POST ENDO 2022

1ER SEPTEMBRE 2022, BERN

HOT TOPICS: THYROID

Dr. Ilaria Giordani

Prof. Dr. Gerasimos Sykiotis

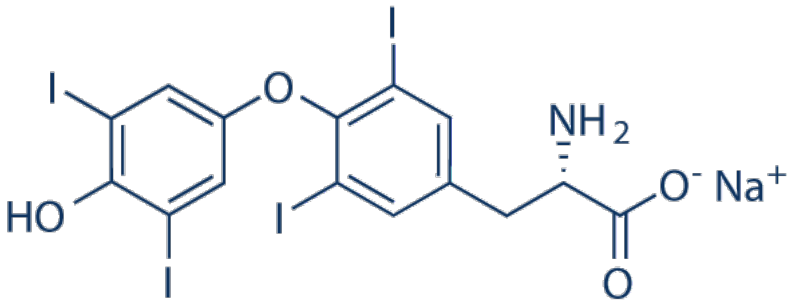
Service d'endocrinologie , diabétologie et métabolisme

CHUV - Lausanne

ENDO2022 JUNE 11-14, 2022 ATLANTA, GEORGIA

CHUV Centre hospitalier universitaire vaudois

UNMET NEEDS OF PATIENTS WITH HYPOTHYROIDISM



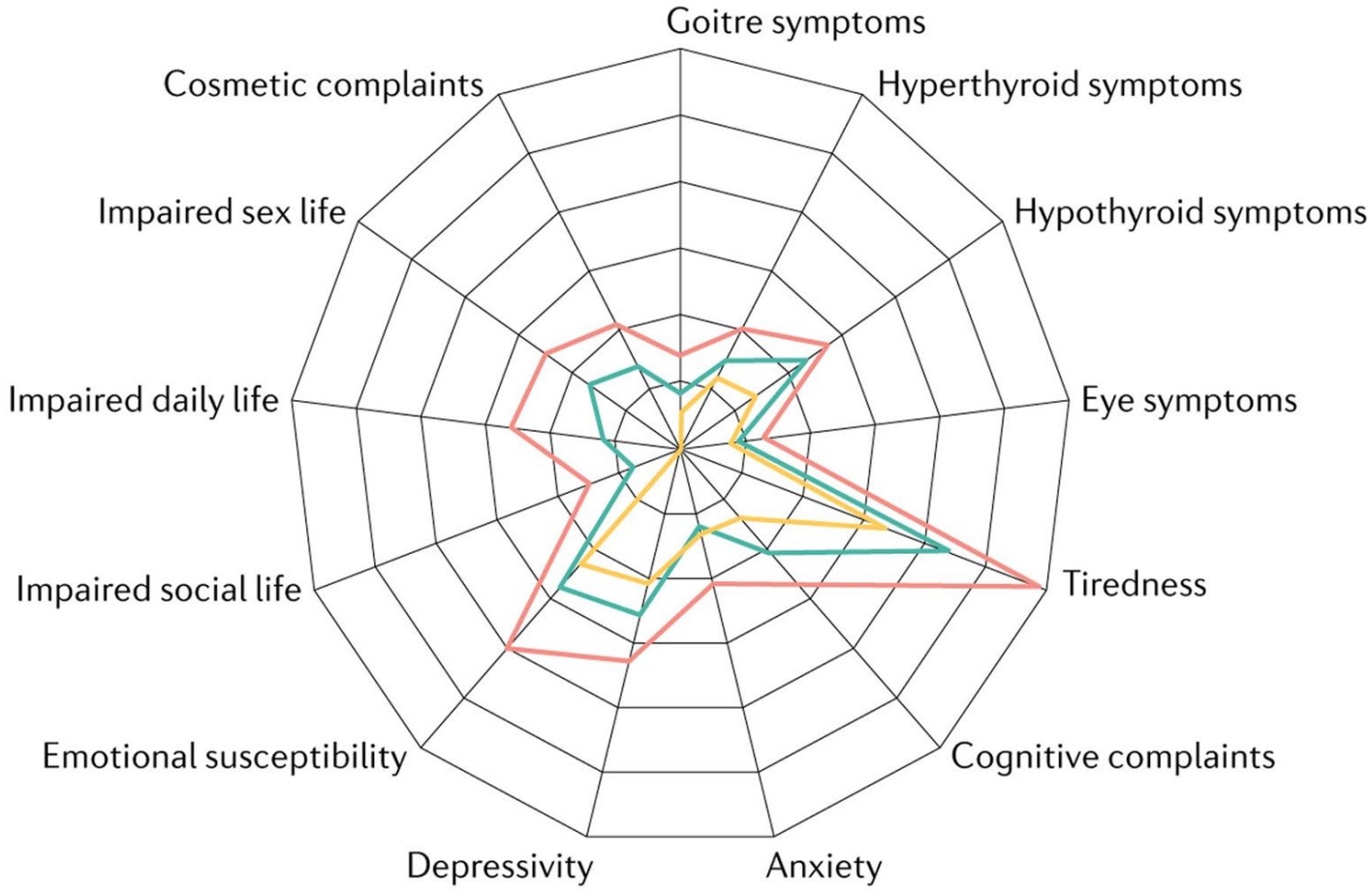
Marco Medici, Rotterdam

Jaqueline Jonklaas, Georgetown

- LT4 monotherapy: **standard of care**
  - Efficacy, long-term experience, safe, long half-life, easy administration, good intestinal absorption, stable T3 levels, low cost

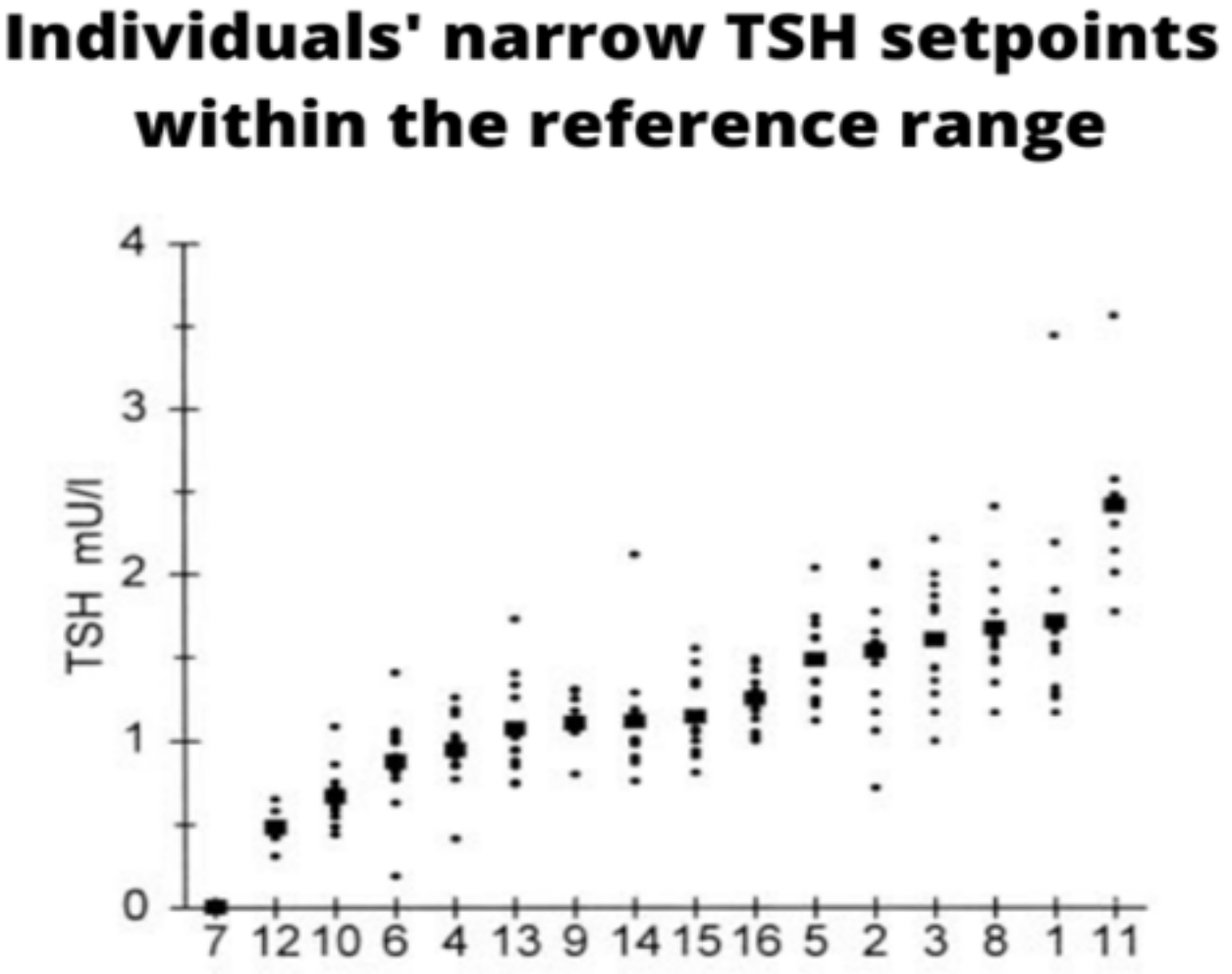
Elizabeth A. McAnich , Stanford

- **TSH within targets** : 50-65% of patients on LT4
- **residual hypothyroid symptoms** despite normal TSH: up to 14% of patients
  - ↑ anxiety, depression, dissatisfaction
  - ↓ QoL



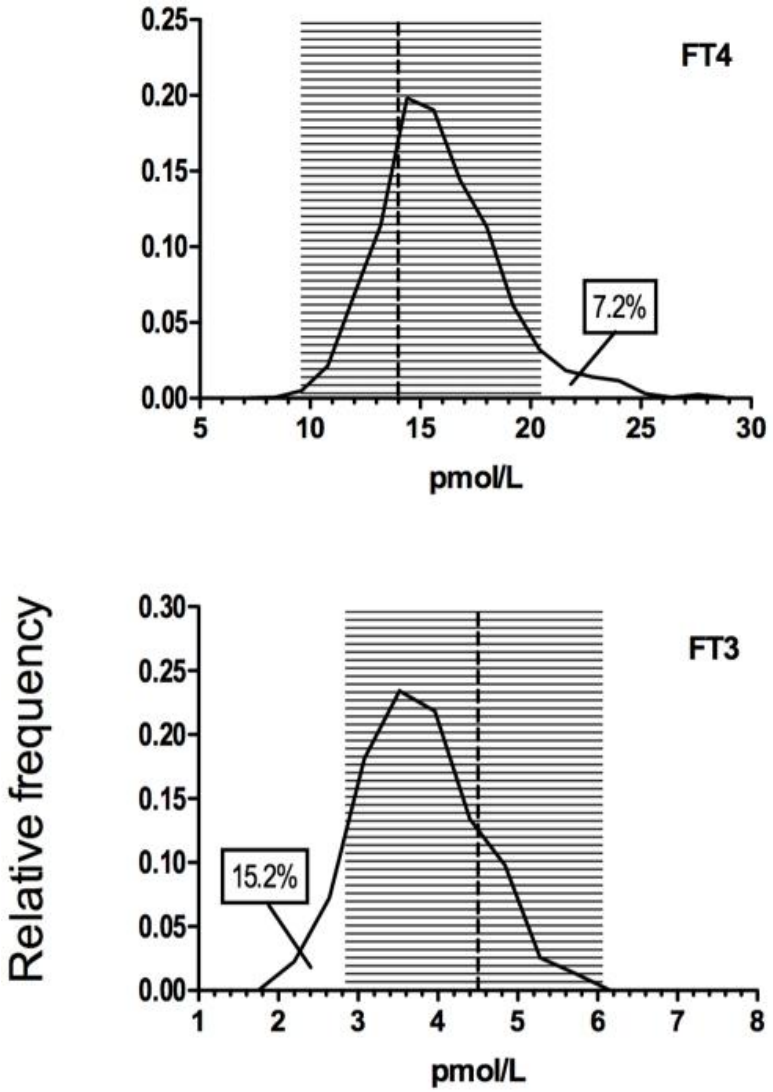
Causes of symptoms and dissatisfaction

- Appropriate TSH not achieved
- Different individual setpoint
- Autoimmunity
- Comorbidities
- Unrealistic expectations
- Awareness of a chronic condition
- Tissue hypothyroidism ?



Endogenous production vs. LT4 therapy

- ↑ FT4 and FT4/FT3 ratio
- ↓ T3
- ↑ LDL and ↓ metabolic rate despite normal TSH



Gullo et al, PLoS One, 2011

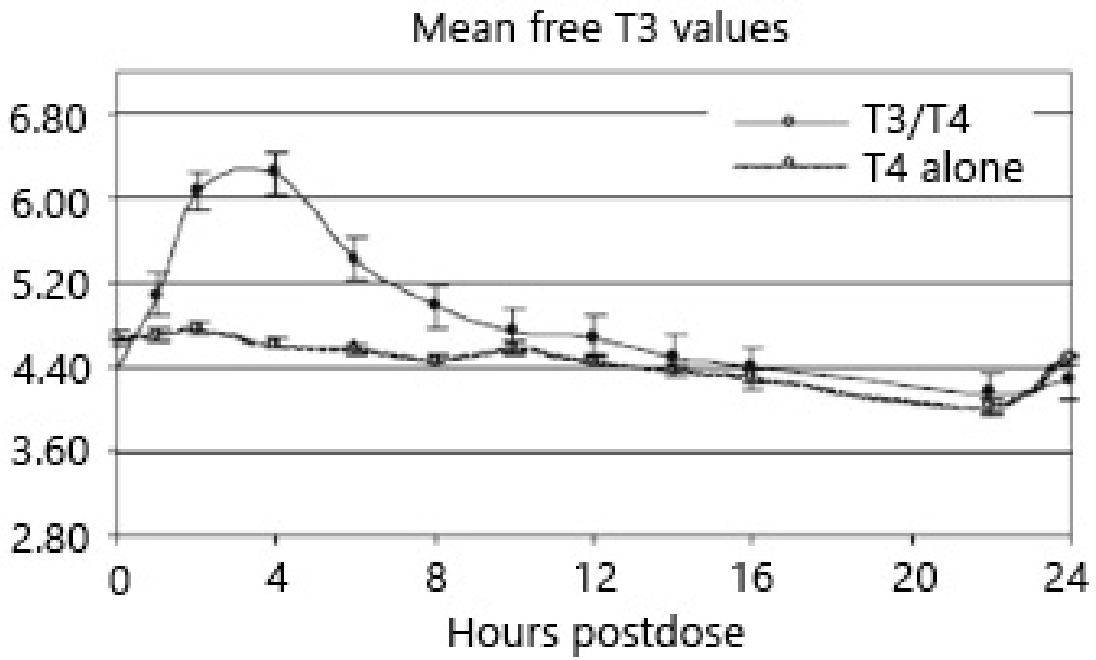
T4+T3 COMBINATION

- Superiority never demonstrated in clinical trials
  - **Limitations** of T4+T3 trials
- 2021 review and meta-analysis :
  - **no difference in clinical outcomes** between T4+T3 and T4 monotherapy
  - higher proportion of patients preferring combination

- ATA/ETA Guidelines:
  - insufficient evidence to support routine use of T4+T3
  - **might be considered** as an experimental approach

T4+T3 COMBINATION

- Current T3 formulations do not reproduce physiologic T3 levels (sustained release?)
- Combination therapy:
  - no increased morbidity or mortality
  - unknown long -term effects



Saravanan et al., Exp Clin Endocrinol Diabetes. 2007

Prescribing T4+T3 :

- ↓T4 by 12-25 mcg/day and add T3 2.5-5 mcg 1-2x/day
- Treatment goals: TSH normalization and optimization of symptoms
- If hyperT3 is a concern: measure total T3 2-4 hours after the morning dose
- T3 does not cross the placenta

Currently recruiting: “T3-4 Hypo trial”

- Multicenter double -blind RCT
- T4+T3 vs. T4+placebo
- 12 months
- Auto -immune hypothyroidism and persistent symptoms despite normal TSH on T4

- Primary endpoints: tiredness and hypothyroid symptoms
- Secondary endpoints: neurocognitive tests, bone markers, lipids
- Parallel group on T4 without symptoms (observation only)

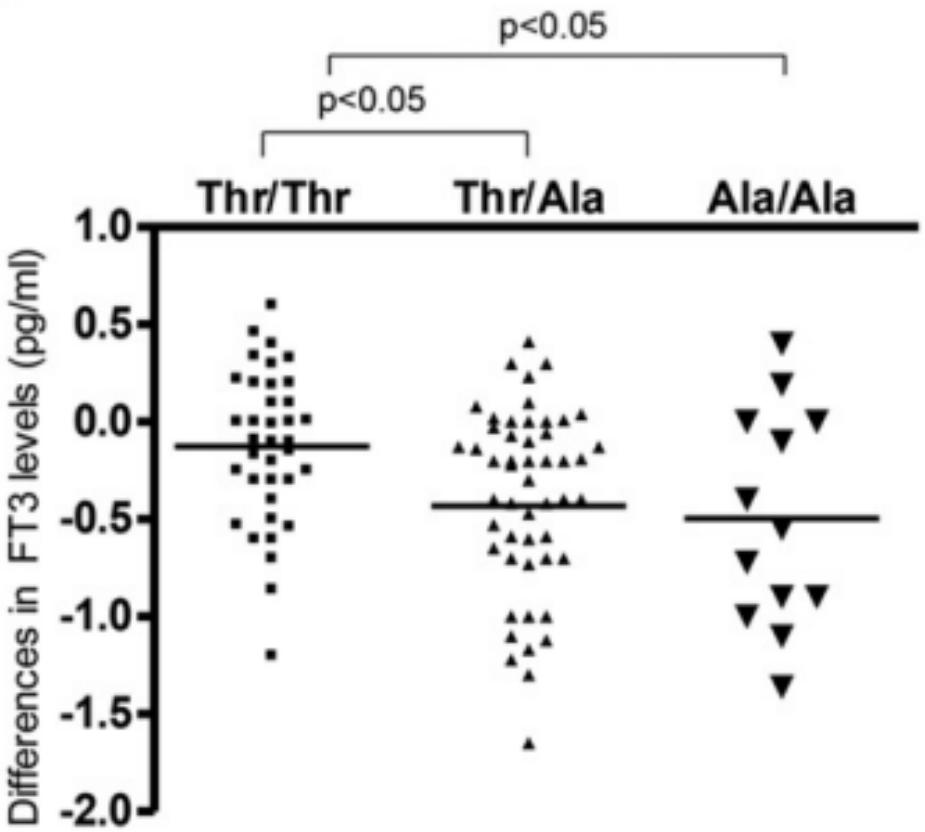
- Testing will include genetic variants

https://t3-4-hypotrial.nl/english/

CURRENT CLINICAL TRIALS

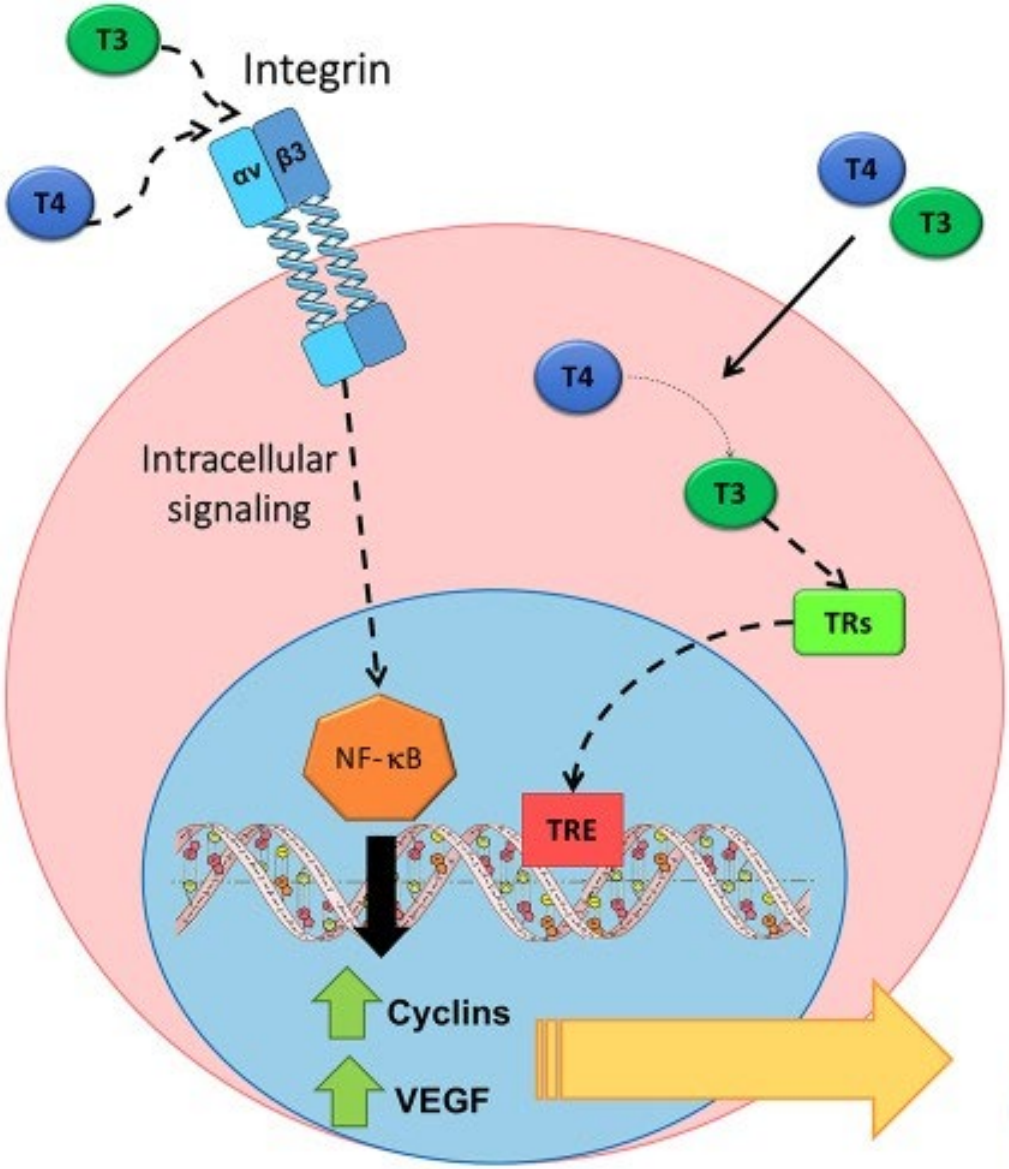
GWAS studies:

- Multiple SNPs associated with thyroid hormone levels
- TSH reference range based on Polygenic Risk Score (personalized TSH target?)
- Polymorphism of deiodinase type 2 (DIO2) ?



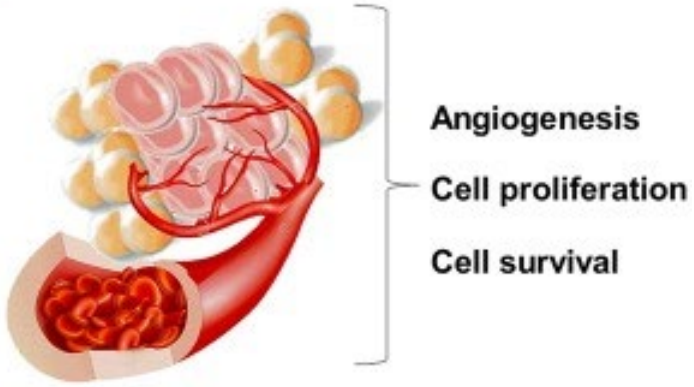
Castagna et al, JCEM, 2017

NON-GENOMIC ACTIONS OF THYROID HORMONES AND CANCER



Integrin αvβ3

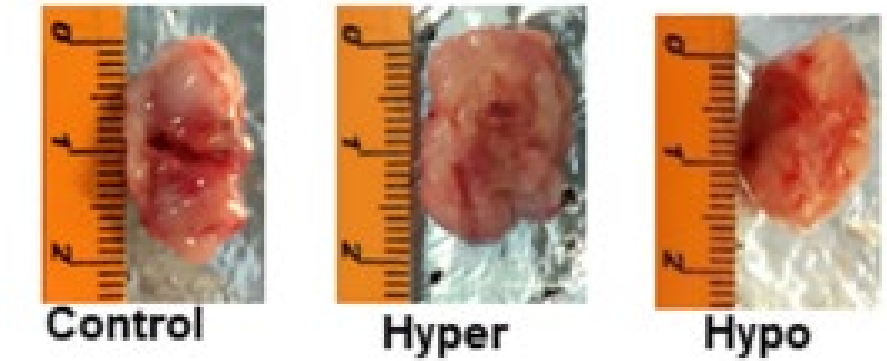
- specific binding sites for T4 (and T3?)
- over-expressed in high-growth endothelial cells, solid tumors and leukemic cells



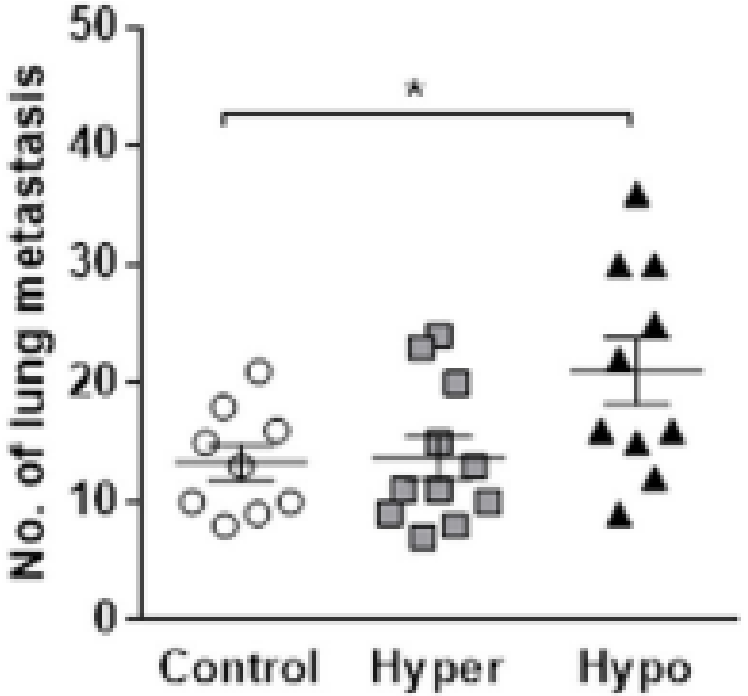
Graciela Cremaschi, Buenos Aires

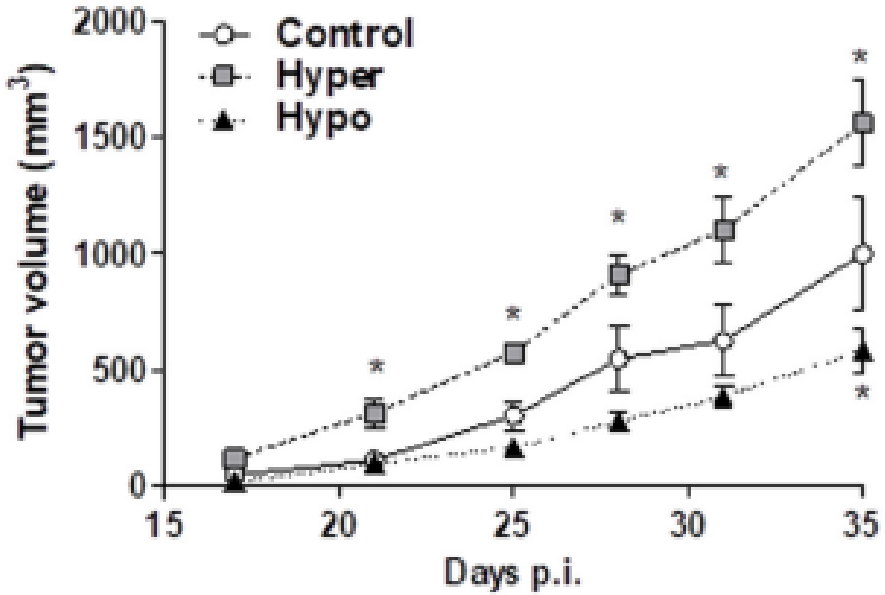
- Non-canonical action: ↑ tumor growth, ↑ angiogenesis
- Canonical action: ↑ anti-tumor immunity

- Potential clinical implications:
  - effects of hypo/hyperthyroidism on cancer?
  - effects of T4 substitution in cancer patients?



Sterle et al, Endocrine-Related Cancer, 2021

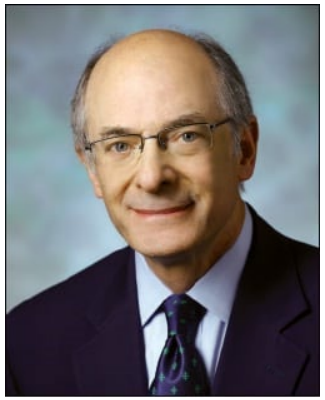




TAKE HOME MESSAGES – Hypothyroidism

- T4+T3 combination could be considered in selected patients with persistent symptoms on T4
- Waiting for T3 sustained release formulations
- Further studies needed to better understand the interactions between thyroid hormones, the immune system (including the immune anti -tumor response) and cancer

ANTITHYROID DRUGS IN GRAVES' DISEASE

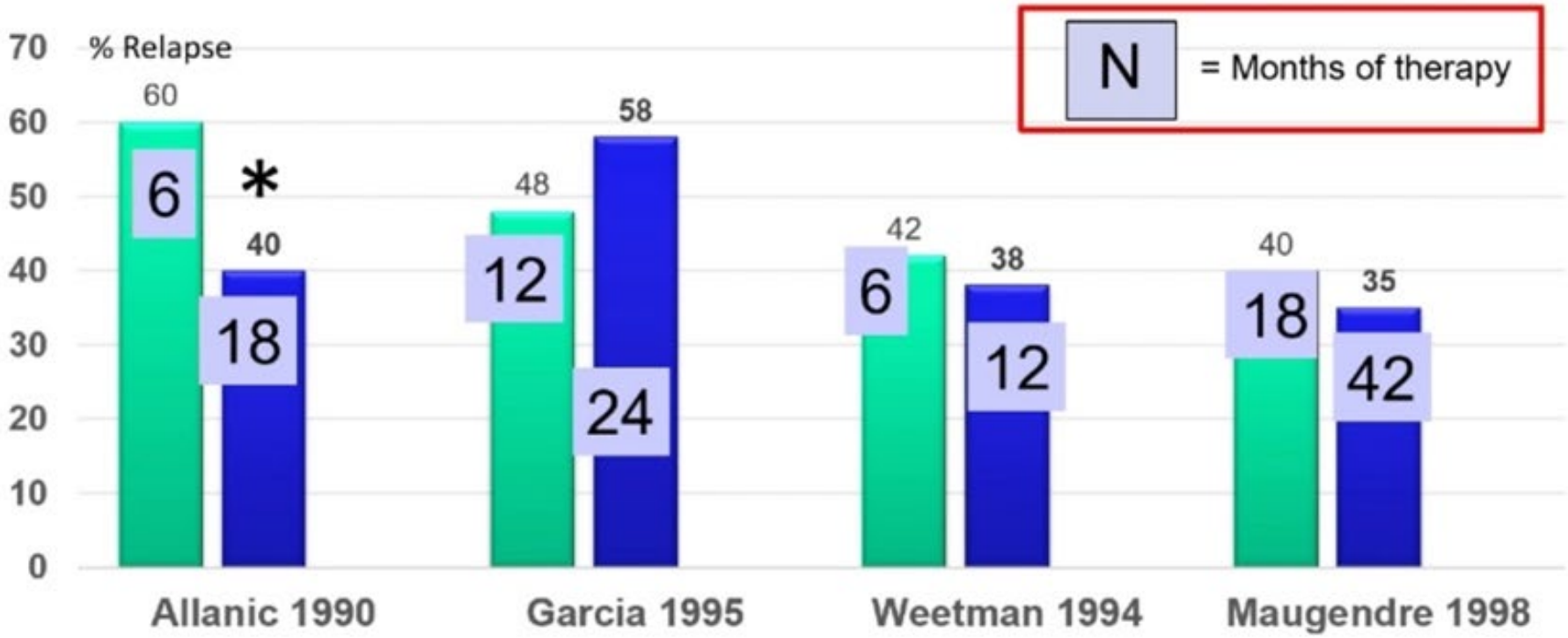


David S. Cooper, Baltimore

- ↑ use of ATDs (vs RAI) in Graves' disease (in US)
- Patients value the possibility of remission and the avoidance of surgery, radioactivity exposure, and lifelong T4 therapy

- Factors predicting non -remission
  - large goiter, eye disease, high T3 -T4, very high TRAb, younger age, tobacco use, male sex?, HLA DR3?
  - NO relation with drug dosage
  - **duration of therapy?**

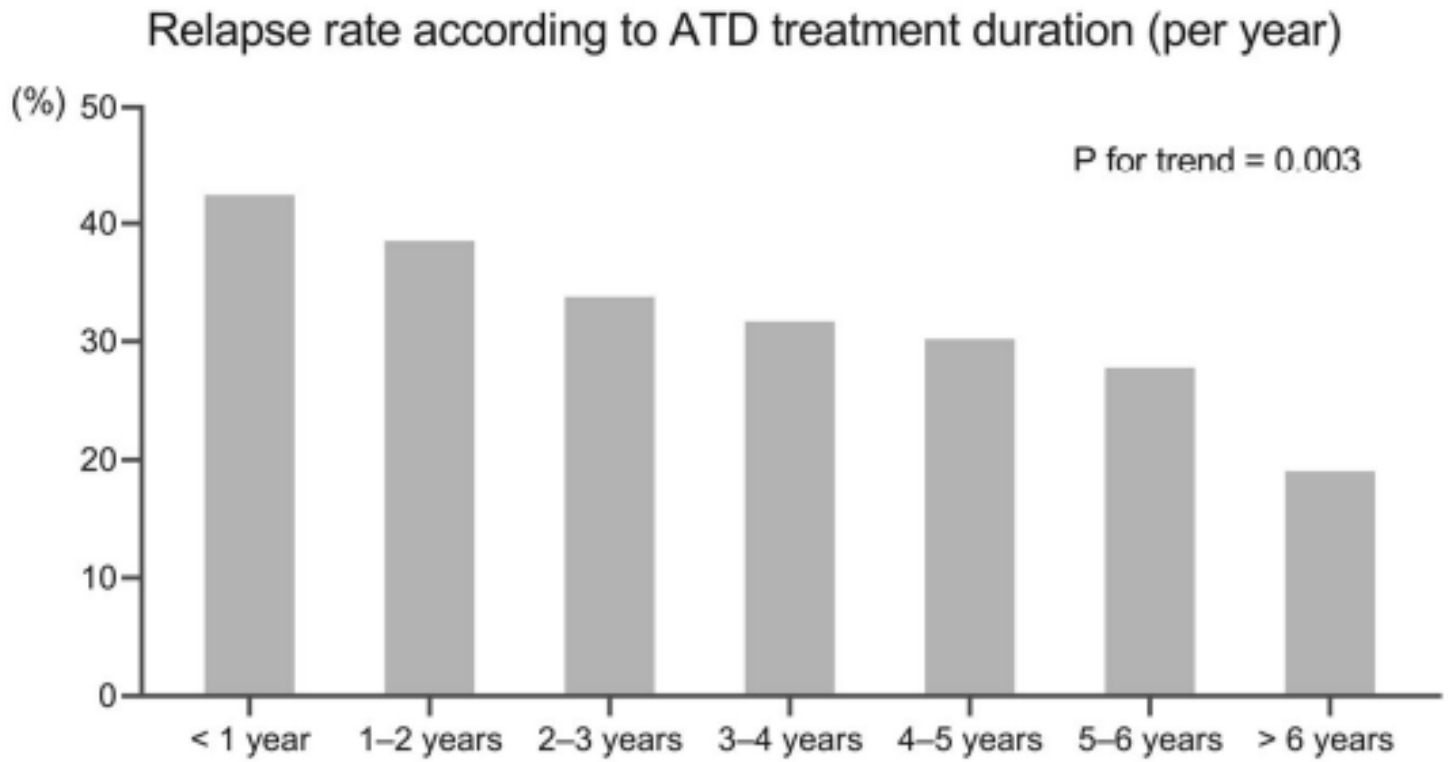
- ATA guidelines recommend treatment for 12 -18 months
  - 4 RCT in the 1990's: the duration of therapy did not have an impact on remission rates
  - no trial > 42 months



The longer the antithyroid drug is used, the lower the relapse rate in Graves' disease: a retrospective multicenter cohort study in Korea

Direct correlation between treatment duration and relapse risk

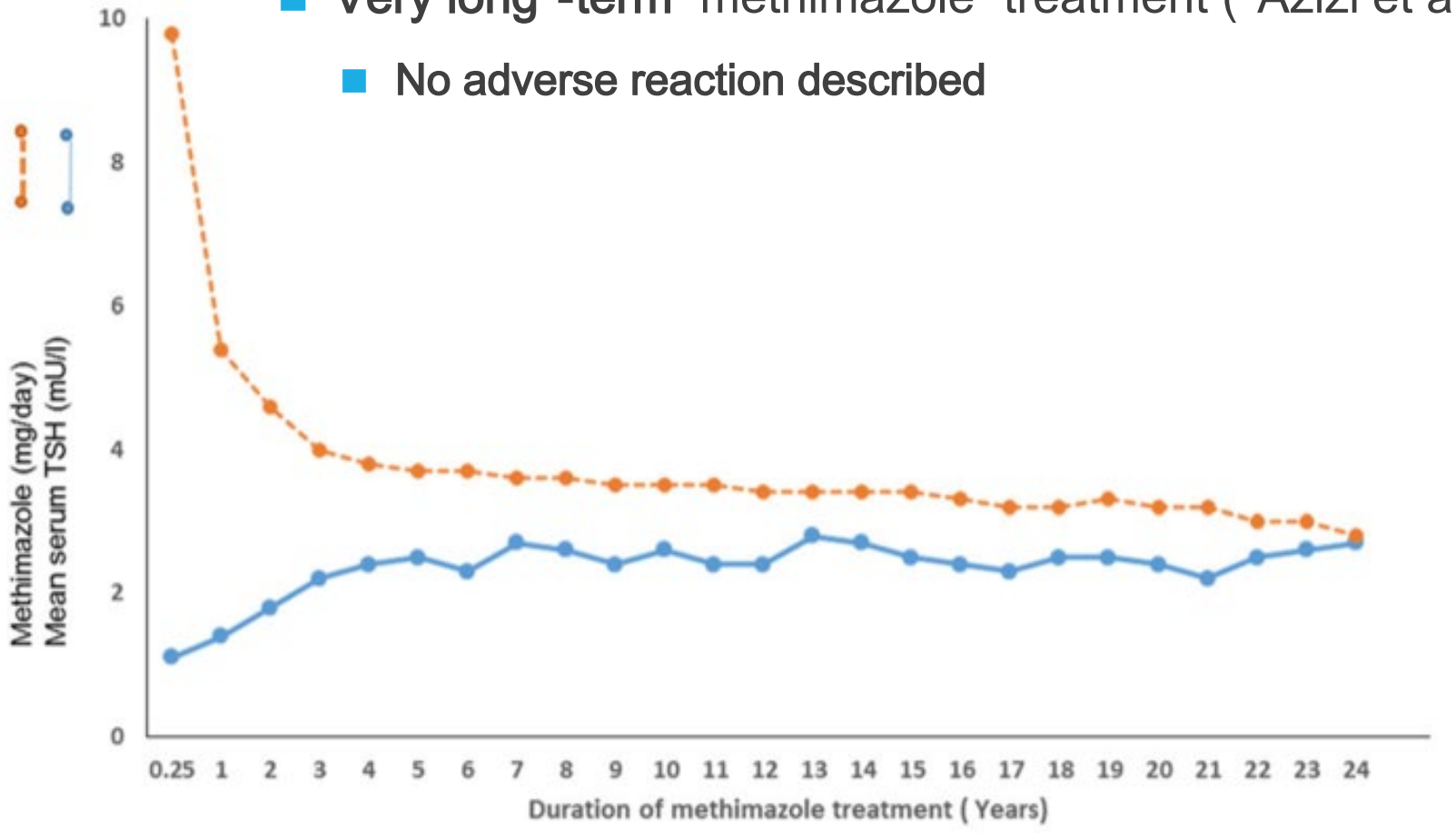
Confirms previous meta-analysis (Azizi et al., Thyroid, 2017)



	< 1 year	1–2 years	2–3 years	3–4 years	4–5 years	5–6 years	> 6 years
Total, n	243	371	133	79	43	18	21
Relapse, n	103	143	45	25	13	5	4
Relapse, %	42.4	38.5	33.8	31.7	30.2	27.8	19.0

Park et al, 2021, Endocrine

- **Very long -term** methimazole treatment (Azizi et al, 2021)
  - **No adverse reaction described**



TSH< 0.4 mU/L No		12	11	5	2	4	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean serum TRAb (IU/ml)				1.2						1.1								1.0							0.9
Methimazole (mg/day)	Mean	9.8	5.4	4.6	4	3.8	3.7	3.7	3.6	3.6	3.5	3.5	3.5	3.4	3.4	3.4	3.4	3.3	3.2	3.2	3.3	3.2	3.2	3.0	3.0	2.8
	SD	1.0	1.6	1.5	1.2	1.1	1.0	1.1	1.0	0.9	1.1	1.2	1.1	1.0	1.1	1.1	1.0	1.1	1.1	1.1	1.3	1.1	1.1	1.7	1.6	1.7

ATDs: most of the side effects in the **first 90 days**

2019 systematic review (Azizi et al, J Endocrinol Invest) **1660 patients** (50% children):

- only **6 adverse reactions after the 1st year** of therapy

TAKE HOME MESSAGES – Hyperthyroidism

- Long-term low dose ATDs treatment may be prescribed effectively and safely for patients with Graves' hyperthyroidism instead of ablation

CANCER RISK ASSOCIATED WITH RAI THERAPY FOR HYPERTHYRO

- Thyroid cancer (≥100 mCi):
  - 2-3x ↑ risk of leukemia
  - 1.2-1.5x ↑ risk of solid cancer (salivary, bone/soft tissue, GI, breast)
  - ↑ risk with ↑ RAI activity?

- Hyperthyroidism (5-30 mCi)?
  - Fewer studies, observational data, short follow-up
  - Confounding factors
  - Reference group?

Cari Kitahara, Bethesda

US/UK Cooperative Thyrotoxicosis Therapy Follow -up study

- 35'593 patients treated for hyperthyroidism between 1946-1964 (US and UK)
  - Overall: ↑ mortality rate for lung, kidney, breast, thyroid cancer deaths
    - first 4 years of follow up
  - RAI-treated patients: cancer risk as expected according to national cancer mortality rates (SMR, 1.02; 95% CI, 0.98-1.07)
    - ↑ mortality rate only for thyroid cancer death (SMR 3.94)
- Conclusion: safe

Ron et al, JAMA, 1998

Table 3. Relative Risks and 95% CIs for Cancer-Specific Mortality Among Patients With Hyperthyroidism Treated With Radioactive Iodine

Cause of Cancer Death[a]	Absorbed Dose, mGy		Dose-Response Relationship			
	Target Organ or Tissue	Organ- or Tissue-Absorbed Dose, Mean (SD)	No. of Deaths	At 100-mGy Organ- or Tissue-Absorbed Dose, RR (95% CI)[b]	*P* Value	Cause-Specific Cancer Death Attributed to Irradiation, No. (%)[c]
Solid cancers						
Thyroid	Thyroid	130 000 (110 000)	15	1.20 (<1.00-6.10)[d]	>.50	
Female breast	Breast	150 (160)	291	1.12 (1.00-1.32)	.04	41.9 (14)
Uterine	Uterus	63 (69)	63	1.54 (0.98-3.42)	.07	
Ovarian	Ovary	38 (42)	104	1.32 (<0.90-2.46)	.30	
Prostate	Prostate	42 (41)	52	1.04 (<0.86-2.42)	>.50	
All other solid cancers	Stomach	170 (180)	242	1.02 (<0.98-1.16)	>.50	
Leukemia (excluding CLL)	Marrow	160 (160)	59	0.97 (<0.96-1.26)	>.50	
Non-Hodgkin lymphoma	Marrow	160 (160)	70	1.07 (<0.96-1.54)	>.50	
Multiple myeloma	Marrow	160 (160)	30	1.69 (<0.97->6.00)	>.50	
All solid cancers combined	Stomach	170 (180)	1984	1.06 (1.02-1.10)	.002	154.7 (8)
All solid cancers excluding female breast	Stomach	170 (180)	1693	1.05 (1.01-1.10)	.01	117.2 (7)

- New analysis after **extended mortality follow -up by 24 years**
- **Organ dose reconstruction** for all RAI-treated patients (model specific to hyperthyroidism)
  → estimated absorbed dose for 26 target organs and tissues
- Exclusion of patients with a cancer diagnosis before study entry

Kitahara et al, JAMA, 2019

Projected estimates of lifetime excess solid cancer deaths

		Excess deaths /1000 patients treated (95% CI)
		Treatment at age 40
10-15 mCi	150 mGy stomach dose	19 (3-40)
	200 mGy stomach dose	25 (4-53)
	250 mGy stomach dose	32 (5-66)

For every 1,000 patients treated with RAI (10-15 mCi) at age 40
→ 20-30 excess solid cancer deaths

= 2-3% of cancers attributable to the radiation exposure

TAKE HOME MESSAGES – Hyperthyroidism

- Long-term low dose ATDs treatment may be prescribed effectively and safely for patients with Graves' hyperthyroidism instead of ablation

- A debated study showed a positive but modest association with risk of death from solid cancer in RAI-treated patients, non confirmed in other cohorts

THERAPIES FOR ADVANCED THYROID CANCER

- 2011-2015: 4 FDA-approved **multikinase inhibitors** for advanced thyroid cancer

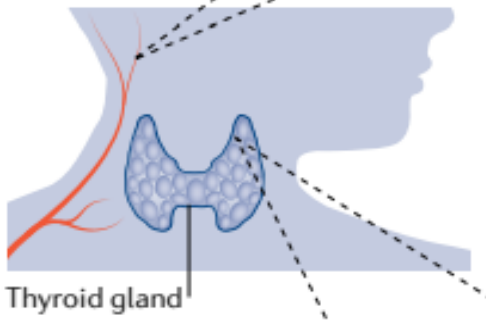
Differentiated Thyroid Carcinoma	Medullary Thyroid Carcinoma
Sorafenib (11/22/2013) Phase III (n=417 pts) PR 12.2% vs. 0.5% placebo mPFS benefit = 5 mos	**Vandetanib** (04/06/2011) Phase III (n=331 pts) PR 45% vs. 13% placebo mPFS benefit = 11.2 mos
Lenvatinib (2/13/2015) Phase III (n=392 pts) ORR 64.8% vs. 1.5% placebo mPFS benefit = 14.7 mos	**Cabozantinib** (11/29/2012) Phase III (n=330 pts) PR 28% vs. 0% placebo mPFS benefit = 7.2 mos

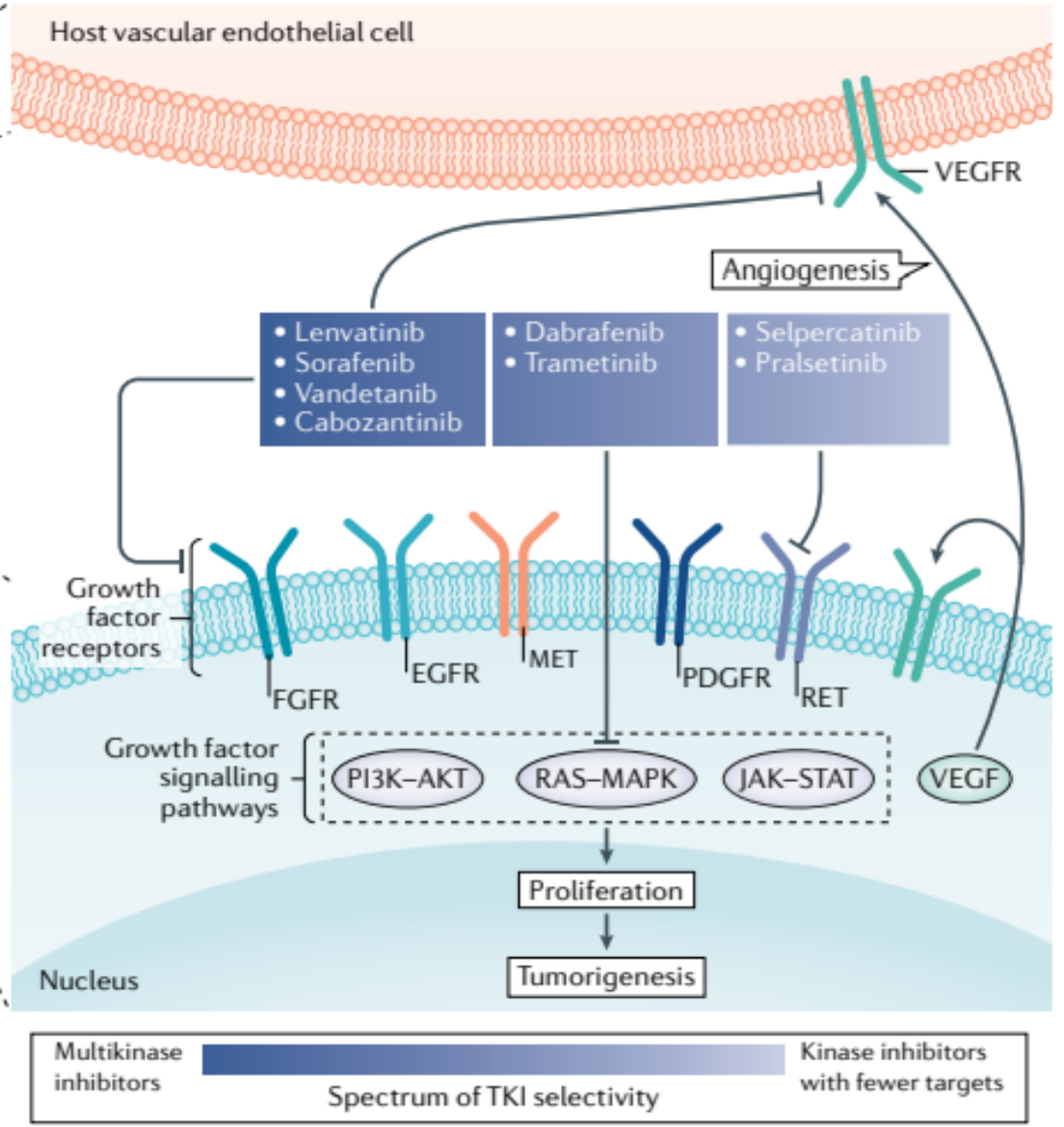
Mimi I. Hu, Houston

- MUTATION -SPECIFIC (TUMOR -AGNOSTIC) THERAPIES
  - $BRAF^{V600E}$: dabrafenib+trametinib
  - RET: selpercatinib , pralsetinib
  - NTRK: larotrectinib , entrectinib
- Less toxicity
- Resistance

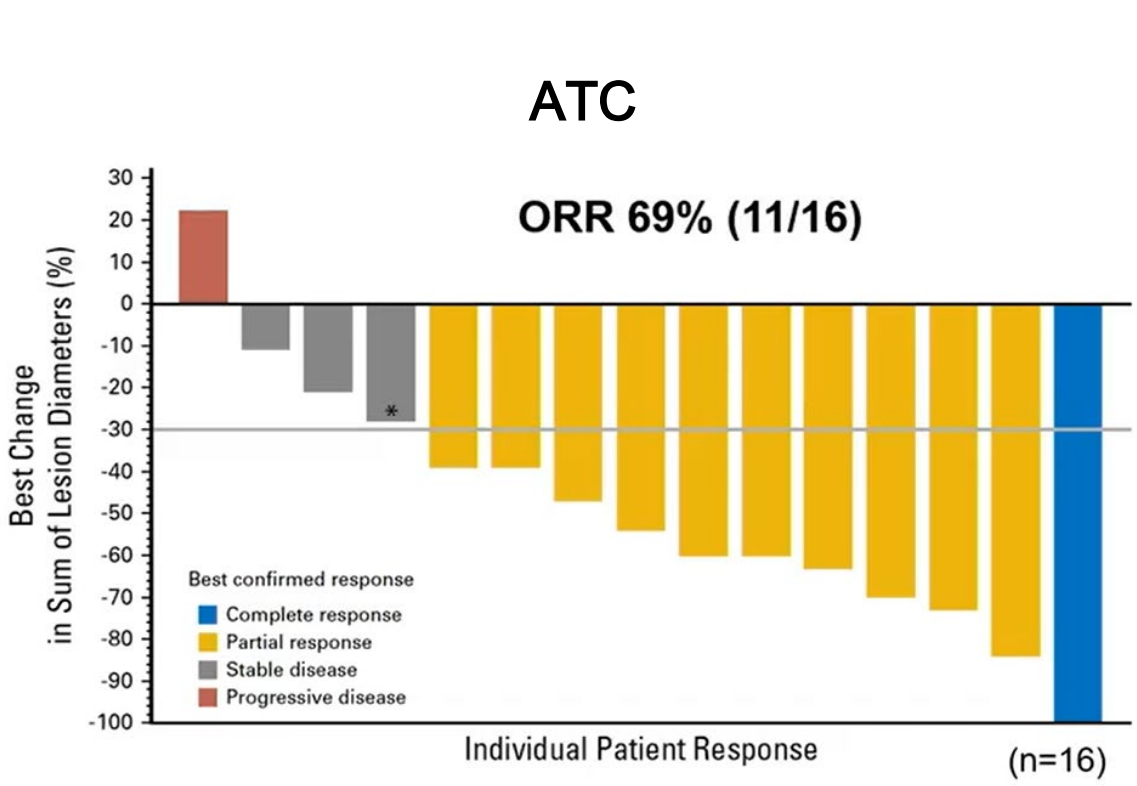
Treatment

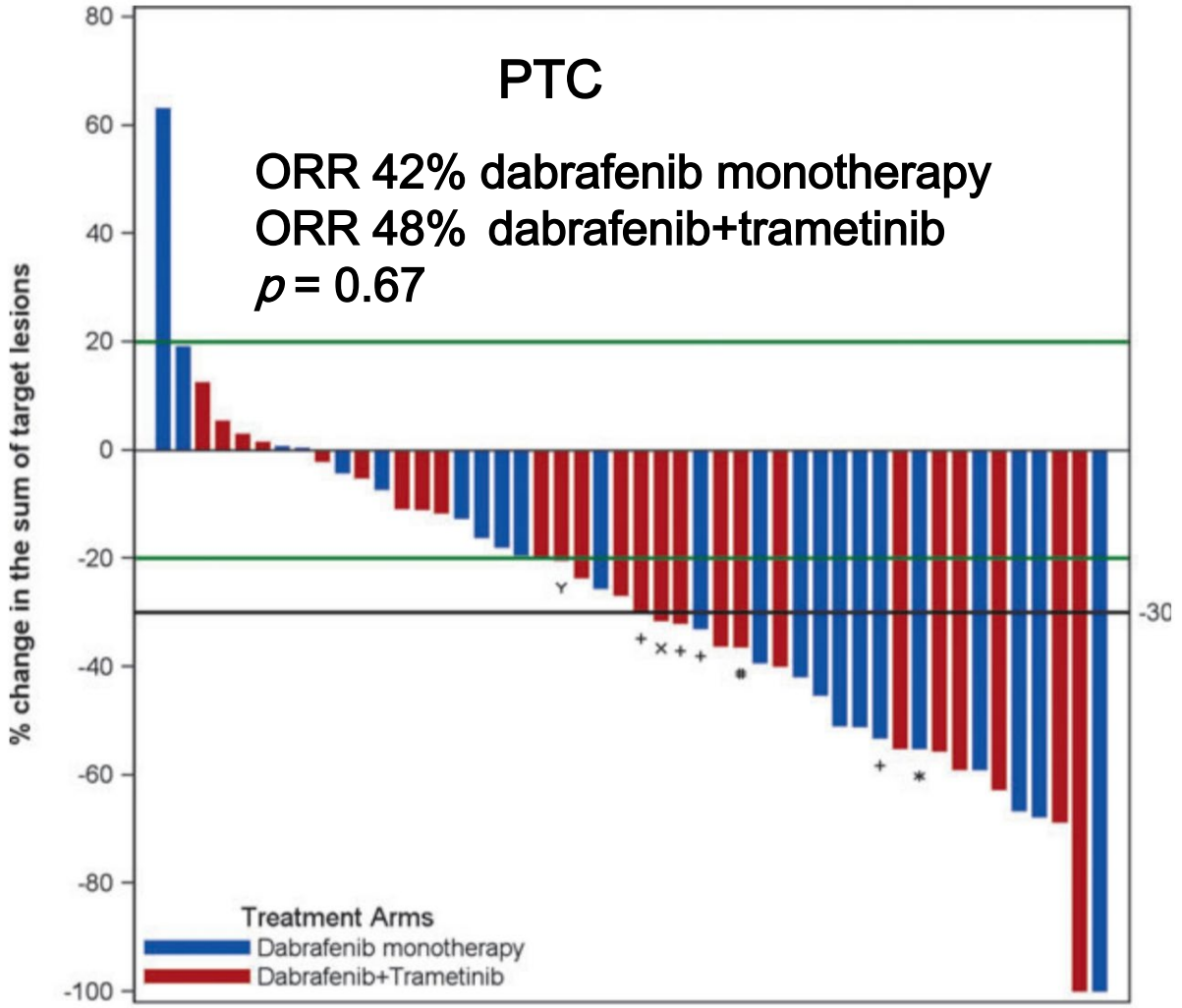
- Palliative
- Redifferentiation
- Neoadjuvant





DABRAFENIB + TRAMETINIB IN BRAF^{V600E}-MUTATED ATC/ PTC



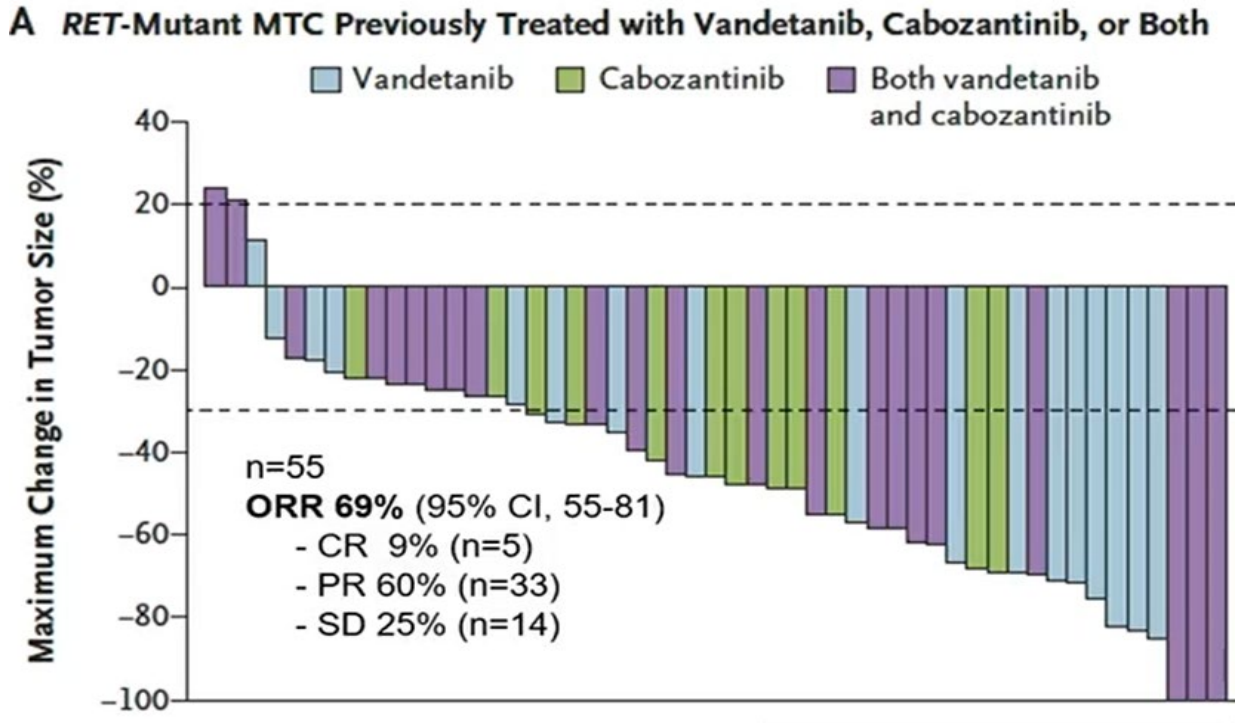


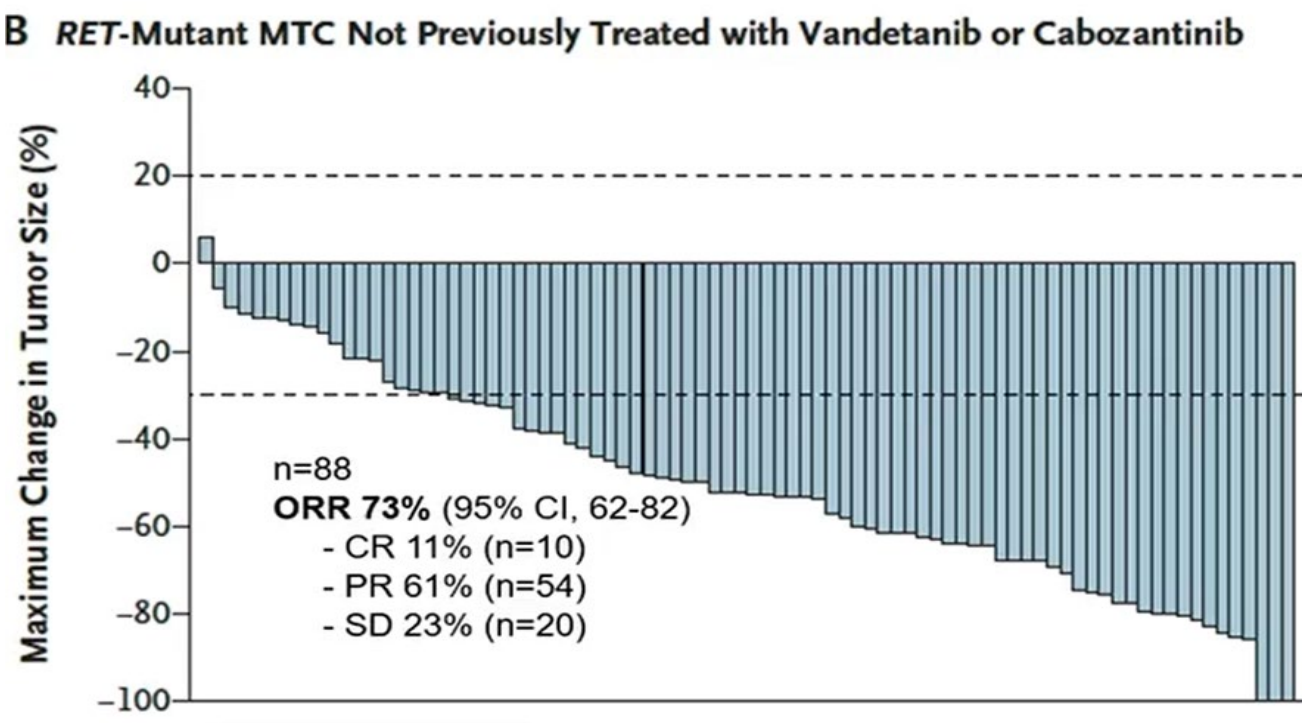
- ATC: robust clinical activity, well tolerated
- PTC: similar efficacy to dabrafenib alone

Subbiah et al, JCO, 2018

Busaidy et al, Thyroid, 2022

SELPERCATINIB IN RET MUTANT MTC

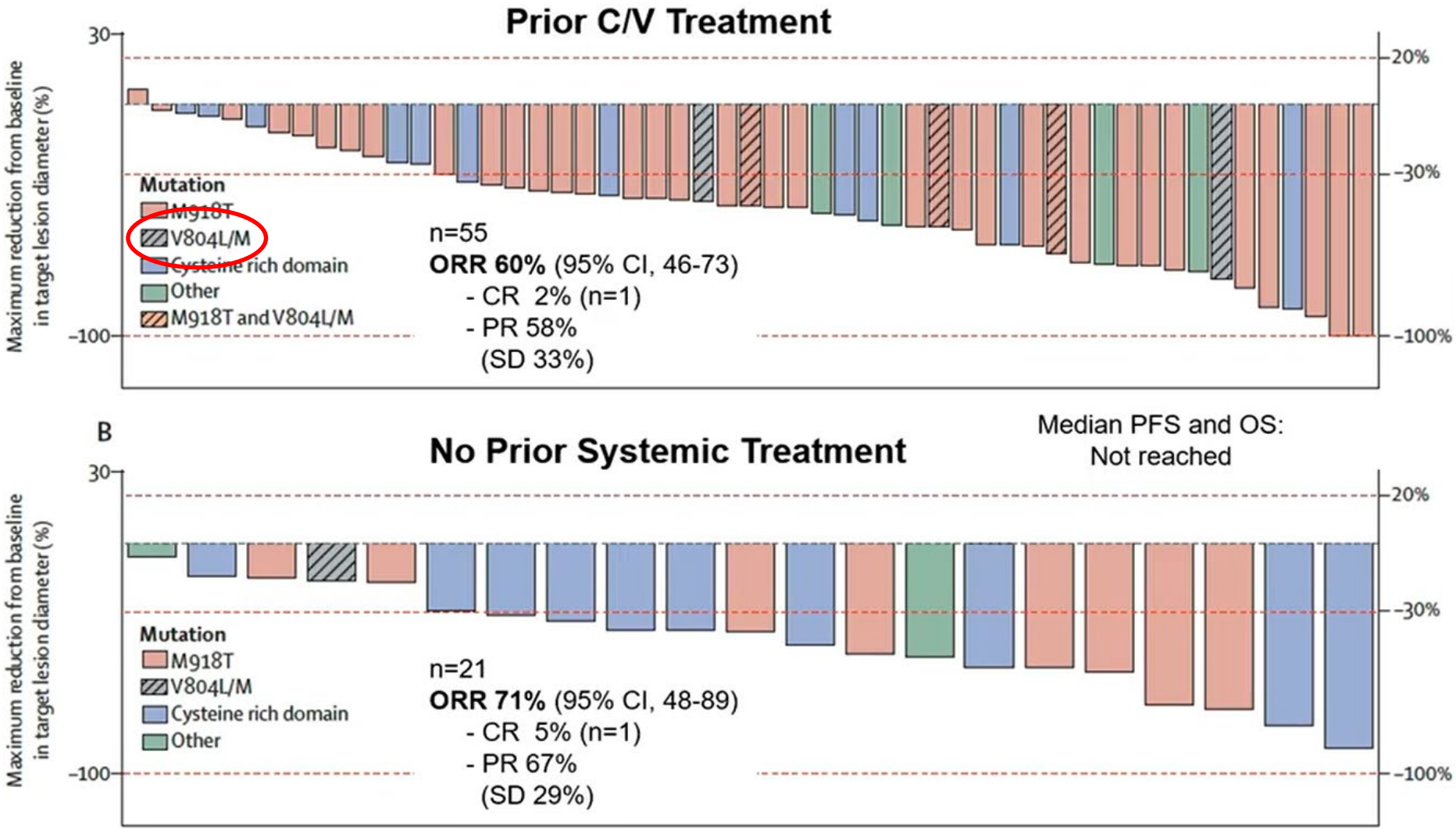




- Durable efficacy
- Patients w/wo previous vandetanib or cabozantinib
- Mainly low -grade toxic effects

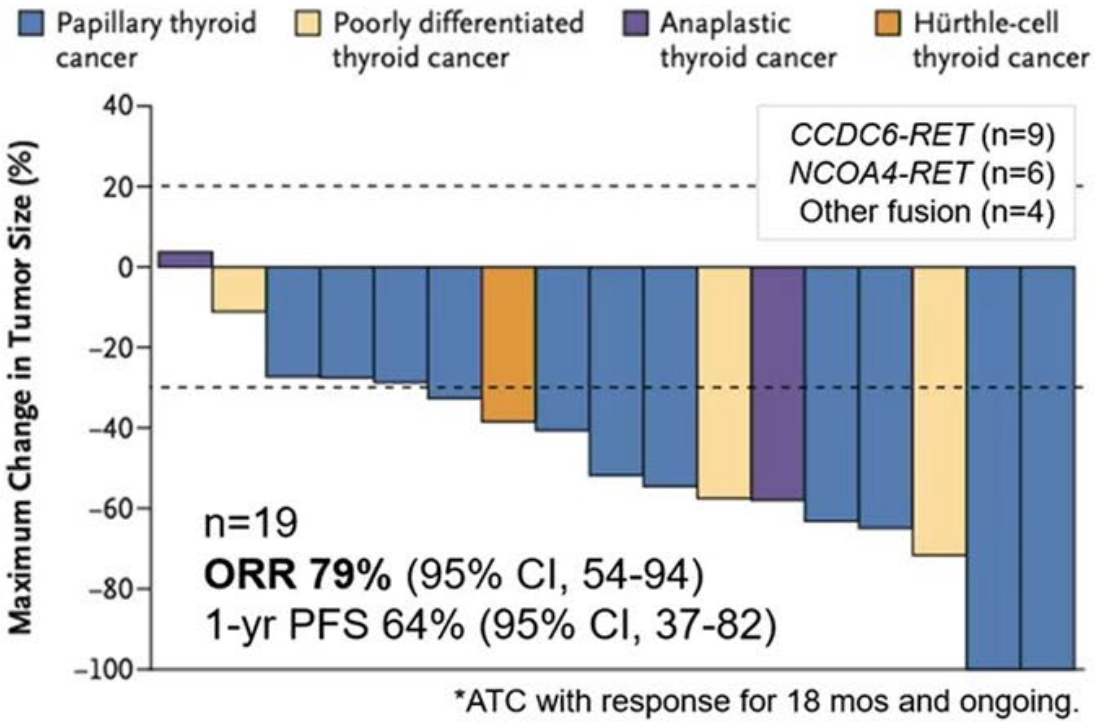
Wirth LJ et al, NEJM, 2020

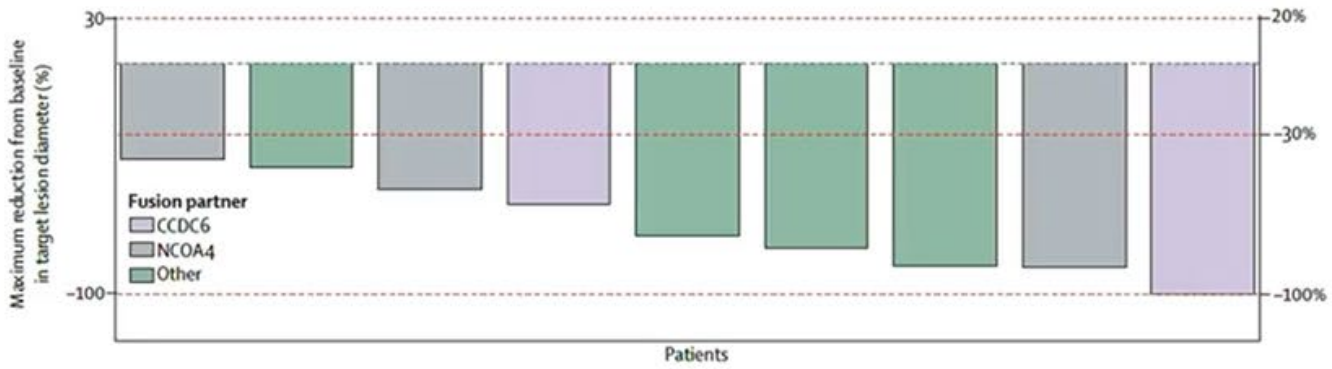
PRALSETINIB IN RET MUTANT MTC



Subbiah V, et al, Lancet Diab Endo, 2021

SELPERCATINIB AND PRALSETINIB IN RET+ THYROID CANCER





n=9
ORR 89% (95% CI, 52-100), all PR
1-yr PFS 81%
mPFS and OS: not reached

Selpercatinib (LIBRETTO-001 trial)

- Multiple histologic types, including 1 ATC

Wirth LJ et al, NEJM 2020

Pralsetinib (ARROW trial)

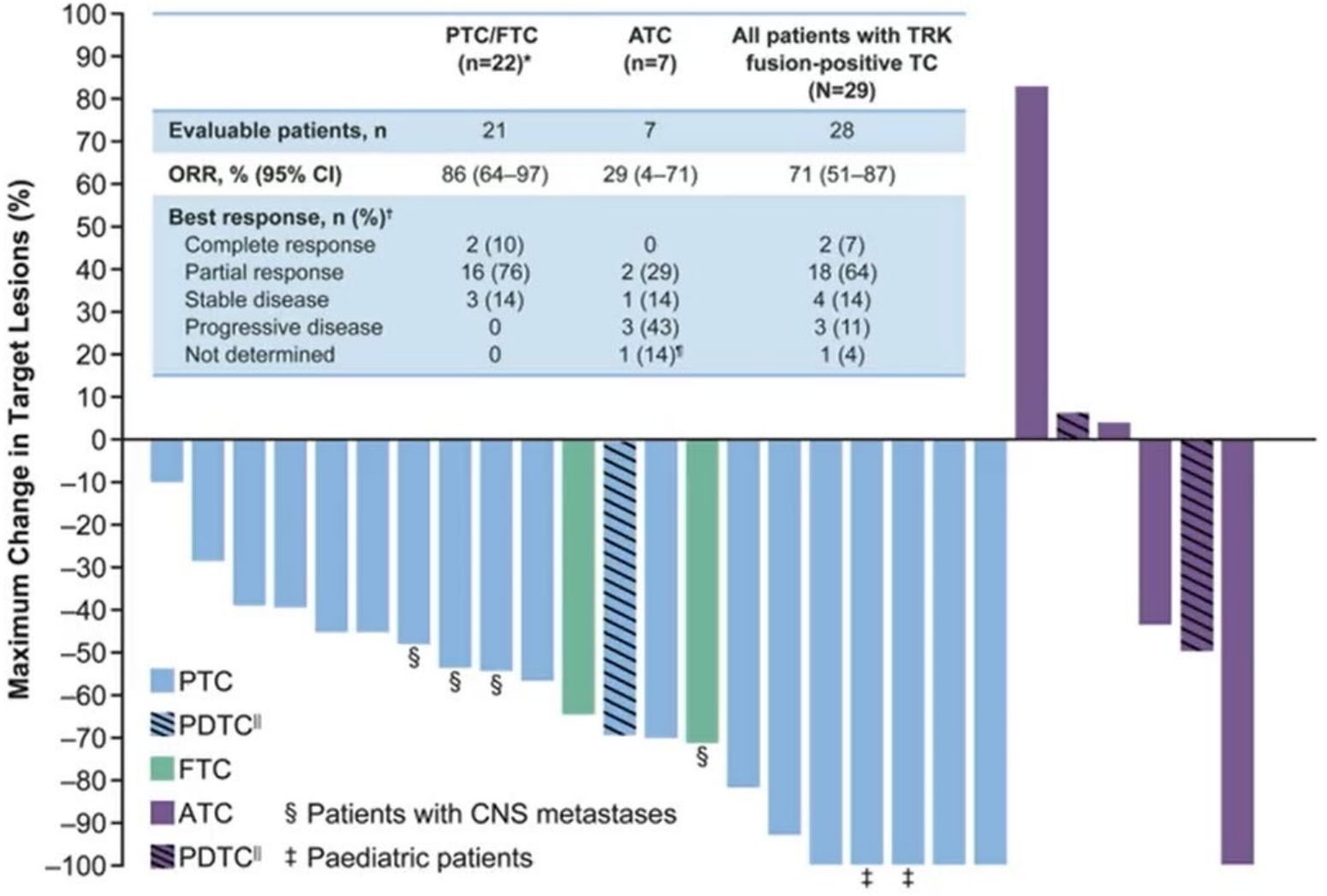
- 8/9 responses
- Well tolerated

Subbiah V, et al, Lancet Diab Endo, 2021

LAROTRECTINIB IN NTRK FUSION THYROID CANCER

- Durable anti -tumour efficacy
- Favorable safety profile

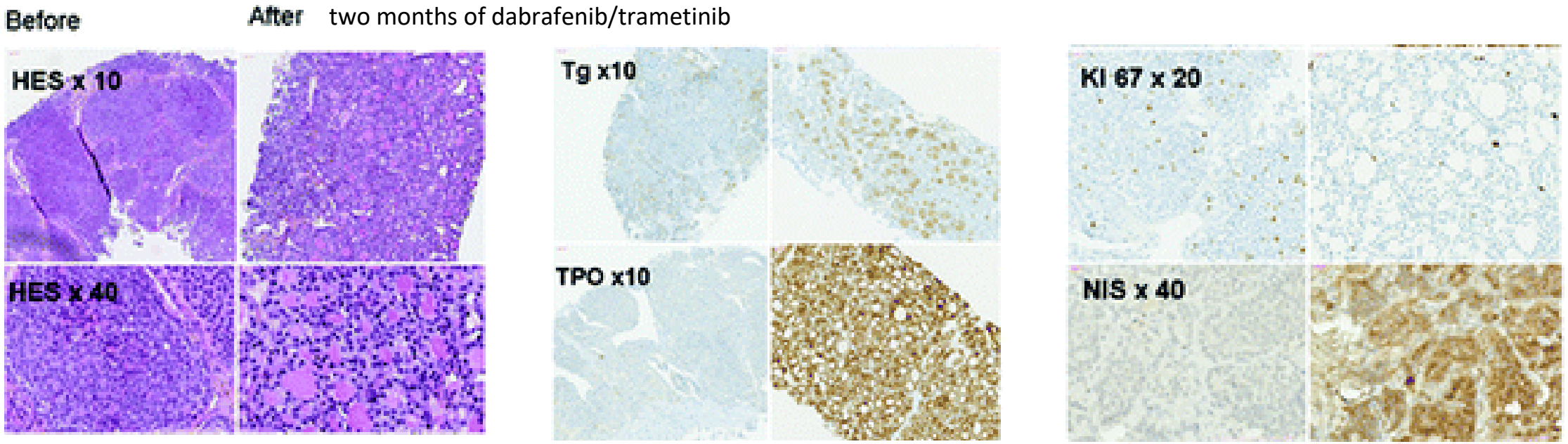
	PTC/FTC (n=22)*	ATC (n=7)	All patients with TRK fusion-positive TC (N=29)
Evaluable patients, n	21	7	28
ORR, % (95% CI)	86 (64–97)	29 (4–71)	71 (51–87)
Best response, n (%)†			
Complete response	2 (10)	0	2 (7)
Partial response	16 (76)	2 (29)	18 (64)
Stable disease	3 (14)	1 (14)	4 (14)
Progressive disease	0	3 (43)	3 (11)
Not determined	0	1 (14)¶	1 (4)



Waguespack AG et al, Eur J Endocrinol,

REDIFFERENTIATION

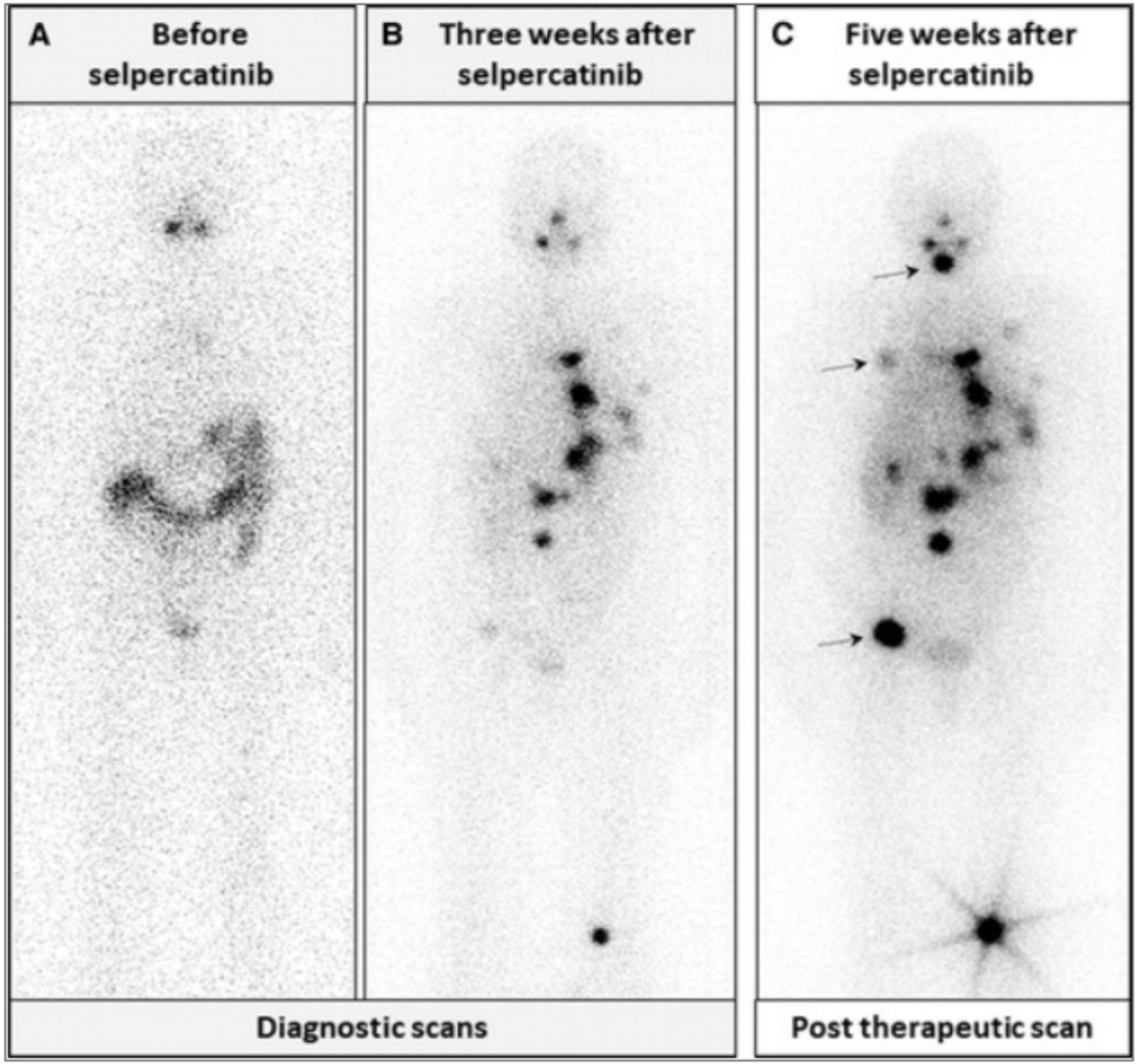
- Gain-of-function mutations in MAPK pathway (BRAF, RAS, RTK) → ↓NIS expression
- Selective MAPK pathway inhibition → ↑ NIS expression → ↑ RAI uptake



Leboulleux et al, Thyroid, 2019

REDIFFERENTIATION

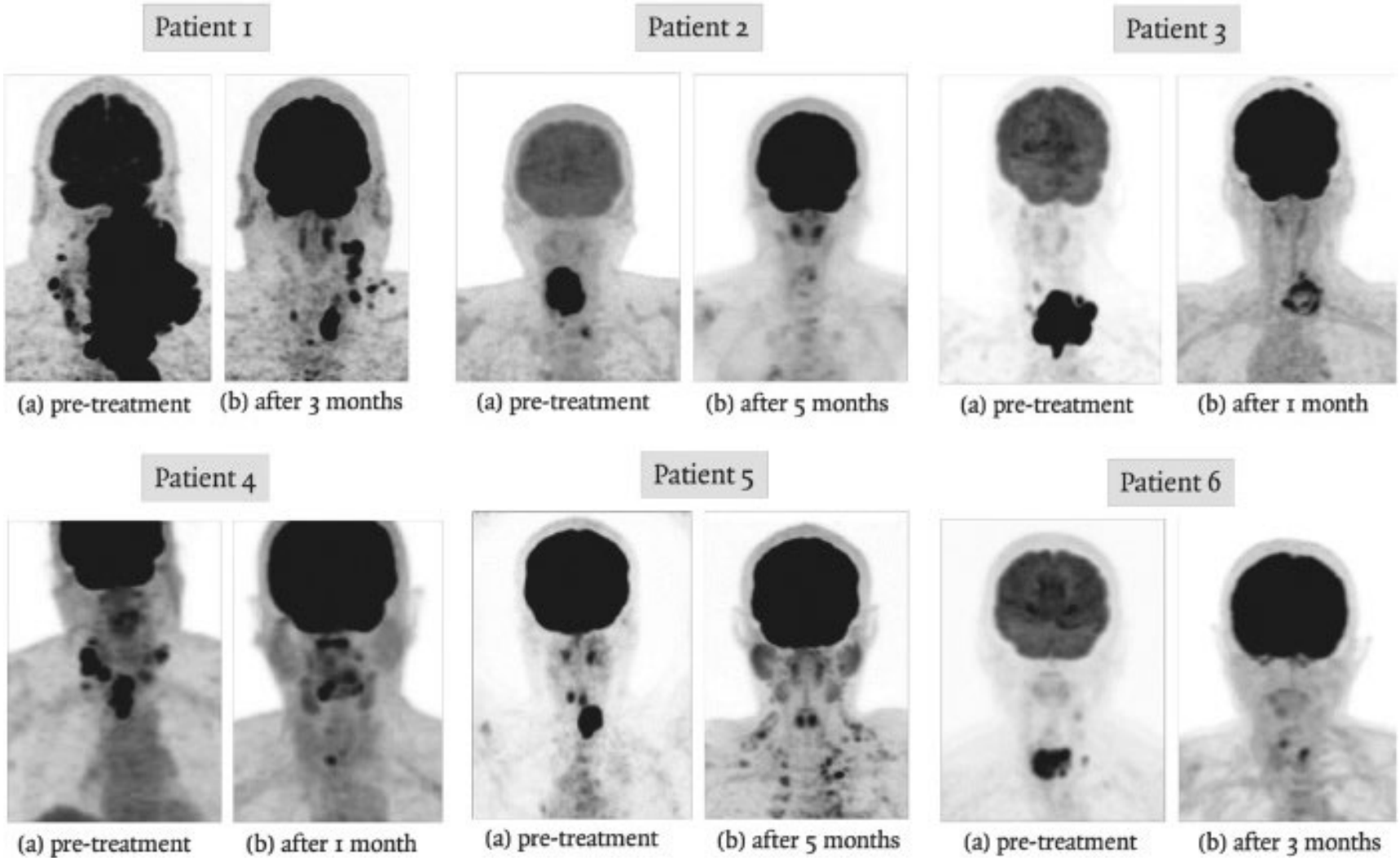
- Dabrafenib (4 weeks): new RAI-avid lesions in 6/10 patients (2 PR, 4 SD)
  - Rothenberg et al, CCR, 2015
- BRAF or MEK inhibition: increased RAI uptake in 9/13 patients (3 PR, 6 SD)
  - Jaber et al, JCEM, 2018
- Case reports with larotrectinib or selpercatinib
- Ongoing MERAIODE trial: phase II trial with trametinib + dabrafenib followed by radioactive iodine for patients with $BRAF^{V600E}$ mutation (Prof. Leboulleux)



Groussin et al, Thyroid, 2021

NEOADJUVANT DABRAFENIB + TRAMETINIB IN $BRAF^{V600E}$-MUTANT ATC

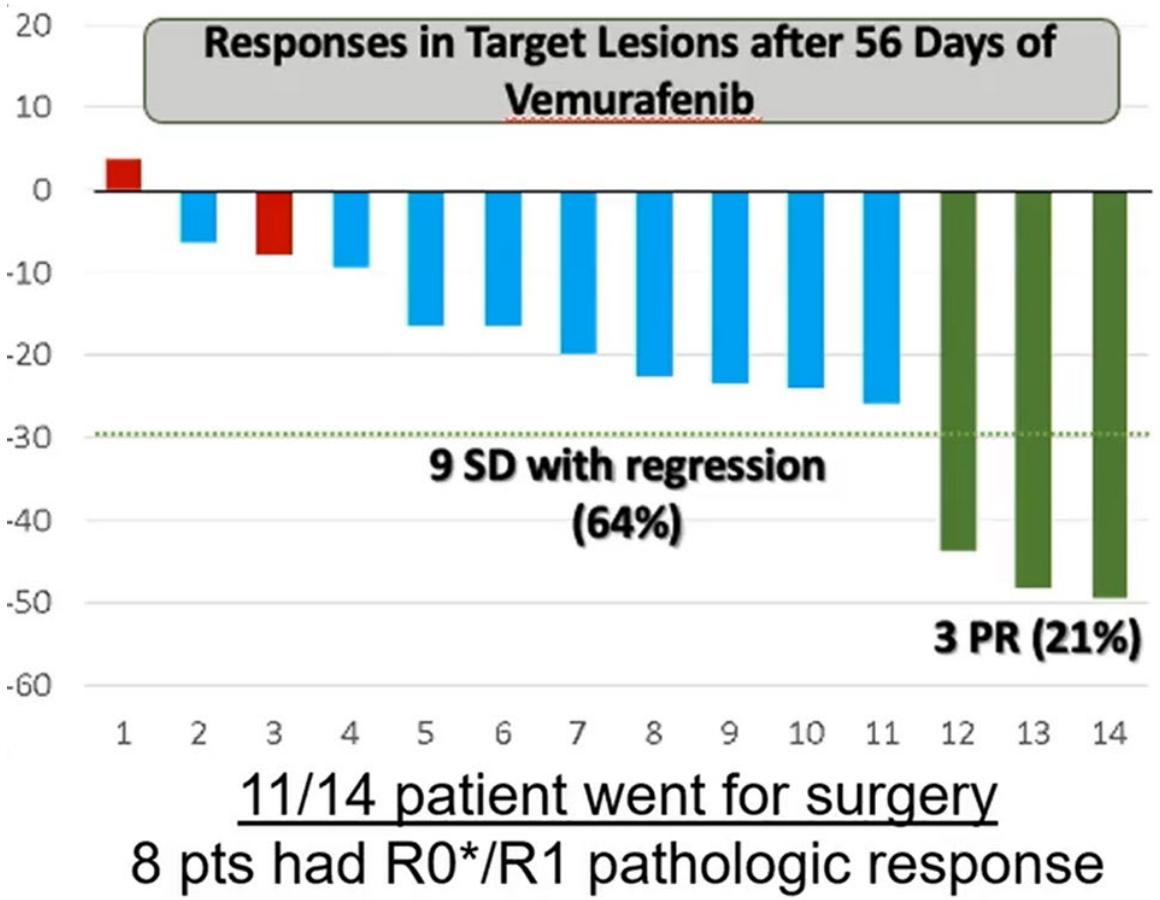
- complete resection possible in all 6 patients
- decreased need for tracheostomy
- high pathologic response rates (R0 in 4/6 and R1 in 2/6)
- durable locoregional control with symptom atic improvement



Wang JR et al. Thyroid. 2019

NEOADJUVANT THERAPY IN LOCALLY AGGRESSIVE DISEASE

- Vemurafenib in $BRAF^{V600E}$-mutant PTC
- Case reports on selpercatinib in RET-mutant sporadic MTC; ongoing phase II trial
- Phase II trial on neoadjuvant lenvatinib for locally advanced DTC



M. Cabanillas, unpublished

ALTERNATIVE APPROACHES IN DEVELOPMENT FOR THYROID CAN

- Tumor vaccines and chimeric antigens (CAR -T)
- Peptide Receptor Radionuclide Therapy (PRRT)
- Immune check -point inhibitors
- PROTACs (PROteolysis TArgeting Chimeras)
- Covalent inhibition of targets
- Super-enhancer gene transcription inhibitors

Matthew D. Ringel
Columbus

TAKE HOME MESSAGES Thyroid cancer

- New targeted therapies for advanced thyroid cancer based on mutational status.
- Redifferentiation therapy using MAPK pathway inhibition shows new RAI -uptake in previous RAI -refractory disease.
- Alternative approaches in thyroid cancer currently in development.

THANK YOU FOR YOUR ATTENTION !