Background Age-associated pro-inflammatory states may result in decreased response to immune checkpoint inhibitors (ICI) in older patients (pts) with cancer. We explored the association of circulating inflammatory markers with response to ICIs, and investigate potential differences in transcriptional and TME signatures of pts ≥80-yr (age) and younger.

Methods We built a multicenter, international database of pts with different tumors treated with ICIs monotherapy between 2011 and 2021 from 11 academic centers in the US and Europe. Retrospective analysis of 885 pts compared objective response rates (ORR; iRECISt), median progression-free survival (mPFS) and overall survival (mOS) between pts ≥80-yr and <80-yr, and stratified them across serum pretreatment levels of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR) and systemic immune-inflammation index (SII=PxN/L). Optimal cut-off values for high (H) vs. low (L) levels were determined using receiver operating characteristic curves.

DNA (592-gene panel/whole exome) and RNA (whole transcriptome) next-generation sequencing, immunohistochemistry (IHC) and TME analysis (MCP-counter) were performed on 24,123 independent samples of non-small cell lung cancer (NSCLC), melanoma (MEL) and renal cell carcinoma (RCC) submitted to a CLIA-certified laboratory (Caris Life Sciences, Phoenix, AZ). Results were compared between pts ≥80-yr and <80-yr.

Results Table 1 summarizes pts baseline characteristics. Pts <80-yr had better ORR (P<0.01), but comparable mOS and mPFS to ≥80-yr (table 2). In pts ≥80-yr, NLR-L and SII-L were associated with higher ORR (P<0.01 and P<0.05; figure 1). All pts with NLR-L, MRL-L and SII-L had lower mOS (P<0.01; figure 1). All PLR-L and SII-L pts had significantly longer mPFS (P<0.01; figure 3).

Compared to pts <80-yr, NSCLC ≥80-yr had increased abundance of fibroblasts, dendritic cells and macrophages (P<0.01) in their TME and lower TMB-H (P<0.001). MEL ≥80-yr pts had fewer TME infiltrating T-lymphocytes (P=0.02), a1.24-fold increased expression of IL-6. RCC ≥80-yr pts had 0.56-fold decreased expression of GZMB, and lower PD-L1 (IHC-SP142, ≥2+ vs 5%) expression (P<0.05; figure 4). Additional correlative biomarkers will be reported in the poster.

Conclusions Lower levels of circulating inflammatory markers associated with significantly longer survival and better response rates to ICIs. SII-L and NLR-L specifically are potential biomarkers of response to ICI in pts ≥80-yr. This is the first study to evaluate the role of serum markers of inflammation as potential biomarkers of response to ICI in older pts with cancer, along with molecular correlate. Circulating inflammatory markers, and associated gene expression and TME composition suggest potential unique, cancer-specific biomarkers of response to ICIs in this population.

Ethics Approval The study was approved by the institutional review board at each participating institution. Written informed consent was waived, given the retrospective nature of the study and the de-identified status of collected data.
Abstract 112 Figure 1  Objective response rates (ORR)
Objective response rates (ORR) in patients < 80 vs. ≥ 80 years, stratified by pre-treatment levels of inflammatory markers: ICI: immune checkpoint inhibitory; NLR: neutrophil-to-lymphocyte ratio; H: high; L: low

Abstract 112 Figure 2A  Kaplan-Meier plot of overall survival by NLR level
Kaplan-Meier plot of overall survival (OS) from ICI initiation, for patients < 80 and ≥ 80 years, stratified according to pre-treatment NLR levels: ICI: immune checkpoint inhibitor; NLR: neutrophil-to-lymphocyte ratio; H: high; L: low; 95%CI: 95% confidence interval

Abstract 112 Figure 2B  Kaplan-Meier plot of overall survival by SII level
Kaplan-Meier plot of overall survival (OS) from ICI initiation, for patients < 80 and ≥ 80 years, stratified according to pre-treatment SII levels: ICI: immune checkpoint inhibitor; SII: Systemic immune-inflammatory index; H: high; L: low; 95%CI: 95% confidence interval

Abstract 112 Figure 2C  Kaplan-Meier plot of overall survival by PLR level
Kaplan-Meier plot of overall survival (OS) from ICI initiation, for patients < 80 and ≥ 80 years, stratified according to pre-treatment PLR levels: ICI: immune checkpoint inhibitor; PLR: platelets-to-lymphocyte ratio; H: high; L: low; 95%CI: 95% confidence interval

Abstract 112 Figure 3A  Kaplan-Meier plot of PFS by PLR level
Kaplan-Meier plot of progression-free survival (PFS) from ICI initiation, for patients < 80 and ≥ 80 years, stratified according to pre-treatment PLR levels: ICI: immune checkpoint inhibitor; PLR: platelets-to-lymphocyte ratio; H: high; L: low; 95%CI: 95% confidence interval

Abstract 112 Figure 3B  Kaplan-Meier plot of PFS by SII level
Kaplan-Meier plot of progression-free survival (PFS) from ICI initiation, for patients < 80 and ≥ 80 years, stratified according to pre-treatment SII levels: ICI: immune checkpoint inhibitor; SII: Systemic immune-inflammatory index; H: high; L: low; 95%CI: 95% confidence interval
SII levels: ICI: immune checkpoint inhibitor; SII: systemic immune-inflammation index; H: high; L: low; 95%CI: 95% confidence interval

Abstract 112 Figure 4
ICI-related biomarkers (A) and composition of the TME (B) in patients ≥ 80 and < 80 years: Fold-changes represent the median value of patients ≥ 80 years compared to those < 80 years. ICI: immune checkpoint inhibitor; TME: tumor microenvironment; TMB-H: high tumor mutation burden; NSCLC: non-small cell lung cancer; MEL: melanoma; PD-L1: programmed-death ligand-1; RCC: renal cell carcinoma