Genomic Testing in the Emerging Era of Precision Medicine: Lessons Learned from Studies in Larotrectinib

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INTRODUCTION

- Identifying the genetic driver of a tumour may allow use of targeted therapies, which typically have fewer side effects than chemotherapy.
- Genomic testing can identify oncogenic alterations, including gene mutations and chromosomal rearrangements, that can be targeted with specific therapies.
- Chromosomal rearrangements may lead to gene fusions, resulting in novel oncogenic fusion proteins.1
  - Selective inhibitors of oncogenic fusion proteins enable precision medicine-based treatment of gene fusion cancers.1
- Molecular testing is essential to identify patients, with rare tumour types, who may benefit from such agents (Figure 1).1,2

Figure 1. Molecular testing for gene fusions1,3

Next-generation sequencing (NGS)
- Tests for different genomic alterations in parallel using DNA or RNA
- RNA is preferred for gene fusions

Reverse transcriptase polymerase chain reaction (RT-PCR)
- Detects known fusion transcripts in RNA
- Detects 5’/3’ imbalance as a fusion signature, but cannot determine novel partners

Fluorescence in situ hybridisation (FISH)
- Detects gene rearrangements in DNA that may generate a fusion transcript

Immunohistochemistry (IHC)
- Detects protein expression, which may result from a fusion event

NGT GENE FUSIONS

- Tropomyosin receptor kinase (TRK) fusions are oncogenic drivers of various tumours; they arise from rearrangements between neurotrophic tyrosine receptor kinase (NTRK) 1, 2, or 3 genes and an unrelated gene (Figure 2).1
- NTRK gene fusions identified in >20 paediatric and adult tumour types, and ~1% of all solid tumours.1
  - Rare in common cancers (e.g., lung, colon) but nearly pathognomonic in certain rare cancers (e.g., infantile fibrosarcoma, secretory carcinoma of the salivary gland, secretory breast carcinoma).
- Larotrectinib is a highly selective, CNS-active TRK inhibitor approved in Brazil, Canada, the US and Europe to treat paediatric and adult patients with advanced solid tumours harbouring NTRK gene fusions.1,4,5
  - In a pooled analysis of 159 patients across three phase I/II trials, objective response rate was 79% and median duration of response was 35.2 months.5
  - Efficacy was seen regardless of tumour type (Figure 3) and age.6
- Larotrectinib was well tolerated. Most adverse events were mild (Grade 1) or moderate (Grade 2) in severity (Table 1).6

Figure 2. TRK fusions are rare but recurrent oncogenic drivers

Table 1. Adverse events in the safety dataset (N=260)6

<table>
<thead>
<tr>
<th>Treatment-related adverse events (%)</th>
<th>Treatment-emergent adverse events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
</tr>
<tr>
<td>Cough</td>
<td>25</td>
</tr>
<tr>
<td>Constipation</td>
<td>27</td>
</tr>
<tr>
<td>Anemia</td>
<td>17</td>
</tr>
<tr>
<td>AST increased</td>
<td>24</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25</td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
</tr>
<tr>
<td>Vomiting</td>
<td>28</td>
</tr>
<tr>
<td>DERMATOLOGY</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15</td>
</tr>
<tr>
<td>Infection</td>
<td>5</td>
</tr>
<tr>
<td>Myalgia</td>
<td>6</td>
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<tr>
<td>Pyrexia</td>
<td>19</td>
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<tr>
<td>Dyspnoea</td>
<td>13</td>
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<tr>
<td>Myelosuppression</td>
<td>16</td>
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<tr>
<td>Oedema/arterial</td>
<td>15</td>
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<tr>
<td>Headache</td>
<td>15</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>7</td>
</tr>
</tbody>
</table>

CONSIDERATIONS OF GENOMIC TESTING

Benefits and drawbacks of different testing methods1,5

- NGS
  - Detects gene fusions as actionable drug targets, highlights the genetic driver of a tumour may allow use of targeted therapies, which typically have fewer side effects than chemotherapy.
  - Genomic testing can identify oncogenic alterations, including gene mutations and chromosomal rearrangements, that can be targeted with specific therapies.
  - Chromosomal rearrangements may lead to gene fusions, resulting in novel oncogenic fusion proteins.1
  - Possible to detect novel fusion partners, and fusions expressed in RNA
  - Ability to test multiple actionable targets in parallel: Relevance of NGS increases as number of actionable targets grows
  - Potential for high sensitivity and specificity

- RT-PCR
  - Location of target within cell is viable
  - High sensitivity and specificity
  - Several fluorophores can be used at once to detect multiple targets in one sample
  - High sensitivity and specificity

- Pan-TRK IHC
  - Low cost
  - Identifies subcellular location of protein
  - Decentralised, available in most laboratories
  - Established reimbursement codes
  - Turnaround time: 1–2 days

- Fluorescence
  - Turnaround time: ~1–3 weeks
  - Technically complex and costly
  - Requires highly centralised testing model and specialty infrastructure
  - Requires centralised and pathology
  - Requires functional protein has been generated

- IHC
  - Low cost
  - Identifies subcellular location of protein
  - Decentralised, available in most laboratories
  - Established reimbursement codes
  - Turnaround time: 1–2 days

- Pro-differentiation genes

- Pro-survival genes

- Genes

- Absent

- Present

- Location of target gene

- Reverse transcriptase polymerase chain reaction (RT-PCR)

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SUMMARY

- Genomic testing is essential and highly recommended to identify patients who may benefit from treatment with targeted therapies.

- Selective inhibitors of oncogenic fusion proteins can enable precision medicine-based treatment of patients with gene fusion cancers.

- Larotrectinib is effective and well tolerated in patients with TRK fusion cancer, regardless of age or tumour type. Rapid and reliable molecular testing is required to identify patients for larotrectinib therapy.

- The identification of NTRK gene fusions as actionable drug targets, highlights the importance of NTRK gene fusion testing across solid tumours.

References

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