

**MERAIODE: A Phase II Redifferentiation Trial with Trametinib and <sup>131</sup>I in Metastatic Radioactive Iodine Refractory RAS Mutated Differentiated thyroid Cancer:**

**Supplementary data**

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**Supplementary Table 1: Inclusion and exclusion criteria, procedures, evaluation criteria, Tissue genotyping and Gene Expression (GE) analysis, Statistical Analysis**

<p><b>Inclusion criteria</b></p>	<ul style="list-style-type: none"> <li>- Patients with thyroid carcinoma of follicular origin (papillary, follicular or poorly differentiated and their respective variants)</li> <li>- Known positive <i>RAS</i> (<i>NRAS</i> or <i>KRAS</i> or <i>HRAS</i>) or <i>BRAF</i> mutation (p.V600E or K601E) (determined on a previous analysis and/or on a representative formalin-fixed paraffin embedded (FFPE) tumor samples sent for central testing or on a biopsy sample sent for central testing).</li> <li>- Radioiodine-refractory disease defined by at least one of the following items:             <ul style="list-style-type: none"> <li>* Distant metastasis without radioiodine uptake on a post-therapeutic radioactive scan</li> <li>* Distant metastasis disclosing RECIST progression within 12 months after a RAI treatment</li> </ul> </li> <li>- Measurable disease with at least one lesion <math>\geq 1.0</math> cm in the longest diameter for a non-lymph node or <math>\geq 1.5</math> cm in the short axis for a lymph node, measured with spiral computed tomography (CT) without iv contrast injection or magnetic resonance imaging (MRI) according to RECIST 1.1</li> <li>- Progressive disease according to RECIST 1.1 criteria within 18 months prior initiation of treatment</li> <li>- Absence of metastatic lesion <math>&gt; 30</math>mm</li> <li>- Previous cumulated activity of radioactive iodine <math>\leq 22.2</math>GBq</li> <li>- Patients may have received prior treatment with either 1 line of Tyrosine Kinase Inhibitor or 1 line of immunotherapy (excluding anti BRAF or anti MEK treatment such as sorafenib, dabrafenib, trametinib and selumetinib) but should be off treatment within 28 days prior to treatment start</li> <li>- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 - Blood pressure (BP) <math>\leq 140/90</math> mm Hg at screening with or without antihypertensive medications and no change in antihypertensive medications within 1 week prior to Cycle 1/Day 1</li> <li>- Creatinine clearance <math>\geq 50</math> mL/min according to the Cockcroft and Gault formula</li> <li>- Adequate bone marrow function with:             <ul style="list-style-type: none"> <li>* Absolute neutrophil count (ANC) <math>\geq 1.5 \times 10^9/L</math></li> <li>* Hemoglobin <math>\geq 9.0</math> g/dL</li> <li>* Platelet count <math>\geq 100 \times 10^9/L</math></li> </ul> </li> <li>* Normal blood coagulation function as evidenced by an International Normalized Ratio (INR) <math>\leq 1.5</math></li> <li>- Adequate liver function with:             <ul style="list-style-type: none"> <li>* Bilirubin <math>\leq 1.5 \times</math> upper limit of normal (ULN) except for unconjugated hyperbilirubinemia or Gilbert's syndrome,</li> <li>* Alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) <math>\leq 3 \times</math> ULN (<math>\leq 5 \times</math> ULN if subject has liver metastases).</li> </ul> </li> <li>- Males or females age <math>\geq 18</math> years at the time of informed consent</li> <li>- Women of childbearing potential must have a negative urine or serum <math>\beta</math>-HCG pregnancy test within 7 days prior to the administration of the first study treatment. Sexually active women of childbearing potential must agree to use a highly effective method of contraception during the study and for at least 12 months after the last study treatment administration. Sexually active males patients must agree to use condom during the study and for at least 12 months after the last study treatment administration. Also, it is recommended their women of childbearing potential partner use a highly effective method of contraception.</li> <li>- In case of previous external beam radiation, all radiation therapy related toxicities must have resolved to <math>&lt;</math> Grade 2 severity per Common Terminology Criteria for Adverse Events (CTCAE v 4.0), except alopecia and infertility.</li> <li>- Voluntary agreement to provide written informed consent and the willingness and ability to comply with all aspects of the protocol - Patient affiliated to a social security regimen or beneficiary of the same</li> </ul>
<p><b>Exclusion</b></p>	<ul style="list-style-type: none"> <li>- Undifferentiated or Medullary (MTC) carcinoma of the thyroid</li> </ul>

<p><b>Criteria</b></p>	<ul style="list-style-type: none"> <li>- Brain metastases (including asymptomatic brain metastases)</li> <li>- Major surgery within 4 weeks prior to the first dose of drug</li> <li>- Subjects having &gt; 1 + proteinuria on urine dipstick testing will undergo 24 h urine collection for quantitative assessment of proteinuria. Subjects with urine protein <math>\geq 1</math> g/24 h will be ineligible.</li> <li>- Need for locoregional treatment such as surgery, external beam radiation or thermoablation at inclusion</li> <li>- Prior RAI therapy &lt; 6 months prior initiation of treatment</li> <li>- External beam radiation &lt; 4 weeks prior initiation of treatment</li> <li>- Iodine contamination defined by a urine ioduria <math>\geq 50</math> <math>\mu\text{g/dl}</math></li> <li>- Gastrointestinal malabsorption or any other condition that in the opinion of the investigator might affect the absorption of the drugs</li> <li>- History of congestive heart failure greater or equal to than New York Heart association (NYHA) Class II, unstable angina, myocardial infarction or stroke within 6 months of the first dose of drug, or cardiac arrhythmia associated with significant cardiovascular impairment and uncontrolled hypertension</li> <li>- Electrocardiogram (ECG) with QT interval (QTc) interval <math>\geq 480</math> msec</li> <li>- Active hemoptysis (bright red blood of at least 0.5 teaspoon) within 2 months prior to the first dose of drug and any other active bleeding, coagulopathy or pathologic condition that would confer a high risk of bleeding.</li> <li>- Active infection requiring systemic therapy</li> <li>- Active malignancy (except for DTC, or definitively treated melanoma in situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix or bladder) within the past 24 months</li> <li>- Any history of or concomitant medical condition that, in the opinion of the investigator, would compromise subject's ability to safely complete the protocol</li> <li>- Females who are pregnant or breastfeeding</li> <li>- Patients with an injection of radio-contrast agent within 8 weeks prior enrolment</li> <li>- Previous history of retinal vein occlusion</li> <li>- Previous history of central serious retinopathy</li> <li>- Known hypersensitivity to the study drugs or to any of the excipients</li> </ul>
<p><b>Procedures</b></p>	<p>After enrolment, the baseline work-up included a brain MRI, a neck-chest-abdomino-pelvic CT scan without contrast, a <math>^{18}\text{F}</math>FDG PET/CT and a <math>^{131}\text{I}</math> diagnostic WBS (dc1-WBS) performed two days after the administration of 185 MBq (5mCi) of <math>^{131}\text{I}</math> following recombinant human (rh)TSH (0.9 mg intra-muscularly for two consecutive days with <math>^{131}\text{I}</math> administration one day after the second injection). Urinary iodine measurement ruled out any iodine overload.</p> <p>At day 1 (D1), patients started treatment with trametinib (2 mg once a day) for 42 days. Between D28 and D35, patients underwent a neck and chest CT-scan without contrast and a second <math>^{131}\text{I}</math> dc-WBS (dc2-WBS) using the same procedure as for the dc1-WBS. At D35 +/-2, and whatever the results of the dc2-WBS, a fixed <math>^{131}\text{I}</math> activity of 5500 MBq (150 mCi) was administered after rhTSH injections with. a post-treatment WBS (T1-WBS) 5 days after <math>^{131}\text{I}</math> administration. The trametinib treatment was maintained until the post-treatment WBS.</p> <p>Radiologic response was assessed according to RECIST version 1.1 at 1, 3, 6, 12 and 18 months after trametinib treatment initiation or until tumor progression (10). Except at baseline and at 1 month, contrast was used for the CT-scans.</p> <p>In case of partial response at 6 or 12 months and according to the investigator assessment, patients could undergo a second course of trametinib-<math>^{131}\text{I}</math> (5500 MBq (150 mCi) after rhTSH), using the same procedures, but brain MRI, dc1-2-WBS and <math>^{18}\text{F}</math>FDG PET/CT were not performed. Following the second treatment course, similar radiologic evaluations were performed.</p> <p>The trial was conducted based on local radiological assessments. The independent central review of the CT scans, WBS and PET/CT was performed at the end of the study. For RECIST evaluation, target lesions defined on the baseline CT scan of the first treatment course were used for the evaluation of the second treatment course. Metabolic</p>

	<p><sup>18</sup>F-DG-response was assessed at 6 months according to PERCIST (11). Patterns of abnormal <sup>131</sup>I uptake on the WBSs were compared in terms of number of metastatic organs with <sup>131</sup>I uptake.</p> <p>Levels of serum thyroglobulin (Tg), and Tg antibodies were measured on site on l-thyroxine treatment at baseline, 3, and 6 months after treatment initiation. Partial response in serum Tg levels was defined as a decrease from baseline &gt;50% in the absence of Tg antibodies.</p> <p>Safety was monitored at D14, 28, 35, 42 and at months 3, 6, 12 and 18, according to the NCI-CTC AE version 4.0.</p> <p>Quality of life (QoL) was evaluated with the EORTC QoL Questionnaire C30 (QLQ-C30) at inclusion, at D14, 28 and 42, and at 3 and 6 months of the first treatment course.</p>
<b>Evaluation criteria</b>	<p>The primary endpoint was the ORR at 6 months according to central review.</p> <p>Secondary endpoints included:</p> <ul style="list-style-type: none"> <li>-ORR (central and local reviews) at 1 and 3 months</li> <li>- ORR (central and local reviews) at 12 and 18 months for patients treated once</li> <li>- ORR (central and local reviews) at 1, 3, 6, 12 and 18 months after the initiation of the second treatment course for patients treated twice</li> <li>- <sup>18</sup>F-DG metabolic response (central review) at 6 months</li> <li>- Progression free-survival (PFS) (central and local RECIST evaluation)</li> <li>- Changes in serum Tg levels, (vii) predictive role on the 6-months ORR of the intensity of <sup>18</sup>F-DG uptake at baseline, of the <sup>131</sup>I uptake on the dc2-WBS and of the 1-month ORR, (viii) safety and (ix) QoL evolution.</li> </ul>
<b>Tissue genotyping and Gene Expression (GE) analysis</b>	<p>Paraffin sections were prepared from tumor tissue blocks, according to the sandwich method. Library preparation, sequencing techniques pipeline were performed with workflow OncoPrint™ Tumor Mutation Load Assay (ThermoFisher Scientific, Courtaboeuf, France), covering 1.65 Mb bases among 409 genes. Sanger sequencing was performed for TERT promoter analysis(12). GE were generated by targeted-RNA sequencing using the HTG EdgeSeq technology and the Oncology Biomarker Panel (13). Details of samples analyses by NGS is available in Supplementary Table 2. GE raw data are available at ArrayExpress under the E-MTAB-12900</p>
<b>Statistical Analysis</b>	<p>The study design is a one-stage Fleming design. The treatment of reference (<sup>131</sup>I alone) was considered ineffective and the treatment under evaluation (trametinib-<sup>131</sup>I) would be considered not effective if the ORR&lt;3% (p0) and of interest if the ORR is ≥ 40% (p1) given the known 80% ORR with selumetinib-<sup>131</sup>I (7).</p> <p>With a risk <math>\alpha = 5\%</math> and a power of 95%, nine patients must be included in a one-stage design: if &gt; 2 responses are observed, the evaluated treatment was considered effective.</p> <p>Continuous variables are described as number of observations, mean value, standard deviation and range. Categorical variables are summarized as counts and percentages.</p> <p>Estimates of the ORR are given with their 95% exact confidence intervals using binomial distribution, considering the small population size. Analyses of the main criteria were performed on the modified intent to treat population in evaluable patients, <i>i.e.</i> in patients who received at least one complete course of treatment with trametinib-<sup>131</sup>I in the absence of iodine contamination. A descriptive exploratory analysis was done on patients who received a second treatment course.</p>

**Supplementary Table 2: Details of samples available for molecular analysis**

Sample ID	Tumor Cell %*	Tissue Type	RAS mutation	Abnormal <sup>131</sup> I uptake on the post-treatment WBS	6-months RECIST evaluation	6-months PERCIST evaluation	NGS*	Expression Analysis**	TERT promoter Status
01-05	80%	M	<i>NRAS</i> (p.G12V)	No	NR	NR	Done	Done	WT
11-11	80%	M	<i>NRAS</i> (p.Q61R)	Yes	R	NA	Done	Done	WT
01-21	90%	PT	<i>NRAS</i> (p.Q61K)	No	NR	NR	Done	Done	WT
03-24	99%	PT	ND	Yes	NR	R	Done	NA	WT
06-30	> 90%	PT	<i>HRAS</i> (p.G13R)	Yes	R	R	Done	Done	WT
11-33	90%	PT	<i>NRAS</i> (p.Q61R)	No	NR	NR	Done	Done	WT
14-34	> 90%	PT	ND	No	NR	NR	Done	Done	WT
14-37	> 90%	PT	<i>NRAS</i> (p.Q61K)	No	NR	NR	Done	Done	WT
01-38	90%	PT	<i>HRAS</i> (p.Q61R)	No	NR	NR	Done	Done	WT

Abbreviations: PT: Primitive Tumor ; M : Metastasis; NR :No Response (stable or progressive disease) ; PR: partial response; Response; NA: not available; RECIST : Response Evaluation Criteria in Solid Tumors; PERCIST : PET response criteria in solid tumors; NGS: next-generation sequencing ; TERT : telomerase reverse transcriptase, NA: not available; WBS: whole body scan performed after the first course of trametinib treatment

\*Only samples with more than 30% tumor cell content were extracted from 10 µm FFPE pellets using Maxwell® RSC DNA FFPE Kit (Promega, Charbonnières-les-Bains, France) according to manufacturer's instructions.

\*\*Tissue Genotyping: the bioinformatics analysis was performed with Ion reporter™ (ThermoFisher Scientific) using OncoPrint Tumor Mutation Load - v3.0 - DNA - Single Sample workflow according to manufacturer's recommendations. Briefly, variant Call and Tumor mutational load were performed for samples with median coverage depth>100X and > 1.15 million bases depth>60X and deamination quality score <100. After filtering, only somatic variants with allele frequency >5% were retained for TMB calculation. Filtered variants quality and annotation were manually reviewed and classified by a molecular geneticist based on public database and literature information. Variants were classified as pathogenic (VP), of uncertain significance (VUS) or probably not pathogenic (VNP). The main hotspot mutational positions in *NRAS*, *HRAS*, *KRAS* genes were visually controlled on bam files.

\*Gene Expression analysis: The samples were run on the S5 (ThermoFisher Scientific) then the HTG EdgeSeq Parser was used to align FASTQ files to probe list. Then, Bioinformatics normalization and analysis were performed using local package as previously described.

**Supplementary Table 3: Radiological assessment (local review) of efficacy with RECIST criteria version 1.1 in 10 evaluable patients**

Local Review	1 <sup>st</sup> course of treatment N=10 patients		
	1 month	3 months	6 months
<b>Objective response rate n (%) [95CI]</b>	<b>0</b>	<b>2 (20%) [2.5-55.6]</b>	<b>3 (30%) [6.6-65.2]</b>
Complete response	0	0	0
Partial Response	0	2 (20%)	3 (30%)
Stable Disease	9 (90%)	7 (70%)	5 (50%)
Progressive disease	1 (10%)	0	1 (10%)
Not evaluable	0	1 (10%) <sup>a</sup>	1 (10%) <sup>b</sup>
CT scan not performed n	0	0	0

Local Review	Patients who did not received a 2 <sup>nd</sup> course of treatment n=7 patients	
	12 months	18 months
<b>Objective response rate n (%) [95CI]</b>	<b>0</b>	<b>0</b>
Complete response	0	0
Partial Response	0	0
Stable Disease	3 (42.8%)	2 (28.6%)
Progressive disease	2 (28.6%)	1 (14.3)
Progressive disease on local assessment prior the time point evaluation and protocol discontinuation:	2 (28.6%)	4 (57.1%)
Not evaluable	0	0

Local Review	Patients who received a 2 <sup>nd</sup> course of treatment n=3 patients				
	1 month after 2 <sup>nd</sup> course	3 months after 2 <sup>nd</sup> course	6 months after 2 <sup>nd</sup> course	12 months after 2 <sup>nd</sup> course	18 months after 2 <sup>nd</sup> course
<b>Objective response rate n (%) [95CI]</b>	<b>3 (100%) [29.2-100]</b>	<b>2 (67%) [9.4-99.2]</b>	<b>2 (67%) [9.4-99.2]</b>	<b>1 (33%)</b>	<b>1 (33%)</b>
Complete response	0	0	0	0	0
Partial Response	3 (100%)	2 (67%)	2 (67%)	1 (33%)	1 (33%)
Stable Disease	0	1 (33%)	0	0	0
Progressive disease	0	0	1 (33%)	0	0
Progressive disease on local assessment prior the time point evaluation and protocol discontinuation:	0	0	0	2 (67%)	2 (67%)
Not evaluable	0	0	0	0	0

a = NE response in a patient who had progressive disease at 1 month

b = NE response in a patient who had progressive disease between 3 and 6 months

**Supplementary Table 4: Toxicity: Adverse event related or unrelated to treatment with trametinib-<sup>131</sup>I**

The adverse events listed here are those that occurred at any grade in at least 2 patients among the 11 included patients, during the first or the second treatment course.

Results are presented as the maximum grade per patient. AEs that occurred in 1 patient only are in the footnote.

Patient n (%)	Adverse Event, regardless the attribution					Treatment-related (TR) adverse event				
	All AE	Grade 1	Grade 2	Grade 3	Grade 4	All AE	Grade 1	Grade 2	Grade 3	Grade 4
<b>Patients with any AE</b>	9 (82)	4 (36)	3 (27)	2 (18)	0	9 (82)	4 (36)	4 (36)	1 (9)	0
<i>By type</i>										
Diarrhea	6 (55)	5 (45)	1 (9)			4 (36)	3 (27)	1 (9)		
Cutaneous eruption	5 (45)	3 (27)	2 (18)			5 (45)	3 (27)	2 (18)		
Asthenia	5 (45)	4 (36)	1 (9)			4 (36)	3 (27)	1 (9)		
Acne	4 (36)	3 (27)	1 (9)			4 (36)	3 (27)	1 (9)		
Abdominal pain	4 (36)	3 (27)	1 (9)			4 (36)	3 (27)	1 (9)		
ASAT increase	3 (27)	3 (27)				2 (18)	2 (18)			
Nausea	3 (27)	3 (27)				2 (18)	2 (18)			
Amnesia	2 (18)	1 (9)	1 (9)			2 (18)	1 (9)	1 (9)		
Rash	2 (18)	1 (9)	1 (9)			2 (18)	1 (9)	1 (9)		

Abbreviations: AE: adverse event

AE that occurred in 1 patient only (9%) include: Grade 1 AE: Atrioventricular block, candidiasis, cardiac disorders, dyspnea, constipation, epistaxis, hair loss, headache, hyperglycemia, hypertension, lactate dehydrogenase increase, lower limb pain, mucositis, pain, visual blur, pruritus, QTc prolongation, TSH increase; Grade 2 AE: Peripheral edema, skin and subcutaneous tissue disorder, vomiting; Grade 3 AE: alkaline phosphatase increase, colitis, gamma-glutamyl transferase increase

### Supplementary Table 5: QoL scores of the QLQ-C30 questionnaire, by visit time

The QLQ-C30 is a 30-items cancer-specific questionnaire that incorporates 5 functioning dimensions (physical, role, cognition, emotional, and social), 9 symptom dimensions (fatigue, pain, nausea/vomiting, dyspnea, insomnia, loss of appetite, constipation, diarrhea, financial problems), and a global health dimension. According to the EORTC scoring manual, standard scores in the range of 0–100 were calculated for each dimension, if at least half of the dimension's items were not missing. Higher scores in the global and functioning dimensions indicate a high level of QoL, whereas a high score in symptom dimensions indicates severe symptoms.

		<b>Baseline</b>	<b>D14</b>	<b>D28</b>	<b>End of treatment</b>	<b>3 months</b>	<b>6 months</b>
<b>Global health status / QoL</b>	n (m.d.)	11	7 (4)	11	9 (2)	6 (4)	6 (4)
	Mean (sd)	71.2 (22.2)	64.3 (17.2)	68.2 (13.9)	59.3 (23.4)	81.9 (18.6)	62.5 (30.2)
	Median (Q1 ; Q3)	75 (67 ; 83)	67 (50 ; 75)	67 (58 ; 83)	50 (42 ; 83)	83 (75 ; 100)	63 (42 ; 83)
	Min ; Max	33 ; 100	33 ; 83	42 ; 83	33 ; 83	50 ; 100	25 ; 100
<b>Physical Functioning</b>	n (m.d.)	11	7 (4)	11	9 (2)	6 (4)	6 (4)
	Mean (sd)	87.9 (16.8)	87.6 (17.8)	83.6 (21.2)	80.7 (24.6)	92.2 (19.1)	78.9 (34.4)
	Median (Q1 ; Q3)	93 (80 ; 100)	93 (73 ; 100)	100 (60 ; 100)	93 (60 ; 100)	100 (100 ; 100)	100 (53 ; 100)
	Min ; Max	47 ; 100	53 ; 100	47 ; 100	40 ; 100	53 ; 100	20 ; 100
<b>Role Functioning</b>	n (m.d.)	11	7 (4)	11	9 (2)	6 (4)	6 (4)
	Mean (sd)	81.8 (26.3)	78.6 (32.9)	75.8 (30.2)	77.8 (37.3)	86.1 (34.0)	61.1 (43.0)
	Median (Q1 ; Q3)	100 (67 ; 100)	100 (50 ; 100)	83 (50 ; 100)	100 (67 ; 100)	100 (100 ; 100)	67 (17 ; 100)
	Min ; Max	33 ; 100	17 ; 100	17 ; 100	0 ; 100	17 ; 100	17 ; 100
<b>Emotional Functioning</b>	n (m.d.)	11	7 (4)	11	9 (2)	6 (4)	6 (4)
	Mean (sd)	78.8 (25.4)	82.1 (14.8)	76.8 (25.5)	80.6 (25.7)	94.4 (6.8)	81.9 (26.0)
	Median (Q1 ; Q3)	92 (67 ; 100)	83 (67 ; 92)	83 (56 ; 100)	92 (75 ; 92)	96 (92 ; 100)	92 (75 ; 100)
	Min ; Max	33 ; 100	58 ; 100	17 ; 100	17 ; 100	83 ; 100	33 ; 100
<b>Cognitive Functioning</b>	n (m.d.)	11	7 (4)	11	9 (2)	6 (4)	6 (4)
	Mean (sd)	84.8 (20.4)	90.5 (13.1)	86.4 (22.1)	88.9 (22.0)	94.4 (8.6)	88.9 (17.2)
	Median (Q1 ; Q3)	83 (83 ; 100)	100 (83 ; 100)	100 (67 ; 100)	100 (83 ; 100)	100 (83 ; 100)	100 (67 ; 100)
	Min ; Max	33 ; 100	67 ; 100	33 ; 100	33 ; 100	83 ; 100	67 ; 100
<b>Social Functioning</b>	n (m.d.)	11	7 (4)	11	9 (2)	6 (4)	6 (4)
	Mean (sd)	84.8 (32.0)	95.2 (8.1)	81.8 (25.2)	85.2 (28.2)	97.2 (6.8)	75.0 (34.6)
	Median (Q1 ; Q3)	100 (83 ; 100)	100 (83 ; 100)	83 (83 ; 100)	100 (83 ; 100)	100 (100 ; 100)	92 (50 ; 100)
	Min ; Max	0 ; 100	83 ; 100	33 ; 100	17 ; 100	83 ; 100	17 ; 100
<b>Fatigue</b>	n (m.d.)	11	7 (4)	11	9 (2)	6 (4)	6 (4)
	Mean (sd)	24.2 (24.3)	33.3 (28.0)	43.4 (26.0)	46.9 (32.3)	14.8 (19.5)	31.5 (28.5)
	Median (Q1 ; Q3)	22 (0 ; 33)	33 (11 ; 33)	33 (33 ; 56)	44 (22 ; 56)	6 (0 ; 33)	33 (0 ; 56)
	Min ; Max	0 ; 78	0 ; 89	0 ; 100	0 ; 100	0 ; 44	0 ; 67
<b>Nausea / Vomiting</b>	n (m.d.)	11	7 (4)	11	9 (2)	6 (4)	6 (4)
	Mean (sd)	3.0 (6.7)	4.8 (8.1)	7.6 (11.5)	13.0 (7.3)	0.0 (0.0)	0.0 (0.0)
	Median (Q1 ; Q3)	0 (0 ; 0)	0 (0 ; 17)	0 (0 ; 17)	17 (17 ; 17)	0 (0 ; 0)	0 (0 ; 0)
	Min ; Max	0 ; 17	0 ; 17	0 ; 33	0 ; 17	0 ; 0	0 ; 0

<b>Pain</b>	n (m.d.)	11	7 (4)	11	9 (2)	6 (4)	6 (4)
	Mean (sd)	21.2 (32.6)	21.4 (26.7)	19.7 (22.1)	20.4 (21.7)	5.6 (13.6)	30.6 (40.0)
	Median (Q1 ; Q3)	0 (0 ; 33)	0 (0 ; 50)	17 (0 ; 50)	17 (0 ; 33)	0 (0 ; 0)	17 (0 ; 50)
	Min ; Max	0 ; 83	0 ; 50	0 ; 50	0 ; 50	0 ; 33	0 ; 100
<b>Dyspnea</b>	n (m.d.)	11	7 (4)	11	9 (2)	6 (4)	6 (4)
	Mean (sd)	15.2 (22.9)	14.3 (26.2)	15.2 (22.9)	11.1 (23.6)	16.7 (27.9)	5.6 (13.6)
	Median (Q1 ; Q3)	0 (0 ; 33)	0 (0 ; 33)	0 (0 ; 33)	0 (0 ; 0)	0 (0 ; 33)	0 (0 ; 0)
	Min ; Max	0 ; 67	0 ; 67	0 ; 67	0 ; 67	0 ; 67	0 ; 33
<b>Insomnia</b>	n (m.d.)	11	7 (4)	11	9 (2)	6 (4)	6 (4)
	Mean (sd)	21.2 (34.2)	14.3 (26.2)	18.2 (22.9)	22.2 (28.9)	5.6 (13.6)	27.8 (39.0)
	Median (Q1 ; Q3)	0 (0 ; 33)	0 (0 ; 33)	0 (0 ; 33)	0 (0 ; 33)	0 (0 ; 0)	17 (0 ; 33)
	Min ; Max	0 ; 100	0 ; 67	0 ; 67	0 ; 67	0 ; 33	0 ; 100
<b>Appetite loss</b>	n (m.d.)	11	7 (4)	11	9 (2)	6 (4)	6 (4)
	Mean (sd)	9.1 (15.6)	4.8 (12.6)	6.1 (13.5)	22.2 (28.9)	0.0 (0.0)	16.7 (18.3)
	Median (Q1 ; Q3)	0 (0 ; 33)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 33)	0 (0 ; 0)	17 (0 ; 33)
	Min ; Max	0 ; 33	0 ; 33	0 ; 33	0 ; 67	0 ; 0	0 ; 33
<b>Constipation</b>	n (m.d.)	11	7 (4)	10 (1)	9 (2)	6 (4)	6 (4)
	Mean (sd)	6.1 (13.5)	19.0 (17.8)	13.3 (17.2)	3.7 (11.1)	11.1 (17.2)	16.7 (18.3)
	Median (Q1 ; Q3)	0 (0 ; 0)	33 (0 ; 33)	0 (0 ; 33)	0 (0 ; 0)	0 (0 ; 33)	17 (0 ; 33)
	Min ; Max	0 ; 33	0 ; 33	0 ; 33	0 ; 33	0 ; 33	0 ; 33
<b>Diarrhea</b>	n (m.d.)	11	7 (4)	11	9 (2)	6 (4)	6 (4)
	Mean (sd)	15.2 (31.1)	28.6 (30.0)	27.3 (32.7)	44.4 (37.3)	0.0 (0.0)	5.6 (13.6)
	Median (Q1 ; Q3)	0 (0 ; 33)	33 (0 ; 67)	33 (0 ; 33)	33 (33 ; 67)	0 (0 ; 0)	0 (0 ; 0)
	Min ; Max	0 ; 100	0 ; 67	0 ; 100	0 ; 100	0 ; 0	0 ; 33
<b>Financial Problems</b>	n (m.d.)	11	7 (4)	10 (1)	9 (2)	6 (4)	6 (4)
	Mean (sd)	0.0 (0.0)	4.8 (12.6)	3.3 (10.5)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
	Median (Q1 ; Q3)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)
	Min ; Max	0 ; 0	0 ; 33	0 ; 33	0 ; 0	0 ; 0	0 ; 0

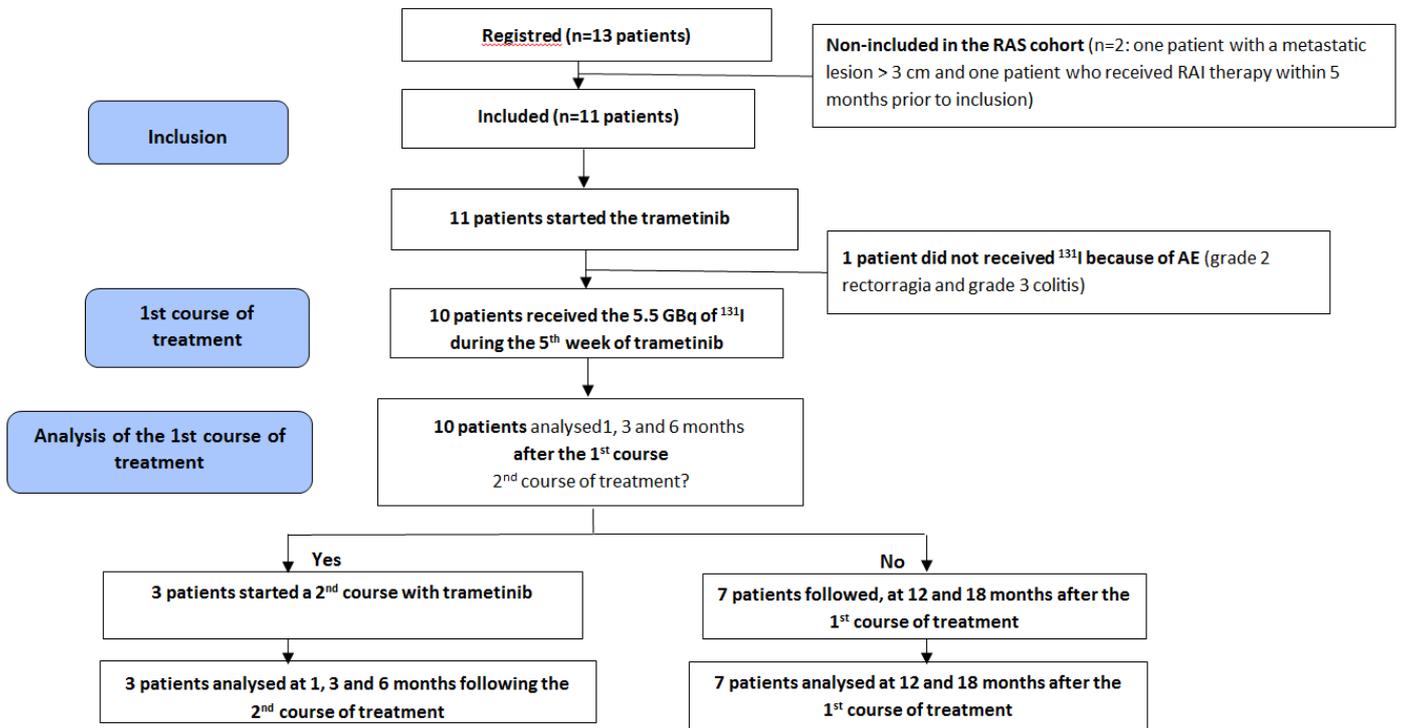
Sd= standard-deviation, min = minimum, max = maximum; m.d.: missing data

**Supplementary Table 6: Tissue genotyping of patients with evaluable response: pathogenic variant (PV) and variant of unknown significance detected (VUS).**

Sample	Gene Name	Protein Nomenclature	Nucleotide Nomenclature	PV/VUS Classification	Reference transcript	hCG37 # locus	Type of mutation	6 months-RECIST evaluation (central
01-05	<i>NRAS</i>	p.Gly12Val	c.35G>T	PV	NM_002524.4	chr1:115258747	SNV	NR
01-05	<i>FLT4</i>	p.Glu740Lys	c.2218G>A	VUS	NM_182925.4	chr5:180047957	SNV	NR
01-05	<i>MDM2</i>	p.Ile208Thr	c.623T>C	VUS	NM_002392.5	chr12:69222650	SNV	NR
11-11	<i>NRAS</i>	p.Gln61Arg	c.182A>G	PV	NM_002524.4	chr1:115256529	SNV	NA
11-11	<i>IKBKE</i>	p.Ala346Asp	c.1037C>A	VUS	NM_014002.3	chr1:206652330	SNV	NA
11-11	<i>KMT2D</i>	p.Ala3549_Lys3550delinsAspGln	c.10646_10648delinsACC	VUS	NM_003482.3	chr12:49427944	MNV	NA
11-11	<i>FOXO1</i>	p.Asp69Asn	c.205G>A	VUS	NM_002015.3	chr13:41240145	SNV	NA
11-11	<i>MYCN</i>	p.Ser145Pro	c.433T>C	VUS	NM_001293228.1	chr2:16082619	SNV	NA
01-21	<i>NRAS</i>	p.Gln61Lys	c.181C>A	PV	NM_002524.4	chr1:115256530	SNV	NR
03-24	<i>PTPN11</i>	p.Gln510Leu	c.1529A>T	PV	NM_002834.3	chr12:112926909	SNV	R
06-30	<i>HRAS</i>	p.Gly13Arg	c.37G>C	PV	NM_005343.2	chr11:534286	SNV	R
11-33	<i>NRAS</i>	p.Gln61Arg	c.182A>G	PV	NM_002524.4	chr1:115256529	SNV	NR
14-34	<i>PTEN</i>	p.Val317fs	c.950_953delTACT	PV	NM_000314.4	chr10:89720798	INDEL	R
14-34	<i>MSH2</i>	p.Leu762*	c.2285T>A	PV	NM_000251.2	chr2:47705485	SNV	R
14-34	<i>NUMA1</i>	p.Thr2093Ala	c.6277A>G	VUS	NM_006185.3	chr11:71714992	SNV	R
14-34	<i>ESR1</i>	p.Ala66Pro	c.196G>C	VUS	NM_000125.3	chr6:152129243	SNV	R
14-34	<i>HNF1A</i>	p.Leu44Val	c.130C>G	VUS	NM_000545.5	chr12:121416701	SNV	R
14-34	<i>NF1</i>	p.Phe1357Ser	c.4070T>C	VUS	NM_001042492.2	chr17:29576097	SNV	R
14-37	<i>NRAS</i>	p.Gln61Lys	c.181C>A	PV	NM_002524.4	chr1:115256530	SNV	NR
14-37	<i>FANCD2</i>	Splice	c.438+1_438+2delGT	PV	NM_033084.3	chr3:10076917	INDEL	NR
01-38	<i>HRAS</i>	p.Gln61Arg	c.182A>G	PV	NM_005343.2	chr11:533874	SNV	NR
01-38	<i>FGFR3</i>	p.Val229Ile	c.685G>A	VUS	NM_000142.4	chr4:1803416	SNV	NR
01-38	<i>CDK12</i>	p.Val595Leu	c.1783G>C	VUS	NM_016507.3	chr17:37627868	SNV	NR

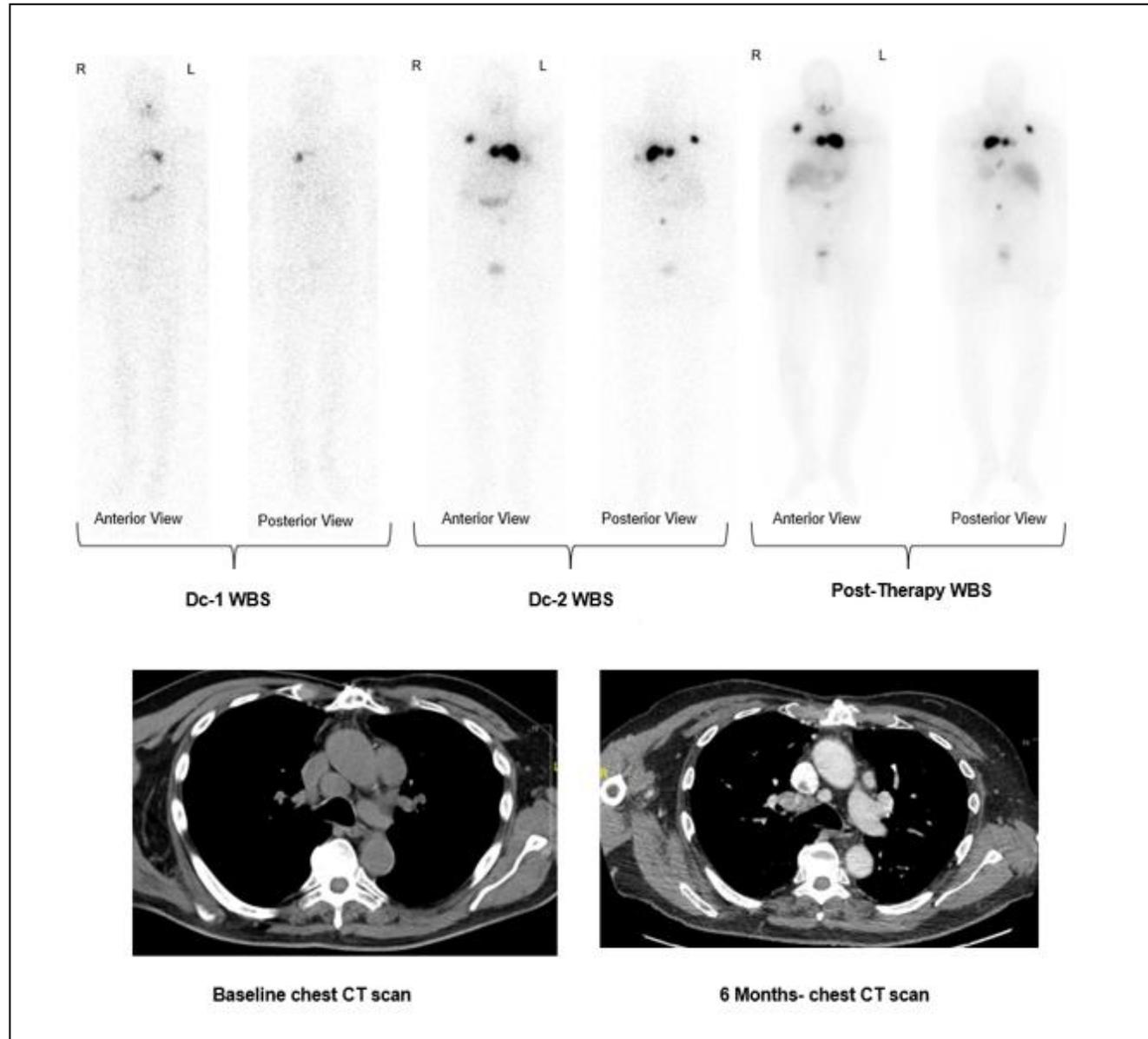
**Abbreviations: VUS: variant of unknown significance, PV: Pathogenic Variant; SNV: Single Nucleotide Variation; Indel : Insertion-deletion; NR :No Response (stable or progressive disease) ; PR: partial response; Response; NA: not available**

**Supplementary Figure 1: MERAIODE flow diagram for RAS-mutated patients**



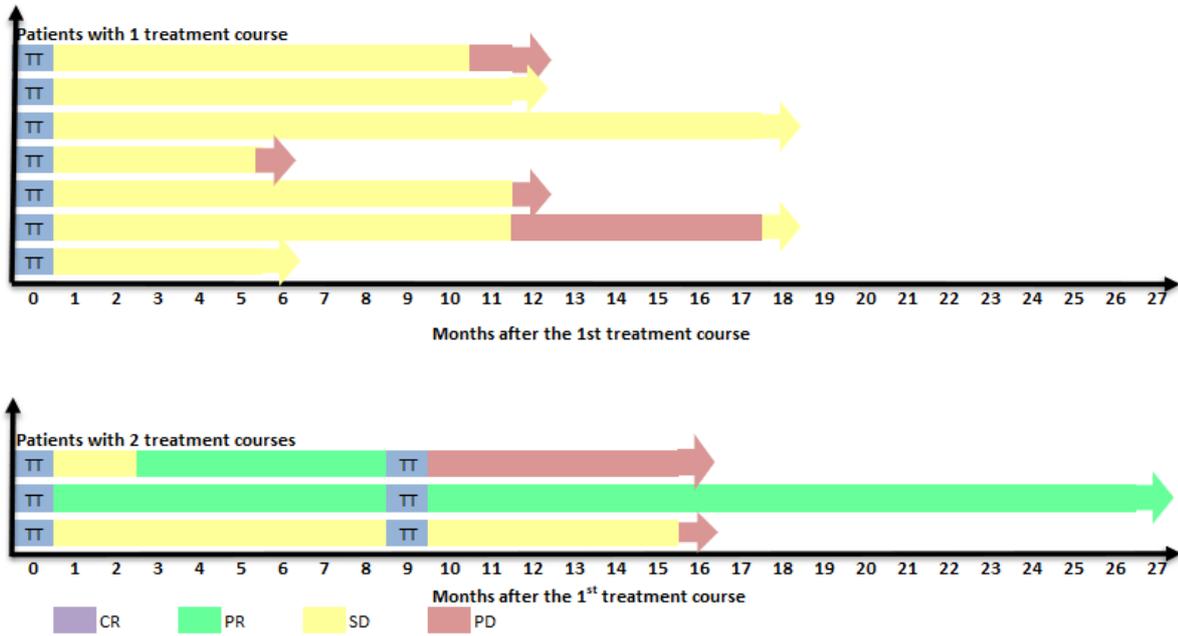
Supplementary Figure 2: dc-1 WBS, dc-2 WBS, post therapy WBS, baseline chest CT and 6-months chest CT scan of one of the patients with increase <sup>131</sup>I uptake after trametinib treatment seen on the dc-2 and post therapy WBS (mediastinal lymph node and bone uptakes on post therapy WBS) and a 6-Response

dc2-WBS and months Partial

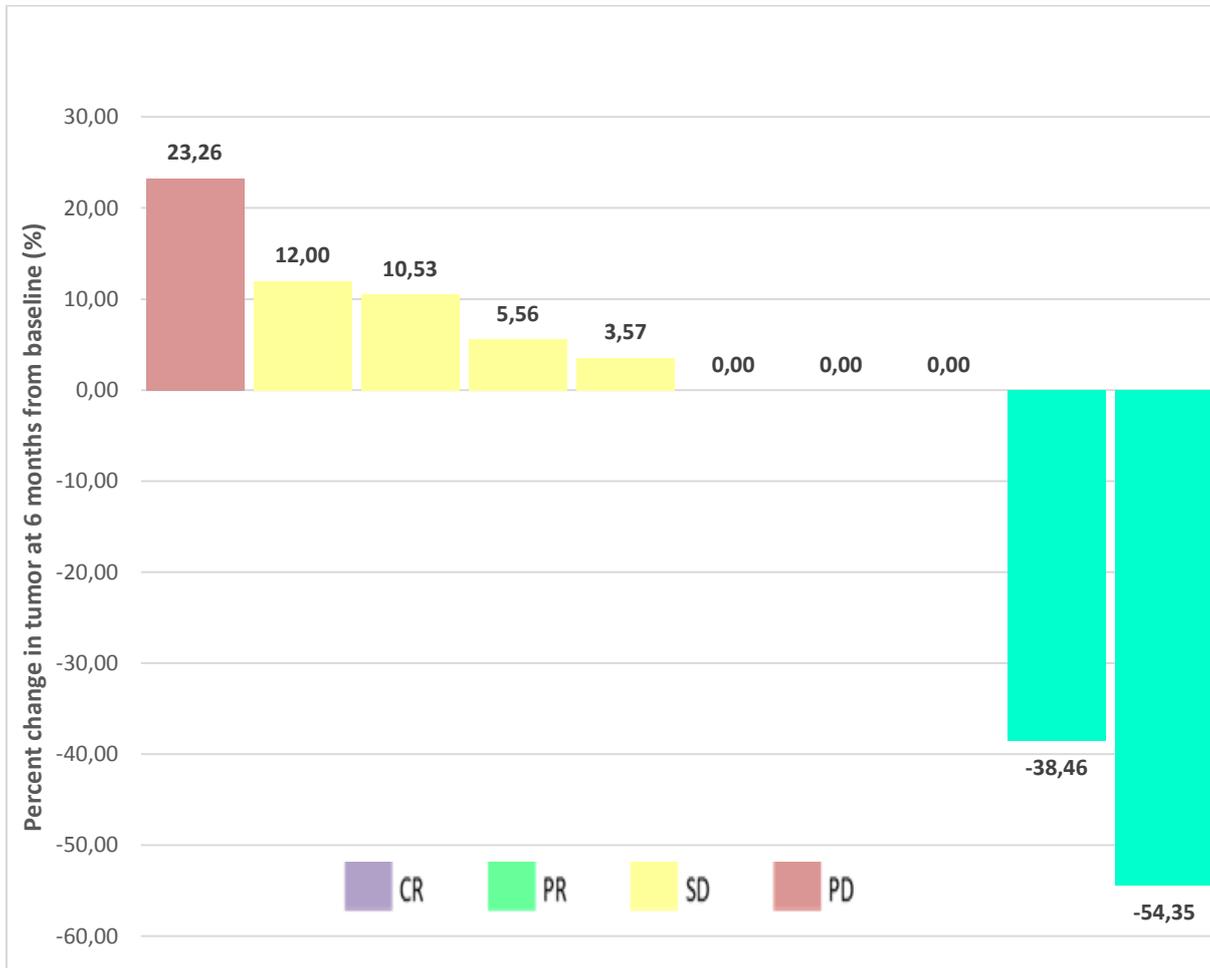




Supplementary Figure 3 Swimmer plot of central RECIST response, for the patients respectively treated by one or two courses of treatment

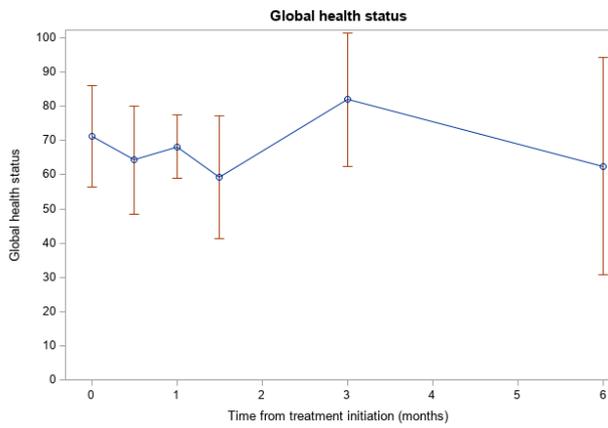


**Supplementary Figure 4: Waterfall plot of the RECIST response 6 months after the first trametinib-<sup>131</sup>I response**

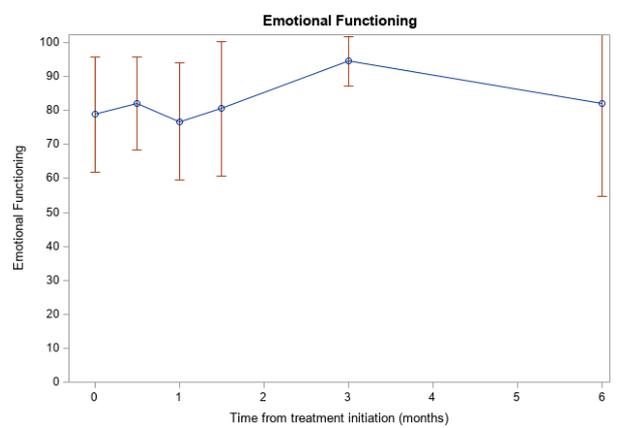


## Supplementary Figure 5: Quality of life score according to the QLQ-C30 questionnaire

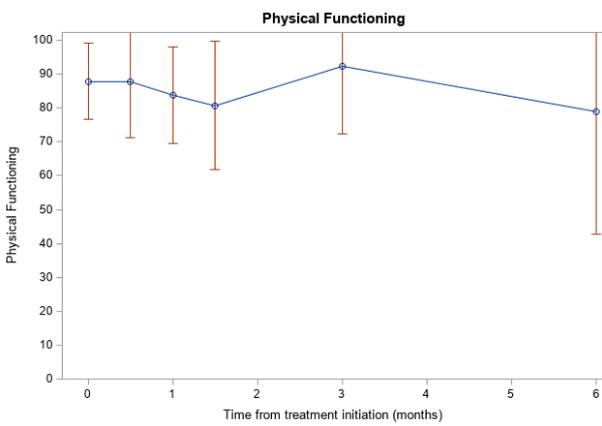
### A – Global Health Status



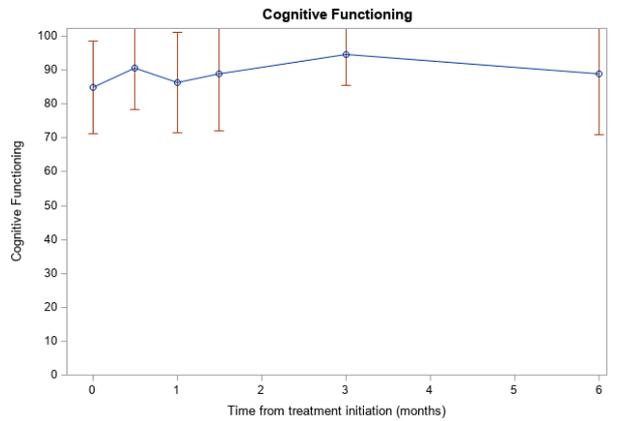
### D – Emotional Functioning



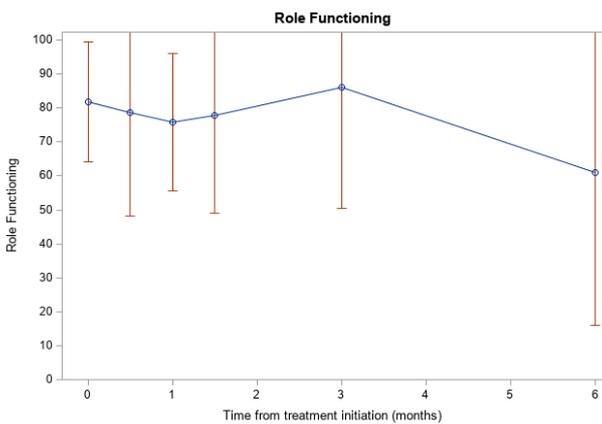
### B – Physical Functioning



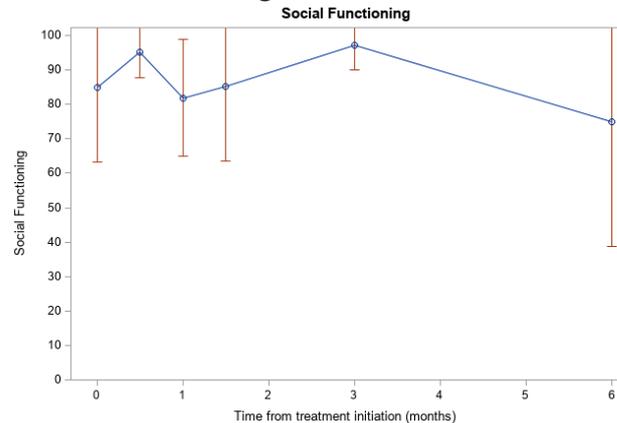
### E – Cognitive Functioning



### C – Role Functioning

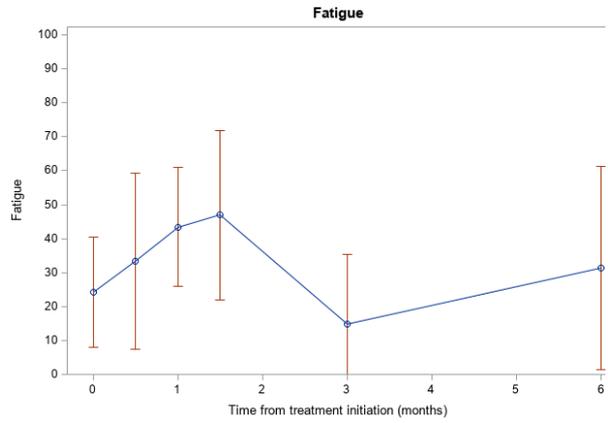


### F – Social Functioning

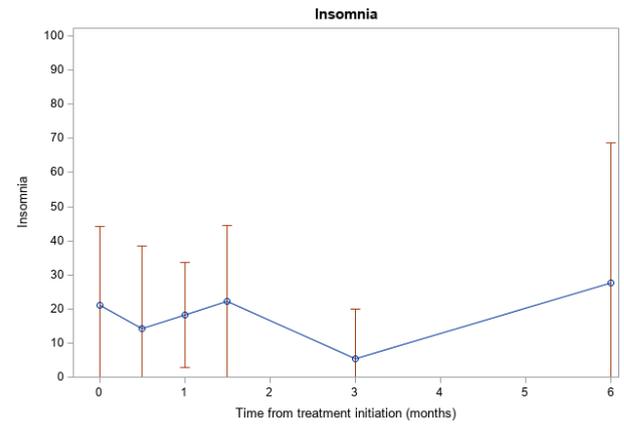


# SYMPTOMS

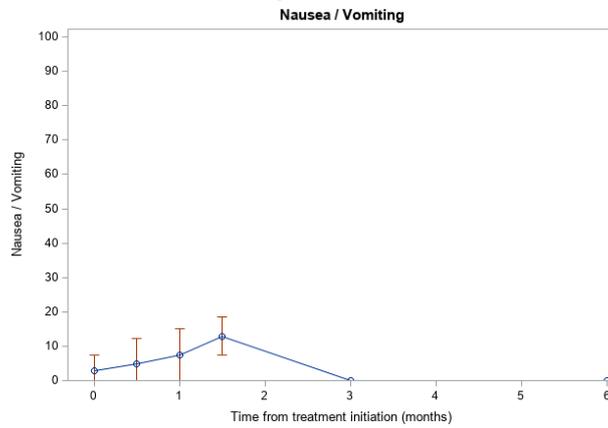
## G – Fatigue



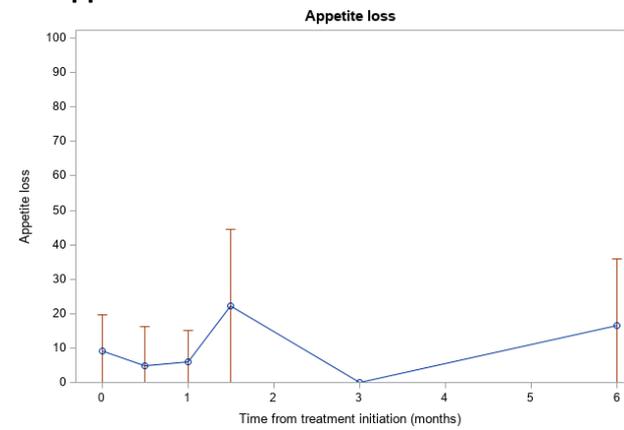
## K – Insomnia



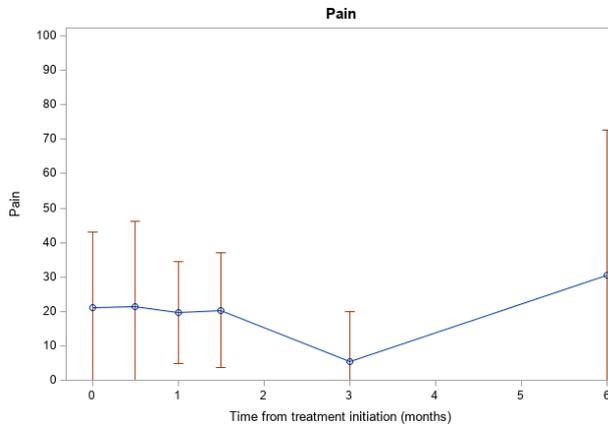
## H – Nausea & vomiting



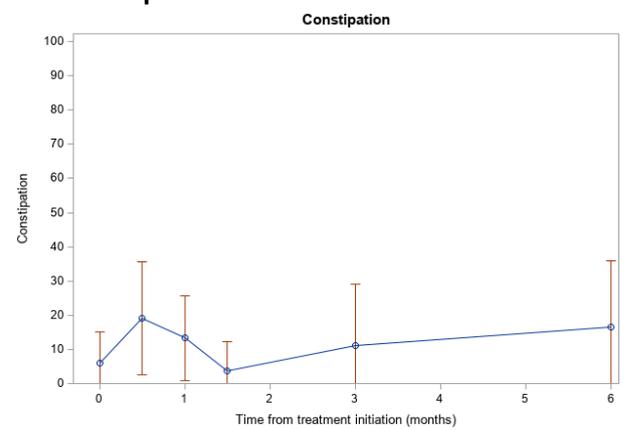
## L – Appetite Loss



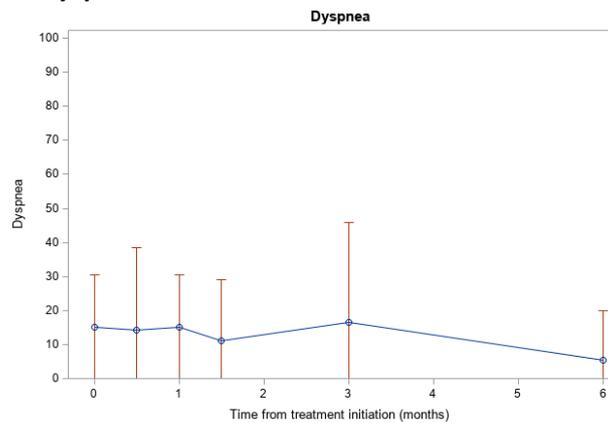
## I – Pain



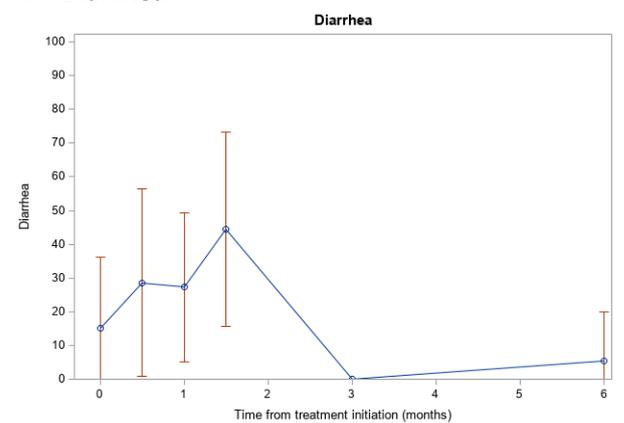
## M – Constipation



## J – Dyspnea



## N – Diarrhea



## O – Financial problems

