Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 1

Extract from the Clinical Evaluation Report for Bevacizumab

Proprietary Product Name: Avastin

Sponsor: Roche Products Pty Ltd

July 2013

TGA Health Safety Regulation

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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

1. List of commonly used abbreviations

Abbreviation	Meaning
AE	Adverse event
AESI	Adverse events of special interest
AUC	Area under plasma concentration versus time curve
C_{max}	Peak plasma concentration
DDI	Drug to drug interaction
GBM	Glioblastoma multiforme
IV	Intravenous
PPK	Population pharmacokinetics
PsPD	Pseudo progression
RT	Radiotherapy
T_{max}	Time to peak plasma concentration
TMZ	Temozolomide

2. Clinical rationale

It is worth noting that around the same time as Study BO21990 started the NCI sponsored an inter-group phase III multicentre study in the USA and Canada which was a randomised placebo controlled study in which patients with newly diagnosed GBM investigated the efficacy and safety of BVZ at a dose of 10mg/kg every two weeks with the standard radiotherapy and TMZ. This is an ongoing study.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

Module 5 contains data on four population pharmacokinetic studies namely a population pharmacokinetic report BO17704 which determines the population pharmacokinetics of BVZ in non-small cell lung cancer patients compared to population pharmacokinetics previously described in an oncology patient population with different types of cancer. Population pharmacokinetics report BO17706 which assessed the pharmacokinetics in metastatic pancreatic cancer patients and compared these to pharmacokinetics previously characterised for Bevacizumab in oncology patient populations with different types of cancer. A Genentech report involving population pharmacokinetics of BVZ report no. 03-0324-1751. A final analysis report on the population pharmacokinetic analyses of BVZ [information redacted].

A pivotal efficacy and safety Study BO21990, a randomised double-blind placebo controlled multicentre phase III trial of BVZ-placebo with TMZ and radiotherapy followed by BVZ-placebo and TMZ in patients with newly diagnosed glioblastoma. Full study reports together with tabular and written summaries are provided for all these studies.

3.2. Paediatric data

Not applicable to this submission.

3.3. Good clinical practice

All aspects of good clinical practice were observed in this submission.

4. Pharmacokinetics

In this section apart from discussing the four population pharmacokinetic analyses, a sub-study of the pivotal trial BO21990, a drug to drug interaction sub-study was undertaken and is presented here. This is performed to allow for an assessment of potential PK effect of BVZ on TMZ by comparing primarily the area under the concentration/time curve from time zero to last measurable concentration ($AUC_{0\text{-last}}$). On the basis of clearance mechanism for BVZ there was no expectation that BVZ would alter the PK of TMZ. This sub-study was undertaken during the maintenance phase in the patients with newly diagnosed glioblastoma when BVZ and TMZ were administered concurrently. The sub-study was undertaken following a treatment break after the concurrent treatment phase of Study BO21990 in which patients received TMZ and BVZ or placebo for six 28 day cycles to disease progression or unacceptable toxicity. During the first cycle of the maintenance phase TMZ was to be taken orally for the first five days of the 28 day cycle at a dose 150mg/m^2 per day and for subsequent cycles a dose of TMZ was to be escalated to 200mg/m^2 if the patient's toxicity profile permitted. BVZ or placebo in a dose of 10 mg/kg every two weeks was administered to patients of days 1 and 15 of each 28 day cycle.

PK assessments of plasma TMZ concentrations and serum BVZ concentrations were performed during the maintenance phase.

The PK outcome measures for this sub-study were to summarise the observed plasma TMZ concentrations and estimate the PK parameters (AUC, T_{max}, C_{max}) for patients in the placebo (placebo + RT + TMZ) and BVZ (BVZ + RT + TMZ) treatment arms at cycle 1, day 1 of the maintenance phase. In addition the observed serum BVZ trough and PK concentrations in patients in the BVZ treatment arms during cycles 1, 2 and 3 during the maintenance phase were to be summarised and the observed BVZ exposures compared with the predicted exposure from PPK simulations based on a dose regimen in Study BO21990.

A total of 20 patients participated in the DDI sub-study and had serum samples collected for BVZ concentration measurements. Of these 20 patients 14 were in the BVZ treatment arm and six in the control arm. BVZ concentration results based on nominal sample collection times are indicated in Table 1.

Table 1. Study BO21990 DDI Substudy: Observed serum BVZ concentrations

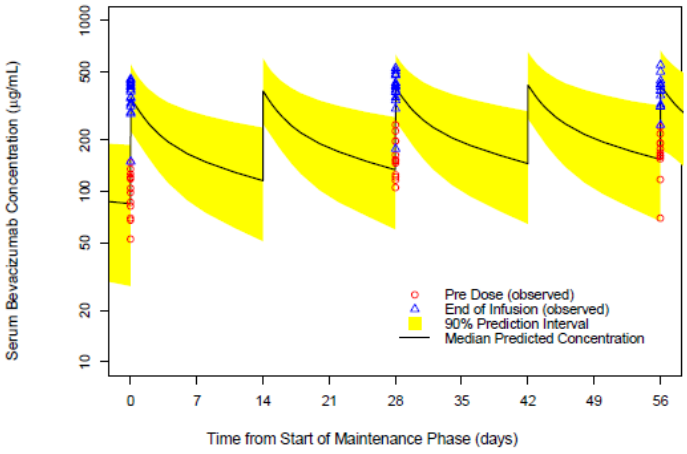
	Cycle 1, Day 1		Cycle 2, Day 1		Cycle 3, Day 1	
	Predose	Postdose	Predose	Postdose	Predose	Postdose
n	13	14	13	13	12	12
Mean	102.1	356.7	161.2	399.8	169.8	397.7
SD	29.0	81.2	43.0	94.1	44.4	83.0
%CV	28.4	22.7	26.7	23.5	26.1	20.9
Minimum	52.4	149.0	105.0	177.0	69.5	244.0
Maximum	148.0	454.0	245.0	527.0	239.0	549.0
Median	104.0	369.5	153.0	407.0	172.5	399.5

CV = coefficient of variation; DDI = drug–drug interaction; SD = standard deviation.

The observed serum BVZ concentrations for patients in the DDI sub-study relative to predictions for the median and 5th and 95th percentiles for BVZ concentrations derived from PPK simulations using the BVZ dosage regimen in Study BO21990 is indicated in Figure 1.

Figure 1. Study BO21990 DDI Substudy: Observed serum BVZ concentrations and visual predictive check

Observed serum BVZ concentrations compared with 90% prediction interval based on nominal dosing and collection times.



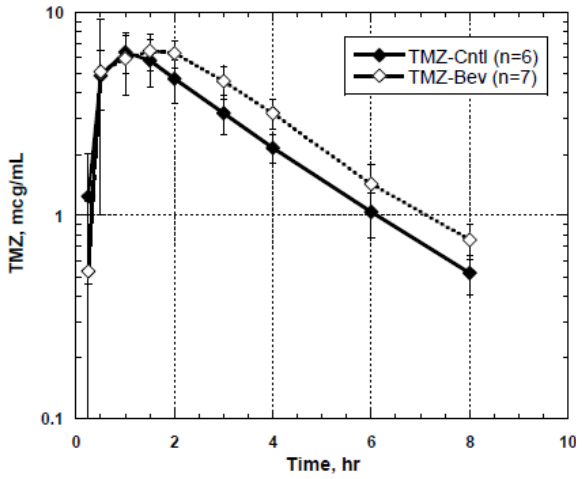
The observed median BVZ concentrations relative to the predictive median and 5th and 95th percentiles are summarised in Table 2. As indicated the observed pre-dose and post-dose BVZ concentrations during cycles 1-3 of the maintenance phase DDI sub-study had similar medians and fell within the 90% prediction interval based on simulations from the BVZ reference PPK model. Therefore the PK of BVZ in patients with newly diagnosed glioblastoma are considered to be similar to the PK of BVZ in patients with different types of cancer contained in the reference BVZ PPK model and BVZ exposure did not appear to be influenced by the presence of TMZ.

Table 2. Study BO21990 DDI Substudy: Observed and predicted serum BVZ concentrations

	Cycle 1, Day 1		Cycle 2, Day 1		Cycle 3, Day 1	
	Predose	Postdose	Predose	Postdose	Predose	Postdose
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 interval	27.8	225.6	59.9	258.2	66.5	174.5
Prediction: 95th interval	186.9	554.5	269.3	632.0	312.6	667.0

In evaluating the TMZ pharmacokinetics, 13 patients were considered evaluable for this analysis. Of the 13 patients evaluated for TMZ PK, six were in the control arm and seven in the treatment arm. The mean plus or minus SD plasma TMZ concentration/time profiles for patients in the placebo and BVZ arms of the sub-study is indicated in Figure 2. TMZ PK parameter estimates for patients in the placebo and BVZ arms are summarised in Tables 3 and 4, respectively.

Figure 2. Study BO21990 DDI Substudy: Mean ± SD plasma temozolomide concentration time profiles by treatment arm



Bev=bevacizumab; Cntrl=control; SD=standard deviation; TMZ=temozolomide.

Table 3. Study 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

AUC_{all}=area under the total concentration–time curve; C_{max}=maximum concentration; CV=coefficient of variation; PI=placebo; RT=radiotherapy; SD=standard deviation; T=temozolomide; T_{max}=time to maximum concentration; $t_{1/2}$=half-life.

Table 4. Study BO21990 DDI Substudy: temozolomide pharmacokinetics in the BVZ arm (BVZ+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

AUC_{all}=area under the total concentration–time curve; Bv=bevacizumab; C_{max}=maximum concentration; CV=coefficient of variation; Pl=placebo; RT=radiotherapy; SD=standard deviation; T=temozolomide; T_{max}=time to maximum concentration; $t_{1/2}$=half-life.

TMZ was rapidly absorbed with a mean T_{max} 0.92 hours in the control arm and 1.43 hours in the BVZ arm. TMZ was also rapidly eliminated with a half-life (T½) of 1.9 hours for the placebo arm and 1.92 hours for the BVZ arm. TMZ (AUC_{all})) was estimated to be 21mcg/hour/ml for placebo and 25.9mcg/hour/ml for the BVZ arm. TMZ C_{max} was estimated to be 6.71mcg/ml for the placebo arm 7.83mcg/ml for the BVZ arm.

The mean TMZ exposure (AUC_{all}) in the BVZ arm appears to be moderately increased by approximately 23% compared with the TMZ exposure in the placebo arm. T_{max} was slightly delayed by 30 minutes and the maximum concentrations C_{max} were similar. However owing to the limited number of patients in each treatment arm the evaluation of the effect of BVZ on TMZ pharmacokinetics must be observed with caution. These data are similar to that already published for TMZ PK. In the TMZ concentrations observed in patients in the two treatment cohorts are within the expected variability predicted from a TMZ PPK model.

> Comment: Accepting the fact that the number of patients in this sub-study were relatively small the moderate difference in TMZ exposure observed between the treatment groups is probably not clinically significant. It is to be noted that TMZ and BVZ do not share the same clearance pathways and therefore are not expected to have potential interactions with one another.

4.1. Population pharmacokinetics

Comprehensive PPK analyses have been conducted over the years. A comprehensive PPK analysis initially conducted using a first order estimation method in non-linear mixed effect modelling in eight (Phase I-III) clinical trials in which several dosage regimens of concomitant anti-neoplastic regimens were evaluated, that is, Study PK03-0324-1751.

The analysis included a total of 491 patients who received IV dose of BVZ ranging from 1-21mg/kg at a dosing frequency of once weekly, every two weeks or every three weeks. Of the 491 patients included in the PPK model 276 were female and 215 were male. The final model estimates of individual parameters are summarised by study in Table 5. This is considered the reference PPK model for other PK analyses. It is noted that the model estimate terminal half-life of BVZ to be approximately 20 days with a range of 11-50 days in a predicted time to steady state of approximately 100 days. The slow CL and long terminal $T_{½}$ of BVZ allows the BVZ to be administered at every 2-3 weeks in combination with other chemotherapeutic agents depending upon respective chemotherapy administration schedules.

Table 5. Mean (CV%) of pharmacokinetic parameters and co-variates by study

	Study, Concomitant Chemotherapy, and Tumor Type								
	AVF0737g	AVF0757g	AVF0761g	AVF0775g	AVF0776g	AVF0780g	AVF2107g	AVF2119g	
Parameter	None (Single Agent) ST	Carboplatin/ Paclitaxel NSCLC	Doxorubicin Carboplatin/ Paclitaxel 5-FU/LV ST	None (Single Agent) HRPC	None (Single Agent) MBC	5-FU/LV CRC	5-FU/LV/ Irinotecan 5-FU/LV CRC	Capecitabine MBC	All Studies
n	15	60	12	15	74	65	215	35	491
CL (L/day)	0.225 (38.2)	0.233 (39.6)	0.230 (23.5)	0.270 (33.5)	0.196 (29.3)	0.248 (29.5)	0.246 (30.5)	0.178 (25.7)	0.232 (33.1)
V_c (L)	2.7 (17.2)	2.8 (21.2)	3.3 (25.0)	3.6 (18.2)	2.5 (17.0)	3.1 (19.8)	3.1 (20.6)	2.6 (19.7)	2.9 (22.0)
K_{12} (day^{-1})	0.223	0.223	0.223	0.223	0.223	0.223	0.223	0.223	0.223
K_{21} (day^{-1})	0.215	0.215	0.215	0.215	0.215	0.215	0.215	0.215	0.215
K_{10} (day^{-1})	0.0826 (33.0)	0.0823 (29.5)	0.0704 (17.1)	0.0749 (26.3)	0.0784 (23.0)	0.0804 (23.2)	0.0793 (19.7)	0.0695 (21.7)	0.0787 (23.2)
$t_{1/2\alpha}$ (days)	1.43 (3.4)	1.43 (3.0)	1.45 (1.5)	1.45 (2.4)	1.44 (2.2)	1.44 (2.3)	1.44 (1.9)	1.46 (1.9)	1.44 (2.3)
$t_{1/2\beta}$ (days)	20.6 (27.4)	20.4 (25.4)	22.5 (17.2)	21.7 (19.9)	20.9 (24.0)	20.6 (27.9)	20.4 (21.3)	23.1 (21.6)	20.8 (23.4)
Weight (kg)	75.1 (19.3)	71.3 (24.6)	78.0 (22.2)	93.5 (24.7)	68.1 (20.4)	74.9 (24.1)	81.3 (26.5)	74.7 (22.3)	76.9 (25.8)
ALK (U/L)	107.1 (58.2)	104.2 (30.4)	104.5 (58.0)	131.3 (76.2)	139.4 (81.1)	226.8 (96.3)	164.0 (93.2)	101.9 (38.6)	152.7 (93.7)
SGOT (U/L)	41.9 (77.4)	28.4 (73.8)	36.4 (54.3)	22.8 (36.6)	51.5 (129.5)	47.7 (102.3)	36.7 (78.2)	37.9 (87.6)	39.2 (100.9)
Albumin (g/L)	38.5 (7.2)	36.2 (16.0)	40.6 (11.4)	41.9 (7.6)	35.8 (8.9)	34.1 (13.7)	37.6 (12.2)	38.8 (10.1)	37.0 (12.8)
Male (n)	3	32	6	15	0	30	129	0	215

ALK = alkaline phosphatase; CL = clearance; CRC = colorectal cancer; CV = coefficient of variation; 5-FU = 5-fluorouracil; HRPC = hormone-refractory prostate cancer; K_{10} = elimination rate constant; K_{12} = distribution rate constant from first compartment to second compartment; K_{21} = distribution rate constant from second compartment to first compartment; LV = leucovorin; MBC = metastatic breast cancer; NSCLC = non–small cell lung cancer; SGOT (AST) = aspartate aminotransferase; ST = solid tumor; $t_{1/2}$ = elimination half-life; V_c = volume of central compartment.

It is noted that this PPK model also included additional co-variates which accounted for inter-individual variability in the PK of BVZ such as different chemotherapeutic agents used in combination. This allowed for the assessment of the effect co-administered chemotherapy evaluated on the PK of BVZ. It is noted that CL of BVZ given in combination with bolus Irinotecan, 5-FU and Leucovorin was not different from that of BVZ as a single agent but for the other BVZ combination the CL of BVZ was 17% slower.

Overall the PK parameters were similar for BVZ at all doses in the studies whether the drug was administered as a single agent or in combination with chemotherapy suggesting that the PK of BVZ is not markedly affected by concomitant administration of chemotherapy drugs evaluated to date.

> Comment: This analysis demonstrated the population PK parameters for BVZ are similar to that estimated for other IgG antibodies. Weight and gender were the most influential co-variates on BVZ CL and V_c. Given the low inter-patient variability and the modest effects of co-variates on BVZ CL and V_c this analysis supports the weight based dosing regimen proposed for BVZ.

Study BO17704 was a population PK analysis of BVZ in patients with advanced or recurrent non-squamous non-small cell lung cancer who had not received prior chemotherapy. This was undertaken to determine whether the PK of this patient population was comparable with population PK previously described in an oncology patient population with different types of cancer. It was a randomised three-arm double-blind phase III study assessing two doses of BVZ in combination with Cisplatin and Gemcitabine versus Cisplatin and Gemcitabine plus placebo as first line treatment. Population PK samples for BVZ were taken at pre-dose and immediately after end of IV infusion of cycle 1-6 and at pre-dose only to cycle 7 in a sub-set of 210 patients. The number of patients included in the population PK data set was 138 with 68 at the BVZ dose of 7.5mg/kg and 70 at the BVZ dose of 15mg/kg.

A Bayesian feedback analysis of the BVZ serum PK concentrations were performed and individual PK parameter estimates for the patient population were obtained based on a previously developed population PK model for patients with different types of cancer. These PK parameters for the lung cancer population were compared to the reference model.

The comparison of the 90% prediction interval for the observed data showed that overall 8.74% of the observations were actually found to lie outside the interval (9.96% outside for low dose and 7.47% for the high dose). As the comparison for the 90% prediction interval with the individual predicted data, showed that overall 4.51% of the individual predictions were to be found to lie outside the interval (4.24% outside for low dose and 4.79% for high dose). No clinically relevant differences in PK parameters, that is, clearance, central and peripheral volumes were found between the lung cancer and reference oncology population. Inspection of the goodness of fit plot showed that the empirical Bayesian estimation based on the reference model was describing the data well without obvious bias.

> Comment: No relevant differences were found in the Bayesian estimates of clearance and central and peripheral volumes between the lung cancer patients and the oncology patients including the pooled data analysis. This finding supports the conclusion that the population PK of BVZ in this lung cancer population is comparable with the population PK of BVZ in other oncology patient population.

In Study BO17706 individual BVZ concentrations/time profile of random individual PK parameters from the Study BO17706 in metastatic pancreatic cancer predicted on the basis of empirical Bayesian estimates from a comprehensive PPK model and was used to assess comparability with a simulated PK profiles and parameters from a reference model.

The observed BVZ trough levels in patients with non-metastatic pancreatic cancer showed a slight increase in serum concentrations from week 3 to week 9 consistent with BVZ $T_{1/2}$ of 20 days.

A comparison of the 90% prediction intervals indicated (a) 7.2% of the observed data within this interval when actual time points were grouped in 24 hour intervals and 88% were within interval when planned time points were used. Overall the results show that the median of the observed data fell within the 95% CI for the majority of the time points when time points were grouped by 24 hour intervals were used and full time points were planned and used.

The individual parameter estimates obtained for the population with pancreatic cancer were similar to those obtained for the reference population. The median volume and mean volume of the central compartment (V_2) were slightly higher in the pancreatic cancer population which can be explained by the difference in co-variate distribution because the ratio of male to females was higher in this population than the reference population.

> Comment: These data again showed that PK in the pancreatic cancer population is comparable to PK in a reference population from which the current model is developed as in line with that from previous population PK analyses.

The population PK analysis of BVZ [information redacted] involved a population PK analysis of patients with various tumour types receiving multiple intravenous infusions of BVZ either as single agents or in combination ranging from 1-21mg/kg with frequencies ranging from weekly to every three weeks. BVZ PK was characterised by a two-compartment model with first order elimination. The data analysed using non-linear mixed effects modelling (NONMEN).

On the 773 patients included for analysis, there were 6108 BVZ samples and for a typical subject treated with BVZ co-administered with other chemotherapy clearance of 9.2ml/hr central volume of distribution 3280ml and inter-compartmental clearance was 15ml/hr and peripheral volume 3850ml corresponding to a disposition elimination half-life of 2.8 days and 27 days respectively. Significant co-variates in order of decreasing influence between subject variability for the parameter were CL clearance/baseline body weight, albumin, tumour burden and sex.

These data when shown as two compartment linear model described the data well with the precise parameter estimates and goodness of fit plots to indicate good model fit. The main co-variate effects, that is, weight, gender and albumin, on clearance of weight and gender and central volume are common between the previous and current population PK model.

Comment: This data from the various population PK studies together with the PK drug to drug interaction sub-study for the pivotal trial showed that for BVZ given in combination with various chemotherapy agents across tumour types showed no obvious potential for PK drug to drug interaction between the various chemotherapy agents and BVZ. This also indicates that there appears to be no requirement for dose modification for other chemotherapeutic agents used in combination with BVZ.

5. Pharmacodynamics

No new data submitted.

6. Dosage selection for the pivotal studies

No formal dose finding study was performed to determine the optimal dose of BVZ for the proposed indication. However previous clinical studies undertaken with doses ranging from 1-20mg/kg every 1 to 3 weeks have revealed a positive benefit/risk ratio of BVZ given the same weekly dose equivalent of 5mg/kg per week as proposed for the pivotal Study BO21990. Furthermore in the relapsed GBM setting this dose schedule has been utilised demonstrating clinical activity and acceptable safety. It is also to be noted that a controlled assessment of benefit from the continuation of BVZ until disease progression including as a single agent after stopping maintenance TMZ as planned in Study BO21990 had not been addressed in the newly diagnosed GBM development programme. It is however considered that as every effort should be undertaken to prolong progression free survival after discontinuation of TMZ that this approach is justified. It is not expected that there would be cumulative toxic risks associated with prolonged usage of BVZ in the maintenance situation.

7. Clinical efficacy

Efficacy data for this submission comes from the pivotal Phase III trial BO21990, a multicentre randomised double blind placebo controlled study comparing the combination of TMZ and radiotherapy with bevacizumab versus TMZ plus radiotherapy and placebo. Overview of the study is indicated in Table 6. It is to be noted that the clinical efficacy data in this evaluation comes from assessment of the co-primary endpoint of progression free survival (PFS) which corresponded to the interim analysis of the co-primary endpoint of overall survival (OS). This data ongoing with the data for the protocol specified final OS anticipated being available at the end of the second quarter 2013.

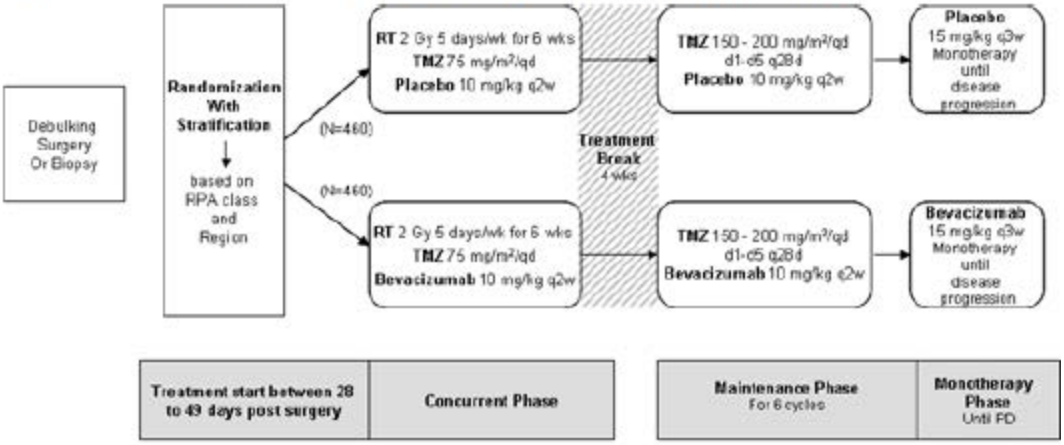
Table 6. Summary of study contributing to efficacy evaluation

Study No. (Phase)	Study Design, Control Type	Population	No. of Patients	Dose, Route, and Regimen
BO21990 (Phase III) 5.3.5.1.1/Vol.4/p.1	Multi-center, randomized, double-blind, placebo controlled	Patients with newly diagnosed GBM, histologically confirmed, with surgical resection or biopsy, no previous chemotherapy or RT	921 (458 Bv+RT/T, 463 Pl+RT/T)	**Concurrent phase** Pl or Bv (10 mg/kg.q2w) for 6 wks concurrent with RT (2.0 Gy fractions 5 days/wk to a total dose of 60.0 Gy) and TMZ (75 mg/m^{2}qd), followed by a treatment break for 4 wks. **Maintenance phase** Pl or Bv (10 mg/kg.q2w) and TMZ (150-200 mg/m^2 day 1-5 of each 28 day cycle) for max 6 cycles.**Monotherapy phase** Pl or Bv (15 mg/kg.q3w) until PD or unacceptable toxicity

AE = adverse event, AESI = AE of special interest, Bv = bevacizumab, Gy = Gray, PD = disease progression, q2w = once every 2 weeks, RT = radiotherapy, T or TMZ = temozolomide, wk = week

In the study, 921 patients with newly diagnosed glioblastoma multiforme (GBM) were randomly assigned on a 1:1 basis to either one of two treatment arms by a central stratified block randomisation procedure and overview of the study design and treatment schedule as indicated in Figure 3.

Figure 3. Overview of study design and treatment schedule



The two primary objectives of the study were to demonstrate the superiority of PFS as assessed by the investigator and superiority in OS when BVZ is added to TMZ with radiotherapy followed by TMZ for the treatment of patients with newly diagnosed GBM. Secondary efficacy objectives included comparison between treatment arms of PFS which were assessed by an independent review facility (IRF), one year and two years survival and health related quality of life (HRQoL) outcomes.

Trial treatment was to start between four and seven weeks after debulking surgery or biopsy of the GBM. Trial treatment for the three phases is indicated in Figure 3 described as concurrent phase, maintenance phase and monotherapy phase. After progressive disease patients were followed for safety, survival and subsequent anticancer therapy every nine weeks.

Evaluation of the disease response to therapy was as via a revised MacDonald response criteria which is based on the combination of radiological tumour assessments, neurological examination and corticosteroid use. This is indicated in Table 7.

Table 7. Disease assessment based on adapted MacDonald criteria.

Response	Macdonald	AVAglio (Adapted Macdonald)
CR[a]	• Disappearance of all enhancing measurable and nonmeasurable disease (sustained for ≥4 weeks) • No new lesions • Clinically stable or improved • No corticosteroids	• 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]	• ≥50% decrease of all measurable enhancing lesions (sustained for ≥4 weeks)[c] • No new lesions • Clinically stable or improved • Stable or reduced corticosteroid dose	• ≥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]	• Does not qualify for CR, PR, or progression • Clinically stable	• Does not qualify for CR, PR, or progression • Improved or stable neurologic symptoms • Corticosteroid dose alone does not affect determination of SD
Progression[b]	• ≥25% increase of enhancing lesions[c] • Any new lesion • Clinical deterioration	• ≥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

CR: complete response; PD: progressive disease; PR: partial response; SD: stable disease.

See **Protocol Appendix 8** 5.3.5.1.1/Vol.20/p.3791 for details in the definition of index and non-index lesions

[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.

[d] Increases and decreases in corticosteroid intake were to be clinically justified. Increases in corticosteroid dose for reasons other than for disease control did not need to be recorded and taken into consideration when making this comparison. The corticosteroid dose was to be kept stable for 5 days prior to the MRI scan in order to minimize interference of corticosteroids in the interpretation of response.

The final analysis of PFS was planned up to 677 patients who had a PFS event either progressive disease or death. Two interim analyses of overall survival were planned and the first when at least 50% of patients for the final OS analysis had been observed and the second at the time of the final PFS analysis when at least 72% of events for the final OS had been observed. The final analysis of OS is planned to be performed when approximately 683 deaths or 100% of events have occurred.

The potential occurrence of pseudo-progression (PsPD) was evaluated at first disease assessment prior to start of maintenance phase according to a strict algorithm. At this time point a >25% increase in index lesions and unequivocal progression of existing non-index lesions relative to the baseline disease assessment were assessed as PsPD thus allowing continuation of trial treatment. Further review was undertaken a period of two months later. If a confirmatory scan showed further tumour progression or death had occurred in the meantime the initial assessment at the end of the treatment break was retrospectively assigned designated

as PD. Conversely if the scan did not show progression then this is confirmed as PsPD and the patient remained on treatment.

All patients MRI scans were assessed by the IRF and the overall assessment of PD or non-PD was determined by a pre-specified algorithm combining the IRF radiological assessment and the investigators neurological evaluation.

As such, changes in health related quality of life were undertaken utilising a core instrument (QLQ/C30) supplemented by a brain cancer specific module EORTC BM20. The QLQ/C30 items self-report questionnaire which patients rate the items on a 4-point scale measuring a number of domains, including physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning etc. The BM20 consisted of four scales comprising multiple items including future uncertainty, visual disorder, motor dysfunction, communication deficit, non-specific symptoms including headache, seizures, drowsiness, hair loss etc. Both instruments have been validated. The primary analysis of HRQol considered to be the most relevant for the current study is supported by literature included the QLQ/C30 global health status/QoL; QLQ/C30 physical functioning; QLQ/C30 social functioning; BM20 motor dysfunction; BM20 communication deficit.

Statistical analyses were undertaken utilising stratified log rank tests and the trial being determined as positive if at the time of the OS interim analysis and final PFS analysis there was a statistically significant difference between treatment arms in PFS in favour of BVZ with a HR <0.769 and a non-detrimental effect on OS (HR<1.0) or a statistically significance difference between the two treatment arms for OS in favour of BVZ. Definitions of key endpoints, statistical tests and significance levels applied are indicated in Table 8. Furthermore several sensitivity and robustness analyses were performed on the co-primary endpoints.

Table 8. Summary of key efficacy endpoints and analysis in Study B021990

Endpoint	Definition of Event	Censoring	Stratification Factor	Test (Sig Level)
Co-primary Endpoints				
OS	death due to any cause	time patient last known to be alive	RPA class and region	log-rank 0.0141[a]
PFS (investigator -assessed)	progression per adapted Macdonald criteria, death due to any cause	last disease assessment of non-PD, or at randomization for those w/o post-BL assessment	RPA class and region	log-rank 0.01
Secondary Endpoints				
IRF-PFS	as for investigator-assessed PFS	as for investigator-assessed PFS	RPA class and region	log-rank
1-year and 2-year survival rates	as for OS	as for OS	RPA class and region	z test
Time to definitive deterioration in HRQoL subscales	change from BL of 10 points with no subsequent improvement or PD or death [b]	at last HRQoL assessment, or at randomization for those w/o post-BL assessment	RPA class and region	log-rank[c]

a Significance level for the second IA of OS according to Lan and DeMets spending function using a O'Brien and Fleming boundary function.

b Standardized scores range from 0 to 100. A 10-point change is considered a clinically relevant deterioration [10415:5.4/Vol.41/p.1817] (10-point decrease for QLQ-C30 selected subscales, 10-point increase for BN20 selected subscales). The analyses were planned including PD as event, and repeated removing PD as an event (posthoc).

c Hochberg's procedure was applied to adjust for the multiplicity of treatment comparisons in the analysis of time until definitive HRQoL deterioration for the five selected subscales.

IRF: independent review facility; OS: overall survival; PFS: progression-free survival; RPA: recursive partitioning analysis;

The primary analysis of HRQoL was time to definitive deterioration which was defined as a change from baseline of 10 points with no subsequent improvement or PD or death. PD was

included in the definitive deterioration competent endpoint because it signified a clinically relevant change in the patients' disease status.

Analyses of corticosteroid use were performed on two sub-sets of patients according to their baseline corticosteroid dose defined as the average Dexamethasone equivalent dose to the GBM control within five days before the first administration of trial treatment. Patients were considered off steroids for 0-<2mg or on steroids at least 2mg. The five day period was in line with the criteria for determining stability at the corticosteroid dose.

Considering the results of the study. The demographic characteristics of the patient population were balanced between the two treatment arms. Most patients were White and the mean age was 56 years in both arms and 22% of patients were >65 years. Distribution across various regions participating demonstrated that Western Europe contributed 51% of patients and the remainder of the regions were well balanced.

Baseline disease characteristics were also well balanced between the two treatment arms. Baseline corticosteroid use was similar between the two arms of treatment with the majority of patients being off steroids and the remainder of patients received daily doses of from 2mg to a maximum of 45mg with the majority at doses of <10mg.

With regards to enzyme inducing anti-epileptic drugs (EIAED) the use of these were well balanced between the two treatment arms with the most commonly reported of these being anticonvulsants such as Phenytoin in 14% of patients in both arms and Carbamazepine in 12% of patients in both arms.

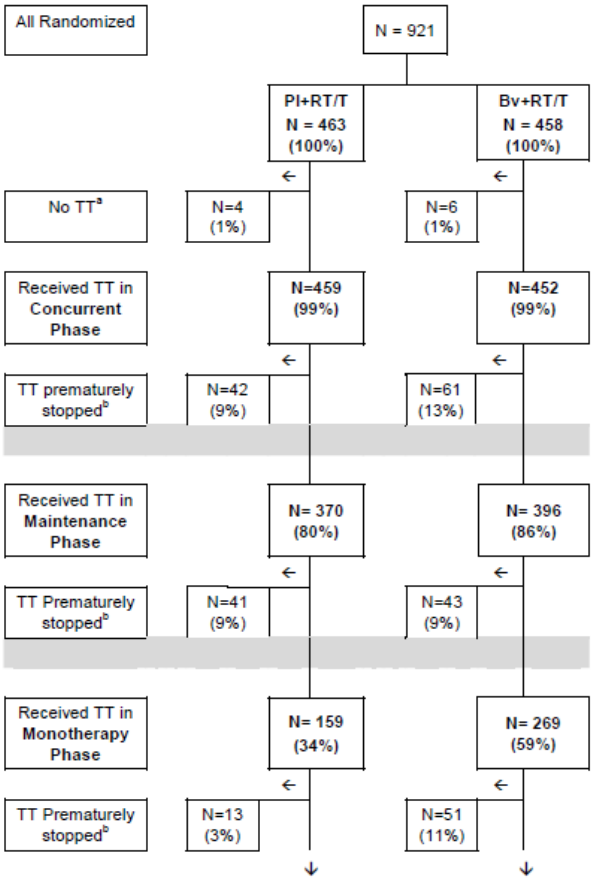
The proportion of patients with abnormal neurological findings at baseline was <20% in both treatment arms with the highest incidence of reported abnormality being motor function and gait followed by speech and language. Patients' neuro-cognitive functions were similar in both arms with MMSE score being a median of 29.

The incidence of signs and symptoms was equivalent in both arms with the most common being headache, memory deficit, motor deficit, speech deficit and visual deficit.

Baseline health related quality of life were similar between the two treatment arms.

Summary of patient disposition at the time of clinical cut-off, that is, 31 March 2012 is indicated in Figure 4. At the time of clinical cut-off the median duration of survival follow up was approximately 14 months in both arms with 174 or 38% of patients alive on treatment or in follow up in the placebo arm and 189 patients or 41% alive on treatment or in follow up in the BVZ arm.

Figure 4. Summary of patient disposition (as randomised)



TT = Trial treatment (Concurrent TT = Bv or PI+RT/T; Maintenance TT = Bv or PI+T; Monotherapy = Bv or PI)

a Reasons for not receiving treatment included: violation of entry criteria (PI+RT/T 1; Bv+RT/T 2), Withdrawn consent (1 Bv+RT/T), Adverse event (1 patient in each arm), Progression prior to treatment (1 PI+RT/T) and administrative/other (PI+RT/T 1, Bv+RT/T 2).

[b] defined as prematurely withdrawn from any component of TT (thus, excluding patients whose reason for stopping TT was PD or death due to PD).

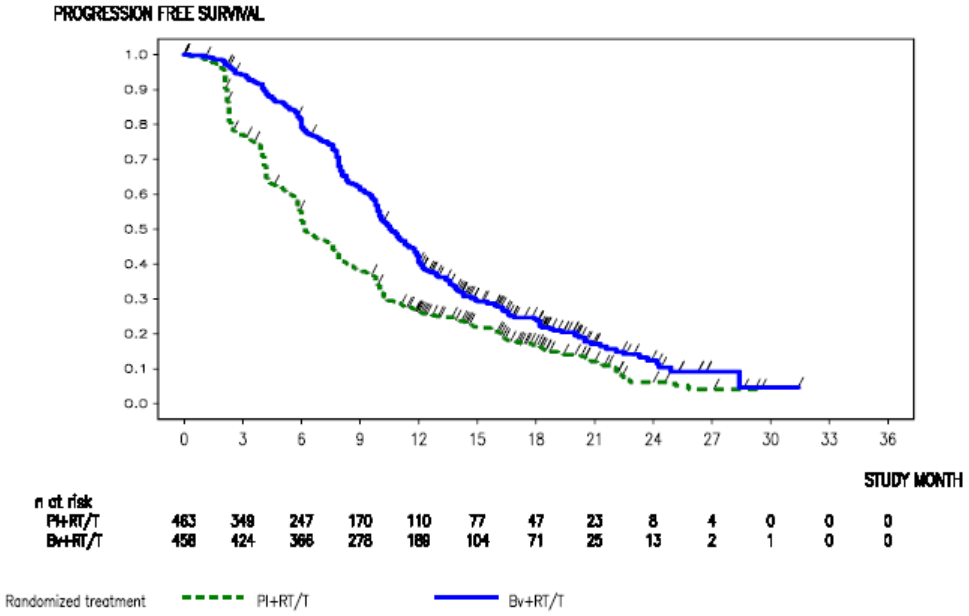
In total 921 patients were randomised, 463 to placebo and 458 to the BVZ arm. Of these four patients in the placebo arm and six in the BVZ arm did not receive any trial treatment thus a total of 911 patients start with the trial treatment.

It is to be noted that more patients on the BVZ arm, that is, 86% than the placebo at 80% continued treatment on the maintenance phase of the trial and more patients on the BVZ arm, that is, 59% continued treatment in the monotherapy phase compared to placebo at 34%.

Patients could be withdrawn from any of the trial treatment components or from any combination however if radiotherapy was discontinued all trial treatment was to be discontinued. The number of patients withdrawn from radiotherapy was small being 5% in each arm, the main reason being adverse events or PD in the placebo arm and adverse events in the BVZ arm. More patients in the BVZ arm, that is, 67% compared to the placebo arm at 40% completed with TMZ per protocol. The most common reason for withdrawal from TMZ treatment was PD 42% for placebo and 13% for BVZ followed by adverse events at 11% for placebo and 14% for BVZ. A total of 89% of patients had withdrawn from placebo and 85% from BVZ at the time of clinical cut-off. The most common reasons for withdrawal from placebo were PD at 70% and BVZ at 52%. More patients withdrew from BVZ due to an adverse event of 22% compared to placebo at 10%. After disease progression patients would be followed for safety and survival only. A total of 31 patients, 20 placebo and 11 BVZ withdrew from survival follow up.

Reviewing the primary efficacy endpoints. Primary analysis of PFS demonstrated clinically meaningful and statistically significant 36% reduction in the risk of experiencing a PFS event, for patients in the BVZ arm compared to the placebo arm with an HR 0.64 and 95% CI 0.55-0.74 P<0.0001 and Kaplan-Meier estimated median of 10.6 versus 6.2 months. The curves separated early and were maintained for up to 24 months as indicated in Figure 5.

Figure 5. Plot of Kaplan-Meier estimates for PFS (ITT)



The distribution of the type of first PFS event was similar across treatment arms. Disease progression was triggered by the radiological assessment alone for 55% of patients in the placebo arm and 56% in the BVZ arm. The neurological assessment included corticosteroid use also as components in the diagnosis of PD in 28% for the placebo and 27% of the BVZ patients. Approximately 9% of patients in each arm were diagnosed with progression based only on clinical grounds. Of the 29 placebo and 32 BVZ patients whose PFS event was determined by death, 8 versus 12 deaths were not considered by the investigator to be due to PD or to the underlying GBM.

Duration of follow up, reasons for lost to follow up and censoring patterns are similar between the treatment arms with a median duration of follow up for patients without progression or death being 16.2 months in the placebo arm compared to 17.5 months in the BVZ arm.

Sensitivity analyses to test the robustness of the results for the co-primary efficacy variable PFS support the primary analysis. It is also noted that review of the results for the per protocol population were consistent with the results for the intent to treat population.

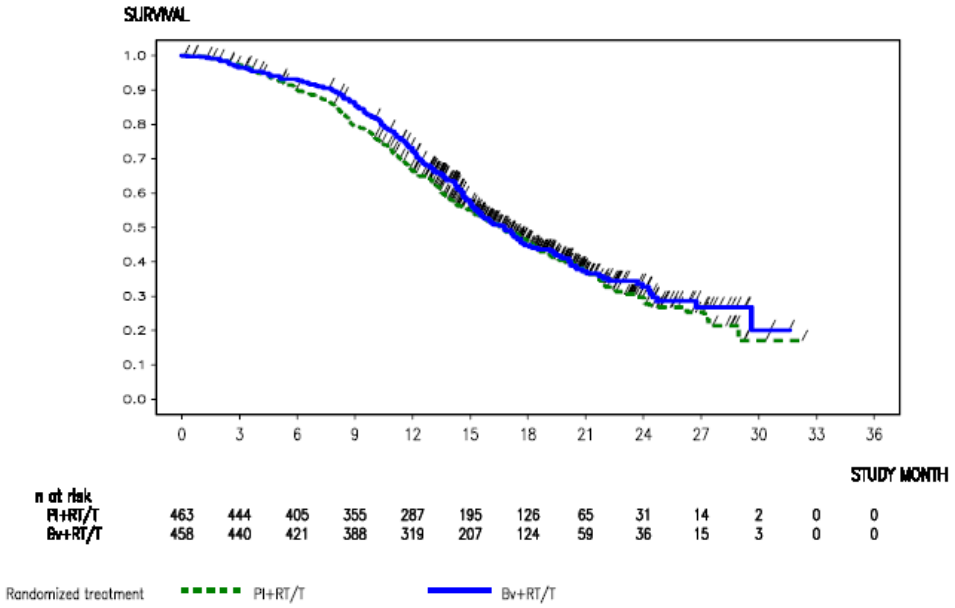
Exploratory Cox regression analyses further assessed robustness and conclusions drawn from the primary analysis of PFS taking into account the prognostic factors, the results were consistent with the overall analyses in a similar reduction of risk of progression or death favouring to the BVZ arm over the control with an HR 0.61.

A total of 20 placebo and 41 BVZ patients received at least one subsequent anti-neoplastic drug therapy prior to experiencing regression, with the most common type of subsequent anti-cancer therapy being TMZ in each treatment arm. It is also to be noted that the rate of confirmed PsPD was low at 9.3% for placebo and 2.2% for BVZ.

Reviewing the data for overall survival at the second interim analysis revealed that the addition of BVZ to RT and TMZ resulted in a 11% reduction in the risk of death with an HR 0.89 P=0.2135 and KM estimated median of 16.8 versus 16.6 months and is indicated in Figure 6. At the time of

the cut-off, 76% of patients or 517 of the deaths required for the final analysis of OS had occurred.

Figure 6. Plot of Kaplan-Meier estimates for overall survival (ITT)



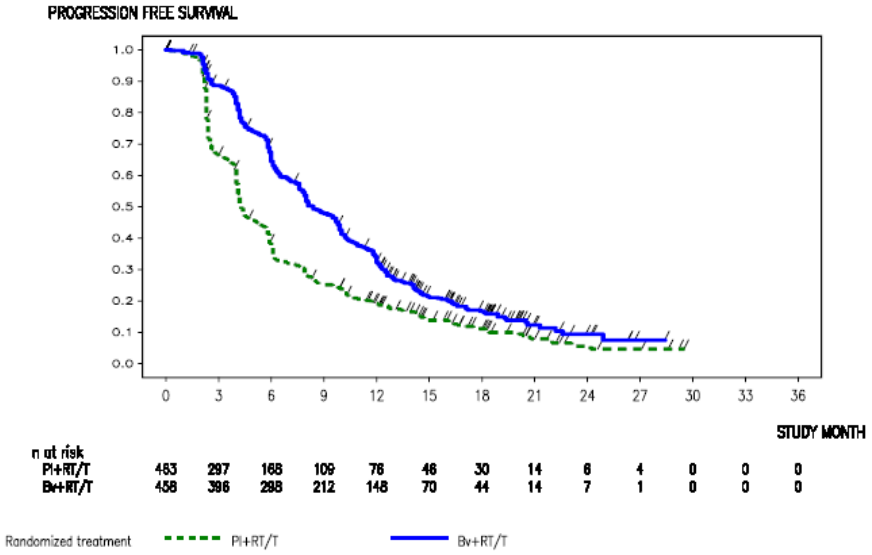
It is noted that the plots of OS separated approximately six months after the time of randomisation and began to converge around 13 months coming back together approximately 15 months.

Sensitivity analyses to test the robustness of the results of the co-primary efficacy endpoint of OS showed similar results to that of the primary analysis.

At the time of the clinical cut-off, 274 placebo patients or 59% and 228 BVZ patients or 50% were retreated receiving at least one subsequent systemic anti-cancer therapy. Substantially more patients in the placebo arm than the BVZ arm received BVZ as part of their management at relapse and TMZ was the most commonly used subsequent therapy in both treatment arms.

Reviewing the secondary efficacy endpoints, the IRF based analysis of PFS showed a similar benefit in the duration of PFS for the BVZ arm compared to the investigator assessment and is indicated Figure 7. However the median duration of PFS was approximately two months shorter in both treatment arms in the IRF based analysis compared with the investigator based analysis. Both treatment arms had more patients with PFS events according to the IRF based analysis compared to the investigator analysis. The majority (52-64%) of the IRF PFS events were based on radiological assessment alone.

Figure 7. Plot of Kaplan-Meier estimates of PFS-IRF (ITT)



The recruitment contributing criteria utilised was similar in both treatment arms.

Sensitivity analyses similar to that performed in the primary PFS analysis applied to the secondary efficacy endpoint of PFS by IRF assessment again showed consistent results.

In relation to one and two year overall survival rates the event free rate at one year was 66% for placebo and 72% for the BVZ arm with a difference of 6% and P=0.052. Review of the two year overall survival rate is difficult because of relatively small numbers involved and is illustrated in Table 9.

Table 9. Summary of one year and two year survival estimates (ITT population).

	Pl+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

7.1. Health related quality of life

It is to be noted that the HRQoL data are considered robust in that compliance of HRQoL assessments were high during patients progression free time with the majority more than 80% of patients who did not progress completed at least one scale and most completed all scales for each of the two monthly HRQoL assessments up to one year of treatment. Furthermore more than 50% of patients completed HRQoL assessed at the time of PD allowing a limited assessment of the changes of HRQoL at the time of progression.

In relation to time to definitive deterioration in HRQoL addition of BVZ to standard therapy resulted in a clinically meaningful and statistically significant delay in the times of definitive deterioration in HRQoL as determined by a 10 point decline in HRQoL score with no subsequent improvement, PD or death for pre-specified scales and is indicated in Table 10.

Table 10. Summary of time to definitive deterioration (TDD) in HRQoL core (ITT)

	Pre-specified analysis: PD included as deterioration event		Post hoc sensitivity analysis: PD excluded 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;0.67] <0.0001		**0.80** [0.66;0.98] 0.0295	
KM-estimated median (months)	4.2	6.9	7.9	10.1

HR estimated using a stratified Cox regression model; p-value determined using a two-sided stratified log rank test. Stratification factors were RPA class and region. NR=not reached

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.

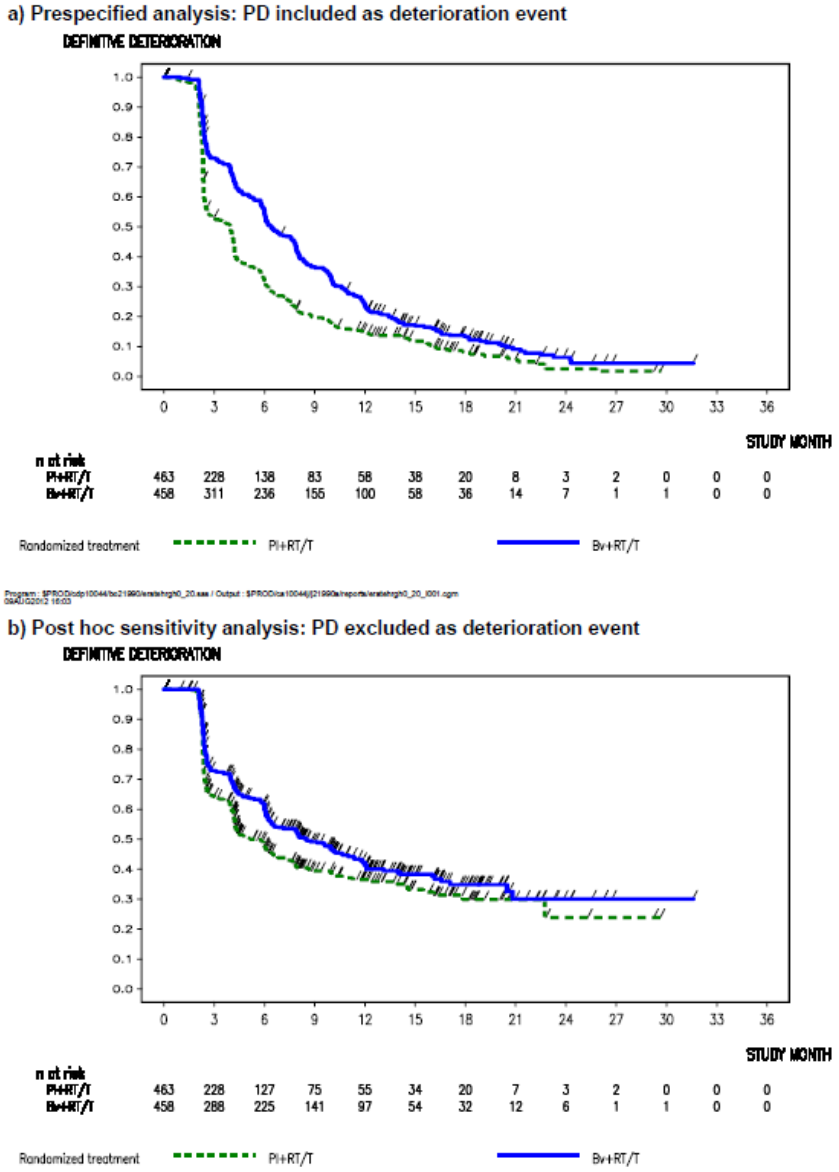
Definitive deterioration was defined as at least a 10-point deterioration in the score from baseline with no subsequent improvement. Death was considered as definitive deterioration in the absence of prior definitive HRQoL deterioration if it occurred within 9 weeks of the last assessment. Otherwise, the patient's data are censored at the date of last assessment. Data for patients who experienced a change of less than 10 points were censored at the date of the last HRQoL assessment. Data for patients with missing baseline or all post-baseline HRQoL assessments were censored at the randomization date. No imputation was performed for missing HRQoL data, i.e., patients' data was not censored at missing scheduled HRQoL assessments that were followed by a completed HRQoL assessment.

A post-hoc sensitivity analysis excluding PD as a deterioration event supported the primary analysis showing that the delay in time to HRQoL deterioration in the BVZ arm was meaningful and robust with a P<0.05 for the scales of global health status social functioning and communication deficit as illustrated in Table 10. Figure 8 shows a KM plot of time to definitive deterioration in the global health status of PD included as an event and without PD as an event.

Figure 8. Plot of Kaplan-Meier estimates for time to definitive deterioration in Global Health Status (ITT)

a) Pre specified analysis: PD included as deterioration event

b) Post hoc sensitivity analysis: PD excluded as deterioration event



Other pre-specified domains showed a consistent benefit from BVZ treatment including cognitive function, weakness in both legs, bladder control, visual disorder, emotional function and role functioning.

During each patient's progression free period there was a consistently greater number of patients in the BVZ arm than the placebo arm with at least one HRQoL assessment that was stable or improved on all five selected scales. The proportion of progression free time for which patients were starting to improve were generally similar in each arm and is indicated in Table 11 the median duration of the patients who were stable or improved were longer for patients in the BVZ arm with a longer progression free time.

Table 11. Summary of HRQoL during PFS 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.

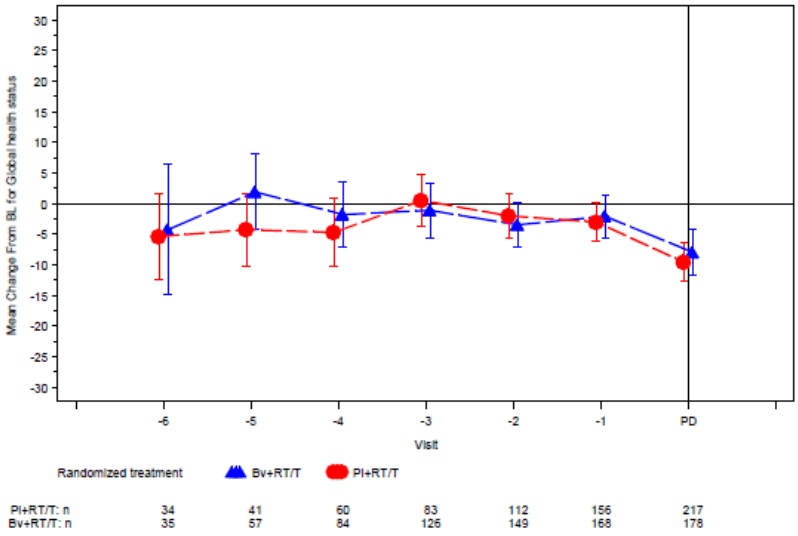
^ median duration of progression-free time improved compared to baseline.

Investingator PFS event/censoring as in main PFS analysis (see Section 8.1.2.1: 5.3.5.1.1/Vol.28/p.5652 of the SAP).

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. The period before missing scheduled assessments is considered in calculating duration as missing.

Based on available HRQoL data at the time of progressive disease involving 217 patients in the placebo arm and 178 in the BVZ arm there was evidence of deterioration in HRQoL compared to baseline in both treatment groups and illustrated in Figure 9.

Figure 9. Mean change from baseline in Global Health Status score at the time of PD compared to previous assessments prior to PD (ITT)



HRQoL assessments (visits) coincided with disease assessments (i.e. every 8 weeks, then every 9 weeks in Monotherapy Phase)

Reviewing other measures of clinical benefit. In relation to Karnofsky performance status (KPS) addition of BVZ to standard therapy resulted in a delay in the time of definitive deterioration in the KPS when compared to the placebo arm and is indicated in Table 12. A post-hoc sensitivity analysis which excluded PD as a deterioration event confirmed a clinically meaningful delay in the time to definitive deterioration in performance status. Nearly all patients with stable or improved KPS during the study maintaining their functional independence through treatment prior to progression. At the time of PD KPS data indicated a trend to deterioration compared to the assessments prior to progression for both treatment groups with a mean decrease from baseline to PD of 7.2 for placebo and 9.1 for BVZ as indicated in Figure 10.

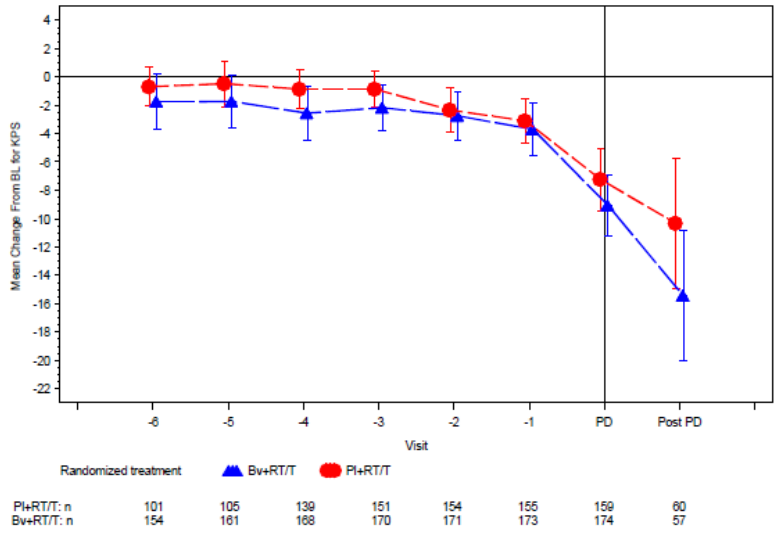
Table 12. Summary of time to definitive deterioration in KPS (ITT)

	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]	

HR estimated using a stratified Cox regression model (stratification factors were RPA class and region).

Definitive deterioration in KPS is defined as a decrease in 20 points from baseline or a KPS ≤50 at any post-baseline assessment, with no later improvement. Death within 9 weeks of the last KPS assessment is also counted as KPS deterioration, in absence of prior deterioration.

Figure 10. Mean KPS at PD and Post-PD compared to assessments prior to PD (ITT)



In relation to corticosteroid use, patients off steroids at baseline had a longer time to initiate corticosteroid therapy in the BVZ arm than the placebo arm and is indicated in Figure 11. Also these patients had a median duration of the sum of the steroid free period was longer for the BVZ arm than the placebo arm and is indicated in Table 13.

Figure 11. Kaplan-Meier Plot of time to initiation of corticosteroid therapy (Patients OFF steroids at baseline)

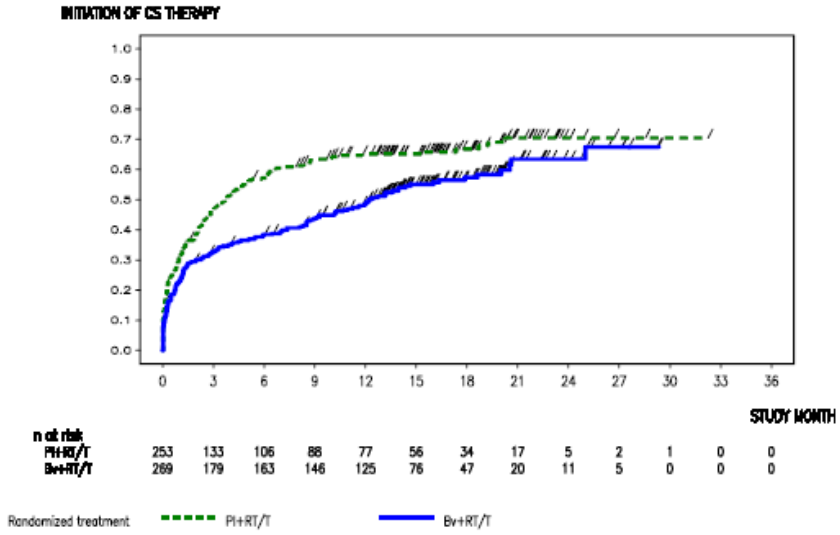


Table 13. Summary of corticosteroid use during patients' progression free time (ITT)

CS dose[a]	Statistic	Patients on[a] CS at Baseline		Patients off[a] CS at Baseline	
		PI+RT/T n=208	Bv+RT/T n=187	PI+RT/T n=253	Bv+RT/T n=269
0 mg	n[b] median duration	98 (47%) 170 days	124 (66%) 195 days	233 (92%) 155 days	252 (94%) 331 days
>0 to < 2mg	n[c] median duration	87 (42%) 30 days	104 (56%) 44 days	80 (32%) 42 days	74 (28%) 33 days
≥2 mg	n[c] median duration	206 (99%) 71 days	179 (96%) 77 days	120 (47%) 52 days	118 (44%) 42 days

CS: corticosteroids

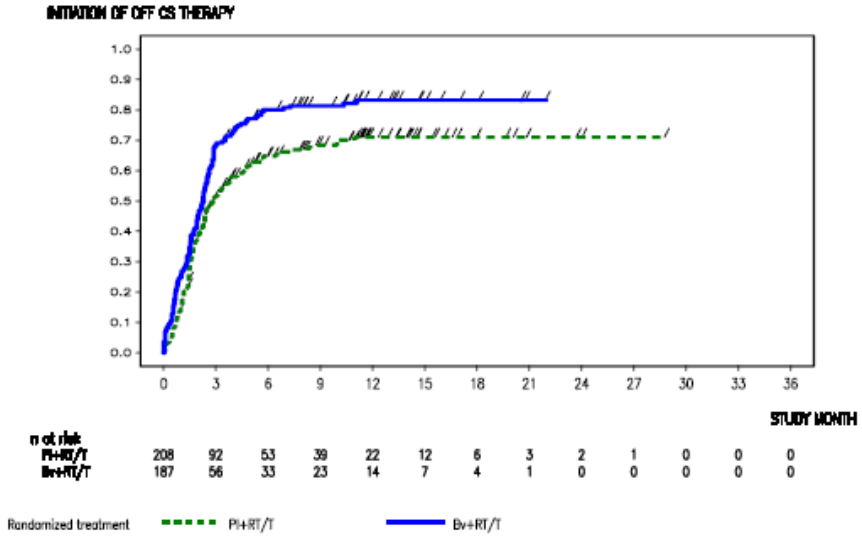
[a] OFF CS defined as <2 mg. ON steroids defined as ≥2 mg mean dexamethasone equivalent dose in 5 days prior to scheduled start of trial treatment.

[b] Number of patients receiving a 0 mg mean dose over a minimum of 5 consecutive days.

[c] Number of patients receiving at least one dose in the given dose category

For those patients on corticosteroids of at least 2mg at baseline more patients in the BVZ arm at 66% than in the placebo arm at 47% were able to discontinue corticosteroids for at least a five consecutive day period during the their progression free time and at an earlier time point as indicated Figure 12. The median duration of the sum of the steroid free period was also slightly longer for the BVZ patients than the placebo patients.

Figure 12. Kaplan-Meier Plot of time to discontinuation corticosteroid therapy (Patients ON steroids at baseline)



In relation to neurological and neuro-cognitive function a high proportion of patients, >80% had normal assessments at baseline and remained stable throughout the duration of treatment with a subsequent trend in neurological status and neuro-cognitive function at PD for both treatment arms.

In relation to signs and symptoms of GBM, these also tended to remain stable throughout the duration of treatment for both treatment arms and consistent with a longer progression free survival duration this stability was greater for the BVZ arm than the placebo arm.

Reviewing response rate data which included those sub-set of patients with lesions at baseline which were either index or non-index lesions and excluding those with confirmed PsPD, the percentage of patients with a best overall response of CR plus PR was higher in the BVZ arm at 38% compared with the placebo arm at 18% and is indicated in Table 14 and indicating that the absolute difference in response rates between the treatment arms was 20% with P<0.0001.

Table 14. Summary of signs and symptoms of GBM during patient's progression-free time (Protocol B Analysis population)

Parameter	Pl+RT/T N=135	Bv+RT/T N=117
Headache		
n (%) patients stable/improved from BL	120 (89%)	109 (93%)
median duration (% PFS time)	5 months (99%)	11 months (99%)
Seizure		
n (%) patients stable/improved from BL	120 (89%)	110 (94%)
median duration (% PFS time)	5 months (99%)	11 months (99%)
Motor Deficit		
n (%) patients stable/improved from BL	118 (87%)	110 (94%)
median duration (% PFS time)	5 months (98%)	10 months (97%)
Speech Deficit		
n (%) patients stable/improved from BL	120 (89%)	110 (94%)
median duration (% PFS time)	5 months (98%)	11 months (98%)
Visual Deficit		
n (%) patients stable/improved from BL	120 (89%)	109 (93%)
median duration (% PFS time)	5 months (99%)	11 months (97%)
Memory Deficit		
n (%) patients stable/improved from BL	120 (89%)	109 (93%)
median duration (% PFS time)	5 months (98%)	10 months (97%)
Sensory Deficit		
n (%) patients stable/improved from BL	120 (89%)	110 (94%)
median duration (% PFS time)	5 months (99%)	10 months (98%)
Consciousness Disturbance		
n (%) patients stable/improved from BL	120 (89%)	110 (94%)
median duration (% PFS time)	5 months (100%)	11 months (97%)
Personality Change		
n (%) patients stable/improved from BL	120 (89%)	109 (93%)
median duration (% PFS time)	5 months (99%)	11 months (98%)
Fatigue		
n (%) patients stable/improved from BL	120 (89%)	109 (93%)
median duration (% PFS time)	5 months (98%)	11 months (98%)

Inv PFS event/censoring as per main PFS analysis.
Considered as a change: for non-focal S&S (fatigue, seizure, headache), a change of 2 levels; for focal S&S (all others), a change of 1 level for two consecutive assessments.

In relation to duration of objective response, 41 patients in the placebo arm and 103 in the BVZ arm had progressed by the time of clinical cut-off and KM estimate of median duration of response was 11.1 months for the placebo arm versus 9.7 months for the BVZ arm with an HR 1.24.

Sub-group analyses for PFS were consistent with the results of the primary analysis in the majority of the sub-groups reporting an estimated hazard ratio of below 1, around 0.65 indicating a PFS benefit for the BVZ arm.

Sub-group analysis for overall survival is also consistent with the results of primary analysis with the majority of sub-groups reported an estimate of a hazard ratio being below 1. A small reduction of risk of death on the BVZ arm compared to the placebo arm.

In relation to bio-marker analyses these were performed on 484 or 53% of patients in the study with demographic characteristics for the patient population similar to those for the overall ITT population. Each bio-marker was analysed using a multiple Cox regression model. The comparison of PFS between treatment arms was performed according to the bio-marker level median, that is, low bio-marker level and high bio-marker level.

In relation to plasma bio-marker analysis, pre-treatment plasma samples obtained between randomisation and treatment start were analysed for the following bio-markers VEGF-A, VEGFR-2, bFGF, ESelectin, ICIM-1, IL-8, PDGF-C, VEGF-C, VEGFR-3, PIGF. Part B Section B, Figures 13 and 14 show the KM plots for PFS VEGF-A and VEGFR-2 respectively dichotomised at the median. Patients with high and low baseline plasma VEGF-A concentrations derived similar benefit in PFS with BVZ treatment with an HR 0.59 and 0.64 with P=0.6104 for high and low baseline plasma VEGF-A levels respectively.

Figure 13. Plot of Kaplan-Meier plot for progression free survival and VEGF-A (dichotomized at median): PI+RT/T versus Bv+RT/T (BEP)

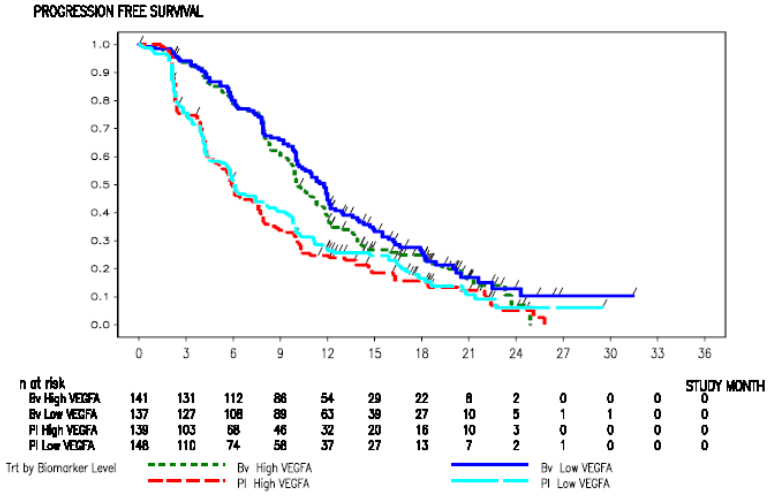
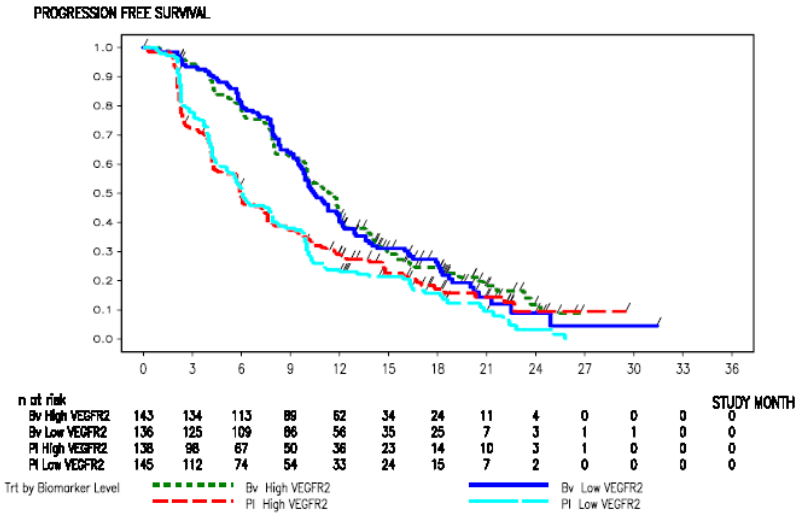


Figure 14. Kaplan-Meier plot for progression free survival and VEGFR-2 (dichotomized at median): PI+RT/T versus Bv+RT/T (BEP)



Similarly no clear evidence of predicted value for BVZ treatment in terms of PFS was observed for any of the other plasma bio-markers. There was no evidence of a prognostic effect of any bio-markers observed in the placebo treatment arm.

In relation to tumour bio-marker analysis, tissue samples obtained during surgery or biopsy were analysed for bio-markers including neuropilin-1 in cytoplasm, CD31, VEGF-A in cytoplasm, VEGFR-2 and VEGFR-1. It is noted that there was a 27% reduction in the risk of progression or death in the high level PtNRP-1 sub-group in the BVZ arm compared to the placebo arm with an HR 0.73. In the low level pNRP-1 sub-group with a 55% reduction in risk of progression or death in the BVZ arm compared to the placebo arm with a HR 0.45.

> Comment: This quite large and well conducted study has demonstrated that for the primary endpoint of PFS the addition of BVZ to the combination of radiotherapy and TMZ for patients with newly diagnosed GBM results in a statistically significant benefit with a 36% reduction by investigator assessed PFS event to the time of data cut-off and a 39% reduction in the risk by IRF assessed PFS events. This is associated with a median PFS of 10.6 months for the BVZ arm and 6.2 months for the placebo arm. Similar benefits were apparent in relation to the various secondary efficacy parameters and were consistent across all sub-groups. It was also noted that in relation to HRQoL that a significant benefit

favoured the BVZ arm of therapy. The one area of uncertainty remains in relation to the co-primary endpoint of overall survival. While there was an 11% reduction in risk of death to data cut-off for the BVZ patients, this is not translated to statistical significance with a P value 0.2135. It is noted that the expected final analysis of overall survival would occur later in 2013. Review of this data at that time will be pertinent.

8. Clinical safety

Evaluation of safety in this submission comes from the pivotal Study BO21990 summarised in Table 15.

Table 15. Summary of studies contributing to safety evaluation

Study / Data Source	Design	Available Safety Info	Treatment Arms and No. of Treated Patients (SAP)
BO21990 CSR	Phase III, multi-center, randomized, double-blind, placebo controlled	Data cut-off March 31, 2012. AEs, SAEs, AESIs, labs, vital signs	• 464 patients - Bv10 mg/kg/q2w for 6 wks concurrent with RT (2.0 Gy fractions 5 days/wk to a total dose of 60.0 Gy) and TMZ (75 mg/m^{2}qd), followed by a treatment break for 4 wks. Then maintenance Bv10 mg/kg/q2w and TMZ (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 until PD. • 447 patients – as above but with placebo instead of Bv

AE = adverse event, AESI = AE of special interest, Bv = bevacizumab, CSR = clinical study report, Gy = Gray, PD = disease progression, q2w = once every 2 weeks, RT = radiotherapy, SAE = serious adverse event, SAP = safety analysis population, TMZ = temozolomide, wk = week

Entry criteria for this study have been mentioned in the Efficacy section but included patients who are at least 18 years of age with newly diagnosed GBM histologically confirmed with surgical resection or biopsy and not been previously treated with chemotherapy or radiotherapy. Key safety related inclusion criteria included adequate healing from previous surgery; stable decrease in corticosteroid dose within five days prior to randomisation; adequate haematological liver and renal function. Exclusion criteria included evidence of recent haemorrhage, inadequately controlled hypertension; clinically significant congestive heart failure; myocardial infarction within the last six months; stroke or TIAs in the last six months; significant vascular disease; Grade II haemoptysis within one month prior to randomisation; evidence of bleeding diaphysis or coagulopathy; history of abdominal fistula or gastrointestinal perforation within six months; history of intracranial abscess within six months; serious non healing wound; active ulcer or untreated bone fracture.

The safety analysis population comprised all randomised patients who received at least one dose of study involving 464 patients from the BVZ arm and 447 patients on the placebo arm as indicated in Table 16.

Table 16. Safety analysis population in Study B021990

	PI+RT/T	Bv+RT/T	Total
No. of patients randomized.	463	458	921
Did not receive study treatment	4	6	10
Received at least one full or partial dose of Bv	12[a]	452	464
No. of patients included in safety analyses	447	464	911

a Patients assigned to Bv+RT/T arm for safety analyses.

Adverse events were documented at each clinical visit and classified and graded according to standard criteria. Adverse events of special interest in relation to BVZ treated patients included evaluation of hypertension, proteinuria, gastrointestinal perforation, wound healing complications, venous thromboembolic events (VTE), arterial thromboembolic events (ATE), bleeding, congestive heart failure, abscesses and fistulae and posterior reversible encephalopathy syndrome (PRES). Safety laboratory assessments included standard haematology, blood chemistry, coagulation with parameters were assessed according to a set schedule. Vital signs were assessed every two weeks.

In relation to exposure to BVZ, it is noted in the three phases of the study BVZ was administered at a dose of 10mg/kg every two weeks during the concurrent and maintenance phases and 15mg/kg every three weeks during the monotherapy phase. A total of 464 patients in the BVZ arm received at least one dose of BVZ following randomisation and by the time of the clinical cut-off date on the 31st March 2012 the median total number of BVZ doses across all phases of study was 18.5 and a maximum number of doses in any one patient was 45.

In relation to exposure to radiotherapy which was delivered during the concurrent phase of the study definitive exposure to radiotherapy was similar for both treatment arms.

In relation to exposure to TMZ which was given during the concurrent phase of therapy at 75mg/m^2 every day and for the first five days of each 28 day cycle during the six cycles of the maintenance phase. In cycle two of the maintenance phase a starting dose of 150mg/m^2 was increased to 200mg/m^2 providing there was no excessive toxicity. The majority of patients in both treatment arms received the planned dose and duration of TMZ treatment during the concurrent phase. In the maintenance phase a higher proportion of patients in the BVZ arm completed the six cycles of TMZ than the placebo arm, 64% versus 37% respectively. These data confirm that the addition of BVZ does not appear to influence tolerance to TMZ.

In relation to duration of safety follow up the median duration of safety follow up was approximately 3.8 months longer in the BVZ arm compared to the placebo arm at 12.3 months versus 8.5 months respectively.

Demographic and other pre-treatment characteristics of the patient population have previously been described in the Efficacy section.

Reviewing the results, the most commonly reported adverse events by individual preferred term are presented in Table 17 and almost all patients in both treatment arms have experienced at least one adverse event, that is,95.7% for placebo and 98.1% for BVZ. It is noted that the adverse events associated with at least a 10% higher incidence in the BVZ arm were those known to be associated with BVZ treatment including bleeding events, hypertension and proteinuria.

Table 17. Summary of adverse events (all grades) with an incidence of ≥10% in either treatment arm (SAP)

Body System/ Adverse Event	Pl+RT/T N = 447 No. (%)	Bv+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)

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.

In relation to adverse events according to system organ class, there was a higher incidence of adverse events in the BVZ arm with several of these including gastrointestinal disorders 78% versus 68%, particularly related to nausea, constipation and vomiting, diarrhoea and abdominal pain, infections and infestations 52% versus 38% most commonly upper respiratory tract infections and urinary tract infections; musculoskeletal and connective tissue disorders 46% versus 30% particularly related to arthralgia, myalgia and musculoskeletal pain; respiratory, thoracic and mediastinal disorders 45% versus 25% mainly due to imbalances in epistaxis and dysphonia; vascular disorders 46% versus 21% mainly due to hypertension; 37% versus 11%; renal and urinary disorders 23% versus 13% primarily due to proteinuria 14% versus 4%.

In relation to grade of adverse events experienced overall 87% of adverse events reported in the study were of Grade I or II severity equivalent for each arm. More patients experienced at least one Grade III or greater adverse event in the BVZ arm at 62.7% compared to placebo arm at 50.1% with most of these related to adverse events associated with BVZ treatment and indicated in Table 18. It is noted that the Grade III adverse events generally did not result in discontinuation of study medication in the majority of cases.

Table 18. Summary of Grade ≥3 Adverse Events with an incidence rate of at least 2%.

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)

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.

In relation to deaths at the time of clinical cut-off 258 or 56% of patients had died in the BVZ arm compared to 253 or 57% of patients in the placebo arm. The greater majority of these were due to progressive disease. Deaths from other causes reported in a similar proportion of patients in each treatment arm being 28 for placebo and 25 for BVZ, the most common being infection 2.2% for BVZ patients and 2.7% for placebo. Overall more non-progressive disease deaths occurred in the BVZ arm during the initial phase of the trial, that is, 11 versus 5 patients and within 90 days of stopping trial treatment, that is,21 versus 12 patients.

As noted during to the concurrent phase of treatment there were more non-PD deaths in the BVZ arm at 11 compared to placebo at 5 with infections being the most common cause and 5 of the 11 non-PD deaths in the BVZ arm potential adverse events of special interest (AESI). Three of these were confirmed or suspected thromboembolic events, one GI perforation and one bleeding event.

During the maintenance phase the number of non-PD events were balanced between the two groups being six patients in the BVZ and seven for placebo. For the mono-therapy phase five non-PD deaths occurred and post-treatment there were more non-PD deaths occurring >90 days after last dose in the placebo group of patients. These are summarised in Table 19.

Table 19. 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**

CVA = cerebrovascular accident; GI = gastrointestinal; MI = myocardial infarction; PE = pulmonary embolism; PD = disease progression.

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)

In relation to serious adverse events there is a higher incidence in the BVZ arm at 36% compared to placebo at 25.7% and is indicated in Table 20. This is partly due to increased incidence of serious AESI although there was also a higher incidence of infections and infestations in the BVZ arm at 10.6% versus 6.5% and thrombocytopenia in 6% versus 3.1%.

Table 20. Summary of most frequent SAEs (incidence ≥1% by preferred term or System Organ Class (SAP)

Body System/* Adverse Event**	Pl+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)
HEPATOBILIARY 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)

* Only body systems with an overall incidence of ≥1% in either arm shown
** Within each body system, only individual preferred terms with and incidence ≥1% in either arm shown
AE Onset between Time of Very First Drug Intake and 90 day(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.
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Adverse events that led to withdrawal of treatment were greater in the BVZ arm at 24.6% compared to placebo at 13.2%. The most common of these being thrombocytopenia and neutropenia in both treatment arms particularly related to TMZ. The increased incidence in the BVZ arm attributable to this agent with infections, infestations; nervous system disorders; renal disorders; general disorders and cardiac disorders.

In relation to adverse events leading to dose modifications or interruptions there was a higher proportion of these in the BVZ arm with 61.7% compared placebo at 37.4%. The most common of these included haemotoxicity particularly thrombocytopenia, vascular disorders primarily hypertension and infections with proteinuria somewhat less common.

In relation to AESIs as expected the overall incidence of this is higher in the BVZ arm at 72.6% compared to placebo at 44.3% with the greatest increases associated with hypertension 37.5% versus 13%, mucocutaneous bleeding 26.7% versus 8.9%, proteinuria 14% versus 4%, ATEs 5% versus 1.6% mainly ischaemic strokes and GI perforations 1.7% versus 0.2% and also the incidence of Grade III adverse AESIs was higher in the BVZ arm at 28.7% versus 15.2%.

There are a greater number of fatal AESIs in the BVZ arm at 7 versus 3 for placebo. Among the BVZ patients the principal deficit seen during the initial phase of treatment with four grade V AESIs in the BVZ arm, two involving pulmonary emboli, one GI perforation and one haemorrhage compared to one haemorrhage for the placebo arm.

8.1. Considering the individual AESIs

8.1.1. Bleeding

The increase in bleeding events seen in the BVZ arm were primarily related to Grade I/II events particular mucocutaneous bleeding events that resolved after specific intervention. Only two of these events were at least Grade III severity both epistaxis and were associated with concomitant Grade III thrombocytopenia requiring platelet transfusion. There was a total of three fatal bleeding events, two in the placebo arm, one due to CVA and one GI haemorrhage and one in the BVZ arm due to tumour haemorrhage.

8.1.2. Arterial thromboembolic events (ATE)

The overall incidence of ATEs of any grade was higher in the BVZ arm 5% versus 1.6% as was the incidence of at least Grade III ATEs at 4.1% versus 1.3%. One in each group was fatal with a CVA in the placebo arm and myocardial infarction in the BVZ arm. ATEs led to discontinuation of therapy for more patients in the BVZ arm at 13 patients compared to one patient in the placebo arm. The majority of the ATE events in the BVZ arm resolved with treatment.

It is noted that the most common ATE events were of ischaemic origin involving 16 of the BVZ patients and six of the placebo patients. As might be expected the incidence of these ATEs were higher in the >65 year age group. Involving 8% of patients who had Grade III ATEs in the BVZ arm compared to none in the placebo arm.

8.1.3. Venous thromboembolic events (VTE)

The overall incidence of VTEs was similar in both arms for any grade being 7.8% for the BVZ and 9.6% for placebo and at least Grade III 7.3% for BVZ and 8.1% for placebo. There were four fatal events all of which were pulmonary embolism, one for placebo and three for BVZ. Similar numbers of patients discontinued treatment or dose modified for VTE events in each arm.

8.1.4. Wound healing complications

Wound healing complications were more frequently reported by the BVZ patients at 3.7% compared to placebo. Seven of these were at least Grade III events compared to three in the placebo arm. There was one fatal wound infection in a BVZ patient. Six patients in the BVZ arm discontinued therapy due to wound healing complications compared to none in the placebo arm.

8.1.5. Hypertension

Hypertension was reported more frequently in the BVZ arm than the placebo arm at 37.5% versus 13% and Grade III in 10.3% versus 2%. Hypertension resolved in the majority >70% of cases. Only four patients required discontinuation of BVZ therapy.

8.1.6. Proteinuria

A higher proportion of patients reported proteinuria in the BVZ arm at 14% compared to 4% for placebo and Grade III/IV in 3.7% versus 0. Proteinuria resolved without specific treatment in

the majority of cases, although 14 patients discontinued BVZ treatment due to proteinuria. One BVZ patient developed Grade IV nephrotic syndrome which resolved with treatment.

8.1.7. Non-GI abscesses and fistulae

Three patients developed abscess and fistula in the BVZ arm compared to two in the placebo arm all of which were Grade III except for one Grade IV event in the BVZ patient. All events resolved with treatment. Two patients withdrew from BVZ therapy because of the events.

8.1.8. GI perforation, abscesses and fistulae

Eight patients in the BVZ arm and one in the placebo arm experienced a GI perforation event, five of which were at least Grade III including one fatal large intestine perforation. Overall three patients in the BVZ arm discontinued due to the event. The event in the placebo arm was Grade IV in severity and led to discontinuation of study.

8.1.9. Congestive heart failure

Two patients in the BVZ arm developed congestive heart failure compared to one in the placebo and both of these in the BVZ arm were Grade III and one patient discontinued treatment.

8.1.10. Thrombocytopenia

The overall incidence of thrombocytopenia of all grades is higher in the BVZ arm at 33.2% compared with placebo at 27.3% and the incidence of at least Grade III thrombocytopenia was also higher in the BVZ than placebo at 14.4% compared to 9.8% but was not associated with clinically significant (at least Grade III) bleeding events. Discontinuation of treatment because of thrombocytopenia was balanced between the arms at 3% versus 3.4% for placebo although the number of patients with dose modification or interruption were slightly increased in the BVZ arm at 24% versus 18%.

KM analysis of time to onset of thrombocytopenia indicated a similar incidence in both treatment arms for the first three months of study then noting a sharp increase in both arms between months four and five when there was a dose increase in TMZ followed by a further plateau of the curve.

8.1.11. Infections

The overall incidence of infections was higher in the BVZ arm than the placebo arm at 52% versus 38% including at least Grade III infections at 12.1% versus 7.6%. The number of fatal infections was similar in both groups at 1.7% and 1.6% respectively.

The curves of time to infection are superimposable over the first three months of study indicating no increased risk of infection related to BVZ during the concurrent phase. There was an increase in the incidence of infections in the BVZ arm after the first three months during the maintenance phases of treatment which may relate to the increased dose of TMZ for these patients between months three to four and more patients in the BVZ arm completing maintenance therapy.

The incidence of Grade III adverse events was commonly related to respiratory tract infections with no imbalance between the two patient groups. The incidence of other Grade III events however was somewhat higher in the BVZ arm with six events compared to the placebo one event.

8.1.12. Clinical laboratory evaluations

There was a higher incidence of newly occurring Grade III or IV laboratory abnormalities for haematological tests in the BVZ arm compared to the placebo arm. In line with the adverse event data the incidence of Grade IV thrombocytopenia was higher in the BVZ arm than the placebo arm being 8% versus 3%. Other test results were well balanced between the treatment arms.

8.1.13. Vital signs

As has previously been observed hypertension has been reported as an adverse effect in BVZ treated patients and small increases from pre-treatment baseline values were observed in the BVZ patient group with median changes from baseline in diastolic and systolic blood pressure at the last visit being 3ml and 4ml of mercury respectively with essentially no change in the placebo arm.

8.1.14. Age

In general the adverse effect profile for patients either above or <65 years were similar with the exception of strokes which the elderly were at higher risk when they were receiving BVZ compared to placebo with the incidence of Grade III or greater ATEs being 8% in those >65 years on BVZ compared to none on placebo and the incidence of at least Grade III cerebral haemorrhage being 4% for those >65 years on BVZ compared to zero for placebo. It is also noted that there was a greater incidence of at least Grade III infection in patients >65 years on BVZ with an incidence of 16% for those on BVZ compared to 8.2% for those on placebo.

8.2. Post-marketing data

There was no post-marketing data in relation to the current proposed indication.

BVZ in combination with intravenous 5-FU based chemotherapy for the first line treatment of patients with metastatic carcinoma of the colon-rectum has been marketed since 2004 and subsequently for several other indications including glioblastoma in patients with progressive disease following prior therapy. The post-marketing experience of BVZ on the basis of safety data contained in the nine previously scheduled periodic safety updated reports (PSUR) was summarised. Adverse event data with a clinical cut-off of the 25th February 2012 was summarised. Overall the incidence of patients reporting adverse events, the proportion of adverse events considered serious and the incidence of adverse events leading to death has remained stable over this period. The most frequent adverse events reported have been GI disorders in 19%, general disorders and administration site disorders in 10.5% and infections and infestations in 9.2%.

> Comment: This safety data has essentially indicated the toxicity profiles recognised for the agents utilised in the combined regimen, namely radiotherapy, TMZ and BVZ. The addition of BVZ to the RT and TMZ have produced additional adverse effects but not had any apparent increase in previously recognised adverse effects for RT plus TMZ. Similarly the extent of adverse effects associated with the BVZ administration is comparable to those for other indications and well recognised in the Product Information. Accordingly while the addition of BVZ to the combination has increased the toxicity profile in general these remain manageable with appropriate surveillance and intervention.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The pivotal Study BO21990 has demonstrated the addition of BVZ to RT plus TMZ therapy in patients with newly diagnosed GBM resulted in a statistically significant improvement in the duration of PFS with a 36% risk of reduction of PFS accompanied by stable or improved HRQoL another measure of clinical benefit during the progression free time. These PFS results are relatively mature with 80% of the randomised patients having had a PFS event.

It is worth commenting that the clinical benefit associated with the prolonged PFS was demonstrated by the stable or improved HRQoL during this period together with symptomatic

stabilisation and reduction in requirements for corticosteroids. All of which represents a worthwhile clinical benefit for patients.

The uncertainty remains however that overall survival was influenced in a significant manner. The interim analysis of overall survival produced an 11% reduction in the addition of BVZ to the RT plus TMZ which was not statistically significant. This represents the second interim analysis in which 56% of randomised patients had died and the final analysis would not be available till later in 2013. The reasons for the lack of statistical significance for overall survival from this quite large and robust study remain uncertain, although it is possible that second-line therapies subsequent to disease progression had an influence. Nevertheless the final analysis of overall survival will provide further relevant information together with that potentially provided from other studies being conducted.

9.2. First round assessment of risks

The safety data provided from the pivotal study essentially indicated the known toxicity profiles of the agents utilised in the combination of RT plus TMZ together with BVZ. This certainly has resulted in an additional mode of toxicities for this patient population but has not resulted in any additive or synergistic adverse effects between the three agents. In general these adverse effects could be adequately managed with appropriate surveillance and early intervention and accordingly the addition of BVZ to the combination cannot be considered to have resulted in unacceptable toxicity for this patient population.

9.3. First round assessment of benefit/risk balance

The data from the pivotal Study BO21990 has certainly indicated a significant and clinically worthwhile improvement in PFS for this population of newly diagnosed GBM patients with the addition of BVZ to the recognised combination of RT plus TMZ. This has been reinforced by the evidence of stable or improved quality of life measures and symptomatic measures as well as corticosteroid use. The adverse effect profile is acceptable in the context for the addition of those toxicities associated with BVZ to those already accepted for RT plus TMZ.

The area of ongoing concern remains with as yet an indeterminate outcome for overall survival with only a minor benefit presently observed. Final analysis of overall survival would be particularly pertinent in this regard as well as results from other studies. Nevertheless at the present time it is reasonable to say that in view of the improvement in PFS and its associated qualitative influence this reviewer is generally supportive of the application.

10. First round recommendation regarding authorisation

On the basis of the favourable outcome for progression free survival from this robust pivotal study together with the qualitative benefits obtained and acceptable safety profile, this reviewer feels that on balance a recommendation in favour of the proposed indication of Avastin in combination with radiotherapy and Temozolomide is indicated for the treatment of adult patients with newly diagnosed glioblastoma is appropriate and supported by this reviewer.

11. Clinical questions

1. It would be desirable to determine results of the final analysis of overall survival for Study BO21990 to become available later in 2013.
2. Results from other similar studies, currently ongoing or in the phase of completion would be desirable.

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