agents selected from i) RB (rituximab and bendamustine); ii) RCHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone); iii) RCVP (rituximab, cyclophosphamide, vincristine sulfate, prednisone); iv) FCMR (fludarabine, cyclophosphamide, mitoxantrone and rituximab); v) fludarabine + rituximab; vi) RFND (rituximab, fludarabine, mitoxantrone,

dexamethasone); and vii) GCHOP (~~Gazyza~~obinutuzumab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone) is to be administered to the subject.

5. The use of any one of claims 1-4, wherein the medicament is to be administered once daily for 28 consecutive days in a 28-day cycle.

6. The use of any one of claims 1-5, wherein the medicament is to be administered for one or more 28-day cycles.

~~8~~7. The use of any one of claims ~~1-7~~1-6, wherein the medicament is to be administered for at least three 28-day cycles,

wherein:

(i) the first two cycles comprise a continuous daily dosing schedule (CS), ~~comprising that~~ wherein the medicament comprising Compound A35~~a compound of Formula (I), or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers~~, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof, is to be administered once daily for 28 consecutive days in a 28-day cycle; and

(ii) the third and subsequent cycles comprise an intermittent dosing schedule (IS), ~~comprising that~~ wherein the medicament comprising Compound A35~~a compound of Formula (I), or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers~~, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof, is to be administered to the subject once daily for 7 consecutive days followed by 21 days without treatment in a 28-day cycle.

~~9~~8. The use of claim ~~8~~7, wherein the IS is continued until progression of disease.

~~10~~9. The use of any one of claims 1-~~9~~8, wherein the subject has progression of disease within 24 months (POD24) of initiating treatment of FL with first-line immunochemotherapy, and wherein the immunochemotherapy comprises that RCHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone) is to be administered to the subject.

~~11~~10. The use of any one of claims 1-~~10~~9, further comprising an additional therapeutic agent.

~~12~~11. The use of claim ~~11~~10, wherein the additional therapeutic agent is rituximab.

~~13~~12. The use of claim ~~12~~11, wherein the rituximab is to be administered to the subject at a dose of about 375 mg/m^2.

~~14~~13. The use of claim ~~12~~11 or ~~13~~12, wherein ~~8 doses of~~ the rituximab ~~are~~is to be administered to the subject in 8 doses over a period of about 6 months.

~~15~~14. The use of any one of claims 1-13, wherein the subject is to be treated for a period of about 6 months.