

Background

The receptor for epidermal growth factor, EGF-R is consistently found to be a relevant molecule in glioblastoma with overexpression, gene-amplification, mutation based variants and constitutive activation. Several reagents have been investigated for targeting the EGF-R molecule or the subsequent intracellular signalling pathway but this is the first phase III with a monoclonal antibody. Proof has been obtained in animal experiments that this antibody to some extent crosses the blood brain barrier (Fig.1). Nimotuzumab has a lower binding affinity than Cetuximab, therefore more selectively binding to cells overexpressing the target molecule.

A multicentre phase III trial in association with the German Glioma Network was designed following the promising results of pediatric phase II and III studies in resistant diffuse intrinsic pontine gliomas. The goal of this phase III in adults with newly diagnosed glioblastoma was to explore the safety and efficacy of the monoclonal anti-EGFR antibody nimotuzumab concomitantly to standard treatment in patients after resection or biopsy. The results are to be correlated to MGMT status and immunohistochemical analysis of EGF-R expression

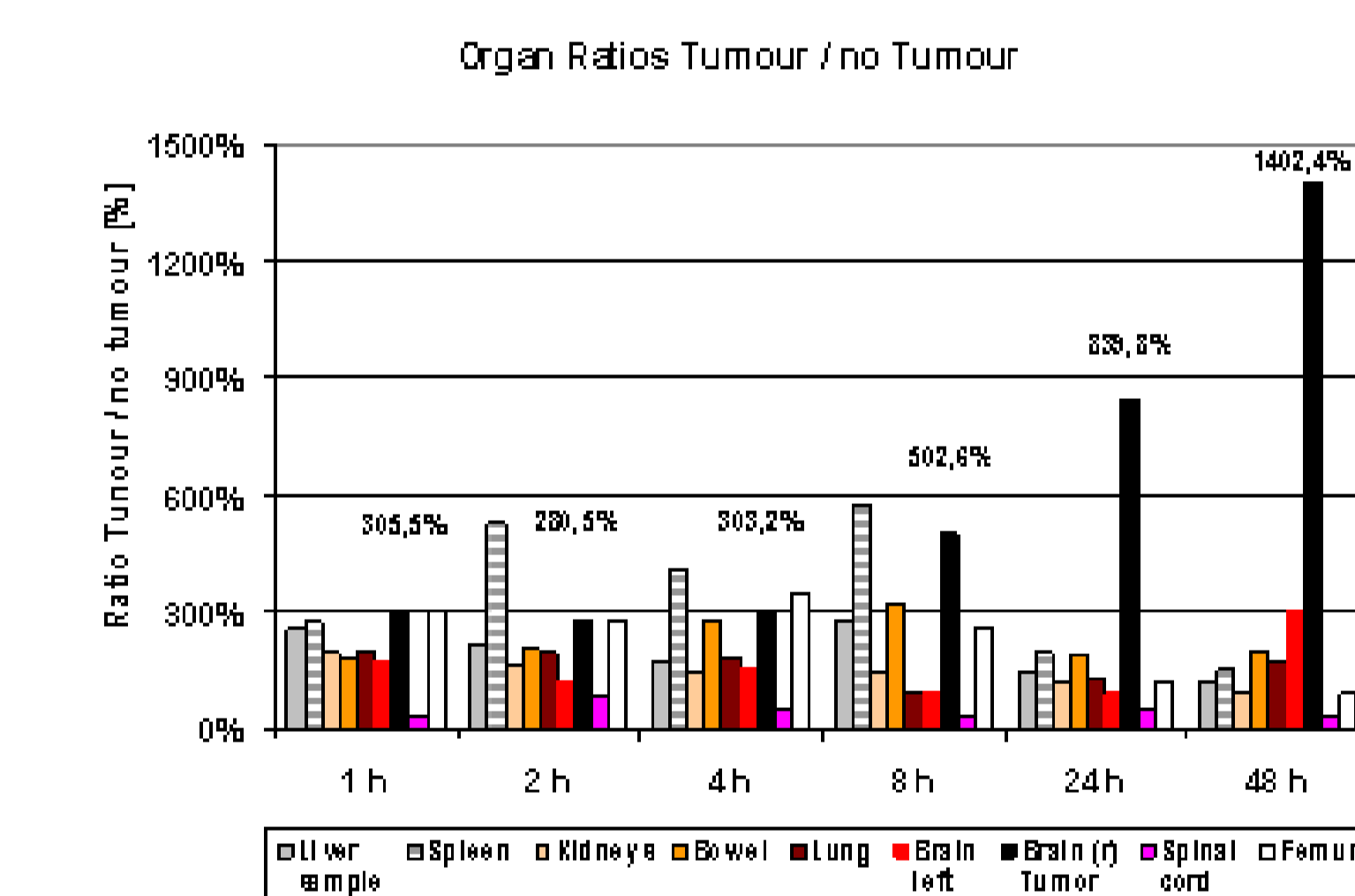


Figure 1 :

Kinetics of uptake of indium 111 labelled nimotuzumab in different organs and xenograft tumor (U87) after intravenous administration

Methods

Design

Multicentre, prospective, randomised, non-blinded, open-label, controlled, phase III study, no specification of resection status

Subject inclusion criteria

- Newly diagnosed GBM proven by histology following resection or biopsy
- Age ≥ 18 years to ≤ 70 years, both gender
- Performance status Karnofsky $\geq 70\%$
- MRI compatibility
- Able to consent
- Treatment in a study centre, availability of the patient during the study treatment and the ability to comply with the study plan

Subject exclusion criteria

- Other severe underlying disease or pre-existing serious conditions which bear the risk of an inadequate study treatment
- Prior antineoplastic therapy (chemo-, immuno-, radiotherapy)
- Prior administration of a recombinant human or murine antibody or known hypersensitivity to antibodies
- Simultaneous antineoplastic therapy other than the study treatment
- Pregnancy, lactating mother or inadequate contraception

Primary and secondary objectives

Primary: Progression-free survival (PFS) with the combination of target therapy with nimotuzumab and standard local radiotherapy

Secondary:

- overall survival
- response rate
- time to re-intervention
- toxicity profile
- symptom control
- quality of life.

Treatment

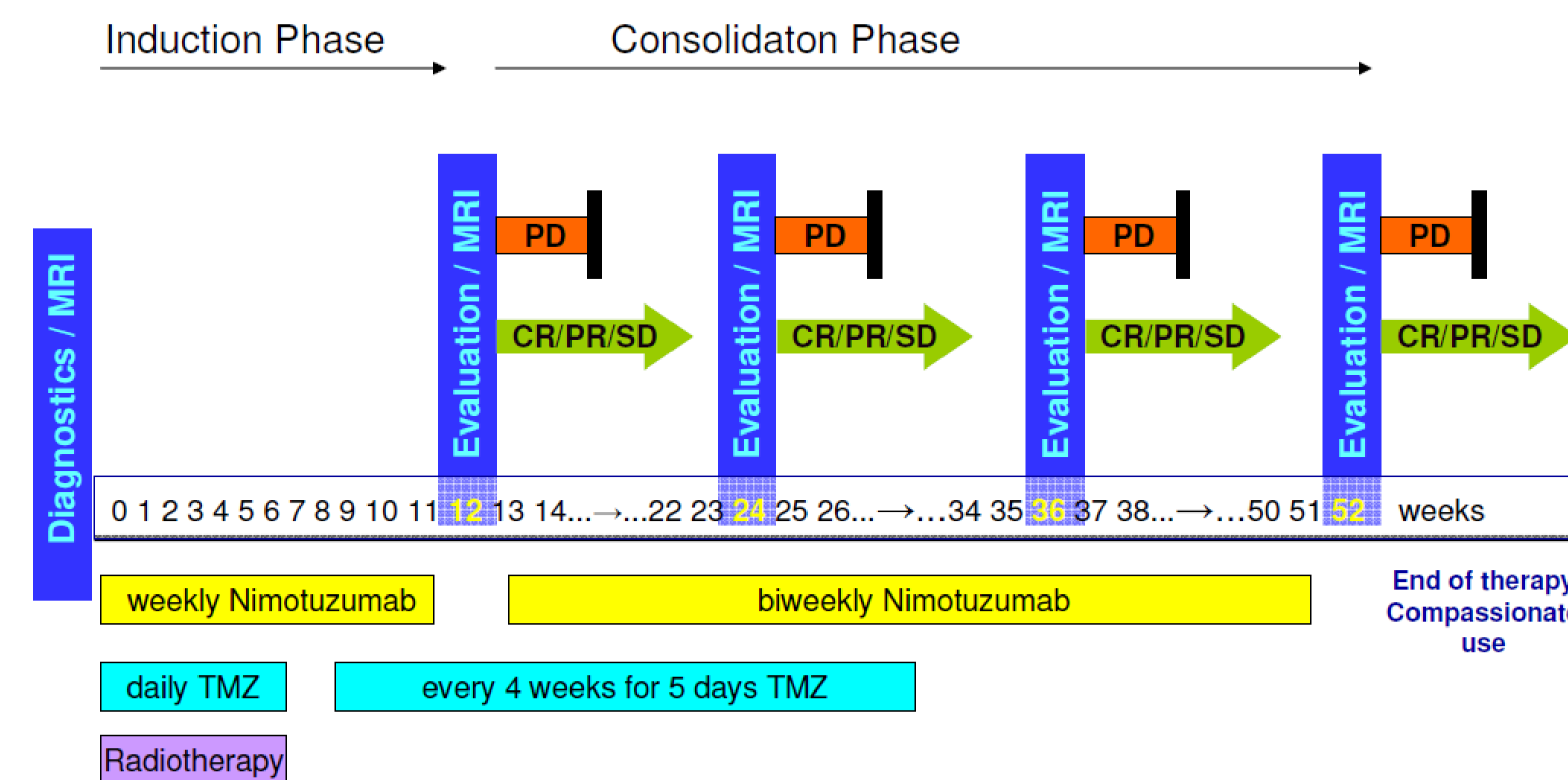


Fig. 2. Treatment regimen of the phase III study: simultaneous target therapy with nimotuzumab and standard focal radiotherapy consisting of induction w0-w11, consolidation I w13-w23, consolidation II w25-w35. MRI and clinical evaluation w12, w24 and w36; in rapidly progressive disease only clinical evaluation was performed. (CR...complete remission, PR...partial remission, SD...stable disease, PD progressive disease)

Results

Between August 2007 and March 2010 148 patients were enrolled in this study. 75 patients were evaluable for a protocol specified interim analysis.

Residual tumour		Arm A, Nimotuzumab (n=39)	Arm B (n=36)
yes	n (%)	21 (53.8)	20 (55.6)
no	n (%)	18 (46.2)	16 (44.4)

Table 1 : Resection Status of the first 75 Patients in the different treatment arms

Demographics

			Arm A (n=39)	Arm B (n=36)
Sex	male	n (%)	25 (64.1)	20 (55.6)
	female		14 (35.9)	16 (44.4)
Age (years)	Mean		54.54	55.44
	SD		10.24	8.95
Height (cm)	Mean		n=38 175.45	173.69
	SD		8.87	9.07
Weight (kg)	Mean		n=38 77.85	80.66
	SD		14.45	16.19
Body surface (m ²)	Mean		n=33 1.93	n=35 1.94
	SD		0.19	0.23

Toxicity

Treatment-emergent adverse events (TEAEs):

TEAEs	OSAG-101	Control
TEAEs	290	230
Pat. w. TEAEs	36 (92.3%)	25 (69.4%)
serious TEAEs	28	23
Pat w. sTEAEs	13 (33.3%)	12 (33.3%)

Most common TEAEs:

	OSAG-101	Control
Fatigue	25	20
Headache	17	15
Nausea	19	14
Vomiting	10	15
Thrombocytopenia	16	6
Rash	8	1
Pruritus	3	3

Conclusions

• Treatment groups are well balanced for demographic characteristics and the substrata of residual tumor and gross total resection

• Repeated applications of nimotuzumab simultaneously to standard therapy (concomitant radiation plus temozolamide followed by temozolamide alone according to the Stupp regimen) were well tolerated and safe in patients with newly diagnosed glioblastoma. Patients maintained an excellent quality of life and showed a favourable profile of adverse events

• No patient discontinued the study treatment due to an adverse event at least possibly related to the study medication

• The cytotoxic efficacy cannot yet be estimated in the first group of patients who completed one year of follow up