24rd Post ADA / Post ENDO-Symposium

Thyroid

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Outline

1. First generation anti-RET and beyond in metastatic medullary thyroid carcinoma
   Julien Hadoux – Gustave Roussy Villejuif, France

2. Regulation of HPT-axis in maternal-foetal health
   Robin Peeters – Rotterdam, Netherlands

3. Thyroid hormone transporter defects
   Edward Visser – Rotterdam, Netherlands

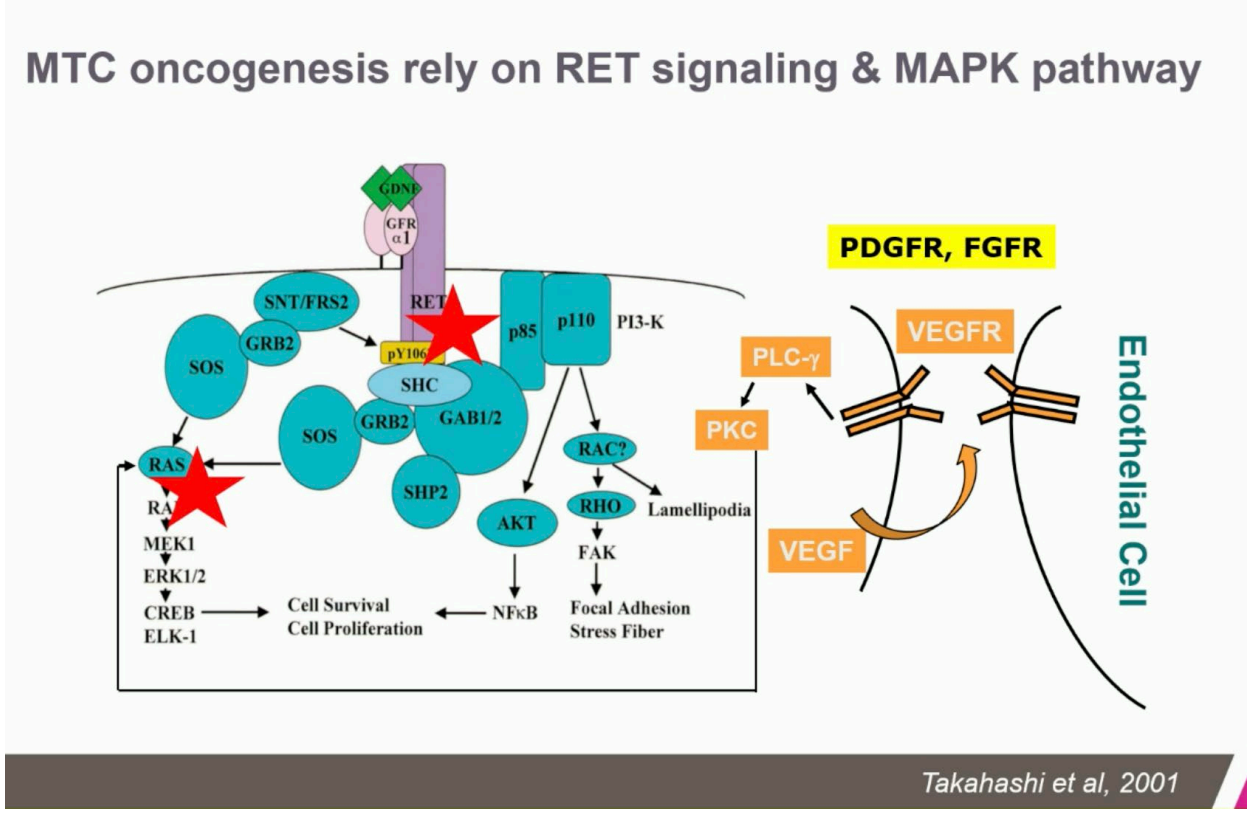
4. Novel therapeutic approaches in radioiodine refractory thyroid cancer
   Christine Spitzweg – Munich, Germany

First generation anti-RET in medullary thyroid carcinoma, and beyond

- Neuroendocrine tumor of the thyroid
- 5% of thyroid cancer
- Sporadically (75%) or in hereditary form (25%)
- MTC oncogenesis rely on RET signaling and MAPK pathway
- RET is constitutively active when mutated

→ RET germline mutation screening for every patient

→ RET somatic mutation screening if a systemic treatment is considered



ESMO 2019, 2022, ATA 2015

First generation anti-RET in MTC, and beyond

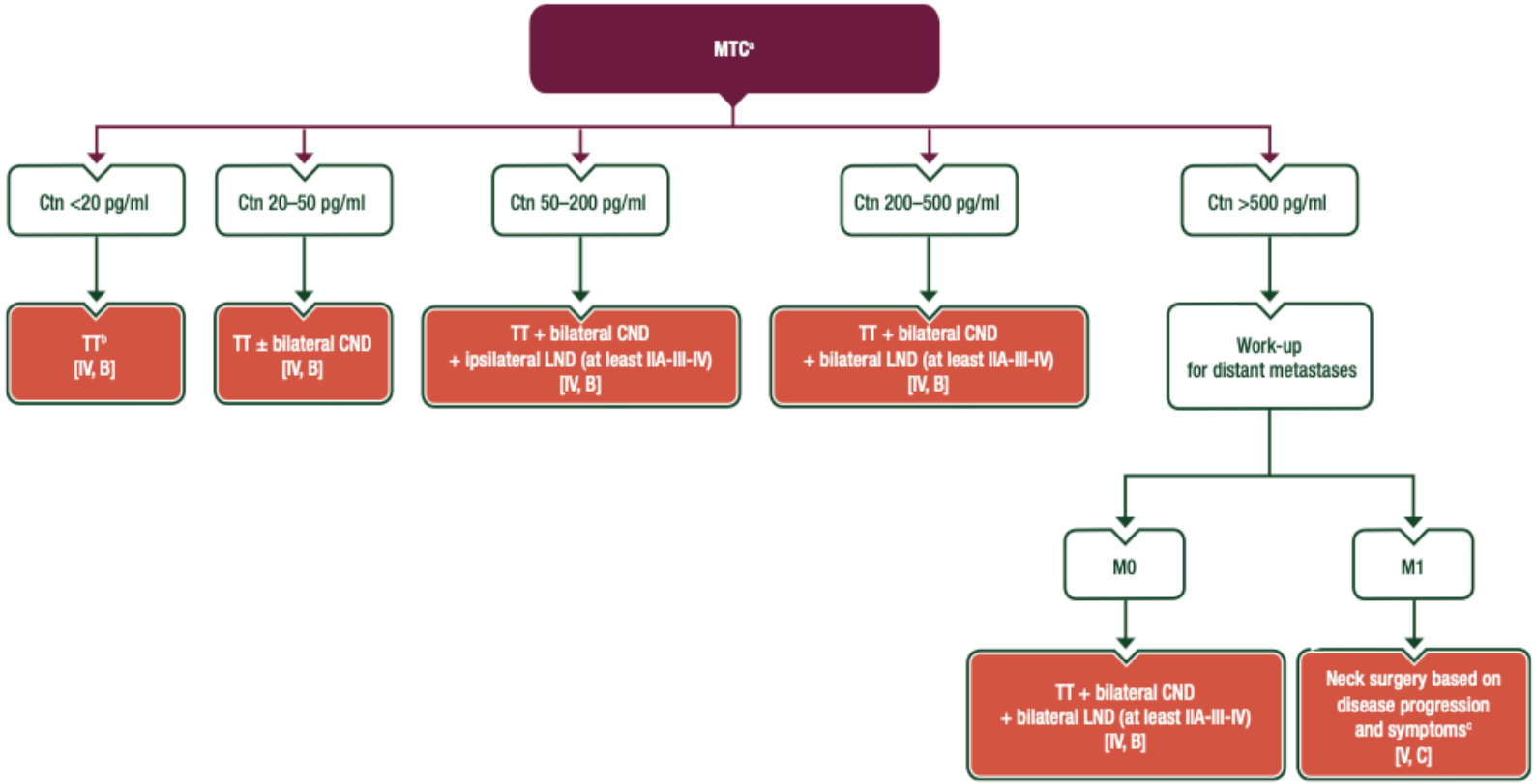
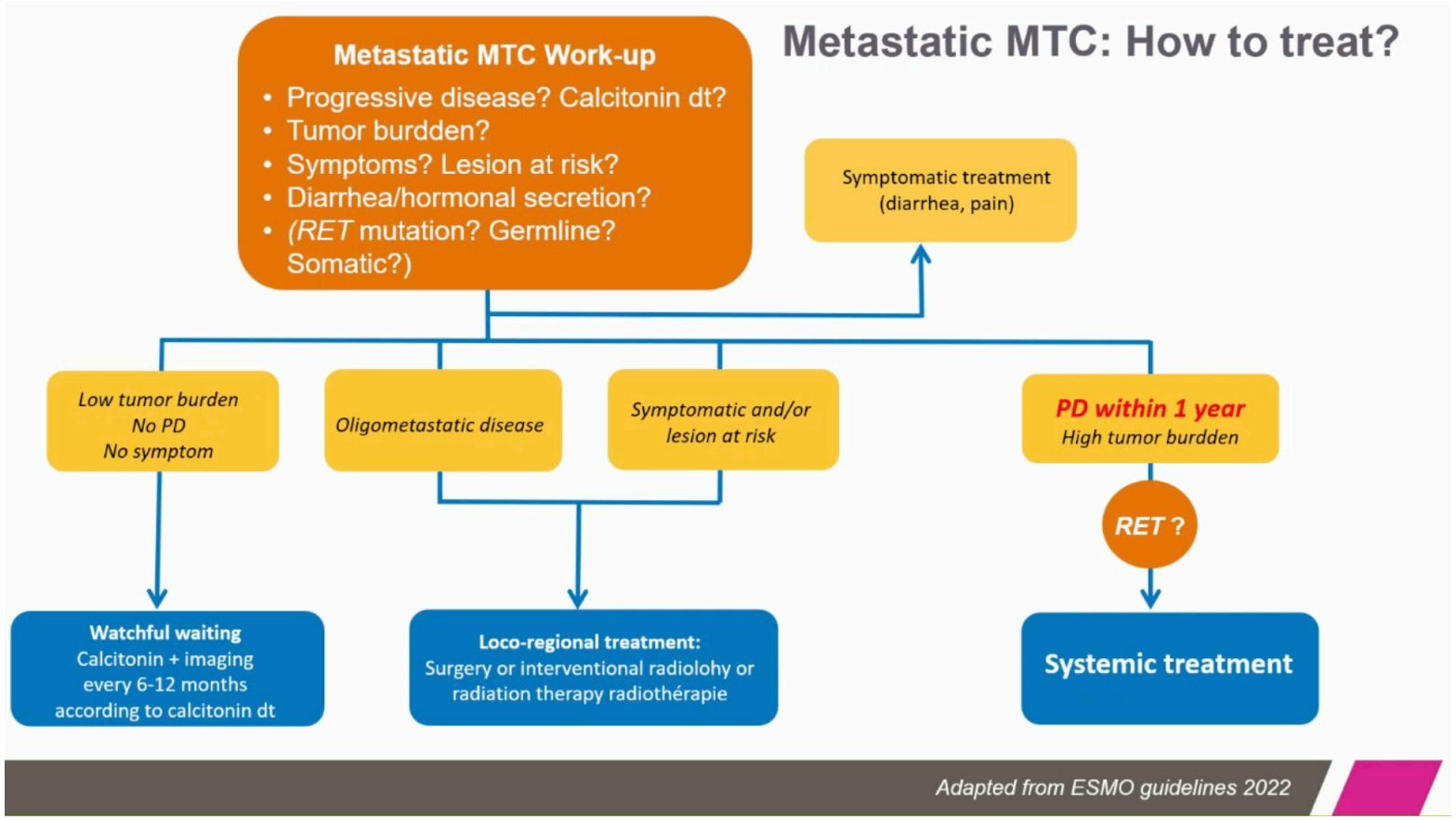


Figure 6. Recommendations for surgical management of MTC patients.

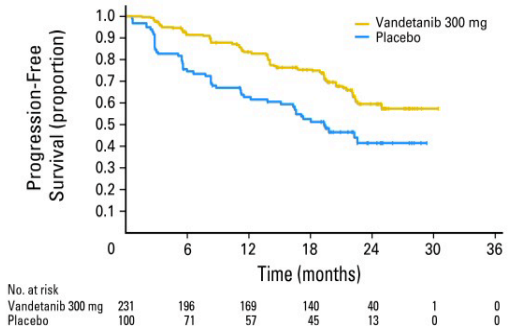
ESMO 2019 and 2022

First generation anti-RET in MTC, and beyond

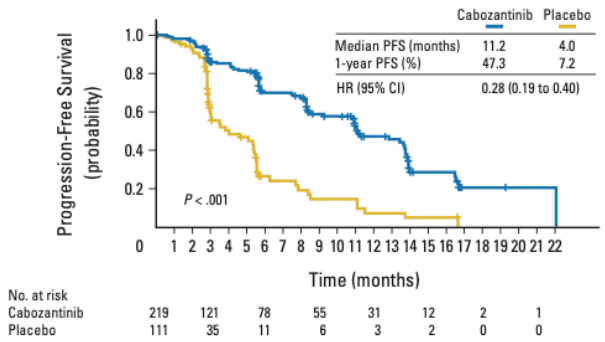


First generation anti-RET in MTC, and beyond

- **First line systemic therapy**: **cabozantinib and vandetanib**
  - Multi kinase inhibitors
  - FDA and EMA approval based on improvement of progression free survival (PFS)



- **ZETA trial (Vandetanib)**
  - Median PFS Placebo 19.3 months vs Vandetanib 30.5 months



- **EXAM trial (Cabozantinib)**
  - Median PFS Placebo 4 months vs. Cabozantinib 11.2 months

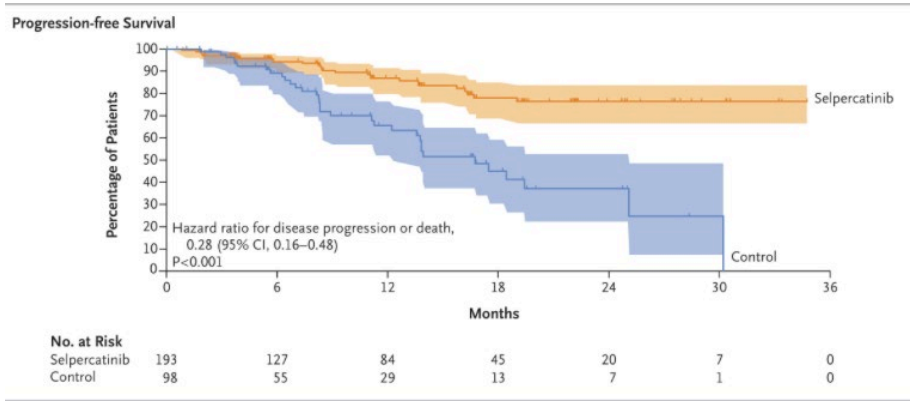
- effective but toxic
  - ≥ Grade 3 toxicities with Vandetanib 55 % , with Cabozantinib 69 %

ESMO 2019, Wells, et al, JCO 2012, Elisei, et al, JCO 2013

First generation anti-RET in MTC, and beyond

- **Selective RET- inhibitors: Selpercatinib**
- **Selpercatinib**
  - Approved by EMA and FDA for treatment of metastatic RET-mutant MTC
  - LIBRETTO-001 (phase I / II)
    - 2 cohorts: treatment naive and previous vantedanib/cabozantinib treatment
    - ORR 82.5% (treatment naive) and 77.6% (previously treated)

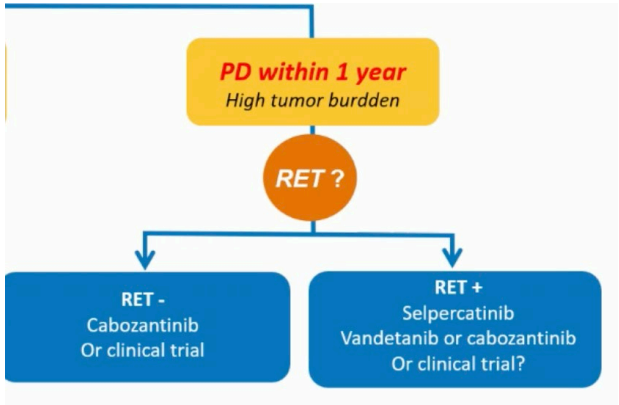
- **LIBRETTO- 531**
  - Selpercatinib vs standard therapy (Vandetanib/Cabozantinib)
  - Median PFS: Selpercatinib not reached vs. Cabozantinib/Vandetanib 16.8 months
  - Safety: tolerability better than MKI
  - More effective as first-line treatment of RET-mutant progressive MTC



Wirth et al, NEJM 2020, Wirth et al, J Clin Oncol, 2024
Hadoux, Elisei et al, NEJM 2023

First generation anti-RET in MTC, and beyond

- **RET mutation: Selpercatinib is the first line preferred option as compared to MKI**



- **Resistance to RET selective inhibitors**
  - On-target or bypass mutations or pathology modifications (increase in KI67 Index)

- **New treatment strategies**
  - Fibroblast- activation protein targeting
    - Overexpressed in MTC
    - ^{68}Ga-CTR-FAPI PET more sensitive in detecting metastatic disease vs. ^{18}FDG PET

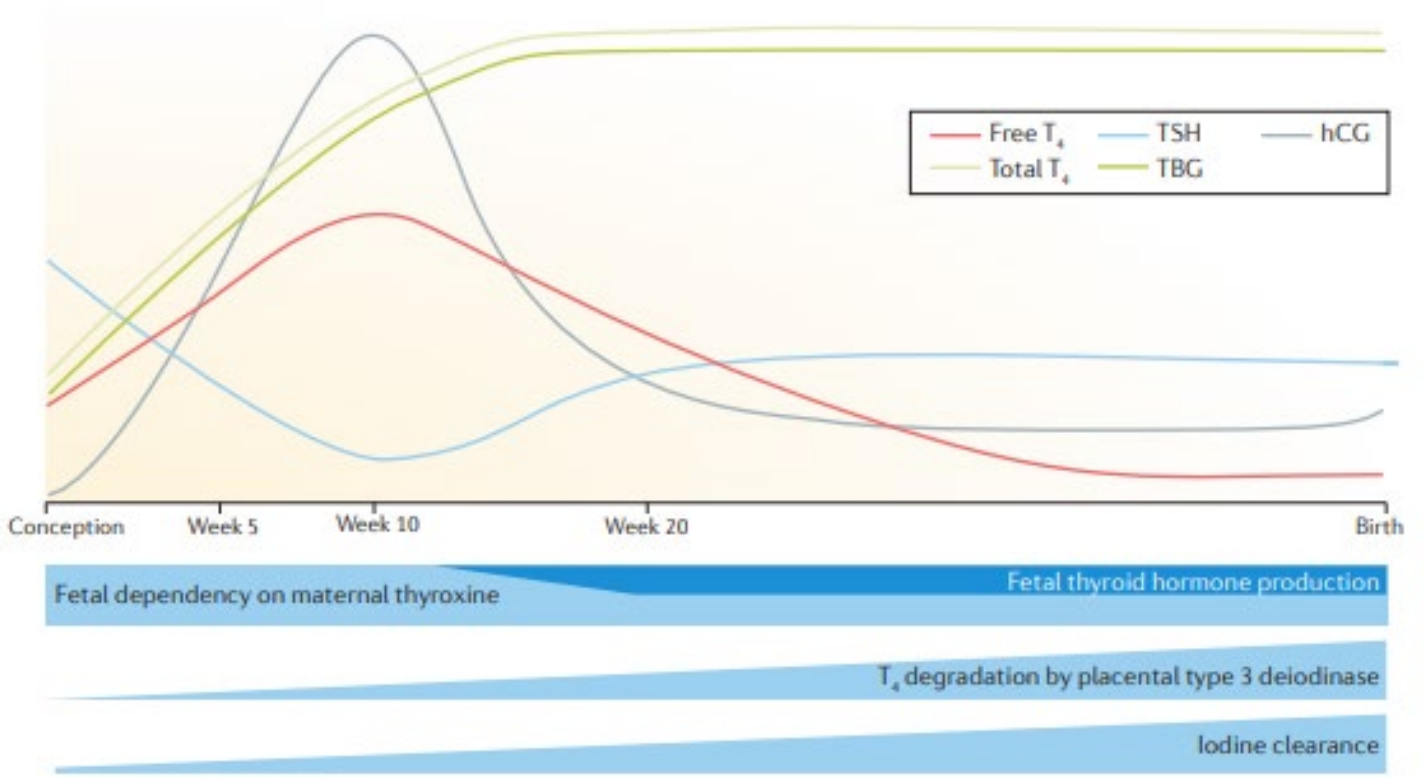
    → FAPI-related radioligand therapy?

Hadoux et al, JCO Precis Oncol, 2023
Kong Z et al, Cancer Discov, 2024

Regulation of HPT-axis

in maternal-foetal health

Regulation of HPT-axis in maternal-foetal health



Korevaar et al, Nature Rev ENDO, 2017, Medici et al, JCEM 2012

- **ATA 2011**
  - First trimester: TSH 0.2-2.5 mIU/L
  - Second and third trimester: TSH 0.2-3.0 mIU/L

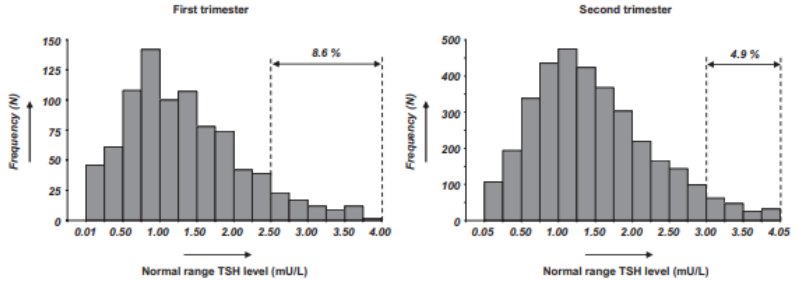


FIG. 1. Distribution of normal range serum TSH levels in the first and second trimesters, after exclusion of women with TPOAb positivity, known thyroid disease, thyroid (interfering) medication usage, twin pregnancies, and pregnancies after fertility treatment. In the first trimester, 8.6% of the women with normal range TSH levels had a TSH level greater than 2.50 mU/liter. In the second trimester, 4.9% of the women with normal range TSH levels had a TSH level greater than 3.00 mU/liter.

- **ATA 2017**
  - Calculate trimester specific reference ranges
  - TSH < 4 mIU/l

Regulation of HPT-axis in maternal-foetal health

Overt hypothyroidism

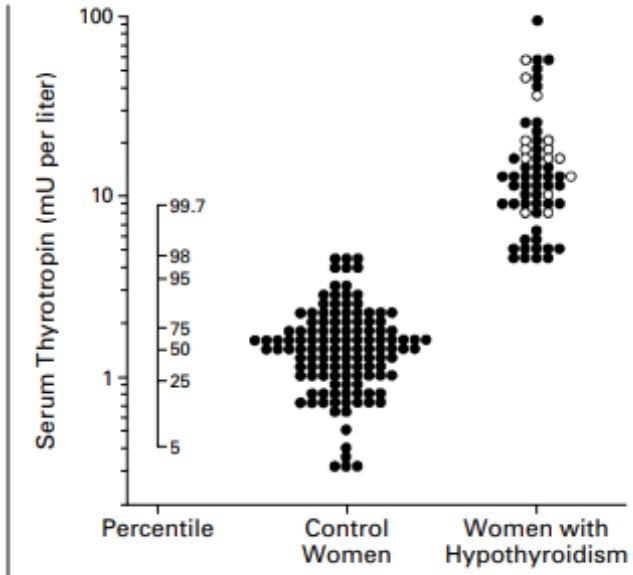


Figure 1. Distribution of Serum Thyrotropin Concentrations during Pregnancy in the 62 Women with Hypothyroidism and the 124 Matched Control Women.

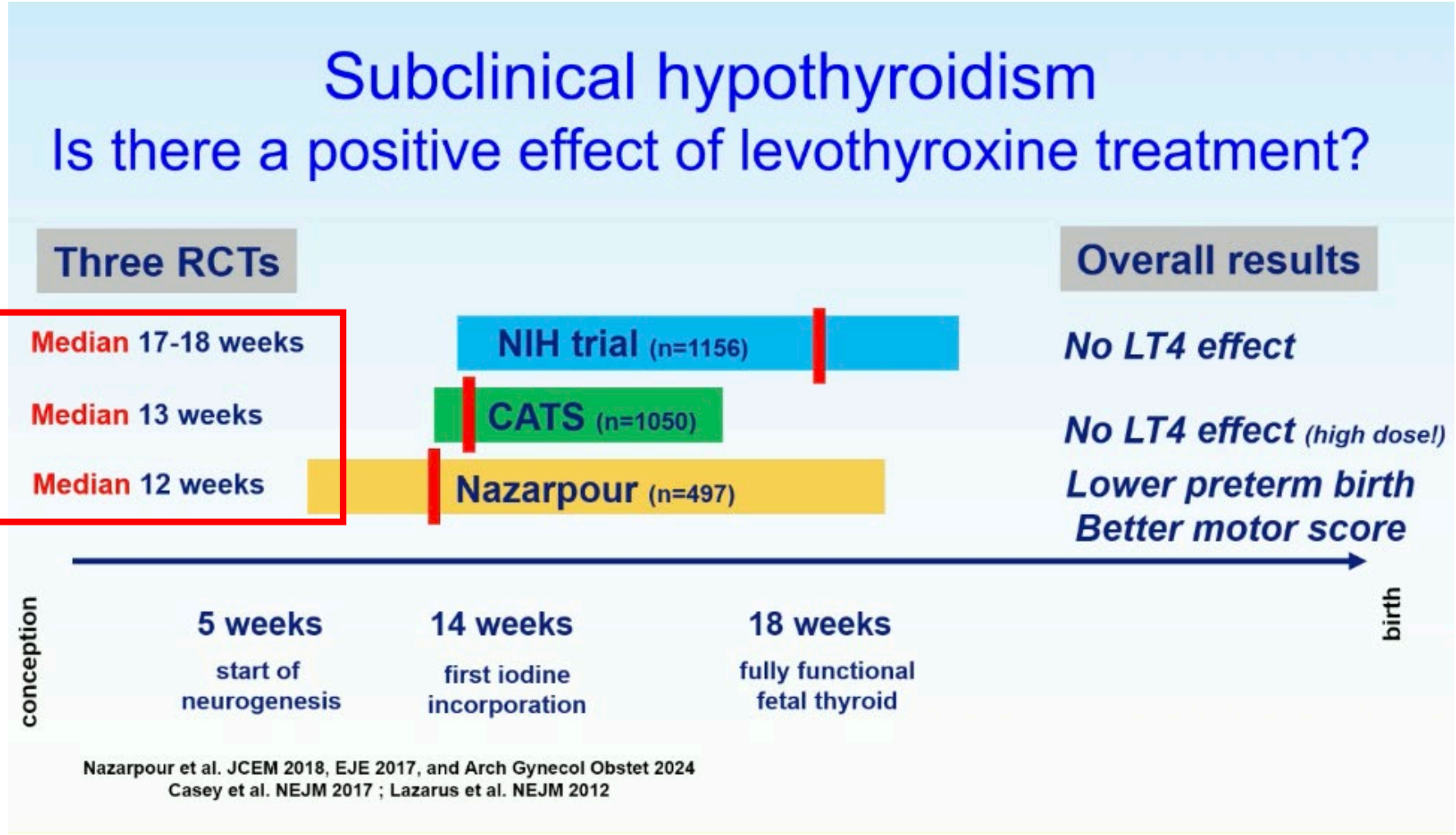
Open circles indicate the 14 women who were treated for hypothyroidism during the pregnancy under study. Selected percentiles are shown for the entire cohort of 25,216 pregnant women.

- **Maternal hypothyroidism and subsequent neuropychological development of the child**
- **62 women with hypothyroidism**
  - 47 women: TSH >99.7th percentile
  - 15 women TSH 98-99.6th percentile fT4 < 99.7th percentile
- 124 euthyroid **matched controls**
- Main outcome: **neuropsychological tests at 7-9 yrs**

→ **Untreated** **Child IQ 100**
→ **Maternal euthyroidism** **Child IQ 107**

Haddow et al, 1999, NEJM

Regulation of HPT-axis in maternal-foetal health



CATS follow-up at age 9

High fT4 in treatment group

- More behavioral problems (22% vs 5%)
- More ADHD symptoms (17% vs 5%)

Hales et al, JCEM 2019

Regulation of HPT-axis in maternal-foetal health

Draft of new ATA Guidelines

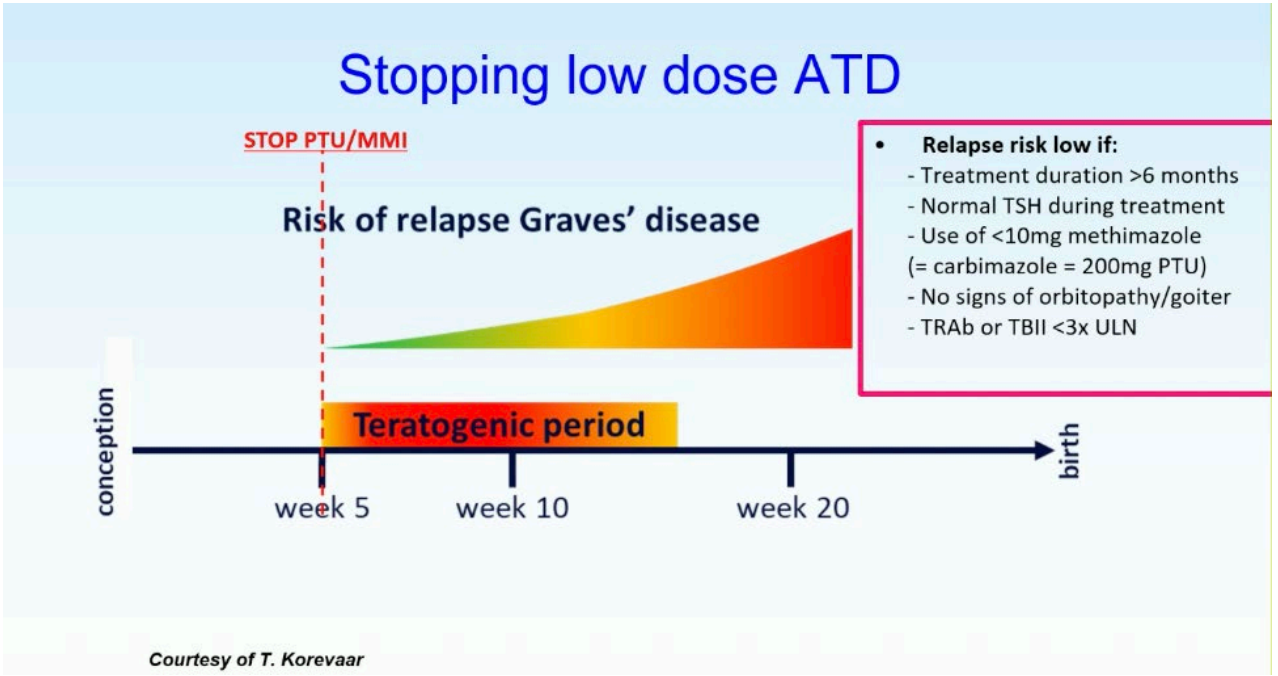
• **TSH > 10 mIU/l**		**always treat**
• **TSH 4 - 10 mIU/l**	first trimester	treatment can be considered
	second& third trimester	no treatment
		follow up testing in 4-6 weeks
• Already using LT4 before pregnancy		target TSH < 2.5 mIU/l, within normal range

Hyperthyroidism in pregnancy

- Propylthiouracil (PTU) remains the preferred drug during pregnancy
- Both PTU and methimazol are associated with increased risk of congenital malformation (2-4%)
- The spectrum of malformations is different
  - PTU-related birth defects are generally less severe

- **PTU:** Face and neck cysts, urinary tract abnormalities

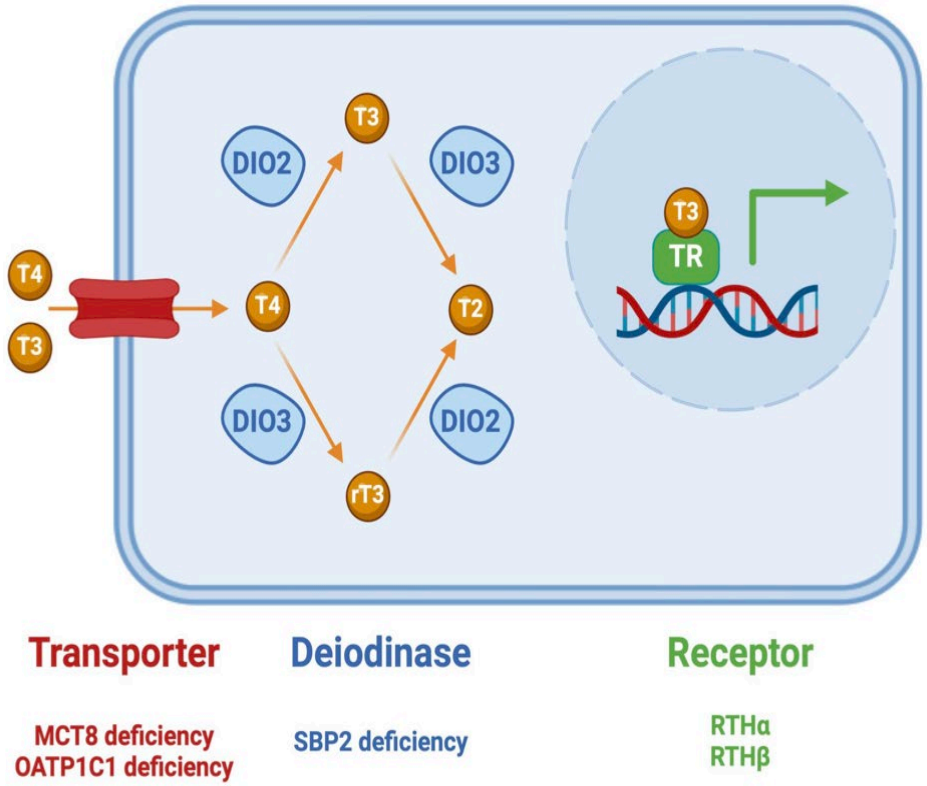
- **Methimazol:** Aplasia cutis, Atresia of oesophagus, Omphalocele



Andersen et al JCEM, November 2013, Seo et al, Annals of int Med 2018
Robin Peeters, ECE Copenhagen 2025

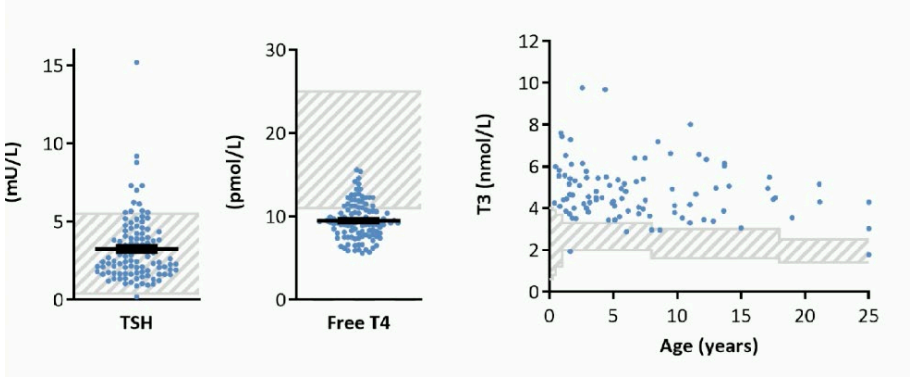
Thyroid hormone transporter defects

Thyroid hormone transporter defects



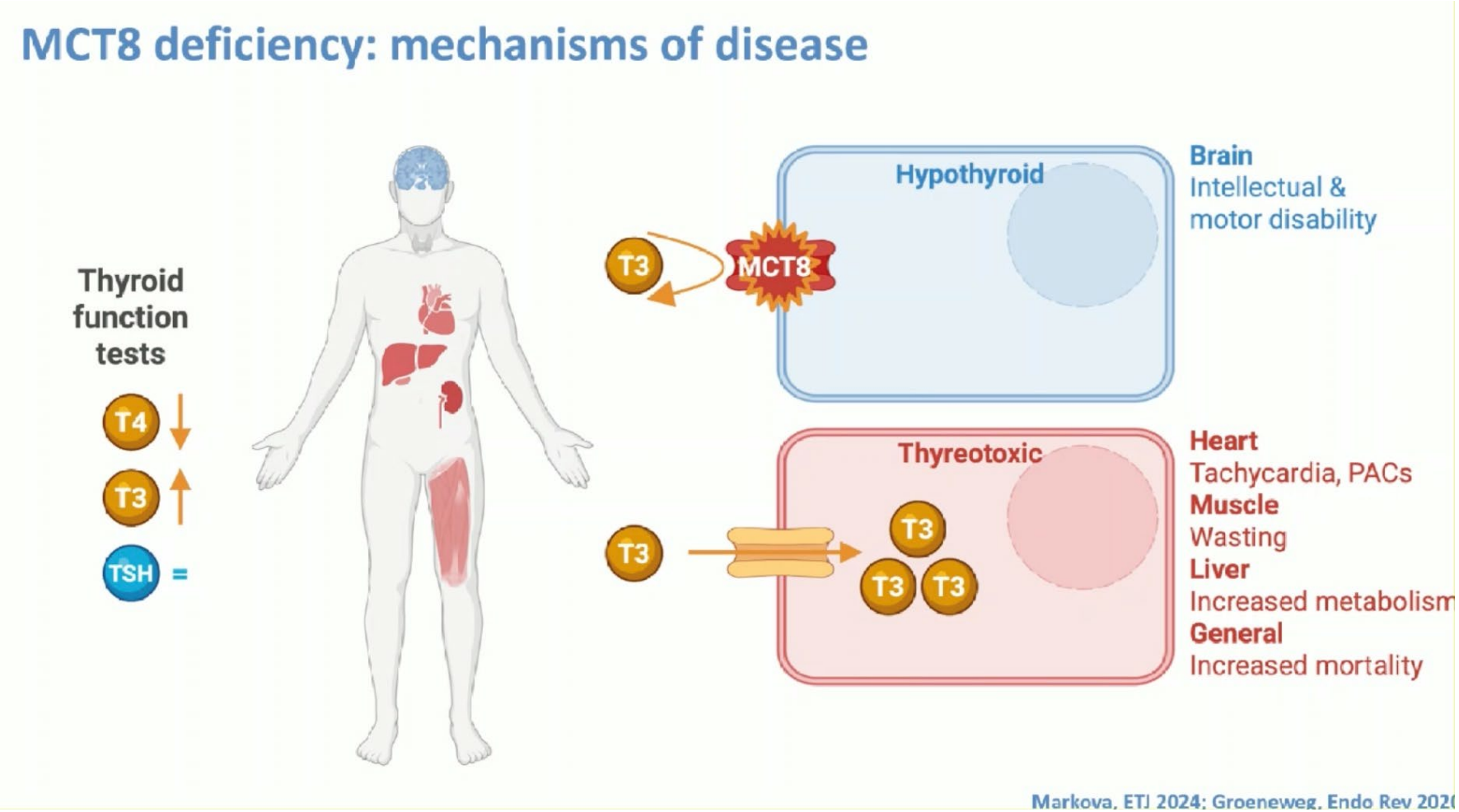
MCT8 Deficiency

- Expressed on the X chromosome → Mainly males affected
- 2 components in the disorder
  - neurodevelopmental
  - metabolic / thyreotoxic (elevated heart rate, body weight deterioration)
- Key features: developmental delay, no head control, central hypotonia, poor weight gain, feeding problems
- High mortality rate



Edward Visser, ECE Copenhagen 2025
Remarand DMCN 2019, Groeneweg Lancet Diabetes Endocrinol, 2020

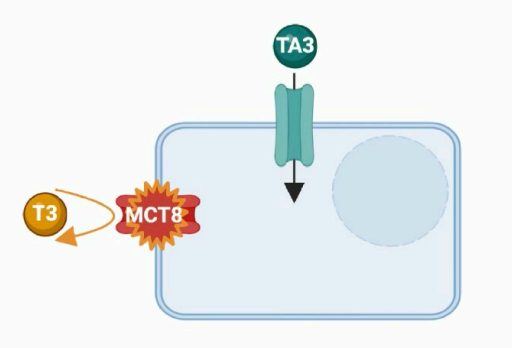
Thyroid hormone transporter defects



Thyroid hormone transporter defects

Treatment

- **LT4**
  - historically (under suspicion of central hypothyroidism, TSH =, fT4 ↓)
  - elevated dejodinase type 1 → aggravates thyreotoxicosis
  - Do not consider
- **PTU + LT4**
  - Beneficial effects on thyroid function tests
  - No evident changes on metabolic parameters, no neurological effects
  - Can be considered if no other therapies available
- **Triac** (Tiratricol, T3 analogue)



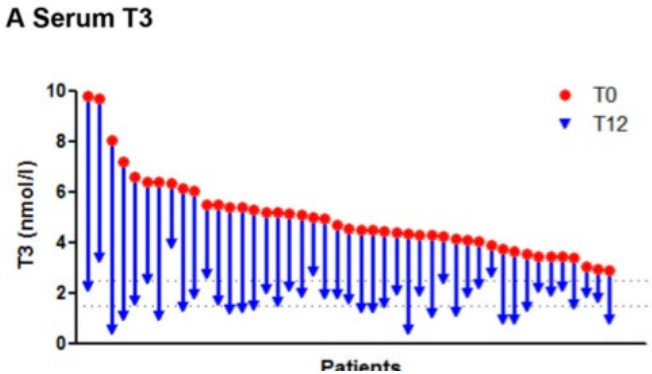
- Metabolic phenotype: negatively influences the pituitary
  → reducing TSH & endogenous thyroid hormon production
- Substitution of T3 in hypothyroid tissue

Weiss Thyroid 2024, Visser, ECE Copenhagen 2025

Thyroid hormone transporter defects

Triac Trial I – metabolic phenotype

- International phase 2 trial, 46 patients, median age 7.1 years, treated for 1 year with Triac
- T3 concentration normalized
- Improvements on body weight and heart rate

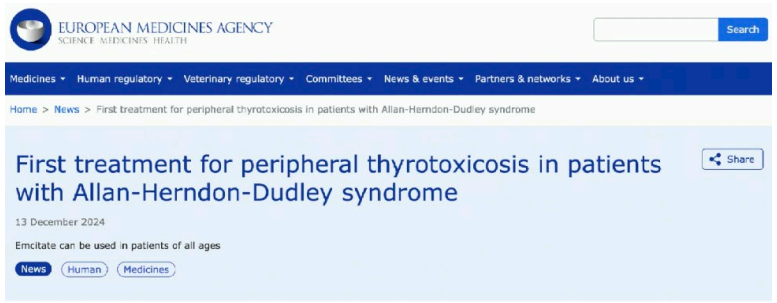


Triac Trial II – neurological phenotype

- Analysis in progress

EMA

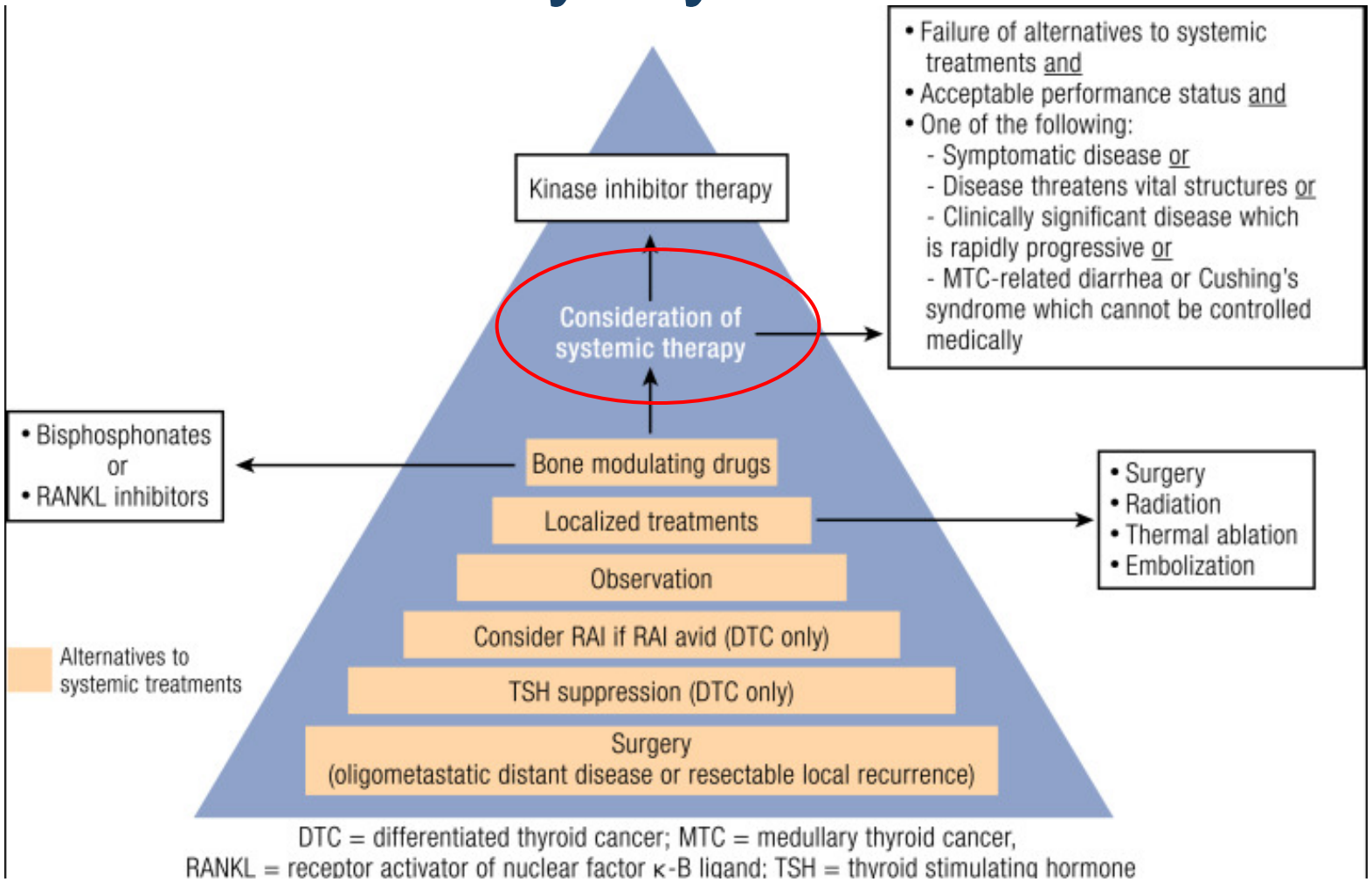
- Recently approved Triac (Emcitate)



Groeneweg, Lancet Diab Endocrinol 2019, Groeneweg, Van Geest, Nat Comm 2025

Novel therapeutic approaches in radioiodine refractory thyroid cancer

Novel therapeutic approaches in radioiodine refractory thyroid cancer



Cabanillas ME et al, Endocrine Rev 2019

Novel therapeutic approaches in radioiodine refractory thyroid cancer

- **No specific target in molecular profile**
  - **Sorafenib /Lenvatinib**
  - **Cabozantinib**
    - Approved by FDA/EMA for second and third line therapy in RAI refractory DTC
    - COSMIC-311 Phase 3 Trial
      - Patients with progression on sorafenib/lenvatinib
      - Significantly prolonged PFS over placebo: 11 months vs 1.9 months

Brose MS et al, The Lancet 2021, Brose MS et al, Cancer, 2022, French J et al, Clin Cancer Res 2024

Novel therapeutic approaches in radioiodine refractory thyroid cancer

Molecular Mechanisms for loss of RAI uptake

- Stimulation of MAPK Pathway
  - Induced by BRAF-mutation, RAS-mutation, RET-fusions, etc.

→ Target MAPK- and BRAF- signaling to reinduce RAI avidity

- **Prospective multicenter, open label phase II trial**
  - BRAF V600 mutated RAI-refractory PTC → Trametinib (MEK inhibitor) + Dabrafenib (BRAF inhibitor)
  - RAS mutated RAI-refractory DTC → Trametinib (MEK inhibitor)

→ **Followed by RAI therapy**

→ BRAF mutated group: RAI uptake in metastatic lesion in 95 %

RAI uptake: dc1-WBS 1/21 ▸ dc2-WBS 11/17 ▸ T-WBS 20/21 (95.2%)

Table 2. Radiologic assessment (central review) of efficacy with RECIST criteria version 1.1 in 21 evaluable patients.

	First course of treatment *N* = 21 patients		
Central review	**1 month**	**3 months**	**6 months**
Patients with a central review	*N* = 21	*N* = 21	*N* = 21
ORR *n* (%) [90CI]	**10 (47.6%) [28.6–67.2]**	**12 (57.1%) [37.2–75.5]**	**8 (38.1%) [20.6–58.3]**
Complete response	0	0	0
PR	10 (47.6%)	12 (57.1%)	8 (38.1%)
Stable disease	10 (47.6%)	9 (42.9%)	11 (52.4%)
PD	1[a] (4.8%)	0	2 (9.5%)
Not evaluable	0	0	0
CT scan not performed *n*	0	0	0

Waterfall plot of the RECIST response 6 months after the first cure

100.0

Spitzweg C et al, Lancet Diabetes&Endocrinology, 2014
Leboulleux S et al, Clin Cancer Res, 2023, Leboulleux et al, Thyroid 2023

Novel therapeutic approaches in radioiodine refractory thyroid cancer

Other molecular targets: Fusions

- **Selective RET inhibitor Selpercatinib**
  - LIBRETTO 001 (phase I/II): previously treated RET fusion positive thyroid cancer
  - Treatment naive patients
  - Approved by FDA/EMA for RET mutated thyroid cancer
- **Selective TRK inhibitor Larotrectinib**
  - Excellent therapeutic efficacy

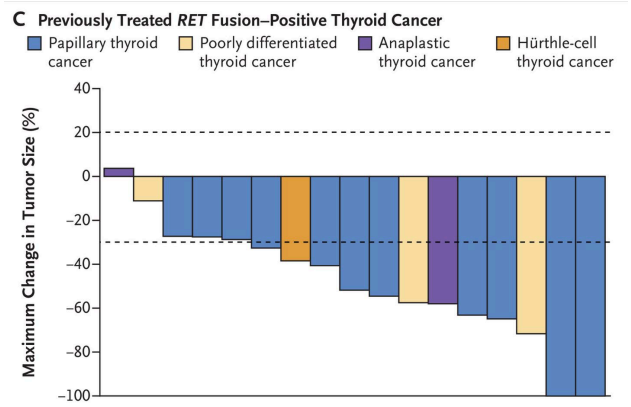
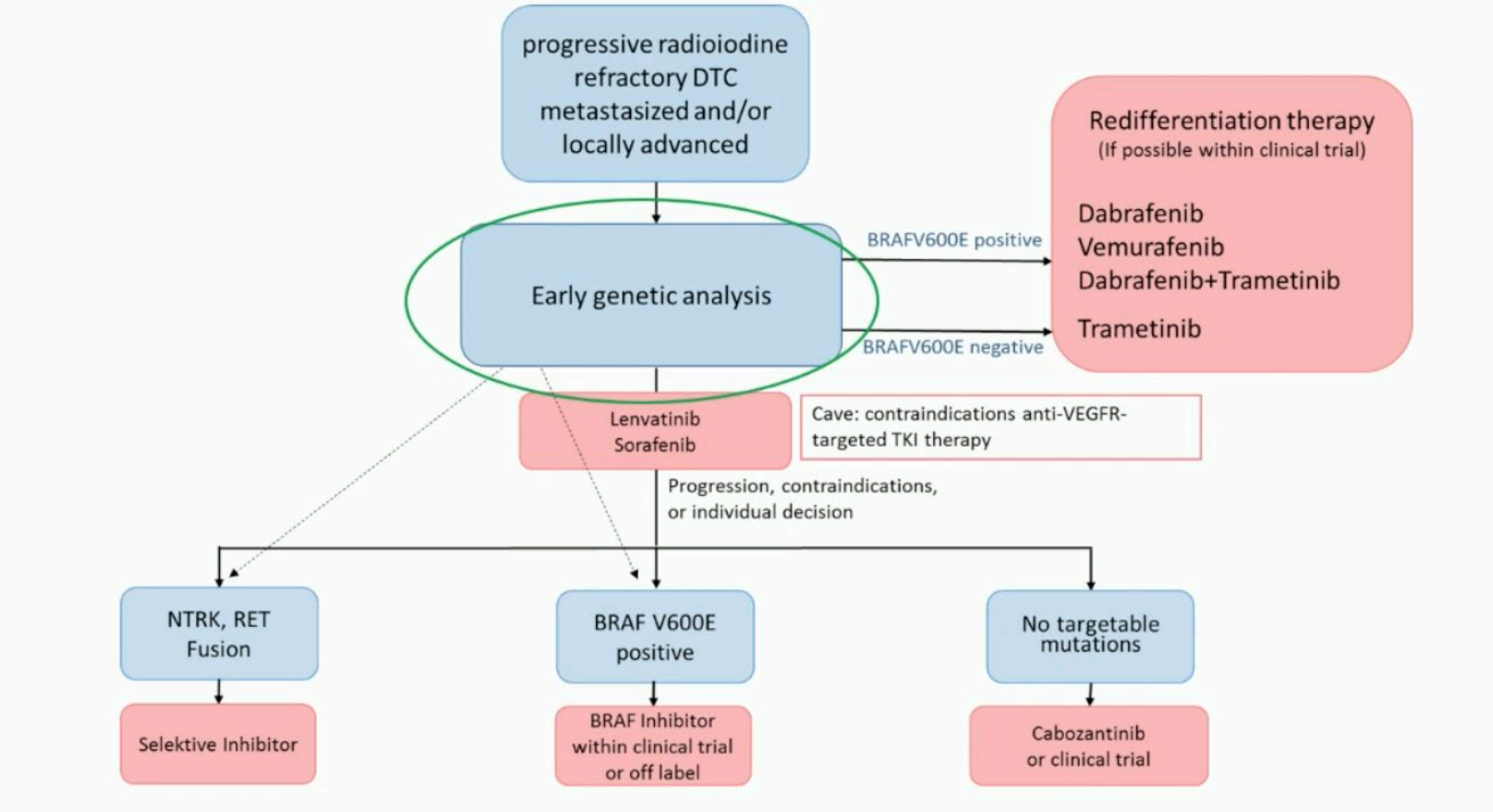


TABLE 2. Efficacy in *RET* Fusion-Positive TC and *RET*-Mutant MTC

	RET Fusion-Positive TC	
Response	Treatment Naïve (n = 24)[a]	Previously Treated (n = 41)
Objective response rate by IRC,[c] % (95% CI)	95.8 (78.9 to 99.9)	85.4 (70.8 to 94.4)
Best overall response		
CR, No. (%)	5 (20.8)	5 (12.2)
PR, No. (%)	18 (75.0)	30 (73.2)
SD, No. (%)	1 (4.2)	6 (14.6)
PD, No. (%)	0	0
Not evaluable	0	0

Wirth L et al, NEJM, 2020, Wirth LJ et al, J Clin Oncol, 2024
Waguespack SG et al, Eur J Endocrinol, 2022

Novel therapeutic approaches in radioiodine refractory thyroid cancer



Key Points

- Medullary thyroid carcinoma
  - RET germline mutation screening for every patient
  - RET somatic mutation screening if a systemic treatment is considered

- Subclinical hypothyroidism in pregnancy
  - Draft of new ATA guidelines: always treat when >10 mIU/l

- RAI refractory DTC
  - Early genetic analysis / molecular profile

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Thank you for your attention