Memorial Sloan Kettering Cancer Center

AACR Abstract #LB-302

# Potential role of larotrectinib (LOXO-101), a selective pan-TRK inhibitor, in NTRK fusion-positive recurrent glioblastoma

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## Background

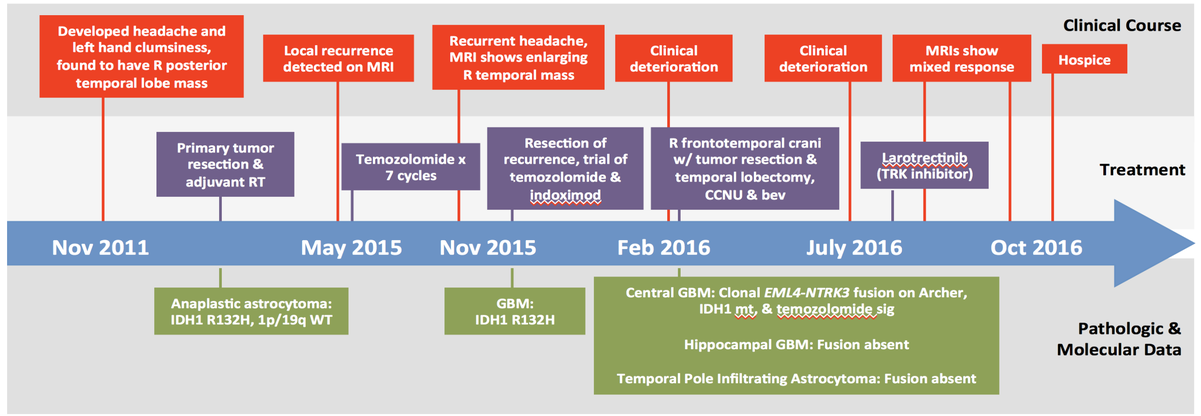
Efforts to develop genomically targeted therapy for glioblastoma (GBM) have been unsuccessful to date. Fusions involving the tropomyosin receptor kinases (TRKA/B/C) encoded by NTRK1/2/3 represent a potential therapeutic target in diffuse gliomas.1,2 Novel TRK inhibitors have shown remarkable efficacy in patients with TRK fusions in a myriad of solid tumor types3,4; however, there is little clinical data on TRK inhibitor efficacy in diffuse gliomas. Here, we report the entirety of the clinical experience to date with larotrectinib, a selective TRK inhibitor, in TRK fusion CNS cancers.

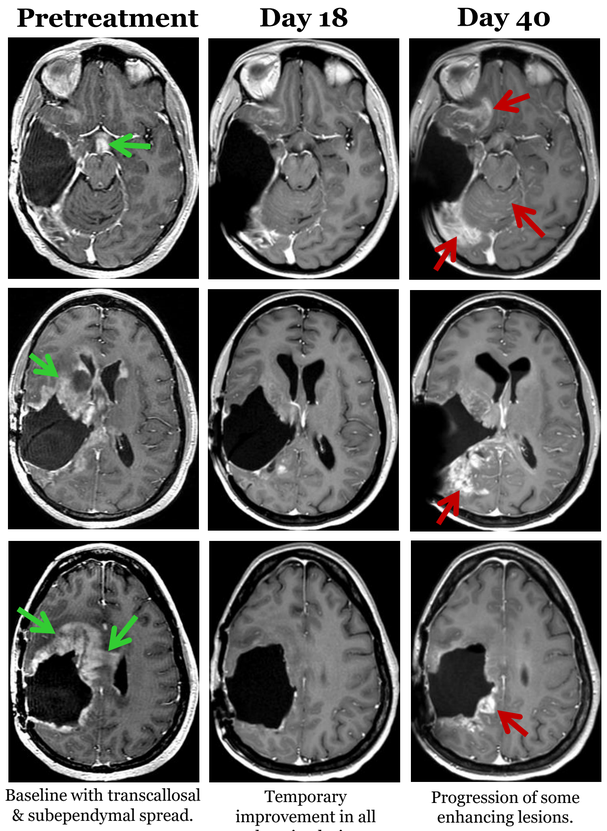
## Case Summary

The index patient described in most detail here was initially diagnosed with an *IDH1* R132H-mutant, 1p/19q intact anaplastic astrocytoma of the right temporal lobe. Three years later, she developed a local recurrence treated with temozolomide with disease progression. Resection identified transformation to GBM for which she received temozolomide and an IDO inhibitor with rapid tumor growth. Urgent piecemeal debulking confirmed GBM in the central and hippocampal components. She was started on CCNU and bevacizumab.

RNA sequencing of her tumor using Archer FusionPlex® revealed an in-frame *EML4-NTRK3* fusion in the dominant clone of the central tumor that was absent from the hippocampal specimen and temporal pole, indicating intratumoral heterogeneity. After clinical deterioration due to progressive disease, she received larotrectinib under expanded access, to which she achieved a partial response by 3 weeks, the degree of which was radiologically discrepant between disease sites, consistent with the subclonality of the fusion oncoprotein. While there was significant periventricular tumor shrinkage (67x52mm to 8x4mm), there was no shrinkage in the right frontal and occipital lobes. A repeat MRI 1 month later showed disease progression with increasing tumor in the latter sites, but ongoing response of periventricular tumor. This led to clinical deterioration and ultimate discontinuation of larotrectinib.

## Case Details




Baseline with transcallosal & subependymal spread.

Temporary improvement in all enhancing lesions.

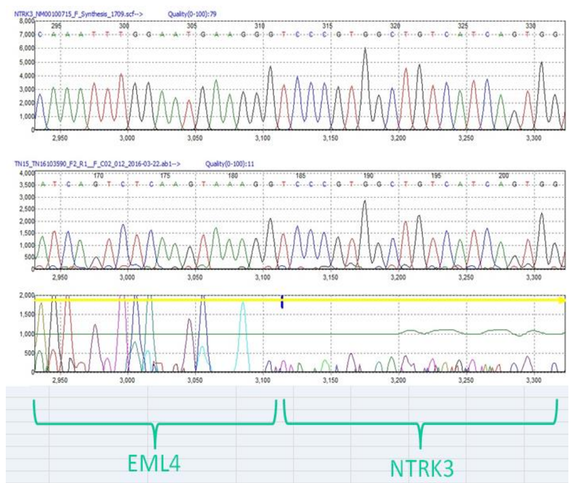
Progression of some enhancing lesions.

Serial contrast T1-weighted images show enhancing disease in the infundibulum, basal ganglia, frontal lobe, subependyma and corpus callosum that subsequently improves (**green arrows**), as well as worsened enhancing disease in the inferior frontal lobe, parietal lobe, occipital lobe and leptomeninges (**red arrows**).

### *EML4-NTRK3* on Archer FusionPlex® (RNA sequencing)

| Location | Read Support for Fusion (%) |
|---|---|
| Central tumor | 85.4% |
| Hippocampal #1 | <0.01% |
| Hippocampal #2 | 0% |
| Temporal Pole | 0% |


### Sanger Sequencing




Sanger sequencing of the central tumor confirms a gene fusion of *EML4* exon 2 and *NTRK3* exon 14

## Additional Cases, from NAVIGATE

| | | |
|---|---|---|
| Pt Info | 79M with GBM | 58M with GBM |
| Molecular | *MGMT* unmethylated *BCR-NTRK2* fusion | *MGMT* unmethylated *AFAP1-NTRK1* fusion |
| Treatment | surgical resection → chemoradiation → temozolomide alone with POD → bevacizumab with POD → larotrectinib | surgical resection → chemoradiation → temozolomide alone with POD → larotrectinib |
| Status | Continues on drug 4 months later with evidence of treatment effect on imaging | Continues on drug 4 months later with evidence of treatment effect on imaging |

- Patient (Pt), Progression of Disease (POD)
- Data cutoff: March 13, 2017

## Conclusions

- This patient's mixed response persisting even at the time of drug discontinuation suggests that the EML4-NTRK3-mutant subclone was sensitive and responded to larotrectinib
- Larotrectinib's signs of anti-tumor activity in these three patients suggests meaningful brain penetration
- TRK fusions may be therapeutic targets in GBM, though the burden of patients with TRK-fused CNS disease is low
- Patients with TRK fusion CNS tumors are eligible for the ongoing NAVIGATE Phase 2 larotrectinib trial

## References

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3. Drilon A, Siena S, Ou S-HI, et al. Safety and Antitumor Activity of the Multi-Targeted Pan-TRK, ROS1, and ALK Inhibitor Entrectinib (RXDX-101): Combined Results from Two Phase 1 Trials (ALKA-372-001 and STARTRK-1). Cancer Discovery. February 2017 [Epub ahead of print].CD-16-1237.
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**AACR Annual Meeting 2017**