elevated tumour PD-L1 levels. (Morgillo F, Della Corte CM, Fasano M, et al. Mechanisms of resistance to EGFR-targeted drugs: lung cancer. ESMO Open 2016;1: e000060)

[008] There is a significant medical need in the art for a satisfactory treatment of cancer driven by EGFR. In addition to the single-agent targeted therapies strategies outlined above in first line and for overcoming the non-responsiveness exhibited by resistant cancers, combination treatments may also provide promise.

SUMMARY

[009] It has been discovered that the combination of an EGFR inhibitor and a triple inhibitor of FAK, SRC and JAK2 provides a robust response in cancers driven by EGFR.

[010] The disclosure provides a method for treating cancer in a host animal, the method comprising the step of administering to the host animal a therapeutically effective amount of a compound that inhibits FAK, SRC and JAK2, in combination with a therapeutically effective amount of at least one additional anti-cancer agent. In some embodiments, the additional anti-cancer agent is an EGFR inhibitor, or a pharmaceutically acceptable salt thereof.

[011] The disclosure provides a compound that inhibits FAK, SRC and JAK2, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer in a patient, in combination with a therapeutically effective amount of at least one additional anti-cancer agent. In some embodiments, the additional anti-cancer agent is an EGFR inhibitor, or a pharmaceutically acceptable salt thereof.

[011a] In one aspect, there is provided use of a compound that inhibits FAK, SRC and JAK2, or a pharmaceutically acceptable salt thereof, and at least one EGFR inhibitor in the manufacture of a combined preparation for simultaneous, separate or sequential administration in the treatment of cancer.

[012] In another aspect, there is provided use of a compound that inhibits FAK, SRC and JAK2, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament comprising a therapeutically effective amount of the compound, for treating cancer in a patient in combination with a therapeutically effective amount of at least one additional anti-cancer agent. In some embodiments, the additional anti-cancer agent is an EGFR inhibitor, or a pharmaceutically acceptable salt thereof.

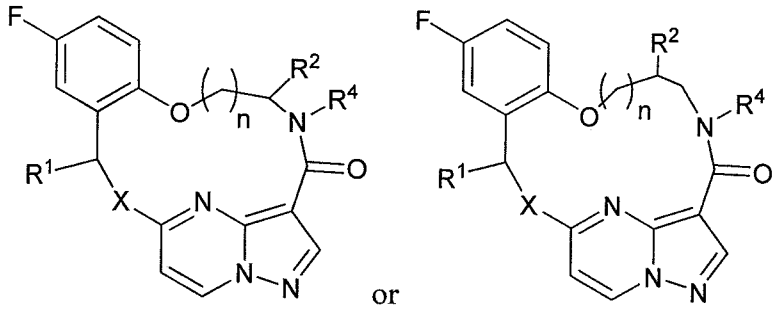
[013] In another aspect, there is provided a composition comprising a compound that inhibits FAK, SRC and JAK2, or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount, for use in the treatment of cancer in a patient, in combination with a therapeutically effective amount of at least one additional anti-cancer agent. In some embodiments, the additional anti-cancer agent is an EGFR inhibitor, or a pharmaceutically acceptable salt thereof.

[014] In another aspect, there is provided a medicament comprising a compound that inhibits FAK, SRC and JAK2, or a pharmaceutically acceptable salt thereof, combined with an EGFR inhibitor, or a pharmaceutically acceptable salt thereof, in fixed or free combination.

[015] In another aspect, there is provided a synergistic composition of a compound that inhibits FAK, SRC and JAK2 and an EGFR inhibitor, where the two components come into contact with each other at a locus.

[016] The disclosure provides a synergistic composition of a compound that inhibits FAK, SRC and JAK2 and an EGFR inhibitor, where the two components come into contact with each other only in the human body.

[017] In some embodiments the compound that inhibits FAK, SRC and JAK2 is of the formula I or II



I or II

[018] wherein

[019] X is NR^3 or CHR^3;

[020] each of R^1 and R^2 is independently H, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, $-OR^5$, $-C(O)OR^5$ or $-C(O)NR^5R^6$; wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl and C_6-C_{10} aryl is independently optionally substituted by deuterium, halogen, -OH, -CN, $-OC_1$-C_6 alkyl, $-NH_2$, $-NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$_2$, $-NHC(O)C_1$-C_6 alkyl, $-N(C_1$-C_6 alkyl)$C(O)C_1$-C_6 alkyl, $-NHC(O)NH_2$, $-NHC(O)NHC_1$-C_6 alkyl, $-N(C_1$-C_6 alkyl)$C(O)NH_2$, $-N(C_1$-C_6 alkyl)$C(O)NHC_1$-C_6 alkyl, $-NHC(O)N(C_1$-C_6 alkyl)$_2$, $-N(C_1$-C_6 alkyl)$C(O)N(C_1$-C_6 alkyl)$_2$, $-NHC(O)OC_1$-C_6 alkyl, $-N(C_1$-C_6 alkyl)$C(O)OC_1$-C_6 alkyl, $-NHS(O)(C_1$-C_6 alkyl), $-NHS(O)_2(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$S(O)(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$S(O)_2(C_1$-C_6 alkyl), $-NHS(O)NH_2$,$-NHS(O)_2NH_2$, $-N(C_1$-C_6 alkyl)$S(O)NH_2$, $-N(C_1$-C_6 alkyl)$S(O)_2NH_2$, $-NHS(O)NH(C_1$-C_6 alkyl), $-NHS(O)_2NH(C_1$-C_6 alkyl), $-NHS(O)N(C_1$-C_6 alkyl)$_2$, $-NHS(O)_2N(C_1$-C_6 alkyl)$_2$, $-N(C_1$-C_6 alkyl)$S(O)NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$S(O)_2NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$S(O)N(C_1$-C_6 alkyl)$_2$, $-N(C_1$-C_6 alkyl)$S(O)_2N(C_1$-C_6 alkyl)$_2$, $-CO_2H$, $-C(O)OC_1$-C_6 alkyl, $-C(O)NH_2$, $-C(O)NH(C_1$-C_6 alkyl), $-C(O)N(C_1$-C_6 alkyl)$_2$, $-SC_1$-C_6 alkyl, $-S(O)C_1$-C_6 alkyl, $-S(O)_2C_1$-C_6 alkyl, $-S(O)NH(C_1$-C_6 alkyl), $-S(O)_2NH(C_1$-C_6 alkyl),

[037] X is NR^3 or CHR^3;

[038] each of R^1 and R^2 is independently H, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, $-OR^5$, $-C(O)OR^5$ or $-C(O)NR^5R^6$; wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl and C_6-C_{10} aryl is independently optionally substituted by deuterium, halogen, -OH, -CN, $-OC_1$-C_6 alkyl, $-NH_2$, $-NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$_2$, $-NHC(O)C_1$-C_6 alkyl, $-N(C_1$-C_6 alkyl)$C(O)C_1$-C_6 alkyl, $-NHC(O)NH_2$, $-NHC(O)NHC_1$-C_6 alkyl, $-N(C_1$-C_6 alkyl)$C(O)NH_2$, $-N(C_1$-C_6 alkyl)$C(O)NHC_1$-C_6 alkyl, $-NHC(O)N(C_1$-C_6 alkyl)$_2$, $-N(C_1$-C_6 alkyl)$C(O)N(C_1$-C_6 alkyl)$_2$, $-NHC(O)OC_1$-C_6 alkyl, $-N(C_1$-C_6 alkyl)$C(O)OC_1$-C_6 alkyl, $-NHS(O)(C_1$-C_6 alkyl), $-NHS(O)_2(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$S(O)(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$S(O)_2(C_1$-C_6 alkyl), $-NHS(O)NH_2$,$-NHS(O)_2NH_2$, $-N(C_1$-C_6 alkyl)$S(O)NH_2$, $-N(C_1$-C_6 alkyl)$S(O)_2NH_2$, $-NHS(O)NH(C_1$-C_6 alkyl), $-NHS(O)_2NH(C_1$-C_6 alkyl), $-NHS(O)N(C_1$-C_6 alkyl)$_2$, $-NHS(O)_2N(C_1$-C_6 alkyl)$_2$, $-N(C_1$-C_6 alkyl)$S(O)NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$S(O)_2NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$S(O)N(C_1$-C_6 alkyl)$_2$, $-N(C_1$-C_6 alkyl)$S(O)_2N(C_1$-C_6 alkyl)$_2$, $-CO_2H$, $-C(O)OC_1$-C_6 alkyl, $-C(O)NH_2$, $-C(O)NH(C_1$-C_6 alkyl), $-C(O)N(C_1$-C_6 alkyl)$_2$, $-SC_1$-C_6 alkyl, $-S(O)C_1$-C_6 alkyl, $-S(O)_2C_1$-C_6 alkyl, $-S(O)NH(C_1$-C_6 alkyl), $-S(O)_2NH(C_1$-C_6 alkyl), $-S(O)N(C_1$-C_6 alkyl)$_2$,$-S(O)_2N(C_1$-C_6 alkyl)$_2$, $-P(C_1$-C_6 alkyl)$_2$, $-P(O)(C_1$-C_6 alkyl)$_2$, $-C_3$-C_6 cycloalkyl, or 3-to 7-membered heterocycloalkyl;

[039] R^3 is independently H, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3-to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or mono- or bicyclic heteroaryl; wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3-to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or mono- or bicyclic heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl or $-OR^5$;

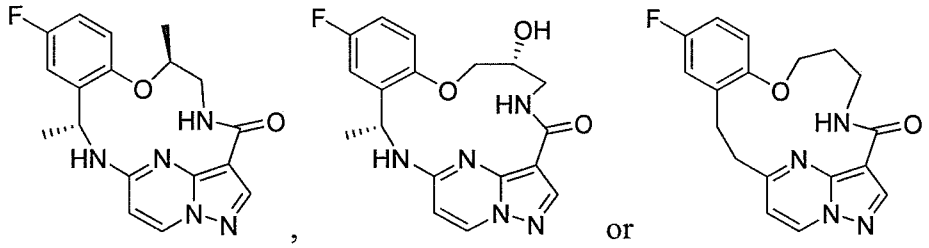
[040] R^4 is H, C_1-C_6 alkyl or 3-to 7-membered heterocycloalkyl, wherein each hydrogen atom in C_1-C_6 alkyl or 3-to 7-membered heterocycloalkyl is independently optionally substituted by halogen, -OH, -CN, $-OC_1$-C_6 alkyl, $-NH_2$, $-NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$_2$, $-CO_2H$, $-C(O)OC_1$-C_6 alkyl, $-C(O)NH_2$, $-C(O)NH(C_1$-C_6 alkyl), $-C(O)N(C_1$-C_6 alkyl)$_2$, C_3-C_6 cycloalkyl, or monocyclic 5- to 7-membered heterocycloalkyl;

[041] each R^5 and R^6 is independently H, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or heteroaryl; and

[042] n is 0 or 1;

[043] or a pharmaceutically acceptable salt thereof.

[044] In some embodiments, the compound that inhibits FAK, SRC and JAK2 is of the formula



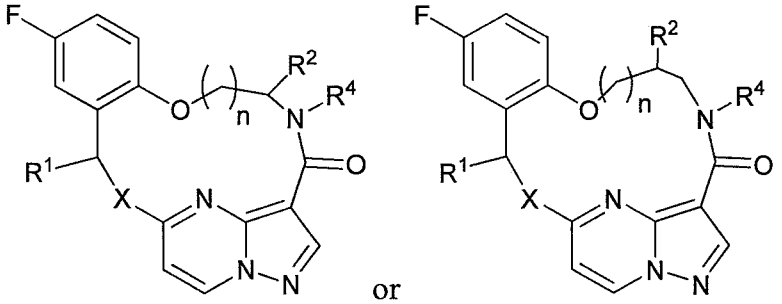
[045] or a pharmaceutically acceptable salt thereof.

[046] In some embodiments, the EGFR inhibitor is an antibody or a small molecule inhibitor. In some embodiments, the EGFR inhibitor is an antibody. In some embodiments, the antibody is cetuximab, necitumumab or panitumumab. In some embodiments, the EGFR inhibitor is a small molecule inhibitor. In some embodiments, the small molecule inhibitor is afatinib, brigatinib, cetuximab, canertinib (CI-1033), dacomitinib, eroltinib, gefitinib, HKI 357, icotinib, lapatinib, osimertinib, naquotinib, nazartinib, necitumumab, neratinib, olmutinib, panitumumab, pelitinib, PF-06747775, rociletinib, vandetanib, WZ 3146, WZ 4002, WZ 8040, or pharmaceutically acceptable salts thereof.

[047] Additional embodiments, features, and advantages of the disclosure will be apparent from the following detailed description and through practice of the disclosure. The compounds of the present disclosure can be described as embodiments in any of the following enumerated clauses. It will be understood that any of the embodiments described herein can be used in connection with any other embodiments described herein to the extent that the embodiments do not contradict one another.

[048] 1. A method for treating cancer in a host animal, the method comprising the step of administering to the host animal a therapeutically effective amount of a compound that inhibits FAK, SRC and JAK2, in combination with a therapeutically effective amount of at least one additional anti-cancer agent.

[049] 2. The method of clause 1, wherein the compound that inhibits FAK, SRC and JAK2 is of the formula I or II



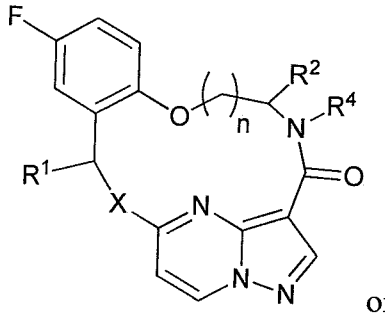
I II

[050] wherein

WHAT IS CLAIMED IS:

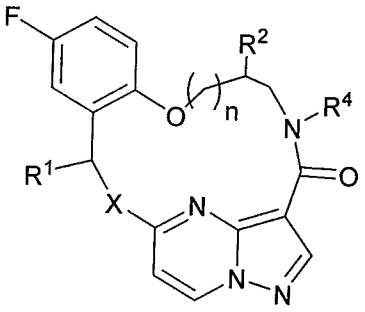
1. Use of a compound that inhibits FAK, SRC and JAK2, or a pharmaceutically acceptable salt thereof, and at least one EGFR inhibitor in the manufacture of a combined preparation for simultaneous, separate or sequential administration in the treatment of cancer.

2. The use of claim 1, wherein the compound that inhibits FAK, SRC and JAK2 is of the formula I or II



I

or



II

wherein

X is NR^3 or CHR^3;

each of R^1 and R^2 is independently H, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, $-OR^5$, $-C(O)OR^5$ or $-C(O)NR^5R^6$; wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl and C_6-C_{10} aryl is independently optionally substituted by deuterium, halogen, -OH, -CN, $-OC_1$-C_6 alkyl, $-NH_2$, $-NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$_2$, $-NHC(O)C_1$-C_6 alkyl, $-N(C_1$-C_6 alkyl)$C(O)C_1$-C_6 alkyl, $-NHC(O)NH_2$, $-NHC(O)NHC_1$-C_6 alkyl, $-N(C_1$-C_6 alkyl)$C(O)NH_2$, $-N(C_1$-C_6 alkyl)$C(O)NHC_1$-C_6 alkyl, $-NHC(O)N(C_1$-C_6 alkyl)$_2$, $-N(C_1$-C_6 alkyl)$C(O)N(C_1$-C_6 alkyl)$_2$, $-NHC(O)OC_1$-C_6 alkyl, $-N(C_1$-C_6 alkyl)$C(O)OC_1$-C_6 alkyl, $-NHS(O)(C_1$-C_6 alkyl), $-NHS(O)_2(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$S(O)(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$S(O)_2(C_1$-C_6 alkyl), $-NHS(O)NH_2$,$-NHS(O)_2NH_2$, $-N(C_1$-C_6 alkyl)$S(O)NH_2$, $-N(C_1$-C_6 alkyl)$S(O)_2NH_2$, $-NHS(O)NH(C_1$-C_6 alkyl), $-NHS(O)_2NH(C_1$-C_6 alkyl), $-NHS(O)N(C_1$-C_6 alkyl)$_2$, $-NHS(O)_2N(C_1$-C_6 alkyl)$_2$, $-N(C_1$-C_6 alkyl)$S(O)NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$S(O)_2NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$S(O)N(C_1$-C_6 alkyl)$_2$, $-N(C_1$-C_6 alkyl)$S(O)_2N(C_1$-C_6 alkyl)$_2$, $-CO_2H$, $-C(O)OC_1$-C_6 alkyl, $-C(O)NH_2$, $-C(O)NH(C_1$-C_6 alkyl), $-C(O)N(C_1$-C_6 alkyl)$_2$, $-SC_1$-C_6 alkyl, $-S(O)C_1$-C_6 alkyl, $-S(O)_2C_1$-C_6 alkyl, $-S(O)NH(C_1$-C_6 alkyl), $-S(O)_2NH(C_1$-C_6 alkyl), $-S(O)N(C_1$-C_6 alkyl)$_2$,$-S(O)_2N(C_1$-C_6 alkyl)$_2$, $-P(C_1$-C_6 alkyl)$_2$, $-P(O)(C_1$-C_6 alkyl)$_2$, $-C_3$-C_6 cycloalkyl, or 3-to 7-membered heterocycloalkyl;

R^3 is independently H, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3-to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or mono- or bicyclic heteroaryl; wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3-to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or mono- or bicyclic heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl or $-OR^5$;

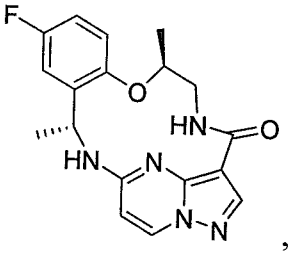
R^4 is H, C_1-C_6 alkyl or 3-to 7-membered heterocycloalkyl, wherein each hydrogen atom in C_1-C_6 alkyl or 3-to 7-membered heterocycloalkyl is independently optionally substituted by halogen, -OH, -CN, $-OC_1$-C_6 alkyl, $-NH_2$, $-NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$_2$, $-CO_2H$, $-C(O)OC_1$-C_6 alkyl, $-C(O)NH_2$, $-C(O)NH(C_1$-C_6 alkyl), $-C(O)N(C_1$-C_6 alkyl)$_2$, C_3-C_6 cycloalkyl, or monocyclic 5- to 7-membered heterocycloalkyl;

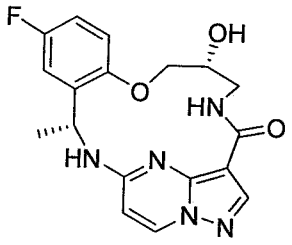
each R^5 and R^6 is independently H, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or heteroaryl; and

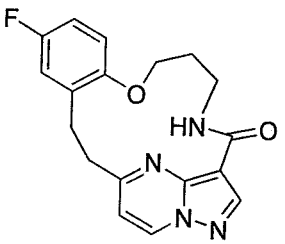
n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

3. The use of claim 1, wherein the compound that inhibits FAK, SRC and JAK2 is a compound of the formula



,


or


or a pharmaceutically acceptable salt thereof.

4. The use of any one of claims 1 to 3, wherein the cancer is selected from the group consisting of ALCL, NSCLC, neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER^+ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, acute myeloid leukemia, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, pediatric glioma CML, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer,

gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer.

5. The use of any one of claims 1 to 4, wherein the at least one EGFR inhibitor is an antibody of EGFR or a small molecule inhibitor of EGFR.

6. The use of any one of claims 1 to 4, wherein the at least one EGFR inhibitor is an antibody of EGFR.

7. The use of claim 6, wherein the antibody is cetuximab, necitumumab or panitumumab.

8. The use of any one of claims 1 to 4, wherein the at least one EGFR inhibitor is a small molecule inhibitor of EGFR.

9. The use of claim 8, wherein the small molecule inhibitor is afatinib, brigatinib, cetuximab, canertinib (CI-1033), dacomitinib, eroltinib, gefitinib, HKI 357, icotinib, lapatinib, osimertinib, naquotinib, nazartinib, necitumumab, neratinib, olmutinib, panitumumab, pelitinib, PF-06747775, rociletinib, vandetanib, or pharmaceutically acceptable salts thereof.

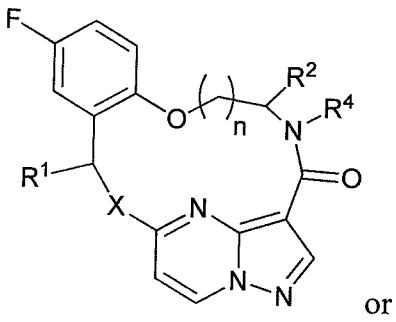
10. The use of claim 9, wherein the small molecule inhibitor is gefitinib, or a pharmaceutically acceptable salt thereof.

11. The use of claim 9, wherein the small molecule inhibitor is osimertinib, or a pharmaceutically acceptable salt thereof.

12. The use of claim 9, wherein the small molecule inhibitor is erlotinib, or a pharmaceutically acceptable salt thereof.

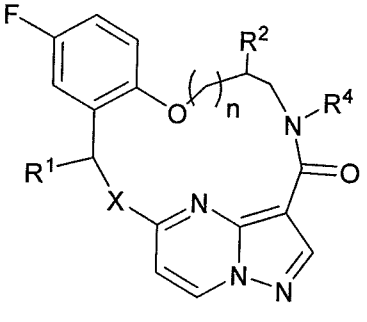
13. Use of a compound that inhibits FAK, SRC and JAK2, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament comprising a therapeutically effective amount of the compound, for treating cancer in a patient in combination with a therapeutically effective amount of at least one additional anti-cancer agent.

14. The use of claim 13, wherein the compound that inhibits FAK, SRC and JAK2 is of the formula I or II



I

or



II

wherein

X is NR^3 or CHR^3;

each of R^1 and R^2 is independently H, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, $-OR^5$, $-C(O)OR^5$ or $-C(O)NR^5R^6$; wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl and C_6-C_{10} aryl is independently optionally substituted by deuterium, halogen, -OH, -CN, -OC_1-C_6 alkyl, $-NH_2$, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, -NHC(O)C_1-C_6 alkyl, -N(C_1-C_6 alkyl)C(O)C_1-C_6 alkyl, $-NHC(O)NH_2$, -NHC(O)NHC_1-C_6 alkyl, -N(C_1-C_6 alkyl)C(O)NH_2, -N(C_1-C_6 alkyl)C(O)NHC_1-C_6 alkyl, -NHC(O)N(C_1-C_6 alkyl)$_2$, -N(C_1-C_6 alkyl)C(O)N(C_1-C_6 alkyl)$_2$, -NHC(O)OC_1-C_6 alkyl, -N(C_1-C_6 alkyl)C(O)OC_1-C_6 alkyl, -NHS(O)(C_1-C_6 alkyl), -$NHS(O)_2$(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)S(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$S(O)_2$(C_1-C_6 alkyl), -$NHS(O)NH_2$,-$NHS(O)_2NH_2$, -N(C_1-C_6 alkyl)$S(O)NH_2$, -N(C_1-C_6 alkyl)$S(O)_2NH_2$, -NHS(O)NH(C_1-C_6 alkyl), -$NHS(O)_2$NH(C_1-C_6 alkyl), -NHS(O)N(C_1-C_6 alkyl)$_2$, -$NHS(O)_2$N(C_1-C_6 alkyl)$_2$, -N(C_1-C_6 alkyl)S(O)NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$S(O)_2$NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)S(O)N(C_1-C_6 alkyl)$_2$, -N(C_1-C_6 alkyl)$S(O)_2$N(C_1-C_6 alkyl)$_2$, $-CO_2H$, -C(O)OC_1-C_6 alkyl, $-C(O)NH_2$, -C(O)NH(C_1-C_6 alkyl), -C(O)N(C_1-C_6 alkyl)$_2$, -SC_1-C_6 alkyl, -S(O)C_1-C_6 alkyl, -$S(O)_2C_1$-C_6 alkyl, -S(O)NH(C_1-C_6 alkyl), -$S(O)_2$NH(C_1-C_6 alkyl), -S(O)N(C_1-C_6 alkyl)$_2$,-$S(O)_2$N(C_1-C_6 alkyl)$_2$, -P(C_1-C_6 alkyl)$_2$, -P(O)(C_1-C_6 alkyl)$_2$, -C_3-C_6 cycloalkyl, or 3-to 7-membered heterocycloalkyl;

R^3 is independently H, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3-to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or mono- or bicyclic heteroaryl; wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3-to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or mono- or bicyclic heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl or $-OR^5$;

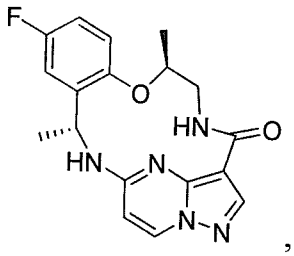
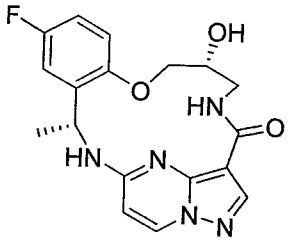
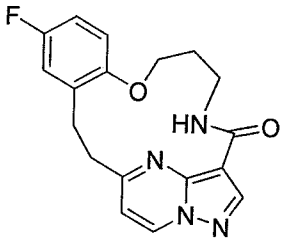
R^4 is H, C_1-C_6 alkyl or 3-to 7-membered heterocycloalkyl, wherein each hydrogen atom in C_1-C_6 alkyl or 3-to 7-membered heterocycloalkyl is independently optionally substituted by halogen, -OH, -CN, -OC_1-C_6 alkyl, $-NH_2$, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, $-CO_2H$, -C(O)OC_1-C_6 alkyl, $-C(O)NH_2$, -C(O)NH(C_1-C_6 alkyl), -C(O)N(C_1-C_6 alkyl)$_2$, C_3-C_6 cycloalkyl, or monocyclic 5- to 7-membered heterocycloalkyl;

each R^5 and R^6 is independently H, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or heteroaryl; and

n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

15. The use of claim 13, wherein the compound that inhibits FAK, SRC and JAK2 is a compound of the formula



or


or a pharmaceutically acceptable salt thereof.

16. The use of any one of claims 13 to 15, wherein the cancer is selected from the group consisting of ALCL, NSCLC, neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER^+ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, acute myeloid leukemia, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, pediatric glioma CML, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer.

17. The use of any one of claims 13 to 15, wherein the additional anti-cancer agent is an EGFR inhibitor, or a pharmaceutically acceptable salt thereof.

18. The use of any one of claims 13 to 15, wherein the additional anti-cancer agent is an antibody of EGFR or a small molecule inhibitor of EGFR.

19. The use of any one of claims 13 to 15, wherein the additional anti-cancer agent is an antibody of EGFR.

20. The use of claim 19, wherein the antibody is cetuximab, necitumumab or panitumumab.

21. The use of any one of claims 13 to 15, wherein the additional anti-cancer agent is a small molecule inhibitor of EGFR.

22. The use of claim 21, wherein the small molecule inhibitor is afatinib, brigatinib, canertinib, dacomitinib, erlotinib, gefitinib, icotinib, HKI 357, lapatinib, osimertinib, naquotinib, nazartinib, neratinib, olmutinib PF-06747775, rociletinib, vandetanib, or

pharmaceutically acceptable salts thereof.

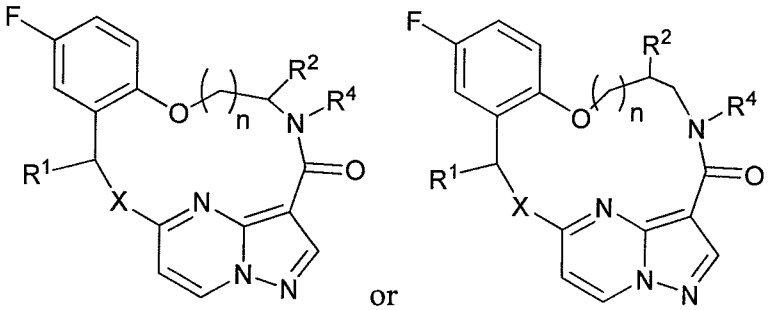
23. The use of claim 22, wherein the small molecule inhibitor is gefitinib, or a pharmaceutically acceptable salt thereof.

24. The use of claim 22, wherein the small molecule inhibitor is osimertinib, or a pharmaceutically acceptable salt thereof.

25. The use of claim 22, wherein the small molecule inhibitor is erlotinib, or a pharmaceutically acceptable salt thereof.

26. A composition comprising a compound that inhibits FAK, SRC and JAK2, or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount, for use in the treatment of cancer in a patient, in combination with a therapeutically effective amount of at least one additional anti-cancer agent.

27. The composition of claim 26, wherein the compound that inhibits FAK, SRC and JAK2 is of the formula I



I or II

wherein

X is NR^3 or CHR^3;

each of R^1 and R^2 is independently H, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, $-OR^5$, $-C(O)OR^5$ or $-C(O)NR^5R^6$; wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl and C_6-C_{10} aryl is independently optionally substituted by deuterium, halogen, -OH, -CN, -OC_1-C_6 alkyl, $-NH_2$, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, -NHC(O)C_1-C_6 alkyl, -N(C_1-C_6 alkyl)C(O)C_1-C_6 alkyl, $-NHC(O)NH_2$, -NHC(O)NHC_1-C_6 alkyl, -N(C_1-C_6 alkyl)$C(O)NH_2$, -N(C_1-C_6 alkyl)C(O)NHC_1-C_6 alkyl, -NHC(O)N(C_1-C_6 alkyl)$_2$, -N(C_1-C_6 alkyl)C(O)N(C_1-C_6 alkyl)$_2$, -NHC(O)OC_1-C_6 alkyl, -N(C_1-C_6 alkyl)C(O)OC_1-C_6 alkyl, -NHS(O)(C_1-C_6 alkyl), $-NHS(O)_2$(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)S(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$S(O)_2$(C_1-C_6 alkyl), $-NHS(O)NH_2$,$-NHS(O)_2NH_2$, -N(C_1-C_6 alkyl)S(O)NH_2, -N(C_1-C_6 alkyl)$S(O)_2NH_2$, -NHS(O)NH(C_1-C_6 alkyl), $-NHS(O)_2NH$(C_1-C_6 alkyl), -NHS(O)N(C_1-C_6 alkyl)$_2$, $-NHS(O)_2N$(C_1-C_6 alkyl)$_2$, -N(C_1-C_6 alkyl)S(O)NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$S(O)_2NH$(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)S(O)N(C_1-C_6 alkyl)$_2$, -N(C_1-C_6 alkyl)$S(O)_2N$(C_1-C_6 alkyl)$_2$, $-CO_2H$,

-C(O)OC$_1$-C$_6$ alkyl, -C(O)NH$_2$, -C(O)NH(C$_1$-C$_6$ alkyl), -C(O)N(C$_1$-C$_6$ alkyl)$_2$, -SC$_1$-C$_6$ alkyl, -S(O)C$_1$-C$_6$ alkyl, -S(O)$_2$C$_1$-C$_6$ alkyl, -S(O)NH(C$_1$-C$_6$ alkyl), -S(O)$_2$NH(C$_1$-C$_6$ alkyl), -S(O)N(C$_1$-C$_6$ alkyl)$_2$,-S(O)$_2$N(C$_1$-C$_6$ alkyl)$_2$, -P(C$_1$-C$_6$ alkyl)$_2$, -P(O)(C$_1$-C$_6$ alkyl)$_2$, -C$_3$-C$_6$ cycloalkyl, or 3-to 7-membered heterocycloalkyl;

R^3 is independently H, deuterium, C$_1$-C$_6$ alkyl, C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkynyl, C$_3$-C$_6$ cycloalkyl, 3-to 7-membered heterocycloalkyl, C$_6$-C$_{10}$ aryl, or mono- or bicyclic heteroaryl; wherein each hydrogen atom in C$_1$-C$_6$ alkyl, C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkynyl, C$_3$-C$_6$ cycloalkyl, 3-to 7-membered heterocycloalkyl, C$_6$-C$_{10}$ aryl, or mono- or bicyclic heteroaryl is independently optionally substituted by deuterium, halogen, C$_1$-C$_6$ alkyl, C$_1$-C$_6$ haloalkyl or -OR^5;

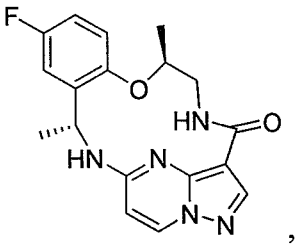
R^4 is H, C$_1$-C$_6$ alkyl or 3-to 7-membered heterocycloalkyl, wherein each hydrogen atom in C$_1$-C$_6$ alkyl or 3-to 7-membered heterocycloalkyl is independently optionally substituted by halogen, -OH, -CN, -OC$_1$-C$_6$ alkyl, -NH$_2$, -NH(C$_1$-C$_6$ alkyl), -N(C$_1$-C$_6$ alkyl)$_2$, -CO$_2$H, -C(O)OC$_1$-C$_6$ alkyl, -C(O)NH$_2$, -C(O)NH(C$_1$-C$_6$ alkyl), -C(O)N(C$_1$-C$_6$ alkyl)$_2$, C$_3$-C$_6$ cycloalkyl, or monocyclic 5- to 7-membered heterocycloalkyl;

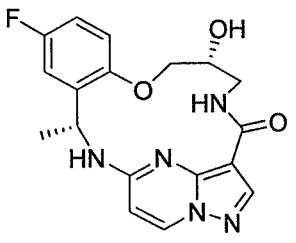
each R^5 and R^6 is independently H, deuterium, C$_1$-C$_6$ alkyl, C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkynyl, C$_3$-C$_6$ cycloalkyl, 3- to 7-membered heterocycloalkyl, C$_6$-C$_{10}$ aryl, or heteroaryl; and

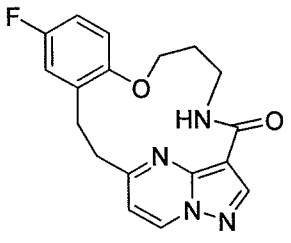
n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

28. The composition of claim 26, wherein the compound that inhibits FAK, SRC and JAK2 is a compound of the formula



,


or


or a pharmaceutically acceptable salt thereof.

29. The composition of any one of claims 26 to 28, wherein the cancer is selected from the group consisting of ALCL, NSCLC, neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER$^+$ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, acute myeloid leukemia, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute

lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, pediatric glioma CML, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer.

30. The composition of any one of claims 26 to 28, wherein the additional anti-cancer agent is an EGFR inhibitor, or a pharmaceutically acceptable salt thereof.

31. The composition of any one of claims 26 to 28, wherein the additional anti-cancer agent is an antibody of EGFR or a small molecule inhibitor of EGFR.

32. The composition of any one of claims 26 to 28, wherein the additional anti-cancer agent is an antibody of EGFR.

33. The composition of claim 32, wherein the antibody is cetuximab, necitumumab or panitumumab.

34. The composition of any one of claims 26 to 28, wherein the additional anti-cancer agent is a small molecule inhibitor of EGFR.

35. The composition of claim 34, wherein the small molecule inhibitor is afatinib, brigatinib, cetuximab, canertinib (CI-1033), dacomitinib, eroltinib, gefitinib, HKI 357, icotinib, lapatinib, osimertinib, naquotinib, nazartinib, necitumumab, neratinib, olmutinib, panitumumab, pelitinib, PF-06747775, rociletinib, vandetanib, or pharmaceutically acceptable salts thereof.

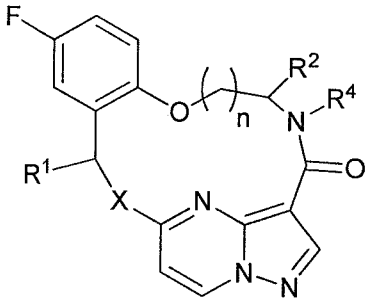
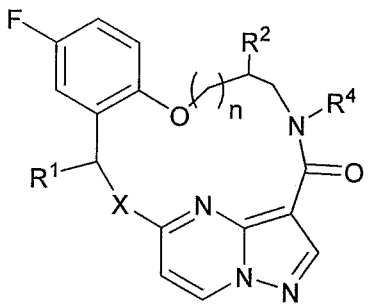
36. The composition of claim 35, wherein the small molecule inhibitor is gefitinib, or a pharmaceutically acceptable salt thereof.

37. The composition of claim 35, wherein the small molecule inhibitor is osimertinib, or a pharmaceutically acceptable salt thereof.

38. The composition of claim 35, wherein the small molecule inhibitor is erlotinib, or a pharmaceutically acceptable salt thereof.

39. A medicament comprising a compound that inhibits FAK, SRC and JAK2, or a pharmaceutically acceptable salt thereof, combined with an EGFR inhibitor, or a pharmaceutically acceptable salt thereof, in fixed or free combination.

40. The medicament of claim 39, wherein the compound that inhibits FAK, SRC and JAK2 is of the formula I or II

I or II

wherein

X is NR^3 or CHR^3;

each of R^1 and R^2 is independently H, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, $-OR^5$, $-C(O)OR^5$ or $-C(O)NR^5R^6$; wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl and C_6-C_{10} aryl is independently optionally substituted by deuterium, halogen, -OH, -CN, $-OC_1$-C_6 alkyl, $-NH_2$, $-NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$_2$, $-NHC(O)C_1$-C_6 alkyl, $-N(C_1$-C_6 alkyl)$C(O)C_1$-C_6 alkyl, $-NHC(O)NH_2$, $-NHC(O)NHC_1$-C_6 alkyl, $-N(C_1$-C_6 alkyl)$C(O)NH_2$, $-N(C_1$-C_6 alkyl)$C(O)NHC_1$-C_6 alkyl, $-NHC(O)N(C_1$-C_6 alkyl)$_2$, $-N(C_1$-C_6 alkyl)$C(O)N(C_1$-C_6 alkyl)$_2$, $-NHC(O)OC_1$-C_6 alkyl, $-N(C_1$-C_6 alkyl)$C(O)OC_1$-C_6 alkyl, $-NHS(O)(C_1$-C_6 alkyl), $-NHS(O)_2(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$S(O)(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$S(O)_2(C_1$-C_6 alkyl), $-NHS(O)NH_2$,$-NHS(O)_2NH_2$, $-N(C_1$-C_6 alkyl)$S(O)NH_2$, $-N(C_1$-C_6 alkyl)$S(O)_2NH_2$, $-NHS(O)NH(C_1$-C_6 alkyl), $-NHS(O)_2NH(C_1$-C_6 alkyl), $-NHS(O)N(C_1$-C_6 alkyl)$_2$, $-NHS(O)_2N(C_1$-C_6 alkyl)$_2$, $-N(C_1$-C_6 alkyl)$S(O)NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$S(O)_2NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$S(O)N(C_1$-C_6 alkyl)$_2$, $-N(C_1$-C_6 alkyl)$S(O)_2N(C_1$-C_6 alkyl)$_2$, $-CO_2H$, $-C(O)OC_1$-C_6 alkyl, $-C(O)NH_2$, $-C(O)NH(C_1$-C_6 alkyl), $-C(O)N(C_1$-C_6 alkyl)$_2$, $-SC_1$-C_6 alkyl, $-S(O)C_1$-C_6 alkyl, $-S(O)_2C_1$-C_6 alkyl, $-S(O)NH(C_1$-C_6 alkyl), $-S(O)_2NH(C_1$-C_6 alkyl), $-S(O)N(C_1$-C_6 alkyl)$_2$,$-S(O)_2N(C_1$-C_6 alkyl)$_2$, $-P(C_1$-C_6 alkyl)$_2$, $-P(O)(C_1$-C_6 alkyl)$_2$, $-C_3$-C_6 cycloalkyl, or 3-to 7-membered heterocycloalkyl;

R^3 is independently H, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3-to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or mono- or bicyclic heteroaryl; wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3-to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or mono- or bicyclic heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl or $-OR^5$;

R^4 is H, C_1-C_6 alkyl or 3-to 7-membered heterocycloalkyl, wherein each hydrogen atom in C_1-C_6 alkyl or 3-to 7-membered heterocycloalkyl is independently optionally substituted by halogen, -OH, -CN, $-OC_1$-C_6 alkyl, $-NH_2$, $-NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$_2$, $-CO_2H$,

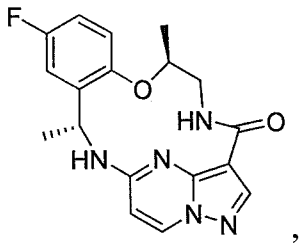
-C(O)OC$_1$-C$_6$ alkyl, -C(O)NH$_2$, -C(O)NH(C$_1$-C$_6$ alkyl), -C(O)N(C$_1$-C$_6$ alkyl)$_2$, C$_3$-C$_6$ cycloalkyl, or monocyclic 5- to 7-membered heterocycloalkyl;

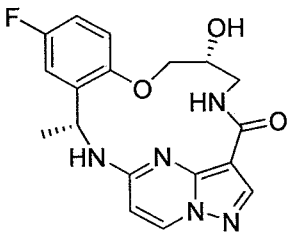
each R^5 and R^6 is independently H, deuterium, C$_1$-C$_6$ alkyl, C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkynyl, C$_3$-C$_6$ cycloalkyl, 3- to 7-membered heterocycloalkyl, C$_6$-C$_{10}$ aryl, or heteroaryl; and

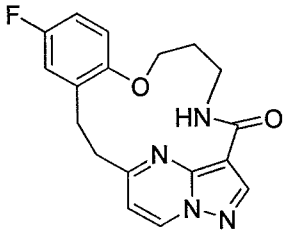
n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

41. The medicament of claim 39, wherein the compound that inhibits FAK, SRC and JAK2 is a compound of the formula



,


or


or a pharmaceutically acceptable salt thereof.

42. The medicament of any one of claims 39 to 41, wherein medicament provides a synergistic effect on a cancer selected from the group consisting of ALCL, NSCLC, neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER^+ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, acute myeloid leukemia, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, pediatric glioma CML, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer.

43. The medicament of any one of claims 39 to 41, wherein the EGFR inhibitor is an antibody or a small molecule inhibitor.

44. The medicament of any one of claims 39 to 41, wherein the EGFR inhibitor is an antibody.

45. The medicament of claim 44, wherein the antibody is cetuximab,

necitumumab or panitumumab.

46. The medicament of any one of claims 39 to 41, wherein the EGFR inhibitor is a small molecule inhibitor.

47. The medicament of claim 46, wherein the small molecule inhibitor is afatinib, brigatinib, cetuximab, canertinib (CI-1033), dacomitinib, eroltinib, gefitinib, HKI 357, icotinib, lapatinib, osimertinib, naquotinib, nazartinib, necitumumab, neratinib, olmutinib, panitumumab, pelitinib, PF-06747775, rociletinib, vandetanib, or pharmaceutically acceptable salts thereof.

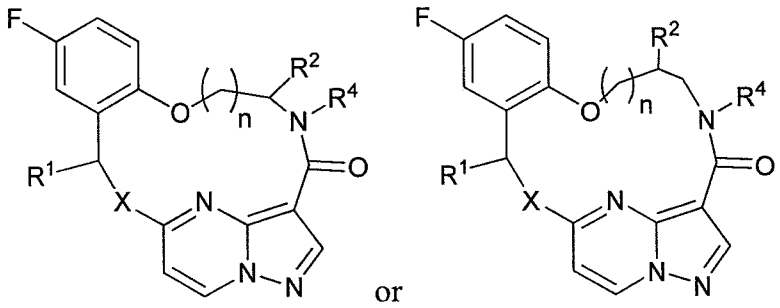
48. The medicament of claim 47, wherein the small molecule inhibitor is gefitinib, or a pharmaceutically acceptable salt thereof.

49. The medicament of claim 47, wherein the small molecule inhibitor is osimertinib, or a pharmaceutically acceptable salt thereof.

50. The medicament of claim 47, wherein the small molecule inhibitor is erlotinib, or a pharmaceutically acceptable salt thereof.

51. A synergistic composition of a compound that inhibits FAK, SRC and JAK2 and an EGFR inhibitor, where the two components come into contact with each other at a locus.

52. The synergistic composition of claim 51, wherein the compound that inhibits FAK, SRC and JAK2 is of the formula I or II



I or II

wherein

X is NR^3 or CHR^3;

each of R^1 and R^2 is independently H, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, $-OR^5$, $-C(O)OR^5$ or $-C(O)NR^5R^6$; wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl and C_6-C_{10} aryl is independently optionally substituted by deuterium, halogen, -OH, -CN, $-OC_1$-C_6 alkyl, $-NH_2$, $-NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$_2$, $-NHC(O)C_1$-C_6 alkyl, $-N(C_1$-C_6 alkyl)$C(O)C_1$-C_6 alkyl, $-NHC(O)NH_2$, $-NHC(O)NHC_1$-C_6 alkyl, $-N(C_1$-C_6 alkyl)$C(O)NH_2$, $-N(C_1$-C_6 alkyl)$C(O)NHC_1$-C_6 alkyl, $-NHC(O)N(C_1$-C_6 alkyl)$_2$, $-N(C_1$-C_6 alkyl)$C(O)N(C_1$-C_6 alkyl)$_2$,

-NHC(O)OC$_1$-C$_6$ alkyl, -N(C$_1$-C$_6$ alkyl)C(O)OC$_1$-C$_6$ alkyl, -NHS(O)(C$_1$-C$_6$ alkyl), -NHS(O)$_2$(C$_1$-C$_6$ alkyl), -N(C$_1$-C$_6$ alkyl)S(O)(C$_1$-C$_6$ alkyl), -N(C$_1$-C$_6$ alkyl)S(O)$_2$(C$_1$-C$_6$ alkyl), -NHS(O)NH$_2$,-NHS(O)$_2$NH$_2$, -N(C$_1$-C$_6$ alkyl)S(O)NH$_2$, -N(C$_1$-C$_6$ alkyl)S(O)$_2$NH$_2$, -NHS(O)NH(C$_1$-C$_6$ alkyl), -NHS(O)$_2$NH(C$_1$-C$_6$ alkyl), -NHS(O)N(C$_1$-C$_6$ alkyl)$_2$, -NHS(O)$_2$N(C$_1$-C$_6$ alkyl)$_2$, -N(C$_1$-C$_6$ alkyl)S(O)NH(C$_1$-C$_6$ alkyl), -N(C$_1$-C$_6$ alkyl)S(O)$_2$NH(C$_1$-C$_6$ alkyl), -N(C$_1$-C$_6$ alkyl)S(O)N(C$_1$-C$_6$ alkyl)$_2$, -N(C$_1$-C$_6$ alkyl)S(O)$_2$N(C$_1$-C$_6$ alkyl)$_2$, -CO$_2$H, -C(O)OC$_1$-C$_6$ alkyl, -C(O)NH$_2$, -C(O)NH(C$_1$-C$_6$ alkyl), -C(O)N(C$_1$-C$_6$ alkyl)$_2$, -SC$_1$-C$_6$ alkyl, -S(O)C$_1$-C$_6$ alkyl, -S(O)$_2$C$_1$-C$_6$ alkyl, -S(O)NH(C$_1$-C$_6$ alkyl), -S(O)$_2$NH(C$_1$-C$_6$ alkyl), -S(O)N(C$_1$-C$_6$ alkyl)$_2$,-S(O)$_2$N(C$_1$-C$_6$ alkyl)$_2$, -P(C$_1$-C$_6$ alkyl)$_2$, -P(O)(C$_1$-C$_6$ alkyl)$_2$, -C$_3$-C$_6$ cycloalkyl, or 3-to 7-membered heterocycloalkyl;

R^3 is independently H, deuterium, C$_1$-C$_6$ alkyl, C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkynyl, C$_3$-C$_6$ cycloalkyl, 3-to 7-membered heterocycloalkyl, C$_6$-C$_{10}$ aryl, or mono- or bicyclic heteroaryl; wherein each hydrogen atom in C$_1$-C$_6$ alkyl, C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkynyl, C$_3$-C$_6$ cycloalkyl, 3-to 7-membered heterocycloalkyl, C$_6$-C$_{10}$ aryl, or mono- or bicyclic heteroaryl is independently optionally substituted by deuterium, halogen, C$_1$-C$_6$ alkyl, C$_1$-C$_6$ haloalkyl or -OR^5;

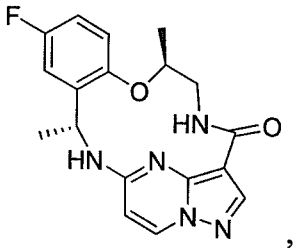
R^4 is H, C$_1$-C$_6$ alkyl or 3-to 7-membered heterocycloalkyl, wherein each hydrogen atom in C$_1$-C$_6$ alkyl or 3-to 7-membered heterocycloalkyl is independently optionally substituted by halogen, -OH, -CN, -OC$_1$-C$_6$ alkyl, -NH$_2$, -NH(C$_1$-C$_6$ alkyl), -N(C$_1$-C$_6$ alkyl)$_2$, -CO$_2$H, -C(O)OC$_1$-C$_6$ alkyl, -C(O)NH$_2$, -C(O)NH(C$_1$-C$_6$ alkyl), -C(O)N(C$_1$-C$_6$ alkyl)$_2$, C$_3$-C$_6$ cycloalkyl, or monocyclic 5- to 7-membered heterocycloalkyl;

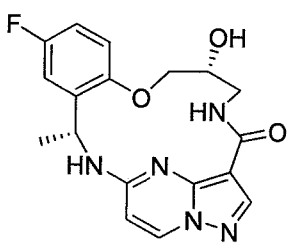
each R^5 and R^6 is independently H, deuterium, C$_1$-C$_6$ alkyl, C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkynyl, C$_3$-C$_6$ cycloalkyl, 3- to 7-membered heterocycloalkyl, C$_6$-C$_{10}$ aryl, or heteroaryl; and

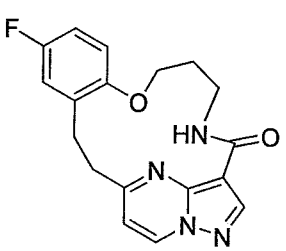
n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

53. The synergistic composition of claim 51, wherein the compound that inhibits FAK, SRC and JAK2 is a compound of the formula



,


or


or a pharmaceutically acceptable salt thereof.

54. The synergistic composition of any one of claims 51 to 53, wherein the locus is a cancer or a cancer cell.

55. The synergistic composition of any one of claims 51 to 53, wherein the

locus is a cancer selected from the group consisting of ALCL, NSCLC, neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, ER^+ breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, acute myeloid leukemia, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, pediatric glioma CML, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer and lung cancer.

56. The synergistic composition of any one of claims 51 to 53, wherein the EGFR inhibitor is an antibody or a small molecule inhibitor.

57. The synergistic composition of any one of claims 51 to 53, wherein the EGFR inhibitor is an antibody.

58. The synergistic composition of claim 57, wherein the antibody is cetuximab, necitumumab or panitumumab.

59. The synergistic composition of any one of claims 51 to 53, wherein the EGFR inhibitor is a small molecule inhibitor.

60. The synergistic composition of claim 59, wherein the small molecule inhibitor is afatinib, brigatinib, cetuximab, canertinib (CI-1033), dacomitinib, eroltinib, gefitinib, HKI 357, icotinib, lapatinib, osimertinib, naquotinib, nazartinib, necitumumab, neratinib, olmutinib, panitumumab, pelitinib, PF-06747775, rociletinib, vandetanib, or pharmaceutically acceptable salts thereof.

61. The synergistic composition of claim 60, wherein the small molecule inhibitor is gefitinib, or a pharmaceutically acceptable salt thereof.

62. The synergistic composition of claim 60, wherein the small molecule inhibitor is osimertinib, or a pharmaceutically acceptable salt thereof.

63. The synergistic composition of claim 60, wherein the small molecule inhibitor is erlotinib, or a pharmaceutically acceptable salt thereof.