Genomic characterisation of metastatic breast cancers

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COI

- FA: research grants from Pfizer, AZ, Lilly, Roche, Novartis, Daiichi , founder: Pegascy
- CL: advisory boards of MSD, BMS, Merck Serono, Amgen, Astra Zeneca, Nanobiotix
- TB: Novartis, Roche, AstraZenzca; Pfizer: Ad board, travel, research grant

Outline

- **Background and scientific question**
- Patients and Methods
- Driver identification
- Mutational processes
- Genomic complexity

Background

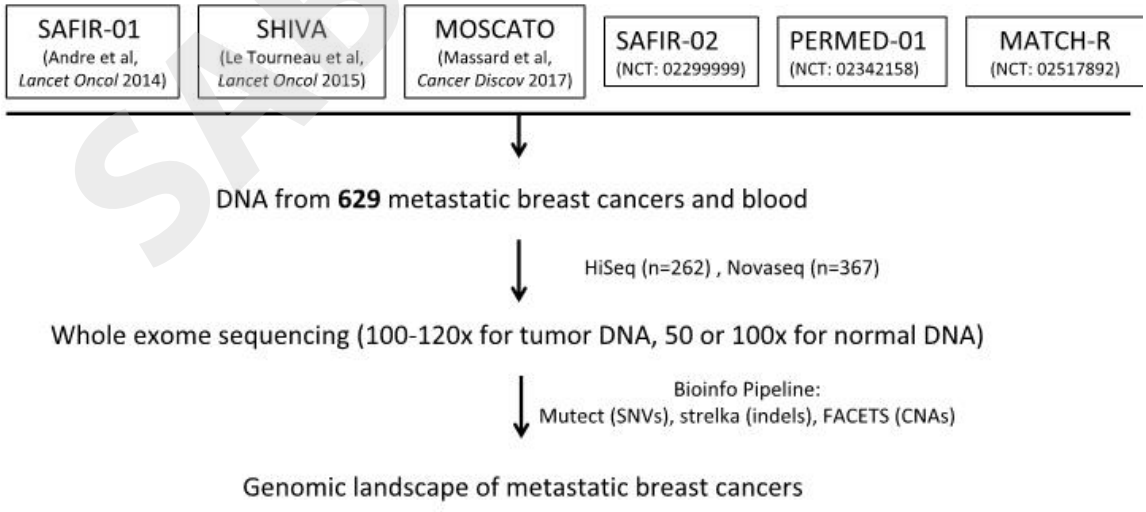
mBC acquire ESR1 mutations under the pressure of endocrine therapy: Evidence of genome evolution

Beyond ESR1, does mBC acquire genomic alterations that contribute to disease progression ?

Outline

- Background
- **Patients and Methods**
- Driver identification
- Mutational processes
- Genomic complexity

Patients and Methods



Patient characteristics

	Overall (n=629)	HR+/HER2- (n=387)	TNBC (n=186)	HER2+ (n=32)	P-value
Age at inclusion					
Median (Range)	54 (26-83)	56 (26-82)	50 (27-83)	53 (37-73)	<0.0001
Site of biopsy					
Liver	272 (43.2)	205 (53%)	43 (23.1%)	9 (28.1%)	
Lymph Node	111 (17.6%)	58 (15%)	43 (23.1%)	7 (21.9%)	
Skin	76 (12.1%)	44 (11.4%)	24 (12.9%)	5 (15.6%)	<0.0001
Breast	74 (11.8%)	38 (9.8%)	33 (17.7%)	2 (6.3%)	
Other	96 (15.3%)	42 (10.8%)	43 (23.2%)	9 (28.1%)	
Previous Endocrine Therapy					
Yes	9 patients pretreated with CDK4 inhibitors				
Number of previous lines of Chemotherapy					
0-1	427 (67.8%)	259 (66.9%)	140 (75.2%)	16 (50%)	
>1	182 (29%)	118 (30.5%)	38 (20.5%)	15 (47%)	0.0019
Missing	20 (3.2%)	10 (2.6%)	8 (4.3%)	1 (3%)	
Delay between biopsy and diagnosis of metastasis					
0-12 months	301 (47.9%)	162 (41.9%)	122 (65.6%)	15 (46.9%)	
> 12 months	183 (29%)	153 (39.5%)	23 (12.4%)	3 (9.3%)	<0.0001
Missing	145 (23%)	72 (18.6%)	41 (22%)	14 (43.8%)	

Outline

- Background
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- **Driver identification**
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Can we identify genomic alterations that drive progression of mBC ?

I. Identification of driver alterations

Driver alterations identified by Mutsig, q<0.1, freq>1%

Driver Alteration: Gene alterations whose characteristics suggests they could alter the phenotype

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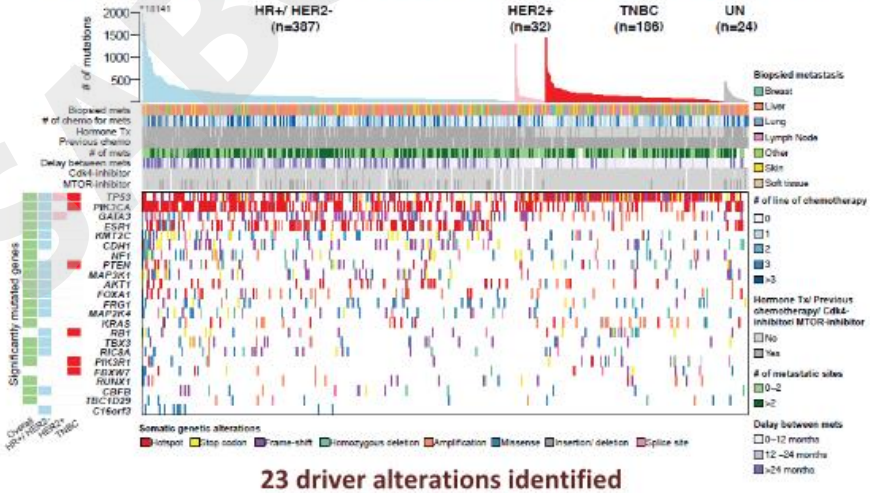
Identification of recurrent driver alterations

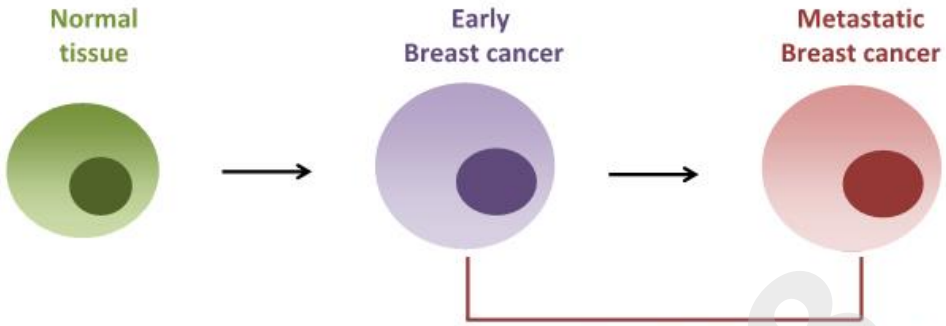


23 driver alterations identified

Are these alterations (or the ones from eBC) more/less frequently mutated in mBC ?

Can we identify genomic alterations that drive progression of mBC ?

II. Comparison with genomic landscape of early Breast Cancers



Comparison with TCGA (Lefebvre, PLoS Med), Fisher's exact test adjusted for multiple comparisons (<0.05)

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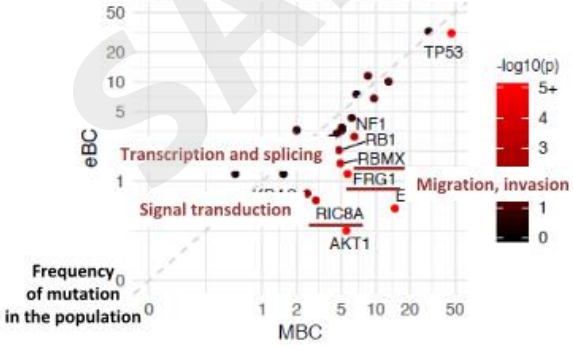
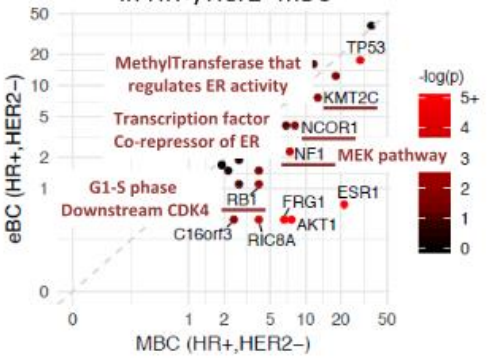
Which genomic alterations are enriched in mBC as compared to eBC ?

Nine gene alterations enriched in the overall population



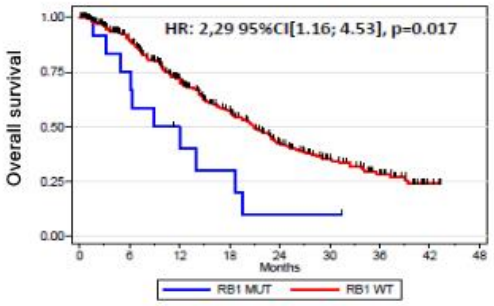
Ten gene alterations enriched in HR+/Her2- mBC



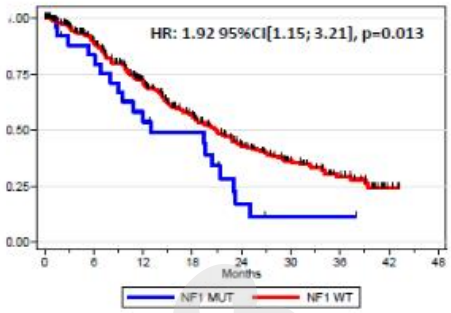
What is the clinical relevance of detecting these alterations (HR+/Her2-) ?

Clinical relevance of RB1 & NF1 mutations

RB1



NF 1



HR: Hazard Ratio (multivariate)

Summary

Metastatic breast cancers acquire new genomic alterations, suggesting a genome evolution and/or clonal selection

Which mutational processes mediate disease evolution ?

Outline

- Background
- Patients and Methods
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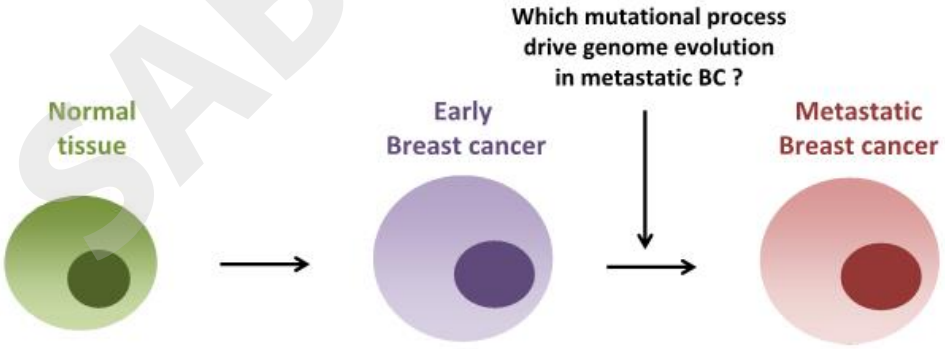
- **Mutational processes**
- Genomic complexity

Which mutational processes drive tumor evolution ?



Which mutational processes drive tumor evolution ?

Mutational signatures associated with mutational processes
(deconstructSigs)
Homologous recombination deficiency
(sign 3 + large scale state transitions)

Which mutational processes drive tumor evolution ?

Comparison with TCGA ($p<0.0001$)

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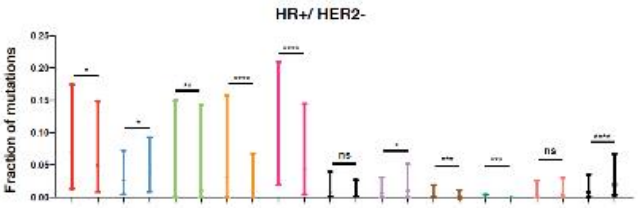
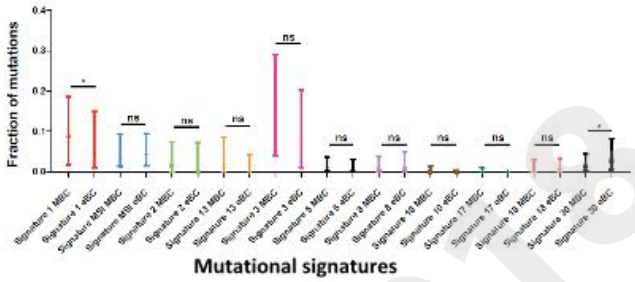
Mutational signatures enriched in mBC as compared to eBC

Four mutational signatures enriched in HR+/Her2- mBC



No mutational signature enriched in mTNBC



*: p<0.05; **: p<0.01; ***: p<0.001; ****: p<0.0001

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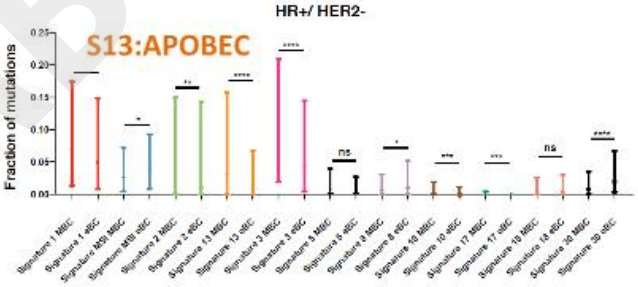
Mutational signatures enriched in mBC as compared to eBC



****: p<0.0001

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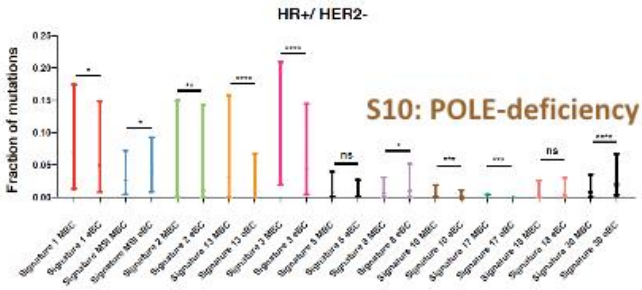
Mutational signatures enriched in mBC as compared to eBC



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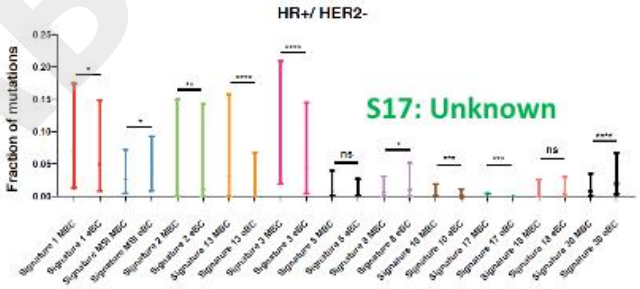
Mutational signatures enriched in mBC as compared to eBC



****: p<0.0001

Since these mutational signatures could indicate a genome evolution, is their detection associated with poor outcome in mBC ?

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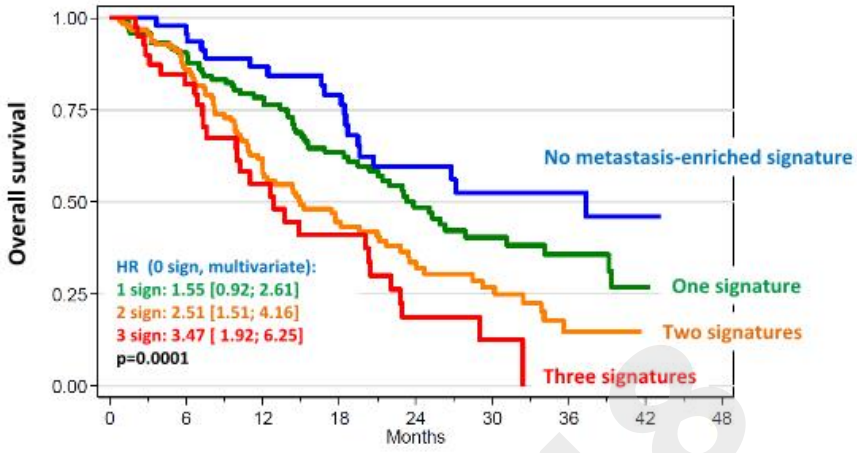
Mutational signatures and outcome



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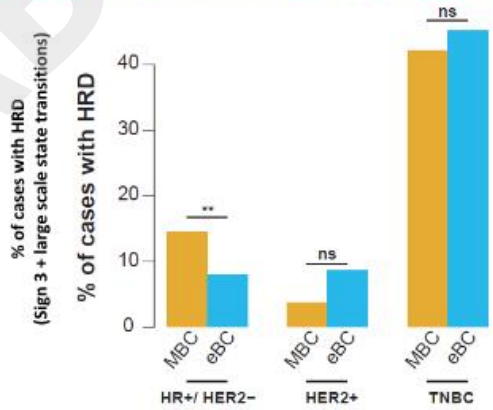
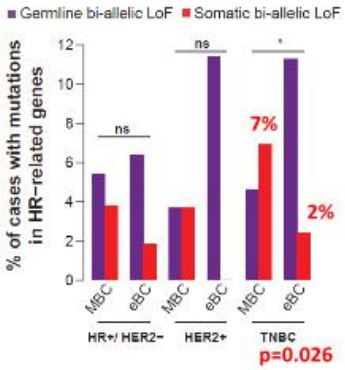
Do metastatic samples present high frequency of Homologous recombination deficiency (HRD) ?

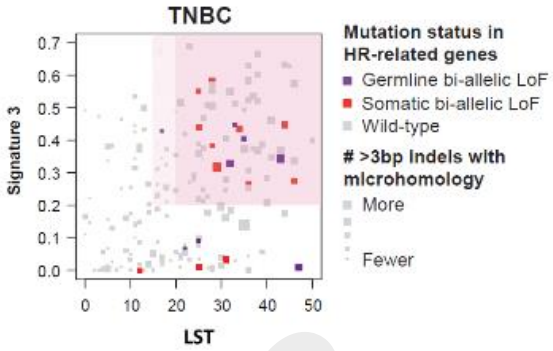


Do mBC present an enrichement of biallelic loss-of-function mutations in genes located on HR-pathway ?

Biallelic loss of function mutations in genes located on HR pathway



Increased frequency of **somatic** biallelic loss-of-function mutations in genes on HR-pathway in mTNBC



75% of mTNBC with somatic bi-allelic LoF present a high HRD

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Take home message

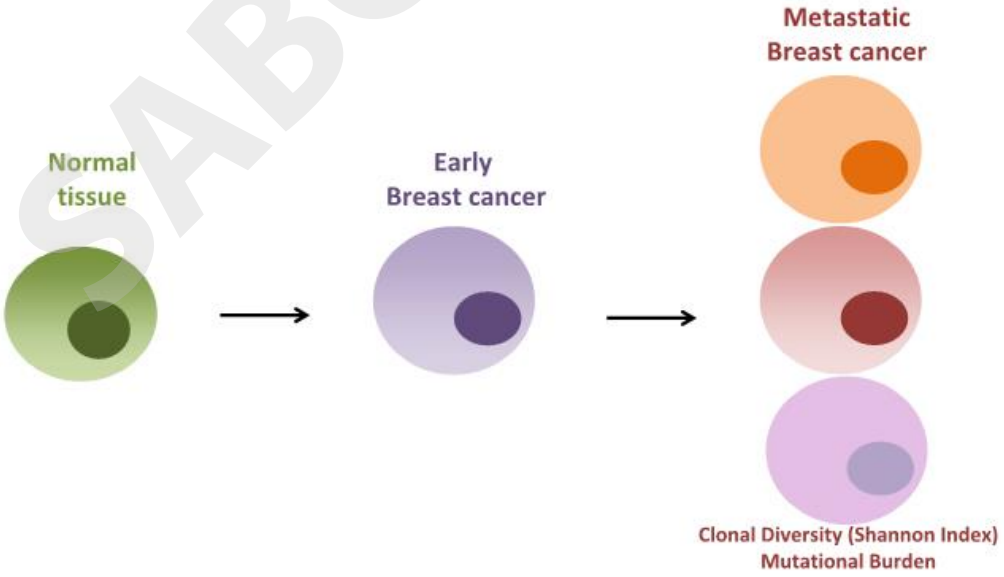
- Mutational signatures 13 (APOBEC), 10 (POLE), 17 are enriched in metastatic samples as compared to early BC
- They could be a surrogate of genome evolution and their detection is associated with poor outcome
- A subset of mTNBC present somatic biallelic loss-of-function mutations on genes located in HR-pathway and could represent a new population of patients eligible for PARP inhibitors

Since mutational processes make the genomes of mBC evolving, is the disease becoming more complex at advanced stages ?

Outline

- Background
- Patients and Methods
- Driver identification
- Mutational processes
- **Genomic complexity**

Are advanced stage BC more complex genetically than eBC ?



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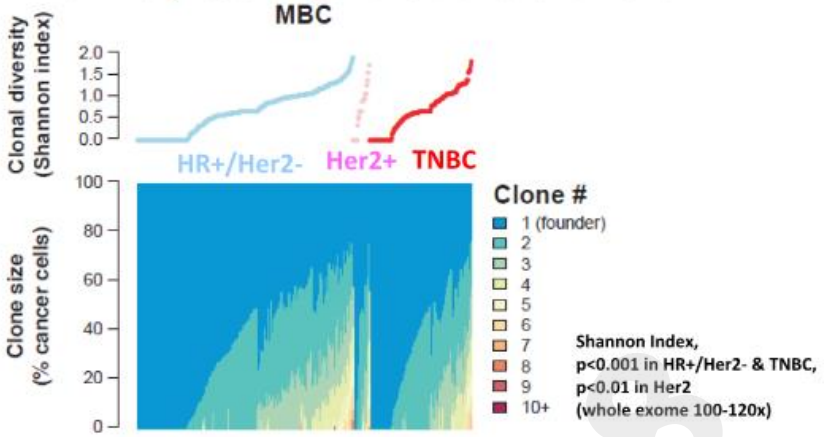
Clonal Diversity

Are mBC presenting more clones than eBC ?



There is a dramatic increase in the clonal diversity in mBC

There is an inter-patient heterogeneity regarding the clonal diversity

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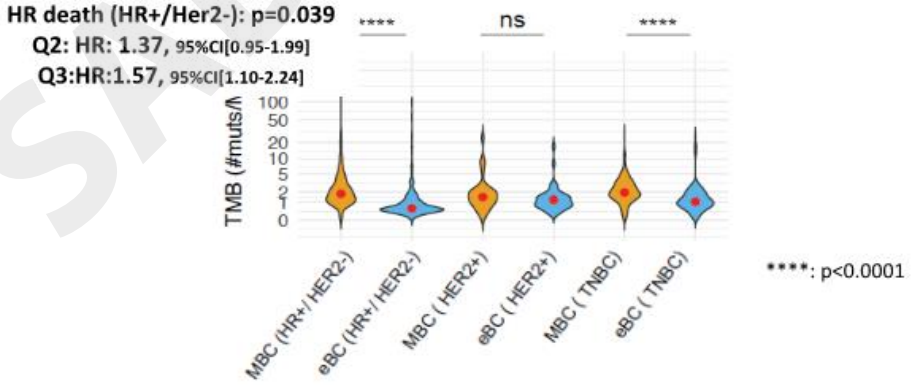
Tumor Mutational Burden

Are mBC presenting more mutations than eBC ?



There is a dramatic increase of mutational load in mBC

There is an inter-patient heterogeneity regarding the mutational load

Conclusion

- 10 driver alterations enriched in HR+/Her2- mBC
- Three signatures enriched in HR+/Her2- mBC that define a group of patients with very poor outcome
- mTNBC includes a group of patients with somatic biallelic LoF mutations in genes located on HR-pathway
- mBC present an increased complexity
- There is an inter-patient heterogeneity regarding clonal diversity and mutational burden

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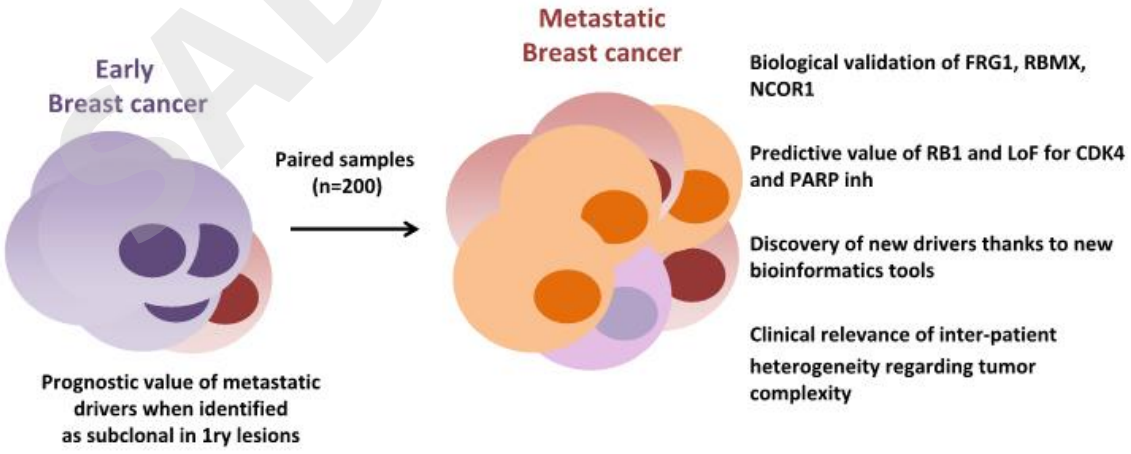
Perspectives



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