MADRID 2014 ESMO congress

Educational Session

Ovarian Cancer

Antiangiogenic therapy: Where in the disease pathway and which patients?

Antonio González Martín

MD Anderson Cancer Center

Madrid·Spain

Disclosure

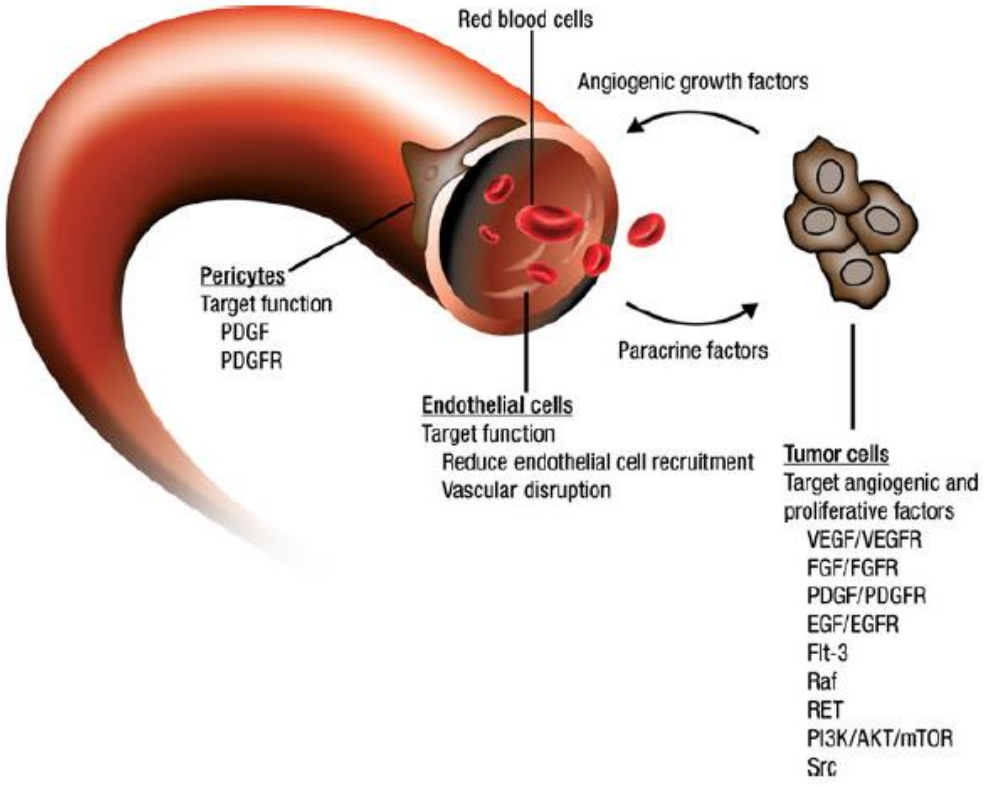
- Advisory compensated: MSD, Roche, Pharmamar.

Learning Objetives

- To review efficacy data of the different randomized clinical trials in the different context of the epithelial ovarian cancer.

- To deal with the different subgroups analysis and biomarkers studies.

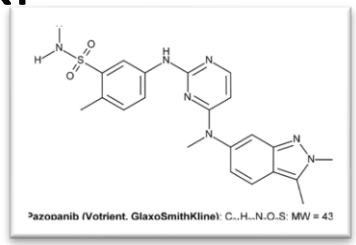
Key angiogenic targets in ovarian cancer

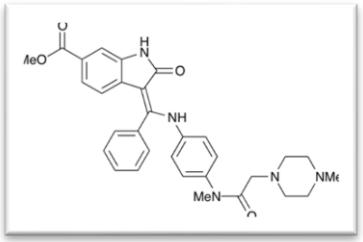


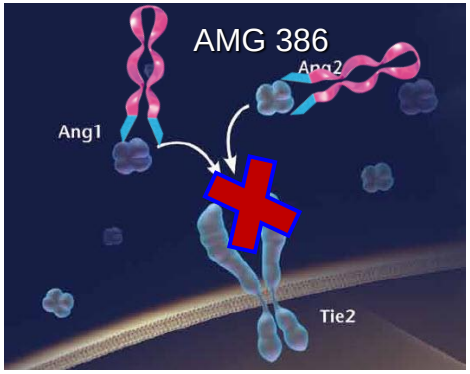
Westin SN et al. Invest New Drugs 2012;Jun 4. [Epub ahead of print]

Anti-angiogenic agents with data in Phase III trials

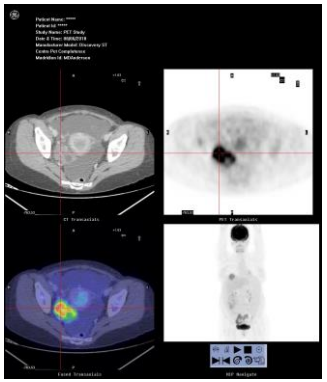
- VEGF-VEGFR pathway:
  - MoAb anti-VEGF
    - Bevacizumab
  - Small molecule-TKI
    - Pazopanib
    - Nintedanib
    - Cediranib
- Angiopoetin pathway:
  - Peptibody anti Ang1-Ang2
    - Trebananib

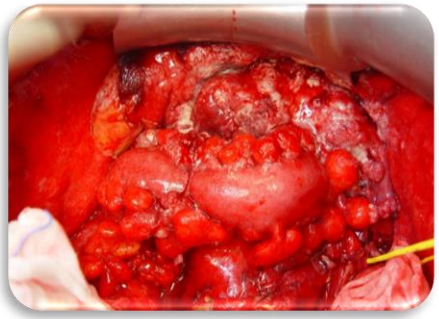






Optimal Up-front Therapy





Diagnosis

Debulking Surgery

Systemic therapy

Anti-angiogenic agents and strategies with data in Phase III trials in front line

- Strategies
  - Concomitant with chemo followed by maintenance
    - Bevacizumab
    - Nintedanib

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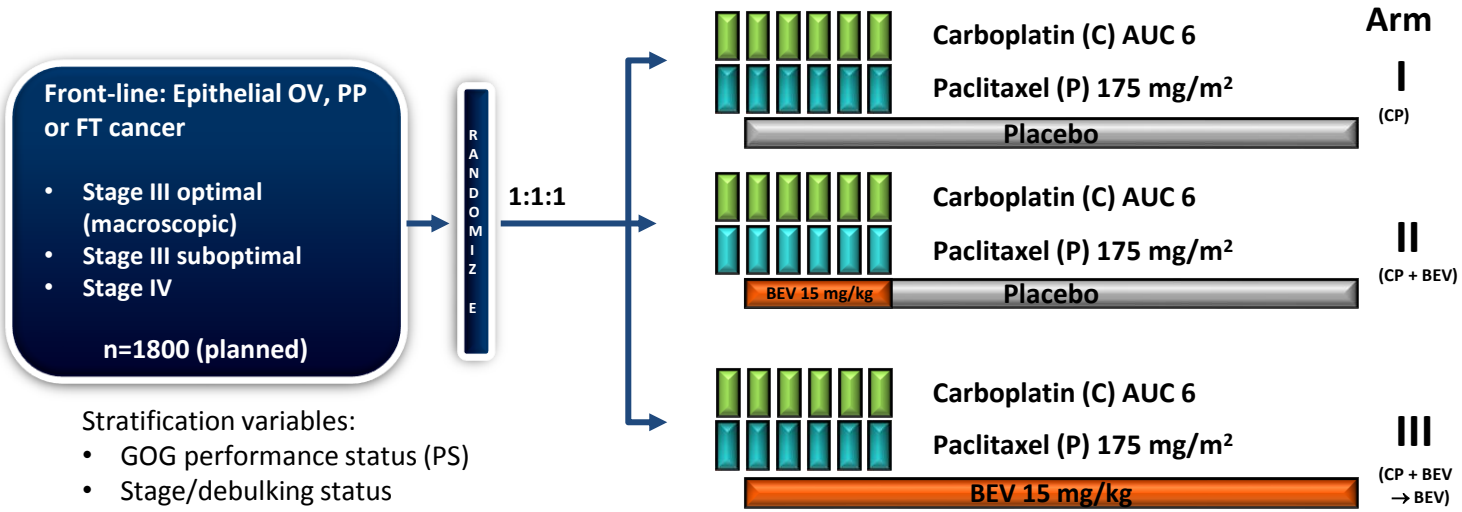
Bevacizumab in front line: GOG-218 & ICON-7



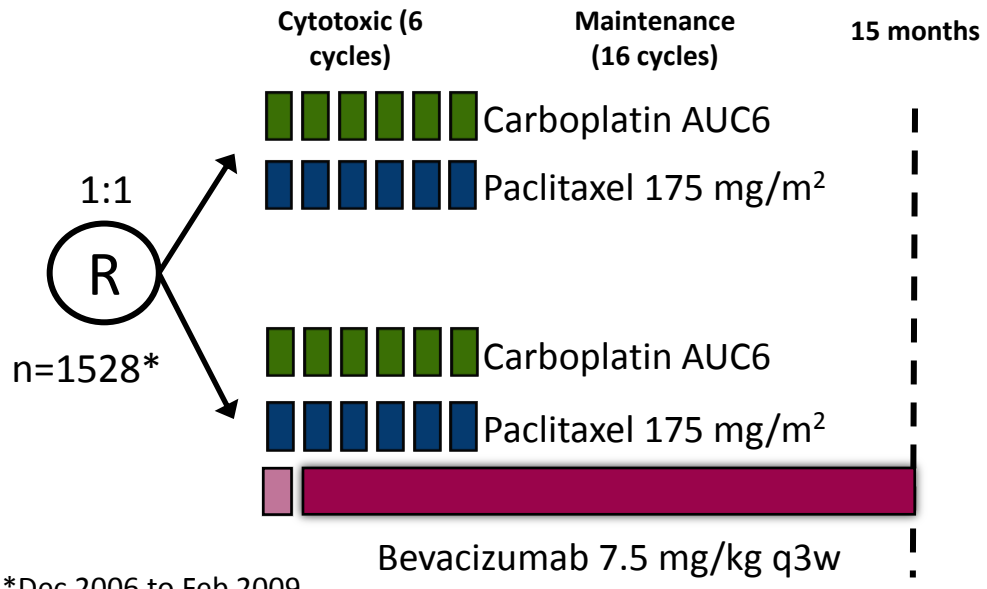
Stratification variables:
- GOG performance status (PS)
- Stage/debulking status

FIGO stage

I–IIA if high risk: Grade 3 or clear cell histology (10%)

IIB–IV: All grades and histological subtypes

Patients with inoperable stage III/IV disease eligible after biopsy only if no further surgery planned



*Dec 2006 to Feb 2009

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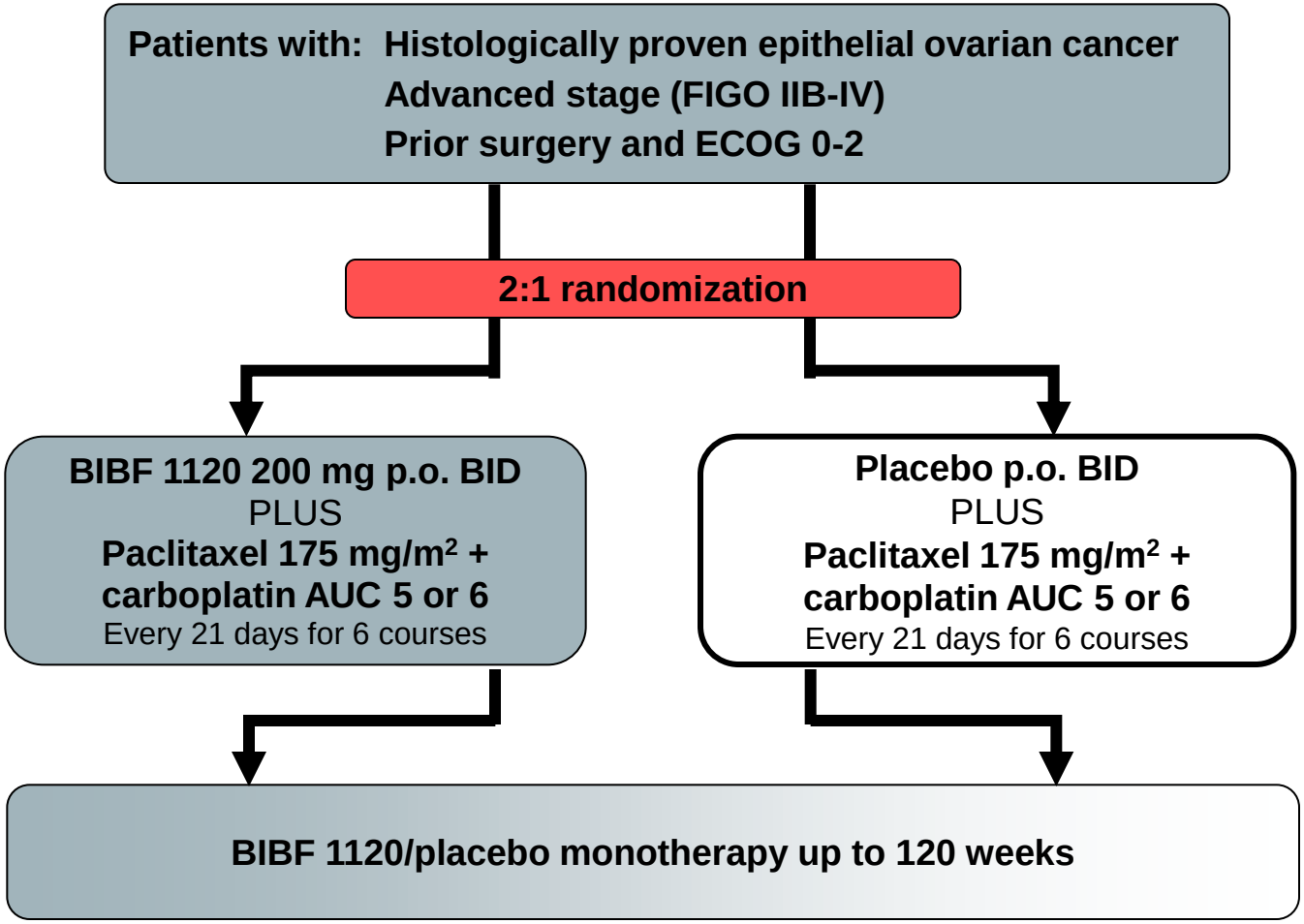
Study Design

- **Phase III randomized, placebo-controlled, double-blind, multicenter**
- **N=1,366 patients randomized (2:1) from December 2009 to July 2012**



Anti-angiogenic agents and strategies with data in Phase III trials in front line

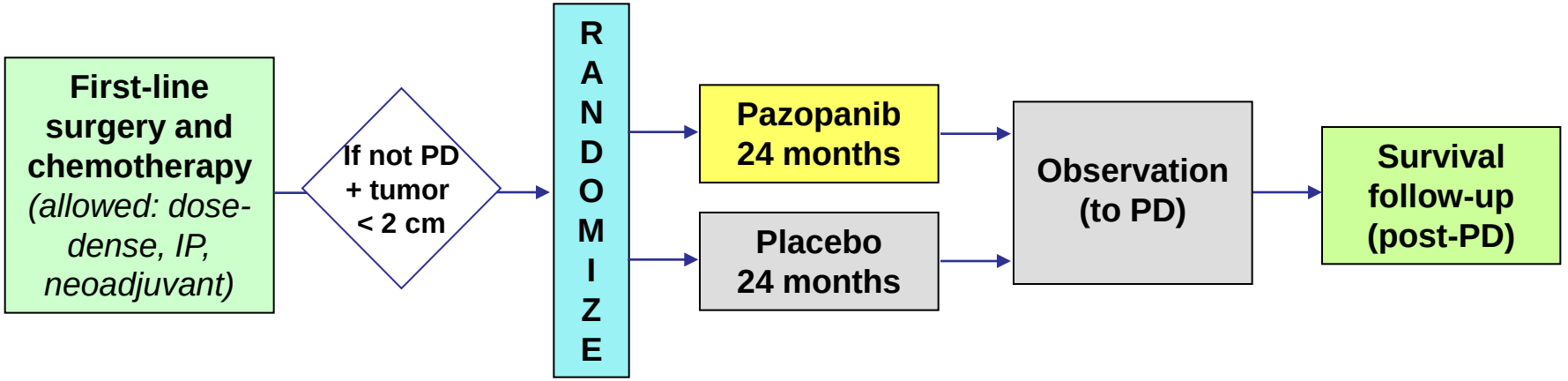
- Strategies
  - Concomitant with chemo followed by maintenance
    - Bevacizumab
    - Nintedanib

  - Maintenance after chemotherapy
    - Pazopanib

AGO-OVAR 16

Study Design

- **Phase III randomized, placebo-controlled, double-blind, multicenter**
- **N=940 patients randomized (1:1) from June 2009 to August 2010**
- **Pazopanib administered at 800 mg daily for up to 24 months***



Median 7 months from diagnosis to randomization

***Original design was for 12 months and later amended to 24 months**

PFS & OS Results

	PURE FRONT-LINE			MAINTENANCE
PFS	**GOG-218**	**ICON-7**	**OVAR-12**	**OVAR-16**
HR (95% CI)	0.71 (0.62-0.82)	0.86 (0.75-0.98)	0.84 (0.72-0.98)	0.77 (0.64-0.91)
Δ Months	+4.1 (10.3 vs 14.4)	+2.4 (16.9 vs 19.3)	+0.6 (16.6 vs 17.3)	5.6 (12.3 vs 17.9)
HR censor (95% CI)	0.62 (0.52-0.75)			
Δ Months (censor)	+6.2 (12 vs 18.2)			
OS	**GOG-218**	**ICON-7**	**OVAR-12**	**OVAR-16**
HR (95% CI)	0.88 (0.75-1.04)	0.99 (85-1.14)	NR	1.07 (0.86-1.33)
Δ Months	+3.2 (40.6 vs 43.8)	58.6 vs 58.0	NR	NR vs 51.8

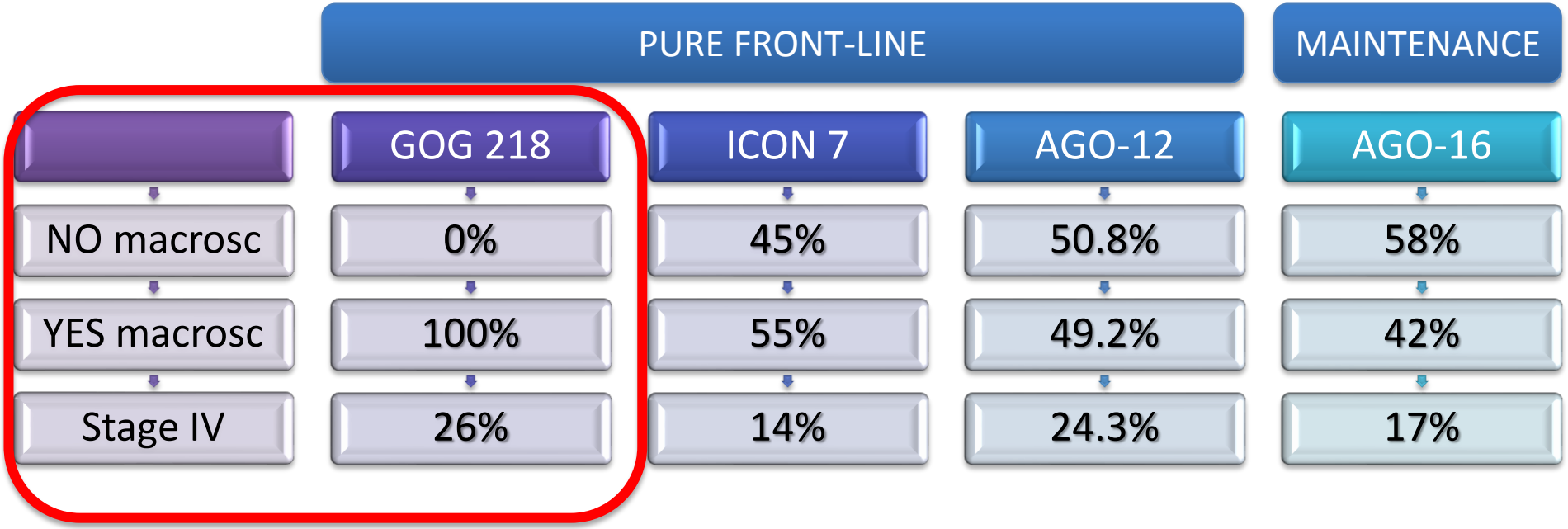
1. Burger et al. NEJM 2011; 2. Perren et al. NEJM 2011;
3. Du Bois et al. ESGO 2013; 4. Du Bois et al. JCO 2014; Nomura et al. ESMO 2014

What anti-angiogenic agent and for which patient in front-line?

- Only bevacizumab has been approved by some health authorities in front-line.
  - The application for pazopanib was withdrawn and the app for nindetanib has not been submitted.

- In the era of personalised medicine…Is there any group of patients obtaining the most benefit from bevacizumab?
  - Selection based on subgroup analysis
  - Selection based on molecular features of the patients

Population in different studies according to stage and residual disease after surgery



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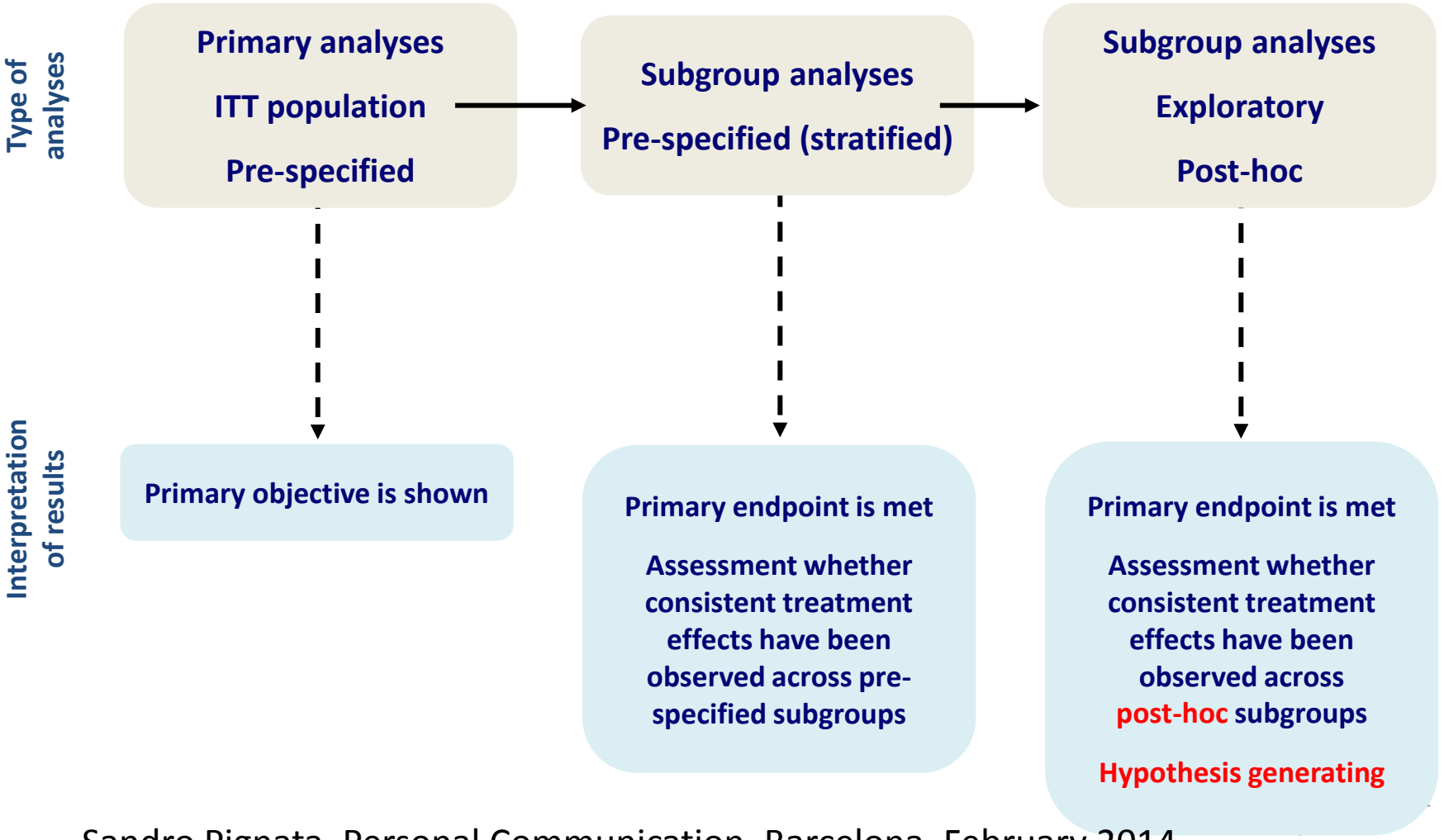
Subgroup Analysis

"Such analyses, which assess the heterogeneity of treatment effects in subgroups of patients, may provide useful information for the care of patients and for future research. However, subgroup analyses also introduce analytic challenges and can lead to overstated and misleading results."

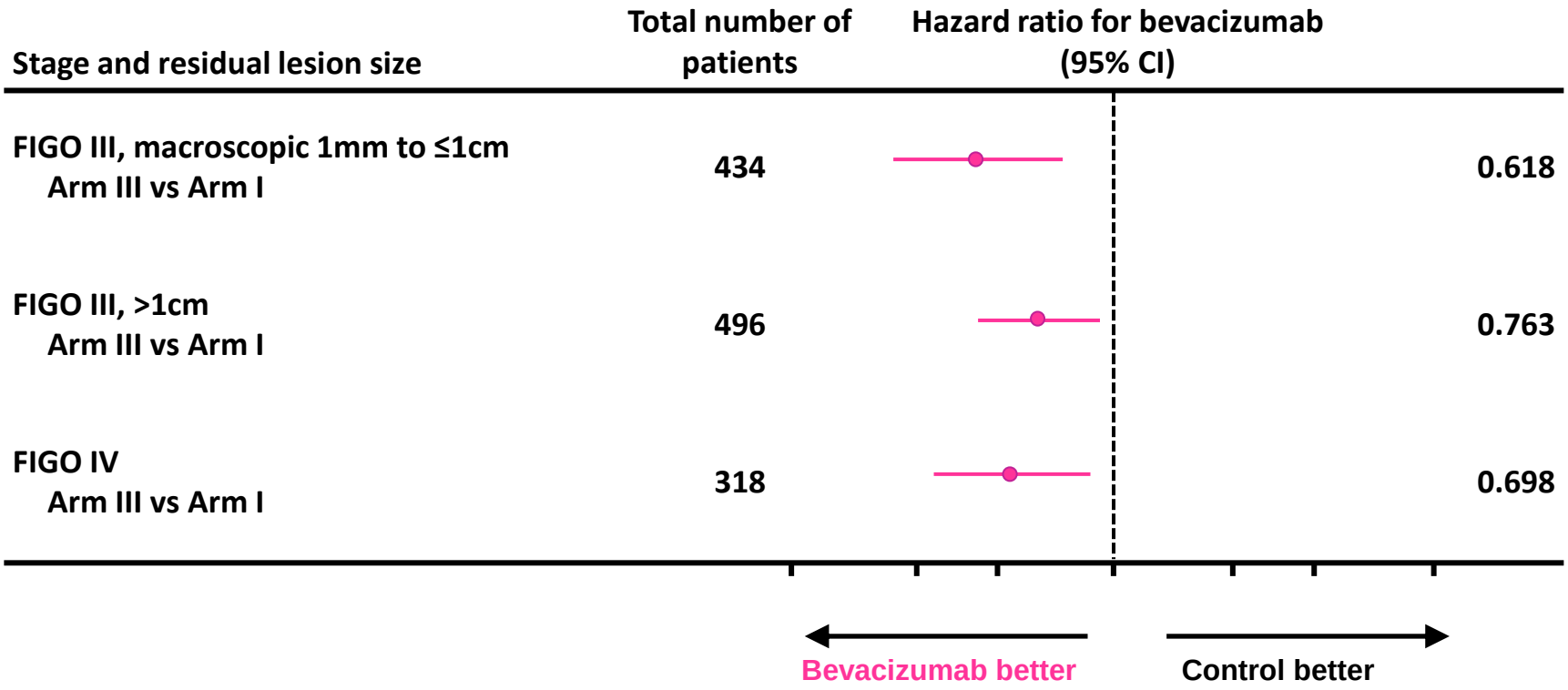
Rui Wang et al. N Eng J Med, Nov 2007

Which data should we consider when making treatment decisions?



Sandro Pignata. Personal Communication. Barcelona, February 2014

Pre-specified Subgroup Analysis in GOG-218



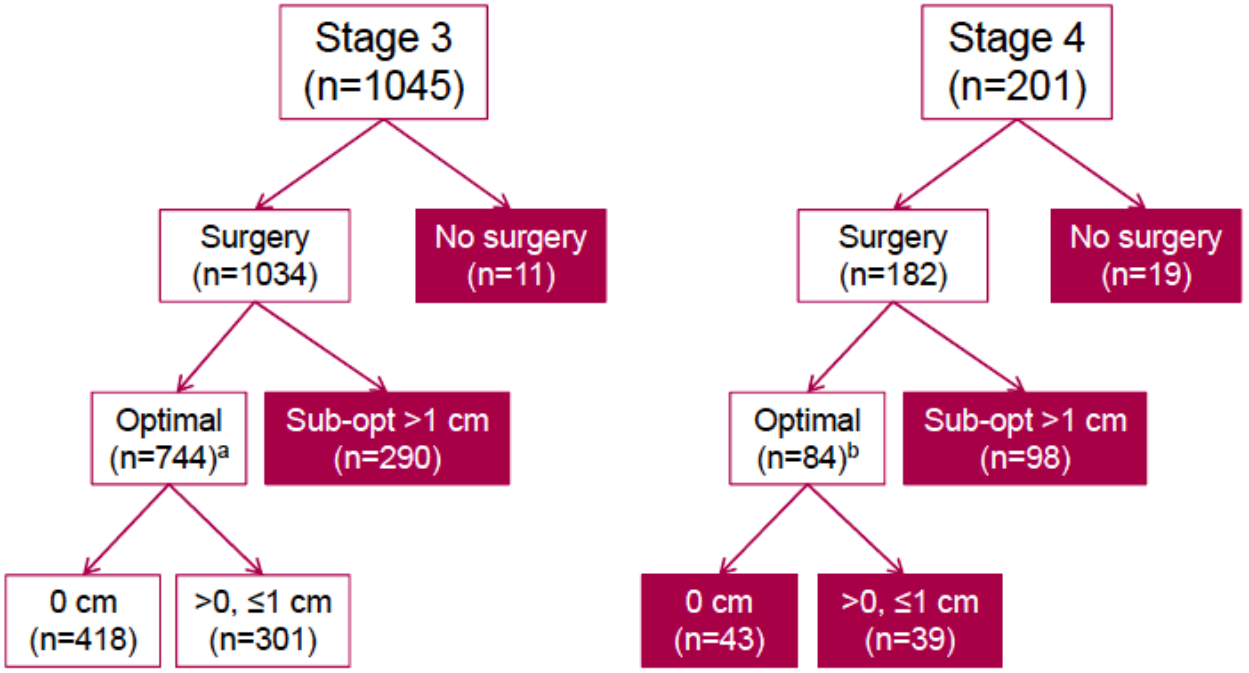
Burger et al. NEJM 2011

ICON7 had a Pre-planned test for interaction in pre-defined subgroups

ICON7
Bevacizumab in Ovarian Cancer

Definition of high-risk subgroup

MRC Clinical Trials Unit



Modified ICON7 high-risk group (n=502)

Original ICON7 high-risk group (n=472)

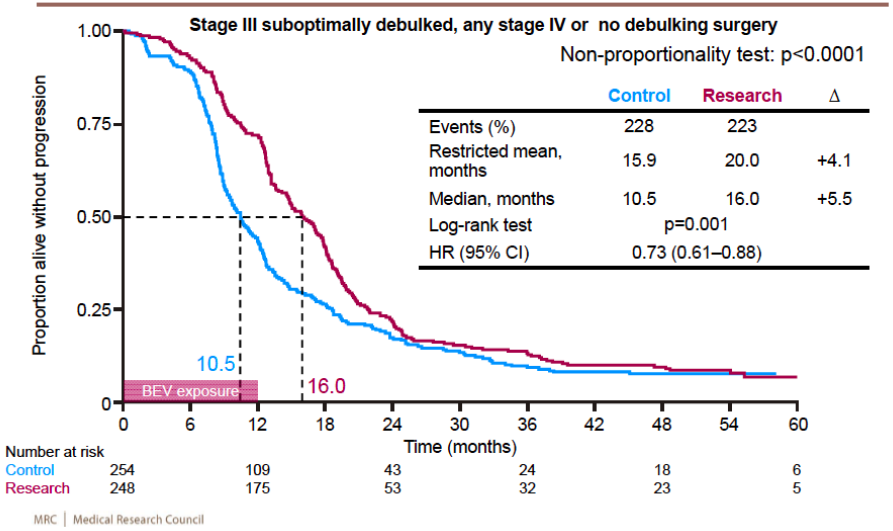
[a]Optimal unknown residual size (n=25)
[b]Optimal unknown residual size (n=2)

Benefit of bevacizumab in high-risk population

ICON7 Bevacizumab in Ovarian Cancer

PFS (2013 update): High-risk (n=502)

MRC Clinical Trials Unit



Final OS analysis

HR 0.73 (0.61-0.88)

Median F/U 49 months

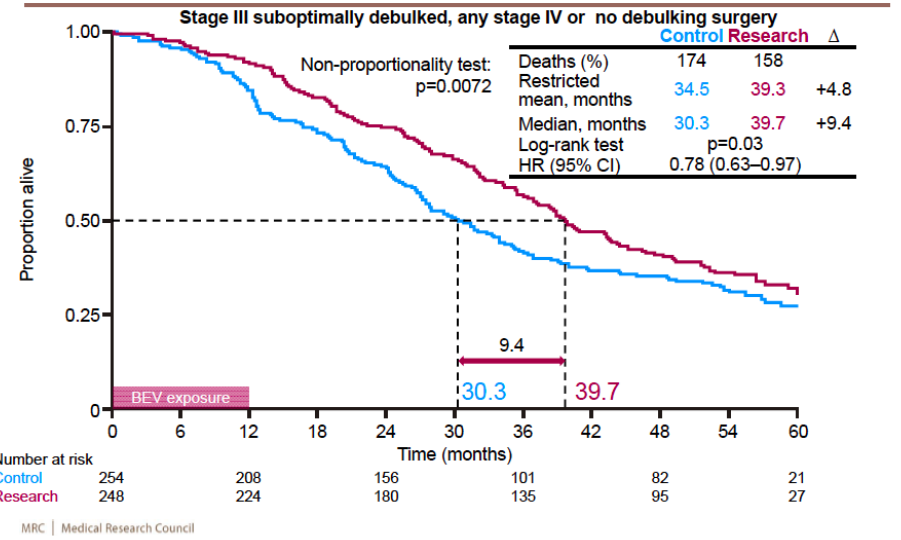
1080 events

Oza. ESMO 2013

ICON7 Bevacizumab in Ovarian Cancer

Final OS: High-risk (n=502)

MRC Clinical Trials Unit



Final OS analysis

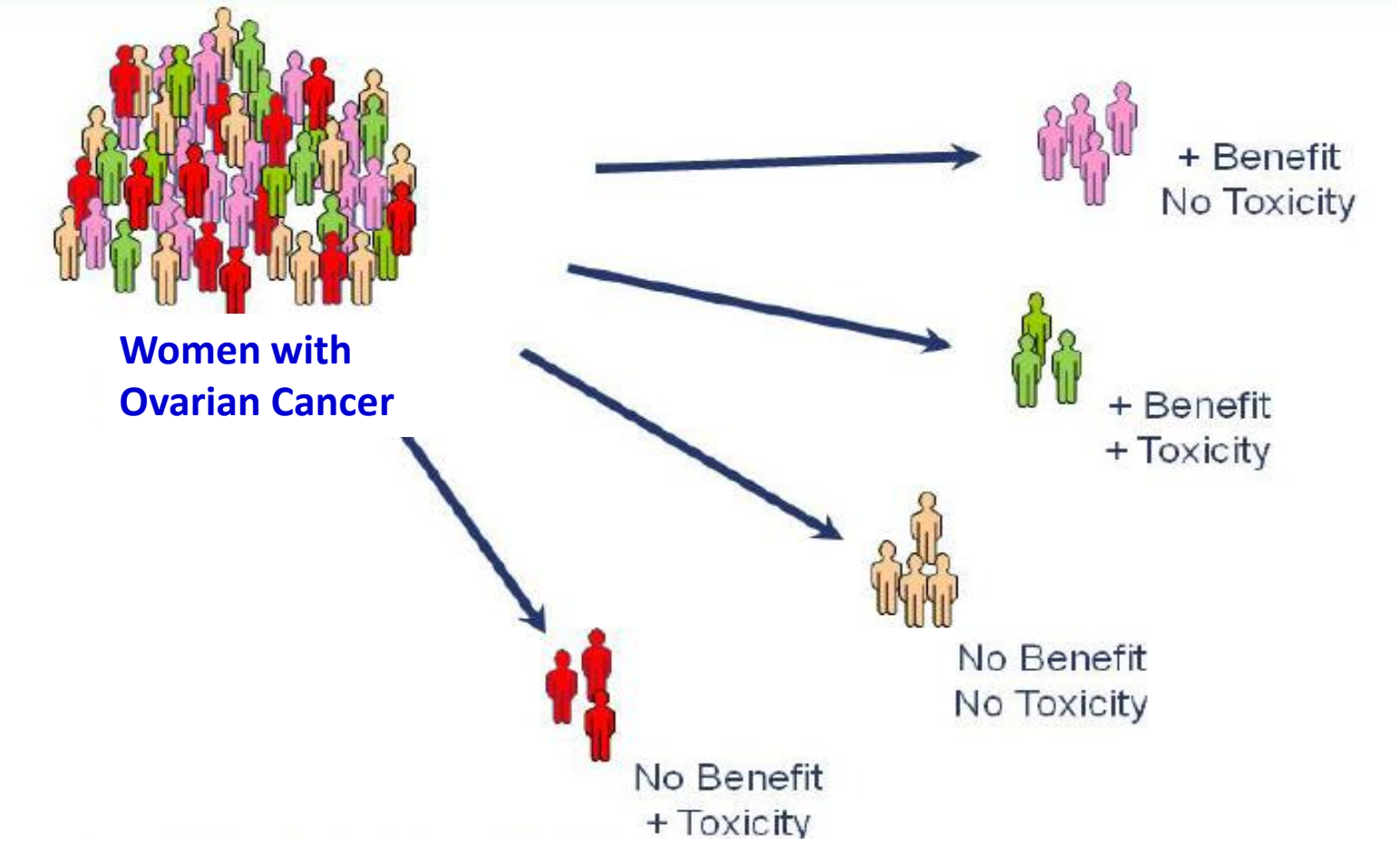
HR 0.78 (0.63-0.97)

Median F/U 49 months

714 events

Oza. ESMO 2013

In the era of personalised medicine…
Is there any group of patients obtaining the most benefit from bevacizumab according to a molecular profile?



Traslational Research in ICON-7

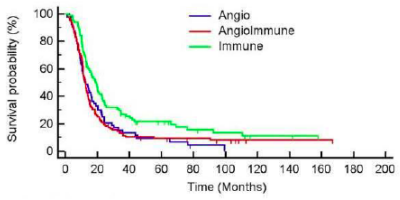
Edimburgh[1]	AGO-Mayo[2]	Toronto[3]
284 HGSOC	359 OC (All subtypes)	400 OC (All subtypes)
FFPE	FFPE	Perpheral blood
Macrodissected	Macrodissected	Germline DNA
ALMAC disease specific array	DASL whole genome array	Illumina exome chip 1.1
63-gene signature	-	GWAS (Genome Wide Association Study)
2 clusters: Inmune and angio-inmune + angio	Reproduce 4 TCGA molecular subtypes	SNPs
Association with PFS and OS	Benefit in PFS for HGS-Proliferative and in OS for HGS-Mesenchymal	Not reach the GWAS level of significance

1. Gourley et al. ASCO 2014, A#5502
2. Winterhoff et al. ASCO 2014, Scientific Symposium
3. Mackay et al. ESMO 2014, 879 PD

- 265 HGS
- All FFPE
- Macrodissected
- Almac Ovarian Disease Specific Array
- 3 clusters

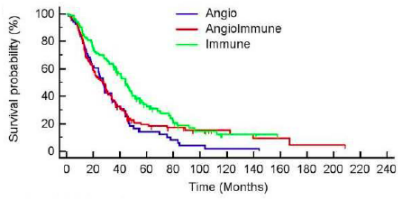
Edinburgh dataset; survival analysis

Progression free survival



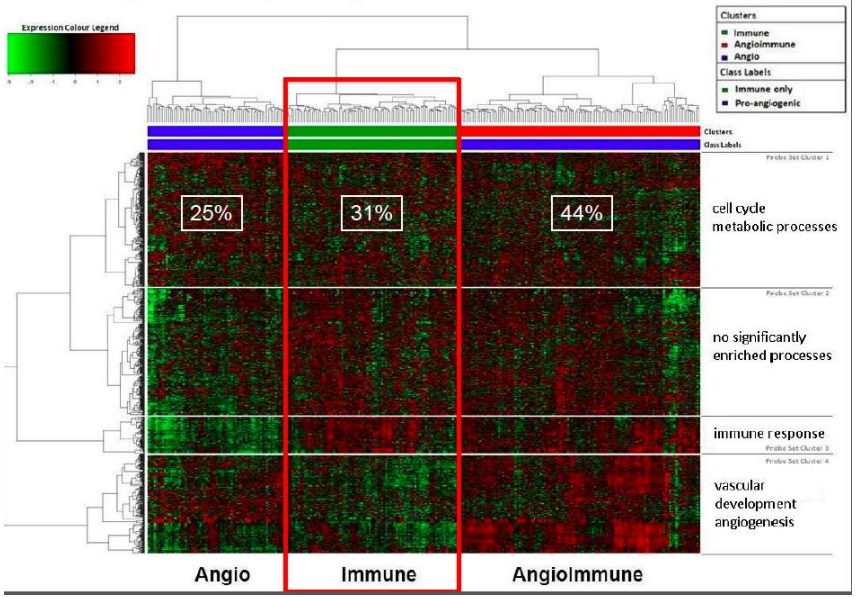
	HR	95% C.I.	p-value
Immune vs Angioimmune	0.60	0.44-0.82	0.002
Immune vs Angio	0.64	0.45-0.92	0.02

Overall survival

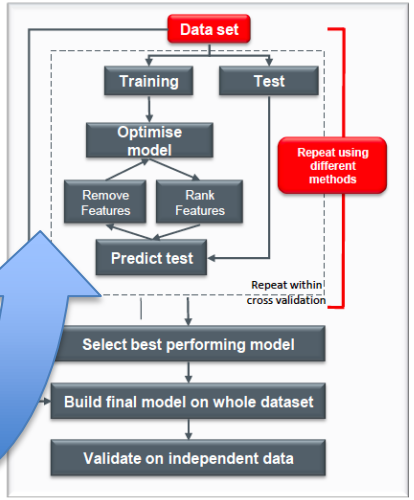


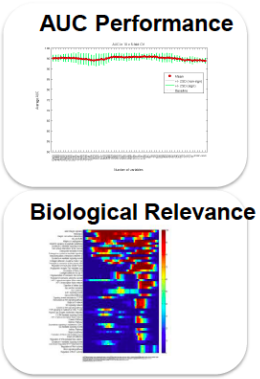
	HR	95% C.I.	p-value
Immune vs Angioimmune	0.58	0.41-0.82	0.001
Immune vs Angio	0.55	0.37-0.80	0.001

Edinburgh dataset; unsupervised hierarchical clustering



Edinburgh dataset; Immune subgroup signature generation





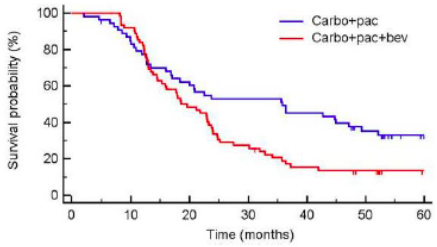
63-gene signature developed to distinguish Immune subgroup patients from those in the Angio and Angioimmune subgroups.

Gourley et al. ASCO 2014

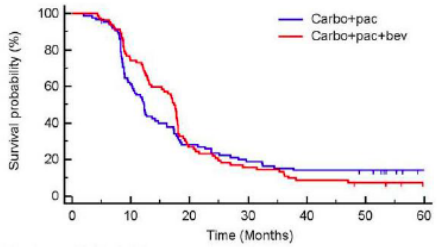
ICON-7 Sub-study
375 Primary FFPE specimens
(No AGO specimens)
284 High grade serous

Immune subgroup patients have inferior progression free survival when treated with bevacizumab

Immune subgroup; 41% of ICON7 TR patients



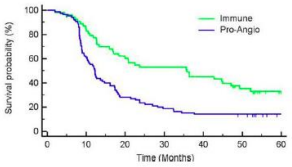
Non-immune (pro-angiogenic) subgroup; 59% of ICON7 TR patients



Test for interaction, p=0.015

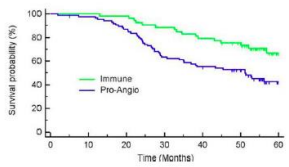
Immune signature prognostic within the control arm of ICON7

PFS



Univariate: HR = 0.47 [0.32-0.71], p < 0.001
Multivariable: HR = 0.52 [0.33-0.81], p = 0.004

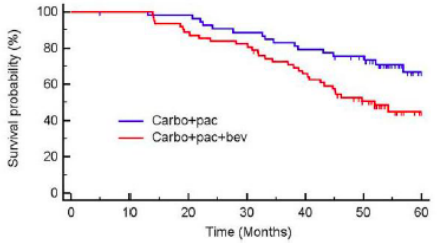
OS



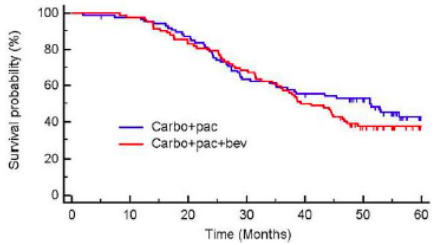
HR = 0.45, [0.26-0.79], p =0.005
HR = 0.53 [0.29-0.96], p = 0.04

Immune subgroup patients have inferior overall survival when treated with bevacizumab

Immune subgroup



Non-immune (pro-angiogenic) subgroup



Test for non-proportionality negative in both molecular subgroups

	Immune subgroup	Proangiogenic subgroup
Univariate	HR 2.00 (1.11-3.61), p=0.022	HR 1.19 (0.80-1.78), p=0.386
	Test for interaction, p=0.075	
Multivariate	HR 2.37 (1.27-4.41), p=0.007	HR 1.10 (0.73-1.66), p=0.637
	Test for interaction, p=0.020	

Gourley et al. ASCO 2014

What do we need from biomarkers or genetic signatures?

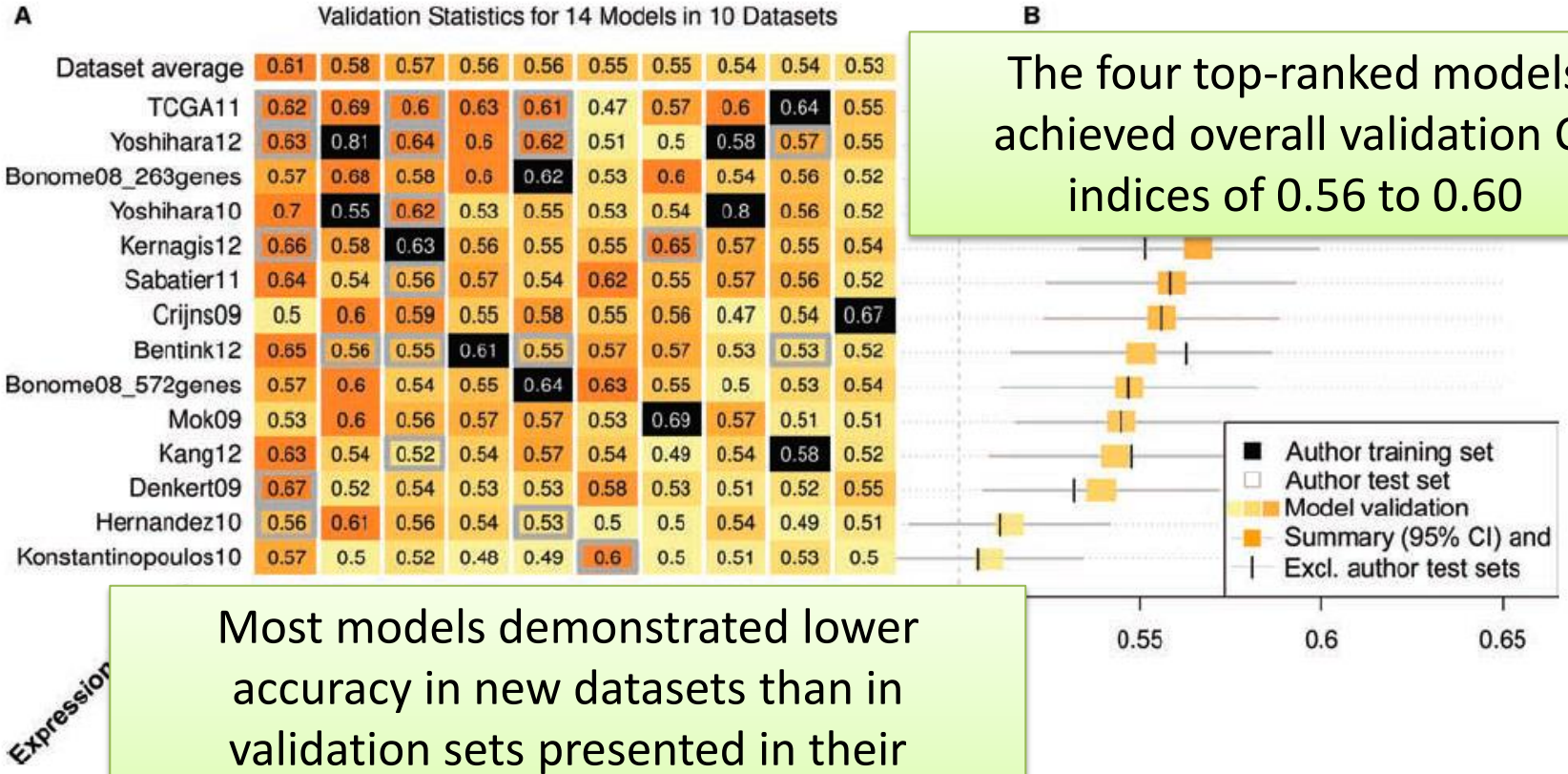
- Need to be robust : reproducible!
  - Validation is crucial.

Michael Birrer. Personal Communication

Comparative Meta-analysis of Prognostic Gene Signatures for Late-Stage Ovarian Cancer

Concordance statistic (C-index) for prediction of overall survival by each of the 14 models in each of the 10 microarray datasets.

14 prognostic signatures



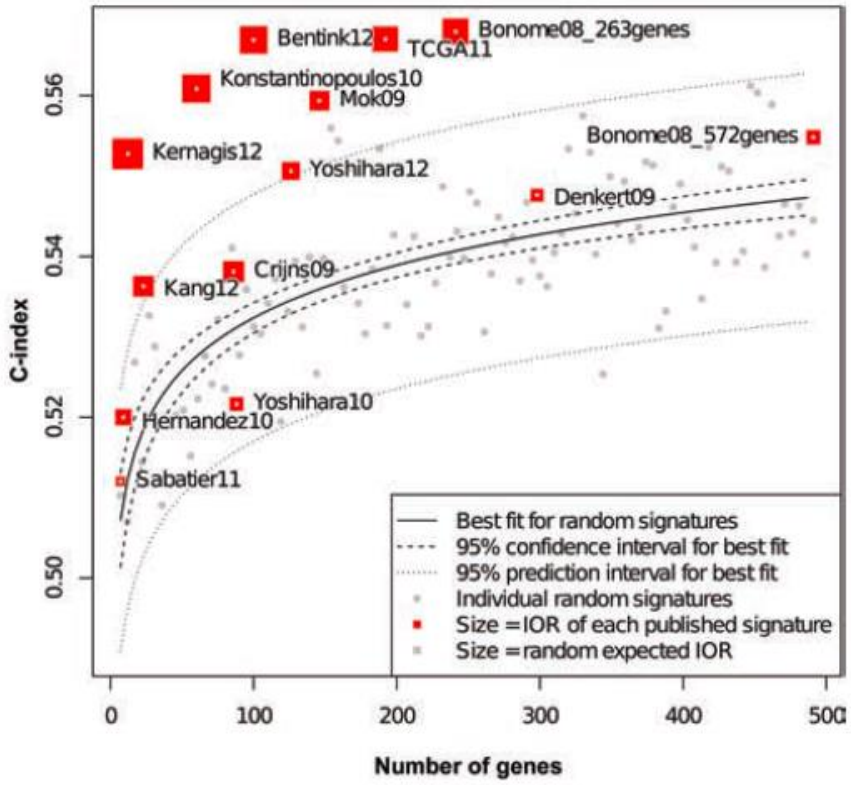
The four top-ranked models achieved overall validation C-indices of 0.56 to 0.60

Most models demonstrated lower accuracy in new datasets than in validation sets presented in their publication.

Waldron L et al. JNCI J Natl Cancer Inst (2014) 106(5):

Comparative Meta-analysis of Prognostic Gene Signatures for Late-Stage Ovarian Cancer

IOR: Improvement Over Random signature score of gene signatures relative to random gene signatures



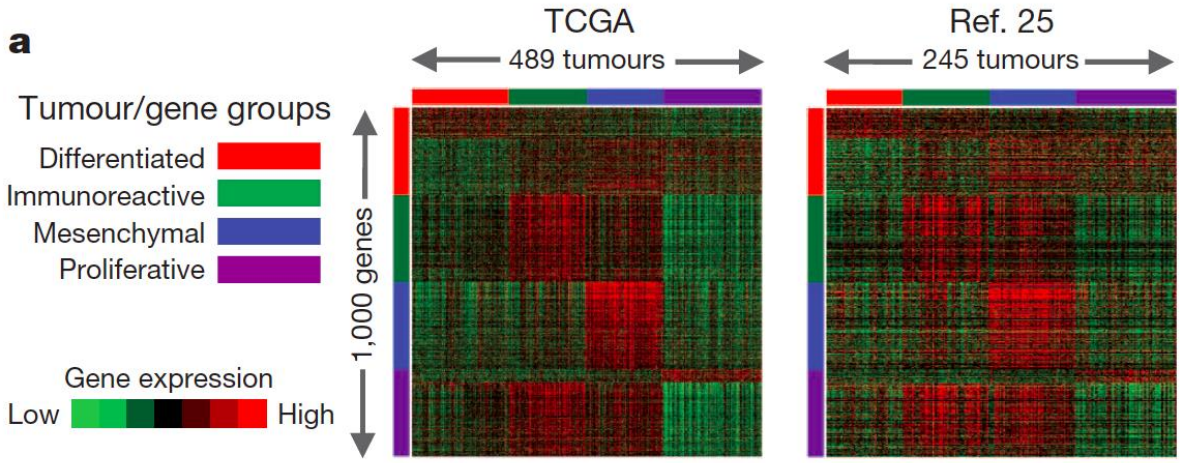
- Most models make better predictions than random
- None of these models are ready for the clinic

Waldron L et al. JNCI J Natl Cancer Inst (2014) 106(5):

What do we need from biomarkers or genetic signatures?

- Need to be robust : reproducible!
  - Validation is crucial.
- Need to be clinically useful:
  - A signature is clinically useful if it alters patient management in a way that positively impacts patient survival or quality of life.

Michael Birrer. Personal Communication



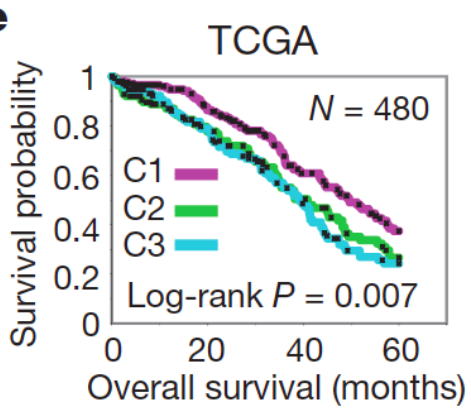
a. Four clusters identified on the basis of gene expression. No differences in survival

b. Tumours separated into three clusters on the basis of miRNA expression, overlapping with genebased clusters.

c. Survival association for miRNA-based clusters

d

		Gene cluster			
		D	I	M	P
miRNA cluster	C1	55	48	15	89
	C2	40	21	51	29
	C3	39	37	43	20



Nature 2011

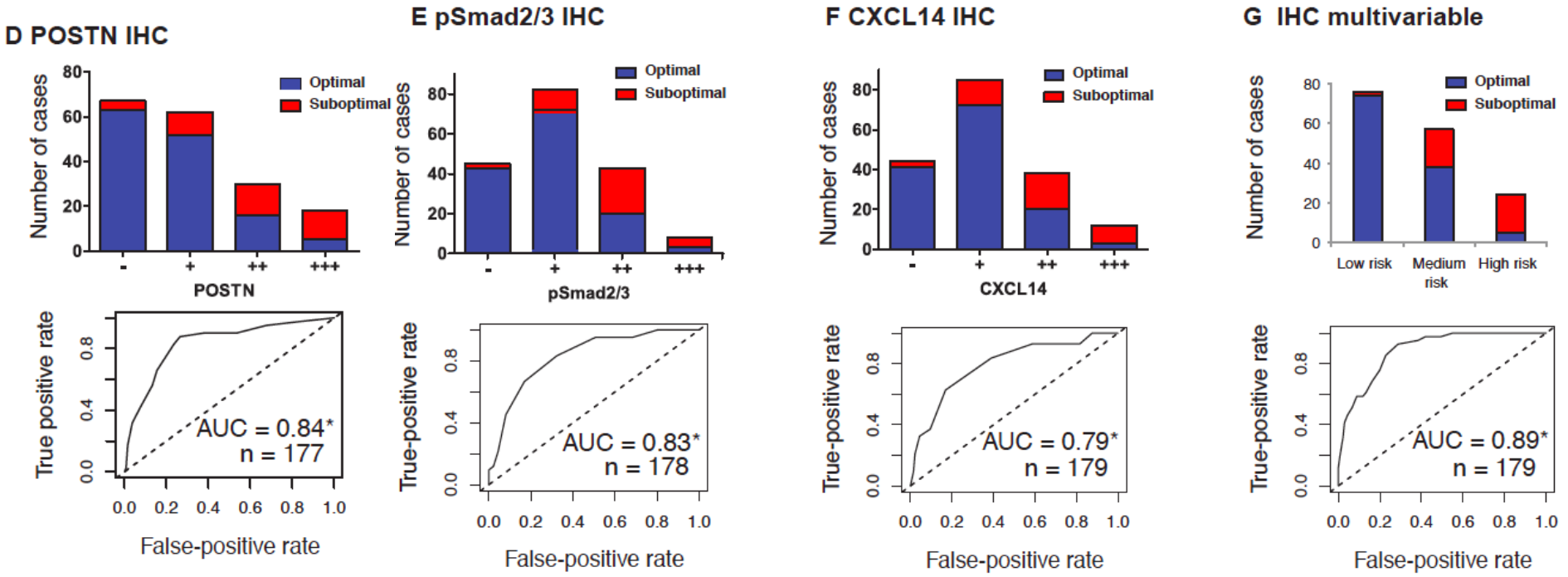
What do we need from biomarkers or genetic signatures?

- Need to be robust : reproducible!
  - Validation is crucial.
- Need to be clinically useful:
  - A signature is clinically useful if it alters patient management in a way that positively impacts patient survival or quality of life.
- How to assess the clinical utility of a biomarker?
  - Is addressing a specific clinical question?
  - Does it lead to a change in clinical management?
  - Does it have a significant clinical impact?

Michael Birrer. Personal Communication

Risk Prediction for Late-Stage Ovarian Cancer by Meta-analysis of 1525 Patient Samples

The sum of immunohistochemistry intensities for these three proteins provided a tool that classified 92.8% of samples correctly in high- and low-risk groups for suboptimal debulking (area under the curve = 0.89; 95% CI = 0.84 to 0.93).



Riester et al. JNCI J Natl Cancer Inst (2014) 106(5):

Evaluation of biomarkers and genetic signatures for the use of bevacizumab in advanced OC

Clinical utility:

- Are addressing a specific clinical question?

  Yes
- Does it lead to a change in clinical management?

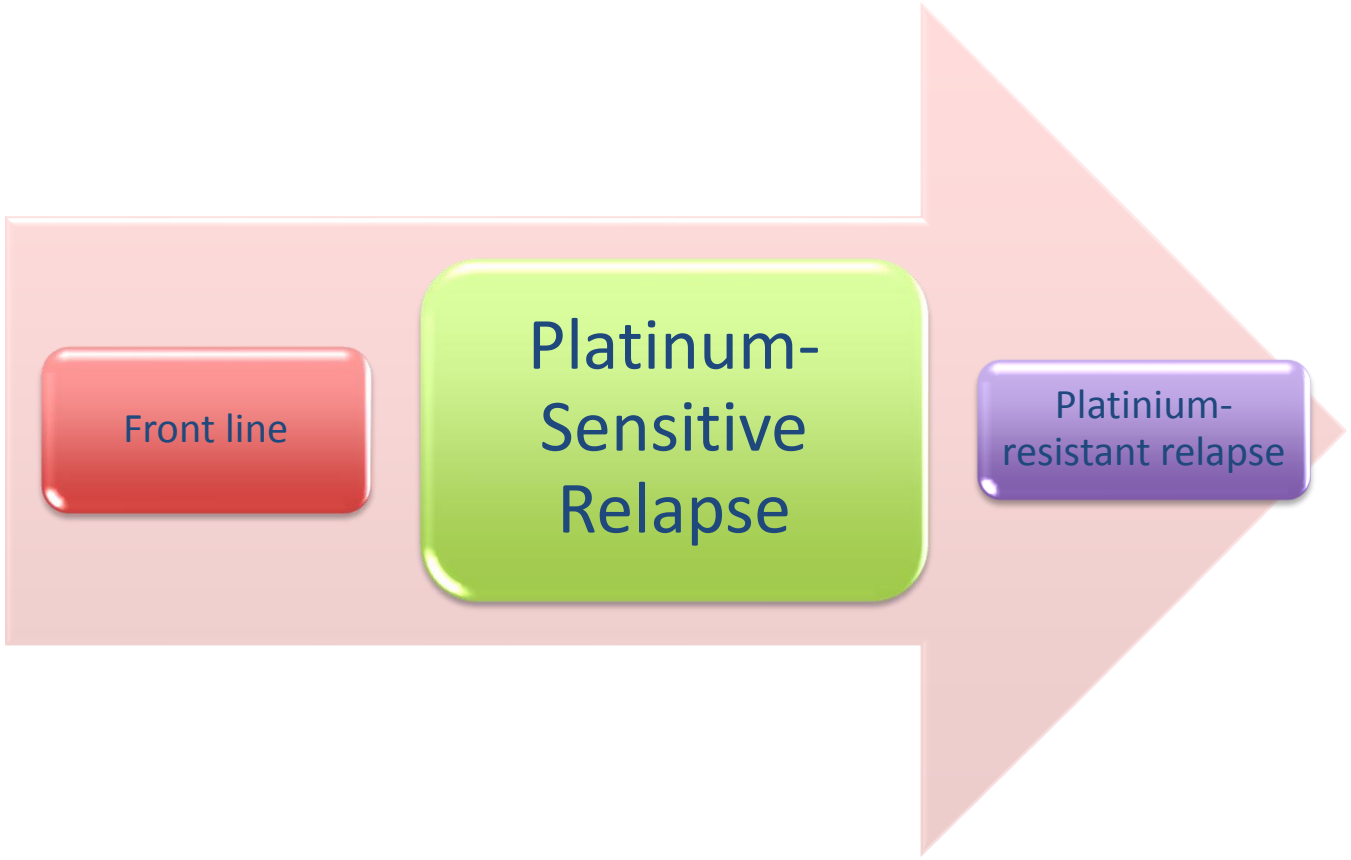
  Probably Yes
- Does it have a significant clinical impact?

  Hopefully Yes

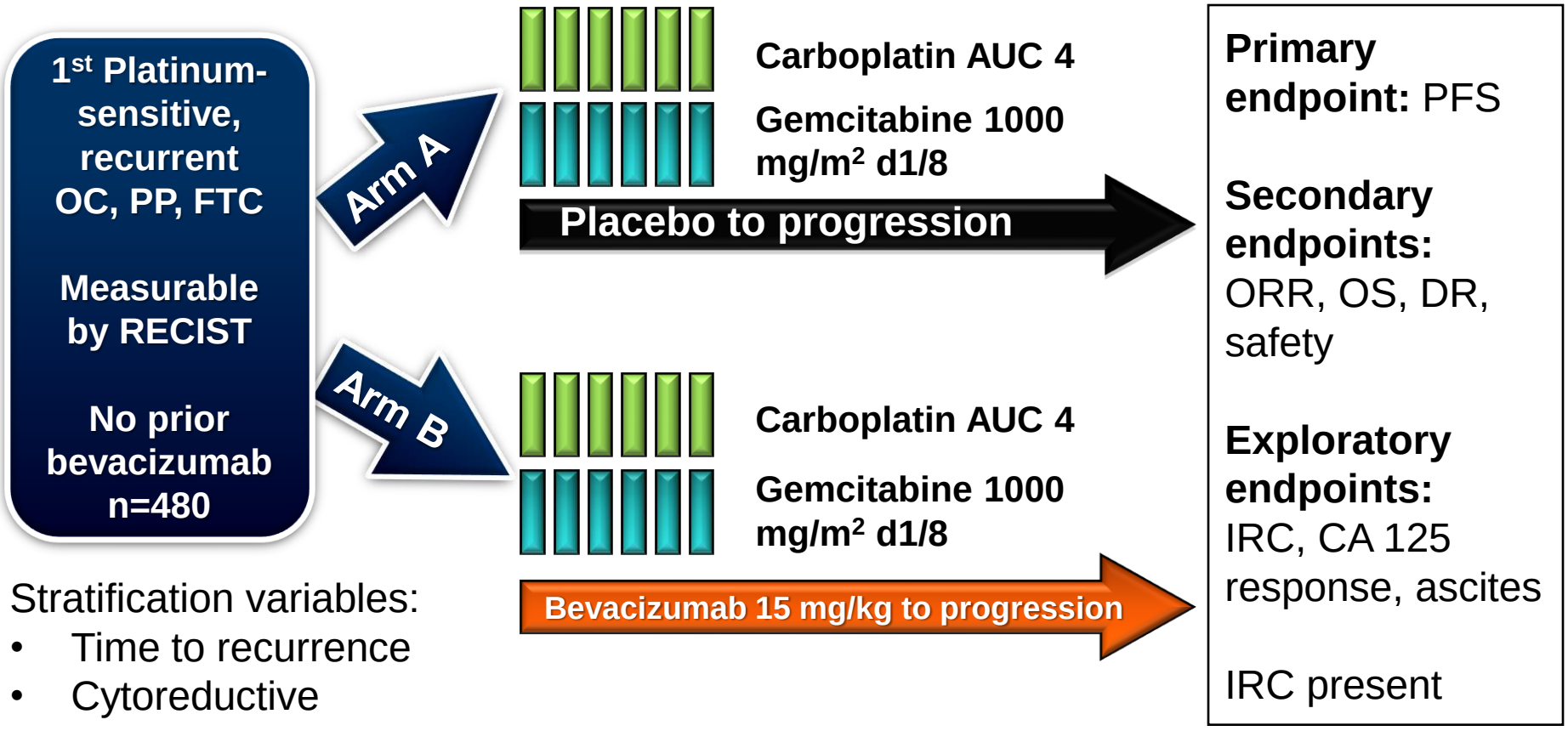
Need to be robust :

- Not yet reproducible.
- Validation is crucial.

Anti-angiogenic therapy in relapsed patients
Platinum-free interval > 6 months



Platinum-Sensitive: OCEANS



Stratification variables:

- Time to recurrence
- Cytoreductive surgery

Aghajanian et al. J Clin Oncol 2012

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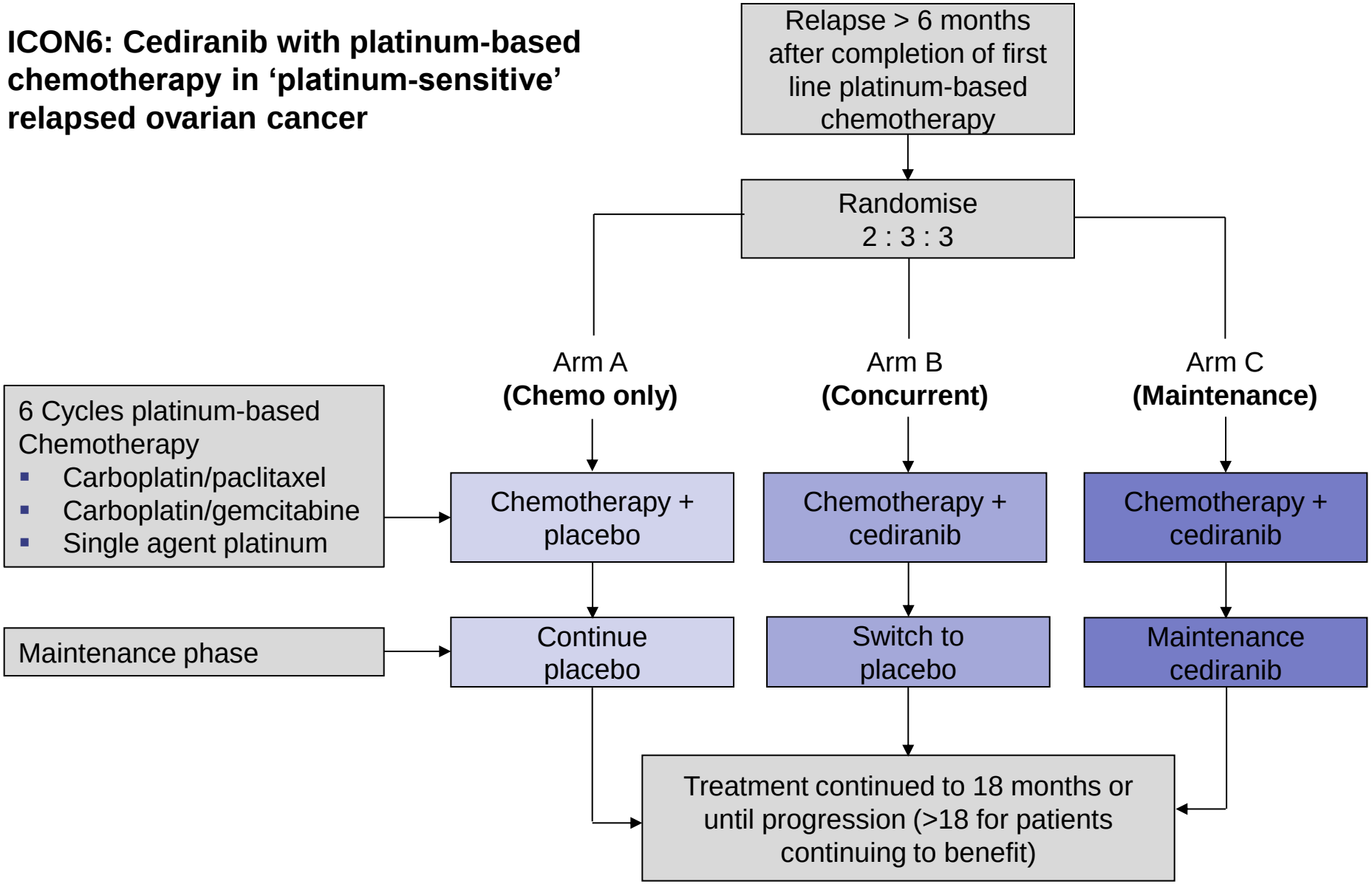
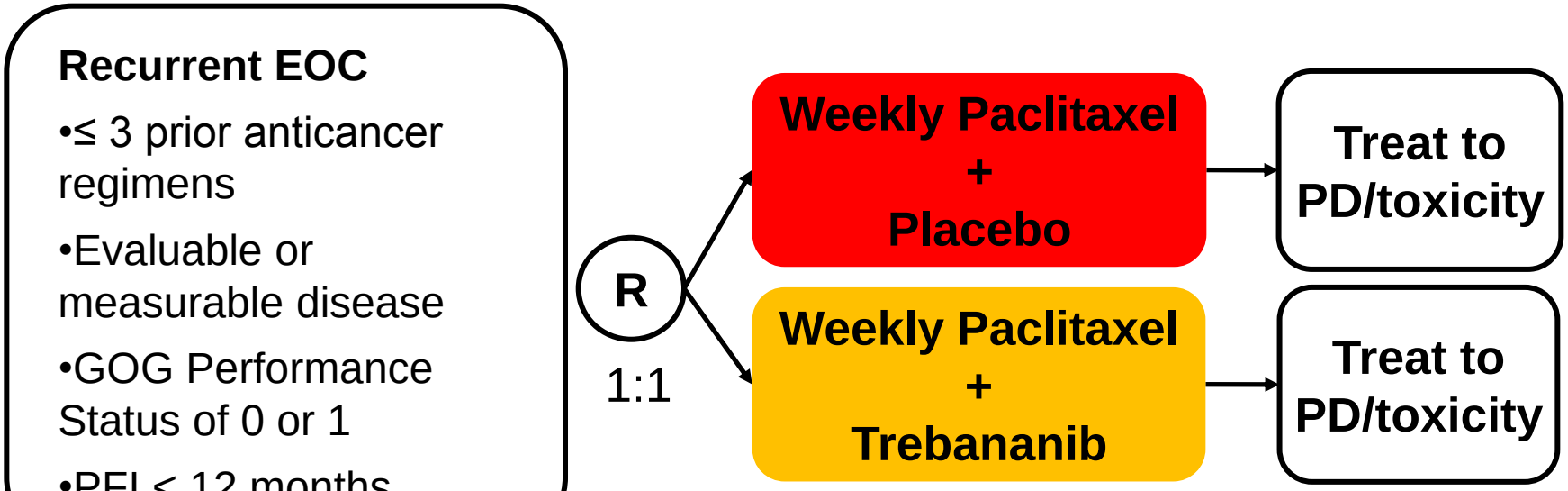
Study schema

ICON6: Cediranib with platinum-based chemotherapy in 'platinum-sensitive' relapsed ovarian cancer



TRINOVA-1: Trial Design



Paclitaxel 80 mg/m^2 IV on days 1, 8, 15 Q4W

Trebananib 15 mg/kg IV QW

ClinicalTrials.gov Identifier: NCT01204749

Stratification factors

- Platinum-free interval (PFI) (≤ 6 vs. > 6 months)
- Measurable disease (Yes/No)
- Region (North America, Western Europe/Australia, Rest of World)

EOC = epithelial ovarian cancer including primary peritoneal, or fallopian tube cancer; PD = progressive disease

Efficacy data with anti-angiogenic agents in phase III trials for recurrent patients with PFI > 6 months

	OCEANS[1]	ICON 6[2]	TRINOVA-1[3(*)]
Drug	Bevacizumab	Cediranib	Trebananib
Class	Mab anti-VEGF	TKI (VEGFR…)	Peptibody (Ang)
HR PFS (95% CI)	0.48 (0.38-0.60)	0.57 (0.44-0.74)	0.66 (0.52-0.84)
Δ mo (median)	+4 (8.4 vs 12.4)	+2.4 (8.7 vs 11.1)	+2 (5.6 vs 7.6)
HR OS (95% CI)	0.96 (0.76-1.20)	0.7 (0.51-0.99)	0.86 (0.69-1.08)
Δ mo (median)	33.7 vs 33.4	+6 (20.3 vs 26.3)	17.0 vs 19.0

1. Aghajanian et al. J Clin Oncol 2012
2. Ledermann et al. ESMO 2013
3. Monk et al. Lancet Oncol 2014. (*) Sub-group of patients with PFI > 6 months.

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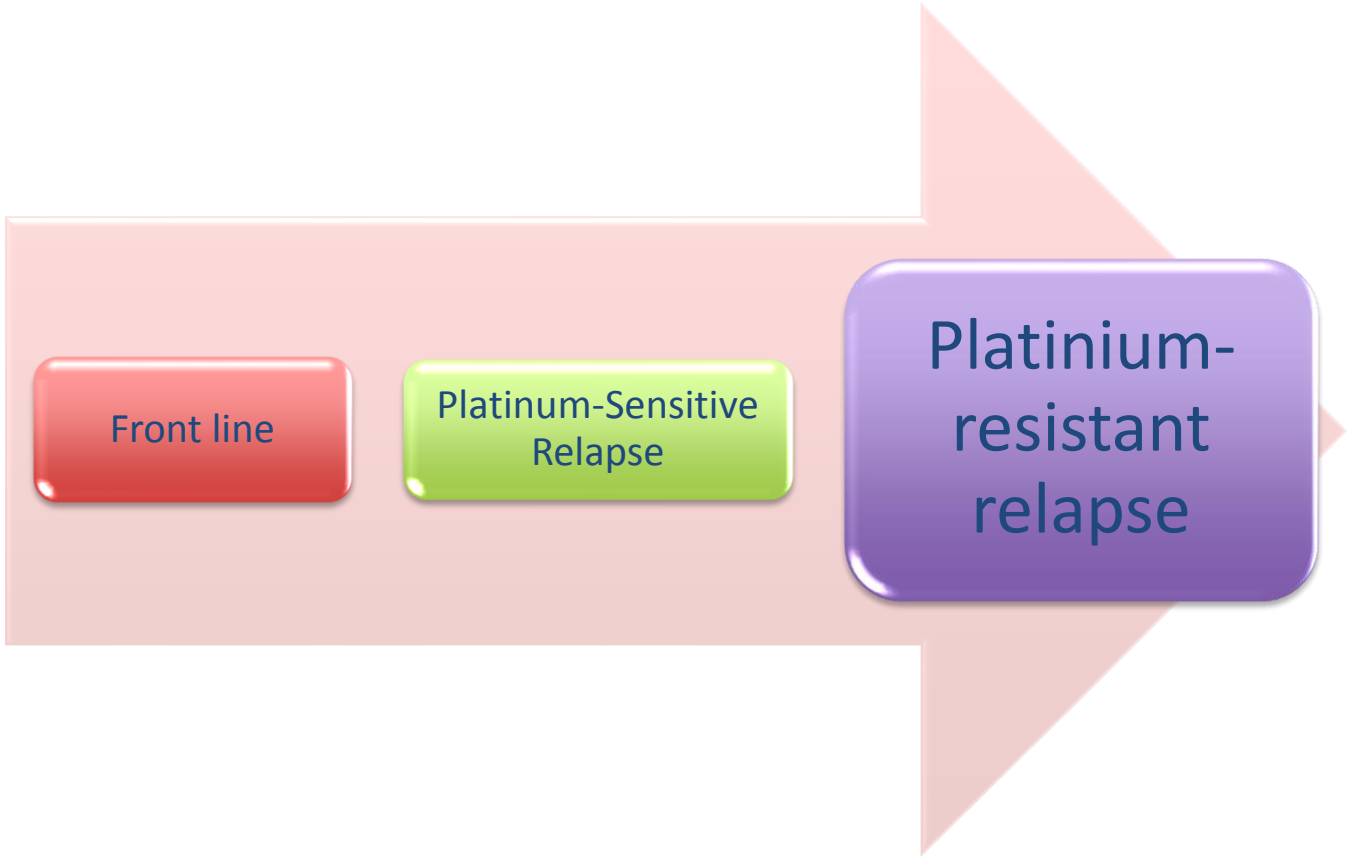
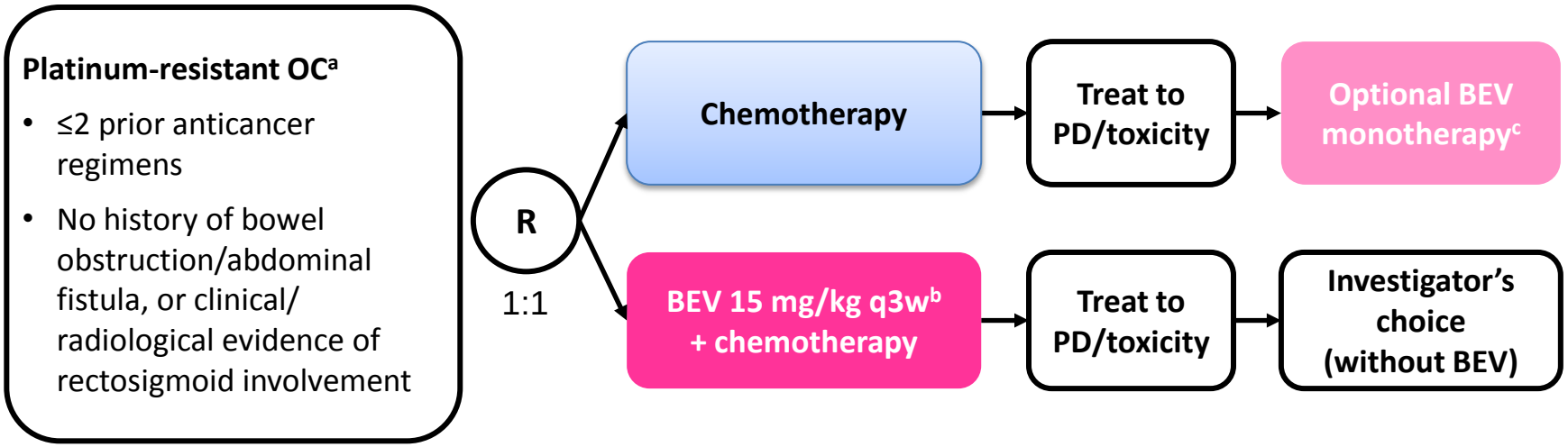
Anti-angiogenic therapy in relapsed patients
Platinum-free interval < 6 months



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)

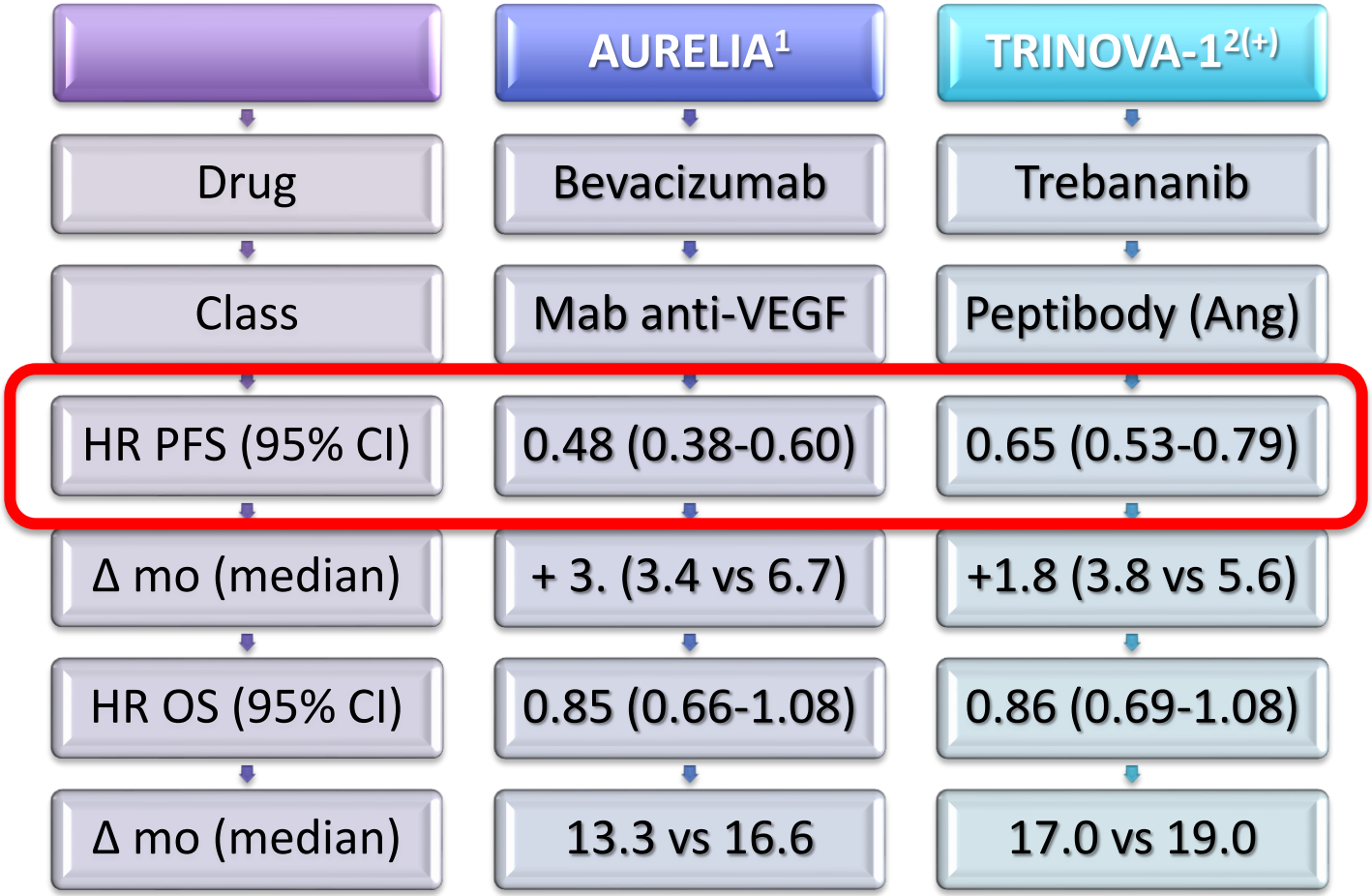
Chemotherapy options (investigator's choice):

- 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

Efficacy data with anti-angiogenic agents in phase III trials for recurrent patients with PFI < 6 months



1. Pujade et al. J Clin Oncol 2014
2. Monk et al. Lancet Oncol 2014. (*) Sub-group of patients with PFI < 6m

PRO in AURELIA Study

Primary PRO hypothesis was that more patients receiving BEV-CT than CT would achieve at least a 15% absolute improvement on the QLQ-OV28 abdominal/GI symptom subscale (items 31-36) at week 8/9.

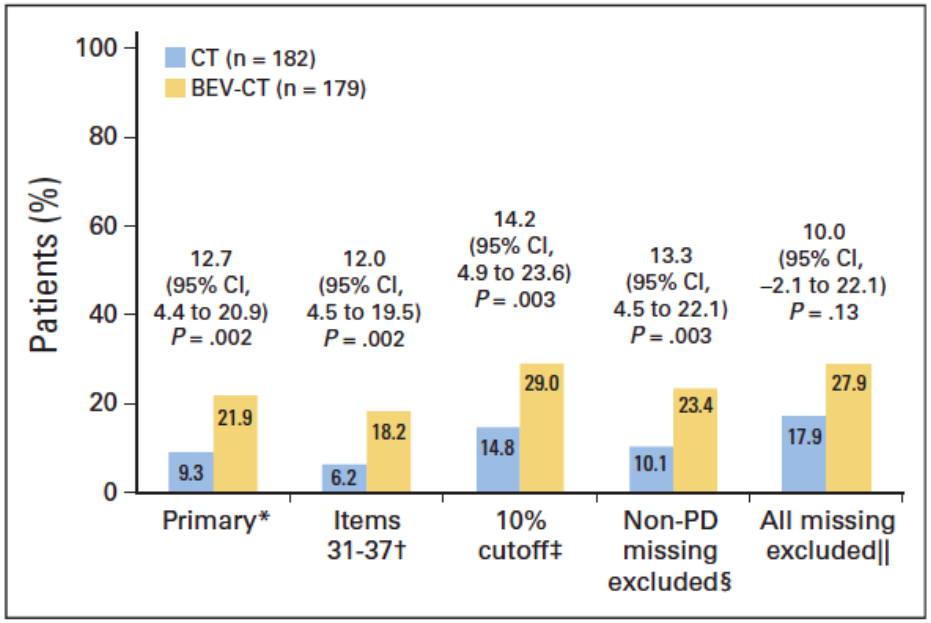


Fig 3. Primary and sensitivity analyses of the primary hypothesis (≥ 15% improvement in abdominal/GI symptoms [European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Ovarian Cancer Module 28]).

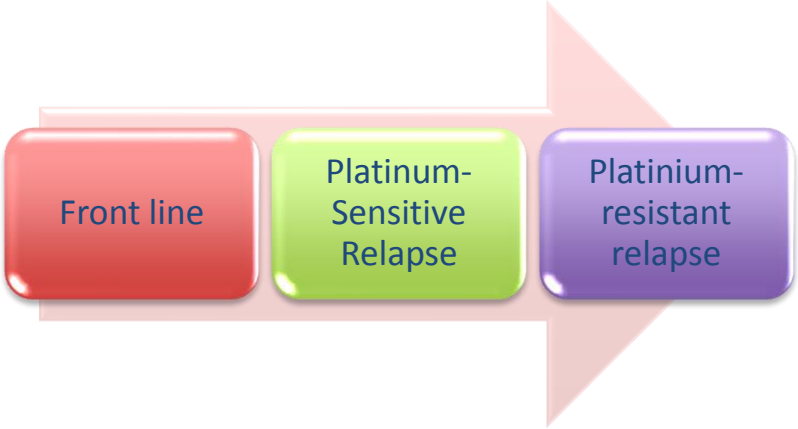
A

Subscale	CT (n = 182) No.	%	BEV-CT (n = 179) No.	%	Difference, % (95% CI)	P
Main analysis	**Patients achieving a ≥ 15% improvement from baseline**					
Physical functional	3 of 170	1.8	20 of 167	12.0		< .001
Role functional	17 of 170	10.0	37 of 167	22.2		.003
Emotional functional	26 of 168	15.5	39 of 164	23.8		.072
Social functional	21 of 167	12.6	37 of 163	22.7		.020
Global health status/QoL score	22 of 169	13.0	40 of 164	24.4		.011
Sensitivity analysis	**Patients achieving a ≥ 10% improvement from baseline**					
Physical functional	6 of 170	3.5	30 of 167	18.0		< .001
Role functional	17 of 170	10.0	37 of 167	22.2		.003
Emotional functional	27 of 168	16.1	43 of 164	26.2		.031
Social functional	21 of 167	12.6	37 of 163	22.7		.020
Global health status/QoL score	22 of 169	13.0	40 of 164	24.4		.011

Figure shows findings for the QLQ-C30 at week 8/9 with subscales for physical, role and social function, and global health/QoL favoring the bevacizumab group

Stockler et al. J Clin Oncol 2014

When in the pathway (2014)?



At any time

- PFS is prolonged in all the scenarios: front-line, PS and PR relapse.
- No differences across the scenarios in terms of safety for bevacizumab (the only drug approved so far).
- No impact in OS in any trial for the ITT population.

Why front-line anti-angiogenic therapy did not reached an OS increase in advanced ovarian cancer?

Impact of Survival Post-progression on OS

- Advanced ovarian cancer has a **long survival post-progression** and subsequent interventions can impact on the OS result, especially the crossover.
  - In GOG 218, OCEANS and AURELIA **≥ 40%** of patients received any anti-angiogenic therapy at relapse.
  - In ICON-7 **less than 5%** of cross-over could explain the OS benefit in high-risk population[2].

- When SPP is long enough, the number of patients required for demonstrating a survival benefit is extremely large (> 2000)[1].

1. Borglio and Berry. J Natl Cancer Inst 2009
2. Oza et al. ESMO 2013

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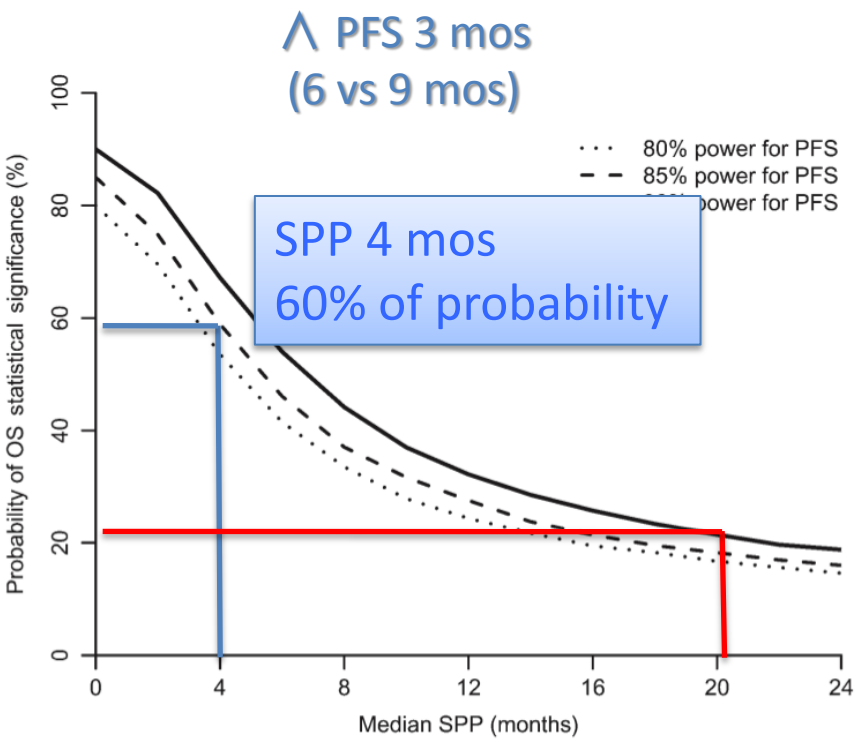
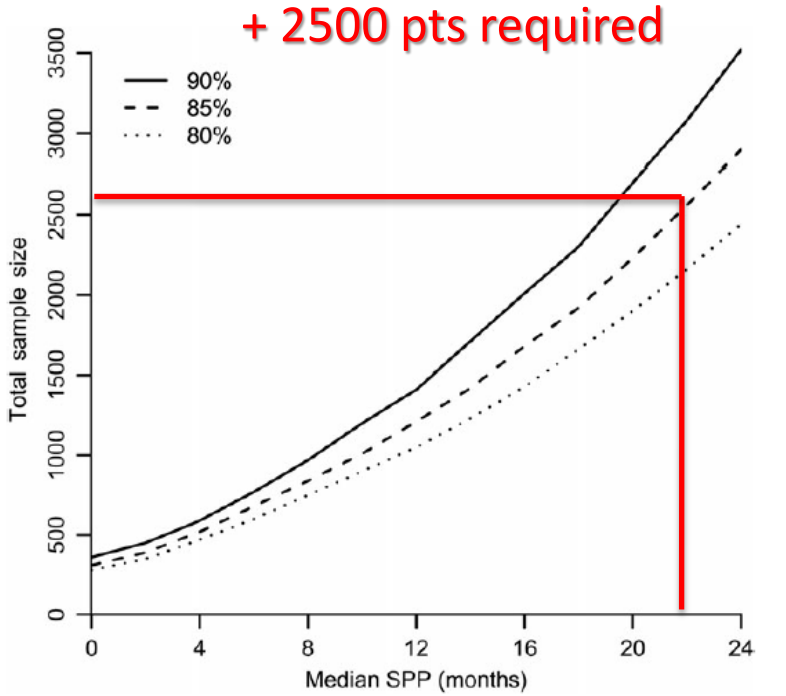
Impact of Survival Post-Progression on OS



Λ PFS 3 mos
(6 vs 9 mos)

SPP 4 mos
60% of probability

SPP 20 mos
< 20% probability

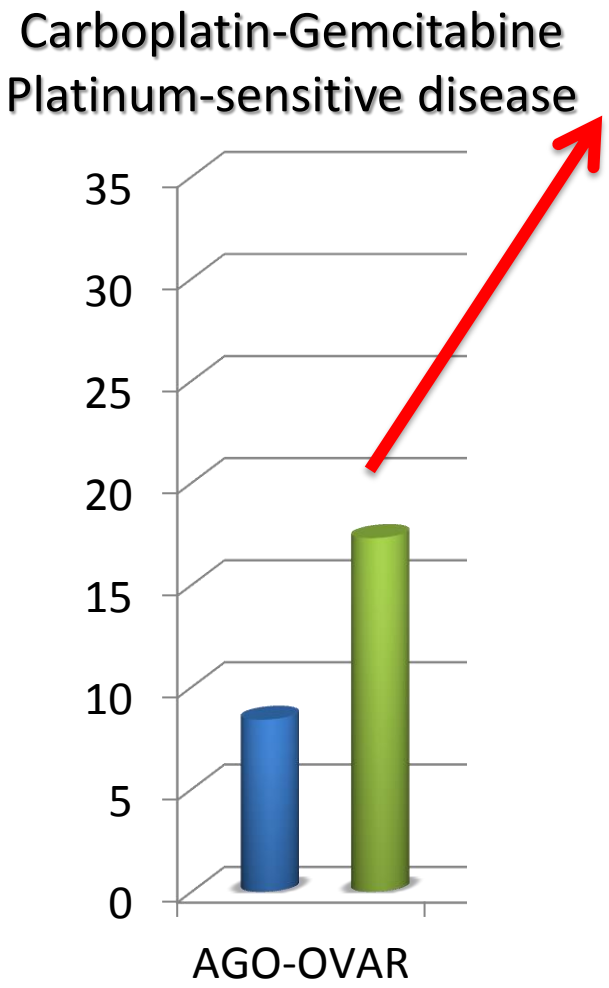


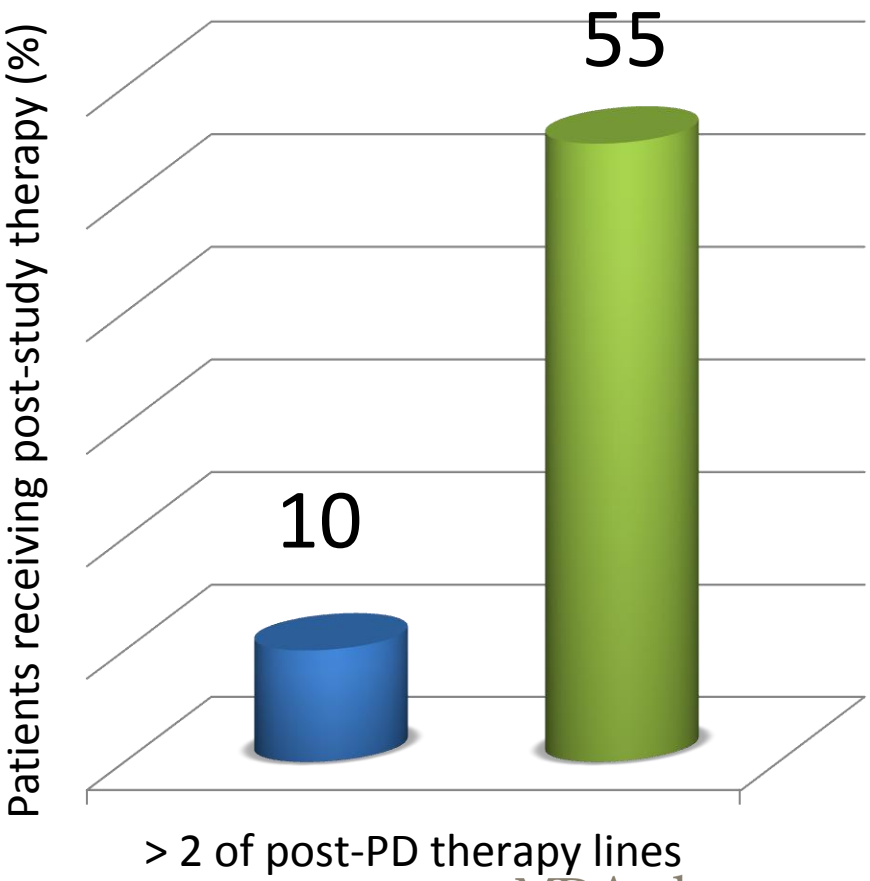
+ 2500 pts required

Figure 3. Sample sizes required for detecting a statistically significant difference in overall survival by median survival postprogression (SPP). The **three curves** were indexed by the power for overall survival (ie, powers of 90%, 85%, and 80%).

Broglio and Berry. J Natl Cancer Inst 2009; 101: 1642-1649

Influence of post-study therapy in OS





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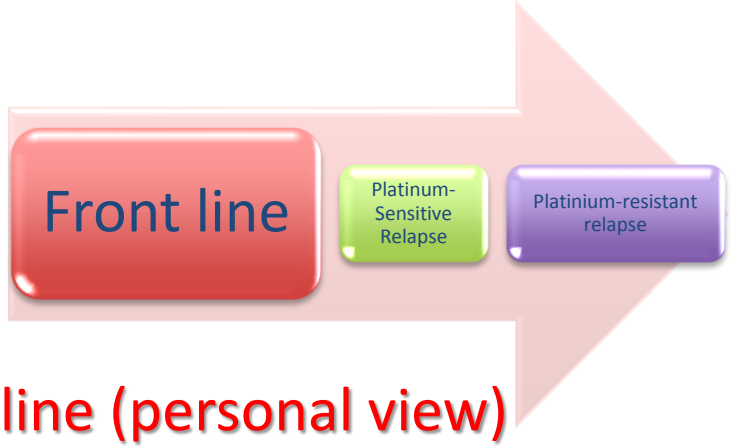
When in the pathway (2014)?



At any time

- PFS is prolonged in all the scenarios: front-line, PS and PR relapse.
- No differences across the scenarios in terms of safety for bevacizumab (the only drug approved so far).
- No impact in OS in any trial for the ITT population.

Front line (personal view)

- Data of predefined subgroup analysis have shown a clinically significant benefit in PFS (GOG-218/ICON-7) and OS (ICON-7)
- In each relapse an unknown percentage of patients will not be eligible for anti-angiogenic therapy and will miss this option.
- Validated predictive signatures should be the more efficient way to select patients.

Thank you!