Figure S1. 30 mg/kg sorafenib was more effective at treating HCC than 10 mg/kg and displayed liver toxicity. **(A)** The anti-tumor efficiency of 10 mg/kg and 30 mg/kg sorafenib were estimated in LPC-H12 and Hepa1-6 subcutaneous tumor model (n=6-8). Tumor growth, relative tumor volume (RTV), and tumor weight were measured. RTV= Day 12 tumor volume/Day 0 tumor volume. **(B)** Body weight changes of mice during different treatment were measured. **(C)** Mouse serum levels of the following liver or renal toxicity-related indices were quantified. Liver toxicity: aspartate aminotransferase (ALT), alanine aminotransferase (AST), and total bilirubin (T-BIL); renal toxicity: blood urea nitrogen (BUN), creatinine (CR), and uric acid (UA). Data are presented as means ± SEM. ns, *P>0.05; *, P <0.05; **, P<0.01.

Figure S2. CKI combined with 10 mg/kg sorafenib showed no obvious side effects in mice. **(A)** Body weight changes of mice during indicated treatment were measured in different tumor models. **(B)** Liver index was measured through ALT, AST, T-BIL in the serum of mice after treatments. **(C)** The index of kidney toxicity was measured through BUN, CR, and UA in the serum of mice after treatments.

Figure S3. The effect of CKI combined with 30 mg/kg sorafenib on tumor growth, tumor weight, the distribution of immune cells, liver and renal toxicity-related indices were observed. **(A)** The anti-tumor efficiency of CKI combined with 10 mg/kg or 30 mg/kg sorafenib were estimated in LPC-H12 subcutaneous tumor model (n=6-10). Tumor growth and tumor weight were measured. **(B)** The infiltration of total immune cells ($CD45^+$) in mice tumors after different treatment were measured by FACX. **(C)** The proportion of tumor-infiltrating immune cells in mice tumor tissues after treatment was quantified by flow cytometry. **(D)** The proportion of immune cells in mice blood after treatment was quantified by flow cytometry. **(E)** The levels of ALT, AST and T-BIL were detected in murine serum after indicated treatments. **(F)** The levels of BUN, CR and UA were detected in murine serum after indicated treatments. Data are presented as means ± SEM. ns, *P>0.05; *, P <0.05; **, P<0.01.

Figure S4. The total immune cells and other type immune cells in mice blood or tumor tissues after CKI and 10mg/kg sorafenib combination treatment. **(A)** The infiltration of total immune cells in tumor tissues in different tumor models after indicated treatments. **(B)** The proportion of M-MDSC, M0, Neutrophil, NK and DC in LPC-H12 or Hepa1-6 subcutaneous tumors. **(C)** $CD4^+$ T, $CD8^+$ T, MDSC, Neutrophil, NK and DC in mice blood were measured by FACS. Data are presented as means ± SEM. **, P<0.01; ***, P<0.001.

Figure S5. CKI combined with 10mg/kg sorafenib shown no anti-tumor effect in nude mice. **(A)** Tumor growth, tumor weight, and body weight of LPC-H12 subcutaneous tumor in nude mice (n=6-8) after the indicated treatments were measured. **(B)** The proportion of $CD4^+$ T, $CD8^+$ T, M1-TAMs, and M2-TAMs were determined by FACS in nude mice tumor tissues. **(C)** The M1/M2 fold changes were quantified after indicated treatments. **(D)** The influence of 0.66mg/mL CKI on the proliferation of CFSE-labeled $CD8^+$ T cells after coculture for 72h. **(E)** After co-incubation with CKI and different doses of sorafenib, the cytotoxicity of Hepa1-6 cells was determined. Data are presented as means ± SEM. *, P <0.05; **, P<0.01.

Figure S6. The $CD8^+$ T cells and macrophages depletion efficiency of neutralizing anti-CD8 antibody and clodronate liposomes. **(A)** The number of $CD4^+$ and $CD8^+$ T cells were analyzed by flow cytometry after 4 days with or without 200μL clodronate liposomes or 200μg neutralizing anti-CD8 antibody treatment in the blood and spleen of C57BL/6 mice. **(B)** The number of $CD11b^+Ly6C^+$ monocytes in blood and $CD11b^{low/int}F4/80^{high}$ macrophages in spleen were detected by FACX after 4 days with or without 200μL clodronate liposomes or 200μg neutralizing anti-CD8 antibody treatment of C57BL/6 mice. Data are presented as means ± SEM. ***, P<0.001.

Figure S7. The other type immune cells in murine blood or tumor tissue with $CD8^+$ T cells or macrophages depletion after CKI and 10mg/kg sorafenib combination treatment. **(A)** The proportion of M-MDSC, M0, Neutrophil, NK and DC in LPC-H12 subcutaneous tumors. **(B)** $CD4^+$ T, $CD8^+$ T, Monocyte, Neutrophil, NK and DC in mice blood were measured by FACS. **(C)** The M1/M2 fold changes were quantified after indicated treatments. Data are presented as means ± SEM. ***, P<0.001.

Figure S8. The tumor growth was measured in different groups with the indicated treatments. Data are presented as means ± SEM. *, P <0.05

Figure S9. The immunosuppressive effect of different time intervals CM-treated macrophages on $CD8^+$ T cells. **(A)** The mRNA expression of related anti-inflammatory markers in macrophages treated with Hepa1-6 CM for 24, 48 or 72h. **(B)** The proliferation of CFSE-labeled $CD8^+$ T cells cocultured with different time intervals CM-treated macrophages. **(C)** The influence of different dose CKI treatment on the proliferation of CFSE-labeled $CD8^+$ T cells cocultured with macrophages (CM treatment for 72h before). **(D)** The representative histograms of CFSE-labeled $CD8^+$ T cells for B. **(E)** The representative histograms of CFSE-labeled $CD8^+$ T cells for C. Data are presented as means ± SEM. *, P <0.05; **, P<0.01; ***, P<0.001.

Figure S10. CKI influenced $M_{hepa1\text{-}6}$ polarization at different times. Data are presented as means ± SEM. *, P <0.05; **, P<0.01; ***, P<0.001.

Figure S11. The expression of cytotoxic markers in $CD8^+$ T cells co-cultured with CKI-primed $M_{hepa1\text{-}6}$ or CKI-primed $M_{hepa1\text{-}6}$ Supernatant was determined by qRT-PCR. Data are presented as means ± SEM.

Figure S12. CKI influenced the expression of receptors and related signaling pathways. **(A)** The expression of pro-inflammatory polarization-related receptors in M1 and M2 with 0.66 mg/mL CKI incubation was measured. **(B)** The expression of pro-inflammation genes in $M_{hepa1\text{-}6}$ exposed to CKI (0.66 mg/mL) along with Sparstolonin B (10μM) or IFN-γR monoclonal antibody (4μg/mL) was measured by qRT-PCR. **(C)** The expression of TNFR1 in $M_{hepa1\text{-}6}$ exposed to CKI (0.66 mg/mL) along with Sparstolonin B (10μM), IFN-γR monoclonal antibody (4μg/mL) or anti-TNFR1 antibody (25μg/mL) was determined by western blotting. **(D)** $M_{hepa1\text{-}6}$ cells were exposed to 0.66 mg/mL CKI for 12h and 10 ng/mL TNF-α for different time intervals, and the amount of TRADD, RIP1, TAB1, phosphorylated and total JNK and ERK was measured. **(E)** Body weight changes of mice during

indicated treatments were measured in LPC-H12 subcutaneous tumor. Data are presented as means ± SEM. **, P<0.01; ***, P<0.001.