CLAIMS

1. A method of evaluating a subject, e.g., evaluating or monitoring the effectiveness of a CAR-expressing cell therapy in a subject, having a cancer, comprising:

acquiring a value of responder or relapser status to a therapy comprising a CAR-expressing cell population (e.g., a CAR19-expressing cell population) for the subject, wherein said value of responder or relapser status comprises a measure of one, two, three, four, five, six, seven, or more (all) of the following:

(i) the level or activity of CD27 and/or CD45RO- (e.g., CD27+ CD45RO-) immune effector cells, e.g., in a CD4+ or a CD8+ T cell population, in a sample (e.g., an apheresis sample or a manufactured CAR-expressing cell product sample);

(ii) the level or activity of one, two, three, or more (*e.g.*, all) of resting T_{EFF} cells, resting T_{REG} cells, younger T cells (*e.g.*, younger CD4 or CD8 cells, or gamma/delta T cells), or early memory T cells, or a combination thereof, in a sample (e.g., an apheresis sample or a manufactured CAR-expressing cell product sample);

(iii) the level or activity of one, two, three, or more (*e.g.*, all) of activated T_{EFF} cells, activated T_{REG} cells, older T cells (*e.g.*, older CD4 or CD8 cells), or late memory T cells, or a combination thereof, in a sample (e.g., an apheresis sample or a manufactured CAR-expressing cell product sample);

(iv) the level or activity of an immune cell exhaustion marker, *e.g.*, one, two or more immune checkpoint inhibitors (e.g., PD-1, TIM-3 and/or LAG-3) in a sample (e.g., an apheresis sample or a manufactured CAR-expressing cell product sample).

(v) the level or activity of one, two, three, four, five, ten, twenty or more of the biomarkers listed in Table 1A, Table 1B, Table 7A, Table 7B, Table 8, Table 9, Table 10, Table 14 (e.g., CCL20, IL-17a and/or IL-6), Table 16, Table 17, Table 18, Table 20, FIG. 2B, PD-1, LAG-3, TIM-3, CD57, CD27, CD122, CD62L, KLRG1, or a CD19 CAR-expressing cell gene set signature;

(vi) a cytokine level or activity (e.g., quality of cytokine repertoire) in a CAR-expressing cell product sample, e.g., CAR19- expressing cell product sample (e.g., CTL019), wherein the cytokine is chosen from one, two, three, four, five or more (or all) of the cytokines listed in Table 16;

(vii) a transduction efficiency of a CAR-expressing cell in a manufactured CAR-expressing cell product sample; or

(viii) a quantity of CD27+ PD-1- cells in a sample (e.g., an apheresis sample or a CAR-expressing cell product sample, e.g., CAR19- expressing cell product sample (e.g., CTL019)), e.g., a quantity greater than or equal to 1 x 10^7 cells,

wherein said value is indicative of the subject's responsiveness or relapsing status to the CAR-expressing cell therapy, thereby evaluating the subject.

2. The method of claim 1, further comprising arranging for one, two, three, four, five, six, seven, or more (e.g., all) of the following to be carried out:

identifying the subject as a complete responder, partial responder or non-responder, or a relapser or a non-relapser;

the administration of a CAR-expressing cell therapy;

the administration of an altered dosing of a CAR-expressing cell therapy;

the alteration of the schedule or time course of a CAR-expressing cell therapy;

the administration of , e.g., to a non-responder or a partial responder, an additional agent in combination with a CAR-expressing cell therapy, e.g., a checkpoint inhibitor, e.g., a checkpoint inhibitor described herein;

the administration of to a non-responder or partial responder a therapy that increases the number of younger T cells in the subject prior to treatment with a CAR-expressing cell therapy;

the modification of a manufacturing process of a CAR-expressing cell therapy, e.g., enriching for younger T cells prior to introducing a nucleic acid encoding a CAR, or increasing the transduction efficiency, e.g., for a subject identified as a non-responder or a partial responder;

the modification of the CAR-expressing cell product prior to infusion into the patient;

the adjustment of the CAR-expressing cell infusion dose to achieve clinical efficacy;

the administration of an alternative therapy, e.g., for a non-responder or partial responder or relapser;

the administration of an alternative therapy, e.g., for a non-responder or partial responder, e.g., a standard of care for a particular cancer type; or

if the subject is, or is identified as, a non-responder or a relapser, the decrease of the T_{REG} cell population and/or T_{REG} gene signature, e.g., by CD25 depletion, administration of cyclophosphamide, anti-GITR antibody, mTOR inhibitor, or a combination thereof.

3. A CAR-expressing cell therapy, for treating a subject that has been identified as being responsive (e.g., identified as a complete responder, partial responder or a non-relapser) to a therapy comprising a CAR-expressing cell population (e.g., a CAR19-expressing cell population), wherein said identifying comprises a measure of one, two, three, four, five, six, seven, or more (all) of the following:

(i) the level or activity of CD27 and/or CD45RO- (e.g., CD27+ CD45RO-) immune effector cells, e.g., in a CD4+ or a CD8+ T cell population, in a sample (e.g., an apheresis sample or a manufactured CAR-expressing cell product sample);

(ii) the level or activity of one, two, three, or more (*e.g.*, all) of resting T_{EFF} cells, resting T_{REG} cells, younger T cells (*e.g.*, younger CD4 or CD8 cells, or gamma/delta cells), or early memory T cells, or a combination thereof, in a sample (e.g., an apheresis sample or a manufactured CAR-expressing cell product sample);

(iii) the level or activity of one, two, three, or more (*e.g.*, all) of activated T_{EFF} cells, activated T_{REG} cells, older T cells (*e.g.*, older CD4 or CD8 cells), or late memory T cells, or a combination thereof, in a sample (e.g., an apheresis sample or a manufactured CAR-expressing cell product sample);

(iv) the level or activity of an immune cell exhaustion marker, *e.g.*, one, two or more immune checkpoint inhibitors (e.g., PD-1, TIM-3 and/or LAG-3) in a sample (e.g., an apheresis sample or a manufactured CAR-expressing cell product sample);

(v) the level or activity of one, two, three, four, five, ten, twenty or more of the biomarkers listed in Table 1A, Table 1B, Table 7A, Table 7B, Table 8, Table 9, Table 10, Table 14 (e.g., CCL20, IL-17a and/or IL-6), Table 16, Table 17, Table 18, Table 20, FIG. 2B, PD-1, LAG-3, TIM-3, CD57, CD27, CD122, CD62L, KLRG1, or a CD19 CAR-expressing cell gene set signature;

(vi) a cytokine level or activity (e.g., quality of cytokine repertoire) in a CAR-expressing cell product sample, e.g., CAR19- expressing cell product sample (e.g., CTL019), wherein the cytokine is chosen from one, two, three, four, five or more (or all) of the cytokines listed in Table 16; or

(vii) a transduction efficiency of a CAR-expressing cell in a manufactured CAR-expressing cell product sample; or

(viii) a quantity of CD27+ PD-1- cells in a sample (e.g., an apheresis sample or a CAR-expressing cell product sample, e.g., CAR19- expressing cell product sample (e.g., CTL019)), e.g., a quantity greater than or equal to 1×10^7 cells.

4. Use of a CAR-expressing cell therapy in the manufacture of a medicament for the treatment of cancer in a subject

wherein the therapeutically effective dose of a CAR-expressing cell therapy in the form of the medicament is to be administered to the subject, if the subject is identified as being responsive (e.g., identified as a complete responder, partial responder or a non-relapser) to a therapy comprising a CAR-expressing cell population (e.g., a CAR19-expressing cell population), wherein said identifying comprises a measure of one, two, three, four, five, six, seven, or more (all) of the following:

(i) the level or activity of CD27 and/or CD45RO- (e.g., CD27+ CD45RO-) immune effector cells, e.g., in a CD4+ or a CD8+ T cell population, in a sample (e.g., an apheresis sample or a manufactured CAR-expressing cell product sample);

(ii) the level or activity of one, two, three, or more (*e.g.*, all) of resting T_{EFF} cells, resting T_{REG} cells, younger T cells (*e.g.*, younger CD4 or CD8 cells, or gamma/delta cells), or early memory T cells, or a combination thereof, in a sample (e.g., an apheresis sample or a manufactured CAR-expressing cell product sample);

(iii) the level or activity of one, two, three, or more (*e.g.*, all) of activated T_{EFF} cells, activated T_{REG} cells, older T cells (*e.g.*, older CD4 or CD8 cells), or late memory T cells, or a combination thereof, in a sample (e.g., an apheresis sample or a manufactured CAR-expressing cell product sample);

(iv) the level or activity of an immune cell exhaustion marker, *e.g.*, one, two or more immune checkpoint inhibitors (e.g., PD-1, TIM-3 and/or LAG-3) in a sample (e.g., an apheresis sample or a manufactured CAR-expressing cell product sample); (v) the level or activity of one, two, three, four, five, ten, twenty or more of the biomarkers listed in Table 1A, Table 1B, Table 7A, Table 7B, Table 8, Table 9, Table 10, Table 14 (e.g., CCL20, IL-17a and/or IL-6), Table 16, Table 17, Table 18, Table 20, FIG. 2B, PD-1, LAG-3, TIM-3, CD57, CD27, CD122, CD62L, KLRG1, or a CD19 CAR-expressing cell gene set signature;

(vi) a cytokine level or activity (e.g., quality of cytokine repertoire) in a CAR-expressing cell product sample, e.g., CAR19- expressing cell product sample (e.g., CTL019), wherein the cytokine is chosen from one, two, three, four, five or more (or all) of the cytokines listed in Table 16; or

(vii) a transduction efficiency of a CAR-expressing cell in a manufactured CAR-expressing cell product sample; or

(viii) a quantity of CD27+ PD-1- cells in a sample (e.g., an apheresis sample or a CAR-expressing cell product sample, e.g., CAR19- expressing cell product sample (e.g., CTL019)), e.g., a quantity greater than or equal to 1 x 10^7 cells,

thereby treating the subject.

5. Use of a CAR-expressing cell therapy in the manufacture of a medicament for the treatment of cancer in a subject,

wherein one first acquires a value of responder or relapser status to a therapy comprising a CAR-expressing cell population (e.g., a CAR19+ cell population) for the subject, wherein said value of responder or relapser status comprises a measure of one, two, three, four, five, six, seven, or more (all) of the following:

(i) the level or activity of CD27 and/or CD45RO- (e.g., CD27+ CD45RO-) immune effector cells, e.g., in a CD4+ or a CD8+ T cell population in a sample (e.g., an apheresis sample or a manufactured CAR-expressing cell product sample);

(ii) the level or activity of one, two, three, or more (*e.g.*, all) of resting T_{EFF} cells, resting T_{REG} cells, younger T cells (*e.g.*, younger CD4 or CD8 cells, or gamma/delta cells), or early memory T cells, or a combination thereof, in a sample (e.g., an apheresis sample or a manufactured CAR-expressing cell product sample);

(iii) the level or activity of one, two, three, or more (*e.g.*, all) of activated T_{EFF} cells, activated T_{REG} cells, older T cells (*e.g.*, older CD4 or CD8 cells), or late memory T cells, or a combination thereof, in a sample (e.g., an apheresis sample or a manufactured CAR-expressing cell product sample);

(iv) the level or activity of an immune cell exhaustion marker, *e.g.*, one, two or more immune checkpoint inhibitors (e.g., PD-1, TIM-3 and/or LAG-3) in a sample (e.g., an apheresis sample or a manufactured CAR-expressing cell product sample); (v) the level or activity of one, two, three, four, five, ten, twenty or more of the biomarkers listed in Table 1A, Table 1B, Table 7A, Table 7B, Table 8, Table 9, Table 10, Table 14 (e.g., CCL20, IL-17a and/or IL-6), Table 16, Table 17, Table 18, Table 20, FIG. 2B, PD-1, LAG-3, TIM-3, CD57, CD27, CD122, CD62L, KLRG1, or a CD19 CAR-expressing cell gene set signature;

(vi) a cytokine level or activity (e.g., quality of cytokine repertoire) in a CAR-expressing cell product sample, e.g., CAR19- expressing cell product sample (e.g., CTL019), wherein the cytokine is chosen from one, two, three, four, five or more (or all) of the cytokines listed in Table 16; or

(vii) a transduction efficiency of a CAR-expressing cell in a manufactured CAR-expressing cell product sample; or

(viii) a quantity of CD27+ PD-1- cells in a sample (e.g., an apheresis sample or a CAR-expressing cell product sample, e.g., CAR19- expressing cell product sample (e.g., CTL019)), e.g., a quantity greater than or equal to 1 x 10^7 cells, and subsequently,

responsive to said value, arranging for one, two, three, four, five, six, seven, or more (e.g., all) of the following to be carried out:

identifying the subject as a complete responder, partial responder or non-responder, or a relapser or a non-relapser;

the administration of e.g., to a responder or a non-relapser, a CAR-expressing cell therapy;

the administration of an altered dosing of a CAR-expressing cell therapy;

the alteration of the schedule or time course of a CAR-expressing cell therapy;

the administration of, e.g., to a non-responder or a partial responder, an additional agent in combination with a CAR-expressing cell therapy, e.g., a checkpoint inhibitor, e.g., a checkpoint inhibitor described herein;

the administration of to a non-responder or partial responder a therapy that increases the number of younger T cells or naïve T cells in the subject prior to treatment with a CAR-expressing cell therapy;

the modification of a manufacturing process of a CAR-expressing cell therapy, e.g., enriching for younger T cells or naïve T cells prior to introducing a nucleic acid encoding a CAR, or increasing the transduction efficiency, e.g., for a subject identified as a non-responder or a partial responder;

the administration of an alternative therapy, e.g., for a non-responder or partial responder or relapser, e.g., a standard of care for a particular cancer type; or

if the subject is, or is identified as, a non-responder or a relapser, decreasing the T_{REG} cell population and/or T_{REG} gene signature, e.g., by depleting CD25 cells, or administration of cyclophosphamide, an anti-GITR antibody, an mTOR inhibitor, or a combination thereof.

6. The method of claim 1 or 2, the therapy of claim 3 or the use of claim 4 or 5, wherein

(a) the CAR-expressing cell therapy comprises a plurality of CAR-expressing immune effector cells.

(b) the CAR-expressing cell therapy is a CAR19 therapy (e.g., CTL019 therapy);

(c) the measure of one or more of (i)-(viii) is obtained from an apheresis sample acquired from the subject, wherein optionally the apheresis sample is evaluated prior to infusion or re-infusion or

the measure of one or more of (i)-(viii) is obtained from a manufactured CAR-expressing cell product sample, e.g., CAR19- expressing cell product sample (e.g., CTL019), wherein optionally the manufactured CAR-expressing cell product is evaluated prior to infusion or re-infusion;

(d) the subject is evaluated prior to, during, or after receiving the CAR-expressing cell therapy; and/or

(e) the cancer is a hematological cancer.

7. The method, therapy or use of claim 6, wherein the hematological cancer is an ALL or a CLL; and/or

the subject is a human patient.

8. The method of claim 1 or 2 or any one of claims 6-7, the therapy of claim 3 or the use of claim 4 or 5, further comprises identifying the subject as a responder (e.g., a complete or partial responder), a non-responder, a relapser or a non-relapser, based on a measure of one or more of (i)-(viii).

9. The method of claim 1 or 2 or any one of claims 6-8, the therapy of claim 3 or the use of claim 4 or 5, wherein

(a)the measure of one or more of (i)-(viii) evaluates a profile for one or more of gene expression, flow cytometry or protein expression;

(b) the level or activity of a CD8+ T cell is evaluated using a profile or signature indicative of the percentage of CD8+ T cell in the sample;

(c) the level or activity of CD27+ CD45RO- immune effector cells is evaluated using a profile or signature indicative of the percentage of CD27+ CD45RO- immune effector cells in the sample;

(d) the level or activity is evaluated using a profile or gene signature according to one, two, three, four, five, ten, twenty, fifty, sixty, seventy, one hundred or more of a biomarker or gene set listed in Tables 1A, 1B, 3, 4, 5, 6, 7A, 7B, or FIG. 2B;

(e) the biomarker is a secreted or a cell surface biomarker listed in Table 8; and/or

(f) a responder (e.g., a complete responder) has, or is identified as having, a greater level or activity of one, two, or more (all) of GZMK, PPF1BP2, or naïve T cells as compared to a non-responder.

10. The method of claim 1 or 2 or any one of claims 6-9, the therapy of claim 3 or the use of claim 4 or 5, wherein

(a) a non-responder has, or is identified as having, a greater level or activity of one, two, three, four, five, six, seven, or more (e.g., all) of IL22, IL-2RA, IL-21, IRF8, IL8, CCL17, CCL22, effector T cells, or regulatory T cells, as compared to a responder;

(b) a complete responder has, or is identified as having, a greater, e.g., a statistically significant greater, percentage of CD8+ T cells compared to a reference value, e.g., a non-responder percentage of CD8+ T cells;

(c) a complete responder has, or is identified as having, a greater percentage (e.g., 7% or greater number) of CD27+ CD45RO- immune effector cells, e.g., in the CD8+ population, compared to a reference value, e.g., a non-responder number of CD27+ CD45RO- immune effector cells;

(d) a complete responder or a partial responder has, or is identified as having, a greater, e.g., a statistically significant greater, percentage of CD4+ T cells compared to a reference value, e.g., a non-responder percentage of CD4+ T cells;

(e) a complete responder has, or is identified as having, a greater percentage of one, two, three, or more (*e.g.*, all) of resting T_{EFF} cells, resting T_{REG} cells, younger T cells (*e.g.*, younger CD4 or CD8 cells, or gamma/delta cells), or early memory T cells, or a combination thereof, compared to a reference value, e.g., a non-responder number of resting T_{EFF} cells, resting T_{REG} cells, younger T cells (*e.g.*, younger CD4 or CD8 cells), early memory T cells;

(f) a non-responder has, or is identified as having, a greater percentage of one, two, three, or more (*e.g.*, all) of activated T_{EFF} cells, activated T_{REG} cells, older T cells (*e.g.*, older CD4 or CD8 cells), or late memory T cells, or a combination thereof, compared to a reference value, e.g., a responder number of activated T_{EFF} cells, activated T_{REG} cells, older T cells (*e.g.*, older CD4 or CD8 cells), or late memory T cells;

(g) a non-responder has, or is identified as having:

a greater percentage of PD-1 or LAG-3 expressing immune effector cells (e.g., CD4+ T cells and/or CD8+ T cells) (e.g., CAR-expressing CD4+ cells and/or CD8+ T cells)

compared to the percentage of PD-1 or LAG-3 expressing immune effector cells from a responder, or a greater percentage of PD-1+/LAG-3+ cells in the CAR-expressing cell population (e.g., a CAR19+ cell population) compared to a responder (e.g., a complete responder) to the CAR-expressing cell therapy,

an exhausted phenotype of PD1+ CAR+ and co-expression of LAG3 in the CAR-expressing cell population (e.g., a CAR19+ cell population), or

a greater percentage of PD-1+/TIM-3+ cells in the CAR-expressing cell population (e.g., a CAR19+ cell population) compared to the responder (e.g., complete responder);

(h) a partial responder has, or is identified as having, a higher percentage of PD-1+/LAG-3+ cells than responders in the CAR-expressing cell population (e.g., a CAR19+ cell population), or

a higher percentage of PD-1+/TIM-3+ cells than responders in the CAR-expressing cell population (e.g., a CAR19+ cell population);

(i) the presence of CD8+ CD27+ CD45RO- T cells in an apheresis sample is a positive predictor of the subject response to a CAR-expressing cell therapy (e.g., a CAR19 therapy (e.g., CTL019 therapy));

(j) a high percentage of PD1+ CAR+ and LAG3+ or TIM3+ T cells in an apheresis sample is a poor prognostic predictor of the subject response to a CAR-expressing cell therapy (e.g., a CAR19 therapy (e.g., CTL019 therapy));

(k) a responder (e.g., a complete responder) to a CAR19 therapy has, or is identified as having, the biomarker profile of Table 9;

(l) a non-responder to a CAR19 therapy has, or is identified as having, the biomarker comprising one or more of PD-1+ immune effector cells, TIM-3+ immune effector cells, LAG-3+ immune effector cells, KLRG1+ immune effector cells, CD27-immune effector cells, activated T_{EFF} cells, activated T_{REG} cells, activated TH1, activated TH2 cells, stimulated memory cells, or late T memory cells, or a combination thereof;

(m) a non-responder to a CAR19 therapy has, or is identified as having, the biomarker profile of Table 10;

(n) gene expression of one, two, three, four or more (all) of KLRG1, CD57, CD27, CD122, or CD62L is predictive of patient response to CTL019 therapy;

(o) a relapser has, or is identified as having, elevated levels of one, two, three, four, five, six, seven, eight, nine, ten or more of C5orf32, CCL17, CSF1, CTSL1, EMP1, EPAS1, GCLM, GK, GPR56, HMOX1, IKBIP, IL10, IL13, IL1RN, IL4, IL5, IL9, MIR155, PANX2,

PGAM4, PRKAR1B, TNFRSF11A, TNFRSF1B, TNFRSF8, VTRNA1-3, or ZNF282; and/or

(p) the responder (e.g., the complete or partial responder) has one, two, three or more (or all) of the following profile:

(i) has a greater number of CD27+ immune effector cells compared to a reference value, e.g., a non-responder number of CD27+ immune effector cells;

(ii) has a greater number of CD8+ T cells compared to a reference value, e.g., a non-responder number of CD8+ T cells;

(iii) has a lower number of cells expressing one or more checkpoint inhibitors, e.g., a checkpoint inhibitor chosen from PD-1, LAG-3, TIM-3, or KLRG-1, or a combination, compared to a reference value, e.g., a non-responder number of cells expressing one or more checkpoint inhibitors; or

(iv) has a greater number of one, two, three, or more (all) of resting T_{EFF} cells, resting T_{REG} cells, younger cells, or early memory T cells, or a combination thereof, compared to a reference value, e.g., a non-responder number of resting T_{EFF} cells, resting T_{REG} cells, naïve CD4 cells, unstimulated memory cells or early memory T cells.

11. The method of claim 1 or 2 or any one of claims 6-10, the therapy of claim 3 or the use of claim 4 or 5, wherein the cytokine level or activity of (vi) is chosen from one, two, three, four, five, six, seven, eight, or more (or all) of cytokine CCL20/MIP3a, IL17A, IL6, GM-CSF, IFNγ, IL10, IL13, IL2, IL21, IL4, IL5, IL9 or TNFα, or a combination thereof; or

wherein a transduction efficiency of 15% or higher in (vii) is indicative of increased responsiveness or decreased relapse.

12. The method of claim 1 or 2 or any one of claims 6-11, the therapy of claim 3 or the use of claim 4 or 5, wherein said value of responder or relapser status comprises a measure of the level or activity of one, two, three, four, five, ten, twenty or more (e.g., all) of the biomarkers having a FDR p-value of below 0.1 or 0.01 listed in Table 1A, 1B, 17, 18, or 20.

13. A method of evaluating the potency of a CAR-expressing cell product, e.g., CAR19- expressing cell product sample (e.g., CTL019), said method comprising:

acquiring a value for one, two, three, four, five, six, seven, eight, or more (e.g., all) of:

(i) the level or activity of CD27 and/or CD45RO- (e.g., CD27+ CD45RO-) immune effector cells, e.g., in a CD4+ or a CD8+ T cell population, in the CAR-expressing cell product;

(ii) the level or activity of one, two, three, or more (*e.g.*, all) of resting T_{EFF} cells, resting T_{REG} cells, younger T cells (*e.g.*, younger CD4 or CD8 cells, or gamma/delta T cells), or early memory T cells, or a combination thereof, in the CAR-expressing cell product;

(iii) the level or activity of one, two, three, or more (*e.g.*, all) of activated T_{EFF} cells, activated T_{REG} cells, older T cells (*e.g.*, older CD4 or CD8 cells), or late memory T cells, or a combination thereof, in the CAR-expressing cell product;

(iv) the level or activity of an immune cell exhaustion marker, *e.g.*, one, two or more immune checkpoint inhibitors (e.g., PD-1, TIM-3 and/or LAG-3) in the CAR-expressing cell product;

(v) the level or activity of one, two, three, four, five, ten, twenty or more of the biomarkers listed in Table 1A, Table 1B, Table 7A, Table 7B, Table 8, Table 9, Table 10, Table 14 (e.g., CCL20, IL-17a and/or IL-6), Table 16, Table 17, Table 18, Table 20, FIG. 2B, PD-1, LAG-3, TIM-3, CD57, CD27, CD122, CD62L, KLRG1, or a CD19 CAR-expressing cell gene set signature;

(vi) a cytokine level or activity (e.g., a cytokine repertoire) in the CAR-expressing cell product sample, e.g., CAR19- expressing cell product sample (e.g., CTL019), wherein the cytokine is chosen from one, two, three, four, five or more (or all) of the cytokines listed in Table 16;

(vii) a transduction efficiency of CAR-expressing cells in the product;

(viii) a quantity of CD27+ PD-1- cells in a sample (e.g., an apheresis sample or a CAR-expressing cell product sample, e.g., CAR19- expressing cell product sample (e.g., CTL019)), e.g., a quantity greater than or equal to 1×10^7 cells; or

(ix) the level or activity of a T_{REG} cell or cell population;

wherein an increase in (i), (ii), (vi), (vii), (viii), or any combination thereof, is indicative of increased potency of the CAR-expressing cell product, and

wherein an increase in (iii), (iv), (ix), or any combination thereof, is indicative of decreased potency of the CAR-expressing cell product.

14. The method of claim 13, wherein the cytokine is chosen from one, two, three, four, five, six, seven, eight, or more (or all) of CCL20/MIP3a, IL17A, IL6, GM-CSF, IFNγ, IL10, IL13, IL2, IL21, IL4, IL5, IL9 or TNFα, or a combination thereof; or wherein a transduction efficiency of 15% or higher is indicative of increased potency.

15. A method for optimizing manufacturing of a CAR-expressing cell product, e.g., CAR19- expressing cell product sample (e.g., CTL019), comprising:

(1) acquiring a sample comprising CAR-expressing cell (e.g., a population of CAR-expressing immune effector cells);

(2) activating the CAR-expressing cell *in vitro*;

(3) evaluating the potency of the potency of the activated CAR-expressing cell by determining one, two, three, four, five, six, seven, eight, or more (e.g., all) of:

(i) the level or activity of CD27 and/or CD45RO- (e.g., CD27+ CD45RO-) immune effector cells, e.g., in a CD4+ or a CD8+ T cell population, in the CAR-expressing cell product;

(ii) the level or activity of one, two, three, or more (*e.g.*, all) of resting T_{EFF} cells, resting T_{REG} cells, younger T cells (*e.g.*, younger CD4 or CD8 cells, or gamma/delta T cells), or early memory T cells, or a combination thereof, in the CAR-expressing cell product;

(iii) the level or activity of one, two, three, or more (*e.g.*, all) of activated T_{EFF} cells, activated T_{REG} cells, older T cells (*e.g.*, older CD4 or CD8 cells), or late memory T cells, or a combination thereof, in the CAR-expressing cell product;

(iv) the level or activity of an immune cell exhaustion marker, *e.g.*, one, two or more immune checkpoint inhibitors (e.g., PD-1, TIM-3 and/or LAG-3) in the CAR-expressing cell product;

(v) the level or activity of one, two, three, four, five, ten, twenty or more of the biomarkers listed in Table 1A, Table 1B, Table 7A, Table 7B, Table 8, Table 9, Table 10, Table 14 (e.g., CCL20, IL-17a and/or IL-6), Table 16, Table 17, Table 18, Table 20, FIG. 2B, PD-1, LAG-3, TIM-3, CD57, CD27, CD122, CD62L, KLRG1, or a CD19 CAR-expressing cell gene set signature;

(vi) a cytokine level or activity in a CAR-expressing cell product sample, e.g., CAR19- expressing cell product sample (e.g., CTL019), wherein the cytokine is chosen from one, two, three, four, five or more (or all) of the cytokines listed in Table 16;

(vii) a transduction efficiency of CAR-expressing cells in the product;

(viii) a quantity of CD27+ PD-1- cells in a sample (e.g., an apheresis sample or a CAR-expressing cell product sample, e.g., CAR19- expressing cell product sample (e.g., CTL019)), e.g., a quantity greater than or equal to 1 x 10^7 cells; or

(ix) the level or activity of a T_{REG} cell or cell population,

wherein an increase in (i), (ii), (vi), (vii), (viii), or any combination thereof, is indicative of increased potency of the CAR-expressing cell product, and

wherein an increase in (iii), (iv), (ix), or any combination thereof, is indicative of decreased potency of the CAR-expressing cell product.

thereby optimizing manufacturing of the product.

16. The method of claim 15, further comprising a step of enriching for, e.g., isolating, cells having an increase in any of (i), (ii), (vi), (vii), (viii), or any combination thereof, or a decrease in any of (iii), (iv), (ix), or any combination thereof, or

wherein the cytokine level or activity is chosen from one or more of cytokine CCL20/MIP3a, IL17A, IL6, GM-CSF, IFNγ, IL10, IL13, IL2, IL21, IL4, IL5, IL9 or TNFα, or a combination thereof.

17. The method of claim 16, further comprising a further step that depletes T_{REG} cells.

18. The method of claim 17, wherein T_{REG} cells are depleted via CD25-depletion, GITR depletion, mTOR inhibition, or a combination thereof.

19. The method of any of claims 13-18, wherein (i), (ii), (iii), (iv), (v), (vi), (vii), (viii), (ix), or any combination thereof (e.g., all) are evaluated following activation *in vitro*, and/or

wherein the CAR-expressing cell therapy comprises CTL019.

20. The method of claim 1 or 2 or any one of claims 6-19, the therapy of claim 3 or the use of claim 4 or 5, wherein

(i) the subject receives treatment, e.g., a pre-treatment or concurrent treatment with an agent, e.g., an mTOR inhibitor, and/or a checkpoint inhibitor, e.g., a pre-treatment prior to

the initiation of a CAR-expressing cell therapy or a treatment post- CAR-expressing cell therapy;

(ii) the cancer is associated with CD19 expression;

(iii) the cancer is a hematological cancer;

(iv) the cancer or hematological cancer is selected from the group consisting of B-cell acute lymphocytic leukemia (B-ALL), T-cell acute lymphocytic leukemia (T-ALL), acute lymphocytic leukemia (ALL), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), B cell promyelocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin lymphoma, Hodgkin lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, and Waldenstrom macroglobulinemia;

(v) the CD19 CAR-expressing cell gene signature comprises a value for expression of at least 5, 6, 7, 8, 9 or 10 genes comprising a CD19 CAR-expressing cell gene signature.

21. The use of a kit for providing a prognosis for success rate of a CAR-expressing cell therapy in a subject having cancer, said kit comprising:

a set of reagents that specifically detects the level or activity of one or more genes listed in Table 1A, Table 1B, Table 7A, Table 7B, Table 8, Table 9, Table 10, Table 14 (e.g., CCL20, IL-17a and/or IL-6), Table 17, Table 18, Table 20, FIG. 2B, PD-1, LAG-3, TIM-3, CD57, CD27, CD122, CD62L, KLRG1, and/or a CD19 CAR-expressing cell gene set signature; and

instructions for using said kit;

wherein said instructions for use provide that if one or more of the detected expression levels is different from, e.g., greater than a reference level, the subject is more likely to respond positively to a CAR-expressing cell therapy in the manufacture of a medicament for the treatment of cancer.

22. The use of claim 21, wherein the set of reagent detects the expression of mRNA expressed from said set of genes, and/or

wherein the set of reagents detects the expression of polypeptides encoded by said set of genes.

23. A system for evaluating cancer in a subject, comprising:

at least one processor operatively connected to a memory, the at least one processor when executing is configured to:

acquire a value of responder or relapser status that comprises a measure of one, two, three, four, five, six, seven, or more (all) of the following:

(i) the level or activity of CD27 and/or CD45RO- (e.g., CD27+ CD45RO-) immune effector cells, e.g., in a CD4+ or a CD8+ T cell population in a sample (e.g., an apheresis sample or a manufactured CAR-expressing cell product sample);

(ii) the level or activity of one, two, three, or more (*e.g.*, all) of resting T_{EFF} cells, resting T_{REG} cells, younger T cells (*e.g.*, younger CD4 or CD8 cells, or gamma/delta T cells), or early memory T cells, or a combination thereof, in a sample (e.g., an apheresis sample or a manufactured CAR-expressing cell product sample);

(iii) the level or activity of one, two, three, or more (*e.g.*, all) of activated T_{EFF} cells, activated T_{REG} cells, older T cells (*e.g.*, older CD4 or CD8 cells), or late memory T cells, or a combination thereof, in a sample (e.g., an apheresis sample or a manufactured CAR-expressing cell product sample);

(iv) the level or activity of an immune cell exhaustion marker, *e.g.*, one, two or more immune checkpoint inhibitors (e.g., PD-1, TIM-3 and/or LAG-3) in a sample (e.g., an apheresis sample or a manufactured CAR-expressing cell product sample); (v) the level or activity of one, two, three, four, five, ten, twenty or more of the biomarkers listed in Table 1A, Table 1B, Table 7A, Table 7B, Table 8, Table 9, Table 10, Table 14 (e.g., CCL20, IL-17a and/or IL-6), Table 16, Table 17, Table 18, Table 20, FIG. 2B, PD-1, LAG-3, TIM-3, CD57, CD27, CD122, CD62L, KLRG1, or a CD19 CAR-expressing cell gene set signature;

(vi) a cytokine level or activity (e.g., quality of cytokine repertoire) in a CAR-expressing cell product sample, e.g., CAR19- expressing cell product sample (e.g., CTL019), wherein the cytokine is chosen from one, two, three, four, five or more (or all) of the cytokines listed in Table 16;

(vii) a transduction efficiency of a CAR-expressing cell in a manufactured CAR-expressing cell product sample; or

(viii) a quantity of CD27+ PD-1- cells in a sample (e.g., an apheresis sample or a CAR-expressing cell product sample, e.g., CAR19- expressing cell product sample (e.g., CTL019)), e.g., a quantity greater than or equal to 1 x 10^7 cells,

responsive to a determination of the value of responder status, perform one, two, three, four, five, six, seven, or more (e.g., all) of:

identify the subject as a complete responder, partial responder, non-responder, relapser or non-relapser;

recommend administering a CAR-expressing cell therapy;

recommend a selection or alteration of a dosing of a CAR-expressing cell therapy;

recommend a selection or alteration of a schedule or time course of a CAR-expressing cell therapy;

recommend administering, e.g., to a non-responder or a partial responder, an additional agent in combination with a CAR-expressing cell therapy, e.g., a checkpoint inhibitor, e.g., a checkpoint inhibitor described herein;

recommend administering to a non-responder or partial responder a therapy that increases the number of naïve T cells in the subject prior to treatment with a CAR-expressing cell therapy;

recommend modifying a manufacturing process of a CAR-expressing cell therapy, e.g., enrich for naïve T cells prior to introducing a nucleic acid encoding a CAR, e.g., for a subject identified as a non-responder or a partial responder;

recommend modifying the CAR-expressing cell product prior to infusion into the patient;

recommend adjusting the CAR-expressing cell infusion dose to achieve clinical efficacy;

recommend administering an alternative therapy, e.g., for a non-responder or partial responder or relapser;

recommend a selection of an alternative therapy, e.g., for a non-responder or partial responder, e.g., a standard of care for a particular cancer type; or

if the subject is, or is identified as, a non-responder or a relapser, recommend decreasing the T_{REG} cell population and/or T_{REG} gene signature, e.g., by CD25 depletion, administration of cyclophosphamide, an anti-GITR antibody, an mTOR inhibitor, or a combination thereof.

24. A method comprising steps of:

providing a blood sample, e.g., a T cell sample, from a subject having cancer;

determining the levels of expression of one or more genes listed in Table 1A, Table 1B, Table 7A, Table 7B, Table 8, Table 9, Table 10, Table 14 (e.g., CCL20, IL-17a and/or IL-6), Table 17, Table 18, Table 20, FIG. 2B, PD-1, LAG-3, TIM-3, CD57, CD27, CD122, CD62L, or KLRG1 to obtain a gene expression pattern for the sample;

comparing the obtained gene expression pattern to that of a reference value, e.g., a historical record of gene expression;

determining a difference between the obtained and the reference value; and

recording the determined difference in a quality control record.

25. The method of claim 24, further comprising a step of comparing the obtained gene expression pattern difference with that of a reference sample.

26. A method of arranging for the treatment of a subject with cancer comprising:

(1) determining if the subject has an increased likelihood to relapse to a CAR-expressing cell therapy by acquiring a value for the level or activity of one or more markers in Table 17 in a sample from the subject, wherein a difference, e.g., a statistically significant difference, in the level or activity of one or more biomarker genes relative to the reference level is indicative of an increased likelihood of relapse to a CAR-expressing cell therapy; and

(2) for a subject with an increased likelihood of relapse, decreasing the T_{REG} cell population and/or decreasing T_{REG} gene signature; and

(3) arranging for a therapeutically effective dose of a CAR-expressing cell therapy to be administered to the subject.

27. The method of claim 26, wherein the T_{REG} cell population and/or T_{REG} gene signature is decreased prior to collection of cells for manufacturing.

28. The method of claim 26, wherein the T_{REG} cell population and/or T_{REG} gene signature is decreased prior to CAR-expressing cell (e.g., T cell, NK cell) therapy.

29. The method of any one of claims 26-28, wherein the T_{REG} cell population and/or T_{REG} gene signature is decreased by administration of cyclophosphamide, anti-GITR antibody, or a combination thereof.