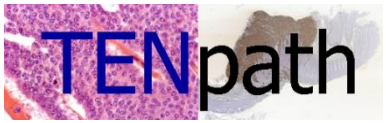
Groupe d'étude des Tumeurs Endocrines

RENATEN
RÉseau NAtional de prise en charge des Tumeurs neuro-ENdocrines Malignes Rares Sporadiques et Héréditaires



NEM1, CMT

Actualités 2015-2016

Pr V.Rohmer

université angers

Groupe d'étude des Tumeurs Endocrines

Carcinome Médullaire de la Thyroïde

Sporadique et Familial

Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma

The American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma

Samuel A. Wells, Jr.,[1,*] Sylvia L. Asa,[2] Henning Dralle,[3] Rossella Elisei,[4] Douglas B. Evans,[5] Robert F. Gagel,[6] Nancy Lee,[7] Andreas Machens,[3] Jeffrey F. Moley,[8] Furio Pacini,[9] Friedhelm Raue,[10] Karin Frank-Raue,[10] Bruce Robinson,[11] M. Sara Rosenthal,[12] Massimo Santoro,[13] Martin Schlumberger,[14] Manisha Shah,[15] and Steven G. Waguespack[6]

Thyroid 2015

La calcitonine au centre de la décision thérapeutique dans les NEM2 A

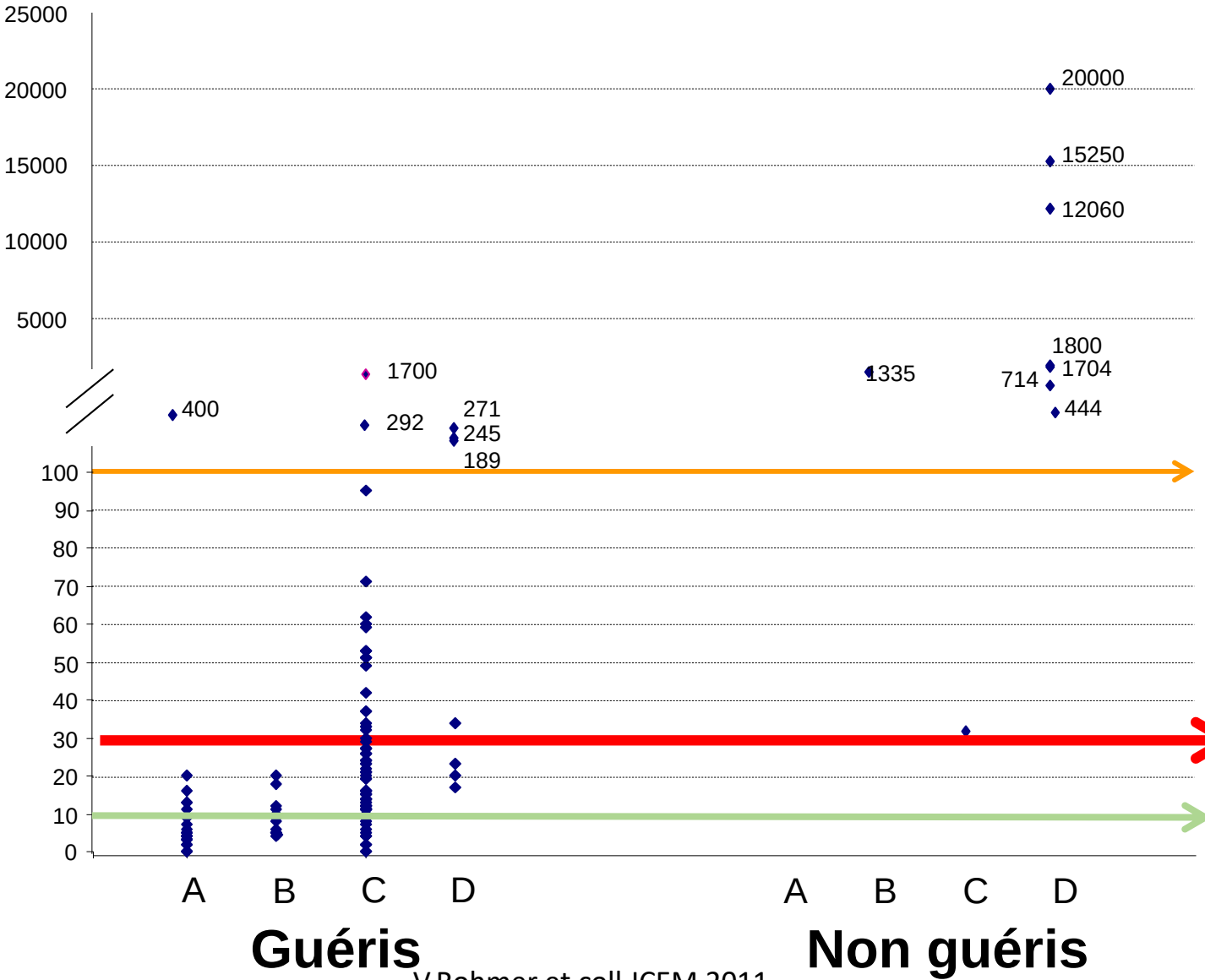
- **RECOMMENDATION 35**

  Children in the ATA-H category should have a thyroidectomy performed at age 5 years, or earlier based on the detection of elevated serum Ctn levels. A central neck dissection should be performed in children with serum Ctn levels above 40 pg/mL, or with evidence on imaging or direct observation of lymph node metastases. The surgeon and pediatrician caring for the patient, in consultation with the child's parents, should decide the timing of thyroidectomy. Grade B Recommendation

- **RECOMMENDATION 36**

  Children in the ATA-MOD category should have a physical examination, US of the neck, and measurement of serum Ctn levels beginning around 5 years of age. The timing of thyroidectomy should be based on the detection of an elevated serum Ctn level; however, 6-month or annual evaluations may extend to several years or decades. Parents who are concerned about a long-term evaluation program may opt to have their child's thyroid gland removed around 5 years of age. The surgeon and pediatrician caring for the patient, in consultation with the child's parents, should decide the timing of thyroidectomy. Grade B Recommendation

Guérison en fonction du niveau préop de la CT basale et des niveaux de risque de l'ATA (132 guéris sur 141 évaluables)



Se 88%

Spe 95%

Se 100%

Spe 82%

Se 100%

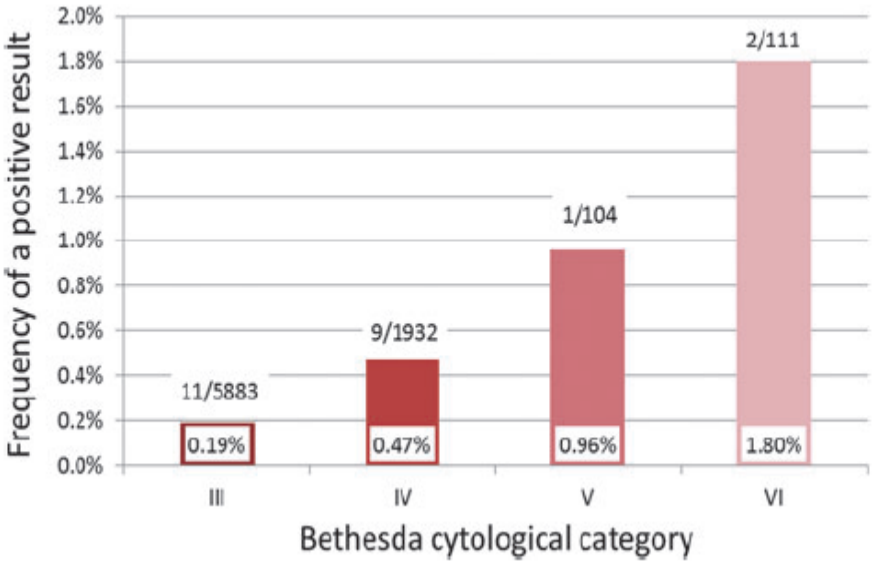
Spe 41%

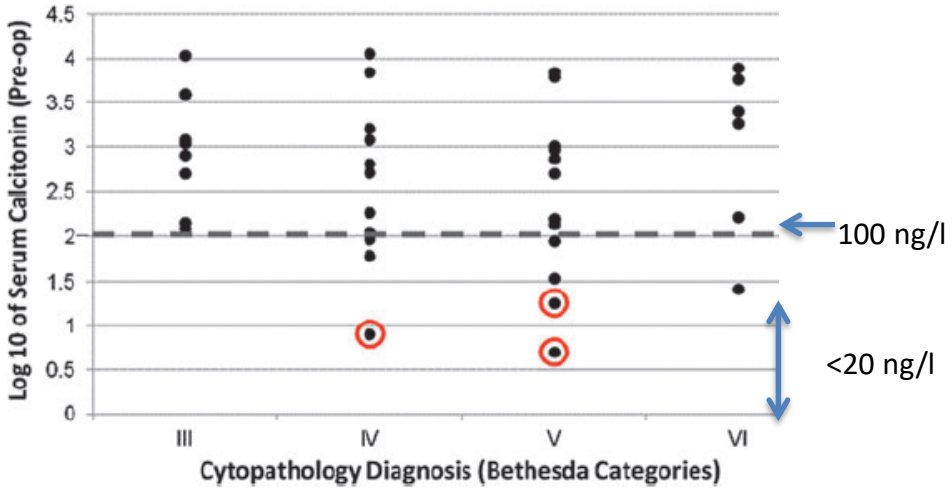
V.Rohmer et coll JCEM 2011

A Genomic Alternative to Identify Medullary Thyroid Cancer Preoperatively in Thyroid Nodules with Indeterminate Cytology

Richard T. Kloos,[1] Robert J. Monroe,[2] S. Thomas Traweek,[3] Richard B. Lanman,[1†] and Giulia C. Kennedy[4]

=L'avenir ???





Utilisation de 5 gènes spécifiques
Résultats: PPV 97,9% NPV 99,8%

JCEM 2016

Macrocalcitonin Is a Novel Pitfall in the Routine of Serum Calcitonin Immunoassay

Thalita G. Alves, Teresa S. Kasamatsu, Ji H. Yang, Maria Cecília Z. Meneghetti, Aline Mendes, Ilda S. Kunii, Susan C. Lindsey, Cléber P. Camacho, Magnus R. Dias da Silva, Rui M. B. Maciel, José Gilberto H. Vieira, and João Roberto M. Martins

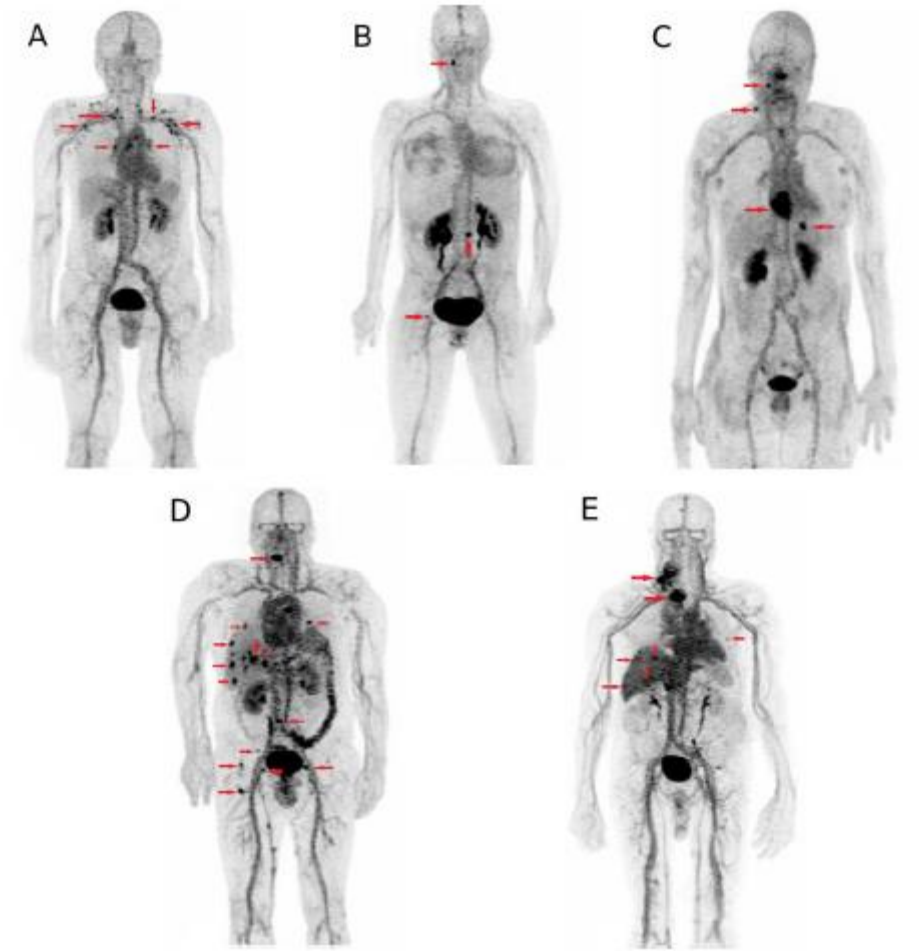
JCEM 2016

Révélée par test de recouvrement au PEG
Confirmé par chromatographie.
A évoquer si chir.du CMT a paru complète.
Fréquence ?

Immuno-PET using anti-CEA bispecific antibody and 68Ga-labeled peptide in metastatic medullary thyroid carcinoma: clinical optimization of the pretargeting parameters in a First-in Human trial.

Bodet-Milin C[1], Faivre-Chauvet A[2], Carlier T[3], Rauscher A[4], Bourgeois M[5], Cerato E[6], Rohmer V[7], Couturier O[8], Drui D[9], Goldenberg DM[10], Sharkey RM[11], Barbet J[12], Kraeber-Bodéré F[13].

JNM 2016

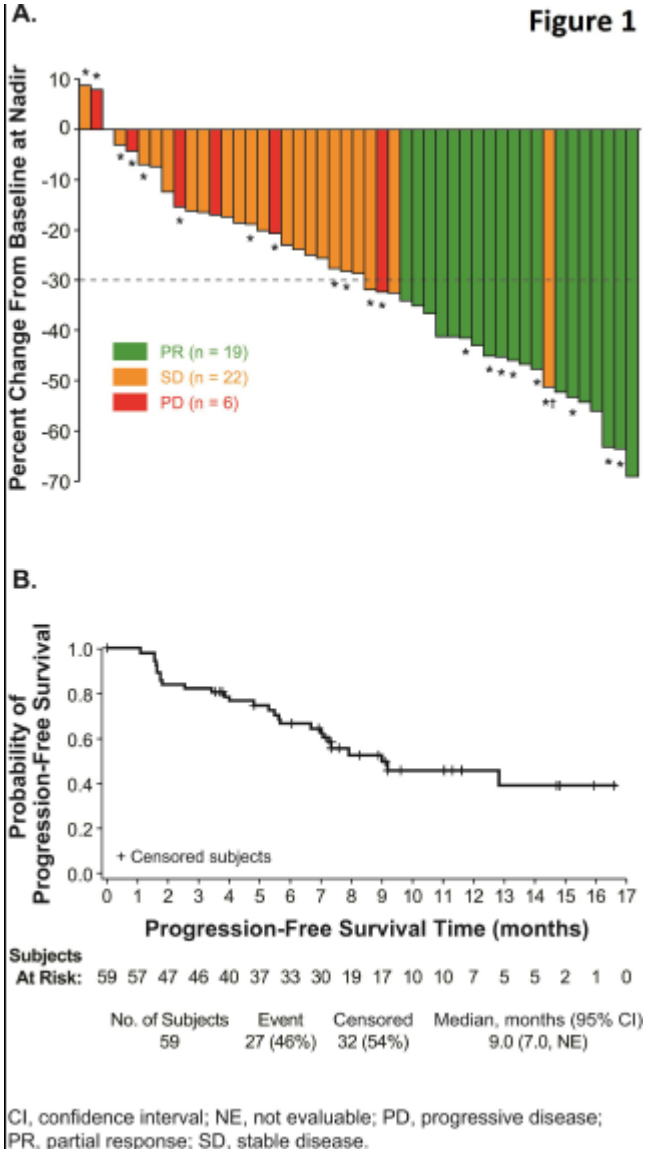


16 patients

Title: A Phase 2 Trial of the Multi-targeted Tyrosine Kinase Inhibitor Lenvatinib (E7080) in Advanced Medullary Thyroid Cancer (MTC)

Authors: Martin Schlumberger,[1] Barbara Jarzab,[2] Maria E. Cabanillas,[3] Bruce Robinson,[4] Furio Pacini,[5] Douglas W. Ball,[6] Judith McCaffrey,[7] Kate Newbold,[8] Roger Allison,[9] Renato G. Martins,[10] Lisa F.Licitra,[11] Manisha H. Shah,[12] Donald Bodenner,[13] Rossella Elisei,[14] Lynn Burmeister,[15] Yasuhiro Funahashi,[16] Min Ren,[17] James P. O'Brien,[17] and Steven I. Sherman[3]

Clinical Cancer Research online aug26,2015



ORR : 36 % (réponses partielles)
Taux de SSP à 6 mois : 67%
SSP médiane : 9 mois

	Molecular target	No.	ORR (%)	Stable disease >6 months (%)
Imatinib	Bcr-Abl, PDGFRα and PDGFRβ, c-Fms, c-Kit, RET	15 9	0	27 56
Gefitinib	EGFR	4	0	0
Motesanib	VEGFR1, VEGFR2 and VEGFR3, PDGFR, c-Kit, RET	91	2	48
Axitinib	VEGFR1, VEGFR2 and VEGFR3	11	18	NR
Sorafenib	RAF, VEGFR2 and VEGFR3, PDGFR, RET	21 15	21 13	53 NR
Vandetanib	VEGFR, EGFR, RET	30 19 331	20 16 45	53 53 NR
Sunitinib	VEGFR1, VEGFR2 and VEGFR3, PDGFR, c-Kit, RET, FLT3	25 15	32 33	NR NR
Lenvatinib	VEGFR1, VEGFR2 and VEGFR3, RET, c-Kit, FGFR1, FGFR2, FGFR3 and FGFR4, PDGFR	59	36	NR
Cabozantinib	VEGFR2, MET, c-Kit, FLT3, Tie2	37 330	27 28	41 NR
Pazopanib	VEGFR 1-3,c-Kit, PDGFR α and -β	35	14	NR

TP Links et al EJE 2015

Etudes difficiles à comparer du fait de l'hétérogénéité des populations incluses…

Exemple:

Comparison of study outcomes and adverse event frequencies from the phase III placebo-controlled trials of vandetanib (ZETA) and cabozantinib (EXAM) in MTC.[16,19,25,26]

Trial	ZETA		EXAM	
Treatment arm	Vandetanib	Placebo	Cabozantinib	Placebo
Entry criteria	Locally advanced or metastatic disease		Documented progression of locally advanced or metastatic disease	
N	231	100	219	111
Median PFS, months	30.5	19.3	11.2	4
Ratio of median PFS, treatment:placebo	1.58		2.80	
Partial response rate (%)	44	1	27	0
Grade 3/4 adverse event rates				
Diarrhea (%)	11	2	16	2
Hypertension (%)	9	1	8	0
QTc prolongation (%)	8	1	0	0
Fatigue (%)	6	1	9	3
Asthenia (%)	3	1	6	1
Death due to adverse event (%)	2	2	6	5

Sherman Oral oncology 2013

Lequel des TKI choisir ???

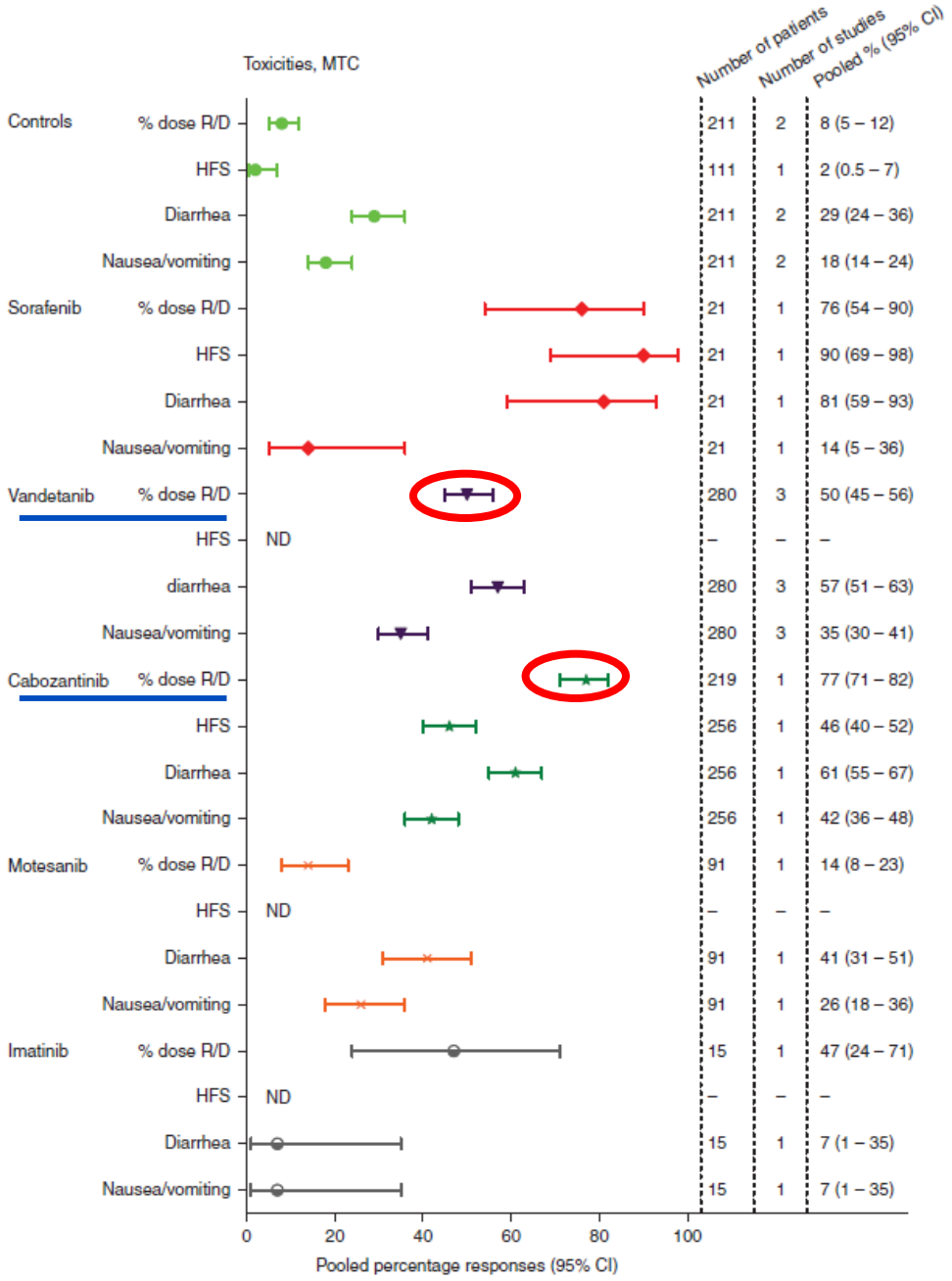
-Comparaison des études difficiles

-Tenir compte des mutations somatiques ? Ex: cabozantinib+ efficace sur CMT sporadique avec mut,somatique 918 (Eliséi JCO2013)

-ou bien des expériences in vitro ? Ex: cabozantinib plus efficace si NEM2A vandetanib si NEM2B

-ou bien d'autres interactions que RET ? EGFR, FGRF,cKIT etc…

-ou surtout des **effets indésirables**…?



Méta-analyse des effets sec.des ITK
EN Klein-Hesselink et al EJE2015

R/D = réduction de dose ou arrêt pour AE

OncoTargets and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

CASE REPORT

Metastatic medullary thyroid cancer: a dramatic response to a systemic chemotherapy (temozolomide and capecitabine) regimen

This article was published in the following Dove Press journal:
OncoTargets and Therapy
13 May 2015
Number of times this article has been viewed

Sahin Lacin
Ece Esin
Yusuf Karakas
Suayib Yalcin

Department of Medical Oncology, Institute of Cancer, Hacettepe University, Ankara, Turkey

Abstract: A 40-year-old male patient presented with increasing serum levels of calcitonin and CEA. He underwent potential curative surgery for medullary thyroid carcinoma, 3 years ago and then 7 months later he had metastasectomy and cervical lymph node dissection for recurrent disease. On admission he had multiple metastatic skin nodules on the chest wall and positron emission tomography–computed tomography revealed multiple visceral metastases as well. The patient had not received any systemic treatment up to that time; therefore, we considered systemic treatment with the new tyrosine kinase inhibitors (vandetanib, cabozantinib, etc). However, since these drugs are only available after cytotoxic chemotherapy, we started temozolomide and capecitabine chemotherapy. After two courses of the treatment all skin nodules disappeared and CEA and calcitonin levels normalized, radiological imaging showed a good partial response.

Is There a Role for Peptide Receptor Radionuclide Therapy in Medullary Thyroid Cancer?

Fernanda Vaisman, MD, PhD, Paulo Henrique Rosado de Castro, MD, PhD,†*
Flavia Paiva Proença Lobo Lopes, MD, PhD,† Daniel Barretto Kendler, MD, MSc,‡
Cencita H.N. Pessoa, MD, PhD, Daniel Alves Bulzico, MD, MSc,* Douglas de Carvalho Leal, MD,§*
*Bruno Vilhena, MD,|| Mario Vaisman, MD, PhD,‡ Michel Carneiro, MD,† and Rossana Corbo, MD, PhD**

Clin nuclear med 2015

16 patients inclus : progression >20% dans les 6 mois
ou apparition de nouvelles lésions cibles +CT et ACE en augmention (TDM +IRM hép)
et Octréoscan +
9 patients octréo + : 1 refus;1 décès donc 7 ont reçu Lu

Evaluation tumorale 8 à 12 mois après

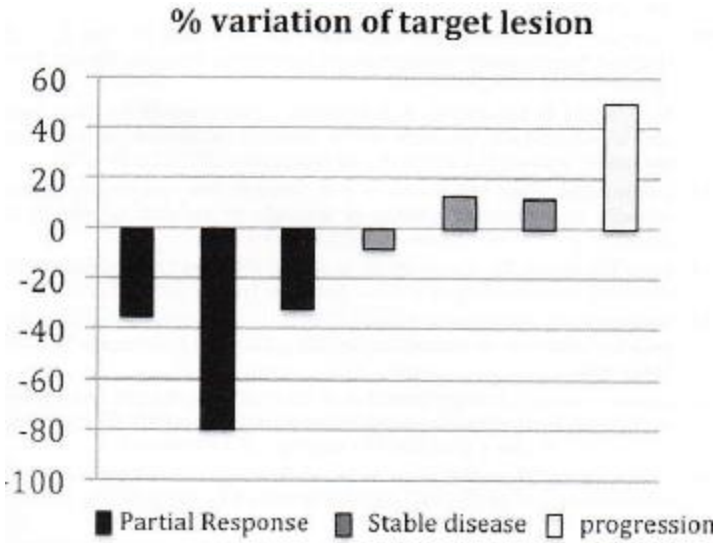


FIGURE 1. Target lesion variation by RECIST 1.1 criteria.

Aucune complication rénale ou hémato

Groupe d'étude des Tumeurs Endocrines

NEM 1

Groupe d'étude des Tumeurs Endocrines

MEN1 disease occurring before 21 years old. A 160-patient cohort study from the GTE (Groupe d'étude des Tumeurs Endocrines).

P. Goudet[1], A. Dalac[2], A. Le Bras [3], C. Cardot-Bauters[4], P. Niccoli[5], N. Lévy-Bohbot[2], H. du Boullay[6], X. Bertagna[7], P. Ruszniewski[8], F. Borson-Chazot[9], B. Vergès[10], JL. Sadoul[11], F. Ménégaux[12], A. Tabarin[13], JM. Kühn[14], P. d'Anella[15], O. Chabre[16], S. Christin-Maitre[17], G. Cadiot[18], C. Binquet[19], B. Delemer[2]

JCEM 2015

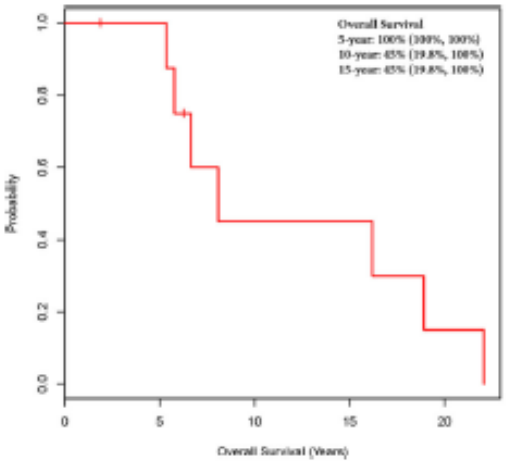
Table 2. Lesions, clinical symptoms and operation rates depending on age

Categories of age	Clinical features	pHPT	Pituitary adenoma	Insulinoma	Gastrinoma	NSPT	Adrenal tumors	Thymic NET
1 to 5 yr	Clinical symptoms	0 (0%)		1 (100%)			1 (100%)	
	Operated cases*	0		1			1	
	Total	**3**		**1**			**1**	
6 to 10 yr	Clinical symptoms	2 (22%)	0 (0%)	4 (100%)	1 (100%)			
	Operated cases*	1	0	3	1			
	Total	**9**	**2**	**4**	**1**			
11 to 15 yr	Clinical symptoms	3 (8%)	9 (36%)	7 (100%)		0 (0%)		
	Operated cases*	5	4	1		4		
	Total	**39**	**25**	**7**		**5**		
16 to 20 yr	Clinical symptoms	16 (22%)	24 (86%)	8 (100%)	2 (100%)	0 (0%)	1 (100%)	1 (100%)
	Operated cases*	32	5	13	0	1	1	1
	Total	**71**	**28**	**8**	**2**	**9**	**1**	1
Total	Clinical symptoms	21 (17%)	30 (55%)	20 (100%)	3 (100%)	0 (0%)	2 (100%)	1 (100%)
	Operated cases<21 yr old	38	9	18	1	5	2	1
	Total	**122**	**55**	**20**	**3**	**14**	**2**	1

Clinical Features, Treatments, and Outcomes of Patients with Thymic Carcinoids and Multiple Endocrine Neoplasia Type 1 Syndrome at MD Anderson Cancer Center

Ioannis Christakis[1] · Wei Qiu[1,2] · Angelica M. Silva Figueroa[1] · Samuel Hyde[3] · Gilbert J. Cote[3] · Naifa L. Busaidy[3] · Michelle Williams[4] · Elizabeth Grubbs[1] · Jeffrey E. Lee[1] · Nancy D. Perrier[1]

Horm Cancer 2016



9 C Thymique / 291 NEM1

Très mauvais pronostic.

Métastases synchrones : 21%

métachrones: 89%

Thymic and Bronchial Carcinoid Tumors in Multiple Endocrine Neoplasia Type 1: The Mayo Clinic Experience from 1977 to 2013

Naykky Singh Ospina[1] · Geoffrey B. Thompson[2] · Francis C. Nichols III[3] · Stephen D. Cassivi[3] · William F. Young Jr[1]

Horm Cancer 2015

348 patients NEM1 : prévalence des carcinoïdes bronchiques: 4,9%

des carcinoïdes thymiques : 2 % (2,6%de 761 NEM1 GTE 2009)

(8% de 85 si prospectif :NIH Gibril 2003

Table 4 Clinical features of thymic (TC) and bronchial carcinoid (BC) tumors in multiple endocrine neoplasia type1 (MEN1)

Feature	BC (n=13)	TC (n=7)
Mean age at diagnosis, years	45.1	43.0
Men, %	61 %	100 %
BC or TC as initial feature of MEN1	31 %	14.3 %
Symptoms at diagnosis	23.1 %	57.1 %
Death [a]	0 %	57.1 %
Distant metastasis	0 %	57.1 %

[a] In the BC tumor group, there were two deaths of unknown cause. In the TC group, the cause of death in one patient was unknown

Symptômes : BC : toux,dyspnée ; en fait ,77% par le seul screening,,

TC : douleur thoracique 4/7

Bronchopulmonary Neuroendocrine Neoplasms and Their Precursor Lesions in Multiple Endocrine Neoplasia Type 1

Detlef K. Bartsch[a] Max B. Albers[a] Caroline L. Lopez[a] Jonas C. Apitzsch[b]
Eduard M. Walthers[b] Ludger Fink[c] Volker Fendrich[a] Emily P. Slater[a]
Jens Waldmann[a] Martin Anlauf[c]

Neuroendocrinology 2015

Prévalence des T bronchiques carcinoides: 6,6% /75NEM1); 7 à 32 mm après un suivi moyen de 134 mois,
En réalité 30% d'images compatibles avec CB si seuil >3mm
Toutes asymptomatiques
Bien diff.pour 5 opérés , 2/5 métas.ganglions , 1 décès

Unraveling the intrafamilial correlations and heritability of tumor types in MEN1: a Groupe d'étude des Tumeurs Endocrines study

J Thevenon, A Bourredjem[1,2], L Faivre, C Cardot-Bauters[3], A Calender[4], M Le Bras[5], S Giraud[4], P Niccoli[6], M F Odou[7], F Borson-Chazot[8], A Barlier[9,10], C Lombard-Bohas[11], E Clauser[12,13], A Tabarin[14], E Pasmant[15], O Chabre[16], E Castermans[17], P Ruszniewski[18], J Bertherat[19], B Delemer[20], S Christin-Maitre[21], A Beckers[22], I Guilhem[23], V Rohmer[24], B Goichot[25], P Caron[26], E Baudin[27], P Chanson[28,29], L Groussin[30,31], H Du Boullay[32], G Weryha[33], P Lecomte[34], F Schillo[35], H Bihan[36], F Archambeaud[37], V Kerlan[38], N Bourcigaux[26], J M Kuhn[39], B Vergès[40], M Rodier[41], M Renard[33], J L Sadoul[42], C Binquet[1,2,43,44] and P Goudet[1,2,43,44,45]

EJE 2015

Table 3 Heritability estimates for seven clinical features of MEN1 (GTE cohort, 797 patients, 2014).

	Heritability		
	Estimate	(±s.d.)	*P*
Parathyroid	88%	(±0.18)	<0.001
Pancreatic	37%	(±0.14)	0.001
Pituitary	64%	(±0.13)	<0.001
Adrenal	65%	(±0.21)	<0.001
Bronchial	60%	(±0.35)	0.037
Thymic	97%	(±0.41)	0.006
Metastasis	19%	(±0.16)	0.104

797 NEM1 dans 265 familles

Très forte hérédité des tumeurs thymiques

Mais l'héritabilité diminue au fil des générations

EUS is superior for detection of pancreatic lesions compared with standard imaging in patients with multiple endocrine neoplasia type 1 (CME)

Sophie J. van Asselt, MD, PhD,[1,2] Adrienne H. Brouwers, MD, PhD,[3] Hendrik M. van Dullemen, MD, PhD,[4] Eric J. van der Jagt, MD, PhD,[5] Alfons H. H. Bongaerts, MD,[2,3] Ido P. Kema, PhD,[6] Klaas P. Koopmans, MD, PhD,[7] Gerlof D. Valk, MD, PhD,[8] Henri J. Timmers, MD, PhD,[9] Wouter W. de Herder, MD, PhD,[10] Richard A. Feelders, MD, PhD,[10] Paul Fockens, MD, PhD,[11] Wim J. Sluiter, PhD,[1] Elisabeth G. E. de Vries, MD, PhD,[2] Thera P. Links, MD, PhD[1]

Groningen, The Netherlands

(Gastrointest Endosc 2015;81:159-67

SJ van Asselt et coll 2015 : 41 NEM1 (35 avec T):
EUS est > aux autre méthodes diagnostiques

TABLE 4. Positive imaging for pancreatic lesions in 35 patients

Imaging modality	Patients no. (%)	*P* value	Lesions no. (%)	*P* value	Lesions > 1 cm no. (%)	*P* value
CT/MRI	14 (40)	–	24 (22)	–	17 (46)	–
SRS	12 (34)	–	13 (12)	–	11 (30)	–
CT/MRI + SRS	18 (51)	–	32 (30)	–	23 (62)	–
^{11}C-5-HTP PET	19 (54)	1*	35 (32)	.74*	19 (51)	.45*
EUS	34 (97)	< .001*	101 (94)	< .001*	36 (97)	< .01*

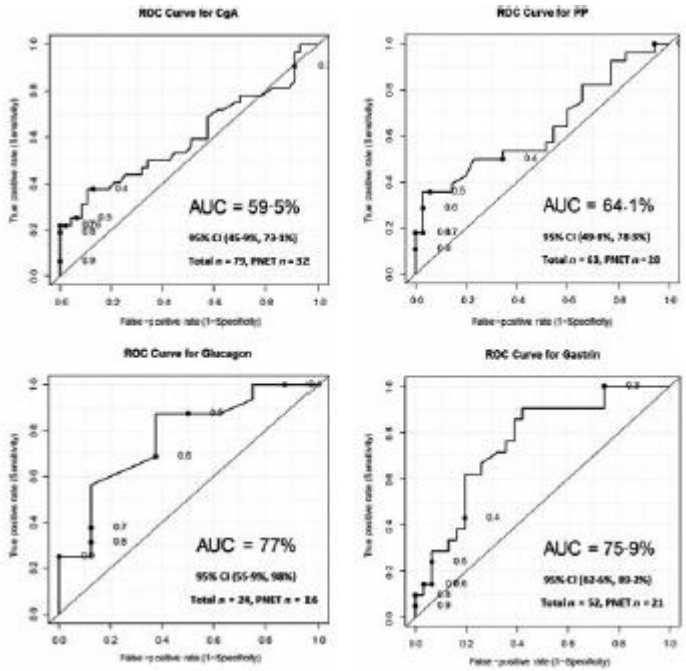
MRI, Magnetic resonance imaging; *SRS*, somatostatin receptor scintigraphy; *^{11}C-5-HTP PET*, ^{11}C-5-hydroxytryptophan positron emission tomography.
*For ^{11}C-5-HTP and EUS, discordance was calculated for the no. of visualized lesions, compared with CT/MRI + SRS.

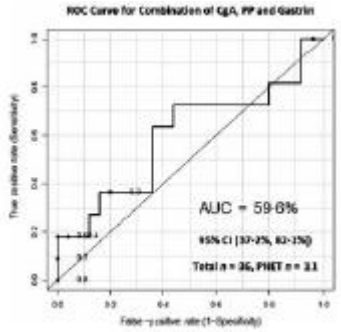
Rappel de l'étude du GTE C.Barbe et coll Digestive and Liver Disease 2012
90 patients NEM1 :EUS et IRM sont complémentaires ;
T >10mm non identifiées: EUS :15,7% IRM: 19,3%

Utility of chromogranin A, pancreatic polypeptide, glucagon and gastrin in the diagnosis and follow-up of pancreatic neuroendocrine tumours in multiple endocrine neoplasia type 1 patients

Wei Qiu*·†, Ioannis Christakis*, Angelica Silva*, Roland L. Bassett Jr‡, Liyun Cao§, Qing H. Meng§, Elizabeth Gardner Grubbs*, Hua Zhao¶, James C. Yao**, Jeffrey E. Lee* and Nancy D. Perrier*

Clin Endoc 2016





MD Anderson center cancer
293 NEM1 dont 55 PNET
Même combinés ces 4 dosages sanguins ont une faible valeur diagnostique

TEP Ga68 :la panacée dans l'exploration des NEM1 ?

Results of ^{68}Gallium-DOTATATE PET/CT Scanning in Patients with Multiple Endocrine Neoplasia Type 1

Samira M Sadowski, MD, Corina Millo, MD, Candice Cottle-Delisle, RN, Roxanne Merkel, RN, Lily A Yang, BS, Peter Herscovitch, MD, Karel Pacak, MD, William F Simonds, MD, Stephen J Marx, MD, Electron Kebebew, MD, FACS

J Am Coll Surg 2015

Role of ^{68}Ga-DOTATATE PET/CT in patients with multiple endocrine neoplasia type 1 (MEN1)

Secondo Lastoria[1] · Francesca Marciello[2] · Antongiulio Faggiano[2] · Luigi Aloj[1] · Corradina Caracò[1] · Michela Aurilio[1] · Laura D'Ambrosio[1] · Francesca Di Gennaro[1] · Valeria Ramundo[2] · Luigi Camera[3] · Leonardo De Luca[4] · Rosa Fonti[5] · Vincenzo Napolitano[6] · Annamaria Colao[2]

Endocrine 2015

Italie :Lastoria...

Etude prospective de 18 apparentés NEM1 +

Explo par CT,EUS,US cervicale,IRM hypoph. Et TEPGa68:

Ga : TNEP 15/15

Ad hypoph.9/12

T surrénale5/8

PTH 5/18

USA :Sadowski…

26 NEM1 connues , suivis; étude prospective;

TEP Ga_{68} > à CT et Octréo (analyse en aveugle)

Chez 10 patients les métas n'étaient pas vues sur octréo

Dans 31 % des cas cela a modifié la décision thérapeutique

Table 2. Concordance of Imaging Study Results per Lesion Analysis

Variable	CT	^{111}In- pentetreotide	DOTATATE
CT, n	48	19	48
^{111}In-pentetreotide, n	—	33*	32
DOTATATE, n	—	—	107

Evaluation of ^{68}Ga-DOTA-TOC PET/CT for the detection of duodenopancreatic neuroendocrine tumors in patients with MEN1

Clément Morgat[1,2,3] · Fritz-Line Vélayoudom-Céphise[4] · Paul Schwartz[3] · Martine Guyot[3] · Delphine Gaye[5] · Delphine Vimont[1,2] · Jürgen Schulz[1,2] · Joachim Mazère[1,2,3] · Marie-Laure Nunes[4] · Denis Smith[6] · Elif Hindié[1,2,3] · Philippe Fernandez[1,2,3] · Antoine Tabarin[4]

Eur.J.Nucl.Med.Mol.Imaging 2016

19 patients

Sensibilités : Ga68 Dota Toc 76%
CT 60%
Octréoscan 20%

GTE

Groupe d'étude des Tumeurs Endocrines

RENATEN

RÉseau NAtional de prise en charge des Tumeurs neuro-ENdocrines Malignes Rares Sporadiques et Héréditaires

TENpath