CLAIMS

1. Use of a composition comprising bacteria of the species *Enterococcus hirae* and bacteria selected from the group consisting of *Akkermansia muciniphila,* ~~*Alistipes shahii, Barnesiella intestinihominis,*~~ *Christensenella minuta* and mixtures thereof, in the manufacture of a medicament in the form of an immunostimulating anti-cancer agent, for the treatment of cancer amenable to treatment by PD1 blockade, in combination with an anti-PD1/PD-L1/PD-L2 Ab-based therapy.

2. The use of claim 1, wherein the composition further comprises bacteria of at least one species selected from the group consisting of *Barnesiella intestinihominis, Alistipes shahii*~~species~~, *Eubacterium* species, *Ruminococcacae, Clostridiales* species, *Bacteroidales* species*, Actinobacteria, Coriobacteriales* species and *Methanobrevibacter smithii*.

3. The use of claim 1 or claim 2, wherein the composition comprises bacteria of the species *Enterococcus hirae* and *Akkermansia muciniphila.*

4. The use of any of claims 1 to 3, wherein said composition further comprises bacteria of the species *Burkholderia cepacia* and/or *Bacteroides fragilis* and/or *Actinotignum schaalii* and/or *Alistipes indistinctus* and/or *onderdonkii.*

5. The use of any of claims 1 to 4, wherein said composition comprises:

- *Clostridiales* bacteria of the species *Christensenella minuta*; and/or
- *Erysipelotrichia* of the species *Dielma fastidiosa or Erysipelatoclostridium ramosum*; and/or
- *Alistipes* bacteria of species selected from the group consisting of *Alistipes shahii, Alistipes indistinctus, Alistipes onderdonkii* and *Alistipes finegoldii*; and/or
- *Eubacterium* bacteria of the species *Eubacterium limosum*; and/or
- *Bacteroidales* bacteria of the species *Bacteroides salyersiae* and/or *Barnesiella intestinihominis*; and/or
- *Actinobacteria* of the species *Actinotignum schaalii;* and/or

- *Coriobacteriales bacteria* of the species *Collinsella intestinalis* and/or *Collinsella tanakaei*; and/or
- *Firmicutes bacteria* of the species *Flavonifractor plautii.*

6. The use of any of claims 1 to 5, wherein said composition comprises:
(i) *Enterococcus hirae* selected from the group consisting of *Enterococcus hirae* strain 13144 deposited on November 7, 2013 at the *Collection Nationale de Cultures de Microorganismes* (CNCM) under the number I-4815, *Enterococcus hirae* strain IGR7 deposited on August 31, 2017 at the CNCM under the number I-5224, *Enterococcus hirae* strain IGR4 deposited on November 27, 2017 at the CNCM under the number CNCM I-5260, *Enterococcus hirae* strain IGR11 deposited on November 27, 2017 at the CNCM under the number CNCM I-5261 and mixtures thereof; and
(ii) *Akkermansia muciniphila* selected from the group consisting of *Akkermansia muciniphila* strains p2261 and p3415, both deposited at the *Collection de souches de l'Unité des Rickettsies* (CSUR) and mixtures thereof; and
(iii) *Eubacterium limosum.*

7. The use of any of claims 1 to 5, wherein said composition comprises:
(i) *Enterococcus hirae* selected from the group consisting of *Enterococcus hirae* strain 13144 deposited on November 7, 2013 at the *Collection Nationale de Cultures de Microorganismes* (CNCM) under the number I-4815, *Enterococcus hirae* strain IGR7 deposited on August 31, 2017 at the CNCM under the number I-5224, *Enterococcus hirae* strain IGR4 deposited on November 27, 2017 at the CNCM under the number CNCM I-5260, *Enterococcus hirae* strain IGR11 deposited on November 27, 2017 at the CNCM under the number CNCM I-5261 and mixtures thereof; and
(ii) *Barnesiella intestinihominis.*

8. The use of any of claims 1 to 5, wherein said composition comprises:
(i) *Enterococcus hirae* selected from the group consisting of *Enterococcus hirae* strain 13144 deposited on November 7, 2013 at the *Collection Nationale de Cultures de Microorganismes* (CNCM) under the number I-4815, *Enterococcus hirae* strain IGR7 deposited on August 31, 2017 at the CNCM under the number

I-5224, *Enterococcus hirae* strain IGR4 deposited on November 27, 2017 at the CNCM under the number CNCM I-5260, *Enterococcus hirae* strain IGR11 deposited on November 27, 2017 at the CNCM under the number CNCM I-5261 and mixtures thereof; and

(ii) *Christensenella minuta.*

9. The use of any of claims 1 to 8, wherein the medicament is for compensating dysbiosis in a cancer patient.

10. The use of any of claim 1 to 9, wherein the medicament is for an individual who is to be treated with anti-PD1 and anti-CTLA4 coblockade or with anti-PD-L2 and anti-CTLA4 coblockade.

~~11. Use of a composition as described in any of claims 1 to 9, for the manufacture of a medicament for preventing a cancer relapse.~~

~~12.~~11. Use of a composition as described in ~~any of claims 1 to 9~~claim 3, for the manufacture of a medicament for decreasing or preventing gut toxicity of an anti-PD1/PD-L1/PD-L2 Ab-based therapy and/or an anti-CTLA-4 Ab-based therapy.

~~13.~~12. Use of a fecal microbial composition comprising *Akkermansia muciniphila* and *Enterococcus hirae* and further comprising bacterial species selected from the group consisting of *Clostridiales* species, *Alistipes* species, *Eubacterium* species, *Bacteroidales* species and *Methanobrevibacter smithii,* in the manufacture of an agent for treating a cancer, in combination with an anti-PD1/PD-L1/PD-L2 Ab-based therapy.

~~14.~~13. The use of claim ~~13~~12, wherein said composition has been enriched with a composition as described in any of claims 1 to 9.

~~15. A theranostic method for determining if a cancer patient needs a bacterial compensation before administration of an anti-PD1/PD-L1/PD-L2 Ab-based therapy, comprising assessing, in a feces sample from said patient, the presence of bacteria from one or several species selected from the group consisting of *Akkermansia muciniphila*, *Enterococcus hirae* and *Dielma fastidiosa* wherein if any one of *Akkermansia muciniphila Enterococcus hirae* and *Dielma*~~

~~*fastidiosa* is absent from said feces sample, the patient needs a bacterial compensation with the composition as described in any of claims 1 to 9 or with the fecal microbial composition as described in claim 13 or claim 14.~~

~~16. A theranostic method for determining if a cancer patient needs a bacterial compensation before administration of an anti-PD1/PD-L1/PD-L2 Ab-based therapy, comprising assessing, in a feces sample from said patient, the presence of *Ruminococcus sp.* CAG:353, *Ruminococcus bacterium* LM158, *Ruminococcus torques 2* and *Ruminococcaceae bacterium* D16, wherein if none of *Ruminococcus sp.* CAG:353, *Ruminococcus bacterium* LM158, *Ruminococcus torques 2* and *Ruminococcaceae bacterium* D16 is present in said feces sample, the patient needs a bacterial compensation with the composition as described in any of claims 1 to 9 or with the fecal microbial composition as described in claim 13 or claim 14.~~

~~17. A theranostic method for determining if a cancer patient needs a bacterial compensation before administration of an anti-PD1/PD-L1/PD-L2 Ab-based therapy, comprising assessing, in a feces sample from said patient, the presence of *Alistipes sp*. CAG:435, *Alistipes sp*. CAG:514, *Alistipes indistinctus* CAG328 and *Alistipes sp*. CAG/268, wherein if none of *Alistipes sp*. CAG:435, *Alistipes sp*. CAG:514, *Alistipes indistinctus* CAG328 and *Alistipes sp*. CAG/268 is present in said feces sample, the patient needs a bacterial compensation with the composition as described inany of claims 1 to 9 or with the fecal microbial composition as described in claim 13 or claim 14.~~

~~18. A theranostic method for determining if a cancer patient needs a bacterial compensation before administration of an anti-PD1/PD-L1/PD-L2 Ab-based therapy, comprising assessing, in a feces sample from said patient, the presence of *Bacteroides xylanosolvens CAG945, Bacteroides uniformis CAG159, Bacteroides ovatus CAG1165, Prevotella CAG :255, CAG163, Ruminococcus bromii CAG611, Roseburia intestinalis CAG291* and *Eubacterium CAG :38, CAG 629*, wherein if *Bacteroides xylanosolvens CAG945, Bacteroides uniformis CAG159, Bacteroides ovatus CAG1165, Prevotella CAG :255, CAG163, Ruminococcus bromii CAG611, Roseburia intestinalis CAG291* or *Eubacterium CAG :38, CAG 629* are present in said feces sample, the patient needs a bacterial compensation with the composition as described inany of

~~claims 1 to 9 or with the fecal microbial composition as described in claim 13 or claim 14.~~

~~19. A theranostic method for determining if a cancer patient needs a bacterial compensation before administration of an anti-PD1/PD-L1/PD-L2 Ab-based therapy, comprising assessing, in a feces sample from said patient, the presence of short chain fatty acid producing *Clostridiaceae* selected from the group consisting *Eubacterium*, *Blautia* and *Roseburia*, wherein the absence of *Eubacterium*, *Blautia* and/or *Roseburia* from said feces sample indicates that the patient needs a bacterial compensation with *Enterococcus hirae* and/or *Akkermansia muciniphila* or with the composition as described inany of claims 1 to 9 or with the fecal microbial composition as described in claim 13 or claim 14.~~

~~20. An *in vitro* theranostic method of determining if a cancer patient is likely to be a good responder to an anti-PD1/PD-L1/PD-L2 Ab-based therapy, comprising assessing, in a feces sample from said patient, the presence of the microorganisms disclosed in Table 1a and Table 2a, wherein the presence of microorganisms disclosed in Table 1a and the absence of microorganisms disclosed in Table 2a are indicative that the patient is likely to be a good responder to the anti-PD1/PD-L1/PD-L2 Ab-based therapy, and wherein the absence of microorganisms disclosed in Table 1a and the presence of microorganisms disclosed in Table 2a are indicative that the patient is likely to be resistant to the anti-PD1/PD-L1/PD-L2 Ab-based therapy.~~

~~21. The method of claim 20, further comprising assessing the presence of additional microorganisms disclosed in Table 1 and Table 2, wherein the presence of microorganisms disclosed in Table 1 and the absence of microorganisms disclosed in Table 2 are indicative that the patient is likely to be a good responder to the anti-PD1/PD-L1/PD-L2 Ab-based therapy, and wherein the absence of microorganisms disclosed in Table 1 and the presence of microorganisms disclosed in Table 2 are indicative that the patient is likely to be resistant to the anti-PD1/PD-L1/PD-L2 Ab-based therapy.~~

~~22. The method of claim 20 or claim 21, wherein the presence of *all the microorganisms disclosed in Table 1 and in Table 2* are assessed.~~

23. The method of any of claims 20 to 22, for determining if a cancer patient is likely to be a good responder to an anti-PD1/PD-L1/PD-L2 Ab-based therapy alone or in combination with anti-CTLA4 Ab or IDO inhibitors or other immunomodulators.

24. The method of any of claims 20 to 23, wherein the patient already received an anti-PD1/PD-L1/PD-L2 antibody.

25. Use of a nucleic acid microarray to perform the method according to any of claims 20 to 24, wherein said nucleic acid microarray comprises nucleic acid probes specific for each of the microorganism species to be detected in said method.

26. Use of a set of primers for performing the method according to any of claims 20 to 25, wherein said set of primers comprises primer pairs for amplifying sequences specific for each of the microorganism species to be detected in said method.

27. An *in vitro* method for assessing whether a cancer patient has a dysbiosis associated with cancer, comprising assessing, in a feces sample from said patient, the presence of *Faecalibacterium* CAG297, *Blautia* CAG179, *Roseburia* CAG55, *Haemophila parainfluenzae* CAG1056, *Clostridiales* CAG1132, *Bifidobacterium adolescentis*, *Firmicutes* CAG1308, *Firmicutes bacterium* CAG713, *Bifidobacterium dentium*, *Enterococcus faecalis*, *Subdoligranulum* CAG140, *Lachnospiricaeae bacterium* CAG14, *Clostridium innocuum* CAG36, *Ruminococcus torques 1*, *Hungatella hathewayi 1* CAG25, *E.coli* CAG 11, *E.coli* CAG 371, *Clostridiales* CAG533 and *Tyzzerella nexilis* CAG311, wherein:

- the presence of *Bifidobacterium dentium*, *Enterococcus faecalis*, *Subdoligranulum* CAG140, *Lachnospiricaeae bacterium* CAG14, *Clostridium innocuum* CAG36, *Ruminococcus torques 1*, *Hungatella hathewayi 1* CAG25, *E.coli* CAG 11, *E.coli* CAG 371, *Clostridiales* CAG533 and *Tyzzerella nexilis* CAG311 and
- the absence of *Faecalibacterium* CAG297, *Blautia* CAG179, *Roseburia* CAG55, *Haemophila parainfluenzae* CAG1056, *Clostridiales* CAG1132, *Bifidobacterium adolescentis*, *Firmicutes* CAG1308 and *Firmicutes bacterium* CAG713

are indicative that the patient has a dysbiosis associated with cancer.

28. A method for predicting relapse in a patient who is treated or who has been treated for a cancer, comprising assessing, in feces samples from said patient obtained at different time-points, the presence of *Faecalibacterium* CAG297, *Blautia* CAG179, *Roseburia* CAG55, *Haemophila parainfluenzae* CAG1056, *Clostridiales* CAG1132, *Bifidobacterium adolescentis*, *Firmicutes* CAG1308, *Firmicutes bacterium* CAG713, *Bifidobacterium dentium*, *Enterococcus faecalis*, *Subdoligranulum* CAG140, *Lachnospiricaeae bacterium* CAG14, *Clostridium innocuum* CAG36, *Ruminococcus torques 1*, *Hungatella hathewayi 1* CAG25, *E.coli* CAG 11, *E.coli* CAG 371, *Clostridiales* CAG533 and *Tyzzerella nexilis* CAG311, wherein:

- an increase of *Bifidobacterium dentium*, *Enterococcus faecalis*, *Subdoligranulum* CAG140, *Lachnospiricaeae bacterium* CAG14, *Clostridium innocuum* CAG36, *Ruminococcus torques 1*, *Hungatella hathewayi 1* CAG25, *E.coli* CAG 11, *E.coli* CAG 371, *Clostridiales* CAG533 and *Tyzzerella nexilis* CAG311 and
- a decrease of *Faecalibacterium* CAG297, *Blautia* CAG179, *Roseburia* CAG55, *Haemophila parainfluenzae* CAG1056, *Clostridiales* CAG1132, *Bifidobacterium adolescentis*, *Firmicutes* CAG1308 and *Firmicutes bacterium* CAG713

are indicative that the patient is likely to relapse.

29. A method for *ex vivo* determining whether a cancer patient is likely to benefit from a treatment with an anti-PD1/PD-L1/PD-L2 Ab-based therapy, comprising assessing the presence of memory Th1 or Tc1 cells towards *Burkholderia cepacia, Enterococcus hirae* and/or *Bacteroides fragilis* in a blood sample from said patient, wherein the presence of memory Th1 or Tc1 cells towards *Burkholderia cepacia* and/or *Enterococcus hirae* indicates that the patient is likely to be a good responder to said treatment, and/or the presence of memory Th1 cells towards *Bacteroides fragilis* indicates that the patient is likely to be a poor responder.

30. A method for *ex vivo* determining whether a cancer patient is likely to benefit from a treatment with an anti-PD1/PD-L1/PD-L2 Ab-based therapy, comprising assessing the presence of memory Th1 or Tr1 cells towards *Akkermansia muciniphila* in a blood sample from said patient, wherein the presence of memory CD4+ Th1 or CD8+ Tc1 (IFNg producing) or CD4+ Tr1 cells

(IL-10 producing) towards *Akkermansia muciniphila* indicates that the patient is likely to be a good responder to said treatment.

31. A method for assessing if a cancer patient who is treated with an anti-PD1/PD-L1/PD-L2 Ab-based therapy is a good responder to said treatment, comprising the following steps:

(i) assessing, in a feces sample from said patient obtained at the beginning of the treatment, the presence or the relative abundance of *Bacteroides xylanosolvens CAG945, Bacteroides uniformis CAG159, Bacteroides ovatus CAG1165, Prevotella CAG :255, CAG163, Ruminococcus bromii CAG611, Roseburia intestinalis CAG291, Eubacterium CAG :38, CAG 629, Ruminococaeae CAG1003, Flavonifractor plautii CAG 439* and *Firmicutes bacterium CAG : 124, CAG 629*;

(ii) assessing, in a feces sample from said patient obtained after three or four administrations of the anti-PD1/PD-L1/PD-L2 Ab, the presence or the relative abundance of the same species as in step (i),

wherein:

- a decrease or complete loss of *Bacteroides xylanosolvens CAG945, Bacteroides uniformis CAG159, Bacteroides ovatus CAG1165, Prevotella CAG :255, CAG163, Ruminococcus bromii CAG611, Roseburia intestinalis CAG291* and *Eubacterium CAG :38, CAG 629*

- and/or in increase or gain of *Ruminococaeae CAG1003, Flavonifractor plautii CAG 439* and *Firmicutes bacterium CAG : 124, CAG 629*

indicate that the patient is a good responder to the treatment.

32. Use of an immunogenic composition comprising fragments of *Akkermansia muciniphila* and *Enterococcus hirae*, in the manufacture of a medicament in the form of an immunostimulating anti-cancer agent, for the treatment of cancer in combination with an anti-PD1/PD-L1/PD-L2 Ab-based therapy .

33. The use of claim 30, wherein the immunogenic composition further comprises fragments of bacteria selected from the group consisting of *Firmicutes* species, *Clostridiales* species, *Alistipes* species, *Eubacterium* species, *Bacteroidales* species, *Methanobrevibacter smithii, Bacteroides fragilis* and *Burkholderia cepacia.*