# A Look to the Future: How to Integrate New Agents Into the Current Treatment Algorithm?

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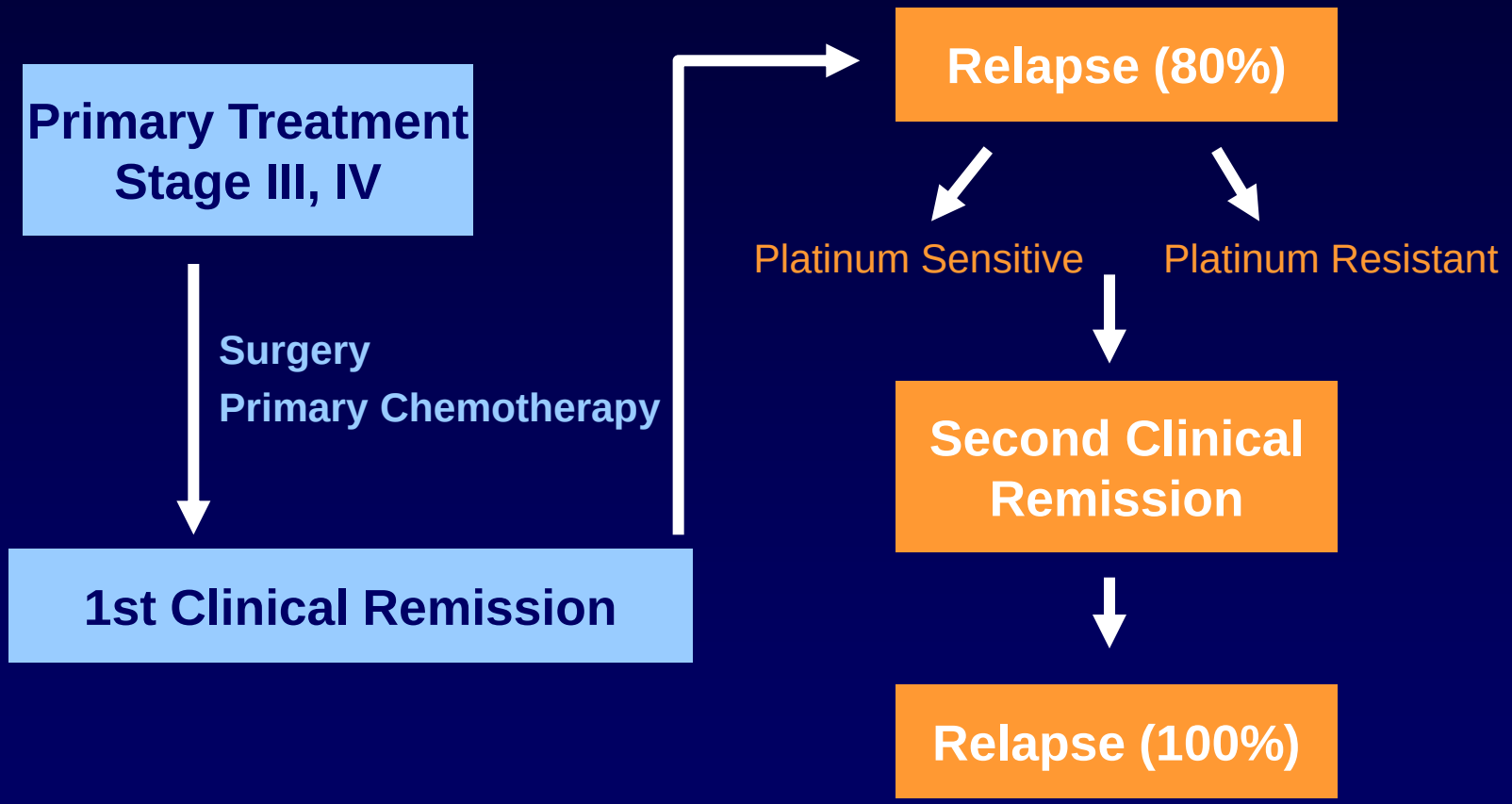
# Ovarian Cancer: A Unique Disease Pattern

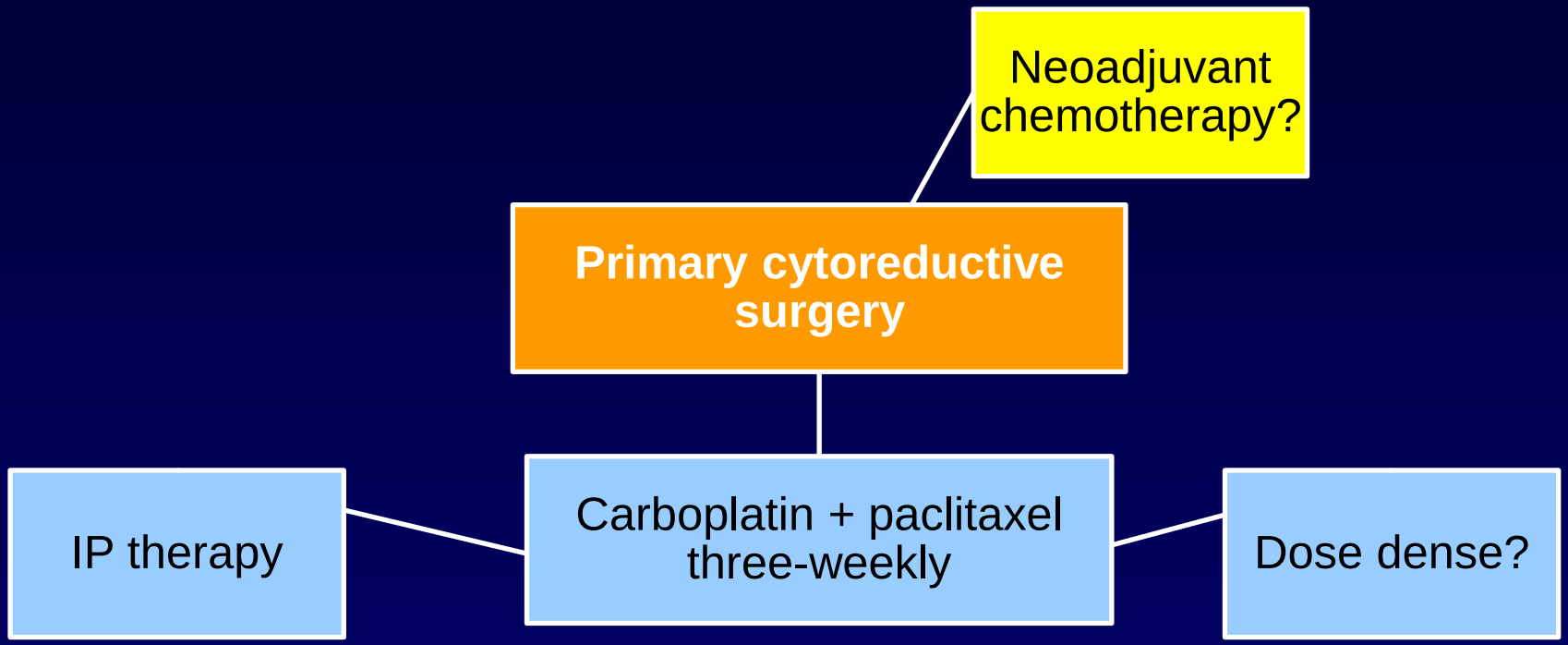


# It’s All Matter of Strategy

# A3: Is the 2004 GCIG recommended standard comparator arm still valid?

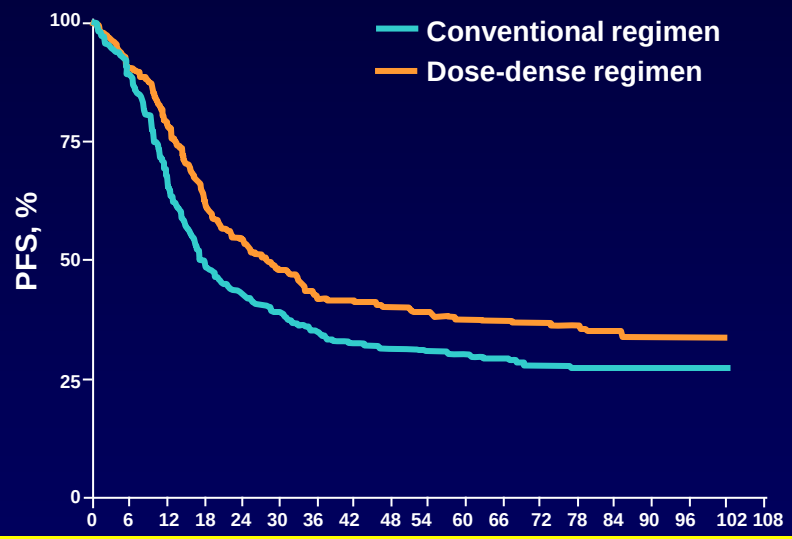
- **The standard arm must contain a taxane and a platinum agent administered for 6 cycles**
- **The recommended regimen is paclitaxel (175 mg/m$^2$) and carboplatin (AUC 5-6) intravenously q3w**

# Ovarian Cancer: First-Line Treatment Algorithm



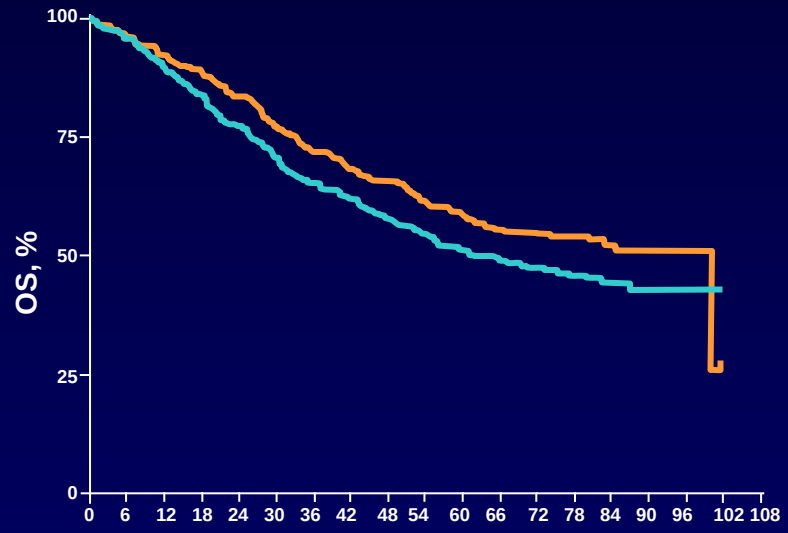
# Possible Variations
# First-Line Dose-Dense in Ovarian Cancer
# JGOG-3016

## PFS




**Median PFS**
**28.2 months vs 17.5 months**
**(HR 0.76, 95% CI 0.62-0.91;**
***P* = .0037).**

## OS

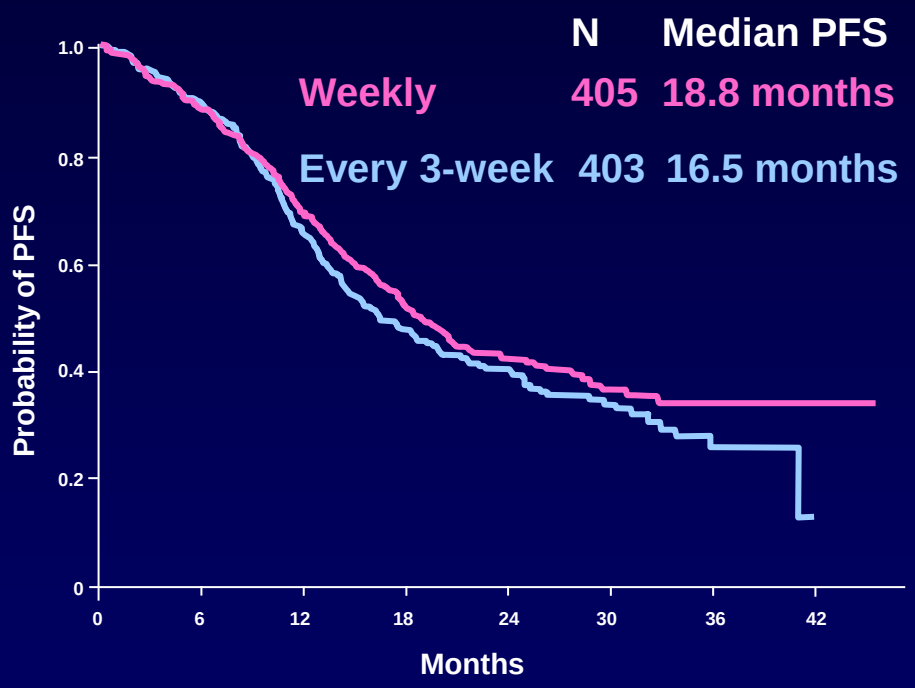



**Median OS was**
**100.5 months vs 62.2 months**
**(HR 0.79, 95% CI 0.63-0.99;**
***P* = .039).**

Katsumata N, et al. *Lancet Oncol.* 2013;14(10):1020-1026.

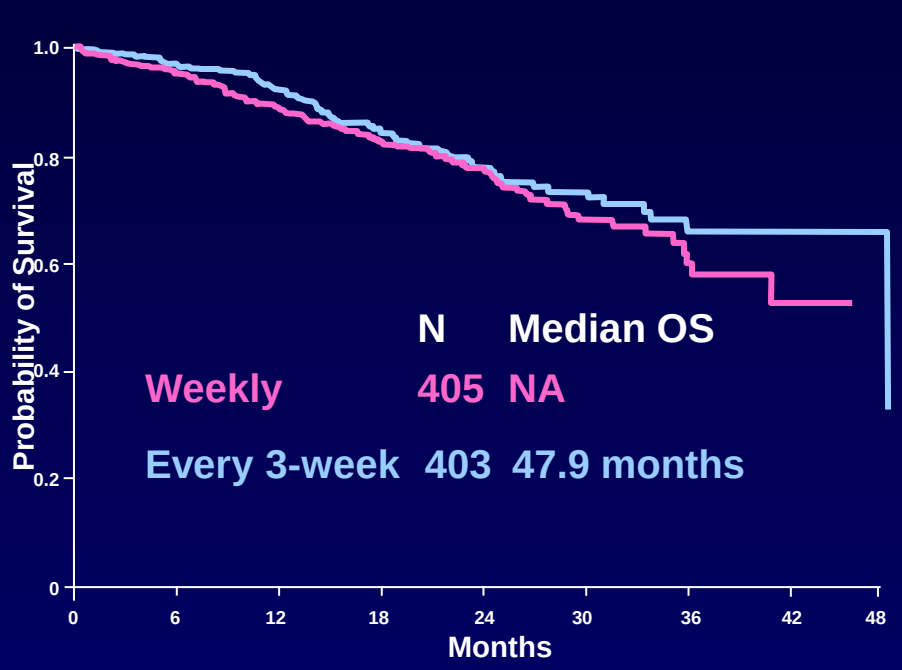
# First-Line Dose-Dense in Ovarian Cancer MITO 7

## PFS




**Median PFS 18.8 months vs 16.5 months**
**Log-rank test *P* = .18**
**Unadjusted HR: 0.88 (0.72-1.06)**

## OS

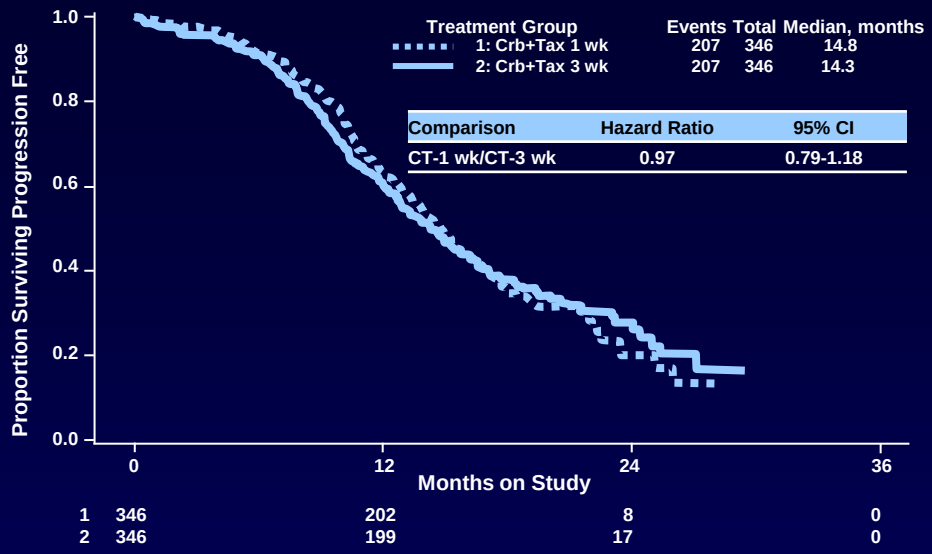



**Median OS NA vs 47.9 months**
**Log-rank test *P* = .24**
**Unadjusted HR: 1.20 (0.88-1.63)**

Pignata S, et al. *Lancet Oncol.* 2014;15(4):396-405.

# Upfront Ovarian Cancer Treatment—Modifying Dose Regimen

## GOG 262 PFS by Randomized Treatment (n = 692)




# Upfront Ovarian Cancer Treatment—Modifying Dose Regimen

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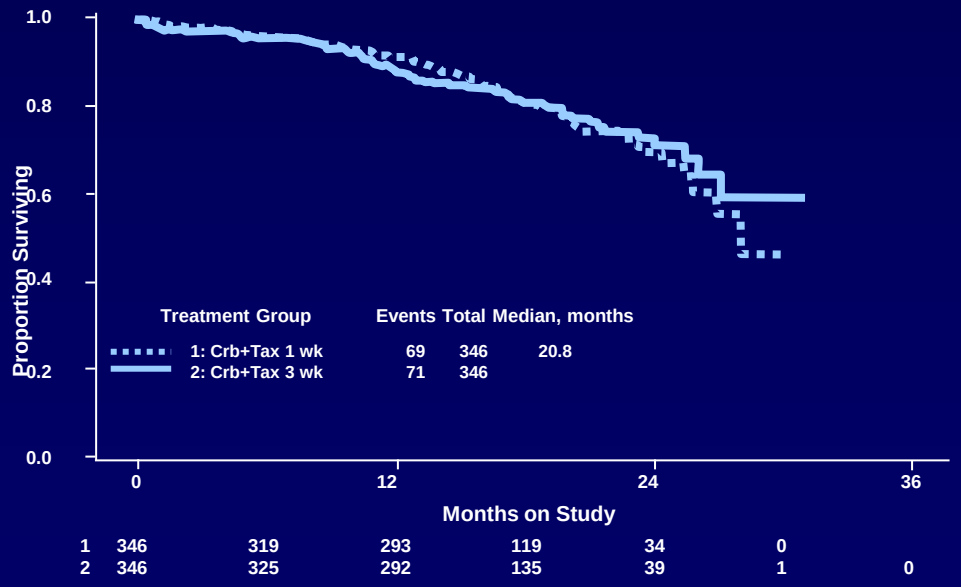
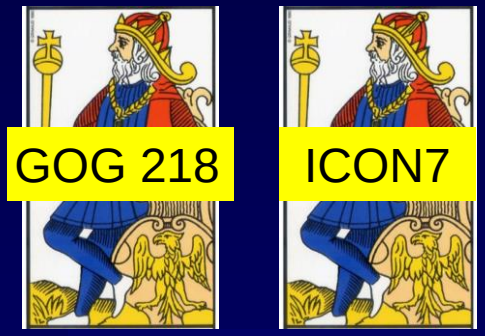



Chan JK, et al. *Int J Gynecol Cancer.* 2013;23(8Suppl1):9-10.

# First Line: How to Integrate New Agents Into the Current Treatment Algorithm?

1st line
Concomitant +
Maintenance




**Bevacizumab**

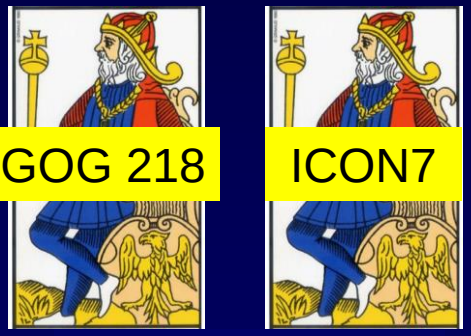

**Nintedanib**

1st line
Maintenance


**Pazopanib**

# First Line: How to Integrate New Agents Into the Current Treatment Algorithm?

1st line
Concomitant +
Maintenance




**Bevacizumab**

Not approved

1st line
Maintenance

Not approved

# First Line: How to Integrate New Agents Into the Current Treatment Algorithm?

| 1st line Concomitant + Maintenance | 1st line Maintenance |
| --- | --- |
| Olaparib | |
| Not approved | |

# First-Line: How to Integrate Olaparib Into the Current Treatment Algorithm?

1. **Treatment based on predictive biomarkers for outcome:**
   - **Bevacizumab?**
   - **Olaparib: *BRCA* mutation**

2. **Combination of bevacizumab and olaparib: Paola 1 study**

# Is It Possible to Predict Benefit From Angiogenesis Inhibitors?

- Multiple studies – exploratory and uncertain
- Discriminatory signature comprising mesothelin, FLT4, AGP and CA-125-ICON7: Collinson et al
- Gourley et al: Immune vs non-immune subgroup
- Winterhoff et al: Benefit related to molecular subtype: ‘mesenchymal and proliferative’

**No validated biomarkers to guide decisions at present**

# Is It Possible to Predict Benefit From Angiogenesis Inhibitors?

- Multiple studies … exploratory and uncertain

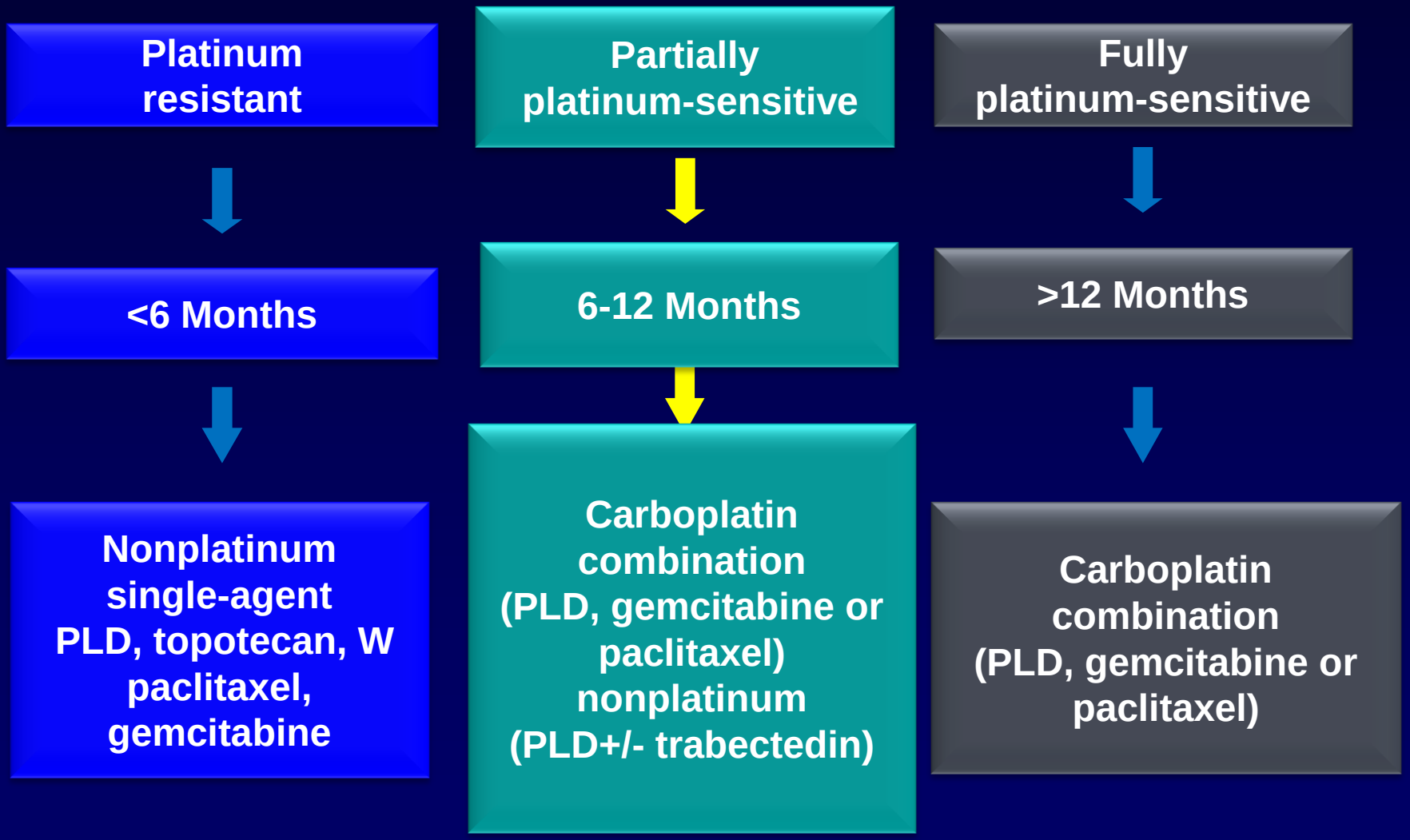
**In which of these groups will tumors with *BRCA* mutation fit? If they belong to the immunogenic group, does this mean they can be less sensitive to bevacizumab?**

- No validated biomarkers to guide decisions at present

# Q1: Which treatment would you recommend for this patient?

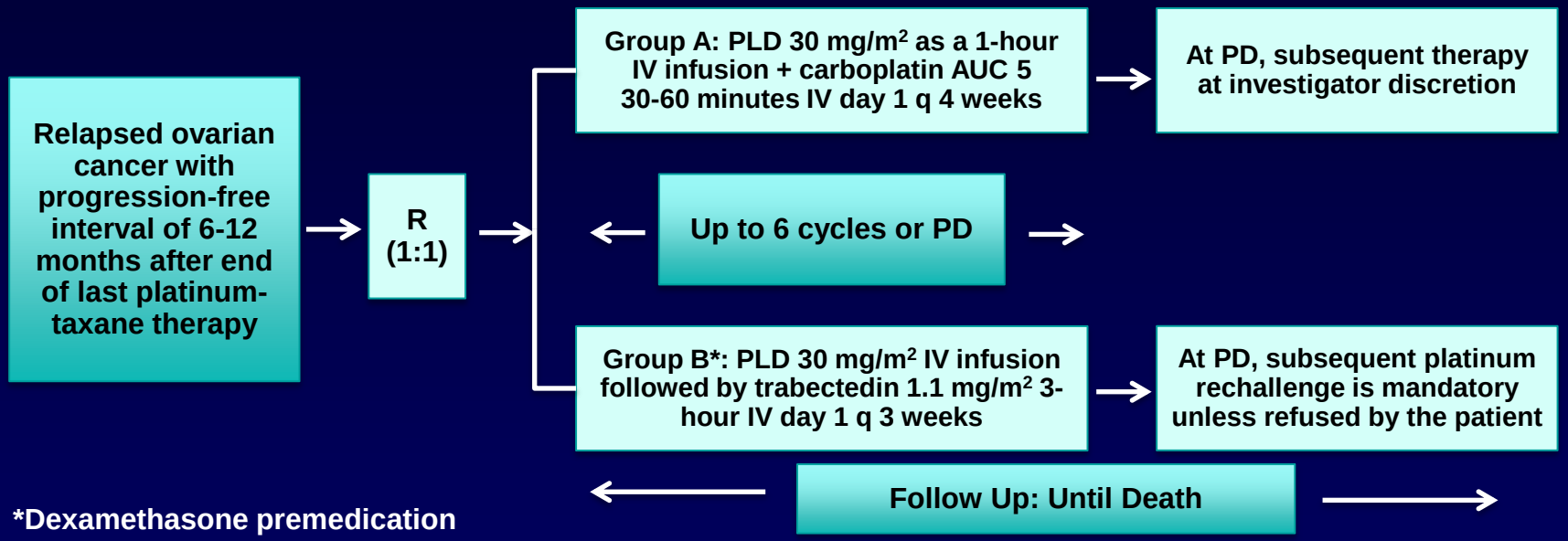
1. Carboplatin-paclitaxel (three-weekly)
2. Carboplatin-paclitaxel (three-weekly) + bevacizumab
3. Carboplatin-paclitaxel (weekly)
4. Carboplatin-paclitaxel (weekly) + bevacizumab
5. Test the patient for *BRCA* mutation and enroll in clinical studies with PARP-inhibitors

# Generally-Accepted Guideline for Chemotherapy at Recurrence



# INOVATYON Study Design

## A multicenter, randomized (1:1) phase III study




*Dexamethasone premedication

### Primary Endpoint

- To evaluate OS in patients with relapsed ovariasn cancer progressing within 6-12 months after end of last platinum

### Sponsor

- MaNGO (Mario Negri Gynecologic Oncology)

### Secondary Endpoints

- To evaluate the time from randomization to subsequent chemotherapy and the OS counted from the administration of subsequent chemotherapy
- To evaluate serologic response of CA-125
- Quality of life
- Safety profile, PFS, ORR

# Subsequent Lines: How to Integrate New Agents Into the Current Treatment Algorithm?

| Resistant (<6 mos) | Sensitive (6-12 mos) | Sensitive (>12 mos) |
|---|---|---|

AURELIA

**bevacizumab**

OCEANS

**bevacizumab**

MITO 11

**pazopanib**

ICON6

**cediranib**

19

**olaparib**

TRINOVA-1

**trebananib**

# Subsequent Lines: How to Integrate New Agents Into the Current Treatment Algorithm?

| Resistant (<6 mos) | Sensitive (6-12 mos) | Sensitive (>12 mos) |
|---|---|---|


**bevacizumab**


**bevacizumab**

Not approved


**olaparib**

# Subsequent Lines: How to Integrate New Agents Into the Current Treatment Algorithm?

| Resistant (<6 mos) | Sensitive (6-12 | Sensitive |
|---|---|---|
| AURELIA<br>bevacizumab | | |
| Not approve | | |

# Subsequent Lines: How to Integrate New Agents Into the Current Treatment Algorithm?

| Re… (< | …sitive | Sensitive (>12 mos) |
|---|---|---|


…OCEANS

…vacizumab


olaparib

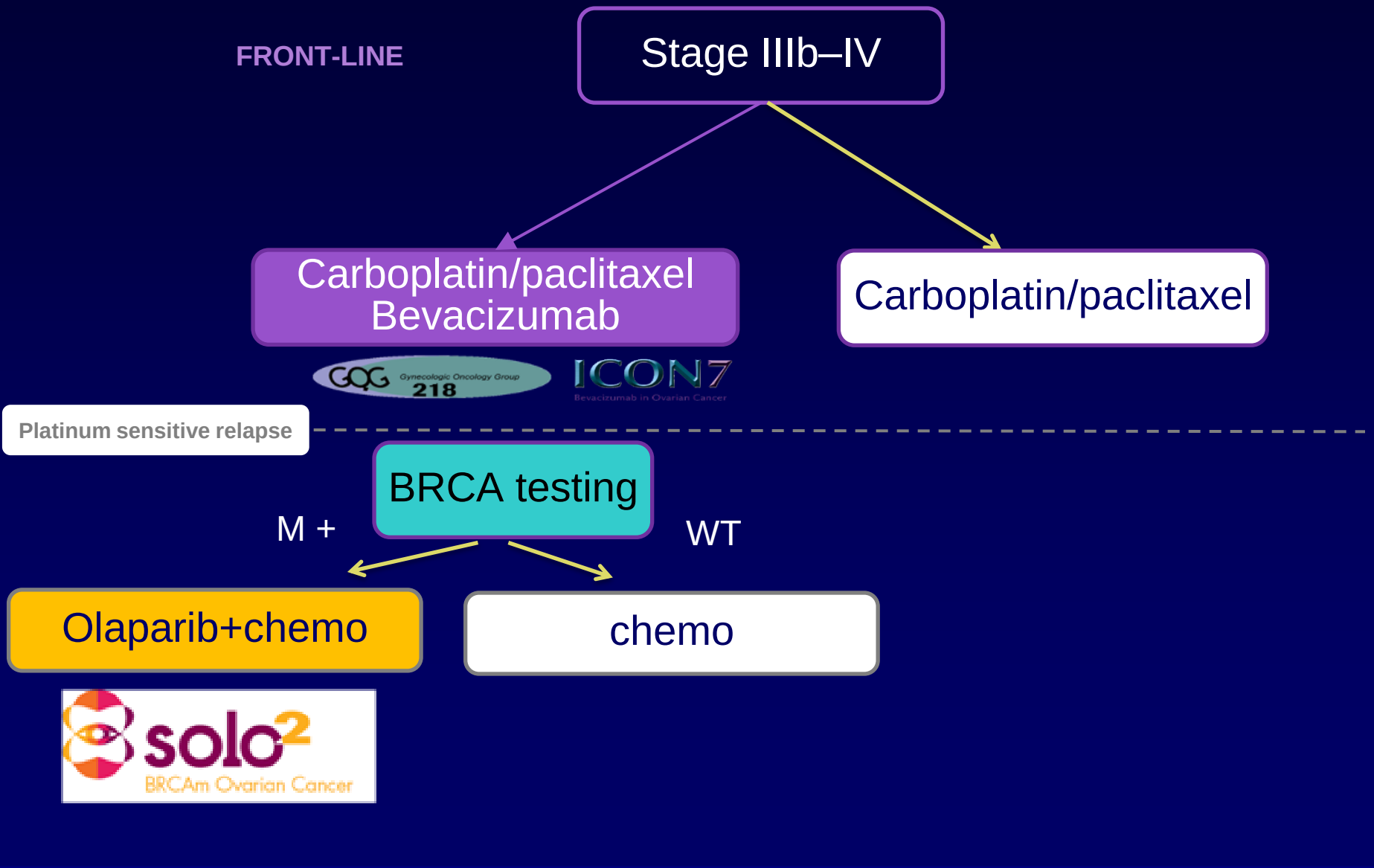
## Q1: Which treatment would you recommend for this patient with platinum-sensitive recurrence?

1. Carboplatin-paclitaxel (three-weekly)
2. Carboplatin-gemcitabine + bevacizumab
3. Enroll the patient in the INOVATYON study (Carboplatin-PLD vs trabectedin-PLD)
4. Test the patient for *BRCA* mutation and, if mutated, treat with platinum-based combination chemotherapy followed by maintenance therapy with olaparib

# Recurrence: Olaparib or Bevacizumab?

1. **Bevacizumab:**
   a. **Platinum sensitive: Approved only with carboplatin and gemcitabine and only for the first recurrence**
   b. **Platinum-resistant: Approved with weekly paclitaxel or PLD or topotecan after ≤2 prior lines**
2. **Olaparib:**
   a. **Platinum sensitive: Approved as maintenance for any platinum-sensitive recurrence**
   b. **Platinum resistant: Not approved**

# Looking at the Future: Ovarian Cancer Treatment Algorithm



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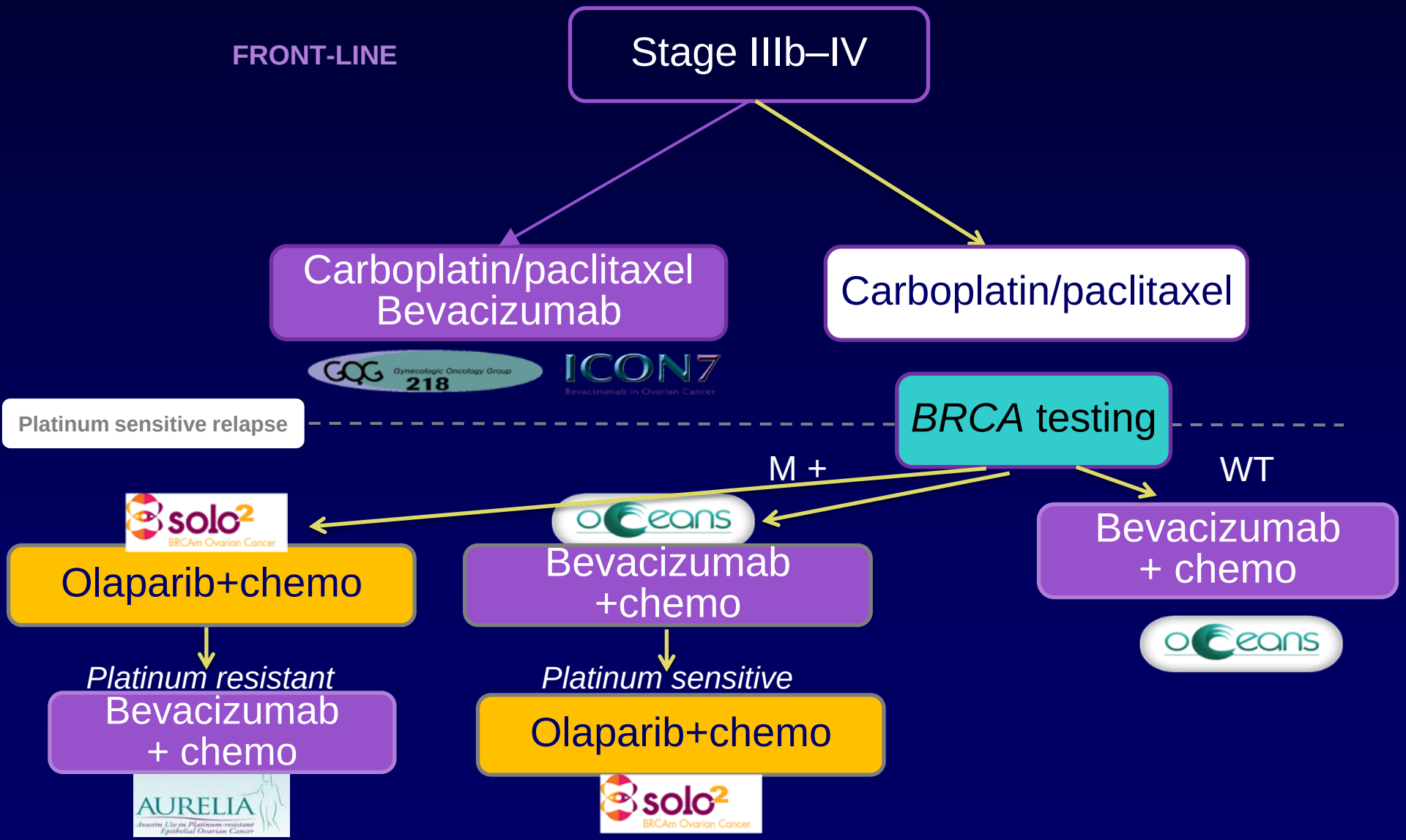

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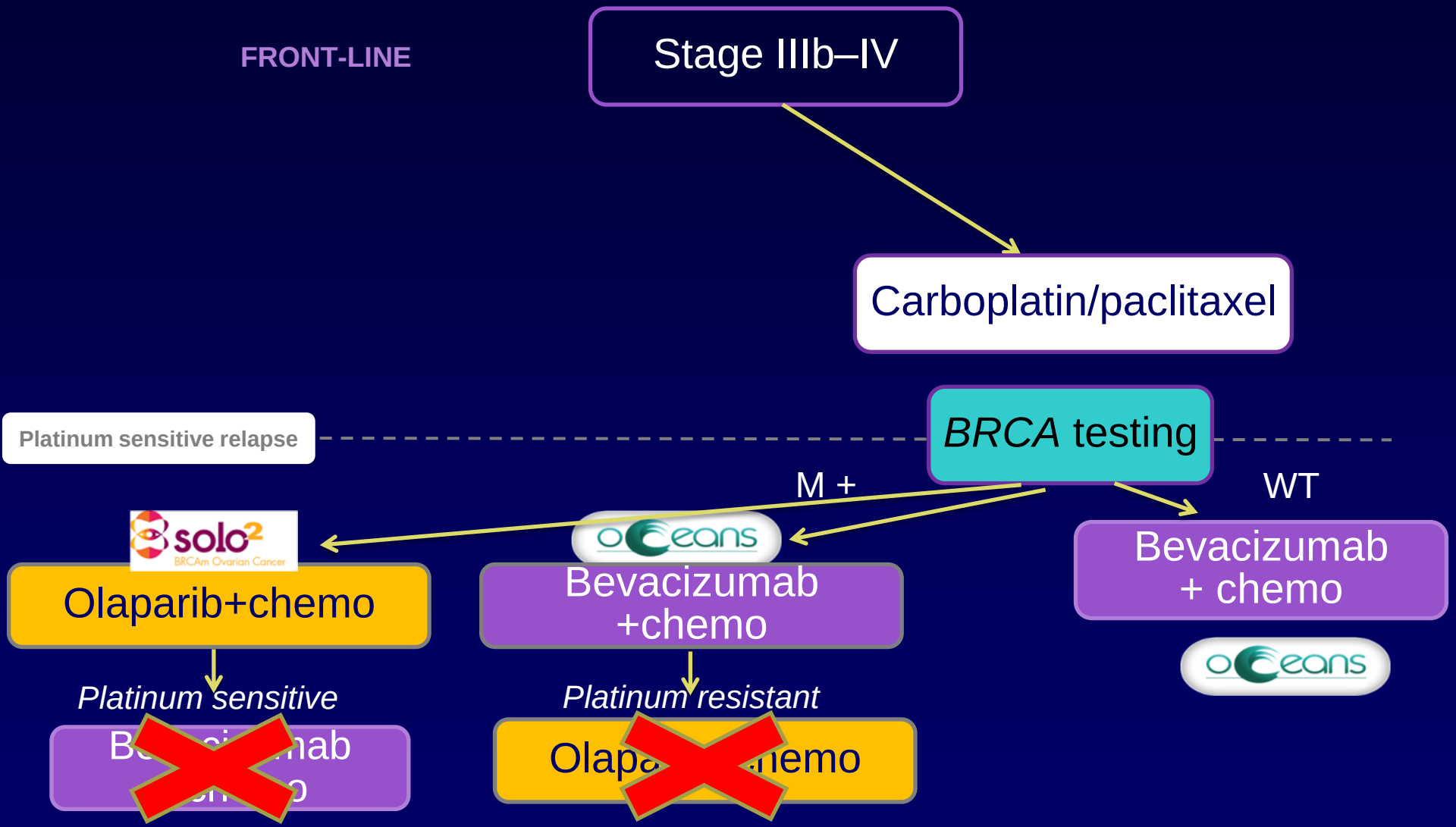

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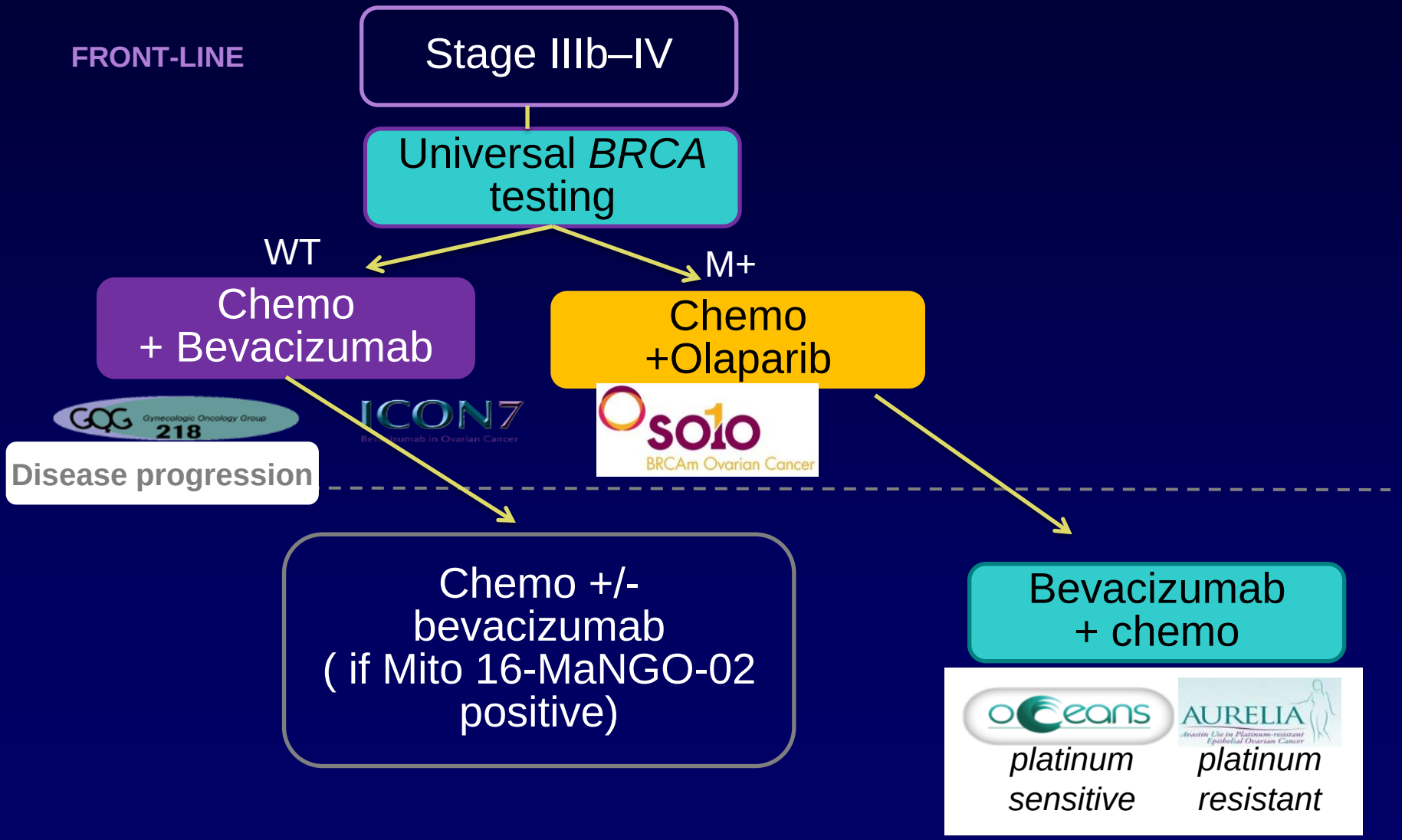

# Conclusions

- Cytoreductive surgery followed by carboplatin/paclitaxel chemotherapy q3 weekly is the mainstay of initial treatment of ovarian cancer
- Intraperitoneal delivery and dose-dense regimens represents alternative schedules of administration of paclitaxel and platinum chemotherapy
- Antiangiogenic therapy is active in ovarian cancer and bevacizumab is currently the only approved antiangiogenic therapy in front-line and in recurrent disease (both platinum-sensitive and resistant)
- There is a lack of specific biomarkers to predict who may benefit from antiangiogenic therapy
- Olaparib is approved as maintenance therapy in patients with platinum-sensitive relapse in response to platinum treatment and *BRCA* mutation (germline and somatic)
- An accurate strategic planning is needed to integrate new agents in the current treatment algorithm, in order to achieve the best outcome

# Integrating New Therapies Into Ovarian Cancer Management: Does *BRCA* Status Matter?