Princess Margaret Consortium

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Stage IB1 (2-4 cm) Cervical cancer treated with Neoadjuvant chemotherapy followed by fertility Sparing Surgery (CONTESSA)

Dre Marie Plante

Neo-Adjuvant Chemotherapy and Conservative Surgery in Cervical Cancer to Preserve Fertility (NEOCON-F)

Dr Frédéric Amant

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Preliminary Proposal

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Dr Frédéric Amant

CONTESSA / NEOCON-F

CONTESSA

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Study Coordinators PMH:

Stephanie LHeureux, Amit Oza

NEOCON-F

PI: F. Amant

Center for Gynaecologic Oncology Amsterdam (CGOA)/Netherlands Cancer Institute (NCI)

Study Coordinator CGOA/NCI:

Nienke van Trommel

Historical background

- Contessa was developed out of the cervical cancer brainstorming day (Melbourne 10/2014)
- Proposal was put on hold 6/2016 (funding issues)
- Proposal reactivated 10/2017 (PMH Consortium)
- Recent opportunity to join forces with NEOCON protocol (Netherlands)

Background

- **Upfront radical trachelectomy : "standard of care" for the management of early-stage cervical in women who wish to preserve fertility (NCCN guideline 2017)**
  - **Validated for lesions < 2 cm**
- **Limited data in the literature regarding the optimal management of women with larger size lesions (2-4 cm) who wish to preserve fertility**

Background

- NACT followed by FPS
  - NACT been shown to be effective in reducing the size of cervical cancer (70%)
  - High rates of fertility preservation (80%)
  - Limited data in the literature (few series / small #); no standardized approach

Specific Hypothesis

- Neoadjuvant chemotherapy (NACT) in node-negative women with stage IB1 (2-4 cm) cervical cancer will enable fertility preserving surgery without compromising oncologic outcome in good chemo-responders

Primary Objective #1

- To evaluate the safety (PFS) of NACT in women with node negative, stage IB1 cervical cancer with lesions measuring 2-4 cm

Primary Objective #2

- To evaluate the **rate of fertility preserving surgery (FPS)** following neoadjuvant chemotherapy (NACT)

Secondary Objectives

- Chemotherapy related adverse events / safety
- Surgical complication rate of FPS
- Requirement for adjuvant radiation therapy (trimodality treatment)
- Requirement for definitive hysterectomy
- Quality of Life
- Ovarian function, rates of pregnancy and obstetrical outcomes

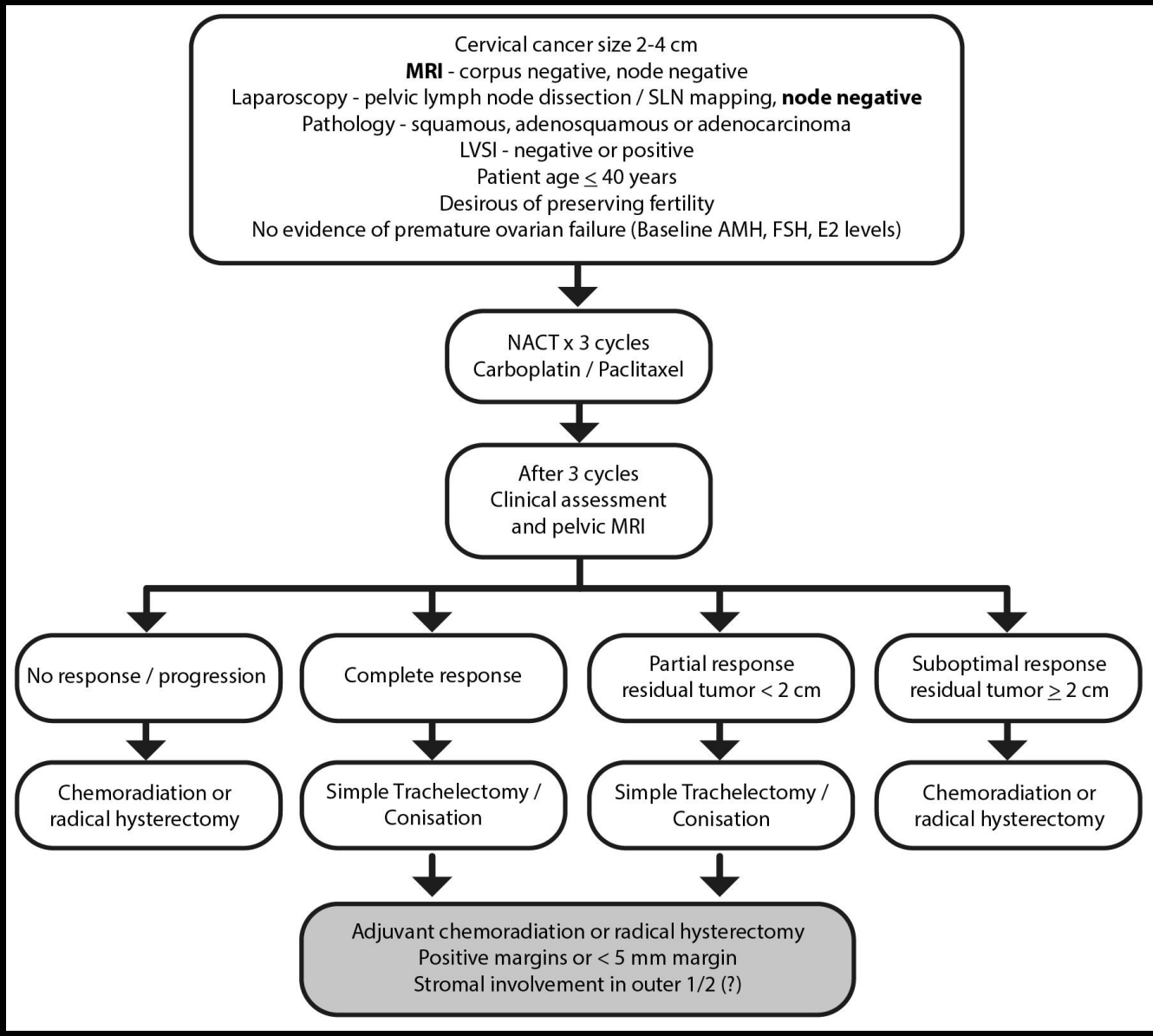
Inclusion criteria

- Invasive cervical cancer
  - adenocarcinoma, adenosquamous or squamous
- LVSI allowed
- Grade 1, 2 and 3
- Stage IB1 measuring 2-4 cm (clinical exam and MRI)
- Age ≤ 40
- No evidence of Premature Ovarian Failure
- Desire to preserve fertility potential

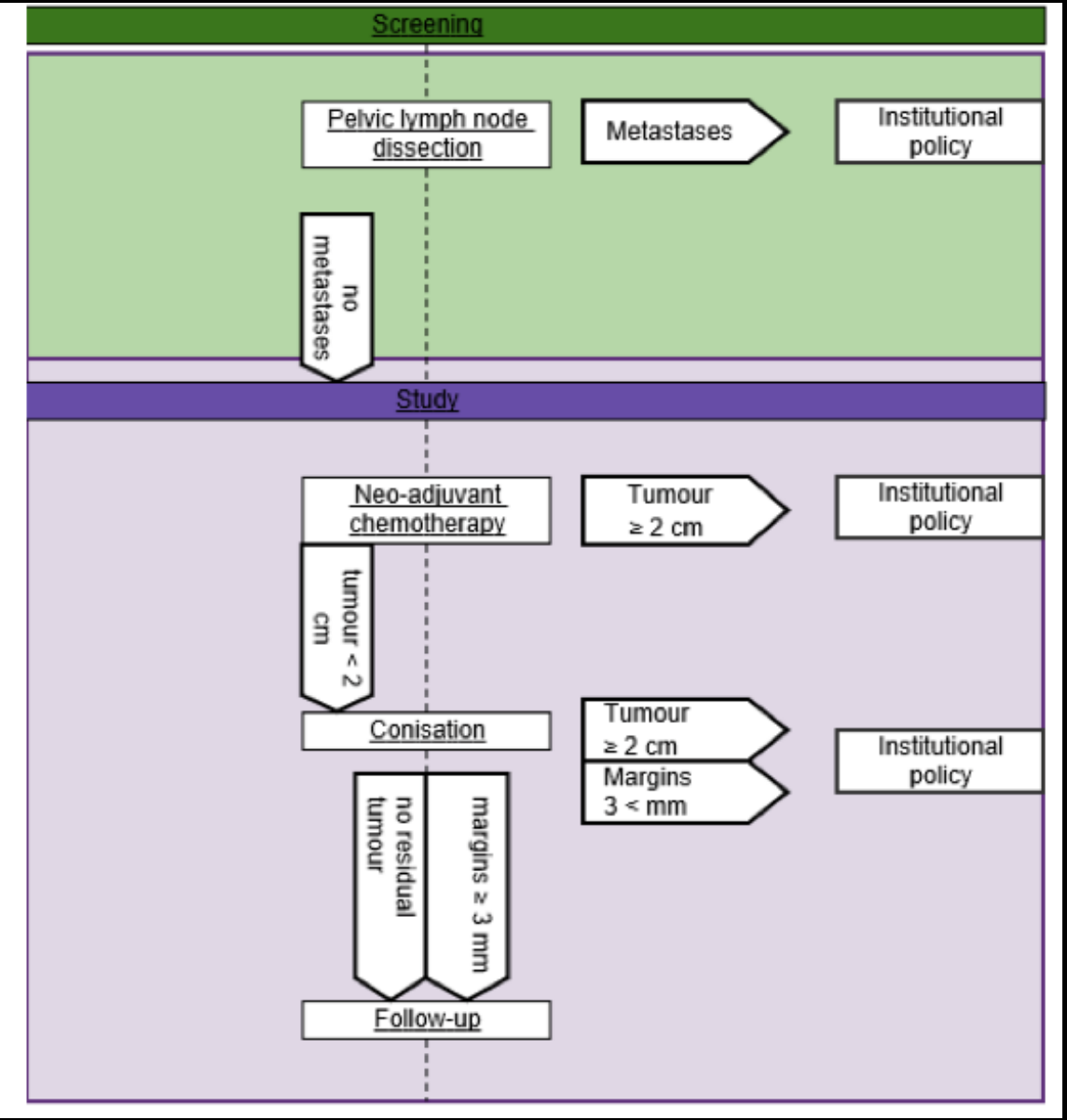
Exclusion criteria

- Uterine corpus invasion or extracervical disease (based on MRI)
- Lymph node metastasis
  - Pre-study laparoscopy to exclude LN mets
    - sentinel lymph node mapping
    - pelvic lymphadenectomy

CONTESSA


Cervical cancer size 2-4 cm
MRI - corpus negative, node negative
Laparoscopy - pelvic lymph node dissection / SLN mapping, node negative
Pathology - squamous, adenosquamous or adenocarcinoma
LVSI - negative or positive
Patient age ≤ 40 years
Desirous of preserving fertility
No evidence of premature ovarian failure (Baseline AMH, FSH, E2 levels)
NACT x 3 cycles
Carboplatin / Paclitaxel
After 3 cycles
Clinical assessment
and pelvic MRI
No response / progression
Complete response
Partial response
residual tumor < 2 cm
Suboptimal response
residual tumor ≥ 2 cm
Chemoradiation or
radical hysterectomy
Simple Trachelectomy /
Conisation
Simple Trachelectomy /
Conisation
Chemoradiation or
radical hysterectomy
Adjuvant chemoradiation or radical hysterectomy
Positive margins or < 5 mm margin
Stromal involvement in outer 1/2 (?)

NEOCON-F


Screening
Pelvic lymph node dissection
Metastases
Institutional policy
no metastases
Study
Neo-adjuvant chemotherapy
Tumour ≥ 2 cm
Institutional policy
tumour < 2 cm
Conisation
Tumour ≥ 2 cm
Margins 3 < mm
Institutional policy
no residual tumour
margins ≥ 3 mm
Follow-up

Trial design

- **Screening phase:** Laparoscopy
  - SLN mapping + pelvic LND
  - Await final pathology analysis
- **Study phase (If LN-):** NACT x 3 cycles
  - Weekly Taxol 80 mg/m2 & Carbo AUC2
  - Q3 weeks Taxol 175 mg/m2 & Carbo AUC6
- **Pelvic MRI** and clinical exam
  - If residual tumor **< 2 cm**
- **Fertility Preserving Surgery** (FPS)
  - Large cone / simple trachelectomy

Primary endpoints

- Recurrence rate/PFS at 2 years (#1)
- Intact functional uterus following NACT and FPS (#2)

Secondary endpoints

- Response rate to NACT
- Adverse events and safety
- Surgical complication rate
- Rates of definitive hysterectomy
- Requirement for adjuvant radiation therapy (trimodality treatment)
- QOL: EORTC QLQ C30 and QLQ CX 24
- Disease Outcomes: PFS at 2 years
- Ovarian function (FSH, estradiol, AMH)
- Pregnancy rates and obstetrical outcomes

Statistical analysis

- Phase II study
- Prospective, multi-center, international trial

Statistics : PRELIMINARY

- N=119 patients
- Expected response rate to NACT: 75%
  - 90 patients should proceed to FPS
- First phase of accrual: 40 patients
  - At least 27 must have responded
- Second phase of accrual: 79 patients
  - At least 83 must have responded

Statistics : PRELIMINARY

- **Safety: defined as number of recurrences within two years in the group receiving FPS (7% recurrence rate expected)**
- **Patients will be monitored continuously in a Bayesian manner and stopping rules will apply when the percentage of recurrences exceeds 12% at two years**

Translational research

- Assessment of **tumor response**
  - Circulating tumor DNA (ctDNA) (PMH)
  - Hypermethylated DNA (Netherlands)

Funding

- PMH Consortium
  - Per case funding for Canadian patients
  - Data collection and data monitoring
- Netherlands (CGOA/NCI)
  - Per case funding for Dutch patients
  - Data collection and data monitoring
- Other groups
  - Will have to secure own funding

Summary

- Feasable study
- Count on international collaboration
- Will provide solid data as to the safety of this approach and standardize the procedure
- In the process of finalizing the “merging” of the 2 protocols