SUMMARY

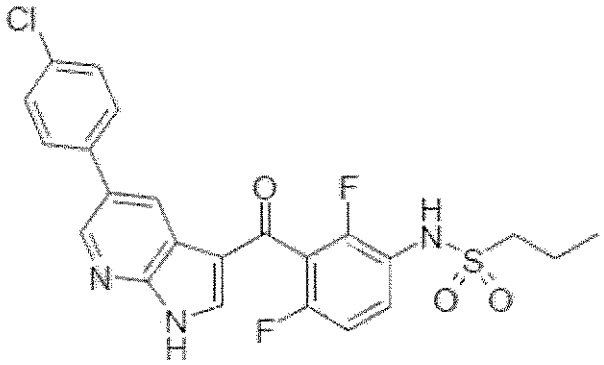
[0009] The present ~~invention~~disclosure contemplates a method of tumor growth inhibition (TGI) in a subject suffering from melanoma comprising administering to the subject an effective amount of an anti-endothelin B receptor (ETBR) antibody drug conjugate in combination with an effective amount of a MAP kinase inhibitor. In one aspect, there is provided a use of an anti-endothelin B receptor (ETBR) antibody in combination with a MAP kinase inhibitor for the preparation of a medicament for tumor growth inhibition (TGI) in a subject suffering from melanoma.

In one ~~aspect~~embodiment, the combination of an anti-ETBR antibody drug conjugate and a MAP kinase inhibitor is synergistic. In another ~~aspect~~embodiment, with respect to the synergistic combination, the TGI is greater than the TGI seen using an anti-ETBR antibody drug conjugate alone or greater than the TGI seen using a MAP kinase inhibitor alone. In yet a further ~~aspect~~embodiment, with respect to the synergistic combination, the TGI is about 10% greater, or about 15% greater, or about 20% greater, or about 25% greater, or about 30% greater, or about 35% greater, or about 40% greater, or about 45% greater, or about 50% greater, or about 55% greater, or about 60% greater, or about 65% greater, or about 70% greater than use of an anti-ETBR antibody drug conjugate alone or the TGI is about 10% greater, or about 15% greater, or about 20% greater, or about 25% greater, or about 30% greater, or about 35% greater, or about 40% greater, or about 45% greater, or about 50% greater, or about 55% greater, or about 60% greater, or about 65% greater, or about 70% greater than use of a MAP kinase inhibitor alone.

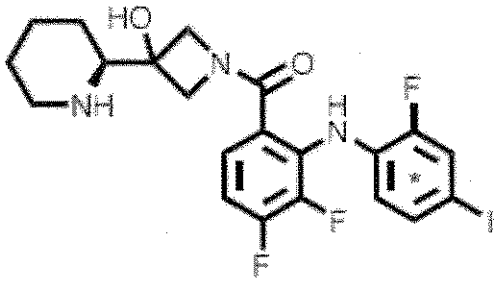
[0010] In another ~~aspect~~ embodiment of the ~~invention~~disclosure described above, the anti-ETBR antibody specifically binds an ETBR epitope consisting of amino acids number 64 to 101 of SEQ ID NO:10. In yet another ~~aspect~~embodiment of the claimed ~~method~~disclosure, the anti-ETBR antibody has three variable heavy chain CDRs and three variable light chain CDRs wherein VH CDR1 is SEQ ID NO:1, VH CDR2 is SEQ ID NO:2, VH CDR3 is SEQ ID NO:3 and wherein VL CDR1 is SEQ ID NO:4, VL CDR2 is SEQ ID NO:5, VL CDR3 is SEQ ID NO:6. In still another ~~aspect~~ embodiment of the claimed ~~method~~disclosure, the anti-ETBR antibody has a variable heavy chain and a variable light chain, wherein said VH is SEQ ID NO:7 or 9. A further ~~aspect~~embodiment of this ~~method~~disclosure also includes an anti-ETBR antibody also having a VL which is SEQ ID NO:8.

[0011] In one ~~aspect~~ embodiment of the claimed ~~method~~disclosure described above, the anti-ETBR antibody is conjugated to a cytotoxin, wherein said cytotoxin is a cytotoxic agent that is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes, and wherein said cytotoxin is a toxin. In another ~~aspect~~ embodiment of the claimed ~~invention~~disclosure, the toxin is selected from the group consisting of maytansinoid, calicheamicin and auristatin. In yet another ~~aspect~~disclosure of the ~~invention~~disclosure, the toxin is a maytansinoid.

[0012] In one embodiment ~~aspect~~ of the claimed ~~method~~disclosure described above, the MAP kinase inhibitor is a BRAF inhibitor. In yet another ~~aspect~~embodiment of the claimed ~~method~~disclosure described above, the BRAF inhibitor is propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide. In another ~~aspect~~embodiment, the BRAF inhibitor has the following chemical structure:



[0013] In another ~~aspect~~embodiment of the claimed ~~method~~disclosure described above, the MAP kinase inhibitor is a MEK inhibitor. In yet another ~~aspect~~embodiment of the claimed ~~method~~disclosure described above, the MEK inhibitor is (S)-(3,4-difuoro-2-((2-fluoro-4-iodophenyl)amino)phenyl)(3-hydoxy-3-(piperidin-2yl)azetidin-1-yl)methanone. In still another ~~aspect~~embodiment of the claimed ~~method~~disclosure described above, the MEK inhibitor has the following chemical structure:



In another aspect, there is provided a use of a MAP kinase inhibitor and an anti-ETBR antibody for the preparation of a medicament for treating melanoma in a subject in need thereof.

[0014] In one ~~aspect~~embodiment of the ~~invention~~disclosure, it is contemplated that a method of treating melanoma comprising administering to a subject in need thereof a therapeutically effective amount of a MAP kinase inhibitor and an anti-ETBR antibody is described. In another ~~aspect~~ embodiment of the claimed ~~method~~disclosure described above, said melanoma is ETBR positive. In yet another ~~aspect~~embodiment of the claimed ~~method~~disclosure, said melanoma is metastatic. In still a further ~~aspect~~embodiment of the claimed ~~method~~disclosure, said subject has not had prior therapy with a MAP kinase inhibitor. In yet a further ~~aspect~~embodiment of the claimed ~~method~~disclosure, said subject has a V600E BRAF gene mutation or said subject is BRAF wildtype, having no V600E BRAF mutation. In still a further ~~aspect~~embodiment of the claimed ~~method~~disclosure, the subject has not had prior therapy with a MAP kinase inhibitor.

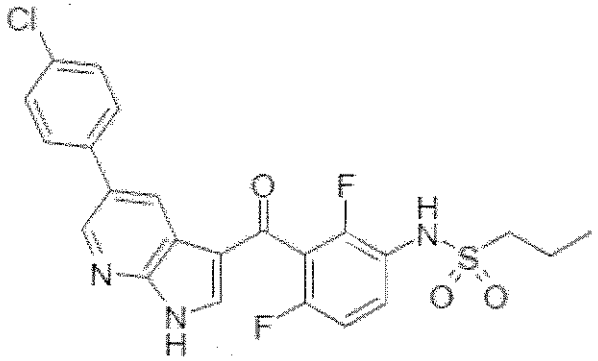
[0015] In another ~~aspect~~ embodiment of the claimed ~~method~~disclosure described above, the combination of an anti-ETBR antibody and a MAP kinase inhibitor is synergistic. In another ~~aspect~~embodiment, with respect to the synergistic combination, the TGI is greater than the TGI seen using an anti-ETBR antibody alone or greater than the TGI seen using a MAP kinase inhibitor alone. In yet a further ~~aspect~~embodiment, with respect to the synergistic combination, the TGI is about 10% greater, or about 15% greater, or about 20% greater, or about 25% greater, or about 30% greater, or about 35% greater, or about 40% greater, or about 45% greater, or about 50% greater, or about 55% greater, or about 60% greater, or about 65% greater, or about 70% greater

than use of an anti-ETBR antibody alone or the TGI is about 10% greater, or about 15% greater, or about 20% greater, or about 25% greater, or about 30% greater, or about 35% greater, or about 40% greater, or about 45% greater, or about 50% greater, or about 55% greater, or about 60% greater, or about 65% greater, or about 70% greater than use of a MAP kinase inhibitor alone.

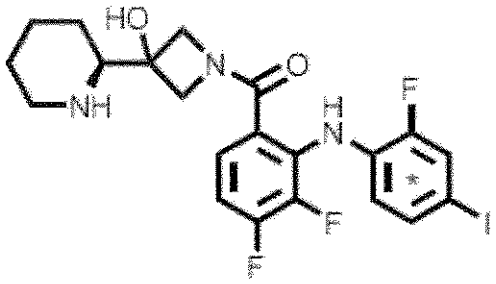
[0016] In another ~~aspect~~ embodiment of the ~~invention~~disclosure described above, the anti-ETBR antibody specifically binds an ETBR epitope consisting of amino acids number 64 to 101 of SEQ ID NO:10. In yet another ~~aspect~~ embodiment of the claimed ~~method~~disclosure, the anti-ETBR antibody has three variable heavy chain CDRs and three variable light chain CDRs wherein VH CDR1 is SEQ ID NO:1, VH CDR2 is SEQ ID NO:2, VH CDR3 is SEQ ID NO:3 and wherein VL CDR1 is SEQ ID NO:4, VL CDR2 is SEQ ID NO:5, VL CDR3 is SEQ ID NO:6. In still another ~~aspect~~ embodiment of the claimed ~~method~~disclosure, the anti-ETBR antibody has a variable heavy chain and a variable light chain, wherein said VH is SEQ ID NO:7 or 9. A further ~~aspect~~ embodiment of this ~~method~~ disclosure also includes an anti-ETBR antibody also having a VL which is SEQ ID NO:8.

[0017] In one ~~aspect~~ embodiment of the claimed ~~method~~ disclosure described above, the anti-ETBR antibody is conjugated to a cytotoxin, wherein said cytotoxin is cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes, and wherein said cytotoxin is a toxin. In another ~~aspect~~ embodiment of the claimed ~~invention~~disclosure, the toxin is selected from the group consisting of maytansinoid, calicheamicin and auristatin. In yet another ~~aspect~~embodiment of the ~~invention~~disclosure, the toxin is a maytansinoid.

[0018] In one ~~aspect~~ embodiment of the claimed ~~method~~ disclosure described above, the MAP kinase inhibitor is a BRAF inhibitor. In yet another ~~aspect~~ embodiment of the ~~method~~disclosure described above, the BRAF inhibitor is propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide. In another ~~aspect~~embodiment, the BRAF inhibitor has the following chemical structure:



[0019] In another ~~aspect~~ embodiment of the claimed ~~method~~ disclosure described above, the MAP kinase inhibitor is a MEK inhibitor. In yet another ~~aspect~~embodiment of the claimed ~~method~~disclosure described above, the MEK inhibitor is (S)-(3,4-difuoro-2-((2-fluoro-4-iodophenyl)amino)phenyl)(3-hydoxy-3-(piperidin-2yl)azetidin-1-yl)methanone. In still another ~~aspect~~embodiment of the claimed ~~method~~disclosure described above, the MEK inhibitor has the following chemical structure:



[0020] In one ~~aspect~~embodiment of the ~~invention~~disclosure, it is contemplated that a method of treating melanoma comprising administering to a subject in need thereof a therapeutically effective amount of a MAP kinase inhibitor and an anti-ETBR antibody drug conjugate is described, wherein the MAP kinase inhibitor is administered first to said subject in need thereof. In another ~~aspect~~embodiment of the ~~invention~~disclosure, said anti-ETBR antibody drug conjugate is administered after administration of said MAP kinase inhibitor. Alternatively, contemplated methods of the ~~invention~~disclosure include where the anti-ETBR antibody and the MAP kinase inhibitor are administered simultaneously.

[0021] In one ~~aspect~~embodiment of the ~~invention~~disclosure, it is contemplated that a method of treating melanoma comprising administering to a subject in need thereof a therapeutically effective amount of a MAP kinase inhibitor and an anti-ETBR antibody drug conjugate is described, wherein the anti-ETBR antibody drug conjugate and the MAP kinase inhibitor are administered sequentially, wherein the anti-ETBR antibody drug conjugate is administered to the subject first and the MAP kinase inhibitor is administered to the subject after administration of the anti-ETBR antibody drug conjugate.

[0022] In one ~~aspect~~embodiment of the ~~invention~~disclosure, it is contemplated that a method of treating melanoma comprising administering to a subject in need thereof a therapeutically effective amount of a MAP kinase inhibitor and an anti-ETBR antibody drug conjugate is described, wherein the MAP kinase inhibitor is administered to the subject first and the anti-ETBR antibody drug conjugate is administered to the subject after administration of the MAP kinase inhibitor.

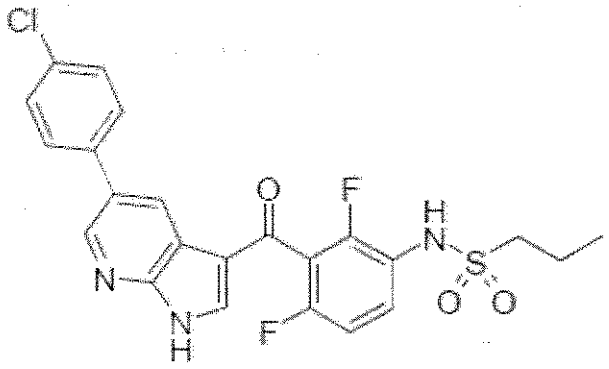
[0023] In furtherance of the above contemplated ~~aspects~~embodiments of the ~~invention~~disclosure, it is further contemplated that a method of treating melanoma comprising administering to a subject in need thereof a therapeutically effective amount of a MAP kinase inhibitor and an anti-ETBR antibody drug conjugate is described, wherein said anti-ETBR antibody drug conjugate is administered intraveneously. It is also contemplated that the anti-ETBR antibody drug conjugate is dosed at about 0.1 mpk, or about 0.2 mpk, or about 0.3 mpk, or about 0.5 mpk, or about 1 mpk, or about 5 mpk, or about 10 mpk, or about 15 mpk, or about 20 mpk, or about 25 mpk, or about 30 mpk in the ~~claimed~~ methods of the ~~invention~~disclosure.

[0024] In furtherance of the above contemplated ~~aspects~~embodiments of the ~~invention~~disclosure, it is further contemplated that a method of treating melanoma comprising administering to a subject in need thereof a therapeutically effective amount of a MAP kinase inhibitor and an anti-ETBR antibody drug conjugate is described, wherein the MAP kinase inhibitor is administered orally. It is also contemplated that the BRAF inhibitor is dosed at about 1 mpk, or about 2 mpk, or about 3 mpk, or about 4 mpk, or about 5 mpk, or about 6 mpk, or about 7 mpk, or about 8 mpk, or about 9 mpk, or about 10 mpk, or about 11 mpk, or about 12 mpk, or about 15 mpk, or about 20 mpk or about 30 mpk in the ~~claimed~~ methods of the ~~invention~~disclosure.

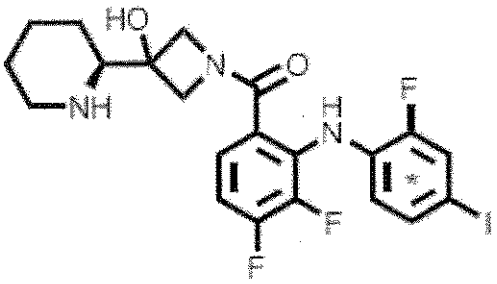
In one aspect, there is provided an article of manufacture for TGI in a subject suffering from melanoma comprising a package comprising an anti-ETBR antibody composition and a MAP kinase inhibitor composition.

[0025] In one ~~aspect~~embodiment of the ~~invention~~disclosure, it is contemplated that an article of manufacture is used for TGI in a subject suffering from melanoma comprising a package comprising an anti-ETBR antibody drug conjugate composition and a MAP kinase inhibitor composition. It is further contemplated that said anti-ETBR antibody drug conjugate specifically binds an ETBR epitope consisting of amino acids number 64 to 101 of SEQ ID NO:10. Alternatively, it is also contemplated that said anti-ETBR antibody has three variable heavy chain CDRs and three variable light chain CDRs wherein VH CDR1 is SEQ ID NO:1, VH CDR2 is SEQ ID NO:2, VH CDR3 is SEQ ID NO:3 and wherein VL CDR1 is SEQ ID NO:4, VL CDR2 is SEQ ID NO:5, VL CDR3 is SEQ ID NO:6. A further alternative that is contemplated is an anti-ETBR antibody has a variable heavy chain and a variable light chain, wherein said VH is SEQ ID NO:7 or 9. In yet another alternative, an anti-ETBR antibody has a variable heavy chain and a variable light chain, wherein said VH is SEQ ID NO:7 or 9 and the VL is SEQ ID NO:8. In another ~~aspect~~ embodiment of the article of manufacture, the anti-ETBR antibody is conjugated to a cytotoxin, wherein said cytotoxin is cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes. In one further ~~aspect~~embodiment, the cytotoxin is a toxin wherein said toxin is selected from the group consisting of maytansinoid, calicheamicin and auristatin. In one ~~aspect~~embodiment, the toxin is a maytansinoid.

[0026] In one embodiment~~aspect~~ of the method of treating melanoma described above, it is also contemplated that the MAP kinase inhibitor is a BRAF inhibitor. In yet another ~~aspect~~ embodiment of the method described above, the BRAF inhibitor is propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide. Further, it is contemplated that the BRAF inhibitor has the following chemical structure:



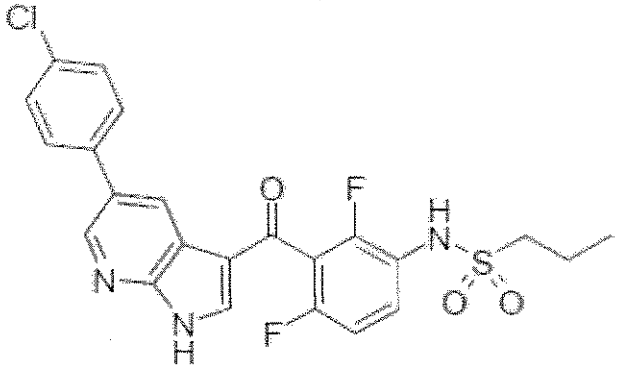
[0027] In another ~~aspect~~ embodiment of the ~~claimed~~ method described above, the MAP kinase inhibitor is a MEK inhibitor. In yet another ~~aspect~~embodiment of the ~~claimed~~ method described above, the MEK inhibitor is (S)-(3,4-difuoro-2-((2-fluoro-4-iodophenyl)amino)phenyl)(3-hydoxy-3-(piperidin-2yl)azetidin-1-yl)methanone. In still another ~~aspect~~embodiment of the ~~claimed~~ method described above, the MEK inhibitor has the following chemical structure:



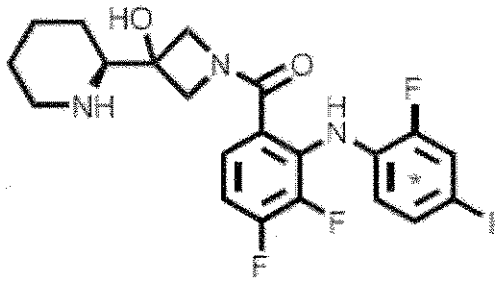
In another aspect, there is provided an article of manufacture for treating melanoma in a subject comprising a package comprising an anti-ETBR antibody composition and a MAP kinase inhibitor composition.

[0028] In one ~~aspect~~embodiment of the ~~invention~~disclosure, it is contemplated that an article of manufacture for treating melanoma in a subject comprising a package comprising an anti-ETBR antibody drug conjugate composition and a MAP kinase inhibitor composition. It is further contemplated that said anti-ETBR antibody specifically binds an ETBR epitope consisting of amino acids number 64 to 101 of SEQ ID NO:10. Alternatively, it is also contemplated that said anti-ETBR antibody has three variable heavy chain CDRs and three variable light chain CDRs wherein VH CDR1 is SEQ ID NO:1, VH CDR2 is SEQ ID NO:2, VH CDR3 is SEQ ID NO:3 and wherein VL CDR1 is SEQ ID NO:4, VL CDR2 is SEQ ID NO:5, VL CDR3 is SEQ ID NO:6. A further alternative that is contemplated is an anti-ETBR antibody has a variable heavy chain and a variable light chain, wherein said VH is SEQ ID NO:7 or 9. In yet another alternative, an anti-ETBR antibody has a variable heavy chain and a variable light chain, wherein said VH is SEQ ID NO:7 or 9 and the VL is SEQ ID NO:8. In another ~~aspect~~embodiment of the article of manufacture, the anti-ETBR antibody is conjugated to a cytotoxin, wherein said cytotoxin is cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes. In one further ~~aspect~~embodiment, the cytotoxin is a toxin wherein said toxin is selected from the group consisting of maytansinoid, calicheamicin and auristatin. In one ~~aspect~~embodiment, the toxin is a maytansinoid.

[0029] In one ~~aspect~~embodiment of the article of manufacture described above, it is also contemplated that the MAP kinase inhibitor is a BRAF inhibitor. In yet another ~~aspect~~embodiment of the article of manufacture described above, the BRAF inhibitor is propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide. Further, it is contemplated that the BRAF inhibitor has the following chemical structure:

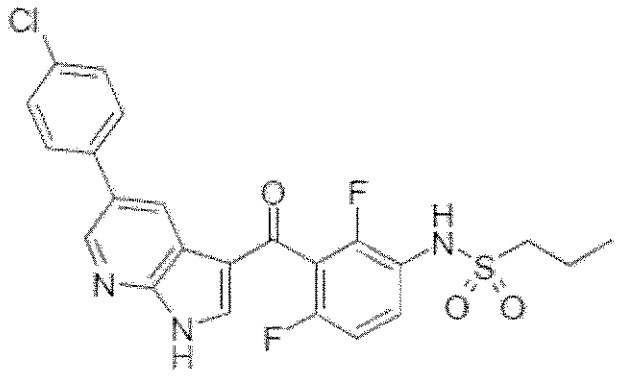


[0030] In another ~~aspect~~embodiment of the article of manufacture described above, the MAP kinase inhibitor is a MEK inhibitor. In yet another ~~aspect~~embodiment of the article of manufacture described above, the MEK inhibitor is (S)-(3,4-difuoro-2-((2-fluoro-4-iodophenyl)amino)phenyl)(3-hydoxy-3-(piperidin-2yl)azetidin-1-yl)methanone. In still another ~~aspect~~embodiment of the article of manufacture described above, the MEK inhibitor has the following chemical structure:

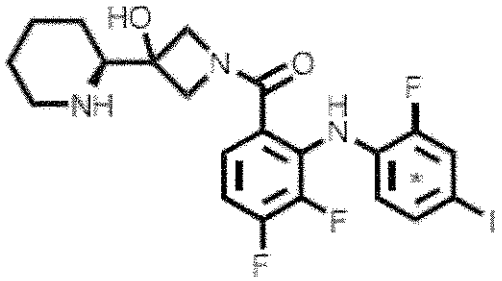


[0031] It is contemplated that one ~~aspect~~embodiment of the ~~invention~~disclosure is use of an anti-ETBR antibody drug conjugate and a MAP kinase inhibitor in the preparation of a medicament for TGI of a melanoma. It is further contemplated that said anti-ETBR antibody specifically binds an ETBR epitope consisting of amino acids number 64 to 101 of SEQ ID NO:10. Alternatively, it is also contemplated that said anti-ETBR antibody has three variable heavy chain CDRs and three variable light chain CDRs wherein VH CDR1 is SEQ ID NO:1, VH CDR2 is SEQ ID NO:2, VH CDR3 is SEQ ID NO:3 and wherein VL CDR1 is SEQ ID NO:4, VL CDR2 is SEQ ID NO:5, VL CDR3 is SEQ ID NO:6. A further alternative that is contemplated is an anti-ETBR antibody has a variable heavy chain and a variable light chain, wherein said VH is SEQ ID NO:7 or 9. In yet another alternative, an anti-ETBR antibody has a variable heavy chain and a variable light chain, wherein said VH is SEQ ID NO:7 or 9 and the VL is SEQ ID NO:8. In another ~~aspect~~embodiment of the article of manufacture, the anti-ETBR antibody is conjugated to a cytotoxin, wherein said cytotoxin is cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes. In one further ~~aspect~~embodiment, the cytotoxin is a toxin wherein said toxin is selected from the group consisting of maytansinoid, calicheamicin and auristatin. In one ~~aspect~~embodiment, the toxin is a maytansinoid.

[0032] In one ~~aspect~~embodiment of the use of the medicament described above, it is also contemplated that the MAP kinase inhibitor is a BRAF inhibitor. In yet another ~~aspect~~embodiment of the use of the medicament described above, the BRAF inhibitor is propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide. Further, it is contemplated that the BRAF inhibitor has the following chemical structure:



[0033] In another ~~aspect~~embodiment of the use of the medicament described above, the MAP kinase inhibitor is a MEK inhibitor. In yet another ~~aspect~~embodiment of the use of the medicament described above, the MEK inhibitor is (S)-(3,4-difuoro-2-((2-fluoro-4-iodophenyl)amino)phenyl)(3-hydoxy-3-(piperidin-2yl)azetidin-1-yl)methanone. In still another ~~aspect~~embodiment of the use of the medicament described above, the MEK inhibitor has the following chemical structure:

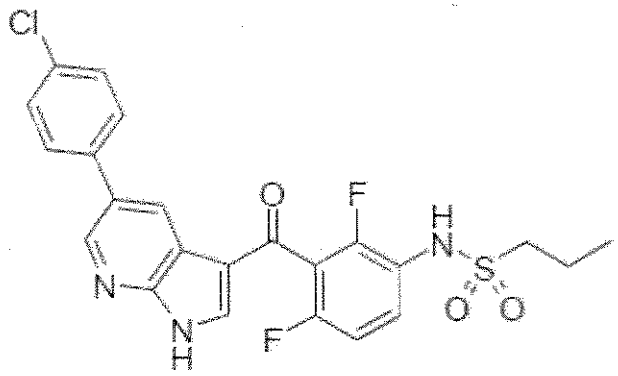


In another aspect, there is provided a use of an article of manufacture as defined above in the preparation of a medicament for TGI of a melanoma.

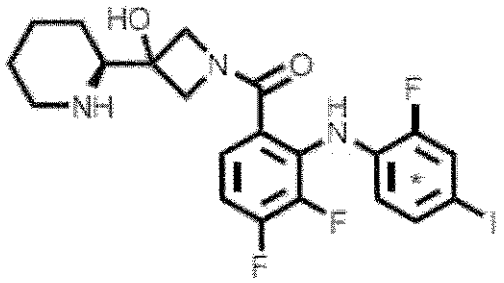
[0034] It is contemplated that one ~~aspect~~embodiment of the ~~invention~~disclosure is use of an article of manufacture comprising an anti-ETBR antibody drug conjugate composition and a MAP kinase inhibitor composition in the preparation of a medicament for TGI of a melanoma. It is further contemplated that said anti-ETBR antibody specifically binds an ETBR epitope consisting of amino acids number 64 to 101 of SEQ ID NO:10. Alternatively, it is also contemplated that said anti-ETBR antibody has three variable heavy chain CDRs and three variable light chain CDRs wherein VH CDR1 is SEQ ID NO:1, VH CDR2 is SEQ ID NO:2, VH CDR3 is SEQ ID NO:3 and wherein VL CDR1 is SEQ ID NO:4, VL CDR2 is SEQ ID NO:5, VL CDR3 is SEQ ID NO:6. A further alternative that is contemplated is an anti-ETBR antibody has a variable heavy chain and a variable light chain, wherein said VH is SEQ ID NO:7 or 9. In yet another alternative, an anti-ETBR antibody has a variable heavy chain and a variable light chain, wherein said VH is SEQ ID NO:7 or 9 and the VL is SEQ ID NO:8. In another ~~aspect~~embodiment of the use of the article of manufacture, the anti-ETBR antibody is conjugated to a cytotoxin, wherein said cytotoxin is cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic

enzymes. In one further ~~aspect~~embodiment, the cytotoxin is a toxin wherein said toxin is selected from the group consisting of maytansinoid, calicheamicin and auristatin. In one ~~aspect~~embodiment, the toxin is a maytansinoid.

[0035] In one ~~aspect~~embodiment of the use of the article of manufacture described above, it is also contemplated that the MAP kinase inhibitor is a BRAF inhibitor. In yet another ~~aspect~~embodiment of the use of the article of manufacture described above, the BRAF inhibitor is propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide. Further, it is contemplated that the BRAF inhibitor has the following chemical structure:



[0036] In another ~~aspect~~embodiment of the use of the article of manufacture described above, the MAP kinase inhibitor is a MEK inhibitor. In yet another ~~aspect~~embodiment of the use of the article of manufacture described above, the MEK inhibitor is (S)-(3,4-difuoro-2-((2-fluoro-4-iodophenyl)amino)phenyl)(3-hydoxy-3-(piperidin-2yl)azetidin-1-yl)methanone. In still another ~~aspect~~embodiment of the use of the article of manufacture described above, the MEK inhibitor has the following chemical structure:



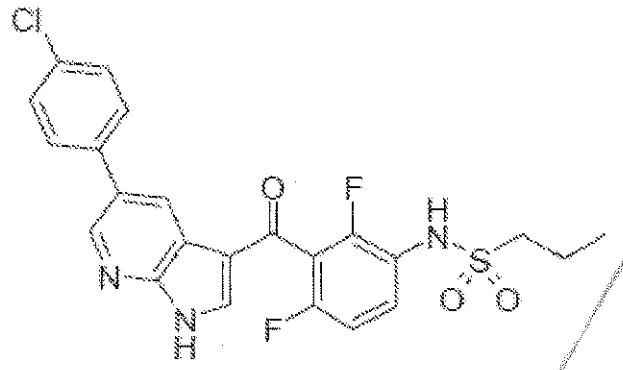
BRIEF DESCRIPTION OF THE FIGURES

[0037] Figure 1 is a schematic of the MAP kinase pathway.

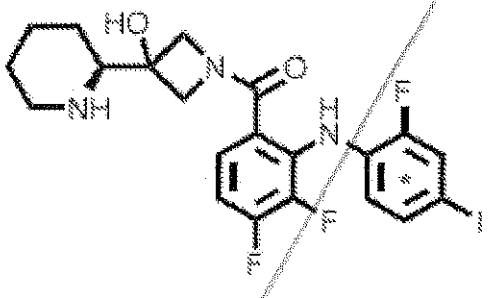
[0038] Figure 2 demonstrates the relationship of receptor level to ADC cell killing *in vitro*. The indicated number of receptor copies/cell was estimated by Scatchard analysis. Panel A shows cell killing by anti-ET_BR ADC titration for the melanoma cell line UACC-257X2.2 and panel B for melanoma cell line A2058. The indicated concentrations of anti-ET_BR ADC (Hu5E9v1-vc-MMAE), control IgG-vc-

WHAT IS CLAIMED IS:

1. A method of tumor growth inhibition (TGI) in a subject suffering from melanoma comprising administering to the subject an effective amount of an anti-endothelin B receptor (ETBR) antibody in combination with an effective amount of a MAP kinase inhibitor.
2. The method of claim 1, wherein said combination is synergistic.
3. The method of claim 1, wherein said TGI is greater than the TGI seen using an anti-ETBR antibody alone.
4. The method of claim 1, wherein said TGI is greater than the TGI seen using a MAP kinase inhibitor alone.
5. The method of claim 3, wherein the TGI is about 10% greater, or about 15% greater, or about 20% greater, or about 25% greater, or about 30% greater, or about 35% greater, or about 40% greater, or about 45% greater, or about 50% greater, or about 55% greater, or about 60% greater, or about 65% greater, or about 70% greater than use of an anti-ETBR antibody alone.
6. The method of claim 4, wherein the TGI is about 10% greater, or about 15% greater, or about 20% greater, or about 25% greater, or about 30% greater, or about 35% greater, or about 40% greater, or about 45% greater, or about 50% greater, or about 55% greater, or about 60% greater, or about 65% greater, or about 70% greater than use of a MAP kinase inhibitor alone.
7. The method of claim 1, wherein said anti-ETBR antibody specifically binds an ETBR epitope consisting of amino acids number 64 to 101 of SEQ ID NO:10.
8. The method of claim 1, wherein said anti-ETBR antibody has three variable heavy chain CDRs and three variable light chain CDRs wherein VH CDR1 is SEQ ID NO:1, VH CDR2 is SEQ ID NO:2, VH CDR3 is SEQ ID NO:3 and wherein VL CDR1 is SEQ ID NO:4, VL CDR2 is SEQ ID NO:5, VL CDR3 is SEQ ID NO:6.
9. The method of claim 1, wherein said anti-ETBR antibody has a variable heavy chain and a variable light chain, wherein said VH is SEQ ID NO:7 or 9.
10. The method of claim 9, wherein said VL is SEQ ID NO:8.
11. The method of claim 1, wherein said anti-ETBR antibody is conjugated to a cytotoxin.
12. The method of claim 11, wherein said cytotoxin is cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.
13. The method of claim 12, wherein said cytotoxin is a toxin.
14. The method of claim 13, wherein said toxin is selected from the group consisting of maytansinoid, calicheamicin and auristatin.
15. The method of claim 14, wherein said toxin is a maytansinoid.
16. The method of claim 1, wherein said MAP kinase inhibitor is a BRAF inhibitor.
17. The method of claim 16, wherein said BRAF inhibitor is propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide.
18. The method of claim 16, wherein said BRAF inhibitor has the following chemical structure:

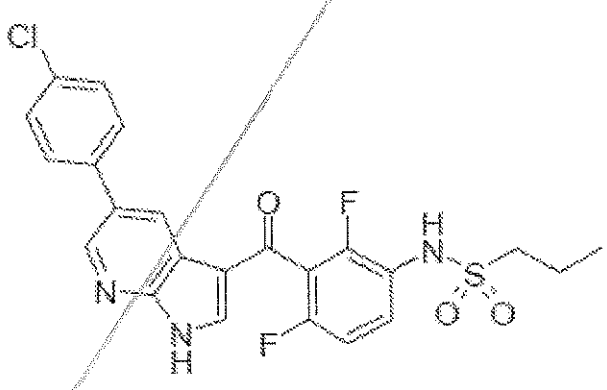


19. The method of claim 1, wherein said MAP kinase inhibitor is a MEK inhibitor.
20. The method of claim 19, wherein said MEK inhibitor is (S)-(3,4-difuoro-2-((2-fluoro-4-iodophenyl)amino)phenyl)(3-hydoxy-3-(piperidin-2yl)azetidin-1-yl)methanone.
21. The method of claim 19, wherein said MEK inhibitor has the following chemical structure:

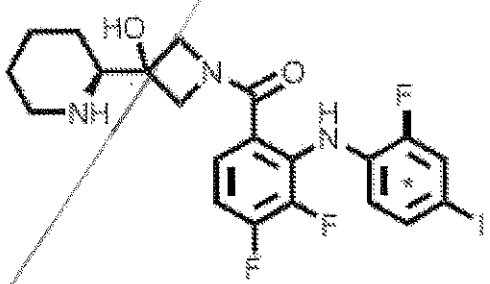


22. A method of treating melanoma comprising administering to a subject in need thereof a therapeutically effective amount of a MAP kinase inhibitor and an anti-ETBR antibody.
23. The method of claim 22, wherein said combination is synergistic.
24. The method of claim 22, wherein said TGI is greater than the TGI seen using an anti-ETBR antibody alone.
25. The method of claim 22, wherein said TGI is greater than the TGI seen using a MAP kinase inhibitor alone.
26. The method of claim 24, wherein the TGI is about 10% greater, or about 15% greater, or about 20% greater, or about 25% greater, or about 30% greater, or about 35% greater, or about 40% greater, or about 45% greater, or about 50% greater, or about 55% greater, or about 60% greater, or about 65% greater, or about 70% greater than use of an anti-ETBR antibody alone.
27. The method of claim 25, wherein the TGI is about 10% greater, or about 15% greater, or about 20% greater, or about 25% greater, or about 30% greater, or about 35% greater, or about 40% greater, or about 45% greater, or about 50% greater, or about 55% greater, or about 60% greater, or about 65% greater, or about 70% greater than use of a MAP kinase inhibitor alone.
28. The method of claim 22, wherein said anti-ETBR antibody specifically binds an ETBR epitope consisting of amino acids number 64 to 101 of SEQ ID NO:10.

29. The method of claim 22, wherein said anti-ETBR antibody has three variable heavy chain CDRs and three variable light chain CDRs wherein VH CDR1 is SEQ ID NO:1, VH CDR2 is SEQ ID NO:2, VH CDR3 is SEQ ID NO:3 and wherein VL CDR1 is SEQ ID NO:4, VL CDR2 is SEQ ID NO:5, VL CDR3 is SEQ ID NO:6.
30. The method of claim 22, wherein said anti-ETBR antibody has a variable heavy chain and a variable light chain, wherein said VH is SEQ ID NO:7 or 9.
31. The method of claim 30, wherein said VL is SEQ ID NO:8.
32. The method of claim 22, wherein said anti-ETBR antibody is conjugated to a cytotoxin.
33. The method of claim 32, wherein said cytotoxin is cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.
34. The method of claim 33, wherein said cytotoxin is a toxin.
35. The method of claim 34, wherein said toxin is selected from the group consisting of maytansinoid, calicheamicin and auristatin.
36. The method of claim 35, wherein said toxin is a maytansinoid.
37. The method of claim 22, wherein said MAP kinase inhibitor is a BRAF inhibitor.
38. The method of claim 37, wherein said BRAF inhibitor is propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide.
39. The method of claim 37, wherein said BRAF inhibitor has the following chemical structure:



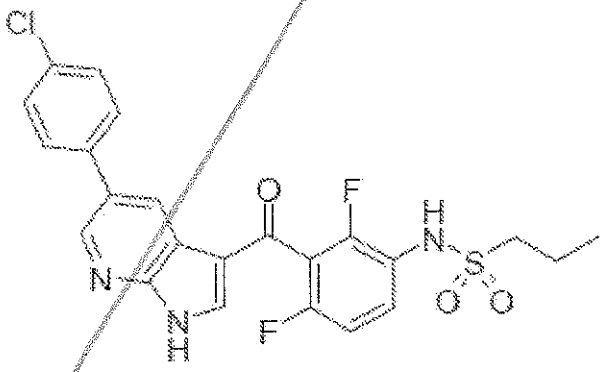
40. The method of claim 22, wherein said MAP kinase inhibitor is a MEK inhibitor.
41. The method of claim 40, wherein said MEK inhibitor is (S)-(3,4-difuoro-2-((2-fluoro-4-iodophenyl)amino)phenyl)(3-hydoxy-3-(piperidin-2yl)azetidin-1-yl)methanone.
42. The method of claim 40, wherein said MEK inhibitor has the following chemical structure:



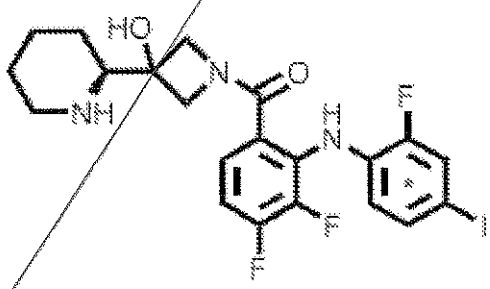
43. The method of claim 22, wherein said melanoma is ETBR positive.

44. The method of claim 22, wherein said melanoma is metastatic.
45. The method of claim 22, wherein said subject has not had prior therapy with a MAP kinase inhibitor.
46. The method of claim 22, wherein said subject has a V600E BRAF gene mutation.
47. The method of claim 22, wherein said subject is V600E wildtype.
48. The method of claim 22, wherein the MAP kinase inhibitor is administered first to said subject in need thereof.
49. The method of claim 22, wherein said anti-ETBR antibody is administered after administration of said MAP kinase inhibitor.
50. The method of claim 22, wherein the anti-ETBR antibody and the MAP kinase inhibitor are administered simultaneously.
51. The method of claim 22, wherein the anti-ETBR antibody and the MAP kinase inhibitor are administered sequentially.
52. The method of claim 51, wherein the anti-ETBR antibody is administered to the subject first.
53. The method of claim 52, wherein the MAP kinase inhibitor is administered to the subject after administration of the anti-ETBR antibody.
54. The method of claim 51, wherein the MAP kinase inhibitor is administered to the subject first.
55. The method of claim 54, wherein the anti-ETBR antibody is administered to the subject after administration of the MAP kinase inhibitor.
56. The method of claim 22, wherein said anti-ETBR antibody is administered intraveneously.
57. The method of claim 22, wherein said anti-ETBR antibody is dosed at about 0.1 mpk, or about 0.2 mpk, or about 0.3 mpk, or about 0.5 mpk, or about 1 mpk, or about 5 mpk, or about 10 mpk, or about 15 mpk, or about 20 mpk, or about 25 mpk, or about 30 mpk.
58. The method of claim 22, wherein the MAP kinase inhibitor is administered orally.
59. The method of claim 22, wherein the MAP kinase inhibitor is dosed at about 1 mpk, or about 2 mpk, or about 3 mpk, or about 4 mpk, or about 5 mpk, or about 6 mpk, or about 7 mpk, or about 8 mpk, or about 9 mpk, or about 10 mpk, or about 11 mpk, or about 12 mpk, or about 15 mpk, or about 20 mpk or about 30 mpk.
60. An article of manufacture for TGI in a subject suffering from melanoma comprising a package comprising an anti-ETBR antibody composition and a MAP kinase inhibitor composition.
61. An article of manufacture for treating melanoma in a subject comprising a package comprising an anti-ETBR antibody composition and a MAP kinase inhibitor composition.
62. The article of manufacture of claim 60 or 61, wherein said anti-ETBR antibody specifically binds an ETBR epitope consisting of amino acids number 64 to 101 of SEQ ID NO:10.
63. The article of manufacture of claim 60 or 61, wherein said anti-ETBR antibody has three variable heavy chain CDRs and three variable light chain CDRs wherein VH CDR1 is SEQ ID NO:1, VH CDR2 is SEQ ID NO:2, VH CDR3 is SEQ ID NO:3 and wherein VL CDR1 is SEQ ID NO:4, VL CDR2 is SEQ ID NO:5, VL CDR3 is SEQ ID NO:6.

64. The article of manufacture of claim 60 or 61, wherein said anti-ETBR antibody has a variable heavy chain and a variable light chain, wherein said VH is SEQ ID NO:7 or 9.
65. The article of manufacture of claim 64, wherein said VL is SEQ ID NO:8.
66. The article of manufacture of claim 60 or 61, wherein said anti-ETBR antibody is conjugated to a cytotoxin.
67. The article of manufacture of claim 66, wherein said cytotoxin is cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.
68. The article of manufacture of claim 67, wherein said cytotoxin is a toxin.
69. The article of manufacture of claim 68, wherein said toxin is selected from the group consisting of maytansinoid, calicheamicin and auristatin.
70. The article of manufacture of claim 69, wherein said toxin is a maytansinoid.
71. The article of manufacture of claim 60 or 61, wherein said MAP kinase inhibitor is a BRAF inhibitor.
72. The article of manufacture of claim 71, wherein said BRAF inhibitor is propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide.
73. The article of manufacture of claim 71, wherein said BRAF inhibitor has the following chemical structure:



74. The article of manufacture of claim 60 or 61, wherein said MAP kinase inhibitor is a MEK inhibitor.
75. The article of manufacture of claim 74, wherein said MEK inhibitor is (S)-(3,4-difuoro-2-((2-fluoro-4-iodophenyl)amino)phenyl)(3-hydoxy-3-(piperidin-2yl)azetidin-1-yl)methanone.
76. The article of manufacture of claim 74, wherein said MEK inhibitor has the following chemical structure:



77. Use of an article of manufacture of claim 60 or 61 in the preparation of a medicament for TGI of a melanoma.

WHAT IS CLAIMED IS:

1. Use of an anti-endothelin B receptor (ETBR) antibody in combination with a MAP kinase inhibitor for the preparation of a medicament for tumor growth inhibition (TGI) in a subject suffering from melanoma.
2. The use of claim 1, selected from a group consisting of:

(a) a use wherein said combination is synergistic,

(b) a use wherein said TGI is greater than the TGI seen using an anti-ETBR antibody alone,

(c) a use wherein said TGI is greater than the TGI seen using a MAP kinase inhibitor alone,

(d) a use wherein said anti-ETBR antibody specifically binds an ETBR epitope consisting of amino acids number 64 to 101 of SEQ ID NO:10,

(e) a use wherein said anti-ETBR antibody has three variable heavy chain CDRs and three variable light chain CDRs wherein VH CDR1 is SEQ ID NO:1, VH CDR2 is SEQ ID NO:2, VH CDR3 is SEQ ID NO:3 and wherein VL CDR1 is SEQ ID NO:4, VL CDR2 is SEQ ID NO:5, VL CDR3 is SEQ ID NO:6,

(f) a use wherein said anti-ETBR antibody has a variable heavy chain and a variable light chain, wherein said VH is SEQ ID NO:7 or 9,

(g) a use wherein said anti-ETBR antibody is conjugated to a cytotoxin,

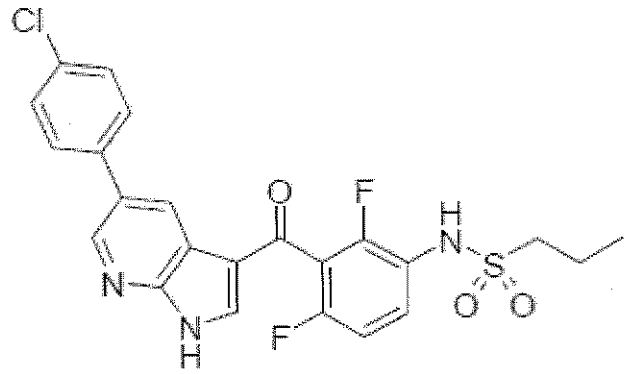
(h) a use wherein said MAP kinase inhibitor is a BRAF inhibitor, and

(i) a use wherein said MAP kinase inhibitor is a MEK inhibitor.

3. The use of claim 2(b), wherein the TGI is about 10% greater, or about 15% greater, or about 20% greater, or about 25% greater, or about 30% greater, or about 35% greater, or about 40% greater, or about 45% greater, or about 50% greater, or about 55% greater, or about 60% greater, or about 65% greater, or about 70% greater than use of an anti-ETBR antibody alone.
4. The use of claim 2(c), wherein the TGI is about 10% greater, or about 15% greater, or about 20% greater, or about 25% greater, or about 30% greater, or about 35% greater, or about 40% greater, or about 45% greater, or about 50% greater, or about 55% greater, or about 60% greater, or about 65% greater, or about 70% greater than use of a MAP kinase inhibitor alone.

5. The use of claim 2(f), wherein said VL is SEQ ID NO:8.
6. The use of claim 2(g), wherein said cytotoxin is cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.
7. The use of claim 6, wherein said cytotoxin is a toxin.
8. The use of claim 7, wherein said toxin is selected from the group consisting of maytansinoid, calicheamicin and auristatin.
9. The use of claim 8, wherein said toxin is a maytansinoid.
10. The use of claim 2(h), selected from a group consisting of:

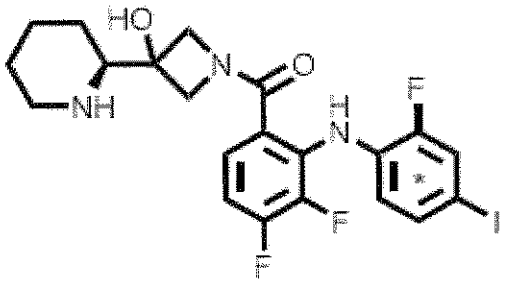
(a) a use wherein said BRAF inhibitor is propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide, and (b) a use wherein said BRAF inhibitor has the following chemical structure:



11. The use of claim 2(i), selected from a group consisting:

(a) a use wherein said MEK inhibitor is (S)-(3,4-difuoro-2-((2-fluoro-4-iodophenyl)amino)phenyl)(3-hydoxy-3-(piperidin-2yl)azetidin-1-yl)methanone, and

(b) a use wherein said MEK inhibitor has the following chemical structure:



12. Use of a MAP kinase inhibitor and an anti-ETBR antibody for the preparation of a medicament for treating melanoma in a subject in need thereof.

13. The use of claim 12, selected from a group consisting of:

(a) a use wherein said combination is synergistic,

(b) a use wherein said TGI is greater than the TGI seen using an anti-ETBR antibody alone,

(c) a use wherein said TGI is greater than the TGI seen using a MAP kinase inhibitor alone,

(d) a use wherein said anti-ETBR antibody specifically binds an ETBR epitope consisting of amino acids number 64 to 101 of SEQ ID NO:10,

(e) a use wherein said anti-ETBR antibody has three variable heavy chain CDRs and three variable light chain CDRs wherein VH CDR1 is SEQ ID NO:1, VH CDR2 is SEQ ID NO:2, VH CDR3 is SEQ ID NO:3 and wherein VL CDR1 is SEQ ID NO:4, VL CDR2 is SEQ ID NO:5, VL CDR3 is SEQ ID NO:6,

(f) a use wherein said anti-ETBR antibody has a variable heavy chain and a variable light chain, wherein said VH is SEQ ID NO:7 or 9,

(g) a use wherein said anti-ETBR antibody is conjugated to a cytotoxin,

(h) a use wherein said MAP kinase inhibitor is a BRAF inhibitor,

(i) a use wherein said MAP kinase inhibitor is a MEK inhibitor,

(j) a use wherein said melanoma is ETBR positive,

(k) a use wherein said melanoma is metastatic,

(l) a use wherein said subject has not had prior therapy with a MAP kinase inhibitor,

(m) a use wherein said subject has a V600E BRAF gene mutation,

(n) a use wherein said subject is V600E wildtype,

(o) a use wherein the MAP kinase inhibitor is to be administered first to said subject in need thereof,

(p) a use wherein said anti-ETBR antibody is to be administered after administration of said MAP kinase inhibitor,

(q) a use wherein the anti-ETBR antibody and the MAP kinase inhibitor are to be administered simultaneously,

(r) a use wherein the anti-ETBR antibody and the MAP kinase inhibitor are to be administered sequentially,

(s) a use wherein said anti-ETBR antibody is to be administered intraveneously,

(t) a use wherein said anti-ETBR antibody is to be dosed at about 0.1 mpk, or about 0.2 mpk, or about 0.3 mpk, or about 0.5 mpk, or about 1 mpk, or about 5 mpk, or about 10 mpk, or about 15 mpk, or about 20 mpk, or about 25 mpk, or about 30 mpk,

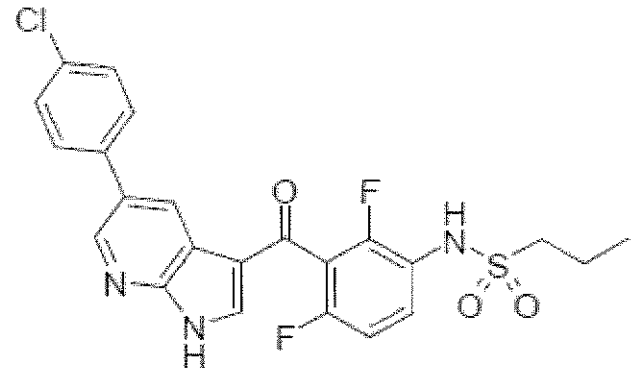
(u) a use wherein the MAP kinase inhibitor is to be administered orally, and

(v) a use wherein the MAP kinase inhibitor is to be dosed at about 1 mpk, or about 2 mpk, or about 3 mpk, or about 4 mpk, or about 5 mpk, or about 6 mpk, or about 7 mpk, or about 8 mpk, or about 9 mpk, or about 10 mpk, or about 11 mpk, or about 12 mpk, or about 15 mpk, or about 20 mpk or about 30 mpk.

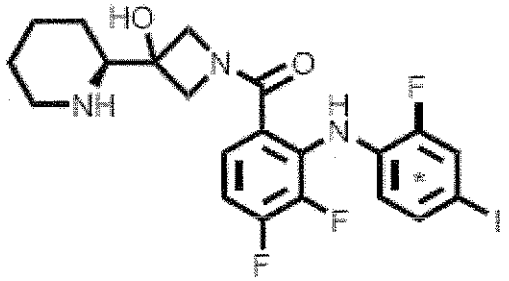
14. The use of claim 13(b), wherein the TGI is about 10% greater, or about 15% greater, or about 20% greater, or about 25% greater, or about 30% greater, or about 35% greater, or about 40% greater, or about 45% greater, or about 50% greater, or about 55% greater, or about 60% greater, or about 65% greater, or about 70% greater than use of an anti-ETBR antibody alone.
15. The use of claim 13(c), wherein the TGI is about 10% greater, or about 15% greater, or about 20% greater, or about 25% greater, or about 30% greater, or about 35% greater, or about 40% greater, or about 45% greater, or about 50% greater, or about 55% greater, or about 60% greater, or about 65% greater, or about 70% greater than use of a MAP kinase inhibitor alone.

16. The use of claim 13(f), wherein said VL is SEQ ID NO:8.
17. The use of claim 13(g), wherein said cytotoxin is cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.
18. The use of claim 17, wherein said cytotoxin is a toxin.

19. The use of claim 18, wherein said toxin is selected from the group consisting of maytansinoid, calicheamicin and auristatin.
20. The use of claim 19, wherein said toxin is a maytansinoid.
21. The use of claim 13(h), selected from a group consisting of:
    a use wherein said BRAF inhibitor is propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide, and
    a use wherein said BRAF inhibitor has the following chemical structure:



22. The use of claim 13(i), selected from a group consisting of:
    (i) a use wherein said MEK inhibitor is (S)-(3,4-difuoro-2-((2-fluoro-4-iodophenyl)amino)phenyl)(3-hydoxy-3-(piperidin-2yl)azetidin-1-yl)methanone, and
    (ii) a use wherein said MEK inhibitor has the following chemical structure:



23. The use of claim 13(r), selected from a group consisting of:
    (i) a use wherein the anti-ETBR antibody is to be administered to the subject first, and
    (ii) a use wherein the MAP kinase inhibitor is to be administered to the subject first.
24. The use of claim 23(i), wherein the MAP kinase inhibitor is to be administered to the subject after administration of the anti-ETBR antibody.
25. The use of claim 23(ii), wherein the anti-ETBR antibody is to be administered to the subject after administration of the MAP kinase inhibitor.
26. An article of manufacture for TGI in a subject suffering from melanoma comprising a package comprising an anti-ETBR antibody composition and a MAP kinase inhibitor composition.
27. An article of manufacture for treating melanoma in a subject comprising a package comprising an anti-ETBR antibody composition and a MAP kinase inhibitor composition.

28. The article of manufacture of claim 26 or 27, selected from a group consisting of:

(a) an article of manufacture wherein said anti-ETBR antibody specifically binds an ETBR epitope consisting of amino acids number 64 to 101 of SEQ ID NO:10,

(b) an article of manufacture wherein said anti-ETBR antibody has three variable heavy chain CDRs and three variable light chain CDRs wherein VH CDR1 is SEQ ID NO:1, VH CDR2 is SEQ ID NO:2, VH CDR3 is SEQ ID NO:3 and wherein VL CDR1 is SEQ ID NO:4, VL CDR2 is SEQ ID NO:5, VL CDR3 is SEQ ID NO:6,

(c) an article of manufacture wherein said anti-ETBR antibody has a variable heavy chain and a variable light chain, wherein said VH is SEQ ID NO:7 or 9,

(d) an article of manufacture wherein said anti-ETBR antibody is conjugated to a cytotoxin,

(e) an article of manufacture wherein said MAP kinase inhibitor is a BRAF inhibitor, and

(f) an article of manufacture, wherein said MAP kinase inhibitor is a MEK inhibitor.

29. The article of manufacture of claim 28(c), wherein said VL is SEQ ID NO:8.

30. The article of manufacture of claim 28(d), wherein said cytotoxin is cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

31. The article of manufacture of claim 30, wherein said cytotoxin is a toxin.

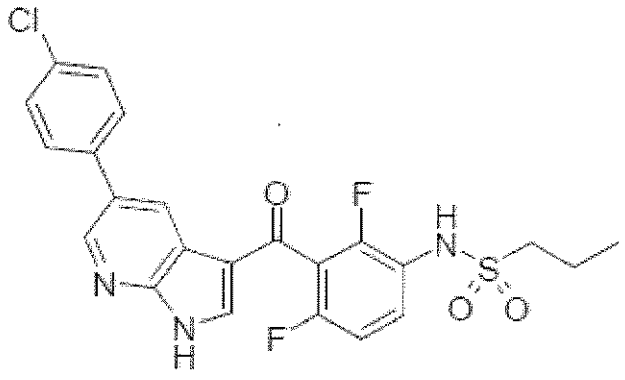
32. The article of manufacture of claim 31, wherein said toxin is selected from the group consisting of maytansinoid, calicheamicin and auristatin.

33. The article of manufacture of claim 32, wherein said toxin is a maytansinoid.

34. The article of manufacture of claim 28(e), selected from a group consisting of:

(i) an article of manufacture wherein said BRAF inhibitor is propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide, and

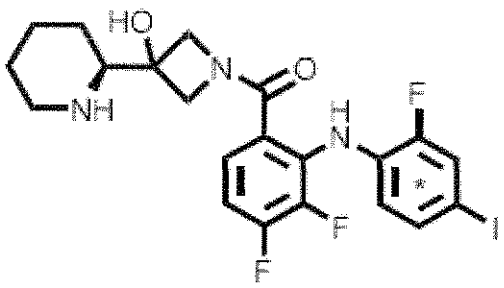
(ii) an article of manufacture wherein said BRAF inhibitor has the following chemical structure:



35. The article of manufacture of claim 28(f), selected from a group consisting of:

(a) an article of manufacture wherein said MEK inhibitor is (S)-(3,4-difuoro-2-((2-fluoro-4-iodophenyl)amino)phenyl)(3-hydoxy-3-(piperidin-2yl)azetidin-1-yl)methanone, and

(b) an article of manufacture wherein said MEK inhibitor has the following chemical structure:



36. Use of an article of manufacture of claim 26 or 27 in the preparation of a medicament for TGI of a melanoma.