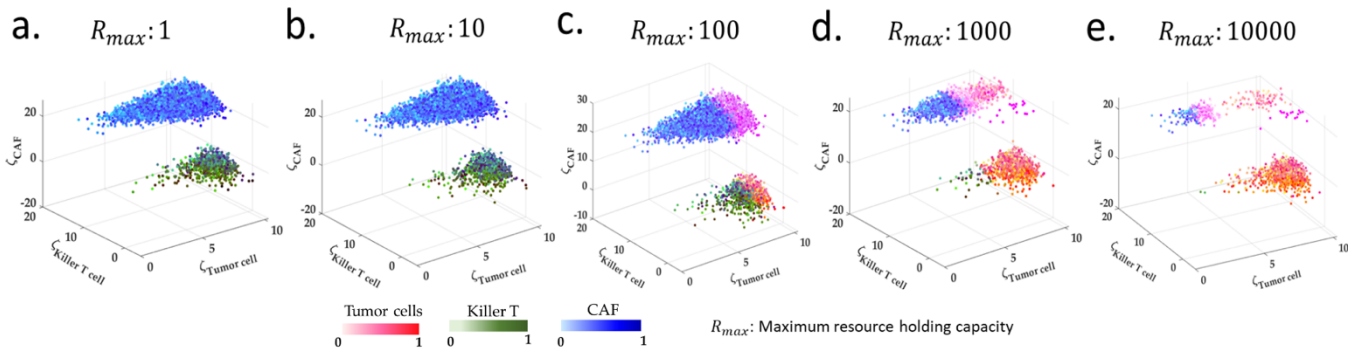

Fig S2. Resource competition leads to different outcomes for different resource capacity. (a-b) Under low-moderate resource availability, the parameter scan for the entire TME system reveals three possible TME composition Immune-dominated, fibro-desert, and desert. Interesting for a fixed resource supply, the parameter scan shows all the five TME subtypes. **(c-e)** The fibro-dominated and immune-desert subtypes emerge beyond a cut-off maximum resource supply rate along with the three mentioned subtypes. The high availability of resource ensures a constant amount of resource to all the different tumor cell types. Further, the elimination of PDL1- tumor cells by killer PD1+ T cells provide a competitive advantage to the PDL1+ tumor cells which, in turn enhances the T-cell exhaustion rate rendering a non-empty immune-desert region.

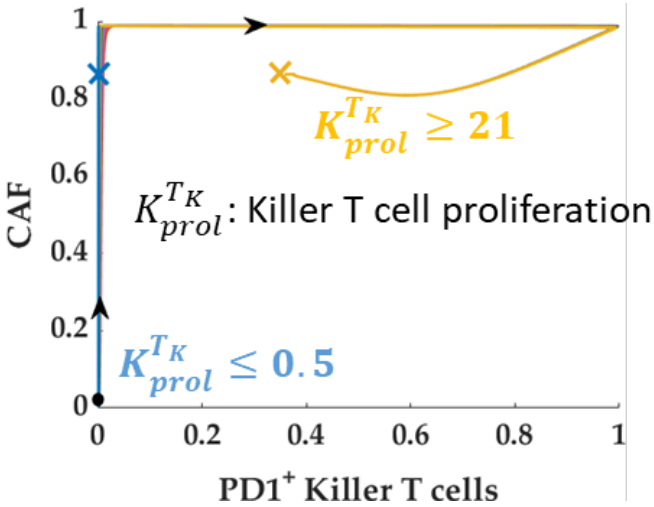

Fig S3. Killer T cell-independent growth of CAF. The proliferation rate governs the pre-ICI population of killer T cells. Below a critical proliferation rate the HNSCC TME model settles in an immune-desert region. Whereas, in both the scenarios (immune-desert and immune-rich), the CAF population remains unaltered indicating a relative independence from the T cell population.

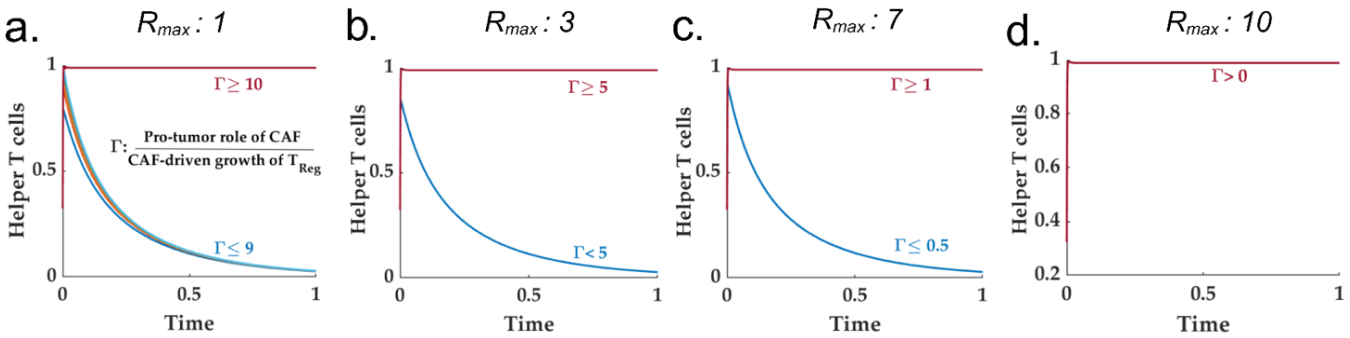

Fig S4. Resource intake governs overall dependence of helper T cell on pro-tumor role of CAF. (a-d) The pro-tumor role of CAF leads to significant pre-ICI, PDL1- tumor cell population. Therefore, beyond a threshold value of the pro-tumor role of CAF (compared to the CAF-driven growth of regulatory T cells), the final helper T cell population remains high. On the other hand, for moderate to low CAF-tumor interaction, the PDL1- tumor cells remain low due to the presence of cytotoxic killer T cells. Therefore, despite an initial increase, the helper T cells settle to a very low value (almost zero). Further, the threshold value of CAF-tumor interaction is dependent on the maximum resource intake in a competitive setting.

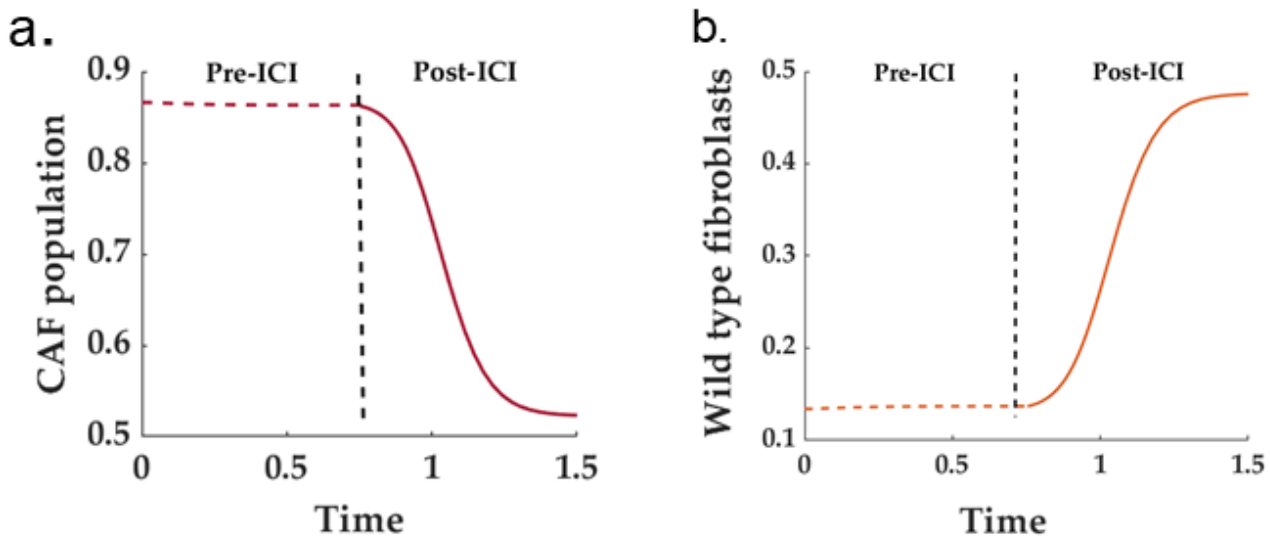

Fig S5. ICI reduces CAF population and increases the wild type fibroblasts in immune rich scenario. (a) The CAF population exhibits a steep increasing tendency owing to multiple paracrine interaction with the tumor cells and tumor associated macrophages. However, the ICI intervention in an immune rich scenario reduces the tumor cells. Further, the reduction in tumor cells-secreted LIF reduces the transition flux from wild type to cancer-associated fibroblasts. Therefore, overall CAF population undergoes a significant reduction during the ICI therapy. **(b)** The wild-type fibroblast population, due to significant reduction in the transition flux towards CAF, increases during an ICI-based therapy in immune rich scenario.

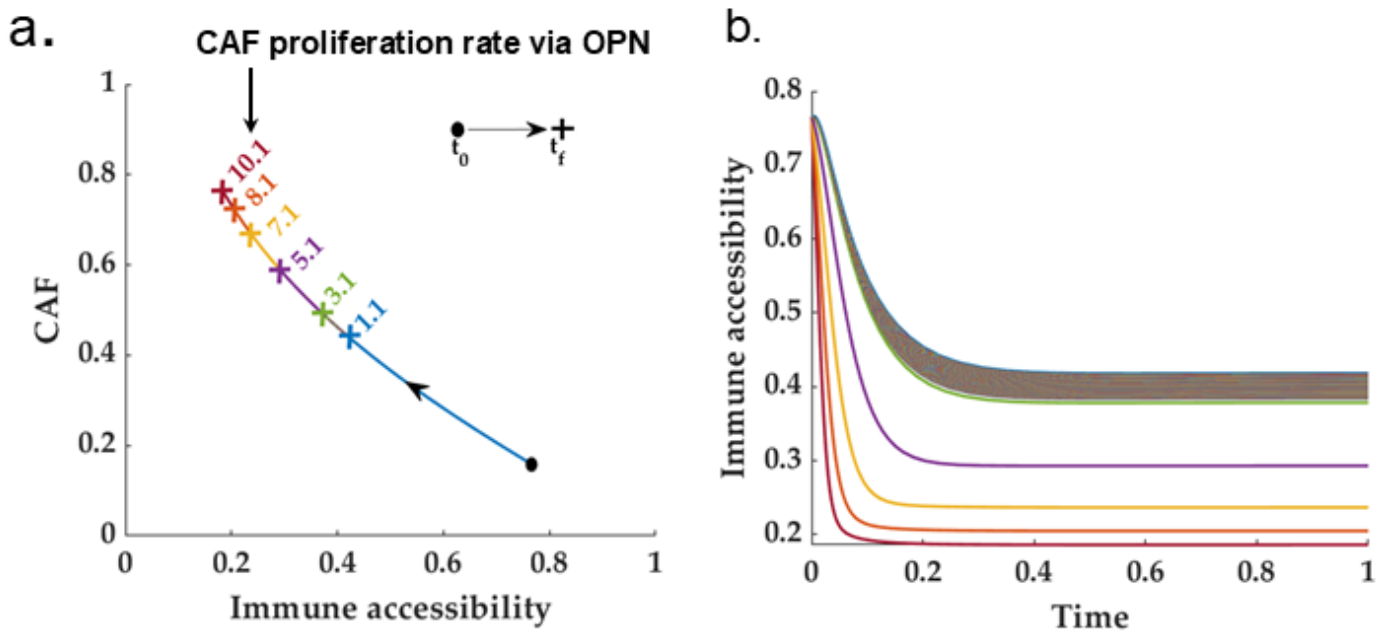

Fig S6. The CAF-immune accessibility story. (a) Demonstrates the phase-space between the immune accessibility and CAF for different CAF proliferation rate. **(b)** The time profile for immune accessibility shows the existence of a threshold time beyond which the immune accessibility deteriorates drastically. Further, this threshold time is dependent on the proliferation rate of CAF. This is due to the fact that a higher proliferation rate renders a faster CAF growth and due to the near-linear trajectory of CAF-immune accessibility trajectory, the immune accessibility adopts a faster time scale.

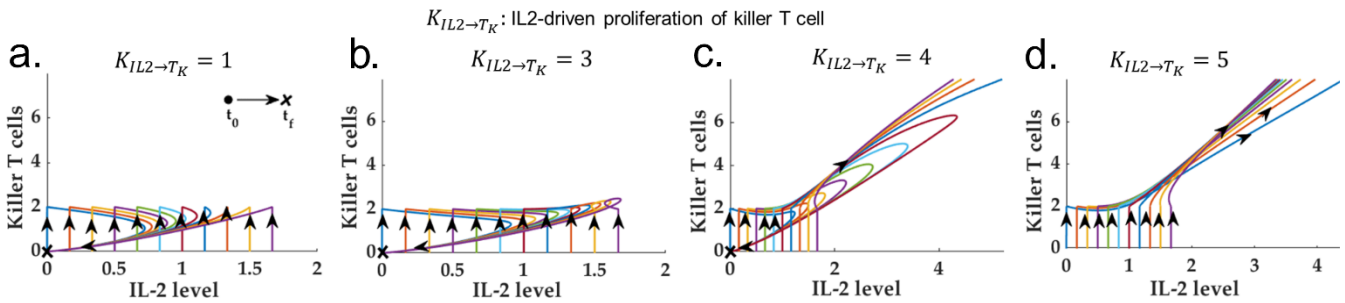

Fig S7. IL2-Killer T cell story. (a-d) Increasing levels of IL-2-induced killer T cell proliferation rate can drive the HNSCC immune-desert TME to an immune hot scenario. However, there exists a threshold IL-2-driven Killer T cell proliferation rate below which the immune-desert scenario can not be circumvented irrespective of the external IL-2 level.

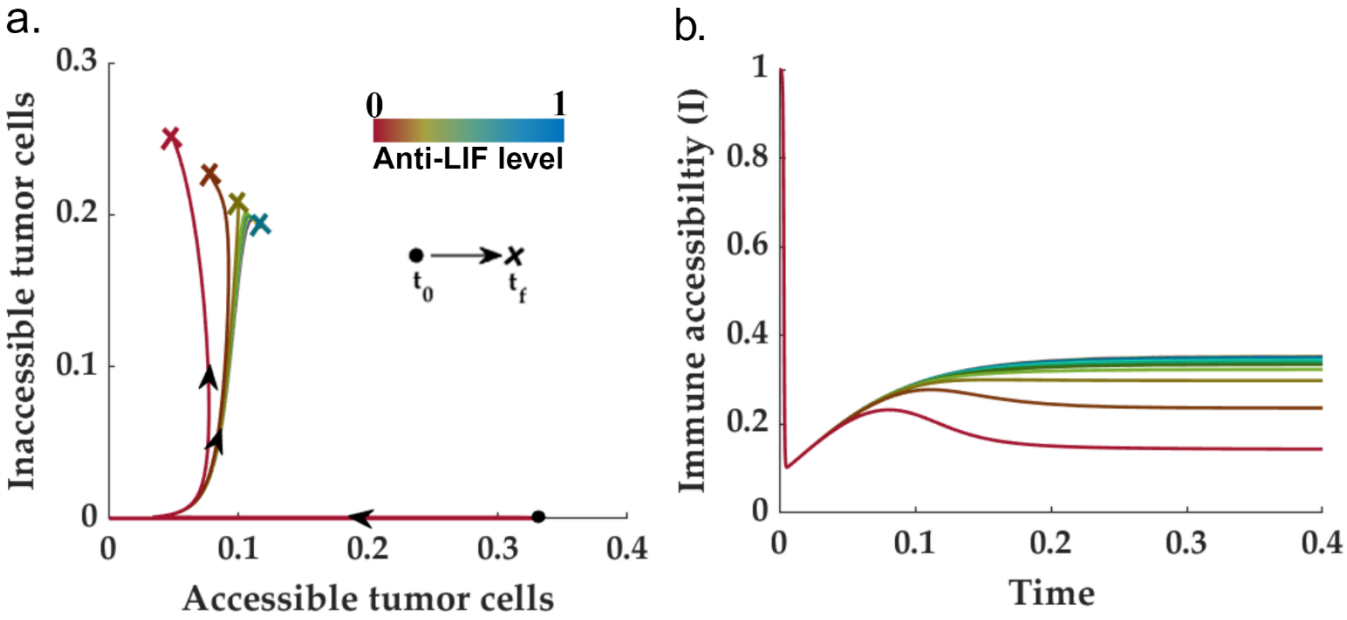

Fig S8. LIF knockout reduces increases immune accessibility. (a) Phase trajectory of different tumor cells vis-à-vis immune accessibility. The LIF knockout significantly reduces the pre-ICI inaccessible tumor cells. However, a complete (or near) complete elimination of inaccessible tumor cells is not possible with only LIF knockout. **(b)** Although a LIF knockout improves the immune accessibility it does not drive the TME system to an immune-dominated situation.

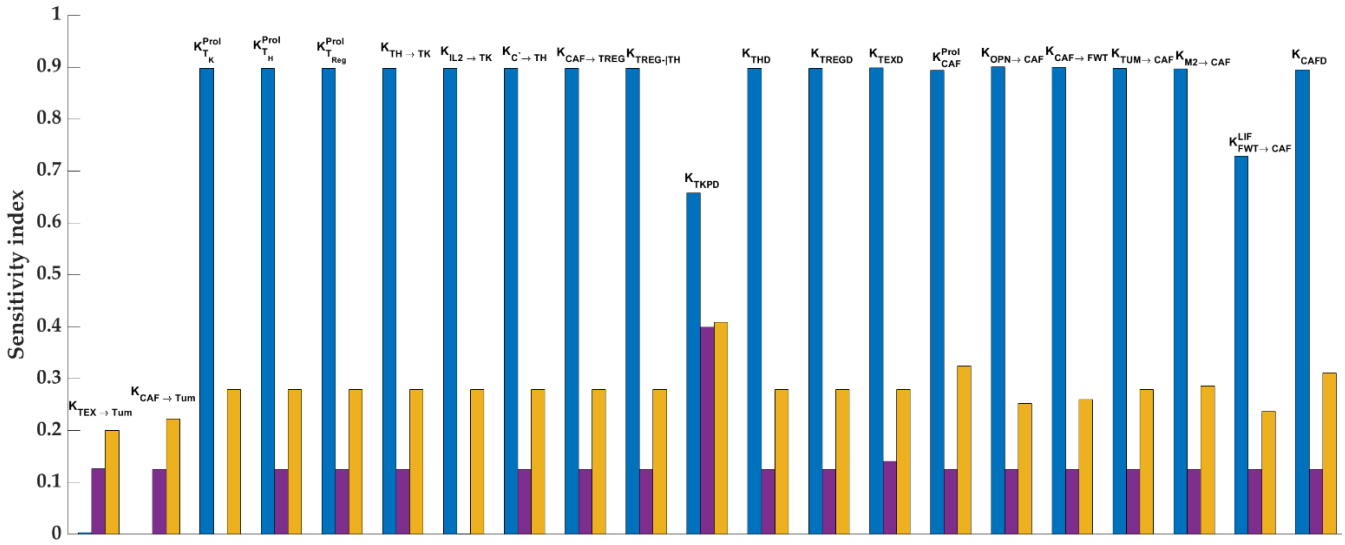

Fig S9. Sensitivity analysis. We chose all the parameters that exhibits an explicit bearing with the proliferation and death and conversion fluxes for Tumor cells (Blue), Killer T cells (Violet), and CAF (Yellow).