



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

London, 22 September 2014
EMA/695902/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Avastin

International non-proprietary name: BEVACIZUMAB

Procedure No.: EMEA/H/C/000582/II/0059

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



Table of contents

1. Background information on the procedure	6
1.1. Type II.....	6
1.2. Steps taken for the assessment of the product.....	7
1.3. Steps taken for the re-examination procedure	7
2. Scientific discussion	8
2.1. Introduction.....	8
2.2. Non-clinical aspects	9
2.2.1. Ecotoxicity/environmental risk assessment	9
2.2.2. Discussion on the non-clinical aspects	9
2.2.3. Conclusion on the non-clinical aspects.....	9
2.3. Clinical aspects	9
2.3.1. Introduction.....	9
2.3.2. Pharmacokinetics.....	10
2.3.3. Discussion on clinical pharmacology.....	13
2.3.4. Conclusion on clinical pharmacology	13
2.4. Clinical efficacy	13
2.4.1. Dose response study	13
2.4.2. Main study.....	14
2.4.3. Discussion on clinical efficacy.....	47
2.4.4. Conclusions on the clinical efficacy.....	51
2.5. Clinical safety	51
2.5.1. Introduction.....	51
2.5.2. Discussion on clinical safety	65
2.5.3. Conclusions on clinical safety	67
3. Benefit-Risk Balance.....	67
4. Recommendations	69
5. Attachments	Error! Bookmark not defined.

List of abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ATE	Arterial thromboembolic event
bFGF	basic fibroblast growth factor
B/R	Benefit/Risk
Bv	Bevacizumab
CHF	Congestive heart failure
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CVA	Cerebrovascular accident
DDI	Drug-drug interaction
EORTC	European Organisation for Research and Treatment of Cancer
FLAIR	Fluid-attenuated inversion recovery
GBM	Glioblastoma
Gd	Gadolinium
GI	Gastrointestinal
KPS	Karnofsky performance status
HR	Hazard ratio
HRQoL	Health-related quality of life
ICAM-1	Intercellular adhesion molecule-1
IHC	Immunohistochemistry
IL-8	Interleukin-8
IRF	Independent review facility
ITT	Intent-to-treat
KM	Kaplan-Meier
KPS	Karnofsky performance status
MAA	Marketing Authorisation Application
mBC	metastatic breast cancer
MedDRA	Medical dictionary for Drug Regulatory Affairs

MGMT	O6-methylguanine-DNA methyltransferase
MI	Myocardial infarction
MMSE	Mini Mental Status Examination
mRCC	metastatic renal cell carcinoma
MRI	Magnetic resonance imaging
NCI	National Cancer Institute (of USA)
NCIC	National Cancer Institute of Canada
NCF	Neurocognitive function
NSCLC	Non-small-cell lung cancer
OS	Overall survival
PD	Progressive disease
PDGF	Platelet-derived growth factor
PFS	Progression-free survival
PK	Pharmacokinetic
PI	Placebo
PIGF	Placental growth factor
PR	Partial response
PRES	Posterior reversible encephalopathy syndrome
PRO	Patient reported outcome
PSPD	Pseudoprogression
QLQ-BN20	Quality of Life Questionnaire-Brain Cancer Module
QLQ C-30	Quality of Life Questionnaire- Core 30
q2w	once every 2 weeks
q3w	once every 3 weeks
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria In Solid Tumors
Roche	F. Hoffmann-La Roche Ltd
RPA	Recursive partitioning analysis
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious AE
SAP	Safety analysis population
SOC	System organ class (MedDRA)

T and TMZ	Temozolomide
VEGF	Vascular endothelial growth factor
VEGFR	VEGF receptor
VTE	Venous thromboembolic event

1. Background information on the procedure

1.1. Type II

Pursuant to Article 16 variation of Commission Regulation (EC) No 1234/2008, Roche Registration Ltd submitted to the European Medicines Agency on 11 March 2013 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	International non-proprietary name:	Presentations:
Avastin	BEVACIZUMAB	See Annex A

The following variation was requested:

Variation requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for a new indication for the treatment of adult patients with newly diagnosed glioblastoma in combination with radiotherapy and temozolomide. Consequently, the MAH proposed the update of sections 4.2, 4.5, 4.8 and 5.1 of the SmPC. The Package Leaflet was proposed to be updated accordingly. Furthermore, the MAH took the opportunity to make some editorial changes in the SmPC and the PL.

The variation proposed amendments to the SmPC and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0235/2012 on the agreement of a Paediatric investigation plan and an EMA Decision CW/1/2011 on a class waiver on conditions.

At the time of submission of the application, the Paediatric investigation plan was not yet completed as the measure was deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 1411/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Dr Jens Ersbøll Co-Rapporteur: Ms Ingunn Hagen Westgaard

Submission date:	11 March 2013
Start of procedure:	29 March 2013
Rapporteur's preliminary assessment report circulated on:	21 May 2013
CoRapporteur's preliminary assessment report circulated on:	22 May 2013
PRAC overview and Advice:	13 June 2013
Rapporteur Revised Assessment Report:	21 June 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	27 June 2013
MAH's responses submitted to the CHMP on:	20 September 2013
PRAC RMP AR:	7 November 2013
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	12 November 2013
2 nd Request for supplementary information and extension of timetable adopted by the CHMP on:	21 November 2013
SAG experts meeting to address questions raised by the CHMP	8 January 2014
MAH's responses submitted to the CHMP on:	20 March 2014
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	23 April 2014
CHMP opinion:	22 May 2014

1.3. Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Robert Hemmings Co-Rapporteur: George Aislaitner

Written notice to the EMA to request a re-examination of Avastin CHMP opinion of 22 May 2014	5 June 2014
Rapporteur's appointment	CHMP meeting 26 June 2014
Detailed grounds for the Re-examination (Appendix 2 of Final Opinion) submitted on	22 July 2014

Start of procedure:	23 July 2014
Rapporteur assessment report	28 August 2014
Co-Rapporteur assessment report (Annex 2).	22 August 2014
Joint Rapporteur's updated assessment report circulated on:	16 September 2014
An Oral explanation on the detailed grounds for re-examination took place on:	22 September 2014
CHMP opinion:	22 September 2014

2. Scientific discussion

2.1. Introduction

Overall, gliomas account for 70% of adult malignant primary brain tumours (Ricard, D., et al., 2012). The incidence of malignant glioma is ~5/100 000 and may develop at all ages, the peak incidence being in the fifth and sixth decades of life. Malignant glioma comprises of glioblastoma [World Health Organization (WHO) Grade IV], anaplastic astrocytoma (WHO Grade III), mixed anaplastic oligoastrocytoma (WHO Grade III) and anaplastic oligodendroglioma (WHO Grade III) (Stupp, R., et al., 2010).

Glioblastoma (GBM) is the most frequent primary malignant brain tumour occurring in adults, and has the worst prognosis. Less than 3% of glioblastoma patients are still alive at 5 years after diagnosis, higher age being the most significant predictor of poor outcome (Ohgaki H, Kleihues P, 2005, Sant M. at al., 2011). GBMs only very rarely disseminate outside the Central Nervous System (CNS) and relapse usually occurs at the original tumour site.

GBM can develop at any site within the central nervous system but is most commonly located in the cerebral hemisphere. Surgical debulking of tumour may diminish or alleviate symptoms associated with mass effect. Symptomatic management is also effective in controlling seizures (anti-epileptic medications) and cerebral edema (corticosteroids). However, all patients with GBM eventually develop tumour progression and associated symptomatic deterioration.

Current treatment option in newly diagnosed glioblastoma include Temozolomide in combination with radiotherapy based on a survival benefit compared to radiotherapy alone.

Bevacizumab (Avastin) is a recombinant humanised monoclonal antibody. It inhibits angiogenesis by neutralising all isoforms of human vascular endothelial growth factor (VEGF), and blocking their binding to VEGF receptors.

Avastin was approved in the European Union (EU) on 12 January 2005 for the first-line treatment of patients with metastatic cancer of the colon or rectum (mCRC), in combination with intravenous 5-fluorouracil/folinic acid or intravenous 5-fluorouracil/folinic acid/irinotecan. Following this, Avastin was approved for the treatment of locally recurrent and metastatic breast cancer, for non-small cell lung cancer (NSCLC), for renal cell cancer, for the first-line ovarian cancer, and in combination with carboplatin and gemcitabine for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents.

This variation concerns an application for extension of the approved indications for Avastin. The MAH applied for the indication:

“Avastin, in combination with radiation and temozolomide, is indicated for the treatment of patients with newly diagnosed gliomas (WHO Grade III or IV)”.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application.

2.2.1. Ecotoxicity/environmental risk assessment

There was no environmental risk assessment submitted as part of this application.

2.2.2. Discussion on the non-clinical aspects

A justification for not providing an updated Environmental Risk assessment for this new indication has been submitted by the MAH. This is in accordance with the Guideline on the Environmental Risk assessment for Human medicinal products (EMA/CHMP/SWP/4447/00, 2006) which states that for certain pharmacologically active substances, among others proteins, such is possible, as these substances are unlikely to result in significant risk to the environment.

Bevacizumab is a monoclonal antibody that is a recombinant humanised immunoglobulin of isotype IgG1 and as a protein bevacizumab is exempted from providing an ERA.

2.2.3. Conclusion on the non-clinical aspects

There are no new non-clinical data submitted as part of this application and the absence of an ERA is considered acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trial was performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Protocol No.	Location of Synopsis (Module 2) Location of Report (Module 5)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
5.3.5 Efficacy and Safety Studies								
BO21990	Synopsis CSR CSR-addendum (BM)	To investigate the efficacy and safety of Bv, temozolomide, and radiotherapy followed by 6 cycles maintenance with Bv and temozolomide. Primary: OS and PFS Secondary: PFS (IRF), 1 and 2 year OS rate, HRQoL, safety	Phase III, randomized, double-blind, multicenter, parallel group, placebo with RT/T active control	(Bv+RT/T arm) Bv10 mg/kg.q2w IV for 6 wks concurrent with RT (2.0 Gy fractions 5 days/wk to a total dose of 60.0 Gy) and T (75 mg/m ² qd p.o.), followed by a treatment break for 4 wks. Then maintenance Bv10 mg/kg.q2w and T (150-200 mg/m ² day 1-5 of each 28 day cycle) for max 6 cycles. Then Bv15 mg/kg.q3w as a single-agent. (PI+RT/T arm) – as above but with PI instead of Bv	Total 921 (458 Bv+RT/T 463 PI+RT/T)	Patients with newly diagnosed supratentorial GBM, histologically confirmed after surgical resection or biopsy, no previous chemotherapy or RT	Bv/PI until PD or unacceptable toxicity. T, 6 wks with RT followed by 6 cycles (each of 28 days duration). RT for up to 6 wks	Follow-up for overall survival. Full CSR

Bv, bevacizumab; GBM, glioblastoma (WHO Grade IV malignant glioma); HRQoL, health-related quality of life; IV, intravenous administration; PD, disease progression; PI, placebo; p.o., oral administration; qd, once daily; q2w, once every 2 weeks; q3w, once every 3 weeks; RT, radiotherapy; T, temozolomide; wks, weeks.

2.3.2. Pharmacokinetics

Pharmacokinetic interaction studies

The potential of drug-drug interaction (DDI) between bevacizumab and temozolomide was evaluated in a substudy of pivotal Study BO21990.

The BO21990 DDI substudy was conducted during the maintenance phase, which followed a treatment break after the concurrent treatment phase in Study BO21990. During the maintenance phase, patients received temozolomide and bevacizumab or placebo for six 28-day cycles or until disease progression or unacceptable toxicity. During the first cycle of the maintenance phase, temozolomide was to be taken orally on the first 5 days of the 28-day cycle at dose of 150 mg/m²/day. For subsequent cycles, the dose of temozolomide was to be escalated to 200/mg/m² if permitted by the patient's haematologic and non-haematologic toxicity profile (according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3). Bevacizumab or placebo (10 mg/kg every 2 weeks) was administered to patients on Days 1 and 15 of each 28-day cycle.

The number of patients included in the substudy was 14 in the temozolomide/bevacizumab (T/B) arm and 6 in the temozolomide/placebo (T/P) arm. Samples for bevacizumab were obtained predose and postdose on Day 1 of Cycles 1, 2, 3 of the maintenance phase. Samples for temozolomide were obtained predose, 15 min, 30 min, 1, 1.5, 2, 3, 4, 6, and 8 hrs postdose on Day 1 of Cycle 1 of the maintenance phase.

The PK outcome measures for the BO21990 DDI substudy were to summarize the observed plasma temozolomide concentrations and estimate the PK parameters (AUC, T_{max}, C_{max}) for patients in the placebo (PI + RT/T) and bevacizumab (Bv + RT/T) treatment arms at Cycle 1, Day 1 of the maintenance phase. In addition, the observed serum bevacizumab trough and peak concentrations in patients in the bevacizumab treatment arm during Cycles 1, 2, and 3 during the maintenance phase were to be summarized and the observed bevacizumab exposures compared with the predicted exposure from PPK simulations based on the dose regimen in Study BO21990.

Results

Figure 1 and Table 1 show the observed Bv concentrations from samples collected pre-dose and post-dose during Maintenance Phase Cycles 1-3.

Figure 1. Observed Bevacizumab Concentrations and Visual Predictive Check

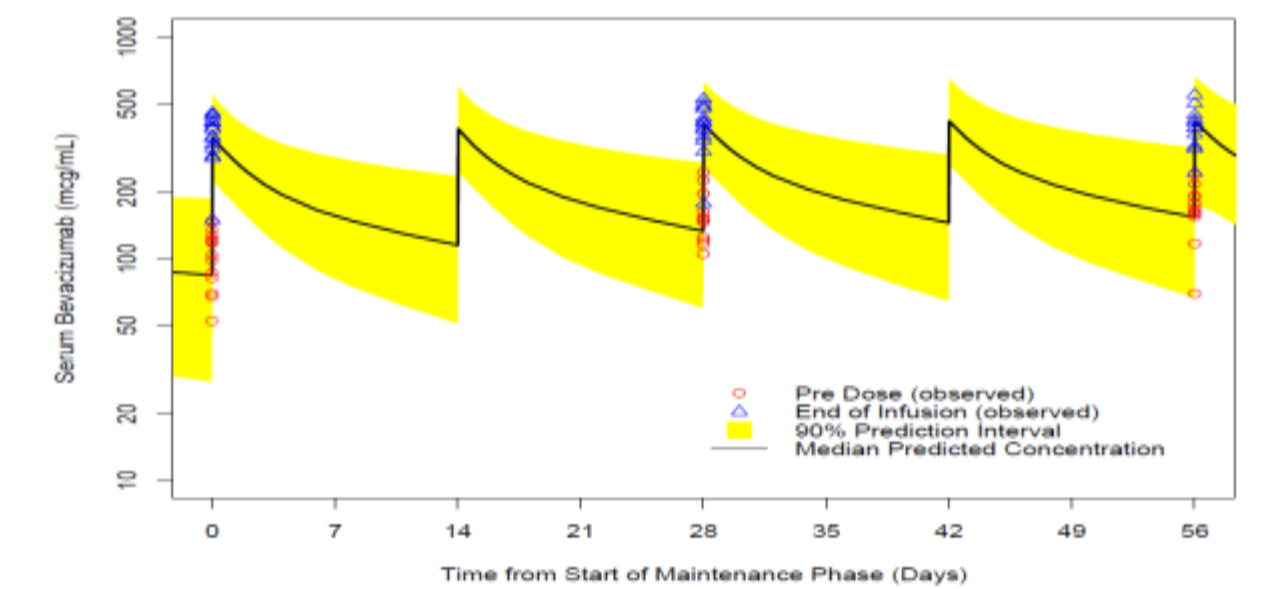
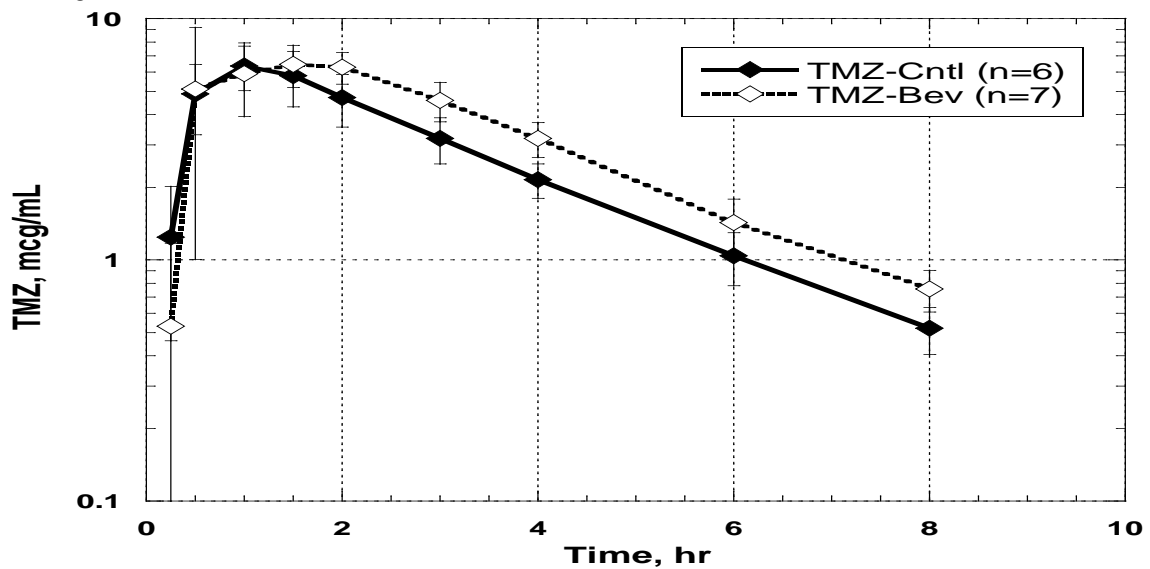


Table 1. Summary of Observed and Predicted Bevacizumab Serum Concentrations

Cycle/Day:	Cycle 1- Day 1 pre-dose	Cycle1 1- Day 1 post-dose	Cycle 2- Day 1 pre-dose	Cycle 2- Day 1 post-dose	Cycle 3- Day 1 pre-dose	Cycle 3- Day1 post-dose
N:	13	14	13	13	12	12
Observed Median:	104.0	369.5	153.0	407.0	172.5	399.5
Predicted - Median:	85.2	354.9	133.4	406.0	152.5	418.5
Prediction - 5th:	27.8	225.6	59.9	258.2	66.5	174.5
Prediction - 95th:	186.9	554.5	269.3	632.0	312.6	667.0

The plasma concentration time profile for TMZ is shown in Figure 2.

Figure 2. B021990 DDD substudy: Mean±SD Temozolomide Plasma Concentration –Time Profiles by Treatment Arm



Temozolomide PK parameter estimates for patients in the placebo and bevacizumab arms are summarized in Tables 2 and 3, respectively.

Table 2. BO21990 DDI Substudy: Temozolomide Pharmacokinetics in the Placebo Arm**(PI + RT/T)**

	AUC _{all} (µg•hr/mL)	T _{max} (hr)	C _{max} (µg/mL)	t _{1/2} (hr)
n	6	6	6	6
Mean	20.98	0.92	6.71	1.91
SD	3.38	0.20	0.74	0.14
%CV	16.1	22.3	11.0	7.6
Minimum	14.20	0.50	6.01	1.66
Maximum	23.60	1.00	8.09	2.06
Median	22.05	1.00	6.46	1.95

Table 3. BO21990 DDI Substudy: Temozolomide Pharmacokinetics in the Bevacizumab Arm**(Bv + RT/T)**

	AUC _{all} (µg•hr/mL)	T _{max} (hr)	C _{max} (µg/mL)	t _{1/2} (hr)
n	7	7	7	7
Mean	25.87	1.43	7.83	1.92
SD	2.52	0.53	2.15	0.24
%CV	9.8	37.4	27.5	12.7
Minimum	22.40	0.50	5.37	1.61
Maximum	29.10	2.00	12.00	2.33
Median	25.80	1.50	7.67	1.90

2.3.3. Discussion on clinical pharmacology

A substudy of BO21990 investigating potential drug-drug interaction when bevacizumab is added to temozolomide treatment did not reveal any influence of temozolomide on bevacizumab exposure. The temozolomide exposure seems to be moderately increased by the presence of bevacizumab. The substudy included only 6 patients treated with temozolomide. No firm conclusions can be drawn on the potential for bevacizumab to modify the exposure of temozolomide. However, no DDI is expected between a monoclonal antibody like bevacizumab and a small molecule like temozolomide.

2.3.4. Conclusion on clinical pharmacology

Although data from a substudy of BO21990 indicate that temozolomide exposure seems to be moderately increased by the presence of bevacizumab, no DDI is expected between a monoclonal antibody like bevacizumab and a small molecule like temozolomide.

2.4. Clinical efficacy

2.4.1. Dose response study

No new studies have been carried out in the claimed population (see discussion on Clinical efficacy).

2.4.2. Main study

BO21990 (Avaglio)

This was a randomized, double-blind, placebo controlled, multicenter Phase III trial of bevacizumab, temozolomide and radiotherapy, followed by bevacizumab and temozolomide versus placebo, temozolomide and radiotherapy followed by placebo and temozolomide in patients with newly diagnosed glioblastoma.

Methods

Study participants

Inclusion Criteria

- Newly diagnosed supratentorial GBM with a tissue diagnosis that has been established following either a surgical resection or biopsy. This includes treatment-naïve - (chemotherapy and radiotherapy) - patients with prior diagnosis of a lower grade astrocytoma that has been upgraded to a histologically verified GBM
- Craniotomy or intracranial biopsy site must be adequately healed, free of drainage or cellulitis, and the underlying cranioplasty must appear intact at the time of randomization. Trial treatment should be initiated > 28 days and ≤ 49 days following the last surgical procedure (including biopsy, surgical resection, wound revision, or any other major surgery involving entry into a body cavity)
- WHO performance status ≤ 2
- At least 1 formalin fixed paraffin embedded tumour tissue block representative of GBM available for pathology central review and analysis of MGMT status. If tumour block was not available or not of adequate quality, sufficient pathology material, representative of GBM, was to be available for central review.
- Stable or decreasing corticosteroids dose within 5 days prior to randomization
- Adequate haematological function: absolute neutrophil count (ANC) ≥ 1.5 x 10⁹/L; platelet count ≥ 100 x 10⁹/L; Haemoglobin ≥ 10 g/dL (may be transfused to maintain or exceed this level)
- Adequate liver function: total bilirubin ≤ 1.5 x ULN; AST and ALT ≤ 2.5 x ULN
- Adequate renal function: creatinine ≤ 1.25xULN; urine dipstick for proteinuria < 2+. Patients discovered to have ≥ 2+ proteinuria on dipstick urinalysis at baseline should undergo a 24 hour urine collection and must demonstrate ≤ 1.0 g of protein in 24 hours OR Urine protein/creatinine ratio (UPC) ≤ 1.0
- International normalized ratio (INR) or PT (secs) and activated partial thromboplastin time (aPTT):
a) in the absence of therapeutic intent to anticoagulate the subject: INR ≤ 1.5 or PT ≤ 1.5 x ULN and aPTT ≤ 1.5 x ULN , b) in the presence of therapeutic intent to anticoagulate the subject: INR or PT and aPTT within therapeutic limits (according to the medical standard in the institution)

Exclusion Criteria

- Evidence of recent haemorrhage on postoperative MRI of the brain. However, patients with clinically asymptomatic presence of hemosiderin, resolving haemorrhagic changes related to surgery, and presence of punctate haemorrhage in the tumour are permitted entry into the study

- Previous centralized screening for MGMT status for enrolment into a clinical trial
- Any prior chemotherapy (including carmustine-containing wafers (Gliadel) or immunotherapy (including vaccine therapy)) for glioblastomas and low grade astrocytomas
- Any prior radiotherapy to the brain or prior radiotherapy resulting in a potential overlap in the radiation field

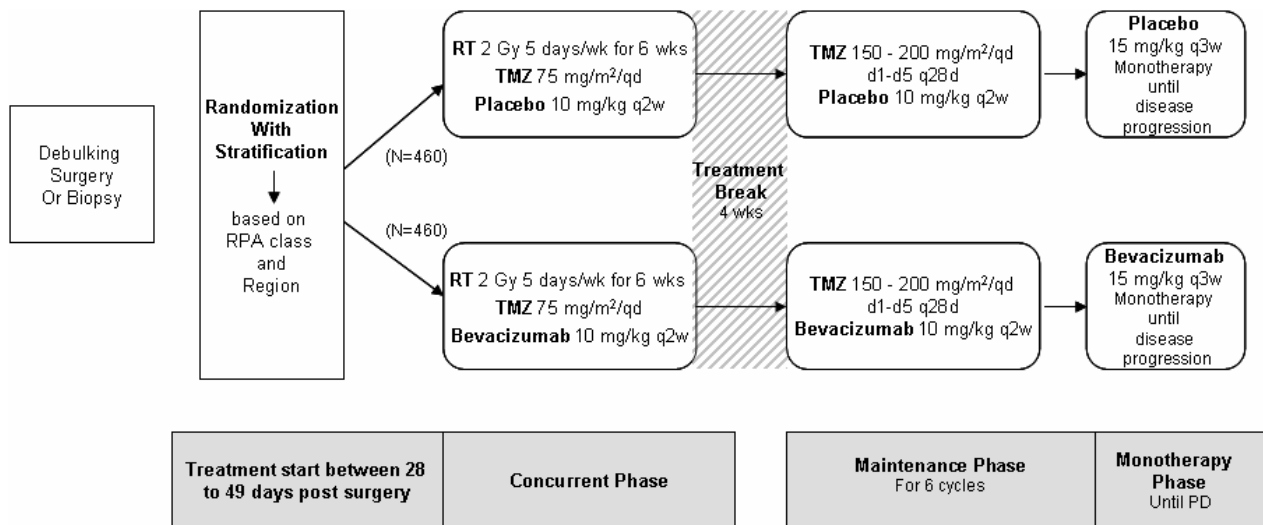
Bv-related Exclusion Criteria

- Inadequately controlled hypertension (defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure >100 m Hg)
- Prior history of hypertensive crisis or hypertensive encephalopathy
- New York Heart Association (NYHA) Grade II or greater congestive heart failure
- History of myocardial infarction or unstable angina within 6 months prior to randomization
- History of stroke or TIAs within 6 months prior to randomization
- Significant vascular disease (e.g. aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to randomization
- History of \geq grade 2 haemoptysis according to the NCI-CTC criteria within 1 month prior to randomization
- Evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic anticoagulation)
- Major surgical procedure, open biopsy, intracranial biopsy, ventriculoperitoneal shunt or significant traumatic injury within 28 days prior to randomization
- Core biopsy (excluding intracranial biopsy) or other minor surgical procedure within 7 days prior to randomization. Placement of a central vascular access device if performed within 2 days prior to Bv/placebo administration
- History of abdominal fistula or gastrointestinal perforation within 6 months prior to randomization
- History of intracranial abscess within 6 months prior to randomization
- Serious non-healing wound, active ulcer or untreated bone fracture

Treatments

Trial treatment was to start between 4 and 7 weeks after debulking surgery or biopsy of the GBM. Trial treatment consisted of three phases as described in Figure 3.

Figure 3. Study design



If adverse events occurred that necessitated delaying bevacizumab, the dose would remain unchanged once treatment resumed. Patients could be withdrawn from any of the trial treatment components (radiotherapy, TMZ or Bv), or from any combination of these three treatment components, however if radiotherapy was discontinued all trial treatment was to be discontinued.

Objectives

The primary objectives of the study were to demonstrate superiority in progression-free survival (PFS) as assessed by the investigator and in overall survival (OS) when Bv is added to TMZ with radiotherapy (Stupp regimen) followed by TMZ for the treatment of patients with newly diagnosed GBM.

Secondary objectives included the comparison of PFS as assessed by an independent review facility (IRF) between treatment arms the comparison of 1-year and 2-year survival rates between treatment arms the evaluation and comparison of the safety profile between treatment arms and the comparison of health-related quality of life (EORTC QLQ C-30, BN-20) between treatment arms.

Exploratory Objectives

To compare the objective response rate (ORR), and the duration of objective response, between treatment arms

To assess and compare OS and PFS between and within arms in relation to MGMT status

To compare neurocognitive function (NCF) using MMSE between treatment arms

To explore and compare the use of corticosteroids between treatment arms

To explore and compare the signs and symptoms related to GBM and patient's KPS between treatment arms

To explore and compare the patterns of tumour progression between treatment arms

Substudy Objectives

To compare neurocognitive function between treatment arms

To explore and compare the correlation between the neurocognitive function and the BO21990 efficacy outcome measures within and between treatment arms

To measure the effect of Bv on the pharmacokinetics of TMZ

To characterize the effect of TMZ on the pharmacokinetics of Bv

Outcomes/endpoints

The co-primary endpoints of this trial were OS defined as the time from randomization to death due to any cause and PFS as assessed by the investigator, defined as the time from randomization until the first date of either objective disease progression (using adapted MacDonald Response Criteria) or death due to any cause. Disease progression was based on radiographic or photographic evidence, and assessments made by the investigator according to RECIST v1.1.

The key secondary endpoints were the following:

- PFS as assessed by an independent review facility (IRF).
- One-year and two-year overall survival defined as the percentage of patients who are still alive at 1 year and 2 years post-randomization, respectively.
- Health-related quality of life (HRQoL) Changes. HRQoL was assessed by a core instrument of the EORTC (EORTC QLQ-C30) supplemented by a brain cancer specific module (EORTC BN20).

The EORTC QLQ-C30 is a 30-item self-report questionnaire on which patients rate the items on a 4-point scale, from 1 "not at all" to 4 "very much" (except for the global health status and QoL items on a 7-point scale, from 1 "very poor" to 7 "excellent"). The instrument measures five functional multi-item scales (physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning), three symptoms scales (fatigue, pain, nausea and vomiting), six single-item measures (dyspnea, insomnia, anorexia, constipation, diarrhea, and financial impact) and a global health status/QoL scale.

The EORTC BN20 consists of four multi-item scales (future uncertainty, visual disorder, motor dysfunction, communication deficit) and seven single-item measures (headache, seizures, drowsiness, hair loss, itching, difficulty with bladder control, and weakness of both legs).

Adapted MacDonald criteria are presented in Table 4 below.

Table 4 . Disease Assessment based on Adapted Macdonald Criteria

Response	Macdonald	AVAglio (Adapted Macdonald)
CR ^a	<ul style="list-style-type: none"> • Disappearance of all enhancing measurable and nonmeasurable disease (sustained for ≥4 weeks) • No new lesions • Clinically stable or improved • No corticosteroids 	<ul style="list-style-type: none"> • Disappearance of all index lesions (enhancing, measurable) sustained for ≥4 weeks) • No worsening of all non-index (non-enhancing and enhancing) lesions (sustained for ≥4 weeks) • No new lesions • Improved or stable neurologic symptoms • Corticosteroid dose must not exceed physiologic levels

PR ^a	<ul style="list-style-type: none"> • ≥50% decrease of all measurable enhancing lesions (sustained for ≥4 weeks)^c • No new lesions • Clinically stable or improved • Stable or reduced corticosteroid dose 	<ul style="list-style-type: none"> • ≥50% decrease of all index lesions (sustained for ≥4 weeks)^c • No progression of non-index (non-enhancing and enhancing) lesions • No new lesions • Improved or stable neurologic symptoms • Stable or reduced corticosteroid dose^d
SD ^a	<ul style="list-style-type: none"> • Does not qualify for CR, PR, or progression • Clinically stable 	<ul style="list-style-type: none"> • Does not qualify for CR, PR, or progression • Improved or stable neurologic symptoms • Corticosteroid dose alone does not affect determination of SD
Progression ^b	<ul style="list-style-type: none"> • ≥25% increase of enhancing lesions^c • Any new lesion • Clinical deterioration 	<ul style="list-style-type: none"> • ≥25% increase of index lesions^c • Unequivocal progression of existing non-index lesions (non-enhancing and enhancing) • Any new lesion • Neurological worsening (only applies if corticosteroid dose^d is stable or increased) with no need for a confirmatory scan

^a Response (CR, PR or SD) required all of the criteria shown to be met;

^b Progression required that any of the criteria shown were met – no confirmatory scan was needed

^c Measured by sum of the products of perpendicular diameters;

Exploratory Parameters

The following exploratory efficacy parameters were defined in the protocol and were analysed descriptively:

Objective response rate (ORR) based on adapted Macdonald criteria.

Duration of response, defined as time between first response and disease progression or death due to any cause. Patients without an event were censored at the date of last follow up for progression.

OS and PFS in relation to MGMT status. Subgroup analyses of OS and PFS by treatment arm according to MGMT status were performed.

Change over time in neurocognitive function (NCF) according to the MMSE.

Extent of corticosteroid use over time.

Change over time in signs and symptoms related to GBM.

Change in KPS over time.

Patterns of tumour progression.

Sample size

The sample size was based on a calculation assuming a 42 month recruitment period and minimum follow up of approximately 17 months for the last patient enrolled.

For the OS endpoint, assuming a median survival duration of 18.3 months in the bevacizumab and temozolomide arm and 14.6 months in the placebo and temozolomide arm (corresponding to a hazard ratio of 0.80, or a reduction in the immediate risk of death by 20%), then 683 events would be required to achieve 80% power of the log rank test at a 2-sided overall 4% alpha level. This calculation included two interim analyses at approximately 50% and 72% of events (the final PFS analysis was to be performed at the time of the second interim analysis).

For the PFS endpoint, assuming a median PFS duration of 9.1 months in the bevacizumab and temozolomide arm and 7 months in the placebo and temozolomide (corresponding to a hazard ratio of

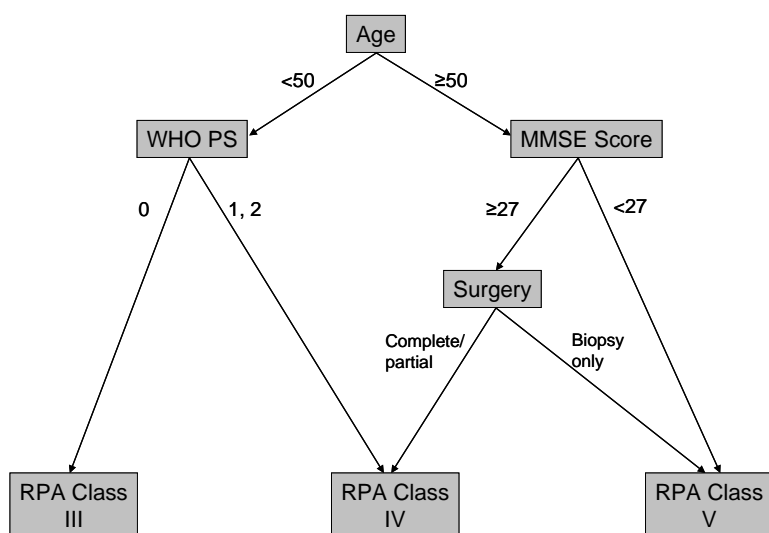
0.769, or a reduction in the immediate risk of progression or death by 23%), 677 events were required to achieve 80% power of the log rank test at a 2-sided 1% alpha level. In the event that less than 72% of OS events had occurred at the time of the PFS analysis (i.e. less than 492 of the 683 death events required), the PFS analysis would be delayed until at least 72% of OS information was available. In order to see the required number of events in the timeframe defined above, and to allow for a 10% dropout rate in PFS at 3 years, and a 5% dropout rate in survival at 4 years, 460 patients per treatment arm was required.

Randomisation

The patients were randomly assigned to receive to RT/TMZ+placebo or RT/TMZ+bevacizumab in a 1:1 ratio. They were stratified by the following factors: Recursive Partitioning Analysis (RPA) Class (III, IV, V) and Region (Western Europe, Eastern Europe, Asia, USA, other).

The definition of RPA class by EORTC is based on WHO performance status, type of surgery, age and MMSE and is categorized as shown in figure 4.

Figure 4. RPA Class Definitions



Randomization and start of treatment was to occur on the same day. When this was not feasible, the delay between randomization and start of treatment was to be kept to a minimum and was not to exceed 3 days.

Blinding (masking)

This was a double-blind trial. Prior to disease progression, the patients' treatment allocation blind was to be maintained. The only exception was in case of an emergency due to safety reasons. Patients' treatment allocation was to remain blinded at disease progression except if it was deemed necessary to unblind by the investigator for deciding on further treatment.

Statistical methods

In order to adjust for multiplicity due to having two primary endpoints, the overall alpha of 5% was split with 4% assigned for OS and 1% for PFS.

The null hypothesis was tested with the stratified log rank test (two-sided) and the trial was determined to be positive if any of the following criteria were met: if, at the time of the OS interim

analysis/final PFS analysis, there was a statistically significant difference between treatment arms in PFS in favour of Bv with a HR<0.769 and a non-detrimental effect on OS (HR <1.0); or if, at the time of the interim or final OS analysis, there was a statistically significant difference between the two treatment arms for OS, in favour of Bv.

Analyses were performed using the following populations:

Intent-to-Treat Population (ITT): all patients randomized into the study. For the analysis, patients were assigned to the treatment arms to which they were randomized.

Per-Protocol Population (PPP): all randomized patients who received any radiotherapy, concomitant TMZ and at least 3 doses of Bv/placebo during the Concurrent phase, as well as patients who stopped treatment prior to this because of toxicity, disease progression or death. Patients had to have at least one disease assessment at baseline and during treatment (unless they died before the first scheduled assessment) and no major protocol violation. Patients were grouped as randomized.

Safety Population: all randomized patients who received at least one dose of trial treatment. Patients were assigned to treatment arms according to the treatment actually received.

In addition the following subsets of the ITT were defined:

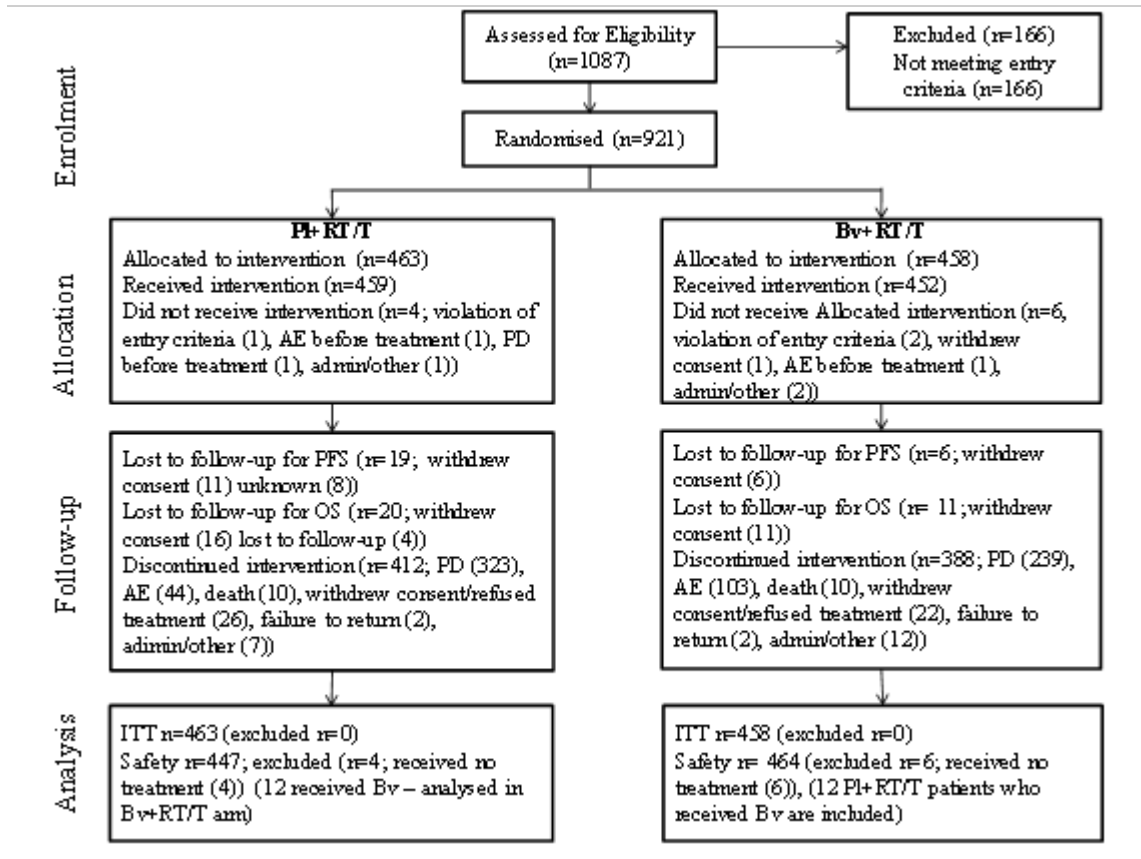
The protocol B population: all randomized patients enrolled under protocol version B. One of the key changes that this amendment implemented was the recording of signs and symptoms of GBM, and accordingly these data were analysed using this population.

The PK population: all randomized patients enrolled in the DDI substudy for whom at least one blood sample could be taken for PK.

The NCF population (subset of the protocol B population): all randomized patients who were enrolled into the NCF substudy and who had a baseline NCF assessment, regardless of whether they received any trial treatment or completed the full course of treatment.

Results

Participant flow



Recruitment

The first patient was randomized on 29 June 2009 and the last on 29 March 2011. A total of 921 patients were enrolled into the study from 120 centers in 23 countries.

Conduct of the study

The protocol was amended once (version B). In total, 786 patients were randomized under version A of the protocol, while 252 patients were randomized under protocol version B.

Key changes to the main protocol as a result of the amendment are summarized below:

- Following a recommendation from the DSMB, an additional interim analysis was introduced to be triggered when approximately 50% of the deaths required for the final OS analysis had occurred.
- The collection of signs and symptoms of GBM was introduced enabling a new exploratory objective “to explore and compare the signs and symptoms related to GBM and patient’s KPS between treatment arms”.
- An additional tumour assessment was added after disease progression was diagnosed enabling the addition of a new exploratory objective “to explore and compare the patterns of tumour progression between treatment arms”.

- The statistical analysis plan was changed with regard to testing of the difference between the arms for the 1-year and 2-year OS rates from a Cochran Mantel Haenzel Test to using a z test.

Baseline data

Baseline demographics and baseline disease characteristics are summarised in the following tables.

Table 5. Summary of Demographic Data by Trial Treatment (ITT)

	PI+RT/T N = 463	Bv+RT/T N = 458
Gender		
FEMALE	165 (36%)	176 (38%)
MALE	298 (64%)	282 (62%)
n	463	458
Age (years)		
Mean	55.9	55.9
SD	10.58	11.26
SEM	0.49	0.53
Median	56.0	57.0
Min-Max	18 - 79	20 - 84
n	463	458
Age Category I (years)		
<65	362 (78%)	359 (78%)
>=65	101 (22%)	99 (22%)
n	463	458
Age Category II (years)		
<50	113 (24%)	116 (25%)
50-59	165 (36%)	158 (34%)
60-69	151 (33%)	145 (32%)
>=70	34 (7%)	39 (9%)
n	463	458
Race		
WHITE	419 (90%)	413 (90%)
BLACK	4 (<1%)	3 (<1%)
ASIAN/INDIAN SUBCONTINENT	2 (<1%)	4 (<1%)
ASIAN/OTHER THAN INDIAN SUBCONTINENT NATIVE	35 (8%)	35 (8%)
HAWAIIAN/OTHER PACIFIC ISLANDER	1 (<1%)	-
OTHER	2 (<1%)	3 (<1%)
n	463	458
Weight (kg)		
Mean	77.39	76.71
SD	15.467	15.116
SEM	0.722	0.706
Median	77.00	76.00
Min-Max	34.2 - 125.0	40.5 - 128.0
n	459	458
Baseline Body Surface Area (m2)		
Mean	1.890	1.879
SD	0.2149	0.2086
SEM	0.0100	0.0098
Median	1.895	1.890
Min-Max	1.23 - 2.43	1.37 - 2.50
n	460	457
Smoking Status		
NEVER SMOKED	233 (50%)	237 (52%)
PAST SMOKER	171 (37%)	159 (35%)
CURRENT SMOKER	58 (13%)	62 (14%)
n	462	458
Region		
WESTERN EUROPE	237 (51%)	236 (52%)
EASTERN EUROPE	80 (17%)	77 (17%)
ASIA	35 (8%)	34 (7%)
USA	18 (4%)	18 (4%)
OTHER	93 (20%)	93 (20%)
n	463	458

Table 6. Baseline Disease Characteristics (ITT)

	Pl+RT/T N = 463	Bv+RT/T N = 458
GBM (Primary or Secondary)		
PRIMARY	461 (100%)	452 (99%)
SECONDARY	2 (<1%)	6 (1%)
n	463	458
Surgical Status		
BIOPSY ONLY	44 (10%)	60 (13%)
PARTIAL RESECTION	223 (48%)	210 (46%)
COMPLETE RESECTION	196 (42%)	188 (41%)
n	463	458
GBM histology		
GBM confirmed	440 (95%)	435 (95%)
GBM not confirmed	13 (3%)	9 (2%)
Missing	10 (2%)	14 (3%)
n	463	458
MGMT gene promoter status		
METHYLATED	120 (26%)	117 (26%)
NON-METHYLATED	236 (51%)	225 (49%)
MISSING	107 (23%)	116 (25%)
n	463	458
Time between surgery and 1st TT (weeks)		
<4	2 (<1%)	3 (<1%)
4-7	438 (95%)	435 (96%)
>7	19 (4%)	14 (3%)
n	459	452
Corticosteroid use at Baseline		
ON	208 (45%)	187 (41%)
OFF	253 (55%)	269 (59%)
MISSING	2 (<1%)	2 (<1%)
n	463	458
EIAEDs at Baseline		
YES	92 (20%)	87 (19%)
NO	371 (80%)	371 (81%)
n	463	458
WHO Performance Status		
0	238 (52%)	227 (50%)
1-2	224 (48%)	231 (50%)
n	462	458
KPS at Baseline		
50-80	140 (30%)	149 (33%)
90-100	322 (70%)	308 (67%)
n	462	457
RPA Class - CRF		
III	75 (16%)	76 (17%)
IV	279 (60%)	261 (57%)
V	108 (23%)	121 (26%)
n	462	458
MMSE score		
<27	108 (24%)	106 (24%)
>=27	351 (76%)	345 (76%)
n	459	451
Signs and Symptoms at BL (Prot B pts)		
YES	80 (59%)	80 (68%)
NO	55 (41%)	37 (32%)
n	135	117

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.

Numbers analysed

A summary of analysis population is presented in Table 7 below.

Table 7. Summary of Analysis Populations by Trial Treatment

	PI+RT/T	Bv+RT/T
No. of Patients Randomized	463	458
No. of patients who did not receive any treatment	4	6
No. of Patients received Randomized Treatment	451	452
No. of Patients received Incorrect Treatment	12	6
No. Included in SAP	447	464
No. Included in PPP	432	432
No. Included in Protocol B	135	117
No. Included in PK	6	14
No. Included in NCF	33	34

Outcomes and estimation

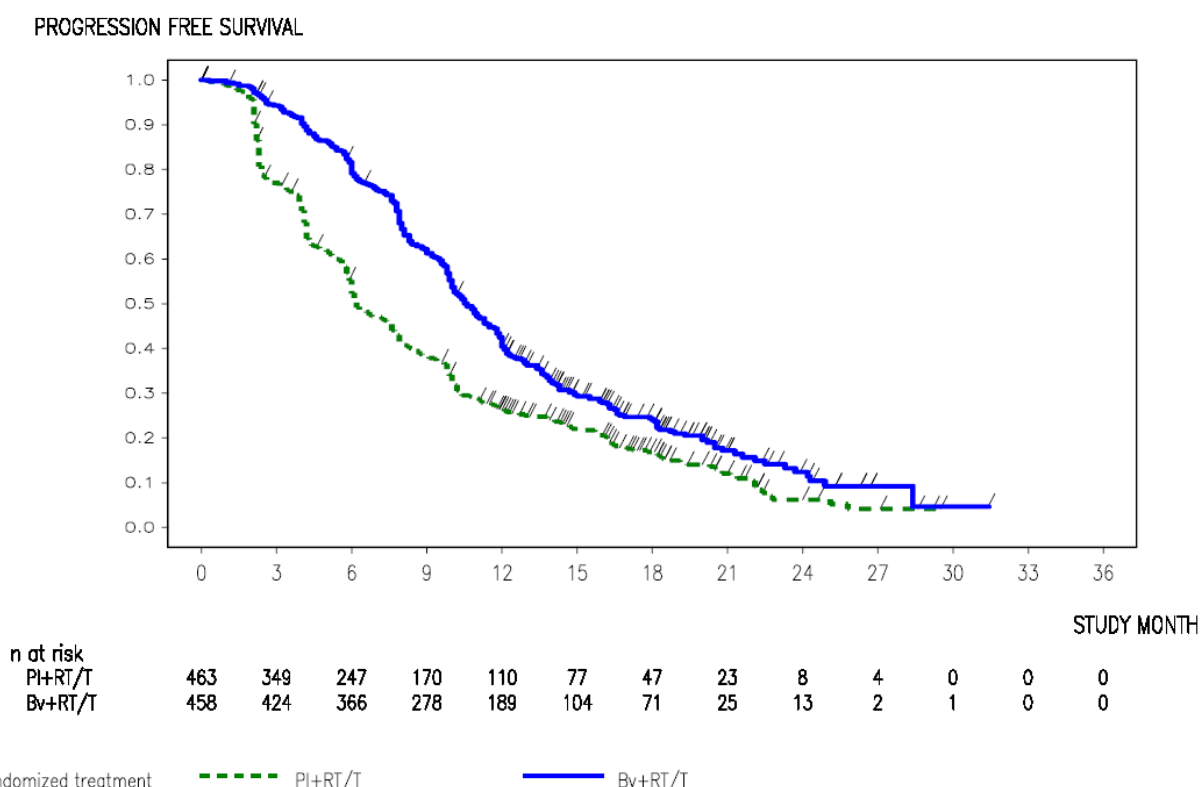
Co-primary endpoints

The efficacy results in terms of the co- primary endpoint of PFS-INV (cut-off date March 31, 2012) are presented in the table 8 and figure 5.

Table 8. Duration of PFS (ITT) Investigator-Assessed (ITT Population; Cut-off: March 31, 2012)

	PI+RT/T	Bv+RT/T
Patients randomised	463	458
Progressive disease or died	387 (83.6%)	354 (77.3%)
Censored	76 (16.4%)	104 (22.7%)
Progression free survival (months)		
Median (95% CI)	6.2 (6.0, 7.5)	10.6 (10.0, 11.4)
Log-rank p-value (stratified)	<0.0001	
Hazard ratio (95% CI)	0.64 (0.55, 0.74)	

Figure 5. Plot of Kaplan-Meier Estimates for PFS, Investigator-Assessed (ITT Population; Cut-off: March 31, 2012)

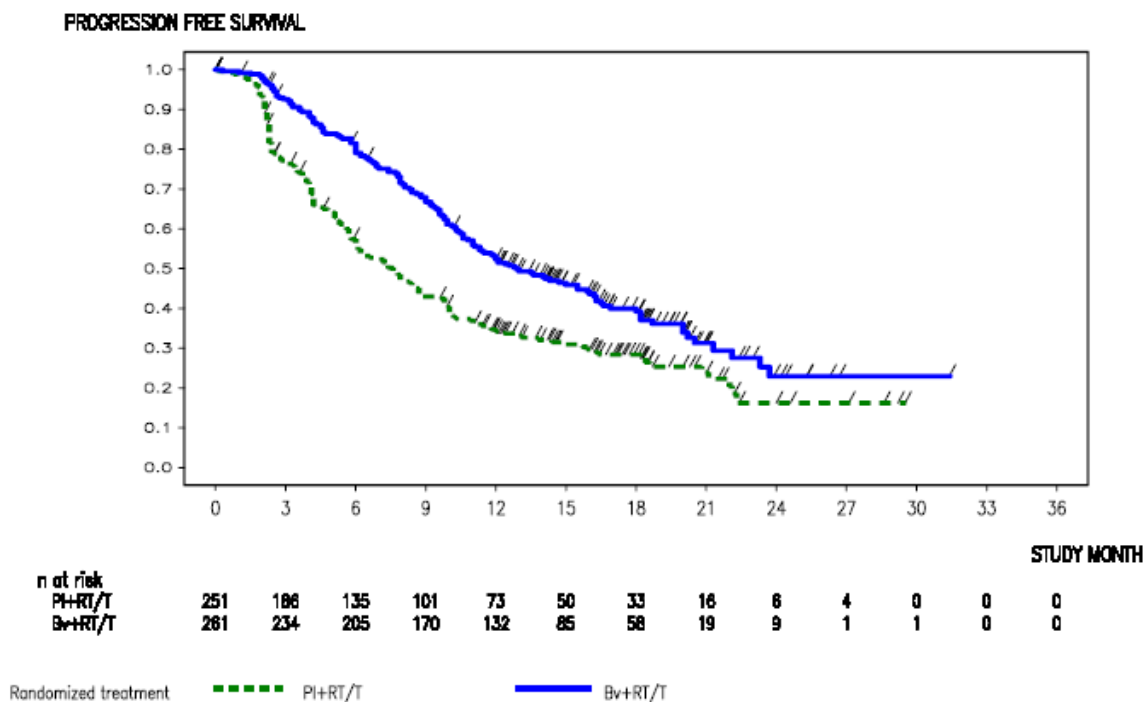


A summary of PFS as assessed by the investigator excluding patients from both arms with PD assessed by radiological scan only and the corresponding Kaplan-Meier curve are presented in Table 9 and figure 6 respectively.

Table 9. Summary of PFS as assessed by the investigator excluding patients from both arms with PD assessed by radiological scan only (cut-off, March 31, 2012)

	PI +RT/T	Bv+RT/T
Patients randomised	251	261
Progressive disease or died	175 (69.7%)	157 (60.2%)
Censored	76 (30.3%)	104 (39.8%)
Progression free survival (months)		
Median (95% CI)	7.6 (6.0, 8.8)	12.9 (11.0, 16.0)
Log-rank p-value (stratified)	<0.0001	
Hazard ratio (95% CI)	0.60 (0.49, 0.75)	

Figure 6. Kaplan-Meier plot of PFS as assessed by the investigator excluding patients from both arms with PD assessed by radiological scan only (cut-off, March 31, 2012)



A summary of the sensitivity analyses of PFS is presented in Table 10 below.

Table 10. Summary Table of Robustness and Sensitivity Analyses (PFS)

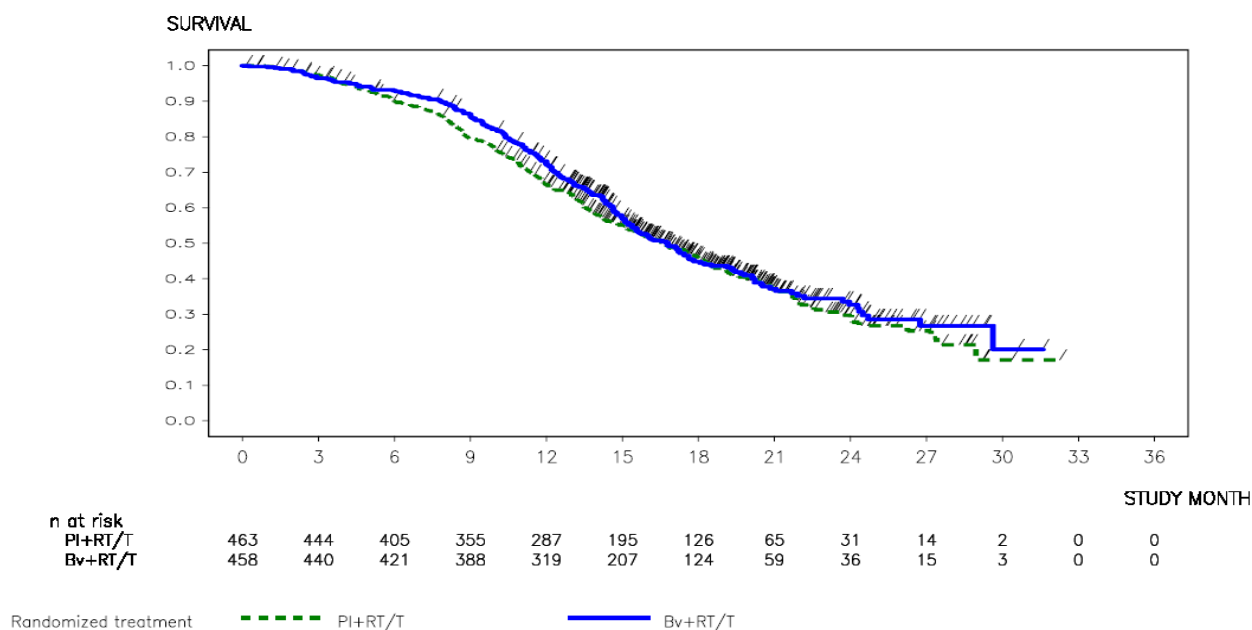
Analysis description	PI+RT/T N=463 Number of patients with events / KM estimated median - months	Bv+RT/T N=458 Number of patients with events / KM estimated median - months	HR (95% CI)	p-value
Investigator (Stratified, CRF) – main analysis*	387 6.2	354 10.6	0.64 (0.55-0.74)	<0.0001
Investigator (Unstratified)	387 6.2	354 10.6	0.65 (0.56-0.75)	<0.0001
Investigator (Stratified, CRF, censoring for NPT)	367 6.2	323 10.9	0.62 (0.53-0.72)	<0.0001
Investigator (Stratified, CRF, censoring for NPT+112days)	363 6.2	320 10.9	0.62 (0.53-0.72)	<0.0001
Investigator (Stratified, CRF, event for Missed Assessment)	395 6.1	362 10.5	0.64 (0.55-0.74)	<0.0001
Investigator (Stratified, CRF, event for Missed Assessment applied to Bv+RT/T arm only)	369 6.2	362 10.5	0.68 (0.59-0.79)	<0.0001

The efficacy results in terms of the co-primary endpoint of Overall Survival and for the primary analysis of 31 March 2012 are summarised in the following table and figure.

Table 11. Duration of Overall Survival (ITT Population; Cut-off: March 31, 2012)

	PI +RT/T	Bv+RT/T
Patients randomised	463	458
Death	263 (56.8%)	254 (55.5%)
Censored	200 (43.2%)	204 (44.5%)
Overall Survival (months)		
Median (95% CI)	16.6 (15.1, 18.2)	16.8 (15.4, 17.8)
Log-rank p-value (stratified)	0.2135	
Hazard ratio (95% CI)	0.89 (0.75, 1.07)	

Figure 7. Plot of Kaplan-Meier Estimates for Overall Survival (ITT Population; Cut-off: March 31, 2012)



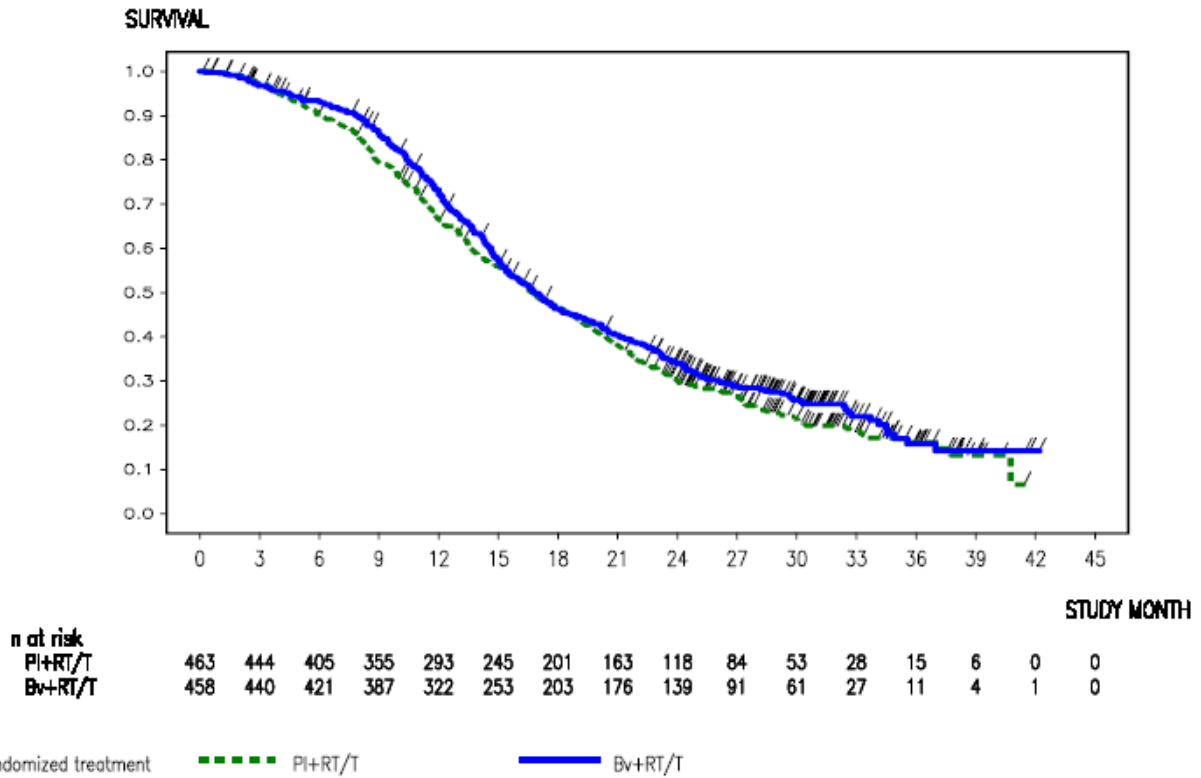
The MAH also submitted the results of an updated OS analysis with a cut-off date of 28 February 2013, which are summarised in the following table and figure.

Table 12. Duration of Overall Survival (ITT Population; Cut-off: February 28, 2013)

	PI +RT/T	Bv+RT/T
Patients randomised	463	458
Death	346 (74.7%)	333 (72.7%)
Censored	117 (25.3%)	125 (27.3%)
Overall Survival (months)		

Median (95% CI)	16.7 (15.4, 18.4)	16.8 (15.5, 18.5)
Log-rank p-value (stratified)	0.0987	
Hazard ratio (95% CI)	0.88 (0.76, 1.02)	

Figure 8. Plot of Kaplan-Meier Estimates for Overall Survival (ITT Population; Cut-off: February 28, 2013)



A summary of the sensitivity analyses of OS is presented in Table 12 below.

Table 13. Summary Table of Robustness and Sensitivity Analyses (OS)

Analysis description	PI+RT/T N=463 Number of patients with events / KM estimated median - months	Bv+RT/T N=458 Number of patients with events / KM estimated median - months	HR (95% CI)	p-value
OS (Stratified, CRF) – main analysis	263 16.6	254 16.8	0.89 (0.75-1.07)	0.2135
OS (Unstratified)	263 16.6	254 16.8	0.92 (0.77-1.09)	0.3171
OS (additional censoring for NPT)	83 NR	94 NR	0.82 (0.61-1.10)	0.1837
OS (accounting for a 33% subsequent line therapy benefit)	263 14.3	254 15.5	0.85 (0.72-1.01)	0.0678

An additional exploratory analysis was conducted investigating post-progression survival for patients receiving bevacizumab or other anticancer treatments as subsequent therapies. The results are summarised in the following table and figure.

Table 14. Summary of post-progression survival for patients receiving bevacizumab or other anticancer treatments as subsequent therapies (ITT population: Cut-off: February 28, 2013)

A) Post-progression survival of patients in PI+RT/T arm receiving Bv or Other

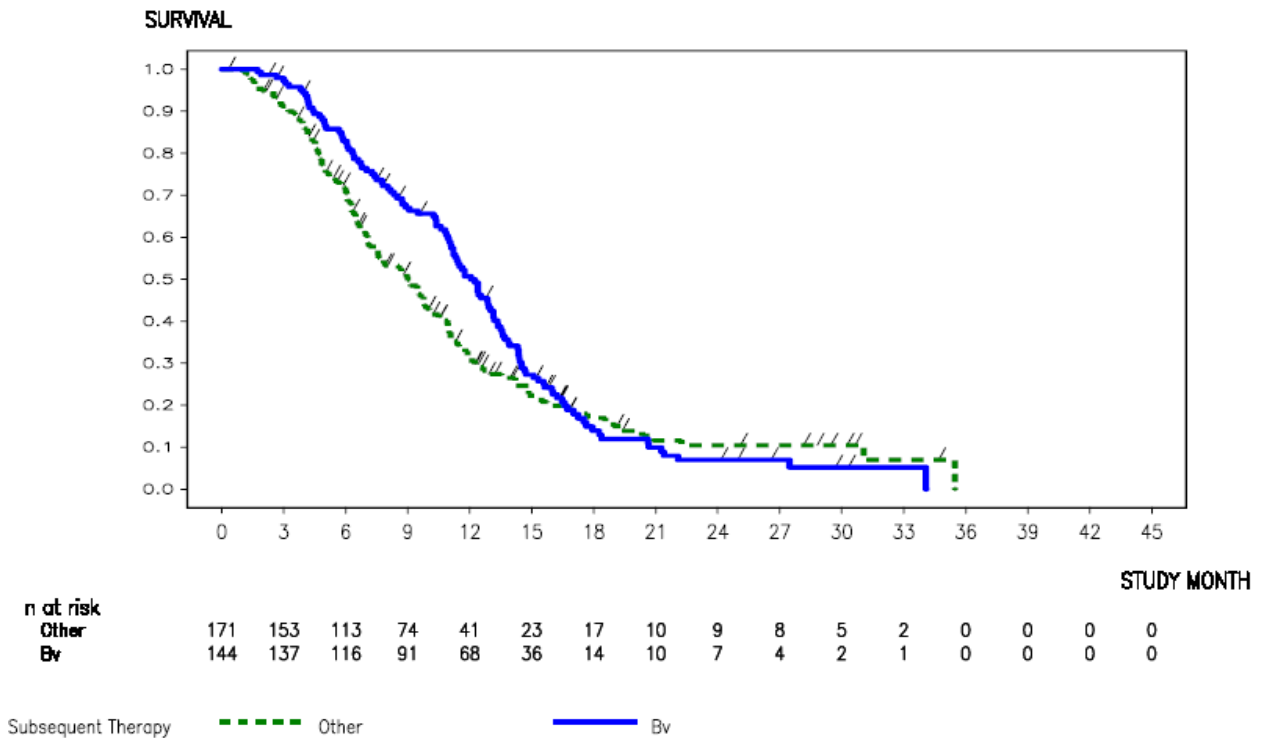
	Other	Bevacizumab
Patients included in the analysis	171	144
Death	131(76.6%)	123 (85.4%)
Censored	40 (23.4%)	21(14.6%)
Post-progression Survival (months)		
Median (95% CI)	9 (7.5, 10.2)	12.1 (11.1, 13.1)
Log-rank p-value (stratified)	0.0955	
Hazard ratio (95% CI)	0.81 (0.63, 1.04)	

B) Post-progression survival of patients in Bv+RT/T arm receiving Bv or Other

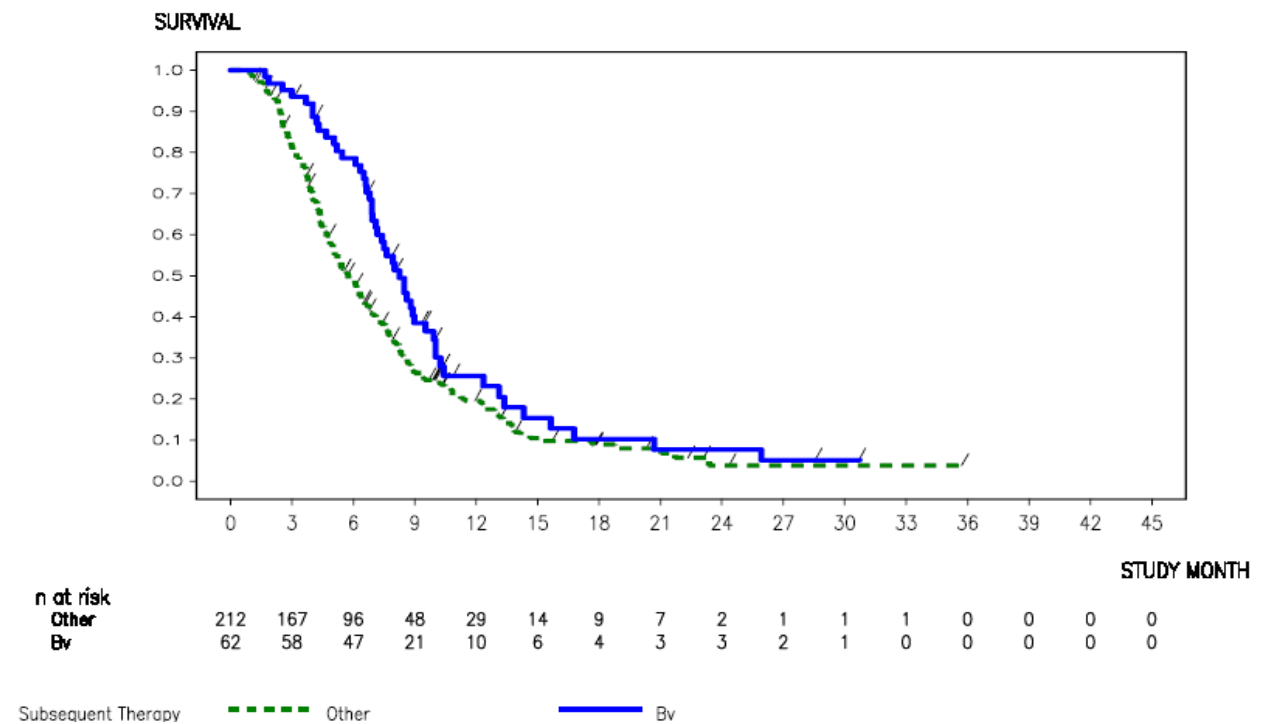
	Other	Bevacizumab
Patients included in the analysis	212	62
Death	177(83.5%)	50(80.6%)
Censored	35 (16.5%)	12(19.4%)
Post-progression Survival (months)		
Median (95% CI)	5.8 (5.0, 16.6)	8.3 (7.1, 9.5)
Log-rank p-value (stratified)	0.0189	
Hazard ratio (95% CI)	0.69 (0.50, 0.94)	

Figure 9. Kaplan-Meier curve of post-progression survival for patients receiving bevacizumab or other anticancer treatments as subsequent therapies (ITT population: Cut-off: February 28, 2013)

A) Post-progression survival of patients in PI+RT/T arm receiving Bv or Other



B) Post-progression survival of patients in Bv+RT/T arm receiving Bv or Other



Pseudoprogression

The rate of confirmed PsPD was 9.3% in the PI+RT/T arm versus 2.2% in the Bv+RT/T arm (Table 15).

Table 15. Summary of Confirmed and Unconfirmed Pseudo Progression at the End of Maintenance Phase Cycle 2 by Trial Treatment

	PI+RT/T N = 463	Bv+RT/T N = 458
End of Treatment Break Patients with potential PsPD	84 (18.1%)	12 (2.6%)
End of Maintenance Phase Cycle 2 Patients with confirmed PsPD	43 (9.3%)	10 (2.2%)
Patients with rejected PsPD	35 (7.6%)	1 (0.2%)
Patients with missing confirmation of PsPD	6 (1.3%)	1 (0.2%)

An additional exploratory analysis comparing PFS and OS for patients with confirmed PsPD is presented in Table 16.

Table 16. Comparison of PFS and OS for patients with confirmed PsPD

	BO21990		Brandes et al. [10462]	
	PI+RT/T		RT/T	
Overall Population (ITT)	n=463		n=103	
	PFS	OS	TTP	OS
Time to event (months) – Median (95% CI)	6.2 (6.0, 7.5)	16.7 (10.3, 27.4)	11.7	20.7
Confirmed PsPD Subgroup Population	n=43		n=32	
	PFS	OS	TTP	OS
Time to event (months) – Median (95% CI)	7.4 (6.10, 8.70)	13.6 (13.0, 20.7)	20.7	38

Source: ahr645_ettpfscspd_10_I001; ahr645_ettoscspd_10_I001.

An additional exploratory analysis investigating the effect of PsPD on OS is presented in Table 17.

Table 17. Summary of OS excluding patients with confirmed PsPD (ITT population; Cut-off March 31, 2013)

	PI +RT/T	Bv+RT/T
Patients randomised	420	448
Death	311(74.0%)	324(72.3%)
Censored	109 (26.0%)	124 (27.7%)
Overall survival (months)		
Median (95% CI)	16.9 (15.7, 18.9)	17.1 (15.6, 18.9)
Log-rank p-value (stratified)	0.1130	
Hazard ratio (95% CI)	0.88 (0.75, 1.03)	

Secondary endpoints

- *Progression-Free Survival (IRF-Assessed)*

Table 18. Duration of PFS - IRF (ITT)

	PI+RT/T	Bv+RT/T
Patients randomised	463	458
Progressive disease or died	396 (85.5%)	368 (80.3%)
Censored	67 (14.5%)	90 (19.7%)
Progression free survival (months)		
Median (95% CI)	4.3 (4.1, 5.1)	8.4 (7.9, 9.7)
Log-rank p-value (stratified)	<0.0001	
Hazard ratio (95% CI)	0.61 (0.53, 0.71)	

Figure 10. Plot of Kaplan-Meier Estimates for PFS - IRF (ITT)

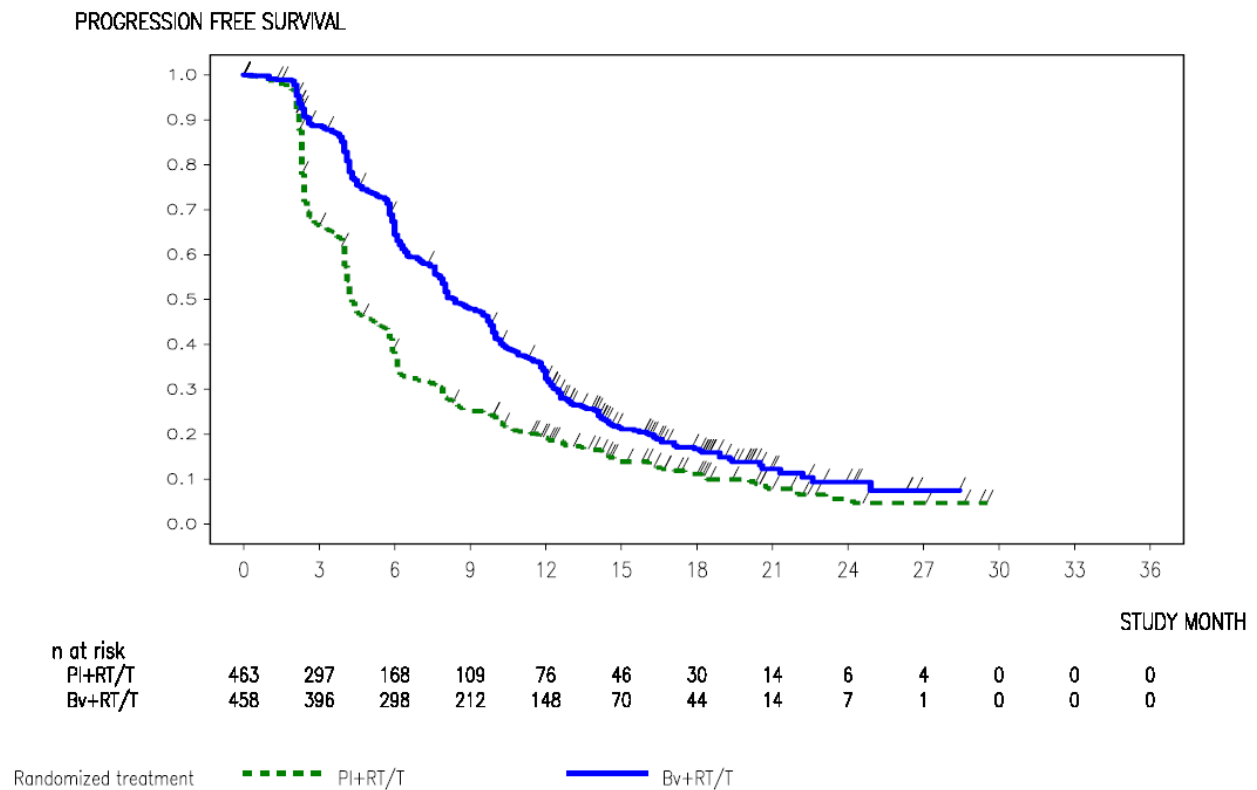


Table 19. Summary Table of Robustness and Sensitivity Analyses for IRF-Based PFS

Analysis description	HR (95% CI)	p-value
IRF (Stratified, CRF) – main analysis*	0.61 (0.53, 0.71)	<0.0001
IRF (Unstratified)	0.63 (0.54, 0.72)	<0.0001
IRF (Stratified, CRF, censoring for NPT)	0.58 (0.50, 0.67)	<0.0001
IRF (Stratified, CRF, censoring for NPT+112days)	0.57 (0.49, 0.67)	<0.0001

- 1-Year and 2-Year Overall Survival Rate

Table 20. Summary of One-Year and Two-Year Survival Estimates (ITT Population)

	P1+RT/T (N=463)	Bv+RT/T (N=458)
Patients with event	263 (56.8 %)	254 (55.5 %)
Patients without events*	200 (43.2 %)	204 (44.5 %)
1 year duration		
Patients remaining at risk	287	319
Event Free Rate	0.66	0.72
95% CI for OS Rate	[0.62;0.71]	[0.68;0.76]
Difference in OS Rates (%)		6
95% CI for Difference in OS Rates#		[-0.1;12.0]
p-value		0.052
2 years duration		
Patients remaining at risk	31	36
Event Free Rate	0.30	0.33
95% CI for OS Rate	[0.24;0.35]	[0.27;0.39]
Difference in OS Rates (%)		3
95% CI for Difference in OS Rates#		[-5.3;11.2]
p-value		0.478

* censored

95% CI using Greenwood's formula

Approximately 75%-80% of patients in each arm had PFS events according to both the investigator and the IRF. In about half of these cases (35-40% of patients in each arm) the investigator and IRF determined PFS events were within approximately one scheduled visit of each other (within 28 days) whereas for the remaining cases, they occurred >28 days apart.

Health Related Quality of Life

- *Time to Definitive Deterioration in HRQoL*

Table 21. Summary of Time to Definitive Deterioration (TDD) in HRQoL Score (ITT)

	Pre-specified analysis: PD included as deterioration event		Post hoc sensitivity analysis: PD <u>excluded</u> as deterioration event	
	PI+RT/T	Bv+RT/T	PI+RT/T	Bv+RT/T
Global health Status QLQ-C30				
No. with event	401 (86.6%)	378 (82.5%)	222 (47.9%)	227 (49.6%)
HR [95% CI] p value	0.64 [0.56;0.74]	<0.0001	0.76 [0.63;0.92]	0.0041
KM-estimated median (months)	3.9	6.4	5.6	8.5
Physical functioning QLQ-C30				
No. with event	407 (87.9%)	385 (84.1%)	221 (47.7%)	249 (54.4%)
HR [95% CI] p value	0.70 [0.61;0.81]	<0.0001	0.90 [0.75;1.08]	0.2394
KM-estimated median (months)	4.2	6.1	6.1	7.3
Social functioning QLQ-C30				
No. with event	401 (86.6%)	379 (82.8%)	212 (45.8%)	223 (48.7%)
HR [95% CI] p value	0.63 [0.55;0.73]	<0.0001	0.78 [0.64;0.95]	0.0113
KM-estimated median (months)	4.1	7.4	6.6	11.8
Motor dysfunction BN20				
No. with event	383 (82.7%)	365 (79.7%)	126 (27.2%)	142 (31.0%)
HR [95% CI] p value	0.67 [0.58;0.78]	<0.0001	0.87 [0.68;1.11]	0.2747
KM-estimated median (months)	5.0	8.6	NR	31.6
Communication deficit BN20				
No. with event	405 (87.5%)	388 (84.7%)	197 (42.5%)	215 (46.9%)
HR [95% CI] p value	0.67 [0.58;0.77]	<0.0001	0.80 [0.66;0.98]	0.0295
KM-estimated median (months)	4.2	6.9	7.9	10.1

- *HRQoL During Patients' Progression-free Time*

Table 22. Summary of HRQoL during Patient's Progression-Free Time (ITT)

HRQoL Scale	PI+RT/T N=463	Bv+RT/T N=458
Global health status – QLQ-C30		
Number of patients stable/improved from baseline	309 (67%)	354 (77%)
median duration* (% PFS time)	4 months (79%)	8 months (74%)
Number of patients improved from baseline	134 (29%)	171 (37%)
median duration^ (% PFS time)	4 months (57%)	6 months (50%)
Physical functioning – QLQ-C30 Functional		

Number of patients stable/improved from baseline	318 (69%)	353 (77%)
median duration* (% PFS time)	5 months (88%)	7 months (72%)
Number of patients improved from baseline	87 (19%)	98 (21%)
median duration^ (% PFS time)	4 months (62%)	6 months (57%)
Social functioning – QLQ-C30 Functional		
Number of patients stable/improved from baseline	327 (71%)	352 (77%)
median duration* (% PFS time)	4 months (77%)	8 months (75%)
Number of patients improved from baseline	165 (36%)	197 (43%)
median duration^ (% PFS time)	4 months (68%)	6 months (60%)
Motor dysfunction – BN20 Functional		
Number of patients stable/improved from baseline	314 (68%)	361 (79%)
median duration* (% PFS time)	4 months (78%)	7 months (72%)
Number of patients improved from baseline	122 (26%)	147 (32%)
median duration^ (% PFS time)	4 months (64%)	6 months (69%)
Communication deficit - BN20 Neurological		
Number of patients stable/improved from baseline	329 (71%)	365 (80%)
median duration* (% PFS time)	4 months (65%)	8 months (68%)
Number of patients improved from baseline	123 (27%)	143 (31%)
median duration^ (% PFS time)	4 months (65%)	6 months (55%)

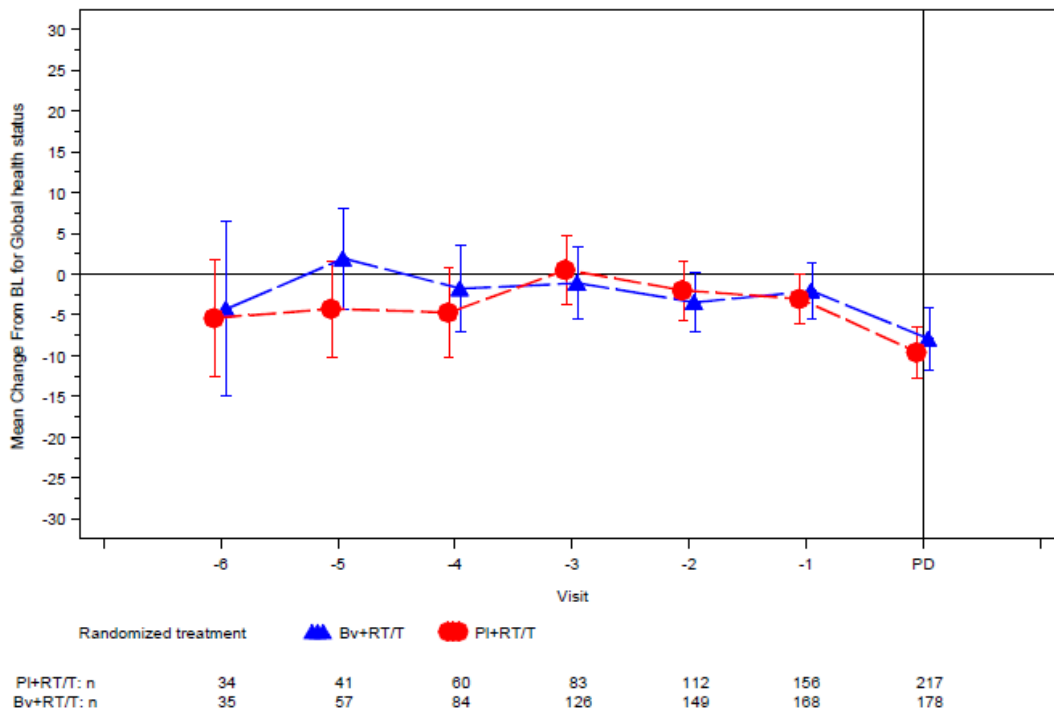
*median duration of progression-free time stable/improved compared to baseline, based on n stable/improved.

^ median duration of progression-free time improved compared to baseline based on n improved.

A linear transformation is used to standardize the raw HRQoL score, so that all scores for the scales and the single-item measures range from 0 to 100. Stable HRQoL is defined as a change within 10 points. Improved HRQoL is defined as an increase of at least 10 points for functioning/global health status, and as a decrease of at least 10 points for symptoms. The period before each scheduled assessment is considered in calculating the total duration of stable and/or improved HRQoL.

- *HRQoL at Progression*

Figure 11. Mean Change from Baseline in Global Health Status Score at the Time of PD Compared to Previous Assessments Prior to PD (ITT)



Exploratory Parameters

- *Time to Definitive Deterioration in KPS*

Table 23. Summary of Time to Definitive Deterioration in KPS (ITT)

	PI+RT/T N=463	Bv+RT/T N=458
Time to Definitive Deterioration - PD included as Deterioration Event		
Number of patients with an Event	399 (86.2%)	371 (81.0%)
KM estimated median (months)	5.5	9.0
HR [95% CI]	0.65 [0.56;0.75]	
Time to Definitive Deterioration - PD excluded as Deterioration Event		
Number of patients with an Event	211 (45.6%)	214 (46.7%)
KM estimated median (months)	11.8	14.2
HR [95% CI]	0.79 [0.65;0.96]	

- *Karnofsky Performance Status during Patients' Progression-free Time*

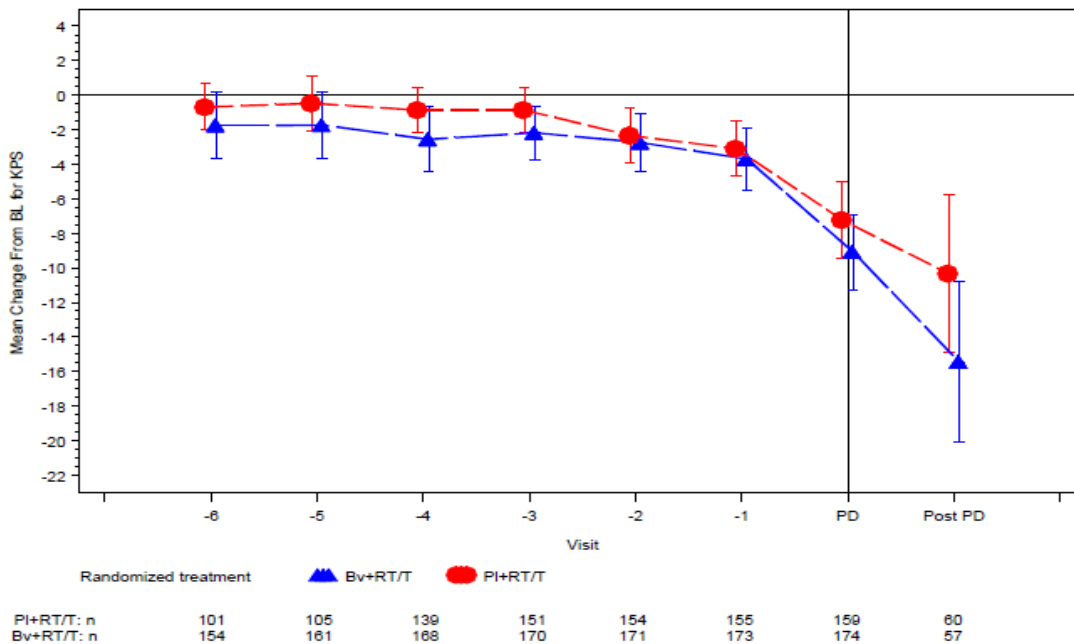
Table 24. Proportion of Progression-Free Time with Stable or Improved KPS (ITT)

	PI+RT/T N=463	Bv+RT/T N=458
Number of patients stable/improved from baseline	455 (98%)	451 (99%)
median duration ^a (% PFS time)	6 months (94%)	9 months (95%)
Number of patients improved from baseline	29 (6%)	36 (8%)
median duration ^a (% PFS time)	3 months (27%)	4 months (44%)
Number of patients with KPS ≥ 70	446 (96%)	450 (98%)
median duration ^a (% PFS time)	6 months (97%)	9 months (96%)

^a median duration during the progression-free time (PFS time)

- *Karnofsky Performance Status at Progression*

Figure 12. Mean KPS at PD and Post-PD Compared to Assessments Prior to PD (ITT)



- *Corticosteroid Use*

Figure 13. Kaplan-Meier Plot of Time to Initiation of Corticosteroid Therapy (Patients OFF steroids at Baseline)

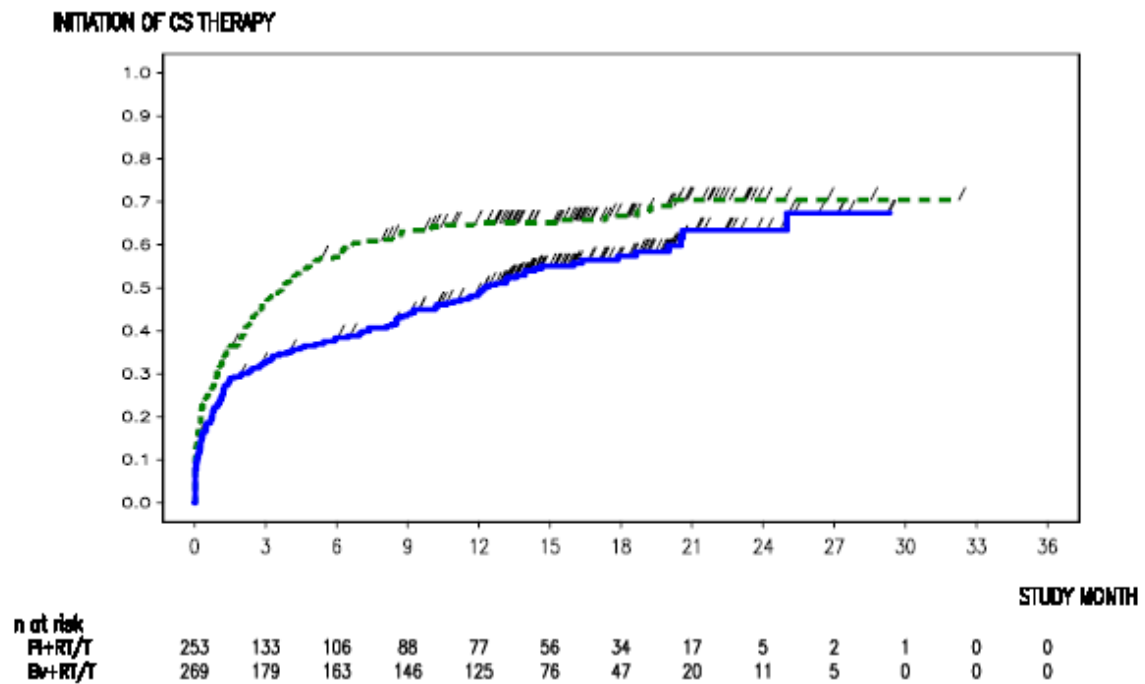


Table 25. Cumulative corticosteroid use by study phase (ITT population)

	P1+RT/T (N=463)	Bv+RT/T (N=458)
Concurrent Phase		
n	459 (100%)	451 (100%)
Number of patients with 0 dose	125 (27%)	161 (36%)
Number of patients with any dose	334 (73%)	290 (64%)
Mean	314.3	265.1
SD	331.11	250.42
Median	225.8	196.5
Min - Max	0.5 - 3060.0	2.0 - 1672.0
Q1 - Q3	115.5 - 400.0	84.0 - 380.5
Maintenance Phase		
n	372 (100%)	399 (100%)
Number of patients with 0 dose	149 (40%)	207 (52%)
Number of patients with any dose	223 (60%)	192 (48%)
Mean	367.1	272.0
SD	682.08	352.74
Median	206.0	146.2
Min - Max	0.5 - 8415.0	0.8 - 2278.5
Q1 - Q3	63.8 - 438.0	46.0 - 388.5
Monotherapy Phase		
n	159 (100%)	268 (100%)
Number of patients with 0 dose	111 (70%)	196 (73%)
Number of patients with any dose	48 (30%)	72 (27%)
Mean	327.3	326.1
SD	599.21	632.95
Median	153.4	98.0
Min - Max	0.5 - 3552.0	0.5 - 4536.0
Q1 - Q3	35.8 - 325.0	15.8 - 381.8

- Tumour Response

Best Objective Response

Table 26. Summary of Best Overall Response (per Adapted Macdonald criteria) Stratified by Treatment

Neurocognitive Function Scale	PI+RT/T N=33	Bv+RT/T N=34
HVLT-R A		
Number of patients stable/improved from baseline	21 (64%)	28 (82%)
median duration (% PFS time)	4.3 months (90%)	8.0 months (70%)
HVLT-R B		
Number of patients stable/improved from baseline	24 (73%)	29 (85%)
median duration (% PFS time)	4.3 months (60%)	8.1 months (70%)
HVLT-R C		
Number of patients stable/improved from baseline	23 (70%)	25 (74%)
median duration (% PFS time)	4.3 months (90%)	10.1 months (80%)
Trail Making Test, Part A		
Number of patients stable/improved from baseline	24 (73%)	27 (79%)
median duration (% PFS time)	2.5 months (100%)	8.1 months (70%)
Trail Making Test, Part B		
Number of patients stable/improved from baseline	22 (67%)	24 (71%)
median duration (% PFS time)	4.2 months (50%)	9.9 months (70%)
COWA		
Number of patients stable/improved from baseline	24 (73%)	29 (85%)
median duration (% PFS time)	4.3 months (70%)	8.8 months (70%)

Patterns of Tumour Progression (IRF)

The results of the exploratory analysis of patterns of tumour progression are presented in table 27 below.

Table 27. Summary of Patterns of Tumour Progression (ITT with Assessment at Time of PD)

a) Tumor Pattern

	PI+RT/T N = 314	Bv+RT/T N = 294
Patients with No changes from Baseline		
From Local to Local	88.8% (214/241)	89.0% (194/218)
From Multifocal to Multifocal	90.4% (66/73)	81.3% (61/75)
Patients with changes from Baseline		
From Local to Multifocal	8.3% (20/241)	7.3% (16/218)
From Local to Distant	2.9% (7/241)	3.7% (8/218)
From Multifocal to Local	8.2% (6/73)	12% (9/75)
From Multifocal to Distant	1.4% (1/73)	6.7% (5/75)

b) Invasiveness (non-enhancing or diffuse)

	PI+RT/T N = 314	Bv+RT/T N = 294
Patients with No changes from Baseline		
From Non-Diffuse to Non-Diffuse	77.2% (98/127)	75.3% (67/89)
From Diffuse to Diffuse	98.4% (184/187)	98% (201/205)
Patients with changes from Baseline		
From Non-Diffuse to Diffuse	22.8% (29/127)	24.7% (22/89)
From Diffuse to Non-Diffuse	1.6% (3/187)	2% (4/205)

Ancillary analyses

- Subgroup analyses

Subgroup analyses for PFS and OS are shown in the following figures.

Figure 14. Forest Plot of Hazard Ratios for PFS, as Assessed by the Investigator, by Subgroup (ITT)

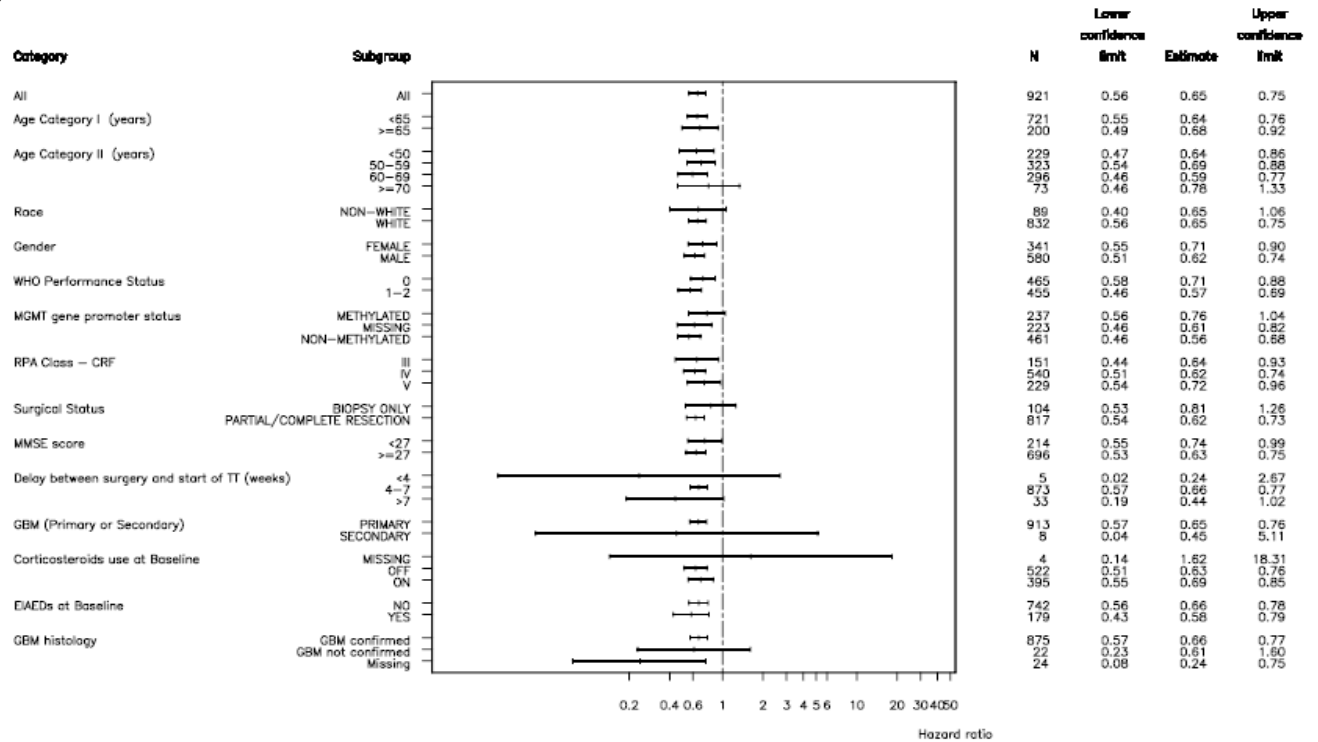
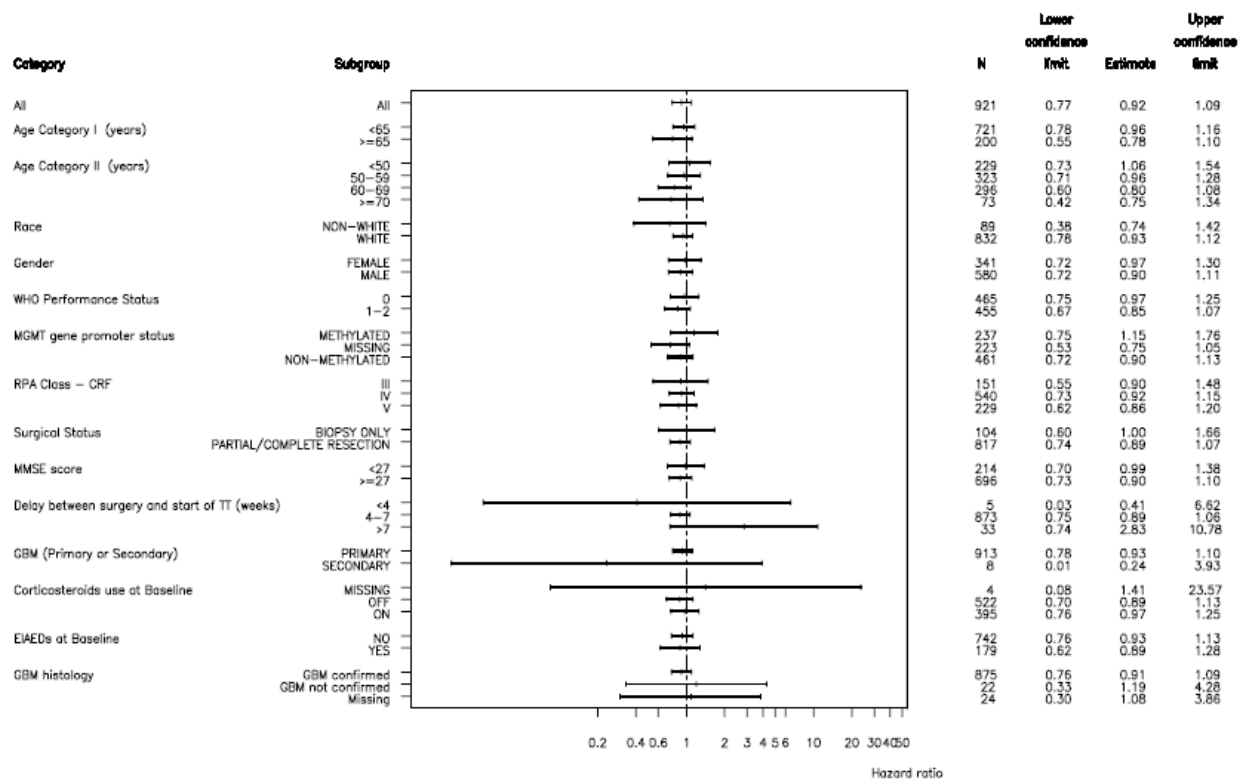


Figure 15. Forest Plot of Hazard Ratios for OS by Subgroup (ITT)



- Biomarker Analysis

Biomarker analyses were performed on those patients in the intent-to-treat (ITT) (all randomized) population who consented separately to participate in the translational research program. Two patient populations were defined: biomarker evaluable protein plasma (BEP) and biomarker evaluable IHC tumour (BEI).

Following biomarkers were investigated: pVEGF-A, pVEGFR-2, tNRP-1, tCD31 (NV), pVEGFR-1, pVEGF-C, pVEGFR-3, PDGF-C, tVEGF-A, tVEGFR-2, tVEGFR-1, bFGF, PIGF, E-selectin, ICAM-1, and IL-8.

No clear evidence of predictive value for Bv treatment in terms of PFS was observed for any of the biomarkers. There was no evidence of a prognostic effect of any biomarkers observed in the PI treatment arm (data not shown).

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 28. Summary of efficacy for trial BO21990

Title: A randomized, double-blind, placebo controlled, multicenter Phase III trial of bevacizumab, temozolomide and radiotherapy, followed by bevacizumab and temozolomide versus placebo, temozolomide and radiotherapy followed by placebo and temozolomide in patients with newly diagnosed glioblastoma.	
Study identifier	BO21990
Design	randomized, double-blind, placebo controlled, multicenter

	Duration of main phase:	Concurrent Phase: 6 weeks Treatment break: 4 weeks Maintenance phase: Six 28-day cycles Monotherapy phase: Placebo/Bv monotherapy (15 mg/kg IV q3w) until disease progression	
Hypothesis	Superiority		
Treatments groups	Placebo + Radiotherapy / Temozolomide	75mg/m ² /qd (N=463)	
	Bevacizumab + Radiotherapy / Temozolomide	10 mg/kg q ² w (N=458)	
Endpoints and definitions	Co-primary endpoint	Progression free survival Investigator – assessed (PFS-INV)	Time between randomization and disease progression (using adapted Macdonald criteria) or death due to any cause
	Co-primary endpoint	Overall survival (OS)	Time between randomization and death due to any cause
	Secondary endpoint	Progression free survival Independent review facility-assessed PFS (IRF)	PFS as assessed by independent review facility
	Secondary endpoint	1-year and 2-year survival rates	As per OS
Database lock	July 2012		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Intent to treat (all patients randomized into the study) cut-off date 31 st March 2012		
Descriptive statistics and estimate variability	Treatment group	PI+RT/T	Bv+RT/T
	Number of subject	463	458
	Co-primary endpoints		
	PFS -Inv (median - months)	6.2	10.6
	95% CI	(6.0, 7.5)	(10.0, 11.4)
	OS (median – months)	16.6	16.8
	95% CI	(15.1, 18.2)	(15.4, 17.8)
	Secondary endpoints		
	PFS-IRF (median – months)	4.3	8.4
	95% CI	(4.1, 5.1)	(7.9, 9.7)
	1-year survival rate (KM estimate and 95%CI)	66% (62-71)	72% (68-72)
2-year survival rate (KM estimate and 95%CI)	30% (24-35)	33% (27-39)	
Effect estimate per	Co-primary endpoints		

comparison	Co-primary endpoint (PFS-Inv)	Comparison groups	PI+RT/T and Bv+RT/T
		HR	0.64
		95% CI	(0.55, 0.74)
		P-value	<0.0001
	Co-primary endpoint (OS)	Comparison groups	PI+RT/T and Bv+RT/T
		HR	0.89
		95% CI	(0.75, 1.07)
	PFS-IRF	Comparison groups	PI+RT/T and Bv+RT/T
		HR	0.61
		95% CI	(0.53, 0.71)
		P-value	<0.0001
	Notes	Stratification factors for the primary analysis (logrank): Recursive Partitioning Analysis (RPA) Class (III, IV, V) and Region (Western Europe, Eastern Europe, Asia, USA, other).	
Analysis description	Updated OS Analysis		
Analysis population and time point description	Intent to treat, (all patients randomized into the study) cut-off date 31st February 2013		
Descriptive statistics and estimate variability	Treatment group	PI+RT/T	Bv+RT/T
	Number of patient	463	458
	OS (median- months)	16.7	16.8
	95% CI	(15.4, 18.4)	(15.5, 18.5)
Effect estimate per comparison	Co-Primary endpoint (OS)	Comparison groups	PI+RT/T and Bv+RT/T
		HR from stratified proportional hazards model	0.88
		95% CI	(0.76, 1.02)
		Log-rank p-value	0.0987

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

N/A

Supportive study

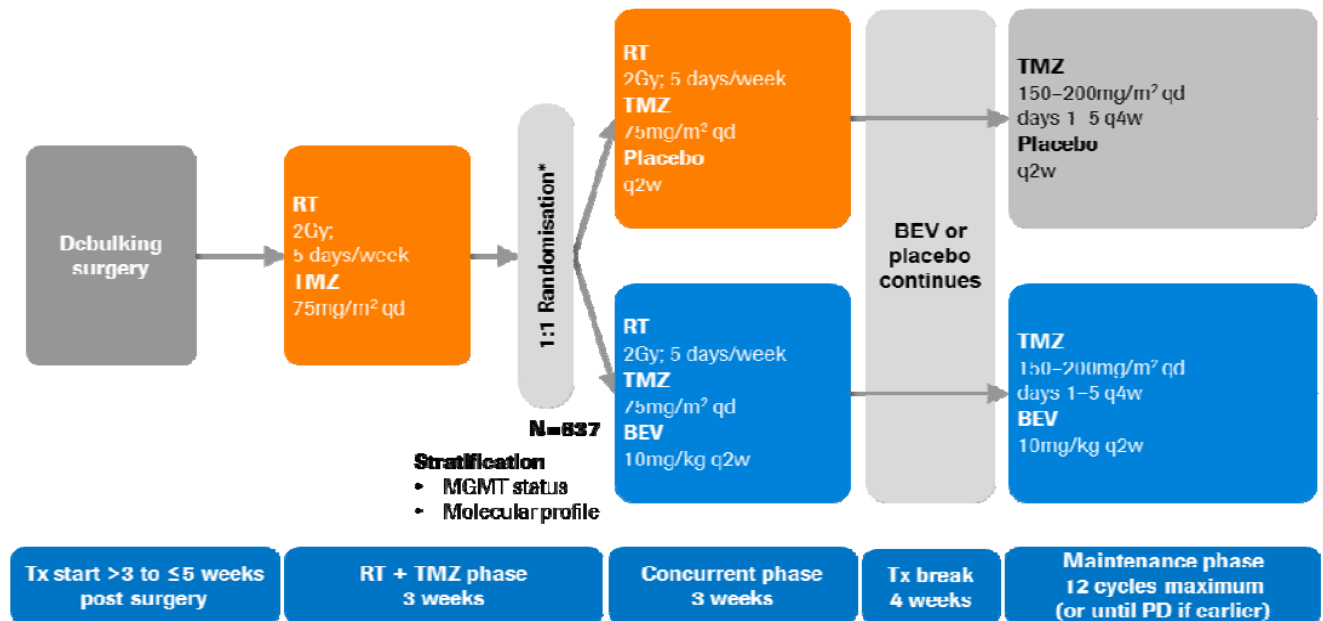
RTOG-0825 STUDY

RTOG-0825 was a study conducted by the Radiation Therapy Oncology Group (RTOG) and funded by the US National Cancer Institute, run mainly in the USA. The applicant presented the publicly available results of the study further to the CHMP's request.

RTOG-0825, was a Phase III, randomized, double-blind, placebo-controlled trial, designed to evaluate the safety and efficacy of Bv combined with standard therapy, consisting of radiotherapy RT and TMZ chemotherapy, in newly diagnosed glioblastoma.

Eligible patients were subsequently randomized in a 1:1 ratio to either the control arm or active arm, and received additional concurrent RT+TMZ concomitantly with placebo or Bv (3-week Concurrent Phase). Treatment with placebo or Bv continued uninterrupted (4 weeks) into a 12-cycle Maintenance Phase until progression of disease (PD). Patients could optionally complete questionnaires evaluating HRQoL (EORTC QLQ-C30 and BN20) and symptom burden (MDASI-BT) (Figure x).

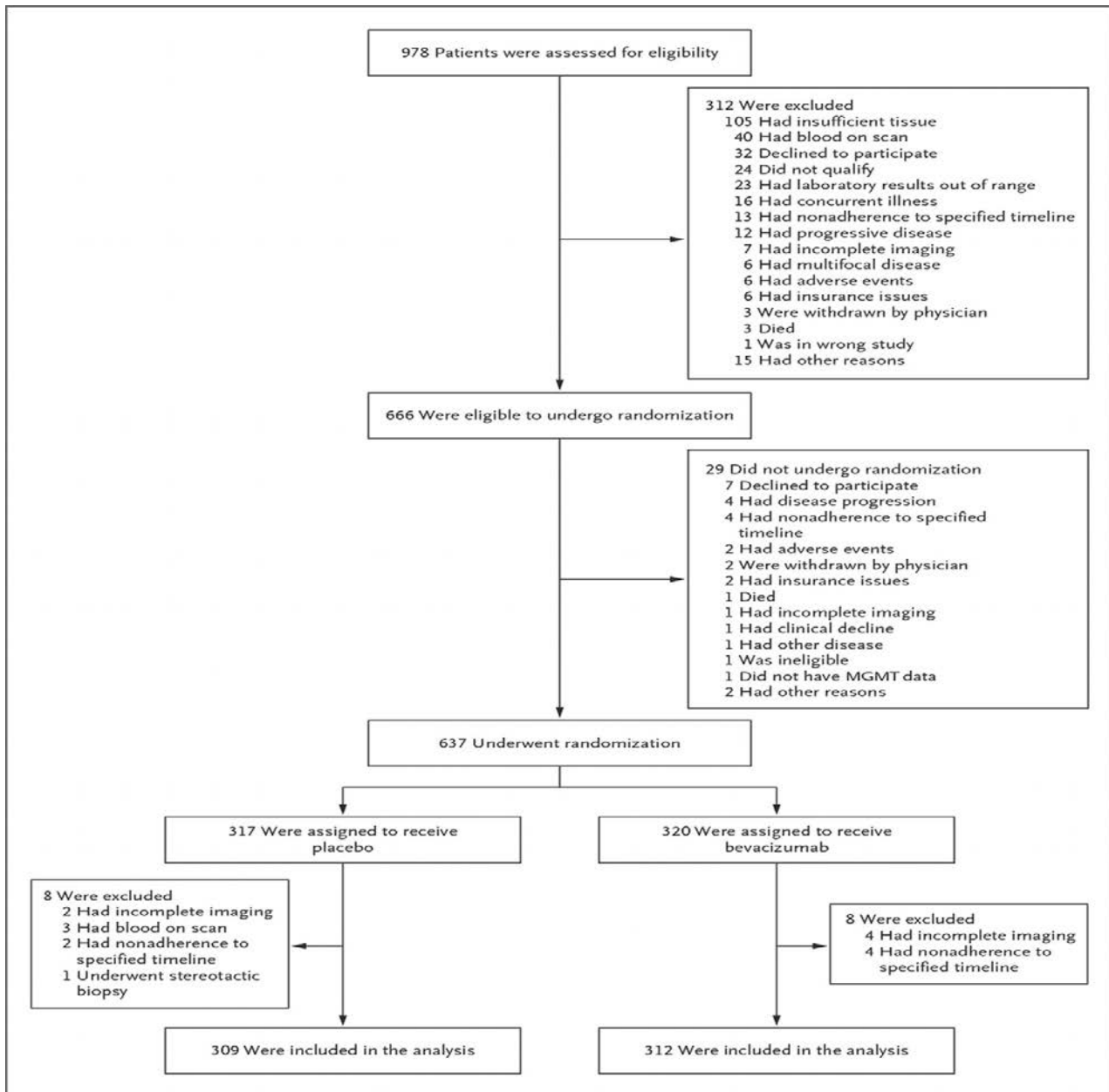
Figure 16. RTOG-0825: Study Design



Cycle=28 days. *≤10 days after start of RT.

In the RTOG-0825 study, only patients who underwent debulking surgery were included, and started concurrent RT/T treatment for 3 weeks within 3–5 weeks after the surgery. After this initial induction phase of 3 weeks, only patients still eligible were subsequently randomized in a 1:1 ratio to either the control arm or active arm, and continued to complete the 3 additional weeks of concurrent RT/T concomitantly with placebo or bevacizumab. 637 patients were randomized in the RTOG-0825 study as compared to the 978 patients initially assessed for eligibility. Following randomization, additional patients were further excluded from the analysis population (Figure 17).

Figure 17. Patient Disposition in RTOG-0825 Study



The co-primary endpoints were PFS and OS. Exploratory analyses were also performed to examine health-related quality of life (HRQoL: EORTC QLQ-C30/BN20), neurocognitive function (NCF: mini mental status examination [MMSE], Hopkins Verbal Learning Test-Revised [HVLTR], Trail-Making Test A & B [TMT A & B], and Controlled Oral Word Association [COWA]), and symptom burden (MDASI-BT tool).

Results showed no difference between the treatment arms for OS (median 16.1 months vs. 15.7 months; HR 1.13, 95% CI: [0.93, 1.37]; $p=0.21$) and showed prolonged PFS in the Bv treatment arm (median 7.3 months vs. 10.7 months; HR 0.79, 95% CI [0.66, 0.94]; $p=0.007$) (Table 29).

Table 29. RTOG-0825: Summary of OS and PFS

	PI+RT/T	Bv+RT/T
Co-primary Efficacy Endpoints:		
OS	N=309	N=312
Number of Patients With an Event	193 (64%)	215 (69%)
Median (months)	16.1	15.7
Hazard Ratio (95% CI)	1.13 (0.93-1.37)	
Log-Rank p-value (stratified).	p = 0.21 ^a	
PFS	N=308	N=311
Number of Patients With an Event	256 (83%)	256 (82.3%)
Median (months)	7.3	10.7
Hazard Ratio (95% CI)	0.79 (0.66-0.94)	
Log-Rank p-value (stratified).	p = 0.007	

The results of the exploratory health-related quality of life endpoints showed neurocognitive functioning deterioration addition of Bv to standard therapy (Armstrong et al. 2013; Wefel et al. 2013).

The safety profile of Bv in RTOG-0825 was consistent with that seen in previous trials across multiple tumour types for approved indications.

2.4.3. Discussion on clinical efficacy

No dose-response finding study was performed to establish the optimal dose of Bv for treatment of patients with newly diagnosed GBM. Only one dose level of bevacizumab has been investigated in patients with newly diagnosed or recurrent glioblastoma, i.e. a dose equivalent to 5mg/kg/week.

The rationale for the use of Avastin in combination with the Stupp regimen has not been satisfactorily explained by the applicant.

Cao et al. have shown that in non-enhancing tumour regions, the uptake of gadolinium-based contrast agents peaks 3-4 weeks into chemo radiotherapy treatment. In this time period the BBB/BTB disruption is most significant and likely the period with most delivery of temozolomide. Three months after RT the effect of RT on gadolinium-uptake is no longer apparent and the delivery of temozolomide is expected to be significantly reduced. Bevacizumab is a much larger molecule than temozolomide and the question remains how bevacizumab can be delivered across the BBB/BTB when the effect of radiotherapy subsides. In addition, bevacizumab has been shown to delay enhancement with gadolinium, reflecting reduced leakage into tumour thought to be due to stabilizing effects of bevacizumab. How bevacizumab is delivered to the tumour after the BBB/BTB has been stabilized is yet to be explained. This effect of bevacizumab may also reduce the delivery of temozolomide.

Design and conduct of clinical studies

BO21990 (Avaglio) study was a randomized (1:1), double-blind, placebo controlled phase III trial investigating the efficacy and safety of adding bevacizumab to the Stupp regimen. The Stupp regimen, consists of radiation therapy (RT) and concomitant temozolomide (TMZ), as well as maintenance treatment with temozolomide.

Limitations regarding radiological assessment (RA) of tumour progression in patients with glioblastoma have been debated in the scientific literature. Pseudo progression is a phenomenon related to oedema and necrosis with temozolomide and radiation which may appear as progressions on images. Pseudo response, i.e. a response seen very rapidly after start of treatment has been observed with antiangiogenic therapy in glioblastoma. It has been suggested that this is due to a normalization of the blood-brain barrier which reduces the gadolinium-enhancement. This lack of enhancement may be wrongly assessed as a decrease in tumour size, i.e. the tumour may be stable or even progressing. Thus on one hand pseudo progression with RT/T may have led to underestimation of PFS in the control arm and on the other hand pseudo response with antiangiogenic treatment may have led to an overestimation of PFS in the bevacizumab arm.

In the Avaglio study, radiological tumour assessments were performed using MRI. To assess progression a set of adapted Macdonald criteria was used, with MRI methodology that was predicted to capture enhancing (Gd-T1 sequence) and non-enhancing tumours (FLAIR/T2) as well as neurological deterioration + corticosteroid use. These criteria are in line with the RANO criteria released while the Avaglio study was under progress.

However, FLAIR/T2 method has its limitations since variations in FLAIR/T2 images are difficult to quantitatively assess [Chinot et al]. Non-enhancing tumours may also be indicative of infiltrative tumours. These may be difficult to differentiate from oedema, gliosis or treatment related leukoencephalopathy. With this method it is not clear whether bevacizumab actually influences tumour development or its effect is just a physiological change in the tumour surroundings.

In addition, conclusion on PD was taken at the end of the 4 week treatment break following the concomitant treatment phase which is considered very early and not in line with clinical practice. This method only takes into consideration early pseudo progression, and does not account for later pseudo progressions which may occur months after chemo radiotherapy [de Wit et al]. Although an algorithm was implemented in the Avaglio trial protocol in an attempt to address bias in terms of pseudoprogression (PsPD), this is considered inadequate since PsPD can occur at later time point during the treatment and premature declaration of PD based on a single scan was possible. In addition, Bv induced pseudo-response (and delayed progression) was not accounted for at all in the Avaglio trial.

No confirmatory scan was required for determination of PD and patients were taken off treatment after one scan showing progression. In cases of suspected PsPD, only one additional scan was required to decide on progression and termination of therapy. Since PsPD may be counteracted by VEGF treatment, PsPD was most frequently determined in the control arm, and consequently many patients in the control arm may have been sub-treated with temozolomide. With the limitations of the imaging techniques as previously mentioned, pseudo-response in the bevacizumab arm was not sufficiently controlled for. Thus the effect of bevacizumab may have been overestimated while patients in the control arm may have performed poorer than otherwise expected. The radiological component was the most common source leading to PD determination whether alone ($\approx 55\%$) or accompanied by neurological deterioration ($\approx 28\%$), while only a minor part of PD events were based on neurological deterioration without radiological PD. Considering the uncertainties regarding RA outlined above it would seem reassuring that the neurological component was part of the decision for a large part of the patients with PD. However, information provided by the applicant regarding the order of assessment of neurological function and radiological assessment reduces the reliability of the neurological assessment; i.e. for the majority of the patients neurological assessment (NA) was performed after the day of RA or at the same day. The investigators may well have been influenced by the results of the RA when assessing NA. Whether the investigator's evaluation of the patient's neurological function was made with or without knowledge of the radiological results was not recorded.

Efficacy data and additional analyses

The final analysis of PFS demonstrated a statistically significant 36% reduction in the risk of progression or death in the absence of prior progression for patients in the Bv+RT/TMZ arm compared to the PI+RT/TMZ arm with an increase in median PFS of 4.4 months (HR 0.64, 95%CI 0.55-0.74; $p < 0.0001$; median 10.6 vs. 6.2 months). However, the clinical relevance of the PFS is questionable in view of methodological problems associated with PFS in glioblastoma and with this type of product (see discussion above).

No improvement in OS has been demonstrated with the addition of bevacizumab to RT/T. Arguably, this may be due to cross-over at the time of progression. A number of exploratory analyses were attempted to address these issue (data not shown). However, it is difficult to draw any conclusions from such types of analyses because in the majority of cases they may be biased by patient selection.

Corticosteroid use has been reduced with the addition of bevacizumab. However, the clinical relevance of this reduction seems limited considering the relatively low dose level. The reason for the reduction may be that the tumour mass is reduced and the need for corticosteroids is diminished. However, it may be that bevacizumab acts as a substitution for corticosteroids since bevacizumab is known to reduce oedema surrounding the tumour.

No detrimental effect was found in Health Related Quality of Life (HRQoL) during treatment with bevacizumab. However, assessment of this endpoint included PD as an event and assessments were not continued beyond progression. In addition, these analyses are not able to document whether there is a difference in HRQoL between early and late progressors. Signs and symptoms of the disease were collected in a subset of the patients (N=252) and did not reveal any significant differences between the treatment arms during treatment, and at the time of PD the majority of the patients reported no signs and symptoms. In both arms nearly all patients had stable or improved KPS. As for HRQoL, signs and symptom of the disease were evaluated until PD, while KPS was also evaluated beyond PD. KPS score showed a decline at PD. However, the number of patients evaluated at and after PD was limited. Furthermore, the evaluation of HRQoL was performed by the investigator, and is likely to be biased by the investigator's knowledge of the disease assessment at PD. In conclusion, data on quality of life secondary endpoints demonstrated that bevacizumab does not have a detrimental effect on the patient's quality of life while on treatment. However, it cannot be concluded based on these analyses that bevacizumab treated patients have a better outcome in quality of life related endpoints than patients who are not treated with bevacizumab.

The publicly available results from RTOG0825 study were submitted and analyzed in relation to the BO21990 (Avaglio) results. Even though there are some methodological differences between these trials, the results are similar. Therefore RTOG0825 study seems to confirm that adding bevacizumab to RT/TMZ improves radiologically determined PFS without any improvement in overall survival. In addition, neurocognitive functioning deterioration was observed during treatment with bevacizumab.

The applicant has performed biomarker analyses to determine if plasma VEGF-A or other plasma or tumour biomarkers has predictive value in PFS. None of the biomarkers included in these analyses can be concluded as predictive of treatment effect of bevacizumab. An extensive biomarker program for Avastin across indications is on-going.

Additional expert consultation

Following the CHMP request, a Scientific Advisory Group meeting was convened on 8 January 2014 to provide advice on the following list of questions:

1. Please discuss the possible impact of the methodological limitations of neuro-imaging of brain tumours by MRI on the determination of progressive disease.

- **Is it likely that the PFS estimate is biased by PsPD induced by TMZ and pseudoresponse induced by bevacizumab?**
- **Is Fluid-attenuated inversion recovery (FLAIR) or T2-weighted sequences as used in the AvaGlio adequate to detect invasive/infiltrative tumour development?**

The SAG concluded that there is a likely and non-negligible bias due to a number of factors, in particular the mechanism of action of bevacizumab, which may influence tumor environment and integrity of the blood-brain barrier and may interfere with the assessment of tumor response.

The FLAIR method cannot be considered adequate because changes in MRI may represent other conditions, in particular oedema and gliosis, and are therefore not specific to the tumor. Furthermore, repeated imaging with FLAIR, T2-weighted and contrast enhanced T1-weighted MRI from multiple institutions are sensitive to variations in image acquisition routines, scanner hardware and operator measurement bias that limits reproducibility. Therefore, although conventional imaging is used in clinical practice to guide treatment decisions, it does not constitute a reliable method to confirm the efficacy of new agents in glioblastoma, particularly VEGF inhibitors. Indeed, even in exploratory studies, overall survival is the preferred endpoint (EORTC experience).

The algorithm implemented to address the bias in terms of pseudo-progression cannot eliminate this bias completely and cannot address important likely bias in terms of pseudo-response (and delayed progression) that is likely to be associated with bevacizumab.

This bias may also impact on the reliability of secondary endpoints related to HR-QoL, as it not possible to rule out knowledge of the status of progression prior to completion of the QoL questionnaires (despite valid efforts to minimize such bias). For similar reasons, the fact that progression was associated with a slight decrease in HR-QoL cannot be used to establish the clinical relevance of the PFS endpoint.

Furthermore, in terms of secondary HR-QoL endpoints, the effect of bevacizumab was similar to placebo or was of small magnitude. Also, there were general methodological issues with this secondary endpoint such as multiplicity and missing data (despite the relatively high compliance and valid efforts to minimize such methodological issues).

Although the PFS endpoint included clinical components (worsening of neurological symptoms or increased corticosteroid used), similar biases might have affected these endpoints since the vast majority of events included radiological progression, which also was the only criterion for progression in the majority of cases. Also, longer follow-up after progression is lacking and it is not possible to assess the reversibility of the worsening in neurological symptoms or corticosteroid use.

Lastly, the long survival observed for a significant number of patients with early progression is counterintuitive and possibly a further indication of the lack of clinical meaningfulness of the PFS endpoint in this disease.

2. Is the improvement in PFS of approximately 4 months of clinical relevance when seen in light of the results of the analyses of OS, HRQL and corticosteroid use? Please discuss the outcome of the AvaGlio study also in the context of the RTOG0825 study results.

Regardless of the size of the effect observed, the clinical relevance of the PFS endpoint is questionable in view of methodological problems associated with PFS in this disease and with this type of product (see answer to question No. 1). The magnitude of the observed effect is not of such an extent that the methodological problems can be considered negligible. Additionally, there is no clinically meaningful

effect that has been established on the basis of other clinically relevant endpoints such as OS or HR-QoL, to corroborate the claimed efficacy.

It is also difficult to discuss the outcome of the AvaGlio study in the context of the RTOG0825 study results because for the latter, results are only available in the format of publicly available presentations. Nevertheless, the claimed results from the RTOG0825 study appear consistent, i.e., no effect on overall survival and no benefit in terms of QoL, possibly even a detriment (neurocognitive functioning). However, although it would most likely not bring supportive evidence of efficacy, detailed results from the RTOG0825 study would need to be assessed (e.g., in the format of a study report, even if abridged) and, specifically, the methodology used in the trial before being able to compare the results from the two studies. Therefore, the SAG recommended that CHMP should assess the RTOG study.

3. Please discuss the possible impact of first line treatment with bevacizumab on the efficacy of subsequent post-progression therapy.

A possible impact on the efficacy of further line therapies is not a major concern, due to the fact that the size of the effect associated with second-line treatments is debatable. The theoretical possibility that treatment with bevacizumab might select more aggressive tumors remains theoretical, at least in this indication, based on the lack of an important detriment in overall survival associated with bevacizumab in this large study.

4. Is the safety profile of the proposed treatment regimen acceptable for the intended patient population?

Bevacizumab was associated with increased toxicity, including Serious Adverse Events and fatal events. However, in view of the high unmet need in this indication, the toxicity associated with bevacizumab did not raise major concerns, at least in principle. However, in the absence of an established and clinically meaningful effect, the additional toxicity associated with bevacizumab cannot be considered acceptable.

2.4.4. Conclusions on the clinical efficacy

In conclusion, there are issues regarding the radiological diagnosis of PD in this disease setting which question the clinical relevance and interpretation of the observed difference in PFS. This difference is not supported by prolonged overall survival. Secondary efficacy endpoints including HRQoL, KPS, corticosteroid use and changes in signs and symptoms of GMB did not provide evidence in support of a clinical benefit of bevacizumab treatment. Overall, the efficacy of bevacizumab in the proposed indication has not been demonstrated.

2.5. Clinical safety

2.5.1. Introduction

The Safety Analysis Population (SAP) comprised all randomized patients who received at least one dose of study treatment; 447 patients in the PI+RT/T arm and 464 patients in the Bv+RT/T arm. Of 921 patients randomized, 10 patients were excluded from the SAP because they did not receive a dose of study treatment (4 from the PI+RT/T arm and 6 from the Bv+RT/T arm). The 911 patients included in the SAP were assigned to treatment arms according to the treatment actually received; 12 of 463 patients randomized to the PI+RT/T arm received at least one dose of Bv and had their safety considered as part of the Bv+RT/T arm.

All AEs and SAEs occurring after initiation of study treatment were collected up to 90 days following the last dose of study treatment, regardless of causality. Adverse events of special interest (AESI), specified in the protocol as of particular interest for Bv safety were collected up to 6 months following the last dose of study treatment. SAEs that were considered to be related to study treatment had to be reported regardless of the time elapsed since last dose of study treatment.

The safety analyses presented for Study BO21990 are based on data collected up to a clinical cut-off date of 31 March 2012. This cut-off date was based on the protocol-specified final PFS analysis with interim OS.

Patient exposure

Table 30. Exposure to Bevacizumab/Placebo (SAP)

	PI+RT/T (N=447)	Bv+RT/T (N=464)
Concurrent Phase (10 mg/kg/q2w for 6-weeks)		
n with ≥ 1 dose	447	464
Duration (weeks)	6.1 (0.1 – 8.3)	6.1 (0.1 – 7.3)
No. of doses	4 (1 - 4)	4 (1 - 5)
No. receiving all planned doses, n %	397 (89%)	415 (89%)
Maintenance Phase (10 mg/kg/q2w for six 4-week cycles)		
No. with ≥ 1 dose, n %	357 (80%)	406 (88%)
Duration (weeks)	20.0 (0.1 - 28.3)	22.1 (0.1 - 31.3)
No. of cycles	5 (1 - 6)	6 (1 - 6)
No. completing 6 cycles, n %*	177 (39.6%)	311 (67.0%)
Monotherapy Phase (15 mg/kg/q3w until PD)		
No. with ≥ 1 dose, n %	152 (34%)	276 (59%)
Duration (weeks)	27.7 (0.1 – 96.9)	19.1 (0.1 – 88.7)
No. of doses	10 (1 – 32)	7 (1 – 29)
Total no. of doses (all phases)	12 (1 - 47)	18.5 (1 – 45)

* % of patients based on SAP

Bv treatment is always given at a fixed dose; 10 mg/kg once every two weeks (q2w) in the maintenance phase. However, for the TMZ in the maintenance phase, there was given the opportunity to escalate or reduce the dose according to defined tolerability criteria. The proportion of patients who were able to dose escalate TMZ was higher in the Bv+RT/T arm (41.3% vs. 34.8%) than in the placebo arm. A higher proportion of patients in the Bv arm also completed the 6 cycles of TMZ than in the placebo arm (64% vs. 37%).

Adverse events

System Organ Class with a ≥ 10% higher incidence rate of AEs (any grade) in the Bv+RT/T arm compared to the PI+RT/T arm were as follows: Gastrointestinal disorders (78% vs. 68%), infections and infestations (52% vs. 38%), musculoskeletal and connective tissue disorders (46% vs. 30%), respiratory, thoracic and mediastinal disorders (45% vs. 25%), vascular disorders (46% vs. 21%) and renal and urinary disorders (23% vs. 13%). A summary of adverse events (all Grades) with an incidence of ≥ 10% in either treatment arm is presented in Table 31 below.

Table 31. Summary of Adverse Events (all Grades) with an Incidence of $\geq 10\%$ in Either Treatment Arm (Safety Population)

Body System/ Adverse Event	Pl+RT/T N = 447 No. (%)	Ev+RT/T N = 464 No. (%)
GASTROINTESTINAL DISORDERS		
NAUSEA	190 (42.5)	221 (47.6)
CONSTIPATION	136 (30.4)	177 (38.1)
VOMITING	101 (22.6)	143 (30.8)
DIARRHOEA	71 (15.9)	92 (19.8)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
ALOPECIA	158 (35.3)	178 (38.4)
RASH	60 (13.4)	75 (16.2)
PRURITUS	35 (7.8)	55 (11.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
FATIGUE	179 (40.0)	189 (40.7)
ASTHENIA	63 (14.1)	80 (17.2)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
THROMBOCYTOPENIA	122 (27.3)	154 (33.2)
NEUTROPENIA	54 (12.1)	66 (14.2)
LEUKOPENIA	40 (8.9)	55 (11.9)
NERVOUS SYSTEM DISORDERS		
HEADACHE	126 (28.2)	170 (36.6)
DIZZINESS	53 (11.9)	46 (9.9)
VASCULAR DISORDERS		
HYPERTENSION	51 (11.4)	171 (36.9)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
EPISTAXIS	20 (4.5)	94 (20.3)
COUGH	39 (8.7)	54 (11.6)
METABOLISM AND NUTRITION DISORDERS		
DECREASED APPETITE	75 (16.8)	114 (24.6)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
ARTHRALGIA	27 (6.0)	68 (14.7)
PAIN IN EXTREMITY	22 (4.9)	47 (10.1)
PSYCHIATRIC DISORDERS		
INSOMNIA	40 (8.9)	52 (11.2)
INFECTIONS AND INFESTATIONS		
NASOPHARYNGITIS	26 (5.8)	60 (12.9)
RENAL AND URINARY DISORDERS		
PROTEINURIA	18 (4.0)	65 (14.0)

More patients experienced at least one grade ≥ 3 AE in the Bv+RT/T arm (62.7%) than in the Pl+RT/T arm (50.1%). A summary of Grade ≥ 3 adverse events with an incidence rate of at least 2% is presented in Table 32.

Table 32. Summary of Grade ≥ 3 Adverse Events with an Incidence Rate of at Least 2% (Safety Population)

Body System/ Adverse Event	Pl+RT/T N = 447 No. (%)	Bv+RT/T N = 464 No. (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
THROMBOCYTOPENIA	44 (9.8)	67 (14.4)
NEUTROPENIA	25 (5.6)	34 (7.3)
LYMPHOPENIA	24 (5.4)	20 (4.3)
LEUKOPENIA	13 (2.9)	18 (3.9)
VASCULAR DISORDERS		
HYPERTENSION	8 (1.8)	48 (10.3)
DEEP VEIN THROMBOSIS	19 (4.3)	13 (2.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
FATIGUE	21 (4.7)	33 (7.1)
ASTHENIA	15 (3.4)	9 (1.9)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
PULMONARY EMBOLISM	12 (2.7)	14 (3.0)
NERVOUS SYSTEM DISORDERS		
CONVULSION	13 (2.9)	8 (1.7)
INFECTIONS AND INFESTATIONS		
PNEUMONIA	7 (1.6)	11 (2.4)
GASTROINTESTINAL DISORDERS		
NAUSEA	10 (2.2)	6 (1.3)
RENAL AND URINARY DISORDERS		
PROTEINURIA	-	16 (3.4)
METABOLISM AND NUTRITION DISORDERS		
HYPERGLYCAEMIA	12 (2.7)	2 (0.4)

Adverse Events of Special Interest

Bleeding

Overall, an increase in bleeding events seen in the Bv+RT/T arm was primarily accounted for by grade 1-2 events, the majority of which were manageable mucocutaneous bleeding events that resolved without specific intervention:

Mucocutaneous bleeding events were more common in the Bv+RT/T arm (124 [26.7%] vs. 40 [8.9%]). Nearly all mucocutaneous bleeding events were grade 1 or 2. Two events (epistaxis), both in the Bv+RT/T arm, were grade ≥ 3 . These grade ≥ 3 bleeding events were treated with platelet transfusions and subsequently resolved.

Events coded under the “cerebral haemorrhage” grouping occurred in a similar number of patients in each arm (12 [2.6%] Bv+RT/T vs. 10 [2.2%] PI+RT/T). While the events in the Bv+RT/T arm tended to be more severe, the difference in the treatment arms was due to the occurrence of strokes (CVA), most of which were determined after medical review to be of ischemic origin.

Bleeding events at other sites (other than mucocutaneous or cerebral) occurred more frequently in the Bv+RT/T arm (54 [11.6%] vs. 36 [8.1%]), with the increase driven primarily by grade 1-2 events.

Arterial Thromboembolic Events (ATEs)

The overall incidence of ATEs (any grade) was higher in the Bv+RT/T arm than in the PI+RT/T arm (23 [5.0%] vs. 7 [1.6%]), respectively) as was the incidence of grade ≥ 3 ATEs (19 [4.1%] vs 6 [1.3%]).

One ATE event in each group was fatal (CVA in the PI+RT/T arm and MI in the Bv+RT/T arm). ATEs led to discontinuation of PI/Bv therapy for more patients in the Bv+RT/T arm (13 patients) than in the PI+RT/T arm (1 patient). The majority of ATE events in the Bv arm resolved with treatment (Table 33).

Table 33. Summary of Arterial Thromboembolic Events (Safety Population)

	PI+RT/T (N=447)	Bv+RT/T (N=464)
No. patients with at least one AE	7	23
No. of patients with Grade 1 AEs	1 (14%)	2 (9%)
No. of patients with Grade 2 AEs	0 (0%)	2 (9%)
No. of patients with Grade 3 AEs	0 (0%)	4 (17%)
No. of patients with Grade 4 AEs	5 (71%)	14 (61%)
No. of patients with Grade 5 AEs	1 (14%)	1 (4%)
No. of patients with Serious AE	5 (71%)	18 (78%)
Total no. of AEs	7	24
Total no. of Grade 1 AEs	1	2
Total no. of Grade 2 AEs	0	2
Total no. of Grade 3 AEs	0	4
Total no. of Grade 4 AEs	5	15
Total no. of Grade 5 AEs	1	1
Total no. of serious AEs	5	19
No. patients with Bv discontinued	1 (14%)	13 (57%)
No. patients with Bv dosage modified	0 (0%)	1 (4%)
No. patients with AE resolved	3 (43%)	14 (61%)
No. patients with trt received for AE	0 (0%)	11 (48%)
No. patients with Bv discontinued	1 (14%)	9 (39%)
No. patients with Bv dosage modified	0 (0%)	1 (4%)
No. patients with AE unresolved	3 (43%)	7 (30%)
No. patients with trt received for AE	2 (29%)	4 (17%)
No. patients with Bv discontinued	0 (0%)	3 (13%)
No. patients with Bv dosage modified	0 (0%)	0 (0%)
No. patients with trt given for AE	2 (29%)	17 (74%)
No. patients without trt given for AE	5 (71%)	6 (26%)

Medical review of all ATE events identified that most of the ATE terms can be grouped under the broad medical concept of “stroke” or cerebrovascular accidents (CVAs) (Table x) and that most of the strokes were of ischemic origin. Thus, 16 of 23 patients in the Bv+RT/T arm and 6 of 7 patients in the PI+RT/T

arm with an ATE experienced a stroke. The non-stroke ATE events included MI, peripheral arterial occlusive disease, embolism, stress cardiomyopathy, and thrombotic microangiopathy.

Table 34. Incidence of Stroke and Non-Stroke Arterial Thromboembolic Events (Safety Population)

AESI/ Adverse Event	PI+RT/T N = 447 No. (%)	Bv+RT/T N = 464 No. (%)
ALL THROMBOEMBOLIC EVENTS - ARTERIAL		
Total Pts with at Least one AE	7 (1.6)	23 (5.0)
Total Number of AEs	7	23
STROKE EVENTS		
Total Pts with at Least one AE	6 (1.3)	16 (3.4)
CEREBROVASCULAR ACCIDENT	2 (0.4)	6 (1.3)
CEREBRAL ISCHAEMIA	3 (0.7)	4 (0.9)
ISCHAEMIC STROKE	1 (0.2)	2 (0.4)
CEREBRAL INFARCTION	-	2 (0.4)
BASAL GANGLIA STROKE	-	1 (0.2)
LACUNAR INFARCTION	-	1 (0.2)
Total Number of AEs	6	16
OTHER ATE EVENTS		
Total Pts with at Least one AE	1 (0.2)	7 (1.5)
MYOCARDIAL INFARCTION	-	3 (0.6)
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE	1 (0.2)	1 (0.2)
EMBOLISM	-	1 (0.2)
STRESS CARDIOMYOPATHY	-	1 (0.2)
THROMBOTIC MICROANGIOPATHY	-	1 (0.2)
Total Number of AEs	1	7

Venous Thromboembolic Events (VTEs)

The overall incidence of VTEs was similar in both arms: any grade, 36 [7.8%] Bv vs. 43 [9.6%] PI; Grade \geq 3, 34 [7.3%] Bv vs. 36 [8.1%] PI. There were four fatal events, all of which were pulmonary embolism (1 PI+RT/T and 3 Bv+RT/T). Similar numbers of patients discontinued PI/Bv treatment or dose modified for VTE events in each arm. The VTE events resolved in a higher proportion in patients in the Bv+RT/T arm (24/36; 67%) than in the PI+RT/T arm (21/43; 49%).

Wound Healing Complications

Wound healing complications (WHC) were more frequently reported by Bv-treated patients (17 [3.7%]) than by PI-treated patients (10 [2.2%]). Seven patients in the Bv+RT/T arm reported grade \geq 3 WHC events compared with three in the PI+RT/T arm. The majority of WHC events resolved with treatment. All grade \geq 3 wound healing complications were related to the craniotomy site.

There was one fatal wound infection in a Bv-treated patient who had developed a post-operative cyst prior to study start. On Day 360, during the Monotherapy Phase of the study, the patient developed Grade 3 head wound infection leading to hospitalization. The patient died on Day 384 reportedly after stopping antibiotic therapy and following discharge from the hospital.

Six patients in the Bv+RT/T arm discontinued therapy due to WHC compared with none in the PI+RT/T arm. Three patients in the Bv+RT/T arm and 2 patients in the PI+RT/T arm had the scheduled de-bulking surgery within four weeks of starting trial treatment. None of these patients experienced significant post-operative wound-healing complications.

Hypertension

Hypertension was reported as an AE more frequently in the Bv+RT/T arm than in the PI+RT/T arm (any grade: 174 [37.5%] vs. 58 [13.0%] patients; grade 3: 48 [10.3%] vs. 9 [2.0%] patients, respectively). Hypertension was reported as resolved in the majority (>70%) of cases. Four patients required discontinuation of Bv therapy.

Proteinuria

A higher proportion of patients reported proteinuria as an AE in the Bv+RT/T arm than in the PI+RT/T arm (any grade: 65 [14.0%] vs. 18 [4.0%]; Grade 3/4, 17 [3.7%] vs. 0 [0.0%], respectively). Proteinuria resolved without specific treatment in the majority of cases; however, 14 patients discontinued Bv treatment due to proteinuria. One Bv-treated patient developed grade 4 nephrotic syndrome, which resolved with treatment.

Non-GI Abscesses and Fistulae

Five patients developed a non-GI abscess or fistula, 3 (0.6%) in the Bv+RT/T arm and 2 (0.4%) in the PI+RT/T arm. All events were grade 3 except for one grade 4 event in the Bv+RT/T arm. All the events resolved with treatment. Two patients in each arm withdrew from Bv/PI therapy for the event.

GI Perforation, Abscesses and Fistulae

Eight (1.7%) patients in the Bv+RT/T arm and one patient (0.2%) in the PI+RT/T arm experienced a "GI perforation" event (including GI abscesses and fistulae). Five of the 8 events in the Bv+RT/T arm were grade ≥ 3 (including one fatal large intestine perforation). Including the patient who died, three patients in the Bv arm discontinued Bv due to the event. Six of the seven non-fatal events had resolved with treatment at the time of the analysis. The event in the PI+RT/T arm (large intestine perforation) was grade 4 in severity, led to discontinuation of all study treatment, and was unresolved at time of the data cut.

Congestive Heart Failure

Three patients had a CHF AE; 2 in the Bv+RT/T arm and 1 in the PI+RT/T arm. Both events in the Bv+RT/T arm were grade 3 whereas a CTC grade was not assigned for the event in the PI+RT/T arm. One patient in the Bv arm discontinued study treatment due to the event. The CHF had resolved at the time of the clinical cut-off for the patient in the PI arm and for the patient who discontinued in the Bv arm, but was still unresolved at the time of the data cut for the second Bv-treated patient.

Posterior Reversible Encephalopathy Syndrome (PRES)

There were no reports of PRES in either treatment arm at the time of the clinical cut-off.

Other Selected AEs

Thrombocytopenia and infections were selected *post hoc* for further analysis since, apart from the AESIs, these were clinically relevant AEs that had a clearly increased overall incidence in the Bv+RT/T arm compared to the PI+RT/T arm.

Thrombocytopenia

The overall incidence of thrombocytopenia AEs (all grades) was higher in the Bv+RT/T arm (154 [33.2%]) than in the PI+RT/T arm (122 [27.3%]). The incidence of grade ≥ 3 thrombocytopenia AEs was also higher with Bv than with PI treatment (67 [14.4%] vs. 44 [9.8%]), but was not associated with clinically significant (grade ≥ 3) bleeding events. Discontinuation of treatment because of thrombocytopenia was balanced between the arms (Bv+RT/T 14 [3.0%]; PI+RT/T 15 [3.4%]), but the number of patients with dose modification/interruption/delay was slightly increased in the Bv+RT/T arm (24% vs. 18%).

Infections

Overall incidence (All treatment phases)

The overall incidence of infections was higher in the Bv+RT/T arm than in the PI+RT/T arm (241 [52%] vs. 170 [38%] patients, respectively). The same was true for grade ≥ 3 infections (56 [12.1%] vs. 34 [7.6%] patients, respectively). The number of fatal (grade 5) infection AEs (occurring during treatment or within 90 days of last dose), however, was similar in both groups (8 [1.7%] vs. 7 [1.6%] patients, respectively). The total number of fatal infections during the study including post-treatment survival follow-up was also similar in each group (10 [2.2%] vs. 12 [2.7%] patients, respectively).

Time to onset of infection

The data over the first 3 months of the study indicate no overall increased risk of infection with the addition of Bv to RT/T during the Concurrent Phase.

After 3 months, the curves of time to onset of infection separate, with the incidence higher in the Bv+RT/T arm. This pattern is not seen for grade ≥ 3 infections, for which the incidence is only slightly higher in the Bv+RT/T arm through the concurrent and maintenance phases of the study up to 6 months. Thus, the difference in incidence over the first 6 months is largely driven by grade 1 and 2 infections occurring during the Maintenance Phase of the study, after the TMZ dose could have been escalated (i.e., between months 3 to 4). Since more patients in the Bv+RT/T arm dose escalated and completed the maintenance phase of treatment this could account for an increased number of events in the Bv+RT/T arm relative to the PI+RT/T arm.

Beyond 6 months, greater numbers of patients were still being followed in the Bv+RT/T arm than in the PI+RT/T arm. The higher overall incidence of grade ≥ 3 AEs of infection in the Bv+RT/T arm appears to be due to AEs with an onset in this later phase of the study and may be related to prolonged treatment exposure and observation in the Bv+RT/T arm.

Sites of Infection

The grade ≥ 3 infection AEs included most commonly respiratory tract infections for which there was no clear overall imbalance across groups. The incidence of grade ≥ 3 sepsis (PTs: sepsis, septic shock, neutropenic sepsis, bacteremia, urosepsis) was higher in the Bv+RT/T arm (6 events) than in the PI+RT/T arm (1 event), as was the occurrence of grade ≥ 3 events reported as wound infections (six events, all in the Bv+RT/T arm, all post-operative cranial wounds) and skin infections (6 events vs. 1 event). There was no clear imbalance in grade ≥ 3 infections at other sites.

A summary of Grade ≥ 3 AEs of Special Interest is presented in Table 35.

Table 35. Summary of Grade ≥ 3 AEs of Special Interest for Bevacizumab (SAP)

AESI/ Adverse Event	Pl+RT/T N = 447 No. (%)	Bv+RT/T N = 464 No. (%)
ALL AESI		
Total Pts with at Least one AE	68 (15.2)	133 (28.7)
Total Number of AEs	81	159
THROMBOEMBOLIC EVENTS - VENOUS		
Total Pts With at Least one AE	36 (8.1)	34 (7.3)
DEEP VEIN THROMBOSIS	20 (4.5)	15 (3.2)
PULMONARY EMBOLISM	15 (3.4)	17 (3.7)
THROMBOSIS	3 (0.7)	3 (0.6)
VENOUS THROMBOSIS LIMB	1 (0.2)	3 (0.6)
EMBOLISM VENOUS	1 (0.2)	1 (0.2)
PELVIC VENOUS THROMBOSIS	-	1 (0.2)
VENOUS THROMBOSIS	1 (0.2)	-
Total Number of AEs	41	40
HYPERTENSION		
Total Pts With at Least one AE	9 (2.0)	48 (10.3)
HYPERTENSION	9 (2.0)	48 (10.3)
Total Number of AEs	9	48
THROMBOEMBOLIC EVENTS - ARTERIAL		
Total Pts With at Least one AE	6 (1.3)	19 (4.1)
CEREBROVASCULAR ACCIDENT*	2 (0.4)	6 (1.3)
CEREBRAL ISCHAEMIA	3 (0.7)	4 (0.9)
MYOCARDIAL INFARCTION	-	3 (0.6)
ISCHAEMIC STROKE	1 (0.2)	1 (0.2)
BASAL GANGLIA STROKE	-	1 (0.2)
CEREBRAL INFARCTION	-	1 (0.2)
EMBOLISM	-	1 (0.2)
LACUNAR INFARCTION	-	1 (0.2)
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE	-	1 (0.2)
Total Number of AEs	6	19
PROTEINURIA		
Total Pts With at Least one AE	-	17 (3.7)
PROTEINURIA	-	16 (3.4)
NEPHROTIC SYNDROME	-	1 (0.2)
Total Number of AEs	-	17
CEREBRAL HAEMORRHAGE		
Total Pts With at Least one AE	3 (0.7)	7 (1.5)
CEREBROVASCULAR ACCIDENT*	2 (0.4)	6 (1.3)
BASAL GANGLIA STROKE	-	1 (0.2)
HAEMORRHAGE INTRACRANIAL	1 (0.2)	-
Total Number of AEs	3	7
WOUND HEALING COMPLICATION		
Total Pts With at Least one AE	3 (0.7)	7 (1.5)
POSTOPERATIVE WOUND INFECTION	-	3 (0.6)
WOUND INFECTION	1 (0.2)	2 (0.4)
IMPAIRED HEALING	-	2 (0.4)
POST PROCEDURAL COMPLICATION	1 (0.2)	-
WOUND COMPLICATION	1 (0.2)	-
Total Number of AEs	3	7
GASTROINTESTINAL PERFORATIONS		
Total Pts With at Least one AE	1 (0.2)	5 (1.1)
LARGE INTESTINE PERFORATION	1 (0.2)	1 (0.2)
ANAL FISTULA	-	1 (0.2)
DIVERTICULAR PERFORATION	-	1 (0.2)
INTESTINAL PERFORATION	-	1 (0.2)
RECTAL PERFORATION	-	1 (0.2)
Total Number of AEs	1	5
FISTULA/ABSCESS		
Total Pts With at Least one AE	2 (0.4)	3 (0.6)
BRAIN ABSCESS	2 (0.4)	1 (0.2)
ABSCESS	-	1 (0.2)
CENTRAL NERVOUS SYSTEM ABSCESS	-	1 (0.2)
Total Number of AEs	2	3

AESI/ Adverse Event	PI+RT/T N = 447 No. (%)	Bv+RT/T N = 464 No. (%)
OTHER HAEMORRHAGES		
Total Pts With at Least one AE	2 (0.4)	3 (0.6)
TUMOUR HAEMORRHAGE	1 (0.2)	2 (0.4)
GASTROINTESTINAL HAEMORRHAGE	1 (0.2)	-
INTRACRANIAL TUMOUR HAEMORRHAGE	-	1 (0.2)
Total Number of AEs	2	3
CHF		
Total Pts With at Least one AE	-	2 (0.4)
CARDIAC FAILURE	-	1 (0.2)
CARDIAC FAILURE CONGESTIVE	-	1 (0.2)
Total Number of AEs	-	2
MUCOCUTANEOUS BLEEDING		
Total Pts With at Least one AE	-	2 (0.4)
EPISTAXIS	-	2 (0.4)
Total Number of AEs	-	2

* CVA codes to the standard medDRA query (SMQ) of 'cerebral haemorrhage'. However, medical review identified these events to be of ischemic origin and not haemorrhagic events. They are also counted under the medical concept of 'ATEs' in this table.

Adverse Event Onset between Time of Very First Drug Intake and 6 month(s) after Very Last Drug Intake Investigator text for Adverse Events encoded using MedDRA version 15.0. Percentages are based on N.

Multiple occurrences of the same adverse event in one individual counted only once.

Serious adverse event/deaths/other significant events

Deaths

At the time of the clinical cut-off, 258/464 (56%) patients had died in the Bv+RT/T arm compared with 253/447 (57%) patients in the PI+RT/T arm (Table 36).

Table 36. Summary of Cause of Death (PD vs. Other) for All Deaths Occurring Until the Clinical Cut-Off – March 31, 2012 (SAP)

Primary Cause of Death	Pl+RT/T N = 447 No. (%)	Bv+RT/T N = 464 No. (%)
Total No. of Deaths	253 (57)	258 (56)
DEATH FROM CAUSES OTHER THAN DISEASE PROGRESSION		
Total No. of Deaths	28 (6.3)	25 (5.4)
INFECTIONS AND INFESTATIONS		
Total no.	12 (2.7)	10 (2.2)
PNEUMONIA	2 (0.4)	3 (0.6)
SEPSIS	-	3 (0.6)
BACTERAEMIA	-	1 (0.2)
LOWER RESPIRATORY TRACT INFECTION	2 (0.4)	-
LUNG INFECTION	2 (0.4)	-
MENINGITIS CHEMICAL	1 (0.2)	-
PERITONITIS	-	1 (0.2)
PNEUMONIA ASPIRATION	-	1 (0.2)
PNEUMOCYSTIS JIROVECI	1 (0.2)	-
PNEUMONIA	-	-
PNEUMONIA RESPIRATORY	1 (0.2)	-
SYNCYTIAL VIRAL	-	-
RESPIRATORY TRACT INFECTION	1 (0.2)	-
SEPTIC SHOCK	2 (0.4)	-
WOUND INFECTION	-	1 (0.2)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total no.	3 (0.7)	5 (1.1)
PULMONARY EMBOLISM	2 (0.4)	3 (0.6)
ACUTE RESPIRATORY DISTRESS SYNDROME	-	1 (0.2)
LUNG DISORDER	-	1 (0.2)
RESPIRATORY FAILURE	1 (0.2)	-
CARDIAC DISORDERS		
Total No.	2 (0.4)	3 (0.6)
CARDIAC ARREST	1 (0.2)	1 (0.2)
CARDIO-RESPIRATORY ARREST	1 (0.2)	-
CARDIOVASCULAR DISORDER	-	1 (0.2)
MYOCARDIAL INFARCTION	-	1 (0.2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total No.	1 (0.2)	2 (0.4)
GENERAL PHYSICAL HEALTH DETERIORATION	-	2 (0.4)
DROWNING	1 (0.2)	-
GASTROINTESTINAL DISORDER		
Total Pts With at Least one AE	2 (0.4)	2 (0.4)
GASTROINTESTINAL HAEMORRHAGE	1 (0.2)	-
INTESTINE PERFORATION	-	1 (0.2)
LARGE INTESTINE PERFORATION	-	1 (0.2)
ACUTE ABDOMEN	1 (0.2)	-
NERVOUS SYSTEM DISORDERS		
Total No.	2 (0.4)	1 (0.2)
BRAIN OEDEMA	-	1 (0.2)
CEREBROVASCULAR ACCIDENT	1 (0.2)	-
CEREBRAL HAEMORRHAGE	1 (0.2)	-
HEPATOBIILIARY DISORDERS		
Total No.	-	1 (0.2)
HEPATOTOXICITY	-	1 (0.2)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
Total No.	-	1 (0.2)
TUMOUR HAEMORRHAGE	-	1 (0.2)
VASCULAR DISORDERS		
Total No.	1	-
EMBOLISM	1 (0.2)	-
DEATH FROM UNKNOWN CAUSES		
Total No.	5 (1.1)	-
DEATH	3 (0.7)	-
UNEVALUABLE EVENT	2 (0.2)	-

Timing of non-PD events leading to death in relation to treatment phase (those occurring during treatment or within 90 days of last dose), as well as those occurring post-treatment (≥ 90 days after last dose), is shown in Table 37.

Table 37. Summary of Non-PD Deaths by Cause and Treatment Phase (SAP)

Treatment Phase Cause	PI+RT/T	Bv+RT/T
During Treatment or ≤ 90 days Post-Treatment (reported as AEs)		
Concurrent/Treatment Break	5	11
Infection	4	3
Haemorrhage	1	1
Thromboembolic events (PE or MI)		3 ^a
GI perforation		1
Other		3 ^b
Maintenance	7	6
Infection	3	2
Pulmonary embolism	1	1 ^c
CVA	1	
Other		3 ^d
Unknown	2 ^e	
Monotherapy	0	5
Infection		4 ^f
MI		1
Total AEs leading to death	12	22^c
> 90 days Post-treatment		
Fatal non-PD events >90 days post-treatment	16	3
Total non-PD deaths	28	25
<small> a: includes PTs 'pulmonary embolism' (PE) in two patients, and 'cardiovascular disorder' suspected due to MI or PE; b: includes PTs 'general health deterioration' (2 pats), and 'ARDS' (1 pat); c: includes a PE that occurred 105 days after the patient stopped trial treatment on day 49. However, the patient subsequently received off-protocol anti-cancer treatment with two cycles of Bv from Day 78 to Day 120 and two cycles of TMZ from Day 78 to Day 134; d: includes PTs 'brain edema', 'cardiac arrest' and 'general physical health deterioration'; e: includes PTs 'cardio-respiratory arrest' and 'death'; f: includes one wound infection and one 'lung disorder' coding to the respiratory SOC (acute pneumopathy/pneumococcal pneumonia) </small>		

Serious adverse events

The summary of the most frequent SAEs is summarized in Table 38.

The incidence of AEs reported as serious was higher in the Bv+RT/T arm (36.6% of patients reported at least one SAE, total of 259 SAEs) than in the PI+RT/T arm (25.7%, 156 SAEs).

Table 38. Summary of Most Frequent SAEs (Incidence \geq 1% by Preferred Term or System Organ Class) (SAP)

Body System/ Adverse Event**	PI+RT/T N = 447 No. (%)	Bv+RT/T N = 464 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	115 (25.7)	170 (36.6)
Total Number of AEs	156	259
INFECTIONS AND INFESTATIONS		
Total Pts With at Least one AE	29 (6.5)	49 (10.6)
PNEUMONIA	6 (1.3)	10 (2.2)
SEPSIS	1 (0.2)	6 (1.3)
NERVOUS SYSTEM DISORDERS		
Total Pts With at Least one AE	31 (6.9)	40 (8.6)
CONVULSION	6 (1.3)	5 (1.1)
CEREBROVASCULAR ACCIDENT	2 (0.4)	6 (1.3)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total Pts With at Least one AE	14 (3.1)	28 (6.0)
THROMBOCYTOPENIA	8 (1.8)	17 (3.7)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total Pts With at Least one AE	14 (3.1)	20 (4.3)
PULMONARY EMBOLISM	12 (2.7)	13 (2.8)
GASTROINTESTINAL DISORDERS		
Total Pts With at Least one AE	10 (2.2)	18 (3.9)
VOMITING	5 (1.1)	5 (1.1)
VASCULAR DISORDERS		
Total Pts With at Least one AE	10 (2.2)	18 (3.9)
DEEP VEIN THROMBOSIS	6 (1.3)	11 (2.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total Pts With at Least one AE	8 (1.8)	13 (2.8)
PYREXIA	3 (0.7)	8 (1.7)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Total Pts With at Least one AE	11 (2.5)	6 (1.3)
METABOLISM AND NUTRITION DISORDERS		
Total Pts With at Least one AE	10 (2.2)	4 (0.9)
HYPERGLYCAEMIA	5 (1.1)	1 (0.2)
CARDIAC DISORDERS		
Total Pts With at Least one AE	2 (0.4)	10 (2.2)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
Total Pts With at Least one AE	1 (0.2)	7 (1.5)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Total Pts With at Least one AE	2 (0.4)	5 (1.1)
HEPATOBIILIARY DISORDERS		
Total Pts With at Least one AE	2 (0.4)	5 (1.1)
PSYCHIATRIC DISORDERS		
Total Pts With at Least one AE	1 (0.2)	5 (1.1)
RENAL AND URINARY DISORDERS		
Total Pts With at Least one AE	-	5 (1.1)

Laboratory findings

There was a higher incidence of newly occurring Grade 3 or 4 laboratory abnormalities for haematological tests in the Bv+RT/T arm compared with the PI+RT/T arm. In line with the AE data, the incidence of grade 4 thrombocytopenia (low platelet counts) was higher in the Bv+RT/T arm than in the PI+RT/T arm (39 [8%] vs. 15 [3%]). Other test results appeared to be balanced between the treatment arms.

Vital Signs

Consistent with the increased incidence of hypertension reported as an AE in Bv-treated patients small increases from pre-treatment baseline values were observed at the last visit in the Bv+RT/T arm for diastolic (DBP) and systolic (SBP) blood pressure. No notable changes were observed in the PI+RT/T arm. Median changes from baseline in DBP and SBP at the last visit were 3.0 and 4.0 mmHg, respectively, in the Bv+RT/T arm compared with 0.0 and -1.5 mmHg, respectively, in the PI+RT/T arm.

Electrocardiograms

Twelve-lead ECGs were recorded at screening and thereafter as clinically indicated and at the 90-day safety follow-up visit. Very few patients had an abnormal ECG result and those who did generally had the abnormal result prior to initiation of study treatment. Approximately 2% of patients with a normal ECG result at baseline had an abnormal result after initiation of treatment (8/464 [1.7%] Bv+RT/T vs. 11/447 [2.5%] PI+RT/T).

Safety in special populations

Age

In general there seems to be more AEs in the Bv+RT/T group when compared to placebo, and slightly more AEs in the ≥ 65 years group. Most striking is the higher rate of cerebral haemorrhage, grade 3/4/5 AEs and serious AEs in the ≥ 65 year group. Furthermore, there is in general a higher discontinuation rate due to AE in patients receiving bevacizumab. There also seems to be higher death rate for patients over ≥ 65 years receiving placebo. Most concerning is the clinically relevant difference in grade 3/4/5 AEs seen between Bv+RT/T and PI+RT/T, and between <65 years and ≥ 65 years.

Sex

With regard to general AEs there seems to be slightly more AEs in females compared to males and more AEs in the Bv+RT/T group. Males seem to have higher and similar death rate in both treatment groups. Looking at AESI to bevacizumab the event rates are comparable between males and females in the bevacizumab group.

Race

Since most patients were white, no comparison between different races has been made.

Discontinuation due to adverse events

Overall, a higher proportion of patients in the Bv+RT/T arm (24.6%) than in the PI+RT/T arm (13.2%) discontinued any component of treatment because of AEs. The most common AEs that led to withdrawal of treatment in both treatment arms were thrombocytopenia and neutropenia, both of which are recognized as dose limiting toxicities for TMZ. The increased incidence in the Bv treatment arm was attributable to AEs in the following SOCs:

- Infections and infestations (21 [4.5%] vs. 8 [1.8%]) – including 6 wound infections in Bv-treated patients vs. none on placebo
- Nervous system disorders (15 [3.2%]) vs. 6 [1.3%]) – including 5 CVAs in the Bv+TR/T arm vs. none in the PI+RT/T arm
- Renal disorders (15 [3.2%] vs. none) – 13 proteinuria, 1 nephrotic syndrome, 1 acute renal failure
- General disorders (7 [1.5%] vs. none) – including pyrexia (3), fatigue (2)
- Neoplasm SOC - the difference due to tumour haemorrhage (7 [1.5%] vs. none)
- Cardiac disorders (4 [0.9%] vs. none) – 2 MI, 1 CHF, 1 coronary artery stenosis

A higher proportion of patients in the Bv+RT/T arm (51.7%) than in the PI+RT/T arm (37.4%) modified any component of treatment because of an AE. The most common reasons were haemotoxicity (primarily thrombocytopenia), vascular disorders (primarily hypertension) and infections, all of which led to dose modifications in a higher proportion of patients in the Bv+RT/T arm. Of the less common reasons ($\leq 5\%$ patients in either arm), proteinuria led to dose modification in notably more patients on Bv treatment (3.0% vs. 0.4%).

Considering individual components of trial treatment, the proportion of patients experiencing an AE leading to dose interruption/delay or discontinuation of Bv/PI was higher in the Bv+RT/T arm than in the PI+RT/T arm. The same was true for AEs leading to dose modification/interruption/delay or discontinuation of TMZ. The increased incidence was mainly attributable to thrombocytopenia, hypertension, and infections for Bv/PI and to thrombocytopenia for TMZ.

A minority of patients in both arms required interruption or discontinuation of their radiotherapy treatment due to an AE (PI+RT/T 19 [4.3%] vs. Bv+RT/T 28 [6.0%]). The SOCs most frequently affected were nervous system, infections, and blood and lymphatic disorders, with no major imbalance between arms in any particular type of AE.

Post marketing experience

Bevacizumab in combination with intravenous 5-fluorouracil-based chemotherapy for the first-line treatment of patients with metastatic carcinoma of the colon or rectum was approved in the United States on 26 February 2004 and in the European Union on 12 January 2005. During the 8-year period from 26 February 2004 to 25 February 2012, a total of 53586 AEs, of which 44427 were serious, were reported in 28252 patients (2.1%). In 3411 cases (0.3%), the outcome was fatal. Overall, the incidence of patients reporting AEs, the proportion of AEs considered serious, and the incidence of patients with AEs leading to death has remained stable over this period.

The most frequently reported SAEs in patients treated with bevacizumab during the reporting period 26 February 2011 to 25 February 2012 were GI disorders (19.0%), general disorders and administration site conditions (10.5%), and infections and infestations (9.2%).

2.5.2. Discussion on clinical safety

The overall exposure and the extent of the safety database are considered satisfactory for the evaluation of safety.

A higher proportion of patients in the Bv arm were able to both dose escalate TMZ (41.3% vs. 34.8%) and to complete the planned 6 cycles of TMZ (64% vs. 37%) compared to the placebo arm, i.e. there was a greater exposure to TMZ therapy in the Bv arm. The difference in the number of patients completing the scheduled 6 cycles of TMZ was primarily due to more patients in the PI+RT/T arm

discontinuing due to PD, not primarily due to toxicity. These data indicate that the addition of Bv did not adversely affect the overall tolerability of the TMZ regimen. The follow-up period for safety assessment was approximately 4 months longer in the Bv arm than in the placebo arm, and both the higher exposure to study medication and duration may explain the differences in incidences of AEs observed across the treatment arms in this study.

Overall, there is a higher incidence of AEs in the Bv+RT/TMZ group. The AEs occurred in a pattern that reflected the safety profile of bevacizumab. These are primarily hypertension, epistaxis, proteinuria, constipation, vomiting, headache, arthralgia, and blood and lymphatic disorders. Higher incidences of grade ≥ 3 adverse events were also seen in the mentioned SOC/PTs in the Bv+RT/T group.

The incidence of SAEs was higher in the Bv (Bv+RT/TMZ) arm (36.6%) than in the Placebo (RT/TMZ) arm (25.7%), and was due partly to increased incidences of serious AESI, but also explained by higher incidences of infections (mainly pneumonia and sepsis) and thrombocytopenia. SAEs assessed as related to study treatment were also higher in the Bv arm than in the Placebo arm (23.9% vs. 14.1%, respectively) and the increased incidence in the Bv arm was primarily attributable to AESIs, thrombocytopenia and infections.

With regard to AESI, arterial thromboembolic events, mainly ischaemic strokes, were observed at a slightly higher incidence rate in this trial (5.0%) than in previous Bv trials (up to 3.8% in combination with different chemotherapies), and higher than in the PI+RT/TMZ arm (1.6%). The potentially increased risk of ATEs elderly Bv-treated patients is reflected in the occurrence of more strokes in the elderly subgroup (≥ 65 years). A review of all cases of ATEs showed that the majority of the patients had co-morbidities or risk-factors.

The overall incidence of infections was higher in the Bv arm than in the PI arm (52% vs. 38%). The same was true for grade ≥ 3 infections (12.1% vs. 7.6%). There was no single SAE with more than 2% increased incidence in the Bv arm compared to the placebo arm, but as a group, analyzed for the SOC 'Infections and infestations' overall, there were more serious infections in the Bv arm than in the PI arm (10.6% vs. 6.5%), the most commonly reported terms were pneumonia and sepsis.

At clinical cut-off date, 56% of patients had died in the Bv arm compared with 57% patients in the placebo arm, mainly due to disease progression. There was also a similar overall incidence of deaths *not* due to PD (non-PD deaths; 6.3% placebo vs. 5.4% Bv) in both treatment arms. However, there were differences in the *timing* of these non-PD deaths. During the actual treatment phases (or within 90 days post treatment), there were more non-PD deaths in the Bv arm (22 deaths) than in the placebo arm (12 deaths). The most common non-PD related cause of death was infection, with similar incidences in both arms – and hence, cannot explain the observed difference in non-PD death rates between the Bv and the control arm. More non-PD deaths occurred in the Bv arm (11) than in the control arm (5) at an *early stage*, i.e. during the concurrent phase and the treatment break. Of these 11 deaths in the Bv arm there were 3 confirmed or suspected thromboembolic events, one GI perforation and one haemorrhage, all of which could potentially be related to bevacizumab. No common pattern or risk factor associated with the early AEs leading to death was found. A causal relationship with bevacizumab cannot be excluded for these additional deaths.

Additional expert consultations

Following the CHMP request, a Scientific Advisory Group meeting was convened on 8 January 2014 to provide advice on the following question:

1. Is the safety profile of the proposed treatment regimen acceptable for the intended patient population?

Bevacizumab was associated with increased toxicity, including Serious Adverse Events and fatal events. However, in view of the high unmet need in this indication, the toxicity associated with bevacizumab did not raise major concerns, at least in principle. However, in the absence of an established and clinically meaningful effect, the additional toxicity associated with bevacizumab cannot be considered acceptable.

2.5.3. Conclusions on clinical safety

Bevacizumab has a well-known safety profile which includes hypertension, proteinuria, wound healing complications, mucocutaneous bleeding, ATEs, VTEs, GI-perforations and fistula. These AEs were also observed in Avaglio.

In combination with temozolomide and radiation there was also an increase in infections (52% vs 38%), including pneumonia, sepsis and skin infections. A higher incidence of ATEs were reported among bevacizumab treated patients in Avaglio than previously reported for bevacizumab, and higher than in the control arm of Avaglio (5% vs 1.6%). There were overall more SAEs in the bevacizumab treated patients than in the control arm; 36.6% vs 25.7%. In addition, there were more non-PD deaths reported as Grade 5 AEs in the bevacizumab arm (22 [4.7%]) than in the control arm (12 [2.7%]) with 11 and 5 out of these occurring in the early phase, i.e. within 70 days from randomisation. A causal relationship with bevacizumab cannot be excluded for these additional deaths.

Overall the risks of adding bevacizumab to the RT/TMZ are associated with increased risk of infections, increased incidence of ATEs and increased non-PD deaths in addition to all the known safety concerns with Avastin.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The assessment of efficacy in GBM is currently based on OS due to a number of limitation with the radiological endpoint PFS. Although standard methods for PFS assessment exist, and although PFS is used in clinical practice to make treatment decisions based on the totality of patient data, this endpoint cannot be considered to be a reliable endpoint to assess the efficacy of new cancer drugs, in particular, if belonging to the class of anti-VEGF drugs, as this further hampers radiological assessment of tumour size.

In the pivotal trial presented (Avaglio), no difference in OS or other clinically relevant endpoint has been observed. A difference in PFS has been observed but the clinical relevance of this observation cannot be considered established. These results were similar to those observed in a similar phase III trial (RTOG0825), also reporting no effect on OS of adding bevacizumab to RT/T whilst observing deterioration of neurocognitive functioning.

Uncertainty in the knowledge about the beneficial effects

There are serious limitations with radiological assessment of tumour response in GBM patients treated with RT/TMZ and RT/TMZ+bev. Currently, PFS cannot be considered a reliable measure of clinically

relevant effect in this disease and class of product (see discussion on clinical efficacy and SAG responses).

Risks

Unfavourable effects

Bevacizumab has a well-known safety profile which includes hypertension, proteinuria, wound healing complications, mucocutaneous bleeding, ATEs, VTEs, GI-perforations and fistula. These AEs were also observed in Avaglio.

The incidence of SAEs was higher in the Bv (Bv+RT/TMZ) arm (36.6%) than in the Placebo (RT/TMZ) arm (25.7%), and was due partly to increased incidences of serious AESI, but also explained by higher incidences of infections (mainly pneumonia and sepsis) and thrombocytopenia. SAEs assessed as related to study treatment were also higher in the Bv arm than in the Placebo arm (23.9% vs. 14.1%, respectively) and the increased incidence in the Bv arm was primarily attributable to AESIs, thrombocytopenia and infections.

With regard to AESI, arterial thromboembolic events, mainly ischaemic strokes, were observed at a slightly higher incidence rate in this trial (5.0%) than in previous Bv trials (up to 3.8% in combination with different chemotherapies), and higher than in the PI+RT/TMZ arm (1.6%). The overall incidence of infections was higher in the Bv arm than in the PI arm (52% vs. 38%).

Uncertainty in the knowledge about the unfavourable effects

There were more non-PD deaths reported as Grade 5 AEs in the bevacizumab arm than in the control arm, i.e. 22 [4.7%] vs 12 [2.7%], respectively, with 11 and 5 out of these occurring in the early phase, i.e. within 70 days from randomisation. A causal relationship with bevacizumab cannot be excluded for these additional deaths.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Based on the data presented, there was no clinically meaningful effect that has been established on the basis of clinically relevant endpoints such as overall survival or health-related quality of life. The claimed improvement in progression-free survival associated with the combination of bevacizumab+ RT/T compared to placebo +RT/T based on the Avaglio trial cannot be considered of clinical relevance in view of methodological problems associated with PFS in this disease and with this type of product.

The bevacizumab + RT/T combination was associated with increased toxicity, including serious adverse events and fatal events.

Discussion on the Benefit-Risk Balance

In the absence of an established clinical efficacy or other clinically relevant benefits, and considering the significant toxicity of the combination of bevacizumab+ RT/T, the benefit-risk cannot be considered positive in the proposed indication.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation not acceptable and therefore does not recommend, by a majority of 21 out of 31 votes, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation rejected		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to include Avastin in combination with radiotherapy and temozolomide for the treatment of adult patients with newly diagnosed glioblastoma.

Grounds for refusal:

Whereas

- The efficacy of bevacizumab in combination with radiotherapy and temozolomide for the treatment of adult patients with newly diagnosed glioblastoma has not been sufficiently demonstrated;
- In the absence of established efficacy, a positive benefit-risk balance has not been established.

the CHMP on the grounds of Article 16 of Regulation 1234/2008/EC has recommended the refusal of the variation to the terms of the Marketing Authorisation.

Re-examination of the CHMP opinion of 22 May 2014

Following the CHMP conclusion that the claimed indication in glioblastoma for Avastin was not approvable, the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

Detailed grounds for re-examination submitted by the applicant

The applicant presented his rationale in writing and at an oral explanation.

A summary of the applicant's grounds for re-examination is presented below.

Study methodology including imaging and disease assessment criteria: The applicant considered that the pivotal study (Avaglio) was designed using standard methodology in GBM for the assessment of tumour growth and followed the current clinical practice. While the applicant acknowledged that there is an on-going evolution of the criteria used to assess disease progression in brain tumours, they contended that the criteria used in Avaglio study represent the most advanced and accepted technology in line with expert recommendations. Several strategies were applied prospectively in Avaglio in order to minimize the possibility of incorrectly interpreting the MRI scan including implementation of an algorithm for the determination of pseudo-progression.

Reliability of PFS: The applicant considered that the robustness and reliability of the primary analysis of PFS was confirmed in a number of predefined and post-hoc sensitivity analyses. Key post-hoc sensitivity analyses that took into account the concerns raised by the CHMP on the reliability of the imaging technique to detect disease progression excluded patients 1) with potential or confirmed pseudo-progression, 2) with possible pseudo-progression in the PI+RT/T arm and possible pseudo-response in the Bv+RT/T arm and 3) with PFS < Day 93 to avoid any potential impact of pseudo-

progression and post-radiation imaging changes at the first disease assessment. The applicant provided an additional post-hoc PFS analysis where all progressions exclusively based on non-index lesions were not regarded as a PFS event.

Finally, the applicant provided a *post-hoc* analysis in line with the RANO criteria (Wen *et al.*, 2010), which are the current standard used in clinical trials. According to this analysis, 84% of the PFS events could be considered unequivocal.

Clinical relevance of PFS: The applicant considered that Avaglio study used a variety of validated and reliable measures to assess the clinical status that captured the patient's perspective (health-related quality of life [HRQOL]), neurocognitive function (Mini Mental Status Examination [MMSE]), and functional status (Karnofsky Performance Status [KPS]). According to the applicant, the KPS results showed a delay in time to definitive deterioration in KPS in favour of bevacizumab irrespective of whether PD was included (pre-specified) or excluded (exploratory) as an event. At the time of disease progression, the data indicated a trend for deterioration in functional status and HRQoL compared to the assessments prior to progression, which underscores the clinical importance for the patients of delaying the time until disease progression. While the Applicant acknowledged that limited data was captured beyond the time of progression, they contended that this does not diminish the value of the data captured on study.

Absence of OS benefit: According to the applicant, the use of subsequent lines of therapy, that often included bevacizumab, may have confounded the result. The applicant concluded that despite the obvious flaws and biases of the exploratory survival analyses these analyses indicated a beneficial effect of bevacizumab.

Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant.

Regarding the MRI evaluation of disease progression, the CHMP maintained the view that the impact of the use of adapted criteria in Study BO21990 remains unclear. The number of PD events may have been overestimated in the placebo arm and underestimated in the bevacizumab arm. The applicant did not convincingly show that the sensitivity analyses performed were able to mitigate the risk of systematic biases in the evaluation of PFS and were adequate to provide sufficient reassurance that bevacizumab produces a PFS increase of clinically important magnitude. In particular, the applicant did not clearly justify how the criteria chosen to exclude specific patients or events in the various sensitivity analyses were able to address the biases/uncertainties around the assessment of progression.

The results of the post hoc analysis according to the RANO criteria were not considered sufficiently robust to resolve the uncertainties around the PFS results. This analysis resulted in an estimated benefit of smaller magnitude, based on an analysis that, necessarily but problematically, introduces some informative censoring. All the additional analyses cannot exclude the possibility of important bias and the estimated effect is not regarded as sufficiently reliable to conclude that a clinically relevant therapeutic efficacy has been established.

Thus, the CHMP maintained the view that it was not possible to estimate with sufficient confidence the magnitude of the gain in tumour control provided by bevacizumab when added to standard of care.

Regarding clinical outcomes, the applicant proposed that only maintenance of QoL to the time of disease progression may be expected, and this can be accepted. However, the CHMP concluded that the positive effects claimed by the applicant are mainly driven by the inclusion of PD as an event in

these analyses, and therefore, they cannot provide independent support or insight into the clinical benefits of delaying progression. Nominally, statistically significant results were retained for some parameters when PD was not counted as a deterioration event. These analyses should be interpreted with caution since relevant data were not collected systematically after disease progression and the consequent impact of (potentially informative) censoring on the results is unclear. In addition, some assessments may have been influenced by knowledge of progression status.

Concerning overall survival, the CHMP acknowledged that no OS benefit had been observed in Study BO21990, a finding consistent with the result of the RTOG 0825 trial. It has not been established that the most likely cause for the failure to demonstrate an OS benefit is confounded by post-progression treatments (including crossover to bevacizumab) rather than lack of an effect.

In conclusion, as the clinical relevance of the efficacy results is uncertain the benefit-risk balance of bevacizumab as an add-on therapy to standard of care for newly diagnosed glioblastoma is considered negative.

Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by majority decision that the efficacy of the above mentioned medicinal product is not sufficiently demonstrated, and, therefore maintains its recommendation for the refusal of the variation to the terms of the Marketing Authorisation for the above mentioned medicinal product. The CHMP considers that:

- The efficacy of bevacizumab in combination with radiotherapy and temozolomide for the treatment of adult patients with newly diagnosed glioblastoma has not been sufficiently demonstrated;
- In the absence of established efficacy, a positive benefit-risk balance has not been established.

Appendix 1
Divergent Positions

DIVERGENT POSITION EXPRESSED BY CHMP MEMBERS

Some members of the CHMP expressed a divergent position as follows:

Divergent opinion

Efficacy

The AVAglio study (BO21990) is a large randomized study that evaluates the effect of the addition of bevacizumab to standard radiotherapy–temozolomide for the treatment of newly diagnosed glioblastoma. The study was designed based on current best practices for disease assessment using MRI for tumour response and progression. Radiographic criteria were adapted to address specific concerns related to the effect of antiangiogenic therapy on imaging. Specifically, assessment of non-enhancing tumor components was included, and a specific algorithm was used to assess pseudoprogression. These adaptations are consistent with current international consensus guidelines.

The ITT analysis included 921 patients (463 in the placebo group and 458 in the bevacizumab group). Two co-primary endpoints (investigator-reported PFS and OS) were used. Median PFS was prolonged by 4.4 months, from 6.2 months (placebo) to 10.6 months (bevacizumab) whereas median OS was almost identical for the two treatment groups (16.6 months vs. 16.8 months). It should be noted that the PFS for the placebo group is consistent with the results of multiple studies using the Stupp regimen.

The PFS gain was associated with diminished use of glucocorticoids, which may be a consequence of improved tumor control (reduced tumor mass) as well as the decreased permeability of tumor vasculature afforded by bevacizumab. More importantly, median time to KPS (Karnofsky Performance Status) deterioration ≥ 20 points was prolonged from 5.5 months (placebo) to 9.0 months (bevacizumab). A KPS of 70 indicates that the patient is capable of self-care but is not able to perform normal activity or work. The median duration of KPS ≥ 70 was 6 months (placebo) as compared to 9 months (bevacizumab). This finding suggests that the PFS gain is associated with important clinical benefit to the patient and KPS assessment is independent of tumour measurement by MRI. The quality of life was maintained during the therapy with bevacizumab. The PFS endpoint was robust across all subgroups.

It is acknowledged that MRI assessment of response and progression poses special challenges when antiangiogenic agents are included in treatment of GBM. Pseudoprogression is a phenomenon related to oedema and necrosis with temozolomide and radiation which may appear as progressions on images. Pseudoresponse, i.e. a response seen very rapidly after start of treatment has been observed with antiangiogenic therapy in glioblastoma. Several sensitivity analyses, as requested by the CHMP, all support the primary estimate. In a sensitivity analysis, where PDs only based on scans are excluded, the PFS estimate supports the primary estimate. As shown by the Applicant, to further investigate the concern with PsPD, a PFS subgroup analysis of patients who were progression-free for at least 93 days, showed a significant difference in favour of the bevacizumab arm. Another exploratory analysis excluding possible PsPD in the PI+RT/T arm and pseudoresponse in the Bv+RT/T arm was also conducted. In the Bv+RT/T arm all patients without a response within the first 92 days after randomisation in the Bv+RT/T arm were included. In the PI+RT/T arm only patients with a unmistakable PFS event in the first 92 days were included. The analysis shows significant difference in favour of Bv+RT/T arm.

The lack of OS benefit should not preclude an approval of a first-line therapy. The influence of subsequent therapies and cross-over from placebo to bevacizumab may have confounded the OS co-primary endpoint.

Several sensitivity analyses including comparison of unequivocal events of progression supported the reliability of the data obtained on PFS.

Safety

Due to the high unmet medical need in this indication, the toxicity associated with bevacizumab therapy does not raise major concerns. No detriments on OS were observed.

Conclusion on the overall B/R

There is high medical need for improved therapy of GBM. Temozolomide was the latest agent approved for the indication (EU MAA 26/01/1999). GBM is a brain tumor with significant differences from other solid tumors both in characteristics and in the presentation of the well being of patients. The applicant has provided data that shows a clinically meaningful gain in PFS when bevacizumab is added to standard radiotherapy/chemotherapy. The PFS gain is associated with a significantly prolonged functional status as measured by KPS and diminished steroid use. Thus, efficacy has been adequately demonstrated despite the lack of significantly superior OS results. The added toxicity associated with bevacizumab therapy does not raise major concerns.

B/R balance is considered favourable.

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