Concordance of genomic alterations between paired tissue and plasma samples analyzed with next generation sequencing panels from patients with HER2-positive metastatic breast cancer

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Background

Analyses of plasma circulating tumor DNA by next generation sequencing (NGS) panels is an emerging useful tool for identifying tumor genomic alterations in BC.
There is scarce data about the concordance of genomic alterations found at the same time point in tissue (T) and plasma (P) samples of patients (pts) with HER2-positive metastatic breast cancer (mBC)[1,2,3].

Methods and Materials

This is a single institution study of a consecutive cohort of HER2-positive mBC pts receiving anti-HER2 therapies. Tumor T and P samples were collected prospectively after obtaining consent. Genomic alterations were analyzed retrospectively using NGS with the VHIO300 panel for T (includes 421 genes) and the VHIO360 panel for P samples (includes 74 genes). HER2 expression in T samples was evaluated using Immunohistochemistry (IHC) and in situ hybridization (ISH) following the 2018 ASCO/CAP guidelines.

Statistical methods

To test the concordance of paired T/P samples between the NGS panels, only the 73 common genes were included (Table 1). General linear models, Pearson and Spearman correlations were used to associate numerical variables.

AKT1	*CCND2*	*ESR1*	*HRAS*	*MLH1*	*PDGFRA*	*SMAD4*
ALK	*CCNE1*	*EZH2*	*IDH1*	*MPL*	*PIK3CA*	*SMO*
APC	*CDH1*	*FBXW7*	*IDH2*	*MTOR*	*PTEN*	*STK11*
AR	*CDK12*	*FGFR1*	*JAK2*	*MYC*	*PTPN11*	*TERT*
ARAF	*CDK4*	*FGFR2*	*JAK3*	*NF1*	*RAF1*	*TP53*
ARID1A	*CDK6*	*FGFR3*	*KIT*	*NFE2L2*	*RB1*	*TSC1*
ATM	*CDKN2A*	*GATA3*	*KRAS*	*NOTCH1*	*RET*	*VHL*
BRAF	*CTNNB1*	*GNA11*	*MAP2K1*	*NPM1*	*RHEB*	
BRCA1	*DDR2*	*GNAQ*	*MAP2K2*	*NRAS*	*RHOA*	
BRCA2	*EGFR*	*GNAS*	*MAPK1*	*NTRK1*	*RIT1*	
CCND1	*ERBB2*	*HNF1A*	*MET*	*NTRK3*	*ROS1*	

Table 1. VHIO300/VHIO360 73 common genes

Results

107 consecutive pts were included in the study, of which 39 had synchronous paired T/P samples.
Out of these 39 pts, a total of 42 T/P pairs of samples were available.

Analysis of NGS panels revealed that ERBB2 amplification status coincided in 71% (30/42) of P and T pairs (Table 2), with copy number correlation reaching statistical significance (Figure 1). In T samples alone, the concordance between ERBB2 amplification detected by two different methodologies, NGS and by IHC-ISH, resulted positive in 83% (35/42) samples (Table 3). Concordance in ERBB2 amplification between P by NGS and paired T samples by IHC-ISH, resulted positive in 64% (27/42) samples (Table 4).

T and P shared at least one pathogenic or likely pathogenic mutation in 76% (32/42) pairs of samples where these variants were present (Bar diagram 1). The overall agreement between genotype status (mutant/ wild-type) for all genes was 78.5%. The number of detected mutations per sample varied from 0 – 6.

For variants of uncertain significance (VUS), 21% (8/38) pairs shared altered variants in both samples (Bar diagram 2). The average percentage of altered shared genes was 35%. The range of VUS variants detected per sample varied from 0 – 14.

For amplifications, 65% (26/40) pairs shared at least one altered gene in both samples. The average percentage of concordant T/P pairs with regards to amplified genes was 60.8% (Bar diagram 3). The range of copies detected per sample varied from 0 - 9. Concordance of genomic alterations found in paired T/P samples is summarized in Table 5.

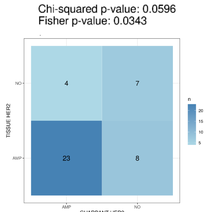


Table 2. VHIO300/VHIO360 ERBB2 amplification

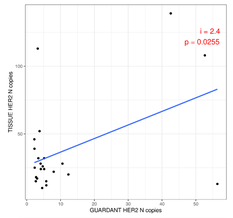


Figure 1. VHIO300/VHIO360 ERBB2 raw copy number

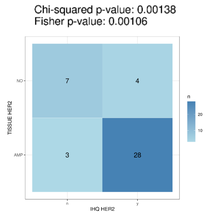


Table 3. VHIO300/IHC-ISH ERBB2 amplification

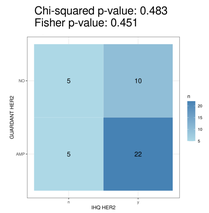
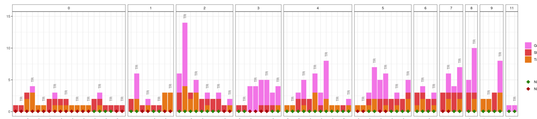
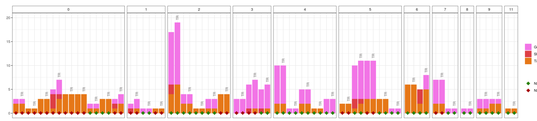


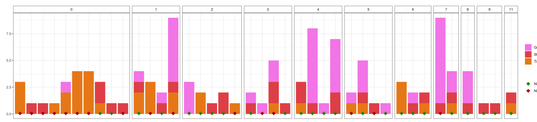
Table 4. VHIO360/IHC-ISH ERBB2 amplification



1.All pathogenic mutations



2. VUS



3. Amplifications

1.2.3. Bar diagrams with genomic alterations found in paired T and P samples sorted by line of treatment. NSF: Non singleton families. TR:Transcript

Genomic alteration	Pathogenic and likely pathogenic mutations		VUS		Amplifications	
	Genes	Number of samples (%)	Genes	Number of samples (%)	Genes	Number of samples (%)
Shared in plasma and tissue	*TP53*	25 (59,5)	*APC*	4 (10,5)	*ERBB2*	23 (57,5)
	PIK3CA	16 (38)	*PIK3CA, CDK12, RB1*	2 (5,2)	*CCND1*	5 (12,5)
	GATA3	4 (9,5)	*ARID1A, CDK6, EGFR, NTRK1*	1 (2,6)	*CDK6, MYC, PIK3CA*	1 (2,5)
	ARID1A	3 (7,1)				
	PTEN	2 (4,8)				
	BRCA2, ESR1, RHOA, SMAD4	1 (2,4)				
Present in plasma (not in tissue)	*TP53*	5 (11,9)	*NF1*	6 (15,8)	*CDK6, PIK3CA*	6 (15)
	ERBB2, ESR1, KRAS	3 (7,1)	*ATM*	5 (13,1)	*BRAF, CCND1, CDK4*	5 (12,5)
	ARID1A, CDKN2A, PIK3CA	2 (4,8)	*APC, CDK12, RAF1*	4 (10,5)	*ERBB2*	4 (10)
	APC, BRCA1, PTEN	1 (2,4)	*MTOR, NTRK1, PDGFRA*	3 (7,9)	*KRAS*	3 (7,5)
Present in tissue (not in plasma)	*TP53*	8 (19) (1 double mutation)	*ERBB2*	9 (23,7)	*ERBB2, MYC*	8 (20)
	BRCA2, CDH1, CDKN2A	2 (4,8)	*EGFR*	6 (15,8)	*FGFR1*	7 (17,5)
	APC	1 (2,4)	*BRCA2, CDK12, KIT, PDGFRA*	5 (13,1)	*CCNE1*	3 (7,5)
	NF1	1 (2,4) (1 double mutation)	*FGFR2, MYC, PTPN11, RAF1, RB1*	3 (7,9)	*AR, CCND1, PIK3CA, RET*	2 (5)

Table 5. Concordance of genomic alterations between tissue and plasma samples

Conclusions

1. A high concordance rate for ERBB2 amplification was detected by NGS in T and P paired samples, as well as in T samples using different approaches, NGS and IHC/ISH.
2. Concordance was high between T and P with regards to pathogenic and likely pathogenic mutations, moderate for amplifications other than ERBB2, and overall low for VUS.
3. The results obtained highlight the complementarity of both NGS techniques, emphasizing the ease of obtaining a plasma liquid biopsy and its panoramic view capturing potential heterogeneity and emerging mutations (e.g. ESR1, ERBB2). In contrast, tissue analysis enables the assessment of a larger set of genes and genomic alterations.

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