Treatment of advanced thyroid cancer.

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I have the following financial relationships to disclose:

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Treatment strategies for cancers derived from thyroid follicular cells:

1. Active surveillance for low volume differentiated thyroid cancer.
2. Surgery.
3. Radioiodine ablation of the thyroid remnant.
4. Adjuvant RAI therapy.
5. RAI treatment of locally recurrent or metastatic thyroid cancer.
6. External beam radiotherapy
7. Systemic therapies for RAI-refractory recurrent or metastatic thyroid cancer.

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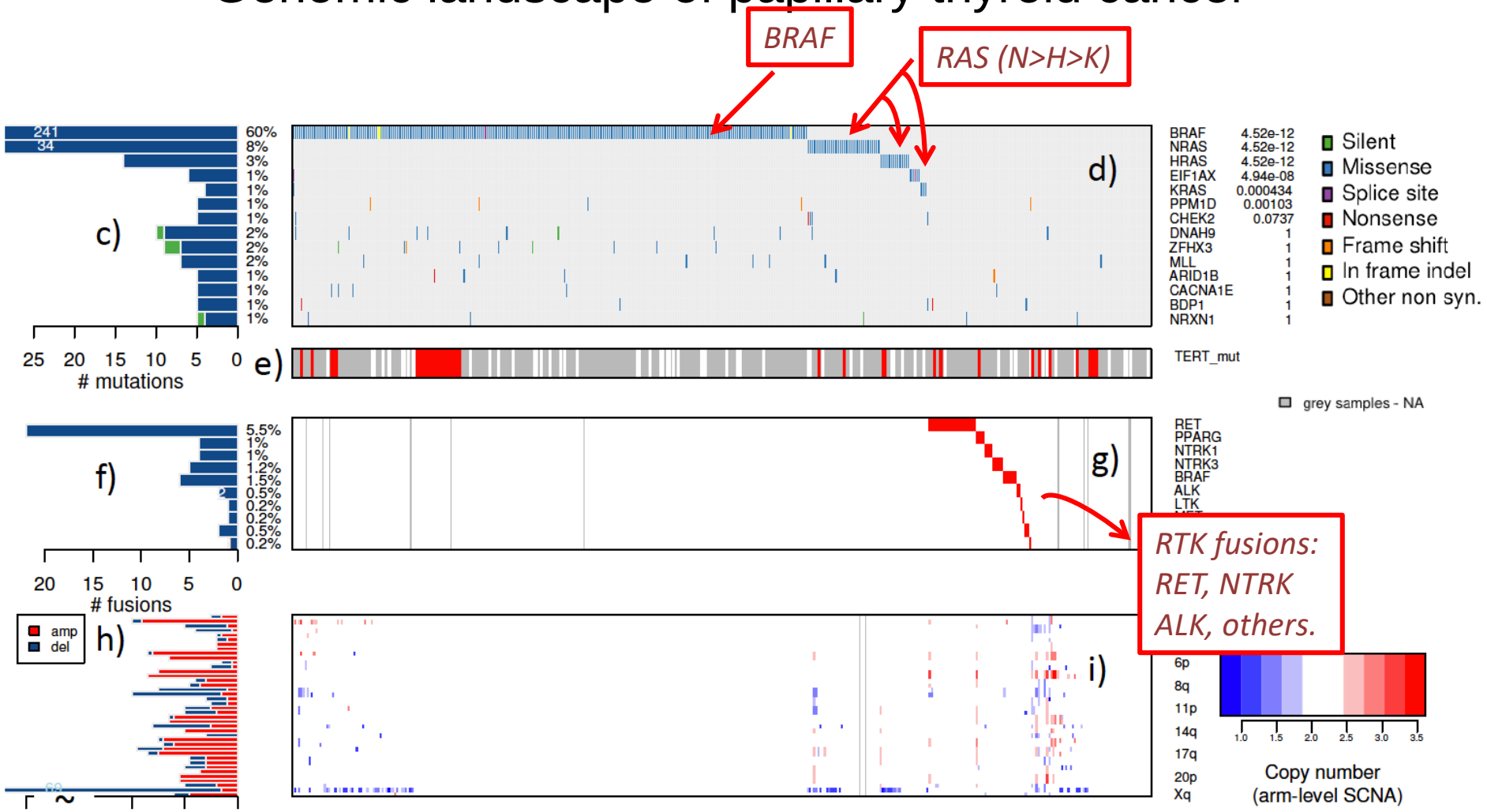
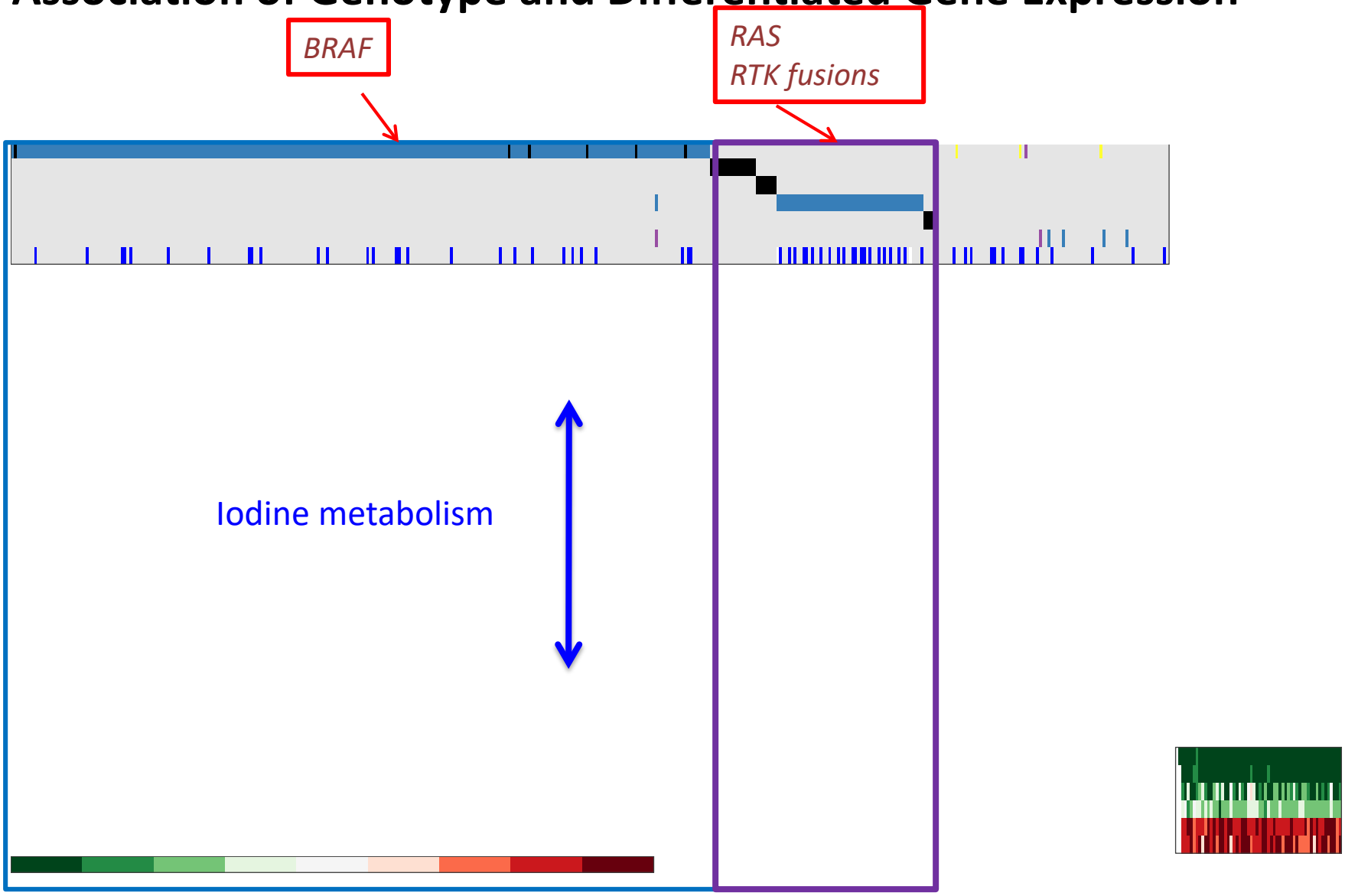
ATA 2015 THYROID CANCER GUIDELINES

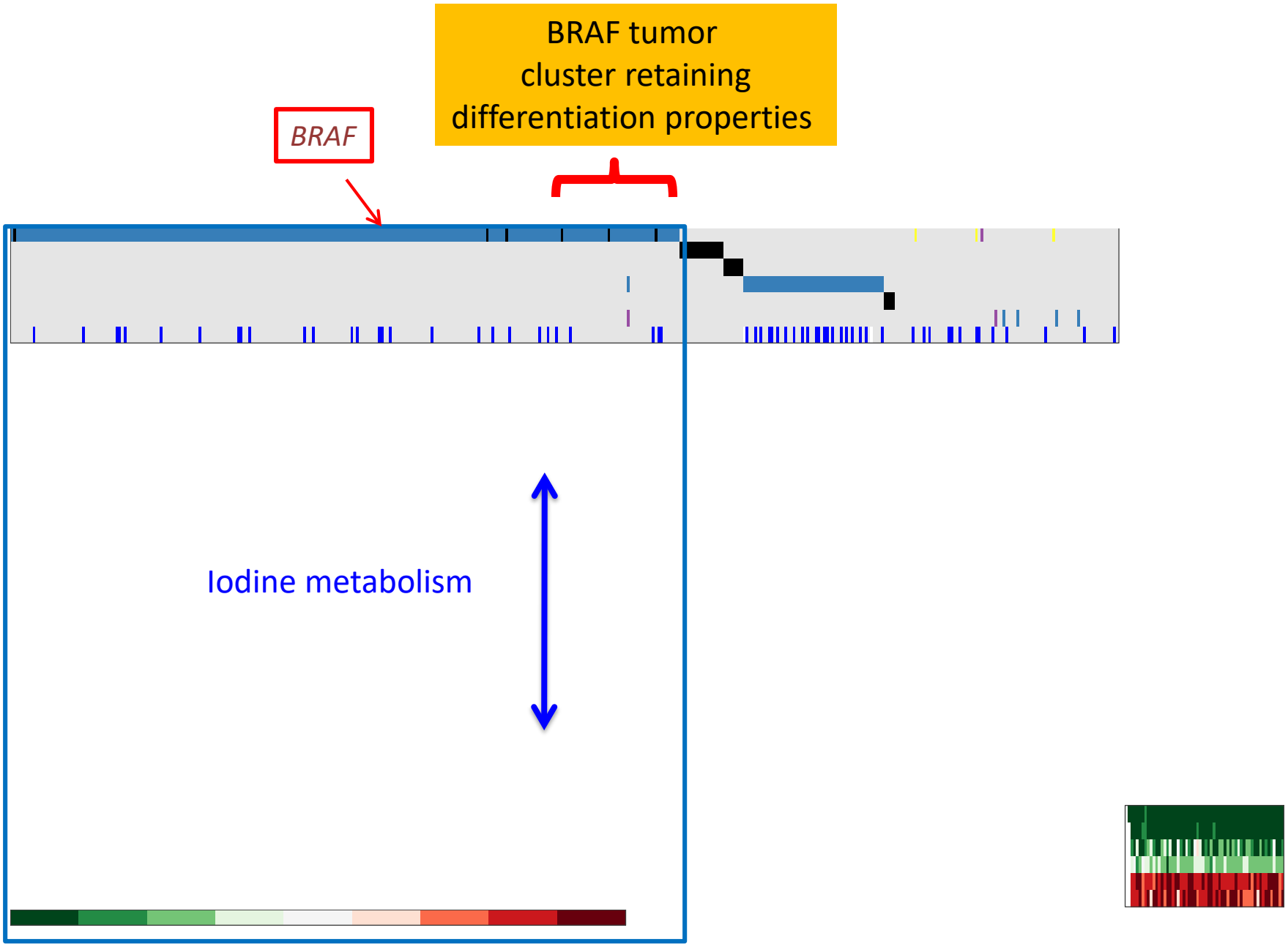
	RAI
ATA LOW RISK: Non-invasive PTCs, no vascular invasion, N0 or < 5 nodal micromets, no "aggressive histology" (e.g. TCV-PTC, hobnail, columnar cell).	NO
ATA INTERMEDIATE RISK: Microscopic perithyroidal invasion, vascular invasion. Clinical N1 or > 5 LN < 3 cm. Micro-PTC with ETE (BRAF mutant).	Consider
ATA HIGH RISK: Gross ETE. Incomplete resection. N1 with any LN > 3 cm. Distant mets. High post-op Tg. FTC with extensive vascular invasion.	Consider

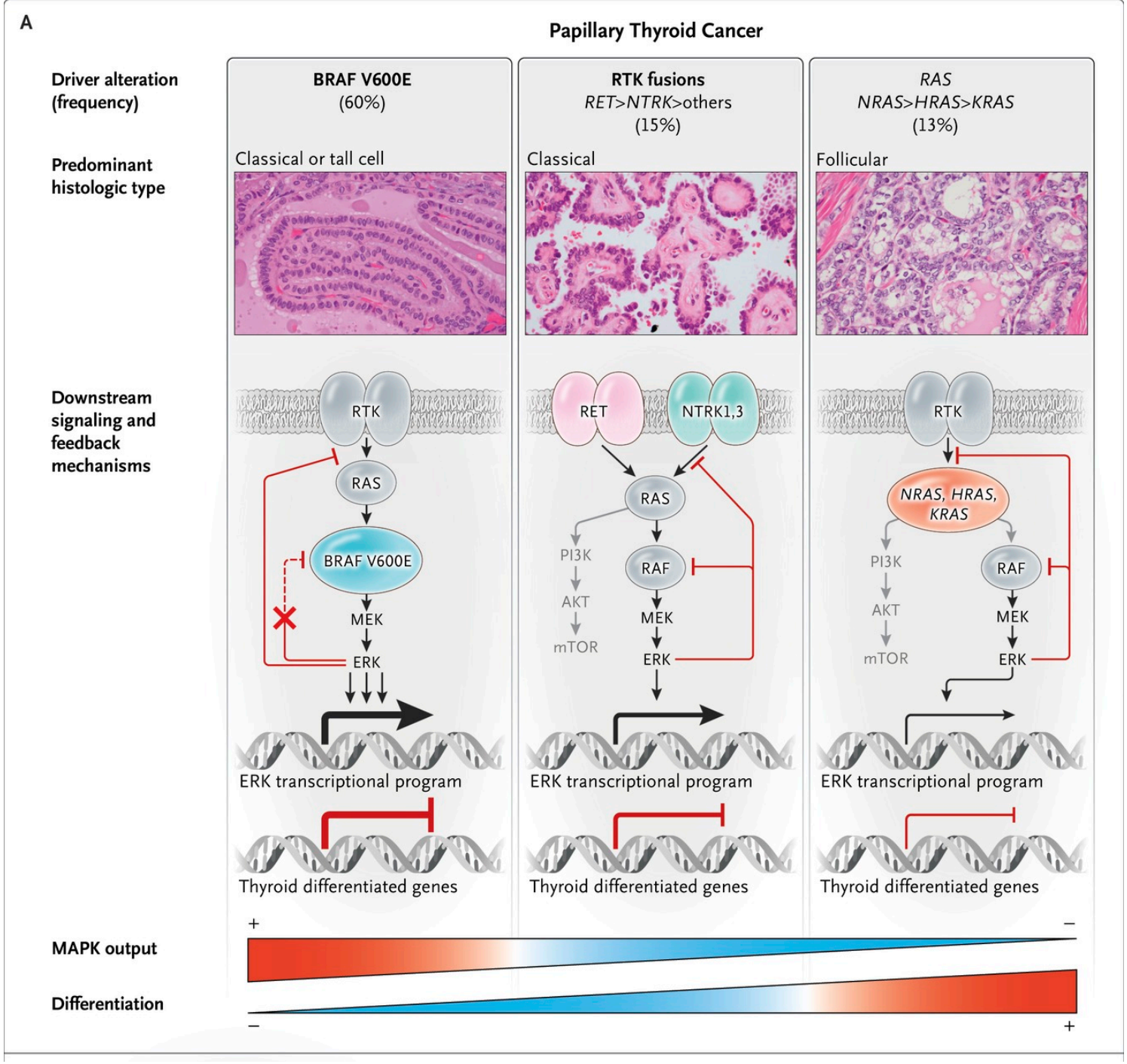
Genomic landscape of papillary thyroid cancer



Association of Genotype and Differentiated Gene Expression




BRAF tumor
cluster retaining
differentiation properties
BRAF
Iodine metabolism



Fagin JA, Wells SA Jr. N Engl J Med 2016

Pathological features enriched in PTCs with BRAF or BRAF-like driver mutations

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- Consensus expert recommendations for adjuvant RAI treatment are based on retrospective studies, despite their methodological weaknesses and biases.

- Most invasive tumors or cancers with significant locoregional nodal disease are tr[illegible] with RAI after surgery

RAI is a **systemic therapy** associated with potentially significant side effects

- Th[illegible] y e[illegible]

- Similarly, patients with persistent or recurrent nodal or distant metastatic disease are treated with RAI irrespective of tumor genotype.

- Measuring efficacy of adjuvant RAI is challenging.

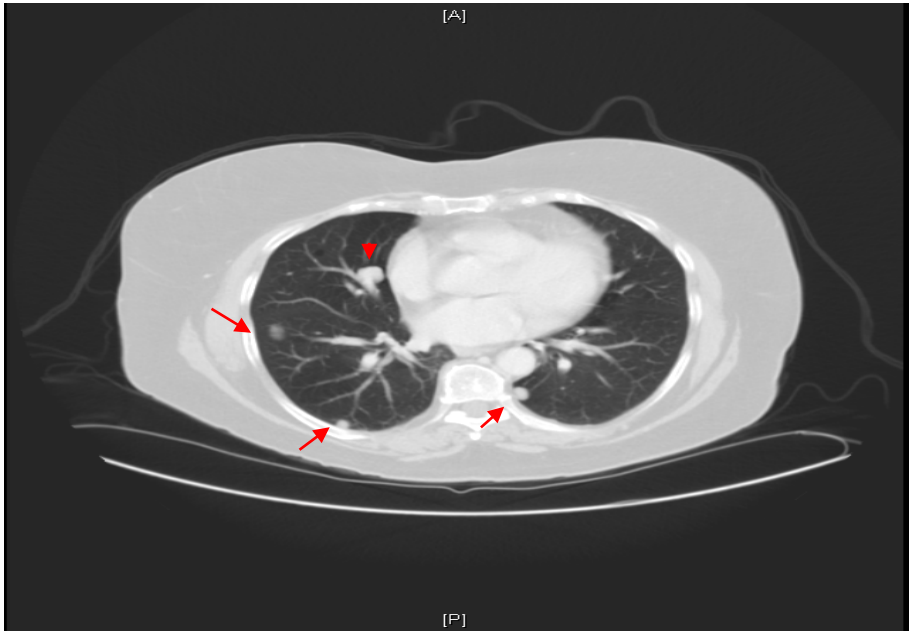
How well does conventional RAI work in metastatic thyroid cancer?

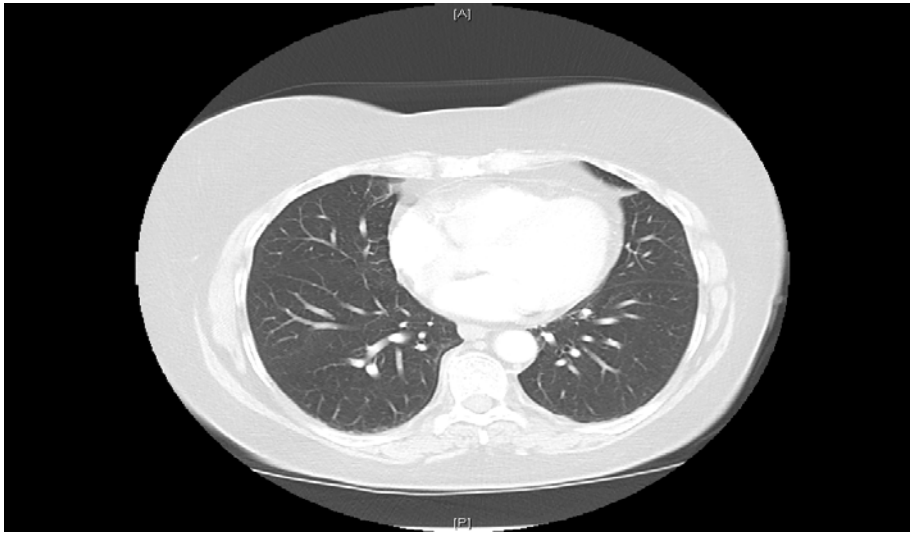
Efficacy of RAI therapy in patients with distant metastases of thyroid cancer

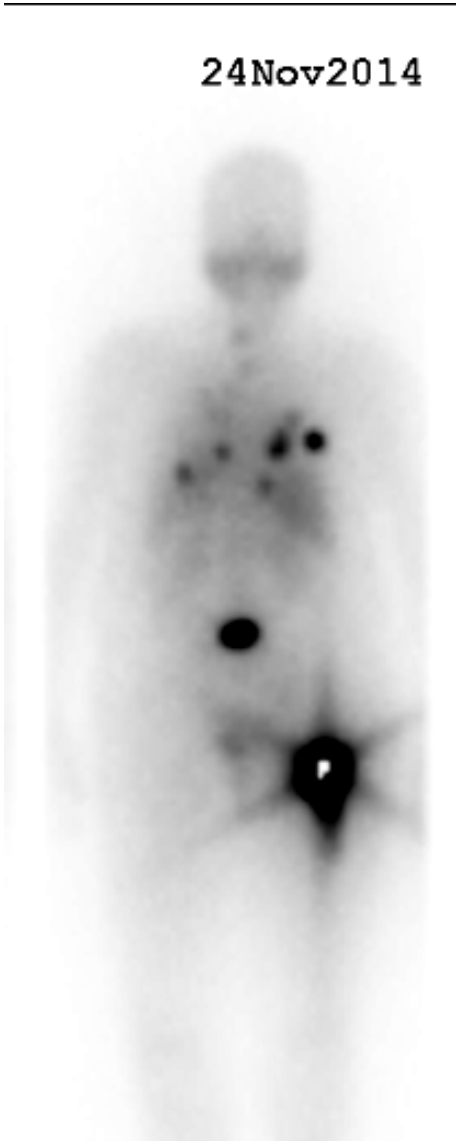
- Among 20,367 unique patients with thyroid cancer treated at MSKCC from 1985 to 2018, 5,863 received RAI therapy within the institution.
- Of these, 3,363 had undetectable TgAb, rendering serum Tg levels interpretable as a biomarker.
- Altogether, 221/3363 patients had Tg levels >200.
- 34/221 ended up with a Tg <20 after RAI, but only 11/221 (5%) had a structural response by RECIST v1.1.

Laura Boucai

Complete response of macronodular lung metastases to “conventional” RAI Rx.







We performed WES on patients with “exceptional” structural responses to conventional RAI.

1. NRAS-Q61R + EIF1AX A113-spl
2. KRAS-Q61R + EIF1AX A113-spl
3. KRAS-G12V
4. BRAF-G469A
5. RET/PTC1.
6. EML4/ALK (Mayo Clinic)

Metastatic thyroid cancers showing major structural responses to RAI are enriched for mutations that constitutively activate RAF dimers (e.g. *RAS*, class 2 *BRAF* mutations, RET fusions).

Treatment strategies for cancers derived from thyroid follicular cells:

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RAI-Refractory (RAIR) Metastatic Thyroid Cancer

- The subset with indolent/slow-growing disease can be closely followed without therapy.
- Systemic therapies for patients with oligometastatic disease can be deferred if individual lesions can be surgically removed or treated with radiotherapy or other ablative treatments.
- Drug therapies for RAIR metastatic disease are administered continuously with palliative intent.

RAI-Refractory (RAIR) Metastatic Thyroid Cancer

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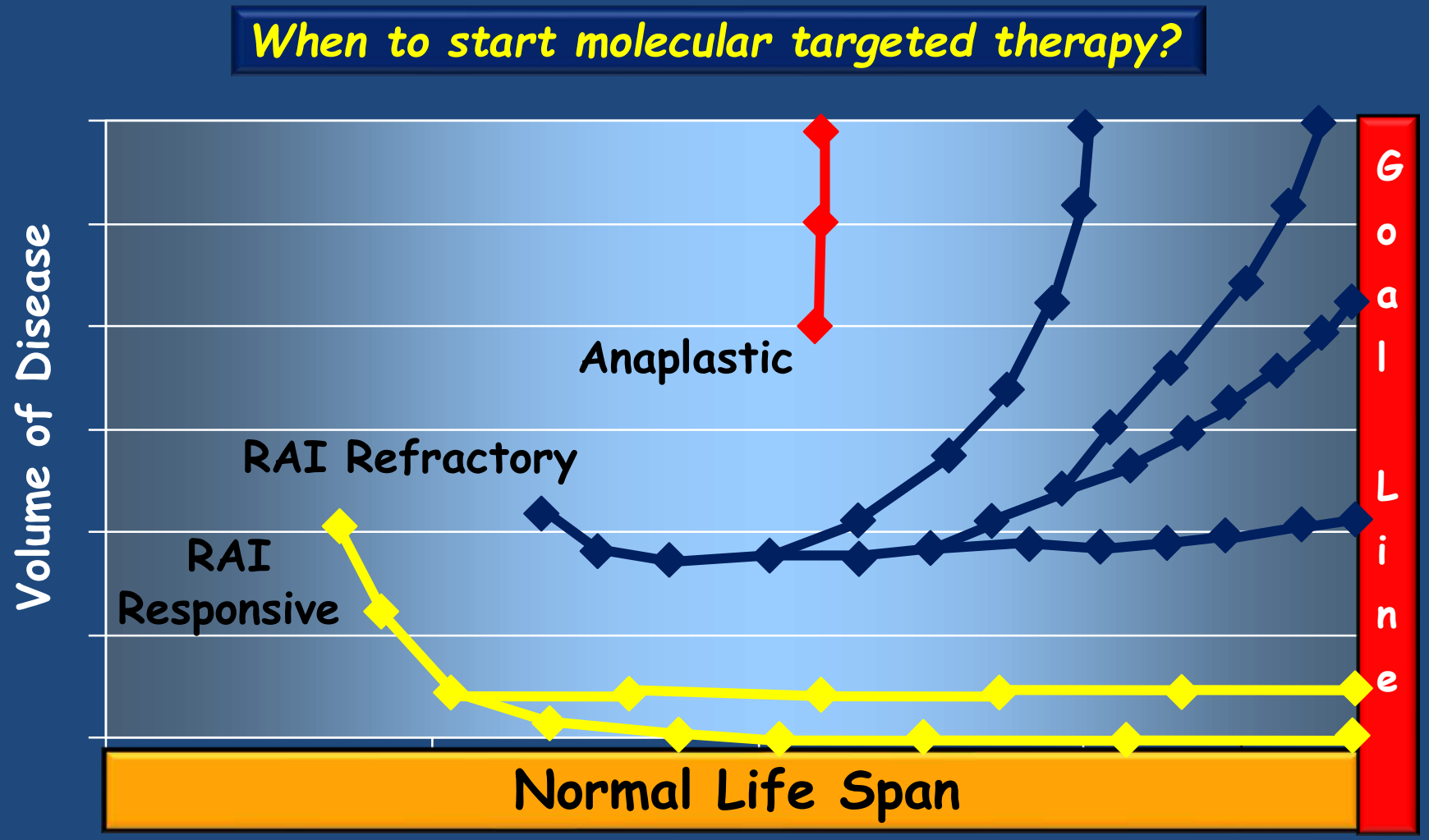
Variations in Rate of Progression in Patients with Metastatic Disease



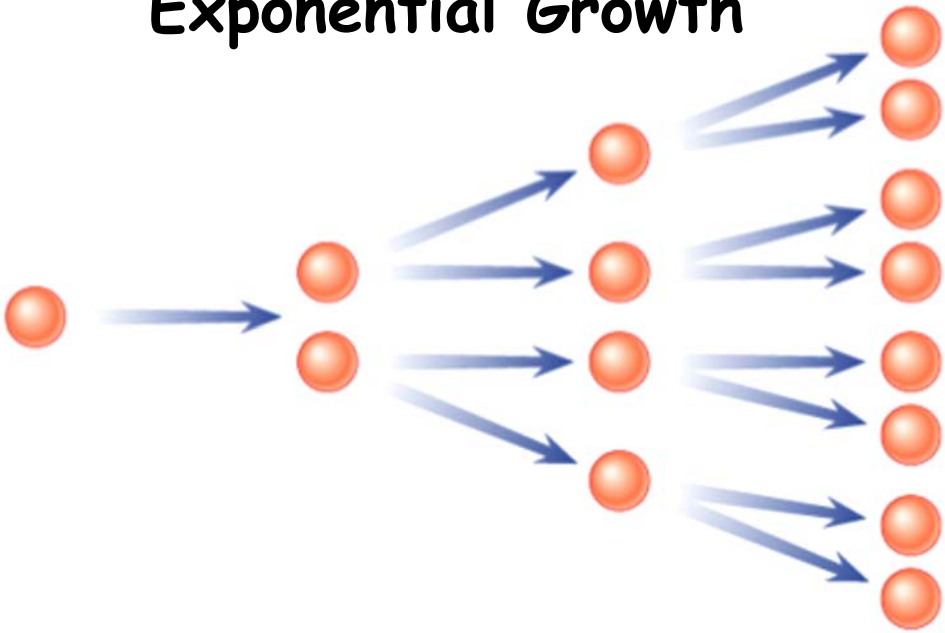
Exponential Growth Curve

1 →2 →4 →8 →16 →32 →62 →128

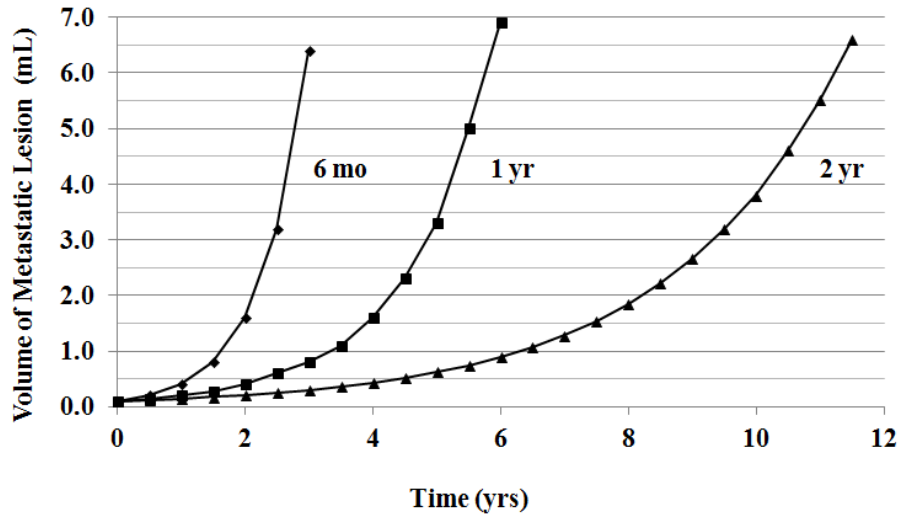
Graphically

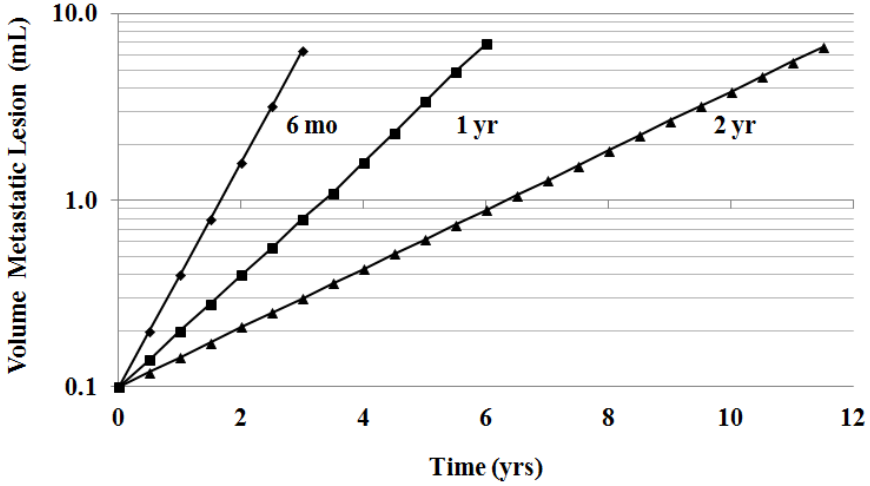
Time

Exponential Growth



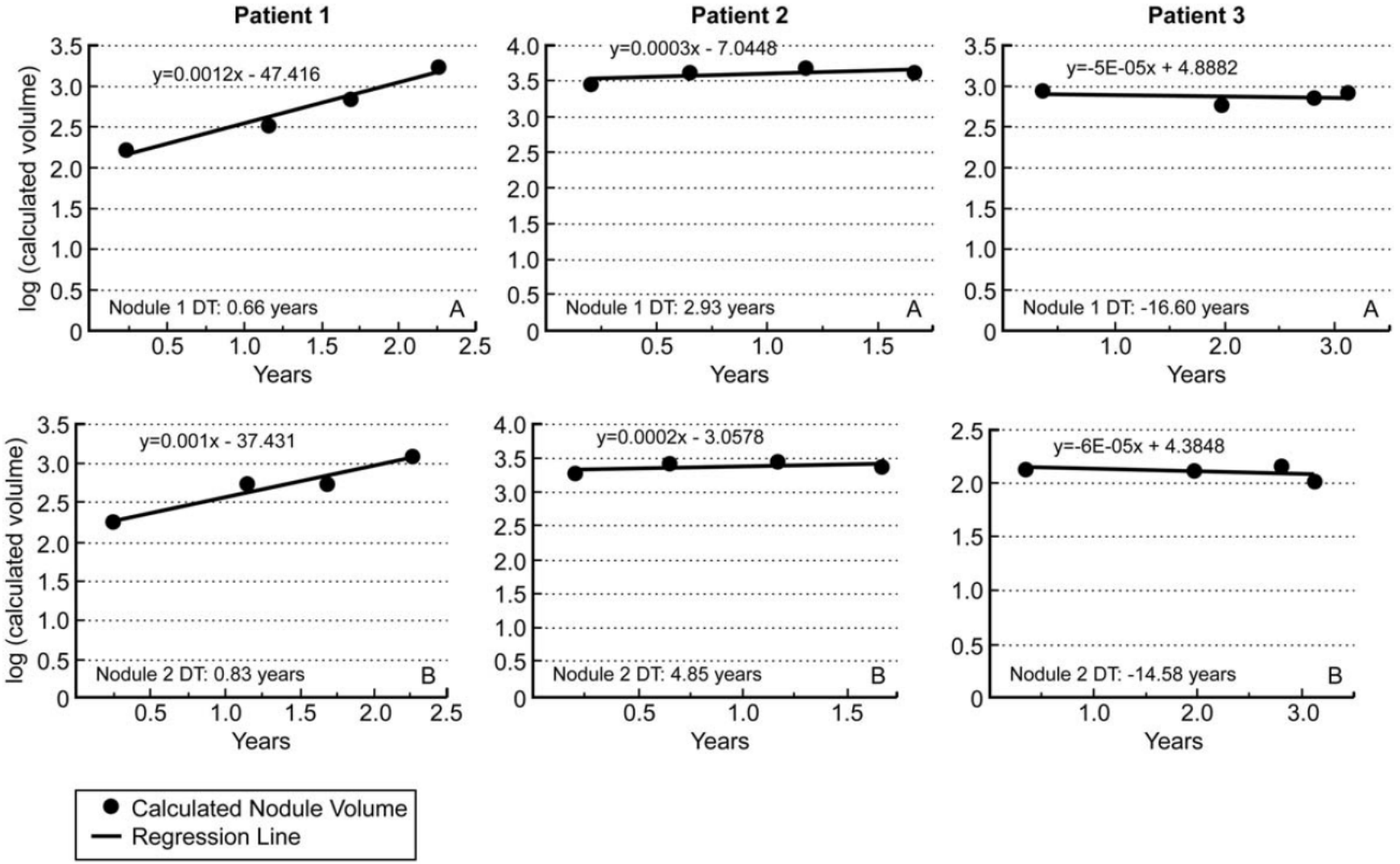
Growth Curves: Exponential Path





Structural Doubling Time In Pulmonary Metastases

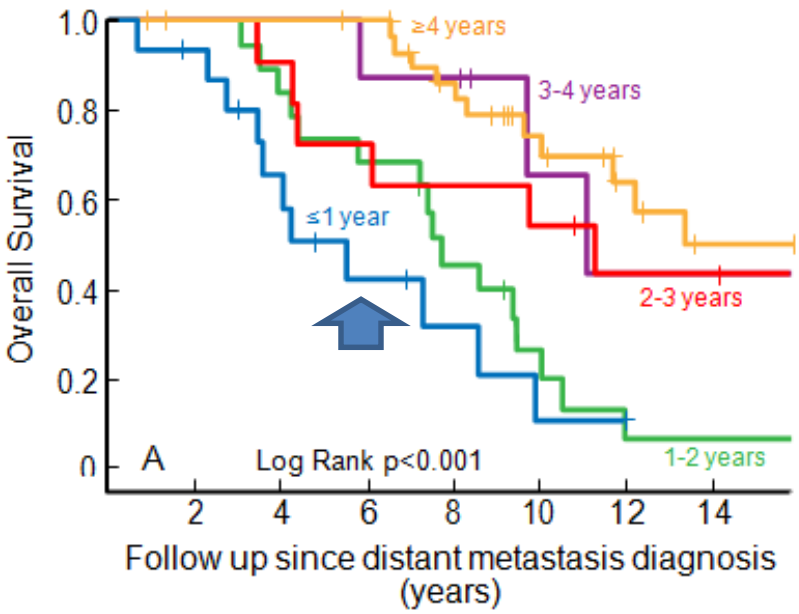
146 progressive pulmonary nodules, median 8.5 yrs, ($r=0.92$, $r^2=0.85$)



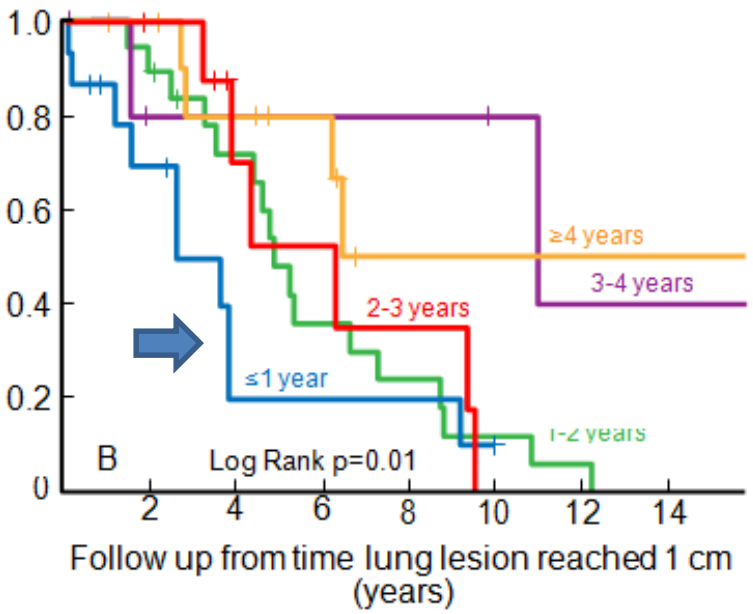
Sabra, Sherman, Tuttle. Cancer 2017

Structural midDT and Overall Survival

OS from DM diagnosis

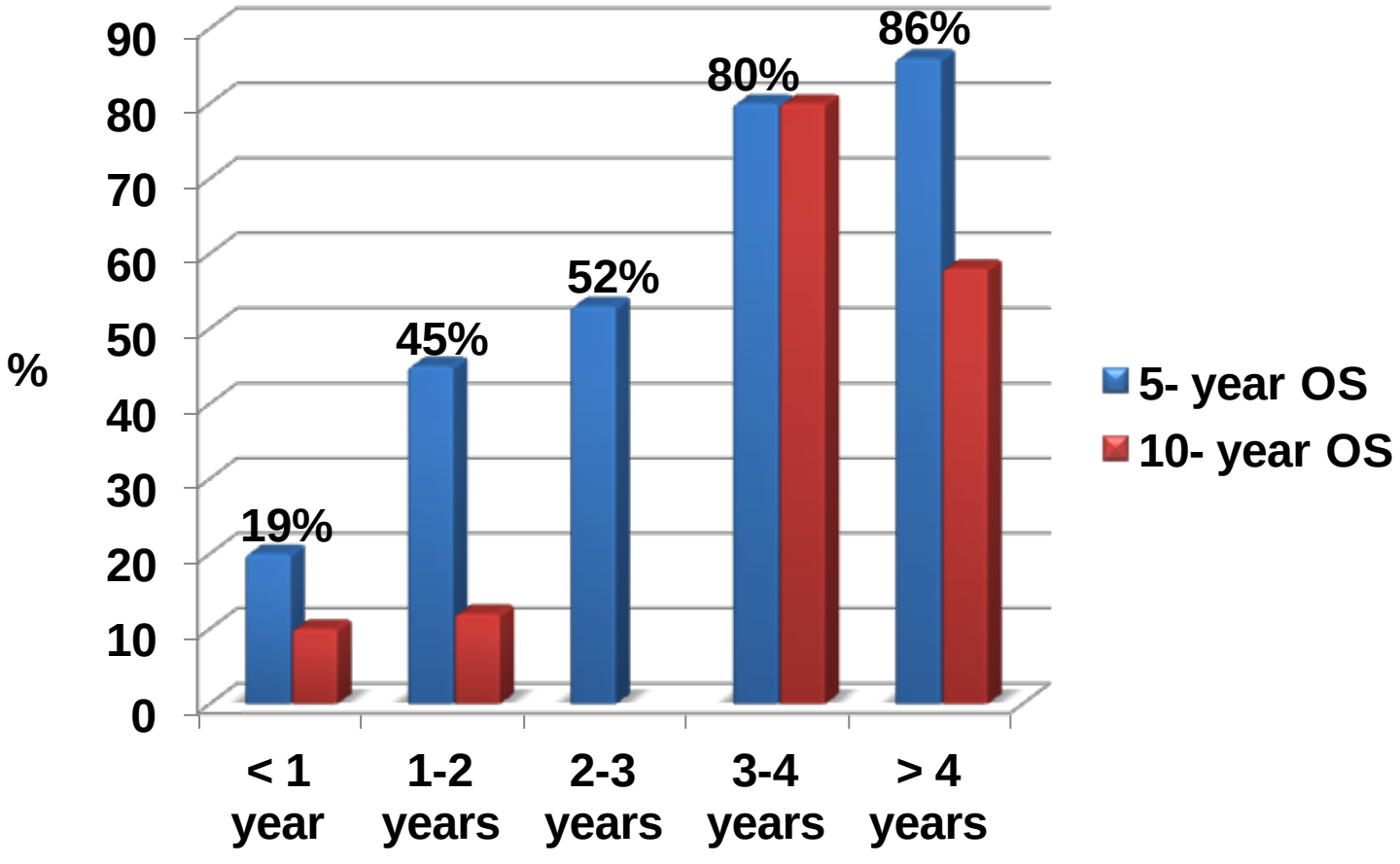


OS from 1 cm time point



Sabra et al. Cancer 2017; 15: 2955-2964

Structural midDT and overall survival from the time lung metastasis was 1 cm

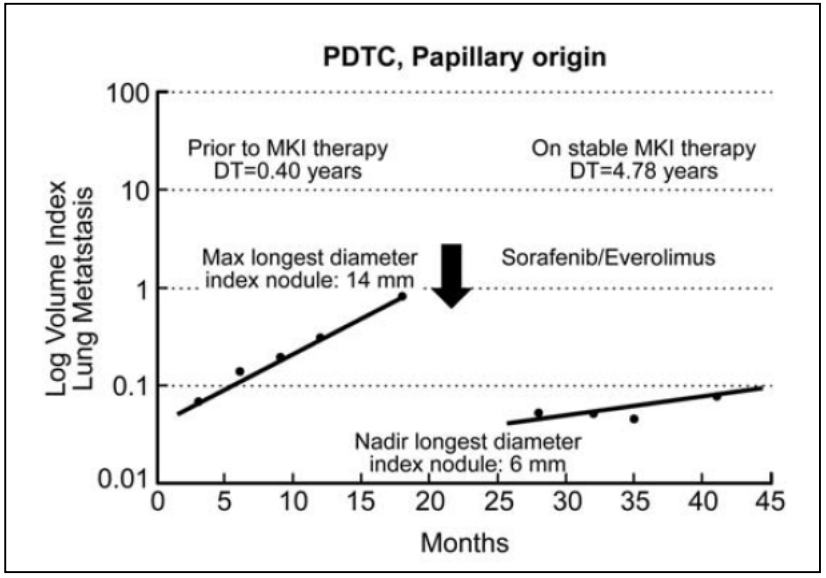


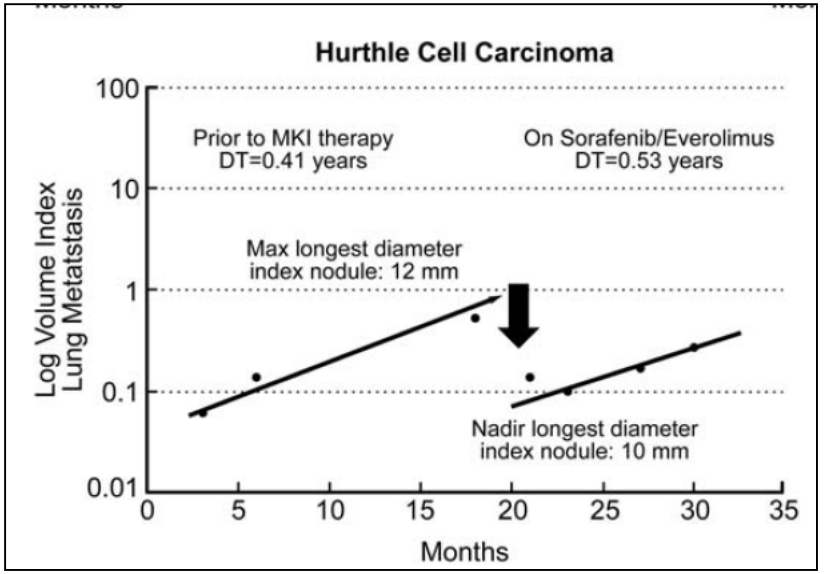
midDT

Sabra et al. Cancer 2017; 15: 2955-2964

Using Tumor Kinetics To Evaluate Effectiveness of Therapy

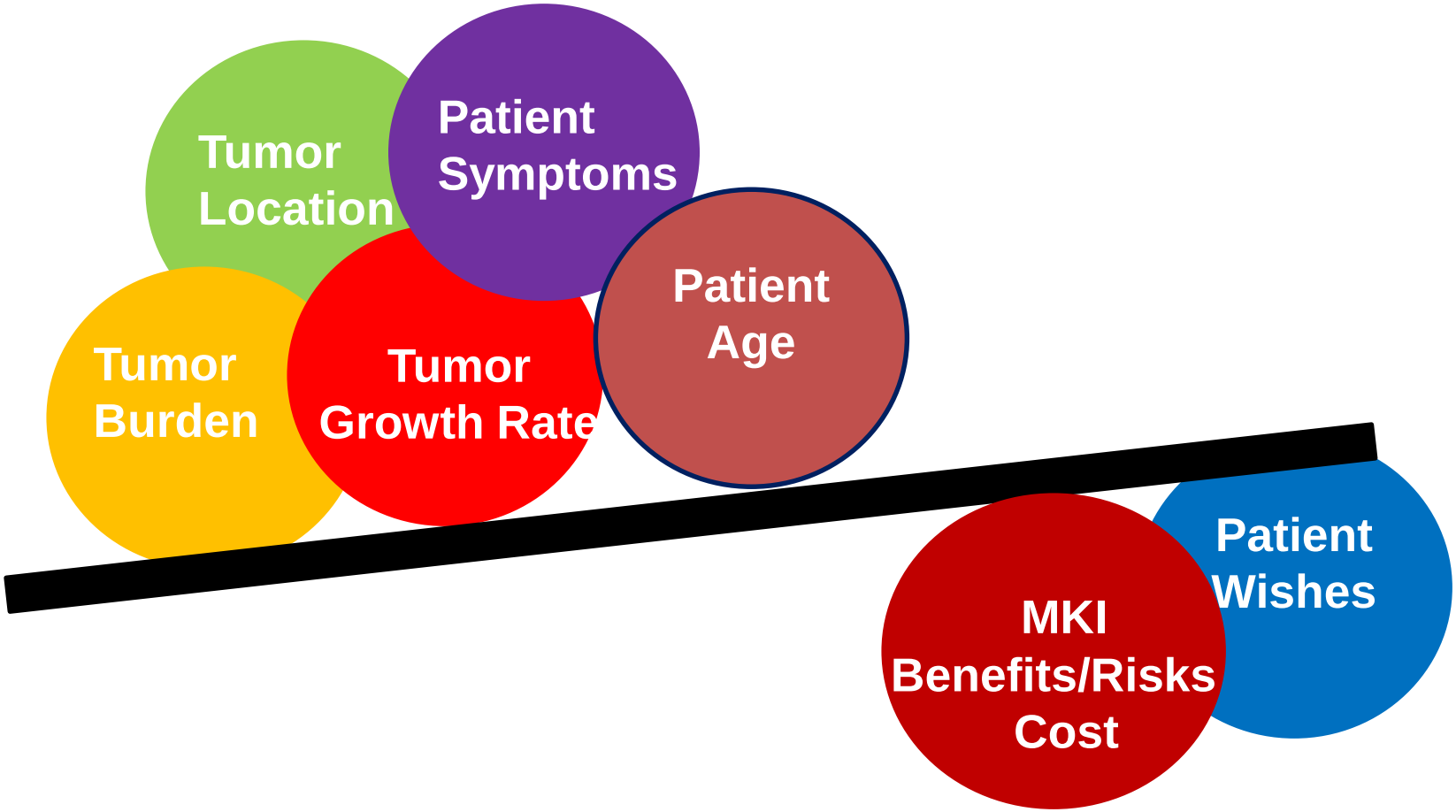
Impact of systemic therapy of the size and growth rates of pulmonary metastases





Sabra, Sherman, Tuttle. Cancer 2017

When to start therapy?



Therapeutic Targets in RAI-Refractory (RAIR) Thyroid Cancer

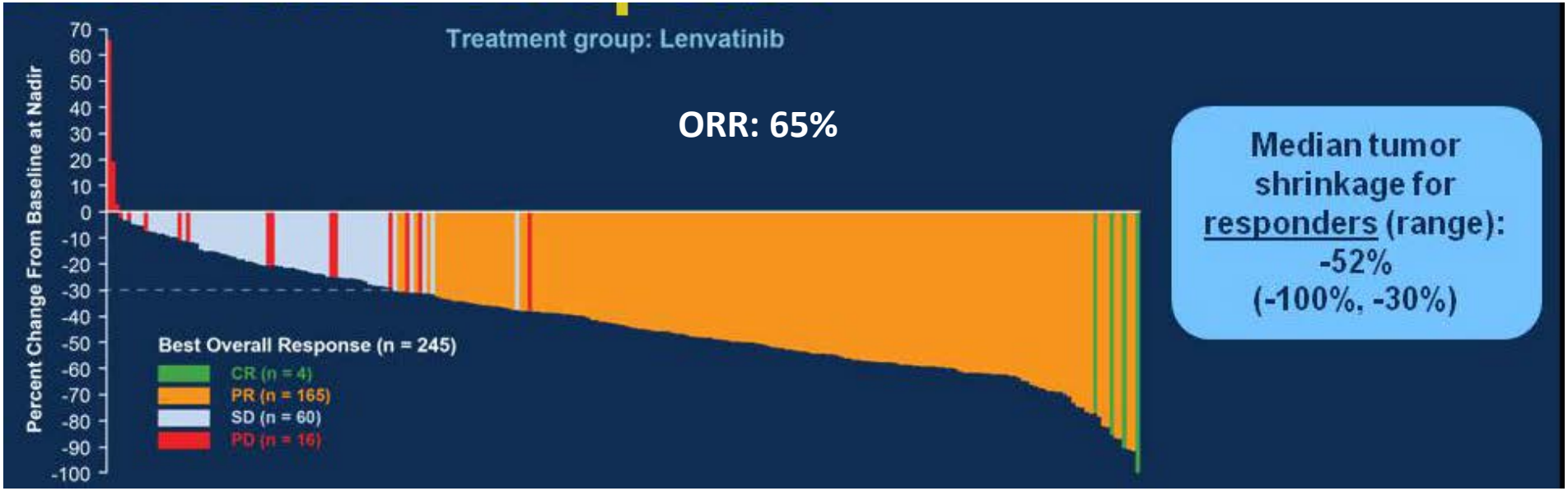
- Tumor vasculature.
- Cell autonomous targets: oncoprotein drivers.
- The immune microenvironment.

Targeting the vasculature:

Multi-targeted VEGFR TKIs Phase II Studies

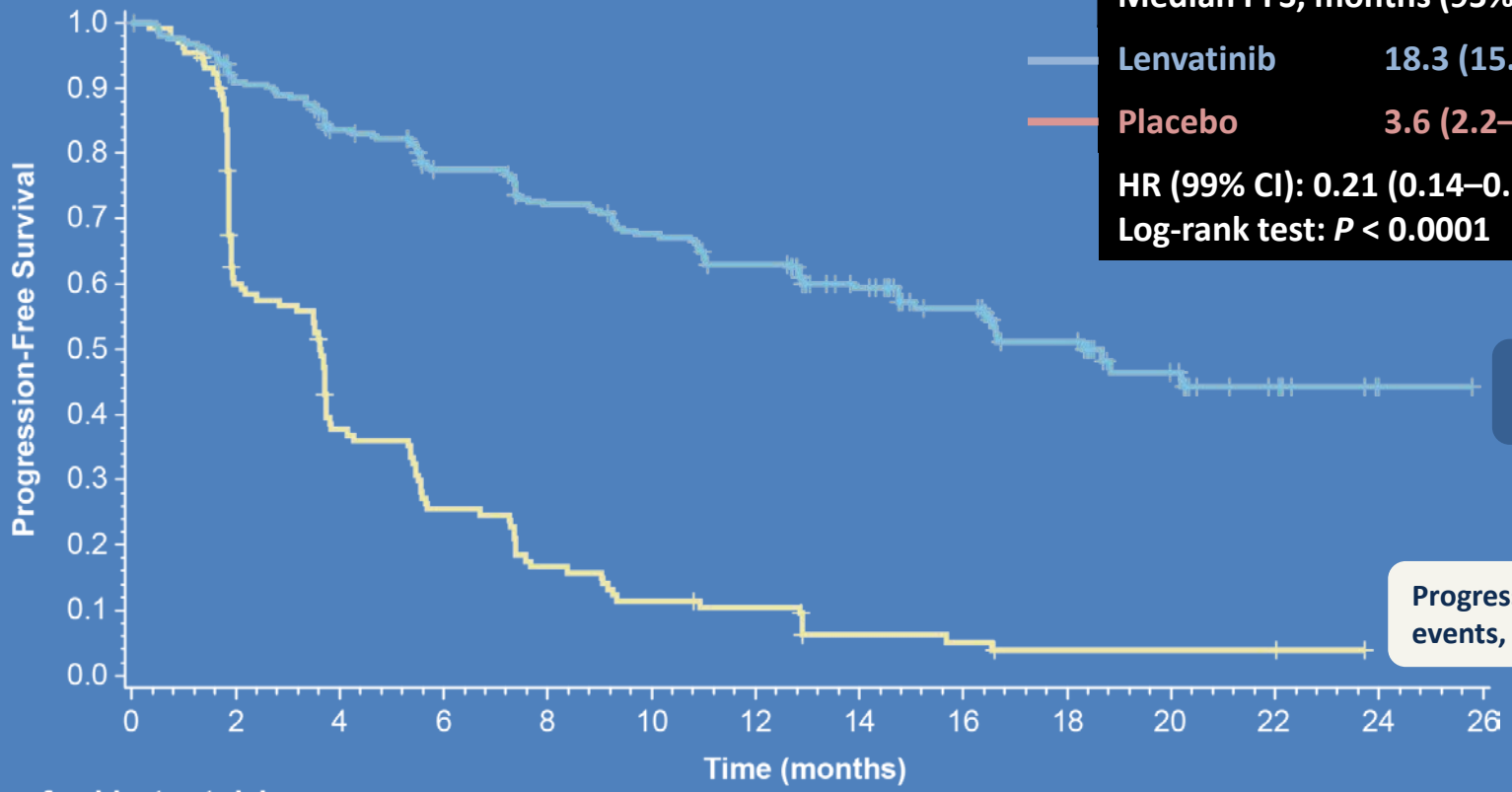
Agent	#	PR/CR	SD	Site
Sorafenib	56	11%	63%	Ohio State
Sorafenib	25	23%	53%	Univ. of Pennsylvania
Sunitinib	29	28%	48% (?)	Univ. of Washington
Sunitinib	35	17%	74%	Univ. of Chicago
Pazopanib	37	49%	43% (?)	Mayo Clinic
Axitinib	45	31%	42%	Multi-Site
Motesanib	93	14%	67%	Amgen
Lenvatinib	58	59%	36%	Multi-Site
VEGFtrap	40	0%	83%	MSKCC
Sorafenib/Everolimus	28	50%	46%	MSKCC

Waterfall of Best Response: Lenvatinib vs. Placebo



Presented By Martin Schlumberger at 2014 ASCO Annual Meeting

Select trial: Kaplan-Meier Estimate of PFS



Number of subjects at risk:

Lenvatinib	261	225	198	176	159	148	136	92	66	44	24	11	3	0
Placebo	131	71	43	29	19	13	11	5	4	2	2	2	0	0

CI, confidence interval; HR, hazard ratio; NR, not reached.

SELECT Trial: Safety Profile

Adverse Reaction	LENVIMA 24 mg, % (n=261)		Placebo, % (n=131)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
Vascular disorders				
Hypertension[a]	73	44	16	4
Hypotension	9	2	2	0
Gastrointestinal disorders				
Diarrhea	67	9	17	0
Nausea	47	2	25	1
Stomatitis[b]	41	5	8	0
Vomiting	36	2	15	0
Abdominal pain[c]	31	2	11	1
Constipation	29	0.4	15	1
Oral pain[d]	25	1	2	0

SELECT Trial: Safety Profile (Cont.)

Adverse Reaction	LENVIMA 24 mg, % (n=261)		Placebo, % (n=131)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
General disorders and administration site conditions				
Fatigue[e]	67	11	35	4
Edema peripheral	21	0.4	8	0
Musculoskeletal and connective tissue disorders				
Arthralgia/myalgia[f]	62	5	28	3
Metabolism and nutrition disorders				
Weight decreased	51	13	15	1
Decreased appetite	54	7	18	1
Dehydration	9	2	2	1
Nervous system disorders				
Headache	38	3	11	1
Renal and urinary disorders				
Proteinuria	34	11	3	0

SELECT Trial: Safety Profile (Cont.)

Adverse Reaction	LENVIMA 24 mg, % (n=261)		Placebo, % (n=131)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
Skin and subcutaneous tissue disorders				
Palmar-plantar erythrodysesthesia	32	3	1	0
Rash[g]	21	0.4	3	0
Respiratory, thoracic, and mediastinal disorders				
Dysphonia	31	1	5	0
Cough	24	0	18	0

DECISION: Phase III Sorafenib vs. Placebo in RAIR, R/M Differentiated Thyroid Cancer

1:1 randomized, double blind Phase III trial in RAIR, progressive LA/metastatic thyroid cancer

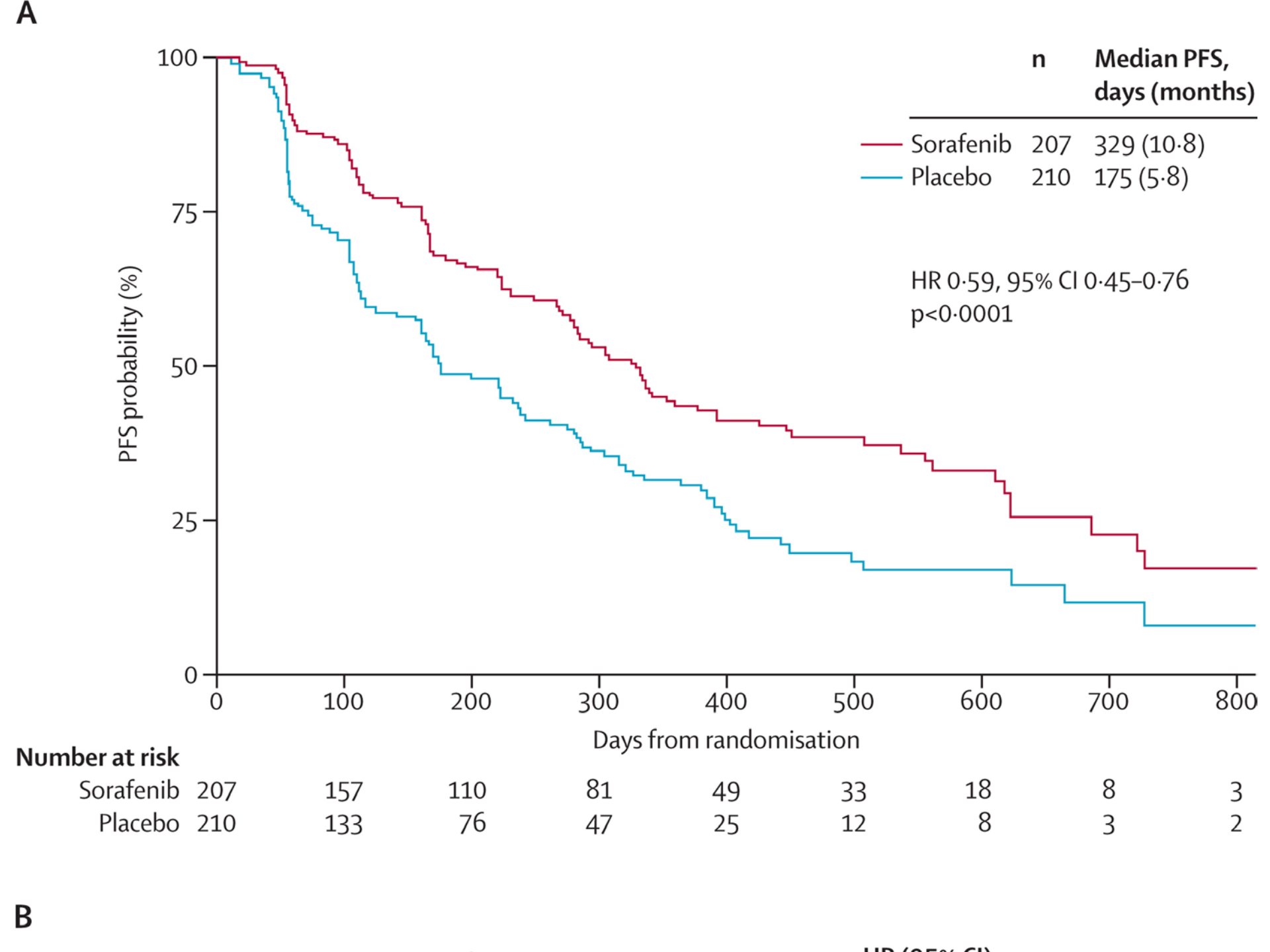
Median Progression-Free Survival (PFS)

Placebo: 5.8 months **HR: 0.59 (95%CI: 0.45-0.76, p< 0.0001)**

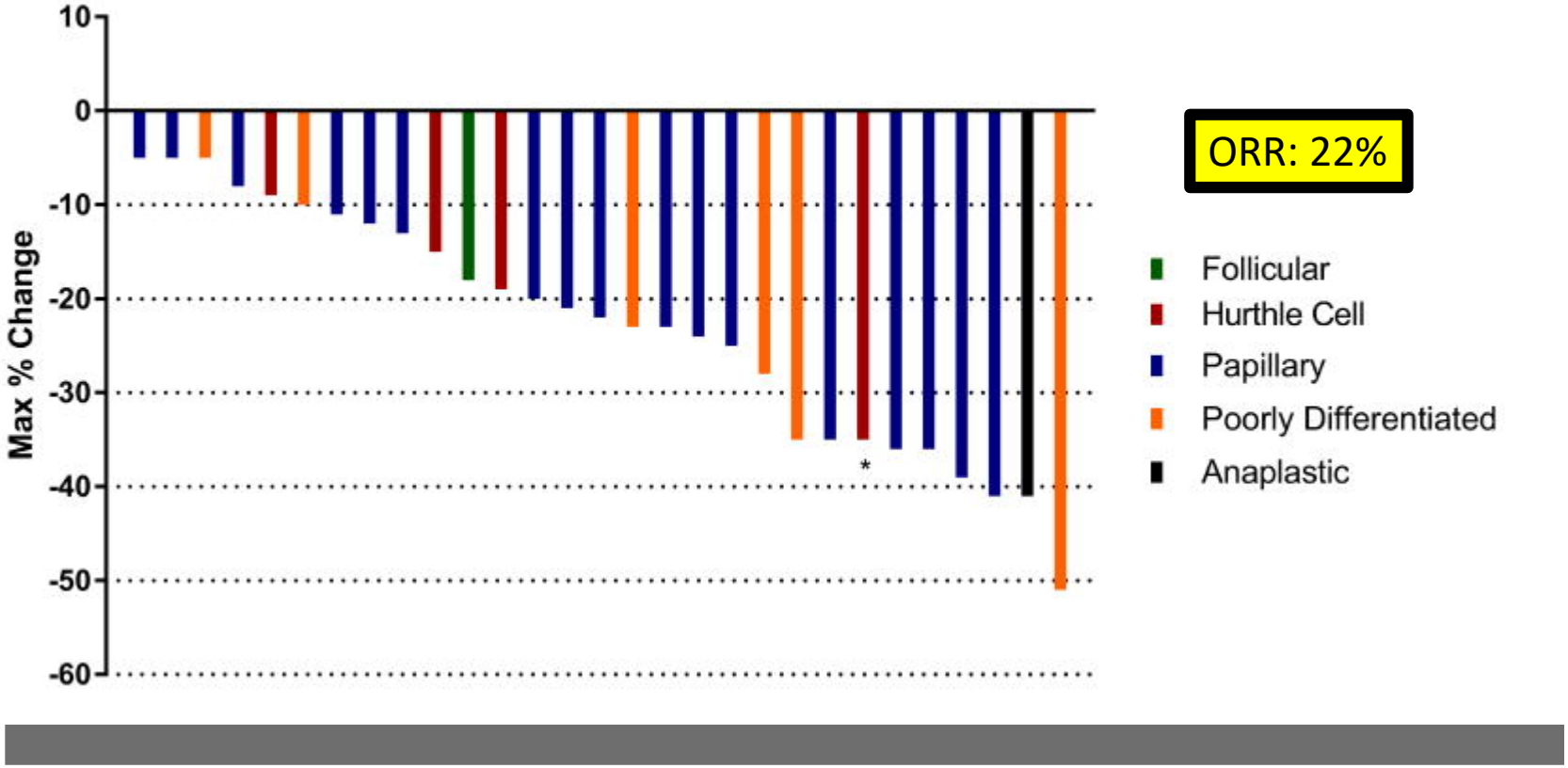
Sorafenib: 10.8 months

	Sorafenib n (%)	Placebo n (%)	p-value
Total Evaluable Patients	196	201	
Overall Response Rate	**24 (12.2)**	**1 (0.05)**	**<0.0001**
Complete Response	0	0	-
Partial Response	24 (12.2)	1 (0.05)	-
Stable Disease ≥ 6 months	82 (41.8)	67 (33.2)	-
DCR (CR+PR+SD)	**106 (54.1)**	**68 (33.8)**	**<0.0001**
Dose interruption due to AEs, %	66.2	25.8	
Dose reduction due to AEs, %	64.3	9.1	
Permanent discontinuation due to AEs, %	18.8	3.8	

Brose, MS et. al., *Lancet*, 384: 319-328, 2014.


A
100
75
50
25
0
PFS probability (%)
n
Median PFS, days (months)
Sorafenib 207 329 (10·8)
Placebo 210 175 (5·8)
HR 0·59, 95% CI 0·45–0·76
p<0·0001
0
100
200
300
400
500
600
700
800
Days from randomisation
Number at risk
Sorafenib 207 157 110 81 49 33 18 8 3
Placebo 210 133 76 47 25 12 8 3 2
B

Combination therapies with sorafenib



Waterfall plot of Best Response per histologic subtype

Phase 2 trial of sorafenib + tensirolimus in RAIR thyroid cancer. Sherman EJ et al. Cancer 2017.

TKI plus mTORC1 Inhibitor: Sorafenib plus Everolimus

Study rationale:

– PI3K/Akt/mTOR pathway alterations in thyroid cancer

– PI3K/Akt/mTOR pathway mediates resistance to TKIs?

	PR	*PR	SD	POD
Papillary	5 (56%)	0	3 (33%)	1 (11%)
Follicular	1 (50%)	0	1 (50%)	0
Hurthle Cell	6 (67%)	1 (11%)	2 (22%)	0
Poorly Differentiated	4 (50%)	0	4 (50%)	0
Medullary[1]	4 (40%)	0	4 (40%)	2 (20%)
Total	**20 (52%)**	**1 (3%)**	**14 (37%)**	**3 (8%)**

[1] Six of 10 patients with medullary thyroid cancer had been on ≥ 1 prior regimens

Eric Sherman

TKIs in RAIR Thyroid: When to Treat?

- Systemic therapy is palliative not curative.
- Spectrum of clinical aggressiveness exists for RAIR thyroid cancers (indolent→aggressive).
- TKI impact upon overall survival has not been demonstrated.
- Therapy requires continuous management of drug toxicities.
  - Common AEs: Hand-foot syndrome, hypertension, fatigue, diarrhea, asthenia, anorexia, proteinuria, alopecia.
  - Mortality: (lenvatinib) 6 drug-related deaths; (sorafenib) 1 drug-related death

BASIC PARADIGM

Treat when risk of *progressive disease* and/or *tumor-related symptoms* outweigh risks of systemic therapy.

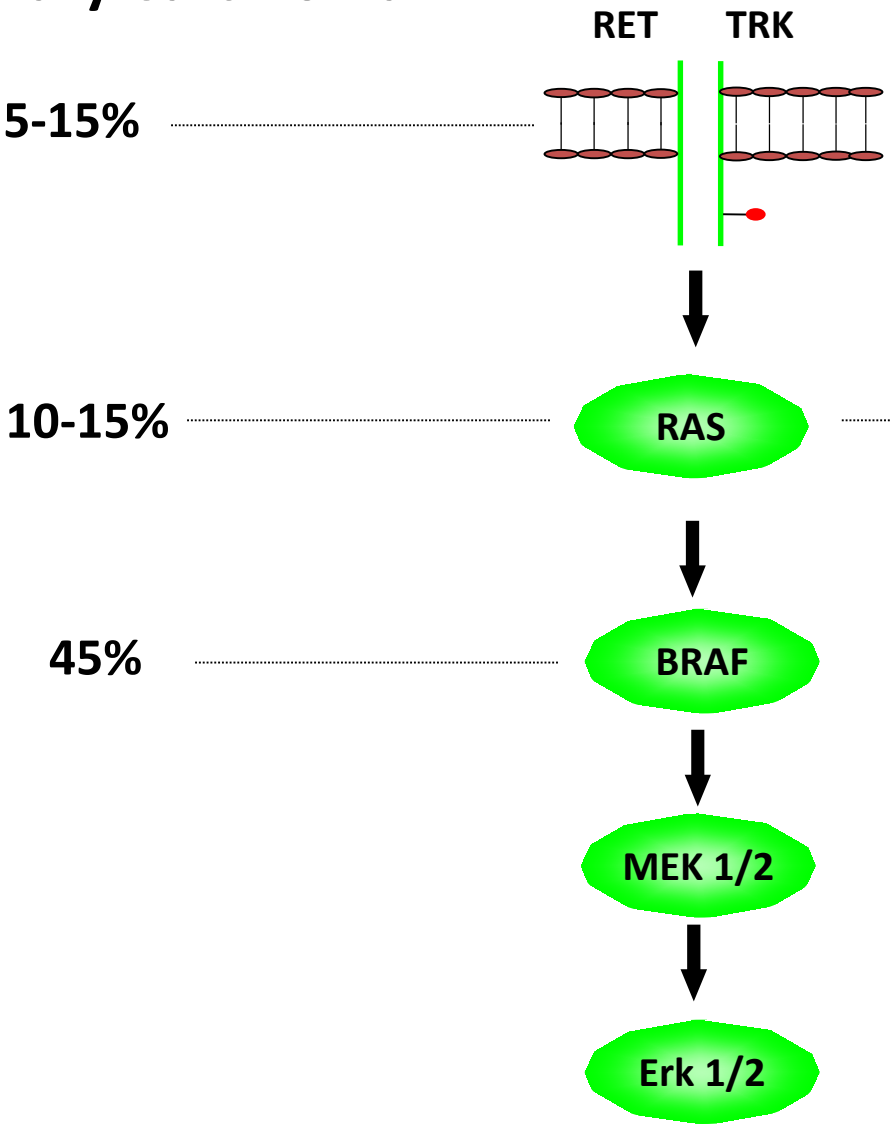
Therapeutic Targets in RAI-Refractory (RAIR) Thyroid Cancer

- Tumor vasculature.
- Cell autonomous targets: oncoprotein drivers.
- The immune microenvironment.

MAPK Pathway Alterations in Differentiated Thyroid Cancers

Papillary Carcinoma

Follicular Carcinoma



Phase II: Vemurafenib in RAIR R/M Thyroid Cancer

- Recurrent, unresectable or metastatic papillary thyroid cancer
- BRAF V600E mutation+
- Radioactive iodine refractory
- Evidence of progression within 14 months
- Prior chemotherapy allowed

→ VEGFR2i-naïve (n=26)

→ VEGFR2i-pretreated (n=25)

→ Vemurafenib 960 mg BID until disease progression or unacceptable toxicity

Vemurafenib (Zelboraf; Genentech/Daiichi Sankyo)

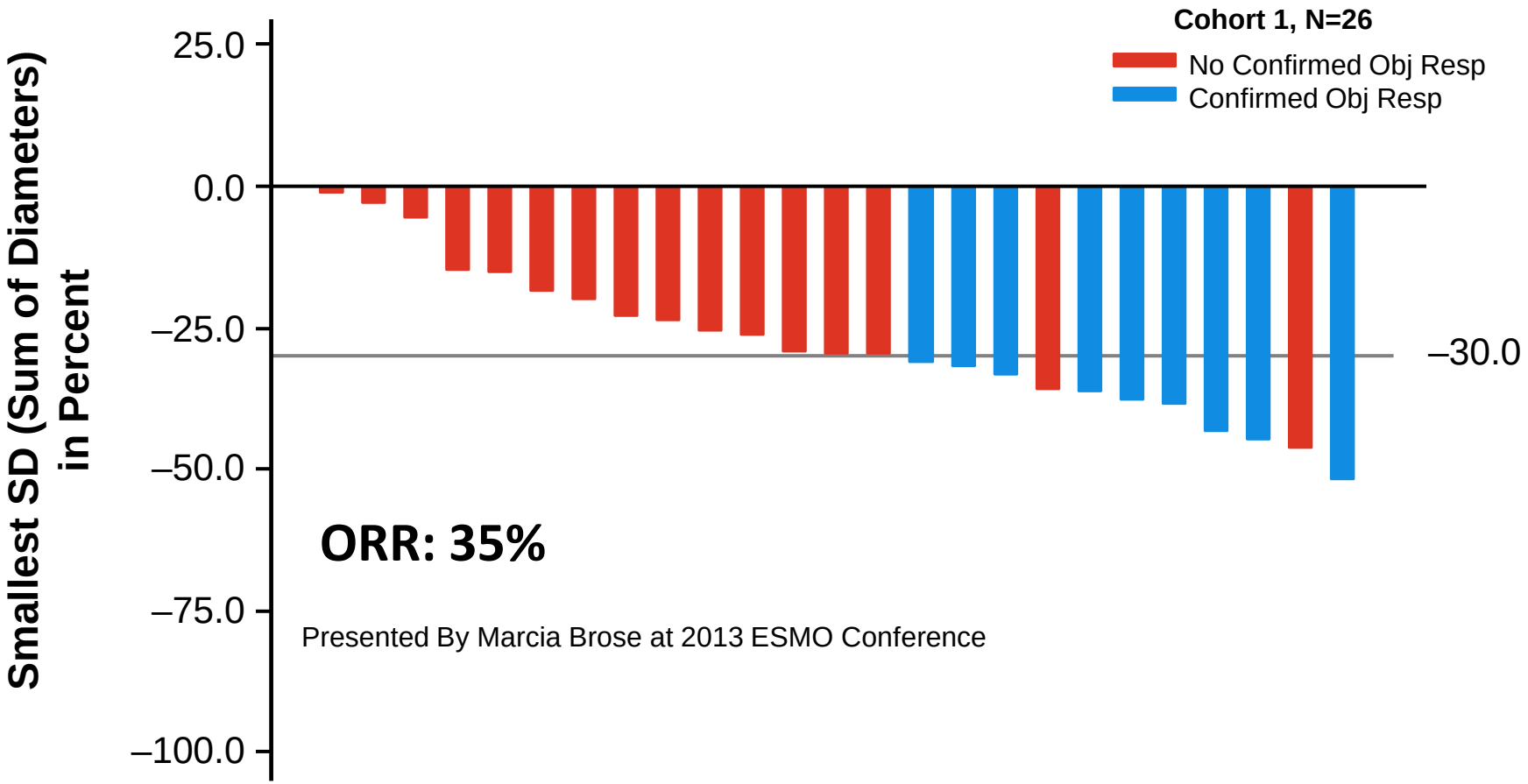
Potent, selective ATP-competitive inhibitor of BRAF (V600E)

FDA approved for unresectable/metastatic, *BRAF*^{V600E} mutant melanoma

IC50 *in vitro* (nM) (purified kinases)	
BRAF^{V600E}	35
BRAF	110
CRAF	48
Brk	240
Kit	610
KDR	5300

Brose M., et. Al., *Lancet Oncol*, 2016

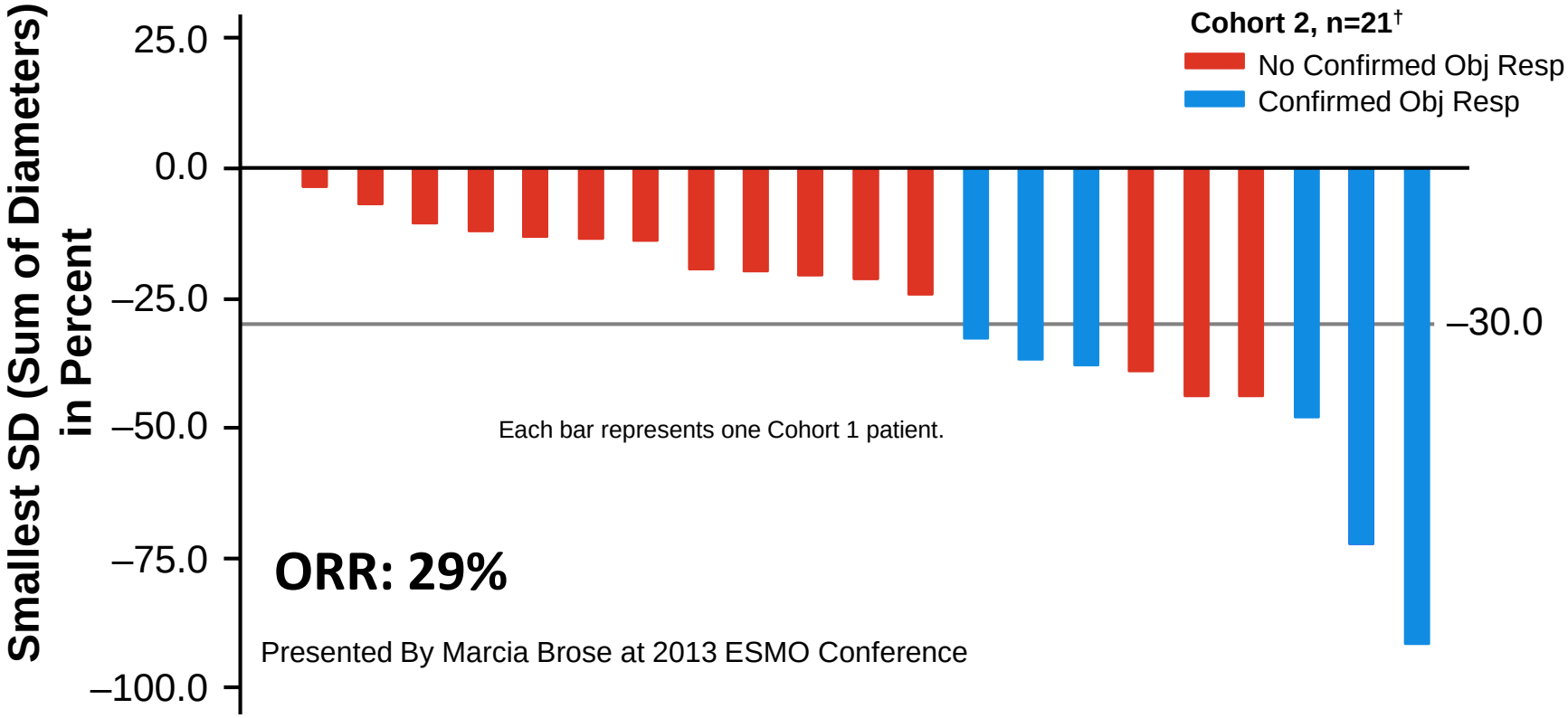
Cohort 1: VEGFR2i-naïve



ORR: 38.5% (10/26)
SD ≥ 6 mos: 35% (9/26)
mPFS: 18.2 mos (95%CI 15.5-29.3mos)
mOS: NR

(Brose M, Lancet Oncol, 2016)

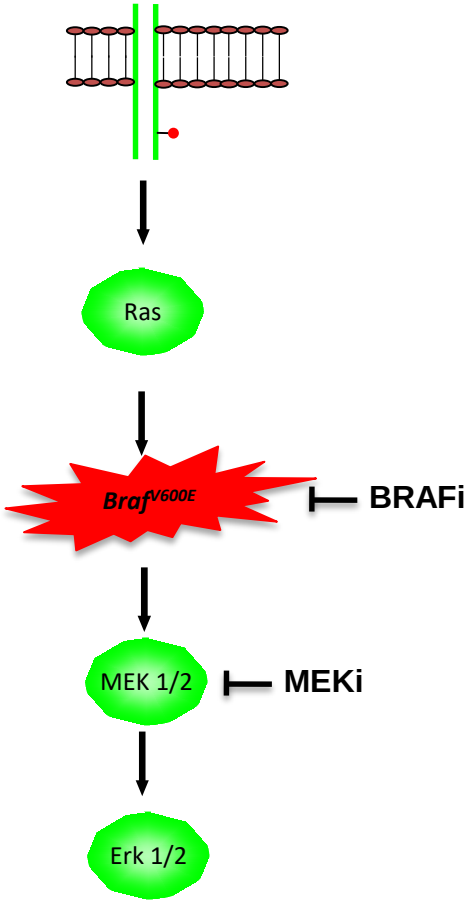
Cohort 2: VEGFR2i-pretreated



ORR: 27.3% (6/22)
SD ≥ 6 mos: 27.3% (6/22)
mPFS: 8.9 mos (95%CI 5.5-NE mos)
mOS: 14.4 mos (8.2-29.5 mos)

(Brose M, Lancet Oncol, 2016)

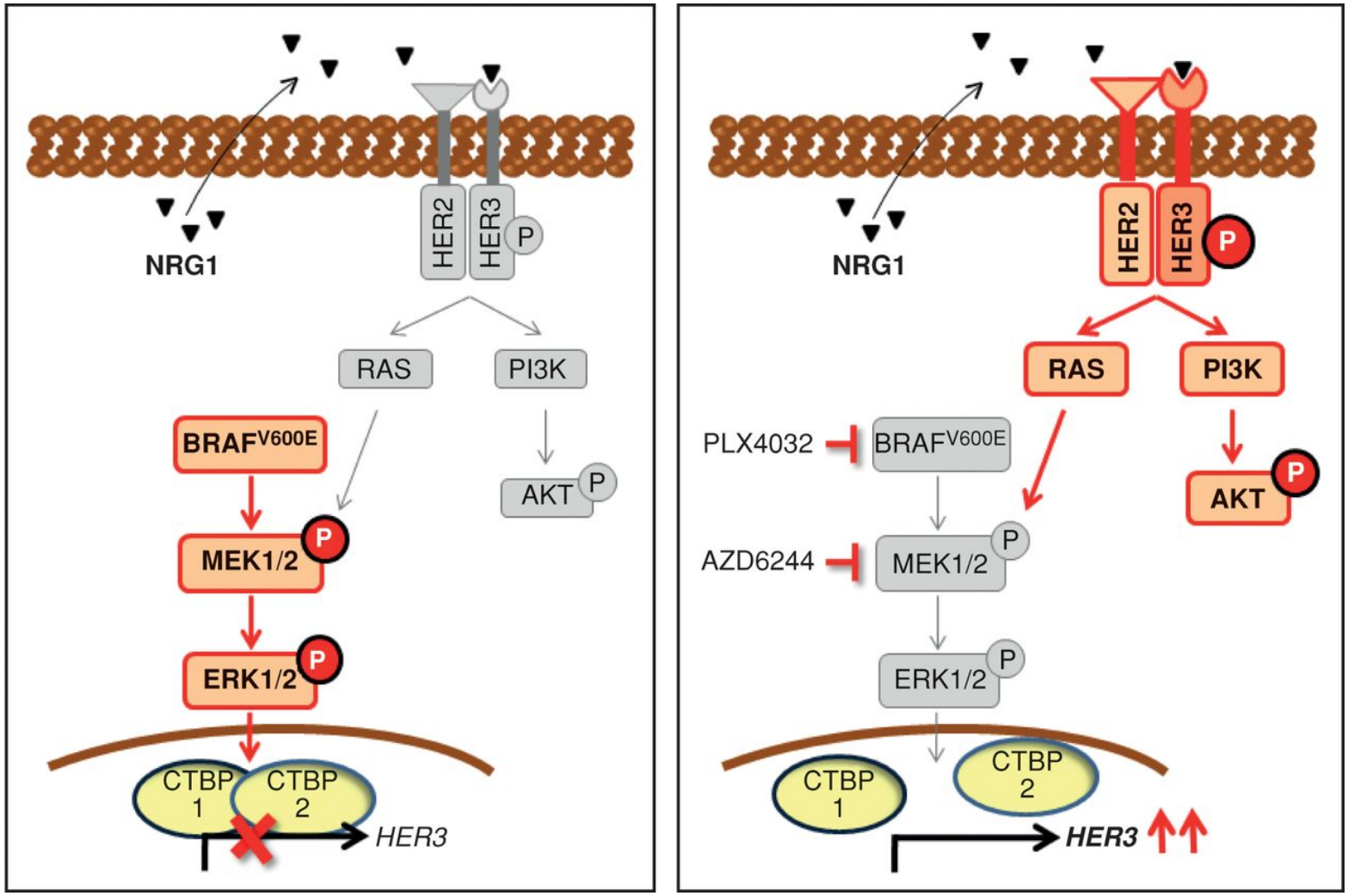
BRAF Inhibitor Combinations



RAIR-DTC	Vemurafenib No Prior RXN	Vemurafenib Prior RXN
PR + CR	10/26 (38%)	6/22 (27%)

Shah, MH *2017 ASCO Annual Meeting*
Sherman, ES *2017 ASCO Annual Meeting*

Model of HER2/HER3-induced primary resistance to MAPK inhibitors in BRAF-mutant thyroid cancer cells.



Cristina Montero-Conde et al. Cancer Discovery 2013;3:520-533

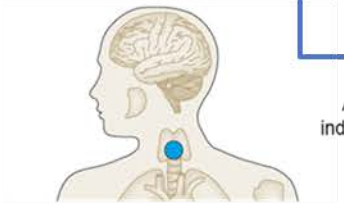
Response Rate in DTC of co-inhibition of $BRAF^{V600E}$ and HER kinases

Dabrafenib/Lapatinib

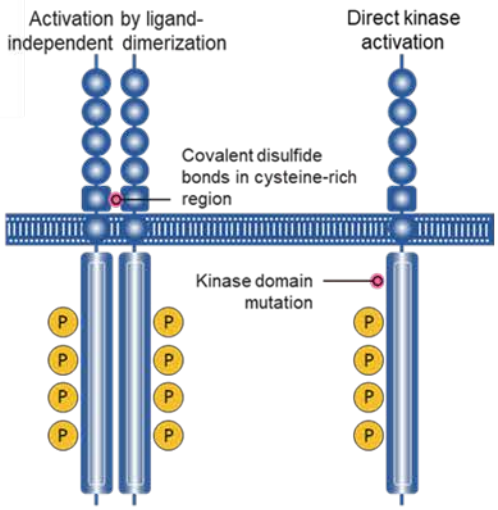
Cohort	#	DTC only	
		Response Rate	Median PFS
DTC Group only	**19**	**58%**	**18m**
1 – Lapatinib 750mg	5	60%	11m
2 – Lapatinib 1250mg	2	50%	27.5m
3 – Lapatinib 1500mg	12	58%	20m
No Prior BRAF inhibitor	14	64%	29m
No Brain Metastases	14	57%	20m
No Prior BRAF inhibitor or Brain Metastases	11	64%	29m

RET is activated by two major mechanisms in thyroid cancer

RET mutations

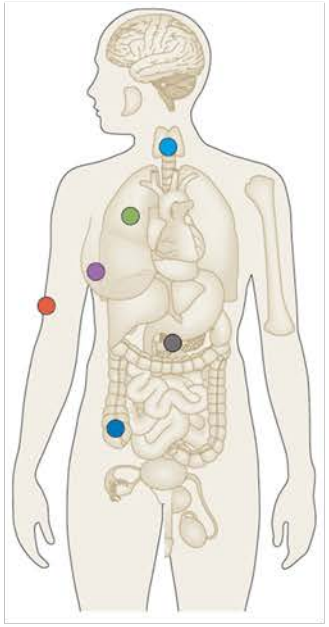


Medullary thyroid cancer
sporadic (>60%)
hereditary (>90%)

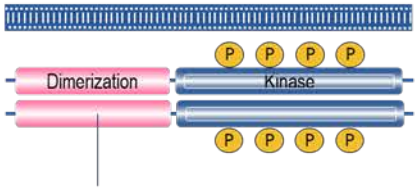


Common mutation: **RET M918T**

RET fusions



Non-small cell lung cancer (2%)
Thyroid cancers (10–20%)
Pancreatic cancer (<1%)
Salivary gland cancer (<1%)
Spitz tumors (<1%)
Colorectal cancer (<1%)
Ovarian cancer (<1%)
Myeloproliferative disorders (<1%)
Many others (<1%)



KIF5B (most common in lung cancer)
CCDC6* or *NCOA4 (most common in thyroid cancer)

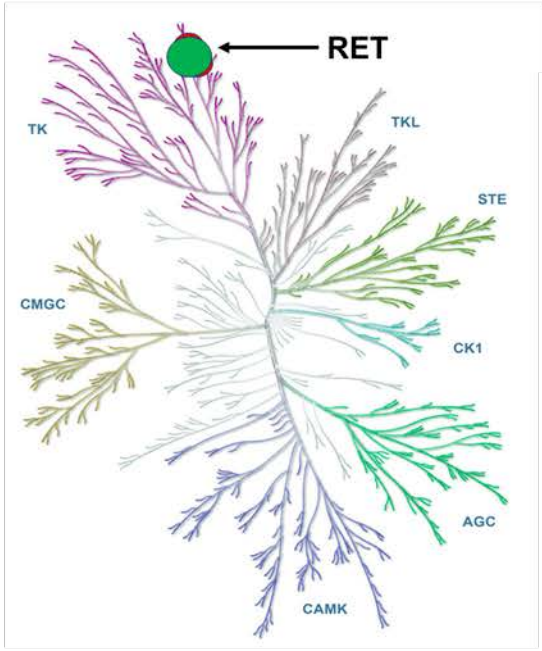
Anti-RET multikinase inhibitors (MKIs): approved for MTC and differentiated thyroid cancers but highly toxic; treatment options after failure of 1st MKI are limited

References: Drilon et al. Nat Rev Clin Oncol. 2018; 15:151–67; Kato et al. Clin Cancer Res. 2017; 23:1988–97; Pietrantonio et al. Ann Oncol. 2018; 29:1394–401; Su et al. PLoS One. 2016; 11:e0165596.

Selpercatinib* (LOXO-292) is a potent and selective *RET* inhibitor

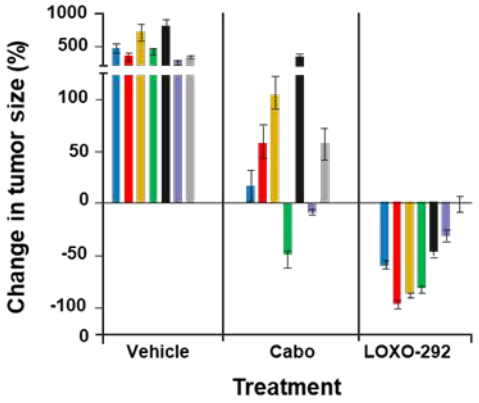
Kinome selectivity

Highly selective for RET



Xenograft models

Multiple fusions/mutations/histologies

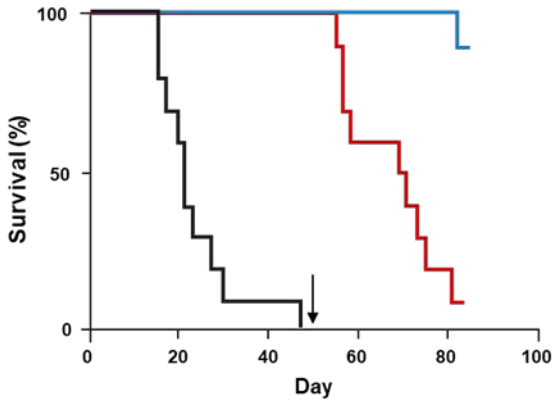


Tumor models

- KIF5B-RET (PDX-NSCLC)
- CCDC6-RET (PDX-CRCA)
- CCDC6-RET-V804M (PDX-CRCA)
- KIF5B-RET (NIH-3T3)
- KIF5B-RET-V804M (NIH-3T3)
- RET C634W (TT cell line-MTC)
- CCDC6-RET (LC-2/ad cell line-NSCLC)

Orthotopic brain model

CCDC6-RET orthotopic brain PDX



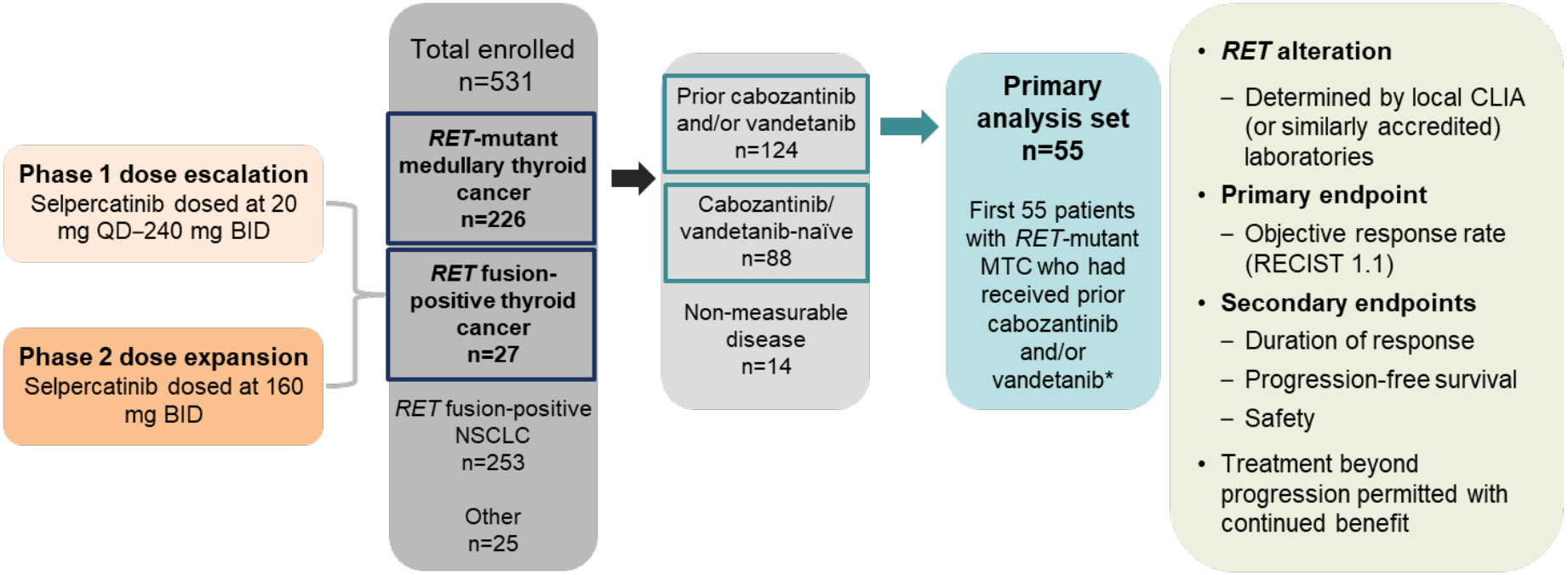
Treatments

- Vehicle
- LOXO-292 30 mg/kg BID → Day 52 → 3 mg/kg BID
- Ponatinib 20 mg/kg QD → Day 52 → 2 mg/kg QD

*PINN, pending USAN approval.

Reference: Subbiah et al. Ann Oncol. 2018; 29:1869–76.

LIBRETTO-001: selpercatinib in *RET*-altered cancers

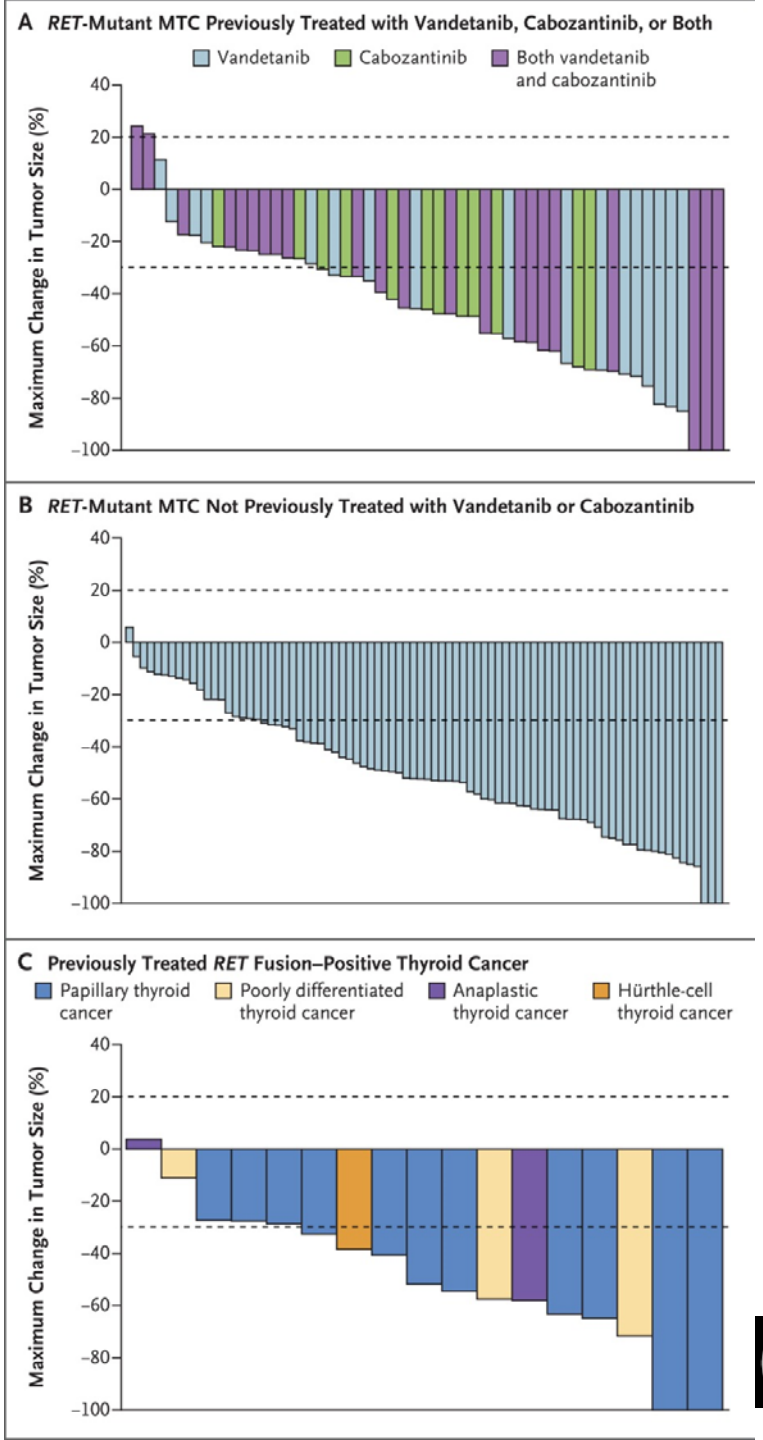


3 populations to be discussed: (1) MTC PAS; (2) MTC, cabozantinib/vandetanib naïve; (3) RET fusion-positive thyroid cancer

NCT03157128; Data cutoff: June 17, 2019.

*Per agreement with FDA, patients with non-measurable disease enrolled during phase 1 dose escalation were eligible for the primary analysis set.

Waterfall Plots of the Maximum Change in Tumor Size.



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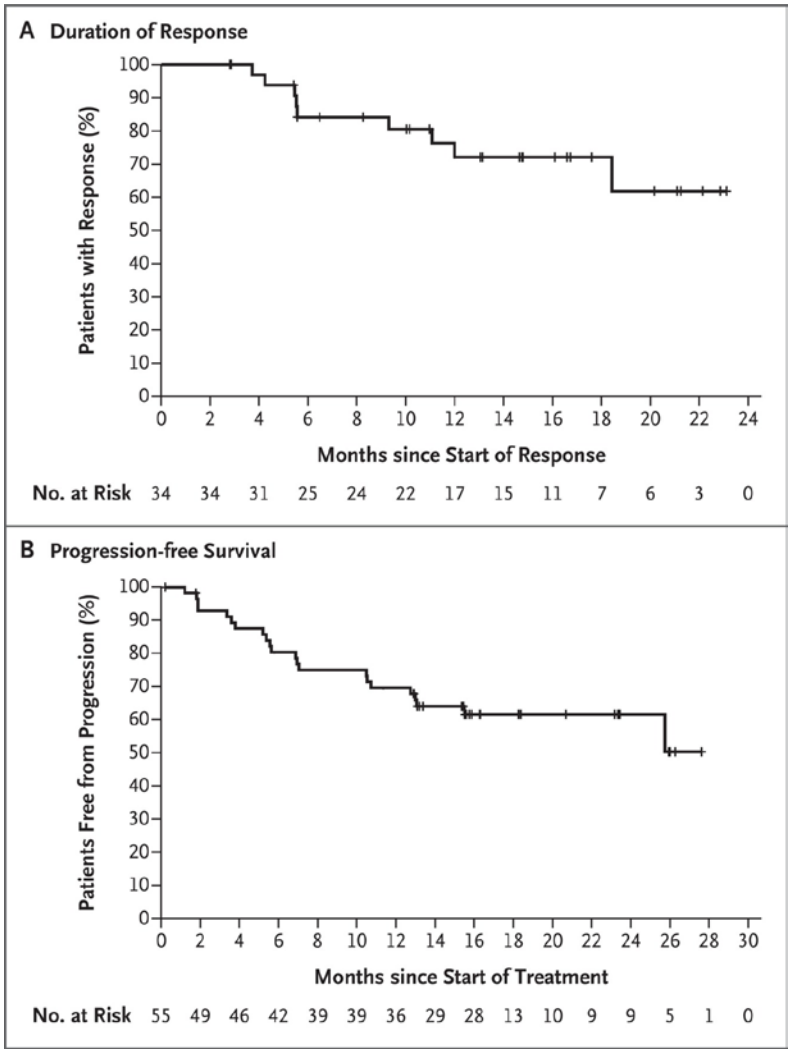
Kaplan–Meier Plots of the Duration of Response and Progression-free Survival among Patients with RET-Mutant MTC Previously Treated with Vandetanib, Cabozantinib, or Both.



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Adverse Events in 162 Patients with RET-Mutant MTC or RET Fusion–Positive Thyroid Cancer Who Received Selpercatinib.

Table 3. Adverse Events in 162 Patients with *RET*-Mutant MTC or *RET* Fusion–Positive Thyroid Cancer Who Received Selpercatinib.*

Adverse Event	Adverse Events, Regardless of Attribution					Treatment-Related Adverse Events		
	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade
	number of patients (percent)							
Any adverse event	9 (6)	42 (26)	95 (59)	11 (7)	162 (100)	45 (28)	3 (2)	153 (94)
Dry mouth	69 (43)	5 (3)	0	0	74 (46)	0	0	63 (39)
Hypertension	10 (6)	25 (15)	34 (21)	0	69 (43)	19 (12)	0	49 (30)
Diarrhea	44 (27)	8 (5)	9 (6)	0	61 (38)	4 (3)	0	27 (17)
Fatigue	35 (22)	24 (15)	2 (1)	0	61 (38)	1 (1)	0	41 (25)
Increased aspartate aminotransferase level	37 (23)	6 (4)	13 (8)	1 (1)	57 (35)	12 (7)	1 (1)	45 (28)
Nausea	44 (27)	13 (8)	0	0	57 (35)	0	0	25 (15)
Constipation	44 (27)	11 (7)	1 (1)	0	56 (35)	0	0	26 (16)
Increased alanine aminotransferase level	26 (16)	7 (4)	17 (10)	1 (1)	51 (31)	16 (10)	1 (1)	42 (26)
Headache	36 (22)	11 (7)	4 (2)	0	51 (31)	1 (1)	0	21 (13)
Peripheral edema	42 (26)	5 (3)	1 (1)	0	48 (30)	0	0	29 (18)
Increased blood creatinine level	27 (17)	12 (7)	0	0	39 (24)	0	0	22 (14)
Abdominal pain	25 (15)	8 (5)	5 (3)	0	38 (23)	0	0	6 (4)
Arthralgia	25 (15)	10 (6)	0	0	35 (22)	0	0	8 (5)
Vomiting	26 (16)	8 (5)	1 (1)	0	35 (22)	0	0	12 (7)
Hypocalcemia	14 (9)	13 (8)	6 (4)	1 (1)	34 (21)	0	0	5 (3)
Back pain	19 (12)	10 (6)	2 (1)	0	31 (19)	0	0	1 (1)
QT interval prolonged on electrocardiography	11 (7)	16 (10)	4 (2)	0	31 (19)	3 (2)	0	21 (13)
Cough	25 (15)	4 (2)	0	0	29 (18)	0	0	2 (1)
Rash	25 (15)	3 (2)	0	0	28 (17)	0	0	13 (8)
Dizziness	25 (15)	2 (1)	0	0	27 (17)	0	0	9 (6)
Abdominal distension	18 (11)	7 (4)	0	0	25 (15)	0	0	12 (7)
Hypothyroidism	14 (9)	11 (7)	0	0	25 (15)	0	0	12 (7)
Weight increased	11 (7)	9 (6)	5 (3)	0	25 (15)	1 (1)	0	8 (5)

* The adverse events listed here are those that occurred at any grade in at least 15% of the patients, regardless of attribution. The relatedness of adverse events to treatment was determined by the investigators. The total percentage for any given adverse event may be different than the sum of the individual grades because of rounding. In total, five patients had grade 5 adverse events including hemoptysis, postprocedure hemorrhage, sepsis, cardiac arrest, and cardiac failure (one patient each), all deemed by the investigators to be unrelated to selpercatinib.

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IMPORTANCE OF GENOTYPING TUMOR SAMPLES OF PATIENTS WITH RAIR METASTATIC THYROID CANCER

1. Multikinase inhibitors are approved as treatments for RAIR thyroid cancer regardless of tumor genotype.

2. Besides RET-driven tumors, NTRK kinase inhibitors (larotrectinib) are approved for treatment of cancers regardless of tumor type (“tissue agnostic”).

3. NCCN guidelines: Selective RAF kinases inhibitors (dabrafenib, vemurafenib) can be considered if there are no clinical trials available.