Supplemental Table 1. Experimental diets composition

Ingredient (g/kg diet)	Control	Ketogenic
Carbohydrates, of which	685	27.5
Sucrose	100	---
Maltodextrin	130	---
Corn starch	400	7.5
Vitamin Mix	20	20
Mineral Mix	35	---
Protein, of which	162.6	270.6
Casein	162	268
DL-methionine	2.6	2.6
Fat, of which	87.97	571.6
Lard	---	480
Soybean oil	87	90
**Fat in casein*	0.97	1.6
Cellulose	64	---
Tert-butylhydroquinone	0.014	0.130
Mineral Mix	---	20
Calcium phosphate dibasic	---	19
Calcium carbonate	---	8

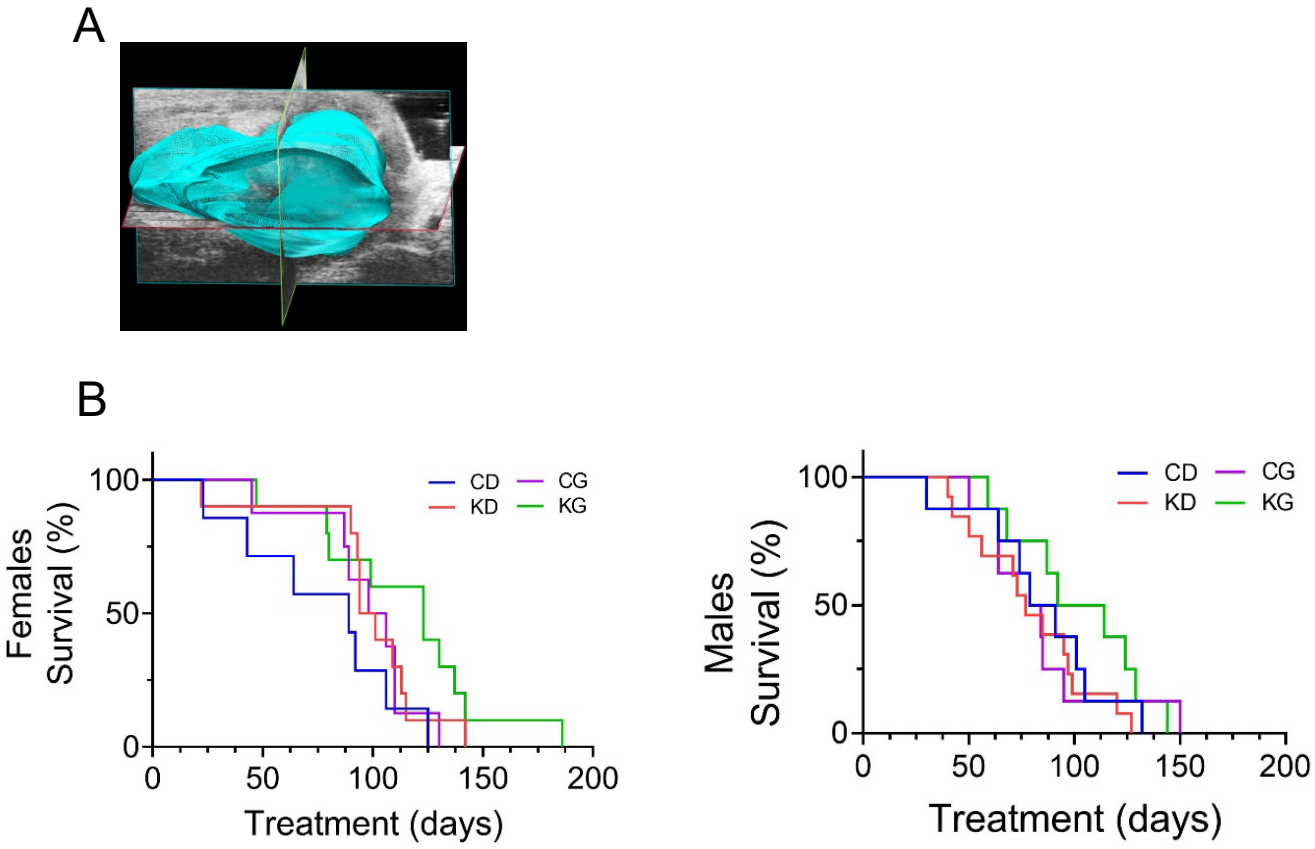

Figure S1. A ketogenic diet plus gemcitabine extends median overall survival in KPC mice. **A**: Representative ultrasound image of a pancreatic tumor in a KPC mouse at enrollment. **B:** Kaplan-Meier survival curves of male and female KPC mice fed a control diet (CD), ketogenic diet (KD), control diet plus gemcitabine (CG) or ketogenic diet plus gemcitabine (KG).

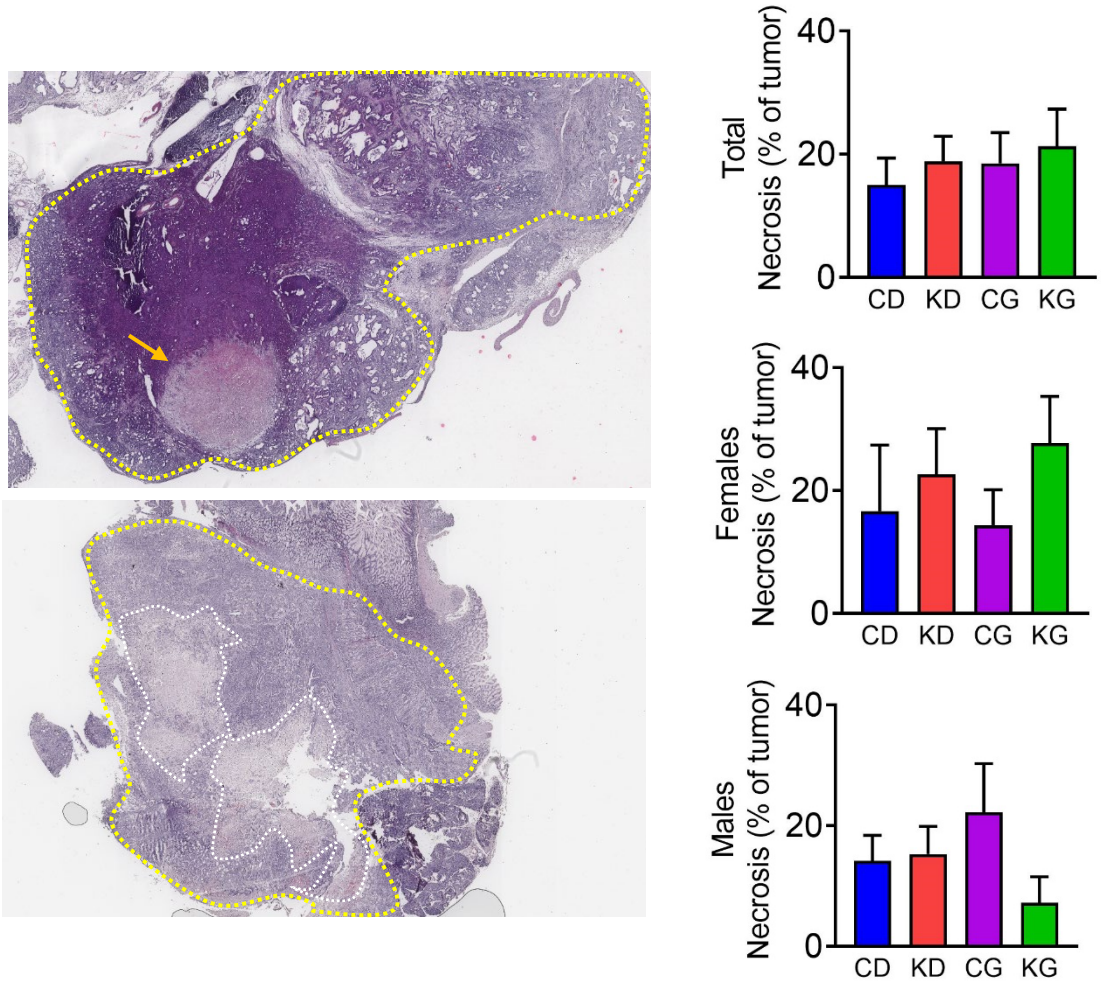

Figure S2: Histopathological analysis of necrosis (**C**) in pancreatic tumor isolated from female and male KPC mice treated with CD, KD, CG or KD. In the ketogenic diet treated groups, more tumor necrosis was noted overall. Representative images: (top) Control diet, (Bottom) Ketogenic diet. Yellow dotted line delineates total tumor surface area. Orange arrow highlights a discrete focus of tumor necrosis. White dotted line delineates more irregular and more extensive tumor necrosis. Hematoxylin and eosin-stained sections. All images digitally scanned at 20X original magnification.

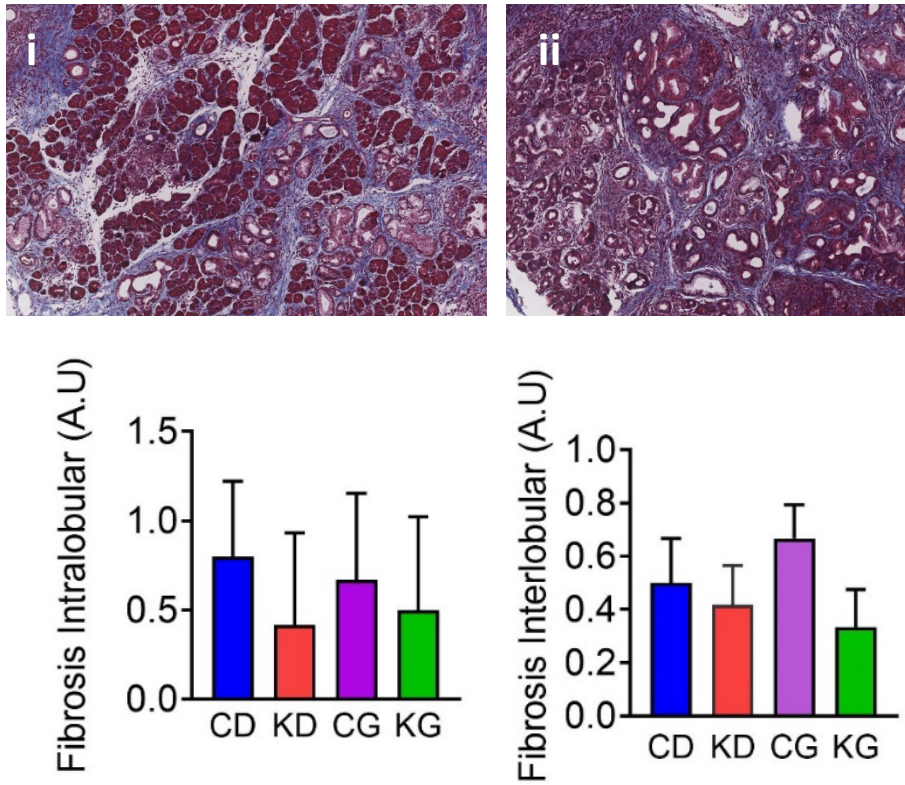

Figure S3: Histopathological analysis of fibrosis in pancreatic tumor isolated from female and male KPC mice treated with CD, KD, CG or KD. In all treatment groups, both intra- and interlobular fibrosis was observed in the background non-neoplastic pancreas. Representative images of Masson trichrome-stained sections: (i) Control diet, (ii) Ketogenic diet.. All images digitally scanned at 20X original magnification.

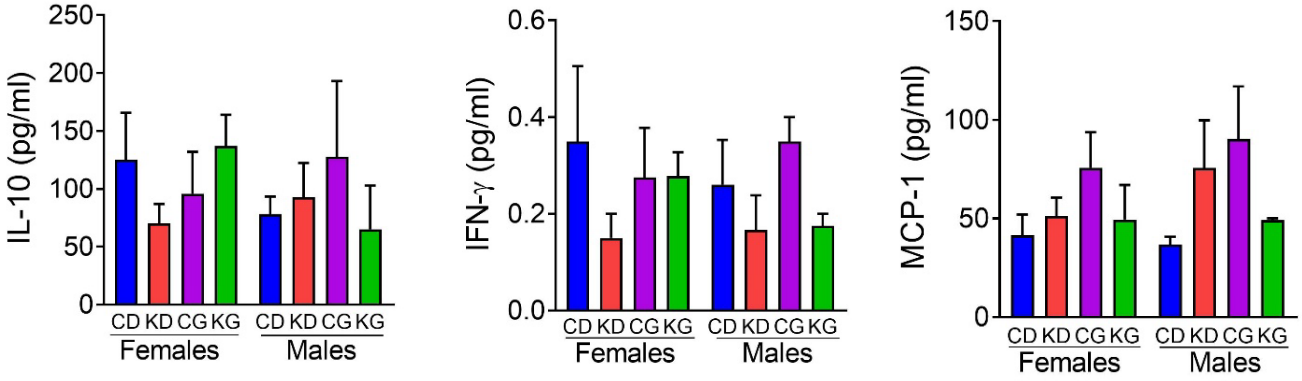

Figure S4: IL-10, IFN-γ and MCP-1 levels were measured in serum obtained from female and male KPC mice fed a CD, KD, CG or KG at euthanasia. Results are expressed as mean ± SD.

Supplemental Figure 5
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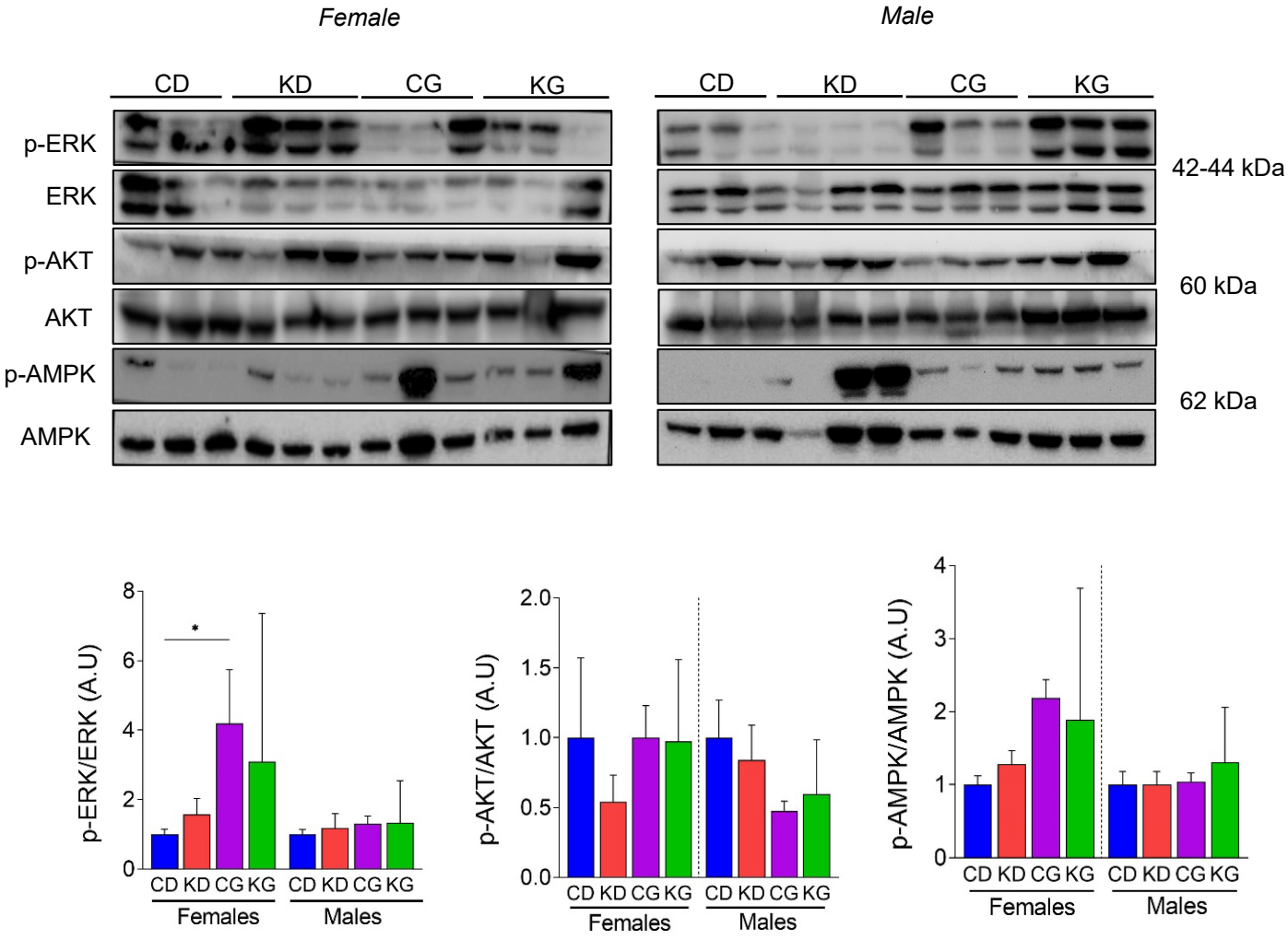

Figure S5. Effect of a ketogenic diet plus gemcitabine on AKT and ERK activation at endpoint. Immunoblots for p-AKT, AKT, p-ERK, ERK, p-AMPK and AMPK, in pancreatic tumor homogenates isolated from CD-, KD-, CG- and KG-treated female and male KPC mice when endpoint was reached. Bands were quantified and results are expressed as % control; **p<0.05.*

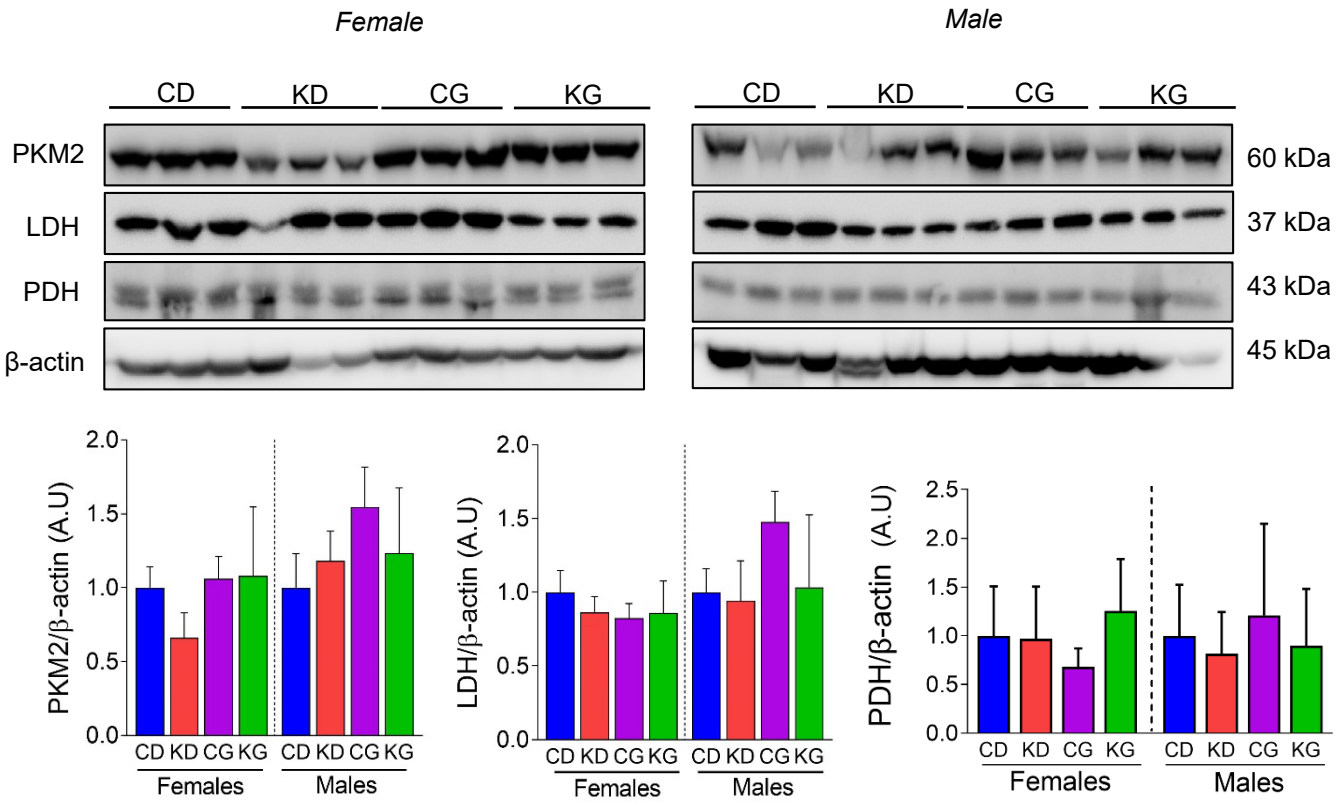

Figure S6. Effect of a ketogenic diet plus gemcitabine on glycolytic pathway in pancreatic tumors. Immunoblots for pyruvate kinase M2 (PKM2), Lactate dehydrogenase (LDH) and pyruvate dehydrogenase (PDH) in pancreatic tumor homogenates isolated from CD-, KD-, CG- and KG-treated female and male KPC mice at endpoint. Loading control: β-actin. Bands were quantified and results are expressed as % control; *$p<0.05$.

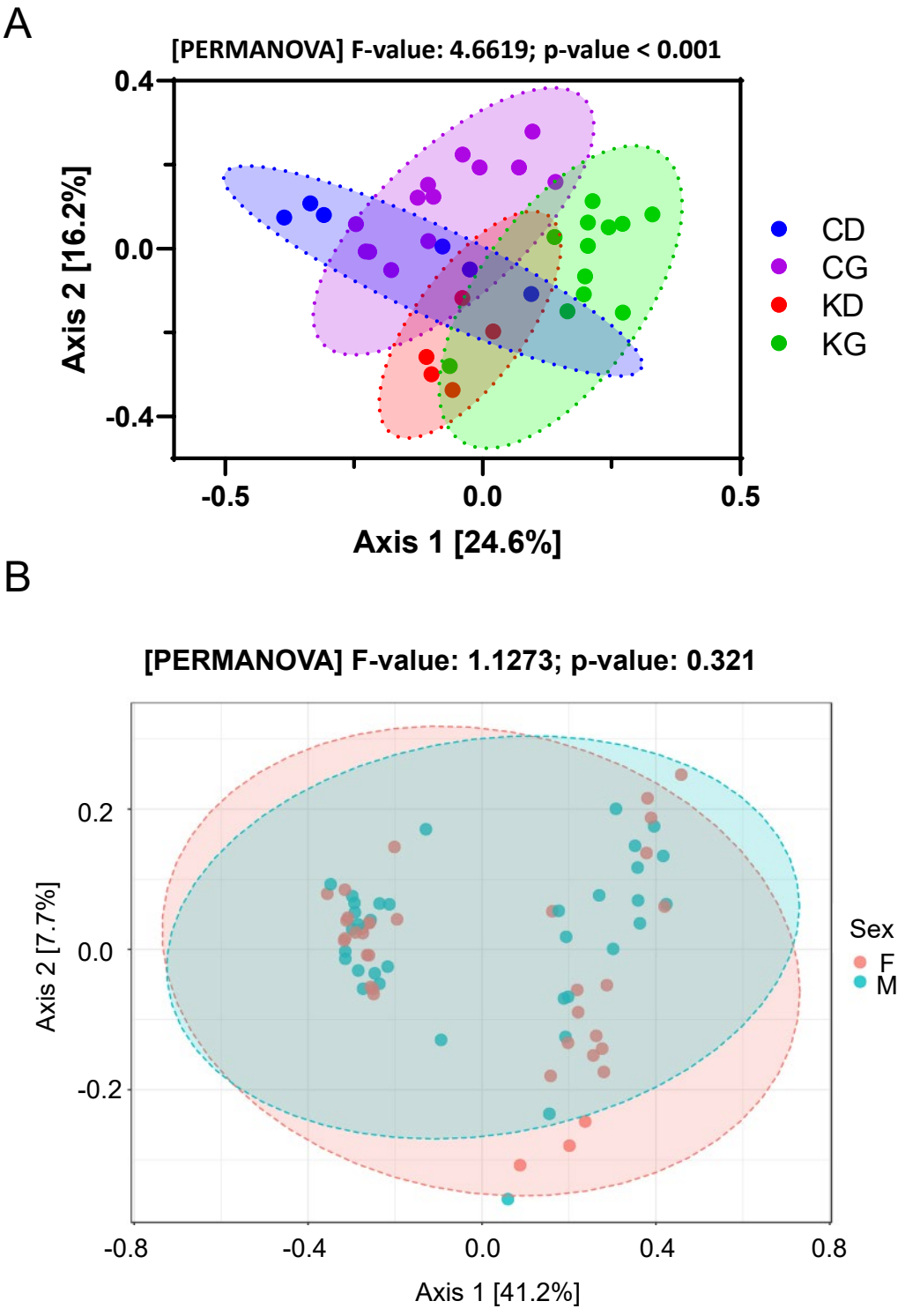

Figure S7: A ketogenic diet plus gemcitabine affects the gut microbiota. A-B: Principal component analysis (PCA). PC1 (axis 1) and PC2 (axis 2) represent the two most principal factors characterizing the bacterial profile among the 4 groups (**A**) or by sex (**B**) and their contribution rates (%) are shown on the axes.

Supplemental Figure 8
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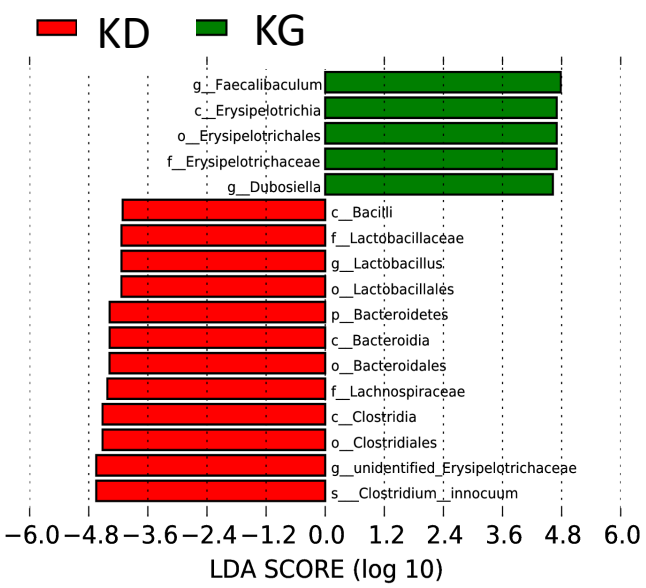

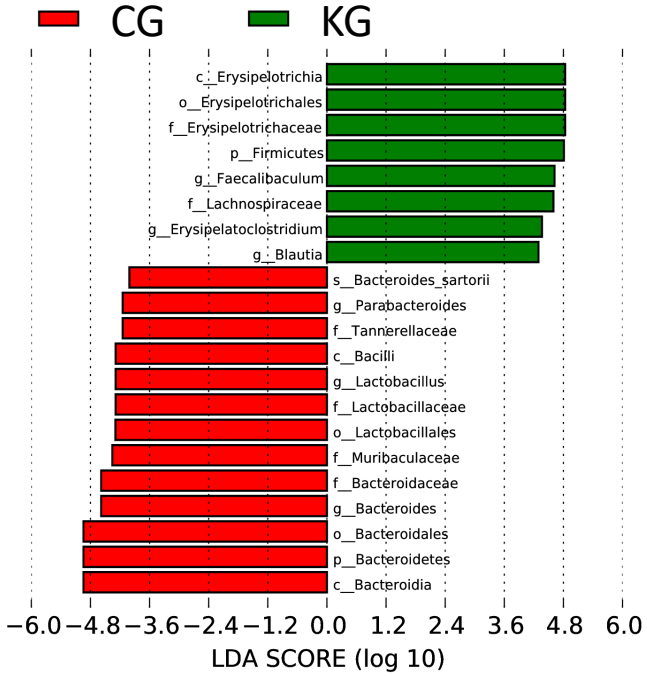

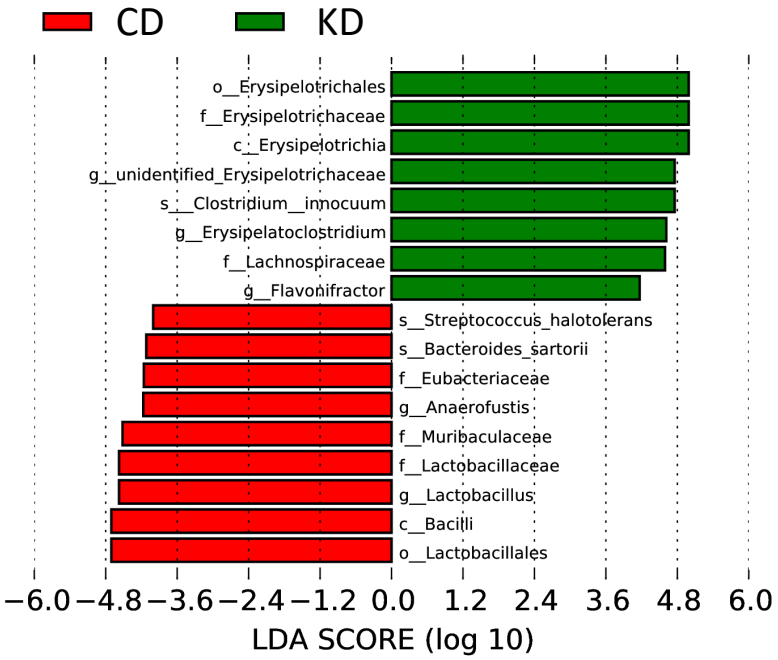

Figure S8: A ketogenic diet affects the gut microbiota. Distribution histogram of the LDA score determined by effect size (LEfSe). Bacterial taxa specifically enriched in groups with an LDA score > 3.6 are shown in the histograms. Comparisons after 1 month of diet/treatment were made between KG and KD (*upper left*), between KG to CG (*upper right*), and between KD and CD (*lower*) to highlight the bacteria taxa differentially enriched in KG-treated mice and in KD-treated mice.