# Angiogenesis in ovarian cancer Discussion

Nicoletta Colombo, MD

University of Milan Bicocca

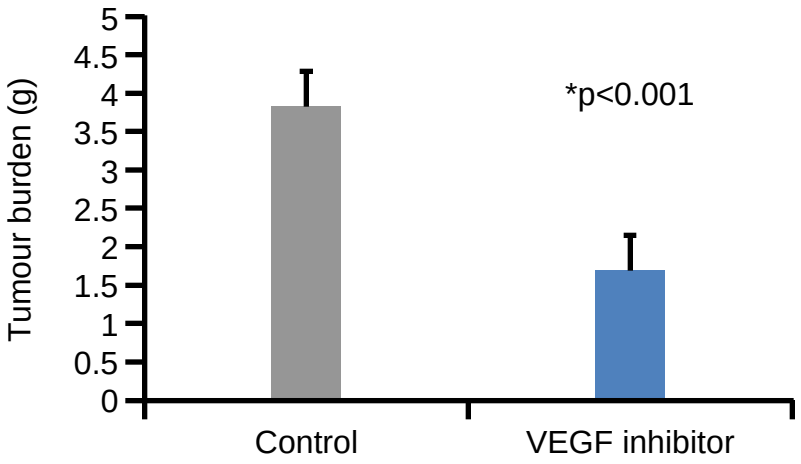
European Institute of Oncology

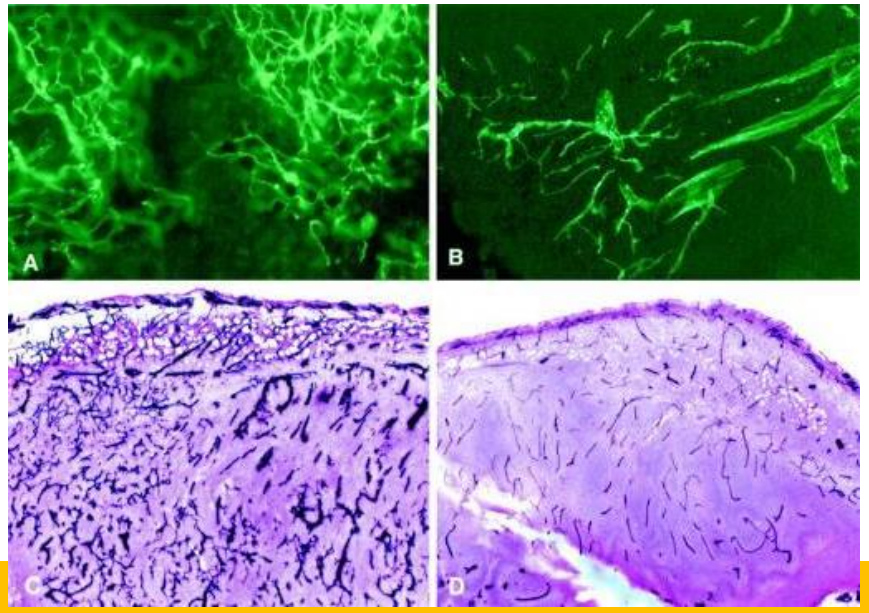
Milan, Italy

# Disclosure slide

- Participation in Roche advisory boards
- Speaker at Roche satellyte symposia

# Angiogenesis (VEGF) in ovarian cancer




**Preclinical data**

Oncogenes (PIK3CA) drive VEGF expression

VEGF inhibitors inhibit tumour growth, abrogate ascites formation and normalise vessels

**Human data**

MVD (CD31 or CD105) and hypoxia associated with poor prognosis

VEGF over-expressed and associated with worse outcome

Associated with ascites and carcinomatosis

VEGF inhibition is synergistic with chemotherapy

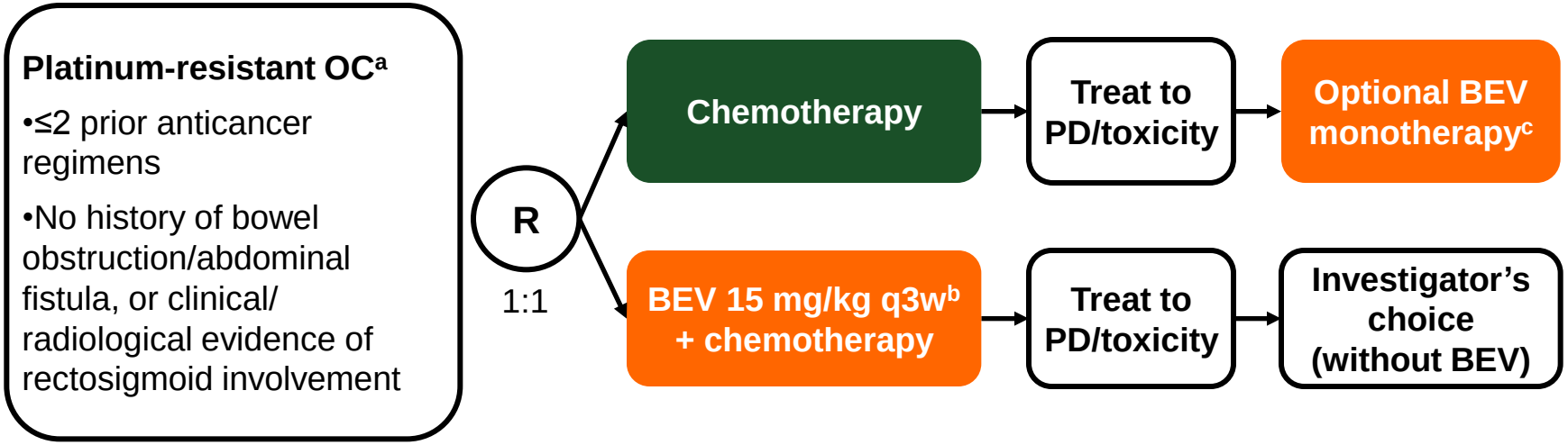
Zhang, et al. Cancer Res 2003; Bozas, et al. Int J Gynecol Cancer 2010; Li, et al. Anticancer Res 2004
Byrne, et al. Clin Cancer Res 2003

# Bevacizumab in ovarian cancer current status

- **Strong biological rationale for effectiveness because epithelial OC is highly VEGF driven**
- **Phase II trials indicate that bevacizumab has single-agent activity in ovarian cancer (more effective than in any other solid tumour except renal)**
- **Two positive phase III clinical trials (GOG-218 and ICON7) in front-line advanced ovarian cancer setting**
- **Positive phase III trials in platinum-sensitive and Platinum-resistant recurrent disease setting (OCEANS and AURELIA)**

# AURELIA trial design

## Analysis by chemotherapy cohort




**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*

# AURELIA trial design

## Analysis by chemotherapy cohort

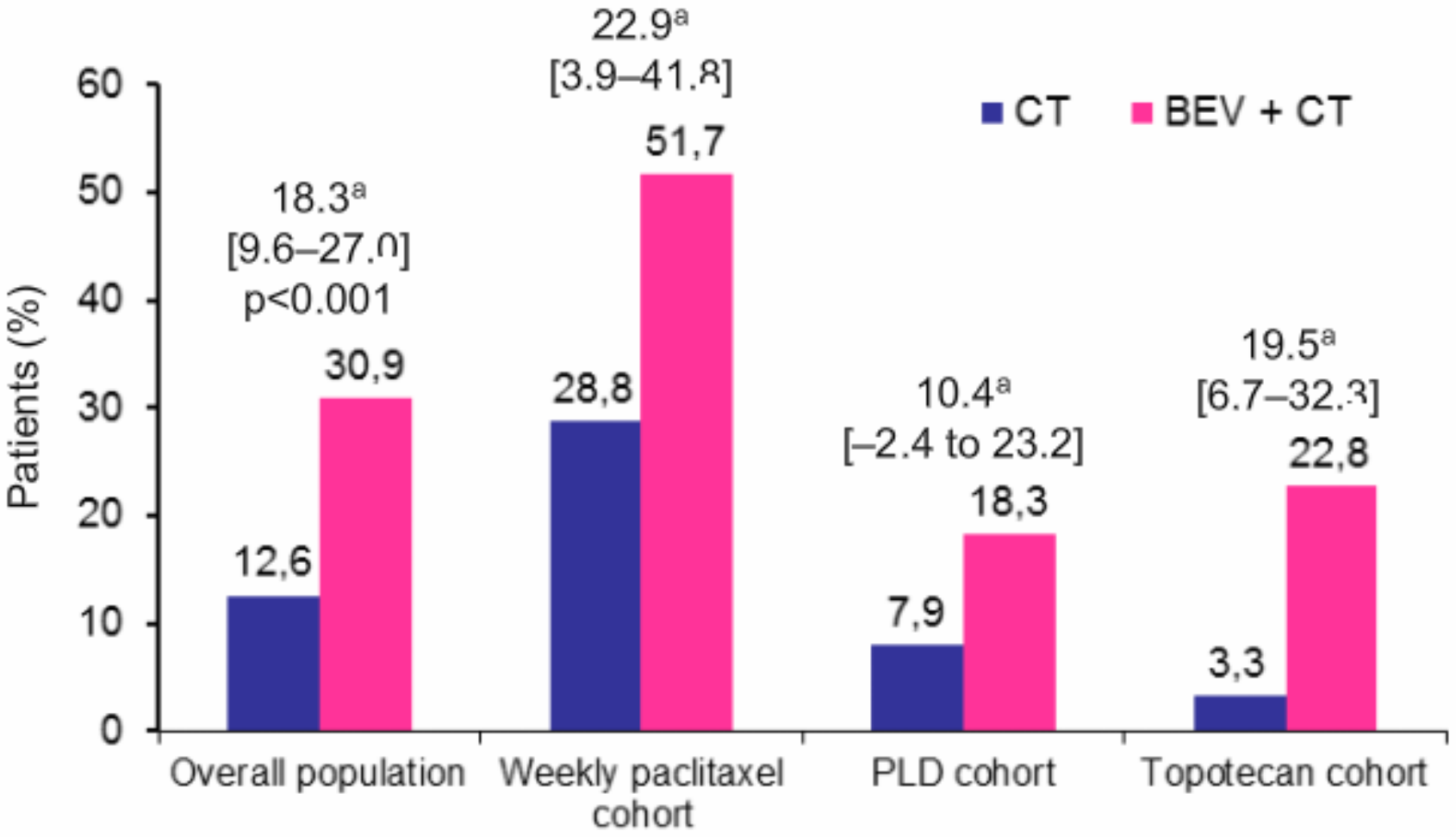
Strenghts:

- Phase III
- Several chemotherapy regimens at the same time
- Solid, convincing results
- **The only positive trial in DDP-resistant disease**

Weaknesses:

- Chemo not randomized
- Slight inbalance in the N° of prior Tx among different regimens
- Gemcitabine not included
- Data on survival and QoL not available

# Summary of best overall response rates (RECIST, CA-125 criteria or both)

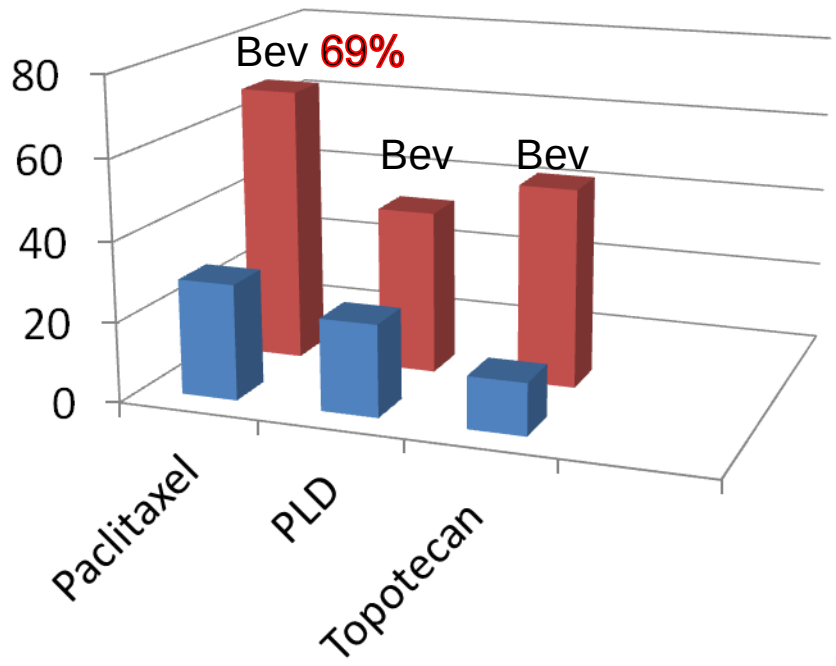



[a]*Difference in overall response rate; 95% CI with Hauck–Anderson continuity correction*

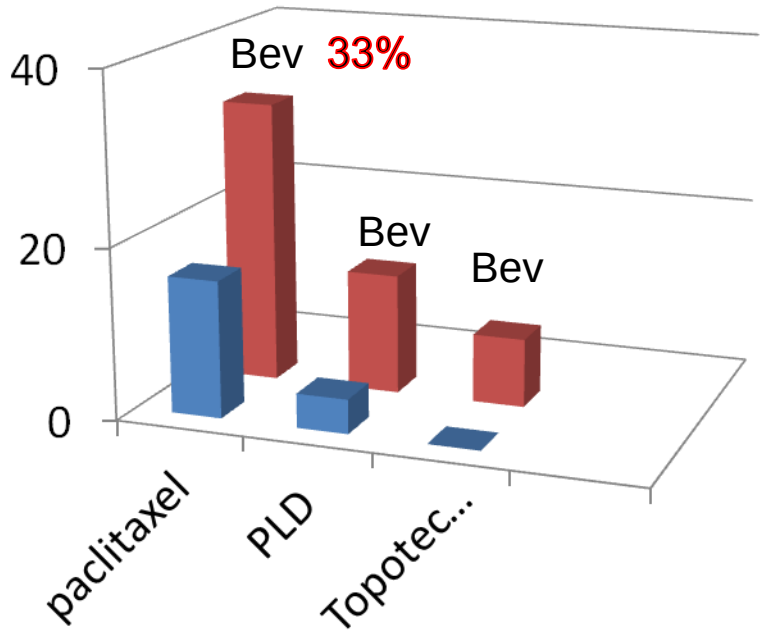
# AURELIA trial design

## Analysis by chemotherapy cohort

### PF survival at 6 months




### PF survival at 12 months



# AURELIA trial design

## Analysis by chemotherapy cohort

The effect of BEV on PFS is seen with any chemotherapy regimen.

**But… in clinical practice**

**The combination of weekly paclitaxel + BEV seems to be the most promising in terms of both response rate and PFS .**

**Is the combination of two anti-angiogenic agents the way to go ?**

**Should weekly paclitaxel be used in front line or second line ?**

# Oceans

## Updated Overall Survival

- 1st interim OS analysis at time of PFS
  - Events in only 29% (far fewer than anticipated)
- 2nd interim OS analysis
  - Unstable and immature data, events in <50% of pts
  - median OS at the median follow-up time
- **3rd interim OS analysis**
  - **More mature with 58% of pts having died**
  - **Median follow-up longer than median OS**
  - **Curves stable to 24 moths due to minimal censoring**

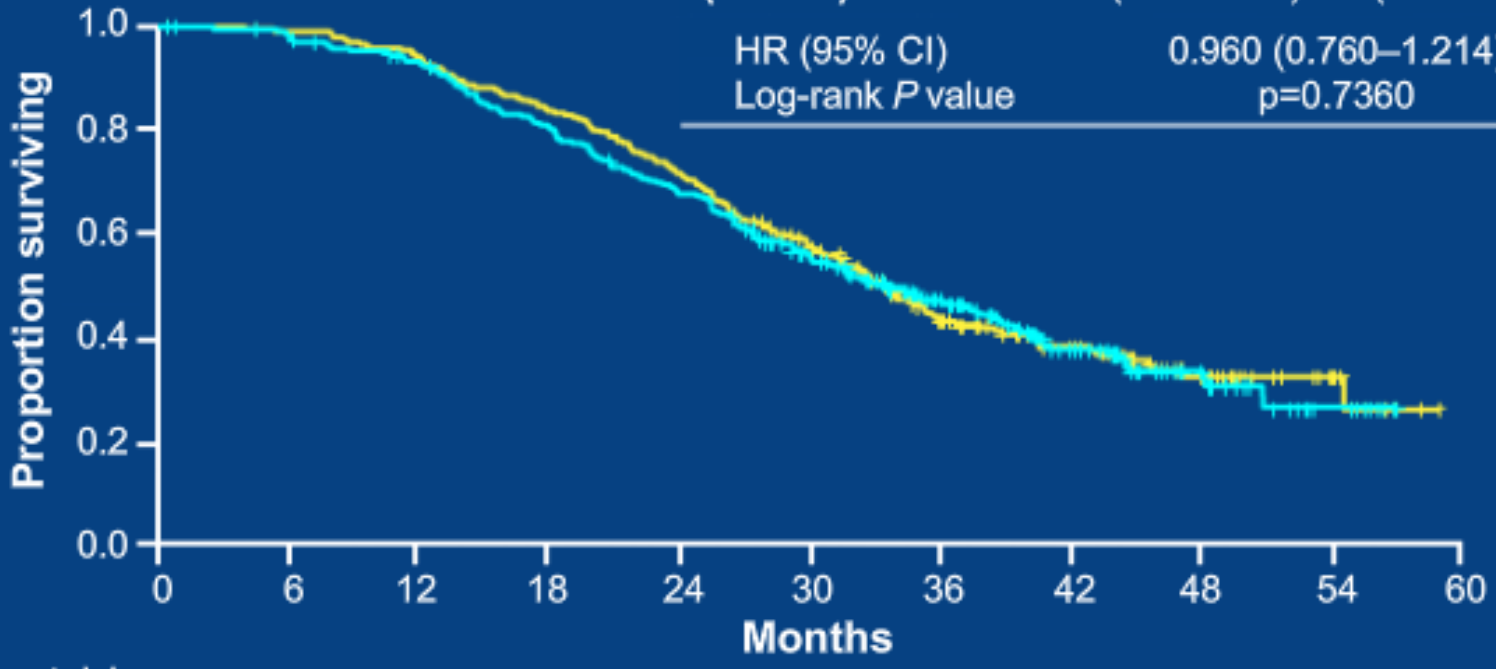
# OCEANS: Summary OS analyses

| | | 1st interim[a] | 2nd interim[b] | 3rd interim[c] |
|---|---|---|---|---|
| **GC + PL** | No. of events (%) | 78 (32.2) | 112 (44.3) | 142 (58.6) |
| | **Median, months** | **29.9** | **35.2** | **33.7** |
| **GC + BV** | No. of events (%) | 63 (26.0) | 123 (50.8) | 144 (59.5) |
| | **Median, months** | **35.5** | **33.3** | **33.4** |
| | HR (95% CI) | 0.751 (0.537,1.052) | 1.027 (0.792,1.331) | 0.960 (0.760,1.214) |
| | Log-rank p-value | 0.0944 | 0.8422 | 0.736 |

[a]Data cutoff date: 17 September 2010
[b]Data cutoff date: 29 August 2011
[C]Data cutoff date: 30 March 2012

# OCEANS: Third Interim OS Analysis[a]

| | GC + PL (n=242) | GC + BV (n=242) |
|---|---|---|
| **Events, n (%)** | 142 (58.7) | 144 (59.5) |
| **Median OS, months (95% CI)** | 33.7 (29.3–38.7) | 33.4 (30.3–35.8) |
| HR (95% CI) | 0.960 (0.760–1.214) | |
| Log-rank *P* value | p=0.7360 | |




Number at risk:

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| GC + PL | 242 | 235 | 221 | 190 | 159 | 117 | 77 | 44 | 23 | 7 | 0 |
| GC + BV | 242 | 239 | 226 | 201 | 171 | 127 | 78 | 48 | 27 | 7 | 0 |

[a]Data cutoff date: March 30, 2012. Median follow-up 41.9 months in PL arm and 42.3 months in BV arm, with 286 deaths (59.1% of patients)

# Why no OS benefit?

- Cross over
- Very long post-progression Survival
- Development of resistance

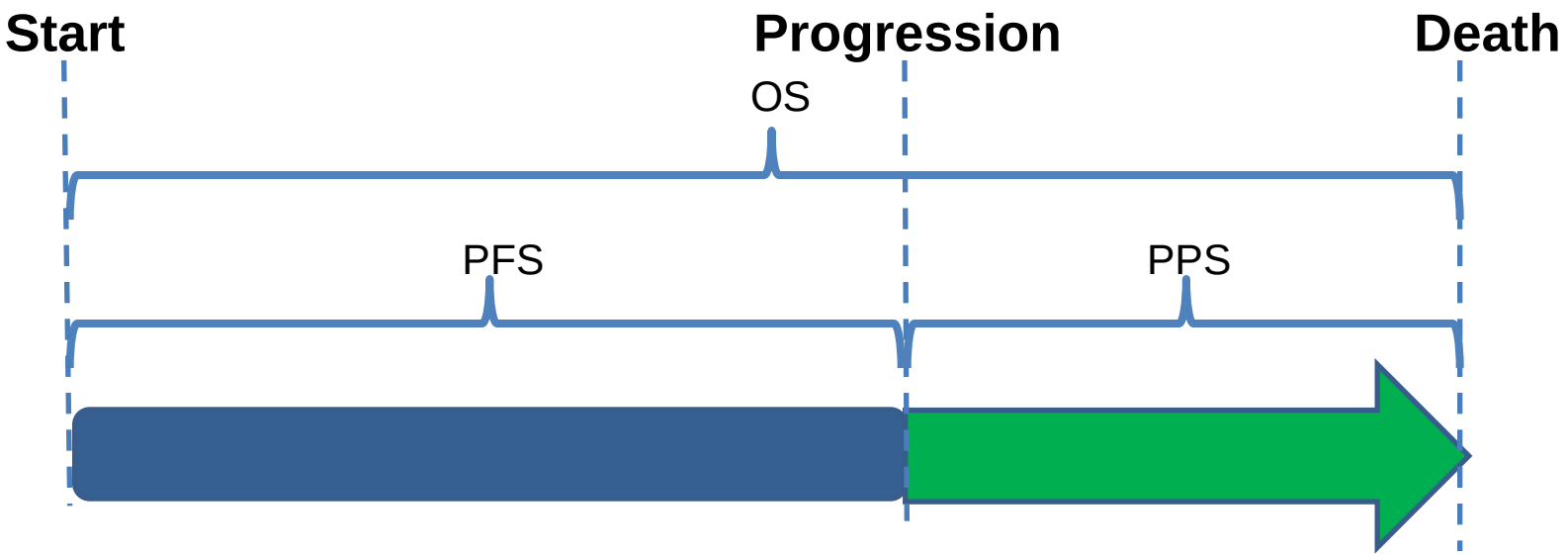
# Why no OS benefit?

- Cross over

| Type of therapy, no. (%)[a] | GC + PL (n=242) | GC + BV (n=242) |
|---|---|---|
| Any subsequent anticancer therapy | 216 (89.3) | 207 (85.5) |
| **Subsequent BV** | **85 (39.4)** | **46 (22.2)** |
| Subsequent chemotherapy[b] | 213 (98.6) | 203 (98.1) |

# What is Post Progression Survival (PPS)?

Post Progression Survival: Time from disease progression till death

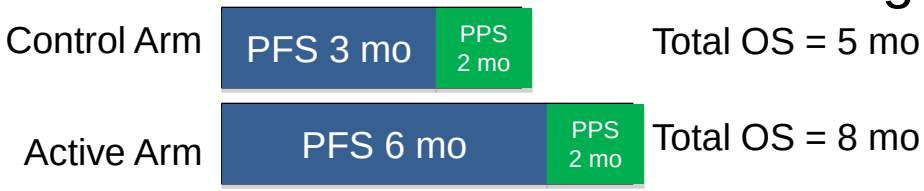


# PPS influences chance to translate PFS into OS benefit

## If PPS = 2 months

PFS and OS benefit = **3 mo**

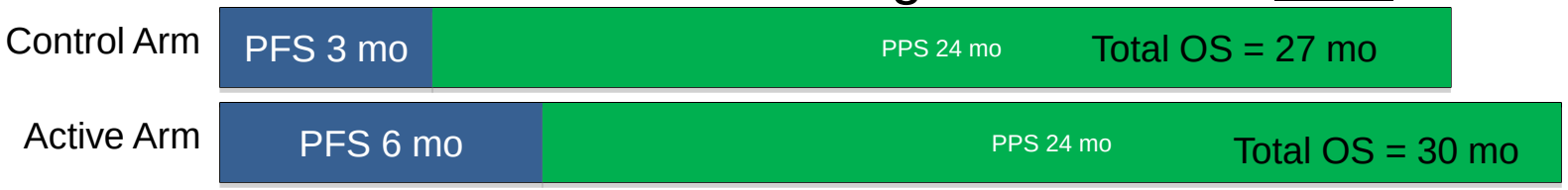
Patients needed to demonstrate significant OS = ***350***




## If PPS = 24 months

PFS and OS benefit = **3 mo**

Patients needed to demonstrate significant OS = **2440**



# Significant OS Improvements are More Difficult to Measure as Patients Survive Longer after Progression

- If PPS is longer than 12 months, there is a less than 30% chance that a trial will report a significant OS, even after reporting a PFS improvement at a high level of significance ($p<0.001$)
- The influence of PPS means that a lack of statistical significance in OS does not imply lack of improvement in OS

Broglio, Berry. J Natl Cancer Inst 2009

# AGO/NCIC/EORTC and OCEANS

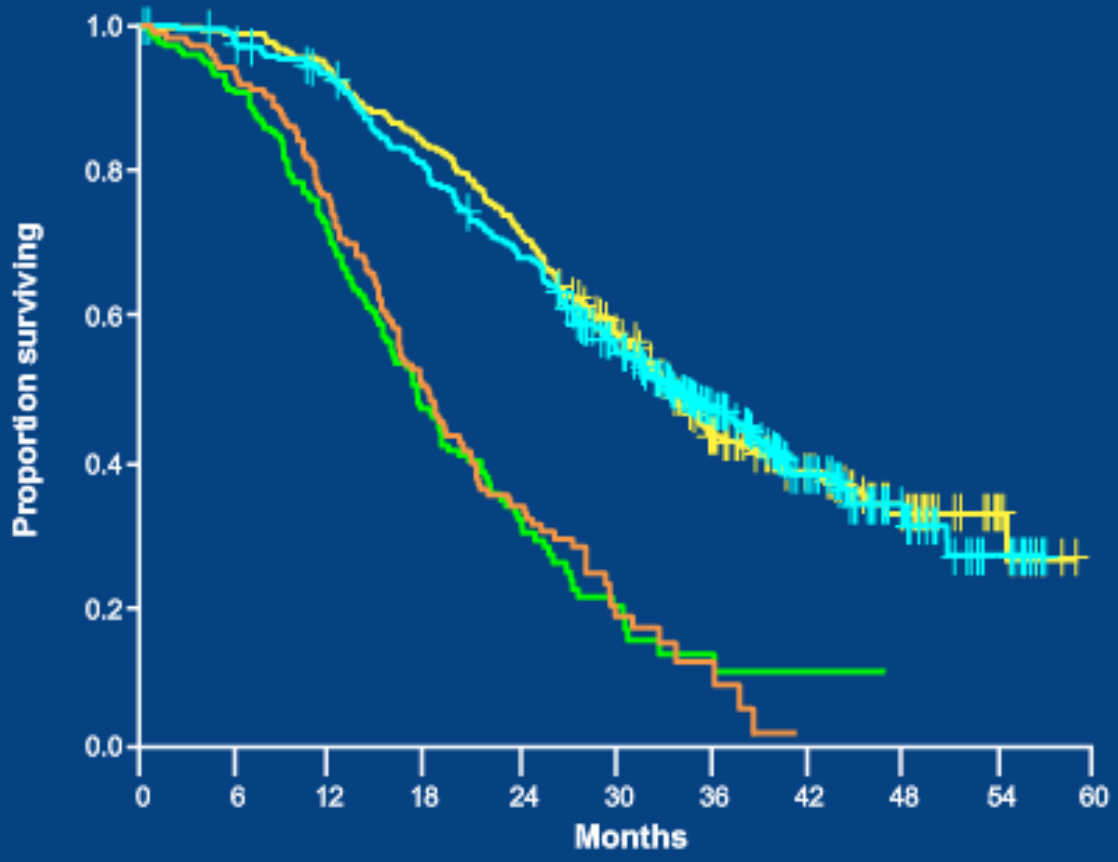
## Overall survival and subsequent treatment

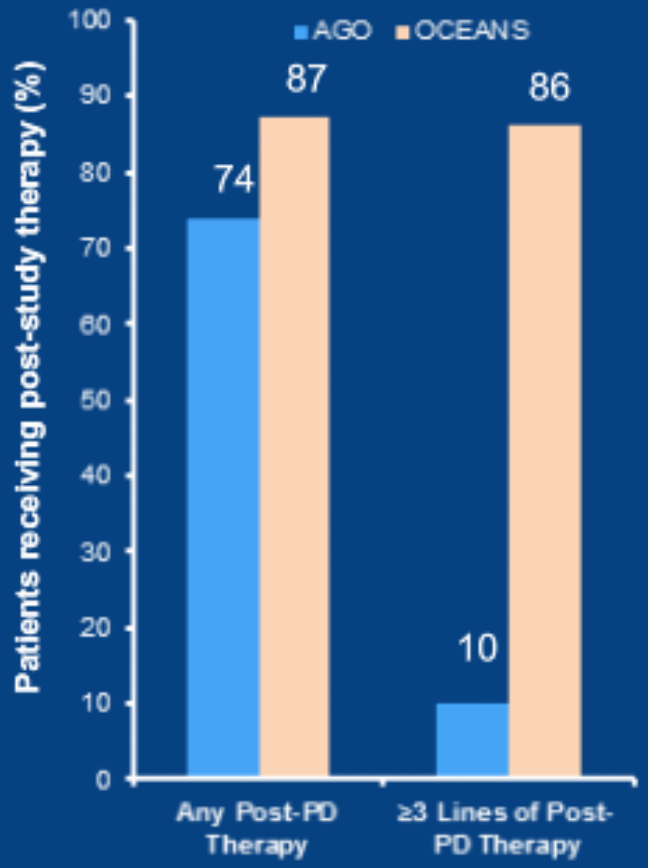
### AGO/NCIC/EORTC: OS[1]

| | C (n=178) | GC + PL (n=178) |
|---|---|---|
| Median OS, mo | 17.3 | 18.0 |
| HR (95% CI) | 0.96 (0.75 – 1.23) | |
| Log-rank *P* value | .7349 | |

### OCEANS: 3rd Interim OS Analysis

| | GC + PL (n=242) | GC + BV (n=242) |
|---|---|---|
| Median OS, mo | 33.7 | 33.4 |
| HR (95% CI) | 0.960 (0.760–1.214) | |
| Log-rank *P* value | .7360 | |



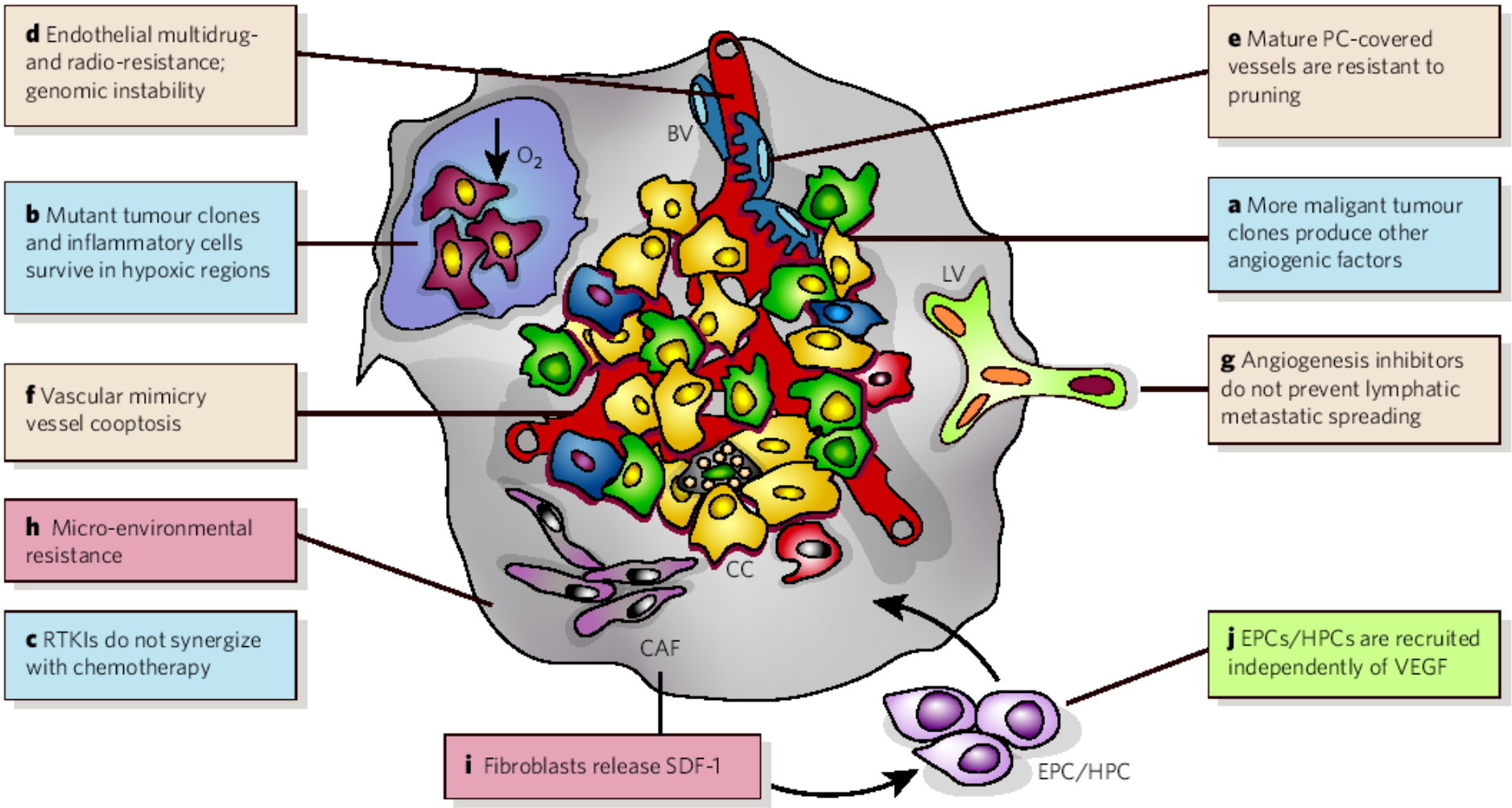




[1]Pfisterer et al. *J Clin Oncol.* 2006

# Why no OS benefit?

- Cross over
- Very long post-progression Survival
- **Development of resistance**

# Resistance to anti-angiogenic therapy



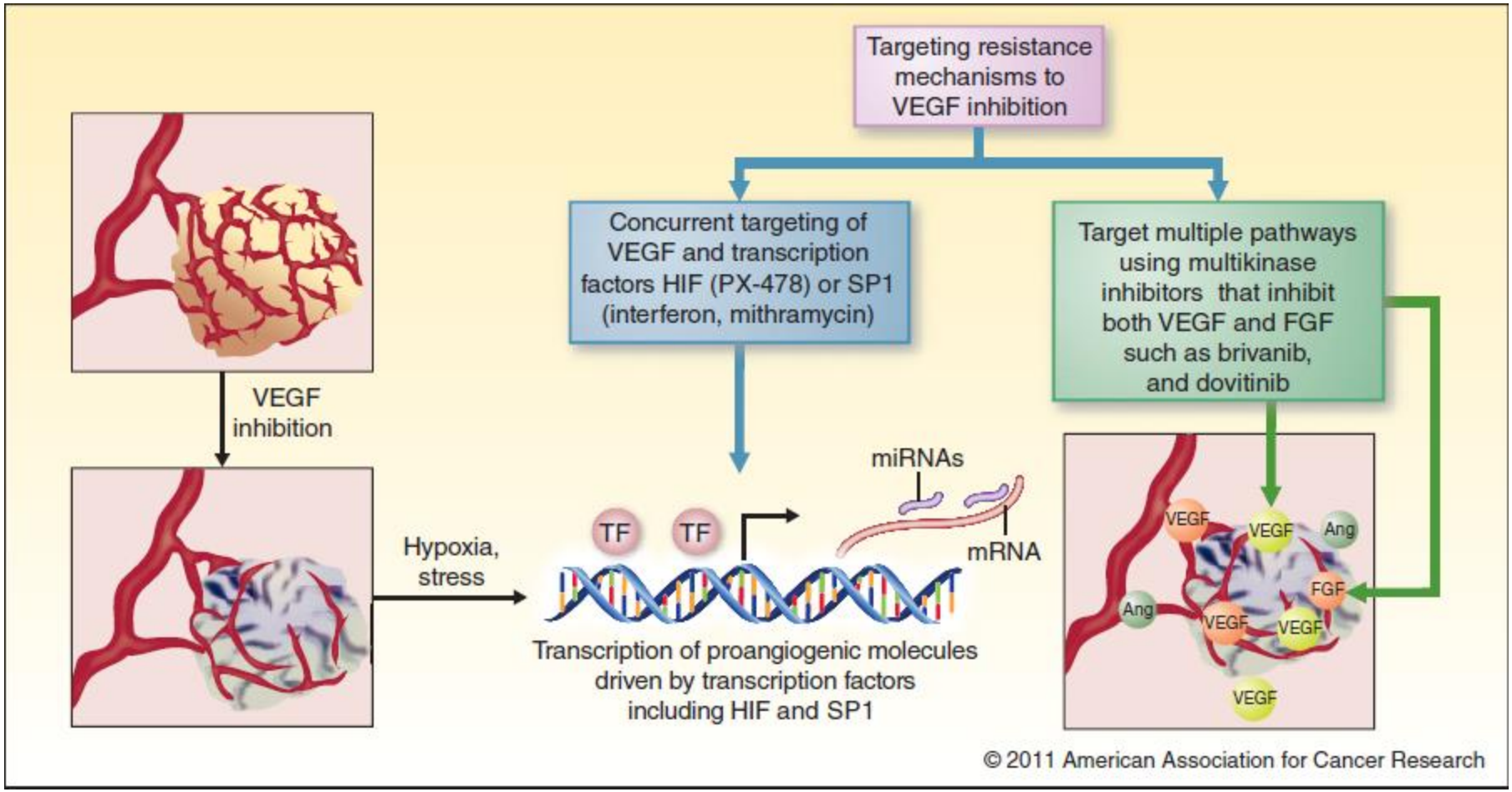



*Carmeliet P. Nature 438, 932-936, 2005*

# FGF

- FGF regulates cell proliferation, differentiation, survival and angiogenesis
- FGF **plays a role in the resistance to ANTI-VEGF** therapy
- Elevation of FGF-2 preceeds the development of anti-VEGF resistance in several tumor types
- In one study of advanced serous ovarian carcinomas, FGF-1 mRNA and protein levels were associated with worse overall survival

# Overcoming Antiangiogenic Resistance



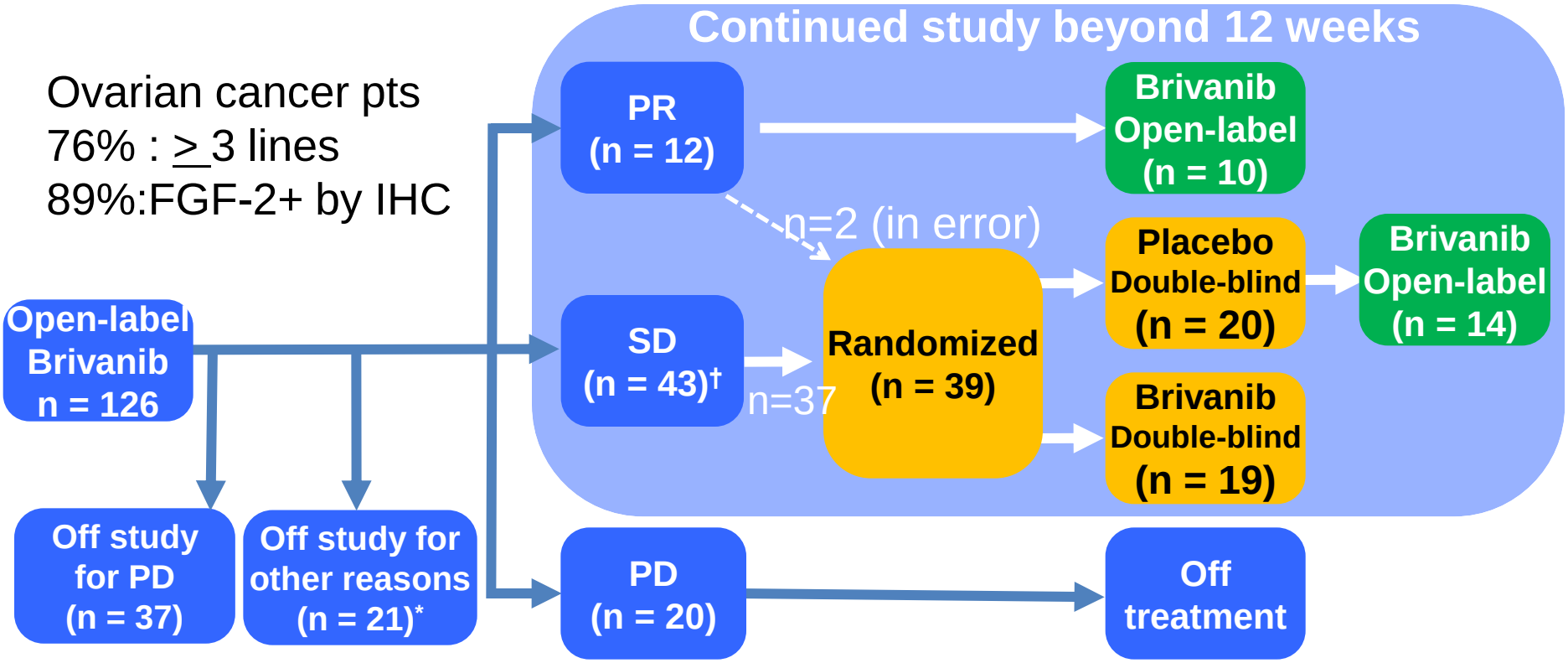

Yao et al. Clin Cancer Res; 17(16) August 15, 2011

# Brivanib (BMS-582664)

- Novel, orally available and selective receptor tyrosine Kinase inhibitor that targets VEGF-R2 and FGF-R1 and 2.
- Preclinical and clinical evidence of activity in several tumor types , also after failure of VEGF inhibition.

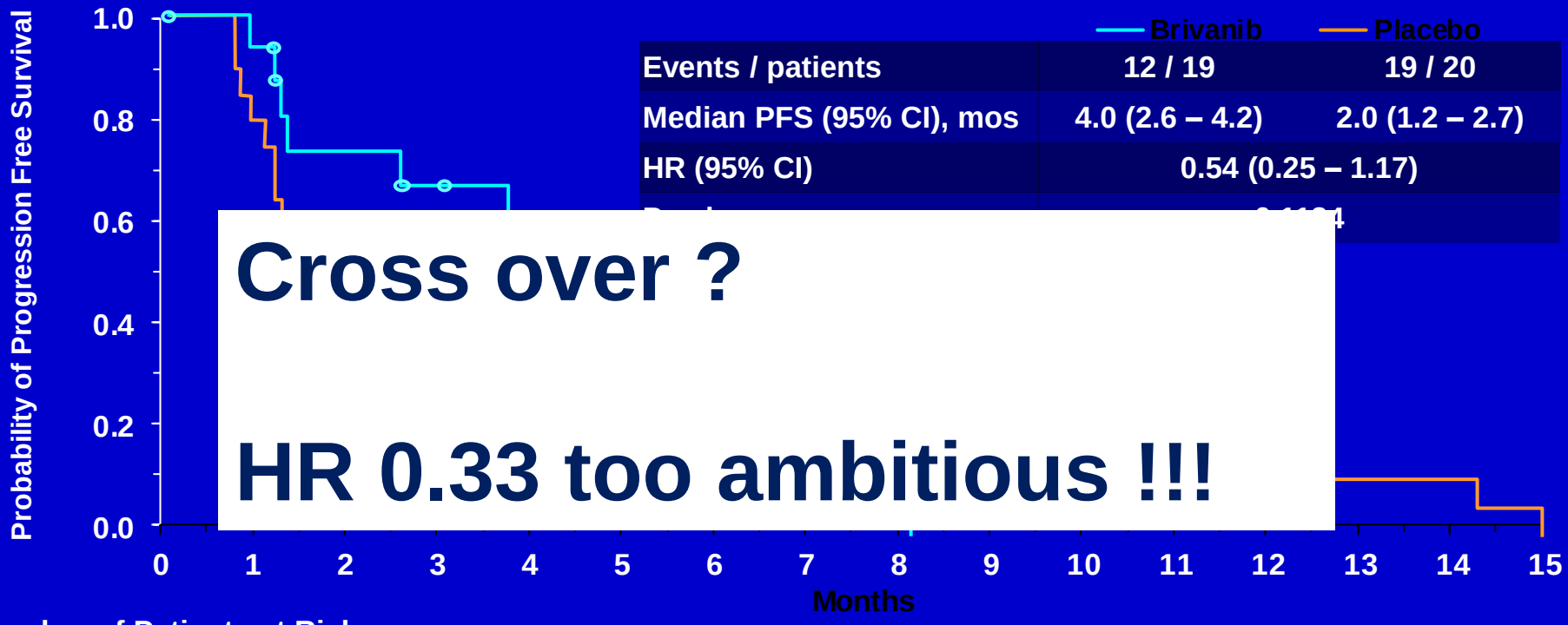
# Ovarian Cancer Patients: Disposition on Randomized Discontinuation Study

Ovarian cancer pts
76% : ≥ 3 lines
89%:FGF-2+ by IHC




**Statistics: 40 randomized patients (regardless of FGF-2 status) needed for 28 events to compare PFS for brivanib vs placebo at HR of 0.33, α of 5%, and power of 80%**

# PFS in All Randomized Ovarian Cancer Patients




| | Brivanib | Placebo |
|---|---|---|
| Events / patients | 12 / 19 | 19 / 20 |
| Median PFS (95% CI), mos | 4.0 (2.6 – 4.2) | 2.0 (1.2 – 2.7) |
| HR (95% CI) | 0.54 (0.25 – 1.17) | |

**Cross over ?**

**HR 0.33 too ambitious !!!**

| Number of Patients at Risk | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Brivanib | 19 | 16 | 11 | 9 | 5 | 2 | 2 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Placebo | 20 | 16 | 10 | 3 | 3 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 0 |

- Nearly identical PFS results in FGF-2+ patients (n = 36)
- Patients who crossed over from placebo to brivanib had a subsequent median PFS of 1.5 mos (95% CI, 1.2-2.8)

# Brivanib Phase II: ovarian cancer

- Response rate: 12%
- Response rate **after anti-VEGF** therapy:
- Tumor assessment at 12 weeks (lead-in)
  - PR = 4 of 23 (17%)
  - SD = 7 of 23 (30%)
  - DCR = 11 of 23 (47%)
- The high frequency of FGF-$2^{+}$ patients precluded the assessment of FGF-2 as a predictive biomarker ( would collagen IV be better?)

# Should Brivanib be further investigated in ovarian cancer ?

- Will combination with chemotherapy be better?
  - In xenograft models, only tumor inhibition but not tumor regression was seen with Brivanib.
  - inhibition of FGF/FGF-R can enhance cisplatin-induced cytotoxicity, suggesting that resistance to cisplatin is mediated, at least in part, by FGF-R

# Should Brivanib be further investigated in ovarian cancer ?

- Timing of FGF/FGF-R directed therapy:
  - The switch to an FGF-R inhibitor during treatment with a VEGF-R inhibitor may be more effective at the time of early revascularization.
  - **Will Brivanib be more active at the time of progression after treatment with VEGF inhibitors??**

# Multitargeted Therapy against VEGF-R and FGF-R : Agents in Phase III Development

| Agent | Class | Target | Phase |
|---|---|---|---|
| Nintedanib (BIBF 1120) | Small-molecule TKI | VEGFR + PDGFR + FGFR | III |
| Cediranib | Small-molecule TKI | VEGFR + PDGFR + FGFR + c-kit | III |

# Summary

1. Clinical benefit of bevacizumab more clearly demonstrated in the setting of high-risk or recurrent disease… but activity demonstrated across all patient population in first and second line ( resistant and sensitive)
2. Several missing pieces (timing, duration, and sequence of bevacizumab administration) will be fixed by ongoing trials
3. The lack of survival benefit will continue to divide the scientific community. The long PPS (and the high rate of cross over) will most likely make impossible to reach a statistical OS improvement in most ovarian cancer trials.
4. Overcoming anti-angiogenesis resistance represents a critical goal to improve outcome and provide a sustained clinical benefit.