Title

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Alliance A071601: Phase II trial of BRAF/MEK inhibition in newly diagnosed papillary craniopharyngiomas.

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Abstract Disclosures

- **Abstract**

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Background: Craniopharyngiomas, a rare brain tumor along the pituitary-hypothalamic axis, can cause significant clinical sequelae. Surgery and radiation, the only effective treatments, can cause significant morbidity. Genetic analysis of craniopharyngiomas revealed that 95% of papillary craniopharyngiomas (PCP) have BRAF *V600E* mutations (Brastianos et al. Nature Genetics 2014). We evaluated the efficacy of BRAF/MEK inhibition in patients (pts) with previously untreated PCP. **Methods:** Eligible pts without prior radiation whose PCP screened positively for BRAF mutations were treated with oral vemurafenib/cobimetinib in 28-day cycles. The primary endpoint of response rate (RR) based on centrally determined volumetric data was evaluated in 16 pts, where a partial response was defined as >20% decrease in volume. This single arm, Simon two-stage phase 2 trial had 89% power to detect a true RR of at least 30% (vs. the null RR 5%; alpha=0.04). In this design, 3 or more observed volumetric responses in 16 evaluable pts would be considered promising activity. **Results:** In the 16 pts evaluated, 56% were female, and the median age was 49.5 years. Median follow-up was 22 months (95% CI: 16-26.5) and median number of treatment cycles was 8. Three patients progressed after therapy was discontinued and none have died. Based on volumetric response criteria, 14 of 15 pts with volumetric data available for central review had response to therapy (93%; 95% CI: 68% to 99.8%). Of 16 patients evaluable based on local review, 15 had response to therapy (93.75%; 95% CI: 70% to 99.8%). The median tumor reduction was -83% (range: -52% to -99%). The one nonresponder received 2 days of treatment before coming off therapy due to toxicity. Median progression-free survival was not reached. Grade 3 toxicities at least possibly related to treatment occurred in 12 pts (rash in 6 pts). Grade 4 toxicities were observed in two pts: hyperglycemia (n=1) and increased CPK (n=1). Three pts discontinued treatment for adverse events. **Conclusions:** Vemurafenib/cobimetinib resulted in an objective response in all pts who received 1 or more cycles of therapy. Our study indicates that BRAF/MEK inhibitors could be a powerful tool in the treatment of previously untreated PCP and warrants further evaluation in larger studies. A second arm of this study is enrolling pts with progressive PCP after prior radiotherapy.
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