ENGOT-CX7 / NSGO / MaRuC

A randomized double-blind placebo-controlled phase II trial of Rucaparib maintenance therapy for patients with locally advanced cervical cancer

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Sponsor: NSGO

Study Chair: Mansoor Raza Mirza

Study Status

- Model A
- Study draft protocol & budget accepted by Clovis
- October/November: Feasibility to be sent out to collaborative groups
- January 18: Protocol finalized
- Q1 18: submissions
- Expected FPI: Q2 2018

Rationale

- **DNA repair in cervical cancer is less established**
- **HPV infection and oncoviral proteins E6 & E7 causes inactivation of p53 & pRB tumour-suppressor genes leading to cell cycle dysfunction and impaired DNA repair**
- **Cells are therefore increasingly dependent on residual repair pathways**
- **A correlation between response to DNA repair pathways has been noted in the clinic:**
  - **Patients treated with chemoradiation have high expression of the nucleotide excision repair protein ERCC1 associated with decreased PFS & OS & activation of the BRCA pathway correlated with treatment failure**
  - **Impaired NHEJ repair was related to increased OS**
- **Early phase trials incorporating modulators of DNA repair such as PARP inhibitors are underway**

Duensing S et al. Cancer Res. 2002; 62:7075–7082
Balacescu O et al. BMC Cancer 2014; 14:246
NCT01281852: Olaparib & radiotherapy in H&N cancer
NCT02686008: Olaparib in patients with HPV positive & HPV negative HNSCC

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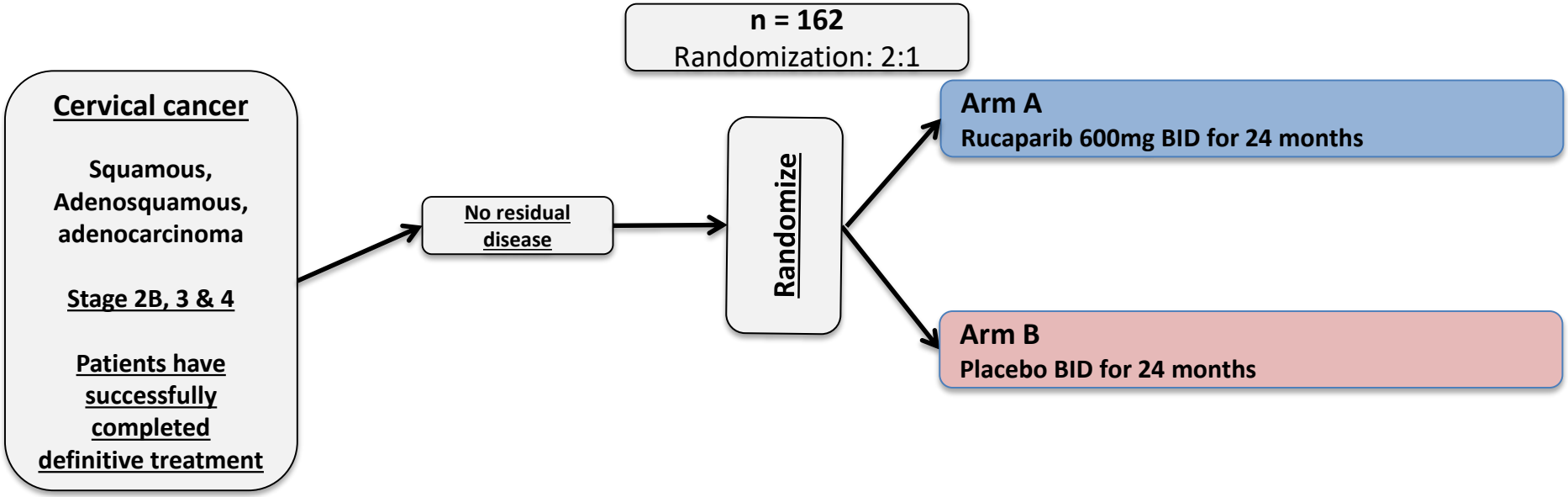

Stratification factors

- Histology (squamous vs adenosquamous, adenocarcinoma)
- FIGO stage (2b-pos. nodes vs. 3 vs 4)

Enrolment of patients with squamous cell histology will be capped once 60% patients with this histo-type are enrolled

Design

- This is a multicenter, phase 2, doubleblind, placebo-controlled trial of maintenance Rucaparib to obtain preliminary evidence of efficacy of rucaparib in locally advanced cervical cancer:

- Randomization: 2:1

- Patients are stratified according to:
  - Histology (squamous vs adenosquamous, adenocarcinoma)
  - FIGO stage (2B with positive nodes vs 3 vs 4)

- Squamous cell carcinoma patients will be capped to 60% of patient population

Study arms

- **Arm A:** rucaparib 600mg BID for 24 months
- **Arm B:** placebo BID for 24 months

Study population

- Squamous cell, adenocarcinoma or adenosquamous carcinoma of the cervix.
- Subject must have completed definitive chemoradiation and is evaluated to be in partial or complete remission 10-12 weeks post chemoradiation
- Initial FIGO stage IIB with positive nodes, IIIA, IIIB, IVA *(biopsy proven)*; or any stage with para-aortic metastases.
- *Toxicities resulting from chemoradiation must resolve to ≤Grade 1 prior to randomization.*

Objectives

Primary objective:

- To prolong Progression-Free Survival (PFS).

Secondary objective:

- To prolong median PFS
- To prolong PFS in sub-population
- To register overall survival (OS).
- To register Patient Reported Outcomes (PROs)
- To register safety and tolerability

Study Statistics

- The study is designed to detect a difference in **PFS at 24 months** corresponding to a hazard ratio of 0.66 (PFS at 24 months to be increased from 46% to 60%) with a power of 80%; one-sided alpha of 15%;
- **The randomization is 2:1 (2 rucaparib; 1 placebo).**
- The number of needed events is 83 corresponding to 144 patients.
- With an expected dropout rate of 10%, and matching the randomization ratio, we shall recruit **a total of 162 patients** (108 patients in the rucaparib arm, and 54 patients in the placebo arm) within 18 months.
- PFS data should be mature after a minimum follow-up of 24 months.