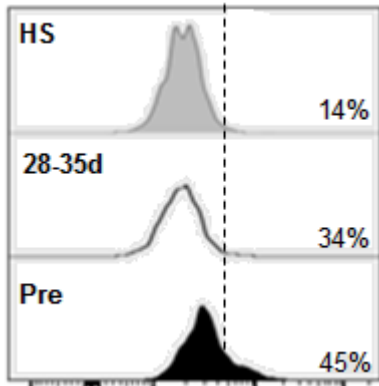


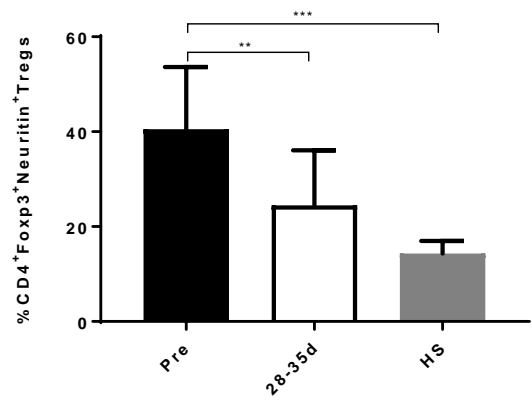
Supplementary Figure 1.

**Supplemental Figure 1. Decrease in Immunosuppressive cell subsets after sorafenib therapy** (A). Frequency and (B) absolute numbers of CD4<sup>+</sup>Foxp3<sup>+</sup> Tregs Pre vs 28-35d (n= 30). (C) Frequency and (D) absolute numbers of MDSCs Pre vs 28-35 (n=30). (E) Ratio of CD4<sup>+</sup>CD127<sup>+</sup> T cells : CD4<sup>+</sup>Foxp3<sup>+</sup> T cells Pre vs 28-35d (n=30). (F) Ratio of CD8<sup>+</sup>CD127<sup>+</sup> T cells : CD4<sup>+</sup>Foxp3<sup>+</sup> T cells Pre vs 28-35d (n=30). (G) Frequency and (H) absolute numbers of Foxp3<sup>+</sup>flt-3<sup>+</sup>pERK<sup>+</sup> Tregs Pre vs 28-35d (n= 30). (I) Frequency and (J) absolute numbers of flt-3<sup>+</sup>pERK<sup>+</sup> MDSCs Pre vs 28-35 (n=30). Each symbol represents an individual HCC patient, \*\*\*\*  $P < 0.0001$ , \*\*\*  $P < 0.001$ , \*\*  $P < 0.01$ , \*  $P < 0.05$ , paired  $t$ -test.

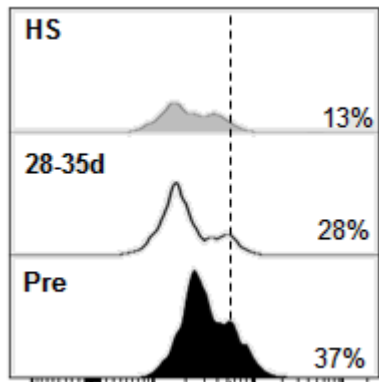
**A CD4<sup>+</sup>Foxp3<sup>+</sup>Neuritin<sup>+</sup>**



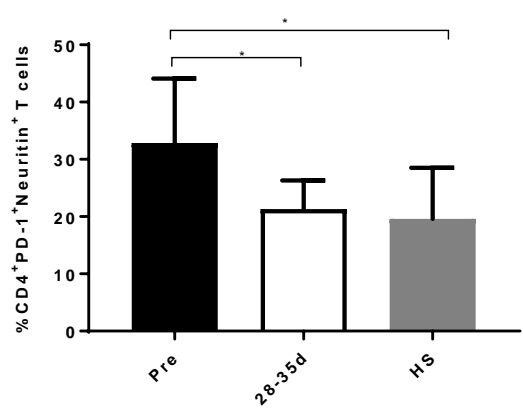
**B**



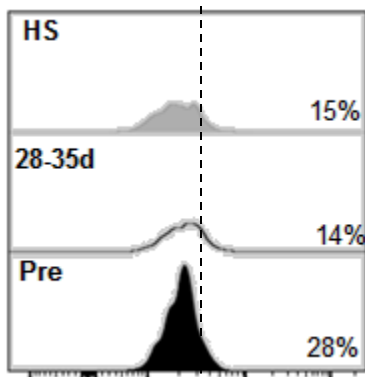
**C CD4<sup>+</sup>PD-1<sup>+</sup>Neuritin<sup>+</sup>**



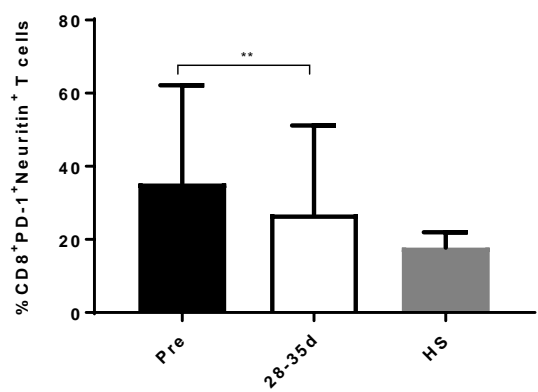
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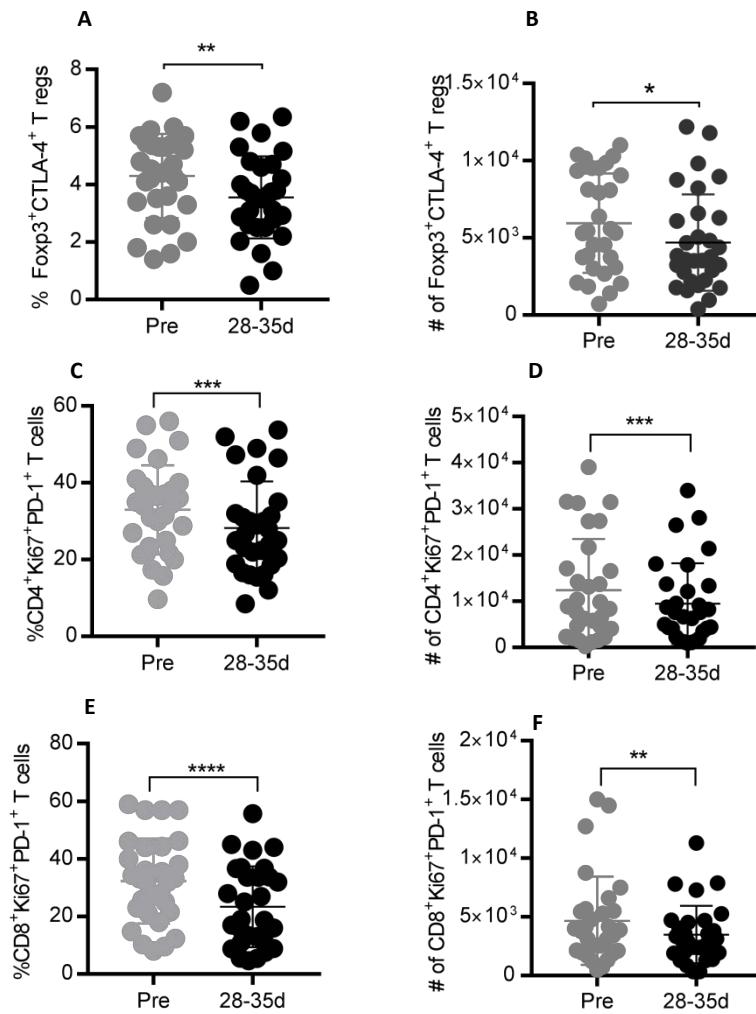
**E CD8<sup>+</sup>PD-1<sup>+</sup>Neuritin<sup>+</sup>**



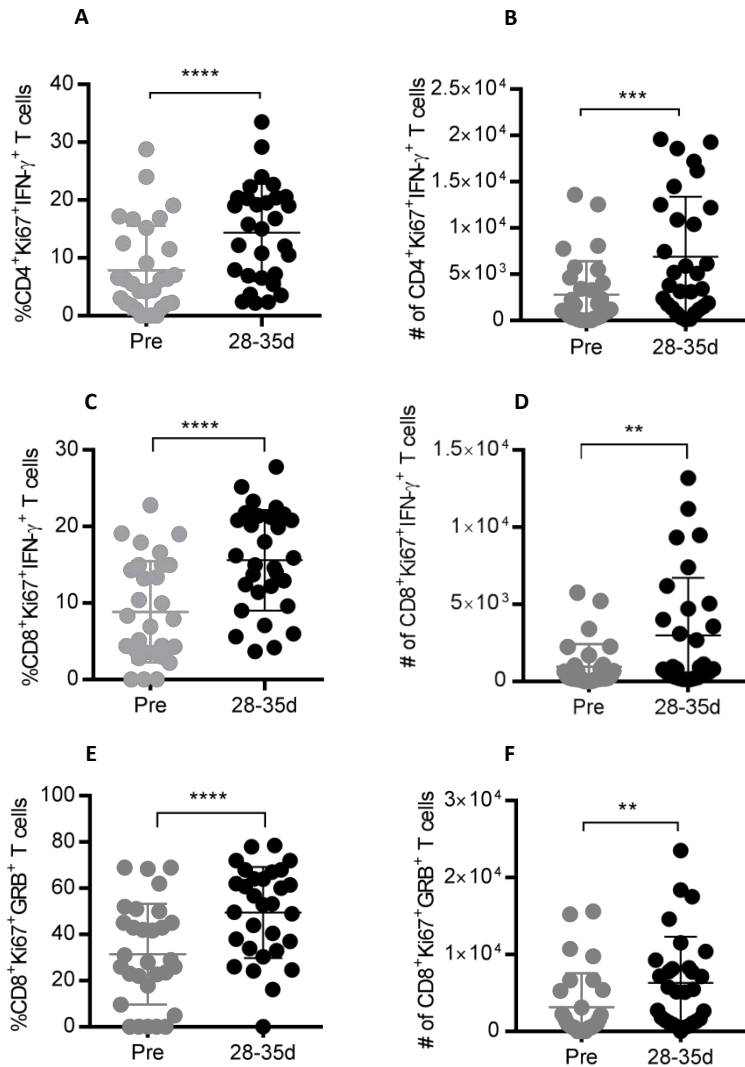
**F**



**Supplemental Figure 2. Effect of sorafenib treatment on Tregs and PD-1<sup>+</sup> T cells co-expressing neurotrophic factor neuritin.** (A) Representative histogram offset and (B) bar graph showing the frequency of CD4<sup>+</sup>Foxp3<sup>+</sup>neuritin<sup>+</sup> Tregs measured at pre and 28-35d of sorafenib treatment in HCC patients and in healthy subjects. (C) Representative histogram offset and (D) bar graph showing the frequency of CD4<sup>+</sup>PD-1<sup>+</sup>neuritin<sup>+</sup> T cells measured at pre and 28-35d of sorafenib treatment in HCC patients and in healthy subjects. (E) Representative histogram offset and (F) bar graph showing the frequency of CD8<sup>+</sup>PD-1<sup>+</sup>neuritin<sup>+</sup> T cells measured at pre and 28-35d of sorafenib treatment in HCC patients and in healthy subjects. In each set, n=6 HCC patients and n=6 healthy subjects were tested. (D). \*\*\*  $P < 0.001$ , \*\*  $P < 0.01$ , \*  $P < 0.05$ , unpaired t-test.



**Supplemental Figure 3. Reduction in T cell exhaustion markers after sorafenib treatment.** Immuno phenotypic analysis of T cells was performed after stimulation of PBMC *in vitro* using anti-CD3/CD28 at pre and 28-35d of sorafenib treatment using flow cytometry. **(A)** Frequency and **(B)** absolute numbers of Foxp3<sup>+</sup>CTLA-4<sup>+</sup> Tregs Pre vs 28-35d (n=30). **(C)** Frequency and **(D)** absolute number of CD4<sup>+</sup> Ki67<sup>+</sup>PD-1<sup>+</sup> T cells Pre vs 28-35d (n= 30). **(E)** Frequency and **(F)** absolute number of CD8<sup>+</sup> Ki67<sup>+</sup>PD-1<sup>+</sup> T cells Pre vs 28-35d (n= 30). Each symbol represents an individual HCC patient. \*\*\*\*  $P < 0.0001$ , \*\*\*  $P < 0.001$ , \*\*  $P < 0.01$ , \*  $P < 0.05$ , paired t-test.



**Supplemental Figure 4. Effect of sorafenib treatment on T effector cells** PBMCs

from HCC patients were stimulated with anti -CD3/CD28 *in vitro* for 48 hrs and immunophenotypic analysis was performed. (A) Frequencies and (B) absolute number of CD4<sup>+</sup>Ki67<sup>+</sup>IFN- $\gamma$ <sup>+</sup> T cells Pre vs 28-35d (n=30). (C) Frequencies and (D) absolute number of CD8<sup>+</sup>Ki67<sup>+</sup>IFN- $\gamma$ <sup>+</sup> T cells Pre vs 28-35d (n= 30). (E) Frequencies and (F) absolute number of CD8<sup>+</sup>Ki67<sup>+</sup>GRB<sup>+</sup> T cells Pre vs 28-35d (n= 30). Each symbol represents an individual HCC patient. \*\*\*\*  $P < 0.0001$ , \*\*\*  $P < 0.001$ , \*\*  $P < 0.01$ , \*  $P < 0.05$ , paired t-test.

**Supplemental Table 1. End of study status/ Reasons for coming of therapy**

Total patients (N)	30			
On treatment	3			
Disease progression	13			
Toxicity	7			
Refused treatment	2			
Death	1			
Other reasons	4			
Accrual between November 20, 2013 to May 12, 2017				

**Supplemental Table 2. PFS and OS results while on sorafenib therapy based on their Child-Pugh score**

Child-Pugh score	PFS (95% CI)			OS (95% CI)		
	6 months	1 year	Median survival rate	6 months	1 year	Median survival rate
A	0.40 (0.19 - 0.60)	0.27 (0.10 - 0.49)	3.7 (1.8 - 9.8)	0.65 (0.40 - 0.82)	0.48 (0.25 - 0.68)	9.7 (2.5 - 27.0)
B	0.40 (0.12 - 0.67)	0.00 (0.05 - 0.56)	4.9 (1.9 - 11.9)	0.60 (0.25 - 0.83)	0.38 (0.10 - 0.66)	7.8 (1.9 - 21.4)