

**Case #3—
Recurrent Platinum-Sensitive
Ovarian Cancer**

Gavin Stuart, MD
University of British Columbia
Vancouver, Canada

Recurrent Platinum-Sensitive Ovarian Cancer Case Summary

- **61-year-old women with history of Stage IIIC G3 ovarian cancer**
- **Suboptimal cytoreduction originally**
- **6 courses of paclitaxel and carboplatin**
- **Normal CA125**
- **Clinical, biochemical, and radiographic evidence of recurrence 18 months since completion of chemotherapy**
- **Surgery—no evidence to support at this time**

Secondary Cytoreduction

- **Controversial**
- **Inconsistent definitions**
- **Benefit appears confined to patients like to respond to additional chemo:**
 - >12 month PFI
 - Isolated site of recurrence
 - Disease completely resectable

Which of the Following Systemic Therapies Would You Recommend for this Patient with “Platinum-Sensitive” Recurrence?

- **Retreat with induction regimen-paclitaxel + carboplatin**
- **Pegylated liposomal doxorubicin + carboplatin (as per CALYPSO trial)**
- **Gemcitabine + carboplatin**
- **Trabectedin + pegylated liposomal doxorubicin**
- **Single-agent platinum chemotherapy**
- **A clinical trial with standard chemotherapy + a targeted agent**

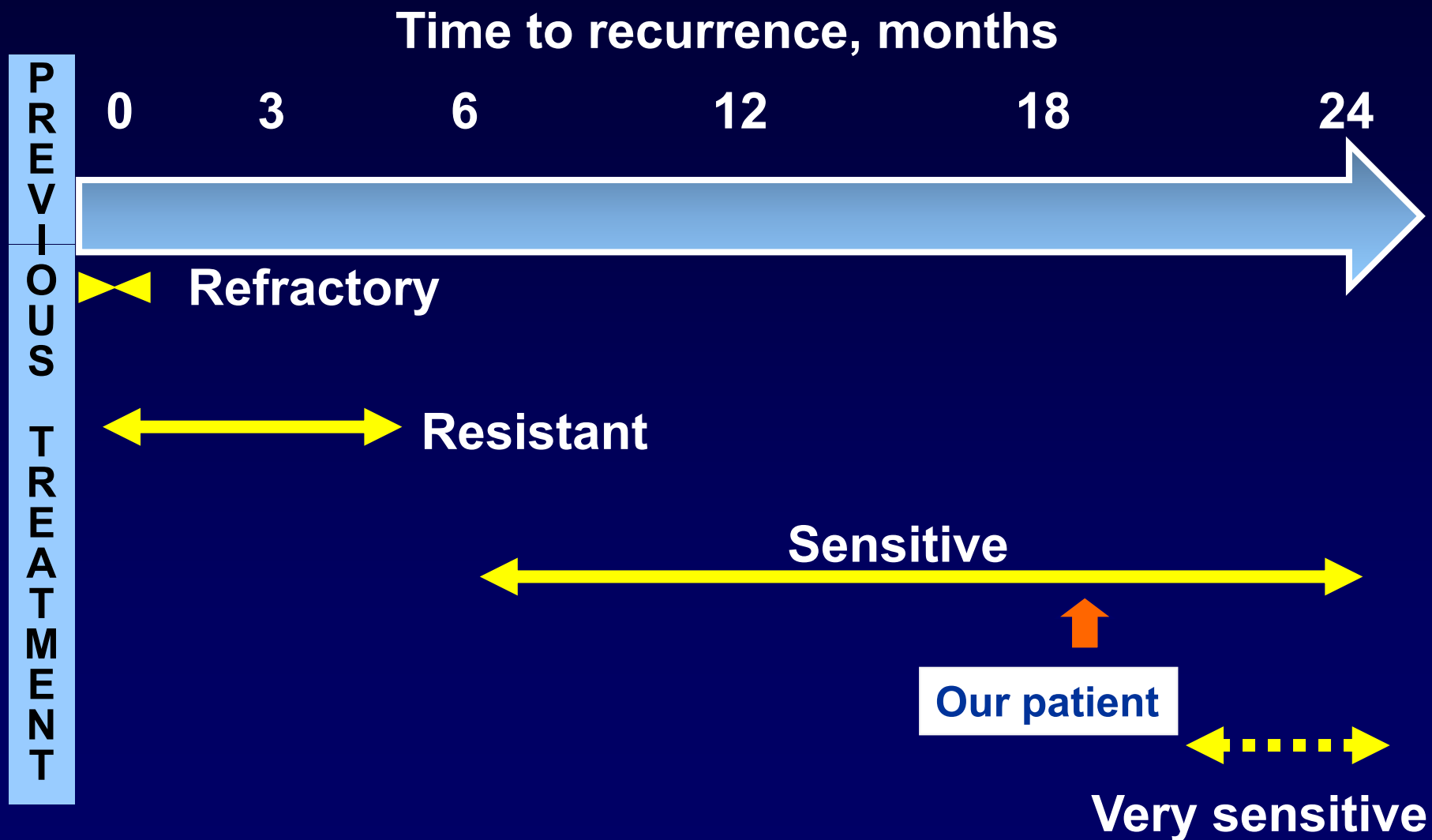
What I Would Recommend?

- **Retreat with induction regimen-paclitaxel + carboplatin**
- Pegylated liposomal doxorubicin + carboplatin (as per CALYPSO trial)
- Gemcitabine + carboplatin
- Trabectedin + pegylated liposomal doxorubicin
- Single-agent platinum chemotherapy
- A clinical trial with standard chemotherapy + a targeted agent

Reasonable Options:

- Retreat with induction regimen-paclitaxel + carboplatin
- **Pegylated liposomal doxorubicin + carboplatin (as per CALYPSO trial)**
- **Gemcitabine + carboplatin**
- Trabectedin + pegylated liposomal doxorubicin
- Single-agent platinum chemotherapy
- A clinical trial with standard chemotherapy + a targeted agent

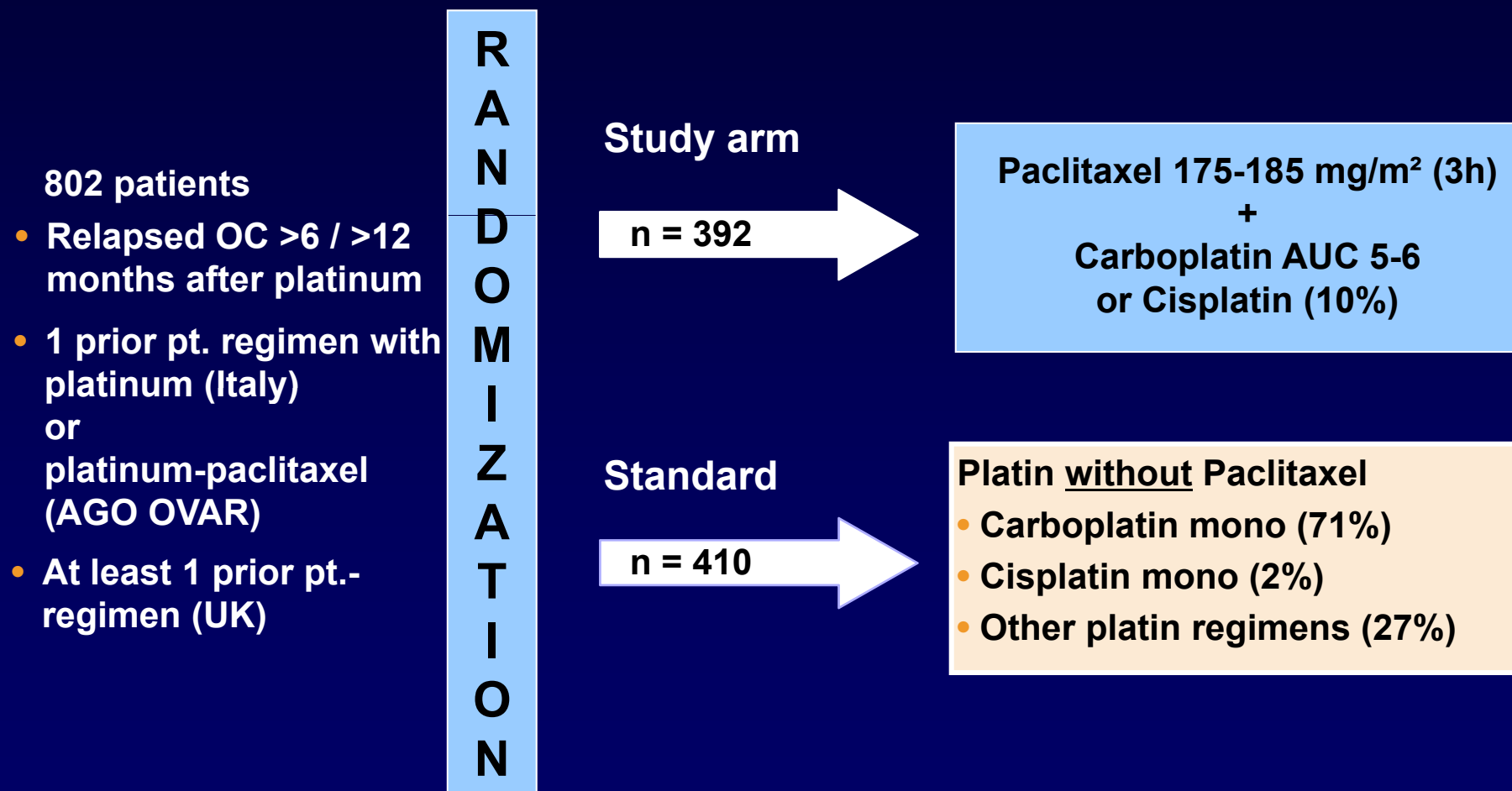
Recurrent Ovarian Cancer— Definition of Disease Sensitivity



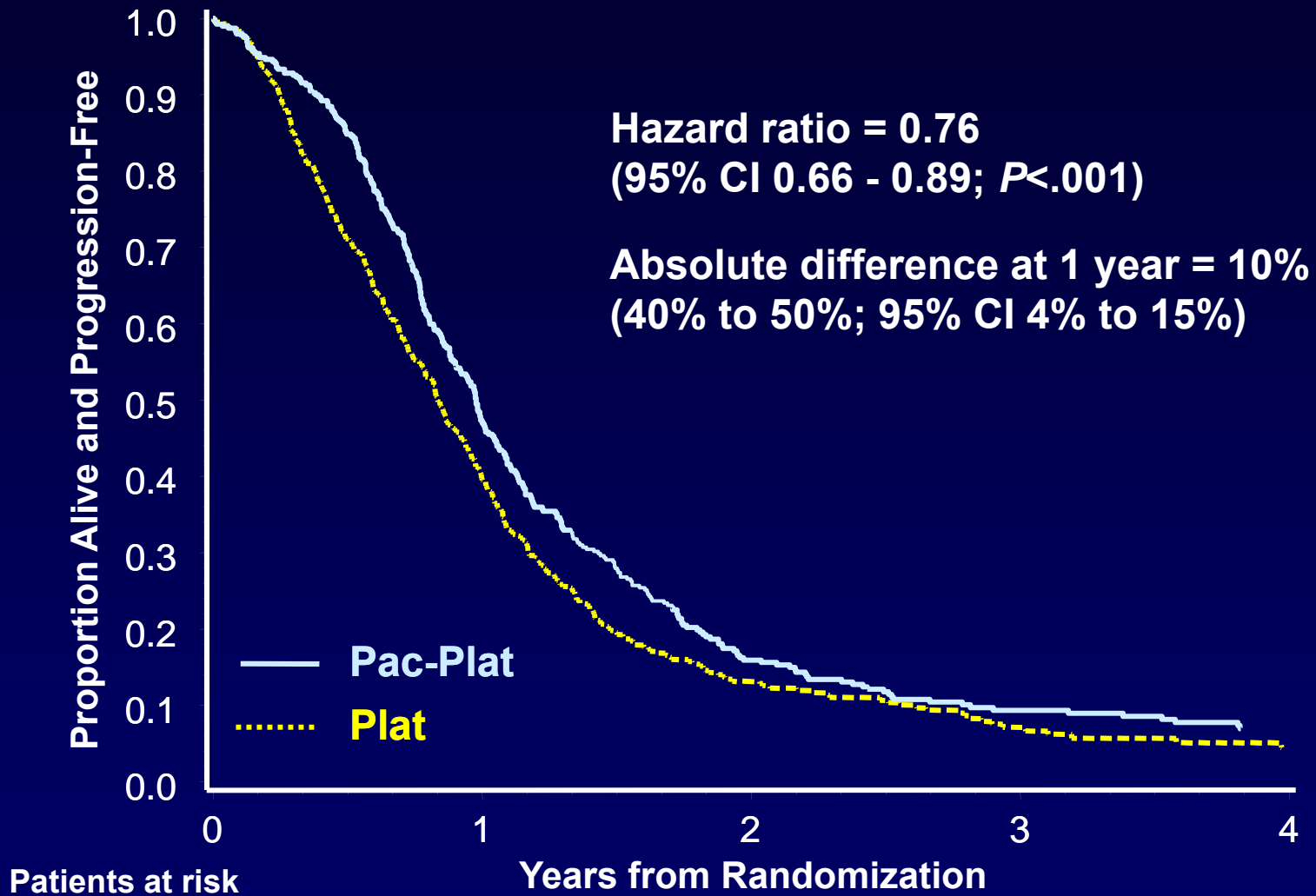
Treatment Selection for Patient With Platinum-Sensitive Disease

- CONSIDER:**
- Patient characteristics
 - PS
 - Comorbidity
 - (Age)
 - Toxicity from prior therapy
 - Neurotoxicity
 - Hematotoxicity
 - Hypersensitivity to previous drug
 - Patient preference
 - Avoid alopecia
 - Ease of administration

ICON4/AGO-OVAR-2.2 Trial: Paclitaxel Plus Platinum–Based Chemotherapy versus Conventional Platinum-Based Chemotherapy in Women with Relapsed Ovarian Cancer

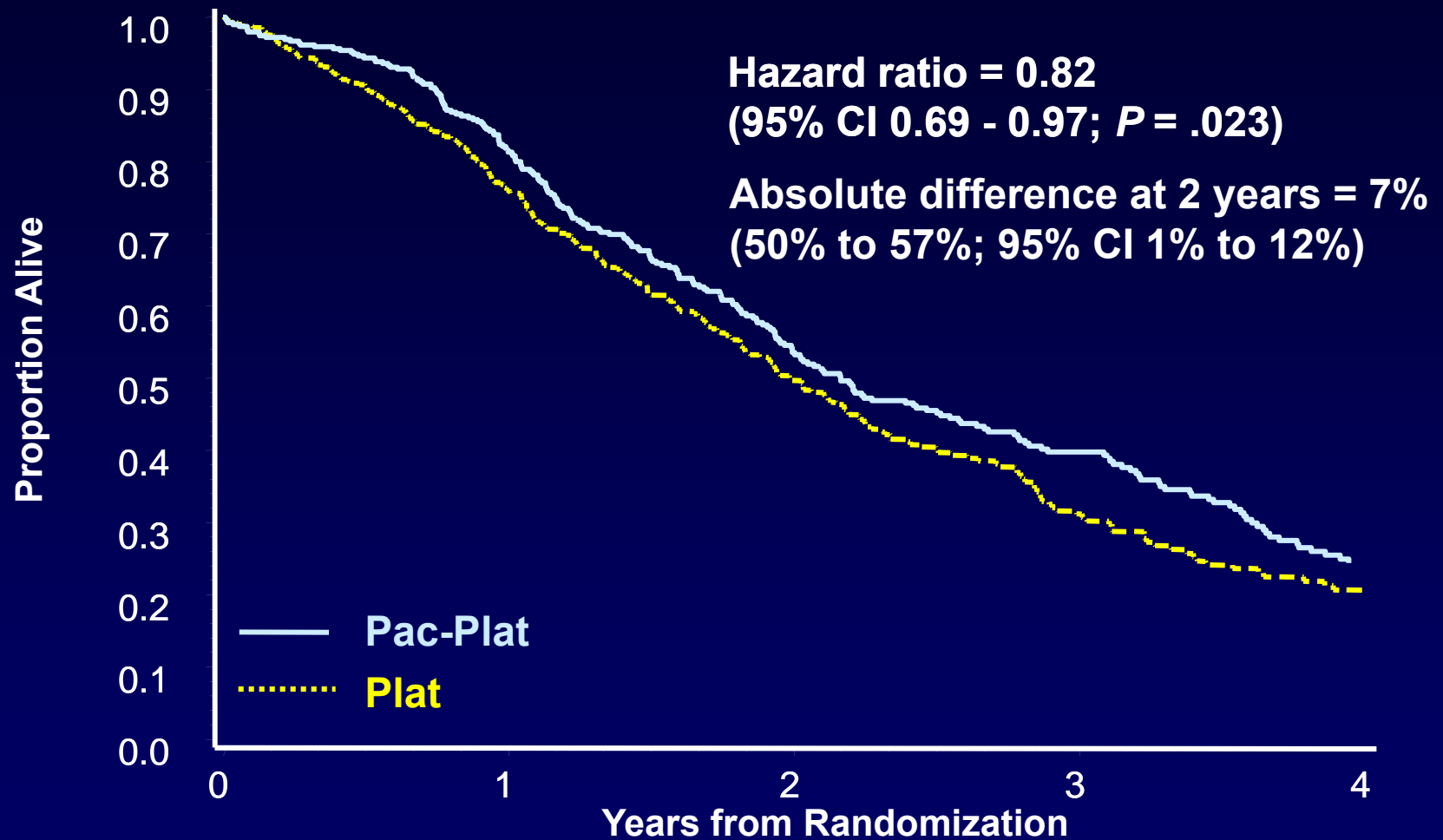


Progression-Free Survival (PFS)



The ICON and AGO Collaborators. *Lancet*. 2003;361(9375):2099-2106.

Overall Survival (OS)



Patients at risk

Pac-Plat	392	306	167	96	43
Plat	410	295	150	68	33

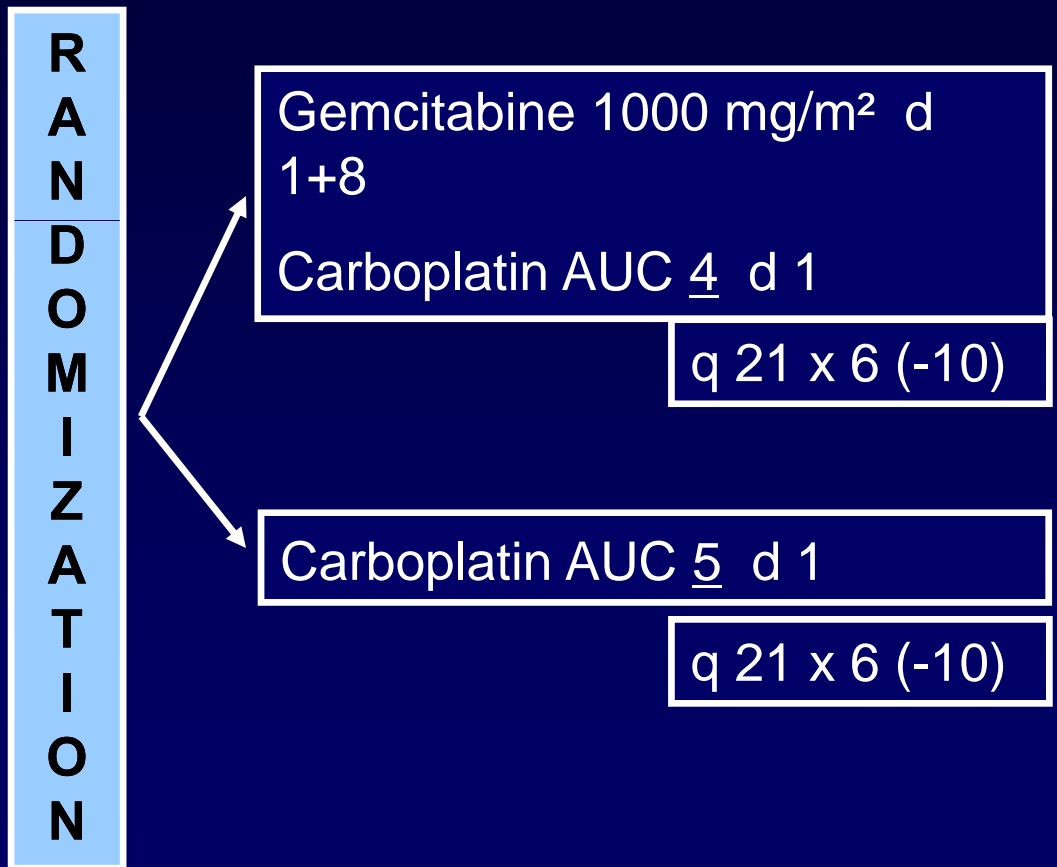
The ICON and AGO Collaborators. *Lancet*. 2003;361(9375):2099-2106.

Moderate or Severe Toxicities

Toxic Effect	Paclitaxel + Platinum (n = 392)	Conventional Platinum Therapy (n = 410)
Neurologic	76 (20%)	4 (1%)
Hematologic	111 (29%)	182 (46%)
Alopecia	322 (86%)	95 (25%)
Nausea + vomiting	131 (35%)	153 (40%)

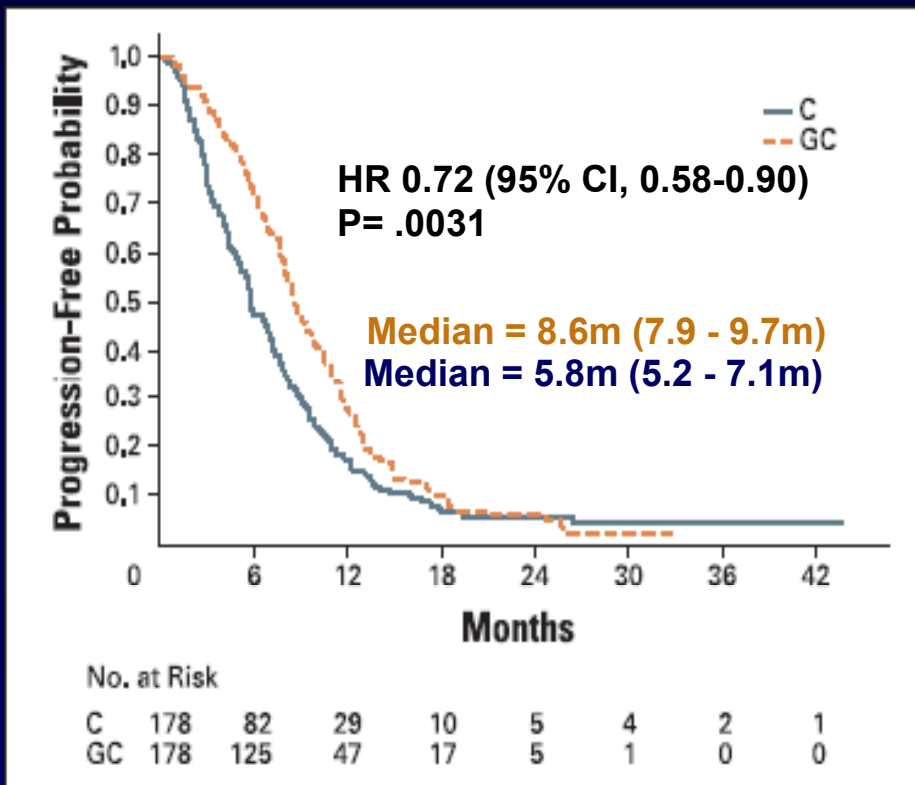
GCIG Trial Gem/Carbo vs. Carbo AGO OVAR – NCIC CTG – EORTC GCG Design

- Recurrent ovarian cancer with at least evaluable disease
- 6+ months after platinum
- Strata:
 - Platinum-free interval (6-12, >12 months)
 - First-line therapy (Plat. +/- Paclitaxel)
 - Measurable disease vs evaluable disease

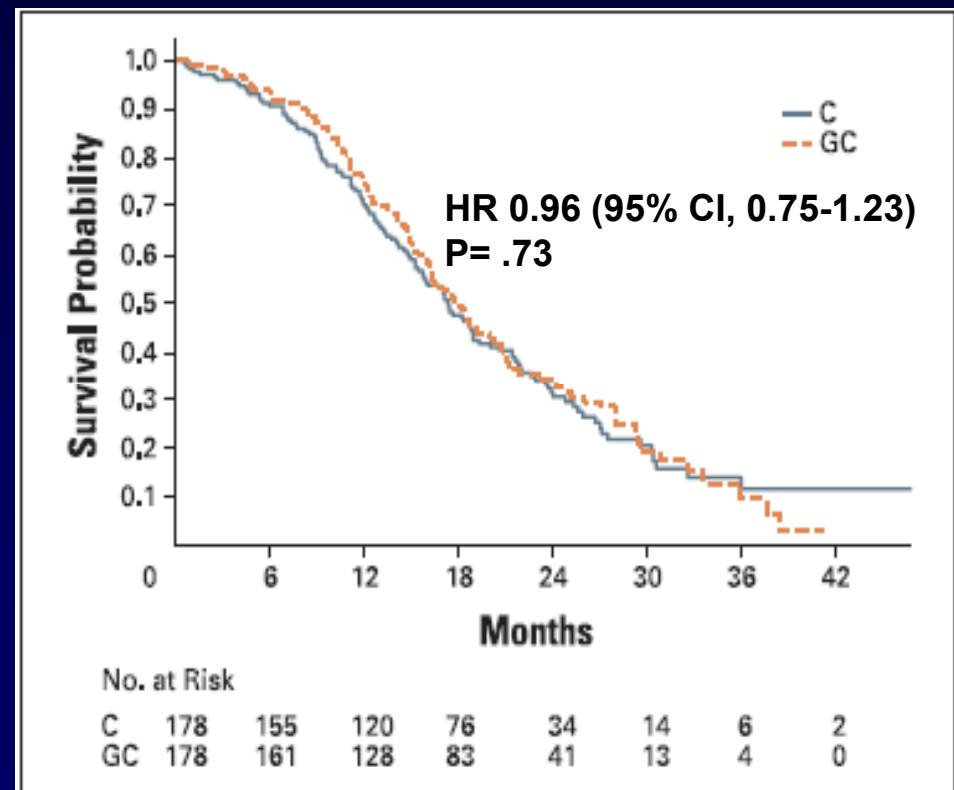


GCIG Trial Gem/Carbo vs Carbo AGO OVAR – NCIC CTG – EORTC GCG PFS and OS by Therapy

PROGRESSION-FREE SURVIVAL



OVERALL SURVIVAL



GCIG Trial Gem/Carbo vs Carbo Hematologic Toxicity

	Gem/Carbo	Carbo	P Value
Grade 3 + 4 (% of patients)	78.3	24.7	<.001
Anemia	27.4	8.0	<.001
Thombocytopenia	34.9	11.5	<.001
Neutropenia	70.3	12.1	<.001
Febrile neutropenia	1.1	0.0	NS
Infection	0.6	0.6	NS
G(M)-CSF	23.6	10.1	<.001
Parenteral antibiotics	8.4	5.1	NS
RBC	27.0	6.7	<.001

CALYPSO Study Schema

International, Intergroup, Open-Label, Randomized Phase III Study

Ovarian cancer in late relapse (>6 months) after first-line or second-line platinum-based therapy (previous taxane required)

Stratification:

- Therapy-free interval (6-12 months vs >12 months)
- Measurable disease (yes vs no)
- Center

R
A
N
D
O
M
I
Z
E

Experimental arm: CD

PLD 30 mg/m² IV d 1

Carboplatin AUC 5 d 1

Q 28 days x 6 courses*

Control arm: CP

Paclitaxel 175 mg/m² IV d 1

Carboplatin AUC 5 d 1

Q 21 days x 6 courses*

*Or progression in patients with SD or PR

Baseline Characteristics (1)

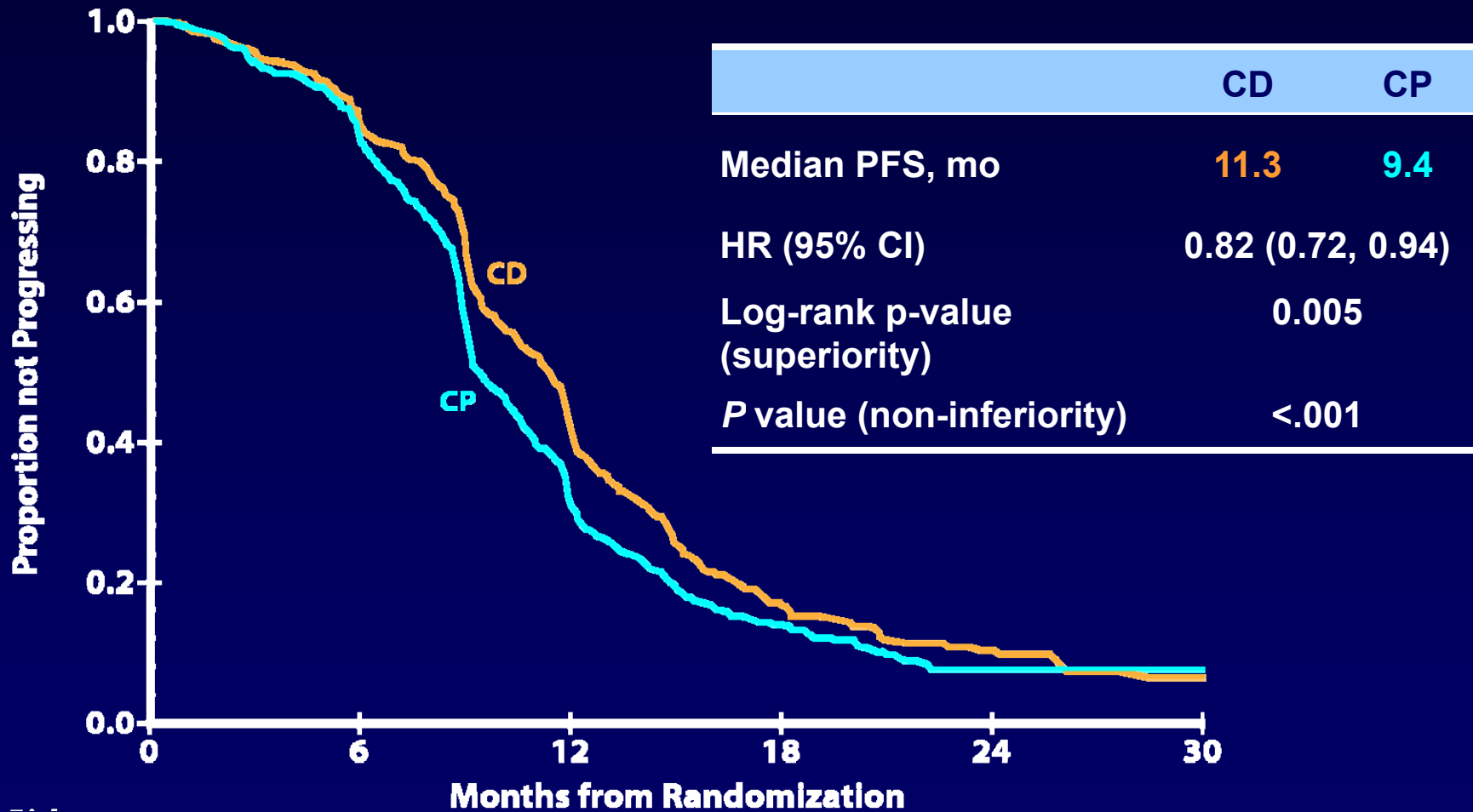
Characteristic	CD (n = 466)	CP (n = 508)
	Number of Patients (%)	
Age, median	60.5	61.0
ECOG performance status*		
0	286 (61)	317 (62)
1	159 (34)	164 (32)
2	13 (3)	15 (3)
Primary site of disease		
Ovarian	415 (89)	451 (89)
Papillary/serous histology	334 (72)	366 (72)
Initial FIGO stage*		
I/II	52 (11)	59 (12)
III/IV	401 (86)	427 (84)
Number of previous lines		
One	408 (88)	421 (83)
Two	58 (12)	87 (17)

* Missing values to attain 100%.

Baseline Characteristics (2)

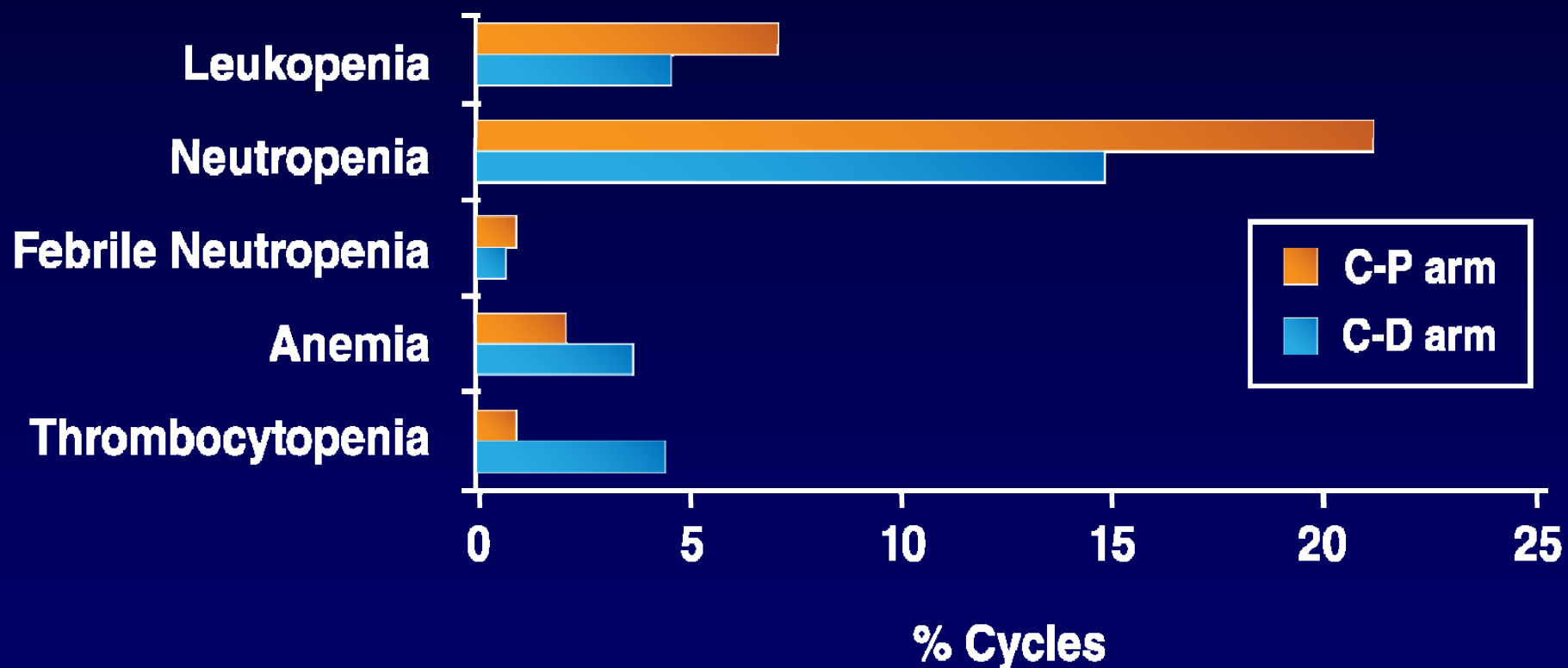
Characteristic	CD (n = 466)	CP (n = 508)
	Number of Patients (%)	
Prior taxane	462 (99)	500 (99)
Interval since prior therapy, median		
6-12 months	162 (35)	182 (36)
>12 months	304 (65)	326 (64)
Measurable disease		
Yes	281 (60)	321 (63)
No	185 (39)	188 (37)
Tumor size		
<5 cm	377 (81)	419 (82)
≥5 cm	89 (19)	90 (18)
Number of sites		
1	217 (47)	245 (48)
>1	249 (53)	264 (52)

CALYPSO: Progression-Free Survival (ITT)



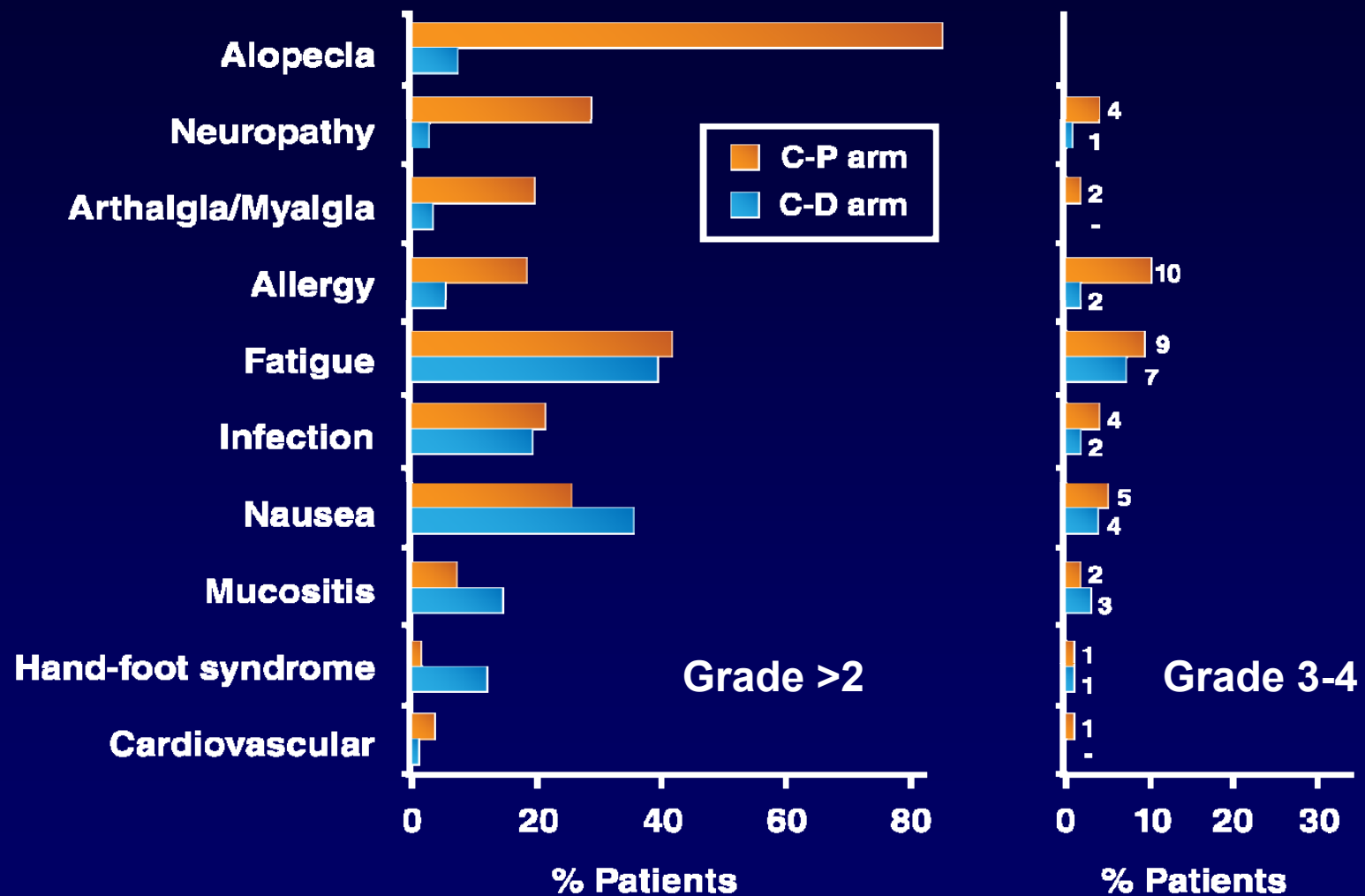
Pujade-Lauraine E, et al. *J Clin Oncol*. 2009;27(18S): Abstract LBA5509.

CALYPSO: Grade 3-4 Hematologic Toxicities



Pujade-Lauraine E, et al. *J Clin Oncol*. 2009;27(18S): Abstract LBA5509.

CALYPSO: Major Nonhematologic Toxicities

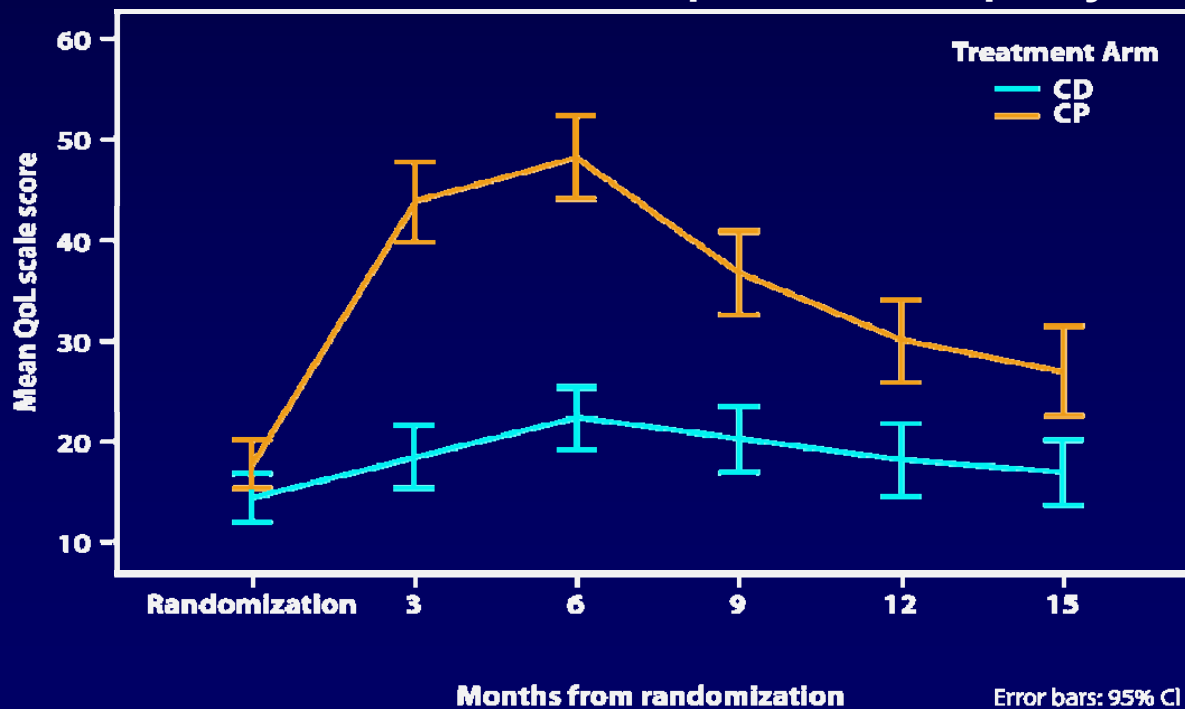


Long-Lasting Neurotoxicity

	CD (n = 466)		CP (n = 501)	
	Grade 2	Grade 3/5	Grade 2	Grade 3/5
Neuropathy*	4%	1%	24%	4%

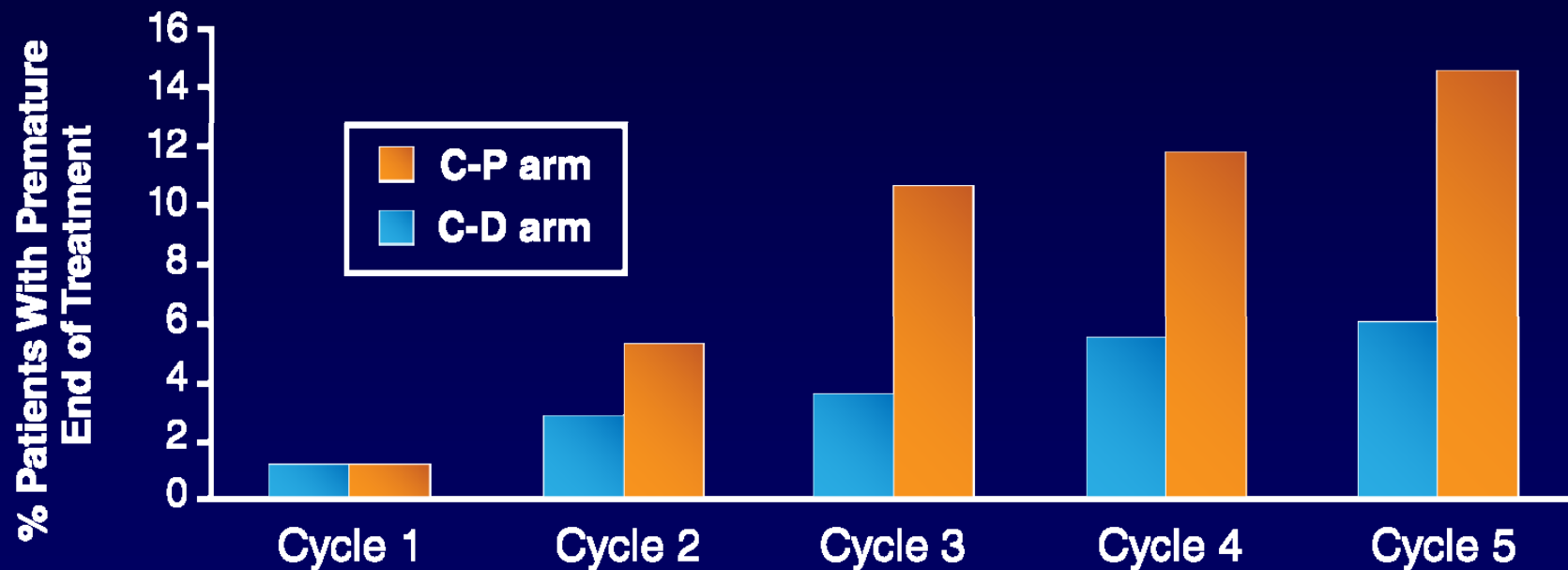
EORTC OV28 – QoL Peripheral Neuropathy

*P<.001



Neuropathy score over time

CALYPSO: Premature End of Treatment Due to Toxicity (< Cycle 6)

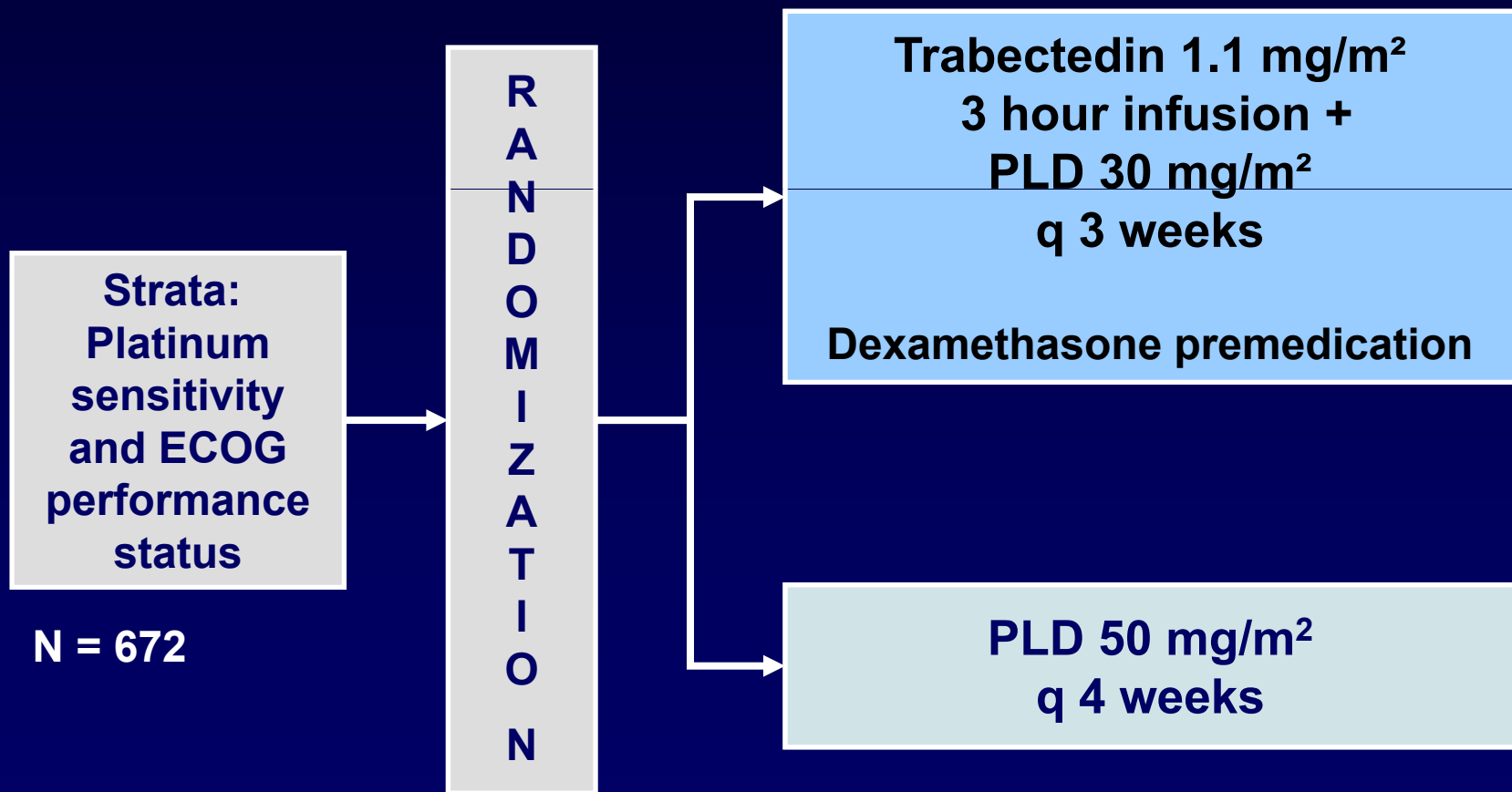


Pujade-Lauraine E, et al. *J Clin Oncol*. 2009;27(18S): Abstract LBA5509.

Platinum-Based Combination Therapies in Platinum Sensitive Recurrent Ovarian Cancer

Paclitaxel + Carboplatin	Gemcitabin + Carboplatin	Pegylated Liposomal Doxorubicin + Carboplatin
Effective (PFS, OS)	Effective (PFS)	Effective (PFS) Superior PFS to Carboplatin/Paclitaxel
Schedule: d1 q 3 w	Schedule: d1 u. 8 q 3 w	Schedule: d1 q 4 w
Neurotoxicity	Hematological Toxicity	Hand Foot Sy (11%)
Alopecia 86%	Alopecia 15%	Alopecia 7%
QoL no worsening	QoL no worsening	QoL data pending

ET743-OVA-301: Randomized Phase III Study of Pegylated Liposomal Doxorubicin (PLD) plus Trabectedin with PLD Alone in Advanced Relapsed Ovarian Cancer



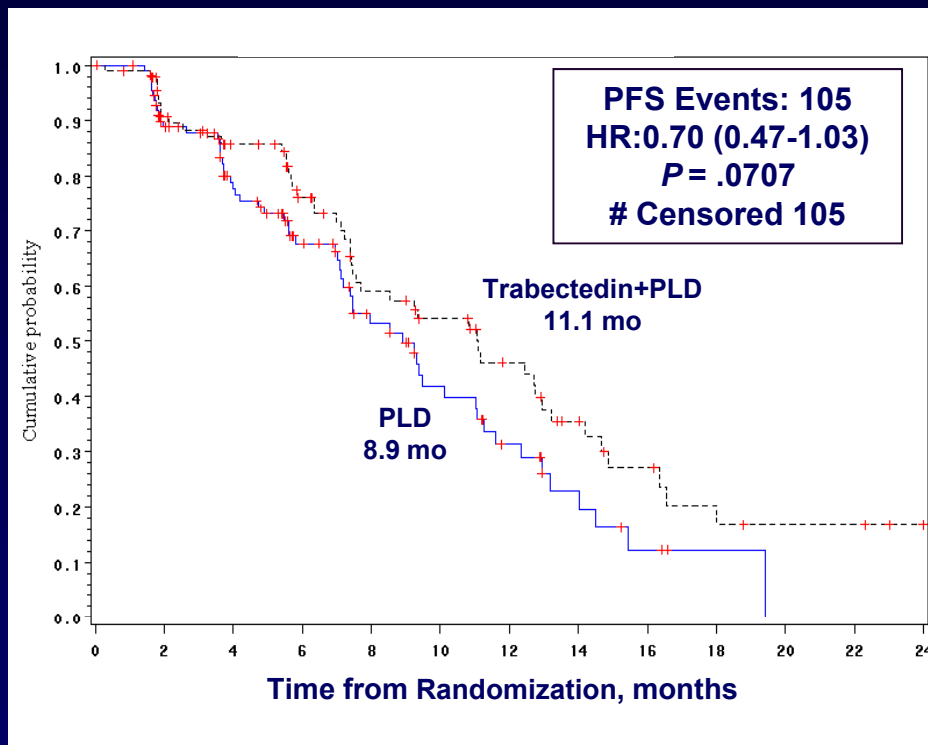
OVA-301

	Trab/PLD	PLD
RR	28%	19%
PFS months	7.3	5.8
Interim OS*	20.5	19.4
<hr/>		
G3/4 Neutro	63%	22%
ALT	31%	1%
HFS	4%	20%
<hr/>		

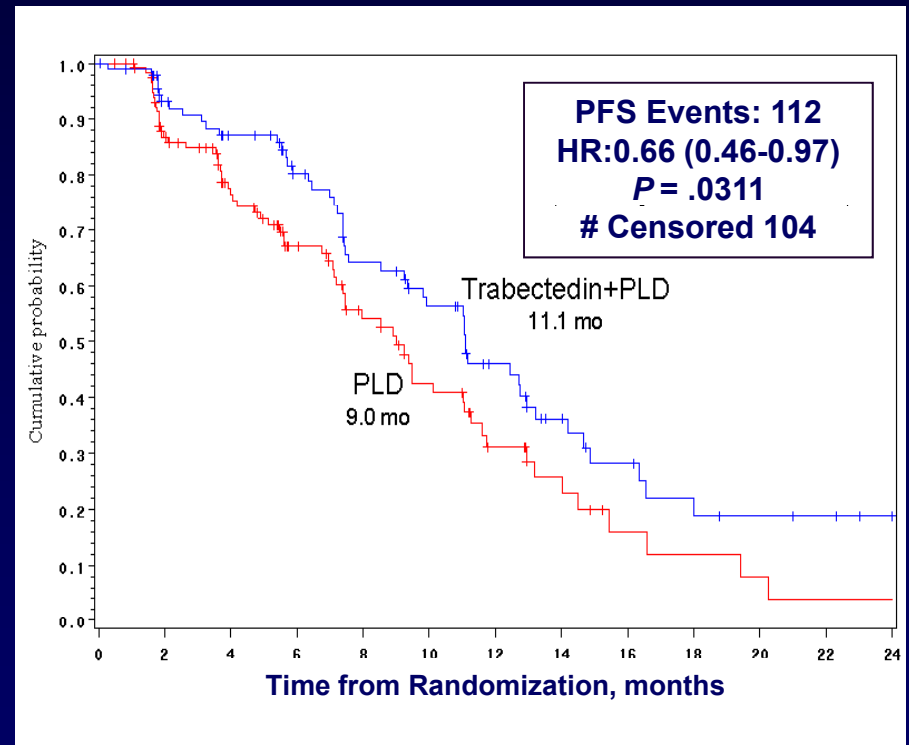
Monk BJ, et al. *Ann Oncol*. 2008;19(Suppl 8): Abstract LBA4.

OVA-301: PFS—Highly Sensitive (PFI >12 months)

Independent Radiology Review (n = 210)



Independent Oncology Review (n = 216)



A Clinical Trial with Standard Chemotherapy + a Targeted Agent

- **Reasonable alternative if there is no indication of response to standard second-line therapy**
- **Bevacizumab**
- **BIBF 1120**
- **PARP inhibitors**

GOG 213: Current Second-Line GOG Trial

Recurrent Ovarian and Peritoneal Cancer
TFI > 6 months

Surgical Candidate?

Yes

Randomize

Surgery

No Surgery

To Chemotherapy
Randomization

No

Randomize

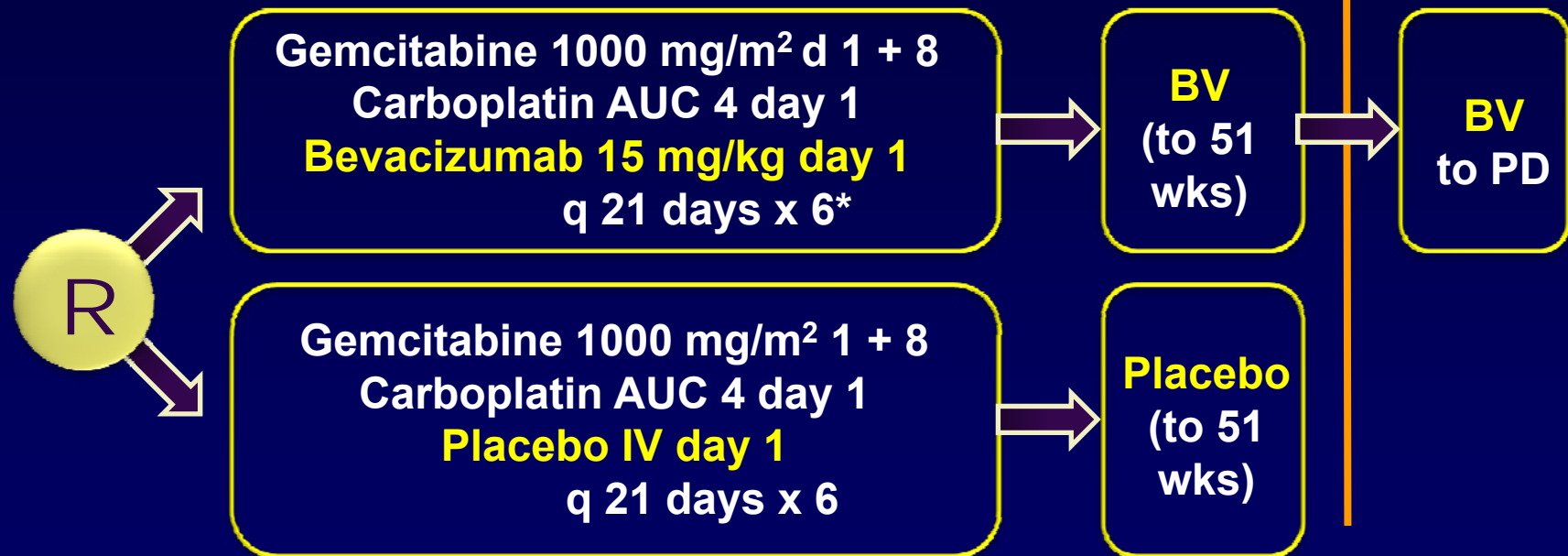
Carboplatin
Paclitaxel

Carboplatin
Paclitaxel
Bevacizumab

Maintenance
Bevacizumab

OCEANS Trial: Study of Carboplatin + Gemcitabine ± Bevacizumab in Patients with Platinum-Sensitive Cancer

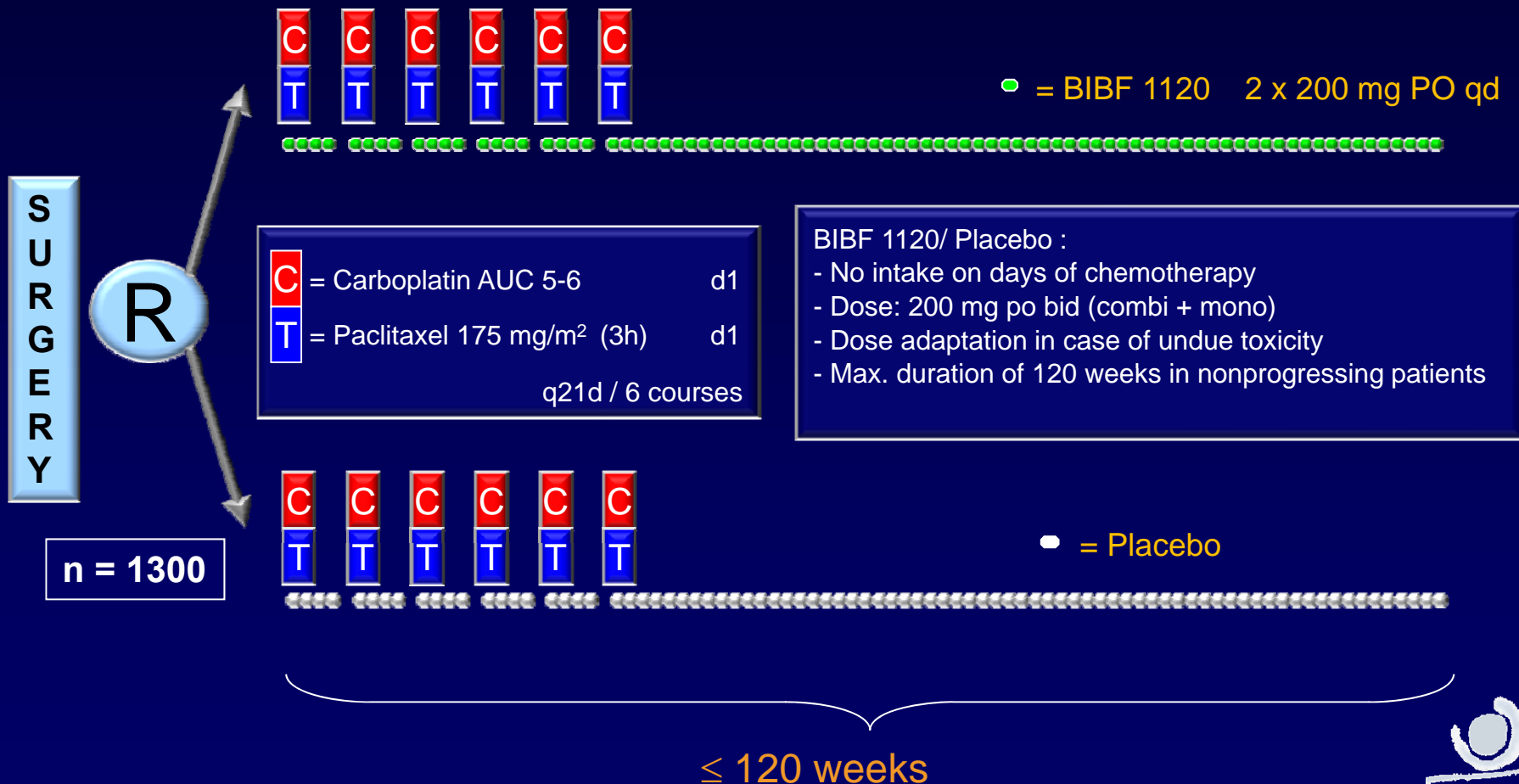
Memorial Sloan-Kettering US [Protocol 07-078]



*Up to 10 cycles allowed

Unblind

AGO-OVAR12: Multicenter Phase III trial of BIBF 1120 in Combination with Standard Treatment of Carboplatin and Paclitaxel Compared to Placebo plus Carboplatin and Paclitaxel in Patients with Advanced Ovarian Cancer



Conclusions

- **The goals of therapy for patients with recurrent ovarian cancer are to improve QOL and extend survival**
- **Platinum-containing combination chemotherapy improves response and survival as compared with single-agent; thus in the absence of contraindications, rechallenge with carboplatin in combination is recommended**
- **The therapeutic index observed with carboplatin-PLD in comparison to carboplatin-paclitaxel suggests that carboplatin-PLD is a preferred alternative**
- **Nonplatinum combination of trabectedin and PLD may be a reasonable alternative for selected patients**
- **Targeted agents in combination with chemotherapy are under investigation**