A phase II trial with cetuximab, bevacizumab and irinotecan for patients with primary glioblastomas and progression after radiation therapy and temozolomide

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Background

- The prognosis of recurrent primary glioblastoma multiforme (GBM) is poor, and no efficacious therapy exist in patients previously treated with radiotherapy and standard chemotherapy
- Angiogenesis is a requirement for growth of GBM and Vascular Endothelial Growth Factor (VEGF) is abundantly produced in gliomas, being a prognostic factor with more VEGF expression correlating with a poor prognosis
- Bevacizumab is a monoclonal antibody which binds to VEGF, thereby inhibiting activation of the VEGF receptor (VEGFR)
- Cetuximab (C) is a chimeric monoclonal antibody that binds to EGFR with high affinity, competes for ligand binding and down regulates receptor expression on the cell surface. Previous studies have shown that cetuximab is effective in inhibiting *in vitro* and *in vivo* growth of glioma cells with amplified EGFR
- Irinotecan is a topoisomerase inhibitor, with limited effect when used as monotherapy for gliomas
- The combination of C and I has shown significantly higher response rate compared to I as monotherapy in colorectal cancer. Furthermore, as shown in the BOND-2 study treating colorectal cancer, Adverse Events (AE) have been observed acceptable when combining C and I with B (CBI)

Aim

To investigate the safety and efficacy of cetuximab, bevacizumab and irinotecan (CBI) in recurrent primary GBM

- Primary objective
  - Determine disease control rate (progression free survival (PFS) and response rate (RR))
- Secondary objective
  - Determine safety, tolerability and toxicity in patients with recurrent or progressive GBM
  - Determine overall survival (OS)

Conclusions

- The CBI regimen is well tolerated, with encouraging response rates, including 2 CR
- The efficacy of the CBI combination seems to be equal or better than treatment with bevacizumab and irinotecan (BI)
- Accordingly, further evaluation of the CBI regimen could be warranted

Methods

- Inclusion criteria:
  - Biopsy verified primary (*de novo*) GBM
  - Recurrent primary GBM with progression < 6 months from standard treatment with radiotherapy and concomitant temozolomide followed by adjuvant temozolomide
  - Progressive disease according to MacDonald criteria and verified by MRI scan
  - Performance status 0-2
  - Minimum 6 weeks from major surgery
  - No hypercholesterolemia
  - No thrombo-embolic event within the last 6 months
  - No anticoagulation therapy
  - Blood pressure < 150/100 mmHg
- Treatment administration:
  - Cetuximab 400 mg/m^2 as starting dose, followed by weekly cetuximab 250 mg/m^2
  - Bevacizumab, 10 mg/kg on day 1 and 15
  - Irinotecan 340 mg/m^2 (patients treated with enzyme inducing anti-epileptic drugs (EIAEDs)) or 125 mg/m^2 (patients without EIAEDs) on day 1 and 15
  - Treatment cycles of 4 weeks until progression
  - Toxicity administration every 2 weeks according to NCI-CTCAE 3.0
- Evaluation:
  - Every second month according to MacDonald criteria

Results

Patients Characteristics

Patient demographics N=43	
Median Age (range)	54 (23-70 years)
Gender Male/Female	25/18
Performance status 0 1 2	 9 26 8
Reoperation before treatment with CBI Yes No	 12 31
Site: Copenhagen Aalborg Odense	 32 8 3

- 43 patients were included between August 2006 and February 2008
- Time from first recurrence until enrollment, including debulking surgery if possible
  - Median 49 days (15 – 162)
- After safety analyses of the first 10 pts, bevacizumab was increased from 5 to 10 mg/kg and this regimen was well tolerated
- All patients were evaluable for toxicity and 32 patients were evaluable for response after receiving at least 2 series of treatment
- Observation time
  - Median 15 months (7-25)

Toxicity

	Grade I-II		Grade III-IV	
	Number	%	Number	%
Nausea	13	30,2%	0	
Vomiting	5	11,6%	1	2,3%
Diarrhea	14	9,3%	3	7%
Stomatitis	12	27,9%	0	
Constipation	16	37,2%	1	2,3%
Loss of appetite	6	14%	1	2,3%
Fatigue	22	51,2%	0	
Neutropenia	5	11,6%	2	4,7%
Fever	5	11,6%	0	
Infection	9	20,9%	6	14%
Alopecia	11	25,6%	0	
Trombosis	0		5	11,6%
CNS hemorrhage	2	4,7%	0	
Skin reaction	26	60,5%	3	7%
Bleeding	6	14%	2	4,7%

- 5 pts had Grade III-IV tromboembolic complications
  - 3 pts with deep vein tromboses -> continued after initiation of LMWH
  - 1 pt had pulmonary embolism (PE) and 1 pt had lacunar infarction. Both pts went off study according to study protocol
- 1 pt had severe GI-bleeding after LMWH was initiated for PE
- No pts went off study due to unmanageable hypertension
- Non-hematological Grade I-II toxicity included transient elevation of transaminases, proteinuria and hyperglycemia
- 3 pts experienced grade III-IV allergic reaction during first cetuximab administration, despite pre-medication
- 1 pt developed severe dyspnoea during second cycle and CT- scan showed pulmonary changes characterized as interstitial pneumonitis, with normalization after discontinuation of cetuximab

Response

Figure 1

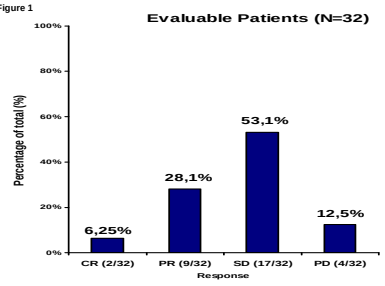

Figure 1: Number of Complete Responses (CR), Partial Responses (PR), Stable Diseases (SD) and Progressive Diseases (PD) according to MacDonald criteria with bi-dimensional measurement at MRI scan

Figure 2A

Serial MRI of a patient with partial remission

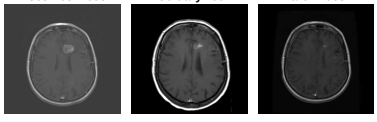

Figure 2B

Serial MRI of a patient with partial remission

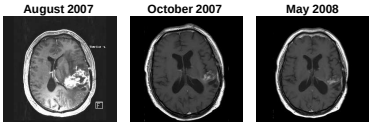

Figure 2: Two pts, both with partial responses. Pt (A) is a 52 year old woman with TTP of 526 days. Pt (B) is a 64 old man which had TTP of 342 days

Main outcome measures

- **Response Rate (RR), Evaluable pts (N=32)**
  - CR + PR (11/32) = 34,4%
  - SD (17/32) = 53,1%
  - Disease controle rate 28/32 = 87,5%
- **Median Overall Survival (OS)**
  - All pts (N=43) = 29 weeks (95% CI: 23-37 weeks)
  - Evaluable pts (N=32) = 34 weeks (95% CI: 25-43 weeks)
- **Median Time To Progression (TTP)**
  - Evaluable pts (N=32) = 24 weeks (95% CI: 16-31 weeks)
- **Progression Free Survival at 6 months (PFS-6)**
  - CR + PR (8/11) = 72,7%
  - SD + PD (5/21) = 23,8%
  - All pts (N=43) (13/43) = 30.2% (95% CI: 17-46%)

Figure 3

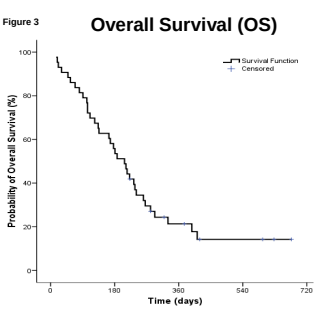

Figure 3: Kaplan-Meier estimate of Overall Survival (OS) for all pts included in this phase II trial (N=43).

Figure 4

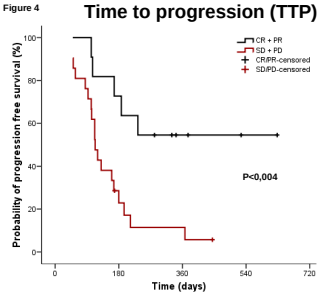

Figure 4: Kaplan Meier estimate showing Time To Progression (TTP) for evaluable pts (N=32). Black curve showing TTP for the total CR and PR pts whereas the red curve shows TTP for the total SD and PD pts.