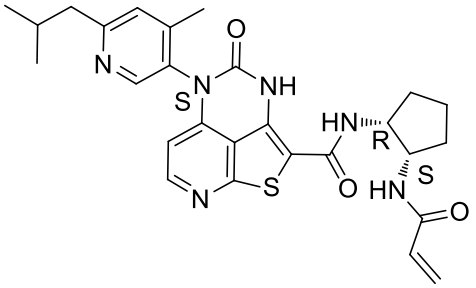
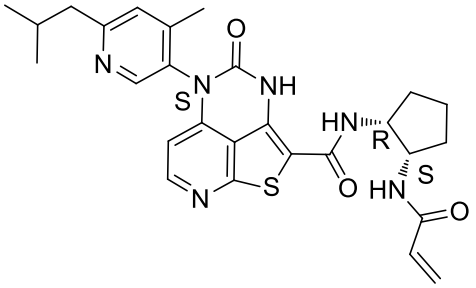
Also described are methods of treating a malignancy in an individual in need thereof, comprising administering a therapeutically effective amount of a compound of Formula (III):



(III)

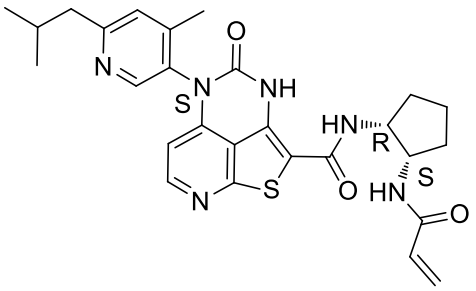
or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof. In one aspect, there is provided use of a compound of Formula (III):



(III)

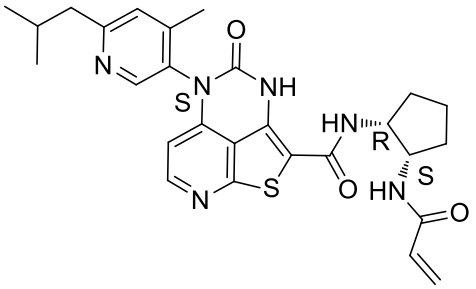
or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof, for the manufacture of a medicament for treating a malignancy. In some examples, the malignancy is selected from the group consisting of a diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and Waldenström macroglobulinemia, Chronic graft versus host disease.

[0007] The present disclosure is also directed to methods of treating chronic graft versus host disease in an individual in need thereof, comprising administering a therapeutically effective amount of a compound of Formula (III):



(III)

or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof. In another aspect, there is provided use of a compound of Formula (III):



(III)

or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof, for the manufacture of a medicament for treating chronic graft versus host disease

[0008] In some examples the therapeutically effective amount of the compound of Formula (III) is from about 140 mg to about 560 mg. In some examples, the therapeutically effective amount of the compound of Formula (III) is administered once a day. In some examples, the therapeutically effective amount of the compound of Formula (III) is administered twice daily. In some examples, the therapeutically effective amount of the compound of Formula (III)is about 140 mg. In some examples, the therapeutically effective amount of the compound of

Formula (III) is about 280 mg. In some examples, the therapeutically effective amount of the compound of Formula (III) is about 560 mg.

[0009] In some examples the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $\boldsymbol{C}_{(\boldsymbol{max},\boldsymbol{day1})}$ of about 59.992 ng/ml to about 2,377.2 ng/ml. In some examples, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $\boldsymbol{C}_{(\boldsymbol{max},\boldsymbol{day1})}$ of about 239.97 ng/ml to about 9,509 ng/ml. In some examples, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $\boldsymbol{C}_{(\boldsymbol{max},ss)}$ of about 66.855 ng/ml to about 2,395.4 ng/ml. In some examples, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $\boldsymbol{C}_{(\boldsymbol{max},ss)}$ of about 267.42 ng/ml to about 9,581.5 ng/ml. In some examples, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a AU$\boldsymbol{C}_{(\text{day 1})}$ of about 312.1 ng.hr/ml to about 11,517 ng.hr/ml. In some examples, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a AU$\boldsymbol{C}_{(\text{day 1})}$ of about 1,248.4 ng.hr/ml to about 46,068 ng.hr/ml. In some examples, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a AU$\boldsymbol{C}_{(ss)}$ of about 312.27 ng.hr/ml to about 13,015 ng.hr/ml. In some examples, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a AU$\boldsymbol{C}_{(ss)}$ of about 1,249.1 ng.hr/ml to about 52,061 ng.hr/ml. In some examples, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 30.9% occupancy to about 99.8% occupancy. In some examples, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 87.1 % occupancy to about 100 % occupancy. In some examples, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of about 59.4% occupancy to about 99.9 % occupancy. In some examples, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of about 90.2 % occupancy to about 100 % occupancy. In some examples, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day1)}$ of about 23.3 % occupancy to about 91.3 % occupancy. In some examples, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day1)}$ of about 63.9 % occupancy to about 97.3 % occupancy. In some examples, the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/ss)}$ of about 50.2 % occupancy to about 95.4 % occupancy. In some examples, the therapeutically effective amount of the compound of Formula

(III) is an amount that results in a $BTKO_{(trough/ss)}$ of about 75.5% occupancy to about 99.3 % occupancy.

[0010] In some examples, the therapeutically effective amount of the compound of Formula (III) is administered once a day. In some examples, the therapeutically effective amount of the compound of Formula (III) is administered twice a day. In some examples, the therapeutically effective amount of the compound of Formula (III) is administered three times a day. In some examples the compound of Formula (III) is administered orally.

[0011] In some examples, the methods described herein further comprise administering 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3- nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin5-yloxy)benzamide). In some examples, the methods described herein further comprise administering cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab.

FIGURES

[0012] Figure 1 depicts a schematic overview of the design for NCT03607513 (MAD=multiple ascending dose; PBO=placebo; SAD=single ascending dose).

[0013] Figure 2 depicts a mechanistic PK/BTKO Model. Aa = Amount of compound of Formula (III) in the depot compartment of the PK model; Ka = absorption rate constant; Q = intercompartmental clearance between compartments 1 and 2; CL = apparent clearance; Syn = synthesis rate constant for free BTK; Kdegf = degradation rate constant of free BTK; Kon = association rate constant; Koff = dissociation rate constant; Kdegi = degradation rate of bound BTK; Kinact = covalent binding rate; BTK = free BTK; BTKb = bound BTK; BTKi = inactivated BTK.

[0014] Figure 3 depicts SAD fasted male cohorts plasma concentrations by time.

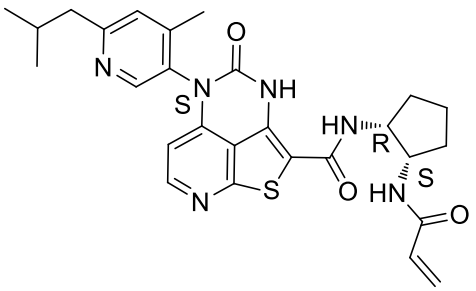
[0015] Figure 4 depicts the arithmetic mean of the compound of formula (III) plasma concentration-time profiles following a single dose of 100 mg of the compound of Formula (III) oral solution in healthy male subjects under fasted or fed conditions (high-fat breakfast) (log-linear) (Phase I Study-SAD part: Pharmacokinetic Analysis Set).

[0016] Figure 5 depicts mean (SD) compound of Formula (III) plasma concentration-time profiles following multiple doses of the compound of Formula (III) oral solution in healthy male and female subjects under fed conditions (standard breakfast).

CLAIMS

What is Claimed:

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



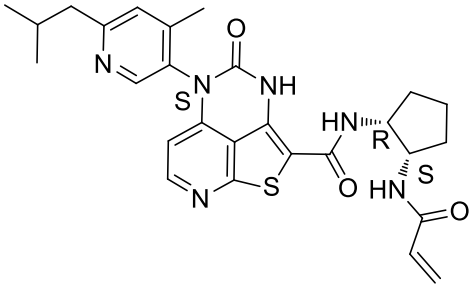
(III)

or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof, for the manufacture of a medicament for treating a malignancy.

2. The use of claim 1, wherein the malignancy is selected from the group consisting of a diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and Waldenström macroglobulinemia, Chronic graft versus host disease.

3. The use of claim 2, further comprising administering 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3- nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin5-yloxy)benzamide).

4. Use of a compound of Formula (III):



(III)

or a pharmaceutically acceptable salt, hydrate, polymorph or solvate thereof, for the manufacture of a medicament for treating chronic graft versus host disease.

5. The use of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is from about 140 mg to about 560 mg.

6. The use of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III)is about 140 mg.

7. The use of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is about 280 mg.

8. The use of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is about 560 mg.

9. The use of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $\boldsymbol{C}_{(\boldsymbol{max},\boldsymbol{day1})}$ of about 59.992 ng/ml to about 2,377.2 ng/ml.

10. The use of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $\boldsymbol{C}_{(\boldsymbol{max},\boldsymbol{day1})}$ of about 239.97 ng/ml to about 9,509 ng/ml.

11. The use of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $\boldsymbol{C}_{(\boldsymbol{max},\mathrm{ss})}$ of about 66.855 ng/ml to about 2,395.4 ng/ml.

12. The use of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $\boldsymbol{C}_{(\boldsymbol{max},\mathrm{ss})}$ of about 267.42 ng/ml to about 9,581.5 ng/ml.

13. The use of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a AU$\boldsymbol{C}_{(\mathrm{day\ 1})}$ of about 312.1 ng.hr/ml to about 11,517 ng.hr/ml.

14. The use of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a AU$\boldsymbol{C}_{(\text{day 1})}$ of about 1,248.4 ng.hr/ml to about 46,068 ng.hr/ml.

15. The use of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a AU$\boldsymbol{C}_{(\text{ss})}$ of about 312.27 ng.hr/ml to about 13,015 ng.hr/ml.

16. The use of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a AU$\boldsymbol{C}_{(\text{ss})}$ of about 1249.1 to about 52061 ng.hr/ml.

17. The use of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 30.9 % occupancy to about 99.8 % occupancy.

18. The use of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/day1)}$ of about 87.1 % occupancy to about 100 % occupancy.

19. The use of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of about 59.4 % occupancy to about 99.9 % occupancy.

20. The use of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(max/ss)}$ of about 90.2 % occupancy to about 100 % occupancy.

21. The use of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day1)}$ of about 23.3 % occupancy to about 91.3 % occupancy.

22. The use of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/day1)}$ of about 63.9 % occupancy to about 97.3 % occupancy.

23. The use of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/ss)}$ of about 50.2 % occupancy to about 95.4 % occupancy.

24. The use of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is an amount that results in a $BTKO_{(trough/ss)}$ of about 75.5 % occupancy to about 99.3 % occupancy.

25. The use of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is administered once a day.

26. The use of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is administered twice a day.

27. The use of any one of claims 1-4, wherein the therapeutically effective amount of the compound of Formula (III) is administered three times a day.

28. The use of any one of claims 1-4, wherein the compound of formula (III) is to be administered orally.

29. The use of any one of claims 1-4, further comprising 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3- nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin5-yloxy)benzamide) to be administered.

30. The use of any one of claims 1-4, further comprising cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab to be administered.