cytosine methyltransferase. Human NSUN5 is located in chromosome 7 and is completely deleted in the Williams-Beuren syndrome, a complex neurodevelopmental disorder. However, RNA targets of NSUN5 in mammals and its role in cancer are unknown. The objective of this project is to determine whether elevated NSUN5 changes rRNA methylation pattern and thereby leads to pro-tumorigenic translational reprogramming and pro-tumorigenic phenotypes in glioblastoma. Western blotting showed that NSUN5 is expressed in 7 out of 9 established glioblastoma cell lines and in 8 out of 12 primary patient-derived glioblastoma cell lines. Bisulfite sequencing confirmed that NSUN5 methylates C3782 of human 28S rRNA in glioblastoma cells. Functionally, overexpression of NSUN5 increases, whereas NSUN5 knockout decreases global protein synthesis and sphere formation in glioblastoma cells. More importantly, mice bearing intracranial NSUN5-expressing U87 tumors survived for a shorter time than mice bearing tumors derived from U87 control cells. Our results suggest that NSUN5 methylates 28S rRNA and may enhance cancer stem cell phenotypes and tumor formation and/or progression in glioblastoma. Experiments are ongoing to determine whether NSUN5 promotes tumor formation and/or progression through translational reprogramming in glioblastoma. This study may help identify novel therapeutic targets for glioblastoma.

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Improvement of hearing with bevacizumab in a patient with neurofibromatosis type 2 and bilateral acoustic schwannomas

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BACKGROUND: Neurofibromatosis type 2 (NF2) is a rare genetic condition caused by mutations in the Merlin gene on chromosome 22. It results in acoustic neuromas (schwannomas) and other CNS tumors including meningiomas and ependymomas. Most patients develop hearing loss as a result of neuroma-driven destruction of auditory nerves. Surgery and radiation therapy remain the two most commonly recommended treatment options. However, there is a risk of further hearing loss with these procedures. There is emerging evidence that bevacizumab, a monoclonal antibody against VEGF-A, can shrink acoustic neuromas and mitigate hearing loss.

CASE PRESENTATION: A 60-year-old female with bilateral acoustic neuromas from NF2 suffered partial hearing loss in the left ear and total hearing loss in the right ear after removal of the right-sided neuroma. Baseline MRI showed a left-sided acoustic neuroma (15 x 13 mm) and recurrence of the right-sided neuroma (18 x 14 mm). Bevacizumab was initiated at 5 mg/kg IV every 14 days. After 8 cycles, the patient reported marked improvement in hearing. At lower frequencies (< 1,000 Hz, the range of human voice), auditory thresholds improved by up to 60% of baseline, while at higher frequencies, improvements of up to 46% were seen. Repeat imaging showed no disease progression.

CONCLUSIONS: Bevacizumab led to hearing improvement and prevention of disease progression after 8 cycles of therapy. This treatment should be considered in patients with NF2 and acoustic neuromas who wish to pursue a less-invasive treatment option with the potential of delaying progression and mitigating hearing loss.

ORAL PRESENTATIONS
11 MAY 2018

1115 - 1200
SESSION SIX ~ Glioblastoma

Durable complete responses observed in patients with recurrent high grade glioma treated with Toca 511 & Toca FC

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Toca 511 (vocimagene amiretrorepvec) is an investigational retroviral replicating vector that selectively infects dividing cancer cells, integrates into the genome and replicates due to immune defects in tumors. Toca 511 spreads through tumors and stably delivers the gene encoding an optimized yeast cytosine deaminase that converts the produrg Toca FC (investigational, extended-release of 5-fluorocytosine) into 5-fluorouracil. In preclinical models, 5-fluorouracil kills infected dividing cancer cells, myeloid derived suppressor cells and tumor associated macrophages, enabling immune activation against the tumor. In this dose ascending Ph1 trial (NCT01470794), Toca 511 was injected into the resection cavity wall of patients with rHGG, followed by courses of oral Toca FC. Additional cohorts included combination with bevacizumab or lomustine. Across the Ph1 program, the safety profile remains favorable. Objective responses (ORs) were assessed by IRR using MRI scans prior to Toca FC treatment as baseline. ORs occurred 6-19 months after Toca 511 administration, suggesting an immunologic mechanism. The ORs were observed in 4 patients with IDH1-wildtype and 2 patients with IDH1-mutant tumors, including 5 complete responses (CRs) with the investigational therapy alone, and 1 CR in combination with bevacizumab. The median duration of response (mDoR) was 35.1+ months. As of AUG2017, all responders were CR and remain alive. In a 23-patient subgroup who received high doses of Toca 511 and met Ph3 trial criteria, mOS was 14.4 months, 3-year survival rate was 26.1%, and mDoR was 35.7+ months with a durable response rate of 21.7%. Data suggest a positive association of durable response with OS.

Timing of adjuvant treatments on glioblastoma survival: A retrospective cohort analysis based on the national cancer database

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Few studies investigated the associations between intervention modalities, timing, and survival in glioblastoma (GBM) patients. A total of 20511 eligible GBM patients underwent biopsy and