

University of Groningen

**Molecular imaging to identify patients with metastatic breast cancer who benefit from endocrine treatment combined with cyclin-dependent kinase inhibition**

Boers, Jorianne; Venema, Clasina M; de Vries, Erik F J; Glaudemans, Andor W J M; Kwee, Thomas C; Schuurin, Ed; Martens, John W M; Elias, Sjoerd G; Hospers, Geke A P; Schröder, Carolina P

*Published in:*  
European Journal of Cancer

*DOI:*  
[10.1016/j.ejca.2019.10.024](https://doi.org/10.1016/j.ejca.2019.10.024)

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*  
Final author's version (accepted by publisher, after peer review)

*Publication date:*  
2020

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Boers, J., Venema, C. M., de Vries, E. F. J., Glaudemans, A. W. J. M., Kwee, T. C., Schuurin, E., Martens, J. W. M., Elias, S. G., Hospers, G. A. P., & Schröder, C. P. (2020). Molecular imaging to identify patients with metastatic breast cancer who benefit from endocrine treatment combined with cyclin-dependent kinase inhibition. *European Journal of Cancer*, 126, 11-20.  
<https://doi.org/10.1016/j.ejca.2019.10.024>

**Copyright**

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

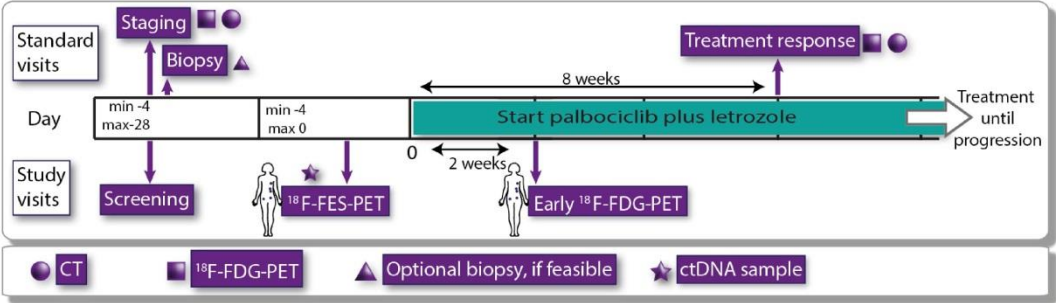
The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

**Take-down policy**

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

**Supplementary Data**

**Appendix A**



**Figure A.1. Study design**

## **Appendix B**

### **2 week FDG-PET related to 8 week FDG-PET**

#### **MATERIAL AND METHODS**

To assess whether response to treatment could be evaluated at an earlier time point, we investigated the response per lesion based on FDG-PET acquired after 2 weeks and compared the results with the 8 week FDG-PET scan. A multilevel model was used to assess the association between the FDG uptake at 2 and 8 weeks.

#### **RESULTS**

Fourteen patients underwent an additional early FDG-PET after 2 weeks of treatment and a total of 341 lesions were analyzed. We compared 2 week FDG uptake to 8 week FDG uptake. The majority of lesions detected on early FDG-PET, showed the same metabolic response category after 8 weeks on FDG-PET (225 of 341; 66%) (Table B.1). After 2 weeks of treatment a relatively high percentage of lesions was classified as stable. Only 43% of the observed (between-lesion) variation in response assessment by FDG-PET at 8 weeks, can be explained by the 2 week FDG-PET response assessment.

#### **DISCUSSION**

We explored whether an early FDG-PET could be of interest as biomarker for response. Unfortunately, the concordance between 2 and 8 week FDG-PET according to the metabolic response evaluation was limited (66%). Implying that the effect of CDK inhibition after 8 weeks cannot already be predicted by the 2 week FDG-PET. Remarkably, a relatively large number of lesions was classified as stable

after 2 weeks. Therefore, early FDG-PET was not suitable to predict early response in our small dataset.

**Table B.1.** Overview of response evaluation per lesion on FDG-PET after 2 and 8 weeks

	<b>FDG – 2 weeks</b>	<b>FDG – 8 weeks</b>	<b>The same metabolic response category</b>
Response	77 (23%)	131 (38%)	64
	34 (20%)	72 (43%)	30
Stable	237 (70%)	158 (46%)	141
	125 (75%)	80 (48%)	74
Progression	27 (8%)	52 (15%)	20
	8 (5%)	15 (9%)	6

Orange: all 341 lesions. Blue: only 167 lesions, corrected for background.

## **FES uptake in lesions with highest baseline FDG uptake in relation to response**

### **MATERIAL AND METHODS**

The 5-lesion analysis is a less laborious method than the all-lesion analysis, and therefore more time efficient. Geometric mean  $SUV_{max}$  on FES-PET was calculated per patient using the 5 lesions (or less if no more available) with highest FDG-PET uptake at baseline. For metabolic response per patient, the percent change in  $SUV_{max}$  of the 5 hottest baseline FDG-PET lesions was calculated from FDG-PET at baseline and after 8 weeks. The lesions used at 8 weeks were the same as were used at baseline. Metabolic response per patient was defined as  $\geq 30\%$  decrease of  $SUV_{max}$  on 8 week FDG-PET, and progression was defined as  $\geq 30\%$  increase. Disease without response or progression was considered stable.

### **RESULTS**

Using the 5 lesions with highest baseline FDG uptake to assess both FES uptake and metabolic response per patient, the estimated geometric mean FES uptake was 3.2 (95%CI 2.3 to 4.4) for patients with stable disease, and 3.9 (2.6 to 6.0;  $P=0.41$ ) for metabolic responding patients. In this secondary analysis, only lesions with high baseline FDG uptake were evaluated and as a consequence no progressive disease was seen based on only these lesions.

## Appendix C

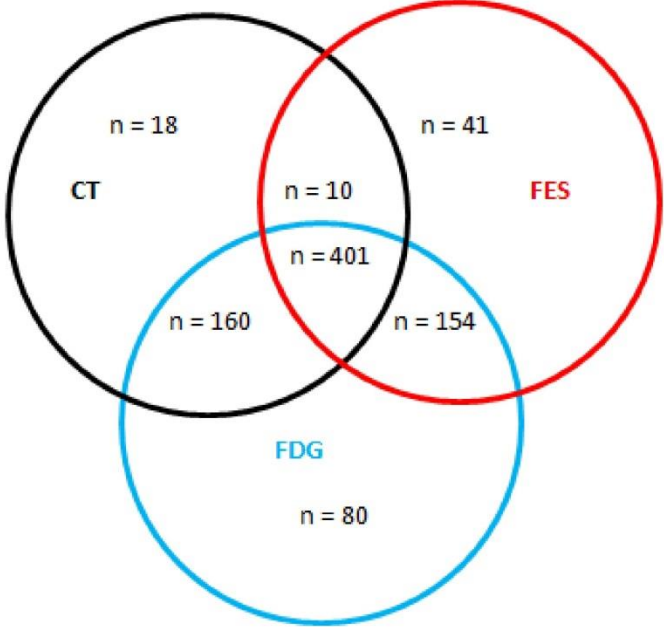
**Table C.1.** Acute toxicity during combined therapy ( $n = 30$  patients)

Events related to study procedures or unknown relationship							
Relation of AE	AE or SAE		Max. grade of AE				Total
			1	2	3	4	
Unknown	AE	Headache		1			1
		Diarrhea	1				1
		Hypercalcemia	2	2	1		5
		Blurry vision	1				1
		Creatinine increased	2				2
		ASAT increased	4	4	1		9
		Nausea		1			1
		Cough	3				3
		Hyponatremia	1		1		2
		Dysphagia		1			1
		Dyspnea	3	3			6
		Fatigue		2			2
		Cardiac tamponade			1		1
		GGT increased	4	3	4	1	12
		Anemia	1				1
		Pain in a part of the body	11	4	1		16
		ALAT increased	6	1	1		8
		AF increased	3	3			6
		Dizziness	1				1
		Hypomagnesemia	1				1
		Walking difficulties	1				1
		Anal fissure		1			1
		Stiffness body	2	1	1		4
		Hoarseness	1				1
		Choledocholithiasis			1		1
		Bilirubin increased		1			1
		Restless legs	1				1
		Grey stool	1				1
		Hypokalemia	1				1
		Insomnia	1				1
		Tingling arm	1				1
		<b>SAE</b>					
			Dural metastases				1
		Cholecystitis				1	1
		Hypercalcemia				1	1
		Dyspnea multifactorial			1		1
		Dyspnea pleural effusion			1		1
		GGT increased due to progressive disease				1	1
		Cholangitis		1			1
	<b>Total</b>						<b>101</b>
(Possibly) related to palbociclib	AE	Decreased appetite	3				3
		Neutropenia	18	19	15		52
		Febrile neutropenia			1		1
		Thrombocytopenia	7	2			9

	ASAT increased	4	1	1		6
	ALAT increased	1				1
	Stomatitis	1				1
	Epistaxis	2				2
	Hyperkalemia	1				1
	Fatigue	10	4	2		16
	Leukopenia	16	16	1		33
	Hot flush	2				2
	Nausea	4	4			8
	Constipation		1			1
	Tingling fingers	2				2
	Alopecia	4				4
	Insomnia		1			1
	Arthralgia	3	1	1		5
	Dyspnea	1				1
	Infection	3	7			10
	Headache	2	1			3
	Anemia	8				8
	Transpiration	1	1			2
	Edema arm	1				1
	Skin irritation	3				3
	Pruritus	1				1
	Vomiting	4	2			6
	Creatinine increased	2				2
	Diarrhea	1				1
	Hypomagnesemia	1				1
	Fever	1				1
	Bruising	1				1
	Malaise		1			1
	Anorexia		1			1
	Hypercalcemia	2				2
	GGT increased	2				2
	Abdominal cramps	1				1
	Dry eye	1				1
	<b>SAE</b> Fever without focus	1				1
	Respiratory infection			1		1
	Cholangitis			2		2
	<b>Total</b>					<b>201</b>
<b>Total AE</b>						<b>291</b>
<b>Total SAE</b>						<b>11</b>
<b>Total</b>						<b>302</b>

The most common toxicity was neutropenia of any grade, reported in 25 of the 30 patients (83%). In 15 patients (50%) a grade  $\geq 3$  neutropenia was observed. Only in one patient neutropenic fever occurred, no hospitalization or antibiotics were needed.

Appendix D



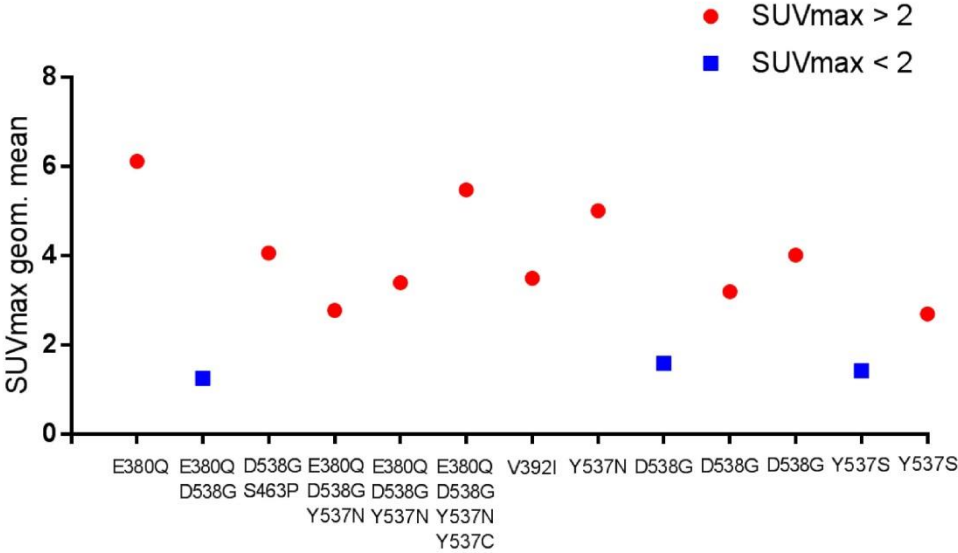
**Figure D.1.** All lesions identified at baseline on FDG-PET, contrast enhanced CT and/or FES-PET.

*CT = black, FES = red, FDG = blue*

In total, 18 lesions were only visible on CT of which all were bone lesions. Also, the majority of lesions only visible on FDG-PET or FES-PET were bone lesions (59% and 56%, respectively).



**Appendix E**



**Figure E.1.** Patients ( $n = 13$ ) with specific mutations in the *ESR1* gene compared with FES uptake.

The geometric mean  $SUV_{max}$  for FES uptake (using response evaluable lesions) was higher in patients with an *ESR1* mutation versus patients without (3.2 (95%CI 2.3 to 4.5) versus 2.4 (1.6 to 3.5);  $P=0.26$ , respectively). Red dots represent FES lesions with a  $SUV_{max}$  geometric mean  $\geq 2.0$ ; Blue dots represent FES lesions with a  $SUV_{max}$  geometric mean  $< 2.0$ .