NEWTON study
(**NEW** dosing maint**T**enance therapy **O**varian ca**N**cer)

A multicenter, open-label phase II trial of a new customized dosing (Rational Adjustment of Dose to reduce Adverse Reactions "RADAR" dosing) of Niraparib as maintenance therapy in platinum sensitive ovarian, fallopian tube or primary peritoneal recurrent cancer patients

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Study Rationale

The NEW ENGLAND JOURNAL of MEDICINE

Table 2. Adverse Events.*

Event	Niraparib (N = 367)		Placebo (N = 179)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Nausea	270 (73.6)	11 (3.0)	63 (35.2)	2 (1.1)
Thrombocytopenia†	225 (61.3)	124 (33.8)	10 (5.6)	1 (0.6)
Fatigue‡	218 (59.4)	30 (8.2)	74 (41.3)	1 (0.6)
Anemia§	184 (50.1)	93 (25.3)	12 (6.7)	0
Constipation	146 (39.8)	2 (0.5)	36 (20.1)	1 (0.6)
Vomiting	126 (34.3)	7 (1.9)	29 (16.2)	1 (0.6)
Neutropenia¶	111 (30.2)	72 (19.6)	11 (6.1)	3 (1.7)

- Most of the hematologic adverse events occurred within the first three 28-day cycles
- After dose adjustment the incidence of grade 3 and 4 adverse events was low and remained unrelated to cumulative dose

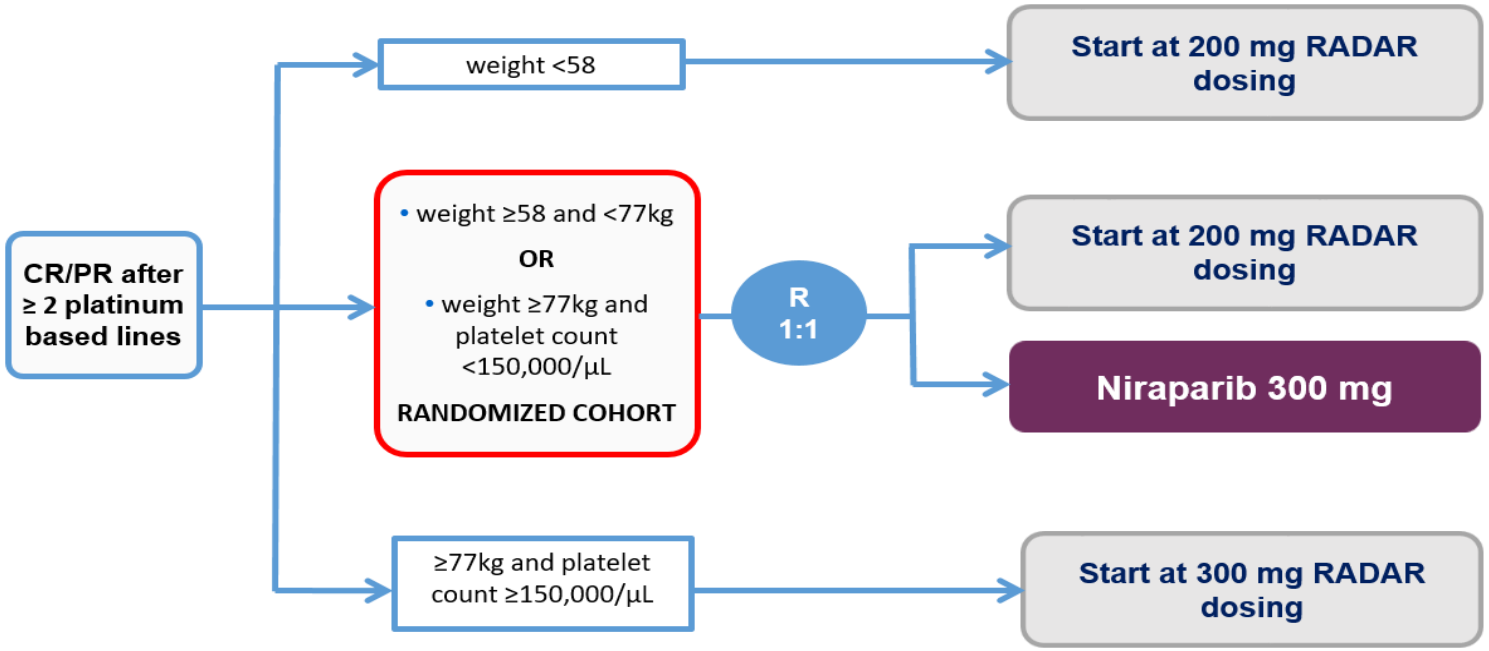
RADAR DOSING

- Patients who either weigh less < 77 Kg **OR** have a baseline platelet count < 150,000/µL
  Initial dose of 200 mg for the first three 28 days cycles therapy.

  N.B: dose can be escalated to 300 mg daily **ONLY** if no hematological toxicities (defined as adverse event of any grade for platelets, or of grade ≥ 3 for neuthrophils and hemoglobin) during the first three cycles occur.

- Patients who weigh less ≥ 77 Kg **AND** a baseline platelet count ≥ 150,000/µL
  Initial dose of 300 mg

Study design



Planned No. of patients: 105

Accrual: 18 months

Follow-up: 24 months

Two primary objectives:

1) **comparison of RADAR vs 300 mg in the randomized cohort** in terms of **safety** (in terms of occurrence of grade ≥ 3 thrombocytopenia in the first three 28-days cycles of therapy)

2) evaluation of RADAR safety in the **entire RADAR cohort** (in terms of occurrence of grade ≥ 3 thrombocytopenia in the first three 28 days cycles of therapy)

Endpoints & Sample size

Primary endpoint: rate of patients experiencing a G3-G4 thrombocytopenia during the first 3 cycle

Secondary endpoints: rate of patients experiencing a G3-G4 thrombocytopenia during the first 6 cycles; PFS; Niraparib pharmacokinetic; compliance, OS

Comparison of RADAR vs 300 mg in the randomized cohort:

- Assuming 15% vs 35% G3-G4 thrombocytopenia (3 cycles)
- Alpha 0.14 (1-sided); power 0.8

Evaluation of RADAR safety in the entire RADAR cohort:

- 34% or more (p0): the new RADAR dosing is not sufficiently safer than the dosing used in NOVA trial;
- 15% or less (p1): the new RADAR dosing is considered interesting for its safety profile.
- Alpha 0.01 (1-sided); power 0.89

Considering 5% drop out rate, we need to enroll in total 105 patients:

- 70 patients in RADAR (half of them randomized to RADAR arm and the other half directly assigned to RADAR from the “weight <58 OR ≥77kg and platelet count ≥150,000/µL” population)
- 35 patients randomized to 300 mg arm

NEWTON sites

Italy

Nr.	Centre	City	Principal Investigator
1	Istituto Europeo di Oncologia (IEO) - Centro coordinatore dello studio	Milano	Nicoletta Colombo - PI dello studio
2	ASST degli Spedali Civili di Brescia	Brescia	Germana Tognon
3	ASST di Lecco	Lecco	Antonio Ardizzoia
4	Ospedale San Gerardo	Monza	Andrea Alberto Lissoni
5	Istituto Oncologico Veneto (IOV)	Padova	Ornella Nicoletto
6	AOU Pisana	Pisa	Angiolo Gadducci
7	AO Arcispedale Santa Maria Nuova	Reggio Emilia	Alessandra Bologna
8	Policlinico Umberto I, Università di Roma "La Sapienza"	Roma	Pierluigi Benedetti Panici
9	AOU Città della Salute e della Scienza di Torino - Ospedale Sant'Anna	Torino	Dionyssios Katsaros
10	AO Ordine Mauriziano	Torino	Annamaria Ferrero

Germany

Nr.	Centre	City	Principal Investigator
1	University Hospital Dresden	University Hospital Dresden	Pauline Wimberger
2	Kliniken Essen Mitte	Essen	Florian Heitz
3	Charité - Universitätsmedizin Berlin	Berlin	Elena Ioana Braicu

Study details and timelines

- Study was submitted on March 28 2019 to AIFA and Italian ECs
- Study approved by CEC (IEO, Milan)
- Final approval from AIFA expected within the first week of July
- First site open: July-September 2019
- First patient in planned for September 2019
- Submission in Germany on-hold due to Brexit