A phase III Trial of postoperative chemotherapy or no further treatment for patients with node-negative stage I-II intermediate or high risk endometrial cancer.

ENGOT-EN2-DGCG / EORTC-55102

Version 2.1

Chief Investigators:

Mansoor Raza Mirza (DGCG); Frederic Amant (EORTC)

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Danish Cancer Society

5-year survival - FIGO

Stage I	G1	G2	G3
Ia	93	91	80
Ib	92	93	82
Ic	91	86	75
Stage II			
IIa	90	84	68
IIb	81	77	65

mansoor@rh.regionh.dk

Creasman et al., IJGO, 2007

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Endometrioid:
Stage I - G3; II
Non-endometrioid:
Stage I-II

→ **Chemotherapy**
Carboplatin-Paclitaxel x 6
+ Brachytherapy

→ **Observation**
+ Brachytherapy

n=678

mansoor@rh.regionh.dk

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Stratifications

1: endometrioid versus non-endometrioid

2: stage 1a vs. 1b vs. 2 disease

3: para-aortic (≥10)and pelvic (≥20) LNE versus lesser LNE

4: Brachytherapy planned yes/no

mansoor@rh.regionh.dk

Inclusion Criteria
Patient Population
FIGO 2009

Only node-negative patients are eligible
Histological confirmed endometrial carcinoma with no macroscopic remaining tumour after primary surgery, with one of the following postoperative FIGO 2009 stage and grade:

Stage I grade 3 endometrioid adenocarcinoma

Stage II endometrioid adenocarcinoma

Stage I and II type 2 histology (clear cell, serous, squamous cell carcinoma or undifferentiated carcinomas)

***Excluded:* Carcinosarcoma, Sarcomas or small cell carcinoma with neuroendocrine differentiation**

mansoor@rh.regionh.dk

Inclusion Criteria
Prior Therapy

• Hysterectomy (total abdominal hysterectomy, radical hysterectomy, laparoscopic or robotic hysterectomy)

• Bilateral salpingo-oopherectomy (BSO)

• pelvic lymphadenectomy (LNE): minimum 12 pelvic nodes (minimum 6 from each side) should be removed. Para-aortic LNE is optional

• Omentectomy recommended in clear cell, serous or undifferentiated carcinoma

• Surgery performed within 10 weeks of randomization. If the dates for hysterectomy and lymph node dissection are different, 10 weeks are counted from the last surgery, and in that case the gap between two surgeries should not exceed 8 weeks.

mansoor@rh.regionh.dk

Exclusion Criteria

Prohibited Treatments and/or Therapies

- External Beam Radiotherapy
- Concurrent cancer therapy
- Concurrent treatment with an investigational agent or participation in another clinical trial.

mansoor@rh.regionh.dk

Central Pathology Review

• Central pathology review confirmation is not required for the patient prior to randomization.

• For central pathology review one H&E stained tissue slide (formalin fixed-paraffin embedded, 3-4 µm) per patient are requested. Slides must be representative for the tumour diagnosed and must optimally contain at least 30% tumour.

• H&E slide for central pathology review must be shipped to Danish CancerBiobank.

• If the site participates in the Translational Research sub-study (TR sub-study) H&E slide for central pathology review must be shipped to Danish CancerBiobank together with additional tissue slides for TR.

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Treatment
Schedule for chemotherapy

Paclitaxel and Carboplatin (TC):

- Paclitaxel 175 mg/m^2 i.v. infusion over 3 hours on day one.
- Carboplatin AUC 5 i.v. infusion over 30-60 minutes on day one.

The treatment is to be repeated every three-weeks for six courses.
Courses 2-6 can be delayed up to 3 days due to administrative reasons.

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Treatment
Vaginal Brachytherapy

The investigator shall decide prior to informed consent and randomization, if VBT is planned for the patient.

In chemotherapy arm, timing of VBT should not cause delay in chemotherapy delivery.

Dose recommendation:

A dose equal to 7Gy weekly x 3 times (total dose 21 Gy) at 5 mm (upper vagina) to 0 mm (mid vagina) from the applicator at the upper half of vagina (HDR/PDR).

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Translational Research

Methods for collection and analysis of tissue samples

• Formalin fixed paraffin embedded (FFPE) tissue blocks representing the tumour of the patient should be selected.

• The FFPE tissue for TR-substudy should be cut into 3-4 m sections.

• Optimally 20 unstained slides (minimum 10) on Super- Frost®Plus glass plates should be shipped together with one slide stained with hema- toxylin and eosin (H&E) to evaluate and confirm tumour tissue in the selected tissue block.

mansoor@rh.regionh.dk

Study End Points

Primary Endpoint

- Overall Survival

Secondary Endpoints

- Disease Specific Survival (DSS)
- Progression-Free Survival (PFS)
- Toxicity
- PRO: (QOL) EORTC QLQ-C30 and EORTC-QLQ-EN24
- Rate of isolated pelvic relapse (central and/or pelvic wall)
- Rate of isolated distant relapse
- Rate of mix local and distant relapse

mansoor@rh.regionh.dk

Statistical plan

To detect an overall absolute difference in five-year survival of 10%, from 72% to 82%, at the 2.5% level with 80% power, 135 deaths corresponding to 644 patients are needed.

In the **endometrioid subgroup** an absolute difference in five-year survival of 12%, from 74% to 86% is expected. Assuming this, 79 deaths corresponding to **438 patients** are needed to yield 80% power at the 2.5% level.

Assuming a dropout rate of 5%, **678 patients** have to be accrued, leaving 644 patients for the overall analysis and 75% of these, or 483 patients, for the analysis in the endometrioid subgroup.

mansoor@rh.regionh.dk

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Group	Country	No. of Institutions	Authorized	Patients randomized
DGCG	Denmark	6	6	22
NSGO	Sweden	4	4	8
	Finland	6	3	0
BGOG	Belgium	11	7	0
EORTC	Belgium	4	4	1
	Austria	1	1	0
	Germany	4	0	0
	Portugal	1	0	0
	Spain	3	0	0
	UK	9	1	0
	Netherlands	1	0	0
MaNGO	Italy	6	0	0
TOTAL		**56**	**26**	**31**

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Trial Specific Satellite Session

Room 5

5pm-5.30pm

mansoor@rh.regionh.dk