Homologous recombination deficiency (HRD) score as a measure to predict the effect of carboplatin on survival in the neoadjuvant phase II GeparSixto trial in triple-negative early breast cancer

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Background & Aim

Homologous recombination–deficient (HRD) tumors have lost the ability to repair double-stranded DNA breaks, resulting in increased susceptibility to DNA-damaging drugs such as platinum agents. Genomic instability and a high frequency of g*BRCA1* and g*BRCA2* mutations are commonly associated with triple-negative breast cancer (TNBC)[1]. Addition of carboplatin to anthracycline/taxane-based neoadjuvant chemotherapy has been shown to increase pathological complete response (pCR; ypT0 ypN0) rates in patients with TNBC in two large phase II studies (GeparSixto[2] and CALGB 40603[3]).

Patients with HRD tumors and those with a g*BRCA*, had in general a higher pCR rate with and without carboplatin[1]. Patients with pCR had in general a better prognosis, irrespective of the g*BRCA* status.

To determine whether HRD can predict the effect of carboplatin on survival in TNBC subgroup from GeparSixto trial, we correlated the HRD status to the event free survival (EFS).

Materials and Methods

GeparSixto (NCT01426880; GBG 66) was a multicenter, prospective, randomized, open-label phase II study. The study design is shown in Figure 1. Pretherapeutic formalin-fixed, paraffin embedded (FFPE) core biopsies from 315 patients with centrally confirmed TNBC enrolled in the GeparSixto study were assessed retrospectively for somatic mutations of *BRCA1/2* (tm*BRCA*) and HRD-score using Myriad's HRD test. The HRD score was defined as an algorithmic assessment of the LOH score (loss of heterozygosity), TAI score (telomeric allelic imbalance) and LST score (long segment transitions). A high HRD score was defined as ≥ 42. tm*BRCA* mutation was defined as a deleterious mutation of *BRCA1* or *BRCA2* in the tumor and *BRCA* intact was defined as no detected mutation in the tumor. HR-deficiency was defined as either HRD score ≥ 42 or a *BRCA* mutation (Figure 2).

Statistical consideration

The significance level was set to a two-sided α=0.05. Fisher's exact test and logistic regression was used to assess the HRD as a predictor of pCR. Kaplan-Meier and Cox proportional hazard methods were used to analyze the EFS.

Results

Figure 1. Study design for the TNBC subgroup

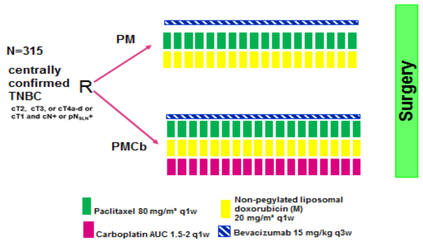


Figure 2. Overlap of HRD & *BRCA* mutations

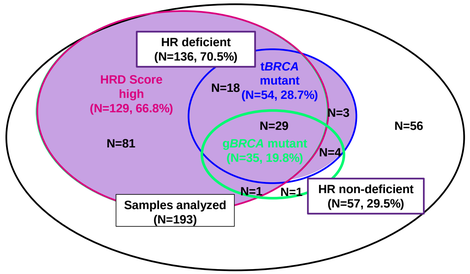
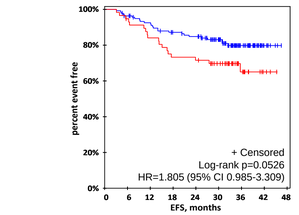


Table 1. Multivariate model for EFS

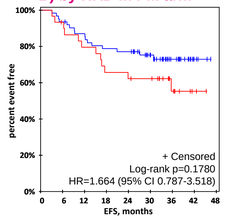
Predictor	Value	HR	95 % CI	p-value
HRD	yes vs. no	0.632	0.333-1.201	0.1662
Arm	PMCb vs. PM	0.478	0.253-0.905	**0.0202**
age	≥ 50 vs. <50	0.576	0.292-1.139	0.1052
cT	cT2-4 vs. cT1	2.507	0.880-7.144	0.0538
cN	N+ vs. N0	2.483	1.301-4.740	**0.0048**
Grading	G3 vs. G1-2	1.088	0.535-2.214	0.8151
Ki67	≥ 60% vs. <60%	1.208	0.578-2.523	0.6116
LPBC	yes vs. no	0.376	0.146-0.967	**0.0231**

Figure 3. EFS by HR-deficiency & according to treatment

A) by HRD status



B) by HRD in PM arm



C) by HRD in PMCb arm

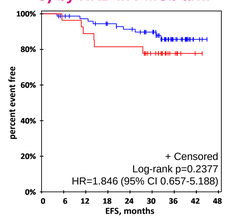
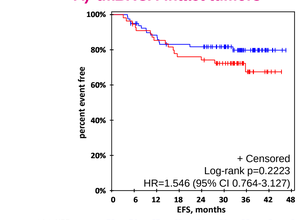
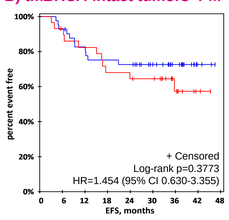


Figure 4. EFS by HRD score (high vs. low) in tm*BRCA* intact tumors & according to treatment

A) tm*BRCA* intact tumors



B) tm*BRCA* intact tumors+PM



C) tm*BRCA* intact tumors+PMCb

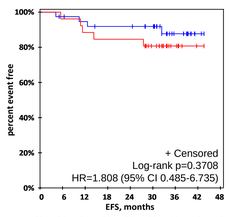
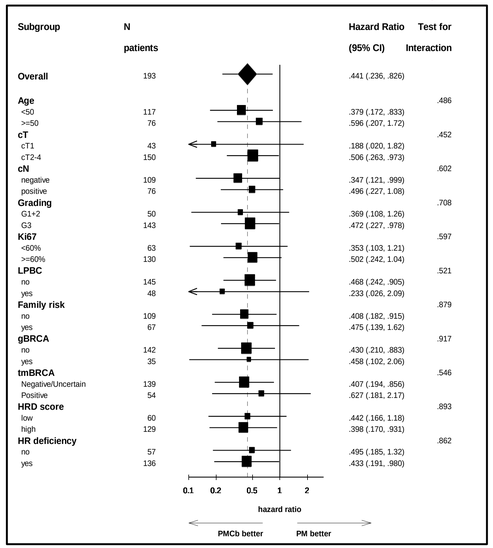


Figure 5. Univariate model for EFS overall & in subgroups



- After median follow-up of 34.3 months for EFS, 43 events have been reported.
- Overall, patients with HR-deficient tumors showed a better EFS than HR-non-deficient ones (p=0.0526, Figure 3).
- Patients with HRD high score and *BRCA* intact tumors had better but not statistically significant EFS rates as compared to HR-non-deficient patients (p=0.2223, Figure 4).
- HR-deficiency did not predict the effect of carboplatin on EFS (Figure 5).
- The multivariate analysis revealed that the therapy (p=0.0202), clinical nodal status before treatment (p=0.0048), and lymphocyte predominant breast cancer (LPBC; p=0.0231) but not HRD (p=0.1662) were independent significant prognostic factors for EFS (Table 1).

Conclusions

Within the GeparSixto study the HR-deficiency (either HRD score high or *BRCA* mutation) was in general associated with a higher pCR rate and an improved EFS. The effect on EFS of adding carboplatin could not be predicted by the HRD score in this underpowered study. However, the results can help to understand the role of HR-deficiency and the value of the HRD score in TNBC especially in patients without *BRCA* mutation. Nodal status and LPBC remained the strongest prognostic factors along with Carboplatin therapy.

References

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