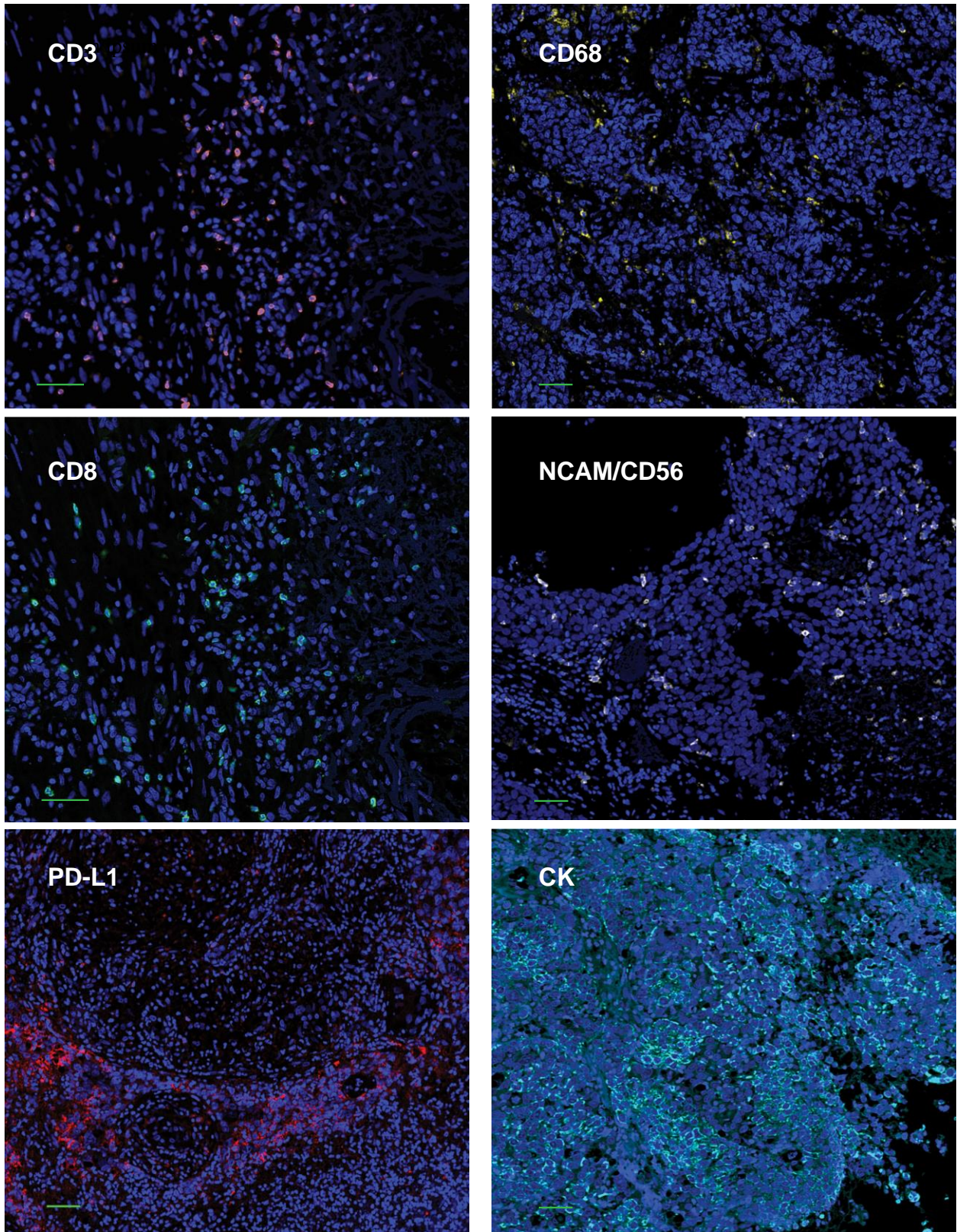
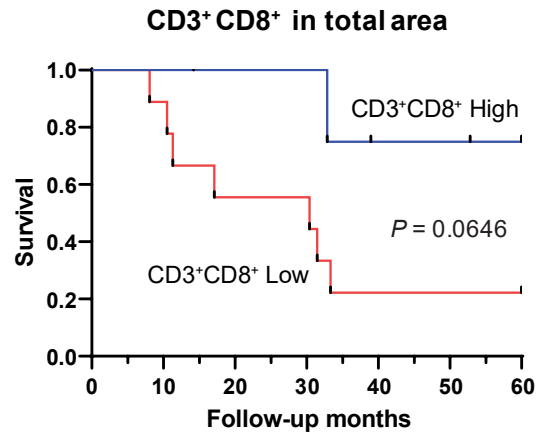


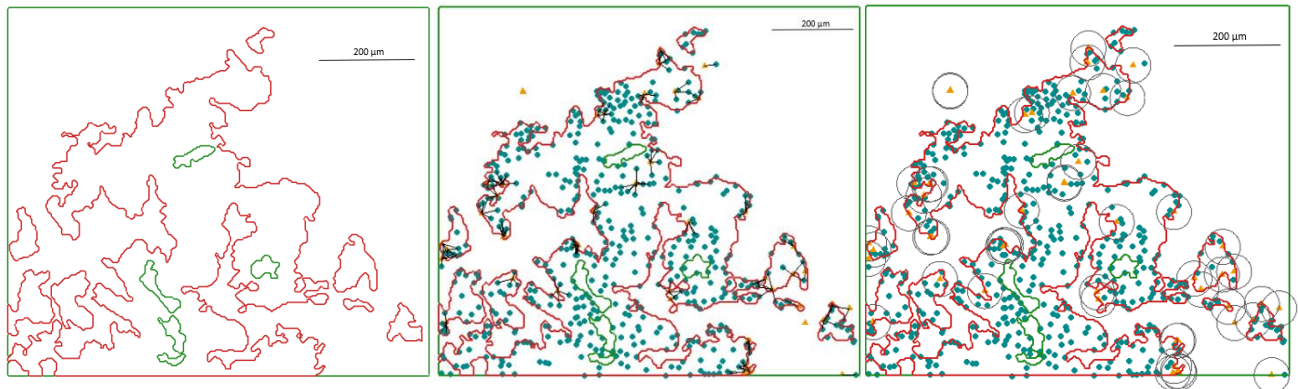
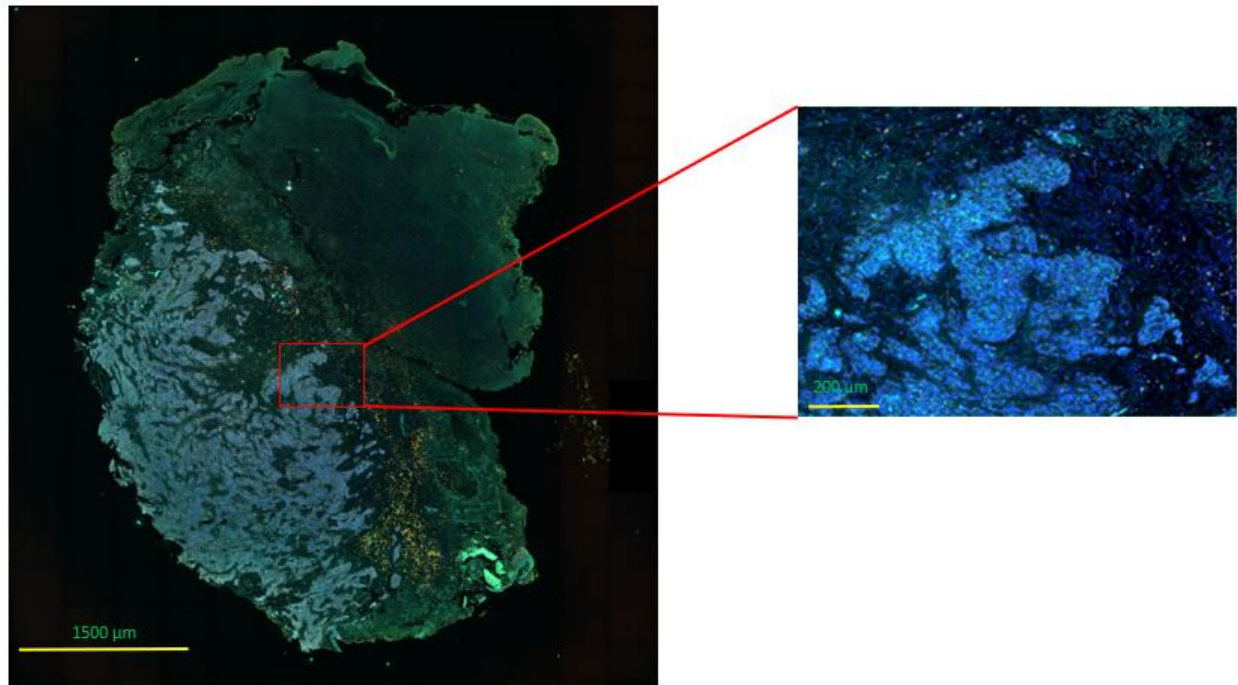
**Supplementary Figure 1.** Experimental workflow for Indium-111 NK cell cytotoxicity assay. **1.** NK cells were isolated from healthy donor PBMCs using a magnetic negative selection kit, further detailed in Materials and Methods. **2.** Freshly isolated NK cells (effector cells) are left untreated or incubated with IL-15 superagonist for 24 hours. **3.** SNUC tumor cells (target cells) labeled with Indium-111 are then incubated in various treatment conditions, depending on the experiment. Treatment conditions include IFN $\gamma$ , anti-PD-L1 antibody, and/or anti-CD16 antibody. Target cells are then plated with NK cells at an E:T ratio of 10:1. **4.** Following 20 hours of assay incubation, experimental supernatants are harvested and gamma radiation release is measured as a surrogate for target cell lysis. Image made using BioRender.



**Supplementary Figure 2.** A representative image for each marker. The scale bars indicate 50 μm.



**Supplementary Figure 3.** Patients with high CD3<sup>+</sup>CD8<sup>+</sup> in total tissue area show a non-statistically significant improvement in 5-year overall survival rate ( $P = 0.065$ ).



**Supplementary Figure 4.** An example of SNUC neighborhood analysis. The upper left panel demonstrates a SNUC tumor section with zoom magnification in the upper right. The lower panel demonstrates segmentation with red indicating tumor region of interest with green indicating stroma region of interest including the surrounding area. Blue circles indicate CK- tumor cells while yellow triangles indicate CD56+ cells. Black lines represent CD56+ neighbors <math><50\mu\text{m}</math> and black circles indicate radius of

Supplementary Table 1. Patient demographics and clinical characteristics

Sample ID	Age	Sex	Race	Primary tumor site	T stage	Lymph node metastasis	Distant metastasis	Clinical stage	Carcinogen exposure	Smoking history	Alcohol use	Vital status	Disease-related death	Recurrence	Response to IC	Regimens
SNUC1	63	Male	White	Maxillary sinus	T4b	N1	M1	IVc	No	Former	Unknown	Deceased	N/A	Unknown	N/A	N/A
SNUC10	80	Female	White	Nasal cavity	T4b	N2C	M0	IVb	No	Never	Never	Deceased	N/A	No	N/A	N/A
SNUC13	83	Male	White	Nasal cavity	T4a	N0	M0	IVa	No	Former	Never	Alive	No	No	No	Cisplatin, etoposide
SNUC15	25	Male	Latin American	Nasal cavity	T4b	N0	M0	IVb	Radiation	Never	Current	Alive	No	No	Yes	Cisplatin, etoposide
SNUC16	74	Male	White	Nasal Cavity	T4b	N0	M0	IVb	No	Former	Never	Deceased	N/A	Yes	Yes	Cisplatin, etoposide
SNUC18	74	Female	White	Maxillary sinus	T4a	N0	M0	IVa	No	Never	Former	Deceased	Yes	Yes	No	Carboplatin, etoposide
SNUC20	52	Male	White	Ethmoid sinus	T4a	N0	M0	IVa	Lead	Never	Former	Alive	No	No	Yes	Cisplatin, etoposide
SNUC22	62	Male	White	Ethmoid sinus	T4a	N0	M0	IVa	No	Never	Never	Alive	No	Yes	Yes	Cisplatin, etoposide
SNUC23	35	Male	Black	Ethmoid sinus	T4a	N0	M0	IVa	No	Former	Current	Deceased	Yes	Yes	Yes	Cisplatin, etoposide
SNUC27	61	Male	Asian	Maxillary sinus	T4b	N0	M0	IVb	chlorinated compounds, dust, vinyl chloride	Former	Former	Alive	No	No	Yes	5-FU, cisplatin, taxotere
SNUC29	65	Female	White	Frontal sinus	T4a	N0	M0	IVa	No	Never	Never	Deceased	N/A	Yes	No	Carboplatin, etoposide
SNUC32	74	Female	White	Nasal cavity	T4a	N0	M0	IVa	No	Former	Current	Deceased	Yes	Yes	No	Carboplatin, etoposide
SNUC33	51	Female	Asian	Ethmoid sinus	T4a	N0	M0	IVa	No	Never	Never	Deceased	No	Yes	Yes	Cisplatin, etoposide
SNUC34	43	Male	White	Ethmoid sinus	T4b	N0	M0	IVb	No	Never	Current	Alive	No	No	Yes	Cisplatin, etoposide

IC: induction chemotherapy

**Supplementary Table 2.** SNUC multi-spectral immunofluorescence panel

Antibody	Vendor/Clone	Catalog #	Dilution	Order of Staining	Opal	Opal Dilution
CD3e	Bethyl Laboratories/BL-298-5D12	A700-016	1:150		1	620 1:100
CD8a	Bethyl Laboratories/BLR044F	A700-044	1:250		2	520 1:100
PD-L1	Bethyl Laboratories/BLR020E	A700-020	1:250		3	690 1:100
CD68	Bethyl Laboratories/KP-1	A500-018A	1:250		4	570 1:100
CK	Invitrogen Thermo Fisher Scientific/80	01-672-060	1:50		5	480 1:100
NCAM/CK56	Bethyl Laboratories/BLR152J	A700-152	1:100		6	780 1:100, TSA-DIG 1:100

**Supplementary Table 3.** Interaction analysis in CKhigh tumor cells

Marker 1	ROI 1	Marker 2	ROI 2	Group	Wilcox	Mean_NI	SD_NI
CK+	Stroma	CD56+	Stroma	Recurrence	0.871	12.43723	12.9055
				No Recurrence		9.760302	10.04758
CK+	Stroma	CD56+	Tumor	Recurrence	0.417	2.014741	2.47381
				No Recurrence		3.570823	3.53775
CK+	Tumor	CD56+	Stroma	Recurrence	0.745	5.982825	11.06346
				No Recurrence		4.425049	4.621642
CK+	Tumor	CD56+	Tumor	Recurrence	0.371	1.697655	2.536259
				No Recurrence		4.958313	5.667206

ROI: Region of interest  
 NI: Number of interactions  
 Mean NI: mm<sup>2</sup>