# Platinum-Sensitive Relapsed Ovarian Cancer: New Options on the Horizon

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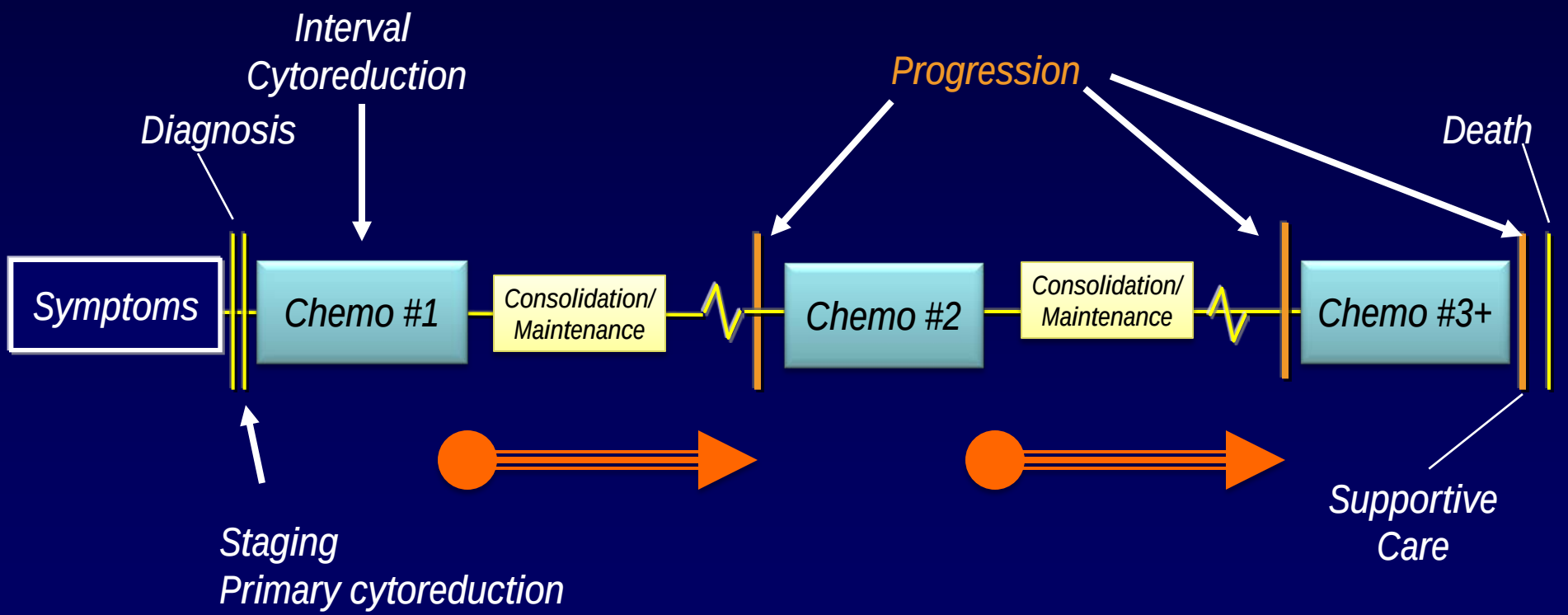
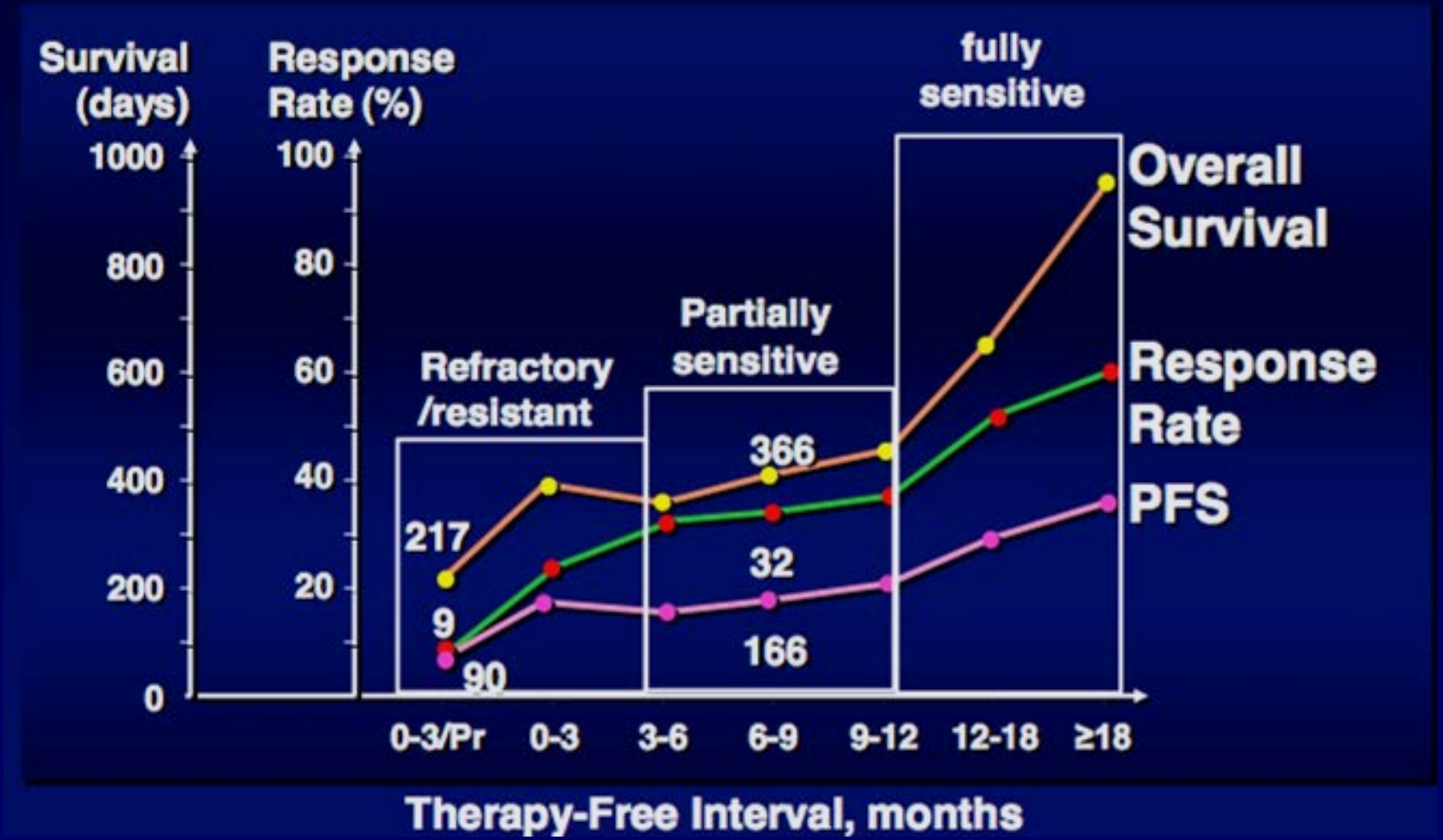
# Ovarian Carcinoma: Clinical Course



# Recurrent Ovarian Cancer

## A GiNECO Study: Therapy-Free Interval and Efficacy




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

# Improving Systemic Therapy Following Recurrence: Sensitive Disease

- Surgery?
- Systemic therapy
  - Platinum Doublets
  - Trabectidin/PLD
- Targeted agents - Concurrent +/- Maintenance:
  - Anti-angiogenics
    - Bevacizumab
    - Cedarinib
  - DNA repair inhibitors
    - Parp inhibitors
    - Wee 1 inhibitor?
- Stem cell targets
  - Hedgehog Inhibitors
- Immunotherapy

# Ovarian Cancer Recurrence Treatment Algorithm

**First-line therapy**
**carboplatin/paclitaxel IV**
**Cisplatin/paclitaxel IP**

| Platinum-sensitive (relapse >12 months) | Partially platinum-sensitive (relapse 6-12 months) | Platinum-resistant / refractory (relapse <6 months or no response) |
|---|---|---|
| Evaluate surgery rechallenge: platin-based combination chemotherapy | PLD/carbo, gemcitabine/carbo, paclitaxel/carbo, trabectedin/PLD | PLD, topotecan, weekly carbo / paclitaxel or paclitaxel weekly Experimental drugs |

**2012: Bevacizumab**

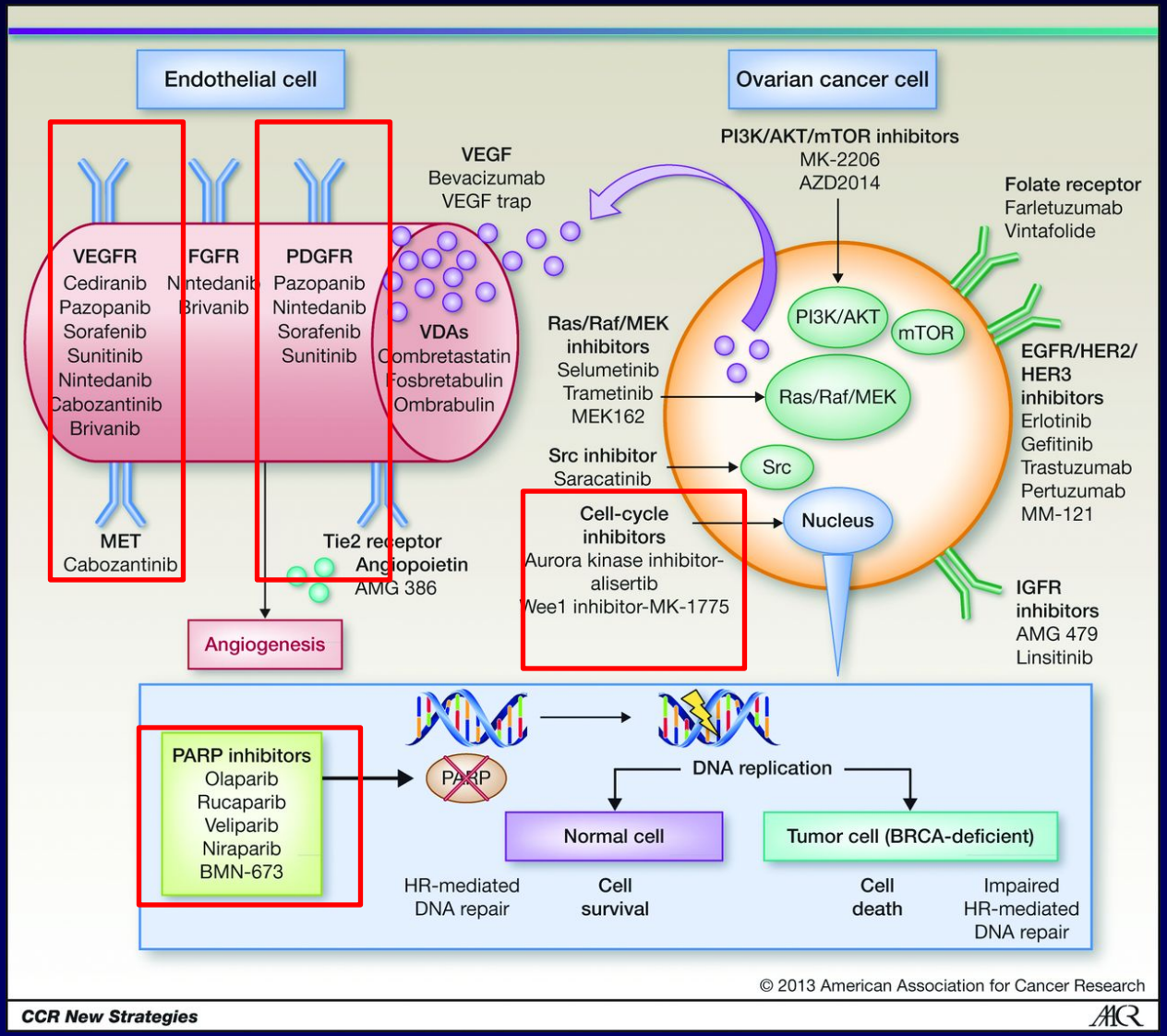
**2014: Olaparib for mBRCA**

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.

# Novel Approaches

- Modulate the microenvironment
- Leverage potential for synthetic lethality
  - Parp inhibition
  - TP53 targeting
- Target driver mutations
- Exploit unique expression on cells
  - Immunologic approaches
- Explore potential to target stem cells

# Targeted Therapies in Ovarian Cancer




Banerjee S, et al. *Clin Cancer Res.* 2013;19(5):961-968.

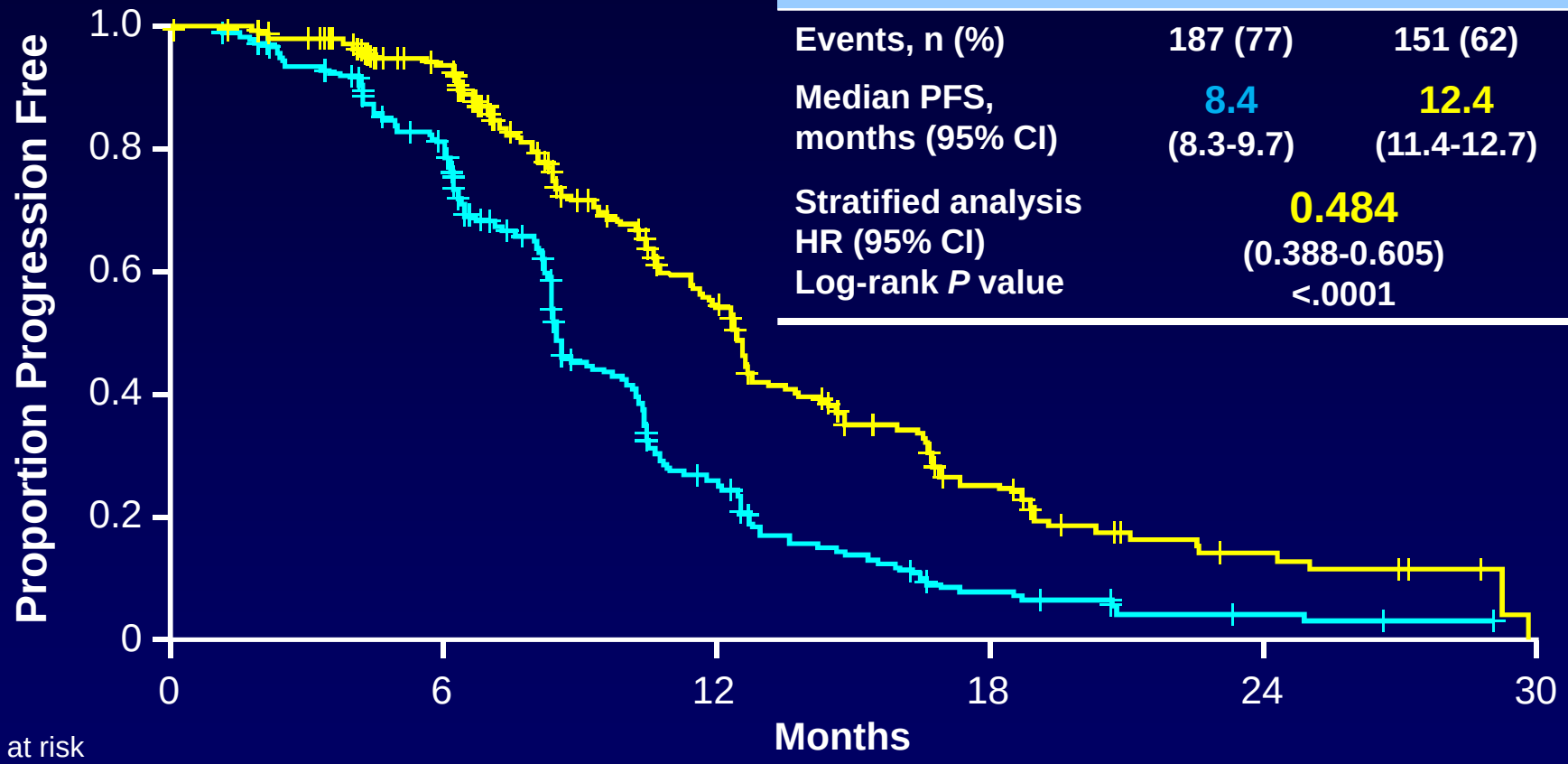
# 1st Platinum-Sensitive Relapse: Antiangiogenic Agents

- **Licensed: Carboplatin/gemcitabine + bevacizumab followed by maintenance bevacizumab**
  - OCEANS[1]:
    - Median PFS improvement 4 months, HR 0.48
    - No overall survival benefit seen
- **Other options: Cedirinib?**
  - ICON6[2]:
    - Median PFS improvement 3.1 months, HR 0.57
    - Overall survival benefit 2.7 months, HR 0.7

**1. Aghajanian C, et al. *J Clin Oncol.* 2012;30(17):2039-2045. 2. Lederman J, et al. *Eur J Cancer.* 2013;49(Suppl2) Abstract LBA10.**

# OCEANS: Primary Analysis of PFS

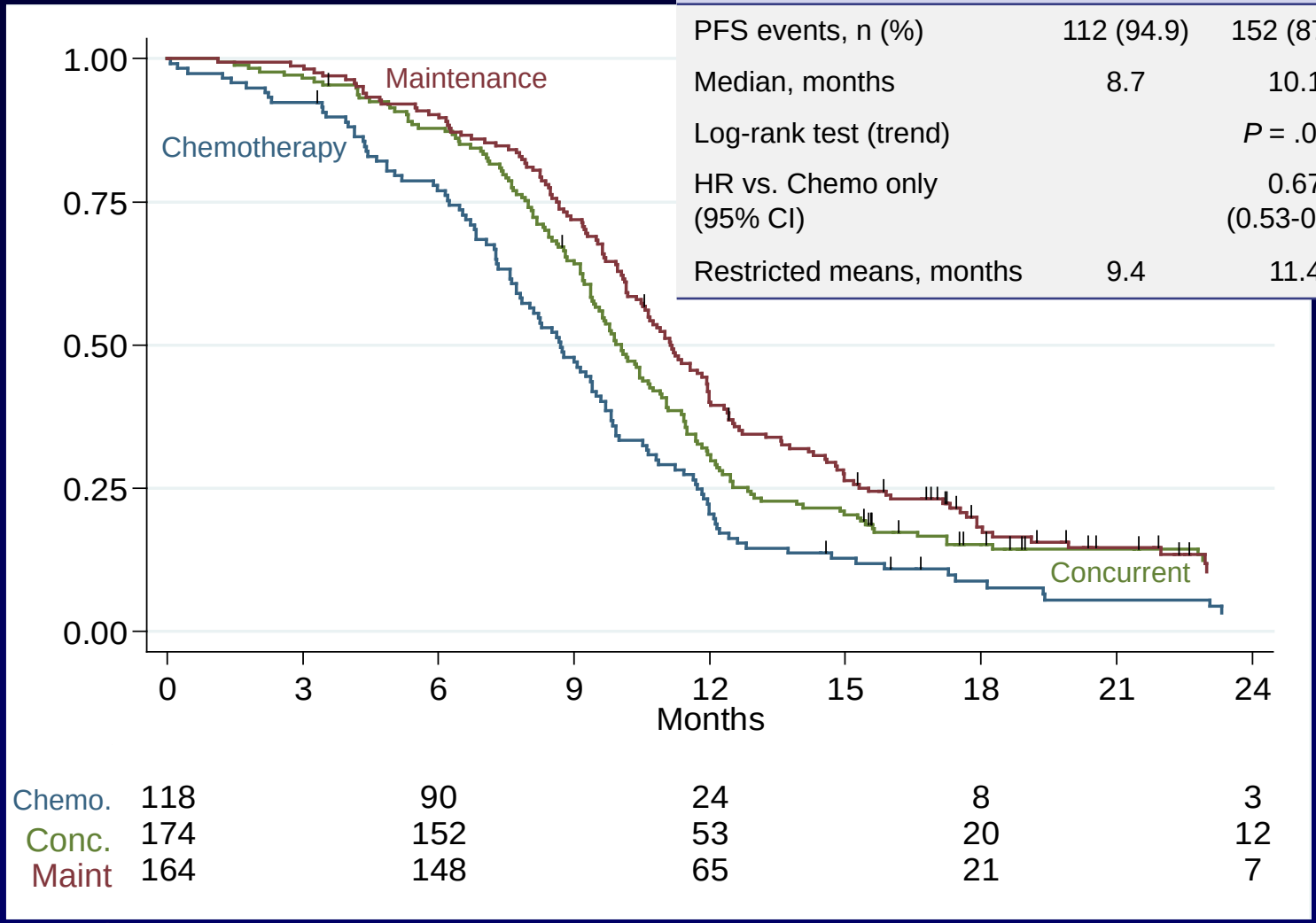
| | CG + PL (n = 242) | CG + BV (n = 242) |
|---|---|---|
| Events, n (%) | 187 (77) | 151 (62) |
| Median PFS, months (95% CI) | 8.4 (8.3-9.7) | 12.4 (11.4-12.7) |
| Stratified analysis HR (95% CI) | 0.484 (0.388-0.605) | |
| Log-rank *P* value | <.0001 | |




Aghajanian C, et al. *J Clin Oncol.* 2012;30(17):2039-2045.

# Progression-Free Survival – All Three Arms

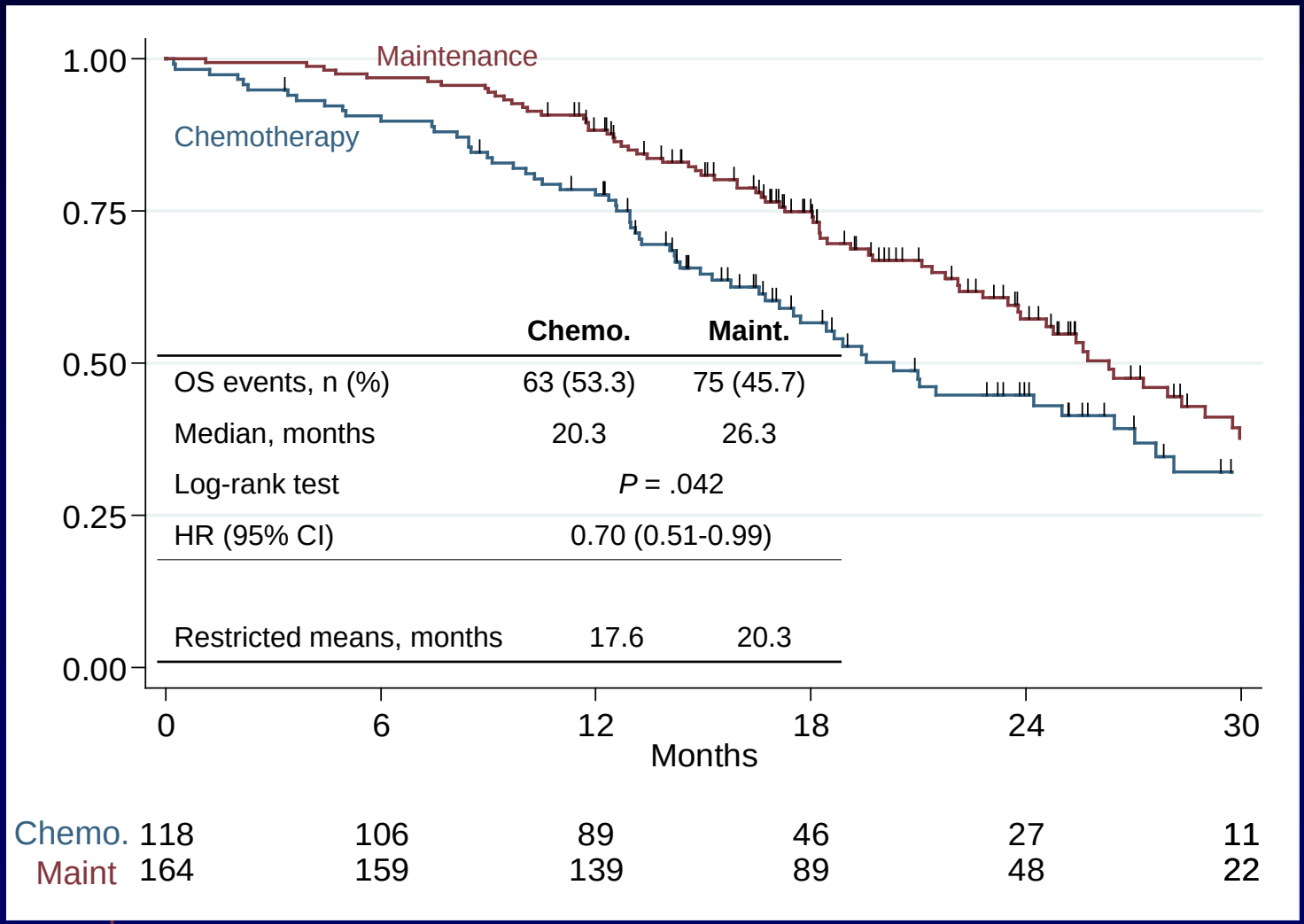
| | Chemo. | Conc. | Maint. |
|---|---|---|---|
| PFS events, n (%) | 112 (94.9) | 152 (87.4) | 139 (84.8) |
| Median, months | 8.7 | 10.1 | 11.1 |
| Log-rank test (trend) | | *P* = .0003 | |
| HR vs. Chemo only (95% CI) | | 0.67 (0.53-0.87) | 0.57 (0.44-0.74) |
| Restricted means, months | 9.4 | 11.4 | 12.5 |




Ledermann JA, et al. *Eur J Cancer.* 2013;49(Suppl 3):Abstract LBA 10.

# Overall Survival

## Restricted mean survival time increases by 2.7 months with maintenance treatment (over two years)




Ledermann JA, et al. *Eur J Cancer.* 2013;49(Suppl 3):Abstract LBA 10.

# Platinum-Sensitive Relapse Treatment Options

## Antiangiogenic agents or PARP inhibitors?

Platinum-sensitive relapse

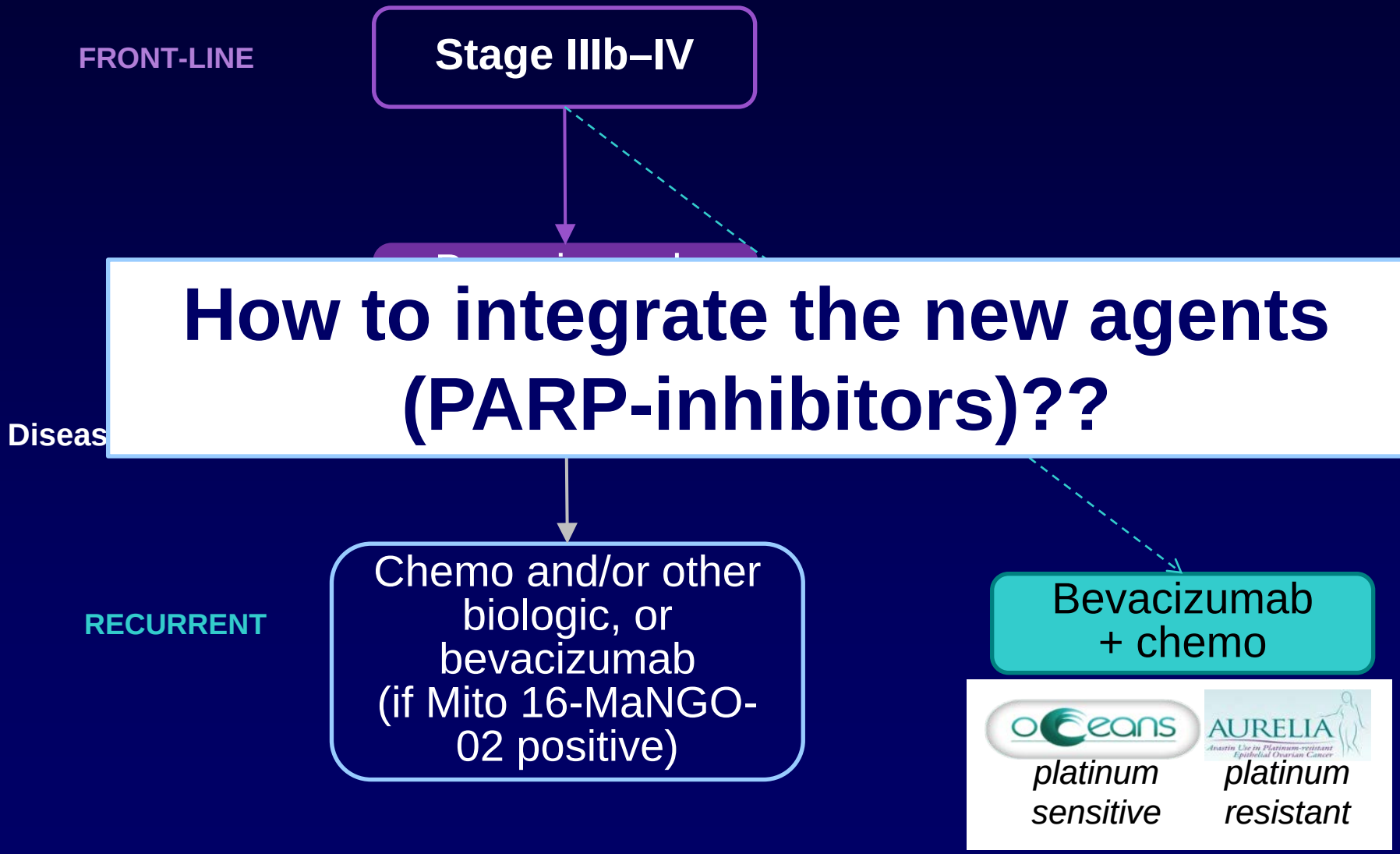
- May be in situation where patients can either have bevaciuzmab or PARP inhibitor

- **Do *BRCA* carriers derive the same benefit from antiangiogenic agents as non-*BRCA* carriers?**
- **Is response to PARP inhibitor affected by prior antiangiogenic agent?**

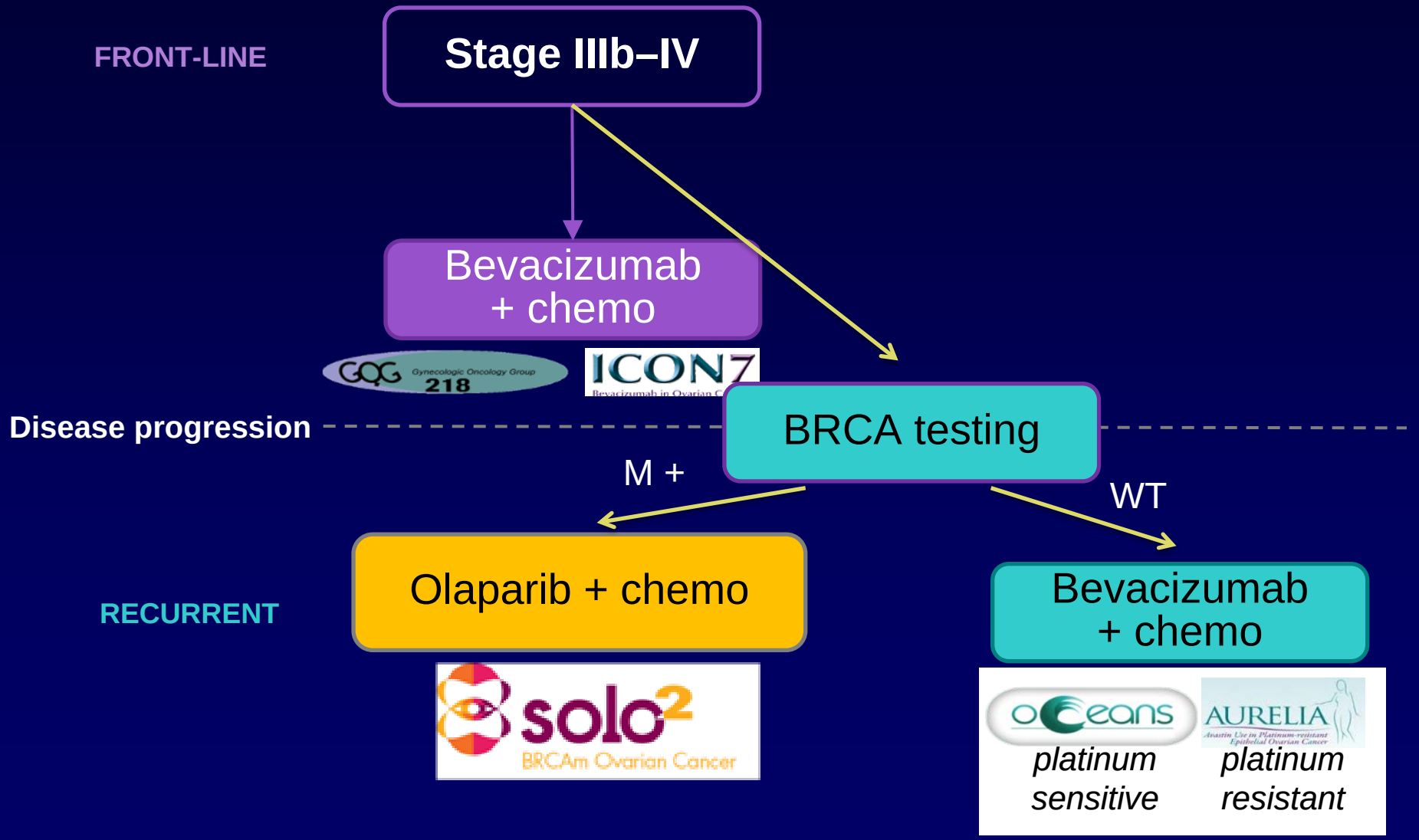
**URGENT NEED FOR BIOMARKER**

Potential for molecular subgroups within high-grade serous predicting outcome with bevacizumab **(Gourley C, et al. *J Clin Oncol.* 2014;32(5S): Abstract 5502.)**

# Ovarian Cancer Treatment Algorithm



# Looking at the Future: Ovarian Cancer Treatment Algorithm

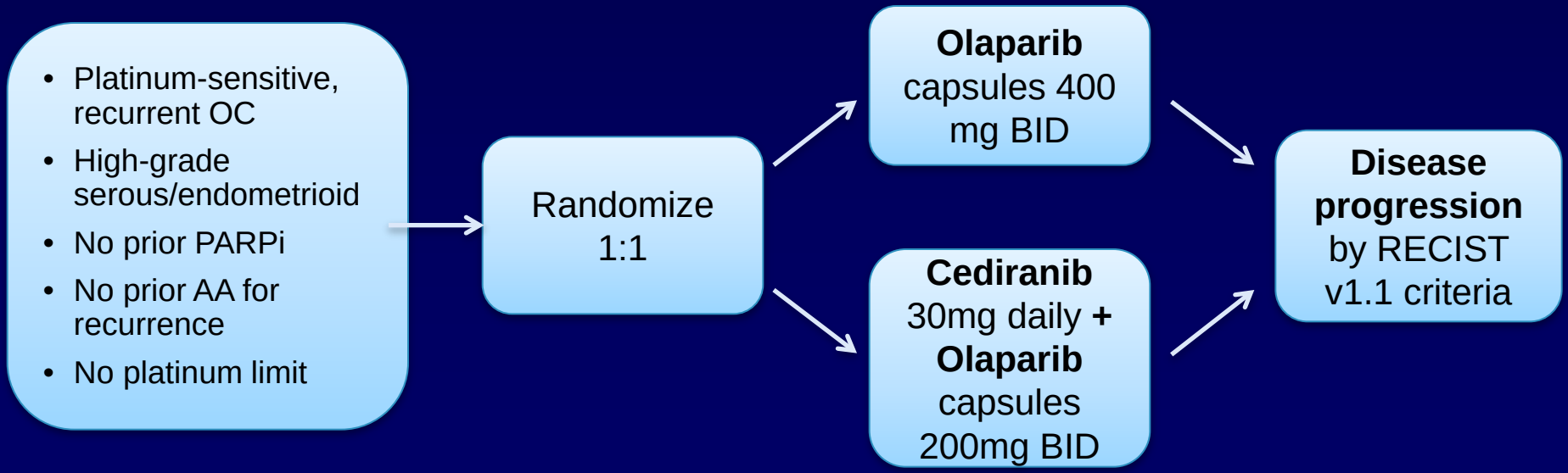


# Platinum-Sensitive Relapse: Cediranib + Olaparib

**Preclinical data potential synergy between PARPi and antiangiogenics**

**PARPi → ↑VEGFR2; VEGFR2i → hypoxia ↓HR → PARPi sensitivity**

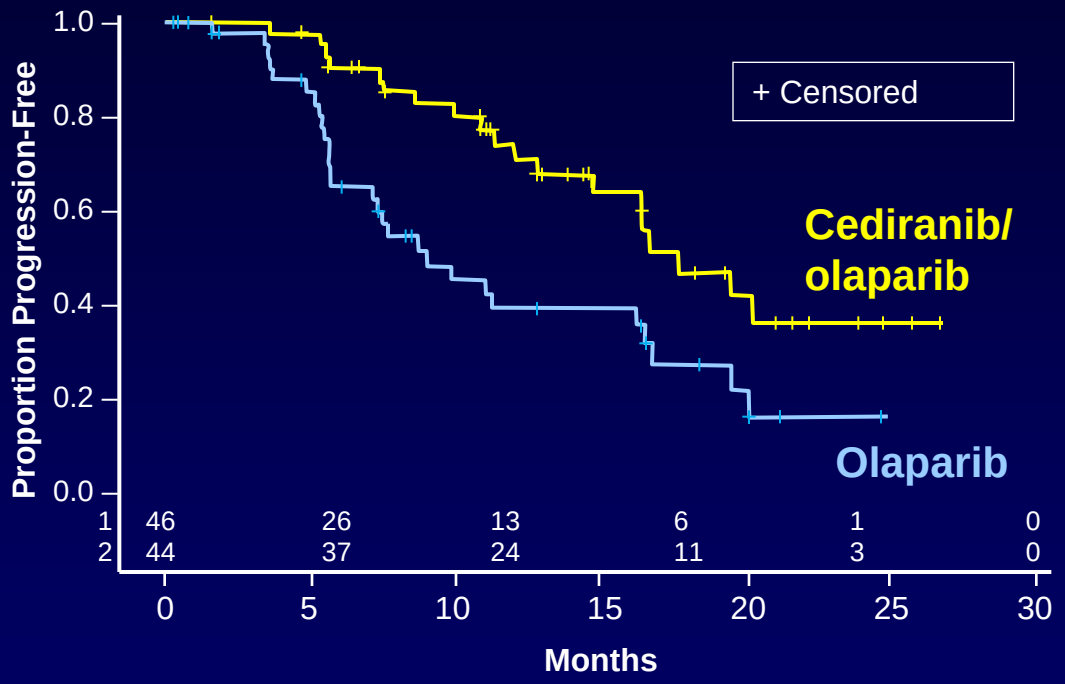
- **Phase II open-label randomized study**
  - **1:1 randomization to cediranib/olaparib combination or single-agent olaparib**
  - **Platinum-sensitive recurrent ovarian, fallopian tube, or primary peritoneal cancer**




Liu J, et al. *J Clin Oncol.* 2014;32(5S): AbstractLBA5500.

# Primary Outcome: Cediranib/Olaparib Significantly Increased PFS Compared to Olaparib Alone

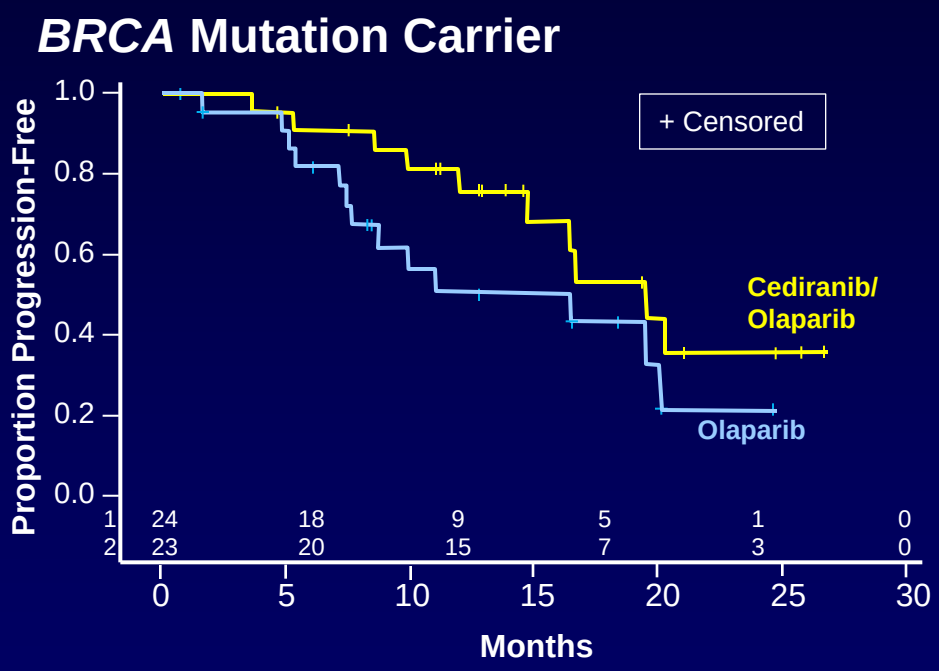
| | Olaparib | Ced/Olap |
|---|---|---|
| PFS events | 28 | 19 |
| Median PFS | 9.0 mo | 17.7 mo |
| | *P* = .005 | |
| | HR 0.42 (95% CI: 0.23-0.76) | |

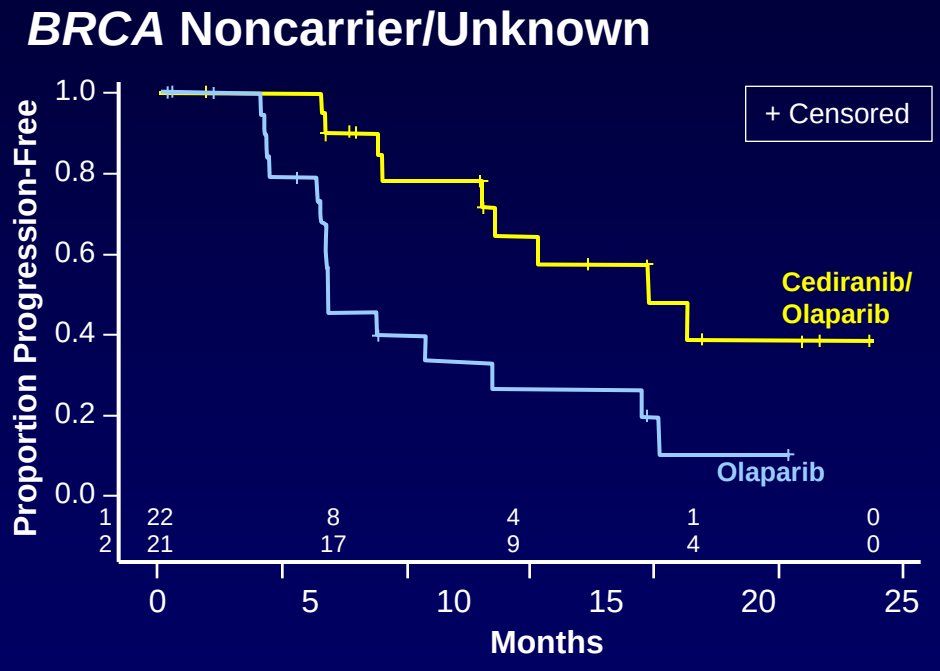



| Arm | ORR N | ORR % |
|---|---|---|
| Olaparib alone | 22 | 47.8 |
| Cediranib/olaparib | 35 | 79.6 |
| | *P* = .002 | |

Liu J, et al. *J Clin Oncol.* 2014;32(5S): AbstractLBA5500.

# Cediranib/Olaparib Significantly Increased PFS in Patients Without a *BRCA* Mutation

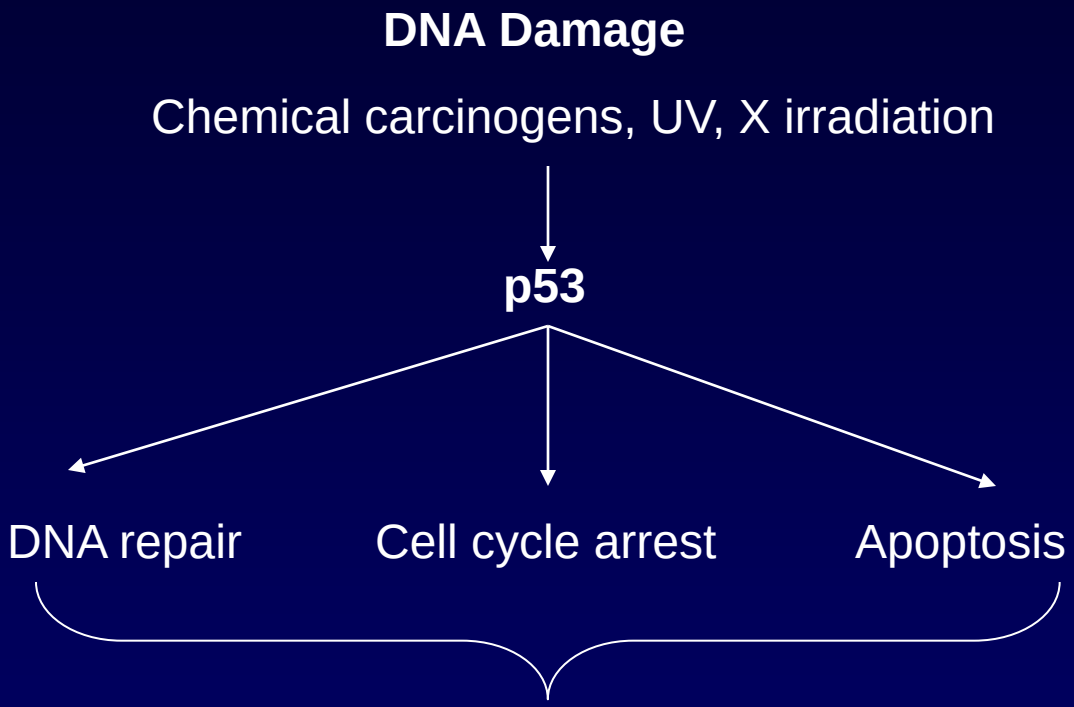



| | *BRCA* Mutation Carrier | | *BRCA* Noncarrier/Unknown | |
|---|---|---|---|---|
| | Olaparib | Ced/Olap | Olaparib | Ced/Olap |
| **PFS events** | 13 | 10 | 15 | 9 |
| **Median PFS** | 16.5 mo | 19.4 mo | 5.7 mo | 16.5 mo |
| | *P* = .16 | | *P* = .008 | |
| | HR 0.55 (95% CI: 0.24-1.27) | | HR 0.32 (95% CI: 0.14-0.74) | |

**Liu J, et al. *J Clin Oncol.* 2014;32(5S): AbstractLBA5500.**

# Normal TP53 Function




**HGS Ovarian Cancer**
**Mutations in >96%**
**?Functional**

# AZ-1775 Compound Profile

- First in class
- Potent, highly selective and ATP competitive Wee1 kinase inhibitor (IC50 = 5.2 nM) with selectivity over other G2/M kinases (~100-200x)
- Potent context specific sensitizer to variety of DNA damaging agents (chemotherapy, radiation) in multiple cell lines (colon, ovarian, breast) *in vitro* and *in vivo*
- Activity only in p53(-) cells not in p53 WT = context specificity

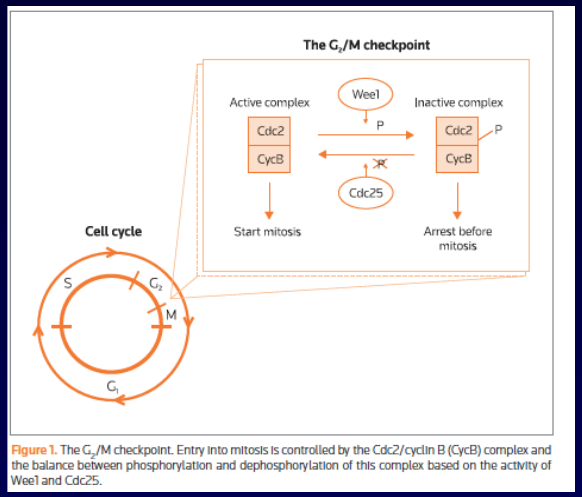
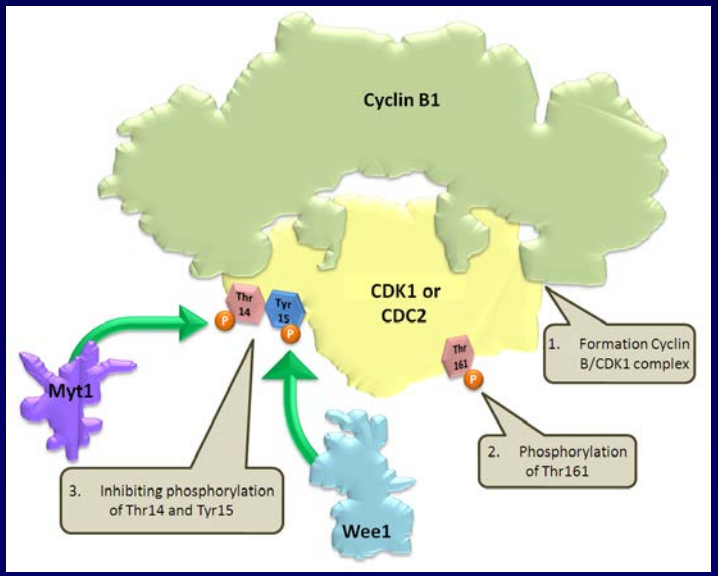
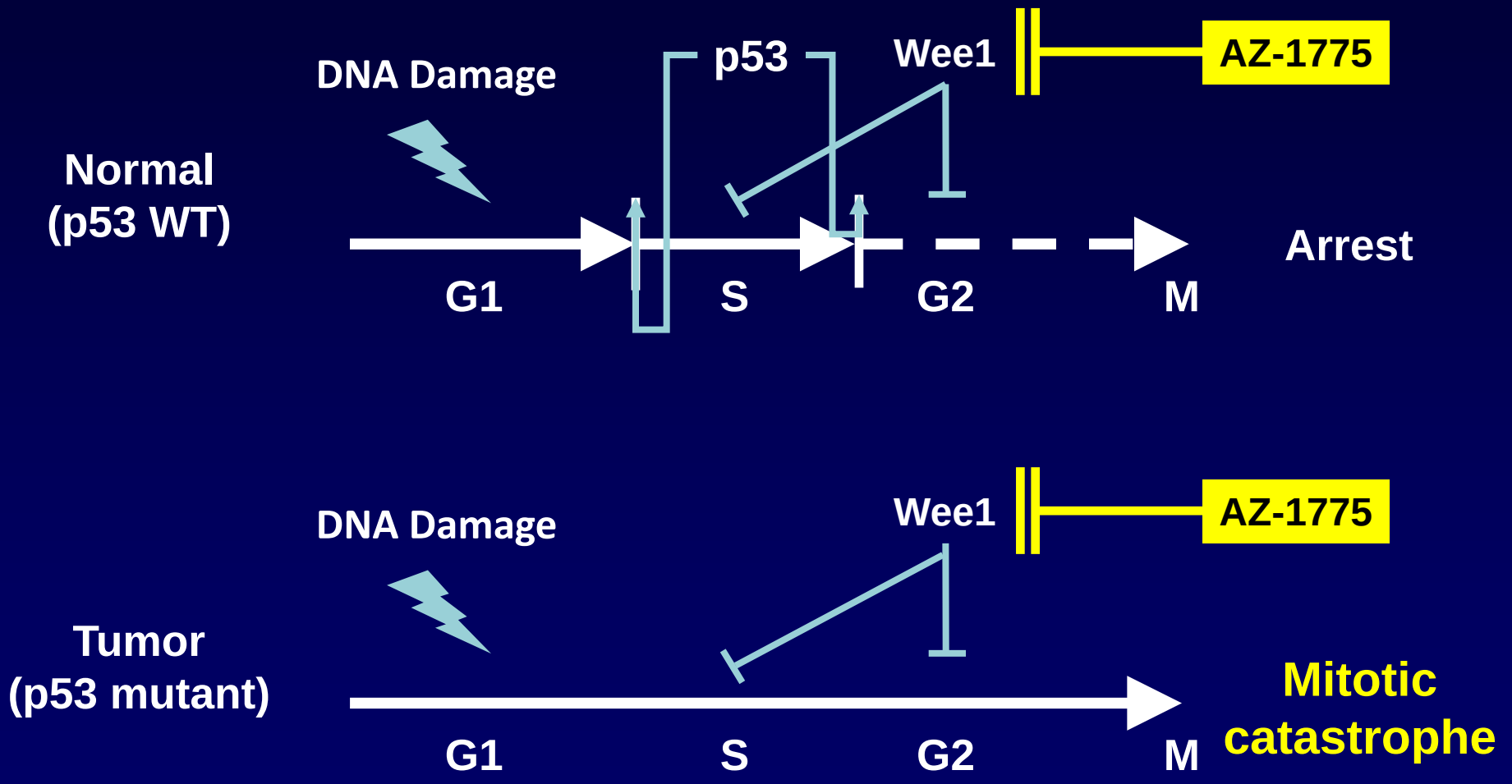


Figure 1. The $G_2$/M checkpoint. Entry into mitosis is controlled by the Cdc2/cyclin B (CycB) complex and the balance between phosphorylation and dephosphorylation of this complex based on the activity of Wee1 and Cdc25.



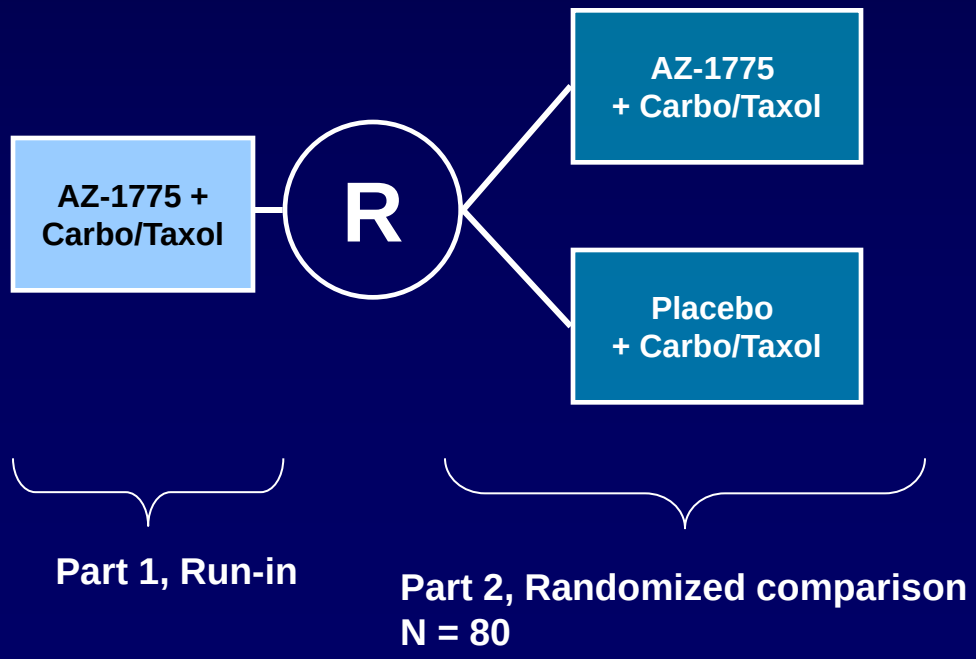
# Scientific Rationale for AZ-1775 Combination Therapies



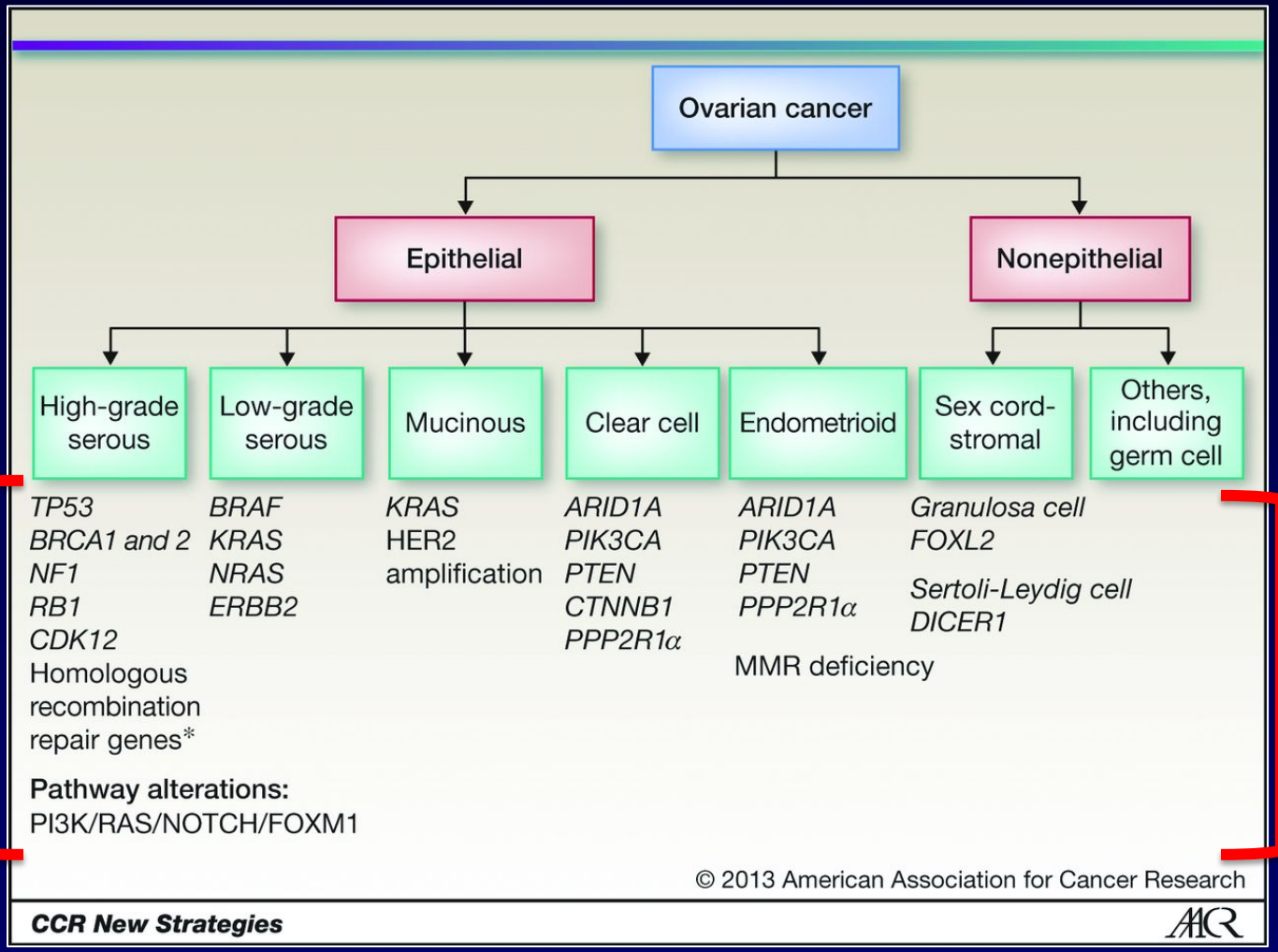
# A Randomized, Phase II Study Evaluating AZ-1775 in Combination With Paclitaxel and Carboplatin vs Paclitaxel and Carboplatin Alone in Adult Patients With Platinum Sensitive p53 Mutant Ovarian Cancer

- Prospective enrollment of P53 mutant patients based on p53 testing by Amplichip
- 2-4L platinum sensitive disease
- Endpoints: Primary EP: PFS
  Secondary EP: OS

- FPI: August 2011
- Efficacy Analysis:
  - N = 80, Power 80%
  - 38 PFS events, 18 months
  - HR 0.5, α = 0.1

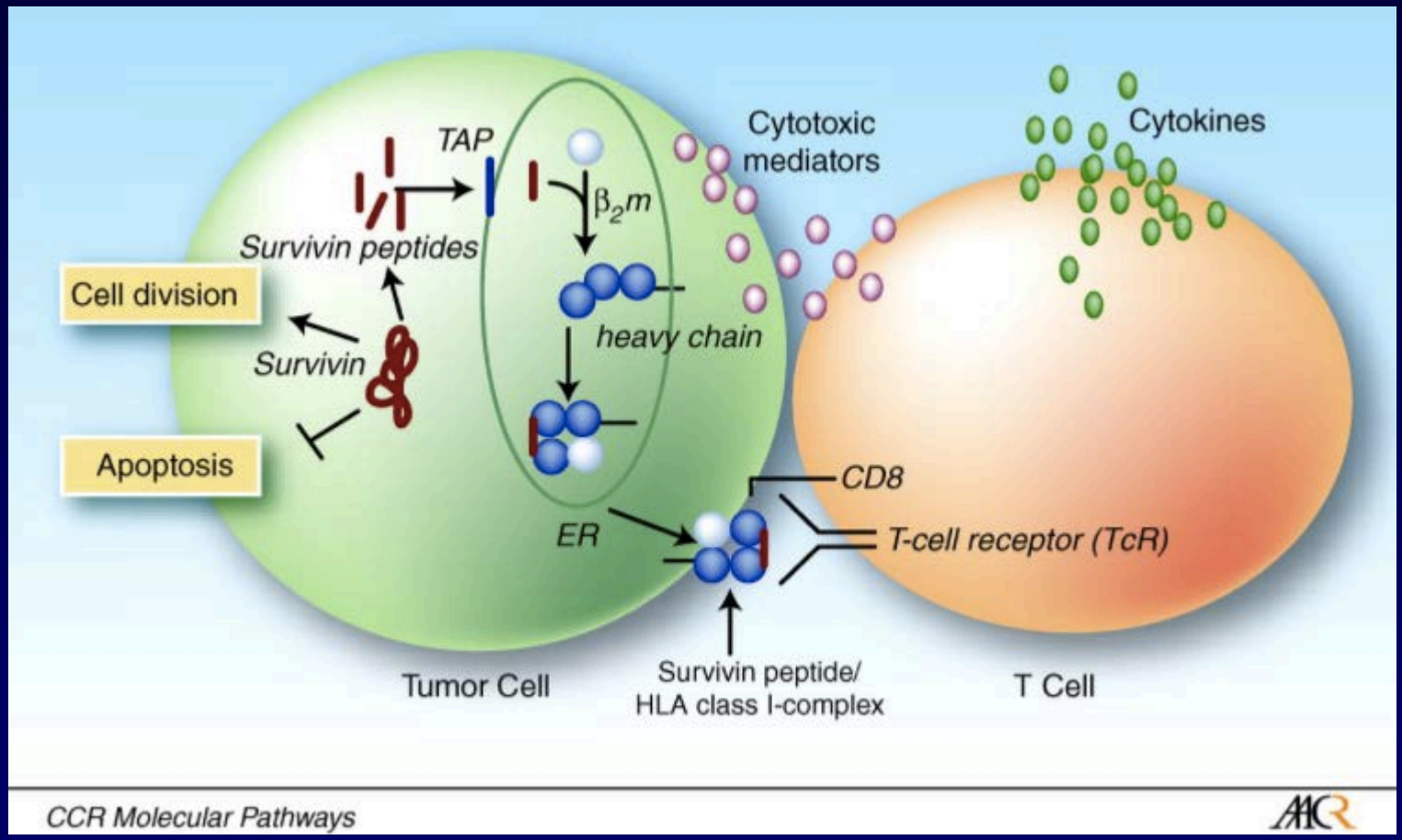


# Histologic Subtypes of Epithelial Ovarian Carcinoma and Associated Mutations/Molecular Aberrations. *, CHK2, BARD1, BRIP1, PALB2, RAD50, RAD51C, ATM, ATR, EMSY, Fanconi Anemia Genes




Banerjee S, et al. *Clin Cancer Res.* 2013;19(5):961-968.

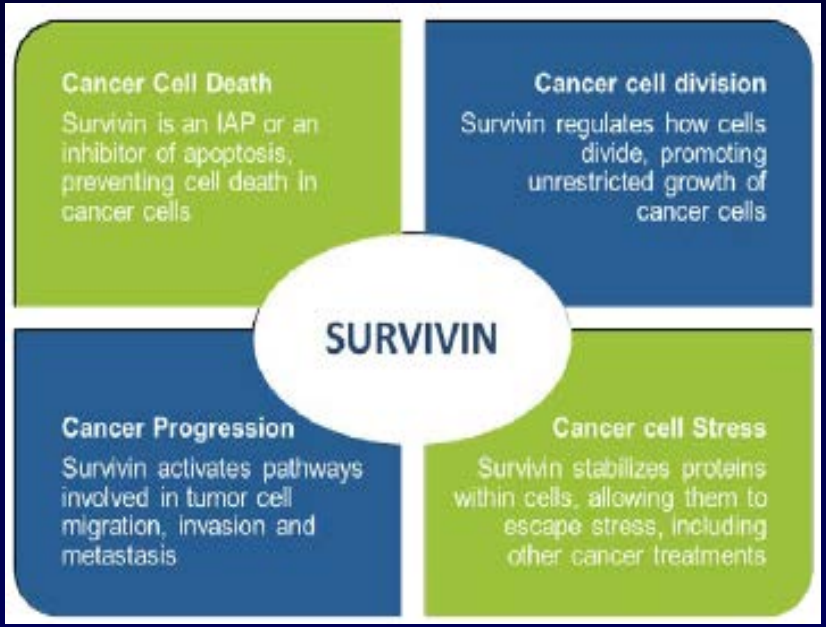
# Survivin

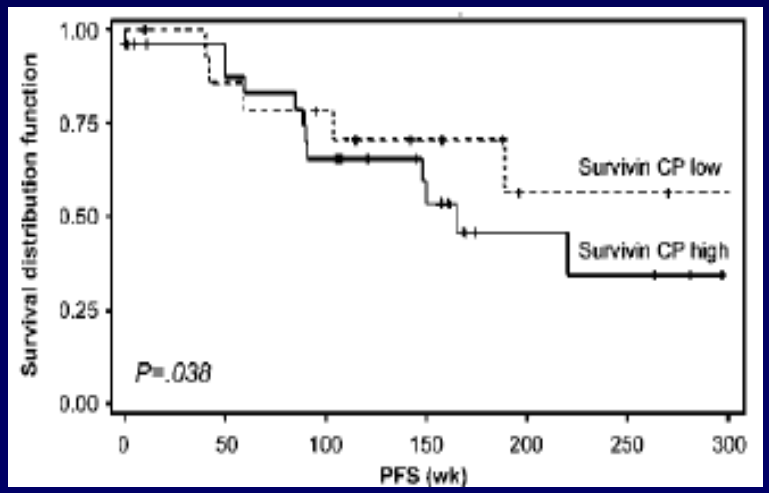



Anderson MH, et al. *Clin Cancer Res.* 2007;13(20):5991-5994.

# Survivin as a Cancer Therapeutic Target

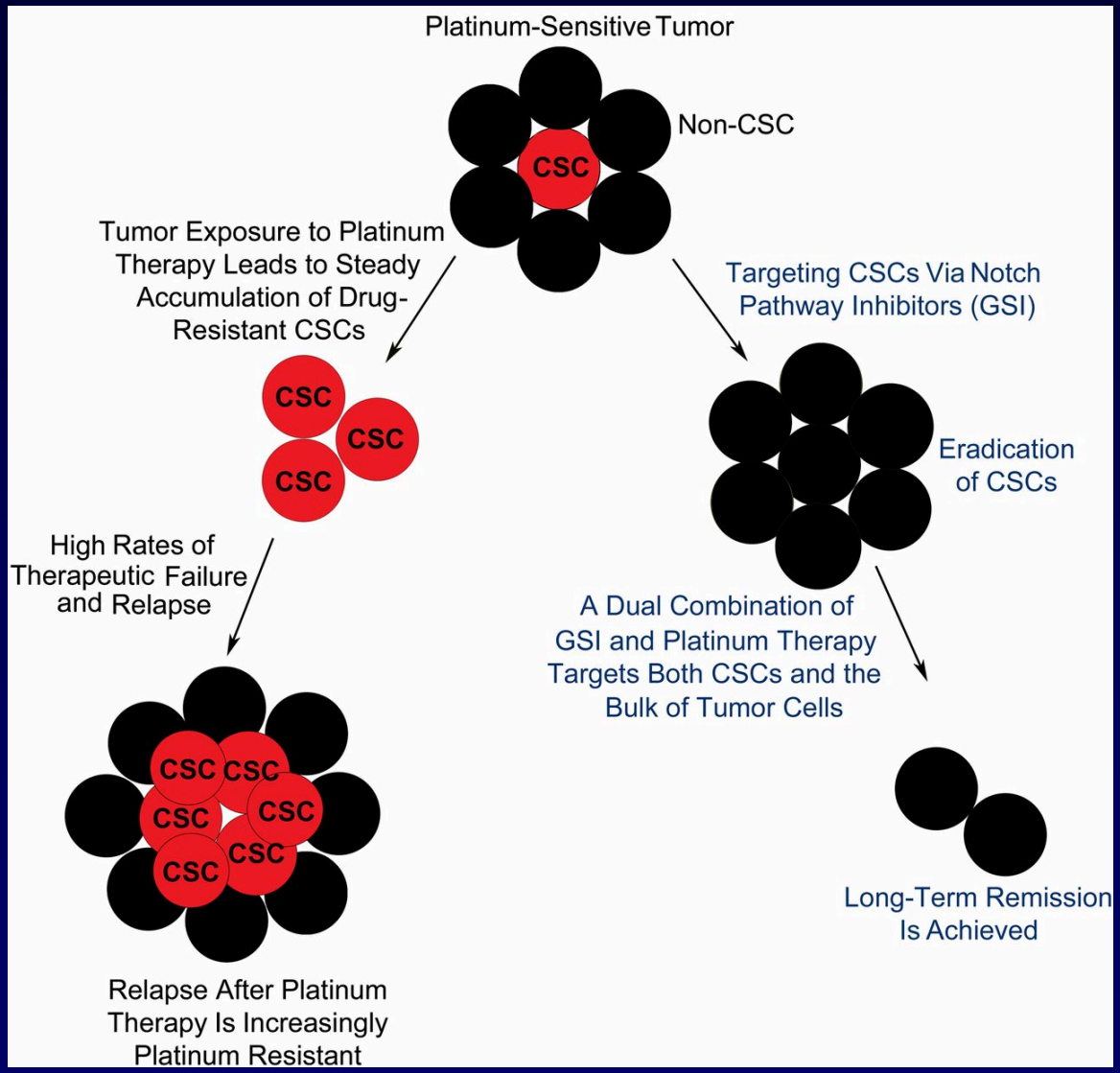
- Plays an important role in the control of:
  - Apoptosis
  - Cell division
  - Cell migration/metastasis
- Expression
  - Not present in most adult tissues
  - Re-expression in numerous human cancers
  - Associated with poor prognosis
  - Downstream of several oncogenes
- Recognized by NCI as an important cancer antigen



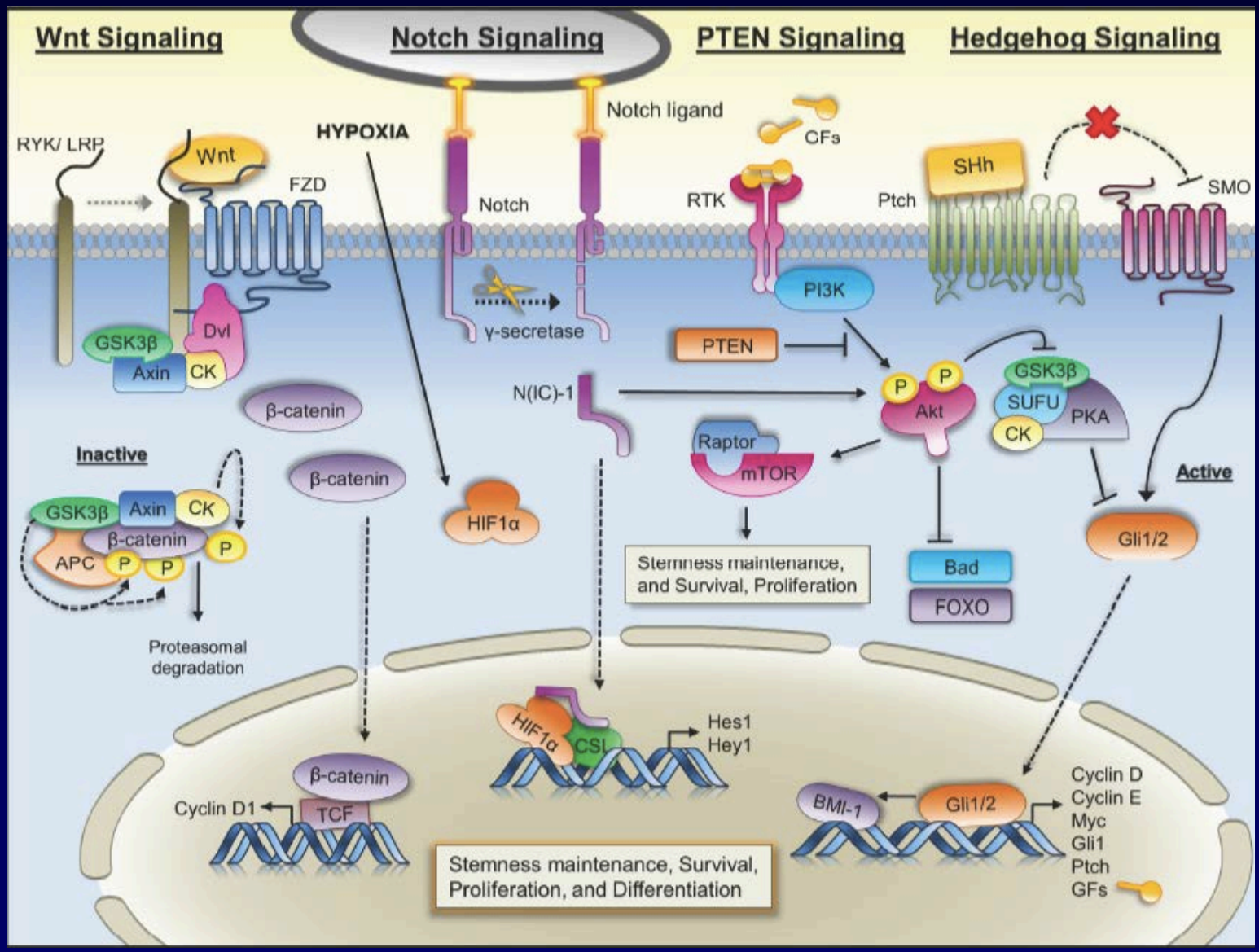




Engels K, et al. *Cancer Res.* 2008;68(13):5159-5166.

# CSCs Are an Important Contributor to Tumor Chemoresistance Because of Their Ability to Survive Platinum-Based Chemotherapies




McAuliffe SM, et al. *Proc Natl Acad Sci U S A*. 2012;109(43):E2939-E2948.




Templeton AK, et al. *Stem Cell Invest.* 2014.

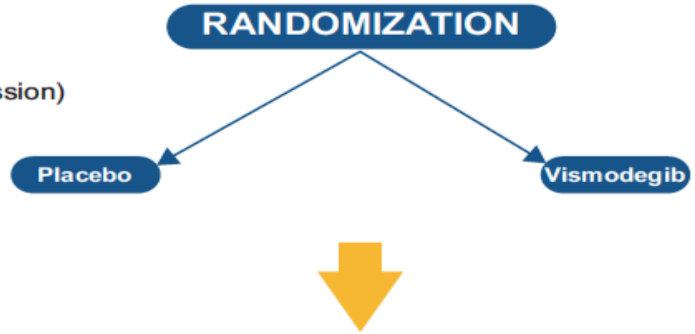
# A Phase II, Randomized, Placebo-Controlled Study of Vismodegib as Maintenance Therapy in Patients With Ovarian Cancer in Second or Third Complete Remission

**Second or third complete remission:**
- Received chemo for relapsed disease (platinum or nonplatinum-based)
- Normal CA-125 & CT scan without evidence of cancer at enrollment

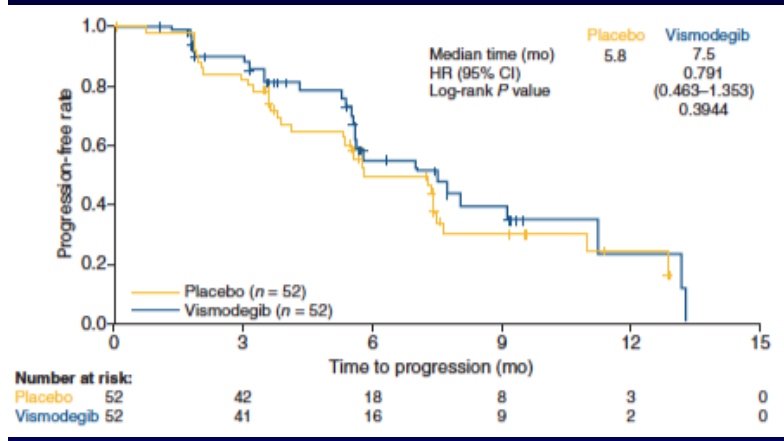
**Time from last therapy to randomization:**
3–14 wks

**Stratification factor:**
Remission status
(second vs third complete remission)

**Primary endpoint:**
PFS from time
of randomization




Treatment until radiographic progression, intolerable adverse event, or withdrawal

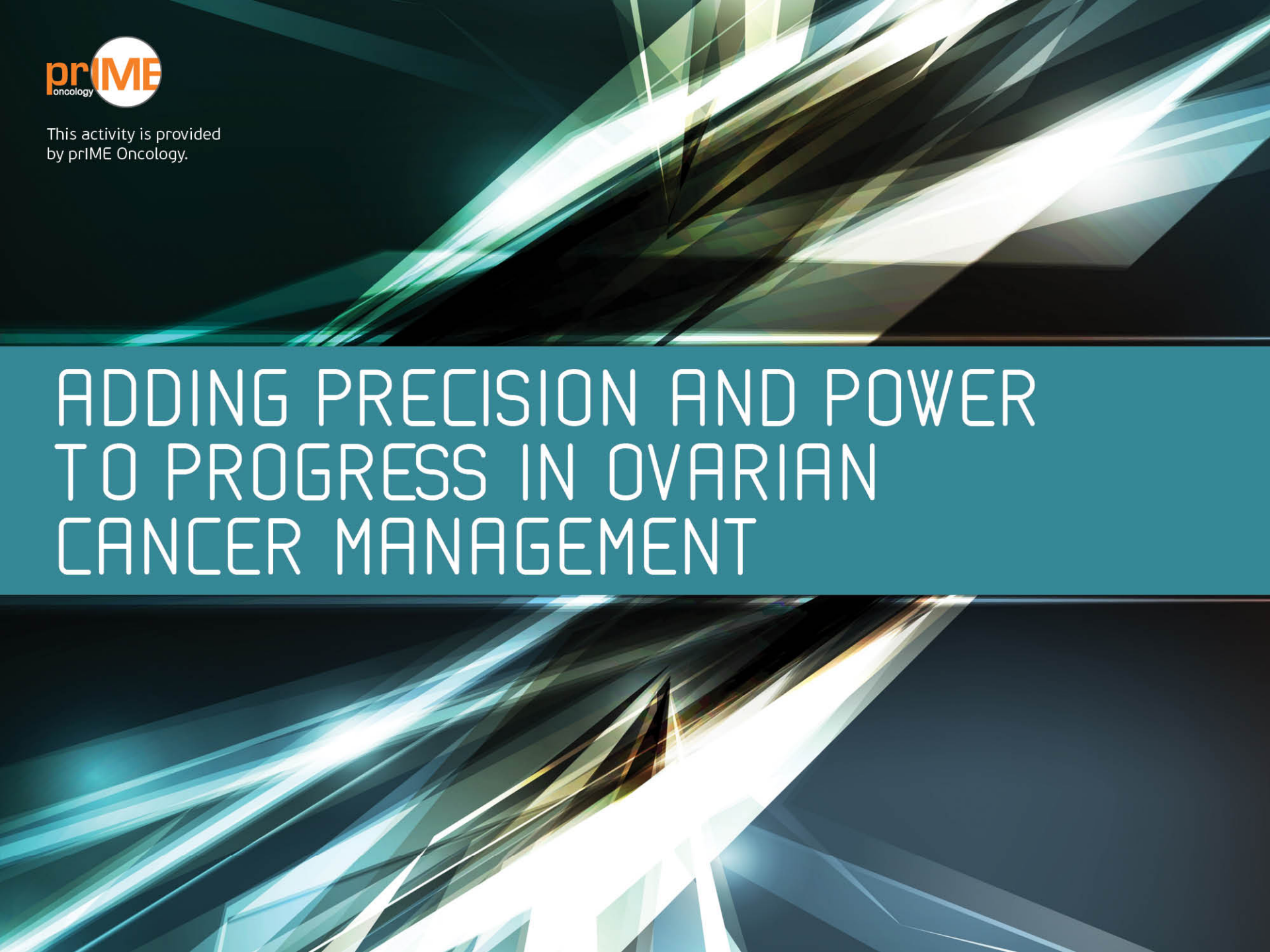



Kaye SB, et al. *Clin Cancer Res.* 2012;18(23):6509-6518.

# Drug Development Program

**Funding**

- **N01 Contract – US NCI**
- **Cancer Care Ontario**
- **US Dept of Defense – Ovarian Cancer Translational Grants**
- **OICR – Translational Research**
- **PMH Foundation**
- **Bras Family**



This activity is provided by prIME Oncology.

# ADDING PRECISION AND POWER TO PROGRESS IN OVARIAN CANCER MANAGEMENT