Prognostic impact of body mass index (BMI) in HER2+ breast cancer treated with anti-HER2 therapies: from preclinical rationale to clinical implications

Francesca Ligorio*, Luca Zambelli*, Giovanni Fucà, Riccardo Lobefaro, Marzia Santamaria, Emma Zattarin, Filippo de Braud and Claudio Vernieri

Abstract: Human Epidermal growth factor Receptor 2 (HER2) overexpression or HER2 gene amplification defines a subset of breast cancers (BCs) characterized by higher biological and clinical aggressiveness. The introduction of anti-HER2 drugs has remarkably improved clinical outcomes in patients with both early-stage and advanced HER2+ BC. However, some HER2+ BC patients still have unfavorable outcomes despite optimal anti-HER2 therapies. Retrospective clinical analyses indicate that overweight and obesity can negatively affect the prognosis of patients with early-stage HER2+ BC. This association could be mediated by the interplay between overweight/obesity, alterations in systemic glucose and lipid metabolism, increased systemic inflammatory status, and the stimulation of proliferation pathways resulting in the stimulation of HER2+ BC cell growth and resistance to anti-HER2 therapies. By contrast, in the context of advanced disease, a few high-quality studies, which were included in a meta-analysis, showed an association between high body mass index (BMI) and better clinical outcomes, possibly reflecting the negative prognostic role of malnourishment and cachexia in this setting. Of note, overweight and obesity are modifiable factors. Therefore, uncovering their prognostic role in patients with early-stage or advanced HER2+ BC could have clinical relevance in terms of defining subsets of patients requiring more or less aggressive pharmacological treatments, as well as of designing clinical trials to investigate the therapeutic impact of lifestyle interventions aimed at modifying body weight and composition. In this review, we summarize and discuss the available preclinical evidence supporting the role of adiposity in modulating HER2+ BC aggressiveness and resistance to therapies, as well as clinical studies reporting on the prognostic role of BMI in patients with early-stage or advanced HER2+ BC.

Keywords: anti-HER2 drugs, BMI, clinical outcomes, HER2+ BC, molecular mechanisms

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Introduction

Human Epidermal growth factor Receptor 2-positive (HER2+) breast cancer (BC) accounts for 20–30% of all BC subtypes. It is defined by Human Epidermal growth factor Receptor 2 (HER2) overexpression or HER2 gene amplification based on an immunohistochemistry (IHC) score for HER2 of 3+, or by an IHC score of 2+ associated with HER2 gene amplification by in situ hybridization (ISH), respectively.1 Of note, HER2+ BC displays an aggressive biological and clinical behavior characterized by high tumor grade and poor patient prognosis in the absence of effective HER2 blockade. According to the expression of hormone receptors (HRs), HER2+ BCs can be classified as HR+/HER2+ [expressing estrogen receptor (ERα) and/or progesterone receptor (PgR) in at least 1% of tumor cells] and HR–/HER2+ (lacking both ERα and PgR expression).
HER2 is a transmembrane glycoprotein and a member of the epidermal growth factor receptor family. It exists as a monomer on cells’ plasma membranes, and it undergoes homodimerization and intracellular domain trans-phosphorylation when it binds its ligands, such as epidermal growth factor (EGF). HER2 heterodimerization with other HER family members, such as HER1 (which is activated by EGF) and HER3, also contributes to HER2 activation. Regardless of the upstream event triggering HER2 dimerization, trans-phosphorylation, and activation, these processes finally lead to the activation of different downstream signaling pathways, primarily the rapidly accelerated fibrosarcoma (RAF)/(Mitogen-Activated Protein Kinase) MAPK, phosphoinositide 3-kinase (PI3K)/Ak strain transforming protein (AKT) (with HER2/HER3 heterodimerization being the most powerful activator), and protein kinase C (PKC) pathways, which, in turn, promote tumor cell proliferation, survival, and angiogenesis.3

The mainstay of HER2+ BC treatment in all disease settings is represented by agents that inhibit HER2 homo- and heterodimerization and/or activation. These drugs include the monoclonal antibodies trastuzumab and pertuzumab; the small tyrosine kinase inhibitor proteins lapatinib, neratinib, and tucatinib; and the antibody-drug conjugates trastuzumab-emtansine (TDM-1) and trastuzumab-duruxtecan. The advent of these anti-HER2 drugs led to significantly increased cure rates in early-stage HER2+ BC and to prolonged patient survival in the metastatic setting. Nevertheless, a non-negligible proportion of early-stage HER2+ BC patients still experiences tumor recurrence after curative surgery, while metastatic BC remains an almost invariably deadly disease.

Different preclinical studies have revealed that HER2+ BC is a lipogenic disease. In particular, fatty acid (FA) de novo biosynthesis and FA uptake crucially contribute to sustain HER2+ BC bioenergetics and resistance to anti-HER2 therapies. However, clinical/translational evidence in this field is lacking, with the only exception of some retrospective studies that revealed an association between intratumor expression of specific metabolic enzymes involved in FA synthesis and patient prognosis. Obesit, as defined as a body mass index (BMI) ≥30 kg/m², and overweight, as defined as a BMI between 25 and 29.9 kg/m², represent not only well-known risk factors for BC development, especially in the post-menopausal age, but also independent negative prognostic factors in patients with early-stage or advanced BC.

Two meta-analyses, the first including 45 studies and the second including 82 studies investigated the association between obesity and BC patient prognosis, showing significantly worse breast cancer–specific survival (BCSS) and overall survival (OS) – with a hazard ratio for both of ~1.3 – in obese as compared with non-obese women, and an association between high BMI and worse BCSS or OS regardless of the time when BMI was ascertained (before versus after BC diagnosis). However, these studies did not perform subgroup analyses according to specific BC subtypes. Recently, a large meta-analysis tried to shed light on this point, showing a detrimental role of obesity on clinical outcomes in patients with all BC subtypes (HR+ BC, HER2+ BC, and Triple Negative BC). However, in all the studies included in this meta-analysis, BMI was measured at diagnosis in patients with early-stage diseases, thus preventing the possibility to evaluate the impact of BMI in patients with advanced BC. Indeed, the literature investigating the BMI-survival association in the metastatic setting is weaker and often contradictory, with initial small studies suggesting a potentially detrimental role of high BMI, while a recent pooled analysis of prospective studies showed a potentially ‘paradoxical’, positive effect of obesity on patient outcomes.

Due to the relevance of identifying modifiable prognostic factors that could crucially impact on patient management and clinical outcomes, here we summarized and discussed the biological bases and the available evidence indicating an association between BMI and prognosis in HER2+ BC patients treated with anti-HER2 drugs.

**Biological background**

Several biological mechanisms might underlie the link between patient adiposity/BMI, systemic lipid metabolism, and clinical outcomes in HER2+ BC patients (Figure 1).

*Insulin receptor and Insulin-like Growth Factor 1 receptor axes*

Insulin is a peptide hormone produced by β cells of the pancreatic islets of Langerhans, and it is secreted in response to increased blood glucose...
Figure 1. Biological mechanisms at the basis of the link between patient adiposity and clinical outcomes in HER2+ BC. Top, left: Increased IGF-1, IGF-2, and insulin levels typical of overweight/obese people could contribute to an overactivation of IR and IGF-1R pathways. These axes in turn lead to the stimulation of PI3K/AKT and MAPK pathways. IGF-1R activation can also stimulate the phosphorylation of HER2 in an Src-dependent manner, and it is able to reverse the p27 Kip1-mediated cell cycle arrest induced by trastuzumab. Finally, IGF-1R induces the expression of FoxM1. Top, right: Leptin, through OB-R, induces the activation of JAK/STAT, MAPK, and PI3K axes; it also can stimulate the expression of cyclin D1, CDK2, and cMyc, as well as of VEGF and VEGF-R2. OB-R can increase HER2 protein levels via STAT3; finally, it can transactivate ERα. Left: Overweight and obesity can affect the pharmacokinetics of anti-HER2 drugs, with an inverse proportional relationship between patient BMI and trastuzumab plasma concentration. Right: In overweight/obese HR+/HER2+ BC patients, an increased activation of the aromatase enzyme in the adipose tissue can lead to increased estradiol concentrations, thus antagonizing the effect of hormonal treatments. Bottom: Given the relevance of plasmatic lipid uptake in modulating HER2+ BC cell growth, proliferation, and resistance to treatments, increased circulating lipid concentrations typical of overweight/obese people could affect HER2+ BC patient outcome.

ACC1, acetyl-CoA carboxylase; AMPK, 5′-adenosine monophosphate-activated protein kinase; ATGs, autophagy-related; BMI, body mass index; CycD1, cyclin D1; ERα, estrogen receptor alpha; ERK, extracellular signal-regulated kinase; FA, fatty acid; FASN, fatty acid synthase; 4EBP1, Eukaryotic Translation Initiation Factor 4E-Binding Protein 1; FoxM1, Forkhead Box M1; Grb2, growth factor receptor-bound protein 2; IGF-1R, Insulin-like Growth Factor 1 receptor; IGF-2R, Insulin-like Growth Factor 2 receptor; IR, insulin receptor; IRS1, insulin receptor substrate 1; LKB1, liver kinase B1; LPL, lipoprotein lipase; MEK, mitogen-activated protein kinase; mTORC1, mammalian Target of Rapamycin Complex 1; OB-R, leptin receptor; PDK1, phosphoinositide-dependent kinase-1; PI2P, phosphatidylinositol 4,5-bisphosphate; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; PTEN, phosphatase and tensin homolog; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma virus; SKP2, S-Phase Kinase Associated Protein 2; SOS, Ras/Rac Guanine Nucleotide Exchange Factor 1; S6K, S6 kinase; TG, triglyceride; TSC1, Tuberous Sclerosis 1; TSC2, Tuberous Sclerosis 2; ULK1, Unc-51 Like Autophagy Activating Kinase 1; VEGF, vascular endothelial growth factor.
levels, thus integrating systemic response to carbohydrate, lipid, and protein metabolism. Insulin-like Growth Factor 1 (IGF-1) and Insulin-like Growth Factor 2 (IGF-2), also known as somatomedines, are anabolic hormones that share structural similarity with insulin; notably, they are mainly produced by the liver in response to increased concentrations of different growth factors, including insulin itself.

Overweight and obesity are associated with systemic resistance to insulin (i.e. an attenuated biological response to normal or elevated insulin levels), higher fasting blood insulin concentration, and, consequently, an increased production of IGF-1 and IGF-2. A large body of preclinical evidence links an increased insulin- and IGF-1-mediated signaling to resistance to anti-HER2 therapies in HER2+ BC cells. The biological activity of insulin, IGF-1, and IGF-2 involves the binding of these ligands to their plasma membrane receptors, of which insulin receptor (IR) and IGF-1 receptor (IGF-1R) are the most relevant ones. IR is frequently overexpressed in BC cell lines and in BC specimens, and it promotes cancer cell proliferation, migration, and inhibition of apoptosis through the activation of the PI3K/AKT and the MAPK pathways. These downstream pathways could also be activated as a result of signaling through IGF-1R, which itself has been shown to be highly overexpressed and/or activated in several BC cells as compared with their normal counterpart.

An enhanced activation of IGF-1R signaling has also been reported as a potential mechanism of acquired resistance to trastuzumab, in that it can activate the PI3K/AKT pathway downstream of HER2 when HER2 is inhibited, finally resulting in an increase of the levels of cyclin D1 and cyclin E through the stimulation of Rb protein phosphorylation, or by inducing IGF-1R/HER2 heterodimerization. In trastuzumab-resistant cells, IGF-1R activation can also stimulate the phosphorylation of HER2 in an Src-dependent manner. Indeed, Src activation has been linked to cancer cell resistance to trastuzumab in various studies, while Src is typically found to be inhibited by trastuzumab in sensitive cells. In trastuzumab-resistant cells, Src promotes tumor cell invasion, possibly through the activation of focal adhesion kinase (FAK). Moreover, IGF-1R overexpression in HER2+ BC cells can reverse trastuzumab-induced cell cycle arrest.

Indeed, in HER2+ BC cells, the activity of the cyclin-dependent kinase inhibitor p27Kip1 is inversely correlated to HER2/neu expression, since HER2 overexpression is associated with reduced expression of p27Kip1 and with ubiquitin-mediated degradation of p27Kip1 protein, while trastuzumab treatment results in an increase in p27Kip1 levels. An enhanced signaling through IGF-1R results in elevated expression of the ubiquitin ligase SKP2, which is responsible for the proteosomal degradation of p27Kip1, which, in turn, antagonizes trastuzumab-induced inhibition of cell growth. Of note, Nahta et al. showed that trastuzumab sensitivity in HER2+ BC cells can be restored by the disruption of IGF-1R/HER2 heterodimerization via IGF-1R blockade, and similar results were reported in other studies. Finally, the expression of Forkhead box protein M1 (FoxM1), which depends on IGF-1R and HER2 activation, has been associated with increased invasiveness in HER2+ BC cells, and it also correlated with poor prognosis in HER2+ BC patients.

Together, the available preclinical evidence points to IR/IGF-1R-mediated signaling as a potential mechanism of HER2+ BC cell resistance to anti-HER2 therapies.

Consistently with preclinical data, high IGF-1R expression or phosphorylation levels in tumor samples have been shown to correlate with lower response rates to neoadjuvant trastuzumab-based bio-chemotherapy in patients with HER2+ BC (50% versus 97%). In addition, high IGF-1R expression has been associated with lower progression-free survival (PFS) in trastuzumab-treated patients with advanced HER2+ BC.

**Leptin and adiponectin**

Leptin is an adipokine mainly produced by adipocytes, placenta, gastric/colonic mucosa, and mammary epithelial cells. Leptin exerts its physiological activities by binding and activating the leptin receptor (OB-R), which, in turn, modulates several downstream transduction pathways. In detail, OB-R can induce the activation of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT), MAPK, and PI3K axes, thus promoting cell proliferation, migration, and apoptosis inhibition. In addition, by activating PKCa, OB-R can induce the expression of several cell cycle regulators, including cyclin D1, cyclin-dependent kinase 2, and c-Myc.
thus promoting cancer cell proliferation. OB-R can also induce the expression of vascular endothelial growth factor (VEGF) and its receptor type two (VEGF-R2), leading to tumor growth and metastatization by promoting tumor-induced angiogenesis. Notably, leptin itself can increase HER2 protein levels through the enhancement of STAT3-mediated expression of the chaperone protein Hsp90. The biological role of leptin axis in HER2+ BC was studied by Fiorio et al., who reported that the co-expression of HER2 and OB-R is common in BC cell lines. In the same work, the authors demonstrated a direct physical interaction between HER2 and OB-R, and they reported on leptin ability to induce HER2 tyrosine phosphorylation and consequent transactivation. In addition, cells expressing high HER2 levels were characterized by low OB-R expression, while moderate HER2 expression correlated with high OB-R expression, thus suggesting that OB-R might reduce tumor cell dependence on HER2 signaling and their sensitivity to anti-HER2 drugs. Finally, OB-R can amplify ER-dependent BC proliferation via trans-activation of ERα. OB-R has been identified in malignant cells of different origin, including lung, stomach, leukemia, and BC, and the correlation between high blood leptin levels and worse BC prognosis has also been demonstrated by different epidemiological studies. In this regard, Ishikawa et al., who evaluated the expression of OB-R by IHC in 76 BC surgical specimens and in normal adjacent mammary tissue, reported that OB-R is expressed in most BC cells, while it is absent in normal breast cells. In addition, they showed a significant association between OB-R expression and the risk of distant tumor relapse, since none of the included patients with OB-R-negative tumors developed distant metastases. Finally, in a series of BC samples, a direct association between leptin/OB-R expression and larger tumor size was shown.

Another important adipokine is represented by adiponectin, which is mainly produced by adipose tissue and acts as an antidiabetic, anti-inflammatory, and cardio-protective hormone. Adiponectin plasma levels are usually low in obese and diabetic patients, and they are inversely associated with insulin resistance and BMI. By binding its receptors AdipoR1 and AdipoR2, adiponectin decreases the phosphorylation of PI3K and AKT, hence suppressing tumor cell proliferation. In addition, adiponectin induces autophagic cell death in BC cells through the activation of the 5′ adenosine monophosphate-activated protein kinase (AMPK)–Unc-51 Like Autophagy Activating Kinase 1 (ULK1) axes. This could justify the association between low adiponectin levels and larger tumor size or worse prognosis in BC patients.

An imbalance between leptin and adiponectin blood levels, which is typically observed in obese patients, can also impact systemic inflammatory status. Indeed, while adiponectin acts as an anti-inflammatory cytokine, leptin induces a pro-inflammatory state by promoting the proliferation of peripheral blood mononuclear cells, by stimulating a T-helper response, and by mediating the production of pro-inflammatory cytokines such as interleukin-2 (IL-2) and interferon-gamma (IFN-γ). High leptin levels have also been shown to stimulate neutrophil differentiation, thus resulting in an increased neutrophil count, and to induce the intratumor recruitment of several immunosuppressor cells, such as T-regulatory cells, myeloid-derived suppressor cells, and tumor-associated macrophages, which are components of the immune system with a well-known pro-tumoral role.

**Lipid metabolism**

The plasmatic levels of several lipids, such as triglycerides, are typically found to be higher in overweight and obese individuals. Cancer cells convert plasma triglycerides into FAs through the sequential action of the lipid-metabolizing enzyme lipoprotein lipase (LPL), which hydrolyzes triglycerides into glycerol and FAs, and the FA transporter, which mediates FA internalization (Figure 1). Of note, CD36 overexpression has been associated with poor cancer prognosis and metastatization in different tumor types.

Lipids play several crucial roles in cancer cells. First, they are structural molecules, since hydrophobic tails of phospholipids and glycolipids, along with cholesterol, represent key components of cell membranes, and they also influence their physical properties, such as fluidity, plasticity, and cell migration. Lipids also play a crucial bioenergetic role via the β-oxidation pathway, in which acetyl-CoA units are removed from FAs to be oxidized in the mitochondrial tricarboxylic acid (TCA) cycle to produce ATP and reducing equivalents.
LPL depletion in HER2 + BC models, and it is associated with worse OS in patients treated with anti-HER2 drugs in the neoadjuvant setting 

More recently, CD36 expression has been associated with tumor immune evasion, showing that CD36 plays a crucial role in modulating Treg cell function. Conversely, CD36-mediated uptake of FAs by tumor-infiltrating CD8+ T cytotoxic cells has been shown to result in reduced cytokine production and impaired antitumor cytotoxic activity, and CD36 expression in CD8+ T cells has been associated with enhanced tumor progression and worse survival in tumor-bearing mice and cancer patients. Of note, the accumulation of different species of FAs, as well as of acyl-carnitines, ceramides, and esterified cholesterol in the tumor microenvironment, likely contributes to an increased CD36 expression in CD8+ tumor-infiltrating lymphocytes, which results in progressive T cell dysfunction. In this view, an increased concentration of plasmatic lipids, which is frequently observed in overweight/obese patients, could contribute to the dysregulation of intratumor lipid metabolism, finally promoting tumor progression and resistance to therapies.

Remarkably, since at least part of the antitumor activity of trastuzumab and pertuzumab is mediated by antibody-dependent cellular cytotoxicity (ADCC), CD36-induced impairment of the activation status of tumor-infiltrating immune cells could crucially contribute to modulate tumor growth and resistance to treatments in HER2+ BC.

**Aromatase expression**

Aromatase, a member of the cytochrome P450 superfamily, is an enzyme that catalyzes the conversion of androgens to estrogens. It is expressed by different tissues, such as gonads, placenta, brain, and stromal cells of adipose...
tissue, with the latter being the main site of extragonadal estrogen formation in non-pregnant premenopausal women, as well as a key source of estrogens in post-menopausal women. Of note, an increased aromatase activity in overweight/obese individuals leads to an enhanced synthesis of peripheral blood estrogens, which could be responsible for the observed increase of BC risk in obese post-menopausal women. Elevated blood estrogen levels have also been associated with worse prognosis in patients with established BC, which is consistent with the association between high BMI and significantly higher rates of local and distant recurrence in BC patients treated with adjuvant anastrozole, a third-generation aromatase inhibitor, or tamoxifen, a selective ER modulator (SERM). This is likely the result of estrogen-mediated activation of the ERα axis, which partially bypasses the biological and antitumor activity of antiestrogens and aromatase inhibitors.

HR+/HER2+ BC accounts for approximately 50% of all HER2+ BCs, and it is characterized by the concomitant activation of ERα and HER2 pathways, which both contribute to stimulate cancer cell growth and proliferation. Since ERα and HER2 axes converge on common downstream pathways that stimulate cancer cell growth and proliferation, HER2 inhibition in HR+/HER2+ BC cells can be compensated by ERα activation and vice versa, thus making HR+/HER2+ BC cells poorly sensitive to single HER2 or ERα inhibition, but exquisitely sensitive to the concomitant blockade of both pathways. In line with the underlying biology, in overweight/obese HR+/HER2+ BC patients, in which aromatase inhibitors and antiestrogens are part of the standard of care therapeutic strategies, an increased expression and activation of the aromatase enzyme in the adipose tissue can be of prognostic relevance.

**Trastuzumab pharmacokinetics**

Anthropometric characteristics of HER2+ BC patients, including overweight and obesity, could significantly affect the pharmacokinetics of anti-HER2 monoclonal antibodies. During the development of trastuzumab, 20 µg/ml was identified as the minimum concentration (Cmin) at which this monoclonal antibody achieves the maximal inhibition of tumor growth. A Spanish prospective study investigated the impact of BMI on trastuzumab pharmacokinetics, administered subcutaneously at the triweekly dose of 600 mg, in 19 patients with non-metastatic HER2+ BC. This study revealed an inverse relationship between patient BMI and trastuzumab plasma concentration, with a Cmin >20 µg/ml being found in 89% of patients with BMI ≤30 kg/m², but only in 10% of patients with BMI >30 kg/m². Moreover, all patients with a weight ≤65 kg had a Cmin >20 µg/ml and no patients weighting >80 kg reached a Cmin >20 µg/ml. Although preliminary, these data indicate that overweight/obese patients could be exposed to reduced trastuzumab concentrations, thus potentially achieving lower clinical benefit from trastuzumab-based therapy.

**Clinical evidence**

Impact of BMI on clinical outcomes in early-stage HER2+ BC

Different studies have investigated the association between BMI and the prognosis of HER2+ BC patients receiving adjuvant or neoadjuvant chemotherapy (Table 1). In the adjuvant setting, Cantini et al. evaluated the correlation between overweight, defined as a BMI ≥25 kg/m², and distant-disease-free survival (DDFS) in 279 early-stage (I–III) HER2+ BC patients treated with adjuvant trastuzumab between 2006 and 2016. In this retrospective study, the authors found a significant correlation between high BMI and worse DDFS, which was limited to the HR−/HER2+ BC cohort. These findings were consistent with results of the study by Mazzarella et al., who published the results of a large retrospective analysis evaluating the impact of obesity on clinical outcomes in 1250 early HER2+ BC patients treated before the introduction of trastuzumab.

In a recently published retrospective series of 505 HER2+ stage I–III BC patients treated with adjuvant trastuzumab-based bio-chemotherapy at Fondazione IRCCS Istituto Nazionale dei Tumori, higher BMI was associated with significantly worse RFS (relapse-free survival) and OS at both univariate and multivariate analysis in the whole study cohort. However, when patients were classified according to tumor HR status, the association between high BMI and worse prognosis was only observed in patients with HR-negative disease, which is consistent with results of previously published studies.
Table 1. Clinical studies investigating the impact of BMI on HER2+ BC prognosis.

| Reference       | Type of study                      | Patients (n) | Setting   | Anti-HER2 therapy                                      | BMI categorization                                                                 | Findings                                                                                                                                   |
|-----------------|------------------------------------|--------------|-----------|--------------------------------------------------------|------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| Cantini et al.  | Retrospective                      | 279          | Adjuvant  | Chemotherapy + trastuzumab                             | BMI < 18.5 kg/m²<br>BMi ≥ 18.5 < 25 kg/m²<br>BMi ≥ 25 < 30 kg/m²<br>BMi ≥ 30 kg/m² | Worse 3-year DDFS in HR−/BMI ≥ 25 patients versus others (hazard ratio: 1.79)                                                                              |
| Ligorio et al.  | Retrospective                      | 505          | Adjuvant  | Chemotherapy + trastuzumab                             | BMI < 27.77 kg/m²<br>BMi ≥ 27.77 kg/m²                                             | Whole population<br>Worse RFS in high versus low BMI patients (hazard ratio: 2.26)<br>Worse OS in high versus low BMI patients (hazard ratio: 2.25)<br>HR−/HER2 subtype<br>Worse RFS in high versus low BMI patients (hazard ratio: 2.20) |
| Crozier et al.  | Analysis of a phase III, randomized| 3505         | Adjuvant  | Arm A: chemotherapy + sequential weekly trastuzumab<br>Arm B: chemotherapy + concomitant weekly trastuzumab | BMI < 25 kg/m²<br>BMi ≥ 25 < 30 kg/m²<br>BMi ≥ 30 kg/m²                             | Worse DFS in overweight versus normal weight patients (hazard ratio: 1.30)<br>Worse DFS in obese versus normal weight patients (hazard ratio: 1.31)<br>No association with BCSS |
| Martel et al.   | Analysis of a phase III, randomized| 3505         | Adjuvant  | Arm A: lapatinib<br>Arm B: trastuzumab<br>Arm C: trastuzumab followed by lapatinib<br>Arm D: trastuzumab + lapatinib | BMI < 18.5 kg/m²<br>BMi ≥ 18.5 < 25 kg/m²<br>BMi ≥ 25 < 30 kg/m²<br>BMi ≥ 30 kg/m² | Whole population<br>Worse DDFS in obese versus normal weight patients (hazard ratio: 1.25)<br>Worse OS in obese versus normal weight patients (hazard ratio: 1.27)<br>Post-menopausal women<br>Worse DDFS, DFS, and OS in obese versus normal weight patients (hazard ratio: 1.27)<br>HR−/HER2 subtype<br>Worse DDFS in obese and overweight versus normal weight patients |
| Yerushalmi et al.| Analysis of a phase III, randomized| 1249         | Adjuvant  | Arm A: chemotherapy + sequential 1-year trastuzumab<br>Arm B: chemotherapy + sequential 2-year trastuzumab | BMI as a continuous variable                                                       | No association with BCFI or OS                                                                                                             |
| Cecchini et al. | Analysis of a phase III, randomized| 2119         | Adjuvant  | Arm A: chemotherapy + concomitant weekly trastuzumab    | BMI < 25 kg/m²<br>BMi ≥ 25 < 30 kg/m²<br>BMi ≥ 30 kg/m²                             | No association with RFS or OS                                                                                                               |

(Continued)
| Reference          | Type of study                  | Patients (n) | Setting  | Anti-HER2 therapy                                    | BMI categorization | Findings                                                                                                                                 |
|--------------------|--------------------------------|--------------|----------|------------------------------------------------------|--------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Di cosimo et al.   | Analysis of a phase III, randomized prospective trial | 455          | Neoadjuvant | Arm A: lapatinib  
Arm B: trastuzumab  
Arm C: lapatinib + trastuzumab                          | BMI < 25 kg/m²  
BMI ≥ 25 < 30 kg/m²  
BMI ≥ 30 kg/m²     | HR+/HER2+ subgroup – higher pCR rate in normal weight versus overweight/obese patients, OR = 0.56 (p = 0.054) |
| Krasniqi et al.    | Retrospective                  | 709          | Metastatic | Pertuzumab-based therapy/T-DM1                        | BMI < 25 kg/m²  
BMI ≥ 25 < 30 kg/m²  
BMI ≥ 30 kg/m²     | Worse OS in obese versus non-obese patients [hazard ratio: 1.29]  
Worse PFS in obese versus non-obese patients, limited to patients with low burden disease and progression within the first 6 months |
| Parolin et al.     | Retrospective                  | 52           | Metastatic | Trastuzumab-based therapy                            | BMI < 25 kg/m²  
BMI ≥ 25 < 30 kg/m²  
BMI ≥ 30 kg/m²     | Worse TTP in normal weight versus overweight versus obese patients [7 versus 7.5 versus 12 months]  
Worse OS in normal weight versus overweight versus obese patients [39 versus 54 versus 67 months] |
| Martel et al.      | Retrospective                  | 329          | Metastatic | Trastuzumab-based therapy                            | BMI < 25 kg/m²  
BMI ≥ 25 kg/m²      | No association with overweight/obesity [BMI ≥ 25 kg/m²] and PFS/OS |
| Modi et al.        | Pooled analysis of clinical trials | 3496        | Metastatic | Trastuzumab or Pertuzumab-based therapy/ T-DM1-based therapy | BMI < 18.5 kg/m²  
BMI ≥ 18.5 < 25 kg/m²  
BMI ≥ 25 < 30 kg/m²  
BMI ≥ 30 kg/m²     | Better OS in obese and overweight versus normal weight patients [hazard ratios: 0.85 and 0.82, respectively]  
Better PFS in obese and overweight versus normal weight patients [hazard ratios: 0.91 and 0.87, respectively] |

BC, breast cancer; BCFI, breast cancer-free interval; BCSS, breast cancer-specific survival; BMI, body mass index; DDFS, distant-disease-free survival; DFS, disease-free survival; HER2+, Human Epidermal growth factor Receptor 2-positive; HR, hormone receptor; OR, odds ratio; OS, overall survival; pCR, pathological complete response; PFS, progression-free survival; RFS, relapse-free survival; TTP, time to progression.
The detrimental impact of high BMI on the prognosis of patients receiving adjuvant trastuzumab was also demonstrated by a post hoc analysis of the prospective N9831 trial.\textsuperscript{121} This study enrolled more than 3500 early-stage HER2\textsuperscript{+} BC patients, who were randomly assigned to one of three treatment arms: arm A (control group), consisting of triweekly doxorubicin plus cyclophosphamide for 4 cycles, followed by weekly paclitaxel for 12 cycles; arm B (the sequential arm), in which patients received the same chemotherapy backbone, followed by trastuzumab for 1 year; and arm C (the concurrent arm), in which patients received chemotherapy concomitant with trastuzumab, followed by trastuzumab alone for additional 40 weeks. In the post hoc analysis, patients were categorized according to their BMI in normal weight (BMI < 18.50 kg/m\textsuperscript{2}), overweight (BMI between 25 and 29.9 kg/m\textsuperscript{2}), and obese (BMI $\geq$ 30 kg/m\textsuperscript{2}). Among 3017 evaluable patients, significantly worse DFS was observed in overweight and obese patients when compared with normal weight patients. Despite the large number of patients included, no statistically significant differences in clinical outcomes were reported according to BMI intervals in individual treatment arms, which could be explained by the fact that these analyses were underpowered.

Similarly, Martel et al. studied the association between HER2\textsuperscript{+} BC patient BMI and clinical outcomes in the ALTTO BIG 2-06 trial population.\textsuperscript{122} ALTTO was a randomized phase III study that investigated the role of adjuvant trastuzumab and/or lapatinib in 8381 patients with early-stage HER2\textsuperscript{+} BC. Specifically, patients were randomized to one of four treatment arms: trastuzumab alone, lapatinib alone, trastuzumab for 12 weeks followed by lapatinib for 34 weeks, or the combination of trastuzumab and lapatinib. BMI categories were defined as underweight (<18.50 kg/m\textsuperscript{2}), normal weight (BMI $\geq$ 18.50 and <25 kg/m\textsuperscript{2}), overweight (BMI $\geq$ 25 and <30 kg/m\textsuperscript{2}), and obese (BMI $\geq$ 30 kg/m\textsuperscript{2}). Obesity at baseline was associated with worse DDFS and OS, but not with worse DFS. The impact of BMI on patient prognosis was then evaluated according to menopausal and HR status; the authors found that obesity negatively affected DDFS, OS, and DFS only in post-menopausal patients, while both obesity and overweight were associated with worse DDFS only in the subgroup of patients with HR tumors, in line with the previously reported studies.\textsuperscript{118-120}

In contrast with data summarized and discussed so far, post hoc analyses of other adjuvant prospective trials – namely, the HERceptin Adjuvant (HERA) and the NSABP B-31 trials – failed to show a significant association between high BMI and the risk of tumor relapse in surgically resected HER2\textsuperscript{+} BC patients receiving adjuvant trastuzumab. Specifically, in the HERA trial, which randomized surgically resected HER2\textsuperscript{+} BC patients to 2 years of adjuvant trastuzumab, 1 year of trastuzumab, or observation after the completion of standard chemotherapy, neither baseline BMI nor BMI changes during the study treatment were associated with breast cancer–free interval (BCFI), BCSS, or OS in 1249 patients enrolled in the 1-year trastuzumab arm for whom BMI data were available.\textsuperscript{123} Similarly, an analysis of the NSABP B-31 trial, which randomized early-stage HER2\textsuperscript{+} BC patients to receive adjuvant doxorubicin plus cyclophosphamide followed by paclitaxel $\pm$ trastuzumab, did not show an association between overweight/obesity and the risk of tumor relapse or OS, neither in the whole patient population nor according to treatment group or ER status.\textsuperscript{124}

It is not easy to explain the conflicting results emerging from this analysis of the NSABP B-31 study and those from the N9831 study, especially because these trials have similar designs and employed the same anti-HER2 treatment schedules. However, the lower number of trastuzumab-treated patients in the NSABP B-31 trial (around 1000 patients versus 1800 patients of the N9831), the different paclitaxel schedule (weekly versus triweekly), and the characteristics of included patients (only node positive in the NSABP B-31 versus either node positive or negative in the N9831 trial) could at least in part account for the observed discrepancies. Regarding the sub-analysis of the HERA trial, the lack of categorization of patient BMI, which was evaluated as a continuous variable, might have in part affected the study results. Indeed, a recent study evaluating updated survival data from more than 5000 patients included in the HERA trial, and which categorized patients in two BMI groups – namely, BMI $\geq$ 25 and <25 kg/m\textsuperscript{2} patients, respectively, actually reported an association between overweight/obesity and worse patient OS.\textsuperscript{23}

Several of the aforementioned studies were included in a very recent meta-analysis that investigated the impact of BMI on OS and DFS in non-metastatic patients with different BC
subtypes (HR+ BC, HER2+ BC, and Triple Negative BC). This study showed that obesity, but not overweight, was associated with worse HER2+ BC patient OS and DFS. Of note, this association was not observed when patients were further classified according to HR status or to the adjuvant treatment received, possibly due to the limited number of patients included in the sub-analyses.22

In the neoadjuvant setting, the available clinical evidence about a potential impact of BMI on patient prognosis is much weaker. Recently, Di Cosimo et al.125 explored the association between BMI and clinical outcomes in early-stage HER2+ BC patients enrolled in the NeoALTTO trial. In this randomized, multicentric, phase III trial, 455 patients were randomly assigned to one of three parallel neoadjuvant treatment groups: daily oral lapatinib, intravenous trastuzumab every 3 weeks, or lapatinib plus trastuzumab. Anti-HER2 blockade was given alone for the first 6 weeks, followed by the addition of weekly paclitaxel for further 12 weeks, before definitive surgery. The rate of pathological complete response (pCR) was the primary endpoint of the NeoALTTO trial. In the analysis reported by Di Cosimo et al., patients were classified according to baseline BMI as underweight (BMI < 18.5 kg/m²), normal weight (BMI between 18.5 and 24.9 kg/m²), overweight (BMI between 25 and 29.9 kg/m²), and obese (BMI ≥ 30 kg/m²). In the whole patient cohort, BMI did not predict pCR rate both at univariate and multivariate analysis; conversely, when patients were evaluated according to tumor HR status, overweight and obesity were found to be independently associated with a significantly lower probability to achieve pCR only in patients with HR+/HER2+ disease. In this study, no data regarding the association between BMI and survival outcomes (i.e. DFS, OS) were reported.

Considering neoadjuvant and adjuvant analyses together, most studies published so far reported an association between high BMI and lower pathological responses or worse clinical outcomes in early-stage HER2+ BC patients treated with anti-HER2 therapies. Regarding the role of HR status in affecting the prognostic role of patient BMI in early-stage HER2+ BC, the available evidence is less conclusive. Indeed, while several studies conducted in the adjuvant setting suggest that the negative prognostic role of BMI might be limited to patients with HR−/HER2+ tumors, the recently published analysis of the neoadjuvant NeoALTTO trial indicated a negative impact of high BMI on pathological responses only in HR+/HER2+ BC patients.

Impact of BMI on clinical outcomes in metastatic HER2+ BC

While a large body of literature supports the role of overweight/obesity as a negative prognostic/predictive factor in early-stage HER2+ BC, only a few studies have investigated the impact of BMI in the metastatic setting (Table 1). In addition, most of these studies are characterized by a small sample size or methodological limitations, or they explored the impact of patient BMI on patient OS rather than PFS, thus precluding the possibility to conclude about the role of overweight/obesity on the efficacy of specific anti-HER2 therapies.126,127 Interestingly, the only large study with a clear clinical endpoint published so far supports an apparently paradoxical, positive prognostic role of overweight and obesity in advanced HER2+ BC.23 Here we summarize the main findings of studies that explored the prognostic role of HER2+ BC BMI in the advanced disease setting so far, highlighting their strengths and limitations.

Krasniqi et al.126 investigated the prognostic role of BMI in 709 metastatic HER2+ BC patients receiving pertuzumab-based therapy and/or T-DM1. In this retrospective, multicentric observational study, obesity was associated with significantly worse OS, but no significant association between BMI and PFS was found. Similarly, in 52 metastatic HER2+ BC patients treated with trastuzumab-based therapy, Parolin et al.127 found an association between high BMI and significantly worse time-to-progression (7 versus 12 months, respectively) in obese versus overweight versus normal weight patients, whereas Martel et al.128 failed to find an association between overweight/obesity (BMI ≥ 25 kg/m²) and PFS/OS in 329 consecutive, metastatic HER2+ BC patients treated with first-line trastuzumab-based regimens. However, the fact that Krasniqi et al. defined OS as the time between BC diagnosis and patient death, rather than as the time between the initiation of first-line treatment for advanced disease and patient death, strongly limits the study conclusions. On the contrary, the study by Parolin et al. only included a very small number of patients, and it has been only published as an abstract.
More recently, Modi et al. published the results of a pooled analysis of data from phase III, randomized clinical trials (CLEOPATRA, MARIANNE, EMILIA, and TH3RESA) that included a total number of 3496 patients with advanced HER2+ BC. In this analysis, the authors found that, when compared with normal weight patients, overweight and obese patients had significantly better PFS (hazard ratios: 0.91 and 0.87, respectively) and OS (hazard ratios: 0.85 and 0.82, respectively).

This obesity ‘paradox’ has been consistently shown in other studies, including metastatic BC patients, as well as patients with other cancer types. The observed differential impact of high BMI on OS in early versus advanced HER2+ BC suggests that the interplay between tumor extrinsic variables, such as adiposity, and clinical outcomes is more complex in patients with advanced disease. For instance, overweight/obese patients with advanced HER2+ BC may be more protected from the risk of cancer-associated cachexia (linked to the advanced disease and resulting in unintentional weight loss), thus compensating the potential effect of obesity (and its associated metabolic/immunological dysfunctions) on promoting HER2+ BC growth and proliferation. Intriguingly, in the study by Modi et al., the association between high BMI and better patient outcome was independent of ECOG performance status and of plasma albumin levels (characteristics that may reflect the status of cancer-associated cachexia), suggesting the need to fully understand the mechanism underlying the ‘obesity paradox’. Due to the low number of studies published in this setting, the potential prognostic role of BMI in patients with metastatic HER2+ BC remains unclear, and further large studies are needed.

Conclusion

Different biological mechanisms underlie the negative impact of increased adiposity on clinical outcomes in HER2+ BC patients. These mechanisms include higher blood insulin, IGF-1 and IGF-2 levels and enhanced IR/IGF-R1 signaling in cancer cells, increased blood leptin and reduced adiponectin levels, an increased concentration of several lipids potentially affecting HER2+ BC growth and response to anti-HER2 therapies, a status of enhanced systemic inflammation, an increased expression of aromatase in cancer cells, and alterations in trastuzumab pharmacokinetics resulting in modifications of its bioavailability.

Of note, the negative impact of high BMI on HER2+ BC patient OS is supported by clinical evidence in the (neo)adjuvant setting, while an ‘obesity paradox’ has been described for patients with HER2+ metastatic BC, in which higher BMI might be associated with better survival.

The solidity of preclinical evidence supporting a link between adiposity-associated metabolic changes and enhanced HER2+ BC progression, together with published clinical studies, highlights the importance of body weight control, accomplished through a healthy diet and regular physical exercise, as part of the management of early-stage HER2+ BC. In this view, it may be useful to implement programs of structured lifestyle interventions in this context. These strategies, which require an active engagement, also represent a promotion of patient participation in the therapeutic process (patient empowerment). In addition, a broader and more solid elucidation of the biological mechanisms underlying the association between overweight/obesity and poor patient survival in the context of limited-stage disease could pave the way to develop specific pharmacological or dietary interventions to be combined with standard treatments in order to improve cure rates in early-stage diseases. Conversely, the understanding of the mechanisms underlying the ‘obesity paradox’ in the metastatic setting could help design adequate nutritional support strategies to prevent patient malnutrition or potentially detrimental alterations in body composition, such as sarcopenia or sarcopenic obesity.

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Author contributions

Francesca Ligorio: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Validation; Visualization; Writing – original draft; Writing – review & editing.

Luca Zambelli: Data curation; Investigation; Methodology; Writing – original draft.
Giovanni Fucà: Data curation; Investigation; Methodology; Writing – review & editing.

Riccardo Lobefaro: Investigation; Writing – review & editing.

Marzia Santamaria: Investigation; Writing – review & editing.

Emma Zattarin: Data curation; Writing – review & editing.

Filippo De Braud: Funding acquisition; Methodology; Resources; Writing – review & editing.

Claudio Vernieri: Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing – review & editing.

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