Journal of Oncology Research and Therapy
Arbib S, et al. Oncol Res Ther 10: 10304.
www.doi.org/10.29011/2574-710X.10304
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Case Report

Extended Treatment with Magnetic Nanoparticle Hyperthermia in a "First-in-Human" Trial Demonstrates Safety and Feasibility in an Advanced Cervical Cancer Case

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Citation: Arbib S, Rukenstein P, Kraus S, Ventura-Bixenshpaner H, Shalev B, et al. (2025) Extended Treatment with Magnetic Nanoparticle Hyperthermia in a "First-in-Human" Trial Demonstrates Safety and Feasibility in an Advanced Cervical Cancer Case. J Oncol Res Ther 10: 10304. DOI: 10.29011/2574-710X.10304

Received Date: 04 September, 2025; **Accepted:** 10 September, 2025; **Published Date:** 12 September, 2025.

Abstract

Background: A patient with advanced cervical cancer was enrolled in a First-in-Human trial examining the safety and feasibility of a novel magnetic nanoparticle-based hyperthermia treatment involving administration of iron oxide multicore encapsulated nanoparticles, termed Sarah Nanoparticles (SaNPs), and exposure to an Alternating Magnetic Field (AMF). **Case Description:** The patient, a 41-year-old woman diagnosed with stage IV cervical cancer, previously treated with first-line hormonal therapy, was treated with seven consecutive treatment cycles of magnetic nanoparticle hyperthermia conducted over a period of 10 months with intervals of approximately one month between each treatment session. The patient received increasing SaNP doses of 0.6 mg/kg and 0.84 mg/kg followed by AMF irradiation for a total duration time of either 10 or 15 minutes. Toxicity assessment was performed using standard criteria for the grading of adverse events during treatment and after a follow-up period of 30 days for each of the treatment cycles, demonstrating that treatment was safe with only few side effects which included mainly local heat and transient pain in the lower back. Blood and urine analyses were mostly normal with some fluctuations in liver function parameters which returned to baseline levels after 30 days. MRI analysis demonstrated SaNP clearance from the liver and spleen after this follow-up period, and according to CT scanning and RECIST 1.1, the disease status was categorized as stable disease. **Conclusion:** Magnetic nanoparticle-based hyperthermia was found to be safe and feasible for repeated treatments with increasing SaNP doses and AMF irradiation times and enabled long-term disease control over a period of 10 months, in a patient with metastatic cervical cancer.

Keywords: Solid Tumors; Cervical Cancer; Magnetic Nanoparticle Hyperthermia; Iron Oxide Nanoparticles; Alternating Magnetic Field.

Abbreviations:

AEs: Adverse Events

AMF: Alternating Magnetic Field

CT: Computed Tomography

CTCAE: Common Terminology Criteria for Adverse Events

ECOG: Eastern Cooperative Oncology Group

EPR: Enhanced Permeability and Retention;

IO: Iron Oxide

MRI: Magnetic Resonance Imaging

NOAEL: No-Observed-Adverse-Effect-Level

SaNPs: Sarah Nanoparticles

SAEs: Serious Adverse Events

Introduction

Despite recent therapeutic advances in cancer treatment, metastatic spread remains the main cause of cancer death. Chemotherapy, radiotherapy, and immunotherapy are the most common treatments used to treat advanced tumors.

Invasive cervical cancer is a highly morbid disease associated with poor treatment efficacy and high mortality rates which have stagnated or risen despite the concerted efforts to find new cancer therapies [1].

Cervical cancer is the fourth most common malignancy in women in terms of both incidence and mortality and it is the second leading cause of cancer mortality in women aged 35 to 64 years [2]. In 2025, the American Cancer Society estimates that about 13,360 new cases of invasive cervical cancer will be diagnosed and about 4,320 women will die from the disease in the U.S. [3]. Previous studies have demonstrated that the survival time of metastatic cervical cancer is only 8-13 months, and only 16.5% will survive for 5 years [4-6]. The survival time for each patient varies from one to another and depends on multiple factors including age, pathological type, disease stage, metastasis spread, physiological condition, health, and fitness [7-8]. Due to morbidity data, poor prognosis, and no obvious symptoms of the disease, metastatic cervical cancer has become one of the main challenges in cancer treatment, trying to slow or stop the growth of cancer cells, reduce symptoms and side effects.

The most prevalent treatment for metastatic cervical cancer is a combination of chemotherapy and radiation therapy. These therapies help reduce tumor burden and prevent cancer cell growth. However, they cause severe side effects, such as nausea, hair loss, fatigue, appetite loss, mouth sores, infections, diarrhea, skin irritation, vaginal pain, and others, which significantly lower the patient's quality of life [1].

In this report, we present a case of a 41-years old female patient with advanced cervical cancer that spread beyond the pelvis into distant organs, and to the iliac vessels as well as to the para-aortic lymph nodes. According to the presented medical history, the patient was previously treated with megestrol acetate, used as primary hormonal therapy, and did not receive any other treatments prior to magnetic nanoparticle-based hyperthermia treatments, conducted within the frame of a First-in-Human clinical trial at the Rabin Medical Center in Petah Tikva, Israel (MOH_2022-09-18_012060).

Recently, magnetic hyperthermia has been recognized as a promising concept for cancer treatment due to its effective heating of solid tumors with minimal damage to healthy surrounding tissues [9-12]. Herein, we present the Sarah Nanotechnology System a novel technology that involves Sarah Nanoparticles (SaNPs) and an Electromagnetic Induction System (EIS), which was designed to treat metastatic (stage IV) solid tumors through the delivery of thermal energy to malignant cells, and induction of thermal damage to cancer cells at a sub-ablative temperature (up to 50±3°C).

SaNPs containing encapsulated iron oxide (IO) covered with a non-toxic, inert, and non-immunogenic material, are intravenously (IV) administered to the patient, and accumulate in tumors and metastases via the Enhanced Permeability and Retention (EPR) effect. Following delivery and accumulation of SaNP on the surrounding malignant tissue, the patient undergoes regional body Alternating Magnetic Field (AMF) application on the torso area (chest to pelvis) with the EIS, at a frequency of 290±10% kHz and field strength between 9-10 mT. The SaNPs absorb the AMF radiation and produce heat through an oscillating magnetic field, thereby heating the malignant cells and causing cell death [13].

Pre-clinical studies conducted in animal models to evaluate the safety and efficacy of the approach demonstrated that the treatment was safe, biocompatible and able to reduce the number and size of metastatic lesions in a murine cancer model, without any adverse effects. Furthermore, pharmacokinetics studies examining SaNP clearance from the body over time showed that after a period of 30 days, most of the SaNP was cleared (~60%), whereas after 90 days and following 3 repeated treatments, almost 90% of SaNP was

safely cleared from the animals' body [14-15]. In a previous case study report, initial results of a breast cancer patient that received one treatment cycle of Sarah Nanotechnology with a SaNP dose of 0.12 mg/kg followed by AMF irradiation were presented, confirming that the approach was safe and feasible, without any treatment-associated toxicities [16].

In the current report, we present a case of a patient with stage IV cervical cancer, that received repeated treatment cycles of Sarah Nanotechnology System over a period of ten months, after which the tumors exhibited a percentage change in tumor size of only 9.37%, considered as stable disease by CT scanning and RECIST criteria. Based on the results of this case, repeated treatment with increasing SaNP doses and AMF irradiation times has proven safe, without any deleterious SaNP accumulation nor treatment-related toxicities.

Case Presentation

Study Design

The trial was conducted at the Rabin Medical Center in Petah Tikva, Israel, and performed following the ethical principles of the Institutional Review Board (IRB), the local Ministry of Health (MOH) and Good Clinical Practice (GCP) guidelines. The patient reviewed and approved a written informed consent before starting the treatments and after receiving instructions regarding the possible risks and benefits and was granted privacy, confidentiality, and anonymity rights. This study was guided by ethical standards and national and international laws.

The primary endpoint of the trial was to assess the safety of treatment/s based on toxicity evaluation which included monitoring the incidence and severity of Adverse Events (AEs) and Serious Adverse Events (SAEs), which were characterized and graded by the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. The secondary endpoint was to evaluate initial signs of efficacy, by assessing disease progression following a 30-day follow-up period, after each treatment cycle, using computed tomography (CT).

To be eligible for the study, the patient had to be age ≥18 with an Eastern Cooperative Oncology Group (ECOG) status of ≤2, diagnosed with histologically advanced metastatic solid cancer (stage IV) excluding brain metastases, with a life expectancy of at least 30 days, progressed disease, or after standard anticancer therapy, or for whom no other approved conventional therapy exists. Inclusion criteria also required that participants in the study must not have received any anticancer treatment, for at least two weeks before starting the study treatment. Before the treatment was initiated, the patient underwent CT scanning to detect any electronic conductive implants or metal that may heat up during the treatment due to AMF exposure and underwent blood testing and urinalysis before and after each treatment. In addition, before, during, and after each treatment, the patient was monitored for vital signs which included an ECG, and measurement of blood pressure, oxygen saturation, heart rate (HR), body surface and oral temperature monitoring. Prior to some of the treatments sessions, the patient was administered with analgesics to alleviate pain. Following each treatment, the patient was required to answer a discomfort questionnaire about pain, or any discomfort experienced during treatments. After 30 days, the patient underwent CT analysis to determine the progression of disease and magnetic resonance imaging (MRI) to detect SaNP clearance from the liver and spleen, and its accumulation in tumors.

Treatment

Sarah Nanotechnology treatment was administered over a period of 10 months after reviewing the CT results obtained 30 days after each treatment cycle and following the clinician's decision on the status of the disease. Thus, the patient was eligible for additional treatment/s in case of stable disease or clinical improvement. The doses were calculated based on the No-Observed-Adverse-Effect-Level (NOAEL) approach and following the FDA guideline [17-18]. As part of the treatment, 4 hours after SaNP administration and before AMF irradiation, the patient received an antacid solution to neutralize gastric acid, minimize electric conductivity, and avoid heating of the stomach. Afterward, the patient underwent AMF irradiation that was administered through the EIS, as previously described [16].

The SaNP and AMF doses for each treatment are described in Table 1. The patient received increasing SaNP doses of 0.6 mg/kg and 0.84 mg/kg, followed by increasing AMF irradiation times of 10 and 15 minutes, while the patient was positioned at either a prone (face down) or supine (face up) position, based on its comfort feedback during the study.

Treatment No.	1	2	3	4	5	6	7
SaNP Dose [mg/kg]	0.6	0.6	0.6	0.6	0.84	0.84	0.84
AMF Dose [minutes]	10	10	10	15	15	15	15
Patient positioning in EIS	Prone	Prone	Prone	Supine	Supine	Supine	Supine

Table 1: SaNP and AMF doses administered to the patient on each treatment cycle and patient positioning in EIS.

Exposure to AMF is known to induce eddy currents which may lead to undesired heating of healthy tissues [19]. To reduce the heating effect on the normal tissues, a chiller-connected circulating water Cooling Blanket System (CBS) was used to cool the patient's irradiated area during AMF application which included the torso area (chest to pelvis). The surface temperature of the irradiated area of the patient was measured and constantly monitored during treatments by using infrared fiber optic temperature probes to provide information on the clinical thermal conditions of the patient during the irradiation. The location of the probes on the patient's skin was determined according to experience gained in pre-clinical studies and a thermal computational model that predicted the occurrence of hot spots in a human body under AMF irradiation at similar field strength conditions [15, 19]. The location of the probes was similar in both prone and supine positions except for one probe (No. 5), which served as a reference point for monitoring the skin temperature outside the CBS shield, and was placed beneath the shoulder in a manner that opposes the direction of each respective position (Figure 1).

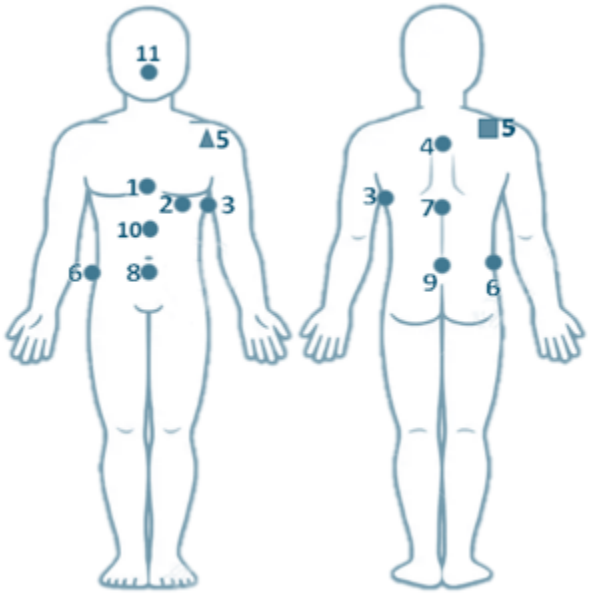

Figure 1: Positions of temperature monitoring infrared probes. Probes 1, 2, 3, and 4 were located on the upper body area and included the sternum (probe 1), inframammary fold (probe 2), right lung (probe 3), and upper back (probe 4). Probes 6, 7, 8, and 9 were located on the lower body area and included the waist (probe 6), mid back (probe 7), abdomen (probe 8), and lower back/lumbar area (probe 9). An additional probe (probe 10) was added around the liver area when the patient was lying in a supine position. Probe 5 was located outside the CBS below the shoulder on the anterior side (for supine position-▲) or on the posterior side (for prone position- ■) and used as a reference. The oral temperature (probe 11) was recorded before and after each AMF irradiation cycle.

Results

Between June 2023 and April 2024, a 41-year-old female patient was enrolled in the study and treated with Sarah Nanotechnology System. In total, the patient received seven repeated treatment sessions at increasing SaNP doses (0.6 mg/kg and 0.84 mg/kg) and AMF irradiation times (10 and 15 minutes) and succeeded in completing the treatments in accordance with the study protocol.

SaNP administration procedure was safe, and no signs of toxicity were observed. In addition, no significant changes were observed in the vital sign parameters measured for oral temperature, HR, blood pressure, saturation, and ECG before, during, and after SaNP administration and AMF exposure except for a rise in HR which was observed during the first treatment cycle at the beginning of AMF irradiation. The HR increased from 67 bpm at baseline to 127 bpm and decreased after a few minutes to 78 bpm, returning to the baseline value by the end of treatment. This could be explained by the patient being under stress during the irradiation procedure and was not considered of clinical significance.

Throughout AMF irradiation, the patient was covered with the CBS, and infrared optic probes were placed as described above to monitor the body's surface and oral temperatures. For the first three treatments the patient was in a prone position, and during the following treatments the patient lay in a supine position to improve its comfort and allow for greater ease of leg movement during the procedure. After the patient was centered in the coil area in a prone or supine position, the CBS chiller was activated and continued to operate during the irradiation breaks to effectively maintain the patient's body temperature within a controlled range. However, several temperature increases were observed at specific locations during the treatments. Changes in temperature appeared mainly during treatments 5 and 6, recorded by probe 2 located under

the inframammary fold area, with increases of 5.7 and 4.6°C, respectively, from the beginning until the end of the irradiation. However, the recorded temperatures did not rise above 39.0°C and remained within a physiological range. The temperature rise in probe 2 is most likely due to incomplete attachment of the CBC to the patient's skin in this area, because of the human anatomical structure. Another temperature rise occurred on the right waist area (probe 6), during treatment 6, which increased by 6.8°C up to 39.0°C. The increase in temperature, particularly in treatments 5 and 6, was probably related to the higher SaNP dose of 0.84 mg/kg and a longer AMF irradiation time of 15 minutes, which may have led to increased heating in the area around the tumors.

Clinical Pathology

The follow-up study examinations included blood testing before the treatment (baseline), 4 hours post SaNP administration, 72 hours, two weeks, and after the follow-up period of 30 days post treatment. Clinical pathology included hematology, chemistry, coagulation, and urinalysis testing. No abnormal clinical pathology or urinalysis results were identified in the blood or urine parameters. Some elevated levels were found in enzymes indicative of liver function, where increased values were detected (Figure 2). Accordingly, alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), and aspartate aminotransferase (AST), showed a transient increase above the normal range as follows.

ALT showed an increase of 1.5-fold during and after the first treatment. The ALT value increased from 17 U/L at baseline to 35 U/L after 30 days and continued to increase to 88 U/L 30 days after the second treatment, However, ALT levels returned to normal 30 days after the third treatment (Figure 2A) with no further increase.

GGT levels (normal range of 0-33U/L) showed an increase to 47 U/L two weeks after the first treatment and then returned to a normal range after 1 month. After the second treatment, GGT levels increased again to 71 U/L and then decreased to 34 U/L 30 days after the third treatment. In the following treatments, GGT levels remained stable within the normal range but increased again before the seventh treatment and remained unchanged during the follow-up (Figure 2D).

ALP levels (normal range of 30-120 U/L) also exhibited an upward trend, reaching 142 U/L two weeks after the first treatment compared to the baseline of 109 U/L, and rising to a value of 220 U/L, 30 days after the second treatment. Subsequently, ALP levels began to gradually decrease reaching 128 U/L in the sixth treatment, increasing again prior to the seventh treatment but remaining unchanged during the follow-up period (Figure 2B).

AST levels at baseline (normal range of 0-31 U/L) showed an abnormal value of 63 U/L before the first treatment which increased to 84 U/L two weeks after treatment. This upward trend continued to a maximum value of 198 U/L before the second treatment, gradually returning to 46 U/L below the patient's baseline levels during the fifth and sixth treatments. However, an increase in the AST levels appeared before and after the seventh treatment (Figure 2C).

The increase in the liver function parameters following treatments may reflect the clinical condition of the patient and advanced disease.

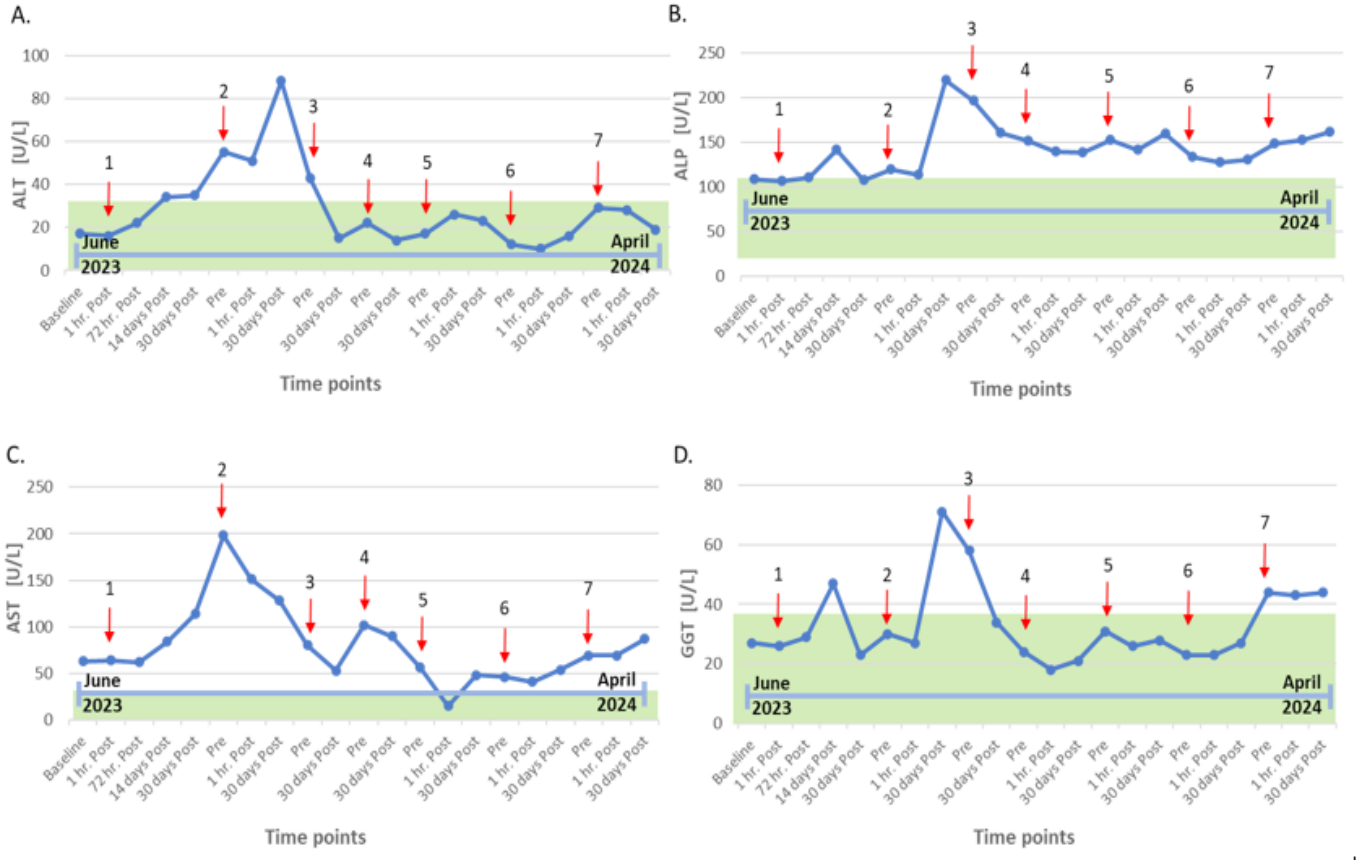

Figure 2: Liver enzyme levels during repeated treatments recorded between June 2023 and April 2024. ALT (A), ALP (B), AST (C), and GGT (D). Blood samples were collected and analyzed before, during, and after each treatment session at various timepoints: Baseline, 1 hr. post SaNP administration, 72 hr., 14 days, and 30 days post treatment. The green area in each graph represents the normal range of values. For each of the parameters, only available results were presented (U/L). The red arrows on the graph indicate the treatment session number.

Another irregular result was the presence of protein in the urinalysis, which was consistently positive in most tests before and after treatments. However, creatinine values and kidney function parameters remained normal in all treatments except for the seventh treatment's follow-up, where the creatinine levels exceeded by 2.7-fold from the normal range compared to the values on the day of treatment before and after, which were in the normal range (56-59 U/L). Proteinuria could be explained by dehydration or intensive exercise practiced by the patient.

MRI and CT Assessments

MRI is a non-invasive technique widely used to diagnose diseases or injuries based on its high soft tissue contrast, with no penetration limit and spatial resolution. Herein, we used MRI as an exploratory tool, still in development stages, to detect the accumulation and/or clearance of SaNPs from the body 30 days after the treatment compared to the baseline and examine whether repeated SaNP administration could impact its accumulation in the body. SaNPs can be detected by MRI due to the superparamagnetic properties of the IO-containing nanoparticles. In particular, IO nanoparticles have been extensively studied as a T2 contrast agent for MRI as they efficiently shorten transverse relaxation times. T2-weighted signals as a function of Echo time (TE) were evaluated in scans conducted in a 3T Ingenia MR scanner (Philips Healthcare) to detect SaNP accumulation in the liver, spleen, and tumors and their clearance as previously described [15].

The measurement of T2-weighted signals reflects the decay of proton spins oriented perpendicular to the main magnetic field (transverse relaxation time). The contrast of the image is determined by an inverse relationship to the relaxation time, therefore, SaNP accumulation leads to a reduction in the transverse relaxation time

by increasing the spin phase coherence loss, lowering the signals on the regions of interest and producing a darker image, compared to the same tissue or organ without SaNP.

Figures 3 and 4 present the SaNP accumulation in the liver, spleen, and tumors. MRI scans were conducted only for the patient's first treatment at a SaNP dose of 0.6 mg/kg at 3 time points: pre-injection (baseline), post-injection, and after the follow-up period of 30 days. The signal intensity of the liver and spleen, as well as the chosen tumors, were analyzed and T2-weighted signals were plotted against TE. As demonstrated by the results, the image contrast became darker at post-injection (Figure 3B) compared to the baseline (Figure 3A) and after 30 days (Figure 3C). It can also be seen that at baseline, T2-weighted signals were high, decreased at post-injection, and increased 30 days after the treatment (Fig 3D-E), suggesting clearance of SaNP from the examined organs, whereas in the liver, the signals after the follow-up period returned to baseline levels and in the spleen the signals were lower than the baseline but higher than at post-injection, indicating partial clearance from this organ. However, no damage to the spleen was observed even after repeated treatments, as reflected by the blood test results.

In addition, two tumors, Tumor 1 (T1) and Tumor 2 (T2) were identified based on a PET-CT scan of the lower abdomen and pelvic area, respectively, and analyzed for their MRI signals to detect SaNP presence (Figure 4). In both tumors, the signals at post-injection were slightly lower than those measured at baseline and remained low after the follow-up period suggesting that SaNPs reached their targets and were not cleared out from the tumors. These results are thought to be related to the EPR effect which enables the SaNP to permeate into the tumor vicinity through the abnormal blood vessels and kept retained in the target areas.

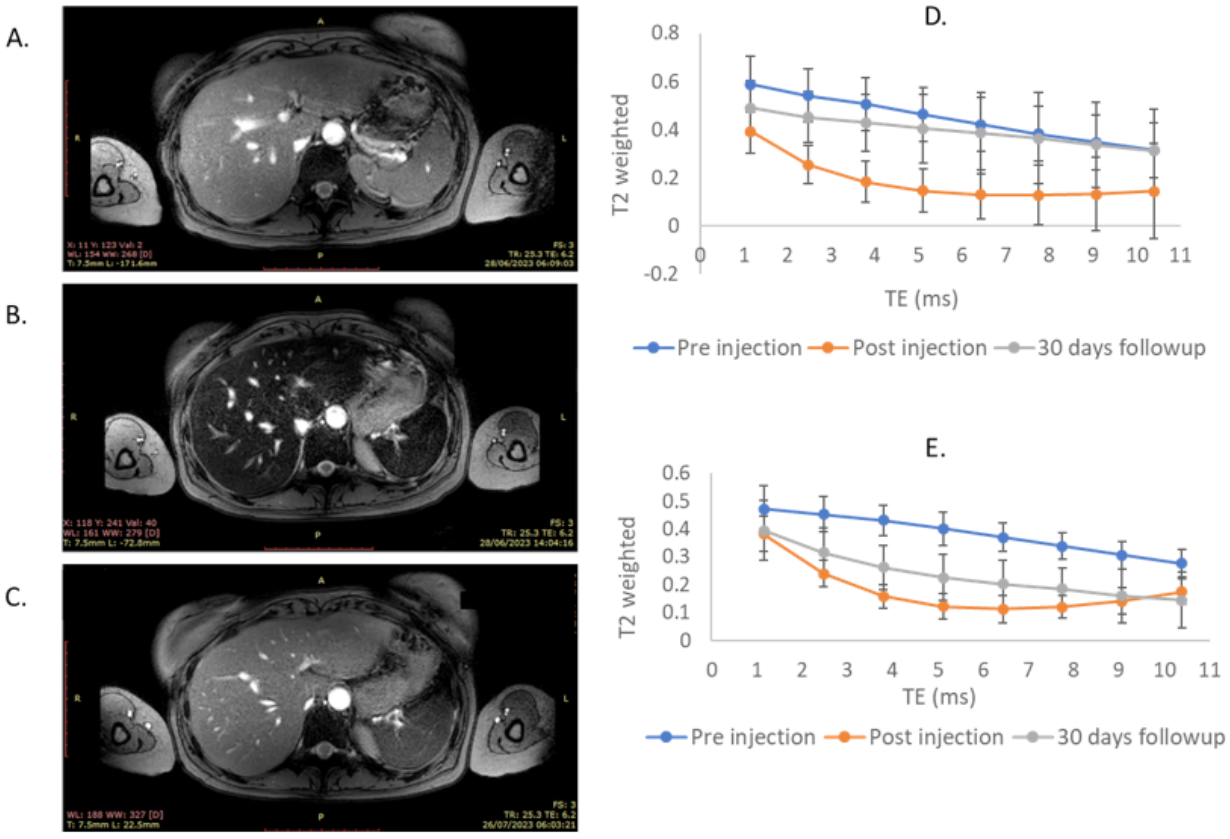

Figure 3: MRI analysis of SaNP accumulation and clearance in and from the liver and spleen. MRI scans were obtained using a T2* scanning mode: MRI scans of liver and spleen at pre-injection (A), post-injection (B), and after 30 days (C) of 1st treatment. T2-weighed signals of liver (D) and spleen (E). Blue line – pre-injection (baseline); Orange line – post-injection (~4hrs.) and grey line – 30 days after treatment. Echo time (TE) was measured in milliseconds (ms).

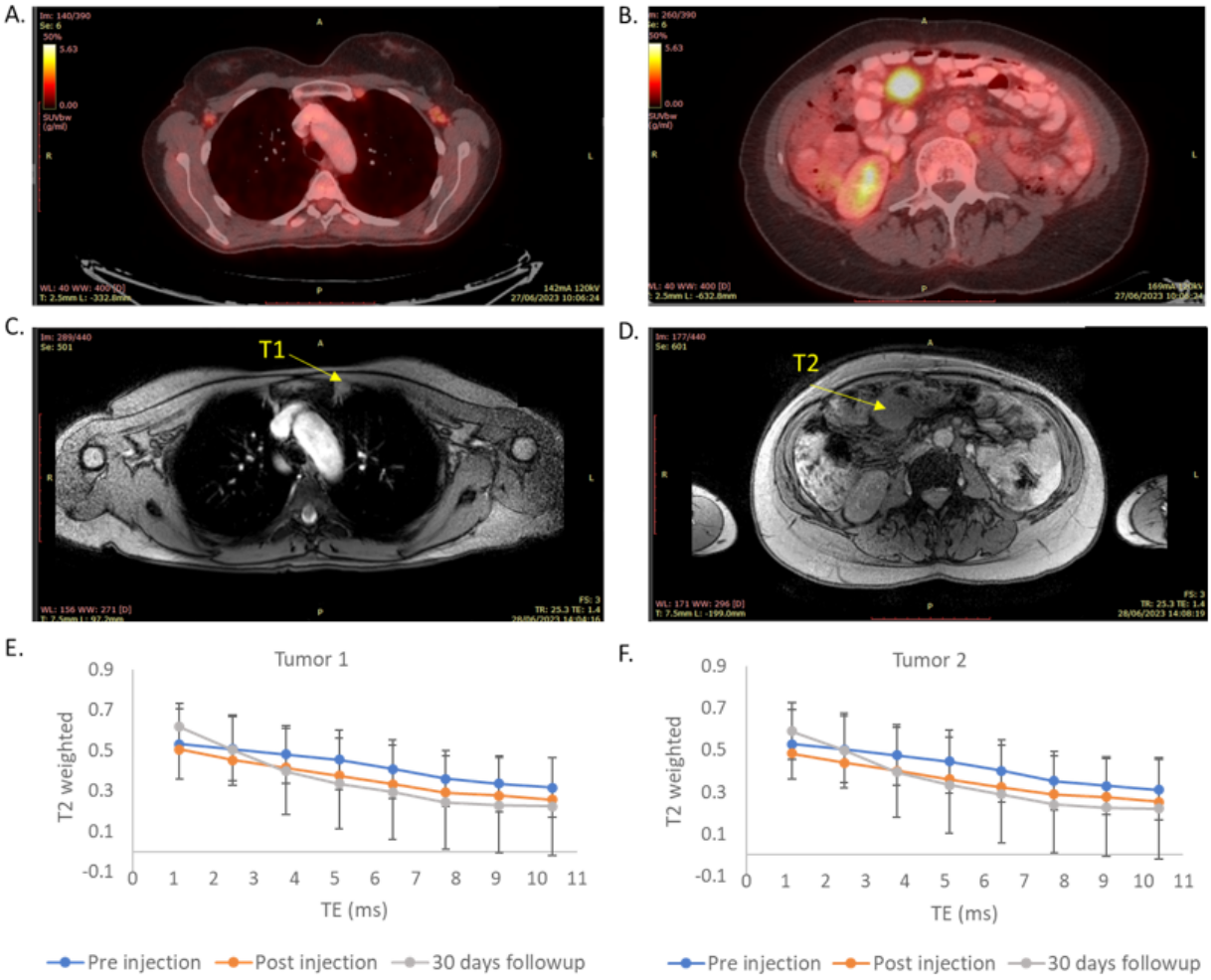

Figure 4: MRI analysis of SaNP accumulation and clearance in and from tumors. Tumors T1 (A, C, E) and T2 (B, D, F). Images from PET-CT scan (A-B), images from MRI scans obtained using a T2* scanning mode (C-D). Yellow arrows indicate tumor locations. T2-weighed signals of tumor T1 (E) and tumor T2 (F).

Disease progression was assessed by CT imaging before treatment (baseline) and after the follow-up period of 30 days by measuring changes in the size of target lesions. The baseline CT results of the patient revealed multiple tumor masses which included a large bilateral tumor mass (LT + RT) in the pelvic area that spread into the iliac and para-aortic lymph nodes.

Table 2 summarizes the size of the target lesions before the treatment/s (baseline) and 30 days after each treatment session. The CT imaging after treatments demonstrated no significant changes in the size of the target lesions, and the patient was categorized as having stable disease (SD) for over 10 months. Notably, no new lesions were observed during this total follow-up period, presumably since the monthly treatments were sufficient to destroy any newly developed metastases, and the patient's clinical condition was improved as determined by the clinician and reported by the patient.

Timeline		Jun-23	Jul-23	Sep-23	Oct-23	Dec-23	Jan-24	Mar-24	Apr-24
Target Lesions #	Organ and Location	Baseline	Treatment No.						
			1	2	3	4	5	6	7
1	Mass: LT pelvis	175	175	175	175	175	180	180	185
2	Mass: RT pelvis	146	146	155	155	158	158	158	167
3	Lymph node: RT iliac vessels	16	16	16	16	16	16	16	18
4	Lymph node: LT para-aortic	15	15	16	15	15	15	15	15
SUM		352	352	361	361	364	369	369	385
%Δ BL				+2.55	2.55+	3.4+	4.8+	4.8+	9.37+
Target Lesion Response		SD	SD	SD	SD	SD	SD	SD	SD

Table 2: CT results and size of target lesions (mm) after each treatment cycle. SD – Stable Disease.

Adverse Events

The treatment was well tolerated, and no clinical signs of toxicity were detected during the treatments or after the 30-day follow-up periods in any of the seven treatments cycles. There weren't any adverse effects related to the SaNP injections and only grade 2 (e.g., mild, and asymptomatic) AEs involving local heat and pain in the lower back area were reported, related to AMF irradiation and eddy currents. This heat and associated pain were attributed to the generation of a hot spot in the above area, as predicted by a thermal simulation model [19]. However, the pain and heat sensations ceased immediately after ending the irradiation procedure.

In addition, during the later treatments when the SaNP dose increased to 0.84 mg/kg, the patient reported heat sensations mainly around the tumors located in the pelvis and abdominal areas. This may indicate selective heating of the tumors due to SaNP permeation and retention in these areas. No additional AEs nor SAEs related to the treatments were observed or reported during the treatments or the follow-up periods. After the last 7th treatment, a SAE was recorded few days after the 30 days follow-up, involving renal failure associated with disease progression but unrelated to treatment. Therefore, the patient could no longer receive additional treatment and trial participation was discontinued. Repeated treatment allowed disease control over a ten-month period; however, the patient died 6 months after treatment discontinuation.

Discussion

Herein, we present a case of a patient with advanced cervical cancer who enrolled in a First-in-Human clinical trial examining the safety of Sarah Nanotechnology System. Throughout the course of the study, the patient received seven consecutive treatment cycles conducted over a period of 10 months with intervals of at least one month between each treatment session. During this long period the overall increase in tumor size (%Δ BL) was only 9.37%.

To our knowledge this is the first report showing the feasibility of extended treatment in a patient that received systemic repeated administration of Sarah Nanotechnology System in the torso area, without any significant AEs, or deleterious SaNP accumulation.

Most treatments that are based on magnetic nanoparticle-based hyperthermia involve local treatment of different cancer types including brain, cervical, prostate carcinoma and soft tissue sarcoma [20-21]. These studies demonstrated that local single-dose treatments were well-tolerated with low or moderate grades of AEs attributed to local heat and/or increased blood pressure due to heating. In a previous case study report, we presented a case of a breast cancer patient that received one treatment cycle of

Sarah Nanotechnology System with an initial SaNP dose of 0.12 mg/kg. This was the first report showing that the treatment was safe and feasible, the ECOG performance status of the patient was not affected, and only local and transient pain in a hot spot was reported [16].

Repeated treatment with Sarah Nanotechnology System resulted in grade 2 AEs involving transient local heat and pain in the lower back during treatments with low SaNP doses of 0.6 mg/kg and pain around the tumors, located in the pelvis and abdominal areas of the patient, after increasing to 0.84 mg/kg SaNP doses and longer irradiation time of 15 minutes. Of note, when pain was reported by the patient, AMF irradiation was immediately discontinued, and the pain and heat sensations immediately ceased. In addition, no significant changes were observed in the clinical pathology parameters, particularly liver enzymes and urine tests during and after treatments. Most liver function parameters returned to baseline levels by the end of treatments.

Notably, according to CT scanning and RECIST criteria, the patient's disease status was categorized as SD, with no evidence of new metastases and a relatively low percentage change from baseline in tumor burden.

Conclusions

The results demonstrate that administration of extended treatment is safe without any toxicities and only few local and transient side effects. Repeated treatment with Sarah Nanotechnology enabled long term control of disease in a patient with no other available treatment options following first-line hormonal therapy. Notably, no signs of progressive disease were observed for over ten months, even though the disease was terminal and already spread into distant sites.

Acknowledgments: The authors would like to thank all the participants in the study, especially Mrs. Cheryl Tal, for her involvement and support, and the clinical team at Rabin Medical Center.

Ethical Guidelines: All experimental procedures were approved by the ethical principles of the Institutional Review Board (IRB), the local Ministry of Health (MOH) and GCP guidelines. This study was guided by ethical standards and national and international laws. The patient signed the consent form after receiving instructions regarding the possible risks and benefits and was granted privacy, confidentiality, and anonymity rights.

Conflicts of Interest: The authors declare the following competing interests: Shir Arbib, Pazit Rukenstein, Sarah Kraus, Hila Ventura-Bixenshpaner, Boaz Shalev, Moshe Eltanani, Udi Ron, Meirav Hirsh-Kovacs, Michal Eck, Doron Suchi, Ofer Shalev, and Arnoldo Cyjon are employees at New Phase Ltd. Efrat Sasson declares no conflict of interest.

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