CANCERS DIFFERENCIES DE LA THYROIDE REFRACTAIRES

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GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

TUmeurs THYroïdiennes Réfractaires : TUTHYREF

CT différencié réfractaire à l'iode
Carcinome médullaire de la thyroïde métastatique
Carcinome anaplasique de la thyroïde

TUTHYREF

INSTITUT NATIONAL DU CANCER

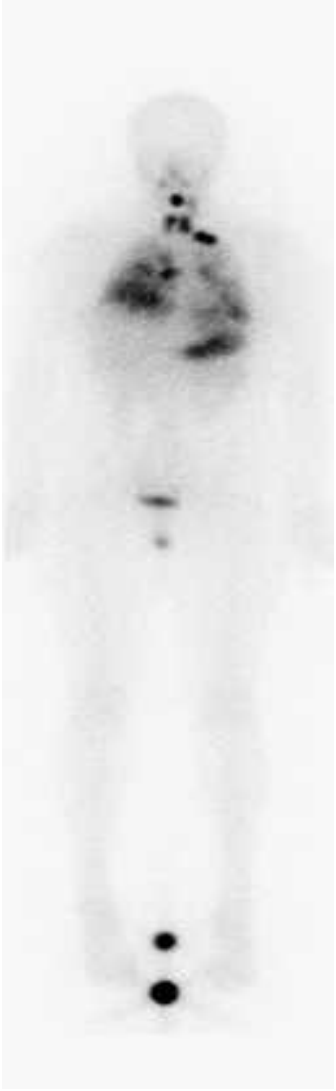
Epidémiologie en quelques chiffres

	Incidence (/100 000)			Mortalité (/100 000)		
	1980	**2012**	**Nbre cas en 2012**	**1980**	**2012**	**Nbre DC/cancer en 2014**
Femme	3,5	17	5900	0,88	0,41	228
Homme	1,4	4	2300	0,63	0,40	173

Courtesy C Hill, Davies 2006, **http://seer.cancer.gov/statfacts/html/thyro.html**

Métastases à distance des cancers différenciés de souche folliculaire

- **Chez moins de < 10% des patients**
- Présentes au diagnostic initial : 50%
- Poumons, Os ++
- Fixation iode 131: 2/3 des cas



Durante et al. 2006

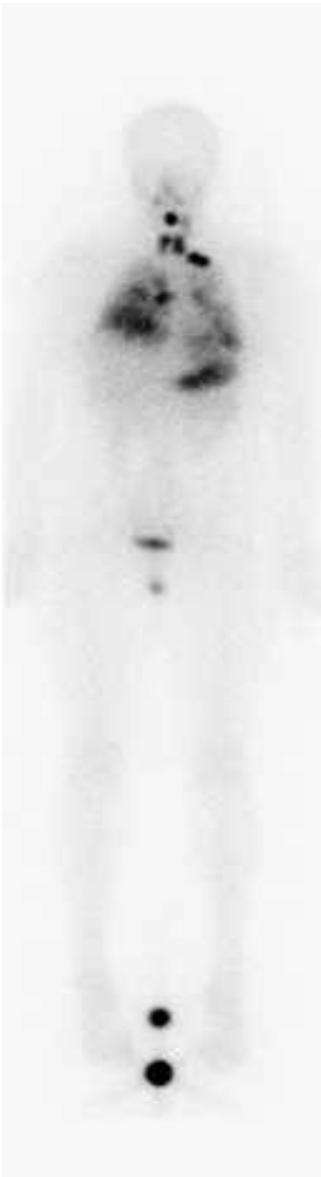
Traitements des métastases à distance par Iode 131

- **Si Fixation d'I 131 :** Traitements successifs tous les 6 mois pendant 2 ans (puis tous les ans) tant que persistent des fixations de l'131I sur la SCE post-thérapeutique

- LT4 à dose suppressive entre 2 traitements

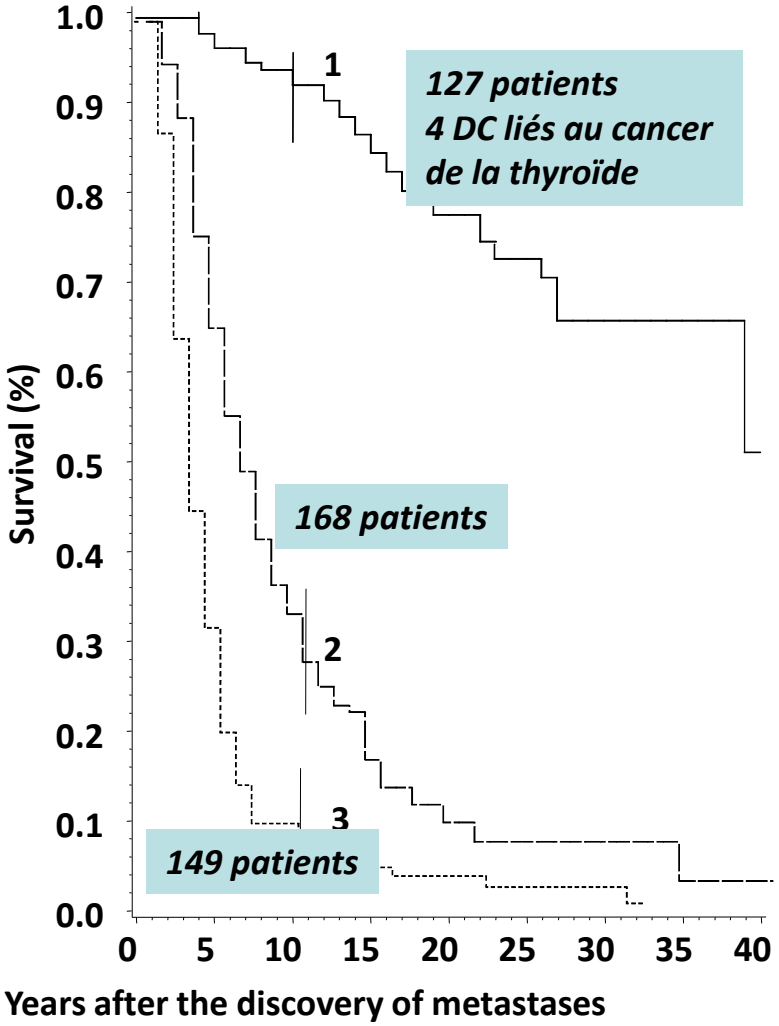
  – Réponse complète après Iode 131 : 43%

  → **1/3 des patients sont guéris par l'I131**



Durante et al. 2006.

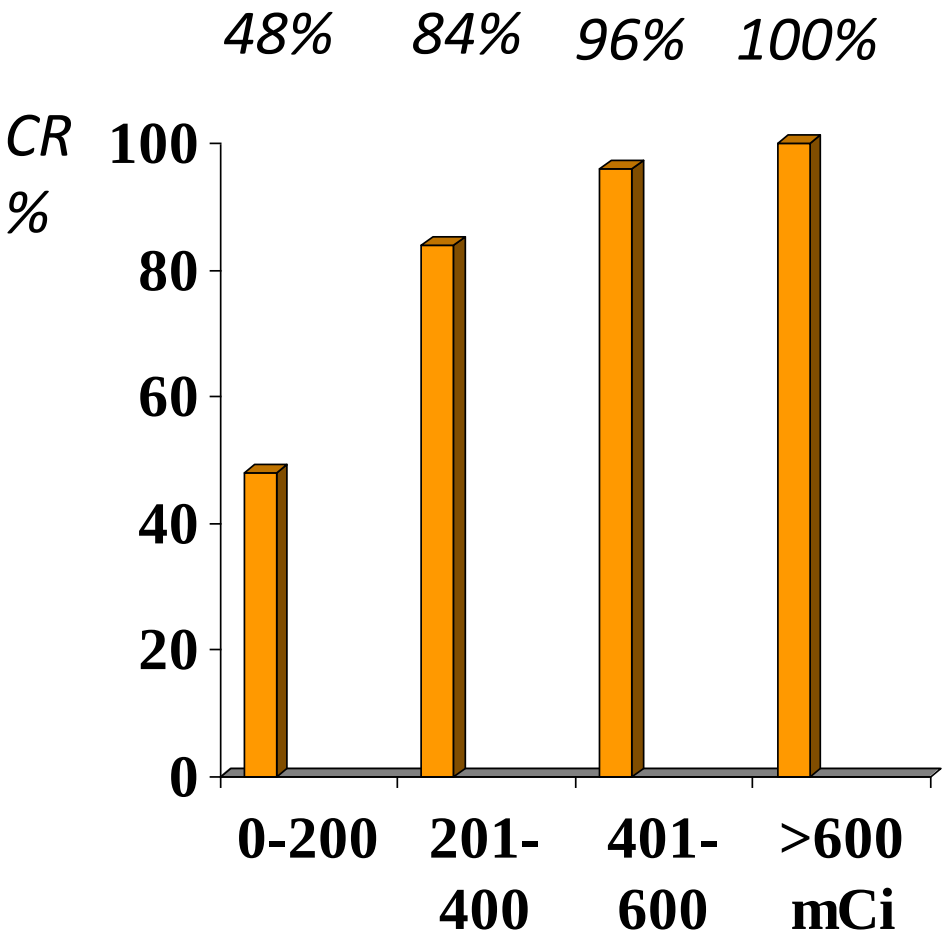
Survie et Réponse au traitement



- Groupe 1: Fixation d'iode et réponse complète:
  - Age < 40 years
  - Cancer bien différencié
  - Petites taille des métastases
- Groupe 2: Fixation d'iode et persistance de fixation
- Groupe 3: pas de fixation d'iode

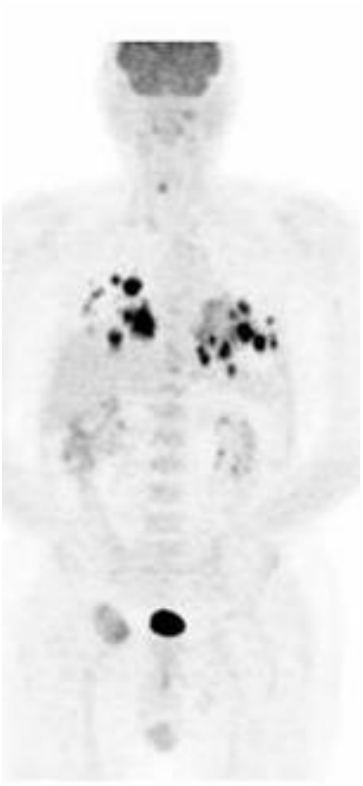
Durante et al. J Clin Endocrinol Metab. 2006;91:2892-2899.

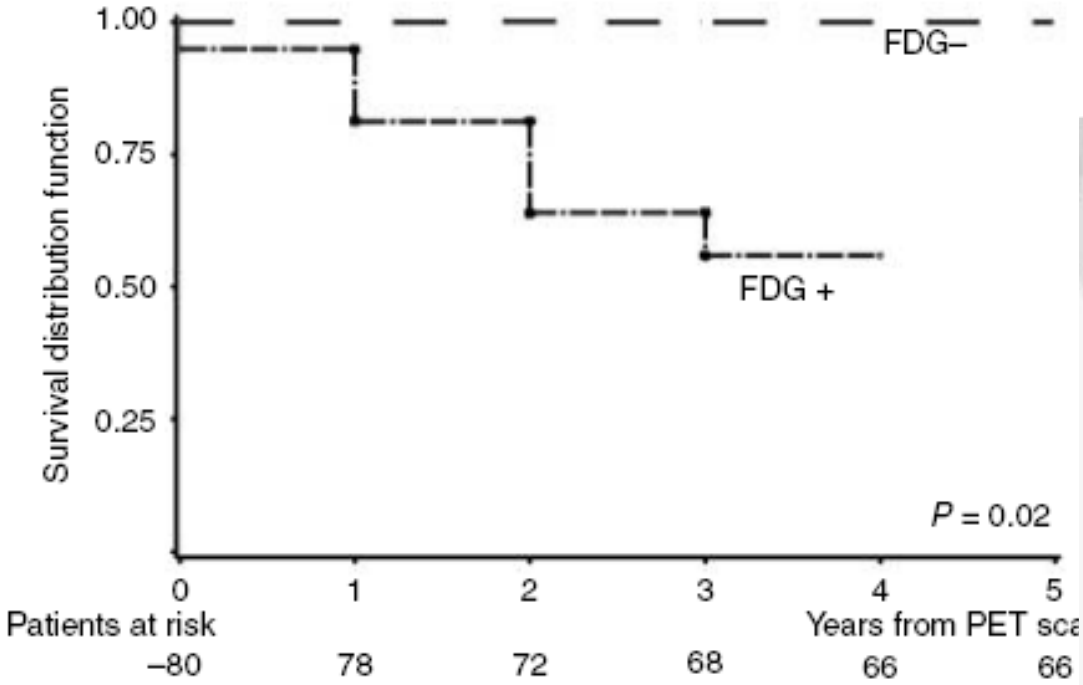
Taux de rémission complète selon l'activité cumulée d'Iode 131

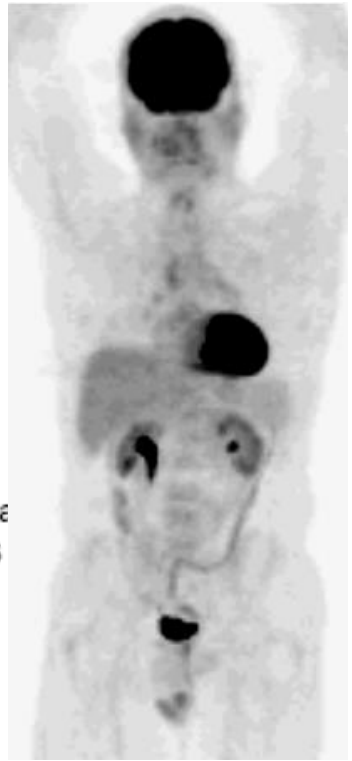


96% des CR sont obtenus avec une activité de 600mCi ou moins.

FDG PET-CT : un facteur pronostic de survie







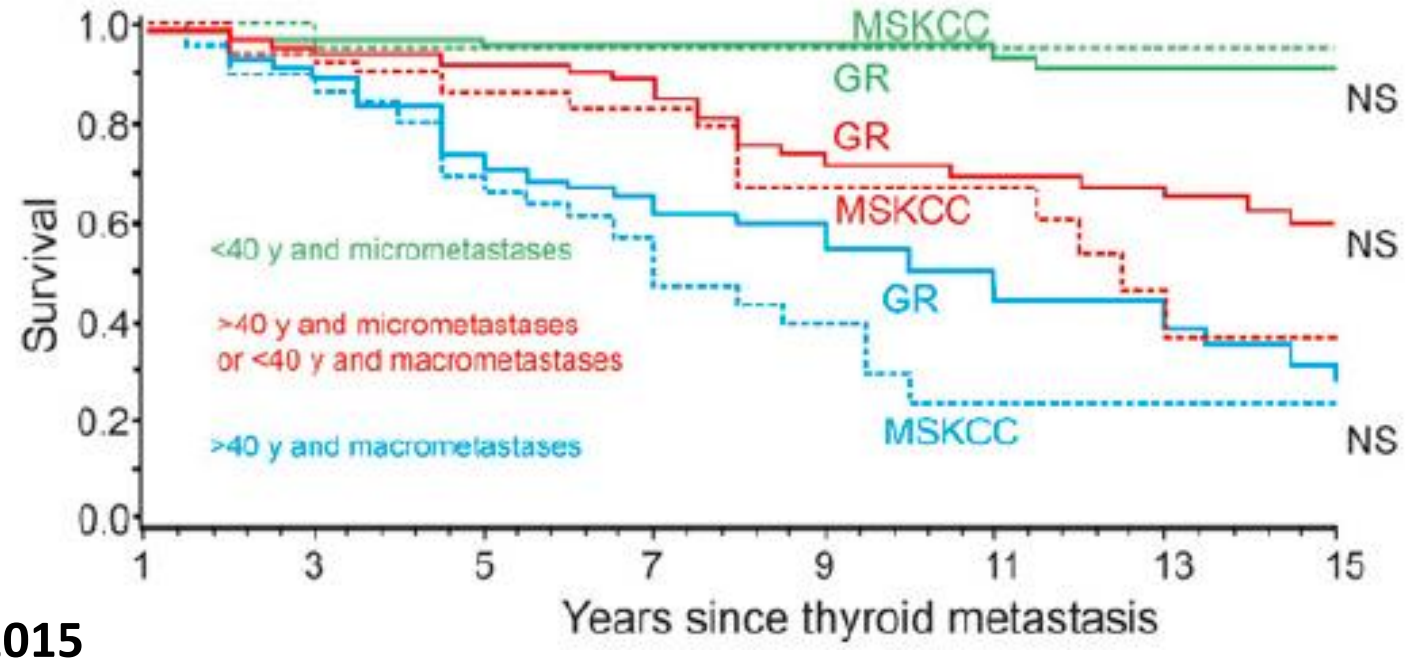
Survie à 2 ans: 60% vs 100%

Deandreis et al, Endocr Relat Cancer 2011

Effect of RAI activity / dosimetry

GR: 231 pts, Fixed repeated activity,
median cumulative activity of 14.8 GBq (range, 1.8–52.5 GBq)

MSKCC :121 pts, personalized activity (2.7–18.6 GBq) based on whole-body/-blood clearance (WB/BC) dosimetry
median cumulative activity of 24.2 GBq (range, 2.7–112 GBq) (P , 0.0001).



Deandreis et al 2015

2 groupes de patients avec métastases à distance de CTD

I131

- **1/3 des patients :**
- **Fixation d'I131**
- **Age jeune**
- **Petites métastases**
- **Tumeurs bien différenciées**

Guérison avec I131

- **2/3 des patients :**
- **Peu ou pas de fixation d'I131**
- **Age élevé**
- **Volumineuses métastases**
- **Tumeurs peu différenciées**
- **Fixation élevée de FDG**

Réfractaire à l'I131

Si progression selon critères RECIST,
Besoin de traitement

CTD réfractaires : définition

- **Absence de fixation d'iode 131 dans l'ensemble des lésions (au diagnostic initial ou en cours de traitement)**
- **Fixation dans certaines lésions mais pas toutes**
- **Progression dans les 12 mois qui suivent un traitement par iode 131**
- **Discussion: maladie persistante après une administration cumulée d'iode 131 de 600 mCi**

→ **Poursuite des traitements par iode au cas par cas**

Schlumberger M et al. Lancet Diabetes & Endocrinol, 2014

Prise en charge des CTD réfractaires

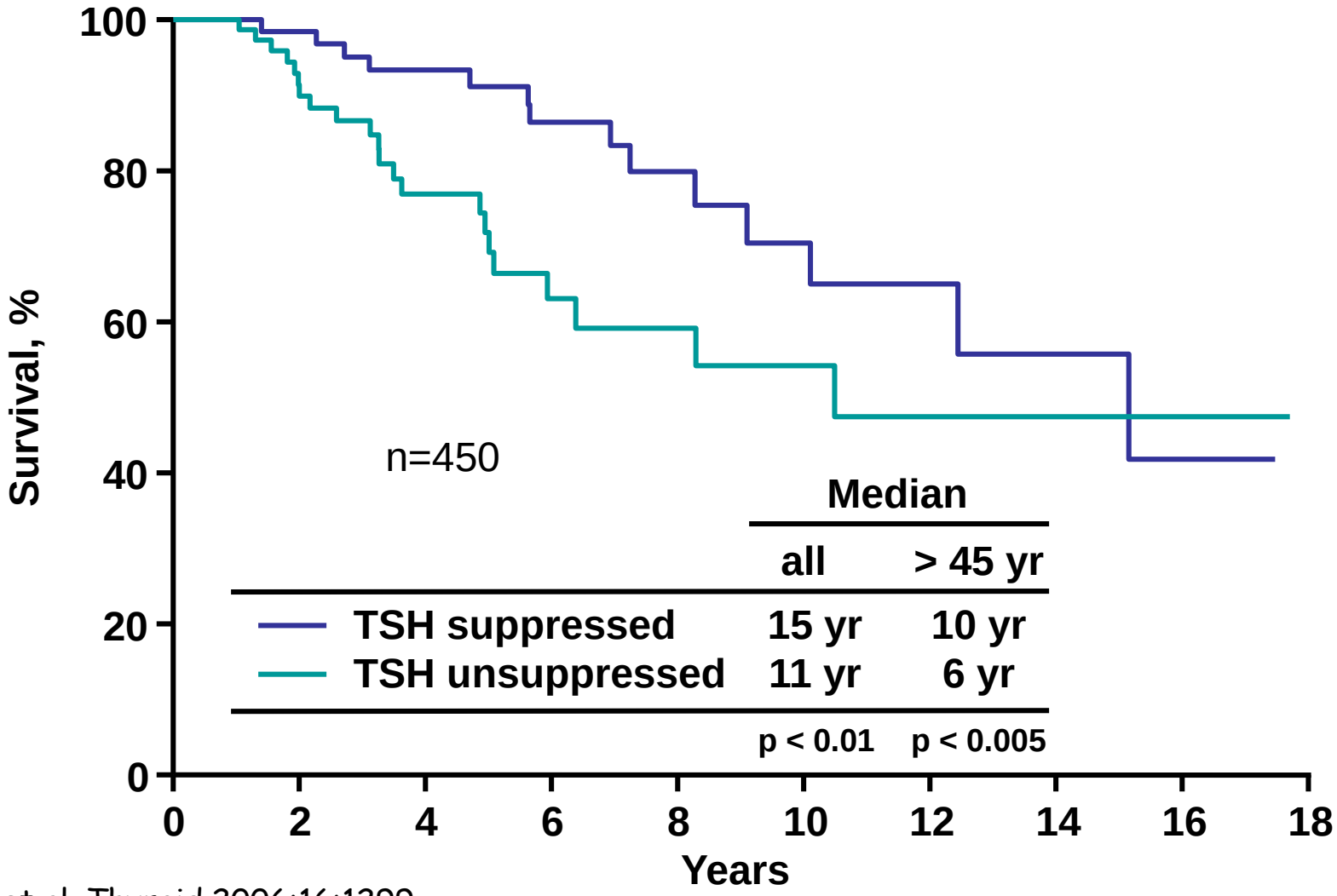
- Traitement par L-T4: TSH < 0.1 mU/L

- Traitements locaux : chirurgie, radiothérapie, radiofréquence, cryo-ablation

- Imagerie tous les 6 mois
  - Si stable: surveillance
  - Si progression (critères RECIST : ≥ 20% en 6-15 mois) : Besoin de traitements systémiques → ITK

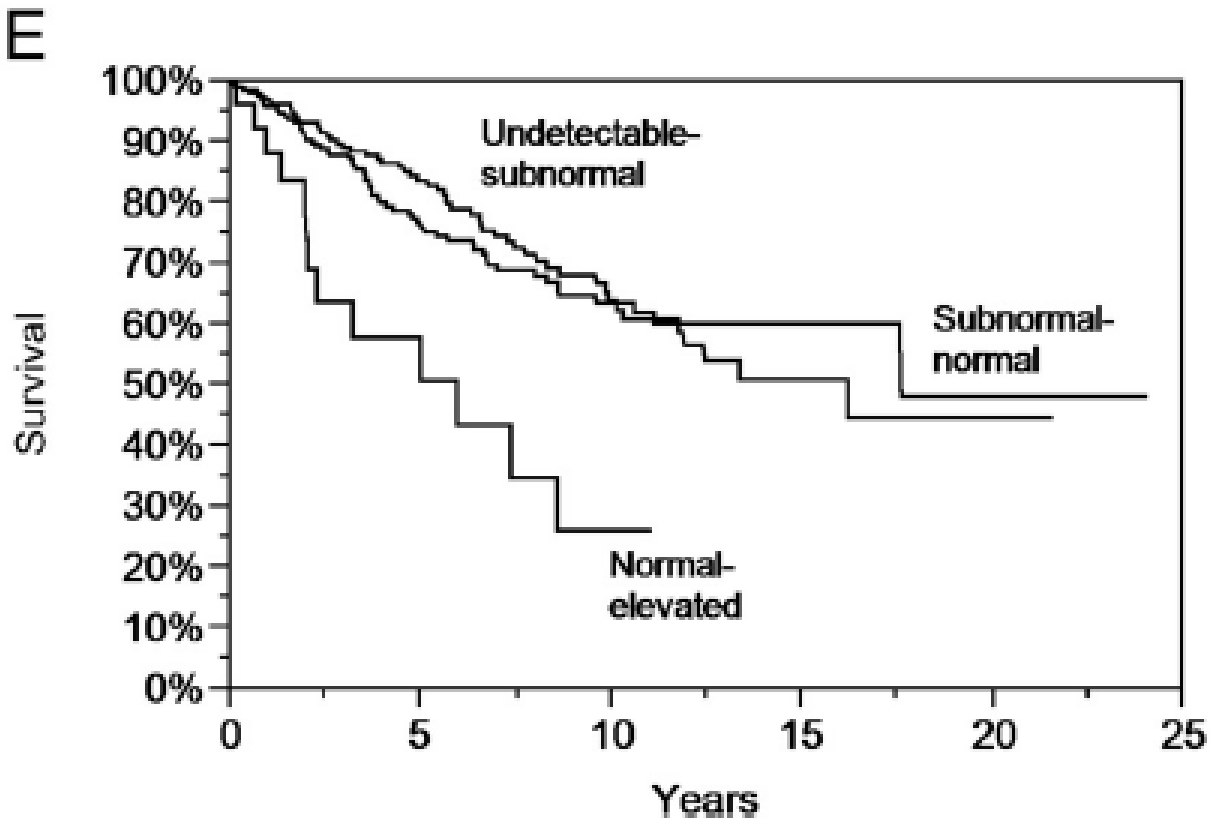
    - **Masse tumorale**
    - **Vitesse de croissance tumorale**
    - **Symptômes**
    - **Localisations des métastases à distance**
    - **Age**
    - **Co-morbidités**

LT4: Amélioration de la survie des patients M1



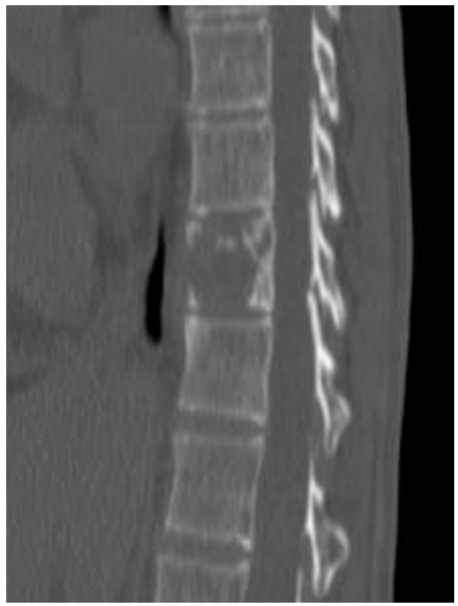
Jonklaas et al. Thyroid 2006;16:1299

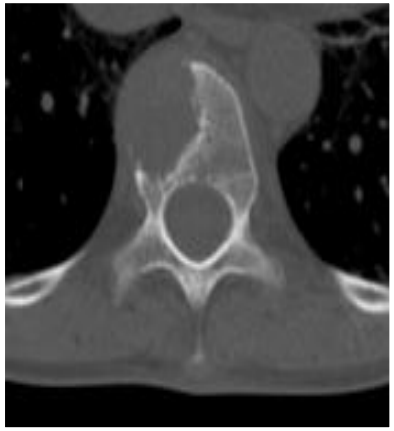
Patients M1: Freiner la TSH, mais pas trop

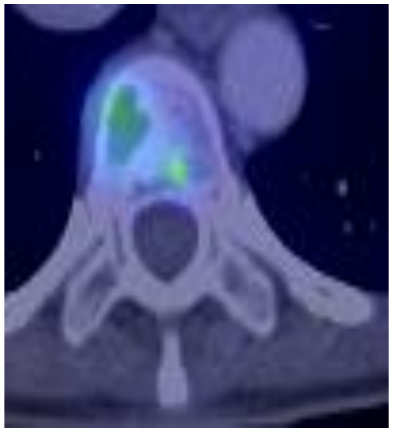


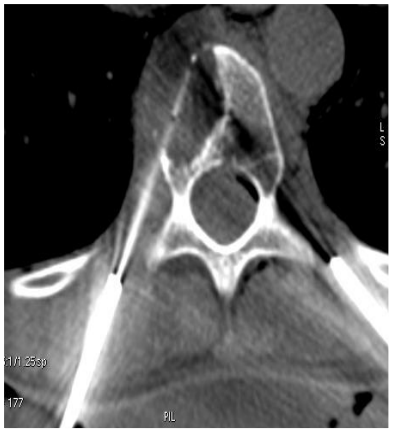
Carhill et al. JCEM 2015

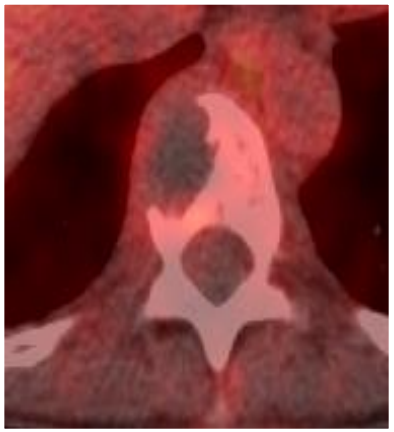
Cryoablation + Cimentoplastie = Contrôle local et consolidation

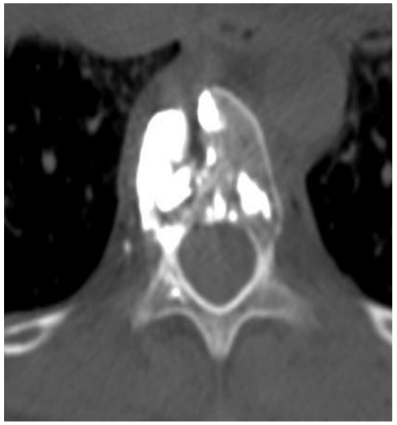


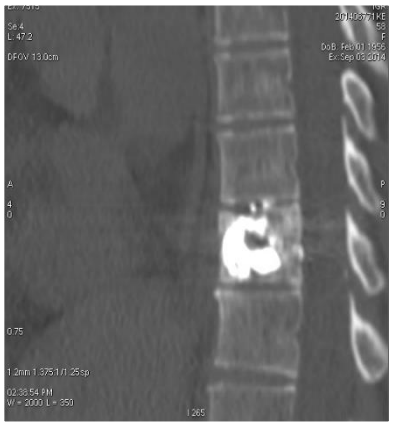






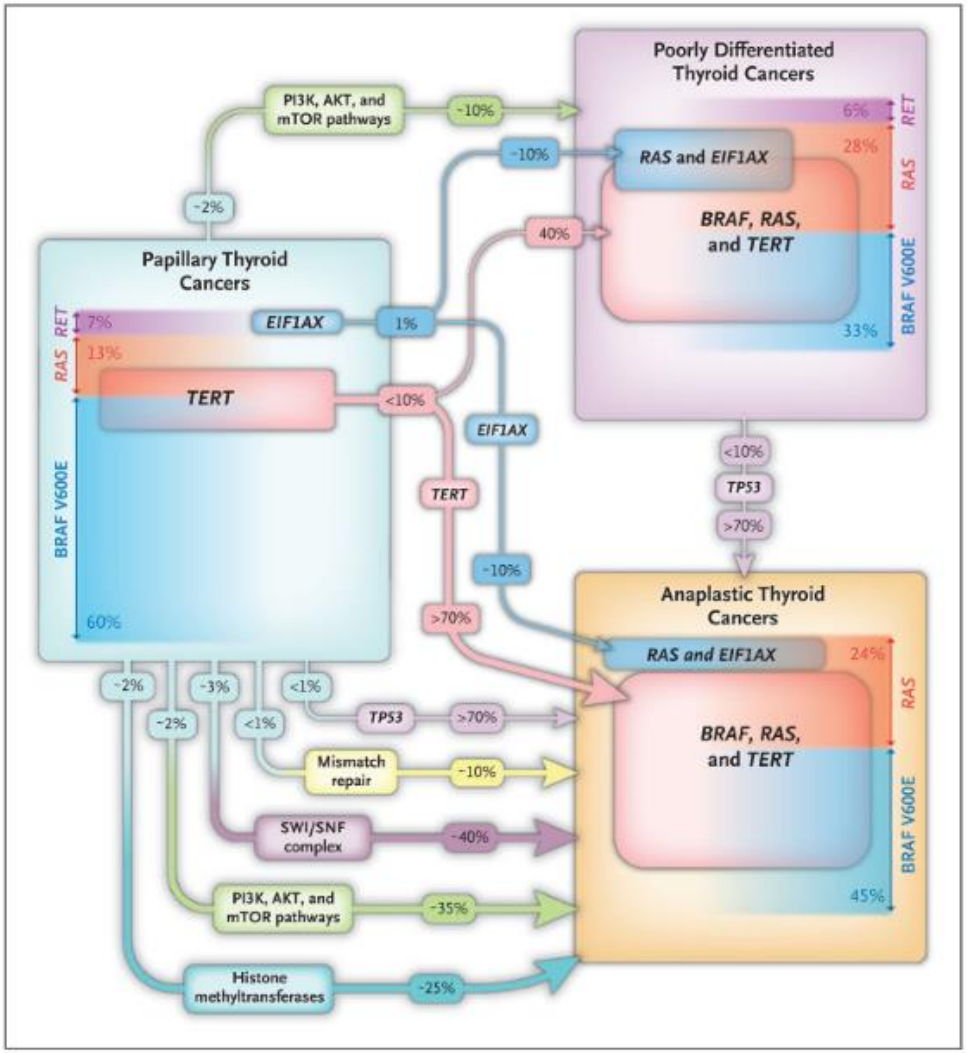






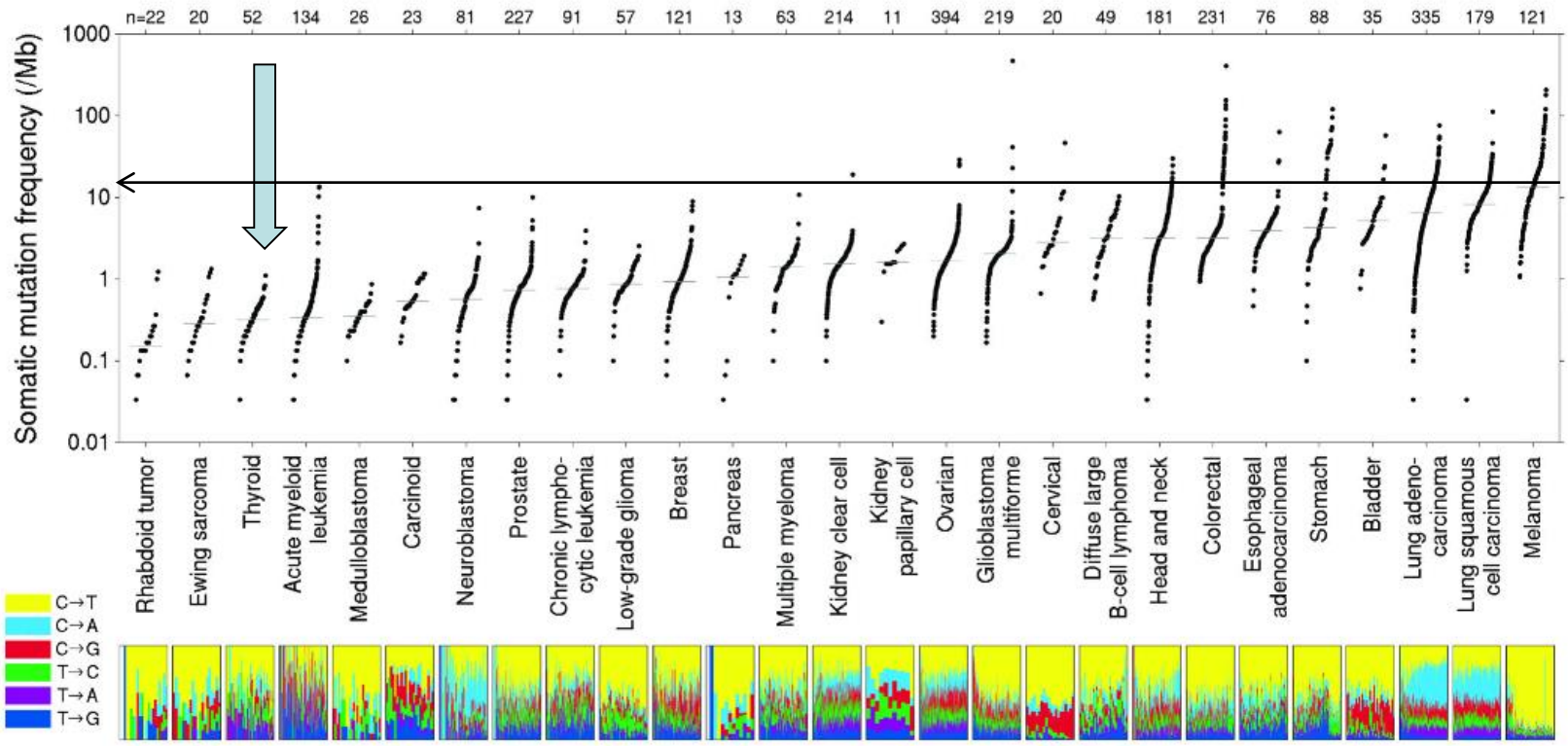
F Deschamps, GR

Carcinome thyroïdien différencié réfractaire à l'iode : Altérations génomiques somatiques



Fagin NEJM 2016

Tumor burden (whole exom sequencing) from 0 to 1/MB

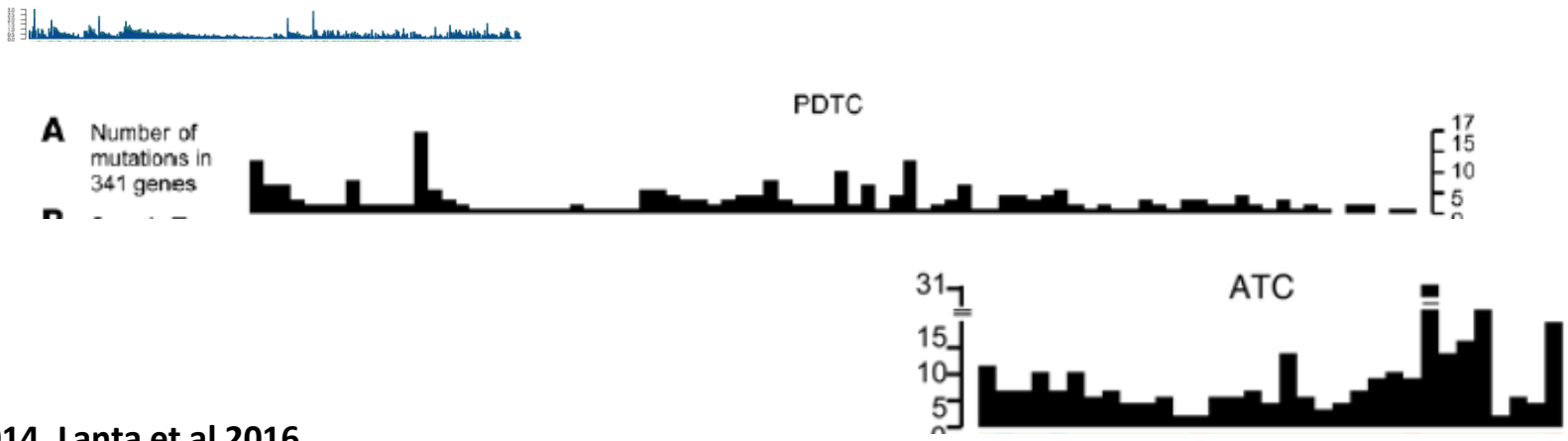


Lawrence et al 2013

Tumor Mutaion burden (whole exom sequencing)

	Cancer Genome Atlas *	Poorly Differentiated TC (Turin 62% et MSKCC 37%)	Anaplastic Thyroid Cancer
N samples	496	84	33
Median density (№ mutations/Mb)	1 +/- 1 (moyenne 0,41)	2 +/- 3	6 +/- 5

*** CPT : classic PTC 69.4%, follicular variant 21.2%, tall cell 7.5%, others 2.0%**



Giordano et al 2014, Lanta et al 2016

Carcinome thyroïdien différencié réfractaire à l'iode
MOLECULAR ALTERATIONS

Mutation	%	
BRAF	**33%**	
RAS (N> H)	28%	
PIK,AKT,MTOR pathway	10%	
TERT promoter mutation	40%	
EIF1AX	≈ 10%	
Mismatch repair	2%	
ALK mutation/translocation	≈1%	
NTRK fusions	1 %	
RET fusions	6%	in young

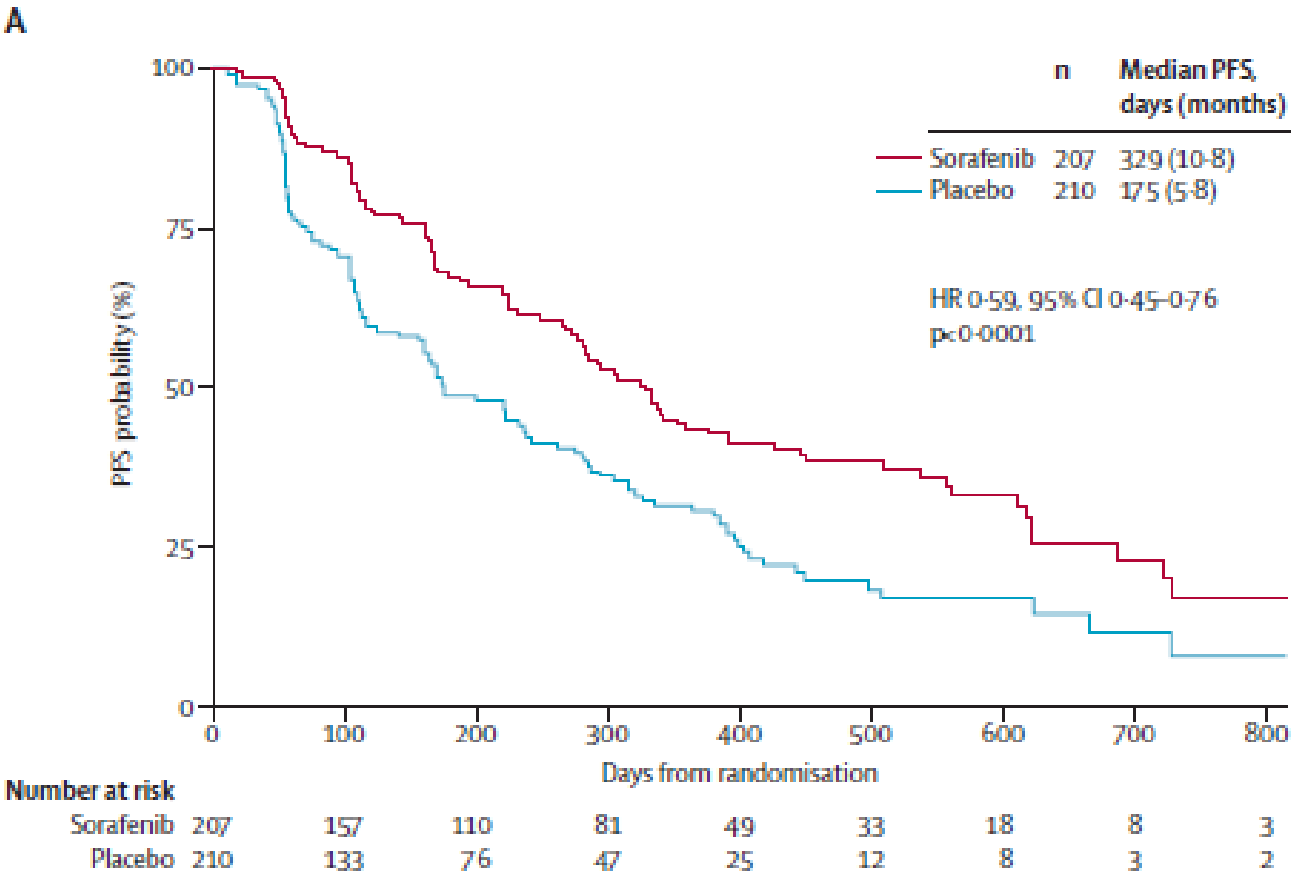
Fagin NEJM 2016, Prasad 2016, Landa 2016, Pozdeyev CCR 2018

CARCINOME THYROÏDIEN DIFFÉRENCIÉ RÉFRACTAIRE À L'IODE : ANTI VEGFR AVEC AMM

		Line	n	CR %	**PR %**	Duration of R (median, months)	PFS (median, months)
Sorafenib	DECISION Brose, 14	1	417	0	**12**	10.2	10.8 (S) vs 5.8 (P)
Lenvatinib	SELECT Schlumberger, 16	1 & 2	392	2	**65**	-	18.3 (L) vs 3.6 (P)

Sorafenib improves PFS in DTC

- **417 radioactive iodine refractory DTC patients**
- **Phase III trial, placebo vs sorafenib 1:1; 800mg/d with cross over**
- **Mutations on 256 samples: BRAF: 30%; RAS: 20%**

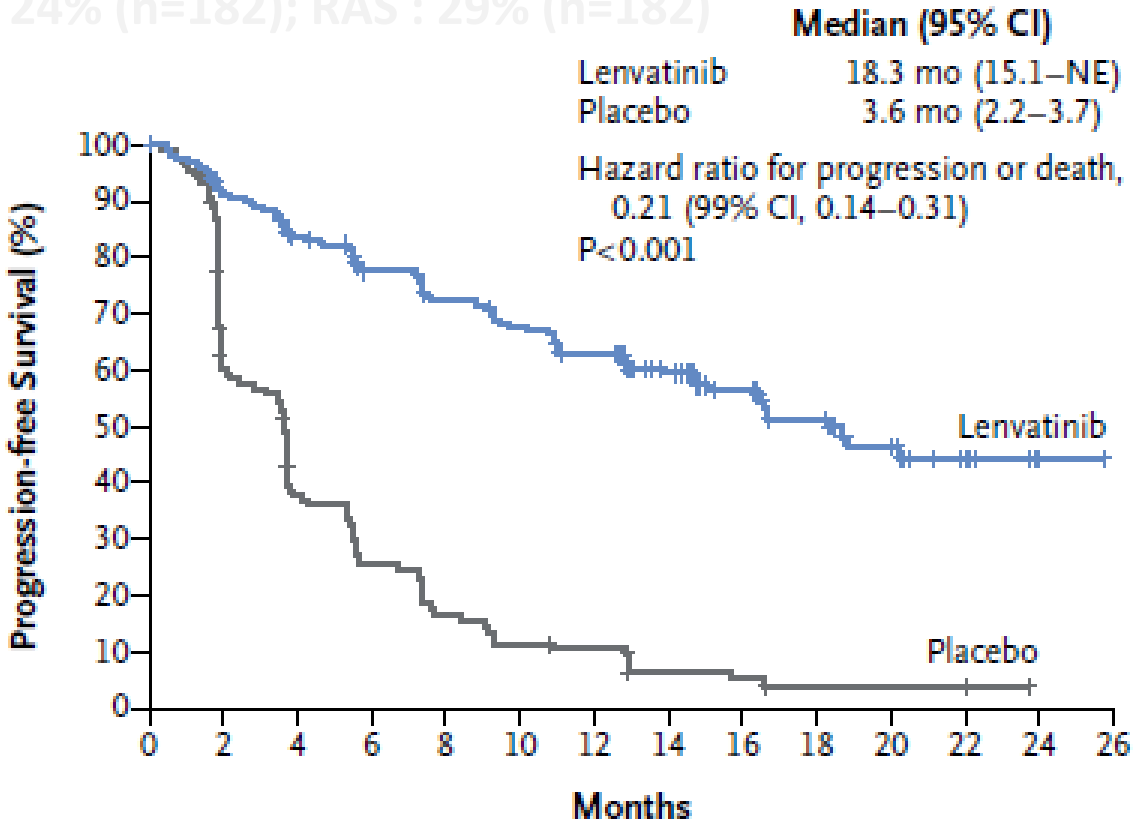


Brose et al. 2014

Response rate : 12%, length : 16.4 months (range: 7.4-16.6)

SELECT: lenvatinib improves PFS in DTC

- **392 radioactive iodine refractory DTC patients**
- **Phase III trial, placebo vs lenvatinib 2:1; 24 mg/d with cross over**
- **Mutation BRAF : 24% (n=182); RAS : 29% (n=182)**



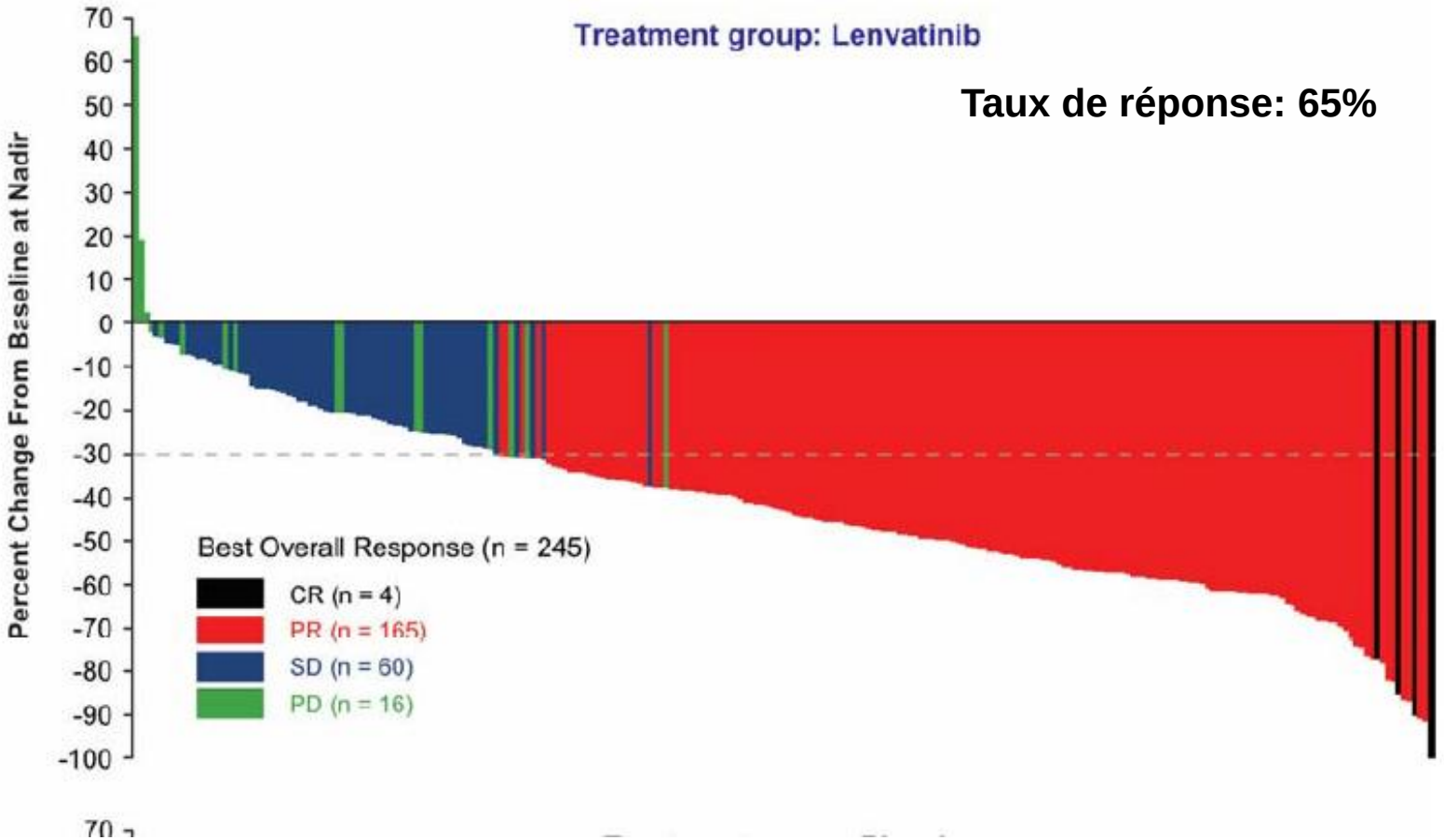
No. at Risk

Lenvatinib	261	225	198	176	159	148	136	92	66	44	24	11	3	0
Placebo	131	71	43	29	19	13	11	5	4	2	2	2	0	0

Schlumberger et al., 2015

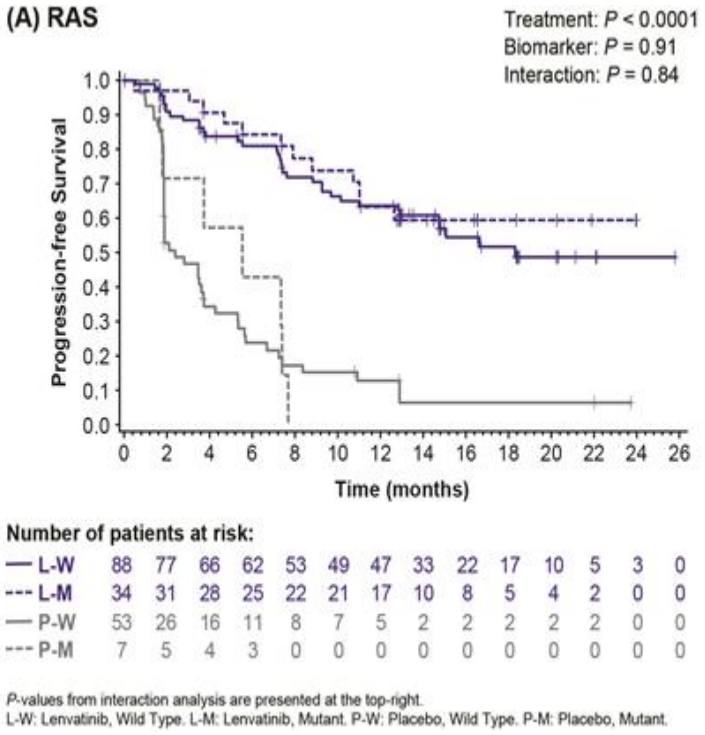
Response rate = 65%

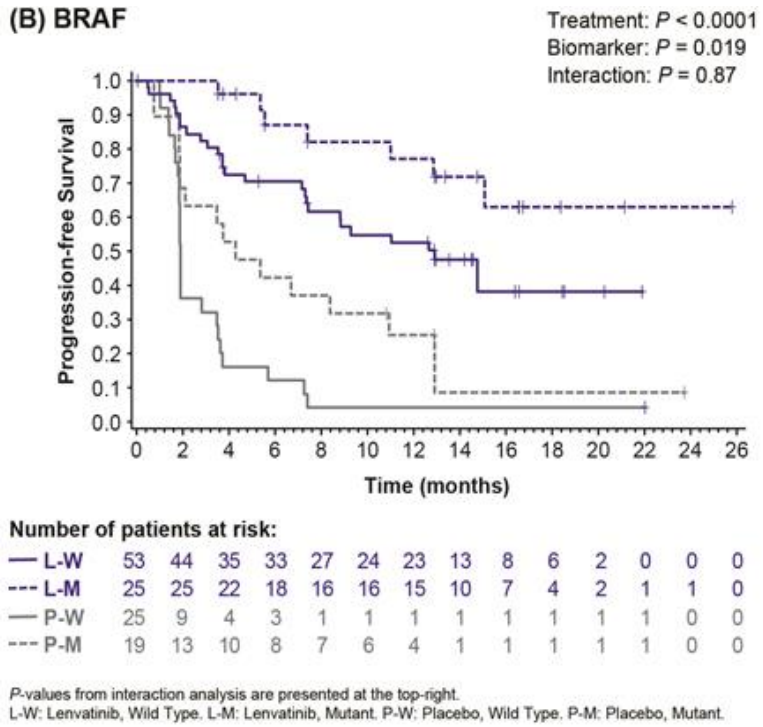
Lenvatinib (E7080) : meilleure réponse tumorale



Schlumberger et al 2015 NEJM

Lenvatinib benefits regardless of BRAF or RAS Status (PFS)

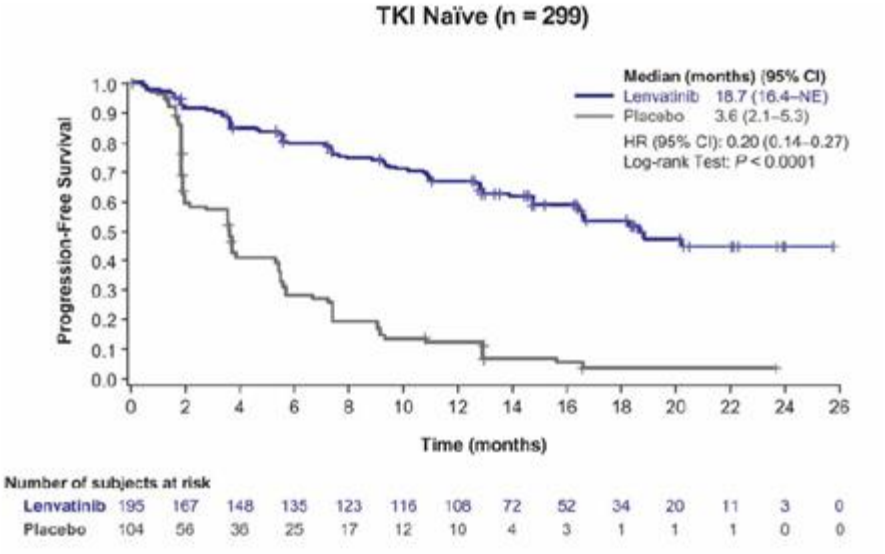


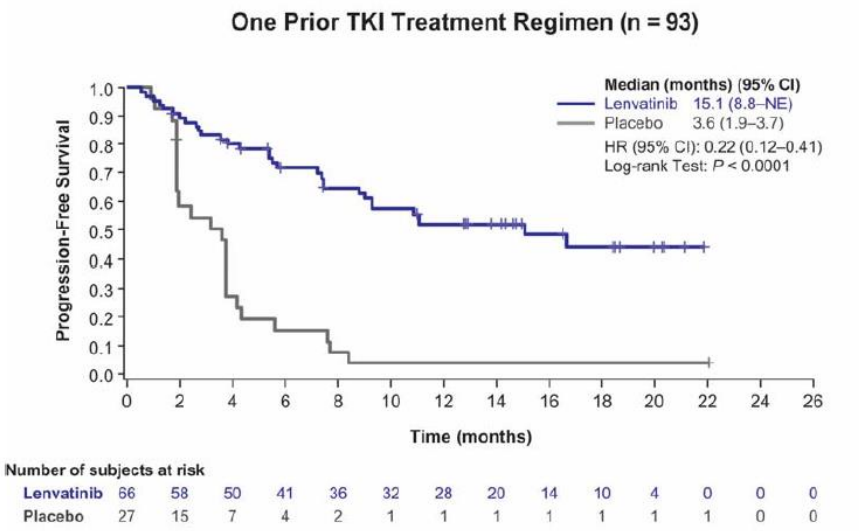


Tahara M. et al., 2016

Lenvatinib improves PFS in TKI naïve & TKI pre treated patients

	TKI naive		Other prior TKI treatment	
	lenvatinib	placebo	lenvatinib	placebo
PFS	16.7	3.6	15.1	3.6





Schlumberger et al., 2015

SELECT: PFS according to metastases sites

M1 location	Sous-groupe	n	Median PFS		HR (95% CI)
			Lenvatinib	Placebo	
Brain	Yes	16	**8.8**	**3.7**	1.00 (0.14–7.10)
	No	376	18.7	3.6	0.21 (0.15–0.28)
Bone	Yes	152	14.8	2.1	0.26 (0.16–0.42)
	No	240	20.2	3.7	0.18 (0.12–0.27)
Liver	Yes	71	7.6	3.7	0.51 (0.27–0.97)
	No	321	20.2	3.6	0.17 (0.12–0.25)
Lungs	Yes	350	18.7	3.6	0.21 (0.15–0.29)
	No	42	14.8	2.4	0.24 (0.08–0.77)
Lymph nodes	Yes	202	14.8	3.6	0.24 (0.16–0.36)
	No	190	Not estimabl	3.6	0.17 (0.11–0.27)

Other parameter studied: age, BMI: not predictive for response

Habra, MA et al. #55. 15th International Thyroid Congress, October 2015

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Toxicities

	DECISION		SELECT	
	Sorafenib	placebo	Lenvatinib	placebo
Dose reduction	64% Mean dose : 651mg	10.8	68%* Mean dose : 17.2 mg	4.6%
Dose interruption	66%	26%	82%	18%
Withdrawal	19%	4%	14%	2%

*** Median time to first dose reduction: 3 months**

Toxicities: sorafenib

	Any grade (%)		Grade 3-4 (%)
	Sorafenib (207)	Placebo (209)	Sorafenib (207)
Hand and foot syndrome	**76**	10	**20**
Diarrhea	**69**	15	6
Alopecia	**67**	8	-
Fatigue	**50**	25	6
Hypertension	**41**	12	**10**
Anorexia	**32**	2	2
Death n (drug related)	12 (1)	6 (1)	

Toxicities: lenvatinib

	Any grade	Grade 3-4
Hypertension	69%	43%
Proteinuria	32%	10%
Arterial thromboembolism	5%	3%
Renal failure	4%	2%
Hepatic failure	-	0.4%
Gastro intestinal fistula	1.5%	0.8%
QT prolongation	8%	1.5%
Posterior reversible encephalopathy Sd	0.4%	0%

Cabozantinib in DTC

- **Phase I clinical trial: Partial response : 53% (4/14)**

- **Phase II clinical trial: NCI-ITOG sponsored trial**

25 patients,
Starting dose : 60 mg/day orally (could be escalated to 80 mg in the absence of response)
Prior TKI : 1 line in 20 cases; 2 lines in 5 cases (sorafenib (52%) and pazopanib (28%))

Median PFS : 12.9 months.

Best Response	PR	SD	PD	Not Evaluable
N (%)	10 (40%)	13 (52%)	0	2 (12%)

Cabanillas et al. 2017

RAIR DIFFERENTIATED THYROID CANCER : ANTI VEGFR (+/- PDGFR, RET, MET, KIT)

		Line	n	CR %	**PR %**	Duration of R (median, months)	PFS (median, months)
Axitinib	Cohen, 08 Locati, 14 Capdevilla, 17	na na 1, 2, 3	45 45 34	0 0 6	**31** **38** **24**	Not reached 17.2 (DTC + MTC) Na	18.1 16.1 9
Sunitinib	Carr, 10	1, 2	28	3	**23**	8.0	12.8 (DTC + MTC)
Motesanib	Sherman, 08	1,2,3	93	0	**14**	8.0	10.0
Vandetanib	Leboulleux, 12 Schlumberger, 16	1 (80%)2,3 1, 2, 3	145 238	0 0	**8%** -	9.0 na	11.1 (V) vs 5.9 (P) 10.0 (V) vs 5.7 (P)
Nindetanib	Schlumberger, 18	1, 2, 3	75	0	**0**	0	2.9 (V) vs 3.1 (P)
Pazobanib	Bible, 10	1, 2, 3	39	0	49	na	11.7
Cabozantinib	Cabanillas, 17	2,3	25	0	40	11.3	12.7
Cabozantinib	Brose, 18	1	35	0	63	na	na

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PHASE III TRIAL

EXELIXIS®

CLINICAL STUDY PROTOCOL

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Cabozantinib (XL184) in Subjects with Radioiodine-Refractory Differentiated Thyroid Cancer Who Have Progressed after Prior VEGFR-Targeted Therapy

RAIR DIFFERENTIATED THYROID CANCER
ANTI BRAF as anti tumor drug

		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 & > 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

Anti BRAF Escape : HER2/HER3 activation

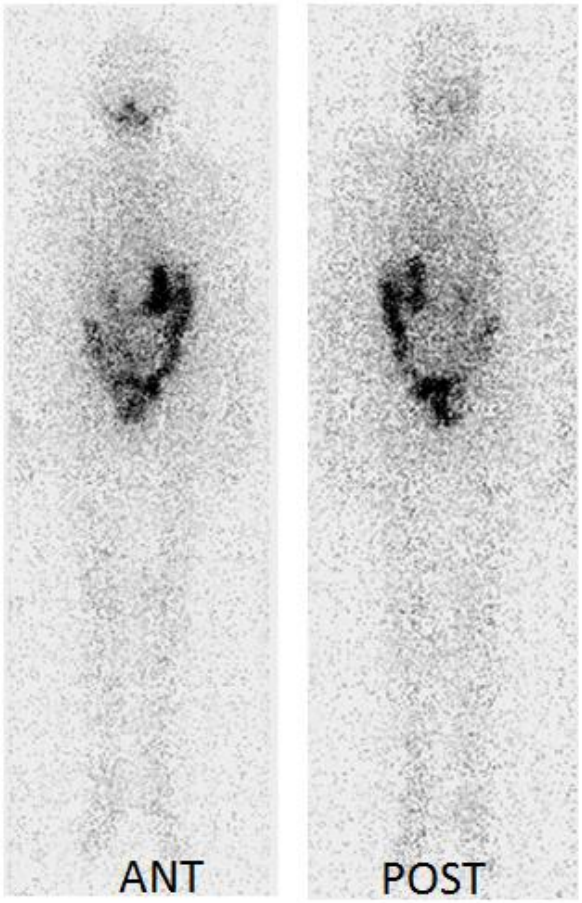
RAIR DIFFERENTIATED THYROID CANCER
ANTI BRAF and drug combination
Dabrafenib + Lapatinib

OUTCOMES

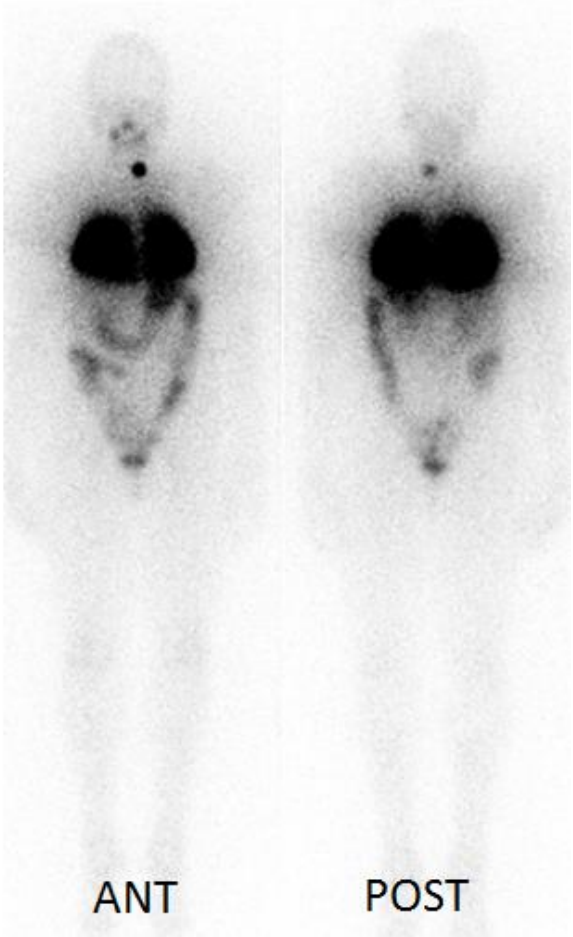
Cohort	#	DTC only	
		Response Rate	Median PFS
DTC Group only	**19**	**58%**	**18m**
1 – Lapatinib 750mg	5	60%	11m
2 – Lapatinib 1250mg	2	50%	27.5m
3 – Lapatinib 1500mg	12	58%	20m
No Prior BRAF inhibitor	14	64%	29m
No Brain Metastases	14	57%	20m
No Prior BRAF inhibitor or Brain Metastases	11	64%	29m

Sherman, ASCO 2018

RAIR DIFFERENTIATED THYROID CANCER : with anti BRAF or anti MEK in BRAF V600E or RAS mutated patient



6 weeks of
Dabrafenib/Trametinib
+ I 131/TSHrh



Best candidate : most probably, small tumor burden, slowly progressive

RAIR DIFFERENTIATED THYROID CANCER REDIFFERENTIATING AGENT

		n	Genetic	Increase in RAI Uptake and ttt with RAI	CR	PR
Ho, 2012	Selumitinib + Iode 131	20	BRAFV600E, RAS & other	8	0	5 (25%)
Rothenberg 2015	Dabrafenib + Iode 131	10	BRAF V600 E	6	0	2 (20%)
Dunn, 2018	Vemurafenib + Iode 131	12	BRAF V600 E	4	0	4 (25%)

Dabrafenib +/- Trametinib NCT03244956

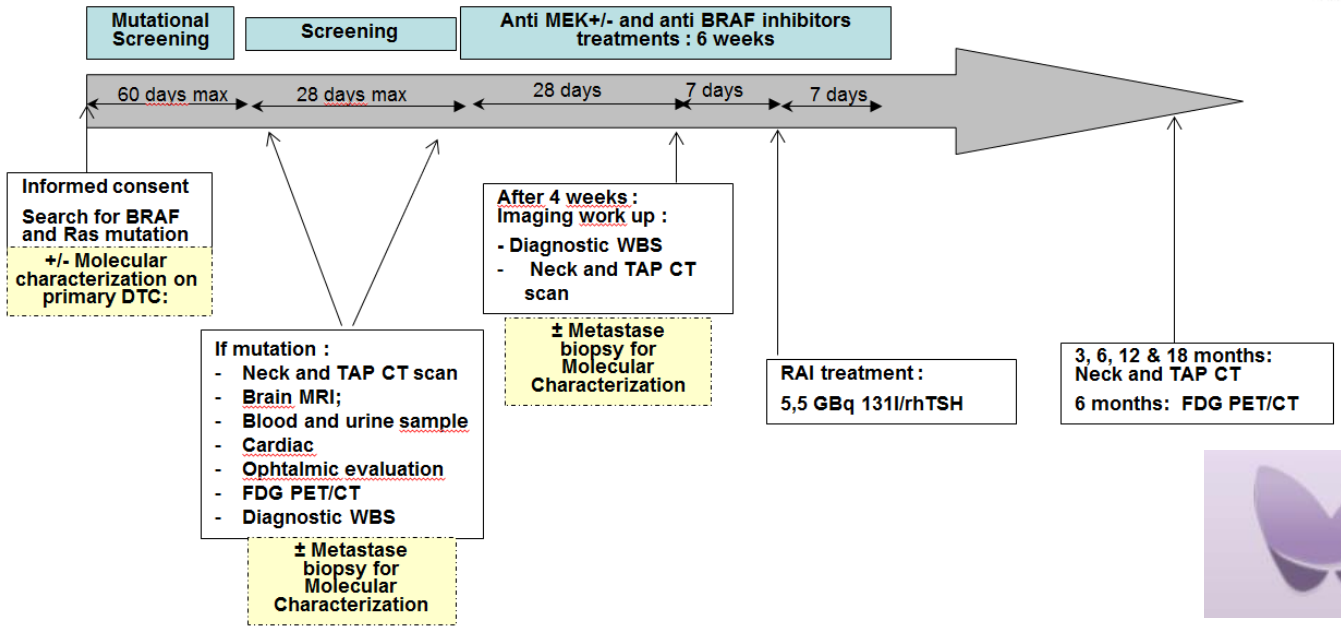
MERAIODE

Reinduction de fixation d'iode par trametinib +/- dabrafenib chez les patients avec mutation RAS/ BRAF

Etude multicentrique Française PHRC 2015

Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE

MINISTÈRE DES AFFAIRES SOCIALES, DE LA SANTÉ ET DES DROITS DES FEMMES



TUTHYREF

RAIR DIFFERENTIATED THYROID CANCER
PIK,AKT,MTOR PATHWAY

		Line	n	CR %	PR %	Duration of R (median, months)	PFS (median, months)
Schneider 2017	Everolimus	>1	28	**0**	**0**	-	9
Hanna, 2018	Everolimus	>1	33	**0**	**3**	na	12.9
Borson-Chazot, 18	Buparlisib	>1	43	**0**	**0**	-	na

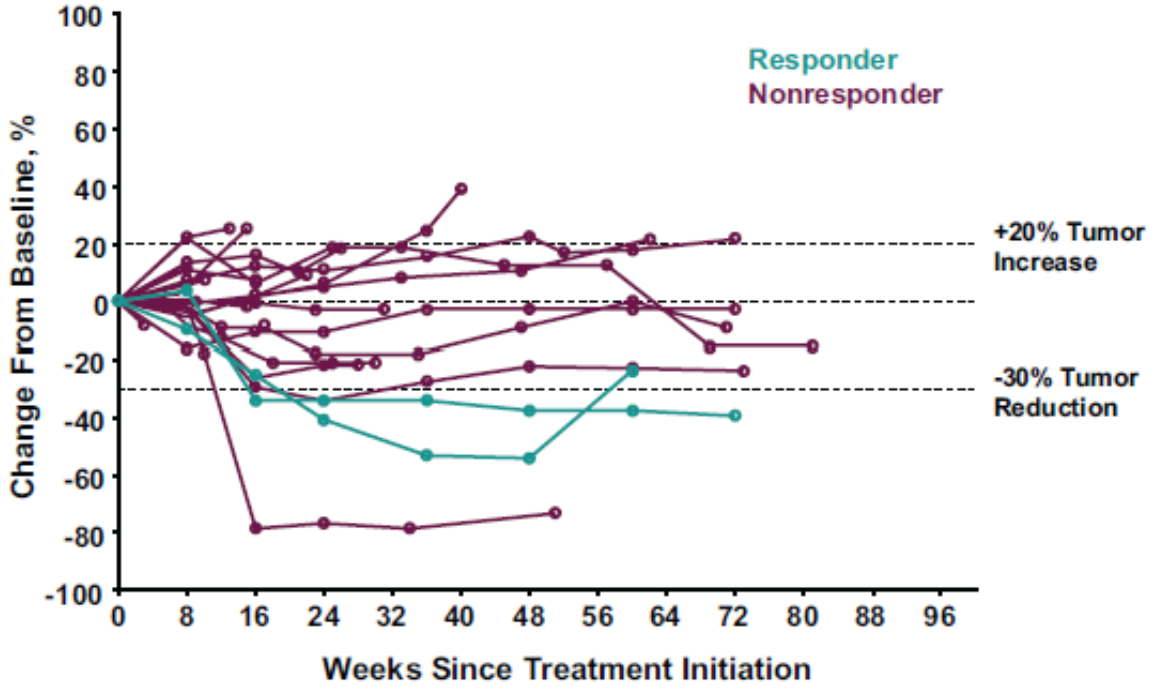
RAIR DIFFERENTIATED THYROID CANCER

Immunotherapy ?

Phase 1 Pembrolizumab

22 PD-L1–positive patients
Complete response = 0%
Partial response = 9%

Figure 3. Percentage change from baseline in the sum of the longest diameters of target lesions over time as assessed per RECIST v1.1 by investigator review (n = 21).



Mehnert 2016

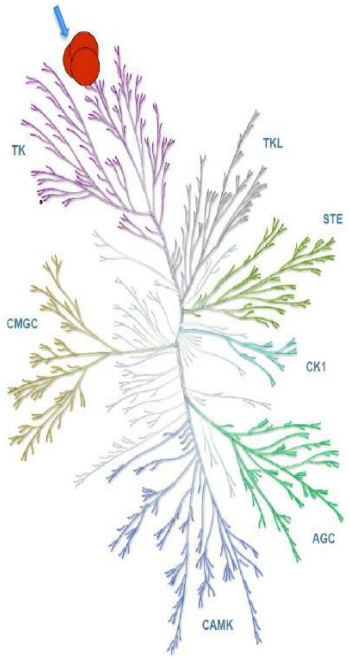
RAIR DIFFERENTIATED THYROID CANCER
ANTI VEGFR and combination therapy

Lenvatinib & Pembrolizumab	Academic and Community Cancer Research United (NCO, ITOG)	**NCT02973997**
Cabozantinib & Azetolizumab	Phase I trial with cohort extension	**NCT03170960**
Regorafenib & Nivolumab	Phase I trial with cohort extension	
Nivolumab & Ipilimumab	Dana Farber Hospital	**NCT03246958**

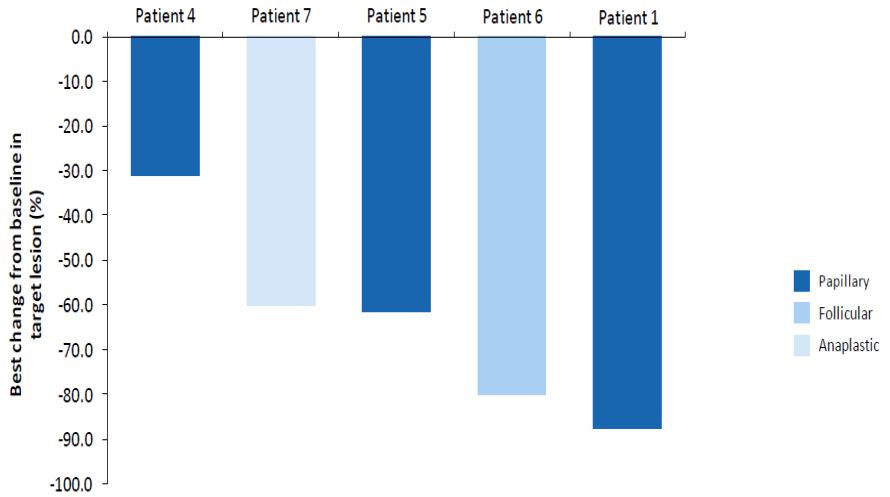
RAIR DIFFERENTIATED THYROID CANCER

ALK/ NTRK : results for Larotrectinib : active against TRK fusion cancer: Phase I-II-Basket

TRKA/B/C

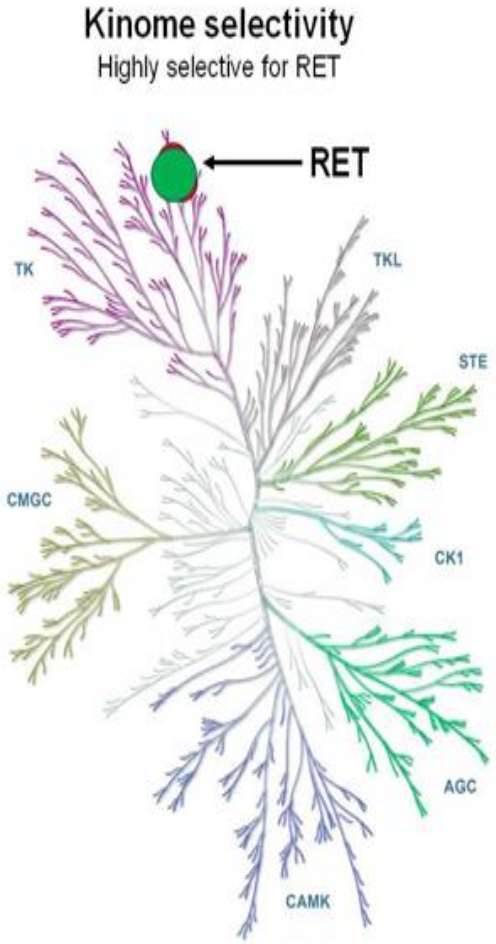


Objective response rate (95% CI)	80% (67–90%)
Partial response	64%
Complete response	16%
Stable disease	9%
Progressive disease	11%

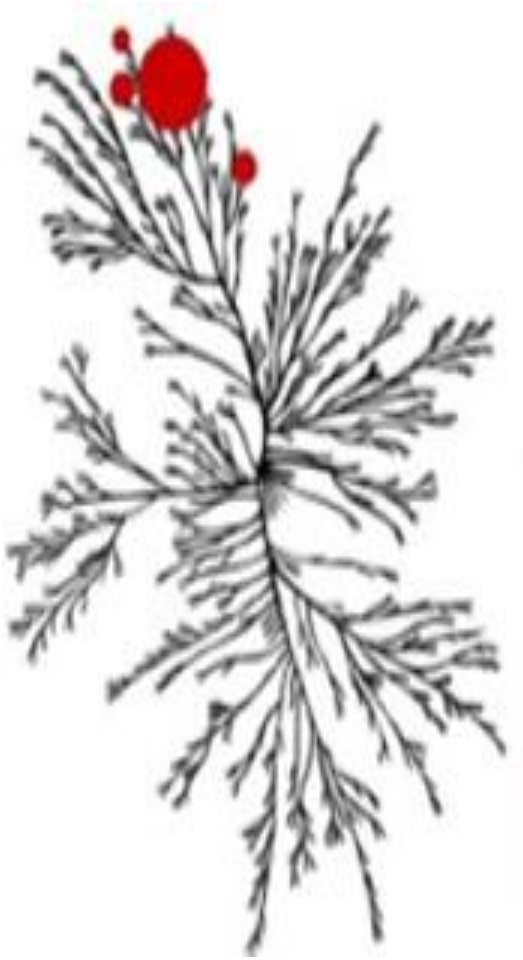


Brose, 2018

SELECTIVE ANTI RET DRUGS



LOXO 292



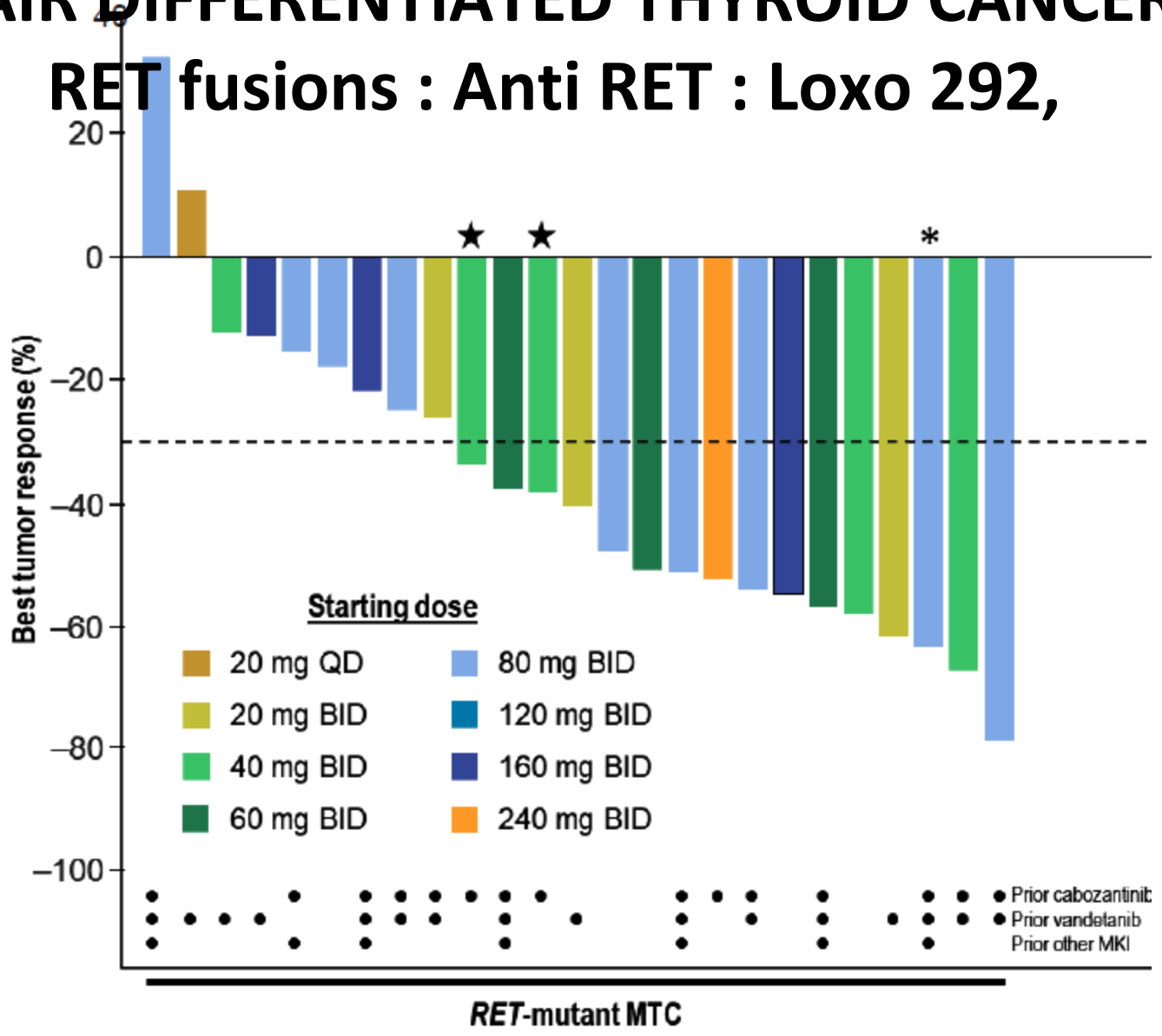
BLU 667

MEDULLARY THYROID CANCER : Efficacy of anti RET

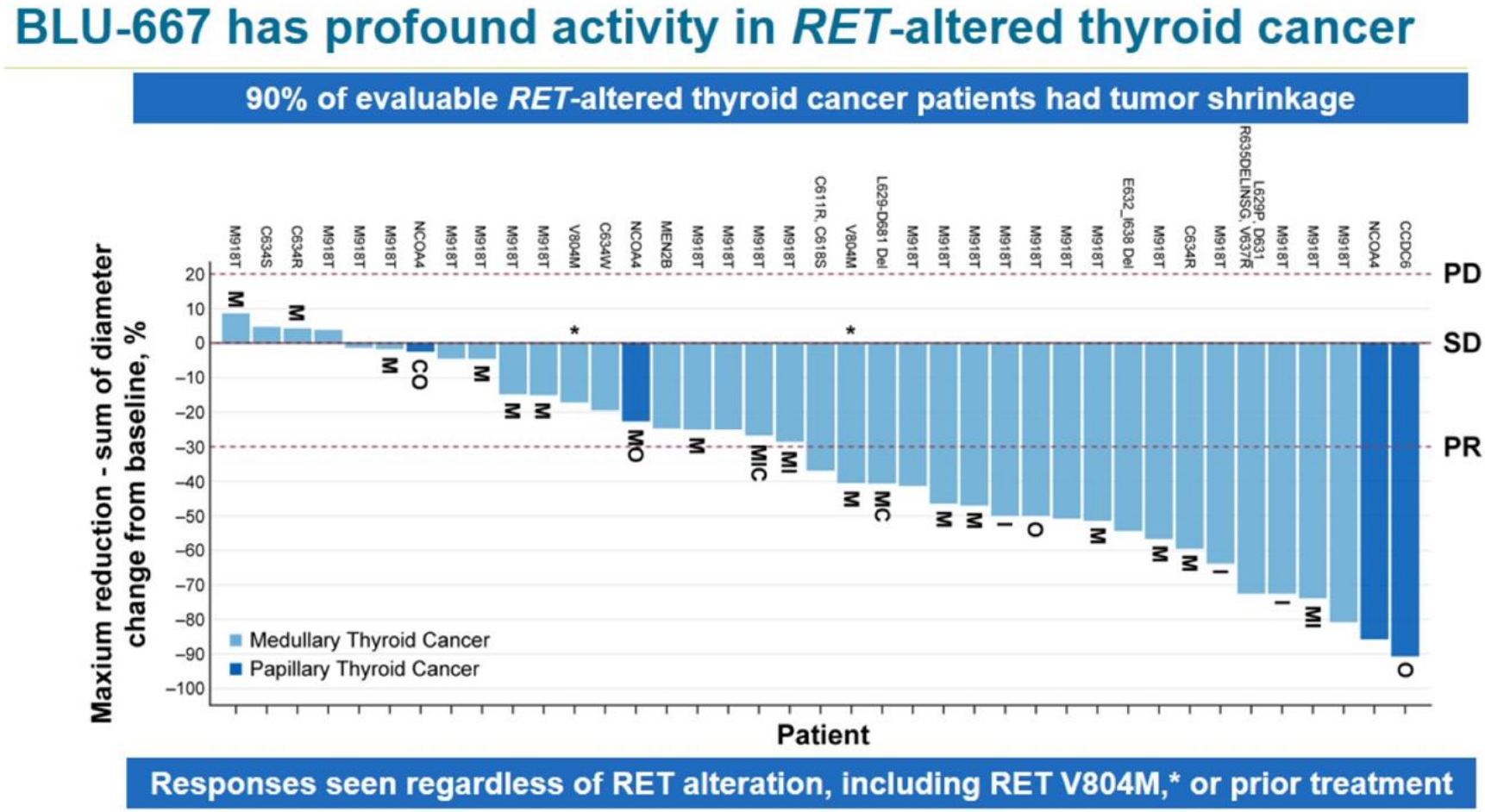
	N included/ evaluated	CR n	PR n	**Response rate**	SD	PD	
Loxo 292 Wirth, 18	29/17	2	15	**59%**	8	2	Not dose related Not RET mutated dependent No effect of prior TKI
Blu 667 Hu, 18	35 (dose of 300-400mg/d)	1	16	**48%**	18	0	Dose related Not RET mutated dependent No effect of prior TKI Response rate of 62% at week 24 (n=13)

RAIR DIFFERENTIATED THYROID CANCER

RET fusions : Anti RET : Loxo 292,



MEDULLARY THYROID CANCER : Efficacy of anti RET



NCO4A, nuclear receptor coactivator 4; CCDC6, coiled-coil domain containing 6; M, prior MKI therapy; C, prior chemotherapy; O, other therapy; I, prior immunotherapy; PD, progressive disease; SD, stable disease; PR, partial response.

Patients Enrolled as of 9 May 2018, Follow-up as of 14 Sep 2018

ITK et CTD

- Taux de réponses
  - Drogues dont le taux de Réponses est de 0-35%
    - Motesanib, Axitinib, Sunitinib, Vandetanib, Vemurafenib, **Sorafenib**
  - Drogues dont le taux de Réponse est >50%
    - **Lenvatinib,** Pazopanib, Cabozantinib, Dabrafenib+/-trametinib si mutation BRAF
- Survie sans progression : essais contre placebo
  - Vandetanib (phase II randomisée) : ZACTHYF
  - Vandetanib (phase III) : VERIFY
  - Sorafenib (phase III) : DECISION
  - Lenvatinib (phase III) : SELECT
- Association anti VEGF-ITK immunotherapie, redifférentiation

RAIR DIFFERENTIATED THYROID CANCER

Screening moléculaire somatique

Si réarrangement ALK, NTRK, RET → ITK Selectif au sein d'un essai

- Programme de Redifférentiation program (si mutation BRAF ou RAS (Première ligne)
- Thérapie combinatoire : anti VEGFR-Immunothérapie ? (1èer ou 2ème ligne)
- Anti BRAF ?
- Anti VEGFR : combien ?

S Leboulleux

MUNICH 2018 ESMO congress

Thank you for your attention