
Pathological Society
Understanding Disease

Angiogenesis in Ovarian Cancer

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Content

1. Epithelial Ovarian Cancer : epidemiology
2. Angiogenesis-normal tissues vs cancer
3. Angiogenic pathways important in ovarian cancer
4. Novel agents targeting angiogenesis in ovarian cancer

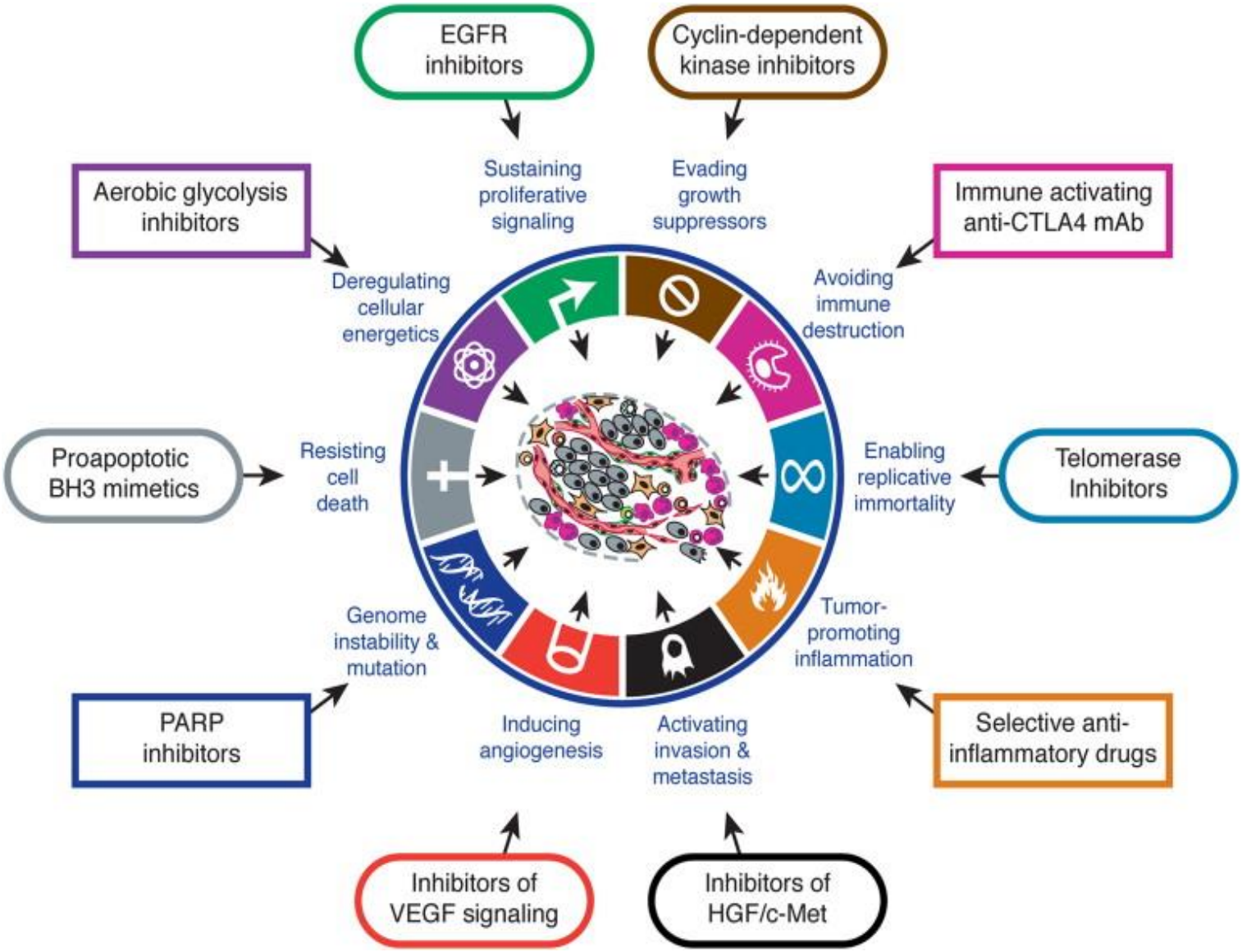
Epithelial Ovarian Cancer (EOC) Incidence and Mortality (UK)

- **Incidence in UK [1]**
  - 6,719 cases in 2007
  - 5th commonest cancer
  - Second most common gynecologic cancer
  - 1.5% lifetime risk of getting ovarian - cancer

- Despite front line surgery and chemotherapy:
  - 70 - 80% women relapse <3 years
  - Majority are retreated with platinum
- Median survival after 1st relapse is 30 months
- Modest improvements over the past 15 years- new treatment paradigms required to improve survival

[1] Cancer Research UK

Hallmarks of cancer

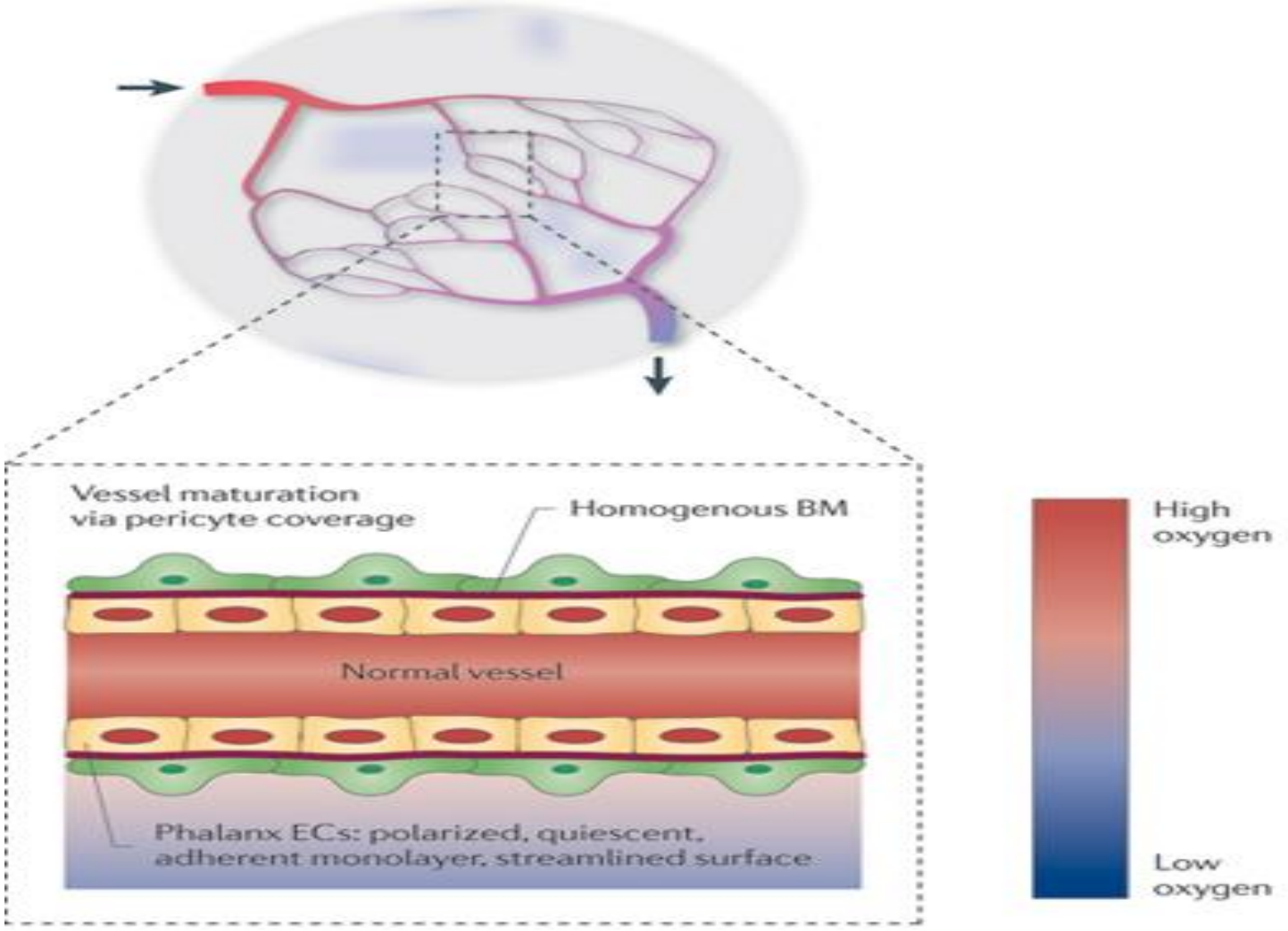


Cell 2011; 144: 646-74.

Angiogenesis

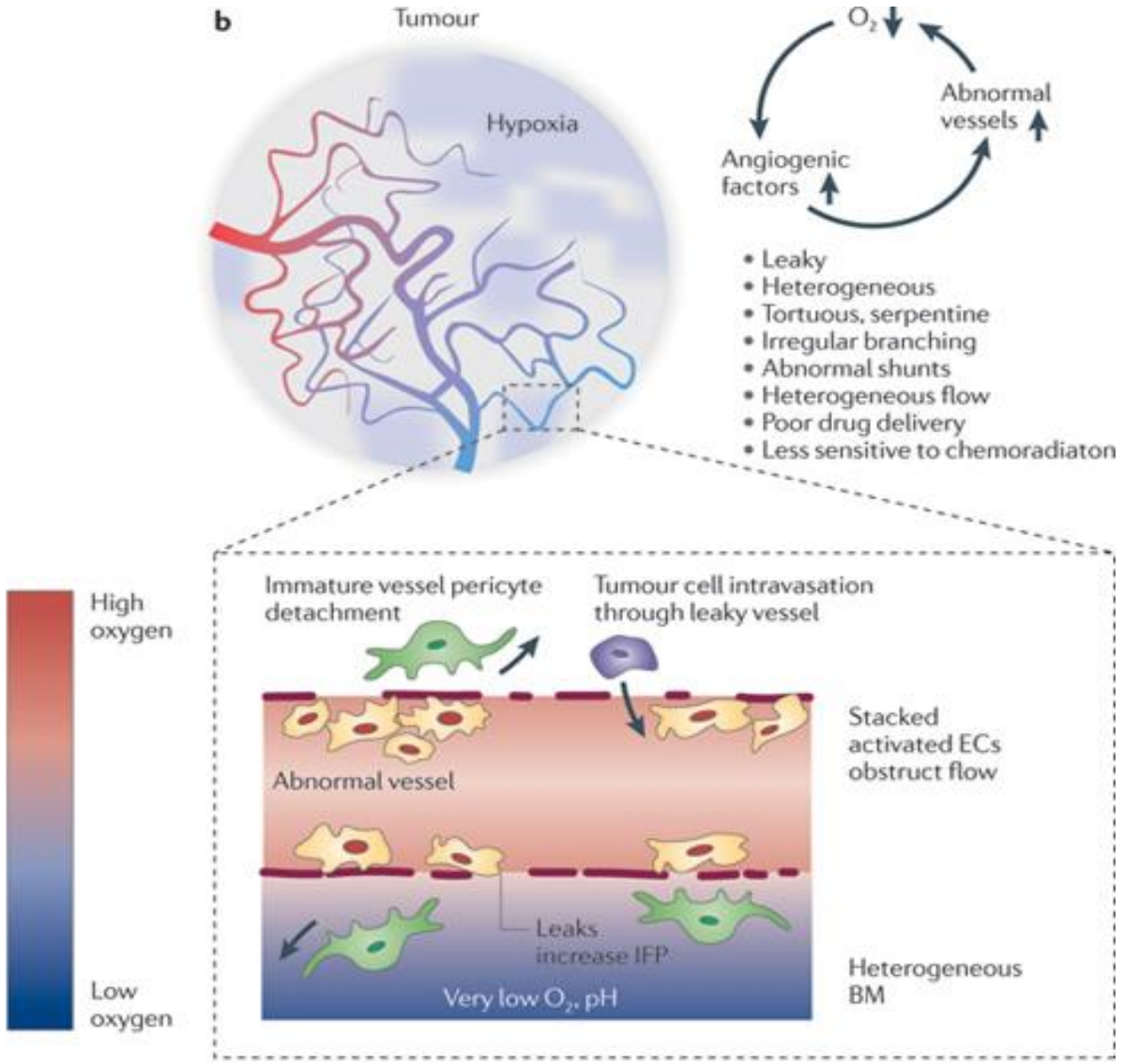
- Angiogenesis refers to the process of the formation of new vessels,
- Complex and involves a large number of cytokines and associated receptors.
- Normal tissues in adult life:
  - occurs sporadically e.g during the menstrual cycle and in wound healing
- Tumours: angiogenesis constitutively active
- Angiogenesis essential process for oncogenesis, tumour growth and progression

Angiogenesis in Normal Tissues



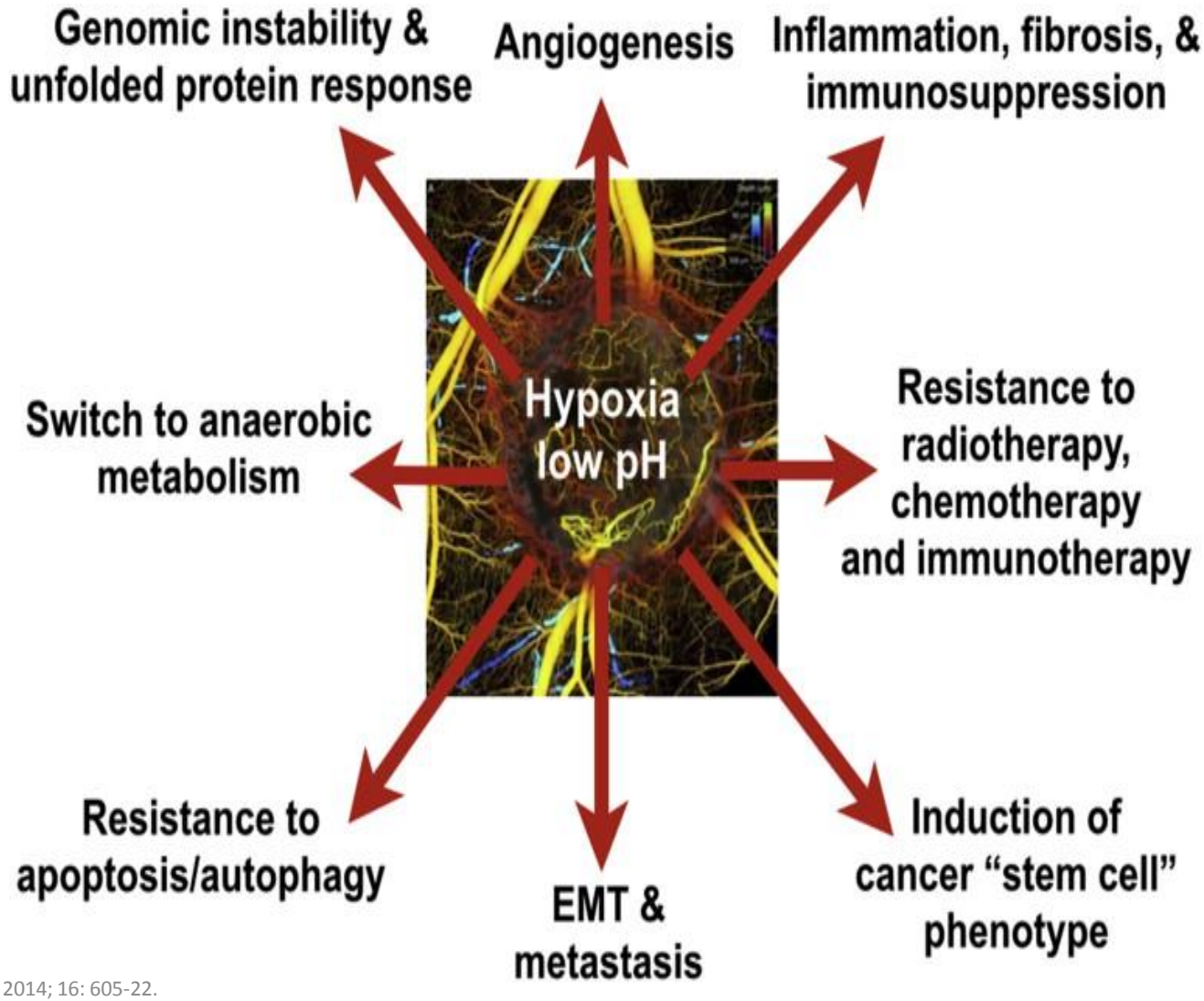
Carmeliet, Nat Rev Drug Discov 2011; 10: 417-27.

Angiogenesis in Tumours: abnormal vessel structure and function



Carmeliet, Nat Rev Drug Discov 2011; 10: 417-27.

Hypoxia and Acidosis Key Features in Tumour Progression and Treatment Resistance



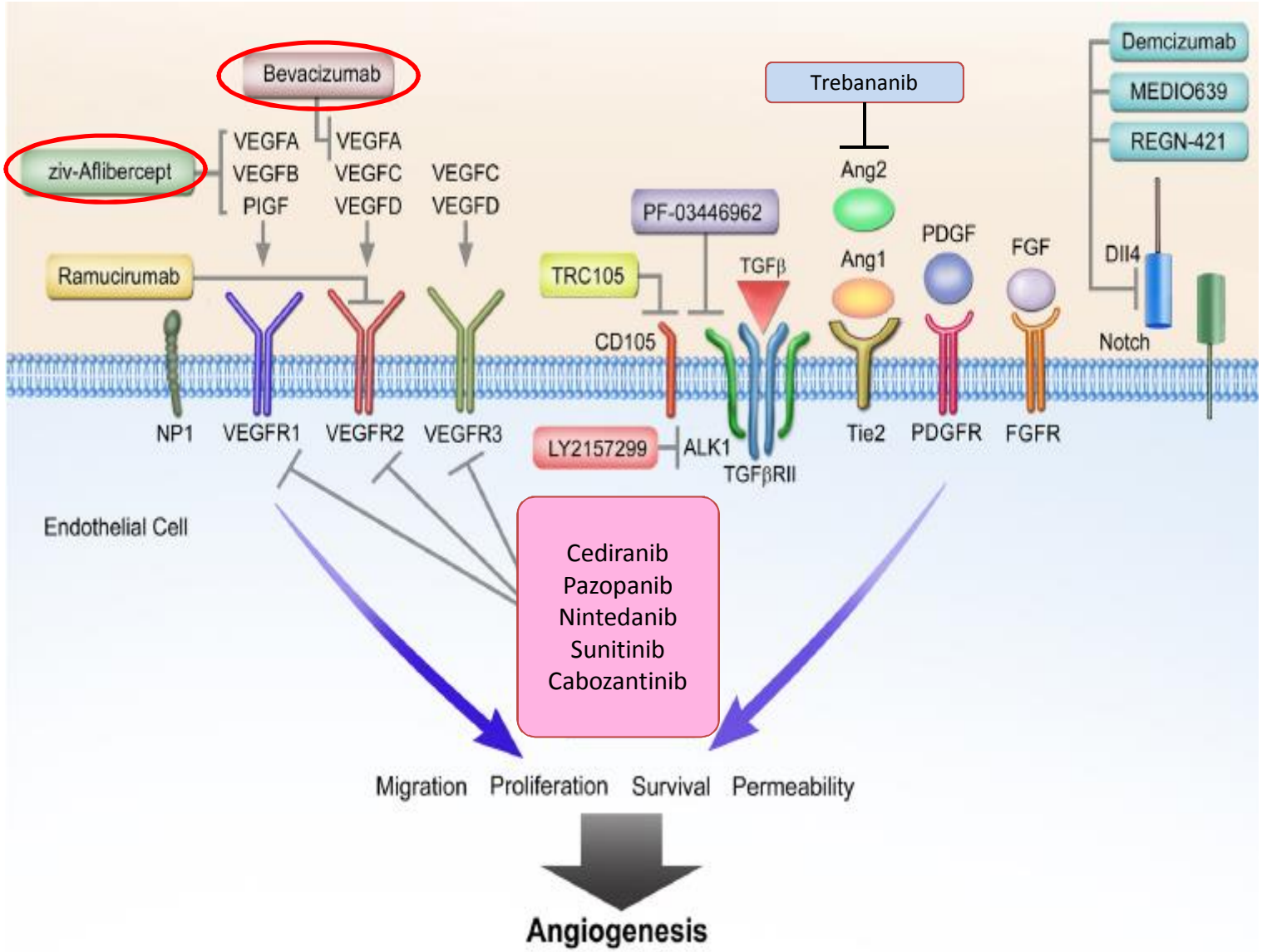
Jain, Cancer Cell 2014; 16: 605-22.

EOC: angiogenic pathways

- Major molecular pathways involved :
  - Vascular Endothelial Growth Factor (VEGF)
  - Angiopoeitin pathway and Tie2 Receptor
  - Platelet Derived Growth Factor (PDGF)
  - Fibroblast Growth Factor (FGF)

- Activation of intracellular pathways such as JAK and STAT, PI3 kinase and MAP kinase pathways are all key components of angiogenesis

Angiogenesis: targeting the angiogenesis pathways in EOC



Clarke and Hurwitz, J of Gastrointestinal Oncology, 2013

EOC - VEGF pathway:

- VEGF: 3 isoforms: VEGF A, B and C
  - regulates new vessel growth and promotes survival of immature vasculature
  - VEGF signals via surface receptors: VEGFR1 ,2, 3
  - VEGFA is main isoform involved in angiogenesis and signals via VEGFR2
  - Activation of intracellular pathways such as JAK and STAT, PI3 kinase and MAP kinase pathways are all key components of angiogenesis

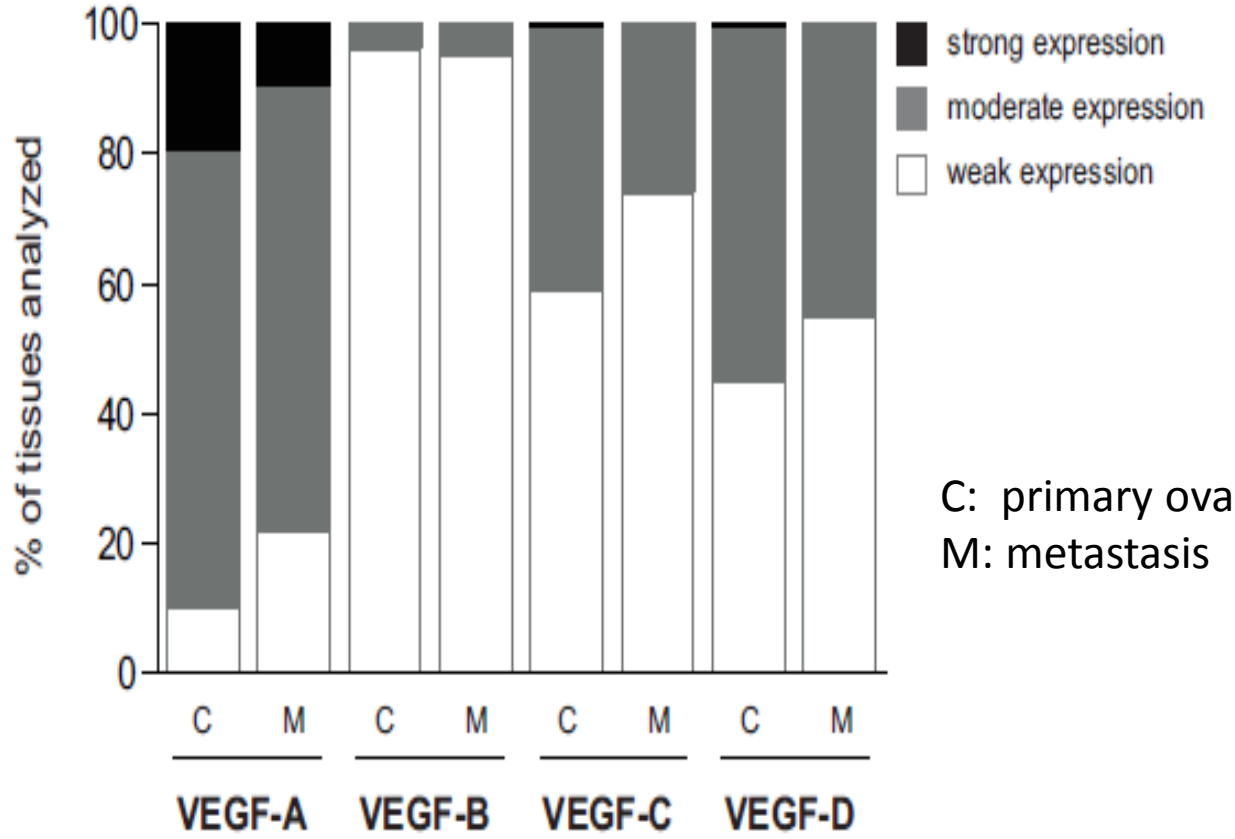
EOC: Rationale for targeting VEGF

- VEGF is dominant pathway in EOC
- VEGF produced by ovarian cancer cells and stimulates ovarian cancer cell proliferation and evasion from apoptosis[2]
- VEGF increases permeability of tumor vasculature- induces formation of malignant ascites[1]
- Tumour selectivity-expression of VEGF and VEGFR is higher in ovarian cancer than in normal ovarian tissue[2,3]

- VEGF ligand overexpressed in ovarian tumors [4]
  - Correlates with ascites formation
  - Poor prognosis
  - Reduced survival

1. Mesiano S, et al. *Am J Pathol.* 1998;153(4):1249-1256.
2. 2. Brown MR, et al. *Baillieres Best Pract Res Clin Obstet Gynaecol.* 2000;14(6):901-918.
3. 3. Chen H, et al. Gynecol Oncol 2004;94(3):630-635.
4. 4. Yamamoto S, et al. *Br J Cancer*. 1997;76(9):1221-1227.

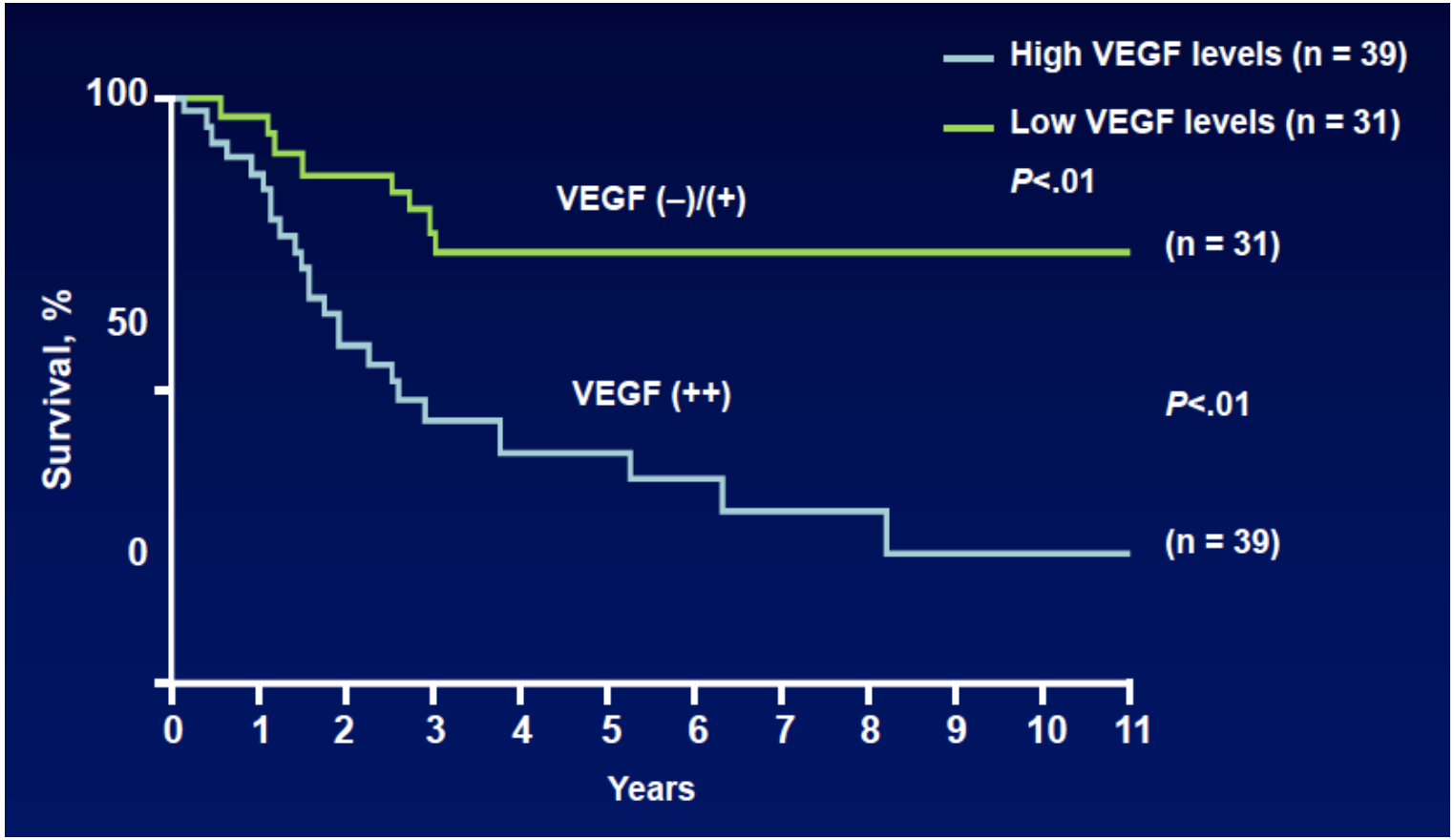
VEGF-A, C and D: over expressed in 40% of ovarian cancers



C: primary ovarian cancer
M: metastasis

Van der Bilt, Cur Pharm Des 2012; 18: 3784-92

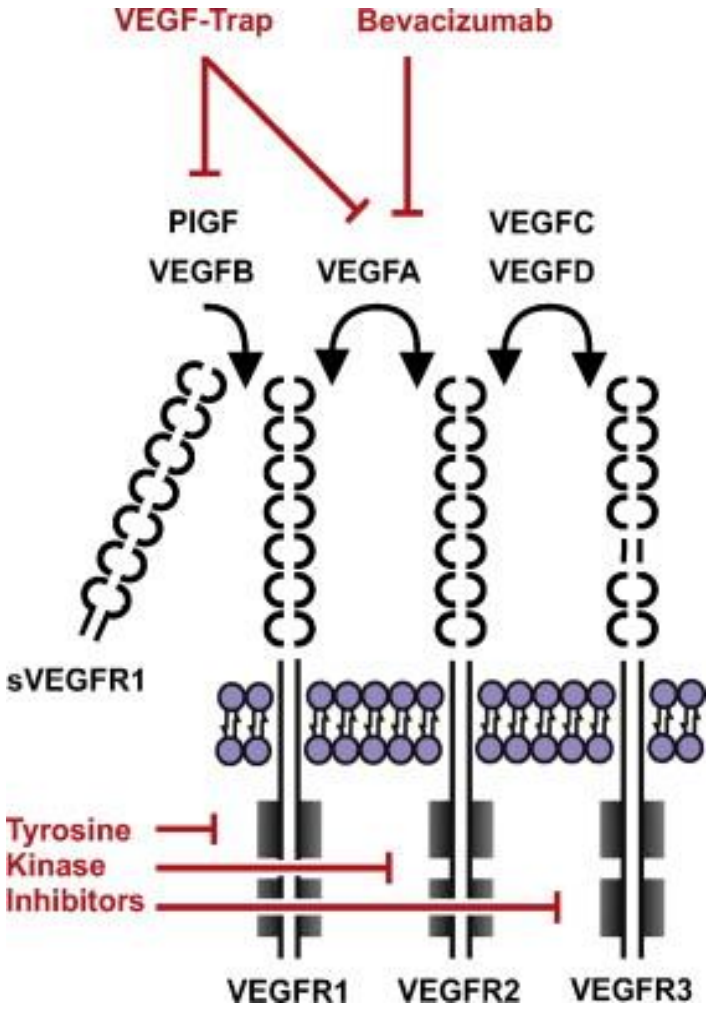
Clinical trials-VEGF Associated with poor survival[1]



1.Yamamoto S, et al. *Br J Cancer*. 1997;76(9):1221-1227.

Anti-angiogenic Agents Targeting the VEGF Pathway

(Aflibercept) Bevacizumab



Cediranib
Pazopanib
Nintedanib

Van der Bilt, Crit Rev Oncol Hematol 2012; 84: 224-42.

Bevacizumab

EOC Novel Agents: Bevacizumab/Avastin

- **Anti-VEGF monoclonal antibody**
  - targets formation of new blood vessels within cancers
  - Binds to VEGF-A extracellularly and prevents its interaction with VEGFR2 receptor, thus inhibiting angiogenesis

- 2 Phase 3 trials demonstrate efficacy: ICON7 and GOG218

- **EMA license 2012:** bevacizumab in combination with carboplatin and taxol in newly diagnosed ovarian cancer

EOC Trials First line: bevacizumab and chemotherapy increases PFS

Study	Regimen(s)	PFS	OS
GOG218[1]	(A) Carboplatin/paclitaxel (B) Carboplatin/paclitaxel/ bevacizumab (C) Carboplatin/paclitaxel/ bevacizumab + bevacizumab maintenance	**10.3 mos** **11.2 mos** **14.1 mos (p<0.001)**	39.3 mos 38.7 mos 39.7 mos
ICON7[2,3]	(A) Carboplatin/paclitaxel (B) Carboplatin/paclitaxel/ bevacizumab + bevacizumab maintenance	**20.3 mos** **21.8 mos (p=0.04)**	44.6 mos 45.5 mos

[1]Burger et al., *N Engl J Med* 2011; [2]Perren et al., *N Engl J Med* 2011;
[3]Oza et al., *Lancet Oncol* 2015; [3]du Bois et al., *ESGO* 2013;
[4]Kristensen et al., *ASCO* 2014; [5]du Bois et al., *J Clin Oncol* 2014

EOC Trials First line: bevacizumab and chemotherapy

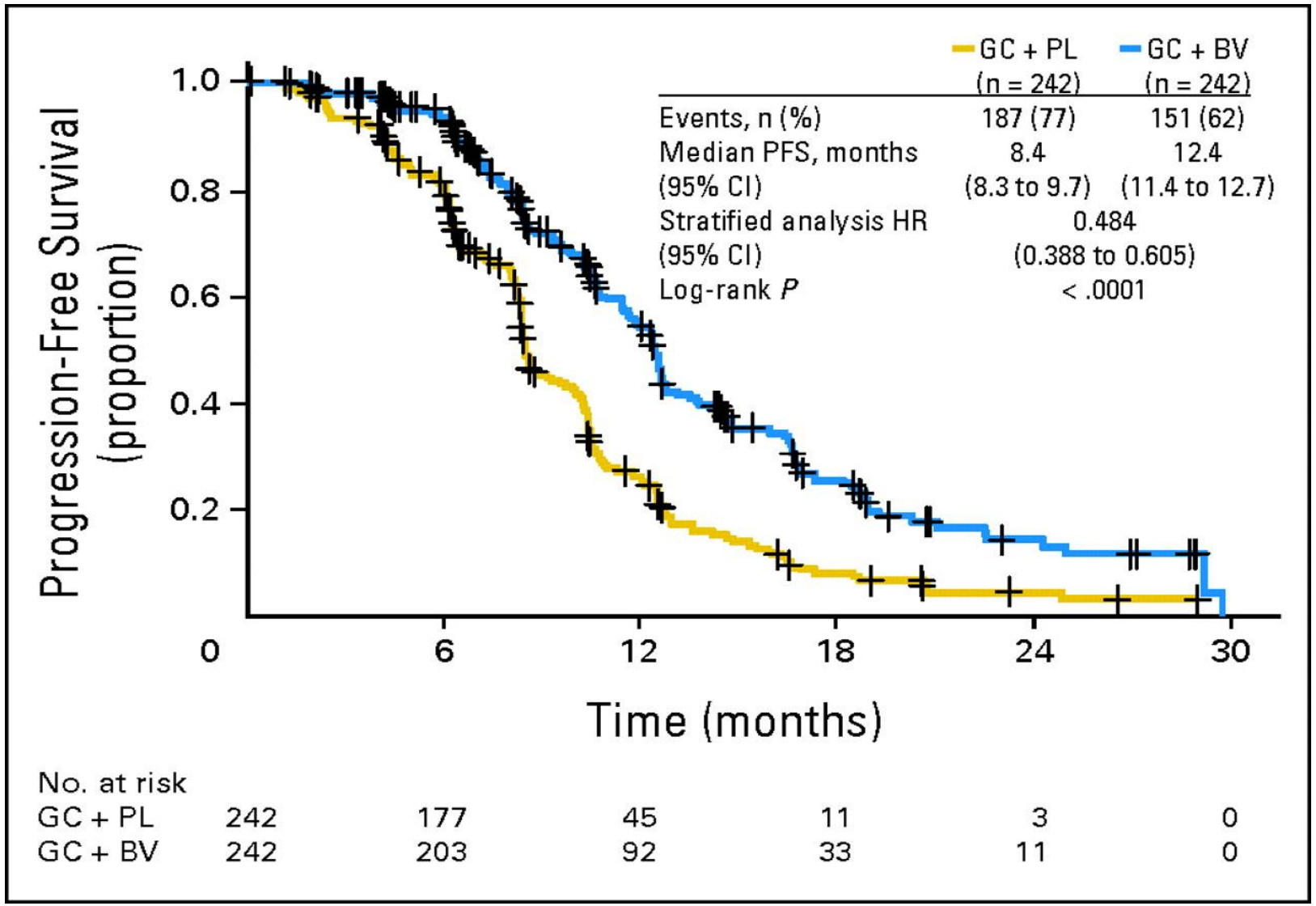
- Bevacizumab well tolerated.
- Main toxicities:
  - hypertension,
  - proteinuria
  - Venous Thromboembolism
- No GI perforation

Recurrent EOC: Bevacizumab

- **Oceans Trial [1]**
- N= 484 patients with Platinum Sensitive Relapse (PSR)
- First relapse >6 months from primary therapy
- Carboplatin (AUC4)/ Gemcitabine (1000mg/m^2) +/- Bevacizumab (15 mg/kg) followed by maintenance therapy; q 3/52 until progression/toxicity
- No prior chemotherapy for relapse
- Cytoreductive surgery for relapse was permitted

[1.] Aghajanian C et al. JCO 2012;30:2039-2045

Oceans Trial: Kaplan-Meier estimates of progression-free survival (PFS) [1]



1. Aghajanian C et al. JCO 2012;30:2039-2045

OC: recurrent disease anti-angiogenics + chemotherapy increase PFS

Study	Regimen(s)	PFS	OS
OCEANS[1] (plat-sens)	(A) Carboplatin/gemcitabine (CG) (B) CG/bevacizumab + bevacizumab maintenance	**8.4 mos** **12.4 mos**	35.2 mos 33.3 mos
GOG213[2] (plat-sens)	(A) Carboplatin/paclitaxel (CP) (B) CP/bevacizumab + bevacizumab maintenance	**10.4 mos** **13.8 mos (p<0.0001)**	37.3 mos 42.2 mos (p=0.056)
AURELIA[3] (plat-res)	(A) Chemotherapy (paclitaxel, PLD, or topotecan) (B) Chemotherapy + bevacizumab	**3.4 mos** **6.7 mos (p<0.001)**	13.3 mos 16.6 mos

[1]Aghajanian et al., *J Clin Oncol* 2012; 2 Coleman et al., *SGO* 2015; [3]Pujade-Lauraine et al., *J Clin Oncol* 2014;

Angiogenesis pathway: PDGF

- PDGF may be activated in response to VEGF inhibition resistance
- PDGF ï four isoforms A-D via PDGFR
- PDGF secreted by endothelial cells at site of angiogenesis and recruits pericytes to stabilise maturing blood vessels.
- Acts in concert with VEGF in order to promote new vessel formation and stabilize newly synthesized vessels
- Activation via PDGF Receptor (PDGFR)
  - up regulation of angiogenic events.
  - signaling via the PI3K/Akt pathway

EOC angiogenesis pathway: PDGF

- PDGFR is expressed in ovarian carcinomas and in malignant ascites
  - associated with a poorer prognosis in EOC [1]

- Negative trials of PDGF/ Kit inhibitors such as Imatinib [2,3]

- But positive trials of agents that target both PDGFR and VEGFR such as Cediranib[4] (ICON6) and Nintedanib[5](AGO-OVAR12)

1 .Lassus et al, Br J Ca, 2004;91
2. Coleman et al, Gynae Oncol 2006, 101
3. Matei et al, Cancer 2008, 113
4.Ledermann, Lancet 2016, 387
5. Dubois, JCO 2013, 31

Anti VEGF/PDGF Oral Tyrosine Kinase Inhibitors (TKI)

VEGF/PDGF Receptor Small Molecule Tyrosine Kinase inhibitors

- **Front line:**
- **Pazopanib** (VEGFR 1-3, PDGFR, c-Kit)
- maintenance: AGO OVAR16;
  - n=940**;** PFS 5.6 months improvement with pazopanib (17.9 mo vs 12.3 mo); No OS benefit. [1]

- **Nintedanib** (VEGFR 1-3, FGFR1-3, PDGFR)
- concurrent chemotherapy and maintenance: AGO OVAR12
- First line/ phase 3 trial/ nintedanib vs placebo;
  - PFS: 17.3 (nintedanib) *vs.* 16.6 months; HR=0.84;
  - **Low risk patients (optimal debulking): PFS 27.1 (Nintedanib) vs 20 months (Placebo).** [2]

1. Dubois,
2. Dubois, JCO 2013

Front Line Treatment EOC: Anti-angiogenics + chemotherapy increases PFS

Study	Regimen(s)	PFS	OS
GOG218[1]	(A) Carboplatin/paclitaxel (B) Carboplatin/paclitaxel/ bevacizumab (C) Carboplatin/paclitaxel/ bevacizumab + bevacizumab maintenance	**10.3 mos** **11.2 mos** **14.1 mos (p<0.001)**	39.3 mos 38.7 mos 39.7 mos
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AGO-OVAR 12[4,5]	(A) Carboplatin/paclitaxel (B) Carboplatin/paclitaxel/ nintedanib + nintedanib maintenance	**17.2 mos** **16.6 mos (p=0.02)**	NR NR
AGO-OVAR 16[6]	(A) Platinum/taxane (B) Platinum/taxane + pazopanib maintenance	**17.9 mos** **12.3 mos (p=0.002)**	OS HR 1.08 (p=0.499)

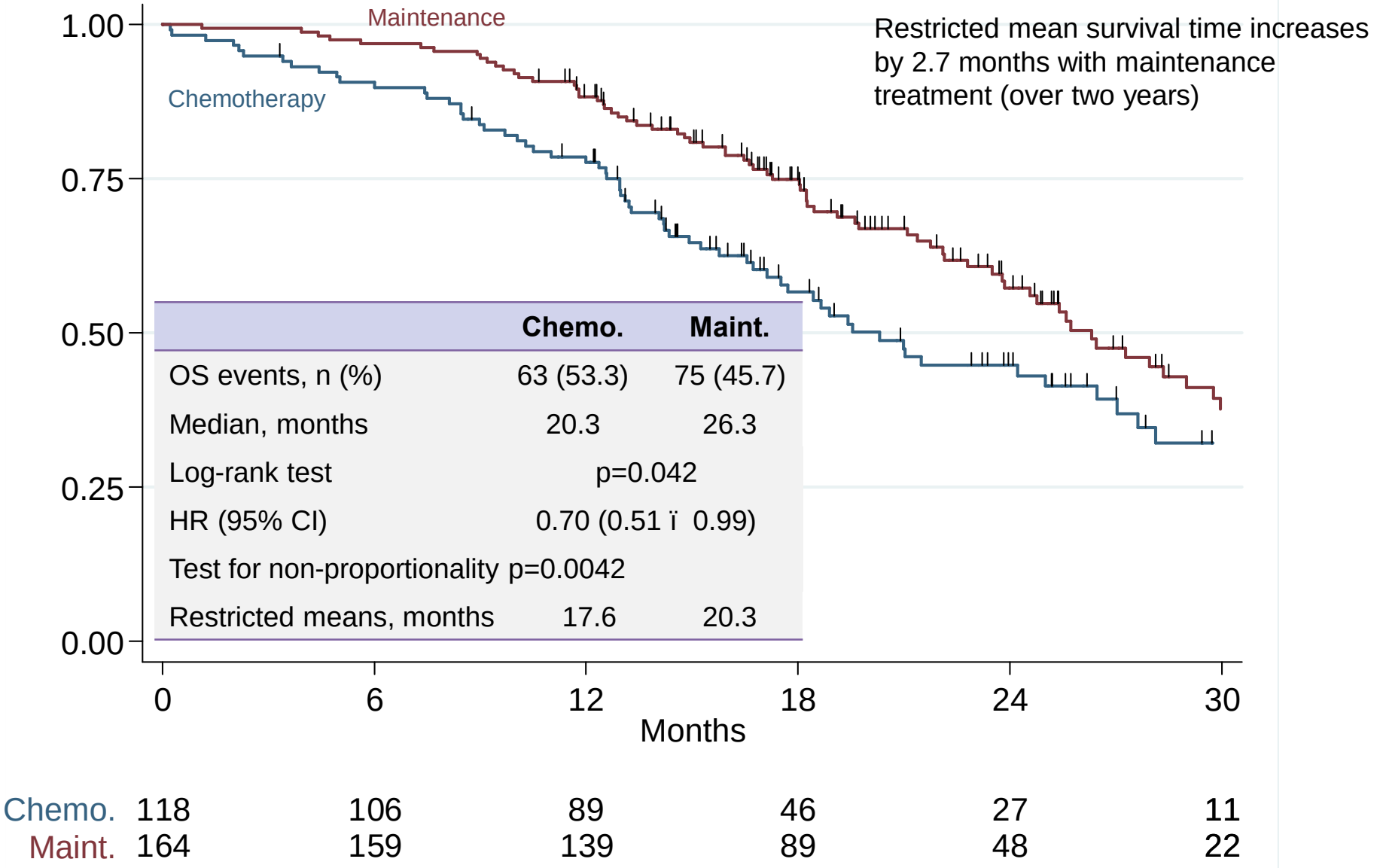
[1]Burger et al., *N Engl J Med* 2011; [2]Perren et al., *N Engl J Med* 2011;
[3]Oza et al., *Lancet Oncol* 2015; [3]du Bois et al., *ESGO* 2013;
[4]Kristensen et al., *ASCO* 2014; [5]du Bois et al., *J Clin Oncol* 2014

Recurrent EOC

- **Cediranib:**
- *in vitro* activity against VEGF1-3, PDGFR, cKit [1]
- >800-5000 fold selectivity for VEGFR-2
- Inhibits growth of established xenografts ï lung, colorectal, prostate, breast and ovary.
- **Phase II trials showed activity as a single agent in ovarian cancer [2.3]**
- **ICON6 Trial –**phase 3 randomised trial; Cediranib (20 mg) concurrent chemotherapy + maintenance [4]

[1] Wedge et al Cancer Res 2005
[2] Matulonis et al 2009;
[3] Hirte et al 2010
[4] Ledermann et al, ESMO 2013

Overall survival [1]



	Chemo.	Maint.
OS events, n (%)	63 (53.3)	75 (45.7)
Median, months	20.3	26.3
Log-rank test	p=0.042	
HR (95% CI)	0.70 (0.51 ï 0.99)	
Test for non-proportionality	p=0.0042	
Restricted means, months	17.6	20.3

[1] Ledermann et al, ESMO 2013

PSR: Anti-angiogenic combinations without chemotherapy Cediranib/Olaparib

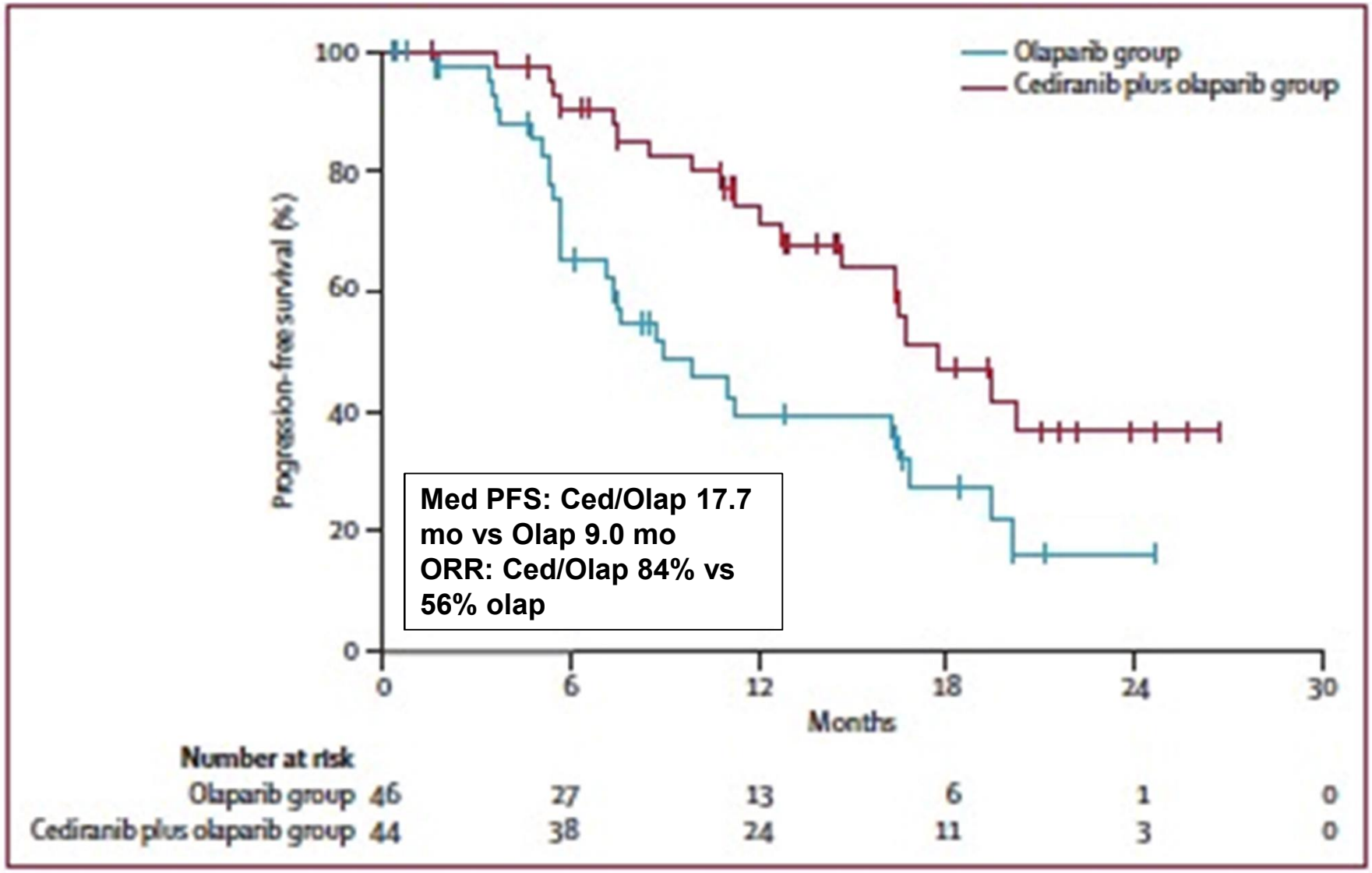
- Randomised Phase II - olaparib v cediranib + olaparib (n=90):
- Relapsed ovarian cancer
- BRCA WT + Mutant
- Cediranib 30 mg/ Olaparib 200mg bd

- **Results** [1]
- Median PFS: Ced/Olap 17.7 mo vs Olap 9.0 mo (HR 0.42, 95% CI 0.23-0.76, p=0.005).
- Toxicity: fatigue (27% Ced/Olap vs 7% Olap), diarrhoea (23% vs 0%), and hypertension (39% vs 0%).

- NCI led Phase III study now enroling

[1.] Lui et al, Lancet Oct 2014

Kaplan-Meier curves for progression-free survival in the ITT population [1]



[1] Lui et al, Lancet Oct 2014

OC: targeting the angiogenesis pathway Angiopoietins

- Angiopoietin (Ang) protein: Ang-1 and Ang-2
  - interact with the Tie2 receptor.[1]
- Ang2 +/- other pro-angiogenic factors e.g VEGF enhance new vessel production
- Ang-2 promotes endothelial cell migration [2]
- Blockage of Ang binding toTie2 receptor leads to decreased sprouting and reduction of the number of tumor vessels. [3]

1. Reiss, Recent Res Can res, 2010,180
2. Petrillo, Exp Opin Investig Drugs, 2012,21
3. Oliner, Cancer Cell 2004, 6

Novel Agents: Trebananib: TRINOVA 1

- **Trebananib: TRINOVA 1**

Å **TRINOVA 1 trial[1]:** Trebananib +/- weekly taxol

Å N = 919; Phase III randomised trial

Å Relapse < 12months from prior therapy

Å Included platinum resistant patients

Å **Results:**

ï PFS: 7·2 months [5·8ï 7·4] vs 5·4 months

ï [95% CI 4·3ï 5·5, hazard ratio 0·66, 95% CI 0·57ï 0·77, p<0·0001)

ï No OS benefit seen: 19.3 months in the Trebananib arm versus 18.3

EOC angiogenesis: FGF pathway

Å FGF may also play a role in angiogenesis acting alongside other pro-angiogenic factors such as VEGF.[1]

- FGF involved in tumor cell proliferation in ovarian cancer [1]
- FGF signaling pathway involves downstream proteins e.g MAPK, PI3K/Akt cascade [2]
- FGF pathway may crosstalk with other pathways such as the Notch pathway [3]

- Nintedanib also targets FGFR- benefit in low risk patients (optimal debulking): PFS 27.1 (Nintedanib) vs 20 months (Placebo). [4]

1. Tebben, Mayo Clin Proc 2005, 80
2. Katoh, Int J Oncol 2006, 29
3. Akai, Genes Dev 2005,19
4. Dubois, JCO 2013

Conclusions

- Angiogenesis plays a key role in ovarian tumour growth
- To date the greatest success has been in targeting the VEGF/ PDGF pathway
- Combination anti-angiogenics together with chemotherapy has led to PFS benefit in multiple settings of ovarian cancer
- Increasing interest in anti-angiogenics + novel agents e.g PARP inhibitors/ Immunotherapy
- Molecular profiles of response still required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