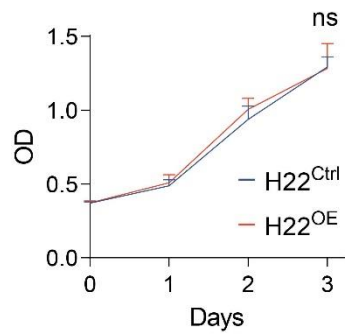


**Supplementary Figure 1. Validation of circTMEM181 expression in HCC**

(A) qPCR analysis validated the circTMEM181 level in 6 patients with PD or PR after anti-PD1 therapy (tests were repeated three times for each patient, t-test, \*\*:  $p < 0.01$ )

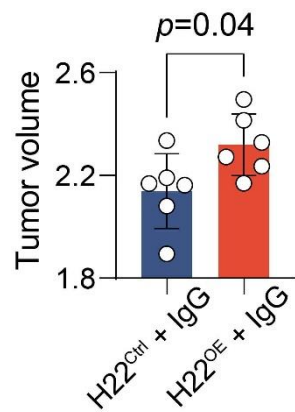
(B) Melt curve plot and gel electrophoresis validated the amplified PCR product by reverse transcription (RT)-PCR utilizing a divergent primer pair of hsa\_circ\_0001663(circTMEM181) in HCC tumor (6 Patients with PD or PR after anti-PD1 therapy).

(C) qPCR analysis indicated that different HCC cell lines stably overexpressing circTMEM181 (OE) or circTMEM181 knock down (sh) were constructed by lentivirus.



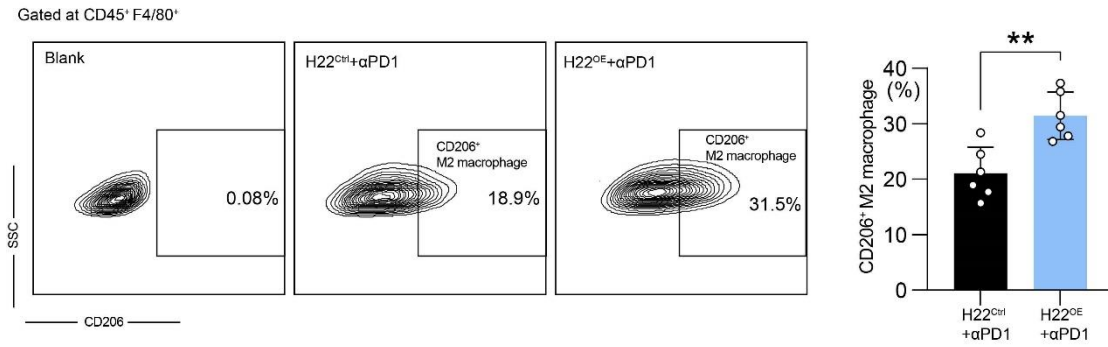
**Supplementary Figure 2. Function of circTMEM181 in H22 cells**

CCK-8 analysis showed no statistical difference in the proliferative capacity between H22 overexpressing circTMEM181(H22<sup>OE</sup>) and the negative control (H22<sup>Ctrl</sup>) at Day 3 (t-test, ns: not significant).



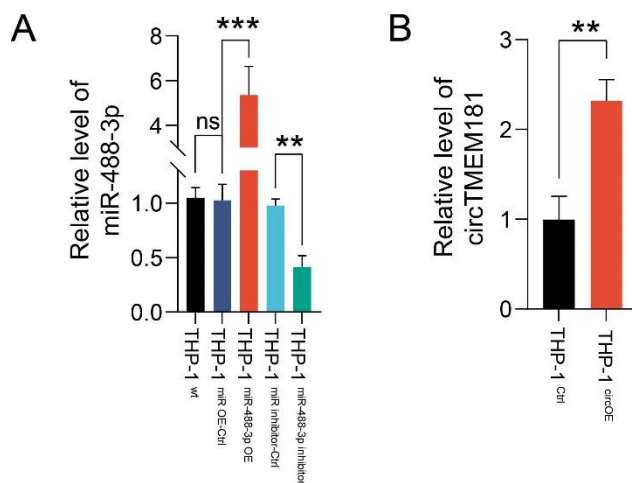
**Supplementary Figure 3. Tumor volume of the H22<sup>Ctrl</sup> + IgG and H22<sup>OE</sup> + IgG**

H22<sup>Ctrl</sup> + IgG and H22<sup>OE</sup> + IgG mice were sacrificed at Day 20 and the tumor volume was measured (t-test).



**Supplementary Figure 4. Detection of CD206<sup>+</sup> macrophage between H22<sup>OE</sup>+αPD1 group and H22<sup>Ctrl</sup>+αPD1 group**

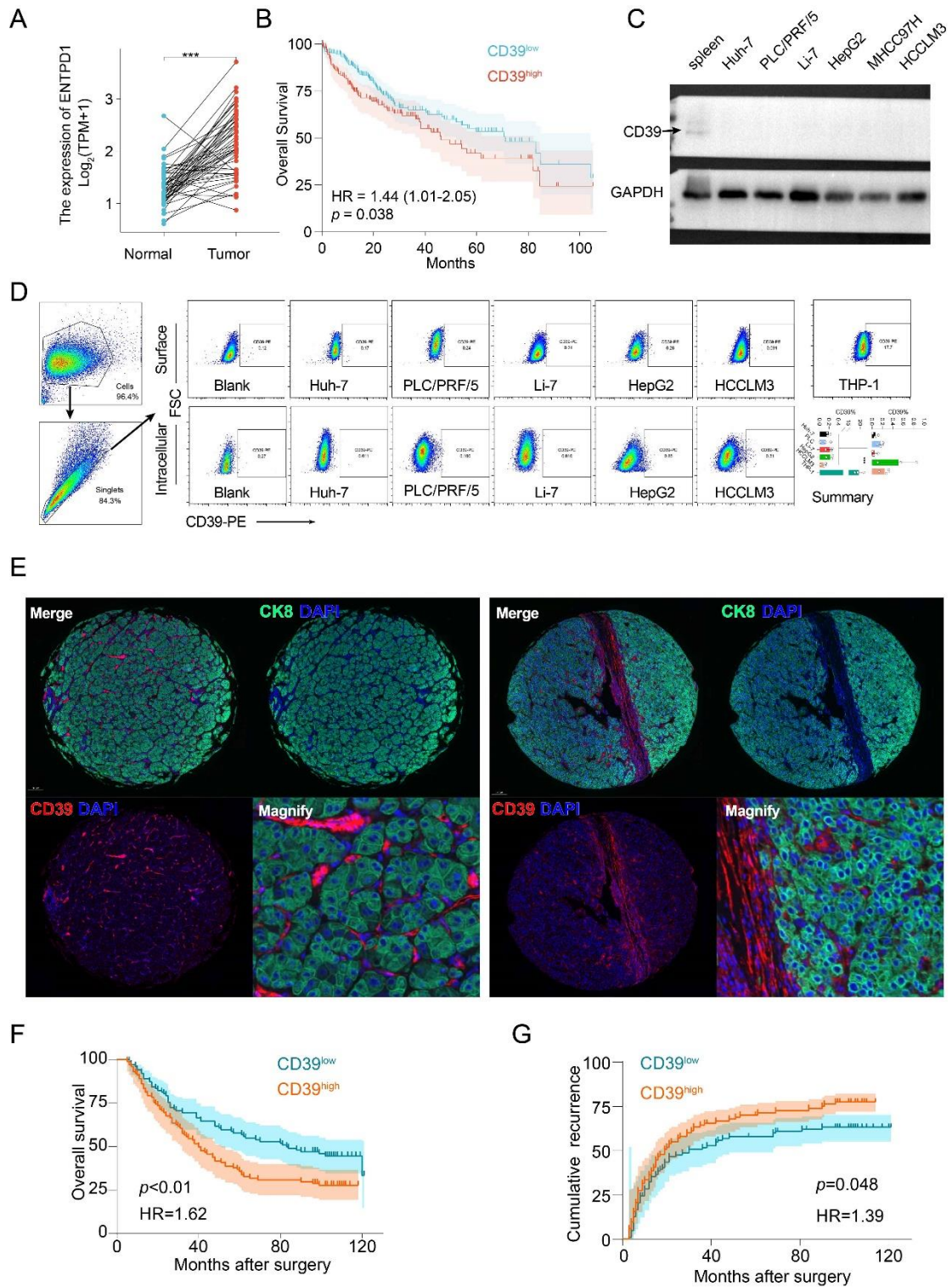
Flow cytometry analysis shows higher proportion of CD206<sup>+</sup> M2 expression in H22<sup>OE</sup>+αPD1 group (t-test, \*\*:  $p < 0.01$ )



**Supplementary Figure 5. Manipulating circTMEM181 and miR-488-3p in THP-1**

(A) qPCR analysis indicated that THP-1 was stably overexpressed or inhibited miR-488-3p (t-test, \*\*:  $p < 0.01$ ).

(B) qPCR analysis indicated that THP-1 was stably overexpressed circTMEM181 (t-test, \*\*:  $p < 0.001$ , \*\*:  $p < 0.01$ , ns: not significant).



### Supplementary Figure 6. Detection of CD39 expression in HCC

(A) Analysis of CD39 expression in 50 paired HCC and corresponding normal tissue from TCGA data (paired-t test, \*\*\*\*:  $p < 0.001$ ).

(B) Kaplan-Meier estimate of overall survival in the TCGA HCC cohort with different levels of CD39 (log-rank test).

(C) WB analysis showed CD39 and GAPDH expression across the HCC cell lines (Huh-7,

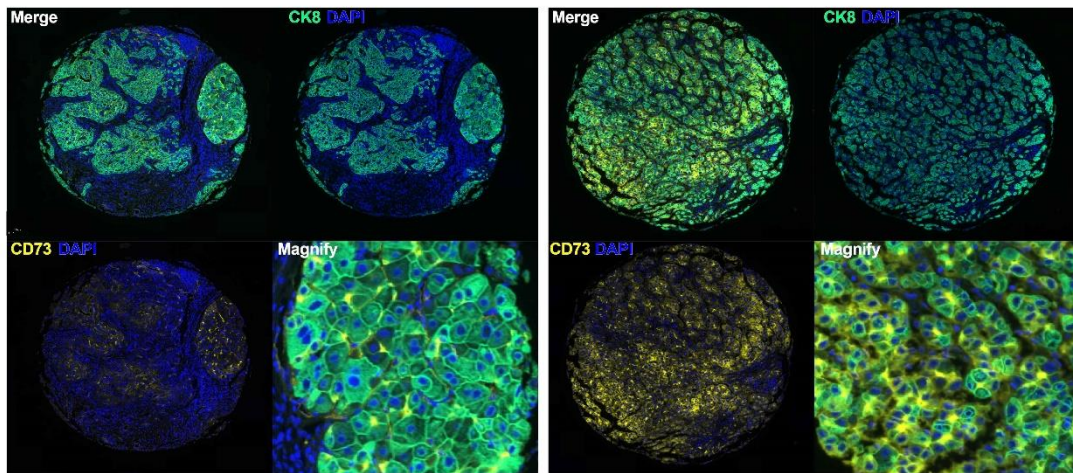
PLC/PRF/5, Li-7, HepG2, 97H and HCCLM3) and the positive control (spleen tissue).

**(D)** Flow cytometry analysis of CD39 expression on the HCC cell lines (Surface or Intracellular), THP-1 (t-test, \*\*\*:  $p < 0.001$ , ns: not significant).

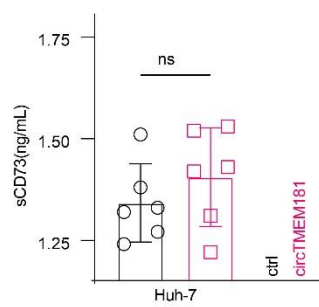
**(E)** Immunofluorescence showed CD39 expression on HCC TMA (Green: CK8, Blue: DAPI, Red: CD39).

**(F and G)** Kaplan-Meier estimate of overall survival or cumulative recurrence in the cohort with different levels of CD39 (n=204, log-rank test).

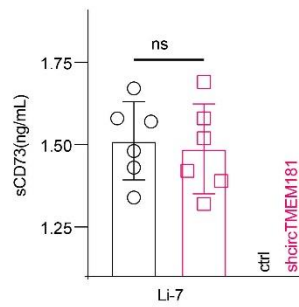
A



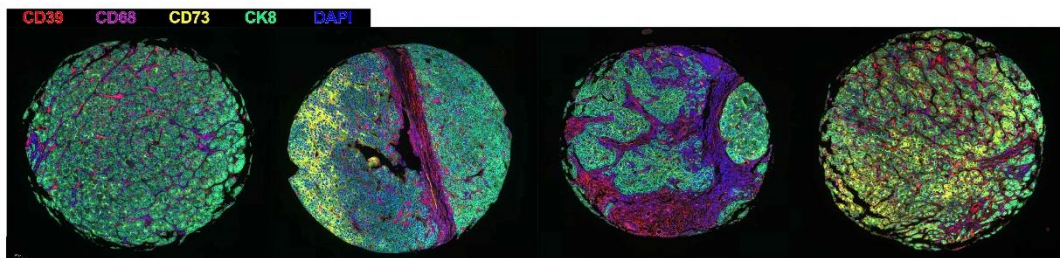
B



C



D

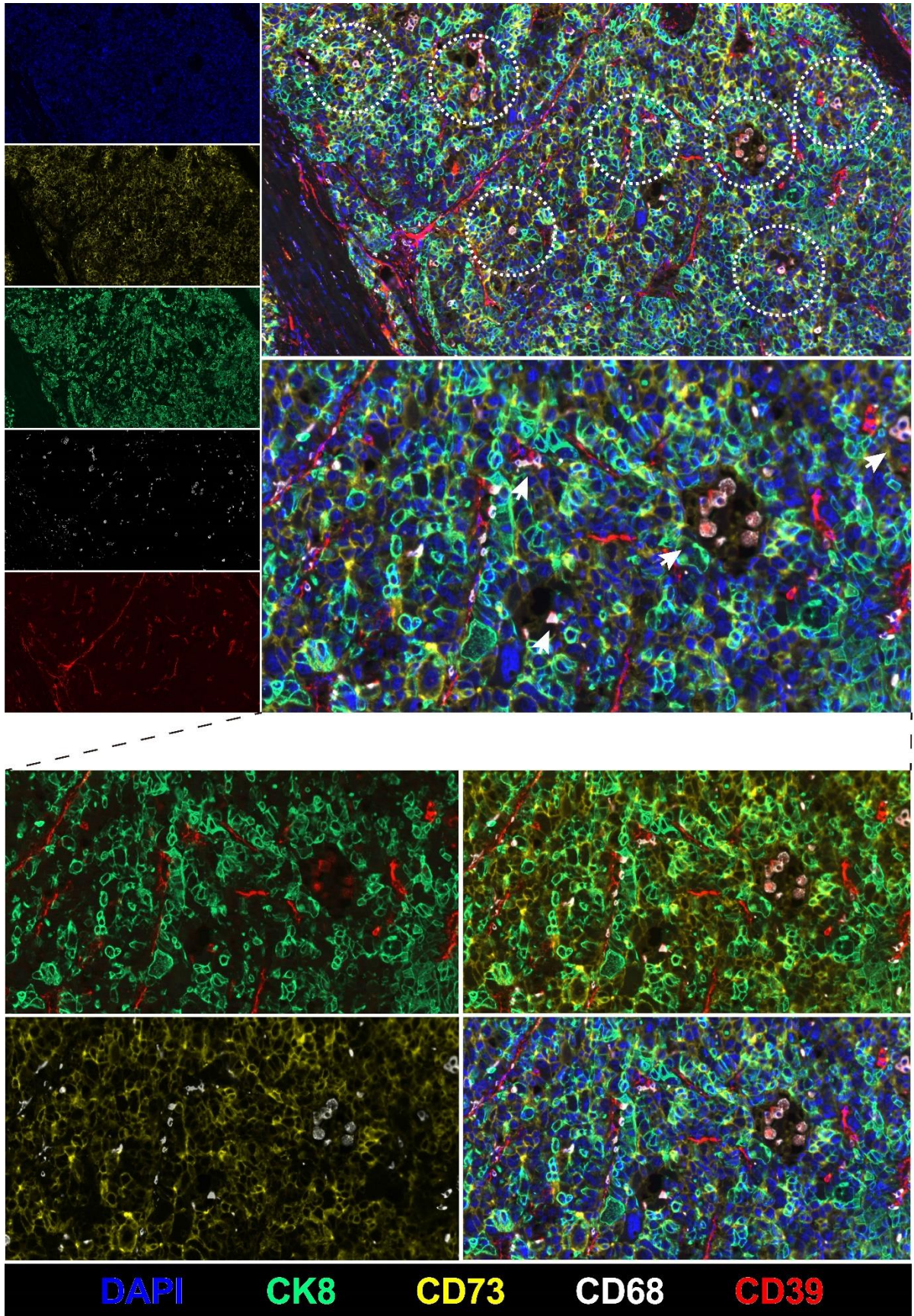


### Supplementary Figure 7. Detection of CD73 expression in HCC

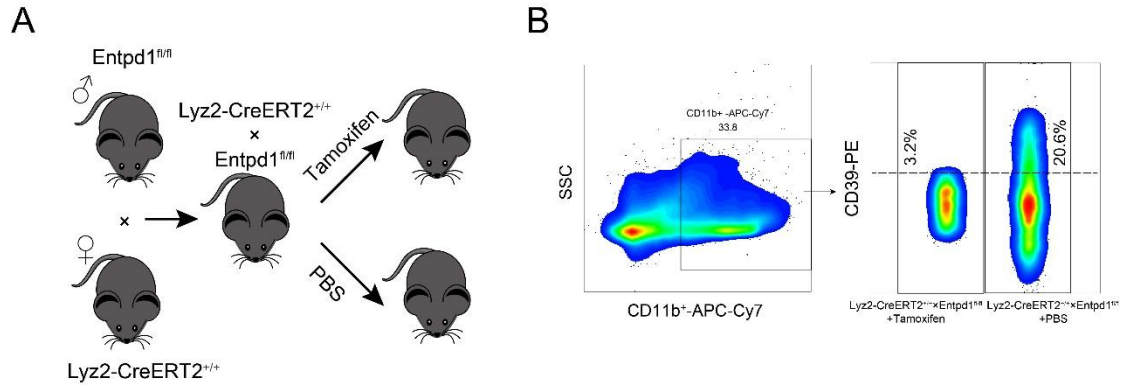
(A) Immunofluorescence showed CD73 expression on HCC TMA (Green: CK8, Blue: DAPI, Yellow: CD73).

(B) Soluble CD73 (sCD73) was detected in indicated conditions (t-test: ns: not significant).

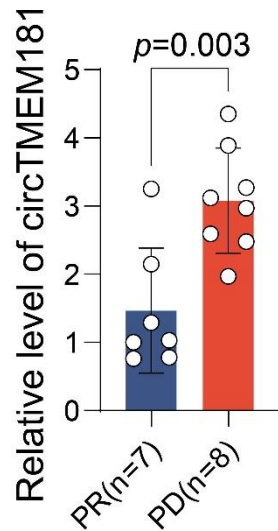
(C) Multi-label-immunofluorescence showing the expression of CD39 (Red) on CD68<sup>+</sup> macrophage (Purple), and the expression of CD73 (Yellow) on CK8<sup>+</sup> HCC tumor cells (Green) in HCC TMA.



Supplementary Figure 8. High resolution picture for Figure 5H



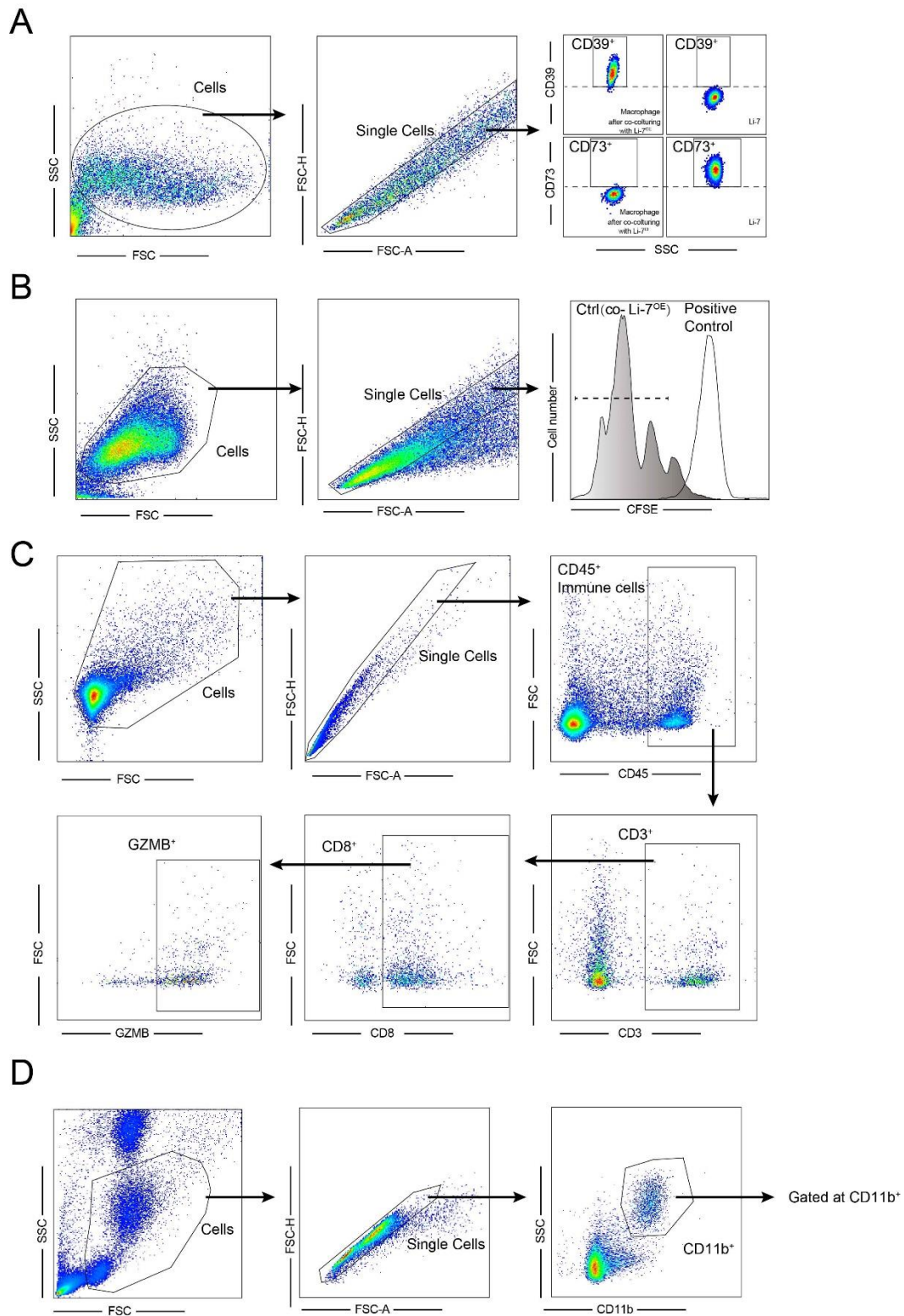
**Supplementary Figure 9. Construction of C57-Lyz2CreERT2 × C57-Entpd1fl/fl mice model**  
**(A)** Schematic illustration indicated the construction of C57-Lyz2<sup>CreERT2</sup> × C57-Entpd1<sup>fl/fl</sup> mice model.  
**(B)** Flow cytometry analysis to verify the selective deletion of CD39 on the macrophage after tamoxifen use.



**Supplementary Figure 10. Expression of circTMEM181 in the discovery cohort and the validation cohort.**

qPCR analysis validated the circTMEM181 level in 15 patients (PD: 8 patients; PR: 7 patients) (t-test).





**Supplementary Figure 11. Flow cytometry gating strategies**

(A) Gating strategies for Figure 5B

(B) Gating strategies for Figure 5E

(C) Gating strategies for Figure 6B, D, J

(D) Gating strategies for Figure 7E, H