TREATMENT OF RELAPSED FOLLICULAR LYMPHOMA

CROSS REFERENCE TO RELATED APPLICATIONS

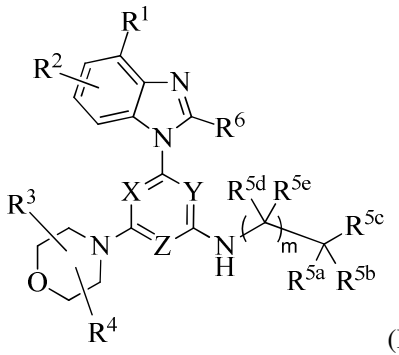
[0001] This application claims the benefit of U.S. Provisional Application No. 62/718,926, filed August 14, 2018 and U.S. Provisional Application No. 62/836,507, filed April 19, 2019; the disclosure of each of the prior applications is considered part of, and is incorporated by reference in, the disclosure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

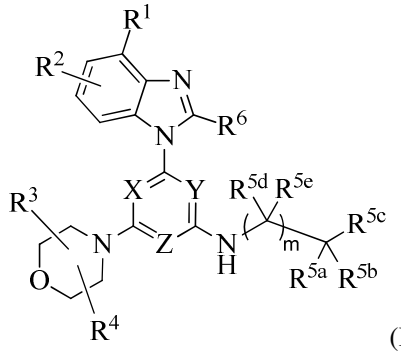
wherein each alkyl, alkylene, heteroalkylene, alkenyl, alkenylene, heteroalkenylene, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl in R^1, R^2, R^3, R^4, R^6, R^X, R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, and R^{5g} is optionally substituted with 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.

[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;

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;

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.

[0004] In some examples of the methods provided herein, 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, or heteroaryl; or (c) $–C(O)R^{1a}$, $–C(O)OR^{1a}$, $–C(O)NR^{1b}R^{1c}$, $–C(NR^{1a})NR^{1b}R^{1c}$, $–OR^{1a}$, $–OC(O)R^{1a}$, $–OC(O)OR^{1a}$, $–OC(O)NR^{1b}R^{1c}$, $–OC(=NR^{1a})NR^{1b}R^{1c}$, $–OS(O)R^{1a}$, $–OS(O)_2R^{1a}$, $–OS(O)NR^{1b}R^{1c}$, $–S(O)_2NR^{1b}R^{1c}$, $–NR^{1b}R^{1c}$, $–NR^{1a}C(O)R^{1d}$, $–NR^{1a}C(O)OR^{1d}$, $–NR^{1a}C(O)NR^{1b}R^{1c}$, $–NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $–NR^{1a}S(O)R^{1d}$, $–NR^{1a}S(O)_2R^{1d}$, $–NR^{1a}S(O)NR^{1b}R^{1c}$, $–NR^{1a}S(O)_2NR^{1b}R^{1c}$, $–SR^{1a}$, $–S(O)R^{1a}$, $–S(O)_2R^{1a}$, $–S(O)NR^{1b}R^{1c}$, or $–S(O)_2NR^{1b}R^{1c}$.

[0005] In some examples of the methods provided herein, R^{5a} and R^{5b} are each independently (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 $–S(O)_2NR^{1b}R^{1c}$.

[0006] In some examples of the methods provided herein, R^{5a} and R^{5b} are each methyl, optionally substituted with one, two, or three halo(s).

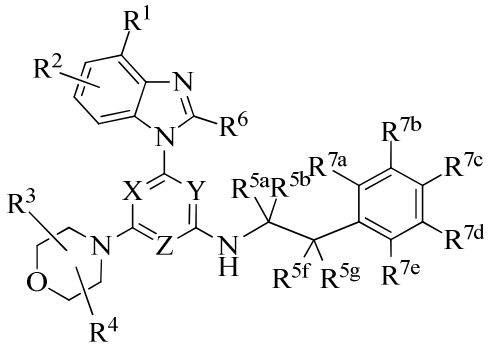
[0007] In some examples of the methods provided herein, n is 1.

[0008] In some examples of the methods provided herein, R^{5f} and R^{5g} are each hydrogen.

[0009] In some examples of the methods provided herein, n is 0.

[0010] In some examples of the methods provided herein, m is 0.

[0011] In some examples of the methods provided herein, the compound of Formula (I) is of Formula (XI):



Formula (XI),

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; wherein:

R^{7a}, R^{7b}, R^{7c}, R^{7d}, and R^{7e} 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, each of which is optionally substituted with one, two, three, or four substituents Q^a; or (c) $–C(O)R^a$, $–C(O)OR^a$, $–C(O)NR^bR^c$, $–C(NR^a)NR^bR^c$, $–OR^a$, $–OC(O)R^a$, $–OC(O)OR^a$, $–OC(O)NR^bR^c$, $–OC(=NR^a)NR^bR^c$, $–OS(O)R^a$, $–OS(O)_2R^a$, $–OS(O)NR^bR^c$, $–OS(O)_2NR^bR^c$, $–NR^bR^c$, $–NR^aC(O)R^d$, $–NR^aC(O)OR^d$, $–NR^aC(O)NR^bR^c$, $–NR^aC(=NR^d)NR^bR^c$, $–NR^aS(O)R^d$, $–NR^aS(O)_2R^d$, $–NR^aS(O)NR^bR^c$, $–NR^aS(O)_2NR^bR^c$, $–SR^a$, $–S(O)R^a$, $–S(O)_2R^a$, $–S(O)NR^bR^c$, or $–S(O)_2NR^bR^c$; or

two of R^{7a}, R^{7b}, R^{7c}, R^{7d}, and R^{7e} that are adjacent to each other form

C_{3-10} cycloalkenyl, C_{6-14} aryl, heteroaryl, or heterocyclyl, each optionally substituted with one, two, three, or four substituents Q^a.

[0012] In some examples of the methods provided herein:

X, Y, and Z are each N;

R^1 and R^2 are each hydrogen;

R^3 and R^4 are each hydrogen;

R^{5a} is C_{1-6} alkyl;

R^{5b} is C_{1-6} alkyl;

R^{5c} is $–(CH_2)–$phenyl, wherein R^{5c} is optionally substituted with one, two, three, or four substituents Q;

R^{5d} and R^{5e} are each hydrogen;

R^6 is CHF_2;

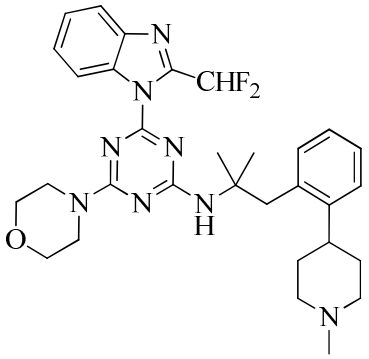
m is 0; and

wherein each alkyl is optionally substituted with one, two, three, or four substituents Q, wherein each substituent Q is independently selected from C_{6-14} aryl, heteroaryl, and heterocyclyl, each of which is further optionally substituted with one, two, three, or four substituents Q^a, wherein the heteroaryl has from 5 to 10 ring atoms and one or more heteroatoms independently selected from O, S, and N, and the heterocyclyl has from 3 to 15 ring atoms and one or more heteroatoms independently selected from O, S, and N;

wherein each Q^a is independently selected from the group consisting of halo, C_{1-6} alkyl, C_{1-6} alkylsulfonyl and $–OR^e$, wherein R^e is hydrogen or C_{1-6} alkyl.

[0013] In some examples of the methods provided herein, R^{5a} and R^{5b} are each methyl, optionally substituted with one or more halos.

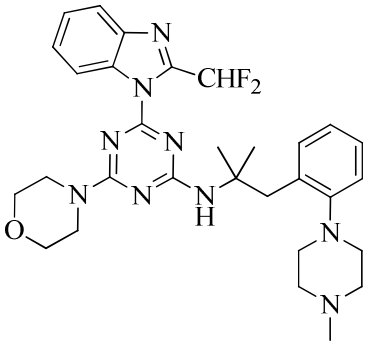
[0014] In some examples of the methods provided herein, the compound of Formula (I) is Compound A35:



Compound A35,

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

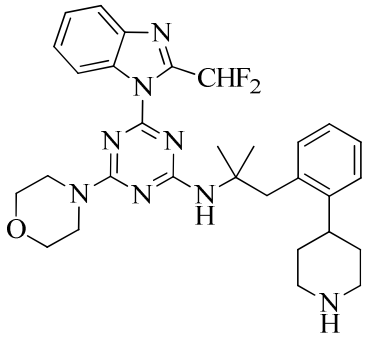
[0015] In some examples of the methods provided herein, the compound of Formula (I) is Compound A36:



Compound A36,

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

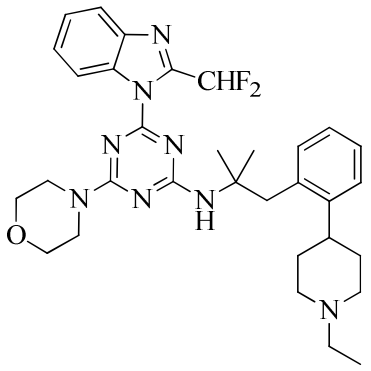
[0016] In some examples of the methods provided herein, the compound of Formula (I) is Compound A68:



Compound A68,

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

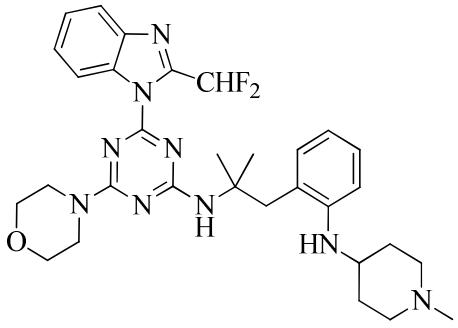
[0017] In some examples of the methods provided herein, the compound of Formula (I) is Compound A70:



Compound A70,

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

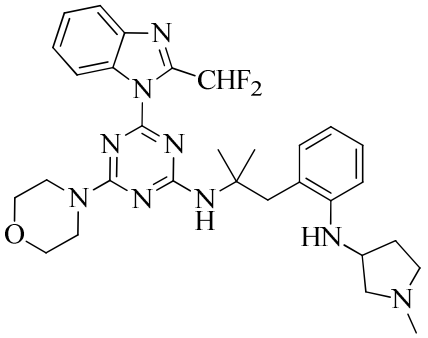
[0018] In some examples of the methods provided herein, the compound of Formula (I) is Compound A37:



Compound A37,

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

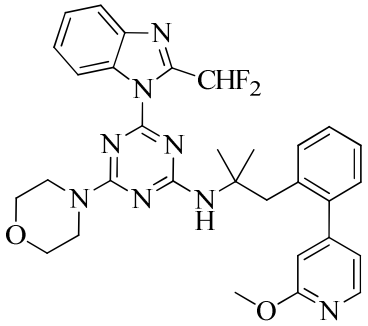
[0019] In some examples of the methods provided herein, the compound of Formula (I) is Compound A38:



Compound A38,

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

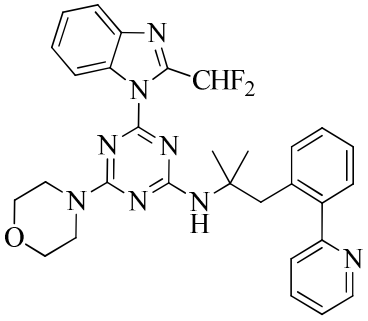
[0020] In some examples of the methods provided herein, the compound of Formula (I) is Compound A41:



Compound A41,

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

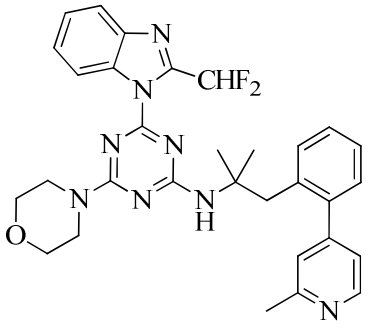
[0021] In some examples of the methods provided herein, the compound of Formula (I) is Compound A42:



Compound A42,

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

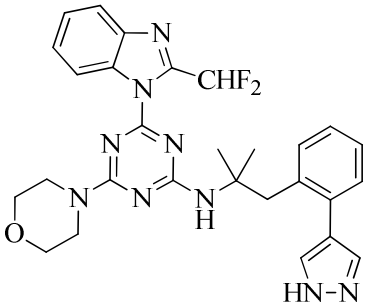
[0022] In some examples of the methods provided herein, the compound of Formula (I) is Compound A43:



Compound A43,

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

[0023] In some examples of the methods provided herein, the compound of Formula (I) is Compound A44:



Compound A44.

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

[0024] In some examples of the methods provided herein, about 30 mg, about 60 mg, about 120 mg, or about 180 mg of 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, hydrate, or prodrug thereof, is administered to the subject.

[0025] In some examples of the methods provided herein, about 60 mg of 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, hydrate, or prodrug thereof, is administered to the subject.

[0026] In some examples of the methods provided herein, 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, is administered to the subject orally.

[0027] In some examples of the methods provided herein, 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, is formulated as a tablet or capsule.

[0028] In some examples of the methods provided herein, 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, is administered to the subject daily.

[0029] In some examples of the methods provided herein, 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, is administered to the subject once per day, twice per day, or three times per day.

[0030] In some examples of the methods provided herein, 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, is administered to the subject once per day.

[0031] In some examples of the methods provided herein, about 60 mg/day of 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, is administered to the subject.

[0032] In some examples of the methods provided herein, the subject has progression of disease within 24 months of initiating treatment of FL with first-line immunochemotherapy.

[0033] In some examples of the methods provided herein, the immunochemotherapy comprises administering to the subject a combination of chemotherapy and immunotherapy agents selected from i) bendamustine and rituximab; 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; and vi) RFND (rituximab, fludarabine, mitoxantrone, dexamethasone).

[0034] In some examples of the methods provided herein, the immunochemotherapy comprises administering to the subject R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone).

[0035] In some examples of the methods provided herein, the immunochemotherapy further comprises administering to the subject a BTK inhibitor

[0036] In some examples of the methods provided herein, the method comprises 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.

[0037] In some examples of the methods provided herein, the CS is continued until at least one incidence of intolerable toxicity occurs/is observed.

[0038] 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.

[0039] In some examples of the methods provided herein, the method comprises at least three 28-day cycles, wherein:

(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, 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:

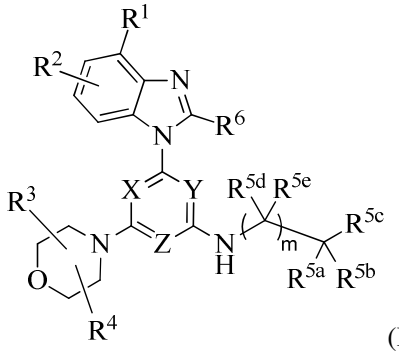
(i) a compound of Formula (I):

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, 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;

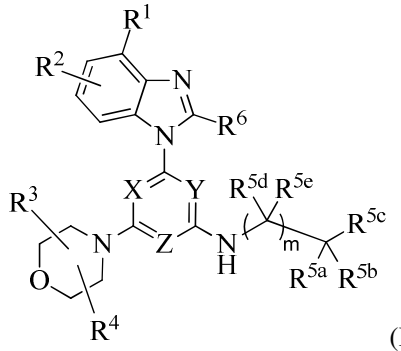
(b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (c) $–C(O)R^{1a}$, $–C(O)OR^{1a}$, $–C(O)NR^{1b}R^{1c}$, $–C(NR^{1a})NR^{1b}R^{1c}$, $–OR^{1a}$, $–OC(O)R^{1a}$, $–OC(O)OR^{1a}$, $–OC(O)NR^{1b}R^{1c}$, $–OC(=NR^{1a})NR^{1b}R^{1c}$,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

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)$_2$R^{1a}, –OS(O)NR^{1b}R^{1c}, –OS(O)$_2$NR^{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)$_2$R^{1d}, –NR^{1a}S(O)NR^{1b}R^{1c}, –NR^{1a}S(O)$_2$NR^{1b}R^{1c}, –SR^{1a}, –S(O)R^{1a}, –S(O)$_2$R^{1a}, –S(O)NR^{1b}R^{1c}, or –S(O)$_2$NR^{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)$_2$R^{1a}, –OS(O)NR^{1b}R^{1c}, –OS(O)$_2$NR^{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)$_2$R^{1d}, –NR^{1a}S(O)NR^{1b}R^{1c}, –NR^{1a}S(O)$_2$NR^{1b}R^{1c}, –SR^{1a}, –S(O)R^{1a}, –S(O)$_2$R^{1a}, –S(O)NR^{1b}R^{1c}, or –S(O)$_2$NR^{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)$_2$R^{1a}, –OS(O)NR^{1b}R^{1c}, –OS(O)$_2$NR^{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)$_2$R^{1d}, –NR^{1a}S(O)NR^{1b}R^{1c}, –NR^{1a}S(O)$_2$NR^{1b}R^{1c}, –SR^{1a}, –S(O)R^{1a}, –S(O)$_2$R^{1a}, –S(O)NR^{1b}R^{1c}; or –S(O)$_2$NR^{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;

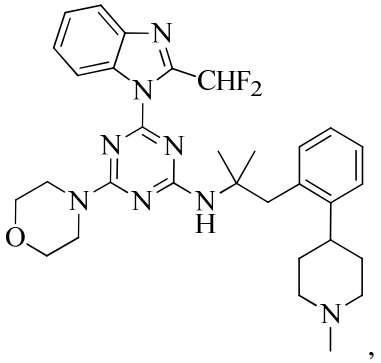
wherein each alkyl, alkylene, heteroalkylene, alkenyl, alkenylene, heteroalkenylene, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl in R^1, R^2, R^3, R^4, R^6, R^X, R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, and R^{5g} is optionally substituted with 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^{b}R^c, –C(NR^a)NR^{b}R^c, –OR^a, –OC(O)R^a, –OC(O)OR^a, –OC(O)NR^{b}R^c, –OC(=NR^a)NR^{b}R^c, –OS(O)R^a, –OS(O)$_2$R^a, –OS(O)NR^{b}R^c, –OS(O)$_2$NR^{b}R^c, –NR^{b}R^c, –NR^{a}C(O)R^d, –NR^{a}C(O)OR^d, –NR^{a}C(O)NR^{b}R^c, –NR^{a}C(=NR^d)NR^{b}R^c, –NR^{a}S(O)R^d, –NR^{a}S(O)$_2$R^d, –NR^{a}S(O)NR^{b}R^c, –NR^{a}S(O)$_2$NR^{b}R^c, –SR^a, –S(O)R^a, –S(O)$_2$R^a, –S(O)NR^{b}R^c, and –S(O)$_2$NR^{b}R^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

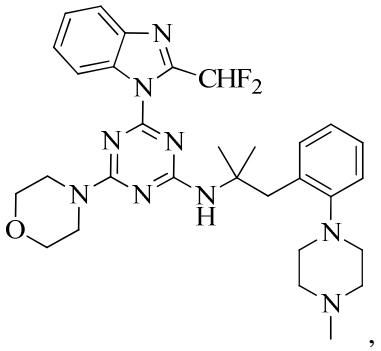
together with the N atom to which they are attached form heterocyclyl, which is further optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a;

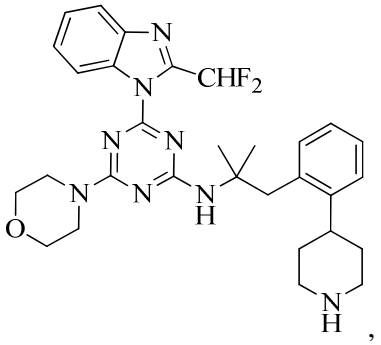
wherein each Q^a is independently selected from the group consisting of (a) oxo, cyano, halo, and nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl; and (c) $–C(O)R^e$, $–C(O)OR^e$, $–C(O)NR^fR^g$, $–C(NR^e)NR^fR^g$,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

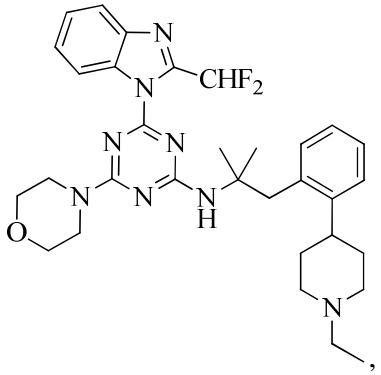
in the manufacture of a medicament for the treatment of follicular lymphoma (FL), wherein the subject has progression of disease within 24 months of initiating treatment of FL with immunochemotherapy (POD24) or the subject has relapsed/refractory FL.

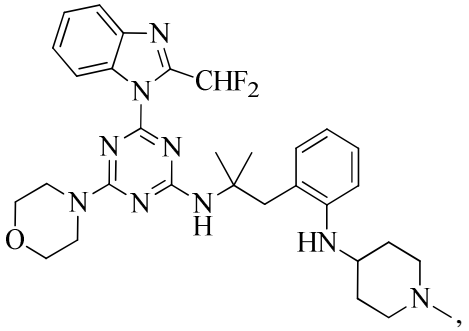
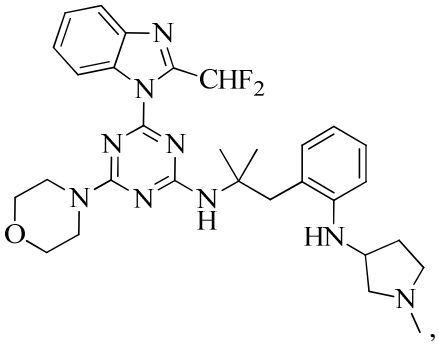
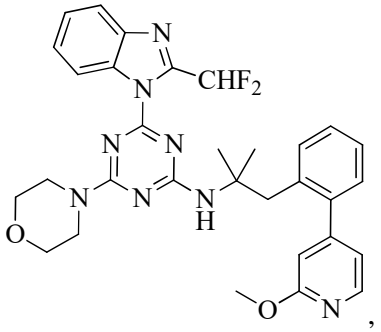
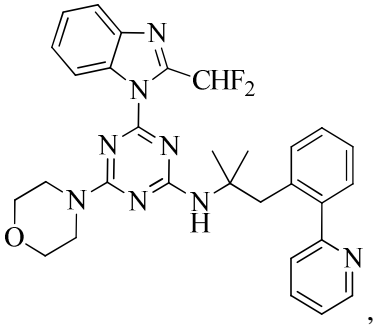
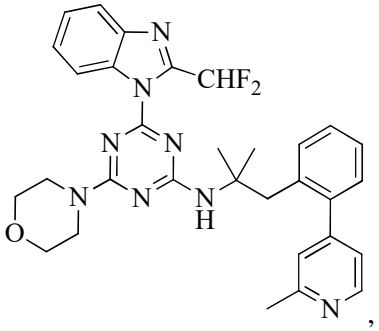
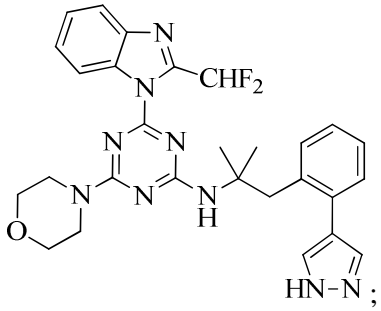
2. The use of claim 1, wherein the compound of Formula (I) is:


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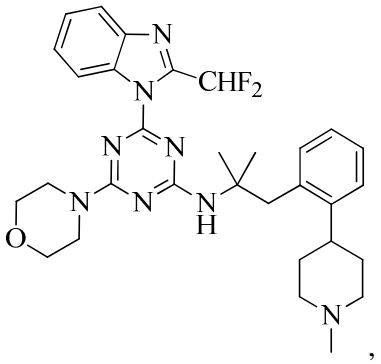
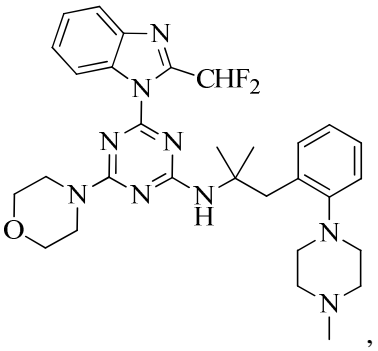

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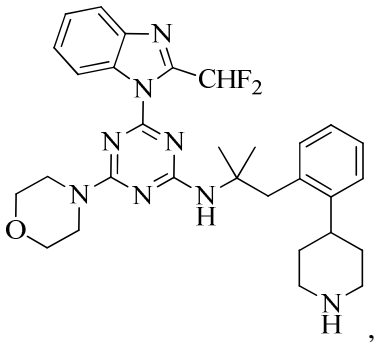
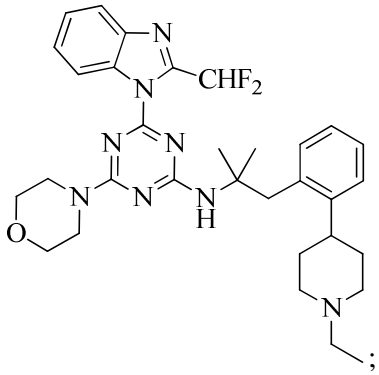

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or

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

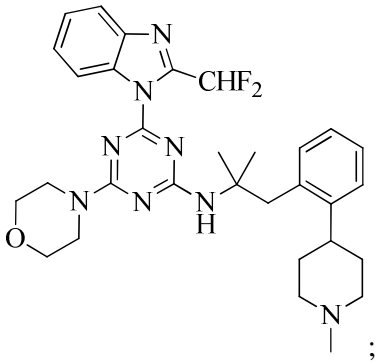
3. The use of claim 1 or 2, wherein the compound of Formula (I) is:


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, or ;

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

4. The use of any one of claims 1-3, wherein the compound of Formula (I) is:

;

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

5. The use of any one of claims 1-4, wherein about 30 mg, about 60 mg, about 120 mg, or about 180 mg of 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.

6. The use of any one of claims 1-5, wherein about 60 mg/day of 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.

7. The use of any one of claims 1-6, 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, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone) is to be administered to the subject.

8. The use of any one of claims 1-7, 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 the medicament comprising 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 the medicament comprising 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. The use of claim 8, wherein the IS is continued until progression of disease.

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

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

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

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

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