What is claimed is:

1. Use of a protein arginine N-methyl transferase 5 (PRMT5) inhibitor for the manufacture of a medicament for treating cancer in a subject, wherein:
a therapeutically effective amount of a Kirsten rat sarcoma viral oncogene homolog glycine-to-cysteine ($KRAS^{G12C}$) inhibitor and a therapeutically effective amount of the PRMT5 inhibitor are to be administered to the subject.

2. Use of a Kirsten rat sarcoma viral oncogene homolog glycine-to-cysteine (KRASG12C) inhibitor for the manufacture of a medicament for treating cancer in a subject, wherein:
a therapeutically effective amount of the $KRAS^{G12C}$ inhibitor and a therapeutically effective amount of a protein arginine N-methyl transferase 5 (PRMT5) inhibitor are to be administered to the subject.

3. The use of claim 1 or claim 2, wherein the cancer comprises methylthioadenosine phosphorylase (MTAP) gene homozygous deletion.

4. The use of claim 1, claim 2 or claim 3, wherein the cancer comprises $KRAS^{G12C}$ gene mutation.

5. The use of claim 3 or 4, wherein the cancer further comprises a cyclin-dependent kinase inhibitor 2A (CDKN2A) gene homozygous deletion.

6. The use of any of claims 1 to 5, wherein the cancer is lung cancer, pancreatic cancer, colon cancer, head and neck cancer, esophageal cancer, or melanoma.

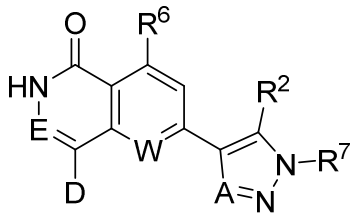
7. The use of any of claims 1 to 6, wherein the $KRAS^{G12C}$ inhibitor is selected from adagrasib, sotorasib, JNJ-74699157, GDC-6036, LY3499446, JDQ443, D-1553, and combinations thereof.

8. The use of any of claims 1 to 6, wherein the $KRAS^{G12C}$ inhibitor is adagrasib or sotorasib.

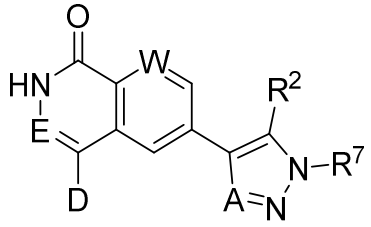
9. The use of any of claims 1 to 8, wherein the PRMT5 inhibitor is a methylthioadenosine (MTA)-cooperative PRMT5 inhibitor.

10. The use of any of claims 1 to 9, wherein

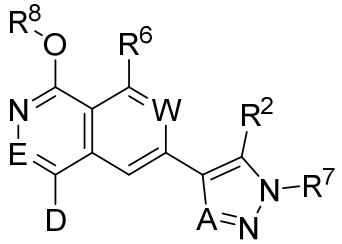
(a) the PRMT5 inhibitor is a compound of Formula IIA, IIB or IIC:



Formula IIA



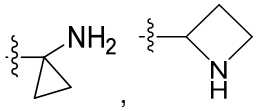
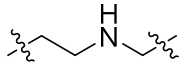
Formula IIB



Formula IIC

or a pharmaceutically acceptable salt thereof, wherein:

A is CR^9 or N;

D is $(C(R^9)_2)_{1\text{-}2}\text{-}NH_2$,  ; or D is  where the methylene is bonded to E where E is C;

E is C, CR^9 or N;

each L is independently a bond or C_1-C_3 alkylene;

W is CR^9 or N;

each X is independently a bond, O, S, $-NR^4-$ or $-NR^4C(O)-$;

each Z is independently a bond, -SO-, $-SO_2-$, -CH(OH)- or -C(O)-;

each R^2 is independently hydroxy, halogen, cyano, cyanomethyl, $-(NR^4)_2$, hydroxyalkyl, alkoxy, $-SO_2C_1$-C_3alkyl, -X-arC_1-C_3alkyl, heteroalkyl, C_2-C_4 alkynyl, -X-haloalkyl, -X-C_1-C_5 alkyl, -Z-C_1-C_5 alkyl, heterocyclyl, -X-L-cycloalkyl, -Z-cycloalkyl, -X-aryl, -Z-aryl, or -X-heteroaryl, wherein the heterocyclyl, the cycloalkyl, the aryl and the heteroaryl are optionally substituted with one or more R^5;

each R^4 is independently hydrogen or C_1-C_3 alkyl;

each R^5 is independently cyano, oxo, halogen, C_1-C_3 alkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxy-C_1-C_3 alkyl, -X-haloalkyl, -Z-cycloalkyl, -X-arC_1-C_3alkyl, -X-arC_1-C_3alkyl substituted with cyano, -X-L-cycloalkyl optionally substituted with C_1-C_3 alkyl or oxo, -X-L-heteroaryl optionally substituted with one or more C_1-C_3 alkyl or oxo, -X-L-heterocyclyl optionally substituted with one or more C_1-C_3 alkyl or oxo, or -X-aryl;

R^6 is hydrogen, halogen, C_1-C_3 alkyl, haloalkyl, hydroxy, alkoxy, C_1-C_3 alkyl-alkoxy, $N(R^9)_2$, $NR^9C(O)R^9$, $C(O)R^9$, oxetane and THF;

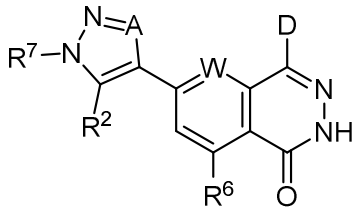
R^7 is H or C_1-C_3 alkyl optionally substituted with one or more halogen;

R^8 is H or C_1-C_3 alkyl; and

each R^9 is independently H or C_1-C_3 alkyl, halogen or haloalkyl;

or

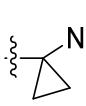
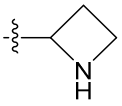
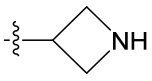
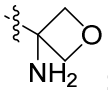
(b) the PRMT5 inhibitor is a compound of Formula IIIA:



(IIIA)

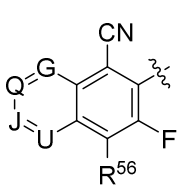
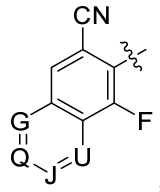
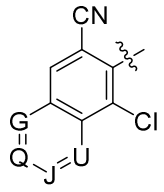
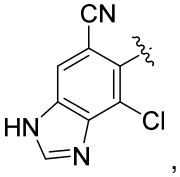
or a pharmaceutically acceptable salt thereof, wherein

A is CR^9 or N;

D is $–CH_2$-NH_2,  ,  ,  ,  , or  ;

W is CR^9 or N, where R^9 is H or C_1-C_3 alkyl;

R^2 is

 ,  ,  , or  ,

where R^{56} is hydrogen, fluoro, chloro, or methyl,

G, Q, J and U are independently selected from C(H), C(R^5), and N, provided only one or two of G, Q, J, and U can be N;

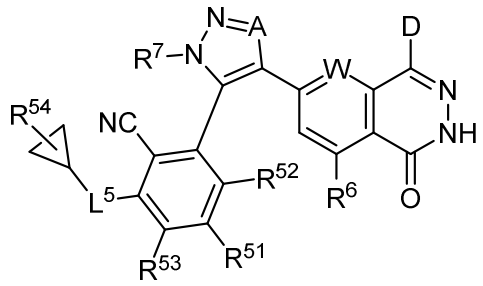
each R^5 is independently hydroxy, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_3-C_6 cycloalkoxy, C_3-C_6 cycloalkyl, C_3-C_6 heterocycloalkyl, or C_1-C_3 alkoxyC_1-C_3 alkyl;

R^6 is hydrogen, halogen, C_1-C_6 alkyl, hydroxy, C_1-C_6 alkoxy, C_1-C_3 alkoxyC_1-C_3 alkyl, C_3-C_6 heterocycloalkyl, -C(O)-C_1-C_3 haloalkyl, or -NR^{15}(CO)R^{16}, where R^{15} is hydrogen or methyl, and R^{16} is C_1-C_3 alkyl; and

R^7 is C_1-C_3 alkyl or C_1-C_3 haloalkyl;

or

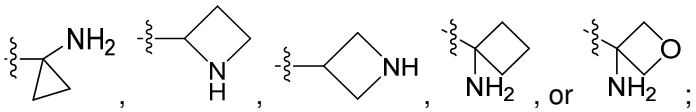
(c) the PRMT5 inhibitor is a compound of Formula IIIB:



(IIIB)

or a pharmaceutically acceptable salt thereof, wherein

A is CR^9 or N;

D is $–CH_2$-NH_2,  ;

W is CR^9 or N, where R^9 is H or C_1-C_3 alkyl;

R^{51} is hydrogen, fluoro, chloro, or methyl, or R^{51} and R^{52} together with atoms to which they are attached form a C_4-C_6 heterocycloalkyl (e.g, hydrofuranyl);

R^{52} is fluoro, chloro, or methyl, or R^{52} and R^{53} together with atoms to which they are attached form a phenyl;

R^{53} is hydrogen, fluoro, chloro, or methyl;

R^{54} is hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 alkoxy;

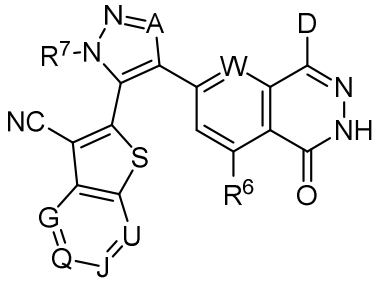
L^5 is –O– or $–CH_2–$;

R^6 is hydrogen, halogen, C_1-C_6 alkyl, hydroxy, C_1-C_6 alkoxy, C_1-C_3 alkoxyC_1-C_3 alkyl, C_3-C_6 heterocycloalkyl, -C(O)-C_1-C_3 haloalkyl, or -NR^{15}(CO)R^{16}, where R^{15} is hydrogen or methyl, and R^{16} is C_1-C_3 alkyl;

R^7 is C_1-C_3 alkyl or C_1-C_3 haloalkyl;

or

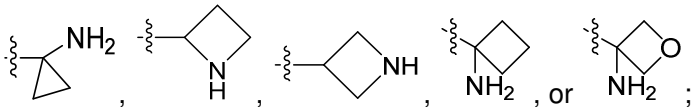
(d) the PRMT5 inhibitor is a compound of Formula IIIC:



(IIIC)

or a pharmaceutically acceptable salt thereof, wherein

A is CR^9 or N;

D is $–CH_2-NH_2$,  ;

W is CR^9 or N, where R^9 is H or C_1-C_3 alkyl;

G, Q, J and U are independently selected from C(H), C(R^5), and N, provided only one or two of G, Q, J, and U can be N;

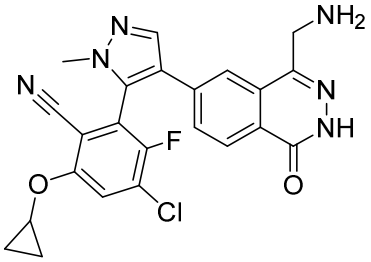
each R^5 is independently hydroxy, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_3-C_6 cycloalkoxy, C_3-C_6 cycloalkyl, C_3-C_6 heterocycloalkyl, or C_1-C_3 alkoxyC_1-C_3 alkyl;

R^6 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, hydroxy, C_1-C_6 alkoxy, C_1-C_3 alkoxyC_1-C_3 alkyl, C_3-C_6 heterocycloalkyl, -C(O)-C_1-C_3 haloalkyl, -N(R^9)$_2$, or -NR^{15}(CO)R^{16},

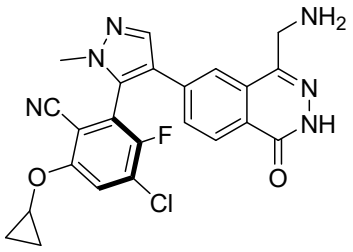
where each R^9 is independently H or C_1-C_3 alkyl, R^{15} is hydrogen or methyl, and R^{16} is C_1-C_3 alkyl; and

R^7 is C_1-C_3 alkyl or C_1-C_3 haloalkyl.

11. The use of claim 10, wherein the PRMT5 inhibitor is:



or a pharmaceutically acceptable salt thereof.

12. The use of claim 10, wherein the PRMT5 inhibitor is: 

(MRTX1719) or a pharmaceutically acceptable salt thereof.

13. The use of any of claims 1 to 6, wherein the PRMT5 inhibitor is MRTX1719 or a pharmaceutically acceptable salt thereof, and the $KRAS^{G12C}$ inhibitor is adagrasib.

14. The use of any of claims 1 to 6, wherein the PRMT5 inhibitor is MRTX1719 or a pharmaceutically acceptable salt thereof, and the $KRAS^{G12C}$ inhibitor is sotorasib.

15. The use of any one of claims 1 to 14, wherein the subject previously received or completed a first-line chemotherapy.