NEWTON study: ***Update***

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NEWTON study

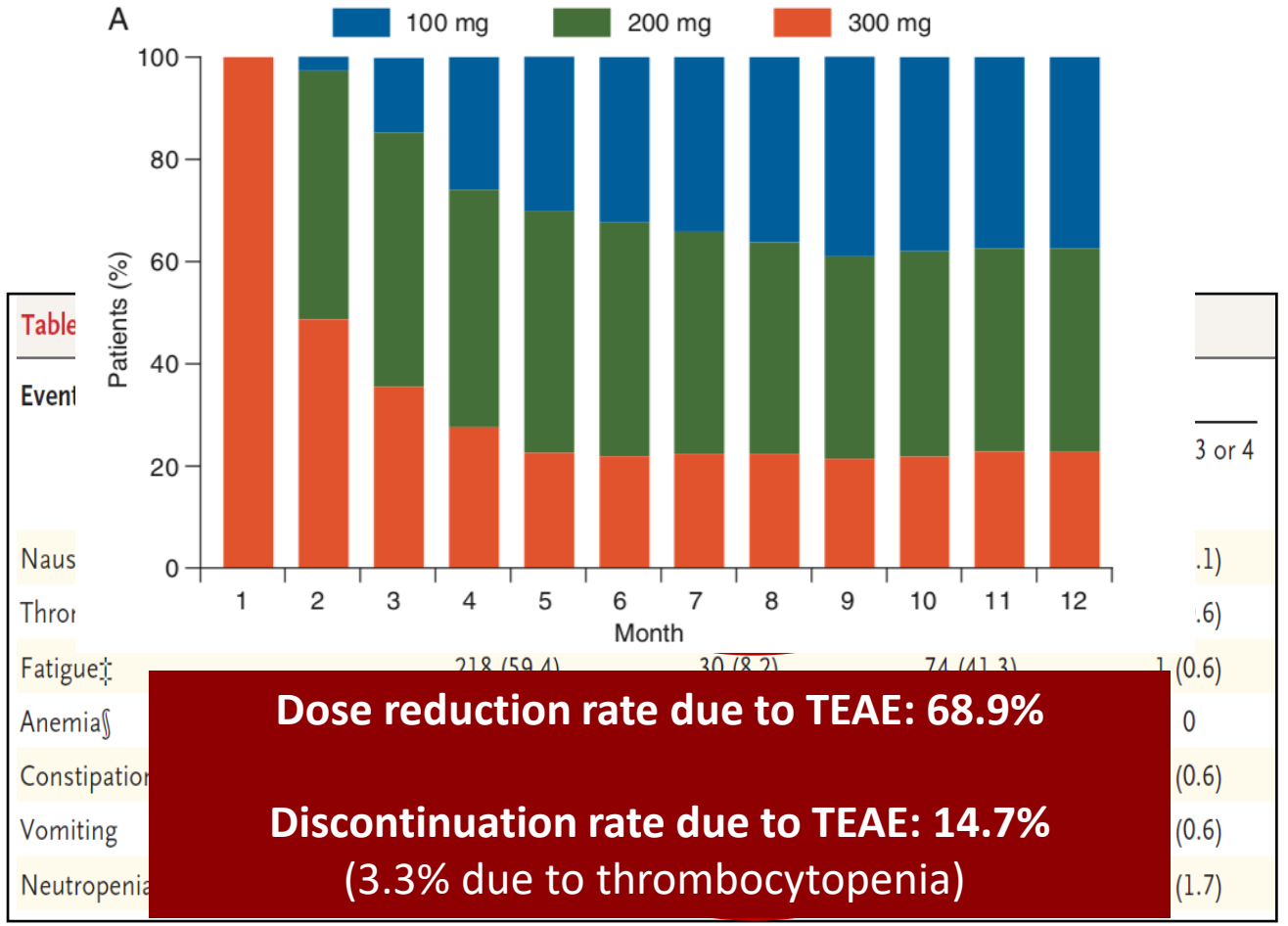
(**NEW** dosing maint**T**enance therapy **O**varian ca**N**cer)

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

Background and rationale

- **Most of the hematologic adverse events occurred within the first three 28-day cycles** (G3-4 thrombocytopenia mostly within the first **two** cycles)

- **Toxicities were manageable with drug suspension and dose reductions:** after dose adjustment the incidence of G3-4 AEs was low and remained unrelated to cumulative dose



Treatment schedule optimization for safety profile improvement:
What we do already know?

Safety and dose modification for patients receiving niraparib

Berek et al. Ann. Onc. 2018

Retrospective analysis on **ENGOT-OV16/NOVA** trial safety population

Body weight and **platelet count** at baseline: risk factors for increased incidence of grade 3-4 thrombocytopenia.

PFS in patients who were dose-reduced was consistent with that of patients who remained at the 300 mg starting dose

Conclusions**: patients with baseline body weight of<77kg or baseline platelets of <150 000/µl may benefit from a starting dose of 200 mg/day.**

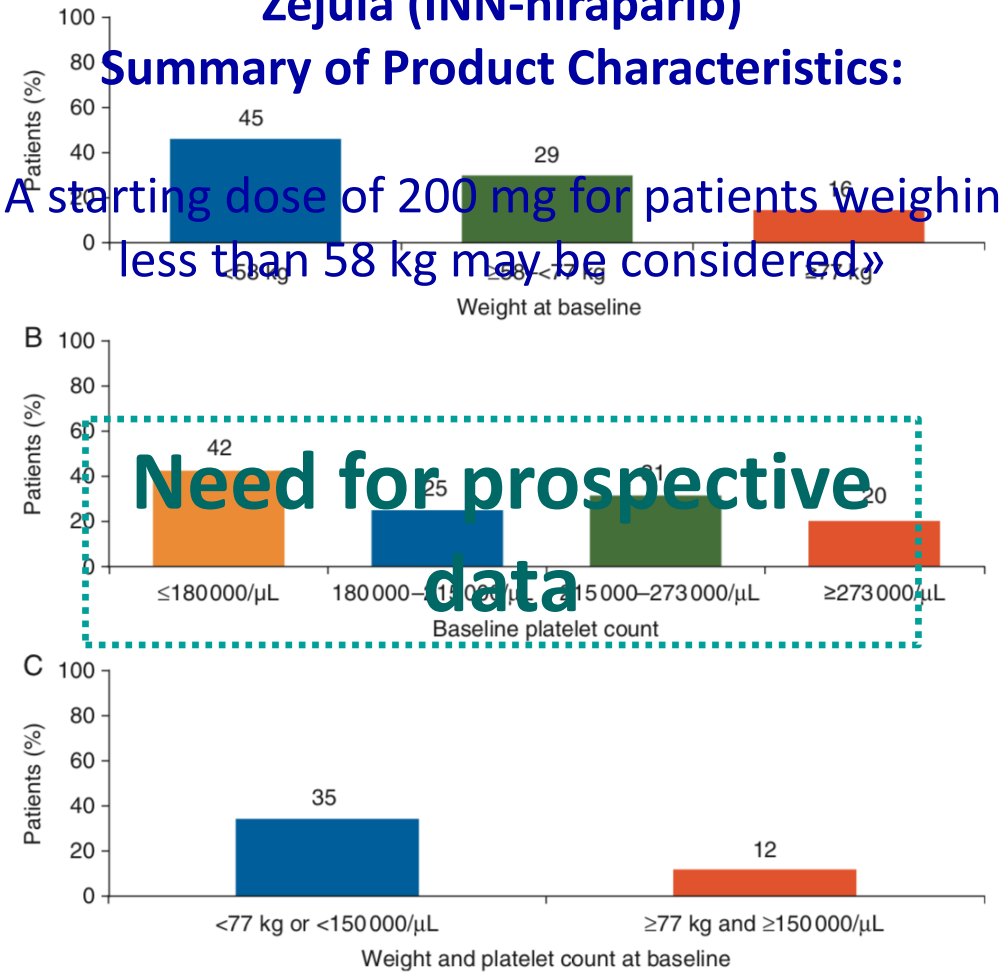
EUROPEAN MEDICINES AGENCY
SCIENCE, MEDICINES, HEALTH

Grade 3/4 thrombocytopenia within 30 days of first dose

Zejula (INN-niraparib)

Summary of Product Characteristics:

«A starting dose of 200 mg for patients weighing less than 58 kg may be considered»



Need for prospective data

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Individualized Starting Dose of Niraparib in Patients with Platinum-Sensitive Recurrent Ovarian Cancer (NORA) : A Randomized, Double-Blind, Placebo-Controlled, Phase III Trial

Late breaking abstract 29
Xiaohua Wu et al.

Main Inclusion Criteria

- Platinum-sensitive, recurrent ovarian cancer;
- High grade serous or high grade predominantly serous histology or known to have g*BRCA*mut;
- Completed at least 2 previous lines of platinum-containing therapy;
- Partial or complete re to the last platinum-ba chemotherapy.

#After initial fixed dose of 300mg (n=16), adopted ISD in protocol amendment:

- **200 mg QD** for Patients with baseline body weight <77 kg or platelets count <150,000/μL;
- **300 mg QD** for Patients with baseline body weight ≥77 kg and platelets count ≥150,000/μL.

Ra → Niraparib#

265 randomized

177 received niraparib

88 received placebo

Starting Dose:
Before protocol amendment:
- 11 patients at 300mg

After protocol amendment:
- 155 patients at 200mg
- 11 patients at 300mg

Starting Dose
Before protocol amendment:
- 5 patients at 300mg

After protocol amendment:
- 80 patients at 200mg
- 3 patients at 300mg

Primary Endpoint

- Progression-free survival (PFS) determined by BICR

Secondary Endpoints

- Safety
- Chemotherapy-free interval (CFI)
  ime to first
  ubsequent therapy
  FST)
  verall survival (OS)

Designed t patients

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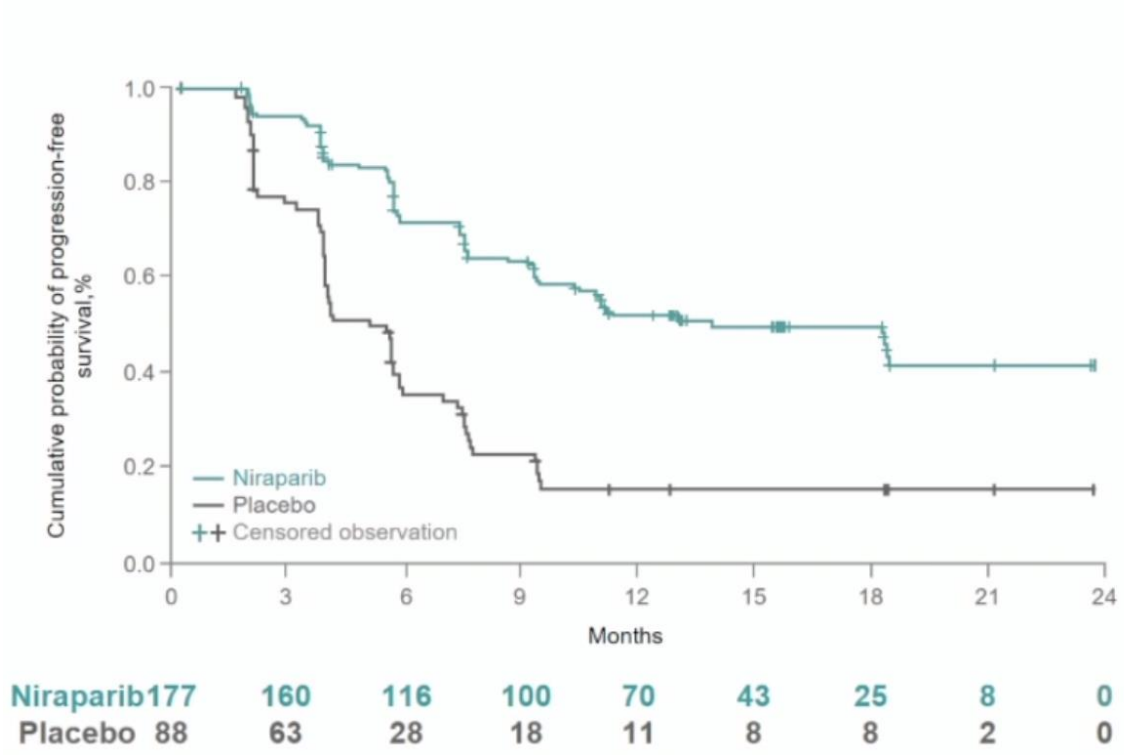
PFS in ITT population



68% reduction of hazard for relapse or death with niraparib

	Niraparib (n=177)	Placebo (n=88)
Median PFS		
Months (95% CI)	18.3 (10.9–NE)	5.4 (3.7–5.7)
Hazard ratio (95% CI)	0.32 (0.23-0.45)	
p-value[1]	<0.0001	

Efficacy

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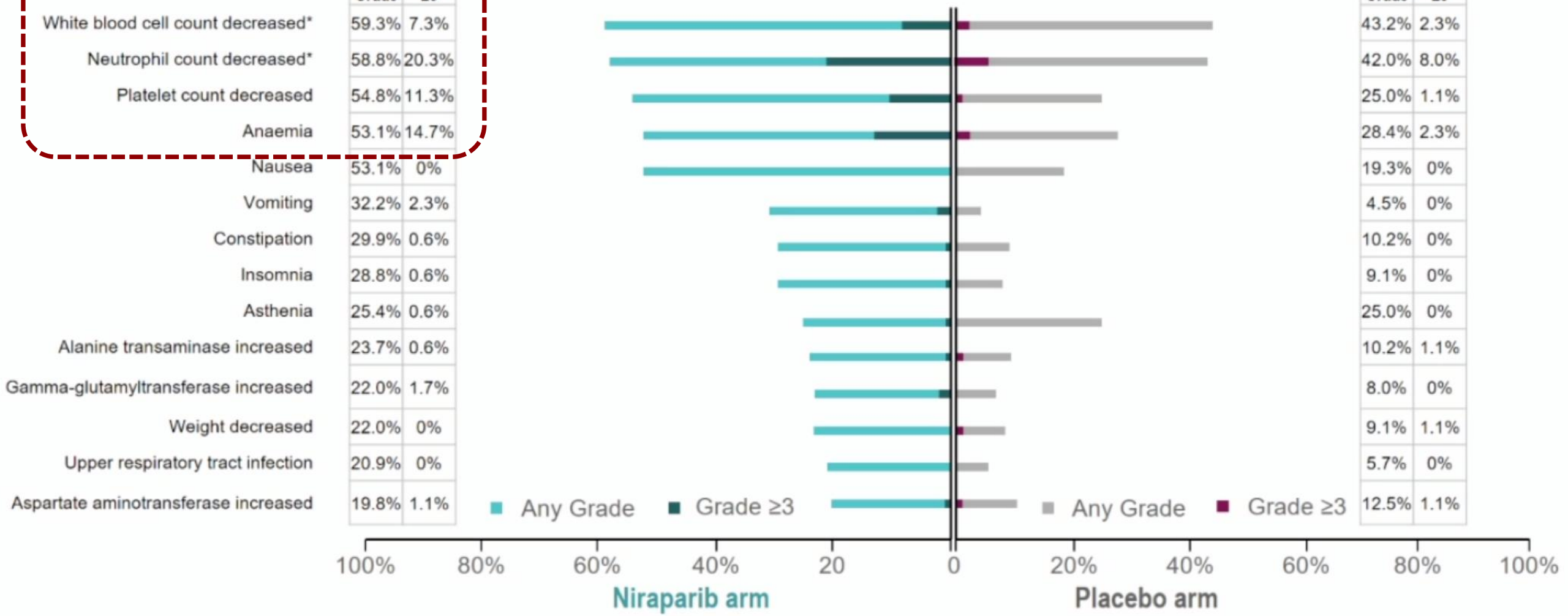
Summary of Adverse Events

Any grade in >10% of patients in either arm and/or grade ≥3 in patients overall

	Niraparib arm		Placebo arm	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
White blood cell count decreased*	59.3%	7.3%	43.2%	2.3%
Neutrophil count decreased*	58.8%	20.3%	42.0%	8.0%
Platelet count decreased	54.8%	11.3%	25.0%	1.1%
Anaemia	53.1%	14.7%	28.4%	2.3%
Nausea	53.1%	0%	19.3%	0%
Vomiting	32.2%	2.3%	4.5%	0%
Constipation	29.9%	0.6%	10.2%	0%
Insomnia	28.8%	0.6%	9.1%	0%
Asthenia	25.4%	0.6%	25.0%	0%
Alanine transaminase increased	23.7%	0.6%	10.2%	1.1%
Gamma-glutamyltransferase increased	22.0%	1.7%	8.0%	0%
Weight decreased	22.0%	0%	9.1%	1.1%
Upper respiratory tract infection	20.9%	0%	5.7%	0%
Aspartate aminotransferase increased	19.8%	1.1%	12.5%	1.1%



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Selective Grade 3/4 TEAEs by PT in NORA and NOVA

NORA

	Niraparib (N=177) n (%)	Placebo (N=88) n (%)
Neutrophil count decreased[a]	36 (20.3)	7 (8.0)
Anaemia[b]	26 (14.7)	2 (2.3)
Platelet count decreased[c]	20 (11.3)	1 (1.1)
Hypertension	2 (1.1)	0

NOVA

	Niraparib (N=367) n (%)	Placebo (N=179) n (%)
Thrombocytopenia[d]	124 (33.8)	1 (0.6)
Anaemia[b]	93 (25.3)	0
Neutropenia[e]	72 (19.6)	3 (1.7)
Hypertension	30 (8.2)	4 (2.2)

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Summary of Adverse Events in NORA

	Niraparib (n=177) n (%)	Placebo (n=88) n (%)
Any TEAE	177 (100.0)	84 (95.5)
≥Grade 3	90 (50.8)	17 (19.3)
Any treatment-related TEAE	176 (99.4)	77 (87.5)
≥Grade 3	79 (44.6)	10 (11.4)
Any serious TEAE	31 (17.5)	10 (11.4)
Any related Serious TEAEs	23 (13.0)	4 (4.5)
Any TEAEs leading to dose reduction	106 (59.9)	12 (13.6)
Any TEAEs leading to treatment discontinuation	7 (4.0)	5 (5.7)
Any TEAE leading to death*	0	1 (1.1)

ISD (Individualised Starting Dose) of niraparib is effective and safe and should be considered a **standard clinical practice** in this patient population.

NOVA

Dose reduction rate due to TEAE: **68.9%**

Discontinuation rate due to TEAE: **14.7%** (3.3% due to thrombocytopenia)

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NORA Baseline Demographic and Disease Characteristics

Characteristic	Niraparib (N=177)	Placebo (N=88)	Total (N=265)
Median age, years (range)	53.0 (35.0, 78.0)	55.0 (38.0,72.0)	54.0 (35.0,78.0)

NOVA

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Germline *BRCA* Mutation		No Germline *BRCA* Mutation	
	Niraparib (N=138)	Placebo (N=65)	Niraparib (N=234)	Placebo (N=116)
Median age (range) — yr	57 (36–83)	58 (38–73)	63 (33–84)	61 (34–82)

Other	2 (1.1)	2 (2.3)	4 (1.5)
Secondary cytoreduction surgery received, n (%)	48 (27.1)	21 (23.9)	69 (26.0%)
Previous bevacizumab use, n (%)	11 (6.2)	7 (8.0)	18 (6.8%)
Number of lines of prior chemotherapy, n (%)			
2	177 (100.0)	88 (100.0)	265 (100.0)

NOVA

Previous lines of chemotherapy — no. (%)‡				
1	1 (0.7)	0	0	0
2	70 (50.7)	30 (46.2)	155 (66.2)	77 (66.4)
≥3	67 (48.6)	35 (53.8)	79 (33.8)	38 (32.8)

gBRCAmut	65 (36.7)	35 (39.8)	100 (37.7)

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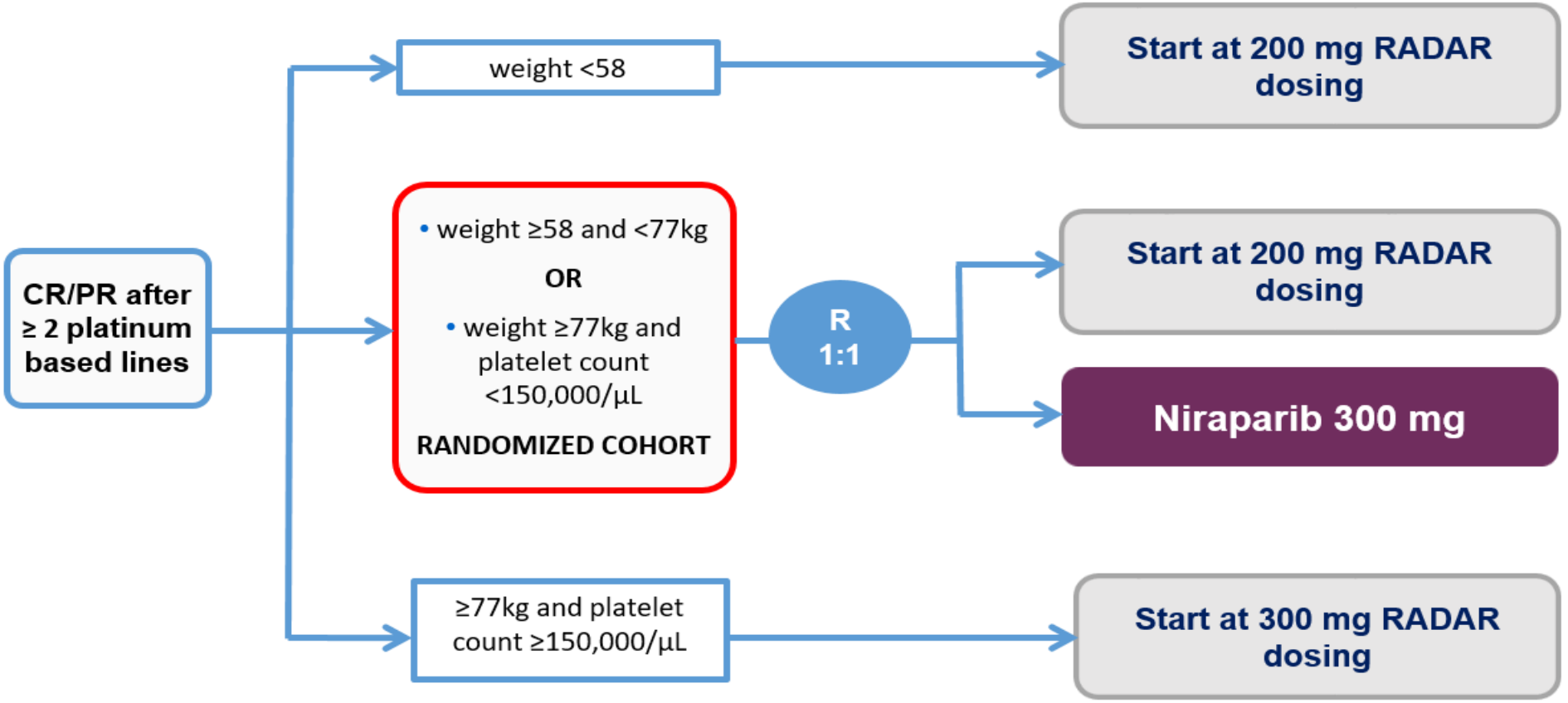

Aim: to evaluate whether the adoption of the **RADAR dosing strategy** could further **improve the safety profile of niraparib, while preserving efficacy.**

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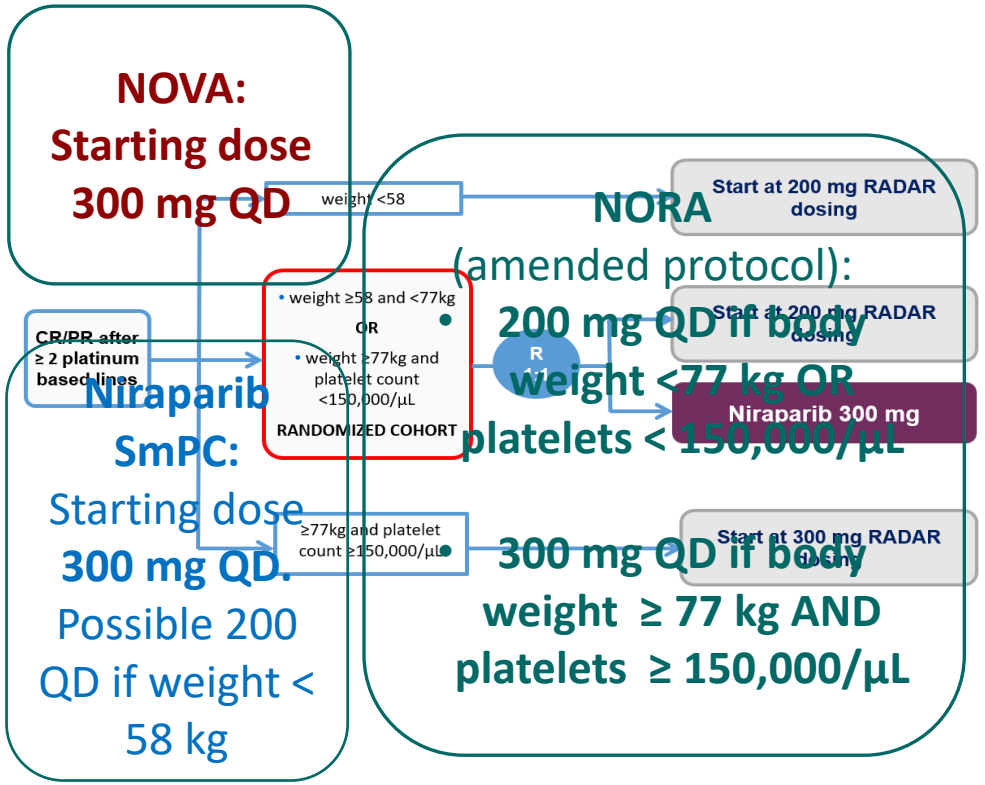


Same dosing, BUT NO dose escalation

RADAR DOSING:

- Patients who either weigh **< 77 Kg OR** have a baseline platelet count **< 150,000/µL**:

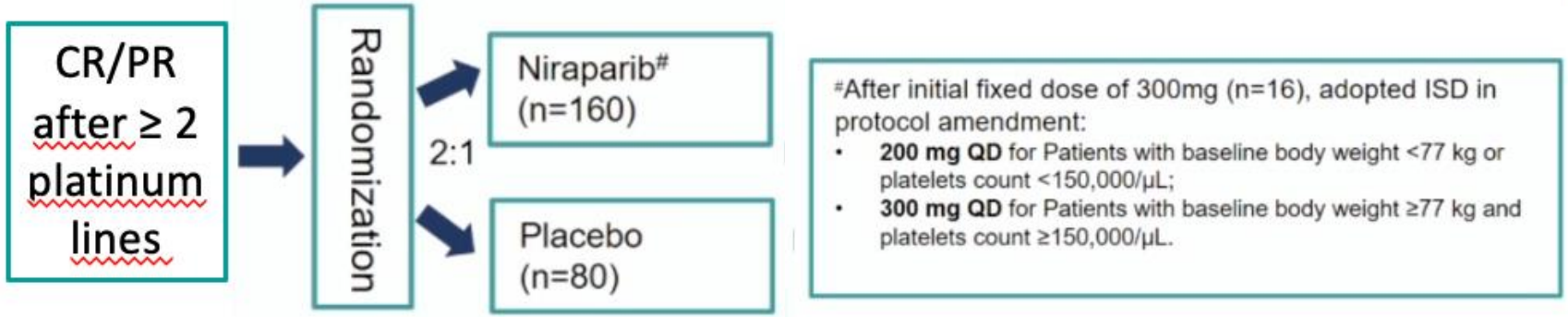
Initial dose of **200 mg** for the first three 28 days cycles therapy.

Dose can be escalated to 300 mg daily ONLY if no hematological toxicities (AE of any grade for platelets, or of grade ≥ 3 for neuthrophils and hemoglobin) during the first three cycles occur.

- Patients who weigh **≥ 77 Kg AND** have a baseline platelet count **≥ 150,000/µL**:

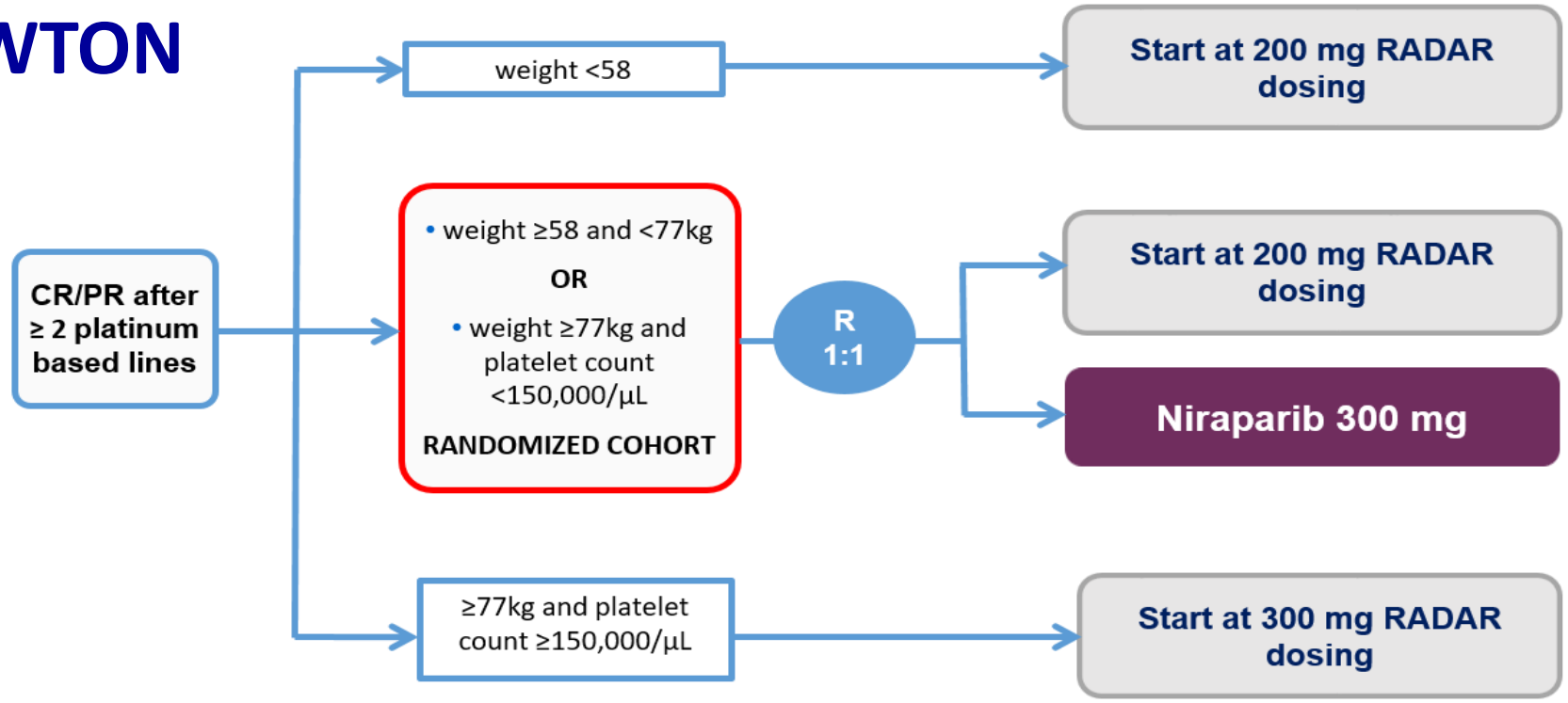
Initial dose of **300 mg**

NORA



Primary endpoint: PFS

NEWTON



Primary endpoint= Safety
(rate of patients experiencing a G ≥3 thrombocytopenia during the first 3 cycles.)

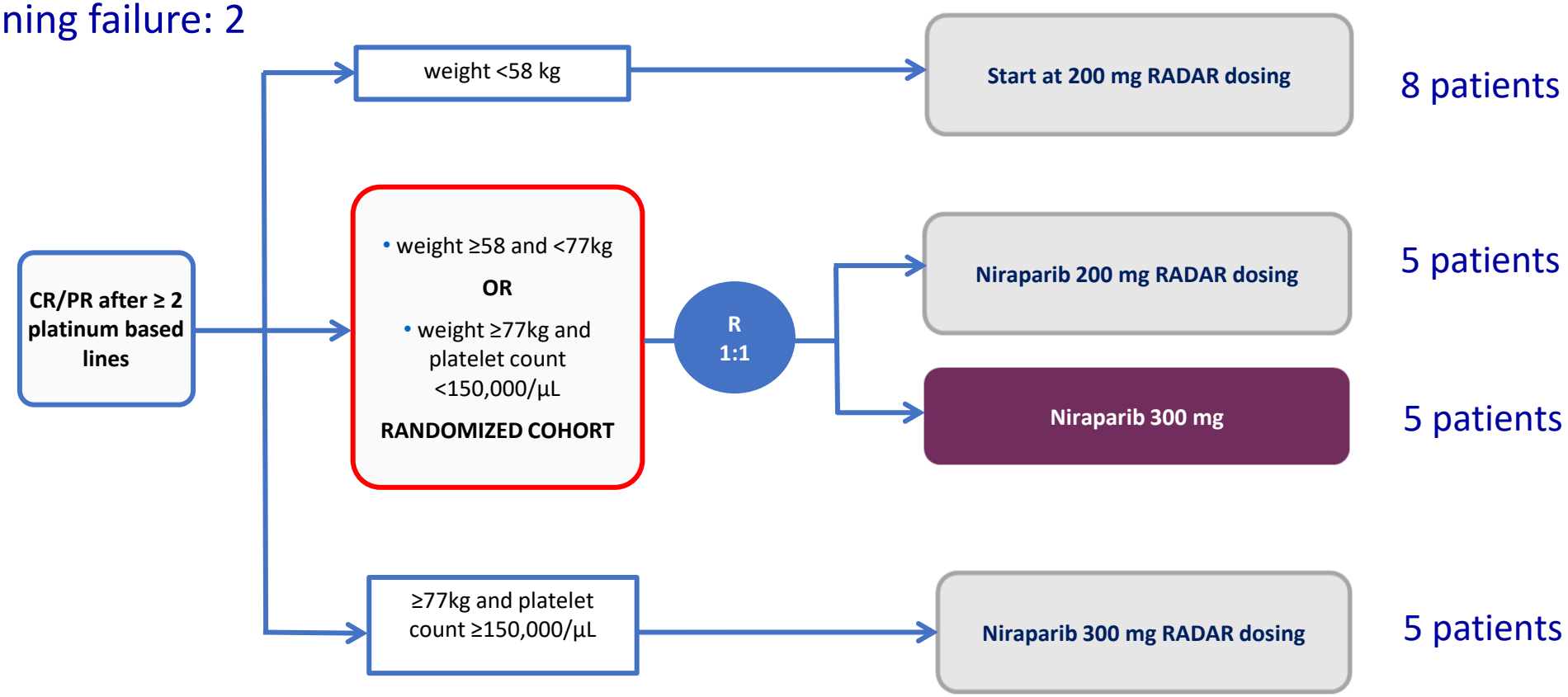
RADAR cohort matching the weight distribution of the NOVA population → correct indirect comparison

NEWTON study: update on accrual

- Patients to be enrolled: 105

- Patients enrolled: 25

- Screning failure: 2



NEWTON study update - Italian sites

- study approval: July 15 2019
- FPI: November 15 2019

Nr.	Centre	City	Principal Investigator	Status	Date of site activation	Enrolment
1	Istituto Europeo di Oncologia (IEO) - Centro coordinatore dello studio	Milano	Nicoletta Colombo - PI dello studio	Active site	October 30 2019	19
2	AO Arcispedale Santa Maria Nuova	Reggio Emilia	Alessandra Bologna	Active site	January 27 2020	Not yet recruiting
3	ASST degli Spedali Civili di Brescia	Brescia	Germana Tognon	Active site	February 28 2020	4
4	Istituto Oncologico Veneto (IOV)	Padova	Giulia Tasca	Active site	September 10 2020	1
5	AO Ordine Mauriziano	Torino	Annamaria Ferrero	Active site	September 15 and 18 2020	1
6	Ospedale San Gerardo	Monza	Andrea Alberto Lissoni	Active site	September 30 2020	Not yet recruiting
7	AOU Città della Salute e della Scienza di Torino - Ospedale Sant'Anna	Torino	Dionyssios Katsaros	Contract under signature (SIV to be planned)		
8	Policlinico Umberto I, Università di Roma "La Sapienza"	Roma	Pierluigi Benedetti Panici	Contract under finalization		
9	AOU Pisana	Pisa	Angiolo Gadducci	Study not submitted to EC		
~~10~~	~~ASST di Lecco~~	Lecco	Antonio Ardizzoia	Study contract not approved		

NEWTON study update - German sites

- Study approval: June 10 2020

- Patients planned to enrol: 30

Nr.	Centre	City	Principal Investigator	Status
1	University Hospital Dresden	University Hospital Dresden	Pauline Wimberger	Contract signed, SIV planned in November 2020
2	Kliniken Essen Mitte	Essen	Florian Heitz	Contract under signature
3	Charité - Universitätsmedizin Berlin	Berlin	Elena Ioana Braicu	Contract under revision

NEWTON study: management during COVID -19 emergency

- Patients received drug at home to guarantee therapy continuation
- Laboratory examinations performed in centres different from those involved in the study

Main issues during COVID-19 emergency

- Site activation on hold
- Slowdown in the administrative process for the sites agreements

Next steps

- Activation of all sites involved in the NEWTON study (by Genuary 2021)

- Protocol and CI amendment (IB v.11 released)
  - Thromboembolic events no longer considered AESI
  - Hypertension
  - Posterior Reversible Encephalopathy Syndrome (PRES)

- Data entry requests

- Pharmacokinetics analyses

Pharmacokinetics analyses

to investigate the relation between PK variables (the trough level and the peak level of niraparib) during different cycles and patients' clinical characteristics, dose administered and toxicities

Cycle	Day	Before taking niraparib *	After taking niraparib (2 hours after)
1	1	X	X
	15	X	
2	1	X	X
3	1	X	X
4 only if dose is escalated (from 200 to 300)	1	X	X
	15	X	
At any cycle at which the dose is reduced	First day of reduction	X	
At the first cycle after dose reduction	1	X	

Goals

- Supporting the sites to insert PK data on time
- Monitoring the right PK collection through the data reported into database
- Requiring sample collections for the analyses

Thanks for your attention !