Treatment of Advanced Ovarian Cancer: Guideline Recommendations and Unmet Needs

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GYNECOLOGIC CANCER INTERGROUP

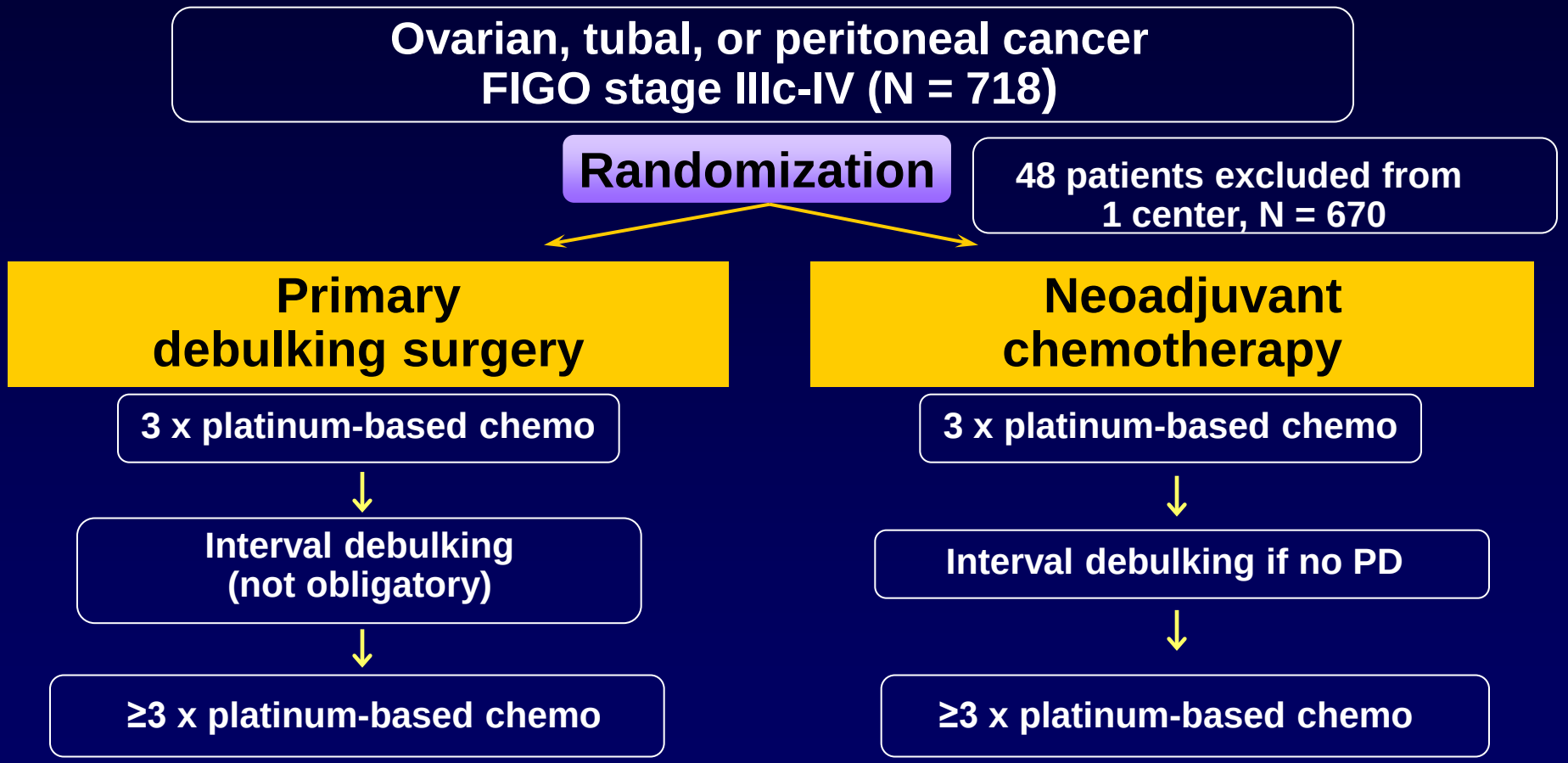
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

4th Ovarian Cancer Consensus Conference
June 25-27, 2010, Vancouver

A5: What Role Does Surgery Play Today at Diagnosis?

- **Surgical staging** should be mandatory and should be performed by a gynecologic oncologist.
- The ultimate goal is cytoreduction to **microscopic disease**. There is evidence that reduction to ≤1 cm macroscopic disease is associated with some benefit. The term "**optimal**" cytoreduction should be reserved for those with no macroscopic residual disease.
- Delayed primary surgery following **neoadjuvant chemotherapy** is an option for selected patients with stage IIIC and IV ovarian cancer as included in EORTC 55971.

Randomized EORTC-GCG/NCIC-CTG Trial on NACT + IDS vs PDS

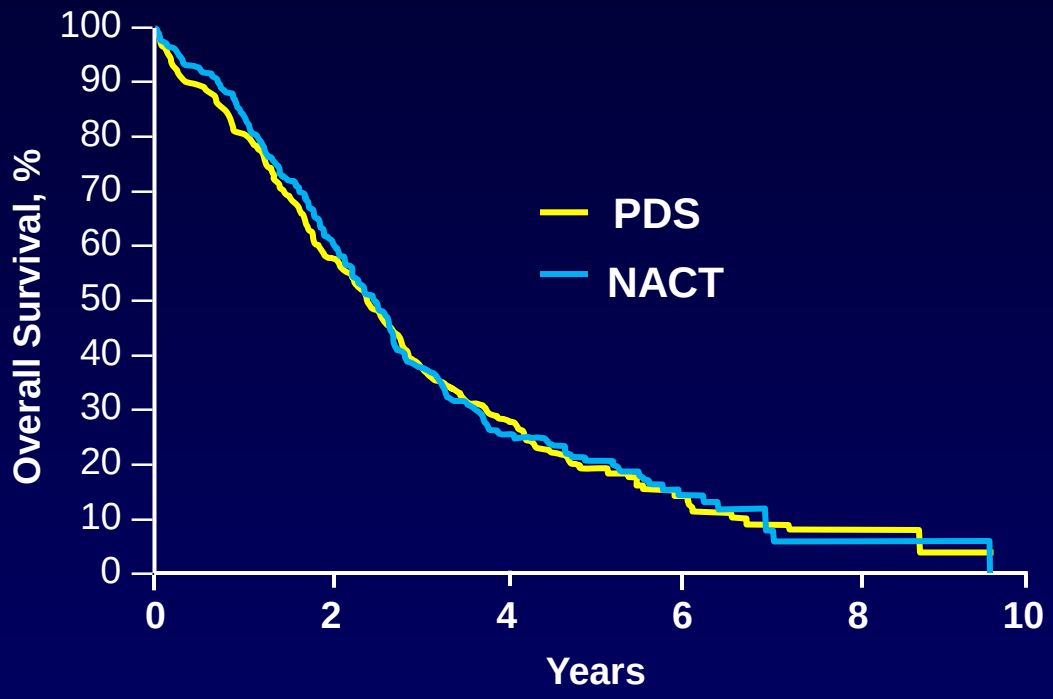


Primary endpoint: Overall survival
Secondary endpoints: Progression-free survival, quality of life, complications

NACT, Neoadjuvant chemotherapy; IDS, Interval debulking surgery; PDS, Primary debulking surgery

Vergote I, et al. *N Engl J Med.* 2010;363(10):943-953.

EORTC: NACT + IDS vs PDS: ITT Overall Survival



Median survival

PDS: 29 months

IDS: 30 months

HR for IDS: 0.98

(0.84, 1.13)

No. of Events						
PDS	253	336	189	62	14	2
NACT	245	334	195	46	13	2

PDS, Primary debulking surgery; NACT, Neoadjuvant chemotherapy

Vergote I, et al. *N Engl J Med.* 2010;363(10):943-953.

Primary Debulking or Neoadjuvant Chemotherapy in Ovarian Carcinoma: Conclusions (1)

- Only patients with (preferentially) biopsy-proven **stage IIIc or IV** are eventually candidates for neoadjuvant chemotherapy.
- Patients with stage **IIIc and metastases <5cm** are generally better treated with primary debulking.
- Patients with **stage IV** disease are generally better treated with neoadjuvant chemotherapy.
- Interval debulking should be planned **after 3 courses** of chemotherapy.

Primary Debulking or Neoadjuvant Chemotherapy in Ovarian Carcinoma: Conclusions (2)

- **No residual tumor is the only goal of debulking surgery. We should never be satisfied with a residual tumor of 1-10 mm, nor call this "optimal"!**
- **In order to select patients for neoadjuvant chemotherapy or primary debulking, laparoscopy, and if available whole body-diffusion +T2 MRI (or PET-CT) are the best tools…**

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A3: Is the 2004 GCIG Recommended Standard Comparator Arm Still Valid?

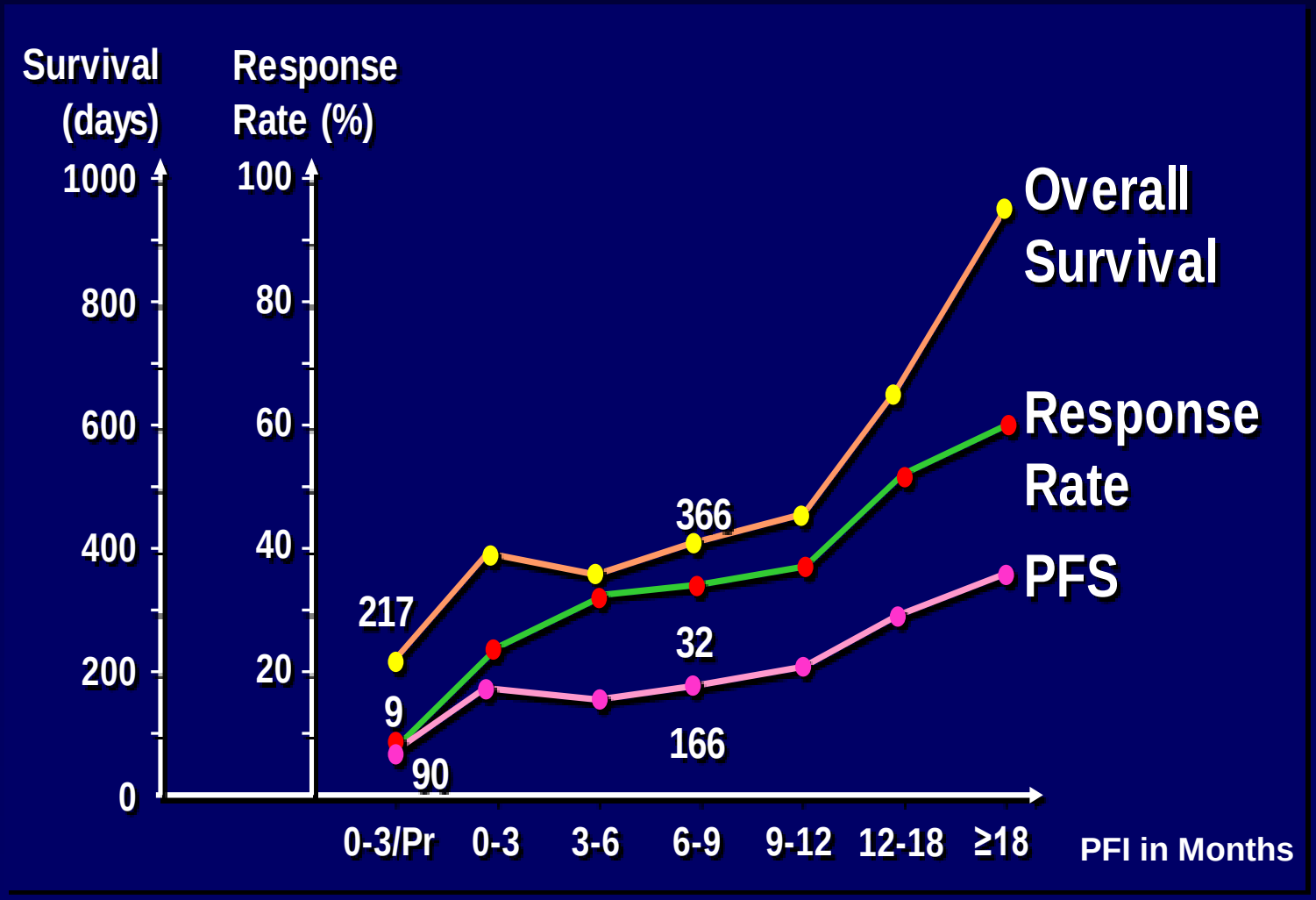
- The standard arm must contain a **taxane and a platinum** agent administered for six cycles. The recommended regimen is paclitaxel (175 mg/m^2) and carboplatin (AUC 5-6) intravenously every 3 weeks.
- Two specific approaches, the alteration of **dose/schedule** and the use of **intraperitoneal** therapy, have been shown to be superior in at least one trial.
- **Bevacizumab** could be incorporated in the control arm of a randomized trial, as a consequence of the results of a trial with bevacizumab that met its primary endpoint.

Recurrent Ovarian Cancer: GCIG Definition

	Treatment-Free Interval (From Last Dose of Platin)
Platinum sensitive	>12 months
Platinum partially sensitive	6-12 months
Platinum resistant	<6 months
Platinum refractory	<4 weeks

Friedlander M, et al. *Int J Gynecol Cancer*. 2011;21(4):771-775.

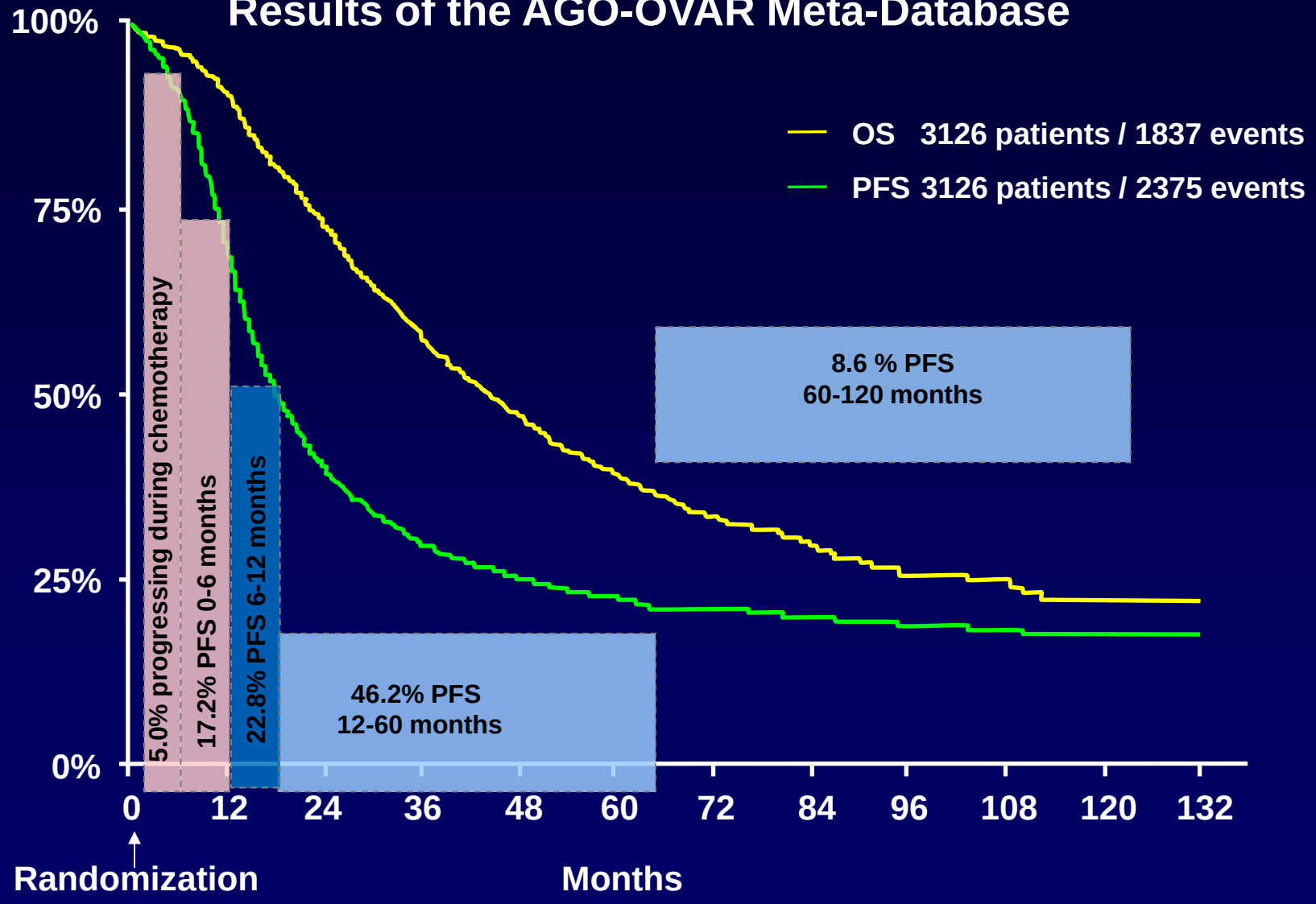
Relevance of Different Types of Recurrences With Respect to Further Therapy



Pujade-Lauraine E, et al. *Proc Am Soc Clin Oncol.* 2002;21: Abstract 829.

PFS and OS After Start of First-Line Chemotherapy

Results of the AGO-OVAR Meta-Database



du Bois A, et al. *Cancer*. 2009;115(6):1234-1244.

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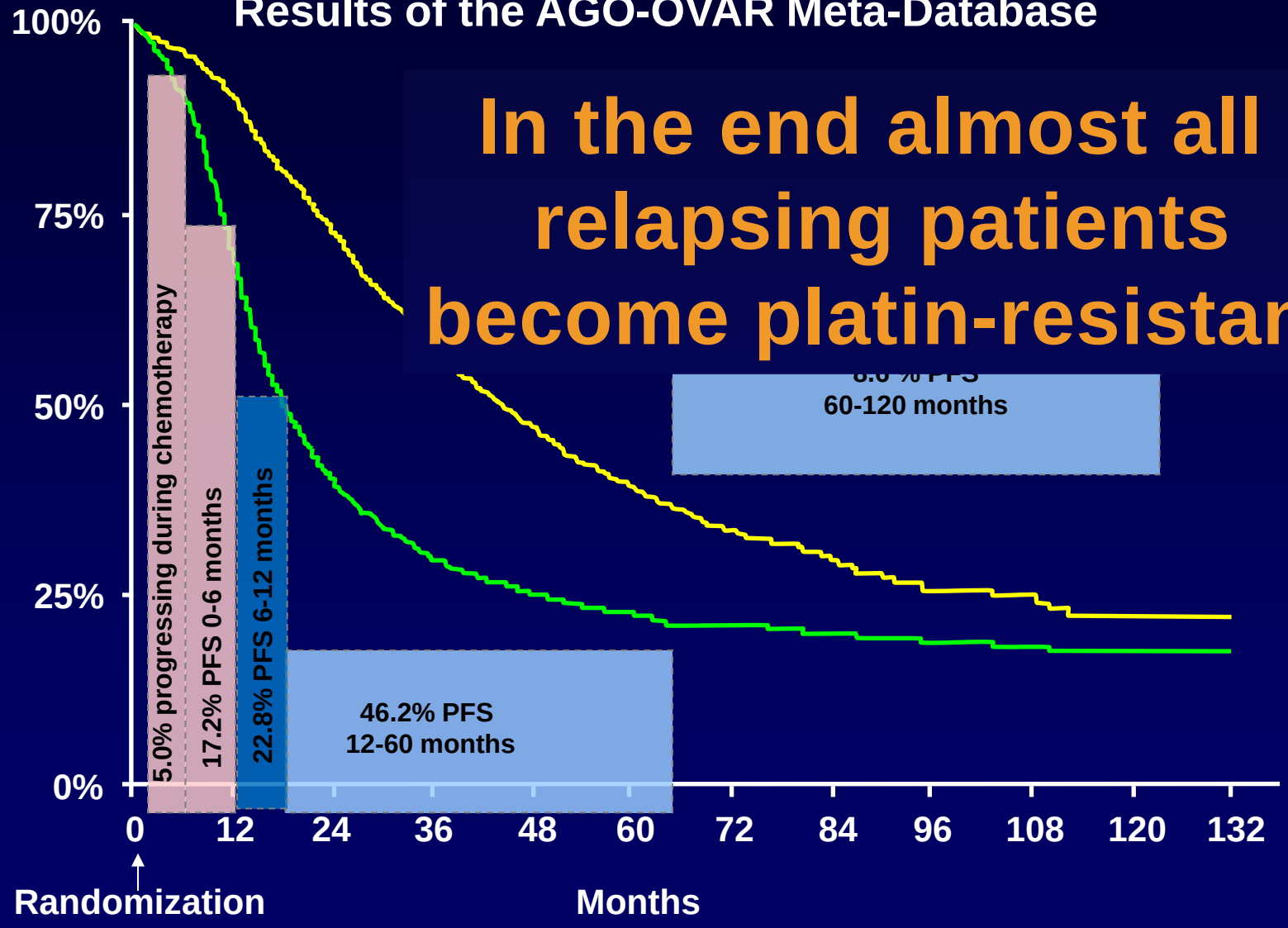

In the end almost all relapsing patients become platin-resistant

du Bois A, et al. *Cancer*. 2009;115(6):1234-1244.

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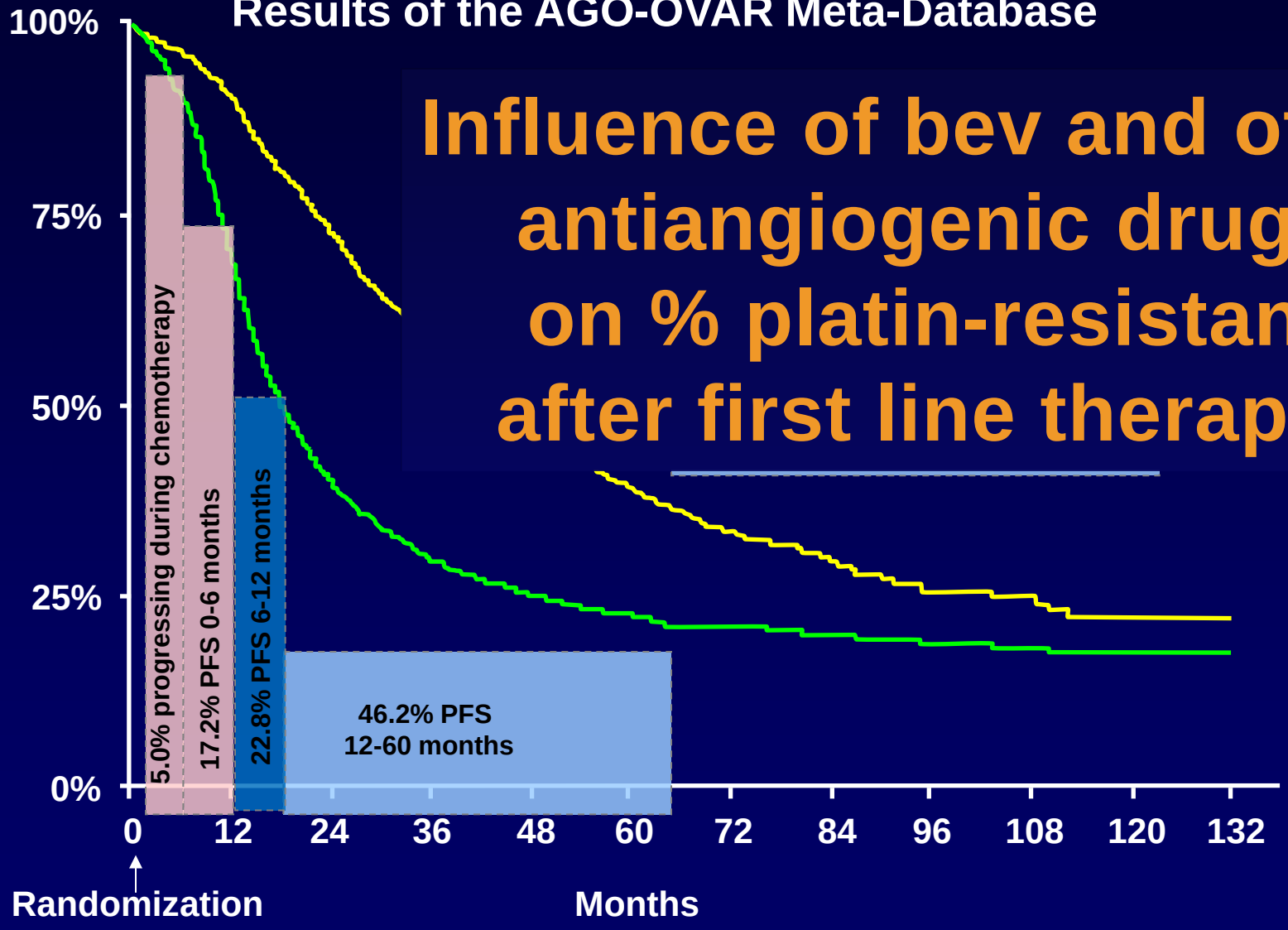
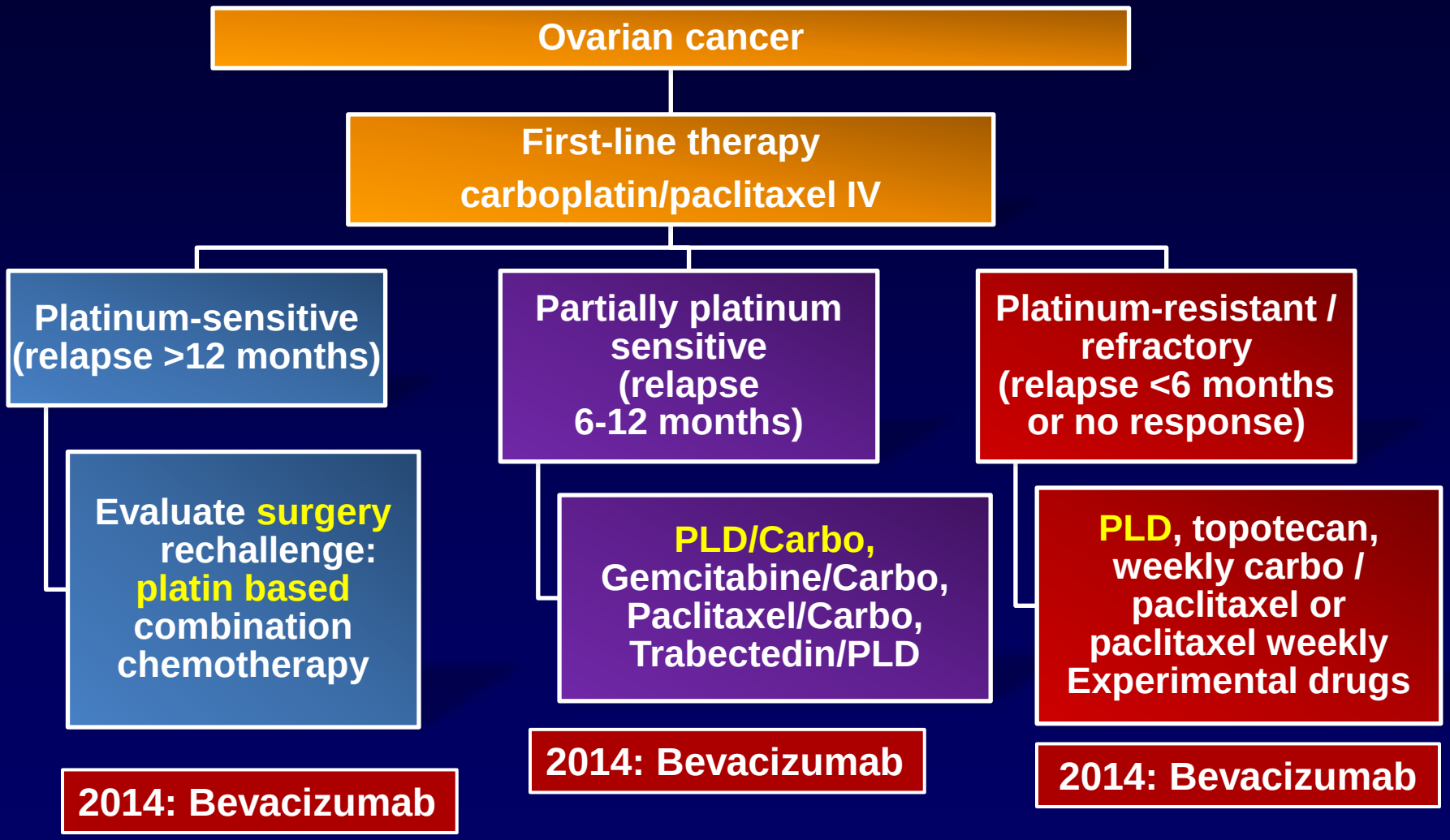


Influence of bev and other antiangiogenic drugs on % platin-resistant after first line therapy!

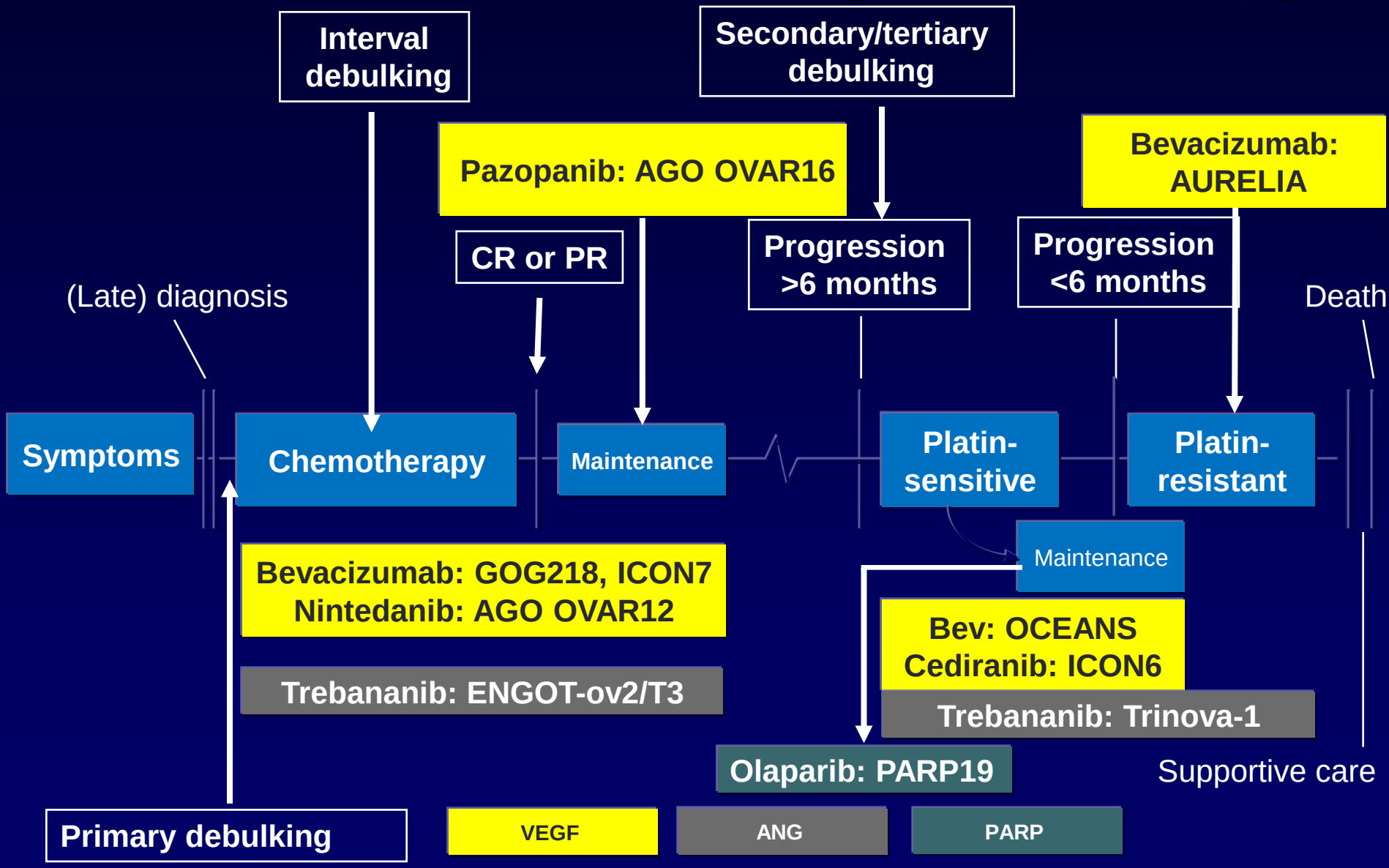
du Bois A, et al. *Cancer*. 2009;115(6):1234-1244.

Ovarian Cancer Recurrence Treatment Algorithm



Vergote I, et al. 2010 College of Oncology National Clinical Guidelines: Ovarian Cancer (Belgium). Available at: www.collegeoncologie.be/files/files/Ovarian_Cancer_V1.2010_(EN).pdf. Accessed: 2014 September 26.

Ovarian Carcinoma: Reported Randomized Trials Targeted Therapy



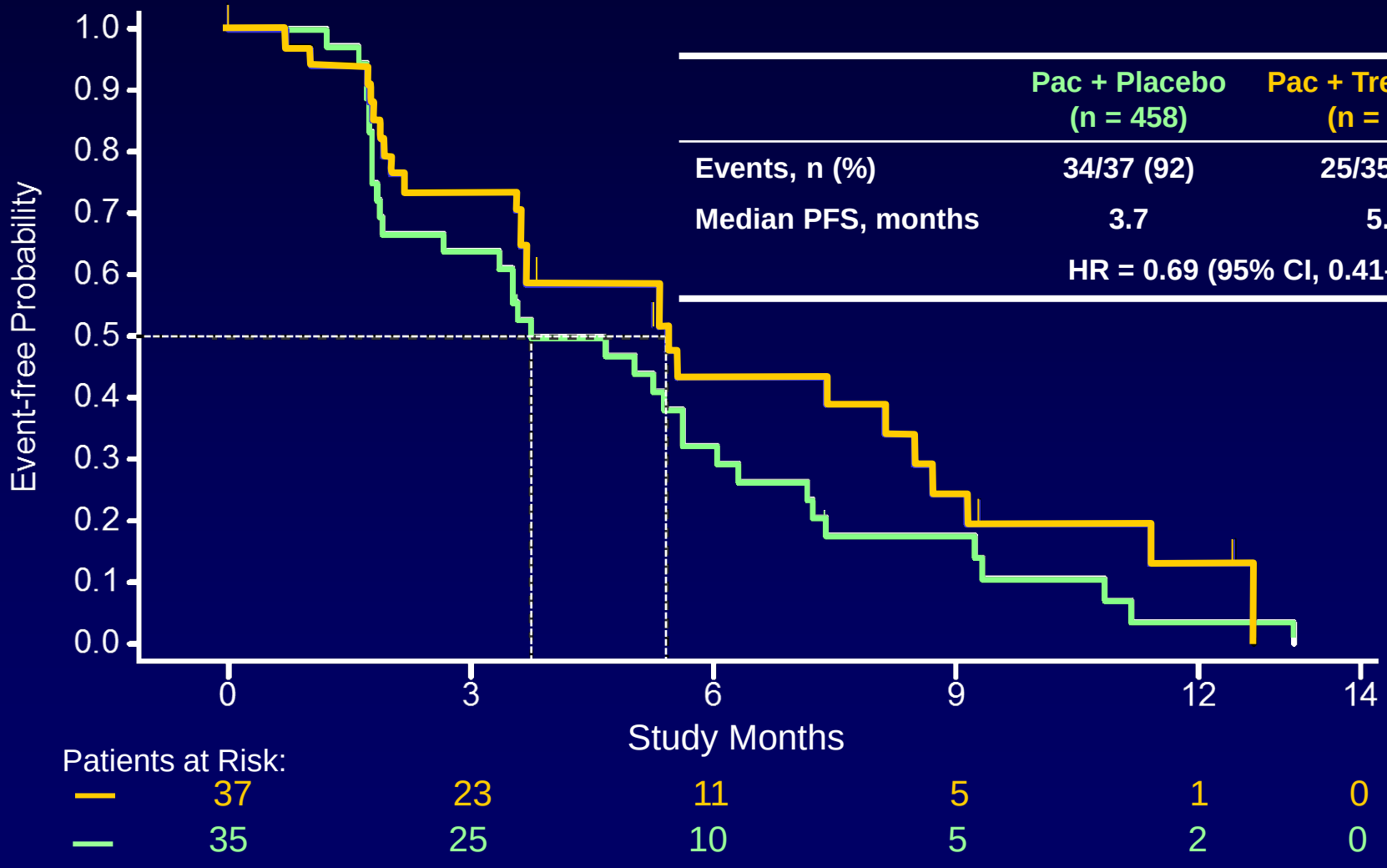
Phase III Studies in Ovarian Cancer With Targeted Drugs

	First Line				Platin Sensitive (>6 months PFI)			0-12 Months	Platin Resistant (< 6 months PFI)
	GOG218 Bev	ICON7 Bev	AGO Pazo	AGO Ninte	OCEANS Bev	ICON6 Ced	PARP Ola**	Trinova-1 Tre	AURELIA Bev
PFS≠*	3.8	1.7	5.6	0.7	4.0	3.1	4.0	1.8	3.3
PFS HR	0.72	0.81	0.77	0.84	0.48	0.57	0.35 BRCA 0.18	0.66	0.48
OS	0.4	0.9	NA	NR	- 1.8	2.7	2.0	1.7	3.3
OS≠ HR	0.91 (NS)***	**0.99 NS (final)**	0.99 (NS)	NR	1.03 (NS)	0.70	0.88 (NS)	0.86 (NS)	**0.85 (NS) (final)**

≠*,difference in months; **phase II

Burger RA, et al. *N Engl J Med*. 2011;365(26):2473-2483. Perren TJ, et al. *N Engl J Med*. 2011;365(26):2484-2496. Oza A, et al. *Eur J Cancer*. 2013;49(Suppl 3): Abstract LBA6. du Bois A, et al. *J Clin Oncol*. 14 September 2014 [Epub ahead of print].;31(Suppl): Abstract LBA5503. Du Bois A, et al. *Int J Gynecol Cancer*. 2013;23(Suppl 8) Abstract. Aghajanian C, et al. *J Clin Oncol*. 2012;30(17):2039-2045. Ledermann J, et al. , et al. *Eur J Cancer*. 2013;49(Suppl 3): Abstract LBA10. Ledermann J, et al. Lancet Oncol. 2014;15(8):852-861. Monk BJ, et al. *Lancet Oncol*. 2014;15(8): 799-808. Pujade-Lauraine E, et al. *J Clin Oncol*. 2012;30(Suppl): Abstract LBA5002. Witteveen P, et al. *Eur J Cancer*. 2013;49(Suppl 3): Abstract LBA5.

TRINOVA-1: Progression-Free Survival Prior Antiangiogenic Therapy



	Pac + Placebo (n = 458)	Pac + Trebananib (n = 461)
Events, n (%)	34/37 (92)	25/35 (71)
Median PFS, months	3.7	5.4
	HR = 0.69 (95% CI, 0.41–1.17)	

Monk BJ, et al. Presented at the 18th International Meeting of the European Society of Gynaecological Oncology; 19-22 October 2013; Liverpool, United Kingdom.

Antiangiogenesis in Ovarian Cancer

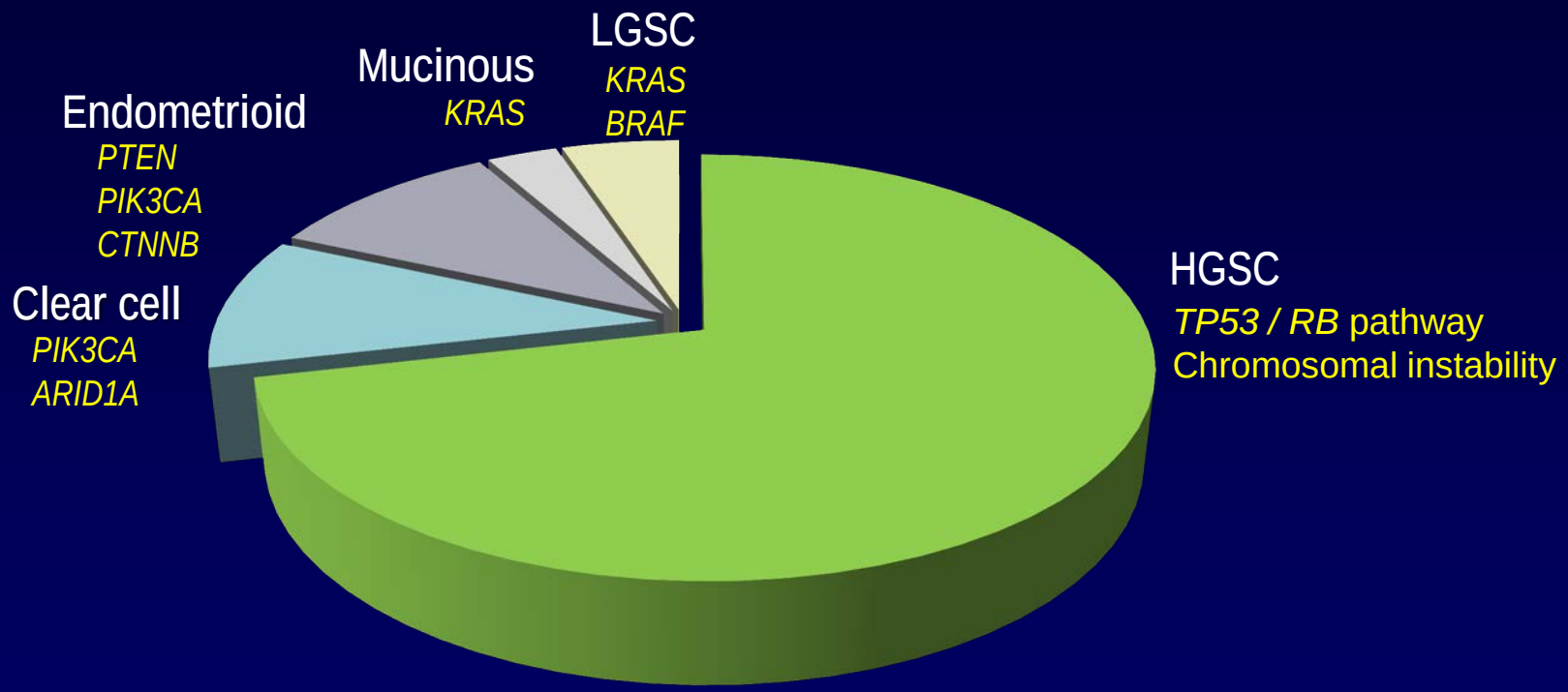
What we know:

- **Antiangiogenic drugs, targeting VEGF or angiopoietin, are active in prolonging PFS and OS in some subgroups of ovarian cancer.**

What we do not know:

- **When should an angiogenesis inhibitor be given (first-line, platin-sensitive, platin-resistant)? Or in all lines? How long?**
- **Which angiogenesis inhibitor should be preferred in which group of ovarian cancer patients? And which are active after progression on another angiogenesis inhibitor?**
- **Biomarkers for efficacy of antiangiogenesis are urgently needed.**
- **What is the potential for combination of VEGF inhibitors with other classes of antiangiogenesis drugs (eg angiogenesis inhibitors) or other targeted therapies (eg PARP, MET, SINE… inhibitors)?**

The Terms “Ovarian Carcinoma” But Also Type I and II Are Outdated!



DISTINCT DISEASES WITH DIFFERENT DRIVER ALTERATIONS

Patient selection, based on robust predictive biomarkers = key to succes!!!!!

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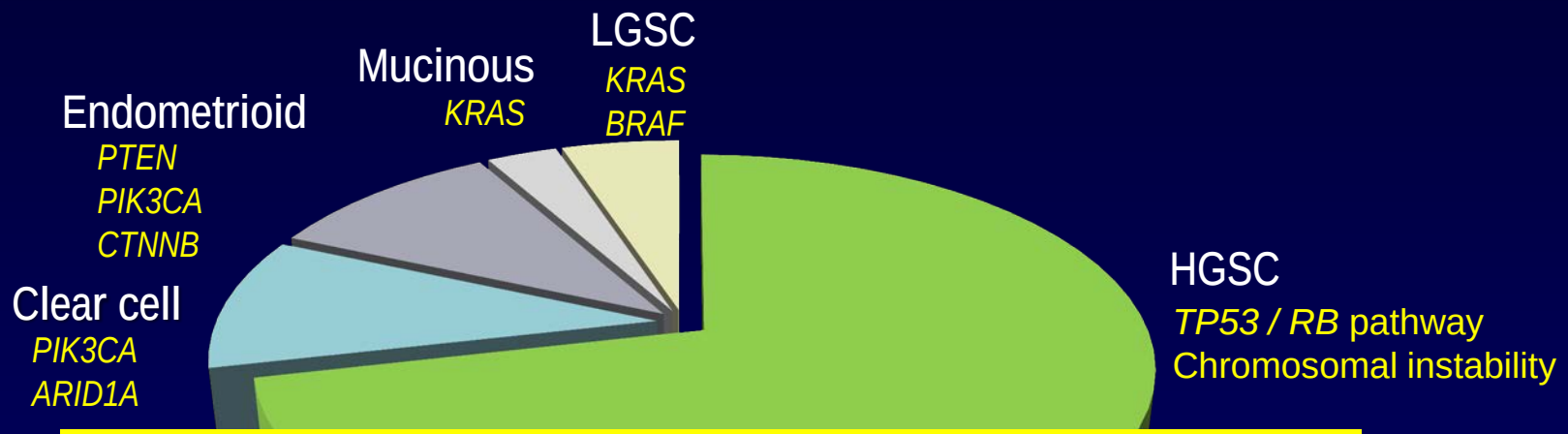


High-grade serous → PARP inhibitors and p53
Low-grade serous → MEK inhibitors
Mucinous → Src / Her2 / MEK inhibitors
Clear cell → PI3K pathway / HIF-1$^{\alpha}$ / MET inhibitors
Endometrioid → PI3K pathway / aromatase inhibitors

DISTINCT DISEASES WITH DIFFERENT DRIVER ALTERATIONS

Patient selection, based on robust predictive biomarkers = key to succes!!!!!

Research in Ovarian Cancer Targeted Therapy

- ✓ Angiogenesis (no predictors)
- ✓ **PARP inhibitors** (high-grade serous, high-grade endometrioid)
- ✓ **RAS-MEK pathway** (low-grade serous)
- ✓ **Folate receptor** (all epithelial ovarian cancer)
- ✓ **EGFR (erlotinib negative in first line)**
- ✓ **ErbB3 (pertuzumab)**
- ✓ **PI3K/AKT/mTOR** (PI3K: clear cell)
- ✓ **IGF-1R, Notch, Hedgehog . . .**
- ✓ **P53 / single target, simultaneous inhibition of multiple oncogenic pathways** (high-grade serous)
- ✓ **Selective inhibition of nuclear export (SINE)** (all epithelial ovarian cancer)

PARP Inhibitors in Ovarian Cancer

What we know now:

- Single-agent olaparib has significant clinical activity in both *BRCA*-mutated (germline and somatic) and sporadic HGSOC, with a favorable toxicity profile and particular potential as maintenance therapy

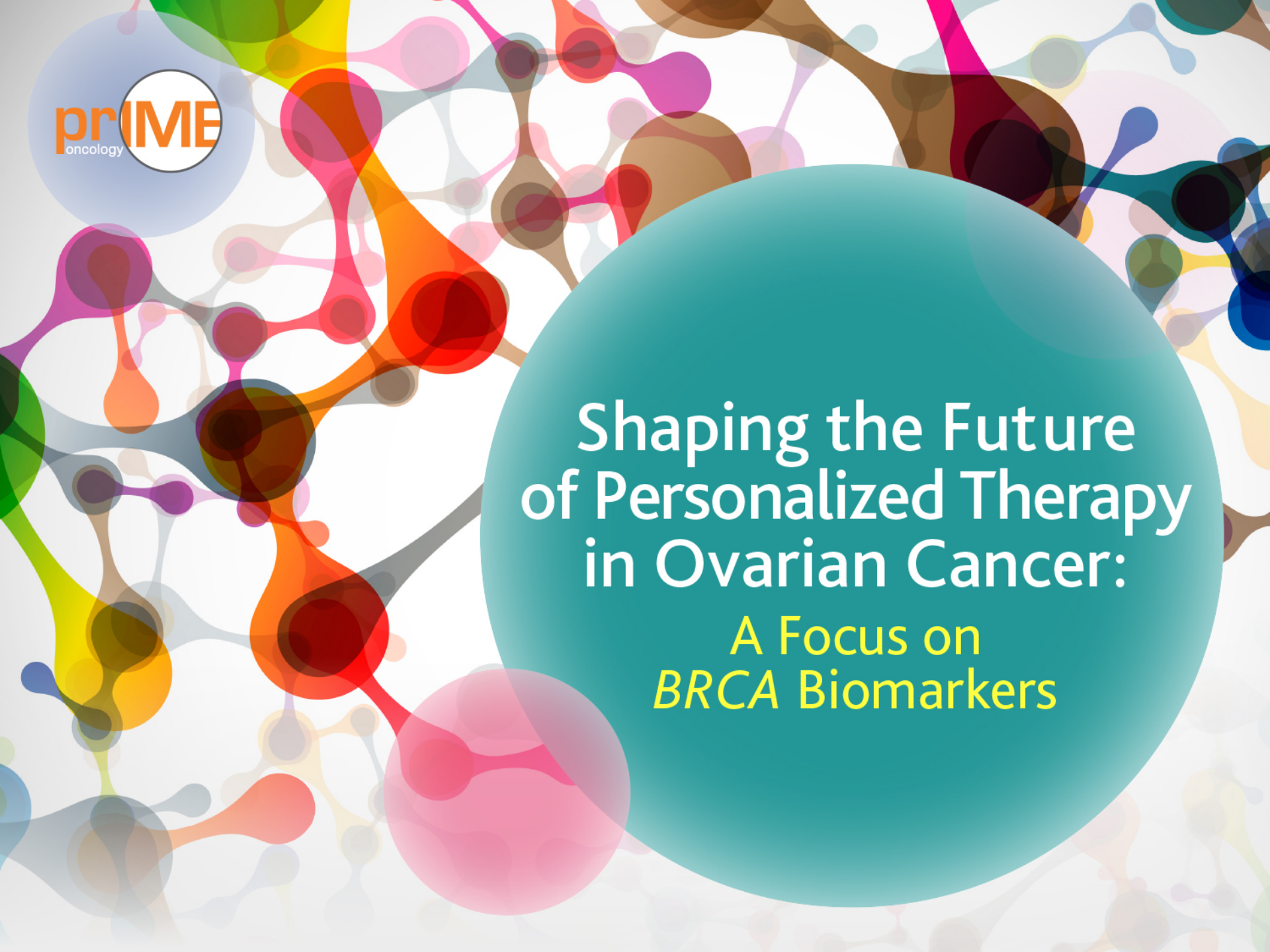
What we still need to know:

- Long-term toxicity
- What after clinical resistance to PARP inhibitor?
- Potential for combination with other approaches, eg, VEGF inhibitors or PI3K inhibitors
- Clinically, myelotoxicity is the most important toxicity


Are we there yet?
No, but making progress

prIME POINTS™ Future Research on Targeted Therapy in Ovarian Cancer

1. Ovarian carcinoma comprises **different tumor types** and should be treated with pathway-dependent targeted therapy according to their **molecular profiles**.
2. Whenever possible, new phase II trials should only include patients with tumors with a **specific mutation or amplification.**
3. **Combinations** of targeted therapies (eg, PARPi and VEGF, PI3K and MEK, or VEGF and MET) are promising.
4. A new group of agents have **one target**, and this target interacts on different pathways or proteins active in ovarian cancer.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oncology
Shaping the Future of Personalized Therapy in Ovarian Cancer:
A Focus on
BRCA Biomarkers