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 cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor and a therapeutically effective amount of the PRMT5 inhibitor are to be administered to the subject.

2. Use of a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor for the manufacture of a medicament for treating cancer in a subject, wherein

a therapeutically effective amount of the CDK4/6 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 and/ or wherein the cancer comprises a cyclin-dependent kinase inhibitor 2A (CDKN2A) gene homozygous deletion.

4. The use of claim 3, wherein the cancer further comprises a Kirsten rat sarcoma viral oncogene homolog glycine-to-cysteine ($KRAS^{G12C}$) gene mutation.

5. The use of any of claims 1 to 4, wherein the cancer is lung cancer, pancreatic cancer, head and neck cancer, bladder cancer, esophageal cancer, lymphoma, stomach cancer, skin cancer, breast cancer, brain cancer, liver cancer, and colon cancer.

6. The use of any of claims 1 to 4, wherein the cancer is lung cancer (e.g., mesothelioma or non-small cell lung cancer (NSCLC) including adenocarcinoma and squamous cell), pancreatic cancer, head and neck cancer, bladder cancer, esophageal cancer, lymphoma (e.g., diffuse large B-cell lymphoma), stomach cancer, melanoma, breast cancer, and brain cancer (e.g., glioblastoma multiforme and glioma).

7. The use of any of claims 1 to 6, wherein the CDK4/6 inhibitor is CDK2/4/6.

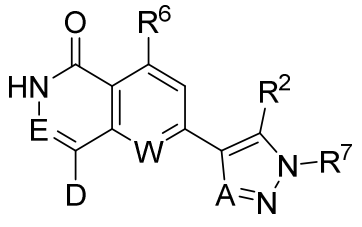
8. The use of any of claims 1 to 6, wherein the CDK4/6 inhibitor is selected from palbociclib, abemaciclib, ribociclib, PF-06873600, and combinations thereof.

9. The use of any of claims 1 to 6, wherein the CDK4/6 inhibitor is palbociclib.

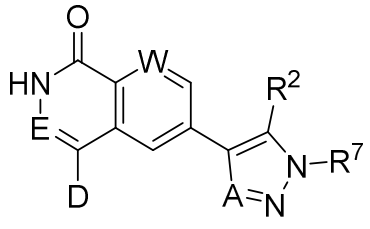
10. The use of any of claims 1 to 9, wherein the PRMT5 inhibitor is a methylthioadenosine (MTA)-cooperative PRMT5 inhibitor.

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

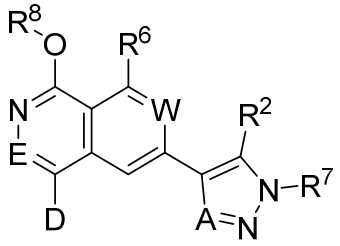
(a) the PRMT5 inhibitor is a compound of Formula IIA, IIB or IIC:



Formula IIA



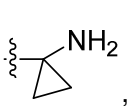
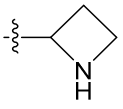
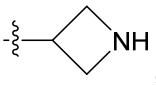
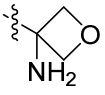
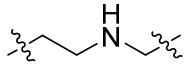
Formula IIB



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 ; 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;

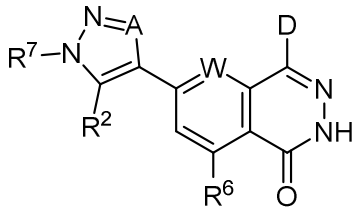
R^6 is hydrogen, halogen, C_1-C_3 alkyl, haloalkyl, hydroxy, alkoxy, C_1-C_3 alkyl-alkoxy, $N(R^9)_2$, $NR^9C(O)R^9$, $C(O)R^9$, oxetane and THF;

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

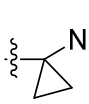
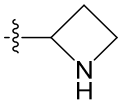
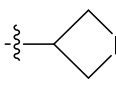
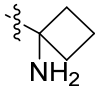
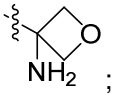
(b) the PRMT5 inhibitor is a compound of Formula IIIA:



(IIIA)

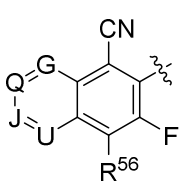
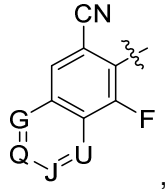
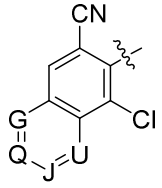
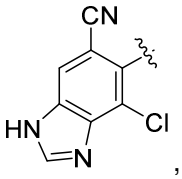
or a pharmaceutically acceptable salt thereof, wherein

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,

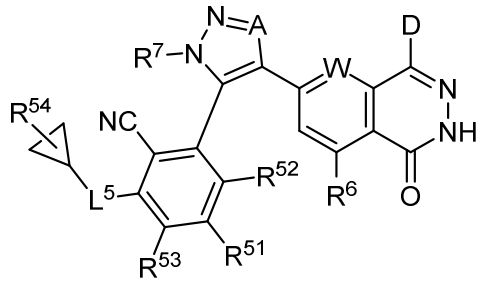
G, Q, J and U are independently selected from C(H), C(R^5), and N, provided only one or two of G, Q, J, and U can be N;

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.

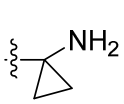
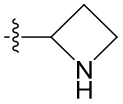
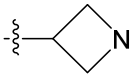
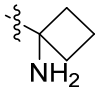
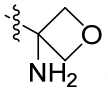
(c) the PRMT5 inhibitor is a compound of Formula IIIB:



(IIIB)

or a pharmaceutically acceptable salt thereof, wherein

A is CR^9 or N;

D is $–CH_2$-NH_2,  ,  ,  ,  , or  ;

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;

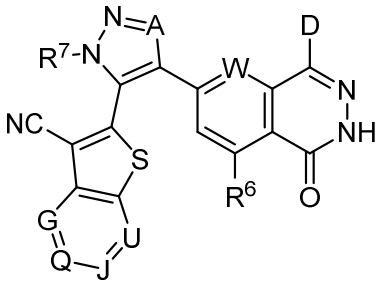
R^{54} is hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 alkoxy;

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

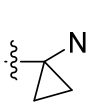
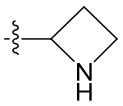
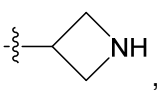
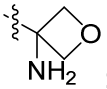
(d) the PRMT5 inhibitor is a compound of Formula IIIC:



(IIIC)

or a pharmaceutically acceptable salt thereof, wherein

A is CR^9 or N;

D is $-CH_2-NH_2$, , , , , or ;

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;

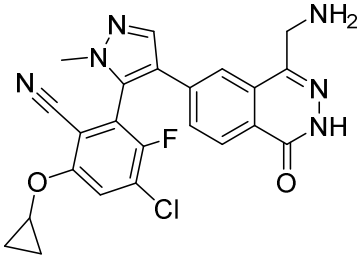
each R^5 is independently hydroxy, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_3-C_6 cycloalkoxy, C_3-C_6 cycloalkyl, C_3-C_6 heterocycloalkyl, or C_1-C_3 alkoxyC_1-C_3 alkyl;

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

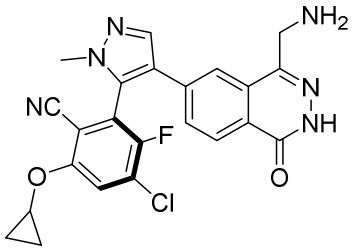
R^7 is C_1-C_3 alkyl or C_1-C_3 haloalkyl.

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



or a pharmaceutically acceptable salt thereof.

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



(MRTX1719) or a pharmaceutically acceptable salt thereof.

14. The use of any of claims 1 to 6, wherein the PRMT5 inhibitor is MRTX1719 or a pharmaceutically acceptable salt thereof, and the CDK4/6 inhibitor is palbociclib.

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