**Supplementary Appendix**

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**Supplementary Tables and Figures**

**Table S1**: Patient characteristics and outcomes

| **Patient characteristics** | n=152 |
|---|---|
| **Median age at infusion** (years; (range)) | 12.5 (<1-26) |
| **Median age at diagnosis** (years; (range)) | 8 (<1-25) |
| **Gender** (male/female) | 93/59 |
| **Race** | |
| Asian | 6 (4%) |
| Black | 7 (5%) |
| Hispanic | 58 (39%) |
| More than 1 race | 2 (1%) |
| White | 76 (51%) |
| *Unknown* | 3 |
| **Initial cytogenetic risk** | |
| Favorable | 22 (19%) |
| Intermediate | 42 (36%) |
| Unfavorable | 53 (45%) |
| *Unknown* | 35 |
| **Pre-infusion disease burden** | |
| No detectable disease | 41 (28%) |
| Low disease | 33 (22%) |
| High disease | 74 (50%) |
| *Unknown* | 4 |
| **Mean time diagnosis to infusion** (months) | 43 (3-164) |
| **Mean number of prior lines of therapy** | 3.5 (1-10) |
| **Prior allo-HCT** | 8 (5%) |
| **Prior CD19 directed therapy** | 33 (22%) |
| **Disease status** | |
| Refractory disease | 24 (16%) |
| ≥1 relapse | 128 (84%) |
| **Overall day 28 response** | |
| No CR | 16 (11%) |
| CR | 131 (86%) |
| Died prior to day28 | 5 (3%) |

| | |
|---|---|
| **CRS grade** | |
| none | 55 (36%) |
| 1 | 36 (24%) |
| 2 | 28 (18%) |
| 3 | 17 (11%) |
| 4 | 15 (10%) |
| 5 | 1 (1%) |
| *Unknown* | 1 |
| **Neurotoxicity grade** | |
| none | 116 (76%) |
| 1 | 17 (11%) |
| 2 | 7 (5%) |
| 3 | 8 (5%) |
| 4 | 3 (2%) |
| 5 | 1 (1%) |
| **Relapsed post CAR** | 55 (36%) |
| CD19-positive relapse | 28 (55%) |
| CD19-negative relapse | 23 (45%) |
| *unknown* | 4 |
| **Loss of BCA post CAR** | 52 (34%) |
| **Survival status** (alive/dead) | 112/40 |
| **Cause of death** | |
| Leukemia | 30 (74%) |
| Infection | 4 (10%) |
| CRS | 1 (2%) |
| Neurotoxicity | 1 (2%) |
| Transplant related | 3 (7%) |
| ARDS/cardiac arrest | 1 (2%) |

allo-HCT, allogeneic hematopoietic cell transplantation; CR, complete remission; CRS, cytokine release syndrome; CAR, chimeric antigen receptor; BCA, B cell aplasia; ARDS, acute respiratory distress syndrome

Table S2: Univariable analysis of disease characteristics and response

| **Characteristics** | Non-responders n=16 | Responders n=131 | p-value |
|---|---|---|---|
| **Age at diagnosis** | | | >0.99 |
| <1 year or >10 years | 8 (12%) | 61 (88%) | |
| 1 to 10 years | 8 (10%) | 70 (90%) | |
| **Gender** (male/female) | 10/6 | 81/50 | >0.99 |
| **Race** | | | 0.025 |
| Black/Hispanic | 12 (19%) | 50 (81%) | |
| Others | 0 (0%) | 8 (100%) | |
| White | 4 (5%) | 70 (95%) | |
| *Unknown* | 0 | 3 | |
| **Initial cytogenetic risk** | | | 0.44 |
| Favorable | 4 (18%) | 18 (82%) | |
| Intermediate | 4 (10%) | 37 (90%) | |
| Unfavorable | 4 (8%) | 46 (92%) | |
| *Unknown* | 4 | 30 | |
| **Pre-infusion disease burden** | | | 0.001 |
| No or low disease | 1 (1%) | 73 (99%) | |
| High disease | 13 (19%) | 56 (81%) | |
| *Unknown* | 2 | 2 | |
| **Time diagnosis to infusion** (months) | 36 (6-117) | 45 (3-164) | 0.44 |
| **Number of prior lines of therapy** | 3.9 (2-7) | 3.4 (1-10) | 0.14 |
| **Prior allo-HCT** | | | 0.56 |
| no | 15 (11%) | 125 (89%) | |
| yes | 1 (14%) | 6 (86%) | |
| **Prior CD19 directed therapy** | | | 0.01 |
| no | 8 (7%) | 106 (93%) | |
| yes | 8 (24%) | 25 (76%) | |
| **Disease status** | | | >0.99 |
| Refractory disease | 2 (8%) | 22 (92%) | |
| ≥1 relapse | 14 (11%) | 109 (89%) | |

allo-HCT, allogeneic hematopoietic cell transplantation

**Table S3:** Univariable and Multivariable analysis of overall survival in all treated patients based on patient characteristics

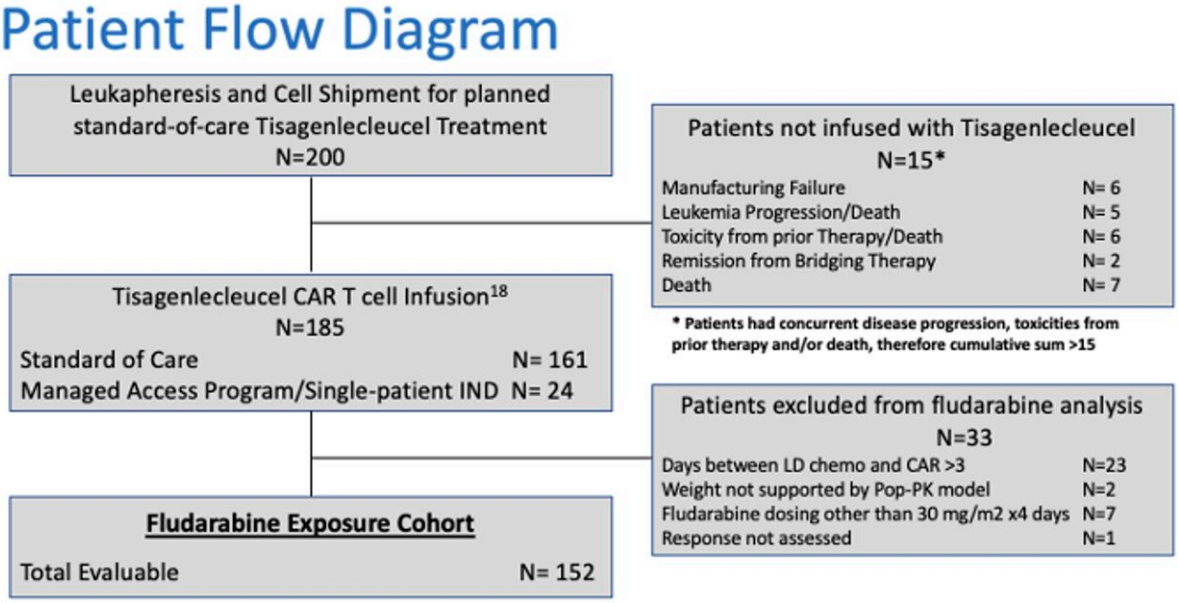
| | Univariable | | | Multivariable | | |
|---|---|---|---|---|---|---|
| **Characteristics** | **HR** | **95% CI** | **p-value** | **HR** | **95% CI** | **p-value** |
| **Sex** | | | 0.092 | | | *0.96* |
| Female | Ref | | | *Ref* | | |
| Male | 0.59 | 0.31-1.09 | | *0.98* | *0.50-1.97* | |
| **Number of prior lines of therapy** | 1.19 | 1.01-1.41 | 0.050 | *1.16* | *0.97-1.38* | *0.11* |
| **Time dx to infusion (months)** | 0.99 | 0.98-1.00 | 0.14 | | | |
| **Age at diagnosis** | | | 0.004 | | 0.21-0.81 | **0.008** |
| <1 or >10 years | Ref | | | Ref | | |
| 1 to 10 years | 0.39 | 0.20-0.75 | | 0.41 | | |
| **Pre-infusion disease burden** | | | <0.001 | | | **<0.001** |
| No or low disease | Ref | | | Ref | | |
| High disease | 4.76 | 2.10-10.8 | | 4.77 | 2.10-10.9 | |
| **Initial cytogenetic risk** | | | 0.15 | | | |
| Favorable | Ref | | | | | |
| Intermediate | 3.06 | 0.87-10.8 | | | | |
| Unfavorable | 2.40 | 0.69-8.32 | | | | |
| **Prior HCT** | | | 0.90 | | | |
| No | Ref | | | | | |
| Yes | 1.09 | 0.26-4.54 | | | | |
| **Prior CD19 directed therapy** | | | 0.69 | | | |
| No | Ref | | | | | |
| Yes | 1.16 | 0.57-2.38 | | | | |
| **Prior relapse** | | | 0.065 | | | *0.055* |
| 1 or more relapse | Ref | | | *Ref* | | |
| Refractory | 0.38 | 0.12-1.24 | | *0.36* | *0.11-1.18* | |
| **CNS or EM disease** | | | 0.64 | | | |
| No | Ref | | | | | |
| Yes | 0.86 | 0.46-1.62 | | | | |
| **Race** | | | 0.32 | | | |
| Black/Hispanic | Ref | | | | | |
| Others | 0.68 | 0.16-2.88 | | | | |
| White | 0.62 | 0.32-1.17 | | | | |
| **Cumulative Flu AUC** (mg*hr/L) | | | 0.22 | | | *0.26* |
| ≥13.8 | Ref | | | *Ref* | | |
| <13.8 | 1.51 | 0.79-2.87 | | *1.53* | *0.73-3.21* | |

HR, hazard ratio; CI, confidence interval; dx, diagnosis; HCT, hematopoetic cell transplantation; CNS, central nervous system; EM, extramedullary disease; flu, fludaraine; AUC, area under the curve; ref, reference

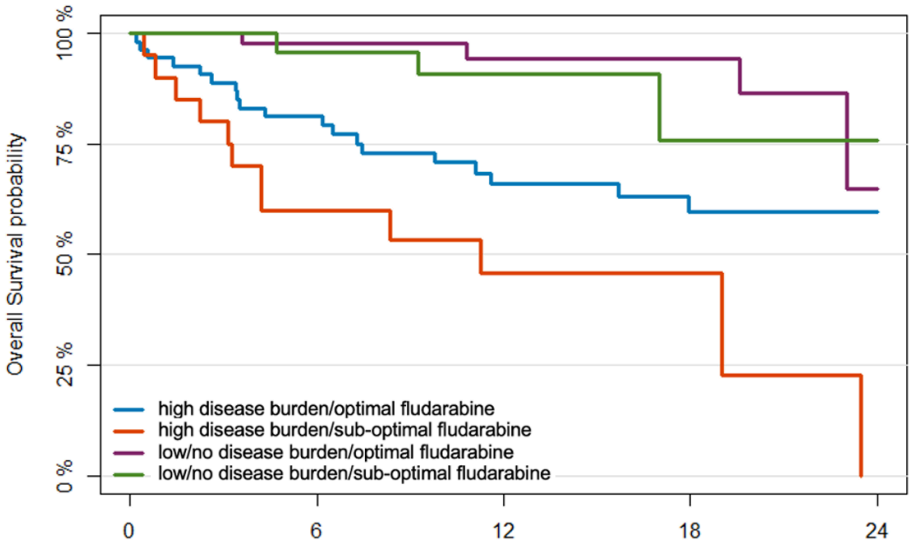
**Table S4**: Univariable analysis of disease characteristics associated with response and fludarabine exposure

| **Characteristics** | Sub-optimal (<13.8mg*hr/L) n=50 | Optimal (≥13.8mg*hr/L) n=102 | p-value |
|---|---|---|---|
| **Race** | | | 0.92 |
| Black/Hispanic | 21 (32%) | 44 (68%) | |
| Others | 2 (25%) | 6 (75%) | |
| White | 26 (34%) | 50 (66%) | |
| *Unknown* | 1 | 2 | |
| **Pre-infusion disease burden** | | | 0.16 |
| No or low disease | 29 (39%) | 45 (61%) | |
| High disease | 20 (27%) | 54 (73%) | |
| *Unknown* | 1 | 3 | |
| **Prior CD19 directed therapy** | | | 0.79 |
| no | 38 (32%) | 81 (68%) | |
| yes | 12 (36%) | 21 (64%) | |

**Supplementary Figure 1:** Patient flow diagram



Supplementary Figure 2: The impact of fludarabine exposure and pre-infusion disease burden on overall survival in all treated patients after tisagenlecleucel infusion.




| At risk | | | | | |
|---|---|---|---|---|---|
| high disease burden/optimal fludarabine: | 54 | 40 | 28 | 17 | 6 |
| high disease burden/sub-optimal fludarabine: | 20 | 10 | 6 | 3 | 0 |
| low/no disease burden/optimal fludarabine: | 45 | 37 | 25 | 14 | 2 |
| low/no disease burden/sub-optimal fludarabine: | 29 | 22 | 13 | 4 | 2 |