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Abstract:

HER2-low expression is associated with hormone receptor expression in luminal breast cancer. We aimed to evaluate its association with androgen receptor (AR) among 196 patients with metastatic triple-negative breast cancer (mTNBC). Central determination of AR showed significant enrichment in HER2-low compared with HER2-0 mTNBC (mean: 33.7% vs. 21.4%, p=0.038), whereas no significant immunological differences were observed. HER2-low/AR-positive patients trended towards longer overall survival, highlighting the potential relevance of these biomarkers.

Main Text

Breast cancer is a heterogenous disease, commonly classified into distinct subtypes based on tumor biology and clinical outcomes. HER2-low expression (immunohistochemistry [IHC] 1+ or 2+/ without amplification by in situ hybridization) is observed in up to 55% of all breast cancers[1] and has emerged as a key biomarker in breast oncology, based on the results of the DESTINY-Breast04 trial and the subsequent approval of trastuzumab deruxtecan for HER2-low metastatic breast cancer.[2] While HER2-low expression is currently utilized to guide treatment choices in clinical practice, its biological correlates remain to be further characterized, particularly within the context of metastatic triple-negative breast cancer (TNBC), a disease that was underrepresented in DESTINY-Breast04.

Initial studies suggested that HER2-low TNBC may have slight biological differences when compared with HER2-0 (IHC 0) TNBC. Molecularly, HER2-low tumors are enriched in luminal genes and enriched in the molecular apocrine phenotype, characterized by androgen receptor (AR) and FOXA1 co-expression.[3,4] AR and HER2 are known to have positive synergistic interactions.[5] FOXA1, a transcription factor co-expressed with AR, is posited to be a determinant of chemoresistance in HER2-low disease.[6] Clinically, the luminal AR subtype within TNBC is associated with postmenopausal status and less aggressive features, including lower tumor grade, lower Ki-67 proliferation index, and longer disease-free survival compared with other TNBC subtypes.[3,7] Taken together, these features of HER2-low TNBC including luminal-gene expression, chemoresistance, and less aggressive disease may hint at a shared biology underlying HER2-low and luminal subtypes, with AR as a potential molecular driver.

Despite these advancements, there is no clear consensus on the prognostic distinction of HER2-low breast cancer within TNBC.[8] One study of over 1 million patients with HER2-

negative breast cancer found only marginal differences in survival between HER2-low and HER2-0 tumors at every tumor stage.[9] A prior cohort study by our group showed no prognostic significance for HER2-low expression.[10] Still, other retrospective analyses have suggested that TNBCs exhibiting HER2-low expression may have a slightly better prognosis compared with HER2-0 TNBC.[9,11]

Of note, in a cohort of 5,235 patients, we had previously reported a positive association between HER2-low expression and estrogen receptor (ER) expression, with increasing probability of identifying HER2-low expression with increasing thresholds of ER expression.[10] We hypothesized that a similar association may exist between HER2-low and AR expression in TNBC, and that this association may be the underlying confounder of mixed results in prognostic analyses.

Herein, we leveraged tissue samples and clinical data from patients who underwent pre-screening for an investigator-initiated prospective clinical trial testing abemaciclib in patients with Rb-positive metastatic TNBC (mTNBC) (NCT03130439),[12] exploring differences in AR expression, immunological variables, and survival between HER2-low and HER2-0 mTNBC.

We analyzed samples and clinicopathologic data from 196 patients with mTNBC, including 69 (35.2%) with HER2-low and 127 (64.8%) with HER2-0 disease. Centralized IHC staining was performed at Brigham and Women's Hospital for AR and PD-L1, and centralized quantification of tumor infiltrating lymphocytes (TILs) was conducted by histopathology according to the International TILs Working Group guidelines.[13]

We first sought to clarify whether HER2-low expression would be associated with distinct outcomes in our cohort. With a median follow up of 4.08 years (IQR 2.35, 6.43), we did not observe significant differences in overall survival (OS) between HER2-low and HER2-0

mTNBC, with a median OS of 1.69 years (95% confidence interval [CI] 1.43, 2.86) and 1.88 years (1.48, 2.36), respectively (p=0.91, **Figure 1A**).

Next, we compared AR expression (in terms of AR-positive cells) in HER2-low and HER2-0 mTNBC. We found the mean AR percentage expression to be 33.7% (standard deviation [SD] 41.1%) in HER2-low disease and 21.4% (SD 34.5%) in HER2-0 disease (**Table 1, Figure 1B-C**), distributions which were found to be significantly different (p=0.038).

We then stratified our sample to compare OS by four subgroups within our mTNBC population: HER2-low/AR-positive, HER2-low/AR-negative, HER2-0/AR-positive, and HER2-0/AR-negative (**Figure 1D**). We observed a trend towards numerically longer OS among patients with HER2-low/AR-positive mTNBC, with a median OS of 2.59 years (95% CI 1.51, 3.99), whereas progressively shorter median OS was observed in patients with AR-positive/HER2-0 disease (2.36 years), AR-negative/HER2-low disease (1.53 years) and AR-negative/HER2-0 disease (1.34 years). These differences were however not statistically significant (p=0.50).

To explore the immunologic profiles underlying the HER2-low subtype in mTNBC, we next compared the expression of PD-L1 and TILs in HER2-low and HER2-0 disease. No significant differences in immunological biomarkers were observed between HER2-low and HER2-0 mTNBC (**Table 2**). The median level of stromal TILs was 5% in both categories. The mean level of stromal TILs was 13.0% (SD 19.0%) in HER2-low tumors and 11.2% (SD 16.5%) in HER2-0 tumors, and the percentage of tumors that were PD-L1 positive (combined positive score [CPS] ≥ 10) were 13.2% for HER2-low and 14.4% for HER2-0 mTNBC (p=1.00). Consistent with this finding, Kaplan-Meier curves also reflected no statistical nor relevant numerical difference in OS for subgroups by PD-L1 and TIL status by HER2-low and HER2-0 (**Figure 1E, 1F**).

Lastly, we evaluated the association of Rb expression with other biomarkers tested in the study (**Supplementary Table 1**). Median Rb expression was found to be significantly higher in HER2-low tumors compared with HER2-0 tumors (median 80 vs. 70; p = 0.032) and was positively correlated with continuous TILs (p = 0.029). No significant associations were identified between Rb expression and the remaining biomarkers evaluated.

In the present correlative study from an investigator-initiated clinical trial, we report an enrichment in AR expression in HER2-low versus HER2-0 mTNBC, with a numerical trend in better prognosis observed among patients having both HER2-low and AR positivity. Between the two biomarkers, AR appeared to be the one associated with the greatest numerical increase in survival.

Our observations add to a growing literature suggesting an association between HER2-low expression and AR expression in breast cancer[4,5,7,14,15], with some studies also linking HER2-low expression to a better prognosis.[16] These results suggest that AR may be a potential driver of the small prognostic differences observed between HER2-low and HER2-0 mTNBC observed in some retrospective studies.[9,11] However, such associations remain controversial, and are not currently utilized for decision making in the clinical setting.

Importantly, anti-androgen therapy has been a target of interest in breast cancer studies for at least a decade.[17] The first clinical trial on anti-androgen therapy for breast cancer was published in 2013, using the AR antagonist bicalutamide.[18] More recently, enzalutamide was found to achieve a clinical benefit rate of 33% and median progression-free survival of 3.3 months among pretreated patients with AR-positive mTNBC, providing the rationale for the design of an ongoing study testing enzalutamide with or without mifepristone compared with physician's choice of chemotherapy for treating AR-positive mTNBC (TBCRC 058 -

NCT06099769).[19,20] Subgroup analyses of the effects of AR antagonists by HER2-low status, as presented in our study, may further elucidate AR and HER2-low as synergistic prognostic markers.

We did not identify differences in PD-L1 expression or TILs in HER2-low compared with HER2-0 mTNBC. This is aligned with a recent report by Baez-Navarro and colleagues, who also found no association between HER2-low status and TILs expression.[21] This suggests that the immune microenvironment may not be significantly influenced by low levels of HER2 expression in mTNBC (as detected by IHC), supporting that HER2-low status alone may not necessitate different immunotherapeutic approaches for mTNBC. Another possibility is that IHC testing for HER2 is not sensitive enough to distinguish immunologically relevant subsets within TNBC, warranting for testing of more sensitive, quantitative HER2 assays.

Limitations of our study include the relatively small sample size, which may have led to little power to detect statistical differences in prognosis depending on the biomarker status. Moreover, the heterogeneity in tissue collection sites and subjectivity of IHC and TILs assessment may have also limited the identification of significant differences in certain biomarkers. Nonetheless, we attempted to limit this through a centralized assessment of AR and immunologic variables conducted by experienced pathologists at Brigham and Women's Hospital, which is expected to provide greater consistency. Lastly, since this cohort was collected within a pre-screening for a clinical trial, detailed demographic information on the study population was not available, limiting the interpretation of our findings.

In summary**,** we confirm our hypothesis that HER2-low mTNBC exhibits significantly higher AR expression compared with HER2-0 disease. While OS did not differ statistically, patients with HER2-low/AR-positive disease demonstrated the numerically longest OS,

suggesting a potential prognostic role of AR in this subtype, to be further elucidated in larger studies. No immunological differences by PD-L1 or TILs levels were observed. Our findings support investigating AR-targeting therapies, such as protein degraders or anti-androgens, to be combined with HER2-targeted antibody-drug conjugates to improve outcomes in HER2-low, AR-positive mTNBC. Larger studies are warranted to further characterize HER2-low mTNBC, with particular attention to AR status as a potential prognostic and therapeutic subgroup.

Methods

Study sample

This study utilized tumor samples and clinical data from the pre-screening phase of 17-024, a phase II trial evaluating abemaciclib in retinoblastoma-positive (Rb-positive) mTNBC (NCT03130439).[12] Patients were required to undergo IHC staining for Rb (clone clone G3-245–RRID: AB_395259, BD Bio, catalog No. 554136), with enrollment restricted to those whose invasive tumors stained ≥50% positive for Rb.

Although patients with Rb-negative disease were excluded from the trial intervention, their tumor samples were retained and the consent forms included permission for further research analyses. In total, 196 patients with mTNBC (regardless of Rb status) completed pre-screening and were included in this present study, with available tissue and OS data. Tumor samples were collected from heterogenous locations (i.e., primary tumors or metastatic biopsies were both eligible for the study). All research was performed in accordance with the Declaration of Helsinki. Institutional review board approval for the conduction of this study was obtained from the Dana-Farber/Harvard Cancer Center and from the Duke Cancer Institute. Written informed consent was obtained from all participants.

Biomarker assessment

Centralized IHC staining was performed for AR (clone clone AR441, Dako, catalog No. M3562–RRID: AB_2060174), and PD-L1 (clone 405.9A11, Cell Signaling Technology, catalog No. 29122–RRID: AB_2798970) by experienced pathologists at Brigham and Women's Hospital. Central quantification of TILs was performed by histopathologic hematoxylin and eosin-stained tissue slides according to the International TILs Working Group guidelines.[13] HER2 statuses were retrieved from pathology reports. Within the TNBC population, HER2 expression was categorized as HER2-low if IHC 1+ or 2+/not-amplified, or HER2-0 if IHC 0. AR expression was assessed both continuously and in discrete categories: negative (0%), intermediate (1-50%), and high (>50%). PD-L1 expression was defined by CPS as is standard, with a threshold of CPS ≥ 10 indicating PD-L1 positivity. TILs were measured both continuously and in discrete categories: absent (0%), intermediate (1-5%), high (>5%) and very high (>30%), with TIL positivity defined by ≥1%. <1% TILs were considered as absent.

Statistical analysis

The primary aim was to evaluate the association between HER2 and AR expression in mTNBC. Secondary analyses explored the relationship between HER2-low status, PD-L1 expression, TIL levels, and OS.

OS was defined as time from metastatic diagnosis to death due to any cause, or censored at date last known alive. OS was analyzed in the full cohort (n = 196) and compared between HER2-low and HER2-0 subgroups. Median OS with 95% CIs was estimated via the Kaplan-Meier method for each group. Log-rank tests were used to assess differences.

Expression levels of AR and PD-L1 were evaluated as both continuous and categorical variables. Association between the biomarkers and HER2 status was compared using Wilcoxon rank-sum test (continuous biomarker) and Chi-square test (categorical biomarker). Box plots and histograms were generated to visualize AR expression by HER2 status.

OS was further stratified by HER2 status and biomarker positivity (AR or PD-L1), with median OS (95% CIs) reported for each subgroup using the Kaplan-Meier estimation method. All analyses were conducted using R version 4.4.1, with two-sided p-values < 0.05 considered statistically significant.

Data availability

Data can be requested from the corresponding authors for academic use, subject to approval of a research plan, a data transfer agreement and ethics committee approval.

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Supervision: PT, SMT, NT

Validation: PT, SMT, NT

Visualization: PT, JC, XC, NT

Writing – original draft: PT, JC

Writing – review & editing: P.T., J.C., B.B.K., X.C., B.J., A.Z., M.H., D.R., M.D., E.W., R.J., N.U.L., J.C., Y.S.C., T.L., N.T., E.M., S.J.S., S.G., S.M.T.

Competing interests

PT reports consulting fees from AstraZeneca, Daiichi-Sankyo, Gilead, Genentech/Roche, Novartis, Menarini/Steamline and Eli Lilly. **NUL** reports institutional research support from Genentech, Pfizer, Merck, Seattle Genetics, Zion Pharmaceuticals, Olema Pharmaceuticals, and AstraZeneca; consulting honoraria from Seattle Genetics, Daiichi-Sankyo, AstraZeneca, Olema Pharmaceuticals, Stemline/Menarini, Artera Inc., Eisai, and Shorla Oncology; royalties from Up to date (book); and travel support from Olema Pharmaceuticals, AstraZeneca, and Daiichi Sankyo. **SMT** reports consulting or advisory roles for Novartis, Pfizer/SeaGen, Merck, Eli Lilly, AstraZeneca, Genentech/Roche, Eisai, Bristol Myers Squibb/Systimmune, Daiichi Sankyo, Gilead, Blueprint Medicines, Reveal Genomics, Sumitovant Biopharma, Artios Pharma, Menarini/Stemline, Aadi Bio, Bayer, Jazz Pharmaceuticals, Natera, Tango Therapeutics, eFFECTOR, Hengrui USA, Cullinan Oncology, Circle Pharma, Arvinas, BioNTech, Johnson&Johnson/Ambrx, Launch Therapeutics, Zuellig Pharma, Bicycle Therapeutics, BeiGene Therapeutics, Mersana, Summit Therapeutics, Avenzo Therapeutics, Aktis Oncology, Celcuity, Boehringer Ingelheim, Samsung Bioepis, Olema Pharmaceuticals, Tempus, and Boundless Bio; research funding from Genentech/Roche, Merck, Exelixis, Pfizer, Lilly, Novartis, Bristol Myers Squibb, AstraZeneca, Gilead, NanoString Technologies, Seattle Genetics, OncoPep, Daiichi Sankyo, Menarini/Stemline, Jazz Pharmaceuticals, and Olema Pharmaceuticals; and travel support from Eli Lilly, Gilead, Jazz Pharmaceuticals, Pfizer, Arvinas, and Roche.

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Figure Legend

Figure 1. Survival outcomes for patients with mTNBC according to AR expression, HER2 expression and level of TILs. 1A. Kaplan-Meier curve for overall survival in HER2-low and HER2-0 mTNBC, N=196. **1B.** Box plot of androgen receptor expression in HER2-low and HER2-0 mTNBC, N=175 (21 patients excluded due to unknown AR information). **1C.** Histogram of androgen receptor expression in HER2-low and HER2-0 mTNBC, N=175 (21 patients excluded due to unknown AR information). **1D.** Kaplan-Meier curve for overall survival in four subgroups: HER2-low AR-positive mTNBC, HER2-low AR-negative mTNBC, HER2-0 AR positive mTNBC, HER2-0 AR negative mTNBC. N=175 (21 patients excluded due to unknown AR information). **1E.** Kaplan-Meier curve for overall survival in four subgroups: PD-L1 positive HER2-low mTNBC, PD-L1 positive HER2-0 mTNBC, PD-L1 negative HER2-low mTNBC, PD-L1 negative HER2-0 mTNBC. N=150 (46 patients excluded due to unknown PD-L1 status). **1F.** Kaplan-Meier curve for overall survival in four subgroups: TILs positive HER2-low mTNBC, TILs positive HER2-0 mTNBC, TILs negative HER2-low mTNBC, TILs negative HER2-0 mTNBC. N=172 (24 patients excluded due to unknown TIL status). TIL positivity defined as ≥ 1%. TILs=tumor infiltrating lymphocytes, mTNBC=metastatic triple negative breast cancer, AR=androgen receptor,

Table 1. Expression of androgen receptor (AR) in HER2-low mTNBC vs. HER2-0 mTNBC. mTNBC=metastatic triple-negative breast cancer, SD=standard deviation.

	HER2-low (%) N= 62	**HER2-0** (%) N=113	P-value*
AR Median (range)	5 (0, 95)	0 (0, 95)	**0.038**
AR Mean (SD)	33.7 (41.1)	21.4 (34.5)	
AR (Categorical)			0.16
Negative (0%)	27 (43.5)	63 (55.8)	
Intermediate (1-50%)	14 (22.6)	26 (23.0)	
High (more than 50%)	21(33.9)	24 (21.2)	

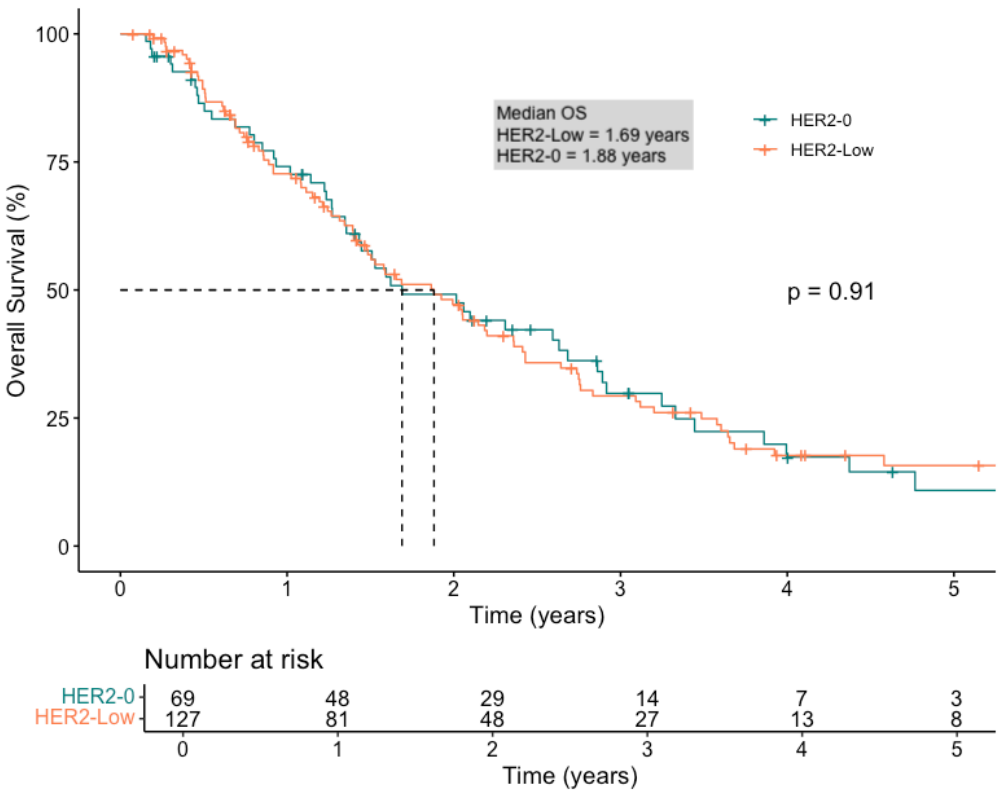
*Wilcox p-value was reported for the continuous variable. Chi-square p-value was reported for the categorical variable. Patients with unknown AR (n=21) are excluded from the comparison.

Table 2. Expression of PD-L1 and TILs in HER2-low mTNBC vs. HER2-0 mTNBC. Patients with unknown AR are not included in the comparison. TILs=tumor infiltrating lymphocyte, mTNBC=metastatic triple negative breast cancer, AR=androgen receptor, CPS=combined positive score.

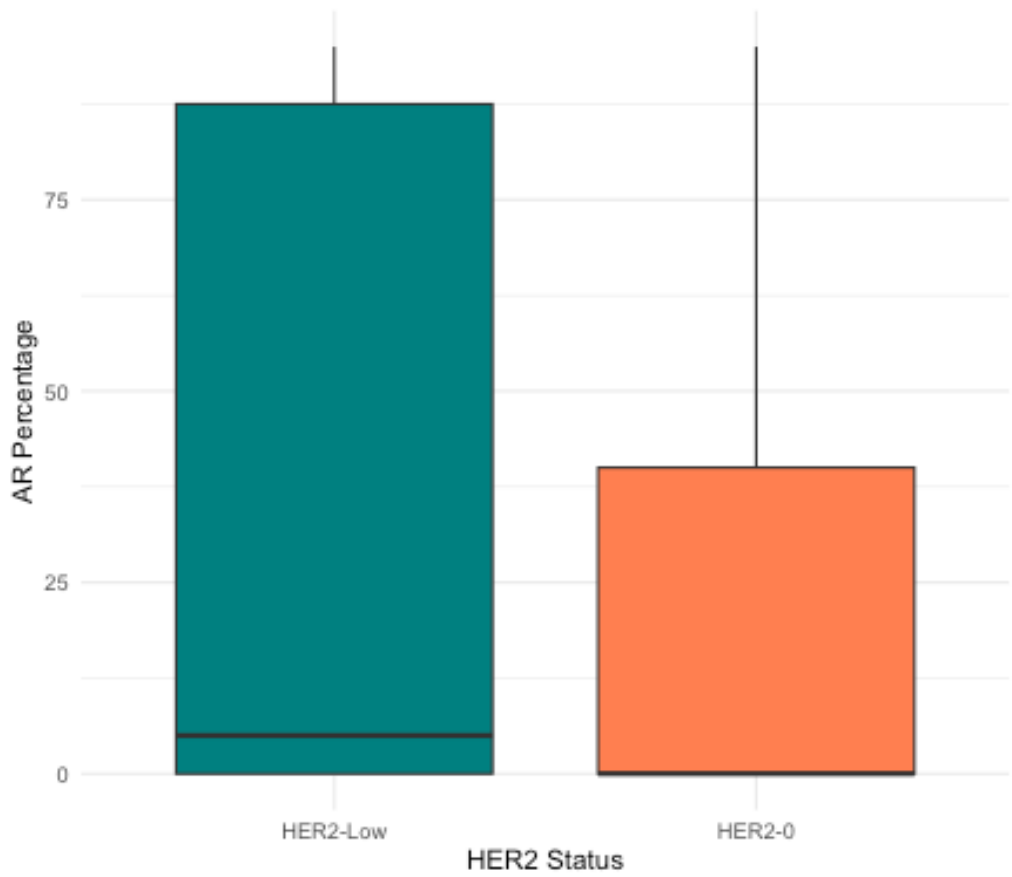
	HER2-low (%) N=69	**HER2-0** (%) N=127	P-value*
PD-L1			1.00
CPS < 10	46 (86.8)	83 (85.6)	
CPS ≥ 10	7 (13.2)	14 (14.4)	
Unknown	16	30	
Stromal TIL Median (range)	5 (0, 90)	5 (0, 70)	0.55
Stromal TIL Mean (SD)	13.0 (19.0)	11.2 (16.5)	
Stromal TIL (30% cut off)			0.85
Absent (0%)	10 (16.1)	21 (19.1)	
Intermediate (1-30%)	44 (71.0)	77 (70.0)	
High (more than 30%)	8 (12.9)	12 (10.9)	
Unknown	7	17	
Stromal TIL (5% cut off)			0.87
Absent (0%)	10 (16.1)	21 (19.1)	
Intermediate (1-5%)	28 (45.2)	50 (45.5)	
High (more than 5%)	24 (38.7)	39 (35.5)	
Unknown	7	17	

*Wilcox p-value reported for the continuous variables. Chi-square p-value reported for the categorical variables.

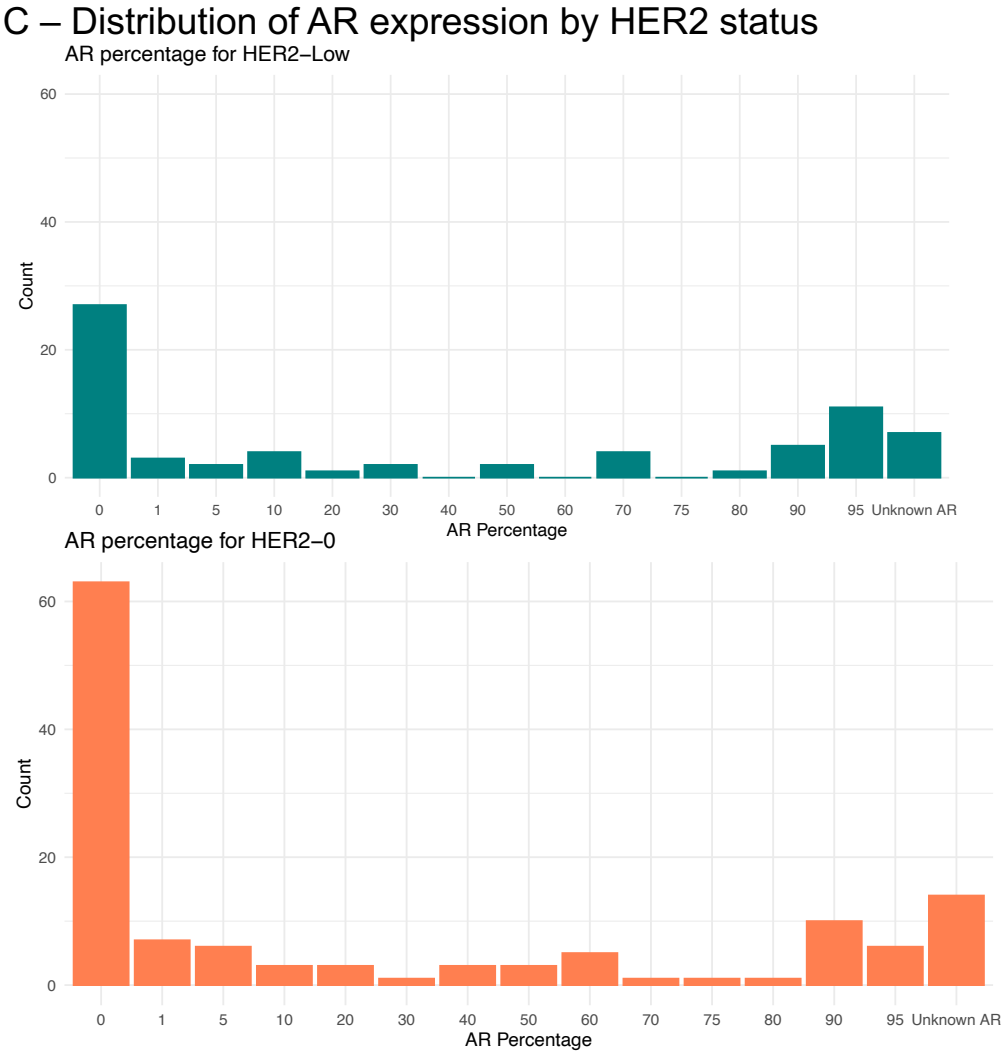
A – OS in HER2-low vs. HER2-0 TNBC



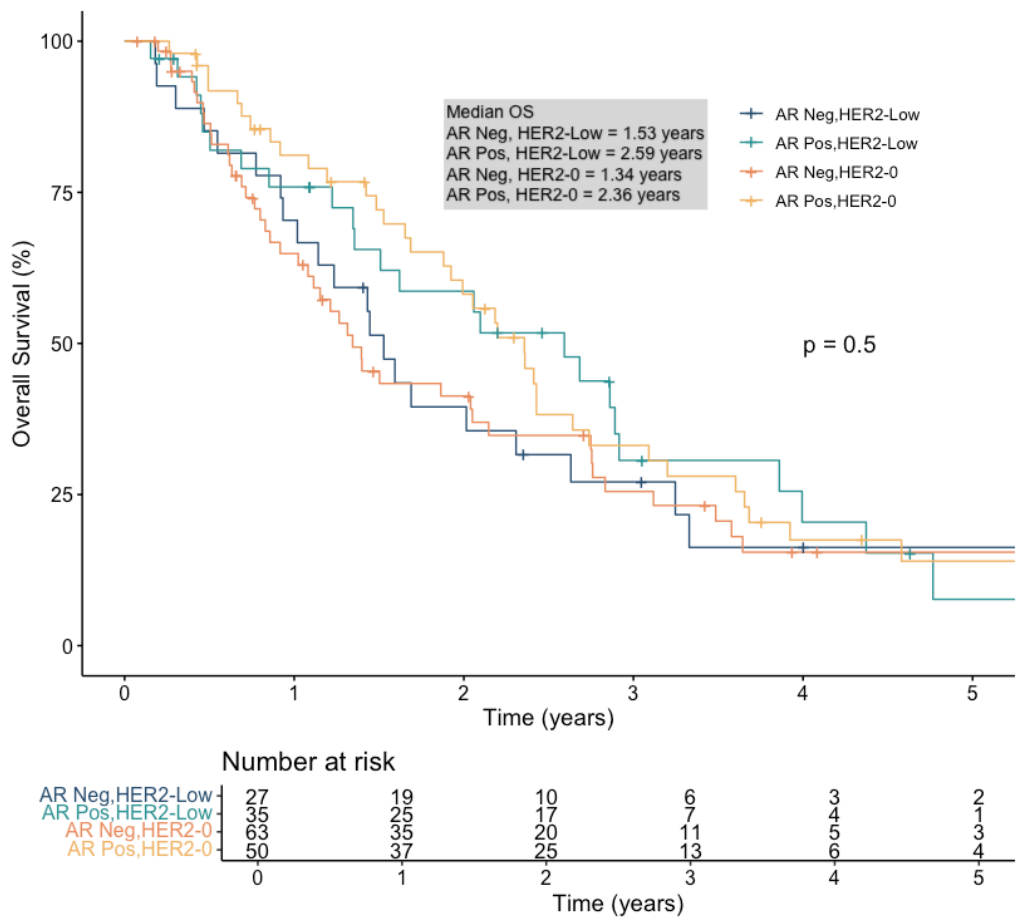
B – Box plot of AR percentage by HER2 status



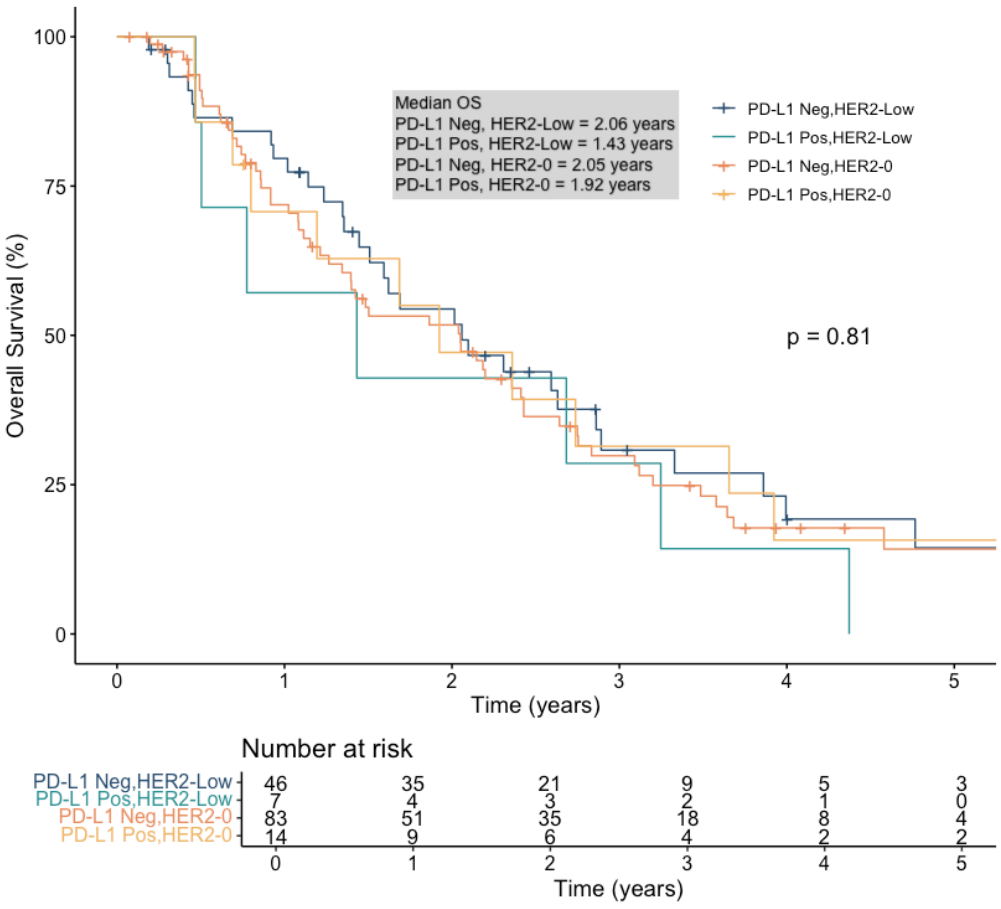
C – Distribution of AR expression by HER2 status



D – OS by AR status and HER2 status



E - OS by PD-L1 and HER2 status



F – OS by TILs and HER2 status