

# Thérapies ciblées et Redifférenciation tumorale dans les cancers thyroïdiens

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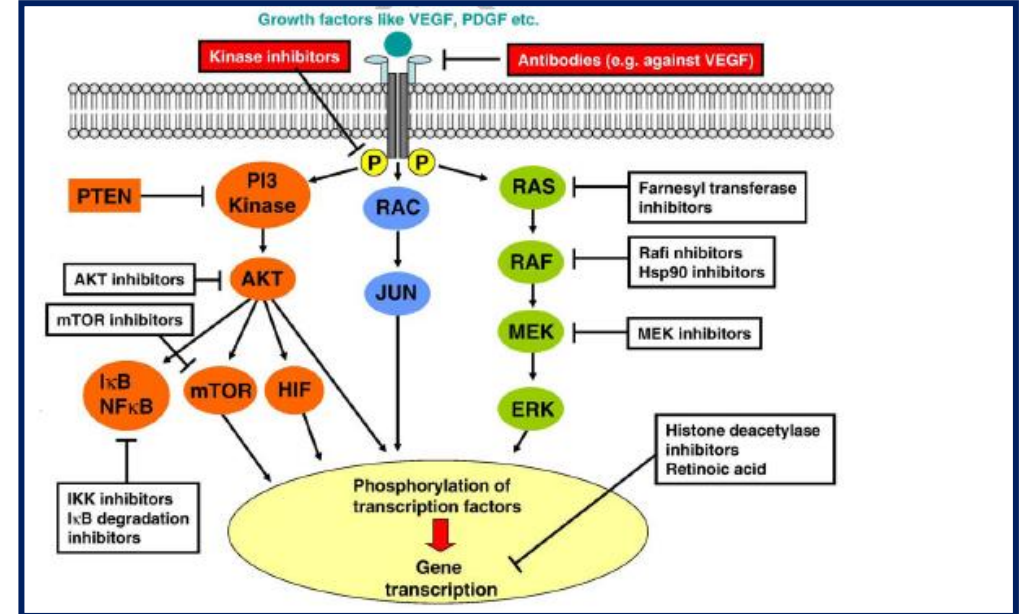
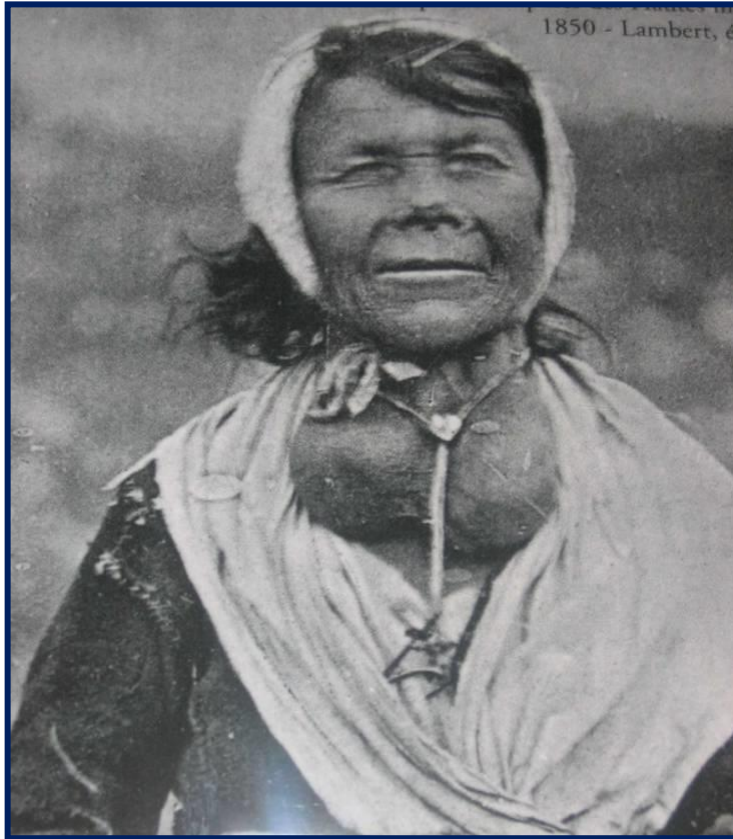
10/02/2022

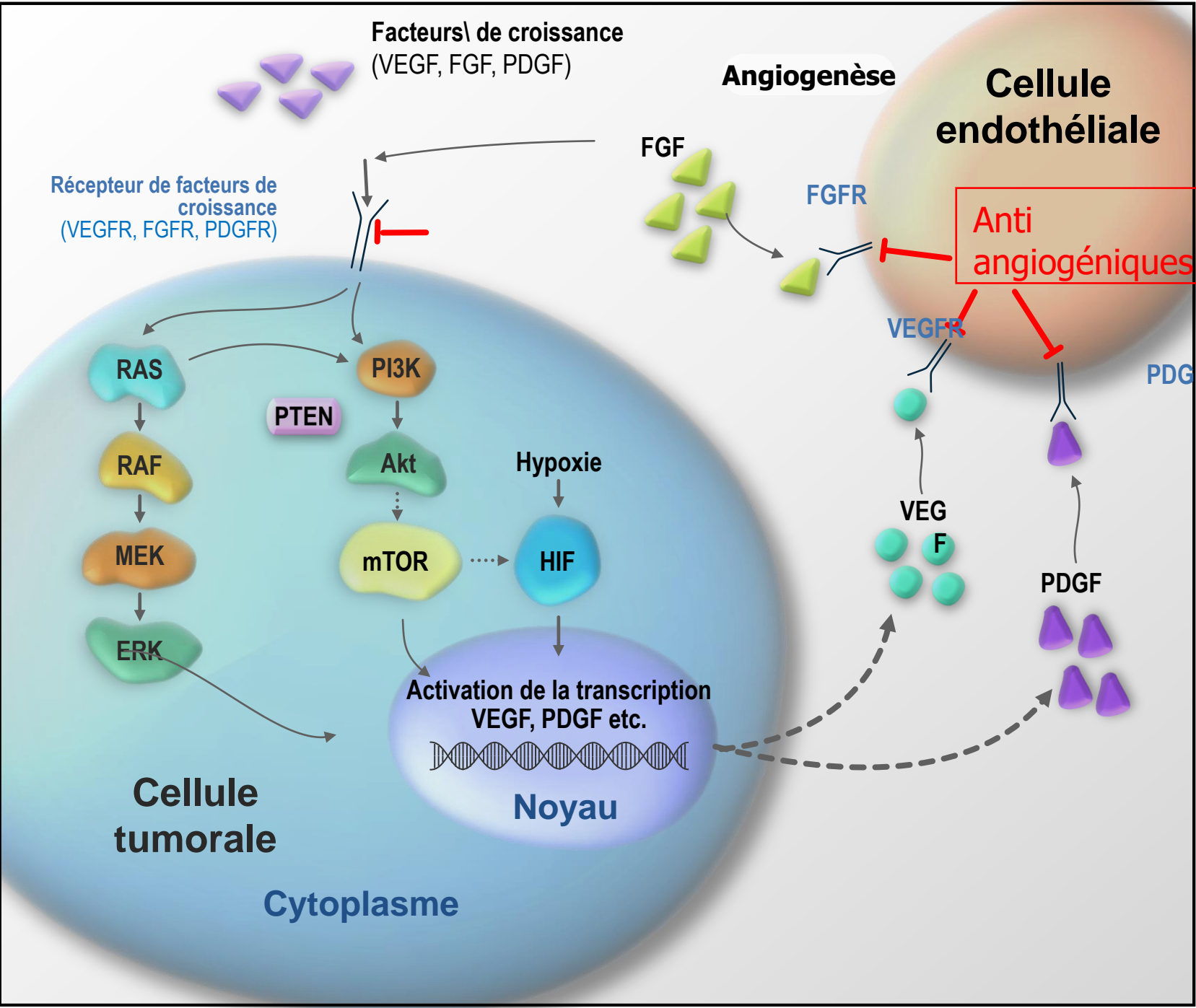
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Dr Yann Godbert

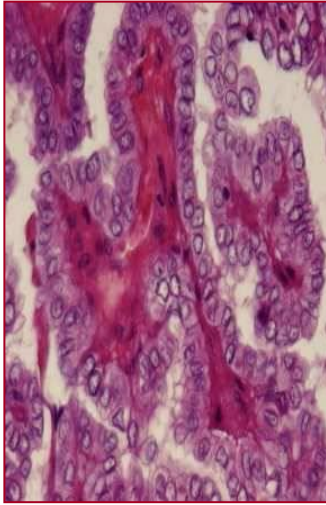
**UPDATE EN MÉDECINE NUCLÉAIRE**

**RADIOTHÉRAPIE INTERNE VECTORISÉE ET THÉRANOSTIQUE**

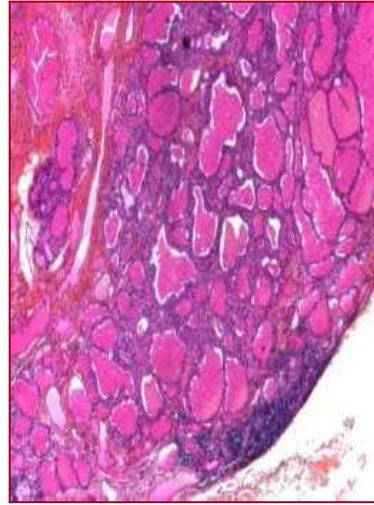




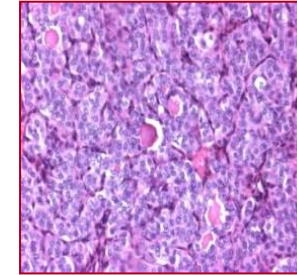
# Cancers thyroïdiens d'origine folliculaire



**Papillaires 90%**  
**Métastases par**  
**voie lymphatique**  
**Ganglions**  
**Micronodules**  
**pulmonaires diffus**



**Folliculaires**  
**Métastases par**  
**voie hématogène**  
**M+ poumons**  
**macronodulaires**  
**M+ os**



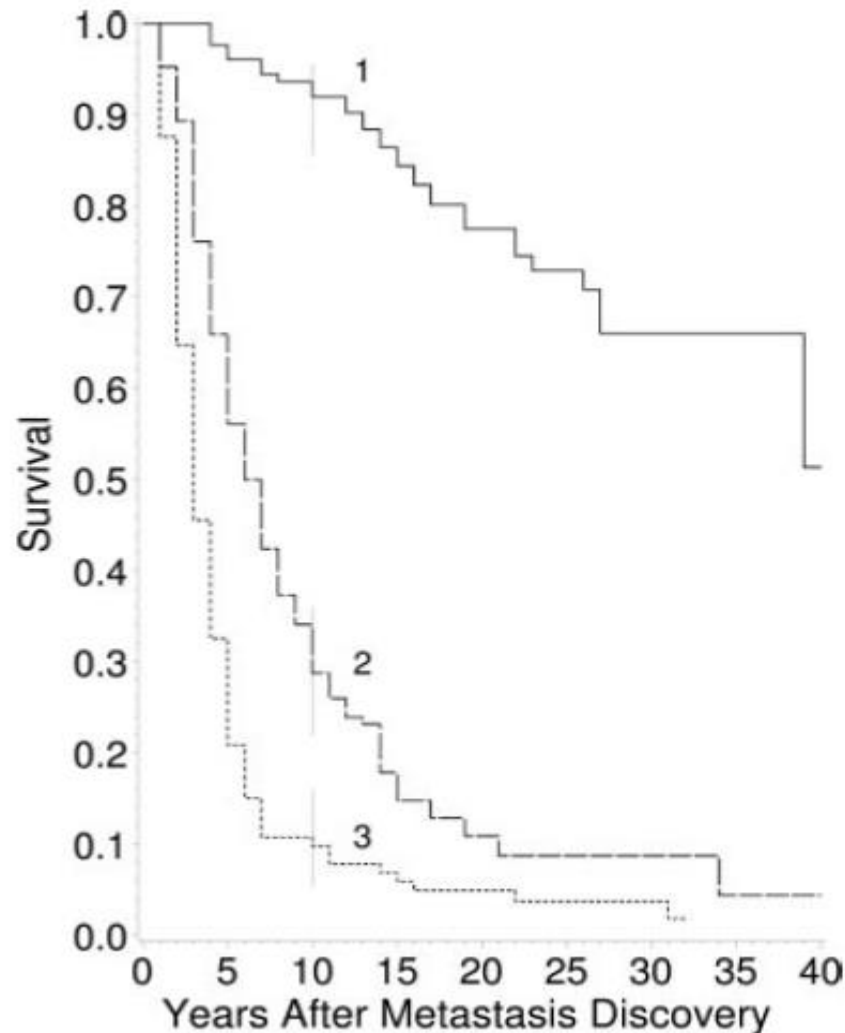
**Anaplasiques très rares**  
**mais très mauvais**  
**pronostic**  
**Pas fixation I131**  
**Chimio+radiothérapie**

Fixation 2/3 cas

Rôle ++ **Iode 131** pour cancers à risque de récurrence, de métastase



# Survie après métastase



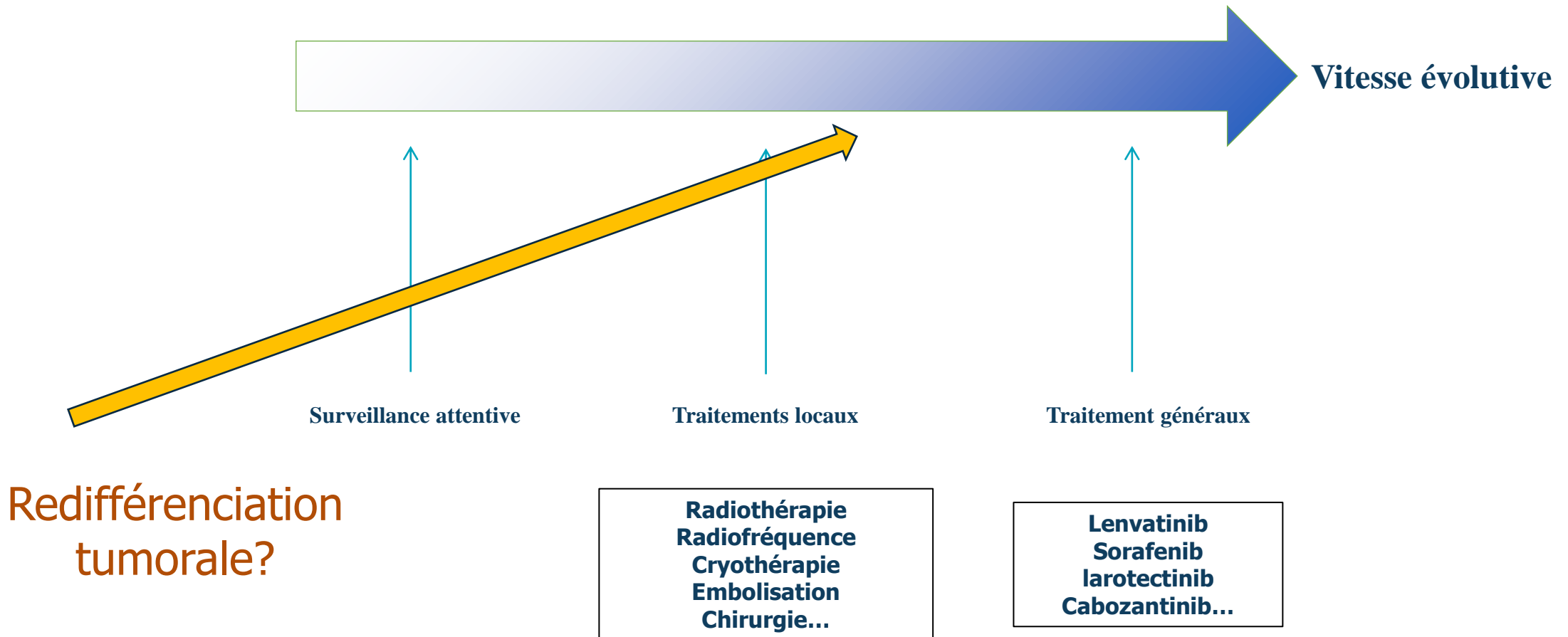
**Groupe 1** : fixation initiale de l'iode 131 + absence maladie résiduelle (jeune , K bien différencié, petites lésions, pas de fixation FDG)

**Groupe 2** : fixation initiale de l'iode131 et maladie résiduelle

**Groupe 3** : pas de fixation de l'iode 131

*D'après Durante Cet al. J Clin Endocrinol Metab 2006 May 9;91(8):2892-9.*

# Principe général de prise en charge



# ALL PATIENTS WITH ADVANCED THYROID CANCER NEED TO HAVE A MOLECULAR TESTING

	RAIR DTC	Anaplastic TC	Medullary TC
Mutation burden	Very low	Low	Very Low
BRAF alterations	<b>33%</b>	45%	-
RAS mutation	28%	24%	-
<b>RET fusion</b>	<b>6%</b>	<b>&lt;1%</b>	-
<b>RET mutation</b>	-	-	<b>60-90%</b>
<b>NTRK fusions</b>	<b>≈ 1%</b>	<b>≈ 1%</b>	-
<b>ALK mutation/translocation</b>	<b>≈ 1%</b>	<b>≈ 1%</b>	-
PIK AKT mTOR pathway	10%	35%	-
C MET	< 1%	-	1-5%

ALK fusion very low 1% in DTC and ATC

Godbert et al jco 2016 Bonhomme 2017 Thyroid 2012, Prasad Cancer 2016, Pozdeyev CCR 2018, Hadoux, 2018



# RAIR DIFFERENTIATED THYROID CANCER: Anti BRAF therapy

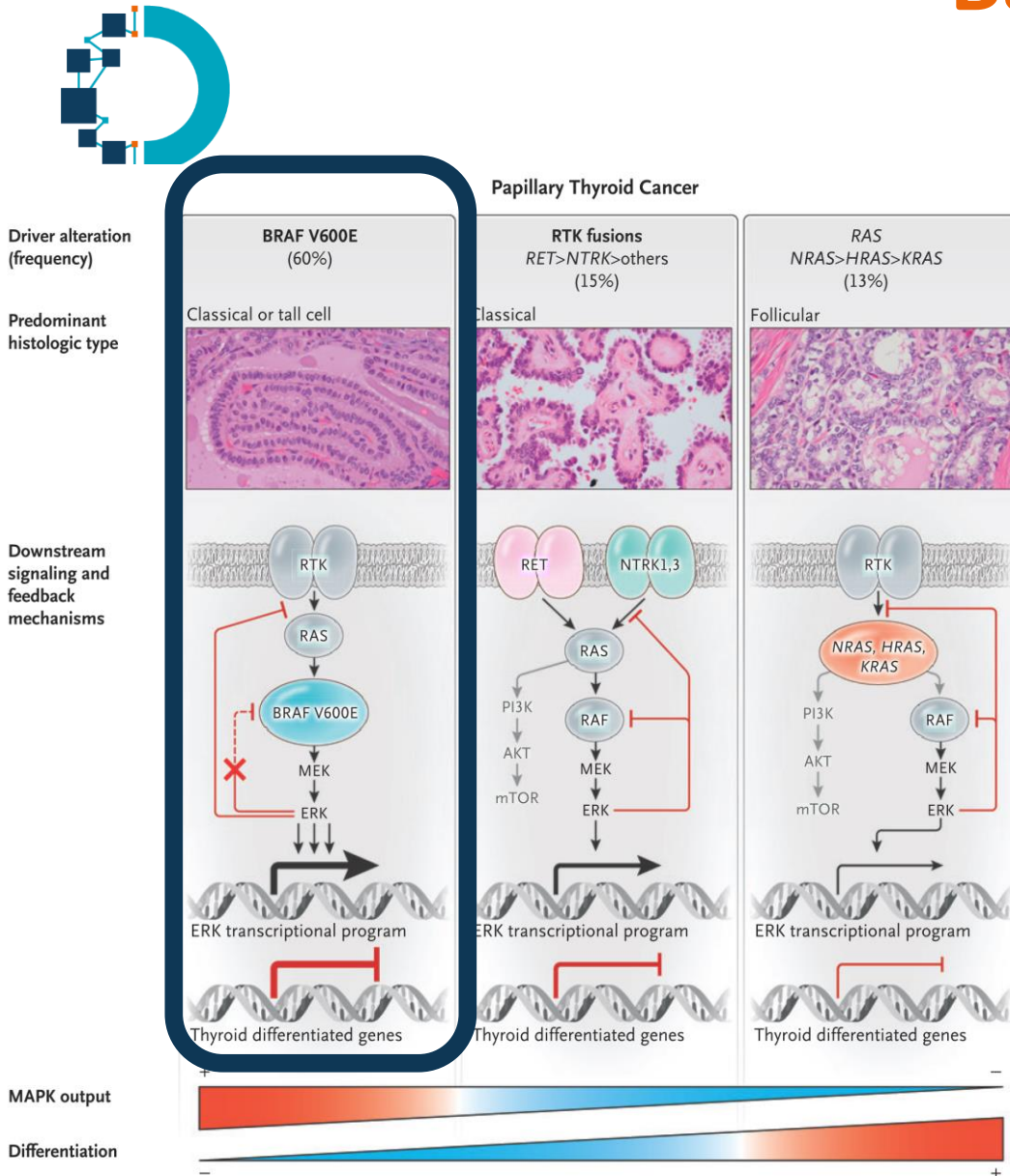
		Line	n	CR %	PR %	Duration of R (median, months)	PFS (median, months)
Brose 2016, Phase 2	Vemurafenib	1	26	0	38.5	16.5	18.2
	Vemurafenib	2	25	0	27.3	8.9	7.4
Falchook 2015 Phase 1	Dabrafenib	≥1	14	0	29	Not reached	11.3
Shah 2017 Phase 2	Dabrafenib	-	22	0	50*	11.5	15.6
	Dabrafenib & Trametinib	-	24	0	54*	15.4	13.3
Taylor M	Encorafenib & Binimetinib +/-Nivolumab: ongoing (NCT04061980)						

\*: modified RECIST criteria

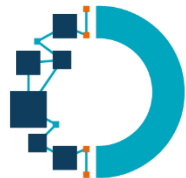


		FDA approval	EMA approval
<i>Sorafenib</i>	<i>Anti VEGFR</i>	<i>Patients with locally recurrent or metastatic, progressive, RAI DTC (2013 &amp; 2014)</i>	
<i>Lenvatinib</i>	<i>Anti VEGFR</i>	<i>Patients with locally recurrent or metastatic, progressive, RAI DTC (2015)</i>	
Larotrectinib	Anti NTRK	Adult and pediatric with NTRK fusion (2018)	
Entrectinib	Anti NTRK	Adults and adolescents aged $\geq 12$ years with NTRK fusion (2020)	
Selpercatinib	Anti RET	<b>Adult and pediatric <math>\geq 12</math> years</b> of age with advanced/metastatic <i>RET</i> fusion-positive thyroid cancer (2020)	Adults with RET fusion-positive thyroid cancer in adults <b>previously treated with sorafenib or lenvatinib or both (2021)</b>
Pralsetinib	Anti RET	<b>Adult and pediatric <math>\geq 12</math> years</b> of age with advanced/metastatic <i>RET</i> fusion-positive thyroid cancer (2020)	No

# Background



- *BRAF<sup>V600E</sup>* is a common oncogenic driver mutation in differentiated thyroid cancer (DTC)
- *BRAF<sup>V600E</sup>* mutation in thyroid tumor cells
  - activates the MAPK pathway
  - correlates to a less differentiated phenotype
- About two thirds of metastatic DTC patients become refractory to radioactive iodine (RAIR)
- Blocking the MAPK pathway in case of *BRAF<sup>V600E</sup>* mutation might up-regulate expression of genes involved in iodine metabolism and restore RAI uptake



# Background

	N patients treated with MAPK Inhibitor		Genetic	N patients treated with <sup>131</sup> I	RECIST Best Tumor Response	
					Complete Response	Partial Response
<i>Ho, 2012</i>	Selumetinib	20	<i>BRAF V600E, RAS &amp; others</i>	8 (40%)	0	5 (25%)
<i>Rothenberg, 2015</i>	Dabrafenib	10	<i>BRAF V600E</i>	6 (60%)	0	2 (20%)
<i>Dunn, 2018</i>	Vemurafenib	12	<i>BRAF V600E</i>	4 (33%)	0	4 (33%)

Ho, et al. N Engl J Med. 2013 Feb 14;368(7):623-32. Rothenberg, et al. Clin Cancer Res. 2015 Mar 1;21(5):1028-35. Dunn, et al. J Clin Endocrinol Metab. 2019 May 1;104(5):1417-1428

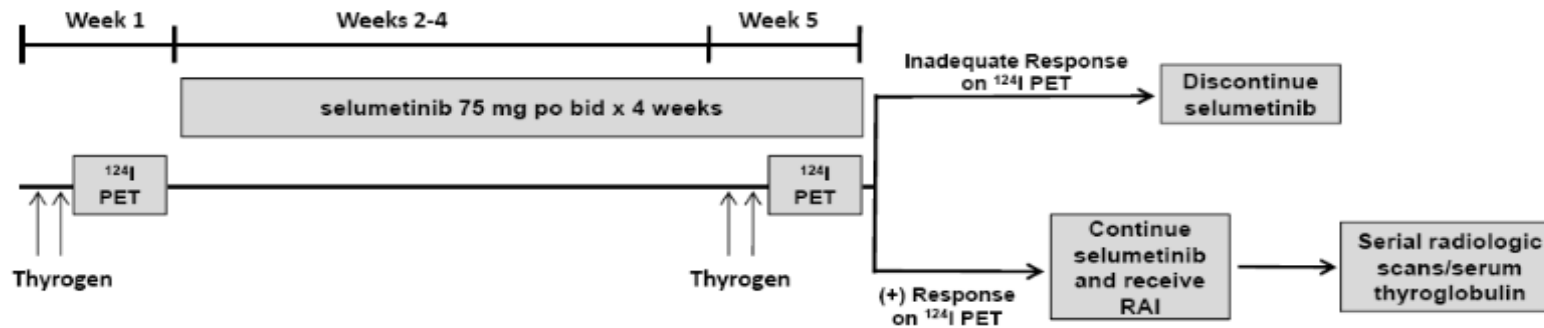


# Selumetinib

Traitement par iode radioactif après  
Selumetinib (anti MEK) : design

Figure 1

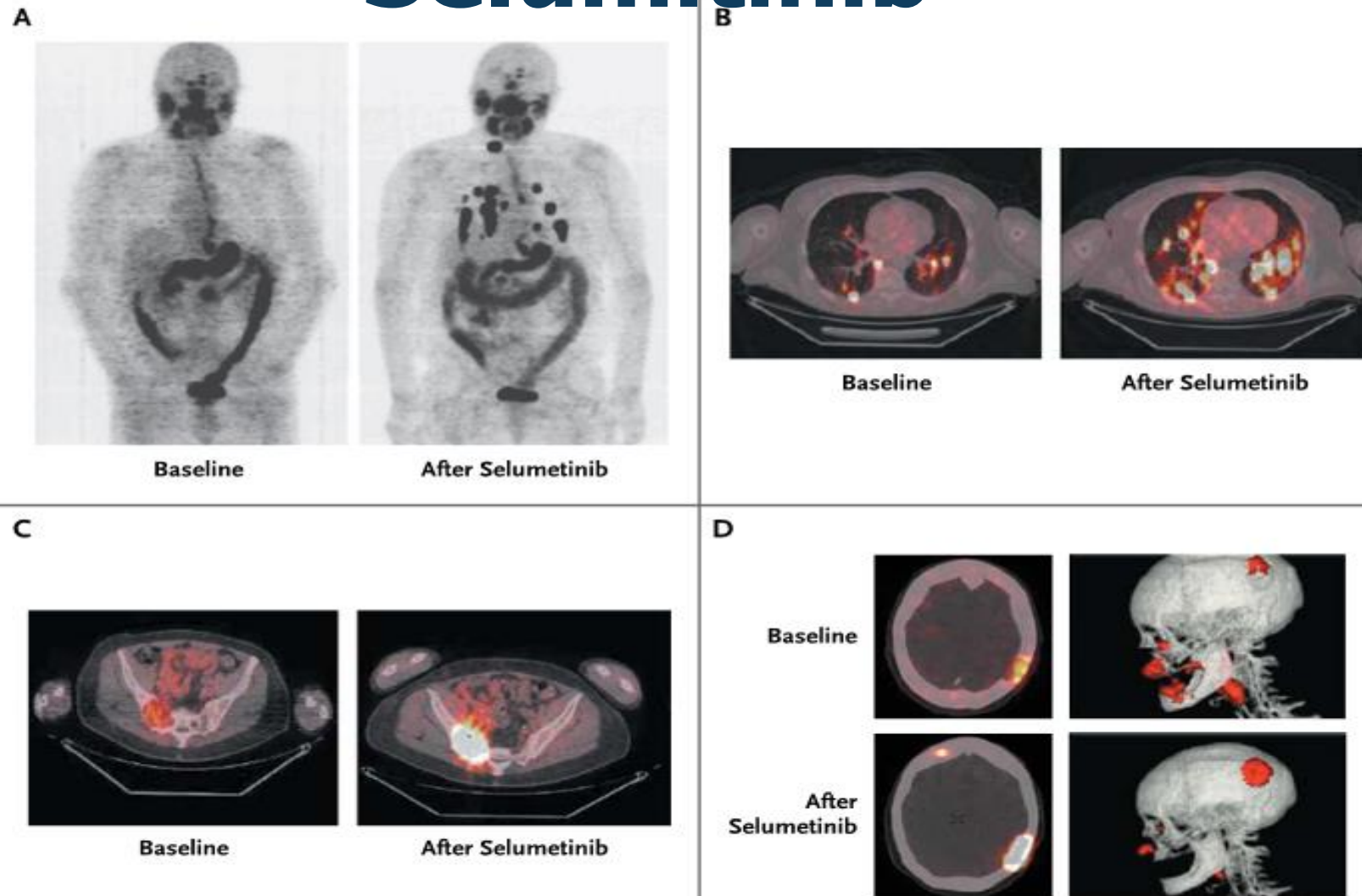
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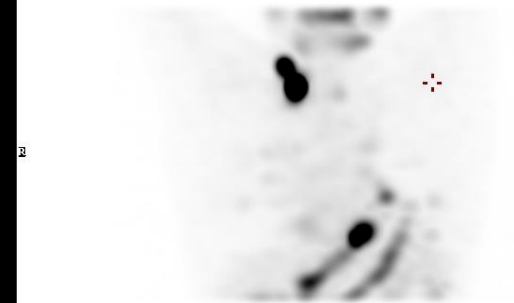
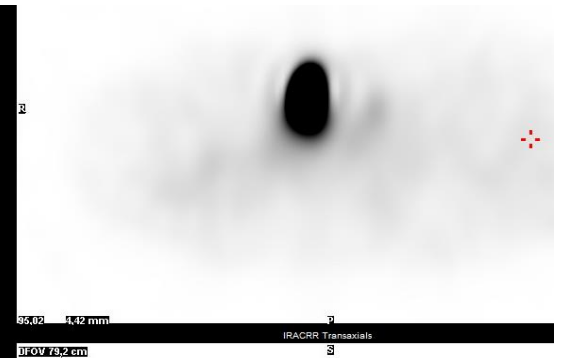
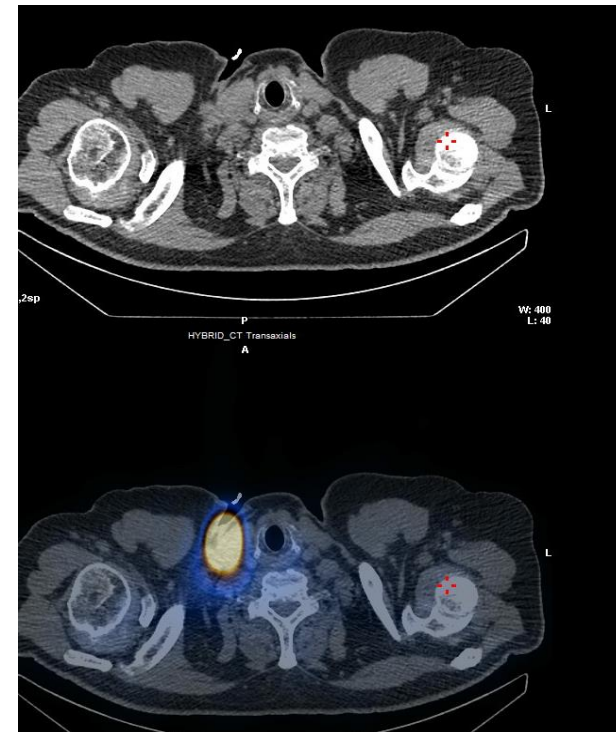
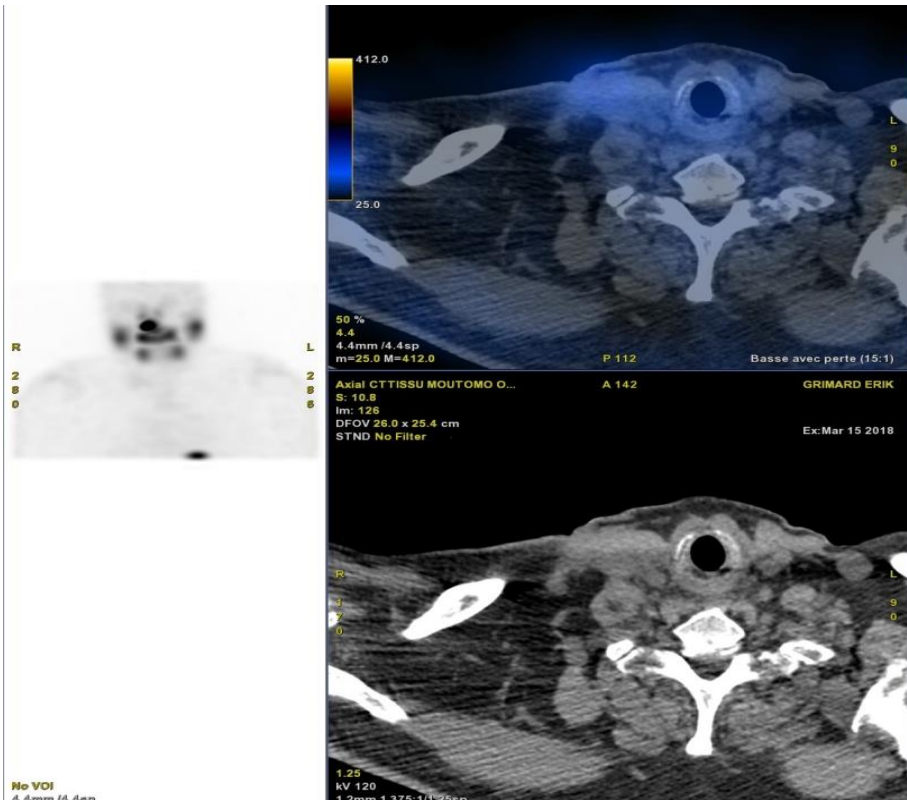
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Ho et al. 2013

# Selumetinib



**Figure 2.** Iodine-124 PET-CT Scans Obtained before and after Selumetinib Treatment in Selected Patients with Positive Responses.



Patient 59 en récurrence locale symptomatique non accessible chirurgicalement en territoire irradié, progressif après multitraitements locaux (RF, embolisation, cryothérapie)  
 Réfractaire à l'iode  
 2 lignes antiangiogéniques (lenvatinib, pazopanib)  
 CP BRAF V600E+ TLS+  
 Traitement par tramétinib, dabrafenib (Cf protocole Méraïode)

Godbert et al SFE 2019



# MERAIODE: A Redifferentiation Phase II Trial With Trametinib and Dabrafenib Followed by Radioactive Iodine Administration for Metastatic Radioactive Iodine Refractory Differentiated Thyroid Cancer Patients With a BRAFV600E Mutation (NCT 03244956)

C Do Cao

For the MERAIODE Study Group

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# Study design



## Initial work up

- Brain MRI
- **Baseline Diagnostic WBS** (185 MBq (5 mCi) <sup>131</sup>I /rhTSH)
- Neck-chest-abdomen-pelvis CT scan (IV-) + thyroglobulin (Tg)/LT4
- **FDG PET/CT**

**Dabrafenib 150 mg twice a day  
Trametinib 2mg/day for a total of 42 days**

## After 4 weeks (Day 28-35)

- Neck-chest-abdomen-pelvis CT scan (IV-) + Tg/LT4
- **D28 Diagnostic WBS** (185 MBq (5 mCi) <sup>131</sup>I/ rhTSH)

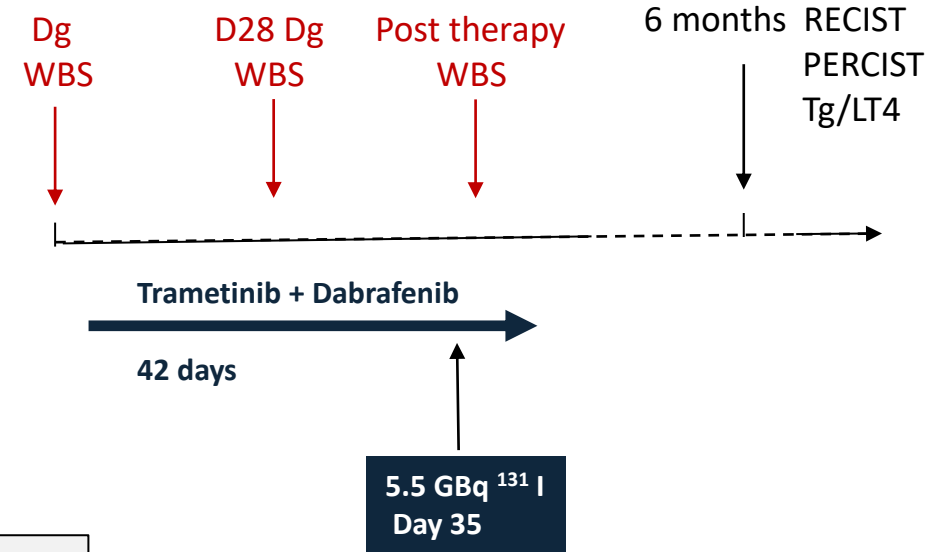
## After 5 weeks (Day 35-42): treatment

- **5.5 GBq (150mCi) of <sup>131</sup>I/ rhTSH**

**Post Therapy  
WBS**

## Follow-up

- Neck-chest-abdomen-pelvis CT scan (IV+) + Tg/LT4 at Month 3, 6 and 12
- **FDG PET/CT at Month 6**

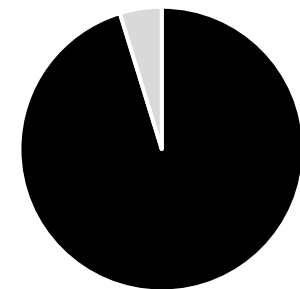
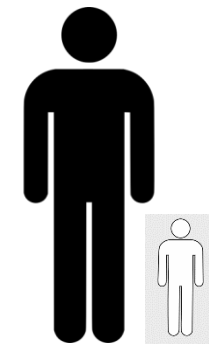
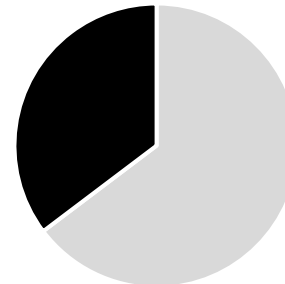
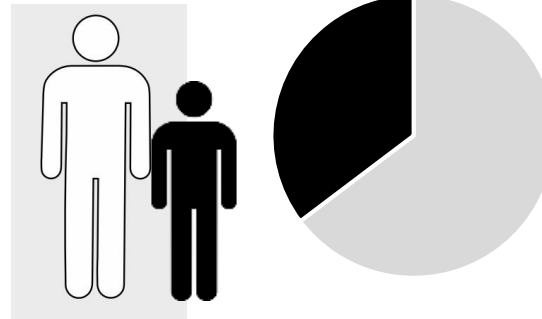
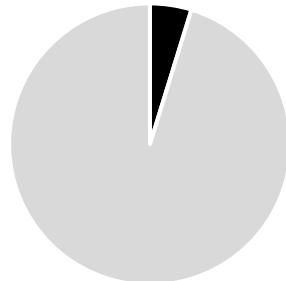
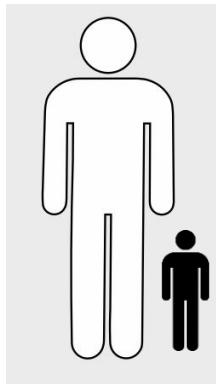




# Rates of patients with abnormal RAI uptake (central review)

Rates of patients with abnormal RAI uptake		
N/Total		
% (95% CI)		
Baseline Diagnostic WBS	Day 28 Diagnostic WBS	Day 35 Post-therapy WBS
1/21 4.8% (0-22.8)	11/17 64.7% (38.3-85.8)	20/21 95.2% (76.1-100)

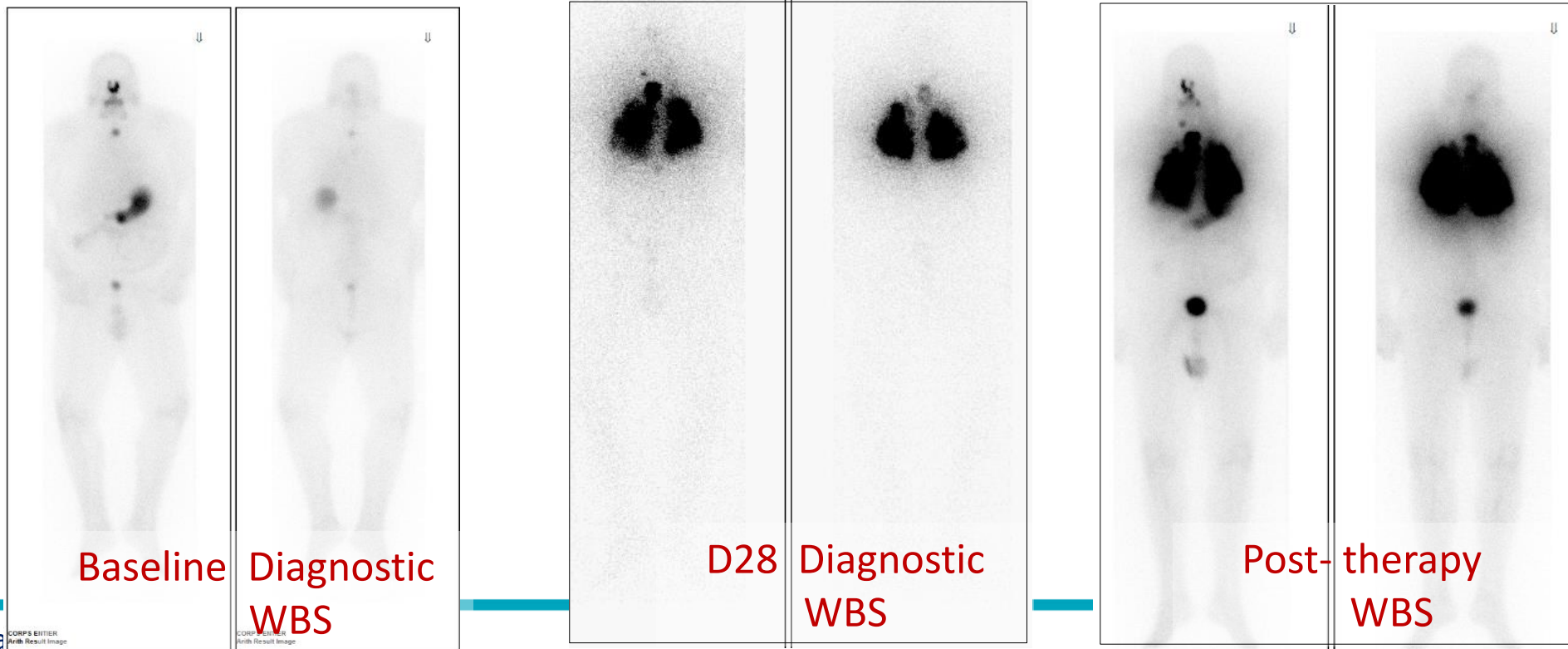
Trametinib + Dabrafenib

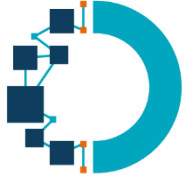


Abnormal uptake  
 No uptake

# Location of abnormal RAI uptake on the post therapy WBS

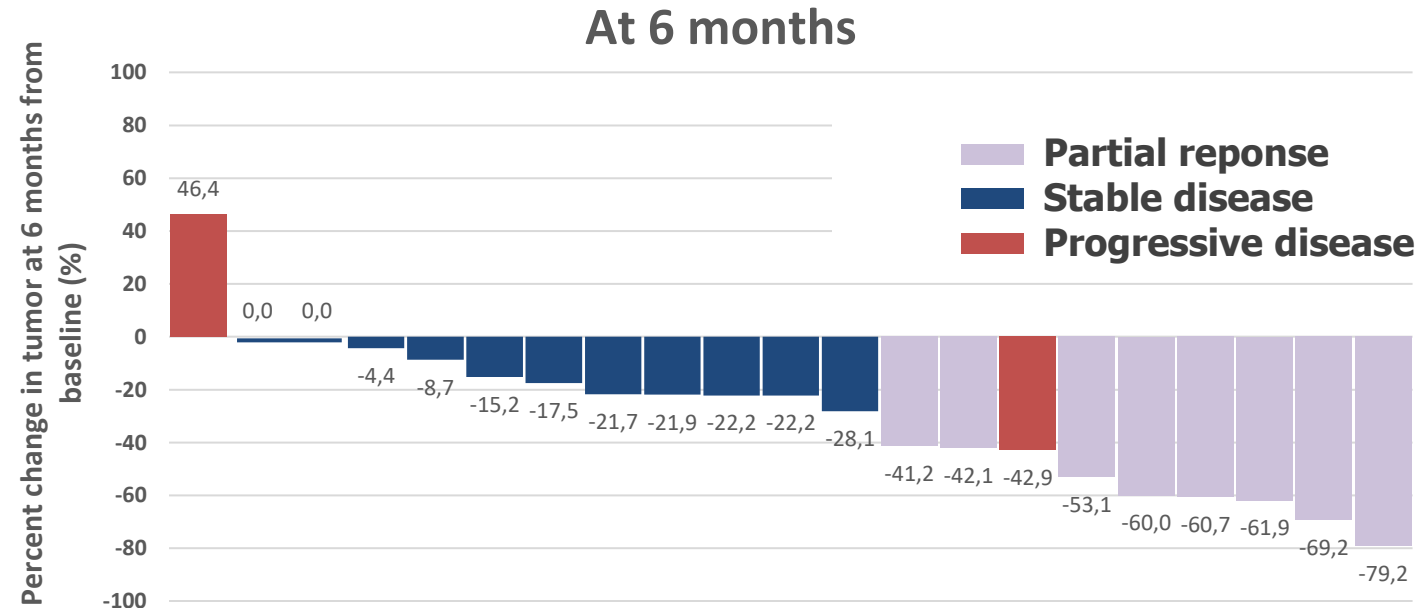
- Main locations
  - lung (20)
  - local recurrence (thyroid bed or neck lymph nodes) (12)
  - mediastinal lymph nodes (6)
  - bones (3)





# MERAIODE - Results: 6 months RECIST v1.1

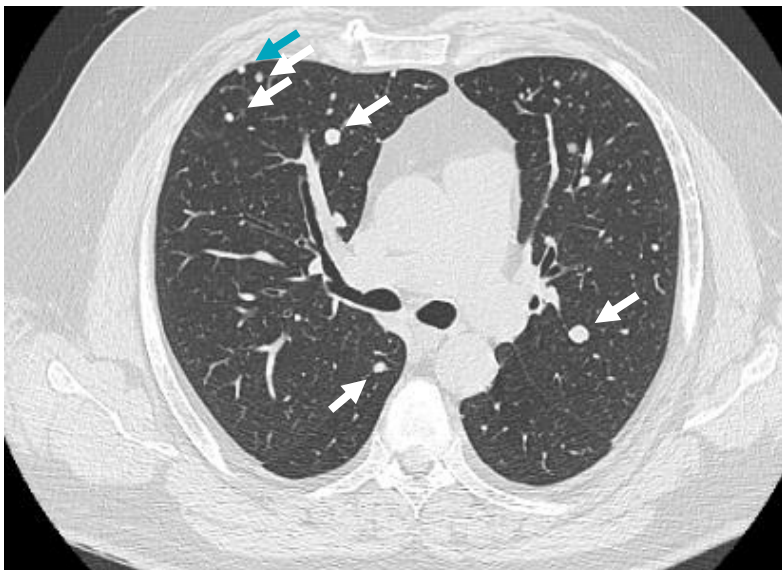
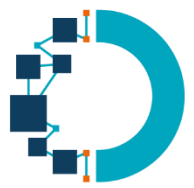
	6 months RECIST evaluation (central review) N (%)
Complete Response	0
Partial Response	8 (38.1%)
Stable Disease	11 (52.4%)
Progressive Disease	2 (9.5%)
Not evaluable	0



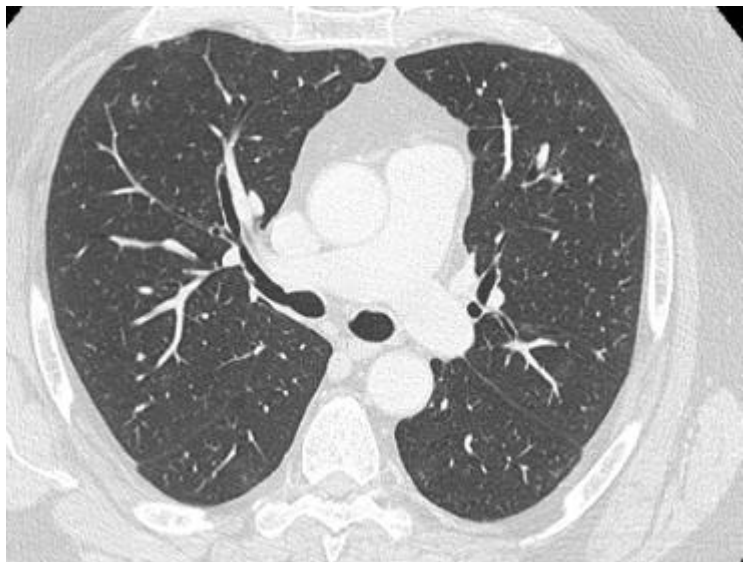
Disease control Rate (CR + PR + SD): 90.5%

Median follow-up : 15.1 months, range [0.8 ; 25.9]

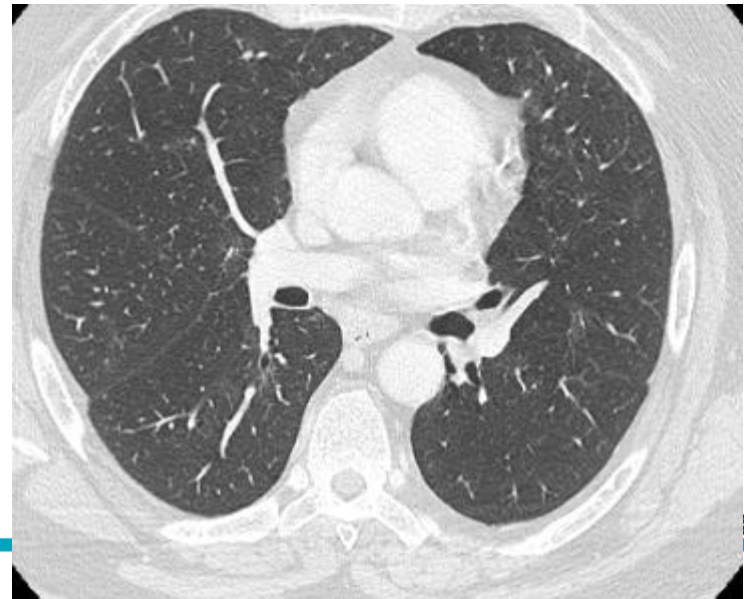
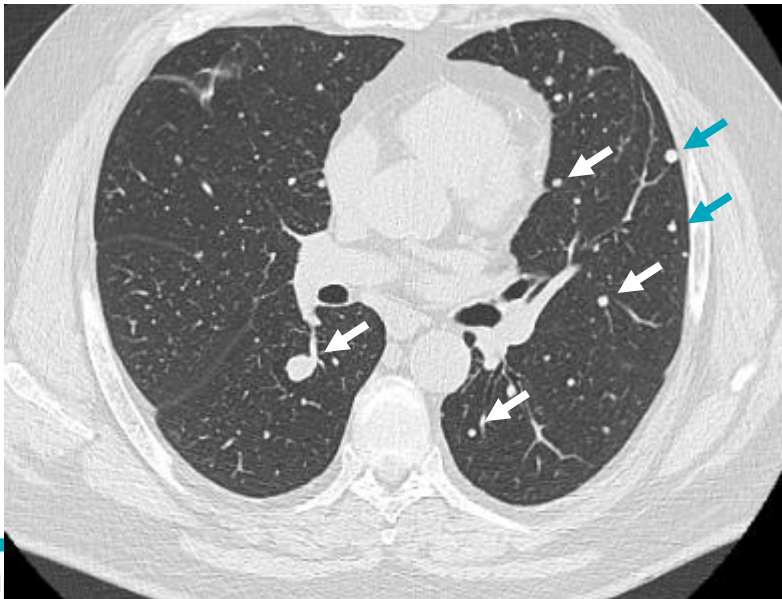
At last follow-up, 8 patients still in PR, median duration of response : 13.2 months, range [6.0 ; 25.9]

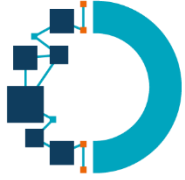


**Baseline**



**6 months**





## Biological response (Tg/LT4)

15 patients without Tg antibodies

Biological Response N (%)	
At 6 months	
Partial Response	5 (35.7%)
Stable disease	8 (57.1%)
Progressive disease	1 (7.1%)
Not evaluable	1

PR : Decrease of Tg level > 50%, Progressive disease : Increase in Tg level > 50%

Evolution of mean Tg (ng/ml) in 15 evaluable patients :

- at baseline :  $96.2 \pm 223.0$  [1.4 – 880]
- at 3 months :  $32.5 \pm 52.2$  [1.4 – 203.7]
- at 6 months :  $23.9 \pm 40.3$  [0.8 – 155.1]

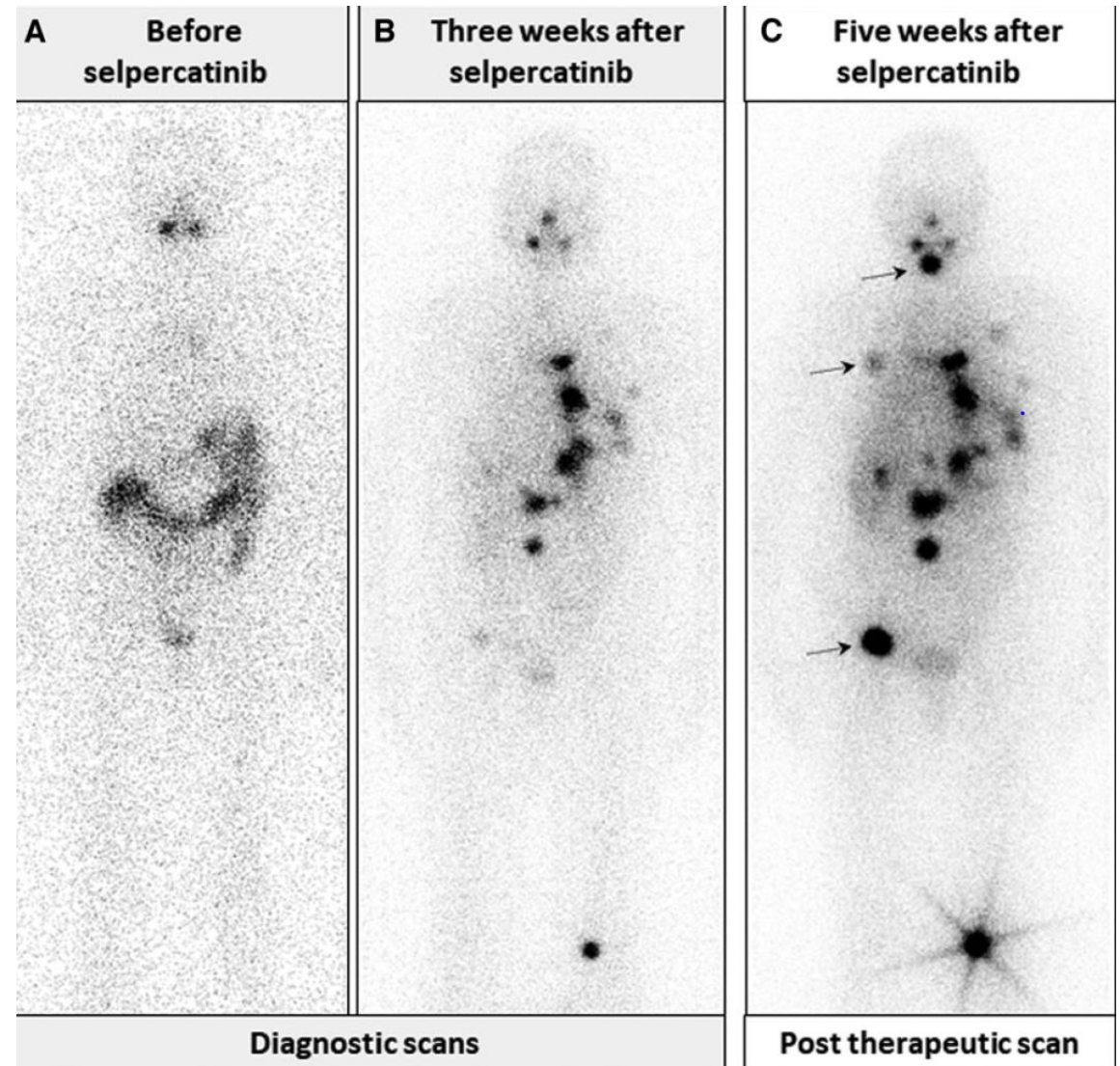
# Avec fusion de RET?

- Cancer papillaire âge de 15 ans
- Rechute 44 ans après : chirurgie et IRAthérapies pour une dose cumulée de 18,5 GBq
- 6 ans après la dernière IRAthérapie, progression multisite. Identification d'un réarrangement RET

## → Selpercatinib

- A S3 : recaptage iode en scintigraphie diagnostique
- A S5 : IRAthérapie 3,7 GBq
- A 15 mois: réponse partielle métabolique. Diminution des lésions connues et reconstruction osseuse des lésions lytiques (pas de cible RECIST)

Donc bénéfice de la séquence sans pouvoir différencier l'effet respectif des traitements



# *Avec fusion de NTRK?*

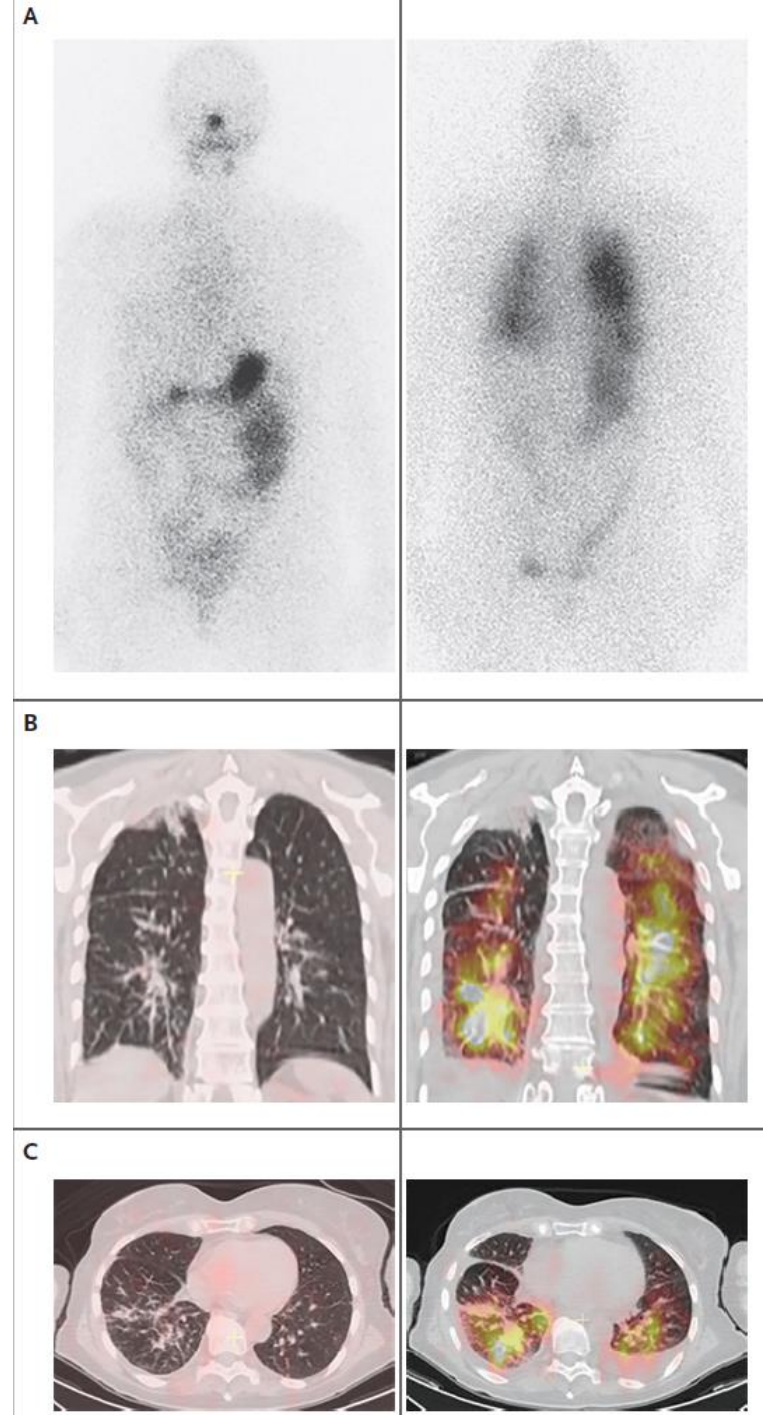
- Cancer papillaire il y a 35 ans
- Nombreuses IRA thérapies (54 GBq)
- Après 12 ans stabilité, progression pleuro pulmonaire et ganglionnaire. Drainage pleural et biopsie confirmant diagnostic et identification réarrangement NTRK

**Lenvatinib** Pas de recaptage en scintigraphie diagnostique. Réponse partielle RECIST. Toxicité limitante.

**Larotrectinib** Recaptage iode scintigraphie diagnostique à S3. Après 20 mois de traitement, réponse partielle.

IRAthérapie 3,6 GBq récente : franche fixation aux niveaux des deux poumons

N Engl J Med. 2020 Oct 22;383(17):1686-1687



# Autre cas réarrangement *NTRK*

48 ans, IRAthérapies (dose cumulée 11 GBq)

Progression pulmonaire métastatique

**Lenvatinib 2 ans** avec réponse partielle, pause pour toxicité et progression

**Larotrectinib** avec recaptage en scintigraphie diagnostique sur tous les sites connus de la maladie

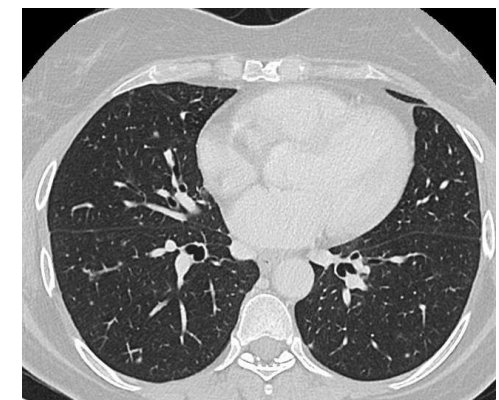
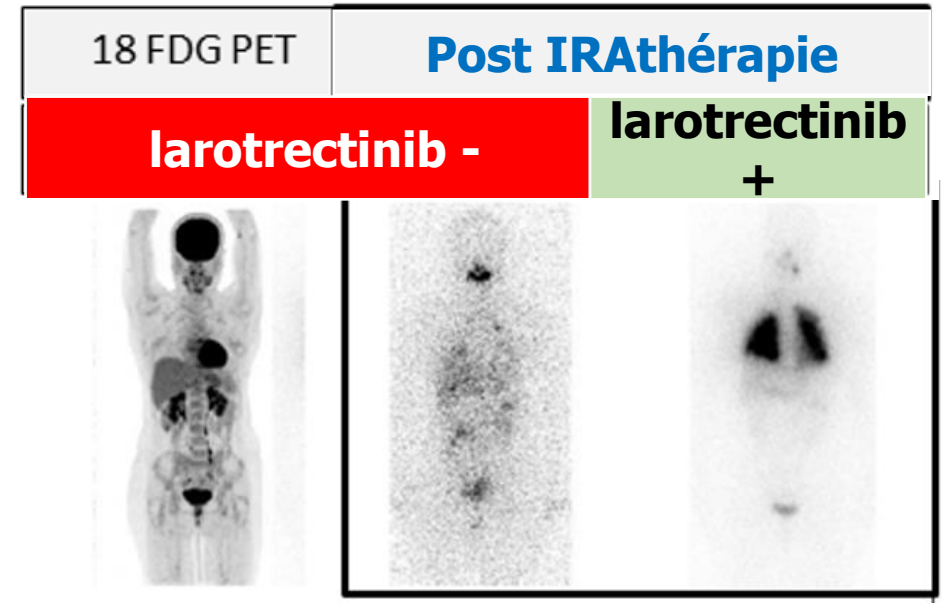
3,8 GBq à **M9** : fixation très intense au niveau 2 champs pulmonaires et formation ganglionnaire

3,9 GBq à **M15** : franche réduction maladie pulmonaire

A **22 mois**, réponse radiologique quasi complète, TG 21.5 ng/mL Ac antiTG < 15 UI/mL

Effet du larotrectinib ? Iode ? des 2?

(Thyroid. Under review)





# Autre cas réarrangement *NTRK*

70 ans. Maladie multimétastatique d'emblée, sans captation d'iode en scintigraphie diagnostique après thyroïdectomie

Atteinte osseuse fracturaire opérée compliquée contre indiquant un traitement antiangiogénique

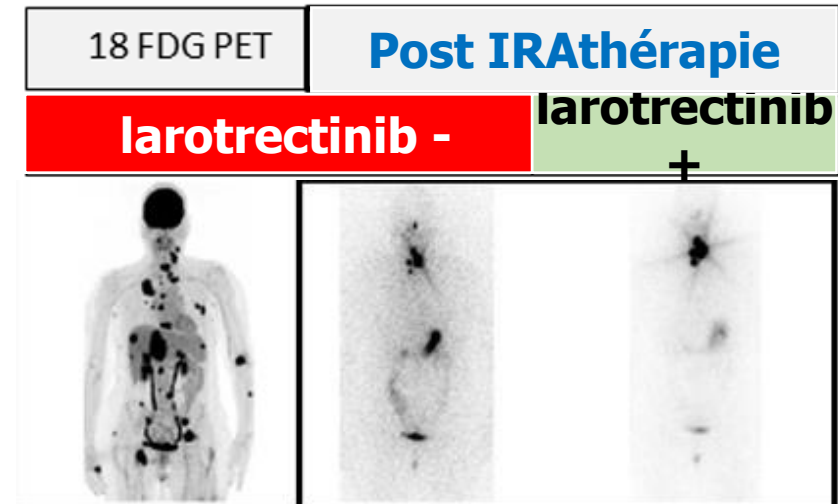
**Larotrectinib**, aucune captation iode en scintigraphie diagnostique

A 15 mois

- Réponse partielle RECIST ensemble sites et réponse métabolique
- Pas de fixation significative en diagnostique

Donc bénéfique du larotrectinib seul

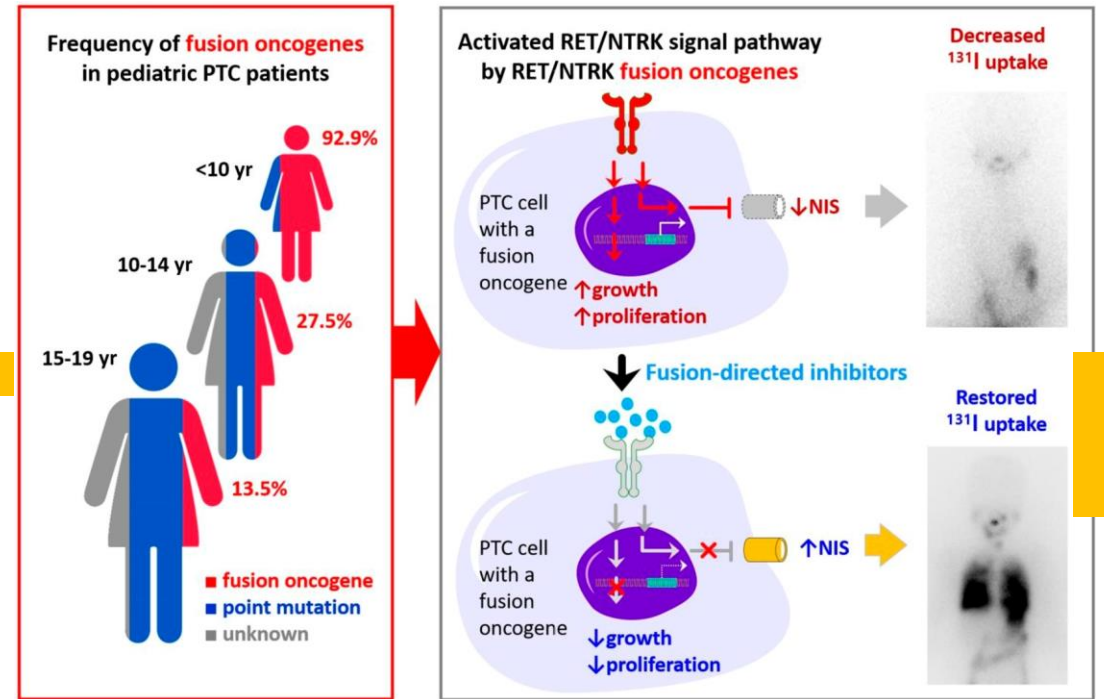
(Thyroid, Under review)



Comme pour mutations BRAF et h,k,nRAS, **redifférenciation possible** mais **pas systématique** avec réarrangements dans notre petite expérience.

Expérience partagée par d'autres (J Clin Invest. **2021 Sep** 15;131(18):e144847.)

Conséquences thérapeutiques incertaines



J Clin Invest. 2021 Sep 15;131(18):e144847.)

# Conclusion

- Ca marche?
- Faible niveau de preuve
- Parait une solution dans les formes de RAIR DTC lentement progressives oligométastatiques avec possibilité de schémas séquentiels répétés bien tolérés le but étant de ralentir l'évolution de la maladie
- Apport exact de l'irathérapie en plus des thérapies ciblées?

## Evaluation prospective...

- Maladie métastatique (Essai ITOG Dr Lori Wirth)
- Adjuvant: PHRC qui débute DT+150mCi rh-tsh dans les hauts risques

