

# HER3 signaling and targeted therapy in cancer

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## Abstract

ERBB family members including epidermal growth factor receptor (EGFR) also known as HER1, ERBB2/HER2/Neu, ERBB3/HER3 and ERBB4/HER4 are aberrantly activated in multiple cancers and hence serve as drug targets and biomarkers in modern precision therapy. The therapeutic potential of HER3 has long been underappreciated, due to impaired kinase activity and relatively low expression in tumors. However, HER3 has received attention in recent years as it is a crucial heterodimeric partner for other EGFR family members and has the potential to regulate EGFR/HER2-mediated resistance. Upregulation of HER3 is associated with several malignancies where it fosters tumor progression via interaction with different receptor tyrosine kinases (RTKs). Studies also implicate HER3 contributing significantly to treatment failure, mostly through the activation of PI3K/AKT, MAPK/ERK and JAK/STAT pathways. Moreover, activating mutations in HER3 have highlighted the role of HER3 as a direct therapeutic target. Therapeutic targeting of HER3 includes abrogating its dimerization partners' kinase activity using small molecule inhibitors (lapatinib, erlotinib, gefitinib, afatinib, neratinib) or direct targeting of its extracellular domain. In this review, we focus on HER3-mediated signaling, its role in drug resistance and discuss the latest advances to overcome resistance by targeting HER3 using mono- and bispecific antibodies and small molecule inhibitors.

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## Introduction

The four members of human epidermal growth receptors (EGFR/HER) family are EGFR/ERBB1/HER1, ERBB2/HER2/Neu, ERBB3/HER3 and ERBB4/HER4. These are expressed widely in numerous cells such as epithelial, neuronal, tumor and mesenchymal cells.<sup>1,2</sup> ERBB family members are known to regulate several cellular processes including cell division, cell proliferation, differentiation, angiogenesis and tumor progression.<sup>1</sup> All ERBB family members share a common molecular structure consisting of an extracellular domain (ECD), a transmembrane domain, an intracellular domain with tyrosine kinase (TK) activity and a c-terminal tail. The ERBB members generally exist in a tethered conformation in equilibrium with an open conformation, except for HER2. HER2 has no known high-affinity ligands and has a constitutive active conformation with its dimerization loop open and exposed.<sup>3</sup> EGFR binds to several ligands including EGF, epiregulin, betacellulin, TGF- $\alpha$ . Neuregulins (NRG) also known as Heregulins (HRG) bind to HER3 and HER4.<sup>4,5</sup> Binding of ligands lead to receptor dimerization, activation of tyrosine kinases and c-terminal tail phosphorylation of tyrosines. This leads to recruitment of adaptor proteins that trigger activation of downstream PI3K/AKT, MAPK and JAK/STAT pathways imparting several biological processes ultimately leading to tumor progression.<sup>2,5,6</sup>

HER3 possesses impaired kinase activity and preferably heterodimerizes with HER2. HER3 heterodimerizes with RTKs to activate oncogenic signaling via the PI3K/AKT pathway. HER3 and downstream PI3K/AKT signaling is a major cause of treatment failure.<sup>7</sup> NRG-1 and NRG-2 are high affinity ligands for HER3. In the absence of ligands, HER3 sub-domain arm II is locked in a tethered auto-inhibitory configuration, refraining from forming homo- or heterodimers. However, HER3 heterodimerizes with HER2 in ligand-independent manner in HER2-amplified cells.<sup>8</sup> Recent clinical strategies focus on direct targeting of HER3 using monoclonal antibodies (mAbs), which avert ligand-induced activation. This review focuses on the latest advances in our understanding regarding the role of HER3 in tumorigenesis and drug resistance in cancer and also discusses novel strategies for therapeutic targeting of HER3 in cancer treatment.

## HER3 structure and role in oncogenesis

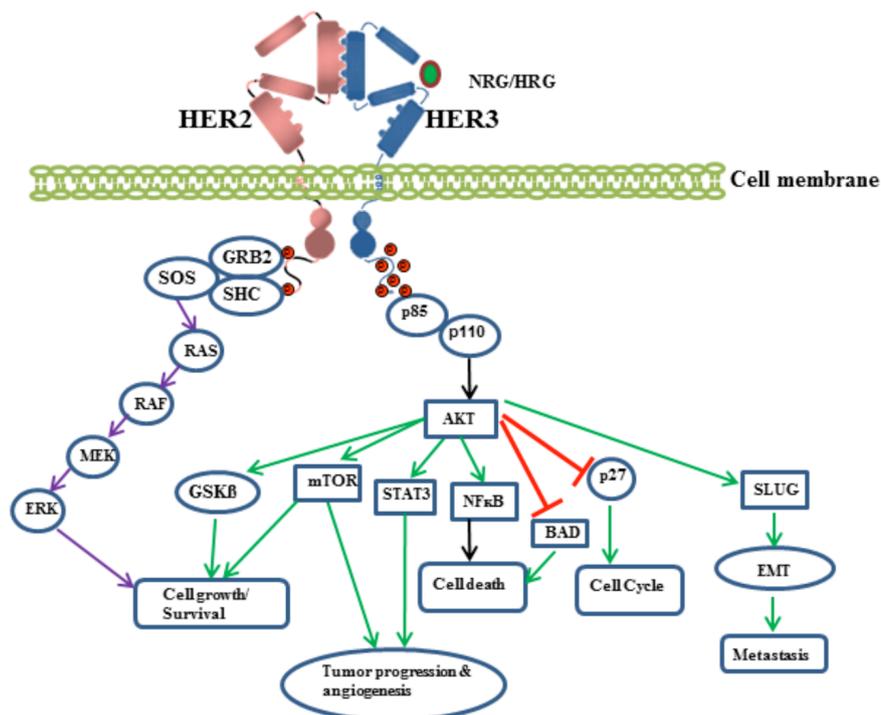
HER3, first identified by Kraus et al. is located on the long arm of chromosome 12 (12q13).<sup>9</sup> It is encoded by 23,651 base pairs and translates into 1342 amino acids. HER3 ECD is divided into four sub-domains (I-IV), which includes two cysteine-rich regions (II and IV) and two flanking domains (I and III) that determine specificity for ligand binding. Cys-721, His-740 and Asn-815 have non-conservative substitutions in HER3 which diminishes the catalytic activity of TK domain of HER3 indicating that HER3 utilizes alternative pathway for its activation.<sup>10</sup>

Enhanced expression of HER3 is associated with malignancies of several cancers including ovarian, breast, prostate, gastric, bladder, lung, melanoma, colorectal and squamous cell carcinoma.<sup>11-19</sup> HER3 is the preferred heterodimeric partner for EGFR in melanoma and pancreatic carcinoma.<sup>17,20</sup> Co-expression of HER2 and HER3 is common in breast cancer and breast cancer derived cell lines.<sup>21</sup> HER3 plays a critical role in HER2-mediated tumorigenesis. Tumors occurring in mice overexpressing the neu transgene exhibit increased expression and activation of HER3.<sup>22</sup> Inhibition of HER2 using tyrosine kinase inhibitors (TKIs) suppresses HER3-mediated downstream activation of PI3K signaling in HER2-overexpressing cells.<sup>23</sup> HER3 is crucial for HER2 for maintaining cell viability in HER2-expressing breast cancer cells.<sup>24</sup> Attenuation of HER3 abrogates HER2-mediated transformation of mammary epithelium in transgenic mice model.<sup>25</sup> HER2 cannot directly bind and activate p85, the regulatory subunit of PI3K. However, HER3 contains six p85-binding motifs, which gets activated by HER2 via heterodimerization, and triggers PI3K signaling. Also, inhibition of HER2 TK activity results in upregulation of HER3 transcription and phosphorylation. This compensatory activation of HER3 partially maintains PI3K/AKT signaling.<sup>26,27</sup> These data suggest that HER2-dependent breast cancers rely on HER3 to drive oncogenic signaling. HER3 is emerging as a crucial biomarker in luminal breast cancers. HER3 mRNA is expressed significantly in estrogen receptor positive (ER+) or luminal tumors, consistent with the observation that HER3 is essential for cell survival in the luminal but not the basal normal mammary epithelium.<sup>28-30</sup> HER3 neutralizing antibodies in combination with anti-estrogen treatment result in decreased tumor cell growth and delayed resistance.<sup>29,31,32</sup> HER3 mutations are more frequently identified in the ECD with fewer mutations in the intracellular KD.<sup>33</sup> The oncogenic potential of most HER3 mutants depends on HER2 for its transforming potential.<sup>34,35</sup> HER3 muta-

tions are common in gastric (12%) and colon cancer (11%). HER3 mutants are reported to transform breast epithelial and colonic cells in a ligand-independent manner.<sup>34</sup> Figure 1 illustrates HER2/HER3-mediated signaling pathways.

### The role of HER3 in resistance to hormonal therapy

Recently, HER3 activation has been linked to resistance to the ER antagonist, tamoxifen. Enhanced HER3 expression helps breast cancer cells to bypass responsiveness to normal endocrine therapies.<sup>36,37</sup> Clinical studies also indicate that breast cancer patients with co-expression of HER2 and HER3 are more likely to relapse on tamoxifen.<sup>38</sup> Liu *et al.* demonstrates that attenuation of HER3 using siRNA abrogates HER2-mediated tamoxifen resistance in breast cancer cells. Inhibition of HER3 significantly increases tamoxifen-induced growth inhibition of MCF7 cells and HER2 overexpressing MCF7 cells via enhanced apoptosis however, does not alter expression or activation of ER $\alpha$ .<sup>39</sup> Increased sensitivity of MCF-7 cells to tamoxifen upon HER3 downregulation could be due to decreased p-AKT levels as AKT signaling is associated with tamoxifen resistance in breast cancer cells.<sup>40,41</sup> Elevated expression of HER3 in Castration-Resistant Prostate Cancer (CRPC) leads to activation of PI3K/AKT signaling and androgen receptor (AR) stabilization.<sup>42</sup> ER+ breast cancer cells when treated with the ER downregulator, fulvestrant induce protein expression and activity of HER3.<sup>43</sup> Another study demonstrates that fulvestrant resistant MCF-7 cells depend on increased HER3 and NRG-2 expression to maintain their growth and survival.<sup>44</sup> Therefore, HER3 might serve as a crucial biomarker in estrogen withdrawal therapy in luminal breast cancers and in regulating ER-mediated pathways.



**Figure 1.** Diagrammatic representation of HER2-HER3 heterodimerization, activation of downstream signaling pathways which regulate several cellular processes including cell proliferation, cell survival, apoptosis, tumor growth and metastasis.

## The role of HER3 in resistance to targeted therapy

The two approaches that are frequently used in ERBB targeted therapy are: i) using monoclonal antibodies or antibody-drug conjugates (pertuzumab, trastuzumab [Herceptin] or T-DM1 to target HER2 and cetuximab, panitumab to target EGFR); or ii) tyrosine kinase inhibitors (erlotinib and gefitinib to target EGFR, lapatinib and neratinib to target HER2). In spite of EGFR and HER2 targeted therapies having shown tremendous success in treating a wide variety of cancers, most tumors are susceptible to resistance to these therapies within months of treatment.

Several studies indicate that activation of HER3 signaling is one major cause of treatment failure to EGFR or anti-estrogen-based therapies.<sup>45,46</sup> Yonesaka *et al.* demonstrates that a subset of colorectal cancer patients acquire resistance to cetuximab-based therapy because of high levels of circulating NRG that induces activation of HER3.<sup>47</sup> Dual targeting of EGFR and HER3 is capable of overcoming acquired resistance to cetuximab and erlotinib further highlighting the role of HER3 in EGFR-targeted therapy.<sup>48</sup> MET amplification in lung cancer leads to gefitinib resistance via activation of HER3 signaling.<sup>49</sup> Additionally, transcriptional upregulation of HER3 is reported to be involved in resistance to MEK/RAF inhibitors in melanoma and thyroid carcinomas.<sup>50,51</sup> The BRAF inhibitor vemurafenib (PLX4032) upregulates HER3 expression through FOXD3 transcription factor leading to resistance in BRAF-mutant melanoma.<sup>50</sup> Vemurafenib increases HER3 signaling via induction of HER3 transcription through decreased promoter occupancy by the transcriptional repressors CtBP1/2, and through autocrine secretion of NRG-1.<sup>51</sup> Targeting HER2 with lapatinib overcomes the resistant phenotype indicating the HER3-induced resistance is dependent on HER2 expression in both melanoma and thyroid carcinoma.<sup>50,51</sup>

Genetic and functional studies on trastuzumab indicate that activation of PI3K/AKT and SRC signaling are major determinants of trastuzumab-induced resistance.<sup>52,53</sup> Studies also indicate that HER3 and IGF-1R-dependent signaling mechanisms contribute to trastuzumab-mediated resistance in several cancers.<sup>53-55</sup>

Huang *et al.* demonstrates that the heterotrimeric complex between HER3/HER2/IGF-1R is a key player in trastuzumab-mediated resistance in breast cancer. The authors also show that specific knockdown of HER3 decreases phosphorylation of AKT, SRC and increases trastuzumab-induced growth suppressing effects in resistant breast cancer cells.<sup>56</sup> Resistance to lapatinib in HER2-positive breast cancer cells is due in part via upregulation of HER3. HER3 mRNA and protein levels are upregulated upon inhibition of the HER2 kinase activity using lapatinib and downstream PI3 kinase using XL147, suggesting that HER3 mediates drug resistance in HER2-enriched breast cancer.<sup>26,57</sup> Research indicates that HER3 signaling contributes to chemotherapy resistance in ovarian cancer. Doxorubicin upregulates NRG to trigger HER3/PI3K pathways in these tumors.<sup>58</sup> Also, activation of HER3 signaling plays a vital role in progression of mCRPC into docetaxel-based chemotherapy.<sup>42</sup> Knufermann *et al.* illustrates that increased resistance to several chemotherapeutic agents like doxorubicin, 5-fluorouracil, paclitaxel, camptothecin and etoposide is associated with co-expression of HER2/HER3 and induced activation of PI3K/AKT signaling.<sup>59</sup> Enhanced expression of HER3 confers paclitaxel resistance in HER2+ breast cancer cells via AKT-mediated upregulation of survivin.<sup>60</sup>

## Anti-HER3 targeted therapies in clinic

Anti-HER3 therapies are based on targeting HER3 in one of the following mechanisms: i) locking HER3 in the tethered confirmation; ii) trapping its ligand, NRG; iii) blocking ligand binding sites; iv) triggering the internalization of the HER3 receptor; v) abrogating dimerization with other EGFR family members; or vi) employing immune cells to kill cancer cells expressing endogenous HER3. The targeted therapies against HER3 include use of mono-/bi-specific antibodies,<sup>61-63</sup> anti-HER3 vaccines,<sup>64</sup> bi-specific ligand traps for HER3,<sup>65,66</sup> HER3-locked nucleic acid based RNA inhibitors,<sup>67</sup> small molecule inhibitors against HER3-pseudokinase activity.<sup>68</sup> Tables 1 and 2 and Figure 2 summarize

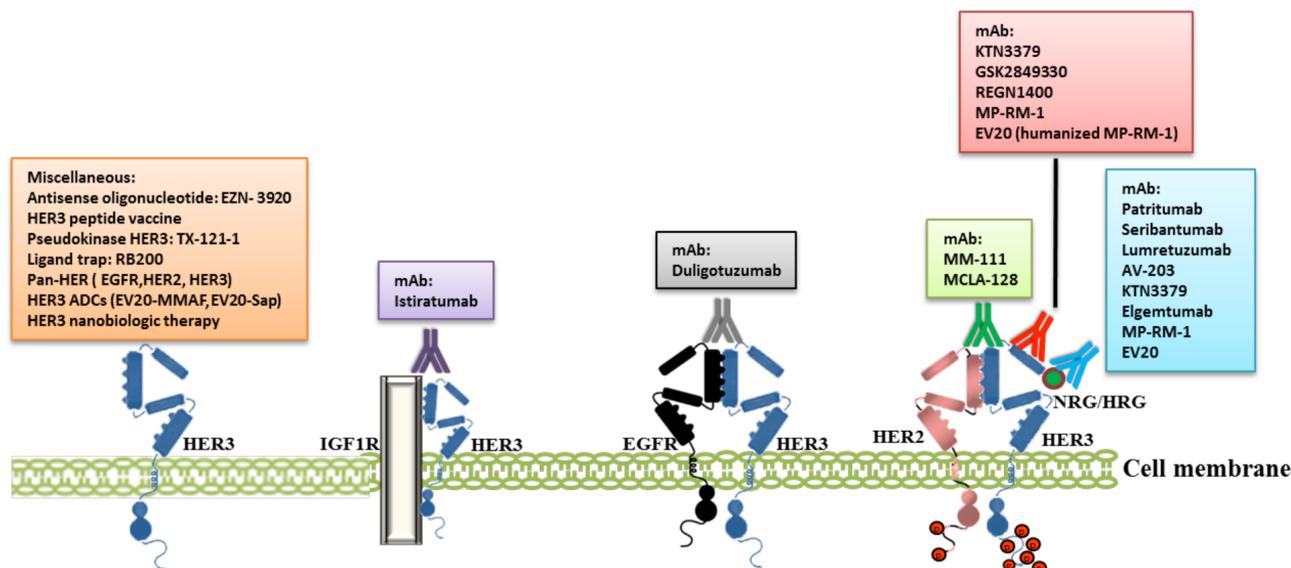


Figure 2. HER3 binding partners and anti-HER3 targeted therapies in preclinical and clinical trials. Several mono and bispecific antibodies targeting HER3 at multiple sub-domains (described in the text). Miscellaneous HER3 targeting therapies including antisense oligonucleotides, HER3 specific peptides vaccines, ligand traps, molecules targeting HER3 pseudokinase activity, pan HER approach, HER3 ADCs and HER3 nanobiologic therapeutic approach.

**Table 1. Anti-HER3 antibody as HER3 therapy.**

HER3 targeted therapy (anti-HER3 antibody)	Target	Cancer types studies	Clinical/preclinical	Sponsor
Patritumab (U3-1287/A888)	HER3	- Colorectal cancer (with cetuximab) [69]	Preclinical	-
		- Advanced solid tumors [70]	Phase I	Daiichi Sankyo
		- Advanced NSCLC (with erlotinib) [71]	Phase I	Daiichi Sankyo
		- Erlotinib induced resistant NSCLC patients [72]	Preclinical	-
		- EGFR wild-type patients with locally advanced or metastatic NSCLC patients (with erlotinib) [73]	Phase III (terminated)	Daiichi Sankyo
U3-1402 (Modified U3-1287)	HER3	- HNSCC (in combination with cetuximab, cisplatin and carboplatin) [74]	Phase II	Daiichi Sankyo
		- MBC patients (with trastuzumab plus paclitaxel) [75]	Phase Ib/II (terminated)	Daiichi Sankyo
U3-1402 (Modified U3-1287)	HER3	- Metastatic or unresectable EGFR-mutant NSCLC [76]	Phase I	Daiichi Sankyo
Seribantumab (MM-121)	HER3	- Locally advanced/metastatic or recurrent ovarian cancer, fallopian tube cancer, primary peritoneal cancer, endometrial cancer, locally advanced/metastatic HER2 non-overexpressing breast cancer (in combination with paclitaxel) [77]	Phase I	Merrimack
		- Colorectal cancer, HNSCC, NSCLC, TNBC and other tumors with EGFR dependence (in combination with cetuximab and irinotecan) [78,81]	Phase I	Merrimack
		- Preoperative TNBC and HR+, HER2- breast cancer (in combination with paclitaxel) [79,82]	Phase II	Merrimack
		- Refractory advanced solid tumors [80,83]	Phase I	Merrimack
		- Advanced platinum resistant/refractory ovarian cancer (in combination with paclitaxel) [84]	Phase II	Merrimack
		- ERBB2-overexpressing breast cancer (along with paclitaxel) [85]	Preclinical	-
		- Trastuzumab-resistant breast cancer [86]	Preclinical	-
		- HNSCC (in combination with cetuximab) [87]	Preclinical	-
		- NSCLC (in combination with docetaxel) [88]	Phase II	Merrimack
		- NRG+, locally advanced or metastatic NSCLC patients (in combination with docetaxel or pemetrexed) [89]	Phase II	Merrimack
		- Advanced NSCLC (in combination with erlotinib) [90]	Phase I/II	Merrimack
		- NRG+, HR+, HER2- MBC in postmenopausal women (in combination with fulvestrant) [91]	Phase II	Merrimack
		- Locally advanced or metastatic ER+ and/or PR+, HER2- breast cancer in post- menopausal women (in combination with exemestane) [92,93]	Phase II	Merrimack
		- Advanced NRG+ NSCLC, HNSCC and colorectal cancer patients (in combination with MM-151, MM-141 or trametinib) [94]	Phase I (terminated)	Merrimack
		- Advanced solid tumors (in combination with gemcitabine, pemetrexed, cabazitaxel and adapted doses of carboplatin) [95]	Phase I	Merrimack
Lumretuzumab (RG7116, RO-5479599)	HER3	- Solid tumors (in combination with SAR245408) [96]	Phase I	Sanofi
		- HER3+ breast cancer expressing HER2 and HER3 protein (in combination with paclitaxel and pertuzumab) [99,100]	Phase I	Roche
		- Metastatic or advanced HER3+ solid tumors [101]	Phase I	Roche
		- Advanced/metastatic NSCLC (in combination with carboplatin and paclitaxel) [102]	Phase Ib/II (terminated)	Roche
Elgemtumab (LJM716)	HER3	- Solid tumors (in combination with cetuximab or erlotinib) [103]	Phase Ib	Roche
		- HER2+ breast cancer [105]	Preclinical	-
		- Platinum-pretreated recurrent/metastatic HNSCC patients (with cetuximab) [106]	Phase Ib/II (withdrawn)	Novartis
		- HER2+ MBC (in combination with BYL719 and trastuzumab) [107]	Phase I	Novartis
		- HER2 overexpressing MBC, gastric cancer (in combination with trastuzumab) [108]	Phase I	Novartis
		- ESCC (in combination with BYL719, paclitaxel, docetaxel, irinotecan) [109]	Phase Ib/II	Novartis
		- ESCC, HNSCC, HER2-overexpressing MBC or gastric cancer [110]	Phase I	Novartis
- Advanced solid tumors [111]	Phase I	Novartis		

Continued on the next page.

HER3-targeted therapies. Table 3 briefly describes the clinical trials, outcomes and adverse effects.

## Monoclonal antibodies against HER3

*Patritumab* (U3-1287/A888) is a mAb directed against HER3 ECD. It induces HER3 internalization by preventing ligand binding, dimerization and suppresses tumor growth in HER3 express-

ing *in vivo* mice models.<sup>69</sup> It has also been investigated in several clinical and preclinical cancer models including colorectal and lung carcinoma.<sup>69-72</sup> Cancer cells treated with patritumab show reduced cellular migration, proliferation, and anchorage-independent growth. In addition, EGFR- and HER3-expressing xenografts treated with patritumab and anti-EGFR antibody, cetuximab exhibit significantly reduced tumor growth compared to single antibody.<sup>69</sup> Patritumab inhibits erlotinib-induced resistance in

**Table 1. Continued from previous page.**

HER3 targeted therapy (anti-HER3 antibody)	Target	Cancer types studies	Clinical/preclinical	Sponsor
KTN3379	HER3	- Advanced tumors [113]	Phase I	Celldex Therapeutics
		- Advanced solid tumors (alone or in combination with erlotinib, vemurafenib, cetuximab and trastuzumab) [114]	Phase Ib	Celldex Therapeutic
		- BRAF mutant melanoma and RAI thyroid cancer (in combination with vemurafenib) [115]	Phase I	Celldex Therapeutic
		- Surgically resectable HNSCC [116]	Phase I	Celldex Therapeutic
AV-203	HER3	- Metastatic or advanced solid tumors [118,119]	Phase I	Aveo
GSK2849330	HER3	- Advanced HER3+ solid tumors [120,121]	Phase I	Glaxo Smith Kline
REGN1400	HER3	- NSCLC, colorectal cancer, HNSCC (in combination with erlotinib or cetuximab) [122]	Phase I	Regeneron
		- HNSCC, colorectal cancer [123]	Preclinical	Regeneron
MP-RM-1	HER3	- Melanoma, gastric, prostate, breast cancer [124]	Preclinical	-
EV20 (humanized MP-RM-1)	HER3	- Prostate cancer, HNSCC, pancreatic cancer, melanoma, breast cancer [125]	Preclinical	-
		- Resistance to vemurafenib in BRAFV600E mutant colon cancer stem cell [127]	Preclinical	-
Duligotuzumab (RG7597, MEHD7945A)	HER3/EGFR	- Solid epithelial tumors [129]	Preclinical	-
		- Locally advanced or metastatic epithelial tumors [130]	Phase I	Genentech
		- Locally advanced or metastatic cancers with mutated KRAS (in combination with cobimetinib) [131,133]	Phase Ib	Genentech
		- KRAS wild-type metastatic colorectal cancer (in combination with FOLFIRI- 5-fluorouracil, folinic acid and irinotecan) [132,134]	Phase II	Genentech
		- Recurrent or metastatic HNSCC (during or following platinum therapy versus cetuximab) [135,136]	Phase II	Genentech
		- Recurrent or metastatic HNSCC (in combination with cisplatin/5'-FU or carboplatin/paclitaxel) [137]	Phase Ib/II	Genentech
MM-111	HER2/HER3	- HER2 expressing carcinomas of the distal esophagus, GE junction and stomach (with paclitaxel and trastuzumab) [138]	Phase II (study interrupted)	Merrimack
		- Advanced, refractory HER2 amplified, NRG+ cancer [139]	Phase I	Merrimack
		- Advanced HER2 amplified, NRG+ breast cancer (in combination with herceptin) [140]	Phase I	Merrimack
		- Advanced HER2+ solid tumors (along with different combination treatment of capecitabine/cisplatin/trastuzumab/lapatinib/paclitaxel or docetaxel) [141]	Phase I	Merrimack
Istiratumab (MM-141)	HER3/IGFR	- Advanced solid tumor (alone or in combination with abraxane/gemcitabine, everolimus or monotherapy) [142,143]	Phase I	Merrimack
		- Metastatic pancreatic cancer (in combination with nab-paclitaxel and gemcitabine) [144]	Phase II	Merrimack
MCLA-128	HER2/HER3	- Malignant solid tumors [145]	Phase I/II	Merus NV
		- Trastuzumab/chemotherapy in HER2+ and with endocrine therapy in ER+ and low HER2 breast cancer [146]	Phase II	Merus NV

HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung carcinoma; MBC, metastatic breast cancer; TNBC, triple negative breast cancer; ESCC, esophageal-squamous cell carcinoma; EGFR, epithelial growth factor receptor; IGFR, insulin like growth factor receptor; HR, hormone receptor; ER, estrogen receptor; 5'-FU, 5'-fluorouracil; NRG, neuregulin; PR, progesterone receptor; RAI, radioiodine-refractory; GE, gastroesophageal.

NSCLC and abrogates HER3-AKT signaling cascade.<sup>72</sup> A combination phase I clinical trial with erlotinib in Japanese patients with advanced stage NSCLC shows an overall response rate of 4.2% and disease control rate of 62.5%.<sup>71</sup> A phase III randomized, double-blind, multi-center, two-part study of patritumab in combination with erlotinib in EGFR wild-type patients with locally advanced or metastatic NSCLC patients who have progressed on at least one prior systemic therapy is terminated.<sup>73</sup> The current phase II trial including patritumab in combination with cetuximab, cisplatin and carboplatin is completed in patients with HNSCC.<sup>74</sup> A phase Ib/II clinical trial evaluating the efficacy of patritumab, trastuzumab plus paclitaxel in metastatic breast cancer is terminated due to variation in patients' standard of care.<sup>75</sup> U3-1402 is a modified antibody consisting of patritumab covalently conjugated with MAAA-1162a, a drug linker with a drug component MAAA-1181a. U3-1402 is in ongoing phase I trial in patients with NSCLC.<sup>76</sup>

*Seribantumab* (MM-121) is a humanized mAb targeting the ECD of HER3 that prevents binding of NRG, blocks heterodimerization and induces HER3 internalization and degradation.<sup>61</sup> Seribantumab is investigated in phase I and II clinical trials in combination with anti-cancer drugs or chemotherapy that covers a broad spectrum of cancer patients.<sup>77-83</sup> The clinical and preclinical studies in ovarian, breast, HNSCC and NSCLC cancers identified NRG as patient response biomarker for seribantumab.<sup>84-88</sup> A phase II study evaluating MM-121 in combination with docetaxel and pemetrexed in NSCLC patients with high NRG expression is still ongoing.<sup>89</sup> Another phase I/II study of MM-121 in combination with erlotinib is completed in patients with NSCLC.<sup>90</sup> There is an ongoing phase II trial where NRG+, HER negative (-) postmenopausal breast cancer patients are subjected to treatment with seribantumab and fulvestrant.<sup>91</sup> A randomized phase II trial of exemestane in combination with seribantumab is completed in postmenopausal women with locally advanced or metastatic ER+ and/or progesterone receptor positive (PR+) HER2- breast cancer.<sup>92,93</sup> Another non-randomized, open-label study of seribantum-

ab plus MM-151, MM-141, or trametinib in patients with advanced NRG+ NSCLC, HNSCC, colorectal cancers initiated by Merrimack is terminated.<sup>94</sup> A phase I study exploring the role of seribantumab indicates that it can be combined at its recommended single agent dose with standard doses of gemcitabine, pemetrexed, cabazitaxel and adapted doses of carboplatin for treatment of patients with advanced solid tumors.<sup>95</sup> A study exploring the role of seribantumab in combination with PI3K inhibitor, SAR245408 is completed in patients with solid tumors.<sup>96</sup>

*Lumretuzumab* (RG7116, RO-5479599) is a humanized glycol-engineered mAb, which suppresses the activation of HER3 signaling by blocking HER3 ECD and preventing NRG binding. It engages immune cells to cause antibody-dependent cell-mediated cytotoxicity (ADCC).<sup>97,98</sup> Currently, there are three clinical trials reported using RG7116. A phase I trial testing the combination of RG7116 with paclitaxel and pertuzumab targeting HER3+ breast cancer has been completed.<sup>99,100</sup> A phase I study with RG7116 illustrates an overall disease control rate of 21% in patients with advanced HER3-positive solid tumors.<sup>101</sup> A phase Ib/II trial of RG7116 in combination with carboplatin and paclitaxel although initiated in patients with NSCLC is terminated.<sup>102</sup> A phase Ib study of RG7116 plus cetuximab/erlotinib identified NRG as potential biomarker in patients with solid tumors.<sup>103</sup>

*Elgemtumab* (LJM716), a human anti-HER3 IgG1 binds to HER3 ECD, locks it in tethered conformation and prevents activation of HER3 and inhibits tumor growth *in vivo*.<sup>104,105</sup> Novartis initiated a phase Ib/II clinical trial of LJM716 in combination with cetuximab in platinum-pretreated recurrent/metastatic patients with HNSCC. However, the study is withdrawn.<sup>106</sup> There is ongoing phase I clinical study of LJM16 in combination with trastuzumab, BYL719 in HER2+ breast cancer patients.<sup>107</sup> A phase I study evaluating the combination of LJM16 with trastuzumab in patients with HER2 expressing metastatic breast or gastric cancer is completed.<sup>108</sup> LJM716 has also been tested for the safety and efficacy in phase I trial for esophageal squamous cell carcinoma.<sup>109,110</sup> A phase I study of LJM716 in Japanese patients states

**Table 2. Miscellaneous HER3 therapies.**

Other HER3 Therapy	Target	Cancer types studies	Clinical/preclinical	Sponsor
Antisense Oligonucleotide (EZN-3920)	HER3	- Lung adenocarcinoma, breast cancer (in combination with lapatinib and gefitinib) [67]	Preclinical	Enzon
HER3 peptide vaccine	HER3	- Breast cancer, pancreatic cancer [64]	Preclinical	-
Ligand traps (RB200)	HER3	- Inflammatory breast cancer, epidermoid carcinoma, colon cancer, NSCLC (alone or in combination with TK inhibitors, AG-825, gefitinib and erlotinib) [65]	Preclinical	-
Pan-HER approach (Pan-HER)	EGFR, HER2, HER3	- Lung and HNSCC (augments radiation response) [149]	Preclinical	Symphogen
HER3 ligands as anti-HER3 target	HER3	- Advanced epithelial malignancies [150]	Phase Ia/IIa	Symphogen
Inhibitor against pseudo kinase activity HER3 (TX-121-1)	Pseudokinase activity of HER3	- Metastatic or advanced tumors in NRG+ patients [153]	Phase I	Aveo
Anti-HER3 ADCs (antibody-drug conjugates)	HER3	- HNSCC [154]	Preclinical	-
		- HER2- amplified breast cancer [155]	Preclinical	-
		- Ovarian cancer, lung adenocarcinoma [68]	Preclinical	-
		- HNSCC, breast cancer, pancreatic cancer, prostate cancer, lung cancer, stomach cancer and melanoma [156]	Preclinical	-
		- EV20-MMAF (cutaneous melanoma) [157]	Preclinical	-
		- EV20-Sap (melanoma) [158]	Preclinical	-
HER3 nanobiologics	HER3	- HerPNK 10 (Her-PBK) recombinant polypeptide in breast cancer [159]	Preclinical	-

HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung carcinoma; NRG, neuregulin.

**Table 3. Summary of clinical trials, outcomes and adverse effects associated with anti-HER3 therapies.**

HER3-targeted therapies in clinical trials	Cancer types	Clinical/preclinical study	Clinical outcomes	Adverse effects
Patritumab (U3-1287/A888)	Advanced solid tumors [70]	Phase I	A dose of 18 mg/kg of patritumab, administered every 3 weeks by IV route was well tolerated in Japanese patients with advanced solid tumors. Acceptable PK profile was obtained. Upon administration, serum soluble HER3 levels increased in all patients.	Increased ALT and AST levels, thrombocytopenia, diarrhea, stomatitis, cheilitis and rash maculopapular. No DLTs were observed.
	Advanced NSCLC (with erlotinib) [71]	Phase I	Patritumab in combination with erlotinib was well tolerated in Japanese patients at a dose of 18 mg/kg administered every 3 weeks by IV route. A significant increase in the serum soluble HER3 levels was observed during treatment. 18 mg/kg of patritumab in combination with p. o. Daily dose of erlotinib (150 mg) was selected for further studies in Japanese patients.	Gastrointestinal and skin toxicities, grade 2 cancer pain (unrelated stomatitis, to the administration of the drug), diarrhea, bacterial pneumonia, abnormal hepatic function, bacterial infection, acneiform rash. No DLT was reported.
	EGFR wild-type patients with locally advanced or metastatic NSCLC patients (with erlotinib) [73]	Phase III (terminated)	Terminated as the pre-defined criteria for continuation were not reached.	-
	HNSCC (in combination with cetuximab, cisplatin and carboplatin) [74]	Phase II	The patients received IV infusion of patritumab (loading dose 18 mg/kg and maintenance dose of 9 mg/kg), every 3 weeks along with 6 cycles of cisplatin (100 mg/m <sup>2</sup> , every 3 weeks) or carboplatin (every 3 weeks by IV); cetuximab (loading dose: 400 mg/m <sup>2</sup> IV and maintenance dose: 250 mg/m <sup>2</sup> IV) weekly.	-
	MBC patients (with trastuzumab plus paclitaxel) [75]	Phase Ib/II (terminated)	Terminated due to an improved standard of care being available.	-
U3-1402 (Modified U3-1287)	Metastatic or unresectable EGFR-mutant NSCLC [76]	Phase I	Actively recruiting.	-
Seribantumab (MM-121)	Locally advanced/metastatic or recurrent ovarian cancer, fallopian tube cancer, primary peritoneal cancer, endometrial cancer, locally advanced/metastatic HER2 non overexpressing breast cancer (in combination with paclitaxel) [77]	Phase I	Dose range for MM-121 in the study was loading dose: 20 to 40 mg/kg; maintenance dose: 12 to 20 mg/kg, administered weekly by IV infusion every 3 weeks by IV. 80 mg/m <sup>2</sup> of paclitaxel was administered weekly by IV route.	Blood and lymphatic disorders, GI disorders, fatigue, mucosal inflammation, pyrexia, UTI, back pain, epistaxis, dyspnea, alopecia, rash.
	Colorectal cancer, HNSCC, NSCLC, TNBC and other tumors with EGFR dependence (in combination with cetuximab and irinotecan) [78,81]	Phase I	MM-121 in the combination with cetuximab and irinotecan had modest activity. Dose range for MM-121: 12 mg/kg to 40 mg/kg, every week via IV infusion route in combination with cetuximab: 400 mg/m <sup>2</sup> (loading dose) followed by 200 or 250 mg/m <sup>2</sup> (maintenance dose) weekly by IV and irinotecan: 180 mg/m <sup>2</sup> , once every 2 weeks by IV route.	Fatigue, dermatitis acneiform, hypomagnesemia, diarrhea, decreased appetite, hypokalemia, mucosal inflammation, dehydration, hypokalemia, nausea, fatigue.
	Preoperative TNBC and HR+, HER2- breast cancer (in combination with paclitaxel) [79,82]	Phase II	The drug alone or in combination exhibited a favorable safety profile. Benefit from MM-121 treatment was only observed in the HR+ group and was not observed in the TNBC group. MM-121 at loading dose of 40 mg/kg in the first week by IV route followed by 20 mg/kg for maintenance dose was administered along with standard doses of paclitaxel IV, doxorubicin IV and cyclophosphamide IV, followed by surgery.	Diarrhea, rash, febrile neutropenia, fatigue, anemia, hypokalemia, pulmonary embolism, hyperglycemia.

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Table 3. Continued from previous page.

HER3-targeted therapies in clinical trials	Cancer types	Clinical/preclinical study	Clinical outcomes	Adverse effects
	Refractory advanced solid tumors [80,83]	Phase I	MM-121 was well tolerated with a favorable safety profile. The dose range of drug was 3.2 mg/kg to 40 mg/kg, weekly via IV infusion followed 20 mg/kg, weekly via IV infusion every 3 weeks by IV route in expansion cohort.	Disease progression, gastrointestinal, renal, urinary and cardiac disorders.
	Advanced platinum resistant/refractory ovarian cancer (in combination with paclitaxel) [84]	Phase II	The addition of seribantumab to paclitaxel failed to exhibit an improved progression free survival in unselected patients. Detectable levels of HRG and low HER2 served as biomarkers linking to the mechanism of action of seribantumab. Loading dose and maintenance dose of seribantumab was 40 mg/kg and 20 mg/kg once a week by IV route, respectively. 80 mg/m <sup>2</sup> of paclitaxel was administered once a week for 3 weeks by IV route followed by weekly administration.	Diarrhea, fatigue, nausea, abdominal pain, alopecia, vomiting, anemia, decreased appetite, hypokalemia, edema.
	NSCLC (in combination with docetaxel) [88]	Phase II	Actively recruiting	-
	NRG+, locally advanced or metastatic NSCLC patients (in combination with docetaxel or pemetrexed) [89]	Phase II	Completed. No result posted.	-
	Advanced NSCLC (in combination with erlotinib) [90]	Phase I/II	Phase I: escalating doses of MM121 and erlotinib were administered. Phase II: MM-121 (20 mg/kg, every other week by IV route in combination with 100 mg erlotinib, p.o.).	Anemia, tachycardia, GI related disorders, fatigue, mucosal inflammation, peripheral edema, paronychia, UTI, hypokalemia, musculoskeletal disorders, nervous system disorders, decreased appetite.
	NRG+, HR+, HER2- MBC in postmenopausal women (in combination with fulvestrant) [91]	Phase II	Actively recruiting.	-
	Locally advanced or metastatic ER+ and/or PR+, HER2- breast cancer in post-menopausal women (in combination with exemestane) [92,93]	Phase II	MM121 (loading dose: 40 mg/kg and maintenance dose: 20 mg/kg) was administered by IV infusion, once a week and exemestane (25 mg) once a day by p.o. route.	Anemia, GI related disorders, fatigue, asthenia, arthralgia, back pain, headache, cough, pruritis.
	Advanced NRG+ NSCLC, HNSCC and colorectal cancer patients (in combination with MM-151, MM-141 or trametinib) [94]	Phase I (terminated)	Study terminated by sponsor.	-
	Advanced solid tumors (in combination with gemcitabine, pemetrexed, cabazitaxel and adapted doses of carboplatin) [95]	Phase I	Of 88% patients recruited, 32% showed an overall clinical benefit. MM-121 can be combined as a single dose or with standard doses of gemcitabine, pemetrexed and cabazitaxel and adapted doses of carboplatin.	Diarrhea, nausea, fatigue, anemia, vomiting, hypokalemia, decreased appetite, thrombocytopenia, peripheral edema, neutropenia, constipation.
	Solid tumors (in combination with SAR245408) [96]	Phase I	Completed, not published.	-

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Table 3. Continued from previous page.

HER3-targeted therapies in clinical trials	Cancer types	Clinical/preclinical study	Clinical outcomes	Adverse effects
Lumretuzumab (RG7116, RO-5479599)	HER3+ breast cancer expressing HER2 and HER3 protein (in combination with paclitaxel and pertuzumab) [99, 100]	Phase I	Participants received escalating doses of lumretuzumab (500 or 1000 mg) every 3 weeks via IV infusion in combination with pertuzumab (loading dose: 840 mg, every 3 weeks via IV infusion and maintenance dose: 420 mg, every 3 weeks via IV infusion) and paclitaxel 80 mg/m <sup>2</sup> , weekly via IV infusion.	Diarrhea, hypokalemia, hypophosphatemia, infusion related reactions.
		Phase I	Dose escalation range was from 100 mg to 2000 mg every 2 weeks, via IV infusion. Lumretuzumab was well tolerated up to dose of 2,000 mg. The linear PK characteristics indicated target-mediated drug deposition saturation. PD effects were observed in serial tumor biopsies and indicated that the active biological dose of the drug is from 400 mg onwards. The disease control rate was 21%. The study has been terminated.	Diarrhea, fatigue, decreased appetite, infusion related reactions, constipation, neutropenia, thrombocytopenia.
	Advanced/metastatic NSCLC (in combination with carboplatin and paclitaxel) [102]	Phase Ib/II (terminated)	-	-
	Solid tumors (in combination with cetuximab or erlotinib) [103]	Phase Ib	The toxicity profile of lumretuzumab (dose range from 400 mg to 2000 mg) with erlotinib or cetuximab was manageable with modest clinical activity observed across tumor type. The study failed to identify a robust biomarker signal that could serve as response prediction biomarker for lumretuzumab. The study concluded that adding HER3 to EGFR targeting therapies is not sufficient to derive clinically meaningful benefit. The combination of trastuzumab with cetuximab or erlotinib demonstrated a modest clinical outcome.	GI related disorders, skin toxicities.
Elgatumab (LJM716) (withdrawn)	Platinum-pretreated recurrent/metastatic HNSCC patients (with cetuximab) [106]	Phase Ib/II	The study has been withdrawn.	-
		Phase I	Actively recruiting.	-
	HER2+ MBC (in combination with BYL719 and trastuzumab) [107]	Phase I	Escalated doses of LJM716 were administered once weekly via IV route. Trastuzumab (2 mg/kg) was administered once weekly by IV route. Dose range of LJM716 was from 10 mg/kg to 40 mg/kg, once weekly by IV infusion. BYL719 (200 mg-400 mg) was administered once daily p.o. Paclitaxel, docetaxel and irinotecan were administered along with the combination in phase 2 of the study.	-
	ESCC (in combination with BYL719, paclitaxel, docetaxel, irinotecan) [109]	Phase Ib/II	LJM716 was found to be tolerated upto 40 mg/kg when administered once weekly via IV infusion. This was also the recommended phase 2 dose. It demonstrated preliminary evidence of antitumor activity.	Diarrhea, chills, infusion-related reactions, reduced appetite, GI disorders, hypokalemia.
	ESCC, HNSCC, HER2-overexpressing MBC or gastric cancer [110]	Phase I	LJM716 was well tolerated in Japanese patients with a manageable safety profile. The recommended dose was established at 40 mg/kg, once a week by IV, route to Japanese patients.	Diarrhea, stomatitis, paronychia, fatigue, pyrexia, pneumonia, decreased lymphocyte count, nausea, vomiting.
Advanced solid tumors [111]	Phase I	-	-	

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Table 3. Continued from previous page.

HER3-targeted therapies in clinical trials	Cancer types	Clinical/preclinical study	Clinical outcomes	Adverse effects
KTN3379	Advanced tumors [113]	Phase I	Completed, not published.	-
	Advanced solid tumors (alone or in combination with erlotinib, vemurafenib, cetuximab and trastuzumab) [114]	Phase Ib	A dose of 20 mg/kg, every 3 weeks via IV route in combination with other agents was safe. The PK data supported a 3 week dosing schedule. NRG maybe used a predictive biomarker to test the response of tumors to KTN3379. Completed, not published.	Diarrhea, rash, anemia, fatigue.
	BRAF mutant melanoma and RAI thyroid cancer (in combination with vemurafenib) [115] Surgically resectable HNSCC [116]	Phase I	Completed, not published.	-
AV-203	Metastatic or advanced solid tumors [118,119]	Phase I	AV-203 was well tolerated in a dose range of 2 mg/kg to 20 mg/kg administered via IV infusion once every 2 weeks. The recommended phase 2 dose was established as 20 mg/kg IV every 2 weeks.	Diarrhea, decreased appetite, hypokalemia, dried skin, hypomagnesemia, headache, dehydration, dizziness, dyspnea, anemia, pruritus.
GSK2849330	Advanced HER3+ solid tumors [120,121]	Phase I	Completed, not published.	-
REGN1400	NSCLC, colorectal cancer, HNSCC (in combination with erlotinib or cetuximab) [122]	Phase I	REGN1400 alone or in combination with erlotinib or cetuximab was well tolerated at the dose range of 2 mg/kg to 20 mg/kg via IV route, once every 2 weeks. The recommended phase 2 dose of 20 mg/kg by IV route, once every 2 weeks. The combination therapy failed to potentiate any anti-EGFR related adverse effects.	Rash, diarrhea, nausea, hypomagnesemia, increased AST, dry skin, fatigue, stomatitis, pneumonia, pyrexia, sepsis
Duligotuzumab (RG7597, MEHD7945A)	Locally advanced or metastatic epithelial tumors [130]	Phase I	MEHD7945A was well tolerated as a single agent with a PD and antitumor activity in HNSCC patients in dose escalating studies with dose range from 1mg/kg to 30 mg/kg administered by IV every 2 weeks. The recommended phase 2 study flat dose was established at 1100 mg twice daily in HNSCC and colorectal cancer patients.	Diarrhea, nausea, chills, headache, fever.
	Locally advanced or metastatic cancers with mutated KRAS (in combination with cobimetinib) [131,133]	Phase Ib	The study did not proceed to expansion stage and was closed for enrollment due to dose limited tolerability and efficacy of the combination.	Hypokalemia, mucosal inflammation, asthenia, dermatitis acneiform.
	KRAS wild-type metastatic colorectal cancer (in combination with FOLFIRI- 5-fluorouracil, folinic acid and irinotecan vs cetuximab) [132,134]	Phase II	Duligotuzumab did appear to improve outcomes in the patients. It dialed to provide progression free survival (PFS) or overall survival (OS) benefit vs cetuximab.	Diarrhea, skin rashes.
	Recurrent or metastatic HNSCC (during or following platinum therapy vs cetuximab) [135,136]	Phase II	Duligotuzumab was 1100 mg, once every 2 weeks by IV route. Cetuximab (loading dose: 400 mg/m <sup>2</sup> and maintenance dose: 250 mg/m <sup>2</sup> ) was administered once weekly by IV route. Dual inhibition of HER3 and EGFR by duligotuzumab demonstrated a comparable activity (in randomized and biomarker positive patients) and not superior activity as compared to single agent cetuximab in HNSCC. HPV-negative HNSCC patients but not HPV-positive HNSCC patients may possibly respond to cetuximab or duligotuzumab.	Infections, GI related disorders.
	Recurrent or metastatic HNSCC (in combination with cisplatin/5'-FU or carboplatin/paclitaxel) [137]	Phase Ib/II	The trial studied the feasibility of combination of duligotuzumab at 1650 mg (recommended phase 2 dose), by IV route, every 3 weeks with combination of cisplatin/5'-FU or carboplatin/paclitaxel. The combinations demonstrated an antitumor effect. But the study was limited by an increased frequency and severity of adverse events.	Neutropenia, hypokalemia, dehydration, anemia, diarrhea, febrile neutropenia, leukopenia, thrombocytopenia, hypomagnesemia.

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Table 3. Continued from previous page.

HER3-targeted therapies in clinical trials	Cancer types	Clinical/preclinical study	Clinical outcomes	Adverse effects
MM-111	HER2 expressing carcinomas of the distal esophagus, GE junction and stomach (with paclitaxel and trastuzumab) [138]	Phase II (Terminated)	The study was terminated due to lack of efficacy.	-
	Advanced, refractory HER2 amplified, NRG+ cancer [139]	Phase I	MM-111 was administered to dose escalation cohorts weekly via IV route.	Fatigue, acute viral myocarditis, pleural effusion.
	Advanced HER2 amplified, NRG+ breast cancer (in combination with herceptin) [140]	Phase I	MM-111 was combined with Herceptin for dose escalation cohorts and administered weekly or bi weekly via IV route.	Anemia, GI related disorders, UTI, decreased appetite, insomnia, anxiety, skin toxicities, pericardial effusion, pleural effusion, deep vein thrombosis.
	Advanced HER2+ solid tumors (along with different combination treatment of capecitabine/cisplatin/trastuzumab/lapatinib/paclitaxel or docetaxel) [141]	Phase I	MM-111 was dosed weekly at 10 mg/kg and where possible, the dose was escalated till 20 mg/kg. In the arm where the patients were treated with MM-111, docetaxel and trastuzumab, the agent was dosed from 30 mg/kg and escalated to 40 mg/kg via IV infusion, once every 3 weeks. The recommended phase 2 dose was established as 20 mg/kg, once a week, via IV infusion and 40 mg/kg every 3 weeks via IV infusion.	Anemia, acute renal failure, chest pain, decreased appetite, diarrhea, febrile neutropenia, hyperuricemia, hypokalemia, hyponatremia, mucosal inflammation, nausea, thrombocytopenia, vomiting.
Istiratumab (MM-141)	Advanced solid tumor (alone or in combination with abraxane/gemcitabine, everolimus or monotherapy) [142,143]	Phase I	No dose limiting toxicities were observed in dose range of 6 mg/kg to 20 mg/kg, administered weekly or 40 mg/kg, administered biweekly. An expansion cohort tested the dosing of MM-141 (20 mg/kg) in patients with hepatocellular carcinoma.	Vomiting, nausea, fatigue, abdominal pain, dyspnea, diarrhea, anemia, increased AST, rash.
	Metastatic pancreatic cancer (in combination with nab-paclitaxel and gemcitabine) [144]	Phase II	Study is active but not recruiting. A fixed dose of istiratumab- 2.8 grams, twice every week by IV route was selected for the study.	-
MCLA-128	Malignant solid tumors [145]	Phase I/II	MCLA-128 was well tolerated and exhibited a favorable safety profile in patients at doses upto 900 mg, every 3 weeks via IV infusion. Based on the PK profile and the anti-tumor activity, the recommended phase 2 dose of MCLA-128 was set at 750 mg, every 3 weeks via IV infusion.	Diarrhea, nausea, vomiting, fatigue, maculopapular rash, oral mucositis, G2 neutropenia
	Trastuzumab/chemotherapy in HER2+ and with endocrine therapy in ER+ and low HER2 breast cancer [146]	Phase II	Actively recruiting.	-
Pan-HER approach	Advanced epithelial malignancies [150]	Phase Ia/IIa	Actively recruiting.	-
HER3 Ligands as anti-HER3 target (AV-203)	Metastatic or advanced tumors in NRG+ patients [153]	Phase I	AV-203 was well tolerated in the dose range from 2 mg/kg to 20 mg/kg, once every 2 weeks via IV route. The recommended phase 2 dose was calculated to be 20 mg/kg, every 2 weeks by IV route.	Diarrhea, decreased appetite, hypokalemia, hypomagnesemia, headache, dehydration, dizziness, dyspnea, dry skin, pruritus.

HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung carcinoma; MBC, metastatic breast cancer; TNBC, triple negative breast cancer; ESCC, esophageal-squamous cell carcinoma; HR, hormone receptor; ER, estrogen receptor; 5'-FU, 5'-fluorouracil; NRG, neuregulin; PR, progesterone receptor; RAI, radioiodine-refractory; GE, gastroesophageal; AST, aspartate aminotransferase; ALT, alanine aminotransferase; DLT, dose limiting toxicity; PK, pharmacokinetic; PD, pharmacodynamic; IV, intravenous; p.o., per oral; GI, gastrointestinal; UTI, urinary tract infection.

that LJM716 is well tolerated with a recommended daily intravenous dose of 40 mg/kg.<sup>111</sup>

*KTN3379*, an anti-HER3 mAb inhibits HER3 activity in ligand-dependent and independent manner.<sup>112</sup> A phase I study evaluating the efficacy of *KTN3379* either alone or in combination with various drugs (cetuximab, erlotinib, vemurafenib, trastuzumab) has been completed in advanced solid tumors.<sup>113,114</sup> A pilot phase I study initiated by Celldex Therapeutics testing whether vemurafenib with the addition of *KTN3379* can restore iodine incorporation in BRAF mutant melanoma and radioiodine-refractory (RAIR) thyroid cancer patients is also completed.<sup>115</sup> A study of *KTN3379* in surgically resectable HNSCC patients is completed which evaluated the effect of *KTN3379* on HER3 activation and other biomarkers in tumor tissues.<sup>116</sup>

*AV-203* is an anti-HER3 IgG1 which binds to the HER3 receptor and prevents NRG binding. *AV-203* shows preclinical activity against patient-derived tumor explant models and suppresses HER3 activation and downstream signaling.<sup>117</sup> Phase I clinical trial in advanced solid tumors is now completed.<sup>118,119</sup>

*GSK2849330* is a HER3 targeting antibody which has completed a phase I clinical trial in HER3+ patients with solid tumors.<sup>120,121</sup> *REGN1400*, another HER3 mAb investigated alone or in combination with erlotinib or cetuximab in several metastatic cancers.<sup>122</sup> *REGN1400* significantly suppresses HER3 downstream signaling and in combination with EGFR mAb, inhibits the growth of xenograft tumors derived from HNSCC and colorectal cancer.<sup>123</sup>

*MP-RM-1* is a murine mAb against HER3 which induces HER3 internalization and degradation and attenuates ligand-dependent and independent HER3 signaling in several cancers including breast, melanoma, prostate and gastric cancer.<sup>124</sup> *EV20*, a humanized version of *MP-RM-1* (Mediapharma S.r.l) inhibits HER2-HER3 heterodimerization, downregulates HER3 and also internalizes it into the tumor.<sup>125,126</sup> It is also shown to reverse the resistance to vemurafenib in BRAF-V600E mutant colon cancer stem cell.<sup>127</sup>

*Duligotuzumab* (RG7597, MEHD7945A) is a phage derived humanized bi-specific antibody targeting both HER3 and EGFR. It prevents ligand binding and favors HER3 internalization and ADCC.<sup>128</sup> It has shown significant efficacy in several *in vivo* models.<sup>48,129</sup> This antibody is explored in phase I & II clinical trials in various metastatic cancers.<sup>130-134</sup> A phase II randomized trial compares the safety and efficacy of MEHD7945A versus cetuximab in metastatic HNSCC patients who have progressed during or following platinum-based chemotherapy.<sup>135,136</sup> A phase Ib study of MEHD7945A plus cisplatin/5-fluorouracil or carboplatin/paclitaxel demonstrates an encouraging clinical activity in patients with recurrent/metastatic HNSCC.<sup>137</sup> A phase Ib, open-label, dose-escalation study exploring the safety, tolerability, and pharmacokinetics of MEHD7945A with cobimetinib in patients with locally advanced or metastatic solid tumors with mutant KRAS is completed.<sup>131,133</sup>

*MM-111* is a bi-specific antibody that forms a trimeric complex with HER2 and HER3. *MM-111* is shown to be more efficient in xenograft tumors derived from HER2+ cancer cell lines where it exhibits significant anti-tumor activity in combination with trastuzumab or lapatinib.<sup>63</sup> However, the phase II clinical trial involving combination of *MM-111* and trastuzumab is terminated in gastric cancer.<sup>138</sup> A phase I clinical trial involving *MM-111* in combination with trastuzumab has been completed in HER2 amplified and NRG+ breast cancer.<sup>139</sup> The other clinical trial sponsored by Merrimack is in advanced HER2 amplified and NRG+ solid tumors.<sup>140</sup> A multi-arm dose escalating study of *MM-111* plus HER2 targeting regimens including capecitabine, cisplatin,

trastuzumab, lapatinib, paclitaxel, docetaxel evaluating the safety, pharmacokinetics (PK), and anti-tumor activity of *MM-111* in patients with advanced HER2+ solid tumors has been completed.<sup>141</sup>

Another bi-specific antibody, *MM-141* (istiratumab) has been developed against HER3 and IGFR by Merrimack.<sup>62</sup> *MM-141* inhibits binding of NRG to HER3 and IGF-1/2 to IGFR and abrogates PI3K/AKT signaling and also increases efficacy of gemcitabine in preclinical models.<sup>62</sup> *MM-141* has been investigated in a phase I clinical trial either alone or in combination with gemcitabine, everolimus or paclitaxel in advanced solid tumors.<sup>142,143</sup> A phase II study exploring the efficacy of *MM-141* in combination with nab-paclitaxel and gemcitabine is still going on in metastatic pancreatic cancer.<sup>144</sup>

*MCLA-128* is a bispecific antibody targeting HER2 and HER3 in phase I/II trial in patients with solid tumors.<sup>145</sup> A phase II study is initiated to evaluate the safety and efficacy of *MCLA-123* in combination with trastuzumab/chemotherapy in HER2+ and with endocrine therapy in ER+ metastatic breast cancer.<sup>146</sup>

## Other anti-HER3 targeted therapies

### Antisense oligonucleotide

RNAi therapy is an emerging anti-HER3 strategy to treat cancers, which are not sensitive to anti-HER3 antibodies. *EZN-3920* is a nucleic acid based HER3 anti-sense oligonucleotide, which inhibits HER3 expression and HER3-mediated downstream signaling and *in vivo* tumor growth.<sup>67</sup> It also demonstrates significant anti-proliferative effects in trastuzumab- and gefitinib-resistant cell lines. *EZN-3920* in combination with lapatinib or gefitinib increases the anti-tumor activity compared to single agent.<sup>67</sup> However, lack of efficient delivery systems of RNA antagonists curtails efficient application in the clinic.<sup>147</sup>

### HER3-peptide vaccine

Peptide vaccines targeting HER3 could induce HER3 neutralizing antibodies in cancer. HER3 epitopes encompassing residues 99-122, 140-162, 237-269 and 461-479 of HER3 are explored as active immune therapy against breast and pancreatic cancer. These mimics show enhanced anti-tumor effects in breast and pancreatic cancer cells.<sup>64</sup>

### Ligand traps

A HER ligand binding molecule which could sequester different ligands for multiple receptors is a recent approach to treat cancers where there is activation of alternate compensatory loops due to other EGFR family members. *RB200* is a bi-specific ligand trap which binds to multiple ligands including HER3 ligand NRG, EGFR ligands including TGF $\alpha$ , heparin binding EGF. *RB200* suppresses EGF- and NRG1- $\beta$ 1-induced phosphorylation of HER family RTKs and cancer cell proliferation as a single agent and in synergy with tyrosine kinase inhibitors, lysophosphatidic acid-induced cell proliferation, and tumor growth in xenograft mice models.<sup>65</sup> However, this strategy has not been applied in the clinic.

### Pan-HER approach

Pan-HER approach includes six antibodies for synergistic targeting of EGFR, HER2 and HER3, with the goal of preventing compensatory activation of EGF receptors where only one receptor is inhibited. This mixture is tested against 100 different cancer cell lines where it significantly attenuates cancer cell proliferation and

outperforms the activity of reference antibodies (cetuximab, trastuzumab and MM-121).<sup>66,148</sup> Sym013 developed by Symphogen is a mixture of six humanized mAbs targeting EGFR, HER2 and HER3, which demonstrates better anti-tumor activity in *in vivo* models.<sup>149</sup> Currently, an open-label, multicenter, phase Ia/Ia trial investigating the safety, tolerability and anti-tumor activity of multiple doses of Sym013 is initiated in patients with advanced epithelial malignancies.<sup>150</sup>

### HER3 ligands as predictive biomarkers and anti-HER3 target

Several preclinical and clinical studies indicate that NRG is a predictive biomarker for HER3-targeted therapies. NRG expression correlates with *in vivo* tumor regression and has been validated in the clinic.<sup>151,152</sup> In a phase I clinical trial, NRG-positive patients with metastatic or advanced tumors show a partial response to HER3-specific mAb, AV-203.<sup>153</sup> Inhibition of HER3 using AV-203 correlates with NRG expression in preclinical studies.<sup>117</sup> Elevated NRG expression corroborates with HER3 activation in head and neck squamous cell carcinomas.<sup>154</sup> However, NRG as a potential biomarker becomes questionable in tumors with HER3 mutations or downstream molecular alterations. Xenograft tumor models with a PTEN mutation show resistance to AV-203 even with elevated NRG expression.<sup>117</sup> In HER2-amplified breast cancer model, HER3 exhibits constitutive activation independent of NRG.<sup>155</sup>

### Inhibitor targeting pseudo kinase activity of HER3

A selective small molecule TX1-85-1 interacts with cys721 in the ATP-binding pocket of HER3. TX-121-1, a derivative of TX1-85-1 causes partial degradation of HER3, interferes with dimerization with c-Met and HER2, perturbs HER3-mediated signaling. More studies are essential to validate the role of these inhibitors in HER3-targeted therapeutics.<sup>68</sup>

### HER3 as target for antibody-drug conjugates

Antibody-drug conjugates (ADCs) are emerging as an attractive strategy to improve the antibody based therapy for treatment of different cancers. HER3-ADCs shows promising anti-tumor efficacy in a wide range of human cancer.<sup>156</sup> Capone *et al.* coupled the humanized anti-HER3 mAb, EV20 to the cytotoxic drug monomethyl auristatin F (MMAF) to generate a novel antibody-drug conjugate (EV20-MMAF). This antibody demonstrates target-dependent cell killing activity in a panel of human melanoma cell lines with HER3 expression independent of BRAF status. A single administration of EV20-MMAF causes long lasting tumor growth inhibition and is superior to vemurafenib in abrogating kidney, liver and lung melanoma metastases.<sup>157</sup> EV20-Sap is another HER3-ADC obtained by coupling EV20 to the plant toxin Saporin (Sap). This complex causes target-dependent cytotoxic activity that correlates with internalization and expression of HER3 on cancer cells. EV20-Sap treatment results in significant reduction of pulmonary metastasis in murine melanoma model.<sup>158</sup>

### HER3 nanobiologic therapeutic approach

Sim *et al.* demonstrates HER3-targeted nanobiologics as a novel approach effective against resistant tumors expressing HER3. The author synthesized a recombinant polypeptide, HerPBK10 (HPK) having a minimal receptor binding domain from NRG-1. This biocarrier combines several functions within a single fusion protein for mediating target cell penetration and non-covalent self-assembly with therapeutic cargo, forming HER3 homing nanobiologics. These nanobiologics show significant affinity and

are effective against tumors showing resistance to inhibitors against HER3 receptor. It is shown that the efficacy of HPK-nanobiologics is dependent on HER3 levels of resistant cells as well as naïve cells.<sup>159</sup>

## Conclusions

Drug resistance is a major reason of treatment failure that limits the efficacy of several targeted therapies including mono-/bi-specific antibodies and small molecule inhibitors against EGFR family members. Targeting other EGFR family members using TKIs leads to feedback upregulation of HER3 encouraging the direct targeting of HER3 as a better option in the clinic. Many HER3 mAbs have been designed and demonstrated significant pre-clinical efficacy, however, a HER3 targeted treatment has not yet received approval based on clinical trials. Studies indicate that HER3 plays a vital role in drug resistance and overall HER signaling. Encouraging clinical studies suggest that concomitant suppression of HER3 along with other RTKs including EGFR family members may be helpful in attaining greater clinical benefits.

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