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► To cite this version:

Sophie Leboulleux, Christine Do Cao, Slimane Zerdoud, Marie Attard, Claire Bournaud, et al.. MERAIODE: A Phase II Redifferentiation Trial with Trametinib and ¹³¹I in Metastatic Radioactive Iodine Refractory RAS Mutated Differentiated thyroid Cancer. *Clinical Cancer Research*, 2023, 29 (13), pp.2401-2409. 10.1158/1078-0432.CCR-23-0046 . inserm-04552345

HAL Id: inserm-04552345

<https://inserm.hal.science/inserm-04552345>

Submitted on 19 Apr 2024

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1 **MERAIODE: A Phase II Redifferentiation Trial with Trametinib and ¹³¹I in Metastatic**
2 **Radioactive Iodine Refractory RAS Mutated Differentiated thyroid Cancer**

3

4

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37

38 Manuscript count: 1800

39 Number of tables: 2

40 Number of figures: 1

41 Online appendix

42 **Running Title: Trametinib-¹³¹I in RAIR RAS mutated DTC**

43

44

45 **Keywords:** refractory thyroid cancer, *RAS* mutation, redifferentiation, trametinib, anti-MEK

46

47 Dear Editor,

48 *RAS* mutations are present in one third of follicular-cell derived thyroid cancer (TC)
49 (1). They are more frequent in follicular TC and in follicular subtype of papillary TC compared
50 with other subtypes, with *NRAS* being more frequently mutated than *HRAS* or *KRAS* (2, 3).
51 In the case of *RAS* mutations, the activation of the Mitogen-Activated Protein (MAP) kinase
52 pathway is less intense than in case of *BRAFp.V600E* mutation. Even though *RAS* mutated
53 tumors are better differentiated than *BRAFp.V600E* mutated tumors, the expression of
54 proteins involved in the iodine metabolism is decreased. These abnormalities may be
55 reverted by the inhibition of the MAPK pathway (4). In a pioneer study on redifferentiation of
56 *RAS* mutated radioactive iodine refractory (RAIR) TC with selumetinib (a MEK inhibitor),
57 significant ¹³¹I tumor uptake reappeared in all 5 patients, resulting in partial tumor responses
58 in 4 (80%) of the patients treated with ¹³¹I (5).

59 In a recent phase II prospective trial in 21 patients with a *BRAFp.V600E* mutated
60 RAIR DTC, dabrafenib-trametinib was associated with reinduction of radioiodine uptake in
61 95% of the patients with a 6-months response rate of 38%, after the administration of a high
62 ¹³¹I activity following rhTSH injections (6). In the present study focused on metastatic RAIR
63 *RAS*-mutated DTC, we investigated the efficacy and safety of trametinib treatment before the
64 administration of a high ¹³¹I activity (following rhTSH injections).

65

66 MERAIODE is a multicentre, prospective phase II trial in patients with RAIR DTC, with
67 two independent cohorts with similar designs, one for *BRAF* p.V600E and one for *RAS*
68 mutated patients (NCT 03244956). The results of *BRAF*pV600E-mutated cohort study were
69 recently published (6). Detailed inclusion and exclusion criteria, procedures and objectives,
70 available in the Supplementary Table 1, were similar to the *BRAFp.V600E* mutated cohort
71 except for treatment consisting in trametinib-¹³¹I.

72 Briefly, RAIR patients were treated with trametinib (2 mg/d) for 42 days. A ¹³¹I
73 diagnostic WBS (185 MBq, 5 mCi) was performed at baseline prior trametinib (dc1-WBS)
74 and between days 28 and 35 (dc2-WBS). A fixed ¹³¹I activity of 5500 MBq (150 mCi) was

75 administered after rhTSH injections at day 35 +/-2 whatever the results of the dc2-WBS.
76 Tumor response was assessed according to RECIST version 1.1 at 1, 3, 6, 12 and 18
77 months after trametinib initiation or until tumor progression (7). Patients with a partial
78 response assessed by the local investigator at 6 or 12 months, could undergo a second
79 course of trametinib-¹³¹I (5500 MBq-150 mCi after rhTSH). The primary endpoint was the
80 overall response rate (ORR) at 6 months according to central review.

81 This investigator-initiated trial was sponsored by Gustave Roussy and conducted
82 within the French Endocan-TuThyRef network. The study was conducted in accordance with
83 the protocol approved by ethics committee (Comité de Protection des Personnes Ouest IV;
84 N.33/17_1-PPRE) in accordance with the 2013 revised Declaration of Helsinki. All patients
85 provided written, informed consent. Detailed statistical analysis is available in the
86 Supplementary Table 1. Tissue genotyping and gene expression analysis were performed in
87 a central laboratory at Gustave Roussy at the end of the study (Supplementary Tables 1 and
88 2).

89

90 From March 2018 to March 2020, among 13 screened patients, 11 were included
91 (Supplementary Figure 1). Ten patients were evaluable for the efficacy of the first treatment
92 course at 6 months. Most patients were men (64%) with poorly differentiated TC (45%)
93 (based on central review) (Table 1). Based on the investigator RECIST assessment, 3
94 patients with PR at 6 or 12 months were re-treated with a second course of trametinib-¹³¹I.

95

96 Abnormal ¹³¹I uptake was present at baseline (dc1-WBS) in 3/10 (30%) patients, on
97 dc2-WBS in 4/9 (44.4%) patients and on the post-treatment WBS in 6/10 (60%) patients.

98 On dc-1-WBS, the 3 patients with abnormal ¹³¹I uptake had one metastatic site with ¹³¹I
99 uptake. Two of them had 2 metastatic sites on the dc-2-WBS and one remained with 1
100 metastatic site on the dc-2-WBS (Supplementary Figure 2). One patient without abnormal
101 dc2-WBS was found to have abnormal uptake on the post-treatment WBS and in 3 patients,

102 the number of metastatic sites with abnormal uptake was higher on the post-treatment WBS
103 compared to the dc2-WBS.

104

105 At 6 months following the 1st treatment course, there were no CR, 2 (20%, CI_{95%}= [3-
106 56]) PR, 7 (70%, CI_{95%}= [34-93]) SD and 1 PD (Table 2, Figure 1, Supplementary Table 3,
107 Supplementary Figures 3 and 4). The median size change of the target lesions was +1.8%
108 (mean = -3.8%; range: -53 to +23) (Figure 1). The ORR at 1 and 3 months were 10 and 20%,
109 respectively. PERCIST evaluation was available in 9 patients at 6 months, and demonstrated
110 PR in 2 cases (22 %), SD in 6 (67 %) and PD in 1 (11 %). Among the 7 patients without
111 serum Tg antibodies, one patient had a biochemical partial response at 3 and 6 months.

112

113 The 3 evaluable patients who had a 2nd treatment course had abnormal ¹³¹I uptake on
114 the post-treatment WBS of the second ¹³¹I administration. The number of metastatic sites on
115 the second post-treatment WBS was similar to the first post-treatment WBS in 2 cases and
116 lower in one case (4 vs.2). Among the 3 patients, 1 had a PR during the 18 months following
117 the 2nd course, whereas the other 2 patients progressed at 3 and 6 months after the 2nd
118 course.

119

120 On September 1st, 2022, the median follow-up time was 34 months (range: 1.1-49.2).
121 The median PFS (central evaluation) was 12.0 months. The 12-month-PFS and 24-month-
122 PFS rates (central evaluation) were 60.0% CI_{95%}= [25.3-82.7] and 40.0% CI_{95%}= [12.3-67.0],
123 respectively. No deaths occurred. None of the patients developed anaplastic transformation
124 during follow-up.

125

126 During trametinib treatment, 9/11 (82%) patients experienced at least one AE, related
127 or not to treatment. Most AEs were grade 1 (36%) and grade 2 (27%) (Supplementary Table
128 4). There were 3 grade 3 AEs in 2 patients, and no grade 4.

129 Treatment was definitively stopped in 2 cases due to AE: at day 12 for a grade 3
130 erythematous colitis; at day 28 for a grade 2 decrease of left ventricular ejection fraction. In
131 this last case, ¹³¹I was administered.

132

133 Following treatment initiation, the global health, the functioning dimensions and the
134 symptoms were impacted with a deterioration from baseline to the end of treatment (D42)
135 which was reversible afterwards (Supplementary Table 5, Supplementary Figure 5).

136 Among the 11 patients included, based on the local *RAS* mutation assessment, 9
137 tissue samples were available for NGS genotyping at the central laboratory. The average
138 coverage depth was 693X (301X to 897X). Tumor mutational load ranked from 1.7 to 135.7
139 mutations per megabase. Five samples harbored a *NRAS* mutation, and two samples
140 harbored a *HRAS* mutation, whereas no *RAS* mutation was detected in two samples. All
141 samples were wild type for *TERT* promoter. Six samples had one to six additional variants,
142 largely of unknown significance. Three pathogenic mutations other than *RAS*, were detected,
143 in *FANCD2*, *PTEN* and *MSH2* (Supplementary Table 6). The gene expression analysis of
144 2,559 transcripts, from genes associated to cancer was performed on 8 samples, which did
145 not show significant differential expression associated to tumor response.

146

147 This phase 2 trial, which included 11 patients, showed that the administration of
148 trametinib for 6 weeks increased the ¹³¹I uptake in two-thirds of RAIR *RAS* mutated tumors
149 with a 6-months response rate of 20%. These results were not as good as expected, given
150 the previous results of redifferentiation with another MEK inhibitor selumetinib (5). Trametinib
151 is also less effective in RAIR *RAS* mutated tumors than the combination of dabrafenib-
152 trametinib in *BRAFp.V600E* mutated RAIR DTC tumors, for patients otherwise meeting
153 similar inclusion criteria i.e. RAIR, progression within 18 months prior to inclusion and no
154 lesion over the size of 30 mm (6) .

155 *RAS* mutated tumors are known to have a better differentiation score than *BRAFp.V600E*
156 mutated tumors. Indeed, despite being RAIR, 3 of the 10 patients had abnormal ¹³¹I uptake

157 on the baseline dc-1 WBS compared to 5% in *BRAFp.V600E* mutated tumors. Furthermore,
158 trametinib was not very efficient in restoring ¹³¹I uptake, with only 44% of the cases showing
159 abnormal ¹³¹I uptake on the dc-2 WBS and 60% on the post-therapy WBS. Subsequently, the
160 response rate at 6 months was only 20% and the response rate was anecdotal in patients
161 who received a second course of trametinib-¹³¹I. The 12-month-PFS and the 24-month-PFS
162 rates were also low, being 60% and 40%, respectively in patients who had a RECIST
163 progression within 18 months prior to inclusion.

164 We did not observe any decrease in tumor size during trametinib treatment and prior to the
165 administration of ¹³¹I, contrary to the association of anti BRAF and anti MEK in
166 *BRAFp.V600E* mutated tumors (6, 8). This observation raises the hypothesis that trametinib
167 alone does not have a major anti-tumor effect. These results also highlight the difficulty in
168 targeting the *RAS* mutation in oncology, with limited efficacy of anti MEK treatment and the
169 occurrence of *RAS* mutation in RAIR DTC as resistance mutation in patients treated with
170 RET or BRAF inhibitors (9, 10) inhibitors. Indeed, the *KRASG12C* mutation for which specific
171 inhibitors such as adagrasib or sotorasib are available, are rarely seen in RAIR TC.

172 The tissue genotyping in this study confirmed a higher frequency of the *NRAS* mutation.
173 Surprisingly in 2 samples, *RAS* mutations, found locally, were not found on the central
174 analysis performed at the end of the study. Since the protocol did not plan to exclude
175 patients based on this central analysis these patients were not excluded. One of them though
176 disclosed ¹³¹I abnormal uptake on the post treatment WBS and had a partial response.

177 Safety of trametinib treatment showed a tolerance concordant to what was expected, with the
178 absence of grade 4 AE event and grade 3 AEs in 18% of the cases.

179 Given the small sample size of the cohort, this study is mainly descriptive, precluding any
180 definitive conclusion. The high rate of poorly differentiated tumors and the absence of *RAS*
181 mutation on the central laboratory analysis in 2 cases might have negatively impacted the
182 present results.

183 However, this is the first prospective study that used trametinib treatment with ¹³¹I treatment
184 administration planned for all patients, and not based on the dc2-WBS findings. It is also the

185 first study to provide long-term follow-up and to explore a second course of trametinib-¹³¹I
186 treatment.

187

188 **Conclusion**

189 The treatment with trametinib in *RAS* mutated DTC is not highly effective for
190 restoring/increasing ¹³¹I uptake and the administration of high activity (150mCi, 3700MBq) of
191 ¹³¹I is followed by a low response rate. Other strategies than trametinib alone should be
192 developed for the redifferentiation of *RAS* mutated RAIR DTC.

193

194 **Acknowledgments**

195 The authors would like to thank the patients, their families, all research staff, and
196 investigators involved in this study, Catherine Richon and Patrick Saulnier from BMO unit in
197 AMMICA UMS3655/US23 for their technical assistance for Tissue genotyping and GE
198 analysis, and finally Bastien Job from Bionformatic unit in AMMICA UMS3655/US23 for GE
199 bioinformatics analysis.

200

201 **Author Contribution**

202 S Leboulleux: Conceptualization, Funding acquisition, Investigation, Methodology,
203 Resources, Visualization, Writing – original draft; Writing – review and editing

204 D Benisvy: Investigation, Resources, Writing –editing

205 D Taieb: Investigation, Resources, Writing –editing

206 M Attard: Resources- editing

207 C Bournaud: Investigation, Resources, Writing –editing

208 M Terroir-Cassou-Mounat: Resources, editing

209 L Lacroix: Resources, Writing – original draft; Writing – review and editing

210 N Anizan: Methodology

211 A Schiazza: Investigation, Resources, Writing –editing

212 ME Garcia: Investigation, Resources, Writing –editing

213 A Al Ghuzlan: Resources- editing
214 Livia Lamartina: Investigation, Resources, Writing –editing
215 M Schlumberger: Investigation, Resources, Writing – review and editing
216 Y Godbert: Investigation, Resources, Writing –editing
217 I Borget : Conceptualization, Data curation, Formal analysis, Methodology, Project
218 administration, Supervision, Validation, Visualization- Writing – review and editing

219
220

221 **Author Disclosure Statement**

222 S. Leboulleux reports advisory boards from Lilly, Eisai, Ipsen
223 L. Lamartina reports advisory boards from Eisai, Lilly, Ipsen; AAA, Novartis and Roche
224 I. Borget reports grants from Roche, BMS, Novartis, Gilead, MSD
225 D. Benisvy, D. Taieb, M. Attard, C. Bournaud, M. Terroir-Cassou-Mounat, L. Lacroix, N.
226 Anizan, M.E. Garcia, A. Al Ghuzlan M. Schlumberger, Y. Godbert reports no competing
227 interests nor personal financial interests

228

229 **Funding:** MERAIODE was financed by the French Ministry of Health, through the National
230 Institute for Cancer (INCa, PHRC2015), Trametinib was provided by Novartis, rhTSH was
231 provided by Sanofi Genzyme. These companies did not participate in any aspect of the study
232 design, data accrual, data analysis, or manuscript preparation and submission. The authors
233 assume responsibility for the accuracy and completeness of the data and analyses (**NCT**
234 **03244956**).

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272

Table 1: Initial characteristics of the 11 included patients

	N = 11 patients
Age years mean \pm std [Range]	66.7 \pm 16.8 [22-77]
Female n (%)	4 (36.4%)
Histology (investigator) n (%)	
Papillary	4 (36.4%)
Follicular	2 (18.2%)
Poorly differentiated	5 (45.5%)
Histology (central review) n (%)	
Papillary	5 (45.4%)
Variant: Tall cell / Variant follicular encapsuled / Cylindric cell/ missing	2/1/1/1
Poorly differentiated	4 (36.4%) *
Oncocytic	1 (9.0%)
Not available	1 (9.0%)
Type of RAS mutation	
NRAS	7 (63.6%)
KRAS	1 (9.1%)
HRAS	3 (27.3%)
pT stage at time of thyroid cancer diagnosis n (%)	
pT1	0
pT2	0
pT3 SLEC	10 (91.9%)
pT4	1 (9.1%)
Neck dissection at time of thyroid cancer diagnosis n (%)	6 (54.5%)
Number of RAI administration prior to enrollment: mean \pm std [Range]	2.2 \pm 1.5 [1-3]
Cumulated activity of ¹³¹ I (GBq): mean \pm std [Range]	8.4 \pm 6.0 [3.4-22.2]
mCi: mean \pm std [Range]	227 \pm 16.2 [92-600]
Previous treatments for thyroid cancer n (%)	
Tyrosine kinase inhibitor	3 (4.2%) **
External beam radiation to the neck	2 (18.2%)
Radiotherapy for lung metastases	1 (9.1%)
Local treatment for bone metastases	2 (18.2%) ***
ECOG status	
0	10 (90.9%)
1	1 (9.1%)

Abbreviations: ECOG: Eastern Cooperative Oncology Group performance status, GBq: GigaBecquerel; mCi: millicurie; std: standard;

*: including one insular, ** 2 pazopanib and 1 lenvatinib, *** one patient with bone RT + cementoplasty and one patient with bone RT only

Table 2: Radiological assessment (central review) of efficacy with RECIST criteria version 1.1, after first trametinib-¹³¹I course (2A), in the absence of second trametinib-¹³¹I course (2B), after second course of trametinib-¹³¹I (2C)

2A	After 1 st course of treatment N=10 patients		
Central Review	1 month	3 months	6 months
Patients with a central review	N=10	N=10	N=10
Objective response rate n (%) [95CI]	1 (10%) [0.3-44.5]	2 (20%) [2.5-55.6]	2 (20%) [2.5-55.6]
Complete response	0	0	0
Partial Response	1 (10%)	2 (20%)	2 (20%)
Stable Disease	9 (90%)	8 (80%)	7 (70%)
Progressive disease	0	0	1 (10%)
Not evaluable	0	0	0

2B	Patients who did not received a 2 nd course of treatment n=7 patients	
Central Review	12 months	18 months
Objective response rate n (%) [95CI]	0	0
Complete response	0	0
Partial Response	0	0
Stable Disease	2 (28.6%)	2 (28.6%)
Progressive disease	3 (42.8%)	1 (14.3%)
Progressive disease on local assessment prior the time point evaluation and protocol discontinuation: CT not available for central review	2 (28.6%)	4 (57.1%)
Not evaluable	0	0
Patients with a central review n	5	3

2C	Patients who received a 2 nd course of treatment n=3 patients				
Central Review	1 month after 2 nd course	3 months after 2 nd course	6 months after 2 nd course	12 months after 2 nd course	18 months after 2 nd course
Objective response rate n (%) [95CI]	1 (33%) [0.8-90.6]	1 (33%) [0.8-90.6]	1 (33%) [0.8-90.6]	1 (33%) [0.8-90.6]	1 (33%) [0.8-90.6]
Complete response	0	0	0	0	0
Partial Response	1 (33%)	1 (33%)	1 (33%)	1 (33%)	1 (33%)
Stable Disease	1 (33%)	1 (33%)	0	0	0
Progressive disease	1 (33%)	1 (33%)	2 (67%)	0	0
Progressive disease on local assessment prior the time point evaluation and protocol discontinuation: CT not available for central review	0	0	0	2	2
Not evaluable	0	0	0	0	0
Patients with a central review	3	3	3	1	1

Figure 1: Efficacy of trametinib-¹³¹I therapy in the 10 evaluable patients

Evolution of the sum of the size of the target lesions based on independent central review (RECIST v1.1), for the patients treated by one or two courses of treatment