Journal for ImmunoTherapy of Cancer

Nemvaleukin alfa monotherapy in patients with advanced melanoma and renal cell carcinoma: results from the phase 1/2 non-randomized ARTISTRY-1 trial

Emiliano Calvo ,[1] Valentina Boni,[1] Olivier Dumas,[2] Sang Joon Shin,[3] Seth D Rosen,[4] Arvind Chaudhry,[5] Philip R Debruyne,[6,7,8] Xiaomin He,[9] Ulka N Vaishampayan ,[10] David F McDermott[11]

To cite: Calvo E, Boni V, Dumas O, *et al*. Nemvaleukin alfa monotherapy in patients with advanced melanoma and renal cell carcinoma: results from the phase 1/2 non-randomized ARTISTRY-1 trial. *Journal for ImmunoTherapy of Cancer* 2025;**13**:e010777. doi:10.1136/jitc-2024-010777

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/jitc-2024-010777).

UNV and DFM are joint senior authors.

Accepted 01 July 2025

For numbered affiliations see end of article.

Correspondence to
Dr Emiliano Calvo;
emiliano.calvo@startmadrid.com

ABSTRACT

Background Despite improved outcomes with immune checkpoint inhibitors (ICIs) and their combinations in advanced solid tumors, a subset of patients remains unresponsive or progresses, highlighting an unmet need for novel treatments with durable benefit. Nemvaleukin alfa (nemvaleukin, ALKS 4230) demonstrated manageable safety and antitumor activity, alone and in combination with pembrolizumab, across heavily pretreated advanced solid tumors in the ARTISTRY-1 study. We report in-depth antitumor activity, safety, pharmacokinetics, and pharmacodynamics of nemvaleukin monotherapy at the recommended phase 2 dose (RP2D) in advanced melanoma and renal cell carcinoma (RCC) cohorts from ARTISTRY-1.

Methods ARTISTRY-1 was a three-part (A, B, and C), multicenter, open-label, phase 1/2 study. Adult patients who had received prior treatment, including ICIs, and had advanced melanoma or RCC were enrolled in Part B. Patients received intravenous nemvaleukin once daily on days 1–5 (21-day cycle) at 6 µg/kg/day (RP2D determined from Part A). Primary endpoints for Part B were overall response rate (ORR) and safety. Secondary endpoints included pharmacokinetic and pharmacodynamic measures.

Results From July 2016 to March 2023, 74 patients in Part B received nemvaleukin monotherapy (melanoma, n=47; RCC, n=27). ORR in melanoma and RCC cohorts was 9% (95% CI, 2% to 21%; n=4) and 14% (95% CI, 3% to 35%; n=3), respectively; disease control rate was 50% (95% CI, 35% to 65%; n=23) and 50% (95% CI, 28% to 72%, n=11), respectively, with stable disease ≥6 months observed in 3 (7%) and 2 (9%) patients, respectively. The most common nemvaleukin-related treatment-emergent adverse event of grade 3–4 was neutropenia (melanoma, n=27 (57%); RCC, n=9 (33%)). No patients in either cohort experienced grade ≥3 treatment-emergent adverse events (TEAEs) of cytokine release syndrome or infusion-related reaction. There were no reported capillary leak syndrome TEAEs. Pharmacokinetic parameters for extent and duration of nemvaleukin exposure were similar between the two cohorts. Increases in peripheral $CD8^+$ T-cell and natural killer cell populations from baseline were similar between the two cohorts, with minimal changes in regulatory T cells observed.

Conclusions Nemvaleukin demonstrated pharmacodynamic proof of mechanism, with single-agent antitumor activity and manageable safety in patients with advanced melanoma and RCC.

Trial registration number NCT02799095.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ For patients with melanoma and advanced renal cell carcinoma (RCC) who do not respond to or develop resistance to first-line immune checkpoint inhibitor (ICI) therapy or subsequent therapies, there is a high unmet need for novel agents with improved treatment index and safety.

⇒ High-dose recombinant human interleukin-2 (rhIL-2) is approved for melanoma and advanced RCC; however, it is associated with severe and life-threatening acute toxicities that restrict its clinical application and it must be administered in an inpatient setting.

WHAT THIS STUDY ADDS

⇒ Nemvaleukin alfa (nemvaleukin, ALKS 4230) is a novel, engineered IL-2 cytokine that demonstrated durable antitumor activity as monotherapy in some patients with advanced melanoma or RCC who were pretreated with ICI therapies.

⇒ Nemvaleukin demonstrated pharmacodynamic proof of mechanism for preferential expansion of $CD8^+$ T cells and natural killer cells, and had a manageable safety profile with a low incidence of treatment discontinuation due to nemvaleukin-related treatment-emergent adverse events and no adverse events of capillary leak syndrome.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Nemvaleukin recapitulates the antitumor activity of high-dose rhIL-2 without its hallmark toxicities, thus confirming its design hypothesis and providing a promising new IL-2 candidate that has potential for improved therapeutic index and safety as well as supporting further evaluation of optimal patient subsets, tumor types, and combination strategies to maximize the therapeutic benefit.

INTRODUCTION

Cytokines and their receptors are key mediators of cell communication in the tumor microenvironment and therapies enhancing the immune-stimulating effects of cytokines have been investigated for decades.[1] High-dose recombinant human interleukin-2 (rhIL-2, aldesleukin) was one of the first immunotherapies approved by the US Food and Drug Administration: it was approved for advanced renal cell carcinoma (RCC) in 1992 and for metastatic melanoma in 1998, with durable efficacy reported in a subset of patients.[2–6] However, the high doses of IL-2 required to achieve clinical efficacy via activation of the intermediate-affinity IL-2 receptor (IL-2Rβγ) also result in a potent interaction with the high-affinity IL-2Rαβγ leading to regulatory T cell (T_{reg}) expansion-mediated immunosuppression, which can potentially limit the antitumor activity of IL-2 treatment.[7] Furthermore, high-dose IL-2 is associated with severe and life-threatening acute toxicities (via vascular endothelial cell activation), such as capillary leak syndrome, which contributes to end-organ injury, thereby severely restricting its clinical application to medically fit patients and in an inpatient setting.[3 8 9]

In comparison, immune checkpoint inhibitors (ICIs), particularly programmed cell death protein-1 (PD-1) inhibitors, have proven effective in treating a diverse spectrum of advanced solid tumors, increasing rates of overall survival compared with standard cancer treatments and allowing long-term remission.[10–14] ICI-based combination therapies, especially those incorporating PD-1 inhibitors, are now the standard of care as the first-line treatments for advanced RCC and metastatic melanoma, and improved survival has been observed with the combination of ipilimumab with nivolumab for both tumor types.[15–17] Despite these positive outcomes, a significant subset of patients remain unresponsive to ICIs, encounter tolerability challenges, or develop resistance to these treatments.[18–20] Additionally, second-line treatment with ICIs or their combinations after progression on prior ICI therapy has not proven effective.[21 22]

Nemvaleukin alfa (nemvaleukin, ALKS 4230) is a novel, engineered IL-2 variant that selectively binds and signals through the intermediate-affinity IL-2R complex (IL-2Rβγ) on $CD8^+$ cells and natural killer (NK) cells in the tumor microenvironment and in the periphery.[23 24] This signaling results in preferential activation and expansion of tumor-killing $CD8^+$ T cells and NK cells, with minimal expansion of T_{regs}, thereby mitigating the risk of toxicities and immunosuppression associated with binding of IL-2 to the high-affinity IL-2R.[23 24] Furthermore, nemvaleukin is inherently active, does not require metabolic or proteolytic conversion, and does not degrade into native IL-2.[23]

ARTISTRY-1 (NCT02799095) is a three-part, first-in-human study that demonstrated antitumor activity of intravenous nemvaleukin monotherapy and nemvaleukin plus pembrolizumab in heavily pretreated adults with advanced solid tumors, and the manageable safety profile allowed for outpatient administration that was previously not achieved with high-dose rhIL-2.[25] We report in-depth results from the dose expansion part B of ARTISTRY-1, which investigated single-agent antitumor activity, safety, pharmacokinetics, and pharmacodynamics of intravenous nemvaleukin monotherapy at the recommended phase 2 dose (RP2D) in patients with heavily pretreated advanced melanoma and RCC.

METHODS

Study design and treatments

ARTISTRY-1 is a global, multicenter, open-label, phase 1/2 study that enrolled patients at 32 sites in seven countries. This was a three-part study comprising Part A (dose-escalation monotherapy), Part B (dose-expansion monotherapy), and Part C (combination therapy with pembrolizumab).

Procedures and dosing details have been described previously.[25] Briefly, RP2D of nemvaleukin was determined to be 6 µg/kg once daily for 5 consecutive days (from day 1 to day 5) in a 21-day cycle based on Part A of ARTISTRY-1. Patients in the nemvaleukin monotherapy dose expansion group (Part B) received nemvaleukin as a 30 min intravenous infusion at the RP2D in an outpatient setting; cycle 1 was 14 days (9 days off treatment), cycles 2+ were 21 days (16 days off treatment).

The study protocol and all amendments were approved by the institutional review board or independent ethics committee at each site. An independent data-monitoring committee monitored safety and efficacy data and overall study conduct. All participants provided written informed consent according to the principles of the Declaration of Helsinki.

Study population

Eligible patients in part B of the ARTISTRY-1 study were aged ≥18 years, had at least one lesion that qualified as a target lesion based on Response Evaluation Criteria In Solid Tumors (RECIST), and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were enrolled in advanced melanoma or RCC cohorts. Patients with advanced melanoma had received an ICI (eg, anti-programmed death/anti-PD ligand-1 (anti-PD(L)1) with or without anti-cytotoxic T-lymphocyte-associated protein-4 (CTLA-4)) and, if appropriate, a molecularly targeted agent (eg, BRAF inhibitor if *BRAF*-mut), and no more than one prior cytotoxic chemotherapy. For the advanced RCC cohort, patients could enroll regardless of

their previous exposure to checkpoint inhibitors. Patients who had received prior anti-PD(L)1 therapy must have received a PD(L)1 ICI, either as a monotherapy or in combination with a CTLA-4 inhibitor or a vascular endothelial growth factor receptor tyrosine kinase inhibitor. Additionally, these patients with prior anti-PD(L)1 therapy exposure were limited to having no more than two prior lines of systemic therapies, including the checkpoint inhibitor-based regimen. Patients previously treated with ICI either as a single-agent or in a combination regimen had experienced objective response or stable disease (by RECIST or RECIST in patients undergoing immunotherapy (iRECIST) as best overall response); patients with progressive disease as best response were eligible on a case-by-case basis with approval by the medical monitor. Patients with active autoimmune disease requiring systemic treatment within the past 3 months or documented history of clinically severe autoimmune disease that required systemic steroids or immunosuppressive agents, or prior IL-2-based or IL-15-based therapy were excluded from the study.

Study objectives and endpoints

The objectives and endpoints of ARTISTRY-1 have been described previously.[25] Primary objectives of Part B were to characterize antitumor activity by overall response rate (ORR) and to assess the safety profile of nemvaleukin monotherapy at the RP2D in patients with melanoma or RCC. The primary endpoints of the ARTISTRY-1 study for Part B were ORR based on RECIST V.1.1 and incidence and severity of treatment-emergent adverse events (TEAEs) according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) V.4.03 or higher. Secondary endpoints were serum concentrations of nemvaleukin and descriptive pharmacokinetic parameters, presence of antidrug antibodies (ADAs) in serum, disease control rate (DCR) and duration of response based on RECIST, progression-free survival (PFS), and numbers of circulating $CD8^+$ T cells, T_{regs}, and NK cells in peripheral blood.

Study assessments

Antitumor activity was determined by the measurement of extent of known disease at baseline and at the end of cycle 2 but before the next treatment cycle. For subsequent cycles, assessments were done at the end of each even-numbered treatment cycle (eg, cycles 4, 6) but before the next treatment cycle. Appropriate radiological procedures (CT scanning, MRI, radionuclide imaging) were conducted to evaluate areas of disease. Superficial skin tumors were measured with calipers and photographed for evaluation. Per RECIST, tumors were assessed for complete response, partial response, stable disease, or progressive disease. The ORR was calculated as the proportion of patients with confirmed complete response or partial response per RECIST V.1.1. PFS was defined as the time from the first dose of nemvaleukin to the first documentation of objective tumor progression or death due to any cause. The DCR was defined as the proportion of patients with objective evidence of complete response, partial response (where complete response or partial response required confirmation), or stable disease (where the stable was required to occur at cycle 4 or later).

Safety was evaluated based on adverse events (AEs), vital signs and weight, clinical laboratory tests, and standard 12-lead electrocardiograms. TEAEs were defined as AEs that occurred or worsened after the first dose of study drug. Reported AE terms were coded using the Medical Dictionary for Regulatory Activities V.25.0. Severity of AEs was graded using NCI CTCAE V.4.03 or higher. A serious AE (SAE) was any AE, occurring at any dose and regardless of causality, that resulted in death, or was life-threatening and posed immediate risk of death from the reaction as it occurred, required inpatient hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability/incapacity or congenital anomaly/birth defect.

Serum samples for evaluation of nemvaleukin pharmacokinetics were obtained from each patient at predetermined time points outlined in the online supplemental methods. Non-compartmental pharmacokinetic analysis was performed to estimate the pharmacokinetic parameters for nemvaleukin. Serum samples for evaluation of ADA induction were obtained from each patient at predetermined time points (online supplemental methods). Concentrations of nemvaleukin and its antibody in human serum were quantified using a validated electrochemiluminescence method using the Meso Scale Discovery platform. The assessment of immune-response induction for each patient was based on the comparison of the predose and postdose sample results. The pharmacodynamic effect of nemvaleukin was assessed by measuring circulating $CD8^+$ T cells, NK cells, and T_{regs} in peripheral blood by flow cytometry from each patient at predetermined time points (online supplemental methods).

Statistical analysis

The nemvaleukin monotherapy dose expansion was designed to enroll patients in each of two cohorts based on tumor type and prior therapy. The sample size of each cohort was chosen based on Simon's two-stage design for phase 2 studies.[26] Enrollment to these cohorts followed a partial response (unconfirmed) Simon's two-stage design enrollment where the target desirable response rate was 20% and the undesirable response rate was 5%, with the assumed alpha of 0.05 and power of 90%. A total of 21 patients could be enrolled for each cohort in the first stage and 20 patients could be enrolled in the second stage if partial response/complete response was ≥2. Enrollment was halted in the RCC cohort due to lower than anticipated response rates observed after sufficient follow-up to allow for an assessment of response among the first 19 patients. The data were presented by expansion cohorts with specified tumor types (melanoma (including cutaneous, mucosal, ocular, and acral subtypes), and RCC)

and overall. No more than five patients with ocular melanoma could be enrolled into the melanoma cohort.

The safety population included all patients who received at least one dose of nemvaleukin. The antitumor evaluable population included patients who completed two cycles of therapy and had at least one follow-up scan. The pharmacokinetics and pharmacodynamics populations included all patients who received at least one dose of nemvaleukin and had at least one measurable serum concentration of nemvaleukin at any scheduled pharmacokinetic time and at least one available postbaseline pharmacodynamic measurement, respectively. Safety data were summarized using descriptive statistics. ORR was summarized by frequency counts, percentage, and 95% CIs. The median PFS was estimated using Kaplan-Meier methodology along with the two-sided 95% CIs based on the antitumor evaluable population.

Patient and public involvement

Although patients made important contributions to this research as study participants, patients and members of the public were not involved with the research study design, recruitment, or conduct of the study presented in this manuscript. Further, they are not involved in the dissemination of study results.

RESULTS

Patients

From July 2016 to June 2021, 299 patients were screened; 56 (19%) did not meet eligibility criteria. Of the 243 patients treated in ARTISTRY-1, 74 from part B in the melanoma (n=47) and RCC (n=27) cohorts received nemvaleukin monotherapy (online supplemental figure 1). At data cut-off (March 27, 2023, for the RCC cohort; September 27, 2023, for the melanoma cohort), 73 of the 74 patients (99%) had discontinued treatment, the most common reason being progressive disease.

Baseline demographics and clinical characteristics are shown in table 1. The median age was 66 years (range 37–82) in the melanoma cohort and 69 years (39–77) in the RCC cohort. The majority of the patients were male (melanoma, 53%; RCC, 89%) and were heavily pretreated, with a median of 2–3 prior lines of therapy (range 1–8). Prior immunotherapy exposure included anti-PD-1/anti-PD-L1 therapy, anti-CTLA-4 therapy, and combination anti-PD-1+anti-CTLA-4 therapy. Some patients received multiple lines or combinations of immunotherapies (table 1). A total of 19 (40%) patients in the melanoma cohort had high baseline lactate dehydrogenase levels; the median (range) level was 438 U/L (233–1921 U/L). A total of 23 (85%) patients in the RCC cohort had clear-cell RCC histology (table 1).

Efficacy

A total of 46 patients from the melanoma cohort and 22 patients from the RCC cohort were included in the antitumor evaluable population. Overall confirmed response rate (95% CI; n) in melanoma and RCC cohorts was 9% (95% CI, 2% to 21%, n=4) and 14% (95% CI, 3% to 35%; n=3), respectively (table 2). All four confirmed responses in the melanoma cohort were partial responses; 3 of 30 (10%) were in patients with cutaneous melanoma, and 1 of 6 (17%) was in mucosal melanoma. DCR in both melanoma and RCC cohorts was 50% (95% CI, 35% to 65%; n=23 and 95% CI, 28% to 72%; n=11), respectively. Within the melanoma cohort, 3 patients with mucosal melanoma, 21 patients with cutaneous melanoma, 5 patients with ocular melanoma, and 4 patients with acral melanoma had stable disease. Two patients from the cutaneous melanoma subgroup and one from the acral melanoma subgroup had stable disease for more than 6 months (table 2). In the RCC cohort, all confirmed responders had partial response and had been treated previously with an ICI. 12 (55%) patients had stable disease, and 2 patients (9%) had stable disease for more than 6 months (table 2). The duration of treatment by overall response for the cutaneous melanoma and mucosal melanoma subgroups and for the RCC cohort is shown in figure 1. Notably, one response in the cutaneous melanoma subgroup lasted for at least 57 weeks, and one response in the mucosal melanoma subgroup lasted for at least 164 weeks; both responses were ongoing at the time of data cut-off. In the RCC cohort, the longest duration of response observed was 94 weeks, with disease progression documented prior to final study closure. Maximum reduction in tumor size of at least 30% was observed in six patients in the melanoma cohort (13%) and in four patients in the RCC cohort (17%) (online supplemental figure 2). Median PFS (95% CI) in the melanoma and RCC cohorts was 16.4 weeks (10.6 to 17.1) and 12.4 weeks (4.4 to 22.6), respectively. In the melanoma cohort, 6-month and 1-year PFS rates were 14% and 11%, respectively. In the RCC cohort, 6-month and 1-year PFS rates were 19% and 10%, respectively (table 2).

Safety

Patients in both melanoma and RCC cohorts received a median of six treatment cycles (online supplemental table 1). The median duration of exposure to nemvaleukin monotherapy in both melanoma and RCC cohorts was 14.7 weeks. The relative dose intensity was high in both melanoma and RCC cohorts, with a median of 98%. Rates of dose interruptions and reductions were consistent across cohorts (online supplemental table 1).

In the melanoma and RCC cohorts, 45 (96%) and 27 (100%) patients, respectively, experienced at least one nemvaleukin-related treatment-emergent adverse event (TRAE), and 36 (77%) and 20 (74%) patients experienced at least one grade 3–4 TRAE (table 3). The most common TRAEs (≥25%) of any grade in the melanoma cohort included fever (n=32 (68%)), nausea (22 (47%)), and neutropenia (22 (47%)). In the RCC cohort, the most common TRAEs (≥25%) of any grade included fever (n=16 (59%)), chills (14 (52%)), and neutropenia (11 (41%)). The most common grade 3–4 TRAE was

Table 1 Baseline demographics and clinical characteristics

Characteristic	Melanoma n=47	RCC n=27	Overall N=74
Age, years, median (range)	66 (37–82)	69 (39–77)	67 (37–82)
Sex			
Male	25 (53)	24 (89)	49 (66)
Female	22 (47)	3 (11)	25 (34)
Race			
White	42 (89)	25 (93)	67 (91)
Black or African American	0	1 (4)	1 (1)
Asian	5 (11)	1 (4)	6 (8)
ECOG performance status			
0	23 (49)	7 (26)	30 (41)
1	24 (51)	20 (74)	44 (60)
Prior lines of therapy, median (range)	3 (1–8)	2 (1–8)	2 (1–8)
Prior lines of therapy			
1	12 (26)	7 (26)	19 (26)
2	9 (19)	10 (37)	19 (26)
3	15 (32)	5 (19)	20 (27)
4	7 (15)	0	7 (10)
5	2 (4)	3 (11)	5 (7)
>5	2 (4)	2 (7)	4 (5)
Prior immune checkpoint inhibitors*			
Anti-PD-1	45 (96)	15 (56)	60 (81)
Anti-PD-L1	3 (6)	2 (7)	5 (7)
Anti-CTLA-4	17 (36)	4 (15)	21 (28)
Anti-PD-1+anti-CTLA-4	3 (6)	1 (4)	4 (5)
Baseline LDH within normal limits			
n	28 (60)	–	–
Median (range), U/L	187 (109–529)	–	–
Baseline LDH above normal limits			
n	19 (40)	–	–
Median (range), U/L	438 (233–1921)	–	–
RCC histology†, n (%)	–		–
Clear-cell	–	20 (74)	–
Clear-cell and oncocytoma	–	1 (4)	–
Clear-cell and non-clear-cell	–	1 (4)	–
Clear-cell with rhabdoid features	–	1 (4)	–

Data are presented as number of patients (%) unless otherwise noted.
*Of 60 patients with prior anti-PD-1 therapy exposure (included nivolumab, pembrolizumab, or unspecified anti-PD-1 therapy), 11 (10 in melanoma cohort, 1 in RCC cohort) had received two lines. All five patients who had received anti-PD-L1 (either atezolizumab or avelumab) as prior immunotherapy had also received anti-PD-1 therapy. All patients who received prior anti-CTLA-4 therapy (ipilimumab) had also received anti-PD-1 therapy, with one patient in the melanoma cohort having received two lines of anti-CTLA-4 therapy and one line of anti-PD-L1 therapy and one patient in the RCC cohort having received one line of anti-PD-1 and one line of anti-PD-1+anti-CTLA-4 therapy. Of four patients who received prior anti-PD-1+anti-CTLA-4 (ipilimumab+nivolumab), three in the melanoma cohort had received anti-PD-1 therapy and one in the RCC cohort had received one line of anti-PD-1 and one line of anti-PD-L1 therapy. No patients were treated with prior anti-PD-1+TKI regimen (pembrolizumab+axitinib).
†Three patients had non-clear cell RCC histology. Histology data were not available per site for one patient.
CTLA-4, cytotoxic T-lymphocyte-associated protein-4; ECOG, Eastern Cooperative Oncology Group; LDH, lactose dehydrogenase; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand 1; RCC, renal cell carcinoma.

Table 2 Summary of nemvaleukin antitumor activity (by RECIST V.1.1)

	Mucosal n=6	Cutaneous n=30	Ocular n=6	Acral n=4	Overall melanoma N=46	RCC N=22	Prior ICI in RCC	
							Yes n=11	No n=11
Overall response rate, n (%) (95% CI)	1 (17) (0.4 to 64.1)	3 (10) (2.1 to 26.5)	0	0	4 (9) (2.4 to 20.8)	3 (14) (2.9 to 34.9)	3 (27) (6.0 to 61.0)	0
Best overall response, n (%)								
Complete response	0	0	0	0	0	0	0	0
Partial response	1 (17)	3 (10)	0	0	4 (9)	3 (14)	3 (27)	0
Stable disease	3 (50)	21 (70)	5 (83)	4 (100)	33 (72)	12 (55)	5 (46)	7 (64)
Stable disease >6 months	0	2 (7)	0	1 (25)	3 (7)	2 (9)	1 (9)	1 (9)
Progressive disease	2 (33)	6 (20)	1 (17)	0	9 (20)	7 (32)	3 (27)	4 (36)
DCR, n (%) (95% CI)	2 (33) (4.3 to 77.7)	15 (50) (31.3 to 68.7)	4 (67) (22.3 to 95.7)	2 (50) (6.8 to 93.2)	23 (50) (34.9 to 65.1)	11 (50) (28.2 to 71.8)	6 (55) (23.4 to 83.3)	5 (46) (16.7 to 76.6)
PFS, weeks, median (95% CI)	13.1 (4.1 to NE)	17.0 (10.6 to 22.3)	16.6 (4.0 to NE)	11.3 (10.6 to NE)	16.4 (10.6 to 17.1)	12.4 (4.4 to 22.6)	–	–
6-month PFS rate (%)	17	18	0	NE	14	19	–	–
1-year PFS rate (%)	17	13	0	NE	11	10	–	–

Responses are assessed as complete response, partial response, stable disease, or progressive disease based on Response Evaluation Criteria In Solid Tumors (RECIST) V.1.1. Only confirmed responses are shown; among patients with stable disease, unconfirmed responses were reported in two with melanoma and in one with RCC. The best overall response is the best response recorded from the start of the study treatment until the disease progression/recurrence. Overall response rate is defined as the percentage of patients who achieve a complete response or partial response based on RECIST V.1.1. DCR is defined as the percentage of patients who achieve a confirmed complete response, partial response, or stable disease at cycle 4 or later based on RECIST V.1.1. For both overall response rate and DCR, the two-sided 95% CI was estimated by Clopper-Pearson method.
DCR, disease control rate; ICI, immune checkpoint inhibitor; NE, not estimable; PFS, progression-free survival; RCC, renal cell carcinoma.

neutropenia (27 (57%) patients in the melanoma cohort and 9 (33%) patients in the RCC cohort). Nemvaleukin-related SAEs were reported in 7 (15%) patients in the melanoma cohort and in 8 (30%) patients in the RCC cohort. Five (7%) patients (1 (2%) in the melanoma cohort and 4 (15%) in the RCC cohort) experienced an infusion-related reaction (IRR). One (2%) patient in the melanoma cohort reported cytokine release syndrome (CRS). No CRS/IRR events of grade ≥3 were observed in any cohort. There were no reported TEAEs of capillary leak syndrome and febrile neutropenia in Part B. Administration of growth factors was permitted for the management of neutropenia, and 4 (5%) patients received filgrastim in Part B. The number of TRAEs leading to treatment discontinuation was low: only 2 (4%) patients from the melanoma cohort and 1 (4%) patient from the RCC cohort. In the melanoma cohort, dose interruptions and dose reductions due to TRAEs were reported in 40% (n=19) and 11% (n=5) of patients, respectively. In the RCC cohort, dose interruptions and dose reductions due to TRAEs were reported in 44% (n=12) and 4% (n=1) patients, respectively. There were no grade 5 TRAEs. One death due to COVID-19 was reported in the RCC cohort and was considered unrelated to study drug treatment (table 3).

Pharmacokinetics and pharmacodynamics

Following the first intravenous infusion of 6 µg/kg nemvaleukin in cycle 1 or cycle 2 in patients with melanoma or RCC (online supplemental figure 3A), mean serum nemvaleukin concentrations were similar between cohorts. Serum nemvaleukin peak concentrations were observed at end of infusion (30 min after start of infusion). Serum nemvaleukin concentrations showed a slow monophasic decline and remained detectable by 24 hours post dose for both cohorts. Serum nemvaleukin mean predose (trough) concentration following once-daily intravenous infusion of 6 µg/kg nemvaleukin for 5 days showed that both the melanoma and RCC cohorts had decreasing trough levels from cycle 1 day 2 up to cycle 1 day 5. Mean serum nemvaleukin trough levels were more stable during cycle 2, where steady state seemed to be reached on cycle 2 day 2 (online supplemental figure 3B). For patients in both the melanoma and RCC cohorts, following the first intravenous infusion of 6 µg/kg nemvaleukin on cycle 1 day 1, serum nemvaleukin area under the concentration-time curve from time 0 to

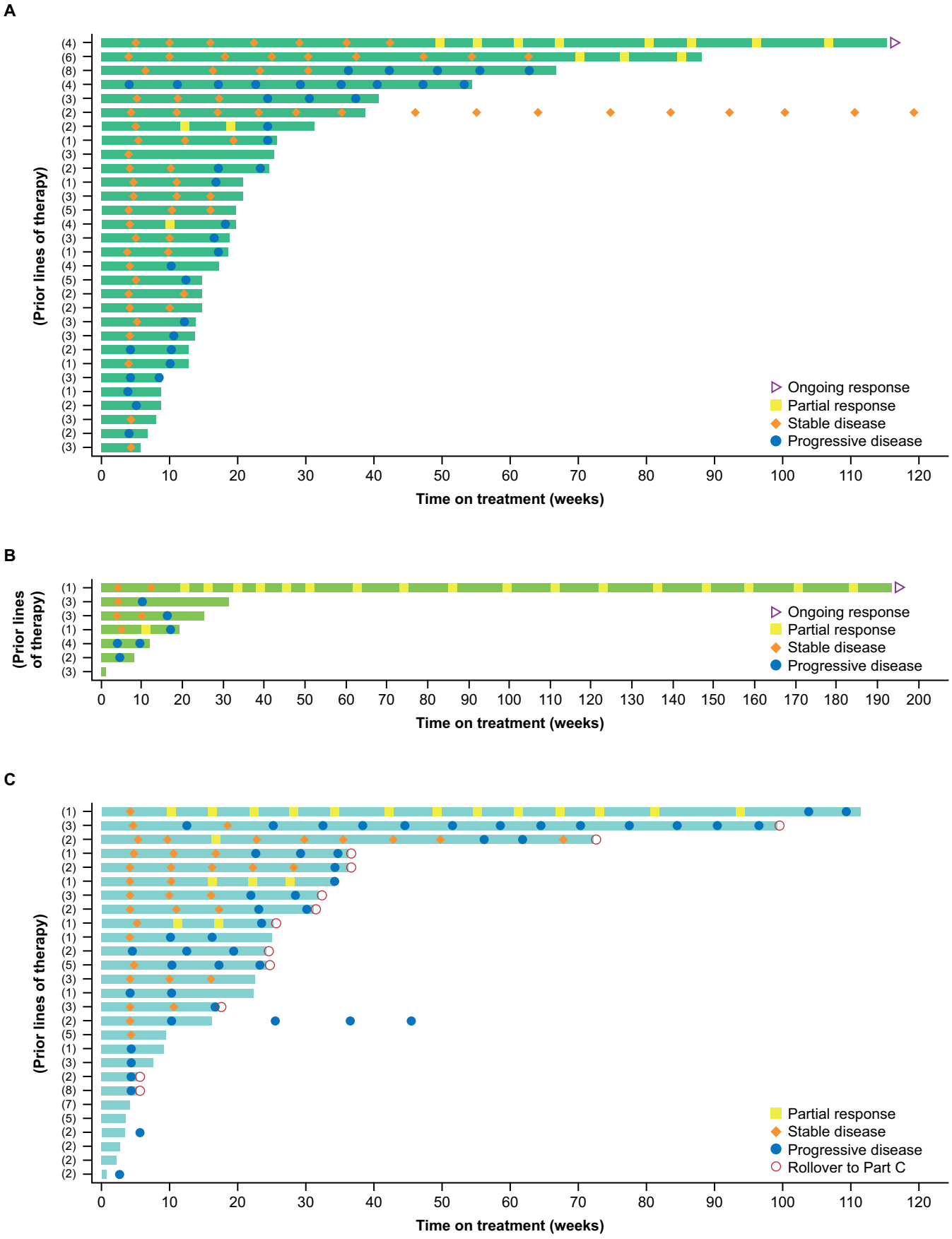

Figure 1 Duration of treatment and response evaluation in (A) cutaneous melanoma (B) mucosal melanoma, (C) renal cell carcinoma. Each bar represents one patient from the first dose until the end of treatment. The number of prior lines of therapy that each patient received is indicated by the number in parentheses. Both confirmed and unconfirmed responses are shown.

Table 3 Summary of nemvaleukin-related treatment-emergent adverse events

	Melanoma N=47	RCC N=27
Any grade nemvaleukin-related TEAEs, n (%)	45 (96)	27 (100)
Nemvaleukin-related grade 3–4 TEAEs, n (%)	36 (77)	20 (74)
Nemvaleukin-related grade 5 TEAEs, n (%)	0	0
Nemvaleukin-related serious TEAEs, n (%)	7 (15)	8 (30)
Nemvaleukin-related TEAEs leading to treatment discontinuation, n (%)	2 (4)	1 (4)
Nemvaleukin-related TEAEs leading to dose interruptions, n (%)*	19 (40)	12 (44)
Nemvaleukin-related TEAEs leading to dose reductions, n (%)†	5 (11)	1 (4)
Most frequent nemvaleukin-related TEAEs (≥25%), n (%)		
Fever	32 (68)	16 (59)
Nausea	22 (47)	6 (22)
Neutropenia	22 (47)	11 (41)
Chills	21 (45)	14 (52)
Hypotension	20 (43)	5 (19)
Aspartate aminotransferase increased	16 (34)	7 (26)
Alanine aminotransferase increased	16 (34)	6 (22)
Anemia	13 (28)	7 (26)
Fatigue	11 (23)	7 (26)
Vomiting	11 (23)	3 (11)
Most frequent grade ≥3 nemvaleukin-related TEAEs (≥5%), n (%)		
Neutropenia	27 (57)	9 (33)
Anemia	5 (11)	2 (7)
Alanine aminotransferase increased	3 (6)	2 (7)
Aspartate aminotransferase increased	3 (6)	1 (4)
Blood pressure increased	1 (2)	2 (7)
Chills	3 (6)	1 (4)
Hyperbilirubinemia	0	2 (7)
Patients with at least 1 CRS TEAE	1 (2)	0
Grade 1–2	1 (2)	0
Grade 3–5	0	0
Patients with at least 1 IRR TEAE	1 (2)	4 (15)
Grade 1–2	1 (2)	4 (15)
Grade 3–5	0	0
Patients with at least 1 CLS TEAE	0	0

*In the melanoma cohort, nemvaleukin-related TEAEs leading to dose interruptions included neutropenia in 9 (19%) patients, alanine aminotransferase increase in 4 (9%) patients, anemia in 3 (6%) patients, aspartate aminotransferase increase in 2 (4%) patients; blood creatinine increase, abnormal liver function test, fatigue, chest discomfort, chest pain, hypertransaminasemia, acute myocardial infarction, hypophosphatemia, arthritis, rash, overdose, hypoesthesia, and hypotension in 1 (2%) patient each. In the RCC cohort, nemvaleukin-related TEAEs leading to dose interruptions included neutropenia, blood creatinine increase, and hyperbilirubinemia in 2 (7%) patients each; thrombocytopenia, alanine aminotransferase increase, aspartate aminotransferase increase, blood bilirubin increase, white blood cell decrease, weight increase, fatigue, asthenia, chills, edema, thirst, bradycardia, hypophosphatemia, myalgia, oliguria, renal failure, and hyperhidrosis in 1 (4%) patient each.
†In melanoma cohort, nemvaleukin-related TEAEs leading to dose reductions included chills in 3 (6%) patients; neutropenia, alanine aminotransferase increase, aspartate aminotransferase increase, and blood bilirubin increase in 1 (2%) patient each. In RCC cohort, nemvaleukin-related TEAEs leading to dose reductions prompted by nemvaleukin-related TEAEs included fatigue in 1 (4%) patient.
CLS, capillary leak syndrome; CRS, cytokine release syndrome; IRR, infusion-related reaction; RCC, renal cell carcinoma; TEAE, treatment-emergent adverse event.

24 hours post dose and to last quantifiable concentration was comparable (online supplemental table 2). Serum nemvaleukin maximum concentration (C_{max}) was 106 ng/mL in the melanoma cohort and 132 ng/mL in the RCC cohort. Serum nemvaleukin mean predose concentration (C_{trough}) values in both cohorts were consistent with previously published animal model data.[24] Median time to C_{max} and time to last quantifiable concentration occurred after approximately 0.5 and 23 hours, respectively (online supplemental table 2).

Of the 74 patients enrolled in the nemvaleukin monotherapy dose expansion phase, 71 had a baseline ADA sample prior to nemvaleukin administration and at least

one ADA sample taken after drug administration and were included in the immunogenicity analysis set. After administration of 6µg/kg daily doses of nemvaleukin intravenous in patients with melanoma or RCC, positive ADA was detected in both cohorts at a frequency of 47%–50%. ADAs were detected after a median of 56 or 22 days after the first dose administration in the melanoma and RCC cohorts, respectively, and ADA positivity was observed for a median of 74 and 12 days, respectively. The median time to resolution was 105 and 21 days in the advanced melanoma and RCC cohorts, respectively (online supplemental table 3).

Immunophenotyping in peripheral blood showed comparable increases from baseline between both treatment cohorts in $CD8^+$ T cell and NK cell populations, with the largest fold change from baseline (FCB) observed at day 8 (cycle 1) and again at day 22 (cycle 2) (figure 2A and B). However, the dynamic changes noted with $CD8^+$ T-cell and NK cell populations were not seen with T_{regs}, in which the largest increase was observed only during cycle 1 (at day 5) (figure 2C). The greatest maximum FCB (FCB_{max}) was observed for total NK cells (sixfold, figure 2D) followed by $CD8^+$ T cells (threefold). T_{regs} showed similar FCB_{max} (twofold) in both cohorts (figure 2D).

DISCUSSION

Single-agent cytokine-based therapies such as high-dose rhIL-2 and interferon-α have limited clinical application due to short half-life, narrow therapeutic window, limited antitumor activity due to upregulation of immunosuppressive molecular pathways, and severe toxicities such as capillary leak syndrome that require inpatient treatment.[1 9] Furthermore, rhIL-2 can only be administered to medically fit patients due to the significant cardiopulmonary sequelae of the CRS toxicity. Nemvaleukin's design incorporates a stable fusion protein of the native IL-2 and IL-2R-α sequences resulting in an inherently active cytokine that does not degrade into native IL-2.[23] The selective activation of the intermediate affinity IL-2R by nemvaleukin has the potential to enable reduction of the severity of CRS and enhance efficacy by activating immune T cells. The present study confirms the hypothesized design principles of nemvaleukin. Single-agent nemvaleukin demonstrated antitumor activity in patients with advanced RCC and melanoma, including the hard-to-treat mucosal melanoma subtype, and a manageable safety profile that was consistent with its mechanism of action. The most frequently reported grade 3 or grade 4 TRAE was neutropenia; events were transient and manageable with or without nemvaleukin dose modifications and supportive treatment. Importantly, there were no reported grade ≥3 CRS or IRR events and no TEAEs of capillary leak syndrome, consistent with the on-target effects of nemvaleukin.

Antitumor responses to nemvaleukin monotherapy were observed in both the melanoma and RCC cohorts. Notably, all responders were ICI pretreated. DCR in both the melanoma and RCC cohorts was 50% and a subset of patients experienced prolonged stable disease of longer than 6 months (7% in the melanoma cohort and 9% in the RCC cohort). Durable objective responses were observed lasting at least 57 weeks in cutaneous melanoma and at least 164 weeks in mucosal melanoma, with both responses ongoing at the time of the data cut-off, and 94 weeks in RCC. Our results are consistent with those of previous studies of ICI monotherapies where responses lasting 6–23 months in melanoma and approximately 13–18 months in RCC have been reported in pretreated patients.[14 27 28] Additionally, ORRs ranging from 16% to 21% have been reported for high-dose rhIL-2, with durable responses and median PFS of ≥5 years in long-term follow-up studies.[3 5] While cross-trial comparisons should be interpreted with caution, the promising results with nemvaleukin monotherapy, particularly in ICI-pretreated patients, suggests that it may have potential as a single-agent therapy for the ICI-resistant patient population for whom not many treatment options are available.

The pharmacokinetic and pharmacodynamic profiles of nemvaleukin were favorable in the context of previous reports of high-dose rhIL-2.[29 30] Pharmacodynamic proof of mechanism of nemvaleukin was also observed in the periphery, with an approximate sixfold increase from baseline in NK cells and a threefold increase for $CD8^+$ T cells consistently during each of the first two cycles of treatment, and minimal expansion observed for T_{regs}. These data are aligned with nemvaleukin's engineering, which enables selective binding to the intermediate-affinity IL-2R leading to preferential expansion of proinflammatory immune cells.[23 24] The results are also in contrast with the pharmacodynamic changes induced by the investigational IL-2 agonist bempegaldesleukin with nivolumab in patients with metastatic melanoma, where an~8–10-fold expansion of T_{regs} from baseline was observed, with relatively smaller increases in $CD8^+$ T cells (~2-fold) and NK cells (~1.5–3-fold), potentially contributing to the lack of added clinical benefit over nivolumab monotherapy.[31] Additionally, nemvaleukin showed no TEAEs of capillary leak syndrome that are associated with IL-2 binding to the high-affinity IL2-R,[9] thereby potentially enhancing the therapeutic index of IL-2.

This study had a few limitations. Owing to the phase 1/2 study design and rare incidence of mucosal melanoma, the sample sizes for each tumor type in this study were small and there was no comparator arm. There were multiple amendments to the study resulting in changes to the definition of efficacy parameters, including updates in timing of samples/data collection. Additionally, the execution of the study and some aspects of the continuum of patient care were impacted during the COVID-19 pandemic. Lastly, limited tissue samples were collected for pharmacodynamic assessment and further validation is needed from larger patient populations.

Overall, nemvaleukin demonstrated preliminary antitumor activity in patients with advanced melanoma and RCC, along with a manageable safety profile, and selective

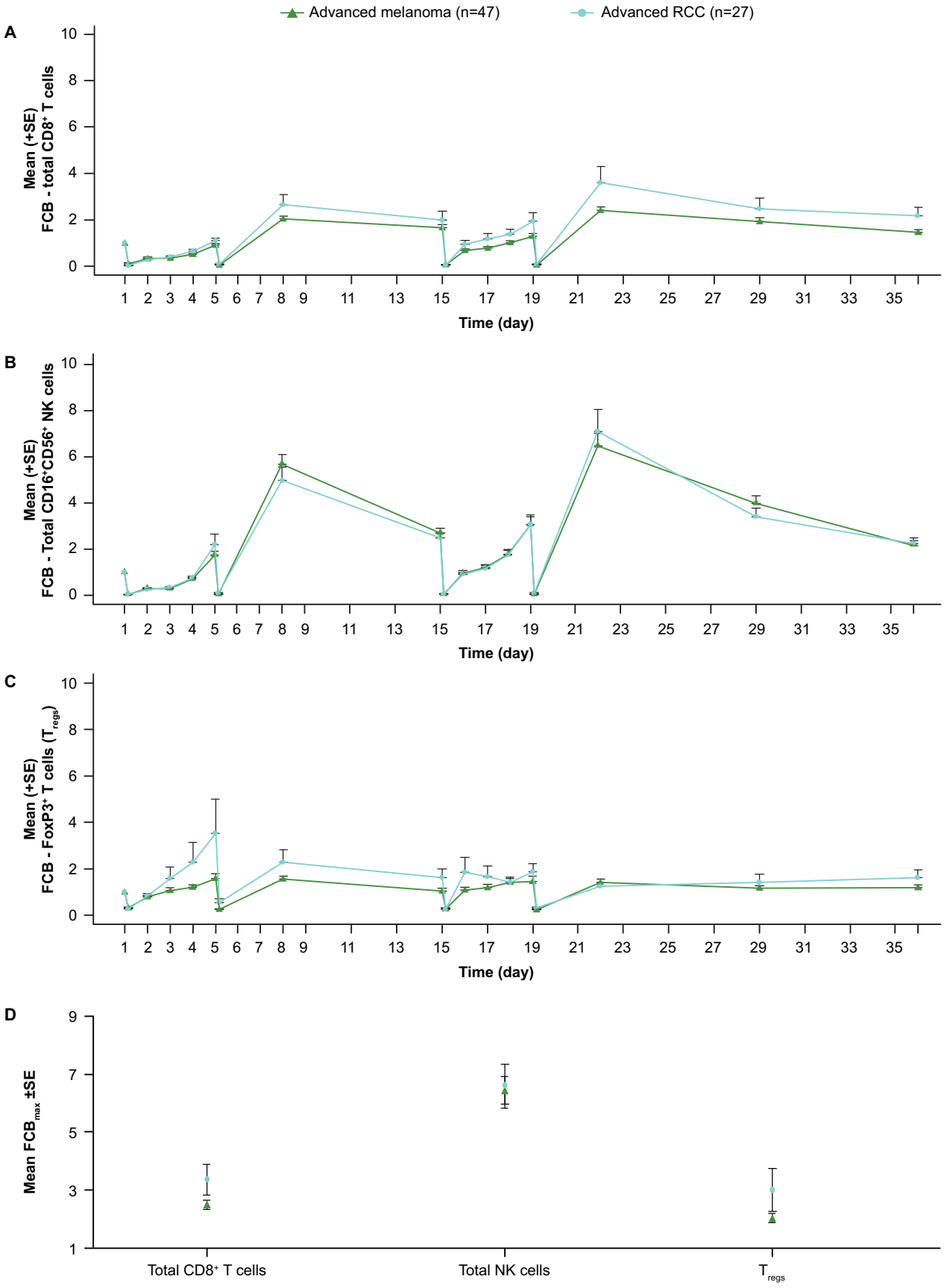

Figure 2 Peripheral immune cell changes following intravenous infusion of 6 µg/kg nemvaleukin in melanoma and renal cell carcinoma (RCC) cohorts. Mean (+SE) fold change from baseline in (A) $CD8^+$ T cells, (B) natural killer (NK) cells, and (C) regulatory T cells (T_{regs}). (D) Pharmacodynamic maximum fold change from baseline in immunophenotypes on cycle 1, day 1. FCB, fold change from baseline. FCB_{max}, maximum fold change from baseline.

activation of the proinflammatory immune pathways, supporting its potential as an active and tolerable cytokine therapy. Future research should focus on identifying optimal patient subsets, tumor types, and combination strategies to maximize the therapeutic benefit.

Author affiliations
[1]START Madrid-CIOCC, Centro Integral Oncológico Clara Campal, Madrid, Spain
[2]CHU de Québec-Université Laval, Québec City, Québec, Canada
[3]Division of Medical Oncology, Yonsei University College of Medicine, Seoul, Korea (the Republic of)
[4]Hematology Oncology Association of the Treasure Coast, Port St. Lucie, Florida, USA
[5]Summit Cancer Centers - Spokane Valley, Spokane, Washington, USA
[6]Kortrijk Cancer Centre, General Hospital AZ Groeninge, Kortrijk, Belgium
[7]Medical Technology Research Centre (MTRC), School of Life Sciences, Anglia Ruskin University, Cambridge, UK
[8]School of Nursing and Midwifery, University of Plymouth, Plymouth, UK
[9]Mural Oncology, Inc, Waltham, Massachusetts, USA
[10]Division of Hematology/Oncology, University of Michigan, Ann Arbor, Michigan, USA
[11]Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

Present affiliations The present affiliation of Valentina Boni is: NEXT Madrid University Hospital Quironsalud, Madrid, Spain.

X Ulka N Vaishampayan @DRUlkaV

Acknowledgements This study was supported by Mural Oncology (part of Alkermes, Inc. at the time of study design and conduct). We thank the patients and their families who made this study possible, and the investigators and the clinical study teams for study support. Professional medical writing and editorial assistance were provided by Mandakini Singh, PhD, of Parexel International and funded by Mural Oncology. Results reported in this manuscript were previously presented in part at the American Society of Clinical Oncology (ASCO) congress (June 3–7, 2022) as an oral presentation (abstract # 2500).

Contributors EC, DFM, UNV, and SDR contributed to the concept and design of the study. Syneos was responsible for the clinical trial conduct and data collection in collaboration with the investigators at the study sites. EC, VB, OD, SJS, SDR, AC, PRD, UNV, and DFM enrolled patients. The analyses were conducted by Syneos for clinical data and by Certara for PK data under the supervision of the sponsor. XH conducted statistical analyses and verified the data. All authors participated in developing and reviewing the manuscript and provided final approval to submit the manuscript for publication. EC had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. EC is the guarantor of this study.

Funding The study was sponsored by Mural Oncology (part of Alkermes, Inc. at the time of study design and conduct).

Competing interests EC declares leadership at BeiGene, EORTC, Merus NV, Novartis, PharmaMar, Sanofi, and START; stock and other ownership interests in Oncoart Associated and START; honoraria fee from HM Hospitales group; consulting fee from or advisory role for Adcendo, Amunix, Anaveon, AstraZeneca/MedImmune, Bristol Myers Squibb, Chugai Pharma, Diaccurate Elevation Oncology, Ellipses Pharma, Genmab, Janssen-Cilag, MonTa, MSD Oncology, Nanobiotix, Nouscom, Novartis, OncoDNA, PharmaMar, Roche/Genentech, Servier, Syneos Health, TargImmune Therapeutics, and T-Knife; research funding from START; and other relationship as president and founder of Foundation INTHEOS (Investigational Therapeutics in Oncological Sciences), the not-for-profit Foundation PharmaMar, and the not-for-profit CRIS Cancer Foundation. VB declares employment and leadership at NEXT Madrid, University Hospital Quirónsalud Pozuelo; stock ownership in 1TRIALSP; consultant or advisory role at Puma Biotechnology, Ideaya Biosciences, Loxo Therapeutics, CytomX Therapeutics, Guidepoint, Oncoart, Lilly, Janssen, EMD Serono, and IDMC Nanobiotix NANORAY-312/Novartis; steering committee membership for CytomX Therapeutics; honoraria (speaking) fee from Eli Lilly, MSD, SOLTI, TACTICS, GETTHI, and GEDEFO; travel, inscription, and accommodation fees from Bayer (ESMO GI); institutional financial support for clinical trials from AbbVie, ACEO, Adaptaimmune, Affimed, Amcure, Amgen, Amunix, Astellas, AstraZeneca, BeiGene, Bicycle, BMS, Boehringer Ingelheim, Boston Therapeutics, Carrick therapeutics, Constellation Pharmaceutical, CytomX; Crescendo Biologics, Cullinan, Daiichi, DebioPharm, Dynavax, Ellipses Pharma, Exelixis, Famawav, GSK, Genentech/Roche, Genmab, Gilead, Incyte, Ipsen, Ideaya Biosciences, Invox Pharma, iOMX Therapeutics, Janssen, Kura, Kronos Bio, Lilly, Loxo Oncology, Macrogenics, Menarini, Merck, Merus, Mersana, Millennium, Moderna, MSD, Navire Pharma, Nektar, Nanobiotix, Novartis, ORCA, Pfizer, PharmaMar; Principia, PsiOxus, PUMA, Regeneron, Ryvu Therapeutics, Ribbon, Sanofi, Salubris Biotherapeutics, Scorpion Therapeutics, Seagen, Seattle Genetics, Spectrum, Stemline Therapeutics, Synthon, Taiho, Tesaro, Transgene, Takeda, Tolrelmo Therapeutics, Totus Medicine, Tyra Biosciences, Vividion Therapeutics, Urogen, Xencor, Zai Biopharmaceutical, and Zenith. OD declares no competing interests. SJS declares no competing interests. SR declares stock ownership in Amgen, Johnson & Johnson, and Pfizer. AC declares stock ownership in Novartis; and speakers' bureau membership at Pharmacyclics. PRD declares grants (to institution) from Pfizer; consulting fees for participation on advisory boards from Astellas Pharma, Bristol Myers Squibb, Ipsen, MSD, and Pfizer; honoraria for lectures from Bayer; travel support from Janssen; (substitute) board membership for the Clinical Trials College, Federal Public Service, Kingdom of Belgium; and stock ownership in Alkermes, Mural Oncology PLC, and Biocartis Group NV. XH declares employment at Mural Oncology. UV declares research support from Bristol Myers Squibb and Merck; consulting fees from Alkermes, Aveo, Bayer, Bristol Myers Squibb, Exelixis, Gilead, Novartis, Pfizer, and Seattle Genetics; and speaker honoraria fees from Exelixis, Bayer, and Pfizer. DFM declares consulting/honoraria fee from BMS, Pfizer, Merck, Eisai, Xilio, Aveo, Genentech, Cullinan, and Exelixis; and research support from Alkermes Bristol Myers Squibb, Exelixis, Genentech, Merck, Pfizer, and X4 Pharma.

Patient consent for publication Not applicable.

Ethics approval Multiple ethics committees and IRBs were involved and the trial protocol was approved by the institutional review boards/independent ethics committees at each site. A complete site and investigator list is provided in the supplement of this article. As corresponding author and guarantor, my institution and site ID are START Madrid-CIOCC, Centro Integral Oncológico Clara Campal, Madrid, Spain: 740108. Additionally, institution details for each site are available at the ARTISTRY-1 ClinicalTrials.gov trial page: https://clinicaltrials.gov/study/NCT02799095?term=artistry-1&rank=2#contacts-and-locations.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. The data sets used and/or analyzed in the current study will be available after review of the request and approval from sponsor and coauthors.

ORCID iDs
Emiliano Calvo http://orcid.org/0000-0003-4921-829X
Ulka N Vaishampayan http://orcid.org/0000-0001-5800-4571

REFERENCES

1 Propper DJ, Balkwill FR. Harnessing cytokines and chemokines for cancer therapy. *Nat Rev Clin Oncol* 2022;19:237–53.
2 Alva A, Daniels GA, Wong MKK, *et al*. Contemporary experience with high-dose interleukin-2 therapy and impact on survival in patients with metastatic melanoma and metastatic renal cell carcinoma. *Cancer Immunol Immunother* 2016;65:1533–44.
3 Amaria RN, Reuben A, Cooper ZA, *et al*. Update on use of aldesleukin for treatment of high-risk metastatic melanoma. *Immunotargets Ther* 2015;4:79–89.

4 Buchbinder EI, Dutcher JP, Daniels GA, *et al*. Therapy with high-dose interleukin-2 (HD IL-2) in metastatic melanoma and renal cell carcinoma following PD1 or PDL1 inhibition. *J Immunother Cancer* 2019;7:49.
5 Clark JI, Curti B, Davis EJ, *et al*. Long-term progression-free survival of patients with metastatic melanoma or renal cell carcinoma following high-dose interleukin-2. *J Investig Med* 2021;69:888–92.
6 Fishman M, Dutcher JP, Clark JI, *et al*. Overall survival by clinical risk category for high dose interleukin-2 (HD IL-2) treated patients with metastatic renal cell cancer (mRCC): data from the PROCLAIM^{SM} registry. *J Immunother Cancer* 2019;7:84.
7 Sim GC, Martin-Orozco N, Jin L, *et al*. IL-2 therapy promotes suppressive ICOS+ Treg expansion in melanoma patients. *J Clin Invest* 2014;124:99–110.
8 Curti B, Daniels GA, McDermott DF, *et al*. Improved survival and tumor control with interleukin-2 is associated with the development of immune-related adverse events: data from the PROCLAIM^{SM} registry. *J Immunother Cancer* 2017;5:102.
9 Jeong GH, Lee KH, Lee IR, *et al*. Incidence of capillary leak syndrome as an adverse effect of drugs in cancer patients: a systematic review and meta-analysis. *J Clin Med* 2019;8:143.
10 Emens LA, Ascierto PA, Darcy PK, *et al*. Cancer immunotherapy: opportunities and challenges in the rapidly evolving clinical landscape. *Eur J Cancer* 2017;81:116–29.
11 Garon EB, Hellmann MD, Rizvi NA, *et al*. Five-year overall survival for patients with advanced non–small-cell lung cancer treated with pembrolizumab: results from the phase I KEYNOTE-001 study. *J Clin Oncol* 2019;37:2518–27.
12 Hamid O, Robert C, Daud A, *et al*. Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. *Ann Oncol* 2019;30:582–8.
13 Khalil DN, Smith EL, Brentjens RJ, *et al*. The future of cancer treatment: immunomodulation, CARs and combination immunotherapy. *Nat Rev Clin Oncol* 2016;13:273–90.
14 Motzer RJ, Escudier B, George S, *et al*. Nivolumab versus everolimus in patients with advanced renal cell carcinoma: updated results with long-term follow-up of the randomized, open-label, phase 3 CheckMate 025 trial. *Cancer* 2020;126:4156–67.
15 Long GV, Stephen Hodi F, Lipson EJ, *et al*. Overall survival and response with nivolumab and relatlimab in advanced melanoma. *NEJM Evid* 2023;2:EVIDoa2200239.
16 Motzer RJ, Tannir NM, McDermott DF, *et al*. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med* 2018;378:1277–90.
17 Wolchok JD, Chiarion-Sileni V, Gonzalez R, *et al*. CheckMate 067: 6.5-year outcomes in patients (pts) with advanced melanoma. *J Clin Oncol* 2021;39:9506.
18 de Miguel M, Calvo E. Clinical challenges of immune checkpoint inhibitors. *Cancer Cell* 2020;38:326–33.
19 Hegde PS, Chen DS. Top 10 challenges in cancer immunotherapy. *Immunity* 2020;52:17–35.
20 Johnson DB, Nebhan CA, Moslehi JJ, *et al*. Immune-checkpoint inhibitors: long-term implications of toxicity. *Nat Rev Clin Oncol* 2022;19:254–67.
21 AVEO Oncology. AVEO Oncology, an LG Chem company, announces phase 3 renal cell carcinoma clinical trial (TiNivo-2) results. Available: https://www.prnewswire.com/news-releases/aveo-oncology-an-lg-chem-company-announces-phase-3-renal-cell-carcinoma-clinical-trial-tinivo-2-results-302199844.html [Accessed 6 Sep 2024].
22 Pal SK, Albiges L, Tomczak P, *et al*. Atezolizumab plus cabozantinib versus cabozantinib monotherapy for patients with renal cell carcinoma after progression with previous immune checkpoint inhibitor treatment (CONTACT-03): a multicentre, randomised, open-label, phase 3 trial. *Lancet* 2023;402:185–95.
23 Lopes JE, Fisher JL, Flick HL, *et al*. ALKS 4230: a novel engineered IL-2 fusion protein with an improved cellular selectivity profile for cancer immunotherapy. *J Immunother Cancer* 2020;8:e000673.
24 Lopes JE, Sun L, Flick HL, *et al*. Pharmacokinetics and pharmacodynamic effects of nemvaleukin alfa, a selective agonist of the intermediate-affinity IL-2 receptor, in cynomolgus monkeys. *J Pharmacol Exp Ther* 2021;379:203–10.
25 Vaishampayan UN, Muzaffar J, Winer I, *et al*. Nemvaleukin alfa, a modified interleukin-2 cytokine, as monotherapy and with pembrolizumab in patients with advanced solid tumors (ARTISTRY-1). *J Immunother Cancer* 2024;12:e010143.
26 Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989;10:1–10.
27 Topalian SL, Hodi FS, Brahmer JR, *et al*. Five-year survival and correlates among patients with advanced melanoma, renal cell carcinoma, or non-small cell lung cancer treated with nivolumab. *JAMA Oncol* 2019;5:1411–20.
28 Ribas A, Puzanov I, Dummer R, *et al*. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *Lancet Oncol* 2015;16:908–18.
29 Dutcher JP, Schwartzentruber DJ, Kaufman HL, *et al*. High dose interleukin-2 (aldesleukin) - expert consensus on best management practices-2014. *J Immunother Cancer* 2014;2:26.
30 Konrad MW, Hemstreet G, Hersh EM, *et al*. Pharmacokinetics of recombinant interleukin 2 in humans. *Cancer Res* 1990;50:2009–17.
31 Gogas H, Ravimohan S, Datta A, *et al*. Baseline biomarkers of efficacy and on-treatment immune-profile changes associated with bempegaldesleukin plus nivolumab. *NPJ Precis Oncol* 2024;8:150.