



Nieuwe ontwikkelingen op het gebied van de angiogeneseremmers

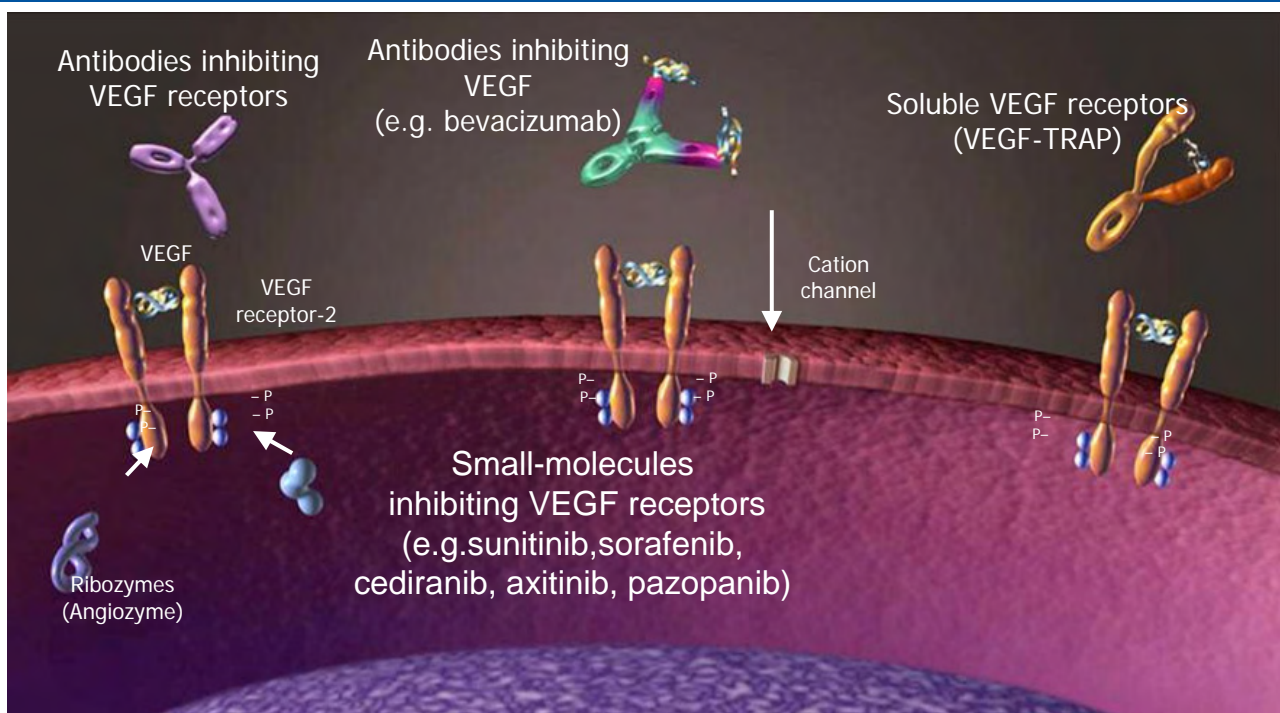
Emile Voest, MD, PhD

*Department of Medical Oncology
University Medical Center Utrecht
the Netherlands*

*4e Nascholing Targeted Therapy
April 2010*

c7

Agents targeting the VEGF pathway



44 VEGF/VEGFR inhibitors in clinical development
Nature Reviews Clinical Oncology 6, 569–579 (1 October 2009)

Dr Voest: please note that we were unable to find a slide with neuropilin represented.
collis_j; 16-9-2005

Bevacizumab prolongs life when combined with chemotherapy in multiple tumors



Chemotherapy combined with bevacizumab	Tumor type	Gain in progression free survival (months)	Hazard ratio
IFL	Colorectal cancer	4.4 (6.2>10.6)	0.54
carboplatin Paclitaxel	Lung cancer	1.7 (4.5>6.2)	0.66
Gemcitabine cisplatin	Lung cancer	0.4 (6.1>6.5)	0.82
Paclitaxel	Breast cancer	5.9 (5.9>11.8)	0.6
Docetaxel	Breast cancer	0.8 (8.0>8.8)	0.79
Gemcitabine	Pancreatic cancer	0.2 (4.7>4.9)	0.99

23 February 2010,

[Phase III Study of Avastin plus Chemotherapy in Advanced Stomach Cancer Did Not Meet Primary Endpoint](#)

Roche (SIX: RO, ROG; OTCQX: RHHBY) announced today the topline results from a global phase III trial investigating the use of Avastin (bevacizumab) in combination with Xeloda (capecitabine) or fluorouracil and cisplatin chemotherapy in patients with inoperable, advanced or metastatic gastric cancer. The study, known as AVAGAST, did not meet its primary endpoint of extending overall survival in patients treated with Avastin in combination with chemotherapy compared to the same chemotherapy plus placebo....



- 08 March 2010
- **RECENTIN did not meet primary endpoint in Horizon III study in metastatic colorectal cancer**
 - Clinical activity was observed in the cediranib arm of the study and there was no statistically significant difference between treatment arms on the efficacy endpoints examined. However, the efficacy did not meet the pre-specified criteria for the primary endpoint of non-inferiority in progression-free survival.

12 March 2010

- **Roche provides update on phase III study of Avastin in men with late stage prostate cancer**
- Roche announced today the results of a phase III trial led by the CALGB and sponsored by the NCI investigating the use of Avastin (bevacizumab) in combination with docetaxel chemotherapy and prednisone in men with HRPC.
- The study, known as CALGB 90401, did **not** meet its primary objective of extending overall survival compared to chemotherapy and prednisone alone.

- June 1, 2009
- **Pfizer Discontinues SUN 1094 Trial of Sunitinib plus Paclitaxel in Advanced Breast Cancer**
- ***Two Other Phase 3 Advanced Breast Cancer Trials of Sunitinib Continue***
- NEW YORK--([BUSINESS WIRE](#))--Pfizer Inc today announced the discontinuation of the SUN 1094 Phase 3 study that evaluated SUTENT® (sunitinib malate) plus paclitaxel versus bevacizumab plus paclitaxel for the first line treatment of patients with advanced breast cancer. The independent Data Monitoring Committee (DMC) found that treatment with sunitinib in combination with paclitaxel would be unable to meet the primary endpoint of superior progression-free survival (PFS) compared to the combination of bevacizumab and paclitaxel. No new safety issues were identified.

- **March 11, 2010**
- **Two Phase 3 Trials Of Sunitinib With Commonly Used Chemotherapies In Advanced Breast Cancer Did Not Meet The Primary Endpoint**
- NEW YORK--Pfizer Inc. announced today that two Phase 3 studies of Sutent® (sunitinib malate) in advanced breast cancer did not meet their primary endpoints. The SUN 1064 Phase 3 study of sunitinib in combination with docetaxel for the first-line treatment of patients with advanced HER-2 negative breast cancer did not show a statistically significant improvement in progression-free survival compared with docetaxel alone. In addition, the SUN 1099 Phase 3 study of sunitinib plus capecitabine, in previously-treated advanced breast cancer patients, did not show a statistically significant improvement in progression-free survival compared with capecitabine alone.

Er zijn echter ook positieve nieuwe toepassingen van VEGF/VEGFR remming

- Sunitinib als 2e lijns behandeling van GIST tumoren
- Sorafenib als behandeling voor gemetastaseerd schildklier carcinoom
- Sorafenib als behandeling van gemetastaseerd HCC
- Nieuwe mogelijke indicaties:
 - EORTC Study 62043; Pazopanib is well tolerated in patients with relapsed, advanced STS and demonstrates interesting activity that warrants additional study in patients with leiomyosarcomas, synovial sarcomas, and other STS types. *JCO 2009, Sleijfer et al.*
 - Phase III Gynecologic Oncology Group (GOG) 0218 (press release feb 25, 2010). Women with ovarian cancer who had maintenance therapy with bevacizumab had longer progression-free survival than the other groups, Genentech said, although the company did not release specific data.

Conclusion (1)

- The concept that VEGF-driven angiogenesis is essential for “all tumors” is not valid anymore
- Clear differences between VEGFR-TKI and bevacizumab in anti-cancer activity
- Toxicity profile of VEGFR-TKI limits their use in combination with chemotherapy
- Mechanism of action is still unclear !!!

What is the optimal duration of anti-VEGF/VEGFR treatment ?

- All studies with VEGFR-TKI were performed with treatment until disease progression regardless of response rate
- Sunitinib in RCC, sorafenib after cytokine failure in RCC
- Other examples: imatinib in GIST, erlotinib in lung cancer, cetuximab/panitumumab in CRC
- Discussion on protracted treatment is now converging on bevacizumab in colorectal cancer
- Why ?

XELOX vs FOLFOX +/- Bevacizumab Roche NO16966 study design

Recruitment
June 2003 – May 2004

XELOX N=317
FOLFOX4 N=317

Recruitment
Feb 2004 – Feb 2005

XELOX + placebo N=350	XELOX + bevacizumab N=350
FOLFOX4 + placebo N=351	FOLFOX4 + bevacizumab N=350

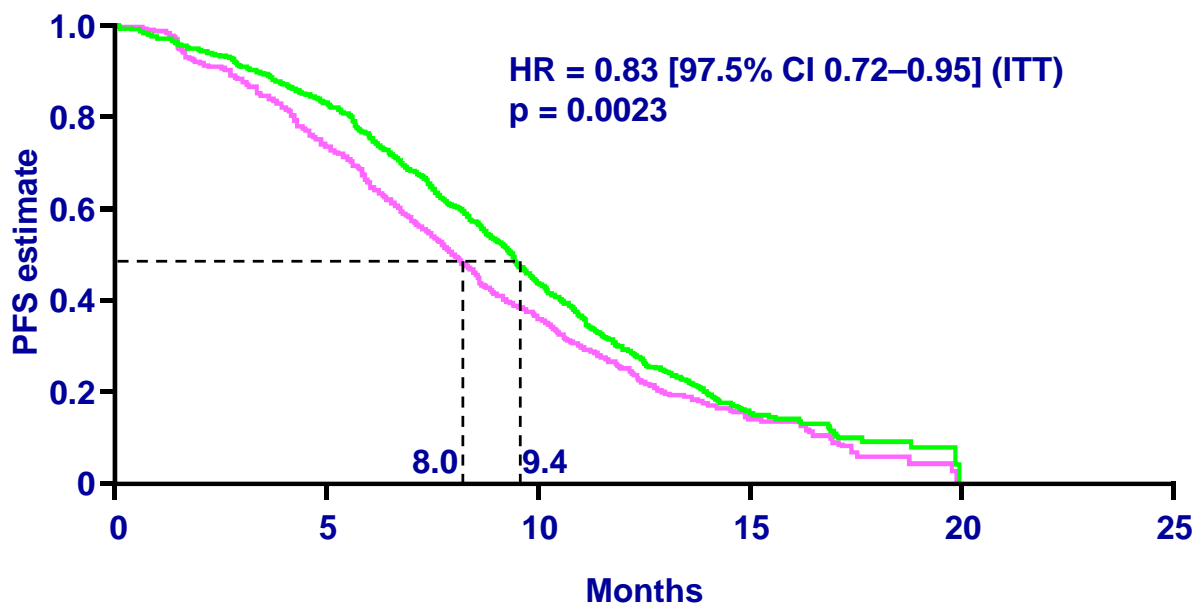
**Initial 2-arm
open-label study
(N=634)**

**Protocol amended to 2x2 placebo-
controlled design after bevacizumab
phase III data¹ became available
(N=1401)**

¹Hurwitz H, et al. Proc ASCO 2003;22 (Abstract 3646)

Cassidy & Saltz, JCO 2008

PFS chemotherapy + bevacizumab superiority: primary objective met



— FOLFOX+placebo/XELOX+placebo N=701; 547 events
— FOLFOX+bevacizumab/XELOX+bevacizumab N=699; 513 events

Saltz et al., JCO 2008

NO16966 Study Drug Exposure – Median Months of Treatment

	FOLFOX +Placebo (N=336)	FOLFOX +Bev (N=341)	XELOX +Placebo (N=339)	XELOX +Bev (N=353)
Oxaliplatin	6.0	6.0	5.5	5.8
Fluoropyrimidine	6.3	6.7	5.6	6.3
Placebo or Bev	6.3	6.0	5.5	6.0

* Per protocol, patients discontinuing oxaliplatin could continue with a fluoropyrimidine + placebo or bevacizumab. Patients could also remain on a fluoropyrimidine alone or placebo or bevacizumab alone but not oxaliplatin alone

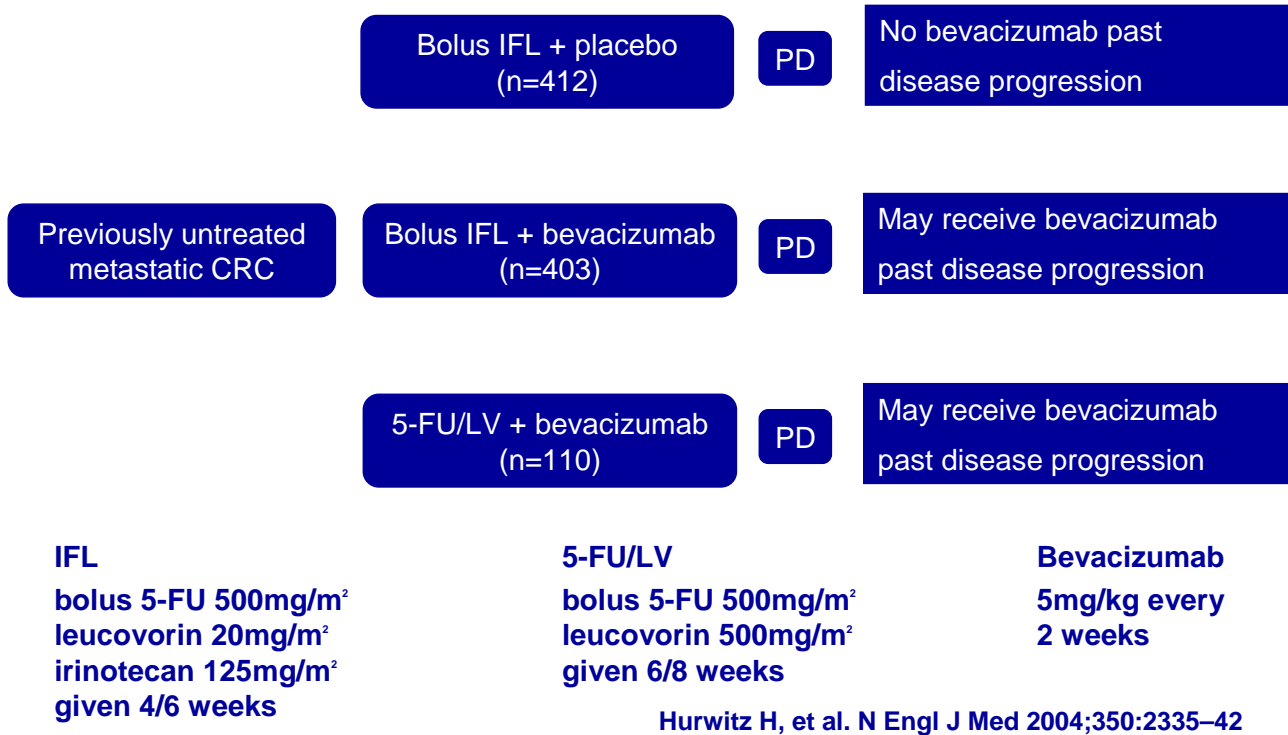
Saltz et al., ASCO GI 2007

NO16966 Study Drug Exposure – Median Months of Treatment

“Analysis of treatment withdrawals showed that, despite protocol allowance of treatment continuation until disease progression, only 29% and 47% of bevacizumab and placebo recipients, respectively, were treated until progression.”

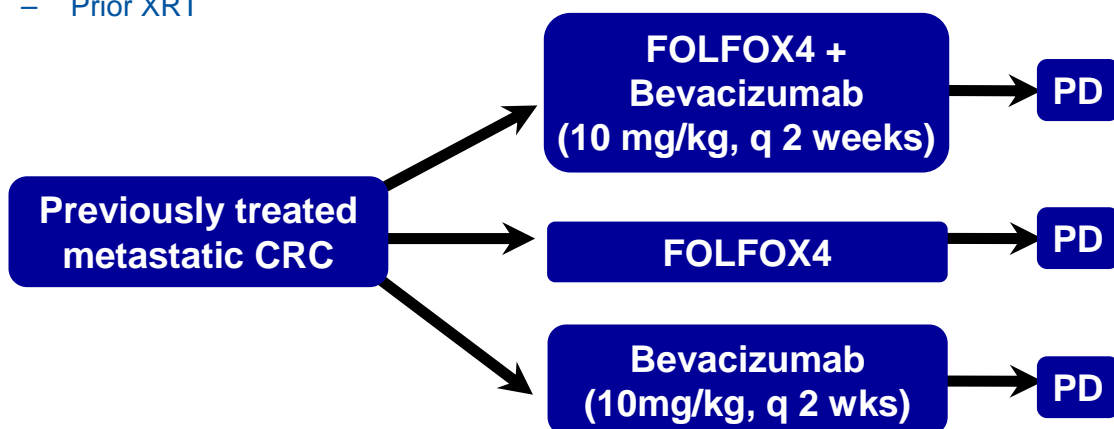
Saltz et al., JCO 2008

Phase III trial of IFL ± bevacizumab in metastatic CRC (AVF2107g): study design



E3200: Study Design

- Stratification factors:
 - ECOG PS: 0 vs 1, 2
 - Prior XRT



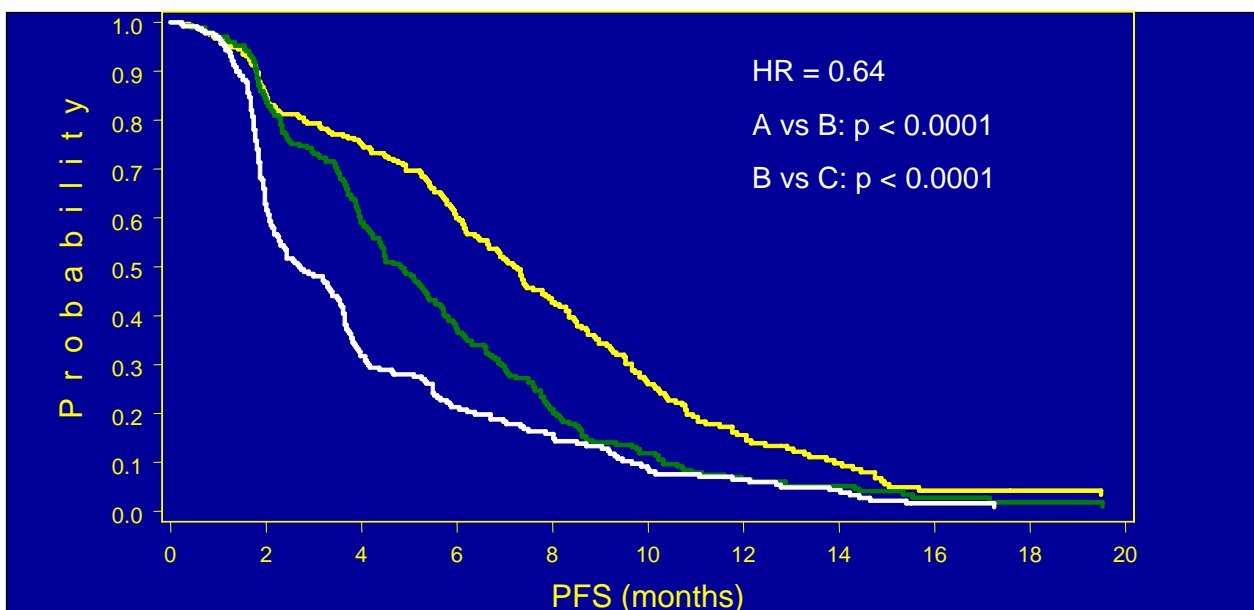
E3200: Response Rates

	FOLFOX4 + bevacizumab 271	FOLFOX4 271	Bevacizumab 230
OR*	21.8%	9.2%	3.0%
CR	1.9%	0.7%	0
PR	19.9%	8.5%	3.0%
SD	51.7%	45.0%	29.1%

***FOLFOX+B vs FOLFOX: P < 0.0001**

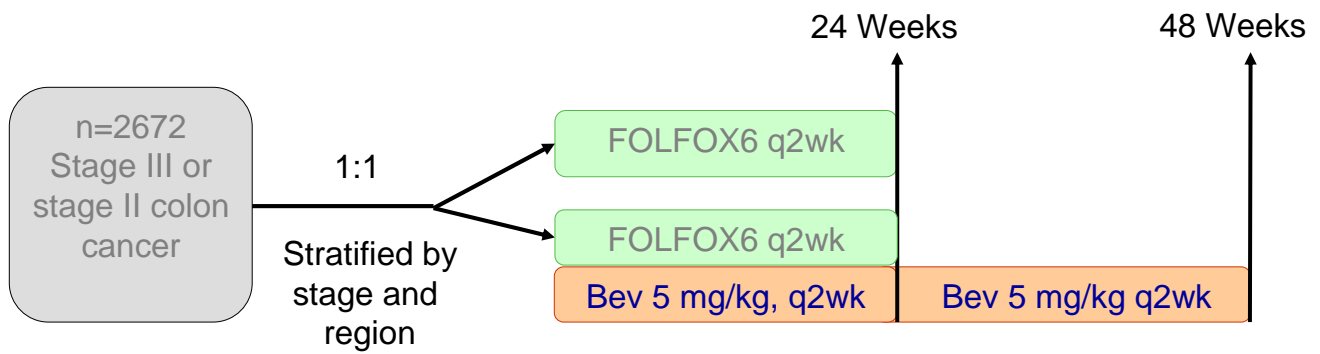
Giantonio BJ, et al. ASCO 2005

E3200: Progression-Free Survival

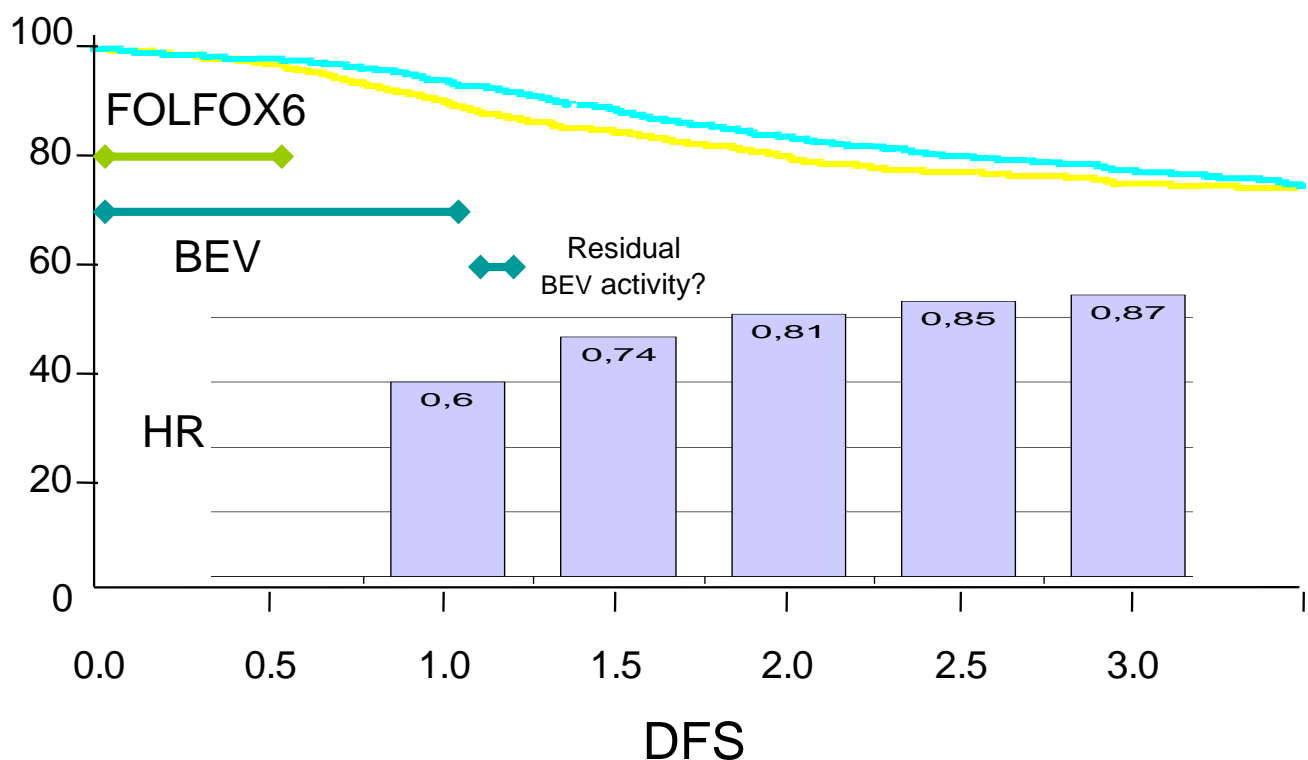


	TOTAL	FAIL	CENS	MEDIAN
— A:FOLFOX4 + bevacizumab	273	228	45	7.2
— B:FOLFOX4	273	241	32	4.8
— C:bevacizumab	229	215	14	2.7

A phase III trial comparing mFOLFOX6 to mFOLFOX6 plus bevacizumab in stage II or III carcinoma of the colon: Results of NSABP Protocol C-08" #LBA4



A phase III trial comparing mFOLFOX6 to mFOLFOX6 plus bevacizumab in stage II or III carcinoma of the colon: Results of NSABP Protocol C-08" (Abstract No: LBA4)



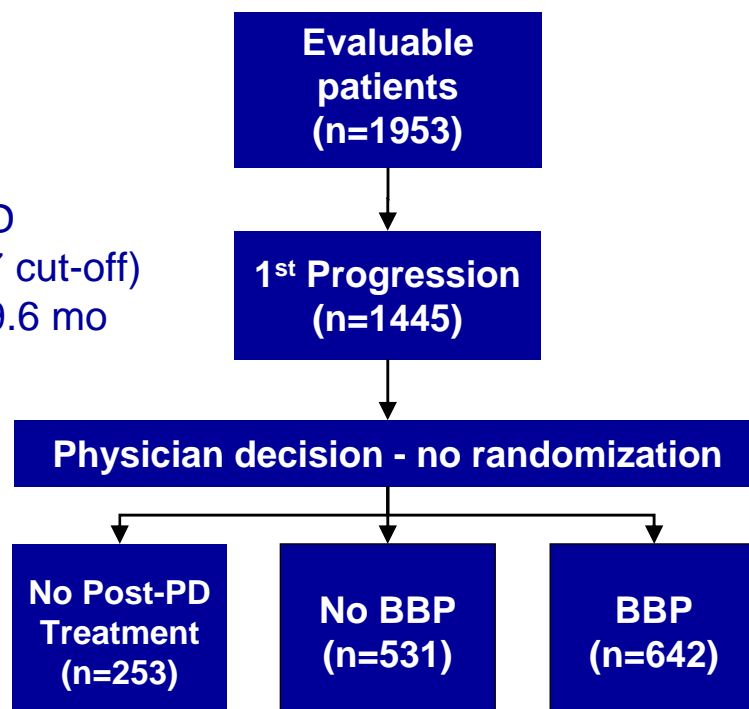
Treatment beyond disease progression ?

- Treatment with anti-VEGF/VEGFR agents beyond progression is not generally accepted nor reimbursed
- No data on continuation of the same VEGFR-TKI beyond progression but activity is seen after VEGFR-TKI rotation in RCC
- Limited data on bevacizumab
- Continuation of Herceptin in Her2 positive metastatic breast cancer patients is already more accepted

BRiTE Registry - Patients with Bevacizumab Beyond Progression (BBP)

BRiTE:

Total N=1953
1445 pts with 1st PD
932 deaths (1/21/07 cut-off)
Median follow-up 19.6 mo



BRiTE: Patient Outcome Based on Treatment Post 1st Progressive Disease

	No Post-PD Treatment (n=253)	No BBP (n=531)	BBP (n=642)
# of deaths (%)	168 (66%)	306 (58%)	260 (41%)
Median OS (mo)	12.6	19.9	31.8
1yr OS rate (%)	52.5	77.3	87.7
OS after 1st PD (mo)	3.6	9.5	19.2

Grothey et al. JCO 2008

Optimal duration of treatment ?

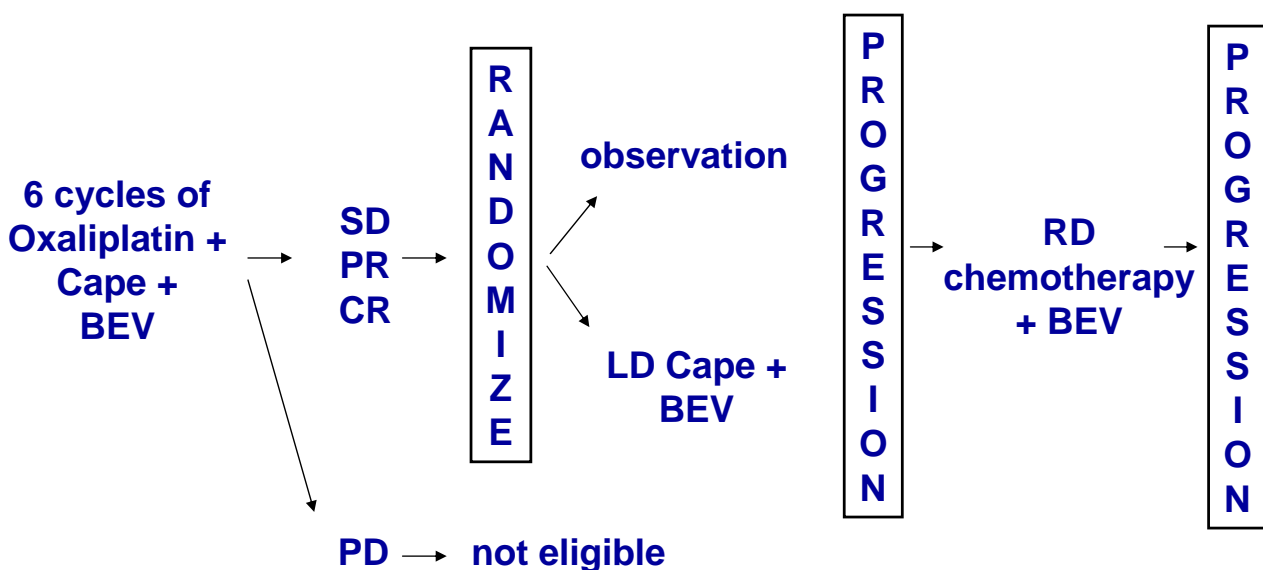
- A Phase III Trial of Carboplatin and Paclitaxel Plus Placebo Versus Carboplatin and Paclitaxel Plus Concurrent Bevacizumab Followed By Placebo, Versus Carboplatin and Paclitaxel Plus Concurrent and Extended Bevacizumab, in Women With Newly Diagnosed, Previously Untreated, Suboptimal Advanced Stage Epithelial Ovarian, Primary Peritoneal Cancer, or Fallopian Tube Cancer
- 1,873 women with newly diagnosed and previously untreated advanced epithelial ovarian, primary peritoneal, or fallopian tube carcinoma.
- Women who had maintenance therapy with bevacizumab had longer progression-free survival than the other groups, Genentech said, although the company did not release specific data.
- Full data are expected to be reported at the American Society of Clinical Oncology meeting in Chicago in June.

Conclusion (2)

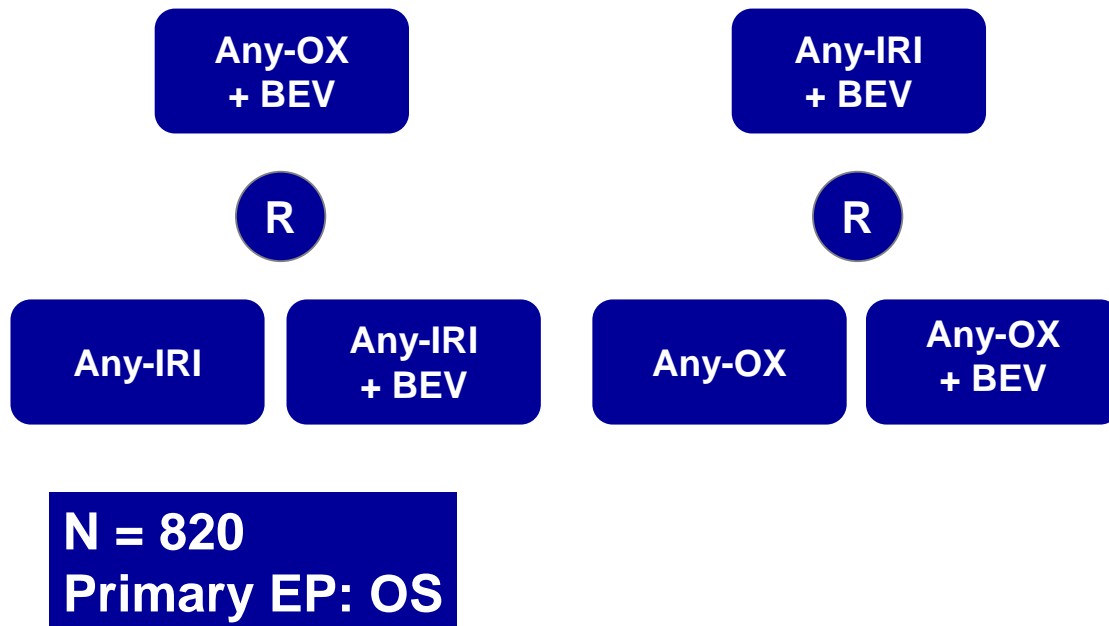
- Continuation of targeted agents is common sense
- Treatment until disease progression with VEGFR-TKI is common practice
- Hurwitz and Saltz trials allowed to treat patients until disease progression but clear differences were seen in maintenance treatment with bevacizumab
- Adjuvant study C08 was negative in colorectal cancer: however different tumor biology (adjuvant versus metastatic disease)
- Ovarian cancer study appears to be in favor of maintenance treatment with bevacizumab
- Clinical trials are underway to provide answers



CAIRO 3



RD = regular dose, LD = low-dose cont.



Final conclusion

- Treatment with inhibitors of the VEGF/VEGFR pathway until disease progression is the current standard of care
- Studies with bevacizumab in metastatic colorectal cancer patients will refine our prescription pattern
- We need to better understand the tumor biology of the various cancers and the role of VEGF in cancer progression to maximize the effects of these expensive but active agents !