

CLINICAL STUDY PROTOCOL

The Effect of tinzaparin on Biomarkers in FIGO Stage III-IV Ovarian Cancer Patients Undergoing Neoadjuvant Chemotherapy – A randomized pilot study

The TABANETOC-trial

(Tinzaparin And Biomarkers After Neoadjuvant Treatment of Ovarian Cancer)

Study code:	TABANETOC
EudraCT number:	2021-000135-31
Sponsor:	Preben Kjølhede
Coordinating Investigators:	Preben Kjølhede Anna-Clara Spetz Holm, Gabriel Lindahl, Anna Karlsson, Tomas Lindahl, Maria Jenmalm

Table Of Contents

1	Synopsis	16
2	Background and rationale	18
3	Benefit-risk evaluation	20
3.1	Benefit-risk evaluation with respect to the ongoing Covid-19 pandemic.....	21
4	Study objectives	21
4.1	Primary objective.....	21
4.2	Secondary objective(s)	22
4.3	Primary endpoint (variable)	22
4.4	Secondary endpoints (variables)	22
4.5	Exploratory endpoints (variables)	22
5	Study design and procedures	22
5.1	Overall study design	22
5.2	Procedures and flow chart	23
5.3	Biological sampling procedures.....	23
5.3.1	Handling, storage, and destruction of biological samples	23
5.3.2	Total volume of blood per subject	23
5.4	Biobank.....	23
5.5	End of Study	23
6	Subject selection	24
6.1	Inclusion criteria	24
6.2	Exclusion criteria	24
6.3	Screening	25
6.4	Withdrawal criteria.....	25
7	Study treatments.....	26
7.1	Description of investigational product(s).....	26
7.2	Dose and administration	26
7.3	Packaging, labeling, and handling of investigational products(s)	27
7.4	Drug accountability and treatment compliance	27
7.5	Randomization.....	27
7.6	Blinding.....	28
7.7	Concomitant medications	28
7.7.1	Background treatment	28
7.7.2	Other concomitant medications.....	28

7.8	Destruction	28
7.9	Treatment after study end	28
8	Methods for measurement of endpoints for clinical efficacy and safety	28
8.1	Methods for measurement of endpoints for clinical efficacy	28
8.1.1	Primary endpoint (variable)	28
8.1.2	Secondary endpoints (variables)	29
8.2	Methods for measurement of endpoints (variables) for clinical safety	29
9	Handling of Adverse Events	29
9.1	Definitions	30
9.1.1	Adverse Event (AE)	30
9.1.2	Adverse Reaction (AR)	30
9.1.3	Serious Adverse Event (SAE)	30
9.1.4	Suspected Unexpected Serious Adverse Reaction (SUSAR)	30
9.2	Assessment of Adverse Events	30
9.2.1	Assessment of causal relationship	30
9.2.2	Assessment of intensity	31
9.2.3	Assessment of seriousness	31
9.3	Reporting and registration of Adverse Events	31
9.3.1	Reporting of Adverse Events (AE)	33
9.3.2	Reporting of Serious Adverse Events (SAE)	33
9.3.3	Reporting of Suspected Unexpected Serious Adverse Reactions (SUSAR)	33
9.4	Follow-up of Adverse Events	33
9.5	Annual Safety Report (Development Safety Update Report, DSUR)	34
9.6	Procedures in case of emergencies, overdose or pregnancy	34
9.7	Reference Safety Information	34
10	Statistics	34
10.1	Analysis population	34
10.2	Statistical analyses	34
10.2.1	Statistical methods	34
10.2.2	Drop-outs	35
10.3	Adjustment of significance and confidence interval	35
10.4	Sample size calculations	35
10.5	Interim analysis (if relevant)	36
11	Quality Control and Quality Assurance	36

11.1	Quality Assurance and Sponsor oversight.....	36
11.2	Monitoring.....	37
11.3	Source data.....	37
11.4	Deviations or serious breaches	37
11.5	Audits and inspections	37
12	Ethics	38
12.1	Compliance to the protocol, GCP and regulations.....	38
12.2	Ethical review of the study	38
12.3	Procedure for obtaining informed consent.....	38
12.4	Data protection	38
12.5	Insurances.....	39
12.6	Publication of results.....	39
13	Substantial changes to the study	39
14	Collection, handling, and archiving data	39
14.1	Case Report Form	40
15	Notification of study completion, reporting, and publication	40
16	References.....	40

Signature page

Sponsor

I am responsible for ensuring that this protocol includes all essential information to be able to conduct this study. I will submit the protocol and all other important study-related information to the responsible investigator(s) so that they can conduct the study correctly. I am aware that it is my responsibility to hold the staff members who work with this study informed and trained.

Sponsor's signature	Date
Preben Kjølhede, MD, PhD; Professor, Senior consultant	

Printed name

Coordinating Investigators / Principal Investigators

I have read this protocol and agree that it includes all essential information to be able to conduct the study. By signing my name below, I agree to conduct the study in compliance with this protocol, the Declaration of Helsinki, ICH GCP (Good Clinical Practice) guidelines and the current national and international regulations governing the conduct of this clinical trial.

I will submit this protocol and all other important study-related information to the staff members and investigators who participate in this study, so that they can conduct the study correctly. I am aware of my responsibility to continuously keep the staff members and investigators who work with this study informed and trained.

I am aware that quality control of this study will be performed in the form of monitoring, audit, and possibly inspection.

Coordinating Investigator / Principal Investigator's signature	Date
Preben Kjølhede, MD, PhD; Professor, Senior consultant	

Printed name

Coordinating Investigator / Principal Investigator's signature	Date
Anna-Clara Spetz Holm, MD, PhD, Associate Professor, Senior Consultant	

Printed name

Coordinating Investigator / Principal Investigator's signature Date

Gabriel Lindahl, MD, PhD, Assistant Professor, Senior Consultant

Printed name

Coordinating Investigator / Principal Investigator's signature Date

Anna Karlsson, MD, Specialist doctor

Printed name

Coordinating Investigator / Principal Investigator's signature Date

Tomas Lindahl, MD, PhD, Professor, Senior Consultant

Printed name

Coordinating Investigator / Principal Investigator's signature Date

Maria Jenmalm, MSc, PhD, Professor

Printed name

Principal Investigator

I have read this protocol and agree that it includes all essential information to be able to conduct the study. By signing my name below, I agree to conduct the study in compliance with this protocol, the Declaration of Helsinki, ICH GCP (Good Clinical Practice) guidelines and the current national and international regulations governing the conduct of this clinical trial.

I will submit this protocol and all other important study-related information to the staff members and investigators who participate in this study, so that they can conduct the study correctly. I am aware of my responsibility to continuously keep the staff members and investigators who work with this study informed and trained.

I am aware that quality control of this study will be performed in the form of monitoring, audit, and possibly inspection.

Principal Investigator's signature

Date

Printed name

Principal Investigator

I have read this protocol and agree that it includes all essential information to be able to conduct the study. By signing my name below, I agree to conduct the study in compliance with this protocol, the Declaration of Helsinki, ICH GCP (Good Clinical Practice) guidelines and the current national and international regulations governing the conduct of this clinical trial.

I will submit this protocol and all other important study-related information to the staff members and investigators who participate in this study, so that they can conduct the study correctly. I am aware of my responsibility to continuously keep the staff members and investigators who work with this study informed and trained.

I am aware that quality control of this study will be performed in the form of monitoring, audit, and possibly inspection.

Principal Investigator's signature

Date

Printed name

Principal Investigator

I have read this protocol and agree that it includes all essential information to be able to conduct the study. By signing my name below, I agree to conduct the study in compliance with this protocol, the Declaration of Helsinki, ICH GCP (Good Clinical Practice) guidelines and the current national and international regulations governing the conduct of this clinical trial.

I will submit this protocol and all other important study-related information to the staff members and investigators who participate in this study, so that they can conduct the study correctly. I am aware of my responsibility to continuously keep the staff members and investigators who work with this study informed and trained.

I am aware that quality control of this study will be performed in the form of monitoring, audit, and possibly inspection.

Principal Investigator's signature

Date

Printed name

Principal Investigator

I have read this protocol and agree that it includes all essential information to be able to conduct the study. By signing my name below, I agree to conduct the study in compliance with this protocol, the Declaration of Helsinki, ICH GCP (Good Clinical Practice) guidelines and the current national and international regulations governing the conduct of this clinical trial.

I will submit this protocol and all other important study-related information to the staff members and investigators who participate in this study, so that they can conduct the study correctly. I am aware of my responsibility to continuously keep the staff members and investigators who work with this study informed and trained.

I am aware that quality control of this study will be performed in the form of monitoring, audit, and possibly inspection.

Principal Investigator's signature

Date

Printed name

Principal Investigator

I have read this protocol and agree that it includes all essential information to be able to conduct the study. By signing my name below, I agree to conduct the study in compliance with this protocol, the Declaration of Helsinki, ICH GCP (Good Clinical Practice) guidelines and the current national and international regulations governing the conduct of this clinical trial.

I will submit this protocol and all other important study-related information to the staff members and investigators who participate in this study, so that they can conduct the study correctly. I am aware of my responsibility to continuously keep the staff members and investigators who work with this study informed and trained.

I am aware that quality control of this study will be performed in the form of monitoring, audit, and possibly inspection.

Principal Investigator's signature

Date

Printed name

Contact information

Role	
Sponsor	<p>Preben Kjølhede, MD, PhD, Professor, Senior Consultant Department of Obstetrics and Gynecology, Department of Clinical and Biomedical Sciences, Linköping University Hospital 58185 Linköping +46705688201 Preben.Kjolhede@liu.se Preben.Kjolhede@regionostergotland.se</p>
Coordinating Investigators / Principal Investigators Linköping (Linköping University Hospital)	<p>Preben Kjølhede, MD, PhD, Professor, Senior Consultant Department of Obstetrics and Gynecology, Department of Clinical and Biomedical Sciences, Linköping University Hospital 58185 Linköping +46705688201 Preben.Kjolhede@liu.se Preben.Kjolhede@regionostergotland.se</p> <p>Anna-Clara Spetz Holm, MD, PhD, Associate Professor, Senior Consultant Department of Obstetrics and Gynecology, Department of Clinical and Biomedical Sciences, Linköping University Hospital 58185 Linköping +4610-1033130 Anna-Clara.Spetz.Holm@liu.se</p> <p>Gabriel Lindahl, MD, PhD, Assistant Professor, Senior Consultant Department of Oncology, Department of Clinical and Biomedical Sciences, Linköping University Hospital 58185 Linköping +46730958174 Gabriel.Lindahl@regionostergotland.se</p>

Role	
	<p>Anna Karlsson, MD, Phd-student, Specialist Doctor Department of Obstetrics and Gynecology, Department of Clinical and Biomedical Sciences, Linköping University Hospital 58185 Linköping +46738366479 Anna.Karlsson@liu.se Anna.Br.Karlsson@regionostergotland.se</p> <p>Tomas Lindahl, MD, PhD, Professor, Senior Consultant Department of Clinical Chemistry, Department of Clinical and Biomedical Sciences, Linköping University Hospital 58185 Linköping +4610-1033227 +46701479660 Tomas.Lindahl@liu.se</p> <p>Maria Jenmalm, MSc, PhD, Professor Division of Inflammation and Infection, Department of Biomedical and Clinical Sciences, Linköping University 58783 Linköping +4613-282418 Maria.Jenmalm@liu.se</p>
Clinical monitoring organization	<p>Forum Östergötland Medicinska Fakulteten 581 85 Linköping forumo@regionostergotland.se</p>
Principal Investigator, Jönköping (Ryhov Hospital)	<p>Laila Falknäs, senior consultant Department of obstetrics and gynecology, Ryhov hospital laila.falknas@rjl.se</p>
Principal Investigator, Värnamo (Värnamo Hospital).	<p>Shefqet Halili, senior consultant Department of obstetrics and gynecology, Värnamo Hospital shefget.halili@rjl.se</p>
Principal Investigator, Eksjö (Höglandssjukhuset i Eksjö)	<p>Malena Tiefenthal Thrane, senior consultant Department of obstetrics and gynecology, Höglandssjukhuset i Eksjö malena.tiefenthal.thrane@rjl.se</p>

Role	
Principal Investigator, Kalmar (Länssjukhuset i Kalmar)	Cecilia Molnar, senior consultant Department of obstetrics and gynecology, Länssjukhuset i Kalmar cecilia.molnar@regionkalmar.se
Principal Investigator, Västervik (Västervik Hospital)	Anders Rosenmüller, senior consultant Department of obstetrics and gynecology, Västervik Hospital anders.rosenmuller@regionkalmar.se
Central Laboratory	Klinisk Kemi Diagnostikcentrum Linköping University Hospital 58185 Linköping
Research Laboratory	Kerstin M Gustafsson, Biomedical Scientist Institutionen för biomedicinska och kliniska vetenskaper Klinisk kemi Universitetssjukhuset, hus 420, plan11 58185 Linköping Kerstin.M.Gustafsson@regionostergotland.se
Olink Laboratory	Olink Proteomics Uppsala Science Park 75137 Uppsala +4618-4443970 info@olink.com

List of used acronyms and abbreviations

Abbreviation	Term/Explanation
AE	Adverse Event = any untoward medical occurrence
AR	Adverse Reaction = all noxious and unintended reactions to the medicinal product, regardless of dose
CRF	Case Report Form
CRP	C-reactive protein
DPDS	Delayed primary debulking surgery
DSUR	Development Safety Update Report = annual safety report
EOC	Epithelial ovarian cancer
EPM	Etikprövningsmyndigheten (English: Swedish Ethical Review Authority)
GCP	Good Clinical Practice
ICH	International Council for Harmonization
ITT	Intention-to-treat = including all data from all subjects who have participated in the study
LMVH	Low molecular weight heparin
LVFS	Läkemedelsverkets författningssamling (English: Swedish Medical Products Agency's statutes)
NACT	Neoadjuvant chemotherapy
OC	Ovarian cancer
PP	Per Protocol analysis = including only data from subjects who have completed the study completely in accordance with the protocol, with no deviations from the protocol
SAE	Serious Adverse Event = serious untoward medical occurrence
SPC or SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
VEGF	Vascular endothelial growth factor
VTE	Venous thromboembolism

1 Synopsis

EudraCT number: 2021-000135-31
<p>Title:</p> <p>The Effects of tinzaparin on Biomarkers in FIGO Stage III-IV Ovarian Cancer Patients Undergoing Neoadjuvant Chemotherapy – A randomized pilot study</p>
Study code: TABANETOC
<p>Short background/ Rationale/Aim:</p> <p>Previous findings have indicated antineoplastic properties of tinzaparin (Innohep®), a commonly used anti-coagulant. Earlier studies have mainly investigated the antineoplastic effects of tinzaparin in animal models and in human cell-lines. In this pilot study we aim to examine the potential antitumoral effects of tinzaparin in vivo in women with epithelial ovarian cancer (EOC).</p>
<p>Study objectives:</p> <p>Primary objective: The primary objective of the study is to evaluate the effects of tinzaparin on changes in levels of CA-125 in EOC patients who receive neoadjuvant chemotherapy (NACT).</p> <p>Secondary objectives: The secondary objective of the study is to explore the impact of tinzaparin on the dynamic of a spectrum of immunological and coagulation factors in EOC patients who receive NACT. Besides, the compliance of tinzaparin injections and adverse events caused by tinzaparin will be described.</p>
<p>Study design:</p> <p>Randomized, open pilot trial</p>
<p>Study population:</p> <p>Women with FIGO stage III-IV EOC receiving NACT</p>
<p>Number of subjects:</p> <p>40 women, 20 in each arm.</p>
<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • The subject has given written consent to participate in the study. • Age 18 and above • Epithelial ovarian, fallopian tube or peritoneal cancer, or abdominal cancer where a biopsy indicates an origin from the ovary, fallopian tube or peritoneum. • Histology diagnosis of either high grade serous carcinoma, endometrioid carcinoma or clear cell carcinoma. • FIGO stage III-IV disease. • Selected for NACT with platinum double regimen at a multidisciplinary conference at Department of Oncology at Linköping University Hospital • Receive treatment at either of the University Hospital in Linköping, or the hospitals in Jönköping (Ryhov Hospital), Eksjö (Höglandssjukhuset Eksjö), Västervik (Västervik Hospital), Kalmar (Länssjukhuset i Kalmar), Värnamo (Värnamo Hospital). • Planned for platinum doublet regimen. • Prior to start of NACT pregnancy should be ruled out by menstrual history or in unclear cases by a urine hCG test. • Women of childbearing potential should use a safe birth control method (combined hormonal contraception, progesterone only hormonal contraception, intra uterine device, bilateral tubal occlusion, vasectomized partner, sexual abstinence, male or female condom, diaphragm with spermicide).

<ul style="list-style-type: none"> • WHO Performance Status 0-1 • Weight 50-150 kg • CA-125-level ≥ 250 kIE/L at diagnosis
<p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Concomitant treatment with heparins, low molecular weight heparins, warfarin or non-vitamin K antagonist oral anticoagulants. Platelet inhibitors are allowed. • Treatment with heparins, low molecular weight heparins or non-vitamin K antagonist oral anticoagulants within the last year. • Known or suspected allergies against any product included in the study • Ongoing pregnancy, independent of gestational age. Breastfeeding or planned pregnancy • EOC disclosed at Cesarean section • Abdominal surgery or other major surgery within the last year • Mental inability, reluctance or language difficulties that result in difficulty understanding the meaning of study participation • Treatment or disease which, according to the investigator, can affect treatment or study results • Known brain metastasis • Participation or recent participation (within the last 30 days) in a clinical study with an investigational product • Ongoing treatment of thromboembolic disease. • Thromboembolic disease within the last year. • Hypersensitivity to the active substance (tinzaparin) or any of the excipients. • Serious hemorrhage or conditions predisposing to serious hemorrhage. Serious hemorrhage is defined as fulfilling any one of these three criteria: <ul style="list-style-type: none"> a) occurs in a critical area or organ (e.g. intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, intra-uterine or intramuscular with compartment syndrome), b) causes a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or c) leads to transfusion of two or more units of whole blood or red blood cells. • Severe coagulation disorder. • Acute gastro duodenal ulcer. • Septic endocarditis. • Previous heparin-induced thrombocytopenia. • WHO Performance Status >1. • Platinum single regimen • E-GFR <30 ml/min (analyzed no more than 14 days before start of treatment with investigational product) • Platelets $<100 \times 10^9$/L (analyzed no more than 14 days before start of treatment with investigational product) • Treatment for other known malignancy within the last year (except basal cell carcinoma)
<p>Investigational product(s), dosage, administration: Innohep® (tinzaparin), 4500 IU/8000 IU daily, subcutaneous injection</p>
<p>Study endpoints:</p> <p>Primary endpoint: Level of CA-125 measured before cycles one-four of chemotherapy and preoperatively.</p> <p>Secondary endpoints: Levels of hemoglobin, platelets, leucocytes, C-reactive protein (CRP), albumin, interleukin 6 (IL-6) and vascular endothelial growth factor (VEGF) before every cycle of chemotherapy, preoperatively and three weeks after the last cycle of chemotherapy.</p>

CA-125 measured before cycles five-seven of chemotherapy and three weeks after the last cycle of chemotherapy

The compliance to tinzaparin injections and occurrence of adverse events related to tinzaparin will be determined.

Objectively confirmed VTE. Death due to VTE.

Exploratory endpoints:

Tissue Factor (TF), D-dimer, soluble P-selectin, thrombin-antithrombin complex and thrombin generation potential will be measured before every cycle of chemotherapy, preoperatively, and three weeks after the last cycle of chemotherapy.

A panel of 92 inflammation-associated proteins will be measured at baseline, at visit 5 and at visit 8 or 9.

Study period:

Q1 2022-Q4 2024

2 Background and rationale

Ovarian cancer (OC) is the gynecological malignancy with the highest mortality rate. In Sweden approximately 700 women are annually diagnosed with OC and in 2018, 568 women died due to OC (1,2). The vast majority of OCs is epithelial OC (EOC). EOC is a heterogeneous disease with different characteristics in carcinogenesis, risk factors, morphology, response to treatment and prognosis. The majority of EOCs is assumed to originate from the fallopian tubes. Although it may be unclear where the cancer started, tubal, ovarian and primary peritoneal cancers have histopathological similarities, and are treated similarly (3-5). From a clinical perspective these three cancers are considered as one entity and are referred to as EOC in this study. To ensure the organ-specific diagnosis a histopathology examination of the ovaries and the fallopian tubes is required. Prior to surgery the diagnosis is therefore not organ-specific, but tentative and is most often based on a core needle biopsy, where the histopathology indicates the genital organs as origin of the cancer. Until the organ-specific diagnosis of the cancer has been determined, the cancer is usually denominated as abdominal cancer.

International guidelines on treatment of advanced stage EOC recommend primary debulking surgery (PDS) followed by adjuvant chemotherapy when it is considered possible to achieve surgical radicality with no macroscopically residual tumor at conclusion of the surgery. However, if this goal is considered not achievable it is recommended to start treatment with NACT followed by delayed primary debulking surgery (DPDS). The choice of primary treatment of advanced stage EOC is dependent on the assessment of the patient and the primary investigation. No unanimous criteria have been suggested to select between the two primary treatment modalities (PDS and NACT). Several clinical, laboratory and imaging factors may influence the decision. When a multidisciplinary team conference deems PDS impossible, based on the primary investigations, the patient is offered NACT (6).

Tinzaparin, a low-molecular weight heparin (LMWH), is an anti-thrombotic drug used in the treatment and prevention of thromboembolism. Tinzaparin acts by activating antithrombin and inactivating factor Xa (7). Moreover, tinzaparin exhibits anti-inflammatory effects indicating immune system modulating properties (8). In addition to its ability to inhibit thrombin and factor Xa, tinzaparin is effective at releasing endothelial tissue factor pathway

inhibitor, the natural inhibitor of both procoagulant and non-coagulant effects of TF. TF acts normally as a cellular receptor for factor VIIa and initiates the coagulation pathway. TF is present on the surface of many tumor cell types and is believed to be responsible for tumor cell procoagulant activity. Animal studies and in vitro studies on human ovarian cancer and breast cancer cells as well as umbilical vein endothelial cells have indicated an anti-metastatic potential of tinzaparin (9). Various mechanisms have been suggested for the anti-metastatic effect, including inhibiting the tissue factor pathway, upregulating E-Cadherin and downregulating von Willebrand-factor. This affects the metastatic process by inhibiting local invasion, the migration of tumor cells, and the promotion of tumor angiogenesis, which are all crucial to the metastatic growth and considered to be hallmarks of cancer (10-17).

EOC most commonly metastasize within the peritoneal cavity and ascites is often found at the time of diagnosis. Malignant cells undergo an epithelial to mesenchymal transition and spread with the ascites. This transition includes changes in cadherin expression and up-regulation of proteolytic pathways. When attaching to peritoneal surfaces the cancer cells return to the epithelial state (18). VEGF is produced by the tumor cells and promotes angiogenesis in the primary tumor as well as in the metastases. Furthermore, VEGF also increases vascular permeability which results in increased ascites production (19)

In colon cancer patients, the use of tinzaparin 4500 IU daily for 30 days postoperatively reduced the levels of VEGF to the preoperative level in the first preoperative month whereas it remained elevated in patients who received lower dose of tinzaparin and/or shorter duration of treatment (20).

Therapeutic doses of tinzaparin have been shown to antagonize cisplatin resistance in an EOC cell line by inhibiting expression of genes that mediate cisplatin resistance (21). The standard treatment for primary EOC includes platinum-based chemotherapy in combinations with paclitaxel. Thus, treatment with tinzaparin may potentially be assumed to counteract the effect of cisplatin resistance in EOC.

Previous studies have suggested various biomarkers as prognostic factors in EOC. The serum level of CRP, an inflammatory biomarker, is a prognostic factor for overall survival, progression free survival and postoperative residual tumor mass (22,23). High levels of IL-6, also an inflammatory biomarker, predicts reduced overall survival and progression free survival (23). Thrombocytosis and anemia are associated with advanced stage EOC, reduced disease-free survival and overall survival (24-27). Low levels of albumin predict of suboptimal debulking as well as of death within six months (28,29). Low levels of hemoglobin and albumin and high levels of platelets and CRP may be indicators of an activated systemic inflammatory response indicating more advanced or maybe generalized malignancy. Other inflammatory markers, such as other interleukins and tumor necrosis factors may also be of interest to analyze.

CA-125, a glycoprotein produced by mesodermally derived tissues, has been found useful as a biomarker of EOC. Higher levels of CA-125 may indicate greater tumor burden and more advanced disease. Studies have also found CA-125 to be of value for predicting suboptimal debulking (30). However, there are contradicting results regarding pre-treatment CA-125 as a predictor for overall survival (31,32). In women with advanced EOC receiving NACT as primary treatment the reduction in CA-125-level has been recognized as a predictor for overall survival as well as optimal cytoreduction when undergoing DPDS (33,34). A decrease

in CA-125 level of more than 50% after the first course of chemotherapy is indicative for better prognosis (35,36)

We have previously shown that the pre-treatment levels of platelets, CRP, albumin and CA-125 in peripheral venous blood were independent predictors of survival in FIGO stage III-IV EOC. Women with low levels of serum albumin or high levels of platelets, CRP or CA-125 had significantly shorter survival than women with normal levels of these biomarkers (37).

In order to evaluate the effect of tinzaparin on these biomarkers in advanced stage EOC we selected patients receiving NACT. Patients undergoing PDS are treated with thromboprophylactic LMWH postoperatively for four weeks and consequently it will not be possible to determine the effect of tinzaparin on the biomarkers. Thus, by selecting only patients for NACT the differences in biomarker levels in patients receiving tinzaparin in addition to NACT in comparison to patients receiving NACT only might indicate anti-neoplastic properties of tinzaparin.

Tinzaparin will have effects on the coagulation system, which is well-known. It promotes the inhibiting effect of Antithrombin III on the activated coagulation factors, mainly factor Xa. However, it is unknown if anti-neoplastic effects are correlated to remaining activation of platelets and coagulation. To evaluate the potential association between the biomarkers and coagulation, D-dimer, soluble P-selectin, thrombin-antithrombin complex and thrombin generation potential will be used.

The clinical effect of tinzaparin on neoplastic growth in EOC is poorly investigated. EOC patients have a higher incidence of venous thromboembolism (VTE) than other cancers (34). The risk of VTE is 20-27% within one year after diagnosing ovarian cancer (38,39) Despite this high incidence the guidelines for treatment of EOC still do not include recommendations on long term antithrombotic prophylaxis. Thus, the long-term effect of tinzaparin on EOC has yet to be elucidated. This pilot study will contribute with knowledge on how tinzaparin affects biomarkers associated with survival and other prognostic factors in patients with EOC.

3 Benefit-risk evaluation

Given that tinzaparin has antitumoral effects, women in the treatment group are expected to have more marked changes in CA125 levels than the control group. This might indicate better response to NACT and a greater chance of achieving macroscopic radicality upon delayed primary debulking surgery. Tinzaparin is a commonly used, well tolerated, anticoagulant, both for treatment of manifest VTE and as prevention of VTE. Women with EOC have an increased risk of VTE compared to healthy women and compared to patients suffering from other cancers. Thus, receiving treatment with tinzaparin may be expected to decrease the risk of VTE, with health benefits for the subjects themselves as well as health economic benefits

Tinzaparin given in thrombosis-prophylactic dosage have few known side effects, they include hematomas and other reactions at the injection site and, rarely, allergic reactions. Anemia and heparin-induced thrombocytopenia have occurred. Subjects included in this study will have blood samples analyzed every three weeks during the course of the study, thus will any anemia or thrombocytopenia be found.

Bleeding events have been reported during treatment with tinzaparin, mainly when high doses of tinzaparin were given. Simultaneous use of drugs that affects the coagulation increases the risk of bleeding events; in this study women with ongoing anticoagulant treatment will be excluded. Treatment with platelet inhibitors will be allowed.

Since this is a pilot study and since the selected end point variables should not be affected by any placebo-effect this study is not blinded.

This study entails small risks, of mainly minor bleeding events. However, the potential benefits concerning antineoplastic effect and risk reduction of thromboembolic events during chemotherapy exceed the risk for minor bleeding adverse events.

3.1 Benefit-risk evaluation with respect to the ongoing Covid-19 pandemic

This study will not generate any extra health care visits as screening, inclusion, randomization and collection of blood samples will be performed during a visit when the subject will attend as part of the clinical routine. Therefore, this study is not to be expected to increase the subjects' risk to be infected by Covid-19. The follow up one week after end of treatment will be implemented as a phone call to further decrease the risk of infection.

In case a subject has been infected by Covid-19 the following chemotherapy will be postponed until the subject has recovered from the infection. In case a subject has to cancel a visit due to Covid-19-infection she will be contacted by phone to assess any adverse events and the blood samples will be collected as soon as possible after she has recovered from the infection/is no longer considered contagious. Treatment with investigational product will continue during the infection. As Covid-19 is associated with increased risk of VTE, treatment with the investigational product might be beneficial for the subject.

The study related procedures (screening, inclusion, randomization, collection of blood samples, follow up of adverse events) are not expected to pose notable extra workload on health care staff and resources as they will be performed during regular health care visits.

The median age of patients diagnosed with EOC is 69 years and few patients are below 40 years of age, thus a majority of the subjects will be vaccinated against Covid-19 at study start. Sponsor will evaluate the virus infection rate and the pandemic situation when all approvals are in place. If the risk-benefit ratio is considered positive, the study will start. Sponsor will continuously evaluate the Covid-19 situation during the study and if the risk-benefit ratio develops in a negative direction the study will temporary be paused by the sponsor.

4 Study objectives

4.1 Primary objective

The primary objective of the study is to evaluate the effects of tinzaparin on changes in levels of CA-125 in EOC patients who receive NACT.

4.2 Secondary objective(s)

The secondary objective of the study is to explore the impact of tinzaparin on the dynamic of a spectrum of immunological and coagulation factors in EOC patients who receive NACT. Besides, the compliance of tinzaparin injections and adverse events caused by tinzaparin will be described. Thromboembolic events will be registered.

4.3 Primary endpoint (variable)

Primary variable: Level of CA-125 measured before cycles one-four of chemotherapy and preoperatively before DPDS.

4.4 Secondary endpoints (variables)

Secondary variables:

Levels of hemoglobin, platelets, leucocytes, CRP, albumin, IL-6 and VEGF before every cycle of chemotherapy, preoperatively before DPDS and three weeks after the last cycle of chemotherapy.

CA-125 measured before cycles five-seven of chemotherapy and three weeks after the last cycle of chemotherapy

The compliance to tinzaparin injections and occurrence of adverse events related to tinzaparin will be evaluated.

Objectively confirmed VTE, i.e. pulmonary embolism, lower-limb deep vein thrombosis or upper extremity deep vein thrombosis. Death due to VTE.

4.5 Exploratory endpoints (variables)

Exploratory variables:

TF, D-dimer, soluble P-selectin, thrombin-antithrombin complex and thrombin generation potential will be measured before every cycle of chemotherapy, preoperatively and three weeks after the last cycle of chemotherapy.

A panel of 92 inflammation-associated proteins will be measured at baseline, at visit 5 and at visit 8 or 9. Blood samples from all visits will be stored in biobanks for possible additional analyzes of the inflammatory panel from the remaining visits.

5 Study design and procedures

5.1 Overall study design

This is an open randomized controlled clinical pilot trial (Phase II). The study includes women with stage III-IV EOC selected for NACT and without signs of thromboembolic disease or ongoing treatment of thromboembolic disease. The women will be allocated 1:1 to treatment with tinzaparin 4500 IU/8000 IU (dose depending on woman's weight) subcutaneously once daily or no tinzaparin. The treatment group starts tinzaparin when the primary treatment (chemotherapy) starts. The control group will not receive tinzaparin or other low molecular weight heparin preparations. The NACT consists of carboplatin and paclitaxel, given

according to the standard regimen with cycle repeats every 21 days. Pre-treatment and before every cycle of chemotherapy venous blood samples will be taken for measuring the biomarkers hemoglobin, platelets, leucocytes, CRP, albumin, CA-125, Tissue Factor, D-dimer, soluble P-selectin, thrombin-antithrombin complex and thrombin generation potential. Furthermore, a panel of 92 inflammation-associated proteins will be analyzed by a by a high-sensitivity Proximity Extension Assay at baseline, visit 5 and visit 8 or 9. After three cycles of NACT, the patient will be evaluated clinically and with imaging diagnostics in order to determine whether the patient should undergo DPDS. In our setting, > 80% of patients receiving NACT for EOC undergo delayed primary debulking surgery. After DPDS, all patients will be treated with tinzaparin for 28 days according to clinical practice concerning postoperative thromboembolic prophylaxis and thereafter continue the chemotherapy for additional two-three courses. The participants who were allocated to tinzaparin during the NACT will continue the tinzaparin after ending the postoperative thromboembolic prophylactic tinzaparin treatment for additional 2-3 courses. The biomarkers will be measured preoperatively and four weeks postoperatively after DPDS and then before each course of chemotherapy given during the primary treatment. The women who do not undergo surgery will remain included in the study for the following three cycles of chemotherapy. Thus, the total study period constitutes 22-29 weeks.

5.2 Procedures and flow chart

See Appendix 1 flowchart and Appendix 2 study design

5.3 Biological sampling procedures

5.3.1 Handling, storage, and destruction of biological samples

Blood samples will be taken before every cycle of chemotherapy, preoperatively and three weeks after the last cycle of chemotherapy. Analyzes will be undertaken at accredited laboratories at sites, at research laboratories at Linköping University Hospital and at Olink Laboratories in Uppsala. For methods see section 8.1.2. Routine blood samples will be analyzed continuously, and the remaining blood samples will be stored in local biobanks at sites until transport to laboratories in Linköping and Uppsala.

5.3.2 Total volume of blood per subject

The total volume of blood taken from each subject during the study is maximum 100 ml.

5.4 Biobank

All samples taken in this study are included in each regional biobank and are then handed out to Biobank Östergötland (registreringsnummer 1) The samples are handled according to the current biobank laws and regulations. The samples are coded/pseudonymized to protect the subject's identification. All samples and the identification/code list are stored securely and separately to prevent unauthorized persons from having access to them.

5.5 End of Study

The study ends when the last subject has completed the last follow-up. The study may be prematurely terminated if it appears that the treatment involved a large number of serious adverse events (SAE) or if recruitment of subjects cannot be met within reasonable time limits. If the study is prematurely terminated or suspended, the investigator should

immediately inform the subjects about this and ensure appropriate treatment and follow-up. The regulatory authority should be informed as soon as possible, but no later than within 15 days. Decisions on premature termination are taken by the sponsor.

6 Subject selection

6.1 Inclusion criteria

To be included in the study, subjects must meet the following criteria:

- The subject has given written consent to participate in the study.
- Age 18 and above
- Epithelial ovarian, fallopian tube or peritoneal cancer, or abdominal cancer where a biopsy indicates an origin from the ovary, fallopian tube or peritoneum.
- Histology diagnosis of either high grade serous carcinoma, endometrioid carcinoma or clear cell carcinoma.
- FIGO stage III-IV disease.
- Selected for NACT with platinum double regimen at a multidisciplinary conference at Department of Oncology at Linköping University Hospital
- Receive treatment at either of the University Hospital in Linköping, or the hospitals in Jönköping (Ryhov Hospital), Eksjö (Höglandssjukhuset Eksjö), Västervik (Västervik sjukhus), Kalmar (Länssjukhuset i Kalmar), Värnamo (Värnamo sjukhus).
- Planned for platinum doublet regimen.
- Prior to start of NACT pregnancy should be ruled out by menstrual history or in unclear cases by a urine hCG test.
- Women of childbearing potential should use a safe birth control method (combined hormonal contraception, progesterone only hormonal contraception, intra uterine device, bilateral tubal occlusion, vasectomized partner, sexual abstinence, male or female condom, diaphragm with spermicide).
- WHO Performance Status 0-1
- Weight 50-150 kg
- CA-125-level ≥ 250 kIE/L at diagnosis

6.2 Exclusion criteria

Subjects must not be included in the study if any of the following criteria are met:

- Concomitant treatment with heparins, low molecular weight heparins, warfarin or non-vitamin K antagonist oral anticoagulants. Platelet inhibitors are allowed.
- Treatment with heparins, low molecular weight heparins or non-vitamin K antagonist oral anticoagulants within the last year.
- Known or suspected allergies against any product included in the study
- Ongoing pregnancy, independent of gestational age. Breastfeeding or planned pregnancy
- EOC disclosed at Cesarean section
- Abdominal surgery or other major surgery within the last year
- Mental inability, reluctance or language difficulties that result in difficulty understanding the meaning of study participation

- Treatment or disease which, according to the investigator, can affect treatment or study results
- Known brain metastasis
- Participation or recent participation (within the last 30 days) in a clinical study with an investigational product
- Ongoing treatment of thromboembolic disease.
- Thromboembolic disease within the last year.
- Hypersensitivity to the active substance (tinzaparin) or any of the excipients.
- Serious hemorrhage or conditions predisposing to serious hemorrhage. Serious hemorrhage is defined as fulfilling any one of these three criteria:
 - a) occurs in a critical area or organ (e.g. intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, intra-uterine or intramuscular with compartment syndrome),
 - b) causes a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or
 - c) leads to transfusion of two or more units of whole blood or red blood cells.
- Severe coagulation disorder.
- Acute gastro duodenal ulcer.
- Septic endocarditis.
- Previous heparin-induced thrombocytopenia.
- WHO Performance Status >1.
- Platinum single regimen
- E-GFR <30ml/min (analyzed no more than 14 days before start of treatment with investigational product)
- Platelets <100 x10⁹/L (analyzed no more than 14 days before start of treatment with investigational product)
- Treatment for other known malignancy within the last year (except basal cell carcinoma)

6.3 Screening

Prescreening will be done during a multidisciplinary conference at Department of Oncology at Linköping University Hospital. Subject eligibility (that subjects fulfill all inclusion criteria and do not meet any exclusion criteria) is established at an inclusion visit at each hospital (site) where the subject will receive treatment.

6.4 Withdrawal criteria

- The study subject may choose to discontinue the study at any time
- The principal investigator can terminate a subject's participation (due to, e.g., non-tolerable adverse events/adverse reactions, pregnancy, etc.).
- A concerned Competent Authority can terminate the study.
- Discontinuation of treatment with curative intention or start of second line-treatment.

The criteria below will result in discontinuation of treatment with investigational product, but the subjects will remain in the intention-to-treat-analyses.

- Other disease that precludes continuation in the study
- VTE occurring during the study.

- Bleeding events resulting in surgical or medical intervention or where discontinuation of treatment with tinzaparin is recommended.
- Significant anemia caused by bleeding.
- Heparin-induced thrombocytopenia.
- Insufficient compliance (>20% missed injections) at visit 5

The criteria below will not result in discontinuation of treatment with investigational product.

- Change from platinum doublet regimen to platinum single regimen.

A platelet count below $50 \times 10^9/L$ will result in a pause in treatment with the investigational product, treatment will restart when the platelet count is equal to or above $50 \times 10^9/L$. If a platelet count below $50 \times 10^9/L$ is discovered, it will be measured daily until the platelet count is equal to or above $50 \times 10^9/L$.

Subjects can discontinue their participation in the study at any time without any consequence to her continued treatment. The investigator/sponsor can at any time terminate the study for a subject due to, e.g., unacceptable adverse events/adverse reactions or because the subject does not follow procedures in the study protocol. If the subject discontinues the study, follow-up of this subject will be performed according to the clinic's routine.

Data for subjects who prematurely discontinue the study will be included and analyzed if they have followed protocol (missed less than 20% of injections) until visit 5. Another subject will be included to achieve the desired number of included subjects according to the sample size calculation if a subject discontinues the study before visit 5.

7 Study treatments

7.1 Description of investigational product(s)

The investigational product will be Innohep® (tinzaparin) solution for injection with either a dosage of 4500 IU once daily for patients weighing below 90 kg or dosage of 8000 IU for patients weighing more than 90 kg. The manufacturer is Leo Pharma AB and there are no replaceable solutions available. As comparative treatment no tinzaparin is used.

The investigational product will be prescribed by an investigator at each site.

7.2 Dose and administration

Tinzaparin will be given in a weight-customized dose. Subjects weighing below 90 kg will be given 4500 IU once daily and subjects weighing 90 kg and above will be given 8000 IU once daily. Tinzaparin will be administered subcutaneously by the subject herself after instructions by a nurse or a doctor. The subjects will also receive a written instruction produced by the manufacturer. The chosen dose is the standard dose for thromboembolic prophylaxis where the wanted effects should occur at the same time as few side effects are expected.

Tinzaparin shall be injected at the same time (± 2 hours) every day, in the evening, for 21-28 weeks.

7.3 Packaging, labeling, and handling of investigational products(s)

The investigational product will be prescribed by an investigator at each site. The prescription will include information about billing address to a study account, the subject will have no cost for the investigational product. The investigational product is stored in room temperature and no temperature monitoring is needed.

As the investigational product will be prescribed and the subjects will retrieve it from a pharmacy of their choice there will be no specific labeling.

7.4 Drug accountability and treatment compliance

The investigational product will be administered by the subject after instructions by a doctor or nurse. At the visits, the subject will be asked if she has taken all injections, if there are any difficulties or side effects from taking them and she will be offered additional instructions if needed.

Missed doses should be taken when discovered if discovered during the same day. Missed doses discovered the next day should not be taken and the next dose should be taken at the same time as it would otherwise have been taken.

>20 % missed doses is considered as insufficient compliance.

The subjects will record the injections and any discovered side effects in a study-specific diary.

7.5 Randomization

Subjects will randomly be assigned into two groups – Group A -receiving tinzaparin (intervention group) and Group B –control group - without tinzaparin. A list of random numbers will be created using a web-based allocator for simple randomization. The allocated method will be written on a paper placed in a sealed envelope. The envelopes are consecutively numbered according to the randomization list from 1 to 40. When the inclusion and exclusion criteria have been checked by the investigator, and the person has signed informed consent, the investigator contacts the coordinating nurse at the department of oncology at the University Hospital in Linköping by telephone. The coordinating nurse opens the randomization envelope (in consecutive number order) and report the allocation to the investigator; in addition, the paper with the allocation is sent to the investigator by fax and the coordination nurse register the allocation and number written on the envelope in the patient file. The investigators will not have access to the outcome of allocation of participants at other sites.

The number of the envelope constitutes the identification number of the participant in the trial.

The randomization will take place at least one workday before start of neoadjuvant chemotherapy and treatment with the investigational product.

Additionally, in order to replace withdrawals a list of 10 random numbers from 1 to 10 with equal number of interventions and controls will be created. The envelopes will be numbered from 41 to 50 and opened consecutively in order to replace a withdrawal.

7.6 Blinding

The study is not blinded for subjects and investigators. The laboratories will be blinded. Code breaking N/A.

7.7 Concomitant medications

7.7.1 Background treatment

All subjects will receive chemotherapy of the platinum double regimen including carboplatin (dose calculated by Calvert formula) and paclitaxel (175 mg/m²) every three weeks. To abate side effects of the chemotherapy subjects will receive corticosteroids, antiemetics and prophylaxis against allergic reactions according to local routine. After clinical evaluation postoperatively some subjects will be given bevacizumab (7,5 mg/kg) in addition to carboplatin and paclitaxel for the remaining treatment with chemotherapy starting 4-6 weeks after surgery. These medications should be reported in the Case Report Form (CRF). The effect of the investigational product might be enhanced by other drugs affecting the coagulation system. None of the background medications has a direct effect on the coagulation system. Corticosteroids as well as the chemotherapy imply an increased risk of bleeding events and thrombocytopenia. All subjects will be monitored regularly with blood samples, thus will any anemia or thrombocytopenia be discovered.

7.7.2 Other concomitant medications

Medications that are considered necessary for the safety and well-being of the subject can be given at the discretion of the investigator, unless otherwise specified as an exclusion criterion. These medications should be reported in the CRF.

7.8 Destruction

Residual investigational products will be returned to a pharmacy by the subjects.

7.9 Treatment after study end

After the study end the subjects will receive no further investigational treatment and will be followed-up according to clinical routine.

8 Methods for measurement of endpoints for clinical efficacy and safety

8.1 Methods for measurement of endpoints for clinical efficacy

8.1.1 Primary endpoint (variable)

CA-125 is a tumor marker used to assess the likelihood of an ovarian mass being a malignancy and during treatment it is used to evaluate the patient's response to the treatment. As CA-125 is used as clinical routine it will be analyzed continuously during the study at all study sites. For subjects outside Region Östergötland CA-125 will also be analyzed continuously or after study end at Linköping University Hospital using Cobas e602, electrochemical luminescence immunoassay, in order to have all samples analyzed with the same method.

8.1.2 Secondary endpoints (variables)

All laboratories at sites are accredited by SWEDAC.

Biomarker	Analyzed	Method	Laboratory
Hemoglobin	Continuously (part of clinical routine)	Photometry	Local laboratory at site
Leucocytes	Continuously (part of clinical routine)	Flow cytometry	Local laboratory at site
Platelets	Continuously (part of clinical routine)	Impedance and fluorescence cytometry or impedance method (RBC/PLT canal)	Local laboratory at site
Albumin	Continuously (part of clinical routine)	Turbidimetric analysis or colorimetry, endpoint	Local laboratory at site
CRP	Continuously (part of clinical routine)	Immunoturbidimetric analysis or turbidimetric fixed point measurement	Local laboratory at site
IL-6	Continuously or after study end	Chemical luminescence	Central laboratory, Linköping University Hospital
VEGF	After study end	ELISA	Research laboratory, Linköping University Hospital
Tissue Factor	After study end	ELISA	Research laboratory, Linköping University Hospital
D-dimer	Continuously or after study end	Latex-enhanced turbidimetry	Central laboratory, Linköping University Hospital
Soluble P-selectin	After study end	ELISA	Research laboratory, Linköping University Hospital
Thrombin-antithrombin complex	After study end	ELISA	Research laboratory, Linköping University Hospital
Thrombin generation potential	After study end	Photometry	Research laboratory, Linköping University Hospital
Panel of 92 inflammation associated proteins	After study end	Proximity Extension Assay technology	Olink laboratory, Uppsala

8.2 Methods for measurement of endpoints (variables) for clinical safety

Anemia and heparin-induced thrombocytopenia are known but very rare side effects of tinzaparin. Subjects in this study will have hemoglobin and platelets measured every three weeks and therefore any anemia or thrombocytopenia will be discovered.

Urine hCG will be taken before every cycle of chemotherapy in women of childbearing potential.

9 Handling of Adverse Events

All AE's and SAE's will be reported in both arms from the visit when the investigational product is given for the first time until one week after last injection.

AE and SAE are followed up until they are fully evaluated or no longer considered clinically significant by the principal investigator.

9.1 Definitions

9.1.1 Adverse Event (AE)

Adverse Event (AE): Any untoward medical occurrence in a clinical investigation subject administered a medicinal product and, which does not necessarily have a causal relationship with the treatment, can be an unfavorable and unintended sign symptom or disease temporally associated with the use of the medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

9.1.2 Adverse Reaction (AR)

All noxious and unintended reactions to the medicinal product related to any dose should be considered an adverse reaction (AR). The phrase “reaction” to a medicinal product means that the causal relationship between the medical product and an adverse event is at least a reasonable possibility, that is the relationship cannot be ruled out.

9.1.3 Serious Adverse Event (SAE)

Serious adverse event (SAE): Any untoward medical occurrence that at any dose:

- results in death
- is life-threatening.
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- results in a congenital anomaly/malformation

Medical and scientific assessment will be made to determine if an event is “serious” and whether it would prompt reporting in other situations, for example important medical events that may not be directly life-threatening or result in death or hospitalization but may compromise the study subject or may require intervention to prevent one of the other results set forth in the definitions above. These should also normally be considered as SAEs.

9.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

SUSAR: A reaction/event that is unexpected, serious, and suspected to be caused by the treatment, i.e. adverse events that are not included in the SPC.

9.2 Assessment of Adverse Events

9.2.1 Assessment of causal relationship

Those AEs which are suspected of having a relationship to the investigational product will be followed up until the subject has recovered or is well taken care of and on their way to good recovery.

All AE will be categorized either as likely related, possibly related, or not related, in accordance with the definitions below:

Likely related: Clinical event, including abnormal results from laboratory analyses, occurring within a reasonable time after administration of the intervention/investigational product. It is unlikely that the event can be attributed to underlying disease or other medications but is

most likely caused by the investigational product and its emergence is reasonable in relationship with use of the investigational product.

Possibly related: Clinical event, including abnormal results from laboratory analyses, occurring within a reasonable time after administration of the intervention/investigational product. The event could be explained by the investigational product and its emergence is reasonable in relationship with use of the investigational product, but there is insufficient information to determine the relationship. The event could be explained by an underlying disease or other medications.

Not related: Clinical event, including abnormal results from laboratory analyses, that is not reasonably related to the use of the intervention/investigational product. The event is unlikely related to the intervention/investigational product and can be explained by other medications or underlying disease.

9.2.2 Assessment of intensity

Each adverse event shall be classified by an investigator as mild, moderate or severe.

Mild: The adverse event is relatively tolerable and transient in nature but does not affect the subject's normal life.

Moderate: The adverse event causes deterioration of function but does not affect health. The event can be sufficiently unpleasant and interferes with normal activities but does not completely obstruct them.

Severe: The adverse event causes deterioration of function or work ability or poses a health risk to the subject.

9.2.3 Assessment of seriousness

The investigator is responsible for assessing the seriousness (serious or non-serious). If the incident is considered serious, this should be reported as a serious adverse event (SAE) by the investigator to the sponsor.

9.3 Reporting and registration of Adverse Events

At each study visit, adverse events (AE) are registered, starting from start of treatment with the investigational product, up to and including 1 week after the subject has ended their treatment with the investigational product. All AE that occur during the study and which are observed by the investigator/study nurse or reported by the subject will be registered in the CRF regardless of whether they are related to the investigational product or not. Assessment of causal relationship, severity, and whether the AE is considered to be an SAE or not will be done by the investigator directly in the CRF. At minimum, for each AE/SAE, a description of the event is recorded (diagnosis/symptom if diagnosis is missing), start and stop dates, causal relationship, severity, if the AE is considered to be an SAE or not, measures and outcome.

The signs and symptoms below are common or very common side effects of the chemotherapy and therefore will not be reported as AE.

- Leucopenia
- Neutropenia

- Infections (aside from infections at injection site)
- Peripheral neuropathy
- Paresthesias
- Sensory disturbances
- Dysgeusia
- Visual disturbances
- Ototoxicity
- Headache
- Dysarthria
- Syncope
- Somnolence
- Cardiovascular disease
- Tachycardia
- Bradycardia
- Hypertension
- Hypotension
- Interstitial lung disease
- Bronchospasm
- Dyspnea
- Rhinitis
- Cough
- Abdominal pain
- Vomiting
- Nausea
- Diarrhea
- Obstipation
- Anorexia
- Dehydration
- Stomatitis
- Mucositis
- Arthralgia
- Myalgia
- Alopecia
- Exfoliative dermatitis
- Palmar-plantar erythrodysesthesia
- Asthenia
- Lethargy
- Pyrexia
- Common postoperative symptoms that are not related to tinzaparin

Innohep® (tinzaparin) is a commonly used anticoagulant with well-known side effects. Side effects are anemia, bleeding, hematomas and bruises, the latter mostly as local reactions at injection sites. The following signs and symptoms can be related to both the investigational product and to the chemotherapy and will therefore be considered AE's:

- Anemia

- Hematoma
- Epistaxis
- Hemoptysis
- Other bleeding events
- Local reactions at injection site

Signs and symptoms not listed in any of the above sections will be considered AE's.

9.3.1 Reporting of Adverse Events (AE)

All AE shall be registered in the CRF within 1 week as above.

9.3.2 Reporting of Serious Adverse Events (SAE)

Serious adverse events (SAE) are reported to the sponsor by sending a special SAE form within 24 hours of the investigator being informed of the SAE to sponsor Preben Kjølhede by email to preben.kjolhede@liu.se and by SMS sent to 070-5688201 informing there is an email regarding a SAE.

Any SAE and AE that is likely related to the investigational product will also be reported to LEO Pharma by the sponsor.

Follow-up information describing the outcome and handling of the SAE is reported as soon as this information is available. The original should be kept in the Investigator Site File.

Based on knowledge of the disease in question and expected clinical course, some events that are otherwise serious are not considered as SAEs in this study.

The following is a list of SAEs that shall not be reported as SAEs:

- Expected events based on the knowledge of the disease in question and expected clinical course.
- If a study subject is hospitalized with a documented cancer-related problem, this will not be reported as an SAE.

9.3.3 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSAR)

Any SUSAR that is fatal or life-threatening will be recorded and reported to the medical products agency (MPA) within seven days on a CIOMS form and with assistance of the MPA also reported into the EudraVigilance Clinical Trials Module. Sponsor will report SUSARs separately to the Ethical review authority. Relevant follow-up information will subsequently be communicated within an additional eight days. All other SUSARs that are not fatal or life-threatening will be reported no later than 15 days after the sponsor learning of them.

Information about SUSAR occurring during the study is compiled by the sponsor and sent out to the principal investigator at all participating centers.

9.4 Follow-up of Adverse Events

Subjects affected by adverse events will be followed-up until the AE/SAE is resolved/stable/persistent. In case of unacceptable adverse events the subject will be withdrawn from the study and followed up according to clinical routine.

9.5 Annual Safety Report (Development Safety Update Report, DSUR)

As long as the study is in process, the sponsor will submit an annual safety report to the Swedish Medical Products Agency. It defines for which time period the report applies and a list of all SAE that have occurred as well as possibly SUSARs. A summary assessment of the safety situation for the subjects and a benefit/risk evaluation for the study should also be described.

9.6 Procedures in case of emergencies, overdose or pregnancy

Since curative treatment of FIGO stage III and IV EOC is not compatible with fertility sparing surgery, pregnancy occurring during the study is highly unlikely.

Tinzaparin is used in pregnancy when the pregnant women have high risk of VTE or manifest VTE with low risk for the fetus. The chemotherapy given to the women included in this study has known teratogenous effects and all women of fertile age are advised on using effective contraceptives.

If a subject becomes pregnant during the study, treatment with tinzaparin will be stopped. She will be followed up until birth and any congenital malformations will be reported as SAE.

9.7 Reference Safety Information

As reference safety information the SPC for Innohep® (Tinzaparin, LeoPharma) is used.

10 Statistics

10.1 Analysis population

The study will include 20 women who are analyzed per protocol which means they have not missed more than 20 % of the injections and 20 women in the control-group. The analyses will be conducted according to both intention to treat principles and to per protocol.

10.2 Statistical analyses

10.2.1 Statistical methods

Descriptive statistics for continuous data will be given as appropriate measures of central tendency (mean and/or median) and dispersion will be provided as standard deviation, range or interquartile range. Categorical nominal or ordinal data will be presented as number and frequency in percent. Univariate comparison of continuous data between groups will be conducted with analysis of variance (ANOVA), t-test or non-parametric tests (Mann-Whitney U-test), as appropriate. Categorical data will be compared using Pearson's chi-squared test or Fisher's exact test, as appropriate.

In order to evaluate the changes in the levels of the biomarkers over time between the treatment arm and the control arm both the primary and the secondary objectives will be analyzed using repeated measures ANOVA models. Continuous variables that are not normally distributed will be transformed using Cox and Box's method in order to achieve the most appropriate transformation of data to a normal distribution.

Outcome of statistical tests will be presented as p-value. Two-sided test for statistical significance will be used and a $p < 0.05$ will be considered statistically significant.

Subgroup analysis will be done for the group of BRCA mutated patients. Although the study is not powered after BRCA mutated participants, the result of such comparison may add interesting scientific knowledge and potentially be hypothesis generating for future studies.

10.2.2 Drop-outs

Repeated measures ANOVA requires measurements on all occasions of measuring. Consequently, missing values must be replaced. We assume that data are missing completely at random (MCAR) and we will use the multiple imputation procedure in SPSS. The number of imputed data sets will depend on the number of missing values but will not be less than ten.

10.3 Adjustment of significance and confidence interval

Not relevant for this pilot study.

10.4 Sample size calculations

This is a pilot study with an exploratory purpose. Sample size estimation is based on the primary outcome CA-125. A reduction in CA-125 between two cycles of chemotherapy of $>50\%$ has been shown to be a strong prognostic factor for survival. A lower response rate in CA-125 has been associated with an unfavorable outcome and a higher risk for suboptimal DPDS. In clinical practice this information is used in the evaluation to determine whether a patient receiving NACT shall be recommended DPDS.

No information is available about the size of effect of tinzaparin on CA-125 levels. In order to be clinically significant we assume that tinzaparin must reduce the response rate on CA-125 level after NACT additionally with at least 25%.

The response of the chemotherapy in patients who receive NACT is evaluated at a multidisciplinary team conference between the third and fourth cycle of chemotherapy. Thus at that time (after cycle 3) information on the clinical blood samples, including CA-125 is available. Provided that the mean level of CA-125 was 2000 at baseline and the standard deviation was 25% of the mean on all occasions of measurement and the mean level of CA-125 decreases at least 50% in the control arm and additional 25% (due to the effect of tinzaparin) in the treatment arm the calculated estimated sample size of the study is 16 in each arm in order to obtain a statistical significance between groups with 80% power at a 5% significance level for two-sided testing.

To compensate for the proportion of women that does not undergo DPDS (approximately 20%) each group should consist of 20 women.

A simple sensitivity analysis concerning different requests to the additional effect of tinzaparin on CA-125 after NACT is presented in the table below. Three various scenarios of reduction in CA-125 levels are depicted. Based on empirical and clinical considerations we find it most likely that the variation in CA-125 will follow scenario B

Table1. Sensitivity analysis with three different scenarios A, B, and C.

	Scenario with reduction in CA-125 at each cycle	Baseline (before cycle 1)	Before cycle 2	Before cycle 3	Before cycle 4
		CA-125 level			
Control group	50%	2000	1000	500	250
Standard deviation		500	250	125	62.5
A) Intervention group	50% + additional 25% on each occasion	2000	750 (1000 - 25%)	282 (50% of 750 - 25%)	106 (50% of 282-25%)
B) Intervention group	25% reduction in relation to the control group	2000	750 (=75% of 1000)	375 (=75% of 500)	187.5 (=75% of 250)
C) Intervention group	20% reduction in relation to the control group	2000	800 (=80% of 1000)	400 (=80% of 500)	200 (=80% of 250)
A Sample size per group				11	3
B Sample size per group				16	16
C Sample size per group				25	25

Power 80%; two-sided $p < 0.05$.

10.5 Interim analysis (if relevant)

No interim analysis is planned since this is a pilot study. Study termination will be considered in case of very severe adverse events and SUSAR's or if change in standard treatment of EOC makes this trial redundant or uninteresting.

11 Quality Control and Quality Assurance

11.1 Quality Assurance and Sponsor oversight

Sponsor will work as principal investigator in the study and hence be well aware of any possible problems that might arise in the study. Sponsor is responsible for making a risk assessment for the study as a whole as well as to take actions to mitigate the identified risks. Monitoring will be one way of mitigating the risks. Monitoring will be performed by Forum Östergötland according to the monitoring plan. Sponsor will read all monitoring reports and take necessary actions. All key personnel involved in the study will receive or have received GCP training.

11.2 Monitoring

An independent quality control (monitoring) of the study will be carried out by qualified personnel from Forum Östergötland, the established support structure for clinical studies at Linköping University Hospital. Monitoring at each site will be carried out before start (initiation), after the first 1-3 subjects have started their participation, at least one time during the study, and after completion of the trial. The study will be monitored according to the study monitoring plan and the monitor will assess integrity of source documents, regulatory compliance and review potential adverse events.

The investigators are obligated to give direct access to medical records and other source data for monitors, inspectors from the MPA and any possible evaluators from the ethical review authority.

Monitoring will ensure that the subject's rights, safety, and well-being are met as well as data in the CRF are complete, correct, and consistent with the source data. It will also check that the study is carried out according to the protocol and that data is collected, documented, and reported according to ICH-GCP and applicable ethical and regulatory requirements.

11.3 Source data

The investigator must keep source documents for each subject in the study. A document describing what has been classified as source data at each site should be included in the Investigator Site File (ISF). The investigator must ensure that all source documents are accessible for monitoring and other quality control activities.

11.4 Deviations or serious breaches

Serious breaches and deviations from the study protocol, GCP and other regulations that significantly and directly affects, or with high likelihood could affect, the subjects or the scientific value of the study, shall be immediately reported within 7 days (from knowledge) to the Swedish Medical Products Agency. It is the sponsor's responsibility to judge the consequences of deviations that have occurred, and thus also to decide whether the Swedish Medical Products Agency should be informed.

Minor deviations that do not affect subjects' integrity or safety, nor significantly affect the study's scientific value, will be documented in the study documentation of the principal investigator and the sponsor.

11.5 Audits and inspections

Authorized representatives for the sponsor and Competent Authorities (CA) may carry out audits or inspections at the study site, including source data verification. The investigator must ensure that all source documents are available for audits and inspections. The purpose of an audit or inspection is to systematically and independently review all study-related activities and documents, to determine whether these activities were performed, registered, analyzed and reported correctly according to the protocol, Good Clinical Practice (GCP) and applicable regulations.

12 Ethics

12.1 Compliance to the protocol, GCP and regulations

The study will be performed in compliance with the study protocol, the Declaration of Helsinki, ICH-GCP (Good Clinical Practice) guidelines and current national and international regulations governing this clinical trial. This is to ensure the safety and integrity of the study subjects as well as the quality of the data collected.

12.2 Ethical review of the study

The final study protocol should be approved by both the Swedish Ethical Review Authority (Etikprövningsmyndigheten, EPM) and the Swedish Medical Products Agency before the trial can be conducted. The final version of the informed consent form and other information provided to subjects, must be approved or given a written positive opinion by EPM. EPM and the Swedish Medical Products Agency must be informed of any changes in the study protocol in accordance with current requirements.

12.3 Procedure for obtaining informed consent

The investigators at each site shall ensure that the subject is given full and adequate oral and written information about the study, its purpose, any risks and benefits as well as inclusion- and exclusion criteria. Subjects should also be informed that they are free to discontinue their participation in the study at any time without having to provide a reason. Subjects should be given the opportunity to ask questions and be allowed time to consider the provided information. If the person chooses to participate, both the subject and the investigator shall sign the informed consent form. A copy of the subject information as well as the informed consent form shall be provided to the subject. The subject's signed and dated informed consent must be obtained before performing any study-specific activity in the study. Each subject who participated in the study will be identified by a subject number on a subject identification list. The subject agrees that monitors, auditors, and inspectors may have access to their medical records and other source data. If new information is added to the study, the subject has the right to reconsider whether he/she will continue their participation.

12.4 Data protection

If any part of the data is handled by any other organization, inside or outside the EU, appropriate agreements and/or other documentation will be established, to ensure that the data processing is performed in accordance with the provisions of the General Data Protection Regulation (GDPR) and other relevant legislation, before any data transfer takes place.

The content of the informed consent form complies with relevant integrity and data protection legislation. In the subject information and the informed consent form, the subject will be given complete information about how collection, use and publication of their study data will take place. The subject information and the informed consent form will explain how study data are stored to maintain confidentiality in accordance with national data legislation. All information processed by the sponsor will be pseudonymized and identified with Study ID. The identification list will be kept on paper and stored in a safety box at Department of Oncology, Linköping University Hospital. The CRFs will be pseudonymized and stored in a safety box.

The informed consent form will also explain that for verification of the data, authorized representatives of the sponsor, as well as relevant authority, may require access to parts of medical records or study records that are relevant to the study, including the subject's medical history.

12.5 Insurances

Study subjects will be covered by the Swedish Pharmaceutical Insurance (Swe: Läkemedelsförsäkringen) in addition to the Patient insurance (Swe: Patientförsäkringen)

12.6 Publication of results

The study will be registered in ClinicalTrials.gov's Protocol Registration and Results System. Reports from the trial will be prepared in scientific manuscripts with the intention of being published in peer reviewed medical journals. Authorship will comply with the recommendations of the International Committee of Journal Medical Editors.

13 Substantial changes to the study

Substantial changes to the signed study protocol are only possible through approved protocol amendments and by agreement from all responsible persons. Information on non-substantial changes should be clearly noted in the amended protocol.

In the event that substantial changes to the protocol (e.g., changing of the main objective, primary or secondary variables, method to measure the primary variable, changing of the investigational product or dosage) will be made during the course of the study, approval from the Swedish Ethical Review Authority (Etikprövningsmyndigheten, EPM) as well as the Swedish Medical Products Agency (Läkemedelsverket) shall be obtained before any changes are implemented. A change that concerns a new site, new investigator or a new study patient information sheet shall only be approved by EPM.

Non-substantial changes will be recorded and later entered in documentation that is submitted, for example in any subsequent notifications of a substantial change or in connection with End of Trial reporting.

The investigator must not make any deviation from or change of the protocol, except which necessary to eliminate an immediate risk to the study subjects, or where the changes only include logistical or administrative aspects of the study (e.g., change of telephone number).

14 Collection, handling, and archiving data

Subjects who participate in the study are coded with a specific study identification number. All subjects are registered in a subject identification list (subject enrolment and identification list) that connects the subject's name and personal number with a study identification number.

Source data will be collected from medical records, CRF's, diaries and laboratory results. All data will be registered, managed, and stored in a manner that enables correct reporting, interpretation, and verification. The complete Trial Master File, as well as source documents,

will be archived for at least 10 years after the study is completed. Source data in the medical records system is stored and archived in accordance with the respective hospital regulations.

14.1 Case Report Form

A paper Case Report Form (CRF) is used for data collection. The investigator must ensure that data is registered and any corrections in the CRF are made as stated in the study protocol and in accordance with the instructions. The investigator must ensure that the registered data is correct, complete, and that reporting takes place according to the timelines that have been predefined and agreed. The principal investigator at each site signs the completed CRF. A copy of the completed CRF will be archived at the study site.

If an examination/test is not performed and data does not exist, ND (Not done) or NK (Not known) is marked. If the question is irrelevant NA (Not applicable) is written. Corrections in the paper CRF are done by striking out the incorrect information and adding the correct information next to the incorrect information, signing, and dating the correction.

15 Notification of study completion, reporting, and publication

After the study is finished The Swedish Medical Products Agency shall be informed of the study's completion at latest 90 days after study end, through submission of a "Declaration of End of Trial Notification" form.

Within one year after the study is completed, the results shall be analyzed, a clinical study report with individual data shall be prepared, and the study results shall also be reported in the EudraCT database.

If the study is prematurely terminated the MPA and EPM shall be notified as soon as possible but no later than within 15 days.

16 References

1. Svenska kvalitetsregistret för gynekologisk cancer. 2018. [In Swedish] Available at: <https://www.cancercentrum.se/samverkan/cancerdiagnoser/gynekologi/kvalitetsregister/> Accessed: February 1st, 2020.
2. Svenska dödsorsaksregistret. 2018. [In Swedish] Available at: <http://www.socialstyrelsen.se/statistik/statistikdatabas/dodsorsaker> Accessed: January 30th, 2020.
3. Meinhold-Heerlein I, Hauptmann S. The heterogeneity of ovarian cancer. Arch Gynecol Obstet. 2014;289(2):237–9.
4. Nik NN, Vang R, Shih I-M, Kurman RJ. Origin and Pathogenesis of Pelvic (Ovarian, Tubal, and Primary Peritoneal) Serous Carcinoma. Annu Rev Pathol Mech Dis. 2014 Jan 24;9(1):27–45.
5. Meinhold-Heerlein I, Fotopoulou C, Harter P, Kurzeder C, Mustea A, Wimberger P, et al. Statement by the Kommission Ovar of the AGO: The New FIGO and WHO Classifications of Ovarian, Fallopian Tube and Primary Peritoneal Cancer. Geburtshilfe Frauenheilkd. 2015;75(10):1021–7.
6. Nationellt vårdprogram äggstockscancer. 2020. [In Swedish] Available at: <https://www.cancercentrum.se/samverkan/cancerdiagnoser/gynekologi/aggstock/vardprogram/> Accessed: April 25th, 2021

7. Hirsh J, Raschke R. Heparin and Low-Molecular-Weight Heparin. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. CHEST 2004;126:188S-203S
8. Mousavi S, Moradi M, Khorshidahmad T, Motamedi M. Anti-inflammatory effects of Heparin and its derivatives: A systematic review. Adv Pharmacol Sci 201; 2015:507151.
9. Dimakakos EP, Vathiotis I, Syrigos K. The Role of Tinzaparin in Oncology. Clin Appl Thromb Hemost. 2018;24(5):697–707.
10. Stevenson JL, Choi SH, Varki A. Differential metastasis inhibition by clinically relevant levels of heparins—correlation with selectin inhibition, not antithrombotic activity. Clin Cancer Res. 2005;11(19 pt 1):7003-7011.
11. Schlesinger M, Roblek M, Ortmann K, et al. The role of VLA-4 binding for experimental melanoma metastasis and its inhibition by heparin. Thromb Res. 2014;133(5):855-862.
12. Harvey JR, Mellor P, Eldaly H, et al. Inhibition of CXCR4- mediated breast cancer metastasis: a potential role for heparinoids?. Clin Cancer Res. 2007;13(5):1562-1570.
13. Alyahya R, Sudha T, Racz M, et al. Anti-metastasis efficacy and safety of non-anticoagulant heparin derivative versus low molecular weight heparin in surgical pancreatic cancer models. Int J Oncol. 2015;46(3):1225-1231.
14. Bauer AT, Suckau J, Frank K, et al. von Willebrand factor fibers promote cancer-associated platelet aggregation in malignant melanoma of mice and humans. Blood. 2015;125(20): 3153-3163.
15. Amirkhosravi A, Mousa SA, Amaya M, Francis JL. Antimetastatic effect of tinzaparin, a low-molecular-weight heparin. J Thromb Haemost. 2003;1(9):1972-1976.
16. Mousa SA, Mohamed S. Anti-angiogenic mechanisms and efficacy of the low molecular weight heparin, tinzaparin: anti-cancer efficacy. Oncol Rep. 2004;12(4):683-688.
17. Mousa SA, Mohamed S. Inhibition of endothelial cell tube formation by the low molecular weight heparin, tinzaparin, is mediated by tissue factor pathway inhibitor. Thromb Haemost. 2004;92(3):627-633.
18. Lengyel E. Ovarian Cancer Development and Metastasis. Am J Pathol. 2010 Sep;177(3):1053-64.
19. Masoumi Moghaddam S, Amini A, Morris DL, Pourgholami MH. Significance of vascular endothelial growth factor in growth and peritoneal dissemination of ovarian cancer. Cancer Metastasis Rev. 2012 Jun;31(1-2):143-62.
20. Mitsis M, Koliou P, Bali C, et al. In Surgical Colon Cancer Patients Extended-Duration Thromboprophylaxis (30 days) with the Highest Dose of Tinzaparin (4,500 IU s.c./q.d.) Normalizes the Postoperative VEGF Levels. J Cancer. 2017;8(15):2899–2906. Published 2017 Aug 25. doi:10.7150/jca.20107
21. Pfankuchen DB, Stölting DP, Schlesinger M et al. Low molecular weight heparin tinzaparin antagonizes cisplatin resistance of ovarian cancer cells. Biochem Pharmacol. 2015 Sep 15;97(2):147-57. doi: 10.1016/j.bcp.2015.07.013. Epub 2015 Jul 31.
22. Hefler LA, Concin N, Hofstetter G, Marth C, Mustea A, Sehouli J et al. Serum C-reactive protein as independent prognostic variable in patients with ovarian cancer. Clin Cancer Res. 2008 Feb 1;14(3):710-4.
23. Dobrzycka B, Mackowiak-Matejczyk B, Terlikowska KM, Kulesza-Bronczyk B, Kinalski M, Terlikowski SJ. Serum levels of IL-6, IL-8 and CRP as prognostic factors in epithelial ovarian cancer. Eur Cytokine Netw. 2013 Jul-Sep;24(3):106-13.
24. Stone RL, Nick AM, McNeish IA, Balkwill F, Han HD, Bottsford-Miller J, Rupairmoole R et al. Paraneoplastic thrombocytosis in ovarian cancer. N Engl J Med. 2012 Feb 16;366(7):610-8.
25. Chen Y, Zhang L, Liu WX, Liu XY. Prognostic significance of preoperative anemia, leukocytosis and thrombocytosis in chinese women with epithelial ovarian cancer. Asian Pac J Cancer Prev. 2015;16(3):933-9.

26. Allensworth SK, Langstraat CL, Martin JR, Lemens MA, McGree ME, Weaver AL et al. Evaluating the prognostic significance of preoperative thrombocytosis in epithelial ovarian cancer. *Gynecol Oncol.* 2013 Sep;130(3):499-504.
27. Altman AD, Liu XQ, Nelson G, Chu P, Nation J, Ghatage P. The effects of anemia and blood transfusion on patients with stage III-IV ovarian cancer. *Int J Gynecol Cancer.* 2013 Nov;23(9):1569-76.
28. Ayhan A, Günakan E, Alyazıcı İ, Haberal N, Altundağ Ö, Dursun P1. The preoperative albumin level is an independent prognostic factor for optimally debulked epithelial ovarian cancer. *Arch Gynecol Obstet.* 2017 Nov;296(5):989-995.
29. Kumar A, Torres ML, Cliby WA, Kalli KR, Bogani G, Aletti G et al. Inflammatory and Nutritional Serum Markers as Predictors of Peri-operative Morbidity and Survival in Ovarian Cancer. *Anticancer Res.* 2017 Jul;37(7):3673-3677.
30. Suidan RS, Ramirez PT, Sarasohn DM, Teitcher JB, Iyer RB, Zhou Q et al. A multicenter assessment of the ability of preoperative computed tomography scan and CA-125 to predict gross residual disease at primary debulking for advanced epithelial ovarian cancer. *Gynecol Oncol.* 2017 Apr;145(1):27-31.
31. Morales-Vásquez F, Pedernera E, Reynaga-Obregón J, López-Basave HN, Gómora MJ, Carlón E et al. High levels of pretreatment CA125 are associated to improved survival in high grade serous ovarian carcinoma. *J Ovarian Res.* 2016 Jul 7;9(1):41.
32. Zorn KK, Tian C, McGuire WP, Hoskins WJ, Markman M, Muggia FM et al. The prognostic value of pretreatment CA 125 in patients with advanced ovarian carcinoma: a Gynecologic Oncology Group study. *Cancer.* 2009 Mar 1;115(5):1028-35.
33. Kessous R, Wissing MD, Piedimonte S, Abitbol J, Kogan L, Laskov I, Yasmeen A, Salvador S, Lau S, Gotlieb WH. CA-125 reduction during neoadjuvant chemotherapy is associated with success of cytoreductive surgery and outcome of patients with advanced high-grade ovarian cancer. *Acta Obstet Gynecol Scand.* 2020 Jan 18.
34. Matsushashi T, Takeshita T, Yamamoto A, Kawase R, Yamada T, Kurose K, Doi D, Konnai K, Onose R, Kato H. Serum CA 125 Level after Neoadjuvant Chemotherapy is Predictive of Prognosis and Debulking Surgery Outcomes in Advanced Epithelial Ovarian Cancer. *J Nippon Med Sch.* 2017;84(4):170-176.
35. J M Riedinger¹, F Bonnetain, J P Basuyau, N Eche, H Larbre, I Dalifard, J Wafflart, G Ricolleau, M F Pichon Change in CA 125 levels after the first cycle of induction chemotherapy is an independent predictor of epithelial ovarian tumour outcome. *Ann Oncol.* 2007 May;18(5):881-5.
36. Maria Lee,^{1,2,*} Min Young Chang,^{3,*} Hanna Yoo,⁴ Kyung Eun Lee,³ Doo Byung Chay,³ Hanbyoul Cho,³ Sunghoon Kim,⁵ Young Tae Kim,⁵ and Jae-Hoon Kim³ Clinical Significance of CA125 Level after the First Cycle of Chemotherapy on Survival of Patients with Advanced Ovarian Cancer. *Yonsei Med J.* 2016 May 1; 57(3): 580–587.
37. Karlsson A, Lundin E, Lukas P, Lindahl G, Kjølhede P. The impact of levels of biomarkers on overall survival in FIGO stage III-IV ovarian cancer. Poster presented at SFOG-veckan. Uppsala, Sweden, August 29th 2018.
38. Abu Saadeh F, Norris L, O'Toole S, Gleeson N. Venous thromboembolism in ovarian cancer: Incidence, risk factors and impact on survival. *Eur J Obstet Gynecol Reprod Biol.* 2013 Sep;170(1):214-8.
39. Kahr HS, Christiansen OB, Grove A, Iyer V, Torp-Pedersen C, Knudsen A, Thorlacius-Ussing O. Venous thromboembolism in epithelial ovarian cancer. A prospective cohort study. *Thromb Res.* 2019 Sep;181:112-119.