Post-Endo 2023

Bern, 31 Aug 2023

Hot topics : thyroid

Dre Stephanie Andrade Lopes

Pre Sophie Leboulleux

Service d'endocrinologie, diabétologie, nutrition et éducation thérapeutique du patient

ENDO 2023

JUNE 15–18, 2023 CHICAGO, IL

Hôpitaux Universitaires Genève

Hyperthyroidism

Radiofrequency ablation for thyroid nodules

Background

- Autonomous functioning thyroid nodules (AFTNs) : 5-10 % of thyroid nodules
- 2nd most common cause of hyperthyroidism (after GD)

- Untreated AFTN (including subclinical hyperthyroidism) is associated with adverse cardiovascular and skeletal complications.

- Standard of care : Radioactive iodine (RAI) or surgery
  - Both associated with permanent post-procedural hypothyroidism.

- Radiofrequency ablation (RFA) has been used in various countries (for both toxic and non-toxic thyroid nodules)
  - Significant nodule volume reduction with improvement in esthetic and compressive symptoms
  - Restoration of normal thyroid function

- Review on Toxic nodules : 10 studies, 254 patients *Muhammad et al, Laryngoscope, Apr 2022*
  - Normalization of thyroid function at last follow-up : 62% (40-94%)
  - Mean Volume reduction rate : 77% (range : 52-86)

Outcomes Of Radiofrequency Ablation For Autonomous Functioning Thyroid Adenoma- Mayo Clinic Experience

Maheswaran Dhanasekaran MBBS[1*]; Aadil Rajwani MD[1]; Regina M. Castro MD[1]; John C. Morris III MD[1]; John Schmitz MD[2]; Robert Alan Lee MD[2]; Matthew R. Callstrom MD., Ph.D[2], Marius N. Stan MD[1]

[1]Department of Endocrinology, Diabetes, Metabolism and Nutrition, Mayo Clinic, Rochester, Minnesota

[2]Department of Diagnostic Radiology, Mayo Clinic, Rochester, Minnesota

- Single-center experience at the Mayo Clinic
- Retrospective chart review of 22 cases

- All patients with AFTN
- Single session of RFA

TABLE 1: Baseline Characteristics Of The 22 Study Patients With AFTN Who Underwent Percutaneous Radiofrequency Ablation (single session)

Total Number of patients	22
Average Age	52.1 [(52.1 ± 14.6); Range: 31- 72]
Median Age	56.29
Gender (F:M)	17:5 (77% F & 23% M)
Avg BMI	27.36 [(27.36 ± 4.67); Range: 19.35- 38.45]
Average pre ablation volume, ml	12.42 [(12.29 ± 10.81); Range: 0.5- 37.48]
Average TSH (mIU/L)	0.41 [(0.41 ± 0.98); Range: 0.001- 4.2]
Average T4 (ng/mL)	1.29 [(1.29 ± 0.33); Range: 0.8-2.3]
Thyroid Function Status	16 (72%), Subclinical Hyperthyroidism 2 (9%), Hyperthyroidism 4 (18%), Euthyroid on ATD

TABLE 2: Comparison of Thyroid function and Nodal Characteristics Pre- and Post-RFA

	Pre- RFA	Post- RFA
Total Number of patients	22	22
Average TSH (mIU/L)	0.41 [(0.41 ± 0.98); Range: 0.001- 4.2]	1.82 [(1.82 ± 1.9); Range: 0.03- 6.9]
Average volume, ml	12.42 [(12.29 ± 10.81); Range: 0.5- 37.48]	4.5 [(4.5 ± 5.1); Range: 0.16- 21.42]
Rate of Restoration of Euthyroidism		91%
Volume Reduction Rate		61.13%

TSH normalisation in all patients within 3-6 months

- 2 recurrent hyperthyroidism
- 2 with transient tachycardia
- 2 developped mild hypothyroidism

None of the nodule grew back during the follow-up period

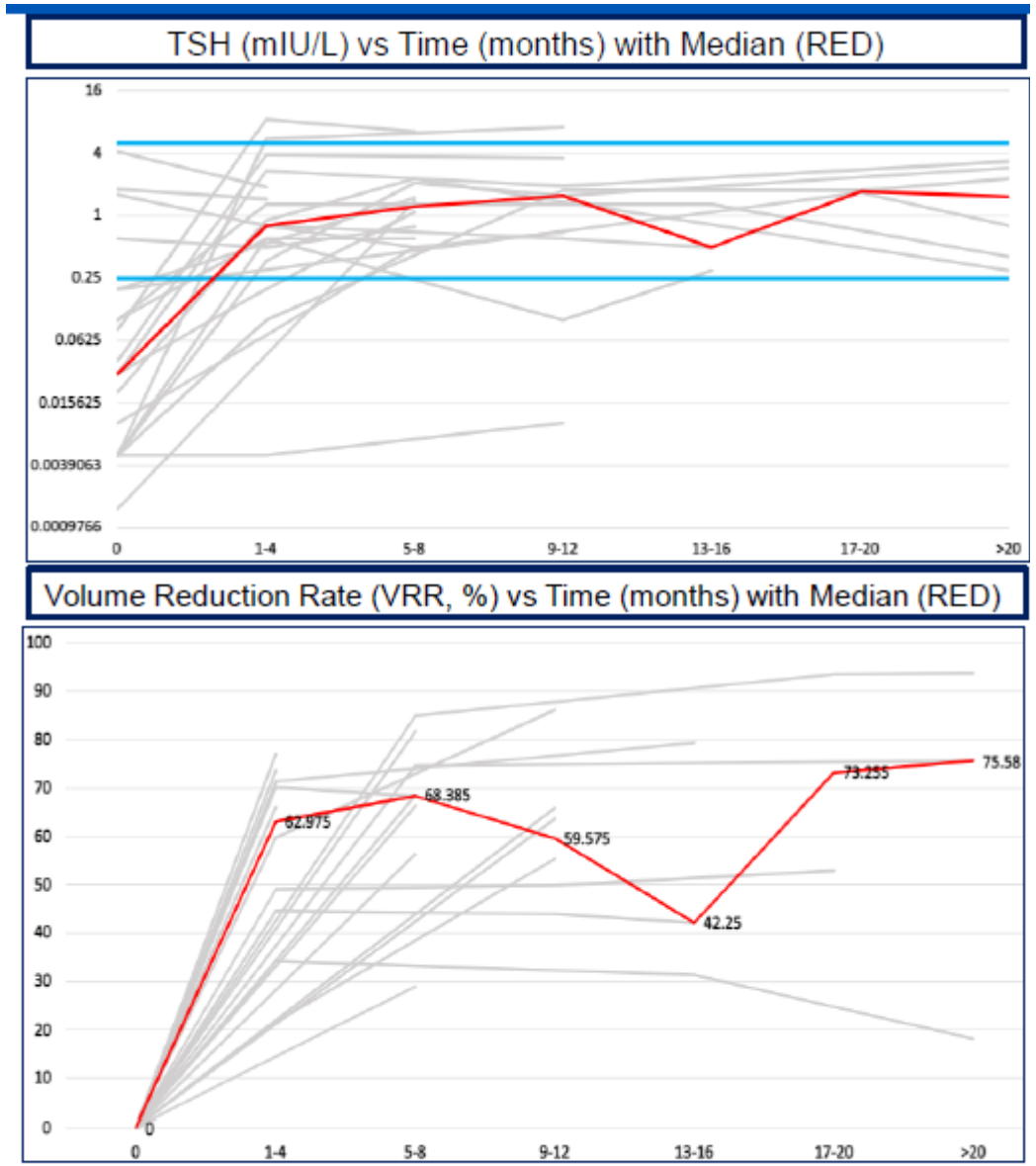


FIGURE 3: Change in TSH (mIU/L) and VRR (%) over time in months following a Sigle RFA Session with the Median TSH Represented in RED and the Blue lines representing normal TSH range

Take home messages- Discussion

- RFA could be an alternative to treatment of AFNTs, in centres with expertise
- Prospective comparison to standard of care needed
- Long term outcome studies needed
  - Predictive factors of complete response
  - Recurrence ?
  - Cardiovascular outcomes?

Hyperthyroidism

Long-term Mortality and Cardiometabolic Effects of Treatment for Hyperthyroidism: EGRET study

Background

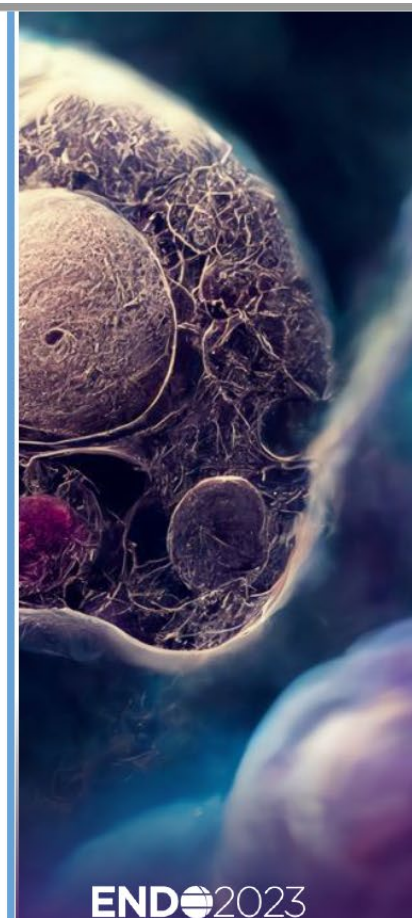
- Multiple options for treatment of Graves disease : ATD, RAI or surgery
- Early and effective control of hyperthyroidism is associated with improved survival when compared to less effective control
- Correction of hyperthyroidism leads to gain weight
- Little is known about the long-term outcomes of each treatment modality

Okosieme et al, Lancet Diab Endoc, 2019
Torlinska et al, Thyroid, 2019

OR 26-05 - Long-term Mortality and Cardiometabolic Effects of Treatment for Hyperthyroidism: EGRET study

Kristien Boelaert, MD, PhD

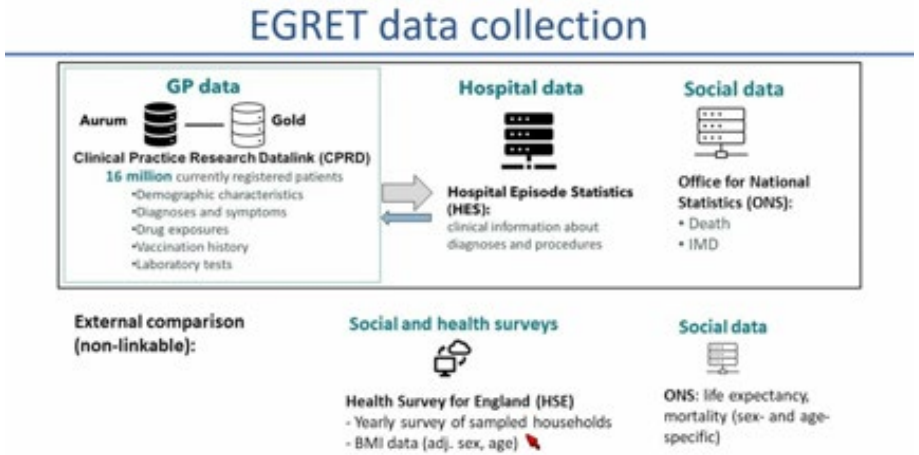
Institute of Applied Health Research, University of Birmingham, UK



Aims :

- Establish the natural history of weight change and risk of obesity in patients with hyperthyroidism
- Investigate the risk of cardiometabolic conditions and death relative to treatment modality

- Inclusion
  - Treatment with ATD, radioiodine or thyroidectomy during the **first** episode of hyperthyroidism between April 1997 and December 2015



- Exclusion criteria
  - ATD less than 6 months as the only treatment for hyperthyroidism
  - Data indicating previous thyroid treatment
  - Thyroid cancer
  - Pregnancy during the first episode

- Proxy data
  - 131-I not well recorded;
  - assumption: long-term levothyroxine in patients not treated with surgery

Baseline characteristics

	Total	ATD	131-I	Surgery	P-value
	N = 55,318	**N = 42,938 (77.6%)**	**N = 8,054 (14.6%)**	**N = 4,326 (7.8%)**	
Age (y): mean (SD)	52 (15)	51 (15)	55 (14)	47 (15)	**<0.001**
Female sex	42,367 (77%)	32,697 (76%)	6,047 (75%)	3,623 (84%)	**<0.001**
Baseline ft4 (pmol/L): mean (SD)	38.6 (22.1)	38.2 (21.7)	40.1 (22.4)	39.6 (26.2)	**<0.001**
Premorbid CVD present	2,142 (3.9%)	1,677 (3.9%)	379 (4.7%)	86 (2.0%)	**<0.001**
Premorbid obesity present	8,688 (15.7%)	6,753 (15.7%)	1,289 (16.0%)	646 (14.9%)	**<0.001**

- **Ethnicity: 80% white**
- **Index of Multiple Deprivation (quintiles)**
- **Smoking status: 41% never smoked – less 131-I in smokers**

BMI change

7 years of follow-up

Women (N = 86,747)

	Coeff.	95% CI		P-value
ATD	**-0.28**	**-0.39**	**-0.18**	**<0.001**
131-I	0.17	-0.01	0.34	0.059
Surgery	**0.83**	**0.58**	**1.08**	**<0.001**
age	0.04	0.03	0.04	<0.001
Const.	25.63	25.43	25.83	

0.83 BMI coefficient:
If 160 cm -> +2.1 kg
If 170 cm -> +2.4 kg

Men (N = 57,429)

	Coeff.	95% CI		P-value
ATD	-0.11	-0.24	0.03	0.117
131-I	-0.22	-0.45	0.02	0.069
Surgery	**1.09**	**0.65**	**1.54**	**<0.001**
age	0.05	0.05	0.05	<0.001
Const	25.17	24.94	25.39	

1.09 BMI coefficient:
If 170 cm -> +3.2 kg
If 190 cm -> +3.5 kg

Risk of developping obesity

Women (N = 86,747)

	OR	95% CI		P-value
ATD	0.98	0.94	1.01	0.22
131-I	**1.12**	**1.05**	**1.19**	**<0.001**
Surgery	**1.27**	**1.16**	**1.39**	**<0.001**
age	1.01	1.01	1.01	<0.001
Const.	0.23	0.21	0.24	

Men (N = 57,429)

	OR	95% CI		P-value
ATD	0.99	0.93	1.06	0.79
131-I	1.03	0.93	1.15	0.55
Surgery	**1.56**	**1.28**	**1.9**	**<0.001**
age	1.01	1.01	1.02	<0.001
Const.	0.17	0.16	0.19	

Risk of death

	Total (55,318)	ATD (N=42,938)	131-I (N=8,054)	Surgery (N=4,326)
In the cohort	7,962 (14.4%)	6,060 (14.1%)	1,504 (18.7%)	398 (9.2%)
Expected	3,138 (5.7%)	2,234 (5.2%)	717 (8.9%)	187 (4.3%)
Mortality Ratio	**2.54**	**2.71**	**2.10**	**2.13**
P-value	<0.0001	<0.0001	<0.0001	<0.0001

Follow up 12.1 years per person

- **Median index date: 22 Jan 2008 -> applied data from ONS tables 2008-2010**
- **Each patient was assigned sex- and age-specific (at-index) expected time of survival**
- **Expected death was defined as an event when expected survival was shorter than observed follow-up**

Mortality Cox PH regression analysis

	HR	95% CI		P-value
Treatment (ref. ATD):				
131-I	**0.87**	**0.82-**	**0.92**	**<0.0001**
Surgery	**0.80**	**0.73-**	**0.89**	**<0.0001**
Age (y)	1.12	1.11-	1.12	<0.0001
Female	0.74	0.71-	0.78	<0.0001
IMD	1.12	1.10-	1.14	<0.0001
Premorbid CVD	1.74	1.62-	1.88	<0.0001
Smoking (ref: non-smoker)				
Current smoker	1.72	1.62-	1.83	<0.0001
Ex-smoker	1.31	1.23-	1.40	<0.0001
BMI (ref: normal BMI)				
Overweight	0.99	0.93-	1.05	0.68
Obese	1.19	1.12-	1.27	<0.0001

*** Model was additionally adjusted for baseline fT4 and ethnicity**

- Included: N = 53,176 patients; MACE: N = 5,468 (10.3%)
- Follow-up: 630,478 patient years; avg. 11.9 y per patient

Risk of MACE

	Total	ATD	131-I	Surgery	P-value
MACE	**5,468 (10.3%)**	4,100 (9.9%)	1,027 (13.4%)	341 (8.0%)	<0.001

MACE Cox PH regression analysis

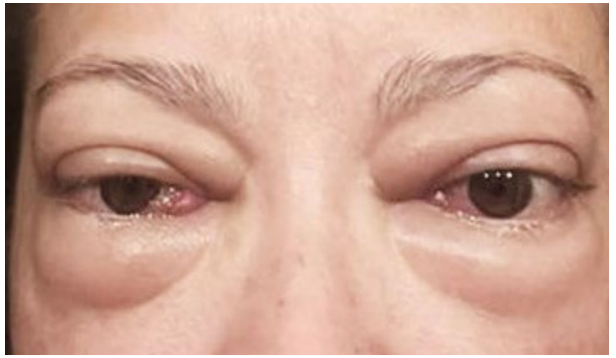
	HR	95% CI	P-value
Treatment (ref. ATD):			
131-I	**1.00**	**0.93 - 1.07**	**0.94**
Surgery	**0.97**	**0.86 - 1.09**	**0.61**
Age (y)	1.07	1.06 - 1.07	<0.0001
Female	0.58	0.55 - 0.62	<0.0001
IMD	1.08	1.06 - 1.10	<0.0001
Smoking (ref: non-smoker)			
Current smoker	1.41	1.32 - 1.52	<0.0001
Ex-smoker	1.20	1.11 - 1.29	<0.0001
BMI (ref: normal)			
Overweight	1.16	1.07 - 1.25	<0.0001
Obese	1.43	1.32 - 1.55	<0.0001

Take home messages

- Surgery seems associated with higher risk of obesity (with medium gain weight of a few kilos)
- Significant reduction in mortality (HR) following 131-I and surgery
- No differences in risk of MACE following either of the treatment for hyperthyroidism
- Could be use to discuss the treatment options with our patients

Thyroid Eye Disease

Background



- Heterogenous disease, auto-immune mediated, with close link to TRAbs levels, suggesting that TSH R is the primary autoantigen
- Important role of IGF-1R, who forms physical and functional complex with TSH-R, leading to inflammation and tissue expansion

- Treament guidelines for moderate-to-severe, active disease
  - First line recommandations:
    - IV GC
    - teprotumumab (IGF-1R antagonsit) as new treatment in ATA/ETA consensus (2022)

ATA and ETA 2022

Durability of Treatment Response With VRDN-001, a Full Antagonist Antibody to IGF-1 Receptor, in Patients With Thyroid Eye Disease (TED): Phase 1/2 Clinical Study

Raymond S. Douglas[1], Roger E. Turbin[2], Kimberly Cockerham[3], Navdeep Nijhawan[4], Rosa Tang[5], Michael T. Yen[6], Chantal Boisvert[7], David Kaufman[8], Andrea Kossler[3], Wendy W. Lee[9], Michael Yoon[10], Shoaib Ugradar[11], Rochelle Summerfelt[12], Barrett Katz[12]

1. Cedars Sinai Medical Center, Los Angeles, CA. 2. Rutgers New Jersey Medical School, Department of Ophthalmology; Divisions of Neuro-Ophthalmology and Oculoplastic, Orbital, and Reconstructive Surgery, Newark, NJ. 3. Stanford University Ophthalmology at Byers Eye Institute, Stanford, CA. 4. Oshawa Clinic, Oshawa, ON, Canada 5. Eye Wellness Center– Neuro-Eye Clinical Trials, Inc. Bellaire, TX. 6. Baylor College of Medicine, Alkek Eye Center, Houston, TX. 7. Duke Eye Center, Durham, NC. 8. Michigan State University Department of Neurology & Ophthalmology, East Lansing, MI. 9. Bascom Palmer Eye Institute, Miami, FL. 10. Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston, MA. 11. UCLA Stein Eye Institute, Los Angeles, CA. 12. Viridian Therapeutics, Waltham, MA.

VRDN-001 is an investigational therapy not approved in any country.

Poster#
FRI-545

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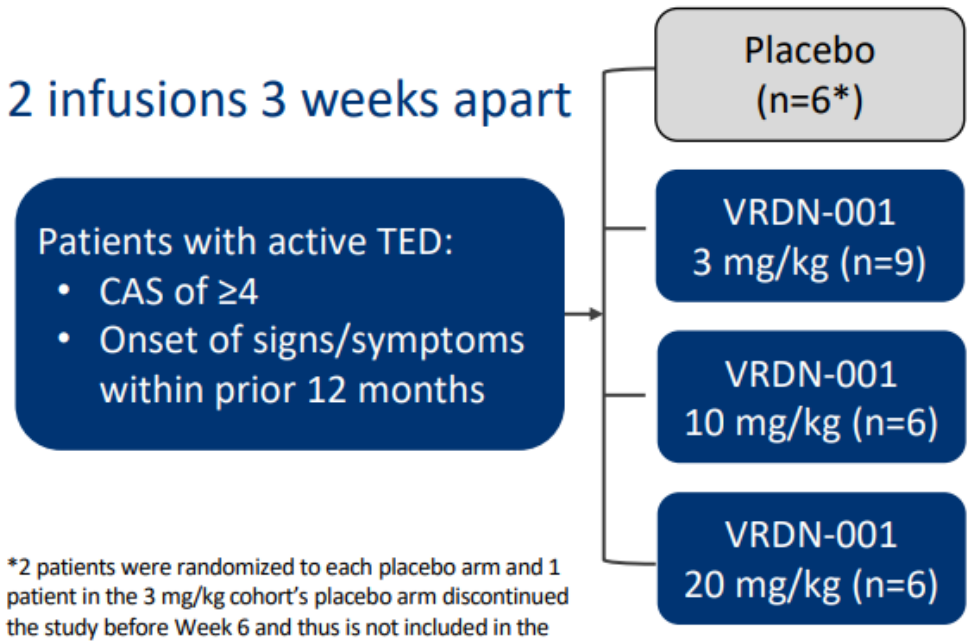
VDRN-001

- Full antagonist antibody to IGF-1R

- Phase 1-2 clinical study
- Inclusion : adults with active moderate-to-severe TED (symptoms <12 months) and CAS ≥4
- Randomized to 2 infusions 3 weeks apart of VRDN-001 at 3 different doses or placebo (3:1)

- Safety, tolerability, and efficacy through 12 weeks

VRDN-001 POC randomized, double-masked trial tested 3 doses in active TED



*2 patients were randomized to each placebo arm and 1 patient in the 3 mg/kg cohort's placebo arm discontinued the study before Week 6 and thus is not included in the efficacy analysis but is included in the safety analysis.
Clinical activity score (CAS) = a composite 0-7 scale scoring signs and symptoms of TED.

Baseline characteristics	Placebo (n=5)	All VRDN-00 (n=21)
Proptosis, mean (SEM)	22.8 (2)	23.7 (0.7)
CAS, mean (SEM)	5.0 (0.5)	5.4 (0.2)
Diplopia, n (%)	3 (60%)	13 (62%)
Diplopia, mean (SEM)	1.6 (0.7)	1.3 (0.3)
Months since onset, mean (SEM)	7.0 (2.0)	7.4 (0.8)
Age, mean years (SEM)	44.2 (4.3)	47 (3.3)
Female, n (%)	3 (60%)	19 (90%)

SEM = Standard error of the mean

	Overall responder rate	Proptosis responder rate	CAS: Score of 0 or 1	CAS: Mean change	Diplopia: Complete resolution*
Placebo (n=5)	20% (1/5)	40% (2/5)	20% (1/5)	-1.75	0
All VRDN-001 (n=21)	**67% (14/21)**	**71% (15/21)**	**62% (13/21)**	**-4.1**	**54% (7/13)**
3 mg/kg (n=9)	56% (5/9)	67% (6/9)	67% (6/9)	-4.2	20% (1/5)
10 mg/kg (n=6)	83% (5/6)	83% (5/6)	83% (5/6)	-4.3	75% (3/4)
20 mg/kg (n=6)	67% (4/6)	67% (4/6)	33% (2/6)	-3.7	75% (3/4)

Preliminary durability of response at 12 weeks in VRDN-001 10 mg/kg cohort:

- Mean proptosis and CAS remained consistent
- 80% (4/5) of VRDN-001 responders at 6 weeks maintained proptosis response, overall response, and CAS decrease to 0 or 1
- Diplopia resolution achieved/maintained for all 4 patients who presented with diplopia at baseline

Safety profile

Data cutoff December 19, 2022

No SAEs, infusion reactions, or discontinuations

Adverse Reactions	Placebo (n=6)	VRDN-001 3 mg/kg (n=9)	VRDN-001 10 mg/kg (n=6)	VRDN-001 20 mg/kg (n=6)
Muscle spasms	-	2	2	2**
Nausea	-	2	-	-
Alopecia	1	-	-	-
Diarrhea	-	1	2**	1*
Fatigue	3	-	1	-
Hyperglycemia	-	1	-	1*
Hearing impairment	-	1	1	-
Dysgeusia	-	-	-	1
Headache	2**	2	1	1
Dry skin	-	1	-	1
Infusion reactions	-	-	-	-

*Deemed unrelated to study drug by the masked investigators.
** 1 patient deemed related and 1 patient deemed unrelated to study drug by the masked investigators.

Data are as of data cut-off of December 19, 2022. Other AE that occurred in more than 1 patient and deemed related to study drug by masked investigators was acne (n=2). Instances were mild and did not require intervention. Muscle spasms were mild and did not require intervention; hearing impairment (n=2) resolved without intervention in both cases. Both patients with hyperglycemia were diabetic at baseline; in 1 case glucose variability was determined by masked PI to be unrelated to drug.

Take home messages

- **VRDN-001 (2 infusions, 3 weeks apart, at 10mg/kg) was well tolerated with rapid and clinically meaningful improvement by 6 weeks, sustained through 12 week**
- **Lower dose and fewer treatments than in prior RCTs of other anti-IGF-1R antibodies.**
- **Results from 3 mg/kg and 20 mg/kg awaited**
- VRDN-001 as potential new treatment for moderate-to-severe TED, with further studies awaited (small number of patients)
  - Ongoing phase 3 clinical trial: THRIVE
  - Prices ? Optimal doses ? Long-term side effects ?

Thyroid cancer

Iodine redifferentiation

Background

- Patients with metastatic differentiated thyroid cancer (DTC) that are radioactive iodine (RAI) refractory (RAIR) have a poor prognosis.
- Redifferentiation therapy (RDT) has emerged as a potential approach to restore RAI avidity in this disease

Prospective trials in BRAFV600E mutated DTC

		N	Genetics	Increase of RAI uptake (according to)	Ttt with RAI	CR	Partial Response
Ho, 2012	Selumitinib +/- Iode 131	9	*BRAFV600E*	4 (60%) (124I PET-CT)	1	0	11% (best PR)
Rothenberg, 2015	Dabrafenib +/- Iode 131	10	*BRAF V600E*	6 (60%) (Dc 131I WBS)	6	0	20% (best PR)
Dunn, 2018	Vemurafenib +/- Iode 131	12	*BRAF V600E*	4 (40%) (Dc 131I WBS)	4	0	25% (best PR)
Tchekmedyian, 2022	Vemurafenib + anti-ErbB3mAbCDX-337 +/- Iode 131	6	*BRAF V600E*	5 (80%) (124I PET-CT)	5	0	33% (6 months PR)
Weber, 2022	Dabrafenib + Trametinib +/- Iode 131	6	*BRAF V600E*	2 (33%) (124I PET-CT)	6	0	17%
Leboulleux, 2023	Dabrafenib + Trametinib +/- Iode 131	21	*BRAF V600E*	20 (95%) (post-T WBS)	21	1	38% (6 months PR)

Adapted from Leboulleux et al, Exp Opinion on Inv Drugs, 2022

Prospective trials in RAS mutated DTC

		N	Genetics	Increase of RAI uptake (according to)	Ttt with RAI	CR	PR
Ho, 2012 NEJM	Selumitinib +/- Iode 131	5	*RAS*	5 (100%) (^{124}I PET-CT)	5	0	80% (best PR)
Leboulleux, 2023 Thyroid	Trametinib +/- Iode 131	10	*RAS*	6 (60%) (post-T WBS)	10	0	20% (6 months PR)
Burman, 2022 ASCO	Trametinib +/- Iode 131	25	*RAS*	22 (88%) (^{124}I PET-CT)	15	0	32% (6 months PR)

Adapted from Leboulleux et al, Exp Opinion on Inv Drugs, 2022

Efficacy of Radioactive Iodine Redifferentiation Therapy in Previously Iodine Refractory Differentiated Thyroid Cancers

David Toro-Tobon, MD[1]; John C. Morris[1], MD; Crystal Hilger[3]; Candy Peskey[2]; Jolanta Durksi, MD[3]; Mabel Ryder, MD[1,2].

[1]Division of Endocrinology, Diabetes, Metabolism and nutrition, Mayo Clinic, Rochester, USA; [2]Division of Medical Oncology, Mayo Clinic, Rochester, USA; [3]Division of Nuclear Medicine, Mayo Clinic, Rochester, USA.

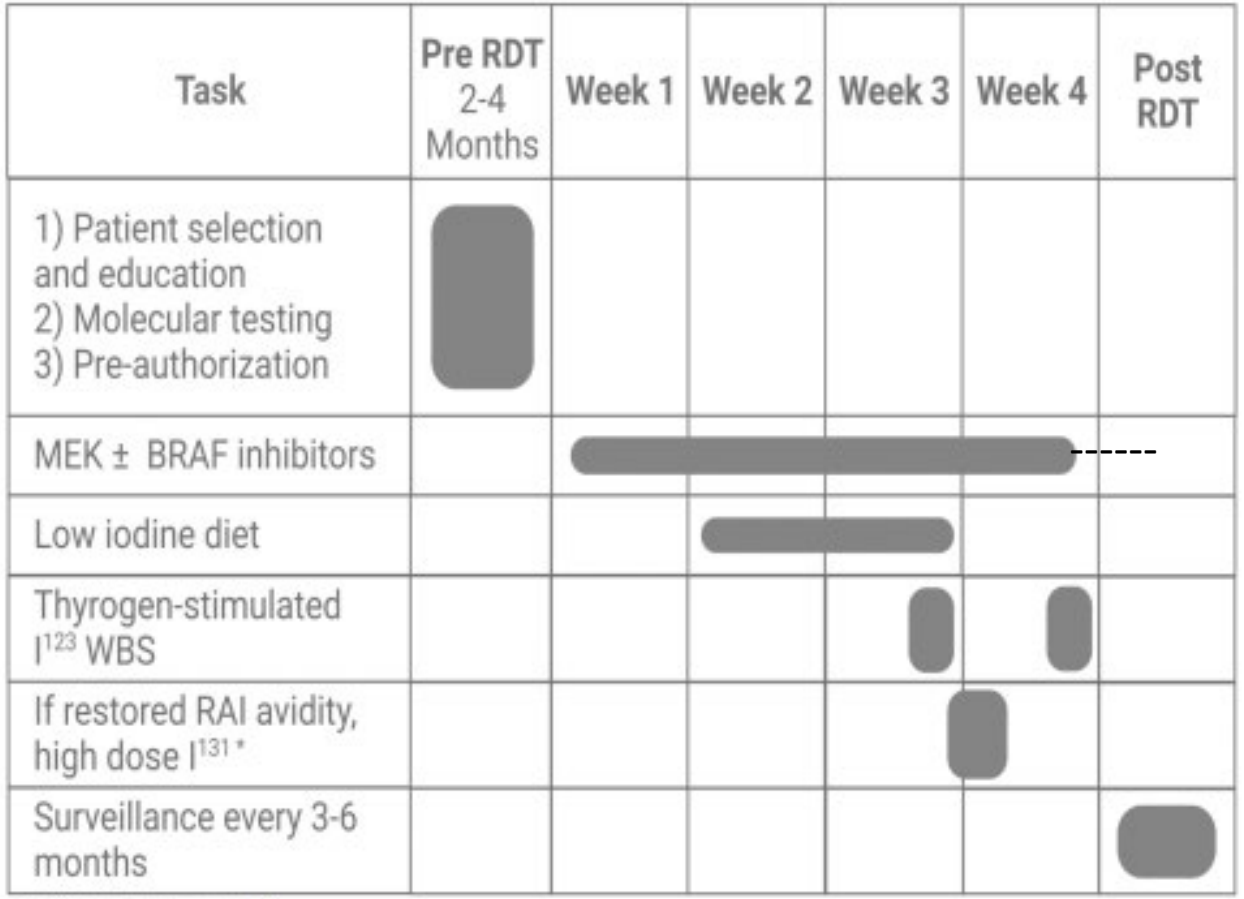
- **Retrospective study** on 33 patients with RECIST-progressive metastatic RAIR-DTC who underwent Redifferentiation therapy (RDT) between 2017 and 2022 at the Mayo Clinic

- **Treatments :**
  - Dabrafenib, trametinib, or both, others

- **Aims :**
  - Efficacy of redifferentiation
  - Predictors of RAI uptake restoration
  - Long term outcomes

  - Responders were defined as patients with RAI restoration, not with RECIST criteria

All patients underwent the following protocol:



*Modified dosimetry protocol [3]
RDT: Redifferentiation therapy; **MEK:** Methyl ethyl ketone; **RAI:** Radioactive iodine; **WBS:** Whole body scan

RAI was given in 64% of the patient
TKI were maintained in 26% -29% of the patients

Characteristics of the patients

Histology	Papillary Thyroid cancer	70% (23)
	Classic	11
	Tall cell	4
	With tall cell variant	4
	Foll cell variant	4
	Poorly differentiated	9% (3)
	Follicular Thyroid Cancer	21% (7)
Mutation	BRAF	55% (18)
	RAS	36% (12)
	RET	12% (4)
	Dabrafenib & Trametinib	55% (18)
	Trametinib	36% (12)
	Other	12% (3)

Nb: TERT mutation present in 50% of the cohort

Restoration of RAI uptake- Treatment Response

		RAI restoration
Histology	Papillary Thyroid cancer Poorly differentiated Follicular Thyroid Cancer	52% (12/23) 0% (0/3) 100% (7/7)
Oncogenic driver	BRAF RAS RET	37% (7/18) 92% (11/12) 25% (1/ 4)
Other mutation	TERT	50% (8/16)

Predictors of RAI uptake restoration

- FTC
- RAS mutation
- Tg of 294 ng/ml or more
- Largest tumor diameter of 1.7 cm or less
- Bone metastasis
- Without locoregional nodal disease

Best Treatment Response (RECIST)

1 Complete Response ; 2 Partial Response

		Best RECIST tumor response	
		Complete Response	Partial Response
RAI Restoration	Yes n=19	0	10% (2)
	No n=14	7% (1)	0

		RAI restoration	Best RECIST tumor response	
			Complete Response	Partial Response
Oncogenic driver	BRAF	37% (7/18)	0	6% (1/18)
	RAS	92% (11/12)	0	8% (1/12)
	RET	25% (1/ 4)	1 (25%)	0

Safety issues :

2 histologic transformation to anaplasic thyroid cancer

Take home messages

- Restoration of RAI avidity in 57% of the cases (RAS > BRAF > RET)
- Low Tumor Response rate in all cohort
- RAI re-uptake restauration does not seem associated to tumor response

- Compared to prospective studies
  - Lower response rate than previously reported (prospective first line with selected patients vs. retrospective data)

  - High redifferentiation rate in RAS mutated patients concordant with the Ho and the Burman study, discordant with the MERAIODE RAS cohort which could be explained by the inclusion of poorly differentiated in the latest study.

Thyroid cancer

Role of molecular markers for long term outcomes

DISEASE-RELATED OUTCOMES IN PATIENTS WITH THYROID CANCER ON LONG TERM FOLLOW-UP: ANALYSIS OF 1487 PATIENTS

WILLIAM R. DOERFLER, ELENA M. MORARIU, SALLY E. CARTY, MARINA N. NIKIFOROVA, YURI E. NIKIFOROV, LINWAH YIP

ENDOCRINE SOCIETY 2023 ANNUAL MEETING
6/18/23

Methods and Aims

HHS Public Access
Author manuscript
Ann Surg. Author manuscript; available in PMC 2017 January 25.

Published in final edited form as:
Ann Surg. 2015 September ; 262(3): 519–525. doi:10.1097/SLA.0000000000001420.

Tumor Genotype Determines Phenotype and Disease-related Outcomes in Thyroid Cancer:

A Study of 1510 Patients

Linwah Yip, MD[†], Marina N. Nikiforova, MD[†], Jenny Y. Yoo, MD[*], Kelly L. McCoy, MD[*], Michael T. Stang, MD[*], Michaele J. Armstrong, PhD[*], Kristina J. Nicholson, MD[*], N. Paul Ohori, MD[†], Christopher Coyne, MD[‡], Steven P. Hodak, MD[‡], Robert L. Ferris, MD, PhD[§], Shane O. LeBeau, MD[‡], Yuri E. Nikiforov, MD, PhD[‡], and Sally E. Carty, MD[†]

- Aim of a study published in 2017

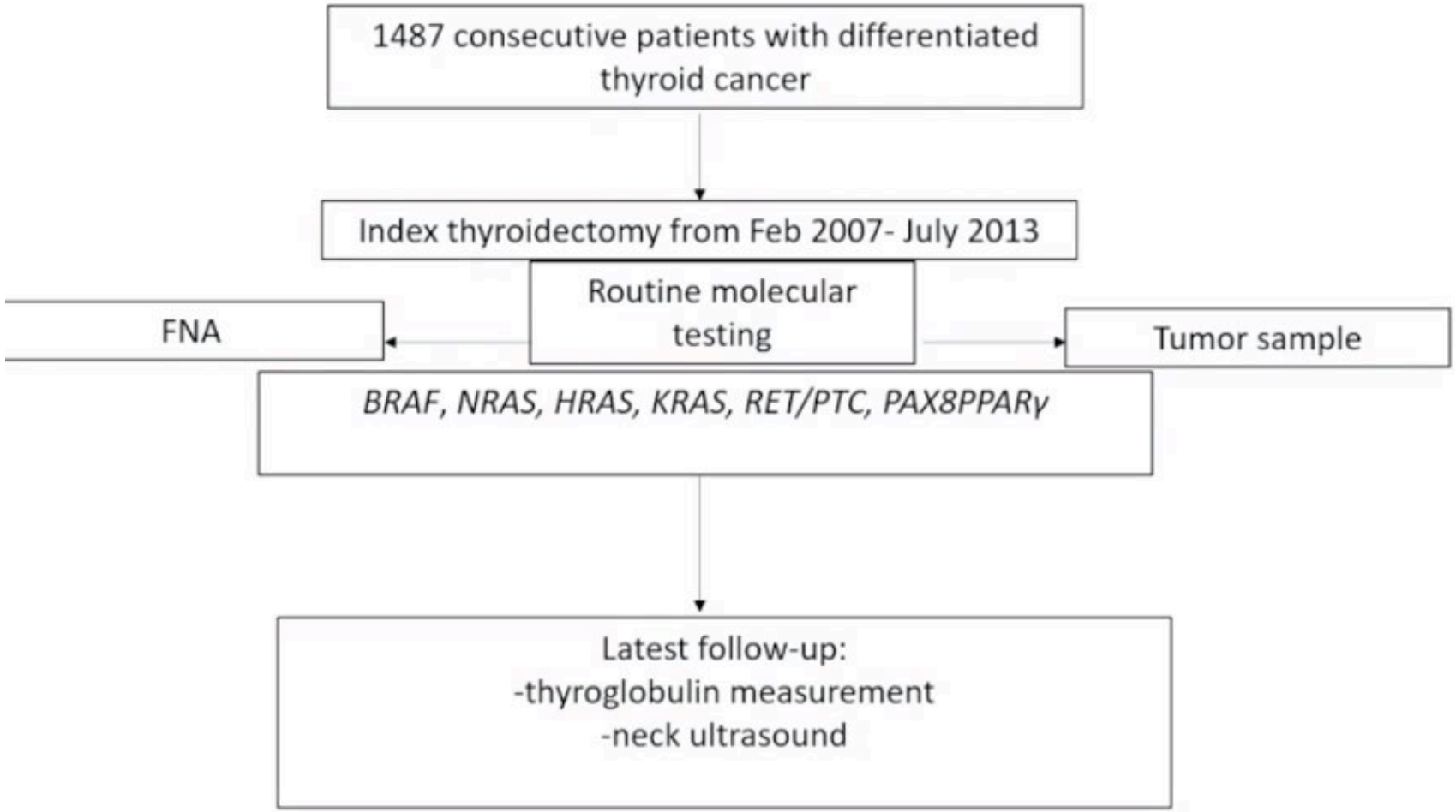
correlate thyroid cancer genotype with histology and outcomes

- 1510 patients with TC treated with total thyroidectomy and RAI according to 2006 and 2009 guidelines
- Routine molecular testing (7 genes panel)

- mean follow-up of 33 +- 21.2 months
  - BRAF-like tumors with higher risk histologic features
  - BRAF-like tumors with higher rates of recurrence compared to RAS like positive tumors

- Present study : long term follow-up to investigate rates of recurrence by genotype

METHODS


1487 consecutive patients with differentiated thyroid cancer
Index thyroidectomy from Feb 2007- July 2013
Routine molecular testing
FNA
Tumor sample
BRAF, NRAS, HRAS, KRAS, RET/PTC, PAX8PPARγ
Latest follow-up:
-thyroglobulin measurement
-neck ultrasound

SUMMARY OF PATIENT AND THYROID CANCER CHARACTERISTICS

Men	333 (22.3%)
Mean age (year)	49.0 ± 15.7
Mean tumor size, cm	2.0 ± 1.5
Type of thyroid cancer	
Papillary thyroid cancer	1468 (98.7%)
Follicular thyroid cancer	10 (0.67%)
Oncocytic carcinoma	10 (0.67%)
Multifocal	769 (51.7%)
Extrathyroidal extension	439 (29.5%)
Received radioactive iodine (RAI)	1054 (70.9%)
Number with central lymph node metastases	396 (26.6%)

Somatic mutations on a 7 gene panel

Number with mutations	1027 (69%)
Negative	460 (31%)
$BRAF^{V600E}$	640 (62.3%)
NRAS	221 (21.5%)
KRAS	8 (0.78%)
HRAS	87 (8.5%)
PAX8/PPARG	15 (1.5%)
RET/PTC	37 (3.6%)
$BRAF^{K601E}$	11 (1.07%)
$BRAF^{K601E}$, HRAS	1 (0.01%)
Complex BRAF mutation	1 (0.01%)
BRAF variant	1 (0.01%)

Recurrences

Median follow-up 7.3 +- 4.1 years

94 recurrences in 1390 patients : 6.7%

Biochemical : 0,6%

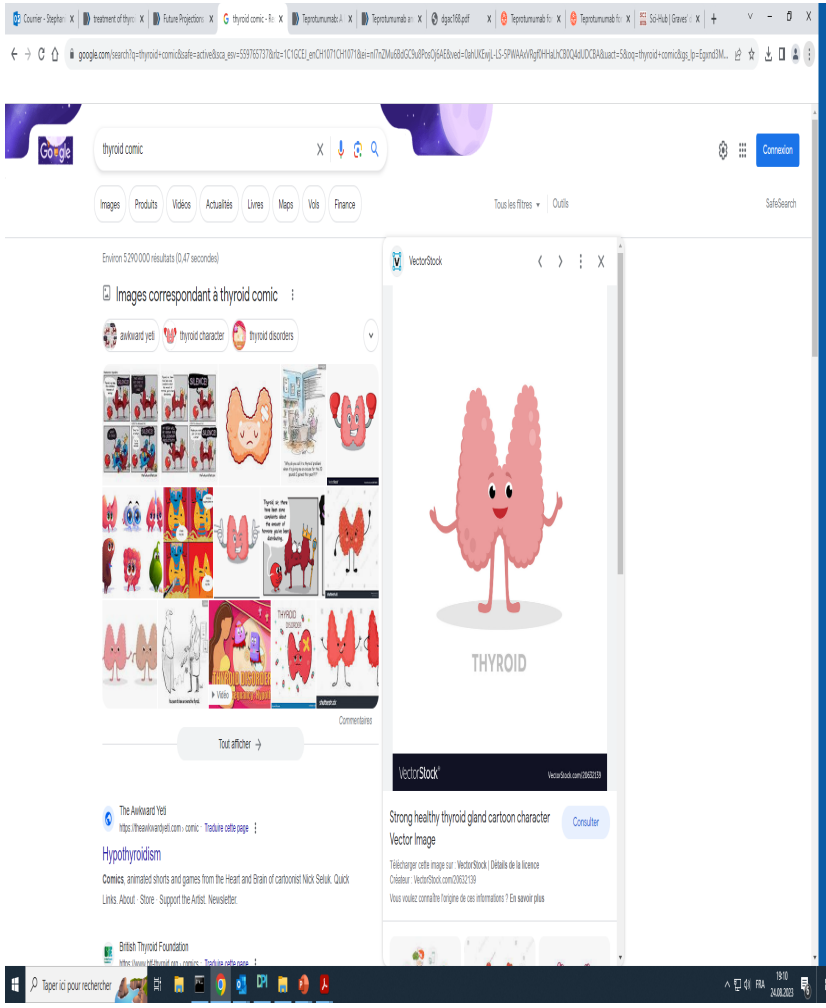
Structural : 6.1% : (Locoregional in 91% of the cases, distant metastases in 9% of the cases)

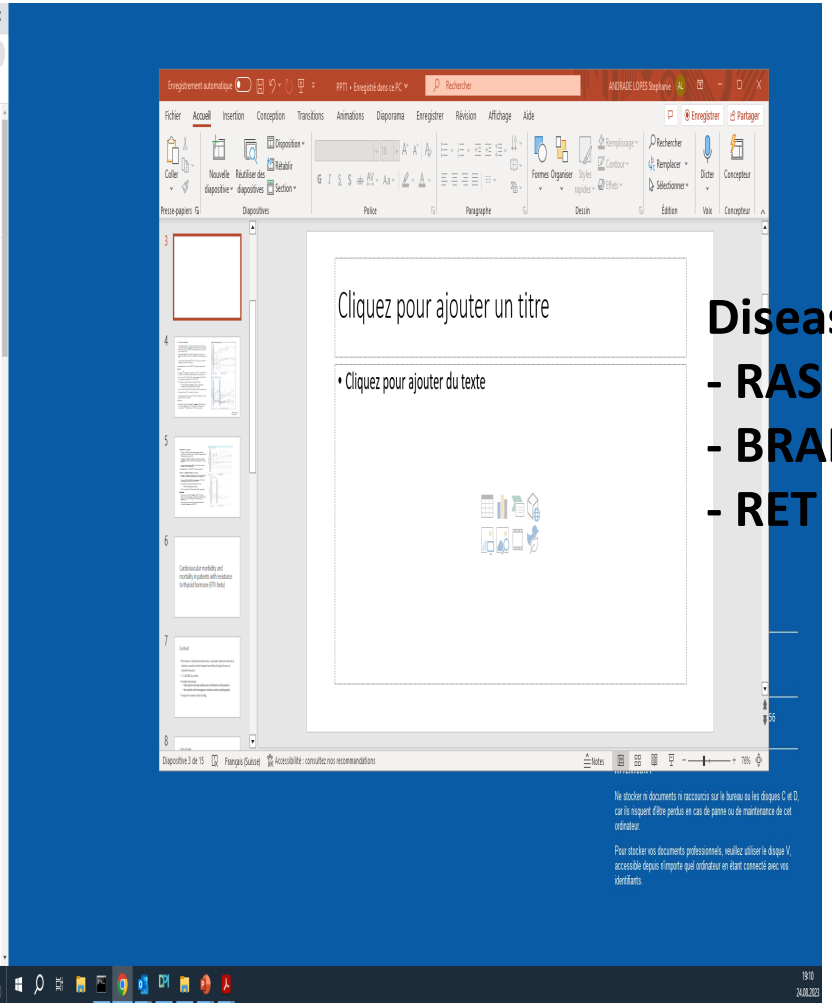
	Total	<2 years	2-5 years	> 5 years
N recurrence	94	58.5% 55/94	27.6% 26/94	13.8% 13/94
N structural recurrence	85	62% 53/85	27% 23/85	10.6% 9/85
N Biochemical recurrence	9	22% 2/9	33% 3/9	44% 4/9

Risk of recurrence according to somatic mutation

	N total	N With recurrence	% of recurrence
BRAFV600E	640	68	**10.6%**
RAS	316	3	**0.9%**
RET/PTC	37	3	**8.1%**
No mutation	460	19	**4.1%**

Disease free survival according to somatic mutation





Disease Free Survival at 5 years

- RAS ans PAX8PPAR Gamma: 99-100%

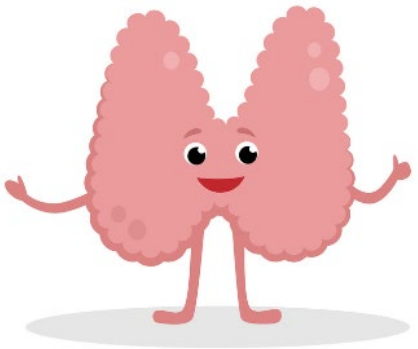
- BRAF V600E 88%

- RET PTC 87%

Take home message

- Risk of recurrence was 7% with 60% of the recurrences occurring within the first two years
- Most recurrences were locoregional
- 5 years DFS higher for patients with RAS-like mutations than BRAF-V600E mutations

- Limitations
  - 7 gene mutation analysis: no analysis of P53 or TERT mutations
  - Changes in postoperative treatment guidelines
  - Absence of multivariate analysis including known prognostic factors including tumor size, number of N1, size of N1…



Thank you for your attention