**Supplementary materials**

Table 1 The information of patients treated with anti-PD-1 antibodies (RNA-seq)

Table 2 HCC Patients information treated with anti-PD-1 antibodies (T cells)

Table 3 HCC Patients information (T cells)

Table 4 Fluorescent-labeled antibodies

Table 5 Primary antibodies and dilutions

Table 6 Gene biotype in cluster 4

**Figure S1. Analysis of FGF7 and VEGFA on survival and infiltration of immune cells**

Kaplan-Meier’s curves for OS in grade 3 **(A)** and 4 **(B)** HCC patients in different groups of FGF7 expression; Kaplan-Meier’s curves for OS in HCC patients in different groups of FGFR1 **(C)** and VEGFA expression **(D)** analyzed by KM plotter; Bioinformatics analysis for the effect of FGF7 on immune cells infiltration in LIHC analyzed by TIMER **(E, F)**.

**Figure S2. The effect of VEGFA and bFGF on T cells and HUVEC**

The T cells derived from healthy donors and HCC patients with or without PD-1 antibodies treatment were analyzed for PD-1, CTLA-4 and Tim-3 expression and IFNG or GZMB secretion. **(A)** Healthy donor derived T cells were separated. RNA expression of VEGFA was analyzed in rest T cells, activated T cells by CD3 antibody (5ng/ml) and CD28 antibody (2.5ng/ml) and activated T cells treated with lenvatinib (100nM), sorafenib (100nM) and BGJ398 (100nM); **(B)** Healthy donor derived T cells were activated with CD3 antibody (10 ng/ml) and then stimulated by VEGFA with gradient concentrations (0, 20, 50, 100 ng/ml); **(C)** Healthy donor derived T cells were activated with CD3 antibody (10 ng/ml) and then stimulated by bFGF with gradient concentrations (0, 20, 50, 100 ng/ml); **(D)** Healthy donor derived T cells were activated with CD3 antibody with gradient concentrations (0, 0.5, 3, 10 ng/ml) and then stimulated by VEGFA (50 ng/ml); **(E)** Healthy donor derived T cells were activated with CD3 antibody with gradient concentrations (0, 0.5, 3, 10 ng/ml) and then stimulated by bFGF (50 ng/ml); **(D)** Healthy donor derived T cells were activated with CD3 antibody (10 ng/ml) as well as stimulated by VEGFA (50 ng/ml), bFGF (50ng/ml) respectively or the combination and then treated with lenvatinib with gradient concentrations (4, 30, 100 ng/ml). The PD-1 expression **(F)**, CTLA-4 expression and Tim-3 expression **(G)** were detected by flow cytometry. **(H)** HUVEC (EC) cells were treated with VEGFA (50ng/ml), bFGF (50ng/ml), VF (VEGFA 50ng/ml+ bFGF 50ng/ml), SOR+ bFGF (sorafenib 100nM+ bFGF 50ng/ml), SOR+VEGFA (sorafenib 100nM+ VEGFA 50ng/ml), LVF (lenvatinib 100nM+ VEGFA 50ng/ml+ bFGF 50ng/ml), SVF (sorafenib 100nM+ VEGFA 50ng/ml+ bFGF 50ng/ml), FVF (BGJ398 100nM+ VEGFA 50ng/ml+ bFGF 50ng/ml ), FSVF (BGJ398 100nM+sorafenib 100nM+ VEGFA 50ng/ml+ bFGF 50ng/ml). \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001, \*\*\*\*p < 0.0001 (Two-way ANOVA).

**Figure S3. lenvatinib has no effect on the proliferation and cell cycle of tumor cells and normal cells**

**(A)** The effect of lenvatinib with different concentration gradient (0, 30, 60, 120, 240, 480, 960, 2000, 3000 ng/ml) on tumor cell lines proliferation tested by CCK8; **(B)** Representative images of the effect of lenvatinib (120nM) on cell cycle tested by flow cytometry; **(C)** Metabolic detection for HUVEC treated by IFNG (20ng/ml), lenvatinib (120nM) or sorafenib (120nM) tested by YSI analysis; **(D)** Flow cytometry analysis for the apoptosis of tumor cells treated by lenvatinib (120nM).

**Figure S4. The effect of lenvatinib on T cells**

**(A)** Representative images showing VEGFR2 expression on CD3+CD8+T cells dissociated from the spleens and tumors in bal/bc mice with H22 tested by flow cytometry; **(B)** VEGFR2 expression in healthy donor derived T cells and HCC patients derived T cells tested by western blot; HCC patients derived T cells were treated with VEGFA (20ng/ml), IFNG (20ng/ml) and VEGFA (50ng/ml)+ lenvatinib with different concentration gradient (4, 30, 300, 3000 ng/ml) and then were collected for western blot; **(C)** Representative images of the effect of lenvatinib (10mg/kg) on PD-1 expression on T cells in different treatment groups dissociated from the tumors in bal/bc mice with H22 tested by flow cytometry.

**Figure S5. The effect of VEGFA and bFGF on T cells**

The T cells derived from healthy donors stimulated by VEGFA and bFGF were analyzed for PD-1 expression. **(A)** Representative images showing PD-1 expression on three different cell populations tested by flow cytometry; **(B)** Representative images showing PD-1 expression on the T cells of different cell populations after treated with VEGFA (50ng/ml), bFGF (50ng/ml) and VF+ LEN100 (VEGFA 50ng/ml+ bFGF 50ng/ml + lenvatinib 100nM) tested by flow cytometry.

**Figure S6. The anti-tumor and immunoregulation effect of lenvatinib and sorafenib**

After 10 days treatment, scatter showing mean number of tumor volume in different administered groups **(A)**; **(B)** Tumor growth curve in different administered groups; **(C)** Histogram showing mean number of the infiltration of CD4 and CD8 T cells ± SD in each group in tumor; **(D)** The scheme showing the treatment timing of drugs and cells injection; **(E)** The markers of macrophages polarization analysis in different treatment groups tested by RNA-seq. \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001, \*\*\*\*p < 0.0001 (Two-way ANOVA).

**Figure S7. The effect of combination lenvatinib and anti-PD-1 antibody therapy in the tumor microenvironment**

Histogram showing infiltration of CD4, CD8, NK and the proportion of PD-1+ NK cells, and infiltration of dendritic cells and the portion of MHC+/PD-L1+ dendritic cells of Balb/C and C57BL/6 mice measured by flow cytometry. \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001, \*\*\*\*p < 0.0001 (Two-way ANOVA). LEN = lenvatinib.

**Figure S8. Lenvatinb has no effect on the expression of PD-L1 in tumor cells and normal cells**

Western blot analysis for the expression of PD-L1 on tumor cells **(A)** and tumor cells stimulated by IFNG (20ng/ml) **(B).**