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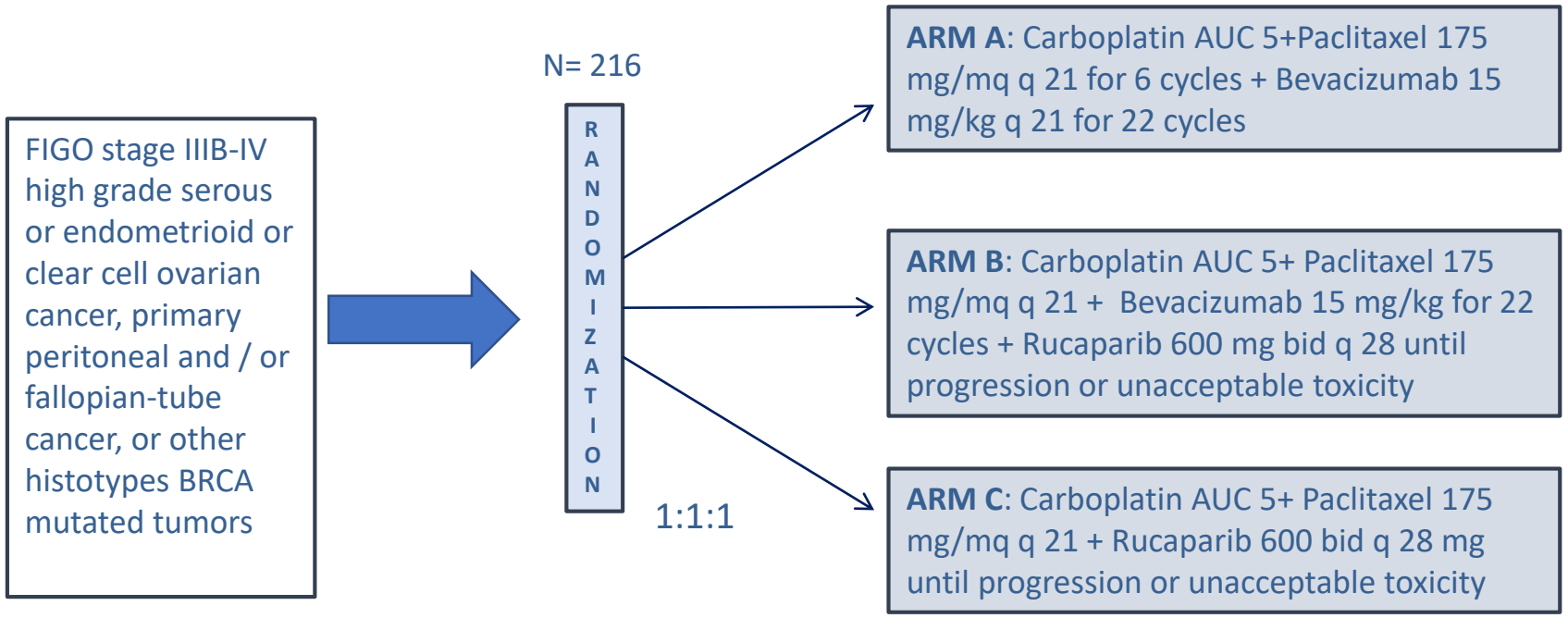
A randomized phase II trial of Carboplatin-Paclitaxel-Bevacizumab vs Carboplatin-Paclitaxel-Bevacizumab-Rucaparib vs Carboplatin-Paclitaxel-Rucaparib in patients with advanced (stage III B-IV) ovarian, primary peritoneal and Fallopian tube cancer preceded by a phase I dose escalation study on Rucaparib-Bevacizumab combination

Phase II - Study design



Stratification Factor:

- Residual tumor at primary surgery;
- Stage of disease;
- HRD status (BRCA mutated vs HRD positive)

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Phase I - Study design

(Only INT-Milan)

A single arm phase 1 study which will be conducted only in the coordinator center, aiming at evaluating the MTD of the combination Rucaparib-Bevacizumab. Once the MTD has been reached the randomized study will start.

Approximately 15-18 patients will be enrolled in the phase 1 part

PATIENT POPULATION:
FIGO stage IIIB-IV high grade serous or endometrioid or clear cell ovarian cancer, primary peritoneal or fallopian-tube cancer, or other histotypes BRCA mutated tumors

SINGLE ARM

Carboplatin AUC 5+ Paclitaxel 175 mg/m2 q 21+ Bevacizumab 15 mg/kg q 21 for 6 cycles followed by Bevacizumab 15 mg/kg q 21 for 22 cycles+ Rucaparib at escalating dosages **(200-400-600)** bid q 28 for 24 cycles as maintenance, until progression or unacceptable toxicity

Phase II - Objectives

Primary:

Progression free survival (PFS)

The trial will test the hypothesis that Carboplatin-Paclitaxel-Bevacizumab-Rucaparib and the Carboplatin-Paclitaxel–Rucaparib arms will improve the progression-free survival in comparison to standard Carboplatin-Paclitaxel-Bevacizumab arm.

Phase II - Objectives

Secondary:

•Overall survival (**OS**) defined as the time from the date of randomization to the date of death;
•Progression-free survival 2 (**PFS2**) defined as time from randomisation to second objective disease progression or death;
•To compare the time from randomisation to first subsequent therapy or death (**TFST**) of patients receiving Carboplatin-Paclitaxel-Bevacizumab vs Carboplatin-Paclitaxel-Bevacizumab-Rucaparib or Carboplatin-Paclitaxel-Rucaparib;
•Time to second subsequent therapy (**TSST**) defined as time from randomisation to the initiation of second subsequent therapy or death.
•Best target lesion **response**, defined as best change in sum of the target lesions from baseline to disease progression or by the modifications of CA 125 according to GCIG criteria;
•**Safety and tolerability;**
•Patient-reported outcome (**PRO**) of disease-related symptoms utilizing the disease-related symptoms – physical (DRS–P) subscale of the National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy (NCCN-FACT) FACT-Ovarian Symptom Index 18 (FOSI-18)Changes and using Euro-Quality of Life 5D (EQ-5D) tool.

Phase I/II - Inclusion Criteria

•Female aged ≥ 18 years at the time of study inclusion;
•Patients with newly diagnosed, histologically confirmed, FIGO stage IIIB-IV high grade (based on local histopathological findings) serous or endometrioid or clear cell ovarian cancer, primary peritoneal and / or fallopian-tube cancer; BRCA mutated other histotypes. Patients with mixed histology are eligible providing that high grade tumor represent more than 70% of the total histology.
•Stage III patients should have had one attempt at optimal debulking surgery (upfront or interval debulking). Stage IV patients must have had either a biopsy and/or upfront or interval debulking surgery;
•Archivial tumor tissue available. At progression fresh biopsy is optional for patients willing/able to submit;
•ECOG Performance Status of 0–1;
•Measurable and not measurable disease;
•Adequate renal and hepatic function;
•Adequate bone marrow function, defined as:
•Able to understand and give written informed consent;
•Females of childbearing potential must have a negative serum pregnancy test within 7 days prior to study enrollment.

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Phase II - Rationale for Number of Patients

The study is dimensioned considering two parallel comparisons (Arm B vs Arm A and Arm C vs Arm A). For each comparison, considering a prolongation in term of PFS of 6 months expected with the experimental Arm (from 15 months to 21 months) corresponding to an HR of 0.71, 96 events are needed to perform the final analysis with an 80% power and a one-tailed alpha of 0.2. Supposing a recruitment period of ~30 months and a follow-up of ~30 months, the sample size of the study amounts to 195 patients (65 in each group). Assuming a 10% drop out, a total of 216 patients (72 in each group) will be randomized in a 1: 1 : 1 ratio to ensure a evaluable 195 patients.

Administrative Information

- Academic trial
- NCI of Milan sponsor
- Data center: NCI of Milan (MITO center)
- Planned study start: January 2018
- HRD EVALUATION CENTRALIZED BY Clovis (~ 14 days)
- Assurance and Rucaparib provided
- Centralized revision of imaging for primary end point PFS (INT Milan-piattaforma immagini MITO)
- Phase I: INT-Milan
- Phase II: 24 Italian sites

To information please contact:

domenica.lorusso@istitutotumori.mi.it

Iolanda.pulice@istitutotumori.mi.it

Phase II – Italian Sites (24 centres)

Principal Invastigator	Site
Domenica Lorusso (Phase I - single site)	***Fondazione IRCCS Istituto Nazionale dei Tumori (Milano)***
Sandro Pignata	Istituto Tumori Pascale-IRCCS (Napoli)
Anna Maria Mosconi	Ospedale Santa Maria della Misericordia (Perugia)
Antonella Savarese	Istituto Nazionale dei Tumori Regina Elena (Roma)
Giovanni Scambia	Fondazione Policlinico Agostino Gemelli (Roma)
Roberto Sorio	Centro di Riferimento Oncologico IRCCS (Aviano)
Oscar Alabiso	AOU Maggiore della Carità SC Oncologia (Novara)
Saverio Cinieri	P.O. "A.Perrino"-ASL Brindisi (Brindisi)
Antonio Nuzzo	Ospedale Renzetti (Lanciano)
Patrizia Vici	Istituto Nazionale Regina Elena-IRE (Roma)
Ugo De Giorgi	IRCCS IRST (Meldola)
Roberto Angioli	Università Campo Biomedico (Roma)
Laura Zavallone	Ospedale degli Infermi (Ponderano-Biella)
Sabino de Placido	AOU Federico II UOC di Oncologia Medica (Napoli)
Giorgio Valabrega	IRCCS Candiolo (Candiolo-Torino)
Claudio Graiff	Azienda Sanitaria dell'Alto Adige Comprensorio Sanitario di Bolzano- Oncologia Medica (Bolzano)
Gennaro Cormio	UO Ginecologia e Ostetricia Policlinico di Bari (Bari)
Filippo Greco	Ospedale Mater Salutis (Legnago)
Claudia Andreetta	Azienda Ospedaliero-Universitaria di Udine (Udine)
Elena Zafarana	UO Oncologia Nuovo Ospedale di Prato (Prato)
Stefano Tamberi	Presidio Ospedaliero di Lugo (Lugo)
Stefano Tamberi	UO Complessa-Presidio Ospedaliero di Ravenna (Ravenna)
Stefano Tamberi	UO Complessa di Oncologia Ospedale Civile degli Infermi (Faenza)
Michele Orditura	Oncologia Medica Seconda Università degli Studi di Napoli (Napoli)