ESMO 2012
three abstracts…

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ESMO central nervous tumors track

- Assigned role: discuss three presentations
  - One on surgery
  - One on CD133
  - One on anti-angiogenesis
- Unifying factor: it's all glioblastoma …

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Re-surgery for recurrent glioblastoma: outcome analysis and correlation with *MGMT* status

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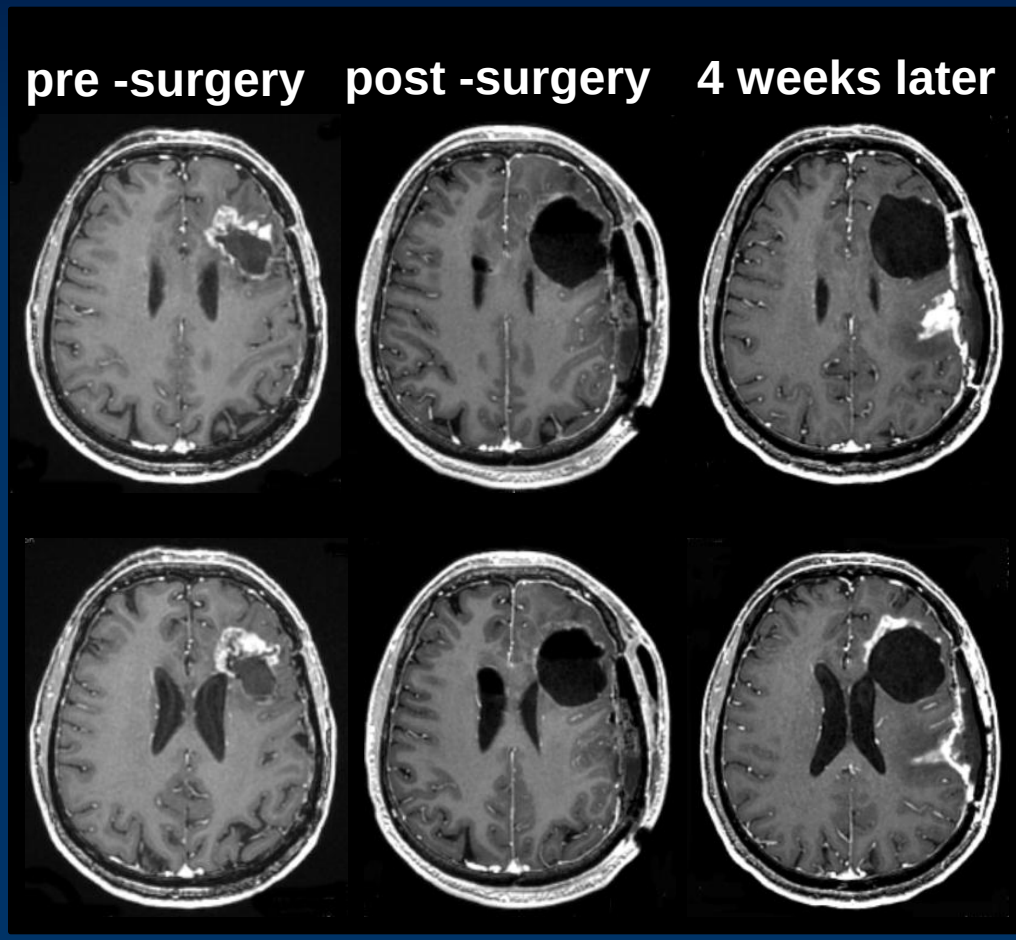
Surgery for recurrent glioblastoma: removing the tip of the iceberg?

- Male, 51 yrs
- Surgery for recurrent glioblastoma
- Immediate post-resection MRI: no residual tumor
- Baseline scan 4 weeks later prior to start bevacizumab
- Did the resection benefit the patient?



Inclusion criteria

- A retrospective analysis was made for glioblastoma patients treated between 01/2005 and 06/2010.

- **Inclusion criteria were:**
  - age ≥18;
  - ECOG PS 0-2;
  - chemotherapy at disease progression after RT/TMZ;
  - availability of data about second progression

Pts characteristics and results

		Population (N=232)
MGMT methylation status	**Evaluable** methylated unmethylated	165 62 103
Age	Median (range)	52 (18-77)
Treatment at progression	Re-surgery + chemotherapy Chemotherapy alone	102 (44%) 130 (66%)

Median time between 1st and 2nd surgery was 13.1 months:

- ***MGMT* methylated : 19.3 months**
- ***MGMT* unmethylated : 13 months (p=0.001)**

OS : 22.4 months

- **OS in pts with 2nd surgery : 25.8 months**
- **OS in pts without 2nd surgery : 18.6 months (p=0.003)**

At multivariate analysis,
re-surgery DID NOT affect OS (p=0.11) while age (p=0.001), *MGMT* methylation (p=0.002) and PFS6 (p=0.0001) were significantly correlated

Is surgery a prognostic marker for improved 6-month PFS or OS in recurrent glioblastoma?

- Two data sets were analyzed.
  - 511 patients enrolled period 1998-2005
  - 247 patients enrolled during 2005-2008,
  - 208 underwent surgery during the clinical trial or immediately prior to study registration.
- No statistically significant difference in PFS6 or OS between the surgery and nonsurgery groups
  - in either data set alone or in the combined data set (P > .45)

Clarke et al, Neuro Oncol 2011;13:1118-24

The ultimate question in glioma surgery

- Candidates for surgery at progression:
  - Young patients, good clinical condition
  - Longer interval from first surgery
  - Smaller, more superficially located lesions in non-eloquent area's

- Are surgeons improving prognosis?
- Or are they operating good prognosis patients?

Questions and Observations

- How many operated cases were methylated?
- At present most analysis of impact of surgery on outcome focuses on clinical variables
  - Unclear impact of molecular factors
  - If MGMT promoter methylation identifies patients with longer PFS: 2nd surgery more likely
- These data support the hypothesis that surgeons operate favorable prognosis patients
  - Which may be a good thing, if proven effective

A Phase 2 Trial of the Multitargeted Kinase Inhibitor Lenvatinib (E7080) in Patients (pts) With Recurrent Glioblastoma (GBM) and Disease Progression Following Prior Bevacizumab Treatment

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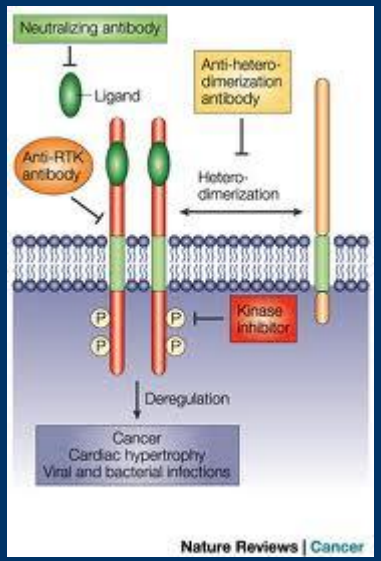
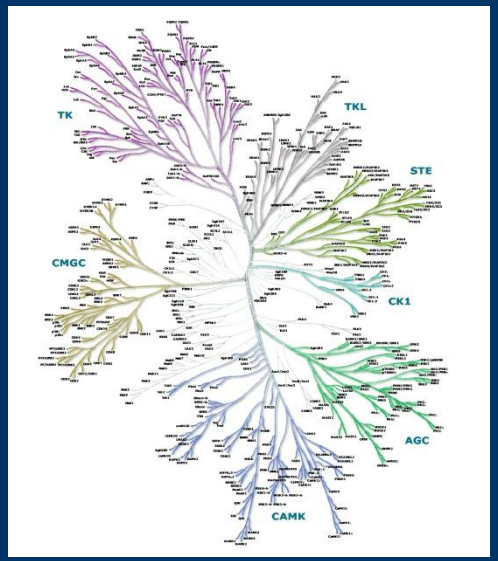
Not all anti-VEGF drugs are created alike…

compound		VEGF R-1	VEGFR-2	VEGFR-3	VEGF-A	EGFR	PlGF	C-kit	PDGF-Rβ	ORR	6 mo PFS
cediranib	TKI		x	x						15.3%	16.2%
vandetanib	TKI		x			x				13%	6.3%
aflibercept	'AB'				x		x			24%	7.7
bevacizumab	AB				x					28.2%	42.6%
pazopanib	TKI	x	x	x				x	x	6%	3%
vatalanib	TKI	x	x	x			x		x	4%	25% (?)
sunitinib	TKI		x					x		0%	16.7%





Pazopanib Neuro Oncol 2010;12:855-61
Bevacizumab JCO 2009;27:4733-4740
Cediranib REGAL data
Vatalanib Neuro-oncology 2010;12:304-316
Aflibercept J Clin Oncol 2011;29:2689-95
Sunitinib J Neurooncol 2012;110:111-8

Some conclusions from REGAL and other anti-VEGF projects

- Are PFS & ORR valuable endpoints?
  - Trends towards improved PFS, ORR
  - However: not supported by OS signal in the right direction
  - Classical T1 MRI with contrast has limited prediction for the OS endpoint

    'patient benefit'
- 6 mo PFS in phase II of 28% does not translate in OS benefit
  - benchmark for anti-VEGF agents?

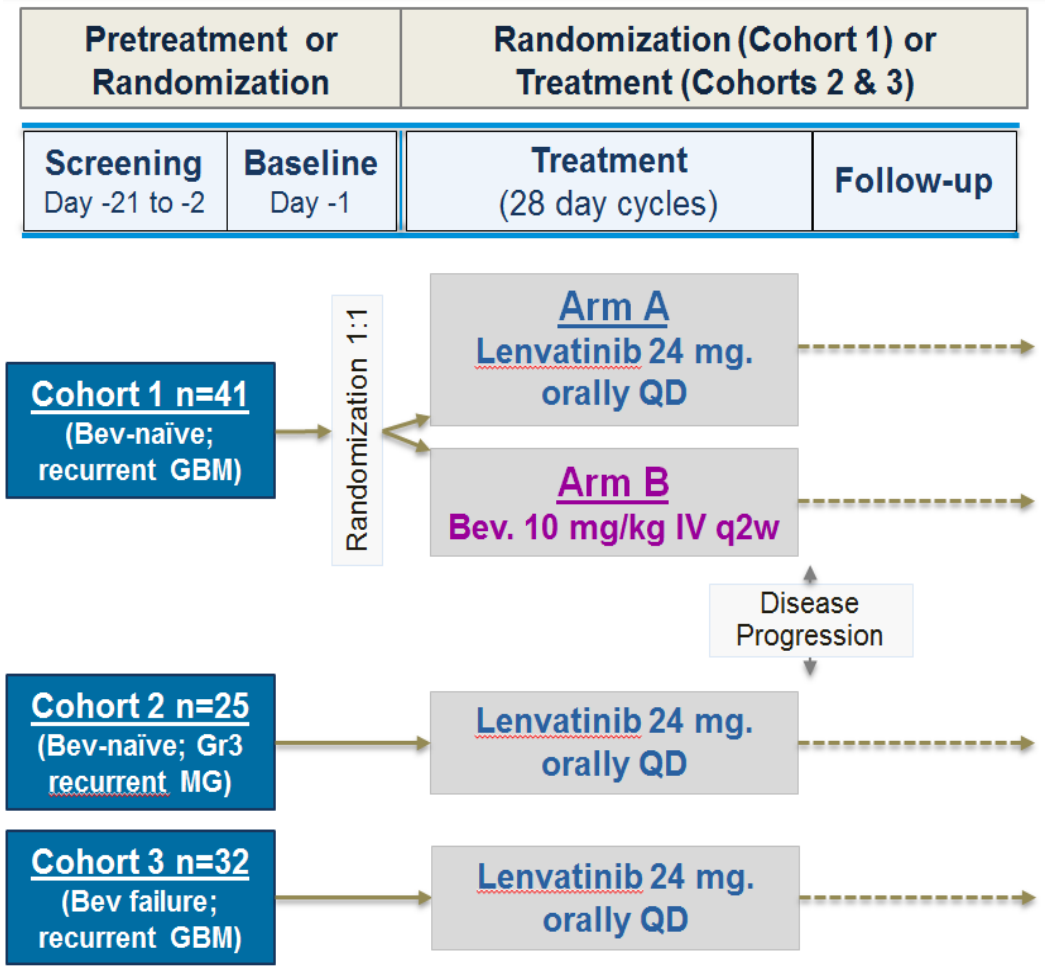
2nd line treatment with bevacizumab after failure to anti-VEGF TKR inhibitor

- Two series (n = 24 and n = 14) with recurrent glioblastoma and bevacizumab-containing regimens after failure to anti-VEGF TKR inhibitor
  - 1st series 6 of 24 patients (25%) had a PR to TKRI treatment, 6-mo PFS was 16.7%
  - 2nd series on 14 patients: no ORR to TKI
- Response to bevacizumab: ORR 21-29% PR, PFS-6 12.5-29%, median OS after start of Bev 5.2 – 7.8 mo

Scott et all, Neuro Oncol 2010;12:603-7, Goldlust et al J Neurooncol 2012;107:407-11

Background and Study Design

- **Essentially all GBM recur after initial therapy and the majority of patients do not survive more than 1 year after the diagnosis of recurrent disease (1 y: 20%-25%)[1]**
- **GBMs are highly vascularized tumors and this was a rationale for the evaluation of the antiangiogenic bevacizumab as a treatment**
  - **Single-agent PFS-6 rate = 42.6% and median OS = 9.2 months[2]; PFS-6 rate after a bevacizumab-containing regimen in recurrent disease = 2%; median PFS = 37.5 days[3]**
- **Lenvatinib is an antiangiogenic agent that, in addition to inhibiting VEGFRs, inhibits several signaling drivers (ie, FGFRs, PDGFRs, and RET) that may become activated and compensate for VEGFR inhibition[4-6]**



1. Chamberlain MC. *Clin Med Insights Oncol*. 2011;5:117-129.
2. Friedman HS et al. *J Clin Oncol.* 2009;27(28):4733-4740.
3. Quant et al. *Neuro Oncol*. 2009;11:550-555.
4. Matsui J et al. *Clin Cancer Res*. 2008;14(17):5459-5465.
5. Matsui J et al. *Int J Cancer*. 2008;122(3):664-671.
6. Glen H et al. *Clin Cancer Res*. 2011;17(8):2528-2537.

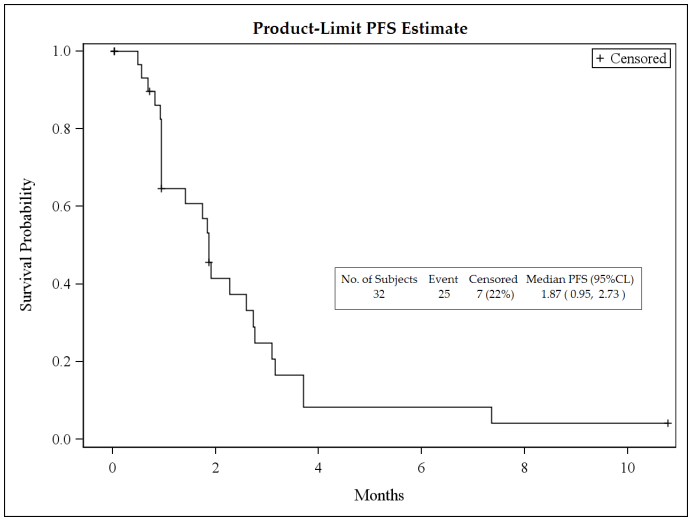
Patient Demographics

Category	Cohort 3 (n=32) n (%)
Age, y, median (range)	52 (27-74)
Gender, male	18 (56.3)
Race, white	32 (100)
Baseline Karnofsky Performance score	
100% = Normal, no complaints; no evidence of disease	3 (9.4)
90% = Able to carry on normal activity; minor signs or symptoms of disease	11 (34.4)
80% = Normal activity with effort; some signs or symptoms of disease	12 (37.5)
70% = Cares for self; unable to carry on normal activity or to do active work	6 (18.8)

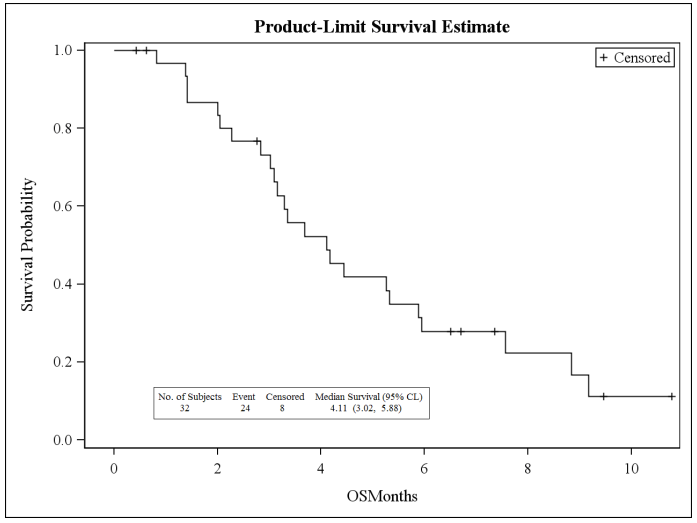
- **All patients were previously treated (with up to 2 systemic treatments)**

Results and Conclusion

PFS



OS



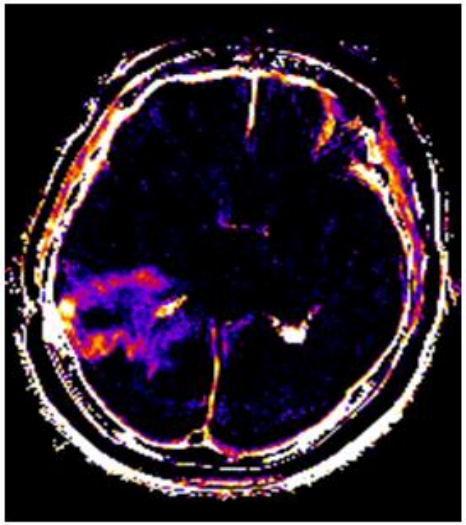
- **Most common AEs were hypertension, 47% (Grade 3: 18.8%; Grade 4: 3.1%); fatigue, 44% (Grade 3: 15.6%; Grade 4: 3.1%); headache, 41%; proteinuria 31% (Grade 3: 6.3%); and diarrhea 31% (no Grade 3 or 4)**

Lenvatinib After Heavily Pretreated Recurrent GBM With Prior Bevacizumab-Containing Regimen for Recurrent Disease

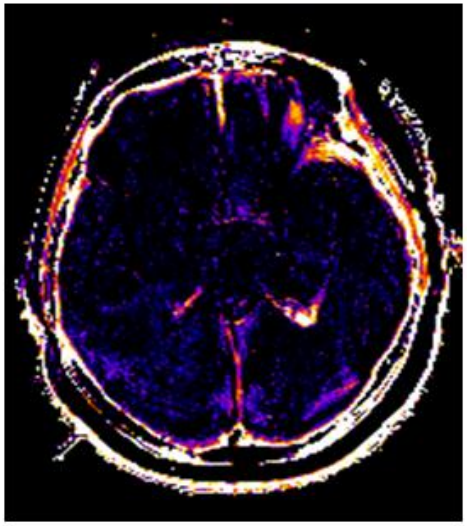
Tumor Response	**N=32**
PFS-6, %	8.3
Median PFS, mos (95% CI)	1.87 (0.95-2.73)
OS-6, %	28
OS-12, %	11.15
Median OS, mos (95% CI)	4.11 (3.02-5.88)
Complete response (CR), n (%)	0
Partial response (PR), n (%)	0
Stable disease (SD), n (%)	9 (28.13)
Progressive disease (PD), n (%)	14 (43.75)
Unknown, n (%)	9 (28.13)
Objective response rate (CR + PR)	0

- **Key conclusion:**
  - **Lenvatinib provided a modest benefit in a difficult-to-treat disease setting with poor prognosis and no effective treatments**

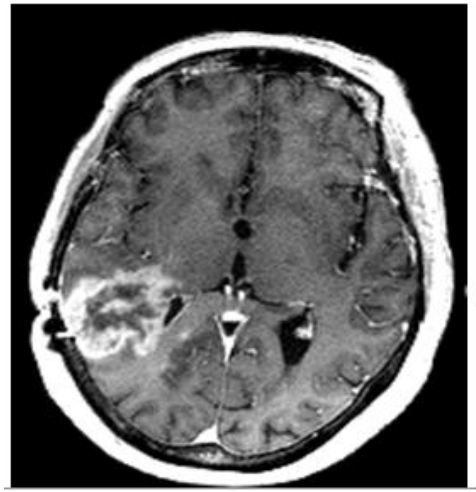
Radiographic Response With Lenvatinib



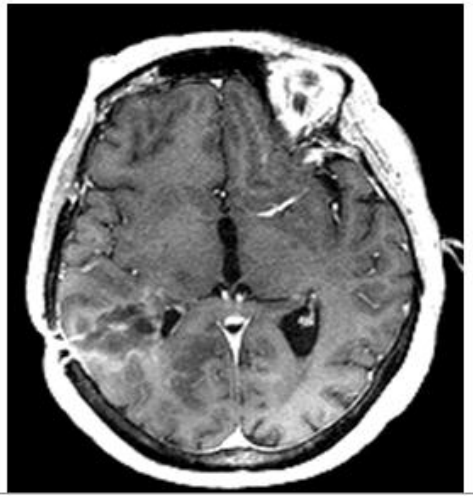
A. Before lenvatinib



A. After lenvatinib



B. Before lenvatinib



B. After lenvatinib

Case

A. Axial maps of K^{trans} derived from evaluation of DCE-MRI analyzed using extended Tofts model in patient with glioblastoma before and after single dose of lenvatinib demonstrate 96.3% decreased K^{trans} in right temporal parietal tumor

B. Corresponding reformatted axial contrast-enhanced T1-weighted 3D fast low-angle shot (3D FLASH) images show decrease in the size of contrast-enhancing abnormality at the corresponding time points (pre-lenvatinib, post-lenvatinib, 81.7% decrease in lesion volume)

Results: 16 patients performed DCE-MRI. 33% reduction in mean K^{trans} was observed in 10 patients (63%) and a significant decrease in lesion volume (mean reduction: 33%, P=0.00287) was found 1 day after therapy, indicating L affected tumor vascularity and vascular permeability

Some observations

- Most anti-VEGF agents do not come close to the results in recurrent glioblastoma observed with bevacizumab
- Bevacizumab still not fully evaluated
- Results in 2nd line anti-VEGF agents worse
- Recurrent glioblastoma after bevacizumab still stage in which most drugs are likely to fail

Association between cancer stem cells and CD133+ blood vessels in glioblastoma multiforme

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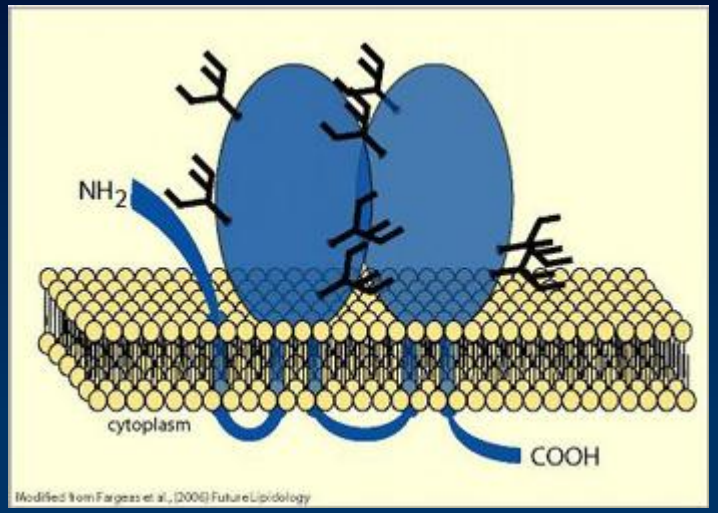
Tartu Ülikooli Kliinikum

CD133 (prominin-1): markers of stem cells?



- Originally described as a marker of hematopoetic CD34+ progenitor cells
- Antibody for CD133 recognizes certain glycosylated epitopes (AC133, AC14)
- Rapid down regulation during cell differentiation
  - or only the AC133 epitope and not the CD133 protein???

- Cancer stem cells: capacity to self-renew, driving tumor growth and generate tumor cell progeny that form tumor bulk
  - More resistant against radiotherapy and chemotherapy
- Does expression of CD133 epitopes AC133 and AC141 define Brain Tumor Stem Cells? Unresolved issue …

Kemper et al, Canc Res 2010;70:719, Bidlingmaier J Molmed 2008;86:1025-32

The expression of CD133 predicts poor prognosis in glioma

- Several studies have shown prognostic significance of CD133 expression in glioma
  - Both CD133+ proportion and CD133+ expression in clusters
  - Stem cell related expression signature related to poor survival in GBM treated with RT/TMZ
- Series of 44 glioblastoma patients
  - CSC generation and CD133+/Ki67+ prognostic for progression and poor outcome

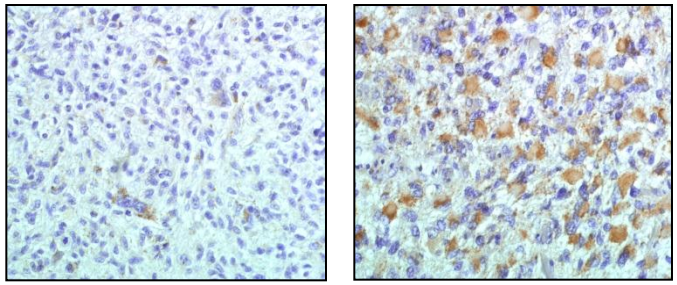
Zeppernick et al, Clin Canc Res 2008;14:123-9 Murat et al, J Clin Oncol 2008;26:3015-24, Cheng et al, Canc Treatment Rev 2009;35:403-408

What is the source of endothelial cells in glioblastoma?

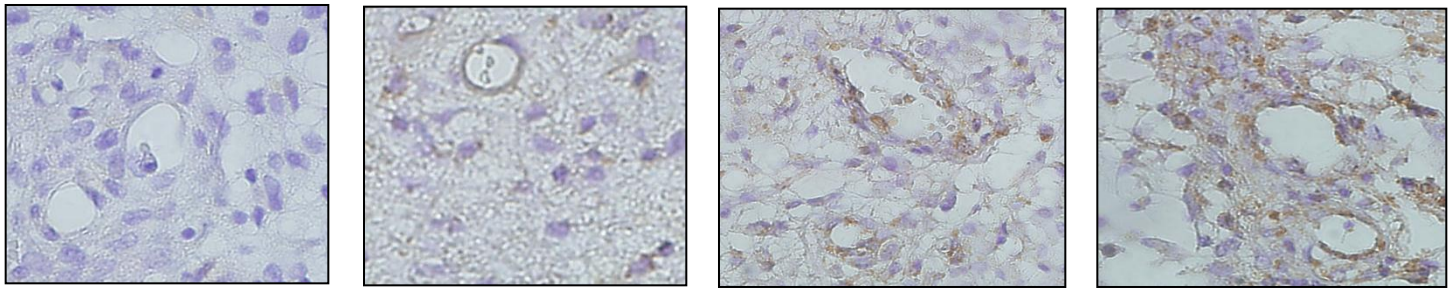
- Usual hypothesis: derived from bone marrow stem cells, endothelial precursor cells
- Alternative: blood vessels originating from tumor stem cells?
  - In glioblastoma: copious CD133+ or Nestin+ blood vessels in regions with CD133+ or Nestin+ cells
  - Niches with CD133+/nestin+ GSC with blood vessels distributed around the surroundings
  - GSC can co-express CD133, Nestin and CD31

He et al, Oncology Reports 2012;27:45-50, Wang et al Nature 2010;468:829-833

CD133+ stem cells and CD133+ blood vessels

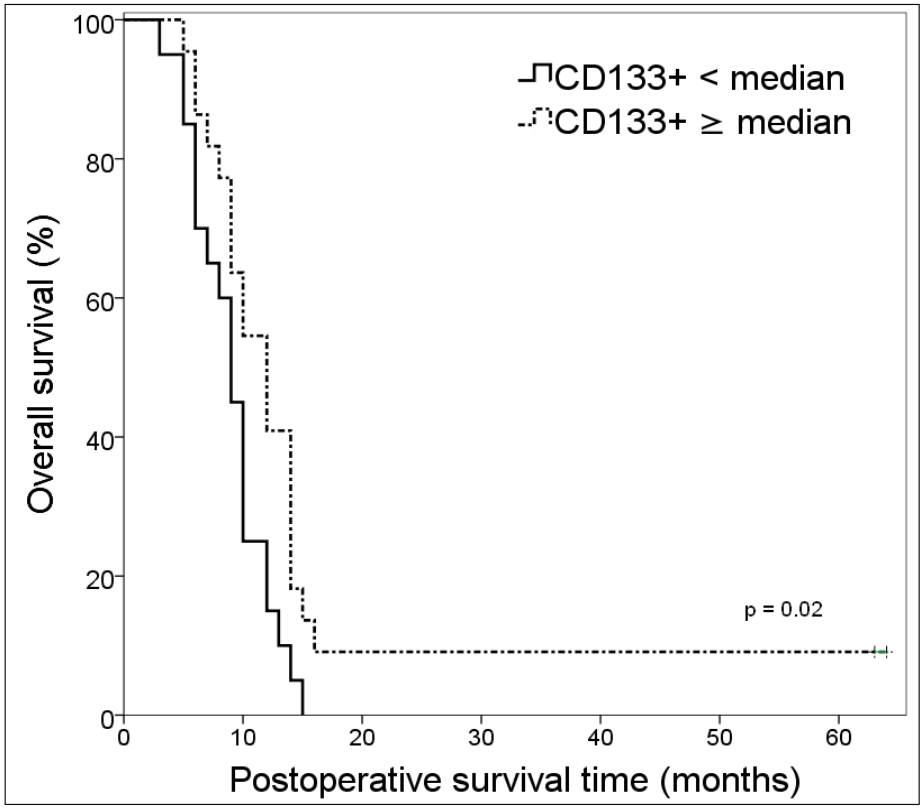


Photos illustrate low (A) and high (B) proportions of CD133+ GBM stem cells in GBM tissue.



Photos depict CD133+ blood vessels (0= no staining, figure 2A; 1= weak staining, figure 2B; 2= moderate staining, figure 2C; 3= strong staining, figure 2D**). A significant association was found between the proportion of CD133+ stem cells and the number of CD133+ blood vessels (p=0.004).** Moreover, a correlation between the number of CD133+ blood vessels and the endothelial CD133 staining intensity was detected (p<0.001

Kaplan-Meier analysis of overall survival (OS) according to CD133+ stem cell proportion



Median survival of patients with low (<median) and high (≥median) proportion of GBM stem cells were 9.0 months (95% CI 7.6-10.5) and 12.0 months (95% CI 9.3-14.7) respectively (p=0.02).

In summary

- A significant association was found between the proportion of CD133+ stem cells and the number of CD133+ blood vessels ($p=0.004$).
- Moreover, a correlation between the number of CD133+ blood vessels and the endothelial CD133 staining intensity was detected ($p<0.001$).
- In multivariate analysis, the proportion of CD133+ GBM stem cells emerged as a significant independent predictor for overall survival.
- Favourable CD133+ expression has to be taken into account in the strategies under preclinical or clinical development for GBM stem cell targeting.

Some observations

- Role of CD133+ for identication of BTSC still matter of debate
- Prognostic role of CD133 expression in most studies
- Intriguing interplay between BTSC and endothelial cells
  - Exchange of proteines?
  - GCS participating to endothelial cell formation?