Ther Adv Med Oncol
2022, Vol. 14: 1–18
DOI: 10.1177/17588359221079123

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

Received: 2 December 2021; revised manuscript accepted: 21 January 2022.

Correspondence to:
Francesca Ligorio
Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Venezian 1, 20133 Milan, Italy.
francesca.ligorio@istitutotumori.mi.it

Claudio Vernieri
Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Venezian 1, 20133 Milan, Italy.
claudio.vernieri@istitutotumori.mi.it
claudio.vernieri@ifom.eu

Fondazione Istituto FIRC di Oncologia Molecolare (IFOM), Milan, Italy

Luca Zambelli
Giovanni Fucà
Riccardo Lobefaro
Emma Zattarin
Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Marzia Santamaria
Fondazione Istituto FIRC di Oncologia Molecolare (IFOM), Milan, Italy

Filippo de Braud
Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy

*Francesca Ligorio and Luca Zambelli contributed equally to this work.

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).[2] 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[4] and pertuzumab;[5] the small tyrosine kinase inhibitor proteins lapatinib,[6] neratinib,[7] and tucatinib;[8] and the antibody-drug conjugates trastuzumab-emtansine (TDM-1)[9] and trastuzumab-deruxtecan.[10] The advent of these anti-HER2 drugs led to significantly increased cure rates in early-stage HER2+ BC[4,11–13] and to prolonged patient survival in the metastatic setting.[5–10,14] 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.[15] 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.[16] Obesity, as defined as a body mass index (BMI) $\geqslant$30 kg/m^2, and overweight, as defined as a BMI between 25 and 29.9 kg/m^2,[17] 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.[18,19]

Two meta-analyses, the first including 45 studies[20] and the second including 82 studies,[21] investigated the association between obesity and BC patient prognosis, showing significantly worse breast cancer–specific survival (BCSS) and overall survival (OS) – with an 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).[22] 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[23] 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,[24] and it is secreted in response to increased blood glucose

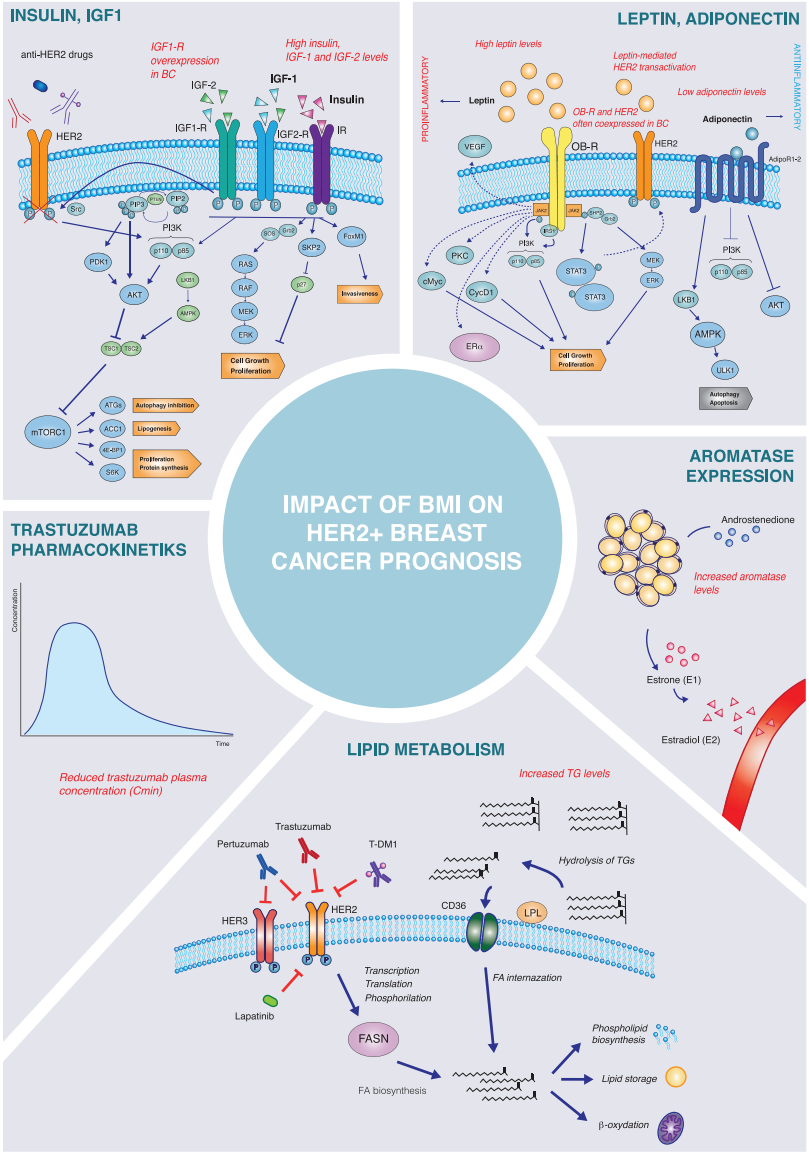

Figure 1. Biological mechanisms at the basis of the link between patient adiposity and clinical outcomes in HER2+ BC. Top, left: Increased IGF-1, IGF-2, and insulin levels typical of overweight/obese people could contribute to an overactivation of IR and IGF-1R pathways. These axes in turn lead to the 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 kinase; mTORC1, mammalian Target of Rapamycin Complex 1; OB-R, leptin receptor; PDK1, phosphoinositide-dependent kinase-1; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-trisphosphate; 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,[25] lipid,[26] and protein[27] 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.[28]

Overweight and obesity are associated with systemic resistance to insulin (i.e. an attenuated biological response to normal or elevated insulin levels),[29] higher fasting blood insulin concentration,[30,31] 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,[32,33] and it promotes cancer cell proliferation, migration, and inhibition of apoptosis through the activation of the PI3K/AKT and the MAPK pathways.[34,35] These downstream pathways could be also activated as a result of signaling through IGF-1R, which itself has been shown to be highly overexpressed[36,37] and/or activated[38] 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,[39,40] 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,[41] 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.[42] Indeed, Src activation has been linked to cancer cell resistance to trastuzumab in various studies,[43–45] while Src is typically found to be inhibited by trastuzumab in sensitive cells.[46] In trastuzumab-resistant cells, Src promotes tumor cell invasion, possibly through the activation of focal adhesion kinase (FAK).[47] 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 $p27^{Kip1}$ is inversely correlated to HER2/neu expression, since HER2 overexpression is associated with reduced expression of $p27^{Kip1}$ and with ubiquitin-mediated degradation of $p27^{Kip1}$ protein,[48] while trastuzumab treatment results in an increase in $p27^{Kip1}$ levels. An enhanced signaling through IGF-1R results in elevated expression of the ubiquitin ligase SKP2, which is responsible for the proteasomal degradation of $p27^{Kip1}$, which, in turn, antagonizes trastuzumab-induced inhibition of cell growth.[49] Of note, Nahta *et al.*[40] 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.[50–52] Finally, the expression of Forkhead box protein M1 (FoxM1), which depends on IGF-1R and HER2 activation,[42] has been associated with increased invasiveness in HER2+ BC cells, and it also correlated with poor prognosis in HER2+ BC patients.[53,54]

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%).[55] In addition, high IGF-1R expression has been associated with lower progression-free survival (PFS) in trastuzumab-treated patients with advanced HER2+ BC.[56]

Leptin and adiponectin

Leptin is an adipokine mainly produced by adipocytes,[57] placenta,[58] gastric/colonic mucosa,[59] and mammary epithelial cells.[60] 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,[61] thus promoting cell proliferation, migration, and apoptosis inhibition. In addition, by activating PKCα, OB-R can induce the expression of several cell cycle regulators, including cyclin D1, cyclin-dependent kinase 2,[62] and c-Myc,[63]

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),[64] 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.[65] The biological role of leptin axis in HER2+ BC was studied by Fiorio *et al.*,[66] 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* transactivation of ERα.[67] OB-R has been identified in malignant cells of different origin, including lung,[68] stomach,[69] leukemia,[70] and BC, and the correlation between high blood leptin levels and worse BC prognosis has also been demonstrated by different epidemiological studies.[71,72] 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.[73]

Another important adipokine is represented by adiponectin, which is mainly produced by adipose tissue[74] and acts as an antidiabetic, anti-inflammatory, and cardio-protective hormone.[75] Adiponectin plasma levels are usually low in obese and diabetic patients, and they are inversely associated with insulin resistance[76] and BMI.[75] By binding its receptors AdipoR1 and AdipoR2, adiponectin decreases the phosphorylation of PI3K and AKT,[77] 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.[78] This could justify the association between low adiponectin levels and larger tumor size or worse prognosis in BC patients.[79]

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).[80,81] 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,[82,83] 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.[84,85] 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.[86,87]

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 (nicotinamide adenine dinucleotide

– NADH, falvin adenin dinucleotide – FADH2). FAs can also modulate intracellular signaling pathways involved in proliferation and survival,[88] acting as precursor of second messengers, such as phosphatidyl inositols,[89] which participate in the activation of several signaling molecules, for example, rat sarcoma virus (RAS) farnesylation.[90] Finally, lipids play a key role in modulating systemic inflammation. For instance, eicosanoids are known to be key immunomodulators mediating the crosstalk between epithelial cells and stromal cells in the tumor microenvironment,[91] and they contribute to the functional maturation of immunosuppressive regulatory T cells (Treg).

In parallel to FA uptake from the extracellular environment, another important source of FAs for cancer cells is their synthesis, which occurs through three sequential reactions that lead to the conversion of citrate to acetyl-CoA, malonyl-CoA, and, finally, to long-chain FAs through the enzymatic activity of fatty acid synthase (FASN). FASN is frequently overexpressed in several malignancies,[92] and its overexpression in human breast epithelial cells is sufficient to induce a malignant-like phenotype.[93] In addition, FASN has been shown to protect cancer cells from anticancer drug–induced oxidation and apoptosis,[94] and its overexpression is associated with more aggressive tumor biology and clinical course. Of note, FASN is frequently overexpressed and/or activated in approximately 85% of HER2+ BC, which typically displays a lipogenic phenotype that crucially sustains tumor cell growth, proliferation, dissemination, and resistance to pharmacological treatments.[92,95] In HER2+ BC models, FASN-induced biosynthesis of FAs promotes the interaction between HER2 and other signaling proteins at lipid raft domains, resulting in an enhanced activation of the PI3K–AKT–mechanistic target of rapamycin (mTOR) pathway. Moreover, FASN stimulates *HER2* gene transcription and HER2 protein expression. In addition, FASN transfection in mammary cells was shown to activate HER2 *via* phosphorylation of its tyrosine residues,[93] while FASN inhibition resulted in reduced transcription of the *HER2* gene.[95] While FASN promotes HER2 expression and activation through different mechanisms, HER2-mediated signaling results in FASN overexpression and enhanced FASN activation, thus generating a positive feedback loop (PFL) of reciprocal stimulation between HER2 and FASN, which potentiates both HER2 and FASN activity.[16,93] As a consequence of this PFL, pharmacological inhibition of HER2 (e.g. through trastuzumab or lapatinib) reduces FASN activity and FA biosynthesis,[96] thus making HER2+ BC cells dependent on the uptake of FAs from the extracellular environment and, as such, dependent on LPL and CD36.[97] The relevance of LPL/CD36 in HER2+ BC growth, proliferation, and survival is supported by preclinical and clinical evidence. Indeed, *in vitro* LPL depletion in HER2+ BC cells hampers tumor cell proliferation.[98] Furthermore, high CD36 expression has been shown to mediate acquired resistance to lapatinib in preclinical HER2+ BC models, and it is associated with worse OS in patients treated with anti-HER2 drugs in the neoadjuvant setting[99] (Ligorio *et al.*, under revision).

More recently, CD36 expression has been associated with tumor immune evasion, showing that CD36 plays a crucial role in modulating Treg cell function.[100] 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.[101] Of note, the accumulation of different species of FAs, as well as of acyl-carnitines, ceramides, and esterified cholesterol in the tumor microenvironment,[102,103] likely contributes to an increased CD36 expression in CD8+ tumor-infiltrating lymphocytes, which results in progressive T cell dysfunction.[104] 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),[105] 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.[106] It is expressed by different tissues, such as gonads, placenta, brain, and stromal cells of adipose

tissue,[107] 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,[108] which could be responsible for the observed increase of BC risk in obese post-menopausal women.[109] Elevated blood estrogen levels have also been associated with worse prognosis in patients with established BC,[110,111] 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).[112] 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,[14,113,114] 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.[115] 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,[116] 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 (C_{min}) at which this monoclonal antibody achieves the maximal inhibition of tumor growth. A Spanish prospective study[117] 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 C_{min} >20 μg/ml being found in 89% of patients with BMI ⩽30 kg/m^2, but only in 10% of patients with BMI >30 kg/m^2. Moreover, all patients with a weight ⩽65 kg had a C_{min} >20 μg/ml, and no patients weighting ⩾80 kg reached a C_{min} >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 bio-chemotherapy (Table 1). In the adjuvant setting, Cantini *et al.*[118] evaluated the correlation between overweight, defined as a BMI ⩾25 kg/m^2, 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.*,[119] 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.[120] 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.[118,119]

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.*[118]	Retrospective	279	Adjuvant	Chemotherapy + trastuzumab	BMI <18.5 kg/m^2 BMI ⩾18.5 <25 kg/m^2 BMI ⩾25 <30 kg/m^2 BMI ⩾30 kg/m^2	Worse 3-year DDFS in HR−/BMI ⩾25 patients *versus* others (hazard ratio: 1.79)
Ligorio *et al.*[120]	Retrospective	505	Adjuvant	Chemotherapy + trastuzumab	BMI <27.77 kg/m^2 BMI ⩾27.77 kg/m^2	*Whole population* Worse RFS in high *versus* low BMI patients (hazard ratio: 2.26) Worse OS in high *versus* low BMI patients (hazard ratio: 2.25) *HR−/HER2 subtype* Worse RFS in high *versus* low BMI patients (hazard ratio: 2.20)
Crozier *et al.*[121]	Analysis of a phase III, randomized prospective trial	3505	Adjuvant	Arm A: chemotherapy Arm B: chemotherapy + sequential weekly trastuzumab Arm C: chemotherapy + concomitant weekly trastuzumab	BMI <25 kg/m^2 BMI ⩾25 <30 kg/m^2 BMI ⩾30 kg/m^2	Worse DFS in overweight *versus* normal weight patients (hazard ratio: 1.30) Worse DFS in obese *versus* normal weight patients (hazard ratio: 1.31) No association with BCSS
Martel *et al.*[122]	Analysis of a phase III, randomized prospective trial	3505	Adjuvant	Arm A: lapatinib Arm B: trastuzumab Arm C: trastuzumab followed by lapatinib Arm D: trastuzumab + lapatinib	BMI <18.5 kg/m^2 BMI ⩾18.5 <25 kg/m^2 BMI ⩾25 <30 kg/m^2 BMI ⩾30 kg/m^2	*Whole population* Worse DDFS in obese *versus* normal weight patients (hazard ratio: 1.25) Worse OS in obese *versus* normal weight patients (hazard ratio: 1.27) *Post-menopausal women* Worse DDFS, DFS, and OS in obese *versus* normal weight patients *HR−/HER2 subtype* Worse DDFS in obese and overweight *versus* normal weight patients
Yerushalmi *et al.*[123]	Analysis of a phase III, randomized prospective trial	1249	Adjuvant	Arm A: chemotherapy Arm B: chemotherapy + sequential 1-year trastuzumab Arm C: chemotherapy + sequential 2-year trastuzumab	BMI as a continuous variable	No association with BCFI or OS
Cecchini *et al.*[124]	Analysis of a phase III, randomized prospective trial	2119	Adjuvant	Arm A: chemotherapy Arm B: chemotherapy + concomitant weekly trastuzumab	BMI <25 kg/m^2 BMI ⩾25 <30 kg/m^2 BMI ⩾30 kg/m^2	No association with RFS or OS

(Continued)

Table 1. (Continued)

Reference	Type of study	Patients (*n*)	Setting	Anti-HER2 therapy	BMI categorization	Findings
Di cosimo *et al.*[125]	Analysis of a phase III, randomized prospective trial	455	Neoadjuvant	Arm A: lapatinib Arm B: trastuzumab Arm C: lapatinib + trastuzumab	BMI <25 kg/m^2 BMI $\geqslant 25$ <30 kg/m^2 BMI $\geqslant 30$ kg/m^2	HR+/HER2+ subgroup – higher pCR rate in normal weight *versus* overweight/obese patients, OR = 0.56 ($p = 0.054$)
Krasniqi *et al.*[126]	Retrospective	709	Metastatic	Pertuzumab-based therapy/T-DM1	BMI <25 kg/m^2 BMI $\geqslant 25$ <30 kg/m^2 BMI $\geqslant 30$ kg/m^2	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.*[127]	Retrospective	52	Metastatic	Trastuzumab-based therapy	BMI <25 kg/m^2 BMI $\geqslant 25$ <30 kg/m^2 BMI $\geqslant 30$ kg/m^2	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.*[128]	Retrospective	329	Metastatic	Trastuzumab-based therapy	BMI <25 kg/m^2 BMI $\geqslant 25$ kg/m^2	No association with overweight/obesity (BMI $\geqslant 25$ kg/m^2) and PFS/OS
Modi *et al.*[23]	Pooled analysis of clinical trials	3496	Metastatic	Trastuzumab- or Pertuzumab-based therapy T-DM1-based therapy	BMI <18.5 kg/m^2 BMI $\geqslant 18.5$ <25 kg/m^2 BMI $\geqslant 25$ <30 kg/m^2 BMI $\geqslant 30$ kg/m^2	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.[121] This study enrolled more than 3500 early-stage HER2+ 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 <25 kg/m^2), overweight (BMI between 25 and 29.9 kg/m^2), and obese (BMI $\geqslant 30$ kg/m^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+ BC patient BMI and clinical outcomes in the ALTTO BIG 2-06 trial population.[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+ 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^2), normal weight (BMI $\geqslant 18.50$ and <25 kg/m^2), overweight (BMI $\geqslant 25$ and <30 kg/m^2), and obese (BMI $\geqslant 30$ kg/m^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.[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+ BC patients receiving adjuvant trastuzumab. Specifically, in the HERA trial, which randomized surgically resected HER2+ 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.[123] Similarly, an analysis of the NSABP B-31 trial, which randomized early-stage HER2+ BC patients to receive adjuvant doxorubicin plus cyclophosphamide followed by paclitaxel ± 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.[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 $\geqslant 25$ and <25 kg/m^2 patients, respectively, actually reported an association between overweight/obesity and worse patient OS.[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 $<18.5\,kg/m^2$), normal weight (BMI between 18.5 and $24.9\,kg/m^2$), overweight (BMI between 25 and 29.9 kg/m^2), and obese (BMI $\geqslant 30\ kg/m^2$). 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* 7.5 *versus* 12 months in obese *versus* overweight *versus* normal weight patients, respectively) or OS (39 *versus* 54 *versus* 67 months, respectively), whereas Martel *et al.*[128] failed to find an association between overweight/obesity (BMI $\geqslant 25\ kg/m^2$) 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.[23] 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,[129,130] as well as patients with other cancer types.[131,132] 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.

Acknowledgements

We would like to thank the 'Associazione Italiana per la Ricerca sul Cancro' (AIRC) (MFAG 2019-22977, Dr Claudio Vernieri) and the Scientific Directorate of Fondazione IRCCS Istituto Nazionale dei Tumori for funding our research.

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.

Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Filippo de Braud – Consulting Fees: Tiziana Life Sciences, BMS, Celgene, Novartis, Servier, Pharm Research Associates, Daiichi Sankyo, Ignyta, Amgen, Pfizer, Octimet Oncology, Incyte, Pierre Fabre, Eli Lilly, Roche, Astra Zeneca, Gentili, Dephaforum, MSD, Bayer, Fondazione Menarini; Travel/Accommodation/Expenses: BMS, Roche, Celgene, Amgen; Speaker Bureau: BMS, Roche, MSD, Bayer, Ignyta, Dephaforum, Biotechespert Ltd, Prime Oncology, Pfizer; Research Grant/Funding (institution): Novartis, Roche, BMS, Celgene, Incyte, NMS, Merck KGAA, Kymab, Pfizer, Tesaro, MSD. Claudio Vernieri – Consulting Fees: Novartis. All other authors declare no conflict of interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the Associazione Italiana per la Ricerca sul Cancro (AIRC) (MFAG 2019-22977, PI Dr Claudio Vernieri) and the Scientific Directorate of Fondazione IRCCS Istituto Nazionale dei Tumori.

References

1. Wolff AC, Hammond MEH, Hicks DG, *et al.* Recommendations for Human Epidermal growth factor Receptor 2 testing in breast. *J Clin Oncol* 2013; 31: 3997–4013.
2. Rubin I and Yarden Y. The basic biology of HER2. *Ann Oncol* 2001; 12(Suppl. 1): S3–S8.
3. Moasser MM. The oncogene HER2: its signaling and transforming functions and its role in human cancer pathogenesis. *Oncogene* 2007; 26: 6469–6487.
4. Cameron D, Piccart-Gebhart MJ, Gelber RD, *et al.* 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet* 2017; 389: 1195–1205.
5. Cardoso F, Paluch-Shimon S, Senkus E, *et al.* 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol* 2020; 31: 1623–1649.
6. Geyer CE, Forster J and Lindquist D. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *Adv Breast Cancer* 2008; 5: 45.
7. Saura C, Oliveira M, Feng YH, *et al.* Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with ⩾2 HER2-directed regimens: phase III NALA trial. *J Clin Oncol* 2020; 38: 3138–3149.
8. DeBusk K, Abeysinghe S, Vickers A, *et al.* Efficacy of tucatinib for HER2-positive metastatic breast cancer after HER2-targeted therapy: a network meta-analysis. *Future Oncol* 2021; 17: 4635–4647.
9. Verma S, Miles D, Gianni L, *et al.* Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012; 367: 1783–1791.
10. Modi S, Saura C, Yamashita T, *et al.* Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med* 2020; 382: 610–621.
11. Gianni L, Eiermann W, Semiglazov V, *et al.* Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet Oncol* 2014; 15: 640–647.
12. Gianni L, Pienkowski T, Im YH, *et al.* 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol* 2016; 17: 791–800.
13. von Minckwitz G, Huang C-S, Mano MS, *et al.* Trastuzumab emtansine for residual invasive

HER2-positive breast cancer. *N Engl J Med* 2019; 380: 617–628.

14. Swain SM, Miles D, Kim SB, *et al*. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol* 2020; 21: 519–530.
15. Ligorio F, Pellegrini I, Castagnoli L, *et al*. Targeting lipid metabolism is an emerging strategy to enhance the efficacy of anti-HER2 therapies in HER2-positive breast cancer. *Cancer Lett* 2021; 511: 77–87.
16. Corominas-Faja B, Vellon L, Cuyàs E, *et al*. Clinical and therapeutic relevance of the metabolic oncogene fatty acid synthase in HER2+ breast cancer. *Histol Histopathol* 2017; 32: 687–698.
17. World Health Organization. Obesity and overweight, https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (accessed 6 June 2020).
18. Ryan DH and Kushner R. The state of obesity and obesity research. *J Am Med Assoc* 2010; 304: 1835–1836.
19. Renehan AG, Tyson M, Egger M, *et al*. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008; 371: 569–578.
20. Protani M, Coory M and Martin JH. Effect of obesity on survival of women with breast cancer: systematic review and meta-analysis. *Breast Cancer Res Treat* 2010; 123: 627–635.
21. Chan DSM, Vieira AR, Aune D, *et al*. Body mass index and survival in women with breast cancer – systematic literature review and meta-analysis of 82 follow-up studies. *Ann Oncol* 2014; 25: 1901–1914.
22. Lohmann AE, Soldera SV, Pimentel I, *et al*. Association of obesity with breast cancer outcome in relation to cancer subtypes: a meta-analysis. *J Natl Cancer Inst* 2021; 113: 1465–1475.
23. Modi ND, Tan JQE, Rowland A, *et al*. The obesity paradox in early and advanced HER2 positive breast cancer: pooled analysis of clinical trial data. *NPJ Breast Cancer* 2021; 7: 30.
24. Weiss M, Steiner DF and Philipson LH. Insulin biosynthesis, secretion, structure, and structure-activity relationships. In: *Endotext*. 2014, https://www.ncbi.nlm.nih.gov/books/NBK279029/ (accessed 8 August 2021).
25. González-Sánchez JL and Serrano-Ríos M. Molecular basis of insulin action. *Drug News Perspect* 2007; 20: 527–531.
26. Hunter SJ and Garvey WT. Insulin action and insulin resistance: diseases involving defects in insulin receptors, signal transduction, and the glucose transport effector system 1. *Am J Med* 1998; 105: 331–345.
27. Liu Z and Barrett EJ. Human protein metabolism: its measurement and regulation. *Am J Physiol Endocrinol Metab* 2002; 283: E1105–E1112.
28. Werner H, Weinstein D and Bentov I. Similarities and differences between insulin and IGF-I: structures, receptors, and signalling pathways. *Arch Physiol Biochem* 2008; 114: 17–22.
29. Cefalu WT. Insulin resistance: cellular and clinical concepts. *Exp Biol Med* 2001; 226: 13–26.
30. Scheen A. Insulin action in man, https://orbi.uliege.be/handle/2268/13970 (accessed 25 July 2021).
31. Whitelaw DC and Gilbey SG. Insulin resistance. *Ann Clin Biochem* 2016; 35: 567–583.
32. Milazzo G, Giorgino F, Damante G, *et al*. Insulin receptor expression and function in human breast cancer cell lines. *Cancer Res* 1992; 52: 3924–3930.
33. Papa V, Pezzino V, Costantino A, *et al*. Elevated insulin receptor content in human breast cancer. *J Clin Invest* 1990; 86: 1503–1510.
34. Avruch J. Insulin signal transduction through protein kinase cascades. *Mol Cell Biochem* 1998; 182: 31–48.
35. Gallagher EJ and LeRoith D. The proliferating role of insulin and insulin-like growth factors in cancer. *Trends Endocrinol Metab* 2010; 21: 610–618.
36. Peyrat JP and Bonneterre J. Type 1 IGF receptor in human breast diseases. *Breast Cancer Res Treat* 1992; 22: 59–67.
37. Goldfine ID, McGuire WL, Vigneri R, *et al*. Insulin-like Growth Factor-I receptors are overexpressed and predict a low risk in human breast cancer. *Cancer Res* 1993; 53: 3736–3740.
38. Resnik JL, Reichart DB, Huey K, *et al*. Elevated Insulin-like Growth Factor I receptor autophosphorylation and kinase activity in human breast cancer. *Cancer Res* 1998; 58: 1159–1164.
39. Lu Y, Zi X, Zhao Y, *et al*. Insulin-like Growth Factor-I receptor signaling and resistance to

transtuzumab (Herceptin). *J Natl Cancer Inst* 2001; 93: 1852–1857.

40. Nahta R, Yuan LXH, Zhang B, *et al*. Insulin-like Growth Factor-I receptor/Human Epidermal growth factor Receptor 2 heterodimerization contributes to trastuzumab resistance of breast cancer cells. *Cancer Res* 2005; 65: 11118–11128.
41. Dufourny B, Alblas J, Van Teeffelen HA, *et al*. Mitogenic signaling of Insulin-like Growth Factor I in MCF-7 human breast cancer cells requires phosphatidylinositol 3-kinase and is independent of mitogen-activated protein kinase. *J Biol Chem* 1997; 272: 31163–31171.
42. Sanabria-Figueroa E, Donnelly SM, Foy KC, *et al*. Insulin-like Growth Factor-1 receptor signaling increases the invasive potential of Human Epidermal growth factor Receptor 2–overexpressing breast cancer cells via Src-focal adhesion kinase and Forkhead box protein M1. *Mol Pharmacol* 2015; 87: 150–161.
43. Zhang S, Huang WC, Li P, *et al*. Combating trastuzumab resistance by targeting SRC, a common node downstream of multiple resistance pathways. *Nat Med* 2011; 17: 461–469.
44. Wang SE, Xiang B, Zent R, *et al*. Transforming growth factor β induces clustering of HER2 and integrins by activating Src-FAK and receptor association to the cytoskeleton. *Cancer Res* 2009; 69: 475–482.
45. Zhuang G, Brantley-Sieders DM, Vaught D, *et al*. Elevation of receptor tyrosine kinase EphA2 mediates resistance to trastuzumab therapy. *Cancer Res* 2010; 70: 299–308.
46. Nagata Y, Lan KH, Zhou X, *et al*. PTEN activation contributes to tumor inhibition by trastuzumab, and loss of PTEN predicts trastuzumab resistance in patients. *Cancer Cell* 2004; 6: 117–127.
47. Vadlamudi RK, Sahin AA, Adam L, *et al*. Heregulin and HER2 signaling selectively activates c-Src phosphorylation at tyrosine 215. *FEBS Lett* 2003; 543: 76–80.
48. Yang H-Y, Zhou BP, Hung M-C, *et al*. Oncogenic signals of HER-2/neu in regulating the stability of the cyclin-dependent kinase inhibitor p27. *J Biol Chem* 2000; 275: 24735–24739.
49. Lu Y, Zi X and Pollak M. Molecular mechanisms underlying IGF-I-induced attenuation of the growth-inhibitory activity of trastuzumab (herceptin) on SKBR3 breast cancer cells. *Int J Cancer* 2004; 108: 334–341.
50. Esparís-Ogando A, Ocaña A, Rodríguez-Barrueco R, *et al*. Synergic antitumoral effect of an IGF-IR inhibitor and trastuzumab on HER2-overexpressing breast cancer cells. *Ann Oncol* 2008; 19: 1860–1869.
51. Huang X, Gao L, Wang S, *et al*. Heterotrimerization of the growth factor receptors erbB2, erbB3, and Insulin-like Growth Factor-I receptor in breast cancer cells resistant to herceptin. *Cancer Res* 2010; 70: 1204–1214.
52. Jerome L, Alami N, Belanger S, *et al*. Recombinant human Insulin-like Growth Factor binding protein 3 inhibits growth of Human Epidermal growth factor Receptor-2–overexpressing breast tumors and potentiates herceptin activity in vivo. *Cancer Res* 2006; 66: 7245–7252.
53. Bektas N, ten Haaf A, Veeck J, *et al*. Tight correlation between expression of the Forkhead transcription factor FOXM1 and HER2 in human breast cancer. *BMC Cancer* 2008; 8: 42.
54. Francis RE, Myatt SS, Krol J, *et al*. FoxM1 is a downstream target and marker of HER2 overexpression in breast cancer. *Int J Oncol* 2009; 35: 57–68.
55. Harris LN, You F, Schnitt SJ, *et al*. Predictors of resistance to preoperative trastuzumab and vinorelbine for HER2-positive early breast cancer. *Clin Cancer Res* 2007; 13: 1198–1207.
56. Gallardo A, Lerma E, Escuin D, *et al*. Increased signalling of EGFR and IGF1R, and deregulation of PTEN/PI3K/Akt pathway are related with trastuzumab resistance in HER2 breast carcinomas. *Br J Cancer* 2012; 106: 1367–1373.
57. Zhang Y, Proenca R, Maffei M, *et al*. Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994; 372: 425–432.
58. Hoggard N, Hunter L, Duncan JS, *et al*. Leptin and leptin receptor mRNA and protein expression in the murine fetus and placenta. *Proc Natl Acad Sci U S A* 1997; 94: 11073–11078.
59. Bado A, Levasseur S, Attoub S, *et al*. The stomach is a source of leptin. *Nature* 1998; 394: 790–793.
60. Smith-Kirwin SM, O'Connor DM, De Johnston J, *et al*. Leptin expression in human mammary epithelial cells and breast milk. *J Clin Endocrinol Metab* 1998; 83: 1810–1813.
61. Andò S and Catalano S. The multifactorial role of leptin in driving the breast cancer microenvironment. *Nat Rev Endocrinol* 2012; 8: 263–275.
62. Okumura M, Yamamoto M, Sakuma H, *et al*. Leptin and high glucose stimulate cell proliferation in MCF-7 human breast cancer cells: reciprocal involvement of PKC-α and

PPAR expression. *Biochim Biophys Acta Mol Cell Res* 2002; 1592: 107–116.

63. Chen C, Chang YC, Liu CL, *et al*. Leptin-induced growth of human ZR-75-1 breast cancer cells is associated with up-regulation of cyclin D1 and c-Myc and down-regulation of tumor suppressor p53 and p21WAF1/CIP1. *Breast Cancer Res Treat* 2006; 98: 121–132.
64. Gonzalez RR, Cherfils S, Escobar M, *et al*. Leptin signaling promotes the growth of mammary tumors and increases the expression of vascular endothelial growth factor (VEGF) and its receptor type two (VEGF-R2). *J Biol Chem* 2006; 281: 263208–262632.
65. Giordano C, Vizza D, Panza S, *et al*. Leptin increases HER2 protein levels through a STAT3-mediated up-regulation of Hsp90 in breast cancer cells. *Mol Oncol* 2013; 7: 379–391.
66. Fiorio E, Mercanti A, Terrasi M, *et al*. Leptin/HER2 crosstalk in breast cancer: in vitro study and preliminary in vivo analysis. *BMC Cancer* 2008; 8: 305.
67. Catalano S, Marsico S, Giordano C, *et al*. Leptin enhances, via AP-1, expression of aromatase in the MCF-7 cell line. *J Biol Chem* 2003; 278: 28668–28676.
68. Tsuchiya T, Shimizu H, Horie T, *et al*. Expression of leptin receptor in lung: leptin as a growth factor. *Eur J Pharmacol* 1999; 365: 273–279.
69. Mix H, Widjaja A, Jandl O, *et al*. Expression of leptin and leptin receptor isoforms in the human stomach. *Gut* 2000; 47: 481–486.
70. Hino M, Nakao T, Yamane T, *et al*. Leptin receptor and leukemia. *Leuk Lymphoma* 2000; 36: 457–461.
71. Wu MH, Chou YC, Chou WY, *et al*. Circulating levels of leptin, adiposity and breast cancer risk. *Br J Cancer* 2009; 100: 578–582.
72. Guo S, Liu M, Wang G, *et al*. Oncogenic role and therapeutic target of leptin signaling in breast cancer and cancer stem cells. *Biochim Biophys Acta* 2012; 1825: 207–222.
73. Ishikawa M, Kitayama J and Nagawa H. Enhanced expression of leptin and leptin receptor (OB-R) in human breast cancer. *Clin Cancer Res* 2004; 10: 4325–4331.
74. Martinez-Huenchullan SF, Tam CS, Ban LA, *et al*. Skeletal muscle adiponectin induction in obesity and exercise. *Metabolism* 2020; 102: 154008.
75. Kern PA, Gregorio GB, Di Lu T, *et al*. Adiponectin expression from human adipose tissue. *Diabetes* 2003; 52: 1779–1785.
76. Hotta K, Funahashi T, Arita Y, *et al*. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol* 2000; 20: 1595–1599.
77. Kim AY, Lee YS, Kim KH, *et al*. Adiponectin represses colon cancer cell proliferation via AdipoR1- and -R2-mediated AMPK activation. *Mol Endocrinol* 2010; 24: 1441–1452.
78. Chung SJ, Nagaraju GP, Nagalingam A, *et al*. ADIPOQ/adiponectin induces cytotoxic autophagy in breast cancer cells through STK11/LKB1-mediated activation of the AMPK-ULK1 axis. *Autophagy* 2017; 13: 1386–1403.
79. Nagaraju GP, Rajitha B, Aliya S, *et al*. The role of adiponectin in obesity-associated female-specific carcinogenesis. *Cytokine Growth Factor Rev* 2016; 31: 37–48.
80. Martín-Romero C, Santos-Alvarez J, Goberna R, *et al*. Human leptin enhances activation and proliferation of human circulating T lymphocytes. *Cell Immunol* 2000; 199: 15–24.
81. Sánchez-Margalet V, Martín-Romero C, Santos-Alvarez J, *et al*. Role of leptin as an immunomodulator of blood mononuclear cells: mechanisms of action. *Clin Exp Immunol* 2003; 133: 11–19.
82. de la Cruz-Merino L, Chiesa M, Caballero R, *et al*. Breast cancer immunology and immunotherapy: current status and future perspectives. In: *International review of cell and molecular biology* (Vol. 331). Academic Press, 2017, pp. 1–53. DOI: 10.1016/bs.ircmb.2016.09.008.
83. Reggiani F, Labanca V, Mancuso P, *et al*. Adipose progenitor cell secretion of GM-CSF and MMP9 promotes a stromal and immunological microenvironment that supports breast cancer progression. *Cancer Res* 2017; 77: 5169–5182.
84. Bhatti MS, Akbri MZ and Shakoor M. Lipid profile in obesity. *J Ayub Med Coll Abbottabad* 2001; 13: 31–33, https://europepmc.org/article/med/11706638 (accessed 28 August 2021).
85. Feingold KR. Obesity and dyslipidemia. In: *Endotext*. 2020, https://www.ncbi.nlm.nih.gov/books/NBK305895/ (accessed 28 August 2021).
86. Pascual G, Avgustinova A, Mejetta S, *et al*. Targeting metastasis-initiating cells through the

fatty acid receptor CD36. *Nature* 2017; 541: 41–45.

87. Koundouros N and Poulogiannis G. Reprogramming of fatty acid metabolism in cancer. *Br J Cancer* 2019; 122: 4–22.
88. Röhrig F and Schulze A. The multifaceted roles of fatty acid synthesis in cancer. *Nat Rev Cancer* 2016; 16: 732–749.
89. Liu X, Yin Y, Wu J, *et al*. Structure and mechanism of an intramembrane liponucleotide synthetase central for phospholipid biosynthesis. *Nat Commun* 2014; 5: 4244.
90. Ventura R, Mordec K, Waszczuk J, *et al*. Inhibition of de novo palmitate synthesis by fatty acid synthase induces apoptosis in tumor cells by remodeling cell membranes, inhibiting signaling pathways, and reprogramming gene expression. *EBioMedicine* 2015; 2: 808–824.
91. Wang D and DuBois RN. Eicosanoids and cancer. *Nat Rev Cancer* 2010; 10: 181–193.
92. Menendez JA and Lupu R. Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis. *Nat Rev Cancer* 2007; 7: 763–777.
93. Vazquez-Martin A, Colomer R, Brunet J, *et al*. Overexpression of fatty acid synthase gene activates HER1/HER2 tyrosine kinase receptors in human breast epithelial cells. *Cell Prolif* 2008; 41: 59–85.
94. Rysman E, Brusselmans K, Scheys K, *et al*. De novo lipogenesis protects cancer cells from free radicals and chemotherapeutics by promoting membrane lipid saturation. *Cancer Res* 2010; 70: 8117–8126.
95. Menendez JA. Fine-tuning the lipogenic/lipolytic balance to optimize the metabolic requirements of cancer cell growth: molecular mechanisms and therapeutic perspectives. *Biochim Biophys Acta* 2010; 1801: 381–391.
96. Ravacci GR, Brentani MM, Tortelli TC, *et al*. Docosahexaenoic acid modulates a HER2-associated lipogenic phenotype, induces apoptosis, and increases trastuzumab action in HER2-overexpressing breast carcinoma cells. *Biomed Res Int* 2015; 2015: 838652.
97. Goldberg IJ, Eckel RH and Abumrad NA. Regulation of fatty acid uptake into tissues: lipoprotein lipase- and CD36-mediated pathways. *J Lipid Res* 2009; 50: S86–S90.
98. Nair R, Roden DL, Teo WS, *et al*. C-Myc and Her2 cooperate to drive a stem-like phenotype with poor prognosis in breast cancer. *Oncogene* 2014; 33: 3992–4002.
99. Feng WW, Wilkins O, Bang S, *et al*. CD36-mediated metabolic rewiring of breast cancer cells promotes resistance to HER2-targeted therapies. *Cell Rep* 2019; 29: 3405–3420.e5.
100. Wang H, Franco F, Tsui Y-C, *et al*. CD36-mediated metabolic adaptation supports regulatory T cell survival and function in tumors. *Nat Immunol* 2020; 21: 298–308.
101. Ma X, Xiao L, Liu L, *et al*. CD36-mediated ferroptosis dampens intratumoral CD8+ T cell effector function and impairs their antitumor ability. *Cell Metab* 2021; 33: 1001–1012.e5.
102. Ma X, Bi E, Lu Y, *et al*. Cholesterol induces CD8+ T cell exhaustion in the tumor microenvironment. *Cell Metab* 2019; 30: 143–156.e5.
103. Zhang Y, Kurupati R, Liu L, *et al*. Enhancing CD8+ T cell fatty acid catabolism within a metabolically challenging tumor microenvironment increases the efficacy of melanoma immunotherapy. *Cancer Cell* 2017; 32: 377–391.e9.
104. Xu S, Chaudhary O, Rodríguez-Morales P, *et al*. Uptake of oxidized lipids by the scavenger receptor CD36 promotes lipid peroxidation and dysfunction in CD8+ T cells in tumors. *Immunity* 2021; 54: 1561–1577.e7.
105. Scheuer W, Friess T, Burtscher H, *et al*. Strongly enhanced antitumor activity of trastuzumab and pertuzumab combination treatment on HER2-positive human xenograft tumor models. *Cancer Res* 2009; 69: 9330–9336.
106. Mills LJ, Gutjahr-Gobell RE, Zaroogian GE, *et al*. Modulation of aromatase activity as a mode of action for endocrine disrupting chemicals in a marine fish. *Aquat Toxicol* 2014; 147: 140–150.
107. Cleland WH, Mendelson CR and Simpson ER. Aromatase activity of membrane fractions of human adipose tissue stromal cells and adipocytes. *Endocrinology* 1983; 113: 2155–2160.
108. Austin H, Austin JM, Partridge EE, *et al*. Endometrial cancer, obesity, and body fat distribution. *Cancer Res* 1991; 51: 568–572.
109. Grodin JM, Siiteri PK and MacDonald PC. Source of estrogen production in postmenopausal women. *J Clin Endocrinol Metab* 1973; 36: 207–214.
110. Lønning PE, Helle SI, Johannessen DC, *et al*. Influence of plasma estrogen levels on the length of the disease-free interval in postmenopausal women with breast cancer. *Breast Cancer Res Treat* 1996; 39: 335–341.

111. Kim J-Y, Han W, Moon H-G, *et al*. Prognostic effect of preoperative serum estradiol level in postmenopausal breast cancer. *BMC Cancer* 2013; 13: 503.

112. Sestak I, Distler W, Forbes JF, *et al*. Effect of body mass index on recurrences in tamoxifen and anastrozole treated women: an exploratory analysis from the ATAC trial. *J Clin Oncol* 2010; 28: 3411–3415.

113. Howlader N, Altekruse SF, Li CI, *et al*. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J Natl Cancer Inst* 2014; 106: dju055.

114. Gianni L, Pienkowski T, Im YH, *et al*. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012; 13: 25–32.

115. Arpino G, Wiechmann L, Osborne CK, *et al*. Crosstalk between the estrogen receptor and the HER tyrosine kinase receptor family: molecular mechanism and clinical implications for endocrine therapy resistance. *Endocr Rev* 2008; 29: 217–233.

116. Cardoso F, Kyriakides S, Ohno S, *et al*. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2019; 30: 1194–1220.

117. González García J, Gutiérrez Nicolás F, Nazco Casariego GJ, *et al*. Influence of anthropometric characteristics in patients with Her2-positive breast cancer on initial plasma concentrations of trastuzumab. *Ann Pharmacother* 2017; 51: 976–980.

118. Cantini L, Pistelli M, Merloni F, *et al*. Body mass index and hormone receptor status influence recurrence risk in HER2-positive early breast cancer patients. *Clin Breast Cancer* 2020; 20: e89–e98.

119. Mazzarella L, Disalvatore D, Bagnardi V, *et al*. Obesity increases the incidence of distant metastases in oestrogen receptor-negative Human Epidermal growth factor Receptor 2-positive breast cancer patients. *Eur J Cancer* 2013; 49: 3588–3597.

120. Ligorio F, Zambelli L, Bottiglieri A, *et al*. Hormone receptor status influences the impact of body mass index and hyperglycemia on the risk of tumor relapse in early-stage HER2-positive breast cancer patients. *Ther Adv Med Oncol* 2021. DOI: 10.1177/17588359211006960.

121. Crozier JA, Moreno-Aspitia A and Ballman KV. Effect of body mass index on tumor characteristics and disease-free survival in patients from the HER2-positive adjuvant trastuzumab trial N9831. *Cancer* 2013; 119: 2447–2454.

122. Martel S, Lambertini M, Agbor-Tarh D, *et al*. Body mass index and weight change in patients with HER2-positive early breast cancer: exploratory analysis of the ALTTOBIG 2-06 trial. *J Natl Compr Cancer Netw* 2021; 19: 181–189.

123. Yerushalmi R, Dong B, Chapman JW, *et al*. Impact of baseline BMI and weight change in CCTG adjuvant breast cancer trials. *Ann Oncol* 2017; 28: 1560–1568.

124. Cecchini RS, Swain SM, Costantino JP, *et al*. Body mass index at diagnosis and breast cancer survival prognosis in clinical trial populations from NRG oncology/NSABP B-30, B-31, B-34, and B-38. *Cancer Epidemiol Biomarkers Prev* 2016; 25: 51–59.

125. Di Cosimo S, Porcu L, Agbor-tarh D, *et al*. Effect of body mass index on response to neo-adjuvant therapy in HER2-positive breast cancer: an exploratory analysis of the NeoALTTO trial. *Breast Cancer Res* 2020; 22: 115.

126. Krasniqi E, Pizzuti L, Barchiesi G, *et al*. Impact of BMI on HER2+ metastatic breast cancer patients treated with pertuzumab and/or trastuzumab emtansine. Real-world evidence. *J Cell Physiol* 2020; 235: 7900–7910.

127. Parolin V, Fiorio E, Mercanti A, *et al*. Impact of BMI on clinical outcome of HER2-positive breast cancer. *J Clin Oncol* 2010; 28(Suppl. 15): 1130–1130.

128. Martel S, Poletto E, Ferreira AR, *et al*. Impact of body mass index on the clinical outcomes of patients with HER2-positive metastatic breast cancer. *Breast* 2018; 37: 142–147.

129. Pizzuti L, Sergi D, Sperduti I, *et al*. Body mass index in HER2-negative metastatic breast cancer treated with first-line paclitaxel and bevacizumab. *Cancer Biol Ther* 2018; 19: 328–334.

130. Alarfi H, Salamoon M, Kadri M, *et al*. The impact of baseline body mass index on clinical outcomes in metastatic breast cancer: a prospective study. *BMC Res Notes* 2017; 10: 550.

131. Simkens LHJ, Koopman M, Mol L, *et al*. Influence of body mass index on outcome in advanced colorectal cancer patients receiving chemotherapy with or without targeted therapy. *Eur J Cancer* 2011; 47: 2560–2567.

132. McQuade JL, Daniel CR, Hess KR, *et al*. Association of body-mass index and outcomes in patients with metastatic melanoma treated with targeted therapy, immunotherapy, or chemotherapy: a retrospective, multicohort analysis. *Lancet Oncol* 2018; 19: 310–322.