El papel de la biopsia liquida en cancer de tiroides

The role of liquid biopsy in thyroid cancer

Thursday, September 24th 2026
18.15 – 18.30

Dr Julien Hadoux
Endocrine oncology unit & UMR INSERM 981
Gustave Roussy, Villejuif, France
& ENDOCAN network



Personal financial interests:

- **Consultancy or advisory role**: Roche, Lilly, IPSEN, Pharma Mar, AAA , EISAI, Bayer, ITM
- **Congress attendance and travel:** IPSEN, AAA, Roche
- **Speaker, leadership roles, stock ownership, licensing fees or royalties**: None

Research funding: Novartis, Sanofi

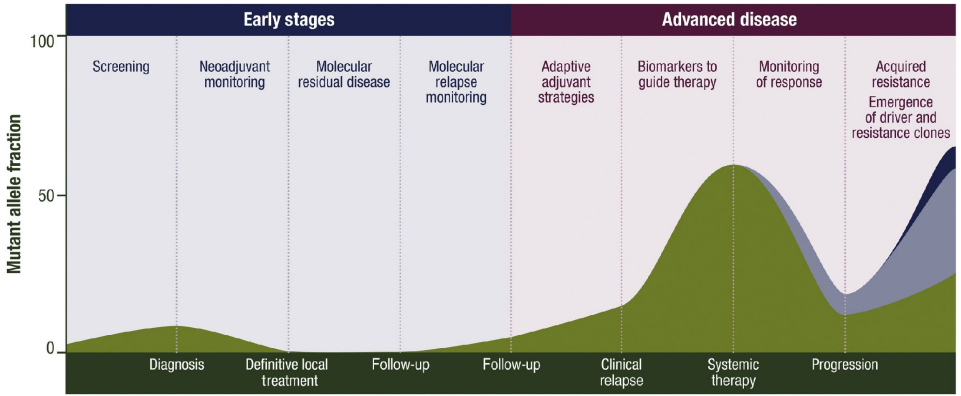
Institutional financial interests: Lilly, EISAI

Non-financial interests: Coordination of the ENDOCAN (Endocrine cancers) network in France

With the help of Dr Ludovic Lacroix & Dr Livia Lamartina

Agenda: can we detect ? Does it change management?

- Introduction
- Genotyping without tissue
- Pre-operative setting
- Surveillance / residual disease
- Monitoring & resistance
- Guidelines



Pascual et al, ESMO guidelines on Ct DNA, 2022

biomedicines

MDPI

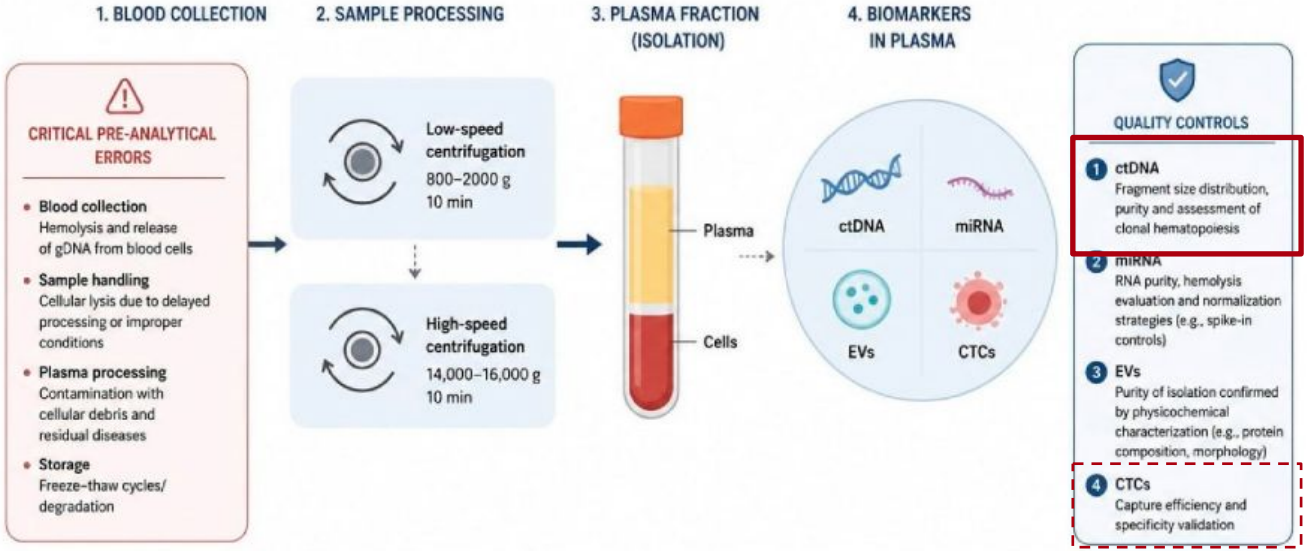
If you want to know everything on liquid biopsys in thyroid K…

Review

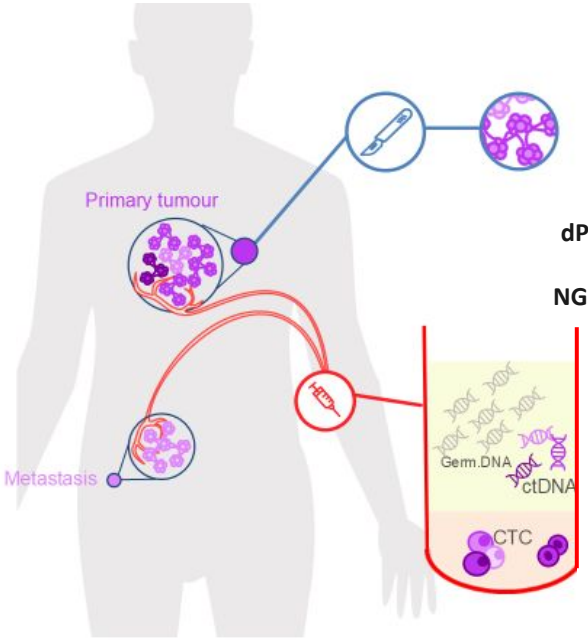
Where Does Liquid Biopsy Add Value in Thyroid Cancer? Biological Rationale, Technological Innovation, and Clinical Utility

María Alonso-Chamorro [1], Ainhoa Palacios Mejorada [1] and Garcilaso Riesco-Eizaguirre [1,2,*]

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Tissue DNA and plasma DNA can both be used to determine the tumour's molecular profile.



Tumour tissue Biopsy

2 main techniques:
dPCR : Higher Se but simplex
&
NGS panel: lower Se but more comprehensive

It is the "gold standard"
tDNA comes from a limited area
(no spatial or temporal heterogeneity)
Multi-step process

Pathology + molecular turnaround: >2 weeks

Blood/plasma is a source of **cell-free DNA (cfDNA)**, part of which comes from **tumour cells (ctDNA)**.
The amount of ctDNA is related to **tumour size and tumour cell activity**.
(heterogeneous origin)
Sampling is **less invasive, simpler and faster**

Sampling + molecular turnaround: 1–2 weeks

The biological sensitivity depends on the situation (≠ analytical sensitivity)

- Not all tumours shed DNA equally
- **Low in localised stages (20%) // response vs progression**
- **Approx. 50–90% in metastatic tumours (depending on primary site)**
- Specificity ~100% (but CHIP / subclones / etc.)

CTC: circulating cancer cell; ctDNA: circulating tumour DNA.

adapted from Scherer, F. (2020) in Recent Results in Cancer Research: Tumor Liquid Biopsies. Springer.

Courtesy of Dr Ludovic Lacroix, molecular biologist

Liquid Biopsy for genotyping: ESMO guidelines

Table 2. Tumour-specific table for advanced cancer genotyping

Tumour type	Indications		ESCAT tier and level of evidence	Recommendation
Thyroid cancer	*BRAF* mutations *RET* mutations *NTRK* 1/2/3 fusions	**+ TMB & MSI**	IB[160,161] IB[162,163] IC[134]	ctDNA testing if tissue not available.

- **Collection of LB** for genotyping should be done **when cancer is progressing, either treatment naive or after prior lines of therapy**. Samples collected when a tumour is responding to therapy = decreased sensitivity.
- The choice between **RT-PCR, digital PCR and NGS** assays in a clinical practice setting should be **defined by availability, reimbursement status and the actionable genetic aberrations** in a tumour-specific context.
- A **negative LB should prompt reflex tissue testing**.
- ctDNA assays have **lower sensitivity for fusions and copy number events** □ **Tissue** prefered,
- All oncology physicians should have **access to a molecular tumour board**, to ensure correct interpretation of results, and for discussion of difficult cases to ensure appropriate decisions are made.

Pascual et al, ESMO guidelines on Ct DNA, 2022

BRAF, *RET*, Fusions, TMB, MSI : which molecular biology technique?

Alteration	Sample	Simplex methods	Small/large panel	Comprehensive Gene Panel	WES/WTS WGS
BRAF mutation	Tissue	**IHC/qPCR/dPCR p.V600**	suitable/DNAseq (or RNAseq)	suitable /DNAseq	suitable
	Plasma	**qPCR/dPCR p.V600**	suitable (DNAseq)	suitable DNAseq LoD <1% TF>1%	**NO**
RET mutation	Tissue	(little value except p.M918T)	suitable/DNAseq (rare in RNAseq)	suitable DNAseq	suitable
	Plasma	(little value except p.M918T)	suitable/DNAseq	suitable (DNAseq LoD <1%)	**NO**
RET/ALK/NTRK fusions	Tissue	**FISH/qPCR/dPCR (IHC-ALK)**	suitable RNAseq/DNAseq	suitable (rearrangement)	suitable
	Plasma	**NO**	DNAseq (no RNAseq)	suitable (rearrangement) (DNAseq LoD <1% TF>1%)	**NO**
MSI	Tissue	**IHC MMR PCR MSI (colon)**	suitable/DNAseq	suitable/DNAseq	suitable
	Plasma	**NO**	Possible DNAseq	DNAseq LoD <1% TF>10%	**NO**
TMB	Tissue	**NO**	**NO**	suitable/DNAseq	suitable
	Plasma	**NO**	**NO**	DNAseq LoD <1% TF>10%	**NO**

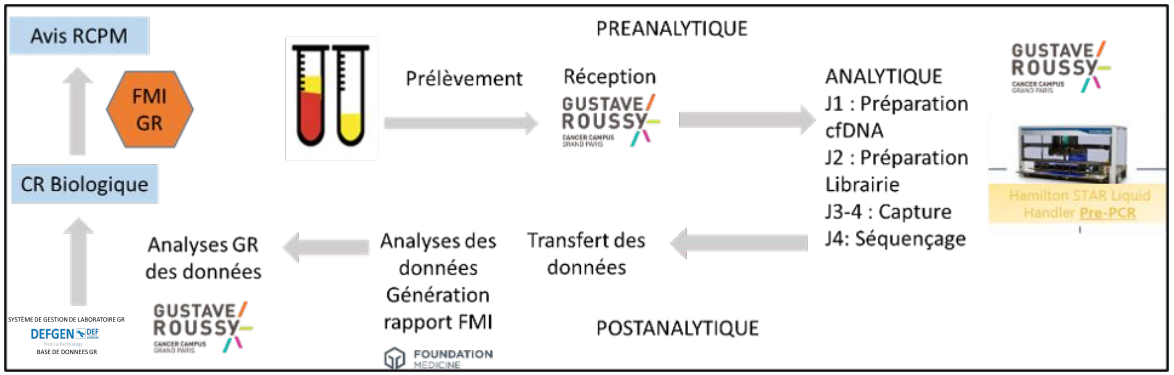
Courtesy of Dr Ludovic Lacroix, molecular biologist

Liquid biopsy: Genotyping without Tissue at Gustave Roussy

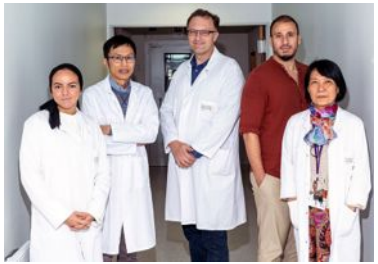
Gustave Roussy – Roche FMI partnership

Internalisation of FMI technology at GR

=> Went into production on 27 June 2024



324 genes:
SNV/CNV/FUSIONS/MSI/TMB/TF
Biological and clinical annotation databases
Turnaround < 15 days (98%)



Gustave Roussy team

- **Technology choice for reagents/process/bioinformatics = FMI partnership**
- Integrated within GR's Department of Medical Biology and Pathology, in the Tumour Genetics Unit – Dr E. Rouleau.
- Compliant with French Public Health Code (CdSP) regulations – ISO15189-COFRAC accreditation / hospital environment
- Data reviewed by medical biologists: interpretation and medical report.
- **Reports discussed at the MTB (VUS, polyclonal resistance, CHIP, oncogenetics referral, variants to verify)**
- Opportunity for clinical and translational research
- Testing available for the whole of France.

Courtesy of Dr Ludovic Lacroix, molecular biologist

Liquid biopsy: Genotyping without Tissue Thyroid Cancer

Gustave Roussy experience on Liquid Biopsy (FMI Liquid) in thyroid cancers

39.5 %

DTC

Related to higher aggressivity and tumor burdden

Moneta et al, ETA 2024, in revision

86 %

MTC

Proportion of patients with RETi mutation of resistance in liquid Biopsy

Hadoux et al, JCO PO 2023

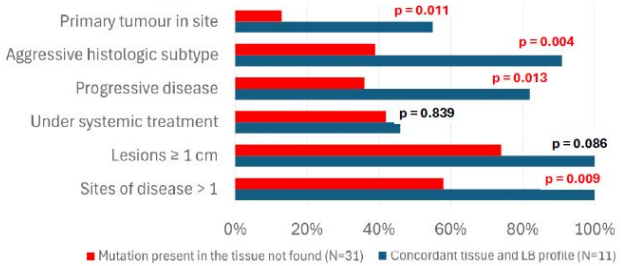
88 %

ATC

Proportion of ATC patients at baseline with at least 1 mutation

Succi et al, ETA 2024

Comparison of clinicopathological features of 42 patients with mutations present in tissue found or not in LB



- Liquid biopsy is very useful and less invasive to capture molecular alterations and tumor heterogenity
- The higher the aggressivity and tumor burdden, the higher the chance to get a result

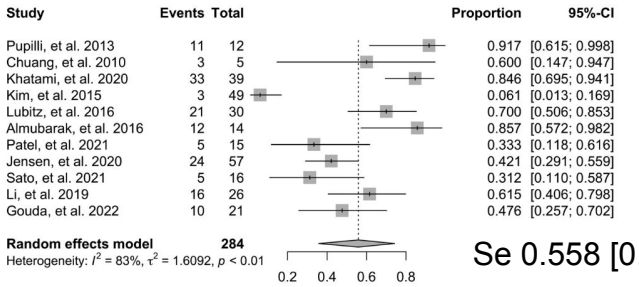
Main issue: no tissue

GUSTAVE ROUSSY
PARIS CANCER CAMPUS

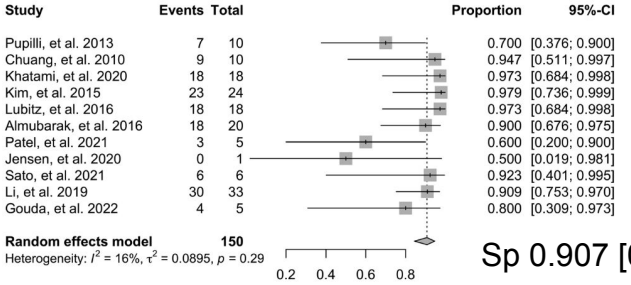
Detecting *BRAF* mutation with ctDNA

Low Se, High Sp in DTC / High Se & Sp in ATC

DTC - metanalysis



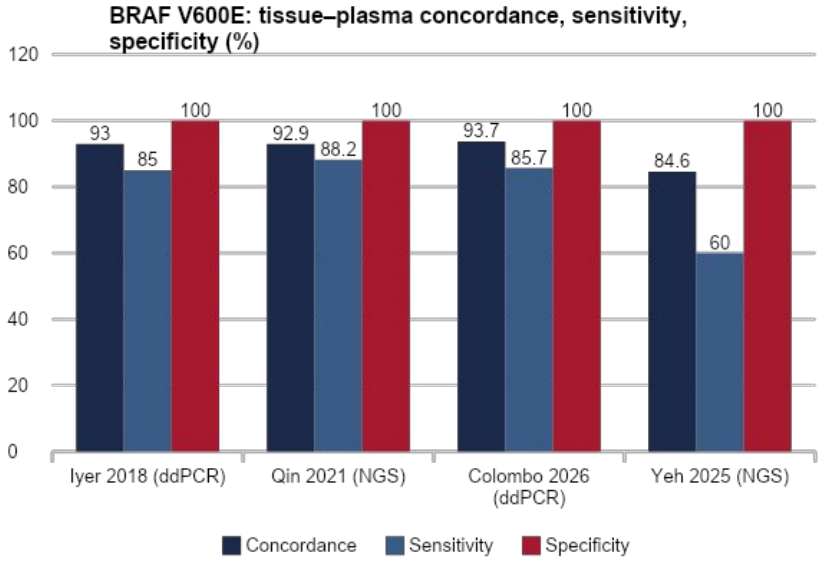
Se 0.558 [0.357;0.742]



Sp 0.907 [0.844;0.946]

Zeyghami et al, ERC 2023

ATC – 4 studies



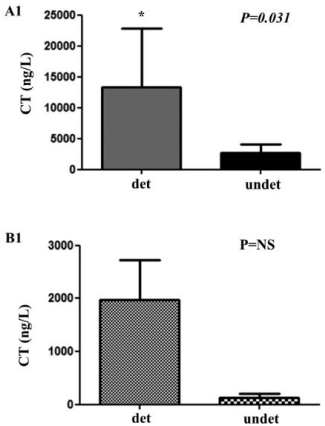
Iyer et al. JCO Precis Oncol 2018; Qin et al. Thyroid 2021; Colombo et al. Endocrine 2026; Yeh et al. NPJ Precis Oncol 2025

Liquid biopsy in the pre-operative setting: Not useful?…

MTC - CtDNA

Monocentric study Pisa

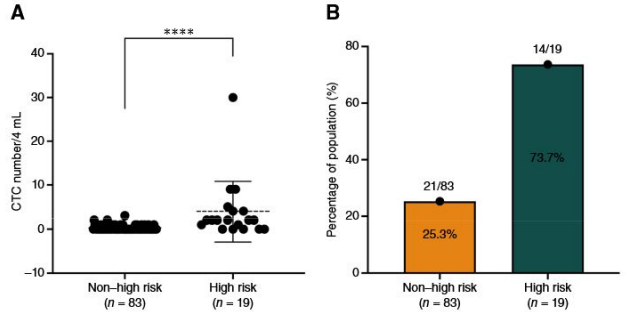
- N= 26 pts pre-op
- 4/26 (15.4%) pre-op ctDNA +
- mean VAF= 1.9% (range, 0.6%-3.8%)
- Correlated to Calcitonin!

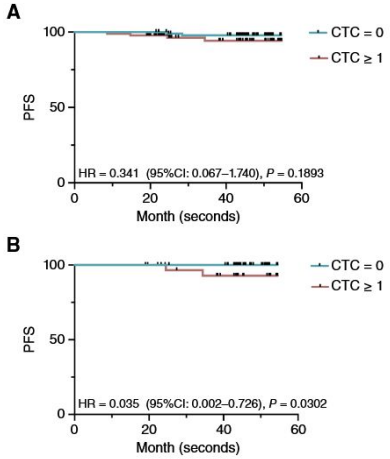


Ciampi et al, JCEM 2022

DTC - CTC

- N= 210 pts tested for CTC before surgery
- 93% specificity for high-risk nodal disease (≥2 CTC/4 mL)





Maybe interesting:

- 25% high risk with 0 CTC
- 25% non high risk with CTC

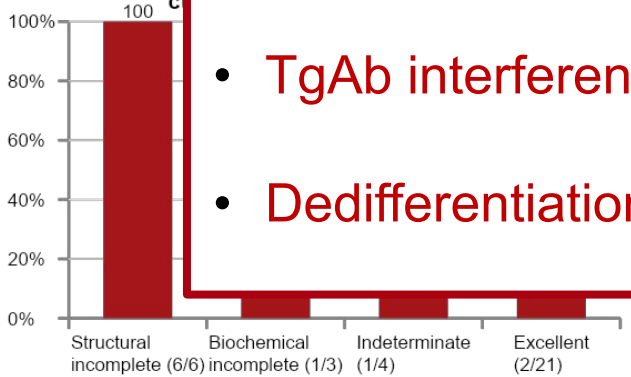
Would CTC help refine risk classification?

Jiang et al, Clin Canc Res 2026

Liquid biopsy for surveillance: Our old school markers still the best and cheapest

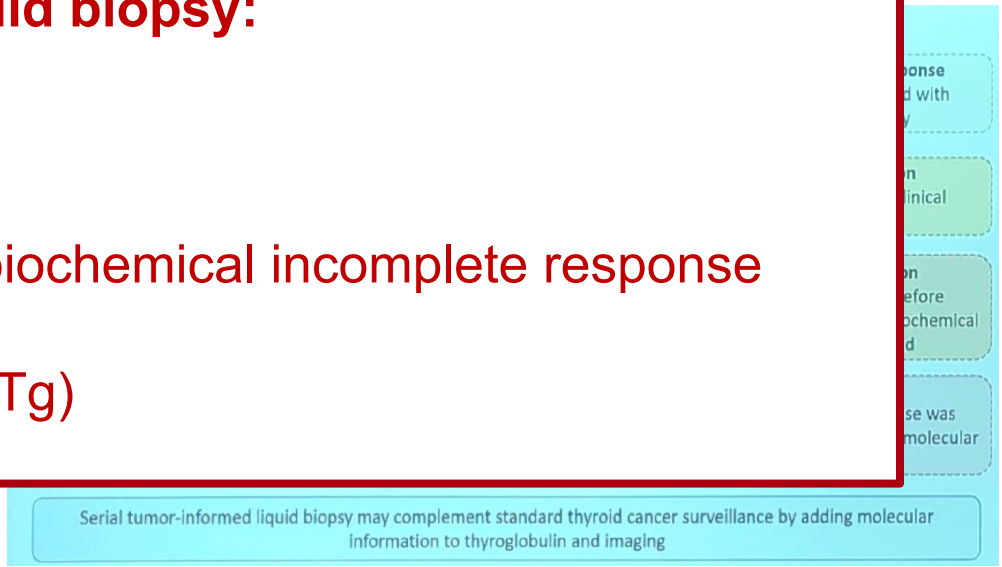
> ***"Currently the only blood-based biomarkers used in thyroid cancer monitoring are thyroglobulin for DTC, and calcitonin and CEA for MTC."***
>
> *Ruz-Caracuel et al, SEAP-GETNE consensus 2026*

- Monocentri
- N= 34 pts
- Patient-spe
- Positive in 2



Area of interest for liquid biopsy:

- Post lobectomy
- TgAb interference biochemical incomplete response
- Dedifferentiation (low Tg)

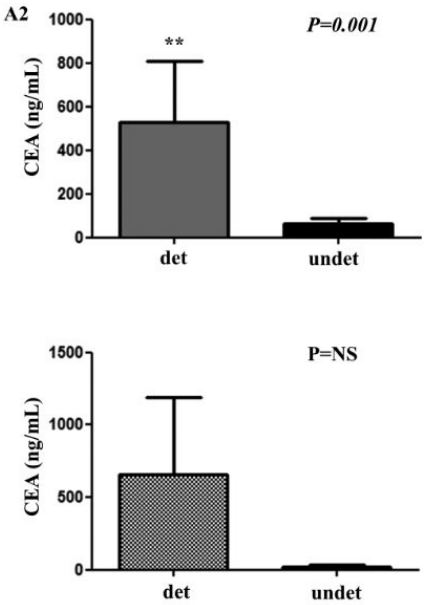


Adapted from Mota DiasThomaz D et al. Eur Thyroid J 2026

Mota DiasThomaz D et al. ETA congress 2026

Liquid biopsy for surveillance: Calcitonin for MTC; what about ATC?

MTC – CtDNA post op



Ciampi et al, JCEM 2022

ATC – CtDNA Follow-up



MD Anderson monocentric
ATC
n=45 baseline / n=31

Metric	Recurrence detection (n=60)
Sensitivity	77%
Specificity	100%
PPV	100%
NPV	92%

Hamidi et al, JCO PO 2025

Clinical case: Resistance induce molecular and clinical heterogeneity

67 year-old male, BMI 40 kg/m²

High grade MTC (ki67 10%),

Metastatic to the lung, liver & lymph nodes

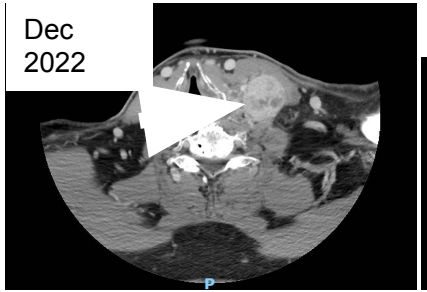
L1 Vandetanib Nov 2015 – June 2019 RECIST -20%

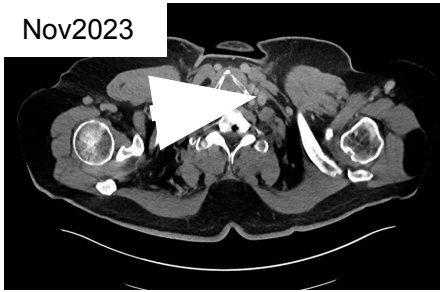
L2 Cabozantinib sep 2019 – Nov 2020, RECIST -18%

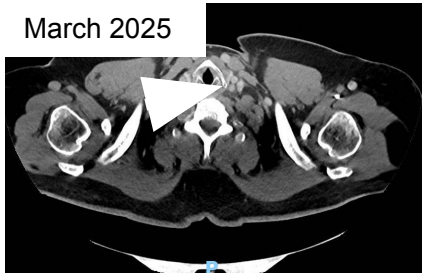
L3 RET selective inh BOS 172738 - dec 2020 – dec 2022, SD

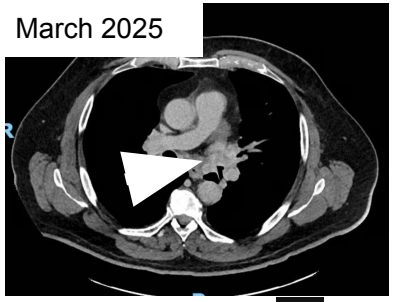
No resistance mutation on liquid biopsy

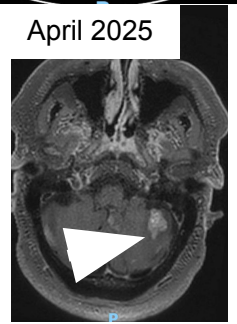
L4 Selpercatinib jan 2023 – March 2025: calcitonin raise from 2000 to 5500 pg/ml **Dissociated progression**









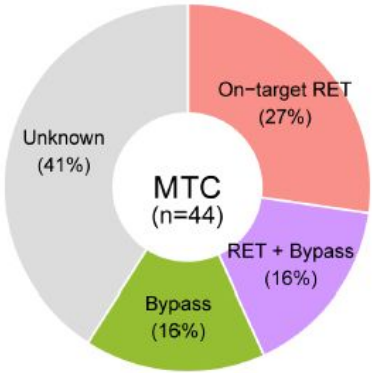


- **Liquid biopsy Jan 2025: TMB low: 1.26 Mut/Mb**
- ***RET* - p.(Ala883Phe) - FA 0.36%**
- ***TP53* - p.(Arg110Pro) - FA 0.15% = Aggressiveness mutation**
- ***PPP1CB::ALK - fusion* - FA 0.09% = Bypass resistance alteration**

L5: Brain stereotactic RT and then **Brigatinib + selpercatinib:** objective response

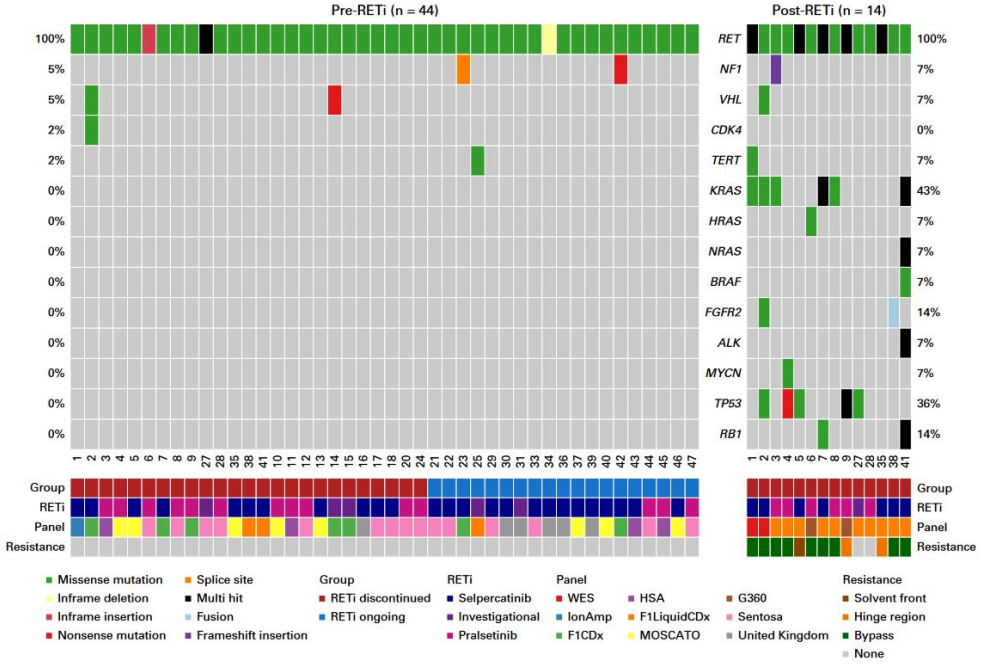
RETi Resistance: 25% on target & 75% bypass

Capture by liquid biopsy



	MTC N (%)
Resistance mechanism	26 (59)
Unknown/No shedding*	18 (41)
On-target	19 (43)
RET Solvent Front G810C/S/R	16
RET V804M/L**	8
RET V804M/L** and G810C/S	5
Bypass	14 (32)
*BRAF*V600E/Amplification	5
KRAS G12D/R	4
MET Amplification	2
NTRK1 fusion	1
Other***	2

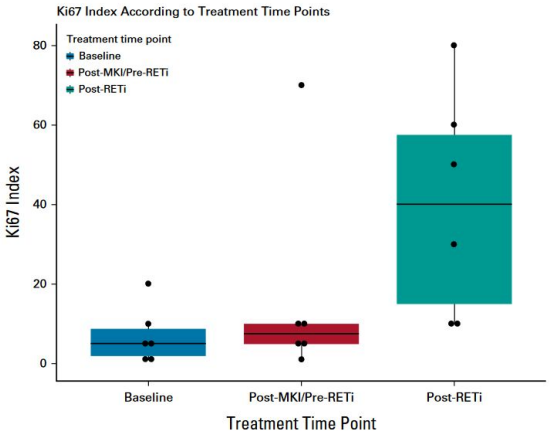
*patients with no oncogenic alterations detected at
**1 NSCLC and 1 MTC patient acquired *RET* V804had clonal expansion of
on-target *RET* alterations; 3 MTC patients acquired cquired on-target *RET*
***EGFR/MYC* amplification, *FGFR2* N82S/ P253L/ation, *KRAS* Q61H, *PIK*

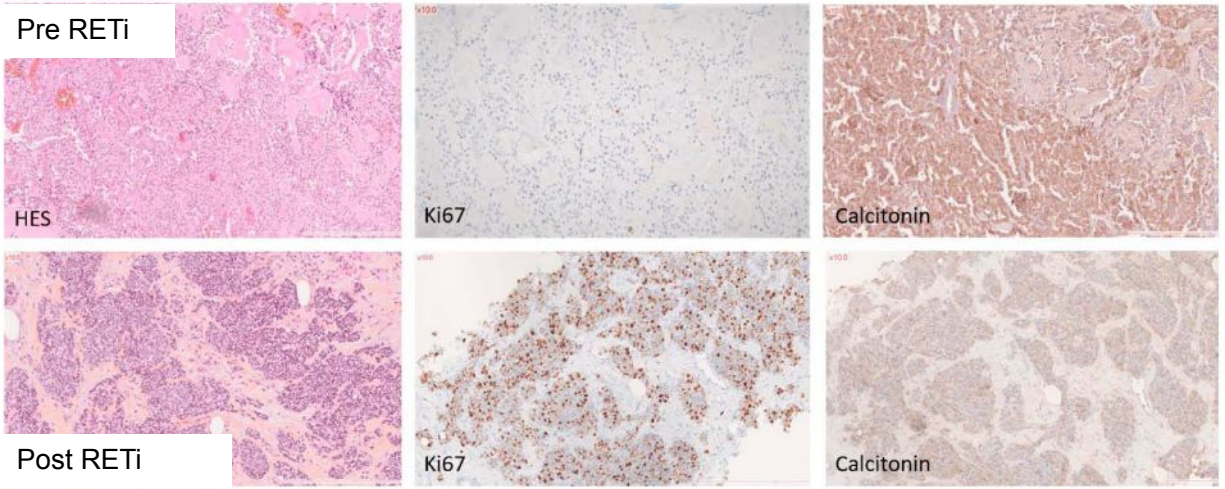


Data from the LIBRETTO 001 phase I trial
Solomon et al, ESMO 2024

Gustave Roussy case series, Hadoux et al, JCO PO 2023

The « all liquid » management: can we work without tissue?





In some patients, IMTCGS grade increase upon progression under RETi

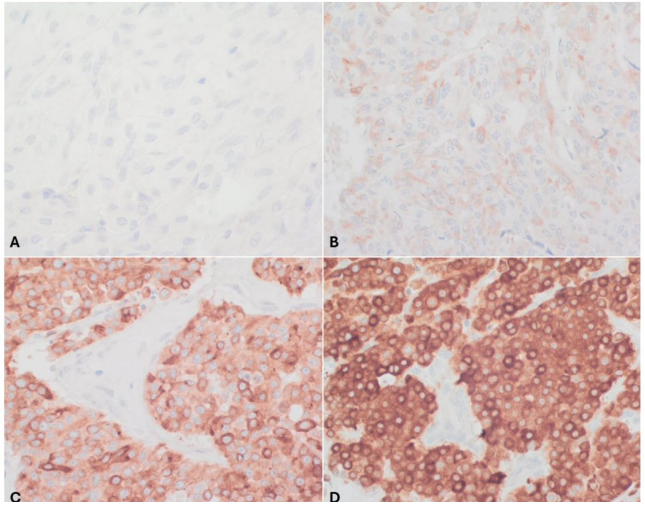
Low grade MTC → **Selective RETi** → **High grade MTC**

Hadoux et al, JCO PO 2023

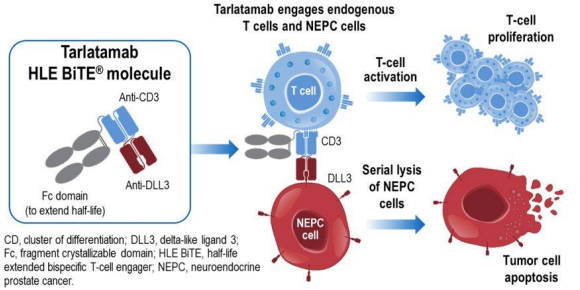
Tumor tissue is necessary for prot biomarker (ADC, bi Spe, etc…)

Ex: DLL3 targeting in MTC

Delta-like ligand 3 (DLL3, inhibitory Notch ligand) expression is correlated to IMTCGS grade and advanced stage

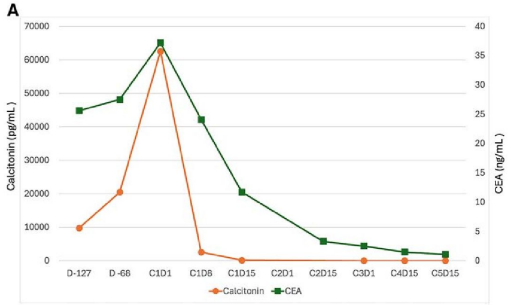


Ruz-Caracuel et al, Endocrine Pathology 2025



Tarlatamab
Bi specific Ab Anti CD3/anti DLL3

Tarlatamab in MTC: case report





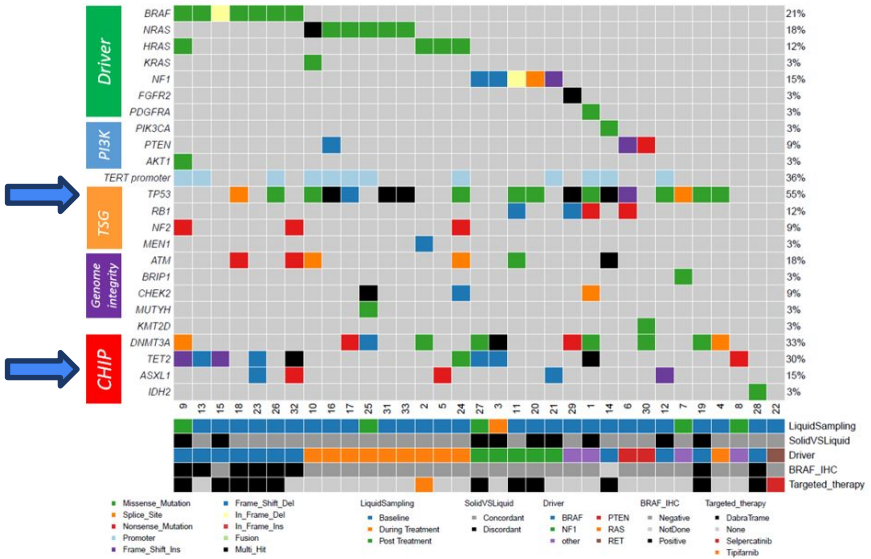


Roberts et al, Thyroid 2026

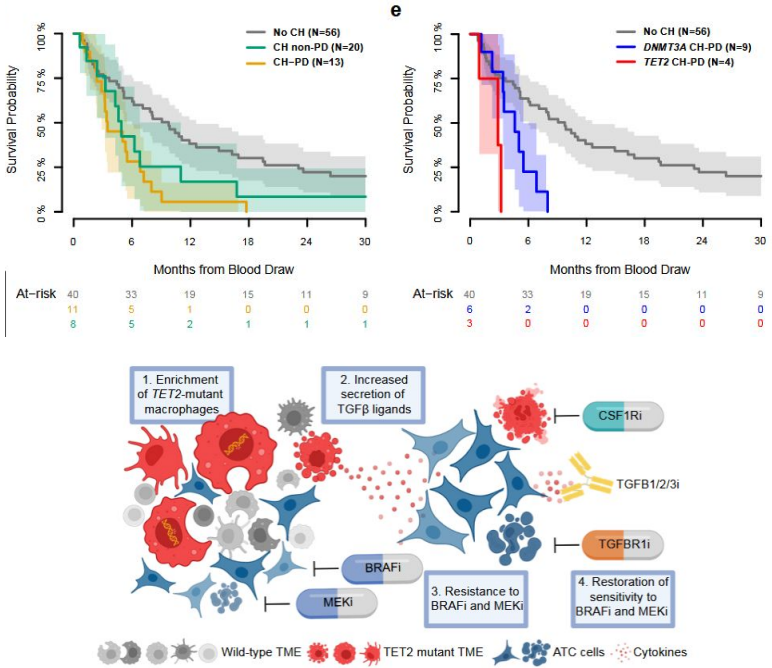
TARMAC Phase II trial to be launched in Europe

Clonal hematopoiesis detection in LB: false positive, really?

Gustave Roussy monocentric study
N= 33 liquid biopsies



MSKCC translational study



Succi M et al, ETA 2024

Tiedje V et al, BioRxiv 2024

Thyroid guidelines 2025–2026: tissue first, plasma when tissue fails, monitoring still research

Source	Statement on liquid biopsy
ATA 2025 (DTC)	Surgical or core biopsy preferred; ctDNA if biopsy impossible (weak, low evidence)
European consensus 2025	ctDNA data preliminary; applicable mainly with high tumor burden
ESMO ctDNA 2022	Genotyping acceptable with validated assays; monitoring and resistance = research
SEAP-GETNE 2026	***"Currently the only blood-based biomarkers used in thyroid cancer monitoring are thyroglobulin for DTC, and calcitonin and CEA for MTC."***

Open questions:

- What is the cost effectiveness?
- How to deal with ChiP?
- Design of clinical trials will be a challenge to implement this into follow-up/surveillance strategies

Ringel Thyroid 2025; Ryška Eur Thyroid J 2025; Pascual Ann Oncol 2022; Ruz-Caracuel Rev Esp Patol 2026

Comité 070: Thyroid cancer group at Gustave Roussy

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Personalized medicine group:
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PDx facility: Ludovic Bigot

Experimental pathology platform (PETRA)
Olivia Bawa, Jean-Yves Scoazec
& all collaborators



Thank you for your attention

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PARIS CANCER CAMPUS