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Intraperitoneal infusion of stem cell-derived natural killer cells in recurrent epithelial ovarian cancer patients: Results of the phase 1 INTRO-01 trial

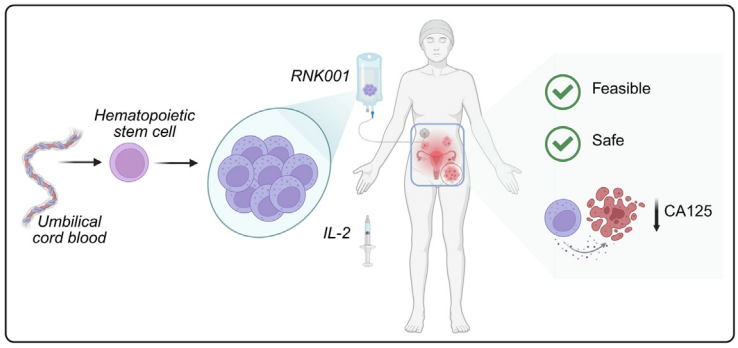
Janneke S Hoogstad-van Evert [a,b,1], Paul K J D de Jonge [a,1], Petra L M Zusterzeel [c], Willemijn Hobo [a], Anniek B van der Waart [a], Hanny Fredrix [a], Lisanne Janssen [a], Maud Wuts [a], Lynn Bosmans [a], Ellen Spijkers [a], Merlize Djojoatmo [a], Veronica Castaño Rodriguez [a], Anna L de Goede [d], Bert van der Reijden [a], Arnold van der Meer [e], Nicolaas Schaap [f], Ruud Bekkers [c,h,i], Joop H Jansen [a], Nelleke Ottevanger [g,1], Harry Dolstra [a,*,1]

[a] Department of Laboratory Medicine, Laboratory of Hematology, Radboud university medical center, Nijmegen, the Netherlands
[b] Department of Gynecology, Amphia hospital, Breda, the Netherlands
[c] Department of Gynecology, Radboud university medical center, Nijmegen, the Netherlands
[d] Department of Pharmacy, Pharmacology and Toxicology, Radboud university medical center, Nijmegen, the Netherlands
[e] Department of Laboratory Medicine, Laboratory of Medical Immunology, Radboud university medical center, Nijmegen, the Netherlands
[f] Department of Hematology, Radboud university medical center, Nijmegen, the Netherlands
[g] Department of Medical Oncology, Radboud university medical center, Nijmegen, the Netherlands
[h] Department of Obstetrics and Gynecology, Catharina Hospital Eindhoven, the Netherlands
[i] GROW school for oncology and reproduction, Maastricht University, Maastricht, the Netherlands

HIGHLIGHTS

- Intraperitoneal NK cell therapy is safe and feasible in recurrent ovarian cancer, with no severe toxicity.
- Five out seven patients demonstrated a transient reduction in CA125 serum levels of 20–53 % after NK cell infusion.
- This study in seven recurrent ovarian cancer patients warrants further development of a repeated NK cell infusion protocol.

GRAPHICAL ABSTRACT



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ABSTRACT

Introduction. Epithelial ovarian cancer (EOC) patients exhibit a poor 5-year overall survival rate of approximately 40 %, underscoring the urgent need for innovative therapies. Allogeneic natural killer (NK) cell therapy presents a promising and safe therapeutic option, given its ability to discriminate between normal and malignant cells with potent cytotoxic effects against malignant cells.

Methods. We present the first-in-human study exploiting the safety of the NK cell product designated RNK001, derived *ex vivo* from umbilical cord blood-derived hematopoietic stem and progenitor cells. This phase 1 INTRO-01 trial (NCT03539406) was initiated to assess the feasibility, safety, and toxicity of

* Corresponding author at: Department of Laboratory Medicine – Laboratory of Hematology, Radboudumc, Geert Grooteplein Zuid 10, P.O. Box 9101, 6500, HB, Nijmegen, The Netherlands.
E-mail address: harry.dolstra@radboudumc.nl (H. Dolstra).
[1] These authors contributed equally to this work.

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Epithelial ovarian cancer
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Clinical trial

intraperitoneal (IP) infusion of RNK001 in EOC patients exhibiting elevated CA125 levels at the second recurrence. RNK001 infusion was supported by IP IL-2 in six patients, and was preceded in one patient by lymphodepleting chemotherapy with cyclophosphamide/fludarabine.

Results. RNK001 consisted of 1.2 to 3.0 × 10^9 highly activated $CD56^+CD3^-$ NK cells and was well tolerated, with neither evidence of graft-*versus*-host disease nor cytokine release syndrome. One patient experienced a grade 3 transient elevation in liver enzymes, another patient exhibited grade 3 ileus caused by disease progression. Notably, five out seven patients demonstrated a reduction in CA125 serum levels of 20–53 % at 14 days post-infusion. Furthermore, one patient achieved a clinical and biochemical response with radiological stable disease and a progression-free survival of 9 months.

Conclusion. These findings suggest that intraperitoneal RNK001-based immunotherapy can be safely administered to recurrent EOC patients without inducing severe toxicity, while clinical and biochemical responses warrant further development.

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1. Introduction

Epithelial Ovarian cancer (EOC) presents challenges due to late-stage diagnosis, high recurrence rates, and limited treatment options [1]. Despite advances in therapies like poly ADP-ribose polymerase (PARP) inhibitors [2–4], intraperitoneal (IP) chemotherapy and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) [5], effective adjuvant treatments remain crucial. Recurrence is typically incurable and managed through combination therapies with platinum-based chemotherapy in case of platinum-sensitive disease, alongside paclitaxel, gemcitabine, liposomal doxorubicin, bevacizumab and PARP inhibitors [6]. Yet, 80 % of patients relapse, with a median survival of two years [1]. Presence of tumor-infiltrating lymphocytes has been correlated with improved survival [7,8]. Consequently, adoptive cell therapy (ACT) exploiting cytotoxic lymphocytes has gained interest in the context of EOC treatment.

ACT using allogeneic natural killer (NK) cells is an attractive approach as NK cells mediate cytotoxicity against tumor cells without prior sensitization [9,10]. Their capacity to recognize and eliminate malignant cells through increased signaling *via* activating receptors and reduced signaling *via* inhibitory receptors renders them pivotal in cancer immune surveillance [9,10]. NK cell ACT has shown promise in the treatment of acute myeloid leukemia (AML) [11,12]. Allogeneic NK cell ACT showed clinical benefit as a consolidation therapy in AML, with reports of complete remissions in case of refractory disease [13,14]. Growing evidence supports allogeneic NK cell reactivity in solid tumors while being well tolerated further supporting their safety [15].

Given EOC's peritoneal spread, IP therapies allow more direct cancer targeting. IP chemotherapy improves absorption, increased susceptibility of cancer cells, and prolongs persistence in the peritoneal cavity. Notably, IP chemotherapy in the adjuvant setting did not negatively affect quality-of-life after 1 year and an improvement in median OS of 16 months [16]. Furthermore, HIPEC has shown to improve mean OS with 11 months [5]. Thus, IP infusion of NK cells in EOC treatment is an appealing approach. We developed a scalable allogeneic NK cell product generated *ex vivo* from umbilical cord blood-derived hematopoietic stem and progenitor cells (named RNK001 [17,18]). In a SKOV-3 mouse model, we have demonstrated that IP RNK001 infusion is effective prolonging survival [17]. Several researchers have shown that IP infusion of chimeric antigen receptor (CAR) engineered T cells in tumor-bearing mice lead to more disease remission and increased survival compared to the IV route [19,20]. Prior clinical studies, such as the APOLLO study (NCT00652899) showed that IP delivery of an allogeneic NK cell product (FATE-NK100) was safe, with persistence for weeks and clinical benefit in three out of nine patients [21]. These encouraging findings prompted the initiation of the first-in-human INTRO-01 study (NCT0353940) utilizing our RNK001 product in EOC patients [22].

This study aimed to assess the safety and toxicity of a single IP RNK001 infusion, with and without a preceding immunosuppressive conditioning, in patients with second recurrence of EOC. Secondary objectives included evaluating RNK001's peritoneal lifespan and its impact on serum CA125 levels.

2. Materials and methods

2.1. Study design

The INTRO-01 trial was designed to include 12 patients with second recurrence EOC detected by elevated serum levels of CA125 on two successive timepoints without the need to start chemotherapy immediately due to disease progression. Prior to RNK001 infusion, laparoscopy was performed to place a Bard port® for IP infusion and to assess whether fluid could effectively disperse throughout the abdominal cavity. The first cohort of six patients received a single IP infusion of RNK001, without non-myeloablative conditioning chemotherapy. The second cohort of ultimately 1 out of 6 intended patients, underwent treatment with RNK001 following conditioning with cyclophosphamide (Cy) 900 mg/m^2/day and fludarabine (Flu) 30 mg/m^2/day from days −6 to −3. Both cohorts received a RNK001 product of similar dose (1.2–3.0 × 10^9 NK cells).

The protocol has been previously published by Hoogstad et al. in 2019 [22]. Study was approved by the Central Committee on Research Involving Human Subjects (CCMO registration number NL160937.000.17, EudraCT number 2016 000299–78) and registered in the clinical trial registry (NCT03539406). Written informed consent was given by all participants in accordance with the Declaration of Helsinki.

2.2. RNK001 manufacturing

We developed a good manufacturing practice (GMP)-compliant scalable manufacturing process to obtain the allogeneic cell-based ATMP RNK001 from $CD34^+$ progenitor cells *ex vivo* as detailed by De Jonge et al. [18]. This manufacturing process incorporates various essential cytokines, including IL-15 and IL-12, and the aryl hydrocarbon receptor antagonist StemRegenin-1 (SR1) to produce 1.5–3.0 NK cells of high purity, viability and a 24 h shelf life. The protocol was optimized to yield NK cells with the necessary expansion and differentiation capacity in GMP-compliant closed system cell culture bags. Phenotype, antitumor potency, proliferative capacity, and metabolic activity were assessed to characterize the RNK001 product. Subsequently, seven batches were produced to qualify the manufacturing process, which demonstrated consistent results in terms of proliferation, differentiation, and antitumor potency, and specifications for the investigational medicinal product for early clinical phase trials were established [18].

2.3. Donor UCB selection

$CD34^+$ starting material was isolated from umbilical cord blood (UCB) units from the Cord Blood Bank Nijmegen, that were banked between 1996 and 2009 after written informed consent to use the material for research purposes. UCB units were selected based on the best possible HLA match for HLA-A, —B and —C, with minimal 1 out of 6 matching. UCB units were negative for viral (HIV-1, HIV-2, HBV, HCV, HTLV-1, HTLV-2 and Lues), bacterial and fungal contamination and contained at least 2.0×10^6 $CD34^+$ cells prior to CD34 selection.

2.4. Product description

RNK001 products and $CD34^+$ starting materials were characterized as described [18]. Briefly, the Radboudumc Laboratory for Hematology (ISO15189 certified) determined $CD34^+$ purity and viability after selection at day 0, as well as $CD56^+CD3^-$ viability, purity and absolute number, and $CD3^+$ T cell and $CD19^+$ B cell content at day 28/29 and day 35/36. RNK001 products were further characterized by flow cytometry by analyzing NKG2A, NKG2D, NKp46, NKp44, NKp30 and DNAM-1 expression as described [18]. Sterility and endotoxin content were tested according to Ph. Eur. 2.6.1 and Ph. Eur. 2.6.14 at day 14/15 and day 35/36 of the manufacturing. Quality control testing was performed in-house (GMP authorization number 16721 F) or outsourced. As RNK001 cells need to be infused within 24 h after manufacturing, the cells were provisionally released by a Qualified Person based on the product characteristics on day 35/36 and sterility and endotoxin results of day 14/15. Final release was performed after sterility and endotoxin results of day 35/36 were available. RNK001 potency was determined by challenging them with K562 cells as described [18].

2.5. RNK001 infusion

Six patients received a single IP infusion of 500 mL $1.2–3.0 \times 10^9$ RNK001 cells in one bag. Six administrations of IL-2 cytokine support (6.0×10^6 Units/administration) were provided through IP infusion every other day, the first being administered on the same day as the RNK001 infusion. The one patient that received NK cells after Flu/Cy conditioning, received 2.3×10^9 RNK001 cells and 6 gifts of IL-2 cytokine support.

2.6. Immunological and biochemical evaluation

Peripheral blood (PB) and peritoneal fluid (PF) samples were collected at days −6, −1/0, 6/7, 13/15 and 27/28 for immunological and biochemical (PB only) analyses; the IP catheter was subsequently removed. PB samples were analyzed for hematological cell counts and CA125 at the Radboudumc Laboratory for Diagnostics (ISO15189 certified). The composition of T, B, and NK cells was analyzed using the Aquios flow cytometer (Beckman Coulter) at the Radboudumc Laboratory for Hematology (ISO15189 certified). PB samples were evaluated for IFNγ, TNF and IL-6 using ELISA according to manufacturer's instructions and measured on a Fluostar ELISA reader. PF samples were phenotyped to determine NK and T cell percentages. Briefly, 1×10^6 cells were stained for CD45 (ECD), CD56 (PE-Cy7), CD3 (FITC) and 7-AAD (live/dead) and analyzed with the FC500 or Gallios flow cytometer (both Beckman Coulter) and analyzed using Kaluza v2.2 software.

2.7. HLA-KIR typing and HLA antibodies

HLA-A/B/C genotyping was performed by PCR-SSOP using Luminex technology (Lifecodes HLA SSO typing, Werfen, Barcelona, Spain) at the Radboudumc Laboratory of Medical Immunology (ISO15189 certified). HLA antibodies were determined using a Luminex screening assay (Lifecodes LifeScreen, Werfen, Barcelona, Spain). Positive sera were tested with a single antigen assay (Lifecodes LSA Class I or Class II kit, Werfen, Barcelona, Spain). We used the cut-off as defined by the manufacturer.

2.8. Chimerism analysis

Chimerism status was determined using quantitative PCR amplifying patient and donor specific DNA polymorphisms with a sensitivity of 0.1 % according previous reports [23,24] at the Radboudumc Laboratory for Hematology (ISO15189 certified).

3. Results

3.1. Patient characteristics and treatment

We investigated feasibility, safety and impact on the CA125 tumor marker of intraperitoneal RNK001 infusion, with and without preceding non-myeloablative immunosuppressive Cy/Flu conditioning, in patients with high-grade serous EOC. A total of 15 patients were enrolled: 8 patients in the first cohort without conditioning and 7 patients in the second cohort with Cy/Flu conditioning (Fig. 1A). In the first cohort, one patient was excluded due to disease progression prior to infusion. In the second cohort, five eligible patients withdrew from participation as those patients were hoping to participate in the study arm without chemotherapy. One patient withdrew consent after inclusion, as she found another phase I study that better suited her personal situation. For 8 patients, a laparoscopy was performed to insert a catheter in the peritoneal cavity prior to RNK001 infusion. This was performed 3–9 weeks prior to RNK001 infusion (Fig. 1B, Table 1). No complications were reported during laparoscopy, and no IP catheter complications occurred. The median peritoneal adhesion index (PAI) was 2, with a range of 0–4 (Table 1). For 8 patients RNK001 product manufacturing was initiated, however, one patient (INTRO-02) was excluded during RNK001 production due to rapid disease progression and started palliative chemotherapy. Ultimately, seven patients received RNK001: six without and one with Cy/Flu conditioning (Fig. 1B). Patient characteristics and their respective UCB-donor for RNK001 manufacturing are displayed in Table 1. Although the peritoneal cancer index (PCI) [28] was not initially considered an eligibility criterion, we revised the protocol after treating three patients in the first cohort (INTRO-01, 03, and 04) and included a PCI threshold of more than 15 out of 36 as an exclusion criterion. Median PCI of all included patients was 12.5 (range 3–26; Table 1). All patients had a Karnofsky score between 80 and 100. In the second cohort, one patient was treated with RNK001 after preceding Cy/Flu chemotherapy, which was well tolerated by this patient, without severe toxicities.

3.2. RNK001 NK cell products

For the generation of allogeneic RNK001 products, partially HLA-matched UCB units were selected based on the patient HLA type. Although KIR mismatch was not a primary focus of this study, six out of seven patients exhibited a KIR receptor-ligand mismatch, wherein the UCB donor carried inhibitory KIR genes lacking the corresponding HLA ligand in the patient (Table 1; Supplementary Table 1). KIR genotype of the used UCB units was of the AB haplotype in all cases. Production of RNK001 was successful for all patients and met release criteria except for the dose in one of eight batches (Table 2, INTRO-03). This product was infused as an out of specification product. One batch was not infused due to disease progression (INTRO-02). Cell numbers and key parameters at each step of the manufacturing process with accompanying release criteria are shown in Table 2. After UCB thawing and CD34 selection, a mean of 3.00×10^6 $CD34^+$ cells (range 1.19–6.99) were placed in culture. The mean purity of the $CD34^+$ cell product was 88 % (range 69 % - 98 %). The starting material met the release criteria ($\geq 1.0 \times 10^6$ $CD34^+$ content, ≥70 % viability and no microbiological contamination) in all cases.

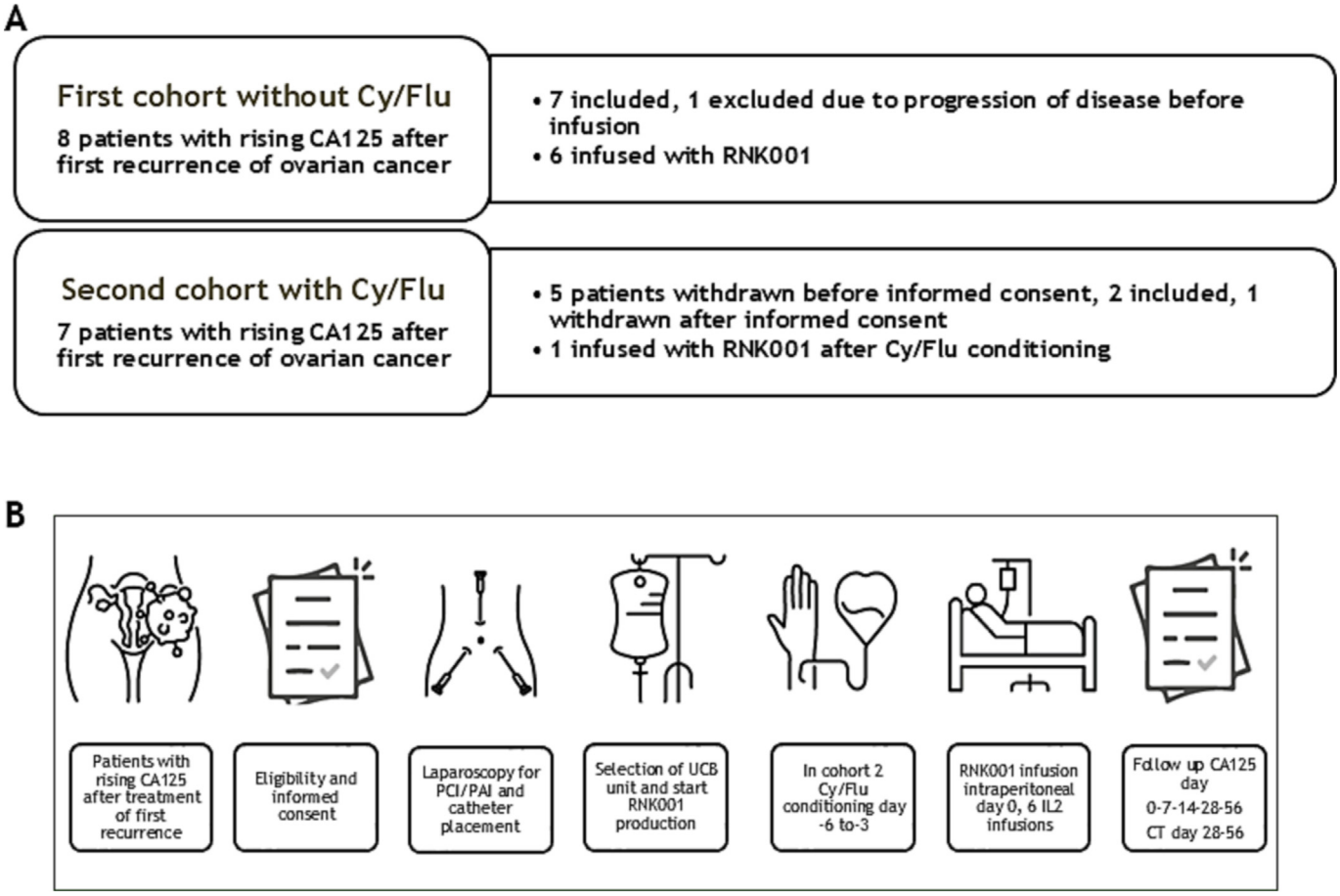

Fig. 1. Patient inclusion and study scheme. (A) Patient inclusion scheme. (B) Patients with rising CA125 after treatment of first OC recurrence were included in the study. After informed consent, patients underwent laparoscopy for PAI/PCI examination and catheter placement. Thereafter, a cryopreserved UCB unit was selected and RNK001 cells were generated. RNK001 cells were infused at day 0 without (cohort 1) or with Cy/Flu (cohort 2) lymphodepletion. Patients were monitored for toxicity, GVHD, CA125, and *in vivo* RNK001 persistence in peritoneal cavity.

After 35 days of culture, the mean RNK001 dose was 2.2×10^9 (range $1.2–3.0 \times 10^9$) with a high purity of 90 % $CD56^+CD3^-$ cells (mean, range 76 %–98 %) and high viability of 99 % $7AAD^-CD56^+CD3^-$ cells (mean, range 97 %–100 %). Minimal T and B cell contamination was present in RNK001 products of 0.1×10^5 $CD3^+$/kg (mean, range $0.0–0.2 \times 10^5$) and 0.2×10^5 (mean, range $0.0–0.2 \times 10^5$) CD19+/kg (Table 2). The mean expression of key NK cell markers NKG2A was 64 % (range 34–83 %), NKG2D 98 % (range 95–100 %), NKp46 85 % (range 64–99 %), NKp44 79 % (range 46–98 %), NKp30 99 % (range 98–100 %) and DNAM-1 76 % (range 60–90 %) (Fig. 2; Supplementary Table 2). CD107a-based degranulation assays showed a mean frequency of $CD107a^+$ degranulating NK cells of 48.0 % (range 40.3–58.4 %). The mean frequency of $CD107a^+IFN\gamma^+$ NK cells was 8.0 % (range 2.8–13.4 %). All products were sterile and had low (< 0.3 EU/ml) endotoxin burden. In process controls (sterility, endotoxin content, purity and viability) met criteria in all cases except for one where the purity at day 28 was only 47 % $CD56^+CD3^-$ (criteria ≥50 %; Table 1). This was the same batch that did not reach the minimal dose ultimately. These results demonstrate feasibility to generate GMP-compliant RNK001 products meeting release criteria for infusion with potent functional activity against K562 *ex vivo* (Fig. 2B).

3.3. Safety and toxicity of RNK001 infusion

RNK001 product was administered in seven patients and IL-2 infusions were completed in all of them. RNK001 infusion was well tolerated with no NK cell infusion-related toxicities. Furthermore, we did not observe any signs of graft-*versus*-host disease (GVHD) nor of cytokine release syndrome, which is supported by undetectable IFNγ and IL-6 levels in plasma and stable TNF levels compared to pre-infusion (day −1/0) (Supplementary Fig. 1). In the period of 4 h between RNK001 and IL-2 administration, patients did not develop fever or chills. But, six out of seven patients experienced fever after the IL-2 infusions with cold chills, resolving with acetaminophen. This was an expected side effect of the IL-2. In two patients, a grade 3 adverse event was recorded based on CTCAE III-IV. In INTRO-01, we observed a sevenfold increase of alkaline phosphatase and a fivefold increase in gamma-glutamyl transferase on day 7, without any accompanying symptoms or abnormalities in other laboratory findings. Both alkaline phosphatase and gamma-glutamyl transferase normalized within two weeks. INTRO-04 was readmitted to the hospital due to an ileus resulting from progression of disease. This adverse event required a prolonged hospital stay, parenteral feeding, and drainage of ascites. During the pre-infusion laparoscopy, a significant amount of disease was already visible in the abdominal cavity (PCI: 26). Given the disease progression, we decided (in consultation with the Data Safety Monitoring Board), to amend the protocol to exclude patients with a PCI more than 15 out of 36. These toxicity data demonstrate that IP infusion of RNK001 is safe and well tolerated in EOC patients.

3.4. Immune effects post-intraperitoneal RNK001 infusion with IL-2 support

Collection of PF was difficult, even after saline infusion of up to 500 ml. Nevertheless, PF collection at day 6/7 after RNK001 infusion

Table 1
Demographic, disease characteristics, and UCB donor characteristics of INTRO-01 ovarian cancer participants.

Patient	Age (years)	FIGO stage	Histology	BRCA mutation	Initial treatment	Relapse treatment	Last maintenance treatment	Platinum free interval (months)	PAI/PCI	Time between IP-port and infusion (weeks)	CA125 day − 1/0	Karnofsky	KIR receptor-ligand mismatch	Donor KIR haplotype	Total infused RNK001 ($x10^9$)
INTRO-01	62	3c	High grade serous	Wt	IDS complete	Caelyx/Beva	Bevacuzimab	9	4/20	5	260	100	C2	AB	2.2
INTRO-02	65	3c	Undifferentiated	Wt	PDS complete	Carbo/Gem	Niraparib	NA	4/19	NA	530	90	–	AB	Not infused due to progression
INTRO-03	62	2b	High grade serous	Wt	PDS complete	Carbo/Gem	Olaparib	9	2/6	5	310	90	C1	AB	1.2[#]
INTRO-04	36	3c	High grade serous	Wt	PDS complete/ IPchemo	Tamoxifen	Tamoxifen	2	2/26	9	270	100	C2,Bw4	AB	3.0
INTRO-05	67	4b	High grade serous	Wt	IDS optimal	Carbo/Pacli	Olaparib	7	3/13	6	790	80	C2,Bw4	AB	1.5
INTRO-06	54	2b	High grade serous	Wt	PDS complete/ IPchemo	Carbo/Caelyx	Niraparib	12	1/3	6	1500	90	C2,Bw4	AB	2.6
INTRO-07	57	3a	High grade serous	Wt	PDS complete	Carbo/Pacli	Niraparib	18	0/6	5	5500	100	–	AB	1.7
INTRO-10	70	4b	High grade serous	Wt	IDS complete	Carbo/Pacli	Olaparib	16	0/14	3	110	80	C2,Bw4	AB	2.3

Abbreviations: FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; CA125, Cancer antigen nr 125; NA, not applicable; PCI, Peritoneal Cancer Index based on laparoscopic assessment; PAI, Peritoneal Adhesion Index based on laparoscopic assessment; HLA, Human Leucocyt Antigen; KIR, killer-cell Ig-like receptors; BRCA, BReast Cancer; IDS, Interval Debulking Surgery; PDS, Primary Debulking Surgery; IP, Intraperitoneal; Chemo, chemotherapy; Beva, Bevacizumab; Caelyx, pegylated liposomal doxorubicin; Carbo, Carbotaxol; Gem, Gemcitabin; Pacli, Paclitaxel; Wt, Wild type. [#]Out of specification-release IP dose $<1.5 \times 10^9$.

was possible in 6 patients (INTRO-01,-03,-04,-05,-06 and − 07) but extracted volumes were low ranging 1–54 ml. As a result not all analyses were feasible. In three patients, donor NK cells were detected 6/7 days after RNK001 infusion through DNA chimerism analysis, while in the other patients donor cell levels were below the assay detection limit of 0.1 % (Supplementary Fig. 2 A). For INTRO-01, INTRO-04 and INTRO-05 donor chimerism in all cells was 0.24 %, 1.02 % and 0.78 %, respectively. Flow cytometry analysis revealed a clear population of $CD56^{++}CD3^{-}$ NK cells in PF obtained at day 6/7 from INTRO-01, −04 and − 06 (no flow cytometry data available for INTRO-05 day 6, Supplementary Fig. 2B) compared to only $CD56^{+}CD3^{-}$ NK cells in the other patients.

To determine systemic immune effects, we analyzed absolute lymphocyte subsets and HLA antibodies in PB at specified timepoints. Absolute numbers of $CD4^{+}$ T cells, $CD8^{+}$ T cells and $CD56^{+}CD3^{-}$ NK cells were elevated at day 13–15 likely due to the peritoneal IL-2 infusions (Supplementary Fig. 3). Thereafter, numbers declined to pre-treatment levels. As anticipated, Cy/Flu chemotherapy induced lymphopenia in INTRO-10. Absolute numbers of $CD4^{+}$ T cells, $CD8^{+}$ T cells, $CD56^{+}CD3^{-}$ NK cells and $CD19^{+}$ B cells were depleted to $<0.1 \times 10^9$/L at the time of infusion (Supplementary Fig. 3). From day 13/15 onward, repopulation of patient' NK cells and T cells was observed. Regarding HLA class I antibodies, five patients did not have HLA class I antibodies pre-infusion of whom one (INTRO-10) remained negative after infusion (Supplementary Table 3). In four cases, HLA class I antibodies were present post-infusion (INTRO-01, −03, −04 and − 05). For three patients the target antigens were present on the infused RNK001 cells, and for one patient (INTRO-05) antibodies targeted the HLA-A*02 antigen despite matching of the patient and donor. Two patients already had HLA class I antibodies present before RNK001 infusion (INTRO-06 and -07), of which one patient (INTRO-06) had antibodies against HLA-B*15 that were significantly increased post-treatment. INTRO-07 developed antibodies at high MFI against the HLA-B*44 antigen present on the infused RNK001 product.

These data suggest that RNK001 cells transiently persist in the peritoneal cavity in the presence of IL-2 support, while combined treatment boosted HLA class I antibody levels.

3.5. Clinical outcome and effect on CA125 levels

At the time of RNK001 infusion, all patients exhibited elevated CA125 levels (Table 1). In five out of seven patients (71 %) we observed a decline in CA125 levels at day 7 ranging 15–40 % and at day 14 ranging 7–53 % (Table 3, Fig. 3A). At day 28, two out of seven patients showed still a decline of 9–12 %, but other patients showed progressive increase. Two patients (INTRO-01 and -07) maintained stable disease according to RECIST 1.1 criteria; however, five patients (including INTRO-10 with Cy/Flu chemotherapy) experienced progression of disease shortly after RNK001 infusion (Table 3). Most patients started palliative chemotherapy treatment between 1 and 4.5 months post-infusion. Notably, INTRO-07 patient had a longer PFS of 9 months, while a PFS of approximately 3 months is typically expected after the initial raise of CA125. At day 0 prior to RNK001 infusion, CT analysis showed 3 tumor lesions of which one in the peritoneal cavity (lesion 1; diameter 38 mm) and two in the liver (lesions 2 and 3; diameters 59 and 37 mm, respectively; Fig. 3B)). The peritoneal tumor lesion 1 showed a significant reduction to 19 mm (50 % decrease) at 3 months and 14 mm (63 % decrease) at 6 months (Fig. 3C). Also the smaller liver tumor lesion 2 decreased from 37 mm at baseline to 23 mm (38 % decrease) at 3 months and 19 mm (49 % decrease) at 6 month. No major change was observed in the bigger liver tumor lesion 3. At 9.5 months, the disease progressed and this patient was treated with cisplatin, gemcitabine and bevacizumab with a very good response, and she is still alive 42 months after the infusion of RNK001. The mean OS for patients treated with RNK001 was 18 months. These findings suggest that one infusion of RNK001 cells with IL-2 support exerts a transient effect on EOC.

Table 2
Batch characteristics of clinical RNK001 products.

Patient	HPC(CB) CD34-enriched cell product			Intermediate expanded RNK001 NK cell product				Final RNK001 NK cell product						
	#CD34+ cells (x10^6)	Viability CD34+ cells (%)	Microbial control	Endotoxin (EU/ml) D14/15	Sterility D14/15	Viable CD56+ CD3- cells D28 (%)	Viability CD56+ CD3- cells D28 (%)	#CD45+ CD56+ CD3- cells (x10^9)	Purity CD56+ CD3- cells (%)	ViabilityCD56 + CD3- cells (%)	T cell content (x10^5/kg)	B cell content (x10^5/kg)	Endotoxin (EU/ml)	Sterility
	≥ 1.0	≥ 70	Neg	< 0.3	Sterile	≥ 50 %	≥ 70 %	1.5–3.0	≥ 70 %	≥ 70 %	< 1.0	< 3.0	< 0.7	Sterile
INTRO-01	1.19	88	Neg	<0.3	Sterile	52	100	2.2	89	100	0.1	0.2	<0.3	Sterile
INTRO-02*	3.94	89	Neg	<0.3	Sterile	80	100	3.0	98	99	0.2	0.2	<0.3	Sterile
INTRO-03	1.71	79	Neg	<0.3	Sterile	47$^{\$}$	100	1.2$^{\#}$	76	97	0.1	0.2	<0.3	Sterile
INTRO-04	6.99	91	Neg	<0.3	Sterile	63	81	3.0	96	100	0.1	0.1	<0.3	Sterile
INTRO-05	1.42	69	Neg	<0.3	Sterile	73	100	1.5	87	99	0.1	0.1	<0.3	Sterile
INTRO-06	2.72	98	Neg	<0.3	Sterile	67	100	2.6	90	99	0.1	0.2	<0.3	Sterile
INTRO-07	2.84	95	Neg	<0.3	Sterile	53	100	1.7	88	100	0.1	0.2	<0.3	Sterile
INTRO-10	1.88	97	Neg	<0.3	Sterile	54	100	2.3	92	100	0.0	0.0	<0.3	Sterile
Mean	3.00	88	NA	NA	NA	61	98	2.2	90	99	0.1	0.2	NA	NA
Range	1.19–6.99	69–98	NA	NA	NA	47–80	81–100	1.2–3.0	76–98	97–100	0.0–0.2	0.0–0.2	NA	NA

Abbreviations: HPC, hematopoietic progenitor cells; CB, cord blood; NA, not applicable; Neg, Negative. * Product not infused due to disease progression. $ In process criterium of 50 % viable CD56$^+$CD3$^-$ cells was not met. # Out of specification-release IP dose <1.5 × 10^9.

4. Discussion

We evaluated the safety, toxicity and anti-tumor effect of a single IP infusion of UCB-derived HSPC-NK cells (RNK001) with IL-2 support in EOC patients experiencing second recurrence (NCT0353940). Utilizing UCB units allows partial HLA matching, thereby optimizing either KIR receptor-ligand mismatch and/or favorable KIR B haplotype. Seven platinum-sensitive EOC patients with rising CA125 levels received RNK001 (1.2–3.0 × 10^9 flat dose), six without and one with Cy/Flu conditioning. Treatment was well tolerated, with no GVHD, cytokine release syndrome, or severe infections. Five patients experienced a CA125 decrease of 20–53 %, two weeks after RNK001 infusion. One patient had a clinical and biochemical response with radiological stable disease and a PFS of 9 months.

RNK001 production from CD34$^+$ UCB cells was feasible, though one batch fell below the required dose (1.2 instead of 1.5 × 10^9 RNK001 cells). The 6–13 week consent-to-infusion time proved challenging given rapid disease progression. To expedite availability, we modified the manufacturing process with cryopreservation to produce off-the-shelf products [25]. On demand availability improves accessibility for clinical trials, especially for EOC patients with high-risk of rapidly progressing disease. Moreover, it facilitates centralized manufacturing and multi-site trials, repeated dosing regimens, and simplifies manufacturing logistics.

To support RNK001 persistence, IL-2 was co-infused due to its clinical availability. Intraperitoneal IL-2 appeared to have a systemic immune effect by elevating absolute numbers of CD4$^+$ T cells, CD8$^+$ T cells and CD56$^+$CD3$^-$ NK cells in blood at day 13–15 post infusion. Six out of seven patients also experienced fever/chills after IL-2 infusions. Although, we have not tested any control patients who received the IL-2 peritoneal infusions only we expect these effects to be driven by IL-2. Donor RNK001 cells were detected in PF from three patients one week post-infusion, without lymphodepleting chemotherapy. No donor chimerism was found in the other patients, possibly due to PF sampling limitations. Furthermore, RNK001 cells infiltrated into tumor lesions cannot be detected in the PF, which should be evaluated in next studies by taking tumor biopsies. Preclinical data demonstrated RNK001 migration, infiltration, and cytotoxic activity in EOC spheroids

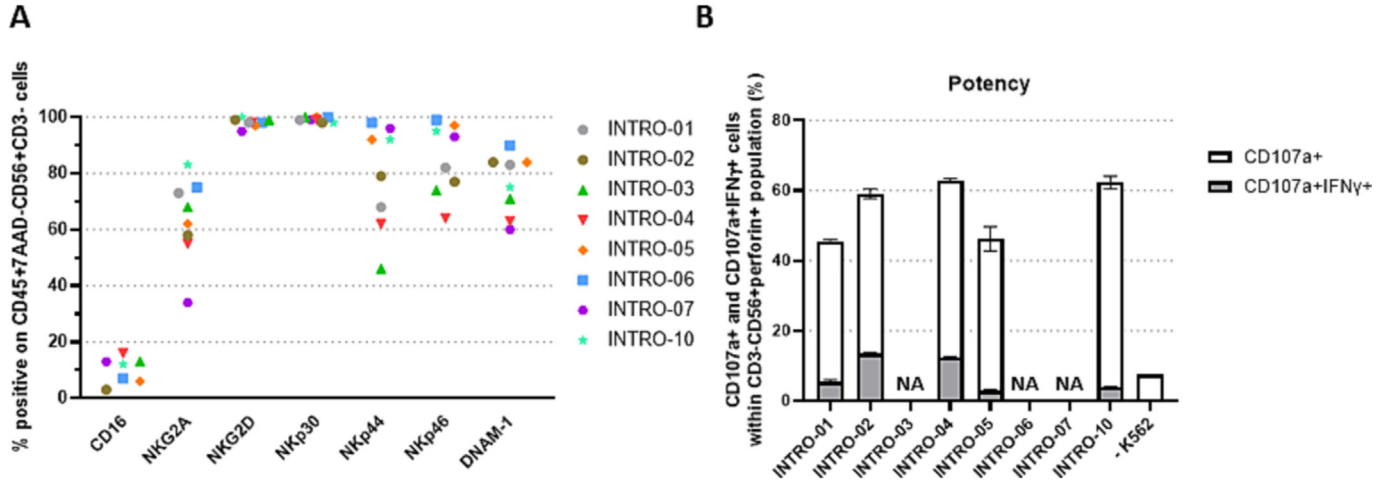

Fig. 2. RNK001 product information. RNK001 products express high levels of activating ligands and show potent functional activity. RNK001 cells were generated for patients included in the study according to our GMP-grade culture protocol. The phenotype of RNK001 products at the day of infusion (day 0) was determined by FCM. (A) Expression of NK cell receptors on CD45$^+$7AAD$^-$CD56$^+$CD3$^-$ RNK001 cells at the day of infusion. (B) Degranulation of RNK001 cells during co-culture with K562 target cells was measured by cell surface expression of CD107a and intracellular IFNγ. After 4 h of incubation at 37 °C, the percentage of CD107a$^+$ and CD107a$^+$IFNγ$^+$ cells was determined by FCM.

Table 3
Clinical outcome and long-term follow-up in RNK001-treated OC patients.

Patient	CA125 compared to day − 1/0*			RECIST 1.1	Progression free survival (months)	First treatment following RNK001 infusion	Interval between RNK001 infusion and next treatment (months)	Time to second subsequent therapy (months)	Survival after RNK001 treatment (months)
	Day 7	Day 14	Day 28						
INTRO-01	220 (−15 %)	170 (−35 %)	230 (−12 %)	SD	3	Carboplatin Paclitaxel	3.5	3	11
INTRO-03	320 (+3 %)	410 (+32 %)	650 (+110 %)	PD	4	Caelyx Bevacizumab	4	4	11
INTRO-04	170 (−37 %)	130 (−52 %)	400 (+48 %)	PD	0	Carboplatin Paclitaxel	1	8	24
INTRO-05	830 (+5 %)	940 (+19 %)	1300 (+65 %)	PD	2	Carboplatin CaelyxNiraparib	2.5	Unknown	13
INTRO-06	1200 (−20 %)	1400 (−7 %)	1500 (0 %)	PD	2	Carboplatin	3	Unknown	21
INTRO-07	3300 (−40 %)	2600 (−53 %)	5000 (−9 %)	SD	9	Carboplatin	9.5	37	Alive (49 m October 2025)
INTRO-10	78 (−29 %)	54 (−51 %)	180 (+64 %)	PD	4	Carboplatin Paclitaxel	4.5	Unknown	6

Abbreviations: CA125, Cancer antigen nr 125; m: months, following treatment: first treatment after progression after RNK001 therapy. SD: stable disease, PD: progressive disease. *CA125 was measured either 1 day before infusion (INTRO-03, −04, −05, −06 and − 07) or on day of infusion, before infusion (INTRO-1 and -10). CA125 was then determined again after 7, 14 and 28 days. Negative value indicates a decrease in CA125.

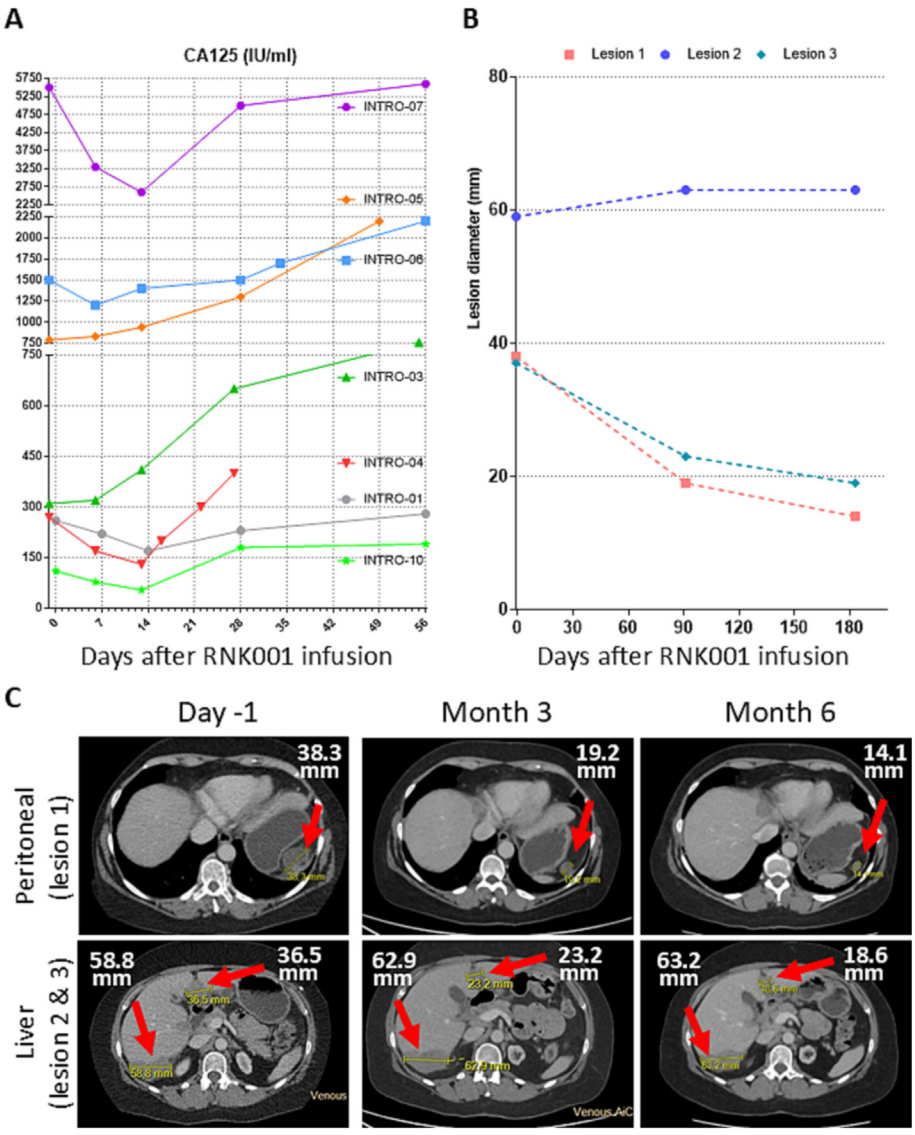

Fig. 3. Effect on CA125 and tumor lesions in patient INTRO-07 after RNK001 cell therapy.
(A) After RNK001 NK cell infusion a transient reduction in CA125 was observed during the first 14 days in five out of seven patients. (B) Size of tumor lesions identified on CT scans for INTRO-07 patient on the day before RNK001 infusion, three and nine months after RNK001 infusion. Three tumor lesions were identified of which one in the peritoneal cavity (lesion 1; diameter 38 mm) and two in the liver (lesions 2 and 3; diameters 59 and 37 mm, respectively). Lesion 1 and 3 showed a significant reduction at 3 and 6 months post RNK001 infusion, while no major change was observed in the bigger liver tumor lesion 3. (C) CT images of intraperitoneal lesion 1 as well as liver lesions 2 and 3 used to identify lesion size.

and EOC-bearing NOD/SCID-IL2Rγ^{null} (NSG) mice [17]. While IL-2 supports NK cells, it also stimulates regulatory T cells (Tregs), potentially reducing efficacy and causing unwanted side effects [26]. IL-15, a more suitable cytokine, is not clinically available and has a short half-life [27]. Novel IL-15 superagonists, such as N-803, are under clinical investigation, though systemic administration can cause inflammatory side-effects [28–30]. An alternative strategy would be to deliver IL-15 locally alongside the NK cells and/or to the tumor microenvironment. This could be achievable by modifying RNK001 to stably express IL-15 by genetic engineering [31] or by (targeted) delivery of mRNA that can transiently result in the production of IL-15 in the tumor microenvironment [32].

Although NK cell therapy is well studied in hematological malignancies, clinical evidence in EOC remains limited. Several trials have assessed intravenous NK cell therapy in EOC [33], with the APOLLO trial demonstrating promise for IP delivery in patients with recurrent disease [21]. Our study further supports that IP delivery of RNK001 can also show clinical benefit without Cy/Flu conditioning. Cy/Flu lymphodepletion is typically used in adoptive NK cell therapy [34]. It eliminates host T cells that reject allogeneic NK cells based on HLA mismatch, and creates a favorable microenvironment for activation, tumor reactivity and proliferation by reducing immune cells competing for endogenous cytokines and depletion of immunosuppressive cells. In a pivotal study by Miller et al. [13] Cy/Flu was found to be the most effective preparative regimen for AML patients. However, its toxicity including prolonged pancytopenia, limits its application in EOC. Our trial was prematurely stopped due to challenges in recruiting patients willing to undergo Cy/Flu chemotherapy in a phase 1 study. As only one patient was enrolled who received a preceding immunosuppressive conditioning, this limited the ability to draw conclusions of the impact of immunosuppressive conditioning on RNK001's peritoneal lifespan. Nonetheless, RNK001 infusion through the IP catheter proved to be feasible, without obstructions or immediate infusion reactions. Platinum-based carboplatin-paclitaxel (CP) chemotherapy, widely used in EOC, may offer a safer lymphodepletion strategy. CP chemotherapy significantly reduces circulating lymphocytes to less than 1000/μl between 5 and 14 days, creating a window for immunotherapy [35]. CP also demonstrated to reduce Treg and immunosuppressive myeloid cell frequencies [36], potentially enhancing NK cell tumor efficacy. Additionally, CP may prevent HLA class I antibody boosting by sufficiently depleting host B cells and CD4+ T helper cells. This is particularly relevant as we observed an increase in HLA class I antibodies in patients treated with allogeneic RNK001 cells without preceding Cy/Flu chemotherapy, which might hinder NK cell persistence and expansion post infusion [12,13,14,34].

RNK001 treatment transiently reduced CA125 levels in five out of seven EOC patients, underscoring its potential for further HSPC-NK cell product development. Enhancing *in vivo* persistence and cytotoxicity through genetic engineering could optimize therapeutic efficacy. Overexpressed EOC antigens, such as EpCAM, MUC1, and FOLR1, are being explored for chimeric antigen receptor (CAR) T cell therapy [37–39]. Modifying our HSPC-NK cells to express a CAR targeting these proteins may improve tumor targeting and efficacy of the anti-EOC response. CAR-NK cell trials in other cancers showed promising results with increased efficacy, long-term survival and minimal side-effects [31, [40]. To maximize therapeutic benefit, we propose repeated CAR-modified HSPC-NK cell infusions combined with CP chemotherapy for EOC patients. While lymphodepletion is critical for native NK cells, its requirement may be precluded by CAR-NK cell engineering and favorable genetic manipulations to enhance self-sustained proliferation, persistence, and resistance to rejection by host T cells and HLA class I antibodies.

In conclusion, intraperitoneal RNK001 infusion in recurrent EOC is feasible and well tolerated, with notable CA125 reductions at day 14. One patient exhibited a clinical and biochemical response with radiologically stable disease. This HSPC-NK cell-based immunotherapy could serve as an additional therapy for recurrent EOC patients in combination with CP for platinum-sensitive EOC patients.

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CRediT authorship contribution statement

Janneke Hoogstad-van Evert: Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Paul de Jonge:** Writing – review & editing, Writing – original draft, Visualization, Validation, Investigation, Data curation. **Petra Zusterzeel:** Writing – review & editing, Supervision, Methodology, Investigation. **Willemijn Hobo:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Anniek van der Waart:** Writing – review & editing, Supervision, Investigation. **Hanny Fredrix:** Writing – review & editing, Validation, Investigation. **Lisanne Janssen:** Writing – review & editing, Validation, Investigation. **Maud Wuts:** Writing – review & editing, Validation, Investigation. **Lynn Bosmans:** Writing – review & editing, Investigation. **Ellen Spijkers:** Writing – review & editing, Validation. **Merlize Djojoatmo:** Writing – review & editing, Resources. **Veronica Castaño Rodriguez:** Writing – review & editing, Resources. **Anna de Goede:** Writing – review & editing, Validation, Methodology, Formal analysis. **Bert van der Reijden:** Writing – review & editing, Investigation. **Arnold van der Meer:** Writing – review & editing, Resources, Investigation. **Nicolaas Schaap:** Writing – review & editing, Funding acquisition, Conceptualization. **Ruud Bekkers:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Joop Jansen:** Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition, Conceptualization. **Nelleke Ottevanger:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Harry Dolstra:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

All authors report no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2025.11.006.

Data availability

Data can be requested from the corresponding author.

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