**Supplementary Figures**

**Supplementary Fig S1 Guardant360 ctDNA Sequencing Gene Panel**

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The Guardant360 panel version GH2.9 reports single nucleotide variants (SNVs) in 70 genes, gene copy number amplifications in 18 genes, fusions/rearrangements in 6 genes as well as indels in 3 genes. Complete exons are sequenced for all exons in 30 genes, including ERBB2, and the critical exons in 40 genes (597 exons total). Thus, a 146,000 base pair targeted region is sequenced for each patient sample. 2,720 probes. Average GC 47%.

**Supplementary Fig S2 Consort Diagram**



**Supplementary Fig S3. Distribution of *HER2* activating mutations identified by plasma ctDNA sequencing in 1,584 breast cancer patients**



Each circle represents a single patient.

**SUPPLEMENTARY TABLES**

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| **Supplementary Table S1 *HER2* Activating Mutations Detection by Tumor DNA** **versus Plasma Cell-free DNA Sequencing** |
|  | *HER2* mutation by tumor DNA sequencing\*  |
| *HER2* mutation by ctDNA sequencing\* | Pos | Neg |
| Pos (concordant with tumor sequencing) | 11 | 0 |
| Pos (discordant with tumor sequencing) | 1 | NA |
| Neg | 2 | 32 |
| No detectable ctDNA mutation  | 0 | 8 |
| Total | 14 | 40 |
| Comparing the tumor DNA sequencing, the sensitivity and specificity of ctDNA for the detection of *HER2* activating mutation was 11/14 (79%, 90% CI: 53-94%) and 32/32 (100%, 90% CI: 91-100%), respectively. The overall concordance rate was 43/46 (93.5%, 90% CI 87-100%). \* Mutation data is detailed in Supplementary Table S2. NA, not applicable |

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| **Supplementary Table S2 *HER2* Mutation by Tumor or ctDNA sequencing, ctDNA *HER2* mutation Variant Allele Frequency, and Tumor Response in Individual Patient with Activating *HER2* Mutations (n=14)** |
| Pt ID | *HER2* Mutationby tumor sequencing | ctDNA *HER2* Mutation Variant Allele Frequency | Best Response% change in tumor size | PFS (Weeks) |
| Baseline ctDNA *HER2* Mutation  | Baseline | 4-week | Progression |
| 13 | P780\_Y781insGSP | Not detected (Neg) | 0%  | 0% | NA | SD | NM | 75  |
| 16 | L869R | L869R | 15.44% | 0.27% | 1.6% | SD | -12% | 37 |
| 14 | S310F,V842I | Not detected | 0%, 0%  | 0%, 0% | 0.34%, 0% | SD | NM | 32 |
| Not detected | D769Y  | 0.94% | 0% | 0.2% |
| Not detected | I767M | 0%  | 0% | 0.25% |
| Not detected | T862A | 0%  | 0% | 17.79% |
| Not detected | T798I | 0%  | 0% | 0.39% |
| Not detected | L869R | 7.47% | 0.55% | 22.86% |
| 15 | V777\_G778insGSP | V777\_G778insGSP | 0.19% | 0% | 0.82% | CR | -100% | 32 |
| 9 | L755S | L755S | 0.96% | 0.15% | 14.82% | PR | -35% | 31 |
| 8 | L755S | L755S | 45.98% | 1.11% | NA | SD | NM | 22 |
| 2 | A775\_G776insYVMA | A775\_G776insYVMA | 10.28% | 0.11% | 15.65% | SD | 5% | 20 |
| 6 | D769H | D769H | 2.85% | 0.25% | 3.76% | SD | -23% | 12 |
| 3 | S310F | Not detected (Neg) | 0% | 0% | 0% | PD | 11% | 9 |
| 1 | P780\_Y781insGSP | P780\_Y781insGSP | 14.27% | 2.01% | 8.84% | PD | 17% | 8 |
| 12 | L755S | L755S | 4.22% | 1.71% | 5.04% | PD | 33% | 8 |
| 11 | L755S | L755S | 32.41% | 43% | NA | PD | 0% | 8 |
| 7 | L755S | L755S | 4.63% | 16.41% | NA | PD | 41% | 4 |
| 10 | L755S | L755S | 15.20% | NA | NA | PD | 17% | 3 |
| NA, Sample Not available; NM, no measurable disease by RECIST; SD, Stable Disease; CR, Complete Response; PR, Partial Response; PD, Progressive Disease; PFS, Progression free survival; Shaded VAFs data were used for the plot in Figure 2d. |