Major Types of Cancer Therapies

- **Chemotherapy**
  - Systemic, kills all fast-growing cells ("cytotoxic")

- **Immunotherapy**
  - Helps your own immune system fight cancer (immune checkpoint inhibitors)

- **Targeted Therapy**
  - Attacks specific types of cancer cells, with less harm to healthy cells

Targeted Therapies for RET+ Cancers

- Multikinase RET inhibitors: vandetinib, lenvatinib, cabozantinib
- Orally bioavailable, more selective than multikinase inhibitors
  - Selpercatinib (LOXO-292; Retevmo)
  - Pralsetinib (BLU-667; Gavreto)
Selective RET-targeted Kinase Inhibitors

Selpercatinib and Pralsetinib FDA Approvals

- **Non-small cell lung cancer:** Adult patients with metastatic RET fusion–positive NSCLC
- **Thyroid cancer:**
  - Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer who require systemic therapy
  - Patients with advanced or metastatic RET fusion–positive thyroid cancer who require systemic therapy and who are radioactive iodine refractory

Selpercatinib in RET+ Cancers

From Phase I/II LIBRETTO-001 Study

<table>
<thead>
<tr>
<th>Indication</th>
<th>N</th>
<th>ORR</th>
<th>Category</th>
<th>Ongoing response at 6 mo for responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>RET Fusion+ NSCLC</td>
<td>105</td>
<td>64%</td>
<td>Prev treated(^1)</td>
<td>81%</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>85%</td>
<td>Prev untreated</td>
<td>90%</td>
</tr>
<tr>
<td>RET+ Medullary Thyroid (MTC)</td>
<td>55</td>
<td>69%</td>
<td>Prev treated(^2)</td>
<td>76%</td>
</tr>
<tr>
<td></td>
<td>88</td>
<td>73%</td>
<td>Prev untreated</td>
<td>61%</td>
</tr>
<tr>
<td>RET Fusion+ Thyroid (other)</td>
<td>19</td>
<td>79%</td>
<td>Prev treated(^2)</td>
<td>87%</td>
</tr>
</tbody>
</table>

\(^1\)Received platinum-containing chemotherapy
\(^2\)Received vandetanib, cabozantinib, or both

### Pralsetinib in RET+ Cancers

#### From Phase I/II ARROW Study

<table>
<thead>
<tr>
<th>Indication</th>
<th>N</th>
<th>ORR</th>
<th>Category</th>
<th>Ongoing response at 6 mo for responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>RET Fusion+ NSCLC</td>
<td>87</td>
<td>61%</td>
<td>Prev treated¹</td>
<td>83%</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>70%</td>
<td>Prev untreated</td>
<td>74%</td>
</tr>
<tr>
<td>RET+ Medullary Thyroid (MTC)</td>
<td>55</td>
<td>60%</td>
<td>Prev treated²</td>
<td>96%</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>71%</td>
<td>Prev untreated</td>
<td>93%</td>
</tr>
<tr>
<td>RET Fusion+ Thyroid (other)</td>
<td>9</td>
<td>89%</td>
<td>Prev treated²</td>
<td>100%</td>
</tr>
</tbody>
</table>

¹Received platinum-containing chemotherapy  
²Received vandetanib, cabozantinib, or both


### Distribution of RET Fusions in Solid Tumors

- RET fusions occur predominantly in NSCLC and thyroid cancer
- RET fusions are rare, recurrent events in other malignancies
- The therapeutic relevance of RET fusions occurring outside NSCLC and thyroid cancers is not established, but trials are underway for selpercatinib and pralsetinib.

- Non-small cell lung cancer (2%)
- Papillary & other thyroid cancers (10-20%)
- Pancreatic cancer (<1%)
- Salivary gland cancer (<1%)
- Colorectal cancer (<1%)
- Ovarian cancer (<1%)
If an actionable mutation such as RET exists, targeted therapy is the best therapy to start with.

Molecular testing to identify any of these mutations is **KEY**

Comparing targeted therapies to chemotherapy in those with specific mutations:
- Response rates are superior
- Tumor shrinkage is greater in the vast majority of patients
- Safety profile is better (fewer side effects)

While it can be distressing to wait two weeks without treatment, it is important to be able to get the best possible therapy for an individual’s cancer.

*Neither targeted therapy nor immunotherapy should be given without receiving results of genetic testing.*

One cycle of chemotherapy for those who are experiencing severe symptoms, may be appropriate while waiting for genetic results.
• Older drugs were less selective, causing many off target side effects. Newer drugs, such as selpercatinib and pralsetinib were optimized to minimize that effect.

• Adverse events include:
  – Selpercatinib – dry mouth, EKG changes (QT prolongation)
  – Pralsetinib – neutropenia (tends to occur early)
  – Both – diarrhea/constipation/other GI, fatigue, elevated liver enzymes, hypertension (some patients require antihypertensives)

• Pneumonitis and other serious side effects are rare, but can occur

Strategies to address adverse events:
  – Hold therapy until toxicity improves
  – If the toxicity keeps happening, lowering the dose may work.
  – Switching to a different selective RET inhibitor may help if holding therapy and dose reduction are not sufficient