Thank you for joining us.
The program will commence momentarily.

Virtual Molecular Tumor Board: Recognition and Management of Targetable Tumor Mutations in Less Common Cancer Types

Friday, August 14, 2020

9:00 AM – 10:00 AM ET

Faculty

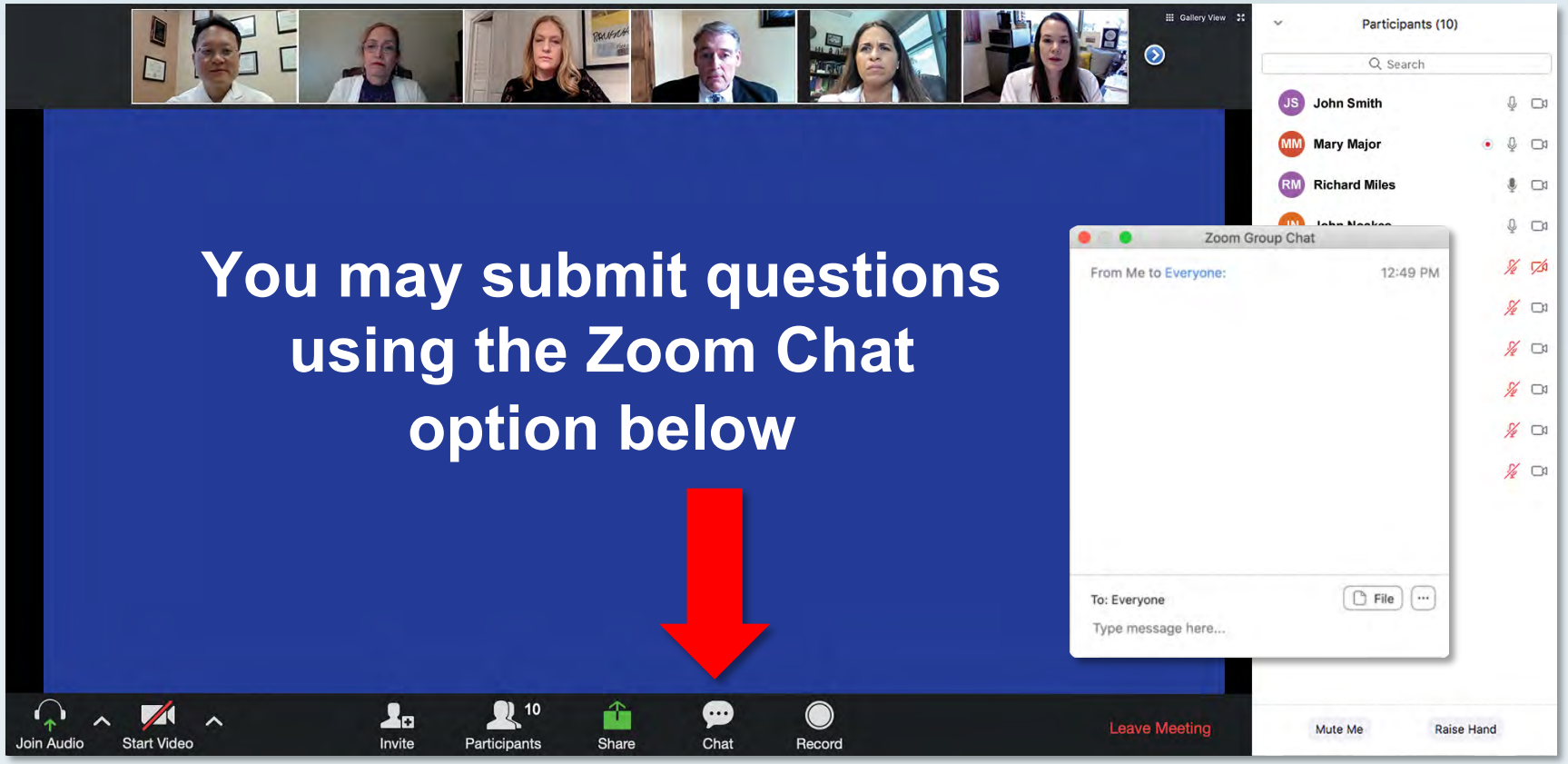
Marcia S Brose, MD, PhD
Andrew McKenzie, PhD
Milan Radovich, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Dr Love and Faculty Encourage You to Ask Questions



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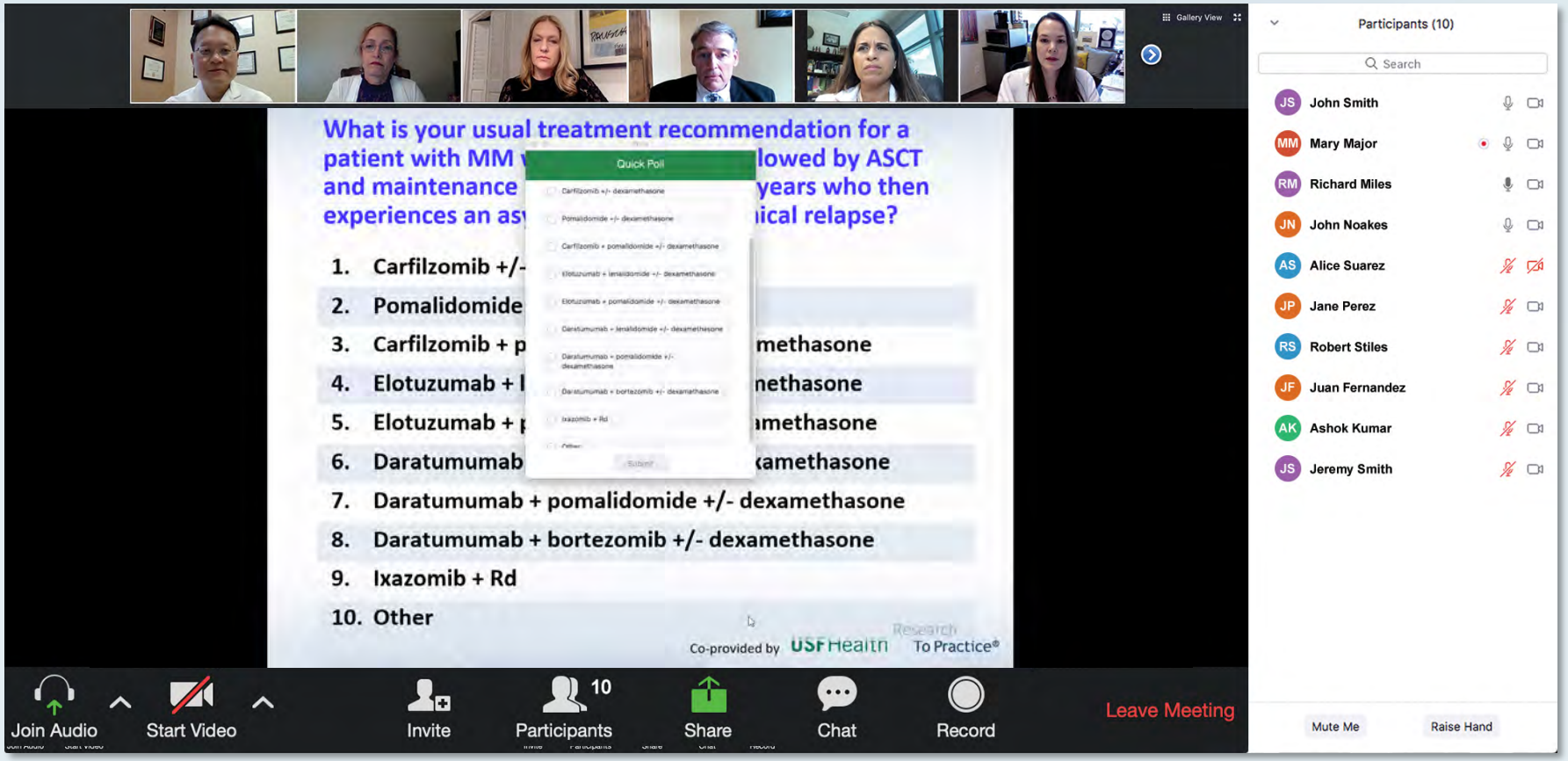
Familiarizing yourself with the Zoom interface
How to answer poll questions



When a poll question pops up, click your answer choice from the available options. Results will be shown after everyone has answered.

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Dr Brose — Disclosures

Consulting Agreements and Contracted Research	Blueprint Medicines, Exelixis Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company

Dr McKenzie — Disclosures

No relevant conflicts of interest to disclose

Dr Radovich — Disclosures

Contracted Research	Boston Biomedical Inc, Lilly
Ownership Interest	Immunomedics Inc, LifeOmic Health LLC, Tyme Inc

Upcoming Live Webinars

Monday, August 17, 2020
5:00 PM – 6:00 PM ET

Recent Advances in Medical Oncology: ER-Positive Breast Cancer

Faculty
Virginia Kaklamani, MD, DSc
Sara M Tolaney, MD, MPH

Moderator
Neil Love, MD

Tuesday, August 18, 2020
5:00 PM – 6:00 PM ET

Current Questions and Controversies in the Management of Lung Cancer

Faculty
Leora Horn, MD, MSc

Moderator
Neil Love, MD

Upcoming Live Webinars

Wednesday, August 19, 2020
12:00 PM – 1:00 PM ET

Clinical Investigator Perspectives on the Current and Future Management of Multiple Myeloma

Faculty
Noopur Raje, MD

Moderator
Neil Love, MD

Thursday, August 20, 2020
5:00 PM – 6:00 PM ET

Clinical Investigator Perspectives on the Current and Future Role of PARP Inhibition in the Management of Ovarian Cancer

Faculty
Don S Dizon, MD

Moderator
Neil Love, MD

Upcoming Live Webinars

Friday, August 21, 2020
12:00 PM – 1:00 PM ET

Optimizing the Selection and Sequencing of Therapy for Patients with Chronic Lymphocytic Leukemia

Faculty
Brad S Kahl, MD

Moderator
Neil Love, MD

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Philadelphia, Pennsylvania

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Indiana University Melvin and Bren Simon Comprehensive Cancer Center
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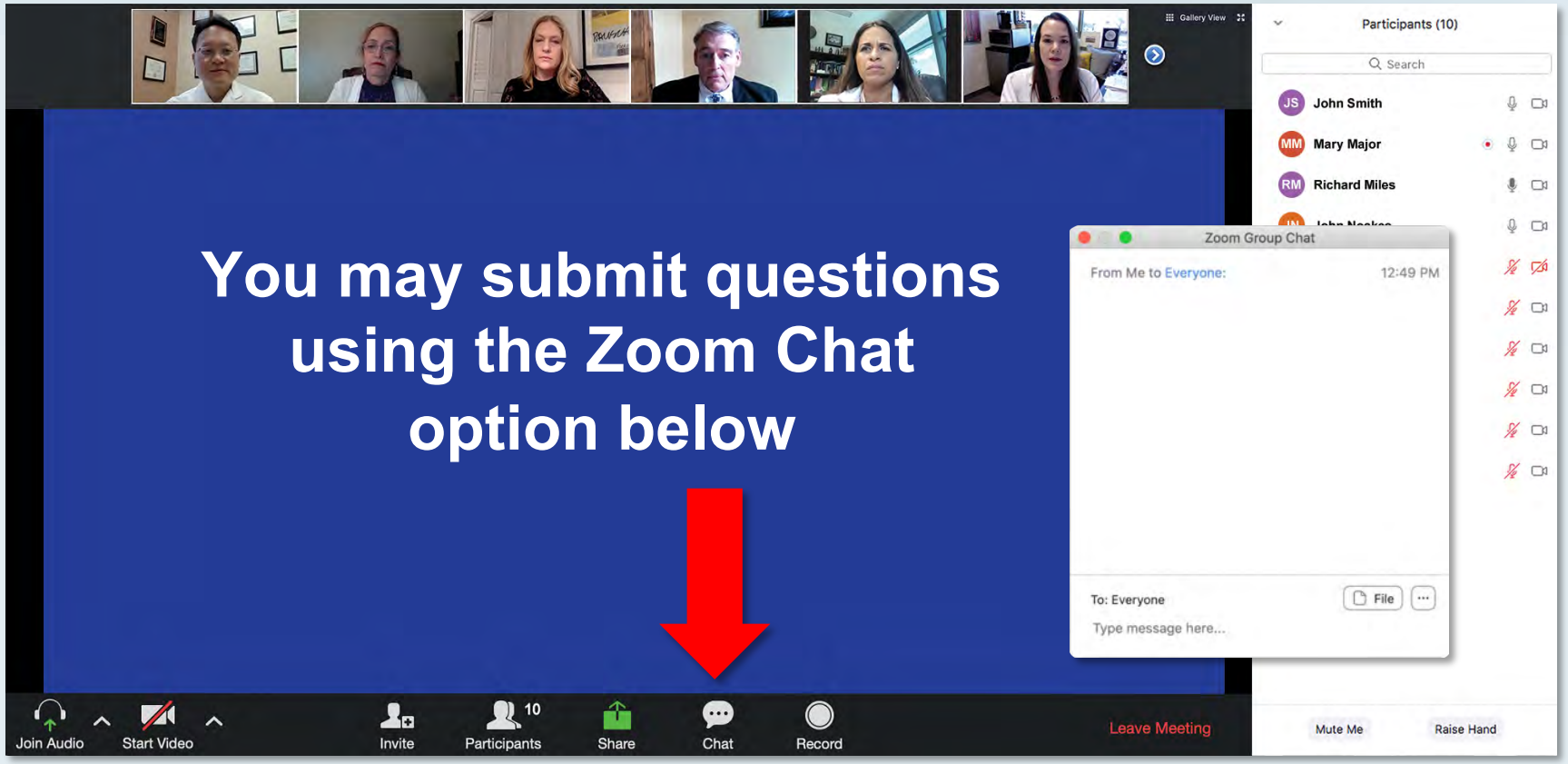
Andrew McKenzie, PhD
Director, Personalized Medicine
Sarah Cannon Research Institute
Nashville, Tennessee

Dr Love and Faculty Encourage You to Ask Questions



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Exploring the Role of Immune Checkpoint Inhibitor Therapy and Other Novel Strategies in Gynecologic Cancers

A Virtual Meet The Professor Series

Starting August 2020

Participating Faculty

Michael J Birrer, MD, PhD
Robert L Coleman, MD
David M O'Malley, MD
Richard T Penson, MD, MRCP
Matthew A Powell, MD
Brian M Slomovitz, MD
Krishnansu S Tewari, MD

Moderator

Neil Love, MD

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RESEARCH TO PRACTICE

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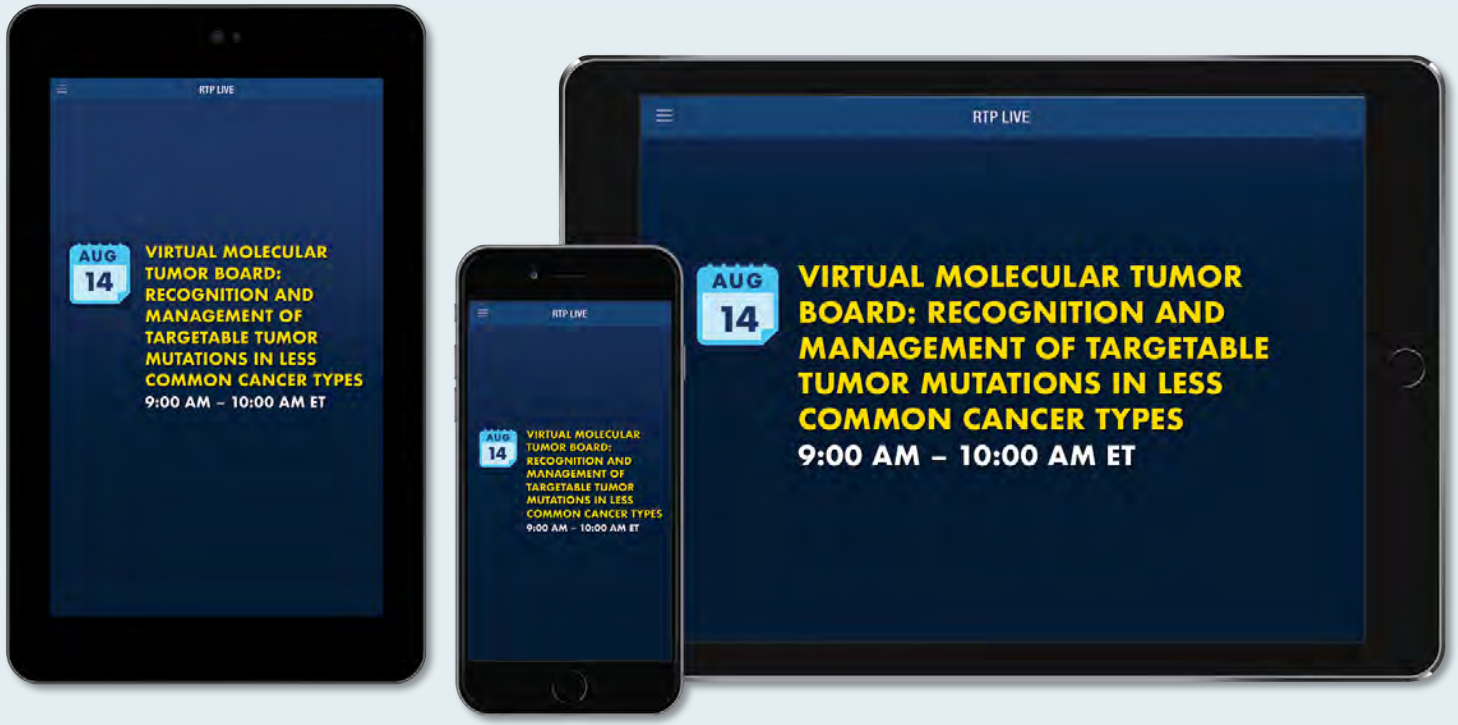

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RTP RESEARCH TO PRACTICE

Community Oncologists

Justin Peter Favaro, MD, PhD
Oncology Specialists of Charlotte
Charlotte, North Carolina

Sulfi Ibrahim, MD
Hematology/Oncology
Reid Health
Richmond, Indiana

Agenda

Part 1: Molecular Tumor Board

Part 2: New Molecular Targets in Thyroid Cancer

Part 3: Targeting the FGFR Signaling Pathway in Cholangiocarcinoma

Part 4: New Options in the Management of GIST Harboring PDGFR Mutations

Part 5: Molecular Tumor Board (Continued)

Agenda

Part 1: Molecular Tumor Board

- Case 1 – Dr Ibrahim: A 77-year-old woman with ER-positive, HER2-negative metastatic breast cancer – ESR, CHEK2 and RET mutations
- Case 2 – Dr Radovich: A 44-year-old woman with metastatic thymoma – MTOR gain-of-function mutation
- Case 3 – Dr McKenzie: A patient with leiomyosarcoma – BRCA germline mutation
- Case 4 – Dr Ibrahim: A patient with bone-only disease

Case Presentation – Dr Ibrahim: A 77-year-old woman with ER-positive, HER2-negative metastatic breast cancer – ESR, CHEK2 and RET mutations

Sulfi Ibrahim, MD

- Stage IIA hormone receptor-positive, HER2 non-amplified, left breast cancer about 7 years ago treated with neoadjuvant chemotherapy followed by a lumpectomy and adjuvant radiation therapy
- Completed 5 years of adjuvant anastrazole and then presented about 2 years later with multiple bone metastases and liver metastasis
- Plasma based NGS obtained and started on palbociclib and letrozole
  - No response to therapy.
- Capecitabine but develops disease progression
- Declining performance status at this and having a discussion on the whether to pursue any further systemic therapy

Questions

- Does something in her genomic profile predict rapid progression through a CDK4/6 inhibitor, with no response, such as the ESR mutation? Should I have used fulvestrant as a partner?
- Is the RET alteration actionable, with a drug like selpercatinib?
- Are there simple guidelines about how to determine which RET alterations are actionable vs not?
- Is the CHEK2 mutation potentially actionable on any clinical trials?

Case Presentation – Dr Ibrahim: A 77-year-old woman with ER-positive, HER2-negative metastatic breast cancer – ESR, CHEK2 and RET mutations

Sulfi Ibrahim, MD

BIOMARKER FINDINGS			ACTIONABILITY	
MSI Status Undetermined				
GENOMIC FINDINGS		MAF %	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
ESR1 -	D538G	2.2%	Fulvestrant 1 ⚠ Anastrozole[1] ⚠ Exemestane[1] ⚠ Letrozole[1]	None
10 Trials see p. 12				
CHEK2 -	I74fs*1	0.12%	None	None
10 Trials see p. 10				
RET -	M918T	4.4%	None	None
10 Trials see p. 14				

Case Presentation – Dr Radovich: A 44-year-old woman with metastatic thymoma – MTOR gain-of-function mutation

- **HISTORY OF PRESENT ILLNESS:**
  - 44-year-old woman with metastatic thymoma.
  - In August 2014, was found to have locally advanced thymoma for which she underwent mediastinal resection. This revealed a 9cm WHO type B1 thymoma. She received postop radiation.
  - In April 2017 she was found to have multiple pleural metastases, and was started on PAC chemotherapy. She later developed progressive disease and was treated with pemetrexed until April 2018.
  - Genomic analysis was performed in April 2018 revealing a gain-of-function mutation in MTOR. She subsequently started everolimus, for which she had disease response for 1 year.
- **PAST MEDICAL HISTORY:** None.
- **FHx:** None.

Case Presentation – Dr Radovich: A 44-year-old woman with metastatic thymoma – MTOR gain-of-function mutation

OTHER ALTERATIONS & BIOMARKERS IDENTIFIED

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See *professional services* section for additional information.

Microsatellite status Cannot Be Determined §

Tumor Mutational Burden Cannot Be Determined §

ERBB4 amplification §

MTOR E1799K

TP53 R248Q

§ Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, MSI or TMB result in this section.

Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).

Case Presentation – Dr McKenzie: A patient with leiomyosarcoma – BRCA germline mutation

- No clinical data submitted
- Clinician was wondering about potential germline involvement

Diagnosis: Leiomyosarcoma | Test Number 1 — Therapy Finder Page

REPORTING		PHYSICIAN
Report Date:	SEP-26-2019	Account:
Receipt Date:	SEP-18-2019	Address
Collection Date:	SEP-17-2019	Additional Recipient: N/A
Specimen:	Blood	
Status:	FINAL	

Complete Tumor Response Map on page 2

Summary of Somatic Alterations & Associated Treatment Options

KEY ✓ Approved in indication — Approved in other indication — ⊗ Lack of response

Alteration	% cfDNA or Amplification	Associated FDA-approved therapies	Clinical trial availability (see page 3)
BRCA2 Splice Site SNV	52.0%	Niraparib, Olaparib, Rucaparib, Talazoparib	Yes

SARAH CANNON

Case Presentation – Dr Ibrahim: A patient with bone-only disease

Sulfi Ibrahim, MD

Questions

- What is the best way to do next-generation sequencing on bone-only disease? Should techniques such as cell transfer – where the tumor material can be aspirated out – be used?
- For a patient who cannot undergo biopsy on the metastasis is it sufficient to do next-generation sequencing on tissue from the primary site? Would there be any added value in evaluating the metastatic site?

Agenda

Part 2: New Molecular Targets in Thyroid Cancer

- Case 5 – Dr Brose: A 39-year-old woman with RAI-refractory papillary thyroid cancer
- Case 6 – Dr Brose: A 69-year-old man with papillary thyroid cancer
- Case 7 – Dr Brose: An 18-year-old woman with locally advanced medullary thyroid cancer
- Case 8 – Dr Ibrahim: A 77-year-old frail woman with metastatic papillary thyroid cancer
- Case 9 – Dr Radovich: A 57-year-old man with metastatic thyroid cancer – RET M918T gain-of-function mutation
- Case 10 – Dr Ibrahim: A 50-year-old woman with metastatic medullary thyroid cancer

New Molecular Targets in Thyroid Cancer

Marcia S Brose, MD, PhD
Professor
Director, Center for Rare Cancers and Personalized Therapy
Abramson Cancer Center
Department of Medicine, Division of Hematology/Oncology
Department of Otorhinolaryngology: Head and Neck Surgery
Philadelphia, Pennsylvania

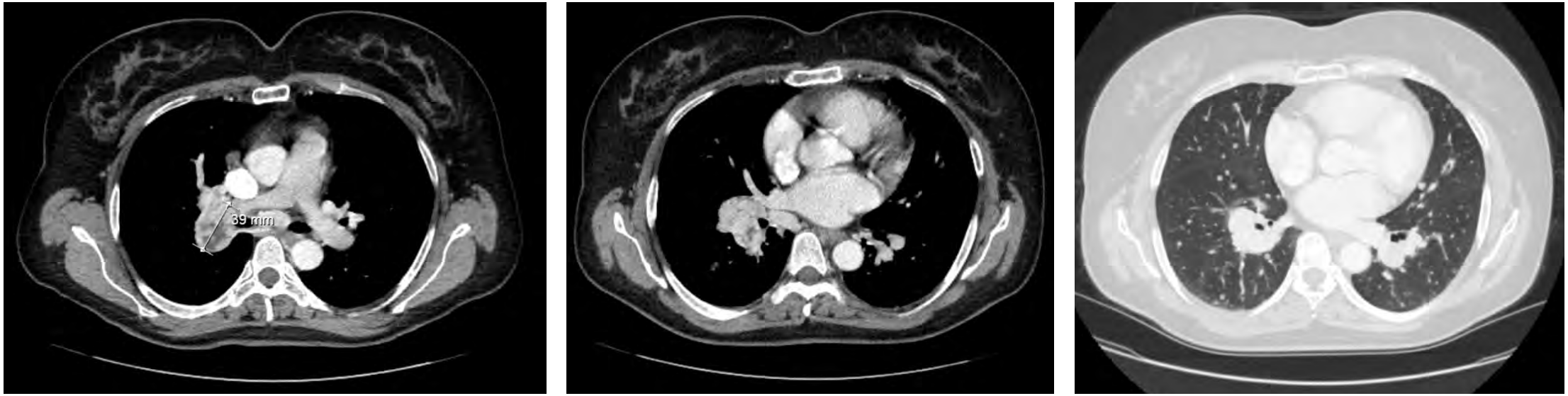
Friday, August 14, 2020

Case Presentation – Dr Brose: A 39-year-old woman with RAI-refractory papillary thyroid cancer

- 39 y.o diagnosed with a papillary thyroid carcinoma, who received 104 mC of I-131 in November 2006.
- May 2009 due to rising thyroglobulin levels, she received 155 mCi of I-131. She had diffuse uptake in the lungs bilaterally.
- On follow up CT of the neck, she was found to have a lesion at C2. She received 3000 cGy to C2 spine from April through May 10, 2010.
- On December 6, 2010 she received dosimetry 312 mCi and her post-therapy scan showed uptake within the bilateral lung metastases as well as subtle uptake within the known C2.

Case Presentation – Dr Brose: A 39-year-old woman with RAI-refractory papillary thyroid cancer (cont)

8/2018 Referral to Oncology



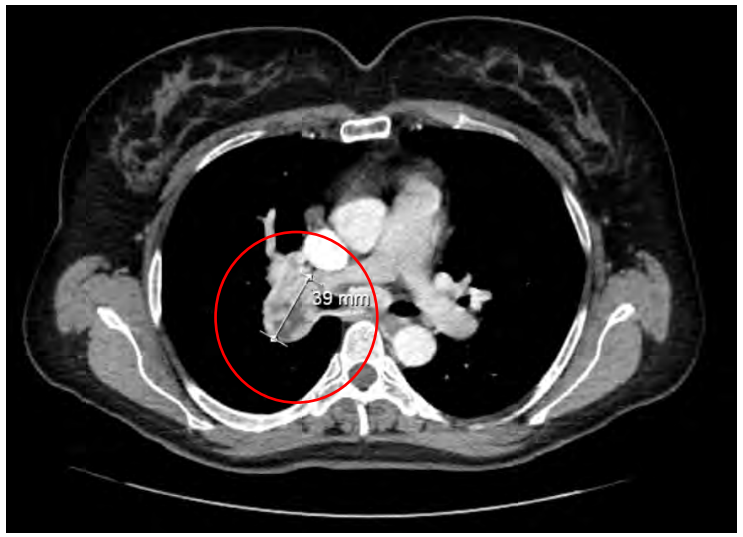
- From 2010 to 2018 she had multiple recurrences in her neck and progression of metastatic disease in the lungs and hilar lymph nodes.

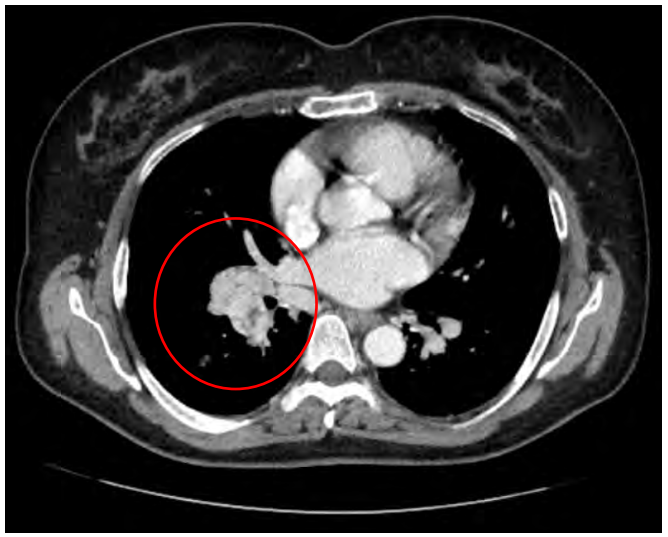
Case Presentation – Dr Brose: A 39-year-old woman with RAI-refractory papillary thyroid cancer – Systemic treatment options

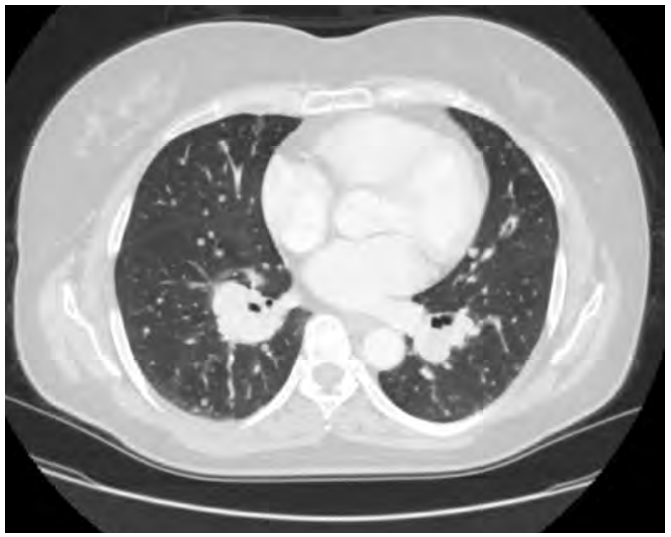
- Systemic Treatment Options for her in May 2018 Included:
  - Sorafenib or Lenvatinib multikinase inhibitors targeting primarily VEGFR among others
  - Vemurafenib or Dabrafenib for patients whose tumors harbor BRAF V600E mutation (up to 50% of patients with papillary histology)
- Prognosis may also be affected by the presence of other mutation
- Genetic analysis was obtained for both point mutations and gene fusions.
  - ETV6-TRK gene fusion identified – Patient was enrolled in clinical trial for larotrectinib

Case Presentation – Dr Brose: A 39-year-old woman with RAI-refractory papillary thyroid cancer – ETV6-TRK fusion

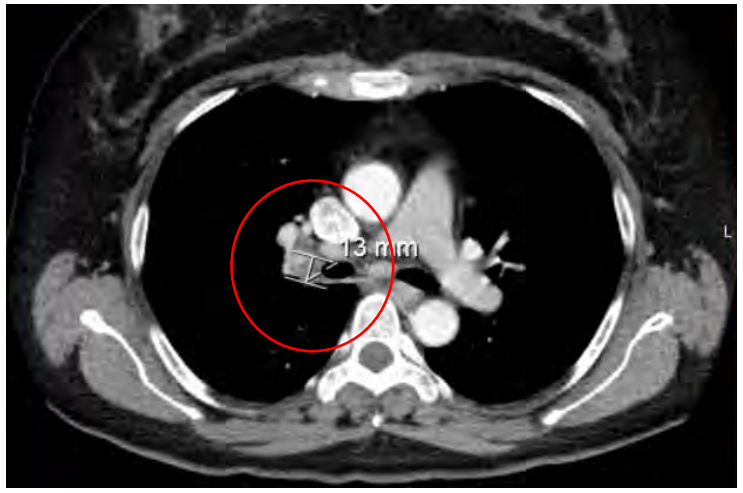
8/2018

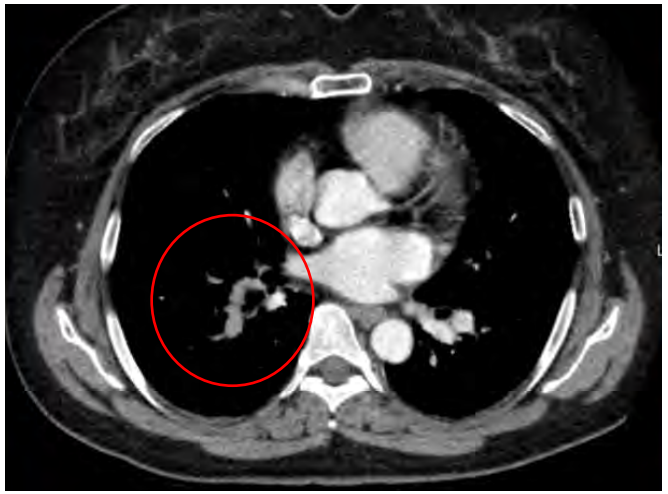


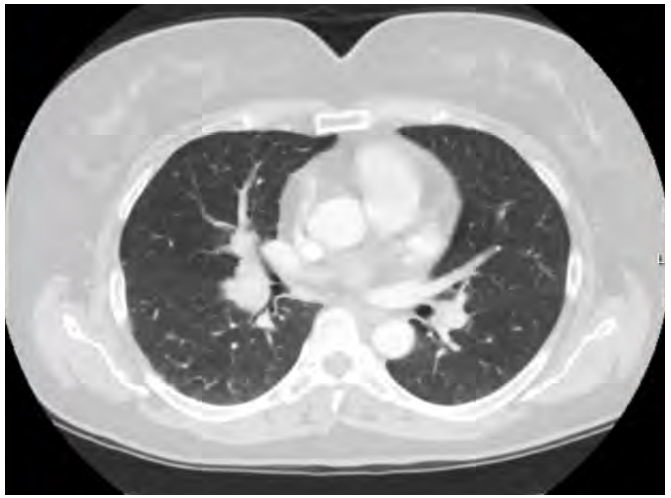




3/2020







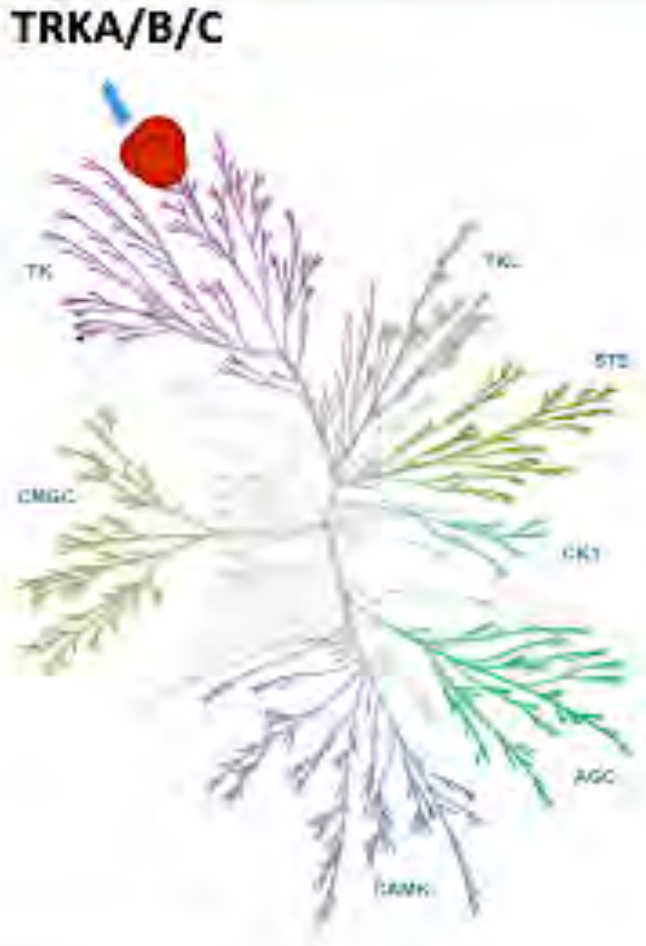
So. . . What Testing Method for *TRK or RET* Fusions Is Best?

Method	Pros	Cons	Comments
IHC	Potential local implementation	Significant FN, FP Requires dedicated tissue and limits multi-target testing	May be used as screening diagnostic, but confirmation of *NTRK* gene fusion is recommended
FISH	Potential local implementation	Interpretation can be challenging Significant FN, FP Requires dedicated tissue and limits multi-target testing	In order to detect fusions at multiple locations, such as the 3 *NTRK* genes, multiple FISH tests would need to be run
RT-PCR	Fast, relatively inexpensive	No novel fusion partner detection May or may not be multiplexed with other fusion targets	Designed to identify only known translocation partners and breakpoints
NGS	Sensitive, specific molecular testing Simultaneously get mutation information for multiple targets	Expensive and longer turn-around time	RNA-NGS testing may be preferable to DNA-NGS testing because it identifies actively transcribed chimeric fusions

Courtesy of Marcia Brose, MD, PhD

Larotrectinib for TRK Fusion Cancers

- Larotrectinib is a highly potent TRK inhibitor against TRKA, TRKB, TRKC (5–11 nM IC_{50} in cellular assays)[1]
- Highly selective, with little or no interaction with other kinase and non-kinase targets
  - limited inhibition of other kinases and >1,000x selective over other off targets[1]
- Larotrectinib is highly active against TRK fusion cancer with durable responses in both children and adults
- TRK fusions are extimated to be present in 5-25% of recurrent DTC

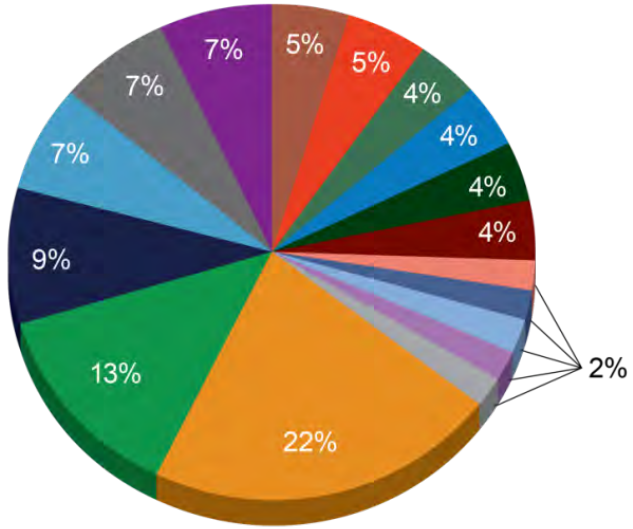


References 1. Doebele et al. Cancer Discov. 2015 Dec;5(12):1049-57. 2. Chartier et al. 2012 KinomeRender: a stand-alone and Web-accessible tool to annotate the human protein kinome tree. PeerJ 1:e126

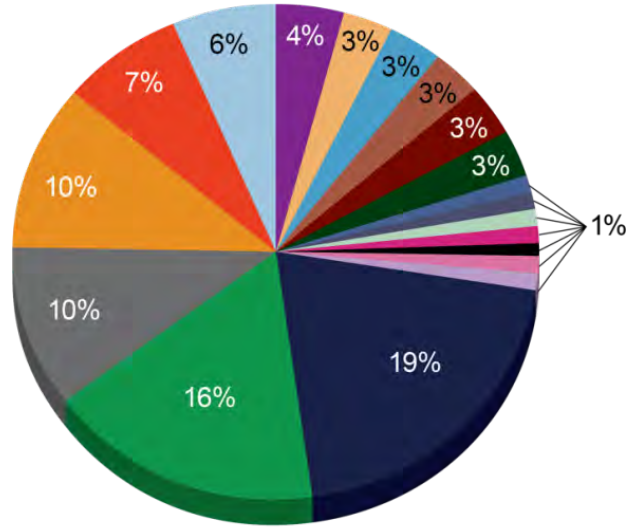
Courtesy of Marcia Brose, MD, PhD

Diversity of TRK Fusion Cancers Treated With Larotrectinib[1,2]

Primary Dataset (n = 55)



Supplementary Dataset (n = 67)



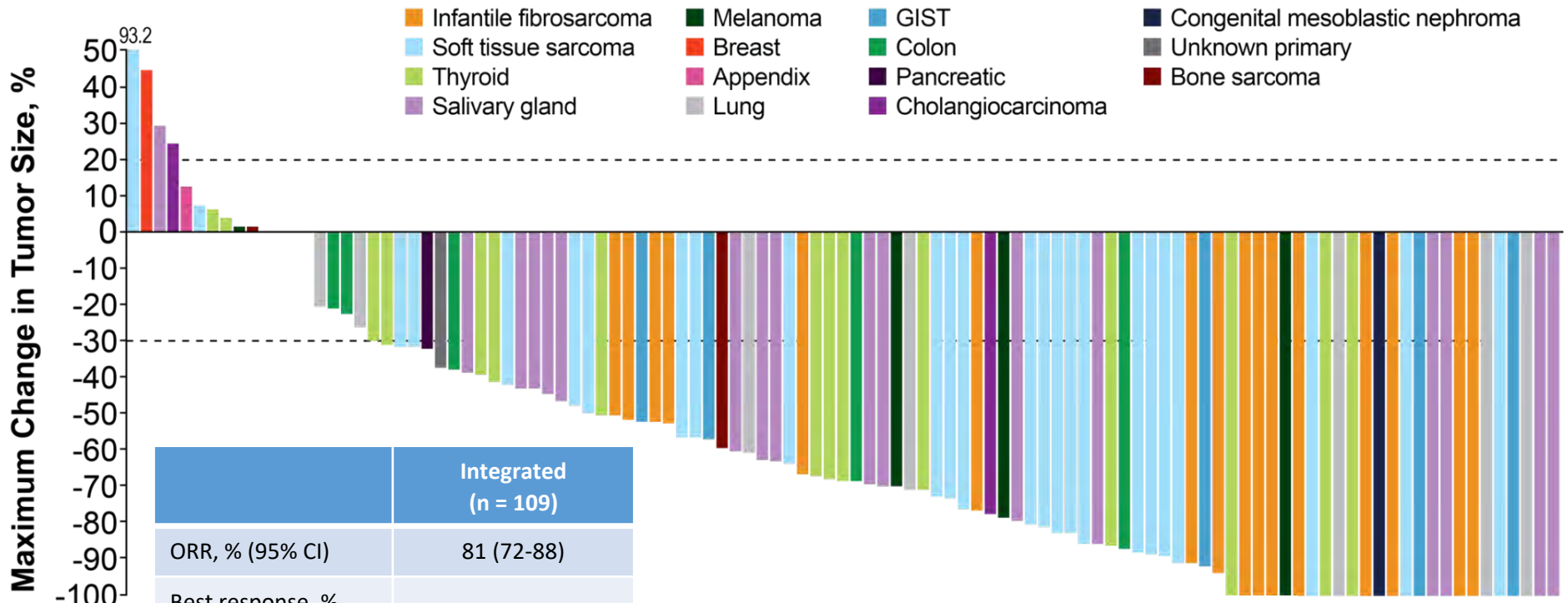
Subtypes of STS

- Appendix
- Bone sarcoma
- Breast
- Cholangiocarcinoma
- Colon
- Congenital mesoblastic nephroma
- Gastrointestinal stromal tumor
- Infantile fibrosarcoma
- Lung
- Melanoma
- Pancreas
- Salivary gland
- Thyroid
- Unknown primary
- Infantile myofibromatosis
- Inflammatory myofibroblastic kidney tumor
- Inflammatory myofibroblastic tumor
- Lipofibromatosis
- Myopericytoma
- Peripheral nerve sheath
- Sarcoma NOS
- Small round-cell sarcoma
- Spindle-cell sarcoma
- Stromal sarcoma
- Not determined

1. Drilon A et al. *New Engl J Med.* 2018;378:731-739. 2. Lanssen U et al. ESMO 2018. Abstract 409O.

Courtesy of Marcia Brose, MD, PhD

Integrated Dataset: Larotrectinib Is Efficacious Regardless of Tumor Type[1]



	Integrated (n = 109)
ORR, % (95% CI)	81 (72-88)
Best response, %	
PR	63
CR	17

Investigator response assessments, as of July 30, 2018

1. Drilon A et al. *New Engl J Med.* 2018;378:731-739. 2. Lanssen U et al. ESMO 2018. Abstract 409O.

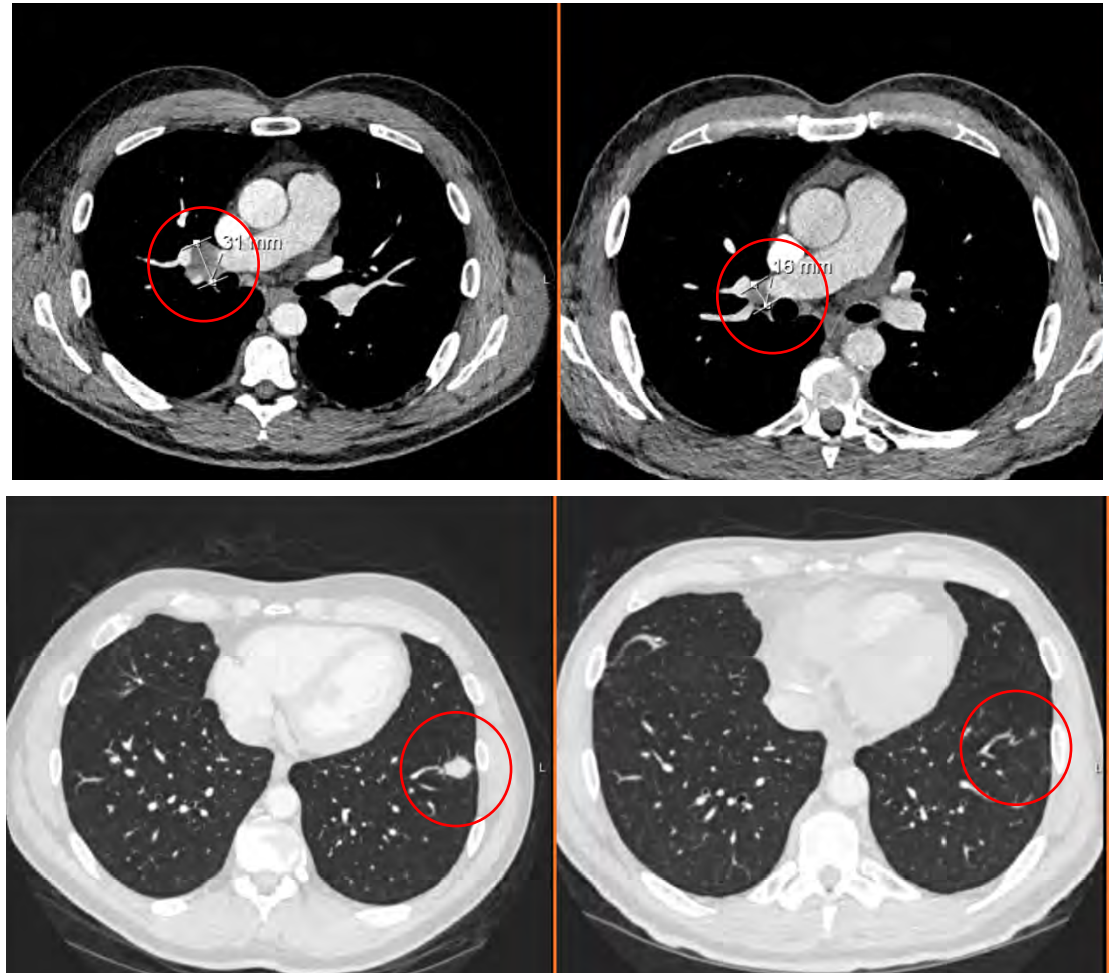
1. Lanssen U et al. ESMO 2018. Abstract 409O.

Courtesy of Marcia Brose, MD, PhD

Case Presentation – Dr Brose: A 69-year-old man with papillary thyroid cancer

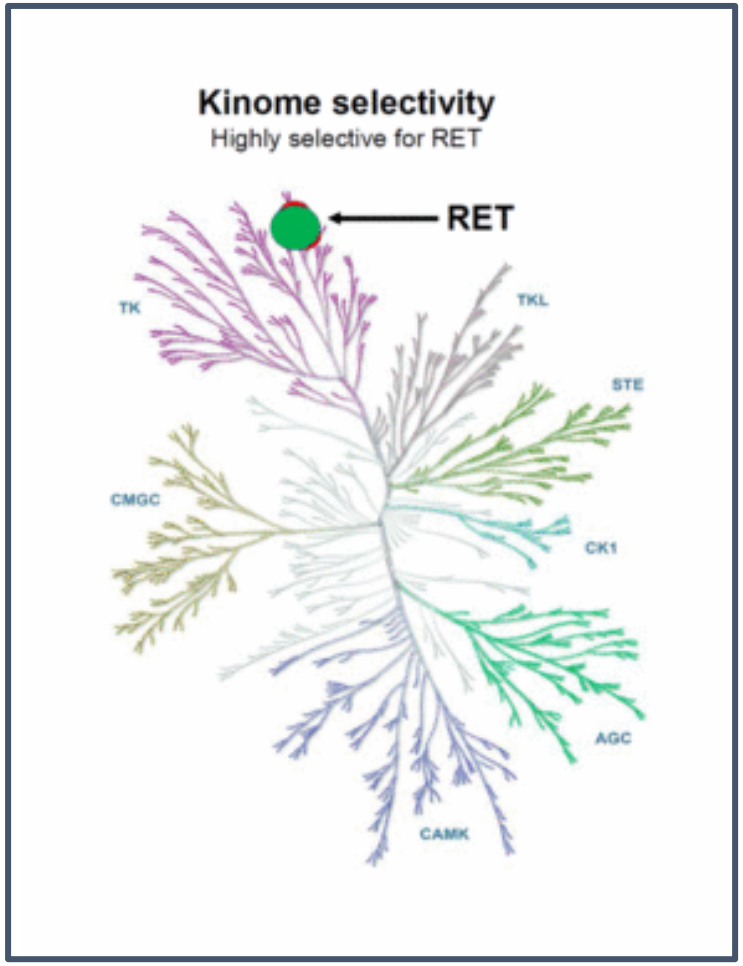
- 69-year-old man who underwent a thyroidectomy February of 2000 with pathology showing multifocal left papillary thyroid carcinoma. From 2000 to 2005 he had multiple rounds of RAI but was deemed RAI refractory in 2005.
- From 2001 to 2017 he was followed for progressing disease in his lungs (for which he underwent a wedge resection) and a metastatic lesion in C7 which was treated with XRT.
- On May 15, 2017 showed increased size of multiple hilar and pulmonary metastatic nodules, most concerning for disease progression. He was referred to Medical Oncology
- As part of his workup, in addition to staging studies, his tumor from his most recent lung resection revealed a molecular profile for both point mutations and gene fusions (DNA and RNA based NGS) was obtained and detected an NCOA4/RET fusion. He was started on Selpercatinib as part of LIBRETTO-001 clinical trial in 3/2019

Case Presentation – Dr Brose: A 69-year-old man with papillary thyroid cancer – NCOA4/RET Fusion PTC treated with selpercatinib from 3/2019 to 7/2020

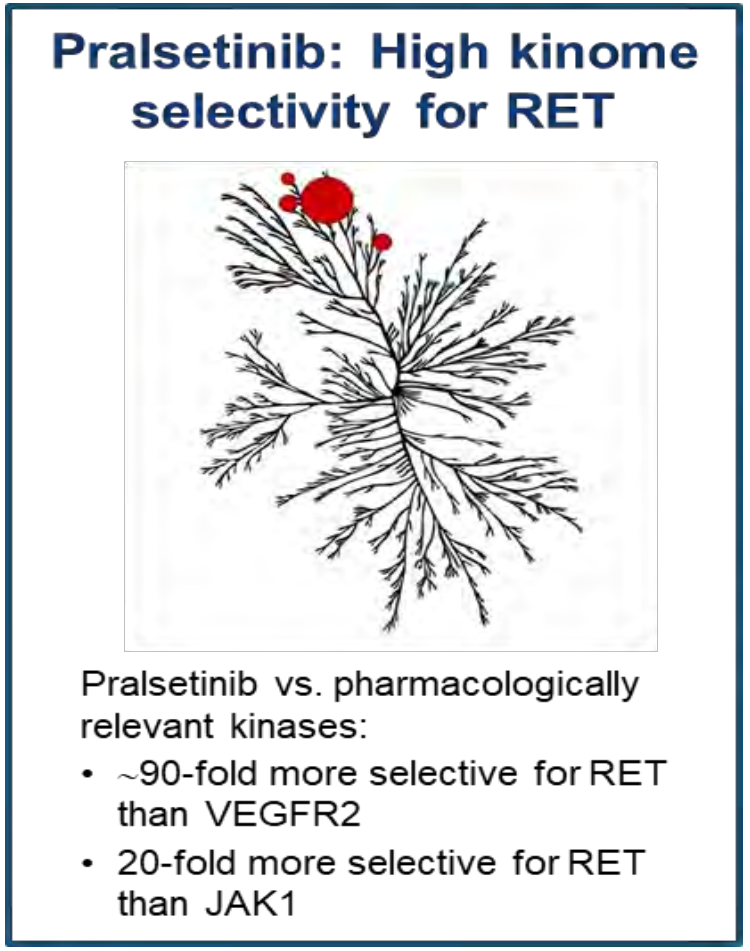


New Selective RET inhibitors: selpercatinib (Loxo-292) and pralsetinib (BLU-667)

Selpercatinib

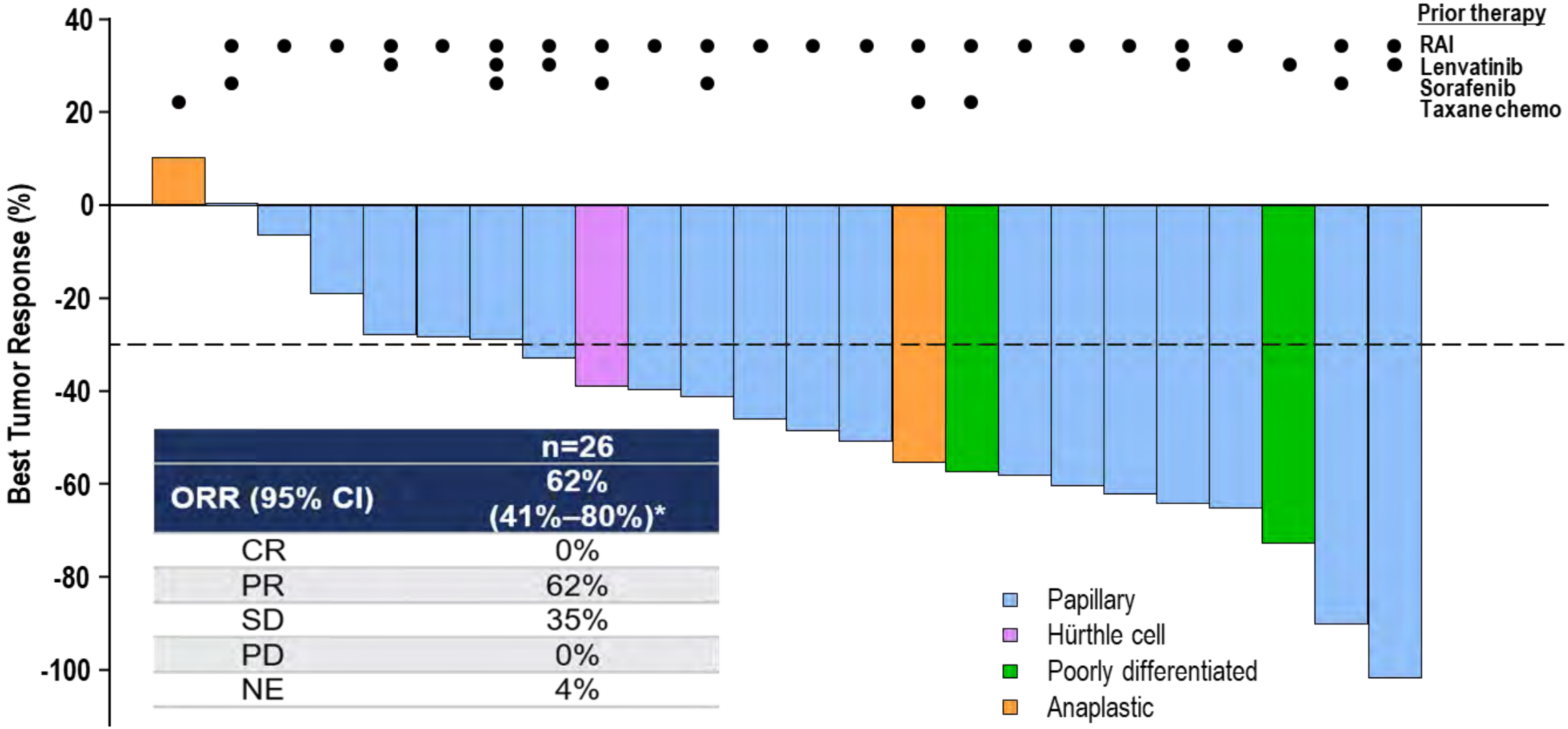


Pralsetinib



Courtesy of Marcia Brose, MD, PhD

Activity of selpercatinib: *RET* fusion-positive thyroid cancer (n=26)



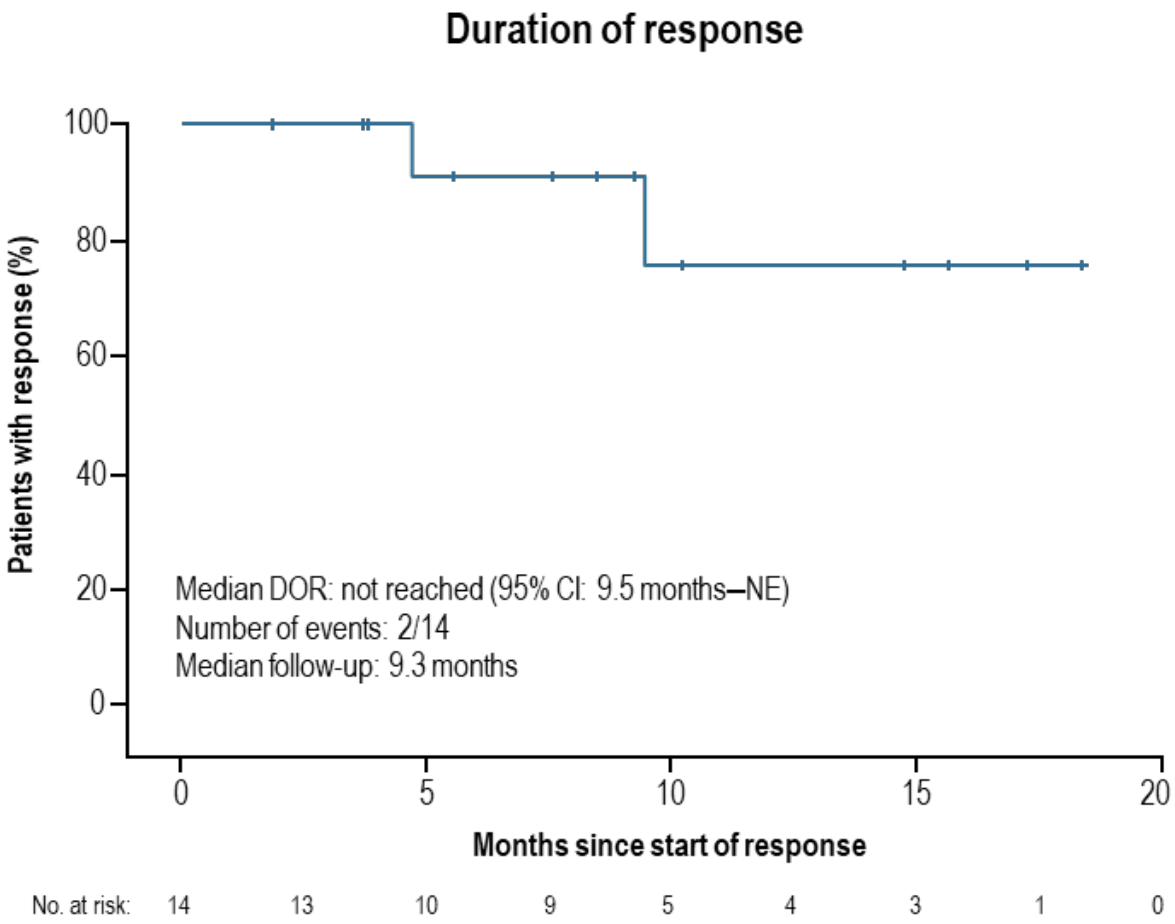
	n=26
ORR (95% CI)	62% (41%–80%)*
CR	0%
PR	62%
SD	35%
PD	0%
NE	4%

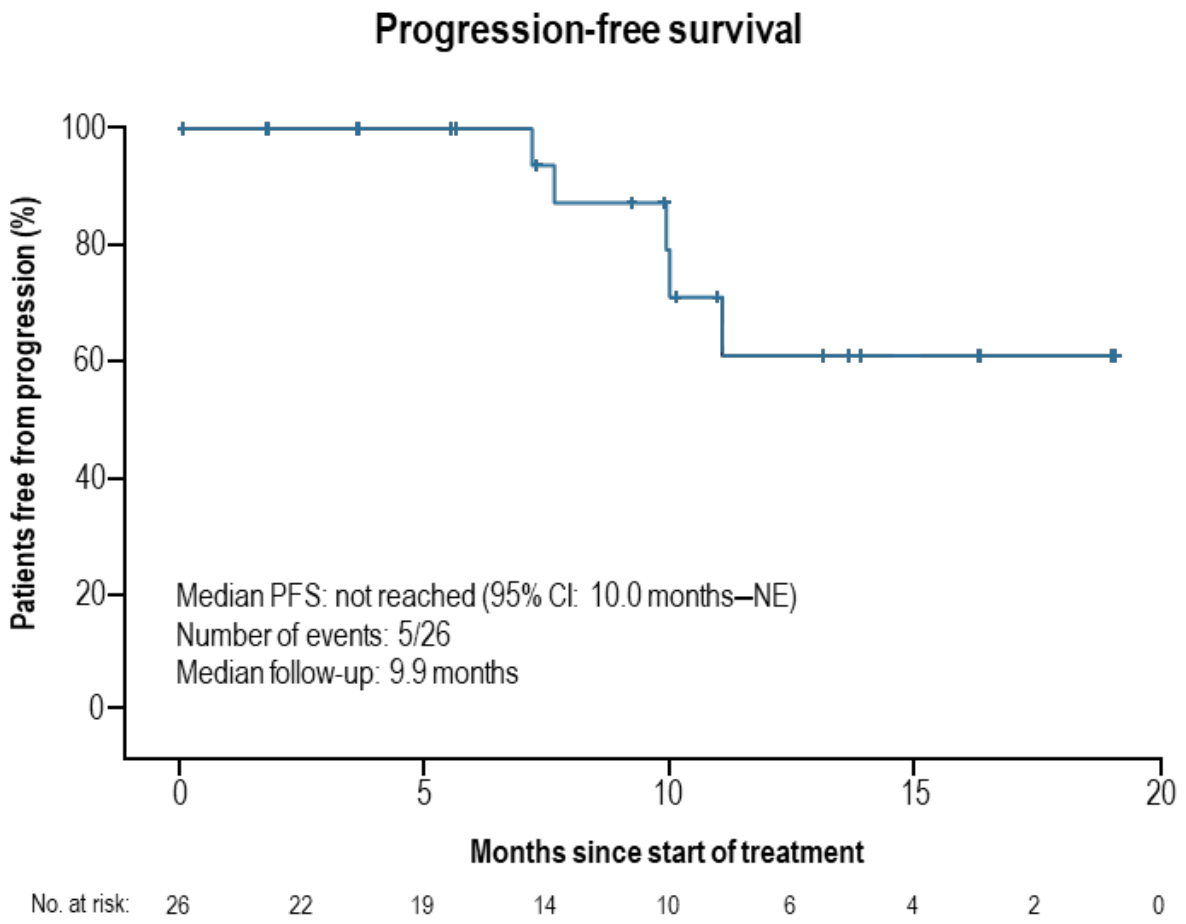
Investigator response assessments as of June 17, 2019. Total % may be different than the sum of the individual due to rounding.
Data include patients with at least one evaluable post-baseline assessment and those who discontinued therapy prior to any post-baseline imaging assessment. 2 patients not shown in waterfall plot: 1 did not have measurable disease at baseline, and 1 deemed not evaluable on study by the investigator. *Includes 2 unconfirmed PRs awaiting confirmatory response assessments. NE—not evaluable, n=1 patient deemed not evaluable on study by the investigator; RAI–radioactive iodine.

BARCELONA 2019 ESMO congress

Courtesy of Marcia Brose, MD, PhD

Durability of selpercatinib benefit: *RET* fusion-positive thyroid cancer





- Of 5 patients that progressed, 5 continued treatment post-progression, for 0.4–8.5+ months

BARCELONA 2019 ESMO congress

Data cutoff: June 17, 2019. No shading to show 95% confidence band due to a very low number of events.

Courtesy of Marcia Brose, MD, PhD

Summary: RAI refractory DTC 2019

- As all patients will ultimately progress on sorafenib and lenvatinib, both agents will be needed and will be used sequentially, as well as additional strategies.
- Molecular testing is recommended prior to treatment with systemic therapies for thyroid cancer. Testing should include detection of point mutations and gene fusions.
- Larotrectinib is FDA and EMA approved for patients with TRK/Fusion cancers
- Selpercatinib (Loxo-292, FDA approved) and pralsetinib (BLU-667) second generation RET inhibitors may have a role for RET/PTC DTC.
- Vemurafenib and dabrafenib are both shown to have single agent activity for patients with BRAF V600E point mutations. While no large phase III studies have been conducted, these should be considered for second line treatment following sorafenib and lenvatinib in patients with BRAFV600E mutations

Courtesy of Marcia Brose, MD, PhD

Medullary Thyroid Cancer: Rationale for RET as a Therapeutic Target

- RET is activated by mutations in ~50% of cases (>60% of progressive cases presenting for clinical trials)
- Hereditary RET mutations associated with familial MTC and MEN 2B are found in 25-35% of the cases and should be screened for in all patients
- Somatic mutation of RET associated with poor prognosis in patients with metastatic MTC
- Limited expression outside the thyroid provides potentially high therapeutic index

Courtesy of Marcia Brose, MD, PhD

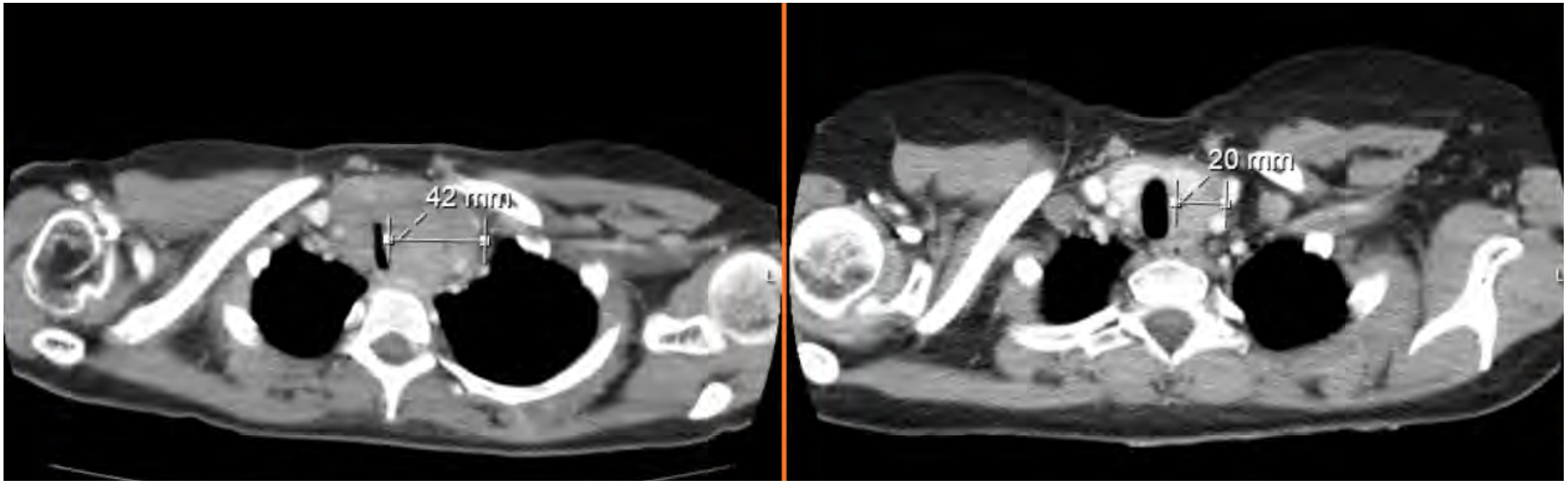
Case Presentation – Dr Brose: An 18-year-old woman with locally advanced medullary thyroid cancer

- 18 y.o. with medullary thyroid cancer with significant mediastinal invasion. She had an US guided bx of thyroid mass. Cytology findings consistent with medullary thyroid carcinoma. On imaging her trachea was narrowed by 85%. She states that she first found the lump around January or February of 2019.
- She ultimately underwent an FNA of the nodule and cytology on 5/30/2019 as well as a core biopsy of the left thyroid revealed medullary thyroid carcinoma
- She underwent genetic screening for MEN2B and was negative for hereditary RET mutation
- Somatic genetic testing for point mutations and gene fusions by DNA and RNA based NGS testing revealed RET p.L629_D631delinsH c.1886_1891delTGTGCG or inframe deletion.
- She was started on treatment with pralsetinib on 08/02/19. Symptoms of mild dysphagia and shortness of breath on exertion as well as voice changes were reversed in one month.

Case Presentation – Dr Brose: An 18-year-old woman with locally advanced medullary thyroid cancer – MTC RET del treated with pralsetinib

August 2019

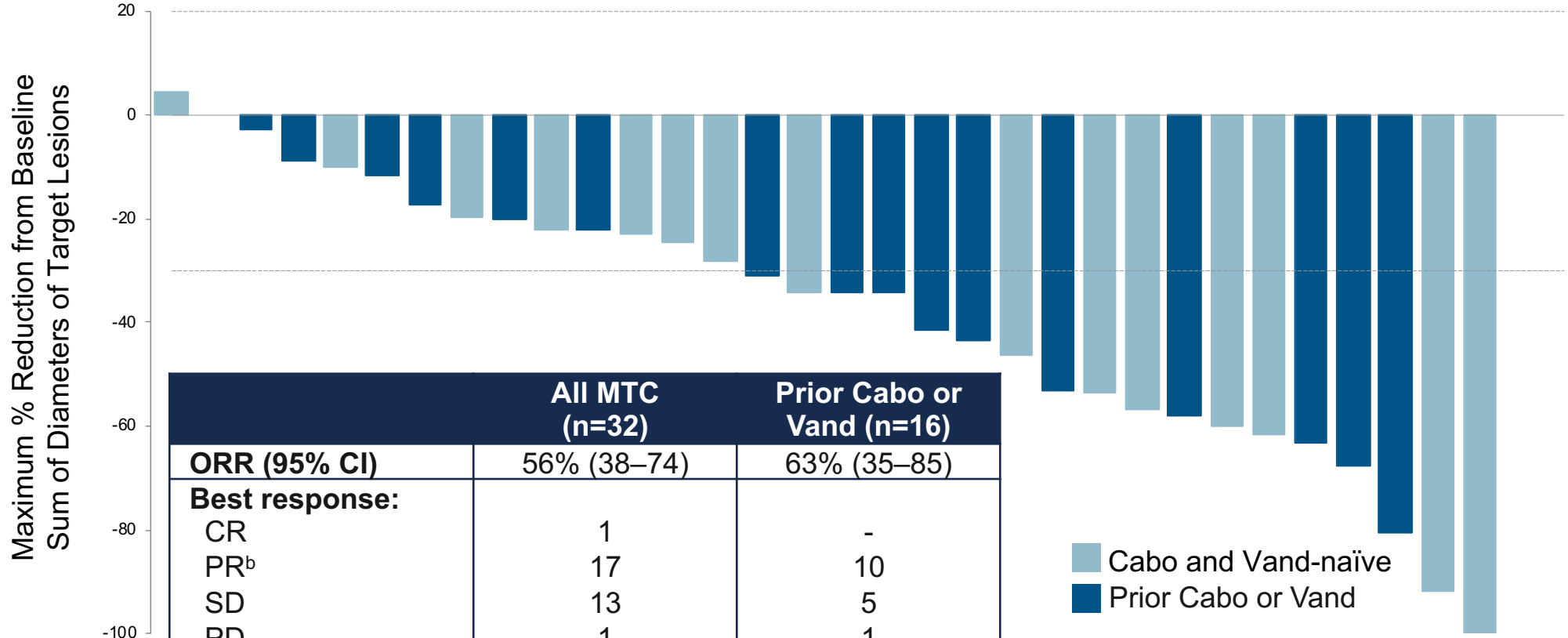
May 2019



ARROW (BLU-667, PRALSETINIB): ADVANCED RET-MUTATED MTC

Antitumor Activity: Tumor Response

RET-mutated MTC (400 mg QD starting dose)[a]

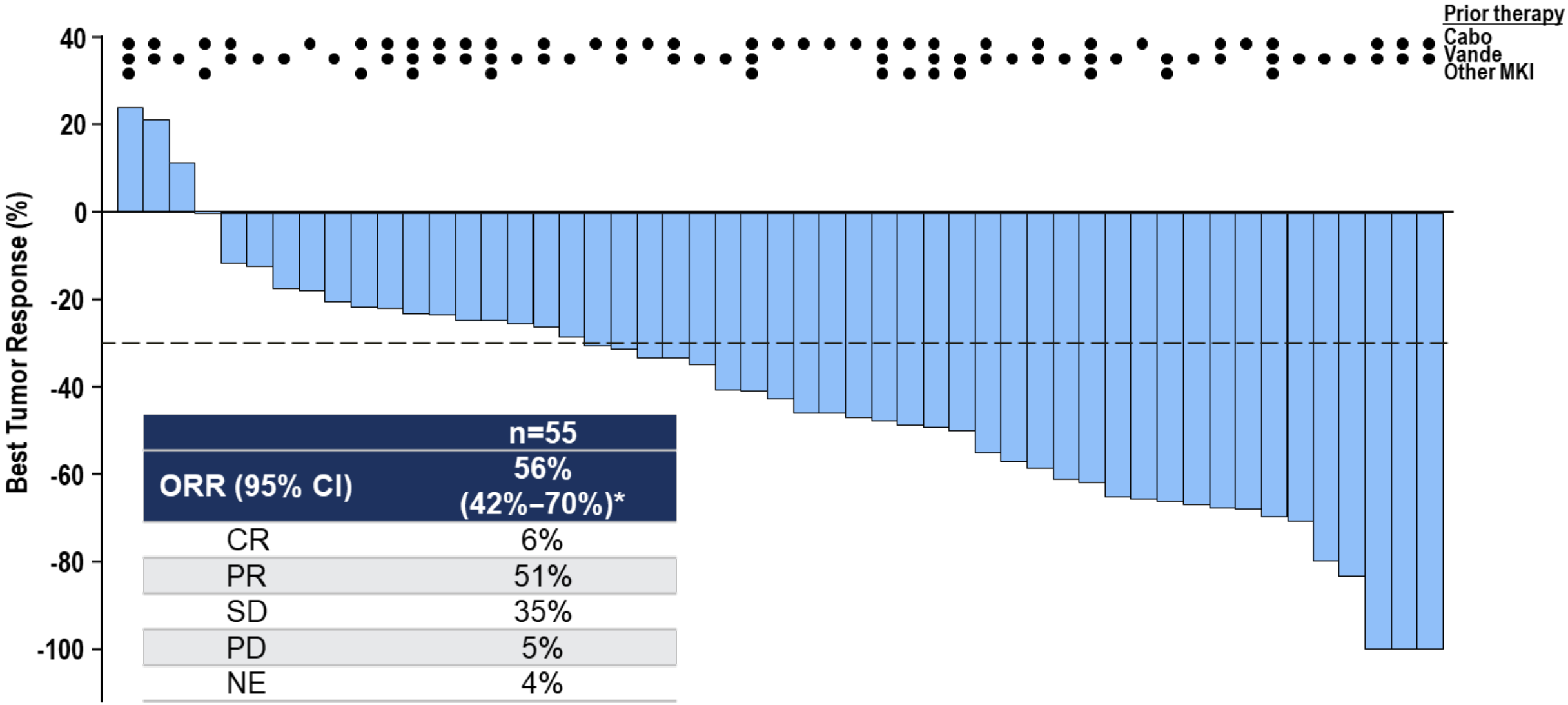


	All MTC (n=32)	Prior Cabo or Vand (n=16)
ORR (95% CI)	56% (38–74)	63% (35–85)
Best response:		
CR	1	-
PR[b]	17	10
SD	13	5
PD	1	1
DCR (95% CI)	97% (84–100)	94% (70–100)
Tumor shrinkage	94%	100%

Courtesy of Marcia Brose, MD, PhD

[a]Data for response-evaluable patients enrolled by 14 Nov 2019. Response-evaluable population includes patients with measurable disease and ≥1 evaluable post-treatment disease assessment. [b]Two patients (one previously received vand, one cabo/vand-naïve) are pending confirmation of response. Cabo, cabozantinib; DCR, disease control rate (best response of SD or better); ORR, overall response rate; vand, vandetanib.

Activity of selpercatinib: *RET*-mutant MTC PAS (n=55)



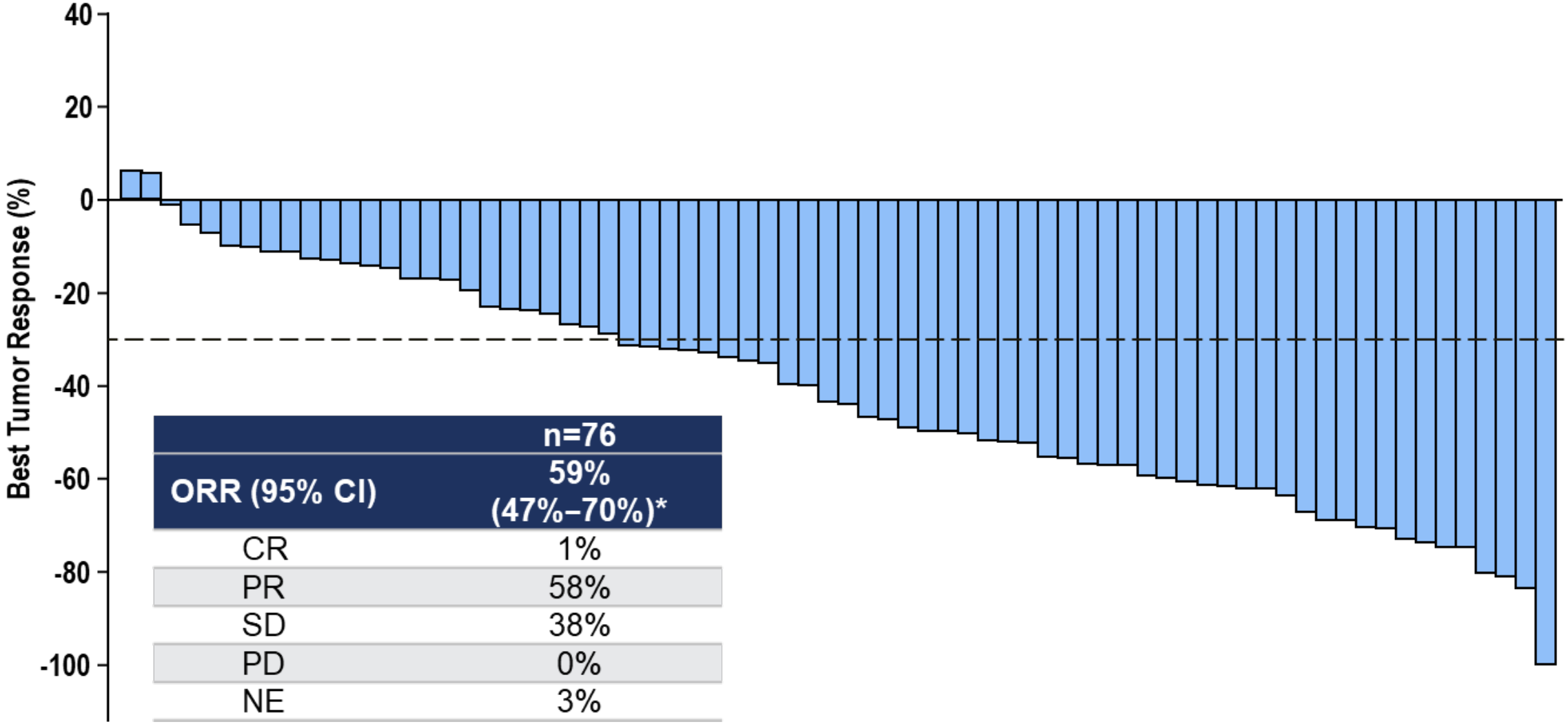
	n=55
ORR (95% CI)	56% (42%–70%)*
CR	6%
PR	51%
SD	35%
PD	5%
NE	4%

Courtesy of Marcia Brose, MD, PhD

Investigator response assessments as of June 17, 2019. Total % may be different than the sum of the individual due to rounding.

4 patients not shown in waterfall plot: 2 discontinued prior to any post-baseline imaging assessments, and 2 did not have measurable disease at baseline. *Includes 2 unconfirmed PRs awaiting confirmatory response assessments. Cabo–cabozantinib; NE—not evaluable, n=2 patients who discontinued prior to any post-baseline imaging assessments. Vande–vandetanib.

Activity of selpercatinib: cabozantinib/vandetanib-naïve *RET*-mutant MTC (n=76)



	n=76
ORR (95% CI)	59% (47%–70%)*
CR	1%
PR	58%
SD	38%
PD	0%
NE	3%

Courtesy of Marcia Brose, MD, PhD

Investigator response assessments as of June 17, 2019. Total % may be different than the sum of the individual due to rounding.
Data include patients with at least one evaluable post-baseline imaging assessment and those who discontinued therapy prior to any post-baseline imaging assessment. 4 patients not shown in waterfall plot: 2 patients discontinued prior to any post-baseline imaging assessments and 2 did not have measurable disease at baseline. *Includes 9 unconfirmed PRs awaiting confirmatory response assessments. NE—not evaluable, n=2 patients who discontinued prior to any post-baseline imaging assessments.

Summary Targeted Therapy for MTC

- Currently there are two approved FDA drugs for MTC, vandetanib and cabozantinib

- New Highly Specific RET inhibitors are in clinical trials and may provide strong responses with lesser toxicity which may change the treatment landscape for patients with MTC who are in need of systemic therapy.

Courtesy of Marcia Brose, MD, PhD

Case Presentation – Dr Ibrahim: A 77-year-old frail woman with metastatic papillary thyroid cancer – CAD

Sulfi Ibrahim, MD

- Papillary thyroid cancer about 3-4 years ago treated with thyroidectomy
- Recently, she developed biopsy-proven metastatic disease in the lungs, bilaterally
- Radioactive iodine therapy, but progressive disease after a few doses

Questions

- Lenvatinib would be the standard of care TKI for differentiated thyroid cancer, but it does have some cardiac toxicity. Should I consider lenvatinib for her?
- Should I obtain next-generation sequencing looking, for example, for a BRAF alteration? And if I do find a BRAF alteration, would it be better to start with BRAF-directed therapy or lenvatinib? If she does have BRAF-positive disease, what would be the optimal way to target that? Would that be combination BRAF/MEK inhibitor therapy or single-agent BRAF-directed therapy?
- What is the probability of finding a RET fusion alteration in a woman with differentiated thyroid cancer?

Case Presentation – Dr Radovich: A 57-year-old man with metastatic thyroid cancer – RET M918T gain-of-function mutation

- **HISTORY OF PRESENT ILLNESS:**
  - 57 year old male with metastatic thyroid cancer.
  - Initially underwent a thyroidectomy and central neck dissection. More recently he presented with extensive mediastinal lymphadenopathy with additional recurrent cervical nodes and at least one pulmonary nodule.
  - Was started on vandetanib in August 2019 and remains on this to-date.
  - Patient underwent genomic sequencing in October 2019 and was found to have a RET M918T gain-of-function mutation with a plan for selpercatinib on progression.

Case Presentation – Dr Radovich: A 57-year-old man with metastatic thyroid cancer – RET M918T gain-of-function mutation

OTHER ALTERATIONS & BIOMARKERS IDENTIFIED

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See *professional services* section for additional information.

Microsatellite status MS-Stable §

Tumor Mutational Burden 5 Muts/Mb §

RET M918T

§ Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, BRCA1/2 alterations, LOH, MSI, or TMB results in this section.

Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).

Case Presentation – Dr McKenzie: A 73-year-old man with metastatic medullary thyroid cancer – RET mutation

- 73yr Male
- Diagnosed 2009 with stage IV medullary thyroid cancer (MTC)
  - 5/2009 Total thyroidectomy and lymph node resection
  - 2/2010 Supraclavicular lymph nodes removed and metastatic
  - 5/2011 Neck lymph nodes removed - positive for metastatic MTC
  - 6/2013 4.6 cm Supraclavicular mass s/p left neck dissection and upper spinal accessory LN excision. Level V node positive for metastatic MTC
  - 8/2014 Removal of 2 metastatic lesions in the mediastinum - positive for metastatic MTC
  - Recurrence in mediastinal mass s/p right posterior thoractomy for resection by Dr. Sommers 3/2015 followed by XRT to the chest 6/2015
  - Liver and T9 metastases s/p 6 surgical tumor resections
  - Molecular testing positive for RET M918T

Case Presentation – Dr McKenzie: A 73-year-old man with metastatic medullary thyroid cancer – RET mutation (cont)

TUMOR TYPE: THYROID MEDULLARY CARCINOMA

Genomic Alteration Identified†

RET M918T

"On a clinical trial LOXO292 (selpercatinib). Since starting clinical trial in 7/21/2019 his calcitonin has normalized, CEA has improved substantially from 270 range to 90 range"
– Jul 2020

Table 10 **Mutations used to Identify and Enroll Patients with *RET*-Mutant MTC in LIBRETTO-001**

RET Mutation Type[1]	Previously Treated (n = 55)	Cabozantinib/ Vandetanib Naïve (n = 88)	Total (n = 143)
M918T	33	49	82
Extracellular cysteine mutation[2]	7	20	27
V804M or V804L	5[4]	6	11
Other[3]	10	13	23

[1] Somatic or germline mutations; protein change.
[2] Extracellular cysteine mutations involving cysteine residues 609, 611, 618, 620, 630, and 634
[3] Other included: K666N (1), D631_L633delinsV (2), D631_L633delinsE (5), D378_G385delinsE (1), D898_E901del (2), A883F (4), E632_L633del (4), L790F (2), T636_V637insCRT(1), D898_E901del + D903_S904delinsEP (1)
[4] One patient also had a M918T mutation

Table 11 **Efficacy Results in LIBRETTO-001 (*RET*-Mutant MTC Previously Treated with Cabozantinib or Vandetanib)**

	RETEVMO (n = 55)
Overall Response Rate[1] (95% CI)	69% (55%, 81%)
Complete response	9%
Partial response	60%
Duration of Response	
Median in months (95% CI)	NE (19.1, NE)
% with ≥ 6 months[2]	76

Case Presentation – Dr Ibrahim: A 50-year-old woman with metastatic medullary thyroid cancer

Sulfi Ibrahim, MD

- Metastatic medullary thyroid cancer, involving the lung, liver and bone
- Initially seen at a tertiary care center and started on sorafenib, with response
  - Plantar/palmar erythrodysesthesia, managed with a dose reduction
- Subsequently developed disease progression
- Cabozantinib
  - Difficulty tolerating, even with dose reduction due to plantar/palmar erythrodysesthesia, fatigue, and mucositis
- Ultimately passed away from her disease
  - Remembered her vividly because she was still relatively young and motivated to try further therapy

Questions

- If you were to see a patient with metastatic medullary thyroid cancer, would selpercatinib automatically be the front-line therapy you would be suggest?
- Is there any role for next-generation sequencing in patients with metastatic medullary thyroid cancer?
- Are there any particular findings in a patient with metastatic medullary thyroid cancer that may direct you towards any other systemic therapy rather than selpercatinib?

Agenda

Part 3: Targeting the FGFR Signaling Pathway in Cholangiocarcinoma

- Case 11 – Dr McKenzie: A 67-year-old man with metastatic cholangiocarcinoma – FGFR2 fusion
- Case 12 – Dr Radovich: A 58-year-old woman with metastatic cholangiocarcinoma – FGFR2-BICC1 fusion
- Case 13 – Dr McKenzie: A 65-year-old woman with metastatic cholangiocarcinoma – FGFR2 fusion
- Case 14 – Dr Radovich: A 74-year-old woman with unresectable intrahepatic cholangiocarcinoma – gain-of-function FGFR2 W290C mutation

Part 4: New Options in the Management of GIST Harboring PDGFR Mutations

- Case 15 – Dr McKenzie: A patient with GIST – PDGFRA
- Case 16 – Dr Radovich: A 61-year-old woman with metastatic GIST – gain-of-function PDGFRA D842Y mutation

Case Presentation – Dr McKenzie: A 67-year-old man with metastatic cholangiocarcinoma – FGFR2 fusion

- 67yr male with metastatic cholangiocarcinoma.
  - 08/2017, biopsy liver lesion showed adenocarcinoma and CAT scans 08/11/2017 showed a right hepatic lobe lesion, 5.2 x 5.7 x 5.9 cm.
  - 08/2017 to 02/2018 cisplatin and gemcitabine.
  - 10/2018 to 03/2019 FOLFOX and 08/2019 to 12/2019 FOLFIRI.
  - 11/20/2019, CAT scans showed progression of intrahepatic metastasis. He has also received radiation therapy, local regional therapy, ablation, arterially directed therapies, then sick on treatment with side effects while getting FOLFOX/FOLFIRI. The last CAT scan 11/2019 showed progression of disease.
  - On 01/24/2020, he had a CT scan showing multifocal pulmonary and hepatic metastases. He had a liver mass, 5.8 x 3.2 cm, previously 6.6 x 5.3 cm. Biopsy 01/28/2020.
- NGS testing revealed FGFR2-BICC1 fusion and patient started pemigatinib 05/2020

Case Presentation – Dr McKenzie: A 67-year-old man with metastatic cholangiocarcinoma – FGFR2 fusion (cont)

Patient

Name:
Date of Birth:
Sex: Male
Case Number:
Diagnosis: Adenocarcinoma, NOS

Specimen Information

Primary Tumor Site: Intrahepatic bile duct
Specimen Site: Liver
Specimen ID:
Specimen Collected: 27-Apr-2020
All Testing Completed: 18-May-2020

Ordered By

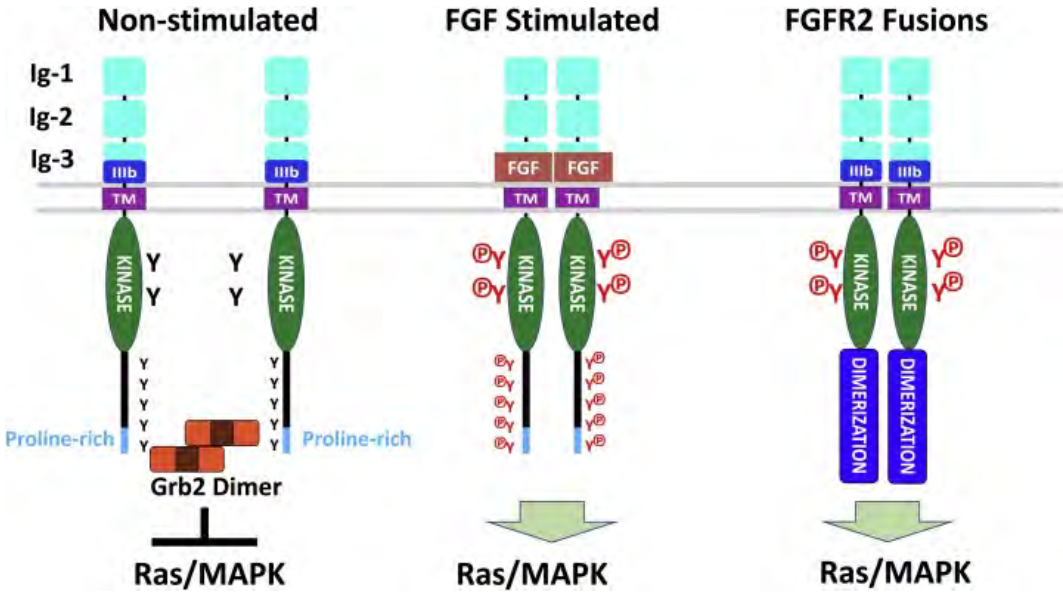
Results with Therapy Associations

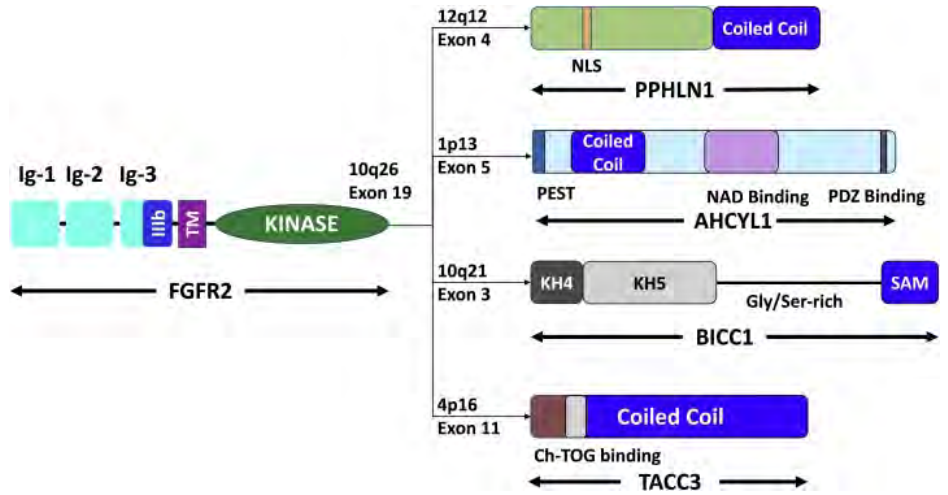
BIOMARKER	METHOD	ANALYTE	RESULT	THERAPY ASSOCIATION		BIOMARKER LEVEL*
FGFR2	**Seq**	**RNA-Tumor**	**Fusion Detected**	**BENEFIT**	**pemigatinib**	**Level 1**
ERBB2 (Her2/Neu)	CISH	DNA-Tumor	Not Amplified	LACK OF BENEFIT	pertuzumab, trastuzumab	Level 3A
	IHC	Protein	Negative | 0			

Cancer Type Relevant Biomarkers

Biomarker	Method	Analyte	Result
MSI	Seq	DNA-Tumor	Stable
Mismatch Repair Status	IHC	Protein	Proficient
NTRK1/2/3	Seq	RNA-Tumor	Fusion Not Detected
Tumor Mutational Burden	**Seq**	**DNA-Tumor**	**Intermediate | 8 Mutations/Mb**
BAP1	**Seq**	**DNA-Tumor**	**Pathogenic Variant Exon 7 | p.Y173C**
BRCA1	Seq	DNA-Tumor	Mutation Not Detected

Biomarker	Method	Analyte	Result
BRCA2	Seq	DNA-Tumor	Mutation Not Detected
ERBB2 (Her2/Neu)	CNA-Seq	DNA-Tumor	Amplification Not Detected
	Seq	DNA-Tumor	Mutation Not Detected
FGFR3	Seq	RNA-Tumor	Fusion Not Detected
IDH1	Seq	DNA-Tumor	Mutation Not Detected
IDH2	Seq	DNA-Tumor	Mutation Not Detected
NRG1	Seq	RNA-Tumor	Fusion Not Detected





Case Presentation – Dr Radovich: A 58-year-old woman with metastatic cholangiocarcinoma – FGFR2-BICC1 fusion

- **HISTORY OF PRESENT ILLNESS:**
  - 58 year old woman with metastatic cholangiocarcinoma.
  - She initially presented in March 2020 with a 4 x7 cm left hepatic lobe mass with intrahepatic biliary ductal dilatation. CT of the chest showed multiple bilateral solid pulmonary nodules.
  - Patient was started on cisplatin and gemcitabine which she continues to date.
  - In April 2020, patient was found on NGS to have an FGFR2-BICC1 fusion with a plan to start pemigatinib on progression.

Case Presentation – Dr Radovich: A 58-year-old woman with metastatic cholangiocarcinoma – FGFR2-BICC1 fusion

OTHER ALTERATIONS & BIOMARKERS IDENTIFIED

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See *professional services* section for additional information.

Microsatellite status MS-Stable §

Tumor Mutational Burden 1 Muts/Mb §

BAP1 W196*

FGFR2 FGFR2(NM_000141)-BICC1(NM_001080512) fusion (F17; B3) §

§ Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, BRCA1/2 alterations, LOH, MSI, or TMB results in this section.

Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).

Case Presentation – Dr McKenzie: A 65-year-old woman with metastatic cholangiocarcinoma – FGFR2 fusion (tissue v blood)

- 65yr Female
- Diagnosed 2012 with metastatic cholangiocarcinoma
  - Undergoes mesenteric nodule bx PATH+ metastatic adenocarcinoma, c/w cholangiocarcinoma primary (STAGE IV)
  - 3/2014-5/2015 Gemcitabine + Oxaliplatin + CyberKnife XRT to 3 sites 3/4/15 (L lung, R lung, abd wall lesions), best response PR, then treatment break (1st Metastatic Tx)
  - 4/2016 Undergoes omentectomy with resection omental tumor PATH+ metastatic adenocarcinoma
  - 2/2017 – XRT for new lung lesion
  - 4/2018 – new progression and initiation of Nivolumab (7/2018 – 7/2019)
  - pemigatinib on trial 9/2019 – 8/2020 until progression
- Blood and tissue-based NGS
  - Blood based revealed no actionable alterations
  - Tissue based revealed FGFR2 fusion

Case Presentation – Dr McKenzie: A 65-year-old woman with metastatic cholangiocarcinoma – FGFR2 fusion (tissue v blood) (cont)

Date of Birth		Medical Facility			
Sex	Female	Ordering Physician		Specimen Received	15 May 2018
FMI Case #		Additional Recipient	Not Given	Date of Collection	15 May 2018
Medical Record #		Medical Facility ID #		Specimen Type	Blood
Specimen ID	Not Given	Pathologist	Not Provided	Median Exon Coverage	4,244x

ABOUT THE TEST:

FoundationACT® (Assay for Circulating Tumor DNA) is a next-generation sequencing (NGS) assay that identifies clinically relevant genomic alterations in circulating tumor DNA and matches them to targeted therapies and clinical trials.

PATIENT RESULTS[‖]

- 0 genomic alterations
- 0 therapies associated with potential clinical benefit
- 0 therapies associated with lack of response
- 0 clinical trials

‖ Reduced sensitivity due to sample quality – See Appendix: Performance Specifications for details.

TUMOR TYPE: LIVER CHOLANGIOCARCINOMA

Genomic Alterations Identified†

No Reportable genomic alterations were detected

Interpretive content on this page and subsequent pages is provided as a professional service, and is not reviewed or approved by the FDA.

PATIENT

DISEASE Pancreatobiliary carcinoma (NOS)
NAME
DATE OF BIRTH
SEX Female
MEDICAL RECORD #

PHYSICIAN

ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIEN
MEDICAL FACILITY ID
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Omentum
SPECIMEN ID USS16-07751 A2
SPECIMEN TYPE Block
DATE OF COLLECTION 12 April 2016
SPECIMEN RECEIVED 12 May 2018

Biomarker Findings

Microsatellite Status - MS-Stable
Tumor Mutational Burden - TMB-Low (5 Muts/Mb)

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

FGFR2 TTC28-FGFR2 fusion

2 Therapies with Clinical Benefit
0 Therapies with Lack of Response
6 Clinical Trials

SARAH CANNON

Case Presentation – Dr Radovich: A 74-year-old woman with unresectable intrahepatic cholangiocarcinoma – gain-of-function FGFR2 W290C mutation

- **HISTORY OF PRESENT ILLNESS:**
  - 74-year-old woman with unresectable intrahepatic cholangiocarcinoma.
  - She initially presented in February 2020 with progressively worsening fatigue, anorexia, weight loss, and right upper quadrant pain. Imaging showed numerous liver metastases. Further pathology workup confirmed cholangiocarcinoma.
  - Patient was started on gemcitabine, cisplatin, and *nab* paclitaxel with disease progression in June 2020.
  - In July 2020, was started on FOLFOX.
  - Genomic sequencing revealed a gain-of-function FGFR2 W290C mutation
  - Plan is to start a clinical trial of infigratinib for FGFR mutated tumors upon disease progression.

Case Presentation – Dr Radovich: A 74-year-old woman with unresectable intrahepatic cholangiocarcinoma – gain-of-function FGFR2 W290C mutation

OTHER ALTERATIONS & BIOMARKERS IDENTIFIED

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See *professional services* section for additional information.

Microsatellite status MS-Stable §

Tumor Mutational Burden 0 Muts/Mb §

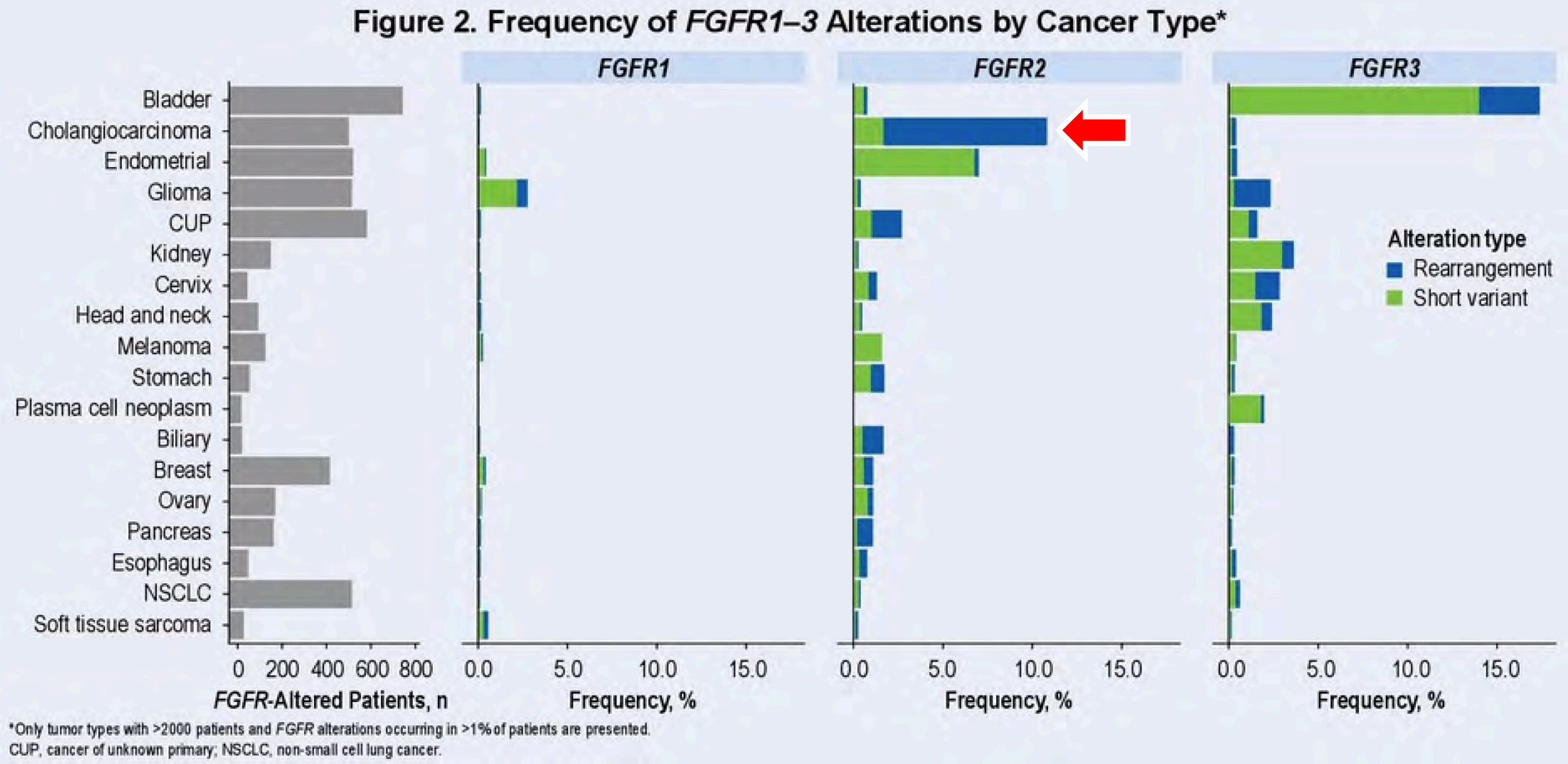
BAP1 Q684*

FGFR2 W290C

§ Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, BRCA1/2 alterations, LOH, MSI, or TMB results in this section.

Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).

Pan-Cancer Analysis of FGFR1-3 Genomic Alterations



Krook MA et al. ASCO 2020;Abstract 3620.

FDA grants accelerated approval to pemigatinib for cholangiocarcinoma with an FGFR2 rearrangement or fusion

Press Release – April 17, 2020

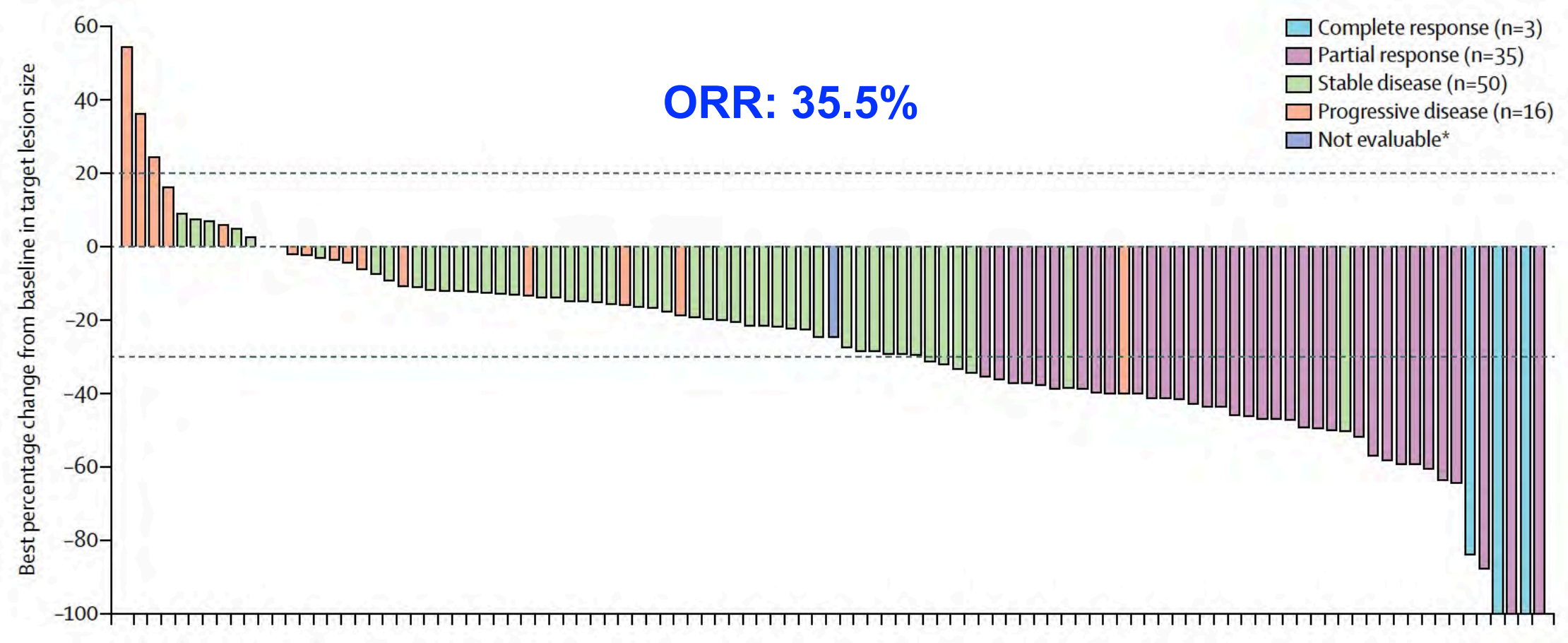
The Food and Drug Administration granted accelerated approval to pemigatinib for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test.

The FDA also approved the Foundation One® CDX (Foundation Medicine, Inc.) as a companion diagnostic for patient selection.

Efficacy was investigated in FIGHT-202 (NCT02924376), a multicenter open-label single-arm trial, in 107 patients with locally advanced unresectable or metastatic cholangiocarcinoma whose disease had progressed on or after at least one prior therapy and had an FGFR2 gene fusion or rearrangement (clinical trial assay performed at a central laboratory). Patients received pemigatinib, 13.5 mg orally, once daily for 14 consecutive days, followed by 7 days off therapy.

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pemigatinib-cholangiocarcinoma-fgfr2-rearrangement-or-fusion

FIGHT-202: Best Percentage Change from Baseline in Target Lesion Size in Patients with FGFR2 Fusions or Rearrangements



Abou-Alfa GK et al. *Lancet Oncol* 2020;21:671-84.

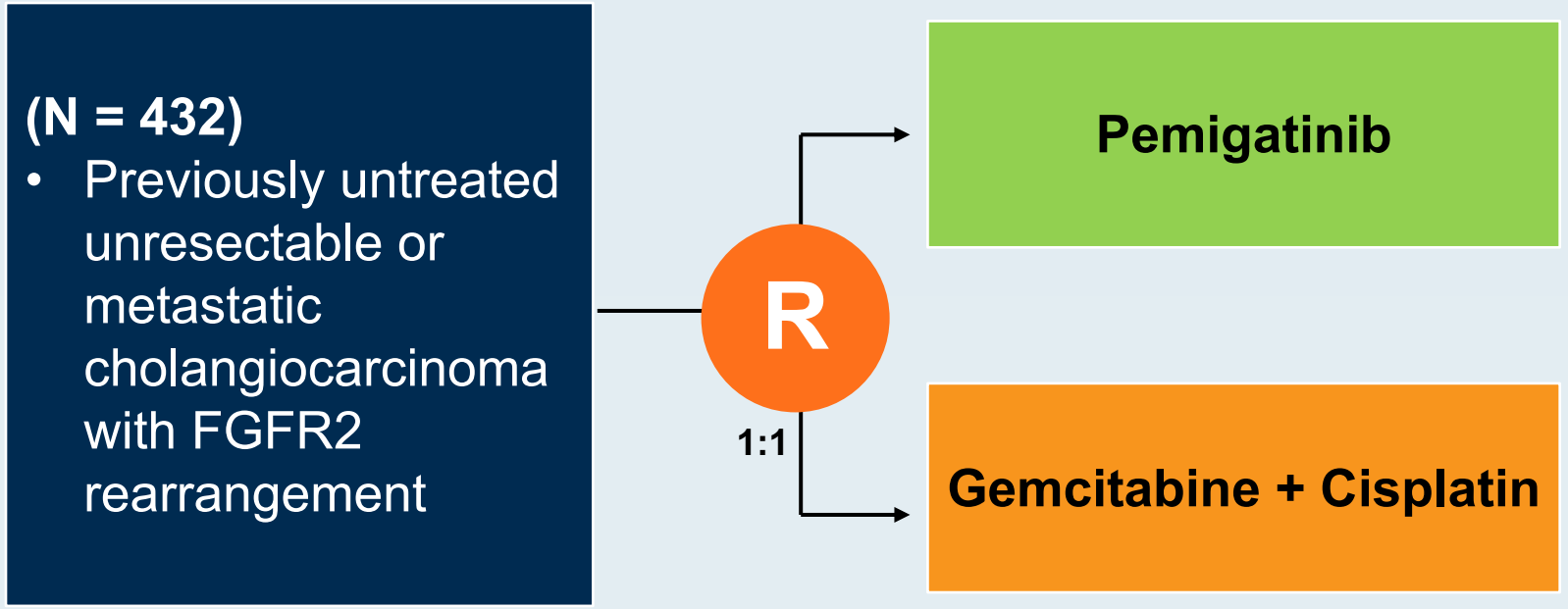
Courtesy of Ghassan Abou-Alfa, MD, MBA

FIGHT-202: Select Treatment-Related Adverse Events

Adverse Event	Grade 1-2	Grade 3	Grade 4
Hyperphosphatemia	55%	0	0
Alopecia	46%	0	0
Dysgeusia	38%	0	0
Diarrhea	34%	3%	0
Fatigue	31%	1%	0
Stomatitis	27%	5%	0
Arthralgia	11%	4%	0
Palmar-plantar erythrodysesthesia	11%	4%	
Hypophosphatemia	5%	7%	0

Abou-Alfa GK et al. *Lancet Oncol* 2020;21:671-84.

FIGHT-302 Phase III Study Schema



Primary endpoint: Progression-free survival

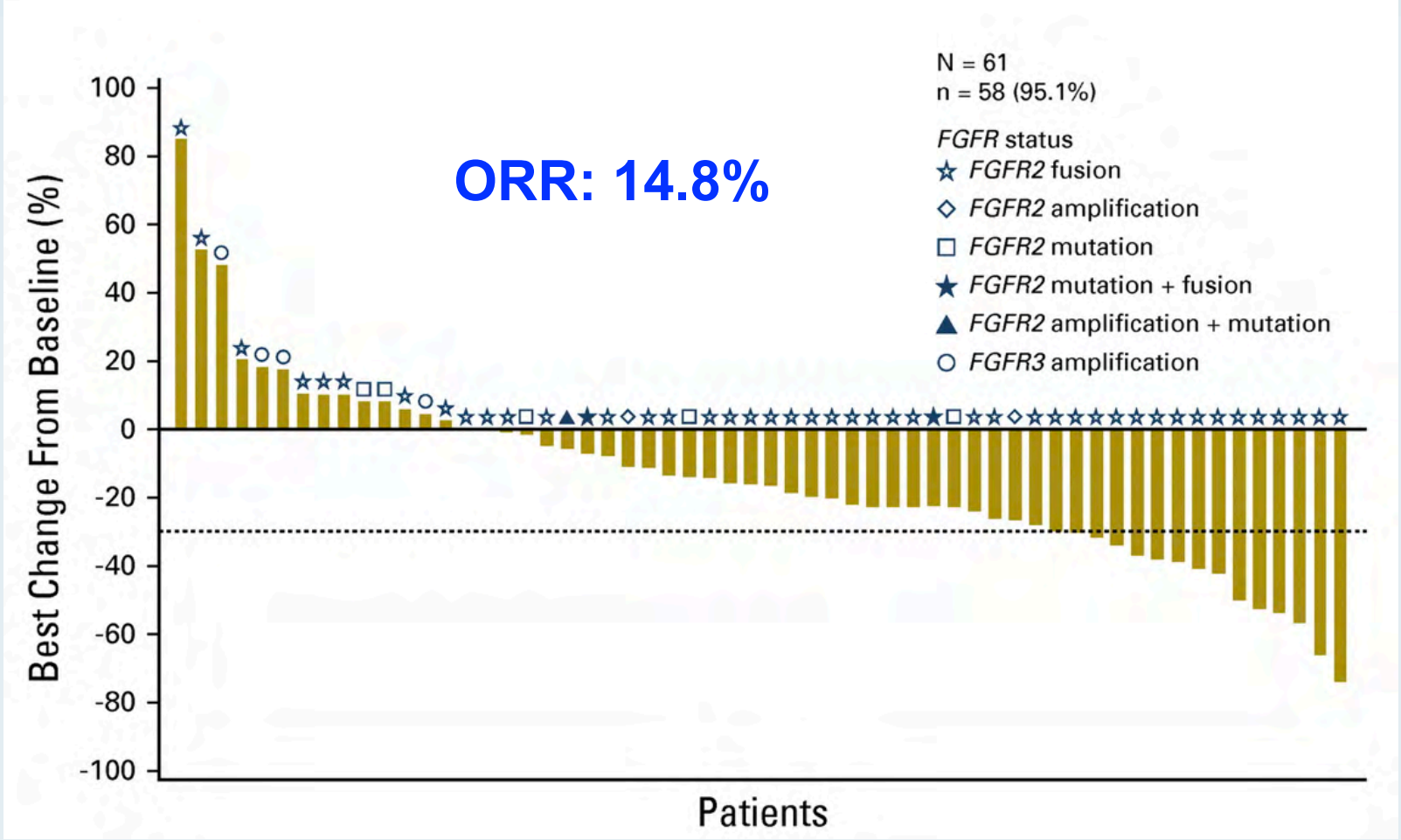
Clinicaltrials.gov, Accessed Aug 12, 2020 (NCT03656536)

FGF Landscape

Drug	Target	Indication	Status
Infigratinib (BGJ398)	FGFR1-3 TKI	Cholangiocarcinoma	First line Phase III
Pemigatinib	FGFR1-3 TKI	Cholangiocarcinoma	First line Phase III
TAS-120	Pan-FGFR TKI	Solid tumors	Phase I
Derazantinib (ARQ 087)	Pan-FGFR TKI	Cholangiocarcinoma	Phase II
Debio 1347	Pan-FGFR TKI	Solid tumors	

Courtesy of Ghassan Abou-Alfa, MD, MBA

Phase II Study of Infigratinib (BGJ398) in FGFR-Altered Cholangiocarcinoma



Javle, M. et al. *Journal of Clinical Oncology* 2018;36:276-282.

Courtesy of Ghassan Abou-Alfa, MD, MBA

Agenda

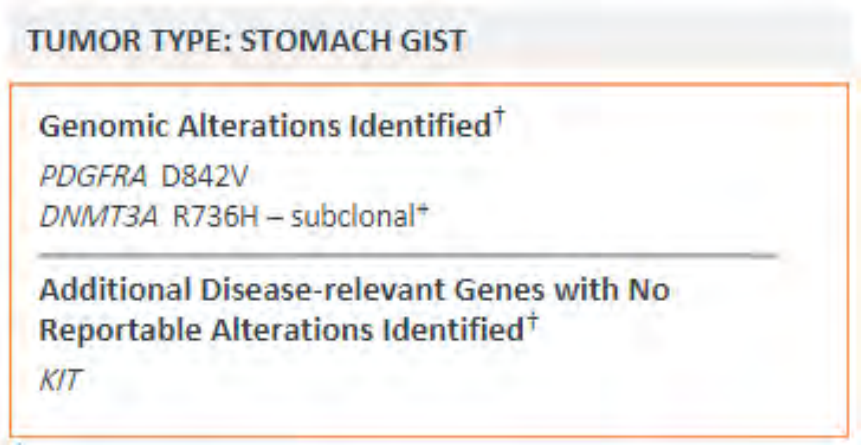
Part 3: Targeting the FGFR Signaling Pathway in Cholangiocarcinoma

- Case 11 – Dr McKenzie: a 67-year-old man with metastatic cholangiocarcinoma – FGFR2 fusion
- Case 12 – Dr Radovich: A 58-year-old woman with metastatic cholangiocarcinoma – FGFR2-BICC1 fusion
- Case 13 – Dr McKenzie: A 65-year-old woman with metastatic cholangiocarcinoma – FGFR2 fusion
- Case 14 – Dr Radovich: A 74-year-old woman with unresectable intrahepatic cholangiocarcinoma – gain-of-function FGFR2 W290C mutation

Part 4: New Options in the Management of GIST Harboring PDGFR Mutations

- Case 15 – Dr McKenzie: A patient with GIST – PDGFRA
- Case 16 – Dr Radovich: A 61-year-old woman with metastatic GIST – gain-of-function PDGFRA D842Y mutation

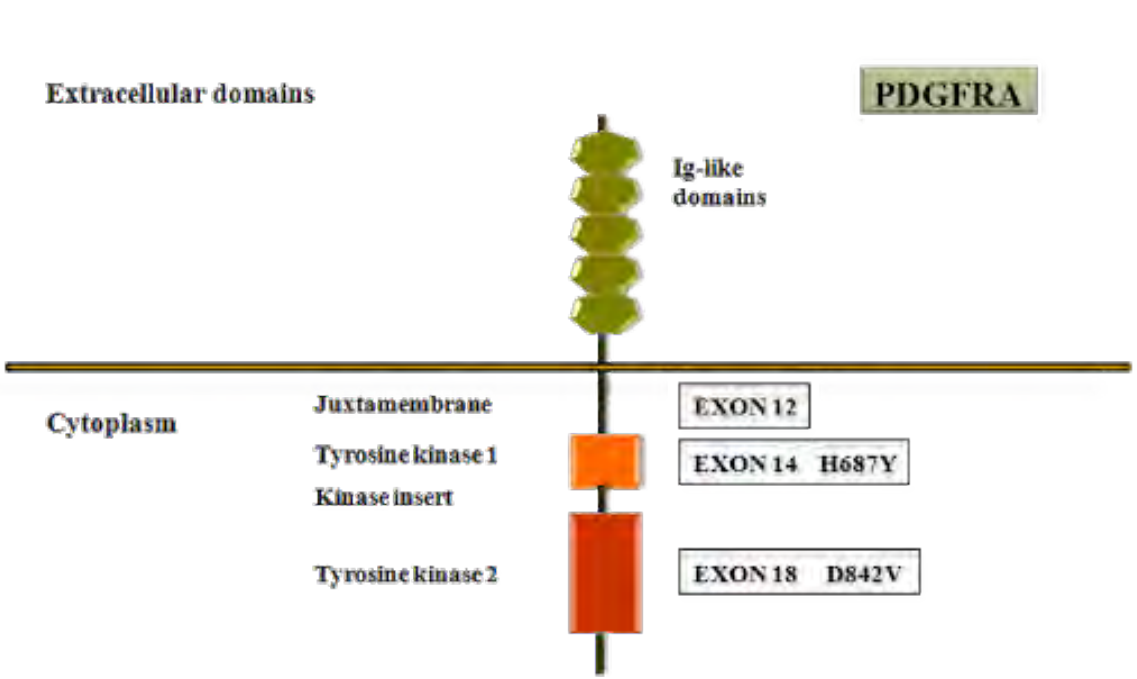
Case Presentation – Dr McKenzie: A patient with GIST – PDGFRA

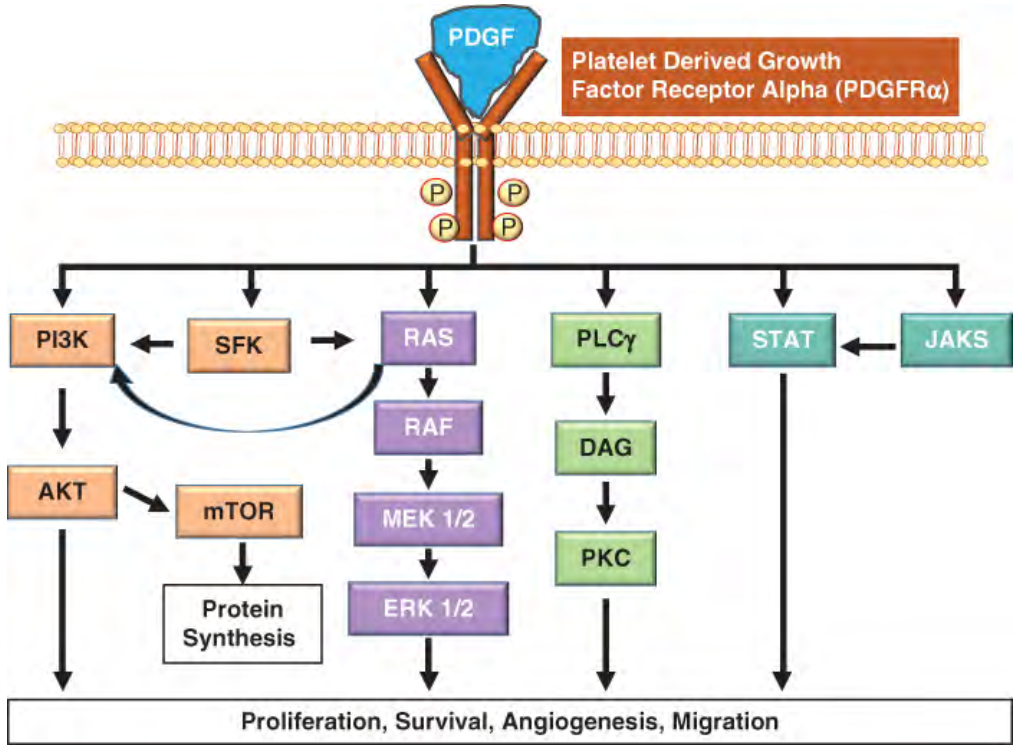


- 4/3/2017: Gastrointestinal Stromal Tumor (GIST) (Soft Tissue Sarcoma) - Pathologic Gastric or Omental Stage IA (AJCCv7) TNM: pT2, pN0, cM0; Mitotic Rate Category: Low
- 3/31/2017 GIST appearing tumor in the stomach. 4/3/2017: Robotic subtotal gastrectomy/gastrojejunostomy. Tumor size 2.9 cm, Negative margins. 5/16/2017: IV ferumoxytol 7/2019: EGD. Gastritis. + H pylori
- Currently being followed every 12 months.
- Tissue testing revealed PDGFRA mutation that is a target for avapritinib

SARAH CANNON

Case Presentation – Dr McKenzie: A patient with GIST – PDGFRA (cont)





Courtesy of Andrew McKenzie, PhD

Case Presentation – Dr Radovich: A 61-year-old woman with metastatic GIST – gain-of-function PDGFRA D842Y mutation

- **HISTORY OF PRESENT ILLNESS:**
  - 61-year-old woman with metastatic GIST.
  - In November 2012, was diagnosed with a 12.4cm epithelioid GIST tumor removed by partial gastrectomy.
  - She received 3 years of adjuvant imatinib ending in February 2016.
  - She did well until November 2019 when she presented with worsening abdominal pain. CT scan showed evidence of disease recurrence with a large jejunal tumor and peritoneal deposits. Biopsy was consistent with recurrent GIST.
  - She was started on imatinib and recently had disease progression.
  - Sequencing of the recurrent GIST revealed a gain-of-function PDGFRA D842Y mutation for which was avapritinib was recently prescribed.

Case Presentation – Dr Radovich: A 61-year-old woman with metastatic GIST – gain-of-function PDGFRA D842Y mutation

OTHER ALTERATIONS & BIOMARKERS IDENTIFIED

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See *professional services* section for additional information.

Microsatellite status MS-Stable §

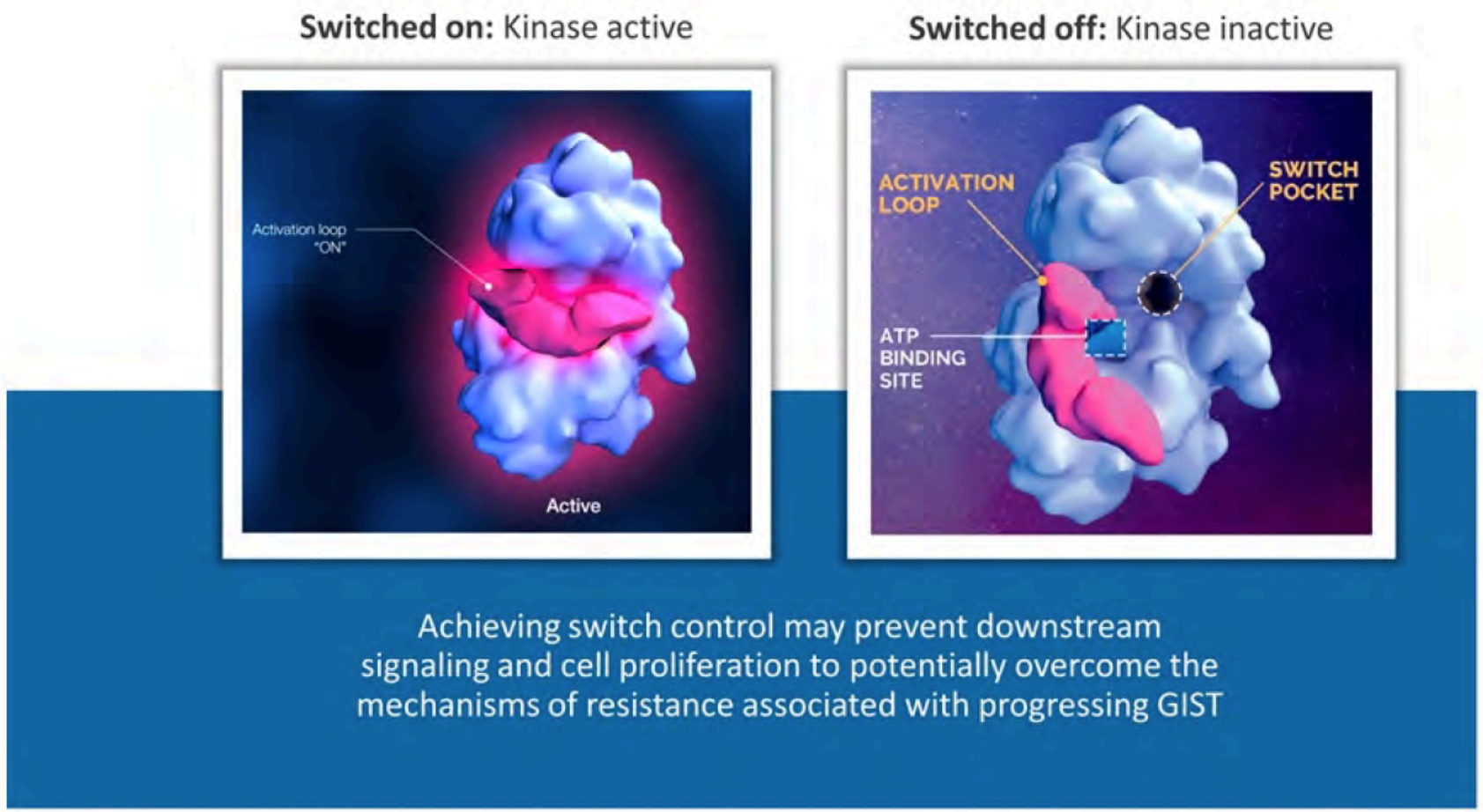
Tumor Mutational Burden 0 Muts/Mb §

PDGFRA D842Y

§ Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, BRCA1/2 alterations, LOH, MSI, or TMB results in this section.

Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).

Ripretinib: A Novel Kinase Switch Control Inhibitor



A unique dual mechanism of action that regulates the kinase switch pocket and activation loop

- Prevents the activation loop from binding to the switch pocket
- Locks the kinase in the inactive ("off") state

https://investors.deciphera.com/static-files/6a6e8459-fca8-47fe-947e-991bc2942431

FDA approves ripretinib for advanced gastrointestinal stromal tumor

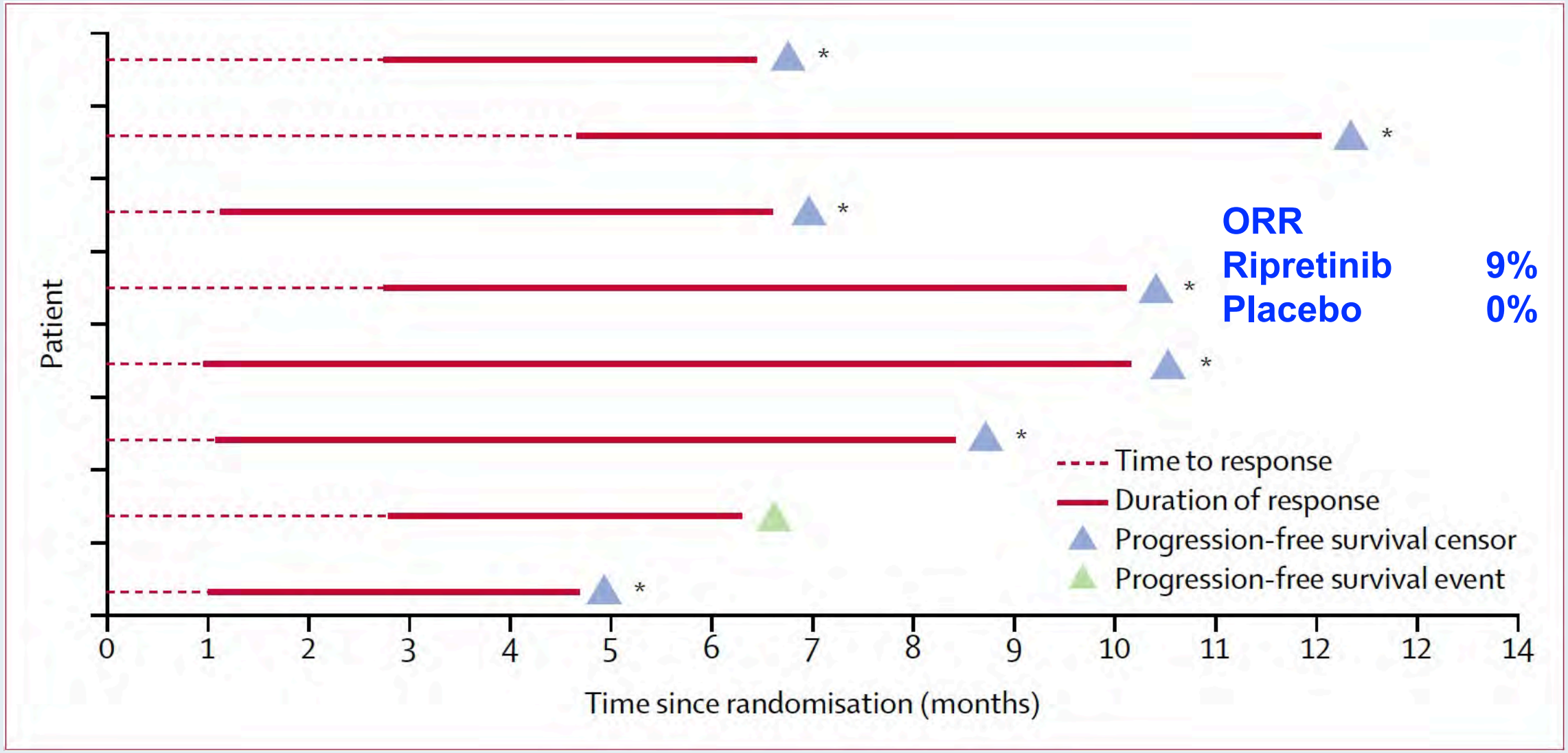
Press Release – May 15, 2020

The Food and Drug Administration approved ripretinib, for adult patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with 3 or more kinase inhibitors, including imatinib.

Efficacy was evaluated in INVICTUS (NCT03353753), an international, multi-center, randomized (2:1), double-blind, placebo-controlled trial in 129 patients with GIST who were previously treated with imatinib, sunitinib, and regorafenib. Patients received ripretinib 150 mg or placebo orally once daily until disease progression or unacceptable toxicity. Crossover was permitted at disease progression for patients randomized to receive placebo.

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-ripretinib-advanced-gastrointestinal-stromal-tumor

INVICTUS: Response Rate, Time to Response, and Duration of Response



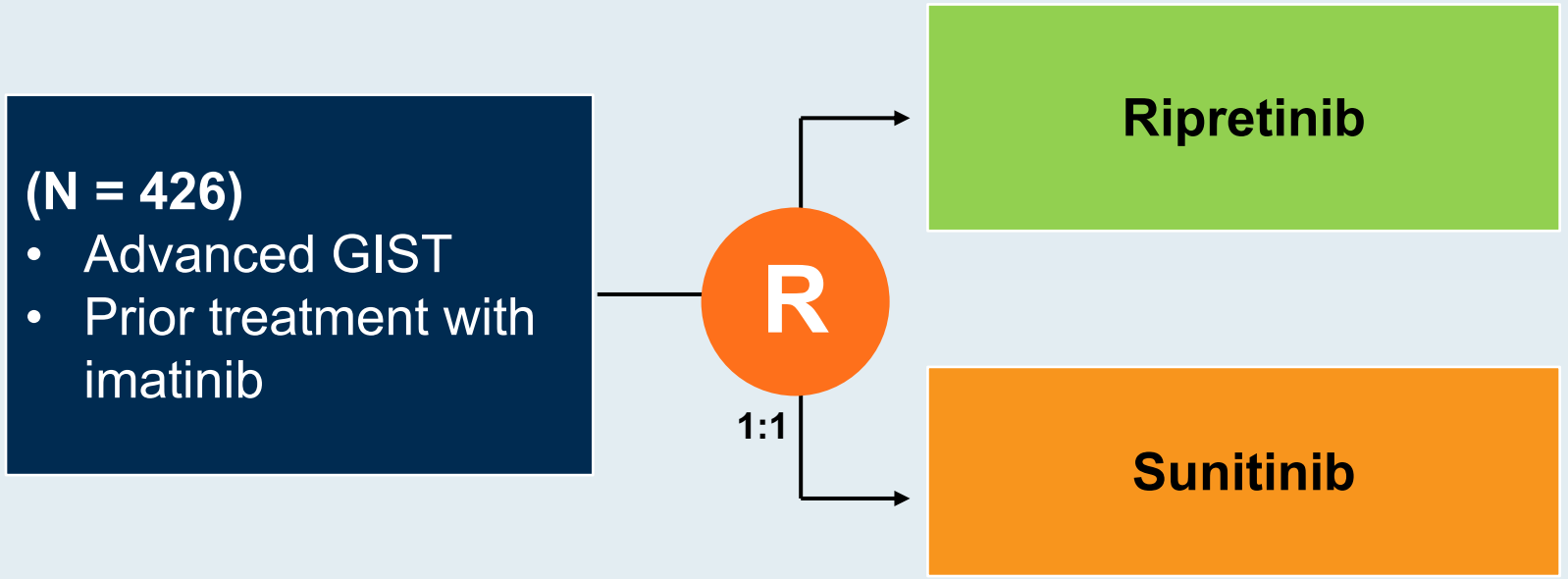
Blay JY et al. *Lancet Oncol* 2020;21:923-34.

INVICTUS: Select Treatment-Related Adverse Events

Adverse Event	Ripretinib (n = 85)		Placebo (n = 43)	
	Grade 1-2	Grade ≥3	Grade 1-2	Grade ≥3
Common AEs				
Alopecia	49%	0	2%	0
Nausea	25%	1%	2%	0
Palmar-plantar erthrodysesthesia	21%	0	0	0
Diarrhea	20%	1%	5%	2%
Most Frequent Grade 3 AEs				
Fatigue	24%	2%	14%	2%
Hypertension	5%	4%	2%	0
Lipase increase	5%	5%	0	0
Hypophosphatemia	4%	2%	0	0

Blay JY et al. *Lancet Oncol* 2020;21:923-34.

INTRIGUE Phase III Study Schema



Primary endpoint: Progression-free survival

Clinicaltrials.gov, Accessed Aug 12, 2020 (NCT03673501)

Agenda

Part 5: Molecular Tumor Board (Continued)

- Case 17 – Dr Favaro: A 79-year-old man with metastatic pancreatic cancer – EGFR exon 19 deletion
- Case 18 – Dr McKenzie: A patient with metastatic pancreatic cancer and an incidental finding of papillary thyroid cancer – BRCA, BRAF
- Case 19 – Dr Ibrahim: A 64-year-old woman with recurrent ameloblastoma – PD-L1 of 100%, FGFR2, SMO mutation
- Case 20 – Dr Ibrahim: A 38-year-old woman with ER-positive, HER2-negative metastatic breast cancer – CHEK2 mutation

FDA Approves First Liquid Biopsy Next-Generation Sequencing Companion Diagnostic Test

Press Release – August 7, 2020

The U.S. Food and Drug Administration approved the first liquid biopsy companion diagnostic that also uses next-generation sequencing (NGS) technology to identify patients with specific types of mutations of the epidermal growth factor receptor (EGFR) gene in a deadly form of metastatic non-small cell lung cancer (NSCLC). This is the first approval to combine two technologies — NGS and liquid biopsy — in one diagnostic test in order to guide treatment decisions.

The Guardant360 CDx assay utilizes two technologies. The first is called liquid biopsy, which uses a blood sample to provide health care professionals with genetic information about the patient's tumor. It is less invasive and more easily repeatable in comparison to standard tissue biopsies. Furthermore, liquid biopsy tests can be used in cases in which standard tissue biopsies are not feasible, for instance, due to the location of the tumor.

The second technology is NGS, which uses large-panel genetic sequencing, known as high-throughput tumor profiling. Compared to older technologies, NGS requires only one test in order to allow clinicians better assessment of tumor composition, giving providers an advantage in evaluating which mutations are problematic. The Guardant360 CDx assay uses NGS technology to simultaneously detect mutations in 55 tumor genes, rather than one gene at a time.

https://www.fda.gov/news-events/press-announcements/fda-approves-first-liquid-biopsy-next-generation-sequencing-companion-diagnostic-test?utm_campaign=080720_PR_FDA%20Approves%20First%20Liquid%20Biopsy%20NGS%20Companion%20Diagnostic%20Test&utm_medium=email&utm_source=Eloqua

Case Presentation – Dr Favaro: A 79-year-old man with metastatic pancreatic cancer – EGFR exon 19 deletion

Justin Peter Favaro, MD, PhD

- 12/2018: Diagnosed with Stage IV pancreatic cancer
  - Pancreatic mass, lymphadenopathy, a few lung mets, a supraclavicular node; Minimally symptomatic
- NGS: EGFR exon 19 deletion
- Modified FOLFIRINOX, with CR
- Currently, receiving 5-FU, low-dose irinotecan

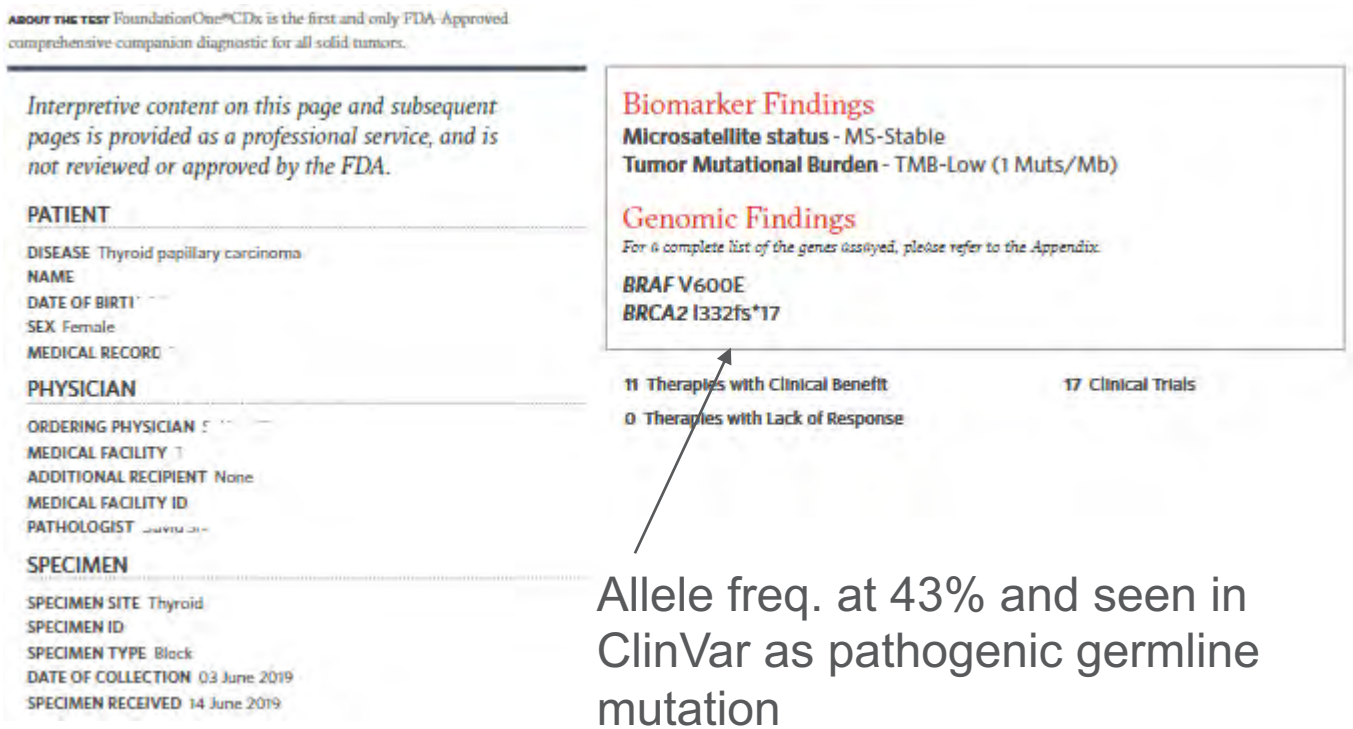
Questions:

- What is the role of EGFR exon 19 deletion in the biology of this disease?
- What is the role of EGFR TKIs in these patients?
- What treatments should be considered next?

Case Presentation – Dr McKenzie: A patient with metastatic pancreatic cancer and an incidental finding of papillary thyroid cancer – BRCA, BRAF

- Pancreatic Adenocarcinoma (IV mesenteric metastasis)
  - Current status:
    - Gemcitabine monotherapy
    - 7/1/2019: Folfirinox attempted x 1, stopped due to toxicity (fatigue) wishes to watch and wait until symptomatic.
    - 1/2020 7/2020: Resumed FOLFIRINOX (abd pain)
    - 7/14/2020 Gemcitabine
- Papillary thyroid cancer
  - 6/2019 Incidentally found on PET CT for pancreatic cancer and confirmed on biopsy.
    - Molecular profiling done and revealed potential germline BRCA2 mutation
    - Deferring intervention until pancreatic cancer treated.

Case Presentation – Dr McKenzie: A patient with metastatic pancreatic cancer and an incidental finding of papillary thyroid cancer – BRCA, BRAF (cont)



ABOUT THE TEST FoundationOne®CDx is the first and only FDA-Approved comprehensive companion diagnostic for all solid tumors.

Interpretive content on this page and subsequent pages is provided as a professional service, and is not reviewed or approved by the FDA.

PATIENT

DISEASE Thyroid papillary carcinoma
NAME
DATE OF BIRTH
SEX Female
MEDICAL RECORD

PHYSICIAN

ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN

SPECIMEN SITE Thyroid
SPECIMEN ID
SPECIMEN TYPE Block
DATE OF COLLECTION 03 June 2019
SPECIMEN RECEIVED 14 June 2019

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - TMB-Low (1 Muts/Mb)

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

BRAF V600E
BRCA2 I332fs*17

11 Therapies with Clinical Benefit
0 Therapies with Lack of Response
17 Clinical Trials

Allele freq. at 43% and seen in ClinVar as pathogenic germline mutation

NM_000059.3(BRCA2):c.994del (p.Ile332fs)

Interpretation:	**Pathogenic**
Review status:	★★★☆ reviewed by expert panel
Submissions:	10 (Most recent: May 19, 2020)
Last evaluated:	Sep 8, 2016
Accession:	VCV000052924.4
Variation ID:	52924
Description:	1bp deletion

National Center for Biotechnology Information. ClinVar; [VCV000052924.4], https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV000052924.4 (accessed Aug. 12, 2020).

Case Presentation – Dr Ibrahim: A 64-year-old woman with recurrent ameloblastoma – PD-L1 of 100%, FGFR2, SMO mutation

Sulfi Ibrahim, MD

- First presented in 1994 and was treated with surgical resection
- Subsequent local recurrence in 2000 and 2008 both again treated with surgical resection
- Next recurrence was in 2012 which was treated with surgery and adjuvant radiation therapy
- Now with further recurrence, which was resected and NGS was sent on the resection specimen
- Now with further disease progression in the neck. Treating physician attempted to get immunotherapy and erdafitinib, both of which were denied by the insurance company
- Referred to our hospital because we had the MATCH trial with vismodegib targeting the SMO mutation

Questions

- What is the SMO mutation and what makes it a target for vismodegib?
- Assuming we could get access to either single-agent PD-1 therapy or combination CTLA4/PD-1 inhibitor therapy, given that PD-L1 level of 100%, is that the better way to go for this disease rather than targeted therapy with vismodegib?
- With the FGFR2 alteration, if we could get off-label access to erdafitinib would that be the better way to go, rather than targeting the SMO mutation?

Case Presentation – Dr Ibrahim: A 38-year-old woman with ER-positive, HER2-negative metastatic breast cancer – CHEK2 mutation

Sulfi Ibrahim, MD

- Hormone receptor-positive, HER2-negative left breast cancer treated with mastectomy
  - Could not tolerate tamoxifen
- Develops metastatic disease to liver and bone
- Chooses alternative therapy, then sees me when she has disease progression
- Abemaciclib and letrozole with initial response and then progression after one year
- Switched to capecitabine with good response in the liver
- Develops metastatic disease to the brain and spinal cord → WBRT
- Plasma based NGS: CHEK2 mutation
- Seen at tertiary care center and a clinical trial is suggested based on the CHEK2 mutation

Questions

- What is the optimal way to target CHEK2 mutations, either using off-label medications or in clinical trials?
- Is there something about a CHEK2 mutation that might predict for a more aggressive disease biology in a patient with hormone receptor-positive disease?

Case Presentation – Dr Ibrahim: A 38-year-old woman with ER-positive, HER2-negative metastatic breast cancer – NGS-based recommendation

4. I also spent time discussing a clinical trial OSU 19183 (A Multicenter, Non-Randomized, Open-Label Phase Ib Study to Determine the Maximum Tolerated and Recommended Phase II Dose of the ATR Inhibitor BAY 1895344 in Combination with Pembrolizumab and to Characterize its Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumor Activity in Patients with Advanced Solid Tumors). This study is enrolling patients with tumors that have mutations in DNA damage response genes and given prior Foundation Medicine testing she would be a good fit for the study (her tumor harbors CHEK2 mutation). I provided her with the informed consent via email.

Recent Advances in Medical Oncology: ER-Positive Breast Cancer

Monday, August 17, 2020

5:00 PM – 6:00 PM ET

Faculty

Virginia Kaklamani, MD, DSc

Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 days.