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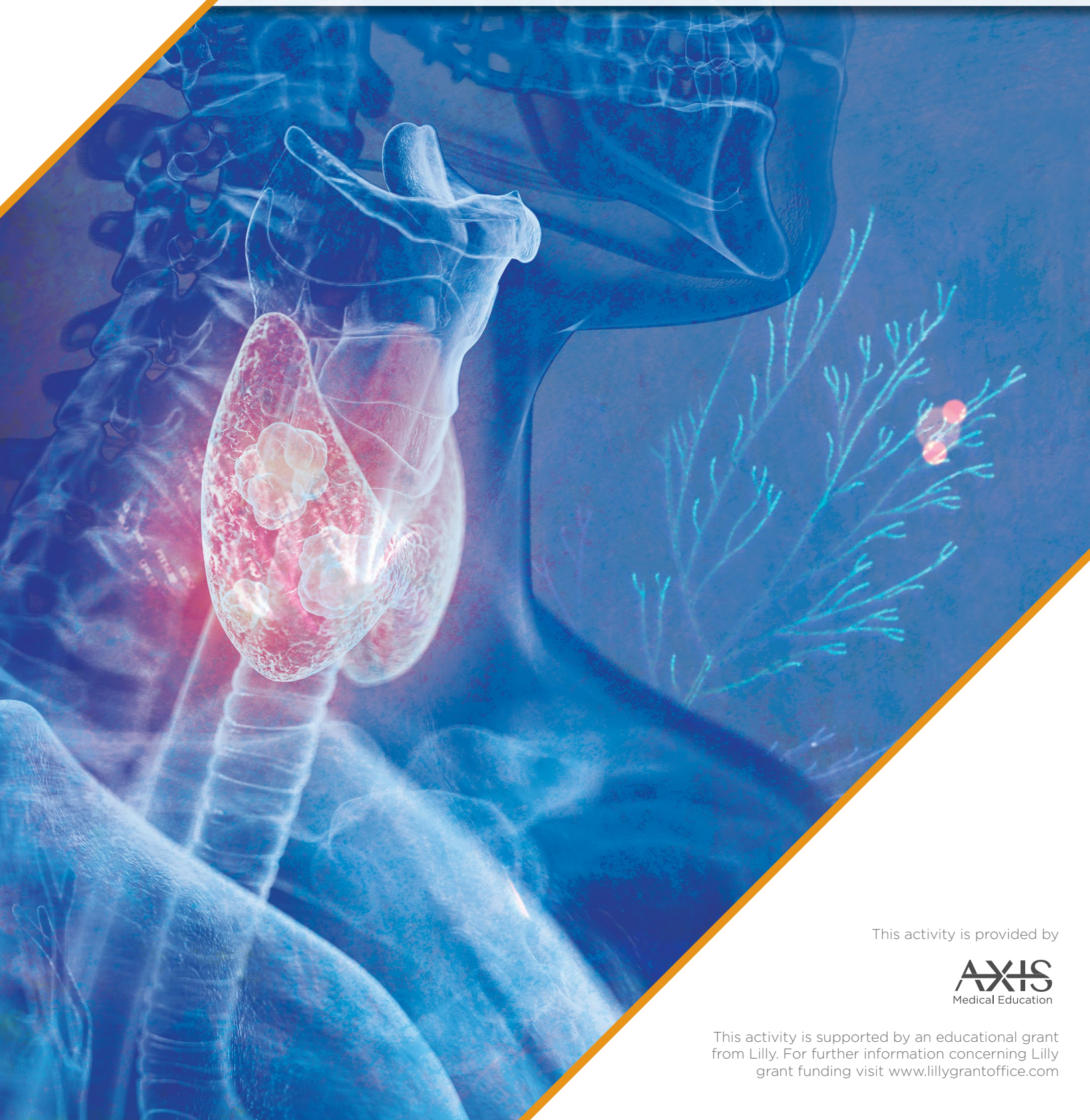
A New Chapter for Oral Precision Therapies in Thyroid Cancer:

RET Inhibitors

This transcript has been edited for style and clarity and includes all slides from the presentation.



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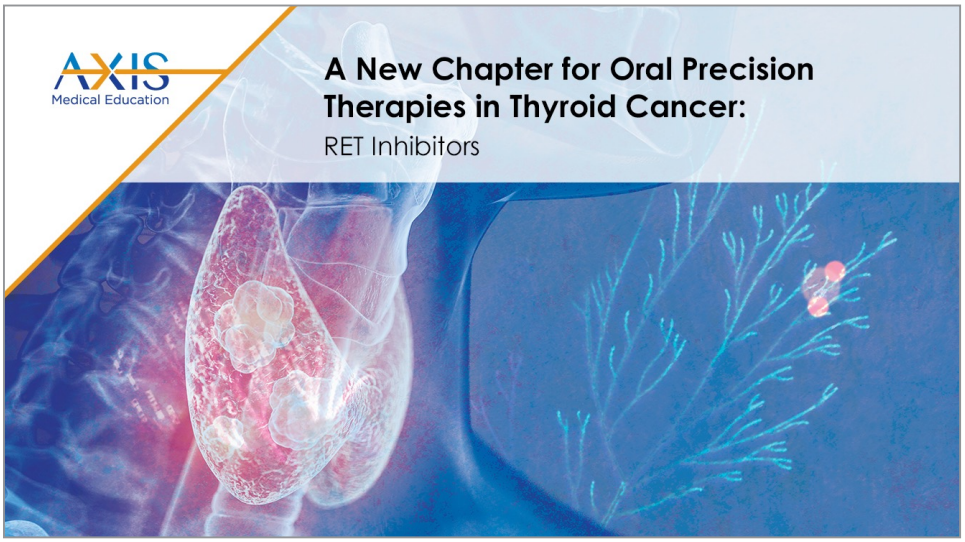
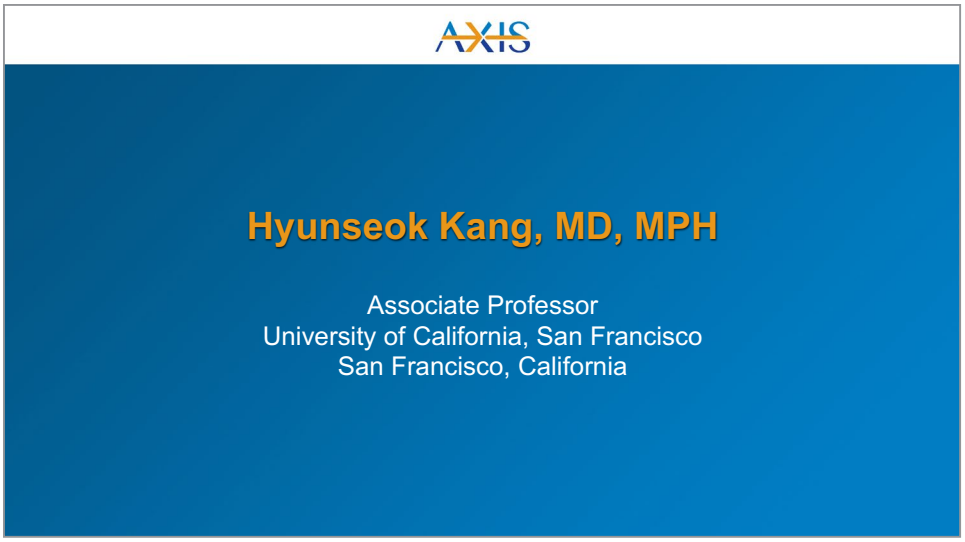
A New Chapter for Oral Precision Therapies in Thyroid Cancer: RET Inhibitors

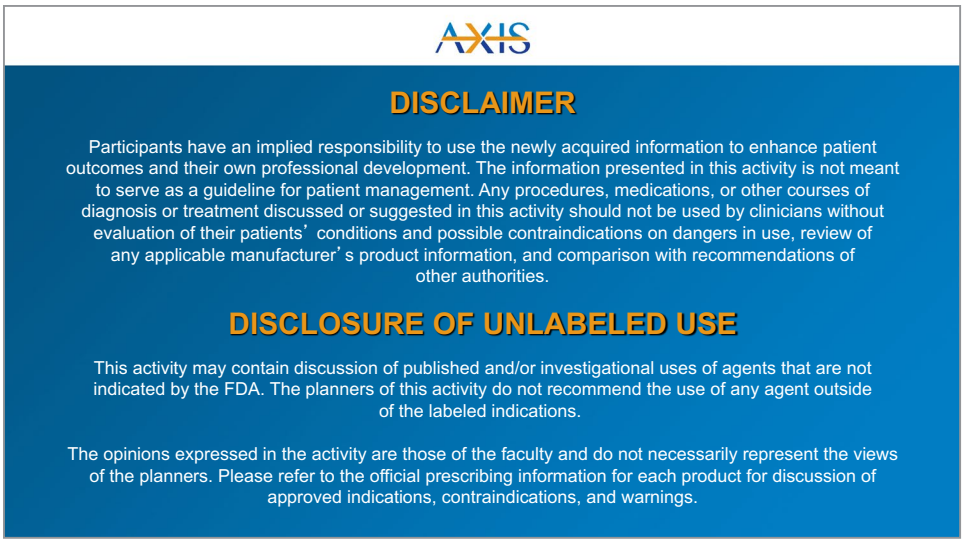
Hyunseok Kang, MD, MPH & Jochen Lorch, MD



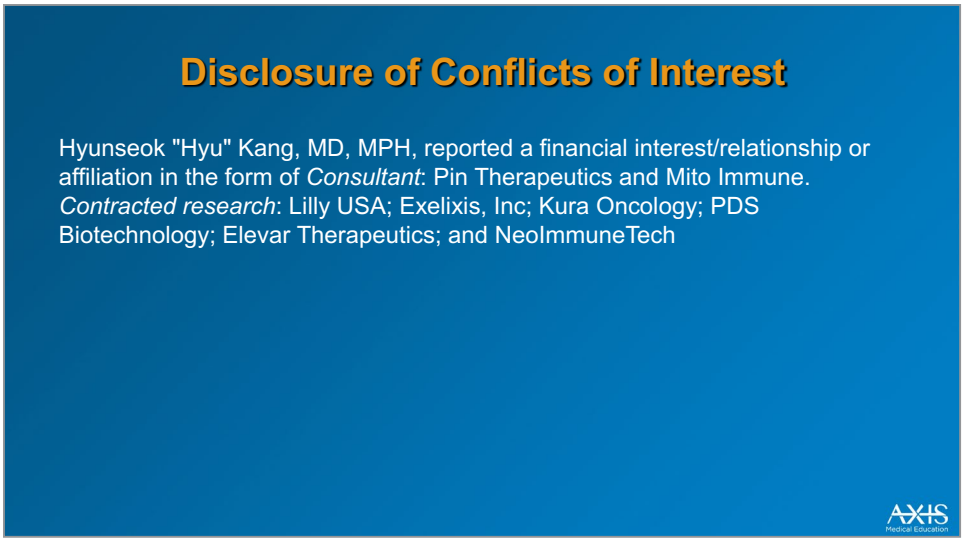
Hyunseok Kang, MD, MPH: Hello and welcome to this educational activity *A New Chapter for Oral Precision Therapies in Thyroid Cancer: RET Inhibitors*.



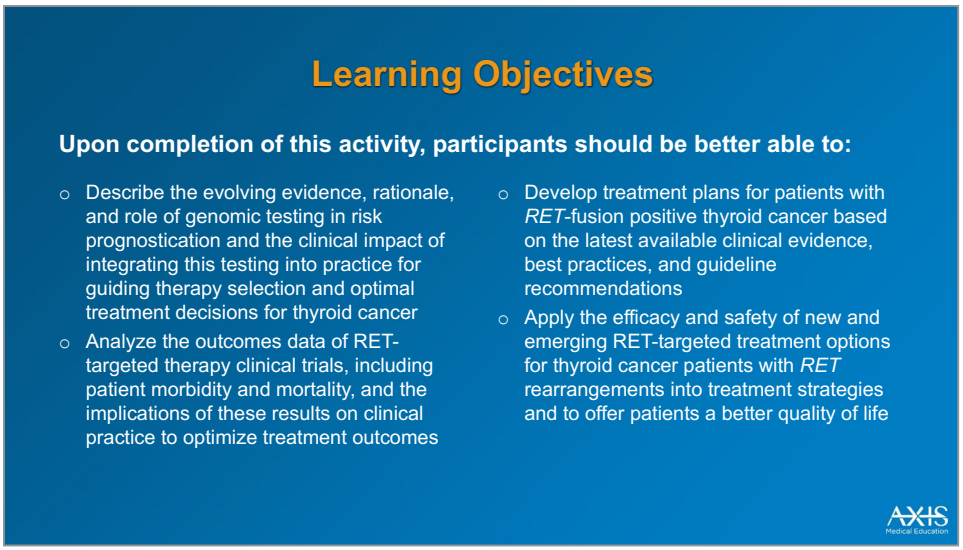
My name is Hyunseok Kang. I'm an associate professor at University of California San Francisco.



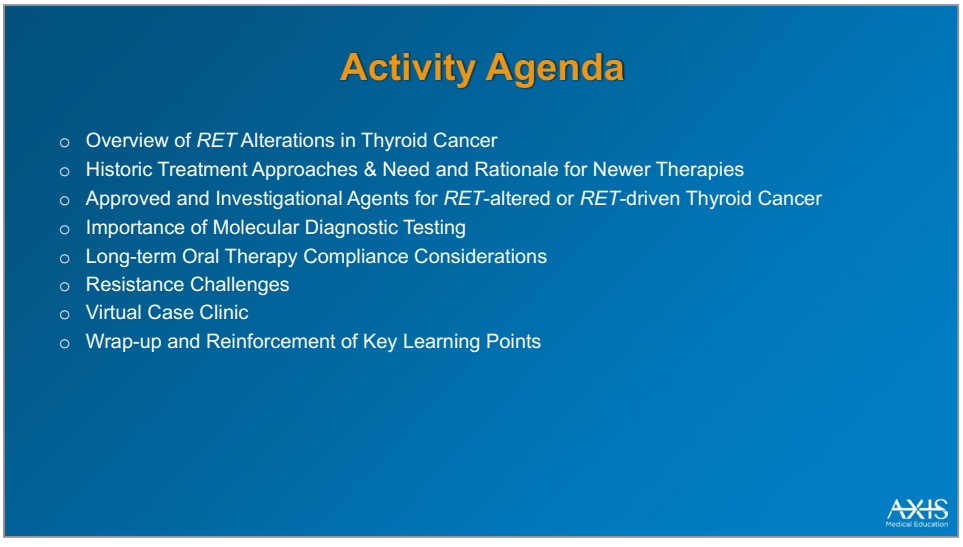
- First a disclaimer and disclosure indicating that we may be discussing off-label use of approved agents or agents that are in development



- And my financial disclosure information.



- Here are the learning objectives for this activity. We expect our participants to better able to describe the evolving evidence, rationale, and role of genomic testing in risk prognostication and the clinical impact of integrating this testing into practice for guiding therapy selection for thyroid cancer. And analyzing the outcome data for RET inhibitor therapy in clinical trials, including patient morbidity and mortality and the implication of these results on clinical practice. Third, develop treatment plans for patients with *RET* fusion-positive thyroid cancer based on the latest available clinical evidence, best practices, and guideline recommendations. And finally, apply the efficacy and safety of new, emerging RET-targeted therapy options for thyroid cancer patients with *RET* rearrangements into treatment strategies and to offer patients a better quality of life.

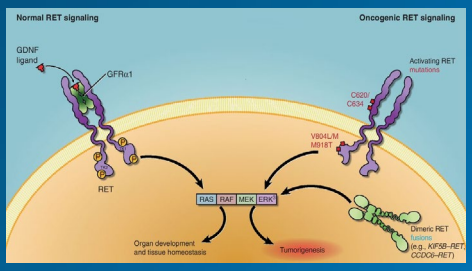


- Today I will be reviewing the overview of *RET* alterations in thyroid cancer, historic treatment approaches and need and rationale for newer therapies, approved and investigational agents for *RET*-altered or *RET*-driven thyroid cancer. The importance of molecular diagnostic testing, long-term oral therapy compliance considerations, resistance challenges, and we'll have a brief virtual case clinic and wrap-up and reinforcement of key learning points.

Overview of *RET* Alterations in Thyroid Cancer

- Let's begin with overview of *RET* alterations in thyroid cancer.

Proto-Oncogene *RE*arrangement During *T*ransfection (*RET*) and Its Significance



- RET is the receptor for glial cell-derived neurotrophic factor (GDNF) family of ligands
- It is a key molecule for organ development and tissue homeostasis
- Activating mutations and chromosomal rearrangements can cause constitutive activation of RET

Subbiah and Cote. *Cancer Discov* 2020;10(4):498-505.

- Proto-oncogene rearrangements during transfection is the full name of *RET*. And it is a receptor for the glial cell-derived neurotrophic factor family of ligands. It is a key molecule for organ development and tissue homeostasis. Activating mutations and chromosomal rearrangements can cause constitutive activation of this gene.

Medullary Thyroid Cancer

- A form of thyroid carcinoma arising from the parafollicular cells (C-cells) that produce calcitonin
- Accounts for <5% of thyroid cancer in the US with an estimated incidence of 0.21 cases per 100,000 population per year

Randle et al. *Surgery* 2017;161(1):137-146.

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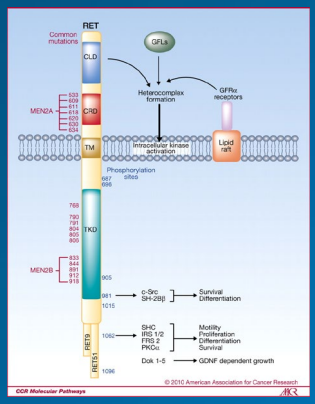
- Medullary thyroid cancer is a form of thyroid carcinoma arising from parafollicular T cells that produce calcitonin. It accounts for less than 5% of thyroid cancers in the US with an estimated incidence of 0.21 cases per 100,000 population per year.

Activating *RET* Mutations in MTC



- 25% of MTC occurs as a hereditary monogenic autosomal dominant disorder in MEN2 syndrome (germline mutations)
- 55%-85% of patients with MTC have somatic *RET* mutations
  - M918T is the most prevalent, found in up to 40% of cases

MTC, medullary thyroid cancer.
Phay and Shah. *Clin Cancer Res.* 2010;16(24):5936-5941.
Salvatore et al. *Nat Rev Endocrinol.* 2021;17:296-306.

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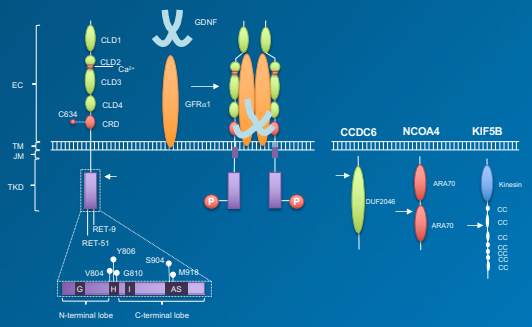
- About 25% of medullary thyroid cancer, which is also called MTC, occurs as a hereditary monogenic autosomal dominant disorder as part of MEN2 syndrome. This mutation happens in germline. So patients were born with these mutations and are predisposed to the development of MTC. About 55 to 85% of patients with MTC have somatic *RET* mutations, which means that they acquire this mutation later in their life. And *M918T* mutation is the most prevalent, found in up to 40% of cases.

Activating *RET* Fusions in PTC and Other TCs



- *RET* kinase fusions occur in <10%-20% of patients with PTCs
- Most common in PTCs occurring after radiation exposure
- Can be present in poorly differentiated thyroid carcinoma and anaplastic thyroid carcinoma

PTC, papillary thyroid cancer; TC, thyroid cancer.
Adapted from Salvatore et al. *Nat Rev Endocrinol*. 2021;17:296-306.

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- Activating *RET* fusions are seen in papillary thyroid cancers and other thyroid cancers. This fusion can occur in 10% to 20% of patients with papillary thyroid cancer. This alteration commonly occurs after radiation exposure. *RET* fusions can be also present in poorly differentiated thyroid carcinoma and anaplastic thyroid carcinoma.

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Historic Treatment Approaches & Need and Rationale for Newer Therapies

- Historically, we've been treating thyroid cancers with total thyroidectomy and neck dissection if needed. This remains as the preferred treatment option. At the time of locoregional recurrence, surgical resection is preferred followed by radiation therapy.

Surgery Options

- Total thyroidectomy +/- neck dissection is the preferred treatment option
- Surgical resection is preferred for locoregional recurrence, followed by radiation therapy

NCCN Clinical Practice Guidelines in Oncology. Thyroid Carcinoma. Version 3.2021. https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf

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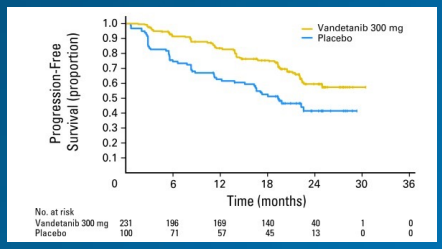
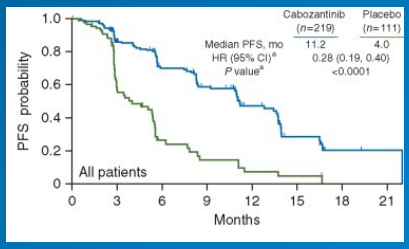
Multikinase Inhibitors for MTC

Vandetanib



Compared to placebo:
- ORR: 45% versus 13%
- mPFS: not reached (predicted 30.5 months by Weibull model) versus 19.3 months

Cabozantinib



Compared to placebo:
- ORR: 28% versus 0%
- mPFS: 11.2 months versus 4.0 months

mPFS, median progression-free survival; MTC, medullary thyroid cancer; ORR, overall response rate.
Wells et al. *J Clin Oncol* 2012;30:134-141. Schulmberger et al. *Ann Oncol* 2017;28:2813-2819.

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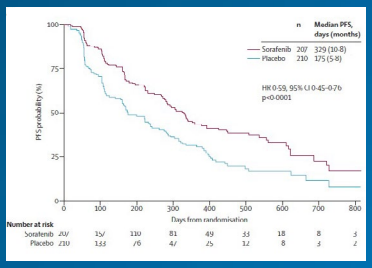
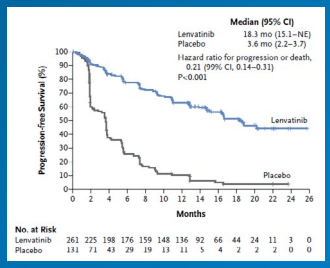
Multikinase Inhibitors for DTC

Sorafenib



Compared to placebo:
- ORR: 12.2% versus 0.5%
- mPFS: 10.8 months versus 5.8 months

Lenvatinib



Compared to placebo:
- ORR: 64.8% versus 1.5%
- mPFS: 18.3 months versus 3.6 months

DTC, differentiated thyroid cancer; mPFS, median progression-free survival; ORR, overall response rate.
Brose et al. *Lancet* 2014;384:319-328; Schlumberger et al. *N Engl J Med* 2015;372:621-630.

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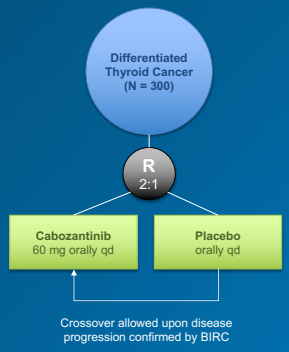
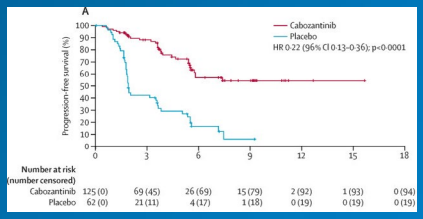
- We do use systemic therapy for thyroid cancers when there is a metastasis or recurrence. For medullary thyroid cancers, there are 2 multikinase inhibitors that have been approved by the FDA. Vandetanib was investigated in comparison with placebo and demonstrated overall response rate of 45% versus 13% seen in placebo and median progression-free survival of 30.5 months versus 19.3 months. Another multikinase inhibitor, cabozantinib, was also investigated in comparison with a placebo. In a clinical trial, cabozantinib demonstrated an overall response rate of 28% versus 0% in placebo arm, and a median progression-free survival of 11.2 months versus 4.0 months.

- For differentiated thyroid cancer, we use multikinase inhibitors after radioactive iodine treatment fails. These drugs have been investigated in the context of radioactive iodine-refractory disease. And currently 3 drugs are approved by FDA, and 2 drugs are approved in the treatment-naïve setting with multikinase inhibitors. First one is sorafenib, which was studied in comparison with placebo and demonstrated an overall response rate of 12.2% versus 0.5% in placebo with a median progression-free survival of 10.8 months versus 5.8 months. Lenvatinib was also investigated in radioactive iodine (RAI)–refractory patients and treatment naïve with multikinase inhibitors and showed an overall response rate of 64.8% versus 1.5% in the placebo arm and a median progression-free survival of 15.1 months versus 3.6 months.

Multikinase Inhibitors for DTC: Cabozantinib (2nd Line) COSMIC-311





Compared to placebo:

- ORR: 15% versus 0%
- mPFS: not reached versus 1.9 months

BIRC, Blinded Independent Review Committee; DTC, differentiated thyroid cancer; mPFS, median progression-free survival; ORR, overall response rate.
Brose. *Lancet Oncol* 2021;22:1126-1138.

- More recently, cabozantinib was studied for patients who had prior treatment with a multikinase inhibitor—either sorafenib or lenvatinib. This was a randomized study between placebo and cabozantinib. Crossover was allowed after open progression. This clinical trial showed the superiority of cabozantinib in terms of median progression-free survival, which was not reached at the time of analysis versus 1.9 months with placebo. An overall response rate was 15% versus 0% in placebo arm.

Multikinase Inhibitors in MTC and DTC

- Vandetanib and cabozantinib demonstrated significant PFS benefits in MTC patients
- Sorafenib, lenvatinib and cabozantinib demonstrated significant PFS benefits in DTC patients
- However, these agents cause significant treatment related adverse events which limits their tolerability for patients
  - Hypertension, proteinuria, decreased appetite, electrolyte abnormalities, hand-foot syndrome, bleeding events, etc.
- Discontinuation rates:
  - Vandetanib: 12%
  - Cabozantinib: 16%
  - Sorafenib: 19%
  - Lenvatinib: 14%

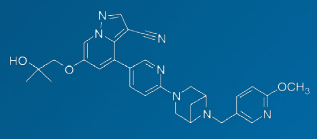
DTC, differentiated thyroid cancer; MTC, medullary thyroid cancer; PFS, progression-free survival.
Wells et al. *J Clin Oncol* 2012;30:134-141; Elisei et al. *J Clin Oncol* 2013;31:3639-3646; Brose et al. *Lancet* 2014;364:319-328; Schlumberger et al. *N Engl J Med* 2015;372:621-630.

- So currently, sorafenib and lenvatinib are approved for patients who have radioactive iodine–refractory differentiated thyroid cancer who are treatment naïve with multikinase inhibitors. And cabozantinib is approved for patients who had prior line of multikinase inhibitor therapy. However, these agents cause significant treatment-related adverse events, and that limits their tolerability for patients. Generally, these agents target the VEGFR pathway and cause hypertension, proteinuria, decreased appetite, electrolyte abnormalities, and hand-foot syndrome. These side effects typically leads us to do dose reduction for these agents, which limits their clinical utility in patients with thyroid cancer.

Approved and Investigational Agents for *RET*-altered or *RET*-driven Thyroid Cancer

- Now, let's move on for approved and investigational agents for *RET*-altered or *RET*-driven thyroid cancer.

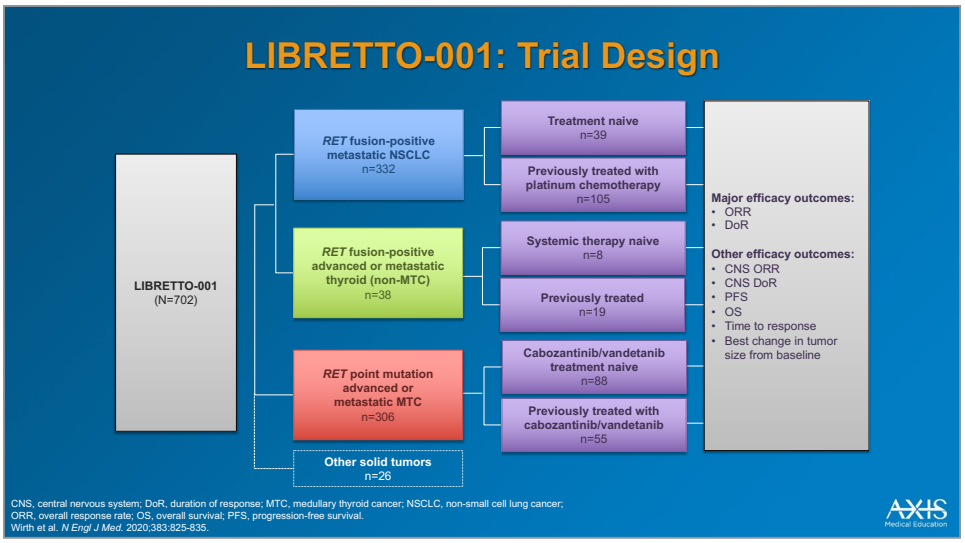
Selpercatinib



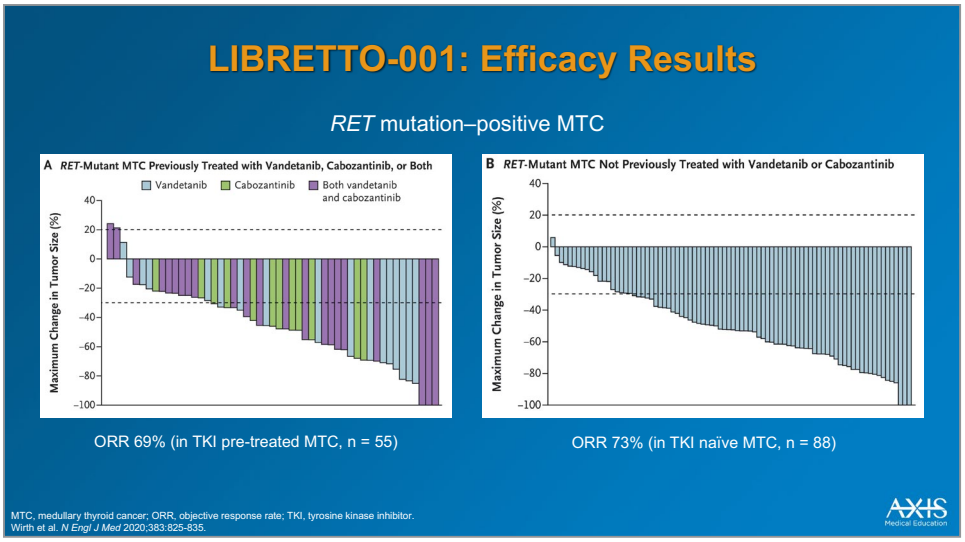
- A highly selective RET inhibitor
- Oral administration based on weight:
  - Less than 50 kg: 120 mg orally twice daily
  - 50 kg or greater: 160 mg orally twice daily
- Approved for metastatic *RET* fusion–positive NSCLC, advanced or metastatic *RET*-mutant MTC, and advanced or metastatic RAI-refractory *RET* fusion-positive thyroid cancer

MTC, medullary thyroid cancer; NSCLC, non-small cell lung cancer; RAI, radioactive iodine.
Wirth et al. *N Engl J Med* 2020; 383:825-835.

- Selpercatinib is a highly selective RET inhibitor, given orally at a dosage of 160 mg twice daily. It is approved for metastatic *RET* fusion-positive non–small cell lung cancer, advanced or metastatic *RET* mutation–positive medullary thyroid cancer, and advanced or metastatic RAI-refractory *RET* fusion-positive thyroid cancer.



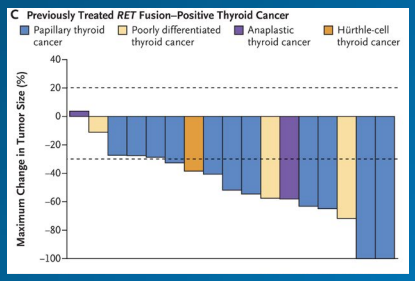
- Selpercatinib was studied in the LIBRETTO-001 study, which was a multi-arm, phase 1/2 study and was investigated in *RET* fusion-positive advanced or metastatic thyroid cancer and *RET* point mutation–positive advanced or metastatic medullary thyroid cancer.



- The efficacy results showed a dramatic overall response rate in *RET* mutation–positive medullary thyroid cancer. The overall response rate for patients who were not previously treated with vandetanib or cabozantinib was 73%. The overall response rate for *RET* mutant–positive MTC previously treated with vandetanib, cabozantinib, or both was 69%.

LIBRETTO-001: Efficacy Results

RET fusion–positive thyroid cancers



- ORR 71% (n = 19)
- Responders include 1 patient with anaplastic thyroid cancer and 2 patients with poorly-differentiated thyroid cancer

MTC, medullary thyroid cancer; ORR, overall response rate; TKI, tyrosine kinase inhibitor.
Wirth et al. *N Engl J Med* 2020;383:825-835.

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- Selpercatinib was shown to have response rate of 71% in *RET* fusion–positive thyroid cancer. This was studied in 19 patients, which included one patient with anaplastic thyroid cancer and two patients with poorly differentiated thyroid cancer.

LIBRETTO-001: Updated Analysis

RET-altered thyroid cancer

	Primary Analysis Set (the first 55 enrolled patients; n = 55)	Integrated Analysis Set (TKI-pretreated MTC; n = 143)	Cabozantinib/ Vandetanib-naïve MTC (n = 112)	RET-Fusion TC (with prior systemic treatment; n = 22)
ORR, %	69.1	69.2	71.4	77.3
CBR, %	92.7	90.9	93.8	100.0
DoR, median, months	NE	NE	21.95	18.4
Duration of follow-up, months	17.45	10.05	9.26	20.27
Rate (%) PFS, > 12 months	82.3	76.9	92.9	68.6

Phase 3 trial (LIBRETTO-531) evaluating selpercatinib compared to cabozantinib/vandetanib in kinase inhibitor-naïve MTC patients is ongoing

CBR, clinical benefit rate; DoR, duration of response; NE, not estimated; ORR, overall response rate; PFS, progression-free survival; TC, thyroid cancer.
Integrated analysis set (IAS, n = 143) includes efficacy evaluable MTC pts previously treated with cabozantinib and/or vandetanib.
The primary analysis set (PAS), a subset of IAS, is the first 55 enrolled pts. Cabo/vande naïve MTC pts (N = 112) and TC pts with prior systemic treatment (N = 22) were also analyzed.
Sherman et al. *J Clin Oncol*. 2021;39(15):6073.

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- In an updated analysis of LIBRETTO-001 study, the preliminary analysis results are upheld. This was an update with a longer follow-up and additional enrollment. The results showed response rates of 70% with multikinase inhibitor–naïve patients and 77% in *RET* fusion–positive thyroid cancer. There is an ongoing phase 3 study, LIBRETTO-531, evaluating selpercatinib compared to cabozantinib and vandetanib in kinase inhibitor–naïve medullary thyroid cancer.

LIBRETTO-001: Safety and Adverse Events

RET-altered thyroid cancer

Treatment-related AEs

Number of patients (%)	Grade 3	Grade 4
Any AE	45 (28)	3 (2)
Hypertension	19 (12)	0
Diarrhea	4 (3)	0
Fatigue	1 (1)	0
Elevated AST	12 (7)	1 (1)
Elevated ALT	16 (10)	1 (1)
Headache	1 (1)	0
QT prolongation	3 (2)	0
Weight gain	1 (1)	0

- Generally well tolerated with few grade 4 AEs
- Common AEs:
  - Dry mouth, hypertension, elevated AST/ALT
- Discontinuation rate for toxicity:
  - 2% (12 of 531)

AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
Wirth et al. *N Engl J Med* 2020;383:825-835.

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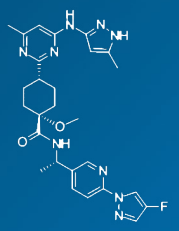
Let's look at the safety and adverse events data of the LIBRETTO-001 study. Generally, selpercatinib was well tolerated with few grade 4 adverse events. The most common adverse events that occurred in more than 40% of patients were dry mouth and hypertension. Less common adverse events, which were seen more than 30% of patients, were diarrhea, nausea, constipation, headache, elevated liver enzymes, and peripheral edema. Generally, selpercatinib was very well tolerated.

Pralsetinib



- A highly selective RET inhibitor
- Oral administration at 400 mg once daily
- Approved for metastatic *RET* fusion–positive NSCLC, advanced or metastatic *RET*-mutant MTC, and advanced or metastatic RAI-refractory *RET* fusion-positive thyroid cancers

MTC, medullary thyroid cancer; NSCLC, non-small cell lung cancer; RAI, radioactive iodine.

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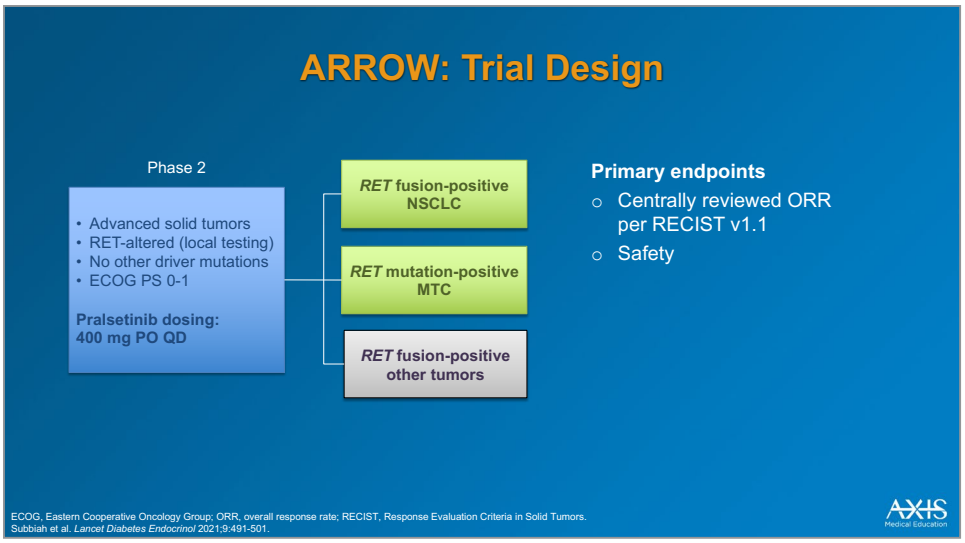
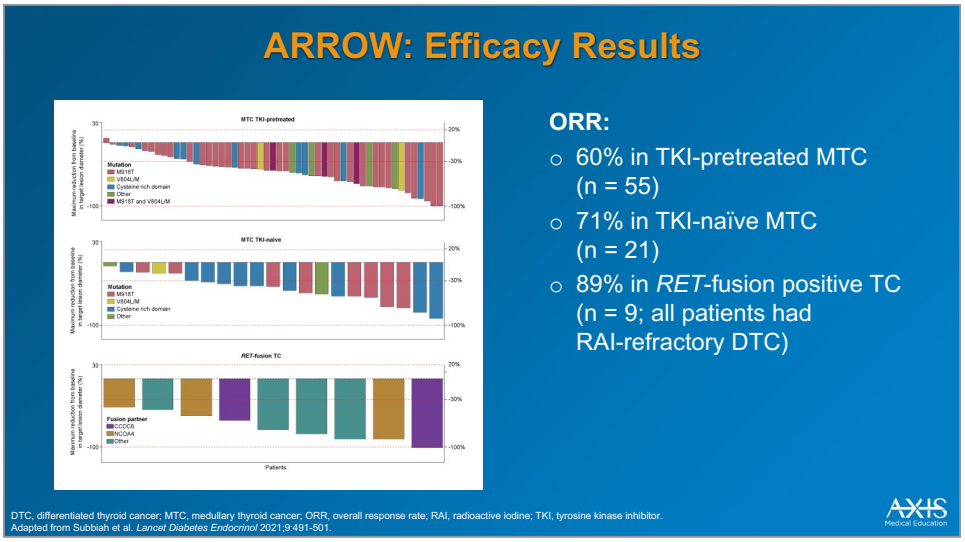
The second agent approved for *RET* fusion–positive thyroid cancers is pralsetinib. This is a highly selective RET inhibitor, orally administered at 400 mg once daily. It is approved for metastatic *RET* fusion–positive non–small cell lung cancer, advanced or metastatic *RET* mutation–positive medullary thyroid cancer, and advanced or metastatic RAI-refractory *RET* fusion–positive thyroid cancers.



- Pralsetinib was studied in the ARROW trial, which is a phase 2 multi-arm study that included *RET* mutation–positive medullary thyroid cancer and *RET* fusion–positive other cancer arms.



- In ARROW study, the overall response rate for multikinase inhibitor–pretreated MTC was 60%, and overall response rate for multikinase inhibitor–naïve MTC was 71%. The response rate for patients with *RET* fusion–positive thyroid cancers—and in this trial all patients had RAI-refractory differentiated thyroid cancer—it was 89%.

ARROW: Safety and Adverse Events

Treatment-related AEs

Number of patients (%)	Grade 3	Grade 4/5
Any AE	67 (47)	9 (7)
Hypertension	24 (17)	0
Neutropenia	18 (13)	1 (1)
Anemia	14 (10)	0
Lymphopenia	15 (11)	2 (1)
Asthenia	6 (4)	0
Pneumonitis	4 (3)	0
Diarrhea	3 (2)	0
Thrombocytopenia	2 (1)	2 (1)
Pneumonia	0	1 (grade 5)

- Generally well tolerated with few grade 4 AEs
- Common AEs:
  - Elevated AST/ALT, decreased WBC, neutropenia, hypertension
- Discontinuation rate for toxicity:
  - 4% (5 of 142)

AEs, adverse events; AST, aspartate aminotransferase.
Subbiah et al. *Lancet Diabetes Endocrinol* 2021;9:491-501.

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The ARROW trial also showed a very favorable safety profile for pralsetinib. Generally, this was very well tolerated with few grade 4 adverse events. The most common adverse events, which were seen more than 40% of patients, were anemia, musculoskeletal pain, constipation, elevated AST, and hypertension.

Highlights Selpercatinib and Pralsetinib

	Selpercatinib	Pralsetinib
Administration, dose	Oral, 160 mg ***twice daily*** (< 50 kg: 120 mg)	Oral, 400 mg ***once daily***
ORR		
TKI-naïve MTC	73% (n = 88)	60% (n = 55)
TKI pre-treated MTC	69% (n = 55)	71% (n = 21)
RET fusion-positive TC	71% (n = 19)	89% (n = 9)
Adverse events		
Any Grade 3-5 Treatment-related AE	30%	53%

AE, adverse event; MTC, medullary thyroid cancer; ORR, overall response rate; TKI, tyrosine kinase inhibitor.
Subbiah et al. *Lancet Diabetes Endocrinol* 2021;9:491-501; Wirth et al. *N Engl J Med* 2020;383:825-835.

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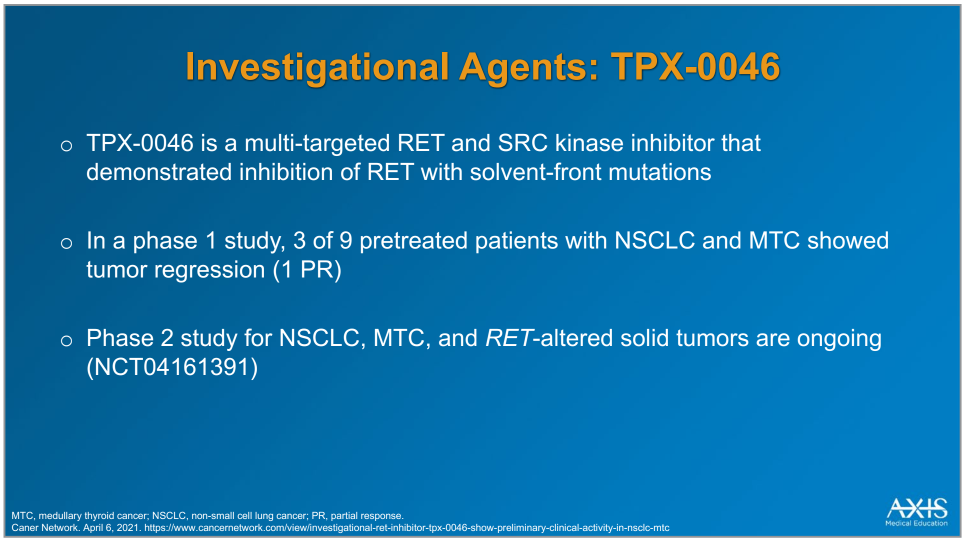
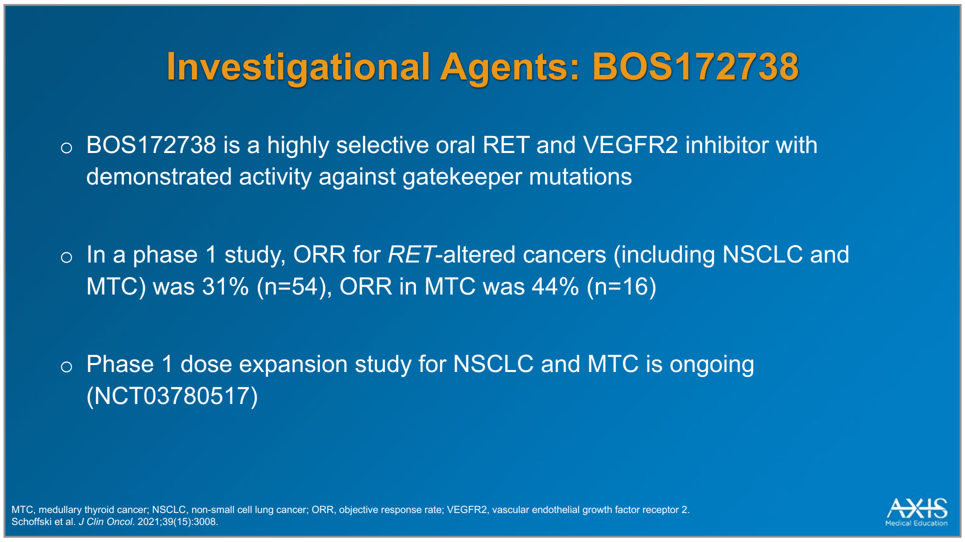
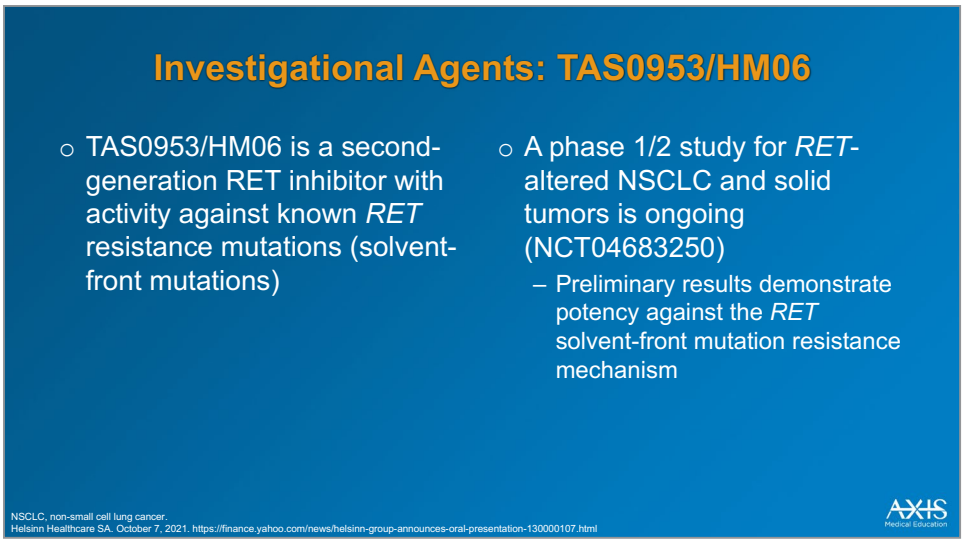
To summarize, comparing selpercatinib and pralsetinib, both agents are orally administered. There is a slight difference between selpercatinib and pralsetinib as selpercatinib is given twice daily, and pralsetinib is given once daily. Response rates of both agents were similar. The tyrosine kinase inhibitor–naïve MTC response rate of selpercatinib was 73% versus 60% in pralsetinib. The tyrosine kinase inhibitor–pretreated MTC response rate was 69% versus 71%. And for *RET* fusion–positive thyroid cancer, selpercatinib's response rate was 71% versus 89% in pralsetinib, which are very comparable. The rates of grade 3 to 5 adverse events were 30% in selpercatinib and 54% in pralsetinib. And the most common adverse events were slightly different with dry mouth and hypertension in selpercatinib; anemia, musculoskeletal pain, constipation, elevated AST, and hypertension in pralsetinib. However, these are very minor differences. In summary, both agents are very safe, very effective in *RET* fusion–positive thyroid cancers or RET mutation–positive MTCs.



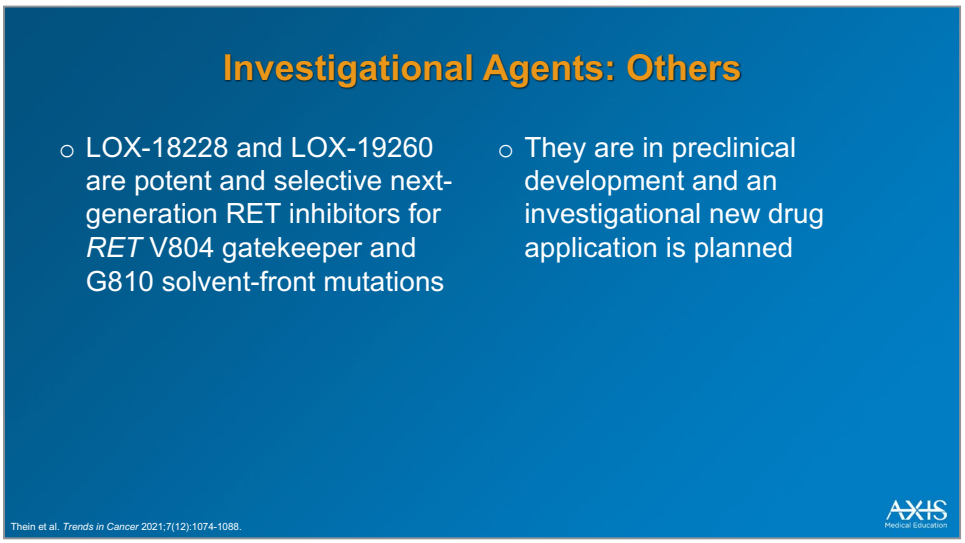
- There are other investigational agents in the horizon. TPX-0046 is a multitargeted RET and SRC kinase inhibitor that demonstrated inhibition of RET with solvent-front mutation. Selpercatinib and pralsetinib were developed to be active against gatekeeper mutations, but with solvent-front mutations, these agents are not expected to work very well. So TPX-0046 has been developed specifically to deal with solvent-front mutations in mind. And in a phase 1 study, 3 of 9 pretreated patients with non–small cell lung cancer or MTC showed tumor regression. A phase 2 studies for non–small cell lung cancer, MTC, and *RET*-altered solid tumors are ongoing.



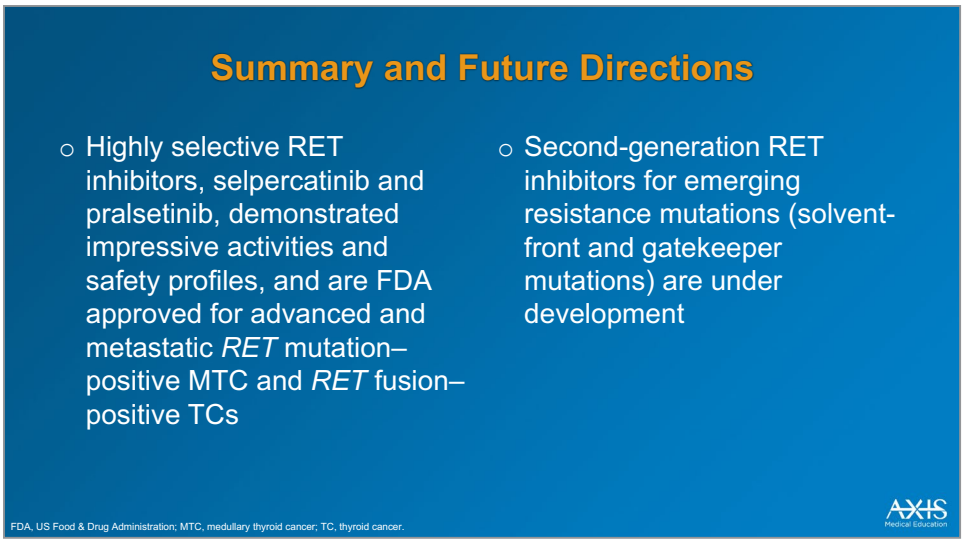
- Another investigational agent, BOS172738, is a highly selective oral RET and VEGFR2 inhibitor that demonstrated activity against gatekeeper mutations similar to selpercatinib and pralsetinib. In a phase 1 study, the overall response rate for *RET*-altered cancers was 31%, and the overall response rate in MTC was 44%. A phase 1 dose expansion study for non–small cell lung cancer and MTC is currently ongoing.



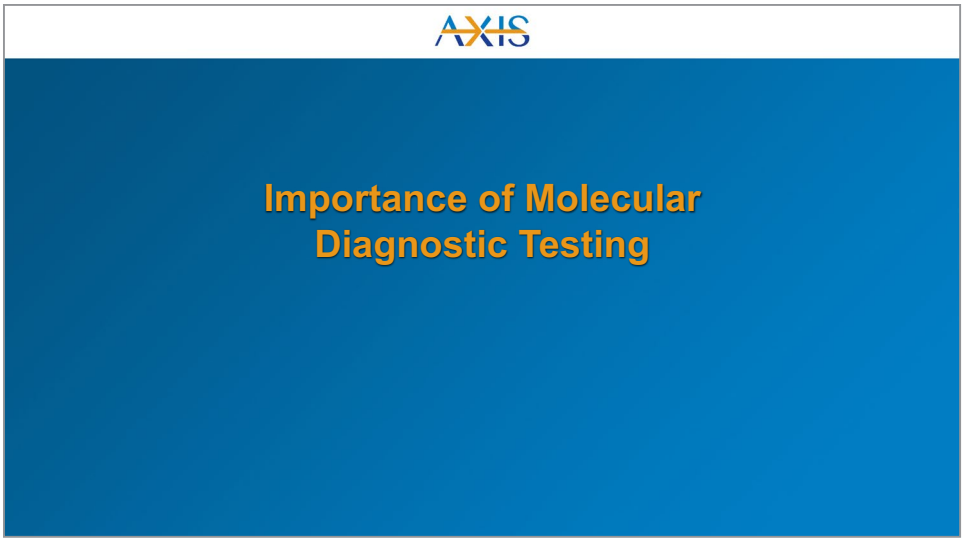
- TAS0953/HM06 is a second-generation RET inhibitor with activity against known *RET*-resistant mutation, including solvent-front mutation. And a phase 1/2 study for *RET*-altered non–small cell lung cancer and other solid tumors is currently ongoing. Preliminary results of this trial demonstrated potency against *RET* solvent-front mutation resistance mechanisms.



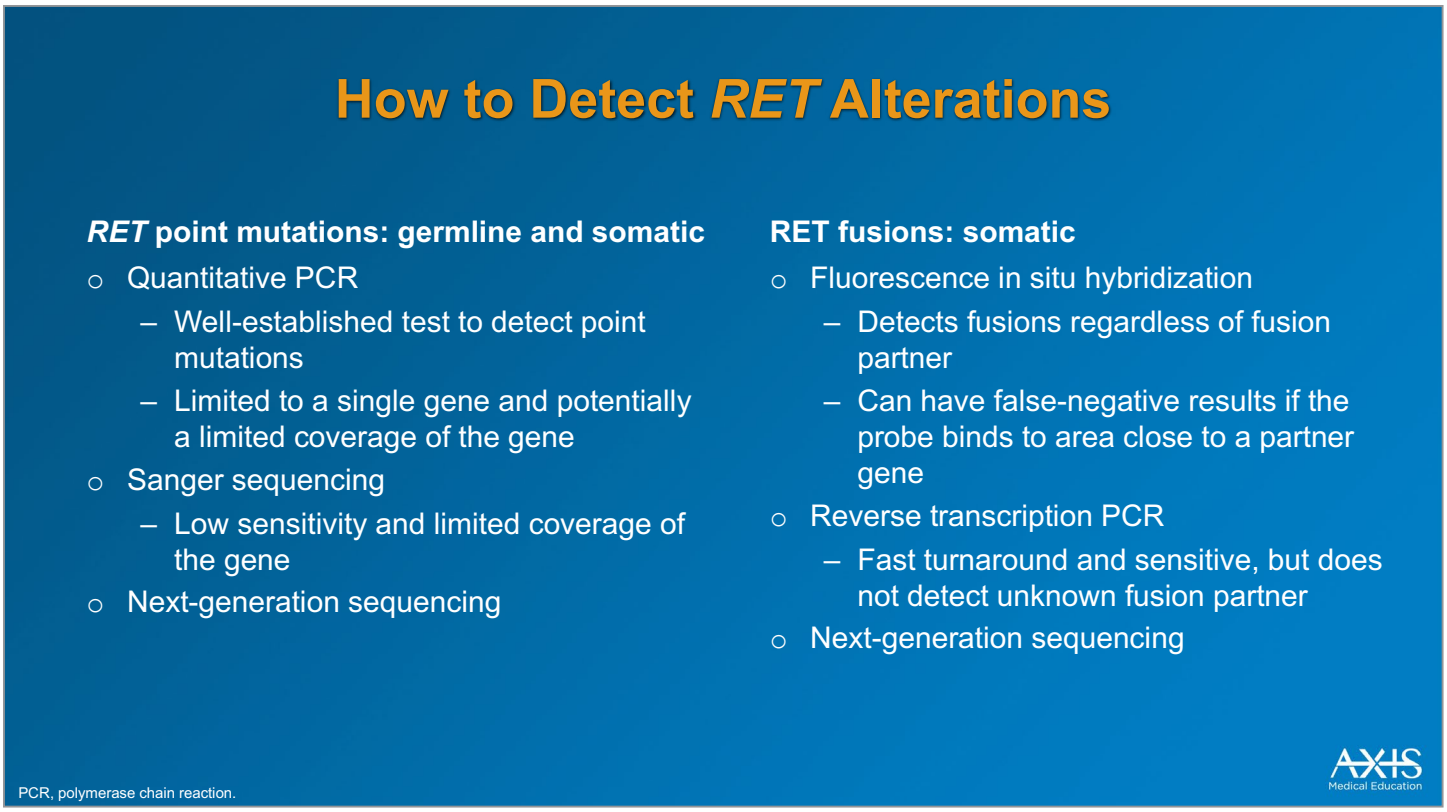
- There are other agents in development, including LOX-18228 and LOX-19260. These are potent and selective next-generation RET inhibitors targeting the *RET* gatekeeper mutation and solvent-front mutations. These agents are in preclinical development and are expected to enter clinical trials in 2022.



- To summarize, the highly selective RET inhibitors, selpercatinib and pralsetinib, demonstrated impressive activities and safety profiles and are FDA approved for advanced and metastatic *RET* mutation–positive MTC and *RET* fusion–positive thyroid cancers. Second-generation RET inhibitors that are active against solvent-front and gatekeeper mutations are under development.

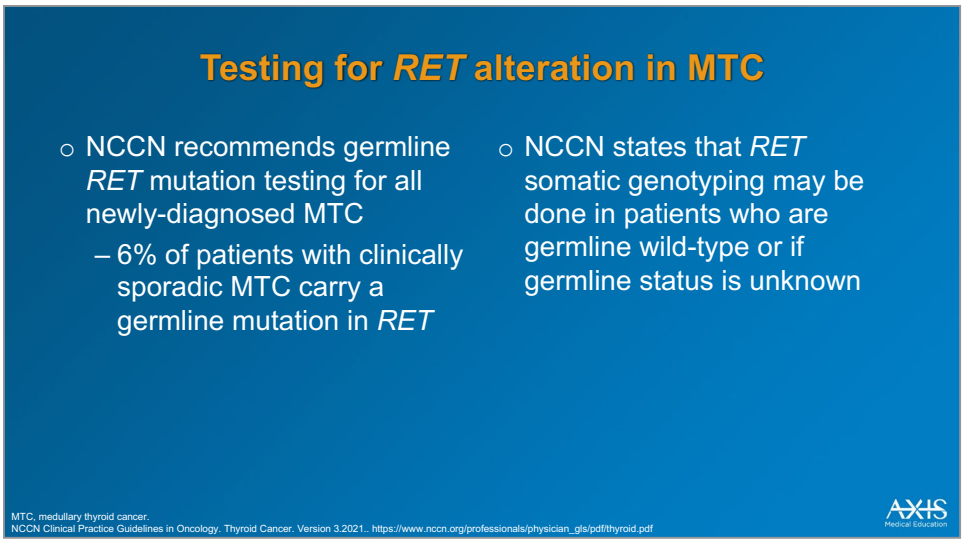


- Next, we will discuss briefly about the importance of molecular diagnostic testing.

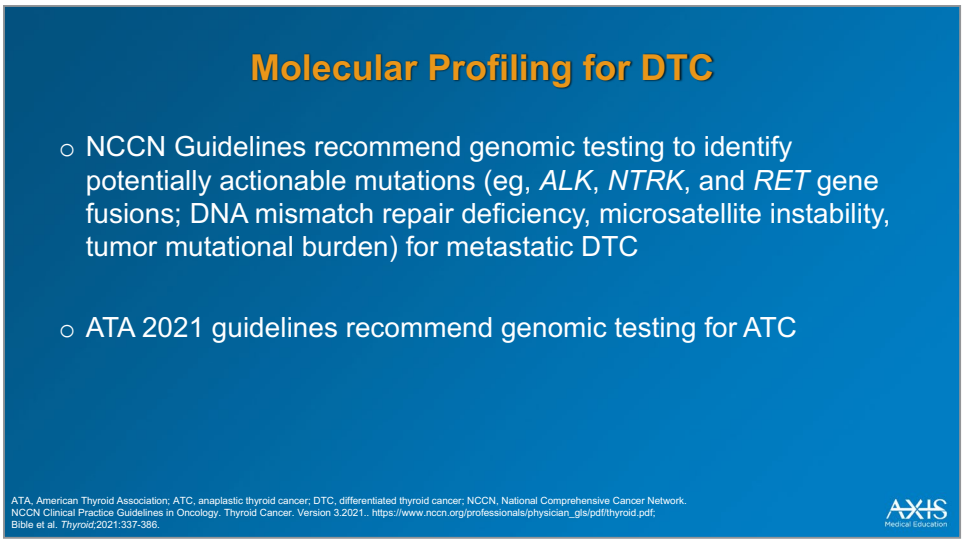


There are several different ways to detect *RET* alterations. *RET* point mutations can be found in either germline or somatic. And these mutations can be detected by quantitative polymerase chain reaction (PCR), Sanger sequencing, or next-generation sequencing. Quantitative PCR is a well-established test to detect point mutations, but it's limited to a single gene and potentially has a very limited coverage of the gene. Sanger sequencing is also even more limited with low sensitivity and is not very frequently used at this time. Next-generation sequencing has a larger, broader panel and can have better sequencing depths. We'll discuss this later in more detail.

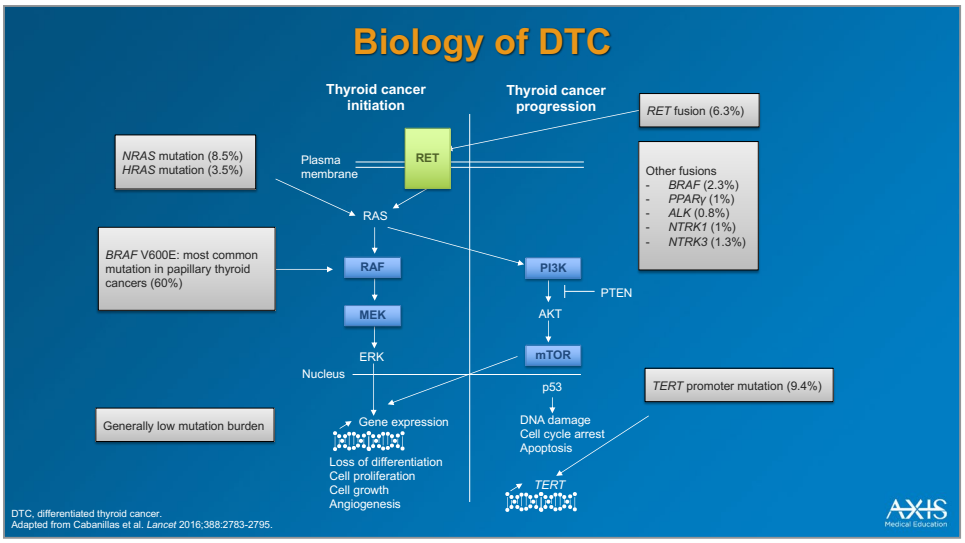
RET fusions always have been in somatic changes. And this can be detected by fluorescence in situ hybridization, which is called FISH. FISH detects fusions regardless of fusion partner but can have false-negative results if the probe binds to area close to a partner gene. Reverse-transcription PCR has a very fast turnaround time and is sensitive. But this only works when we have a known fusion partner, so it does not detect unknown fusion partner. Next-generation sequencing can detect fusions with slight limitation. It relates to the depth of sequencing.



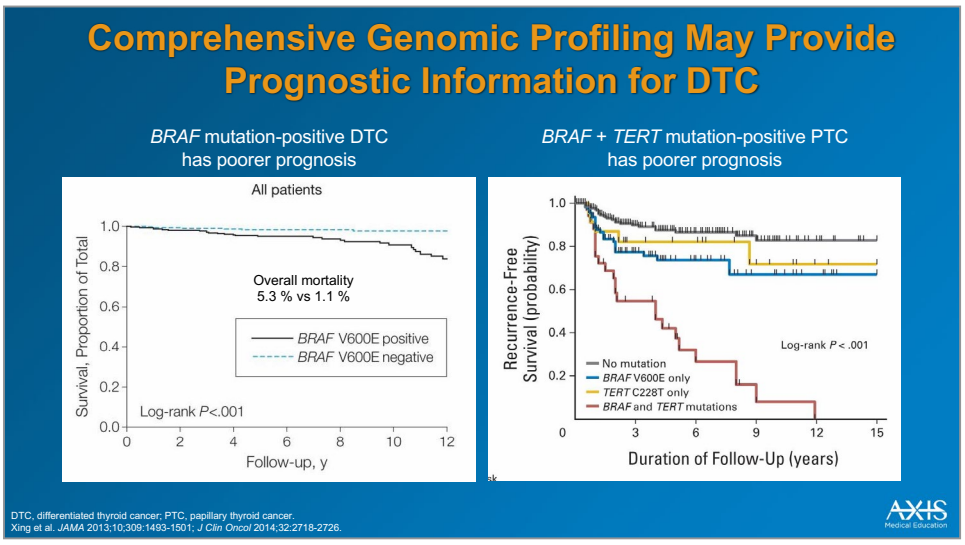
- Testing for *RET* alterations in MTC is recommended by the NCCN. NCCN Guidelines recommend germline *RET* mutation testing for all new diagnoses of MTC. Approximately 6% of patients with clinically sporadic MTCs also carry a germline mutation in *RET*, which means that we can observe *RET* germline mutations even in patients who don't have any family history. The NCCN Guidelines also state that *RET* somatic genotyping may be done in patients who are germline wild-type or if germline status is unknown.



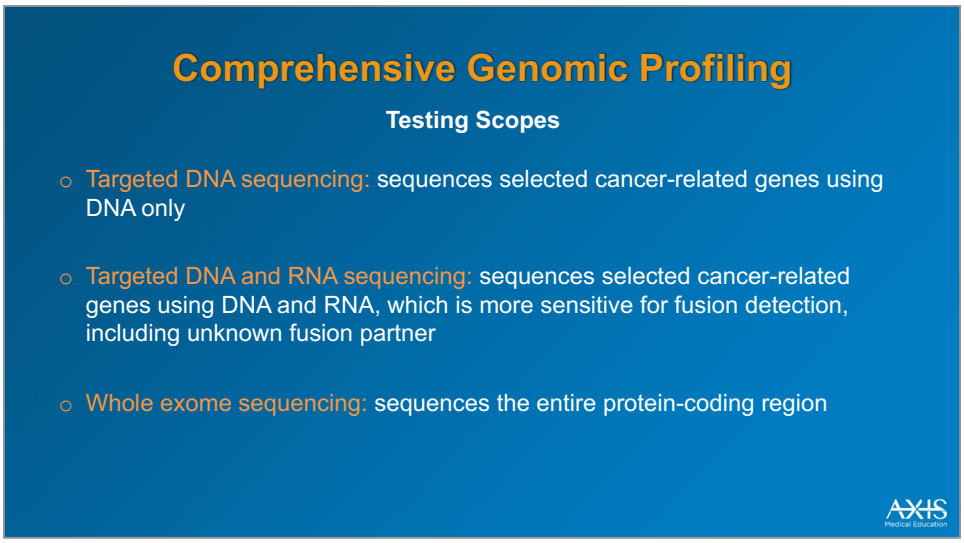
- For differentiated thyroid cancer (DTC), NCCN Guidelines recommend genomic testing to identify potentially actionable mutations. For example, *ALK*, *NTRK*, and *RET* gene fusions, DNA mismatch repair deficiency, microsatellite instability, and tumor mutational burden for metastatic DTC.



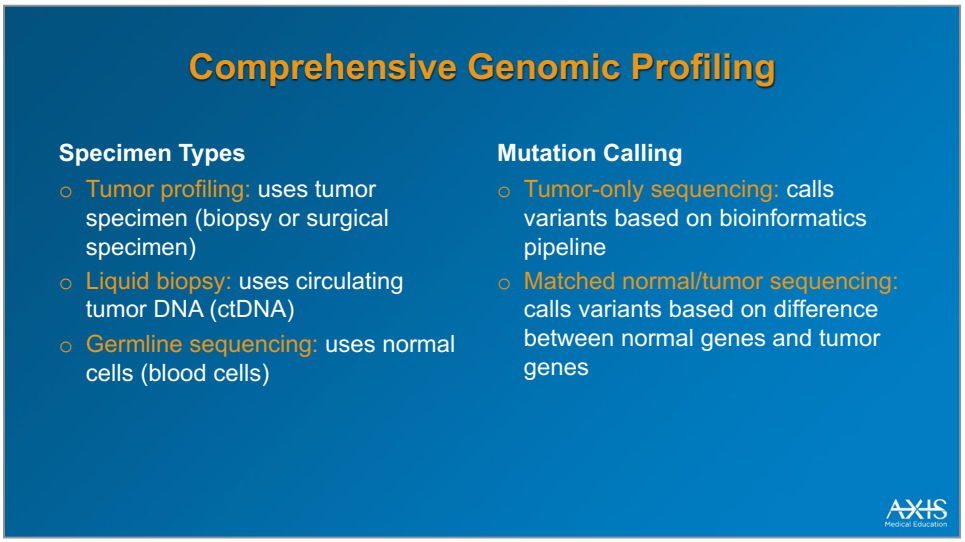
- If you look at the biology of DTC a little deeper, there are few well-known oncogenes altered in studies looking at the genomic alterations. *NRAS* mutation is seen in 8.5% of differentiated thyroid cancer. *HRAS* mutation is also seen in 3.5% of DTC. *RAS* mutations are not quite actionable at this time, but in future, we may be able to develop agents targeting these mutations. *BRAF* V600E is a very well-known oncogene and is the most common mutation in papillary thyroid cancers. Thyroid cancers are known to have, generally, very low mutational burden. But there are quite frequent fusion events with *RET* fusion being the most common at 6.3% of DTC. And other fusions, including *BRAF, PPARγ, ALK*, and *NTRK* are seen in DTC.



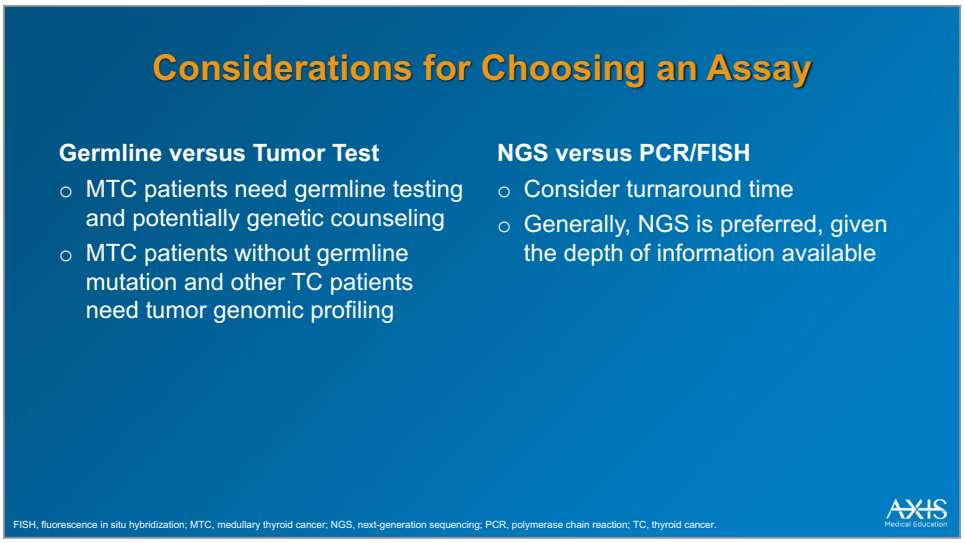
- Comprehensive genomic profiling may provide prognostic information for DTC. It is known that *BRAF* mutation–positive DTC has a poorer prognosis of overall mortality of 5.3% in *BRAF* V600E–positive disease versus 1.1% in *BRAF* V600E–negative disease. If you look at *BRAF* and *TERT* mutation status at the same time, the dual-mutant patient has the poorest prognosis, whereas patients who do not have either of the mutations have the best prognosis. So having the information for mutational status can provide prognostic information for patients.



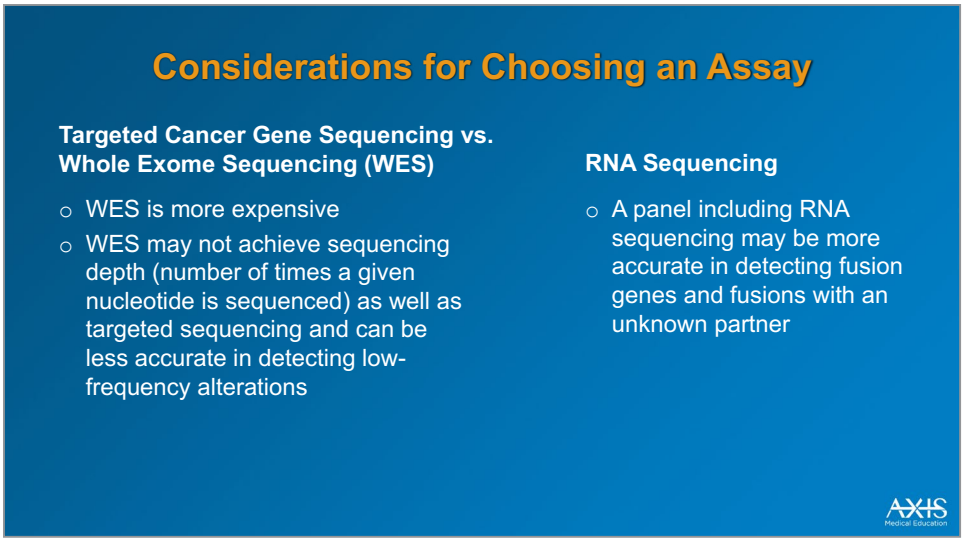
- Comprehensive genomic profiling can be done in several different ways. A common way of doing it is to perform targeted DNA sequencing, which sequences selected cancer-related genes using DNA only. And some test platforms offer targeted DNA and RNA sequencing, and it sequences selected cancer-related genes using DNA and RNA. And RNA sequencing provides more information for fusion detection, including unknown fusion partner. So it can be more sensitive to detect fusion events. Whole exome sequencing sequences the entire protein-coding regions, and it can provide a broader panel, but there could be limited in terms of sequencing that.



- Tumor profiling uses a tumor specimen from biopsy or surgery; or this profiling can be done with blood, which we call liquid biopsy. this test platform uses circulating tumor DNA. Germline sequencing uses normal cells, and we frequently use white blood cells for this. So for germline sequencing, frequently the sample type that we need is blood collection. If the sequencing is only done for the tumor, then the variant calling is based on bioinformatics pipeline because we don't have a germline sequencing information. Some platforms offer matched normal and tumor sequencing, and those platforms sequence both tumor and normal tissue and calls variants based on differences between normal genes and tumor genes. So, generally matched tumor and normal sequencing is known to be more accurate than variant calling, but tumor-only sequencing with an extensive bioinformatics pipeline can perform as well as matched normal/tumor sequencing.



- When choosing an assay, we should be cognizant of assay type. MTC patients need germline testing and potentially genetic counseling because a significant portion of them can be hereditary. And MTC patients without germline mutation and other thyroid cancer patients need tumor genomic profiling, which is mainly somatic sequencing. Next-generation sequencing versus PCR/FISH—PCR and FISH have a significantly faster turnaround time, but generally next-generation sequencing is preferred given the depths of information available through the test.



- Targeted cancer gene sequencing is more commonly performed than whole exome sequencing because whole exome sequencing is more expensive and may not achieve sequencing depth as well as targeted sequencing and can be less accurate in detecting low-frequency alterations. RNA sequencing is preferred when we expect to detect fusion proteins. Especially when you're suspicious for fusions with unknown partner, RNA sequencing can provide the most accurate information.

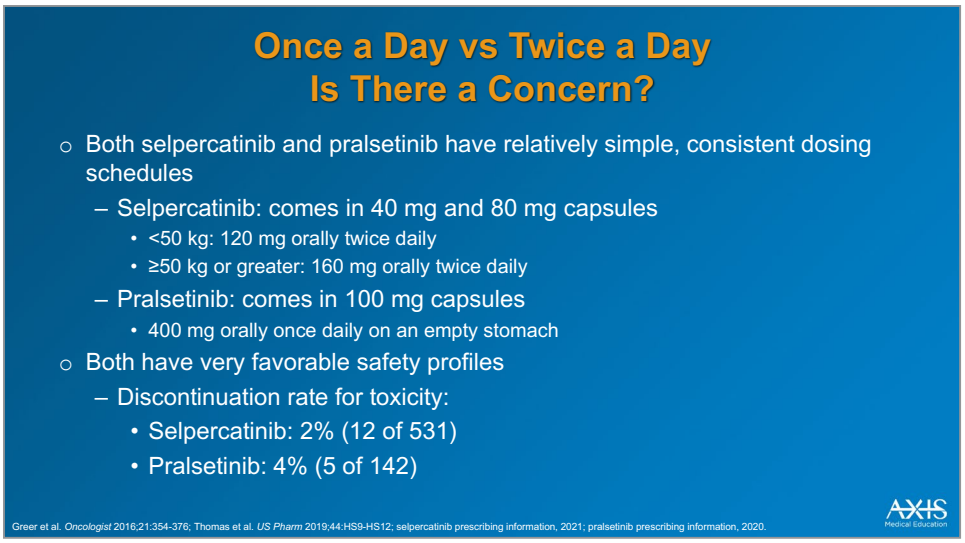
- We'll turn to considerations for long-term oral therapy compliance.

Once a Day vs Twice a Day Is There a Concern?

- Adherence to oral cancer therapy has been a problem
- A systematic literature review suggests that the rate of adherence to oral cancer drugs is as low as 46%
- Factors associated with nonadherence include:
  - Complex treatment regimen
  - Substantial behavior change required
  - Inadequate supervision
  - Poor communication

Greer et al. *Oncologist* 2016;21:354-376.
Thomas et al. *US Pharm* 2019;44:HS9-HS12.

- The major difference between selpercatinib and pralsetinib is once a day versus twice a day. And there might be a concern of compliance in this treatment regimen. In research, adherence to oral cancer therapy has been a problem. A systematic literature review suggests that the rate of adherence to oral cancer drugs can be as low as 46%. Factors associated with nonadherence include complex treatment regimen, substantial behavior change required, inadequate supervision, and poor communication.



- Both selpercatinib and pralsetinib have relatively simple, consistent dosing schedules. One is twice a day, and the other is once a day. But it is easy to remember, and both have very favorable safety profiles. If you look at the discontinuation rate for toxicity, selpercatinib had a 2% rate and pralsetinib had a 4% rate. So both treatments are very well tolerated, and compliance was really good.

- Next, we'll move onto resistant challenges.

Resistance Mechanisms

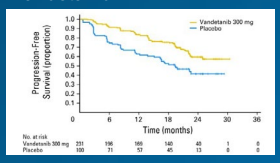
- Resistance to RET inhibitors was studied mainly in *RET* fusion–positive NSCLC
  - Acquired alterations in other genes (MET or KRAS amplification)
  - Acquired mutation in RET G810 (solvent-front mutation)
  - Selpercatinib and pralsetinib are active against *RET* gatekeeper mutations

NSCLC, non-small cell lung cancer.
Lin et al. *Ann Oncol* 2020;31:1725-1733.

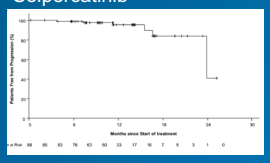
- Resistance to RET inhibitors was mainly studied in *RET* fusion–positive non–small cell lung cancer. There are few mechanisms of action, which include acquired alteration in other genes such as *MET* or *KRAS* amplification; acquired mutation in *RET* G810, which is a solvent-front mutation that we discussed; and there are gatekeeper mutations but both selpercatinib and pralsetinib are active against *RET* gatekeeper mutations.

MKI vs Selective RET Inhibitor in Treatment-Naïve MTC Patients: PFS

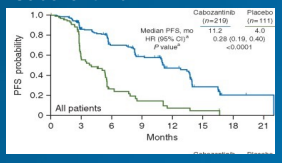
Vandetanib



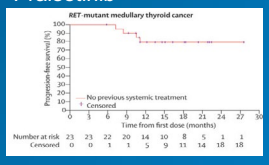
Selpercatinib



Cabozantinib



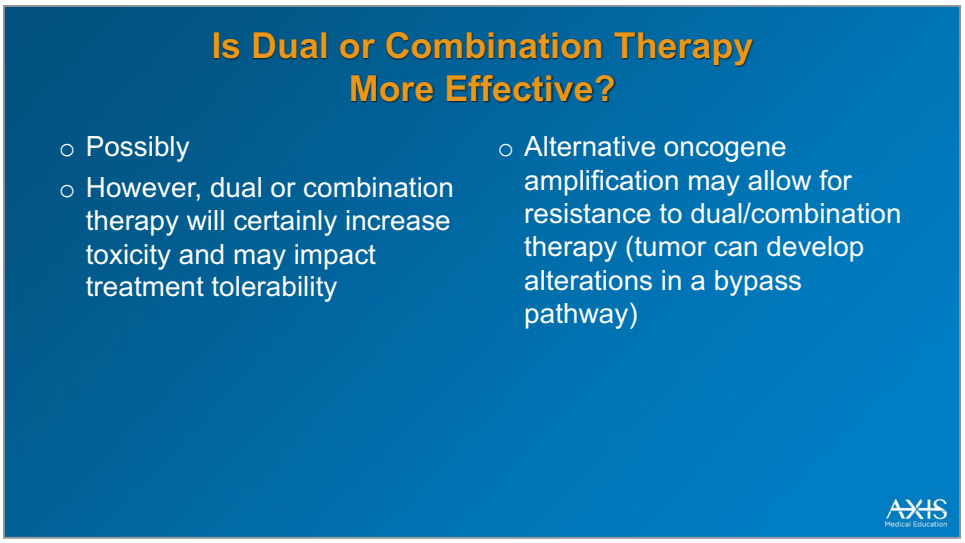
Pralsetinib



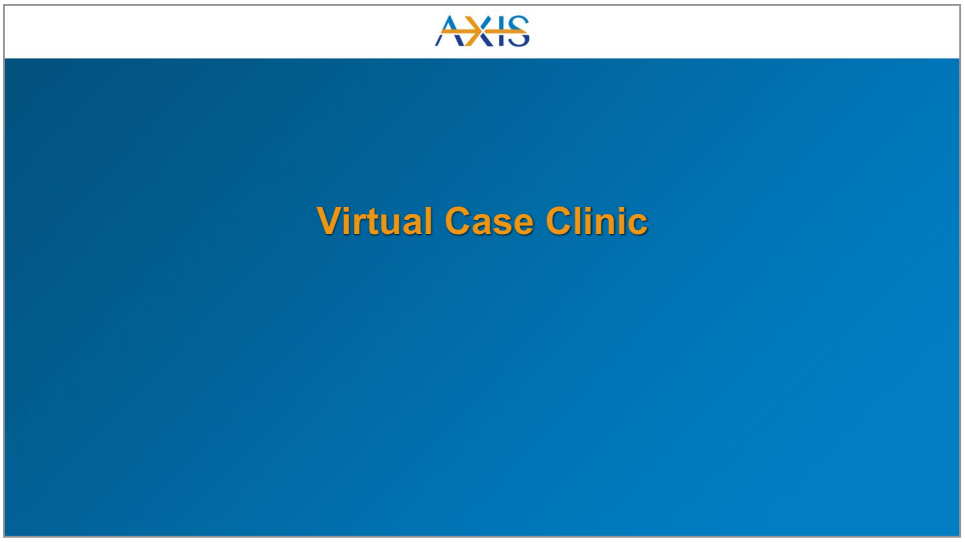
- PFS curves do not suggest more resistance development in patients treated with highly selective RET inhibitor, compared to MKIs

MKI, multikinase inhibitor; MTC, medullary thyroid cancer; PFS, progression-free survival.
Wells et al. *J Clin Oncol*. 2012;30:134-141; Elisei et al. *J Clin Oncol*. 2013;31:3639-3646;
Wirth et al. *N Engl J Med*. 2020;383(9):825–835; Subbiah et al. *Lancet Diabetes Endocrinol*. 2021;9(8):491-501.

- If you look at the pattern of progression-free survival, both selpercatinib and pralsetinib achieved very high progression-free survival at 24 months. Comparing that curve to vandetanib or cabozantinib, it doesn't seem like these highly specific RET inhibitor is associated with development of more resistance compared to previous generation multikinase inhibitors.



- And there's a question whether dual or combination therapy would be more effective. Dual therapy may be more effective; however, dual or combination therapy will certainly increase toxicity and may impact treatment tolerability. Alternative oncogene amplification may allow for resistance to dual/combination therapy because a tumor always can develop alterations in a bypass pathway.



- Next, let's look at the virtual case clinic.

  I am joined by Dr. Jochen Lorch, Professor of Medicine at Northwestern Chicago. We are going to discuss a patient case example to highlight the use of RET inhibitors in clinical practice for the treatment of advanced thyroid cancer.

Case: Patient Presentation and Medical History

Presentation

- 42-year-old female, never smoker
- Experienced chest pain and palpitations
  - Cardiac work-up was negative
- A CT chest scan identified a few pulmonary nodules and mediastinal lymphadenopathy
- Endobronchial ultrasound (EBUS) FNA of hilar lymph node positive for metastatic adenocarcinoma, most likely of thyroid origin
- Underwent neck ultrasound
  - Multinodular, diffusely heterogenous thyroid gland
  - Left thyroid gland is highly vascular, heterogenous and multinodular with nodular borders difficult to discern

Medical History

- No significant medical history
- Lived close to Chernobyl as a child at the time of the nuclear disaster
- No regular medications, just NSAIDs

FNA, fine needle aspiration.

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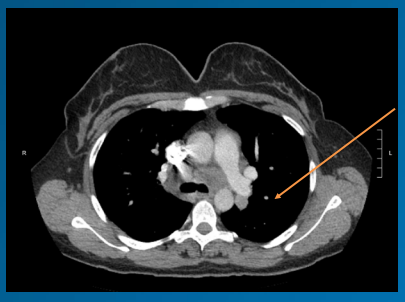
We brought a case of a 42-year-old woman who was a never smoker and experienced chest pain and palpitations, and her cardiac workups were unrevealing. She had CT scan that showed a few pulmonary nodules and mediastinal lymphadenopathy. And she had endobronchial ultrasound-guided fine needle aspiration of the hilar lymph node that showed metastatic adenocarcinoma, most likely of thyroid origin. She then had a neck ultrasound that showed multinodular diffusely heterogenous bilateral thyroid gland. The left thyroid gland was markedly and highly vascular, heterogenous, and multinodular with borders of nodules difficult to discern. She does not have any significant medical history, but she did live very close to Chernobyl as a child at the time of the nuclear disaster. She was a never smoker, no regular medications, just nonsteroidal anti-inflammatory drugs from time to time.

Case: Key Imaging Findings

Chest CT



Thyroid Ultrasound

- There is a multinodular, diffusely heterogenous thyroid gland seen on both sides
- There is an irregular heterogenous, highly vascular area with varying echotexture in the medial mid-pole of the left thyroid lobe, measuring 1.5 x 1.38 x 1.67 cm
- A mid anechoic structure is seen in the left thyroid lobe, measuring 0.44 x 0.42 x 0.18 cm

CT, computed tomography.

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Here are our images of her chest, which showed distinct mediastinal lymph nodes and hilar lymph nodes. And on the ultrasound, there were multiple nodules throughout the thyroid.

Case: Tissue Diagnosis/Current Status

- FNA of the thyroid is positive for papillary thyroid carcinoma
- Clinical stage T1b N1b M1
- Patient is referred to an endocrine surgeon and an endocrinologist
- Thyroglobulin 7.4 ug/L
- Anti-thyroglobulin Ab 378 IU/mL

FNA, fine needle aspiration.

AXIS Medical Education

- She then had a fine needle aspiration of the thyroid, which showed papillary thyroid cancer, so she was staged as T1b N1b M1 papillary thyroid carcinoma and was referred to endocrine surgeon and endocrinologist. At the time of the diagnosis, her thyroglobulin level was 7.4 ug/L, but she did have anti-thyroglobulin antibody titer which was pretty high.

Case: Next Step?

- What do you recommend next for treatment?
  a) Radioactive iodine ablation
  b) Total thyroidectomy and central neck dissection
  c) PET scan and brain MRI
  d) Initiate neoadjuvant therapy in anticipation of subsequent surgery
  e) Unsure

MRI, magnetic resonance imaging; PET, positron emission tomography.

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- This is the first question. What do you recommend next for the treatment? Radioactive iodine ablation, total thyroidectomy and central neck dissection, PET scan and brain MRI, initiate new adjuvant therapy in anticipation of subsequent surgery, what would you do?

Jochen Lorch, MD: I'm unsure. This is an unusual case because most cases in young women with thyroid cancer, thyroid nodules are diagnosed because a scan was obtained or perhaps because of a physical exam. To find somebody with a relatively small primary tumor and such widespread disease is very unusual. Nonetheless, the histology is papillary thyroid cancer, and it seems that it was a well-differentiated type.

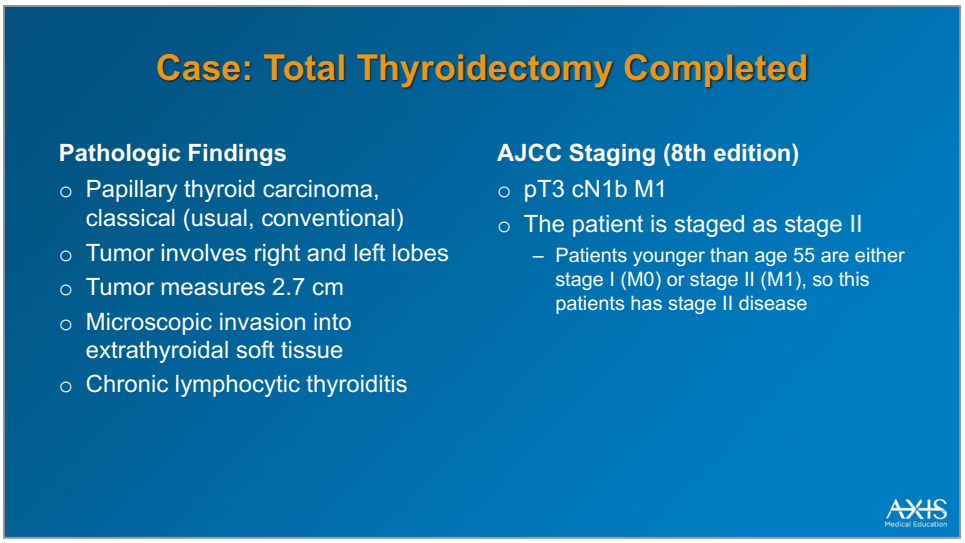
With this, my choice would be a total thyroidectomy and central neck dissection for two reasons. First, to take the tumor out, although in this case where you have widely metastatic disease, taking care of the primary tumor is probably not that big of a priority. However, to use radioactive iodine, you have to get rid of the thyroid tissue first, so then I would say a thyroidectomy is the treatment of choice. What you're achieving with a central neck dissection you could probably argue about, because that's not going to change the extent of the tumor, but you're already there so you might as well. But that would be my choice. I was tempted to also get a PET scan.

Now, I think the brain MRI would not necessarily be recommended at this stage, but with such widespread disease and again, with this unusual pattern of relatively small primary tumor and multiple areas of distant metastatic disease, I would have also ordered a PET scan.

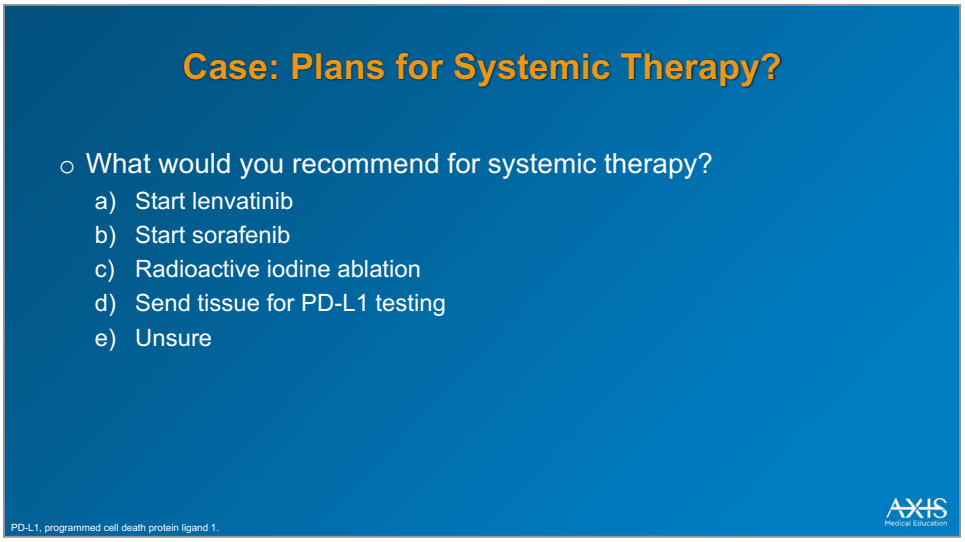
Kang: Exactly. Actually, that was in line with my thought as well. I intended to choose total thyroidectomy just to remove thyroid so that we could use radioactive iodine ablation. I agree with you that central neck dissection might be controversial, but since we are there, I thought that it would be reasonable to complete the staging with doing the neck dissection. PET scan, I think, would be useful. There is some data suggesting that PET avid disease is less iodine avid, but I think we still would need to give a benefit of doubt and probably use radioactive iodine anyway for this young lady with differentiated thyroid cancer.

Any other point to add?

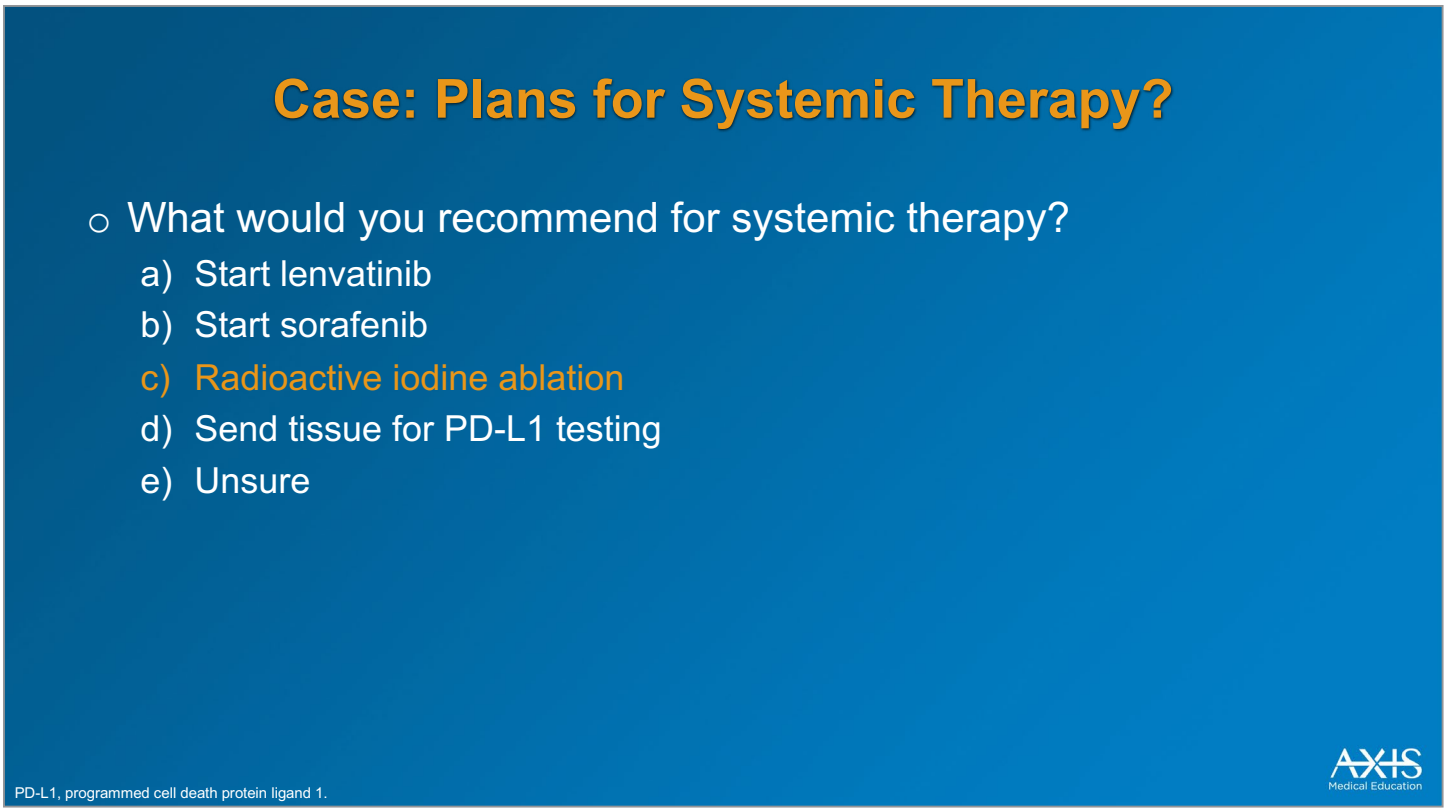
Lorch: As you mentioned, there is this inverse relationship between PET avidity and iodine avidity. So, you learn something about the biology through a PET scan, but then also you would see, I mean it's such widespread disease it might be worthwhile also taking a general look. If those tumors are PET-positive, then you might detect other areas of disease that could potentially cause a problem.



- **Kang:** I agree. She did have total thyroidectomy next, and the pathology showed papillary thyroid carcinoma classical type. And tumor was involving the right and left lobes, measured 2.7 cm at the largest, and there was microscopic invasion into extrathyroidal soft tissue. She also had chronic lymphocytic thyroiditis in the background. This was staged as pT3 cN1b M1. Following the AJCC staging, she is still stage II because she's younger than age 55, and with M1 disease she's classified as stage II.



- Next step, what should we do for systemic therapy? Should we do lenvatinib, sorafenib, radioactive iodine ablation, or send tissue for PD-L1 testing?



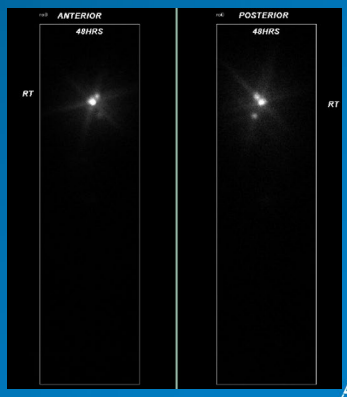
Lorch: So now that the thyroid gland is out, you definitely want to give radioactive iodine a shot. This is a very aggressive thyroid cancer so I'm not sure how much radioactive iodine will be effective under these circumstances, but it's a relatively easy treatment. And that would definitely be something to consider. The question is, should you also get a diagnostic radioiodine scan to make sure that there is sufficient uptake, just because of the unusual biology, but that's debatable.

Kang: Is it your standard practice to get radioactive iodine dose symmetry before RAI ablation?

Lorch: No, not routinely, but again this is an unusual case, and one could consider it, especially since you're also dealing with a fairly high volume of disease. You want to treat with a reasonably high dose. There are lung metastases, some dose symmetry might be useful. But again, that's debatable. As far as other options go, obviously for lenvatinib and sorafenib we have not established that this is an iodine-refractory tumor. And for sending tissue for PD-L1 testing, there is very limited experience with immunotherapy in differentiated thyroid cancer. Generally, the response rates tend not to be very high. And again, while you have the option of treating with radioactive iodine which is a one-time treatment, pretty well-tolerated, that's what you would try first.

Case: Radioactive Iodine Ablation

- I-131 radioactive iodine ablation performed (375 mCi)
- Post-therapy scan showed multiple areas of uptake in left cervical lymph nodes and mediastinal lymph nodes

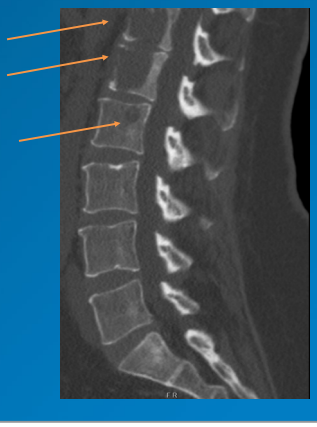


Kang: I agree. I intended to use radioactive iodine, as we have extensively discussed. So that's where we are.

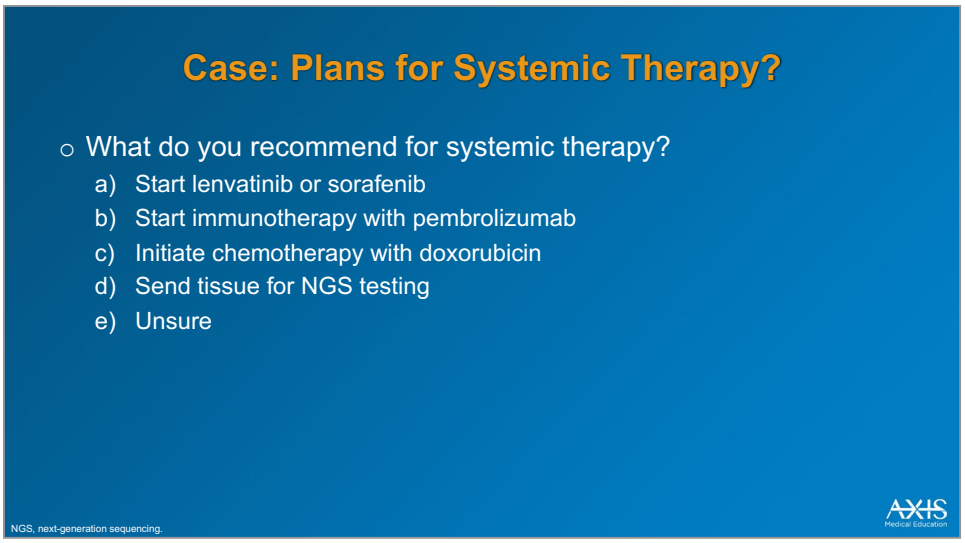
She did have radioactive iodine treatment, and she did have a fairly high dose of radioactive iodine treatment, 375 mCi. Post-therapy scan actually showed multiple areas of uptake in left cervical lymph nodes and mediastinal lymph nodes but not in the lung nodules.

Case: Progression

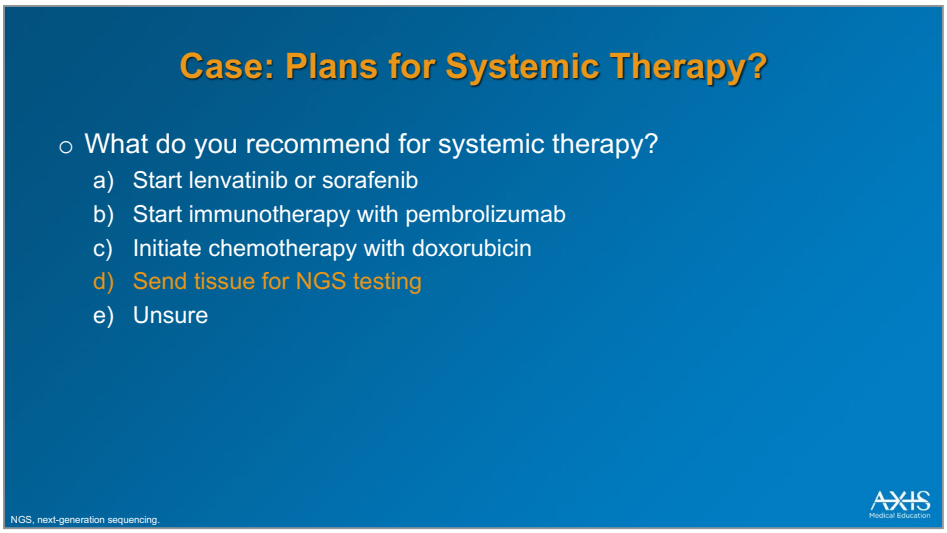
- 2 months later, the patient complained of new lower back pain
- A CT scan of the chest/abdomen/pelvis identified a new lytic bone lesion in sacrum and iliac bones as well as multi-level vertebral body lytic lesions



Then, 2 months later she complained of new lower back pain, and she had CT scan of the chest, abdomen, and pelvis. And showed a new lytic lesion in the sacrum and iliac bones, as well as multilevel vertebral body lytic lesions.



- Now she has clear evidence of progression, what would you recommend for systemic therapy? Start lenvatinib or sorafenib, start immunotherapy with pembrolizumab, initiate chemotherapy with doxorubicin, or send tissue for next-generation sequencing (NGS)?



Lorch: One of the difficult parts about treating patients with thyroid cancer is that sometimes it's difficult to decide whether or not there is actual disease progression. From the imaging that we've received so far, I'm not sure if we've so far imaged the lumbar spine, where she now has pain and where she has these lytic metastases. Now, on scan they do seem quite extensive, so I think something should be done about them. But I think the question whether or not you would treat these as an area of painful metastases, bone metastases, and treat with a course of radiation versus starting out with systemic therapy is not an easy question to answer.

Again, unless there is previous imaging, these lesions could have been there already.

Kang: Unfortunately, this care was done before I saw her, so this is actually what happened. Let's assume that we had baseline images that didn't show this, and she had radiation to palliate. Then as a next step what would you prefer to do? Would you start with lenvatinib or sorafenib or would you do NGS?

Lorch: She clearly need systemic therapy and soon, because this is obviously very aggressive, very rapidly progressing. And so, I think starting the FDA-approved standard of care, lenvatinib or sorafenib, I typically prefer lenvatinib because of the efficacy data, although the two drugs have never been compared head-to-head, so both are reasonable choices. Again, my preference would be lenvatinib. At the same time, it's definitely the right moment to send for NGS to determine what the next steps could be. Is this tumor *BRAF*-mutant?

Typically, pathologists can tell by the appearance of the tumor under the microscope whether or not these are *BRAF*-positive. There is also immune histochemistry that could be used as a quicker way to determine whether a BRAF inhibitor is even a consideration. NGS would detect fusions and other rare abnormalities, such as *RET* fusions, *NTRK* fusions, and would be reasonable to initiate, especially since getting the results back typically takes between 2 and 8 weeks.

Kang: Does her history of radiation exposure as a child make you more suspicious for one genetic alteration over the others?

Lorch: That's a good question. From my experience and from what I read and talked about or heard from my colleagues, I find that some of the *NTRK* fusion ones and also the *RET* fusion positive cases often have this very unrelenting progression. Although I don't think there is any published data, but I'm not sure if they tend to be more aggressive than other cases of DTC. And especially as aggressive, if this is a typical case for the level of aggressiveness for one of these cases. In general in my experience, you usually cannot tell based on the clinical history alone. Again, there are features, just tall cell features and some other abnormalities that typically indicate whether a tumor is *BRAF* mutant or not. But for these rare alterations, *RET* and *NTRK*, typically without NGS, it's typically very difficult to tell or impossible to tell.

Case: Molecular Marker Testing

Comprehensive genomic profiling with NGS

Formalin-Fixed Paraffin-Embedded Tissue Thyroidectomy specimen, Comprehensive Genomic Analysis
Genomic Alterations Detected
FGFR2 A315T, *RET NCOA4-RET* fusion (N7;R12), *RET-NAALADL2* fusion (R11;N13), *TERT* promoter -124C>T
Microsatellite Status (MSI)
MS-Stable
PD-L1 22C3 FDA (Pembrolizumab) Status
High Expression, Tumor Proportion Score: 95%
Tumor Mutational Burden
0 Muts/Mb

PD-L1, programmed cell death protein ligand 1.

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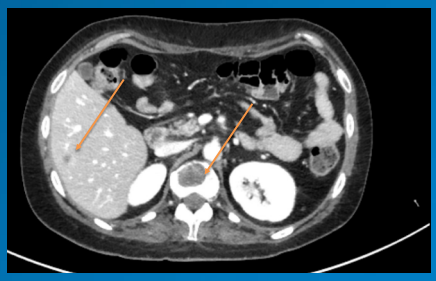
Kang: Right. I've seen reports of clusters of *RET* alterations in the survivors of Hiroshima and Nagasaki, so I was alluding to that.

She did have NGS, which showed two different *RET* fusions; NCOA4 *RET* fusion and *RET*-NAALADL2 fusion. She did also have a *TERT* promotor mutation and *FGFR2* mutation, MS-stable, PD-L1 was very high, tumor proportion score (TPS) score was 95%, but tumor mutational burden was very low, 0/Mb.

Case: Progression

- Patient started palliative lenvatinib immediately, which she tolerated after 1 dose reduction
- A re-staging scan reported progression of multiple lytic bone lesions and new liver metastases



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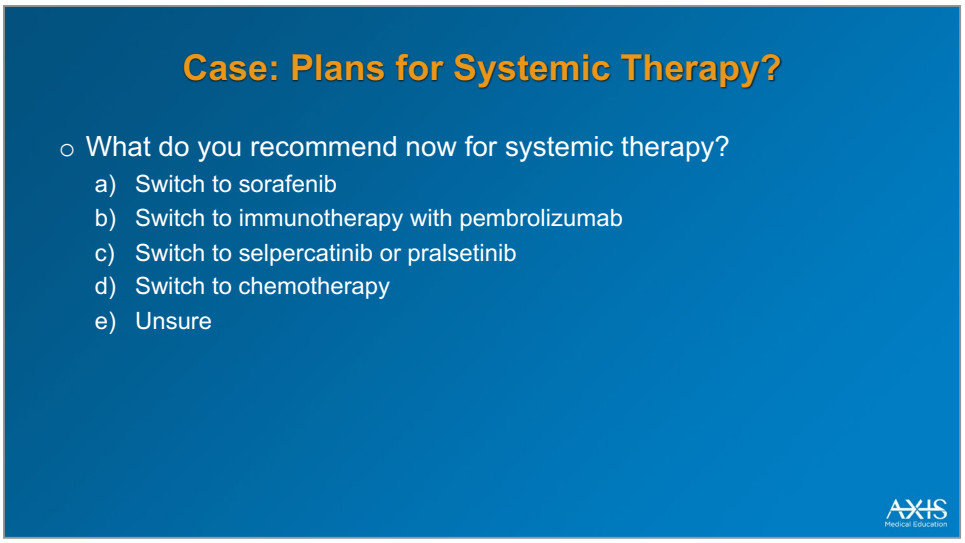
She was started on palliative lenvatinib immediately, given the symptom burden. And she tolerated treatment well after one dose reduction. However, a re-staging scan showed multiple new lytic bone lesions and new liver metastases.



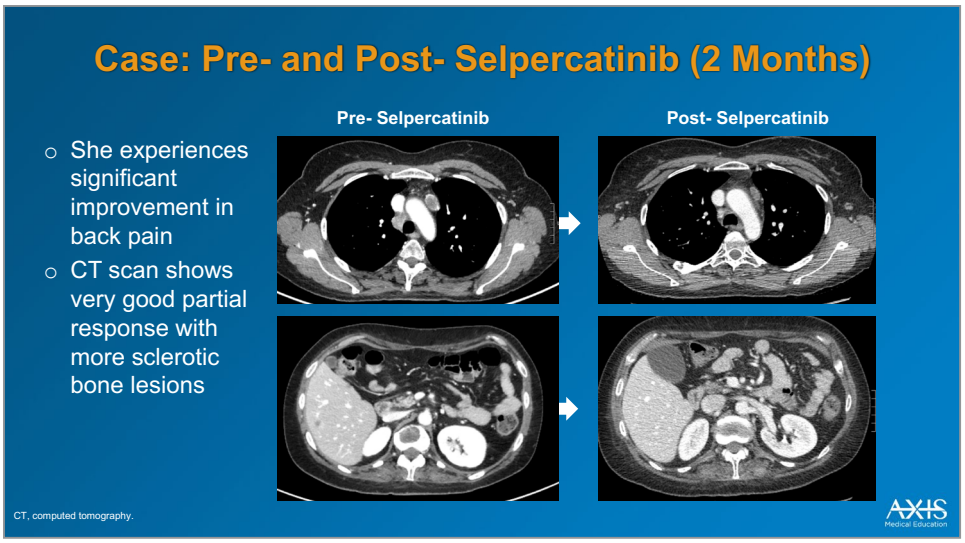
- Now what should we do? Should we switch to sorafenib, switch to immunotherapy given high TPS, or switch to selpercatinib or pralsetinib, or switch to chemotherapy?

- **Lorch:** Luckily, a *RET* fusion was detected, and this is actually one of the more typical ones. So I think a RET inhibitor would be a logical next choice. Again, this is an unusually aggressive case. Lenvatinib often does work quite well even in these *RET* fusion–positive cases. Overall, the biology seems to be very unfavorable, and I think the prognosis with or without RET inhibitors is probably somewhat guarded. Now, with respect to the high PD-L1 expression, we don't know how well PD-L1 expression correlates with response to immunotherapy in DTC.

  There is some indication that in an aplastic thyroid cancer there is a connection, but in DTC that is not established. And, as I mentioned before, responses are somewhat unusual, so that alone would not sway me to use immunotherapy at this point. It may be a useful treatment down the road, but currently I would not use this.

  Kang: Do you think there is any role for chemo at all if a case is unusually aggressive?

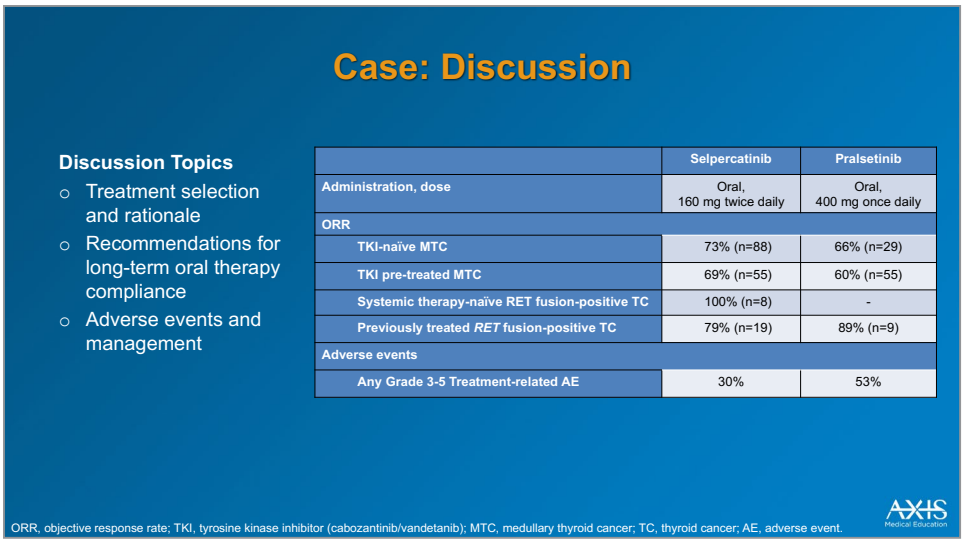
  Lorch: That's also a good question. The short answer is yes, I think there are some, doxorubicin and then some of the more aggressive ones, traditional standard chemotherapy like platinum-based with a taxane, paclitaxel and carboplatin for example, does have a certain level of efficacy. However, that's relatively low, and in the case of doxorubicin, side effects are significant. So, it's actually been a long time that I've used traditional chemotherapy in a case like this.



Kang: Same here, so thank you.

She was started on selpercatinib.

She started experiencing significant improvement in back pain after she started the drug. A CT scan after 2 months showed a very good partial response with more sclerotic bone lesions. This story ended happily, and I think it highlights the need for NGS and molecular targeted therapy for specific genomic alterations.



I do want to discuss a little bit more about two different options for thyroid cancer. We know that there are selpercatinib and pralsetinib in the same space. Do you have any preference or any opinion on differences?

Lorch: I do not. I use them alternatingly. So, one patient I treat with selpercatinib, the next I'll treat with pralsetinib. I have not noticed any major changes in terms of efficacy or side effect profile. I like both drugs, and I'm using both basically.

Kang: On paper at least, QT prolongation was seen with selpercatinib and not much on pralsetinib. Is that what you see in the actual practice as well?

Lorch: Yeah, rarely I've seen it, but again I have not come across a case where I've had to alter the dose for example, that would probably then be a reason to switch to the other drug. But again, so far I have not encountered that.

Kang: Yeah. I've had patients who had pneumonitis develop with pralsetinib and then switched to selpercatinib and still maintained a good response. And the patient developed QT prolongations with pralsetinib who maintained a response very well. So, I agree that the two drugs seem to be very comparable in terms of efficacy. But there might be a little bit of difference in terms of toxicities, but I don't think we have enough data.

I think the key takeaways from today's case discussion were that somatic NGS testing including *RET* should be considered for all cases of RAI-refractory DTC, and selpercatinib and pralsetinib are highly selective RET inhibitors with favorable safety profiles that are FDA approved and should be considered as options for *RET* fusion–positive thyroid cancer.

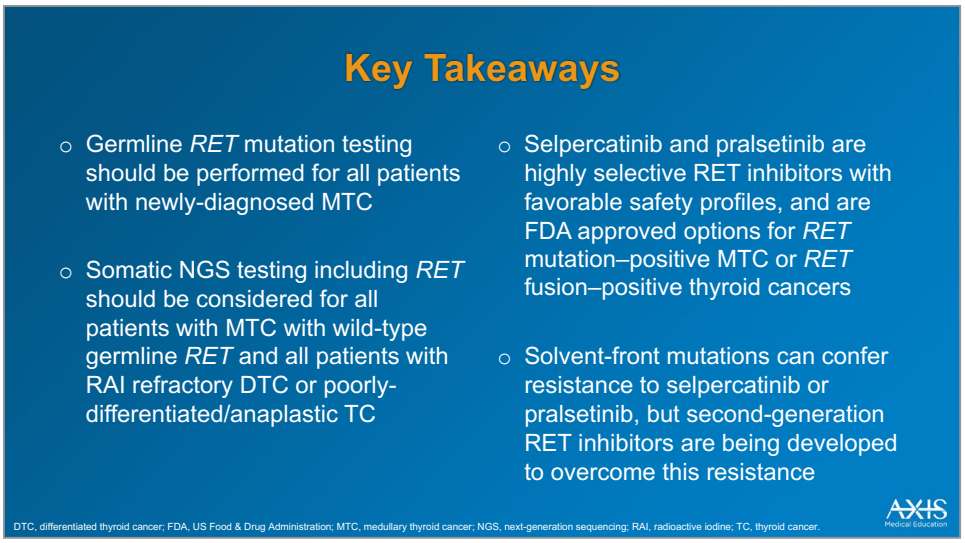
Anything else to add?

Lorch: I agree with that. One thing to keep in mind is that obviously these treatments, as good as they are, they are not curative, and the question is always what are you going to do after one of these drugs fails? Do you switch to the other drug from selpercatinib to pralsetinib or the other way around? There are also a number of second-generation RET inhibitors that are in development. If you have access to those, that would be often a relatively easy choice. The other part is that in DTC, the duration of response seems to be quite good. In an aplastic thyroid cancer, which were also included in these studies, for the most part the duration of response was relatively disappointing.

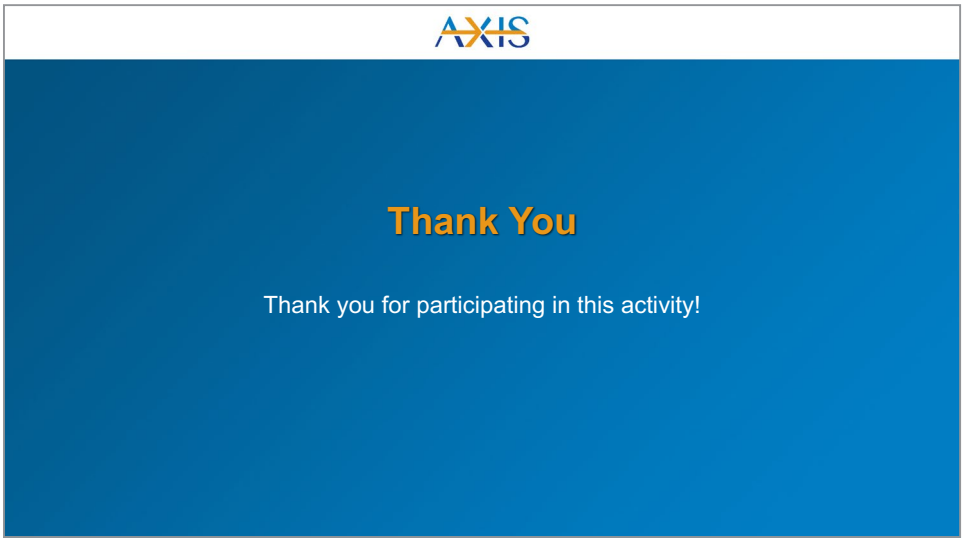
It's definitely the treatment that you could or should try. But again, there are limitations, and in the case of anaplastic thyroid cancer, I think there are perhaps other treatments that I would use before such as immunotherapy, which in anaplastic thyroid cancer tends to work rather well. Otherwise, I agree. This is a big step forward, especially compared to the traditional multi-tyrosine kinase inhibitors, you can typically tell when you walk into the room whether a patient is on one of these RET-specific inhibitors versus one of the older broad-spectrum TKIs such as lenvatinib or sorafenib, just because of the way they look and feel.

Kang: Great. Thank you very much.

Lorch: Thank you.



Kang: So in summary, key takeaways from this presentation. First, germline *RET* mutation testing should be performed for all patients with newly diagnosed MTC. Second, somatic NGS testing, including *RET*, should be considered for all patients with MTC with wild-type germline *RET* and all patients with RAI-refractory DTC or poorly differentiated or anaplastic thyroid cancer. And third, selpercatinib and pralsetinib are highly selective RET inhibitors with favorable safety profiles and are FDA approved options for *RET* mutation–positive MTC or *RET* fusion–positive thyroid cancers. Solvent-front mutations can confer resistance to selpercatinib or pralsetinib, but second-generation RET inhibitors to overcome the limitations are under development.



With that, I thank everybody for participating in this activity.

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