## Supplementary Figures

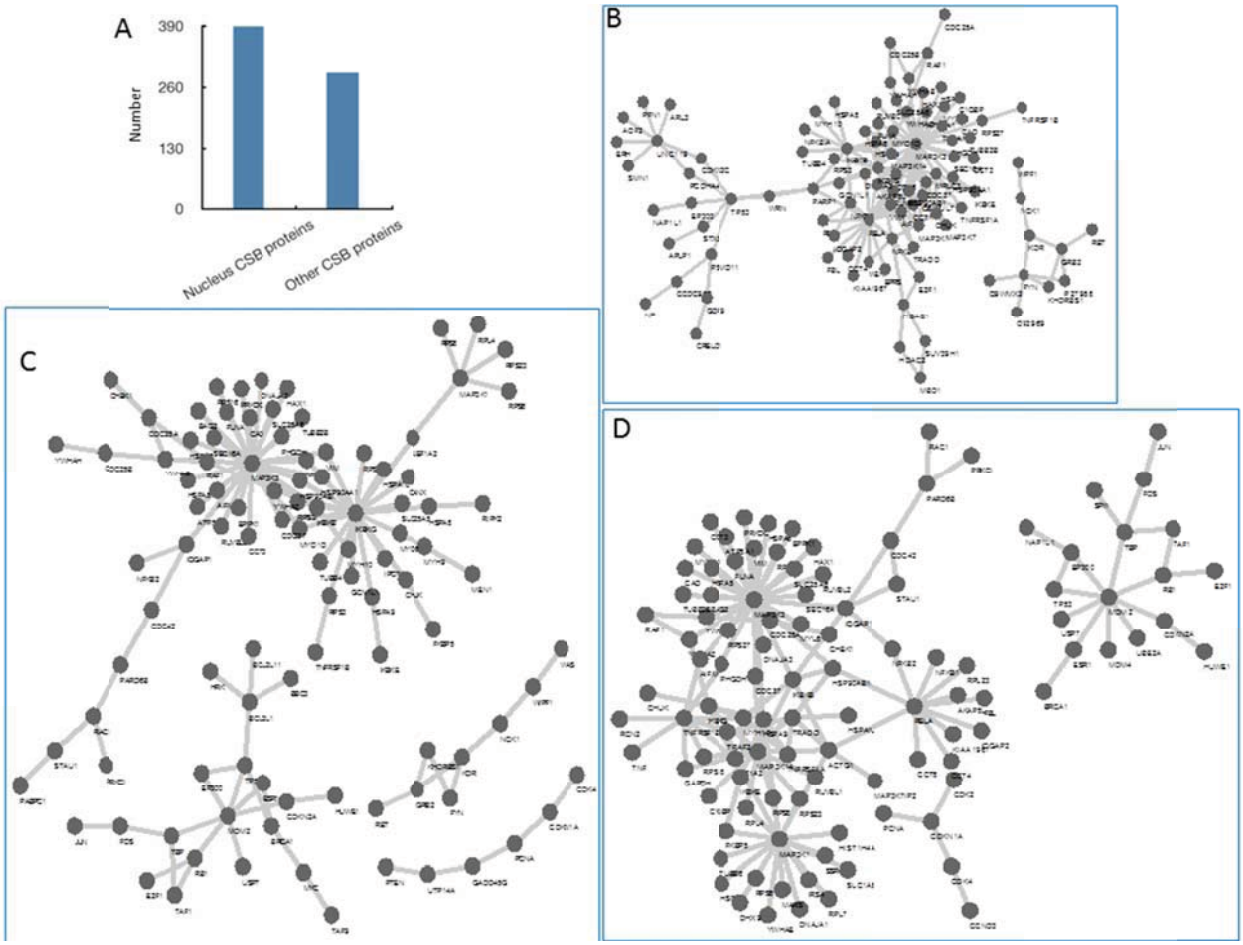


Fig. S1. CSB derived signaling networks for distinct breast cancer metastases.

A. The subcellular localization of CSB proteins. B. CSB derived protein signaling network for breast cancer brain metastases. C. CSB derived protein signaling network for breast cancer bone metastases. D CSB derived protein signaling network for breast cancer lung metastasis.

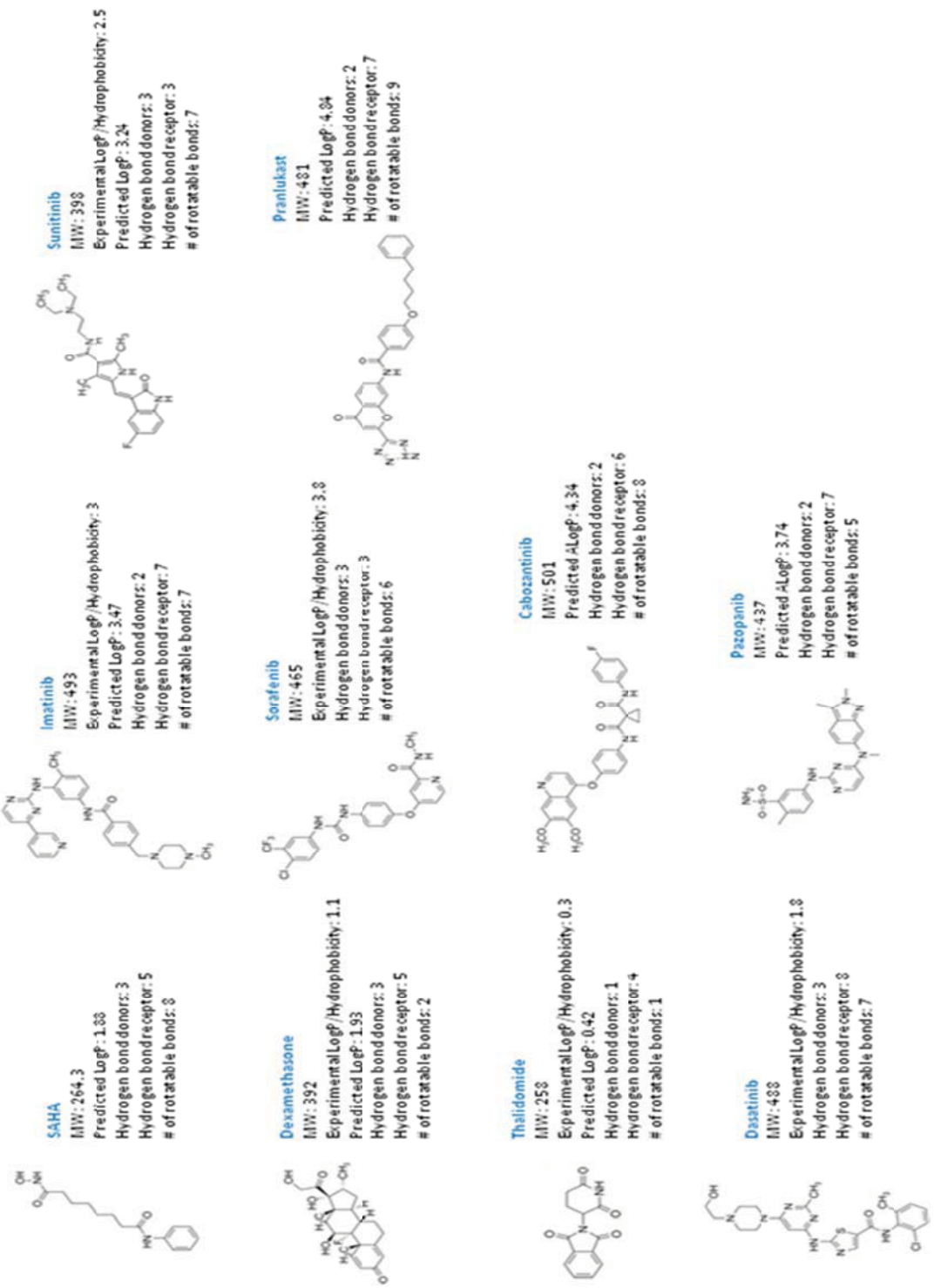


Fig S2. Chemical structures of the candidate repositioned drugs and their parameters for the "Rule of Five."

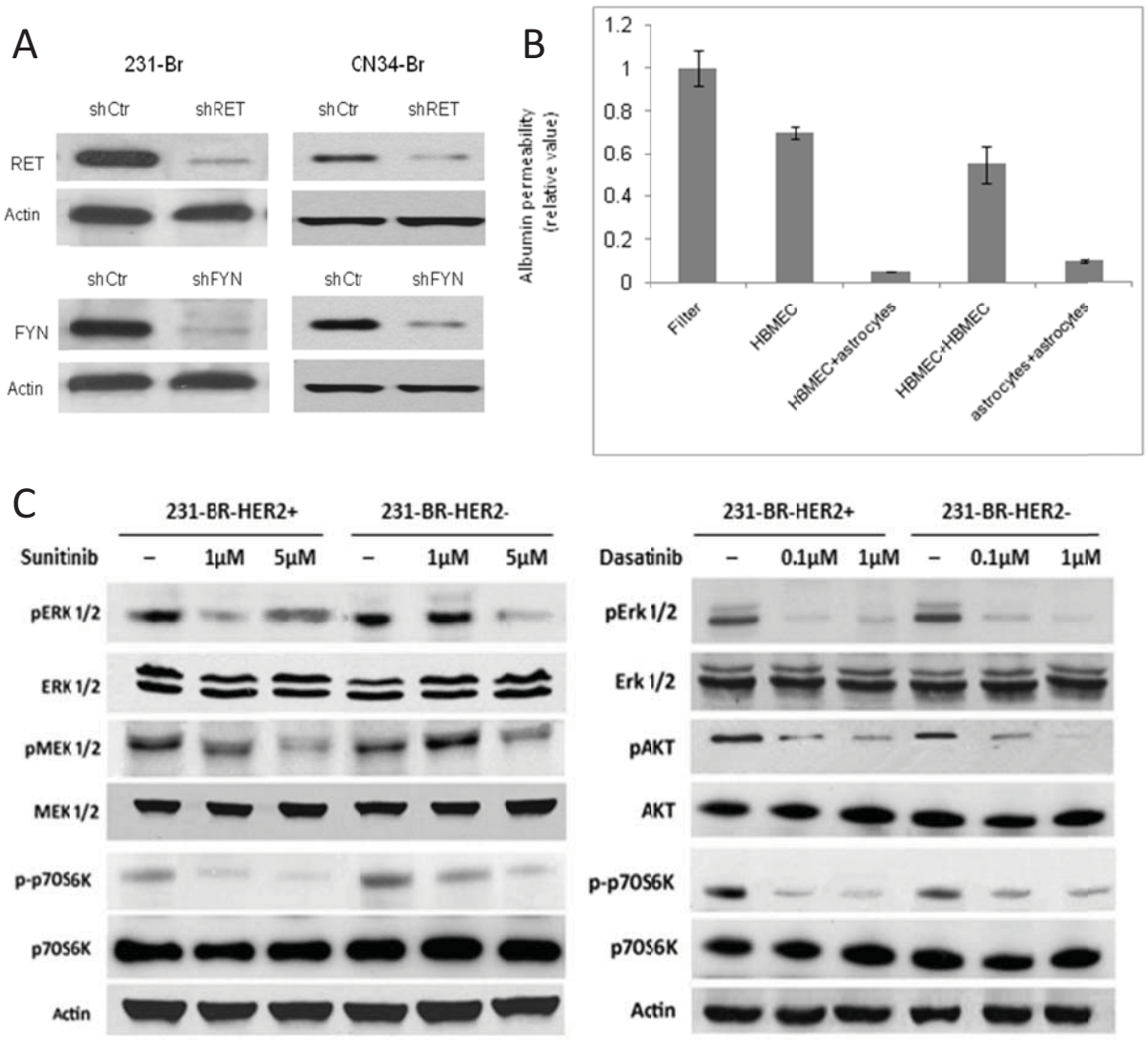


Fig S3. Western immunoblot analysis of RET, FYN and the down-stream pathway proteins in indicated cell lines.

A. Expression of RET and FYN in the shRNA knockdown 231-Br and CN34-Br cell lines. B. Albumin permeability analysis of the *in vitro* BBB assay. Absorbance at 620nm is shown relative to an empty tissue culture insert. Data are the average of triplicate determinations ± s.d.. C. Expression of down-stream pathway proteins under the treatment of Sunitinib and Dasatinib at indicated concentrations in indicated cell lines.


Fig S4. Relationship between the brain metastasis core signaling network and ER, PR, HER2 status in different breast tumor cohorts.

A. The Kaplan-Meier curve for brain metastasis-free survival on the basis of brain metastasis core signaling network (BrMNS) and ER, PR, HER2 status in the EMC286 cohort. B. The Kaplan-Meier curve for brain metastasis-free survival on the basis of BrMNS and ER, PR, HER2 status in the EMC192 cohort. C. The Kaplan-Meier curve for BrMNS and ER, PR, HER2 status in the MSK82 cohort. P value for the indicated comparison is calculated by Fisher's exact test.

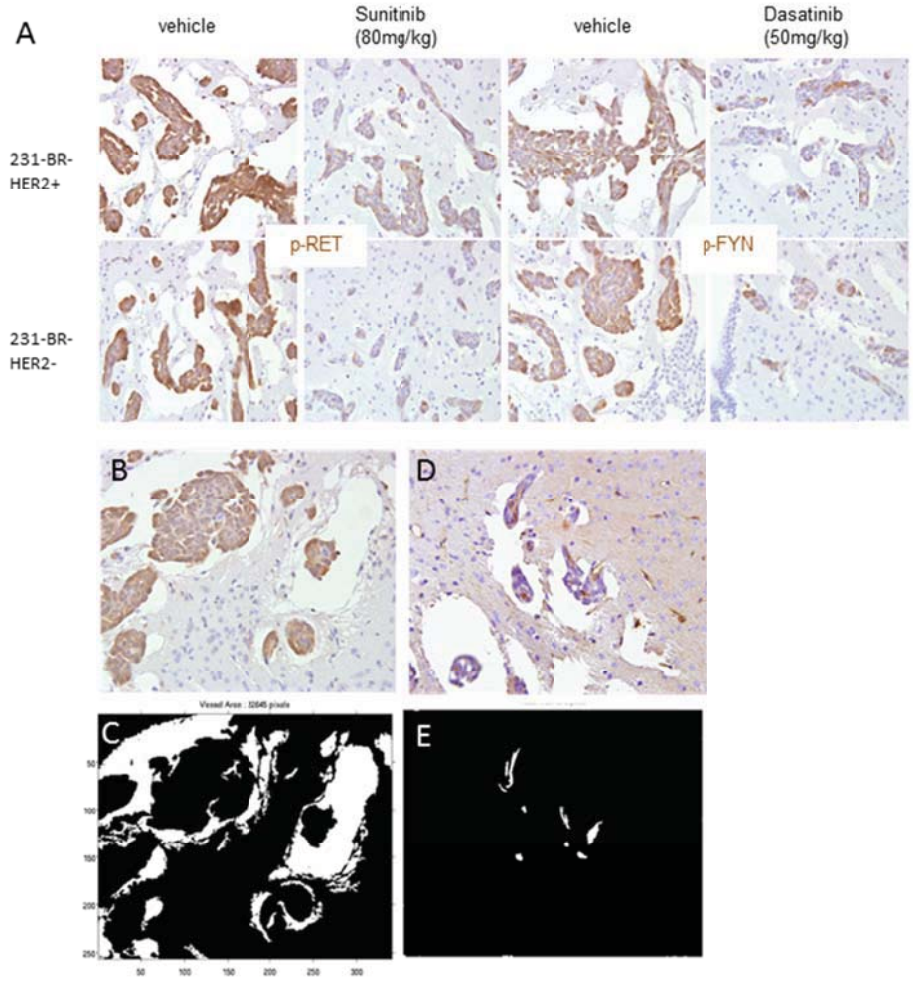


Fig S5. Evaluation of p-FYN and p-RET activation and tumor loci surrounding edema and vessels in the brain metastasis mouse models.

A. Immunohistochemical evaluation of p-FYN and p-RET activation *in vivo* in response to Sunitinib or Dasatinib treatment. Frozen sections (4μm thick) of brains from mice injected with 231-BR-HER2+ or 231-BR-HER2- cells and treated with Sunitinib (80 mg/kg body weight), Dasatinib (50 mg/kg body weight) or vehicle (n = 5 mice per group) were stained with antibodies specific for phosphorylated FYN (p-FYN; Thr12) or phosphorylated RET (p-RET; Tyr905). Representative images of large metastases for each group are shown. Images were taken under 20× objective. The presence of p-FYN or p-RET antigen is indicated by brown staining; nuclei were counterstained purple with hematoxylin. B. Representative brain metastasis image used for the loci surrounding edema area analysis. Tumor cells are brown. C. The segmented areas for edema area are white. D. Representative anti-CD31 immunohistochemistry images used for the brain metastasis vessel analysis. Vessel endothelial cells are brown. E. The segmented areas for vessels are white.

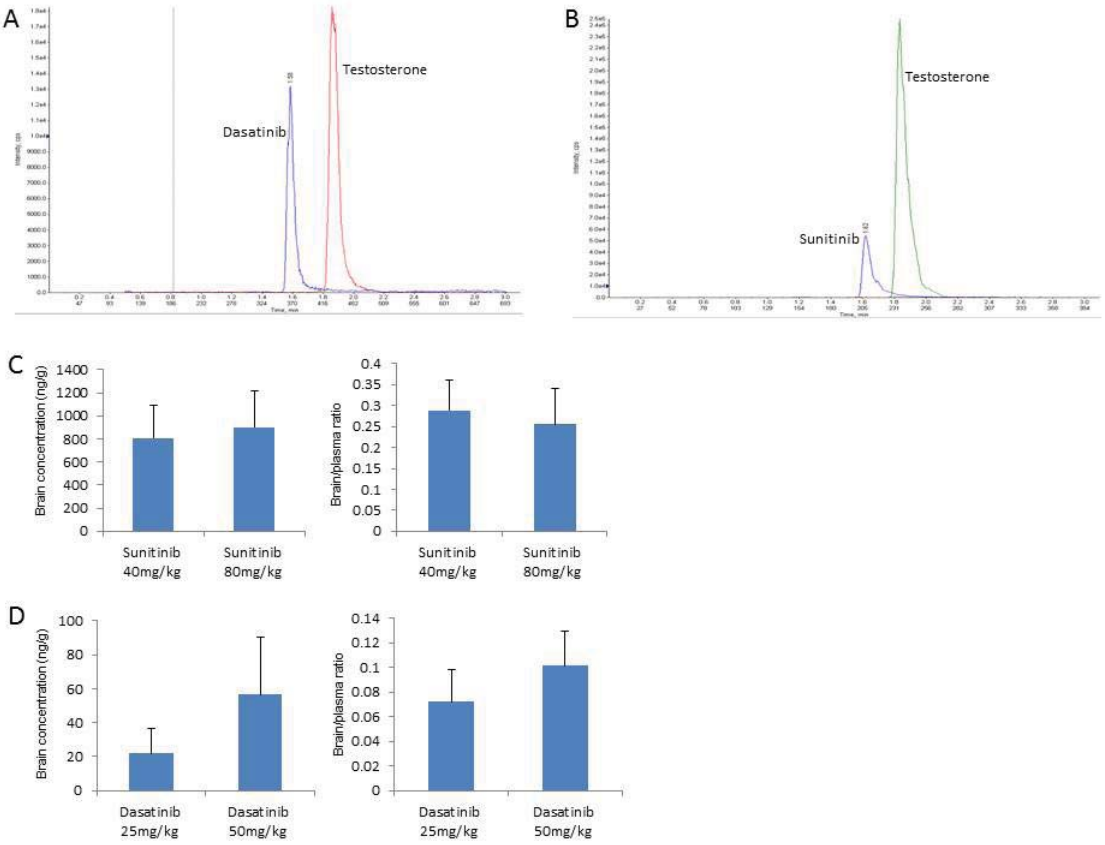


Fig. S6. Pharmacokinetic study of Sunitinib and Dasatinib accumulated in brain of the xenograft models.

A-B. Chromatograms of Dasatinib, Sunitinib and Testosterone for Authentic Plasma Sample 6hr post last dose. C-D. The brain distribution of Sunitinib and Dasatinib in the xenograft animal models.

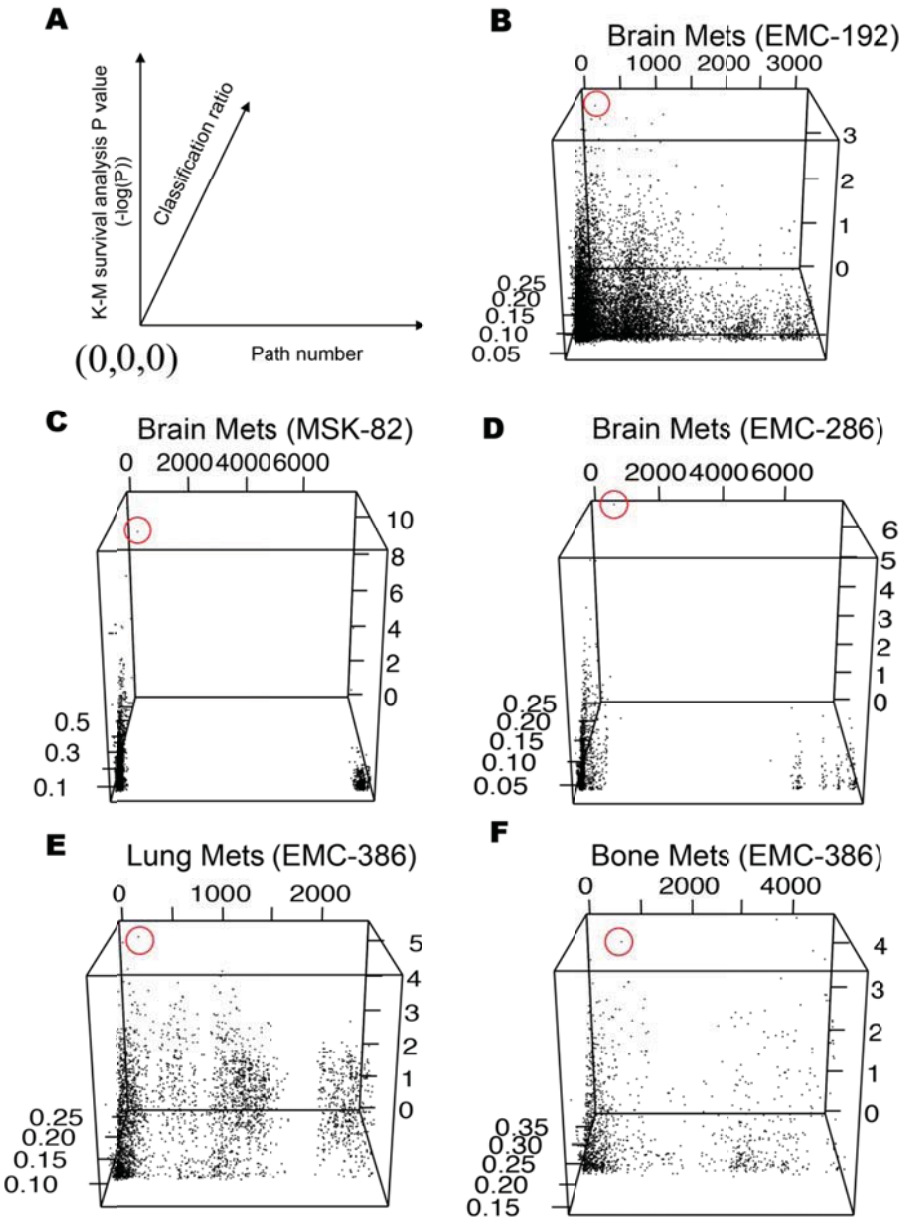


Fig S7. The three-dimensional cubes for the best subtrees in the survival analysis.