**Background** Nanrilkefusp alfa (SOT101, RLI-15) is a high affinity superagonist fusion protein of interleukin (IL)-15 and the IL-15 receptor α (IL-15Rα) sushi+ domain representing a promising clinical candidate for the treatment of cancer. Nanrilkefusp alfa induces proliferation and activation of CD8⁺ T cells, memory CD8⁺ T cells, NK cells, γδ T cells and NKT cells but not Tregs.

**Methods** Blood and tumor samples from patients with advanced/metastatic solid tumors participating in a Phase clinical I study (NCT04234113) were analyzed by flow cytometry, immunohistochemistry and NanoString analyses for immune cell activation and tumor infiltration induced by Nanrilkefusp alfa monotherapy or in combination with pembrolizumab.

**Results** Nanrilkefusp alfa monotherapy or combined with pembrolizumab markedly increased proliferation of CD8⁺ T cells, memory CD8⁺ T cells, NK cells, γδ T cells and NKT cells, as well as IFN-γ levels without concomitantly increasing Tregs in peripheral blood. Whereas strong proliferation of NK cells was detected already at the lowest dose level of 0.25 μg/kg, proliferation of CD8⁺ T cells, memory CD8⁺ T cells and NKT cells was dose-dependent, reaching maximal activity at 12 μg/kg. High NK-cell proliferation was maintained over repeated cycles of the treatment, while NKT and CD8⁺ T cell proliferation peaked in cycle 1 and then declined slightly. In tumor tissues, nanrilkefusp alfa increased the density of NK cells, CD3⁺, CD4⁺ and CD8⁺ tumor-infiltrating lymphocytes (TILs), the CD8⁺/Treg ratio and the densities of proliferating CD8⁺ and CD4⁺ TILs, while Tregs in the tumor remained low. Consistent with the increased number of TILs, nanrilkefusp alfa increased the expression of gene sets related to innate and adaptive immune responses, including NK cell function, Th1 activation, regulation of the immune response, chemokines, and γδ T cells. Pharmacodynamic responses were the most pronounced in patients showing a clinical benefit as determined by stable disease or partial response.

**Conclusions** Nanrilkefusp alfa boosts both the innate and adaptive immune system and induces proinflammatory changes in the microenvironment of multiple tumor types as single-agent and in combination with pembrolizumab. An extended evaluation of nanrilkefusp alfa in combination with pembrolizumab or cetuximab is currently ongoing in phase 2 clinical trials in patients with advanced solid tumors (NCT05256381, NCT05619172).

**Ethics Approval** The study obtained ethics approval and participants gave informed consent before taking part. Comite de Protection des Personnes, CPP Ouest 6 – CPP 1157 ME1; CElm Hospital Universitari Vall d’Hebron, ID-RTF096; Western Institutional Review Board, 20192896; U.T.MD Anderson Cancer Center Institutional Review Board, 20192896; Multi-center ethics committee University Hospital Brno, 82/20MEK; Ethics committee Masaryk Memorial Cancer Institute, R 22/20.