

## SUPPLEMENTAL MATERIAL

### ***Effect of Granulocyte Colony-Stimulating Factor on Toxicities after CAR T cell Therapy for Lymphoma and Myeloma***

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**Supplemental Table 1.** Logistic Regression Model for Severe Neutropenia in Lymphoma Cohort

| Variable                                           | Univariate Analysis <sup>§</sup> |              |              |          | Multivariate Analysis |              |              |          |
|----------------------------------------------------|----------------------------------|--------------|--------------|----------|-----------------------|--------------|--------------|----------|
|                                                    | OR                               | Lower 95% CI | Upper 95% CI | P value* | OR                    | Lower 95% CI | Upper 95% CI | P value* |
| Age at CAR T <sup>†</sup>                          | <b>1.005</b>                     | 0.981        | 1.029        | 0.7      |                       |              |              |          |
| Sex (male)                                         | <b>0.71</b>                      | 0.35         | 1.41         | 0.3      |                       |              |              |          |
| CAR T construct (axi-cel)                          | <b>2.45</b>                      | 1.06         | 5.50         | 0.03*    | <b>5.96</b>           | 1.90         | 21.20        | <0.01*   |
| ECOG ≥1                                            | <b>2.20</b>                      | 1.12         | 4.41         | 0.02*    | <b>1.67</b>           | 0.79         | 3.59         | 0.2      |
| Lines of therapy prior to CAR T <sup>†</sup>       | <b>1.280</b>                     | 1.009        | 1.671        | 0.05     | <b>1.001</b>          | 0.999        | 1.004        | 0.07     |
| Bridging therapy prior to CAR T                    | <b>1.44</b>                      | 0.73         | 2.95         | 0.3      |                       |              |              |          |
| Time from Diagnosis to CAR T (months) <sup>†</sup> | <b>1.001</b>                     | 0.995        | 1.007        | 0.9      |                       |              |              |          |
| ANC <sup>†</sup>                                   | <b>1.083</b>                     | 0.965        | 1.242        | 0.2      |                       |              |              |          |
| Hemoglobin <sup>†</sup>                            | <b>0.810</b>                     | 0.668        | 0.972        | 0.03*    | <b>0.906</b>          | 0.720        | 1.137        | 0.4      |
| Platelets <sup>†</sup>                             | <b>0.998</b>                     | 0.995        | 1.002        | 0.4      |                       |              |              |          |
| LDH <sup>†</sup>                                   | <b>1.002</b>                     | 1.000        | 1.004        | 0.06     | <b>1.001</b>          | 0.999        | 1.004        | 0.3      |
| Albumin <sup>†</sup>                               | <b>0.408</b>                     | 0.171        | 0.900        | 0.03*    | <b>0.656</b>          | 0.233        | 1.797        | 0.4      |
| Prophylactic G-CSF <sup>‡</sup>                    | <b>0.83</b>                      | 0.38         | 1.72         | 0.6      | <b>0.33</b>           | 0.10         | 0.93         | 0.05     |

\*P<0.05, indicating statistical significance in univariate or multivariate models, is denoted by asterisks.

<sup>†</sup>Continuous hazard ratio (per unit change in regressor).

<sup>‡</sup>Prophylactic G-CSF refers to exposure to G-CSF prior to CAR T cell infusion.

<sup>§</sup>Variables with P<0.10 in univariate logistic regression model were included in the multivariate model (represented by grey shading). The variable of interest, prophylactic G-CSF, was included in the multivariate model to study its effect on the development of severe neutropenia.

**Supplemental Table 2.** Logistic Regression Model for Severe Thrombocytopenia in Lymphoma Cohort

| Variable                                           | Univariate Analysis <sup>§</sup> |              |              |          | Multivariate Analysis |              |              |          |
|----------------------------------------------------|----------------------------------|--------------|--------------|----------|-----------------------|--------------|--------------|----------|
|                                                    | OR                               | Lower 95% CI | Upper 95% CI | P value* | OR                    | Lower 95% CI | Upper 95% CI | P value* |
| Age at CAR T <sup>†</sup>                          | <b>0.998</b>                     | 0.975        | 1.023        | 0.9      |                       |              |              |          |
| Sex (male)                                         | <b>0.74</b>                      | 0.39         | 1.43         | 0.4      |                       |              |              |          |
| CAR T construct (axi-cel)                          | <b>1.50</b>                      | 0.61         | 4.26         | 0.4      |                       |              |              |          |
| ECOG $\geq 1$                                      | <b>2.79</b>                      | 1.42         | 5.67         | <0.01*   | <b>1.66</b>           | 0.72         | 3.91         | 0.2      |
| Lines of therapy prior to CAR T <sup>†</sup>       | <b>1.343</b>                     | 1.095        | 1.659        | 0.01*    | <b>1.316</b>          | 1.023        | 1.710        | 0.03*    |
| Bridging therapy prior to CAR T                    | <b>2.55</b>                      | 1.33         | 4.94         | 0.01*    | <b>1.70</b>           | 0.69         | 4.19         | 0.3      |
| Time from Diagnosis to CAR T (months) <sup>†</sup> | <b>0.997</b>                     | 0.990        | 1.003        | 0.4      |                       |              |              |          |
| ANC <sup>†</sup>                                   | <b>1.074</b>                     | 0.972        | 1.187        | 0.2      |                       |              |              |          |
| Hemoglobin <sup>†</sup>                            | <b>0.556</b>                     | 0.443        | 0.683        | <0.01*   | <b>0.702</b>          | 0.533        | 0.910        | 0.01*    |
| Platelets <sup>†</sup>                             | <b>0.989</b>                     | 0.984        | 0.994        | <0.01*   | <b>0.992</b>          | 0.987        | 0.997        | <0.01*   |
| LDH <sup>†</sup>                                   | <b>1.003</b>                     | 1.002        | 1.005        | <0.01*   | <b>1.002</b>          | 1.000        | 1.004        | 0.04*    |
| Albumin <sup>†</sup>                               | <b>0.172</b>                     | 0.074        | 0.367        | <0.01*   | <b>0.427</b>          | 0.140        | 1.216        | 0.1      |
| Prophylactic G-CSF <sup>‡</sup>                    | <b>0.82</b>                      | 0.41         | 1.67         | 0.6      | <b>1.02</b>           | 0.41         | 2.66         | 1.0      |

\*P<0.05, indicating statistical significance in univariate or multivariate models, is denoted by asterisks.

<sup>†</sup>Continuous hazard ratio (per unit change in regressor).

<sup>‡</sup>Prophylactic G-CSF refers to exposure to G-CSF prior to CAR T cell infusion.

<sup>§</sup>Variables with P<0.10 in univariate logistic regression model were included in the multivariate model (represented by grey shading). The variable of interest, prophylactic G-CSF, was included in the model to study its effect on the development of severe thrombocytopenia.

**Supplemental Table 3.** Maximum CRS and ICANS in Lymphoma Cohort by G-CSF Exposure

|                    | Prophylactic<br>G-CSF*<br>(N=140) | G-CSF<br>after CAR T†<br>(N=42) | G-CSF<br>non-exposed†<br>(N=15) | Overall<br>(N=197) |
|--------------------|-----------------------------------|---------------------------------|---------------------------------|--------------------|
| <b>CRS grade</b>   |                                   |                                 |                                 |                    |
| 0                  | 19 (13.6%)                        | 10 (23.8%)                      | 5 (33.3%)                       | 34 (17.3%)         |
| 1                  | 48 (34.3%)                        | 23 (54.8%)                      | 8 (53.3%)                       | 79 (40.1%)         |
| 2                  | 64 (45.7%)                        | 7 (16.7%)                       | 2 (13.3%)                       | 73 (37.1%)         |
| 3                  | 5 (3.6%)                          | 2 (4.8%)                        | 0 (0%)                          | 7 (3.6%)           |
| 4                  | 4 (2.9%)                          | 0 (0%)                          | 0 (0%)                          | 4 (2.0%)           |
| <b>ICANS grade</b> |                                   |                                 |                                 |                    |
| 0                  | 60 (42.9%)                        | 26 (61.9%)                      | 10 (66.7%)                      | 96 (48.7%)         |
| 1                  | 28 (20.0%)                        | 3 (7.1%)                        | 1 (6.7%)                        | 32 (16.2%)         |
| 2                  | 28 (20.0%)                        | 3 (7.1%)                        | 1 (6.7%)                        | 32 (16.2%)         |
| 3                  | 22 (15.7%)                        | 8 (19.0%)                       | 3 (20.0%)                       | 33 (16.8%)         |
| 4                  | 2 (1.4%)                          | 2 (4.8%)                        | 0 (0%)                          | 4 (2.0%)           |

\*Prophylactic G-CSF refers to exposure to G-CSF prior to CAR T cell infusion.

†Within 30 days after CAR T cell infusion.

**Supplemental Table 4.** Cox Proportional Hazards Model for Grade  $\geq 2$  CRS in Lymphoma Patients treated with axicabtagene ciloleucel

| <i>Variable</i>                                          | <i>Univariate Analysis<sup>§</sup></i> |                         |                         |                 | <i>Multivariate Analysis</i> |                         |                         |                 |
|----------------------------------------------------------|----------------------------------------|-------------------------|-------------------------|-----------------|------------------------------|-------------------------|-------------------------|-----------------|
|                                                          | <b>HR</b>                              | <i>Lower<br/>95% CI</i> | <i>Upper<br/>95% CI</i> | <i>P value*</i> | <b>HR</b>                    | <i>Lower<br/>95% CI</i> | <i>Upper<br/>95% CI</i> | <i>P value*</i> |
| <i>Age at CAR T<sup>†</sup></i>                          | <b>1.009</b>                           | 0.992                   | 1.027                   | 0.3             |                              |                         |                         |                 |
| <i>Sex (male)</i>                                        | <b>0.68</b>                            | 0.44                    | 1.06                    | 0.1             |                              |                         |                         |                 |
| <i>ECOG <math>\geq 1</math></i>                          | <b>1.42</b>                            | 0.91                    | 2.21                    | 0.1             |                              |                         |                         |                 |
| <i>Lines of therapy prior to CAR T<sup>†</sup></i>       | <b>0.874</b>                           | 0.746                   | 1.024                   | 0.1             |                              |                         |                         |                 |
| <i>Bridging therapy prior to CAR T</i>                   | <b>0.88</b>                            | 0.54                    | 1.43                    | 0.6             |                              |                         |                         |                 |
| <i>Time from Diagnosis to CAR T (months)<sup>†</sup></i> | <b>0.998</b>                           | 0.994                   | 1.003                   | 0.5             |                              |                         |                         |                 |
| <i>ANC<sup>†</sup></i>                                   | <b>1.042</b>                           | 0.983                   | 1.106                   | 0.2             |                              |                         |                         |                 |
| <i>Hemoglobin<sup>†</sup></i>                            | <b>0.935</b>                           | 0.836                   | 1.045                   | 0.2             |                              |                         |                         |                 |
| <i>Platelets<sup>†</sup></i>                             | <b>1.002</b>                           | 0.999                   | 1.004                   | 0.08            | <b>1.002</b>                 | 0.999                   | 1.004                   | 0.07            |
| <i>LDH<sup>†</sup></i>                                   | <b>1.001</b>                           | 1.001                   | 1.002                   | <0.01*          | <b>1.002</b>                 | 1.001                   | 1.002                   | <0.01*          |
| <i>Albumin<sup>†</sup></i>                               | <b>0.728</b>                           | 0.479                   | 1.108                   | 0.1             |                              |                         |                         |                 |
| <i>Prophylactic G-CSF<sup>‡</sup></i>                    | <b>1.90</b>                            | 0.98                    | 3.69                    | 0.06            | <b>2.00</b>                  | 1.03                    | 3.90                    | 0.04*           |

\* $P < 0.05$ , indicating statistical significance in univariate or multivariate models, is denoted by asterisks.

<sup>†</sup>Continuous hazard ratio (per unit change in regressor).

<sup>‡</sup>Prophylactic G-CSF refers to exposure to G-CSF prior to CAR T cell infusion.

<sup>§</sup>Variables with  $P < 0.10$  in Cox univariate proportional hazards model were included in the multivariate model (represented by grey shading).

**Supplemental Table 5.** Cox Proportional Hazards Model for Grade  $\geq 2$  ICANS in Lymphoma Patients treated with axicabtagene ciloleucel

| <i>Variable</i>                                          | <i>Univariate Analysis<sup>§</sup></i> |                         |                         |                 | <i>Multivariate Analysis</i> |                         |                         |                 |
|----------------------------------------------------------|----------------------------------------|-------------------------|-------------------------|-----------------|------------------------------|-------------------------|-------------------------|-----------------|
|                                                          | <b>HR</b>                              | <i>Lower<br/>95% CI</i> | <i>Upper<br/>95% CI</i> | <i>P value*</i> | <b>HR</b>                    | <i>Lower<br/>95% CI</i> | <i>Upper<br/>95% CI</i> | <i>P value*</i> |
| <i>Age at CAR T<sup>†</sup></i>                          | <b>1.012</b>                           | 0.992                   | 1.033                   | 0.2             |                              |                         |                         |                 |
| <i>Sex (male)</i>                                        | <b>0.83</b>                            | 0.50                    | 1.36                    | 0.5             |                              |                         |                         |                 |
| <i>ECOG <math>\geq 1</math></i>                          | <b>2.20</b>                            | 1.31                    | 3.71                    | <0.01*          | <b>1.74</b>                  | 1.02                    | 2.98                    | 0.04*           |
| <i>Lines of therapy prior to CAR T<sup>†</sup></i>       | <b>1.007</b>                           | 0.862                   | 1.176                   | 0.9             |                              |                         |                         |                 |
| <i>Bridging therapy prior to CAR T</i>                   | <b>1.10</b>                            | 0.66                    | 1.86                    | 0.7             |                              |                         |                         |                 |
| <i>Time from Diagnosis to CAR T (months)<sup>†</sup></i> | <b>0.996</b>                           | 0.991                   | 1.002                   | 0.2             |                              |                         |                         |                 |
| <i>ANC<sup>†</sup></i>                                   | <b>1.058</b>                           | 0.989                   | 1.131                   | 0.1             |                              |                         |                         |                 |
| <i>Hemoglobin<sup>†</sup></i>                            | <b>0.782</b>                           | 0.684                   | 0.894                   | <0.01*          | <b>0.942</b>                 | 0.795                   | 1.117                   | 0.5             |
| <i>Platelets<sup>†</sup></i>                             | <b>0.999</b>                           | 0.997                   | 1.002                   | 0.7             |                              |                         |                         |                 |
| <i>LDH<sup>†</sup></i>                                   | <b>1.002</b>                           | 1.001                   | 1.003                   | <0.01*          | <b>1.002</b>                 | 1.000                   | 1.003                   | 0.01*           |
| <i>Albumin<sup>†</sup></i>                               | <b>0.377</b>                           | 0.250                   | 0.567                   | <0.01*          | <b>0.674</b>                 | 0.403                   | 1.129                   | 0.1             |
| <i>Prophylactic G-CSF<sup>‡</sup></i>                    | <b>1.01</b>                            | 0.54                    | 1.89                    | 1.0             | <b>1.36</b>                  | 0.71                    | 2.61                    | 0.4             |

\* $P < 0.05$ , indicating statistical significance in univariate or multivariate models, is denoted by asterisks.

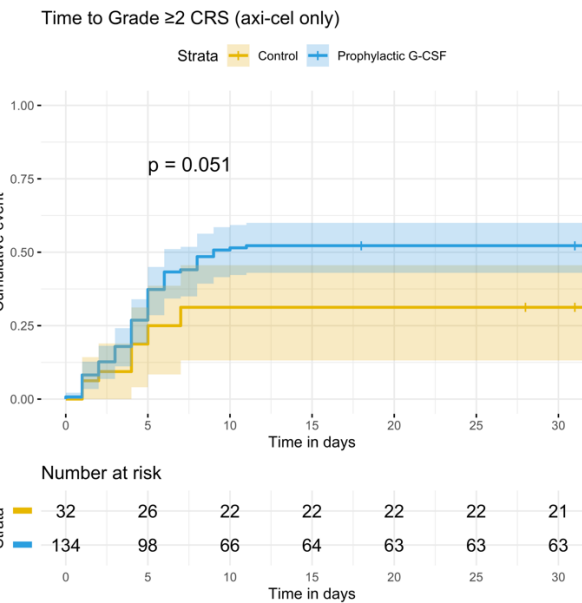
<sup>†</sup>Continuous hazard ratio (per unit change in regressor).

<sup>‡</sup>Prophylactic G-CSF refers to exposure to G-CSF prior to CAR T cell infusion.

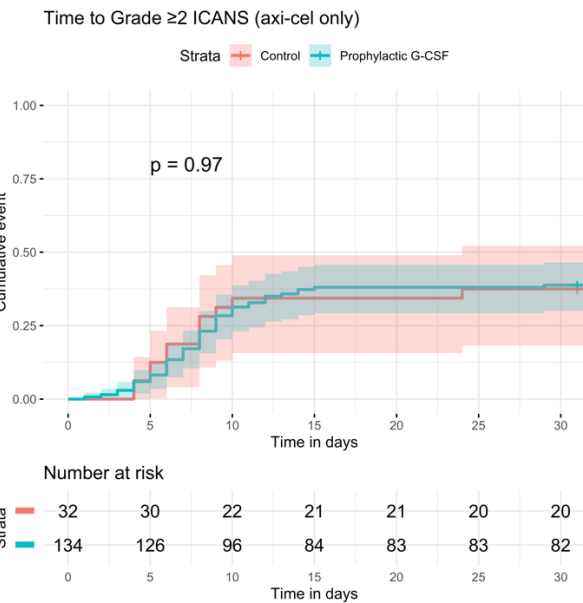
<sup>§</sup>Variables with  $P < 0.10$  in Cox univariate proportional hazards model were included in the multivariate model (represented by grey shading). The variable of interest, prophylactic G-CSF, was included in the model to study its effect on the development of Grade  $\geq 2$  ICANS.

Supplemental Figure 1.

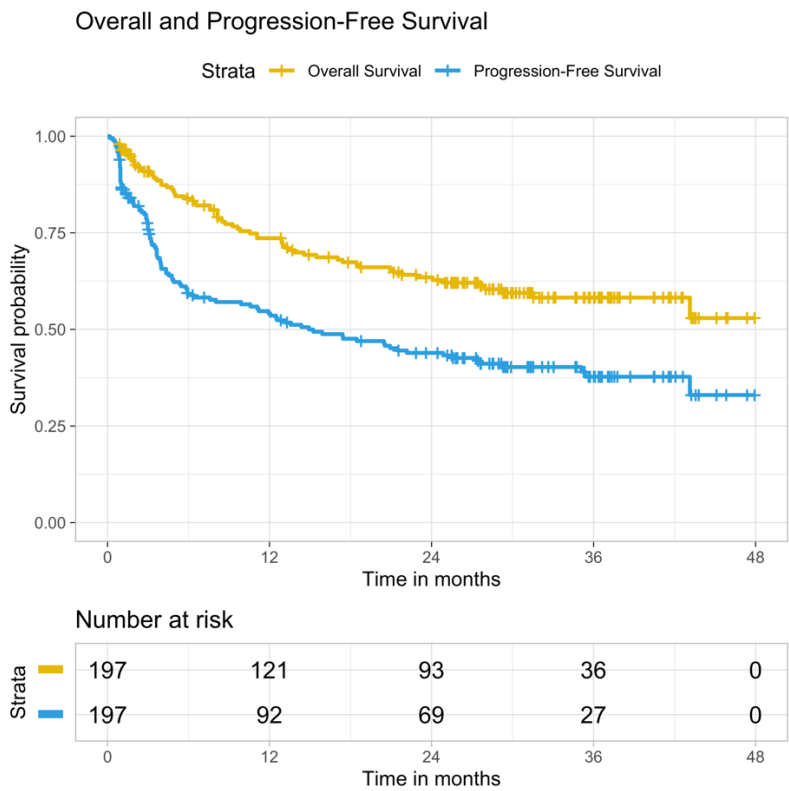
A.



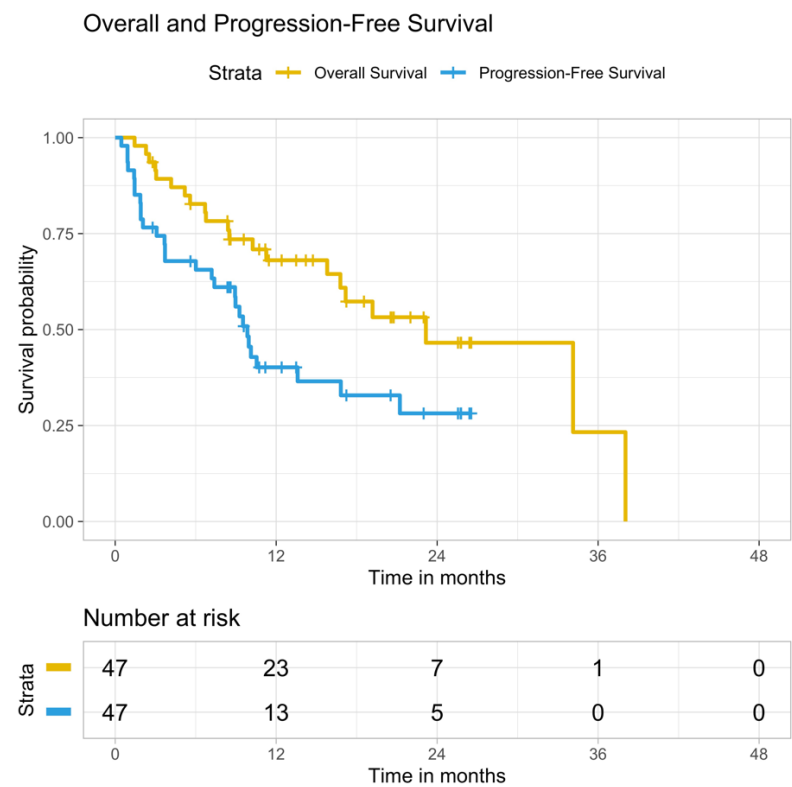
B.



Supplemental Figure 2.



Supplemental Figure 3.



## SUPPLEMENTAL FIGURE LEGENDS

### **Supplemental Figure 1.**

Cumulative incidence of CRS and ICANS for the subset of lymphoma patients treated with axicabtagene ciloleucel (N=166). Time to grade  $\geq 2$  CRS (**Panel A**) and grade  $\geq 2$  ICANS (**Panel B**) were estimated. Patients were stratified by whether they received prophylactic G-CSF (N=134) or not (control, N=32). There was a trend toward a greater cumulative incidence of grade  $\geq 2$  CRS in the prophylactic G-CSF group (Gray test,  $P=0.051$ ). However, in a multivariate analysis (see Supplemental Table 4), prophylactic G-CSF was significantly associated with grade  $\geq 2$  CRS (HR 2.00, 95% CI 1.03-3.90,  $P=0.04$ ). There was no significant difference in grade  $\geq 2$  ICANS between the two groups. 95% confidence intervals are represented by shading.

### **Supplemental Figure 2.**

Progression-free survival (PFS) and overall survival (OS) for patients with lymphoma who received anti-CD19 CAR T cells. 2-year PFS was 43.9% (95% CI 37.1-51.9%). 2-year OS was 63.5% (95% CI 56.6-71.2%).

### **Supplemental Figure 3.**

Progression-free survival (PFS) and overall survival (OS) for patients with multiple myeloma who received anti-BCMA CAR T cells. Median PFS was 9.9 months (95% CI 7.4-21.2). Median OS was 23.2 months (95% CI 16.3-not reached).