SUPPLEMENTAL INFORMATION

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Table S1. Mass cytometry antibody panel- list of targets and heavy metal conjugants

| 151Eu_CD107a | 153Eu_HLA_DR | 154Sm_CD69 | 156Gd_CXCR3 | 165Ho_LAG3 | 175Lu_PERFORIN | 142Ce_NKG2C | 148Nd_CD161 | 152Sm_KIR2DL1 | 167Er_KIR3DL1 | 143Nd_CPARP | 145Nd_CD137 | 149Sm_CD244 | 155Gd_CD27 | 158Gd_CXCR4 | 159Tb_NKP30 | 160Gd_CXCR6 | 164Dy_FAS | 166Er_NKG2D | 169Tm_NKG2A | 170Er_TIM3 | 172Yb_NKP80 | 174Yb_CD94 | 161Dy_Ki67 | 146Nd_NKP44 | 157Gd_TIGIT | 162Dy_NKP46 | 163Dy_CD56 | 171Yb_DNAM1 | 173Yb_KIR2DL2-DL3 | 176Yb_CD57 | 115In_CD45 | 113In_CD3 | 209Bi_CD16 |
| Patient | KIR2DS2 | KIR2DL2 | KIR2DL3 | KIR2DL5A/B | KIR2DS3 | KIR2DS5 | KIR2DP1 | KIR2DL1 | KIR3DL1 | KIR3DS1 | KIR2DS4 | KIR2DS1 |
|---------|---------|---------|---------|-------------|---------|---------|---------|---------|---------|---------|---------|---------|
| 1       | -       | -       | +       | +           | -       | +       | +       | +       | +       | +       | +       | +       |
| 3       | -       | -       | +       | -           | -       | -       | +       | +       | -       | +       | -       |
| 4       | +       | +       | +       | -           | -       | -       | +       | +       | -       | -       | +       | -       |
| 5       | -       | -       | +       | -           | -       | -       | +       | +       | -       | -       | +       | -       |
| 6       | +       | +       | +       | +           | +       | +       | +       | +       | +       | +       | +       | +       |
| 7       | +       | +       | +       | +           | +       | +       | +       | +       | +       | +       | +       | +       |
| 8       | -       | -       | +       | -           | -       | -       | +       | +       | +       | -       | +       | -       |
| 9       | -       | -       | +       | -           | -       | -       | +       | +       | -       | -       | +       | -       |
| 10      | -       | -       | +       | +           | +       | -       | +       | +       | -       | +       | +       | -       |
| 11      | -       | -       | +       | -           | -       | -       | +       | +       | +       | -       | +       | -       |
| 12      | -       | -       | +       | -           | -       | -       | +       | +       | -       | +       | +       | +       |
| 13      | -       | +       | +       | +           | +       | -       | +       | +       | -       | +       | -       | +       |
| 14      | +       | +       | +       | +           | +       | +       | +       | +       | +       | -       | -       | +       |
| 15      | +       | +       | +       | +           | -       | +       | +       | +       | +       | +       | -       | +       |
| 16      | +       | +       | +       | +           | -       | +       | +       | +       | -       | +       | -       | +       |
| 17      | -       | -       | +       | -           | -       | -       | +       | +       | +       | -       | +       | -       |
| 18      | -       | -       | +       | -           | -       | -       | +       | +       | +       | -       | +       | -       |
| 19      | +       | +       | +       | +           | +       | -       | +       | +       | -       | +       | +       | +       |
| 20      | +       | +       | +       | -           | -       | -       | +       | +       | +       | -       | +       | -       |
| 21      | +       | +       | +       | +           | +       | +       | +       | +       | +       | -       | +       | +       |
| 22      | +       | +       | +       | +           | -       | +       | +       | +       | +       | +       | -       | +       |
| 23      | +       | +       | +       | +           | +       | -       | +       | +       | +       | +       | +       | +       |
| 24      | -       | -       | +       | -           | -       | -       | +       | +       | +       | -       | +       | +       |
| 25      | +       | +       | +       | +           | -       | +       | +       | +       | -       | +       | -       | +       |
**Table S3. Donor KIR characteristics**

| Donor | KIR2DS2 | KIR2DL2 | KIR2DL3 | KIR2DL5A/B | KIR2DS3 | KIR2DS5 | KIR2DP1 | KIR2DL1 | KIR3DL1 | KIR3DS1 | KIR2DS4 | KIR2DS1 |
|-------|---------|---------|---------|-------------|---------|---------|---------|---------|---------|---------|---------|---------|
| 1     | -       | -       | -       | -           | -       | -       | -       | -       | -       | -       | -       | +       |
| 3     | -       | -       | +       | -           | -       | -       | +       | -       | -       | -       | +       | +       |
| 4     | +       | +       | +       | -           | -       | -       | -       | -       | -       | +       | +       | +       |
| 5     | -       | -       | +       | -           | -       | -       | -       | +       | -       | +       | -       | -       |
| 6     | -       | -       | +       | -           | -       | -       | -       | -       | -       | +       | +       | +       |
| 7     | +       | +       | +       | -           | -       | +       | -       | +       | -       | +       | +       | +       |
| 8     | +       | +       | +       | -           | -       | +       | +       | -       | +       | +       | +       | +       |
| 9     | -       | -       | +       | -           | -       | -       | +       | -       | +       | +       | +       | +       |
| 10    | -       | +       | +       | +           | -       | -       | +       | -       | +       | +       | +       | +       |
| 11    | +       | +       | +       | -           | -       | +       | -       | +       | +       | +       | +       | +       |
| 12    | -       | -       | +       | -           | -       | +       | -       | -       | +       | -       | +       | +       |
| 13    | -       | +       | +       | -           | -       | +       | +       | +       | +       | +       | -       | -       |
| 14    | -       | -       | +       | -           | -       | -       | +       | -       | -       | -       | +       | -       |
| 15    | -       | +       | +       | -           | -       | +       | +       | -       | -       | +       | -       | -       |
| 16    | +       | +       | +       | -           | -       | +       | +       | +       | +       | -       | -       | +       |
| 17    | -       | +       | +       | -           | -       | +       | +       | +       | +       | -       | +       | -       |
| 18    | +       | +       | +       | -           | -       | +       | +       | +       | +       | -       | +       | -       |
| 19    | +       | +       | +       | +           | +       | +       | +       | +       | +       | +       | +       | -       |
| 20    | +       | +       | +       | -           | -       | +       | +       | +       | +       | -       | +       | -       |
| 21    | +       | +       | +       | -           | -       | +       | +       | +       | +       | -       | +       | -       |
| 22    | +       | +       | +       | -           | +       | +       | +       | -       | +       | +       | +       | -       |
| 23    | +       | +       | +       | -           | -       | +       | +       | +       | +       | -       | +       | -       |
| 24    | +       | +       | +       | +           | +       | +       | +       | +       | +       | +       | +       | +       |
| 25    | +       | +       | +       | -           | +       | +       | +       | +       | +       | +       | +       | +       |
**Table S4.** Characteristics of the NK-cell products of 12 patients treated in the phase II extension study

| Patient | Viability, % | Viable CD32+, APCs, % | CD3+ cells x 10^5/Kg | CD3-CD(16,56+), NK cells, % | CD19+, B cells, % | CD14+ cells, monocytes, % |
|---------|--------------|------------------------|-----------------------|----------------------------|------------------|--------------------------|
| 1       | 95           | 0.13                   | 0.02                  | 0.2                        | 97.08            | not detected             |
| 2       | 95           | not detected           | 0.01                  | 0.1                        | 97.92            | not detected             |
| 3       | 94           | not detected           | 0.02                  | 0.2                        | 98.76            | not detected             |
| 4       | 95           | 0.33                   | 0.02                  | 0.06                       | 99.06            | not detected             |
| 5       | 87           | 0.38                   | 0.02                  | 0.063                      | 95.88            | not detected             |
| 6       | 96           | not detected           | 0.04                  | 0.4                        | 98.70            | 0.03                     |
| 7       | 94           | 0.05                   | 0.04                  | 0.4                        | 99.09            | 0.01                     |
| 8       | 96           | 0.08                   | 0.05                  | 0.5                        | 99.32            | not detected             |
| 9       | 97           | not detected           | 0.01                  | 0.1                        | 99.27            | 0.06                     |
| 10      | 95           | not detected           | 0.01                  | 0.1                        | 99.39            | 0.01                     |
| 11      | 93           | 0.08                   | 0.02                  | 0.2                        | 97.13            | not detected             |
| 12      | 88           | 0.01                   | 0.01                  | 0.1                        | 98.28            | not detected             |

**Table S5.** Causes of death in treatment and CIBMTR control group.

|                      | CASES (N=7) | CONTROLS (N=67) | MAC controls (N=31) | RIC controls (N=36) |
|----------------------|-------------|-----------------|---------------------|---------------------|
| Primary disease      | 0           | 36 (54%)        | 14 (45%)            | 22 (61%)            |
| Graft failure        | 1 (14%) (secondary graft failure) | 1 (1%) | 1 (3%) | 0 |
| GVHD                 | 1 (14%)     | 5 (7%)          | 3 (10%)             | 2 (6%)              |
| Infection            | 2 (28%)     | 3 (4%)          | 1 (3%)              | 2 (6%)              |
| Interstitial pneumonia/ARDS | 1 (14%) | 4 (6%) | 3 (10%) | 1 (3%) |
| Organ failure        | 0           | 9 (13%)         | 2 (6%)              | 7 (19%)             |
| Second malignancy    | 0           | 1 (1%)          | 0                   | 1 (3%)              |
| Other causes         | 2 (28%) (1 unidentified cause of death, 1 hemorrhage) | 8 (12%) | 7 (23%) | 1 (3%) |
Table S6. Immunologic cell recoveries after transplant stratified by NK cell dose

|                | Total (N=5) | Low dose (N=7) | Intermediate dose (N=12) | High dose (N=12) | P value
|----------------|-------------|----------------|--------------------------|------------------|---------
|                | Mean  | SD   | Mean  | SD   | Mean  | SD   | Mean  | SD   | Mean  | SD   |---------|
| WBC            | 4263  | 2399 | 4950  | 2397 | 3833  | 1969 | 4177  | 2836 | 0.773 |
| Absolute lymphocytes | 407   | 294  | 216   | 83  | 320   | 215  | 564   | 347  | 0.189 |
| NK cells       | 636   | 964  | 122   | 136 | 284   | 305  | 1084  | 1282 | 0.064 |
| CD3            | 91    | 145  | 89    | 22  | 40    | 35   | 136   | 207  | 0.397 |
| CD4            | 47    | 81   | 23    | 1.4 | 24    | 29   | 74    | 115  | 0.848 |
| CD8            | 41    | 77   | 66    | 24  | 15    | 11   | 56    | 113  | 0.217 |
| CD19           | 2.8   | 2.7  | 1.5   | 0.7 | 3.1   | 3.2  | 2.9   | 2.7  | 0.909 |
| CD25           | 12    | 13   | 6     | 7.1 | 11    | 8.3  | 15    | 17   | 0.824 |
| CD45RO         | 67    | 130  | 14    | 7.8 | 23    | 21.1 | 119   | 183  | 0.876 |
| CD45RA         | 2.7   | 3.1  | 0.5   | 0.7 | 3.8   | 3.4  | NA    | NA   | 0.140 |
| Day 90         |        |      |       |     |       |      |       |      |       |
| WBC            | 3819  | 1694 | 3425  | 2410 | 4457  | 1786 | 3530  | 1830 | 0.421 |
| Absolute lymphocytes | 757   | 495  | 780   | 744  | 638   | 372  | 862   | 501  | 0.703 |
| NK cells       | 269   | 240  | 190   | 132 | 256   | 164  | 314   | 324  | 0.695 |
| CD3            | 442   | 616  | 1022  | 1109 | 209   | 164  | 365   | 443  | 0.689 |
| CD4            | 170   | 220  | 215   | 314 | 11    | 32   | 196   | 269  | 0.737 |
| CD8            | 264   | 485  | 781   | 870  | 100   | 148  | 161   | 301  | 0.335 |
| CD19           | 82    | 102  | 97    | 114 | 116   | 115  | 50    | 88   | 0.325 |
| CD25           | 19    | 26   | 15    | 4.2 | 42    | 38   | 6.3   | 5.1  | 0.005 |
| CD45RO         | 155   | 190  | 58    | 41  | 111   | 59   | 228   | 258  | 0.424 |
| CD45RA         | 13    | 20   | 2.3   | 1.7 | 25    | 24   | NA    | NA   | 0.148 |
| Day 180        |        |      |       |     |       |      |       |      |       |
| WBC            | 5877  | 2767 | 6175  | 3309 | 5871  | 2219 | 5714  | 3346 | 0.988 |
| Absolute lymphocytes | 1649  | 1582 | 1926  | 804  | 1260  | 1341 | 1879  | 2164 | 0.231 |
| NK cells       | 342   | 191  | 391   | 162 | 313   | 141  | 334   | 260  | 0.650 |
| CD3            | 1254  | 1545 | 1082  | 440  | 1181  | 1296 | 1429  | 2271 | 0.577 |
| CD4            | 401   | 297  | 326   | 50   | 378   | 241  | 470   | 435  | 0.881 |
| CD8            | 794   | 1233 | 745   | 415  | 705   | 1042 | 900   | 1807 | 0.811 |
| CD19           | 178   | 146  | 221   | 197 | 152   | 116  | 171   | 153  | 0.796 |
| CD25           | 54    | 66   | 151   | 108 | 66    | 44   | 16    | 14   | 0.025 |
| CD45RO         | 820   | 1327 | 415   | 213 | 630   | 411  | 1050  | 1815 | 0.716 |
| CD45RA         | 39    | 20   | 30    | 18  | 57    | NA   | NA    | NA   | 0.221 |
| Day 360        |        |      |       |     |       |      |       |      |       |
| WBC            | 6392  | 2667 | 3500  | NA  | 5566  | 2566 | 7700  | 2540 | 0.257 |
| Absolute lymphocytes | 2229  | 1142 | 1270  | NA  | 1832  | 1097 | 2786  | 1087 | 0.149 |
| NK             | 334   | 174  | 164   | 46  | 338   | 194  | 433   | 136  | 0.114 |
| CD3            | 1193  | 609  | 769   | 254 | 1194  | 783  | 1147  | 503  | 0.285 |
| CD4            | 608   | 319  | 365   | 149 | 537   | 229  | 806   | 381  | 0.126 |
| CD8            | 514   | 357  | 370   | 152 | 559   | 475  | 556   | 353  | 0.572 |
| CD19           | 496   | 341  | 383   | 171 | 609   | 389  | 450   | 393  | 0.673 |
| CD25           | 35    | 19   | 24    | NA  | 40    | 28   | 31    | 6    | 0.456 |
| CD45RO         | 606   | 262  | 338   | NA  | 526   | 177  | 802   | 295  | 0.143 |
| CD45RA         | NA    | NA   | NA    | NA  | NA    | NA   | NA    | NA   | NA    |

*Definitions: Low dose was <1 x10^6/Kg/dose; Intermediate dose was 1 x10^6-3x10^6/Kg/dose; High dose was 1 x10^7/Kg/dose

**Abbreviations: SD: standard deviation, NA: not available**
Table S7. Multivariable analysis of relapse, NRM, DFS, and OS: RIC controls vs. cases

|      | Number Events / Evaluable | Hazard Ratio (95% Confidence Interval) | P-value |
|------|---------------------------|----------------------------------------|---------|
| **DFS** |                           |                                        |         |
| Cases | 8/24                      | 1.00<sup>a</sup>                        |         |
| RIC Controls | 48/79                    | 2.28 (1.08 - 4.82)                      | 0.03    |
| **NRM** |                           |                                        |         |
| Cases | 7/24                      | 1.00<sup>a</sup>                        |         |
| RIC Controls | 12/79                   | 0.60 (0.22 - 1.68)                      | 0.33    |
| **Relapse** |                        |                                        |         |
| Cases | 1/24                      | 1.00<sup>a</sup>                        |         |
| RIC Controls | 36/79                   | 14.18 (1.75 - 115.00)                    | 0.013   |
| **OS**  |                           |                                        |         |
| Cases | 7/24                      | 1.00<sup>a</sup>                        |         |
| RIC Controls | 36/79                   | 1.66 (0.71 - 3.88)                      | 0.24    |

<sup>a</sup> Reference group

Variables considered for analysis: recipient age, recipient gender, recipient race and ethnicity, HCT-CI, performance score, CMV serostatus, graft type, year of transplant

There were no significant factors in the DFS, NRM, relapse, and OS models. The results shown are from the models with only the main effect.

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Table S8. Multivariable analysis of relapse, NRM, DFS, and OS of MAC controls vs. cases

|      | Number Events / Evaluable | Hazard Ratio (95% Confidence Interval) | P-value |
|------|---------------------------|----------------------------------------|---------|
| **DFS** |                           |                                        |         |
| Cases | 8/24                      | 1.00<sup>a</sup>                        |         |
| MAC Controls | 39/81                    | 1.55 (0.67 - 3.55)                      | 0.30    |
| **NRM** |                           |                                        |         |
| Cases | 7/24                      | 1.00<sup>a</sup>                        |         |
| MAC Controls | 16/81                   | 0.73 (0.29 - 1.85)                      | 0.51    |
| **Relapse** |                        |                                        |         |
| Cases | 1/24                      | 1.00<sup>a</sup>                        |         |
| MAC Controls | 23/81                   | 7.24 (0.95 - 55.16)                    | 0.06    |
| **OS**  |                           |                                        |         |
| Cases | 7/24                      | 1.00<sup>a</sup>                        |         |
| MAC Controls | 31/81                   | 1.31 (0.56 - 3.04)                      | 0.39    |

<sup>a</sup> Reference group

Variables considered for analysis: recipient age, recipient gender, recipient race and ethnicity, HCT-CI, performance score, CMV serostatus, graft type, year of transplant

There were no significant factors in the DFS, NRM, relapse, and OS models. The results shown are from the models with only the main effect.
### Table S9. Multivariable analysis of NRM, DFS, and OS: RIC controls vs. cases without DSA

|       | Number Events / Evaluable | Hazard Ratio (95% Confidence Interval) | P-value |
|-------|---------------------------|----------------------------------------|---------|
| **DFS** |                           |                                        |         |
| Cases  | 5/19                      | 1.00<sup>a</sup>                      |         |
| RIC Controls | 36/62                | 3.33 (1.30 - 8.52)                   | 0.012   |
| **NRM** |                           |                                        |         |
| Cases  | 5/19                      | 1.00<sup>a</sup>                      |         |
| RIC Controls | 8/62                  | 0.63 (0.21 - 1.95)                   | 0.43    |
| **OS**  |                           |                                        |         |
| Cases  | 5/19                      | 1.00<sup>a</sup>                      |         |
| RIC Controls | 28/62                | 1.84 (0.67 - 5.04)                   | 0.24    |

<sup>a</sup> Reference group

Variables considered for analysis: recipient age, recipient gender, recipient race and ethnicity, HCT-CI, performance score, cmv serostatus, graft type, year of transplant

There were no significant factors in the DFS, NRM, relapse, and OS models. The results shown are from the models with only the main effect.

### Table S10. Multivariable analysis of NRM, DFS, and OS: MAC controls vs cases without DSA

|       | Number Events / Evaluable | Hazard Ratio (95% Confidence Interval) | P-value |
|-------|---------------------------|----------------------------------------|---------|
| **DFS** |                           |                                        |         |
| Cases  | 5/19                      | 1.00<sup>a</sup>                      |         |
| MAC Controls | 30/63             | 2.08 (0.87 - 4.95)                   | 0.10    |
| **NRM** |                           |                                        |         |
| Cases  | 5/19                      | 1.00<sup>a</sup>                      |         |
| MAC Controls | 13/63             | 0.90 (0.35 - 2.29)                   | 0.83    |
| **OS**  |                           |                                        |         |
| Cases  | 5/19                      | 1.00<sup>a</sup>                      |         |
| MAC Controls | 23/63             | 1.44 (0.61 - 3.43)                   | 0.41    |

<sup>a</sup> Reference group

Variables considered for analysis: recipient age, recipient gender, recipient race and ethnicity, HCT-CI, performance score, cmv serostatus, graft type, year of transplant

There were no significant factors in the DFS, NRM, relapse, and OS models. The results shown are from the models with only the main effect.
Figure S1. FC21-NK cell expansion and product characteristics

Panel (A) shows fold expansion was calculated as the ratio of the NK cell content (CD3-CD56+) of the final product for infusion to the NK cell content of the starting MNC product after CD3 depletion and adjusted for occurrences in which only a portion of the product was processed, cultured, or carried forward in culture.

Panel (B) shows viability and NK cell content (CD3-CD56+) of the final fresh product prepared for infusion.

Panel (C) shows residual FC21 (CD19 or CD32+, and CD56-), FC21 or B cell (CD19+), and T cell (CD3+) content in the final NK cell product.

Panel (D) shows viability and recovery of 31 cryopreserved NK cell products assessed after thawing and preparing for infusion. Bars and whiskers represent median ± interquartile range.
**Figure S2.** Mass cytometry stochastic clustering by NK cell markers by individual patients and timepoints.

Peripheral blood was obtained at the indicated timepoints, and mononuclear cells (MNC) were isolated, processed, and assessed for 34 parameters (Supplemental Table S1) along with healthy subject MNC and expanded FC21-NK cell products as reference samples. Samples were gated on live cells, singlets, and cPARP-/CD45+ events. ViSNE plots were constructed by clustering on eight parameters. Shown are plots from all patients at all timepoints, healthy subjects, and NK cell products, showing expression of CD56 as a reference for each sample. Cluster 1 (bottom left) consists of CD3+ T cells, Cluster 2 (top middle) of CD3-CD56dimNKG2DdimCD57+ “standard” NK cells, Cluster 3 (top right) of CD56brNKG2DbrNKp46brCD57- NK cells corresponding to the phenotype of the infused FC21-NK cell product, and Cluster 4 (bottom middle) of all remaining cells. Cluster 3 identifies a unique phenotypic signature associated with the FC21-NK cells that is not present in healthy subjects and persists in patients after adoptive transfer.