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Safety and Tolerability of OncoRob © in Patients with Advanced Solid Tumors under Compassionate Use

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Abstract

Relevance: *OncoRob © is the fourth generation of bacteriophage-based, highly selective oncolytic Bio-Robot for systemic, intravenous administration in cancer patients. It can target, destroy cancer cells and avoid innate and adaptive immune response. In addition, it can distinguish between early and late stage cancer.*

Purpose: *The primary purpose is to provide treatment to terminally ill patients, and to evaluate any therapeutic benefit. The secondary purpose is to test the tolerability, safety, and to find a therapeutic dose of OncoRob © after systemic administration in patients with advanced stage III-IV solid tumor malignancies.*

Material and Methods: *OncoRob © was administered to 17 patients in a dose and frequency escalating regimen for an initial period of 6 weeks or 24 doses. Under compassionate use, treatment was continued up to 11 months. The patients were suffering from head & neck, esophageal, skin squamous cell carcinoma (SCC), colorectal, prostate, gastric, melanoma, breast, serous ovarian and clear cell renal carcinoma. OncoRob © was administered in escalating doses twice a week, and after reaching the maximum tolerated dose, the patients were treated at that dose four times a week. Clinical lab parameters, vital signs, electrocardiogram and patients own-reported adverse events were used for evaluation of safety. The maximum dose was based on the first sign of any minor toxic side effect likely related to OncoRob ©. No further concomitant anti-tumor treatment was administered during the study period. All patients were informed about the experimental treatment and signed consent forms. The patients were continuously treated until remission or stable disease was reached. The treatment was stopped after disease progression, non-compliance or upon patient decision. Consequently, the therapeutic effects were evaluated.*

Results: *17 patients range 48-87 years old received OncoRob © starting at a dose of $5x10^9$ particles and increasing to the final dose of $5x10^{10}$ four times weekly. Total doses of 687 were used. The median treatment period was 4 months and the longest 11 months. During the study period 4 patients contracted COVID-19 and therefore, the treatment needed to be interrupted for two weeks. This interruption caused a worsening of cancer conditions. Treatment-related adverse events were fatigue (26/687), increase or decrease in blood pressure (113/687), increase of body temperature (maximum 38.5C, 8/687), pain on the tumor sites (107/687), shivering (130/687), nausea/vomiting (46/687). These side effects were minor and lasted between 20min and 3 hours. The increase of body temperature occurred 5 hours after the treatments and was observed randomly during the treatment. No patient died during the treatment period and no other events were reported. All clinical lab and vital functions remained unaffected. An increase or stable body weight (16/17) and an improvement of general condition (15/17) could be observed in patients. Reductions of tumor size and tumor markers were observed in 15 out of 17 patients. At the end of the 6 week-treatment period, 2 patients were in total remission, 4 with stable disease, 9 with partial response. The survival rate is 10 out of 17 patients after one-year surveillance. Two patients died within one month after termination of the treatment due to progressive diseases.*

Conclusions: *OncoRob © is tolerated without any side effects and dose-limiting toxicities were not observed. Despite extensive prior treatments in some patients, and final stage of disease in 15 out of 17 patients, a positive response or stable disease has been reached during the treatment period. Patients with advanced cancer and large tumor loads should receive more frequent and higher doses under intensive care conditions. Patients in early stage and smaller tumor loads may be treated less intensively.*

Keywords: Cancer, Solid Tumor, Bacteriophage, Biological Robots, OncoRob ©, Oncolytic, Apoptosis

1. Introduction

Gene therapy relies on the delivery of foreign DNA into cells. More than 60% of all reported clinical trials for gene therapy are for cancer [1]. Successful systemic gene therapy has been hindered by vector-related limitations, including toxicity and inefficient gene delivery to tumor cells after intravenous administration [2]. For detailed information it can be referred to many review articles presenting the pros and cons of those gene transporters [3-5]. Gene transfer vectors can be broadly categorized into two groups: mammalian-viral and non-viral vectors. In general, viral vectors tend to provide for longer-term gene expression but often come with additional safety concerns, ranging from fears of generating replication competent virus during vector production, random insertion of the transgene into the genome following treatment, or development of a harmful immune response [6]. Non-viral vectors are less efficient in transferring the genetic cargo through all cellular barriers, they lead often only to a transient gene expression and after systemic application they are quickly inactivated [7]. The immune response can further hinder the repeated dosing for cancer treatment. In order to circumvent this problem, the gene carrier needs to be camouflaged from humoral, cellular and innate immune system. Further, the cargo DNA introduced into the targeted cells are recognized by GMP–AMP synthase (cGAS) and interferon-γ (IFNγ)- inducible protein 16 (IFI16) leading to production of pro-inflammatory cytokines such as interferons [3,8-12]. cGAS-stimulator of interferon genes (STING) pathway is a crucial signaling cascade of the innate immune system activated by cytosol DNA. Recognizing DNA as an immune-stimulatory molecule is an evolutionarily preserved mechanism in initiating rapid innate immune responses against microbial pathogens [13].

Understandably, due to the need for extensive modifications of mammalian and non-mammalian viruses such as bacteriophages or insect viruses (baculovirus) for systemic gene transfer, the success of gene transport in the treatment of cancer and other diseases have made hardly any tangible advance during the last three decades [14-24]. Systemic administration of the wild type bacteriophages, also known as Bacteriophage therapy for infectious diseases has been reviewed and it has shown a very good safety records in clinical trials [25-28]. There are merely a few researchers advocating the use of bacteriophages for gene therapy, and even for systemic administration, over a long period of more than two decades. Their works, however, did not progress beyond in vitro and preclinical studies [29,30]. All clinical trials so far, including all different type of gene-carrier remained limited to a local administration, for example local injection into the tumor tissue. Allvec-1 was the first bacteriophage gene transporter used for systemic cancer treatment in patients [31]. In this study, the safety and efficacy was studied in a small number of patients with solid tumors. Allvec-1 showed no medicine related side effects and a positive response in 1 out of 6 patients. The side effects were related to the tumor destruction rather than to Allvec-1. The next generation of this gene carrier (MetaVec) was given under compassionate-use to two patients with ovarian cancer and colorectal cancer. No adverse reaction was noted in those treatments [32].

OncoRob © is the fourth generation and a new type of DNA and protein transporter based on an extensively modified bacteriophage, and it is especially designed for the targeted treatment of cancer. OncoRob © was designed and manufactured by Novother Cancer Research in New Zealand. It is the first bio-robots of its type that have ever been used in animals and humans for systemic administrations. The preclinical safety of OncoRob © was studied in vitro cell cultures and in several toxicity studies in rats and rabbits. All these studies are not published and were conducted during the research and development and are part of the internal reporting data base. The apoptotic effects were measured by several methods: FACS (Fluorescence Activated Cell Sorting), MTT assay, DNA laddering, intracellular ATP and microscopy. The cancer cell lines in those studies were: breast cancer MCF-7 & 231, cervical cancer Hela, osteosarcoma Saos, esophageal cancer KYSE-30, NSCLC A549, lung adenocarcinoma LXF-289, NSCLC D51, colon cancer HCT-116. OncoRob © could induce complete apoptosis in all cell lines, however, the time point for the maximum effect differed between the cell lines ranging from 2 to 48 hours. In contrast, OncoRob © was inert in healthy Mouse embryonic fibroblasts as control. Four acute toxicity studies in rabbits and four chronic toxicity studies in rats (6 to 8 weeks) all were free of any sign of toxicity. Tissue distribution of OncoRob © in rats showed infiltration of OncoRob © in all organs including the CNS, without expressing its cargo. OncoRob © could be detected in plasma after repeated dosing showing its ability to avoid the immune response in contrast to the wild type bacteriophage.

OncoRob © is designed to target and destroy cancer cells selectively through apoptosis. In order to exert their effects every drug that are used to treat cancer (chemotherapeutics, immunological, monoclonal antibodies, nanoparticles, radionuclides) must reach the targeted cells through the tumor environment at adequate concentrations. For any of these agents to reach the targeted cells, they must overcome a number of impediments created by the tumor microenvironment (TME), beginning with tumor interstitial fluid pressure (TIFP), and a multifactorial increase in composition of the extracellular matrix (ECM) [33, 34]. After IV administration, OncoRob © can find the cancer cells in body and penetrate into larger tumor mass (preclinical data). The surface of OncoRob © can mask it from the innate, adaptive immune and intracellular immune response (in animal studies and clinical data). Therefore, after repeated dosing, its therapeutic effects can be maintained. Foreign nucleotides can induce an intracellular innate immune response. OncoRob © contains specific structures blocking this immune response and hence avoiding the release of cytokines from cells being penetrated by OncoRob ©. After entering the cancer cells, OncoRob © can distinguish between early and late stage of cancer by screening the intracellular make-up of cancer cells and initiate different apoptotic pathways as required. Although, the original design of this

study was focused mainly on safety and tolerability, due to the therapeutic benefit observed during the initial six weeks, the treatment was extended to several months.

2. Material and Methods

This treatment protocol was designed according to the preclinical data generated during the development of OncoRob © and the clinical data of safety and tolerability with Allvec-1 and MetaVec, the predecessor gene carriers to OncoRob ©. The treatment protocol and the clinical facility were approved by the ethics committee. The medication was produced under manufacturing-controlled procedures. Prior to the release of the batch for clinical study, 4 batches of OncoRob © were produced until the best manufacturing procedures were established. All batches are tested for sterility, level of endotoxin according to Ep and USP for injectable solutions, and the quantity of OncoRob © per milliliter.

2.1. Eligibility

Patients with advanced solid tumor malignancies with no therapeutic options available with other standard treatments or refusing the standard treatment, but with a minimum life-expectancy of few weeks were admitted to this treatment protocol. Patients with severe cardiac malfunctions were excluded from the study (table 1). All patients and a first degree relative had to sign a consent form. The consent form, the treatment protocol and medical facility were approved by ethics committee (NZ Proclaimed Hapu "Te Hapu Hoani Haora Hoani O Nu Tireni"). The ethics committee was informed about all deviations from treatment protocol and regularly informed about the progress of the treatment. Further, the treatments were under *NZ Section 25 Medicine Act 1981*.

Inclusion criteria	Exclusion criteria
1. Written consent from both the patient and a close relative/ witness. 2. All patients must have tumor imaging results including chest and abdomen before the study. 3. If signs of brain metastasis presented, then brain CT scan or at least other radiographic images as well. 4. All patient male and females with tumor size of T1-T4. 5. All patient male and female with lymph node involvement including N0-N3. 6. All patient male and female with distant metastasis including M0-M1. 7. Any New Zealand citizen or permanent resident who are member of Hapu.	1. Moderate to severe renal impairment. 2. Moderate to severe hepatic impairment. 3. Patients with tumor induced cardiac tamponade. 4. Patients with systolic and diastolic blood pressure below 60/110 mmHg. 5. Patients with systolic and diastolic blood pressure above 100/160 mmHg. 6. Patients with cardiac arrhythmia. 7. Patients with a general life-expectancy of less than 4 weeks. 8. Pregnant or lactating women. The safety of this therapy on unborn children is not known. Female study participants of reproductive potential must have a negative serum or urine pregnancy test performed within 48 hours before infusion. 9. Uncontrolled active infection. 10. Previously treatment with any gene therapy products. 11. Any uncontrolled active medical disorder that would preclude participation.

Table 1: Inclusion and Exclusion Criteria

2.2. Treatment Protocol

In a safety and tolerability, open-label, single center, dose escalation treatment, the safety, tolerability, as well as the tumor response of OncoRob © was evaluated. Patients started the treatment receiving intravenous twice weekly doses of OncoRob © at 5x109 and increased to 5x1010 four times a week. The treatment was aimed for 24 doses in 6 weeks. The treatment period was 14 months. OncoRob © was given into a 500 ml saline bag and the infusion was run for 60 min. The decision to increase the doses and the frequency of doses was made individually for each patient. The maximum tolerated dose (MTD) was defined as the highest dose level at which a patient experienced dose-limiting toxicities (DLT) after an injection. As premedication 1g paracetamol tablet was given before starting the OncoRob © infusion. During the 14-month treatment period, prednisolone tablets 10mg was also given for 8 weeks to few patients as an additional premedication, which is standard treatment in oncology. We discovered, however, that prednisolone reduces the efficacy of OncoRob © by generally suppressing mRNA synthesis, and therefore it was stopped.

2.3. Treatment Assessment

Safety and toxicity evaluation at baseline included a physical examination, review of systems vital signs, 12-lead electrocardiogram (ECG), and complete blood cell count with differential, hepatic, and renal function assessment. Efficacy was evaluated by the measurements of tumor marker, C-reactive protein (CRP), all visible and palpable tumors, imaging chest radiographs, computer tomography, Magnetic Resonance Imaging (MRI), sonography, or bone scans. The cardiac function was assessed at the beginning

and if necessary on suspected side effects.

2.4. Analytic Methods

Patients were evaluable for safety if at least three low doses of study medication were received. Adverse events and laboratory tests were summarized by normal range. Cumulative dose, dose intensity, and overall dose were summarized descriptively (n, median, range). Tumor response included objective response (complete and partial response) and stable disease. Objective response and stable disease were defined as patients' base values and consequent values during and after treatment. Evaluation of efficacy was a secondary objective of this study. Complete response was defined as disappearance of all clinical evidence of tumor. Partial response was defined as >30% decrease in the sum of the tumor diameters without an increase in any lesions or the appearance of new lesions at the end of the study period. Progressive disease was defined as an increase in lesion by >25% or appearance of new lesions. The patient could achieve stable disease status if criteria for complete or partial response were not met, and progressive disease did not occur within the first 6 weeks of treatment. Data is provided within the manuscript and available upon request from authors. In addition, data is stored by the New Zealand Northland District Health Board.

3. Safety Results

3.1. Patients' Baseline Characteristics

Eighteen patients were screened, and 17 patients entered this treatment. All patients were from the Northland Environmental Health Clinic in Whangarei New Zealand. Their treatment data prior to OncoRob © treatment are summarized in table 2. None of the patients have received any other treatment during OncoRob © period. All other treatments, if any, were stopped at least two weeks prior to the OncoRob © treatments.

Variables	
No. patients (male/female)	17(12/5)
Median age, y (range)	69 (48-86)
Tumor types, n	
Metastatic head and neck squamous cell cancer	1
Metastatic colorectal cancer	2
Metastatic gastric cancer	1
Renal clear cell carcinoma	1
Metastatic oesophageal cancer	1
Skin squamous cell carcinoma	1
Metastatic breast (adenocarcinoma)	1
Prostate cancer	6
Metastatic serous ovarian cancer	1
Metastatic melanoma	2
Previous treatments, n	
Cytotoxic therapy	3
Radiotherapy	4
Surgery	5
Vitamin C	7

Table 2: Safety and Tolerability of OncoRob © in Patients with Solid Tumors: Baseline Characteristics

3.2. Drug Delivery and DLTs

The starting dose of OncoRob © was 5x109 within 3-4 consecutive injections it was increased to the final dose of 5x1010 four times weekly. The patients were observed for 3 hours after each infusion and released from the clinic. There was no sign of toxicity in any patient. The lab parameters were all unaffected by OncoRob © treatment. Therefore, a clear DLT, as known by chemotherapy, could not be observed in this study. Since this study was the first study with OncoRob © in humans, and in order to avoid any risk to the patients, it was decided to stop the dose escalation at the presence of the first potential side effect.

3.3. Patient Disposition

14 out of 17 patients received at least 24 injections within a time period of 6 weeks and were assessable for safety and toxicity. None of the patients experienced side effects related to OncoRob © or stopped the treatment. No patient stopped treatment due to progression of disease. The median treatment period was 4 months, the shortest was 2 months, and the longest survival period 7 years, so far including treatment with previous versions of OncoRob © (table 3).

Type of cancer and number of patients	Number of doses	Treatment duration in months	Incidence of toxic side effects	Survival in months
1x Breast cancer IV	76	8.5	0	13
1x Clear cell renal carcinoma III	14	2	0	>24 remission
2x Colorectal Cancer IV	79	4 and 5	0	>18 and 6
1x Gastric cancer IV	28	2	0	>15
2x SSC head and neck IV	155	8 and 9	0	8 and 9
2x Melanoma IV	31	0.3 and 2	0	2 and 3
1x Serous ovarian cancer	37	3.5	0	>18
6x Prostate cancer I-II &IV	227	1.5, 2, 2.5, 6, 11, 24	0	8 and >12 and >17 and >22 and >24 remission and >84
1x Oesophageal cancer	40	4.5	0	4.5
Total 17 patients	687	Median: 4	0	

Table 3: Pool of Patients, Length of Treatment and Survival

3.4. Toxicity Assessment

Although there were no direct OncoRob © caused side effects, the tumor lysis effect of OncoRob © induced several reactions. Treatment-related adverse events were increase of heart rate and blood pressure, nausea, shivering / shaking, specific pain on the tumor sites in body, fatigue, and slight increase of body temperature 38°C (table 4 and figure 1). These side effects were minor and lasted between 30 min. to 3 hours. These effects could be related to the antitumor effects of OncoRob © rather than a toxic effect. Hence, the highest dose was set at $5x10^{10}$.

Events	N	%	h
Pain on tumor site	107	15.6	1.6
Shivering /Shaking	130	18.9	0.4
Nausea / Vomiting	43	6.2	0.5
Blood pressure change	113	16.4	0.7
Heart rate increase	61	8.9	0.5
Fatigue	26	3.8	3
Increase body temperature	8	1.1	0.5

Table 4: Number of Events After 687 doses (n), Percentage of Events %, Average Recovery Time in Hours (h)

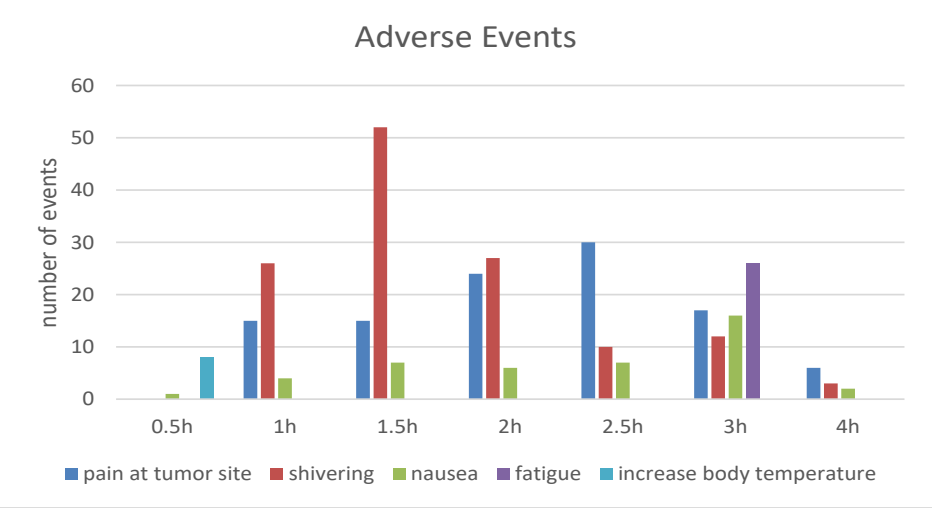


Figure 1: Frequency of Adverse Events and Their Occurrence After the Infusion of OncoRob ©: n= Number of the Events

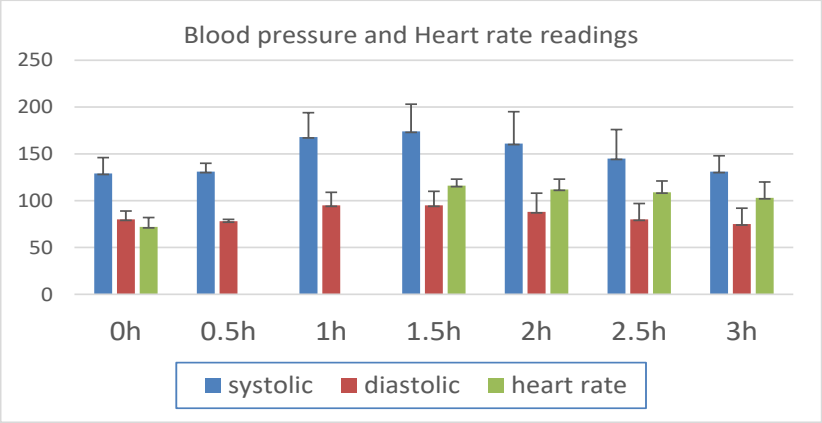


Figure 2: Average Blood Pressure and Heart Rate Readings Pre and Post OncoRob © Infusion. Data Presented with SD; Significant Increase of Blood Pressure (F-test) Between 0.5 h and 1 to 1.5h

The median duration of treatment was 4 months. A total of 488 adverse events were observed. None was OncoRob © related toxicity. None of the patients experienced any severe side effects (Table 3).

3.5. Efficacy Results

All 17 patients were evaluated for tumor response and no patient was withdrawn due to toxicity. Since the primary objective of this study was the safety and tolerability of OncoRob ©, the time points and the frequency of radiological imagines were not optimized and therefore, in the following, the tumor responses for each patient are described.

3.6. Head & Neck Squamous Cell Cancer (SCC)

A 69-year-old male patient entered the treatment in stage T4N3bM1, which was diagnosed 10 years earlier. He had rejected all conventional treatments during the entire period of disease. He was receiving, prior to the treatment with OncoRob ©, only high doses of intravenous vitamin C. This treatment might have had some therapeutic benefit for this patient during the previous years as his disease did not progress. However, vitamin C showed to be ineffective during the last 12 months. No concurrent treatment with OncoRob © was noted. He had received 80 doses of OncoRob © in a period of 8 months. The tumor size was measured and its surface protruding the skin was calculated (figures 3 and 4). The exudates aspirated from the parotid tumor showed only necrotic cells (data not shown). In addition to paracetamol, the patient was also pre-medicated with prednisolone during weeks 5 and 10 of treatment as presented in figure 4. There was an initial decrease in tumor size during the weeks before introducing prednisolone by 62%. It seems that prednisolone antagonized the therapeutic effects of OncoRob © and as the result the tumor size increased rapidly. The sharp increase of tumor load during the period could not be combated by OncoRob © due to the limitation of clinical facility to increase the dose and frequency of treatments.

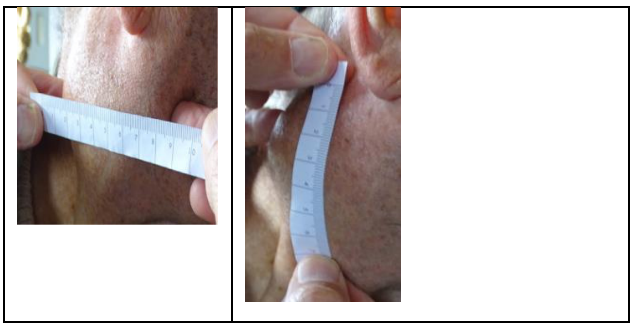


Figure 3: Squamous Cell Carcinoma Stage T4N3bM1 of 69 Years Old Male Pre OncoRob © treatment

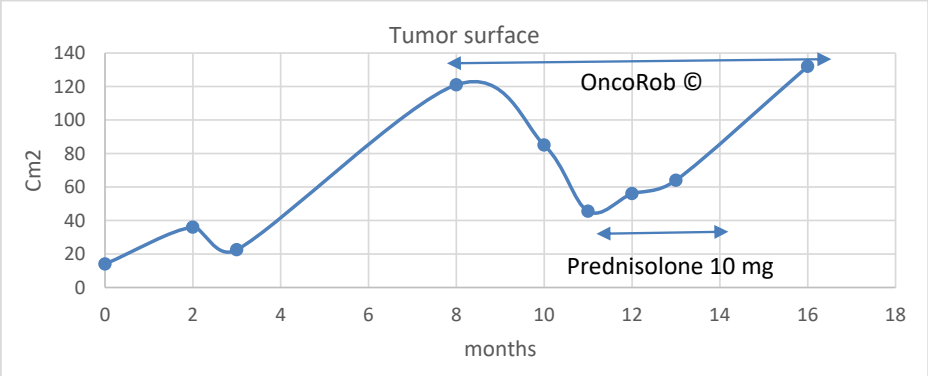


Figure 4: Tumor Measurements Over Time Pre and with OncoRob © Treatment

The literature indicates a doubling time of 30 to 90 days for aggressive SCC [35]. In figure 5, the volume of tumor in the CT scan of 14 months prior to the OncoRob © treatment and the volume of tumor after 16 weeks of treatment with OncoRob © are presented. These real measurements are compared with a projected tumor volume assuming 40 days for doubling (figure 5). The patient decided to end his life using euthanasia.

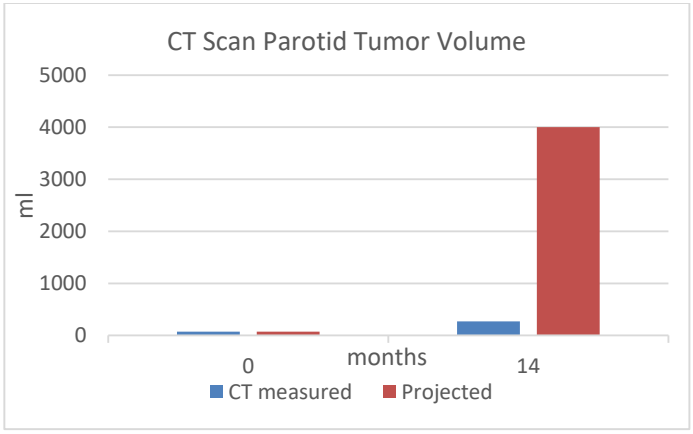


Figure 5: Comparison of the Projected Tumor Volume and the Real Tumor Volume after OncoRob © Treatment

3.7. Head and neck SCC

A male 74 years old with recurrent SCC in stage T4aN2bM0 entered the OncoRob © treatment. He had parotidectomy and lymph nodes resection but rejected any further standard treatment. No concurrent treatment was noted during this study. He had received 75 doses of OncoRob © in a period of 9 months. Prior to the treatment with OncoRob © two tumor masses were visible located on mandibular and cervical regions. Figure 6 shows the diameters of these lesions over the period of treatment with OncoRob ©. There was a clear reduction in tumor size (cervical mass by 57%) until the commencement with prednisolone premedication. Again, prednisolone treatment reduced OncoRob © efficacy. The patient decided to end his life by euthanasia.

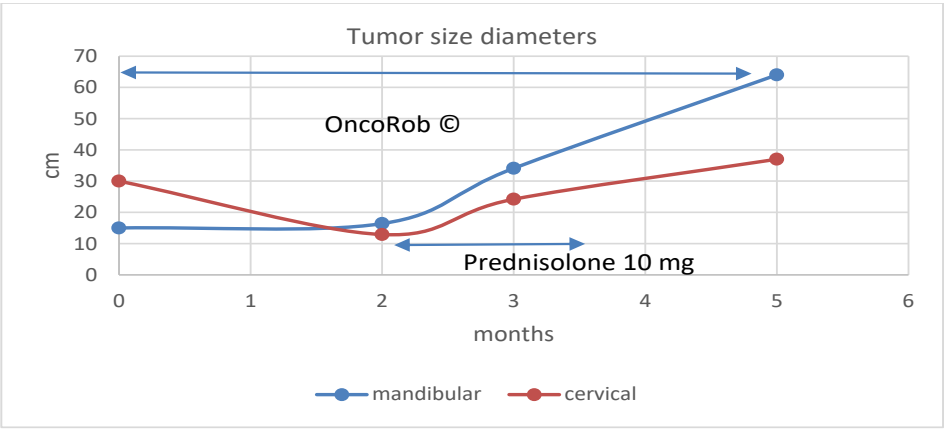


Figure 6: Mandibular and Cervical Tumor Size on OncoRob © Treatment with and Without Prednisone

Citation: Nosovich, A. A., Fournier, S. (2026). Safety and Tolerability of OncoRob © in Patients with Advanced Solid Tumors under Compassionate Use. *J Cancer Res, 4*(2), 1-28.

3.8. Oesophageal Cancer

A 64-year-old female patient in stage T4N4M1 entered the treatment with OncoRob ©. She had severe problem swallowing and she was scheduled for an esophageal stent. There was also multiple liver metastasis presented in MRI. She had no previous or concurrent treatments. She received 40 doses of OncoRob © over a period of 19 weeks. No side effect was recorded during the OncoRob © treatment. There were episodes of nausea and shivering during and after OncoRob © treatment which can be related to the tumor destruction and release of inflammatory cytokines and they did not last more than 20 min. She had contracted COVID-19 and the treatment with OncoRob © was paused for 3 weeks. In addition, from 2nd to 17th weeks of OncoRob © treatment, she was pre-medicated with prednisolone. These two factors have reduced the chances to maximize the therapeutic effects of OncoRob © for this patient. Nonetheless, we could see a reduction of oesophageal tumor size in Positron Emission Tomography scan compared to CT scan five months after the start of treatment with OncoRob © (figure 7 and 8). This reduction of tumor size, by 37%, was accompanied by clinical improvement, including ability to swallow normal food, during the treatment. OncoRob © did not have any effect on liver metastasis (figure 8). The metastatic disease on liver site was progressive. One month after ending OncoRob © treatment, the patient passed away due to the metastatic diseases in liver.

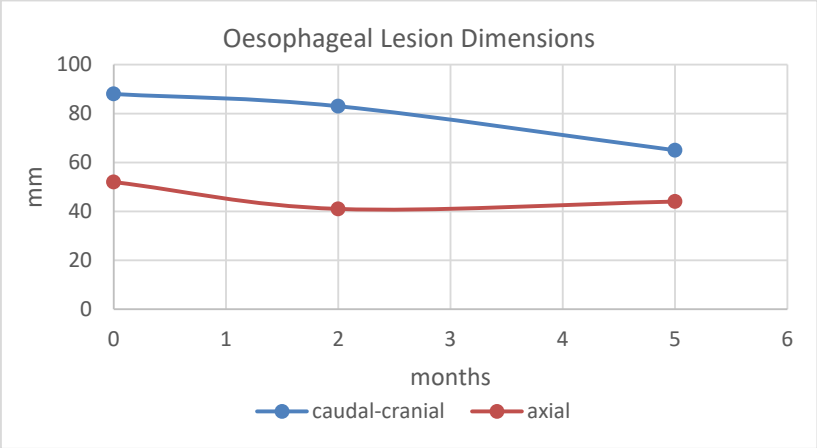


Figure 7: Measurements of Primary Tumor Site in Oesophagus. Start of OncoRob © Treatment was Months 0

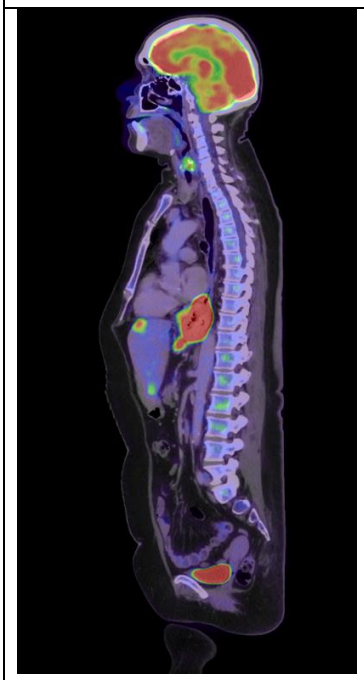
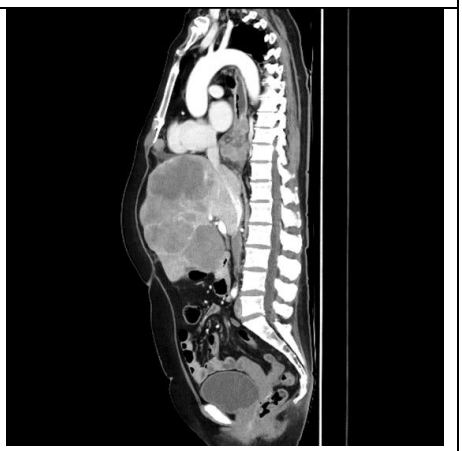
CT/PET scan: before OncoRob ©.	CT scan: 5 Months after OncoRob ©.
	

Figure 8: Oesophageal Patient's CT/PET Scan Images, Pre and Post OncoRob © Treatment

3.9. Adenocarcinoma Breast

A 73-year-old patient with estrogen and progesterone positive and human epidermal growth factor recepton 2 (Her-2) negative receptors type of breast adenocarcinoma in stage T4N4M2 entered the treatment with OncoRob ©. Prior to the treatment with OncoRob © she had already substantial tumor deposits in pleura severely affecting normal breathing. She underwent previously 3 years treatment with chemo and hormonal therapies. She did not have any concurrent treatment. She was treated with 76 doses of OncoRob © for a period of 8.5 months. The treatment was well tolerated and no OncoRob © inherent side effect on any lab parameters or clinical observations were noted. According to the patient wish OncoRob © treatment was stopped. The patient survived 14 months after the beginning of treatment with OncoRob ©. Figure 9 shows the level of tumor marker cancer antigen 15-3 (CA153) dependent on the frequency of OncoRob © administrations. The serum level of CA153 was stabilized or increased depending on the frequency of OncoRob © administrations (figure 9). During the pre-treatment period with OncoRob © the serum level of CA-153 was continuously increasing. This increase came to a hold when 24 doses of OncoRob © was administered during the first 2.5 months. CA-153 level increased again when the frequency of OncoRob © treatment was reduced.

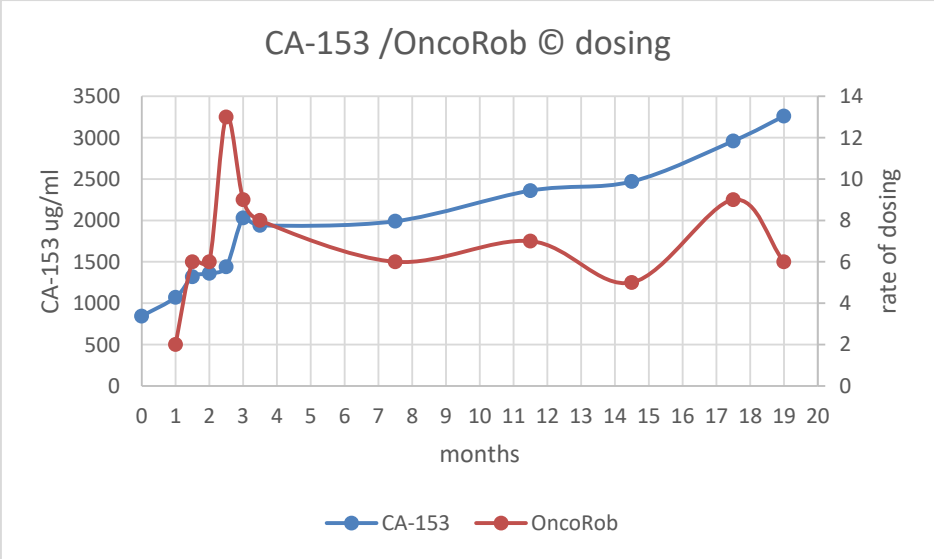


Figure 9: Correlation Between Tumor Marker CA-153 (ug/ml) and the Number of OncoRob © Doses (n) Between Measuring Time Points

3.10. Gastric Adenocarcinoma

A 71-years-old male patient with gastric adenocarcinoma in stage T4N4M1 with multiple lymph nodes and liver metastasis was treated with 28 doses of OncoRob © for a period of 2 months. OncoRob © did not cause any side effect and the treatment was very well tolerated. During the weeks 0 and 6, prior to OncoRob © treatment there was a steep increase of Carbohydrate antigen 19-9 (CA-199) plasma level. There was a reduction in the plasma level of the tumor marker CA-199 after the treatment with OncoRob © (figure10).

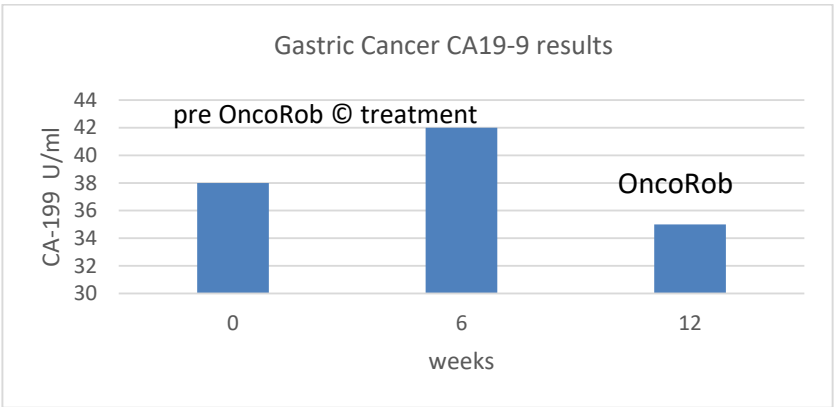


Figure 10: Gastric Cancer Patient's Tumor Marker Results Pre and During OncoRob © Treatment

Citation: Nosovich, A. A., Fournier, S. (2026). Safety and Tolerability of OncoRob © in Patients with Advanced Solid Tumors under Compassionate Use. *J Cancer Res, 4*(2), 1-28.

Prior to OncoRob © treatment two CT scans were obtained and those images showed a rapid increase of tumor size within 4 weeks. OncoRob © treatment was started 4 weeks after the last CT scan. During this period the disease may have progressed but no images immediately before the start of OncoRob © treatment are available. Therefore, the therapeutic benefit of the treatment might be underestimated. Nonetheless, the results of CT scans showed a reduction of gastric tumor site by 19% on the major curvature, and increase of the angle of the curvature indicating improvement of normal anatomical shape of this gastric region affected by the tumor (figures 11 and 12).

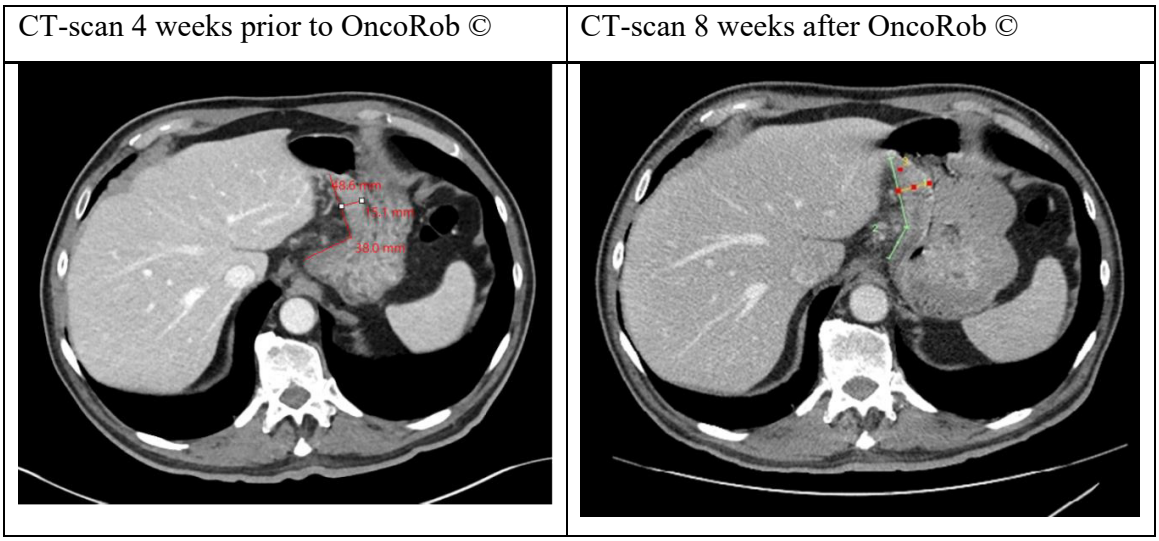


Figure 11: Gastric Cancer Patient's CT Scan Results Pre and Post OncoRob © Treatment

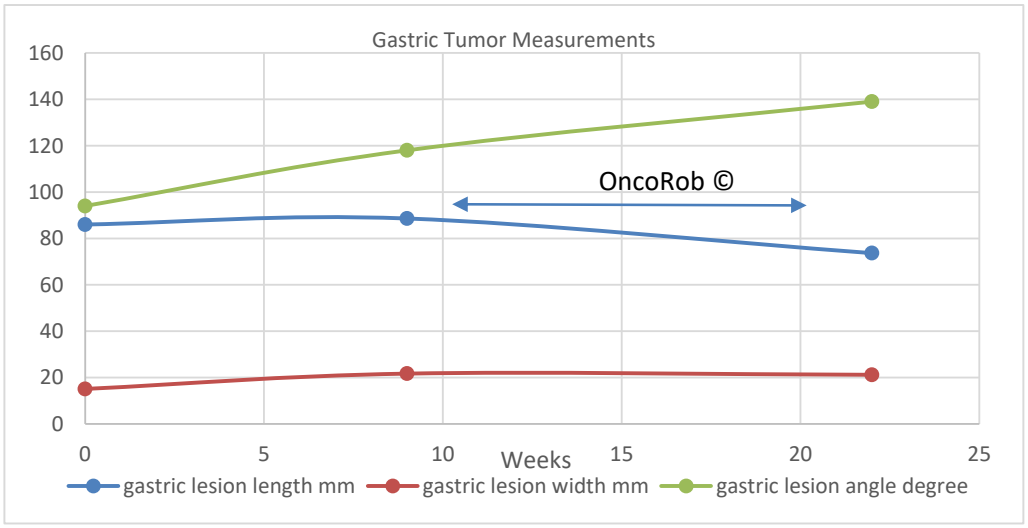


Figure 12: Gastric Tumor Measurements Pre and Post OncoRob © Treatment

Figure 13 shows the diameter of the liver lesions in segment 8 and 2. The lesion in segment 2 has resolved totally but there was a slight diffuse increase in the size of the lesion in segment 8 (figure 14). As explained before due to the lack of images immediately before the start of the treatment the extend of therapeutic effect on this lesion might be underestimated. Another explanation for the increase in size for this lesion is an inflammatory reaction caused by apoptosis.

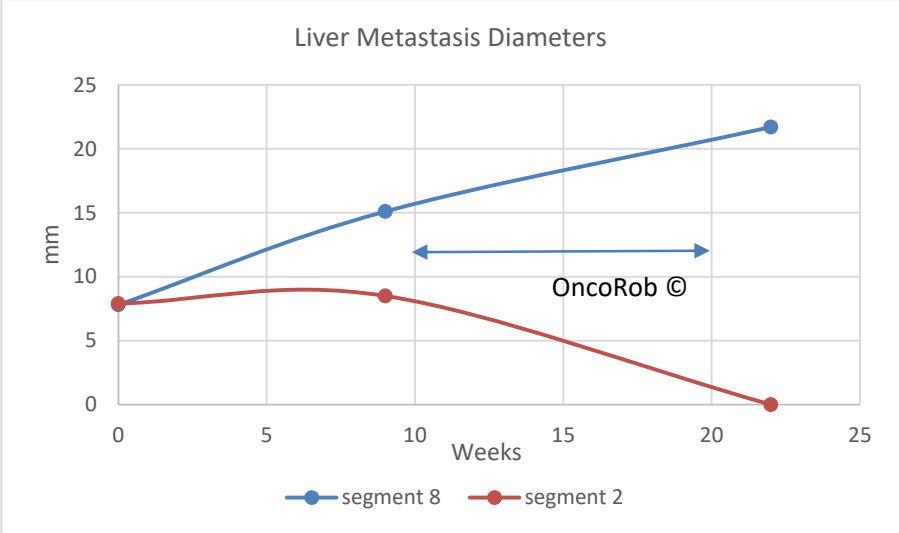


Figure 13: Gastric Cancer Patient's Liver Metastasis Pre and Post OncoRob © Treatment

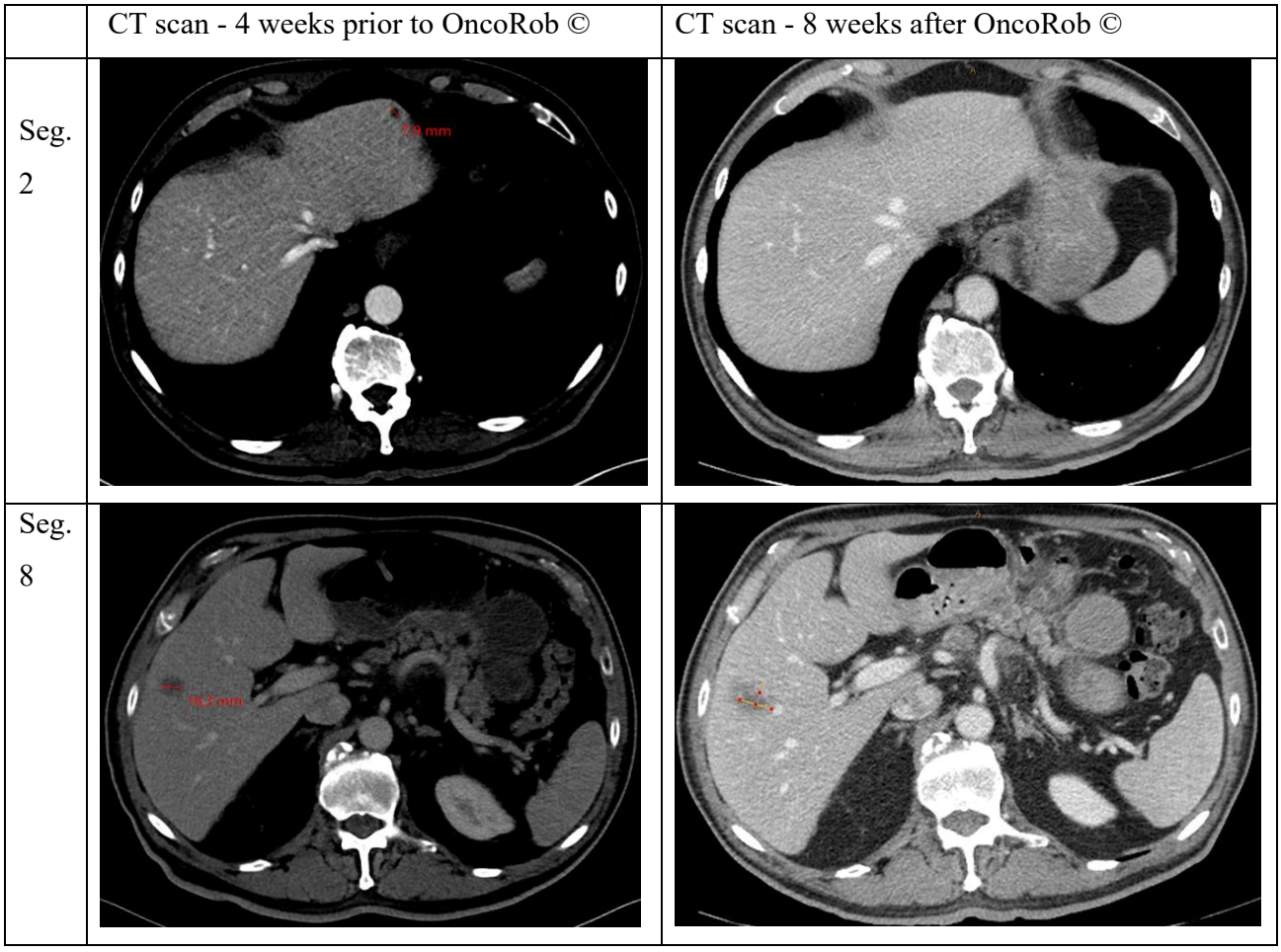


Figure 14: Liver Images of Gastric Cancer Patient's Pre and Post OncoRob © Treatment

3.11. Sigmoid and Prostate Adenocarcinoma

A 71-year-old patient with dual cancer of sigmoid stage T4N4M1with extensive metastasis in liver and severely affecting the patency of sigmoid, and prostate stage T3N2M1has entered the treatment with OncoRob ©. The patient was given only few weeks survival prognosis. The patient did not receive any previous treatment for sigmoid cancer but had received anti-testosterone treatment two years earlier. During the treatment with OncoRob © the patient did not have any other concomitant treatment. The

patient was treated with 45 doses of OncoRob © for a period of 5 months and it was well tolerated. Shivering and nausea were the main reactions and they lasted only for few minutes during the treatments. Few weeks after the start of the treatment the patient could pass again normal stool. As the CT images (figure 15 and16) show OncoRob © reduced the tumor size on the primary tumor site by 31% in sigmoid but it had limited effects on the liver metastasis. The reduction of the sigmoid tumor size was also accompanied by a reduction of serum carcinoembryonic antigen (CEA) level 3.5 months after the start of the treatment (figure 17).

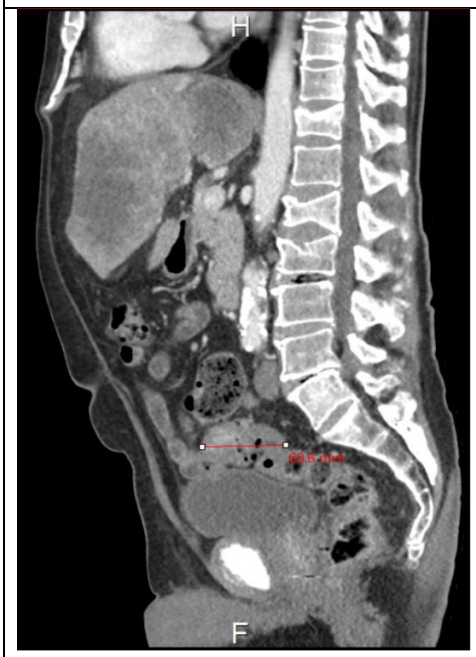
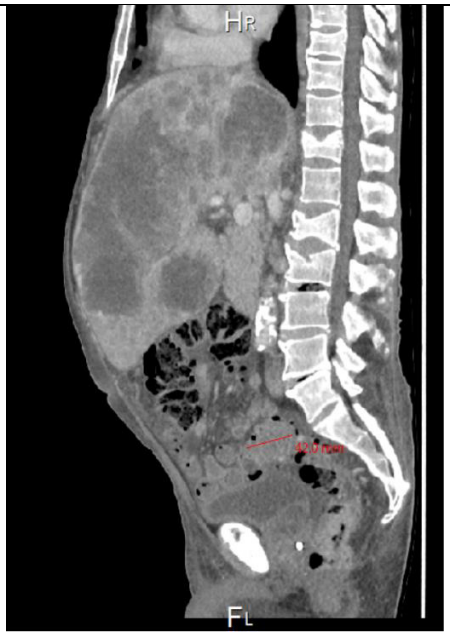
6 weeks prior to OncoRob © treatment.	4.5 months after the start of OncoRob © treatment.
	

Figure 15: Sigmoid and Prostate Patients's CT Scan Images Pre and Post OncoRob © Treatment

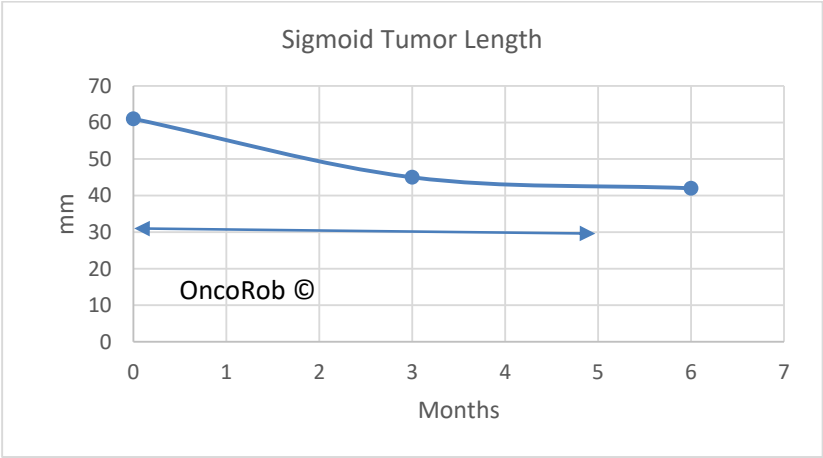


Figure 16: Sigmoid Tumor Size During OncoRob © Treatment

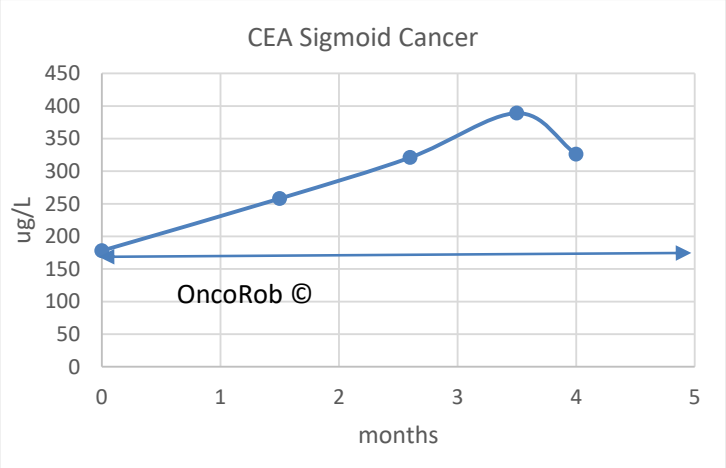


Figure 17: Sigmoid Cancer Patient's CEA Tumor Marker During OncoRob © Treatment

Further, the prostate-specific antigen (PSA) level declined 1.5 months after the start of treatment with OncoRob © (figure 18). Despite very good tolerability and improved clinical status of the patient, the liver metastasis had increased in size and as the result liver parameters and function continued to worsen. Therefore, the treatment after 3 months was stopped. The patient survived 2 months after the end of the OncoRob © treatment.

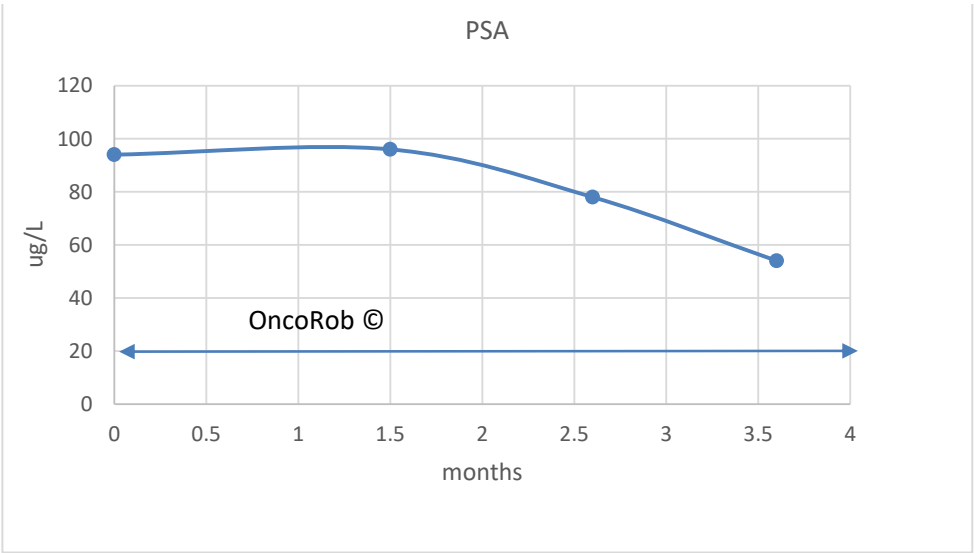


Figure 18: Sigmoid and Prostate Cancer Patient's PSA Levels During OncoRob © Treatment

3.12. Rectal Adenocarcinoma

A 58-years-old female patient with stage T4N2M1 of adenocarcinoma of rectum was admitted to the treatment with OncoRob ©. She did not have any previous or concomitant treatment. In the CT images there have been already two liver lesions prior to the OncoRob © treatment. The central liver metastasis in the vicinity of the major portal vessels was deemed to be surgical non-operable. As the result no further attempt was made to remove the tumor from primary rectal site. Therefore, prior to the treatment with OncoRob © a survival time of 4-6 months was given. In a period of 4 months, 34 doses of OncoRob © were administered. OncoRob © was well tolerated and only mild shivering, slight decrease of blood pressure and back pain surrounding the lumbar area were recorded. These effects lasted only for few minutes. We could see a delayed response, 2-5 weeks, of OncoRob © on serum levels of CEA. There was a decrease of CEA level depending on the frequency of the treatment, figure 19. Nineteen doses of OncoRob © decreased the CEA level between week 4-7. There were only 2 treatments between weeks 7-10 as the result CEA level increased again. Ten doses of OncoRob © between weeks 10-14 decreased the CEA level on week 19th of treatment.

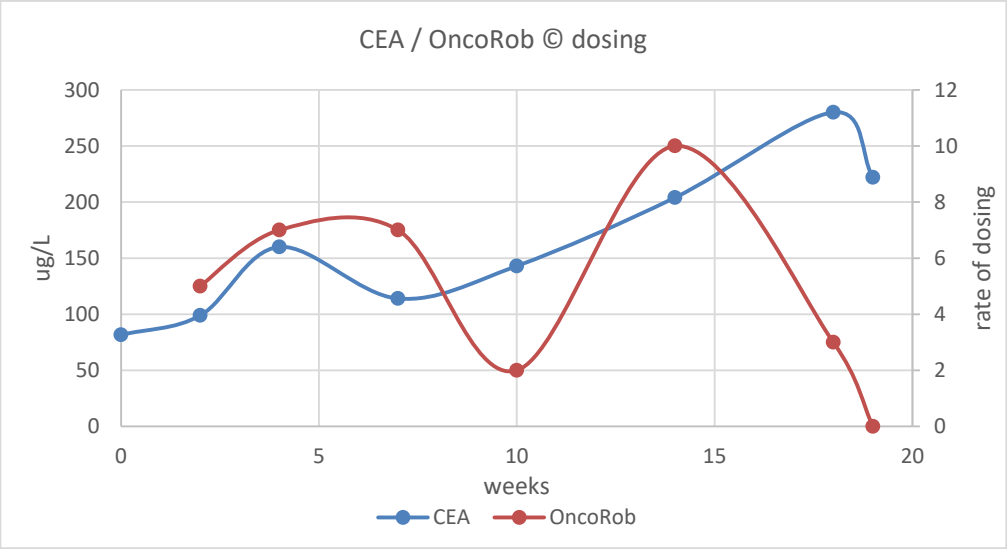


Figure 19: Correlation Between Serum CEA and the Number of OncoRob © Doses (n) Between Measuring Time

MRI also showed a reduction of primary tumor size in rectum by 34% after 15 weeks of treatment (figure 20 and 21). During the same period the peripheral liver lesion was stable and the growth of the lesion in central lobe was slowed down (figure 22).

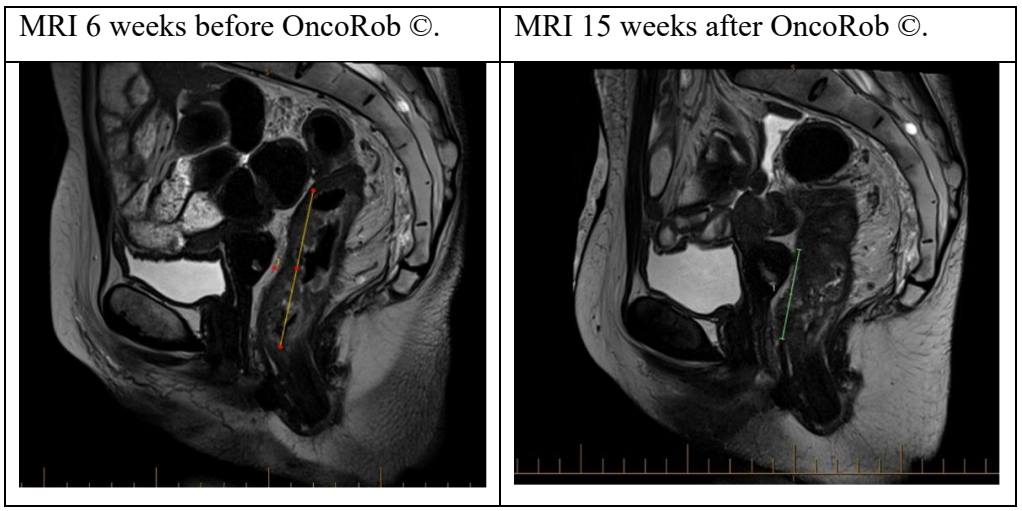


Figure 20: Rectal Cancer Patient's MRI Images 6 Weeks Prior and 15 Weeks Post OncoRob © Treatment

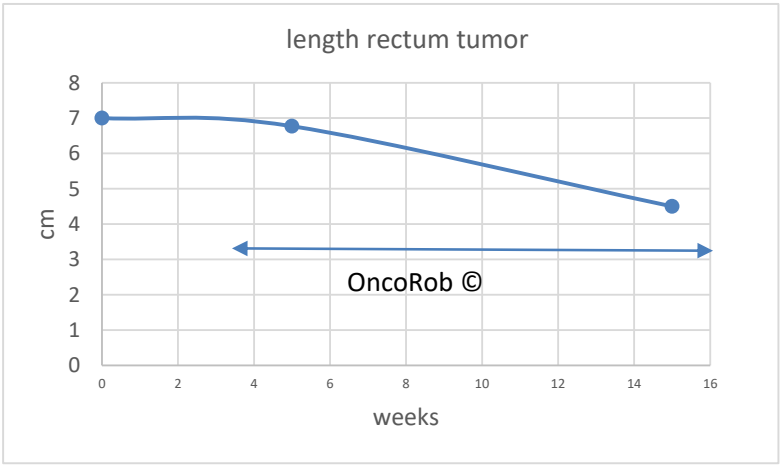


Figure 21: Rectum Tumor Measurement Pre and During OncoRob © Treatment

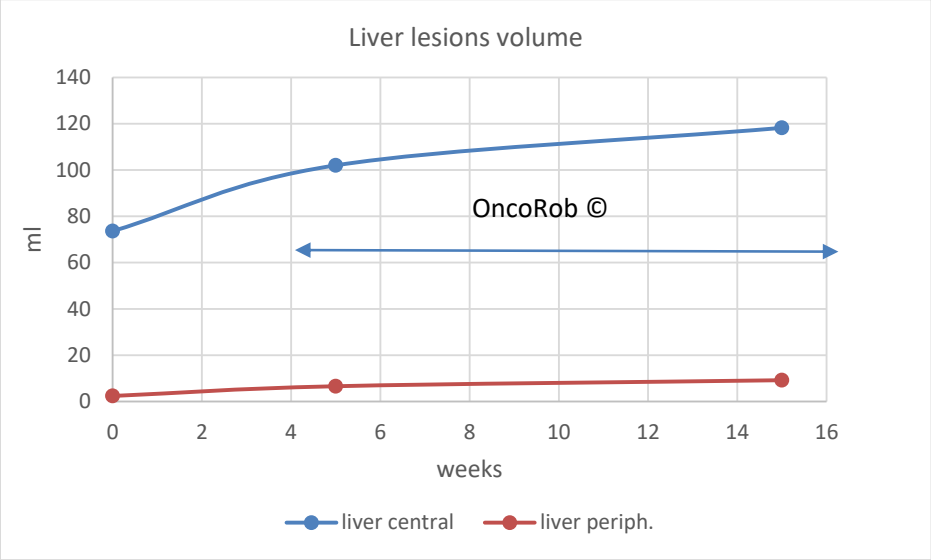


Figure 22: Rectal Patient's Liver Lesions Volume Pre and During OncoRob © Treatment

OncoRob © treatment was stopped after 19 weeks and the patient entered a surveillance period. The patient is still alive after 18 months from the beginning of treatment.

3.13. Clear Renal Cell Carcinoma

A 48-year-old male patient with clear renal cell carcinoma in stage T3N0M0 entered the treatment with OncoRob ©. The patient did not have any previous or concomitant treatments, but he was scheduled for nephrectomy later in 6 weeks. During this period, he was treated with 9 doses of OncoRob ©. The treatment was well tolerated and major events were moderate pain on tumor site during and after treatment with OncoRob © and shivering. These effects lasted for less than 45 min. The histological finding of the tumor after nephrectomy indicated 20% of apoptotic and necrotic region in the total tumor mass (figure 23) and extension of tumor in renal vein within its segmental branches and in inferior vena cava. Despite invasive tumor the margin of the tumor was not involved.

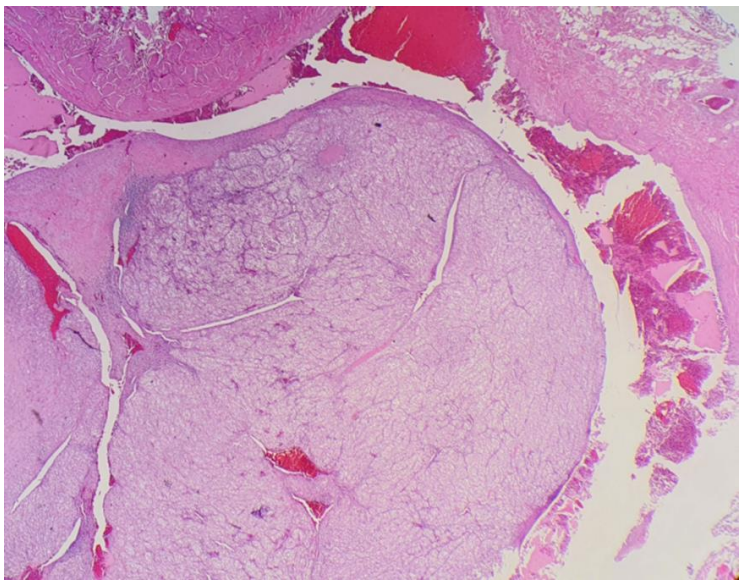


Figure 23: Clear Renal Cell Carcinoma: Image of the Tumor after Nephrectomy

The patient started a new course with 5 doses of OncoRob © after the operation. Patient showed moderate to severe pain in the site of nephrectomy. The pain lasted for 45 min. and the pain became less as more doses of OncoRob © was administered. The patient received in total (pre- and post-operation) 14 doses of OncoRob ©. He is still under surveillance and in total remission after 2 years.

3.14. Serous Ovarian Cancer

An 88-year-old patient with serous ovarian cancer in stage T4N4M1 with peritoneal metastases along the surface of the spleen and liver and lymphadenopathy along the para-aortic region, and in the bilateral iliac entered the treatment with OncoRob ©. She had previously hysterectomy but she rejected all other conventional treatments. She was treated

with 37 doses of OncoRob © in a period of 3.5 months. The treatment was very well tolerated. The patient experienced moderate pain in iliac and in retroperitoneal region starting about an hour after OncoRob ©. This pain lasted up to an hour. No further effects were noted. The effect of OncoRob © on tumor marker cancer antigen 125 (CA-125) was monitored during the course of treatment. We could observe a reduction of CA125 during the first 8 weeks of treatment with 28 doses of OncoRob ©. During the following 4 weeks the frequency of OncoRob © was dropped to 6 doses. As the result CA-125 increased again. This increase became more significant as the treatment was stopped (figure 24). The patient is alive after 16 months of surveillance.

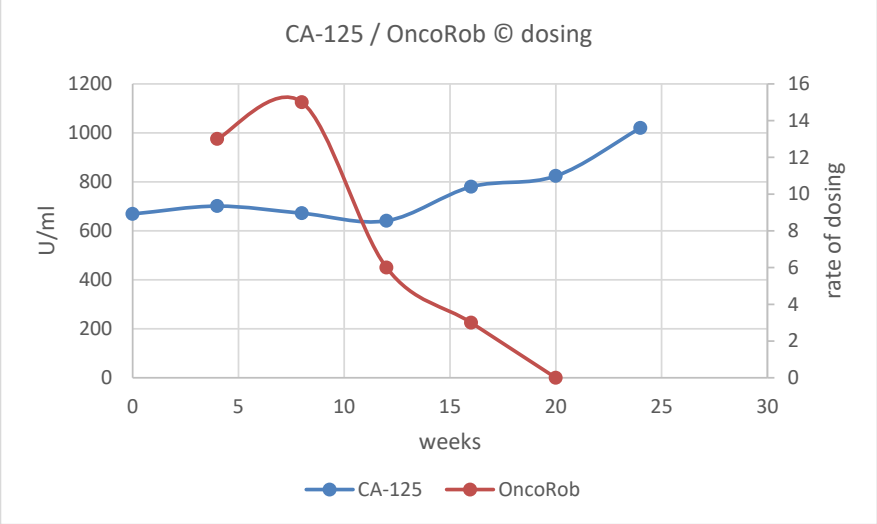


Figure 24: Correlation Between Plasma Level of CA-125 and the Number of OncoRob © Doses (n) Between Measuring Time Points

3.15. Adenocarcinoma Prostate

A 61-year-old patient with prostate cancer in stage T4N2M0 had commenced the treatment with OncoRob ©. Despite histological Gleason 9 (4+5) he had rejected all conventional treatments before and during the treatment with OncoRob ©. Prior to the OncoRob © treatment he showed a large right transitional zone lesion with extra-prostatic extension anteriorly with bladder infiltration and right seminal vesicle involvement. The patient complained about severe outflow obstruction with chronic urinary retention and infection. Therefore, the patient underwent urethra-cystoscopic laser surgery. The patient has received in total 85 doses of OncoRob © over a period of 11 months. OncoRob © was very well tolerated. The patient presented slight shivering and cold feeling about an hour after the infusion of OncoRob ©. Interestingly, the patient complained about slight biting pains in lower pelvis and iliac region. The pain coincided with shivering and lasted for few hours. MR images showed a reduction in volume of both prostate and lesion by 50% (25 and 26).

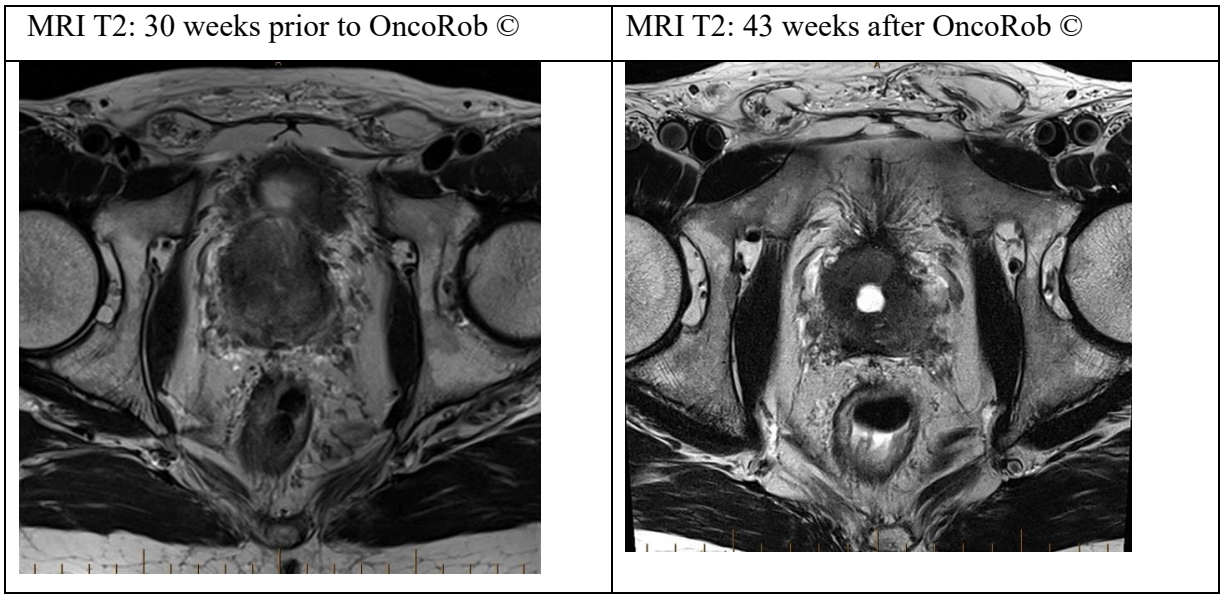


Figure 25: Prostate Cancer Patient's MRI Images Pre and Post OncoRob © Treatment

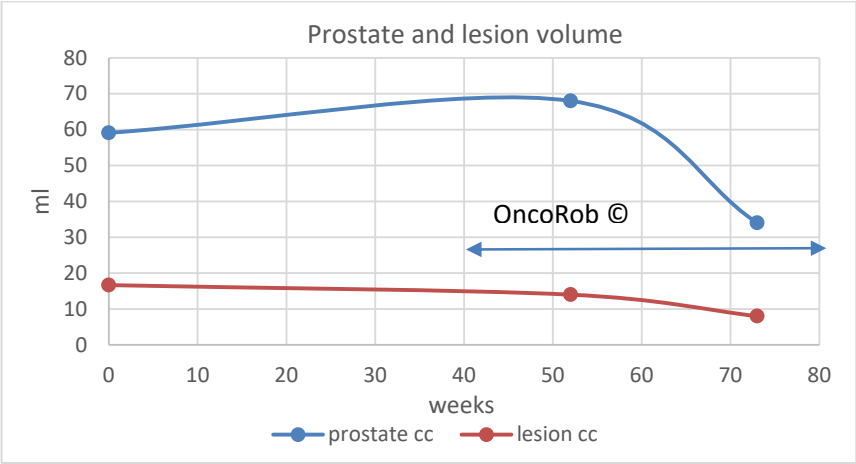


Figure 26: Prostate and Lesion Volumes Pre and During OncoRob © Treatment

Further, OncoRob © could stop the spread of metastasis to new lymph nodes, and already affected lymph nodes were unchanged. These therapeutic effects of OncoRob © were accompanied by changes of plasma PSA levels. The PSA level well correlated with the frequency of OncoRob © dosing (Figure 27).

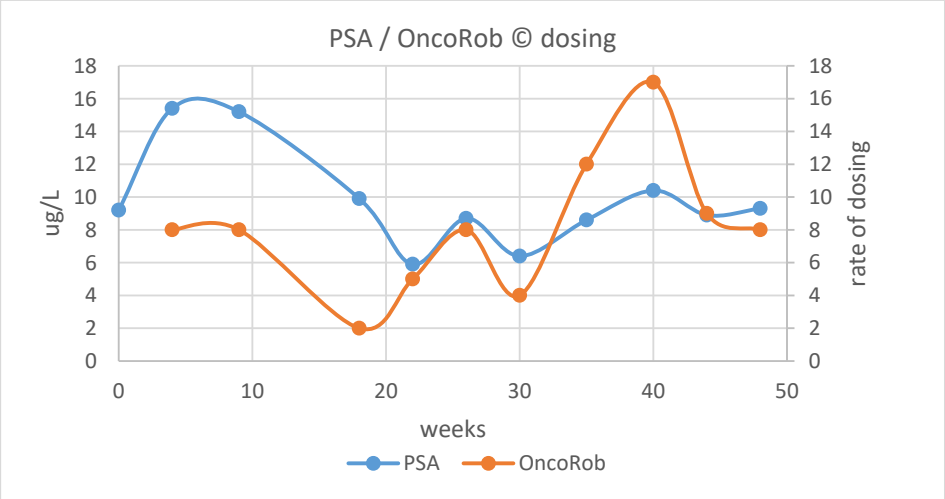


Figure 27: Correlation Between Plasma Level of PSA and the Number of OncoRob © Doses (n) Between Measuring Time Points

Although the original length of treatment was planned for only 26 doses of OncoRob ©, due to the good clinical results, excellent safety and the wish of the patient, the treatment was continued for 85 doses for a period of 11 months. After this period the patient was encouraged to stop the treatment with OncoRob © and to consider standard conventional treatments. The patient has received testosterone blocker and underwent radiotherapy 4 months after the end of OncoRob © treatment. Following the completion of radiation therapy, the images showed metastatic deposition in cervical vertebra. MR images showed that there was no bony metastasis during and after OncoRob © treatment.

3.16. Prostatic Adenocarcinoma

An 80-year-old patient with most aggressive (ISUP 5) metastatic prostate adenocarcinoma in stage T4N4M1 with extended bone metastasis of entire skeleton had entered the treatment with OncoRob ©. Prior to the treatment with OncoRob © the patient presented hematuria and clot retention. The patient underwent emergency resection of tumor mass within his bladder, but rejected all other conventional treatments and was receiving only high dose intravenous vitamin C. He was treated with 38 doses of OncoRob © over a period of 6 months. There was an increase of blood pressure and shivering starting about an hour after the infusion with OncoRob ©. The high blood pressure was treated only with Nitro spray and it returned to normal values after 20-30 min. No other reactions were noted during and after the treatment. The patient responded very well on OncoRob © treatment. There was a drop on serum PSA level to the normal values coinciding with the frequency of OncoRob © dosing (figure 28).

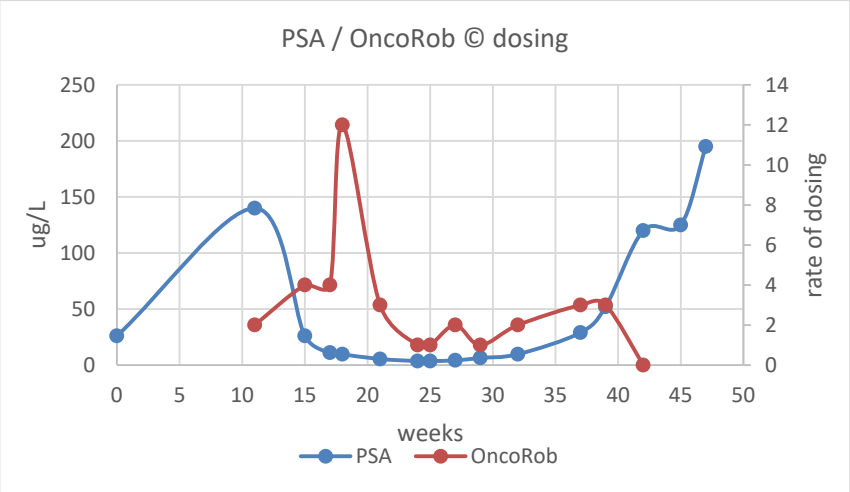


Figure 28: Correlation Between Plasma Level of PSA and the Number of OncoRob © Doses (n) Between Measuring Time Points

The patient complained about pain in his bones, due to bony metastasis, before the treatment with OncoRob ©. Therefore, the high alkaline phosphatase was used as parameter to monitor the disease progression. There was a significant reduction of serum Alkaline Phosphatase (ALP) after the treatment with OncoRob © correlating with the frequency of dosing. During the treatment the pain in bones ceased completely (figure 29).

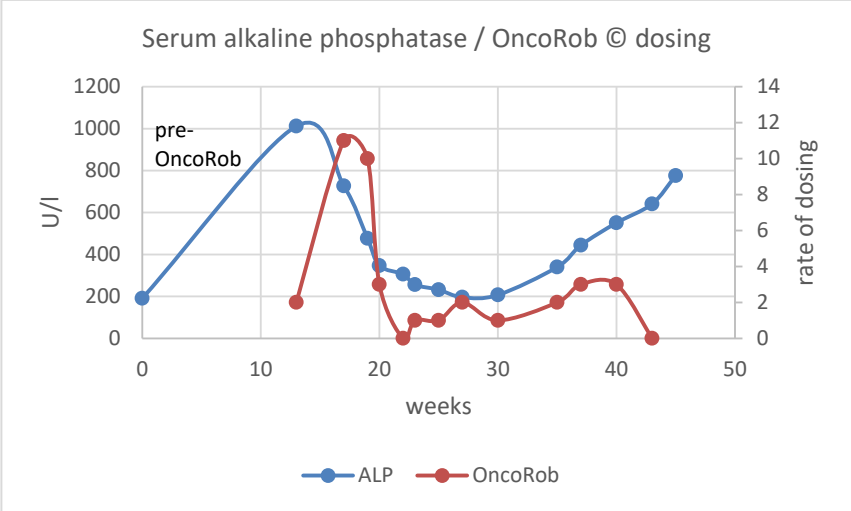


Figure 29: Correlation Between ALP and the number of OncoRob © doses (n) between measuring time points

The urinary retention prior to the treatment with OncoRob © led to hydronephrosis with increase of serum creatinine levels. During the treatment with OncoRob © creatinine levels improved and the patient did not complain about urine retention. These changes seemed to be dependent on the frequency of dosing (figure 30).

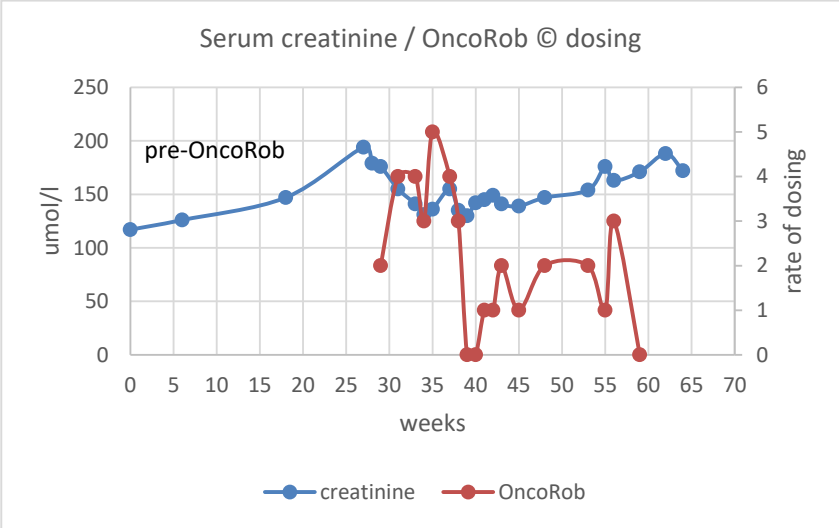


Figure 30: Correlation Between Serum Creatinine and the Number of OncoRob © Doses (n) Between Measuring Time Points

The patient was advised to continue the regular treatment due to the advanced stage of his disease and the high level of malignancy with his prostate cancer. However, due to the improvement of clinical symptoms and lab parameters, the patient decided to stop regular treatment with OncoRob ©. The condition of the patient worsened dramatically and the bony metastasis reappeared leading to severe bone marrow depression. None of the standard treatments were effective. The patient survived two months after stopping OncoRob ©.

3.17. Adenocarcinoma Prostate

A 75-year-old patient with extensive involvement of both prostate lobes with ISUP grade 1in stage T2cN0 has entered the treatment with OncoRob © without having any other concurrent treatment for prostate cancer. The patient showed mild urinary retention. MRI scan showed, prior to OncoRob © treatment, lesions in left midgland transitional zone (PIRADS-2) and broad diffusion restriction in the posterior peripheral zone bilaterally suspicious for tumor PIRADS-5. In addition, benign hypertrophic prostate (BHP) was noted with the prostate volume of 45 ml. He was treated with 14 doses of OncoRob © in a period of 7 weeks. Patient tolerated the treatment very well. The reactions to the treatment were feeling cold and low blood pressure. These effects lasted up to 20 min. There was a clear reduction of serum PSA after the treatment with OncoRob © (figure 31).

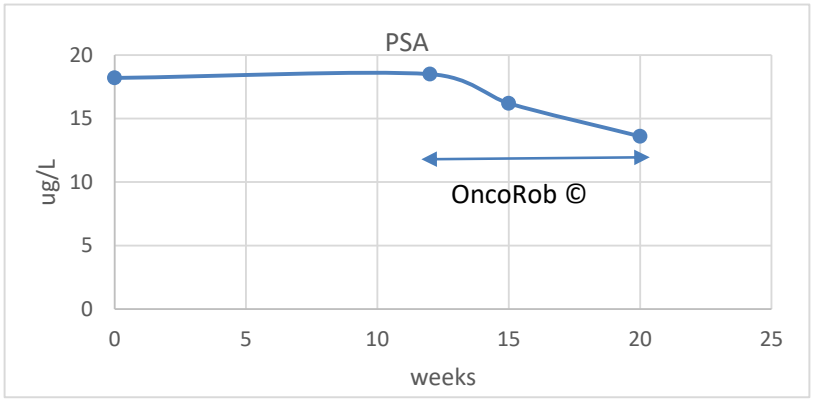


Figure 31: PSA Levels Pre and During OncoRob © Treatment

The MRI scan in Apparent Diffusion Coefficient (ADC) analysis showed extensive focal restriction of diffusion including midline of the peripheral zone and reaching from mid gland to the apex. This lesion doubled in size within 16 weeks prior to OncoRob © treatment. OncoRob © treatment reduced the length and volume of this lesion by 18% (figure 32 and 33). The pre-treatment MRI was performed 4 months prior to the start with OncoRob © treatment. Therefore, the real therapeutic benefit observed here might have been even greater if the images were obtained immediately before the start of the treatment.

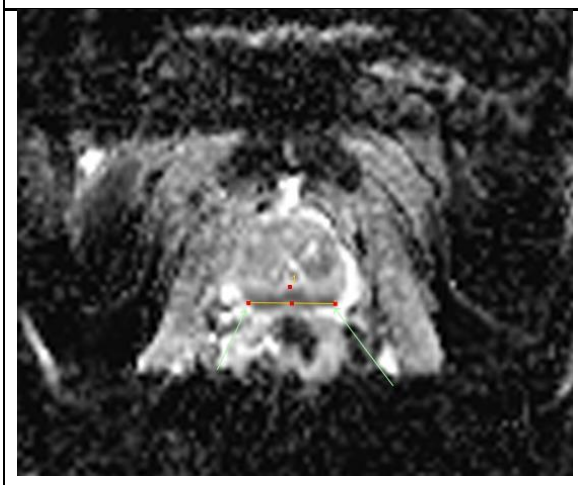
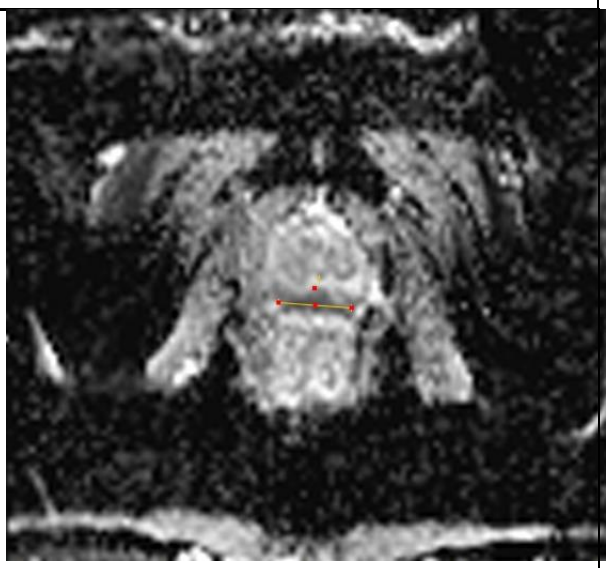
ADC MRI peripheral zone 4 months prior to OncoRob ©.	ADC MRI peripheral zone 7 weeks after OncoRob ©.
	

Figure 32: Prostate Cancer Patient's MRI Images Pre and Post OncoRob © Treatment

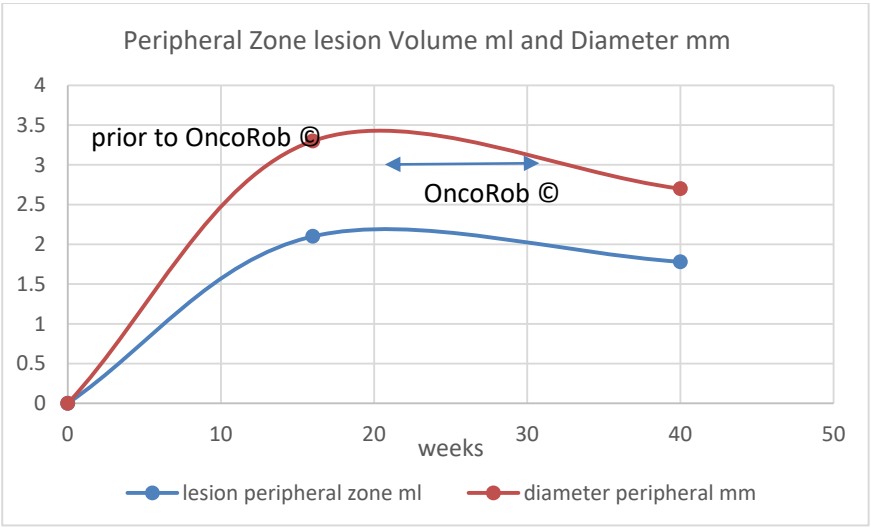


Figure 33: Peripheral Zone Lesion Volume and Diameter Pre and Post OncoRob ©

Further, ADC analysis of the MRI scans in pre and post OncoRob © treatment could show a reduction in size of the lesion in transitional zone by 53% (figures 34 and 35).

MRI ADC transitional zone 4 months prior to OncoRob ©	MRI ADC transitional zone 7 weeks after OncoRob ©

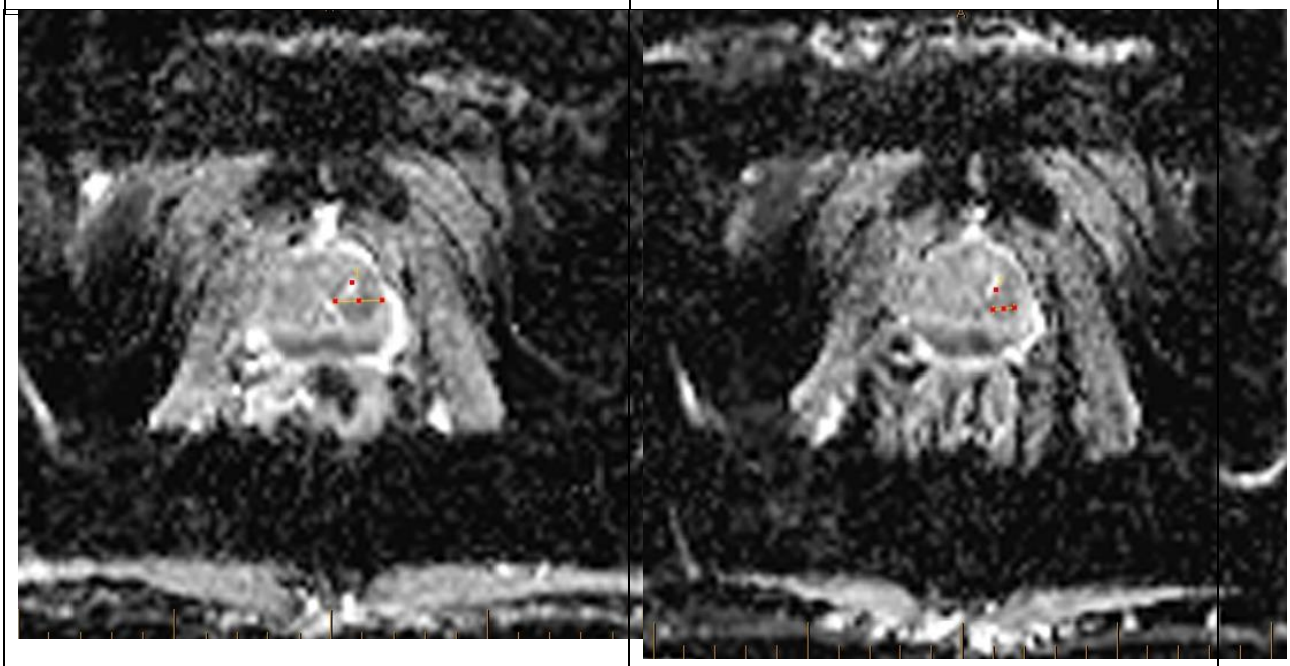


Figure 34: Prostate Cancer Patient's MRI (Magnetic Resonance Imaging) Images Pre and Post OncoRob © Treatment

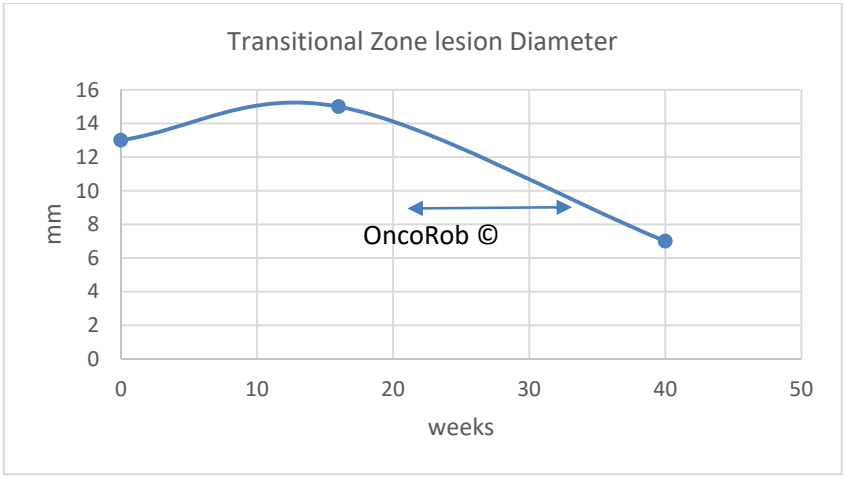


Figure 35: Prostate Transitional Zone Lesion Diameter Pre and Post OncoRob © Treatment

The BHP observed in patient was also affected by this treatment leading to a reduction in prostate volume (figure 36 and 37).

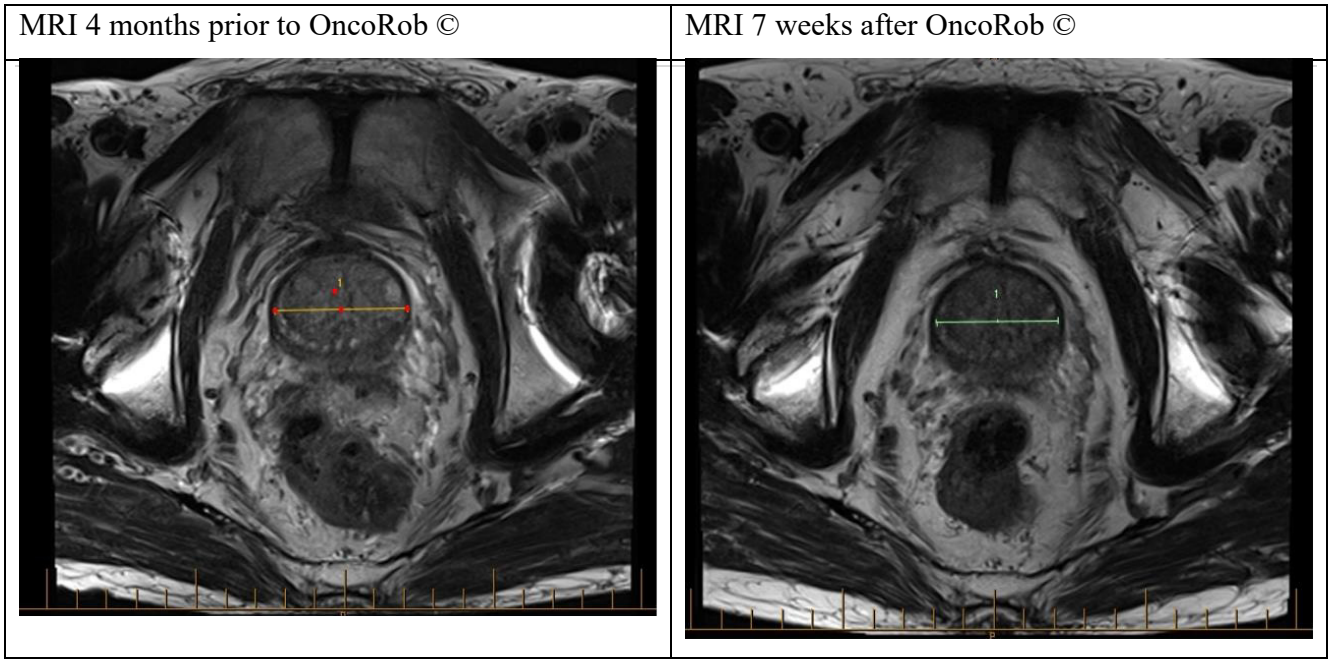


Figure 36: Prostate Cancer Patient's MRI Images Pre and Post OncoRob ©

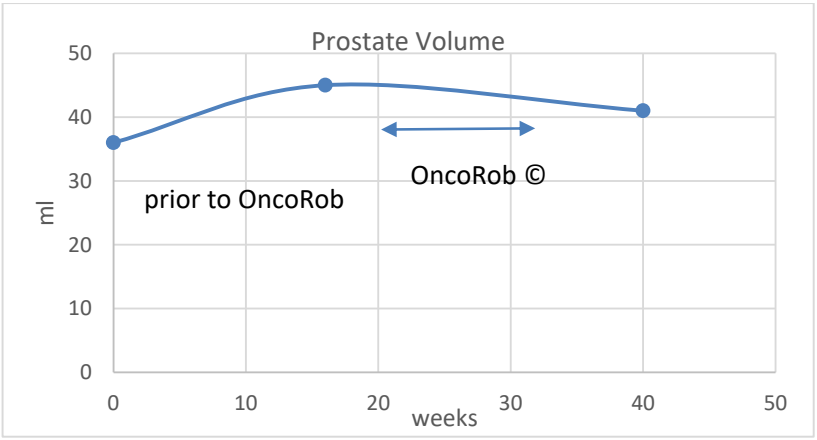


Figure 37: Prostate Volume Pre and Post OncoRob © Treatment

The patient was scheduled for a robotic prostatectomy after the end of OncoRob © treatment and he is in remission for 1.5 years.

3.18. Prostatic Adenocarcinoma

A 74-year-old patient diagnosed with prostate cancer 9 years earlier entered the treatment with OncoRob © in stage T2N0M0. He refused any other standard treatments before or during the treatment with OncoRob ©. Biopsies of 4 years and MRI of 2 years earlier confirmed Gleason (3+3) 6 and a lesion within the left posterolateral peripheral zone abutting the prostate capsule (PIRAD 4), respectively. A CT scan before the start of treatment with OncoRob © could show that the prostatic lesion was unchanged but he had atelectasis of right middle and lower lobe of lung. The patient has received 25 doses of OncoRob © over a period of 10 weeks. The treatment was very well tolerated and only short episode of mild nausea, low blood pressure and cold were experienced about an hour after the start of the OncoRob © infusion. These effects disappeared after 20-30 min. There was a sharp increase of serum PSA before the treatment with OncoRob © but the PSA level dropped after the treatment (figure 38). The comparison of MRI results 3 years prior to and post OncoRob © treatment indicated that the size of the lesion was stable or even reduced. Further, post OncoRob © treatment showed that there is no evidence of extracapsular tumor extension.

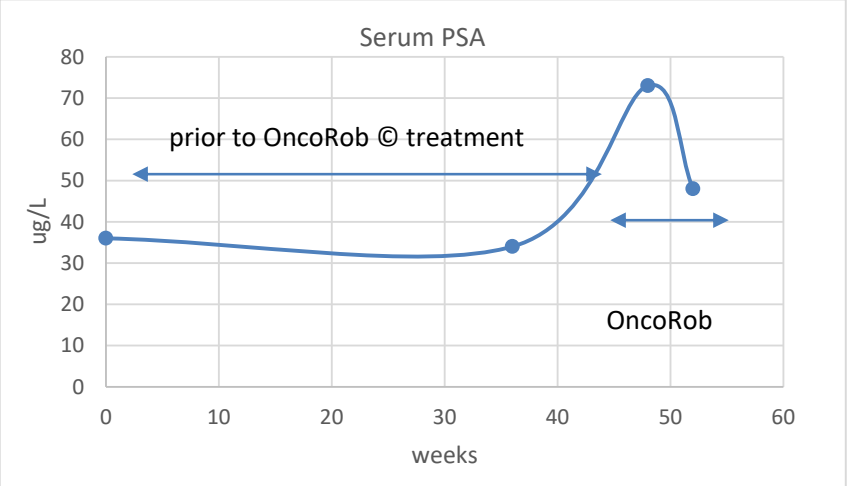


Figure 38: PSA Level Pre and During OncoRob ©

3.19. Prostate Cancer

A 63-year-old patient 5 years after radical prostatectomy, bilateral lymph node dissection and radiation to remove a Gleason (3+4) 7 had entered the treatment with OncoRob ©. Despite the surgery and radiation, the serum PSA level had been increasing during the last years. The patient had received 22 doses of OncoRob © in a period of 5 weeks without any other concurrent treatments. The treatment was very well tolerated and only short episodes of cold feeling were reported. The sharp increase of serum PSA prior to OncoRob © treatment flattened (figure 39) but it was still above the normal values. This indicates the presence of metastasis in the body. Therefore, the patient was encouraged to continue the treatment with OncoRob © or undergoing standard treatments. The patient, however, could not comply for personal reasons. During the surveillance period of 12 months the patient has developed bony metastasis.

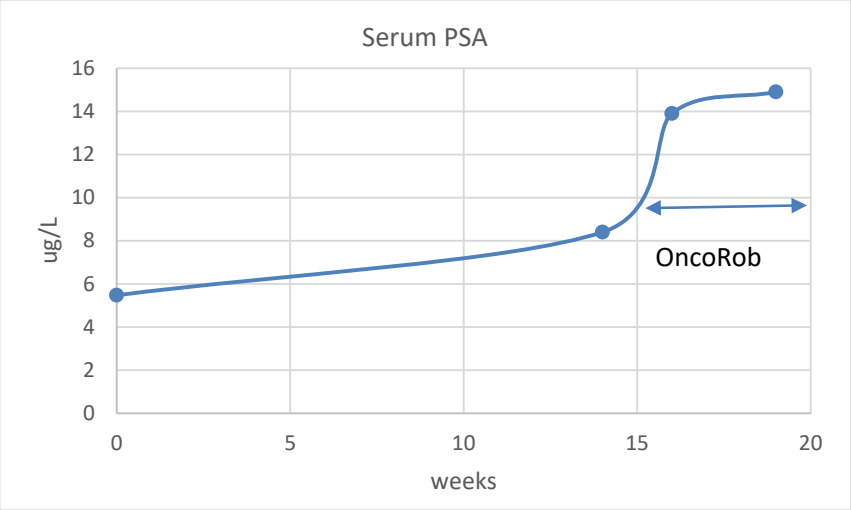


Figure 39: PSA Level Pre and During OncoRob ©

3.20. Suspected Prostate Cancer

A 65-year-old patient with suspected prostate cancer for 5 years had been treated with 42 doses OncoRob © over a period of 2 years. He was treated previously with earlier version of OncoRob © called MetaVec. The treatment was well tolerated. The reactions to the treatment were increase of blood pressure (lasted only few minutes), back pain and slight nausea (lasted for few hours). The recent MRI showed suspicious focal lesion within middle 3rd of right peripheral zone measuring 11 mm demonstrating T2 hypo intensity and restricted diffusion. These findings are stable comparing to a 4 years older MRI and consistent with PIRAD-4. Further, in the earlier MRI there was another lesion in the right transitional zone which was not present in the recent MRI (figure 40). The patient shows a large benign prostate hypertrophy but he does not have any urinary retention or any other clinical symptoms. The serum PSA levels are constant and it shows a slight increase during the last 5 years.

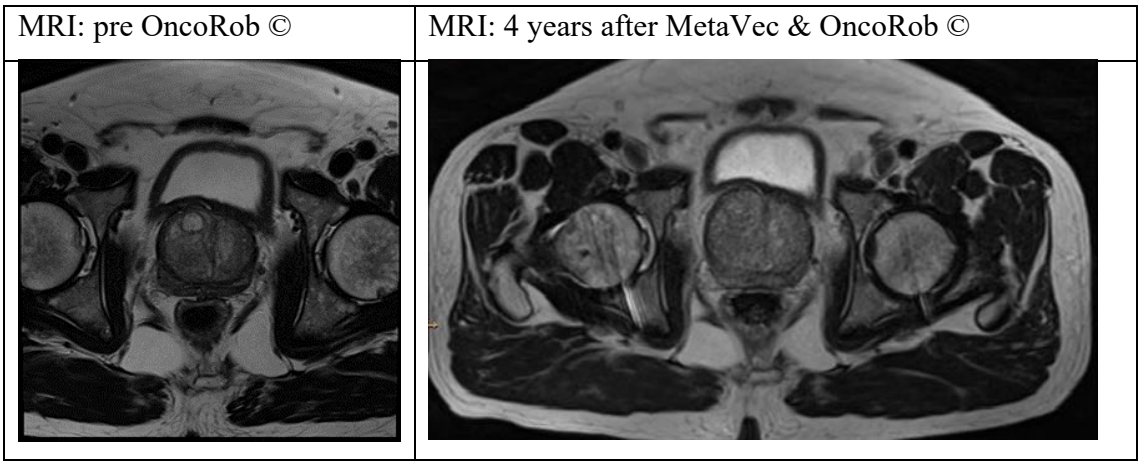


Figure 40: MRI Images Pre and Post OncoRob © Treatment

3.21. Metastatic Melanoma

A 66-year-old female patient with extensive metastatic melanoma diagnosed 3 years prior to treatment with OncoRob © had joined this treatment. She had metastasis in brain, abdomen, mesentery, large neoplastic mass in pancreas, in par-aortic lymph nodes and multiple other solid subcutaneous metastatic nodules ranging from 4 to 44 mm in diameters. She was receiving 4 mg daily dexamethasone as concomitant treatment. She received 24 doses of OncoRob © in a period of 8 weeks. OncoRob © was very well tolerated and not a single side effect was observed. Due to dexamethasone, OncoRob © was ineffective. She succumbed her disease 4 weeks after the end of OncoRob © treatment.

3.22. Metastatic Melanoma

A 60-year-old female patient with widespread cervical, inguinal mesenteric lymphadenopathy, large splenic and left adrenal gland lesions was introduced to the clinic. Based on compassionate ground and despite poor clinical conditions, signs of cardiac ischemia, with some lesions already ulcerating the skin, she was admitted to the treatment with OncoRob ©. She has received 6 doses of OncoRob © in a period of 9 days without any other concomitant treatment. The major treatment related reaction were pain on the cervical tumor site, shaking and nausea. Due to the poor general condition of the patient OncoRob © treatment was, however, stopped. She survived 9 weeks after the end of the treatment.

4. Discussions

There has been enormous progress developing new approaches for treatment of different types of cancer during the last decades. Just to mention a few of them it would include immune checkpoint inhibitors, monoclonal antibodies, anti-angiogenesis, tumor immunotherapy, and more recently tumor vaccines. All these therapies have better tolerability compared to the classical chemotherapy. However, they target one selective pathway among many different pathological mechanisms, and since tumor cells utilize different pathways to survive, they have limited therapeutic efficacy. On the other hand, a surgical resection of tumor in or without combination with pharmacological treatment seems to give the best results in cancer treatment. OncoRob © utilizes the benefits of both therapies approaches by selectively penetrating into the tumor tissue and eliminates cancer cells by apoptosis.

Gene therapy or oncolytic viruses have received several setbacks during the last decades due to the adverse events and lack of efficacy. These can be attributed to the use of mammalian-viral vectors [36-38]. OncoRob © is the fourth generation of gene carrier using bacteriophage as a starting point for construction of these vehicles. The first generation of this therapy was Allvec-1 which showed excellent tolerability and safety in terminal stage cancer patients. However, Allvec-1 could show a positive response only in about 10% of cases31. The oncolytic mechanisms of the second generation was more superior to Allvec-1. However, due to the lack of its ability to penetrate large tumor mass it was superseded by the third generation called MetaVec [32]. MetaVec was administered to two patients with serous ovarian and colon cancer with positive response but it seemed that after repeated dosing the response was reduced indicating deactivating of MetaVec by immune response (internal reports, not published). This finding led to the generation of OncoRob © which can evade adaptive and innate immune responses. In addition, OncoRob © can distinguish between early stage of cancer cell abnormalities compared to the late stage and use different part of its genome to combat cancer cells. In other words, OncoRob © has been given an autonomy to use its genomic cargo to combat cancer cells at different stages by utilizing several molecular sensors. Therefore, the term OncoRob © for oncolytic robots.

The fact that from 17 patients admitted to this treatment protocol, 15 were in advanced stage of cancer disease and no other therapeutic measures were available, these could have challenged the proof of safety right from the beginning. Nonetheless, this treatment has shown that OncoRob © is safe and well tolerated at doses up 5x1010 four times weekly for a minimum of 24 cycles. No sign of toxicity was observed at any time during the treatment with 687 doses, up to 11 months, and during the post-treatment surveillance period of

up to12 months. In order to evaluate the real adverse events caused by OncoRob © toxicity, we need to distinguish those body reactions caused by destruction of tumor cells and the release of inflammatory mediators from inherent side effects caused by OncoRob © itself. The adverse reactions reported during this treatment were an increase or decrease of blood pressure, shivering and nausea. Several studies have reported the release of cytokines such as interleukin's (IL), tumor necrosis factor (TNF) from cancer cells after apoptosis or necrosis [39,40]. These cytokines can induce the adverse reactions seen after OncoRob © treatment. Further, it seems to be a correlation between the rate and the extend of therapeutic benefit and the occurrence of those reactions. This has become very clear after introducing prednisolone or dexamethasone, as a premedication, to some patients. Prednisolone and dexamethasone suppressed all OncoRob © related reactions but on the other hand tumor progressed clearly in those patients after the start of premedication figures 4 and 6. This can be explained by the molecular mode of action of corticosteroids which in general suppresses the synthesis of mRNA [41-43]. OncoRob © in order to exert its apoptotic effects also need to synthesize its own mRNA. Further, the adverse reactions occurred in phases, after an hour, 24 and sometimes after 40 hours (in form of reappearance of fatigues). It is of interest to note that apoptosis starts also after few hours and can last up to 72 hours, depending of cancer cell sensitivity. The preclinical data with OncoRob © could demonstrate that protein expressions leads to apoptosis as mode of action in several tumor cell lines. Therefore, the adverse reaction seen in this treatment can be caused by tumor cell apoptosis. Pain on tumor specific sites coincided with other adverse reactions which can be explained by OncoRob © effects on tumor tissue. All these provides us with some causality between those reactions and the therapeutic effects of OncoRob © and therefore, they are regarded as non-toxicity related drug adverse reactions.

Although higher doses could have been tolerated, due to lack of clinical facility to provide intensive care and the terminal stage of the diseases in all patients, no risk was taken. Therefore, the maximum dose was set at the appearance of the first adverse event related to the treatment. This approach has limited the ability of this treatment protocol to maximize the therapeutic benefits of OncoRob © for those patients. Nonetheless, there are many clinical, lab and imaging results showing the therapeutic benefits and efficacy in this treatment protocol. The improvement of patients' conditions during this treatment encouraged us to continue the treatment beyond the intended period initially mentioned in the treatment protocol. Since the original goal of this treatment protocol was to present safety and tolerability for OncoRob ©, the CT and MR images of patients do not coincide well with the beginning and end of the treatment. Therefore, some readers might suggest to present this study only as safety followed by several case reports. The author, however, believes that this would have disjointed the merits of having a treatment with no toxic side effects from the therapeutic benefits for cancer patients. Nonetheless, from 17 patients, 15 of them presented a positive response ranging in total remission, reduction of tumor size in primary location, resolving some metastatic lesions and stable disease. Even those patients who ultimately succumbed their underlying disease showed some reduction of tumor size and improvement of their general conditions during the treatment with OncoRob © without having any sign of toxicity. This was also confirmed by the improvement of the clinical conditions for patients with digestive track and prostate cancer. Both patients with colorectal cancer were suffering from an imminent intestinal closure. After the treatment with OncoRob © they could pass large volume of stool. The patient with esophageal cancer was able to swallow only liquid food before but solid food after the treatment with OncoRob ©. Although two of these patients succumbed their cancer disease, their primary tumor site reduced in size. The cause of their death was rather liver metastasis. There are many studies showings that viral particles, advanced glycation end products and modified Low-Density Lipoprotein (LDL) cholesterol can be cleared from blood circulation by liver [44,45]. It is conceivable that OncoRob © may also be removed and destroyed by this pathway. As a result, the number of OncoRob © reaching the metastatic cells in liver could be limited and large deposits of cancer cells in liver can escape.

The stimulation of tumor growth by dead cell debris is of high clinical relevance. Whether surgery, chemotherapy, radiation, anti-angiogenic, immunotherapy, or targeted therapy, interventions involve tissue injury and cell death in the tumor bed [46]. From numerous pre-clinical studies, the dead cell debris production has emerged as the material source of this stimulation of tumor growth associated with treatment, which underlies the inherent limitation of cancer treatment [47,48]. Paradoxically, these studies suggest that cancer cell apoptosis can instruct the proliferation of neighboring cancer cells, an insidious interaction that is currently not taken into consideration when designing cancer therapies [49,50]. By designing OncoRob © I have avoided to utilize any mechanism leading to failed or non-lethal apoptosis. Several preclinical studies with OncoRob © could show a significant better apoptotic efficacy than chemotherapy at high concentrations. None of the patients in this treatment protocol, even after three years surveillance, suffered from an accelerated tumor growth. OncoRob © might have only a limited therapeutic effect in one patient with melanoma due to the use of dexamethasone for brain metastasis and another patient with melanoma due to the short period of treatment. In this patient the therapy was hampered by an existing coronary heart disease.

The therapeutic effects of OncoRob © on broad spectrum of cancer cases show (gastrointestinal, head and neck, breast, esophagus, ovarian and prostate) that it is possible to attack cancer cells with one therapeutic tool. Since OncoRob © attacks the tumor tissue and cancer cell at multiple different molecular targets, it presents the benefits of combination treatments known for other type of oncological protocols. The fact that OncoRob © proved to be safe and effective after

repeated dosing for several months shows that the concept of avoiding both innate and adaptive immune response has worked. It is possible that immune stimulation through cell killing can also contribute to tumor cell removal and help to generate a long-term systemic immunity to other tumor deposits [51,52]. The unfortunate contracting of COVID-19 by four patients and the interruption of the treatment with OncoRob © for two weeks has shown a worsening of disease in those patients. This may emphasize the importance of continuous treatment for terminally ill patients.

5. Conclusions

OncoRob © proved to be safe and well tolerated after repeated dosing up to 11 months in terminally ill cancer patients. Despite the limited number of patients for each type of cancer and their stage of disease, we may come to a preliminary conclusion that OncoRob © might lead to remission in early stage of disease and to prolong the survival in late stage of cancer without any toxic effect. The effect of OncoRob © on metastatic disease seems to be more favorable for bones than liver. This can be explained by the ability of liver and spleen as a macromolecule clearing organs and removal of OncoRob ©. Therefore, it is logical to assume that large metastatic tumor masses in liver could not receive sufficient number of OncoRob © to achieve a tangible therapeutic benefit. However, OncoRob © can remove small tumor depositions in liver and reduce the size of primary tumor site. This finding encourages the author to develop additional features for OncoRob © to improve its efficacy for large hepatic tumor deposits.

Declarations

Ethical Approval

The consent form, the treatment protocol and medical facility were approved by ethics committee (NZ Proclaimed Hapu "Te Hapu Hoani Haora Hoani O Nu Tireni"). The ethics committee was informed about all deviations from protocol and regularly informed about the progress of the treatment. Further, the treatments were given under *NZ Section 25 Medicine Act 1981*. All patients received voluntary informed consent to be treated in accordance with the World Medical Association Declaration of Helsinki (WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects, 2013) and the processing of personal data.

Consent to Participate

All patients were informed of the purpose, procedures, and risks. They signed voluntary informed consent form in the presence of a witness.

Consent to Publish

The authors consent to publish this study. Consent for publication of information and images leading to identification of patients is not applicable.

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Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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