CLAIMS

1. An immunomodulator for use in the treatment, reduction, inhibition or control of cancer in a patient intended to undergo checkpoint inhibition therapy, wherein thecheckpoint inhibition therapy comprises administration of a blocking agent, selected from a cell, protein, peptide, antibody or antigen binding fragment thereof, directed against CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, B7 -H3, B7-H4, B7-H6, A2AR, or IDO, and combinations thereof, wherein the immunomodulator comprises a whole cell, non-pathogenic heat-killed *Mycobacterium* and wherein the immunomodulator is to be administered simultaneously, separately or sequentially with administration of the checkpoint inhibition therapy .

2. Use of an immunomodulator in the manufacture of a medicament for the treatment, reduction, inhibition or control of cancer in a patient intended to undergo checkpoint inhibition therapy, wherein the checkpoint inhibition therapy comprises administration of a blocking agent, selected from a cell, protein, peptide, antibody or antigen binding fragment thereof, directed against CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, B7 -H3, B7-H4, B7-H6, A2AR, or IDO, and combinations thereof, wherein the immunomodulator comprises a whole cell, non-pathogenic heat-killed *Mycobacterium* and wherein the immunomodulator is to be administered simultaneously, separately or sequentially with the administration of the checkpoint inhibition therapy.

3. The use according to claim 2, wherein the checkpoint inhibition therapy comprises a sub-therapeutic amount and/or duration of the blocking agent which is to be administered.

4. The use according to claim 2 or claim 3, wherein the blocking agent is selected from a cell, protein, peptide, antibody, or antigen binding fragment thereof, directed against CTLA-4, PD-1, or PD-L1, and combinations thereof.

5. The use according to any one of claims 2-4, wherein the
blocking agent is an antibody selected from ipilimumab, nivolumab, pembrolizumab, azetolizumab, tremelimumab, and combinations thereof.

6. The use according to claim 5, wherein the blocking agent is pembrolizumab and wherein the patient has mismatch-repair deficient tumours associated with the cancer and/or exhibits PD-L1 expression in at least 10%, or 20%, or 30%, or 40%, or 50% or more of tumour cells, as measured using the SP142 immunohistochemistry antibody assay.

7. The use according to claim 5, wherein the blocking agent is ipilimumab and is to be administered intravenously at a dose of 2 mg/kg or less every three weeks, optionally for a maximum of four infusions.

8. The use according to claim 5, wherein the blocking agent is nivolumab and is to be administered intravenously at a dose of at least 3, or 5 or 10 mg/kg or more every four weeks, optionally wherein the patient exhibits PD-L1 expression in at least 1%, 5% or 10% or more of tumour cells, as measured using the SP142 immunohistochemistry antibody assay.

9. The use according to claim 5, wherein the blocking agent is azetolizumab and is to be administered intravenously at a dose of at least 10 or 15 mg/kg or more every three weeks, optionally wherein the patient exhibits PD-L1 expression in at least 1%, 5% or 10% or more of tumour cells and/or tumour infiltrating immune cells selected from B-cells and NK cells, as measured using the SP142 immunohistochemistry antibody assay.

10. The use according to claim 2 or claim 3, wherein the blocking agent is an antibody selected from AMP-224, BMS-986016, MGA-271, and combinations thereof.

11. The use according to claim 10, wherein the blocking agent is BMS-986016 and is to be administered intravenously at a dose of between about 20 mg and about 8000 mg, every two weeks, optionally for a maximum of forty eight infusions.

12. The immunomodulator according to any one of claims 2-11, wherein the cancer selected from prostate cancer, liver cancer, renal cancer, lung cancer, breast cancer, colorectal cancer, breast cancer, pancreatic cancer, brain cancer, hepatocellular cancer, lymphoma, leukemia,

gastric cancer, cervical cancer, ovarian cancer, thyroid cancer, melanoma, carcinoma, head and neck cancer, skin cancer and soft tissue sarcoma.

13. The use according to any one of claims 2-12, wherein the cancer is selected from pancreatic, colorectal, prostate or ovarian cancer.

14. The use according to any one of claims 2-13, wherein cancer is metastatic.

15. The use according to any one of preceding claims 2-14, wherein the whole cell non-pathogenic heat-killed *Mycobacterium* is selected from *M. vaccae, M. obuense, M. parafortuitum, M. aurum, M. indicus pranii, M. phlei* and combinations thereof.

16. The use according to any one of claims 2-15, wherein the non-pathogenic heat-killed *Mycobacterium* is preferentially the rough variant.

17. The use according to any one of claims 2-16, wherein the non-pathogenic heat-killed *Mycobacterium* and/or blocking agent is for administration via the parenteral, oral, sublingual, nasal or pulmonary route.

18. The use according to claim 17, wherein the parenteral route is selected from subcutaneous, intradermal, subdermal, intraperitoneal, or intravenous.

19. The use according to claim 17or claim 18, wherein the parenteral route comprises intratumoural injection.

20. The use according to any one of claims 2-19, wherein
administration of the immunomodulator is prior to and/or after the checkpoint inhibition therapy.

21. Use of:(i) a checkpoint inhibitor, selected from a cell, protein, peptide, antibody or anti-gen binding fragment thereof, directed against CTLA-4, PO-1, PO-L 1, PO-L2, LAG-3, B7 -H3, B7 -H4, B7-H6, A2AR, or IDO, and combinations thereof, and (ii) an immunomodulator, in the

manufacture of a medicament for the treatment, reduction, inhibition or control of aneoplasma, tumour or cancer in a subject wherein the use results in enhanced therapeutic efficacy relative to administration of the checkpoint inhibitor or immunomodulator alone, and wherein the immunomodulator comprises a whole cell, non-pathogenic heat killed *Mycobacterium*.

22. The use according to claim 21, wherein a sub-therapeutic amount of the checkpoint inhibitor is to be administered.

23. The use according to claim 21 or claim 22, wherein the checkpoint inhibitor is selected from a cell, protein, peptide, antibody, or antigen fragment thereof, directed against CTLA-4, PD-1, or PD-L1, and combinations thereof.

24. The use according to any one of claims 21or claim 23, wherein the checkpoint inhibitor is an antibody selected from ipilimumab, nivolumab, pembrolizumab, azetolizumab, tremelimumab, and combinations thereof.

25. The use according to claim 24, wherein the checkpoint inhibitor is pembrolizumab and wherein the patient has mismatch-repair deficient tumours and/or exhibits PD-L1 expression in at least 10%, or 20%, or 30%, or 40%, or 50% or more of tumour cells, as measured using the SP142 immunohistochemistry antibody assay.

26. The use according to claim 24, wherein the checkpoint inhibitor is ipilimumab, and wherein the ipilimumab is to be administered intravenously at a dose of 2 mg/kg or less every three weeks, optionally for a maximum of four infusions.

27. The use according to claim 24, wherein the checkpoint inhibitor is nivolumab, and wherein the nivolumab is to be administered intravenously at a dose of at least 3, or 5 or 10 mg/kg or more every four weeks, optionally wherein the patient exhibits PD-L1 expression in at least 1%, 5% or 10% or more of tumour cells, as measured using the SP142 immunohistochemistry antibody assay.

28. The use according to claim 24, wherein the checkpoint inhibitor is azetolizumamb, and wherein the azetolizumab is to be administered intravenously at a dose of at least 10 or 15 mg/kg or more every three weeks, optionally wherein the patient exhibits PD-L1 expression in at least 1%, 5% or 10% or more of tumour cells and/or tumour-infiltrating immune cells selected from B-cells and NK cells, as measured using the SP142 immunohistochemistry antibody assay.

29. The use according to claim 21 or claim 22, wherein the checkpoint inhibitor is an antibody selected from AMP-224, BMS-986016, MGA-271, and combinations thereof.

30. The use according to claim 29, wherein the checkpoint inhibitor is BMS-986016 and is to be administered intravenously at a dose of between about 20 mg and about 8000 mg, every two weeks, optionally for a maximum of forty eight infusions.

31. The use according to claim 21 or claim 22, wherein the neoplasia, tumour or cancer is associated witl1 a cancer selected from prostate cancer, liver cancer, renal cancer, lung cancer, breast cancer, colorectal cancer, breast cancer, pancreatic cancer, brain cancer, hepatocellular cancer, lymph-oma, leukaemia, gastric cancer, cervical cancer, ovarian cancer, thyroid cancer, melanoma, carcinoma, head and neck cancer, skin cancer and soft tissue sarcoma.

32. The use according to claim 31, wherein the neoplasia, tumour or cancer is associated with pancreatic, colorectal, prostate or ovarian cancer.

33. The use according to claim 21or claim 22 or claim 31or claim 32, wherein the neoplasia, tumour or cancer is metastatic.

34. The use according to claim 21 or claim 22 or any one of claims 31-33, wherein the whole cell, non-pathogenic heat-killed *Mycobacterium* is selected from *M. vaccae, M. obuense, M. parafortui-tum, M. aurum, M. indicus pranii, M. ph lei* and combinations thereof.

35. The use according to claim 21 or claim 22 or any one of claims 31-34, wherein the non-pathogenic heat-killed *Mycobacterium* is the rough variant.

36. The use according to claim 35, wherein the whole cell non-pathogenic heat-killed *Mycobacterium* and/or checkpoint inhibitor is to be administered via the parenteral, oral, sublingual, nasal or pulmonary route.

37. The use according to claim 36, wherein the parenteral route is selected from subcutaneous, intradermal, subdermal, intraperitoneal, or intravenous.

38. The use according to claim 36or claim 37, wherein the parenteral route comprises intra-tumoural injection.

39. The use according to claim 21or claim 22 or any one of claims 31-38, wherein the amount of non-pathogenic heat-killed *Mycobacterium* is to be administered is from 10^7 to 10^9 cells.

40. The use according to claim 21 or claim 22, wherein enhanced therapeutic efficacy is measured by increased overall survival time.

41. The use according to claim 21 or claim 22, wherein enhanced therapeutic efficacy is measured by increased progression-free survival.

42. The use according to claim 21 or claim 22, wherein enhanced therapeutic efficacy is measured by a decrease or stabilisation of tumour size.

43. The use according to claim 21 or claim 22, wherein enhanced therapeutic efficacy is measured by an improved overall response rate and/or increased quality of life.