c-MET as a Potential Resistance Mechanism to Everolimus in Breast Cancer: From a Case Report to Patient Cohort Analysis

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- No disclosure

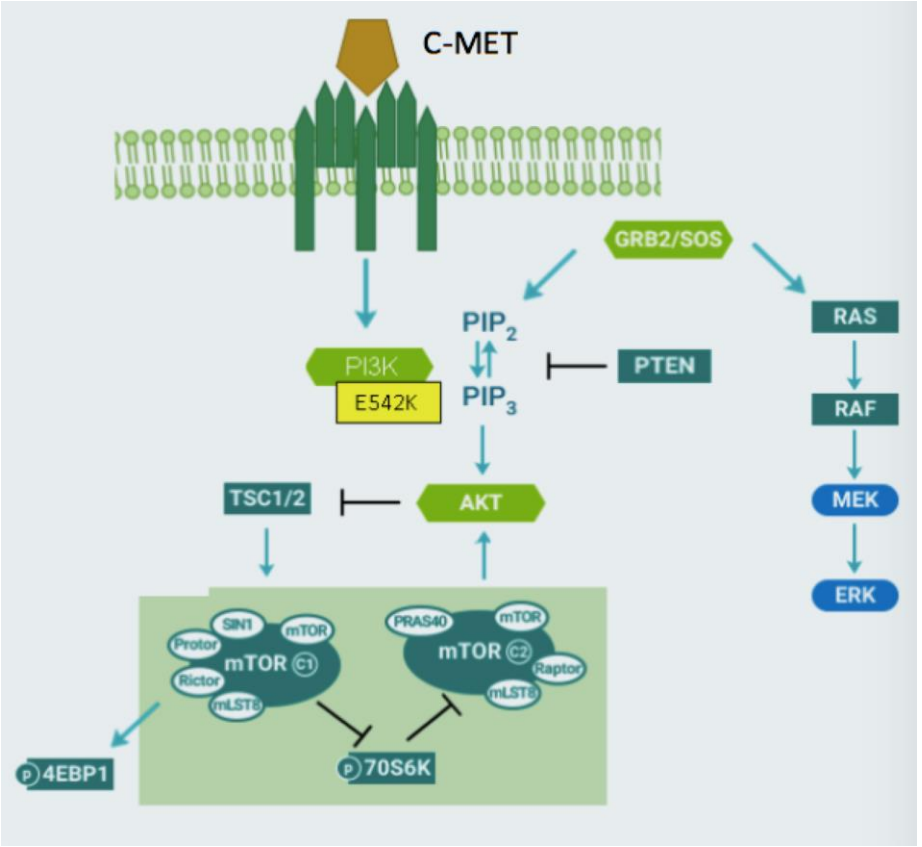
Background

- Endocrine therapy is the key treatment in HR (+) Breast Cancer
  - ➔ First line setting in mBC includes ET + CDK4/6 inhibitor

- The PI3K/Akt/mTOR pathway is activated in >50% of mBC
  - ➔ Everolimus is used in combination with ET
  - ➔ Primary or secondary resistance to everolimus is common

- c-MET is a tyrosine kinase receptor associated
  with agressiveness of cancer
  and poor prognosis

- **Association between c-MET expression and resistance to everolimus ?**



Starting from a clinical case :

a highly sensitive patient to everolimus

Case-report : mBC in a 69-yo woman

1998: locally advanced breast cancer treated with surgery, chemotherapy (6FEC), RT and tamoxifen 5 y

2012: resurgence with lung metastases.

Ductal Carcinoma

ER 7/8, PR 0/8

HER2 0

KI67 70%

➔ Letrozole

EVEROLIMUS + exemestane

Progression-free survival (PFS) = 17 months
Best response rate : 75% decrease of lesions

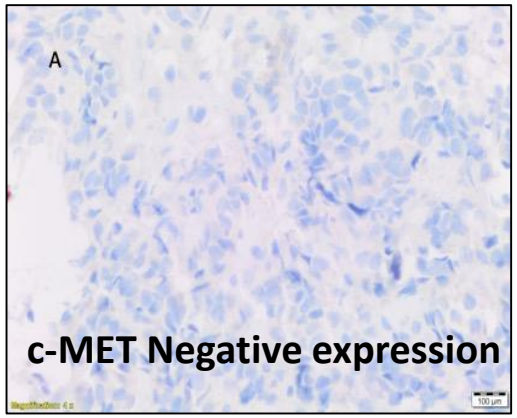
EVEROLIMUS + EXEMESTANE

Biopsy 1 = Before everolimus

Biopsy 2 = at progression

PIK3CA E542K ➔ could explain the sensitivity to everolimus

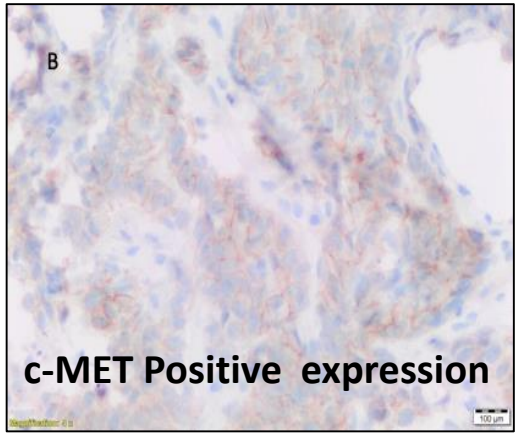
p-4EBP1 +++ ➔ could explain the sensitivity to everolimus



c-MET Negative expression

p-ERK Low expression

c-MET – ERK axis



c-MET Positive expression

p-ERK High expression

At progression on everolimus, different regimens were tested (taxane, capecitabine)

Due to c-MET and p-ERK expression

-> **cabozantinib** = tyrosine kinase inhibitor

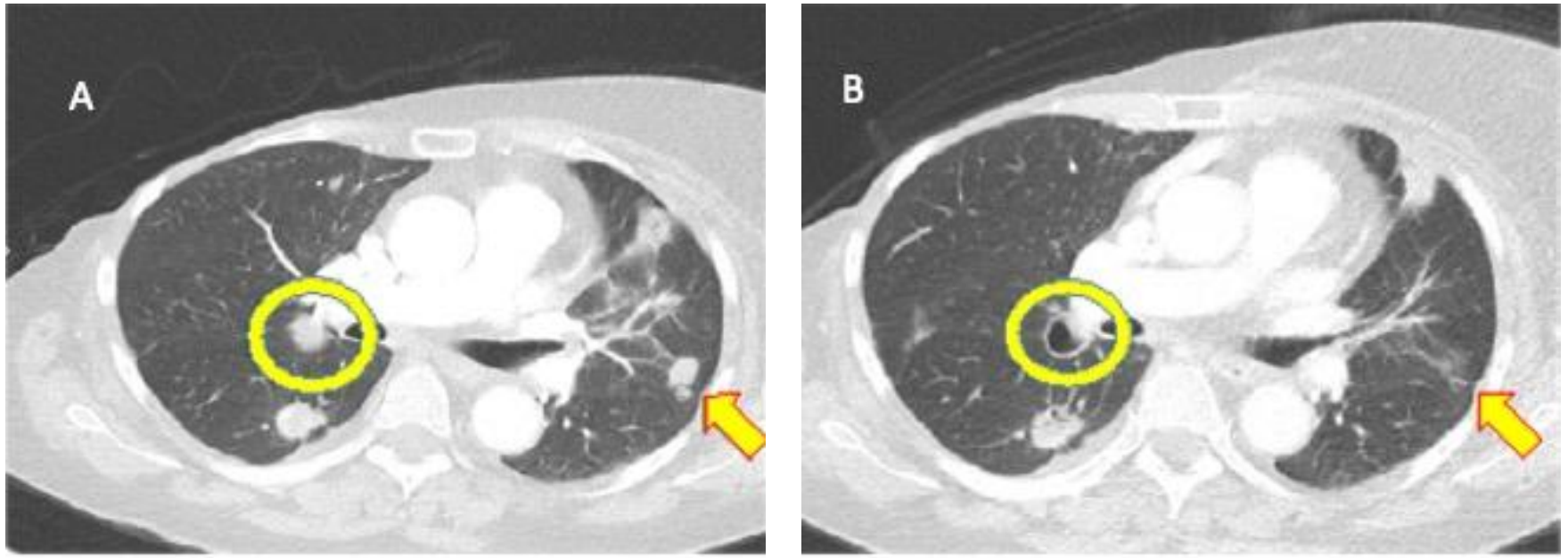


Fig. 3 : Chest tomography (A) before and (B) at 1 month of cabozantinib initiation

PFS of 7 months

Analyzing a patients cohort:

A link between c-MET and Everolimus efficacy ?

Materials and methods :

- **Retrospective** analysis of a cohort of postmenopausal mBC patients treated with **everolimus** 10mg daily + exemestane as **2nd line ET** in Jolimont between 2012 and 2017

- All mBC with ER and/or PR, previous ET line, none had received CDK4/6 inhibitors

- Available biopsy performed within 12 months before everolimus initiation

- c-MET expression assessed by IHC : positive if ≥ 50% of tumor cells with moderate/high membranous staining

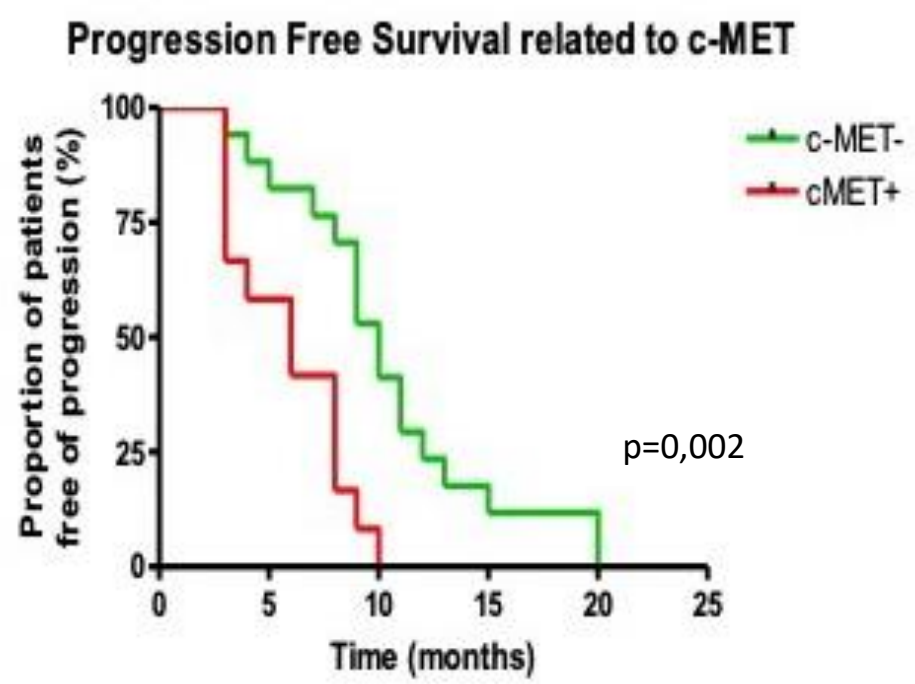
- Response rate, progression-free survival (PFS) and overall survival (OS)

Results : Demographic and tumor characteristics of the patient cohort

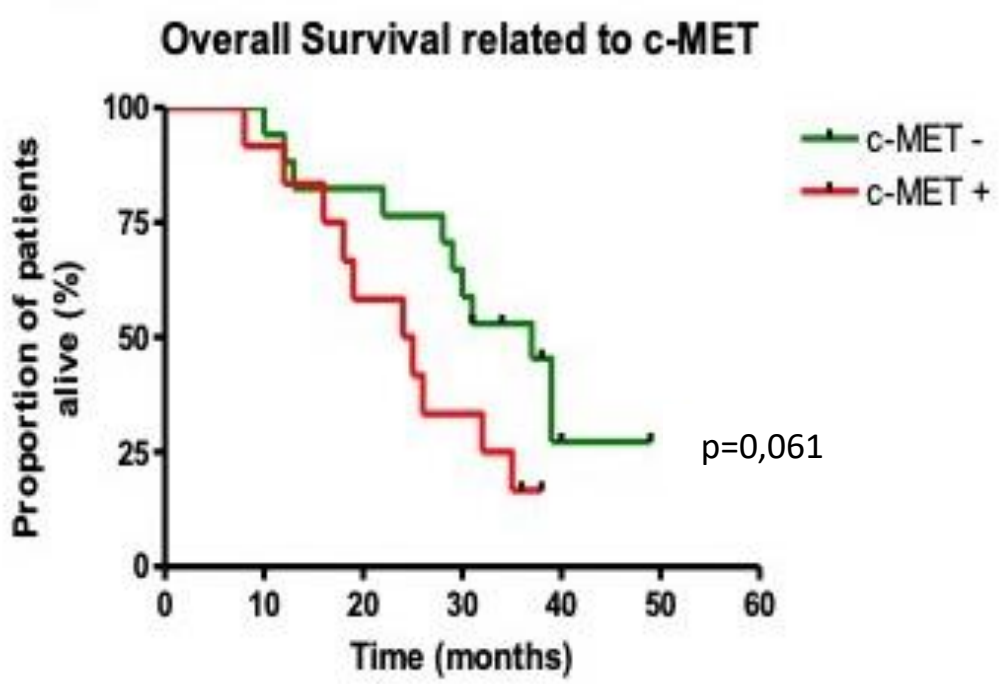
Characteristics	c-MET positive ($n=12$)	c-MET negative ($n=17$)
Median age, years (range)	59 (33–78)	60 (40–76)
Ethnicity, Caucasian, *n* (%)	12 (100)	17 (100)
Ductal carcinoma, *n* (%)	9 (75)	11 (65)
Lobular carcinoma, *n* (%)	3 (25)	6 (35)
Grade in metastatic setting, *n* (%)		
1	0 (0)	2 (12)
2	7 (59)	11 (65)
3	5 (41)	4 (23)
De novo metastatic, *n* (%)	3 (25)	3 (17)
Previous chemotherapy, *n* (%)		
Adjuvant/neoadjuvant only	5 (42)	6 (35)
Treatment of metastatic disease (with or without adjuvant/neoadjuvant), *n* (%)	3 (25)	3 (17)
Previous endocrine therapy, *n* (%)		
Adjuvant	9 (75)	14 (82)
Metastatic disease	12 (100)	17 (100)
Previous therapies (including those used in adjuvant or metastatic setting), *n* (%)		
1	1 (8)	2 (12)
2	5 (42)	9 (53)
3 or more	6 (50)	6 (35)
Endocrine therapy sensitivity, *n* (%)	7 (59)	14 (82)
Metastases location at initiation of everolimus, *n* (%)		
Visceral metastasis only	4 (33)	4 (24)
Bone metastases/lymph nodes	4 (33)	8 (48)
Visceral + bone metastases/lymph nodes	4 (33)	5 (29)
Measurable disease, *n* (%)	10 (83)	15 (88)
Phospho-c-MET positive, *n* (%)	8/10 (80) 2 pts not evaluable	0/14 (0) 3 pts not evaluable

ET sensitivity :
≥ 24 weeks of response or disease stabilization

A



B



	c-MET +	c-MET -	p-value
mPFS (months)	6,1	10,5	**0,002**
OS (months)	24,5	37	0,061

Limitations

- Retrospective analysis with limited number of patients
- Before the era of CDK4/6 inhibitors ! (although not pointless)
- No validated assay for c-MET and phospho-c-MET evaluation

Conclusions & perspectives

- TK receptor c-MET could be associated with cancer progression and resistance to everolimus.
- It opens the era of targeted therapy in breast cancer
- Need for prospective and randomized trials