Chinese Medical Journal Pulmonary and Critical Care Medicine 1 (2023) 11–17

Contents lists available at ScienceDirect

Chinese Medical Journal Pulmonary and Critical Care Medicine

journal homepage: www.elsevier.com/locate/pccm

Review Article

HER3-targeted therapeutic antibodies and antibody–drug conjugates in non-small cell lung cancer refractory to EGFR-tyrosine kinase inhibitors

Margaret E. Larsen, Hui Lyu, Bolin Liu

Departments of Interdisciplinary Oncology and Genetics, Stanley S. Scott Cancer Center, School of Medicine, Louisiana State University (LSU) Health Sciences Center, New Orleans, LA 70112, USA

ARTICLE INFO

Edited by: Peifang Wei

Keywords:
Human epidermal growth factor receptor 3 (HER3)
Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI)
Resistance
Antibody
Antibody-drug conjugate (ADC)
Non-small cell lung cancer (NSCLC)

ABSTRACT

Human epidermal growth factor receptor 3 (HER3) is a unique member of the human epidermal growth factor receptor (HER/EGFR) family, since it has negligible kinase activity. Therefore, HER3 must interact with a kinase-proficient receptor to form a heterodimer, leading to the activation of signaling cascades. Overexpression of HER3 is observed in various human cancers, including non-small cell lung cancer (NSCLC), and correlates with poor clinical outcomes in patients. Studies on the underlying mechanism demonstrate that HER3-initiated signaling promotes tumor metastasis and causes treatment failure in human cancers. Upregulation of HER3 is frequently observed in *EGFR*-mutant NSCLC treated with EGFR-tyrosine kinase inhibitors (TKIs). Increased expression of HER3 triggers the so-called EGFR-independent mechanism via interactions with other receptors to activate "bypass signaling pathways", thereby resulting in resistance to EGFR-TKIs. To date, no HER3-targeted therapy has been approved for cancer treatment. In both preclinical and clinical studies, targeting HER3 with a blocking antibody (Ab) is the only strategy being examined. Recent evaluations of an anti-HER3 Ab-drug conjugate (ADC) show promising results in patients with EGFR-TKI-resistant NSCLC. Herein, we summarize our understanding of the unique biology of HER3 in NSCLC refractory to EGFR-TKIs, with a focus on its dimerization partners and subsequent activation of signaling pathways. We also discuss the latest development of the therapeutic Abs and ADCs targeting HER3 to abrogate EGFR-TKI resistance in NSCLC.

Introduction

Human epidermal growth factor receptor 3 (HER3 or erbB3) belongs to the human epidermal growth factor receptor (HER) family, which also includes the epidermal growth factor receptor (EGFR, HER1/erbB1), HER2 (erbB2), and HER4 (erbB4). The HER receptors are arguably the most characterized receptor tyrosine kinases (RTKs) contributing to both normal cell development and tumorigenesis.[1,2] They are commonly overexpressed in human cancers and play important roles in tumor initiation and progression.[3,4] Both EGFR and HER2 are excellent targets and a number of targeted therapies against EGFR and/or HER2 have been successfully used in the clinic to treat cancer patients. Unlike other family members, HER3 has negligible kinase activity.[5–7] Studies on the biology of HER3 indicate that activation of HER3 signaling promotes tumor progression via enhancement of metastatic potential and induction of treatment failure in human cancers.[8–10] Increasing evidence supports HER3 as an attractive target and inhibition of HER3 is thought to be required to overcome therapeutic resistance, enhance efficacy, and increase patient survival.[9,11–13] To date, there is no Food and Drug Administration (FDA)-approved HER3-targeted therapy for cancer treatment. Targeting HER3 with a blocking antibody (Ab) is the major strategy currently being examined in both preclinical studies and clinical evaluations.[9,11,14] A recent report of phase I trial shows that the HER3 Ab-drug conjugate (ADC, patritumab deruxtecan, U3-1402, HER3-DXd) exhibits a good safety profile and provides meaningful benefit in patients with EGFR-tyrosine kinase inhibitor (TKI)-resistant non-small cell lung cancer (NSCLC).[15] In this review, we describe our current knowledge of HER3 dimerization with a kinase-proficient receptor to activate "bypass signaling pathways", thereby resulting in resistance to EGFR-TKIs in NSCLC. We also discuss the latest development of HER3-targeted therapy, including monoclonal and bispecific Abs as well as ADCs to abrogate EGFR-TKI resistance.

Elevated expression of HER3 causes EGFR-TKI resistance to promote NSCLC progression

Immunohistochemistry analyses of clinical samples indicate that overexpression of HER3 is associated with worse overall survival in patients with various human cancers, including colorectal cancer, gastric cancer, breast cancer, melanoma, ovarian cancer, head and neck

Correspondence to: Bolin Liu, Departments of Interdisciplinary Oncology and Genetics, Stanley S. Scott Cancer Center, School of Medicine, Louisiana State University (LSU) Health Sciences Center, 1700 Tulane Ave., New Orleans, LA 70112, USA.

E-mail address: bliu2@lsuhsc.edu

https://doi.org/10.1016/j.pccm.2022.12.001
Received 31 August 2022; Available online 27 February 2023

cancer, pancreatic cancer, and cervical cancer.[16] Elevated expression of HER3 is also frequently observed in NSCLC and has been correlated with a poor prognosis and increased risk of metastasis in the patients.[17–19] It is well-documented that HER3-initiated signaling promotes cancer progression mainly through two mechanisms of action: enhancement of metastatic potential of tumor cells and induction of drug resistance in cancer treatment.[8–10] HER3 expression has been implicated as a major cause of treatment failure in cancer therapy.[10,20] Activation of HER3 signaling contributes to the drug-resistant phenotypes of HER2-positive breast cancer,[21,22] castration-resistant prostate cancer,[23] and platinum-resistant/refractory ovarian cancer.[24,25] Accumulating evidence supports a crucial role of HER3 in the development of resistance to EGFR-targeted therapy in NSCLC.[26–29] It has been shown that EGFR-TKIs, including the first-generation TKIs gefitinib and erlotinib and the third-generation TKI osimertinib, can induce HER3 expression during the treatment of *EGFR*-mutant NSCLC. The compensatory upregulation of HER3 triggers the activation of "bypass signaling pathways" via an EGFR-independent mechanism,[26,27,30] thereby resulting in resistance to gefitinib,[31,32] erlotinib,[33,34] and osimertinib.[35–37] These data suggest that elevated expression of HER3 induces EGFR-TKI resistance to promote NSCLC progression. Gene amplification of *HER3* is rare in NSCLC.[19] The underlying mechanisms of HER3 overexpression and its adaptive induction by EGFR-TKIs remain elusive. A recent study showed that osimertinib upregulated HER3 via an inositol-requiring enzyme 1α (IRE1α)-dependent mechanism in NSCLC cells;[37] however, different EGFR-TKIs may utilize distinct mechanisms to induce HER3 expression. While overexpression of HER2 has been shown to negatively impact the effectiveness of EGFR-TKIs in a subgroup of NSCLC patients with *EGFR*-mutant tumors,[38,39] it is currently unclear if HER3 has the potential to serve as a predictive biomarker for the efficacy of EGFR-TKIs in NSCLC.

HER3 forms dimerization with kinase-proficient receptors to activate "bypass signaling pathways", resulting in resistance to EGFR-TKIs in NSCLC

HER3 is unique among the HER family members. Unlike EGFR, HER2, and HER4, HER3 has limited intrinsic kinase activity.[5–7] Thus, HER3 must interact with a kinase-proficient receptor to form heterodimers. This interaction leads to the activation of multiple signaling cascades, thereby promoting cell proliferation and survival.[8–10] EGFR and HER2 are the most preferred dimerization partners for HER3 to activate downstream signaling pathways.[9] While clinical analysis confirms that overexpression of HER3 significantly correlates with worse overall survival in patients with various solid tumors, it also suggests that the influence of HER3 expression on patient survival may be greater in tumors with overexpression of HER2.[16] These data reveal that heterodimerization of HER2/HER3 plays a pivotal role in cancer progression, further emphasizing the importance of understanding the unique features of HER3 dimerization with a kinase-proficient RTK in cancer biology. Gene amplification and/or overexpression of several RTKs, including mesenchymal–epithelial transition (MET) factor, also known as hepatocyte growth factor receptor (HGFR), wild-type EGFR, HER2, HER3 and Axl (tyrosine-protein kinase receptor UFO, a member of the TAM family that also includes TYRO3 and myeloid-epithelial-reproductive tyrosine kinase (MERTK) have been observed in NSCLC cells with acquired resistance to EGFR-TKIs.[28,30,40–44] In studying the underlying mechanisms through which increased HER3 causes resistance to EGFR-TKIs, HER3 has been found to interact with some of those RTKs, leading to activation of the so-called "bypass signaling pathways" in EGFR-TKI refractory NSCLC. Heterodimerization of EGFR/HER3 and HER2/HER3-stimulated by the HER3 ligand heregulin (HRG) critically contributes to EGFR-TKI (gefitinib) resistance in NSCLC, while inhibition of HRG production potently suppresses HER3 signaling and significantly enhances the efficacy of gefitinib in NSCLC.[45] Elevated levels of HRG were observed in the plasma of NSCLC patients who had received the EGFR-TKI erlotinib.[46] Increased HRG seemed to induce resistance to the first-generation EGFR-TKIs (gefitinib or erlotinib), but not the second-generation EGFR-TKI (afatinib, a pan-HER family inhibitor).[46,47] In addition to HRG, activation of the G-protein-coupled receptors bombesin receptor (BnR) and PAC1 can also promote the formation of the EGFR/HER3 and HER2/HER3 heterodimers, thereby stimulating the growth of NSCLC cells mainly through the phosphoinositide 3-kinase (PI-3K)/protein kinase B (Akt) and mitogen-activated protein kinase kinase (MEK)/mitogen-activated protein kinase (MAPK) signaling pathways.[48,49] Interestingly, recent studies show that overexpression of DARRP-32 (dopamine- and cyclic-adenosine monophosphate [AMP]-regulated phosphoprotein of molecular weight 32,000) increases EGFR/HER3 heterodimers to promote HER3-dependent gefitinib resistance in gastric cancer[50] and NSCLC.[51] *MET* gene amplification or protein overexpression has become an important resistance mechanism to multiple EGFR-TKIs in *EGFR*-mutant NSCLC.[31,52,53] Inhibition of MET has been actively evaluated as an effective strategy in combination with EGFR-TKIs to overcome therapeutic resistance.[41,43,54] However, MET does not work in isolation and can form heterodimers with EGFR, HER2, HER3, or rearranged during transfection (RET) in lung cancer with *MET* amplification.[55] Elevated expression of MET interacts with and activates HER3 in NSCLC cell lines and/or tumor specimens resistant to gefitinib or erlotinib.[31,56] Axl is another RTK whose expression is upregulated in osimertinib-resistant NSCLC cell lines and tumor samples.[57] It has been shown that activation of Axl via its interaction with EGFR and HER3 results in intrinsic and acquired resistance to osimertinib.[58]

In addition, numerous studies reveal that activation or overexpression of insulin-like growth factor-1 receptor (IGF-1R) or fibroblast growth factor receptor 1 (FGFR1) plays an important role in the acquired resistance to EGFR-TKIs in NSCLC.[27,59–62] HER3 has been shown to interact with IGF-1R in herceptin-resistant breast cancer cells [63] and with FGFR3 in glioblastoma.[64] Currently, it is unclear if HER3 may also form heterodimers with IGF-1R or FGFR3 in NSCLC to cause EGFR-TKI resistance. To bypass EGFR signaling, HER3-containing heterodimers activate multiple signaling pathways, including the PI-3K/Akt, MEK/extracellular regulated protein kinases (ERK), and Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) pathways [Fig. 1], resulting in resistance to EGFR-TKIs in NSCLC.[30,41,43] The PI-3K/Akt signaling pathway is a well-known survival pathway, leading to multi-drug resistance in a wide variety of human cancers. Mounting evidence indicates that activation of the MEK/ERK signaling pathway seems to play a crucial role in NSCLC resistant to EGFR-TKIs.[26,40,65] Indeed, inhibition of MEK or ERK not only abrogates acquired resistance to EGFR-TKIs, but also delays the acquisition of the resistant phenotype in NSCLC.[66–68] Current clinical trials are testing the efficacy of a MEK inhibitor in combination with an EGFR-TKI in NSCLC patients.

Therapeutic antibodies and ADCs targeting HER3 to abrogate the resistance to EGFR-TKIs in NSCLC

Effective inhibition of HER3 signaling is believed to be required to overcome resistance, enhance efficacy, and increase patient survival. Due to its lack of or impaired kinase activity[5–7], HER3 is rarely targeted by small-molecule inhibitors. Targeting HER3 with a blocking Ab is the major therapeutic strategy currently under both preclinical and clinical evaluations.[9,11,14] A number of anti-HER3 Abs, including monoclonal Ab (mAb) and HER3-containing heterodimer-targeting bispecific Ab,[33,69] show antitumor activity in laboratory studies of various cancer types and some of them have been tested in clinical evaluations. [9,70,71] Here, we focus on the recent development of mAbs, bispecific Abs, and ADCs that are directly against HER3 in NSCLC, especially those refractory to EGFR-TKIs. Table 1 lists the ongoing clinical trials testing the efficacy of HER3-targeted therapeutic Abs and ADCs in cancer patients.

Table 1
Ongoing clinical trials of HER3-targeted ADCs or Abs in patients with various cancers (ClinicalTrials.gov).

Abs	Targets	Trial phases	Clinicaltrials.gov identifier	Cancer types	Sponsor
ADCs					
U3-1402/HER3-DXd	HER3	Early phase I	NCT04610528	Breast cancer	SOLTI Breast Cancer Research Group
U3-1402	HER3	Phase II	NCT04699630	Advanced/metastatic breast cancer	SCRI Development Innovations, LLC
U3-1402	HER3	Phase II	NCT04965766	Advanced/metastatic breast cancer	Gustave Roussy, Cancer Campus, Grand Paris
U3-1402	HER3	Phase I/II	NCT02980341	HER3-positive metastatic breast cancer	Daiichi Sankyo Co., Ltd.
U3-1402	HER3	Phase I	NCT03260491	Metastatic NSCLC	Daiichi Sankyo, Inc.
U3-1402	HER3	Phase II	NCT04619004	Metastatic *EGFR*-mutated NSCLC	Daiichi Sankyo, Inc.
U3-1402 (+osimertinib)	HER3	Phase I	NCT04676477	Metastatic *EGFR*-mutated NSCLC	Daiichi Sankyo, Inc.
U3-1402	HER3	Phase III	NCT05338970	Metastatic *EGFR*-mutated NSCLC after EGFR-TKI	Daiichi Sankyo, Inc.
mAbs					
MM-121/seribantumab	HER3	Phase II	NCT04383210	Advanced solid tumors with *HRG* gene fusion	Elevation Oncology
HMBD-001	HER3	Phase I/II	NCT05057013	Advanced solid tumors with HER3 expression	Cancer Research UK
SIBP-03	HER3	Phase I	NCT05203601	Advanced solid tumors (head & neck and breast cancer)	Shanghai Institute of Biological Products
Bispecific Abs					
MCLA-128/zenocutuzumab	HER2/HER3	Phase II	NCT02912949	Advanced solid tumors with *HRG* gene fusion	Merus N.V.
MCLA-128	HER2/HER3	Expanded access	NCT04100694	Advanced solid tumors with *HRG* gene fusion	Merus N.V.
MCLA-128	HER2/HER3	Phase II	NCT03321981	Metastatic breast cancer	Merus N.V.

Abs: Antibodies; ADCs: Ab-drug conjugates; EGFR: Epidermal growth factor receptor; HER: Human epidermal growth factor receptor; mAb: Monoclonal Ab; NSCLC: Non-small cell lung cancer; TKI: Tyrosine kinase inhibitor.

HER3-targeted therapeutic Abs

Among many anti-HER3 mAbs being investigated in a wide variety of human cancers, three of them (patritumab, seribantumab, and lumretuzumab) are most studied in preclinical investigations and show antitumor activity in different phases of clinical trials.[15] Patritumab (also known as U3-1287/AMG-888) is a fully humanized anti-HER3 immunoglobulin G (IgG) 1 mAb that has been clinically tested in patients with advanced solid tumors, including NSCLC.[71] Patritumab exhibits potent inhibitory effects on cell proliferation and survival in both *in vitro* and *in vivo* xenograft models of human cancers, including NSCLC.[34] It has been shown that patritumab is able to abrogate HRG (the ligand for HER3)-mediated resistance to EGFR-TKIs in the models of colorectal cancer and NSCLC,[34,72] suggesting that this Ab's antitumor activity depends on the expression levels of HRG. Indeed, circulating levels of HRG seem to serve as a predictive biomarker for the efficacy of patritumab in combination with EGFR-TKIs in clinical trials of NSCLC patients.[73–75] Seribantumab (or MM-121) is a fully human anti-HER3 IgG2 mAb with the capability to block HRG binding to HER3, thus preventing HER3 dimerization with another RTK and inhibiting downstream signaling. Along with others, we have shown that seribantumab exerts potent antitumor activity in preclinical studies of various human cancers, including HER2-positive breast cancer and NSCLC.[76–79] Further studies found that seribantumab was the most effective in repressing the growth of the tumors with ligand-dependent activation of HER3 in *in vivo* xenograft models, and it abrogated gefitinib resistance-induced by exogenous HRG in *EGFR*-mutant NSCLC cells.[76] These data are consistent with recent observations that higher *HRG* mRNA and low HER2 levels predict that the addition of seribantumab to a standard of care in patients with platinum-resistant ovarian cancer, hormone receptor-positive HER2-low breast cancer, or EGFR wild-type NSCLC will be beneficial.[80,81] Another humanized anti-HER3 IgG1 mAb, lumretuzumab (RG7116) effectively blocks HRG binding with high-affinity binding to the extracellular domain of HER3.[82] It is a glycoengineered mAb which enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) activity.[83] A phase I trial reported that lumretuzumab was well tolerated and showed evidence of clinical activity.[84] However, recent studies revealed that the combinations of lumretuzumab and an EGFR-targeted therapy, cetuximab or erlotinib, exhibited minimal clinical benefit in patients with various cancers, although the toxicity profile of the combinations was manageable.[85]

A newly developed anti-HER3 mAb GSK2849330 is a humanized IgG1/IgG3. It specifically binds to the extracellular domain III of HER3 with high affinity, preventing HRG binding to HER3, and subsequently blocks receptor dimerization and downstream signaling. In studies of HER3-expressing cancer cell lines, GSK2849330 showed potent anti-proliferative/anti-survival effects via enhanced ADCC and complement-dependent cytotoxicity (CDC) activity.[86] The promising findings prompted a phase I clinical trial of GSK2849330 in patients with HER3-positive solid tumors. A favorable safety profile was observed.[87] Most adverse events (AEs), including diarrhea (66%), fatigue (62%), and decreased appetite (31%)-caused by GSK2849330 were Grade 1 or 2. But the antitumor activity of this Ab as a monotherapy in patients was minimal. Despite this, an exceptional response was seen in an NSCLC patient with *CD74-HRG*-fusion.[87] It is currently unclear if *HRG*-fusions may serve as a useful biomarker for patient selection to further evaluate the efficacy of GSK2849330. HMBD-001 is a unique anti-HER3 IgG1 mAb. It inhibits both ligand-dependent and -independent HER3 activation via high-affinity binding to the HER3 dimerization interface. It is designed to block the formation of all HER3-containing heterodimers, regardless of ligand binding or HER2/EGFR overexpression. Preclinical studies indicate that HMBD-001 exerts robust and sustained antitumor activity in multiple HER3-positive cancer models, including those with *HRG*-fusions.[88] Ongoing phase I/II clinical

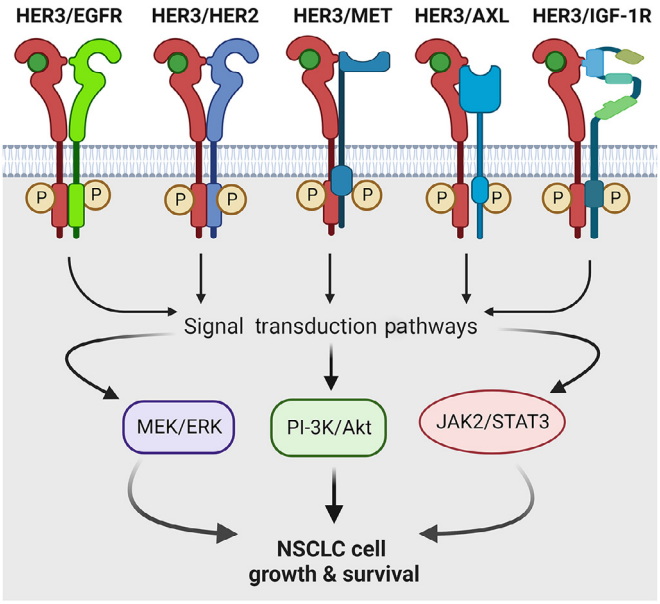

Fig. 1. Diagram of HER3 signaling-mediated promotion of NSCLC cell proliferation and survival. Increased expression of HER3 interacts with EGFR, HER2, MET, AXL, or IGF-1R to form heterodimers, which in turn activate multiple signal transduction pathways, thereby increasing the growth and survival of NSCLC cells. Created with biorender.com. Akt: Protein kinase B; AXL: Tyrosine-protein kinase receptor UFO; EGFR: Epidermal growth factor receptor; ERK: Extracellular regulated protein kinase; HER: Human epidermal growth factor receptor; IGF-1R: Insulin-like growth factor-1 receptor; JAK2: Janus kinase 2; MEK: Mitogen-activated protein kinase kinase; MET: Mesenchymal–epithelial transition; NSCLC: Non-small cell lung cancer; PI-3K: Phosphoinositide 3-kinase; P: Phosphorylation; STAT3: Signal transducer and activator of transcription 3.

trials (NCT05057013) aim to test the safety and efficacy of HMBD-001 in patients with advanced HER3-positive solid tumors, including NSCLC. In addition, a recently generated murine mAb33 against human HER3 shows the potential to prevent or overcome EGFR-TKI resistance. The mAb33 in combination with the anti-EGFR mAb cetuximab and anti-HER2 mAb trastuzumab (3xmAbs) promotes the degradation of EGFR/HER2/HER3 and induces cellular senescence. Moreover, combinations of the 3xmAbs with osimertinib exhibit synergistic effects to eliminate tumors. Thus, the 3xmAbs, either alone or in combination with EGFR-TKIs, potentially attenuate the emergence of resistance to EGFR-TKIs.[89] Interestingly, mAb33, when combined with both osimertinib and cetuximab, is also able to block the emergence of osimertinib resistance, suggesting that the combinations of mAb33, osimertinib, and cetuximab likely prevent osimertinib-induced upregulation of HER3.[90] These novel combinations may offer opportunities to prevent or overcome EGFR-TKI resistance; however, their clinical activity remains unknown.

Several bispecific Abs targeting HER3-containing heterodimers have been reported.[9,11] Among them, MCLA-128 (zenocutuzumab) seems to be the most studied HER2/HER3 bispecific Ab. It is a humanized IgG1 with two distinct Fab arms simultaneously targeting the extracellular domains of HER2 and HER3.[91] MCLA-128 showed a good safety profile and was well tolerated in clinical evaluations of patients with metastatic breast cancer.[92] This Ab-related diarrhea (all Grade 1 or 2) was observed in about 20% of patients. Recent studies reveal that MCLA-128 exhibits potent antitumor activity in *HRG* gene fusion-positive cell lines and/or patient-derived xenograft (PDX) models of lung, breast, ovarian, and pancreatic cancers. Moreover, MCLA-128 treatment achieves rapid responses in two patients with *ATP1B1-HRG* fusion-positive pancreatic cancer and partial response in a patient with *CD74-HRG* fusion-positive NSCLC.[93] Currently, three clinical trials are ongoing to test the therapeutic efficacy of MCLA-128 in patients with advanced solid tumors with *HRG* rearrangements.

HER3-targeted ADCs

Preclinical studies reveal that the majority of the anti-HER3 Abs potently induce growth inhibition and/or cell death in various cancers, especially in those with high *HRG* expression levels, and some of them demonstrate favorable toxicity profiles in clinical evaluations. However, the therapeutic efficacy of the anti-HER3 mAbs has been limited in the clinical trials of patients with solid tumors, including NSCLC.[9,14] As a result, the clinical development for most of the anti-HER3 mAbs has been discontinued. There are only a couple of active studies of the newly developed HER3 mAbs in the early phases of clinical trials [Table 1]. The underlying mechanisms of this discrepancy between preclinical and clinical antitumor activities of the anti-HER3 mAbs remain unclear. The majority of the anti-HER3 mAbs are able to delay tumor growth, but not shrink the tumors in xenografted mouse models. This suggests that although targeting HER3 with a blocking Ab by itself may not be effective, it is still a good strategy for cancer treatment, despite possibly requiring modification through drug conjugation.[14] The recent development of the HER3 ADC provides a new avenue to identify effective HER3-targeted therapy for human cancers, including NSCLC.[9,94,95]

Patritumab deruxtecan (HER3-DXd or U3-1402) is a novel anti-HER3 ADC that is composed of the mAb patritumab, a tetrapeptide-based linker, and the topoisomerase I inhibitor DX-8951 (exatecan) derivative (DXd).[96] It has been shown that HER3-DXd specifically binds to membrane HER3 with high efficiency to trigger internalization into cells. Subsequently, HER3-DXd releases its payload DXd upon linker cleavage, thereby promoting apoptosis via DNA damage.[96] Preclinical studies indicate that HER3-DXd exerts potent antitumor activity in cell line-derived xenograft (CDX) and PDX models of breast cancer, NSCLC, colon cancer, and gastric cancer with HER3 expression.[96–98] A recent analysis of the paired NSCLC samples showed that the expression of *HER3* was increased in *EGFR*-mutant tumors with acquired resistance to EGFR-TKIs as compared to those of the paired pretreatment tumor samples, supporting the rationale to examine the antitumor activity of HER3-DXd and/or osimertinib in *EGFR*-mutant NSCLC cells. Indeed, *in vitro* studies revealed that HER3-DXd in combination with osimertinib markedly inhibited the proliferation of EGFR-TKI-resistant NSCLC cells with increased expression of *HER3*.[99] Further studies were carried out by taking advantage of the PDX models-derived from EGFR-TKI-resistant NSCLC tumors. Pretreatment of the PDX models with osimertinib increased the expression of *HER3* on the cell membrane, which resulted in enhanced internalization and antitumor activity of HER3-DXd.[100] Thus, both *in vitro* and *in vivo* studies support the notion that combinations of osimertinib and HER3-DXd may be a useful approach to treat *EGFR*-mutant NSCLC. This strategy provides a new avenue for identifying effective therapy for patients with *EGFR*-mutant NSCLC.[101] Several clinical trials have been initiated to evaluate the safety and antitumor activity of HER3-DXd in patients with various human cancers, including NSCLC. In a recent phase I clinical trial, HER3-DXd exhibited a good safety profile in patients with EGFR-TKI-resistant NSCLC.[15] The most common AEs-caused by HER3-DXd were fatigue (64%) and nausea (60%). All patients ($n = 81$) had at least one AE. The most common Grade ≥3 AEs were thrombocytopenia (39%) and neutropenia (25%), both of them occurred early and transiently. While treatment was discontinued due to AEs in 9% of patients, none of them were due to thrombocytopenia. Importantly, treatment with HER3-DXd provided clinically meaningful efficacy in the patients.[15] These findings support the development of HER3-DXd as a novel therapy to overcome EGFR-TKI resistance in NSCLC.[102] It is worth mentioning that two additional HER3-targeted ADCs (EV20-Sap and EV20/MMAF) have been developed. Both EV20-Sap and EV20/MMAF have been examined in preclinical models and have shown some activity against melanoma and/or breast cancer.[103–105] To date, no studies of

EV20-Sap and EV20/MMAF in NSCLC models have been reported and there is currently no clinical evaluation of these two ADCs.

Conclusions

HER3 has been recognized as an excellent target for cancer therapy. Among many HER3-targeted Abs and ADCs being actively studied in preclinical and/or clinical settings, HER3-DXd has high potential to be developed as a promising HER3-targeted therapy for cancer patients, especially those with EGFR-TKI-resistant NSCLC.[101,102] Due to the importance of increased *HER3* expression in the emergence of resistance to EGFR-TKIs, many studies focus on testing the antitumor activity of HER3-DXd in combination with osimertinib in EGFR-TKI-resistant NSCLC.[99,100] However, the molecular basis of HER3 upregulation during EGFR-TKIs treatment remains unclear. Elucidating the underlying mechanisms will not only improve our understanding of the unique biology of HER3 in NSCLC, but also provide valuable data to facilitate the development of novel therapy for NSCLC refractory to EGFR-TKIs. Interestingly, recent studies show that HER3-DXd is able to induce antitumor immunity and enhance the efficacy of immune checkpoint blockade against *HER3*-expressing tumors, suggesting that HER3-DXd in combination with immunotherapy could be a useful approach for cancer treatment.[106] However, the scientific rationale behind this combinatorial effect is not fully understood. Clearly, HER3 must interact and act in concert with another RTK to activate multiple signaling pathways, resulting in cancer progression. Further investigations are warranted to define the key partners of HER3 during the process, which may assist with the discovery of rational drug combinations for the effective treatment of human cancers.

Acknowledgments

We are grateful to Dr. Shi-Yong Sun (Emory University School of Medicine and Winship Cancer Institute) for his critical reading of the manuscript. This work was supported in part by a translational research grant from METAvivor Research and Support Inc. and a start-up fund provided by the Stanley S. Scott Cancer Center at Louisiana State University (LSU) Health Sciences Center (to BL).

Conflicts of interest

None.

References

1. Baselga J, Swain SM. Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. *Nat Rev Cancer*. 2009;9:463–475. doi:10.1038/nrc2656.
2. Hynes N, Macdonald G. ErbB receptors and signaling pathways in cancer. *Curr Opin Cell Biol*. 2009;21:177–184. doi:10.1016/j.ceb.2008.12.010.
3. DeFazio A, Chiew YE, Sini RL, Janes PW, Sutherland RL. Expression of c-erbB receptors, heregulin and oestrogen receptor in human breast cell lines. *Int J Cancer*. 2000;87:487–498.
4. Olayioye MA, Neve RM, Lane HA, Hynes NE. The ErbB signaling network: receptor heterodimerization in development and cancer. *EMBO J*. 2000;19:3159. doi:10.1093/emboj/19.13.3159.
5. Boudeau J, Miranda-Saavedra D, Barton GJ, Alessi DR. Emerging roles of pseudokinases. *Trends Cell Biol*. 2006;16:443–452. doi:10.1016/j.tcb.2006.07.003.
6. Citri A, Skaria KB, Yarden Y. The deaf and the dumb: the biology of ErbB-2 and ErbB-3. *Exp Cell Res*. 2003;284:54–65. doi:10.1016/S0014-4827(02)00101-5.
7. Shi F, Telesco SE, Liu Y, Radhakrishnan R, Lemmon MA. ErbB3/HER3 intracellular domain is competent to bind ATP and catalyze autophosphorylation. *Proc Natl Acad Sci U S A*. 2010;107:7692–7697. doi:10.1073/pnas.1002753107.
8. Lyu H, Han A, Polsdofer E, Liu S, Liu B. Understanding the biology of HER3 receptor as a therapeutic target in human cancer. *Acta Pharm Sin B*. 2018;8:503–510. doi:10.1016/j.apsb.2018.05.010.
9. Haikala HM, Janne PA. Thirty years of HER3: from basic biology to therapeutic interventions. *Clin Cancer Res*. 2021;27:3528–3539. doi:10.1158/1078-0432.CCR-20-4465.
10. Amin DN, Campbell MR, Moasser MM. The role of HER3, the unpretentious member of the HER family, in cancer biology and cancer therapeutics. *Semin Cell Dev Biol*. 2010;21:944–950. doi:10.1016/j.semcdb.2010.08.007.
11. Liu X, Liu S, Lyu H, Riker AI, Zhang Y, Liu B. Development of effective therapeutics targeting HER3 for cancer treatment. *Biol Proced Online*. 2019;21:5. doi:10.1186/s12575-019-0093-1.
12. Ma J, Lyu H, Huang J, Liu B. Targeting of erbB3 receptor to overcome resistance in cancer treatment. *Mol Cancer*. 2014;13:105. doi:10.1186/1476-4598-13-105.
13. Zhang N, Chang Y, Rios A, An Z. HER3/ErbB3, an emerging cancer therapeutic target. *Acta Biochim Biophys Sin*. 2016;48:39–48. doi:10.1093/abbs/gmv103.
14. Yonesaka K. HER2-/HER3-targeting antibody-drug conjugates for treating lung and colorectal cancers resistant to EGFR inhibitors. *Cancers*. 2021;13:1047. doi:10.3390/cancers13051047.
15. Jänne PA, Baik C, Su WC, et al. Efficacy and safety of patritumab deruxtecan (HER3-DXd) in EGFR inhibitor-resistant, EGFR-mutated non-small cell lung cancer. *Cancer Discov*. 2022;12:74–89. doi:10.1158/2159-8290.CD-21-0715.
16. Ocana A, Vera-Badillo F, Seruga B, Templeton A, Pandiella A, Amir E. HER3 overexpression and survival in solid tumors: a meta-analysis. *J Natl Cancer Inst*. 2013;105:266–273. doi:10.1093/jnci/djs501.
17. Yi ES, Harclerode D, Gondo M, et al. High c-erbB-3 protein expression is associated with shorter survival in advanced non-small cell lung carcinomas. *Mod Pathol*. 1997;10:142–148.
18. Scharpenseel H, Hanssen A, Loges S, et al. EGFR and HER3 expression in circulating tumor cells and tumor tissue from non-small cell lung cancer patients. *Sci Rep*. 2019;9:7406. doi:10.1038/s41598-019-43678-6.
19. Manickavasagar T, Yuan W, Carreira S, et al. HER3 expression and MEK activation in non-small-cell lung carcinoma. *Lung Cancer Manag*. 2021;10:LMT48. doi:10.2217/lmt-2020-0031.
20. Gala K, Chandarlapaty S. Molecular pathways: HER3 targeted therapy. *Clin Cancer Res*. 2014;20:1410–1416. doi:10.1158/1078-0432.CCR-13-1549.
21. Holbro T, Beerli RR, Maurer F, Koziczak M, Barbas 3rd CF, Hynes NE. The ErbB2/ErbB3 heterodimer functions as an oncogenic unit: ErbB2 requires ErbB3 to drive breast tumor cell proliferation. *Proc Natl Acad Sci USA*. 2003;100:8933–8938. doi:10.1073/pnas.1537685100.
22. Lee-Hoeflich ST, Crocker L, Yao E, et al. A central role for HER3 in HER2-amplified breast cancer: implications for targeted therapy. *Cancer Res*. 2008;68:5878–5887. doi:10.1158/0008-5472.CAN-08-0380.
23. Jathal MK, Chen L, Mudryj M, Ghosh PM. Targeting ErbB3: the new RTK(id) on the prostate cancer block. *Immunol Endocr Metab Agents Med Chem*. 2011;11:131–149. doi:10.2174/187152211795495643.
24. Mills GB, Yarden Y. The rebirth of a phoenix: ovarian cancers are addicted to ErbB-3. *Cancer Cell*. 2010;17:217–218. doi:10.1016/j.ccr.2010.02.023.
25. Sheng Q, Liu X, Fleming E, et al. An activated ErbB3/NRG1 autocrine loop supports in vivo proliferation in ovarian cancer cells. *Cancer Cell*. 2010;17:298–310. doi:10.1016/j.ccr.2009.12.047.
26. Rotow J, Bivona TG. Understanding and targeting resistance mechanisms in NSCLC. *Nat Rev Cancer*. 2017;17:637–658. doi:10.1038/nrc.2017.84.
27. Lim SM, Syn NL, Cho BC, Soo RA. Acquired resistance to EGFR targeted therapy in non-small cell lung cancer: mechanisms and therapeutic strategies. *Cancer Treat Rev*. 2018;65:1–10. doi:10.1016/j.ctrv.2018.02.006.
28. Tomasello C, Baldessari C, Napolitano M, et al. Resistance to EGFR inhibitors in non-small cell lung cancer: clinical management and future perspectives. *Crit Rev Oncol Hematol*. 2018;123:149–161. doi:10.1016/j.critrevonc.2018.01.013.
29. Rosell R, Cardona AF, Arrieta O, et al. Coregulation of pathways in lung cancer patients with EGFR mutation: therapeutic opportunities. *Br J Cancer*. 2021;125:1602–1611. doi:10.1038/s41416-021-01519-2.
30. Liu Q, Yu S, Zhao W, Qin S, Chu Q, Wu K. EGFR-TKIs resistance via EGFR-independent signaling pathways. *Mol Cancer*. 2018;17:53. doi:10.1186/s12943-018-0793-1.
31. Engelman JA, Zejnullahu K, Mitsudomi T, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science*. 2007;316:1039–1043. doi:10.1126/science.1141478.
32. Sergina NV, Rausch M, Wang D, et al. Escape from HER-family tyrosine kinase inhibitor therapy by the kinase-inactive HER3. *Nature*. 2007;445:437–441. doi:10.1038/nature05474.
33. Huang S, Li C, Armstrong EA, et al. Dual targeting of EGFR and HER3 with MEHD7945A overcomes acquired resistance to EGFR inhibitors and radiation. *Cancer Res*. 2013;73:824–833. doi:10.1158/0008-5472.CAN-12-1611.
34. Yonesaka K, Hirotani K, Kawakami H, et al. Anti-HER3 monoclonal antibody patritumab sensitizes refractory non-small cell lung cancer to the epidermal growth factor receptor inhibitor erlotinib. *Oncogene*. 2016;35:878–886. doi:10.1038/onc.2015.142.
35. Du X, Yang B, An Q, Assaraf YG, Cao X, Xia J. Acquired resistance to third-generation EGFR-TKIs and emerging next-generation EGFR inhibitors. *Innovation*. 2021;2:100103. doi:10.1016/j.xinn.2021.100103.
36. Di Noia V, D'Aveni A, D'Argento E, et al. Treating disease progression with osimertinib in EGFR-mutated non-small-cell lung cancer: novel targeted agents and combination strategies. *ESMO Open*. 2021;6:100280. doi:10.1016/j.esmoop.2021.100280.
37. Vicencio JM, Evans R, Green R, et al. Osimertinib and anti-HER3 combination therapy engages immune dependent tumor toxicity via STING activation in trans. *Cell Death Dis*. 2022;13:274. doi:10.1038/s41419-022-04701-3.
38. Ohashi K, Ninomiya K, Yoshioka H, et al. Impact of HER2 expression on EGFR-TKI treatment outcomes in lung tumors harboring EGFR mutations: a HER2-CS study subset analysis. *Lung Cancer*. 2020;150:83–89. doi:10.1016/j.lungcan.2020.09.024.
39. Yu X, Ji X, Su C. HER2-altered non-small cell lung cancer: biology, clinicopathologic features, and emerging therapies. *Front Oncol*. 2022;12:860313. doi:10.3389/fonc.2022.860313.

40. Blakely CM, Bivona TG. Resiliency of lung cancers to EGFR inhibitor treatment unveiled, offering opportunities to divide and conquer EGFR inhibitor resistance. *Cancer Discov*. 2012;2:872–875. doi:10.1158/2159-8290.CD-12-0387.
41. Cooper AJ, Sequist LV, Lin JJ. Third-generation EGFR and ALK inhibitors: mechanisms of resistance and management. *Nat Rev Clin Oncol*. 2022;19:499–514. doi:10.1038/s41571-022-00639-9.
42. Johnson M, Garassino MC, Mok T, Mitsudomi T. Treatment strategies and outcomes for patients with EGFR-mutant non-small cell lung cancer resistant to EGFR tyrosine kinase inhibitors: focus on novel therapies. *Lung Cancer*. 2022;170:41–51. doi:10.1016/j.lungcan.2022.05.011.
43. Tian X, Gu T, Lee MH, Dong Z. Challenge and countermeasures for EGFR targeted therapy in non-small cell lung cancer. *Biochim Biophys Acta Rev Cancer*. 2022;1877:188645. doi:10.1016/j.bbcan.2021.188645.
44. Nukaga S, Yasuda H, Tsuchihara K, et al. Amplification of EGFR wild-type alleles in non-small cell lung cancer cells confers acquired resistance to mutation-selective EGFR tyrosine kinase inhibitors. *Cancer Res*. 2017;77:2078–2089. doi:10.1158/0008-5472.CAN-16-2359.
45. Zhou BB, Peyton M, He B, et al. Targeting ADAM-mediated ligand cleavage to inhibit HER3 and EGFR pathways in non-small cell lung cancer. *Cancer Cell*. 2006;10:39–50. doi:10.1016/j.ccr.2006.05.024.
46. Yonesaka K, Kudo K, Nishida S, et al. The pan-HER family tyrosine kinase inhibitor afatinib overcomes HER3 ligand heregulin-mediated resistance to EGFR inhibitors in non-small cell lung cancer. *Oncotarget*. 2015;6:33602–33611. doi:10.18632/oncotarget.5286.
47. Yonesaka K, Iwama E, Hayashi H, et al. Heregulin expression and its clinical implication for patients with EGFR-mutant non-small cell lung cancer treated with EGFR-tyrosine kinase inhibitors. *Sci Rep*. 2019;9:19501. doi:10.1038/s41598-019-55939-5.
48. Lee L, Ramos-Alvarez I, Moody TW, Mantey SA, Jensen RT. Neuropeptide bombesin receptor activation stimulates growth of lung cancer cells through HER3 with a MAPK-dependent mechanism. *Biochim Biophys Acta Mol Cell Res*. 2020;1867:118625. doi:10.1016/j.bbamcr.2019.118625.
49. Moody TW, Lee L, Jensen RT. The G protein-coupled receptor PAC1 regulates transactivation of the receptor tyrosine kinase HER3. *J Mol Neurosci*. 2021;71:1589–1597. doi:10.1007/s12031-020-01711-8.
50. Zhu S, Belkhiri A, El-Rifai W. DARPP-32 increases interactions between epidermal growth factor receptor and ERBB3 to promote tumor resistance to gefitinib. *Gastroenterology*. 2011;141:1738–1748.e1-2. doi:10.1053/j.gastro.2011.06.070.
51. Alam SK, Zhang Y, Wang L, et al. DARPP-32 promotes ERBB3-mediated resistance to molecular targeted therapy in EGFR-mutated lung adenocarcinoma. *Oncogene*. 2022;41:83–98. doi:10.1038/s41388-021-02028-5.
52. Roper N, Brown AL, Wei JS, et al. Clonal evolution and heterogeneity of osimertinib acquired resistance mechanisms in EGFR mutant lung cancer. *Cell Rep Med*. 2020;1:100007. doi:10.1016/j.xcrm.2020.100007.
53. Shi P, Oh YT, Zhang G, et al. Met gene amplification and protein hyperactivation is a mechanism of resistance to both first and third generation EGFR inhibitors in lung cancer treatment. *Cancer Lett*. 2016;380:494–504. doi:10.1016/j.canlet.2016.07.021.
54. Wang Q, Yang S, Wang K, Sun SY. MET inhibitors for targeted therapy of EGFR TKI-resistant lung cancer. *J Hematol Oncol*. 2019;12:63. doi:10.1186/s13045-019-0759-9.
55. Tanizaki J, Okamoto I, Sakai K, Nakagawa K. Differential roles of transphosphorylated EGFR, HER2, HER3, and RET as heterodimerisation partners of MET in lung cancer with MET amplification. *Br J Cancer*. 2011;105:807–813. doi:10.1038/bjc.2011.322.
56. Arteaga CL. HER3 and mutant EGFR meet MET. *Nat Med*. 2007;13:675–677. doi:10.1038/nm0607-675.
57. Murakami Y, Kusakabe D, Watari K, et al. AXL/CDCP1/SRC axis confers acquired resistance to osimertinib in lung cancer. *Sci Rep*. 2022;12:8983. doi:10.1038/s41598-022-12995-8.
58. Taniguchi H, Yamada T, Wang R, et al. AXL confers intrinsic resistance to osimertinib and advances the emergence of tolerant cells. *Nat Commun*. 2019;10:259. doi:10.1038/s41467-018-08074-0.
59. Cortot AB, Repellin CE, Shimamura T, et al. Resistance to irreversible EGF receptor tyrosine kinase inhibitors through a multistep mechanism involving the IGF1R pathway. *Cancer Res*. 2013;73:834–843. doi:10.1158/0008-5472.CAN-12-2066.
60. Hayakawa D, Takahashi F, Mitsuishi Y, et al. Activation of insulin-like growth factor-1 receptor confers acquired resistance to osimertinib in non-small cell lung cancer with EGFR T790M mutation. *Thorac Cancer*. 2020;11:140–149. doi:10.1111/1759-7714.13255.
61. Park JH, Choi YJ, Kim SY, et al. Activation of the IGF1R pathway potentially mediates acquired resistance to mutant-selective 3rd-generation EGF receptor tyrosine kinase inhibitors in advanced non-small cell lung cancer. *Oncotarget*. 2016;7:22005–22015. doi:10.18632/oncotarget.8013.
62. Kim TM, Song A, Kim DW, et al. Mechanisms of acquired resistance to AZD9291: a mutation-selective, irreversible EGFR inhibitor. *J Thorac Oncol*. 2015;10:1736–1744. doi:10.1097/JTO.0000000000000688.
63. 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. doi:10.1158/0008-5472.CAN-09-3321.
64. De Bacco F, Orzan F, Erriquez J, et al. ERBB3 overexpression due to miR-205 inactivation confers sensitivity to FGF, metabolic activation, and liability to ERBB3 targeting in glioblastoma. *Cell Rep*. 2021;36:109455. doi:10.1016/j.celrep.2021.109455.
65. Ercan D, Xu C, Yanagita M, et al. Reactivation of ERK signaling causes resistance to EGFR kinase inhibitors. *Cancer Discov*. 2012;2:934–947. doi:10.1158/2159-8290.CD-12-0103.
66. Li Y, Zang H, Qian G, Owonikoko TK, Ramalingam SR, Sun SY. ERK inhibition effectively overcomes acquired resistance of epidermal growth factor receptor-mutant non-small cell lung cancer cells to osimertinib. *Cancer*. 2020;126:1339–1350. doi:10.1002/cncr.32655.
67. Tricker EM, Xu C, Uddin S, et al. Combined EGFR/MEK inhibition prevents the emergence of resistance in EGFR-mutant lung cancer. *Cancer Discov*. 2015;5:960–971. doi:10.1158/2159-8290.CD-15-0063.
68. Gu J, Yao W, Shi P, et al. MEK or ERK inhibition effectively abrogates emergence of acquired osimertinib resistance in the treatment of epidermal growth factor receptor-mutant lung cancers. *Cancer*. 2020;126:3788–3799. doi:10.1002/cncr.32996.
69. McDonagh CF, Huhalov A, Harms BD, et al. Antitumor activity of a novel bispecific antibody that targets the ErbB2/ErbB3 oncogenic unit and inhibits heregulin-induced activation of ErbB3. *Mol Cancer Ther*. 2012;11:582–593. doi:10.1158/1535-7163.MCT-11-0820.
70. Malm M, Frejd FY, Ståhl S, Löfblom J. Targeting HER3 using mono- and bispecific antibodies or alternative scaffolds. *MAbs*. 2016;8:1195–1209. doi:10.1080/19420862.2016.1212147.
71. Jacob W, James I, Hasmann M, Weisser M. Clinical development of HER3-targeting monoclonal antibodies: perils and progress. *Cancer Treat Rev*. 2018;68:111–123. doi:10.1016/j.ctrv.2018.06.011.
72. Kawakami H, Okamoto I, Yonesaka K, et al. The anti-HER3 antibody patritumab abrogates cetuximab resistance mediated by heregulin in colorectal cancer cells. *Oncotarget*. 2014;5:11847–11856. doi:10.18632/oncotarget.2663.
73. Yonesaka K, Hirotani K, von Pawel J, et al. Circulating heregulin level is associated with the efficacy of patritumab combined with erlotinib in patients with non-small cell lung cancer. *Lung Cancer*. 2017;105:1–6. doi:10.1016/j.lungcan.2016.12.018.
74. Horinouchi H. The prospect of patritumab for treating non-small cell lung cancer. *Expert Opin Biol Ther*. 2016;16:1549–1555. doi:10.1080/14712598.2016.1249846.
75. Shimizu T, Yonesaka K, Hayashi H, et al. Phase 1 study of new formulation of patritumab (U3-1287) process 2, a fully human anti-HER3 monoclonal antibody in combination with erlotinib in Japanese patients with advanced non-small cell lung cancer. *Cancer Chemother Pharmacol*. 2017;79:489–495. doi:10.1007/s00280-016-3231-3.
76. Schoeberl B, Faber AC, Li D, et al. An ErbB3 antibody, MM-121, is active in cancers with ligand-dependent activation. *Cancer Res*. 2010;70:2485–2494. doi:10.1158/0008-5472.CAN-09-3145.
77. Schoeberl B, Pace EA, Fitzgerald JB, et al. Therapeutically targeting ErbB3: a key node in ligand-induced activation of the ErbB receptor-PI3K axis. *Sci Signal*. 2009;2:ra31. doi:10.1126/scisignal.2000352.
78. Huang J, Wang S, Lyu H, et al. The anti-erbB3 antibody MM-121/SAR256212 in combination with trastuzumab exerts potent antitumor activity against trastuzumab-resistant breast cancer cells. *Mol Cancer*. 2013;12:134. doi:10.1186/1476-4598-12-134.
79. Wang S, Huang J, Lyu H, et al. Therapeutic targeting of erbB3 with MM-121/SAR256212 enhances antitumor activity of paclitaxel against erbB2-overexpressing breast cancer. *Breast Cancer Res*. 2013;15:R101. doi:10.1186/bcr3563.
80. Liu JF, Ray-Coquard I, Selle F, et al. Randomized phase II trial of seribantumab in combination with paclitaxel in patients with advanced platinum-resistant or –refractory ovarian cancer. *J Clin Oncol*. 2016;34:4345–4353. doi:10.1200/JCO.2016.67.1891.
81. Schoeberl B, Kudla A, Masson K, et al. Systems biology driving drug development: from design to the clinical testing of the anti-ErbB3 antibody seribantumab (MM-121). *NPJ Syst Biol Appl*. 2017;3:16034. doi:10.1038/npjsba.2016.34.
82. Mirschberger C, Schiller CB, Schraml M, et al. RG7116, a therapeutic antibody that binds the inactive HER3 receptor and is optimized for immune effector activation. *Cancer Res*. 2013;73:5183–5194. doi:10.1158/0008-5472.CAN-13-0099.
83. Kawakami H, Yonesaka K. HER3 and its ligand, heregulin, as targets for cancer therapy. *Recent Pat Anticancer Drug Discov*. 2016;11:267–274. doi:10.2174/1574892811666160418123221.
84. Meulendijks D, Jacob W, Martinez-Garcia M, et al. First-in-human phase I study of lumretuzumab, a glycoengineered humanized anti-HER3 monoclonal antibody, in patients with metastatic or advanced HER3-positive solid tumors. *Clin Cancer Res*. 2016;22:877–885. doi:10.1158/1078-0432.CCR-15-1683.
85. Meulendijks D, Jacob W, Voest EE, et al. Phase Ib study of lumretuzumab plus cetuximab or erlotinib in solid tumor patients and evaluation of HER3 and heregulin as potential biomarkers of clinical activity. *Clin Cancer Res*. 2017;23:5406–5415. doi:10.1158/1078-0432.CCR-17-0812.
86. Clarke N, Hopson C, Hahn A, et al. 300 Preclinical pharmacologic characterization of GSK2849330, a monoclonal AccretaMab® antibody with optimized ADCC and CDC activity directed against HER3. *Eur J Cancer*. 2014;50(Suppl 6):98–99.
87. Gan HK, Millward M, Jalving M, et al. A phase I, first-in-human study of GSK2849330, an anti-HER3 monoclonal antibody, in HER3-expressing solid tumors. *Oncologist*. 2021;26:e1844–e1853. doi:10.1002/onco.13860.
88. Thakkar D, Paliwal S, Kar S, et al. Abstract P197: an anti-HER3 antibody, HMBD-001, that uniquely binds to and blocks the HER3 heterodimerization interface, shows superior tumor growth inhibition in biomarker-defined preclinical cancer models including NRG1-fusion driven cancers. *Mol Cancer Ther*. 2021;20(12_Suppl):P197. doi:10.1158/1535-7163.TARG-21-P197.
89. Mancini M, Gal H, Gaborit N, et al. An oligoclonal antibody durably overcomes resistance of lung cancer to third-generation EGFR inhibitors. *EMBO Mol Med*. 2018;10:294–308. doi:10.15252/emmm.201708076.

90. Romaniello D, Marrocco I, Belugali Nataraj N, et al. Targeting HER3, a catalytically defective receptor tyrosine kinase, prevents resistance of lung cancer to a third-generation EGFR kinase inhibitor. *Cancers*. 2020;12:2394. doi:10.3390/cancers12092394.
91. Geuijen CAW, De Nardis C, Maussang D, et al. Unbiased combinatorial screening identifies a bispecific IgG1 that potently inhibits HER3 signaling via HER2-guided ligand blockade. *Cancer Cell*. 2018;33:922–936. e10. doi:10.1016/j.ccell.2018.04.003.
92. Alsina M, Boni V, Schellens JHM, et al. First-in-human phase 1/2 study of MCLA-128, a full length IgG1 bispecific antibody targeting HER2 and HER3: final phase 1 data and preliminary activity in HER2+ metastatic breast cancer (MBC). *J Clin Oncol*. 2017;35:2522. doi:10.1200/JCO.2017.35.15_suppl.2522.
93. Schram AM, Odintsov I, Espinosa-Cotton M, et al. Zenocutuzumab, a HER2xHER3 bispecific antibody, is effective therapy for tumors driven by NRG1 gene rearrangements. *Cancer Discov*. 2022;12:1233–1247. doi:10.1158/2159-8290.CD-21-1119.
94. Marks S, Naidoo J. Antibody drug conjugates in non-small cell lung cancer: an emerging therapeutic approach. *Lung Cancer*. 2022;163:59–68. doi:10.1016/j.lungcan.2021.11.016.
95. Desai A, Abdayem P, Adjei AA, Planchard D. Antibody-drug conjugates: a promising novel therapeutic approach in lung cancer. *Lung Cancer*. 2022;163:96–106. doi:10.1016/j.lungcan.2021.12.002.
96. Hashimoto Y, Koyama K, Kamai Y, et al. A novel HER3-targeting antibody-drug conjugate, U3-1402, exhibits potent therapeutic efficacy through the delivery of cytotoxic payload by efficient internalization. *Clin Cancer Res*. 2019;25:7151–7161. doi:10.1158/1078-0432.CCR-19-1745.
97. Koganemaru S, Kuboki Y, Koga Y, et al. U3-1402, a novel HER3-targeting antibody-drug conjugate, for the treatment of colorectal cancer. *Mol Cancer Ther*. 2019;18:2043–2050. doi:10.1158/1535-7163.MCT-19-0452.
98. Yonesaka K, Takegawa N, Watanabe S, et al. An HER3-targeting antibody-drug conjugate incorporating a DNA topoisomerase I inhibitor U3-1402 conquers EGFR tyrosine kinase inhibitor-resistant NSCLC. *Oncogene*. 2019;38:1398–1409. doi:10.1038/s41388-018-0517-4.
99. Yonesaka K, Tanizaki J, Maenishi O, et al. HER3 augmentation via blockade of EGFR/AKT signaling enhances anticancer activity of HER3-targeting patritumab deruxtecan in EGFR-mutated non-small cell lung cancer. *Clin Cancer Res*. 2022;28:390–403. doi:10.1158/1078-0432.CCR-21-3359.
100. Haikala HM, Lopez T, Kohler J, et al. EGFR inhibition enhances the cellular uptake and antitumor-activity of the HER3 antibody-drug conjugate HER3-DXd. *Cancer Res*. 2022;82:130–141. doi:10.1158/0008-5472.CAN-21-2426.
101. Lim SM, Kim CG, Cho BC. Antibody-drug conjugates: a new addition to the treatment landscape of EGFR-mutant non-small cell lung cancer. *Cancer Res*. 2022;82:18–20. doi:10.1158/0008-5472.CAN-21-3481.
102. Lim SM, Kim CG, Lee JB, Cho BC. Patritumab deruxtecan: paving the way for EGFR-TKI-resistant NSCLC. *Cancer Discov*. 2022;12:16–19. doi:10.1158/2159-8290.CD-21-1429.
103. Capone E, Giansanti F, Ponziani S, et al. EV20-Sap, a novel anti-HER-3 antibody-drug conjugate, displays promising antitumor activity in melanoma. *Oncotarget*. 2017;8:95412–95424. doi:10.18632/oncotarget.20728.
104. Capone E, Lamolinara A, D'Agostino D, et al. EV20-mediated delivery of cytotoxic auristatin MMAF exhibits potent therapeutic efficacy in cutaneous melanoma. *J Control Release*. 2018;277:48–56. doi:10.1016/j.jconrel.2018.03.016.
105. Gandullo-Sánchez L, Capone E, Ocaña A, Iacobelli S, Sala G, Pandiella A. HER3 targeting with an antibody-drug conjugate bypasses resistance to anti-HER2 therapies. *EMBO Mol Med*. 2020;12:e11498. doi:10.15252/emmm.201911498.
106. Haratani K, Yonesaka K, Takamura S, et al. U3-1402 sensitizes HER3-expressing tumors to PD-1 blockade by immune activation. *J Clin Invest*. 2020;130:374–388. doi:10.1172/JCI126598.