

LA PLACE DE LA BIOLOGIE MOLÉCULAIRE EN PRATIQUE DANS LA PRISE EN CHARGE DES TUMEURS THYROÏDIENNES

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07/11/2019



4 au 7 novembre
Palais des Congrès Paris



www.carrefour-pathologie.org

Absence de liens d'intérêt sur le sujet



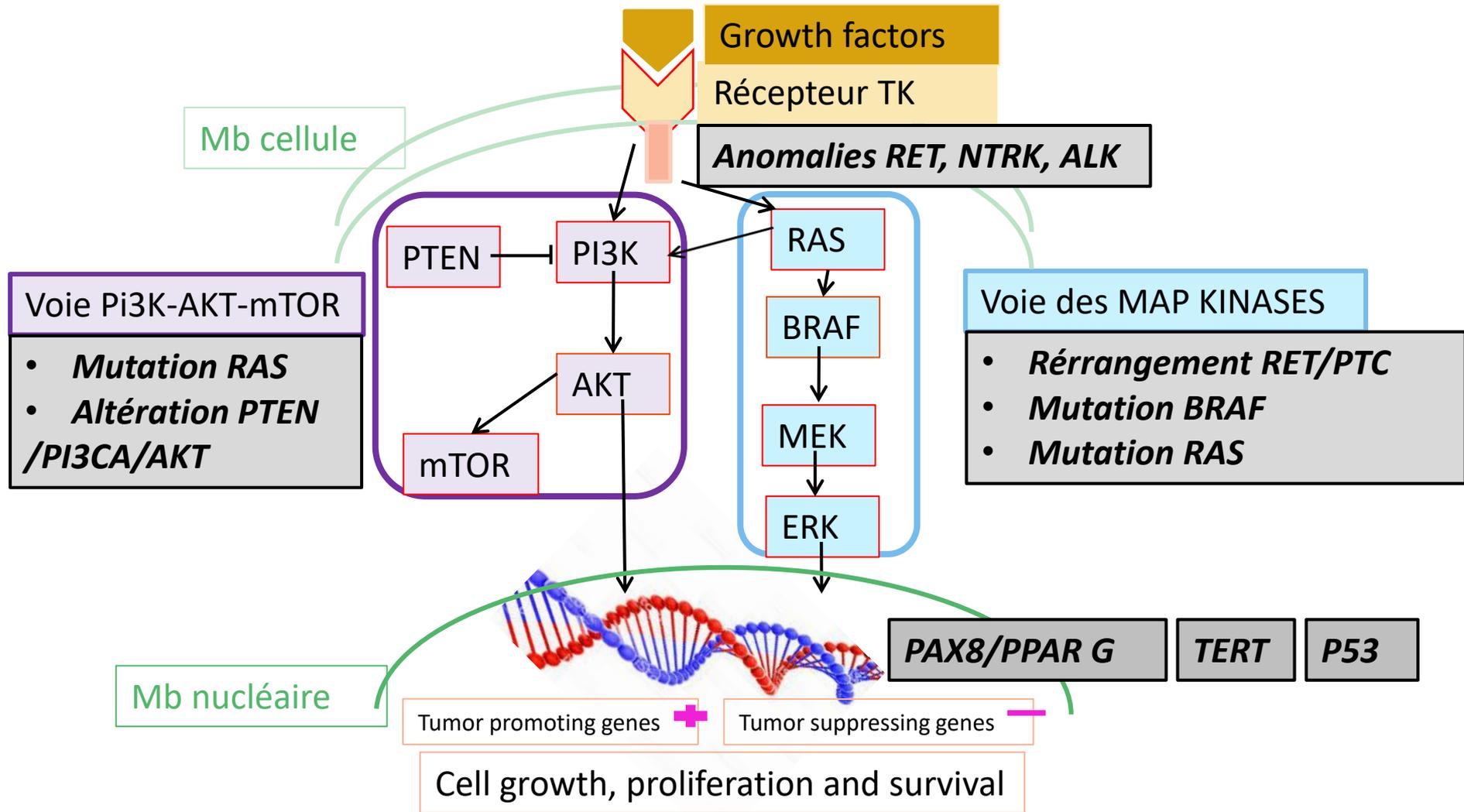
le mot latin nodus, “nœud”, est à l’origine du terme nodules,
Le “sac de nœuds”, qui décrit des “situations compliquées, sans solution, qui provoquent des conflits”, convient bien à la problématique thyroïdienne.

-> intérêt de la biologie moléculaire pour démêler ce sac de nœuds?

OBJECTIFS

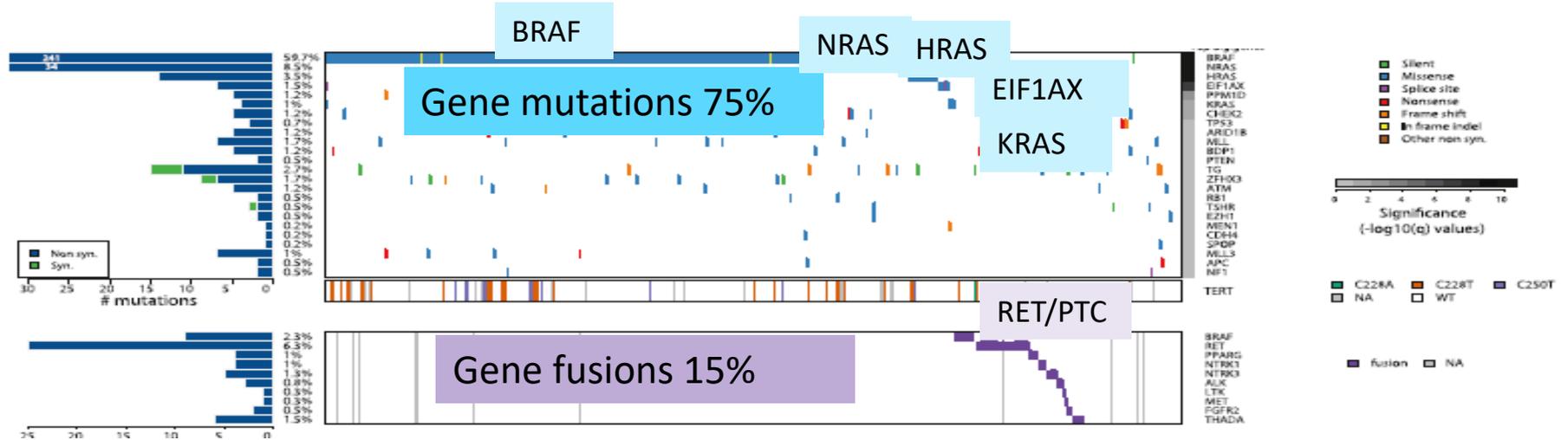


1. Screening des nodules par cytoponction
 - Intérêt de la BM pour améliorer le diagnostic de la cytologie?
2. augmentation du nombre des cancers thyroïdiens (x 3 en 40 ans)
 - BM : outil pour classification diagnostique /pronostic ?
3. Les formes agressives/réfractaires sont rares :
 - BM : aide pour le choix thérapeutique : thérapie ciblée?



The Cancer genome Atlas (TCGA)

Figure 1. Landscape of Genomic Alterations in 402 Papillary Thyroid Carcinomas



Découverte de 97% des altérations génétiques des carc.papillaires

Integrated Genomic Characterization of Papillary Thyroid Carcinoma

The Cancer Genome Atlas Research Network^{1,*}

¹The Cancer Genome Atlas Program Office, National Cancer Institute at NIH, 31 Center Drive, Bldg. 31, Suite 3A20, Bethesda, MD 20892, USA

*Correspondence: gjordano@umich.edu (T.J.G.), gadgetz@broadinstitute.org (G.G.)

<http://dx.doi.org/10.1016/j.cell.2014.09.050>

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The Cancer genome Atlas (TCGA)

690 Cell 159, 676-690, October 23, 2014 ©2014 The Authors

« BRAF V600E-Like »
ou « RAS-like » =
carcinomes
papillaires avec des
caractéristiques
biologiques et
cliniques différentes

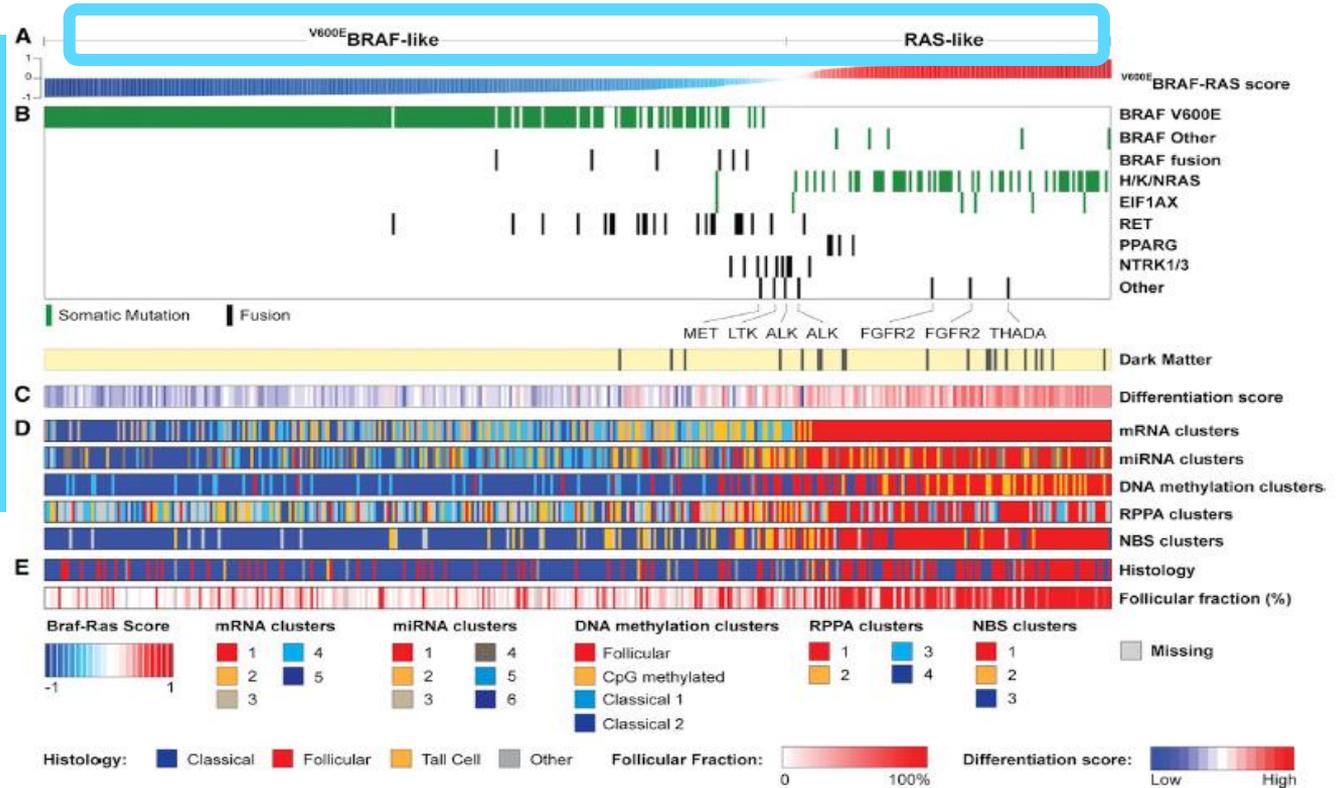


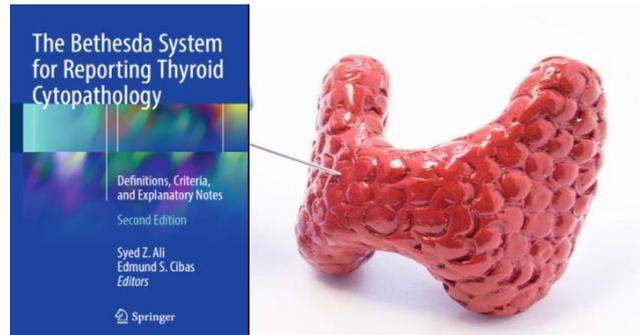
Figure 4. The $BRAF^{V600E}$ -RAS Score

(A–E) Thyroid samples (A) ($n = 391$) were ranked by $BRAF^{V600E}$ -RAS score (BRS), with $BRAF^{V600E}$ -like and RAS-like samples having negative (-1 to 0) and positive scores (0 to 1), respectively. The BRS is strongly associated with: (B) driver mutation status; (C) thyroid differentiation score (TDS); (D) single data-type clusters; and (E) histology and follicular fraction. The RAS-like samples (normalized score > 0 , in red on the top bar) consistently emerged as a distinct subgroup characterized by a higher TDS. See also Figures S6, S7A, and S7B and Tables S2 and S4B.

OBJECTIFS



- Biologie moléculaire et cytologie
- Biologie moléculaire et diagnostic/pronostic
- Biologie moléculaire et thérapeutique



Biologie moléculaire et cytologie



Cytologie :
Diagnostic fiable dans 60 à 80% des cas

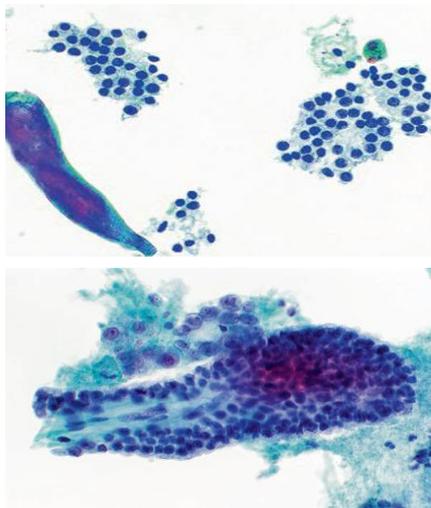


Table 1.1 The Bethesda System for Reporting Thyroid Cytopathology: diagnostic categories

I. Nondiagnostic or Unsatisfactory ^a
Cyst fluid only
Virtually acellular specimen
II. Benign
Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.)
Consistent with chronic lymphocytic (Hashimoto) thyroiditis in the proper clinical context
Consistent with granulomatous (subacute) thyroiditis
Other
III. Follicular Neoplasm or Suspicious for a Follicular Neoplasm ^b
Specify if oncocytic (Hürthle cell) type
IV. Follicular Neoplasm or Suspicious for a Follicular Neoplasm ^b
Specify if oncocytic (Hürthle cell) type
V. Suspicious for Malignancy
Suspicious for papillary thyroid carcinoma
Suspicious for medullary thyroid carcinoma
Suspicious for metastatic carcinoma
Suspicious for lymphoma
VI. Malignant
Papillary thyroid carcinoma
Poorly differentiated carcinoma
Medullary thyroid carcinoma
Undifferentiated (anaplastic) carcinoma
Squamous cell carcinoma
Carcinoma with mixed features (specify)
Metastatic malignancy
Non-Hodgkin lymphoma
Other

Biologie moléculaire et cytologie



Cytologie indéterminée (15 à 30% des cas)

- **Bethesda III / AUS :**
Atypies de signification indéterminée
- **Bethesda IV / FN :**
Néoplasme folliculaire
- **Bethesda V / SM :**
Suspects de malignité

Table 1.1 The Bethesda System for Reporting Thyroid Cytopathology: diagnostic categories

I. Nondiagnostic or Unsatisfactory ^a
Cyst fluid only
Virtually acellular specimen
Other (obscuring blood, clotting artifact, drying artifact, etc.)
II. Benign
Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.)
Consistent with chronic lymphocytic (Hashimoto) thyroiditis in the proper clinical context
Consistent with granulomatous (subacute) thyroiditis
Other
III. Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance ^a
IV. Follicular Neoplasm or Suspicious for a Follicular Neoplasm ^a
Specify if oncocytic (Hürthle cell) type
V. Suspicious for Malignancy
Suspicious for papillary thyroid carcinoma
Suspicious for medullary thyroid carcinoma
Suspicious for metastatic carcinoma
Suspicious for lymphoma
Other
VI. Malignant
Papillary thyroid carcinoma
Poorly differentiated carcinoma
Medullary thyroid carcinoma
Undifferentiated (anaplastic) carcinoma
Squamous cell carcinoma
Carcinoma with mixed features (specify)
Metastatic malignancy
Non-Hodgkin lymphoma
Other

D'après Cibas, The Bethesda System for Reporting Thyroid Cytopathology, 2017

Biologie moléculaire et cytologie



Cytologie indéterminée

Diagnostic category	Risk of malignancy (%)	Usual management ^a
Nondiagnostic or Unsatisfactory	5–10 ^b	Repeat FNA with ultrasound guidance
Benign	0–3 ^c	Clinical and sonographic follow-up
Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance	~10–30 ^d	Repeat FNA, molecular testing, or lobectomy
Follicular Neoplasm or Suspicious for a Follicular Neoplasm ^e	25–40 ^f	Molecular testing, lobectomy
Suspicious for Malignancy	50–75	Near-total thyroidectomy or lobectomy ^{g,1}
Malignant	97–99	Near-total thyroidectomy or lobectomy ^h

Analyse moléculaire?



- ETAPE 1 : analyse de gènes isolés:

- Mutation BRAF V600E

BRAF V600E= carcinome papillaire

- ETAPE 2 : panel

- BRAF + RAS + RET/PTC ou PAX8/PPARG

= 70% des cancers thyroïdiens

Biologie moléculaire et cytologie



○ ETAPE 1 : analyse de gènes isolés: ➤ **BRAF**

○ ETAPE 2 : panel ➤ **BRAF + RAS + RET/PTC ou PAX 8/PPARG**

○ ETAPE 3 : screening large Sur matériel dédié et congelé

- **GEC (Genes Classifier) : Afirm**
- **NGS : Thyroseq** (V3 : *formol et congelé*)
- **miRNA : ThygenX/ThyraMIR et Rosetta**

“molecular testing for indeterminate thyroid nodules has become increasingly common and is widely used as an adjunct diagnostic tool for thyroid nodules diagnosed as indeterminate on FNA.”



Et en pratique ?

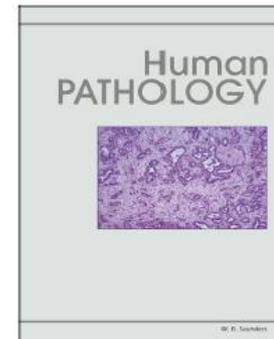
In today's endocrine clinics, **molecular testing of thyroid fine-needle aspiration samples has become routine**. Many academic laboratories have testing done in their own laboratories; many clinics send samples for molecular testing to commercial entities

Z. Baloch and V.A. LiVolsi, 50-years of thyroid pathology: concepts and developments, *Human Pathology* (2019)

Journal Pre-proof

50-years of thyroid pathology: concepts and developments

Zubair Baloch, Virginia A. LiVolsi





Et en pratique ?

- Pas de tests remboursés en France



ORIGINAL ARTICLE

WILEY

Molecular testing of *BRAF*, *RAS* and *TERT* on thyroid FNAs with indeterminate cytology improves diagnostic accuracy

M. Decaussin-Petrucci^{1,6*} | F. Descotes^{2*} | L. Depaepé¹ | V. Lapras³ | M.-L. Denier³ | F. Borson-Chazot⁴ | J.-C. Lifante⁵ | J. Lopez^{2,6} 

Conclusions: Mutation profiling can be successfully performed on thyroid LB-FNA without any dedicated sample in a pathology laboratory. It is an easy way to improve diagnostic accuracy of routine LB-FNA and may help to better select patients for surgery and to avoid unnecessary thyroidectomies.

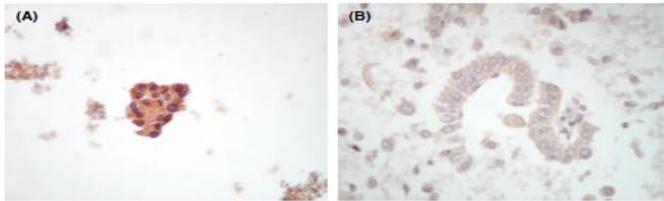


Et en pratique ?

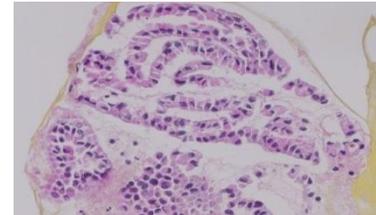
■ ICC BRAF V600E :

- Anticorps monoclonal VE1 qui cible la protéine V600E mutée
- Sensibilité : 61-100% et Spécificité : 77-73% (FNA/cell block)
- Économique et fiable : permet de restreindre la biologie moléculaire aux cas positifs

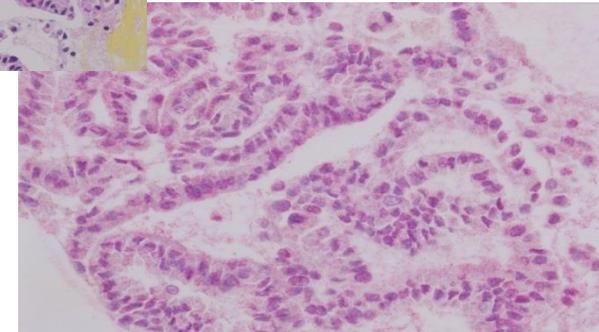
Cytopathology. 2019;30:460–467



(A) Liquid-based preparation. Image of immunocytochemical cytoplasmic staining in a specimen that was on liquid-based cytology reveals positivity 3+ for the monoclonal V600E antibody (VE1) in tumour cells (anal magnification $\times 250$). (B) Cell block preparation. Image of immunocytochemical cytoplasmic staining in a specimen that was on cell block method reveals positivity 3+ for the VE1 in tumour cells (avidin-biotin method, anal magnification $\times 250$). This image was diagnosed as papillary thyroid carcinoma tall cell variant



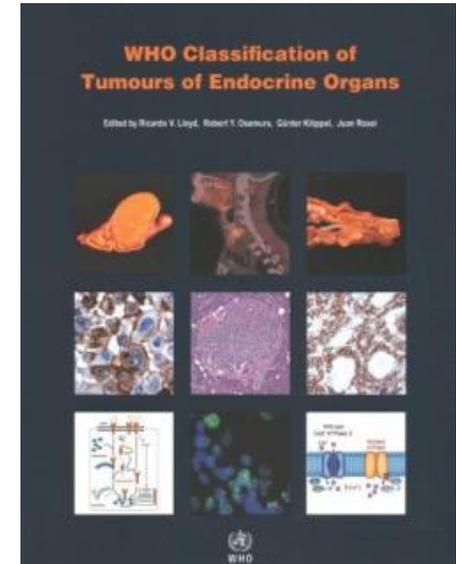
ICC BRAF sur
cytobloc



OBJECTIFS



- Biologie moléculaire et cytologie
- Biologie moléculaire et diagnostic/pronostic
- Biologie moléculaire et thérapeutique



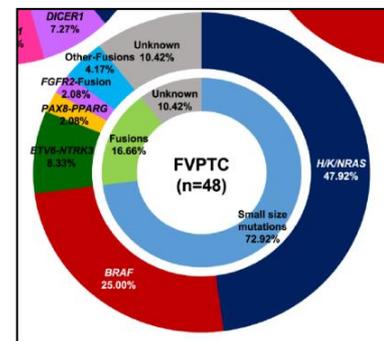
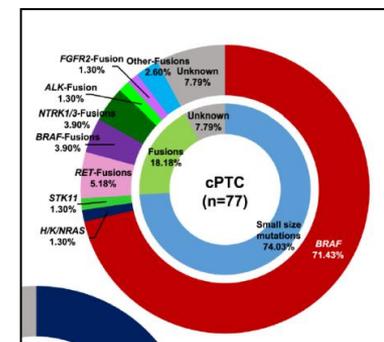


Carcinome PAPILLAIRE : biologie moléculaire

- Anomalies moléculaires mutuellement exclusives (sauf TERT)

BRAF V600E = CARCINOME PAPILLAIRE
RET/PTC = CARCINOME PAPILLAIRE
TERT = PRONOSTIC

Type de carcinome papillaire	Mutation BRAF V600E	Réarrangement RET/PTC	Mutation RAS	Mutation du promoteur de TERT
Tous types	30-90%	5-35%	0-35%	5-25%
Papillaire classique	45-80%	5-25%	0-15%	5-15%
Papillaire cellules hautes	60-95%	35%	0%	5-30%
Papillaire variant vésiculaire	5-25%	5-25%	15-35%	5-15%





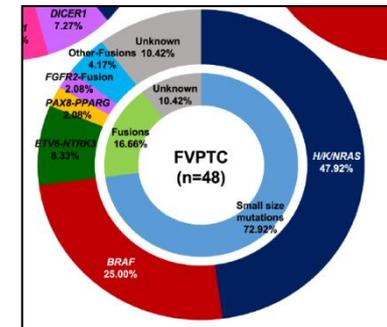
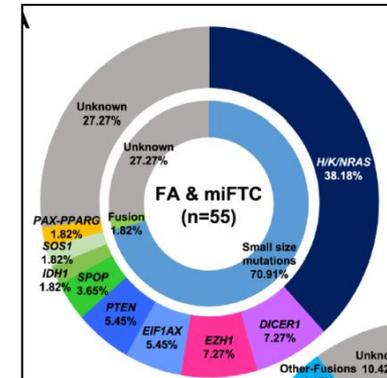
Carcinome VÉSICULAIRE : biologie moléculaire

- Mutations RAS et réarrangement PAX8/PPARgamma

**RAS et PAX8/PPARg = NON SPECIFIQUES DU CANCER
TERT = PRONOSTIC**

Type de tumeur	Mutation RAS	Réarrangement PAX8/PPAR g	Mutation du promoteur de TERT
Carcinome vésiculaire	40-50%	10-40%	20%
Carc. oncocytaire	10-15%	0-5%	
Adénome	20-30%	8%	
NIFTP	30-54%	-	
Papillaire variant vésiculaire	15-35%	1-5%	

PLOS Genetics | August 5, 2016



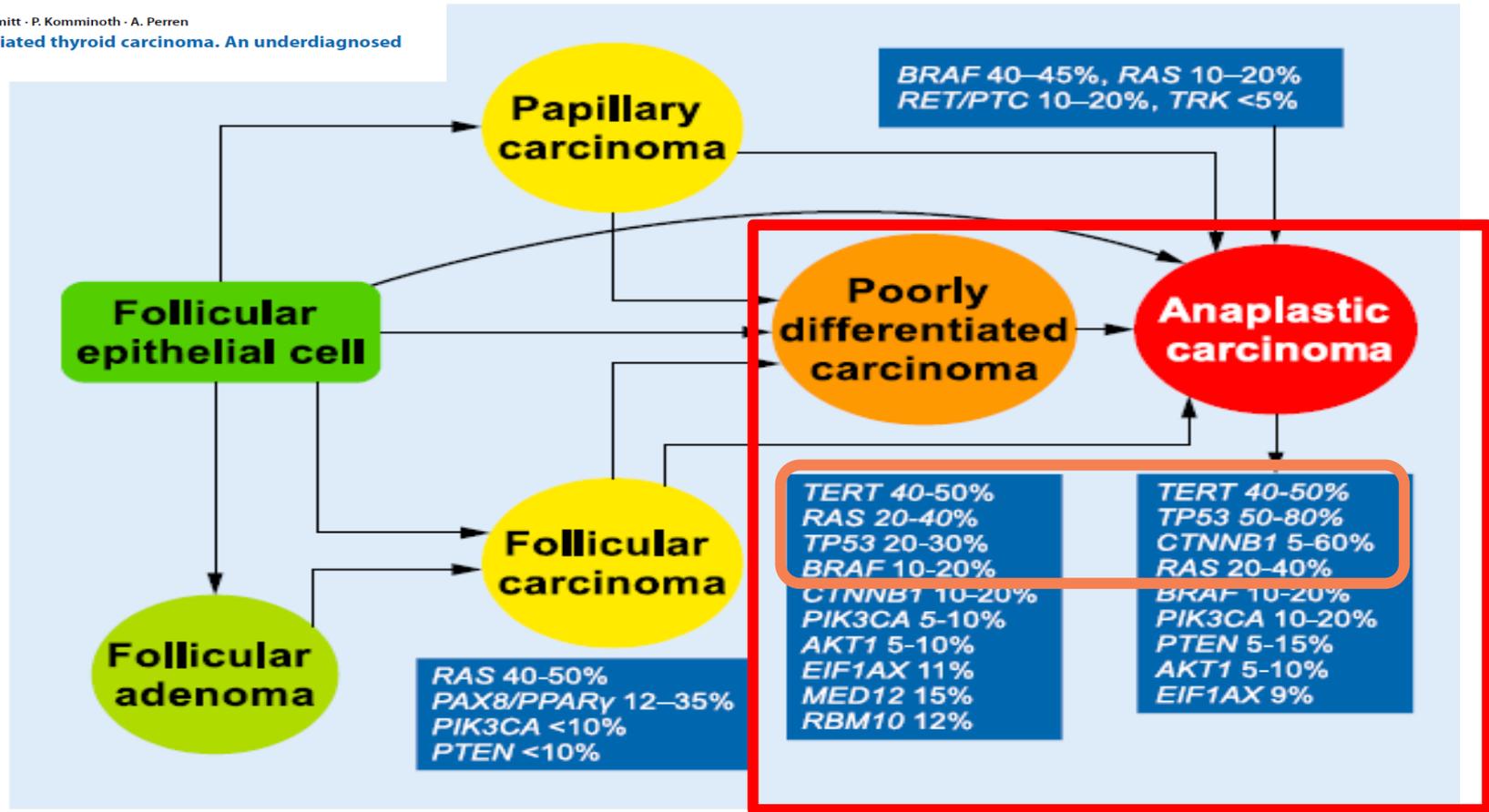


Fig. 3 ▲ Stepwise de-differentiation of thyroid carcinomas derived from follicular epithelial cell



Carcinome médullaire

	RET (mutation germinale)	RET (mutation somatique)
Médullaire héréditaire	100%	
Médullaire sporadique		40%



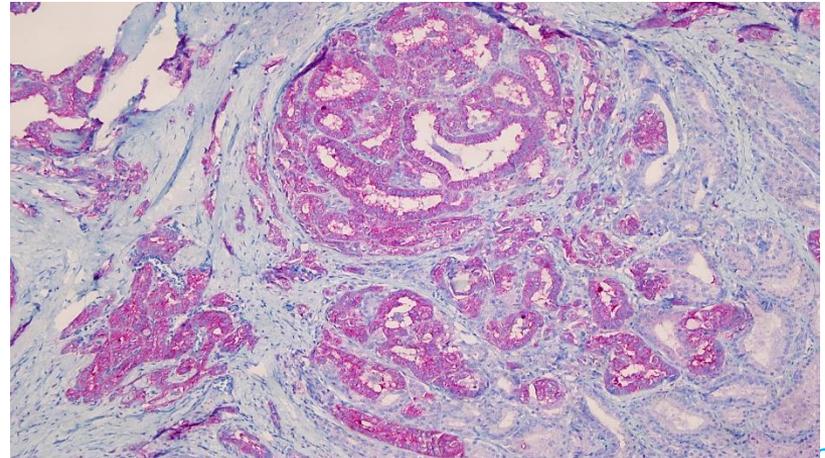
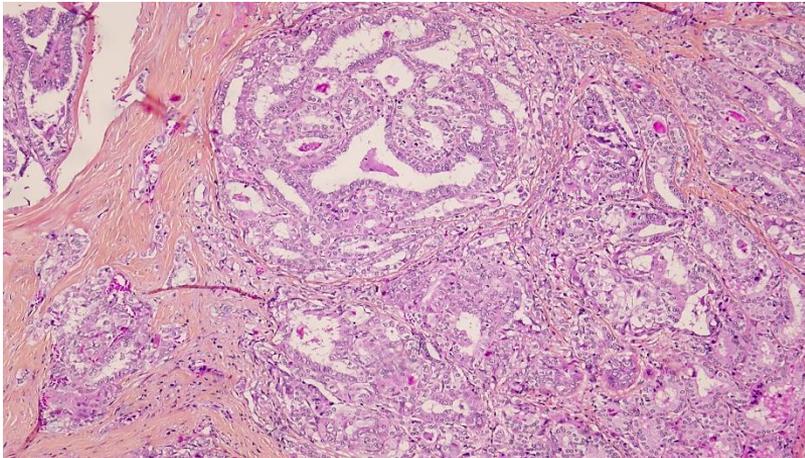
Et en pratique : diagnostic?

- BRAF V600 E + Immuno = carcinome papillaire
 - Sensibilité : 96,8%
 - Spécificité : 86,3%

Endocrine Pathology 2019

A Systematic Review and Meta-Analysis of the Diagnostic Performance of BRAF V600E Immunohistochemistry in Thyroid Histopathology.

Ranjit Singarayer Ozgur Mete et al





Et en pratique: pronostic ?

- BRAF V600E seul n'est pas un facteur pronostique indépendant
- BRAF+ : plus souvent N+ : outil pour la chirurgie?
 - BRAF - : pas de curage, moins de surveillance?
 - BRAF + : curage étendu??



Et en pratique: pronostic ?

- Mutation BRAF V600E
- Mutation du promoteur de TERT : pronostic ++++
 - Traitement complémentaire plus agressif?

European Journal of Cancer 398 (2019) 41–49



Original Research

TERT promoter mutations identify a high-risk group in metastasis-free advanced thyroid carcinoma

Claire Bournaud^{a,*}, Françoise Descotes^b, Myriam Decaussin-Petrucci^{c,d}, Julien Berthiller^e, Christelle de la Fouchardière^f, Anne-Laure Giraudet^g, Mireille Bertholon-Gregoire^h, Philip Robinson^h, Jean-Christophe Lifante^h, Jonathan Lopez^{h,d}, Françoise Borson-Chazot^{h,k}

J Clin Endocrin Metab. First published ahead of print July 5, 2013 as doi:10.1210/jc.2013-2383

JCEM ONLINE

Brief Report—Endocrine Research

Frequent Somatic *TERT* Promoter Mutations in Thyroid Cancer: Higher Prevalence in Advanced Forms of the Disease

Íñigo Landa, Ian Ganly, Timothy A. Chan, Norisato Mitsutake, Michiko Matsuse, Tihana Ibrahimspasic, Ronald A. Ghossein, and James A. Fagin





Prise en charge des cancers thyroïdiens

Recommandations de l'American Thyroid Association (ATA)

**Risque élevé
(30 - 50 %)**
**¹³¹I recommandé
en routine**

**Risque
intermédiaire
(5-30 %)**
¹³¹I à discuter

**Risque faible
(1 - 4 %)**
**¹³¹I non
recommandé
en routine**

Risque de récurrence morphologique

CV, invasion vasculaire large
pT4a extension extrathyroïdienne large
pN1 avec rupture capsulaire, > 3 gg envahis
CP > 1 cm, **TERT +/- BRAF muté**
pN1, gg > 3 cm

CP, BRAF muté, extrathyroïdien
CP, invasion vasculaire
N1 clinique
pN1, > 5 gg envahis
CP intrathyroïdien, < 4 cm, BRAF muté
pT3 extension extrathyroïdienne minime
pN1, gg tous < 0,2 cm
pN1, <= 5 gg

CP 2-4 cm intrathyroïdien
Micro CP multifocal
pN1 sans rupture capsulaire, ≤ 3 ganglions
CV à invasion minime
CP intrathyroïdien, < 4 cm, BRAF sauvage
Micro CP unifocal intrathyroïdien, BRAF muté
CP variant folliculaire encapsulé, intrathyroïdien
Micro CP unifocal

THYROID

Volume 26, Number 1, 2016

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DOI: 10.1089/thy.2015.0020

→ **Comment sélectionner les patients pour l'¹³¹I ?**

OBJECTIFS



- Biologie moléculaire et cytologie
- Biologie moléculaire et diagnostic/pronostic
- Biologie moléculaire et thérapeutique



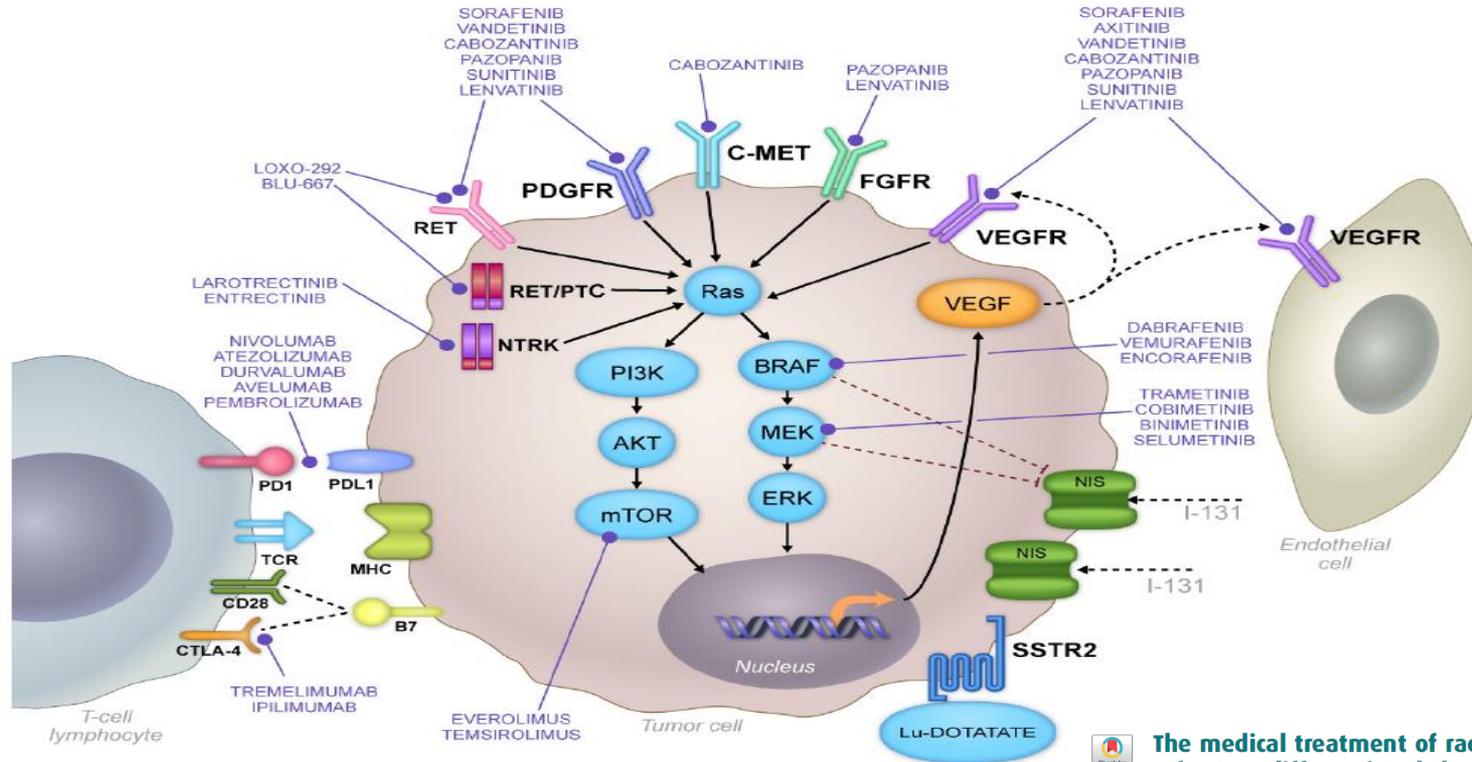
- Pronostic du cancer de la thyroïde excellent avec survie globale de 90% à 10 ans
- Traitement de référence : **chirurgie, +/- iode radioactif**
- **Les cancers localement avancés ou M+** : survie de 6 mois – 5 ans
 - Carcinomes réfractaires à l'iode
 - Carcinome peu différencié
 - Carcinome anaplasique
 - Carcinome médullaire M+
- Recherche de thérapeutiques alternatives : réseau TUTHYREF
 - 28 centres
 - RCP régionales et nationale



The medical treatment of radioiodine-refractory differentiated thyroid cancers in 2019. A TUTHYREF® network review

Bull Cancer 2019; 106: 812–819

Biologie moléculaire et thérapeutique



Targeted Therapy for Advanced Thyroid Cancer: Kinase Inhibitors and Beyond

The University of Texas MD Anderson Cancer Center

The medical treatment of radioiodine-refractory differentiated thyroid cancers in 2019. A TUTHYREF® network review

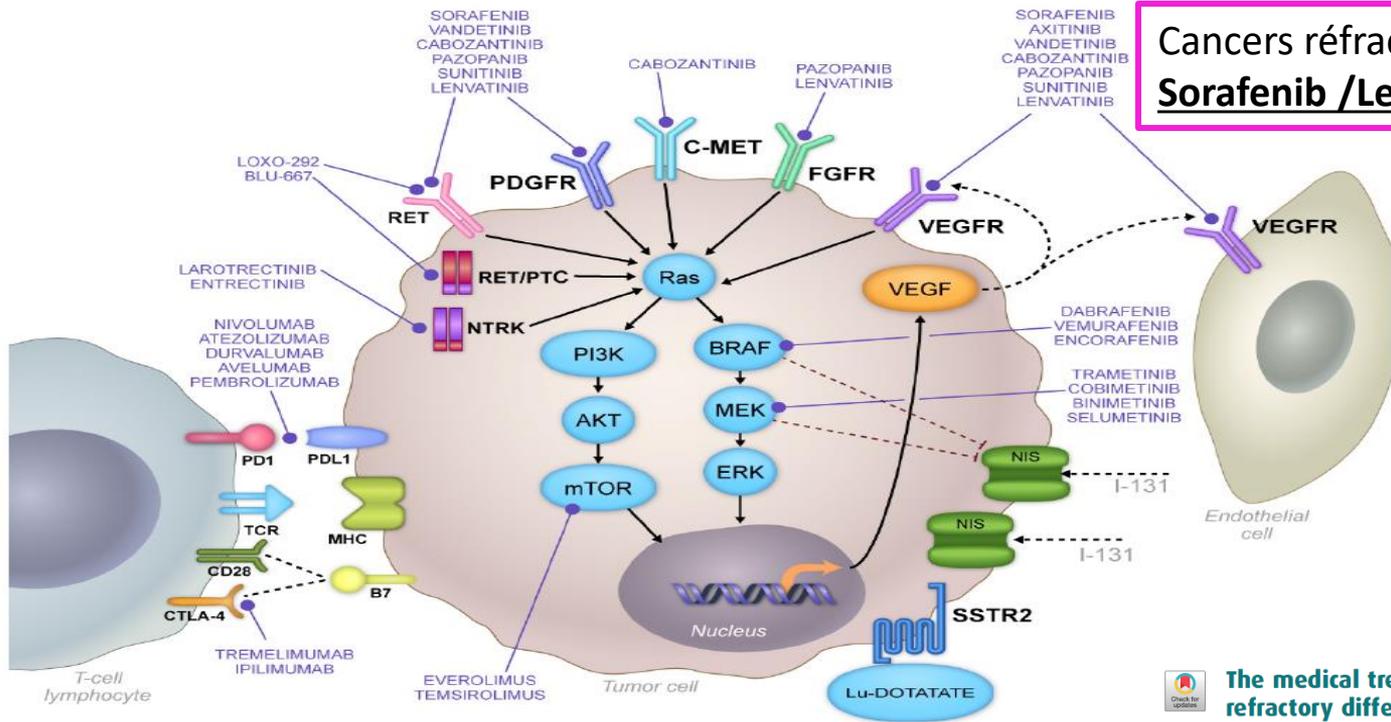
Endocrine Reviews; Copyright 2019 DOI: 10.1210/er.2019-00007
 Maria E. Cabanillas, Mabel Ryder, and Camilo Jimenez

Bull Cancer 2019; 106: 812–819





Cancers réfractaires :
Sorafenib /Lenvatinib : TKI



Targeted Therapy for Advanced Thyroid Cancer: Kinase Inhibitors and Beyond

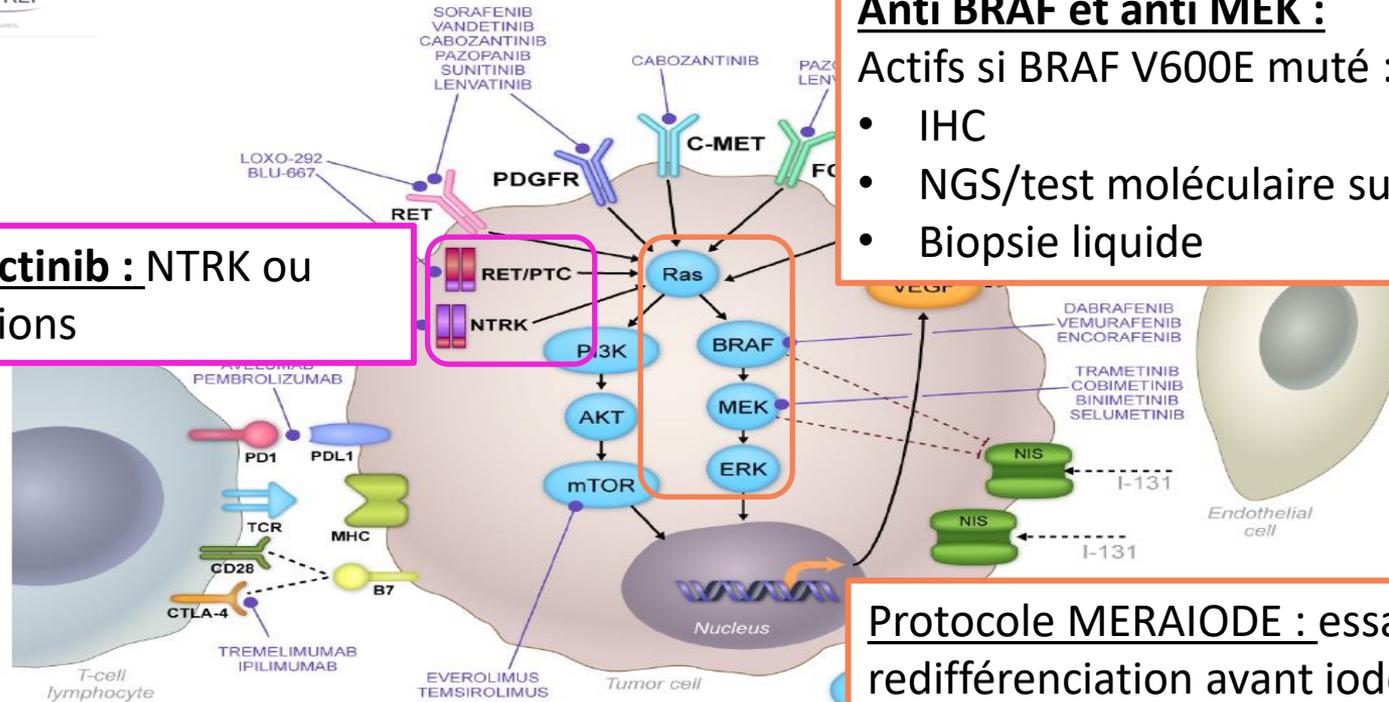
University of Texas MD Anderson Cancer Center



The medical treatment of radioiodine-refractory differentiated thyroid cancers in 2019. A TUTHYREF® network review



Biologie moléculaire et thérapeutique



Larotrectinib : NTRK ou RET fusions

Anti BRAF et anti MEK :
Actifs si BRAF V600E muté :

- IHC
- NGS/test moléculaire sur tissu
- Biopsie liquide

Protocole MERAIODE : essai de redifférenciation avant iode :

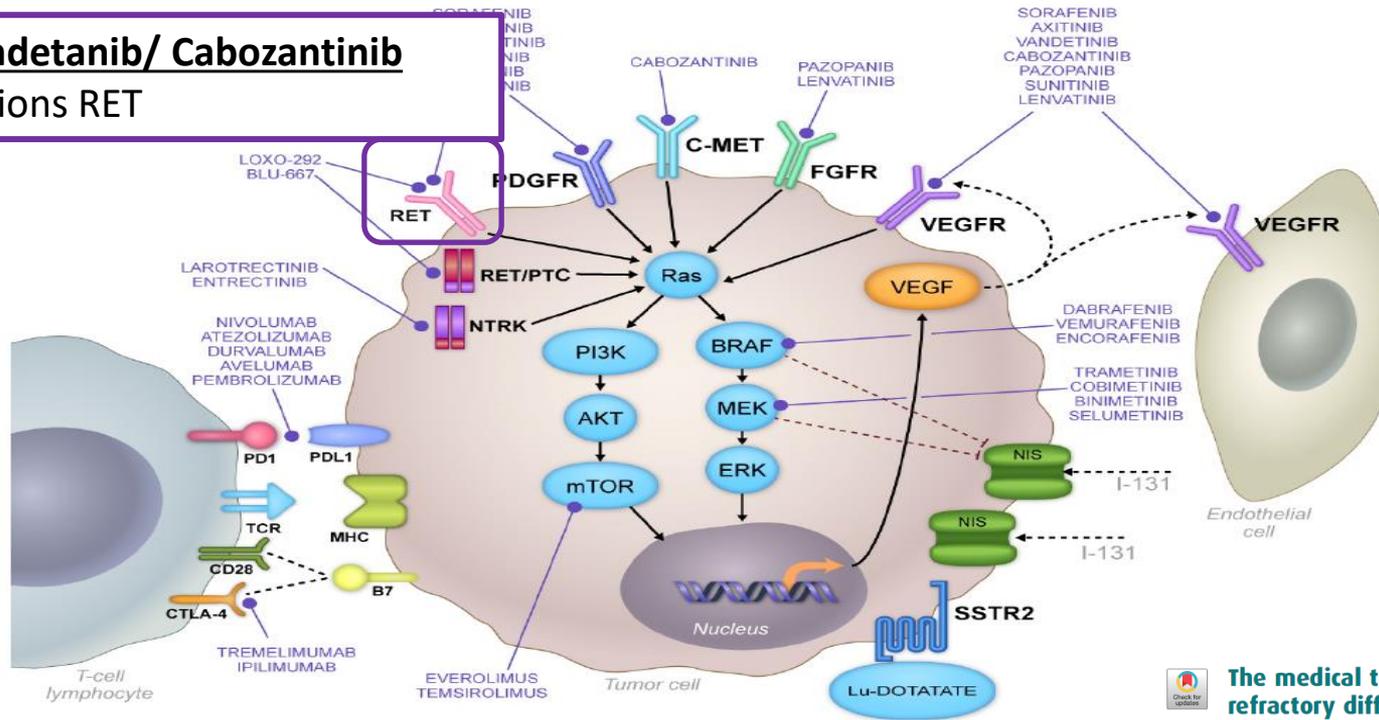
- 1-recherche mutation RAS/BRAF
- 2- Trametinib/Dabrafenib
- 3- Iode

Visual Art: © 2018 The University of Texas MD Anderson Cancer Center



CMT : Vandetanib/ Cabozantinib

- Mutations RET



Targeted Therapy for Advanced Thyroid Cancer: Kinase Inhibitors and Beyond

Endocrine Reviews; Copyright 2019 DOI: 10.1210/er.2019-00007

Maria E. Cabanillas, Mabel Ryder, and Camilo Jimenez

University of Texas MD Anderson Cancer Center



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Bull Cancer 2019; 106: 812–819



Biologie moléculaire EN PRATIQUE



■ Cytologie :

- Intérêt pour mieux classer les lésions indéterminées
 - Meilleure prise en charge
 - Éviter thyroïdectomies inutiles
- BRAF/RAS/ Réarrangements/ ou panel de gènes ou NGS



Biologie moléculaire EN PRATIQUE



- **Cytologie :**
 - Intérêt pour mieux classer les lésions indéterminées
- **Diagnostic et pronostic :**
 - Marqueurs diagnostiques : BRAF V600E= Carc. papillaire
 - Marqueurs pronostiques : TERT
- **Thérapeutique : Screening moléculaire indispensable**
 - Les cancers localement avancés ou M+

MERCI DE VOTRE ATTENTION

