

# Randomized phase II study of neoadjuvant bevacizumab and irinotecan versus bevacizumab and temozolomide followed by concomitant chemoradiotherapy in newly diagnosed primary glioblastoma multiforme

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## Background

**Background:** Concomitant temozolomide (T) and radiotherapy (RT) is standard of care in patients with newly diagnosed Glioblastoma multiforme (GBM) and good performance status (PS). Bevacizumab (B) and irinotecan (I) has shown activity in patients with recurrent disease with a significant number of responders. The response rate of temozolomide is around 10%, and increased response rates may indicate survival benefit. We tested bevacizumab combined with either temozolomide or irinotecan and concomitant radiotherapy as 1. line therapy in patients with newly diagnosed GBM. The aim of the study was to investigate if the combination of bevacizumab and irinotecan was sufficiently active to warrant a head-to-head comparison to Stupp's regimen combined with bevacizumab in a future randomized phase III trial.

## Methods

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**Endpoints:** The primary endpoint was response at 8 weeks. Secondary endpoints were 6 and 12-months PFS, overall survival (OS), safety and feasibility. Response was assessed every 8 weeks. Toxicity was assessed every 2 weeks.

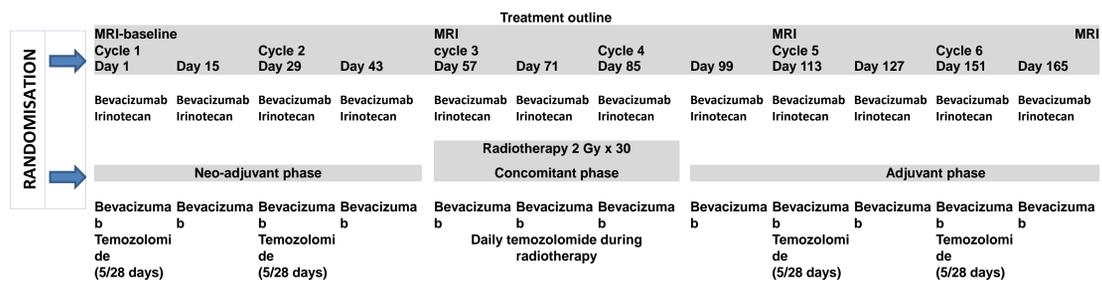
**Methods:** Pts with newly diagnosed GBM (previously untreated except for primary surgery/biopsy), were randomized to bevacizumab and irinotecan on days 1 and 14 (BI regimen) or to bevacizumab on days 1 and 14 and temozolomide on days 1-5 in a 28-day cycle (BT regimen) for 8 weeks, followed by radiotherapy (60 Gy/30 fractions/5 fractions per week) and concomitant BI or BT. Post-radiotherapy, chemotherapy was continued for 8 weeks.

**Protocol procedure:** A "two-stage" design was employed. A true response rate of 30% was considered worthy of further study, while a response rate of 10% would not. If  $\leq 1$  response was observed among the first 10 pts, inclusion to that specific experimental arm should be terminated. If  $\geq 2$  responses were observed, the inclusion was to be continued.

**Inclusion criteria:** 1) Signed informed consent, 2) Primary GBM, 3) No prior therapy except primary surgical resection or biopsy, 4) PS 0-2; 5) Age > 18 years, 6) Expected OS > 3 months, 7) Adequate organ function. 8) No sign of cerebral bleeding on cerebral MR-scanning at baseline

**Chemotherapy:** **Bevacizumab** was dosed 10 mg/kg every 14. days, intravenously. **Irinotecan** was dosed every 14. days. The dose was dependent on use of enzyme-inducing anti-epileptic drugs (EIAID) so the patients not on EIAED were dosed with irinotecan 125 mg/m<sup>2</sup> and patients on EIAED were dosed with 340 mg/m<sup>2</sup>. **Temozolomide** was administered differentially during the study: During the neo-adjuvant and the adjuvant part, temozolomide 200 mg/m<sup>2</sup> was given daily for 5 days followed by 23 days off (The dose in the first cycle was 150 mg/m<sup>2</sup> though). During radiotherapy, temozolomide 75 mg/m<sup>2</sup> was given daily.

**Radiotherapy:** Target was determined from fusion of CTC and baseline MRC. If PD after neo-adjuvant part, the largest target (baseline or 8-week MRC was used for radiotherapy planning. Planning is with Eclipse-system (Varian Medical Systems). **GTV** : The enhancing tumor on the post-contrast T1 image and/or the none-enhancing area on the T2 image on the baseline MR-scan. **CTV** : GTV + 2 cm margin, except for bony structures. Meningeal structures were considered anatomic barriers to tumor spread when appropriate. If present, operation cavity were included in the tumor volume. **ITV**: ITV=CTV. **PTV** : CTV + 0.5 cm margin for patient setup inconsistencies. Tolerance doses for organs at risk were as by Emami et al, IJROBP 1991, 21; 109-122. Radiotherapy was performed using a linear accelerator.



**Response evaluation:** Response evaluation was according to the MacDonald criteria, modified as described below.

**Complete response (CR):** A complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks with no new lesions. Patient should be off corticosteroids and with stable or improved clinical status.

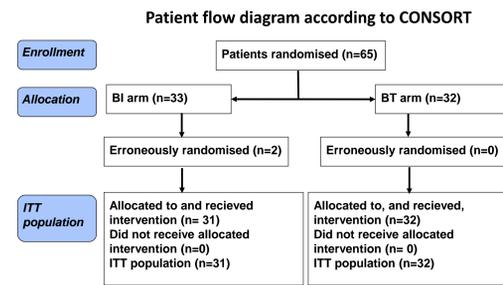
**Partial response (PR)** required a  $\geq 50\%$  decrease in the sum of products of perpendicular diameters of all measurable enhancing lesions compared with baseline with no new lesions, on stable or reduced corticosteroid dose and with stable or improved clinical status. **A minor response (mPR)** required a decrease of 25% or more of the product of perpendicular diameters of all measurable enhancing lesions compared to baseline but less than 50%, thus not qualifying for a formal PR. As with CR and PR, there could be no new lesions and corticosteroids and neurological status should be stable.

**Progressive disease (PD)** was defined as an increase of  $\geq 25\%$  in the sum of the products of perpendicular diameters of enhancing lesions, the appearance of new enhancing lesions or signs of clinical deterioration. **Stable disease (SD)** was declared if the patient did not qualify for complete response, partial response or progressive disease and was stable clinically. Because of the neo-adjuvant study design, it was not mandatory that PR or mPR could be confirmed at subsequent evaluations.

**Contrast enhancing (CE)** lesions <10 mm in diameter at baseline were not measurable but were evaluable. When such lesions increased in size to  $\geq 10$  mm they were included as measurable. CE lesions that were  $\geq 10$  mm in diameter at baseline were measurable and were followed as measurable, even if they decreased in diameter to <10 mm during therapy. Immediately following the chemo-radiotherapy, an aggravation of neurological symptoms necessitating dose-escalation of corticosteroids may be seen; however, this should not in itself be considered evidence of PD. In case of radiological progression on MRI within 2 months following the chemo-radiotherapy, PD was declared if this was confirmed on subsequent MRI or if the clinical condition deteriorated. If PD on MRI could not be confirmed, the increase in size of the lesion following chemo-radiotherapy was defined as **pseudoprogression (PsPD)**, and the status of the patient was SD. All MRI were reviewed by an expert neuroradiologist, blinded to treatment.

In some cases, the **blinded MRI review** diagnosed radiological progression in pts at a time when the evaluation clinically as well as determined by the day-to-day radiological service had not found progression, and PD was determined at the time of PD per the date determined by the blinded review. In other cases, the MRI review could not confirm radiological progression where this had been determined during the study, and these pts were censored for PD at the time they were taken off-study.

## Results



	Response after 8 weeks of neoadjuvant therapy	
	Bevacizumab - Temozolomide	Bevacizumab - Irinotecan
Complete response	0	0
Partial response	10	6
Minor response*	11	7
Stable disease	6	7
Progressive disease	4	6
Not evaluable	***1	**5

MRI were reviewed by an expert neuroradiologist, blinded to treatment. (\*) 50-75% of baseline. (\*\*) three patients had non-enhancing tumors at baseline, 2 had poor quality MR at 8 wks. All were clinical non-PD and received planned chemoRT. (\*\*\*) One patient had a non-enhancing tumor at baseline.

	ITT population: Patient characteristics	
	BT (n=32)	BI (n=31)
Median age (range)	62 (30 - 73)	59 (36 - 77)
ECOG performance status		
0	12	20
1	18	10
2	2	1
Male / Female	21 / 11	18 / 13
Surgical resection / biopsy only	30 / 2	28 / 3
Median dose prednisolone	25 mg	25 mg
25% - 75% range of doses	10 - 50 mg	12 - 50 mg*

Data on the prednisolone dose were missing from 5 patients on the BI-arm.

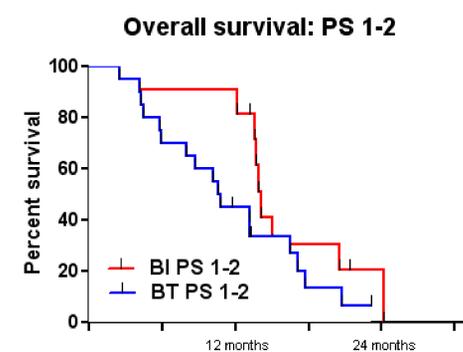
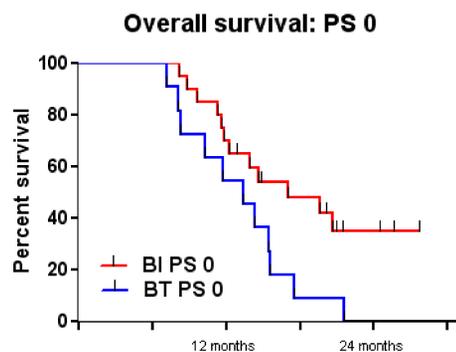
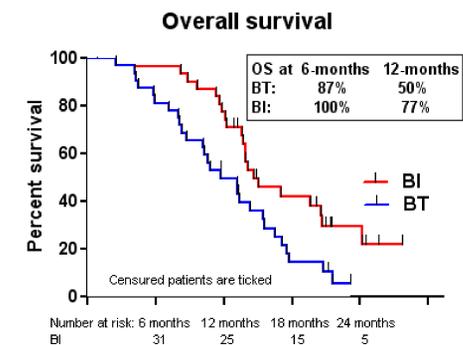
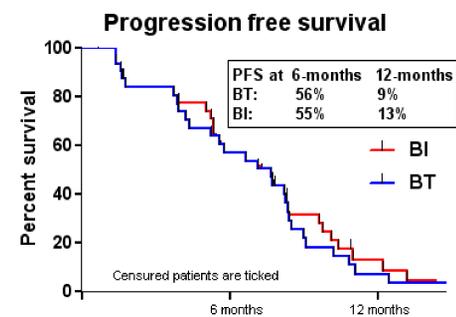
Two pts on the BI arm were not included in the analysis: One was claustrophobic and refused the MRI, and the other had a bleeding on the baseline MRI. Both were excluded from the study and were not included in the ITT population.

### Non-hematological toxicity from neoadjuvant therapy

Toxicity graded according to CTCAE criteria version 3.0	Bevacizumab-Temozolomide				Bevacizumab-Irinotecan			
	I	II	III	IV	I	II	III	IV
Nausea	8	4			11	2		
Emesis	7	1			2	1		
Diarrhoea	6				5	3		
Constipation	8	1			3			
Thrombosis	0							1
Alopecia	0				6	1		
Hypertension	7	5	3		7	3		
Fatigue	19	3	2		19	4		

The most severe toxicity for each patient during the first 2 cycles of neoadjuvant therapy is shown. The more common chemotherapy-induced toxicities are shown, as well as the types of toxicity that resulted in grade III or worse toxicity, are shown here. There were no wound-healing complications.

Side-effects were manageable and there were no apparent increased toxicity from the combined chemotherapy, bevacizumab and radiotherapy.



**PFS and survival:** The 6- and 12 months PFS were similar between the two treatment arms. **Survival** was significantly prolonged on the BI arm with a median survival of 445 days on the BI-arm vs. 337 days on the BT arm (p-value = 0.014 (Log-rank)). The median follow-up was 405 days (SD: 181). The number of pts were relatively small and the distribution of performance status was unbalanced, favouring the BI-arm and the observed survival benefit should be interpreted cautiously. When survival was stratified for PS (0 vs. 1-2), the improved survival from BI was still observed, most clearly in the good PS group. All pts were allowed to cross-over to the alternative regimen at time of PD.

## Conclusion

**The response rate** at 8 weeks seemed to favor the combination of bevacizumab and temozolomide compared to bevacizumab and irinotecan: If true PR and "minor responses" were combined for the analysis, then the increased response rate on the BT-arm was borderline statistically significant. However, it should be remembered that no formal statistical comparison of efficacy data were pre-planned, due to the relatively small sample sizes.

**PFS at 6- and 12 months** were similar between the arms., **Survival** was significantly better on the BI-arm. This may in part be explained by slightly unbalanced pt characteristics with regard to PS in favor of the BI-arm. Nevertheless, when analysis was stratified for PS (0 vs. 1-2) a survival benefit from BI was still suggested, most clearly in the good PS group. We will continue to update the survival data in the future.

**Neo-adjuvant chemotherapy** combined with bevacizumab did not seem to compromise outcome compared to historical results. Our response data support the strategy of combining bevacizumab with Stupp's regimen in 1. line therapy of GBM. On the other hand, the observed improved survival from BI was indeed intriguing and needs further consideration. If the current study had demonstrated a consistent significant benefit from BI compared to BT, we would have suggested a randomized study to compare BI plus radiotherapy to BT plus radiotherapy in the first line setting.

**The use of blinded critical review** of all MRI perhaps deflated our response rates as well as the 6- and 12 months PFS. The discussion of the validity of radiological evaluation of response/relapse in GBM is ongoing; however, in this study, it ensured unbiased and similar evaluations of all patients.