CLAIMS

1. Use of a primary cell-derived biologic comprising IL-1β, IL-2, IL-6, IL-8, TNF-α, and IFN-γ in the manufacture of a dosage regimen for the treatment of cancer, wherein the primary cell-derived biologic is to be administered with an antagonist of programmed cell death-ligand 1 (PD-L1) or of programmed cell death 1 (PD-1) or of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) in a subject in effective amounts at different locations and/or at different times, wherein the effective amount of the primary cell-derived biologic includes a ratio of IL-1β International Units (IU) to IL-2 IU of 0.45 to 1.37, a ratio of IFN-γ IU to IL-2 IU of 0.19 to 0.39, a ratio of TNF-α IU to IL-2 IU of 0.53 to 1.26, a ratio of IL-6 IU to IL-2 IU of 1.16 to 6.06, and a ratio of IL-8 IU to IL-2 IU of 0.15 to 0.51, and wherein the antagonist is an antibody.

2. The use of claim 1 wherein the primary cell-derived biologic is to be administered prior to the antagonist, or wherein the antagonist is to be administered prior to the primary cell-derived biologic.

3. The use of any one of the preceding claims wherein a further dose of the primary cell-derived biologic is to be administered after the antagonist; or wherein a further dose of the antagonist is to be administered after the primary cell-derived biologic.

4. The use of any one of the preceding claims wherein the primary cell-derived biologic is to be administered subcutaneously or perilymphatically; and wherein the antagonist is to be administered intravenously or orally; and wherein the primary cell-derived biologic is to be administered once a day up to 10 days; and wherein the antagonist of PD-L1 or PD-1 is to be administered once every two to four weeks; and wherein the CTLA-4 antagonist is to be administered once every three to twelve weeks.

5. The use of any one of the preceding claims, wherein the subject is refractory to treatment with the antagonist prior to the administration of the primary cell-derived biologic, and wherein a level of PD-L1 in a tumor of the subject increases after the administration of the primary cell-derived biologic; and wherein a level of CTLA-4 in a tumor of the subject increases after the administration of the primary cell-derived biologic.

6. The use of any one of the preceding claims, wherein the dosage regimen is to be administered to the subject with a chemical inhibitor selected from the group consisting of alkylating agents, antimetabolites, antibiotics, and immunomodulating agents; or with an NSAID selected from the group consisting of indomethacin, ibuprofen, celecoxib, rofecoxib, and combinations thereof; or with zinc.

7. The use of claim 6 wherein the alkylating agent is cyclophosphamide.

8. A method of selecting a subject for treatment, the method comprising the step of determining a level of PD-L1 in a tumor sample obtained from a subject having cancer who has been administered a primary cell-derived biologic comprising IL-1β, IL-2, IL-6, IL-8, TNF-α, and IFN-γ, wherein the effective amount of the primary cell-derived biologic includes a ratio of IL-1β International Units (IU) to IL-2 IU of 0.45 to 1.37, a ratio of IFN-γ IU to IL-2 IU of 0.19 to 0.39, a ratio of TNF-α IU to IL-2 IU of 0.53 to 1.26, a ratio of IL-6 IU to IL-2 IU of 1.16 to 6.06, and a ratio of IL-8 IU to IL-2 IU of 0.15 to 0.51; wherein the treatment comprises an effective amount of an antagonist of PD-L1 or PD-1 to be administered to the subject if the level of PD-L1 in the tumor sample is higher than a threshold level of PD-L1, wherein the threshold level of PD-L1 corresponds to a level in a negative control sample, and wherein the antagonist is an antibody.

9. The method of claim 8 wherein the step of determining comprises the step of performing an assay to detect the level of PD-L1 or the step of performing an immunohistochemistry assay, wherein the threshold level of PD-L1 is partial or complete cell membrane staining in 49% of viable tumor cells in the tumor sample.

10. A method of assessing the likelihood that a subject will be responsive to an antagonist of PD-L1 or PD-1, wherein the subject has a cancer that has been determined to express a first level of PD-L1 that is below a threshold level of PD-L1, wherein the threshold level of PD-L1 corresponds to a level in a negative control sample, the method comprising the step of determining a second level of PD-L1 in a tumor sample obtained from the subject after the administration of a primary cell-derived biologic comprising IL-1β, IL-2, IL-6, IL-8, TNF-α, and IFN-γ to the subject, wherein the effective amount

of the primary cell-derived biologic includes a ratio of IL-1β International Units (IU) to IL-2 IU of 0.45 to 1.37, a ratio of IFN-γ IU to IL-2 IU of 0.19 to 0.39, a ratio of TNF-α IU to IL-2 IU of 0.53 to 1.26, a ratio of IL-6 IU to IL-2 IU of 1.16 to 6.06, and a ratio of IL-8 IU to IL-2 IU of 0.15 to 0.51; wherein a second level of PD-L1 that is above the threshold level of PD-L1 is indicative that the subject will be responsive to the antagonist of PD-L1 or PD-1, and wherein the antagonist is an antibody.

11. The method of claim 10 wherein the step of determining comprises the step of performing an assay to detect the second level of PD-L1 or the step of performing an immunohistochemistry assay, wherein the threshold level of PD-L1 is partial or complete cell membrane staining in 49% of viable tumor cells in the tumor sample.

12. A method of selecting a subject for treatment, the method comprising the step of determining a level of CTLA-4 in a tumor sample obtained from a subject having cancer who has been administered a primary cell-derived biologic comprising IL-1β, IL-2, IL-6, IL-8, TNF-α, and IFN-γ, wherein the effective amount of the primary cell-derived biologic includes a ratio of IL-1β International Units (IU) to IL-2 IU of 0.45 to 1.37, a ratio of IFN-γ IU to IL-2 IU of 0.19 to 0.39, a ratio of TNF-α IU to IL-2 IU of 0.53 to 1.26, a ratio of IL-6 IU to IL-2 IU of 1.16 to 6.06, and a ratio of IL-8 IU to IL-2 IU of 0.15 to 0.51; and wherein the treatment comprises an effective amount of an antagonist of CTLA-4 to be administered to the subject if the level of CTLA-4 in the tumor sample is higher than a threshold level of CTLA-4, wherein the threshold level of CTLA-4 corresponds to a level in a negative control sample, and wherein the antagonist is an antibody.

13. The method of claim 12 wherein the step of determining comprises the step of performing an assay to detect the level of CTLA-4.

14. A method of assessing the likelihood that a subject will be responsive to an antagonist of CTLA-4, wherein the subject has a cancer that has been determined to express a first level of CTLA-4 that is below a threshold level of CTLA-4, wherein the threshold level of CTLA-4 corresponds to a level in a negative control sample, the method comprising the step of determining a second level of CTLA-4 in a tumor sample obtained from the subject after the administration of a primary cell-derived biologic comprising IL-1β,

IL-2, IL-6, IL-8, TNF-α, and IFN-γ to the subject , wherein the effective amount of the primary cell-derived biologic includes a ratio of IL-1β International Units (IU) to IL-2 IU of 0.45 to 1.37, a ratio of IFN-γ IU to IL-2 IU of 0.19 to 0.39, a ratio of TNF-α IU to IL-2 IU of 0.53 to 1.26, a ratio of IL-6 IU to IL-2 IU of 1.16 to 6.06, and a ratio of IL-8 IU to IL-2 IU of 0.15 to 0.51; wherein a second level of CTLA-4 that is above the threshold level of CTLA-4 is indicative that the subject will be responsive to the antagonist of CTLA-4, and wherein the antagonist is an antibody.

15. The method of claim 14 wherein the step of determining comprises the step of performing an assay to detect the second level of CTLA-4.

16. The use of any one of claims 1 to 7, or the method of any one of claims 8 to 15, wherein the antibody is a human or humanized antibody; or wherein the antibody is specific for PD-L1; or wherein the antibody is selected from the group consisting of atezolizumab, durvalumab, BMS-936559, and avelumab; or wherein the antibody is specific for PD-1; or wherein the antibody is selected from the group consisting of nivolumab, pidilizumab, pembrolizumab, MEDI-0680, and REGN2810; or wherein the antibody is selected from a group consisting of ipilimumab and tremelimumab.

17. The use of any one of claims 1 to 7, or the method of any one of claims 8 to 15, wherein the effective amount of the primary cell-derived biologic to be administered to the subject includes at least 1 IU of each of IL-1β, IL-2, IL-6, IL-8, and TNF-α; or wherein the effective amount of the primary cell-derived biologic to be administered to the subject includes 22-657 International Units (IU) or 220-6,700 pcg of IL-1β, 29-478 IU or 1730-28,100 pcg of IL-2, 10-185 IU or 560-10,900 pcg of IFN-γ, 29-600 IU or 580-12,000 pcg of TNF-α, 34-2,895 IU or 260-22,100 pcg of IL-6 and 5-244 IU or 4,610-243,600 of IL-8.

18. The method of any one of claims 9, 11, 13 or 15, wherein the assay is selected from the group consisting of in situ hybridization, RT-qPCR, microarray analysis, multiplexed RNA expression analysis, RNA-seq, an immunohistochemistry assay, flow cytometry, a multiplexed protein assay and a Western blot assay.

19. The method of any one of claims 8 to 11 wherein the level of PD-L1 in the tumor sample is a level of PD-L1 in cell membranes in the tumor sample.

20. The use of any one of claims 1 to 7, or the method of any one of claims 8 to 15, wherein the primary cell-derived biologic further comprises GM-CSF and G-CSF.

21. The use of any one of claims 1 to 7, or the method of any one of claims 8 to 15, wherein the cancer is selected from the group consisting of melanoma, lung cancer (such as non-small-cell lung cancer (NSCLC)), renal cell carcinoma (RCC), prostate cancer, ovarian cancer, colorectal cancer (CRC), kidney cancer, gastric cancer, breast cancer, diffuse large B cell lymphoma (DLBCL), hematological malignancies (e.g., acute myelogenous leukemia (AML), multiple myeloma (MM), chronic lymphocytic leukemia (CLL), Chronic myelogenous leukemia (CML), Hodgkin's lymphoma, non-Hodgkin's lymphoma, B-cell lymphoma, follicular lymphoma, cutaneous T-cell lymphoma), pancreatic cancer, bladder cancer, squamous cell carcinoma of the head and neck, genitourinary cancer, advanced cutaneous squamous cell carcinoma, liver metastases, mesothelioma, gastroesophageal cancer, Merkel cell carcinoma, and urothelial carcinoma.

22. The use of any one of claims 1 to 7 or 16 to 21, wherein the antagonist of PD-L1 or PD-1 is selected from the group consisting of MEDI-0680, REGN2810, atezolizumab, durvalumab, avelumab, and CA-170.