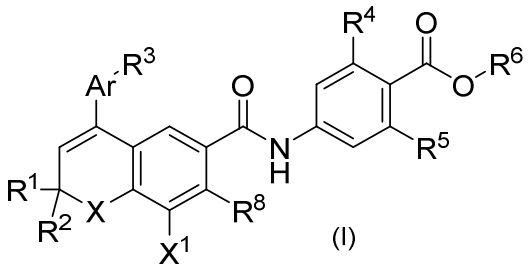
the same treatment session). In still other embodiments, the multiple RAR/RXR active agents are formulated together as a single, common medicament.

[0004a] In one aspect, there is provided a use of at least one retinoid active agent and/or rexinoid active agent (RAR/RXR active agent) in the preparation of a medicament for the treatment of cancer; wherein said medicament to be administered with chimeric antigen receptor (CAR)-modified immune cells.

[0005] In some embodiments, the CAR-modified immune cells are, or comprise, CAR-modified T cells. In some embodiments, the CAR-modified immune cells are, or comprise, CAR-modified NK cells. In some embodiments, the CAR-modified immune cells are, or comprise, CAR-modified NKT cells. In some embodiments, the CAR-modified immune cells are, or comprise, CAR-modified macrophages. Further embodiments can comprise mixtures of these cell types. Most typically such cellular preparations are administered by infusion, for example intravenous infusion. In contrast, the RAR/RXR active agents are small molecules that can be administered orally, for example as pills or capsules and the like. Thus the RAR/RXR active agents and the CAR-modified immune cells may be administered on independent schedules.

[0006] In some embodiments, the retinoid active agent is a RARα antagonist. In some embodiments, the RARα antagonist is a compound of general formula (I):



(I)

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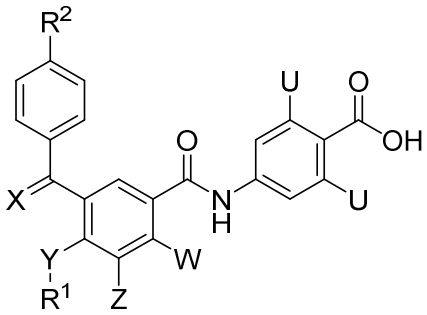
wherein R^1, R^2, R^3, and R^6 are independently H or C_{1-6} alkyl; R^4 and R^5 are independently H or F; Ar is phenyl, pyridyl, thienyl, furyl, or naphthyl; X is $C(CH_3)_2$, O, S, or NR^7, wherein R^7 is H or C_{1-6} alkyl; X^1 is H or halogen such as F, Cl or Br; and R^8 is H or OH.

[0007] In some embodiments, the RARα antagonist is AGN194301, AGN193491, AGN193618, AGN194202, or AGN194574.

[0008] In some embodiments, the RARα antagonist is a compound of general formula (II):



(II)

[0017] In some embodiments, the methods comprise additionally administering at least one cancer chemotherapy agent.

[0018] In some embodiments, the methods comprise administering at least two retinoid active agents. In some embodiments, the two retinoid active agents are a RARα antagonist and a RARɣ agonist.

[0019] In some embodiments, the methods further comprise administering to the subject at least one immune checkpoint inhibitor. In some embodiments, the immune checkpoint inhibitor is an inhibitor of at least one of CTLA-4, PD-1, TIM-3, LAG-3, PD-L1 ligand, B7-H3, B7-H4, BTLA, or is an ICOS, or OX40 agonist. In some embodiments, the immune checkpoint inhibitor is an antibody specific for at least one of CTLA-4, PD-1, TIM-3, LAG-3, PD-L1 ligand, B7-H3, B7-H4, BTLA, ICOS, or OX40.

[0020] Also disclosed herein are methods of prolonging the disease-free survival of a cancer patient comprising administering CAR-modified immune cells and at least one retinoid active agent and/or rexinoid active agent.

[0020a] In another aspect, there is provided a use of at least one retinoid active agent and/or rexinoid active agent in the preparation of a medicament for prolonging the disease-free survival of a cancer patient, wherein the medicament is to be administered with CAR-modified immune cells.

[0021] Also disclosed herein are methods of decreasing toxicity of CAR-modified immune cells comprising administering to a subject in need thereof at least one retinoid active agent and/or rexinoid active agent in combination with the CAR-modified immune cells such that as a result of the combination, a lower dose of CAR-modified immune cells are administered more safely and equally effectively than if the CAR-modified immune cells were administered alone; or that a higher dose of CAR-MIC can be administered with greater efficacy and equal safety.

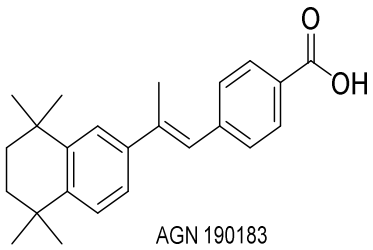
[0021a] In yet another aspect, there is provided a use of at least one retinoid active agent and/or rexinoid active agent in the preparation of a medicament for decreasing the toxicity of CAR modified immune cells, wherein the medicament is to be administered in combination with the CAR-modified immune cells, such that as a result of the combination, a lower dose of CAR-modified immune cells are administered than if the CAR-modified immune cells were administered alone

[0022] Also disclosed herein are methods of expanding the number of CAR-modified immune cells comprising culturing the CAR-modified immune cells in a culture medium

comprising at least one retinoid active agent and/or rexinoid active agent. In some embodiments this is done instead of administering RAR/RXR active agent(s) to the patient. In other embodiments this is done in addition to administering RAR/RXR active agent(s) to the patient. In various embodiments the RAR/RXR active agent(s) used in the CAR-modified immune cell culture and those administered to the patient are different, the same, or one set constitutes a subset of the other.

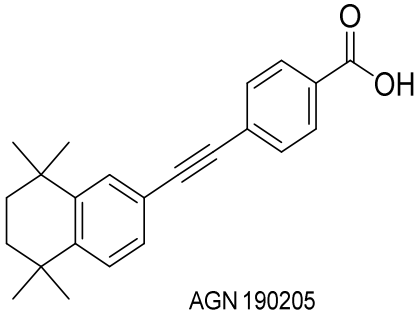
[0023] Also disclosed herein are methods of treating cancer comprising administering to a subject in need thereof, chimeric antigen receptor (CAR)-modified immune cells, at least one retinoid active agent and/or rexinoid active agent, and at least one immune checkpoint inhibitor.

[0023a] In yet another aspect, there is provided a use of, at least one retinoid active agent and/or rexinoid active agent in the preparation of a medicament for the treatment of cancer in a subject, wherein said medicament is to be administered with CAR-modified immune cells and at least one immune checkpoint inhibitor



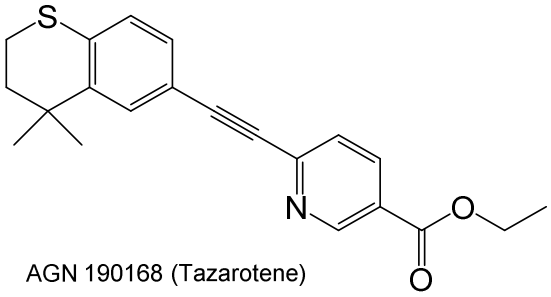
AGN 190183

and



AGN 190205 .

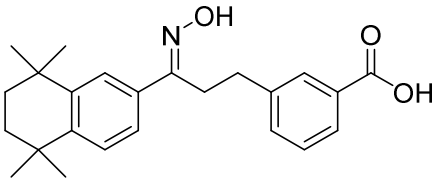
[0050] Another exemplary RARɣ agonist is AGN 190168.



AGN 190168 (Tazarotene)

[0051] Although compounds such as AGN190183, AGN190205, AGN190168 (tazarotene) are RARɣ agonists they are not RARɣ selective since they activate RARα and/or RARβ as well. It may be preferable to use RARɣ selective agonists since activation of RARα may negate the T effector cell activation effects produced by RARɣ activation by increasing production of Treg cells. RARɣ selective agonists, on the other hand, will potentiate the anti-tumor effects of cancer immunotherapeutics.

[0052] An example of a highly selective RARɣ agonist is the compound:



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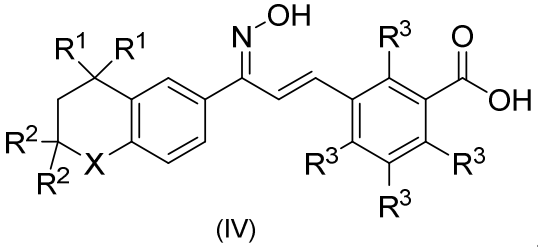
[0053] Other RARɣ selective agonists are members of the family of compounds of general formula (IV):



(IV) ,

What is claimed is:

1. Use of at least one retinoid active agent and/or rexinoid active agent (RAR/RXR active agent) in the preparation of a medicament for the treatment of cancer; wherein said medicament to be administered with chimeric antigen receptor (CAR)-modified immune cells.

2. The use of claim 1, wherein the RAR/RXR active agent comprises a Retinoic Acid Receptor (RAR) active agent.

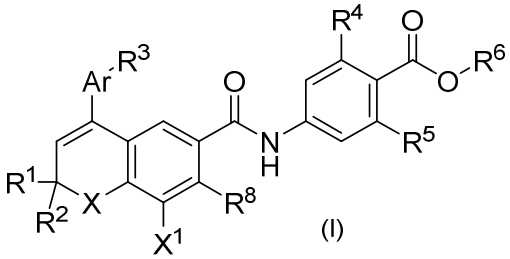
3. The use of claim 1, wherein the RAR/RXR active agent comprises a Retinoid X Receptor (RXR) active agent.

4. The use of claim 2, wherein the RAR active agent is a RARα antagonist.

5. The use of claim 1, wherein two RAR active agents are to be administered.

6. The use of claim 5, wherein a first RAR active agent is a RARα selective antagonist, and a second RAR active agent is a RARɣ agonist.

7. The use of claim 4, wherein the RARα antagonist is a compound of general formula (I)



(I)

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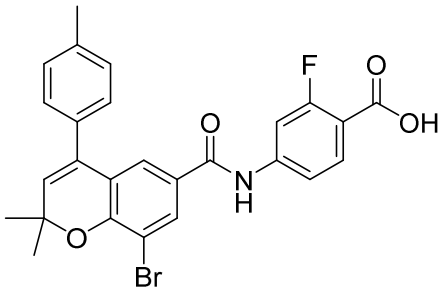
wherein R^1, R^2, R^3, and R^6 are independently H or C_{1-6} alkyl; R^4 and R^5 are independently H or F; Ar is phenyl, pyridyl, thienyl, furyl, or naphthyl; X is $C(CH_3)_2$, O, S, or NR^7, wherein R^7 is H or C_{1-6} alkyl; X^1 is H or halogen such as F, Cl or Br; and R^8 is H or OH.

8. The use of claim 7, wherein the RARα antagonist is:



AGN 194301

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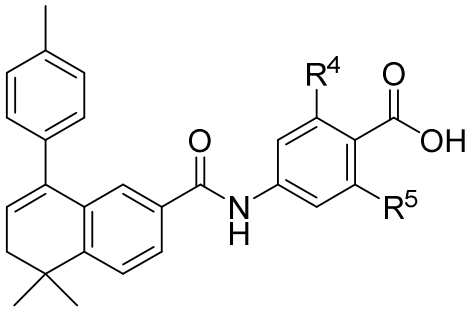
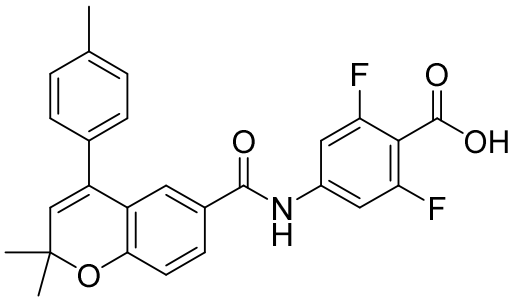


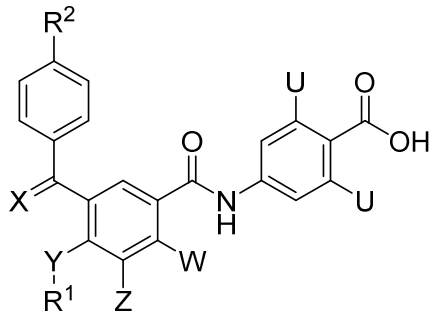
R^4 and R^5 both H; AGN193491
R^4 = F, R^5 = H; AGN193618
R^4 and R^5 both F; AGN194202

, or



AGN 194574

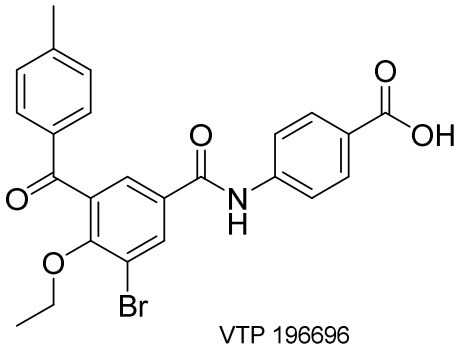
9. The use of claim 4, wherein the RARα antagonist is a compound of general formula (II)



(II)

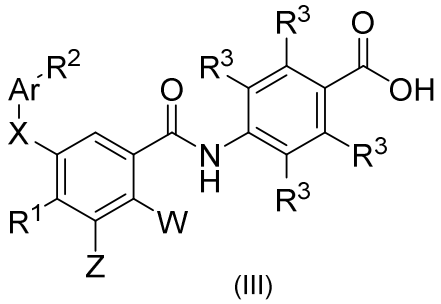
wherein R^1 and R^2 are independently $C_{1\text{-}6}$ alkyl; X is O, S, or CH_2; Y is O, S, CH_2, or NR^3, wherein R^3 is $C_{1\text{-}6}$ alkyl; Z is Cl or Br; W is H or OH; and U is independently H or F.

10. The use of claim 9, wherein the RARα antagonist is:



VTP 196696

11. The use of claim 4, wherein the RARα antagonist is a compound of general formula (III):

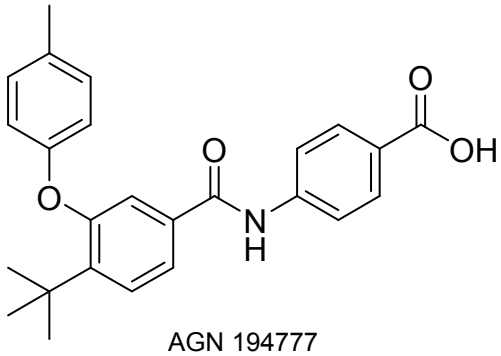


(III)

,

wherein R^1 and R^2 are independently H or C_{1-6} alkyl; R^3 is H or F; Ar is phenyl, pyridyl, thienyl, furyl, or naphthyl; X is O, S, N, or CH_2; W is H or OH; and Z is Cl or Br.

12. The use of claim 4, wherein the RARα antagonist is:

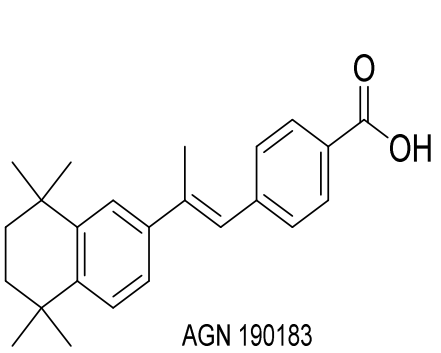


AGN 194777 .

13. The use of claim 4, wherein the RARα antagonist is BMS185411, BMS614, Ro41-5253, or Ro46-5471.

14. The use of claim 2, wherein the RAR active agent is a RARɣ agonist.

15. The use of claim 14, wherein the RARɣ agonist is:



AGN 190183

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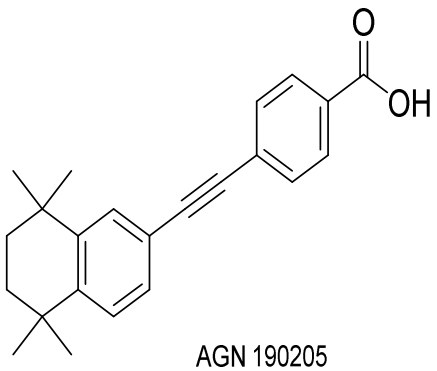
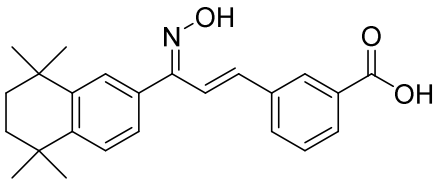
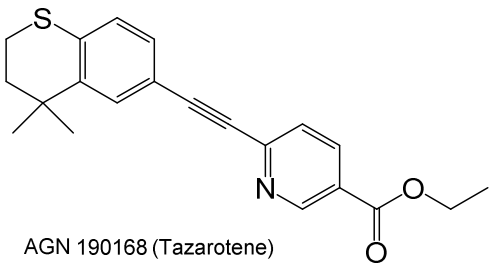


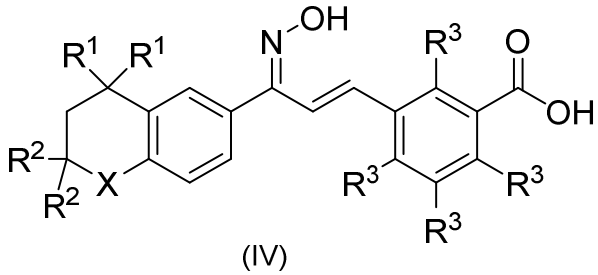
AGN 190205 ,



, or


AGN 190168 (Tazarotene) .

16. The use of claim 14, wherein the RAR agonist is a RARγ selective agonist of general formula IV



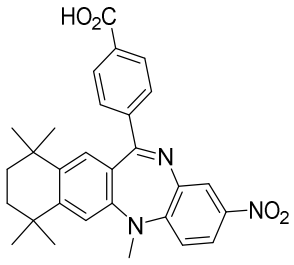
(IV)

wherein R^1 and R^2 are independently H or C_{1-6} alkyl; R^3 is H or F; and X is O, S, CH_2, $C(R^4)_2$, or NR^5, wherein R^4 and R^5 are independently H or C_{1-6} alkyl.

17. The use of claim 14, wherein the RAR agonist is a RARγ selective agonist selected from CD437, CD2325, CD666, and BMS961.

18. The use of claim 3, wherein the RXR active agent is a RXR antagonist.

19. The use of claim 18, wherein the RXR antagonist is selected from



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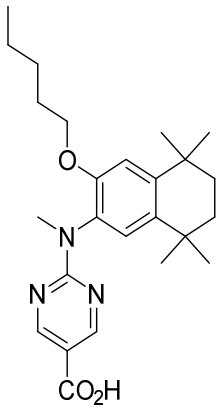
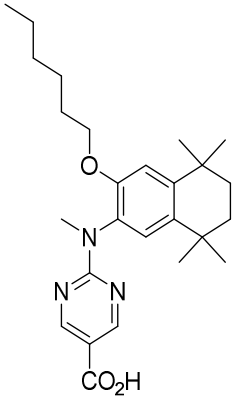
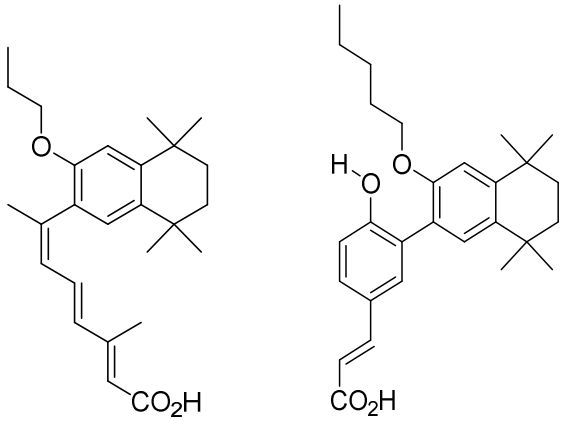


PA 451 ,


PA 452 ,



LG 100754 , or UVI 3003

20. The use of claim 19, wherein the RXR antagonist is AGN195393, or LGN100849.

21. The use of claim 1, wherein the medicament is to be administered with at least one cancer chemotherapy agent.

22. The use of claim 1, wherein the medicament is to be administered with at least one immune checkpoint inhibitor.

23. The use of claim 1, wherein the immune checkpoint inhibitor is an inhibitor of at least one of CTLA-4, PD-1, TIM-3, LAG-3, PD-L1 ligand, B7-H3, B7-H4, BTLA, or is an ICOS, or OX40 agonist.

24. The use of claim 1, wherein the immune checkpoint inhibitor is an antibody specific for at least one of CTLA-4, PD-1, TIM-3, LAG-3, PD-L1 ligand, B7-H3, B7-H4, BTLA, ICOS, or OX40.

25. Use of at least one retinoid active agent and/or rexinoid active agent in the preparation of a medicament for prolonging the disease-free survival of a cancer patient, wherein the medicament is to be administered with CAR-modified immune cells.

26. Use of at least one retinoid active agent and/or rexinoid active agent in the preparation of a medicament for decreasing the toxicity of CAR modified immune cells, wherein the medicament is to be administered in combination with the CAR-modified immune cells, such that as a result of the combination, a lower dose of CAR-modified immune cells are administered than if the CAR-modified immune cells were administered alone.

27. A method of expanding the number of CAR-modified immune cells comprising culturing the CAR-modified immune cells in a culture medium comprising at least one retinoid active agent and/or rexinoid active agent.

28. Use of, at least one retinoid active agent and/or rexinoid active agent in the preparation of a medicament for the treatment of cancer in a subject, wherein said medicament is to be administered with CAR-modified immune cells and at least one immune checkpoint inhibitor .

29. The use of claims 1, 25, 26 or 28, wherein the medicament is to be administered prior to, simultaneously with, or after the CAR modified immune cells.