Thyroid Cancer Cases

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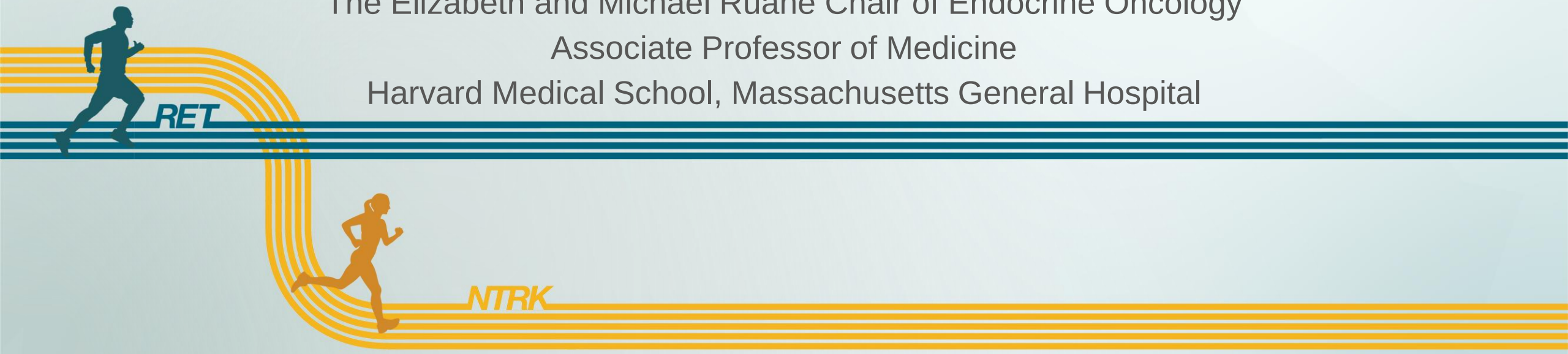


Case Study 1

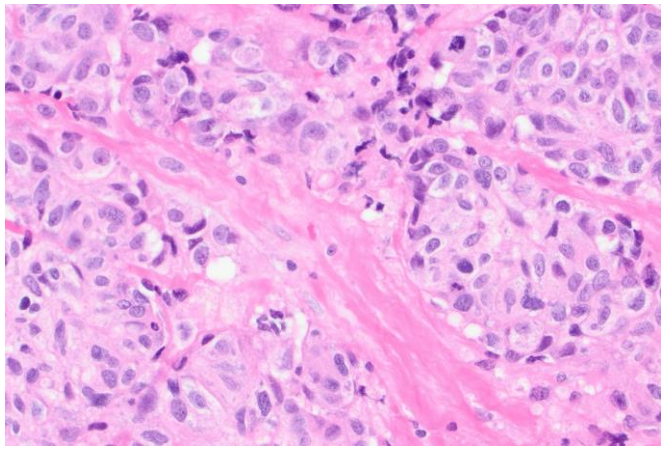
- 2012: **52-year-old man**, non-smoker, originally from Morocco presented to an outside hospital with a left **neck mass**
  - **History of lymphoma** at 22 years of age, treated with chemotherapy
  - Schizophrenia
- April, 2012 biopsy: Adenocarcinoma, **CK7+, TTF-1+**
- Chest CT: **No obvious lung primary**
- PET/CT: FDG+ L supraclavicular adenopathy, FDG+ liver lesions, and FDG+ T9 lesion
- Received **palliative RT** to L neck, 30 Gy

Case Study 1

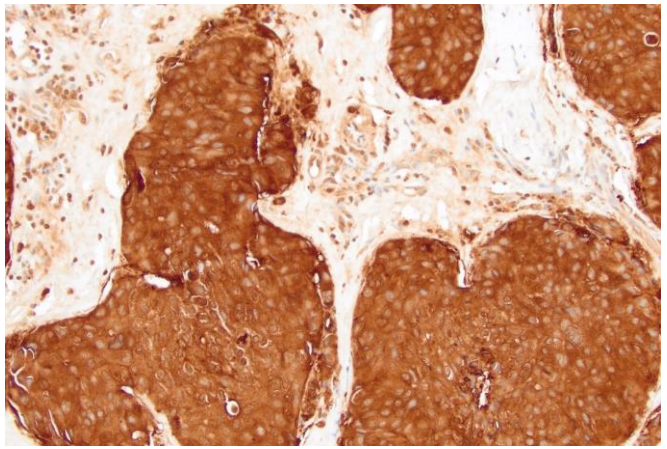
- Referred to Massachusetts General Hospital (MGH)
- Pathology review
  - Additional IHC CK 5/6, CK20, CD99, p63, napsin, TG, mucicarmine negative
  - Synaptophysin, chromogranin, calcitonin, p16 positive
  - Dx changed to metastatic **medullary thyroid carcinoma** (MTC)

Case Study 1: Path RVW at MGH

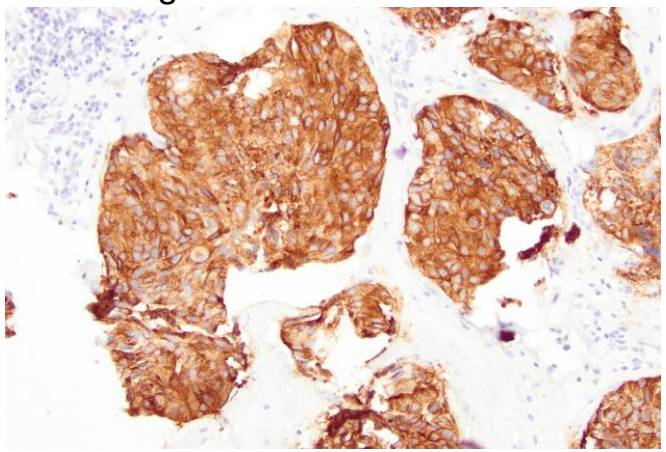
40X



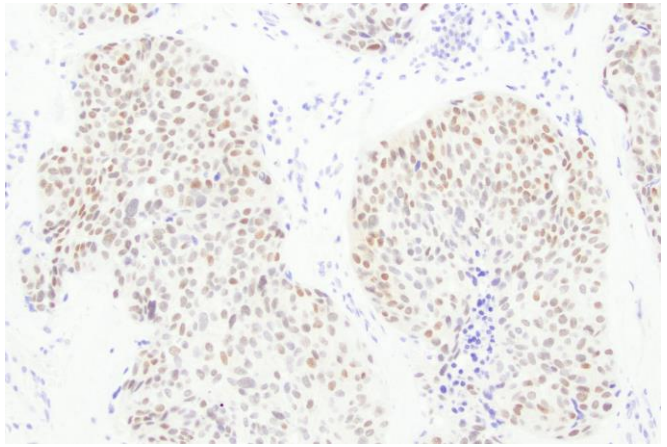
CEA 20X



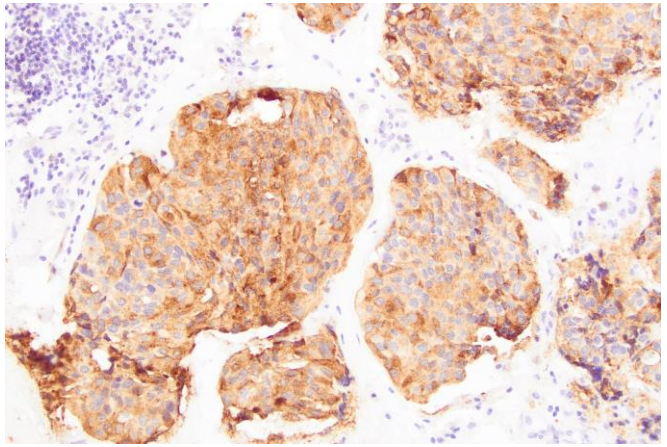
Chromogranin 20X



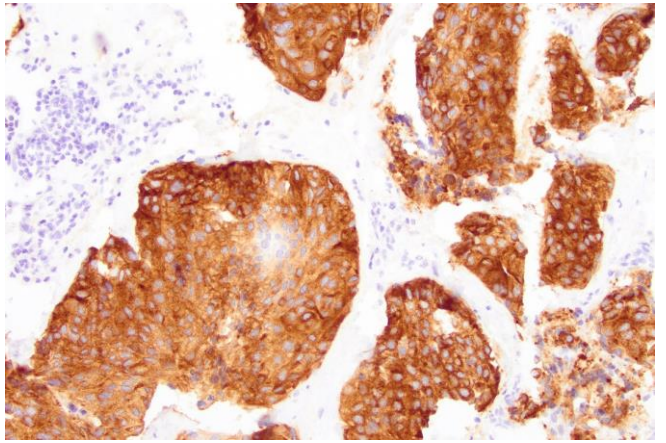
TTF-1 20X



Calcitonin 20X



Synaptophysin 20X



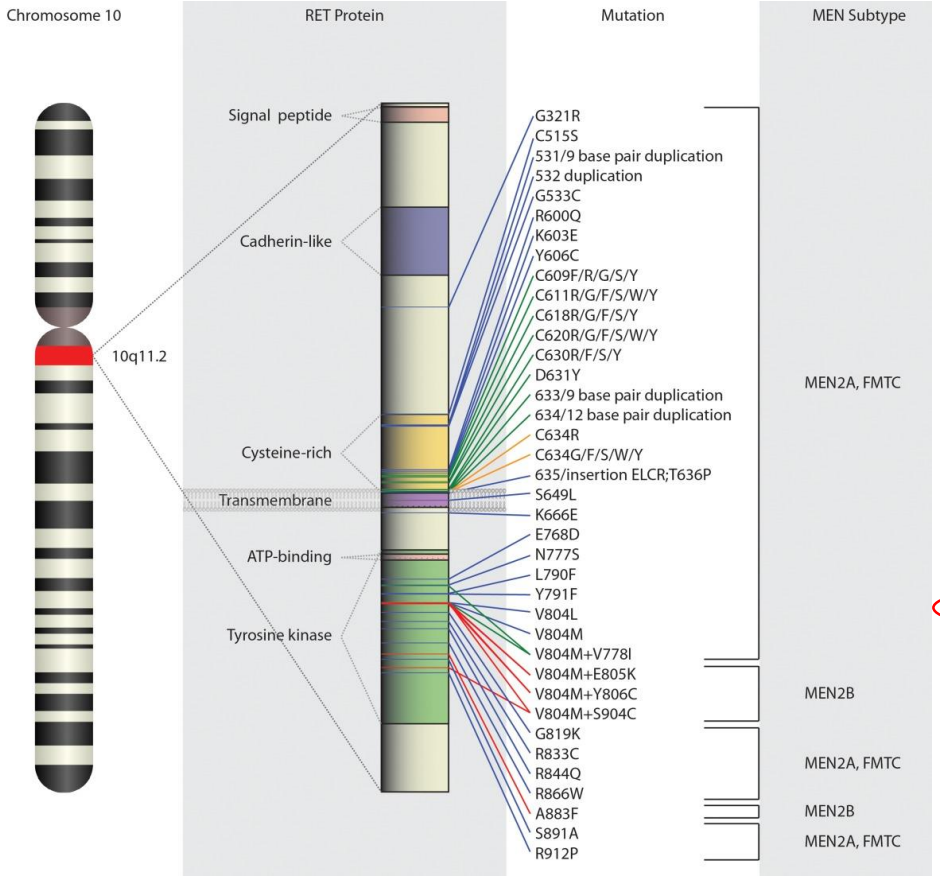
Images courtesy of Adam Fisch MD, PhD

Case Study 1

- Bulky neck disease **unresectable**
- Serum calcitonin = 467, CEA = 25.3
- **Germline *RET* testing ordered**
  - Genomic DNA
  - *RET* exons 10, 11, 13, 14, 15 and 16 analyzed by PCR
  - Covering majority of MEN2A and 2B mutations
- **Cabozantinib started** November, 2012

Case Study 1

- Germline testing + for *RET V804M*, MEN2A[1]



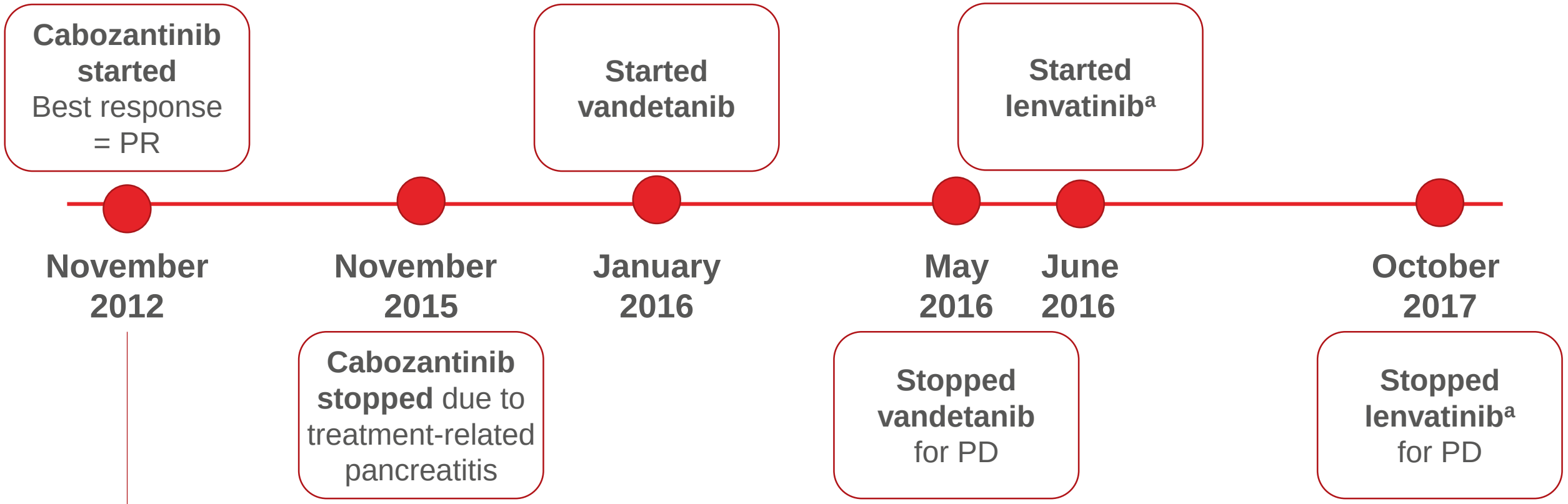
- MTC genotype-phenotype correlation[2]

TABLE 4. RELATIONSHIP OF COMMON *RET* MUTATIONS TO RISK OF AGGRESSIVE MTC IN MEN2A AND MEN2B, AND TO THE INCIDENCE OF PHEO, HPTH, CLA, AND HD IN MEN2A

RET *mutation*[a]	*Exon*	*MTC risk level*[b]	*Incidence of PHEO*[c]	*Incidence of HPTH*[c]	*CLA*[d]	*HD*[d]
G533C	8	MOD	+	–	N	N
C609F/G/R/S/Y	10	MOD	+/++	+	N	Y
C611F/G/S/Y/W	10	MOD	+/++	+	N	Y
C618F/R/S	10	MOD	+/++	+	N	Y
C620F/R/S	10	MOD	+/++	+	N	Y
C630R/Y	11	MOD	+/++	+	N	N
D631Y	11	MOD	+++	–	N	N
C634F/G/R/S/W/Y	11	H	+++	++	Y	N
K666E	11	MOD	+	–	N	N
E768D	13	MOD	–	–	N	N
L790F	13	MOD	+	–	N	N
V804L	14	MOD	+	+	N	N
V804M	14	MOD	+	+	Y	N
A883F	15	H	+++	–	N	N
S891A	15	MOD	+	+	N	N
R912P	16	MOD	–	–	N	N
M918T	16	HST	+++	–	N	N

1. Krampitz GW, Norton JA. *Cancer* 2014;120:1920–31; 2. Wells SA Jr, et al. *Thyroid* 2015;25:567–610.

Case Study 1

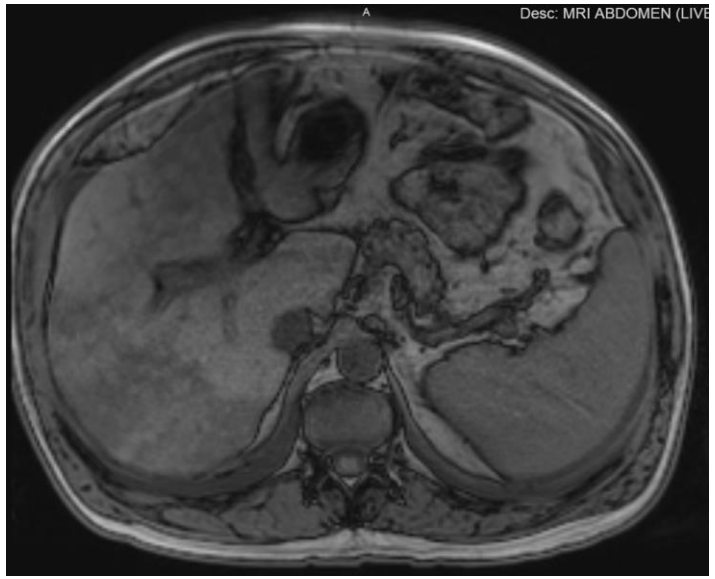


In meantime, 2 children found + for germline *RET V804M* and underwent prophylactic thyroidectomy; *22* siblings in Morocco were notified of risk for MEN2A

[a]Lenvatinib is not approved by EMA and Swissmedic for patients with MTC.

Case Study 1

- October, 2017: Enrolled on LIBRETTO-001, phase 1/2 trial of RET-specific inhibitor, selpercatinib[a], in dose escalation phase, 80 mg BID



MRI: Liver diffusely infiltrated with mets

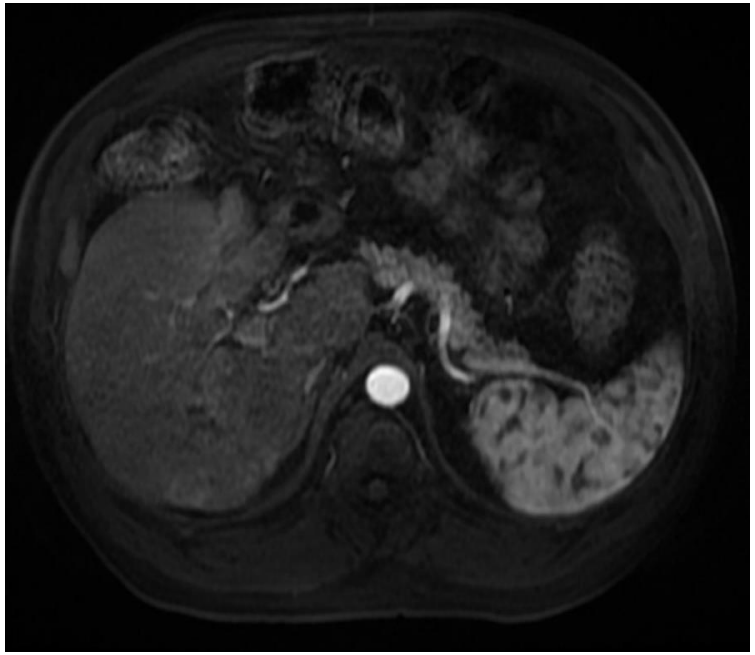
Calcitonin = 1576
CEA = 70.4

Ga68-DOTATATE PET/CT: axillary/subpectoral, mediastinal, portocaval/precaval LNs, T5-T7 vertebral body lesions

[a]Approved dose of selpercatinib is 160 mg BID.

Case Study 1

- By week 8, complete response (CR) by RECIST v1.1 (December, 2017)



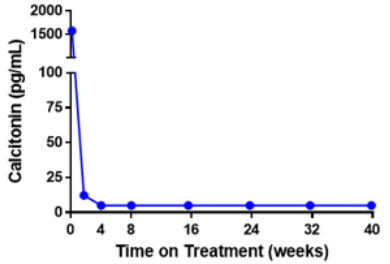
MRI: Resolution of diffuse infiltration of liver with mets

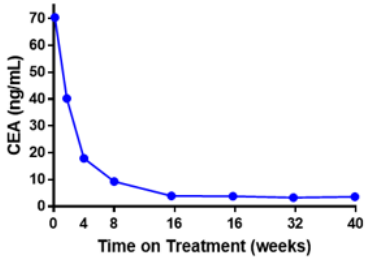
Ga68-DOTATATE PET/CT: Complete resolution of PET+ disease

Calcitonin < 5.0
CEA = 3.2 (normal)

- Remained in CR throughout 2018, 2019 & 2020

Tumor marker decreases





Case Study 1

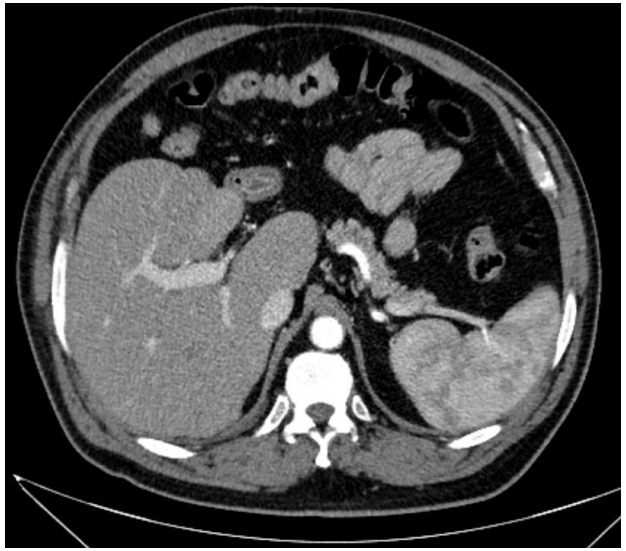
- February, 2021: Hip arthroplasty done, selpercatinib held
- Complicated by wound infection requiring further selpercatinib hold for *6 more weeks!*

Calcitonin

1/5/2021 0758	<5.0 *
3/23/2021 1208	<5.0 *
6/16/2021 0809	<5.0 *
9/8/2021 0743	<5.0 *

CEA

1/5/2021 0758	3.2
3/23/2021 1208	2.8
6/16/2021 0809	2.7
9/8/2021 0743	3.0

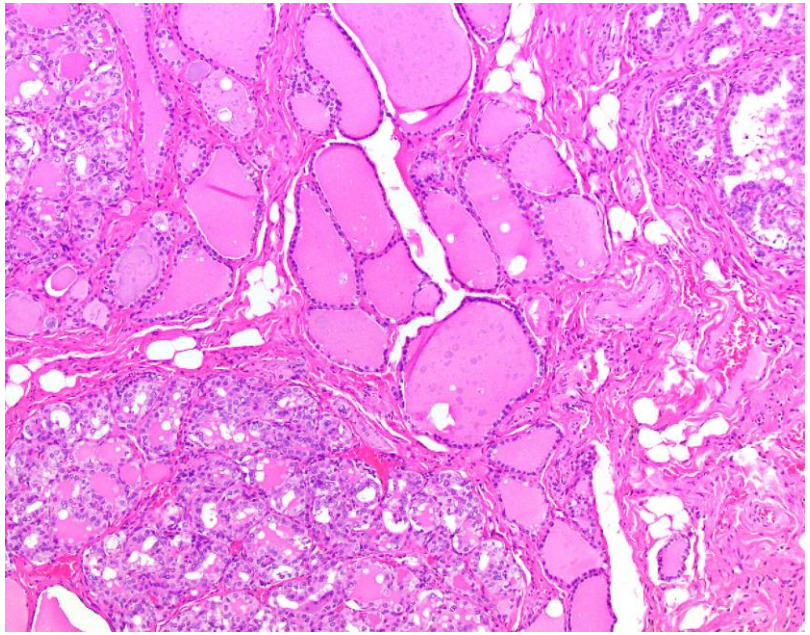


- Remained in response entire period off drug. Resumed protocol treatment April, 2021. Still on study in CR today

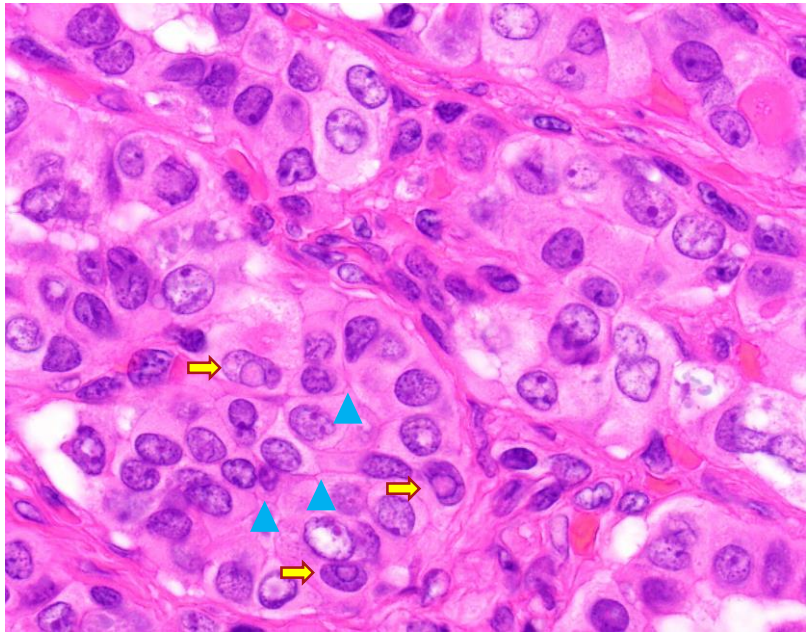
Case Study 2

- **62-year-old man** diagnosed with PTC after paratracheal mass found incidentally on chest CT, 2013
- Underwent thoracoscopic resection of mediastinal disease, then **total thyroidectomy** and **central/lateral neck dissection**
  - Path: PTC, >4 cm, diffuse sclerosing variant, present throughout the entire gland, ETE into soft tissue, multifocal LVI including extrathyroidal LV1, no PNI. Numerous + LNs, with ENE, largest 3.2 cm

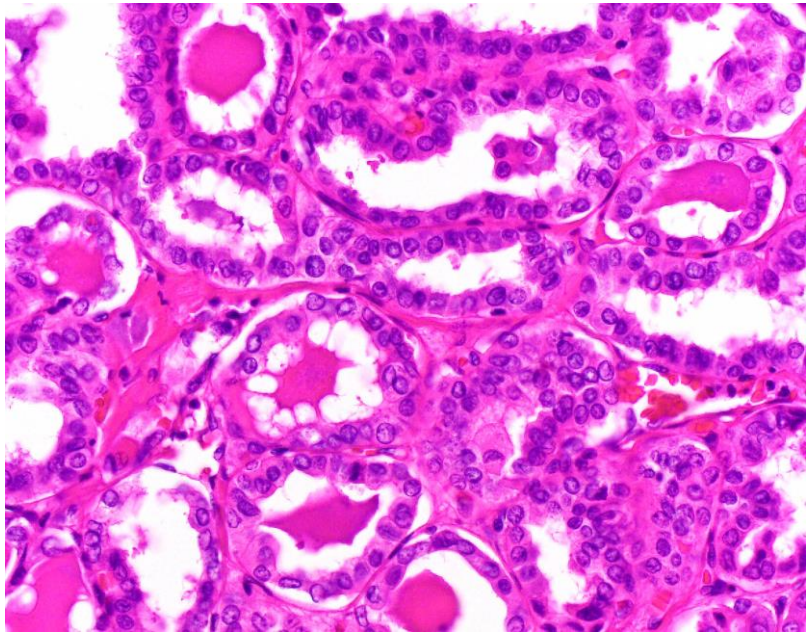
Case Study 2



Higher power (100X magnification) H&E stain shows the distinct tumor clusters (T) amongst normal thyroid follicles (N)



Oil immersion (1000X) shows somewhat squamoid features notable in diffuse sclerosing variant with prominent pink desmosomes separating the cells (blue arrowheads), nuclear clearing and distinct intranuclear pseudoinclusions (yellow arrows)



H&E stain shows entirely follicular architecture in this focus (400X). This pattern, when seen in combination with other patterns (solid growth, classic papillary growth and squamous features) is practically diagnostic of a kinase fusion-related carcinoma

Images courtesy of Peter Sadow MD, PhD.

Case Study 2

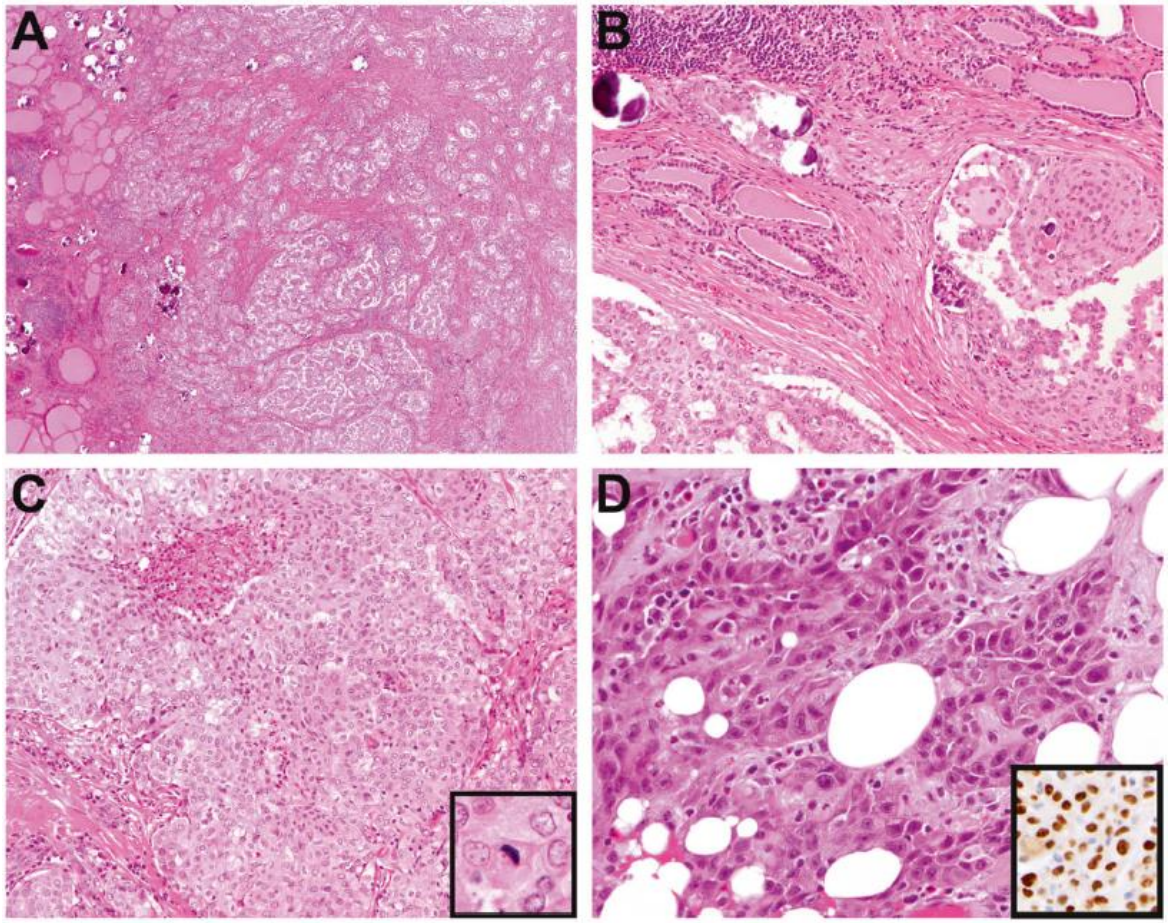
- PCR for *BRAF V600E* and our in-house SNaPshot: **Negative for mutations in K/H/N *RAS* & *BRAF***
- Received 125 mCi I-131, post-treatment WBS – uptake in thyroid bed only

Case Study 2

- Over next 3 years, thyroglobulin (Tg) steadily rose
- April, 2016: MEK inhibitor, trametinib, given with intention to “redifferentiate” with I-131, 150 mCi, unsuccessfully
- November, 2016 PET/CT: Multiple new & increasing lung nodules
- In-house fusion assay v. 1 ordered: Targeted RNA NGS using Anchored Multiplex PCR (AMP) detected no reportable fusion transcripts
  - NEGATIVE for *ALK*/*RET*/*ROS1*/*BRD4*/*NUTM1*/*EGFR*/*EWSR1* rearrangement and *MET* exon 14 skipping
    - Additional analysis showed an intergenic fusion involving *PPL* Exon22 (ENST00000345988) and *NTRK1* Exon13 (ENST00000524377), consistent with an *NTRK1* rearrangement
    - Confirmed by FISH

Case Study 2

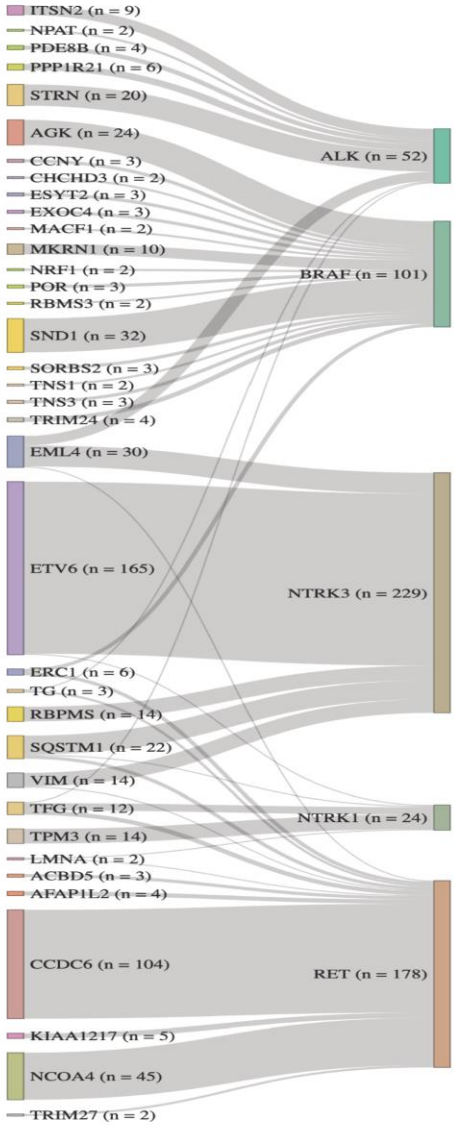
- Characteristic histologic triad seen in 95% of kinase fusion-positive cases
  - Multinodularity
  - Prominent fibrosis
  - Extensive lymphovascular invasion
- High rates of other features
  - ETE
  - LN involvement
  - Distant mets
- Features should prompt evaluation for oncogenic fusions, if not already performed



Chu YH, et al. *Mod Pathol* 2020;33:2458–72.

ALK, *BRAF*, *NTRK* and *RET* Fusions in Thyroid Cancer

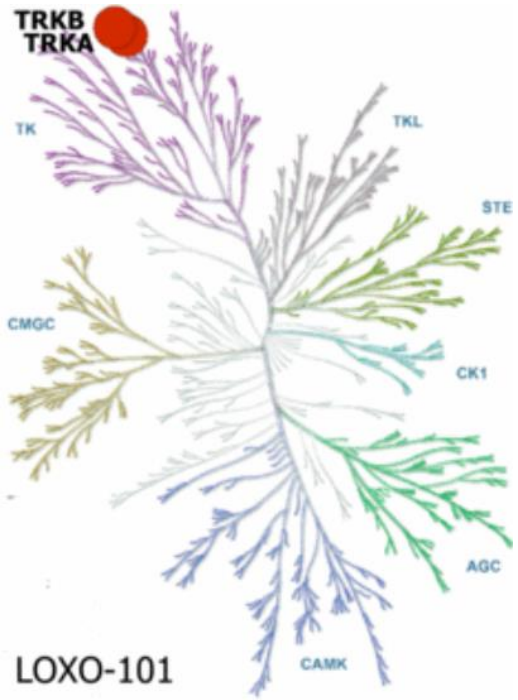
- Sankey diagram shows 5' partner genes on the left, and the key kinase genes on the right
- Highest diversity of fusions, with each kinase gene harboring numerous 5' partners
- When searching for oncogenic fusions, optimal assay will include not only the relevant kinase genes but also have the capability of detecting numerous 5' partners



Wirth L, et al. *J Clin Oncol* 2021;39(suppl):Abstract 6083.

Case Study 2

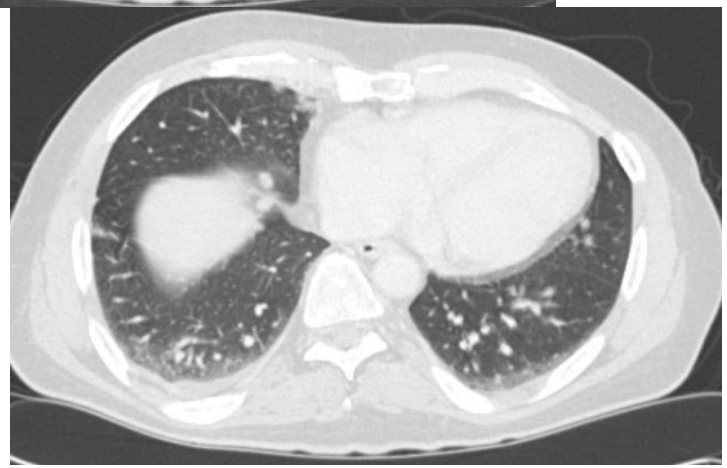
- December, 2016: Enrolled on phase 2 basket trial of LOXO-101 (larotrectinib)



- First-in-class highly selective small molecule TRK 1/2/3 inhibitor
- First gene-specific, tissue agnostic FDA approval in oncology

Scott LJ. *Drugs* 2019;79:201–6.

Case Study 2



Tg = 1185

4 mos

March, 2017

Tg = 66

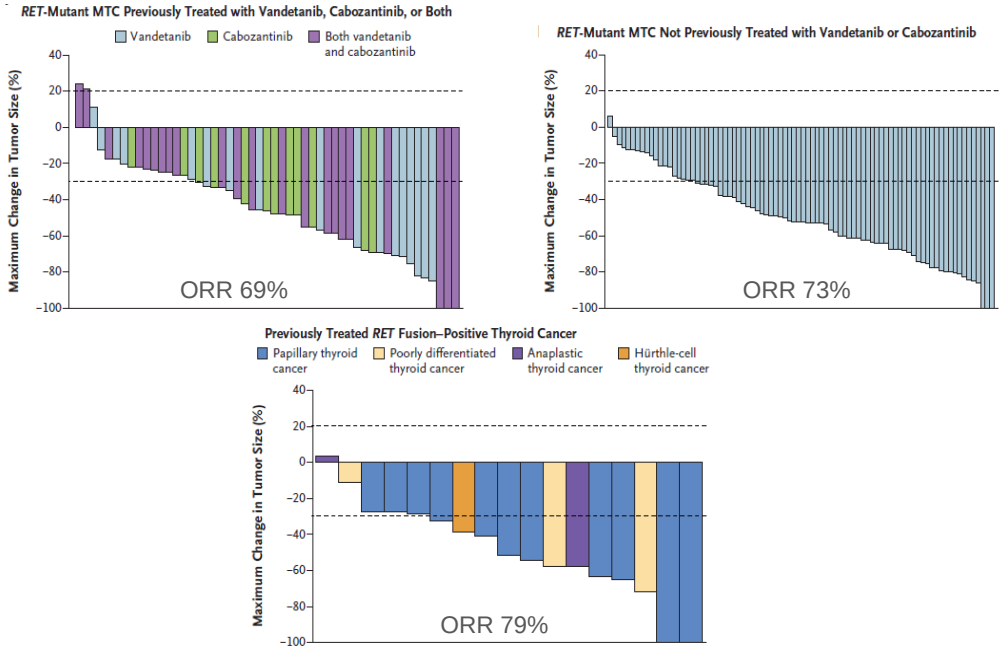
Complete response

- AEs: Gr 1 fatigue
- Today still on study, in CR

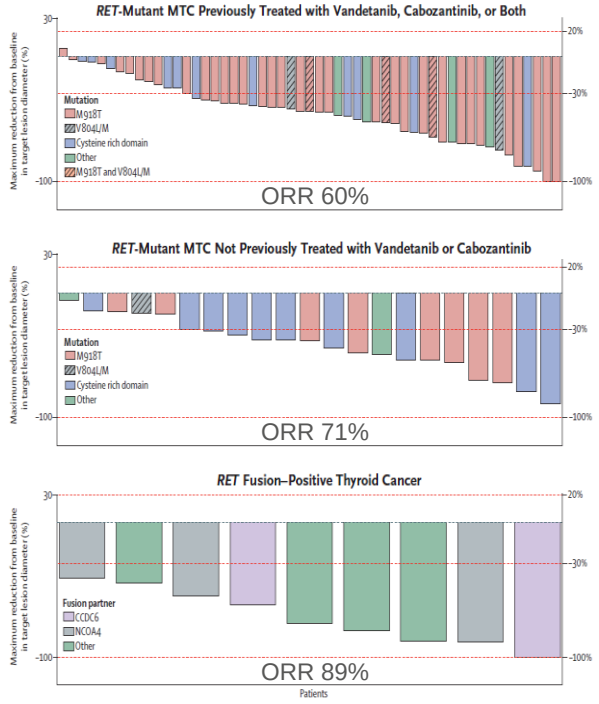
Conclusions

- Identification of actionable molecular alterations for precision targeted therapy in every case of advanced thyroid cancer critical
- Efficacy of RET-targeted therapy in thyroid cancer

Selpercatinib[1]

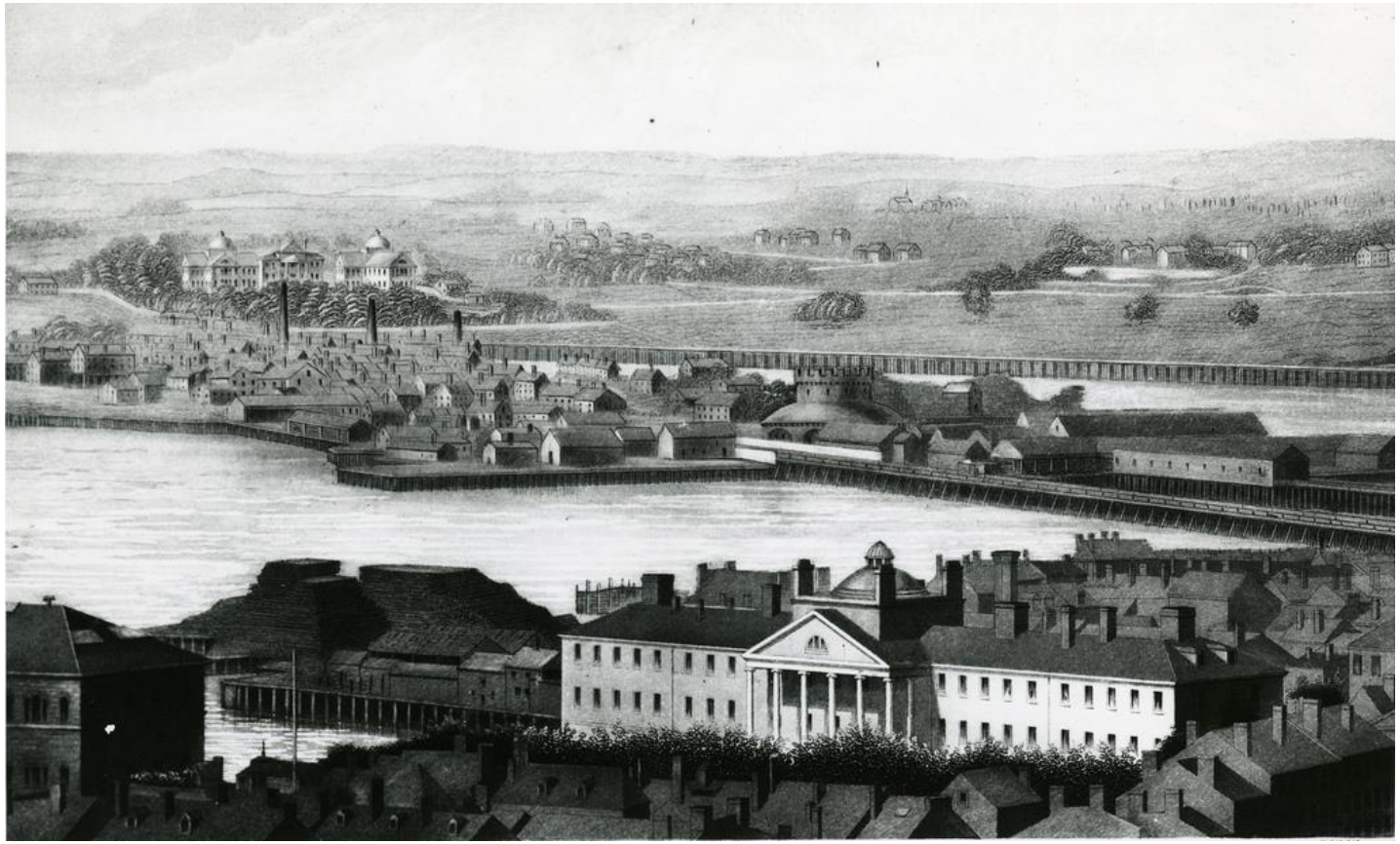


Pralsetinib[2]



1. Wirth L, et al. *N Engl J Med* 2020;383:825–35; 2. Subbiah V, et al. *Lancet Diabetes Endocrinol* 2021;9:491–501.

Thank You



Massachusetts General Hospital
founded in 1811