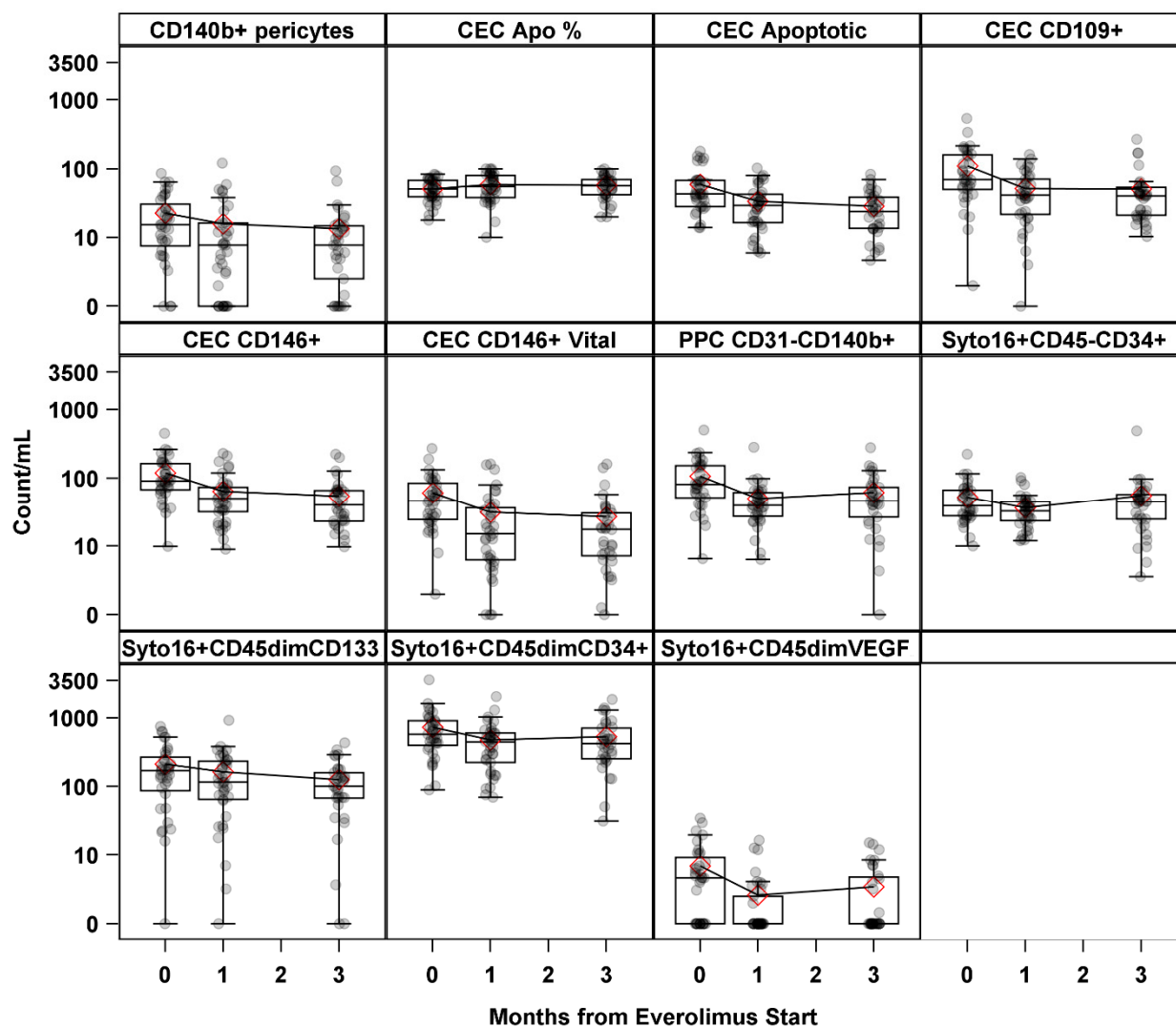
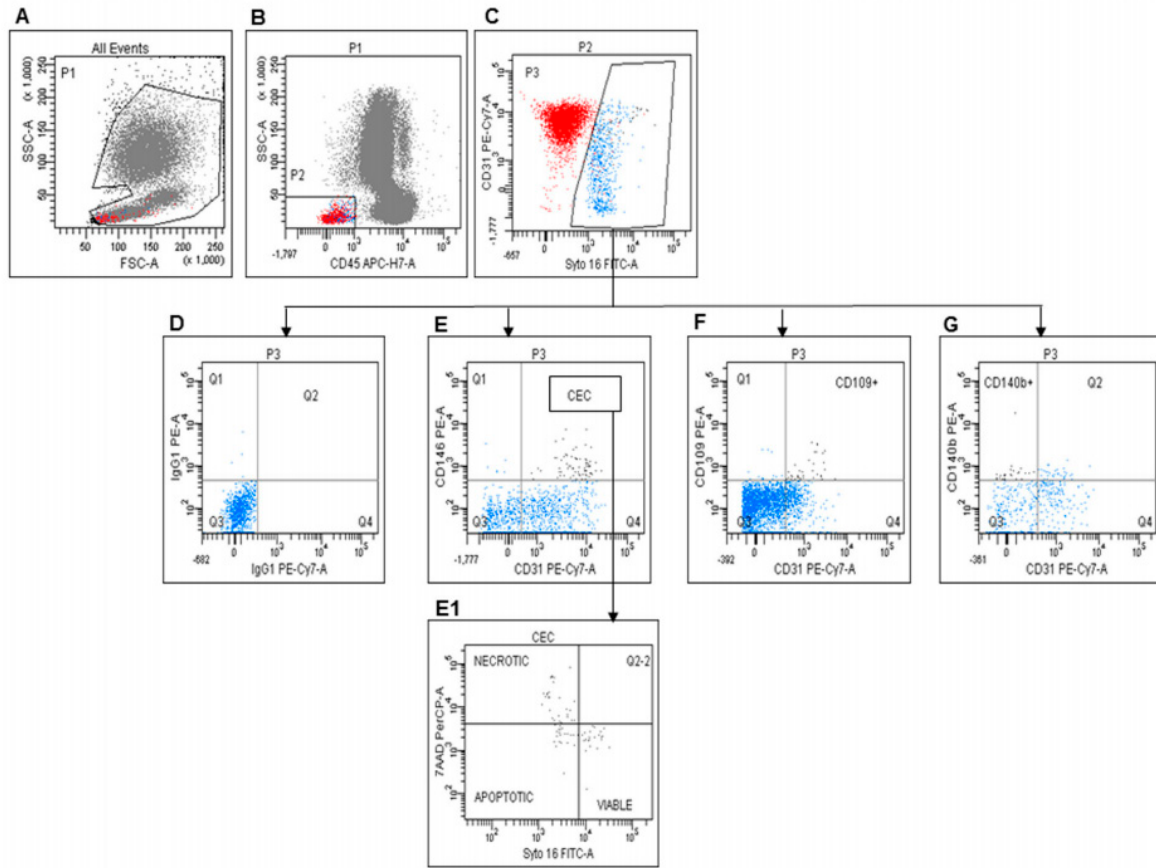


Supplementary materials



**Figure S1.** CCs (CECS and CEPs) by time from Everolimus start.



**Figure S2.** CCs evaluation by flow cytometry. **A:** Gate used to exclude cell fragments and debris. **B:** Gate made to identify CD45- cells. **C:** CD31 expression and Syto16 staining in CD45- cells. **D:** Negative control for **E** (CD31+ CD146+, CECs), **F** (CD31+ CD109+ CECs) and **G** (CD31+CD140b+, PPCs). **E1:** Distribution of viable, apoptotic, and necrotic CECs.

**Table S1.** Summary Statistics of serum BAT by time from EVE start.

|                | Time     | N  | Mean (IQR) <sup>1</sup> | adj p-value <sup>2</sup> |
|----------------|----------|----|-------------------------|--------------------------|
| TPS-1 (ng/mL)  | Baseline | 38 | 152 (111-203)           | -                        |
|                | Month 1  | 28 | 142 (96-179)            | 0.55                     |
|                | Month 3  | 17 | 166 (114-216)           | 0.95                     |
|                | at PD    | 13 | 151 (103-169)           | 0.94                     |
| VEGF (pg/mL)   | Baseline | 38 | 448 (234-574)           | -                        |
|                | Month 1  | 28 | 612 (246-585)           | 0.02                     |
|                | Month 3  | 17 | 578 (345-654)           | 0.09                     |
|                | at PD    | 13 | 566 (356-692)           | 0.16                     |
| VEGFR2 (pg/mL) | Baseline | 38 | 1689 (1418-1917)        | -                        |
|                | Month 1  | 28 | 1279 (1095-1440)        | < .001                   |
|                | Month 3  | 17 | 1247 (1007-1374)        | < .001                   |
|                | at PD    | 13 | 1583 (1375-1766)        | 0.05                     |
| bFGF (pg/mL)   | Baseline | 38 | 4.3 (1.5-6.4)           | -                        |
|                | Month 1  | 28 | 4.1 (1.7-5.0)           | 1.00                     |
|                | Month 3  | 17 | 4.8 (1.7-6.5)           | 0.96                     |
|                | at PD    | 13 | 4.0 (2.0-4.8)           | 0.97                     |

<sup>1</sup> IQR = Inter Quartile Range; <sup>2</sup> Repeated Measures Adjusted p-values for Multiple comparisons vs Baseline.

**Table S2.** Progression Free Survival according to the first (Q1), the median and the third quartile (Q3) of the CCs at baseline.

|                     |        | Cut-off<br>value | No. Failures<br>/At risk | Hazard Ratio<br>(95% CI) | adj p-value <sup>1</sup> |
|---------------------|--------|------------------|--------------------------|--------------------------|--------------------------|
| CEC CD146           | Q1     | > 67.7           | 15/29                    | Ref                      |                          |
|                     |        | ≤ 67.7           | 6/9                      | 1.83 (0.71-4.74)         | 0.21                     |
|                     | Median | > 90.9           | 10/20                    | Ref                      |                          |
|                     |        | ≤ 90.9           | 11/18                    | 1.42 (0.60-3.35)         | 0.42                     |
|                     | Q3     | > 163            | 4/11                     | Ref                      |                          |
|                     |        | ≤ 163            | 17/27                    | 2.57 (0.86-7.66)         | 0.09                     |
| CEC Apo (%)         | Q1     | > 39.0           | 2/9                      | Ref                      |                          |
|                     |        | ≤ 39.0           | 19/29                    | 3.30 (0.78-14.2)         | 0.11                     |
|                     | Median | > 51.0           | 8/18                     | Ref                      |                          |
|                     |        | ≤ 51.0           | 13/20                    | 1.41 (0.58-3.40)         | 0.45                     |
|                     | Q3     | > 68.0           | 14/27                    | Ref                      |                          |
|                     |        | ≤ 68.0           | 7/11                     | 1.11 (0.45-2.76)         | 0.82                     |
| CEC CD146 Vital     | Q1     | > 24.5           | 16/29                    | Ref                      |                          |
|                     |        | ≤ 24.5           | 5/9                      | 1.13 (0.41-3.09)         | 0.81                     |
|                     | Median | > 46.5           | 11/18                    | Ref                      |                          |
|                     |        | ≤ 46.5           | 10/20                    | 1.24 (0.53-2.93)         | 0.62                     |
|                     | Q3     | > 84.3           | 17/27                    | Ref                      |                          |
|                     |        | ≤ 84.3           | 4/11                     | 1.11 (0.45-2.76)         | 0.82                     |
| Apoptotic CEC       | Q1     | > 24.5           | 15/28                    | Ref                      |                          |
|                     |        | ≤ 24.5           | 5/9                      | 1.11 (0.40-3.05)         | 0.84                     |
|                     | Median | > 43.0           | 9/19                     | Ref                      |                          |
|                     |        | ≤ 43.0           | 11/18                    | 1.77 (0.50-3.82)         | 0.53                     |
|                     | Q3     | > 68.0           | 5/11                     | Ref                      |                          |
|                     |        | ≤ 68.0           | 15/26                    | 1.39 (0.45-2.76)         | 0.82                     |
| CD140b+ pericytes   | Q1     | > 7.6            | 17/29                    | Ref                      |                          |
|                     |        | ≤ 7.6            | 4/9                      | 0.73 (0.25-2.18)         | 0.57                     |
|                     | Median | > 15.5           | 10/19                    | Ref                      |                          |
|                     |        | ≤ 15.5           | 11/19                    | 1.09 (0.46-2.56)         | 0.85                     |
|                     | Q3     | > 30.8           | 4/11                     | Ref                      |                          |
|                     |        | ≤ 30.8           | 17/27                    | 2.24 (0.75-6.69)         | 0.15                     |
| CEC CD109+          | Q1     | > 50.4           | 15/29                    | Ref                      |                          |
|                     |        | ≤ 50.4           | 6/9                      | 1.57 (0.61-4.07)         | 0.35                     |
|                     | Median | > 69.8           | 11/21                    | Ref                      |                          |
|                     |        | ≤ 69.8           | 10/17                    | 1.19 (0.50-2.79)         | 0.70                     |
|                     | Q3     | > 160            | 5/12                     | Ref                      |                          |
|                     |        | ≤ 160            | 16/26                    | 1.58 (0.58-4.32)         | 0.37                     |
| PPC CD31 + CD140b+  | Q1     | > 51.4           | 13/29                    | Ref                      |                          |
|                     |        | ≤ 51.4           | 8/9                      | 3.78 (1.53-9.33)         | 0.01                     |
|                     | Median | > 81.0           | 10/20                    | Ref                      |                          |
|                     |        | ≤ 81.0           | 11/18                    | 1.50 (0.64-3.54)         | 0.35                     |
|                     | Q3     | > 153            | 7/11                     | Ref                      |                          |
|                     |        | ≤ 153            | 14/27                    | 0.97 (0.39-2.41)         | 0.95                     |
| Syto16+CD45dimCD34+ | Q1     | > 401            | 15/29                    | Ref                      |                          |
|                     |        | ≤ 401            | 6/9                      | 1.76 (0.68-4.56)         | 0.25                     |
|                     | Median | > 582            | 10/20                    | Ref                      |                          |
|                     |        | ≤ 582            | 11/18                    | 1.73 (0.73-4.09)         | 0.21                     |
|                     | Q3     | > 909            | 5/11                     | Ref                      |                          |

|                           |        |   |      |       |                  |      |
|---------------------------|--------|---|------|-------|------------------|------|
| Syto16+CD45-CD34+         |        | ≤ | 909  | 16/27 | 1.56 (0.57-4.28) | 0.39 |
|                           | Q1     | > | 27.8 | 17/29 | Ref              |      |
|                           |        | ≤ | 27.8 | 4/9   | 0.75 (0.25-2.23) | 0.60 |
|                           | Median | > | 39.0 | 13/20 | Ref              |      |
|                           |        | ≤ | 39.0 | 8/18  | 0.58 (0.24-1.41) | 0.23 |
|                           | Q3     | > | 67.2 | 7/11  | Ref              |      |
| Syto16+CD45dimCD133+CD34+ |        | ≤ | 67.2 | 14/27 | 0.76 (0.31-1.88) | 0.55 |
|                           | Q1     | > | 87.4 | 14/29 | Ref              |      |
|                           |        | ≤ | 87.4 | 7/9   | 2.70 (1.07-6.79) | 0.06 |
|                           | Median | > | 171  | 10/20 | Ref              |      |
|                           |        | ≤ | 171  | 11/18 | 1.70 (0.72-4.01) | 0.23 |
|                           | Q3     | > | 269  | 4/11  | Ref              |      |
| Syto16+CD45dimVEGFR2+     |        | ≤ | 269  | 17/27 | 2.38 (0.80-7.09) | 0.12 |
|                           | Q1     | > | 0.0  | 11/24 | Ref              |      |
|                           |        | = | 0.0  | 10/14 | 1.70 (0.72-4.02) | 0.23 |
|                           | Median | > | 4.7  | 10/19 | Ref              |      |
|                           |        | ≤ | 4.7  | 11/19 | 1.21 (0.52-2.87) | 0.65 |
|                           | Q3     | > | 9.3  | 5/11  | Ref              |      |
|                           |        | ≤ | 9.3  | 16/27 | 1.57 (0.58-4.29) | 0.38 |

<sup>1</sup>Family-wise Error Rate for multiple comparisons adjusted p-value.