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**Volumetric response quantified using T1 subtraction predicts long-term survival benefit from cabozantinib monotherapy in recurrent glioblastoma**

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Conflicts of Interest related to this Manuscript:

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## Abstract

**Background:** To overcome challenges with traditional response assessment in anti-angiogenic agents, the current study uses T1 subtraction maps to quantify volumetric radiographic response in cabozantinib monotherapy, an orally bioavailable tyrosine kinase inhibitor with activity against VEGFR2, MET, and AXL, in an open-label, phase II trial in patients with recurrent glioblastoma (NCT00704288).

**Methods:** A total of 108 patients with adequate imaging data and confirmed recurrent GBM were included in this retrospective study from a phase II multicenter trial of cabozantinib monotherapy (XL184-201) at either 100mg (N=87) or 140mg (N=21) per day. Contrast enhanced T1-weighted digital subtraction maps were used to define volume of contrast enhancing tumor at baseline and subsequent follow-up time points. Volumetric radiographic response (>65% reduction in contrast enhancing tumor volume from pre-treatment baseline tumor volume sustained for more than 4 weeks) was tested as an independent predictor of overall survival (OS).

**Results:** Volumetric response rate (VRR) for all therapeutic doses was 38.9% (41.4% and 28.6% for 100mg and 140mg doses, respectively). A log-linear association between baseline tumor volume and OS ( $P=0.0006$ ) and a linear correlation between initial change in tumor volume and OS ( $P=0.0256$ ) were observed. A significant difference in OS was observed between responders (median OS=20.6 months) and non-responders (median OS=8.0 months) (HR=0.3050,  $P<0.0001$ ). Multivariable analyses showed continuous measures of baseline tumor volume (HR=1.0233,  $P<0.0001$ ) and volumetric response (HR=0.2240,  $P<0.0001$ ) were independent predictors of OS.

**Conclusions:** T1 subtraction maps provide value in determining response in recurrent GBM treated with cabozantinib and correlated with survival benefit.

## IMPORTANCE OF THE STUDY

GBM is the most common malignant brain tumor in adults and treatment options for patients with recurrent GBM are significantly limited. Cabozantinib is an oral inhibitor of tyrosine kinases including VEGFR2, MET, and AXL, which are implicated in the pathophysiology of GBM. Previous studies examining radiographic response in anti-VEGF therapies have been challenging due to reduction in vascular permeability; however, T1 subtraction maps may overcome these challenges and allow for more accurate estimates of tumor burden. The current study demonstrates that patients with recurrent GBM who exhibit a significant and sustained reduction in contrast enhancing tumor volume on T1 subtraction maps following treatment with cabozantinib exhibit a significant survival advantage. This suggests T1 subtraction may be a better way of estimating tumor burden and that early changes may be a surrogate for clinical activity of cabozantinib.

## INTRODUCTION

Glioblastoma (GBM) is the most common malignant brain tumor in adults and accounts for more than 54% of all gliomas and 45% of all malignant primary brain and CNS tumors<sup>1</sup>. Median survival for non-elderly patients with GBM is only around 14 months,<sup>2</sup> with fewer than 10% of patients surviving beyond 5 years following initial diagnosis.<sup>3</sup> Standard of care for newly diagnosed GBM patients includes maximum surgical resection, followed by radiotherapy plus concomitant temozolomide<sup>4</sup> until tumor recurrence or relapse. Upon recurrence, however, very few effective therapeutic options exist. Thus, there continues to be an unmet need for drug development in the setting of recurrent GBM.

GBM is a highly-vascularized tumor, which is thought to result from overproduction of pro-angiogenic growth factors including vascular epithelial growth factor (VEGF)<sup>5,6</sup>. However, targeted inhibition of VEGF alone using bevacizumab, a humanized monoclonal antibody for VEGF-A, has shown only limited efficacy<sup>7-11</sup>. Preclinical data suggest that overexpression of hepatocyte growth factor receptor (MET) in GBM may aid in eventual resistance to bevacizumab<sup>12,13</sup>, suggesting targeted inhibition of both MET and VEGF may overcome these challenges. Further, studies in a variety of tumor types have suggested that chronic inhibition of VEGF results in upregulation of both MET and AXL<sup>14,15</sup>, and inhibition of AXL during anti-VEGF therapy also increases efficacy through prolonging resistance<sup>16,17</sup>. Further, both MET<sup>13,18-20</sup> and AXL<sup>21-24</sup> have been implicated in GBM pathogenesis and are associated with poor prognosis in patients with GBM. Thus, inhibition of MET, AXL, and VEGF may have a significant impact on outcomes in patients with recurrent GBM.

Cabozantinib is an oral tyrosine kinase inhibitor (TKI) with activity against VEGF receptors, MET, and AXL<sup>25,26</sup>. Preclinical data has shown suppression of MET and VEGFR2 signaling with improved survival in a mouse xenograft model<sup>27</sup>, and clinical trials in solid

tumors have demonstrated tumor regression<sup>28-30</sup>. A recent open-label, phase II trial in patients with recurrent GBM has shown some evidence of clinical activity<sup>31,32</sup>; however, radiographic response evaluation in patients treated with anti-VEGF therapy can be particularly challenging due to the dramatic changes in contrast enhancement from decreased vascular permeability regardless of anti-tumor activity<sup>33-38</sup>. Previous studies have shown that digital subtraction of pre- from post-contrast T1-weighted images, or “T1 subtraction maps”, improves visualization and volumetric quantification of subtly enhancing tumor. Additionally, early changes in contrast enhancing tumor volume defined using T1 subtraction maps have been shown to predict long-term clinical outcome in recurrent GBM treated with bevacizumab<sup>39</sup>. Therefore, in the current study we examine whether early radiographic response defined using quantitative tumor volume estimates from T1 subtraction maps could predict overall survival in an open-label, phase II, multicenter clinical trial of bevacizumab-naïve recurrent GBM patients treated with cabozantinib (NCT00704288).

## METHODS

### *Patients*

A total of 152 patients who did not previously fail anti-angiogenic therapy (e.g. bevacizumab, cediranib, or pazopanib) of the 222 total patients enrolled in XL184-201, a multicenter (8 sites), phase II, open-label, uncontrolled study of cabozantinib, a tyrosine kinase inhibitor with principal targets of MET, VEGFR2, AXL, and RET, at a dose of 140 or 100 mg (free base equivalent weight, oral, daily) in patients with recurrent GBM at first or second relapse, were included in the current retrospective study. Of these patients, a total of 108 patients (N=87 for 100mg and N=21 for 140mg) had serial MR images (at least 3 to confirm response) with sufficient quality available for volumetric analyses. The median age for these patients was 56.5 years (range = 21 – 73) and, of the patients included, approximately 65% of the patients were male. All patients included had Karnofsky Performance Status (KPS) of more than 70 at baseline. The study spanned from June 2008 through July 2014. In all patients, initial standard radiation therapy and chemotherapy (concurrent radiation therapy and temozolomide treatment) failed, and radiation therapy (or previous investigational drugs) had been completed more than 12 weeks previously. Baseline images were obtained within 14 days prior to treatment according to study guidelines and follow up imaging was performed every 6 to 8 weeks until disease progression. The current imaging analysis was performed retrospectively using data from the study sponsor (Exelixis). All participants in XL184-201 signed an institutional review board-approved informed consent at their respective institution prior to enrolling in the multicenter clinical trial. Specific inclusion and exclusion criteria for this trial can be found at [clinicaltrials.gov/ct2/show/NCT00704288](https://clinicaltrials.gov/ct2/show/NCT00704288).

## *Magnetic Resonance Imaging*

Anatomic MR images were acquired for all patients in the current study using a 1.5T or 3T clinical MR scanner using pulse sequences supplied by their respective manufacturers and according to their local standard of care protocols. Standard anatomic images consisted of pre-contrast, 2D axial T1-weighted fast spin-echo images (repetition time (msec)/echo time (msec) = 400–3209/3.6– 21.9; slice thickness = 3–6.5 mm; intersection gap = 0–2.5 mm; number of averages = 1-2; matrix size = 176–512 x 256–512; and field of view = 24–25.6 cm) along with T2-weighted fast spin-echo and fluid-attenuated inversion-recovery (FLAIR) images. In addition, parameter matched axial 2D T1-weighted fast spin echo images enhanced with gadopentetate dimeglumine (Magnevist; Berlex), 0.1 mmol/kg, were acquired shortly after contrast material injection, followed by 3D magnetization-prepared rapid acquisition gradient-echo (MPRAGE) sequences in most patients.

## *Contrast-Enhanced T1-Weighted Digital Subtraction Maps*

Contrast-enhanced T1-weighted subtraction maps (**Fig. 1**) were created using parameter matched pre- and post-contrast axial 2D T1-weighted images and techniques previously described<sup>39</sup>. First, linear registration was performed between all images including contrast enhanced T1-weighted images and T2-weighted and/or FLAIR images to nonenhanced T1-weighted images using a 12-degree-of-freedom transformation and a correlation coefficient cost function in FSL (FLIRT; FMRIB Software Library, Oxford, England; [http:// www.fmrib.ox.ac.uk/fsl/](http://www.fmrib.ox.ac.uk/fsl/)). Next, “Gaussian normalization” of image intensity for both nonenhanced and contrast enhanced T1-weighted images was performed using custom *c*- code and bash scripts, courtesy of the National Institutes of Mental Health Magnetoencephalography 3Core Facility (3dNormalize; NIMH MEG Core, Bethesda, MD;



*kurage.nimh.nih.gov/ meglab/Med/3dNormalize*), which normalizes image intensity by dividing each voxel by the standard deviation of the image intensity from the whole brain [ $S_{Nor}(x,y,z) = S(x,y,z)/\sigma_{WB}$ ], where  $S$  is raw image signal intensity,  $Nor$  is normalized,  $x,y,z$  are voxel coordinates, and  $WB$  is whole brain. Next, bias field correction was performed (FAST segmentation; FLIRT; FMRIB Software Library, Oxford, England; <https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FAST>) and voxel-by-voxel subtraction between normalized nonenhanced and contrast-enhanced T1-weighted images was performed. Image voxels with a positive (greater than zero) before-to-after change in normalized contrast enhancement signal intensity (ie, voxels increasing in MR signal after contrast agent administration) within T2-weighted FLAIR hyperintense regions were isolated to create the final T1 subtraction maps by thresholding the T2-weighted FLAIR images based on relative signal intensity (i.e. intersection of binary mask created by empirical thresholding by FLAIR hyperintensity and positive contrast from T1 subtraction). Estimates of tumor volume included areas of contrast enhancement on T1 subtraction maps including central necrosis (defined as being enclosed by contiguous, positive enhancing disease). A team of trained lab technologists created initial segmentations and all final volumes were reviewed by a single investigator (B.M.E.) who was blinded to other relevant metrics until study completion. Volumetric response (VR) was defined as a sustained decrease on enhancing volume greater than 65% for at least 4 weeks, as described previously<sup>40-42</sup>.

### *Statistical Analysis*

A log-linear regression model was created to examine the association between baseline enhancing tumor volume and OS [ $OS = a \cdot \log_{10}(Volume) + b$ ] in patients who were not censored (82 of 108). Similarly, a linear model was used to explore the influence of initial



changes (i.e. post-treatment volume minus pre-treatment volume) in enhancing volume and OS ( $OS = a \cdot (\text{Change in Volume}) + b$ ) in patients who were not censored. Univariate, log-rank analysis on Kaplan Meier data were performed to compare durable volumetric radiographic responders, as defined by a sustained decrease on enhancing volume greater than 65% for at least 4 weeks, to non-responders for patients treated with 100mg, 140mg, and pooled patients from both doses. A multivariable Cox regression model including age, baseline tumor volume, treatment dose, and radiographic response was used to predict OS. All statistical tests were performed using GraphPad Prism v7.0c (LaJolla, CA) or Stata v12 (College Station, TX).

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## RESULTS

T1 subtraction maps provided clear benefit for delineating contrast enhancing tumor from surrounding tissue in patients treated with cabozantinib. **Fig. 1** illustrates representative images from two patients with recurrent GBM that experienced a sustained volumetric response using T1 subtraction maps after treatment with cabozantinib at a dose of 100mg. In both of these cases, as with many patients who experienced volumetric response, a significant level of T1 shortening (hyperintensity) was observed on pre-contrast T1-weighted images following initial treatment (**Fig. 1B, D**). After T1 subtraction it was apparent that most of the observed residual contrast enhancement on post-contrast T1-weighted images following therapy was likely attributed to pre-contrast T1 shortening, resulting in a relatively small volume of post-treatment contrast enhancement tumor burden.

Approximately 38.9% of patients (42 of 108) with recurrent GBM treated with cabozantinib at either dose experienced a durable volumetric radiographic response (VRR), as defined by a sustained decrease on enhancing volume greater than 65% for at least 4 weeks (**Table 1**). In patients treated with 100mg of cabozantinib (N=87) and patients treated with 140mg of cabozantinib (N=21), 41.4% (36 of 87) and 28.6% (6 of 21) experienced a confirmed volumetric response, respectively.

As reported previously, baseline enhancing tumor volume is an independent and significant prognostic factor for OS in patients treated with cabozantinib<sup>43</sup>. A re-examination of this previous data suggests a simple log-linear model can be used to predict OS given only the volume of contrast enhancing tumor prior to treatment

(**Fig. 2A**;  $OS = -4.7 \cdot \log_{10}(Volume) + 31.7 \text{ months}$ ;  $P = 0.0006$ ). Examination of the initial change in contrast enhancing tumor volume following administration of cabozantinib (**Fig. 2B**)

suggests a linear relationship between the degree of tumor shrinkage is directly proportional to OS benefit ( $OS = -0.04 \cdot (\text{Change in Volume}) + 10.6 \text{ months}$ ;  $P = 0.0256$ ).

Univariate log-rank analysis suggested a significant survival advantage in patients exhibiting a confirmed volumetric response (median OS = 20.6 months) compared with patients that did not respond (median OS = 8.0 months) when pooling patients from both dose levels (**Fig. 3A**;  $HR = 0.3050$ ,  $P < 0.0001$ ). When splitting patients by dose, significant survival differences still remained between volumetric responders and non-responders (**Fig. 3B**). In particular, patients treated with either 100mg or 140mg of cabozantinib that exhibited a sustained volumetric response had a significantly longer OS ( $HR = 0.3842$  and  $HR = 0.1132$ , respectively;  $P < 0.0001$ ). Additionally, patients that responded to 140mg had a significantly longer OS compared with responders treated with 100mg ( $HR = 0.3448$ ,  $P = 0.0211$ ), suggesting there may be dose dependent survival benefit for patients with recurrent GBM treated with cabozantinib. Multivariable Cox regression showed that continuous baseline tumor volume ( $HR = 1.0233$ ,  $P < 0.0001$ ) and confirmed volumetric response ( $HR = 0.2240$ ,  $P < 0.0001$ ) were independent predictors of OS, while age ( $HR = 1.0038$ ,  $P = 0.7022$ ) and dose level ( $HR = 0.9885$ ,  $P = 0.1368$ ) were not statistically significant independent predictors when accounting for these other covariates (**Table 2**).

## DISCUSSION

The current study indicates that T1 subtraction maps provide equivalent (e.g. **Fig. 1A, C**) or improved (e.g. **Fig. 1B, D**) visualization and detailed demarcation for quantitation of enhancing disease burden in GBM. Results from the current trial provide additional support for the use of T1 subtraction maps to estimate change in contrast enhancing tumor volume as an early surrogate of treatment efficacy in recurrent GBM based on *initial response*, similar to those reported previously after treatment with bevacizumab<sup>39</sup>. A recent study by Gahrman *et al.*<sup>44</sup> examining bevacizumab therapy in the BELOB trial suggests T1 subtraction maps provided only equivalent performance for identifying time-to-progression (TTP) when compared with post-contrast T1-weighted images alone. This suggests the largest added value of T1 subtraction in recurrent GBM may be in assessment of early response, rather than early disease progression, in anti-angiogenic therapies. Importantly, the current study indicates that patients with a large and sustained reduction in contrast enhancing tumor volume following cabozantinib therapy will experience more than twice the survival benefit compared with patients who do not. This large and clinically meaningful difference in OS implies early changes in contrast enhancing tumor volume using T1 subtraction may be a robust imaging biomarker for OS benefit in recurrent GBM.

The rates of confirmed volumetric response (38.9% overall, 41.1% for 100mg, and 28.6% for 140mg) in the current study (N=108) were substantially higher than the objective response rates reported for this same trial (N=152) by an independent radiological facility using RANO (14.5% and 17.6% for 100mg and 140mg doses, respectively<sup>31</sup>). These rates were similar to response rates reported for bevacizumab using traditional post-contrast T1-weighted images and a modified Macdonald or RANO criteria<sup>7,45,46</sup> (28%-63%), yet higher than traditional chemotherapies like irinotecan<sup>47,48</sup>.

Interestingly, patients treated with cabozantinib that had long post-treatment OS had notable T1 shortening on pre-contrast T1-weighted images. This was in notable contrast to patients with long post-treatment OS following bevacizumab, in which significant T1 hypointensity was observed. Subsequent studies aimed at determining the source of post-cabozantinib T1 shortening in recurrent GBM may be warranted to determine whether it has biologic or prognostic significance.

Despite occurring less frequently, patients who experienced a volumetric response when treated with 140mg appeared to experience a longer OS compared with responders treated at 100mg. Although speculative given the small sample size, this may suggest increased therapeutic efficacy with increased dose, so long as tumor shrinkage is observed early after the start of therapy. Additional studies at higher doses may be warranted given they are safe and tolerated<sup>31</sup>, as the 140-mg/day dose has been approved for treatment of medullary thyroid cancer based on results from the pivotal phase 3 trials.<sup>28,49</sup>

The current study had a few limitations that should be addressed. First, this study was retrospective and as such the conclusions were solely based on the data available for advanced image analyses wherein only 108 of the 152 patients treated in the trial had sufficient imaging for analysis<sup>32</sup>. Additionally, lesion segmentation was not fully automated or controlled and involved multiple layers of human interpretation. Thus, some variability in lesion size measurement and response rate may have been present and unaccounted for. Lastly, the current study does not involve a formal comparison to the traditional RANO criteria, so questions still remain regarding the added value of the current technique with respect to other more accepted approaches commonly used in clinical trials.

In conclusion, results from the current study suggest that volumetric analysis using T1-subtraction maps represents a detailed and informative assessment method to evaluate

response of GBM patients treated with anti-angiogenic therapy. Results support the hypothesis that volumetric response predicts OS in patients treated with cabozantinib and suggests cabozantinib may have clinical activity in more than one third of recurrent anti-angiogenic therapy naïve GBM patients as evidenced by a durable volumetric response using T1 subtraction maps that are associated with a significant survival benefit.

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## Figure Captions:

**Fig. 1. Pre-contrast T1-weighted images, post-contrast T1-weighted images, and contrast-enhanced T1-weighted digital subtraction maps in two representative recurrent GBM patients with a sustained volumetric response following treatment with 100mg of cabozantinib.** A) Pre-treatment and B) post-treatment MRI scans showing pre-contrast T1-weighted images (left column), post-contrast T1-weighted images (middle column), and T1 subtraction maps (right column) in a 62-year-old patient with an OS of 16.8 months following treatment. C) Pre-treatment and D) post-treatment MRI scans showing pre-contrast T1-weighted images, post-contrast T1-weighted images, and T1 subtraction maps in a 57-year-old patient who was still alive (censored) 20.5 months following treatment. Note that in both cases, as in many patients exhibiting a durable response, we observed significant T1 shortening on pre-contrast T1-weighted images following therapy, which resulted in a significant decrease in true contrast enhancing tumor burden following digital subtraction.

**Fig. 2. Log-linear or linear associations between baseline or change in contrast enhancing tumor burden and overall survival (OS) following treatment with cabozantinib in recurrent GBM.** A) Log-linear ( $OS = a \cdot \log_{10}(Volume) + b$ ) association between baseline tumor volume and OS. B) Linear ( $OS = a \cdot (\text{Change in Volume}) + b$ ) association between initial change in tumor volume and OS. Solid lines represent best fit line after log-linear or linear regression and dashed lines represent 95% confident intervals for the respective model fits.

**Fig. 3. Kaplan-Meier plots showing the association between confirmed volumetric response (VR) and overall survival (OS) in recurrent GBM patients treated with cabozantinib.** A) Kaplan-Meier plots demonstrating a significant survival advantage in patients with a confirmed VR treated with cabozantinib pooled across both 100mg and 140mg dose levels (*Log-rank, P<0.0001, HR=0.3050*). B) Kaplan-Meier survival plots showing a significant survival advantage in patients with confirmed VR treated with 100mg and 140mg. Note that patients with confirmed response treated with 140mg had a significantly longer OS compared with volumetric responders treated with 100mg (*Log-rank, P=0.0211*).

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**Table 1. Analysis of Overall Survival (OS) by Durable Volumetric Response (VR)**

Variable	100 mg (N=87)			140 mg (N=21)			All (N=108)		
	VR (N=36)	Non-VR (N=51)	Total (N=87)	VR (N=6)	Non-VR (N=15)	Total (N=21)	VR (N=42)	Non-VR (N=66)	Total (N=108)
Deaths - n (%)	22 (61.1%)	41 (80.4%)	63 (72.4%)	4 (66.7%)	15 (100%)	19 (90.5%)	26 (61.9%)	56 (84.8%)	82 (75.9%)
Censored - n (%)	14 (38.9%)	10 (19.6%)	24 (27.6%)	2 (33.3%)	0 (0%)	2 (9.5%)	16 (38.1%)	10 (15.2%)	26 (24.1%)
Median OS (Months)	16.8	8.3	12.1	34.4	5.9	6.9	20.6	8.0	11.0

N = number of subjects in the specified population.



**Table 2:** Multivariate Cox regression model results including age, treatment dose (100mg vs. 140mg), baseline contrast enhancing lesion volume, and confirmed volumetric responders versus non-responders.

Variable	Coefficient	Hazard Ratio	95% C.I.	P-Value
Age	0.0038 ± 0.0100	1.0038	(0.9844 – 1.0236)	0.7022
(Continuous)				
Dose	0.0115 ± 0.0077	1.0116	(0.9964 – 1.0270)	0.1368
(100mg or 140mg),				
Pre-Treatment Volume	0.0231 ± 0.0055	1.0233	(1.0123 – 1.0345)	< 0.0001
[uL] (Continuous)				
Responders vs. Non-Responders	-1.4963 ± 0.2662	0.2240	(0.1329 – 0.3774)	< 0.0001

Figure 1

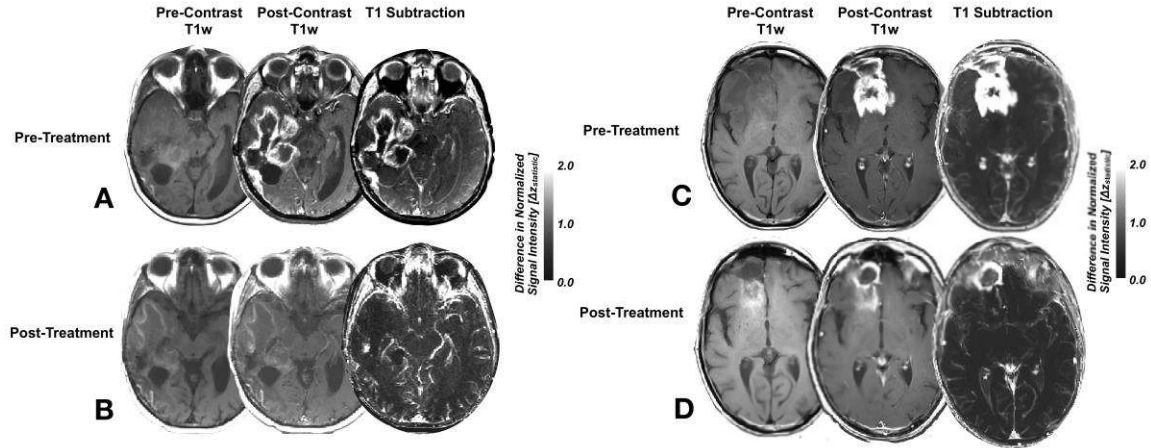
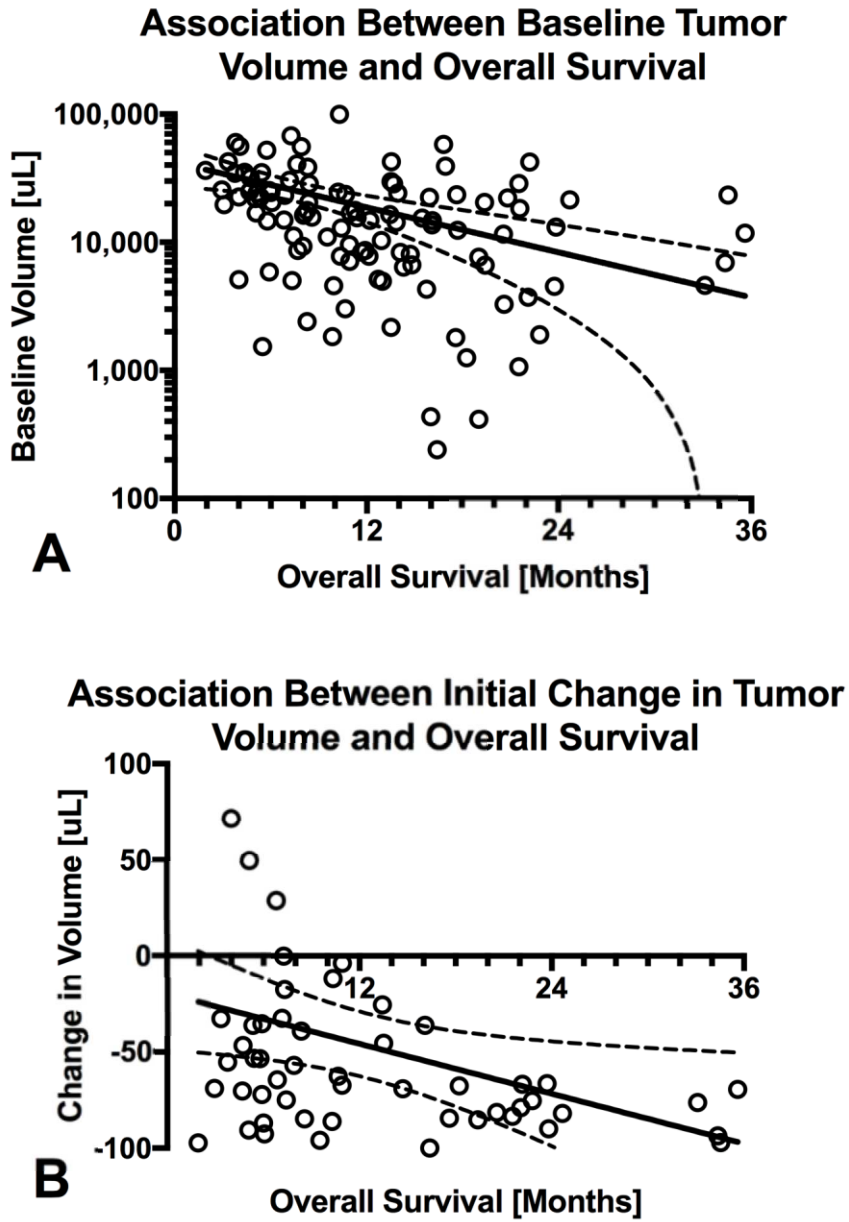
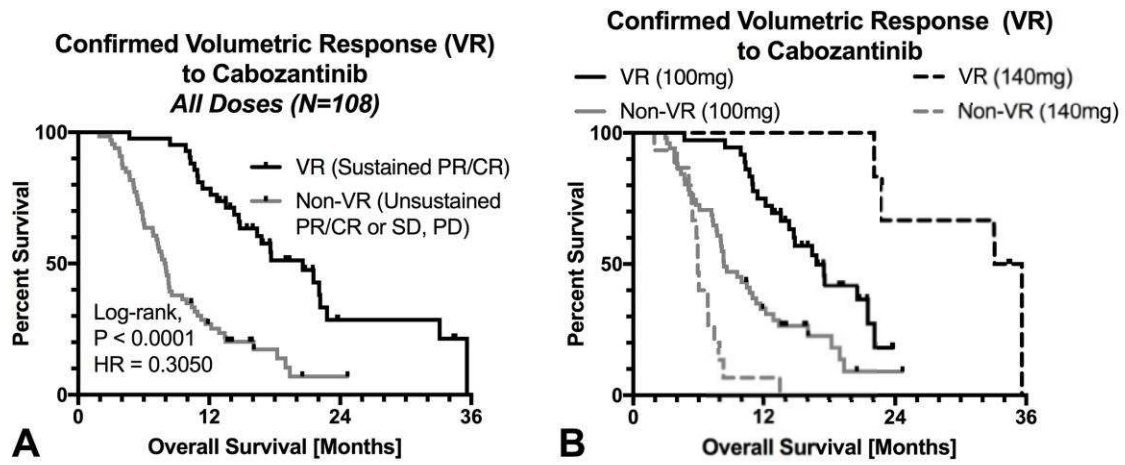


Figure 2



script

Figure 3



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