Reply to J.C. Lindsey et al

After the first report by Tabori et al1 and our article2 published in Journal of Clinical Oncology, the potential impact of TP53 mutation status in sporadic medulloblastoma has been controversially discussed in the field of neurooncology.

The latest report by Lindsey et al3 conducted in another completely independent cohort investigating TP53 and CTNNB1 mutation status in 30 patients with primary medulloblastoma supports our recently published data. In our study2 investigating 310 patients with primary medulloblastoma, TP53 mutations were detected in all major cytogenetic and transcriptomic subgroups of medulloblastoma but were clearly overrepresented among Wnt/Wingless (WNT) -driven tumors characterized by mutations in the CTNNB1 gene. This finding was confirmed by Lindsey et al in their cohort, given that three of five tumors harboring a TP53 mutation belonged to the WNT-subgroup. In addition, we found an overrepresentation in MYCN-amplified medulloblastoma that remains to be confirmed in independent cohorts.

The results of a recent study by Gibson et al4 indicate that, in CTNNB1-mutated mice, the deletion of TP53 might be necessary for the accumulation of further mutations and therefore the development of medulloblastoma.4 Notably, these tumors anatomically resemble human WNT-subgroup medulloblastoma. Taken together, these data provide the first in vivo evidence of a cooperative role of concomitant mutations of CTNNB1 and TP53 in WNT-medulloblastoma tumorigenesis.

Our cohort included two patients with Li-Fraumeni syndrome (LFS) as confirmed by the detection of TP53 germline mutation; one of the patients had not previously received a diagnosis of LFS. Interestingly, Lindsey et al3 also report one patient with a newly identified TP53 germline mutation (LFS) who died about one year after diagnosis. Accordingly, undiagnosed patients with hidden LFS might constitute a significant proportion of supposedly sporadic medulloblastoma with TP53 mutation.

Concerning the patient outcome, the observations of Lindsey et al are in line with our results, showing that TP53 mutation is not associated with a poor patient outcome, in contrast with the report by Tabori et al.1

To evaluate the value of TP53 mutation status as a prognostic marker in medulloblastoma, it is essential to take into account that molecular characteristics of the tumor might determine the patient’s outcome (ie, WNT-driven tumors being associated with a favorable prognosis), that the clinical course of patients with LFS may differ from that of patients with medulloblastoma harboring a sporadic TP53 mutation, and that the impact of the TP53 mutation status on prognosis might depend on the different therapy regimen applied. Thus, it would be preferable to separately evaluate—ideally prospectively—the effect of TP53 mutation status on prognosis in the different trial arms within a randomized multicenter clinical trial.

In conclusion, the study by Lindsey et al3 supports our findings that TP53 mutations occur in all molecular subgroups and are not perse an adverse prognostic marker across all subgroups of medulloblastoma. This supports the notion that medulloblastoma comprises distinct entities with specific genetic alterations that are decisive for the patient’s outcome.

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