

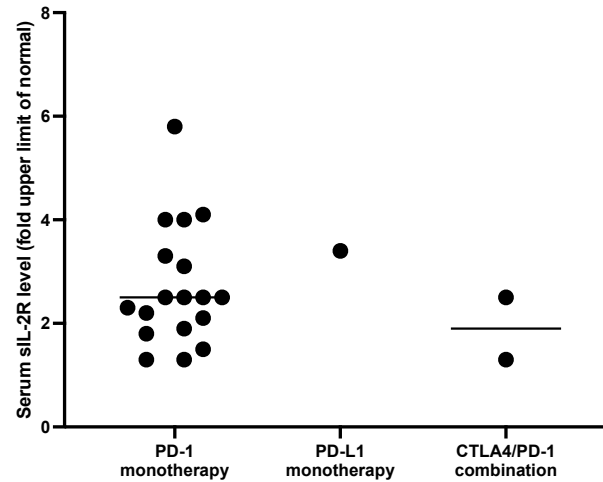
Supplemental Figure 1. sIL-2R levels of ICI-nephritis cases by ICI class

Figure S1. sIL-2R levels of ICI-nephritis cases by ICI class. PD-1 monotherapy includes cemiplimab, nivolumab and pembrolizumab; PD-L1 monotherapy includes atezolizumab; CTLA-4/PD-1 combination includes ipilimumab/nivolumab. Symbols represent unique individuals; bars represent median.

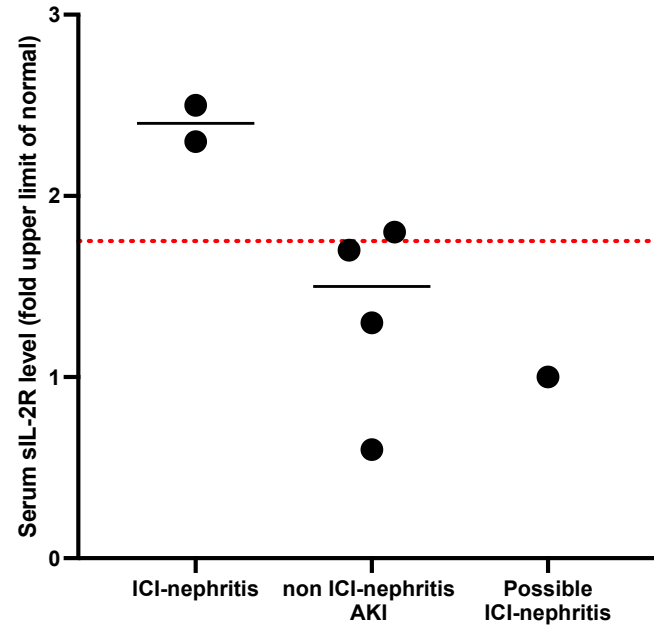
Supplemental Figure 2. External validation cohort for diagnostic performance of sIL-2R in ICI-treated patients who developed AKI

Figure S2. External validation cohort for diagnostic performance of sIL-2R in ICI-treated patients who developed AKI. ICI-nephritis include biopsy-proven ICI-nephritis (N=1) and clinically adjudicated ICI-nephritis (N=1); non ICI-nephritis AKI include biopsy-proven acute tubular necrosis (N=1) and clinically adjudicated hemodynamic AKI (N=3).

Supplemental Figure 3. Linear correlation between B cell phenotypes and CD8+ T cells and within different B cell phenotypes

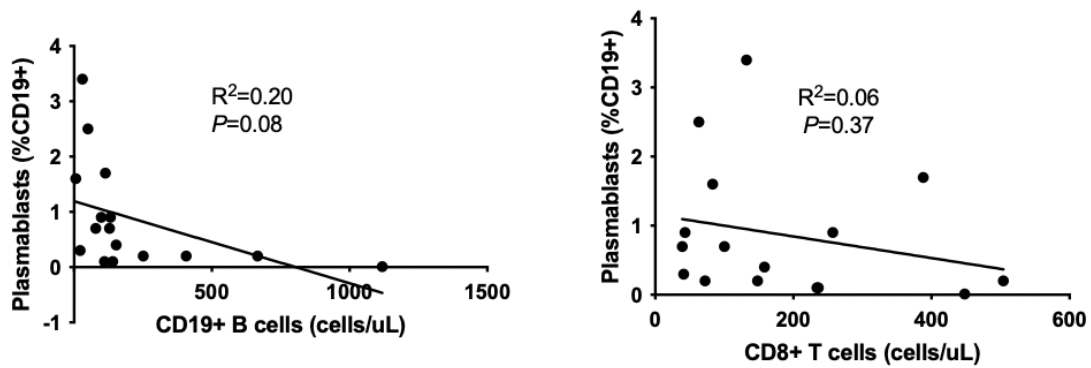


Figure S3. Linear correlation between percentage of plasmablasts and total CD19+ B cell count (left), percentage of plasmablast and CD8+ T cells (right). Symbols represent unique individuals; straight line represents fitted regression line; R^2 and P values are indicated in the graphs.

Supplemental Figure 4. Comparison of sIL-2R level, peripheral T and B cell markers in patients with ICI-nephritis who were diagnosed with kidney biopsy and who were diagnosed by clinical adjudication

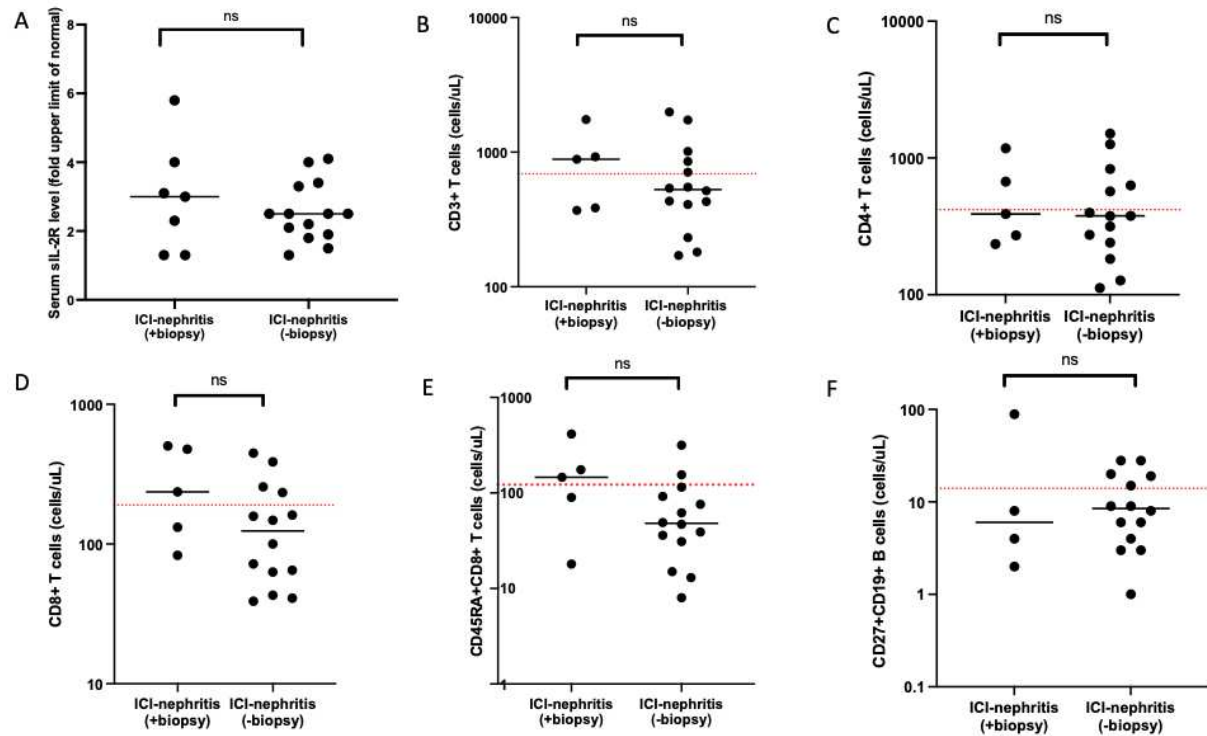


Figure S4. (A) Fold ULN of serum sIL-2R level were compared between patients with ICI-nephritis (N=7) who were diagnosed with kidney biopsy and who were diagnosed by clinical criteria (N=14). (B–F) Absolute total lymphocyte counts as indicated (cells/uL), shown in log scale, were compared between patients with ICI-nephritis who were diagnosed with kidney biopsy (N=5) and who were diagnosed by clinical criteria (N=14) who received concurrent chemotherapy (N=4). Symbols represent unique individuals; bars represent geometric means (95% confidence intervals) of total indicated patients; red dotted line represent lower limit of normal of the assay. ns=non-significant

Supplemental Figure 5. Comparison of peripheral T and B cell markers in patients with ICI-nephritis who received concurrent chemotherapy with ICI or who received ICI therapy alone

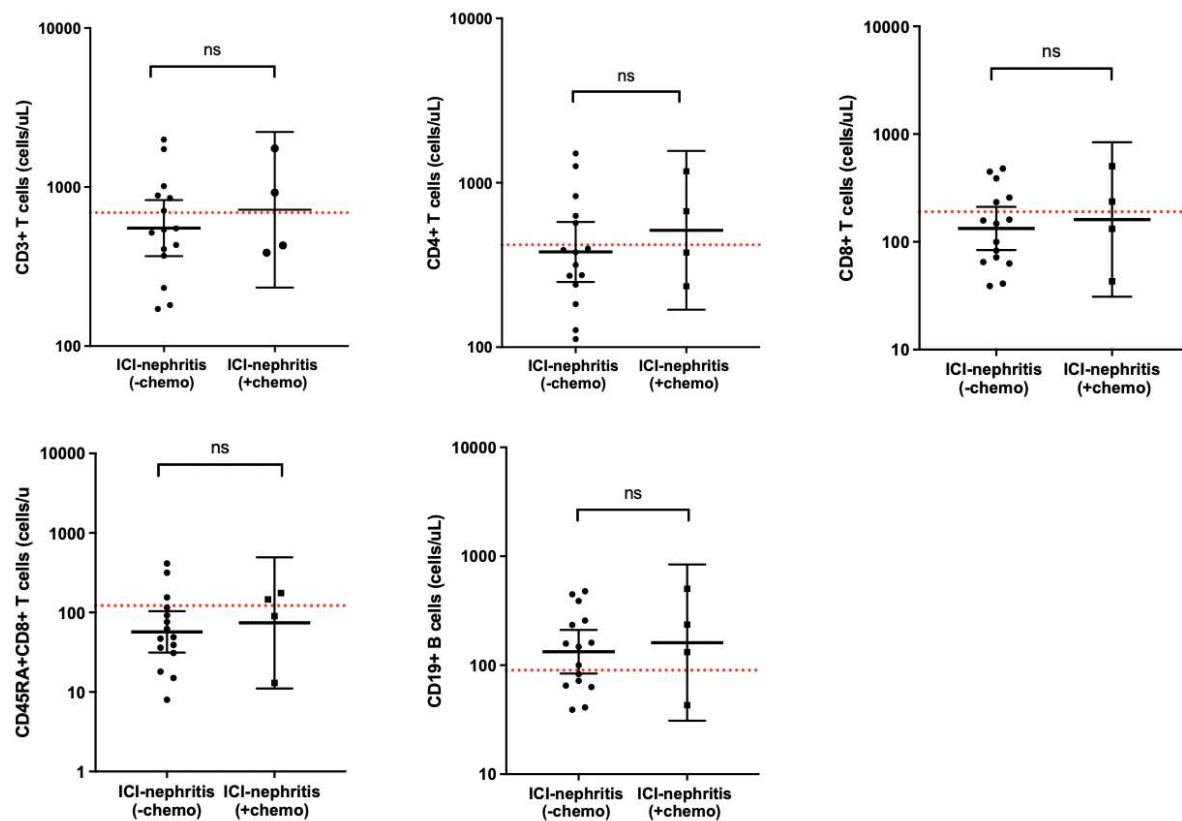


Figure S5. Absolute total lymphocyte counts as indicated (cells/uL), shown in log scale, compared between patients with ICI-nephritis who were treated with ICI alone (N=15) and who received concurrent chemotherapy (N=4). Symbols represent unique individuals; bars represent geometric means (95% confidence intervals) of total indicated patients; red dotted line represent lower limit of normal of the assay. ns=non-significant.

Supplemental Table 1. Case summaries for hemodynamic AKI control group

| Patient ID | Age/race | Baseline creatinine (mg/dL) ^a | Peak creatinine (mg/dL) | sIL-2R (fold ULN) | Diagnosis |
|------------|-------------|--|-------------------------|-------------------|----------------------------|
| 1 | 80-90 yo HF | 1.3 | 3.0 | 1.1 | Cardiorenal syndrome |
| 2 | 70-80 yo WM | 1.2 | Required RRT | 1.7 | Ischemic ATN |
| 3 | 40-50 yo WF | 0.7 | 2.3 | 0.5 | Myoglobin cast nephropathy |
| 4 | 50-60 yo AM | 1.5 | 3.4 | 0.8 | Ischemic ATN |
| 5 | 50-60 yo BM | 1.0 | 4.4 | 1.0 | Ischemic ATN |
| 6 | 70-80 yo HM | 1.4 | 1.9 | 0.7 | Ischemic ATN |

Table S1. Case summaries for hemodynamic AKI control group. a. case 3,4 and 6 do not have pre-AKI creatinine available within 90 days. Their baseline creatinine was imputed from creatinine nadir during hospitalization. Age ranges in 10-year intervals are used to protect patients' confidentiality. Abbreviations: sIL-2R=soluble interleukin 2 receptor; HF=Hispanic female; WM=White male; WF=White female; AM=Asian male; BM=Black male; HM=Hispanic male; RRT=renal replacement therapy; AKI=acute kidney injury; ATN=acute tubular necrosis; CKD=chronic kidney disease

Supplemental Table 2. Case summaries for non-ICI AIN group

| Patient ID | Age/race | Baseline creatinine (mg/dL) | Peak creatinine (mg/dL) | sIL-2R (fold ULN) | Diagnosis |
|------------|-------------|-----------------------------|-------------------------|-------------------|----------------------|
| 1 | 50-60 yo WF | 0.8 | 1.6 | 1.2 | TINU syndrome |
| 2 | 70-80 yo AM | 1.5 ^a | 5.3 | 4.1 | IgG4-related disease |
| 3 | 30-40 yo WF | 0.9 | 2.7 | 2.5 | TINU syndrome |
| 4 | 30-40 yo WF | 0.9 | 1.1 | 2.8 | TINU syndrome |
| 5 | 70-80 yo BM | 3.0 | 4.5 | 1.6 | PPI-associated AIN |

Table S2. Case summaries for non-ICI-nephritis group. a. case 2 does not have pre-AKI baseline creatinine available within 90 days. Baseline creatinine was imputed from creatinine nadir during follow-up course. Age ranges in 10-year intervals are used to protect patients' confidentiality. Abbreviations: sIL-2R=soluble interleukin 2 receptor; WF=White female; AM=Asian male; BM=Black male; TINU=tubulointerstitial nephritis and uveitis syndrome; PPI=proton pump inhibitor; AIN=acute interstitial nephritis

Supplemental Table 3. Genes included in IL-2 family pathway score and T cell receptor pathway score

| IL-2 family pathway score | T cell receptor pathway score | |
|---------------------------|-------------------------------|---------------|
| <i>HAVCR2</i> | <i>CD247</i> | <i>IL5</i> |
| <i>IL15</i> | <i>CD28</i> | <i>INPP5D</i> |
| <i>IL2</i> | <i>CD3D</i> | <i>JUN</i> |
| <i>IL21</i> | <i>CD3E</i> | <i>LCK</i> |
| <i>IL21R</i> | <i>CD3G</i> | <i>LCP2</i> |
| <i>IL2RA</i> | <i>CD4</i> | <i>MAPK11</i> |
| <i>IL2RB</i> | <i>CD40LG</i> | <i>MAPK12</i> |
| <i>IL2RG</i> | <i>CD45R0</i> | <i>MAPK13</i> |
| <i>IL5</i> | <i>CD45RA</i> | <i>MAPK14</i> |
| <i>INPP5D</i> | <i>CD45RB</i> | <i>NFATC1</i> |
| <i>JAK1</i> | <i>CD8A</i> | <i>NFATC2</i> |
| <i>JAK2</i> | <i>CD8B</i> | <i>NFKB1</i> |
| <i>JAK3</i> | <i>CHUK</i> | <i>NFKBIA</i> |
| <i>LCK</i> | <i>CSF2</i> | <i>PDCD1</i> |
| <i>PIK3CD</i> | <i>CTLA4</i> | <i>PIK3CD</i> |
| <i>PTPN6</i> | <i>FOS</i> | <i>PPP3CA</i> |
| <i>STAT1</i> | <i>FYN</i> | <i>PSMB10</i> |
| <i>STAT3</i> | <i>HAVCR1</i> | <i>PSMB8</i> |
| <i>STAT4</i> | <i>HLA-DPA1</i> | <i>PSMB9</i> |
| <i>STAT5A</i> | <i>HLA-DPB1</i> | <i>PSME1</i> |
| <i>STAT5B</i> | <i>HLA-DQA1</i> | <i>PSME2</i> |
| <i>SYK</i> | <i>HLA-DQB1</i> | <i>PTPN22</i> |
| | <i>HLA-DRA</i> | <i>PTPN6</i> |
| | <i>HLA-DRB1</i> | <i>PTPRC</i> |
| | <i>HLA-DRB3</i> | <i>RAF1</i> |
| | <i>ICOS</i> | <i>RELA</i> |
| | <i>IFNG</i> | <i>SLA</i> |
| | <i>IKBKB</i> | <i>TNF</i> |
| | <i>IKBKG</i> | <i>TRAF6</i> |
| | <i>IL10</i> | <i>TRAT1</i> |
| | <i>IL2</i> | <i>TRDC</i> |
| | <i>IL4</i> | <i>TRDV3</i> |
| | | <i>ZAP70</i> |

Supplemental Table 3. The pathway score is equal to the first principal component of the gene set.

Supplemental Table 4. Case summaries for external validation cohort

| Patient ID | Age/race | Baseline creatinine (mg/dL) | Peak creatinine (mg/dL) | Cancer Type | ICI therapy | sIL-2R (fold ULN) | Diagnosis |
|------------|----------------|-----------------------------|-------------------------|-------------------------|-------------|-------------------|--------------------------------------|
| 1 | 60—70 yo AM | 0.9 | 3.3 | SCC of larynx | Pembro | 2.5 | ICI-nephritis (biopsy proven) |
| 2 | 70—80 yo WF | 1.6 | 2.9 | Sacral sarcoma | Pembro | 2.3 | ICI-nephritis (clinically diagnosed) |
| 3 | 70—80 yo WM | 1.1 | 1.8 | Peritoneal mesothelioma | Ipi/nivo | 1.8 | ATN (biopsy proven) |
| 4 | 60—70 yo WM | 1.1 | 3.7 | Lung adenocarcinoma | Pembro | 0.6 | Ischemic ATN (clinically diagnosed) |
| 5 | 60—70 yo WF | 1.2 | 2.2 | Pleural mesothelioma | Ipi/nivo | 1.7 | Pre-renal AKI |
| 6 | 60—70 yo HM | 1.2 | 1.9 | Metastatic RCC | Nivo | 0.3 | Pre-renal AKI |
| 7 | 60—70 yo WF | 0.9 | 1.4 | Metastatic RCC | Ipi/nivo | 1.0 | Possible ICI-nephritis |

Table S4. Case summaries for the external validation cohort. Age ranges in 10-year intervals are used to protect patients' confidentiality. Abbreviations: sIL-2R=soluble interleukin 2 receptor; AM=Asian male; WF=White female; WM=White male; HM=Hispanic male; SCC=squamous cell cancer; RCC=renal cell carcinoma; pembro=pembrolizumab; ipi/nivo=ipilimumab/nivolumab; AKI=acute kidney injury; ATN=acute tubular necrosis