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

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Supplementary Data

Appendix A

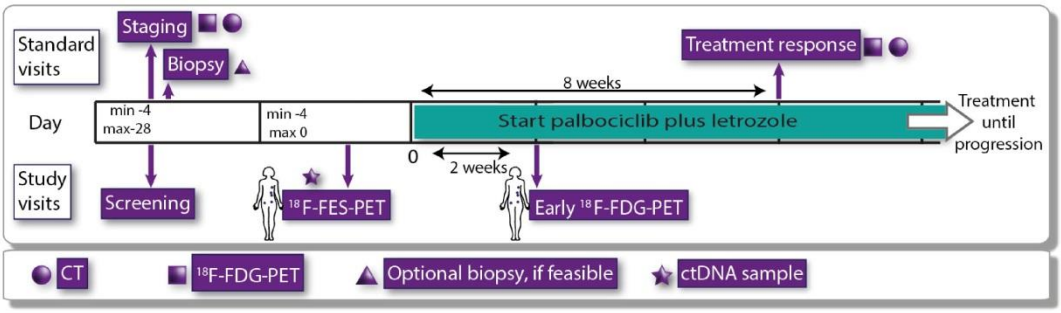

Figure A.1. Study design

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

	FDG – 2 weeks	**FDG – 8 weeks**	**The same metabolic response category**
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 ≥ 30% decrease of SUV_{max} on 8 week FDG-PET, and progression was defined as ≥ 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
	SAE	Dural metastases				1	**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**
	Total						**101**
(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
	SAE	Fever without focus	1				**1**
		Respiratory infection			1		**1**
		Cholangitis			2		**2**
	Total						**201**
Total AE							**291**
Total SAE							**11**
Total							**302**

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

Appendix D

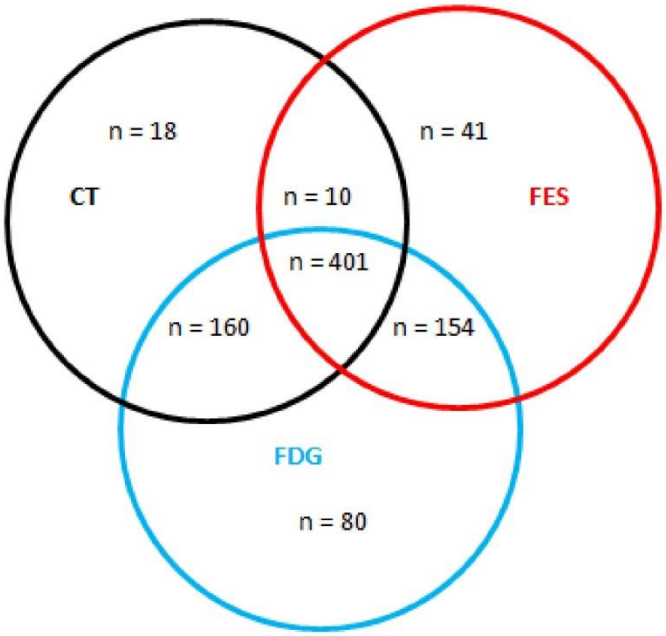

Figure D.1. All lesions identified at baseline on FDG-PET, contrast enhanced CT and/or FES-PET.

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

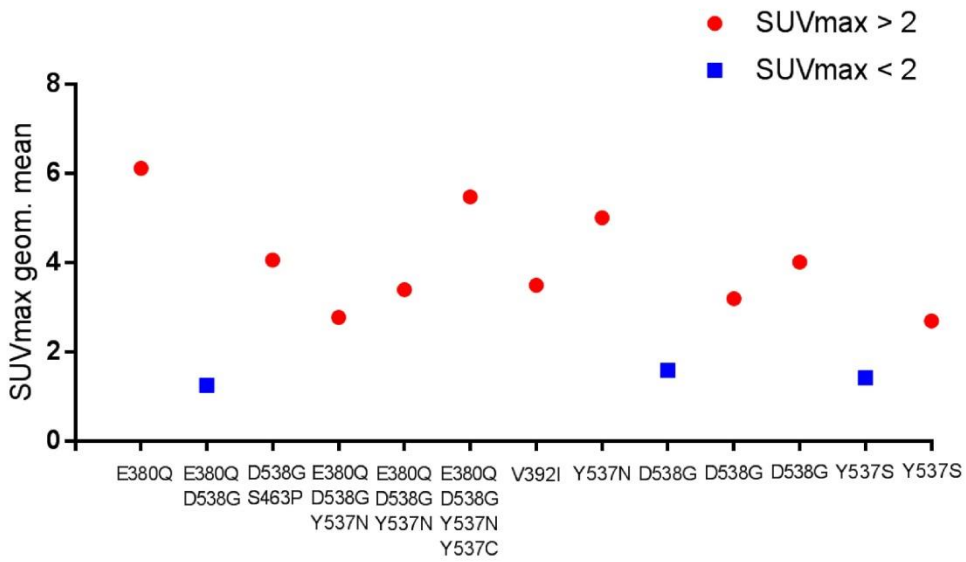

Figure E.1. Patients (*n* = 13) with specific mutations in the *ESR1* gene compared with FES uptake.

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 $SUV_{max\ geometric\ mean} < 2.0$.