PROTOCOL TITLE

Neo-Adjuvant Chemotherapy and **Con**servative Surgery in Cervical Cancer to Preserve **F**ertility

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
ANC	**Absolute Neutrophil Count**
AR	**Adverse Reaction**
BD	**Blue Dye**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CKC	**Cold-Knife Cone**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
eCRF	**Electronic Case Report Form**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
ICG	**Indocyanine Green**
INCIP	**International Network on Cancer, Infertility and Pregnancy**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
LEEP	**Loop Electrosurgical Excision Procedure**
LRS	**Less radical surgery**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
nSLN	**Non sentinel node**
(S)AE	**(Serious) Adverse Event**
SLN	**Sentinel Lymph Node**
SLP	**Sentinel lymphnode procedure**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance**

	of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: The standard treatment of stage Ib1 2-4 cm cervical cancer in women who wish to preserve fertility is an abdominal radical trachelectomy with pelvic lymph node dissection. Since the number of take home babies after completing this procedure is below 10%, there is a need for exploration of alternative treatment modalities with better chances of preserving fertility at equal risk of recurrence. Since low fertility rates after abdominal radical trachelectomy are observed due to the radical surgery performed on the uterine cervix, less radical surgery is warranted. To enable less radical surgery by cervical conisation, neo-adjuvant chemotherapy to reduce tumor size is incorporated to the multi-modal treatment scheme of these patients.

Objective: The primary objective is to determine the efficacy of neo-adjuvant chemotherapy to reduce tumour size below 2 cm in diameter and thus enabling less radical surgery (LRS). At the same time safety, defined as number of women who get recurrence within two years, after LRS will be monitored continuously.

Secondary objectives are number of patients who kept the possibility to conceive (no hysterectomy performed, no radiation to pelvic area performed), ovarian function after treatment, quality of life, registration of pregnancies if they occur during follow-up, registration of concerns about fertility prior and after treatment. Translational research to predict response to neo-adjuvant chemotherapy.

Primary outcome: response to neo-adjuvant chemotherapy.

Secondary outcomes are: recurrence free survival, need for adjuvant therapy (radical hysterectomy or (chemo)radiation, preservation of ovarian function, quality of life.

Study design: One arm two-stage Simon's design with response to neo-adjuvant chemotherapy as the primary endpoint. Safety, defined as number of recurrences within two years in the group receiving LRS, will be monitored continuously in a Bayesian manner.

Study population: women ≥18 and ≤ 40 years with FIGO stage Ib1 cervical carcinoma with tumor measuring ≥ 2 cm and ≤ 4 cm on physical examination and imaging. Histologic types: squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma with or without lymph vascular space invasion. Patients will undergo pelvic lymph node dissection.

Intervention (if applicable): If no metastases are observed, patients will start a short protocol of four courses of weekly neo-adjuvant chemotherapy (12 weeks). If response to chemotherapy results in a tumor of less than 2 cm, LRS will be performed.

Main study parameters/endpoints: Primary endpoint is response to the neo-adjuvant treatment. Success of the trial will be determined on the basis of the boundaries given by the Simon's design (at least 27 responders in the first stage and at least 83 responders in total)

Additionally a point estimate and 95% confidence bound for the response rate will be calculated.
Safety will be monitored in a Bayesian setting using continuous monitoring via posterior probability. Stopping rules for safety will be applied only to patients who receive LRS (exact number unknown, expected number is 75% of the total sample size, expected approximately 90 patients). If 17% of patients who received LRS have recurrence within 2 years the treatment is considered unsafe. The study will stop if P(proportion of patients without recurrence by 2 years < 0.83 | data from the trial) > 0.7

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:
Burden: Patients will undergo a sequential treatment of surgery (pelvic lymph node dissection), followed by neo-adjuvant chemotherapy and LRS. This process takes several months and is more time consuming than the current standard treatment of radical abdominal trachelectomy with pelvic lymph node dissection in one session. Patients will be asked to fill in QoL questionnaires at 4 time points in this trial. One extra blood sample is taken prior to study registration. Extra biopsies are taken while under general anesthesia in the operating theatre just before scheduled surgery (pelvic lymph node dissection and LRS). Follow-up visits and examinations are according to standard Dutch national guidelines for follow-up.
Risk: recurrence of disease, short-term and long-term side effects of chemotherapy (bone marrow depression, opportunistic infections, neurotoxic side effects, reduced fertility).
Benefit: women are expected to have better chances to become pregnant and have less immature and premature deliveries. Due to less radical surgery, women are expected to have less side effects on rectal-, bladder and sexual function.

1. INTRODUCTION AND RATIONALE

Background:

The standard treatment modality for women with stage Ib1 cervical cancer is a radical hysterectomy (removal of uterus, upper vagina and parametrium) with pelvic lymph node dissection (Querleu et al, 2008). Radical hysterectomy with pelvic lymph node dissection in women with stage Ib1 cervical cancer measuring 2-4 cm, results in a good local control, this procedure is associated with significant morbidity due to removal of the parametrium where autonomic fibers enabling bowel-, bladder- and sexual function, are resected (Derks et al, 2016). Due to the removal of the uterus, women are no longer able to become pregnant.

In 1997, Smith et al introduced an uterus sparing treatment modality for women with cervical cancer measuring 2- 4 cm without parametrial involvement (stage Ib1 cervical cancer measuring 2-4 cm) in case women wished to preserve their fertility. In this abdominal radical trachelectomy (ART) cervix and parametrium are resected and the uterine corpus is preserved with an anastomosis to the vagina (Smith et al, 1997). In cases of lymph node metastases, parametrial involvement or two or more of the Sedlis criteria (lymph vascular space invasion, tumor >4 m or deep stromal invasion) patients are treated with adjuvant (chemo)radiation in the Western world. With chances of one or more of these factors to be present in more bulky tumors, considerable numbers of patients are offered adjuvant treatment in patients with stage Ib1 2-4 cervical cancer. The reported incidence of pelvic lymph node metastases in stage Ib1 cervical cancer measuring 2-4 cm is reported to be 18-27 % (Park et al, 2011, Sakuragi et al, 2011, Xianlan et al, 2015, Derks 2017). In the up to now largest review by Plante et al (136 patients treated with ART), 1 in 3 patients in this group lost their fertility after adjuvant treatment for intended fertility sparing therapy. If fertility is preserved, a considerable amount of women encounter problems in becoming pregnant and staying pregnant. Only 6% of women who choose for a radical trachelectomy in the group of patients with Ib1 2-4 cm cervical cancer, fell pregnant and were able to take a healthy baby home (Plante et al, 2015) .

Due to these poor numbers in ART, neo-adjuvant chemotherapy has drawn more interest to fertility sparing management of women with stage Ib1 2-4 cm disease. The rationale is that cervical cancer is considered as a chemo-sensitive malignancy. In some centres, neo-adjuvant chemotherapy is used to reduce tumor size before radical surgery. The reported response rate in advanced stage cervical cancer is 60-95% (Rob et al, 2011, Robova et al, 2013, Kenter et al, 2016) and the response rate is higher when combination chemotherapy is administered. If neo-adjuvant chemotherapy reduces the size of the tumor considerably, less radical surgery can be performed comprising of conisation of the uterine cervix (NACT-FS) . In this way, a cone is excised from the uterine cervix and the parametrium is left untouched.

Platinum containing chemotherapy is considered as an intermediate risk agent of resulting in secondary ovarian failure in cancer survivors (richtlijn fertiliteitsbehoud bij vrouwen met kanker). Gershenson et al reported on 132 patients with germ cell ovarian cancer who were treated with platinum based chemotherapy. Mean age was 35 and 87% of women still had a menstrual cycle after treatment (Gersheson et al, 2007). There are no studies on gonadotoxicity of taxanes including women who are treated with taxanes only since these agents are often incorporated in multi-agent regimen. In a review by Zoa et al, regimen incorporating taxanes for the treatment of breast cancer showed an OR 1.24 (95% confidence level 1.03-1.50, P=0.02) for chemotherapy induced amenorrhea in women treated for breast cancer (Zao et al, 014). The ASCO guideline " Fertility preservation for patients with cancer, considers the risk of taxanes fertility as "unknown" (ASCO guideline 2006).

Data on oncologic- and fertility outcomes in patients with Ib1 2-4 cervical cancer is scarce. The largest set of data is presented by Bentivegna et al and comprises 1219 patients in whom ART was intended and 114 patients in whom NACT-FS was planned. The authors noted that data on tumor characteristics and recurrences were only documented in 209 patients in whom ART was intended and 52 patients in whom NACT-FS was intended. In this review both stage Ib1 tumors <2 cm and >2 cm were analysed together and the reported rate of recurrence was 4% (with 1 % died of disease) in the ART group and recurrence rate was 6% (with 1 % died of disease) in the NACT-FS group. Due to inclusion of smaller sized Ib1 tumors, recurrence rates can be underestimated for the group of patients with Ib1 2-4 cm cervical cancer (Bentivegna et al, 2016).
In a review by Plante et al. in which the group of patients with stage Ib1 2-4 cervical cancer (136 patients in whom ART was intended and 77 patients in whom NACT-FS was intended) was analysed separately, the recurrence rate was 4% (1.6% died of disease) after ART and recurrence rate was 7% (3% died of disease) after NACT-FS. After ART, 69% of women were considered to have kept their fertility (no radiation to uterus/ovaries) but only 6% of women fell pregnant and took a healthy baby home afterwards. In case of NACT-FS, 80% of women were considered to have kept their fertility and 31% of women took a healthy baby home (Plante et al, 2015).

There is still an ongoing debate whether lymph node dissection should be performed before or after neo-adjuvant chemotherapy. In a review by Kim et al, 1784 women with stage Ib1-IIa cervical cancer who were either treated by neo-adjuvant chemotherapy followed by radical surgery or radical surgery alone, neo-adjuvant chemotherapy reduced the need of adjuvant radiotherapy (RT) in all studies (OR, 0.57; 95% CI, 0.33-0.98). In observational studies overall survival was poorer in patients treated with neo-adjuvant chemotherapy when

compared to primary radical surgery (HR 1.68, 95% CI 1.12-2.53). It is hypothesed that the adjuvant radiotherapy has a “concealing” effect on small metastatic tumor depositions in the lymph nodes. Therefore, after NACT, a subgroup of patients could be withheld erroneously adjuvant radiotherapy because these small metastases could be concealed (Kim et al, 2013). On the other hand, microscopic metastasis could be sterilized by neo-adjuvant chemotherapy. This would result in less women needing post-operative radiation therapy which will result in lower numbers of women suffering from early and late radiation effects. In this selected group of women with low stage cervical cervical cancer who wish to try to better preserve their fertility, we choose to follow the safest option of starting with pelvic lymph node dissection and in case no metastases are found, to continue to neo-adjuvant chemotherapy.

Three groups have reported on this scheme of pelvic lymph node dissection, neo-adjuvant chemotherapy and fertility sparing surgery in this order: Slama et al reported on 44 (stage IA2: N=7, IB1; N=23, IB2: N=2) women. In 32 women, fertility sparing surgery was performed (reasons for not performing fertility sparing surgery: lymph node metastases (N=7 patients) and progression during chemotherapy (N=2). Fertility sparing surgery consisted of conisation (N=11) or simple vaginal trachelectomy (N=21). Four out of 32 women had a recurrence of whom 1 died. Nine of these 32 women tried to conceive, 6 out of 32 women fell pregnant and 5 children were born of whom one prematurely. Mean follow-up was 23 months (range 3-53 months) (Slama et al, Gynecol Oncol 2016). In a second study by Lanowska et al. on 20 patients with stage Ib1 2-4 cm tumors and no lymph node metastases were included, two patients were treated with chemoradiation because of “insufficient pathologic response” and the remaining 18 patients were treated with a radical vaginal trachelectomy after neo-adjuvant chemotherapy. One patient faced recurrence of disease. Seven out of these 18 women tried to conceive, 5 out of these 7 women fell pregnant and 4 children were born (of whom 2 prematurely). Mean follow-up 23 months (range 1-88 months) (Lanowska et al 2014). Finally, Salihi et al reported on 11 patients with stage Ib1 or Ib2 cervical cancer who had been proven to have no pelvic lymph node metastases on dissection. Four women were treated with chemoradiation due to poor response (N=3) or progression during neo-adjuvant chemotherapy (N=1).The remaining 7 patients were treated with a conisation after neo-adjuvant chemotherapy. All patients tried to conceive and 6 fell pregnant if whom 5 women delivered in total 7 children (2 children were born prematurely). One patient faced recurrence of disease. Mean follow-up was 58 months (range 13-122 months) (Salihi, 2015). Remarkably, few women (28% in the Slama study and 39% in the Lanowska study), tried to conceive after their fertility sparing treatment. To the contrary, all women in Salihi’s trial tried to conceive. This difference might be explained to the shorter median follow-up (23 months in

both Slama's and Lanowska's trial vs 58 months in Salihi's trial) but reasons for women to decide to conceive after fertility sparing surgery should be further explored.

In this protocol, we will investigate the efficacy and safety and of neo-adjuvant chemotherapy in order to be able to perform less radical surgery in women with stage Ib1 2-4 cervical cancer. In order to reduce recurrence risks and futile chemotherapy, close stopping rules have been formulated to be able to stop the study if too little patients respond to neo-adjuvant chemotherapy or recurrence rates are unexpectedly high.

2. OBJECTIVES

Primary Objective:

To evaluate the **efficacy** of neo-adjuvant chemotherapy on tumor response in women who wish to preserve their fertility with stage Ib1 carcinoma of the cervix measuring 2-4 cm.
At the same time safety, defined as number of women who get recurrence within two years, after LRS will be monitored continuously.

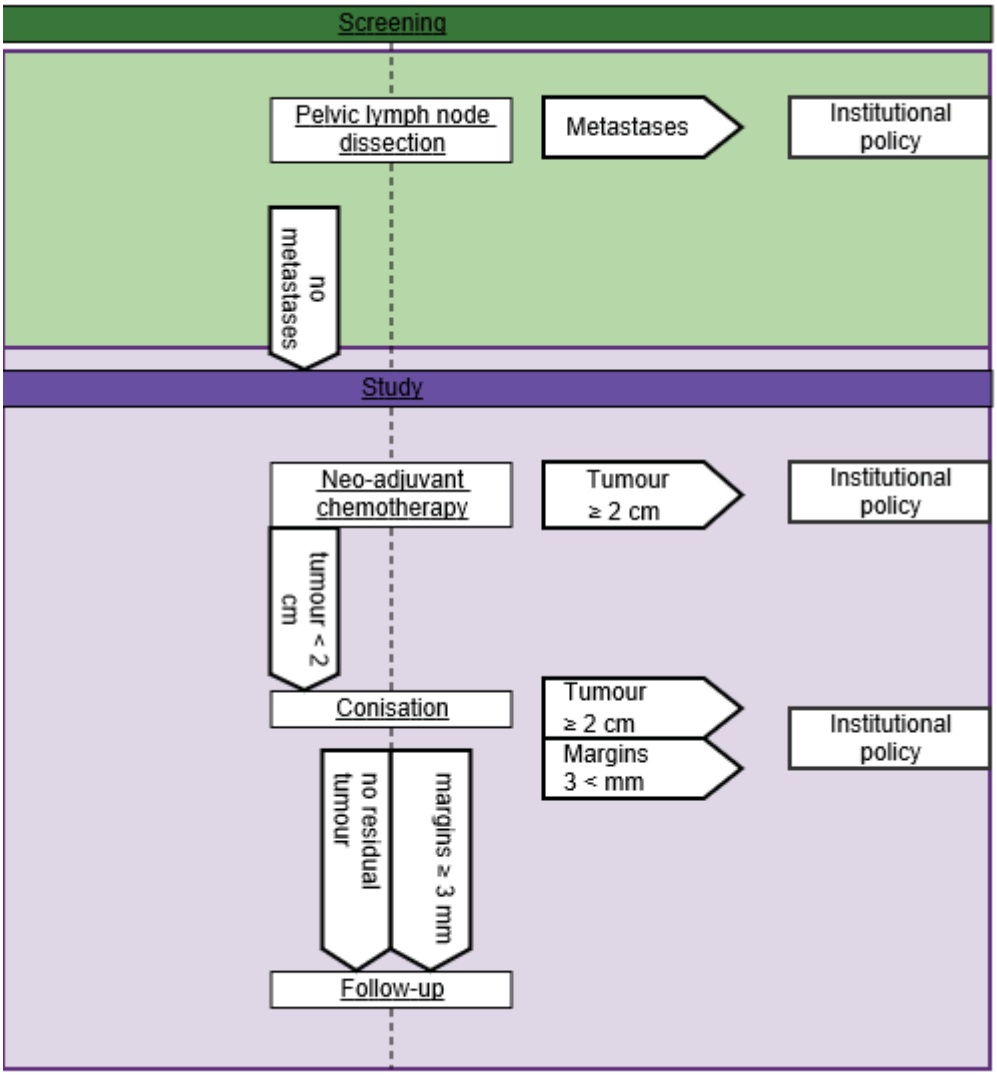
Secondary Objective(s):

To determine number of patients who kept the possibility to conceive (no hysterectomy performed, no radiation to pelvic area performed), to assess ovarian function after treatment, quality of life, registration of pregnancies if they occur during follow-up, registration of concerns about fertility prior and after treatment. Translational research to predict response to neo-adjuvant chemotherapy.

3. STUDY DESIGN

This is a prospective, multi-center phase II open label non-randomized trial evaluating the outcomes of performing less radical surgery in women with stage Ib1 2-4 cm cervical cancer with no pelvic lymph node metastases and adequate response to neo-adjuvant chemotherapy, who wish to preserve their fertility with an accrual of 119 evaluable patients.

Study flowchart:



4. STUDY POPULATION

4.1 Population (base)

Cervical cancer is a rare condition in the developed world with an incidence of 6/100.000 women per year. In The Netherlands, 846 women were diagnosed with cervical cancer in

2016. Of these women, 109 were 39 years or younger (www.cijfersoverkanker.nl). We will include women aged 18 - 40 years with FIGO stage Ib1 cervical carcinoma with tumor measuring ≥ 2 cm and ≤ 4 cm who wish to preserve their fertility.

4.2 Inclusion criteria

- Stage Ib1 cervical cancer measuring ≥2 - ≤4 cm on physical examination and imaging in any direction
- Histologic type: squamous cell carcinoma (SCC), adeno cell carcinoma (ACC), adeno-squamous cell carcinoma (ASC)
- Lymph vascular space invasion allowed (LVSI)
- Age ≥18 years and ≤ 40 years
- Wish to preserve fertility
- Written and signed informed consent
- Negative serum or urine pregnancy test within 14 days prior to registration, and an effective method of contraception must be used during treatment
- MRI abdomen and pelvis, chest X-ray must be performed and negative for metastatic disease within 12 weeks of enrolment
- No metastases on pelvic lymph node dissection
- Laboratory values: serum creatinine < 140 µmol/L; creatinine clearance > 60 ml/min(Cockroft formula); white blood cell count > 3.5 x 109/l; platelets > 100 x 109 /l

4.3 Exclusion criteria

- Other high grade histologies like neuro-endocrine and clearcell carcinoma
- FIGO stage Ia, Ib1< 2 cm, Ib2, II, III and IV disease
- Involvement of tumor in uterine corpus on MRI or hysteroscopy if performed
- Evidence of metastatic disease on imagining performed within 12 weeks of enrolment
- other diagnosis of malignancy or evidence of other malignancy for 5 years before screening for this study (except non-melanoma skin cancer).

4.4 Sample size calculation

Sample size calculation was done for the efficacy endpoint. An optimal Simon's two-stage design will be used. The null hypothesis that the true response rate is 61% (clinically unacceptable) will be tested against one-sided alternative. The expected response rate is 75%. For a total of 119 patients this design yields a one-sided type I error of 2.5% and power of 85%. In the first stage 40 patients will be accrued. The study will continue to the second

stage if at least 27 patients will respond to the neo-adjuvant treatment. The second stage will accrue additional 79 patients. At the end of the study there must be at least 83 responders to declare the treatment as successful.

4.5 Treatment of subjects

4.5.1 Investigational product/treatment

This study will enrol patients with stage Ib1 2-4 cm cervical cancer, age ≥18- ≤ 40 years who wish to preserve their fertility and have the most common histologic tumor types (SCC, ASC and ACC) of cervical cancer. The patients are given weekly paclitaxel 80 mg/m2 + carboplatin AUC=2 (or AUC=6 per three weeks) during 12 weeks/4 courses. The combination treatment with carboplatin (AUC=6) and paclitaxel (175 mg/m2) has proven tolerable and effective and is already considered standard of care for patients with cervical cancer.

4.5.2 Screening: Pelvic lymph node dissection

Patients will (including patients undergoing lymphatic mapping and sentinel lymph node biopsy) undergo a complete bilateral pelvic lymph node dissection with removal of the lymph nodes along the external iliac artery, the internal iliac artery and the common iliac artery as well as in the obturator fossa. If suspicious lymph nodes are noted at the time of surgery, they will be removed and sent for intra-operative pathologic evaluation. If the intra-operative pathologic evaluation shows metastatic disease to the lymph nodes, the patient will be treated at the discretion of her physician. The number of removed lymph nodes does not influence disease free survival (DFS) in lymph node negative patients. If a positive lymph node is found, DFS increases with the amount of nodes removed (Pieterse et al, 2007). Different guidelines mention different numbers of the minimal amount of lymph nodes to be removed (GOG: 4 lymph nodes; EORTC 11 lymph nodes). Therefore the minimal amount of lymph nodes to be removed is set at 11 according to European guidelines (Verleye et al, 2009).

Patient’s consent will be asked to obtain four extra biopsies for translational research purposes (under general anesthesia, at the lymph node dissection). Ideally, if permitted by local facilities, biopsy material will be frozen (two frozen, two formalin-fixed and paraffin-embedded). If frozen material is precluded by local facilities, all biopsy material should be formalin-fixed and paraffin-embedded. Three biopsies (two fresh frozen and one paraffin embedded) will be collected and centrally stored at the LUMC after the completion of patient

accrual or during the study period depending on the number of biopsies and storage capacity of the local site. One paraffin biopsy is stored at the NKI-AVL. If consented for by the patient that extra study biopsies are taken, an additional blood sample (1x 10ml blood in EDTA tube) and a cervical smear in thin prep will be collected at baseline and before LRS and stored at the NKI-AVL. These additional sample collections are optional for individual patients as well as for individual participating centers.

Sentinel lymphnode procedure (SLP): a sentinel node procedure is advised to be performed to verify the first basin of lymphatic drainage is examined by identifying the sentinel lymph node (SLN). All three currently available techniques (blue dye, radiocolloid, indocyanine-green) for SLN detection are acceptable in the trial, however combined technique using blue dye and radiocolloid or indocyanine-green are the preferred techniques due to the largest evidence available in the literature and the highest detection rate reported (Rob et al, 2013, Kadkhodayan et al, 2015). Preoperative lymphoscintigraphy is not required by the protocol.
The following principles of SLN detection techniques should be followed:

a) Blue dye (BD)

At the beginning of the procedure, after induction of anesthesia, 2 ml non-diluted (or 2 ml diluted in 2 ml of saline) of blue dye is applied slowly into the cervical stroma, preferably superficially, submucosally, next to the visible lesion, into the four quadrants (or at the 3 and 9 o'clock positions).

b) Radiocolloid (RC)

The radioactive tracer with 99m technetium is installed into the uterine cervix following the identical principles as with blue dye for small and large tumors. The most often-used activity in small tumors is about 110 MBq. The application timing must correspond to the type of radioactive tracer, since the size of particles determines both time to visualization and retention time in SLN[13]. Ultra-short protocol when radiocolloid is applied at the beginning of the surgery is preferred with a small particle agent, while long protocol when the application is performed a day before the surgery (preferably 12 hours) is better with a larger particle agent.

c) Indocyanine-green (ICG)

At the beginning of the procedure, after induction of anesthesia, 2 ml diluted ICG is applied slowly into the cervical stroma, preferably superficially, submucosally, next to the visible lesion, into the four quadrants (or at the 3 and 9 o'clock positions).

Pathologic examination/ultrastaging:

All sentinel lymph nodes as well as all other non-sentinel lymph nodes will be fixed in 10% buffered formalin. After fixation, all SLNs will be sliced at 2 mm intervals, embedded in paraffin and further examined by **ultrastaging protocol**. This protocol consists of 2 consecutive sections (4 µm-thick) obtained in regular 250 µm intervals, which will be cut from each paraffin block. The first section from each level will be stained with H&E and the second section examined immunohistochemically with antibody against cytokeratins (AE1/AE3) . Non-SLNs (nSLN) will be sliced at 2 mm intervals in their entirety, embedded in paraffin and examined via a single section stained with H&E.

The type of metastasis will be classified according to the TNM system. Macrometastases are defined as metastasis > 2 mm in diameter, micrometastases are metastasis >0.2 and ≤ 2 mm, and isolated tumor cells (ITCs) as individual tumor cells or small clusters of cells up to 0.2 mm in diameter or < 200 cells. Final lymph node status combines the results from the evaluation of all pelvic nodes together with SLN ultrastaging (SLN + nSLN).

4.5.3 Treatment

If on **pathologic** examination **no (macro)metastases** in the examined pelvic lymph nodes are detected, patients will be registered for the study. In case isolated tumor cells are detected in the sentinel node(s), it is allowed but not obligatory to include women in this study and institutional policy of treatment is allowed.

Women will start neo-adjuvant chemotherapy within six weeks after pelvic lymph node surgery The first course of chemotherapy is named week 5-7. See treatment summary table (table 1).

Treatment schedule of neo-adjuvant chemotherapy: Weekly paclitaxel 80 mg/m2 + carboplatin AUC=2 during 12 weeks. Paclitaxel and carboplatin doses will be based on blood counts obtained <72 hour before each treatment, except for the first cycle of treatment in which doses may be based on the blood counts obtained within two weeks before treatment.

Patient monitoring

A doctor must be readily available during paclitaxel and carboplatin infusions. In case of allergic reactions, local guidelines must be followed.

Dose adjustments

If the absolute neutrophil count (ANC) is ≥1.0 x 109/l and platelet count is ≥75 x 109/l, full doses will be administered. If the ANC is <1.0 x 109/l or the platelet count is <75 x 109/l treatment will be delayed until bone marrow recovery with a maximum of two weeks.

Treatment-related non-hematological toxicity > grade 2 or polyneuropathy > grade 1 also warrants treatment interruption with a maximum total interruption of two weeks (i.e., consecutive or segregated). Chemotherapy in reduced dose can be resumed if non-hematological toxicity has recovered to maximum grade 2 or baseline toxicity or grade 1 in case of polyneuropathy.

In case of dose delay >1 week, paclitaxel and carboplatin doses should both be reduced with 25% for all subsequent doses, unless the toxicity can unambiguously be related to a specific agent. In such cases, the study team may determine specific dose adjustments. If more than two dose reductions per agent are required, further patient management will be individually discussed with the study team. Doses cannot be re-escalated.

Co-medication

Premedication, medication in case of allergic reaction and anti-emetic medication are given according to local guidelines.

Concomitant medication

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded in the patient file including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids.

Response evaluation will be performed in week 10 before the start of 10th weekly administration by physical examination and MRI. Physical examination is repeated in week 13. To reduce inter-observer bias, the same physician will perform the pre-assessment and response evaluation. Response evaluation will be documented by:

- Physical examination (complete response: no visible tumor; partial response: tumor in largest diameter < 2 cm , poor: tumor > 2cm, or no response: tumor unchanged
- MRI following RECIST 1.1 criteria (see appendix 1).

If a complete clinical and radiological response on physical examination and MRI is observed at first evaluation after nine administrations of chemotherapy, no additional doses will be

given. If the tumour diameter is ≥2 cm in largest diameter on physical examination or imaging after the last dose of chemotherapy, the patient will not be considered eligible for LRS.

4.5.4 Surgery

Less radical surgery (LRS): if the largest tumor diameter is < 2 cm on physical examination and imaging, and a radical conisation seems feasible by the surgeon, a conisation will be performed. In this procedure, a cone shaped specimen is excised from the uterine cervix in one piece in the operating theatre. It is preferred that the cone is a cold-knife cone (CKC) but a loop electrosurgical excision procedure (LEEP) is also acceptable.
In case if a conisation seems NOT possible due to residual tumor < 2cm, a simple trachelectomy/portio amputation with application of a cerclage is allowed. The parametrium should be left untouched at all times. If parametrectomy is deemed necessary, the patient will be treated according to “institutional policy”.

. If on pathological examination:

- No residual tumor is found: follow-up
- Residual tumor is found, free margins over 3 mm or more: follow-up
- Residual tumor is found, free margins less than 3 mm or in margins of specimen: local policy.

In case of tumor after NACT ≥ 2 cm

- Institutional policy

In case of progression during NACT:

- Institutional policy

This specimen is examined by a gynecopathologist.

4.5.5 Follow-up

Patients will visit for follow-up according to the Dutch guideline every 3 months for the first two years, 6 monthly in year 3 and 4 and once in year five. At 4-6 weeks and 24 months after LRS, ovarian function will be tested with an AMH, FSH and oestradiol measurement. On every visit physical examination is performed. Cervical cytology using a ThinPrep vial (Hologic) is performed every six months. Assessment of distant disease is performed if indicated.

4.5.6 Quality of life questionnaires

QOL (QoL) is assessed at baseline, 12, 24 and 60 months post study entry. Quality of life will be assessed by the EORTC QLQ-C30 self-administered multi-dimensional scale cancer-specific questionnaire and the cervical cancer supplement: QLQ-CX24, which is validated in 81 languages. It consists of 5 function scales, three symptom scales, six single-items, and a global QoL score. According to validation studies, it takes patients less than 15 minutes to complete it.

At baseline women will be asked to fill in questionnaires on:

- SDM-Q9NL
- Decisional conflict Scale DCS

After 12, 24 and 60 months of follow-up, women will be asked to fill in:

- Decisional Regret Scale RCS
- Questionnaire on concerns regarding fertility

Women will be asked if they agree to be registered in the **INCIP** database (International Network on Cancer, Infertility and Pregnancy (INCIP) during follow-up to learn about pregnancy outcomes.

4.6 Study procedures

All study procedures at each time point can be schematically reviewed in the summary table.

4.6.1 Before pelvic lymph node dissection

When patients are eligible according to the inclusion criteria the following investigations should be performed within 28 days prior to registration:

- Written and signed informed consent
- Check in -and exclusion criteria (except status pelvic lymph nodes not yet possible due to operation in the future)
- Registration for screening in ALEA
- Past medical history and baseline signs and symptoms
- Demography
- Physical examination including: performance status, vital signs, weight, height, pelvic exam, registration of visible tumor diameter in two directions, cervical cytology using ThinPrep vial.
- MRI and X thorax

- Quality of life questionnaire
- Reproductive Concerns Scale
- Laboratory blood test: Hemoglobin, hematocrit, red blood cell count (RBC), white blood cell count (WBC) with differential, platelet count, Blood group, irregular antibodies, type and screen
- sodium, potassium, calcium, serum creatinine, total bilirubin, alkaline phosphatase, eGFR, γGT, ASAT, ALAT, magnesium, total protein, albumin, urea, LDH
- 1x 10ml blood in EDTA tube if consented for translational research
- Tumor markers: CA 125, CEA, SCC
- Ovarian function: oestradiol, FSH, AMH

- ***14 days prior treatment: pregnancy test***

4.6.2 During Treatment

Week 0

On admission for pelvic lymph node dissection:

- type and screen
- vital signs

During surgery:

- pelvic lymph node dissection
- Sampling of tumor tissue for FFPE (usual care)
- Sampling of tumor tissue for freezing procedure (translational research)
- Obtaining cervical cytology in ThinPrep vial
- After pelvic lymph node dissection: registration of adverse events according to CTCAE 4.03

Week 3

- Study registration if no metastatic disease in pelvic lymph node dissection
- Policlinic visit to learn pathology results
- registration of adverse events according to CTCAE 4.03

Week 5-7

Before chemotherapy course 1:

- Hemoglobin, hematocrit, red blood cell count (RBC), white blood cell count (WBC) with differential, platelet count
- sodium, potassium, calcium, serum creatinine, total bilirubin, alkaline phosphatase, eGFR, γGT, ASAT, ALAT, magnesium, total protein, albumin, urea, LDH
- vital signs
- registration of adverse events according *CTCAE 4.03*

Week 8-9

Before chemotherapy course 2:

- Hemoglobin, hematocrit, red blood cell count (RBC), white blood cell count (WBC) with differential, platelet count
- sodium, potassium, calcium, serum creatinine, total bilirubin, alkaline phosphatase, eGFR, γGT, ASAT, ALAT, magnesium, total protein, albumin, urea, LDH
- vital signs
- registration of adverse events according *CTCAE 4.03*

Week 10

- pelvic exam, registration of visible tumor diameter in two directions
- MRI

Week 11-13

Before chemotherapy course 3:

- Hemoglobin, hematocrit, red blood cell count (RBC), white blood cell count (WBC) with differential, platelet count
- sodium, potassium, calcium, serum creatinine, total bilirubin, alkaline phosphatase, eGFR, γGT, ASAT, ALAT, magnesium, total protein, albumin, urea, LDH
- Tumor markers: CA 125, CEA, SCCvital signs
- registration of averse outcomes according *CTCAE 4.03*

Week 13

- pelvic exam, registration of visible tumor diameter in two directions
- If complete clinical and radiological response on physical examination and MRI: no additional 4th course is given.

Week 14-15

Before chemotherapy course 4:

- Hemoglobin, hematocrit, red blood cell count (RBC), white blood cell count (WBC) with differential, platelet count
- sodium, potassium, calcium, serum creatinine, total bilirubin, alkaline phosphatase, eGFR, γGT, ASAT, ALAT, magnesium, total protein, albumin, urea, LDH
- vital signs
- registration of averse outcomes according *CTCAE 4.03*

Week 17-18

- If response of tumour adequate ie <2 cm on all directions on physical examination and MRI and surgeon deems radical LRS possible: LRS
- registration of adverse events according *CTCAE 4.03*
- Type and screen on admission and 1x 10ml blood in EDTA tube if consented for translational research

During surgery:

- Sampling of tumor tissue for FFPE (usual care)
- Sampling of tumor tissue for freezing procedure(translational research)
- Cervical smear in thin prep

4 to 6 weeks post LRS

- Physical examination including gynaecological examination
- Ovarian function: oestradiol, FSH, AMH
- registration of adverse events according CTCAE 4.03

4.6.3 Follow-up

Follow-up scheme (see table 2):

- Year 1 and 2: 3 monthly, year 3 and 4: 6 monthly, year 5: once with Physical examination: performance status, vital signs, weight, pelvic exam
- QoL and Reproductive Concerns Scale 12, 24, 60 months
- 24 months: ovarian function: oestradiol, FSH, AMH

Table 1

	Screening			Study								
Summary table		**On admission for pelvic lymph node disscetion**	**Pelvic Lymph node dissection**		**Neo-adjuvant chemotherapy course 1**	**Neo-adjuvant chemotherapy course 2**	**Before course 3**	**Neo-adjuvant chemotherapy course 3**	**Before course 4**	**Neo-adjuvant chemotherapy course 4**	**Conization**	**4-6 weeks post-conization**
Study week	week -4 until 0	week -1	0	week 3	week 5-7	week 8-9	week 10	week 11-12	week 13	week 14-15	week 17-18	
registration screening	X											
registration study				X								
informed consent	X											
in-& exclusion criteria	X											
demography	X											
medical history	X											
baselin signs & symptoms	X											
WHO preformance	X											
Physical exam	X											X
Hematology	X[1&2]	X[2]			X[1]	X[1]		X[1]		X[1]	X[2]	
Biochemistry[3]	X				X	X		X		X		
Pregnancy test	X[4]											
pelvic exam[11]	X						X		X			
height/weight[5]	X											
vital signs[6]	X	X			X	X		X		X		
Tumor markers[7]	X							X[11]				X[11]
Ovarian function[8]	X											X
additional blood sample[9]	X										X	
MRI	X						X					
X-thorax	X											
Tumour biopsy[10]			X								X	
Quality of life	X											
reproductive concerns scale	X											
adverse events			X	X	X	X		X		X	X	X
cervical smear	X										X	

1. White blood cell count with differential, red blood cell count, granulocytes, platelet count, hematocrit and hemoglobin,
2. blood group, irregular antibodies, type and screen
3. sodium, potassium, calcium, serum creatinine, total bilirubin, alkaline phosphatase, eGFR, γGT, ASAT, ALAT, magnesium, total protein, albumin, urea, LDH
4. Pregnancy test no older than 2 weeks
5. barefooted and lightly clothed, height only at baseline
6. temperature, pulse and resting systolic and diastolic blood pressure
7. SCC, CEA, CA 125
8. oestradiol, FSH, AMH
9. 1x 10ml blood in EDTA tube if consented for translational research
10. two frozen, one formalin-fixed and paraffin-embedded if consented for translational research
11. tumor markers only when elevated at start study

Table 2

Follow-up scheme	Year 1 and 2								year 3 and 4				Year 5
Months post conization	3	6	9	12	15	18	21	24	30	36	42	48	60
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X
QoL				X				X					X
Reproductive Concerns Scale				X				X					X
Ovarian function								X					
tumor markers[7, 11]	X	X	X	X	X	X	X	X	X	X	X	X	X

5. METHODS

5.1 Study parameters/endpoints

5.1.1 Main study parameter/endpoint

The primary endpoint is response to neo-adjuvant chemotherapy.

Safety endpoint is defined as recurrence within 2 years since start of neo-adjuvant chemotherapy.

5.1.2 Secondary study parameters/endpoints (if applicable)

Secondary endpoints are recurrence-free survival for patients who received LRS, number of patients who kept the possibility to conceive (no hysterectomy performed, no radiation to pelvic area performed), ovarian function after treatment, quality of life, registration of pregnancies if they occur during follow-up, registration of concerns about fertility prior and after treatment. Translational research to predict response to neo-adjuvant chemotherapy.

5.1.3 Other study parameters (if applicable)

Smoking habits, obstetrical history, menstrual cycle

5.2 Randomisation, blinding and treatment allocation

Not applicable

5.3 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

5.3.1 Specific criteria for withdrawal (if applicable)

Pregnancy during treatment

5.4 Replacement of individual subjects after withdrawal

If a patient is registered after pelvic lymph node dissection but does not start with chemotherapy, this patient is replaced.

5.5 Follow-up of subjects withdrawn from treatment

Patients will be offered standard care and follow-up after withdrawal from the study.

5.6 Premature termination of the study

The trial can stop either due to lack of evidence of efficacy (at the interim analysis) or due to safety (at any time after 10 evaluable patients).

Efficacy will be evaluated according to Simon's two-stage design with an interim analysis after 40 evaluable patients. The trial will be put on hold after 40th patient has been accrued and until evaluation of the first stage. The study will close for futility if less than 27 responses will be observed.

Safety will be monitored continuously. The stopping boundaries are provided in the Appendix. The number of patients in the stopping criteria corresponds to the number of evaluable patients who underwent LRS.

If the trial is stopped, we will contact all included patients and will offer adjuvant treatment as and if deemed appropriate.

5.7 Translational Research

If funding is acquired, the following translational research will be executed.

Prediction of adequate response to neo-adjuvant chemotherapy is the main translational research question in the translational research project linked to this clinical trial. Hence cell cycle analysis (since platinum based therapy is known to be especially effective in cells in particular phases of the cell cycle), the activity of DNA repair mechanisms (e.g RAD51) will be analysed using different assays and chemotherapy sensitivity assays will be performed using tumoroids. In order to do so a cervical biopsy will be taken during pelvic lymphadenectomie. This cervical biopsy will be stored in a media supplied and send by courier to the LUMC for immediate work up. Apart from tumor tissue bloodsamples (serum, plasma and thrombocytes) will be taken and stored.

In order to evaluate the effect of chemotherapy on tumor characteristics; a cervical biopsy will be taken under general anesthesia during the pelvic lymph node dissection and a fresh frozen sample will be stored in a biobank. This material will be compared with tumor material which will be derived from the LRS specimen after regular diagnostic tests have been performed. If tumor response is not enough to justify a LRS, this has to be proven by a biopsy for histologic examination. In this scenario, one extra biopsy specimen will be taken and freshly frozen and stored in a biobank.

6. SAFETY REPORTING

6.1 Section 10 WMO event

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC with undue delay of a temporary halt including the reason for such an action. The study will be suspended pending further review by the accredited METC. The investigator will take care that all subjects are kept informed.

6.2 AEs, SAEs and SUSARs

6.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a patient during a clinical trial, whether or not considered related to the investigational treatment (i.e. can also be related to the core biopsies). All adverse events reported spontaneously by the patient or observed by the investigator or his staff starting on the the day of PLN dissection until 30 days after conization will be recorded.

6.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the patients, such as an unexpected outcome of an adverse reaction.

*Life threatening***:** the term 'life threatening' in the definition of 'serious' refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.

*Hospitalization***:** any adverse event leading to hospitalization or prolongation of hospitalization will be considered as 'serious', UNLESS at least one of the following exceptions are met:

- the admission is pre-planned (e.g. elective or scheduled surgery arranged prior to the start of the study, documented in the patient's file);
- prolonged hospitalization for technical, practical or social reasons, in the absence of an adverse event.

All SAEs will be reported to the accredited METC that approved the protocol, according to the requirements of that METC.

6.2.3 Suspected unexpected serious adverse reactions (SUSAR)

SUSARs are unexpected adverse reactions with a suspected relationship to the investigational medicinal product. Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (e.g.

Summary of Product Characteristics (SPC)). All serious adverse reactions not mentioned in this product information are considered unexpected.

6.3 Recording of AEs

At each contact with the patient, the study personnel must seek information on (serious) adverse events by specific questioning and, as appropriate, by examination. Information on all (serious) adverse events should be recorded promptly in the patient's medical records. This information must be as complete as possible and preferably include start and stop date of the event, CTC grading (see below) and the relation to study medication. At a later moment this information will be transferred from the medical records to the Case Report Forms.

All adverse events starting on the day of PLN dissection until 30 days after conization must be recorded. The clinical course of each event must be followed until resolution or stabilization. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist

6.4 Recording of SAEs

Besides recording in the patient's medical record, for each serious adverse event, the study specific Serious Adverse Event Form must be completed. On the SAE form all clearly related signs, symptoms and abnormal diagnostic procedures must be recorded as a single diagnosis. The component parts of the diagnosis may be listed for verification.

The following definitions will be used to assess causality:

Not related: The clinical adverse event is definitely unrelated to the study treatment (e.g., does not follow a reasonable temporal sequence from study drug administration, present prior to receiving study medication, etc.)

The study treatment is not likely to have had reasonable association with the observed experience; however, relationship cannot be definitely excluded.

Related: The connection with study treatment appears unlikely, but cannot be excluded with certainty (e.g., follows a reasonable temporal sequence from drug administration, may be related to known characteristics of the patients' clinical state or other modes of therapy administered to the patient, etc.).

The clinical adverse event appears related to the study treatment with a high degree of certainty (e.g., follows a reasonable temporal sequence from drug administration and abates upon discontinuation of the drug, cannot be reasonably explained by known characteristics of the patient's clinical state or other modes of therapy administered to the patient, etc.).

The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the patient’s condition, therapeutic interventions or concomitant drugs; AND occurs immediately following study drug administration, improves on stopping the drug, or reappears on re-exposure.

The intensity of an adverse event will be graded according to the NCI Common Toxicity Criteria v 4.030. Adverse events that cannot be graded using the NCI Common Toxicity Criteria will be graded as mild (asymptomatic), moderate (symptomatic but not interfering significantly with function) or severe (causing significant interference with function).

Table 3. Adverse Event Grading (Severity) Scale

Grade	Severity	Alternate Description [a]
1	Mild (apply event-specific NCI CTCAE grading criteria)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate (apply event-specific NCI CTCAE grading criteria)	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[b]
3	Severe (apply event-specific NCI CTCAE grading criteria)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare ADL[c]
4	Very severe, life threatening, or disabling (apply event-specific NCI CTCAE grading criteria)	Life-threatening consequences; urgent intervention indicated
5	Death related to AE	

6.5 Reporting of SAEs

All serious adverse events (including pregnancy) starting on the day of PLN dissection and within 30 days after surgery, whether considered by the investigator to be related to study treatment or not, must be medically well documented and reported to the Antoni van Leeuwenhoek Data Centre within 24 hours or, at the latest, on the following working day.

The report must be sent by **email (drugsafety@nki.nl)** to the **Antoni van Leeuwenhoek Data Centre.** The Data Centre can also be contacted by **fax** (+31 20 512 2679) or **telephone** (+31 20 512 2668) between **09.00 and 17.00 hours (GMT+1)** Monday to Friday**.**

Reporting must be done using the study specific Serious Adverse Event Form of the study. The forms will be filed at the Antoni van Leeuwenhoek Data Centre. Serious adverse events that are not considered to be SUSARs will not be reported to the Ethics Committee.
All serious adverse events must be followed up until resolution or stabilization, and this information must be reported to the Data Centre as soon as it becomes available, using a follow-up Serious Adverse Event Form. This form will be signed by the investigator and filed together with the initial report.

All SAE's will be reported once yearly, as described in the section Annual Safety Report. All SAE's for this multicentre oncological study will not be reported through the web portal ToetsingOnline to the METC.

6.6 Reporting of SUSARs

The Antoni van Leeuwenhoek is the sponsor of this study. The Data Centre will represent the Antoni van Leeuwenhoek for the sponsor task of reporting safety data according to the WMO requirements. The Antoni van Leeuwenhoek Data Centre personnel will notify the study

coordinator of any serious adverse event reported. The study coordinator will evaluate the SAE and will decide whether the event reported could be related to the protocol treatment and whether it is, both, unexpected and serious (SUSAR).

The Data Centre will report all SUSARs through the web portal ToetsingOnline to the METC. The expedited reporting of SUSARs through the web portal ToetsingOnline is sufficient as notification to the Dutch competent authority. The Data centre will report all SUSARS through EVWEB to EudraVigilance of the EMA and all competent authorities from the applicable countries.
This reporting will be expedited and will occur not later than 15 days after the Data Centre its first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.
The expedited reporting of SUSARs through the web portal ToetsingOnline is sufficient as notification to the competent authority.

6.6.1 Six-monthly line listing

SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that have no immediate consequences for the safety of the subjects involved in this clinical trial, will be reported to the accredited METC in a 6-monthly line listing accompanied by a brief report by the investigator highlighting the main points for concern.

The Principal Investigators of participating sites will also be informed about the SUSARs.

6.7 Annual safety report

In addition to the expedited reporting of SUSARs, the study coordinator (in collaboration with the Data Centre) will submit, once a year throughout the clinical trial, a safety report to the accredited METC and the CCMO.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation

7. STATISTICAL ANALYSIS

7.1 Primary study parameter(s)

Primary endpoint is response to the neo-adjuvant treatment. Success of the trial will be determined on the basis of the boundaries given by the Simon’s design (at least 27 responders in the first stage and at least 83 responders in total) Additionally a point estimate and 95% confidence bound for the response rate will be calculated.

7.2 Secondary study parameter(s)

Safety endpoint.

Safety will be monitored in a Bayesian setting using continuous monitoring via posterior probability. Stopping rules for safety will be applied only to patients who receive LRS (exact number unknown, expected number is 75% of the total sample size, so about 90 patients). We will follow each patient for at least 2 years. If 17% of patients who received LRS have recurrence within 2 years the treatment is considered unsafe. Thus, the proportion of patient without recurrence by 2 years (θ) which would be considered futile equals 0.83. Prior distribution for this proportion was set as Beta(46, 9.42) This prior corresponds to mean θ of 0.83 and standard deviation of 0.05. The continuous monitoring will start after 10 patients have been treated and evaluated for safety (either have recurrence within 2 years or are followed for 2 years without signs of recurrence). After evaluation for recurrence by 2 years of every consecutive patient, the prior distribution will be updated and the trial will be considered unsafe if Probability($\theta < 0.83$ | data from the trial) > 0.7. Based on this rule the maximum number of acceptable failures can be determined. Stopping boundaries can be found in the Appendix. The calculations of the stopping boundaries were done using Shiny application written by Jack Lee at al. (https://biostatistics.mdanderson.org/softwareOnline/).

The stopping boundaries take into account evaluable patients, so in principle patients with at least 2 years of follow-up. However the monitoring is performed in the continuous manner. In case if the stopping boundary is crossed, but the outcome from some accrued patients is still unknown, the trial will be put on hold until the outcome of all accrued patients is known. The results will then be updated. If the stopping boundary is still crossed, the trial will be considered unsafe. If the stopping boundary is not crossed anymore for the updated data, the trial will reopen.

Exact operating characteristics depend on the final sample size, which is unknown, but at the moment it's assumed to be 90 patients. In case if the true θ is only 0.6 then the trial will stop after average number of 13 evaluable patients. Similarly, the expected number of evaluable patients in case of $\theta=0.7$ is 20. If the true θ is 0.9 or higher the probability of stopping the study for safety is at most 7%.

7.3 Other study parameters

Recurrence-free survival will be calculated for all patients and separately for patients who received LRS. Recurrence-free survival will be defined as time from registration until recurrence or death from any cause. Kaplan-Meier method will be used to calculate the survival estimates. The need for adjuvant therapy (radical hysterectomy or (chemo)radiation will be registered, preservation of ovarian function will be assessed by questionnaires on menstrual cycle and hormonal laboratory tests. Quality of life will be analysed as longitudinal outcome. Mixed models will be used to account for missing data.

7.4 Interim analysis (if applicable)

One interim analysis is planned according to the Simon's design. The interim analysis will take place after accruing 40 patients. The trial will be put on hold and the results of the first

stage will be evaluated. If at least 27 patients respond to the neo-adjuvant chemotherapy the trial will be reopened for the second stage.

8. ETHICAL CONSIDERATIONS

8.1 Regulation statement

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/index.html) or the laws and regulations of the country, whichever provides the greatest protection of the patient. The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice (ref: http://www.ifpma.org/pdfifpma/e6.pdf). The protocol will be approved by the Local, Regional or National Ethics Committees.

8.2 Recruitment and consent

The investigator must fully explain the trial to the patient. A patient information sheet giving details of the trial will be provided for the patient to read and retain. After the patient had time to consider the information and has been encouraged to ask questions, he/she will be asked to give informed consent by signing and dating an informed consent form. All informed consent forms should be countersigned and dated by the investigator. If the patient is unable to read or write, the informed consent forms should be signed and dated by the investigator and an independent witness, to indicate that the patient apparently understood the information and consented freely.

Written informed consent will be obtained before any study procedures, including study-specific screening procedures, has been performed. Procedures that are part of standard care and not done for study-specific purposes for this study, may occur before informed consent is obtained. The original of the informed consent form will be filed.

A copy will be given to the patient. The patients have the right to withdraw from the study at any time, without giving an explanation and without prejudice to their subsequent care

8.3 Subject identification

Each patient will be assigned a Patient Allocation Number on registration. The Patient Allocation Number and the Patient Verification Code (Verification Code consist of the months (2 digits mm) and year (4 digits yyyy) of the date of birth of the patient) are to be entered on the Case Report Form. The investigator will retain all pertinent information for a period of maximum 15 years from study completion.

The investigator will be responsible for retaining sufficient information about each patient (e.g. name, address, phone number, and identity in the study) so that regulatory agencies or participating investigators may access this information should the need to do so arise. These records should be retained in a confidential manner for as long as legally mandated according to local requirements Patients will not be asked in the future for information in relation to this study.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.5 Replacement of individual subjects after withdrawal

Patients who refuse after prior informed consent before start of protocol treatment will be replaced. Patients who discontinue for reasons not related to the study treatment after the first administration will be replaced, but will be analysed as per “intention-to-treat” principles. Patients who discontinue due to toxicity related to study treatment will NOT be replaced but will be analysed as per “intention-to-treat” principles.

8.6 Benefits and risk assessment, group relatedness

Combination treatment with carboplatin (AUC=2) and paclitaxel (80 mg/m2) has proven tolerable and effective for this indication. This group could benefit from the chemotherapy by reducing the tumor size and therefore a limited surgery.. This limit surgery could lead to a higher pregnancy rate. Although this is a low dose, the extra chemotherapy could give more side effects, but we expect the benefits the outweigh the possible disadvantages of the chemotherapy.

8.7 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

8.8 Trial Insurance

The sponsor/investigator has a liability insurance that is in accordance with article 7 of the WMO. The sponsor (also) has an insurance that is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research

subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

9.1 Central data centre

The central Data Management, data processing and statistical analysis of this study will be performed at the Biometric Department of the Antoni van Leeuwenhoek. Randomization will be done after the written informed consent is obtained and after verification of eligibility.

Registration will be performed using the TENALEA® registration package run by the Antoni van Leeuwenhoek Data Centre. When the system is not accessible it will be done centrally at the Data Centre (+31 20 512 2668). For every patient confirmation letters will be sent by e-mail to the Principal Investigator of the site, the responsible Data Manager and the study coordinator of the study, stating the Patient Allocation Number and if applicable the randomization arm.

Data will be collected on the electronic case report forms (eCRFs), specially designed for this study, by the local Data Manager of each participating institute. The eCRF system specific for this study will be developed by the Antoni van Leeuwenhoek Data Centre. The system can be accessed via internet by the sites to include data directly in the Data Centre Servers. The Data Centre will supply accounts to the local data managers to enter data into the system. Checks will be incorporated into the eCRF system to prompt queries at the moment that data is entered facilitating the work of the local data manager who could quickly correct errors. Additional checks will be programmed using statistical programs with the goal of obtaining a clean file.

9.2 Handling and storage of data and documents

The Study Coordinators (in cooperation with the Data Centre) will be responsible for writing the protocol, reviewing all case report forms, reporting of serious adverse events (SAE) and documenting his/her review on evaluation forms, discussing the contents of the reports with the Data Manager and the Statistician, and for publishing the study results. They will also generally be responsible for answering all clinical questions concerning eligibility, treatment, and the evaluation of the patients.

9.3 Monitoring and Quality Assurance

9.3.1 Site Monitoring

The study will be risk based monitored according to ICH GCP. This study will be considered as a low risk study. The standard chemotherapy for cervical cancer has been proven

tolerable and effective. Since we use a lower dose than the standard dose, we don't foresee any major problems concerning the safety. Site monitoring will be performed by an independent Clinical Research Monitor or the person to whom the monitoring tasks have been delegated.

Amongst others the following will be reviewed:

- Compliance with the protocol, ICH-GCP and all applicable regulatory requirements.
- Informed Consent
- Source Data Verification
- Investigator Study File
- (Serious) Adverse Events / SUSAR

A monitoring plan specific to the study and describing the nature and frequency of the monitoring will be written by the appointed monitor and approved by the Principal Investigator and the Head of the Data Centre.

9.3.2 Central monitoring

Data from all patients will also be centrally checked at the Data Centre. Through central monitoring of the data collected, the Data Centre will be able to detect outliers or apparently spurious data. When persistent irregularities or protocol violations are detected, the Data Centre will inform the local investigator (and Principal Investigators) and queries will be sent to the local Data Manager

9.4 Quality Assurance

To ensure compliance with ICH-GCP and all applicable regulatory requirements, as part of the quality system, a quality assurance audit may be conducted. For this purpose the investigator must agree to allocate time and grant access to all relevant documents.

Regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

9.5 Amendments

Amendments are changes made to the protocol after a favorable opinion by the accredited METC and the Competent Authority has been given. A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial
- the scientific value of the trial
- the conduct or management of the trial
- the quality or safety of any intervention used in the trial

All substantial amendments will be notified to the METC and to the Competent Authority. Non substantial amendments will not be notified to the accredited METC and the Competent Authority, but will be recorded and filed by the sponsor.

9.6 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems and amendments.

9.7 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit. The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

9.8 Publication policy

The final publication of the trial results will be written by the Study Coordinators on the basis of the final analysis performed at the AVL Data Centre. A draft manuscript will be submitted by the study coordinators to the Data Centre for review no later than six months after receiving the Data Centre report. After revision by the Data Centre and other co-authors the manuscript will be sent to a major scientific journal.

Authors of the manuscript will include at least the Study Coordinators, the investigators who have included more than 5% of the eligible patients in the trial (by order of inclusion), and members of the Data Centre team who have contributed to the trial.

All manuscripts will include an appropriate acknowledgment section, mentioning all investigators who have contributed to the trial, as well as supporting bodies. The Study Coordinators and the Data Centre must approve all publications, abstracts and presentations based on patients included in this study. This is applicable to any individual patient registered/randomized in the trial, or any subgroup of the trial patients.

10. STRUCTURED RISK ANALYSIS

10.1 Potential issues of concern

The combination treatment with carboplatin (AUC=6) and paclitaxel (175 mg/m^2) is already considered standard of care for ovarium cancer and has proven tolerable. Since we use a lower dose for cervical cancer than the standard dose used for ovarium cancer, we don't foresee any major problems concerning the safety.

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Appendix 1 Response Evaluation Criteria in Solid Tumors (RECIST), v.1.1

Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (Eisenhauer 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with niraparib.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pneumonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published ENREF 51. In addition, the Gynecologic Cancer Intergroup has developed CA-

125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer_ENREF_54.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that

is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	

CR	Not evaluated	No	PR	≥4 wks. Confirmation**
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration.” Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* ‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

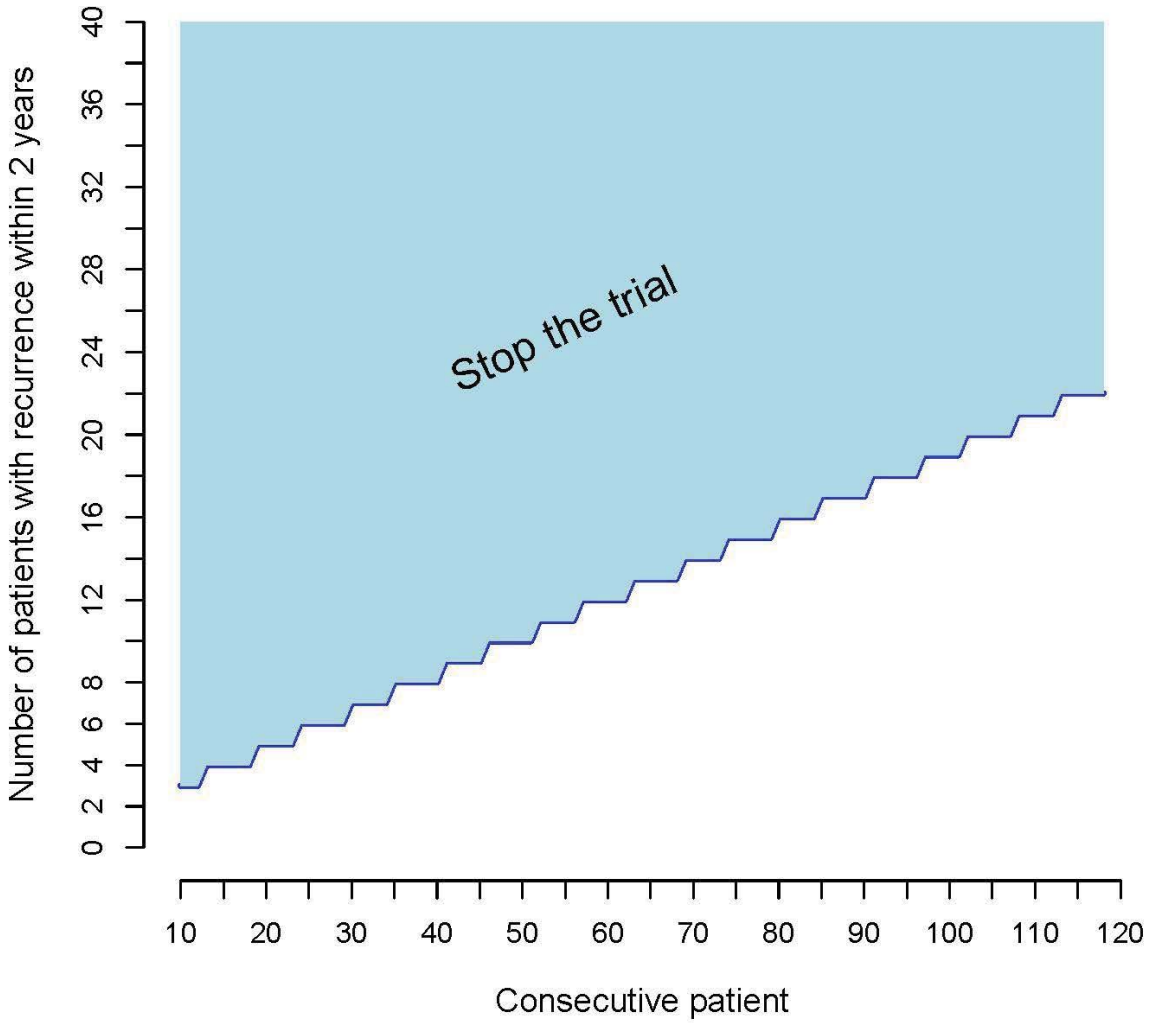
The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

Appendix 2. Stopping rules



NEOCON-F stopping rule for safety	**If the number of patients with recurrence within 2 years is** **greater than this column, the trial should stop for safety**
consecutive patient	maximum number of failures
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