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the Experts  
WEB SERIES  
Hosted by Dr. Vivek Subbiah

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# RET Targeting Therapies

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## 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

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

<sup>1</sup>Received platinum-containing chemotherapy

<sup>2</sup>Received vandetanib, cabozantinib, or both

Wirth LJ, et al. *New Engl J Med.* 2020; Drilon A, et al. *New Engl J Med.* 2020;  
<https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-selpercatinib-lung-and-thyroid-cancers-ret-gene-mutations-or-fusions>.

## Pralsetinib in RET+ Cancers

### From Phase I/II ARROW Study

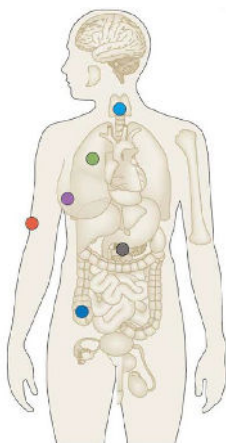
Indication	N	ORR	Category	Ongoing response at 6 mo for responders
RET Fusion+ NSCLC	87	61%	Prev treated <sup>1</sup>	83%
	27	70%	Prev untreated	74%
RET+ Medullary Thyroid (MTC)	55	60%	Prev treated <sup>2</sup>	96%
	21	71%	Prev untreated	93%
RET Fusion+ Thyroid (other)	9	89%	Prev treated <sup>2</sup>	100%

<sup>1</sup>Received platinum-containing chemotherapy

<sup>2</sup>Received vandetanib, cabozantinib, or both

Gainor J, et al. *Lancet Oncol.* 2021; Subbiah V, et al. *Lancet Diabetes Endocrinol.* 2021.

## Distribution of RET Fusions in Solid Tumors



- 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%)

- 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.

## Optimal Sequencing of Therapy

- 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)

## Rationale for Waiting for Testing Results

- 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.

## RET Inhibitor Adverse Events

- 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

FDA Prescribing Information.

## Strategies to Reduce Side Effects

- 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