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REVIEW

Emerging anti-cancer antibodies and combination therapies targeting HER3/ERBB3

Nadège Gaborit, Moshit Lindzen, and Yosef Yarden

Department of Biological Regulation, Weizmann Institute of Science, Rehovot, Israel

ABSTRACT

Cancer progression depends on stepwise accumulation of oncogenic mutations and a select group of growth factors essential for tumor growth, metastasis and angiogenesis. Agents blocking the epidermal growth factor receptor (EGFR, also called HER1 and ERBB1) and the co-receptor called HER2/ERBB2 have been approved over the last decade as anti-cancer drugs. Because the catalytically defective member of the family, HER3/ERBB3, plays critical roles in emergence of resistance of carcinomas to various drugs, current efforts focus on antibodies and other anti-HER3/ERBB3 agents, which we review herein with an emphasis on drug combinations and some unique biochemical features of HER3/ERBB3.

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Introduction

Despite significant progress in the development of new anti-cancer drugs, more than 14 million new cases of cancer were diagnosed globally in 2012, and approximately 8.2 million patients died in 2012 due to their disease.[1] Solid tumors are characterized by stepwise accumulation of oncogenic mutations, which present an immense pharmacological challenge. However, tumor cell survival, migration and ability to attract blood and lymph vessels depend on a multitude of growth factors, and some of these bind with cell surface localized receptor tyrosine kinases (RTKs).[2] Due to their accessibility and the ability to block the catalytic kinase function using small molecule, tyrosine kinase inhibitors (TKIs), RTKs have become a sustained source of attractive targets for cancer drugs.[3] For example, type 1 RTKs, a group containing the epidermal growth factor receptor (EGFR, also called ERBB1) and the co-receptor called HER2/ERBB2, is one of the most studied and targeted groups of molecules in cancer therapy.[4] Importantly, currently available drugs target only 2 members of the HER/ERBB family, namely EGFR and HER2. Nevertheless, many new agents targeting HER3 are in various stages of clinical development, and some mAbs are approaching phase 3 trials. Hence, it is both timely and important to overview the large efforts invested to develop novel pharmacological interceptors of HER3 (see Fig. 1). This review provides a systematic description of the biology of HER3 and its family members, and critically relates to the multiple experimental interceptors, with an emphasis on potentially effective drug combinations.

Targeted cancer therapy directed at the EGFR (HER/ERBB) family

All members of the EGF family of growth factors, which includes 11 ligands, bind with moderate or high affinity to type 1 RTKs.[2,4,5] The founding member of this first RTK sub-family was discovered in 1982 by Stanley Cohen and colleagues.[6] Three similar receptors have later been characterized. These are human EGFR 2, HER2 (also called ERBB2), HER3 (ERBB3) and HER4 (ERBB4). All four HER/ERBB proteins contain an extracellular ligand binding domain, a transmembrane region and an intracellular domain harbouring a catalytic tyrosine kinase function. The extracellular portion consists of 4 subdomains, referred to as domains I-IV, of which domains I and III (of EGFR) are necessary for ligand binding (see Fig. 2A).[7] Following ligand binding, a relatively large structural conformation converts an untethered, inactive form to a tethered/active form, thereby enables homo- or hetero-dimerization with a similar or different member of the EGFR/ERBB family.[8] In this context, one of the favorite partners for dimer formation is HER2, which binds no known EGF-like ligand and its conformation is constitutively tethered, ready for dimerization.[9] Once dimerization occurred, receptor activation and phosphorylation initiate, leading to a cascade of phosphorylation events, which activates 2 main signaling pathways, namely the mitogen-activated protein kinase (MAPK/ERK) pathway and the phosphatidylinositol 3-kinase (PI3K) to AKT pathway (Fig. 3). These pathways control numerous cellular responses, such as proliferation, cell cycle entry, survival, metabolic pathway activation, apoptosis and angiogenesis.[5,10-14]

Because EGFR is involved in survival of epithelial cells, including cancer cells, and both EGFR and HER2 are frequently overexpressed or mutated in cancer, several therapies have been developed with the aim of intercepting their signaling, and arresting tumor growth. Two major pharmacological strategies have been developed, and they are concisely reviewed below: these are low molecular weight compounds, called TKIs, which target the intracellular domain of the receptor, and monoclonal antibodies (mAbs) targeting the extracellular domain of the receptor. Multiple TKIs have been designed to target the EGFR family. These compounds inhibit the catalytic tyrosine kinase

CONTACT Yosef Yarden yosef.yarden@weizmann.ac.il

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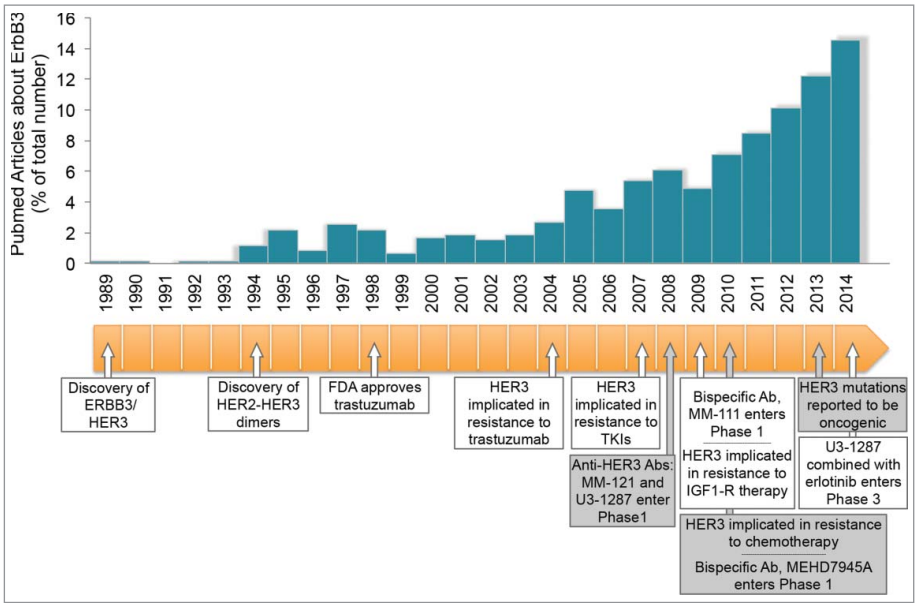


Figure 1. An avalanche of HER3 studies. The histogram depicts the yearly number of HER3/ERBB3 reports, which became available through Pubmed since the early 1990s. The timeline at the bottom identifies and dates some milestones in HER3 research since the discovery of the protein and transcript in 1989.

function by binding to the nucleotide-binding site of the target receptor.[15] Initially, mono-specific TKIs were developed. For example reversible, ATP-competitive EGFR inhibitors (e.g., gefitinib/Iressa and erlotinib/Tarceva) were found to be selective to mutant forms of EGFR found in 10–40% of non-small cell lung cancer (NSCLC).[16-18] In addition to lung cancer, since 2005 erlotinib is used in combination with chemotherapy for the treatment of metastatic pancreatic carcinoma.[19] Unlike erlotinib and gefitinib, lapatinib (Tykerb/Tyverb) is a dual tyrosine kinase inhibitor that forms relatively selective and unique complexes with both EGFR and HER2.[20] Several clinical trials established lapatinib's activity, together with chemotherapy, in the treatment of patients with HER2-positive advanced breast cancer previously treated with trastuzumab and chemotherapy.[21] Afatinib is the first clinically approved TKI of the second generation of HER/ERBB inhibitors, designed to have more potent inhibition of EGFR and to overcome the EGFR T790M resistance mutation. Afatinib is an oral, irreversible PanHER family blocker, which selectively and potently blocks signaling from the 3 catalytically active HER-family receptors, and also inhibits transphosphorylation of the inactive member, HER3/ERBB3.[22] In lung cancer patients with EGFR mutations,

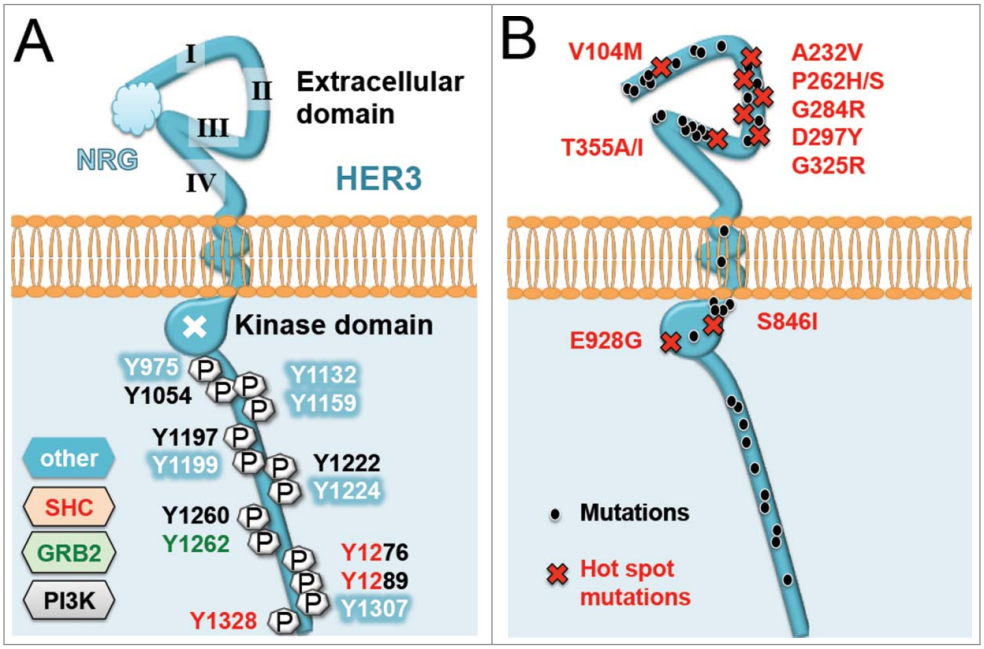


Figure 2. Key sites of HER3. (A) Shown are phosphotyrosine phosphorylation sites of HER3/ERBB3 able to dock binding proteins involved in MAPK (ERK) or PI3K/AKT signaling pathways, such as SHC, GRB2 or the α subunit of PI3K. (B) Reported sites of mutations within HER3/ERBB3 reported in different types of tumors. Note that hot spot mutations (red) are more frequently detected in cancer.

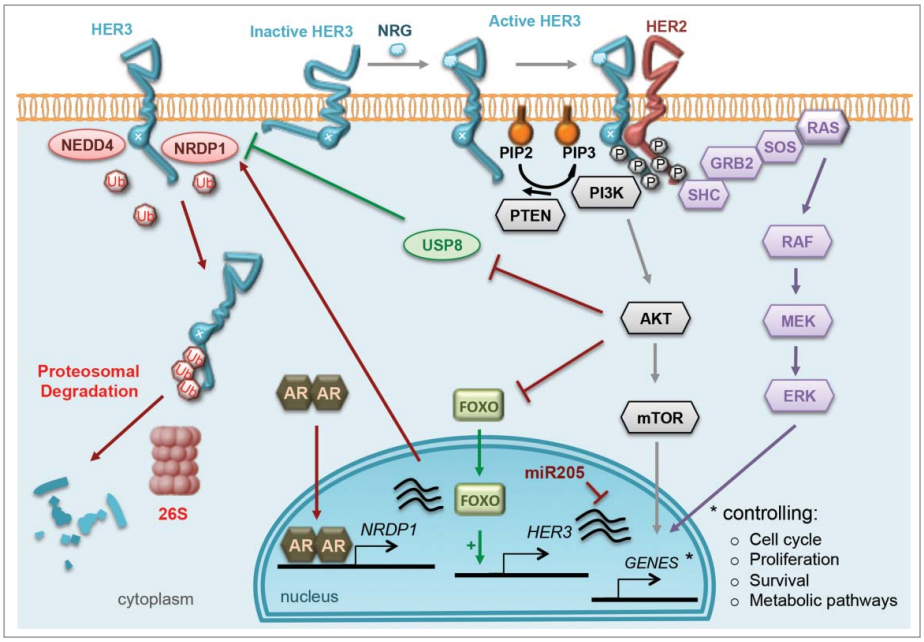


Figure 3. Regulation of HER3 and downstream signaling. HER3/ERBB3 adopts an active conformation following binding of a ligand, called neuregulin (NRG), in between domains I and III of the extracellular domain. Since the tyrosine kinase domain is impaired, HER3/ERBB3 can undergo only weak auto-phosphorylation. In addition, HER3/ERBB3 can form heterodimers with other receptor tyrosine kinases (RTKs), leading to efficient trans-phosphorylation of the cytoplasmic domain. The main dimerization partner of HER3 is HER2/ERBB2 . Both the MAPK pathway (ERK, shown in purple) and the AKT pathway (gray) are activated when such heterodimers form. Nuclear translocation of the downstream effectors of these pathways permits transcriptional and translational regulation of genes involved in numerous cellular responses, such as cell cycle control, proliferation, survival, metabolism, apoptosis and angiogenesis. On its own, HER3 is regulated at different levels: 2 ubiquitin ligases, NEDD4 and NRDP1, have been reported to mediate its ubiquitination and proteosomal degradation. The deubiquitinating enzyme USP8, which is regulated by AKT, negatively regulates NRDP1. The activated androgen receptor (AR) also controls HER3 levels by binding to the *NRDP1* promoter regions and activating *NRDP1* transcription. In addition, several miRNA molecules, such as miR205, miR125a and miR125b, have been reported to control HER3/ERBB3 expression.

afatinib has been associated with prolonged progression-free survival, compared to chemotherapy. This led to approval of oral afatinib, in 2013, for the first-line treatment of patients with metastatic NSCLC who have tumors with EGFR mutations.[23] Third generation TKIs were developed to inhibit EGFR ^{T790M} while sparring wild type EGFR, consequently they show less toxicities. AZD9291,[24] CO-1686 (also called rociletinib),[25] and HM61713[26] are under clinical development, and early phase results are in general quite encouraging. An example is given by rocetinib, which has been awarded breakthrough therapy designation (BTD) by FDA and has been studied in phase 2 and 3.

The first mAbs to EGFR were generated by Mendelsohn and colleagues in the early 1980s.[27] Sela and colleagues later demonstrated that anti-EGFR antibodies can synergize with platinum-based chemotherapy, when administered to tumor-bearing animals.[28] Mendelsohn's murine antibody is the father of cetuximab (Erbitux^{TM}), a chimeric human/mouse mAb that inhibits binding of EGF and downstream signaling.[29] The antibody was clinically developed and eventually approved in 2004, together with chemotherapy, for the treatment of metastatic colorectal cancer (mCRC).[30] Panitumumab (Vectibix^{TM}), a fully human antibody, binds to the same site of EGFR. An acquired mutation in EGFR (S492R) prevents cetuximab binding but retains panitumumab binding.[31] Importantly, it was noted that the effects of both panitumumab and cetuximab were limited to patients with wild type KRAS tumors; antibody treatment did not benefit patients whose tumors expressed a mutant form of KRAS.[32–35] Multiple determinants of resistance to anti EGFR therapy have been described recently, among them, mutation in the receptor itself - changing its interactions with the drug molecule – or in downstream transducers and deregulation of parallel signaling pathways.[36] For example recent data suggest that the mutation status of KRAS, NRAS, BRAF and/or PIK3CA genes may be a signature for EGFR dependency in CRC.[37]

Studying a mutant form of the rodent HER2 (also called NEU), Greene, Weinberg and colleagues showed that ectopic expression of the oncoprotein in rat fibroblast enabled them to grow as tumors, but a corresponding mAb reverted this transformed phenotype.[38] Another murine antibody, 4D5, specifically inhibited the growth of human breast tumor-derived cell lines overexpressing HER2/ERBB2.[39] Humanization of 4D5, the predecessor of trastuzumab (Herceptin^{TM}), along with genetic engineering that enhanced binding affinity[40] and recruitment of killer lymphocytes to the human Fcγ receptors (especially FcγRIIIa), to augment antibody-dependent cell-mediated cytotoxicity (ADCC), readied the antibody for clinical trials. In the pivotal clinical trials that applied trastuzumab on HER2-positive advanced breast cancer, the mAb conferred significant improvements in progression-free survival (PFS) and overall survival (OS), which led to the approval of a combination of trastuzumab and chemotherapy.[41] Unlike trastuzumab, pertuzumab is a mAb that inhibits heterodimerization of HER2 with other family members.[42] A large clinical trial that combined pertuzumab, trastuzumab and chemotherapy[43,44] demonstrated significant improvement in patient outcome, along with serious adverse events in 36% of patients who received pertuzumab, trastuzumab, and docetaxel. These results led to the approval of a combination of pertuzumab, trastuzumab and docetaxel for the

treatment of patients with HER2-positive breast cancer, whose disease progressed during prior trastuzumab-based therapy.[45] Because pertuzumab inhibits recruitment of HER3 to HER2,[42] some side effects of the combination might be due to HER3 blockade. Another lesson from HER2 that might be applicable to anti-HER3 antibodies is Trastuzumab-DM1 (T-DM1). This is an antibody drug conjugate comprising trastuzumab and emtansine (DM1), a tubulin polymerization inhibitor. Following successful trials, which showed high efficacy and relatively mild side effects,[46,47] T-DM1 has been approved for the treatment of HER2-positive metastatic breast cancer patients, who previously received trastuzumab and chemotherapy.

HER3/ERBB3: How did the black sheep of the family become a prime target?

The third member of the EGFR family, HER3, has been discovered some 25 y ago (see Fig. 1).[48,49] Initially, HER3, unlike EGFR and HER2, has been considered an unsuitable target for cancer treatments. This was due to an overall moderate expression levels in cancer cells, a catalytically impaired kinase domain,[50] a presumed lack of ability to form homodimeric HER3-HER3 complexes, and an initial inability to detect oncogenic mutations of HER3/ERBB3. Yet, it has been clear early on that HER3-containing heterodimers, especially with HER2, generate strong survival signals.[51,52] Moreover, ablation of HER3 uncovered one of its cellular roles, which is to couple active HER2 to the phosphatidylinositol 3-kinase/protein kinase B pathway (PI3K-AKT).[53] More recent studies were able to detect low but intrinsic tyrosine kinase activity of HER3, which prompted a model suggesting that transient HER3-HER2 hetero-interactions set the stage for signaling competent HER3 homodimers.[54] Another unique feature of HER3 relates to its constitutive (ligand-independent) endocytosis.[55,56] and its up-regulation when the AKT pathway is inhibited.[57] Unlike CBL-mediated downregulation of the majority of growth factor receptors, HER3 downregulation is mediated by a dedicated cascade involving a deubiquitinating enzyme, USP8, and 2 E3 ubiquitin ligases, NRDP1 and NEDD4.[58,59] In addition to regulation by means of ubiquitination, several microRNAs are reportedly able to modulate HER3 levels (see Fig. 3).[60–63] As we describe below, 2 major lines of evidence motivated the current intensified interest in intercepting HER3 in human tumors: First, oncogenic mutant forms have recently been identified in approximately 10% of solid tumors and second, several studies indicated that HER3 plays pivotal roles in several compensatory processes that underlay emergence of resistance to certain cancer drugs.[64,65]

Aberrant HER3 in human cancer

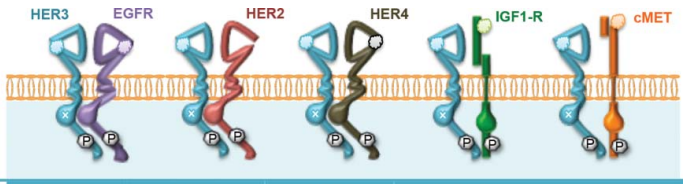
According to a recent report, somatic mutations exist in ~11% of colon and gastric cancers (Fig. 2B).[66] Moreover, when tested in vitro, the mutants were able to transform colonic and breast epithelial cells in a ligand-independent but HER2-dependent manner. In addition, co-expression of HER2 and HER3 is commonly detected in breast cancer.[67] In fact, a large fraction of human mammary tumors present an overexpressed HER3.[68] Although initially controversial, according to recent meta-analyses, relatively high expression levels of HER3 might associate with shorter survival of patients with breast, colorectal, melanoma, pancreatic, head and neck, and ovarian cancer.[69] Once again, co-expression of HER2 appears to strengthen this clinical association with poorer survival.

Roles for HER3 in drug resistance

Unlike primary resistance, tolerance to HER/ERBB-intercepting drugs emerges in the majority of patients while under treatment with TKIs or with mAbs.[70,71] Mechanisms underlying resistance often involves compensatory pathways that preempt pharmacological intervention. Two features of HER3 make this receptor especially competent to launch such bypass loops, namely the ability to strongly stimulate the PI3K-AKT pathway and its propensity to form heterodimers not only with HER2 and EGFR but also with MET and IGF1-R. Figure 4 presents the major interaction partners of HER3, as well as drugs that target these partners, either alone or in combination with HER3. For example, HER3 expression is substantially increased after long-term exposure of breast cancer cells to trastuzumab.[72] Similarly, upregulation of HER3 accompanies inhibition of EGFR and HER2 using TKIs, such as gefitinib, erlotinib and lapatinib.[73,74] Yet another indirect effect underlies resistance of lung cancer to gefitinib; this involves focal amplification of MET, which confers resistance by driving HER3-dependent activation of PI3K.[75] HER3 has also been implicated in development of resistance to cetuximab: resistant NSCLC and HNSCC cancer cells manifested strong activation of HER2, HER3 and MET, along with coupling to PI3K-AKT.[76] Interestingly, IGF1-R inhibition in liver cancer cells evokes an analogous EGFR-dependent mechanism that involves HER3.[77] The roles of HER3 in evolving resistance extends to chemotherapy, such as resistance of HER2-overexpressing breast cancer cells to paclitaxel[65,78] and acquisition of resistance to tamoxifen by luminal B breast cancer.[79]

Signature of HER3 activation and use as a biomarker

As aforementioned, HER3 is trans-activated by its dimerization partners. This activation leads to phosphorylation of some of the 14 tyrosine residues located at the C-terminal tail of HER3 (Fig. 2A).[80] Several studies have identified phospho-sites able to dock SH2 (Src homology region 2) and PTB (phosphotyrosine-binding) domains of proteins involved in signaling pathways, such as SHC, GRB2 or the PI3K complex. Importantly, unlike EGFR and HER2, HER3 contains multiple phosphotyrosine binding sites for the regulatory subunit of PI3K complexes.[81] This unique feature of HER3 might explain HER2s action in breast cancer, such as inflammatory breast tumors overexpressing HER2.[82] In such patients, coexpression of pHER2 and pHER3 in tumors seems to predict for a favorable response to lapatinib, a HER2-specific TKI. Moreover, resistance of HER2-overexpressing breast cancer cells to lapatinib might be due to autocrine stimulation of HER3 by neuregulin and consequent transactivation of EGFR and the PI3K pathway.[83] In conclusion, the phosphorylated form of HER3, or a relevant phosphoprotein signature,[84,85] might serve as a biomarker enabling patient selection.



Targets	Drug type	EGFR	HER2	HER4	IGF1-R	cMET
HER3 partners	Anti-ligand Ab	Anti-TGFα Anti-HB-EGF Anti-AREG (experimental)	-	Anti-HB-EGF (experimental)	MEDI-573	Rilotumumab LGG7/TAK-701 Ficlatuzumab
	Anti-receptor Ab	Cetuximab* Panitumumab	Trastuzumab* Pertuzumab	Anti-ErbB4 mAbs (experimental)	Figitumumab Cixutumumab Ganitumab Dalotuzumab R1507	LY2875358 H224G11/ABT700 Onartuzumab
	ADC	-	T-DM1	-	-	-
	TKI	Gefitinib* Erlotinib* Lapatinib* Rociletinib AZD-9291	Lapatinib*	-	Linsitinib BMS-754807 BVP51004 XL228 INSM-18	XL880 XL184 SGX523 PF-02341066 JNJ-38877605 ARQ197 MGCD265
HER3 + HER3 partners	Anti-ligand Ab	-	-	Anti-NRG1 (experimental)		
	PanHER TKI	Afatinib AZD-8931 CI-1033/Canertifinib Dacomitinib			-	-
	HDAC inhibitor	-	Entinostat	-	-	-
	HSP90 inhibitor	Tanespimycin (17-AAG)			-	-
	Bispecific Ab	MEHD7945A	MM-111	-	MM-141	-
	PanHER Ab	Sym013 (experimental)			-	-
	Tetraspecific Ab	CRTB6 (experimental)		-	-	-

Figure 4. Drugs targeting HER3s interaction partners. Listed are the main protein partners of HER3. Clinically approved drugs targeting HER3 partners are underlined. Other than afatinib, no drug targeting both HER3 and a direct partner (lower part of the table) has so far been approved. Asterisks indicate drugs and resistance mechanisms that might involve HER3.

Indirect Strategies Targeting HER3/ERBB3

Several structural and functional features inherent to HER3 present a pharmacological challenge: attempts to intercept the protein must take into account its very low kinase activity.[50] In addition, HER3 seems to act as an auxiliary subunit of driver oncogenes, such as HER2/ERBB2 and EGFR, rather than a bona fide driver. Yet another feature, which is less understood, is the ability of HER3 to instigate compensatory feedback regulatory loops that adapt and compensate for inhibition of other receptors of the HER/ERBB family. Presumably, engagement of HER3 upon pathway inhibition involves multiple mechanisms, such as complex formation, de-phosphorylation, trans-phosphorylation and translocation to the plasma membrane, along with feedback regulation of the PI3K-AKT pathway, the major downstream effector of HER3.[74] Specific elements of the HER3 promoter might also be involved.[86] It is therefore conceivable that pharmacological elimination of HER3 would be accompanied by indirect side effects. Although immunological approaches have dominated the field of HER3 targeting, several additional strategies, which we briefly review below and in Figure 5, might be effective by their own, or they might assist other strategies.

HER3 strategies involving ligand targeting

The potential of NRG targeting to inhibit tumorigenicity and metastasis of breast cancer has been first demonstrated by Tsai and colleagues, who applied an NRG-based antisense scenario.[87] Later approaches employed monoclonal antibodies to NRG. Some of the mAbs show synergy with chemotherapy on lung cancer cells.[88] Notably, because NRG1 binds both HER3/ERBB3 and HER4/ERBB4, and the latter receptor is expressed in cardiac and neural tissues, toxicity might become an issue when targeting NRGs. Another way to target the ligands is a decoy receptor strategy. This entails a recombinant fusion protein linking the Fc domain of human IgG1 to the truncated extracellular domains of EGFR and ERBB4/HER4.[89] This decoy molecule showed an ability to inhibit tumor growth and metastasis in several cancer models. Finally, an original strategy based on HER3 restricted ability to autophosphorylate was developed by Jay and colleagues, who made use of bivalent ligands.[90] In principle, the engineered ligands lock HER3/ERBB3 in a homodimeric conformation, thereby prevent HER3 from forming powerful heterodimers, such as HER2-HER3 or EGFR-HER3.

Tyrosine kinase inhibitors preventing HER3 auto- and trans-phosphorylation

An important approach to target HER3/ERBB3 entails inactivation of its own, very weak, kinase activity, as well as the catalytic activity of it dimerization partners, such as EGFR and HER2/ERBB2. As mentioned previously, tumors exhibiting hyper-activation of EGFR or HER2/ERBB2 often develop resistance following treatment with reversible TKIs, such as erlotinib, gefitinib or lapatinib, and this might involve up-regulation of HER3/ERBB3. PanHER inhibitors, which target all

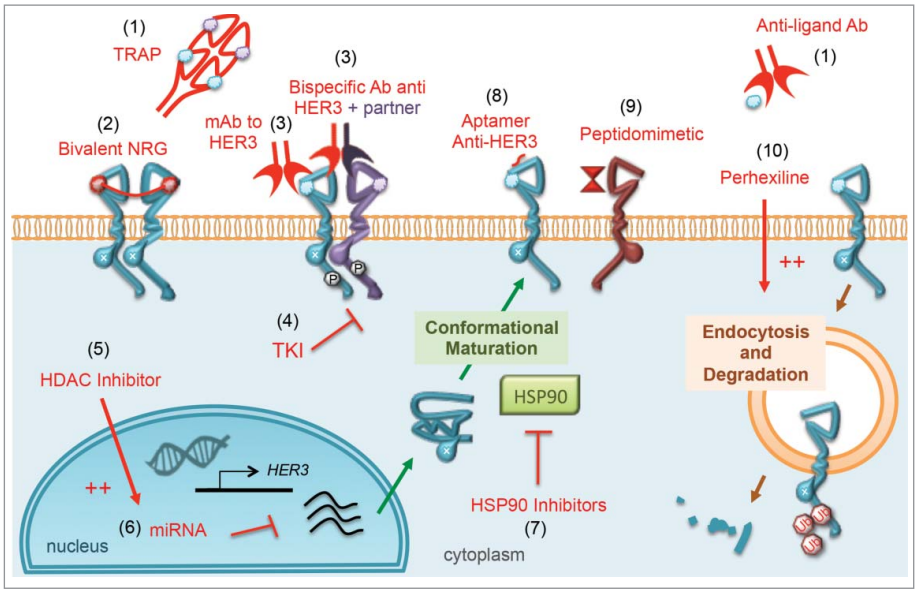


Figure 5. Direct and indirect inhibition of HER3. The last decade has witnessed the introduction of several experimental strategies able to target HER3/ERBB3. (1) The ligand trapping strategy consists of developing recombinant decoys (aka TRAP).[89] or anti-NRG antibodies,[88] thereby avoiding ligand-induced activation of HER3. (2) Since HER3 homodimers are weakly active compared to the heterodimers HER3-HER2 and HER3-EGFR, a recombinant bivalent-NRG has been developed that locks HER3 in the homodimeric conformation and restricts its ability to form heterodimers.[90] (3) Several monoclonal and multispecific antibodies have been developed to target HER3 and its dimerization partners, leading them to degradation or/and avoiding their phosphorylation.[172] Some of these antibodies are able to trigger CDC or ADCC. For example, the glycoengineered mAb RO5479599 causes enhanced ADCC, due to higher affinity to the human Fc-gamma receptor RIIIa expressed on the surface of immune effector cells. Antibodies competing with NRG and avoiding ligand-induced phosphorylation of HER3 have also been reported.[137,156] (4) Tyrosine kinase inhibitors (TKIs) have been widely used to inactivate the tyrosine kinase activity of HER3s partners, and several panHER TKIs (targeting all EGFR family members) have been developed, leading to inactive heterodimers.[94] (5) HDAC inhibitors (such as entinostat) can inhibit HER3 at the transcriptional level by inducing several miRNAs, such as miR125a, miR125b and miR205.[63] (6) Several other nucleotide-based drugs, such as the locked nucleic acid (LNA) called EZN-3920 and miR-450b-3p, might downregulate HER3. (7) Inhibiting the heat shock protein 90 (HSP90), and consequently HER3 maturation and refolding, is another way to reduce HER3 stabilization.[97] (8) HER3 can be targeted by small RNA aptamer molecules, which bind with the extracellular domain of HER3 and inhibit downstream signaling.[98] (9) Using a peptidomimetic molecule binding HER2 and mimicking HER2-HER3s dimerization site is another way to prevent HER3 activation.[99] (10) Recently, screening of approved drugs for their ability to selectively internalize and degrade HER3, identified an anti-anginal drug, perhexiline, as an agent that can target HER3.[100]

members of the HER/ERBB family, have been developed, as a default strategy that potentially overcomes this adaptive reaction. For example, afatinib (BIBW2992, Gilotrif), dacomitimib (PF299804), AZD-8931,[91] CI-1033[92,93] and several other PanHER TKIs are in different phases of clinical development.[94] Among these, dacomitinib and afatinib.[22] are particularly well advanced, and they possess novel features, such as irreversible binding to the target receptors and prevention of downstream signals. However, it has not been clearly documented in the clinic that panHER TKIs directly impact HER3 function. Specifically, IGF1-R, MET or other growth factor receptors might activate the HER3 signaling pathway and bypass inactivated EGFR or HER2.

Others indirect strategies

Entinostat (SNDX-275), a specific inhibitor of class I histone deacetylases (HDACs), appears capable of targeting HER3 at the transcriptional level. HDACs are involved in the de-acetylation of core nucleosomal histones, a process involved in aberrant cancer gene expression. Entinostat recently received BTD from FDA due to exciting data from Phase 2b data, showing a significant improvement of overall survival in patients with ER/PR positive breast cancer. Entinostat downregulates HER3 and HER2 via induction of specific microRNAs (miR-125a, miR125b, and miR205) in HER2-overexpressing breast cancer cells.[63] Likewise, several antisense oligonucleotides or microRNAs seems able to downregulate HER3, such as a locked nucleic acid (LNA)-based HER3 antisense oligonucleotide called EZN-3920,[95] which improves the anti-tumor activity of TKIs, and miR-450b-3p, which inhibits proliferation of breast cancer cells.[60] Targeting mRNAs with LNA EZN-3920 provided promising preclinical strategy but further development remains a challenge. Another indirect strategy is the use of HSP90 inhibitors, such as tanespimycin (17-AAG). The Heat Shock Protein 90 (HSP90) assists conformational maturation and refolding of various proteins, including the HER/ERBB family, IGF1-R and MET.[96] Inhibiting HSP90 reduces stability of these proteins and arrests subsequent signaling pathways. A phase 2 clinical trial showed efficacy of an HSP90 inhibitor when combined with trastuzumab in the treatment of HER2-overexpressing metastatic breast cancer.[97] Nevertheless, the HSP90 approach has been in development for over a decade in patients with advanced breast cancer without clear evidence of clinical efficacy. A30, an RNA aptamer specific to the extracellular domain of HER3, is able to inhibit NRG-induced signaling.[98] Likewise, a peptidomimetic molecule that binds HER2s domain IV and reduces HER2 dimerization with HER3 might inhibit HER2-HER3 signaling.[99] Lastly, Ren and associates recently re-purposed Perhexiline, an anti-anginal drug that inhibits mitochondrial carnitine palmitoyltransferase I (CPT1), as a promoter of HER3 internalization and degradation, as well as an inhibitor of breast cancer in an animal model.[100]

Monoclonal Antibodies Targeting HER3

Monospecific antibodies to HER3

The first monoclonal antibody specific to human HER3 was generated in our lab in 1996,[101] but many more antibodies were generated later, following the understanding that HER3 acts as a partner of HER2/ERBB2 and serves as a node responsible for resistance to several cancer drugs. Table 1 lists reagents specifically targeting HER3. By now, several antibodies have reached clinical trials (see a list in Table 2). The first fully human antibody has been patritumab (U3–1287/AMG888).[102–104] Patritumab inhibits ligand-induced phosphorylation of HER3, as well as downstream signaling to AKT and ERK. In phase 1 trials patritumab was well tolerated, and showed some evidence of disease stabilization.[105] It is notable that clinical tests of patritumab and other anti-HER3 drugs in phase 1 and phase 2 studies has been conducted in unselected patient populations. Hence, lacklustre results are not surprising. When applied to lung and head and neck carcinoma, the antibody enhanced efficacy of radiation therapy.[106] It might also prevent cetuximab resistance in colorectal cancer.[107] This mAb is currently being tested in phase 2 trials on newly diagnosed HER2-positive metastatic breast cancer, in combination with trastuzumab and paclitaxel. Based on results of the HERALD trial[108] showing a statistically significant difference in PFS over placebo in NRG-high patient with advanced NSCLC, patritumab in combination with erlotinib is currently tested in trials that recruited patients with locally advanced and metastatic lung cancer.

MM-121(SAR256212, seribantumab) is a fully humanized IgG2 mAb that inhibits ligand –induced signaling by competing with NRG for binding to HER3. MM-121 decreases formation of HER2-HER3 dimers.[109,110] When singly applied, MM-121 decreased growth of pancreatic tumor cells (AsPC-1),[111] ovarian cancer cells (OVCAR8)[112] and also cisplatin-resistant cancer cells.[113] Multiple combinations of MM-121 with others drugs have been studied. Notably, the combination MM-121 and trastuzumab has been tested on a tumor xenograft model established from trastuzumab-resistant breast cancer cells, and dramatically inhibited tumor growth by activating apoptosis.[114] In combination with erlotinib, MM-121 inhibits growth of pancreatic ductal adenocarcinoma by abolishing AKT pathway activation.[112] Henry and colleagues examined the benefit of combining MM-121 and either a PanPI3K inhibitor (SAR245408) or a microtubule inhibitor (cabazitaxel), while treating lung (A549, NSCLC) and gastric cancer cells (N87, HER2-overexpressing), respectively. In both cases mAb-induced downregulation of HER3 enhanced the inhibitory activity of the other drug.[115] In the same vein, Curley and colleagues showed that MM-121 can re-sensitize estrogen receptor (ER) positive breast cancer to letrozole, an oral non-steroidal aromatase inhibitor.[116] Finally, the combination of MM-121 and cetuximab has been reported to inhibit head and neck tumors, in animals.[117] As reported in Table 2, several clinical trials currently examine safety and efficacy of these and additional combinations of anti-HER3 antibodies. Based on results reported in conferences, the safety of MM-121 combined with several chemotherapies (platinium or taxol)[118] or cetuximab and irinotecan[119] have been confirmed. The results from phase 2 trials in NSCLC (MM121 + Erlotinib),[120] or in ovarian cancer (MM121 + Paclitaxel),[121] showed the importance of patient selection, with improved PFS compared to TKI or chemotherapy alone, especially in a subgroup of patients who were NRG positive.

LJM716 is a fully human mAb that can lock HER3 in an inactive conformation by binding with an epitope localized in between domains II and IV of HER3. It has been reported to inhibit both ligand–dependent and ligand–independent HER3 activity in vitro, and prevent tumor growth in both NRG-dependent and HER2-driven cancer models. Importantly, this mAb does not inhibit NRG binding, and it acts synergistically with anti-EGFR (cetuximab) and anti-HER2 (trastuzumab) antibodies.[122] The result of a phase 1 clinical trial testing the safety LJM716 in combination with trastuzumab in HER2 positive patients (breast and gastric cancer), show mild to moderate adverse effects and some encouraging case of partial response (6%) and stable disease (36%).[123] In combination with BYL719 (a PI3K inhibitor), either alone or with trastuzumab, LJM716 showed promising results on HER2-positive breast cancer cells.[124] These data prompted additional clinical trials, which are currently ongoing (see Table 2).

Another interesting mAb is AV-203, a humanized IgG1 directed to HER3.[125,126] AV-203 inhibits both NRG-induced

Table 1. Experimental pharmacological agents specifically targeting HER3/ERBB3, along with their respective binding sites.

	Names	Binding sites	Blocking of NRG binding
Antibodies (in clinical trials)	MM-121 (Seranbitumab)	Unknown	Yes
	U3-1287 (Patritumab)	Unknown	Unknown
	LJM716	Between domains II-IV	No
	AV-203	Unknown	Yes
	REGN1400	Unknown	Yes
	GSK2849330	Domain III	Yes
	RG7116 (Lumretuzumab)	Domain I	Yes
Other antibodies	TK-A3 and TK-A4	Domain II / Unknown	Yes / Yes
	MP-RM-1 (EV-20)	Unknown	No
	9F7-F11 and 16D3-C1	Domain I / Domain I	No / Yes
	NG33	Unknown	Yes
	A5/F4	Domains I and III	Yes
LNA	EZN-3920	*ERBB3/HER3* mRNA	-
miRNAs	miR-450b-3p	*ERBB3/HER3* 3′ UTR	-
	miR-205		-
RNA aptamers	A30	HER3 ECD	No

Table 2. Anti-HER3/ERBB3 antibodies currently in clinical trials.

Anti-HER3 mAbs	Target	Phase	Combination with	Cancer Types	CT Number	Recruitment
MM-121 (SAR256212, Seribantumab)	HER3	1	Alone	Refractory Advanced Solid Tumors	NCT00734305	Completed
		1/2	Erlotinib	Advanced Non-Small-Cell Lung (NSCLC)	NCT00994123	Completed
		2	Paclitaxel	Platinum Resistant/ Refractory Advanced Ovarian Cancers	NCT01447706	Completed
		1	Gemcitabine or carboplatin or pemetrexed or cabazitaxel	Solid Tumors	NCT01447225	Completed
		1	Cetuximab and irinotecan	Colorectal Cancer/Head and Neck Squamous Cell Carcinoma (HNSCC) /NSCLC/Triple Negative Breast Cancer/ More	NCT01451632	Completed
		1	SAR245408	Solid Tumors	NCT01436565	Completed
		2	Exemestane	Locally Advanced or Metastatic ER+ and/or PR+ HER2 Negative Breast Cancer	NCT01151046	Completed
		2	Paclitaxel	HER2-Negative Breast Cancer	NCT01421472	Completed
Patritumab (U3-1287, AMG888)	HER3	1	Alone	Solid Tumors	NCT01957280	Completed
		1	Alone	Advanced Solid Tumors	NCT00730470	Completed
		1/2	Trastuzumab and paclitaxel	Newly Diagnosed Metastatic Breast Cancer	NCT01512199	Ongoing
		1/2	Erlotinib	Advanced NSCLC	NCT01211483	Completed
		3	Erlotinib	Locally Advanced or Metastatic NSCLC	NCT02134015	Ongoing
		1	Cetuximab and platinum	HNSCC	NCT02350712	Ongoing
LJM716	HER3	1/2	BYL719	Previously Treated Esophageal Squamous Cell Carcinoma (ESCC)	NCT01822613	Ongoing
		1	BYL719 and trastuzumab	Metastatic HER2 plus Breast Cancer	NCT02167854	Ongoing
		1	Trastuzumab	HER2 Overexpressing Metastatic Breast or Gastric Cancer	NCT01602406	Completed
		1	Alone	HNSCC, or HER2 plus Breast or Gastric Cancer	NCT01598077	Completed
		1	Alone	Advanced Solid Tumors	NCT01911936	Completed
AV-203	HER3	1	Alone	Solid Tumors	NCT01603979	Completed
REGN1400	HER3	1	Erlotinib or cetuximab	Unresectable or Metastatic Tumors (without brain metastases)	NCT01727869	Completed
GSK2849330*	HER3	1	Alone	HER3 Positive Solid Tumors	NCT01966445	Ongoing
		1	Alone	HER3 Positive Solid Tumors	NCT02345174	Ongoing
RG7116* RO5479599 (GE-huMab-HER3, Lumretuzumab)	HER3	1	Alone, or with cetuximab, or erlotinib	Metastatic and/or Locally Advanced Malignant HER3-Positive Solid Tumors	NCT01482377	Completed
		1	Carboplatin and paclitaxel	Advanced or Metastatic NSCLC of Squamous Histology	NCT02204345	Suspended
		1	Pertuzumab and paclitaxel	Metastatic Breast Cancer Expressing HER2 and HER3	NCT01918254	Ongoing

Bispecific Abs	Target	Phase	Combination with	Cancer Types	Number CT	Recruitment
MM-111	HER2 HER3	1	Alone	HER2 Amplified Solid Tumors / Metastatic Breast Cancer	NCT00911898	Completed
		1	Trastuzumab	Advanced HER2 Amplified, Heregulin Positive Breast Cancer	NCT01097460	Completed
		1	Cisplatin, capecitabine, trastu, lapatinib, paclitaxel, docetaxel	HER2 Positive Cancer	NCT01304784	Completed
		2	Trastuzumab and paclitaxel	HER2 Positive Carcinomas of the Distal Esophagus, Gastroesophageal (GE) Junction and Stomach	NCT01774851	Completed
MEHD7945A (Duligotuzmab, RG7597)	EGFR HER3	1	Alone	Locally Advanced or Metastatic Epithelial Tumors	NCT01207323	Completed
		1	Cisplatin and 5-FU or paclitaxel and carboplatin	Recurrent/Metastatic HNSCC	NCT01911598	Completed
		2	Alone	Recurrent/Metastatic HNSCC	NCT01577173	Completed
		2	FOLFIRI	KRAS Wild-Type Metastatic Colorectal Cancer	NCT01652482	Completed
		1	Alone	Locally Advanced or Metastatic Cancers With Mutant KRAS	NCT01986166	Ongoing
MM-141	IGF-IR HER3	1	Alone, or with everolimus or abraxane and gemcitabine	Advanced Solid Tumors	NCT01733004	Ongoing
		2	Nab-paclitaxel and gemcitabine	Metastatic Pancreatic Cancer	NCT02399137	Ongoing

* Glycoengineered mAbs

and HER2-dependent activation of HER3, and it acts as a potent inhibitor of downstream signaling pathways by preventing HER2-HER3 dimerization. This mAb appears to be effective when tested in several cancer models, such as breast and pancreatic tumors; its safety has been successfully tested in a phase 1 clinical trial on patients with metastatic or advanced solid tumors.[127] TK-A3 and TK-A4 (aka, A3 and A4) are humanized IgG1 mAbs that inhibit NRG-dependent phosphorylation of HER3 and promote HER3 internalization and degradation. These mAbs showed an ability to decrease growth of several tumor types, especially melanoma, in animal models. TK-A3 recognizes the dimerization loop in domain II of HER3s extracellular domain.[128] According to recent reports, TK-A3 and TK-A4 can reduce melanoma resistance to BRAF/MEK inhibitors.[129]

MP-RM-1 and its humanized form, EV-20, is a weak affinity anti-HER3 mAb, which is able to inhibit NRG-induced activation of HER3 and downstream pathways, by promoting HER3 degradation and inhibiting HER2-HER3 dimers. Notably, the antibody cannot displace HER3-bound NRG, yet able to decrease tumor growth in several animal models.[130,131] REGN1400 is a fully human IgG molecule directed to HER3 and able to inhibit NRG binding.[132] In combination with anti-EGFR antibodies, REGN1400 can synergistically promote regression of HNSCC (FaDu) and colorectal cancer (LIM1215) models in animals. The safety of REGN1400 in combination with erlotinib or cetuximab has been tested in a phase 1 trial, showing an acceptable safety profile. Stable disease cases have been reported when used in combination with cetuximab (23%) or with erlotinib (18%). An expansion cohort is planned in HNSCC and CRC.[133] SGP1 is another mAb that competes with NRG binding and cooperates with trastuzumab when tested in vitro on breast cancer cells (SKBR3 and MDA-MB-361).[134]

Lazrek and colleagues generated mouse antibodies directed to domain I, III and IV of HER3. Although some of their mAbs do not inhibit NRG binding, they are still able to diminish tumorigenic growth in nude mice xenografted with epidermoid (A431), pancreatic (BxPC3), or triple-negative breast cancer cells (MDA-MB-468). Mech-anistically, these mAbs arrested cells at the G1 phase of the cell cycle and induced apoptosis, while reducing HER2-HER3 dimers and AKT-induced phosphorylation of MDM-2, XIAP and FOXO1.[135] It was further reported that the combination of anti-HER3 mAbs and trastuzumab effectively inhibited growth of xenografts expressing relatively low HER2 levels (e.g., A431 and A549 cells). Similarly, a combination of pertuzumab and an antibody to HER3 (denoted 9F7-F11) enhanced pancreatic tumor inhibition in mice, in line with an added benefit of antibody mixtures containing mAbs to both HER3 and HER2.[136]

Glycoengineered mAb to HER3

RG7116, also called RO5479599 (GE-huMab-HER3),[137] is a humanized glycoengineered IgG1 directed to domain I of HER3. This antibody prevents ligand binding and receptor heterodimerization, thereby blocks receptor phosphorylation and prevents downstream activation ok AKT.[138] Remarkably, the engineered glycosylation within the antibody's Fc region represents a novel feature allowing very high affinity recognition of the human Fc-gamma receptor RIIIa of immune effector cells. Hence, this mAb is expected to strongly trigger ADCC. Consistent with this attribute, RG7116/RO5479599 effectively inhibited NSCLC mouse models. RG7116s efficacy was tested in combination with an anti-EGFR (RG7160) or anti-HER2 (pertuzumab) mAbs in an animal model of HNSCC (FaDu), or in a subcutaneous patient-derived tumor xenograft model, respectively.[138] Several clinical trials are currently ongoing to test safety of RG7116/RO5479599, either alone or in combination with other drugs (Table 2). According to initial reports, RG7116 was well tolerated when used alone to treat patients with metastatic HER3 positive tumors.[139]

GSK2849330[140] is an IgG1/IgG3 chimeric, glycoengineered humanized monoclonal antibody directed against domain III of HER3s extracellular domain and presenting enhanced ability to mediate ADCC and complement dependent cytoxicity (CDC) due to high binding affinity to human Fc-gamma receptor RIIIa and to human complement protein C1q, respectively. This mAb can block NRG binding, receptor dimerization and activation. It is currently being tested in phase 1 clinical studies.

In summary, despite encouraging preliminary results, glycoengineered mAbs against HER3 are still in an initial phase of clinical development. It is worthwhile, however, referring to a similar EGFR-targeting strategy, which yielded moderate efficacy and increased skin toxicity.[141] Hence, further clinical development has been discontinued.[142]

Antibodies engaging 2 non-overlapping epitopes of HER3

Extensive animal studies observed synergistic anti-tumor effects of combining 2–3 anti-HER2 antibodies able to recognize distinct portions of HER2,[143-145] including a dimerization-inhibitory mAb.[146] In vitro, the more effective mAb mixture was also more effective than the respective single mAbs in inducing receptor degradation[147] and ADCC.[145] Synergistic anti-tumor effects were confirmed, as well as associated with receptor degradation, using another set of mAbs.[143] As aforementioned, a mixture of 2 mAbs to HER2, trastuzumab and pertuzumab, in combination with chemotherapy, significantly prolonged OS of breast cancer patients whose tumors overexpress HER2 compared to a mixture of placebo and trastuzumab combined with chemotherapy:[148,149] The median overall survival was 56.5 months in the group receiving the pertuzumab combination, as compared with 40.8 months in the group receiving the placebo combination. Surprisingly, clinical data did not support combination of T-DM1, a drug-conjugated analog of trastuzumab, and pertuzumab. Nevertheless, future mAb combinations might be identified by systematic selections of cooperating anti-HER2 antibodies that can improve efficacy relative to the trastuzumab/pertuzumab combination.[150] In analogy to anti-HER2 combinations, we noted that certain pairs of anti-EGFR antibodies could accelerate EGFR degradation[144] and they synergized in terms of inhibiting tumorigenic growth of triple negative breast cancer cells.[151] Sym004, a therapeutic antibody mixture comprising several mAbs targeting EGFR, was shown to elicit superior cancer cell inhibition and has already completed safety trials.[152] Using cellular models, it

was shown that Sym004 might overcome acquired resistance to cetuximab.[153] In line with this, preclinical[154] data supported tumor dependency on EGFR signaling. Moreover, recent clinical data provide evidence of clinical activity in patients with mCRC whose disease progressed while on anti-EGFR therapies.[155]

Whether or not anti-HER3 antibodies can collaborate when administered in mixtures of 2 or more antibodies is still an open question. When studying in vitro mixtures of 2 mAbs to HER3/ERBB3, involving one mAb, which inhibits NRG binding, we observed clear benefit of combining 2 anti-HER3 mAbs in terms of inhibition of several cancer cells types. However, this cooperative effect was minimal in an animal model of pancreatic tumors.[156] In the same vein, D'Ouza and colleagues developed a bispecific molecule, called A5/F4, comprising 2 single chain variable fragments (ScFv) directed to HER3s domains I and III.[157] They later showed that the bispecific molecule, better than each mAb alone, inhibited cell proliferation in vitro. This result was extended to an in vivo model of gastric cancer, but no comparison to single mAbs was presented. In conclusion, combining 2 or more mAbs to EGFR and HER2 holds promise in terms of anti-tumor efficacy. Yet, not all antibodies targeting non-overlapping epitopes of EGFR or HER2 provide improved efficacy in preclinical studies, and the value of combining 2 or more anti-HER3 mAbs is still questionable.

Multispecific antibodies targeting HER3 and one of its direct partners

In line with the above-described antibody combinations, several bispecific and multispecific molecules have been developed in the past 5 y MEHD7945A is a 2-in-one human IgG1 molecule targeting both EGFR and HER3 with significantly different affinities to these receptors. By inhibiting EGFR, as well as signaling downstream to HER2-HER3 dimers, MEHD7945A strongly inhibited cancer cell growth in vitro and in vivo (cell lines NCI-H292, BxPC3, A431), especially in combination with chemotherapy (gemcitabine).[158] In later studies, MEHD7945A was shown to inhibit proliferation of cells that were resistant to anti-EGFR drugs, such as erlotinib and cetuximab,[159] and it could synergize with PI3K inhibitors in preclinical models of triple negative breast cancer.[160] Several clinical trials testing MEHD7945A alone, or in combination with chemotherapeutic agents, are currently in progress (see Table 2). In phase 1 trials, MEHD7945A showed pharmacodynamic evidence supporting target inhibition, as well as anti-tumor activity in 25% of evaluable patients with head and neck squamous cell carcinoma (HNSCC; n = 3), mCRC (n = 6), and NSCLC (n = 3). However, these results were associated with grade 3 gastro-intestinal toxicities.[161] In addition, clinical data from randomized phase 2 studies failed to provide evidence of improved efficacy in patients with advanced HNSCC[162] or in patients with metastatic CRC (NCT01652482).[163]

MM-111 is an engineered antibody fusion molecule directed to both HER2 and HER3. This bispecific antibody demonstrated an ability to decrease tumor growth in preclinical models of HER2-overexpressing cancer cells (cell lines BT474, breast cancer and N87, gastric carcinoma), especially when combined with lapatinib or with trastuzumab (see Table 2).[164] The safety of MM-111 combined with several drugs, such as chemotherapy (taxol, platinium) or anti-HER2 therapies (TKI or mAbs), has been demonstrated in a phase 1 trial performed with patients with HER2-positive cancer.[165] Similarly, MM-141 is a tetravalent bispecific antibody harbouring 4 high-affinity binding sites, 2 are specific to the insulin-like growth factor 1 receptor (IGF1-R) and 2 to HER3.[166] Notably, MM-141 displaces both NRG and IGFs (I and II) from their respective receptors. This bispecific antibody could potentiate anti-tumoral effects of chemotherapy in animal models. Similarly, MM-141 potentiated the activity of everolimus (an mTOR inhibitor) in Caki-1 xenografted mice. Presumably, MM-141s efficacy is due to suppression of signaling downstream to both HER3 and IGF-1 receptors.[166]

FL518 and CRTB6 are tetraspecific antibodies that recognize EGFR, HER2, HER3 and VEGF.[167] They were made out of 2 2-in-one antibodies, namely MEHD7945A, directed against EGFR and HER3 (as described above) and bH1–44, which binds both VEGF and HER2. Importantly, these tetraspecific molecules are able to strongly impact the crosstalk between HER proteins and the MET pathway. Accordingly, they were more effective, both in vitro and animals, than the corresponding bispecific antibodies in terms of inhibiting growth of drug-resistant cancer cells exhibiting elevated activation of MET. Similarly, Tab6 is a tetravalent antibody made out of trastuzumab and MM-121 (see above). Consequently, Tab6 binds both HER3 and HER2. So far, Tab6 was used in vitro, either alone or in combination with lapatinib, and showed an ability to decrease proliferation of breast cancer cells overexpressing HER2.[168]

Sym013 (Pan-HER) is a mixture of 6 mAbs, comprising 3 pairs of synergistic mAbs, each targeting EGFR, HER2 and HER3.[169] The mixture has been reported to effectively inhibit growth of lung (NSCLC) and head and neck (HNSCC) cancer models in vitro and in vivo. Sym013 triggers degradation of EGFR, HER2 and HER3, prevents ligand binding to EGFR and HER3, and strongly inhibits subsequent activation of the AKT and MAPK/ERK pathways. Similarly, our team, recently demonstrated anti-cancer effects of a combination of 3 mouse mAbs directed to EGFR, HER2 and HER3.[170] The mixture was able to decrease tumorigenic growth of 2 lung cancer models expressing mutant forms of EGFR, which are resistant to erlotinib (PC9-ER and H1975 cell models). Importantly, when applied alone, anti-EGFR antibodies induced a feedback compensatory loop that up-regulated both HER2 and HER3, and resulted in robust activation of the ERK pathway. Importantly, the triple antibody mixture nullified compensatory activation of ERK and, accordingly, strongly inhibited tumorigenic growth of lung cancer models both in vitro and in animals.

Epilog and the power of drug combinations

While it is presently difficult predicting the true clinical potential of HER3 interceptors, experience gained in other domains of molecular targeted cancer therapy provide a glimpse of the future.[171] Thus, following the example of trastuzumab, which targets the major partner of HER3 and is commonly combined with paclitaxel for the treatment of patients with metastatic breast cancer overexpressing HER2,[41] it seems safe predicting

that anti-HER3 agents, especially mAbs, will likely be combined with chemotherapy. It is also predictable that HER3 interceptors will induce growth arrest rather than blatant apoptosis or other types of cell death. The frequent involvement of HER3 in tumor recurrence following emergence of drug resistance raises another prediction: HER3 blockers might be especially effective in delaying onset of drug resistance in the context of genetically aberrant forms of HER/ERBB family members. Other than drug efficacy and emergence of resistance, application of the new drugs and especially their combinations, is expected to elicit mild or moderate adverse clinical effects. In similarity to other HER/ERBB-targeting agents, and in line with the phenotypes of HER3-ablated mice, side effects are expected to involve primarily skin, gastrointestinal tract, cardiac and neural tissues. In fact, serious gastrointestinal toxicities were reported when simultaneously targeting EGFR and HER3.[161] Nevertheless, the very large number of experimental drugs targeting EGFR and HER2, along with their manageable toxicities, promise that HER3 targeting will greatly expand the armamentarium available for therapy of patients with relatively hard to treat solid tumors.

Abbreviations

ADCC	Antibody-Dependent Cell-mediated Cytotoxicity
ADC	Antibody Drug Conjugate
AKT	Protein kinase B
BTD	Breakthrough Therapy Designation
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
FDA	Food and Drug Administration (USA)
MAPK	Mitogen-activated Protein Kinase
HDAC	Histone Deacetylase
HER	Human EGF Receptor
HGF	Hepatocyte Growth Factor
HNSCC	Head and Neck Squamous Cell Cancer
HSP90	Heat Shock Protein 90
IGF	Insulin-like Growth Factor
IGF1-R	Insulin-like Growth Factor 1 Receptor
IgG	Immunoglobuline G
mAb	Monoclonal Antibody
mCRC	Metastatic Colorectal Cancer
MET	Hepatocyte Growth Factor Receptor
NRG	Neuregulin
NSCLC	Non-Small Cell Lung Cancer
PFS	Progression-Free Survival
PI3K	Phosphatidylinositol 3-Kinase
RTK	Receptor Tyrosine Kinase
TKI	Tyrosine Kinase Inhibitor

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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