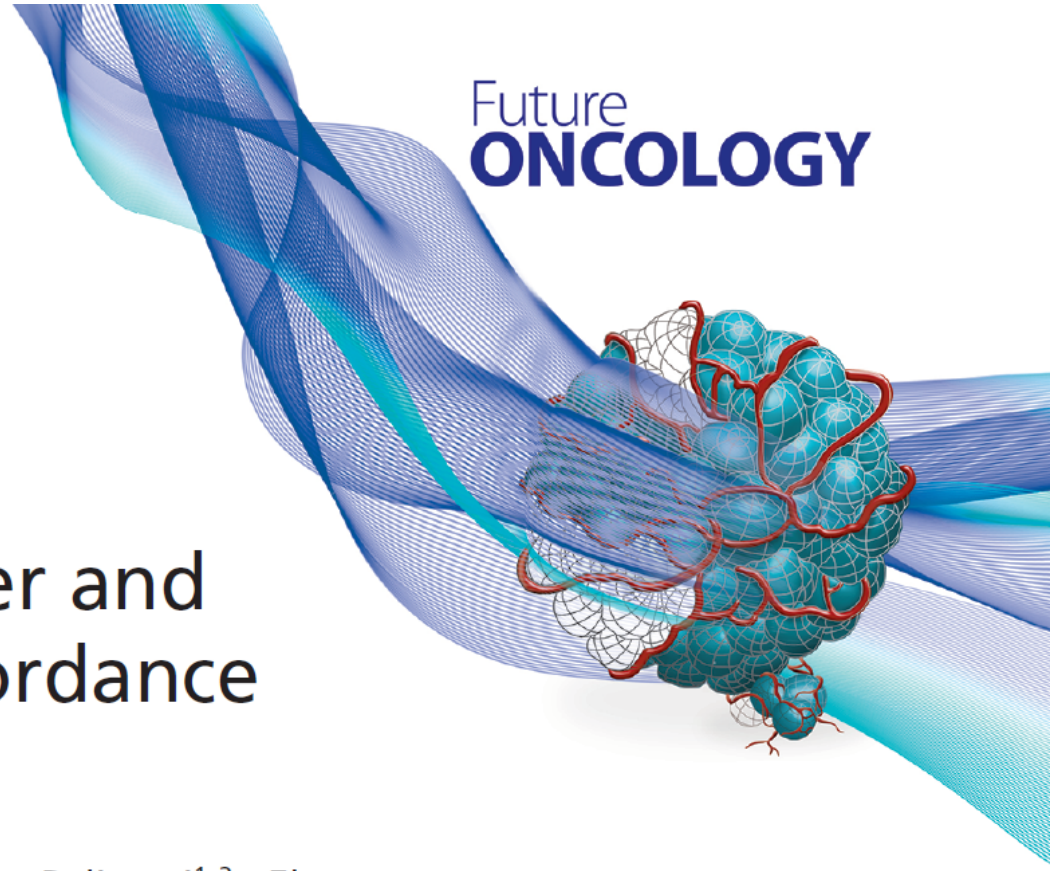
Cremona 15 Marzo 2019
LECTURES FOR TRAINING

Comparison of primary breast cancer and paired metastases: biomarkers discordance influence on outcome and therapy

Dr.ssa Elena Ongaro

Research Article

Future ONCOLOGY



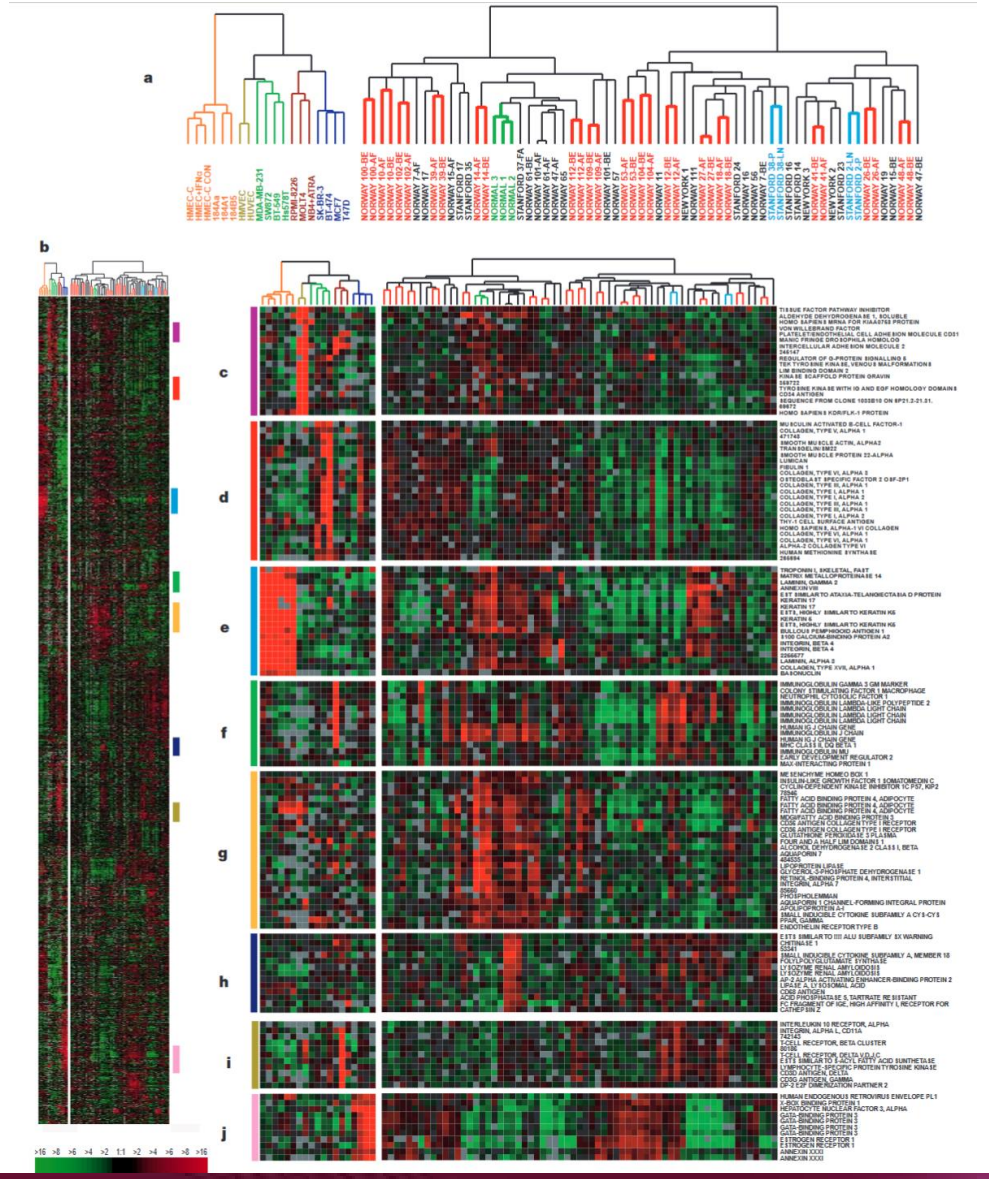
Comparison of primary breast cancer and paired metastases: biomarkers discordance influence on outcome and therapy

Elena Ongaro[1,2], Lorenzo Gerratana*[,1,3], Marika Cinausero[1,2], Giacomo Pelizzari[1,3], Elena Poletto[1], Manuela Giangreco[3,4], Claudia Andreetta[1], Stefano Pizzolitto[5], Carla Di Loreto[3,6], Alessandro Marco Minisini[1], Mauro Mansutti[1], Stefania Russo[1], Gianpiero Fasola[1] & Fabio Puglisi[3,7]

Background

The high heterogeneity of breast cancer led to the definition of different molecular subtypes (luminal A and B, HER2-enriched and triple negative) with distinctive biological features and clinical outcomes

→ immunohistochemical-defined surrogates based on the assessment of ER, PR, HER2 and Ki67 expression



Perou et al. Nature 2000

Background

- It is commonly thought that distant metastases resemble the same profile of the primary tumor, systemic palliative therapy is usually assigned according to the primitive biological phenotype

- Discordance rates for ER, PR and HER2 expression between primary BC and paired metastases are described, suggesting both biological and therapeutic implications

Aurilio et al. EJC 2014

- Metastasis biopsy is not strictly required, but NCCN guidelines recommend the re-biopsy of metastatic sites when feasible

Goetz et al. J Nat Compr Canc Netw 2019

Aim

- To evaluate the discordance in ER, PR, HER2 and Ki67 expression in a retrospective, real-world series of metastatic breast cancer

- To investigate the possible impact of antineoplastic treatments on biomarkers expression with an exploratory hypothesis generating purpose

Methods

- From January 2004 to July 2013 we retrospectively analyzed a cohort of 544 patients with metastatic breast cancer receiving anticancer treatments at the Department of Oncology, University Hospital of Udine, Italy.

- We selected patients that underwent biopsy of local or distant recurrence with available archival ER, PR, HER2 and Ki67 data.

- Biopsies from both primary and metastatic sites were analyzed at the Pathology Department of the University Hospital of Udine.

Statistical analysis

- Descriptive analysis of clinical and pathological characteristics was performed.
  - ER and PR variations were defined according to a 1% cut off, while for Ki67 a cut off of 14, 20 and 30% was applied.
  - Modifications of both hormonal receptors and Ki67 were analyzed also on a percent basis.

- To estimate the association between received therapies and ER, PR and Ki67 changes, OR with the 95% CI were calculated through uni- and multivariate logistic regression.

- Prognostic impact of changes in ER, PR and Ki67 in terms of OS was investigated through uni- and multivariate Cox regression and described by means of Kaplan–Meier estimator plot.

Baseline features

Table 1. Population's main characteristics.

Baseline features	Number	%
Age at stage IV diagnosis:		
– <35	2	0.8
– 35–65	137	59.1
– 65–70		
– >70		
Grading:		
– G1		
– G2		
– G3		
– Gx		
pT:		
– T0		
– T1		
– T2		
– T3		
– T4		
– Tx		

Table 1. Population's main characteristics.

Baseline features	Number	%
pN:		
– N0	56	24.1
– N1mi	2	0.9
– N1	44	19.0
– N2	28	12.1
– N3	38	16.4
– Nx	64	27.5
Stage IV at diagnosis:		
– Yes	42	18.0
– No	164	70.7
– Unknown	24	10.3
Previous treatments:		
– Anthracyclines	117	50.4
– Taxanes	78	33.6
– Antiestrogens	114	49.1
– Aromatase inhibitors	91	39.2

Molecular characteristics

	Primary Biopsy		*Secondary Biopsy*	
	Number	*%*	*Number*	*%*
Tumor Phenotype	166		178	
Luminal A	26	15.66	10	5.62
Luminal B	88	53.01	100	56.18
Luminal HER2	16	9.64	16	8.99
HER2 Positive	17	10.24	19	10.67
Triple Negative (TNBC)	19	11.45	33	18.54

Molecular discordance

	Number	*%*	*p value*
ER (n=166)			
Discordant	21	12.65	*p = 0.0072*
Gain	4	10.25	
Loss	17	13.38	
ER continuous (n=127)			
Lower	58	45.67	*p = 0.2437*
Higher or Stable	69	54.33	
PgR (n=171)			
Discordant	85	49.71	*p < 0.0001*
Gain	13	20.63	
Loss	72	66.67	
PgR continuous (n=108)			
Lower	88	81.48	*p < 0.0001*
Higher or Stable	20	18.52	

HER2 (n=175)			
Discordant	6	3.43	*p = 0.6875*
Gain	4	2.79	
Loss	2	6.25	
Ki67 >14 (n=120)			
Discordant	39	32.5	*p = 0.0003*
<14 to ≥14	31	73.80	
≥14 to <14	8	10.25	
Ki67 ≥20 (n=120)			
Discordant	42	35.0	*p < 0.0001*
<20 to ≥20	35	67.30	
≥20 to <20	7	10.29	
Ki67 ≥30 (n=120)			
Discordant	45	37.5	*p < 0.0001*
<30 to ≥30	38	52.77	
≥30 to <30	7	14.58	

Molecular discordance

Tumor phenotype (n=126)			
Discordant	28	22.2	
Luminal A to B	7	63.6	
Luminal B to A	2	2.89	
Luminal A/B to TNBC	11	13.75	
Luminal A/B to HER2 positive	1	1.25	
Luminal A/B to Luminal HER2	2	2.50	
Luminal HER2 to Luminal A/B	1	7.69	
Luminal HER2 to HER2 positive	3	23.07	
HER2 positive to Luminal HER2	1	7.14	

Uni- and multivariate analyses

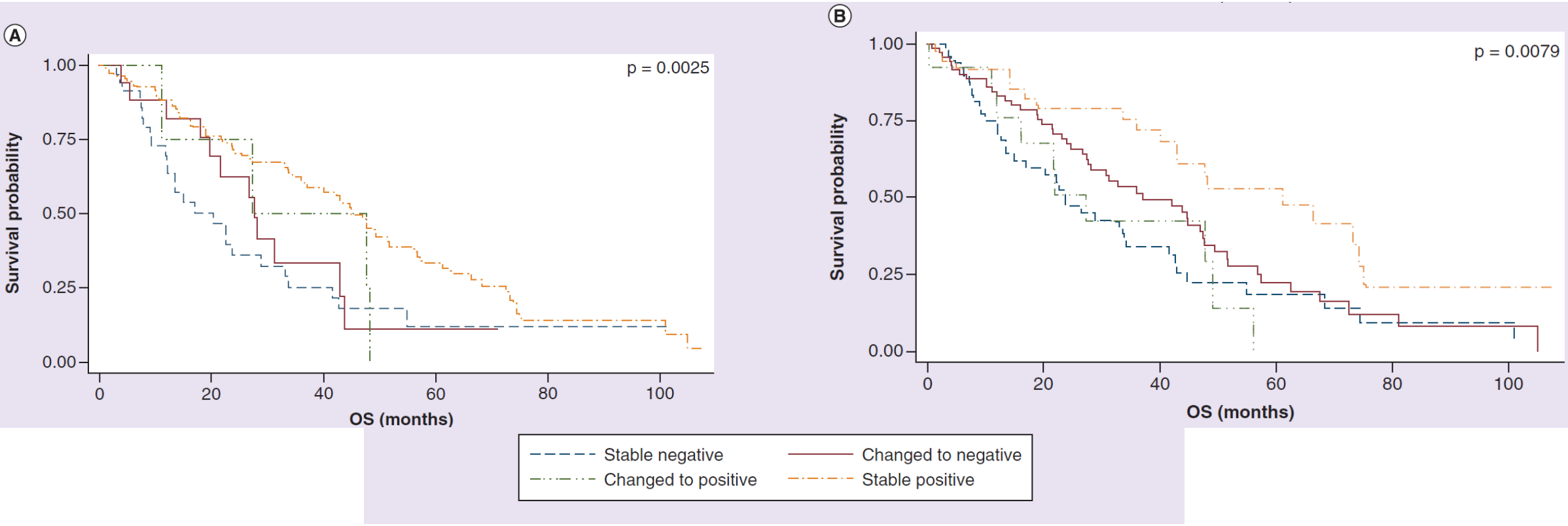
Table 4. Uni- and multivariate analyses.[†]

Phenotype modification	Anthracyclines[‡]		Taxanes[§]		Antiestrogens[¶]		Aromatase inhibitors[#]	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
ER loss:								
– Univariate	1.85 (0.61–5.63)	ns	1.43 (0.51–4.01)	ns	0.81 (0.28–2.31)	ns	3.02 (0.92–9.84)	ns
– Multivariate	–		–		–		–	
ER reduction (min. 1%):								
– Univariate	1.33 (0.65–2.71)	ns	4.03 (1.89–8.58)	<0.001	0.81 (0.39–1.67)	ns	2.51 (1.21–5.19)	0.013
– Multivariate	–		3.59 (1.66–7.77)	0.001	–		2.07 (0.96–4.44)	ns
PR loss:								
– Univariate	6.47 (2.68–15.61)	<0.001	3.7 (1.48–9.2)	0.005	1.14 (0.47–2.74)	ns	1.85 (0.82–4.16)	ns
– Multivariate	5.20	0.02	1.52	ns	–		–	
PgR reduction (min. 1%):								
– Univariate	5.27 (1.82–15.18)	0.002	5.17 (1.41–18.92)	0.013	2.45 (0.89–6.70)	ns	2.33 (0.84–6.40)	ns
– Multivariate	3.35 (0.99–11.28)	ns	2.61 (0.58–11.61)	ns	–		–	
K-67 <14 to ≥4:								
– Univariate	0.37 (0.16–0.87)	0.023	0.31 (0.12–0.79)	0.015	3.24 (1.36–7.69)	0.008	0.87 (0.38–1.98)	ns
– Multivariate	0.40 (0.13–1.17)	ns	0.55 (0.17–1.72)	ns	3.71 (1.45–9.47)	0.006	–	

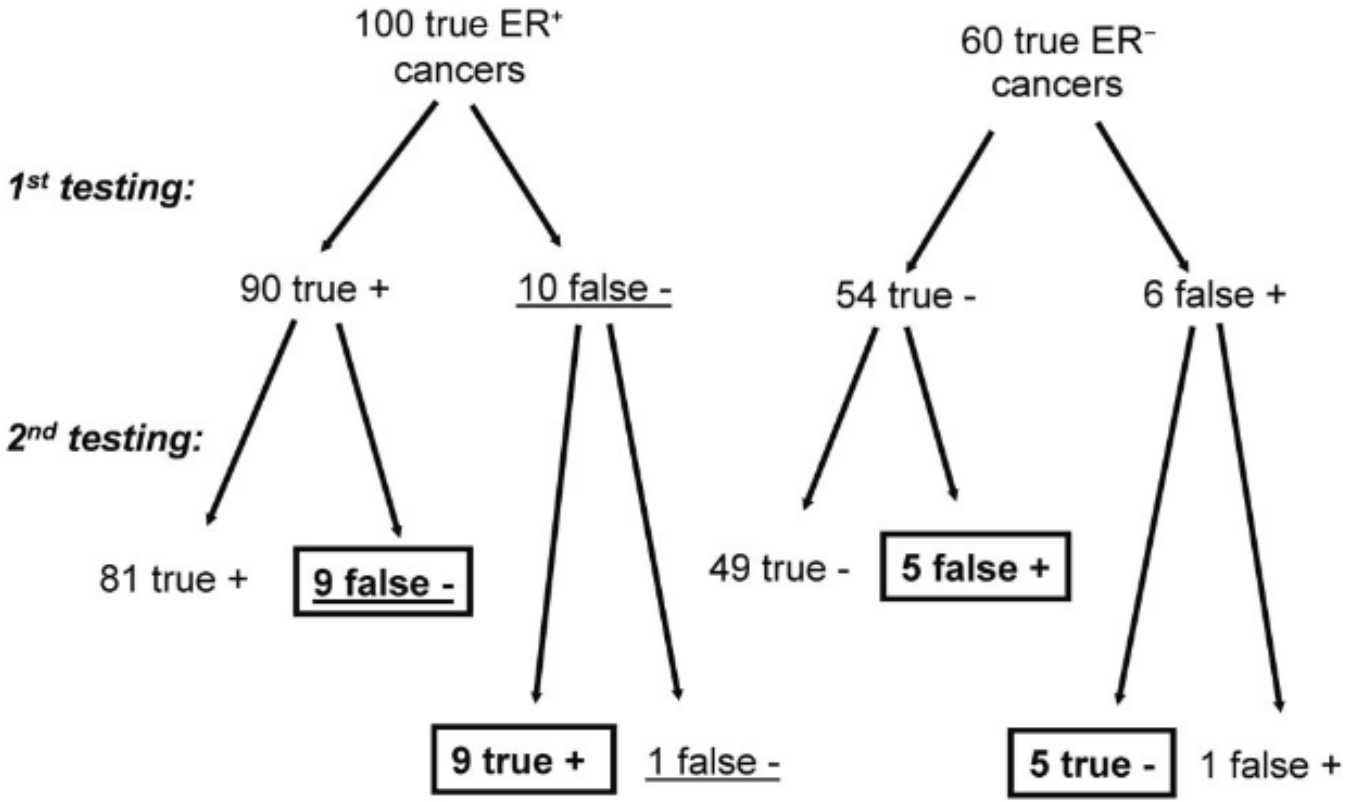
Survival analysis

ER

PgR



Discordance: a technical issue…?



Pusztai et al. The Oncologist 2010

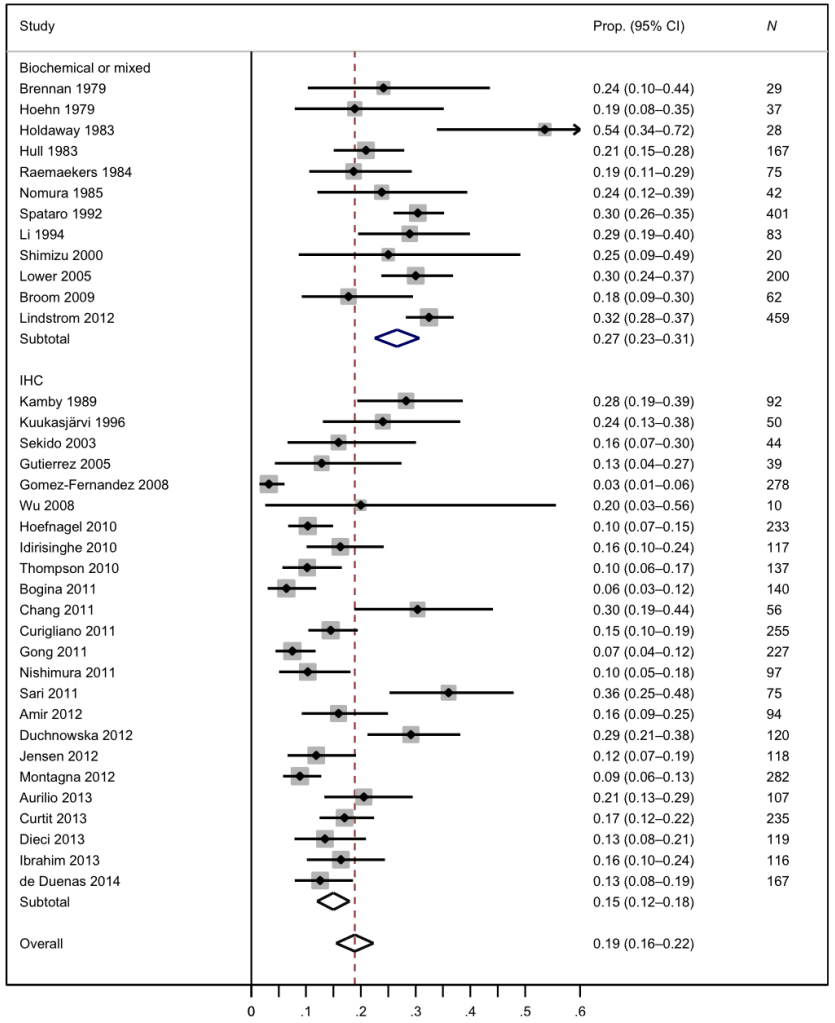
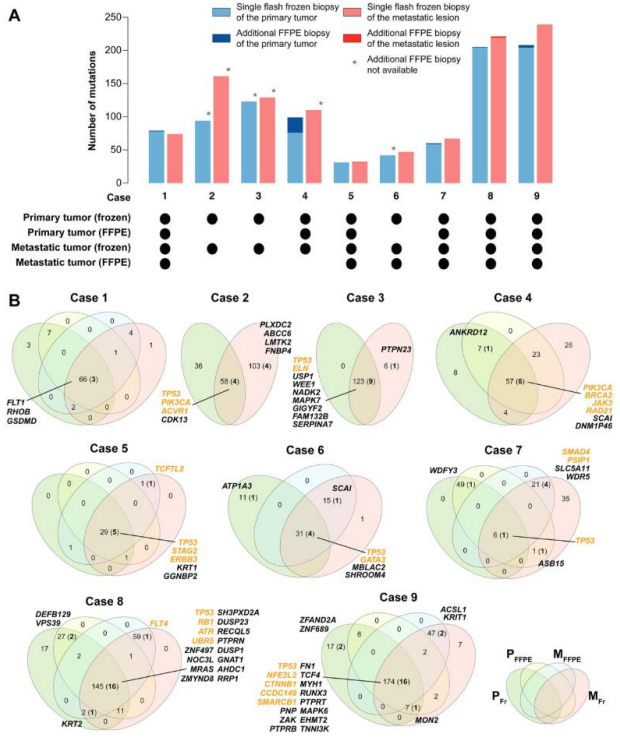


Figure 2. Meta-analysis of the proportion of estrogen receptor discordance by type of assay. Abbreviations: CI, confidence interval; Prop., proportion.

Sighoko et al. The Oncologist 2014

…or a real fact?



Ng et al. Clin Canc Res 2017

Fig. 1. Spatial and temporal heterogeneity in primary and metastatic lesions in treatment-naïve synchronous metastatic breast cancer

(A) Barplots depict the number of somatic mutations identified in single frozen biopsies of the primary tumors and metastatic lesions, and for seven patients, the additional mutations identified by analyzing an additional FFPE biopsy of the corresponding tumor. Available biopsy samples are indicated by black dots below the barplots. **(B)** Venn diagrams illustrate the number of somatic mutations and the number of likely pathogenic mutations (in bold) present in each of the biopsies. Genes affected by likely pathogenic mutations are listed, with those affecting cancer genes (31–33) labeled in orange. P_{Fr}: frozen biopsy of primary; P_{FFPE}: FFPE biopsy of primary; M_{Fr}: frozen biopsy of metastasis; M_{FFPE}: FFPE biopsy of metastasis. FFPE, formalin-fixed paraffin-embedded.

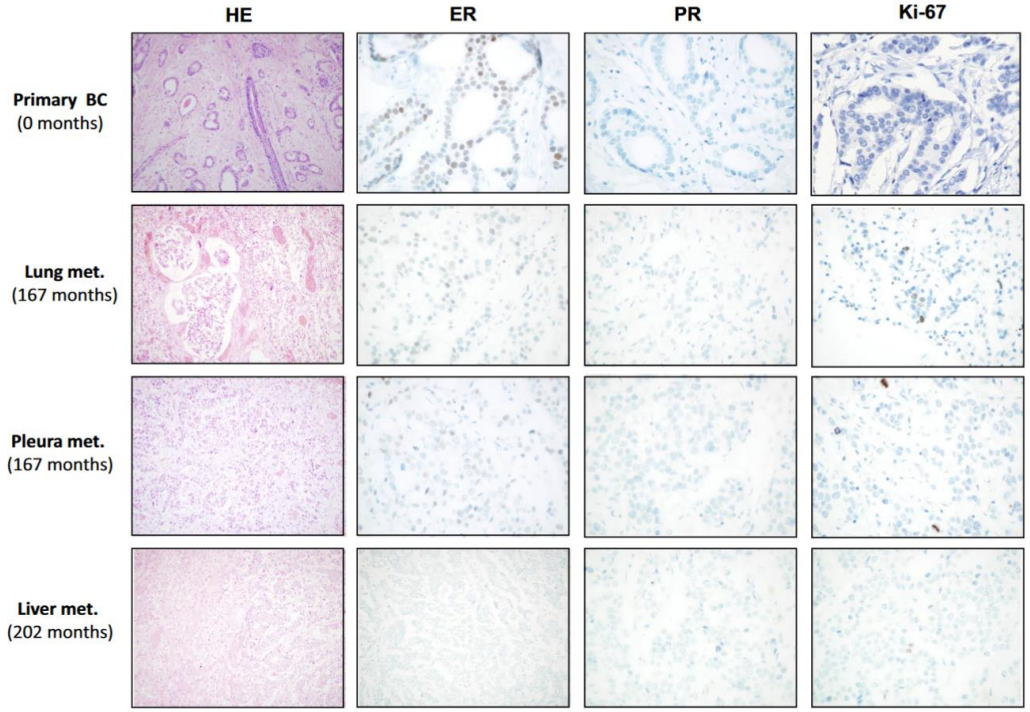


Fig. 3 Photomicrographs of the primary tumor and distant metastases of patient 10. The primary tumor was a LumB (ER+, PR− and Ki67 low, HER2 neg) IDC. After lumpectomy and sentinel lymph node biopsy (SLNB) the patient received radiation therapy, but declined any other adjuvant treatment. 14 years later metastases were discovered in the lung and pleura; the patient received multiple lines of chemotherapy and endocrine treatment. At 17 years liver metastases occurred, treatment was switched back to chemotherapy, the patient passed away 4 months later due to progression of the disease. The lung and pleura metastases were ER weakly positive, but the liver metastasis was detected as TN

Szekely et al. Clin Exp Metastasis 2017

Discussion

- In our series ER discordance determined a therapeutic change. Among patients with PR discordance, the driver of therapeutic decisions was the ER status.

- Our results suggest a potential positive prognostic role of stability in positive ER and PR expression.

- Possible role of previous exposure to anthracyclines, taxanes or aromatase inhibitors in hormonal receptor variations. Whether this phenomenon is due to an early clonal selection or to a real ER or PR loss is not clear and needs to be further investigated.

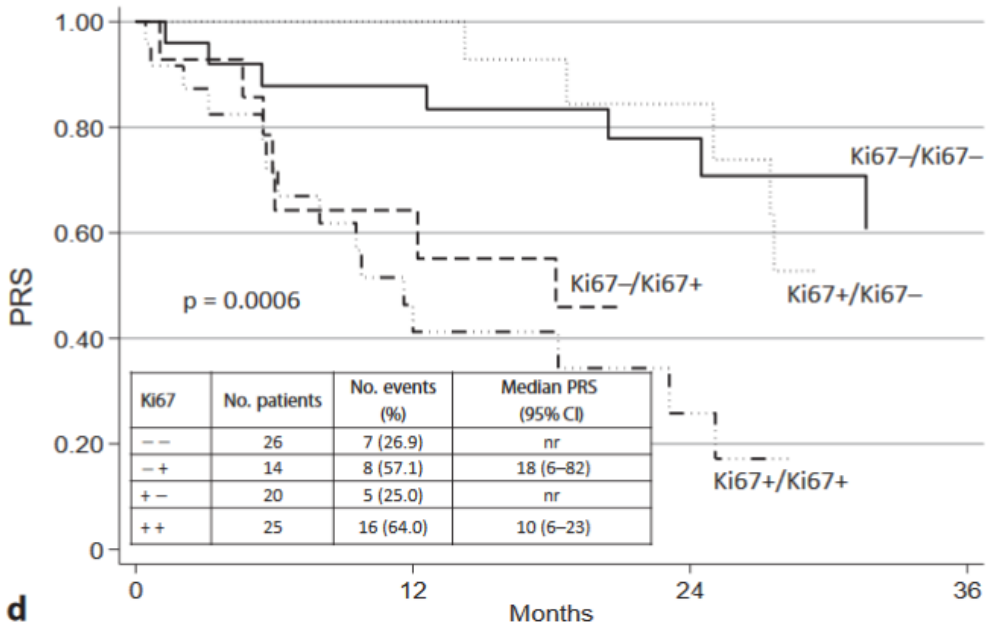
Ki-67 variation: metastatic like neoadjuvant?

Table 6 Uni- and multivariate analysis of factors for overall survival after recurrence

			Univariate analysis		Multivariate
Variables	**Category**	**primary/recurrence**	**Relative risk**	**P value**	**P value**
Primary Tumor					
Tumor size	2.0 cm </≤2.0 cm	primary tumor	0.98	0.93	
Nodal status	0/1-3/4+	primary tumor	1.39	0.15	
Nuclear Grade	1/2/3	primary tumor	1.55	0.22	
Ki-67	50%≤/< 50%	primary tumor	5.67	0.0002	0.0006
ER	+/-	primary tumor	0.49	0.07	0.09
PgR	+/-	primary tumor	0.43	0.037	0.35
p53	+/-	primary tumor	2.18	0.058	0.11
HER2	+/-	primary tumor	0.9	0.82	
Recurrent Tumor					
DFI	5y≤/2y≤/< 2y	at recurrence	0.73	0.22	
Ki-67	50%≤/< 50%	recurrent tumor	2.88	0.009	0.32
ER	+/-	recurrent tumor	0.36	0.013	0.51
PgR	+/-	recurrent tumor	0.25	0.005	0.046
p53	+/-	recurrent tumor	1.78	0.16	
HER2	+/-	recurrent tumor	0.95	0.91	
Distant metastasis	+/-	at recurrence	2.56	0.017	0.043

ER: estrogen receptor; PgR: progesterone receptor; DFI: disease-free interval
*27 cases died of only breast cancer.

Nishimura et al. World J Surg Oncol 2011



Ki67	No. patients	No. events (%)	Median PRS (95% CI)
– –	26	7 (26.9)	nr
– +	14	8 (57.1)	18 (6–82)
+ –	20	5 (25.0)	nr
+ +	25	16 (64.0)	10 (6–23)

Ibrahim et al. Oncology 2013

Conclusions

- Our results corroborate the importance of Ki67 as a prognostic factor and suggest a possible role for a proxy of acquired disease aggressiveness, consistently with data derived from the neoadjuvant setting

- These results may represent the basis for further prospective studies focused on the validation of Ki67 as a dynamic marker of prognosis, capable of representing the disease's evolution also in consideration of previous treatments

- If confirmed, these data could be integrated in the current follow-up strategies for a higher tailorization and precise approach.

Conclusions

- The molecular evaluation of metastatic lesions may influence the clinical decision-making process.

- Moreover, our results suggest the possible role of therapy exposure in modifying hormonal receptor status and Ki67 percentage of expression, and consequently biological behavior of metastatic BC.

eleongaro@gmail.com