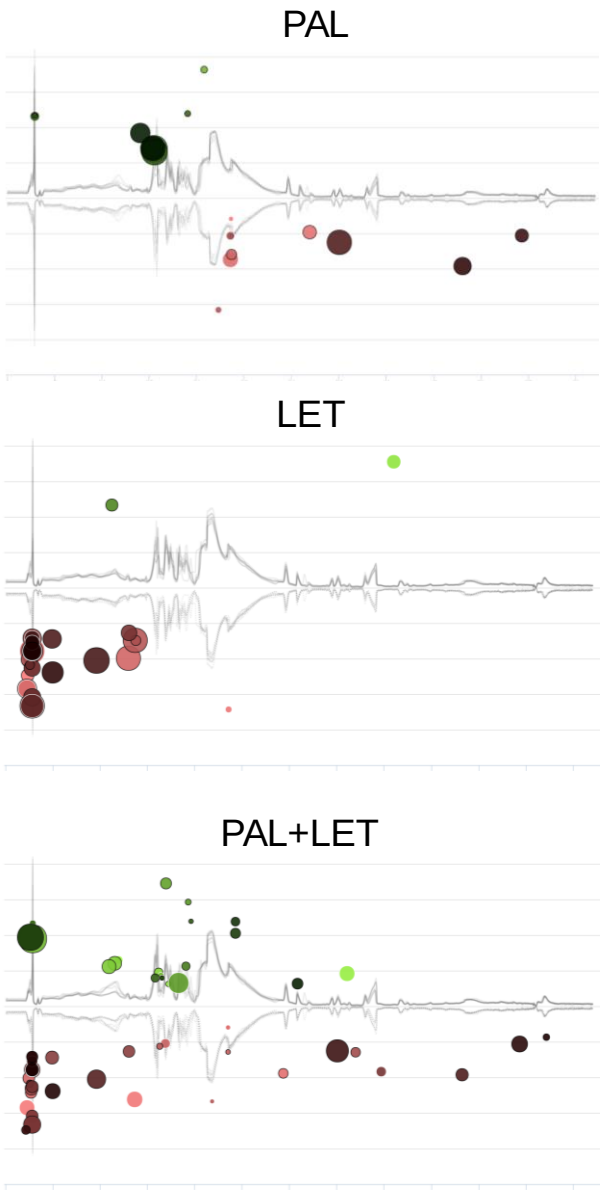

Fig. S1 Pair-wise metabolomics cloud-plot analysis between the control and either PAL, LET, or PAL+LET as obtained for HILIC-LC-ESI-neg-MS measurements in MCF-7 treated cells. Related to Figure 2. Palbociclib (200 nM), letrozole (10 nM), and the combination of both were compared to the vehicle (control) after 48 h of drug exposure to show the overall response of the metabolome following the individual or combined treatments. Following the combined treatment, there are clearly more metabolic features altered than following the individual treatments. Cloud plots show all highly significantly dysregulated metabolites (fold change > 1.5, *p*-value < 0.001). Metabolic features whose intensity were increased after treatment are shown on the upper part of the plot as green circles and those with decreases intensities are shown on the bottom as red circles. Bigger and brighter circles (features) correspond to larger fold changes and lower *p*-values, respectively. The x- and y-axis represent the retention time and the *m/z* and in the background the total ion chromatogram (TIC) of the overlaid samples is shown.

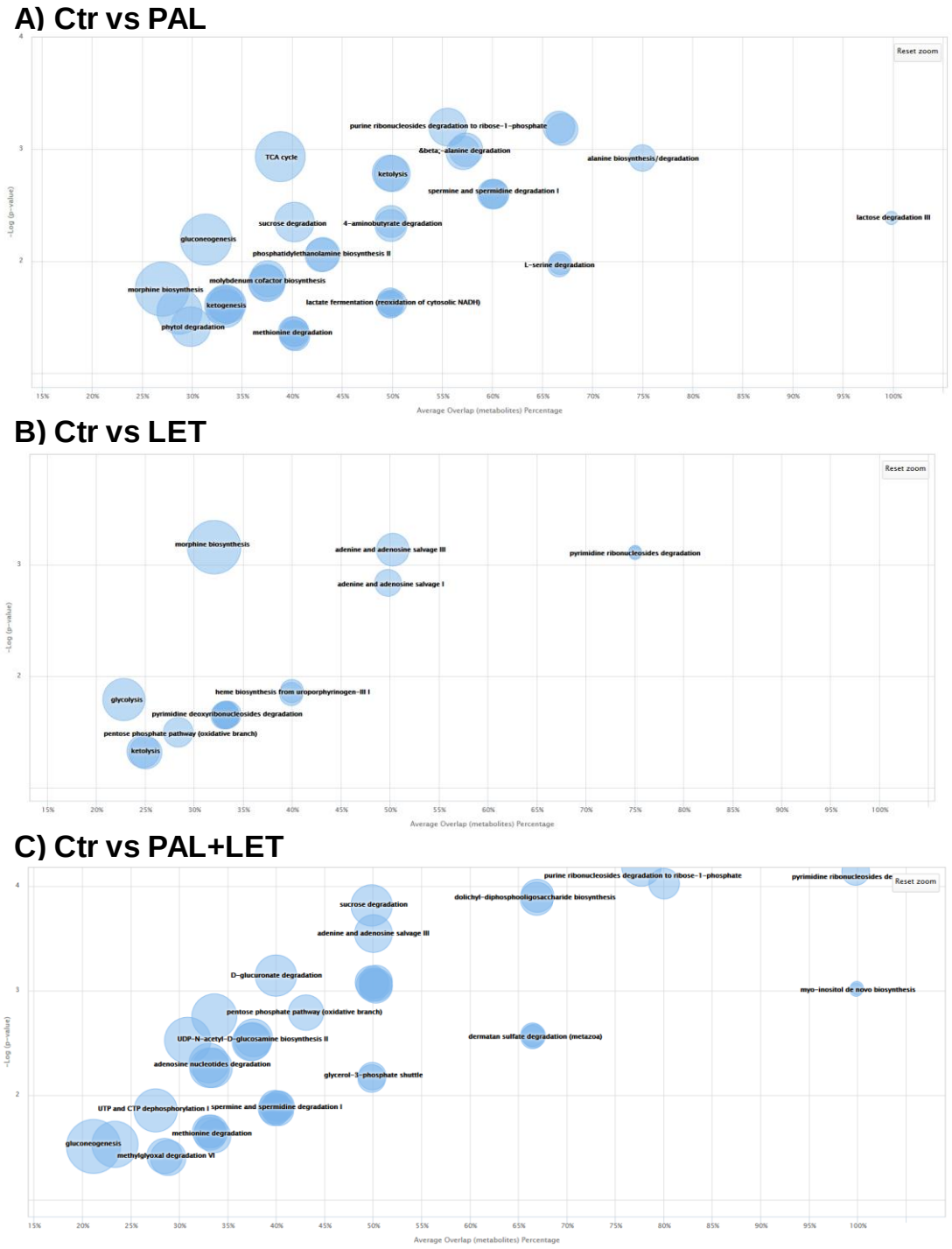

Fig. S2 Predicted metabolic pathways highlighting the effect of the individual and combined agent dosing. Related to Figure 2. Samples were generated after 48 h treatment with palbociclib (A), letrozole (B), and the combined treatment (C). Plots were generated using XCMS Online with the *p*-value threshold filter set to 0.05. The radius of a circle represents the size of the metabolic pathway; significantly dysregulated pathways appear in the upper right-hand quadrant of the plot. Pathways are plotted as a function of pathway significance versus average metabolic pathway overlap. The x- and y-axis represent the average metabolite overlap as percentage and the -log (*p*-value), respectively.

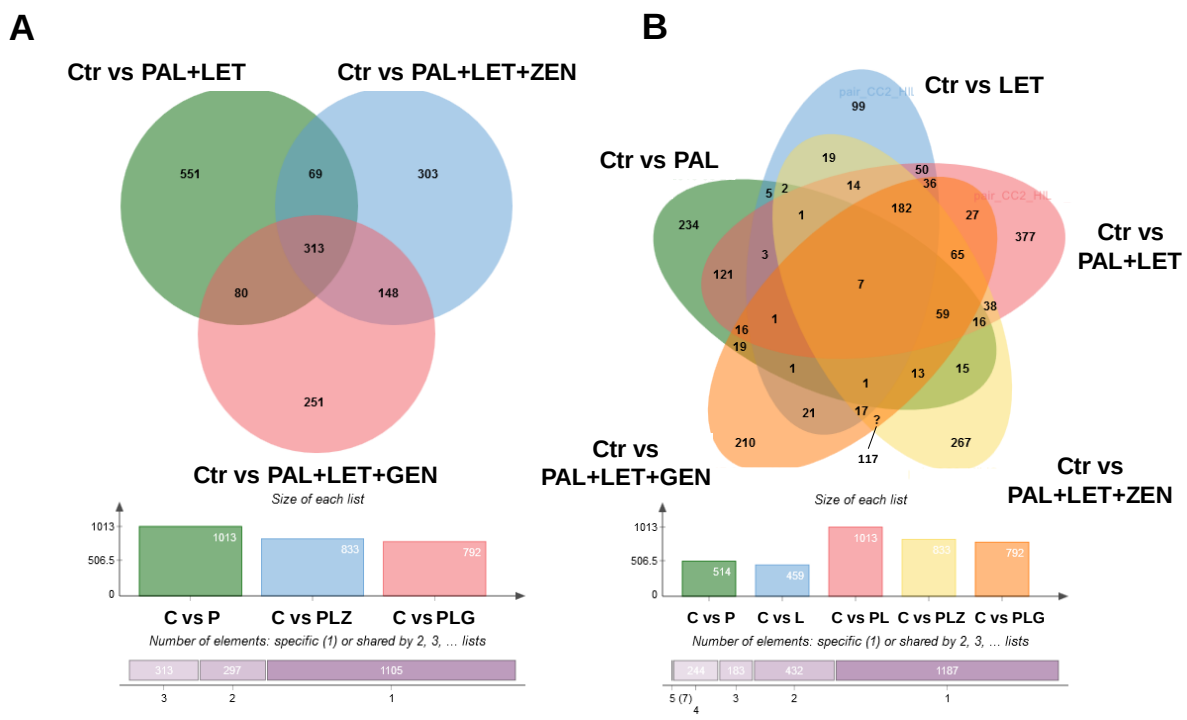

Fig. S3 Venn diagrams of meta-analyses demonstrating the effect of xenoestrogens on the combined agents based on the HILIC-LC-MS measurements from cell extracts. Related to Figure 3. (A) Compares the combined palbociclib and letrozole treatment alone (green) to cells exposed to ZEN (blue) or GEN (red) additionally. In (B) also the single agents were included in the analysis for the sake of completeness. Numbers indicate significantly dysregulated metabolic features compared to the control group (fold change >1.5, *p*-value <0.05).