

# A phase II trial with bevacizumab and irinotecan for patients with primary brain tumors and progression after standard therapy



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## Background

- Primary brain tumors are devastating diseases that generally carry a poor prognosis.
- The combination of bevacizumab (B) and irinotecan (I) has shown promising efficacy in treating recurrent glioblastoma.
- The efficacy of B+I in the treatment of other primary brain tumors has not been established.

## Aim

- To investigate the efficacy of B +I in heavily pretreated patients with various recurrent brain tumors in a prospective phase II trial.
- Primary endpoints were progression free survival (PFS) and response rates (RR).
- Secondary endpoints were safety and overall survival.
- In case of promising response rates, more specific phase II trials were to be carried out for individual histologies.

## Materials and methods

- Patients were treated with intravenous bevacizumab 10 mg/kg and irinotecan 125/340 mg/m<sup>2</sup> every 14 days. Irinotecan dose according to use of EIAED or not. 2 treatments = 1 cycle.
- Evaluation was carried out every 8 weeks using magnetic resonance imaging (MRI) and Macdonald response criteria.
- On-study treatment consisted of 6 cycles of therapy. In case of clinical benefit, treatment could continue until progression, unmanageable toxicity or death.

Baseline patient characteristics	n= 85
Median age, years (range)	51 (21-71)
Gender	
male	45 (53%)
ECOG Performance status	
0	28 (33%)
1	39 (46%)
2	17 (20%)
Previous therapy	
radiation therapy	85 (100%)
extent of primary surgery	
needle biopsy only	17 (20%)
partial resection	36 (42%)
gross total resection	25 (29%)
re-resection(s) at any time	49 (58%)
chemotherapy	
1 line	71 (84%)
2 lines or more	10 (12%)

## Results

- 85 patients with various recurrent primary brain tumors were included (for histological diagnosis, please refer to table 2 below).
- 78 of these patients were evaluable after 2 cycles of chemotherapy.
- Follow-up for all patients was at least 6 months.
- Patients received a median of 4 cycles (range 0,5 – 25 cycles).

Table 2. Best Macdonald response for all histologies

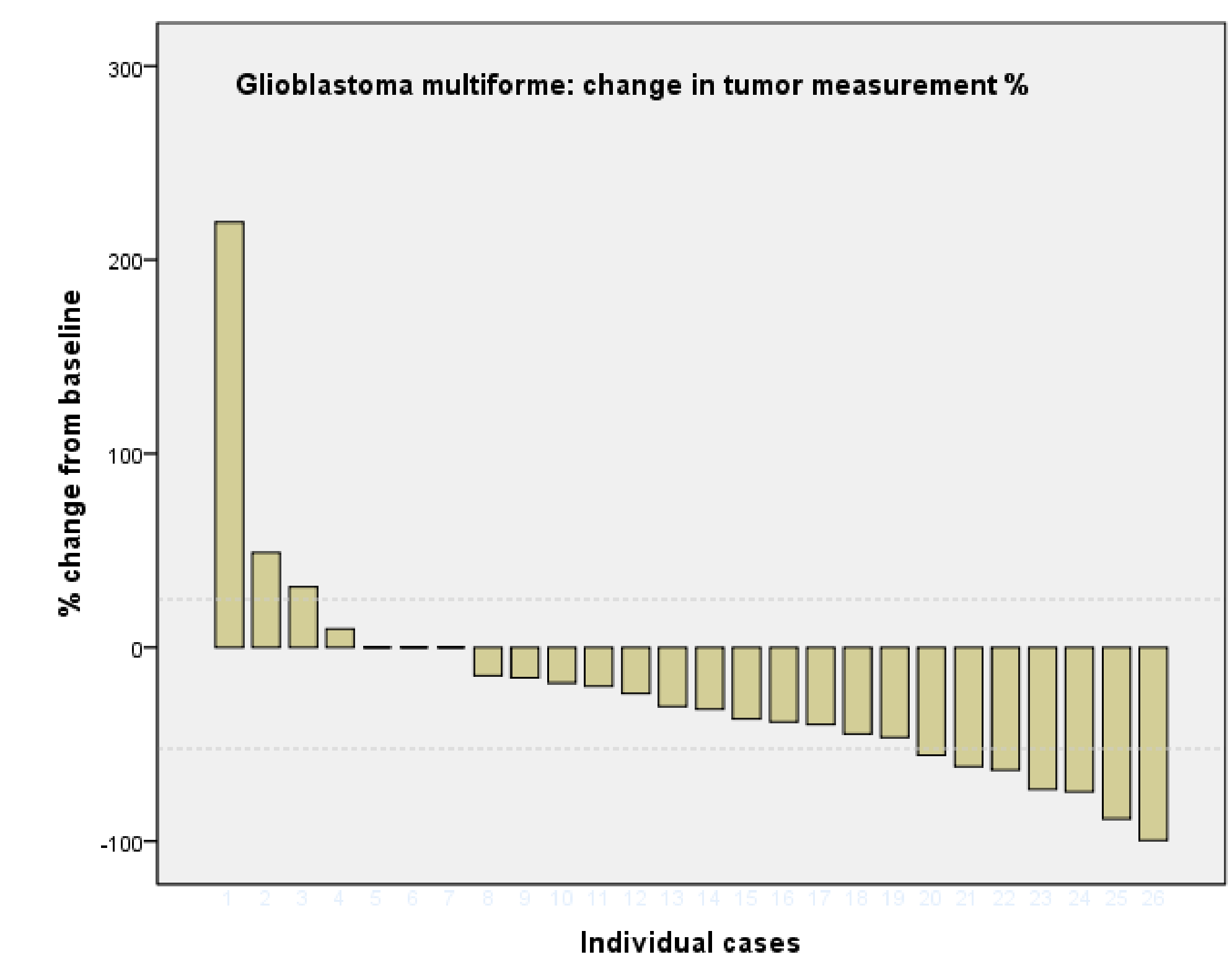
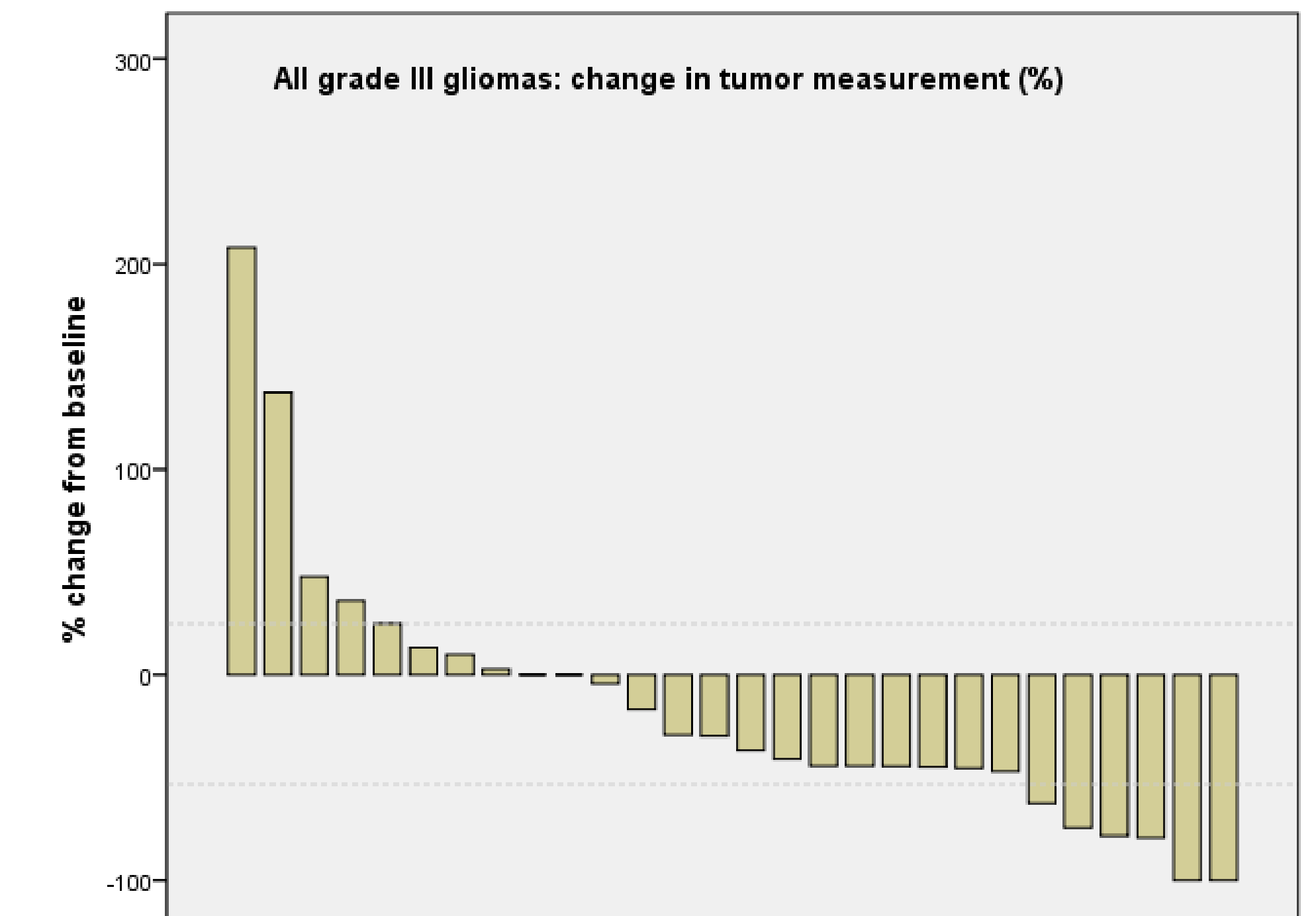
	CR	PR	SD	PD	NE	Total
Glioblastoma Multiforme WHO gr. IV	0	7 (22%)	18 (56%)	3 (9%)	4 (12%)	32
Anaplastic astrocytoma WHO gr. III	0	1 (6%)	8 (50%)	5 (31%)	2 (12%)	16
Anaplastic oligodendroglioma WHO gr. III	1 (11%)	2 (22%)	4 (44%)	2 (22%)	0	9
Anaplastic oligoastrocytoma WHO gr. III	1	1	3	2	0	7
Ependymoma WHO gr. III	0	0	1	1	0	2
Oligodendroglioma WHO gr. II	0	0	2	0	0	2
Oligoastrocytoma WHO gr. II	0	0	1	1	0	2
Astrocytoma WHO gr. II	0	1 (11%)	6 (67%)	1 (11%)	1 (11%)	9
Gliosarcoma	0	0	2	0	0	2
Medulloblastoma WHO gr. IV	0	1	0	0	0	1
Meningeoma WHO gr. III	0	0	1	0	0	1
Malignant Schwannoma WHO gr. IV	0	0	1	0	0	1
Prolactinoma	0	0	1	0	0	1
<b>Total</b>	<b>2</b>	<b>13</b>	<b>48</b>	<b>15</b>	<b>7</b>	<b>85</b>

Table 3. Endpoints for GBM, all grade III and all grade II gliomas

	ORR (CR+PR)	PFS Median (weeks)	PFS6	OS Median (weeks)
<b>Glioblastoma Multiforme (n=32)</b>	<b>21.8%</b>	<b>22.1</b>	<b>36 %</b>	<b>34</b>
<b>Glioma WHO gr. III (AA, AOD, AOA, ependymoma gr. III) (n=34)</b>	<b>17.6%</b>	<b>16.0</b>	<b>33%</b>	<b>29</b>
<b>Glioma WHO gr. II (astrocytoma, oligodendroglioma, oligoastrocytoma) (n=13)</b>	<b>7.6%</b>	<b>17.1</b>	<b>19%</b>	<b>28</b>

Table 4. Toxicity by CTCAE ver. 3.0

Toxicity	Grade I-II	Grade III-V
Fatigue	48.3 %	7.1 %
Nausea	51.8 %	1.2 %
Diarrhea	40.0 %	0 %
Proteinuria, all grades	15.3 %	
Hypertension	17.6 %	3.5 %
Neutropenia	11.7 %	4.8 %
Bleeding/thromboembolism	23.6 %	8.3 %
Gastrointestinal perforation		1.2 %



## Discussion

- Despite moderate Macdonald responses, B+I causes tumor regression in a majority of patients with grade III glioma or GBM.
- PFS and PFS6-rates in these groups compare favorably with historical results.
- Clinical benefit (CR+PR+SD) was also observed in non-glioma tumors.
- Only 1 partial response was observed among 13 patients with grade II histologies.
- Toxicity is frequent but mostly mild; the most common serious side effect was bleeding/thromboembolic events seen in 8.3% of patients.

## Conclusion

- B+I shows efficacy against grade III glioma and GBM and prolongs the median progression free survival.
- Non-glioma primary brain tumors are very rare and difficult to include in prospective clinical trials.