References

1. Berendsen S, Varkila M, Kroonen J, et al. Prognostic relevance of epilepsy at presentation in glioblastoma patients. *Neuro Oncol*. 2015;18(5):700–706.
2. Kerkhof M, Vecht CJ. Seizure characteristics and prognostic factors of gliomas. *Epilepsia*. 2013;54(Suppl 9):12–17.
3. Ruda R, Bello L, Duffau H, Soffietti R. Seizures in low-grade gliomas: natural history, pathogenesis, and outcome after treatments. *Neuro Oncol*. 2012;14(Suppl 4):iv55–iv64.
4. Capelle L, Fontaine D, Mandonnet E, et al. Spontaneous and therapeutic prognostic factors in adult hemispheric World Health Organization Grade II gliomas: a series of 1097 cases: clinical article. *J Neurosurg*. 2013;118(6):1157–1168.

Received 21 May 2016; accepted 23 May 2016
Advance Access date 1 July 2016

doi:10.1093/neuonc/now140

Reply to Letter

Response to: "Prognostic relevance of epilepsy at presentation in lower-grade gliomas"

We thank Zhou et al for their interest and comments regarding our article.[1]

We acknowledge the theoretical interest of taking the isocitrate dehydrogenase 1 (IDH1) mutational status of tumors into account in the multivariable survival analysis of glioblastoma patients presenting with or without epilepsy. We also agree that the inclusion of IDH1 status in this analysis should not depend on its mere correlation with epilepsy and have indeed not to proceed in such a way in our analysis. As discussed in our article, tissue to determine IDH1 status was only available for 360 of the 647 glioblastoma patients, a limitation of our retrospective study. However, restricting our analysis to these patients would have led to selection bias. Indeed, and as stated in our manuscript, these 360 patients showed significant differences with respect to age, tumor location, resection and postoperative treatment, and proportion of patients presenting with epilepsy compared with our complete patient cohort.[1] Moreover, these patients showed a significantly longer survival (median overall survival [OS]: 376.0 days from surgery, 95% CI: 337.4–414.6) compared with patients not included in the IDH1 analysis (median OS: 196.0, 95% CI: 159.2–232.8, log-rank test, $P<.0005$). Of note as well, IDH1 mutation was observed in only 21 of 360 patients (5.8%). Since IDH1 status did not correlate to epilepsy at presentation (χ^2 test, $P=.98$), it is unlikely that IDH1 mutation is the underlying factor that explains the prognostic effect of epilepsy at presentation in glioblastoma patients.

We also thank Zhou et al for sharing their preliminary analysis on the prognostic relevance of epilepsy at presentation in an institutional cohort of 113 lower-grade gliomas and in 477 patients from The Cancer Genome Atlas (tumor grade undescribed). With use of a univariable log-rank test, they did not observe any significant association between survival and epilepsy at presentation in their institutional cohort ($P=.131$). In the dataset of The Cancer Genome Atlas, a *history* of seizure was associated with survival in univariable analysis ($P=.048$), but not after correction for age, KPS, tumor location, World Health Organization grade, histological classification, radiotherapy, or chemotherapy ($P=.682$). This analysis of Zhou et al in fact addresses a different research question than that investigated in our paper, as they report on the prognostic relevance of epilepsy in lower-grade gliomas. In order to interpret the results of this analysis, however, more information regarding baseline characteristics of the patients included in their study is needed, in particular regarding the distribution of grade II and grade III patients in their cohorts. Indeed, the median follow-up of their institutional cohort (37 mo) seems very short for low-grade glioma patients compared with the published median survival of grade II glioma patients,[2] suggesting an overrepresentation of grade III astrocytic tumors or immature follow-up data. Additionally, it would be very interesting for Zhou et al to address their own question on the role of IDH1 mutational status, which is more frequently found in lower-grade tumors.[3] We are looking forward to reading a future report of their analyses, and in particular the results of a multivariable analysis with their institutional data.

Conflict of interest statement. The authors have no competing interests to declare.

Sharon Berendsen MD, Tom J. Snijders MD PhD, Pierre A. Robe MD PhD
Brain Center Rudolf Magnus, Department of Neurology and Neurosurgery (S.B., T.J.S., P.A.R.), University Medical Center of Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands; Department of Human Genetics, GIGA Research Center (P.A.R.), Liège University Hospital (CHU), Avenue de l'Hôpital, 1, 4000 Liège, Belgium.

Corresponding Author: Pierre A Robe, MD PhD, Department of Neurosurgery, University Medical Center of Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands (p.robe@umcutrecht.nl.)

References

1. Berendsen S, Varkila M, Kroonen J, et al. Prognostic relevance of epilepsy at presentation in glioblastoma patients. *Neuro Oncol*. 2015;Sep 29. pii: nov238. [Epub ahead of print].
2. Gorlia T, Wu W, Wang M, et al. New validated prognostic models and prognostic calculators in patients with low-grade glio-

mas diagnosed by central pathology review: a pooled analysis of EORTC/RTOG/NCCTG phase III clinical trials. *Neuro Oncol*. 2013;15(11):1568–1579.

3. Eckel-Passow JE, Lachance DH, Molinaro AM, et al. Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors. *N Engl J Med*. 2015;372(26):2499–508.

Received 20 June 2016; accepted 22 June 2016

doi:10.1093/neuonc/now161