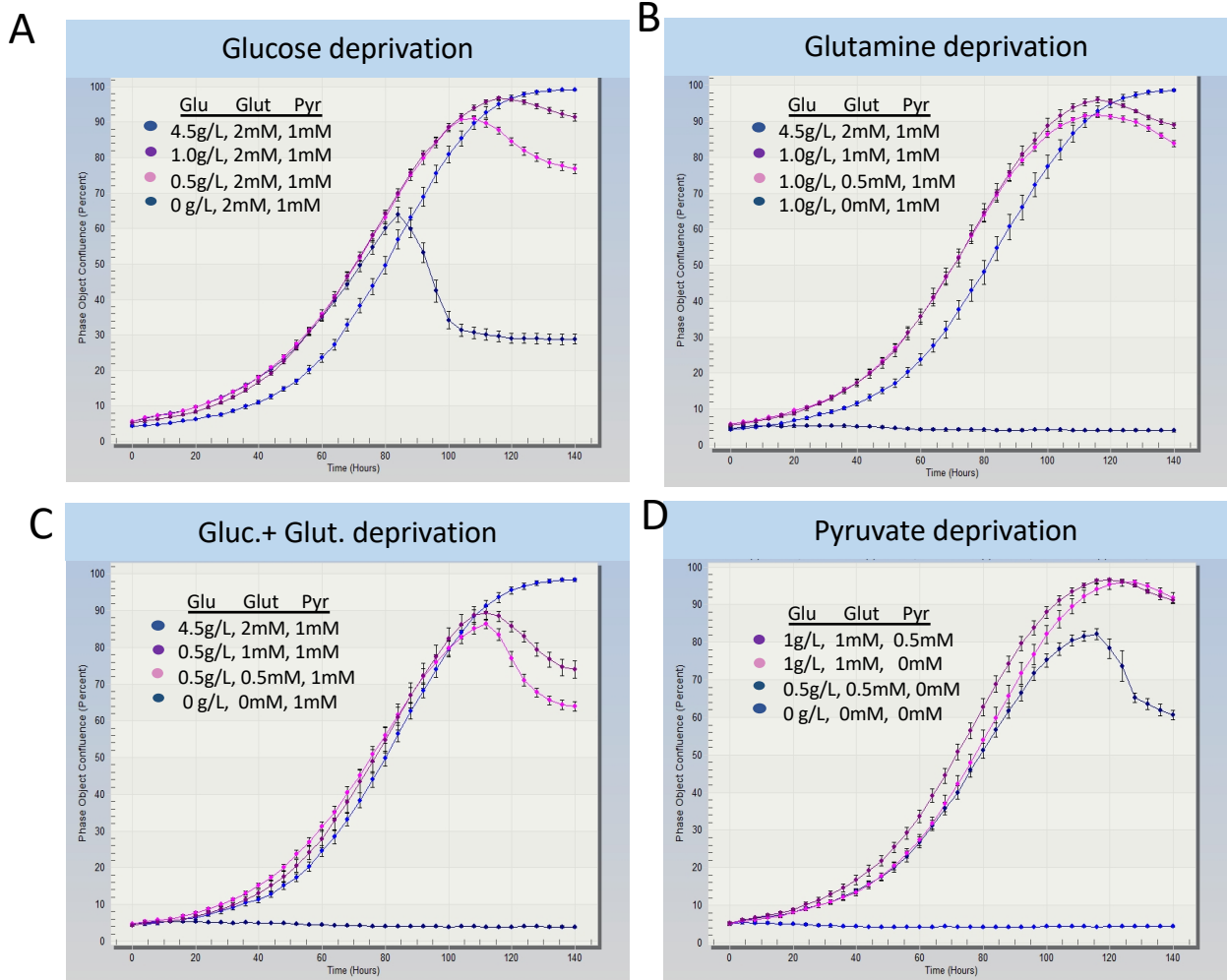
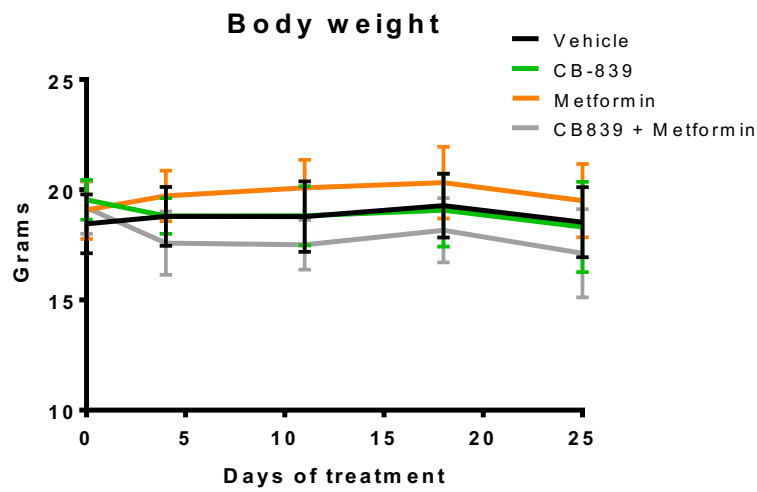


FIGURE S1



Murine OS cells K7M2 are sensitive to glutamine depletion. The proliferation responses of murine OS K7M2 cells to the deprivation of three carbon source nutrients: glucose (**A**), glutamine (**B**), both glucose and glutamine (**C**) or pyruvate (**D**) for 6 days.

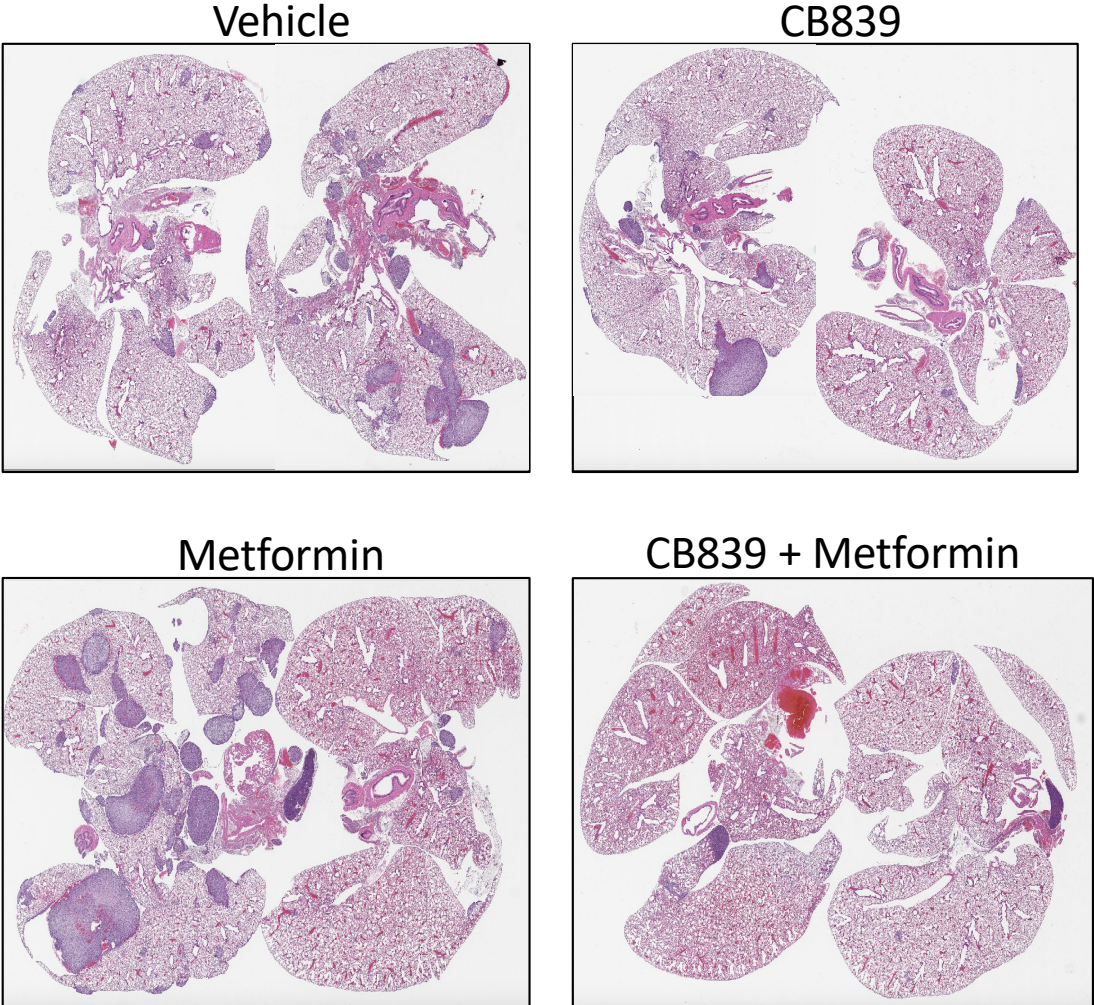
FIGURE S2



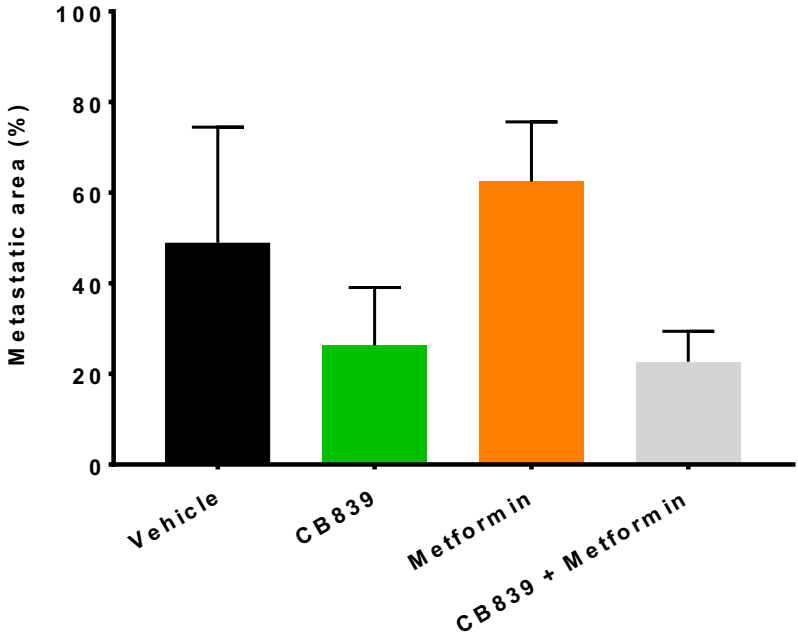
Body weights of mice treated with CB-839, metformin and combination: The measurements were taken once a week after tumor cells injection. No significant difference was found for mice body weigh through treatment period.

FIGURE S3

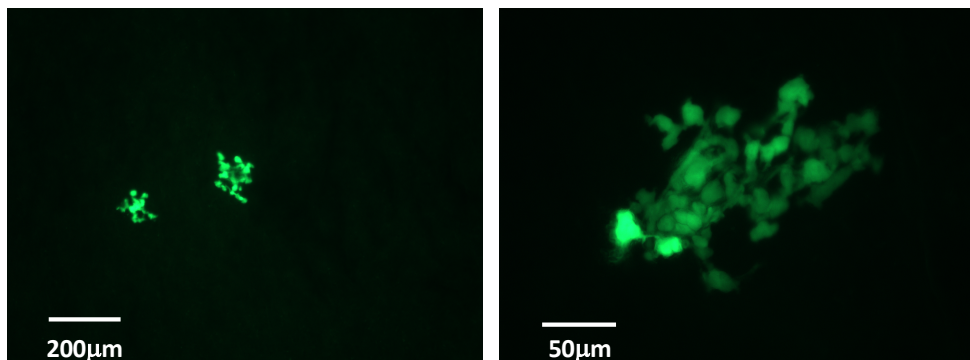
A



B



C



A. Representative H&E stained whole lung sections of the mice treated with CB-839, metformin and the combination.
B. The experimental metastasis model of murine osteosarcoma K7M2 cells. Half million cells were intravenously injected into Balb/c mice. Mice received daily gavage of vehicle, CB-839 (200 mg/kg, twice a day), metformin (300 mg/kg, once a day) or combination of CB-839 and Metformin (n = 4). The treatments were started at day 2 for a total of 25 days. Data displayed as bar plots and SD representing the percentage of lung metastatic area over the whole lung section. **C.** Representative fluorescent images of the lung micro-metastases 9 days after the intravenous injection of OS MG63.3/GFP cells. Measurement as shown by the bars.

FIGURE S4

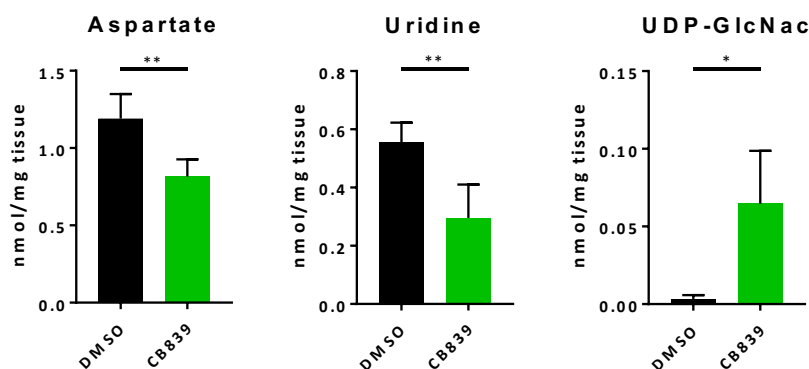


Figure S4. Metabolites found to be significantly dysregulated *via* ^1H NMR upon CB-839 treatment alone: Aspartate, uridine and UDP-N-acetylglucosamine (GlcNac) concentrations as nmol/mg tissue. t-test followed by Welch correction, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

FIGURE S5

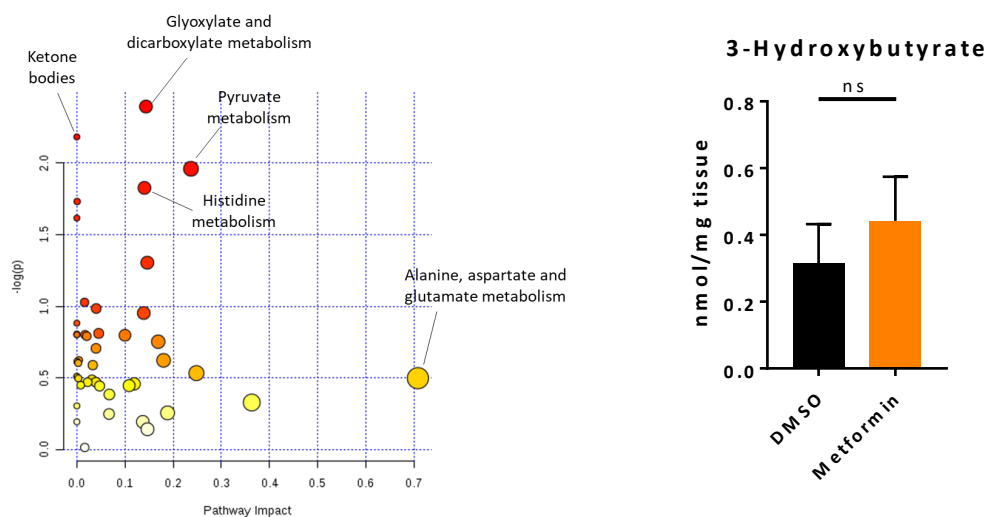


Figure S5. Pathways analysis and 3-HB levels from mice treated with metformin alone: A, Pathway analysis performed using the concentration of all the metabolites identified by ^1H NMR. Only relevant pathways are labeled for clarity purposes. B, 3-Hydroxybutyrate concentration obtained by ^1H NMR ($p = 0.082$, t-test followed by Welch correction).

FIGURE S6

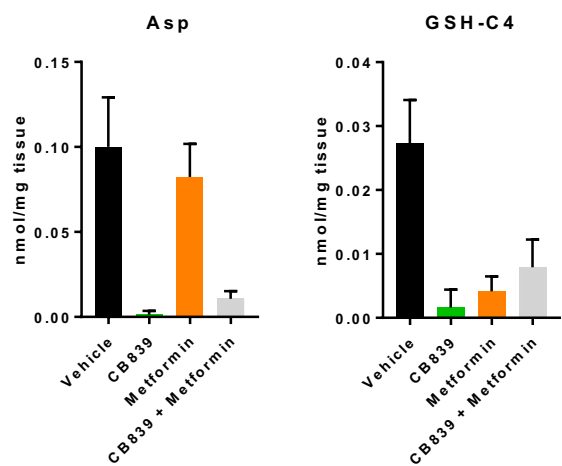


Figure S6. ^{13}C -Glutamine derived metabolites quantified by NMR: Concentrations of ^{13}C -Gln-derived-aspartate and GSH from mice treated with metformin, CB-839 or combination.