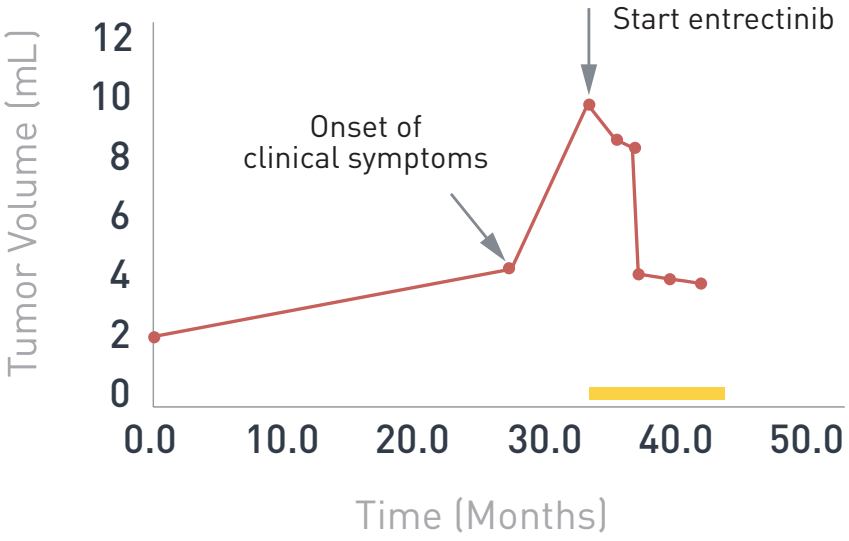
MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

ADVANCES AT **MASS GENERAL CANCER CENTER** FEBRUARY 2018

# New Genetic-Based Treatment for Glioneuronal Tumors

***Can identifying oncogene fusions that are susceptible to treatment help with reducing these tumors?***




## Glioneuronal Tumor Volume With TNK Inhibitor Therapy

Radiologic analysis demonstrated 60% reduction in tumor size after nine months of entrectinib therapy. The yellow line indicates time and duration of treatment.

Glioneuronal tumors are a rare group of uncommon, diverse primary central nervous system tumors with few treatment options aside from surgical resection. Radiation is offered if the tumor is not totally resected or if it displays high-grade aggressive behavioral features or recurrence. Historically, the molecular understanding of these tumors has been quite limited, confounding the ability to treat them with targeted therapy.

Now Priscilla K. Brastianos, MD, director of the Central Nervous System Metastasis Program at the Massachusetts General Hospital Cancer Center, has discovered a new clinically actionable genetic target in glioneuronal tumors: oncogene fusions involving the neurotrophic tropomyosin receptor kinase (*NTRK*) gene family. Oncogene fusions are a combination of two separate genes that, when combined, often lead to activation of a gene. Activation of the *NTRK* gene family is known to promote cell growth, survival, and differentiation in other cancers.

Further, Dr. Brastianos and her team have discovered that treatment of a patient with one of the *NTRK* fusions with entrectinib, a TRK inhibitor, led to a 60% reduction of the tumor over time. Their findings were published in *Nature Precision Oncology* in March 2017.[1]

"This is the first time a TRK inhibitor has been used for a glioneuronal tumor with a positive response," says Dr. Brastianos, whose laboratory focuses on identifying molecular drivers of progressive brain tumors and metastatic brain tumors. Dr. Brastianos' research findings show that there are clinically actionable targets in these tumors; and that clinicians should test glioneuronal tumors for oncogenic fusions and mutations, since targeted therapies may already be available.

### NOVEL ONCOGENE FUSIONS DISCOVERED IN GLIONEURONAL TUMORS

Dr. Brastianos initiated a genomic analysis in 26 glioneuronal tumors from adult patients to identify the molecular characteristics of this under-studied tumor type. Her team discovered that 34% (9 of 26) of the

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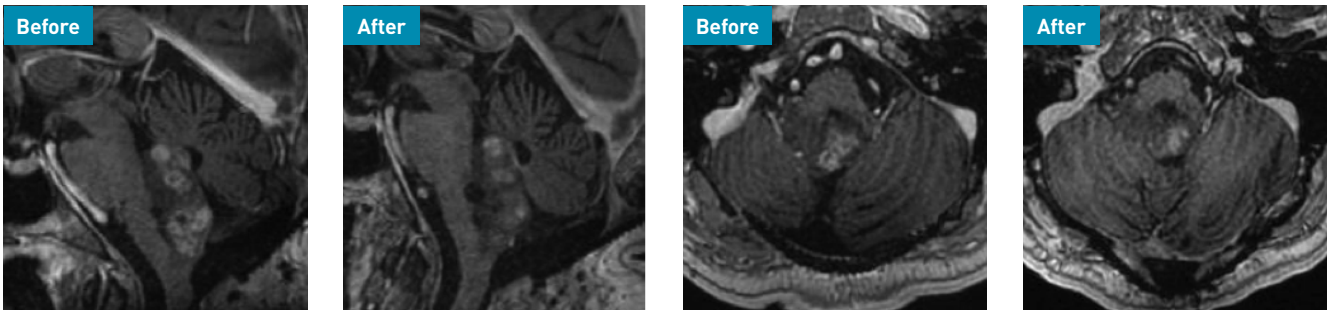
## Radiographic Analysis of Targeted Glioneuronal Tumor Treatment

MRI images show reduction in tumor size from the start of entrectinib treatment and at nine months after therapy.




Sagittal Axial

tumors exhibited BRAF mutations and 27% (7 tumors) had oncogenic fusions. Of the 7 oncogenic fusions, three involved *NTRK* gene fusions—the first time this fusion type has been linked with glioneuronal tumors.

"Finding three out of 26 tumors with this *NTRK* gene fusion is significant," says Dr. Brastianos. "We have seen *NTRK* gene fusions in other cancers, such as non–small cell lung cancer, colorectal cancer and sarcoma, but not previously in glioneuronal tumors."

Looking ahead, Dr. Brastianos suggests a clinical trial involving a larger number of glioneuronal tumor patients with *NTRK* fusions.

### TRACK RECORD OF FINDING GENETIC DRIVERS

Dr. Brastianos' work in glioneuronal tumors follows from similar molecular investigations of other tumors—including craniopharyngiomas, another uncommon, under-studied brain tumor. Her team was the first to discover BRAF mutations in craniopharyngiomas and to show that a patient with this mutation responded to targeted therapy with BRAF and MEK inhibitors. That research was published in *Nature Genetics* in 2014[2] and in the *Journal of the National Cancer Institute* in 2015.[3]

As a result, her team opened an ongoing national Alliance-sponsored clinical trial in multiple sites in the United States, investigating BRAF inhibitors in craniopharyngiomas. The Alliance is an affiliation of over 850 medical oncology institutions throughout the world; it oversees oncological clinical trials.

In addition, Dr. Brastianos and colleagues have discovered mutations in the *AKT* and *SMO* genes in meningiomas, one of the most common types of CNS tumors. From that discovery, they initiated an Alliance-sponsored, multicenter clinical trial in 2015 for meningioma patients to receive treatment with AKT and SMO inhibitors. To date, 550 hospitals are participating in that study.

This work is enhanced by the multidisciplinary brain metastasis clinic at Mass General Cancer Center—the first of its kind in the United States—which not only provides treatment for these patients, but also conducts clinical and translational research. Its goal is to understand the molecular pathways that drive progressive primary and metastatic brain tumors, and to apply this understanding to the clinical setting.

"It is tremendously rewarding to see our patients benefit from

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the cutting-edge work performed in the laboratory. All of these studies fit the pattern of what our laboratory does, which is to find new therapeutic targets, especially in under-studied brain tumors, then move forward with clinical trials," says Dr. Brastianos. "Now that we have found several targets and opened several clinical trials as a direct result, it's important that genetic testing be considered for patients with primary and metastatic tumors."

1 Alvarez-Breckenridge C, Miller JJ, Nayyar N, et al. Clinical and radiographic response following targeting of BCAN-NTRK1 fusion in glioneuronal tumor. ***NPJ precision oncology***. 2017 Mar; 1(5).

2 Brastianos PK, Taylor-Weiner A, Maney PE, et al. Exome sequencing identifies BRAF mutation in papillary craniopharyngiomas. ***Nat Genet***. 2014 Feb; 46(2):161-5.

3 Brastianos PK, Shankar GM, Gill CM, et al. Dramatic response of BRAF V600E mutant papillary craniopharyngioma to targeted therapy. ***J Natl Cancer Inst.*** 2015 Oct; 45(3):285-9.

## Contributor

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