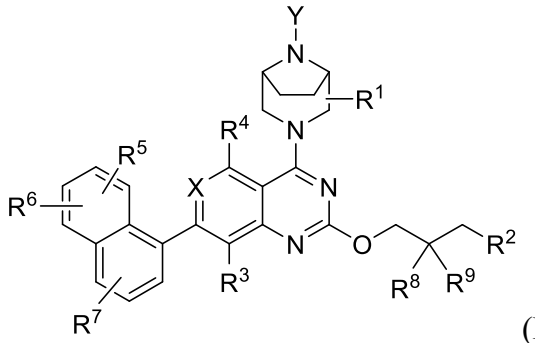
Nature, 2013, 503: 548-51). The G12D mutation moreover provides a unique chemical moiety-binding space due to the encoding of an acidic amino acid residue (D) in place of a small flexible amino acid residue possessing only a hydrogen side chain (G). This alteration of the KRAS protein structure provides a unique space that may be targeted with small molecules drugs that specifically inhibit KRAS(G12D) oncogenic activity. It is therefore desirable to design and develop small molecule drugs that target KRAS(G12D) with sufficient bioavailability to treat diseases such as cancer.

SUMMARY

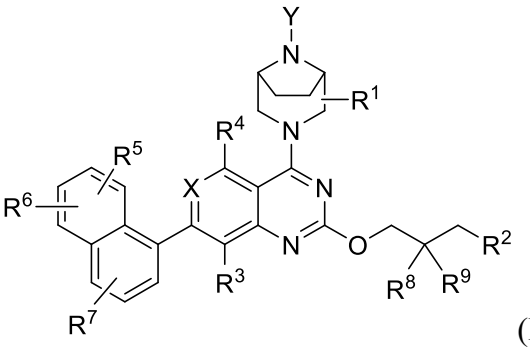
Provided herein are small molecule inhibitors of the KRAS(G12D) mutant oncoprotein. Inhibitors of KRAS(G12D) include those having the structural formula **I**:



(**I**)

and pharmaceutically acceptable salts and compositions comprising such, wherein Y, X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, and R^9 are as defined herein.

In one aspect, the present disclosure relates to a compound of the Formula I:



(**I**);

or a pharmaceutically acceptable salt thereof, wherein

Y is hydrogen or -C(O)OCHR^{a}OC(O)R^b;

X is N;

R^1 is hydrogen, halo, OH, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, (C_1-C_4)hydroxyalkyl, -CHO, -C(O)OR^b, -C(O)ONR^{a}R^b or a 5- to 6-membered heteroaryl optionally substituted with 1 to 3 groups selected from halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, and cyano;

R^2 is a 6- to 10-membered bicyclic heterocyclyl optionally substituted with 1 to 3 groups selected from R^d;

R^3 is selected from hydrogen, halo, (C_1-C_4)alkyl, cyano, and (C_3-C_6)cycloalkyl optionally substituted with 1 to 3 groups selected from halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, and cyano;

R^4 is selected from hydrogen, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, (C_1-C_4)alkoxy, deuterated(C_1-C_4)alkoxy, (C_1-C_4)haloalkoxy, (C_1-C_4)alkynyl, (C_1-C_4)alkenyl, halo, (C_3-C_6)cycloalkyl, -O(C_3-C_6)cycloalkyl, cyano, NH_2, -NH(C_1-C_4)alkyl, -N[(C_1-C_4)alkyl]$_2$, -P(O)[(C_1-C_4)alkyl]$_2$, and -S(C_1-C_4)alkyl, wherein said (C_3-C_6)cycloalkyl and said (C_3-C_6)cycloalkyl of -O(C_3-C_6)cycloalkyl are optionally substituted with 1 to 3 groups selected from halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, and cyano;

R^5 is (C_2-C_4)alkynyl;

R^6 is hydrogen or halo;

R^7 is hydrogen or OH;

R^8 and R^9 are taken together to form cyclopropyl;

R^a and R^b are each independently selected from hydrogen and (C_1-C_4)alkyl; and

R^c and R^d are each independently selected from halo, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, (C_1-C_4)alkoxy, (C_1-C_4)haloalkoxy, cyano, OH, oxo, -C(O)OR^a, -C(O)R^a, -SO_2R^a, -S(O)R^a, -$SO_2NR^aR^b$, -$NR^aC(O)R^b$, -$NR^aSO_2R^b$, -NR^aR^b, and NO_2;

provided that R^2 is not piperazinyl substituted with (C_1-C_4)alkyl, -C(O)OR^a, or -C(O)R^a when R^4 is (C_3)alkyl.

The use of these compounds, salts, and compositions for treating diseases responsive to the inhibition of KRAS(G12D), such as cancer, is also disclosed. In one example, disclosed compounds show improved bioavailability. See e.g., **Table 3**.

In another aspect, the present disclosure relates to a pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

In yet another aspect, the present disclosure relates to use of the compound as described herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable composition as described herein, in the manufacture of a medicament for treating cancer.

In yet another aspect, the present disclosure relates to the compound as described herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable composition as described herein, for use in therapy.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows the tumor growth inhibition data of female NOD SCID mice treated with **Compound 3**.

FIG. 2 shows the body weight percent change of female NOD SCID mice treated with **Compound 3**.

FIG. 3 shows the tumor growth inhibition data of female NOD SCID mice treated with **Compound 34**.

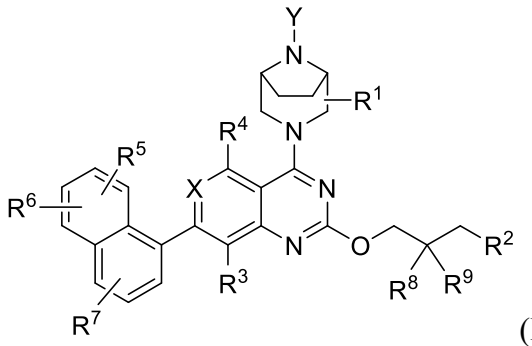
FIG. 4 shows the body weight percent change of female NOD SCID mice treated with **Compound 34**.

DETAILED DESCRIPTION

CLAIMS

Listing of Claims:

1. A compound of the Formula **I**:



(**I**);

or a pharmaceutically acceptable salt thereof, wherein

Y is hydrogen or -C(O)OCHR^{a}OC(O)R^b;

X is N;

R^1 is hydrogen, halo, OH, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, (C_1-C_4)hydroxyalkyl, -CHO, -C(O)OR^b, -C(O)ONR^{a}R^b or a 5- to 6-membered heteroaryl optionally substituted with 1 to 3 groups selected from halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, and cyano;

R^2 is a 6- to 10-membered bicyclic heterocyclyl optionally substituted with 1 to 3 groups selected from R^d;

R^3 is selected from hydrogen, halo, (C_1-C_4)alkyl, cyano, and (C_3-C_6)cycloalkyl optionally substituted with 1 to 3 groups selected from halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, and cyano;

R^4 is selected from hydrogen, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, (C_1-C_4)alkoxy, deuterated(C_1-C_4)alkoxy, (C_1-C_4)haloalkoxy, (C_1-C_4)alkynyl, (C_1-C_4)alkenyl, halo, (C_3-C_6)cycloalkyl, -O(C_3-C_6)cycloalkyl, cyano, NH_2, -NH(C_1-C_4)alkyl, -N[(C_1-C_4)alkyl]$_2$, -P(O)[(C_1-C_4)alkyl]$_2$, and -S(C_1-C_4)alkyl, wherein said (C_3-C_6)cycloalkyl and said (C_3-C_6)cycloalkyl of -O(C_3-C_6)cycloalkyl are optionally substituted with 1 to 3 groups selected from halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, and cyano;

R^5 is (C_2-C_4)alkynyl;

R^6 is hydrogen or halo;

R^7 is hydrogen or OH;

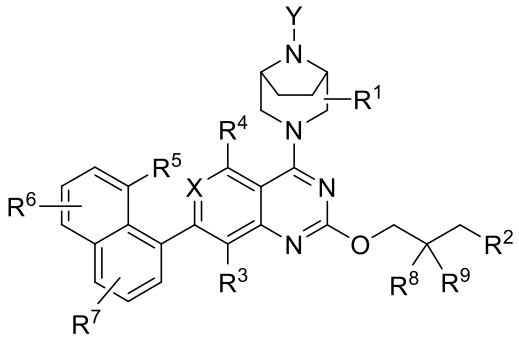
R^8 and R^9 are taken together to form cyclopropyl;

R^a and R^b are each independently selected from hydrogen and (C_1-C_4)alkyl; and

R^c and R^d are each independently selected from halo, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$haloalkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$haloalkoxy, cyano, OH, oxo, $-C(O)OR^a$, $-C(O)R^a$, $-SO_2R^a$, $-S(O)R^a$, $-SO_2NR^aR^b$, $-NR^aC(O)R^b$, $-NR^aSO_2R^b$, $-NR^aR^b$, and NO_2;

provided that R^2 is not piperazinyl substituted with $(C_1$-$C_4)$alkyl, $-C(O)OR^a$, or $-C(O)R^a$ when R^4 is (C_3)alkyl.

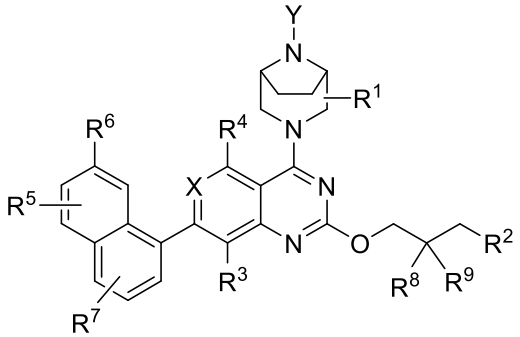
2. The compound of Claim 1, wherein the compound is of the Formula **II**:



(**II**);

or a pharmaceutically acceptable salt thereof.

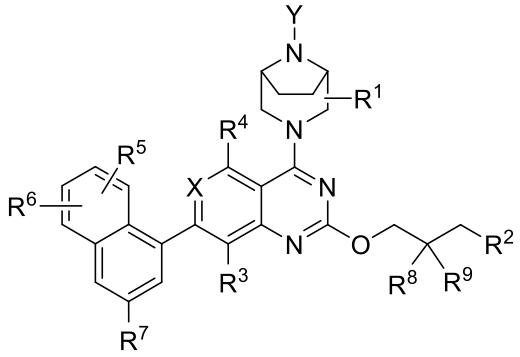
3. The compound of Claim 1, wherein the compound is of the Formula **III**:



(**III**);

or a pharmaceutically acceptable salt thereof.

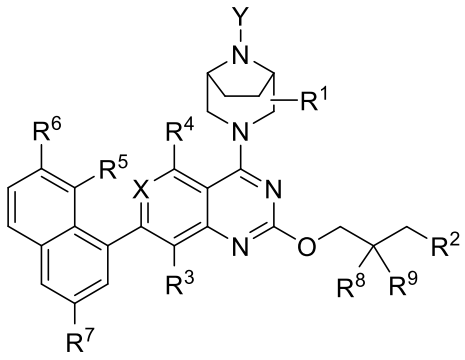
4. The compound of Claim 1, wherein the compound is of the Formula **IV**:



(**IV**);

or a pharmaceutically acceptable salt thereof.

5. The compound of any one of Claims 1 to 4, wherein the compound is of the Formula **V**:



(**V**);

or a pharmaceutically acceptable salt thereof.

6. The compound of any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen.

7. The compound of any one of Claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein R^3 is halo.

8. The compound of any one of Claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein R^3 is fluoro.

9. The compound of any one of Claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein R^5 is (C_2)alkynyl.

10. The compound of any one of Claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^6 is halo.

11. The compound of any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein R^6 is fluoro.

12. The compound of any one of Claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein R^7 is OH.

13. The compound of any one of Claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from hydrogen, $(C_1\text{-}C_4)$alkoxy, deuterated$(C_1\text{-}C_4)$alkoxy, -$N[(C_1\text{-}C_4)\text{alkyl}]_2$, halo, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_4)$haloalkoxy, $(C_1\text{-}C_4)$alkyl, and NH_2.

14. The compound of any one of Claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from hydrogen, methyl, methoxy, isopropoxy, $OCDF_2$, $OCHF_2$, -$N(CH_3)_2$, NH_2, chloro, and cyclopropyl.

15. The compound of any one of Claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein R^2 is a 7- to 10-membered nitrogen containing fused or spiro bicyclic heterocyclyl optionally substituted with 1 to 3 groups selected from R^d.

16. The compound of any one of Claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein R^2 is 3-azabicyclo[3.1.0]hexanyl, 2-azabicyclo[3.1.0]hexanyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, or 1,2,3,6-tetrahydropyridinyl, each of which being optionally substituted with 1 to 3 groups selected from R^d.

17. The compound of any one of Claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein R^c and R^d are each independently selected from halo, cyano, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkoxy, -$S(O)R^a$, and -$SO_2NR^aR^b$.

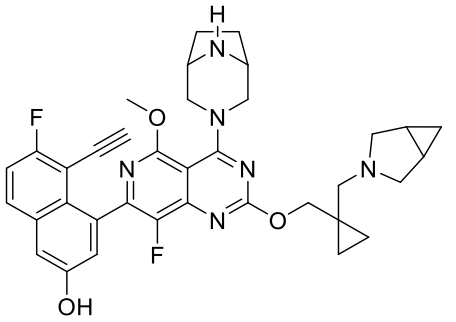
18. The compound of any one of Claims 1 to 17, or a pharmaceutically acceptable salt thereof, wherein R^c and R^d are each independently selected from fluoro, cyano, CF_3, methoxy, isopropyl, OCF_3, -$S(O)CH_3$, and -$SO_2N(CH_3)_2$.

19. The compound of any one of Claims 1 to 18, or a pharmaceutically acceptable salt thereof, wherein R^8 and R^9 are taken together to form cyclopropyl.

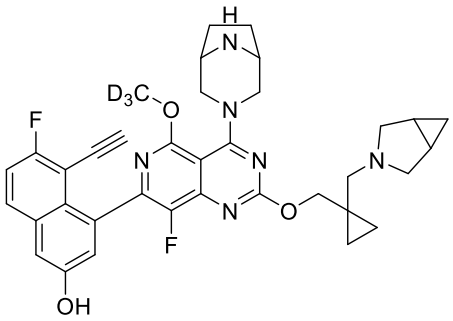
20. The compound of any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, wherein Y is hydrogen or -C(O)OCH(CH_3)OC(O)CH_3.

21. The compound of any one of Claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein Y is hydrogen.

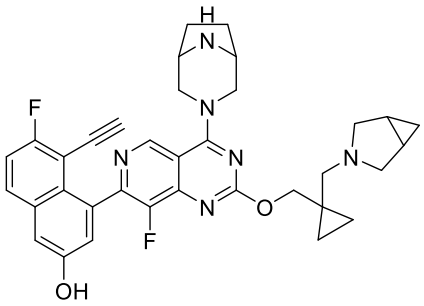
22. The compound of Claim 1, wherein the compound is selected from

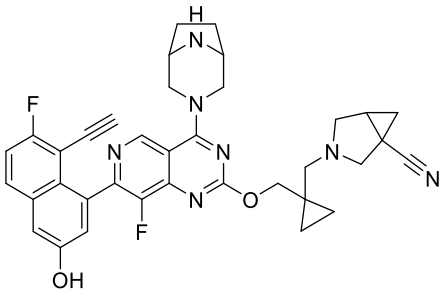


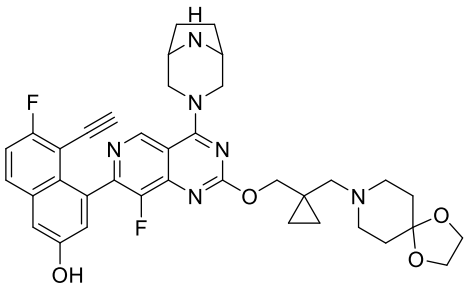
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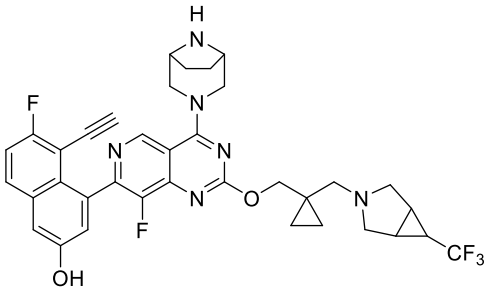


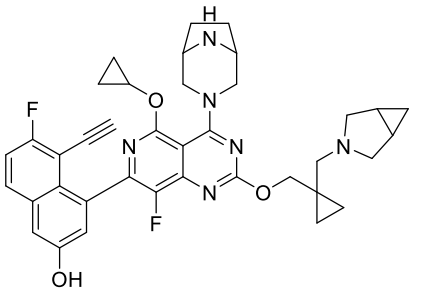
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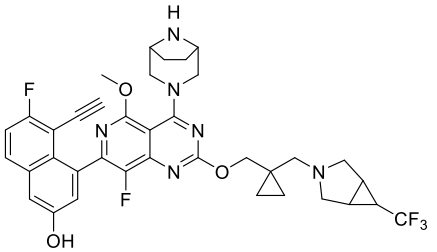

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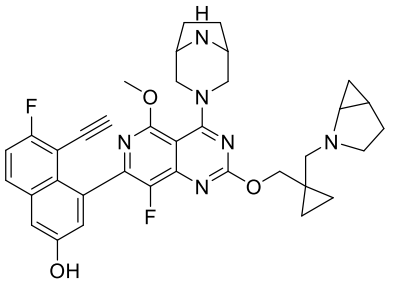

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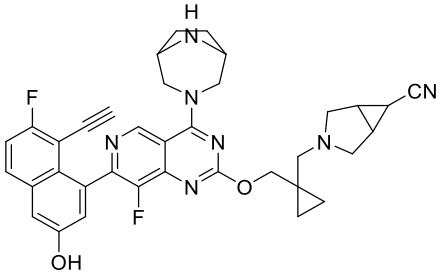

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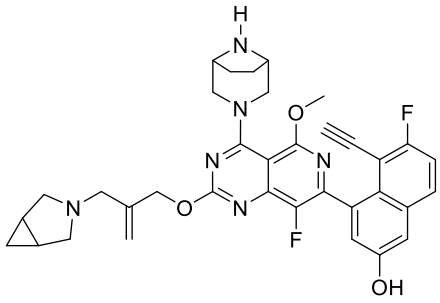

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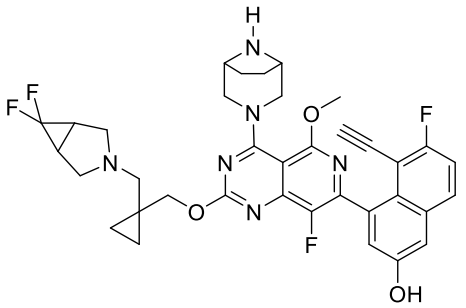

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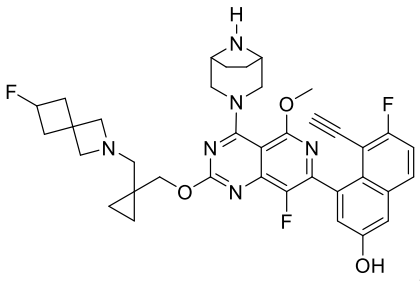

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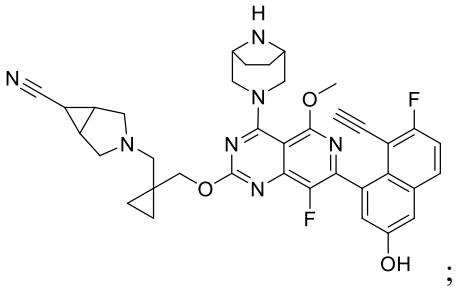

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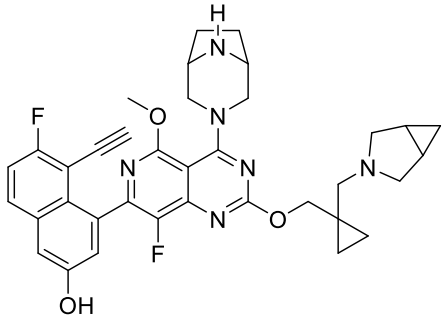

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, and


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or a pharmaceutically acceptable salt of any of the foregoing.

23. The compound of Claim 1, wherein the compound is of the structural formula:


; or a pharmaceutically acceptable salt thereof.

24. A pharmaceutical composition comprising a compound of any one of Claims 1 to 23, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

25. Use of the compound of any one of Claims 1 to 23, or a pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable composition of Claim 24, in the manufacture of a medicament for treating cancer.

26. The compound of any one of Claims 1 to 23, or a pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable composition of Claim 24, for use in therapy.