WHICH IS THE PATIENT PROFILE ELIGIBLE FOR A REDIFFERENTIATION STRATEGY

Simone de Leo

ASST Santi Paolo e Carlo

simone.deleo@asst-santipaolocarlo.it

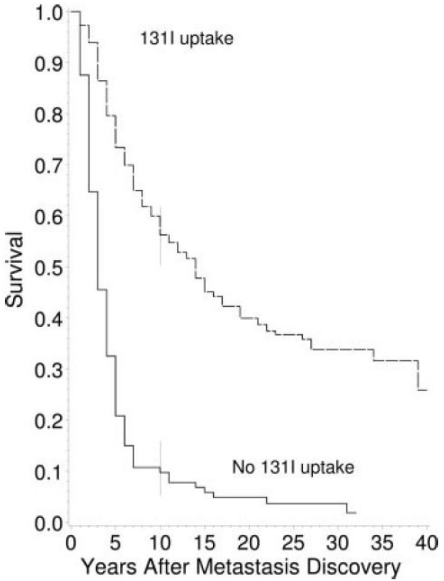
Sistema Socio Sanitario

Regione Lombardia

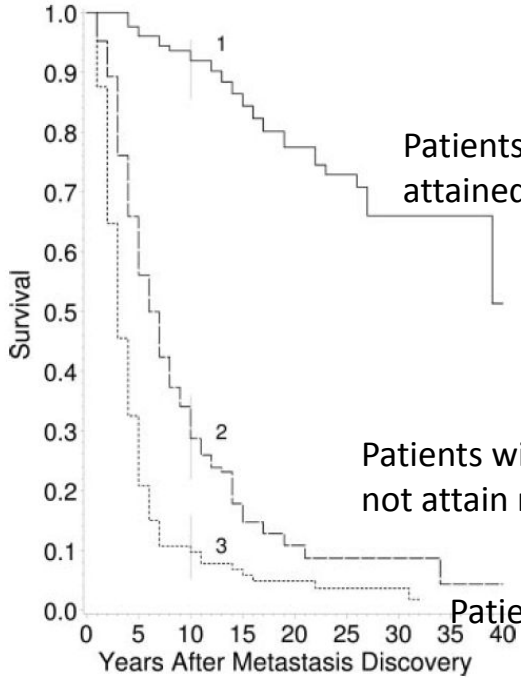
ASST Santi Paolo e Carlo

Radioactive iodine treatment

RAI therapy with 131I is a well-established treatment for patients with differentiated thyroid cancer



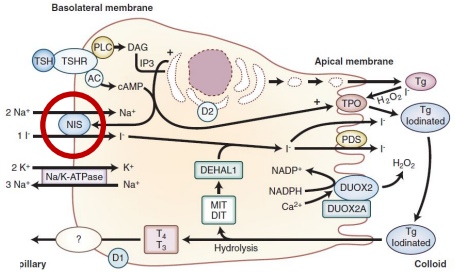
Survival after the discovery of metastases according to 131I uptake in the metastases



Patients with 131I uptake who attained negative imaging studies

Patients with 131I uptake who did not attain negative imaging studies

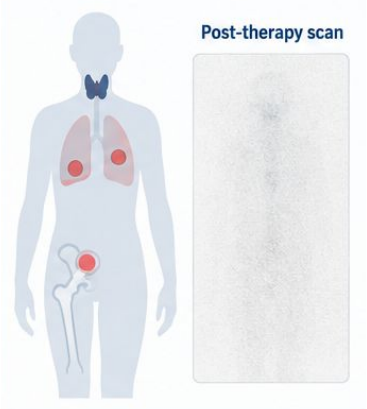
Patients with no 131I uptake



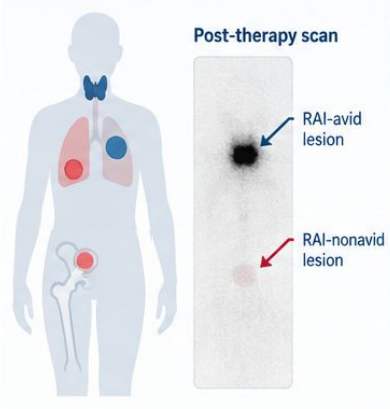
Durante et al. 2006, JCEM

Definitions of RAI refractoriness

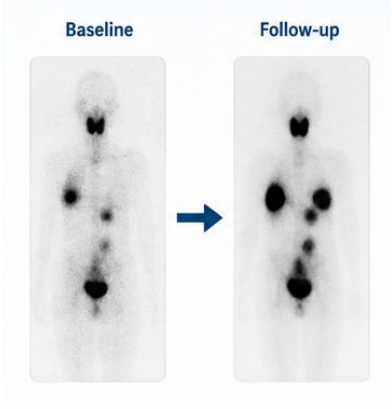
ABSENCE OF RAI UPTAKE ON WBS



ABSENCE OF UPTAKE IN SOME BUT NOT ALL LESIONS

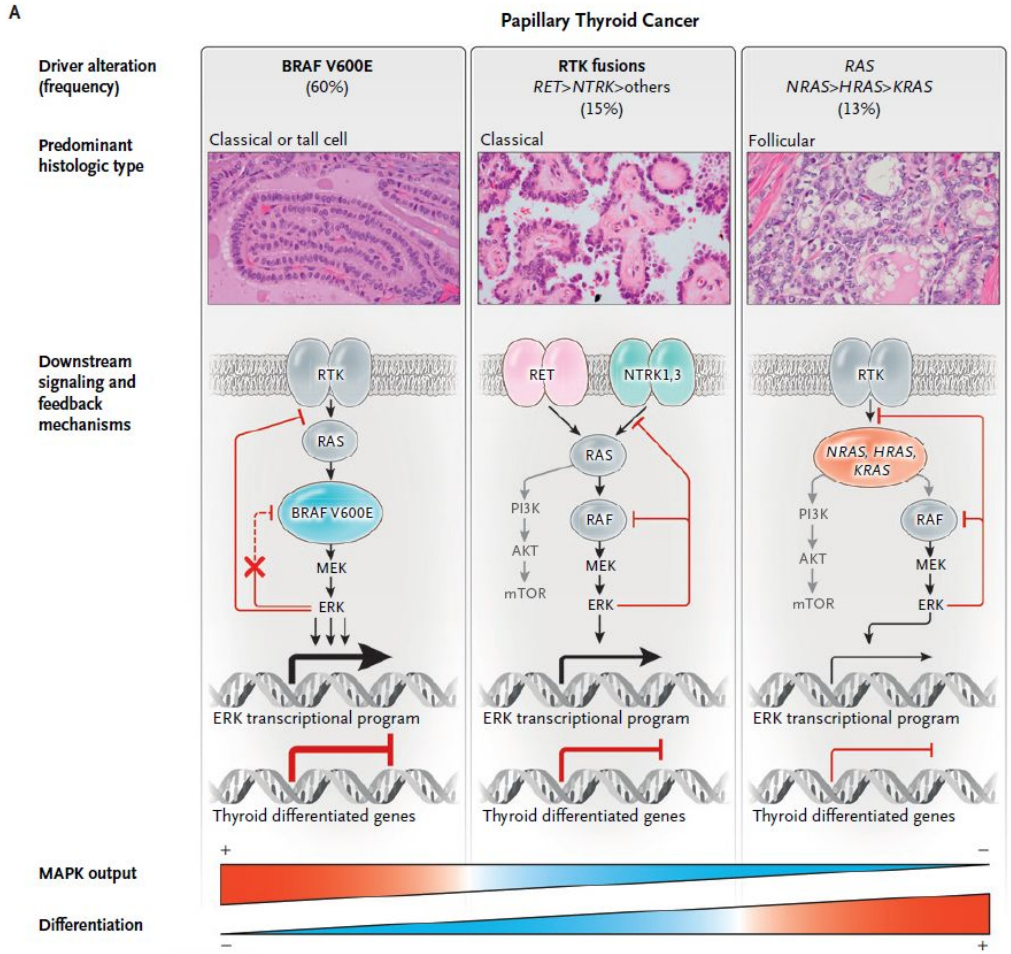


PROGRESSION DESPITE UPTAKE OF RAI



REACHING THE MAXIMUM ACTIVITY OF RAI

Haugen et al. 2015, Thyroid; Fugazzola et al. 2019 ETJ



Molecular drivers determine the degree of thyroid differentiation

- **RAS-mutated PTC** → relatively lower MAPK output → greater preservation of thyroid differentiation.
- **RTK fusion-driven PTC** → intermediate phenotype.
- **BRAF V600E PTC** → high MAPK output because of strong ERK activation and impaired negative feedback → greatest suppression of thyroid differentiation genes

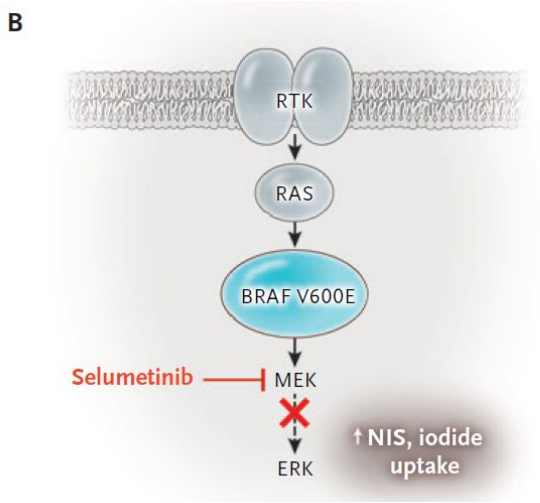
Fagin and Wells, 2016 NEJM

Can we reverse RAI refractoriness?

Research article

Small-molecule MAPK inhibitors restore radioiodine incorporation in mouse thyroid cancers with conditional BRAF activation

Debyani Chakravarty,[1] Elmer Santos,[2] Mabel Ryder,[1,3] Jeffrey A. Knauf,[1] Xiao-Hui Liao,[4] Brian L. West,[5] Gideon Bollag,[5] Richard Kolesnick,[3,6] Tin Htwe Thin,[6] Neal Rosen,[3,6] Pat Zanzonico,[2,7] Steven M. Larson,[2,6] Samuel Refetoff,[4,8,9] Ronald Ghossein,[10] and James A. Fagin[1,3]



Pharmacological inhibition of the MAPK pathway may reduce ERK activation and increase thyroid-specific gene expression

↑ thyroid-specific gene expression

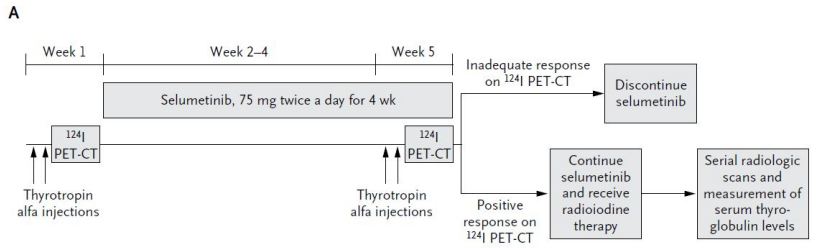
- ↑ NIS expression/function
- ↑ Thyroid peroxidase expression

↑ RAI uptake and organification

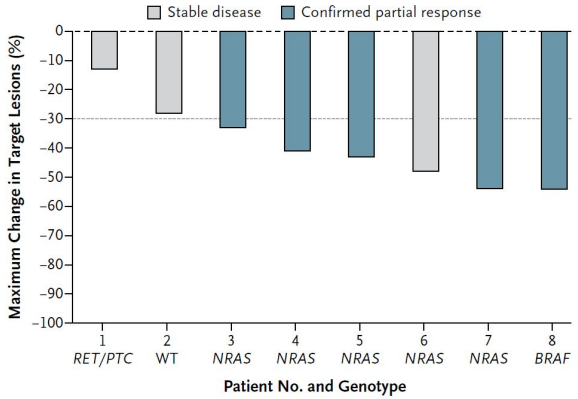
Potentially effective 131I therapy

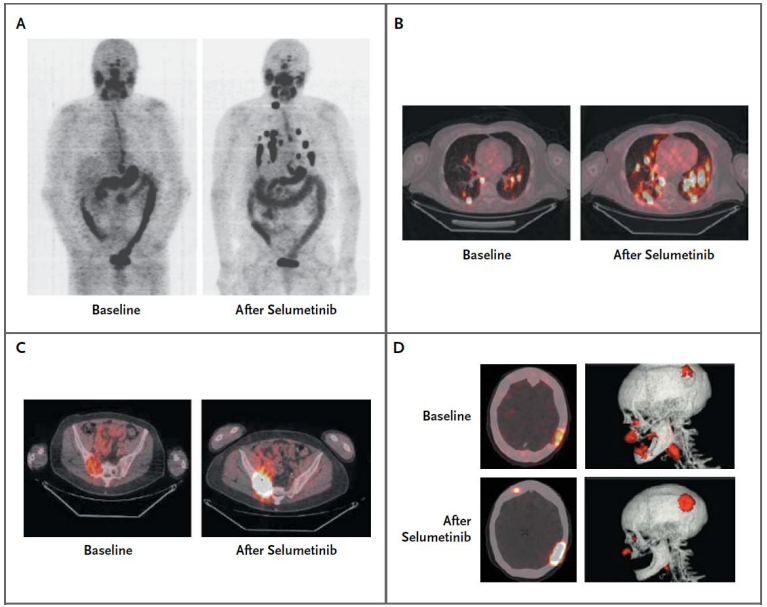
Chakravarty D et al 2011 JCI; Fagin and Wells, 2016 NEJM

Selumetinib pilot trial



Tumor Genotype	Patients with Increased Iodine Uptake in a Lesion after Selumetinib	Patients Who Received Radioiodine
	no./total no. of patients	
BRAF	4/9	1/9
NRAS	5/5	5/5
RET/PTC	2/3	1/3
Wild-type	1/3	1/3
Total	12/20	8/20





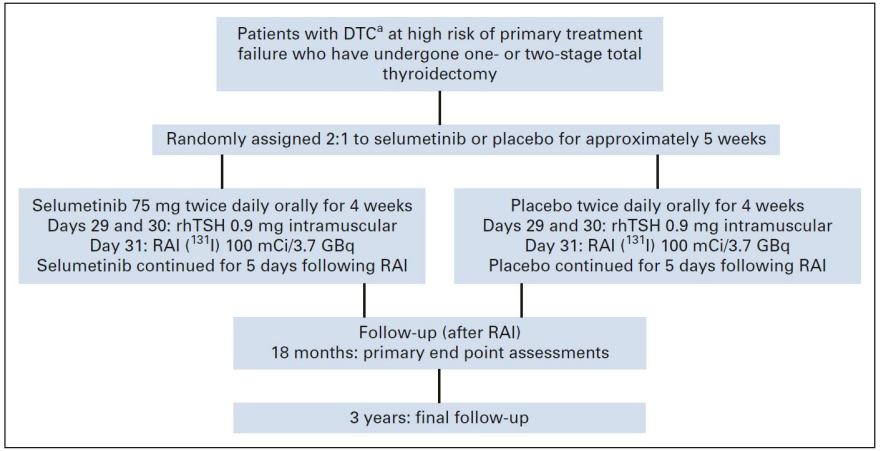
Biological redifferentation ≠ therapeutic efficacy ≠ clinical benefit

Ho et al, 2013 NEJM

Selumetinib Plus Adjuvant Radioactive Iodine in Patients With High-Risk Differentiated Thyroid Cancer: A Phase III, Randomized, Placebo-Controlled Trial (ASTRA)

Alan L. Ho, MD, PhD[1]; Marek Dedecjus, PhD[2]; Lori J. Wirth, MD[3]; R. Michael Tuttle, MD[4]; William B. Inabnet III, MD[5,6]; Jan Tennvall, PhD[7]; Fernanda Vaisman, PhD[8]; Lars Bastholt, MD[9]; Andrew G. Gianoukakis, MD[10,11]; Patrice Rodien, PhD[12]; Ralf Paschke, PhD[13]; Rossella Elisei, MD[14]; David Viola, MD[14]; Karen So, MD[15]; Danielle Carroll, MD[15]; Tina Hovey, MSc[16]; Bhavana Thakre, MD[17]; and James A. Fagin, MD[4]; the ASTRA investigator group

ASTRA is an international, phase III, randomized, placebo controlled, double-blind trial (NCT01843062).
233 randomly assigned (selumetinib, n=155 [67%]; placebo, n=78 [33%])



CR Rate	Selumetinib plus RAI	Placebo plus RAI
CR rate at 18 months, No. (%)		
Full analysis set (primary analysis)	62/155 (40)	30/78 (38)
	OR 1.07 (95% CI, 0.61 to 1.87); P = .8205	
Treatment compliant analysis set[a]	56/120 (47)	27/72 (38)
	OR 1.46 (95% CI, 0.81 to 2.67); P = .2131	

[a]Patients who received selumetinib/placebo twice daily from 7 days before to 5 days after RAI, as a minimum.

The addition of selumetinib to adjuvant RAI failed to improve the CR rate for patients with DTC at high risk of primary treatment failure

Ho et al, 2022 JCO

	Patients included (patients evaluated)	Inclusion criteria	Type of mutation (number)	PTC	FTC	PDTC	First-line treatment	Second-line treatment
Ho et al (2013)[13]	24 (20)	RAIR disease defined by (a) a non-RAI-avid metastatic lesion on a diagnostic whole body scan <2 years before enrolment, or (b) an RAI-avid lesion stable or progressive in size despite therapeutic ^{131}I >6 months before study entry, or (c) at least one [^{18}F]FDG-avid lesion with SUV_{max} ≥5; and measurable disease according to RECIST; and at least one [^{18}F]FDG-avid lesion	*BRAF*^{V600E} 9; *NRAS* 5; *RET/PTC* 3; wild-type 3	13	0	7	18	2*
Rothenberg et al (2015)[20]	10 (10)	Somatic *BRAF*^{V600E} mutation and metastatic or unresectable disease; and no ^{131}I uptake on a whole body scan (diagnostic or post treatment) within 14 months of study entry; and evaluable by CT scan; and ECOG ≥1	*BRAF*^{V600E} 10	10	0	0	10	0
Dunn et al (2019)[15]	12 (10)	*BRAF*^{V600E} mutation and RAIR disease defined by (a) a non-RAI-avid metastatic lesion on a diagnostic WBS <2 years before enrolment, or (b) an RAI-avid lesion of stable size or which progressed despite therapeutic ^{131}I >6 months before study entry, or (c) at least one [^{18}F]FDG-avid lesion with SUV_{max} ≥5; and no ^{131}I treatment <6 months before study entry	*BRAF*^{V600E} 12	9	0	3	11	1†
Tchekmedyian et al (2022)[16]	7 (7)	*BRAF*^{V600E} mutation and RAIR disease defined by (a) a non-RAI-avid metastatic lesion on a diagnostic whole body scan <2 years before enrolment, or (b) an RAI-avid lesion of stable size or an RAI-avid lesion that progressed despite therapeutic ^{131}I >6 months before study entry, or (c) at least one [^{18}F]FDG-avid lesion with SUV_{max} ≥5; and measurable disease according to RECIST	*BRAF*^{V600E} 7	4	0	3	7	0
Weber et al (2022)[21]	20 (20)	Unresectable or RAIR disease, or both; or RAIR disease defined by at least one metastatic lesion without therapeutically sufficient RAI accumulation on a diagnostic or therapeutic RAI scan performed less than 1 year before enrolment, or both; and at least one lesion ≥15 mm (short-axis diameter for nodes; long-axis diameter for other lesions)	*BRAF*^{V600E} 6; *NRAS* 2; *KRAS* 1; *APC* 1; *AKT* 1; *PTEN* 3; no mutation 6	10	7	3	20	0
Leboulleux et al (2023)[18]	24 (21)	*BRAF*^{V600E} mutation and RAIR disease defined by (a) presence of distant metastases without ^{131}I uptake on a post-therapy whole body scan, or (b) distant metastases disclosing RECIST version 1.1 progression within 12 months after a therapeutic ^{131}I administration, or both; and patients had measurable disease according to RECIST version 1.1 criteria; and no lesion >3 cm; and RECIST version 1.1 progression within 18 months before enrolment	*BRAF*^{V600E} 21; unknown 4	24	0	0	20	1‡
Leboulleux et al (2023)[17]	11 (10)	*RAS* mutation and RAIR disease defined by (a) the presence of distant metastases without ^{131}I uptake on a post-therapy whole body scan, or (b) distant metastases disclosing RECIST version 1.1 progression within 12 months after a therapeutic ^{131}I administration, or both; and patients had measurable disease according to RECIST version 1.1 criteria; and no lesion >3 cm; and RECIST version 1.1 progression within 18 months before enrolment	*RAS* 11	4	2	5	8	3§
Wadsley et al (2023)[19]	28 (28)	RAIR disease defined by (a) the presence of a measurable non-RAI avid lesion on a previous whole body scan, or (b) at least one measurable lesion had progressed within 12 months of RAI therapy, or both; and RECIST version 1.1 progression within 12 months before enrolment	NA	11	17	0	28	0

Leboulleux et al, 2025 Lancet Diabetes Endocrinol

Study	Drug (days)	Basis for ^{131}I administration	Patients receiving ^{131}I (treated/total)	^{131}I activity determination	Mean (range) ^{131}I activity
Ho 2013	Selumetinib (35)	^{124}I PET/CT: predicted dose ≥20 Gy to at least one metastatic lesion; maximum ^{131}I activity 300 mCi	1/9	MSKCC dosimetry protocol	NA
Dunn 2019	Vemurafenib (35)	^{124}I PET/CT: predicted dose ≥20 Gy to at least one metastatic lesion; maximum ^{131}I activity 300 mCi	4/12	MSKCC dosimetry protocol	253 mCi (130–401); 47–93% of MTA
Tchekmedyian 2022	Vemurafenib + anti-ErbB3 mAb (35)	^{124}I PET/CT: predicted dose ≥20 Gy to at least one metastatic lesion; maximum ^{131}I activity 300 mCi	4/7	MSKCC dosimetry protocol	236 mCi (197–299); 30–97% of MTA
Rothenberg 2015	Dabrafenib (42)	^{131}I WBS with 4 mCi after rhTSH; uptake seen in any abnormal site	6/10	Fixed activity	150 mCi
Weber 2022	Dabrafenib + trametinib (24)	^{123}I WBS + SPECT/CT (visual assessment)	2/6	^{124}I PET dosimetry	300 mCi (273–421)
Leboulleux 2023	Dabrafenib + trametinib (42)	All patients received therapeutic ^{131}I regardless of diagnostic scan result	21/21	Fixed activity	150 mCi
Wadsley 2023	Selumetinib (28)	Clinically relevant uptake or ≥30% increase in RAI uptake	11/28	Fixed activity	150 mCi

Leboulleux et al, 2025 Lancet Diabetes Endocrinol

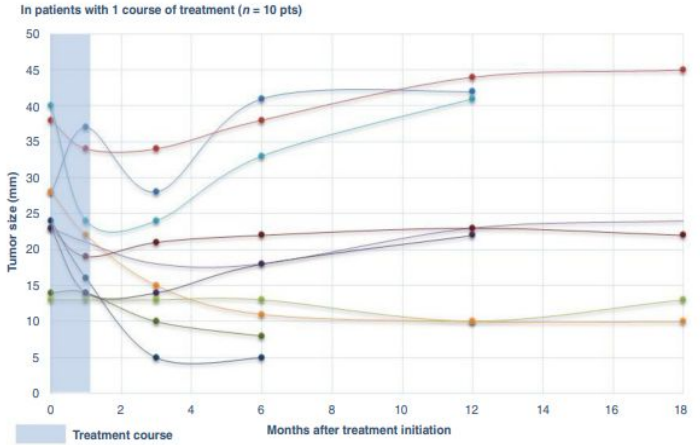
Redifferentiation in RAIR TC

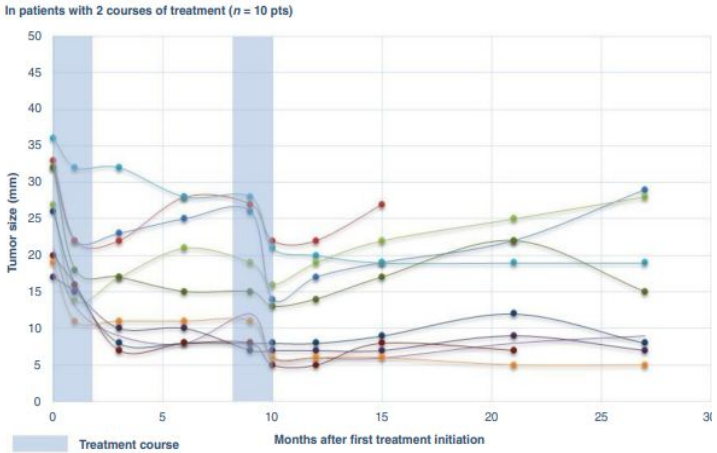
	Treatment	Number of patients included (number evaluable)	Iodine uptake evaluation method	Number of patients with increased iodine uptake	Number of patients treated with ^{131}I	Number of patients with complete response	Partial response
***BRAF*^{V600E} mutation**							
Ho et al (2013)[13]	Selumetinib with or without ^{131}I	NA (9)	^{124}I PET–CT	4 (44%)	1	0	11% (best)
Rothenberg et al (2015)[20]	Dabrafenib with or without ^{131}I	10 (10)	Diagnostic ^{131}I whole body scan	6 (60%)	6	0	20% (best)
Dunn et al (2019)[15]	Vemurafenib with or without ^{131}I	12 (10)	^{124}I PET–CT	6 (60%)	4	0	20% (best)
Tchekmedyian et al (2022)[16]	Vemurafenib and anti-ErbB3mAb with or without ^{131}I	7 (6)	^{124}I PET–CT	5 (80%)	4	0	33% (6 months)
Weber et al (2022);[21]	Dabrafenib and trametinib with or without ^{131}I	6 (6)	^{124}I PET–CT	2 (33%)	6	0	0% (best)
Leboulleux et al (2023)[18]	Dabrafenib and trametinib with or without ^{131}I	21 (24)	Post-treatment ^{131}I whole body scan	20 (95%)	21	1	38% (6 months); 57% (best)
***RAS* mutation**							
Ho et al (2013)[13]	Selumetinib with or without ^{131}I	NA (5)	^{124}I PET–CT	5 (100%)	5	0	80% (best)
Leboulleux et al (2023)[17]	Trametinib with or without ^{131}I	11 (10)	post-treatment whole body scan	6 (60%)	10	0	20% (6 months and best)
Burman et al (2022)[28]	Trametinib with or without ^{131}I	NA (25)	^{124}I PET–CT	22 (88%)	15	0	32% (6 months)

Data are RECIST tumour response.

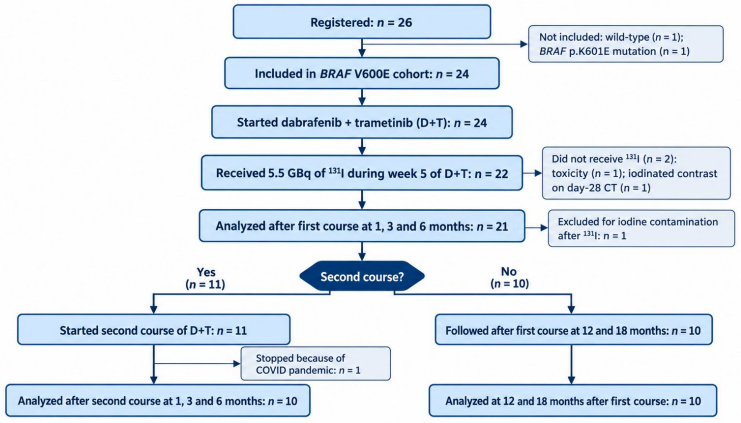
Table 3: Tumour response in thyroid cancer with *BRAF*^{V600E} or *RAS* mutations

Leboulleux et al, 2025 Lancet Diabetes Endocrinol





MERAIODE - BRAF

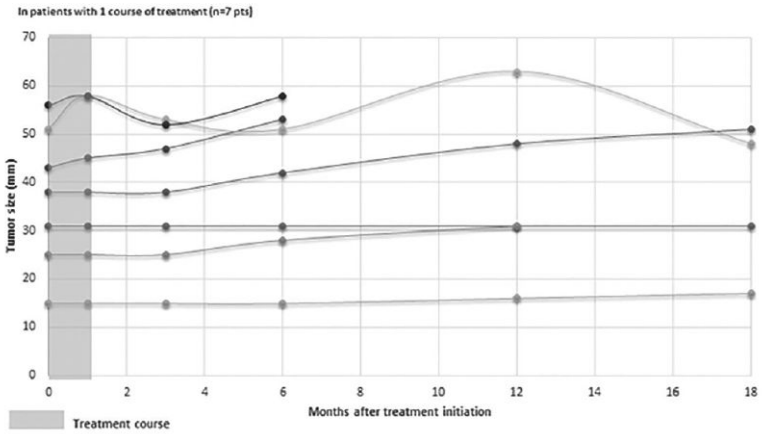


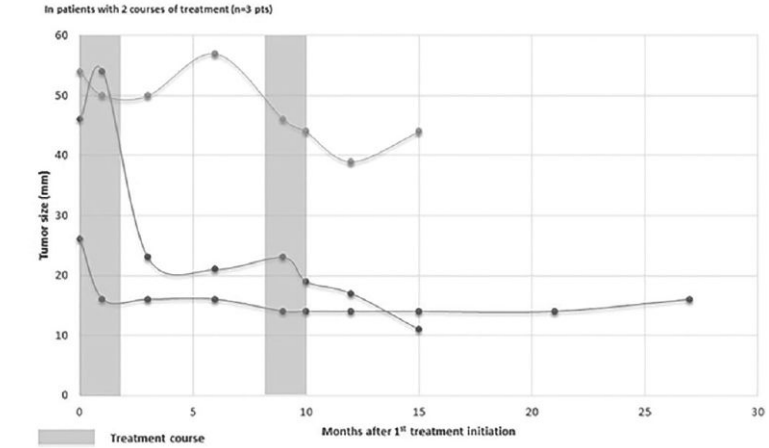
Dabrafenib-trametinib is effective in BRAF p.V600E mutated DTC patients for restoring 131I uptake.

6 months after 131I administration

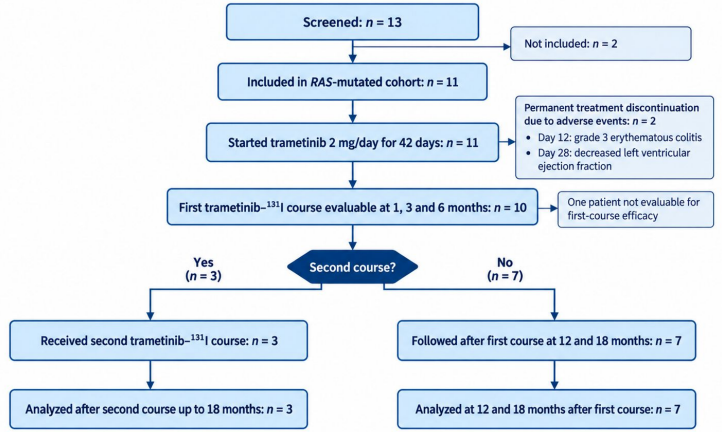
- PR observed in 38% of patients
- SD observed in 52% of patients

Leboulleux et al, 2023 Clin Cancer Res





MERAIODE - RAS



Trametinib in RAS mutated DTC seems less effective for restoring/increasing 131I uptake, and the administration of high activity (150 mCi) of 131I is followed by a low response rate:

- PR observed in 20% of patients
- SD observed in 70% of patients

Leboulleux et al, 2023 Thyroid

Redifferentiation in RAIR TC with RET mutation

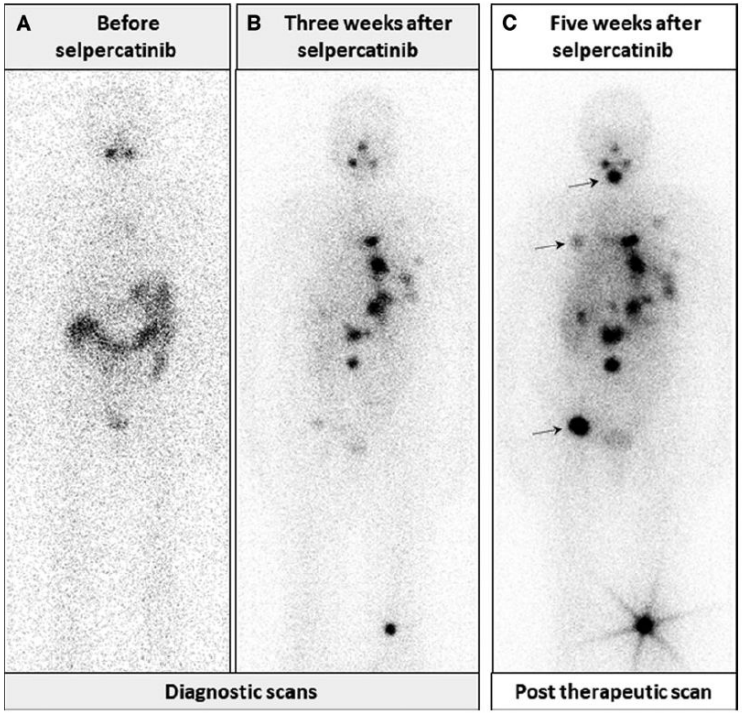


FIG. 1. Post-iodine 131 scans obtained before and after selpercatinib treatment. **(A, B)** Diagnostic scans were obtained with the use of iodine 131 (295 MBq [8 mCi]) before treatment with selpercatinib and 3 weeks after the initiation of treatment. At baseline, anterior image of the whole-body scan shows no iodine uptake in metastases with only physiological gastrointestinal tract elimination. After selpercatinib, the whole-body scan shows restored iodine uptake in almost all metastases that had previously shown no uptake, including bone metastases. **(C)** Additional metastatic foci of iodine uptake (three arrows) can be observed on the post-therapeutic (3700 MBq [100 mCi]) scan after 5 weeks of selpercatinib treatment.

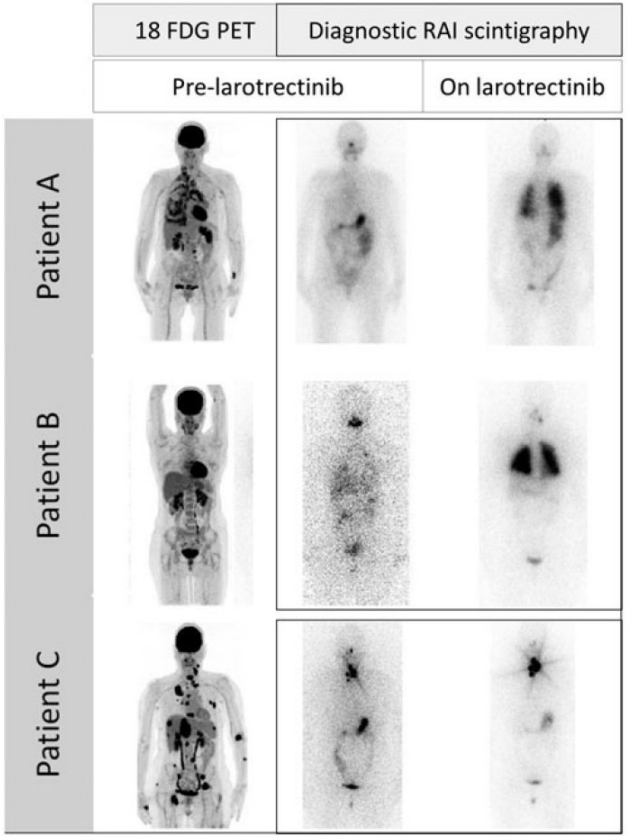
Groussin et al, 2021 Thyroid

Redifferentiation in RAIR TC with RET mutation

Author	Year of publication	Number of patients	RET fusion	Selpercatinib dose	Time to redifferentiation	Iodine avidity restoration based on	Tg before ^{131}I therapy	^{131}I therapy	Tg after ^{131}I therapy
Groussin L, et al.	2021	1	NCOA4-RET	160 mg bid	3 weeks	^{131}I scan	Basal Tg of 253 ng/ml (before Selpercatinib)	100 mCi (3700 MBq)	Basal Tg of 441 ng/ml
Lee YA, et al.	2021	1	CCDC6-RET	80 mg bid	5 months	^{123}I scan	Stimulated Tg of 5990 ng/mL (before Selpercatinib)	1°after 5 months-60 mCi (0.11GBq/kg) 2°after 19 months-60 mCi (0.11 GBq/kg)	Stimulated Tg after 1° RAI- 1930 ng/mL Stimulated Tg after 2° RAI- 855 ng/mL
Werner RA, et al.	2022	1	RET fusion positive (*not specified*)	*not specified*	15.5 months	^{131}I scan	Basal Tg of 148 ng/ml	1°after 15.5 months-9.4 GBq 2°after 20.5 months-7.5 GBq	Basal Tg of 21 ng/ml
Weiler D, et al.	2024	1	RET fusion positive (*not specified*)	160 mg bid	9 months	_	Basal Tg of 6.76 ng/ml	6672 MBq	Basal Tg of 2.48 ng/ml
Chiu HK, et al.	2024	1	RET fusion positive (*not specified*)	120 mg bid	9 months	_	Basal Tg of 5.7 ng/ml	162 mCi (103.5 mCi/m2, 3.1 mCi/kg)	Basal Tg of 0.8 ng/mL
Barbry F, et al.	2025	1	NCOA4-RET	*not specified*	6 weeks	_	Basal 6.94 ng/mL (before Selpercatinib)	3.7 GBq	Undetectable
Tarasova V D, et al.	2025	1	NCOA4-RET	160 mg bid	3 months	^{123}I scan	Basal 79.8 ng/mL	146 mCi (5402 MBq)	Basal Tg of 14.7 ng/mL

Talpacci et al, 2026 Front Oncol

Redifferentiation in RAIR TC with NTRK fusion



diffuse reuptake of RAI is seen in pulmonary lesions but neither in the metastatic lymph nodes nor in the fourth lumbar vertebra lesion

RAI reuptake can be seen in all known pulmonary metastases

only cervical lymph node shows RAI uptake, despite multiple 18FDG avid lesions are present on PET

Groussin et al, 2020 NEJM; Groussin et al, 2022 Thyroid

2025 American Thyroid Association Management Guidelines for Adult Patients with Differentiated Thyroid Cancer

Matthew D. Ringel,[1,*] Julie Ann Sosa,[2,*] Zubair Baloch,[3] Lindsay Bischoff,[4] Gary Bloom,[5] Gregory A. Brent,[6] Pamela L. Brock,[7] Roger Chou,[8] Robert R. Flavell,[9] Whitney Goldner,[10] Elizabeth G. Grubbs,[11] Megan Haymart,[12] Steven M. Larson,[13] Angela M. Leung,[5,14] Joseph Osborne,[15] John A. Ridge,[16] Bruce Robinson,[17] David L. Steward,[18] Ralph P. Tufano,[19] and Lori J. Wirth[20]

For patients with RAIR DTC, what is the role for kinase inhibitor redifferentiation therapy?

■ **RECOMMENDATION 74**

A. Redifferentiation by MAPK pathway blockade in patients with progressive RAIR DTC harboring targetable mutations may be considered in selected patients. Clinical trial participation is encouraged. ***(Conditional recommendation, Low certainty evidence)***

B. Redifferentiation approaches in adjuvant RAI treatment for patients with high-risk, non-gene selected DTC are not recommended. ***(Strong recommendation, Moderate certainty evidence)***

MERAIODE

ASTRA

Predictive factors of tumor response

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

A Phase II Redifferentiation Trial with Dabrafenib-Trametinib and ^{131}I in Metastatic Radioactive Iodine Refractory *BRAF* p.V600E-Mutated Differentiated Thyroid Cancer

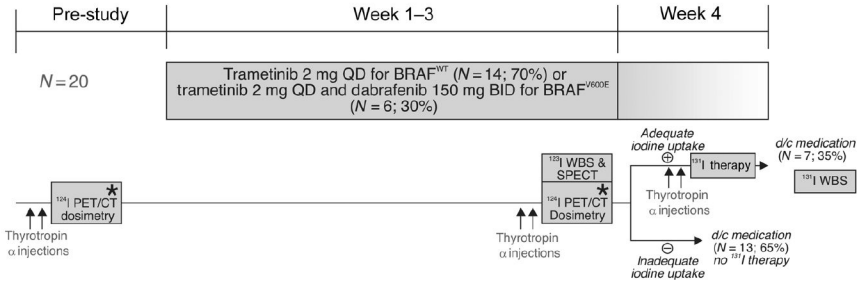
Sophie Leboulleux[1,2], Christine Do Cao[3], Slimane Zerdoud[4], Marie Attard[5], Claire Bournaud[6], Ludovic Lacroix[7,8], Danielle Benisvy[9], David Taïeb[10], Stéphane Bardet[11], Marie Terroir-Cassou-Mounat[1,4], Nadège Anizan[1,12], Emilie Bouvier-Morel[13], Livia Lamartina[1], Georges Lion[14], Sarah Betrian[15], Christophe Sajous[16], Aurélie Schiazza[9], Marie-Eve Garcia[10], Renaud Ciappuccini[11], Martin Schlumberger[1], Abir Al Ghuzlan[7], Yann Godbert[17], and Isabelle Borget[13]

MERAIODE BRAF

	Patients with 6 months RECIST response/Total n. of patients	Exact-Odds ratio CI: 95%	p-value
Baseline FDG uptake			
SUVmax> 14.7 (median)	4/10 (40%)	1	0.86
SUVmax≤ 14.7 (median)	4/11 (36%)	0.86 [0.11-7.0]	
1-month RECIST response			
Yes	5/10 (50%)	1	0.38
No	3/11 (27%)	0.39 [0.32- 24.5]	

Leboulleux et al, 2023 Clin Cancer Res

Predictive factors of tumor response



7/20 (35%) patients demonstrated successful redifferentiation: **5/14** (36%) in the **BRAF-WT**, **2/6** (33%) in the **BRAF-MUT** arm

Table 3. Predictors of successful redifferentiation.

Parameter		Successful redifferentiation, *n* (%) No	Yes	*P*
Histopathology	PTC/FTC	11 (65)	6 (35)	1.00
	PDTC	2 (67)	1 (33)	
Cumulative previous radioiodine activity	≤432 mCi (~16 GBq)	12 (75)	4 (25)	0.10
	>432 mCi (~16 GBq)	1 (25)	3 (75)	
$BRAF^{V600E}$ mutation	No	9 (64)	5 (36)	1.00
	Yes	4 (67)	2 (33)	
SUV_{peak} (FDG-PET)[a]	≤10	3 (33)	6 (67)	0.01[b]
	>10	7 (100)	0 (0)	
Unstimulated Tg pre-redifferentiation (ng/mL)	≤66	6 (100)	0 (0)	0.05
	>66	7 (50)	7 (50)	
Histopathology/$BRAF^{V600E}$ mutation[c]	FTC/no	4 (57)	3 (43)	1.00
	PTC/no	3 (60)	2 (40)	

[a]Mean of five lesions with highest uptake.
[b]$P < 0.05$ by Fisher exact test.
[c]The lower row presents a subgroup analysis for BRAF-WT PTC versus FTC.

Redifferentiation was successful in patients with
- a mean SUV_{peak} <10
- unstimulated Tg > median (66 ng/mL)

Weber et al, 2022 Clin Cancer Res

Predictive factors of tumor response

Clinical Outcomes of Radioactive Iodine Redifferentiation Therapy in Previously Iodine Refractory Differentiated Thyroid Cancers

David Toro-Tobon,[1] John C. Morris,[1,2] Crystal Hilger,[2] Candy Peskey,[2] Jolanta M. Durski,[3] and Mabel Ryder[1,2]

Characteristic	*Redifferentiated* (n=19)	*Non-redifferentiated* (n=14)	*Total sample* (n=33)	p
Non-stimulated thyroglobulin, median in ng/mL (IQR)				
Total sample	294 (103–1264)	29 (6–83.7)	103 (16–294)	0.03
PTC subgroup	66.5 (16.2–124.2)	46 (6.4–95.2)	46 (13.5–109)	0.18
IEFV-PTC subgroup	845 (294–1762)	—	—	—
FTC subgroup	342 (148–808)	—	—	—
Redifferentiation agent, *n* (%)				
Dabrafenib+Trametinib	7 (36.8)	11 (78.7)	18 (54.5)	0.01
Trametinib	12 (63.2)	0 (0)	12 (36.5)	<0.001
Pralsetinib	0 (0)	1 (7.1)	1 (3)	0.24
Alectinib	0 (0)	1 (7.1)	1 (3)	0.24
Selpercatinib	0 (0)	1 (7.1)	1 (3)	0.24
Histology, *n* (%)				
PTC	8 (42.1)	11 (78.6)	19 (57.6)	0.03
Classic	4 (21.1)	7 (50.0)	11 (33.4)	0.08
Tall cell subtype	2 (10.6)	2 (14.3)	4 (12.1)	0.75
With tall cell features	2 (10.6)	2 (14.3)	4 (12.1)	0.75
Infiltrative encapsulated follicular variant PTC	4 (21.1)	0 (0)	4 (12.1)	0.07
FTC	7 (36.6)	0 (0)	7 (21.2)	0.01
Poorly differentiated thyroid cancer	0 (0)	3 (21.4)	3 (9.1)	0.03
Main mutation(s), *n* (%)				
BRAF	7 (36.8)	11 (78.6)	18 (54.5)	0.01
RAS	11 (57.9)	0 (0)	12 (36.4)	<0.001
RET	1 (5.3)	2 (14.3)	3 (9.1)	0.38
TERT	8 (42.1)	8 (57.1)	16 (48.5)	0.40
NKX2	4 (21.1)	0 (0)	4 (12.1)	0.07
BRCA2	1 (5.3)	1 (7.1)	2 (6.1)	0.82
CDKN2A	1 (5.3)	1 (7.1)	2 (6.1)	0.82
Alk rearrangement	0 (0)	1 (5.3)	1 (3.0)	0.32

MEK inhibitor monotherapy for RAS mutant disease, combination BRAF-MEK inhibitors for BRAF mutant disease, RET inhibitor for RET fusion, and ALK inhibitor for ALK mutant disease (n.=33)

Redifferentiation was successful in patients with
- higher unstimulated Tg levels
- FTC histotype (worse in PTC and PDTC)
- RAS mutation (worse in BRAF)

	Rediff.	Non rediff.	p
CR	0 (0)	1 (8.3)	0.23
PR	2 (11.8%)	0 (0)	0.22
SD	6 (35.2)	6 (50)	0.43
PD	2 (11.8)	3 (25)	0.35
Non-CR/non-PD	7 (41.2)	2 (16.7)	0.16

Toro-Tobon et al, 2024 Thyroid

Mutation in the SWI/SNF pathway: predictive for inefficacy?

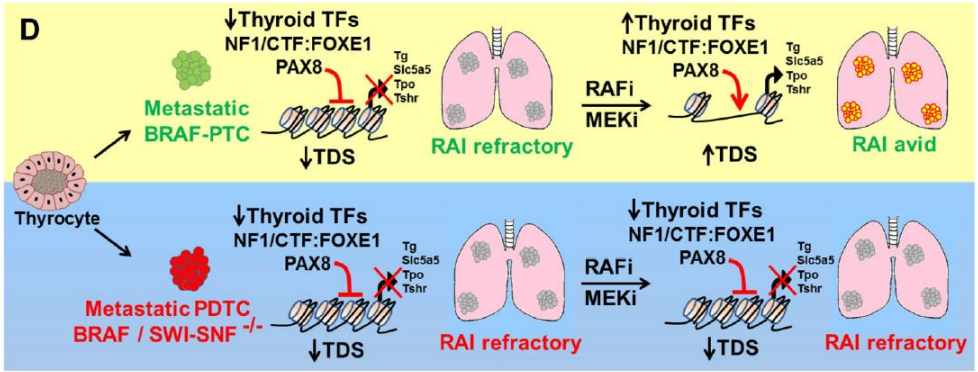


Figure 7: Thyroid cancers with *ARID1A*, *ARID2*, or *SMARCB1* mutations are resistant to redifferentiation by MAPK pathway inhibitors.

SWI/SNF complexes are ATP-dependent chromatin-remodeling complexes

SWI/SNF activity helps maintain the thyroid differentiation program by allowing transcription factors such as PAX8, NKX2-1, and FOXE1 to access their target genes, including genes involved in iodine handling such as SLC5A5/NIS

SWI/SNF loss-of-function alterations, particularly in ARID1A, ARID2, or SMARCB1, may lock thyroid cancer cells in a dedifferentiated state and confer resistance to MAPK inhibitor-induced restoration of RAI uptake.

Saqcena et al, 2021 Cancer Discov

Which is the patient profile eligible for a redifferentiation strategy?

- ✔ Low-moderate FDG uptake
- ✔ Higher serum thyroglobulin levels
- ✔ Preserved follicular phenotype/FTC
- ✔ RAS mutation (?)
- ✔ No clear SWI/SNF-loss resistance signal

Open questions

- Which patients are most likely to derive a clinically meaningful benefit?

Trial	Population / molecular profile	Redifferentiation strategy
NCT06440850	High-risk DTC, **BRAF V600E**, before initial RAI	Vemurafenib + cobimetinib
NCT06007924	Progressive **RAI-refractory DTC with RAF-dimer–driven alterations**; separate ATC cohort	Avutometinib + defactinib
NCT05783323 – LANTERN	Metastatic DTC with **NTRK fusion**, including pediatric/AYA patients	Larotrectinib
NCT06458036 – RAISE	Newly diagnosed metastatic DTC with **RET fusion**, age 2–25 yr	Selpercatinib
NCT05668962	Restoration of RAI uptake in RAI-R TC with **RET fusion**	Selpercatinib
NCT05733013	Prospective MSK **real-world observational registry** of patients receiving redifferentiating agents in routine practice	

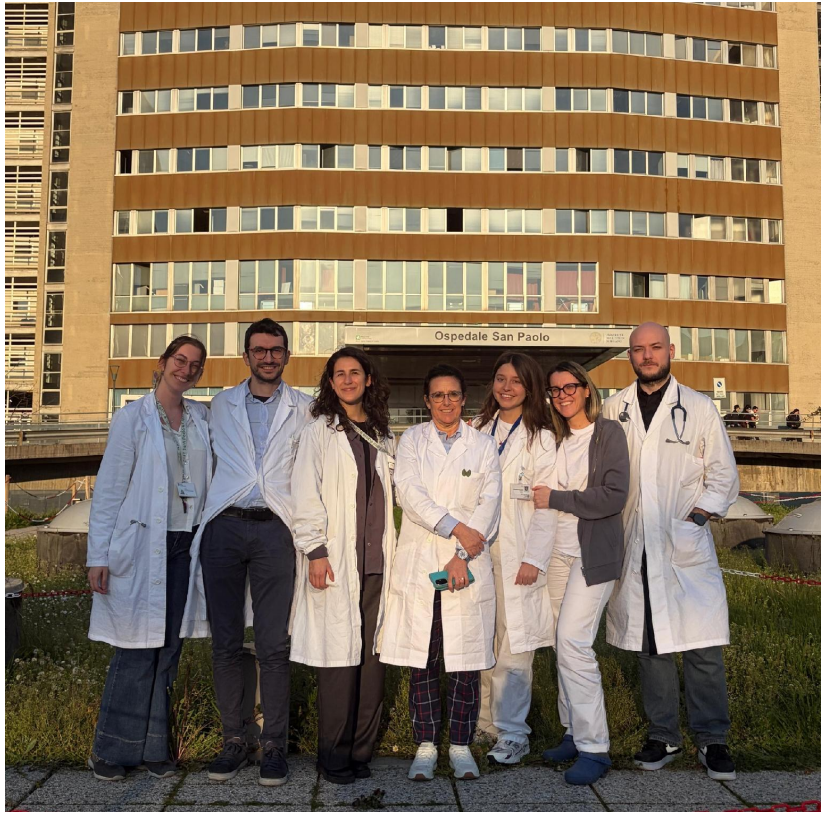
Trial	Population / molecular profile	Redifferentiation strategy
NCT06440850	High-risk DTC, **BRAF V600E**, before initial RAI	Vemurafenib + cobimetinib
NCT06007924	Progressive **RAI-refractory DTC with RAF-dimer–driven alterations**; separate ATC cohort	Avutometinib + defactinib
NCT05783323 – LANTERN	Metastatic DTC with **NTRK fusion**, including pediatric/AYA patients	Larotrectinib
NCT06458036 – RAISE	Newly diagnosed metastatic DTC with **RET fusion**, age 2–25 yr	Selpercatinib
NCT05668962	Restoration of RAI uptake in RAI-R TC with **RET fusion**	Selpercatinib
NCT05733013	Prospective MSK **real-world observational registry** of patients receiving redifferentiating agents in routine practice	

Open questions

- Which patients are most likely to derive a clinically meaningful benefit?
- Can redifferentiation be successfully repeated?
- What disease burden/lesion size remains amenable to effective RAI therapy?
- What is the optimal duration of redifferentiation treatment before ^{131}I?
- What is the optimal treatment schedule?
- How much restored RAI uptake is enough?

Thank you for your attention

Sistema Socio Sanitario
Regione Lombardia
ASST Santi Paolo e Carlo



Dr Simone De Leo

Medico Chirurgo
simone.deleo@asst-santipaolocarlo.it

