Homologous recombination deficiency, RB-loss gene signatures, intrinsic subtype and response to neoadjuvant treatment in HR+/HER2- early breast cancer: a correlative analysis of two phase II trials

Gaia Griguolo[1,2], Federica Miglietta[1,2], Laia Paré[3], Daniele Giulio Generali[4], Antonio Frassoldati[5], Antonino Musolino[6], Simon Spazzapan[7], Grazia Maria Vernaci[2], Tommaso Giarratano[2], Marcello Lo Mele[8], Giancarlo Bisagni[9], Federico Piacentini[10], Enrico Tagliafico[10], Katia Cagossi[11], Francesca Schiavi[12], Claudia Pinato[12], Aleix Prat[3,12], Valentina Guarneri[1,2], Maria Vittoria Dieci[1,2]

1. Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, IT; 2. Oncology 2, Istituto Oncologico Veneto IRCCS, Padova, IT; 3. Reveal Genomics, Barcelona, ES; 4. UO Patologia Mammaria , ASST of Cremona, Cremona, IT; 5. Azienda Ospedaliero Universitaria di Ferrara-Arcispedale Sant'Anna, Ferrara, IT; 6. University of Parma, Parma, IT; 7. Centro di Riferimento Oncologico (CRO) IRCCS, Aviano, IT; 8. Azienda Ospedaliera Universitaria di Padova, Padova, IT; 9. IRCCS AUSL Reggio Emilia, IT; 10. University of Modena and Reggio Emilia, Modena, IT; 11. Ospedale Bernardino Ramazzini, Carpi, IT; 12. Istituto Oncologico Veneto IRCCS, Padova, IT; 12. IDIBAPS, Barcelona, ES.

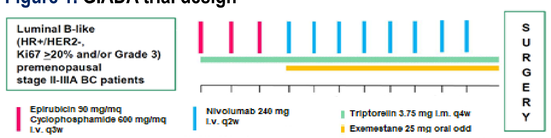
Background

- Hormone-receptor (HR)+/HER2- breast cancer (BC) is an heterogeneous disease.
- Homologous recombination deficiency (HRD) and BRCA mutations have been previously associated with worse outcomes in HR+/HER2- metastatic BC patients (pts) receiving CDK4/6 inhibitors and endocrine therapy[1-2].
- We assess the relation between HRD and RB-loss signatures, PAM50 subtyping and chemo-endocrine score, and response to treatment in HR+/HER2- early BC.

Patients and Methods

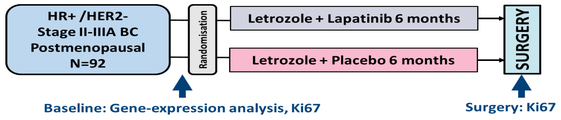
- The phase II GIADA trial treated premenopausal patients with Luminal B (LumB)-like BC with a combination of chemo, immuno and endocrine treatment[3] (**Fig.1**). Baseline expression of 758 genes was quantified from 43 pts using nCounter.

Figure 1. GIADA trial design



- The LETLOB phase II trial randomized postmenopausal women with HR+/HER2- BC to neoadjuvant letrozole +/- lapatinib[4] (**Fig.2**). Baseline gene-expression (Affymetrix) was available from 66 pts.

Figure 2. LETLOB trial design



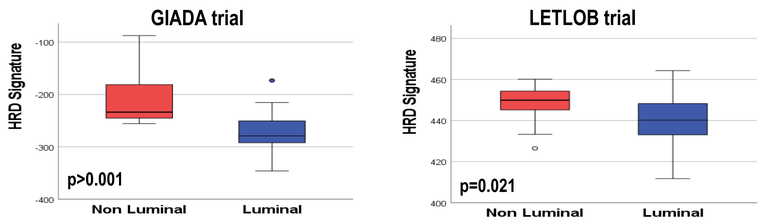
- Intrinsic subtype was assigned using the PAM50 subtype predictor[5].
- A published HRD signature[6] and a signature of RB loss (RBsig)[7], previously reported to potentially predict resistance to CDK4/6 inhibitors in HR+/HER2- BC were computed.
- The PAM50 based chemo-endocrine score (CES) was calculated[8]. High values of CES indicate increased endocrine sensitivity, while low values indicate chemosensitivity.
- Association of genomic signatures with pCR was assessed through logistic regression and association with PEPI scores was assessed through Kruskal-Wallis test.

Results

Association between HRD signature, PAM50 subtyping and other gene-signatures

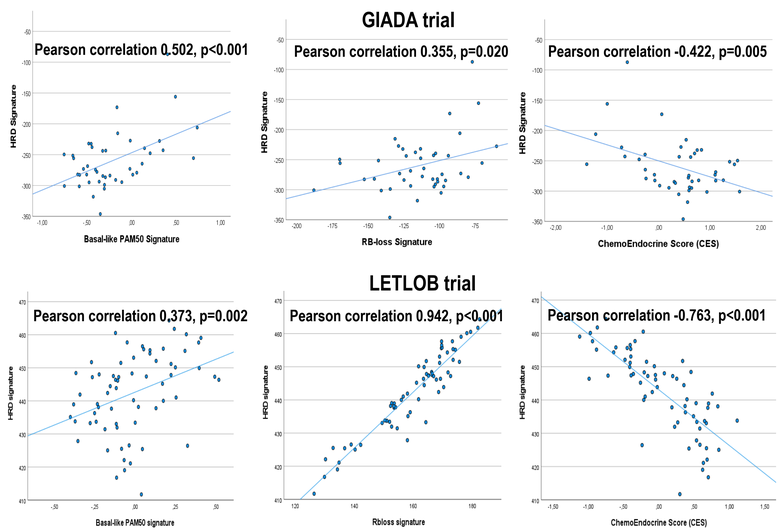
HRD signature levels were significantly higher in non-luminal HR+/HER2- BCs (Basal-like and HER2-enriched) as compared to Luminal (A or B) tumors (**Fig. 3**).

Figure 3. HRD signature levels according to intrinsic subtyping



Higher levels of HRD signature were associated with higher levels of PAM50 Basal-like and RB-loss signatures, and lower levels of CES, indicative of chemosensitivity (**Fig.4**).

Figure 4. Association between gene-expression signatures in the two trials

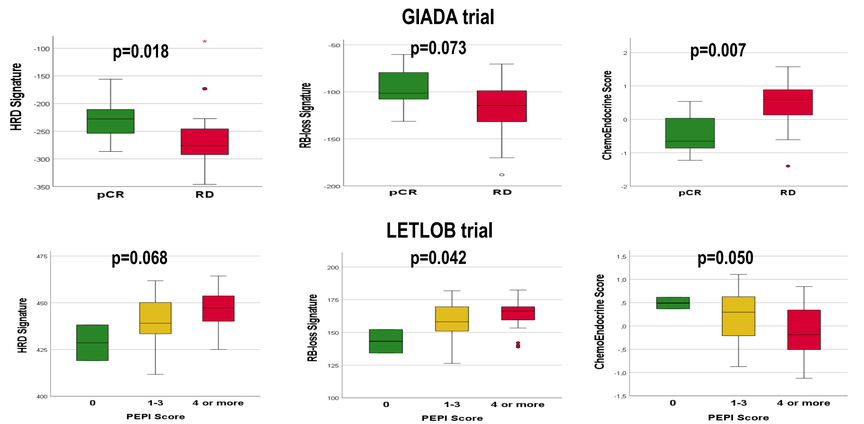


Association between gene signatures and response to neoadjuvant treatment

In the GIADA trial, higher levels of HRD signature and RBloss signature and lower levels of CES were associated with higher pCR rates after chemo, endocrine and immunotherapy.

In the LETLOB trial, lower levels of HRD signature and RBloss signature and higher levels of CES were associated with higher sensitivity to endocrine treatment (lower PEPI scores, 0 vs 1-3 vs 4 or more, after neoadjuvant letrozole) (**Fig. 5**).

Figure 5. Association between gene-expression signatures and response to treatment



Conclusions

- **In HR+/HER- early BC, HRD gene signatures, RB-loss gene signatures and non-luminal intrinsic subtyping are all associated with each other.**
- **These biological features are associated with higher sensitivity to chemotherapy-based therapy and lower sensitivity to endocrine treatment.**
- **These observations might help correctly tailor systemic therapy, including biologic agents, in patients with HR+/HER2- early and advanced BC.**

References

1. Park et al ASCO 2021
2. Marra A et al, ESMO 2022
3. Dieci MV et al, CCR 2022
4. Guarneri V et al, JCO 2014
5. Parker J et a. JCO 2009
6. Peng et al, Nat Commun 2014
7. Malorni, Oncotarget 2016
8. Prat A et al, CCR 2017