Supplementary Methods

Semi-quantitative histological scores

ISN/RPS classification (Weening JJ et al.,*J Am Soc Nephrol.* 2004), NIH chronicity and activity index (CI, AI) (Bajema IM et al., *Kidney Int.* 2017) and sclerosis scores were retrieved from medical records. Sclerosis scores are semi-quantitative scores on PAS and trichrome-stained FFPE sections, on a scale of 0-6, obtained by adding glomerulosclerosis score (<30% of glomeruli affected: +1, 30-60%: +2, > 60%: +3) to interstitial fibrosis score (mild: +1, moderate: +2, extensive: +3).

Semi-quantitative PSR staining score (scale: 2-6) was obtained by adding the median glomerular fibrosis score (low: 1, intermediate: 2, high: 3) and the median interstitial fibrosis score (low: 1, intermediate: 2, high: 3), provided by three (blinded) scorers.

Immunohistochemistry and PSR staining

Slides were incubated with mouse anti-human CD8 (mouse monoclonal antibody clone C8/144B, Dako; dilution 1/24) or anti-human $p16^{INK4a}$ (mouse monoclonal antibody clone E6H4, Roche Ventana CINtec Histology; prediluted ready-to-use), using the Benchmark ultra Ventana autostainer. Bound antibodies were labeled with ultraview universal horseradish peroxidase-labeled multimer (brown color, Roche Ventana). PSR staining was performed as previously described (Courtoy GE et al., *Biomolecules* 2020).

Supplementary Figure Legends

Supplementary Figure 1: Per-glomerulus quantification of p16^{INK4a}, CD8 and fibrosis. Representative images illustrating per-glomerulus analysis strategy on serial sections immuno-stained for p16^{INK4a} and CD8, and PSR-stained for collagen deposits. **Top:** Detection of p16^{INK4a}-positive cells (green, right panel) within glomerulus (delineated by maroon circle, left panel). **Middle:** Detection of CD8-positive cells within a 30μm radius (yellow from 0-10μm, orange from 10-20μm, red from 20-30μm, right panel) around glomerulus (delineated by maroon circle, left panel). **Bottom:** Detection of fibrous tissue (blue, right panel) surrounding the Bowman's capsule, normalized to the area of the glomerulus (delineated by purple circle), on PSR-stained section. Per-glomerulus p16^{INK4a}: number of positive cells/μm2 within glomerulus, CD8: number of positive cells within 30μm radius around glomerulus, Bowman's capsule thickness: area of fibrous tissue surrounding capsule, normalized to area of glomerulus section.

Supplementary Figure 2: Representative images of p16^{INK4a}, CD8 and PSR staining of kidney biopsies from patients with active LN. A-D. p16^{INK4a}, CD8 and PSR staining of FFPE serial sections from four different LN kidney biopsies harvested at baseline. Overview (left panels), close-up (right) showing p16^{INK4a}-positive cells within a glomerulus, periglomerular CD8-positive cells, and collagen deposits in and around Bowman's capsule of the same glomerulus. Examples of low-to-moderate p16^{INK4a}-stained samples (<75th percentile, "Q3") **(A-C)**, and a high p16^{INK4a} sample (>Q3) **(D)**.

Supplementary Figure 3: Correlation between glomerular and interstitial p16^{INK4a} staining in LN baseline biopsies. Significant positive correlation between p16^{INK4a}

(positive cells/μm^2) in glomerular and interstitial areas of biopsies. Spearman's rank-order correlation coefficient: r=0.7591, *p<0.0001*.

Supplementary Figure 4: $p16^{INK4a}$ accumulation is not associated with demographic parameters of LN patients. A. Distribution of age of LN patients with $p16^{INK4a}$ low-to-moderate (<75th percentile, "Q3") *vs.* $p16^{INK4a}$-high (>Q3) baseline kidney biopsies. **B.** $p16^{INK4a}$ values (positive cells/μm^2) in biopsies from female *vs.* male LN patients. **C.** $p16^{INK4a}$ values (positive cells/μm^2) in biopsies from patients of different ethnicities. Horizontal bars: medians. *p values*: Mann-Whitney (two groups) or Kruskal-Wallis test (three groups).

Supplementary Figure 5: Association of severe proteinuria with higher glomerular but not interstitial $p16^{INK4a}$ in LN baseline biopsies. A, B. Significantly higher $p16^{INK4a}$ (positive cells/μm^2) in glomerular **(A)** and interstitial **(B)** areas of biopsies from patients with low eGFR (<60 mL/min/1.73m^2). **C,D.** Significantly higher proteinuria (urinary protein/creatinine ratio, uP/C, g/g) associated with high (>75th percentile, "Q3") *vs.* low-to-moderate (<Q3) $p16^{INK4a}$ (positive cells/μm^2) in glomerular areas **(C)** but not interstitial areas **(D)** of baseline kidney biopsies. Horizontal bars: medians. *p values*: Mann-Whitney test.

Supplementary Figure 6: $p16^{INK4a}$ accumulation in LN baseline biopsies is not associated with parameters of systemic disease and ISN/RPS classification. A, B. Similar baseline levels of serum anti double-stranded DNA (dsDNA) antibody (U/mL) **(A)**

or C3 (g/L) **(B)** in patients with p16^{INK4a}-high (>75th percentile, "Q3") *vs.* p16^{INK4a} low-to-moderate (<Q3) baseline kidney biopsies. **C,D.** No significant differences in p16^{INK4a} (positive cells/μm^2) between ISN/RPS classifications (III (+V) *vs.* IV (+V), III/IV *vs.* III/IV+V). Horizontal bars: medians. *p values*: Mann-Whitney test.

Supplementary Figure 7: p16^{INK4a} accumulation is associated with lower eGFR in incident LN biopsies. A. Longer (non-significant) duration between SLE and LN diagnosis (in years) in patients with p16^{INK4a}-high (>75th percentile, "Q3") *vs.* p16^{INK4a} low-to-moderate (<Q3) baseline kidney biopsies. **B.** Higher (non-significant) p16^{INK4a} (positive cells/μm^2) in relapse *vs.* incident nephritis. **C.** Significantly higher p16^{INK4a} (positive cells/μm^2) is associated with low eGFR (<60 mL/min/1.73m^2) in incident LN cases. Horizontal bars: medians. *p values*: Mann-Whitney test.