Angiogenesis and Endometrial Cancer

Christian Marth

Department of Obstetrics and Gynecology
Medical University Innsbruck

AGO AUSTRIA

ENGOT
European Network of
Gynaecological Oncological Trial groups

DISCLOSURE INFORMATION

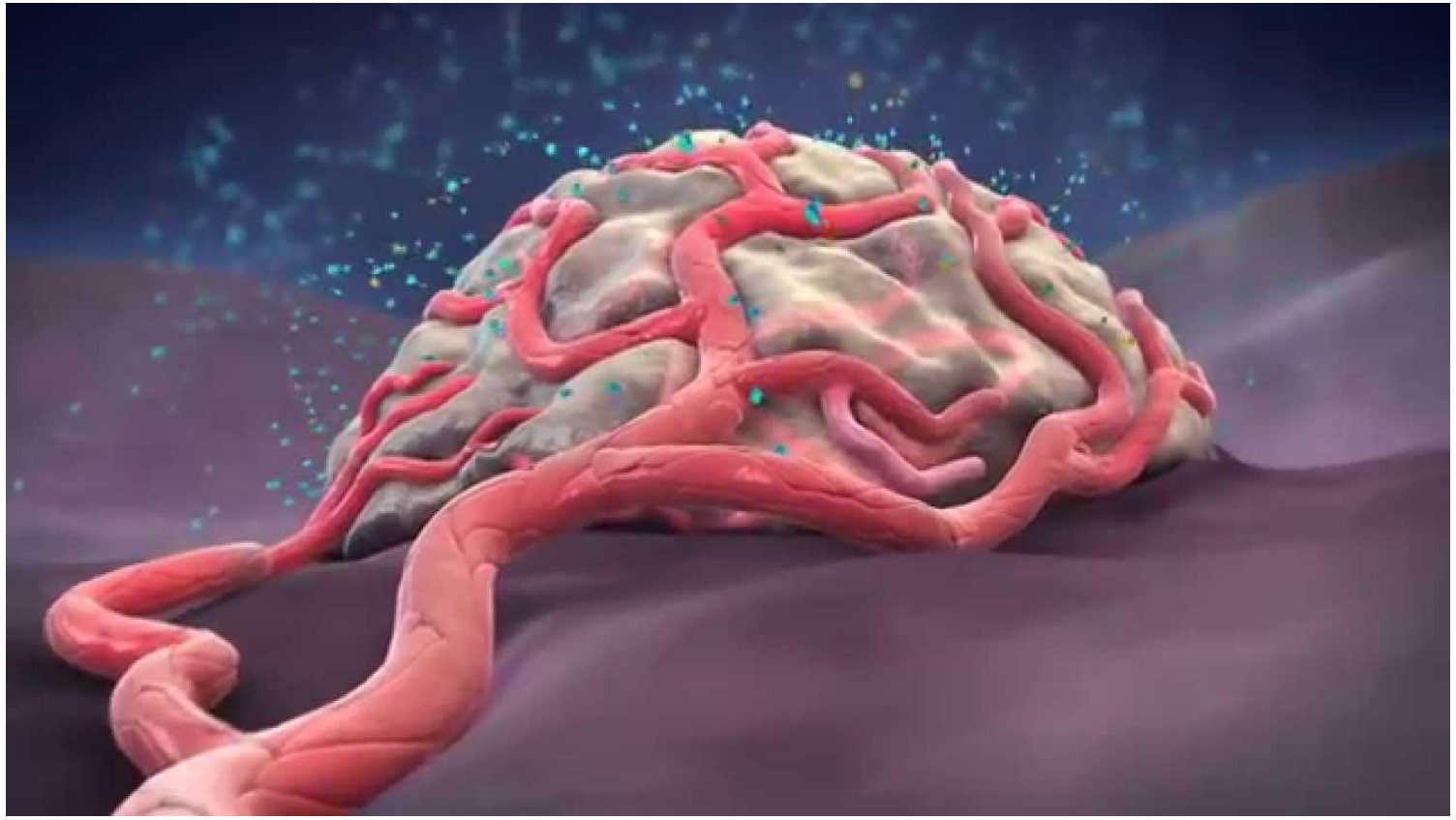
Funded Research: EU, FWF, Astra Zeneca, Roche

Honoraria/Expenses: Roche, Novartis, Amgen, MSD, Pharmamar, Astra Zeneca, Tesaro, GSK

Consulting/Advisory Board: Roche, Novartis, Amgen, MSD, Astra Zeneca, Pfizer, Pharmamar, Cerulean, Vertex, Tesaro, GSK

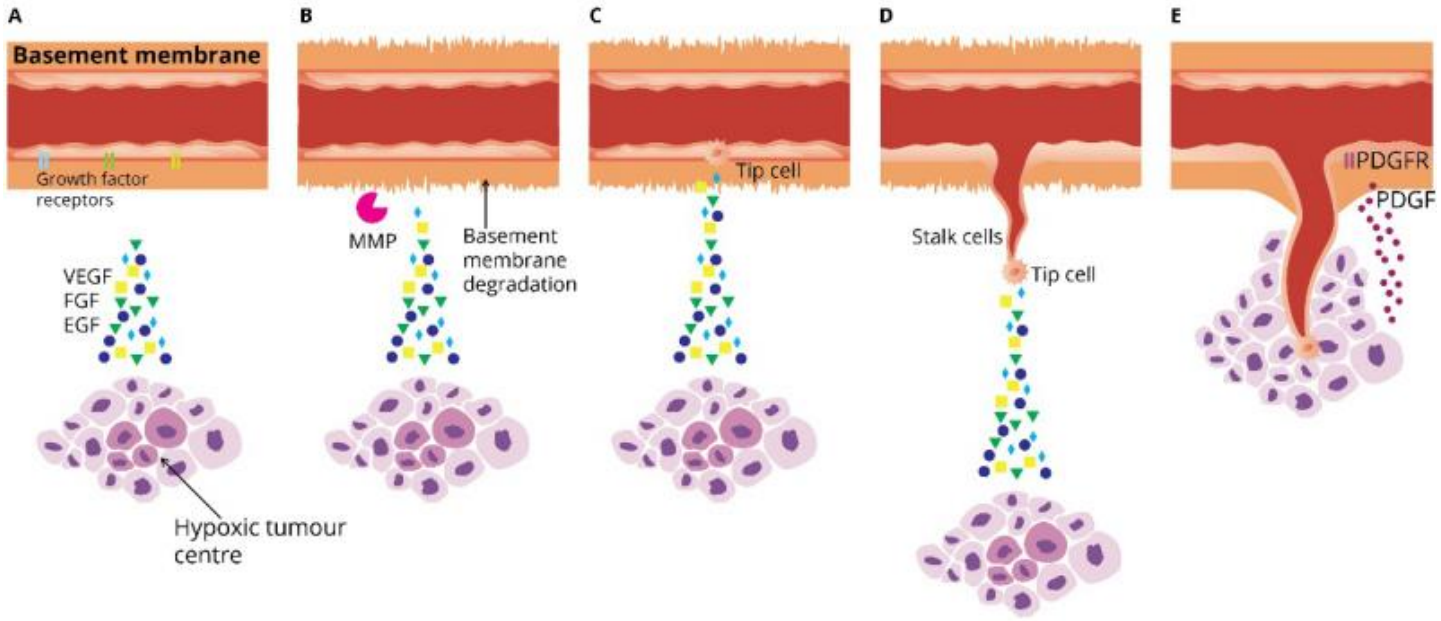
Angiogenesis

- Angiogenesis is the process of vessel formation (arterial, venous, or lymphatics).



Angiogenesis

- Angiogenesis is the process of vessel formation (arterial, venous, or lymphatics).
- The process of angiogenesis involves the degradation of the basement membrane by matrix metalloproteinases (MMPs), movement of endothelial cells through the degraded matrix, their proliferation and organization into new vessels, and the subsequent production of new basement membranes



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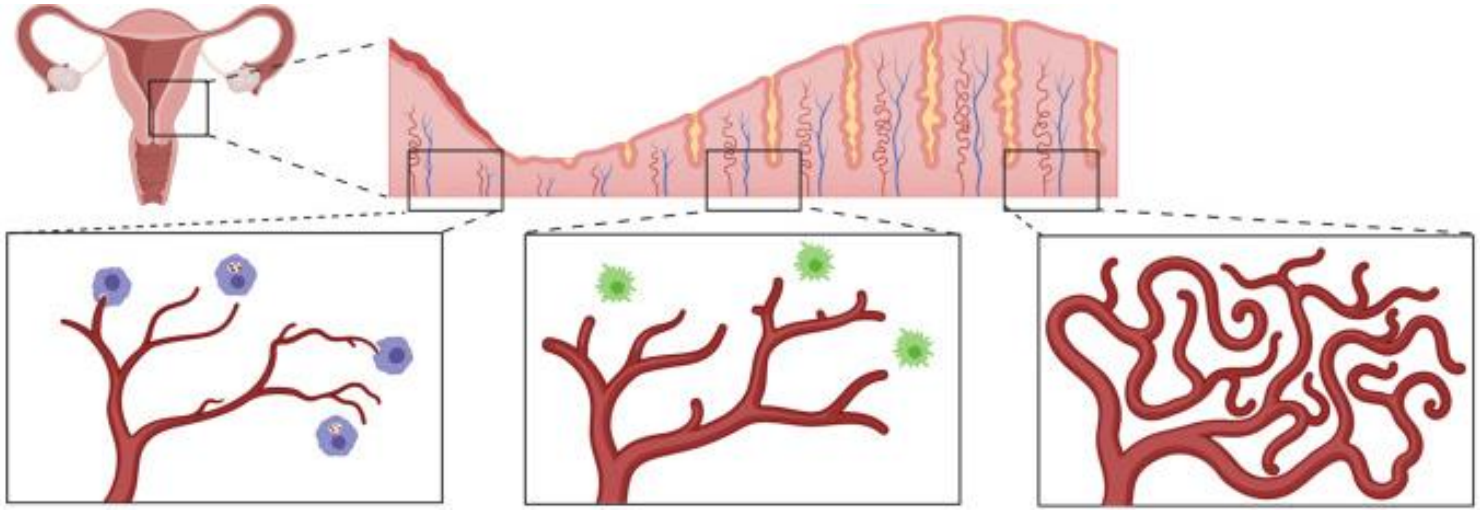
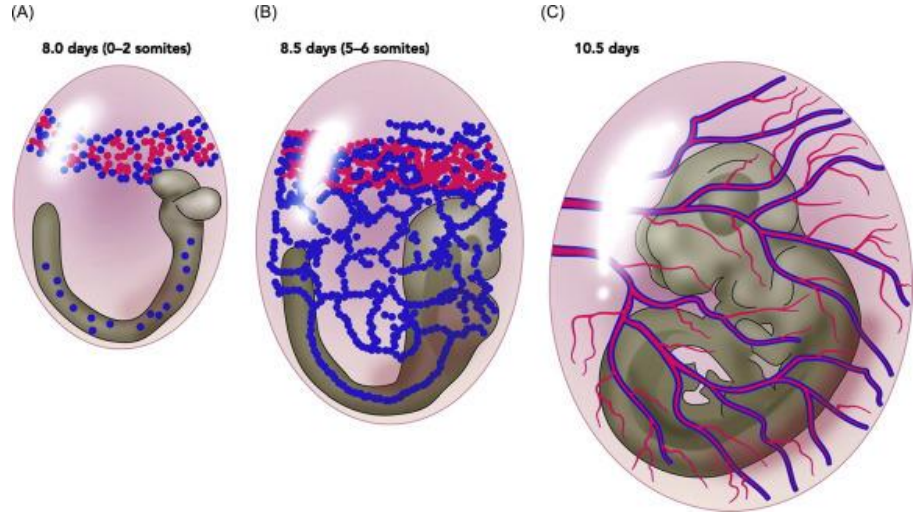
- Angiogenesis is important for embryo development, wound healing, menstrual cycling, and other normally occurring processes in the adult body





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- The process of angiogenesis involves the degradation of the basement membrane by matrix metalloproteinases (MMPs), movement of endothelial cells through the degraded matrix, their proliferation and organization into new vessels, and the subsequent production of new basement membranes
- Angiogenesis is important for embryo development, wound healing, menstrual cycling, and other normally occurring processes in the adult body
- Associated with pathologic processes, including endometriosis and malignancies
- Human endometrial cells have strong angiogenic potential due to the fact that angiogenesis is required for successful implantation and pregnancy
- Microvessel density (MVD) is increased in EC compared with normal endometrium.
- MVD has also been shown to correlate with EC survival, FIGO stage, as well as other histologic and clinicopathologic parameters

In Tumor Angiogenesis, an Imbalance Between Pro- and Anti-angiogenic Factors Results in Abnormal Proliferation of New Vessels

Antiangiogenic Factors

- Endostatin
- Angiostatin
- Thrombospondin-1
- Interleukin-4,12,18
- Metalloproteinase inhibitors
- Vasostatin
- Interferon-α,β,γ
- Others

Angiogenesis

Proangiogenic Factors

- Vascular endothelial growth factor
- Tumor necrosis factor-α
- Transforming growth factor-α,β
- Basic/acidic fibroblast growth factor
- Nitric oxide
- Angiopoietin-1,2
- Others

Herbst RS. *Expert Opin Emerg Drugs.* 2006;11(4):635-650.

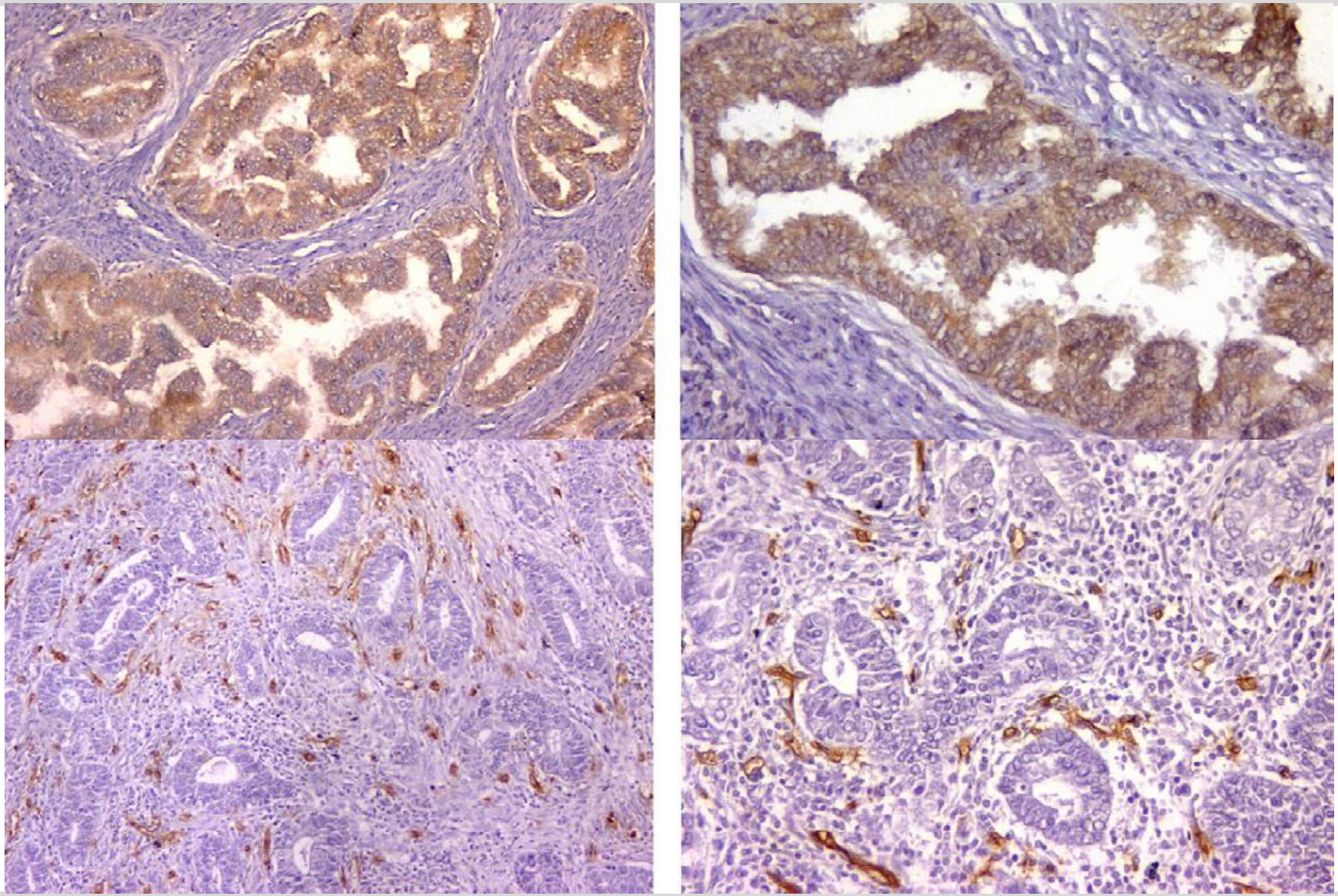
Neoangiogenesis in endometrioid endometrial carcinoma

VEGF

High VEGF immunoreactivity

CD34

Intratumoral neoangiogenesis is shown by means of CD34 immunostaining



Ozbudak IH et al. Gynecol Oncol 2008

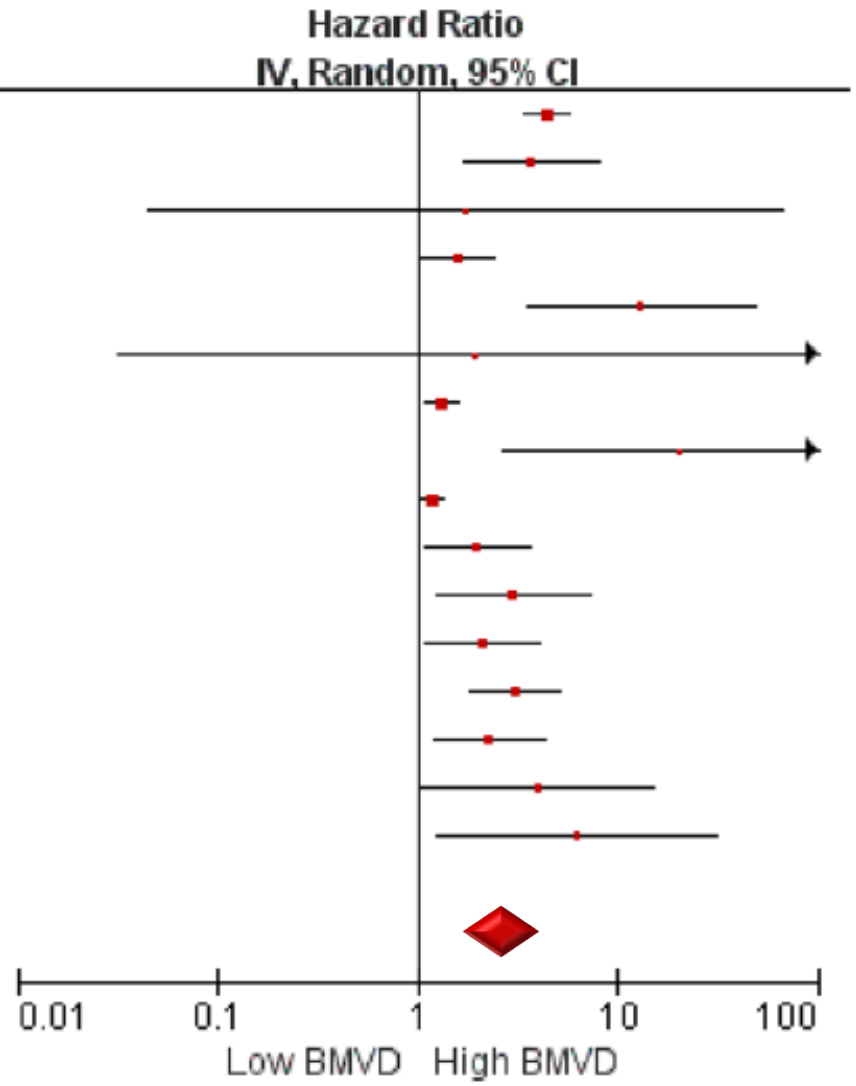
Microvessel Density and Overal Survival in Endometrial Cancer

Overall Survival

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Ai 2009	1.4929	0.131	9.9%	4.45 [3.44, 5.75]
Giatromanolaki 2001	1.3083	0.3941	6.9%	3.70 [1.71, 8.01]
Huang 2008	0.56	1.86	0.9%	1.75 [0.05, 67.06]
Kaku 1997	0.4752	0.2158	9.1%	1.61 [1.05, 2.46]
Kamat 2007	2.5764	0.6753	4.2%	13.15 [3.50, 49.40]
Kirschner 1996	0.68	2.1	0.7%	1.97 [0.03, 121.02]
Li 2010	0.2776	0.0965	10.1%	1.32 [1.09, 1.59]
Merritt 2010	3.0121	1.0415	2.3%	20.33 [2.64, 156.55]
Obermair 1999	0.1823	0.059	10.3%	1.20 [1.07, 1.35]
Ozalp 2003	0.6821	0.3064	8.0%	1.98 [1.08, 3.61]
Salvesen 1999	1.0953	0.4491	6.3%	2.99 [1.24, 7.21]
Salvesen 2000	0.7419	0.3419	7.6%	2.10 [1.07, 4.10]
Stefansson 2006	1.13	0.27	8.4%	3.10 [1.82, 5.26]
Straume 2002	0.8329	0.3276	7.7%	2.30 [1.21, 4.37]
Tan 2003	1.39	0.68	4.2%	4.01 [1.06, 15.22]
Wagatsuma 1998	1.8423	0.8225	3.3%	6.31 [1.26, 31.64]
Total (95% CI)			**100.0%**	**2.65 [1.86, 3.77]**

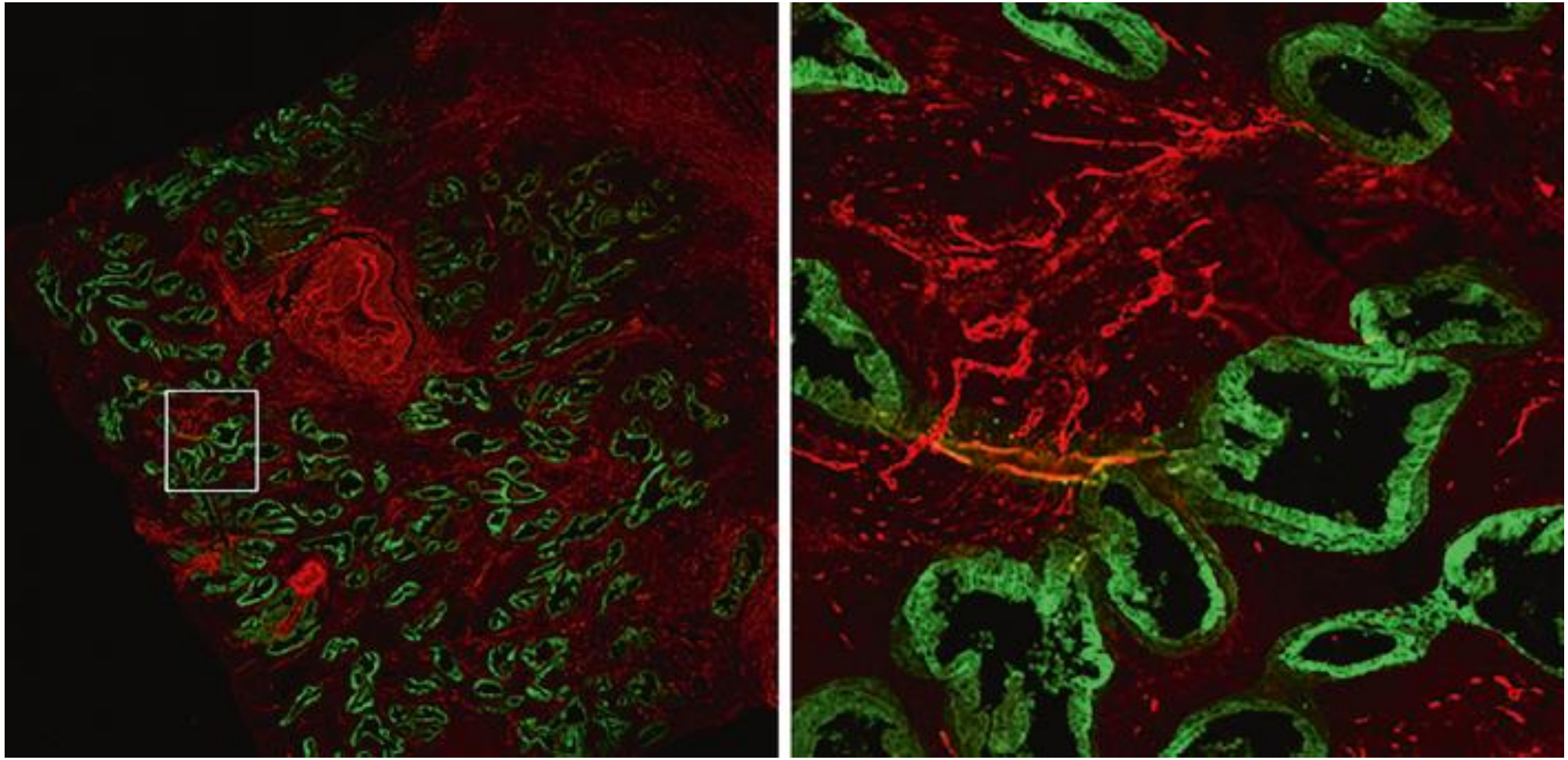
Heterogeneity: $Tau^2 = 0.31$; $Chi^2 = 123.72$, df = 15 ($P < 0.00001$); $I^2 = 88\%$

Test for overall effect: $Z = 5.43$ ($P < 0.00001$)



Wang JZ et al., Arch Gyn Obstet 2018

Poor outcome in hypoxic endometrial carcinoma is related to vascular density

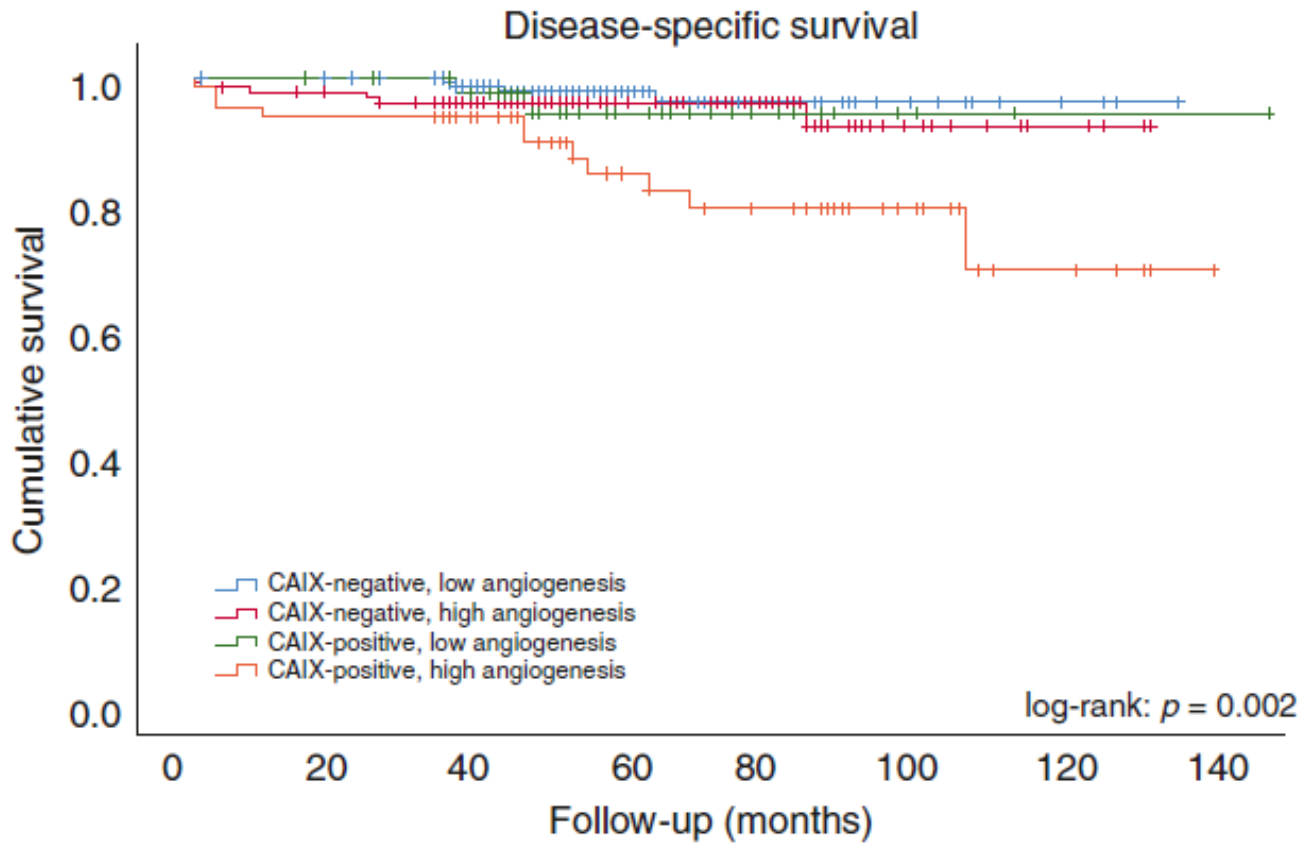


Combined staining of carbonic anhydrase IX (green, key effector proteins of HIF-1 and specifically related to hypoxia) and CD34 staining (red, vasculature) in endometrial cancer

Casper Reijnen, et al. British Journal of Cancer 2019

Poor outcome in hypoxic endometrial carcinoma is related to vascular density

- 16.4% of 385 ECs showed positive CAIX expression with high vascular density.
- These ECs had a reduced DSS compared to tumours with either hypoxia or high vascular density (log-rank p = 0.002).
- Multivariable analysis showed that hypoxic tumours with high vascular density had a reduced DSS (hazard ratio [HR] 3.71, p = 0.002), DDFS (HR 2.68, p = 0.009) and a borderline significance for reduced DFS (HR 1.87, p = 0.054).
- Adverse outcome in hypoxic ECs is seen in the presence of high vascular density

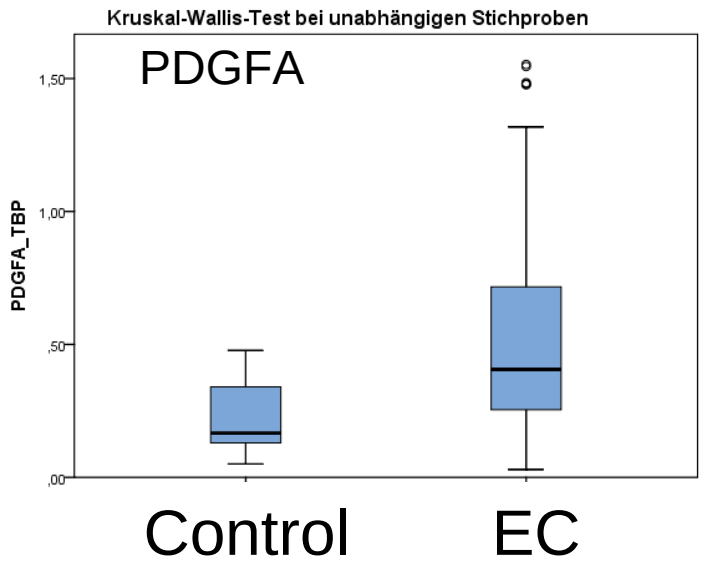


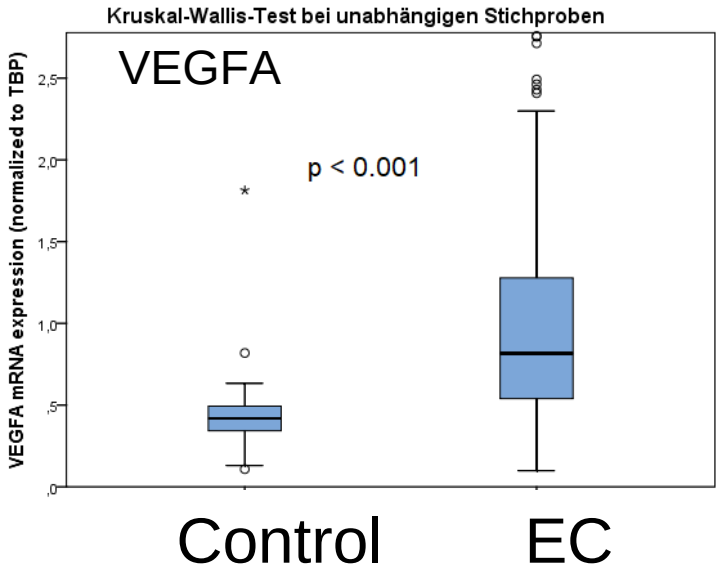
Expression of Angiogenetic Molecules in Endometrial Cancer

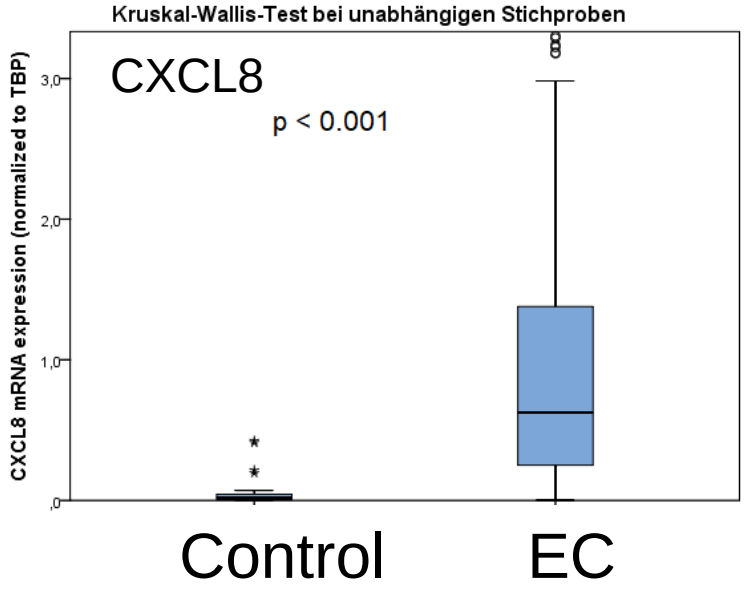
Different expression between EC (n=239) and healthy control tissues (n=25):

- ❑ PDGFA - Expression higher in EC (p<0.001)
- ❑ VEGFA - Expression higher in EC (p<0.001)
- ❑ CXCL8 - Expression higher in EC (p<0.001)

PDGFA and *VEGFA* showed a 2-fold higher expression in EC
CXCL8 almost 42-fold higher expression in EC compared to normal E



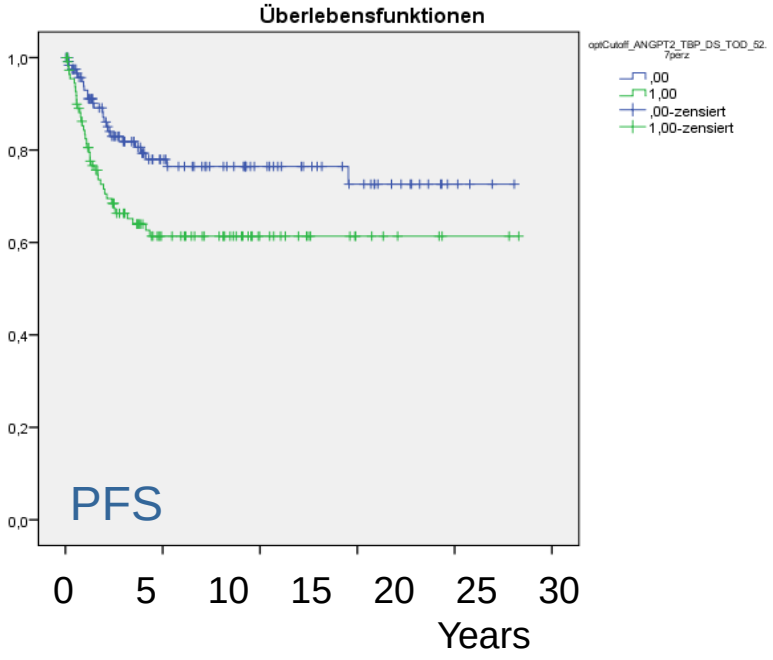


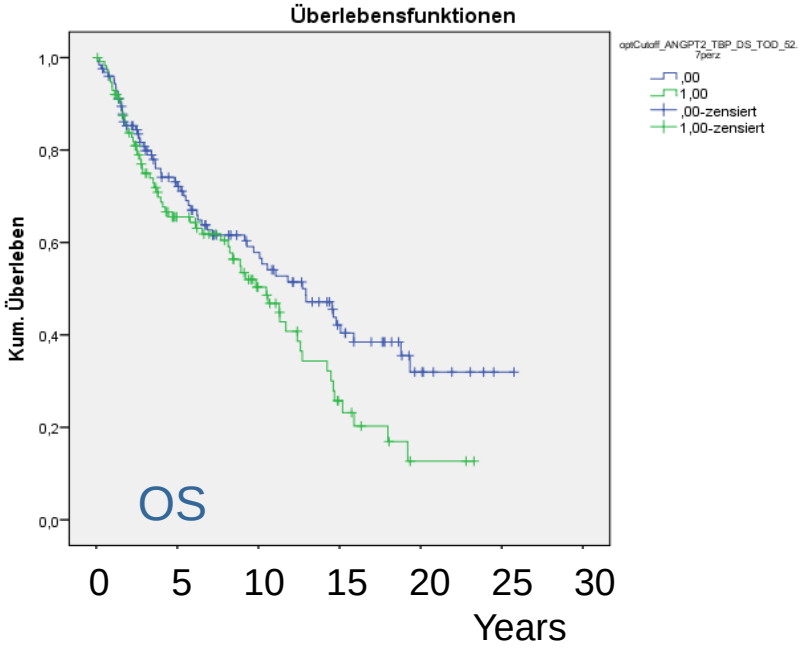


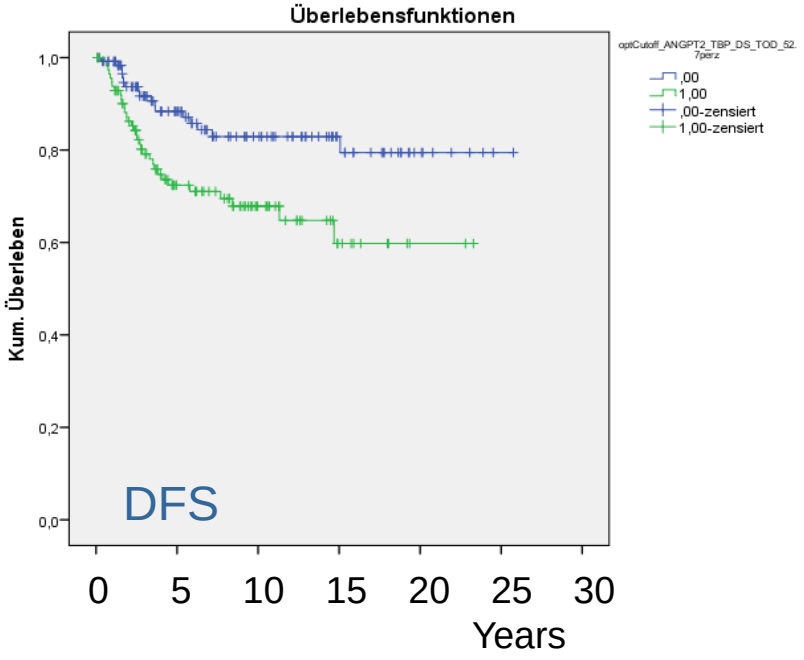
T. Pan et al., 2023

Expression of Angiogenetic Molecules in Endometrial Cancer

ANGPT2 > Angiopoietin 2







- High levels of *ANGPT2* (cut-off 0.94, 52.7 P.) are associated with a reduced RFS (p =0.011) and DSS (p=0.004)
- *OS not statistically significant (p=0.058)*

T. Pan et al., 2023

Phase II trials evaluating anti-angiogenesis agents in recurrent/metastatic endometrial cancer

Study Drug	Target	Prior CT	No. Pts	ORR %	SD %	mTTP/PFS (months)	mOS (months)
Dalantercept (Makker, 2015)	BMP 9/10	1-2	28	0	57	2.1	14.5
Trebananib (Moore, 2015)	Tie2 Receptor	1-2	32	3.1	25	2	6.6
Cediranib (Bender, 2015)	VEGF/c-kit	1-2	48	12.5	37.5	3.7	12.5
Sunitinib (Castonguay, 2014)	VEGF/KIT/PDGFR	≤ 1	33	18.2	18.2	3.0	19.4
Nintedanib (Dizon, 2014)	VEGF/FGFR/PDGFR	1-2	32	9.4	34	3.1	10.1
Lenvatinib (Vergote, 2013)	VEGFR/FGFR/RET/KIT/PDGFRβ	1-2	133	14.3	NR	5.4	10.6
Beva/temsirolimus (Alverez, 2013)	VEGF/mTOR	1 -2	49	24	55	5.6	16.9
Aflibercept (Coleman, 2012)	VEGFR	1-2	44	7	32	2.9	14.6
Bevacizumab (Aghajanian, 2011)	VEGF	1-2	52	13.5	50	4.2	10.6
Sorafenib (Nimeiri, 2010)	VEGF/Raf/Ras	≤ 1	39	5	42.5	3.2	11.4
Thalidomide (McMeekin, 2007)	VEGFR/bFGF	1-2	21	12.5	8	1.7	6.3

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MITO END-2

Patients with advanced (stage III-IV) or recurrent type 1 or type 2 endometrial cancer; 0-1 previous CHT lines; Measurable or evaluable disease (n~108)

R

1:1

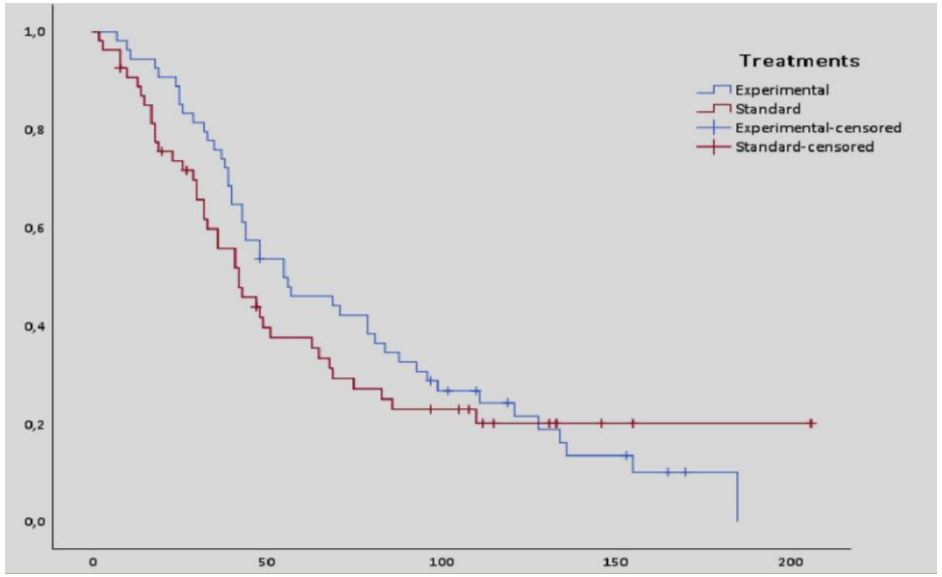
Carboplatin + Paclitaxel for 6-8 cycles

Carboplatin + Paclitaxel for 6-8 cycles

+

Bevacizumab in combination with chemotherapy and maintenance

PFS

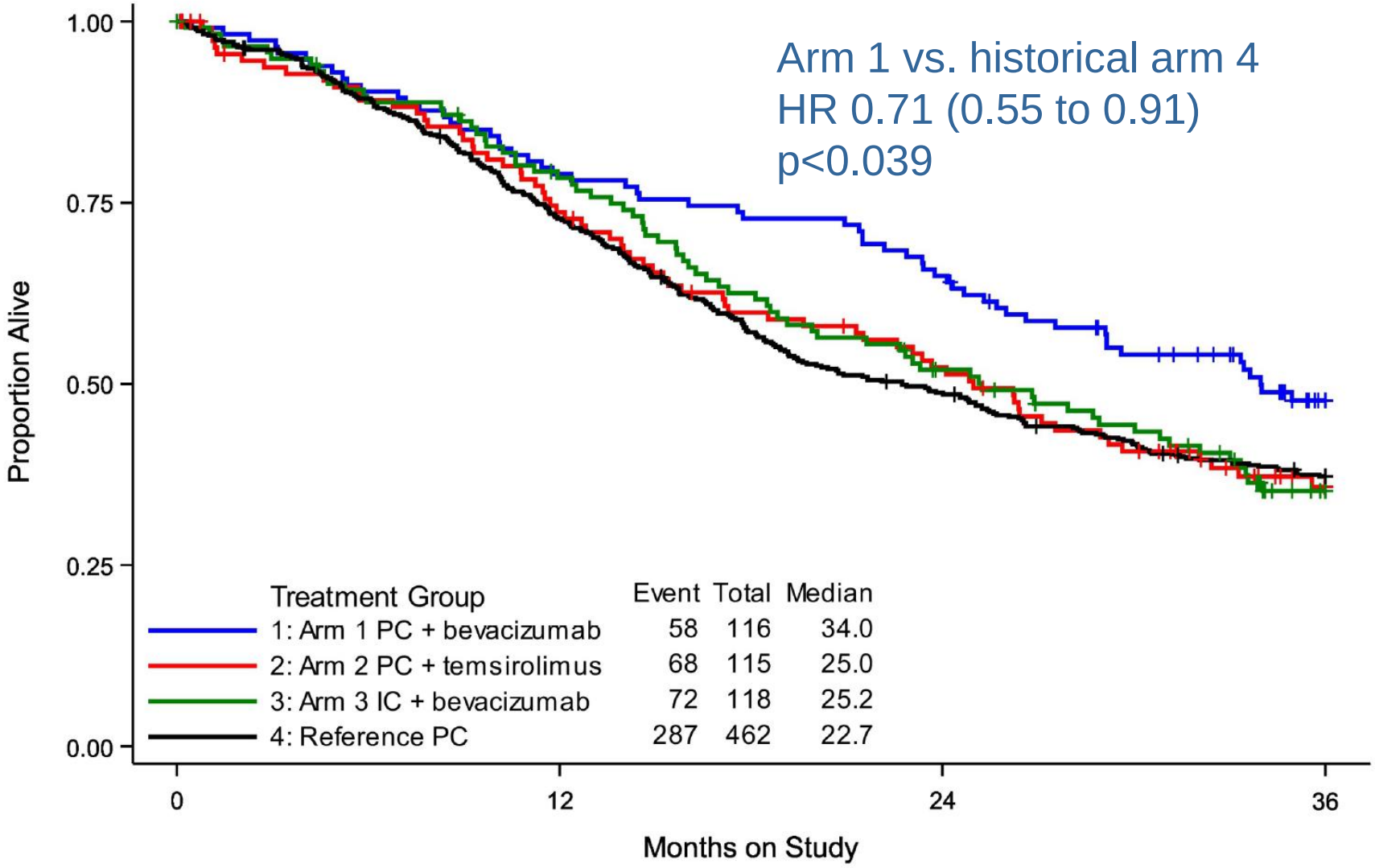


	CT (N=54)	CT-B (N=54)
Events, n	40	46
Median PFS, months **(95% CI)**	10,5 (7.2-13,5)	13.7 (7.5-20,0)
HR (stratified) (95% CI) 2-sided log-rank p-value 2-sided Breslow test p value	0.846 (0.5–1.3) 0.437 0.08*	

* p<0.20

Lorusso D, et al. *J Clin Oncol.* 2015;33(suppl): Abstract 5502, Lorusso D, et al. Gynecologic Oncology 2019

A Phase II Study of Frontline Paclitaxel/Carboplatin/Bevacizumab, Paclitaxel/Carboplatin/Temsirolimus, or Ixabepilone/Carboplatin/Bevacizumab in Advanced/Recurrent Endometrial Cancer

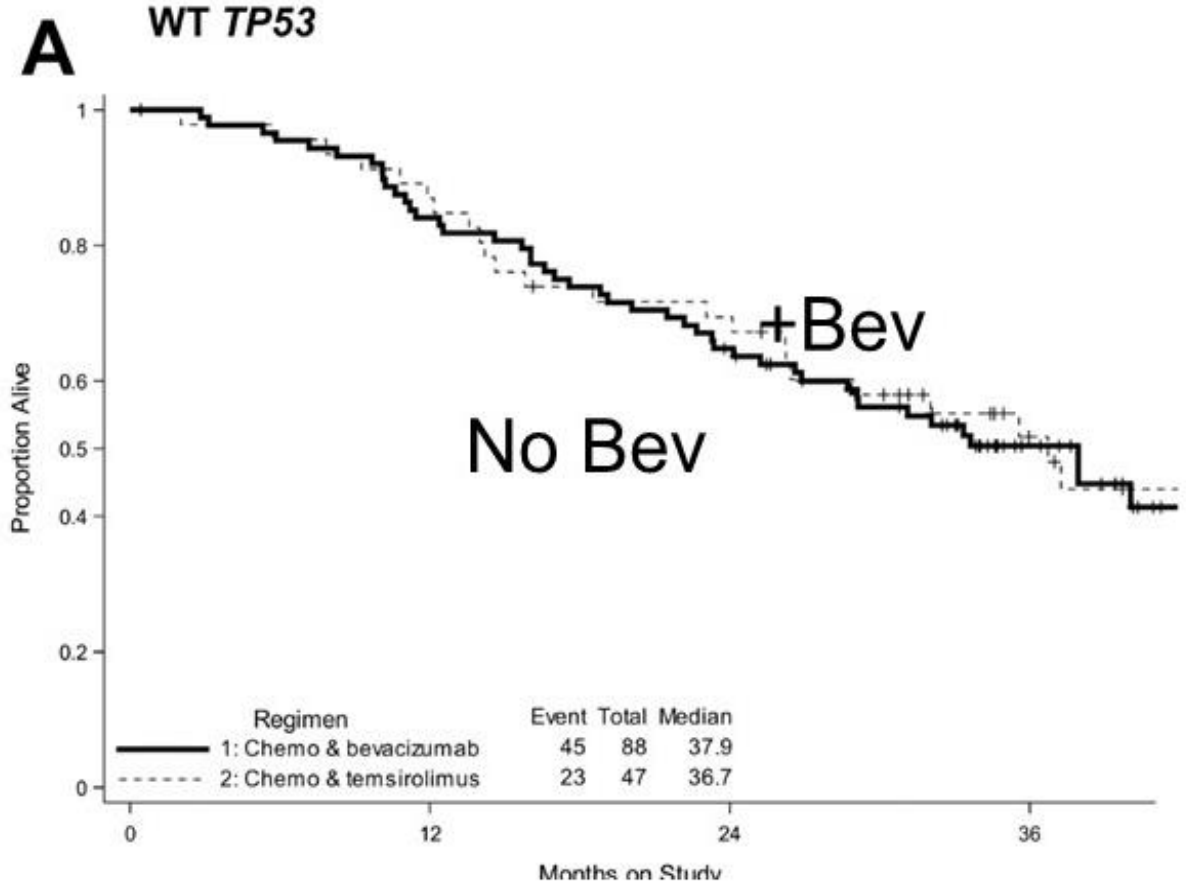


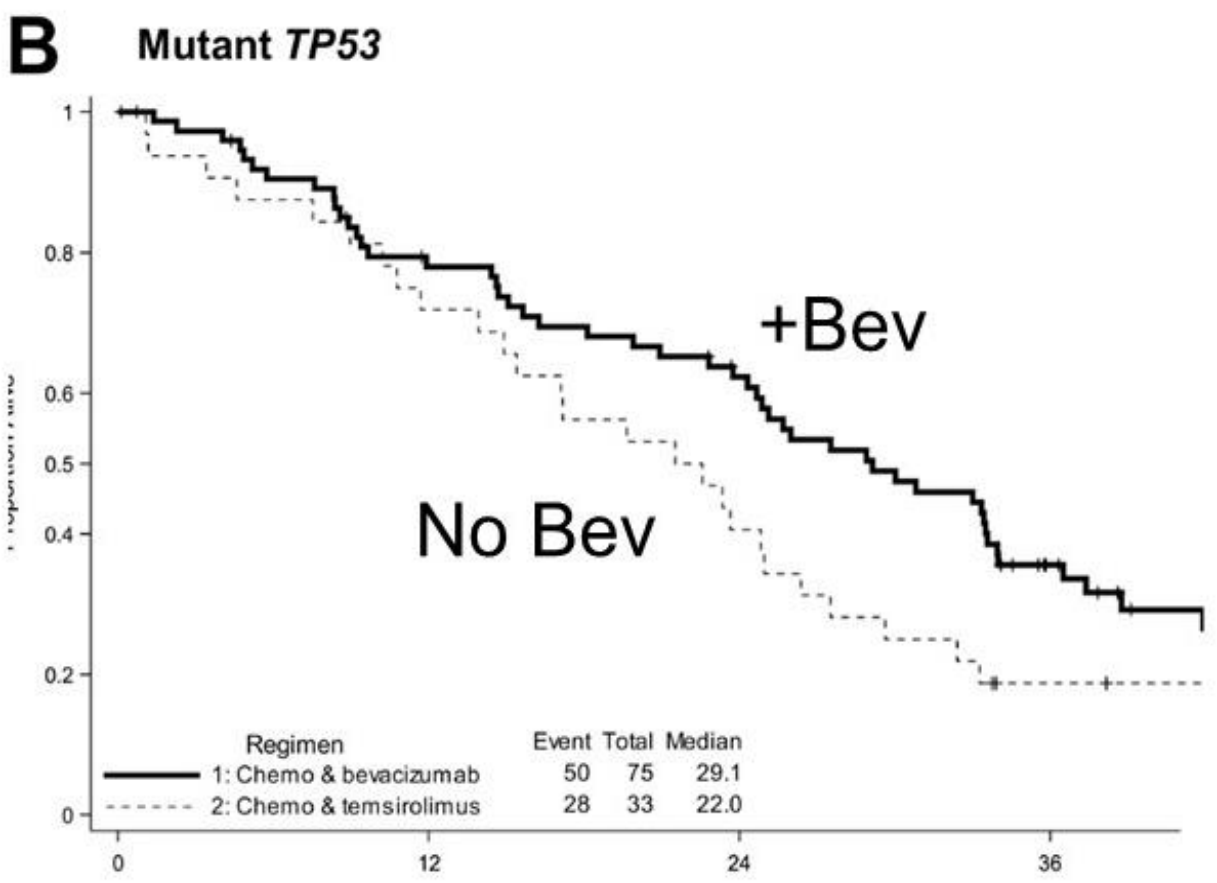
Carol Aghajanian, et al. JCO 2015

TP53 Sequencing and p53 Immunohistochemistry Predict Outcomes When Bevacizumab Is Added to Frontline Chemotherapy in Endometrial Cancer:

An NRG Oncology/GOG Study

Patients based on TP53 status and Bevacizumab



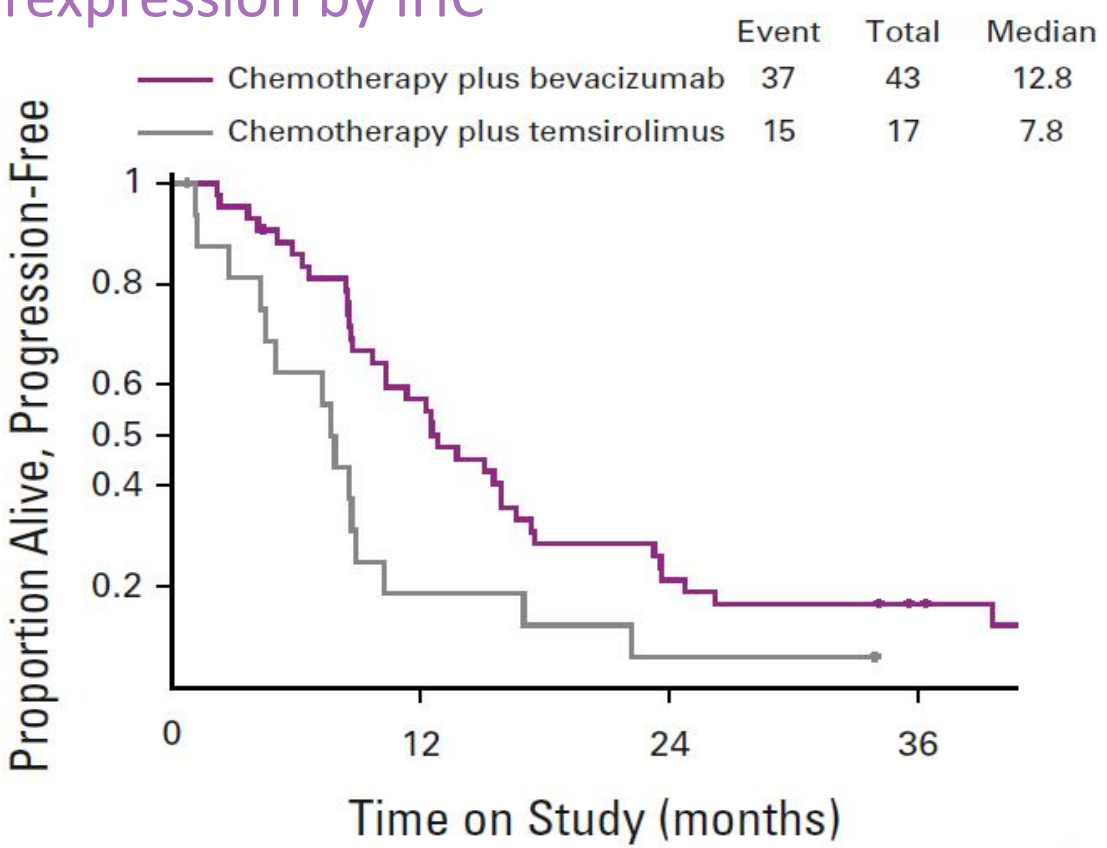


Kristina Thiel, et al. J Clin Oncol 40:3289-3300. © 2022

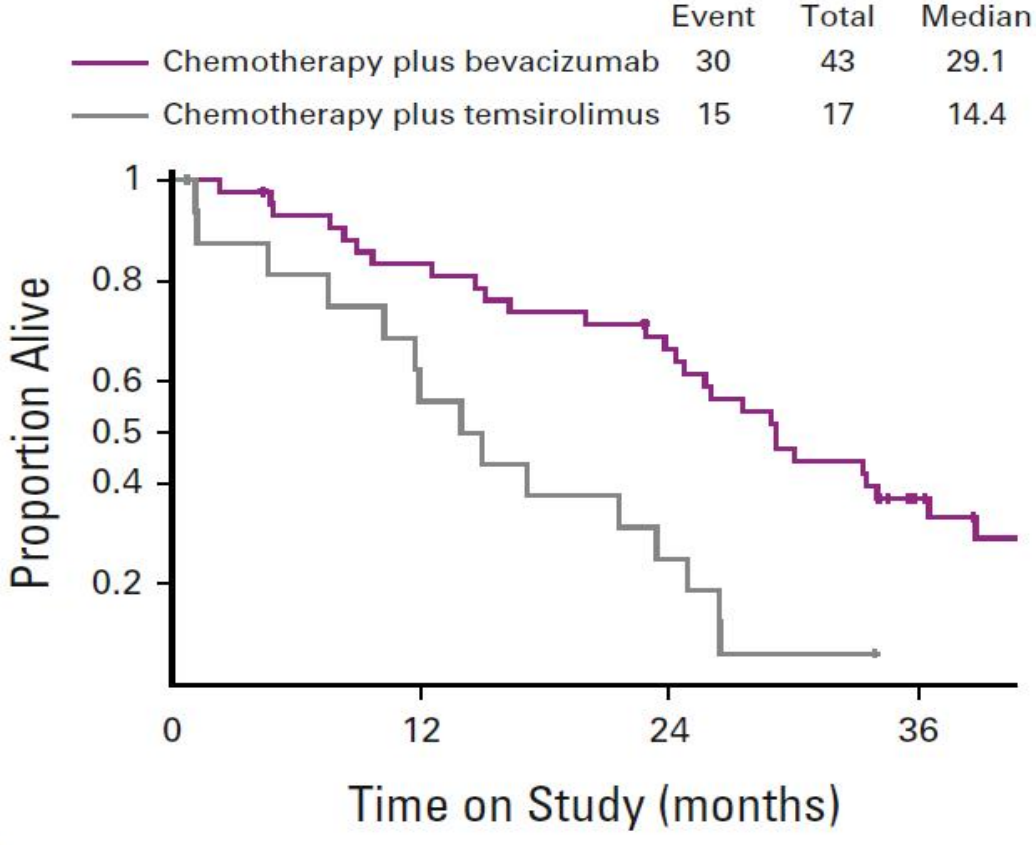
TP53 Sequencing and p53 Immunohistochemistry Predict Outcomes When Bevacizumab Is Added to Frontline Chemotherapy in Endometrial Cancer:

An NRG Oncology/GOG Study

p53 overexpression by IHC



No. at risk:				
Chemotherapy plus bevacizumab	43	24	9	5
Chemotherapy plus temsirolimus	17	3	1	0



No. at risk:				
Chemotherapy plus bevacizumab	43	35	27	11
Chemotherapy plus temsirolimus	17	9	4	0

Kristina Thiel, et al. J Clin Oncol 40:3289-3300. © 2022

TP53 Sequencing and p53 Immunohistochemistry Predict Outcomes When Bevacizumab Is Added to Frontline Chemotherapy in Endometrial Cancer:

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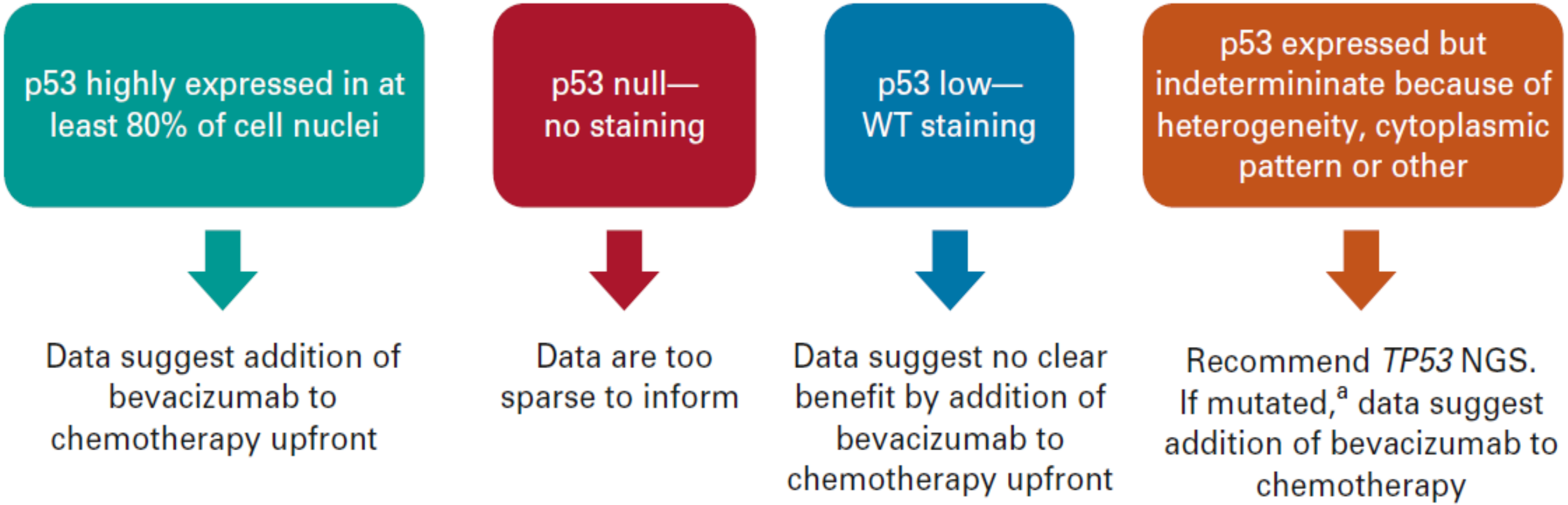


Kristina Thiel, et al. J Clin Oncol 40:3289-3300. © 2022

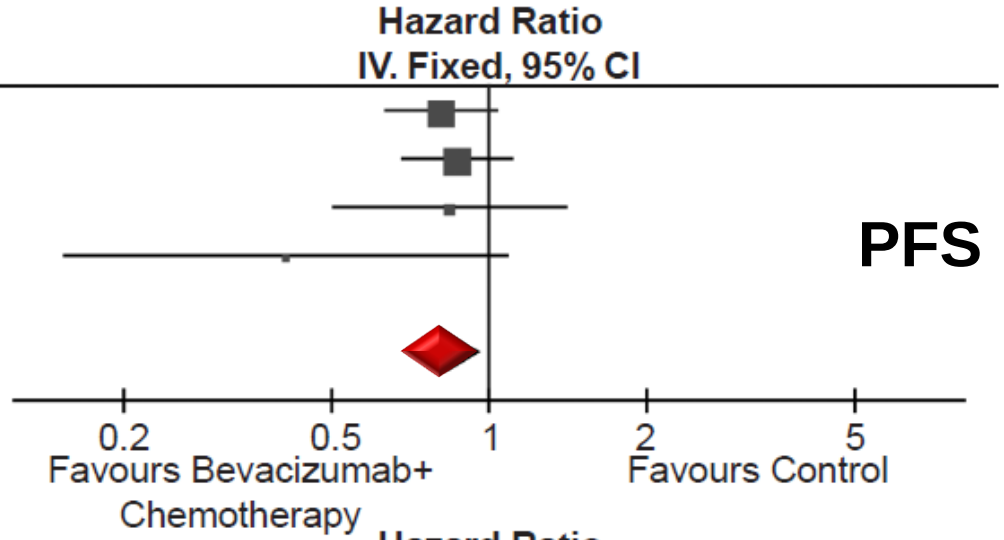
Efficacy and Safety of Bevacizumab-Combined Chemotherapy for Advanced and Recurrent Endometrial Cancer: A Systematic Review and Meta-analysis

a

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV. Fixed, 95% CI
Aghajan C 2018	-0.2107	0.1282	42.7%	0.81 [0.63, 1.04]
Aghajan C 2018	-0.1393	0.1257	44.4%	0.87 [0.68, 1.11]
Lorusso D 2019	-0.1744	0.2647	10.0%	0.84 [0.50, 1.41]
Rose PG 2017	-0.8965	0.5004	2.8%	0.41 [0.15, 1.09]
Total (95% CI)			**100.0%**	**0.82 [0.70, 0.97]**

Heterogeneity: $Chi^2 = 2.18$, $df = 3$ ($P = 0.54$); $I^2 = 0\%$

Test for overall effect: $Z = 2.32$ ($P = 0.02$)



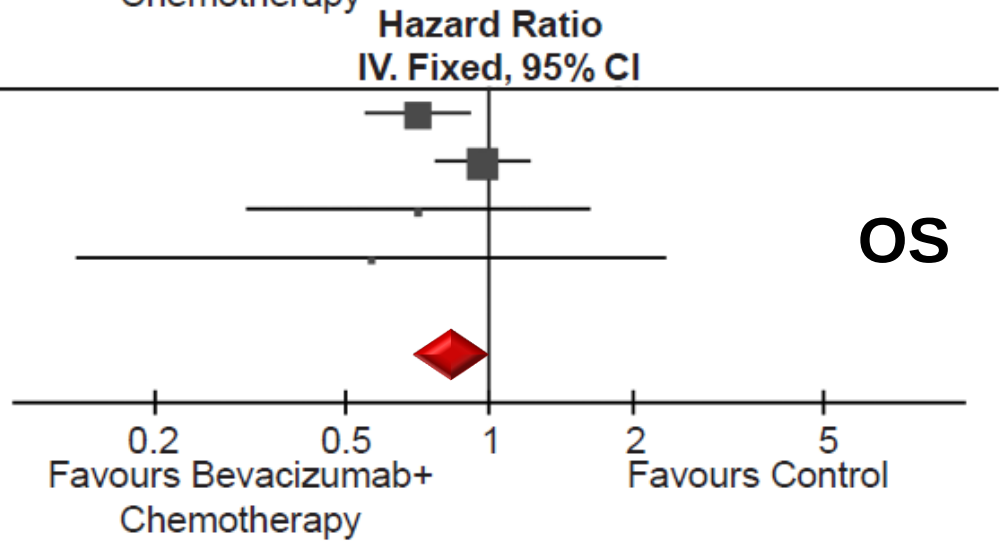
PFS

b

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV. Fixed, 95% CI
Aghajan C 2018	-0.3425	0.1303	42.5%	0.71 [0.55, 0.92]
Aghajan C 2018	-0.0305	0.1178	52.0%	0.97 [0.77, 1.22]
Lorusso D 2019	-0.3425	0.4228	4.0%	0.71 [0.31, 1.63]
Rose PG 2017	-0.5674	0.7247	1.4%	0.57 [0.14, 2.35]
Total (95% CI)			**100.0%**	**0.83 [0.70, 0.98]**

Heterogeneity: $Chi^2 = 3.60$, $df = 3$ ($P = 0.31$); $I^2 = 17\%$

Test for overall effect: $Z = 2.16$ ($P = 0.03$)



OS

Phase II trials evaluating anti-angiogenesis agents in recurrent/metastatic endometrial cancer

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Lenvatinib (Vergote, 2013)	VEGFR/FGFR/RET/KIT/PDGFRβ	1-2	133	**14.3**	NR	5.4	10.6
Beva/temsirolimus (Alverez, 2013)	VEGF/mTOR	1 -2	49	24	55	5.6	16.9
Aflibercept (Coleman, 2012)	VEGFR	1-2	44	7	32	2.9	14.6
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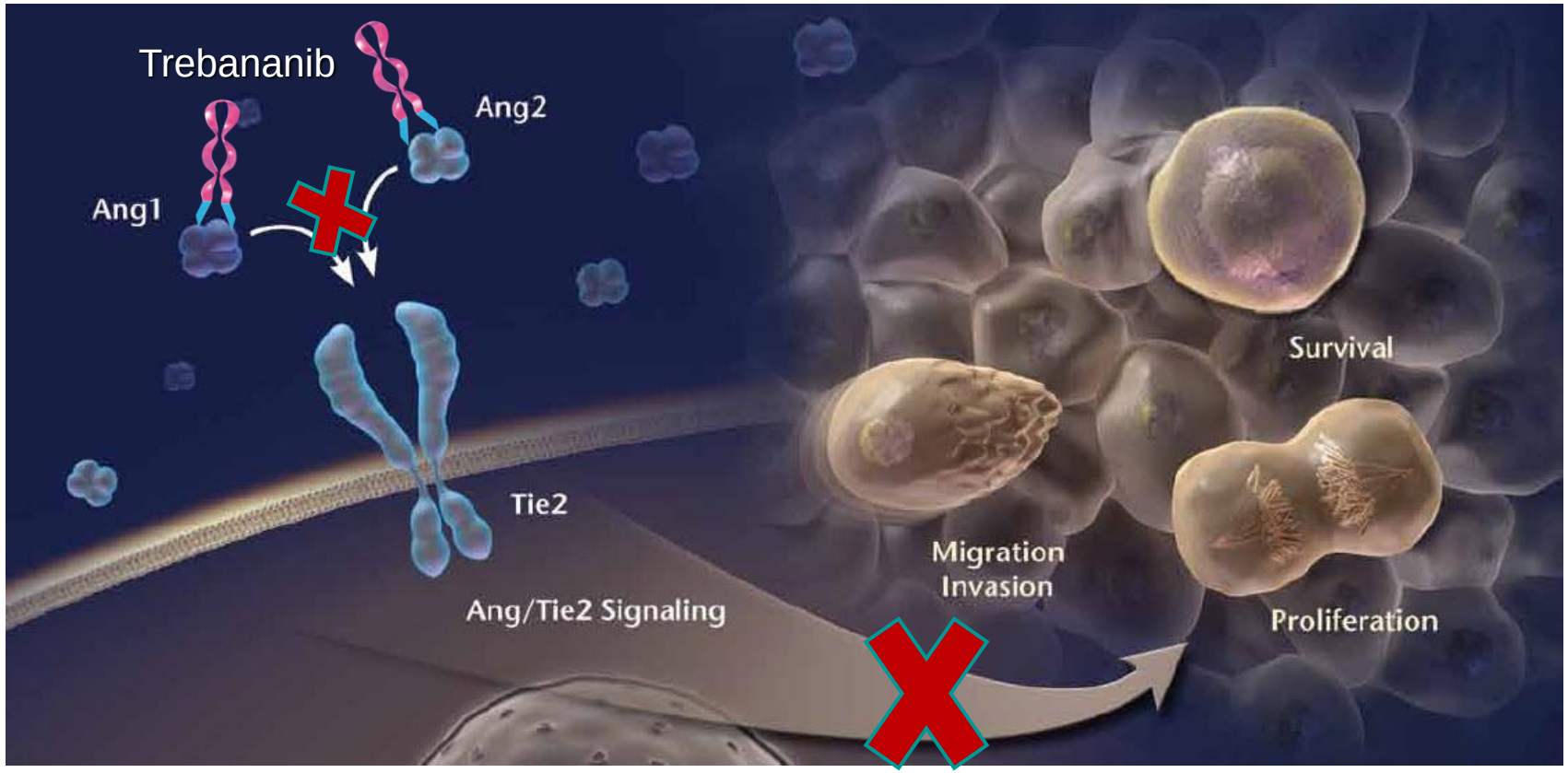
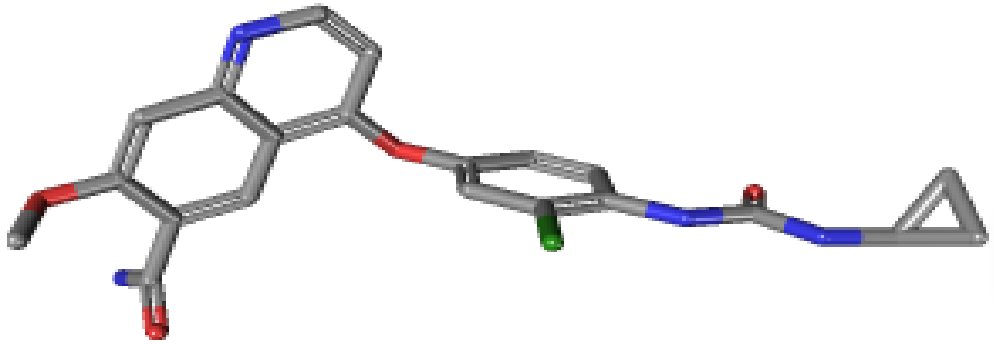
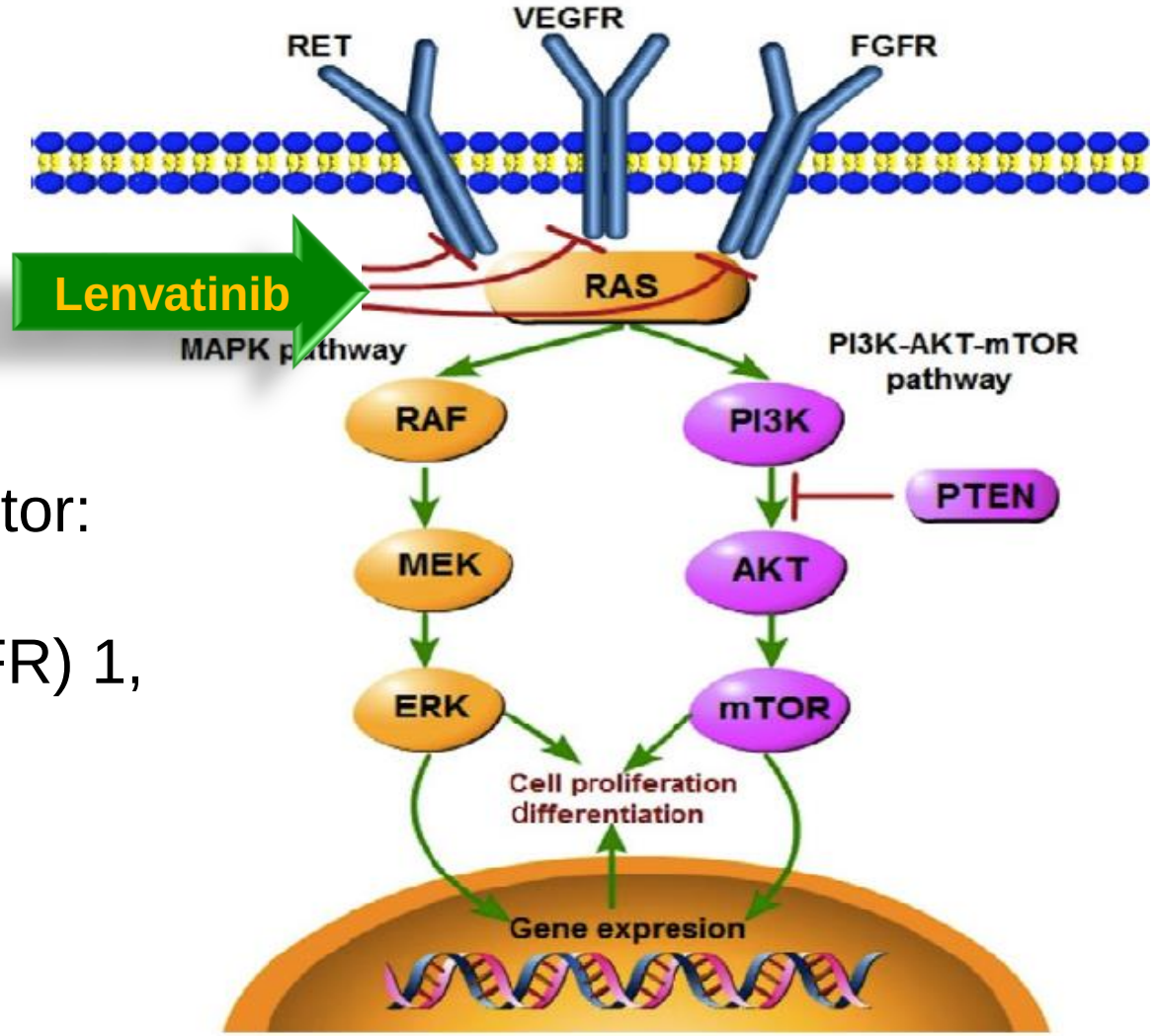
Thalidomide (McMeekin, 2007)	VEGFR/bFGF	1-2	21	**12.5**	8	1.7	6.3


Trebananib
Ang2
Ang1
Tie2
Ang/Tie2 Signaling
Migration
Invasion
Survival
Proliferation

Lenvatinib



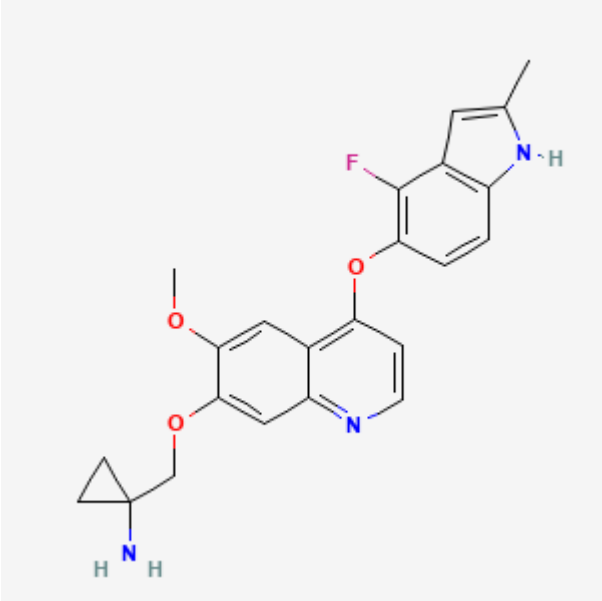


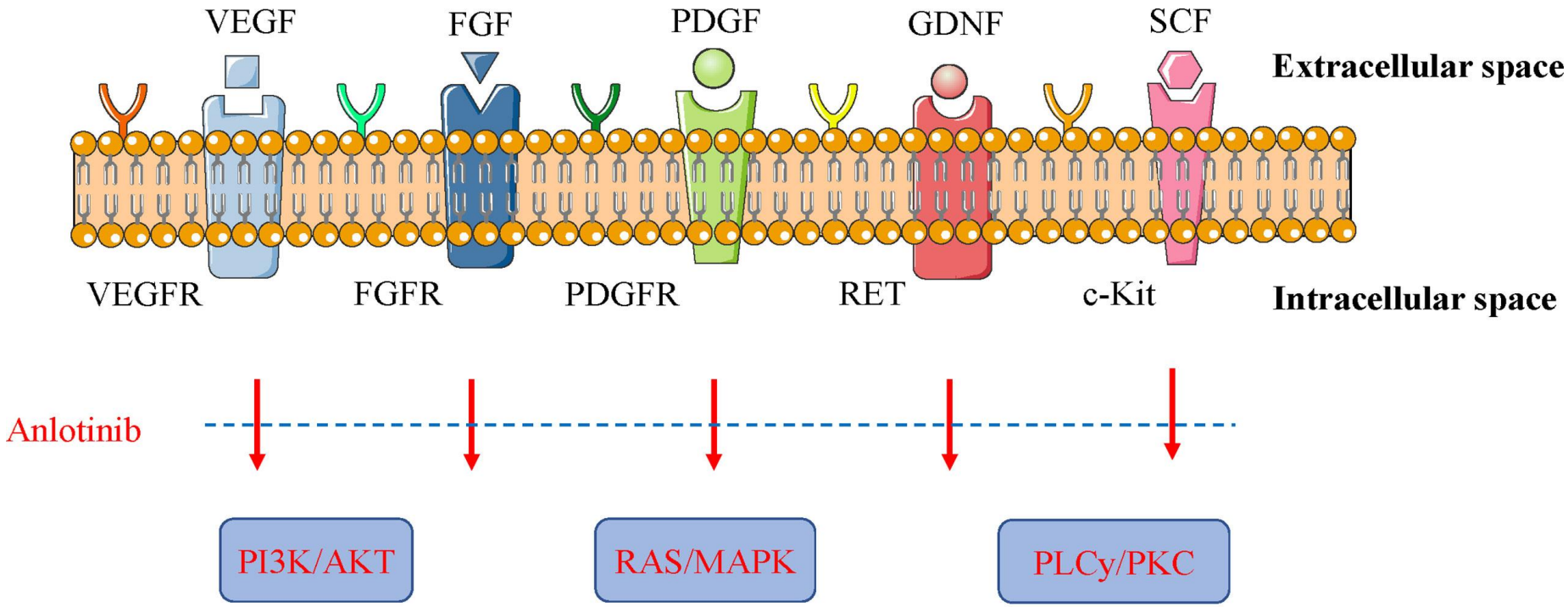
Lenvatinib acts as a multiple kinase inhibitor:

- VEGFR1, 2 and 3, as well as
- Fibroblast growth factor receptors (FGFR) 1, 2, 3 and 4
- Platelet-derived growth factor receptor (PDGFR) alpha
- c-Kit
- RET proto-oncogene

Stjepanovic N and Capdevilla J. Biologics: Targets and Therapy 2014

Anlotinib: a novel multi-targeting tyrosine kinase inhibitor

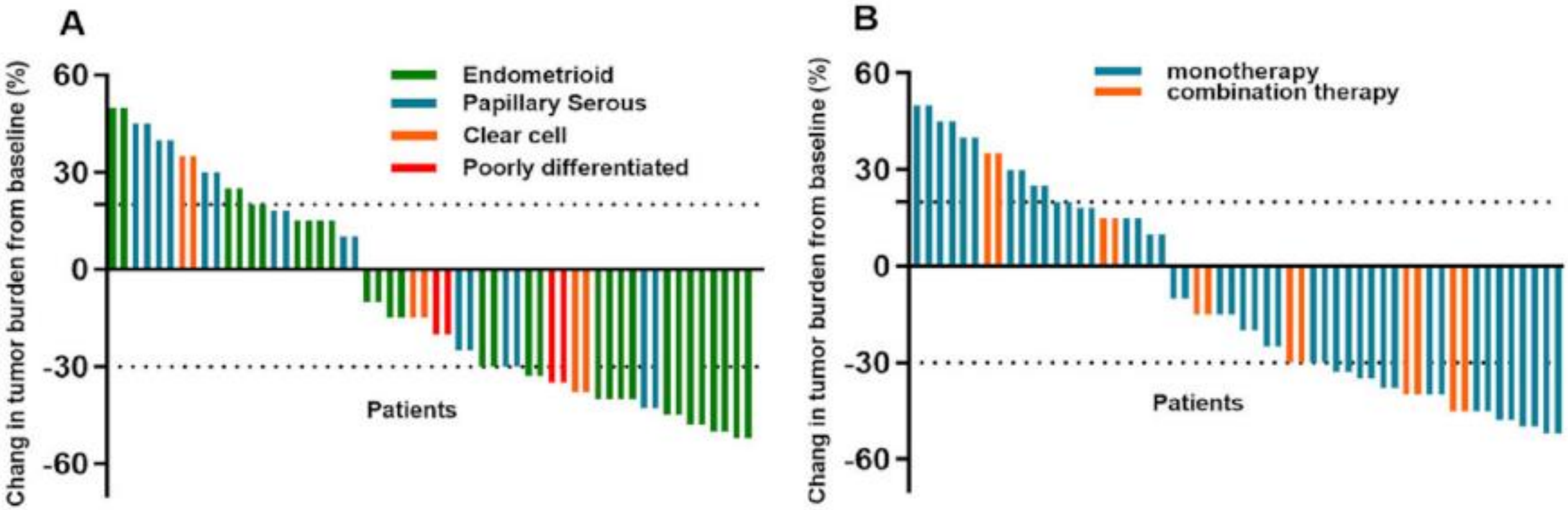




Suppress angiogenesis, survival and cell proliferation

Anlotinib in recurrent or metastatic endometrial cancer

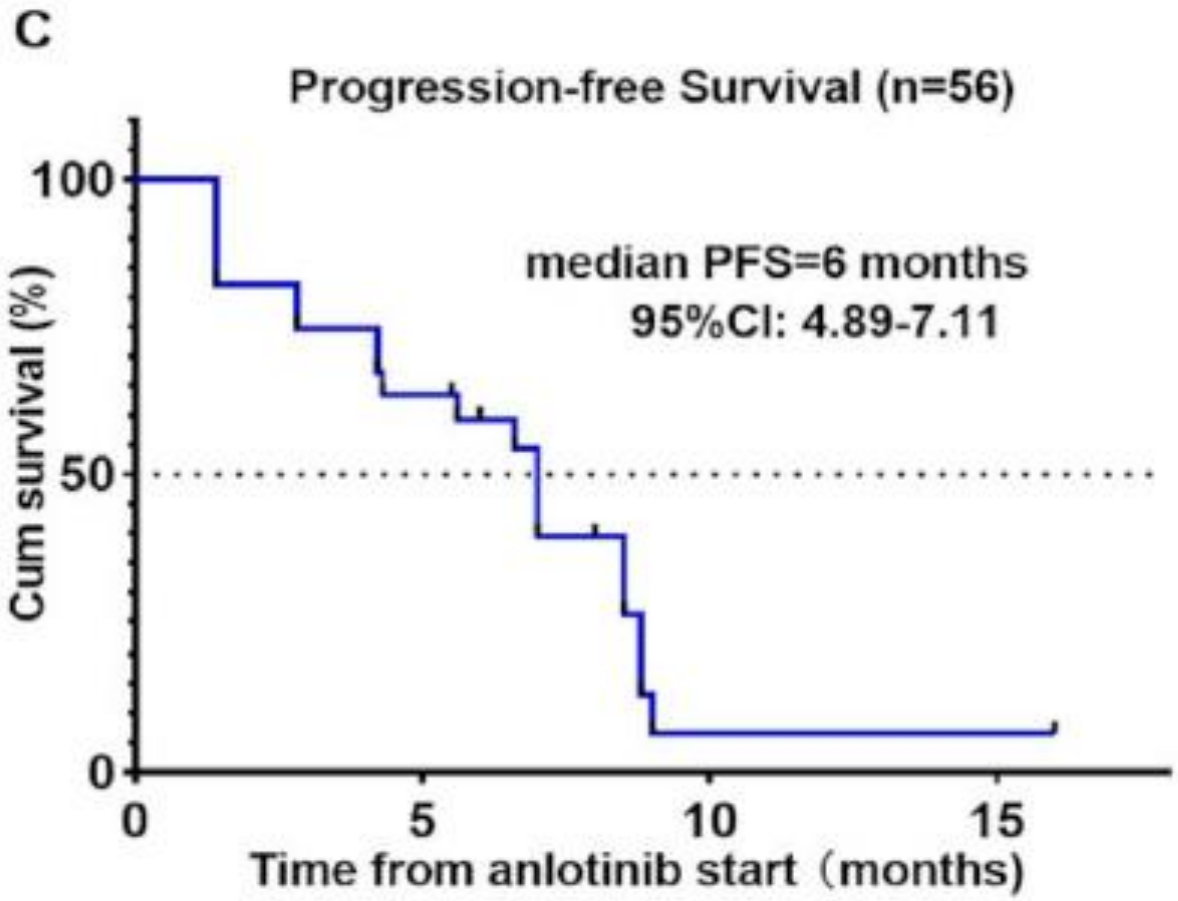
Original research

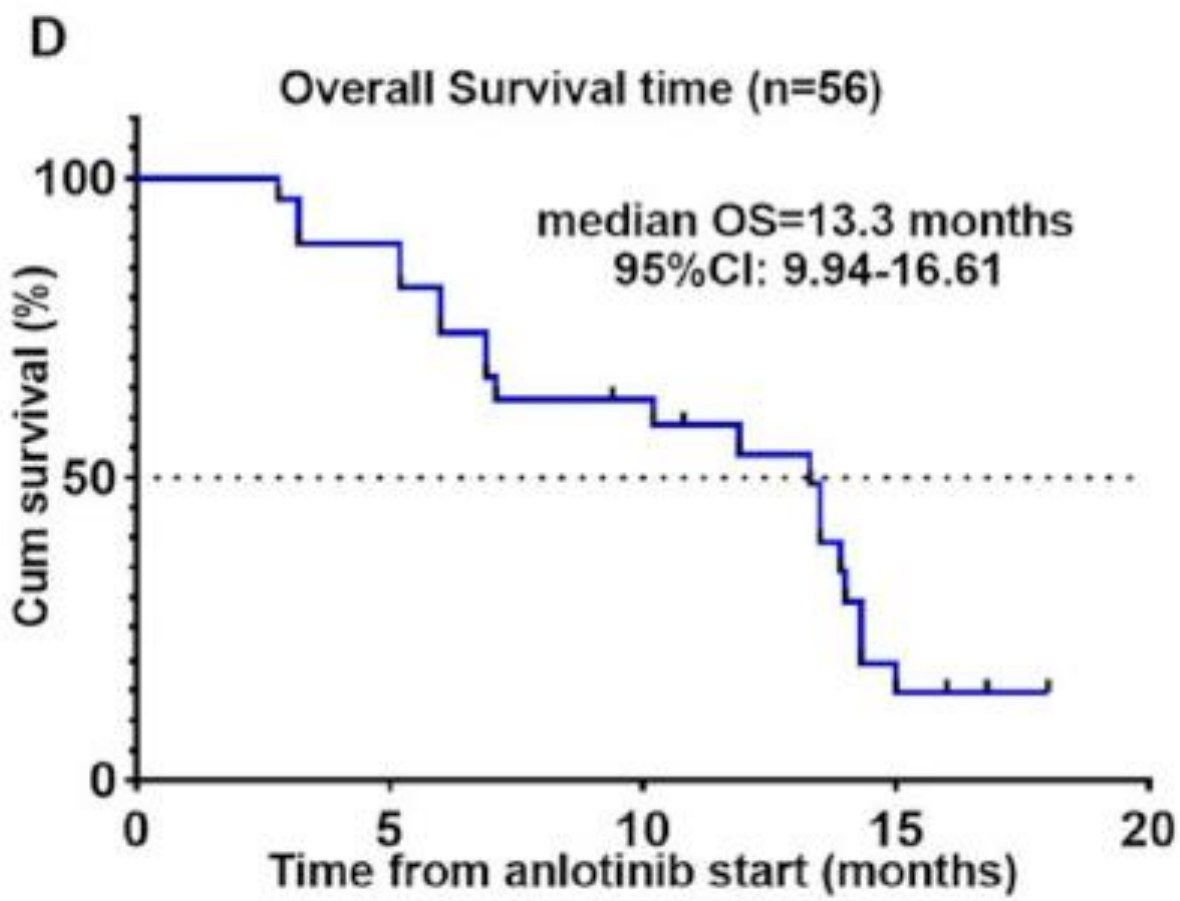


Qingli Cui et al. Int. J. Gynecol Cancer 2022

Anlotinib in recurrent or metastatic endometrial cancer

Original research





Anlotinib in recurrent or metastatic endometrial cancer

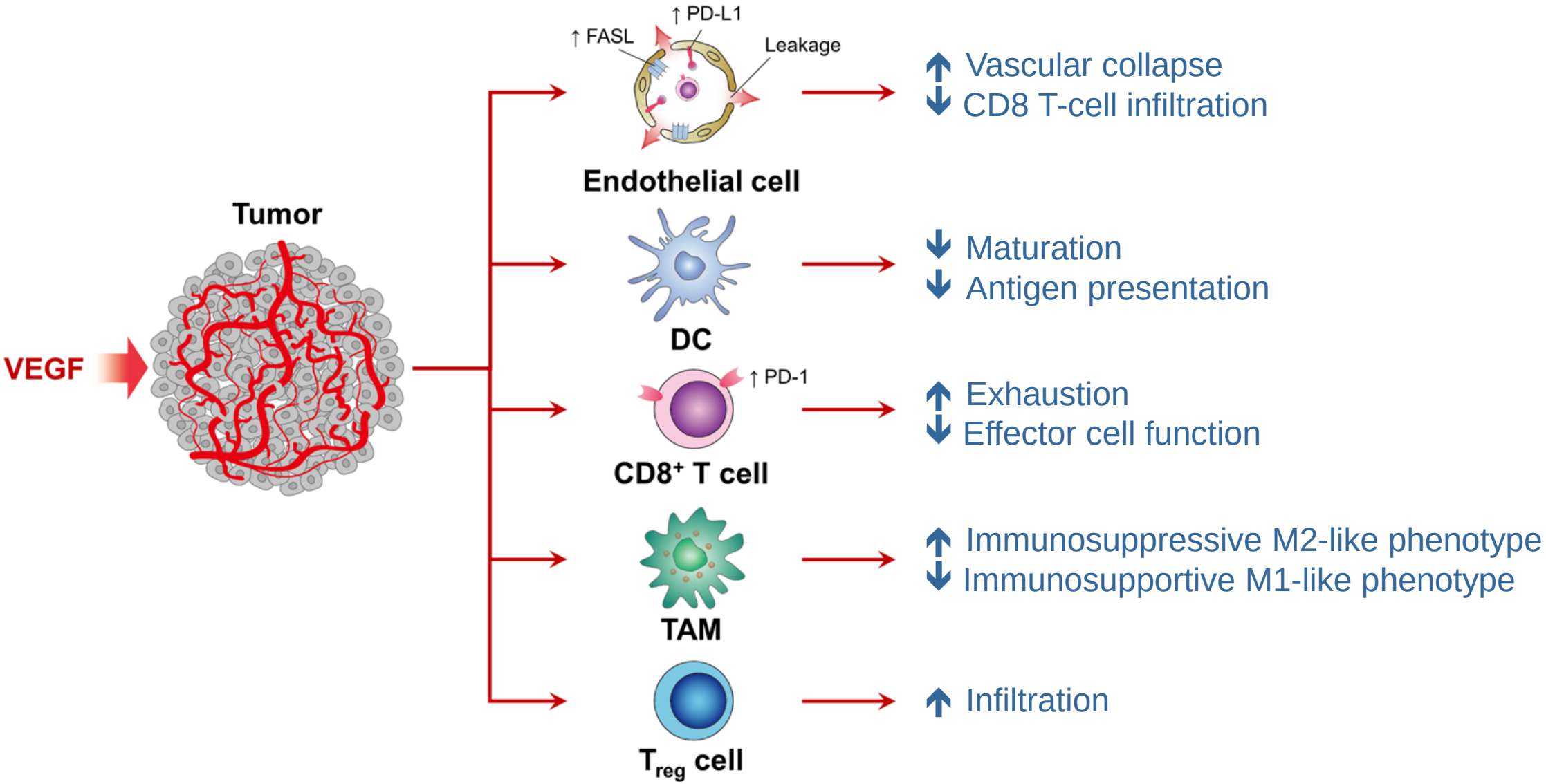
Multivariate analyses of progression-free survival and overall survival

	Progression-free survivalMicrosatellite stable			Overall survival		
Variable	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Age						
≤60	0.287	0.094 to 0.870	0.027	0.323	0.104 to 0.997	0.049
>60	Ref			Ref		
Prior lines of treatment						
2	0.271	0.087 to 0.847	0.025	0.334	0.111 to 1.009	0.052
≥3	Ref			Ref		
Treatment						
Monotherapy	1.828	0.469 to 7.119	0.385	0.844	0.254 to 2.802	0.782
Combination	Ref			Ref		
ECOG status						
0–1	0.663	0.261 to 1.685	0.387	0.579	0.228 to 1.468	0.249
2–3	Ref			Ref		

ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; Ref, reference.

Qingli Cui et al. Int. J. Gynecol Cancer 2022

The abnormal tumor vasculature elicits immune suppression in the tumor microenvironment



Won Suk Lee, et al., Experimental & Molecular Medicine 2020

Combination of Anti –PD/L1 plus antiangiogenic agents in pretreated endometrial carcinoma

Regimen	N	ORR	Median PFS	Patients	Reference
Pembrolizumab + lenvatinib	411	32%	6.6 mos	346 pMMR, 65 dMMR	Makker et al. JCO 2023
Nivolumab + cabozantinib	36	25%	5.3 mos	34 MSS, 2 MSI-high	Lheureux et al. J Immunther Cancer 2022
Camrelizumab + Apatinib	36	44%	6.4 mos	Unselected	Wang et al. ASCO 2023
Avelumab + axitinib	28	39%	7.3 mos	pMMR	Lee et al. ASCO TPS 5628

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KEYNOTE-775: Study Design

Enrollment & Eligibility

- N = ~780 2L advanced EC patients
  - Approximately 120 dMMR and 660 MMRp patients
- Measurable disease per RECIST v1.1
- ECOG PS ≤1
- Stratification factors:
  - dMMR vs MMRp
  - MMRp patients further stratified by ECOG PS, geographic region, and prior history of pelvic radiation

R 1:1

Physician's choice chemotherapy (doxorubicin or paclitaxel)

Pembrolizumab 200 mg IV Q3W + Lenvatinib 20 mg PO QD

Primary End Points

- PFS (BICR) and OS

Secondary End Points

- ORR, HRQoL, safety and tolerability, PK

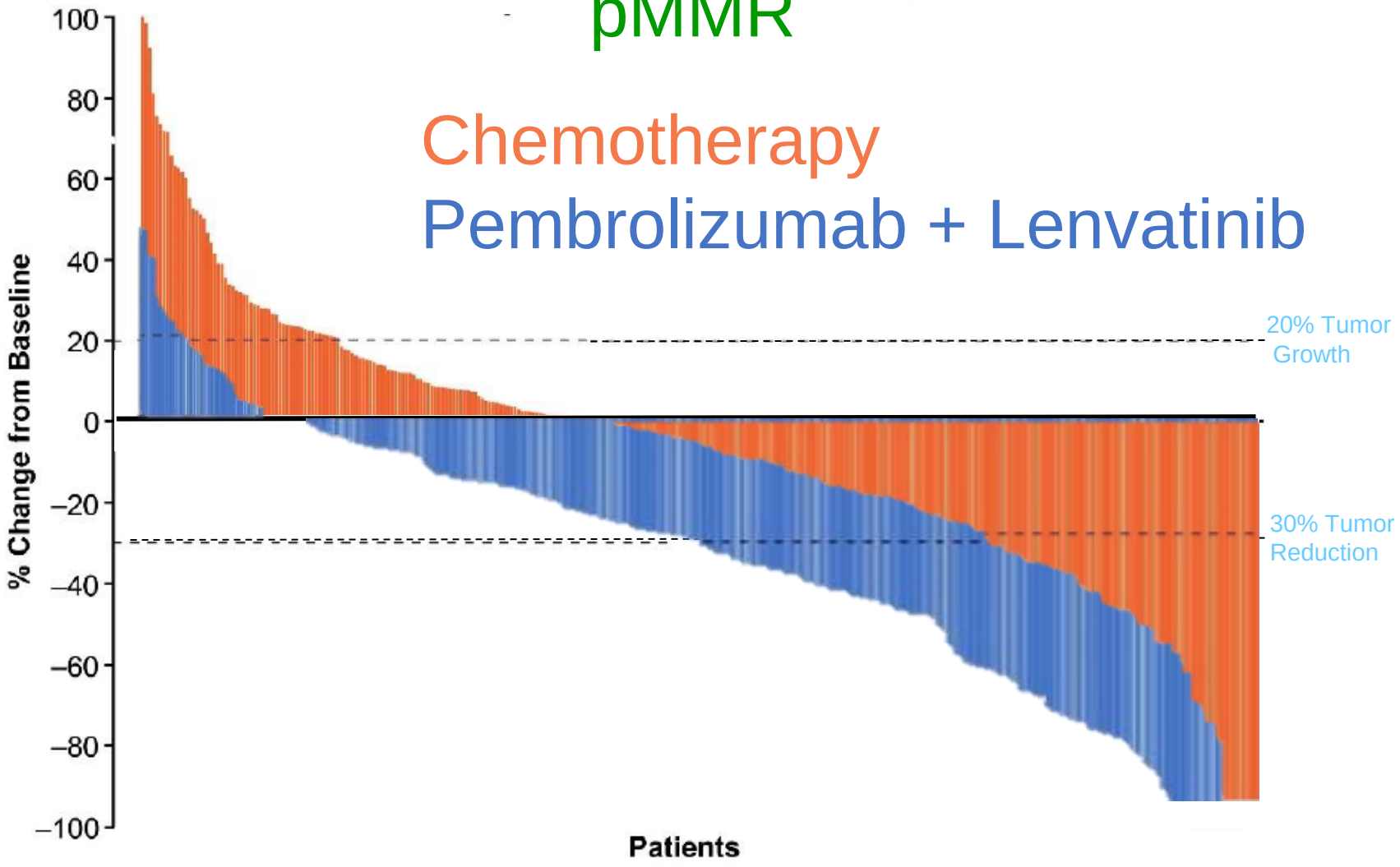
Vicky Makker et al. SGO 2021, Clinicaltrials.gov. NCT03517449. Accessed July 16, 2020.

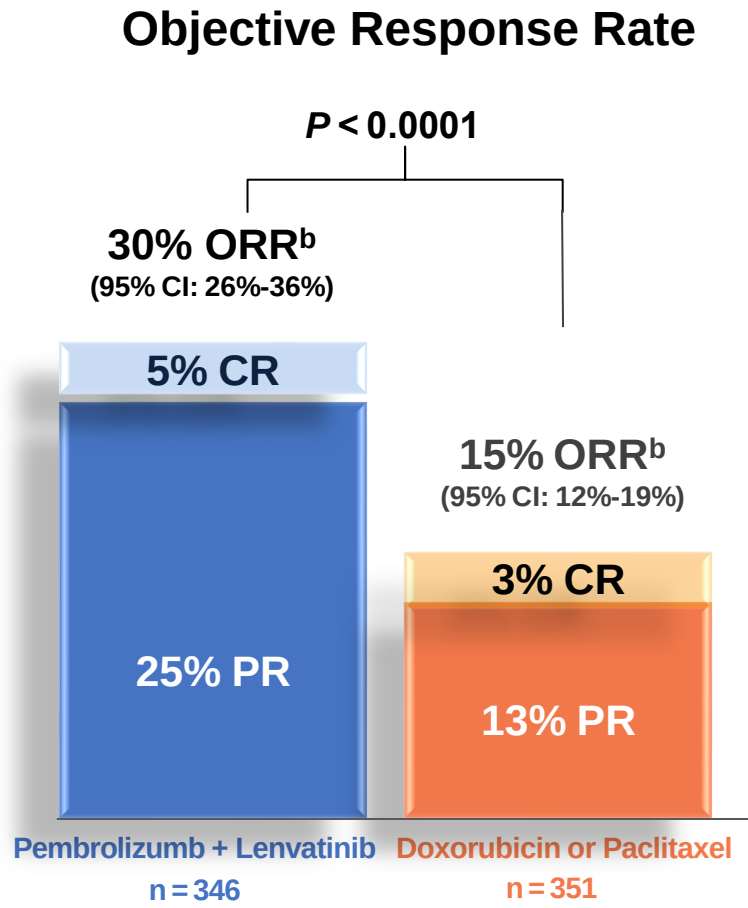
KN 775:Waterfall plots of best percentage change from baseline for target lesions based on BICR assessment per RECIST v1.1 in patients with measurable disease

pMMR

Chemotherapy

Pembrolizumab + Lenvatinib



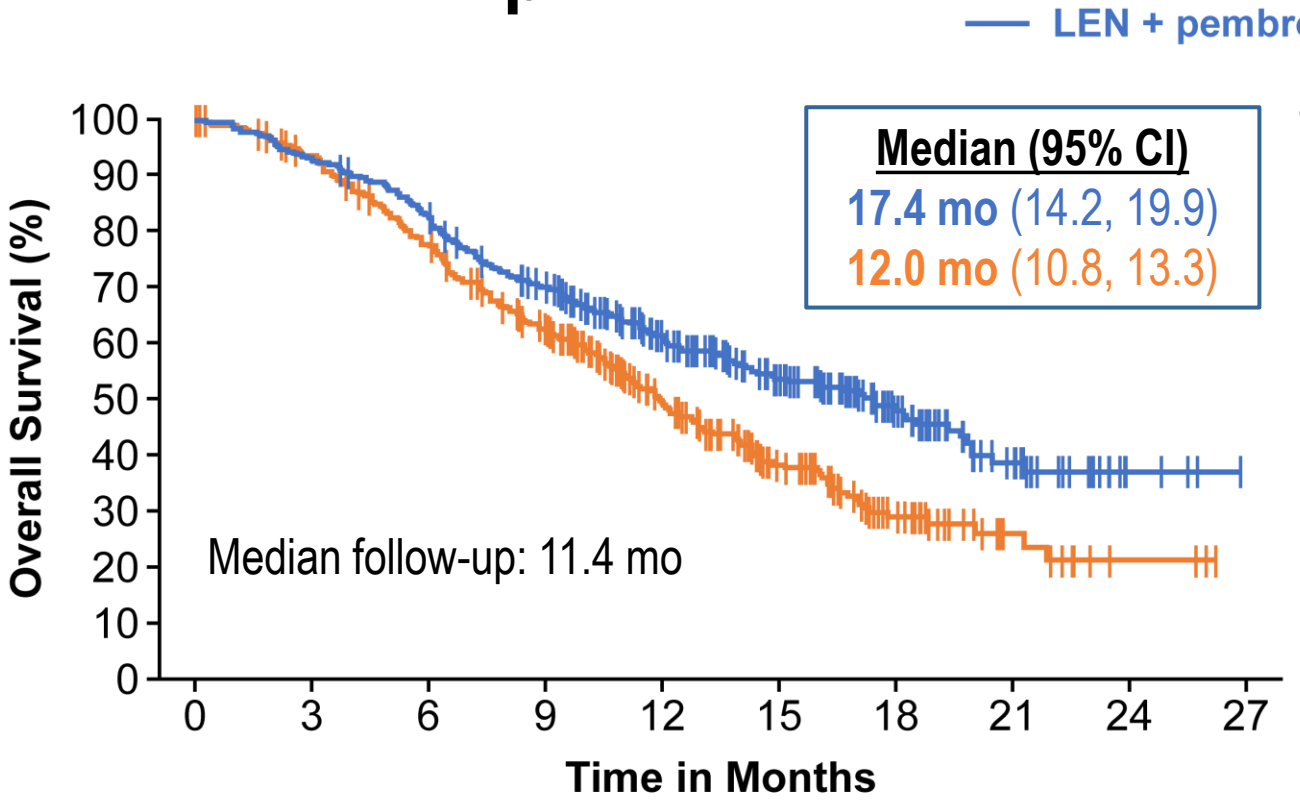


Makker V et al. NEJM 2022

Frauenheilkunde Innsbruck

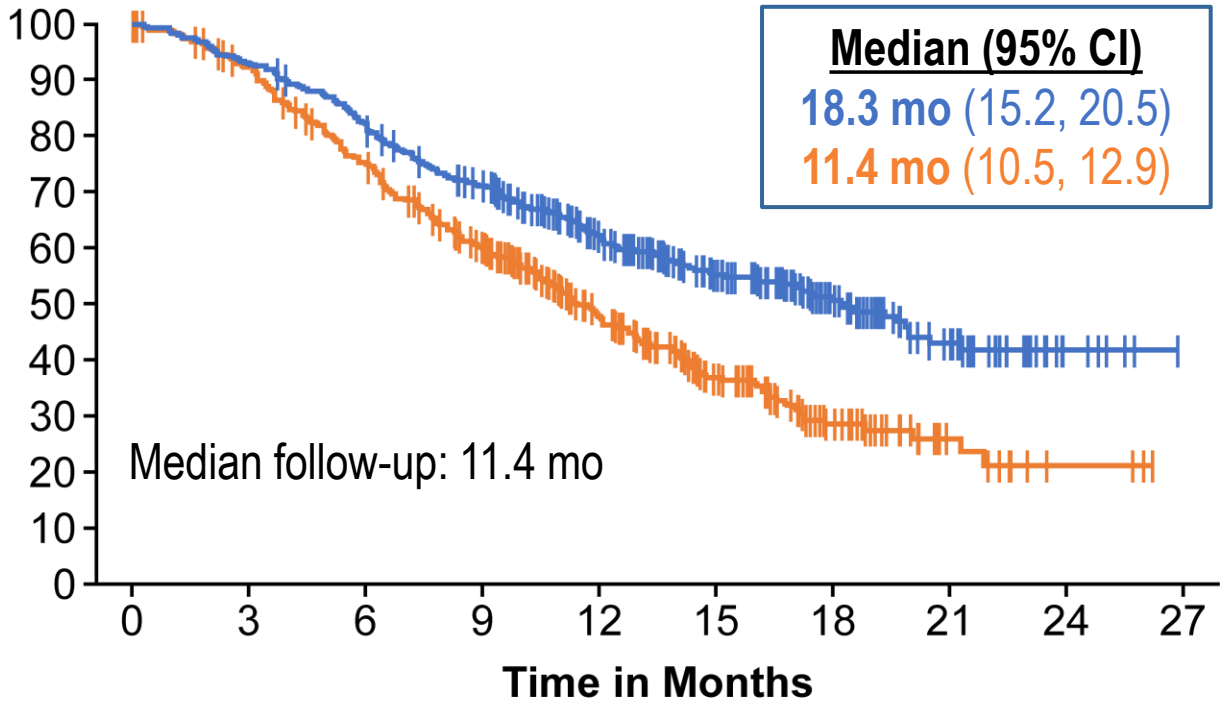
KN-775: Overall Survival

pMMR



	Events	HR (95% CI)	*P*-value
LEN + pembro	165	**0.68** (0.56, 0.84)	0.0001
TPC	203		

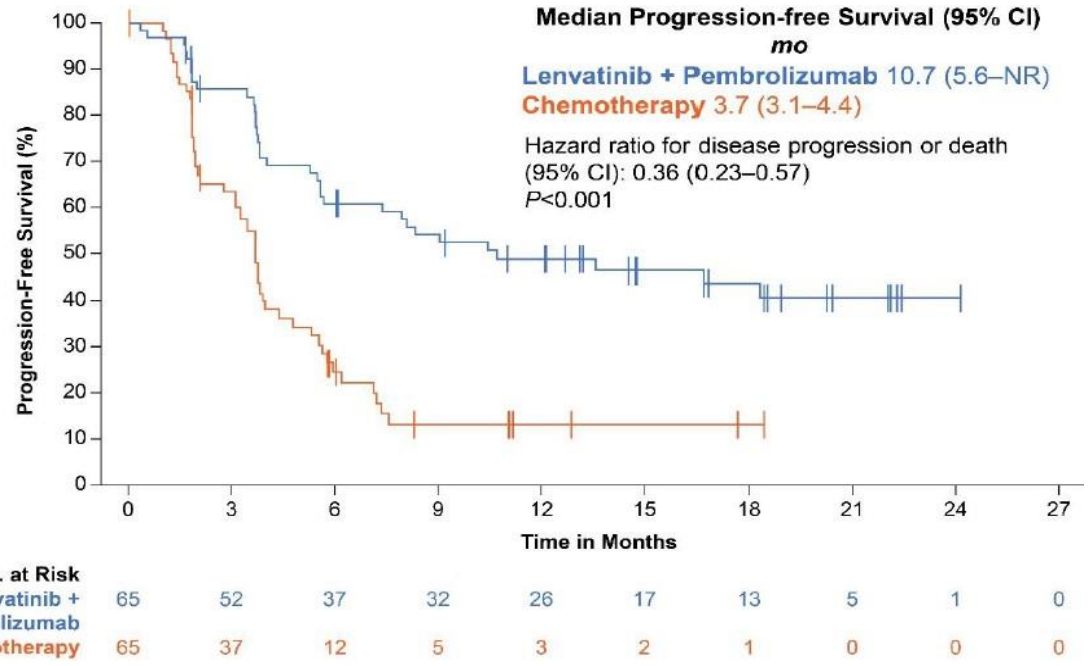
All-comers

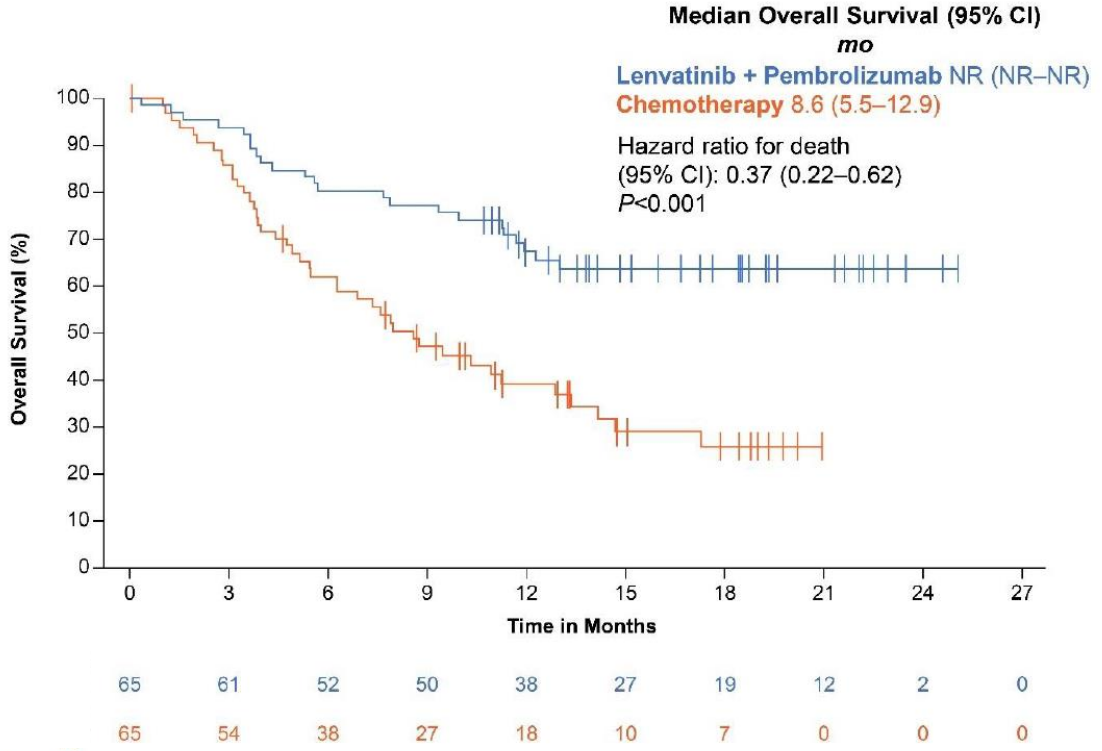


	Events	HR (95% CI)	*P*-value
LEN + pembro	188	**0.62** (0.51, 0.75)	< 0.0001
TPC	245		

A multicenter, open-label, randomized, phase 3 study to compare the efficacy and safety of lenvatinib in combination with pembrolizumab vs treatment of physicia`s choise in patients with advanced endometrial cancer: Study 309/ KEYNOTE-775. Vicky Makker et al. SGO 2021

dMMR Subgroup Analysis in KN 775 – Pembrolizumab-Lenvatinib vs chemotherapy PFS/OS in recurrent endometrial cancer





CI, confidence interval; NR, not reached.

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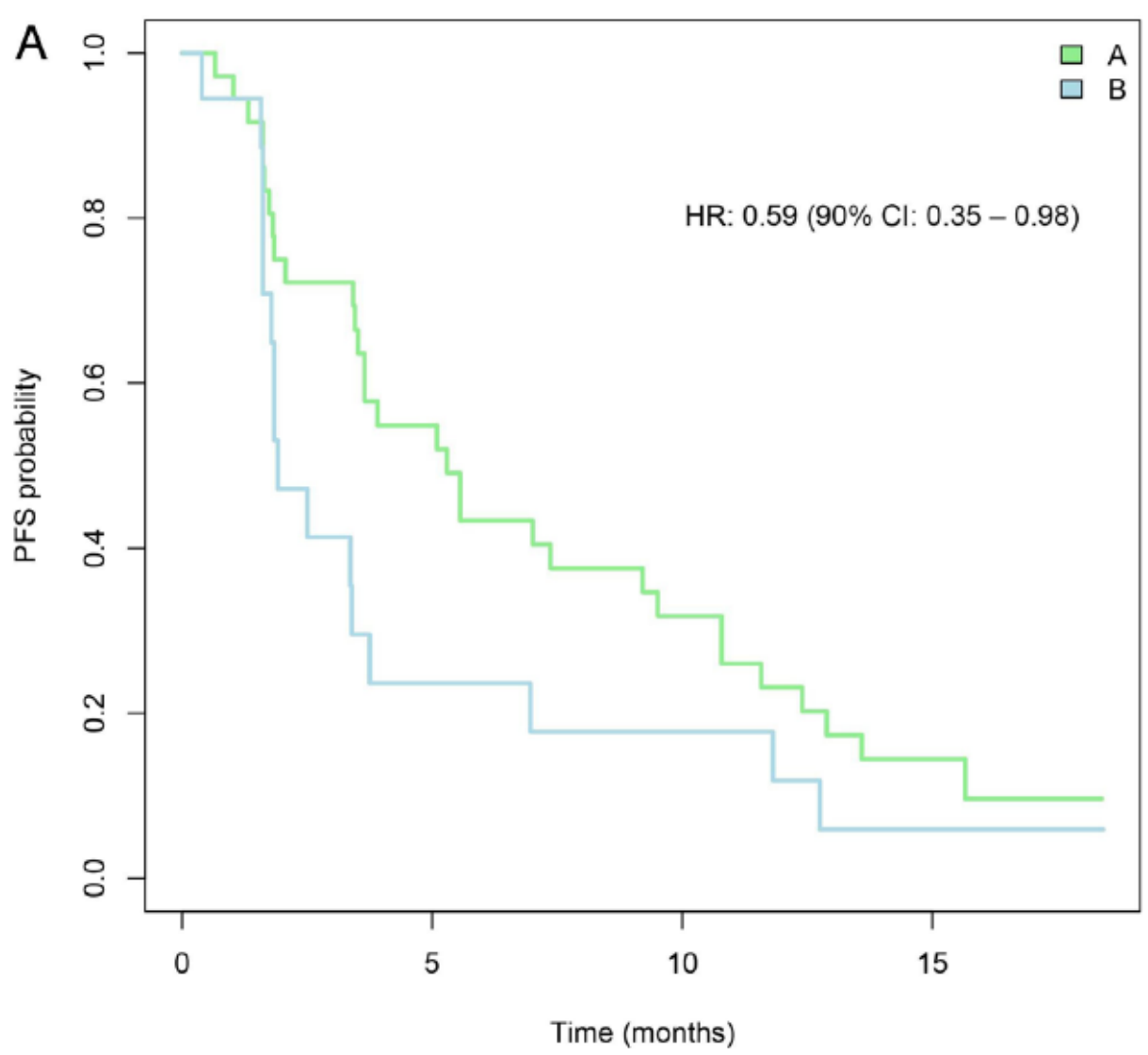
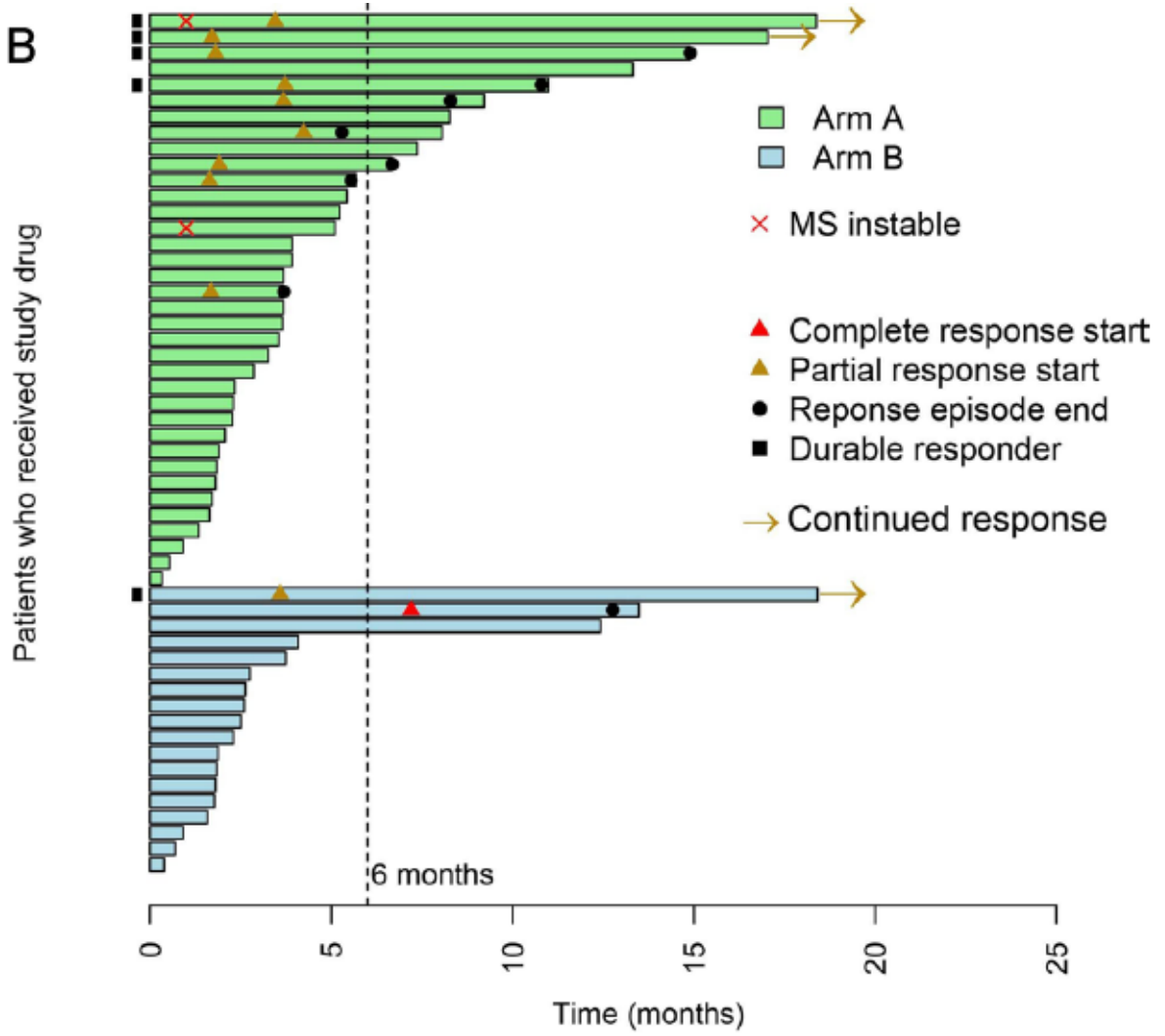
Translational randomized phase II trial of cabozantinib in combination with nivolumab in advanced, recurrent, or metastatic endometrial cancer





Conclusion

- Angiogenesis plays a major role in endometrial carcinoma biology
- Anti-angiogenic drugs show activity in endometrial carcinoma
- P53abn tumors might gain a major benefit
- Combination strategies with immune-checkpoint inhibitors are very promising


christian marth