Synopsis Clinical Study Report

Trial title:	A phase I/II, single-arm clinical trial to evaluate the safety and immune activation of the combination of DCVAC/PCa, an active cellular immunotherapy, and ONCOS-102, an immune-priming adenovirus, in men with advanced metastatic castration-resistant prostate cancer.
Test products:	DCVAC/PCa ONCOS-102
Indication studied:	Pathologically confirmed advanced metastatic adenocarcinoma of the prostate in patients initially treated with hormonal manipulation (abiraterone/enzalutamide) or chemotherapy
Trial sponsor:	SOTIO a.s., Jankovcova 1518/2, 170 00 Prague, Czech Republic
Protocol number/identifier:	SP015
EudraCT:	2015-004314-15
Development phase:	I/II
Trial initiation date (first patient signed the Informed Consent Form):	23-May-2018
Trial completion date:	25-Jan-2021
Reporting period:	From 23-May-2018 to 16-Mar-2021
Principal investigator:	Ladislav Jarolím, doc., M.D., CSc. Department of Urology, University Hospital Motol, Prague, Czech Republic
Sponsor's responsible medical officer:	Richard Sachse, M.D., Ph.D. Chief Medical Officer, SOTIO a.s.
Good Clinical Practice compliance statement:	This trial was conducted in compliance with International Council for Harmonisation Good Clinical Practice, including the archiving of essential documents.
Version of the Synopsis Clinical Study Report:	1.0
Date of the Synopsis Clinical Study Report:	04-May-2021

Due to the limited amount of collected data only a Synopsis of a Clinical Study Report was prepared.

1. Table of contents

2. List of abbreviations and definitions of terms

Acronym	Definition
AE	Adverse Event
CD	Cluster of Differentiation
CPO	Cyclophosphamide
CT	Computed Tomography
CTCAE	Common Terminology Criteria For Adverse Events
DC	Dendritic Cell
DCVAC/PCa	Autologous Active Cellular Immunotherapy Consisting of Dendritic Cells for Prostate Cancer
ECOG	Eastern Cooperative Oncology Group
EoT	End of Treatment
EudraCT	European Clinical Trials Database
GnRH	Gonadotropin-releasing Hormone
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
LHRH	Luteinizing Hormone-Releasing Hormone
LNCaP	Androgen-Sensitive Prostate Cancer Cell Line
NA	Not Applicable
NCI	National Cancer Institute
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PET	Positron Emission Tomography
PFS	Progression-free Survival
Poly(I:C)	Polyinosinic:Polycytidylic Acid
PSA	Prostate-Specific Antigen
RPE	Radical Prostatectomy
RT	Radiotherapy
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SoC	Standard of Care
ULN	Upper Limit of Normal

3. Synopsis

NAME OF SPONSOR

SOTIO a.s., Jankovcova 1518/2, 170 00 Prague, Czech Republic

NAME OF FINISHED PRODUCT(S)

DCVAC/PCa

ONCOS-102

NAME OF ACTIVE INGREDIENT(S)

Autologous dendritic cells pulsed with killed prostate cancer cells and matured by a Toll-like receptor 3 ligand

Oncolytic adenovirus with immunostimulatory cytokine granulocyte-monocyte colony-stimulating factor

TITLE OF TRIAL

A phase I/II, single-arm clinical trial to evaluate the safety and immune activation of the combination of DCVAC/PCa, an active cellular immunotherapy, and ONCOS-102, an immune-priming adenovirus, in men with advanced metastatic castration-resistant prostate cancer.

PRINCIPAL INVESTIGATOR NAME, NUMBER OF TRIAL CENTERS AND COUNTRIES

Ladislav Jarolím, doc., M.D., CSc.

1 site in the Czech Republic participated in the trial and screened 5 patients.

PUBLICATION

No publication to date.

TRIAL PERIOD

Trial initiation date (first patient signed the Informed Consent Form [ICF]): 23-May-2018

Trial completion date: 25-Jan-2021

REPORTING PERIOD

From: 23-May-2018 (first patient signed the ICF)

To: 16-Mar-2021 (database lock)

PHASE OF DEVELOPMENT

I/II

BACKGROUND AND RATIONALE

Prostate cancer is the most common non-skin cancer in men in Europe. Patients with prostate cancer are treated primarily with surgery (radical prostatectomy [RPE]) or radiotherapy (RT). Unfortunately, a high number of the treated patients develop biochemical failure which may be defined by 2 consecutive rising prostate-specific antigen (PSA) values >0.2 ng/mL. A rising PSA level universally precedes metastatic progression and prostate cancer-specific mortality. Treatment options for biochemical failure after RPE include salvage RT and androgen deprivation therapy, and for biochemical failure after RT the options are salvage RPE, cryoablation of the prostate, brachytherapy, and high-intensity focused ultrasound. Novel therapeutic approaches may prevent or delay the onset of metastatic disease and death after PSA failure. One innovative treatment option available to test in this setting is immunotherapy.

DCVAC/PCa is an active cellular immunotherapy which consists of autologous dendritic cells (DCs) activated by ex vivo exposure to killed cells of the prostate cancer cell line LNCaP. The potency of DCVAC/PCa and its biological activity were characterized by extensive *in vitro* studies. These studies

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demonstrated that DCVAC/PCa possesses the capacity to present exogenous antigens of apoptotic tumor cells on major histocompatibility complex class I and II molecules and can activate both $CD4^+$ (helper) and $CD8^+$ (cytotoxic) tumor-specific T lymphocytes.

Combining different treatment modalities may help reduce the tumor mass and enhance the immunogenic response in late stages of prostate cancer. One of such combinations may be immunotherapy administered concurrently with the oncolytic virus ONCOS-102. We hypothesize that ONCOS-102 may enhance the anti-tumor immune responses generated by DCs loaded with tumor antigens and thus assist the immune system to overcome evasive strategies used by tumors. Justification for the combination of these two investigational medicinal products is supported, in addition to the scientific rationale described above, by their favorable safety profiles documented in phase I clinical trial with ONCOS-102 and phase II clinical trials with DCVAC/PCa (SOTIO a.s. data on file).

To test this hypothesis, a clinical trial SP015 was set up, to evaluate the safety and efficacy of the combination of DCVAC/PCa with ONCOS-102 in men with castration-resistant advanced metastatic prostate cancer primed previously with cyclophosphamide (CPO), who have progressed following initial therapy with either hormonal manipulation (e.g., abiraterone and enzalutamide) or chemotherapy.

The trial was terminated prematurely based on the sponsor's decision due to low recruitment rate, significantly affecting the trial duration. The number of patients necessary to proceed with a meaningful evaluation of the primary, secondary, and exploratory endpoints has not been reached.

OBJECTIVES

Primary objective:

The primary objective of this clinical trial was to evaluate the safety of the combination of DCVAC/PCa with ONCOS-102 in men with castration-resistant advanced metastatic prostate cancer, previously primed with CPO, who had progressed following initial therapy with either hormonal manipulation (e.g., abiraterone and enzalutamide) or chemotherapy.

Secondary objectives:

- To evaluate time to disease progression demonstrated by PSA levels
- To evaluate radiographic progression-free survival (PFS) by radiographic evidence of disease progression
- To evaluate overall survival (OS)
- To evaluate the objective response rate

Exploratory objectives:

- To evaluate immune response in the peripheral blood
- To evaluate immune response in the tumor
- To assess expression of potentially cancer-related genes in the peripheral blood and tumor

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ENDPOINTS

Primary endpoint:

- Safety profile as measured by adverse events (AEs), serious adverse events (SAEs), laboratory abnormalities, and vital signs

Secondary endpoints:

- Time to PSA progression demonstrated by a rising PSA value as defined by the Prostate Cancer Working Group 2, i.e., 25% or greater increase and an absolute increase of 2 ng/mL or more from the nadir, which was confirmed by a second value (also 25% or greater increase and an absolute increase of 2 ng/mL or more from the nadir) obtained 3 to 6 weeks later
- Radiographic PFS, a composite of:
  - radiographic progression of bone lesions
  - radiographic progression of soft tissue lesions
  - death due to any cause
- OS
- Objective response rate

Exploratory endpoints:

- Levels of cytokines, anti-virus and anti-tumor antibodies, and viral particles; percentage of virus- and tumor-specific T lymphocytes in the peripheral blood
- Density and characterization of tumor-infiltrating immune cells and characterization of tumor cells in tumor biopsies
- Expression levels of potentially cancer-related genes in the peripheral blood and tumor biopsies

METHODOLOGY

This was a single-arm, phase I/II clinical trial designed to evaluate the safety of combinatory immunotherapy treatments with DCVAC/PCa and ONCOS-102 in men with castration-resistant advanced metastatic prostate cancer, who had progressed following initial therapy with either hormonal manipulation (e.g., abiraterone and enzalutamide) or chemotherapy.

The clinical trial consisted of the following periods and treatments:

Screening period

Patients were screened for eligibility for the clinical trial within a 4-week period.

Leukapheresis period

Leukapheresis period included the Baseline visit of each eligible patient and a leukapheresis within 2 weeks after the Baseline visit. All patients eligible for the clinical trial were to be evaluated for feasibility of leukapheresis at an evaluation visit (or visits – if necessary) that was to be performed not more than 7 days before the leukapheresis procedure itself.

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Treatment period

Patients were to be treated with the following:

ONCOS-102

ONCOS-102 administration was to be started within 3 weeks of leukapheresis at Week 5 (35 days since baseline ± 2 days), and 3 further doses were to be administered on a weekly basis (± 2 days), i.e., at Week 6 (42 days since baseline ± 2 days), Week 7 (49 days since baseline ± 2 days), and Week 8 (56 days since baseline ±2 days). In addition, ONCOS-102 was to be administered at Week 14 (± 3 days) and at Week 23 (±3 days).

Patient monitoring after ONCOS-102 administration: A viral shedding analysis was to be performed in the first 2 patients exposed to ONCOS-102. Samples of blood, saliva, and urine were to be collected from these patients. The samples were to be analyzed by quantitative polymerase chain reaction for the number of gene copies of ONCOS-102 (a selective method for ONCOS-102 determination) and by the culture method for the presence of infectious adenoviruses (non-specific for ONCOS-102). Results of these analyses were to be presented to the Ministry of the Environment of the Czech Republic and the Czech State Institute for Drug Control after completion of the fourth dose of ONCOS-102 of the second patient. Shedding analyses reports are presented in appendix 7.9.

Cyclophosphamide

A priming bolus dose of CPO (300 mg/m^2 intravenously) was to be given 1-3 days before the first (Week 5) and the fifth (Week 14) ONCOS-102 administration.

DCVAC/PCa

DCVAC/PCa therapy was to start 6 weeks after leukapheresis at Week 8. DCVAC/PCa was to be administered subcutaneously in cycles, always on Day 1 (± 3 days) of the corresponding cycle. The initial 3 cycles were to be 3 weeks long and the remaining cycles were to be 6 weeks long. Therefore, Dose 2 (at Week 11), Dose 3 (at Week 14), and Dose 4 (at Week 17) were to be administered 3 weeks (± 3 days) after the previous dose, and subsequent doses were to be administered 6 weeks (± 3 days) after the previous dose (at Weeks 23, 29, 35, 41, 47, and 53). DCVAC/PCa was to be administered in up to 10 doses or until development of intolerance, consent withdrawal, or death.

Standard of care therapy

Patients who did not have a bilateral orchiectomy leading to castrate levels of testosterone before entry into the clinical trial were to use gonadotropin-releasing hormone/luteinizing hormone-releasing hormone (GnRH/LHRH) analogs during their whole participation in the clinical trial. GnRH/LHRH analogs were to be prescribed and administered as per Summary of Product Characteristics.

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End of treatment

After completion of all doses of ONCOS-102 and DCVAC/PCa per protocol or discontinuation for any reason, patients were to be evaluated at the End of treatment (EoT) visit, which was to be scheduled 30 days (+ 3 days) after the last dose of ONCOS-102 or DCVAC/PCa, whichever was later.

Survival follow-up period

Patients who completed or discontinued treatment with ONCOS-102 and DCVAC/PCa were to be contacted for survival information every 3 months (± 1 week) until death, consent withdrawal, or end of the trial.

End of the trial

Last patient last visit.

This trial was not blinded.

NUMBER OF PATIENTS

Planned: 15

Screened: 5

Eligible: 4

Analyzed for efficacy: NA (2 potentially evaluable: received ≥5 DCVAC/PCa and ONCOS-102 administrations)

Analyzed for safety: 5

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION AND EXCLUSION

Diagnosis:

Male patients with castration-resistant advanced metastatic prostate cancer, who have progressed following initial therapy with either hormonal manipulation (e.g., abiraterone and enzalutamide) or chemotherapy.

All patients must have at least one readily accessible soft tissue/nodal tumor lesion (for intratumoral application of ONCOS-102 and biopsy).

Main inclusion criteria:

1 Males 18 years of age and older

2 Histologically or cytologically confirmed adenocarcinoma of the prostate

3 Radiographically documented metastatic disease (presence of skeletal or soft-tissue/visceral/nodal metastases) with evidence of disease according to the following criteria:

- Measurable lymph nodes (short axis ≥15 mm) or visceral lesion measurable per Response Evaluation Criteria In Solid Tumors version 1.1,

NAME OF SPONSOR SOTIO a.s., Jankovcova 1518/2, 170 00 Prague, Czech Republic **NAME OF FINISHED PRODUCT(S)** DCVAC/PCa ONCOS-102 **NAME OF ACTIVE INGREDIENT(S)** Autologous dendritic cells pulsed with killed prostate cancer cells and matured by a Toll-like receptor 3 ligand Oncolytic adenovirus with immunostimulatory cytokine granulocyte-monocyte colony-stimulating factor

OR

- Two or more lesions on bone scan/imaging.

  And with at least one soft tissue or visceral lesion being accessible for intratumoral administration of ONCOS-102 and biopsy.

4 Eastern Cooperative Oncology Group (ECOG) performance status 0-1

5 PSA ≥2 ng/mL

6 Rising PSA levels after previous treatment failure

7 Surgically or medically castrate with serum testosterone levels ≤1.7 nmol/L. Patients who have not had bilateral orchiectomy must be maintained on standard dosing of GnRH/LHRH analog therapy at appropriate frequency for the duration of the clinical trial.

8 Laboratory criteria:

- White blood cell count greater than 4000/mm^3 (4.0×10^9/L)
- Platelet count of at least 100,000/mm^3 (100×10^9/L)
- Total bilirubin within normal limits (benign hereditary hyper-bilirubinemias, e.g., Gilbert's syndrome, are permitted)[1]
- Serum alanine aminotransferase, aspartate aminotransferase, and creatinine <1.5×upper limit of normal (ULN)[1]

9 Patients who have progressed following:

- at least initial therapy (chemotherapy or treatment with a hormonal agent known to impact survival such as abiraterone and enzalutamide); or
- one first-line chemotherapy regimen and one additional hormonal agent known to impact survival such as abiraterone and enzalutamide; or
- failure of two lines of chemotherapy; or
- failure of pre-chemotherapy abiraterone or enzalutamide and subsequent chemotherapy

10 Life expectancy of at least 12 months based on the investigator's judgement

11 Signed ICF

Main exclusion criteria:

1 Patients with neuroendocrine or small cell cancer of the prostate

[1] If the patient has liver metastases, these parameters might not be applicable and the decision on inclusion of the patient into the trial is to be made by the investigator after discussion with the sponsor's medical monitor.

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2	History of other malignant disease (with the exception of the primary prostate cancer and non-melanoma skin tumors) in the past 5 years
3	Systemic immunosuppressive therapy apart from corticosteroids at a dose of less than 10 mg/day
4	Administration of experimental therapy within the last 4 weeks before start of screening
5	Treatment with immunotherapy within the last 3 months before start of screening
6	Treatment with radiopharmaceutical drugs within 8 weeks before start of screening
7	Patient significant co-morbidities (cardiovascular diseases, e.g., unstable angina pectoris, uncontrolled hypertension, myocardial infarction, ventricular arrhythmia, or stroke within a 6-month period before the Baseline visit; congestive heart failure or cardiac arrhythmia not controlled by treatment; active severe infections; uncontrolled metabolic disorders; etc.)
8	Known hypersensitivity or allergic reaction (other than local inflammatory reaction or irritation at injection site) to DCVAC/PCa or its constituents, i.e., CryoStor CS10 freeze medium (Biolife Solutions) containing 10% dimethyl sulfoxide
9	Uncontrolled co-morbidities including social conditions which in the investigator's opinion would prevent participation in/completion of the clinical trial
10	Patients known to be HIV positive or syphilitic
11	Known active (infectious) hepatitis B and active hepatitis C
12	Known central nervous malignancies such as glioma and brain metastases
13	Receipt of oncolytic virus treatment or vaccination with a live virus within 4 weeks of trial start
14	History of organ transplantation
15	Any autoimmune diseases, therapies with monoclonal antibodies, any psychiatric disease, medical history of active tuberculosis and any allogeneic stem cell transplantations in the last 5 years

TEST PRODUCTS, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER(S)

DCVAC/PCa:

DCVAC/OvCa, an active cellular immunotherapy product containing DCs activated by exposure to killed tumor cells of the LNCaP cell line and matured by poly(I:C), a Toll-like receptor 3 ligand.

Dose and mode of administration:

An aliquot of approximately 1×10^7 activated autologous DCs was to be thawed, re-suspended in 0.9% pre-cooled saline solution to a total volume of 5 mL, and divided in two 2.5 mL injections. The two injections were to be administered subcutaneously in the inguinal and axillary regions.

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Batch number:

DCVAC/OvCa was prepared on an individual basis, each product with a unique lot number (list of batches administered to patients is presented in appendix 7.7).

ONCOS-102:

ONCOS-102 is a serotype 5 adenovirus that features a chimeric capsid for enhanced gene delivery to cancer cells and a 24 bp deletion in the E1A gene for cancer cell-restricted replication. In addition, it is armed with granulocyte-macrophage colony-stimulating factor, a potent inducer of anti-tumor immunity.

Dose and mode of administration:

An aliquot of 4×10^{11} viral particles was to be thawed and reconstituted with 0.5 mL of 0.9% saline solution, and injected intratumorally under ultrasound guidance by a radiologist or another trained physician. The suspension could be injected either in one or two viable lesions located in the soft tissue, lymphatic nodes of the neck, the liver, or regional pelvic nodes. Injection into the primary tumor (i.e., prostate gland) was to be avoided. The minimum volume to be injected in one lesion was 0.5 mL.

Batch number:

ONCOS-102 was prepared from 3 received batches (list of batches administered to patients is presented in appendix 7.8).

Cyclophosphamide (Immunomodulatory treatment):

CPO 500 mg powder for solution for injection or infusion was to be used as immunomodulatory treatment.

Dose and mode of administration:

A bolus of 300 mg/m^2 was to be administered intravenously 1-3 days before the first and the fifth ONCOS-102 administration.

Batch number:

A commercially available product containing cyclophosphamidum monohydricum was used.

Standard of care therapy:

Continuous administration of GnRH/LHRH analogs or bilateral orchiectomy resulting in castrate levels of testosterone (i.e., ≤1.7 nmol/L). Best supportive care.

DURATION OF TREATMENT

The treatment period ideally lasted for 52 weeks in total (48 weeks of treatment followed by 30 days of safety follow-up until the EoT visit).

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STATISTICAL METHODS

Only a descriptive statistical analysis was planned for evaluation of safety and efficacy endpoints. The trial reached neither the planned sample size nor even achieved a number of patients adequate for any meaningful statistical evaluation; therefore, a statistical analysis was not performed.

SUMMARY OF AVAILABLE DATA AND CONCLUSION

Patient disposition:

A total of 5 patients were screened in this trial. Study design with inclusion criteria involving presence of soft tissue lesions resulted in low number of recruited patients with short time of life expectancy. Of the 5 screened patients, 4 patients (80%) were eligible and 1 patient (20%) was a screening failure. Of the 4 eligible patients, 3 patients were exposed to DCVAC/PCa, all 4 patients were exposed to ONCOS-102, all 4 patients were exposed to CPO, and all 4 patients were exposed to standard of care therapy (SoC). One of the 3 patients that received DCVAC/PCa received the planned number of doses of DCVAC/PCa (i.e., 10 doses). The other 2 patients discontinued treatment with DCVAC/PCa prematurely (1 due to an AE after 2 doses, 1 due to death after 6 doses). Two of the 4 patients that received ONCOS-102 received the planned number of doses of ONCOS-102 (i.e., 6 doses). The other 2 patients discontinued treatment with ONCOS-102 (1 due to an AE after 4 doses, 1 due to death after 3 doses).

Protocol violations were protocol deviations which might have significantly affected the reliability of trial data. In this trial, no protocol violations were recorded as reportable.

Patient demographics and baseline characteristics:

Demographics and other baseline characteristics of patients were comparable. Median age of the patients was 71 years. At the time of screening, 2 patients exhibited a disease at clinical stage 2, 1 patient at clinical stage 3 and 1 patient at clinical stage 4. Median Gleason score at screening was 8. All patients had a significant medical history at screening, the most prevalent type of disorder/procedure was related to kidneys, eyes, and liver function.

Disease status:

Overall, the evaluation of disease status by analyzing the computed tomography (CT) / magnetic resonance imaging (MRI) imaging and bone scintigraphy values showed consistent results. The overall response of soft tissue/visceral lesions indicated a progressive disease, while the response of bone lesions indicated a non-progressive disease in 1 patient. One patient (SP015C002B001) exhibited very high PSA concentrations at screening and baseline visit. The high PSA concentrations reflect disease relapse. The patient who completed all treatment (SP015C002B005) consistently exhibited PSA concentrations fluctuating above the ULN.

Safety results:

An Independent Data Monitoring Committee (IDMC) consisting of 3 members, including one statistician, assessed the progress of the trial and safety data at regular intervals.

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During the trial, all patients experienced at least 1 AE (in total, 53 AEs occurred during the trial). In total, 9 AEs of NCI CTCAE Grade 3 to 5 AEs were reported in 3 patients. Two SAEs were reported in 2 patients (general physical health deterioration and nystagmus). One SAE was fatal (general physical health deterioration).

One AE was reported as having a suspected causal relationship to leukapheresis (anemia). No AE was reported as having a suspected causal relationship to DCVAC/PCa. 6 occurrences of 3 types of AEs were reported in 1 patient as having a suspected causal relationship to ONCOS-102 (chills, elevated/high temperature, and vomiting). No AE was reported as having a suspected causal relationship to CPO or SoC.

One patient experienced SARS-CoV-2 disease during the trial but recovered without any persisting consequences.

DCVAC/PCa and ONCOS-102 were prematurely discontinued by 1 patient due to an AE of general health deterioration.

Most of the AEs can be explained by the underlying disease of prostate cancer or preexisting baseline status. The most common AEs encountered in the trial were general health deterioration, nausea, chills, and elevated/high temperature. Other common AEs reported were anemia, fatigue, urinary infection suspicion/infection of the lower urinary tract, urine retention, constipation, and vomiting.

Three patients died during the trial. No death was reported to be causally related to DCVAC/PCa, ONCOS-102, CPO, or SoC; the cause of death was reported to be related to underlying disease.

No safety concerns were identified during laboratory data review by the sponsor's medical monitor, nor during the two IDMC meetings and one remote review by the IDMC members.

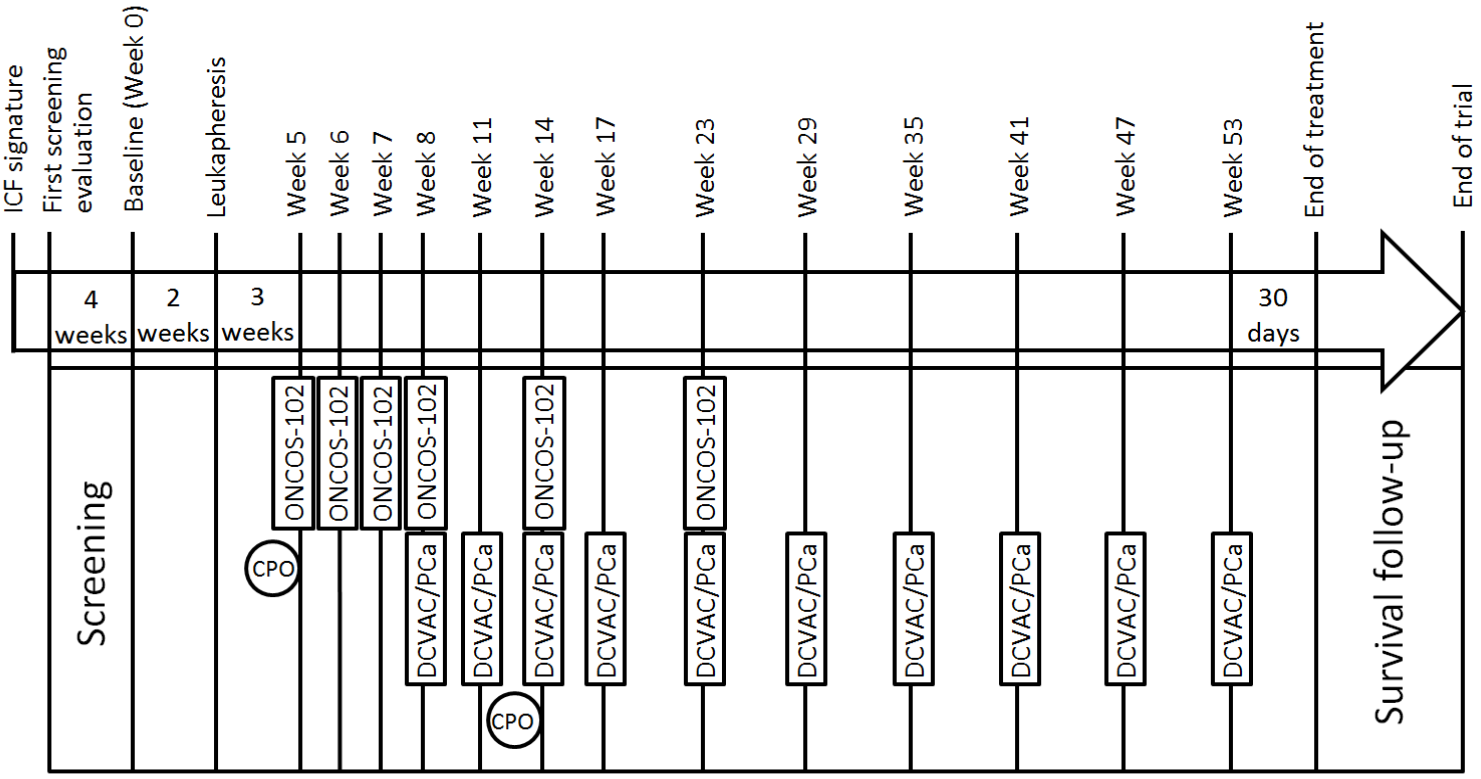
Conclusion:

Due to the low number of recruited patients, in this trial of 4 patients with advanced metastatic castration-resistant prostate cancer who have progressed following initial therapy with hormonal manipulation (abiraterone/enzalutamide) or chemotherapy, no definitive conclusion could be made concerning the safety or preliminary signs of efficacy of the combination of DCVAC/PCa with ONCOS-102. Based on the collected data on concomitant administration of DCVAC/PCa or ONCOS-102, no safety concerns were identified by the sponsor nor the IDMC that could be associated with these investigational products. The profile of the most frequently occurring AEs and laboratory parameter abnormalities might potentially be associated with the underlying conditions or previous treatments received by the patients.

DATE AND VERSION OF THIS SYNOPSIS CLINICAL STUDY REPORT

Version 1.0, 04-May-2021

4. Trial schema



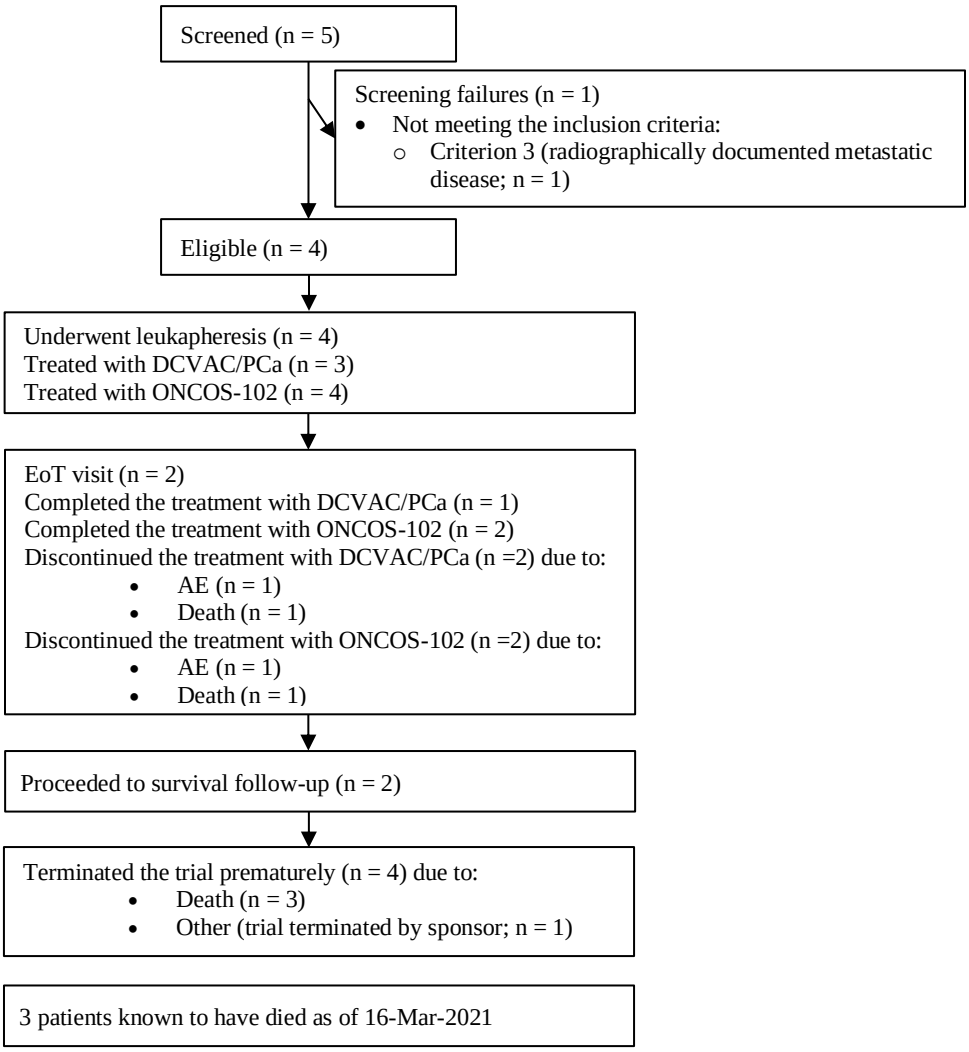
5. Schedule of assessments

Screening period		Leukapheresis period		Treatment period														
Visit	**Screening**	**Baseline**	**Leuka-pheresis**	**Week 5**	**Week 6**	**Week 7**	**Week 8**	**Week 11**	**Week 14**	**Week 17**	**Week 23**	**Week 29**	**Week 35**	**Week 41**	**Week 47**	**Week 53**	**End of treatment**	**Survival follow-up**
DCVAC/PCa cycle							**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycle 7**	**Cycle 8**	**Cycle 9**	**Cycle 10**		
Time since baseline	**Up to -4 weeks**	**0**	**Up to 2 weeks**	**5 weeks (35 +/-2 days)**	**6 weeks (42 +/-2 days)**	**7 weeks (49 +/-2 days)**	**8 weeks (56 +/-2 days)**	**11 weeks (+/-3 days)**	**14 weeks (+/-3 days)**	**17 weeks (+/-3 days)**	**23 weeks (+/-3 days)**	**29 weeks (+/-3 days)**	**35 weeks (+/-3 days)**	**41 weeks (+/-3 days)**	**47 weeks (+/-3 days)**	**53 weeks (+/-3 days)**	**30 (+3) days after the last dose of ONCOS-102 or DCVAC/PCa**	**Every 3 months**
Informed consent	X																	
Demography	X																	
Prostate cancer and medical history	X																	
Vital signs	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination, height, weight	X						X				X						X	
ECOG status	X			X			X				X			X			X	
Hematology	X	X		X			X	X		X		X		X		X	X	
Biochemistry	X	X		X			X	X		X		X		X		X	X	
Urinalysis	X	X		X			X	X		X		X		X		X	X	
Coagulation	X			X[1]			X[1]											
Testosterone levels	X																	
TSH	X											X					X	
Samples of urine and buccal swabs for shedding analysis[2]				X	X	X	X		X		X							
HIV, syphilis, hepatitis B and C	X		X															
PSA levels[3]	X	X					X	X	Every 6 weeks (+/- 3 days) until confirmed PSA progression, thereafter every 12 weeks (+/- 3 days)									
Tumor viability assessment by PET/CT	X																	
Ultrasound[4]	X			X	X	X	X		X		X							
Disease assessment by MRI/CT and bone scan	X[5]	Every 4 months																
Leukapheresis			X															
Cyclophosphamide				X[6]					X[6]									
ONCOS-102				X	X	X	X		X		X							
DCVAC/PCa[7]							X	X	X	X	X	X	X	X	X	X		
Blood samples (serum and whole blood) for research				X[8]	X[8]	X[8]	X[8]		X[8]		X[8]					X[9]	X[9]	
PBMCs for research				X[10,11]			X[11]				X[11]					X[12]	X[12]	
Blood sample for HLA testing		X																

Screening period		Leukapheresis period		Treatment period														
Visit	**Screening**	**Baseline**	**Leuka-pheresis**	**Week 5**	**Week 6**	**Week 7**	**Week 8**	**Week 11**	**Week 14**	**Week 17**	**Week 23**	**Week 29**	**Week 35**	**Week 41**	**Week 47**	**Week 53**	**End of treatment**	**Survival follow-up**
DCVAC/PCa cycle							**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycle 7**	**Cycle 8**	**Cycle 9**	**Cycle 10**		
Time since baseline	**Up to -4 weeks**	**0**	**Up to 2 weeks**	**5 weeks (35 +/-2 days)**	**6 weeks (42 +/-2 days)**	**7 weeks (49 +/-2 days)**	**8 weeks (56 +/-2 days)**	**11 weeks (+/-3 days)**	**14 weeks (+/-3 days)**	**17 weeks (+/-3 days)**	**23 weeks (+/-3 days)**	**29 weeks (+/-3 days)**	**35 weeks (+/-3 days)**	**41 weeks (+/-3 days)**	**47 weeks (+/-3 days)**	**53 weeks (+/-3 days)**	**30 (+3) days after the last dose of ONCOS-102 or DCVAC/PCa**	**Every 3 months**
Tumor biopsy				X			X											
Adverse events	X																	
Concomitant medication / non-drug therapies	X																	
Recording of further antineoplastic therapy																	X[13]	X[13]
Survival follow-up[14]																		X

1) Coagulation results must be available before biopsy.
2) The first 2 or more (as requested by the authorities) patients exposed to ONCOS-102: Samples for shedding analysis will be collected before and 24, 48, 72, and 96 hours after administration of the first dose of ONCOS-102; before and 24 and 48 hours after administration of the second dose of ONCOS-102; and before and 24 hours after administration of all subsequent doses of ONCOS-102. If no modification of shedding analysis schedule is needed, samples for the rest of the patients will be collected before and 24 hours after ONCOS-102 administration only.
3) PSA levels will be assessed until the EoT visit, consent withdrawal, or death.
4) Viable lesions located in the soft tissue, lymphatic nodes of the neck, pelvis or in the liver identified by positron emission tomography PET/CT should be localized by ultrasound at screening. ONCOS-102 will be injected intratumorally under ultrasound guidance by a radiologist or another trained physician.
5) MRI/CT and bone scans at screening can be omitted if results not older than 30 days are available.
6) A priming bolus dose of CPO (300 mg/m^2 intravenously) will be given 1-3 days before the first (Week 5) and the fifth (Week 14) ONCOS-102 administration.
7) DCVAC/PCa to be administered in up to 10 doses or until development of intolerance, consent withdrawal, or death.
8) The first 2 or more (as requested by the authorities) patients exposed to ONCOS-102: Blood samples for research will be collected before and 6, 24, 48, 72, and 96 hours after administration of the first dose of ONCOS-102; before and 6, 24, and 48 hours after administration of the second dose of ONCOS-102; and before and 6 and 24 hours after administration of all subsequent doses of ONCOS-102. If no modification of shedding analysis schedule is needed, samples for the rest of the patients will be collected before and 6 and 24 hours after ONCOS-102 administration only.
9) The last blood sample for research (serum only) will be collected at Week 53 before DCVAC/PCa administration or at the EoT visit in case of premature termination.
10) 1 peripheral blood mononuclear cell (PBMC) sample will be collected before the first administration of priming bolus dose of CPO (300 mg/m^2 intravenously, 1-3 days before ONCOS-102 administration at Week 5).
11) PBMC samples will be collected before DCVAC/PCa and/or ONCOS-102 administration.
12) The last PBMC sample will be collected at Week 53 before DCVAC/PCa administration or at the EoT visit in case of premature termination.
13) Where applicable.
14) Survival follow-up every 3 months until death, consent withdrawal, or end of trial.

6. Patient disposition



7. Appendices

7.1 Protocol and protocol amendments

Provided as separate PDF files.

7.2 IDMC Charter

Provided as a separate PDF file.

7.3 Sample case report form

Provided as separate PDF files.

7.4 List of Ethics committees (name of committee chair included)

Ethics Committee	Address	Chairman
Eticka komise Fakultni nemocnice v Motole	V Uvalu 84, 150 06 Prague, Czech Republic	MUDr. Vratislav Smelhaus

7.5 List and description of investigators and other important participants in the trial

Provided as a separate PDF file.

7.6 Signatures of the principal investigator, the sponsor's responsible medical officer and statistician

TRIAL TITLE: A phase I/II, single-arm clinical trial to evaluate the safety and immune activation of the combination of DCVAC/PCa, an active cellular immunotherapy, and ONCOS-102, an immune-priming adenovirus, in men with advanced metastatic castration-resistant prostate cancer.

PROTOCOL NUMBER/IDENTIFIER: SP015

EUDRACT: 2015-004314-15

SYNOPSIS CLINICAL STUDY REPORT VERSION: Version 1.0, 04-May-2021

TRIAL AUTHORS:

I have read this Synopsis Clinical Study Report and confirm that to the best of my knowledge it accurately describes the conduct and results of the trial.

PRINCIPAL INVESTIGATOR: Ladislav Jarolím, doc., M.D., CSc.

SIGNATURE:

AFFILIATION: Motol University Hospital, V Uvalu 84, 150 06 Prague, Czech Republic

DATE: 7 MAY 2021

SPONSOR'S RESPONSIBLE MEDICAL OFFICER: Richard Sachse, M.D., Ph.D.

SIGNATURE:

AFFILIATION: SOTIO a.s., Prague, Czech Republic

DATE: 5 May 2021

SPONSOR'S RESPONSIBLE STATISTICIAN: Pavla Kadlecova, M.Sc.

SIGNATURE:

AFFILIATION: SOTIO a.s., Prague, Czech Republic

DATE: 06-MAY-2021

7.7 Listing of patients receiving DCVAC/PCa product from specific batches

Patient number	Lot number
SP015C002B001	L1A02520
SP015C002B002	L1A02529
SP015C002B003	L1A02574
SP015C002B005	L1A02580

7.8 Listing of patients receiving ONCOS-102 product from specific batches

Patient number	Lot number	Visit name
SP015C002B001	BX1010808 01	Week 5
SP015C002B001	BX1010808 01	Week 6
SP015C002B001	BX1010808 01	Week 7
SP015C002B002	BX1010808 01	Week 5
SP015C002B002	BX1010808 01	Week 6
SP015C002B002	BX1010808 01	Week 7
SP015C002B002	BX1010808 01	Week 8 / Cycle 1
SP015C002B005	BX1010808 01	Week 5
SP015C002B003	BX1010808 10	Week 5
SP015C002B003	BX1010808 10	Week 6
SP015C002B003	BX1010808 10	Week 7
SP015C002B003	BX1010808 10	Week 8 / Cycle 1
SP015C002B003	BX1010808 10	Week 14 / Cycle 3
SP015C002B005	BX1010808 01	Week 5
SP015C002B005	BX1010808 10	Week 6
SP015C002B005	BX1010808 10	Week 7
SP015C002B005	BX1010808 10	Week 8 / Cycle 1
SP015C002B003	BX1010808 10	Week 23 / Cycle 5
SP015C002B005	BX1010808 10	Week 14 / Cycle 3
SP015C002B005	BX1016142 04	Week 23 / Cycle 5

7.9 Shedding analyses reports

Provided as separate PDF files.