AURELIA: A randomized phase III trial evaluating bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer

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ASCO Annual '12 Meeting

Background

- Ovarian cancer (OC) is a highly VEGF-driven disease
- Bevacizumab (BEV) significantly improves progression-free survival (PFS) when combined with chemotherapy and continued as a single agent in the:
  - Front-line setting (GOG-0218, ICON7)[1,2]
  - Platinum-sensitive recurrent setting (OCEANS)[3]

VEGF = vascular endothelial growth factor

1. Burger NEJM 2011; 2. Perren NEJM 2011; 3. Aghajanian JCO 2012

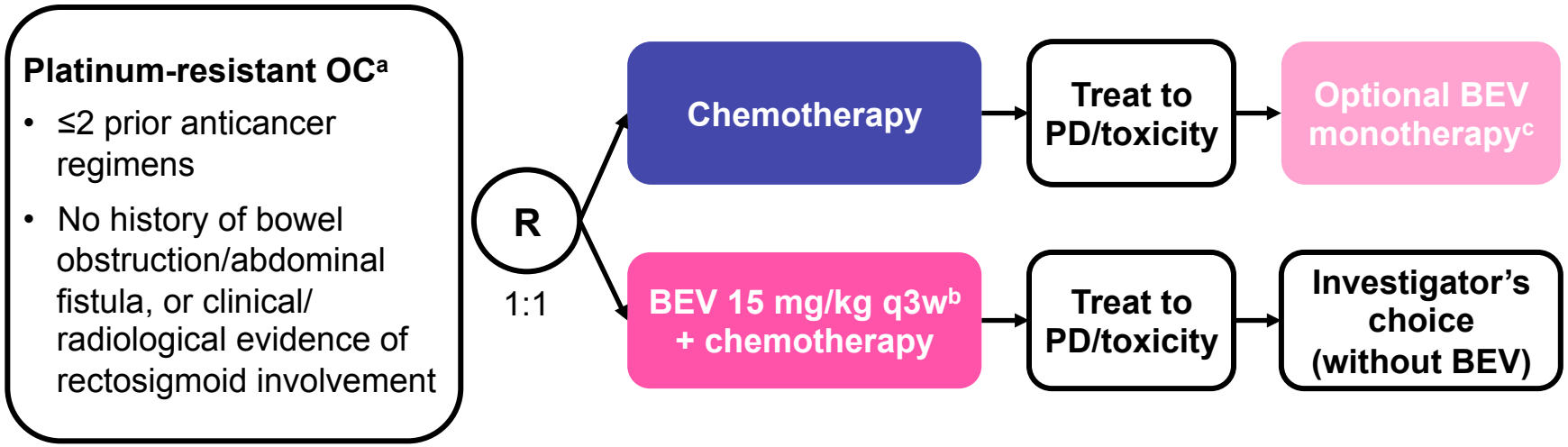
Platinum-resistant OC: A high unmet medical need

- At first relapse, 25% of patients have platinum-resistant OC; almost all patients with recurrent OC will ultimately develop platinum resistance
  - Single-agent therapy (eg weekly paclitaxel, PLD, or topotecan) is standard
  - Combination regimens have failed to improve efficacy vs single-agent chemotherapy
  - Median overall survival is typically <12 months
- BEV has demonstrated single-agent activity in this setting[1,2]
  - Concern about GI perforation in one study[2]
- AURELIA is the first randomized trial to evaluate the addition of BEV to chemotherapy in platinum-resistant OC

PLD = pegylated liposomal doxorubicin. GI = gastrointestinal.

1. Burger JCO 2007; 2. Cannistra JCO 2007

AURELIA trial design



Stratification factors:

- Chemotherapy selected
- Prior anti-angiogenic therapy
- Treatment-free interval (<3 vs 3–6 months from previous platinum to subsequent PD)

Chemotherapy options (investigator's choice):

- Paclitaxel 80 mg/m^2 days 1, 8, 15, & 22 q4w
- Topotecan 4 mg/m^2 days 1, 8, & 15 q4w (or 1.25 mg/m^2, days 1–5 q3w)
- PLD 40 mg/m^2 day 1 q4w

PD = progressive disease

[a]Epithelial ovarian, primary peritoneal, or fallopian tube cancer; [b]Or 10 mg/kg q2w; [c]15 mg/kg q3w, permitted on clear evidence of progression

Statistical design

Primary objective: To compare PFS with chemotherapy (CT) alone vs BEV + CT according to RECIST v1.0

Secondary objectives: To compare

- Objective response rate (ORR) according to RECIST v1.0 and/or GCIG CA-125 criteria
- Overall survival
- Quality of life
- Safety and tolerability

Statistical assumptions

- HR of 0.7 (median PFS 4.0 → 5.7 months with BEV)
- 80% power for 2-sided log-rank test at α=0.05

Primary analysis: PFS events in 301 of 361 patients

- Data cut-off: November 14, 2011

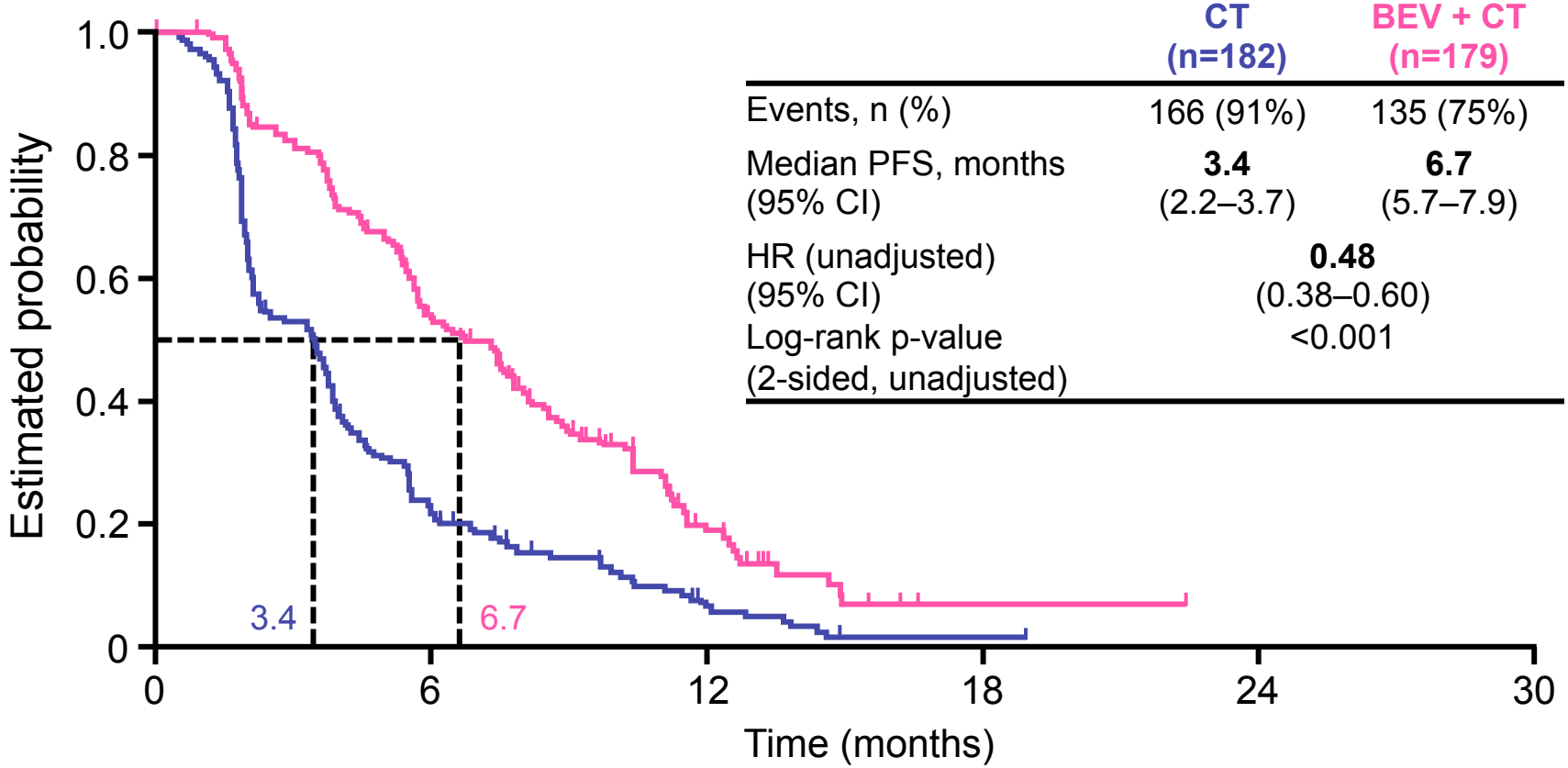
Baseline characteristics

Characteristic	CT (n=182) n (%)	BEV + CT (n=179) n (%)
Median age, years	61	62
(range)	(25–84)	(25–80)
Origin of cancer: Ovary	157 (86)	167 (93)
Serous/adenocarcinoma at diagnosis	152 (84)	156 (87)
Histologic grade at diagnosis		
1	9 (5)	10 (6)
2/3	153 (84)	147 (82)
Prior anti-angiogenic therapy[a]	14 (8)	12 (7)
Two prior chemotherapy regimens	78 (43)	72 (40)
PFI <3 months[a,b]	46 (25)	50 (28)
ECOG PS		
0	99 (54)	107 (60)
1/2	80 (44)	70 (39)
Measurable disease	144 (79)	143 (80)
Ascites	54 (30)	59 (34)

PFI = platinum-free interval

[a]Stratification factor. [b]From last platinum to subsequent PD

Progression-free survival



	CT (n=182)	BEV + CT (n=179)
Events, n (%)	166 (91%)	135 (75%)
Median PFS, months (95% CI)	**3.4** (2.2–3.7)	**6.7** (5.7–7.9)
HR (unadjusted) (95% CI)	**0.48** (0.38–0.60)	
Log-rank p-value (2-sided, unadjusted)	<0.001	

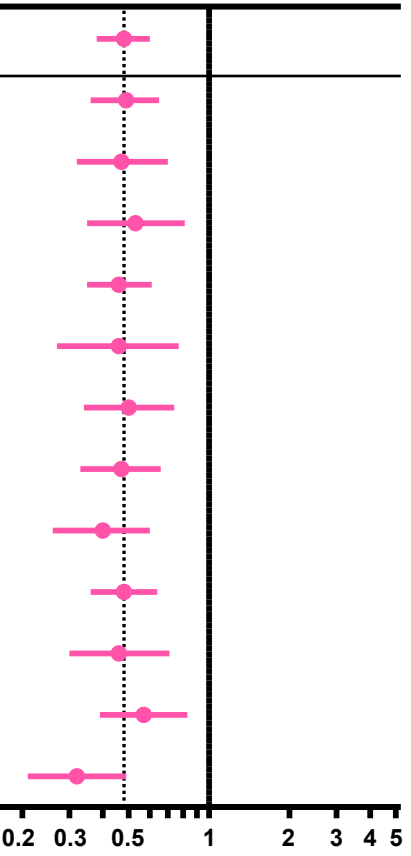
No. at risk:

CT	182	93	37	20	8	1	1	0	0
BEV + CT	179	140	88	49	18	4	1	1	0

Median duration of follow-up: 13.9 months (CT arm) vs 13.0 months (BEV + CT arm)

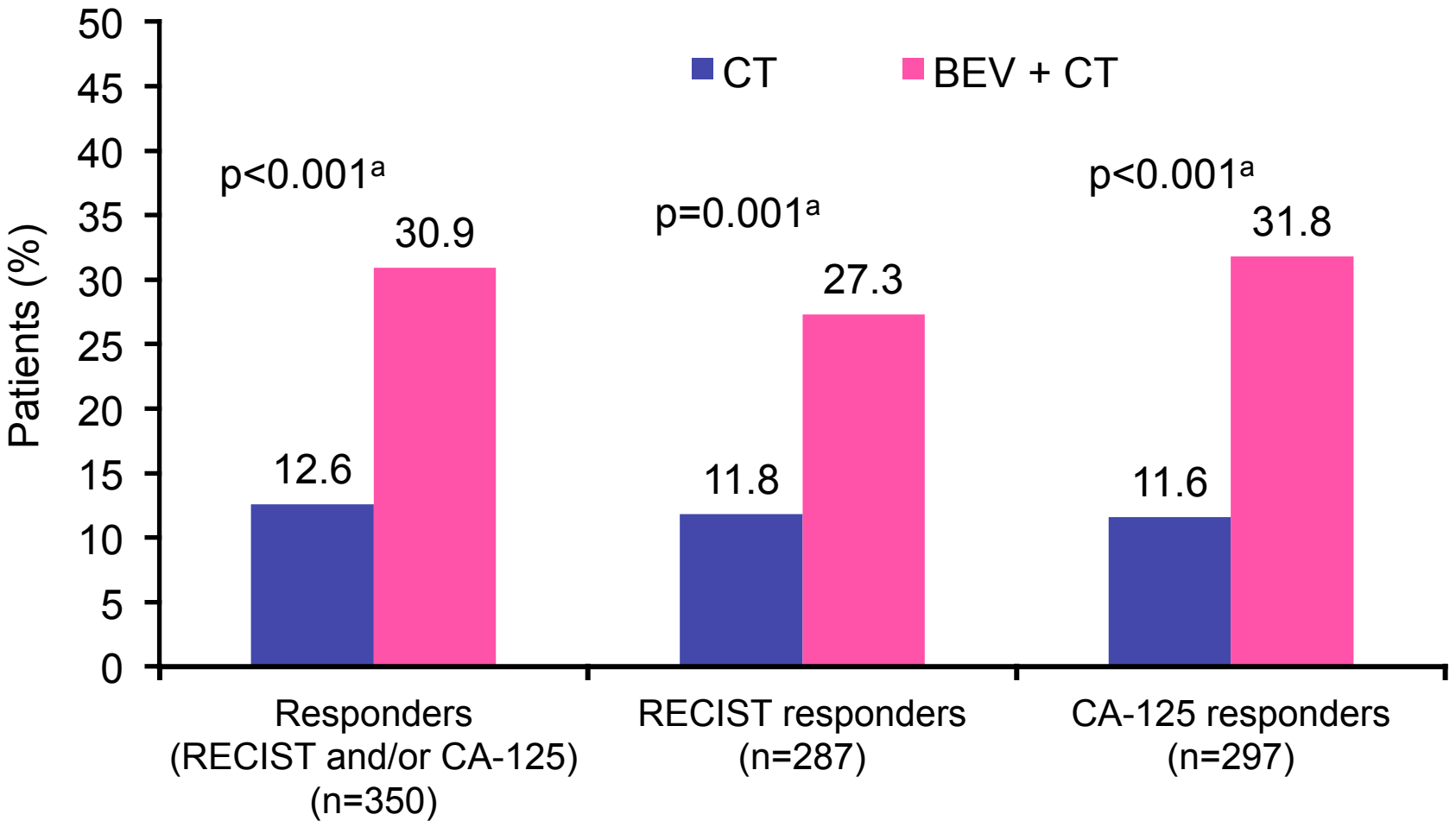
Subgroup analysis of PFS

Subgroup		No. of patients	Median PFS, months: CT	Median PFS, months: BEV + CT	HR[a]
All patients		361	**3.4**	**6.7**	0.48
Age, years	**<65**	228	**3.4**	**6.0**	0.49
	≥65	133	**3.5**	**7.8**	0.47
PFI, months[b]	**<3**	96	**2.1**	**5.4**	0.53
	3–6	257	**3.6**	**7.8**	0.46
Measurable disease, cm	**No (<1)**	74	**3.7**	**7.5**	0.46
	Yes (1–<5)	126	**3.3**	**7.5**	0.50
	Yes (≥5)	161	**3.3**	**6.0**	0.47
Ascites	**Yes**	113	**2.5**	**5.6**	0.40
	No	248	**3.5**	**7.6**	0.48
Chemotherapy	**Paclitaxel**	115	**3.9**	**10.4**	0.46
	PLD	126	**3.5**	**5.4**	0.57
	Topotecan	120	**2.1**	**5.8**	0.32



[a]*Unadjusted.* [b]*Missing n=8*

Summary of best overall response rates



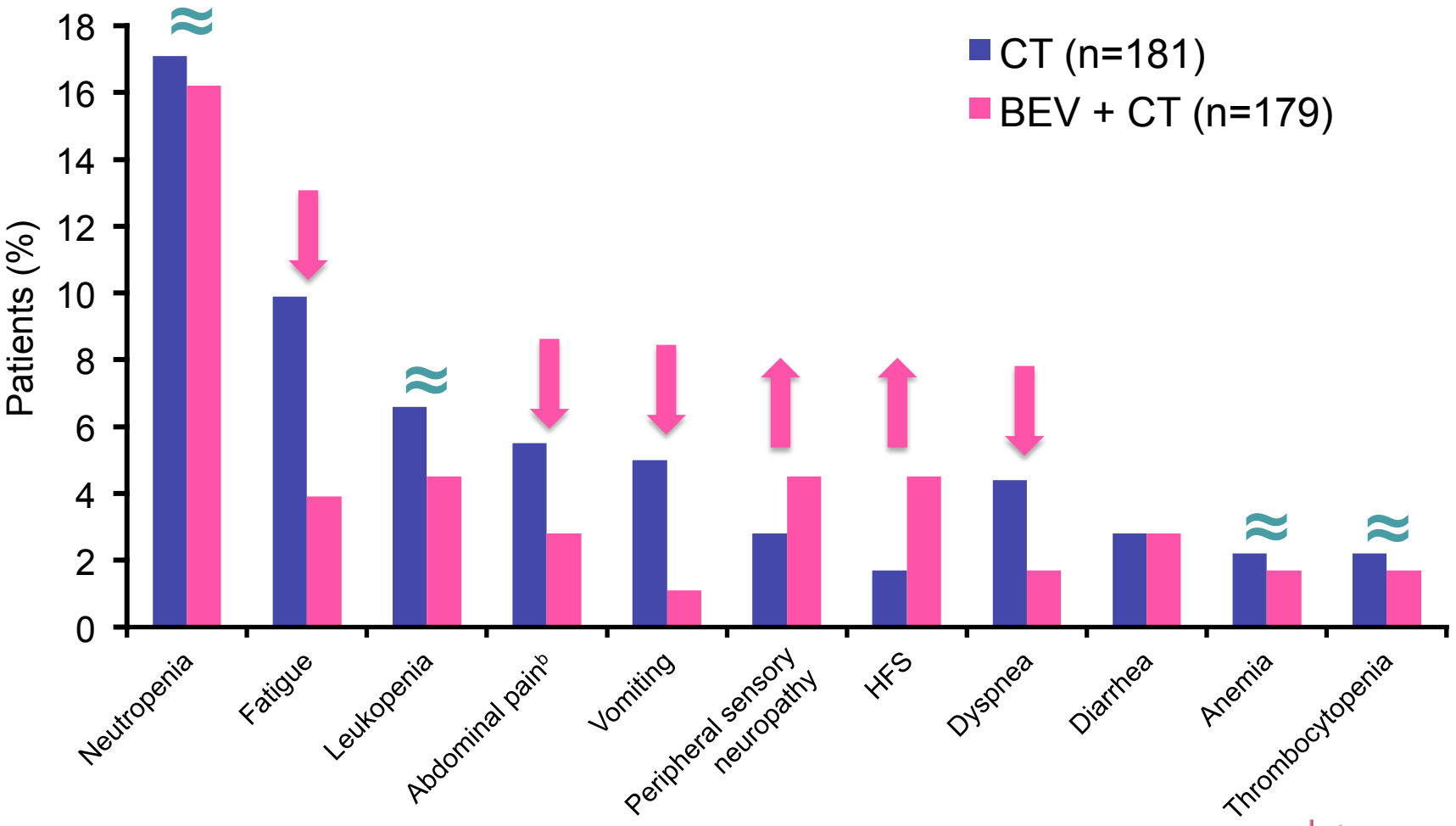
[a]*Two-sided chi-square test with Schouten correction*

Adverse events of special interest

Grade ≥3 adverse events of special interest, n (%)	CT (n=181)	BEV + CT (n=179)
Hypertension	2 (1.1)	13 (7.3)
Grade ≥2	12 (6.6)	36 (20.1)
Proteinuria	0	3 (1.7)
Grade ≥2	1 (0.6)	19 (10.6)
GI perforation	0	3 (1.7)
Grade ≥2	0	4 (2.2)
Fistula/abscess	0	2 (1.1)
Grade ≥2	0	4 (2.2)
Bleeding	2 (1.1)	2 (1.1)
Thromboembolic event	8 (4.4)	9 (5.0)
Arterial	0	4 (2.2)
Venous	8 (4.4)	5 (2.8)
Wound-healing complication	0	0
RPLS	0	1 (0.6)
CHF	1 (0.6)	1 (0.6)
Cardiac disorders (excluding CHF)	0	0

RPLS = reversible posterior leukoencephalopathy syndrome; CHF = congestive heart failure

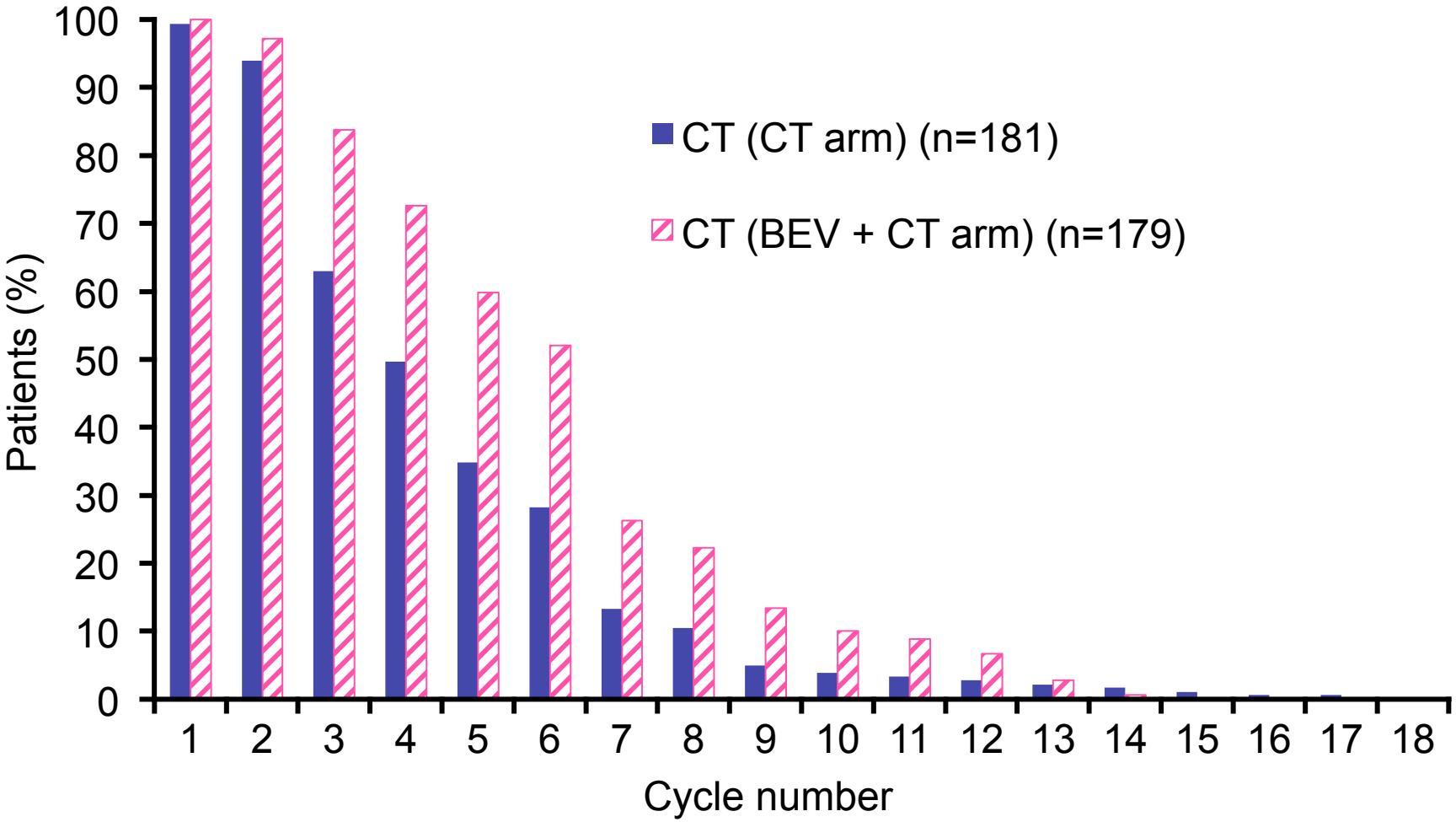
Additional grade ≥3 adverse events[a] in ≥2% of patients in either arm



HFS = hand-foot syndrome

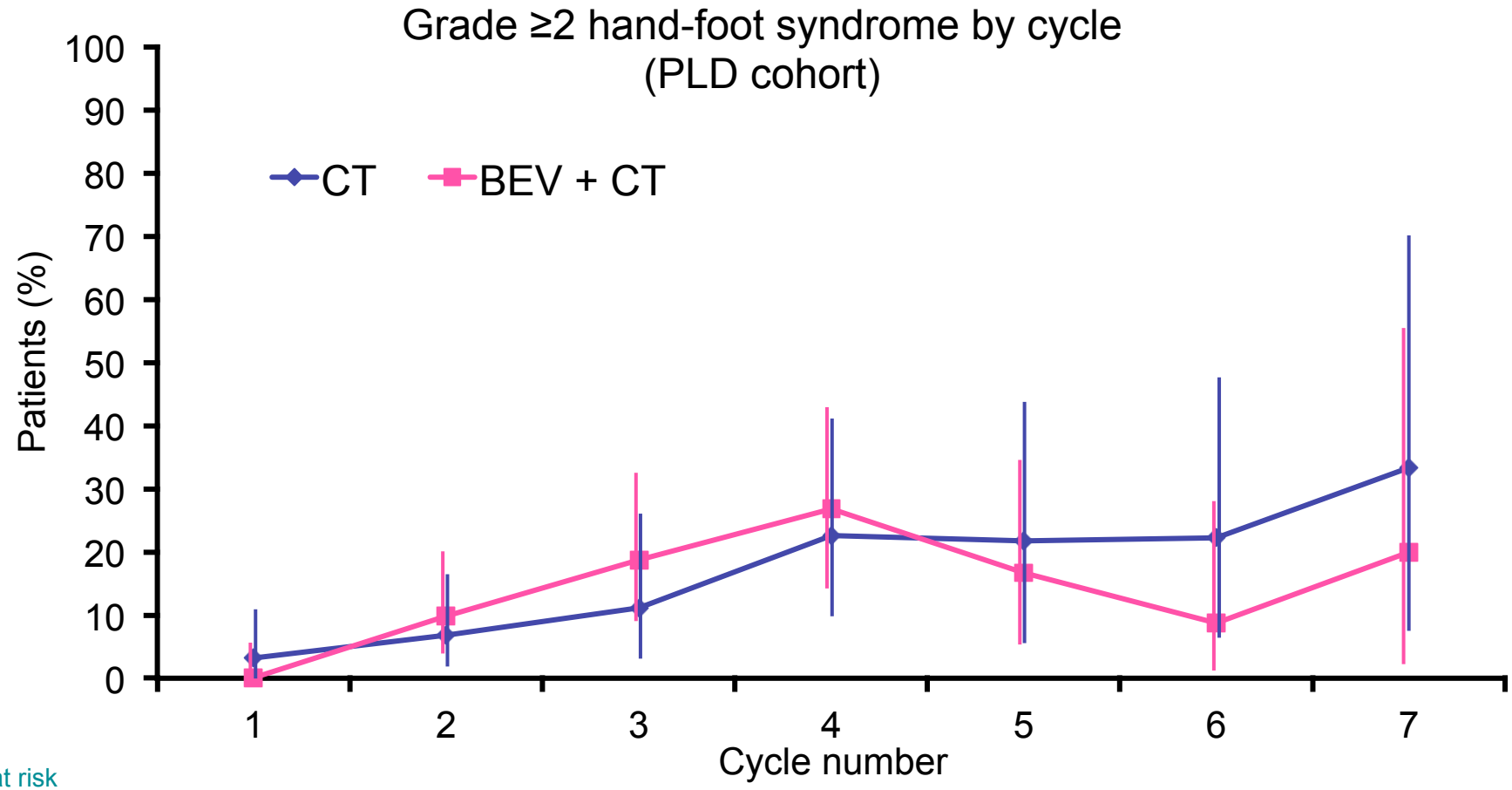
[a]Preferred terms. [b]Includes abdominal pain upper

Higher chemotherapy exposure in the BEV + CT arm than in the CT arm



1 cycle = 4 weeks except for q3w (day 1–5) topotecan

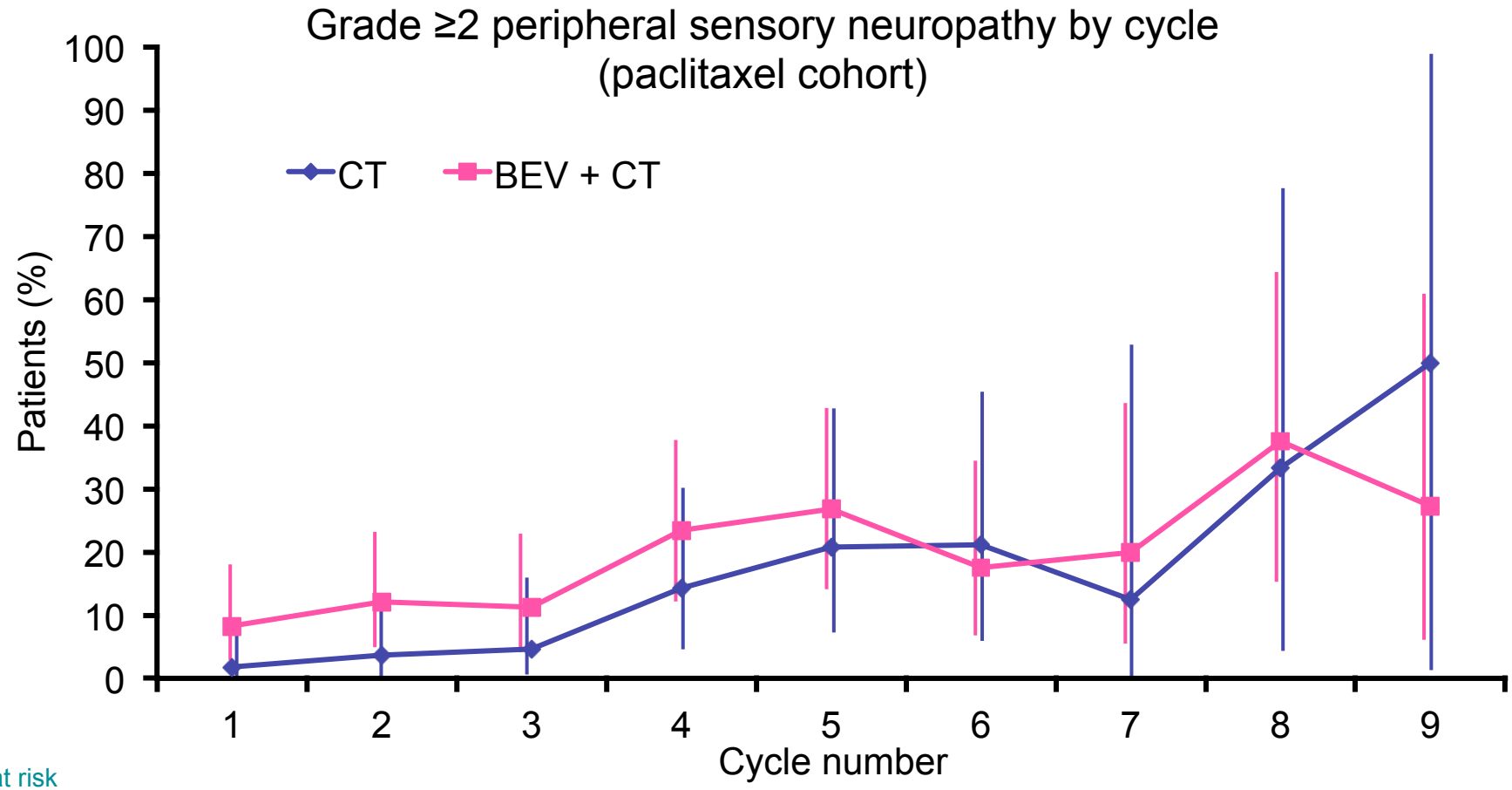
Similar time course of cumulative hand-foot syndrome in the two arms[a]



No. at risk							
CT	63	59	36	31	23	18	9
BEV + CT	62	61	48	41	30	23	10

[a]*Incidence is based on the No. at risk receiving PLD in the respective cycle*
Vertical bars represent 95% Pearson–Clopper confidence intervals
Cycles with <10 patients in each arm not shown

Similar time course of cumulative neuropathy in the two arms[a]



No. at risk									
CT	55	54	43	35	24	19	8	6	2
BEV + CT	60	58	53	47	41	34	20	16	11

[a]Incidence is based on the No. at risk receiving paclitaxel in the respective cycle
Vertical bars represent 95% Pearson–Clopper confidence intervals
Cycles with <10 patients in each arm not shown

Summary

- The primary objective was met
  - PFS HR 0.48 ($p<0.001$) in favor of BEV combination therapy vs single-agent CT
  - Median PFS: 6.7 vs 3.4 months, respectively
- Significant improvement in ORR
  - 30.9% vs 12.6%, respectively ($p=0.001$) by RECIST and/or CA-125
- BEV safety profile consistent with previous experience
  - Patients at high risk of GI perforation were excluded from the study
- Overall survival data expected in 2013

Conclusions

- AURELIA is the first randomized phase III trial in platinum-resistant OC to demonstrate:
  - Benefit with biologic therapy
  - Benefit with a combination regimen versus monotherapy

Bevacizumab combined with chemotherapy should be considered a new standard option in platinum-resistant ovarian cancer

Acknowledgments

The 361 patients and their families, and …

GINECO

E Pujade-Lauraine
I Ray-Coquard
B Weber
D Berton-Rigaud
P Follana
F Selle
M Fabbro
A Lortholary
F Joly
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