

REVIEW

## Targeting HER3 for cancer treatment: a new horizon for an old target

J. Uliano<sup>1,2</sup>, C. Corvaja<sup>1,2,3</sup>, G. Curigliano<sup>1,2</sup> & P. Tarantino<sup>1,2,4,5\*</sup>

<sup>1</sup>Division of New Drugs and Early Drug Development, European Institute of Oncology IRCCS, Milan; <sup>2</sup>Department of Oncology and Hemato-Oncology, University of Milan, Milan; <sup>3</sup>Department of Medicine, University of Udine, Udine, Italy; <sup>4</sup>Breast Oncology Program, Dana-Farber Brigham Cancer Center, Boston; <sup>5</sup>Harvard Medical School, Boston, USA



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Human epidermal growth factor receptor 3 (HER3) is a member of the human epidermal growth factor receptors family, having as its main ligands neuregulins 1 and 2. Although its poor tyrosine kinase activity entails a weak oncogenic power on its own, HER3 can heterodimerize with HER2 and/or epidermal growth factor receptor (EGFR), leading to a drastic enhancement of transphosphorylation and activation of downstream signaling pathways, ultimately promoting oncogenesis, metastatic dissemination, and drug resistance. Given its ubiquitous expression across solid tumors, multiple efforts have been done to therapeutically target HER3 by blocking either the ligand binding domain or its dimerization with other receptors. Treatment with anti-HER3 monoclonal antibodies or bispecific antibodies, both as single agents and in combination with other compounds, unfortunately led to unsatisfactory results across several tumor types. The HER3-directed delivery of cytotoxic payloads through antibody-drug conjugates has recently demonstrated encouraging activity in several tumor types, however, suggesting a potential role for the therapeutic targeting of HER3 in cancer treatment.

**Key words:** HER3, breast cancer, lung cancer, ADCs, patritumab deruxtecan

### BIOLOGICAL BACKGROUND

Human epidermal growth factor receptor 3 (HER3/ErbB3) is a tyrosine kinase receptor belonging to the HER family alongside epidermal growth factor receptor (EGFR; ErbB1 or HER1), HER2 (ErbB2), and HER4 (ErbB4).<sup>1</sup> HER3 is a 180 kDa protein encoded by the *ERBB3* gene on 12q13.<sup>2</sup> Among the HER family members, HER3 is unique for different reasons. First, whereas EGFR binds several ligands and HER2 has none,<sup>3</sup> the preferential activators of HER3 are neuregulins (NRGs) 1-2,<sup>4</sup> also known as heregulins (HRG). Most importantly, HER3 has poor if no intracellular tyrosine kinase activity due to a divergence in critical residues in the intracellular kinase domain, which is locked in an inactive-like conformation, leading to a 1000-fold weaker kinase activity compared with EGFR.<sup>5</sup> Nonetheless, HER3 is able to form heterodimers, preferentially with HER2 and/or EGFR, which dramatically enhance transphosphorylation and the consequent activation of mitogenic downstream pathways.<sup>6</sup> Additionally, unlike other HER family members, HER3

dimerizes also with some non-HER receptors, namely mesenchymal-epithelial transition factor (MET) receptor and fibroblast growth factor receptor 2 (FGFR2).<sup>7,8</sup> Furthermore, through a direct binding with the phosphoinositide-3 kinase (PI3K) p85 subunit, HER3 is a strong activator for PI3K/protein kinase B (AKT) signaling, pivotal for cancer survival.<sup>9</sup> HER3 also activates mitogen-activated protein kinase (MAPK) cascade, janus kinase (JAK) and proto-oncogene c-Src (SRC) signaling pathways, all involved in cancer proliferation<sup>10,11</sup> (Figure 1).

The role of HER3 in cancer biology is multifaceted. Ubiquitous HER3 expression is detected in various solid tumor types<sup>12</sup> (Figure 2), with a proven role in disease progression. Two systematic analyses across multiple solid tumor types showed that HER3 expression was associated with worse overall survival, with a risk of death 1.60-fold higher compared with HER3-negative patients.<sup>12,13</sup>

HER3 cooperates with other receptors not only to promote tumorigenesis and metastatic dissemination, but also to confer resistance to anticancer drugs.

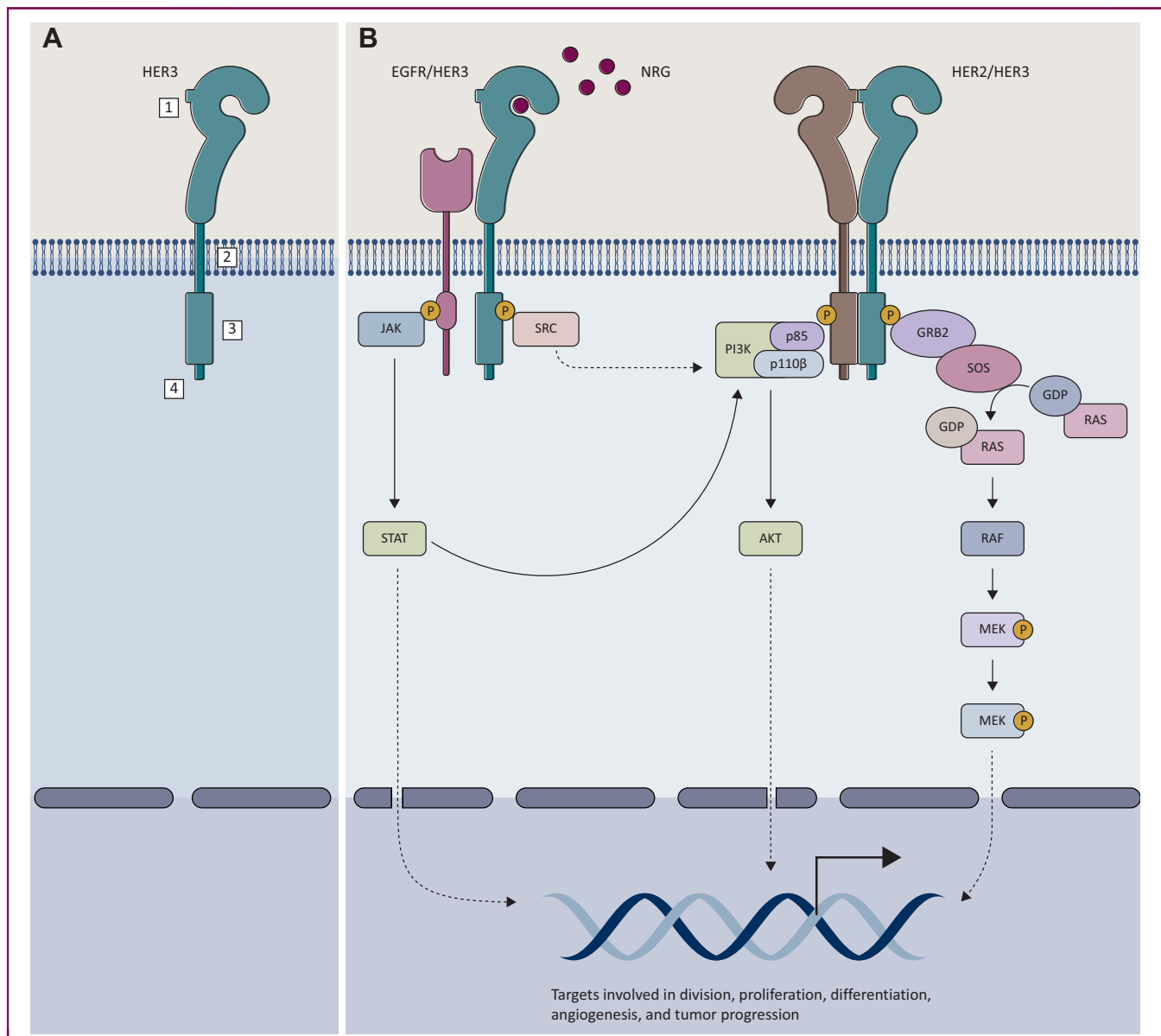
Preclinical data showed that HER3 contributes to HER2-mediated resistance to tamoxifen, and, consequently, reduction of expression of HER3 can reverse this resistance in breast cancer (BC) cell lines.<sup>14</sup> HER3 overexpression is also involved in resistance to fulvestrant: in BC cell lines, exposure to fulvestrant induced the expression and activity of HER3, significantly increasing cell proliferation

\*Correspondence to: Dr Paolo Tarantino, Division of New Drugs and Early Drug Development, IEO, European Institute of Oncology IRCCS, via G. Ripamonti 435, 20141, Milan, Italy. Tel: +39-33-86-60-90-85

E-mail: [paolo.tarantino@unimi.it](mailto:paolo.tarantino@unimi.it) (P. Tarantino).

Twitter handle: [@jacopo\\_uli](https://twitter.com/jacopo_uli) [@carlacorvaja](https://twitter.com/carlacorvaja) [@curiyoey](https://twitter.com/curiyoey) [PTarantinoMD](https://twitter.com/PTarantinoMD).

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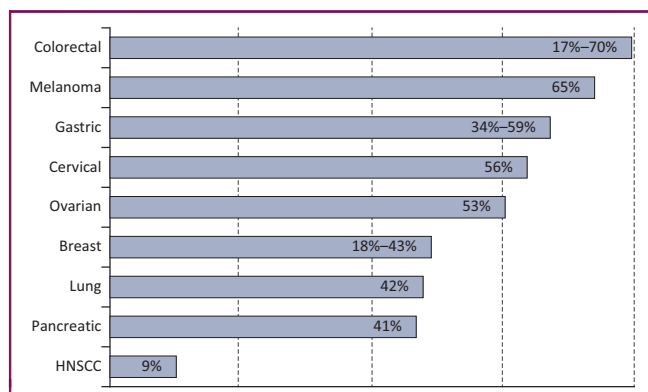


**Figure 1. HER3 and its signaling pathway.** (A) In its monomeric inactivated form, HER3, as the other highly homologous HER family proteins, consists of four structural components playing different key roles: (i) a ligand-binding extracellular domain, (ii) a transmembrane domain, (iii) an intracellular kinase domain, and (iv) a C-terminal tail. (B) The binding between NRG1-2 and HER3 induces a conformational change resulting in its heterodimerization preferentially with EGFR and HER2. This causes a further conformational modification in the intracellular domain, leading to the transphosphorylation of the C-terminal tails, which eventually activates downstream intracellular signaling pathways, such as PI3K/AKT, MAPK, JAK/STAT and SRC, regulating several cellular processes including cell division, proliferation, differentiation, as well as angiogenesis and tumor progression.

AKT, protein kinase B; EGFR, epidermal growth factor receptor; GDP, guanosine diphosphate; GTP, guanosine triphosphate; GRB2, growth factor receptor bound protein 2; HER, human epidermal growth factor receptor; JAK, janus kinase; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated extracellular signal-regulated kinase; NRG, neuregulin; PI3K, phosphoinositide-3 kinase; SOS, son of sevenless; STAT, signal transducer and activator of transcription.

compared with unexposed ones.<sup>15</sup> HER3 confers resistance to HER2-targeted therapy too. Indeed, HER3 activates PI3K/AKT and SRC signaling pathways, two of the major molecular mechanisms involved in trastuzumab and lapatinib resistance, also through heterotrimers with HER2 and insulin-like growth factor-1 receptor (IGF-1R)<sup>11,16,17</sup> and HRG-driven HER3-EGFR-PI3K-PDK1 signaling axis.<sup>18</sup> Lastly, HER3 is linked to resistance to chemotherapy: indeed, combined HER3 and EGFR overexpression worsen BC-specific and distant metastasis-free survival after adjuvant chemotherapy in triple-negative BC (TNBC).<sup>19</sup> Also, HER3

overexpression mediates paclitaxel resistance in HER2-overexpressing BC cell lines in a PI3K/AKT/mTOR signaling pathway-dependent fashion; once again, knocking down ErB3 expression can reverse this resistance mechanism.<sup>20</sup> Up-regulated HER3 signaling is involved in resistance to several other targeted therapies used for treating several tumor types, including anti-EGFR drugs gefitinib and cetuximab.<sup>21,22</sup> One of the multiple genomic alterations known to be involved in acquired resistance to anti-EGFR tyrosine kinase inhibitors (TKIs) in patients with *EGFR*-mutated advanced non-small-cell lung cancer (aNSCLC) is



**Figure 2.** Rate of HER3 overexpression across different tumor types. HNSCC, head and neck squamous cell carcinoma.

HER3 up-regulation induced by osimertinib. Thus blocking HER3/EGFR dimerization is hypothesized to prevent or delay both acquired and primary resistance to EGFR inhibitors.<sup>23</sup> Moreover, MET amplification leads to gefitinib and erlotinib resistance via increased HER3/PI3K signaling.<sup>7</sup> NRG1 and transcriptional HER3 activation are also involved in resistance to anaplastic lymphoma kinase (ALK) inhibitors and BRAF inhibitors, not only in NSCLC, but also in melanoma and thyroid cancer.<sup>24-26</sup>

Overall, there is a strong rationale behind the therapeutic targeting of HER3.

### HER3-TARGETING WITH MONOCLONAL ANTIBODIES

Monoclonal antibodies (MoAbs) target HER3 by blocking the ligand binding or the heterodimerization of the receptors (Table 1; Figure 3A).<sup>27</sup> Several anti-HER3 MoAbs have been tested for therapeutic use in oncology and, despite a favorable toxicity profile in early clinical trials, objective responses were rarely observed, underscoring limited activity as single agents. Only three molecules demonstrated promising preliminary activity and progressed up to phase II and III clinical trials: patritumab (U3-1287), a fully human HER3-directed MoAb that binds to HRG and induces reduction of expression of HER3;<sup>28</sup> seribantumab (MM-121), a fully human immunoglobulin G2 that inhibits HRG-mediated and downstream PI3K/AKT signaling;<sup>29</sup> lumretuzumab (RO5479599), an immun conjugate containing a humanized HER3-directed MoAb that binds to HER3 extracellular domain, inhibiting HER3 dimerization and EGFR-dependent signaling, and activates the immune system to exert antibody-dependent cellular cytotoxicity.<sup>30</sup>

#### Breast cancer

In patients with pretreated HER2-positive metastatic BC (mBC), a phase I study of patritumab, paclitaxel, and trastuzumab demonstrated manageable toxicities and encouraging preliminary activity.<sup>31</sup>

In a phase Ib trial, the addition of lumretuzumab to pertuzumab and paclitaxel in 35 patients with HER3-positive HER2-low (immunohistochemistry 1+ to 2+ and *in situ*

hybridization negative) BC was instead burdened by a high incidence of diarrhea and the narrow therapeutic window limited further clinical development.<sup>32</sup> As for the biomarker analysis, a phase II study of seribantumab plus exemestane in patients with hormone receptor (HR)-positive HER2-negative mBC highlighted a clinical benefit in the HRG-high subgroup.<sup>33</sup> The company, however, prematurely terminated the phase II SHERBOC trial (NCT03241810) of seribantumab and fulvestrant in such population.

#### NSCLC

In the phase II HERALD study, patritumab added to erlotinib did not prolong progression-free survival (PFS) in an unselected population of 215 patients with aNSCLC and increased risk of gastrointestinal toxicity.<sup>34</sup> Notably, PFS was improved for those tumors highly expressing HRG mRNA, although a cut-off point was not prospectively determined. The phase III HER-3Lung trial did not confirm the efficacy of patritumab and erlotinib in the subgroup of *EGFR* wild-type NSCLC patients with high HRG expression, however, leading to the premature termination of the trial.<sup>35</sup>

In *EGFR* wild-type NSCLC patients, the addition of seribantumab to erlotinib failed to improve PFS. Similarly to patritumab, a predefined retrospective analysis highlighted a PFS benefit in patients with detectable HRG mRNA,<sup>36</sup> therefore, seribantumab received fast track designation for patients with HRG-positive aNSCLC. Nonetheless, the role of HRG as a biomarker of response to seribantumab remains controversial, as the company terminated the phase II SHERLOC trial (NCT02387216) of seribantumab and docetaxel in HRG-positive NSCLC patients, after it failed to meet its primary endpoint of improved PFS at the interim analysis.

#### Other tumors

A phase II trial evaluated the combination of the anti-HER3 MoAb CDX-3379 and cetuximab in a population of heavily pretreated patients with head and neck squamous cell carcinoma (HNSCC). Preliminary antitumor activity was observed with an acceptable safety profile, with diarrhea representing the most common treatment-related adverse event (TRAE).<sup>37</sup> In a first-in-human phase I study of ISU104 in patients with advanced solid tumors, mucositis and diarrhea represented the most frequent TRAEs and among the 15 patients enrolled, seven stable disease and one partial response were observed.<sup>38</sup>

#### BEYOND HER3-DIRECTED MOAB: BISPECIFIC ANTIBODIES

To overcome the limits and resistance mechanisms to single-agent HER3-directed MoAb, bispecific antibodies have been tested in clinical trials. The most promising bispecific agent is the HER2/HER3-directed zenocutuzumab (MCLA-128), that inhibits HRG-stimulated HER3-dependent tumor growth and recruits natural killer (NK) cells into the tumor bed. Zenocutuzumab demonstrated clinical activity in patients with *NRG1* fusion-positive solid tumors, including aNSCLC, BC, and pancreatic cancer,<sup>39,40</sup> and it is

**Table 1. HER3-targeted agents under clinical development**

Drug type	Name of the compound	Mechanism of action	Phase of clinical development	Sponsor
Monoclonal antibodies	Patritumab (U3-1287)	HER3-directed MoAb	Phase III	Daiichi Sankyo Co., Ltd
	Seribantumab (MM-121)	HER3-directed MoAb	Phase II	Elevation Oncology
	Lumretuzumab (RO5479599)	Immunoconjugate containing a glycoengineered, humanized HER3-directed MoAb; ADCC	Phase Ib/II	Hoffmann-La Roche
	GSK2849330	HER3-directed MoAb	Phase I	GlaxoSmithKline
	CDX-3379	A human HER3-directed MoAb	Phase II	Celldex Therapeutics
	Barecetamab (ISU104)	A fully human HER3-directed MoAb.	Phase I	ISU Abxix Co., Ltd
	AV-203	A humanized HER3-directed MoAb.	Phase I	AVEO Pharmaceuticals, Inc.
	Elgemtumab (LJM716)	HER3-directed MoAb	Phase I/II	MorphoSys/Novartis
	HMBD-001	Anti-HER3 MoAb	Phase I/II	Hummingbird Bioscience
	U3P1287/01 (AMG888)	Anti-HER3 MoAb	Phase I	U3 Pharma GmbH
SIBP-03	HER3-directed recombinant humanized MoAb	Phase Ia	Shanghai Institute Of Biological Products	
Bispecific antibodies	Zenocutuzumab (MCLA-128)	HER2/HER3-directed IgG bispecific antibody; ADCC	Phase II	Merus N.V.
	Sym013	An antibody mixture composed of six humanized IgG1 MoAbs EGFR, HER2, and HER3 directed	Phase I/II	Symphogen A/S
	Isitarumab (MM-141)	HER3/IGF-1R-directed bispecific antibody	Phase II	Merrimack Pharmaceuticals
	SI-B001	EGFR/HER3-directed bispecific IgG	Phase I	Sichuan Baili Pharmaceutical Co., Ltd
	MM-111 Duligotuzumab (MEHD7954A)	HER2/HER3 bispecific antibody EGFR/HER3-directed bispecific antibody	Phase I Phase II	Merrimack Pharmaceuticals Genentech/Roche
ADCs	Patritumab deruxtecan (U3 1402)	HER3-directed ADC, composed of patritumab, an HER3-directed MoAb, conjugated to the topoisomerase I inhibitor DX 8951	Phase I/II	Daiichi Sankyo Co., Ltd

ADC, antibody–drug conjugate; ADCC, antibody-dependent cellular cytotoxicity; EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; IGF-1R, insulin-like growth factor-1 receptor; IgG, immunoglobulin G; MoAb, monoclonal antibody.

currently under evaluation in the phase I/II eNRGy trial (NCT02912949).

Conversely, duligotuzumab (MEHD7954A), an EGFR/HER3-directed bispecific MoAb, failed to improve clinical outcomes compared with cetuximab in HNSCC in the phase II MEHGAN study, regardless of NRG1 expression, and was found to be burdened by a high incidence of gastrointestinal TRAEs.<sup>41</sup> Moreover, the addition of duligotuzumab to FOLFIRI did not improve clinical outcomes compared with FOLFIRI/cetuximab in patients with *KRAS* wild-type metastatic colorectal cancer.<sup>42</sup>

The development of the bispecific HER3/IGF-1R-directed MoAb istiratumab (MM-141) was discontinued by the Sponsor following the negative results of the phase II CARRIE trial, as its addition to first-line nab-paclitaxel and gemcitabine did not show a clinical benefit in patients with metastatic pancreatic cancer with high IGF-1 serum levels.<sup>43</sup>

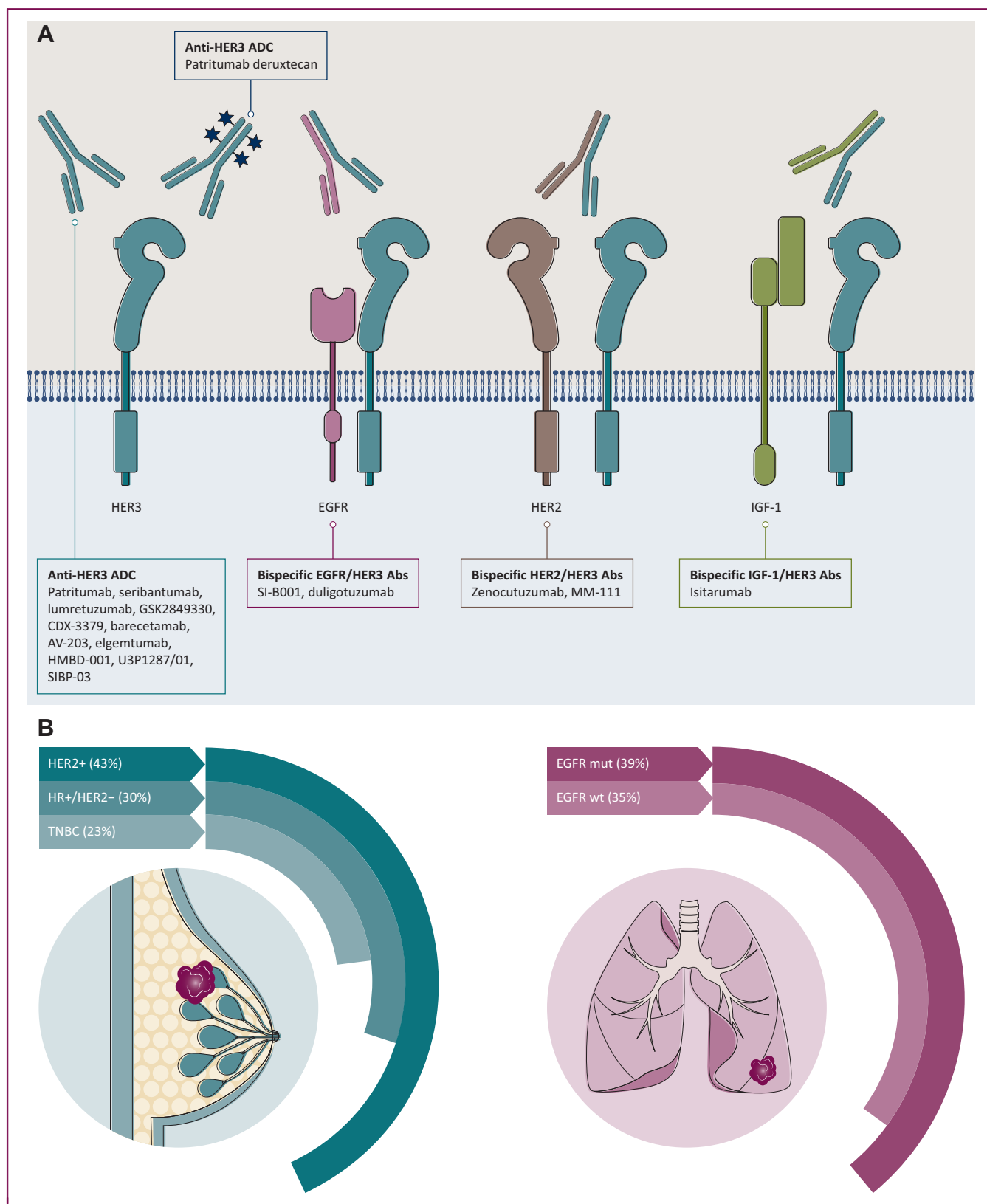
### NEW HORIZON: THE ANTIBODY-DRUG CONJUGATES ERA

The most promising results have been observed with antibody–drug conjugates (ADCs), which allow for HER3-directed delivery of highly cytotoxic molecules to tumor cells. Patritumab deruxtecan (U3 1402; HER3-DXd) consists of patritumab linked, via a tetrapeptide-based cleavable linker, to a topoisomerase I inhibitor payload (DX-8951), that inhibits DNA replication and triggers apoptotic cell

death. In addition, through DXd-induced cell damage and immune activation, HER3-DXd might elicit antitumor immune response.<sup>44</sup> *In vitro* and *in vivo*, HER3-DXd sensitizes HER3-expressing cells for anti-programmed cell death protein 1 inhibition, therefore warranting the investigation of combinations with immune checkpoint inhibitors (ICIs).<sup>45</sup> Table 2 summarizes current ongoing clinical trials on novel anti-HER3 strategies.

### Breast cancer

The phase I/II, first-in-human, U31402-A-J101 study evaluated HER3-DXd in 182 heavily pretreated patients with HER3-expressing mBC, showing promising and durable antitumor activity across all BC subtypes (Figure 3B). Overall, at both doses of 4.8 mg/kg and 6.4 mg/kg every 3 weeks, HER3-DXd showed a manageable toxicity profile and a low rate of discontinuation (9.9%) due to treatment-emergent adverse events (TEAEs), most commonly gastrointestinal and hematologic. Nonetheless, interstitial lung disease (ILD) was observed in 6.6% of patients, mostly grade 1 and 2 although one grade 5 event was observed. Grade 3 or higher hematologic toxicities were observed more frequently at the dose of 6.4 mg/kg and they were managed by dose delay or reduction. Thrombocytopenia occurred frequently (60.4% at 4.8 mg/kg and 71.4% at 6.4 mg/kg), but none resulted in a grade  $\geq 3$  bleeding event.<sup>46</sup>



**Figure 3.** (A) Anti-HER3 therapeutic strategies. In the last decades, several anti-HER3 compounds with different mechanisms have been tested, unfortunately with disappointing results. Amongst them: MoAbs targeting HER3 preventing its heterodimerization with other receptors; bispecific Abs targeting both HER3 and EGFR or HER2 or IGF-1; the ADC patritumab-deruxtecan. (B) ORR of patritumab deruxtecan in pretreated mBC and advanced NSCLC. In BC, durable antitumor activity was observed across the range of HER3 expression in metastatic HR-positive/HER2-negative BC (ORR 30%; median DOR 7.2 months), TNBC (ORR 23%; median DOR 5.9 months) and HER2-positive BC (ORR 43%; median DOR 8.3 months) patients. In pretreated patients with *EGFR*-mutated and wild-type NSCLC, patritumab deruxtecan at the dose of 5.6 mg/kg achieved an ORR of 39% and 35%, respectively.

ADC, antibody–drug conjugate; BC, breast cancer; DOR, duration of response; EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; HR, hormone receptor; IGF-1, insulin-like growth factor-1; mBC, metastatic breast cancer; MoAb, monoclonal antibody; NSCLC, non-small-cell lung cancer; ORR, overall response rate; TNBC, triple-negative breast cancer.

**Table 2.** Current ongoing clinical trials investigating novel anti-HER3 strategies

NCT number	Conditions	Setting	Phase	Treatment arms	Status	Population
NCT04610528 (TOT-HER3)	BC	Early	I	Patritumab deruxtecan	Recruiting	Enrollment: 80
NCT05057013	Solid tumors	Advanced or metastatic	I/II	HMBD-001	Recruiting	Enrollment: 135
NCT02980341	BC	Advanced or metastatic	I/II	Patritumab deruxtecan	Active, not recruiting	Enrollment: 184
NCT05504707 (DecipHER)	TNBC; HER2-negative BC	Early	I	HER2 and HER3 - primed dendritic cells	Recruiting	Enrollment: 30
NCT04348747	TNBC; HER2-positive BC	Advanced with brain metastasis	II	Anti-HER2/HER3 Dendritic cell Vaccine/pembrolizumab	Recruiting	Enrollment: 23
NCT03065387	Solid tumors	Advanced or metastatic	I	Neratinib/everolimus Neratinib/palbociclib Neratinib/trametinib	Recruiting	Enrollment: 120
NCT04603287	Epithelial tumors	Advanced or metastatic	I	SI-B001	Active, not recruiting	Enrollment: 60
NCT03552406	Solid tumors	Advanced	I	ISU104/cetuximab	Active, not recruiting	Enrollment: 33
NCT04965766 (ICARUS-BREAST)	Breast cancer	Advanced or metastatic (second line)	II	Patritumab deruxtecan	Recruiting	Enrollment: 100
NCT02912949 (eNRGy)	Solid tumors	Advanced or metastatic	II	Zenocutuzumab	Recruiting	Enrollment: 250
NCT05338970 (HERTHENA-Lung02)	Non-squamous NSCLC	Advanced or metastatic	III	Patritumab deruxtecan versus platinum-based chemotherapy	Recruiting	Enrollment: 560
NCT05203601	Solid tumors	Advanced or metastatic	I	SIBP-03	Recruiting	Enrollment: 68
NCT04619004 (HERTHENA-Lung01)	EGFR-mutated NSCLC	Advanced or metastatic (>2 lines)	II	Patritumab deruxtecan fixed dose (group 1) Patritumab deruxtecan up-titration (group 2)	Recruiting	Enrollment: 420
NCT04676477	EGFR-mutated NSCLC	Advanced or metastatic	I	Patritumab Deruxtecan/osimertinib	Recruiting	Enrollment: 252
NCT04383210	Solid tumors	Advanced or metastatic	II	Seribantumab	Recruiting	Enrollment: 75
NCT05044897	HNSCC	Recurrent	II	SI-B001	Recruiting	Enrollment: 30
NCT04699630	BC	Advanced or metastatic	II	Patritumab deruxtecan	Recruiting	Enrollment: 120
NCT03260491	NSCLC	Advanced or metastatic	I	Patritumab deruxtecan	Recruiting	Enrollment: 264
NCT04209465	Solid tumors	Advanced or metastatic	I/II	BDTX-189	Active, not recruiting	Enrollment: 91

BC, breast cancer; EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small-cell lung cancer; TNBC, triple-negative breast cancer.

Based on these encouraging results, HER3-DXd was investigated in the early setting. In the window-of-opportunity SOLT1 TOT-HER3 study, patients with untreated HR-positive/HER2-negative resectable BC received a single preoperative dose of HER3-DXd (6.4 mg/kg). The primary endpoint was a variation in a combined score based on tumor cellularity and tumor-infiltrating lymphocytes (CeTIL score), that correlates with pathological complete response.<sup>47</sup> Preoperative HER3-DXd led to clinically meaningful responses, with an ORR of 45% at C1D21 in the first 30 patients enrolled, alongside increased immune infiltration, suppressed proliferation, and increased CeTIL score in responders. No cases of ILD were reported and most frequent grade  $\geq 3$  TRAEs included diarrhea, neutropenia, and increased alanine aminotransferase levels.<sup>48</sup> The TOT-HER3 substudy will continue enrollment in patients with TNBC and the SOLT1-VALENTINE will evaluate neoadjuvant HER3-DXd alone or in combination with endocrine therapy in HR-positive/HER2-negative BC. Furthermore, the phase II ICARUS-BREAST trial (NCT04965766) will investigate

HER3-DXd in HR-positive BC patients with high HER3 expression progressing after cyclin-dependent kinase 4/6 inhibitors.

### NSCLC

In the dose expansion cohort of a phase I trial, HER3-DXd (5.6 mg/Kg) achieved an ORR of 39% (24.4%-54.5%) in 44 patients with EGFR-mutated NSCLC progressed after osimertinib and platinum-based chemotherapy (PBC). At a median follow-up of 10.2 months, median duration of response was 6.9 months with a PFS of 8.2 months. The most common grade  $\geq 3$  TEAE was thrombocytopenia. ILD occurred in 5% of patients with one case of grade 5 event, although it was reported to be not related to study treatment.<sup>49</sup> Based on these results, the phase II HERTENA-Lung01 (NCT04619004) is currently evaluating HER3-DXd in this population whereas the phase III HERTENA-Lung02 (NCT05338970) will compare HER3-DXd with PBC in EGFR-mutated NSCLC after failure of third-generation TKIs. The

combination of HER3-DXd and osimertinib is also under evaluation in a phase I clinical trial (NCT04676477), both in first and second line. Interestingly, HER3-DXd (5.6 mg/kg) also achieved an ORR of 35% in a cohort of 47 patients with *EGFR* wild-type aNSCLC pretreated with PBC and ICIs (Figure 3B). Notably, HER3-DXd was active regardless of the presence of several other oncogenic alterations, including *KRAS/NRAS* mutations and *ALK* fusions. Myelotoxicity was the most common grade  $\geq 3$  TRAE and ILD was observed in 9% of the patients, without any drug-related deaths.<sup>49</sup>

## CONCLUSION

Owing to its intrinsic impaired kinase activity, HER3 has been historically overlooked as a therapeutic target. Only recently, a deeper knowledge of its role and the interplay with other ErbB receptors has driven an interest in the development of HER3-directed agents. Anti-HER3 MoAbs showed limited activity as single agents across several solid tumors. Nonetheless, far more promising results have been observed with the targeted delivery of cytotoxic payloads through the ADC patritumab deruxtecan, although hematologic and potentially life-threatening pulmonary toxicities require prompt diagnosis and management. Biomarkers of response to HER3-directed agents need to be explored and prospectively validated, as the role of HRG mRNA expression remains controversial.

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## DISCLOSURE

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