HIGHLIGHTS IN GYNECOLOGICAL CANCERS

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Disclosure slide

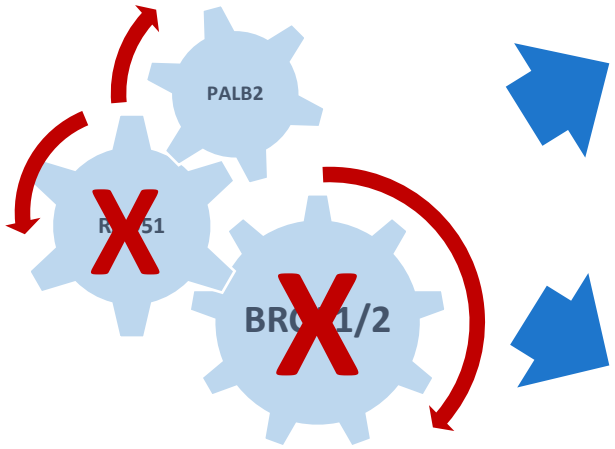
- Research grants from Roche, Genentech, Merck Serono, MSD, Bayer, Amgem, Takeda and Merrimack
- Advisor role in Roche, Lilly and Merck Serono.
- Speaker for Roche, Lilly, Merck Serono, Amgem and Bayer

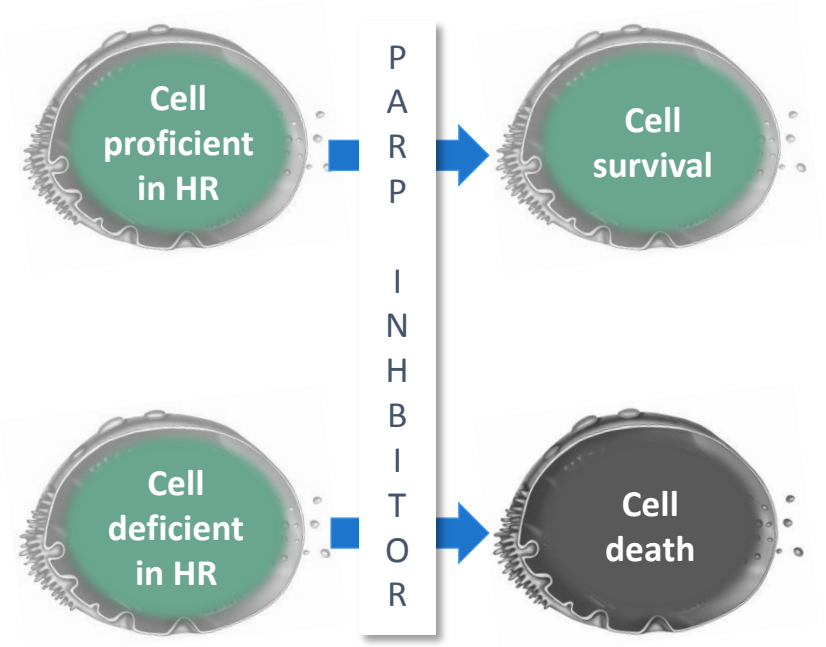
Outline

- **ARIEL 2 TRIAL ON RUCAPARIB AND BRCA MOLECULAR ALTERATIONS**
- **ROSSIA TRIAL: EXTENDED "REAL LIFE" COHORT ON THE PROLONGED USE OF BEVACIZUMAB IN FIRST LINE OVARIAN CANCER TREATMENT**
- **COMPUTED TOMOGRAPHY IS MORE SENSITIVE THAN CA-125 IN DETECTING DISEASE PROGRESSION IN PATIENTS WITH PLATINUM-RESISTANT OVARIAN CANCER: ANALYSIS OF THE AURELIA TRIAL**
- **RELAPSES AFTER FERTILITY SPARING SURGERY IN OVARIAN CANCER**

PARP inhibitors (PARPi) are synthetically lethal to tBRCA^{mut} and tBRCA-like tumor cells with homologous recombination deficiency (HRD)

HR is a complex process requiring coordinated function of many gene products.





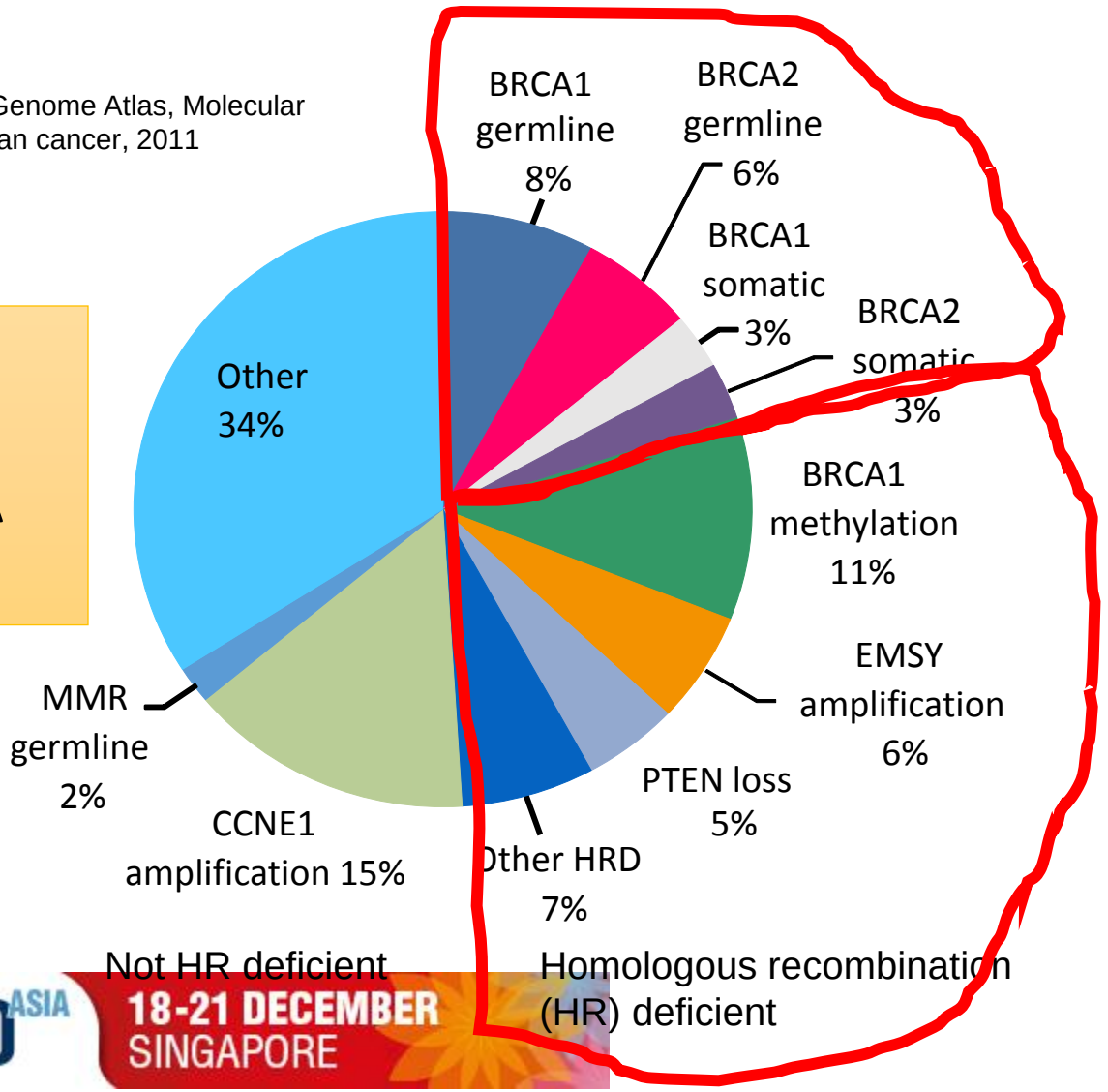
Genetic and epigenetic dysregulation cause HRD, resulting in tBRCA^{mut} and tBRCA-like tumors that are sensitive to PARPi therapy

HR=homologous recombination.

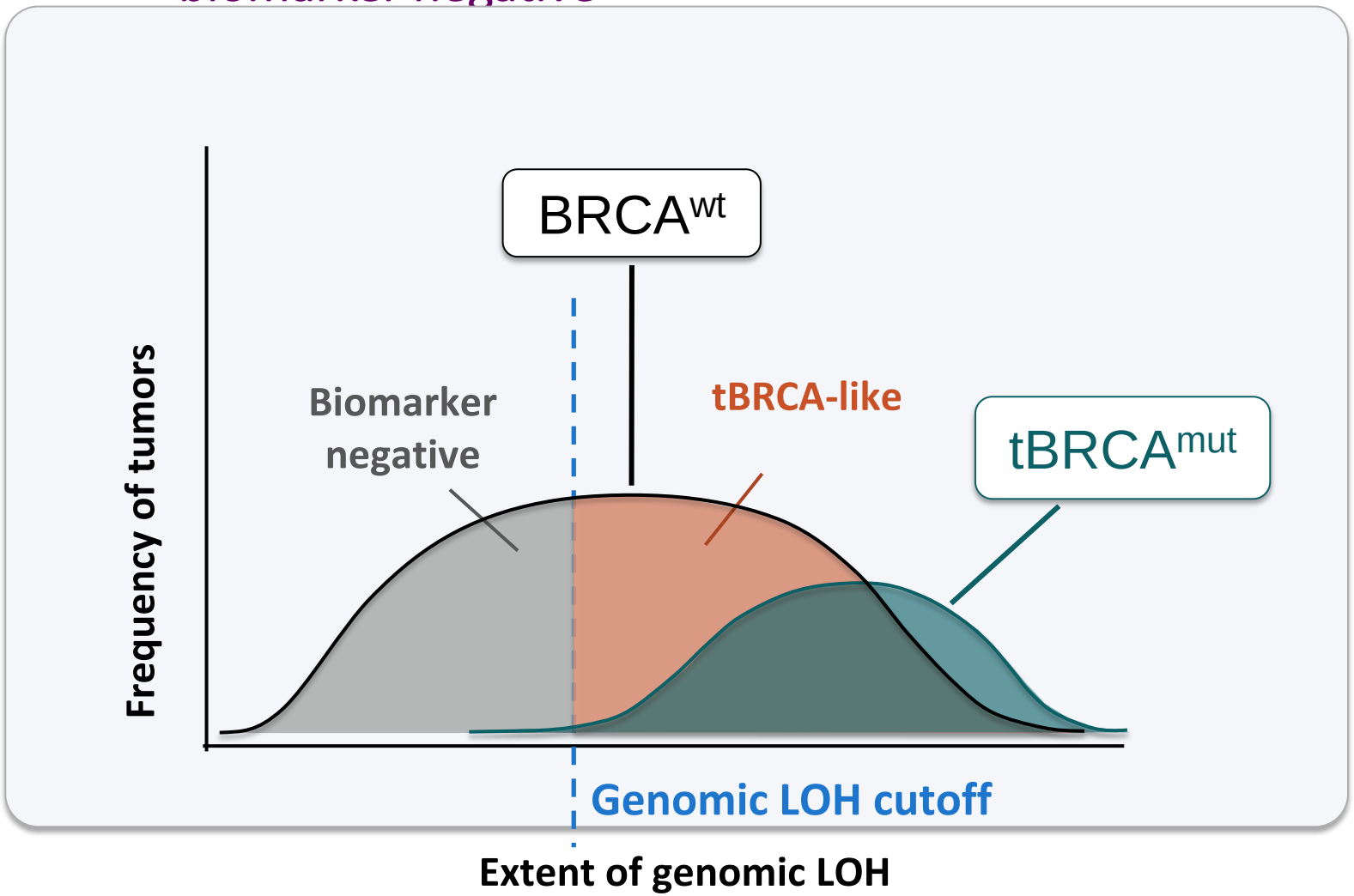
PARP INHIBITORS ARE SYNTHETICALLY LETAL TO TUMOR CELLS WITH HOMOLOGOUS RECOMBINATION DEFICIENCY (HRD)

Levine D. The Cancer Genome Atlas, Molecular profiling of serous ovarian cancer, 2011

How can we define HRD beyond BRCA mutation?



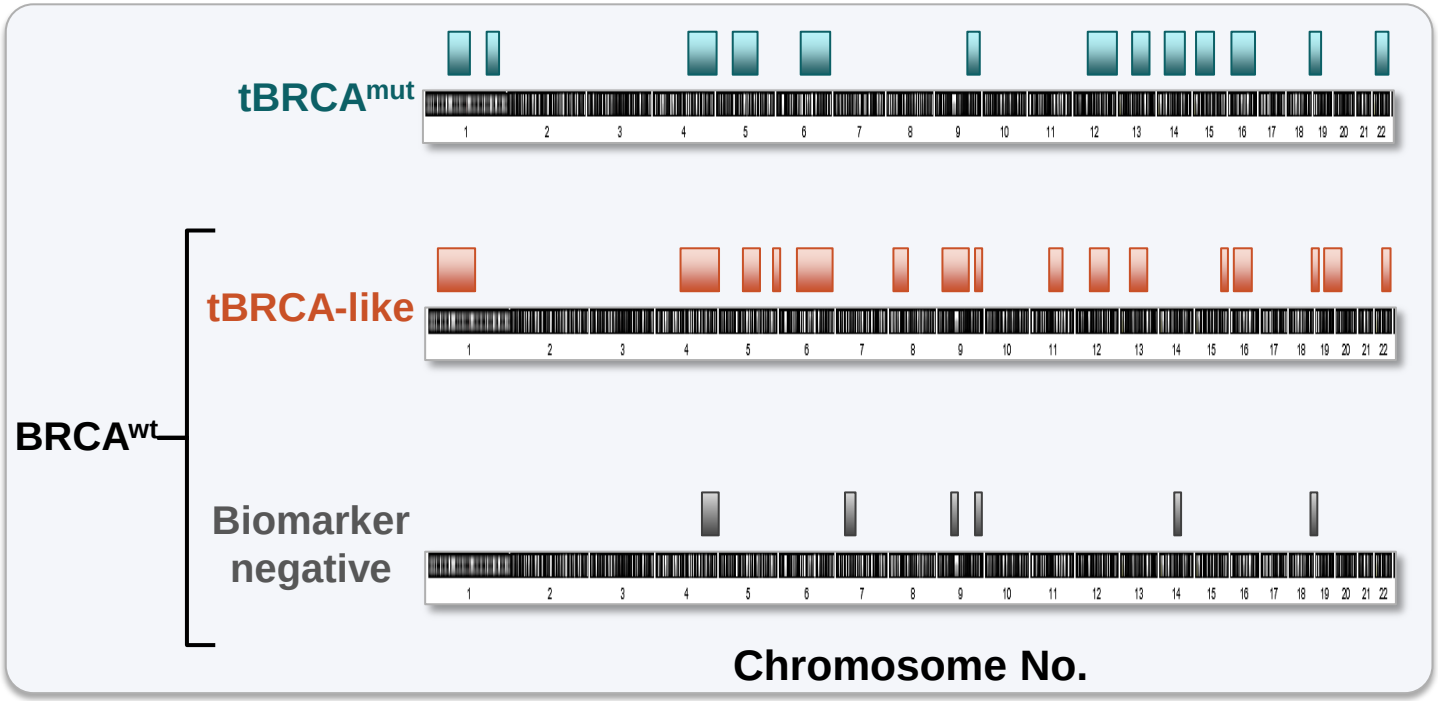
High grade Ovarian Cancer patients can be classified into three molecular subgroups: tBRCA^{mut}, tBRCA-like, and biomarker negative



tBRCA^{mut} includes germline and somatic mutations.
LOH=loss of heterozygosity;
tBRCA^{mut}=tumor BRCA mutation; wt=wild-type.

Loss of heterozygosity (LOH) signature detects tBRCA-like patients

Genomic profiling based on NGS



Hypothesis 1: Ovarian cancer patients with high genomic LOH suggesting tBRCA-like signature will respond to PARPi.

Hypothesis 2: Ovarian cancer patients who are "biomarker negative" (ie, with low genomic LOH) will not respond to PARPi.

NGS=next-generation sequencing.

ARIEL2 (Part 1) designed to assess rucaparib sensitivity in three prospectively defined molecular subgroups

Key Eligibility (N=206)

- High-grade serous or endometrioid OC
  - Known germline BRCA enrollment capped at N=15
- ≥1 prior platinum chemotherapy
- Platinum-sensitive, relapsed, measurable disease
- Tumor tissue (screening biopsy and archival)

NGS of **tumor tissue** allows patients to be classified

600 mg BID rucaparib until disease progression

- **tBRCA^{mut}**
- **tBRCA-like**
- **Biomarker Negative**

Analysis of HRD Subgroups

Primary endpoint

- PFS

Secondary endpoints

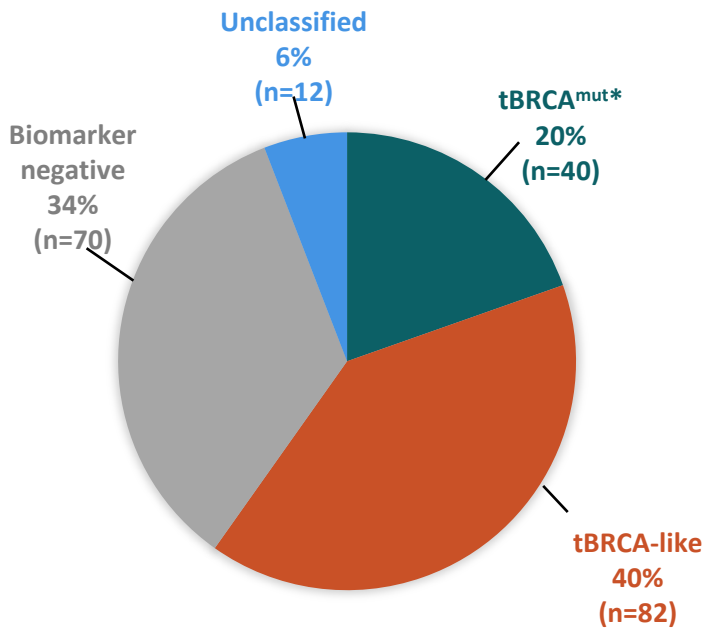
- ORR
  - RECIST
  - RECIST + CA-125
- Safety
- PK

PFS=progression free survival; PK=pharmacokinetics; RECIST=Response Evaluation Criteria In Solid Tumors.

Patient characteristics

Parameter	Total (N=204)
Median age, years (range)	65 (31–86)
ECOG PS grade	
0 / 1 / Pending (%)	65 / 35 / <1
Diagnosis†	
Epithelial ovarian cancer (%)	80
Primary peritoneal / fallopian tube cancer (%)	12 / 8
Histology	
Serous / endometrioid / mixed (%)	97 / 2 / 2
No. of prior treatment regimens	
Median no. of regimens (range)	1 (1–6)
1 (%)	58
≥2 (%)	42
Median no. of platinum-based regimens (range)	1 (1–5)
1 (%)	59
≥2 (%)	41
Platinum-free interval to latest platinum regimen	
6-12 months	48
>12 months	52

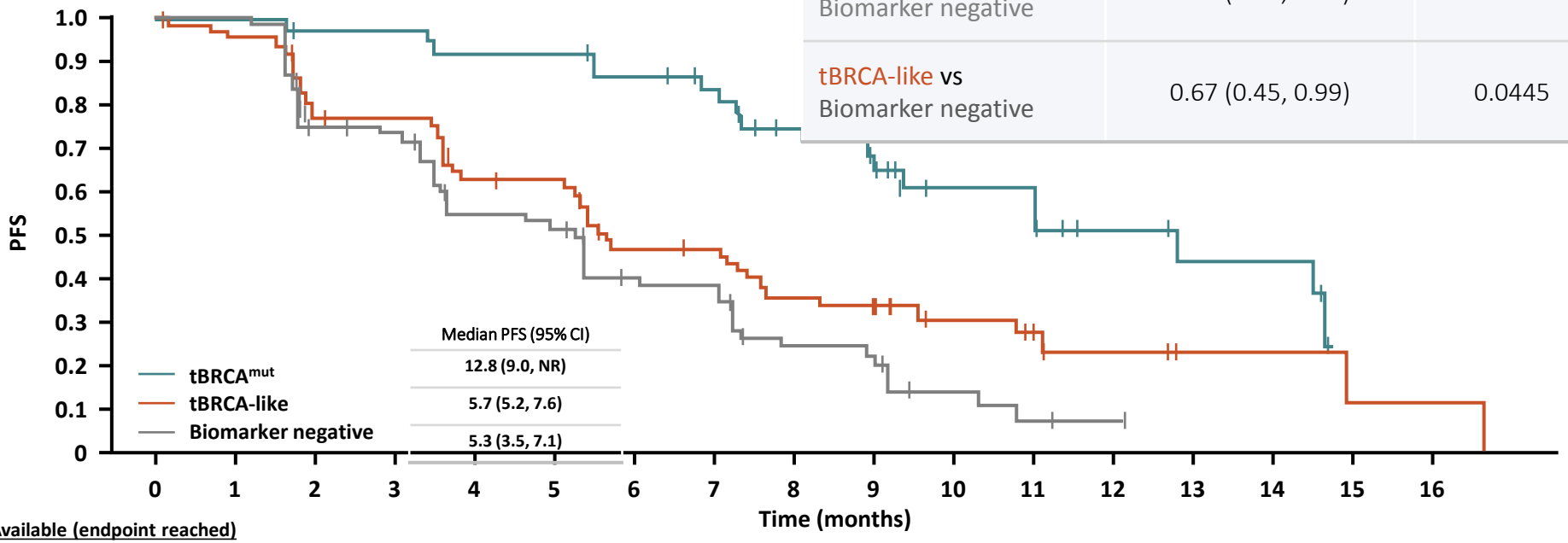
Distribution of HRD molecular subgroups



†1 patient with unknown diagnosis.
*Enrollment of known germline BRCA patients was capped.
Data cut-off date: 01SEP2015.
ECOG=Eastern Cooperative Oncology Group; PS=performance status.

Primary efficacy analysis: PFS in tBRCA^{mut} and tBRCA-like versus biomarker negative patients

Subgroup comparison	HR (95% CI)	p-value
tBRCA^{mut} vs Biomarker negative	0.22 (0.12, 0.40)	<0.0001
tBRCA-like vs Biomarker negative	0.67 (0.45, 0.99)	0.0445



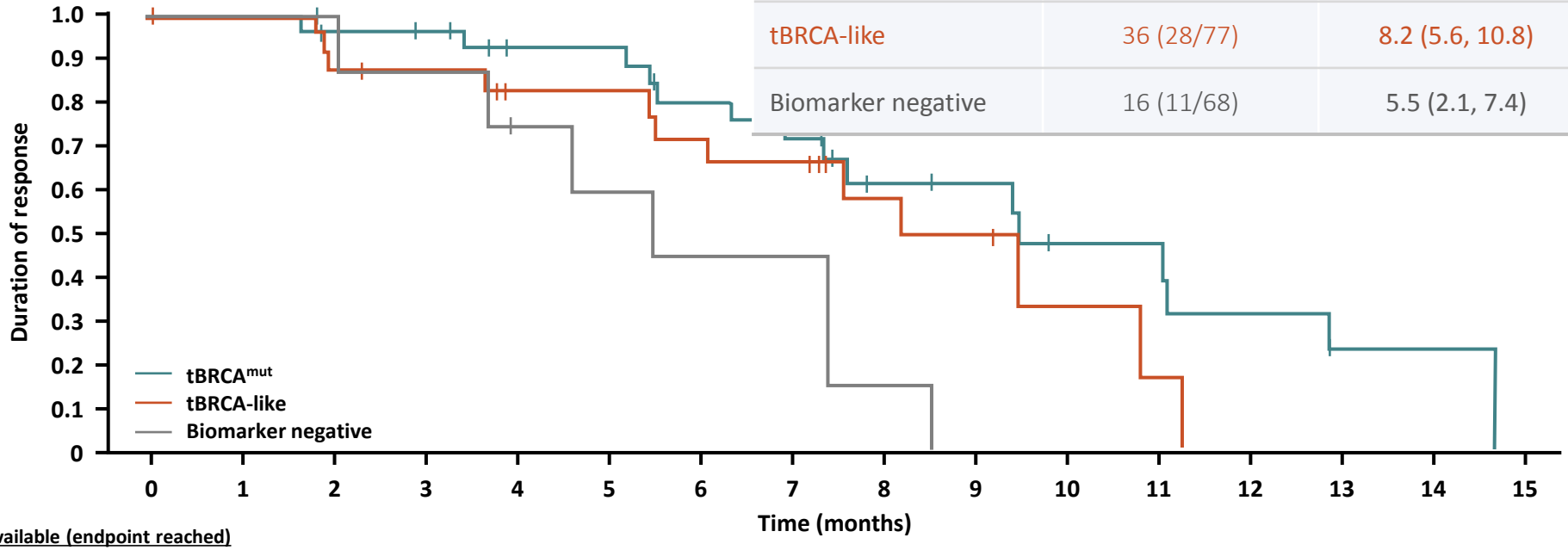
Available (endpoint reached)

tBRCA^{mut}	40 (0)	40 (0)	38 (1)	38 (1)	36 (3)	36 (3)	32 (5)	31 (5)	25 (9)	22 (10)	18 (12)	13 (13)	13 (15)	8 (15)	6 (16)	6 (16)	1 (18)			
tBRCA-like	82 (0)	75 (3)	59 (13)	54 (17)	46 (25)	42 (27)	34 (35)	29 (37)	25 (40)	21 (44)	14 (45)	10 (46)	6 (47)	4 (48)	2 (48)	2 (48)	2 (48)	1 (49)	1 (49)	0 (50)
Biomarker negative	70 (0)	68 (0)	52 (15)	46 (17)	33 (29)	32 (29)	22 (37)	20 (38)	13 (44)	11 (45)	5 (49)	4 (49)	2(51)	1 (51)	0 (51)					

CI=confidence interval; NR=not reached.

Most durable responses in tBRCA^{mut} and tBRCA-like patients

HRD molecular subgroup	Objective RECIST response rate, % (N)	Median duration of response, mo (95% CI)
tBRCA^{mut}	75 (30/40)	9.5 (7.4, 12.9)
tBRCA-like	36 (28/77)	8.2 (5.6, 10.8)
Biomarker negative	16 (11/68)	5.5 (2.1, 7.4)

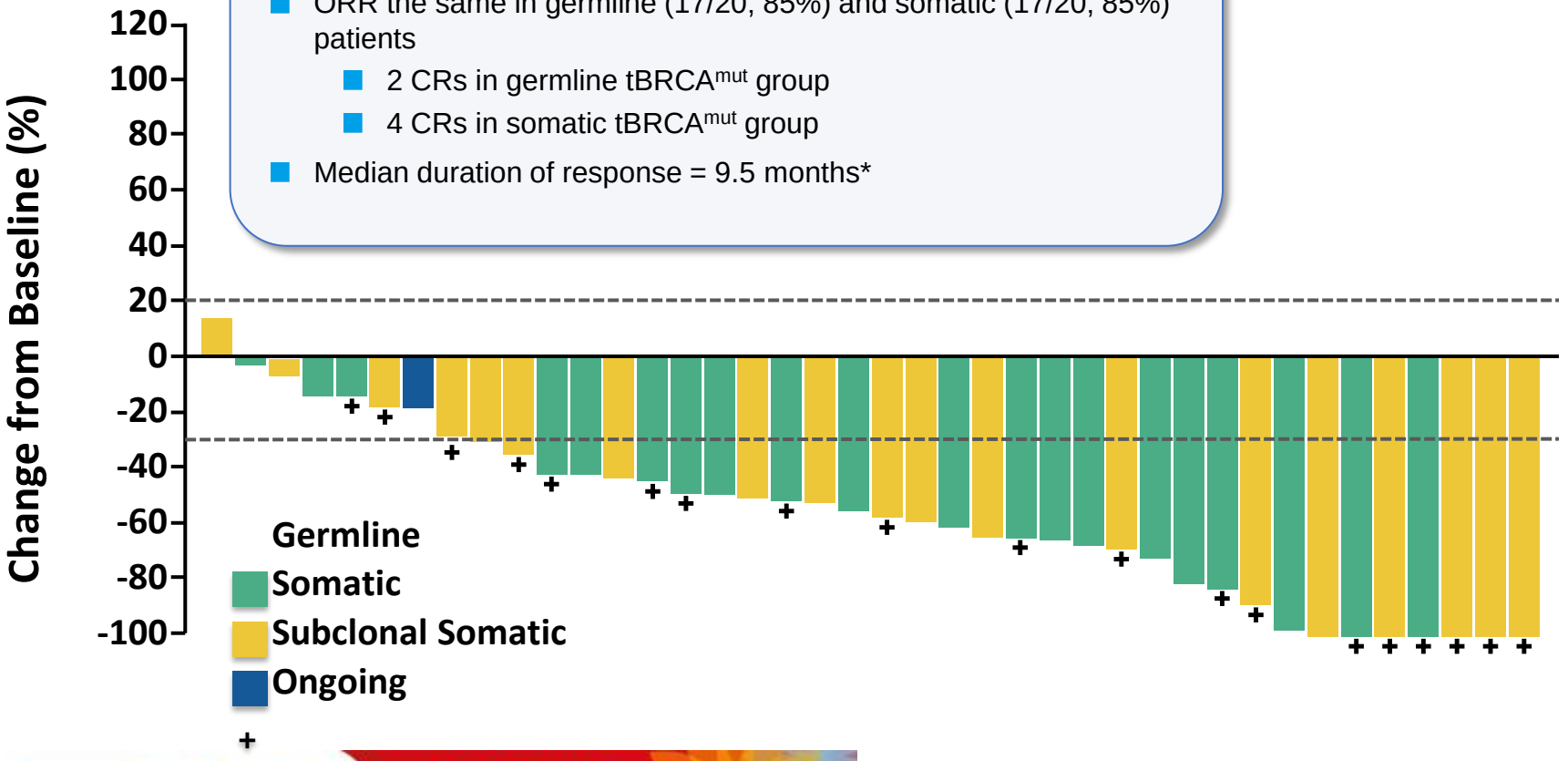


Available (endpoint reached)

tBRCA^{mut}	30 (0)	30 (0)	29 (1)	28 (1)	25 (2)	23 (2)	22 (4)	18 (6)	17 (7)	10 (9)	9 (9)	6 (11)	6 (11)	4 (13)	4 (13)	1 (14)	1(15)
tBRCA-like	28 (0)	26 (0)	26 (0)	19 (3)	19 (3)	15 (4)	15 (5)	12 (7)	10 (7)	6 (9)	6 (9)	2 (10)	1 (11)	0 (12)			
Biomarker negative	10 (0)	9 (0)	9 (0)	7 (1)	7 (1)	5 (2)	4 (4)	3 (4)	3 (4)	1 (6)	0 (7)						

Response rate similar in gBRCA^{mut} and sBRCA patients

- ORR (RECIST or CA-125) 85%
- ORR the same in germline (17/20; 85%) and somatic (17/20; 85%) patients
  - 2 CRs in germline tBRCA^{mut} group
  - 4 CRs in somatic tBRCA^{mut} group
- Median duration of response = 9.5 months*



*48% of patients are still ongoing at the time of the data cut.

Tumors with *RAD51C* alterations are tBRCA-like (high genomic LOH) and responded to rucaparib

HR-pathway gene	Genetic alteration type	Germline/somatic inference	HRD molecular subgroup	RECIST response	CA-125 response
ATM	Truncation	Somatic	Indeterminate	NE	NE
ATM	Homozygous del	Somatic	Indeterminate	SD	Yes
BRIP1	Truncation	Germline	Biomarker negative	PR	No
BRIP1	Splice	Germline	Biomarker negative	SD	No
CHEK2	Splice	Indeterminate	Biomarker negative	SD	No
CHEK2	Truncation	Germline	tBRCA-like	SD	No
FANCA	Homozygous del	Somatic	tBRCA-like	SD	NE
FANCI	Truncation	Germline	Biomarker negative	PD	No
NBN	Truncation	Germline	Biomarker negative	CR	Yes
NBN	Truncation	Germline	Indeterminate	SD	NE
RAD51C	Truncation	Germline	tBRCA-like	PR	Yes
RAD51C	Homozygous del	Somatic	tBRCA-like	PR	Yes
RAD51C	Splice	Germline	tBRCA-like	PR	Yes
RAD51C	Splice	Germline	tBRCA-like	SD	Yes
RAD51L1	Truncation	Indeterminate	Biomarker negative	SD	No
RAD51L3	Truncation	Germline	tBRCA-like	NE	NE
RAD51L3	Truncation	Indeterminate	tBRCA-like	SD	Yes
RAD54L	Truncation	Somatic (subclonal)	Biomarker negative	SD	NE

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; NE=not evaluable.

Rucaparib is generally well tolerated

Adverse event*	Treatment-Related AEs reported in ≥15% of patients Number of patients total N=204, n (%)	
	All grade	Grade 3/4
Nausea	143 (70)	7 (3)
Asthenia/Fatigue	135 (66)	15 (7)
ALT/AST increased**	80 (39)	23 (11)
Dysgeusia	79 (39)	0
Decreased appetite	70 (34)	2 (1)
Anemia/Decreased hemoglobin	62 (30)	38 (19)
Vomiting	61 (30)	2 (1)
Constipation	60 (29)	2 (1)
Diarrhea	40 (20)	3 (2)

*No cases of myelodysplastic syndrome or acute myeloid leukemia reported
**ALT/AST elevations are transient, self-limiting, and not associated with other signs of liver toxicity.

Rucaparib ovarian cancer trials currently enrolling patients

The HRD algorithm will be applied prospectively to two ongoing trials

ARIEL2 Part 2 (N=300)

Single arm in HGOC patients who have received ≥3 prior chemotherapy regimens (NCT01891344)

ARIEL3 (N=540)

Randomized maintenance study rucaparib vs placebo in HGOC patients who have received ≥2 platinum regimens (NCT01968213)

Conclusions

- **Rucaparib is highly active and well tolerated in HGOC patients with tBRCA^{mut}**
  - **The ORR (RECIST + CA-125) was 85% for patients with tBRCA^{mut}**
  - **Patients with germline or somatic BRCA mutant tumors had the same ORR (RECIST + CA-125)**
- **This is the first clinical study to prospectively demonstrate that an HRD signature can identify BRCA^{wt} HGOC patients who may benefit from rucaparib**
  - **Hazard ratio for PFS is 0.67 (95% CI 0.45, 0.99; p=0.045) in tBRCA-like vs biomarker negative tumors, with an approximate doubling of ORR**
- **Rucaparib is now in an expanded ARIEL2 registration-enabling study for the treatment of originally platinum-sensitive recurrent HGOC patients who have received ≥3 prior chemotherapies and have suitable tumor genetics**

Safety and efficacy in ROSiA, a single-arm study of extended-duration front-line bevacizumab-containing therapy in 1021 women with ovarian cancer

Amit M Oza[1], Frédéric Selle[2], Irina Davidenko[3], Jacob Korach[4], Cesar Mendiola[5], Peter Gocze[6], Patricia Pautier[7], Ewa Chmielowska[8], Aristotelis Bamias[9], Andrea DeCensi[10], Zanete Zvirbule[11], Antonio Gonzalez-Martin[12], Roberto Hegg[13], Florence Joly[14], Claudio Zamagni[15], Angiolo Gadducci[16], Nicolas Martin[17], Stephen Robb[17], Nicoletta Colombo[18]

[1]Princess Margaret Hospital, University of Toronto, Toronto, Canada; [2]Tenon Hospital AP-HP and Alliance Pour la Recherche en Cancérologie, Paris, France; [3]Clinical Oncology Dispensary #1, Krasnodar Region Ministry of Healthcare, Krasnodar, Russia; [4]Sheba Medical Center, Tel Hashomer, Israel; [5]University Hospital 12 de Octubre, Madrid, Spain; [6]University of Pécs, Pécs, Hungary; [7]Gustave Roussy, Villejuif, France; [8]Oncology Center Prof. F Lukaszczyka, Bydgoszcz, Poland; [9]Alexandra Peripheral General Hospital, Athens, Greece; [10]EO Ospedali Galliera, Genoa, Italy; [11]Riga East University Hospital, Latvian Oncology Centre, Riga, Latvia;
[12]MD Anderson Cancer Center, Madrid, Spain; [13]Perola Byington Hospital/FMUSP, São Paulo, Brazil; [14]Centre François Baclesse, Caen, France; [15]Policlinico S Orsola-Malpighi, Bologna, Italy; [16]University of Pisa, Pisa, Italy; [17]F Hoffmann-La Roche Ltd, Basel, Switzerland; [18]European Institute of Oncology and University of Milan Bicocca, Milan, Italy

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Background and rationale for ROSiA

- Two randomised phase III trials have shown that adding BEV to front-line chemotherapy significantly improved PFS → EU approval

Characteristic	GOG-0218[1,2]	ICON7[2,3]
Design	Placebo-controlled 3-arm	Open-label 2-arm
BEV dose/duration	15 mg/kg for **15 months**	7.5 mg/kg for **12 months**
PFS HR (95% CI) vs chemo alone	0.62 (0.52–0.75)[a]	0.86 (0.75–0.98)
Median PFS with BEV, months	18.2	19.3

- Safety profile characterised by hypertension and infrequent proteinuria and GI perforation

Roche BEV basket terms (NCI-CTCAE version 3.0)	GOG-0218[1,2]	ICON7[3]
Grade ≥3 hypertension, %	9.9	6.2
Grade ≥3 proteinuria, %	1.6	0.5
Grade ≥3 GI perforation, %	1.6	1.3

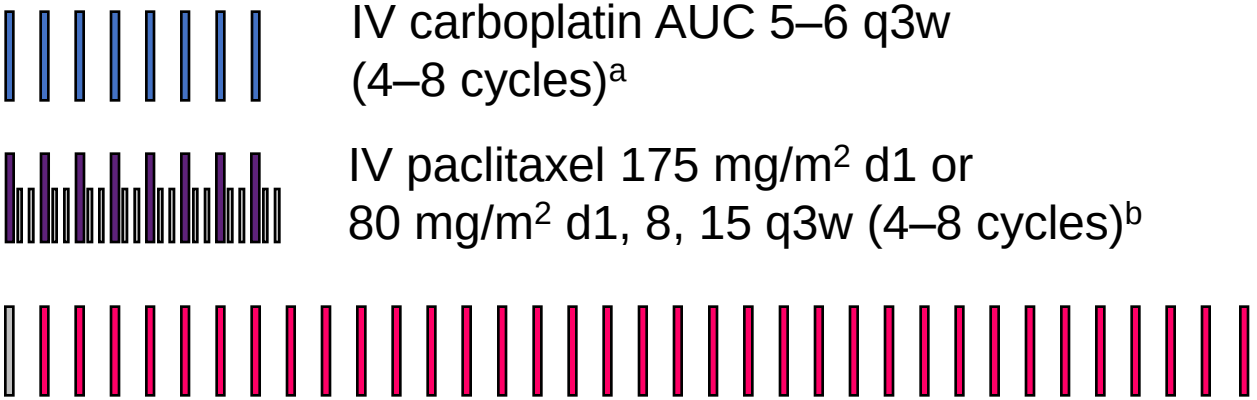
- The single-arm ROSiA trial explored an extended duration of front-line BEV in a broader setting

[1]Burger et al. NEJM 2011
[2]Avastin SmPC
[3]Perren et al. NEJM 2011

Study design

- **Epithelial ovarian, fallopian tube or primary peritoneal cancer:**
  - Stage IIB–IV
  - Grade 3 stage I/IIA
  - Clear-cell carcinoma (any stage)
  - Carcinosarcoma
- **Maximally debulked (prior neoadjuvant chemotherapy allowed)**
- **ECOG PS 0–2**

Dec 2010–May 2012:
1021 patients enrolled



IV carboplatin AUC 5–6 q3w (4–8 cycles)[a]

IV paclitaxel 175 mg/m^2 d1 or 80 mg/m^2 d1, 8, 15 q3w (4–8 cycles)[b]

BEV 15 or 7.5 mg/kg IV q3w for up to 36 cycles (2 years) or until disease progression or unacceptable toxicity

Patients without progression at cycle 36 could continue therapy after discussion with the Steering Committee

- Primary endpoint: Safety (AEs by NCI-CTCAE version 4.03)
- Secondary endpoints: PFS, ORR, duration of response, overall survival
- Exploratory objectives: Optional translational research

[a]Cisplatin permitted in patients with hypersensitivity to carboplatin
[b]A change from one paclitaxel regimen to the alternative during the study was not permitted
ECOG PS = Eastern Cooperative Oncology Group performance status; ORR = overall response rate

ROSiA

Baseline characteristics (N=1021)

Characteristic		No. of patients (%)
Age at screening, years	Median (range)	56 (20–82)
	≥70 years	121 (11.9)
ECOG PS[a]	0	706 (69.1)
	1/2	307 (30.1)
Hypertension at baseline		336 (32.9)
FIGO stage	I/II	167 (16.4)
	III (not further classified)	29 (2.8)
	IIIA	40 (3.9)
	IIIB	60 (5.9)
	IIIC	485 (47.5)
	IV	240 (23.5)
Outcome of debulking surgery (N=967)[b]	>1 cm	328 (33.9)
	≤1 cm	639 (66.1)
	Macroscopic (1–10 mm)	200 (20.7)
	Microscopic (<1 mm)	286 (29.6)
	Unknown/missing	153 (15.8)
High risk (MRC definition)[c]		468 (45.8)

77%

[a]Missing in 8 patients (0.8%). [b]Percentages calculated using a denominator of 967 (patients with debulking surgery).
[c]FIGO stage III and >1 cm residual disease or any FIGO stage IV or no debulking surgery
MRC = Medical Research Council

ROSiA

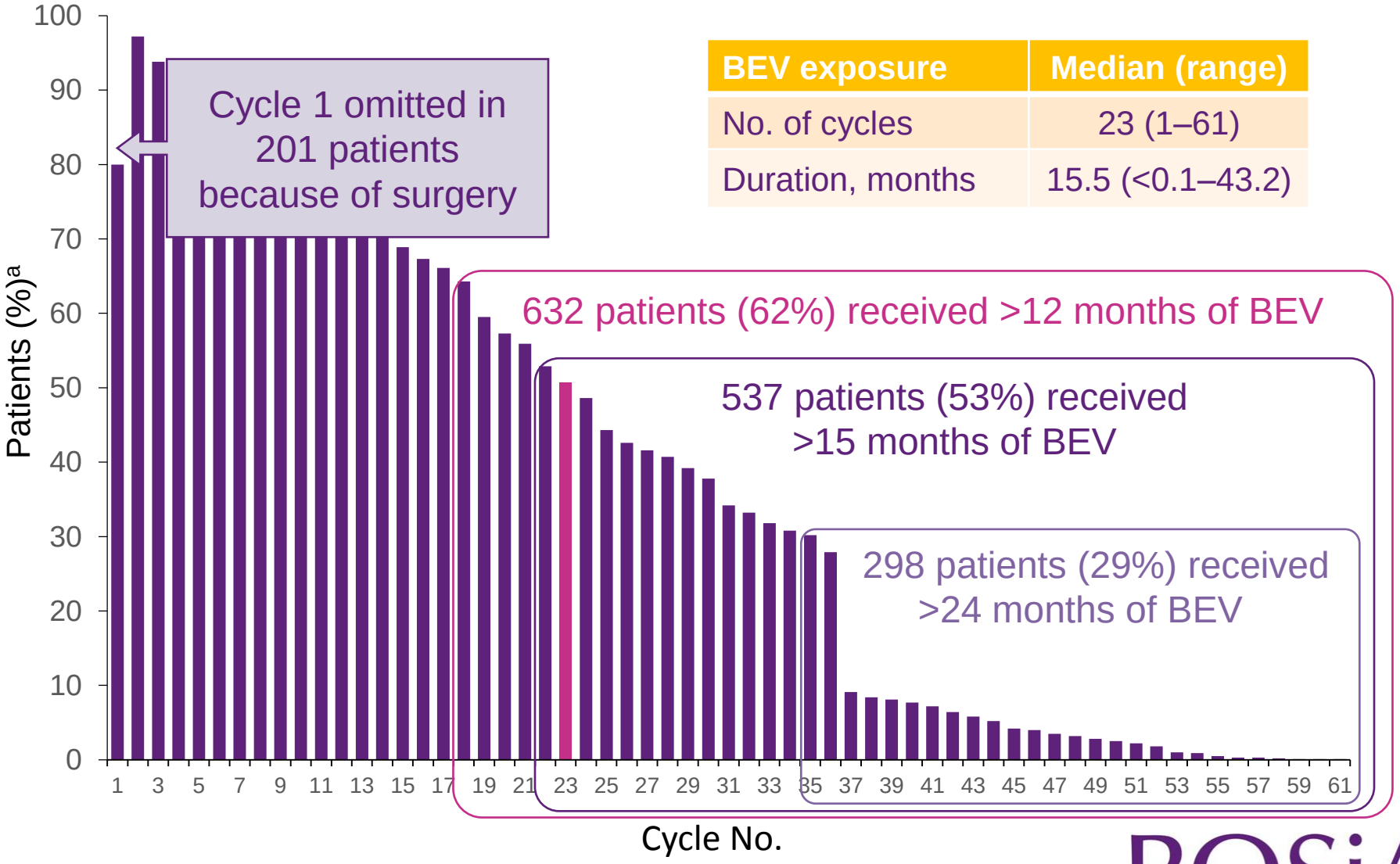
INVESTIGATORS' CHOSEN BEVACIZUMAB DOSE/ CHEMOTHERAPY SCHEDULE AT START OF TREATMENT

Selected dose/schedule	No. of patients (%)
BEV	1021 (100.0)
7.5 mg/kg	106 (10.4)
15 mg/kg	909 (89.0)
Missing	6 (0.6)
Paclitaxel	1021 (100.0)
q3w	950 (93.0)
Weekly	71 (7.0)[a]
Carboplatin	1020 (99.9)
Switched to cisplatin	5 (0.5)
Neoadjuvant chemotherapy before enrolment	206 (20.2)

[a]Of whom 3 later switched to q3w administration

ROSiA

Bevacizumab exposure by cycle



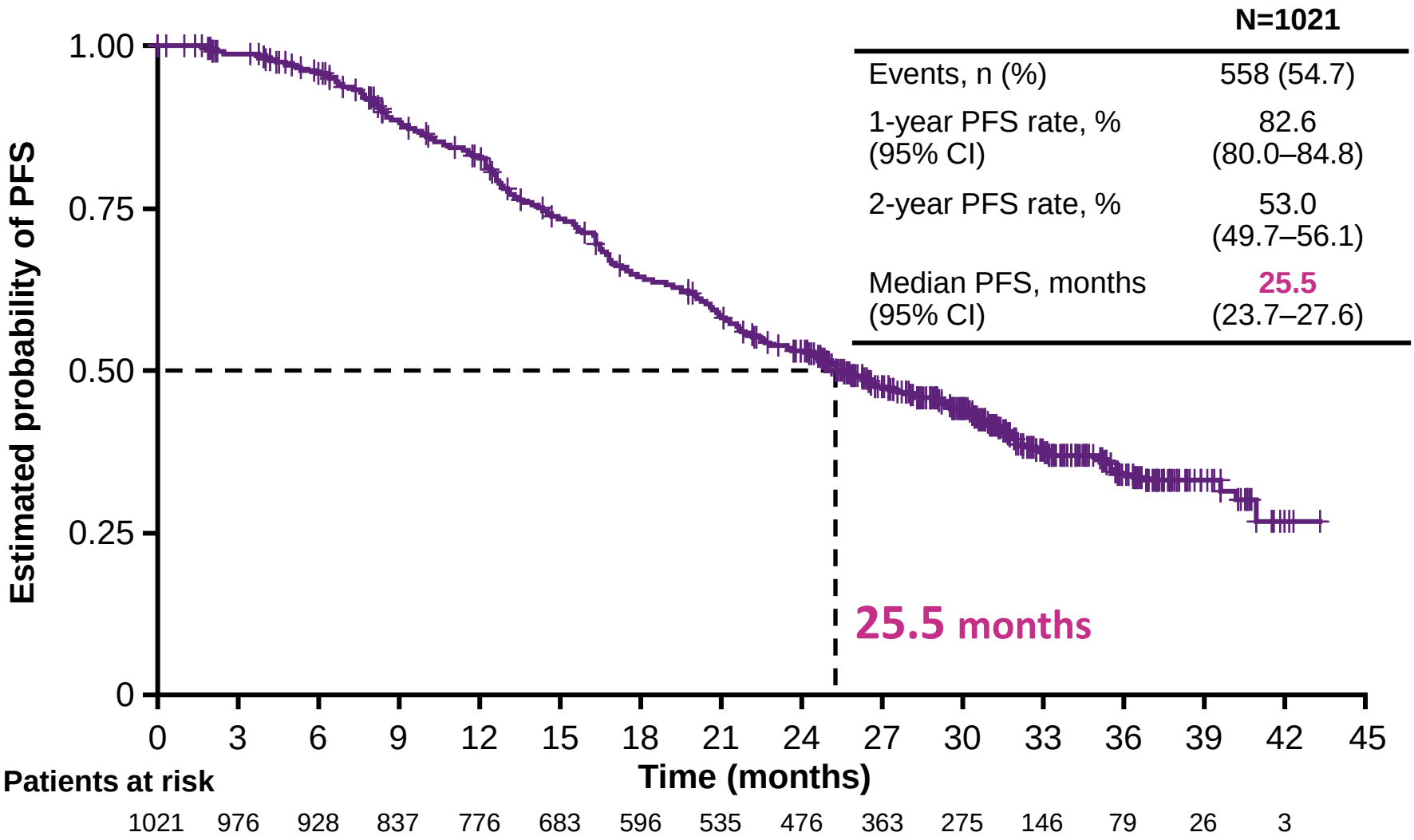
BEV exposure	Median (range)
No. of cycles	23 (1–61)
Duration, months	15.5 (<0.1–43.2)

[a]Denominator at each cycle is 1021

ROSiA

Progression-free survival (ITT population)

Median duration of follow-up: 32.0 months (range 0.7–49.5 months)

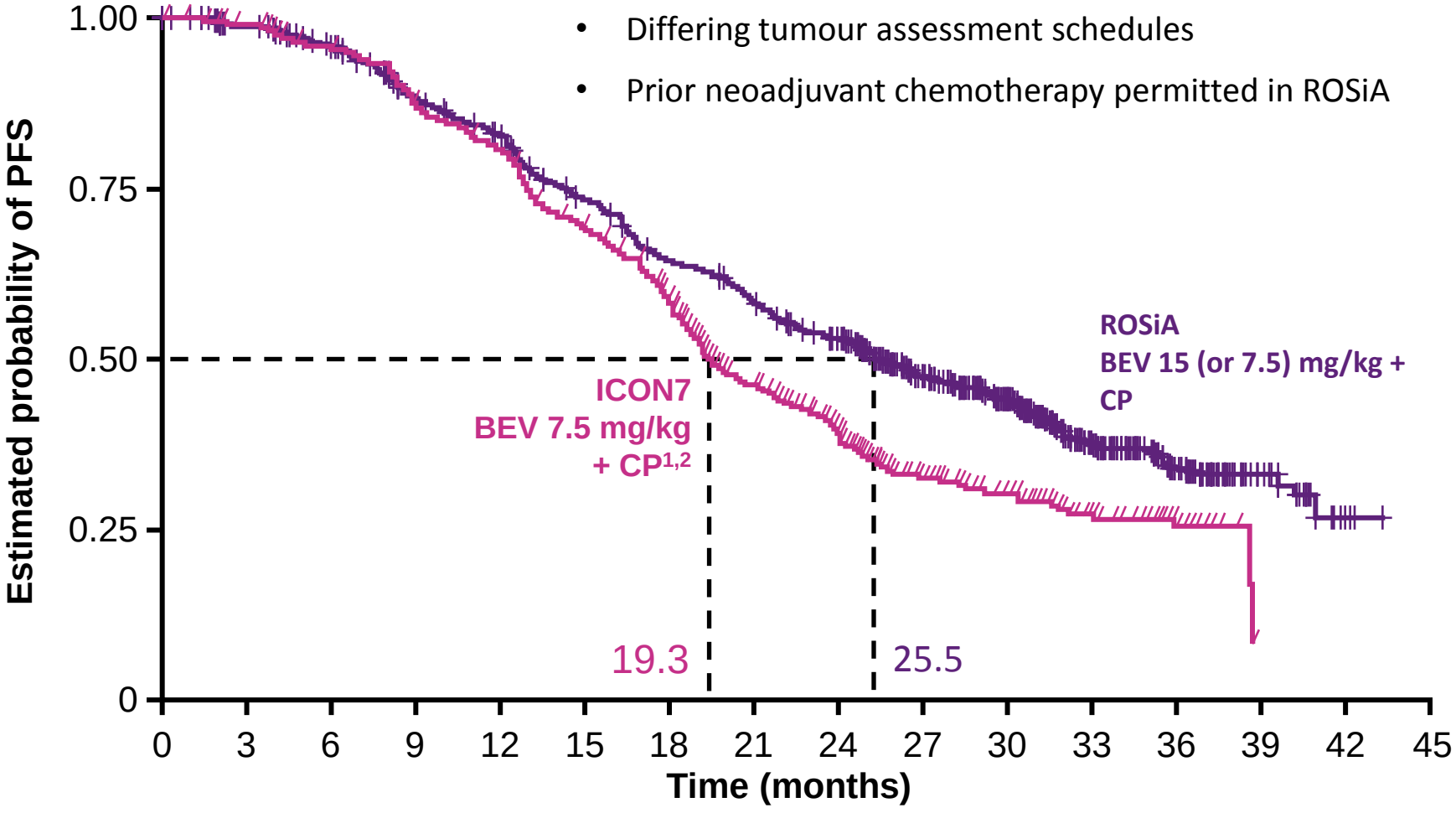


Data cut-off: 7 Dec 2014. ITT = intent-to-treat

PFS in ROSiA and ICON7 (ITT populations)

Caveats

- Differing tumour assessment schedules
- Prior neoadjuvant chemotherapy permitted in ROSiA



CP = carboplatin + paclitaxel

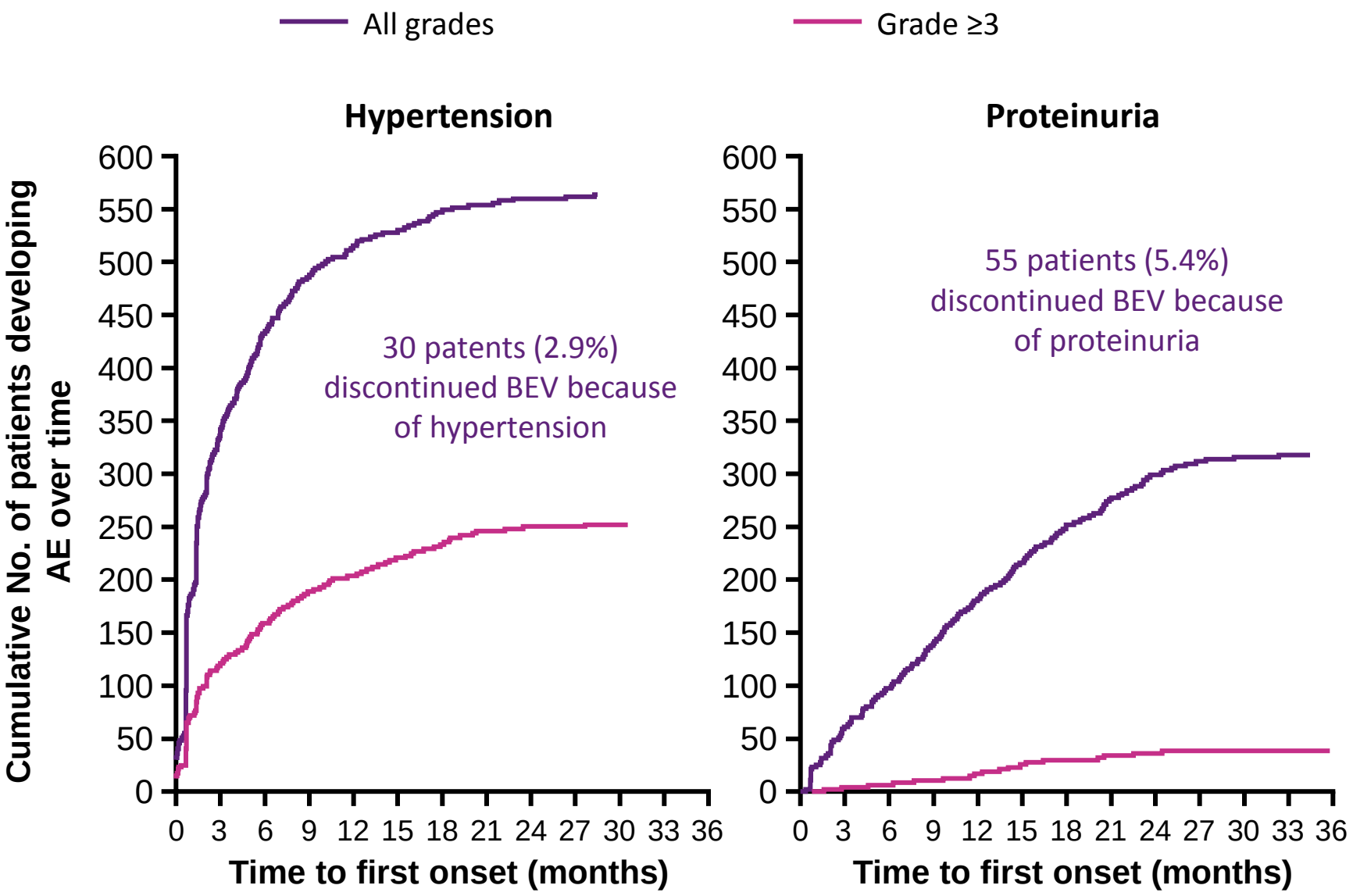
[1]Avastin SmPC;
[2]Roche data on file 2012 (ICON7 CSR addendum).

Summary of grade ≥3 AEs of special interest (N=1021)

Patients (%)	Grade 3	Grade 4	Grade 5	Grade ≥3
Any AE of special interest	**39.6**	**13.6**	**0.6**	**53.8**
Neutropenia and associated complications	18.2	11.0	0.1	29.3
Febrile neutropenia	2.3	0.6	0.1	2.9
Hypertension	24.1	0.6	0	24.7
Thrombocytopenia	8.1	1.7	0	9.8
Proteinuria	3.8	0	0	3.8
Thromboembolic events	1.9	0.8	0.3	2.9
GI perforation[a]	0.9	0.4	0.1	1.4
Bleeding	0.5	0.1	0.2	0.8
Wound-healing complication	0.4	0	0	0.4
Fistula/abscess	0.3	0.1	0	0.4
Congestive heart failure	0	0.1	0.1	0.2
Posterior reversible encephalopathy syndrome	0	0.1	0	0.1

[a]Roche BEV basket terms, comprising: GI perforation (0.4%), abdominal abscess (0.1%), anal abscess (0.1%), anal fistula (0.1%), colonic abscess (0.1%), intestinal perforation (0.1%), jejunal perforation (0.1%), large intestine perforation (0.1%), perineal abscess (0.1%), peritoneal abscess (0.1%), peritonitis (0.1%)

Cumulative incidence of hypertension and proteinuria over time

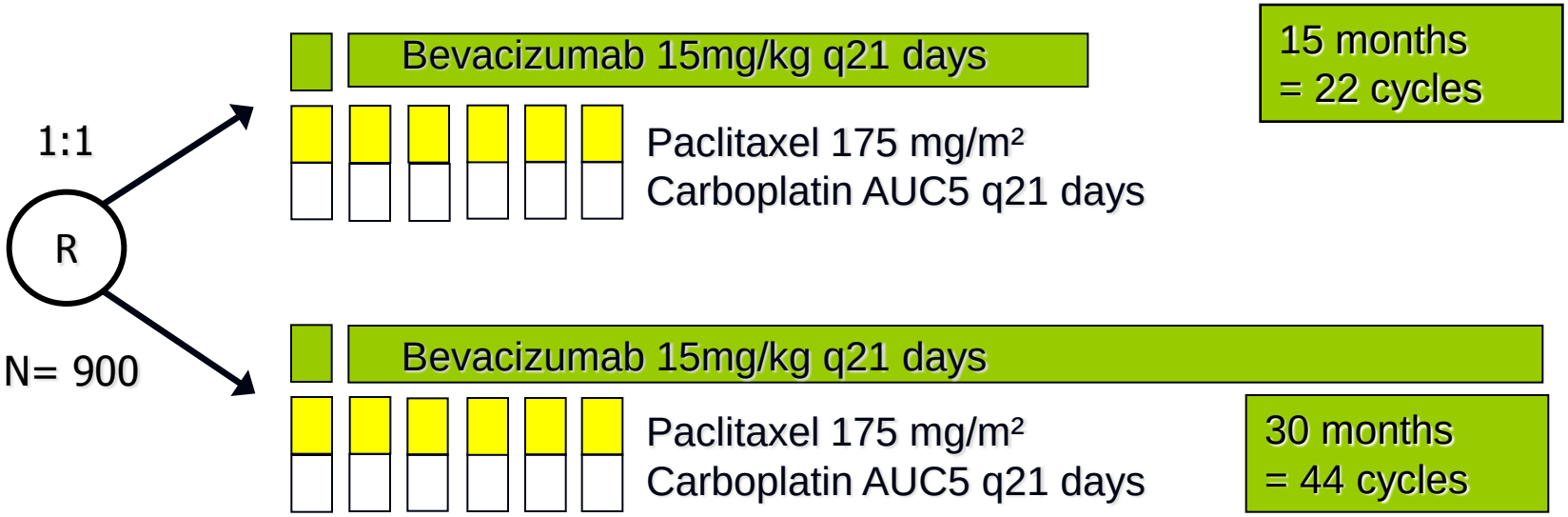


Conclusions

- The BEV duration in ROSiA is the longest investigated to date
- Median PFS is the longest reported to date for front-line BEV-containing therapy: 25.5 months overall
  - Stage IIIB–IV (current label population): 21.6 months
  - MRC-defined high-risk subgroup: 18.3 months
- The safety profile in ROSiA was acceptable and similar to that in ICON7 and GOG-0218 with 12 or 15 months of BEV, respectively
  - Proteinuria and hypertension were more common but relatively few patients discontinued treatment for these events
- The longer duration of BEV in ROSiA may improve PFS without substantially compromising safety – to be confirmed in a phase III trial
  - BOOST trial (NCT01462890): Prospective comparison of BEV 15 mg/kg for 15 vs 30 months both with carboplatin + paclitaxel

ROSiA

ENGOT Ov-15 Trial
AGO-OVAR 17
Study Design



Strata

- macroscopic residual tumor (yes vs no)
- FIGO Stage (IIB-IIIC vs IV)
- Study Group

Primary endpoint:

- PFS (non inferiority -> superiority)

Main question: treatment duration Bev

Computed tomography is more sensitive than CA-125 in detecting disease progression in patients with platinum-resistant ovarian cancer: Analysis of the AURELIA trial

Kristina Lindemann, Gunnar Kristensen, Mansoor Raza Mirza, Lucy Davies, Felix Hilpert, Ignacio Romero, Ali Ayhan, Alexander Burges, Maria Jesus Rubio, Francesco Raspagliesi, Manon Huizing, Geert-Jan Creemers, Maria Lykka, Chee Khoon Lee, Val Gebski, Eric Pujade-Lauraine

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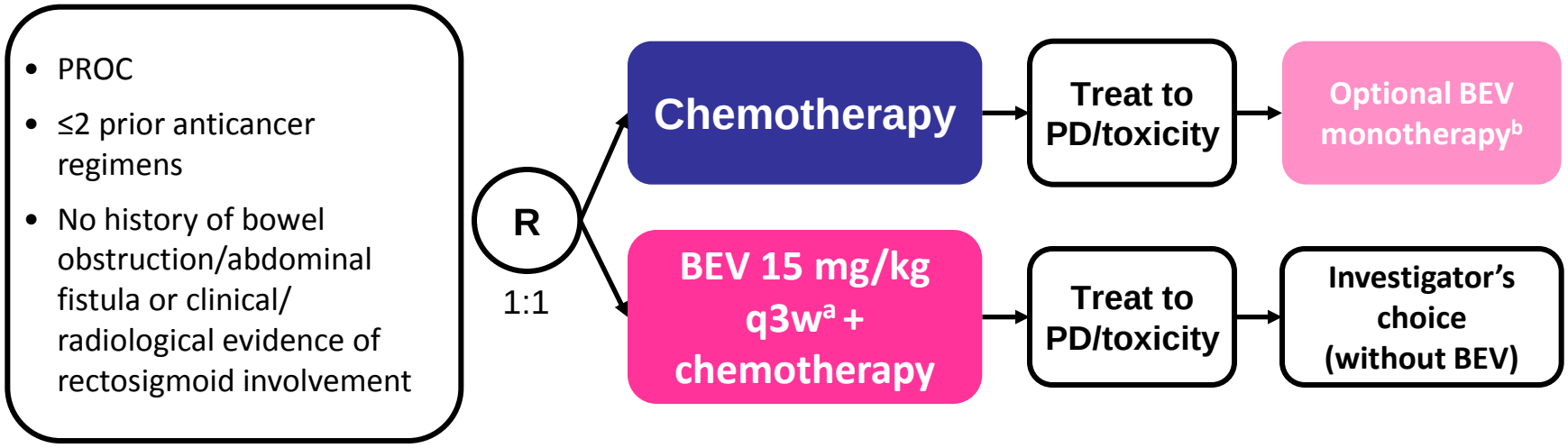
AURELIA: DESIGN AND RESULTS



- Significantly improved PFS and ORR with BEV added to chemotherapy
  - PFS HR 0.48; median PFS 6.7 vs 3.4 months[1]
- Favourable patient-reported outcomes with BEV + chemo[2]

[a]Or 10 mg/kg q2w
[b]15 mg/kg q3w, permitted on clear evidence of PD
HR = hazard ratio; ORR = objective response rate

[1]Pujade-Lauraine E et al. JCO 2014
[2]Stockler M et al. JCO 2014

RATIONAL

- Radiographic studies are the standard for trial reporting and they are required by regulatory agencies for drug approval
- The cost and toxicity of radiography together with patient inconvenience advance the need to develop alternative means of accurate assessment
- Is CA125 a surrogate marker for PFS ?

Abstract 2703, Romero et al.

Correlation between RECIST and CA-125 at the time of PD (Aurelia study)

Disease status by CA-125	PD by RECIST (N=218), n (%)			P value
	Chemo alone (N=125)	Chemo + BEV (N=93)	Total (N=218)	
Non-PD	73 (58)	51 (55)	124 **(57)**	0.60
PD	52 (42)	42 (45)	94 **(43)**	

- **Less than half of the patients with PD by RECIST had PD detected by CA-125 criteria**

ESMO 2015, Abstract 2703

TAKE HOME MESSAGE

- **Although intriguing, this post-hoc analysis presents several caveats and can not lead to a radical change as suggested by the authors**

- **The GCIG recommendation still holds true:**

The GCIG requests that data from all clinical trials using these definitions are made available to GCIG trial centers so that continual validation and improvement can be accomplished

LONG-TERM FOLLOW-UP OF PATIENTS WITH AN ISOLATED OVARIAN RECURRENCE AFTER CONSERVATIVE TREATMENT OF EPITHELIAL OVARIAN CANCER : REVIEW OF THE RESULTS OF A INTERNATIONAL MULTICENTER STUDY COMPRISING 545 PATIENTS

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SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE Abstract 2704

SITE OF RECURRENCE ACCORDING TO GRADE

	Recurrence N (%)	Ovarian recurrence N (%)	Extra-ovarian recurrence N (%)	P value
Total	63 (11.6)	24 (4.4)	39 (7.2)	
Grade 1	32 (9)	19 (59)	13 (41)	
Grade 2	12 (11.2)	4 (33)	8 (67)	.001
Grade 3	19 (23.5)	1 (5)	18 (95)	
DOD		3 (12.5%)	24 (61.5%)	

MAIN ISSUES FOR FERTILITY-SPARING SURGERY

- **What is the incidence of microscopic bilateral involvement?**

  2.5%*

- **What is the risk of recurrence in the spared ovary**

  4%

- **Is prognosis worsened by conservative surgery?**

****Benjamin et al. Gynecol Oncology 1999***

TAKE HOME MESSAGES

- **Isolated ovarian recurrence are rare and they are often salvaged by surgery**
- **The poor prognosis of grade 3 tumors is mainly related to extraovarian recurrences** and it is probably independent from the type of surgery (conservative/demolitive)
- **Patients with grade 3 tumors should be aware that demolitive surgery will not eliminate their risk of recurrence** and decide accordingly.