METHODS AND COMPOSITIONS RELATING TO TREATMENT OF CANCER

REFERENCE TO RELATED APPLICATION

[0001] This application claims priority from U.S. Provisional Patent Application Serial No. 61/740,126, filed December 20, 2012, the entire content of which is incorporated herein by reference.

GOVERNMENT SUPPORT

[0002] This invention was made with government support under Grant No. CA143999, awarded by the National Institutes of Health. The Government has certain rights in the invention.

FIELD OF THE INVENTION

[0003] Methods and compositions for treatment of cancer in a subject in need thereof are provided according to general aspects of the present invention. Methods and compositions for treatment of cancer in a subject in need thereof are provided according to specific aspects of the present invention which include administering both cetuximab and ISC-4, as a combination formulation or as separate formulations.

BACKGROUND OF THE INVENTION

[0004] There is a continuing need for methods and compositions for treatment of cancer in a subject in need thereof. Such methods and compositions are provided according to the present invention.

SUMMARY OF THE ~~INVENTION~~DISCLOSURE

[0005] Methods of treating cancer in a subject in need thereof are provided according to aspects of the present ~~invention~~ disclosure which include administering both cetuximab and ISC-4, as a combination formulation or as separate formulations.

[0006] Methods of treating cancer in a subject in need thereof are provided according to aspects of the present ~~invention~~ disclosure which include administering a combination of cetuximab and ISC-4 as a combination formulation or separately, wherein the cancer is characterized by wild-type KRAS.

[0007] Methods of treating cancer in a subject in need thereof are provided according to aspects of the present ~~invention~~ disclosure which include administering a combination of cetuximab and ISC-4 as a combination formulation or separately, wherein the cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have an activating KRAS mutation.

[0008] Methods of treating cancer in a subject in need thereof are provided according to aspects of the present ~~invention~~ disclosure which include administering a combination of cetuximab and ISC-4 as a combination formulation or separately, wherein the cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have an activating KRAS mutation, in codon 12, 13 or 61, with reference to human KRAS.

[0009] Methods of treating cancer in a subject in need thereof are provided according to aspects of the present ~~invention~~ disclosure which include administering a combination of cetuximab and ISC-4 as a combination formulation or separately, wherein the cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have activating KRAS mutations Q61H, G12S, G12V, G12A or G13D, with reference to human KRAS.

[0010] Methods of treating cancer in a subject in need thereof are provided by the present ~~invention~~ disclosure which include administering a combination of cetuximab and ISC-4 as a combination formulation or separately, wherein the cancer is colorectal cancer characterized by wild-type KRAS.

[0011] Methods of treating colorectal cancer in a subject in need thereof are provided according to aspects of the present ~~invention~~ disclosure which include administering a combination of cetuximab and ISC-4 as a combination formulation or separately, wherein the colorectal cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have an activating KRAS mutation.

[0012] Methods of treating cancer in a subject in need thereof are provided according to aspects of the present ~~invention~~ disclosure which include administering a combination of cetuximab and ISC-4 as a combination formulation or separately, wherein the cancer is colorectal cancer characterized by wild-type KRAS such that the wild-type KRAS does not have an activating KRAS mutation, in codon 12, 13 or 61, with reference to human KRAS.

[0013] Methods of treating cancer in a subject in need thereof are provided according to aspects of the present ~~invention~~ disclosure which include administering a combination of cetuximab and ISC-4 as a combination formulation or separately, wherein the cancer is colorectal cancer

characterized by wild-type KRAS such that the wild-type KRAS does not have activating KRAS mutations Q61H, G12S, G12V, G12A or G13D, with reference to human KRAS.

[0014] Methods of treating cancer in a subject in need thereof are provided according to aspects of the present ~~invention~~ disclosure which include obtaining a first sample containing or suspected of containing cancer cells from the subject prior to administering the combination of cetuximab and ISC-4; administering a combination of cetuximab and ISC-4 as a combination formulation or separately, obtaining a second sample containing or suspected of containing cancer cells from the subject after administering the combination of cetuximab and ISC-4; and assaying the first and second samples for one or more markers of apoptosis, wherein increased apoptosis in the second sample compared to the first sample indicates therapeutic activity of the administered cetuximab and ISC-4, thereby monitoring effectiveness of administering the combination of cetuximab and ISC-4. According to aspects of such methods, the cancer is characterized by wild-type KRAS, such that the wild-type KRAS does not have an activating KRAS mutation. According to aspects of such methods, the cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have an activating KRAS mutation, in codon 12, 13 or 61, with reference to human KRAS. According to aspects of such methods, the cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have activating KRAS mutations Q61H, G12S, G12V, G12A or G13D, with reference to human KRAS. According to aspects of such methods, the cancer is colorectal cancer characterized by wild-type KRAS, such that the wild-type KRAS does not have an activating KRAS mutation. According to aspects of such methods, the cancer is colorectal cancer characterized by wild-type KRAS such that the wild-type KRAS does not have an activating KRAS mutation, in codon 12, 13 or 61, with reference to human KRAS. According to aspects of such methods, the cancer is colorectal cancer characterized by wild-type KRAS such that the wild-type KRAS does not have activating KRAS mutations Q61H, G12S, G12V, G12A or G13D, with reference to human KRAS.

[0015] Methods of treating cancer in a subject in need thereof are provided according to aspects of the present ~~invention~~ disclosure which include obtaining a first sample containing or suspected of containing cancer cells from the subject prior to administering the combination of cetuximab and ISC-4; administering a combination of cetuximab and ISC-4 as a combination formulation or separately; obtaining a second sample containing or suspected of containing cancer cells from the subject after administering the combination of cetuximab and ISC-4; and assaying the first and second samples for phospho-Akt, wherein decreased phospho-Akt in the second sample

compared to the first sample indicates therapeutic activity of the administered cetuximab and ISC-4, thereby monitoring effectiveness of administering the combination of cetuximab and ISC-4. According to aspects of such methods, the cancer is characterized by wild-type KRAS, such that the wild-type KRAS does not have an activating KRAS mutation. According to aspects of such methods, the cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have an activating KRAS mutation, in codon 12, 13 or 61, with reference to human KRAS. According to aspects of such methods, the cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have activating KRAS mutations Q61H, G12S, G12V, G12A or G13D, with reference to human KRAS. According to aspects of such methods, the cancer is colorectal cancer characterized by wild-type KRAS, such that the wild-type KRAS does not have an activating KRAS mutation. According to aspects of such methods, the cancer is colorectal cancer characterized by wild-type KRAS such that the wild-type KRAS does not have an activating KRAS mutation, in codon 12, 13 or 61, with reference to human KRAS. According to aspects of such methods, the cancer is colorectal cancer characterized by wild-type KRAS such that the wild-type KRAS does not have activating KRAS mutations Q61H, G12S, G12V, G12A or G13D, with reference to human KRAS.

[0016] According to aspects of methods of treating cancer of the present ~~invention~~ disclosure, the cetuximab and ISC-4 are administered simultaneously or sequentially. In a non-limiting example, the cetuximab and ISC-4 are administered sequentially within a period of time selected from: one hour, two hours, four hours, eight hours, twelve hours and twenty-four hours.

[0017] Pharmaceutical compositions are provided according to aspects of the present ~~invention~~ disclosure which include both cetuximab and ISC-4.

[0018] Commercial packages are provided according to aspects of the present ~~invention~~ disclosure which include both cetuximab and ISC-4, wherein the cetuximab and ISC-4 are provided as a single pharmaceutical formulation or as separate pharmaceutical formulations.

[0019] Methods of treating cancer in a subject in need thereof are provided by the present ~~invention~~ disclosure which include administering a combination of cetuximab and an ISC-4 prodrug in combination or separately.

[0020] Methods of treating cancer in a subject in need thereof are provided according to aspects of the present ~~invention~~ disclosure which include administering a combination of cetuximab and an ISC-4 prodrug in combination or separately, wherein the cancer is characterized by wild-type KRAS.

[0021] Methods of treating cancer in a subject in need thereof are provided according to aspects of the present ~~invention~~ disclosure which include administering a combination of cetuximab and an ISC-4 prodrug as a combination formulation or separately, wherein the cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have an activating KRAS mutation.

[0022] Methods of treating cancer in a subject in need thereof are provided according to aspects of the present ~~invention~~ disclosure which include administering a combination of cetuximab and an ISC-4 prodrug as a combination formulation or separately, wherein the cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have an activating KRAS mutation, in codon 12, 13 or 61, with reference to human KRAS.

[0023] Methods of treating cancer in a subject in need thereof are provided according to aspects of the present ~~invention~~ disclosure which include administering a combination of cetuximab and an ISC-4 prodrug as a combination formulation or separately, wherein the cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have activating KRAS mutations Q61H, G12S, G12V, G12A or G13D, with reference to human KRAS.

[0024] Methods of treating colorectal cancer in a subject in need thereof are provided according to aspects of the present ~~invention~~ disclosure which include administering a combination of cetuximab and an ISC-4 prodrug in combination or separately, wherein the cancer is colorectal cancer characterized by wild-type KRAS.

[0025] Methods of treating colorectal cancer in a subject in need thereof are provided according to aspects of the present ~~invention~~ disclosure which include administering a combination of cetuximab and an ISC-4 prodrug as a combination formulation or separately, wherein the colorectal cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have an activating KRAS mutation.

[0026] Methods of treating cancer in a subject in need thereof are provided according to aspects of the present ~~invention~~ disclosure which include administering a combination of cetuximab and an ISC-4 prodrug as a combination formulation or separately, wherein the cancer is colorectal cancer characterized by wild-type KRAS such that the wild-type KRAS does not have an activating KRAS mutation, in codon 12, 13 or 61, with reference to human KRAS.

[0027] Methods of treating cancer in a subject in need thereof are provided according to aspects of the present ~~invention~~ disclosure which include administering a combination of cetuximab and an ISC-4 prodrug as a combination formulation or separately, wherein the cancer is colorectal

cancer characterized by wild-type KRAS such that the wild-type KRAS does not have activating KRAS mutations Q61H, G12S, G12V, G12A or G13D, with reference to human KRAS.

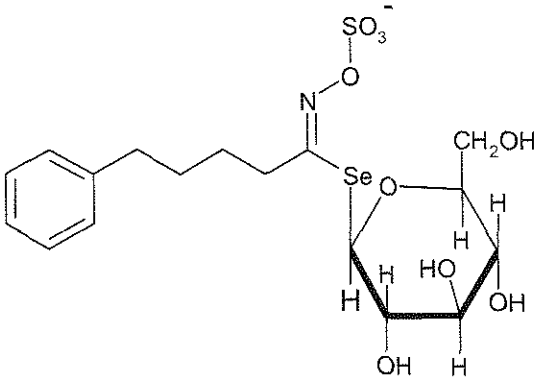
[0028] Methods of treating cancer in a subject in need thereof are provided according to aspects of the present ~~invention~~ disclosure which include obtaining a first sample containing or suspected of containing cancer cells from the subject prior to administering the combination of cetuximab and an ISC-4 prodrug; administering a combination of cetuximab and an ISC-4 prodrug in combination or separately; obtaining a second sample containing or suspected of containing cancer cells from the subject after administering the combination of cetuximab and ISC-4 prodrug; and assaying the first and second samples for one or more markers of apoptosis, wherein increased apoptosis in the second sample compared to the first sample indicates therapeutic activity of the administered cetuximab and ISC-4 prodrug, thereby monitoring effectiveness of administering the combination of cetuximab and ISC-4 prodrug. According to aspects of such methods, the cancer is characterized by wild-type KRAS, such that the wild-type KRAS does not have an activating KRAS mutation. According to aspects of such methods, the cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have an activating KRAS mutation, in codon 12, 13 or 61, with reference to human KRAS. According to aspects of such methods, the cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have activating KRAS mutations Q61H, G12S, G12V, G12A or G13D, with reference to human KRAS. According to aspects of such methods, the cancer is colorectal cancer characterized by wild-type KRAS, such that the wild-type KRAS does not have an activating KRAS mutation. According to aspects of such methods, the cancer is colorectal cancer characterized by wild-type KRAS such that the wild-type KRAS does not have an activating KRAS mutation, in codon 12, 13 or 61, with reference to human KRAS. According to aspects of such methods, the cancer is colorectal cancer characterized by wild-type KRAS such that the wild-type KRAS does not have activating KRAS mutations Q61H, G12S, G12V, G12A or G13D, with reference to human KRAS.

[0029] Methods of treating cancer in a subject in need thereof are provided according to aspects of the present ~~invention~~ disclosure which include obtaining a first sample containing or suspected of containing cancer cells from the subject prior to administering the combination of cetuximab and an ISC-4 prodrug; administering a combination of cetuximab and the ISC-4 prodrug in combination or separately; obtaining a second sample containing or suspected of containing cancer cells from the subject after administering the combination of cetuximab and the ISC-4

prodrug; and assaying the first and second samples for phospho-Akt, wherein decreased phospho-Akt in the second sample compared to the first sample indicates therapeutic activity of the administered cetuximab and the ISC-4 prodrug, thereby monitoring effectiveness of administering the combination of cetuximab and the ISC-4 prodrug. According to aspects of such methods, the cancer is characterized by wild-type KRAS, such that the wild-type KRAS does not have an activating KRAS mutation. According to aspects of such methods, the cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have an activating KRAS mutation, in codon 12, 13 or 61, with reference to human KRAS. According to aspects of such methods, the cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have activating KRAS mutations Q61H, G12S, G12V, G12A or G13D, with reference to human KRAS. According to aspects of such methods, the colorectal cancer is characterized by wild-type KRAS, such that the wild-type KRAS does not have an activating KRAS mutation. According to aspects of such methods, the colorectal cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have an activating KRAS mutation, in codon 12, 13 or 61, with reference to human KRAS. According to aspects of such methods, the colorectal cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have activating KRAS mutations Q61H, G12S, G12V, G12A or G13D, with reference to human KRAS.

[0030] According to aspects of methods of treating cancer of the present ~~invention~~ disclosure, the cetuximab and an ISC-4 prodrug are administered simultaneously or sequentially. In a non-limiting example, the cetuximab and the ISC-4 prodrug are administered sequentially within a period of time selected from: one hour, two hours, four hours, eight hours, twelve hours and twenty-four hours.

[0031] Methods of treating cancer in a subject in need thereof are provided according to aspects of the present ~~invention~~ disclosure which include administering a combination of cetuximab and an ISC-4 prodrug in combination or separately, wherein the ISC-4 prodrug is ISC-4 glucosinolate prodrug or a pharmaceutically acceptable salt thereof. The ISC-4 glucosinolate prodrug has the structural formula:



[0032] Methods of treating cancer in a subject in need thereof are provided according to aspects of the present ~~invention~~ disclosure which include administering a combination of cetuximab and an ISC-4 prodrug in combination or separately, wherein the cancer is characterized by wild-type KRAS and wherein the ISC-4 prodrug is ISC-4 glucosinolate prodrug or a pharmaceutically acceptable salt thereof. According to aspects of such methods, the cancer is characterized by wild-type KRAS, such that the wild-type KRAS does not have an activating KRAS mutation. According to aspects of such methods, the cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have an activating KRAS mutation in codon 12, 13 or 61, with reference to human KRAS. According to aspects of such methods, the cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have activating KRAS mutations Q61H, G12S, G12V, G12A or G13D, with reference to human KRAS.

[0033] Methods of treating cancer in a subject in need thereof are provided according to aspects of the present ~~invention~~ disclosure which include administering a combination of cetuximab and an ISC-4 prodrug in combination or separately, wherein the cancer is colorectal cancer characterized by wild-type KRAS and wherein the ISC-4 prodrug is ISC-4 glucosinolate prodrug or a pharmaceutically acceptable salt thereof. According to aspects of such methods, the colorectal cancer is characterized by wild-type KRAS, such that the wild-type KRAS does not have an activating KRAS mutation. According to aspects of such methods, the colorectal cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have an activating KRAS mutation, in codon 12, 13 or 61, with reference to human KRAS. According to aspects of such methods, the colorectal cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have activating KRAS mutations Q61H, G12S, G12V, G12A or G13D, with reference to human KRAS.

[0034] Methods of treating cancer in a subject in need thereof are provided according to aspects of the present ~~invention~~ disclosure which include obtaining a first sample containing or suspected of containing cancer cells from the subject prior to administering the combination of cetuximab and an ISC-4 prodrug, wherein the ISC-4 prodrug is ISC-4 glucosinolate prodrug or a pharmaceutically acceptable salt thereof; administering a combination of cetuximab and the ISC-4 glucosinolate prodrug or a pharmaceutically acceptable salt thereof in combination or separately; obtaining a second sample containing or suspected of containing cancer cells from the subject after administering the combination of cetuximab and the ISC-4 glucosinolate prodrug or a pharmaceutically acceptable salt thereof; and assaying the first and second samples for one or more markers of apoptosis, thereby monitoring effectiveness of administering the combination of cetuximab and the ISC-4 glucosinolate prodrug or a pharmaceutically acceptable salt thereof. According to aspects of such methods, the cancer is characterized by wild-type KRAS, such that the wild-type KRAS does not have an activating KRAS mutation. According to aspects of such methods, the cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have an activating KRAS mutation, in codon 12, 13 or 61, with reference to human KRAS. According to aspects of such methods, the cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have activating KRAS mutations Q61H, G12S, G12V, G12A or G13D, with reference to human KRAS. According to aspects of such methods, the cancer is colorectal cancer characterized by wild-type KRAS, such that the wild-type KRAS does not have an activating KRAS mutation. According to aspects of such methods, the cancer is colorectal cancer characterized by wild-type KRAS such that the wild-type KRAS does not have an activating KRAS mutation, in codon 12, 13 or 61, with reference to human KRAS. According to aspects of such methods, the cancer is colorectal cancer characterized by wild-type KRAS such that the wild-type KRAS does not have activating KRAS mutations Q61H, G12S, G12V, G12A or G13D, with reference to human KRAS.

[0035] Methods of treating cancer in a subject in need thereof are provided according to aspects of the present ~~invention~~ disclosure which include obtaining a first sample containing or suspected of containing cancer cells from the subject prior to administering the combination of cetuximab and an ISC-4 prodrug, wherein the ISC-4 prodrug is ISC-4 glucosinolate prodrug or a pharmaceutically acceptable salt thereof; administering a combination of cetuximab and the ISC-4 glucosinolate prodrug or a pharmaceutically acceptable salt thereof in combination or separately; obtaining a second sample containing or suspected of containing cancer cells from

the subject after administering the combination of cetuximab and the ISC-4 glucosinolate prodrug or a pharmaceutically acceptable salt thereof; and assaying the first and second samples for phospho-Akt, thereby monitoring effectiveness of administering the combination of cetuximab and the ISC-4 glucosinolate prodrug or a pharmaceutically acceptable salt thereof. According to aspects of such methods, the cancer is characterized by wild-type KRAS, such that the wild-type KRAS does not have an activating KRAS mutation. According to aspects of such methods, the cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have an activating KRAS mutation, in codon 12, 13 or 61, with reference to human KRAS. According to aspects of such methods, the cancer is characterized by wild-type KRAS such that the wild-type KRAS does not have activating KRAS mutations Q61H, G12S, G12V, G12A or G13D, with reference to human KRAS. According to aspects of such methods, the cancer is colorectal cancer characterized by wild-type KRAS, such that the wild-type KRAS does not have an activating KRAS mutation. According to aspects of such methods, the cancer is colorectal cancer characterized by wild-type KRAS such that the wild-type KRAS does not have an activating KRAS mutation, in codon 12, 13 or 61, with reference to human KRAS. According to aspects of such methods, the cancer is colorectal cancer characterized by wild-type KRAS such that the wild-type KRAS does not have activating KRAS mutations Q61H, G12S, G12V, G12A or G13D, with reference to human KRAS.

[0036] According to aspects of methods of treating cancer of the present ~~invention~~ disclosure, the cetuximab and the ISC-4 glucosinolate prodrug or a pharmaceutically acceptable salt thereof, are administered simultaneously or sequentially.

[0037] In a non-limiting example, the cetuximab, and the ISC-4 glucosinolate prodrug or a pharmaceutically acceptable salt thereof, are administered sequentially within a period of time selected from: one hour, two hours, four hours, eight hours, twelve hours and twenty-four hours.

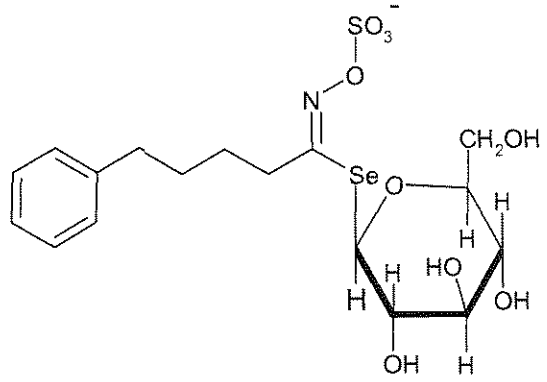
[0038] Pharmaceutical compositions according to aspects of the present ~~invention~~ disclosure include cetuximab, and the ISC-4 glucosinolate prodrug or a pharmaceutically acceptable salt thereof.

[0039] Commercial packages according to aspects of the present ~~invention~~ disclosure include cetuximab and the ISC-4 glucosinolate prodrug or a pharmaceutically acceptable salt thereof.

[0040] Commercial packages according to aspects of the present ~~invention~~ disclosure include a single pharmaceutical formulation including both cetuximab, and the ISC-4 glucosinolate prodrug or a pharmaceutically acceptable salt thereof.

[0041] Commercial packages according to aspects of the present ~~invention~~ disclosure include cetuximab and the ISC-4 glucosinolate prodrug or a pharmaceutically acceptable salt thereof, wherein the cetuximab is provided as a first pharmaceutical formulation and the ISC-4 glucosinolate prodrug or pharmaceutically acceptable salt thereof is provided as a separate second pharmaceutical formulation in the commercial package.

[0042] Compositions according to aspects of the present ~~invention~~ disclosure include the ISC-4 glucosinolate prodrug having the structural formula:



or a pharmaceutically acceptable salt thereof.

[0042a] In one aspect, there is provided the use of cetuximab and ISC-4 in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the cetuximab and ISC-4 are formulated as a combination or separately.

[0042b] In one aspect, there is provided the use of cetuximab and an ISC-4 prodrug in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the cetuximab and ISC-4 prodrug are formulated as a combination or separately.

[0043] Methods of assessing efficacy of treatment of cancer are provided according to aspects of the present ~~invention~~ disclosure which include: obtaining a first sample containing or suspected of containing cancer cells from a subject prior to administering cetuximab and ISC-4 together or separately; obtaining a second sample containing or suspected of containing cancer cells from the subject after administering the cetuximab and ISC-4; and assaying the first and second samples for one or more markers of apoptosis and/or assaying the first and second samples for phospho-Akt, wherein an increase in the one or more markers of apoptosis and a decrease in phosphor-Akt is indicative of therapeutic activity of administering both cetuximab and ISC-4 in combination, together or separately, thereby monitoring effectiveness of administering the combination of cetuximab and ISC-4.

[0044] Methods of assessing efficacy of treatment of cancer are provided according to aspects of the present ~~invention~~ disclosure which include: obtaining a first sample containing or suspected of containing cancer cells from a subject prior to administering cetuximab and an ISC-4 together or separately; obtaining a second sample containing or suspected of containing cancer cells from the subject after administering the cetuximab and the ISC-4 prodrug; and assaying the first and second samples for one or more markers of apoptosis and/or assaying the first and second samples for phospho-Akt, wherein an increase in the one or more markers of apoptosis and a

decrease in phosphor-Akt is indicative of therapeutic activity of administering both cetuximab and the ISC-4 prodrug in combination, together or separately, thereby monitoring effectiveness of administering the combination of cetuximab and the ISC-4 prodrug.

[0045] Methods of assessing efficacy of treatment of cancer are provided according to aspects of the present ~~invention~~ disclosure which include: obtaining a first sample containing or suspected of containing cancer cells from a subject prior to administering cetuximab, and ISC-4 glucosinolate prodrug or pharmaceutically acceptable salt thereof, together or separately; obtaining a second sample containing or suspected of containing cancer cells from the subject after administering the cetuximab and the ISC-4 glucosinolate prodrug or pharmaceutically acceptable salt thereof; and assaying the first and second samples for one or more markers of apoptosis and/or assaying the first and second samples for phospho-Akt, wherein an increase in the one or more markers of apoptosis and a decrease in phosphor-Akt is indicative of therapeutic activity of administering both cetuximab and the ISC-4 glucosinolate prodrug or pharmaceutically acceptable salt thereof in combination, together or separately, thereby monitoring effectiveness of administering the combination of cetuximab and the ISC-4 glucosinolate prodrug or pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0046] Figure 1A is a graph showing results of cell viability assays and calculated EC50 values for indicated cell lines treated with ISC-4 or DMSO;

[0047] Figure 1B is a graph showing the effect of ISC-4 treatment on cell cycle profiles of synchronous and asynchronous HCT116 cells;

[0048] Figure 1C is a graph showing the effect of ISC-4 treatment on cell cycle profiles of synchronous and asynchronous HT-29 cells

[0049] Figure 1D is a graph showing sub-G1 content of indicated colon cancer cell lines following ISC-4 treatment with 0, 1, 2, 4, 8, or 16 μM ISC-4;

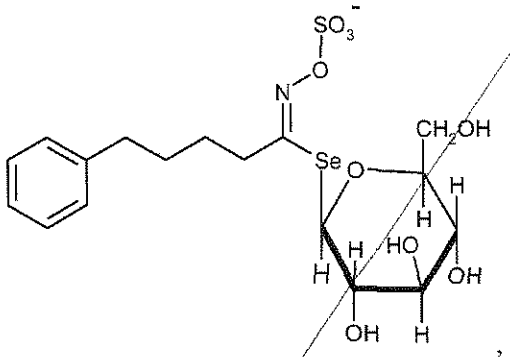
[0050] Figure 2 shows results of cell viability assays in SW480 and RKO colon cancer cell lines treated with ISC-4 (1, 2, or 4 μM) and indicated therapies at putative EC12.5, EC25, and EC50 alone and in combination;

[0051] Figure 3A shows results of cell viability assays of human colon cancer cell line HT-29 treated with ISC-4 and cetuximab at indicated doses for 72 hours;

CLAIMS

1. A pharmaceutical composition comprising: cetuximab and ISC-4; or cetuximab and an ISC-4 prodrug.

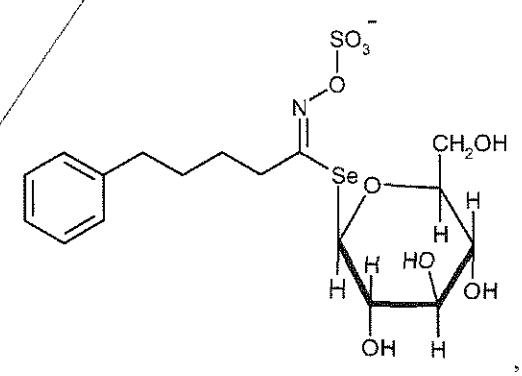
2. The pharmaceutical composition of claim 1, wherein the ISC-4 prodrug is ISC-4 glucosinolate prodrug having the structural formula:



or a pharmaceutically acceptable salt thereof.

3. A commercial package comprising cetuximab and ISC-4; or cetuximab and an ISC-4 prodrug.

4. The commercial package of claim 3 wherein the ISC-4 prodrug is ISC-4 glucosinolate prodrug having the structural formula:



or a pharmaceutically acceptable salt thereof.

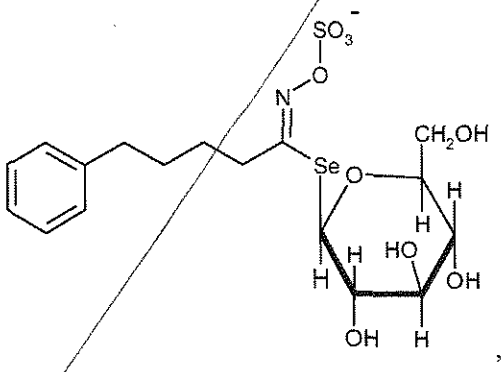
5. The commercial package of claim 3, wherein the cetuximab and ISC-4 are provided as a single pharmaceutical formulation.

6. The commercial package of claim 3, wherein the cetuximab and ISC-4 are provided as separate pharmaceutical formulations.

7. The commercial package of claim 3 or 4, wherein the cetuximab; and the ISC-4 prodrug are provided as a single pharmaceutical formulation.

8. The commercial package of claim 3 or 4, wherein the cetuximab; and the ISC-4 prodrug are provided as separate pharmaceutical formulations.

9. A composition comprising: ISC-4 glucosinolate prodrug having the structural formula:



,

or a pharmaceutically acceptable salt thereof.

10. A *method of treating cancer in a subject in need thereof, comprising:*

administering a combination of cetuximab and ISC-4 as a combination formulation or separately.

11. The method of claim 10, wherein administration of the combination provides a synergistic effect.

12. The method of treating cancer of claim 10 or 11, wherein the cancer is characterized by wild-type KRAS.

13. The method of treating cancer of any of claims 10-12, wherein the cancer is colorectal cancer characterized by wild-type KRAS.

14. The method of treating cancer of any of claims 10-13, further comprising:

obtaining a first sample containing or suspected of containing cancer cells from the subject prior to administering the combination of cetuximab and ISC-4;

obtaining a second sample containing or suspected of containing cancer cells from the subject after administering the combination of cetuximab and ISC-4; and

assaying the first and second samples for one or more markers of apoptosis, thereby monitoring effectiveness of administering the combination of cetuximab and ISC-4.

15. The method of treating cancer of any of claims 10-14, further comprising:

obtaining a first sample containing or suspected of containing cancer cells from the subject prior to administering the combination of cetuximab and ISC-4;

obtaining a second sample containing or suspected of containing cancer cells from the subject after administering the combination of cetuximab and ISC-4; and

assaying the first and second samples for phospho-Akt, thereby monitoring effectiveness of administering the combination of cetuximab and ISC-4.

16. The method of treating cancer of any of claims 10-15, wherein the cetuximab and ISC-4 are administered simultaneously.

17. The method of treating cancer of any of claims 10-15, wherein the cetuximab and ISC-4 are administered sequentially.

18. The method of treating cancer of any of claims 10-15 and 17, wherein the cetuximab and ISC-4 are administered sequentially within a period of time selected from: one hour, two hours, four hours, eight hours, twelve hours and twenty-four hours.

19. A method of treating cancer in a subject in need thereof, comprising:

administering a combination of cetuximab and an ISC-4 prodrug as a combination formulation or separately.

20. The method of treating cancer of claim 19, wherein administration of the combination provides a synergistic effect.

21. The method of treating cancer of claim 19 or 20, wherein the cancer is characterized by wild-type KRAS.

22. The method of treating cancer of any of claims 19-21, wherein the cancer is colorectal cancer characterized by wild-type KRAS.

23. The method of treating cancer of any of claims 19-22, further comprising:

obtaining a first sample containing or suspected of containing cancer cells from the subject prior to administering the combination of cetuximab and ISC-4 prodrug;

obtaining a second sample containing or suspected of containing cancer cells from the subject after administering the combination of cetuximab and ISC-4 prodrug; and

assaying the first and second samples for one or more markers of apoptosis, thereby monitoring effectiveness of administering the combination of cetuximab and ISC-4 prodrug.

24. The method of treating cancer of any of claims 19-23, further comprising:

obtaining a first sample containing or suspected of containing cancer cells from the subject prior to administering the combination of cetuximab and ISC-4 prodrug;

obtaining a second sample containing or suspected of containing cancer cells from the subject after administering the combination of cetuximab and ISC-4 prodrug; and

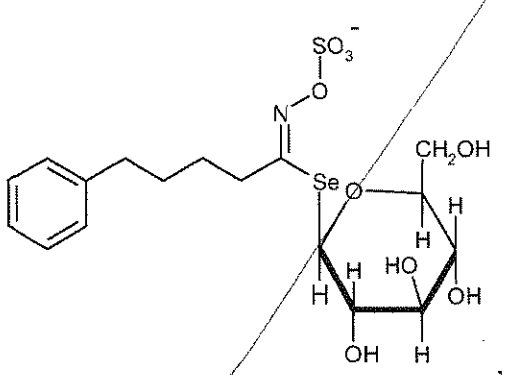
assaying the first and second samples for phospho-Akt, thereby monitoring effectiveness of administering the combination of cetuximab and ISC-4 prodrug.

25. The method of treating cancer of any of claims 19-24, wherein the cetuximab and ISC-4 prodrug are administered simultaneously.

26. The method of treating cancer of any of claims 19-24, wherein the cetuximab and ISC-4 prodrug are administered sequentially.

27. The method of treating cancer of any of claims 19-24 and 26, wherein the cetuximab and ISC-4 prodrug are administered sequentially within a period of time selected from: one hour, two hours, four hours, eight hours, twelve hours and twenty-four hours.

28. The method of treating cancer of any of claims 19-27, wherein the ISC-4 prodrug is ISC-4 glucosinolate prodrug having the structural formula:



,

or a pharmaceutically acceptable salt thereof.

29. The method of treating cancer of any of claims 10-28, wherein the cancer is resistant to 5-fluorouracil.

30. The method of treating cancer of any of claims 10-29, wherein the cancer is resistant to 5-fluorouracil and characterized by wild-type KRAS.

31. The method of treating cancer of any of claims 10-30, wherein the cancer is resistant to 5-fluorouracil and characterized by wild-type KRAS such that the wild-type KRAS does not have an activating KRAS mutation, in codon 12, 13 or 61, with reference to human KRAS.

32. The method of treating cancer of any of claims 10-31, wherein the cancer is resistant to 5-fluorouracil and characterized by wild-type KRAS such that the wild-type KRAS

does not have activating KRAS mutations Q61H, G12S, G12V, G12A or G13D, with reference to human KRAS.

33. Cetuximab and ISC-4 or cetuximab and an ISC-4 prodrug for use in the treatment of cancer.

34. A combination of cetuximab and ISC-4 or cetuximab and an ISC-4 prodrug for use as a medicament.

35. A method of treating cancer in a subject substantially as described herein.

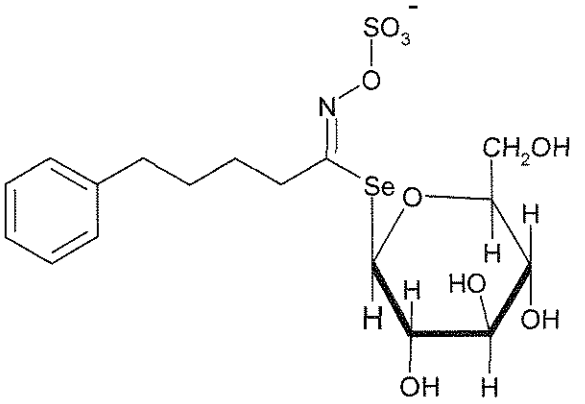
36. A pharmaceutical composition substantially as described herein

37. A commercial package substantially as described herein.

CLAIMS

1. A pharmaceutical composition comprising: cetuximab and ISC-4; or cetuximab and an ISC-4 prodrug.

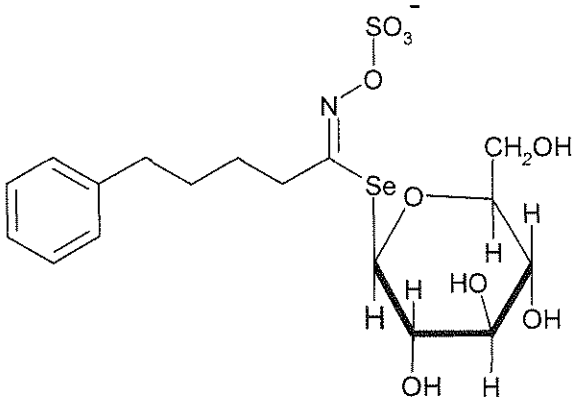
2. The pharmaceutical composition of claim 1, wherein the ISC-4 prodrug is ISC-4 glucosinolate prodrug having the structural formula:



or a pharmaceutically acceptable salt thereof.

3. A commercial package comprising cetuximab and ISC-4; or cetuximab and an ISC-4 prodrug.

4. The commercial package of claim 3 wherein the ISC-4 prodrug is ISC-4 glucosinolate prodrug having the structural formula:



or a pharmaceutically acceptable salt thereof.

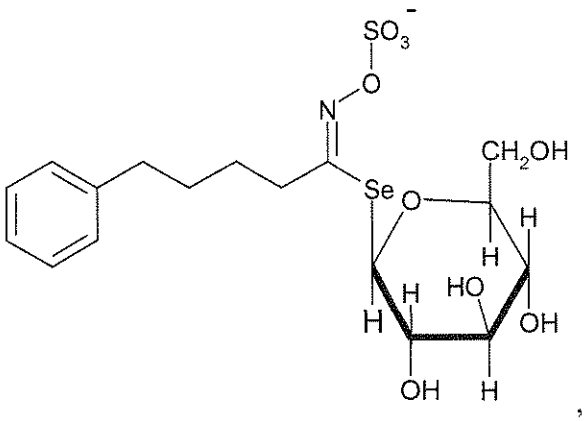
5. The commercial package of claim 3, wherein the cetuximab and ISC-4 are provided as a single pharmaceutical formulation.

6. The commercial package of claim 3, wherein the cetuximab and ISC-4 are provided as separate pharmaceutical formulations.

7. The commercial package of claim 3 or 4, wherein the cetuximab; and the ISC-4 prodrug are provided as a single pharmaceutical formulation.

8. The commercial package of claim 3 or 4, wherein the cetuximab; and the ISC-4 prodrug are provided as separate pharmaceutical formulations.

9. A composition comprising: ISC-4 glucosinolate prodrug having the structural formula:



or a pharmaceutically acceptable salt thereof.

10. Use of cetuximab and ISC-4 in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the cetuximab and ISC-4 are formulated as a combination or separately.

11. The use of claim 10, wherein the medicament provides a synergistic effect.

12. The use of claim 10 or 11, wherein the cancer is characterized by wild-type KRAS.

13. The use of any of claims 10-12, wherein the cancer is colorectal cancer characterized by wild-type KRAS.

14. The use of any of claims 10-13, wherein the cetuximab and ISC-4 are to be administered simultaneously.

15. The use of any of claims 10-13, wherein the cetuximab and ISC-4 are to be administered sequentially.

16. The use of any of claims 10-13 and 15, wherein the cetuximab and ISC-4 are to be administered sequentially within a period of time selected from: one hour, two hours, four hours, eight hours, twelve hours and twenty-four hours.

17. Use of cetuximab and an ISC-4 prodrug in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the cetuximab and ISC-4 prodrug are formulated as a combination or separately.

18. The use of claim 17, wherein the medicament provides a synergistic effect.

19. The use of claim 17 or 18, wherein the cancer is characterized by wild-type KRAS.

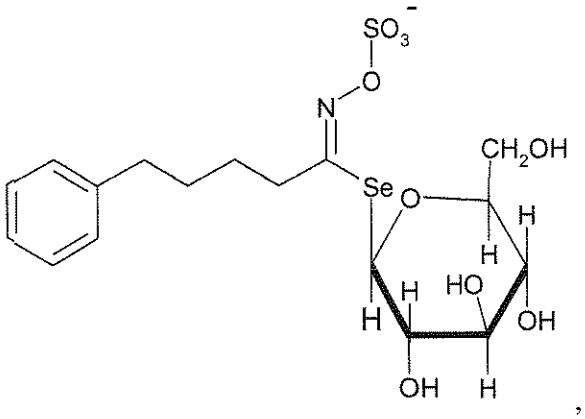
20. The use of any of claims 17-19, wherein the cancer is colorectal cancer characterized by wild-type KRAS.

21. The use of any of claims 17-20, wherein the cetuximab and ISC-4 prodrug are to be administered simultaneously.

22. The use of any of claims 17-20, wherein the cetuximab and ISC-4 prodrug are to be administered sequentially.

23. The use of any of claims 17-20 and 22, wherein the cetuximab and ISC-4 prodrug are to be administered sequentially within a period of time selected from: one hour, two hours, four hours, eight hours, twelve hours and twenty-four hours.

24. The use of any of claims 17-23, wherein the ISC-4 prodrug is ISC-4 glucosinolate prodrug having the structural formula:



or a pharmaceutically acceptable salt thereof.

25. The use of any of claims 10-24, wherein the cancer is resistant to 5-fluorouracil.

26. The use of any of claims 10-25, wherein the cancer is resistant to 5-fluorouracil and characterized by wild-type KRAS.

27. The use of any of claims 10-26, wherein the cancer is resistant to 5-fluorouracil and characterized by wild-type KRAS such that the wild-type KRAS does not have an activating KRAS mutation, in codon 12, 13 or 61, with reference to human KRAS.

28. The use of any of claims 10-27, wherein the cancer is resistant to 5-fluorouracil and characterized by wild-type KRAS such that the wild-type KRAS does not have activating KRAS mutations Q61H, G12S, G12V, G12A or G13D, with reference to human KRAS.

29. Cetuximab and ISC-4 or cetuximab and an ISC-4 prodrug for use in the treatment of cancer.

30. A combination of cetuximab and ISC-4 or cetuximab and an ISC-4 prodrug for use as a medicament.