The role of early MRI in predicting survival while on bevacizumab in recurrent glioblastoma: results from a prospective clinical trial (CABARET)

Running title: Early MRI to predict survival on bevacizumab

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Conflict of Interest

None declared

Author contributions

All authors edited, revised and approved the final version of the manuscript. All agree to be accountable for all aspects of the work.

KF, AN, MR, JS, LC, EH, HR were associated with original trial conception and design, patient recruitment, trial management and interpretation of results.

PP, GF, CG were associated with central radiological review of MRI scans and analysis and interpretation of results

EB and KS were associated with trial management, data integrity, statistical analysis and interpretation of data results

Protection of human and animal subjects

This trial was performed after approval by the relevant ethics committee at each participating site. All principles outlined in the Declaration of Helsinki have been followed.

Informed consent was obtained from each participant

Abstract

Background: Bevacizumab has been associated with prolonged progression-free survival (PFS) in recurrent glioblastoma; however, not all derive benefit. An early indicator of efficacy or futility may allow early discontinuation for nonresponders. We prospectively assessed the role of early MRI (eMRI) and its correlation with subsequent routine MRI results and survival.

Methods. Patients were from a randomized phase 2 clinical trial (CABARET) comparing bevacizumab with bevacizumab plus carboplatin in recurrent glioblastoma. eMRI was conducted after 4 weeks on trial (after two treatments with bevacizumab 10 mg/kg every 2 weeks). Results were compared with results of the subsequent standard 8-week MRI.

Results. 119 of 122 patients had available eMRI, and 111 had the subsequent MRI for comparison. Thirty-six (30%) had early radiological response and 17 (14%) progressive disease. Concordance between eMRI and 8-week MRI was moderate (κ= 0.56), most (*n*=79, 71%) giving the same result. There was strong evidence that progression-free and overall survival were predicted by eMRI response (both P<0.001). Median survival (months) was 8.6 for eMRI response, 6.6 for stable disease, and 3.7 for progressive disease; HR 3.4 (progressive vs stable disease) (95% CI, 1.9–6.0). Landmark analyses showed eMRI progression was a strong predictor of mortality, independent of other potential baseline predictors.

Conclusions. In this study, early progression shown on MRI for patients on bevacizumab appears to be a robust marker of poor prognosis.

Discipline: Neuro-oncology

Condensed abstract

We used data from a prospective randomized phase 2 clinical trial in patients with recurrent glioblastoma to determine whether the MRI result at 4 weeks correlated with survival. Early MRI disease progression was strongly associated with inferior overall survival, independently of other predictors of survival at baseline.

Keywords: bevacizumab; MRI; glioblastoma; clinical trial; radiology; prognosis

Background

Glioblastoma is an aggressive central nervous system malignant cancer. Management options for recurrent disease, which have been limited, are now changing with the advent of targeted therapies. Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF) is now a common option for recurrent disease in some countries. VEGF causes peritumoral angiogenesis with an abnormal vascular network, which is hyperpermeable and results in peritumoral edema.[1] VEGF inhibition can result in rapid normalization of glioma-associated blood vessels, reduction in vascular permeability, and improvement in patients' symptoms.

Whether early radiological changes associated with bevacizumab use truly reflect disease response remains debated in the literature, as on the whole, improvements in progression-free survival (PFS) have not translated into overall survival (OS) in most de novo and recurrent-glioblastoma clinical trials involving bevacizumab.[2-4] Targeted therapies in cancer medicine are not without significant cost and potentially serious toxicities. Bevacizumab is expensive, not readily available in some countries owing to its cost and/or uncertainty about the benefit of PFS without corresponding OS benefit, and may be associated with rare but potentially serious toxicities.[5,6]

It would be ideal if an early indicator of bevacizumab efficacy or futility in an individual patient could help guide management. If such an indicator reliably predicted response or progression, prolonged and expensive use of the drug, with ongoing exposure to the risk of toxicity, could potentially be avoided in those individuals for whom it is unlikely to result in durable benefit. Additionally, an early switch to an alternative form of therapy might be appropriate, especially given the increasing availability of clinical trials of other therapies in this patient population.

Our prospective study aimed to determine whether early magnetic resonance imaging (after 4 weeks, or two bevacizumab treatments) (eMRI) was a reliable predictor of prognosis during bevacizumab treatment, using the usual-care 8-week MRI as the reference investigation. We also documented whether changes on the eMRI were associated with differential survival outcomes and/or changes in clinical status or steroid dose. We used scans and data from patients enrolled on the CABARET trial, a randomized phase 2 study comparing bevacizumab monotherapy with bevacizumab plus carboplatin. Examining the role of eMRI was a preplanned exploratory endpoint for this trial.

Methods

Study population

The CABARET trial included 122 adult patients with recurrent glioblastoma from 18 Australian sites, who had previously received both radiotherapy and temozolomide but no other chemotherapy for glioblastoma. Details of inclusion and exclusion criteria have been published.[7] All patients received bevacizumab 10 mg/kg intravenously every 2 weeks; those randomized to doublet therapy also received carboplatin AUC 5 every 4 weeks. Treatment was continued until disease progression or withdrawal of treatment for other reasons (for example, toxicity). Response Assessment in Neuro-Oncology (RANO) criteria, including clinical status and steroid dose, were used for disease assessment for the trial's primary endpoint: PFS as determined by central radiological review.[8] There was no evidence of differences in survival outcomes between the two randomized treatment arms, so they were combined for this analysis.

Early MRI and protocol

In addition to standard MRIs at baseline and every 8 weeks, each participant also had an eMRI at approximately 4 weeks as part of a prospectively designed exploratory endpoint to determine

the role of eMRI in disease assessment. The results from the eMRI were compared with the baseline MRI but were not used in determining overall disease response or progression; and were not acted upon by treating sites with the exception of any potential safety concerns (for example, central nervous system hemorrhage). Both eMRI and 8-week MRI results for this substudy are based on the trial's central radiology review, which was not conducted in real time and did not take the eMRI into consideration when determining disease response on subsequent MRIs. An individual trial participant's series of scans were reviewed and reported by the same central radiologist. The eMRI, as an exploratory substudy, was reviewed by the central radiologists only after the trial's primary endpoint - a PFS date based on 'standard' timing imaging, or cessation of treatment for any other reason, had been established for that patient. Radiologists were blinded to study treatment, steroid dosing and clinical and neurological findings and these were not included in this substudy comparison, which only compares radiographic findings, without the clinical/steroid dosing component of RANO criteria.

Each site was requested to conduct MRIs in accordance with the acquisition protocol provided for the trial to ensure that, where possible, the quality of MRIs was standardized. Scan series included precontrast and postcontrast T1-weighted imaging (volumetric acquisition) and T2/FLAIR sequences (maximum slice thickness 5 mm with no interslice gap).

Data analysis and statistical methods

Radiological findings from the eMRI were compared with the 8-week MRI, the first 'standard' scan on the trial, to determine the level of correlation between the two. This comparison did not include clinical status and steroid dosing as is described in the RANO criteria, but rather was based on T1 and T2/FLAIR changes alone. A kappa statistic was calculated to determine the concordance between results from the eMRI and the 8-week MRI result.

A preplanned exploratory objective of the trial was to correlate the eMRI response at 4 weeks with PFS and OS. PFS and OS dates were calculated from the date of the eMRI, and were described using the Kaplan-Meier method and compared using proportional-hazards regression models. In additional landmark analyses,[9] OS was modelled from the eMRI as a function of baseline risk factors (including age, ECOG performance status, number of relapses, and extent of initial surgery) and eMRI findings (progression or no progression).

Where the eMRI showed progression, the type of radiological progression (T1 contrast-enhancing measurable lesion, nonmeasurable lesion, T2/FLAIR increase, or new lesion) was documented, and OS for patients with contrast-enhancing (T1C+) versus T2/FLAIR progression was calculated.

We also compared clinical status (improved, stable, or deteriorated) and steroid dose (none, reduced, stable or increased), as formally documented by sites at the week 4 visit—both components of RANO criteria—for patients with a response, stable disease, or progressive disease at the time of eMRI, using a chi-square test.

As part of the CABARET trial, an experimental grading scale for T2/FLAIR change was developed by the neuroradiologists who participated in the central radiology review and was applied at the time of central review ('modified' RANO criteria).[7] This classified T2/FLAIR change into five categories (Supplementary Table 1). As an exploratory approach to determine the potential utility of this grading system, PFS and OS were calculated for patients categorized by amount/grade of T2/FLAIR change on eMRI. We also compared patients with T1C+ versus T2/FLAIR progression at week 4.

Results

In total, 122 patients were randomized and 120 underwent at least one treatment. Data for eMRI was available for 119 of these patients, excluding two patients who withdrew consent after randomization but prior to treatment, and one who did not undergo eMRI. Of these, 111 had both a 4-week and an 8-week MRI; the remainder had no MRI after week 4 owing to cessation of treatment for clinical progression, for toxicities, or by choice.

Concordance

Concordance between the eMRI and 8-week MRI for the 111 patients is shown in Table 1. The kappa statistic indicated moderate concordance (κ 0.58). For 71% (n =79), the eMRI and 8-week MRI resulted in the same disease status finding. The disease status on eMRI was the same or better than the 8-week MRI in 99 patients (91%), which is relevant to the decision to cease futile treatment. For 16 of 17 patients with progressive disease at week 4, radiological progression or death occurred a median of 27.5 days later (range 0–61 days). The one remaining patient was recorded to have decreased tumor volume, but a new lesion that resulted in attribution of progressive disease on eMRI, then subsequently a partial response at 8 weeks with continued decrease in tumor volume and no new lesion documented at this time point. No subsequent MRIs were conducted for this patient, who had treatment 3 days after the 8-week MRI but no subsequent therapy, chose to leave the trial 6 weeks after the 8-week scan and died 1 week later.

Progression-free and overall survival

There was strong evidence of differences in PFS and OS according to the eMRI status (Table 2). Patients with progressive disease at eMRI had shorter survival than patients with either stable disease or a response. Figure 1 shows the OS for all three groups. The hazard ratio (HR) if disease progression was seen on eMRI, relative to stable disease, was 3.35 (95% CI 1.88–5.95).

Proportional-hazards regression models were fitted to time from the eMRI to death from any cause, to assess whether the eMRI result had any prognostic value beyond baseline risk factors (Table 3). For both univariable and multivariable models, patient age and progression on eMRI were the only predictors for which there was evidence of an association with OS. Of these, eMRI progression was the strongest predictor of mortality, independent of other potential predictors (multivariable model HR 3.85, 95% CI 2.2–6.9, *P*<0.001).

Clinical status and steroid dose

Clinical status, determined and formally documented by the site at the week 4 visit, was compared for patients with eMRI response, stable disease, and progressive disease. Most patients (*n*=88, 74%) had stable clinical status at this time, and there was no association between eMRI result and clinical status (*P*=0.30). At week 4, 65 patients (55%) had a stable steroid dosage or were not receiving steroids at baseline and week 4; 45 (38%) were on a decreased dosage or had ceased steroids after baseline. Only nine patients (8%) had increased their steroid dosage. There was no association between eMRI result and steroid use (*P*=0.89).

T2/FLAIR changes

Overall survival was shorter for patients with any increase in T2/FLAIR signal abnormality on eMRI (n=5), compared with any decrease (n=49); however statistical inference is limited due to the small sample size. Table 4 shows a comparison of OS based on T2/FLAIR grading, and Figure 2 shows the Kaplan-Meier curve comparing T2/FLAIR decrease, stability, and increase. When T2/FLAIR signal change was assessed, regardless of any other radiological findings, the degree of T2/FLAIR change as documented by the modified RANO 5-point scale (Supplementary Tables 1 and 2) did not provide any additional information regarding OS beyond that obtained by classifying T2/FLAIR change as decreased, stable, or increased (current RANO criteria classification).

Of the 17 patients who had eMRI disease progression, six had T1/contrast-enhancing progression alone and two had T2/FLAIR increase alone. OS differed according to the type of progression at week 4, although the small sample size limits formal statistical comparison. The median OS for those with T1 progression was 3.7 months, and for those with T2/FLAIR progression, 1.8 months (HR 3.41, 95% CI 0.58-19.9).

Discussion

This prospective study is one of the first in the setting of glioblastoma to show that an early MRI during bevacizumab therapy may predict OS. The multivariable model showed disease progression on eMRI to be a strong predictor of mortality, even when adjusted for baseline risk factors. Knowing a patient's likely prognosis during the early stages of a treatment is useful, especially given the potential costs (both financial and toxicity risks) of therapy, and also that additional therapies including clinical trial therapy may be available to patients. Ceasing a treatment that is likely to be futile before performance status deteriorates could facilitate easier access to alternative treatment options.

There is scant literature regarding the value of early MRI in this context. Kreisl et al, in their phase 2 single-arm trial of bevacizumab in recurrent glioblastoma, compared 4-week partial response on MRI with stable disease (by MacDonald and Levin criteria), reporting that early partial response was associated with improved PFS; although early disease progression was not evaluated.[10] A retrospective study of early MRI as a prognostic marker for patients from the RTOG 0625 clinical trial of bevacizumab with irinotecan or temozolomide found that early progression shown by T1 but not FLAIR on 8- and 16-week scans was prognostic for OS.[11] However, an 8-week MRI is more conventional timing for tumor assessment than our 4-week MRI. Huang and colleagues in 2013 published a retrospective study of 91 patients with recurrent glioblastoma receiving bevacizumab, analyzing the value of early (approximately 30 days)

posttreatment imaging (similar to our MRI time frame), and reporting that post-treatment enhancing tumor volume as well as FLAIR volume were associated with both PFS and OS, although FLAIR change did not remain statistically significant in multivariable analysis.[12] They concluded that early-MRI volumetric analysis could identify patients who were more likely to benefit from bevacizumab therapy. Our study seems to support this, although we have not reported formal volumetric measurements, which may be a more sensitive tool and may potentially have identified even more patients with early progressive disease at the 4-week time point.

Sorensen et al in 2009 described a 'vascular normalization index' incorporating advanced MRI imaging that measured vascular permeability, microvessel volume, and circulating collagen IV level after a single dose of cediranib, a pan-VEGF receptor tyrosine kinase inhibitor.[13] This was able to predict the response to the drug. Several studies have found that early PET imaging is more predictive than MRI of early treatment response or progression in patients with recurrent glioblastoma on bevacizumab;[14-16] however, FLT-PET is not routine and currently has limited use outside of clinical trials in this context in Australia.

The sample size of this study limits our ability to determine an association between early T2/FLAIR progression (alone or mixed with other change) and poorer outcome. Other retrospective studies have resulted in conflicting findings related to whether T2/FLAIR tumor progression is adversely associated with survival.[17-19] While several have not found an association, a retrospective analysis of data from patients who participated in the recurrent glioblastoma AVF3708g clinical trial found that T2/FLAIR assessment was significantly associated with differences in PFS and response rates.[20] Our study has not incorporated advanced MRI techniques such as diffusion restriction, spectroscopy, and cerebral blood volume assessments;

it is acknowledged that given the conflicting studies on the prognostic significance of T2/FLAIR signal change, advanced MRI may enlighten investigators and clinicians in this context.[21-23 24]

We did not find an association between steroid dose and eMRI result. Nevertheless, almost 40% of patients on the trial had decreased or ceased steroids after 4 weeks on study. This highlights the important point that bevacizumab may be associated with clinical benefit independent of radiographic findings. If bevacizumab is able to result in a reduction in steroid dose, this can be argued to be an example of clinical benefit. Bevacizumab has been associated with reduced steroid requirements in multiple studies.[5,25-27] This underpins the importance, when assessing any patient on treatment, of considering both radiological findings and clinical status when determining potential benefit of therapy.

It is also interesting to note that median PFS was similar when patients with eMRI response and stable disease were compared (Table 2). While the exploratory nature of this analysis precludes robust statistical inference, the lack of statistically significant association between response and PFS was also noted in a landmark analysis of scans for patients who participated in the BRAIN study, although response was correlated with OS in their analysis.[28] However, as previously noted, Kreisl et al did find an association between early MRI response and PFS, although RANO criteria were not used for this study.[10] In the CABARET study, eMRI progression was the finding most strongly associated with survival outcome, rather than eMRI response.

There are several limitations to our study. Although two-dimensional quantitation of abnormal enhancement was performed, formal volumetric assessments and advanced MRI sequences were not included. Seventeen patients showed progressive disease on eMRI but only five had any T2/FLAIR increase at the 4-week mark, and only two had solitary T2/FLAIR signal increase at

this time, meaning that robust statistical comparisons of survival for this group are not feasible. Furthermore, our findings apply to MRI after two 2-weekly bevacizumab treatments, and it is unclear how they would apply to bevacizumab given at a 3-weekly interval, whether 4 weeks would be an appropriate timepoint, or whether two treatment cycles are required. Nevertheless, strengths include the prospective study design, uniformity in centralized radiological assessment, and that the majority of patients who participated in the CABARET study had both 4-week and 8-week scans available for assessment.

In summary, we found that an early (4-week) MRI after commencement of 2-weekly bevacizumab therapy correlated at least moderately with subsequent 8-week imaging. Compared with stable disease at 4 weeks, progressive disease was a significant prognostic marker for poorer survival; but partial response at this time point was not a significant prognostic marker for better survival in this patient cohort.

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Figure Legends

Figure 1: Kaplan-Meier curve: overall survival, comparing 4-week MRI complete or partial response (red), stable disease (green), and progressive disease (black)

Figure 2: Kaplan-Meier curve: overall survival, comparing 4-week MRI T2/FLAIR decrease (red), stable (green), and increase (black)

Table 1: Comparison between 4-week and 8-week MRI results[a]

	Week 8				
Week 4	**Complete response[b]**	**Partial response[b]**	**Stable disease**	**Progressive disease**	**Total**
Complete response[b]	0	0	0	1	1
Partial response[b]	1	22	6	5	34
Stable disease	3	7	41	8	59
Progressive disease	0	1	0	16	17
Total	4	30	47	30	111

a Radiological findings only, does not include clinical status or steroid dosing components of RANO criteria.

b Reported on this scan only, not necessarily confirmed on subsequent imaging.

Table 2: PFS and OS based on 4 week MRI response, calculated from date of 4-week MRI[a]

Week 4 MRI result	n	Median survival (months) (95% CI)	HR (95% CI)	*P*
Progression-free survival				
Complete or partial response[b]	33	2.8 (2.8–4.6)	0.99 (0.63–1.55)	
Stable disease	56	2.7 (2.5–2.8)	1.00 (reference)	<0.001
Progressive disease	16	0.9 (0.7–1.0)	8.39 (4.21–17)	
Overall survival				
Complete or partial response[b]	36	8.6 (6.1–10.0)	0.81 (0.54–1.22)	
Stable disease	66	6.6 (4.6–7.4)	1.00 (reference)	<0.001
Progressive disease	17	3.7 (2.2–4.7)	3.35 (1.88–5.95)	

a *n*=105, excluding 14 patients whose disease progressed, measured by clinical deterioration at week 4 visit. Only 1 of these 14 patients had radiological progressive disease at this time point.

b Reported on this scan only, not necessarily confirmed on subsequent imaging.

Table 3: Univariable and multivariable proportional hazards regression models assessing the prognostic value of eMRI beyond baseline risk factors

Predictor	Value	HR (95% CI	*P*
Univariable			
ECOG	2 versus 0 or 1	1.26 (0.84–1.88)	0.27
Initial glioblastoma surgery	Resection versus biopsy or debulking	0.98 (0.67–1.42)	0.89
Age	≥ 65 versus <65	1.56 (1.00–2.44)	0.05
Relapse	1 versus ≥2 or unknown	1.14 (0.77–1.68)	0.50
eMRI	Progression versus not	3.61 (2.06–6.31)	<0.001
Multivariable			
ECOG	2 versus 0 or 1	1.32 (0.88–1.99)	0.18
Initial glioblastoma surgery	Resection versus biopsy or debulking	0.93 (0.63–1.39)	0.73
Age	≥ 65 versus <65	1.63 (1.02–2.63)	0.04
Relapse	1 versus ≥2 or unknown	1.09 (0.73–1.62)	0.69
eMRI	Progression versus not	3.85 (2.16–6.88)	<0.001

Table 4: Overall survival from week 4 by T2/FLAIR at week 4[a]

Week 4 MRI T2/FLAIR	Overall survival from week 4 MRI		
	Median survival (months) (95% CI)	HR (95% CI)	P
Any decrease (*n*=49)	6.7 (4.7–8.1)	0.87 (0.59–1.27)	0.03
Stable (*n*=62)	5.7 (4.3–7.1)	1.00 (reference)	
Any increase (*n*=5)	2.3 (1.3–8.7)	3.02 (1.20–7.62)	

a Excludes 3 patients with unknown T2/FLAIR results at 4 week MRI.

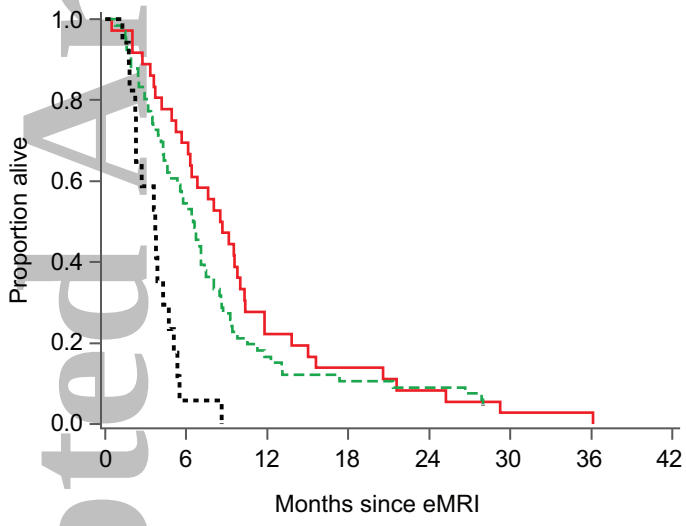

Figure 1

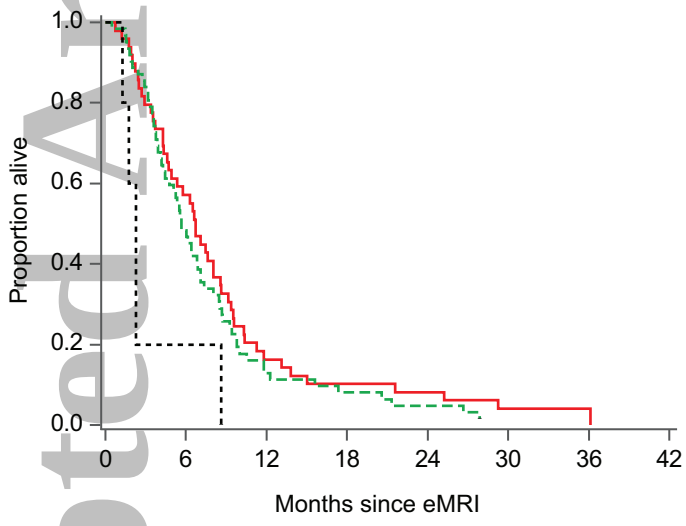

Figure 2

Supplementary table 1: 5-point scale for T2/FLAIR used in 'modified' RANO criteria

Grade	Description
-2	>50% decrease in size of T2 / FLAIR abnormality
-1	25-50% decrease in size of T2 / FLAIR abnormality
0	Stable (+/- 25% from nadir T2/FLAIR appearance)
+1	25-50% increase in size of T2 / FLAIR abnormality
+2	>50% increase in size of T2 / FLAIR abnormality

Supplementary table 2: 'Modified' RANO scale quantifying T2/FLAIR responses at week 4

		PFS (months)		OS (months)	
T2/FLAIR response	**n (%)**	**Median (95% CI)**	**HR (95% CI)**	**Median (95% CI)**	**HR (95% CI)**
Unknown	3 (3%)	6.4 (>0.7)	P=0.013	30 (28 - 32)	P=0.0091
>50% decrease	14 (12%)	3.1 (2.5 – 5.0)	1.00 (ref)	7.5 (4.9 - 10.4)	1.00 (ref)
25-50% decrease	35 (29%)	2.7 (1.1 - 2.8)	1.46 (0.77 - 2.75)	6.3 (4.3 - 8.1)	1.02 (0.54 - 1.92)
-25 to 25% of nadir	62 (52%)	2.7 (2.2 - 2.8)	1.18 (0.64 - 2.16)	6.1 (4.8 - 7.4)	1.10 (0.61 - 1.98)
25-50% Increase	2 (2%)	1.0 (0.9 - 1.1)	7.28 (1.57 - 33.74)	1.8 (1.3 - 2.3)	14.64 (3.02 - 70.88)
>50% Increase	3 (3%)	1.0 (0.9 - 1)	6.23 (1.67 - 23.16)	2.3 (1.8 - 8.7)	2.4 (0.68 - 8.39)