Entrectinib Produces Responses in Children and Adolescents With CNS and Other Cancers That Have Specific Gene Fusions

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ASCO Perspective
“There have been far fewer studies of targeted cancer medicines in pediatric populations than in adults. While these data are very early and more research is needed, they suggest the exciting possibility of the first treatment for childhood cancers that is effective based on tumor genetics instead of tumor type or location,” said ASCO President Monica M. Bertagnolli, MD, FACS, FASCO.

ALEXANDRIA, Va. – In a phase I/IB study of 29 patients, age 4.9 months to 20 years, with rare central nervous system tumors, neuroblastoma, or other solid tumors, responses to entrectinib, a novel targeted treatment, were seen in 12 of the 28 evaluable patients. The 12 pediatric patients who experienced a response to therapy had fusions in \( NTRK1/2/3,\) \( ROS1,\) or \( ALK \) genes (11 patients) or an \( ALK \) mutation (1 patient). The study will be presented at the upcoming 2019 ASCO Annual Meeting in Chicago.

“Our results show that children with life-threatening cancers can benefit greatly even after other conventional therapies have not worked – we’ve seen some rapid and durable responses, which is very gratifying,” said author Giles W. Robinson, MD, a pediatric neuro-oncologist at St. Jude Children’s Research Hospital in Memphis, TN. “These early findings suggest that this therapy holds great promise for those whose tumors have these specific gene fusions.”

Entrectinib is an oral systemic medication that also penetrates the central nervous system (CNS) to inhibit protein pathways related to mutations in \( NTRK1/2/3,\) \( ROS1,\) and \( ALK \) genes, with the goal of promoting cancer cell death. Entrectinib is distinct from other medicines in its class as it has broader activity that targets multiple mutations whereas other medicines are usually effective against just one mutation.

About the Study
As of October 31, 2018, the STARTRK-NG clinical trial had enrolled 29 patients from 4.9 months to 20 years of age, with a median of 7 years of age, who had either CNS tumors, neuroblastoma,
or other solid tumors. Most patients with CNS tumors had undergone surgery to remove the tumors, followed by radiation.

The first phase of the trial was designed to assess optimal dosing, and it was expanded to focus on patients with tumors harboring alterations to \( \text{NTRK}1/2/3, \text{ROS}1, \) and \( \text{ALK} \) genes. In all, 12 of the 29 patients enrolled had tumors with \( \text{NTRK}1/2/3, \text{ROS}1, \) or \( \text{ALK} \) gene fusions or mutations.

A complete response was defined as disappearance of all disease and neurologic improvement or stability. A partial response was 30% or greater reduction in disease for solid tumors and 50% or greater reduction in disease for CNS tumors and neurologic stability. Progressive disease was a 20% or greater increase in disease for solid tumors or 25% or greater increase in disease for CNS tumors or worsening neurologic status, and stable disease was defined as no change in cancer progression or regression.

**Key Findings**

A total of 12 patients had objective responses (tumor shrank or disappeared) to entrectinib, with a median treatment duration of 281 days. The median time to response was 57 days, and all responses occurred at doses of \( 400 \text{ mg/m}^2 \) (milligrams per body surface area squared) or more. No responses were observed among patients lacking the alterations targeted by entrectinib.

Patient responses and corresponding mutation data were:

- **CNS tumors**: Among the five patients with evaluable CNS tumors, all had an objective response - one had a complete response (fusion of \( \text{ETV6-NTRK3} \) genes) and four had a partial response (three confirmed gene fusions in \( \text{TPR-NTRK1}, \text{EEF1G-ROS1}, \text{EML1-NTRK2} \) and one unconfirmed \( \text{GOPC-ROS1} \) gene fusion). One remaining CNS patient is yet to be evaluated (\( \text{KANK1-NTRK2} \) fusion).

- **Extracranial tumors**: Six patients with extracranial tumors (a solid tumor occurring outside the CNS) had objective responses - one patient had a complete response (\( \text{DCTN1-ALK} \) fusion) and five had partial responses (\( \text{TFG1-ROS1}, \text{EML4-NTRK3}, \text{KIF5B-ALK}, \) and two \( \text{ETV6-NTRK3} \) fusions). The types of cancer included three cases of inflammatory myofibroblastic tumors, two cases of infantile fibrosarcomas and one case of melanoma.

- **Neuroblastoma**: One patient had a complete response (\( \text{ALK F1174L} \) mutation).

The medicine was well tolerated and there appears to be no time frame yet studied in which the medicine stops working or toxicities become limiting, according to Dr. Robinson.

The recommended dose of entrectinib in children was \( 550 \text{ mg/m}^2 \) once daily. Some of the noted side effects were fatigue, elevated creatinine levels, dysgeusia resulting in loss of taste, and at higher dose, one incidence of pulmonary edema resulting in fluid in the lungs. One unusual side effect was weight gain, which is not often seen with cancer medicines. These side effects have resulted in dose reductions to \( 400\text{mg/m}^2 \).

**Next Steps**
Accrual to the clinical trial is ongoing. Phase II recruitment will begin soon to establish effectiveness of the medicine. Investigators also hope to determine long-term side effects and duration of response on and off therapy.

This study is sponsored and received funding from F. Hoffman-La Roche Ltd. The study design and conduct was also supported by Alex’s Lemonade Stand Center of Excellence.

**Study at a Glance**

<table>
<thead>
<tr>
<th>Study Focus For your readers:</th>
<th>Responses to a targeted therapy in children and adolescents with central nervous system tumors and recurrent solid tumors with alterations in the TrkA/B/C, ROS1 and ALK kinase pathways</th>
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<tbody>
<tr>
<td>Study Focus:</td>
<td>Central Nervous System Tumors</td>
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<tr>
<td>Trial Type:</td>
<td>Phase I/IB clinical trial</td>
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<tr>
<td>Patients on Trial:</td>
<td>29 in phase I and IB</td>
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<td>Treatment Tested:</td>
<td>Entrectinib</td>
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<tr>
<td>Primary Finding:</td>
<td>A complete or partial response was seen in all trial participants with alterations in specific kinase pathways</td>
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<tr>
<td>Secondary Finding(s):</td>
<td>The results were especially promising in high-grade central nervous system tumors</td>
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**For Dr. Bertagnolli:**

The results were especially promising in high-grade central nervous system tumors.

**Patent and Caregiver Inquiries:**

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