Supplementary material

Table S1. Targeted therapies in MTC.

Drug	Company	Target	Outcome	References
Axitinib	AG-01376, Pfizer	inhibitor of VEGF-R-1-3	SD 27%	Cohen EE et al.[a]
Motesanib	AMG706 Amgen/Takeva	Inhibitor of VEGFR1-3 and PDGF-Rα/β	ORR 2%, SD 81%; PFS 12 months	Schlumberger MJ et al.[b]
Pazopanib	GW786034, Votrient, GlaxoSmithKline	Inhibitor of VEGFR1-3, PDGF-Rα/β and cKit		Unknown/ unpublished data
Sorafenib	Nexavar, BAY43-9006, Bayer-Onyx	Inhibitor of VEGFR2-3, RET, c-Kit, FGF-R1 and p38	SD 88% sporadic MTC and 80% hereditary MTC PFS 17,9 months	Lam ET et al.[c], Hong D et al.[d]
Sunitinib	Sutent, SU011248, Pfizer	Inhibitor of VEGF-R1-3, c-Kit and PDGF-Rα/β	ORR 0-55 % SD 44,4-87,7 %	Gómez-Sáez JM[e]
Vandetanib	Zactima, ZD6474, AstraZeneca	Inhibitor of VEGF-R1-3, RET and EGF-R	ORR MTC with RET 20% SD 53% ORR MTC 45%	Robinson BG et al.[f], Chau NG et al.[g], Wells S et al.[h]
Cabozantinib	XL184, Exlixis	Inhibitor of VEGF-R2, RET and MET	PR 29%	Kurzrock R. et al.[i]

[a] Cohen EE, Rosen LS, Vokes EE, et al. Axitinib is an active treatment for all histologic subtypes of advanced thyroid cancer: results from a phase II study. J Clin Oncol. 2008; 26: 4708-4713.

[b] Schlumberger MJ, Elisei R, Bastholt L, et al. Phase II study of safety and efficacy of motesanib in patients with progressive or symptomatic, advanced or metastatic medullary thyroid cancer. J Clin Oncol. 2009; 27: 3794-3801.

[c] Lam ET, Ringel MD, Kloos RT, et al. Phase II clinical trial of sorafenib in metastatic medullary thyroid cancer. J Clin Oncol. 2010; 28: 2323-2330.

[d] Hong D, Ye L, Gagel R, et al. Medullary thyroid cancer: targeting the RET kinase pathway with sorafenib/tipifarnib. Mol Cancer Ther. 2008; 7: 1001-1006.

[e] Gómez-Sáez JM. Sunitinib for the treatment of thyroid cancer. Expert Opin Investig Drugs. 2016; 25: 1345-1352.

[f] Robinson BG, Paz-Ares L, Krebs A, et al. Vandetanib (100 mg) in patients with locally advanced or metastatic hereditary medullary thyroid cancer. J Clin Endocrinol Metab. 2010; 95: 2664-2671.

[g] Chau NG, Haddad RI. Vandetanib for the treatment of medullary thyroid cancer. Clin Cancer Res. 2013; 19: 524-529.

[h] Wells SA Jr, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol. 2012; 30: 134-141.
[i] Kurzrock R, Sherman SI, Ball DW, et al. Activity of XL184 (Cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer. J Clin Oncol. 2011; 29 :2660-2666.

Table S2. Radiopharmaceuticals of Choice for MTC Imaging

Radiopharmaceutical labelled with γ radiation emitting radionuclide	
Frequently used radiopharmaceuticals	*Less frequently used radiopharmaceuticals*
Metaiodobenzylguanidine (MIBG), labelled with ^{131}I or ^{123}I	^{99m}Tc(V)-dimercaptosuccinic acid (DMSA)
^{111}In-pentetreotide (Octreoscan)	^{201}Thalium (^{201}Tl)
^{99m}Tc-Depreotide (Neospect)[a]	^{99m}Tc-sestamibi (MIBI)
^{99m}Tc-EDDA/HYNIC-Tyr3-Octreotide (Tektrotyd)	Radiolabelled monoclonal anti-CEA antibodies (^{131}I-anti-CEA antibody)
Radiopharmaceutical labelled with a positron-emitting radionuclide (β +)	
^{18}F-fluorodeoxyglucose (^{18}F-FDG)	
^{18}F-fluorodihydroxyphenylalanine (^{18}F-DOPA)	
^{68}Ga-labelled somatostatin analogues (^{68}Ga-DOTA-TATE or DOTA-TOC)	

[a] withdrawn from the market

Table S3. Ethics committee approvals

Name of the Bioethics Committee	Approval number
Jagiellonian University Bioethics Committee	Poland, No 122.61201.4.2015
National Medical Ethics Committee	Slovenia, KME 150/06/12
Medical University of Innsbruck Ethics Committee	Austria, AN2015-0229 353/2.6 354/2.1
Azienda Ospedaliero-Universitaria Pisana Ethics Committee	Italy, Prot. no 36449
Erasmus MC Ethics Committee	The Netherlands, NL55280.078.16, v04

Table S4. Inclusion and exclusion criteria

Inclusion criteria	<u>Related to the medullary cancer of the thyroid</u>: 1. Histologically documented medullary cancer of the thyroid. 2. Presence of more than one distant or nodal, surgically untreatable metastases confirmed with either ^{18}F-FDG PET/CT or enhanced-CT or MRI. 3. Doubling time (DT) of serum calcitonin level less than two years prior to study entry and negative imaging. 4. Karnofsky performance status > 50%. 5. Life expectancy of more than 6 months. <u>Related to the patient</u>: 6. Male or female patients aged >18 years without upper age limit. 7. Ability to understand and willingness to sign a written informed consent document. 8. Written informed consent obtained according to international guidelines and local laws.
Exclusion criteria	<u>Related to the MTC</u>: 1. Patients with surgically treatable medullary thyroid cancer. 2. Patients with history of second malignancy other than basal cell carcinoma of the skin. <u>Related to previous or concomitant therapies</u> : 3. Participation in any other investigational trial within 3 months of study entry. 4. Previous external beam radiation therapy within two years. 5. Organ allograft requiring immunosuppressive therapy. <u>Related to the patient</u>: 6. Pregnancy, breast-feeding. 7. Known hypersensitivity to gastrin analogues. 8. Patients with concurrent illnesses that might preclude study completion or interfere with study results. 9. Patients with bladder outflow obstruction or unmanageable urinary incontinence. 10. Clinical diagnosis of disseminated intravascular coagulation. 11. Serum creatinine >170 μmol/L, GFR < 40 mL/min 12. Known history of hypersensitivity to Gelofusine or any other contraindications to Gelofusine infusion

Table S5. The Study Flowchart

Patient Protocol activities	W0 Screen (day)	Scintigraphic scans and collection of blood and urine samples	Observation period						Follow up Period (month after end of study visit)	
	-14 to 0	2 times in period of 2 weeks x 3-4days of hospitalization (if needed)	Once a week (W)						3	**4**
			W 1	**W 2**	**W 3**	**W 4**	**W 6**	**W8 end of study visit**		
Informed Consent	· (within 4 wks)									
Demographic Data	·									
Medical History / Baseline conditions	·									
Primary Diagnosis / Prior Treatment	·									
Concomitant Diseases & Treatment	·									
ECG, Chest X-ray	·									
Pregnancy Test (if indicated)	·	·								·
Complete Physical Examination	·		·	·	·	·	·	·	·	·	·
Performance Status (ECOG)	·		·	·	·	·	·	·	·	·	·
Haematology: Hb, Ht, WBC with differential, RBC and reticulocytes, platelets, fibrinogen, INR, PTT[a]	·	·	·	·	·	·	·	·	·	·	·
Chemistry: TSH, FT3, FT4, calcitonin[c], procalcitonin, electrolytes, creatinine, GFR, albumin, AST, ALT, total bilirubin , CEA[1]	·	·	·	·	·	·	·	·	·	·	·
Tracer admin low-dose/high-dose[b,]		·								
Gelofusine co-infusion [c]		·								
Dosimetry studies		·								
Toxicity Assessment		· Throughout study								

[a] 1 – 2 days before the therapy cycle the blood samples should be taken for blood morphology, routine coagulation test, renal and liver function parameters, TSH and calcitonin, procalcitonin.
[b] During infusion vital signs will be monitored and blood samples will be drawn for [c] calcitonin determination.