Poster nr. 713

Nanrilkefusp alfa, a high-affinity IL-15Rβγ agonist, promotes an innate and adaptive anti-tumor inflammatory environment as single agent or combined with anti-PD-1 in patients with advanced cancers

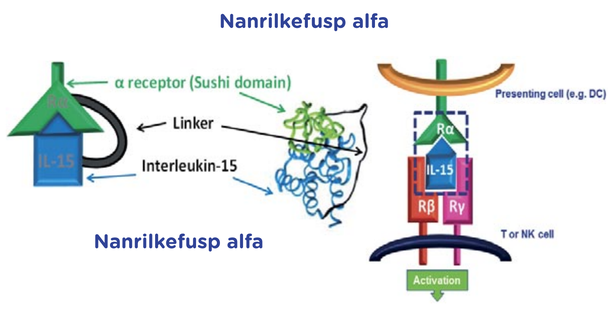
Petr Danek[1], Ekaterina Simonova[1], Nada Hradilova[1], David Bechard[4], Richard Sachse[3], Joachim Kiemle-Kallee[3], Ulrich Moebius[1], Radek Spisek[1,2], Irena Adkins[1,2], Martin Steegmaier[1], Lenka Palova-Jelinkova[1,2]

[1]SOTIO Biotech a.s, Českomoravská 2532/19b, 190 00 Prague 9, Czech Republic; [2]Department of Immunology, 2nd Faculty of Medicine and University Hospital Motol, Charles University, V Uvalu 84, Prague 5, 150 06, Czech Republic; [3]Sotio Biotech AG, Lichtstrasse 35 – WSJ-21, 4056 Basel, Switzerland; [4]Cytune Pharma, 3 Chemin du Pressoir Chênaie, 44100, Nantes, France

Introduction

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 cells 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 and NKT cells, the absolute NK cell, CD8⁺ and memory CD8⁺ T cell counts, 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, 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 selected advanced solid tumors (NCT05256381, NCT05619172).

Figure 1: Time on study and the best clinical response

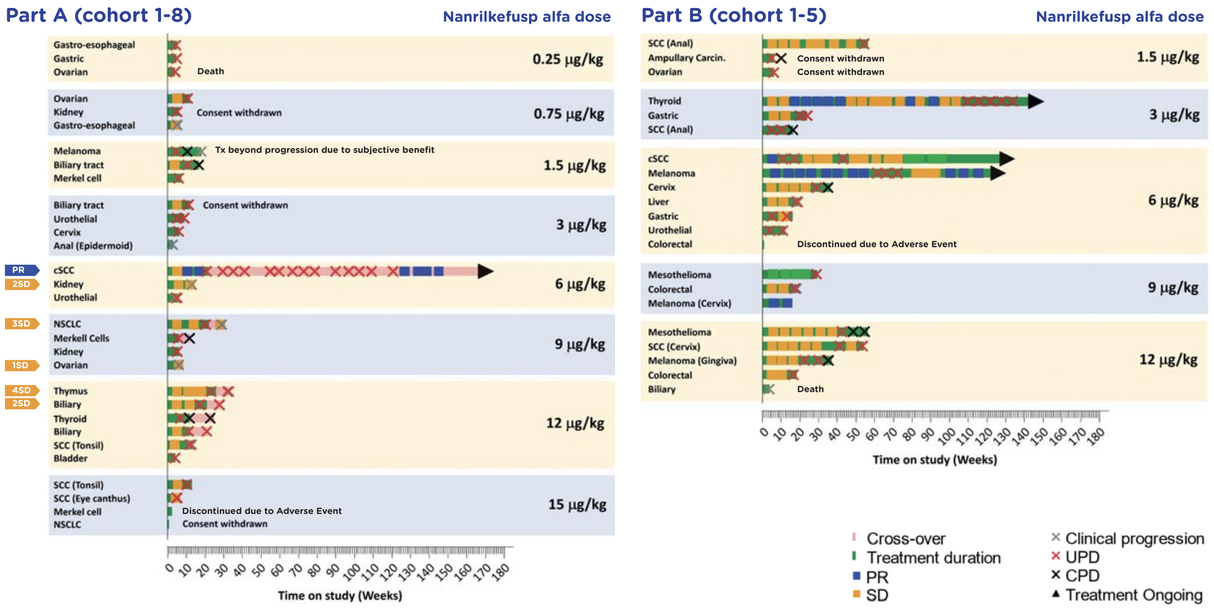


Figure 2: Nanrilkefusp alfa induces pharmacodynamic changes in line with its mode of action in peripheral blood

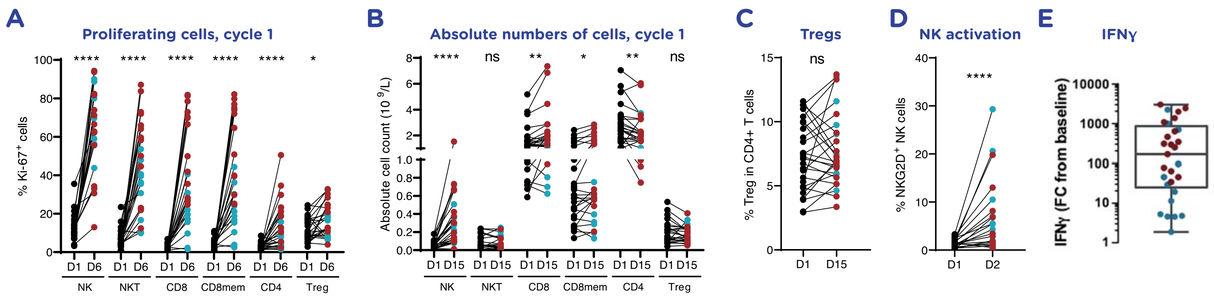


Figure 2: Nanrilkefusp alfa induces pharmacodynamic changes in line with its mode of action in peripheral blood. Pharmacodynamic responses evaluated in peripheral blood from 27 patients during cycle 1 prior to and during therapy with different concentration of nanrilkefusp alfa. **(A)** The percentage of proliferating (Ki67⁺) and **(B)** absolute numbers of NK, NKT, CD8⁺ T cells, memory CD8⁺ T cells, CD4⁺ T cells and Tregs were evaluated by flow cytometry using peripheral blood samples collected pre-dose (Day 1) and at 6 days (Ki67⁺) or 15 days (absolute count) after starting treatment. Strong proliferation of NK cells was apparent at 0.25 µg/kg, while the activation of CD8⁺ T cells, memory CD8⁺ T cells and NKT cells was dose-dependent, reaching a plateau at 12 µg/kg. **(C)** The percentage of Tregs in the total CD4⁺ T-cell counts and **(D)** the percentage of NKG2D⁺NK cells determined by flow cytometry in peripheral blood before treatment and on days 15 and day 2, respectively. **(E)** Maximal fold-change in peripheral blood IFN-γ concentrations from baseline. * p<0.05, **p<0.01. ***p<0.001, ****p<0.0001 (Wilcoxon–Mann–Whitney test). ns, not significant

Methods

Study design

- Phase 1/1b study is a multicenter, open-label, dose escalation study for patients with selected advanced/metastatic solid tumors

Dosing schedule

Part A (Nanrilkefusp alfa monotherapy)

- Nanrilkefusp alfa 0.25-15.0 µg/kg s.c. injection: Day 1, 2, 8, and 9 of each 21-day cycle

Part B (Nanrilkefusp alfa combined with pembrolizumab)

- Nanrilkefusp alfa 1.5-12.0 µg/kg s.c. injection: Day 1, 2, 8, and 9
- Pembrolizumab i.v. 200 mg: Day 1 of each 21-day cycle

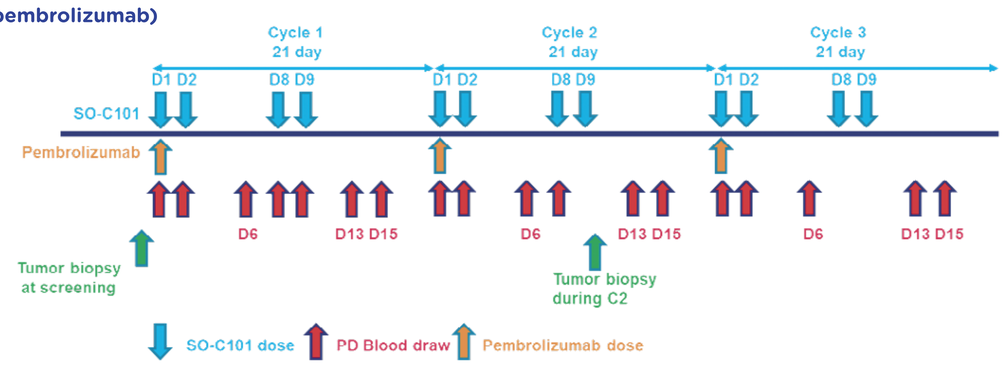


Figure 3: Tumor infiltration and gene expression changes after treatment with nanrilkefusp alfa as a monotherapy

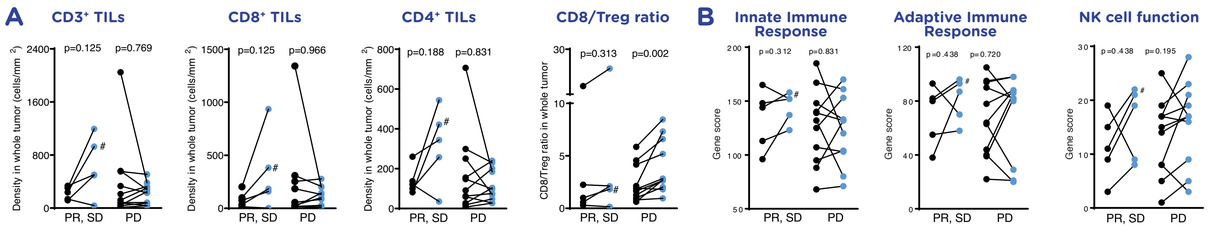


Figure 3. IHC and transcriptomic analysis of the tumor tissue after nanrilkefusp alfa administration. (A) Immune cell infiltration and **(B)** gene scores for the selected immune pathways were evaluated using paired tumor biopsies from 16 patients. Biopsies were collected before treatment and on-treatment (cycle 2) and subjected to immunohistochemistry and NanoString gene analysis. Patients were divided into two groups according to their clinical response. Group 1 includes patients with confirmed PR (labelled #) or SD. Group 2 includes patients with progressive disease (unconfirmed and confirmed). Wilcoxon–Mann–Whitney test. PR, partial response; SD, stable disease; PD, progressive disease.

Figure 4: Tumor infiltration and gene expression changes after treatment with nanrilkefusp alfa in combination with pembrolizumab

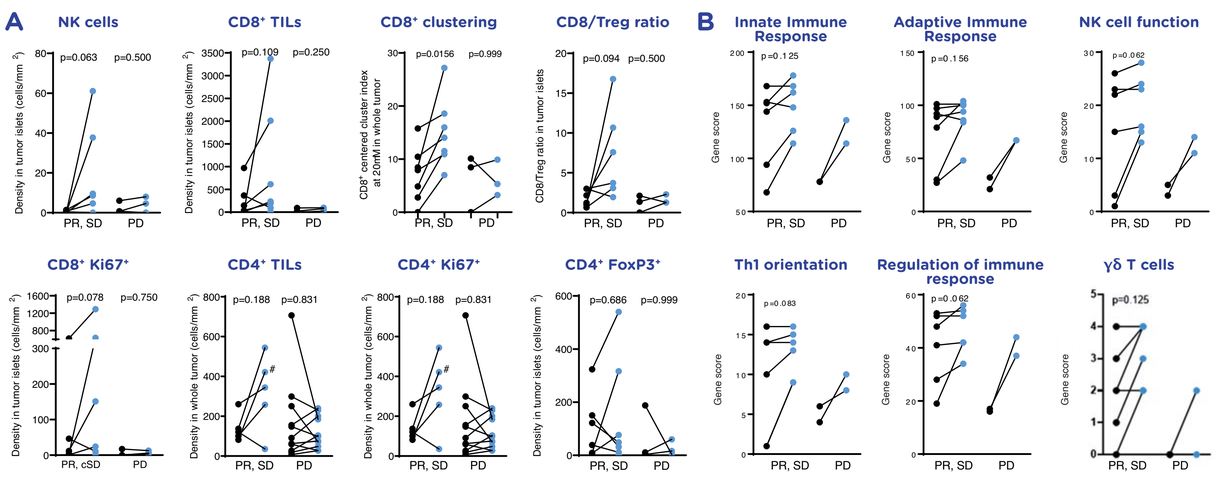
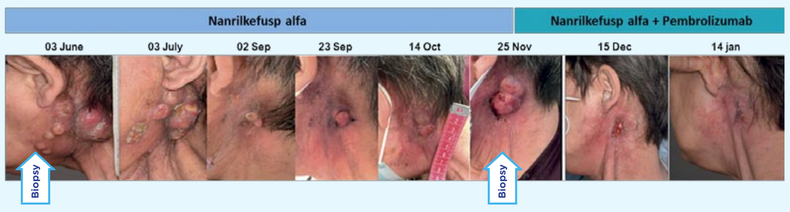


Figure 4. IHC and transcriptomic analysis of the tumor tissue after administration of nanrilkefusp alfa in combination with pembrolizumab. (A) Immune cell infiltration and **(B)** gene scores for the selected immune pathways were evaluated using paired tumor biopsies from 10 patients. Biopsies were collected before treatment and on-treatment (cycle 2) and subjected to immunohistochemistry and NanoString gene analysis. Patients were divided into two groups according to their clinical response. Group 1 includes patients with confirmed PR (labelled #) or SD. Group 2 includes patients with progressive disease (unconfirmed and confirmed). Wilcoxon–Mann–Whitney test. PR, partial response; SD, stable disease; PD, progressive disease

Conclusions

- Nanrilkefusp alfa mode-of-action includes activation of both innate as well as adaptive immunity
- Nanrilkefusp alfa as monotherapy and in combination with pembrolizumab showed a dose-dependent PD responses in blood of all patients, however, clinically responsive patients showed also an increased CD8⁺ T cell and NK cell infiltration in the tumor
- Nanrilkefusp alfa induces robust immune-stimulatory response in in the microenvironment of multiple tumor types as a single-agent and in combination with pembrolizumab
- Nanrilkefusp alfa seems to be able to restore the sensitivity to CPI treatment in CPI refractory/resistant patients as demonstrated by the case study

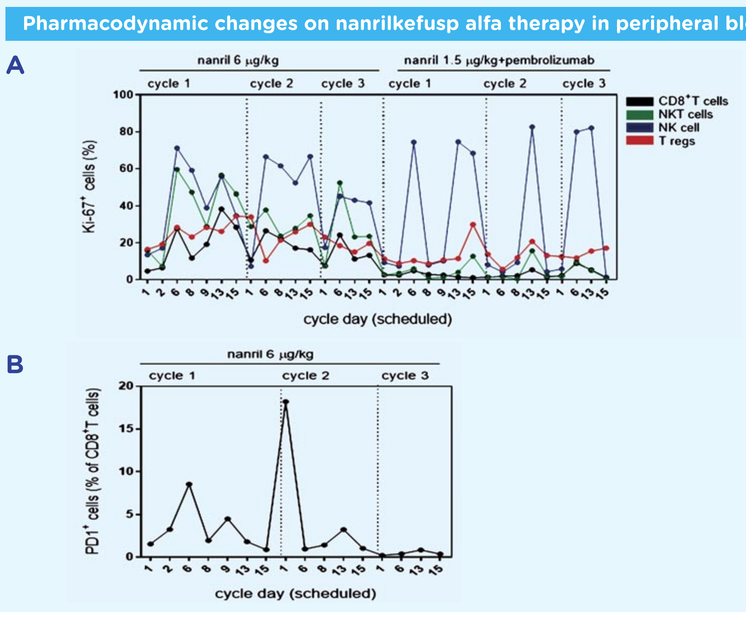
Figure 5: PD changes in peripheral blood and tumor tissue of the patient with skin squamous cell carcinoma previously exposed to an immune checkpoint blocker, treated with nanrilkefusp alfa 6 µg/kg with a best response of partial response



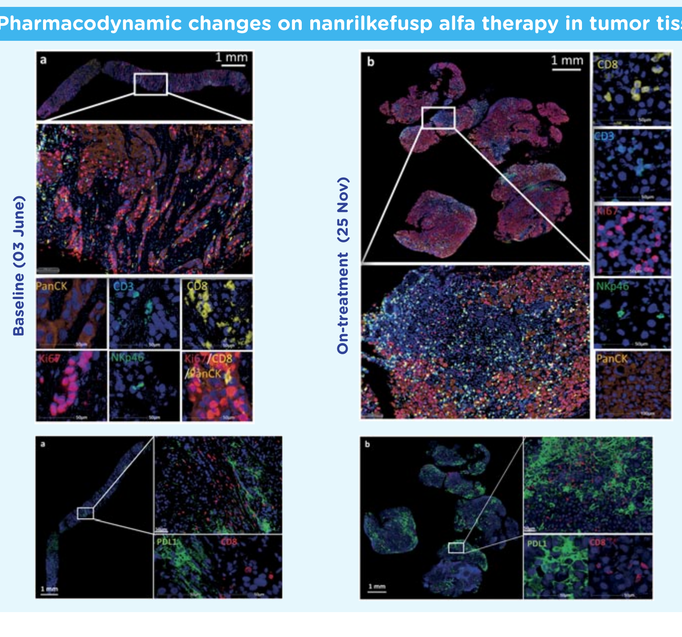
Patient	Treatment history	On-study benefit
Female, age 62, with cutaneous Squamous Cell Carcinoma	• 3 prior lines • Most recent: Cemiplimab (01/2020 -04/2020)	• Nanrilkefusp alfa monotherapy 6 µg/kg started 4 Jun 2020 • PR (-58 % at target lesions) at Cycle 8 (28 Oct 2020) • Crossover to nanrilkefusp alfa 1.5 µg/kg + pembrolizumab 200 mg Q3W on 26 Nov 2020 • PR (-63 % at target lesions) at Cycle 4 (5 Feb 2021) • 5 May 2021: PET-CT showed no „hot spots“ • Patient still on treatment

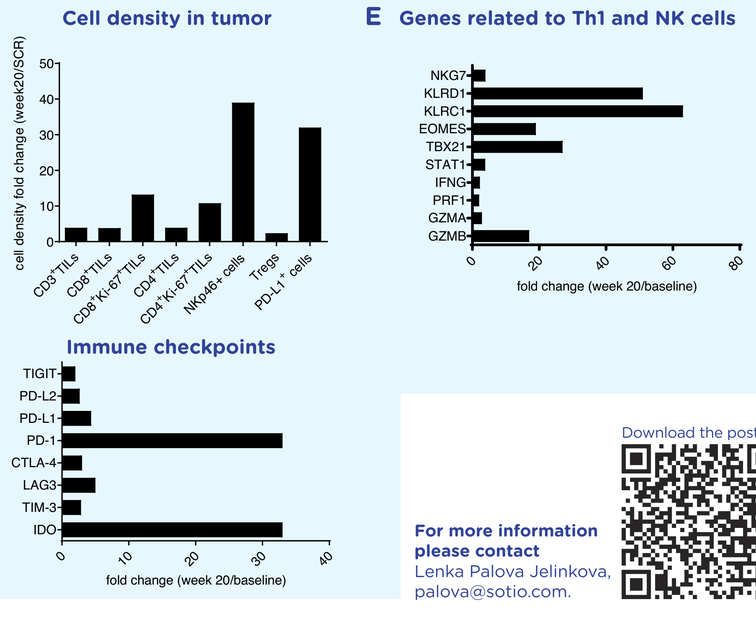
(A) Proliferation of CD8⁺ T cells, NK cells, NKT cells, and Tregs in peripheral blood was analyzed in cycles 1-3 of nanrilkefusp alfa monotherapy and cycles 1-3 of combination therapy by FACS analysis. **(B)** Percentage of PD1⁺CD8⁺ T cells in peripheral blood in cycles 1-3 of nanrilkefusp alfa monotherapy was evaluated by FACS analysis. **(C)** Baseline (a) and relapse (b, week 20) tumor biopsies were stained for immune cell markers by immunohistochemistry. **(D)** The density of immune cells and PD-L1⁺ cells was determined as a fold change from baseline. **(E)** Expression of selected genes related to NK- and T-cell activation, cytotoxicity, and immune checkpoints were analyzed in baseline and relapse tumor biopsies by NanoString analysis.

Pharmacodynamic changes on nanrilkefusp alfa therapy in peripheral blood



Pharmacodynamic changes on nanrilkefusp alfa therapy in tumor tissue





For more information please contact
Lenka Palova Jelinkova, palova@sotio.com.

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