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Research Article

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Androgen Receptor as a Prognostic and Predictive Factor for Response to Trastuzumab Among Female Patients with Invasive HER2-Positive Breast Cancer

Manar Montasser Mohamed[1]*; Marwa A Suliman[2]; Ahmed Mostafa Elzawawy[2]; Wael Abdou Hassan[3]; Soheir Elsayed Abd Elmohsen[2]; Muhammad Solaiman Muhammad[2]

[1]Department of Oncology, Suez Canal Authority Hospitals, Ismailia, Egypt.

[2]Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Suez Canal University, Ismailia, Egypt.

[3]Department of Pathology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt.

Abstract

Introduction: Breast cancers overexpressing Human Epidermal growth factor Receptor-2 (HER2) have relatively poor outcome. Androgen receptor in breast cancer was studied and showed different prognostic data among the different molecular breast cancer subtypes.

Methods: Retrospective-prospective cohort (historical cohort) study of 24 files of female patients with Hormone Receptor (HR)- negative/ Human Epidermal growth factor Receptor positive (HER +ve) invasive breast cancer patients; classified/stratified and tested for Androgen Receptor score of expression, considering Time to Tumor Progression (TTP) as primary end point, and Overall Survival (OS) as second end points.

Results: With a mean follow-up period of 66 months (about 5.5 years), AR (score 5) had the best prognosis in luminal A (50% had TTP to the 7th year and 50% had OS to the 9th year).

Conclusion: AR (score 5 and 7) had the best TTP and AR (score 5) had the best OS in HER2- positive invasive breast cancer female patients. Androgen receptor positivity degree has a great impact on response to Trastuzumab among HER2+ patients.

Keywords: Overall Survival (OS); Time to Tumor Progression (TTP); Androgen Receptor (AR).

Introduction and Rationale

Tumors overexpressing HER2 have a less favorable outcome especially when AR is also co-expressed, suggesting a unique mechanism of tumor survival than that observed in ER positive tumors. Research suggests that AR may play into a positive feedback loop of HER2 activation, promoting tumor survival [1].

Androgen Receptor (AR) influences the growth of HER2+ ER– BC cells in non-genomic way; since in these cells, inhibition of AR by Enzalutamide decreases the HER2 phosphorylation without affecting the total level of HER2 or HER3, and treatment of cells with a combination of enzalutamide and trastuzumab, an approved HER2 target drug, potentiates the inhibitory effect on cell growth due to a single inhibiting drug [2].

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Correspondance: *Manar Montasser Mohamed, Department of Oncology, Suez Canal Authority Hospitals, Ismailia, Egypt.*

Email: manarmontasser@med.suez.edu.eg

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This study was done to evaluate the expression of Androgen receptor and to correlate its degree of expression with the different clinicopathological features for Hormone Receptor – negative/ HER2-positive breast cancer patients; to be able to bring new option of treatment and new hope and of course; for better lifestyle for breast cancer patients attending Clinical Oncology and Nuclear Medicine department at Suez Canal University Hospital.

Subjects & methods

It was a Retrospective-Prospective Cohort Study (to study the correlation between score/degree of androgen receptor expression and the clinicopathological features and prognosis for simple random sample from all triple negative invasive breast cancer patient attending clinical oncology and nuclear medicine department in Suez Canal university hospital in period from January 2015 until December 2019.

Patients with unknown hormonal receptors status and patients who refuse to participate in the study were excluded. When diagnosed as breast cancer patient, the patient is referred to our clinical oncology and nuclear medicine department to start the plan of management. Routinely, the paraffin block is requested to test for hormonal receptors namely: Estrogens-Receptor, Progesterone-Receptor and HER-2neu. Then, the patient will be asked whether to accept or to refuse testing for the Androgen Receptor using his/her same initial paraffin block without any new tissue biopsy. Result of the Androgen receptor expression was correlated to the patient clinicopathological data already present in the patient archive file records in the department. Data was collected and coded then entered as a spread sheets using SPSS. Patients were categorized into groups having the same clinicopathological features and treatment received; in order to avoid confounding.

Data was analyzed using SPSS. Data are presented as tables and graphs; t test was used to compare between quantitative data expressed as mean and standard deviation. P value <0.05 was considered as significant. Kaplan Meier curves were used to estimate survival.

Concerning ethical considerations, Data was collected from archive files in Suez Canal University Hospital Clinical Oncology Department (SCUCOD). Approval of the staff responsible in the SCUCOD and approval of the Ethics committee in the Faculty of Medicine- Suez Canal University were obtained before starting field work. Confidentiality was maintained. The patient had the right to accept or to refuse participating in the study. The study had no harm on the patient; and no invasive maneuver. The patient had the right to cancel his participation in the study at any time and without giving any excuse.

Results

A mean of 162 patients per year attended clinical oncology department in Suez Canal University hospital, in the period between January 2015 and December 2017. Hence, the sample size was calculated to provide 95% confidence interval and to ensure reliability of Data. 107 female patients with breast cancer were tested for androgen receptor on their paraffin block.

Regarding molecular classification; 24 patients were HER2Neu positive Hormonal Receptor (HR) negative, 43 patients were HR positive, HER2Neu negative; 39 had ER, PR +VE/ HER2Neu -ve; and 4 had ER +ve, PR and HER2Neu -ve. 30 patients were triple negative, while only 10 patients had triple positive breast cancer. Here, we study only HER2Neu patients.

24 patients' files were included and studied. 24 paraffin blocks – corresponding to each of the 24 patients/files were tested for androgen receptor expression via immunohistochemistry. Sections from the selected paraffin blocks were cut into 4 micrometers thick sections for Immunohistochemical (IHC) staining. Slides were prepared and incubated with primary anti-AR antibody (Lot and Company). This was followed by incubations with the propriate secondary antibody (Lot and Company). All slides are lightly counterstained with hematoxylin for 30s prior to dehydration and mounting.

Immunohistochemical scoring Invasive tumor cells with nuclear reaction to AR antibody were considered positive. Semiquantitative analysis of stained tissue sections was performed through modified Allred scoring system guidelines**. Positive cells were counted in 3 different high-power fields (hpf) (400x) (Figure 1) and the average number was calculated. Individual scores of the percentage of positive cells (0-5) and the staining intensity of the cytoplasm (0-3) were summed up to obtain the final grades. The percentage of positive cells was set as follows: 1- less than 10 positive cells; 2- from 10 to 20 of positive cells; 3- from 20 to 50 positive cells; 4-from 50 to 70 positive cells; and score 5-more than 70 positive cells. The staining intensity of positivity in the cytoplasm was scored as: 1-weak; 2-moderate; and 3-strong.

Final score was calculated by the sum of number of positive cells in HPF and the intensity of staining of the cytoplasm. Final score of Zero is considered negative. Final score of 3 in addition to Zero is considered low

Androgen receptor expression with Hematoxylin and Eosin staining Androgen receptor degree of expression was estimated by the number of positive cells per high power field plus the intensity of its staining; both yielding a final score (Figure 1).

Final score of androgen receptor expression in our study ranged from 0 then 3 to 8. Score was defined as follows:

1. → Negative/ No androgen receptor expression
2. → Low positive expression
3. → Low to intermediate expression
4. → Intermediate expression
5. → Intermediate to high expression
6. → High expression
7. → Highest / Very high expression

Patients' characteristics including demographic, different clinic-pathological data are summarized in the table below (Table 1).

Table 1: HER2Neu positive patients' characteristics.

Comparison 4 HER2Neu	Number	Percentage
Age at diagnosis	24	100%
– Younger than 35	4	16.7%
– 36-50 years	9	37.5%
– Older than 50 years	11	45.8%
Menopausal status at diagnosis	24	100%
– Premenopausal	13	54.2%
– Postmenopausal	11	45.8%
Body Mass Index at diagnosis	24	100%
– Obese	9	37.5%
– Overweight	15	62.5%
Co-morbidities	24	100%
– No history of any chronic illness	16	66.7%
– Hypertension	4	16.7%
– Hypertension and diabetes mellitus	4	16.7%
Presenting symptom	24	100%
– Breast lump	24	100%
Side	24	100%
– Right breast	15	62.5%
– Left breast	9	37.5%
Operation	24	100%
– Modified Radical Mastectomy	17	70.8%
– Conservative breast surgery	7	29.2%
Histopathological Subtype	24	100%
– Invasive ductal carcinoma	22	91.7%
– Medullary carcinoma	2	8.3%
Grading	24	100%
– Grade 2	22	91.7%
– Grade 3	2	8.3%
Tumor Size	24	100%
– T1	5	20.8%
– T2	13	54.2%
– T3	6	25%
Nodal Status	24	100%
– N0	6	25%
– N1	6	25%
– N2	3	12.5%
– N3	9	37.5%
Distant Metastasis	24	100%
– M0	24	100%
Extranidal Extension	24	100%
– No	11	45.8%
– Positive	13	54.2%
Surgical margins	24	100%
– Free	24	100%
Multicentricity	24	100%
– No multicentricity	24	100%
Multifocality	24	100%
– No multifocality	24	100%
Early versus advanced	24	100%
– Early	11	45.8%
– Locally advanced	4	16.7%
– Respectable advanced	9	37.5%
Neoadjuvant chemotherapy if any	24	100%
– No	17	70.8%
– Yes	7	29.2%
Regimen of neoadjuvant chemotherapy if any	24	100%
– None received	18	75%
– 3 CMF	2	8.3%
– 3 FEC then 3 Vinorelbine/ Cisplatin	2	8.3%
– 2 Docetaxel/ Gemcitabine then 2 Vinorelbine/ Cisplatin	2	8.3%
Adjuvant Chemotherapy	24	100%
– 6 FEC	2	8.3%
– 4 AC then 12 Paclitaxel weekly	2	8.3%
– 4 AC then 4 Paclitaxel/ Trastuzumab every 3 weeks and Trastuzumab continued for 1 year	18	75%
– 4 FEC then 4 Paclitaxel/ Carboplatin	2	8.3%
Post-operative Radiotherapy	24	100%
– 50Gy/25#	24	100%
Maintenance Capecitabine	24	100%
– No	22	91.7%
– Capecitabine alone	2	8.3%
Androgen Receptor Expression Final Score	24	100%
– 4	2	8.3%
– 5	9	37.5%
– 6	4	16.7%
– 7	2	8.3%
– 8	7	29.2%

Regarding time to tumor progression.

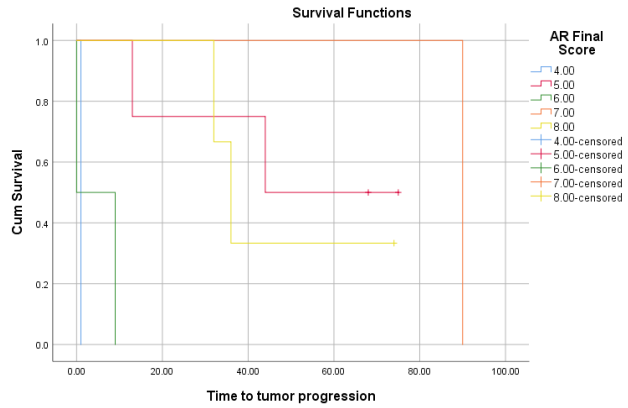

Figure 1: Time to tumor progression in all HER2 positive patients generally.

This Kaplan-Meier curve (Figure 1) shows time to tumor progression when comparing the levels of androgen receptor expression in HER2 positive patients generally; as follows:

- Score 7: 100% of patients survived for → 90 months
- Score 8: 100% → 32 months… 34% → 75 months
- Score 5: 100% → 13 months… 75% → 45 months… 50% → 78 months
- Score 6: 50% → 10 months.
- (With overall maximal standard error: 0.354)

With body mass index

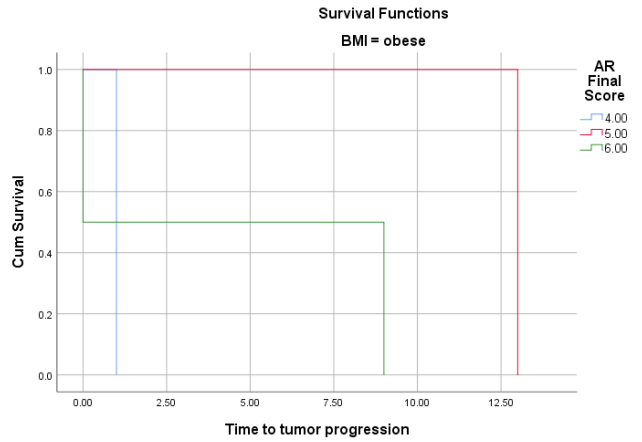

Figure 2: Time to tumor progression in HER2Nneu+ve obese patients.

This Kaplan-Meier curve (Figure 2) shows time to tumor progression when comparing the levels of androgen receptor expression in HER2Nneu +ve obese patients as estimated by body mass index (BMI); as follows:

Score 5: 100% → 13 months

Score 4: 100% → 1 month

Score 6: 50% → 9 months.

(With overall maximal standard error: 0.500)

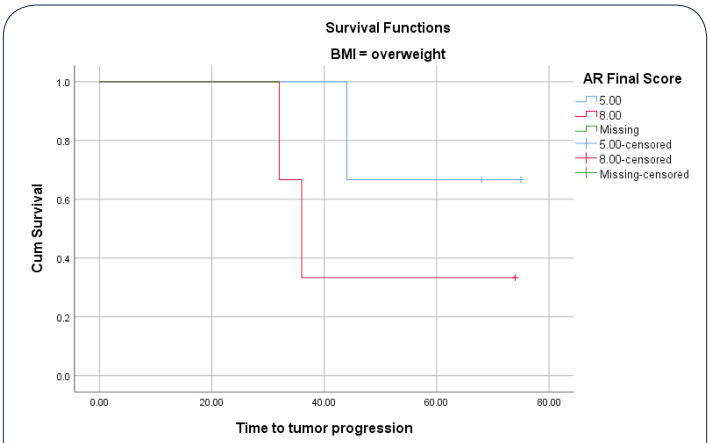

Figure 3: Time to tumor progression in HER2Nneu +ve overweight patients.

This Kaplan-Meier curve (Figure 3) shows time to tumor progression when comparing the levels of androgen receptor expression in HER2Nneu +ve overweight patients as estimated by body mass index (BMI); as follows:

Score 5: 100% → 45 months… 68% → 76 months

Score 8: 100% → 32 months… 33% → 74 months.

(With overall maximal standard error: 0.667)

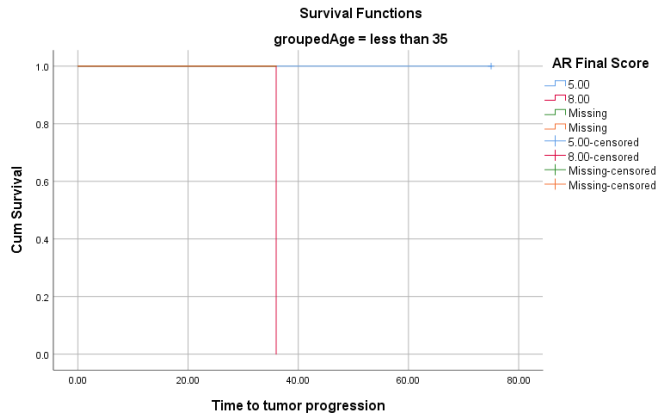

Figure 4: Time to tumor progression in HER2Nneu+ve patients with age less than 35 years.

This Kaplan-Meier curve (Figure 4) shows time to tumor progression when comparing the levels of androgen receptor expression in HER2Nneu +ve patients with regard to age less than 35 years; as follows:

Score 5: 100% → 75 months

Score 8: 100% → 35 months.

(With overall maximal standard error: 0.000)

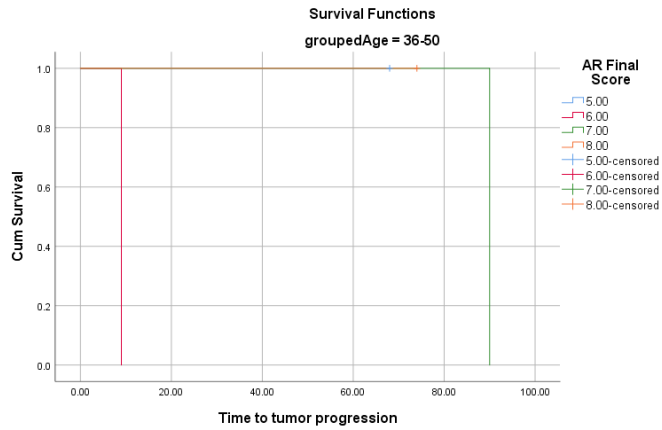

Figure 5: Time to tumor progression in HER2Nneu+ve patients with age 36 to 50 years.

This Kaplan-Meier curve (Figure 5) shows time to tumor progression when comparing the levels of androgen receptor expression in HER2Nneu +ve patients with regard to age 36 to 50 years; as follows:

Score 7: 100% → 90 months

Score 8: 100% → 73 months

Score 5: 100% → 67 months

Score 6: 100% → 8 months.

(With overall maximal standard error: 0.000)

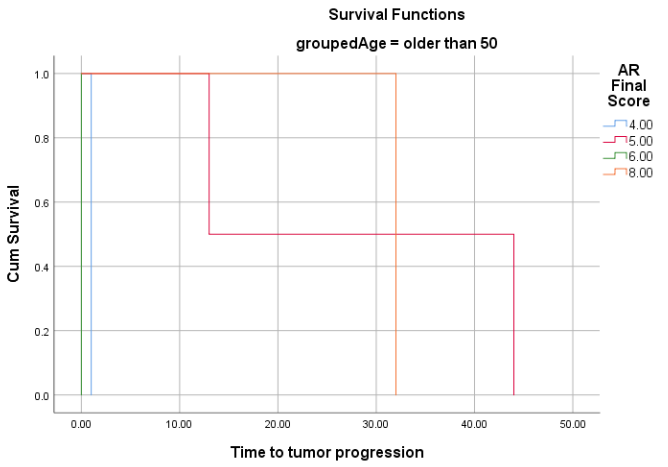

Figure 6: Time to tumor progression in HER2Nneu+ve patients with age older than 50 years.

This Kaplan-Meier curve (Figure 6) shows time to tumor progression when comparing the levels of androgen receptor expression in HER2Nneu +ve patients with regard to age older than 50 years; as follows:

Score 8: 100% → 33 months

Score 5: 100% → 14 months…50% → 44 months

Score 4: 100% → 2 months.

(With overall maximal standard error: 0.500)

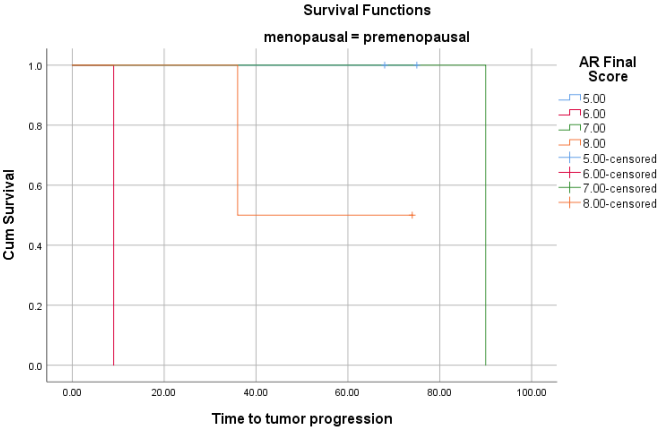

Figure 7: Time to tumor progression in HER2Nneu+ve premenopausal patients.

This Kaplan-Meier curve (Figure 7) shows time to tumor progression when comparing the levels of androgen receptor expression in HER2Nneu +ve premenopausal patients; as follows:

Score 7: 100% → 90 months

Score 5: 100% → 73 months

Score 8: 100% → 35 months… 50% → 75 months

Score 6: 100% → 9 months.

(With overall maximal standard error: 0.500)

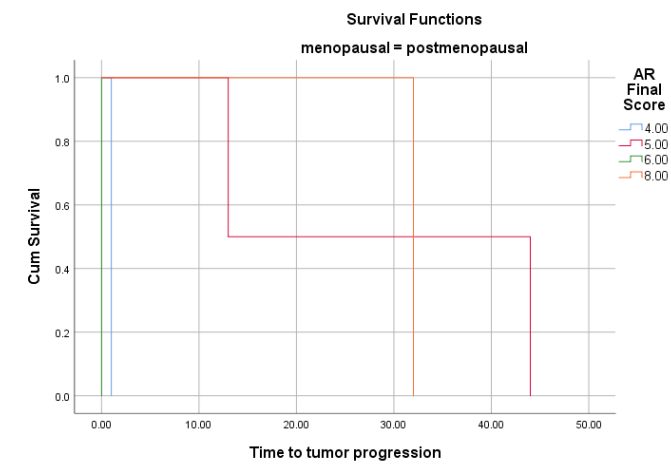

Figure 8: Time to tumor progression in HER2Nneu +ve postmenopausal patients.

This Kaplan-Meier curve (Figure 8) shows time to tumor progression when comparing the levels of androgen receptor expression in HER2Nneu +ve postmenopausal patients; as follows:

Score 8: 100% → 32 months

Score 5: 100% → 13 months… 50% → 44 months

Score 4: 100% → 2 months.

(With overall maximal standard error: 0.500)

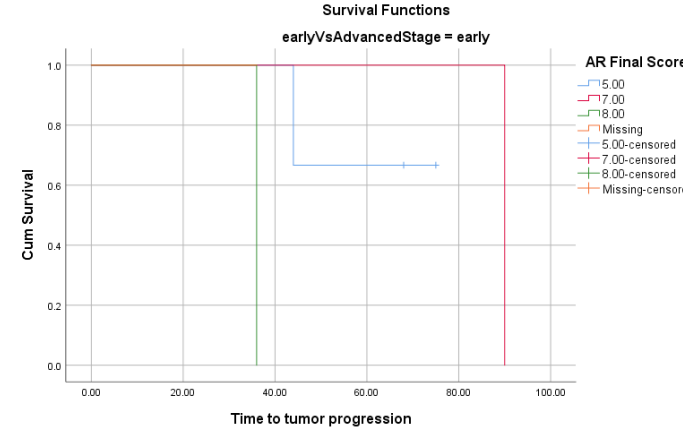

Figure 9: Time to tumor progression in HER2Nneu+ve patients with early stage.

This Kaplan-Meier curve (Figure 9) shows time to tumor progression when comparing the levels of androgen receptor expression in HER2Nneu +ve patients with regard to early stage; as follows:

Score 7: 100% → 90 months

Score 5: 100% → 42 months… 68% → 75 months

Score 8: 100% → 35 months.

(With overall maximal standard error: 0.667)

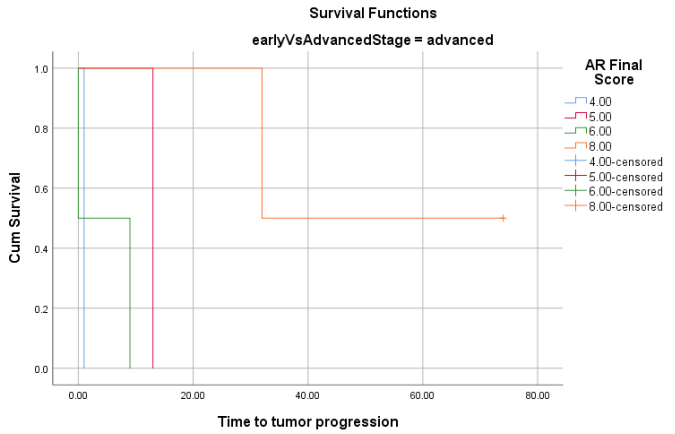

Figure 10: Time to tumor progression in HER2Nneu +ve patients with regard to advanced stage.

This Kaplan-Meier curve (Figure 10) shows time to tumor progression when comparing the levels of androgen receptor expression in HER2Nneu +ve patients with regard to advanced stage; as follows:

Score 8: 100% → 32 months… 50% → 75 months

Score 5: 100% → 13 months

Score 6: 50% → 10 months.

(With overall maximal standard error: 0.500)

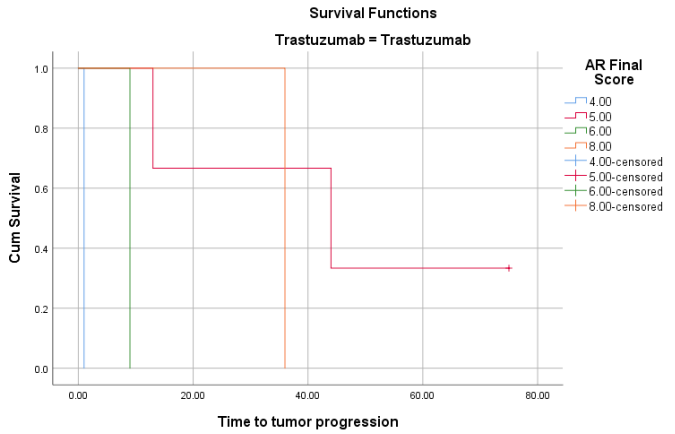

Figure 11: Time to tumor progression in HER2Nneu +ve patients with regard to response to Trastuzumab.

This Kaplan-Meier curve (Figure 11) shows time to tumor progression when comparing the levels of androgen receptor expression in HER2Nneu +ve patients with regard to response to Trastuzumab; as follows:

Score 8: 100% → 35 months

Score 5: 100% → 12 months… 68% → 45 months… 33% → 75 months

Score 6: 100% → 10 months.

(With overall maximal standard error: 0.272)

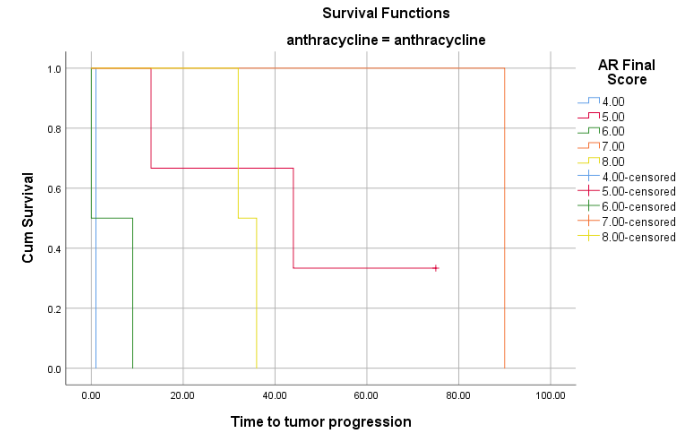

Figure 12: Time to tumor progression in HER2Nneu +ve patients regarding response to anthracyclines.

This Kaplan-Meier curve (Figure 12) shows time to tumor progression when comparing the levels of androgen receptor expression in HER2Nneu +ve patients regarding response to anthracyclines; as follows:

Score 7: 100% → 90 months

Score 5: 100% → 13 months… 67% → 44 months… 33% → 75 months

Score 8: 100% → 32 months… 50% → 36 months.

(With overall maximal standard error: 0.667)

Response to Texans

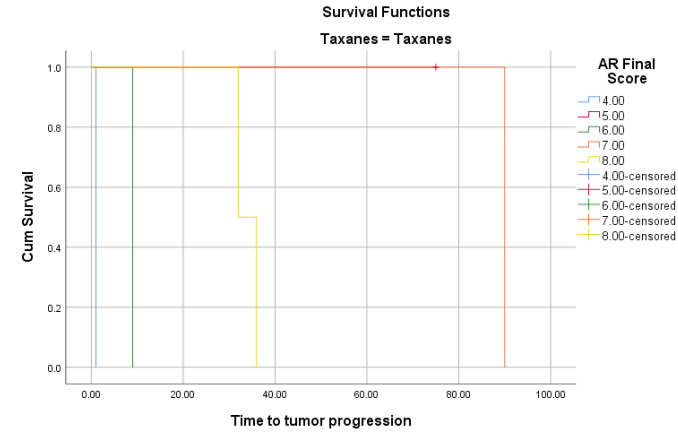

Figure 13: Time to tumor progression in HER2Nneu +ve patients regarding response to Texans.

This Kaplan-Meier curve (Figure 13) shows time to tumor progression when comparing the levels of androgen receptor expression in HER2Nneu +ve patients regarding response to Texans; as follows:

Score 7: 100% → 90 months

Score 5: 100% → 75 months

Score 8: 100% → 32 months… 50% → 36 months

Score 6: 100% → 10 months.

(With overall maximal standard error: 0.354)

Summary of TTP/PFS curves in HER2Neu positive Subgroup

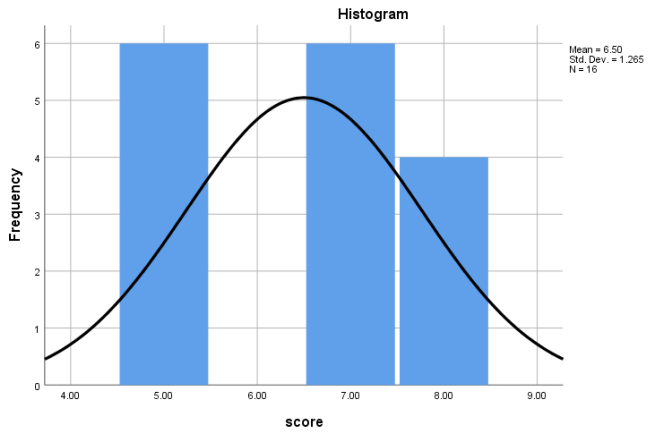

Figure 14: Score 7 and score 5 as degree of androgen receptor expression are the predominant and have the best Time to Tumor Progression (TTP) in all hormonal Receptor (HR)-ve/ HER2Neu positive patients.

This histogram (Figure 14) shows that score 7 and score 5 as degree of androgen receptor expression are the predominant and have the best Time to Tumor Progression (TTP) in all Hormonal Receptor (HR)-ve/HER2Neu positive patients in our study. Z score = 0.931. P-Value is < .00001. (Statistically significant)

Overall survival

Generally

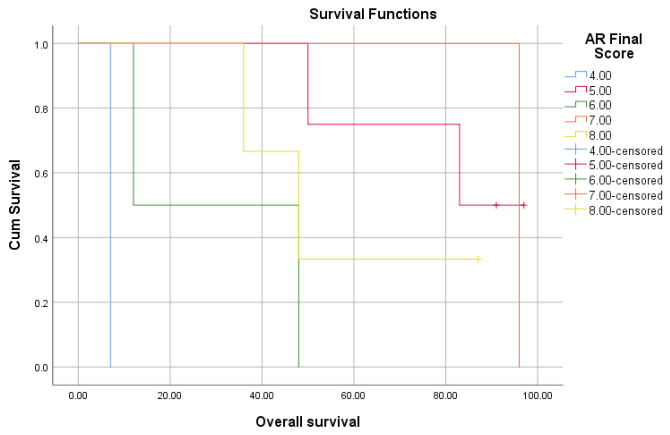

Figure 15: Overall survival in HER2-Neu positive patients generally.

This Kaplan-Meier curve (Figure 15) shows the overall survival in HER2-Neu positive patients generally; as follows:

Score 7: 100% of patients survived for → 95 months

Score 5: 100% → 50 months … 75% → 84 months… 50% → 97 months

Score 8: 100% → 35 months… 68 % → 48 months… 35% → 88 months

Score 6: 100% → 13 months… 50% → 48 months

Score 4: 100% → 8 months

(With maximal standard error: 0.354)

With body mass index

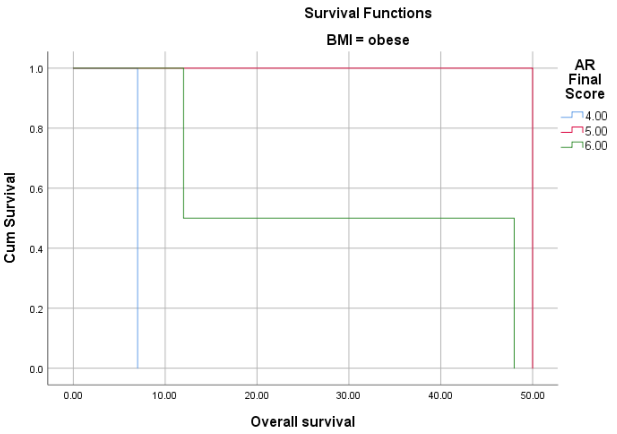

Figure 16: Overall survival in HER2-Neu positive obese patients.

This Kaplan-Meier curve (Figure 16) shows the overall survival in HER2-Neu positive obese patients as estimated by Body Mass Index (BMI); as follows:

Score 5: 100% → 50 months

Score 6: 100% → 13 months … 50% → 46 months

Score 4: 100% → 7 months

(With maximal standard error: 0.354)

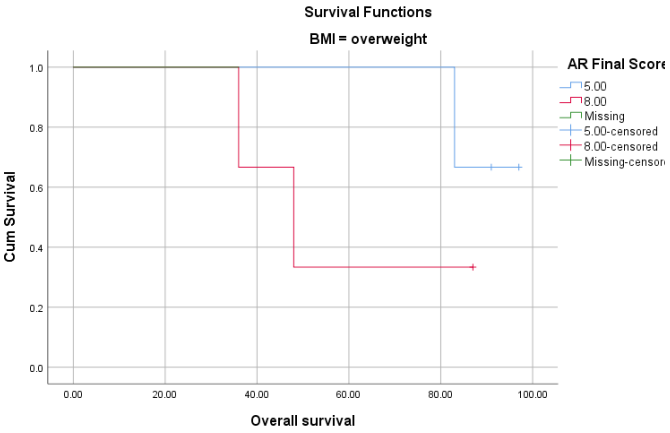

Figure 17: Overall survival in HER2-Neu positive overweight patients.

This Kaplan-Meier curve (Figure 17) shows the overall survival in HER2-Neu positive overweight patients as estimated by Body Mass Index (BMI); as follows:

Score 5: 100% → 84 months… 68% → 97 months

Score 8: 100% → 35 months … 67% → 47 months… 34% → 87 months

(With maximal standard error: 0.272)

With age group

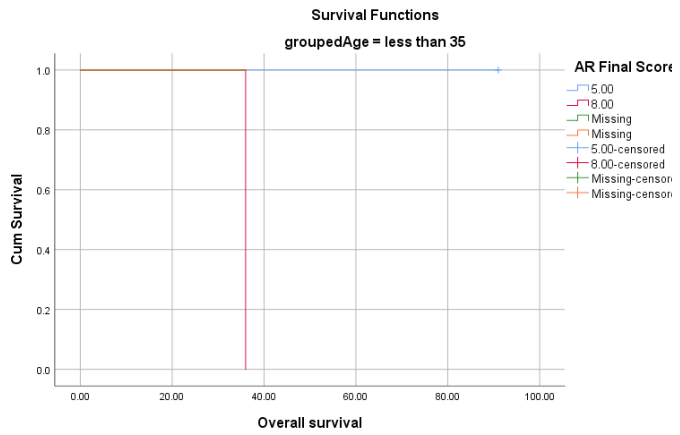

Figure 18: Overall survival in HER2-Neu positive patients aging less than 35 years.

This Kaplan-Meier curve (Figure 18) shows the overall survival in HER2-Neu positive patients aging less than 35 years; as follows:

Score 5: 100% → 90 months

Score 8: 100% → 35 months

(With maximal standard error: 0.000)

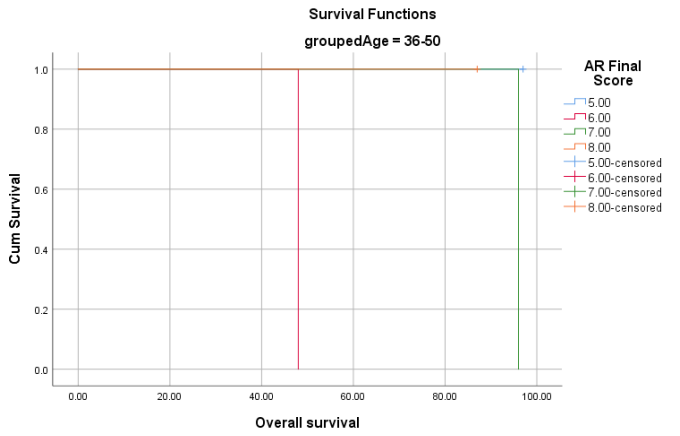

Figure 19: Overall survival in HER2-Neu positive patients aging 36 to 50 years

This Kaplan-Meier curve (Figure 19) shows the overall survival in HER2-Neu positive patients aging 36 to 50 years; as follows:

Score 5: 100% → 98 months

Score 7: 100% → 97 months

Score 8: 100% → 88 months

Score 6: 100% → 48 months.

(With maximal standard error: 0.000)

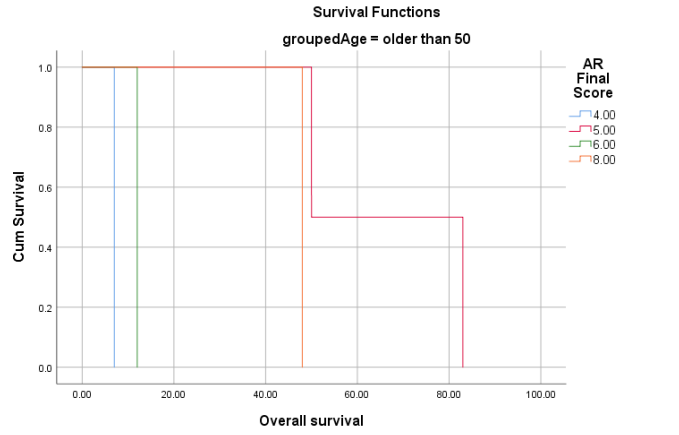

Figure 20: Overall survival in HER2-Neu positive patients aging older than 50 years.

This Kaplan-Meier curve (Figure 20) shows the overall survival in HER2-Neu positive patients aging older than 50 years; as follows:

Score 5: 100% → 50 months… 50% → 84 months

Score 8: 100% → 47 months

Score 6: 100% → 13 months

Score 4: 100% → 8 months.

(With maximal standard error: 0.354)

With menopausal status

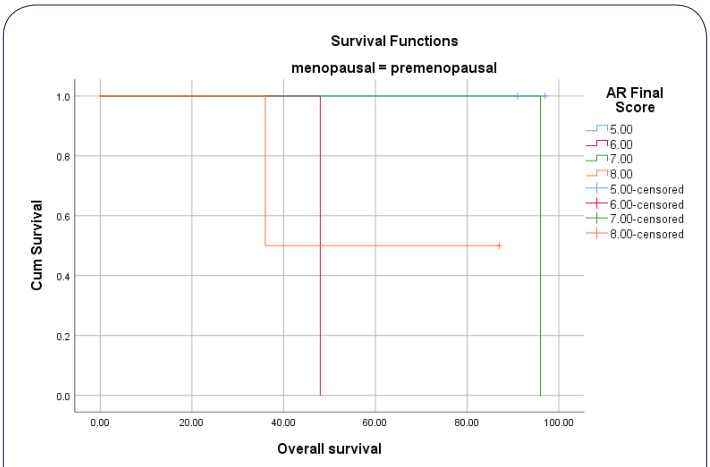

Figure 21: Overall survival in HER2-Neu positive premenopausal patients.

This Kaplan-Meier curve (Figure 21) shows the overall survival in HER2-Neu positive premenopausal patients; as follows:

Score 5: 100% → 97 months

Score 7: 100% → 95 months

Score 6: 100% → 48 months

Score 8: 100% → 36 months… 50% → 87 months

(With maximal standard error: 0.500)

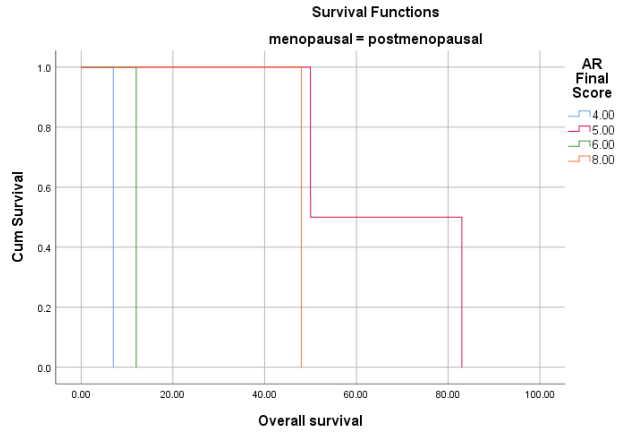

Figure 22: Overall survival in HER2-Neu positive postmenopausal patients.

This Kaplan-Meier curve (Figure 22) shows the overall survival in HER2-Neu positive postmenopausal patients; as follows:

Score 5: 100% → 50 months… 50% → 84 months

Score 8: 100% → 48 months

Score 6: 100% → 13 months

Score 4: 100% → 8 months

(With maximal standard error: 0.500)

With stage early versus advanced

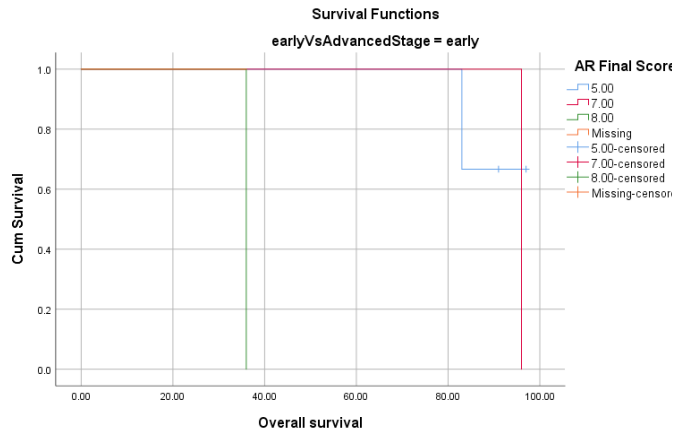

Figure 23: Overall survival in HER2-Neu positive patients with early stage.

This Kaplan-Meier curve (Figure 23) shows the overall survival in HER2-Neu positive patients with early stage; as follows:

Score 7: 100% → 95 months

Score 5: 100% → 84 months … 68% → 97 months

Score 8: 100% → 35 months

(With maximal standard error: 0.272)

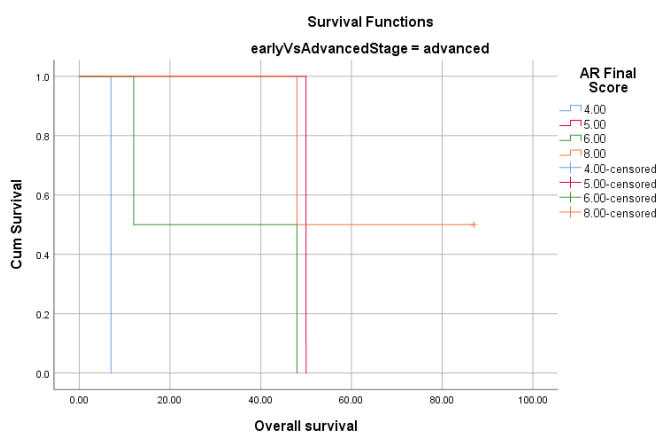

Figure 24: Overall survival in HER2-Neu positive patients with advanced stage.

This Kaplan-Meier curve (Figure 24) shows the overall survival in HER2-Neu positive patients with advanced stage; as follows:

Score 5: 100% → 50 months

Score 8: 100% → 47 months … 50% → 88 months

Score 6: 100% → 13 months… 50 % → 47 months

Score 4: 100% → 8 months

(With maximal standard error: 0.354)

Summary of OS curves of HER2Neu positive Subgroup

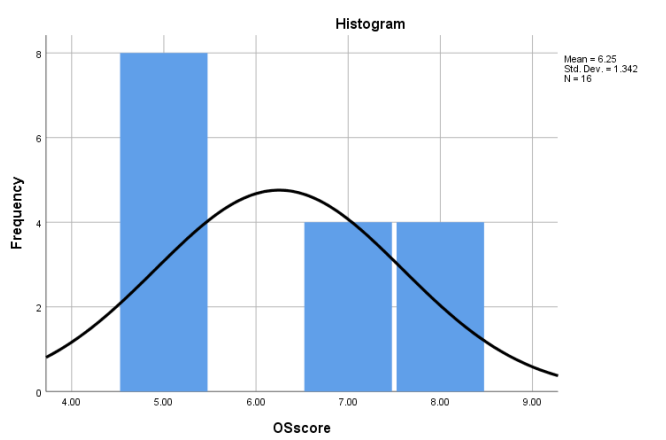

Figure 25: Score 5 androgen receptor expression has the best Overall Survival (OS) in all HR-ve/HER2Neu positive patients.

This histogram (Figure 25) shows that score 5 as degree of androgen receptor expression is the predominant and has the best Overall Survival (OS) in all HR-ve/HER2Neu positive patients in our study. Z score = 3.725. P-Value is 0.000195. (Statistically significant).

Discussion

- He L in 2017 stated that; "the androgen receptor, however, also influences the growth of HER2+ ER– BC cells in non-genomic way. That inhibition of AR by Enzalutamide decreases the HER2 phosphorylation without affecting the total level of HER2 or HER3. Treatment of cells with a combination of enzalutamide

and trastuzumab, an approved HER2 target drug, potentiates the inhibitory effect on cell growth [2].

- Andrew Wardley and his colleagues in 2021 stated that Enzalutamide plus trastuzumab were well tolerated, and a subset of patients in this heavily pretreated population had durable disease control [3].

- Our studied HER2Neu positive breast cancer patients had best Progression free survival and Overall survival with score 7 (not targeted by any anti-androgen) (in contrast to all the other luminal A, triple positive and triple negative groups).

➢ Our study results came in agreement with the study of He L, Andrew Wardley and their colleagues.

§ FDA granted accelerated approval to pertuzumab in 2013 as neoadjuvant treatment. approval was granted to pertuzumab for use in combination with trastuzumab and chemotherapy as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer.

- In our study, in HER2Neu positive group, 18 patients (75%) didn't receive neoadjuvant chemotherapy; while 6 patients (25%) did.

➢ Affordability of anti-tumor therapy is still a potential need especially for patients in the developing countries.

Conclusion

Androgen receptor intermediate expression (score 5) and high expression (score 7) had the best prognosis in HER2Neu positive breast cancer female patients; for Time to Tumor Progression (TTP) and androgen receptor intermediate expression (score 5) had the best Overall Survival (OS).

Regarding HER2Neu positive breast cancer female patients, among those who receive Trastuzumab, highly and intermediately positive androgen receptor showed better response to Trastuzumab than low positive androgen receptor.

References

1. He L, Du Z, Xiong X, et al. Targeting Androgen Receptor in Treating HER2 Positive Breast Cancer. 2017; 7: 14584. 10.1038/s41598-017-14607-2.

2. Andrew Wardley, et al. The efficacy and safety of enzalutamide with trastuzumab in patients with HER2+ and androgen receptor-positive metastatic or locally advanced breast cancer. National Library of Medicine. 2021. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8062601/.

3. Food and Drug Administration. FDA grants regular approval to pertuzumab for adjuvant treatment of HER2-positive breast cancer. FDA. 2017; 12(21). https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-regular-approval-pertuzumab-adjuvant-treatment-her2-positive-breast-cancer.