

Therapeutic significance of hormone receptor positivity in patients with HER-2 positive breast cancer

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Breast cancer with high expression of human epidermal growth factor receptor (HER)-2 represents a biologically and clinically heterogeneous group of neoplastic disorders. Importantly, hormone receptor expression has an effect on biological properties and affects the selection of therapies. On the basis of molecular genetics, four principal subtypes, including luminal A, luminal B, HER2-enriched (HER-2-E), and basal-like can be distinguished. Breast tumors characterized by HER-2 positivity and simultaneous expression of hormone receptors, triple positive breast cancers (TPBC) are of increasing interest owing to the unique biological characteristics associated with complex interactions between HER-2 and hormone receptor signaling pathways. Interactions between hormone receptors and HER-2 explain the decreased efficacy of hormonal therapy in comparison with HER-2-negative patients. The expression of estrogen receptors in HER-2 positive tumors may also be associated with resistance to anti-HER-2 treatment. Multiple available therapeutic options, including hormonal therapy, anti-HER-2 agents and cytotoxic drugs explain favorable prognosis of TPBC. Escalation and de-escalation therapeutic strategies that could result in lower toxicities are being investigated as well as combinations of anti-HER-2 agents with hormonal therapy, immunotherapy, cyclin dependent kinase 4/6 and phosphatidyl inositol-3-kinase inhibitors. Distinction between subtypes of HER-2-positive breast cancer and treatment diversification may result in improved outcomes in TPBC. A response to neoadjuvant therapy may serve in the tailoring of therapy management.

Key words: breast cancer, estrogen receptor, HER-2

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INTRODUCTION

Breast cancer may serve as an example of a tumor whose biological characteristics impact in a fundamental manner on the presentation, behavior and therapy. The presence of hormone receptors (HR) and human epidermal growth factor receptor (HER)-2 is a principal factor determining the clinical management.

HER-2 is a member of a family of transmembrane tyrosine kinase receptors (together with HER-1 (EGFR), HER-3 and HER-4) and a universal partner for heterodimerization with other members of HER receptor family. The amplification of the gene *c-erbB-2* resulting in overexpression or of HER-2 protein stimulates tumor growth, invasion and tumor cell survival by activation of several signaling pathways¹.

HER-2 positive breast cancer is clinically and biologically heterogeneous disease. Based on gene expression profiling, four major molecular subtypes of HER-2 positive tumors have been identified, namely luminal A, luminal B, HER-2 enriched (HER2-E), and basal-like. The most common molecular subtype among them is the HER2-E (in 50-60 % of cases) (ref.²).

Trastuzumab was the first HER-2-directed therapy. The unprecedented activity of trastuzumab paved the way for the introduction of other drugs targeting HER-2, including other monoclonal antibodies (pertuzumab), HER-2- tyrosine kinase inhibitors (lapatinib and neratinib) and antibody conjugates (e.g. trastuzumab emtansine; TDM-1). The medical therapy of HER-2 positive breast cancer is mostly based on concomitant or sequential combinations of HER-2 targeting agents with cytotoxic or hormonal drugs.

About three quarters of breast cancers express HR (ref.³) while HER-2 amplification is present in only 12-15% of cases. Simultaneous positivity of HR and HER-2 amplification is observed in about half of HER-2 positive breast cancer patients^{4,5}.

The tumors positive for HER-2 as well as HR (HER2+/HR+), termed triple positive breast cancer (TPBC) (ref.^{1,6,7}) are characterized by unique biological properties resulting from complex interactions between HER-2 and estrogen receptor (ER) signaling pathways⁸⁻¹².

The expression of ER and progesterone receptor (PR) is, in general, associated with better treatment outcome, at least in the short term. Overall survival (OS), disease-free survival (DFS) and progression-free survival (PFS) positively correlate with ER and PR expression¹³⁻¹⁵. However, although the 5-year relapse rate is higher in ER negative tumors, late relapses are more common in ER-positive tumors, sometimes decades after diagnosis^{12,16}.

In ER positive luminal tumors, preclinical as well as clinical data demonstrate intensive interactions between signaling pathways stimulated by ER engagement and HER-2 amplification.

It has been demonstrated that activation of the ER pathway may be one of the mechanisms of resistance to anti-HER-2 therapy and that TPBC tumors frequently belong to the luminal molecular subtype¹¹. The administration of trastuzumab improved OS in both luminal molecular subtypes in two large adjuvant trials (NSABP B31 and N9831) (ref.^{17,18}). In patients with basal-like subtype, NSABP B31 has demonstrated an OS benefit of trastuzumab, but an OS benefit in these patients was not evident in the N9831 trial.

In the treatment of TPBC anti-HER-2 therapy has to be combined with cytotoxic and hormonal agents^{9,10}. Patients with high HER-2 positivity have statistically significantly lower HR expression compared to patients with lower HER-2 positivity resulting in lower efficacy of hormonal therapy compared to patients with HR-positive, HER-2 negative tumors⁵. On the other hand, ER positivity may be associated with the resistance to anti-HER-2 therapy^{5,19}.

Short-term survival in patients with HR-positive/HER-2-positive tumors

A recently published study based on SEER registry analyzing the 4-year breast cancer-specific survival (BCSS) of 196 094 patients treated between 2010 and 2013 according to tumor subtypes as well as clinical and demographic parameters demonstrated that TPBC patients had 4-year BCSS slightly lower compared to patients with HR-positive, HER-2 negative tumors (92.5% vs 90.3%), with the survival rates in patients with HR-negative, HER-2-positive and triple negative patients being 82.7% and 77.0%, respectively²⁰. The stage was the strongest determinant of survival in this study, and 4-year BCSS in patients with stage I tumor was above 95% regardless of the subtype. Among patients with stage IV tumors, highest survival rates were noted in TPBC, even after correction for clinical and demographic factors.

Long-term survival in HR-positive patients

Colleoni et al. evaluated late relapse in patients with HR-positive tumors treated with adjuvant therapy between 1978 and 1985, i.e. at the time when HER-2 positivity was not evaluated, with a median follow up of 24 years¹². Favorable outcome was noted in patients with ER-positive compared to ER-negative tumors during the 5 years after diagnosis, with a higher incidence of late relapses. The risk of relapse for tumors expressing ER was significantly lower during the first 5 years (9.9% v 11.5%; $P=0.01$). In the subsequent period, the risk of recurrence was higher for ER-positive compared to ER-negative tumors (5 to 10 years: 5.4% v 3.3%; 10 to 15 years: 2.9% v 1.3%; 15 to 20 years: 2.8% v 1.2%; and 20 to 25 years: 1.3% v 1.4%; $P<0.001$). The survival curves of patients with ER-positive and ER-negative tumors cross over and hazard ratio of OS, DFS and BCSS change during the course of the time. Patients with ER-positive tumors have a higher risk of relapse, including distant metastases 5 to 25 years after diagnosis, supporting the need for long-term clinical follow-up.

Long term survival in patients with HR-positive/HER-2-positive breast cancer

A prospective study evaluating the effect of HR status in 3394 stage I - III patients treated in National Comprehensive Cancer Network (NCCN) centers demonstrated that patients with HR-negative, HER-2-positive tumors have a significantly higher risk of early, but not late death compared to TPBC. The hazard ratio for OS during the first two years after diagnosis was 1.92, with 95% confidence intervals (CI) 1.28 - 2.86 ($P=0.002$), hazard ratio 2 to 5 years after diagnosis was 1.55 (95% CI 1.19 to 2.00, $P=0.001$), and hazard ratio after 5 years from diagnosis was 0.81 (95% CI 0.55 to 1.19, $P=0.285$) (ref.²¹).

The association of long-term outcome with molecular subtype was analyzed in a study evaluating HER-2-positive patients treated in the adjuvant setting demonstrating that at 10 years the relapse-free survival (RFS) is best in patients with luminal A molecular subtype (89.8%), followed by luminal B (82.3%), HER2-enriched (76.8%) and basal-like (74.19%) (ref.²²). This study confirmed the difference in the timing of relapse between HR-positive, HER-2-positive and HR-negative, HER-2-positive tumors in patients treated with trastuzumab and chemotherapy. The relapse rate during the initial 5 years was higher in HR-negative, HER-2-positive patients in comparison with TPBC (RFS hazard ratio 0.65, 95% CI 0.56-0.77, $P<0.001$), but this difference disappeared during the subsequent years (RFS hazard ratio 1.32, 95% CI 0.93-1.88, $P=0.12$).

A potential tumor-promoting synergism of stimulating both ER and HER-2 signaling pathways in TPBC may be offset by a wide range of therapeutic targets, including ER and HER-2 which may contribute to better survival in patients with advanced disease. The introduction of dual HER-2 blockade with the combination of trastuzumab, pertuzumab and chemotherapy has changed the therapeutic landscape by reaching a landmark median survival of almost 5 years, almost two years longer than would be

expected in the pre-pertuzumab era²³. Trastuzumab emtansine that combines trastuzumab with a cytotoxic agent represents another therapeutic option. These drugs can be administered in simultaneous or sequential combination or different lines of therapy, including the combinations with hormonal agents. However, prospective data on the combinations of anti-HER-2 therapies with hormonal drugs are currently limited.

The significance of HR expression in TPBC

As outlined above, it appears that some HER-2 positive, HR-positive tumors, specifically tumors with high ER expression are characterized by biological behavior of luminal tumor with favorable prognosis during the initial years after diagnosis, but a relatively high incidence of late relapses, putting the efficacy and importance of anti-HER-2 therapy into question²⁴.

The significance of the extent of hormone dependence on the behavior of TPBC is demonstrated by the results of a retrospective analysis of patients treated with adjuvant chemotherapy alone or in combination with trastuzumab. The administration of trastuzumab resulted in improved RFS as well as BCCS in all subgroups. However, in patients with tumors exhibiting more than 30% of HR-positive cells (and even more in patients with tumors demonstrating more than 50% of HR-positive cells), the differences in survival were not significant. The pattern of relapse was different in patients with tumors exhibiting more than 50% of HR-positive cells with a low risk of relapse during the first 5 years, with a subsequent rise in the relapse rate later, and a limited effect of trastuzumab administration. Multivariate analysis of RFS demonstrated that the benefit of trastuzumab treatment is limited to tumors with $\leq 50\%$ ER-positive cells⁸.

These conclusions are supported by a secondary analysis of the HERA trial that demonstrated significantly lower benefit from adjuvant trastuzumab in patients with ER-positive tumors and low level of HER-2 amplification (low HER-2/CEP17 ratio determined by fluorescent in situ hybridization) compared to patients with tumors characterized by the high level of HER-2 amplification and low expression of hormone receptors determined immunohistochemically. Patients with ER-positive tumors and low HER-2 amplification (ratio 2-5) or higher ESR1 expression show lower benefit from adjuvant trastuzumab administered after chemotherapy. It may be hypothesized that in some cases of TPBC, tumor growth may be more dependent on signaling pathways characteristic for luminal tumors rather than HER-2-related mechanisms²⁵.

Implications for therapy in treatment settings

A number of trials studied the intensification of neoadjuvant therapy aiming at increasing the pathological complete response (pCR) rate or improving survival. The results of several neoadjuvant studies have demonstrated that independent of the anti-HER-2 therapy regimen the pCR rate is markedly lower in TPBC compared to patients with HR-negative, HER-2-positive tumors. Interestingly, the low pCR rate does not affect a generally favorable prognosis of TPBC (ref.²⁴), and it may be speculated

whether the administration of neoadjuvant treatment comprising chemotherapy in early TPBC with favorable prognosis is not an overtreatment²⁶.

In the neoadjuvant setting dual anti-HER-2 blockade was tested in combination with hormonal therapy in the absence of chemotherapy with pCR rate reaching 20-30% (ref.^{2,27}). In the ADAPT trial T-DM1 administered with or without hormonal therapy (aromatase inhibitors) was compared with the combination of trastuzumab with hormonal therapy. T-DM1 resulted in pCR rate above 41% independent of the administration of hormonal therapy, while the pCR rate for the combination of trastuzumab with hormonal therapy was substantially lower (15%) (ref.²⁸).

In the GeparQuinto trial prolonged administration of lapatinib in patients with HR-positive tumors in combination with standard medical therapy that included anthracyclines and taxanes as well as hormonal agents according to local guidelines followed by adjuvant trastuzumab for 12 months resulted in significantly improved OS compared with adjuvant trastuzumab (hazard ratio 0.32; $P=0.019$). The neoadjuvant administration of EGFR/HER-2 inhibitor lapatinib followed by adjuvant trastuzumab may achieve more effective inhibition of growth signaling in endocrine-dependent tumor cells, resulting in improved efficacy in TPBC (ref.^{29,30}).

In the PERELISA trial a repeat biopsy was performed after 2 weeks of neoadjuvant letrozole. In patients with a decrease of Ki67 expression by more than 20%, letrozole was continued in combination with trastuzumab and pertuzumab. In remaining patients, weekly paclitaxel in combination with trastuzumab and pertuzumab was administered. The pCR rate in patients with decreased Ki67 treated with trastuzumab, pertuzumab and letrozole was 20.5% (ref.³¹).

Current standard of medical therapy in TPBC consists of anti-HER-2 agents combined with hormonal, and, with the exception of tumors smaller than 0.5 cm, also cytotoxic drugs. Hormonal therapy is administered sequentially to chemotherapy and concomitantly with maintenance trastuzumab⁹.

The results of SOFT and TEXT trials investigating ovarian function suppression (OFS) as part of adjuvant endocrine therapy indicate the higher benefit of OFS in TPBC compared to patients with HR-positive, HER-2-negative tumors that persists after therapy and is present regardless of anti-HER-2 treatment³².

The data of Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization trial also indicate that patients with amenorrhea during therapy have better outcome³³. However, an optimal regimen of oral endocrine treatment with OFS in TPBC patients has not yet been determined.

The phase III Katherine trial investigated the efficacy of adjuvant administration of T-DM1 in patients who did not achieve pCR after neoadjuvant chemotherapy with trastuzumab. The patients with residual disease in surgical specimens were randomized between T-DM1 or trastuzumab. A significant benefit in invasive disease-free survival at 3 years for T-DM1 (88.3% vs. 77%, $P<0.001$) was observed regardless of HR expression³⁴.

Table 1. HER2 positive breast cancer trials - adjuvant setting.

Clinical trial	Therapy	Control	Design	Results	Ref.
Katherine					
A Randomized, Multicenter, Open-Label Phase III Study to Evaluate the Efficacy and Safety of Trastuzumab Emtansine Versus Trastuzumab as Adjuvant Therapy for Patients With HER2-Positive Primary Breast Cancer Who Have Residual Tumor Present Pathologically in the Breast or Axillary Lymph Nodes Following Preoperative Therapy	trastuzumab emtansine every 3 weeks, 14 cycles	trastuzumab every 3 weeks, 14 cycles	patients without pCR after neoadjuvant chemotherapy + trastuzumab	3-year iDFS 88.3% vs. 77% $P < 0.001$	34
ExteNET					
A Randomized, Double-Blind, Placebo-Controlled Trial Of Neratinib (HKI-272) After Trastuzumab In Women With Early-Stage HER-2/Neu Overexpressed/Amplified Breast Cancer	neratinib 1 year	placebo	12 months of adjuvant trastuzumab + - neratinib 1 year	5-year iDFS HR+ patients: 91,2% vs. 86,8% hazard ratio 0.60, 95% CI 0.43-0.83 $P = 0.002$	35
APT					
A Phase II Trial of Adjuvant Paclitaxel and Trastuzumab for Node-Negative HER2-Positive Breast Cancer	12 x weekly paclitaxel + 1 year trastuzumab	0	a single arm trial	7-year DFS HR+ patients: 94.6% (95% CI 91.8-97.5) HR- patients: 90.7% (95% CI 84.6-97.2)	36

iDFS - invasive disease free survival

DFS - disease free interval

Adjuvant dual blockade was tested in the EXTNET phase III placebo controlled trial investigating the effect of one year treatment with neratinib after standard 12 months of adjuvant trastuzumab³⁵. A significant improvement of invasive disease-free survival at 5 years was observed in patients with tumors expressing hormone receptors (hazard ratio 0.60, 95% CI 0.43-0.83, $P = 0.002$).

APT trial evaluated the efficacy of a non-anthracyclin adjuvant chemotherapy. Patients with tumors < 3 cm and no axillary involvement were treated with 12 weekly doses of paclitaxel with trastuzumab administered for a year. Seven-year DFS in the whole cohort was 93.3% (95% CI 90.4-96.2%), 94.6% (95% CI 91.8-97.5%) in patients with HR-positive tumors, and 90.7% (95% CI 84.6-97.2%) in patients with HR negativity. This regimen is currently considered as an effective treatment in patients with small tumor expressing both HR and HER-2 (ref.³⁶). The results of selected clinical trials investigating adjuvant therapy of HER-2 positive breast cancer are presented in Table 1.

Patients with advanced TPBC were studied in TAnDEM, EGF30008 and eLEcTRA trials that demonstrated a significant prolongation of PFS with the addition of anti-HER-2 therapy to hormonal treatment, but an improvement of OS did not reach statistical significance³⁷⁻⁴⁰.

Retrospective analyses indicate that the combination of hormonal therapy with anti-HER-2 treatment may improve outcomes⁴¹. American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) guidelines consider justified the addition of

endocrine therapy as maintenance in patients with metastatic TPBC (ref.^{10,42}).

A PFS benefit of the combination of dual HER-2 blockade (pertuzumab and trastuzumab) and aromatase inhibitor in patients with metastatic TPBC has been demonstrated in the PERTAIN trial with median PFS in the experimental arm of 18.9 months compared to 15.8 months in the control arm (hazard ratio 0.65; 95% CI 0.48-0.89; $P = 0.007$) (ref.⁴³). In the ALTERNATIVE trial patients who progressed during neoadjuvant or adjuvant treatment with trastuzumab and chemotherapy were treated with an aromatase inhibitor and randomized into three treatment arms of trastuzumab monotherapy, lapatinib monotherapy and the combination of trastuzumab and lapatinib⁴⁴. An improvement of PFS was observed for dual blockade compared to either agent alone (median PFS 11 months compared to 8.3 months for lapatinib and 5.7 months for trastuzumab). The results of selected clinical trials investigating the treatment of advanced TPBC are presented in Table 2.

The significance of tumor infiltrating lymphocytes (TIL)

The presence of TIL is one of the most important predictors of response to therapy and long-term survival in patients with breast cancer⁴⁵. In patients with HER-2-positive breast cancer the presence of TIL is associated with better survival in both early disease⁴⁶⁻⁴⁸ and in metastatic setting⁴⁹.

The presence of TIL is predictive of pCR after anti-HER2 neoadjuvant treatment independently of other

Table 2. Triple positive breast cancer trials (advanced setting).

Clinical Trial	Therapy	Control	Results	Ref.
TAnDEM				
Trastuzumab Plus Anastrozole Versus Anastrozole Alone for the Treatment of Postmenopausal Women With Human Epidermal Growth Factor Receptor 2-Positive, Hormone Receptor-Positive Metastatic Breast Cancer: Results From the Randomized Phase III TAnDEM Study	trastuzumab + anastrozol	anastrozol	median PFS 3.8 months vs. 5.6 months <i>P</i> = 0.006	37
EGF30008				
A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase III Study Comparing GW572016 and Letrozole Versus Letrozole in Subjects With Estrogen/Progesterone Receptor-Positive Advanced or Metastatic Breast Cancer	lapatinib + letrozole	letrozole	PFS 8.2 vs. 3.0 months hazard ratio 0.71; 95% CI, 0.53 - 0.96 <i>P</i> = 0.019	38, 39
eLEcTRA				
An Open Label, Randomized Comparison of Femara® 2.5mg Once Daily With or Without Weekly Herceptin® Until Disease Progression as First-line Treatment in Postmenopausal Women With Advanced Breast Cancer	trastuzumab + letrozole	letrozole	median TTP 14.1 vs. 3.3 months hazard ratio 0.67; 95% CI 0.35-1.29, <i>P</i> = 0.23	40
PERTAIN				
A randomized, two-arm, open-label, multicenter phase II trial assessing the efficacy and safety of pertuzumab given in combination with trastuzumab plus an aromatase inhibitor in first-line patients with HER2-positive and hormone receptor-positive metastatic or locally advanced breast cancer	pertuzumab + trastuzumab + AI	trastuzumab + AI	PFS 18.9 vs. 15.8 months hazard ratio 0.65; 95% CI 0.48-0.89 <i>P</i> =0.007	43
ALTERNATIVE				
progression on trastuzumab Phase III, Randomized Study of Dual Human Epidermal Growth Factor Receptor 2 (HER2) Blockade With Lapatinib Plus Trastuzumab in Combination With an Aromatase Inhibitor in Postmenopausal Women With HER2-Positive, Hormone Receptor-Positive Metastatic Breast Cancer: ALTERNATIVE	lapatinib (L) + trastuzumab (T) + AI	lapatinib + AI (L+AI) vs. trastuzumab + AI (T+AI)	median PFS L+T+AI vs. T+AI: 11.0 vs. 5.7 months hazard ratio 0.62, 95% CI 0.45, 0.88 <i>P</i> =0.0064 median PFS L+AI vs. T+AI: 8.3 vs. 5.7 months hazard ratio 0.71, 95% CI 0.51, 0.98 <i>P</i> = 0.0361	44

PFS - progression free survival
AI - aromatase inhibitors
TTP - time to tumor progression

clinical and pathological parameters. The presence of TIL in HER-2-positive tumors may also predict the response of anti-PD1 immunotherapy as indicated by the results of the phase Ib/II PANACEA trial that investigated the efficacy of pembrolizumab in trastuzumab-resistant metastatic breast cancer⁵⁰. In HER-2-positive tumor TIL counts are higher in non-luminal compared to luminal molecular subtypes as indicated in the analyses of CHERLOB (ref.⁵¹) and PAMELA (ref.⁵²) trials that also demonstrated a positive correlation between TIL counts and pCR.

CDK4/6 inhibitors

Cyclin dependent kinase (CDK) 4/6 inhibitors currently represent an effective therapy of ER-positive, HER-2 negative breast cancer⁵³. Regimens of CDK4/6 inhibitors and hormonal agents have also been tested in combination with anti-HER-2 therapy in TPBC.

In the preliminary analysis of the PATRICIA (SOLTI 13-03) trial that tested the addition of palbociclib to trastuzumab with or without letrozole in patients after 2-4 lines of therapy a longer PFS was noted in patients with luminal tumors (defined by PAM50) compared to patients with non-luminal tumors (median 12.4 vs 4.1 months, adjusted hazard ratio = 0.37; *P*=0.052) (ref.⁵⁴). Palbociclib in combination with trastuzumab may represent a safe and effective therapy in previously treated patients with advanced HER-2 positive breast cancer, specifically TPBC. The detection of non-luminal subtypes using PAM50 may aid in identifying the patients who are unlikely to benefit from this therapy, regardless of hormone receptor status.

In the phase II NA-PHER trial the administration of neoadjuvant therapy regimen combining trastuzumab, pertuzumab, palbociclib and fulvestrant (i.e. not containing cytotoxic drugs) in patients with TPBC resulted

in the significant decrease of Ki67 after both 2 weeks and 16 weeks (at surgery). Ki67 expression significantly decreased during therapy. Complete response was observed in 50% of the patients, and the pCR rate was 27%, indicating that the combined strategy aiming at ER and HER-2 may be an effective approach that avoids the use of cytotoxic agents in TPBC (ref.⁵⁵).

PI3K and mTOR inhibitors

The dysregulation of phosphatidylinositol-3-kinase (PI3K) and mammalian target of rapamycin (mTOR) signaling pathways may represent an important mechanism of trastuzumab resistance⁵⁶.

The trials investigating the utilization of the mTOR inhibitor everolimus in HER-2 positive breast cancer (BOLERO-1 and BOLERO-3) brought negative results. Search of predictive biomarkers of response to everolimus indicated that mutation in the PI3K pathway may predict the response to everolimus⁵⁷. A number of PI3K pathway inhibitors are currently tested in patients with HER-2 positive tumors, but none of these compounds has been registered so far and thus cannot be used outside of clinical trials^{58,59}.

CONCLUSION

The distinction between subtypes of HER-2-positive breast cancer may improve prognostication and leads to diversification of therapeutic options. The unique biology of TPBC resulting from interactions between HER-2 and ER is currently being investigated in numerous clinical trials. The efficacy of hormonal agents, anti-HER-2 therapy and cytotoxic drugs in TPBC is, in general, associated with favorable prognosis, and similarly to other luminal tumors, the prognosis during the initial years is favorable while there are more frequent late relapses.

While the distinction between ER-positive and ER-negative HER-2-positive tumors has in the current guidelines only limited therapeutic implications, strategies investigating hormonal therapy in TPBC are being intensively studied in clinical trials of escalation as well of de-escalation of treatment in selected subgroups. An early evaluation of response to neoadjuvant therapy may represent one approach of tailoring the intensity of therapy with the aim of reducing toxicity. Laboratory methods are an indispensable part of patient management in the era of targeted therapies⁶⁰, and molecular testing using multigene platforms is becoming an essential part of therapeutic decisions.

Search strategy and selection criteria:

In this review, we have evaluated studies on the role of the hormone dependency in patients with HER2-positive breast cancer. Scientific articles from 1990 to 2019 were searched using the PubMed and Web of Science databases. All searches were up to date as of June 2019. The search terms used included „breast cancer”, „triple positive”, „HER-2 positivity”, „estrogen receptor”, „progesterone receptor”, „hormonal therapy“, „anti-HER-2 therapy“,

„prognosis“ and „survival“. Only English language papers were reviewed.

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