

Figure S1. Representative X-ray or CT scan images of GCTB1, GCTB2, GCTB3, GCTB4, and DF1 patients pre-surgery, post surgery and post-denosumab treatment. In the lower panels, explanted tumor specimens used for patient-derived primary culture isolation.

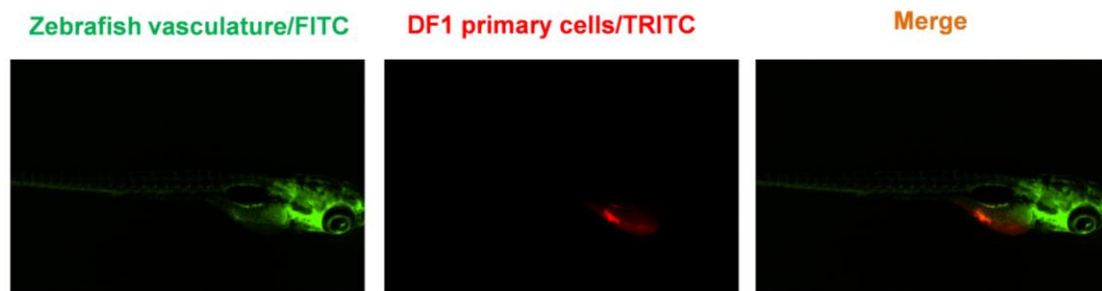


Figure S2. DF1 xenotransplanted zebrafish embryo in perivitelline duct representative images with A1r plus confocal microscopy at 72 hpi. Green probe stain zebrafish vasculature, red probe stain DF1 primary cells and images merged.

Table S1. Table showing relative expression of investigated target genes in GTCB1, GTCB2, GTCB3 and DF1, with related p values. FC, Fold Change. Ct, threshold cycle (average of three replicates). In bold, FC with significant p value (<0.05). B2M was used as reference gene. B2M Cts average were: 21.3 for GTCB1, 21.5 for GTCB2, 21.04 for GTCB3, 23.1 for DF1. Healthy related tissues Cts were ≤ 35 for all genes analyzed.

| Target genes | GCTB1 | | | GCTB2 | | | GCTB3 | | | DF1 | | |
|--------------|-------|--------------|---------|-------|---------------|---------|-------|---------------|---------|-------|--------------|---------|
| | Ct | FC | p value | Ct | FC | p value | Ct | FC | p value | Ct | FC | p value |
| RANK | 30.09 | 8.72 | 0.037 | 30.09 | 21.33 | 0.019 | 30.55 | 10.19 | 0.035 | 35.33 | 1.94 | 0.269 |
| RANK-L | 28.27 | 92.51 | 0.004 | 27.13 | 234.33 | 0.002 | 27.96 | 92.54 | 0.003 | 29.01 | 59.82 | 0.005 |
| OPG | 33.02 | 0.35 | 0.025 | 30.91 | 1.15 | 0.322 | 33.55 | 0.15 | 0.020 | 34.16 | 0.85 | 0.289 |
| CXCR4 | 29.91 | 25.43 | 0.0003 | 30.16 | 21.89 | 0.001 | 32.14 | 5.27 | 0.029 | 31.71 | 94.24 | 0.0002 |
| CXCL12 | 28.93 | 0.06 | 0.003 | 28.94 | 0.07 | 0.003 | 29.60 | 0.03 | 0.005 | 31.05 | 0.25 | 0.0009 |
| OPN | 27.77 | 82.12 | 0.0004 | 25.97 | 329.26 | 0.00002 | 25.54 | 312.03 | 0.00009 | 30.81 | 44.13 | 0.0001 |
| RUNX2 | 27.59 | 71.53 | 0.049 | 26.98 | 125.69 | 0.039 | 28.30 | 35.24 | 0.034 | 30.24 | 49.62 | 0.029 |
| FLT1 | 34.78 | 0.73 | 0.182 | 33.47 | 2.75 | 0.019 | 33.96 | 1.09 | 0.269 | 36.71 | 1.01 | 0.941 |

Table S2. Toxicology profile of DF1 xenotransplanted zebrafish embryos after exposure to DENO, LENVA and DENO + LENVA or untreated.

| Conditions | Injected embryos 2 hpi | Alive embryos 72 hpi | Delta % 72 hpi vs 2 hpi |
|--------------|------------------------|----------------------|-------------------------|
| CTR | 10 | 9 | 10% |
| DENO | 8 | 6 | 25% |
| LENVA | 9 | 5 | 44% |
| DENO + LENVA | 9 | 0 | 100 % |