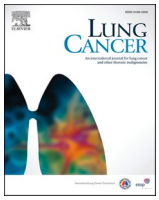
Lung Cancer 186 (2023) 107385

Contents lists available at ScienceDirect

Lung Cancer

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



Review article

Management of HER2 alterations in non-small cell lung cancer – The past, present, and future

Jorn Nützinger [a,1], Jii Bum Lee [b,1], Jia Li Low [a], Puey Ling Chia [c], Silvana Talisa Wijaya [a], Byoung Chul Cho [b], Sun Min Lim [b], Ross A Soo [a,*]

[a] Department of Haematology-Oncology, National University Cancer Institute, Singapore
[b] Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea
[c] Department of Medical Oncology, Tan Tock Seng Hospital, Singapore

ARTICLE INFO

Keywords:
HER2
Non-small cell lung cancer
Exon 20 mutation
Targeted therapy

ABSTRACT

HER2 mutations, which account for 2–4% of non-small cell lung cancer (NSCLC), are distinct molecular alterations identified via next generation sequencing (NGS). Previously, treatment outcomes in *HER2*-mutant metastatic NSCLC were dismal, showing limited clinical benefit with platinum-based chemotherapy with or without immunotherapy. In contrast to HER2-altered breast and gastric cancer, *HER2*-mutant NSCLC does not benefit from HER2 targeting agents such as trastuzumab or TDM1. *HER2* mutations are also inherently different from HER2 overexpression and amplification. Currently, trastuzumab deruxtecan, a HER2 targeting antibody drug conjugate (ADC) is the first and only approved treatment option for patients with *HER2*-mutant metastatic NSCLC after failure with standard treatment. In this review, we summarized the biology of *HER2* and detection of HER2 overexpression, amplification and mutations, as well as general landscape of landmark and ongoing clinical trials encompassing from chemotherapy to targeted agents, including tyrosine kinase inhibitors (TKIs), ADCs and investigational agents.

1. Introduction

Non-small cell lung cancer (NSCLC) is a heterogeneous disease composed of distinct driver oncogenes such as mutations of the epidermal growth factor receptor gene (*EGFR*), Kirsten rat sarcoma virus gene (*KRAS*), and gene rearrangement of anaplastic lymphoma kinase (*ALK*) and *ROS1*. Molecular targeted therapies targeting such molecular alterations have led to major changes in the treatment landscape for NSCLC.

The Human epidermal growth factor receptor 2, also known as HER2 or erbB-2/neu, a well- established oncogene in breast cancer, has recently been identified as a therapeutic target in NSCLC. Several HER2 activating mechanisms have been described including gene mutation, amplification, and overexpression [1].

HER2 mutations in NSCLC were first discovered in 2004 [2], however until recently, developing effective anti-HER2 therapies has been a challenge (Fig. 1) [3]. In August 2022, based on the data from the DESTINY-Lung02, the U.S Food and Drug Administration (FDA) granted accelerated approval to the antibody drug conjugate trastuzumab-deruxtecan, making it the first targeted agent approved for *HER2*-mutant NSCLC.

In this review, we provide an overview of the biology of HER2 including various alterations of HER2, their detection methods, and the treatment of *HER2*-mutant NSCLC (Fig. 2).

Abbreviations: ADC, antibody drug conjugate; ADCC, antibody-dependent cellular cytotoxicity; BID, twice daily; CNS, central nervous system; DAR, drug-to-antibody ratio; DoR, duration of response; ECD, extracellular domain; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; FISH, fluorescence in situ hybridization; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; ILD, interstitial lung disease; mAbs, monoclonal antibodies; NGS, next generation sequencing; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; qPCR, quantitative polymerase chain reaction; qRT-PCR, real-time quantitative reverse transcriptase polymerase chain reaction; T-DXd, trastuzumab deruxtecan; TEAE, Treatment-emergent adverse event; TKD, tyrosine kinase domain; TKIs, tyrosine kinase inhibitors; TMB, tumor mutational burden; TMD, transmembrane domain.

* Corresponding author.
E-mail address: ross_soo@nuhs.edu.sg (R.A. Soo).

[1] These authors contributed equally as first authors.

https://doi.org/10.1016/j.lungcan.2023.107385
Received 6 August 2023; Received in revised form 21 September 2023; Accepted 22 September 2023
Available online 28 September 2023

2. Biology and detection of *HER2*

2.1. Biology

Discovered in the mid 1980′s (Fig. 1), the *HER2* proto-oncogene is located on the long arm of human chromosome 17 (17q11.2-q12) [4]. The *HER2* transcript encodes a transmembrane glycoprotein of 185 kDa (kD) belonging to the ErbB-family of type 1 transmembrane growth factor receptors which consists of HER1 (ErbB1, EGFR), HER2 (ErbB2, HER2/neu), HER3 (ErbB3) and HER4 (ErbB4). Each receptor is composed of three main components: an extracellular ligand binding domain, an α-helical transmembrane segment and an intracellular tyrosine kinase domain. Under physiologic conditions, upon ligand binding to their extracellular domains, HER proteins undergo hetero- or homodimerization between the receptors hereby adhering to a distinct hierarchical order that favors heterodimers over homodimers. Subsequent intracellular transphosphorylation of tyrosine residues initiates a variety of signaling pathways including MAPK, PI3K/AKT, PKC and STAT, leading to cellular proliferation, differentiation, and migration. HER2 exhibits significant structural homology with all other members of its family, but, unlike other members, no direct ligand has been identified for HER2 [5]. Instead, HER2 remains in its active conformation, enabling continuous availability for dimerization, therefore rendering it the favored partner for heterodimerization. HER2 also displays reduced internalization and degradation, leading to prolonged activation on the cell membrane [6]. Combined with HER3, which is devoid of intrinsic tyrosine kinase activity and therefore restricted to heterodimerizing with other HER-receptors, the HER2/HER3 heterodimer is the most potent in terms of strength of their interaction, ligand-induced tyrosine phosphorylation and downstream signaling [7].

Its superior capability for heterodimerization, combined with a distinctive basal tyrosine kinase activity, grants HER2 a crucial function in signal transduction and consequently plays a significant role in carcinogenesis when its function is dysregulated (Fig. 2).

2.2. HER2 alterations

In contrast to breast cancer which is triggered by *HER2* amplification, NSCLC can be activated by gene mutation, amplification, and overexpression of the HER2 leading to downstream activation of the MAPK, PI3K/Akt, phospholipase C, protein kinase C, and the Janus kinase (Jak-STAT) signaling pathways [8,9]. In the following sections, we will discuss the different alterations and their detection methods.

2.3. HER2 overexpression

Prevalence ranges widely from 2.4 to 38 % and is more common in well-differentiated adenocarcinomas [10–12]. The identification and distinction remain debatable due to difference in applied methods, patient groups studied and the different definitions of HER2 positivity [13–15].

The underlying molecular pathogenesis is unclear, but increased HER2 presence on the cell surface increases the formation of HER2-containing heterodimers, consequently altering cell polarity and adhesion and activating several above-mentioned oncogenic signaling pathways [16]. The mechanism of overexpression is attributed to increased copy number from chromosome duplication and polysomy (*HER2* gene copy number higher than 5 or 6, but HER2/CEP17 < 2) [13,17]. Bunnet et al. discovered a strong correlation between HER2 protein expression, assessed by IHC, and *HER2* gene copy number, evaluated by fluorescence in situ hybridization (FISH). Of the cell lines tested, 32 % were HER2 IHC positive. Interestingly, polysomy, rather than genuine amplification, was often detected by FISH. Therefore, in case of moderate or strong HER2 overexpression an additional FISH analysis is advised to distinguish between these possibilities [6,18]. HER2 overexpression is associated with poorer survival, which may be due to chemo-radiotherapy resistance, but results are conflicting [19–21].

There is no consensus on scoring and categorizing HER2 protein overexpression in lung cancer and a universal definition and test are urgently needed. In the absence of a specific testing method, two immunohistochemistry (IHC) scoring systems are used, including scoring using 0–3 + and the H-score [22]. Another method for quantifying HER2 overexpression is the use of quantitative polymerase chain reaction (qPCR) or real-time quantitative reverse transcriptase polymerase chain reaction (qRT-PCR).

2.4. HER2 amplification

HER2 amplification in NSCLC occurs less frequently compared to breast cancer [13], but the reported frequency varies due to a lack of a clear definition and the existence of two distinct mechanisms: amplification as a primary driver in patients who did not receive targeted therapy (3 %) and amplification from acquired EGFR-TKI resistance (13 %) [23].

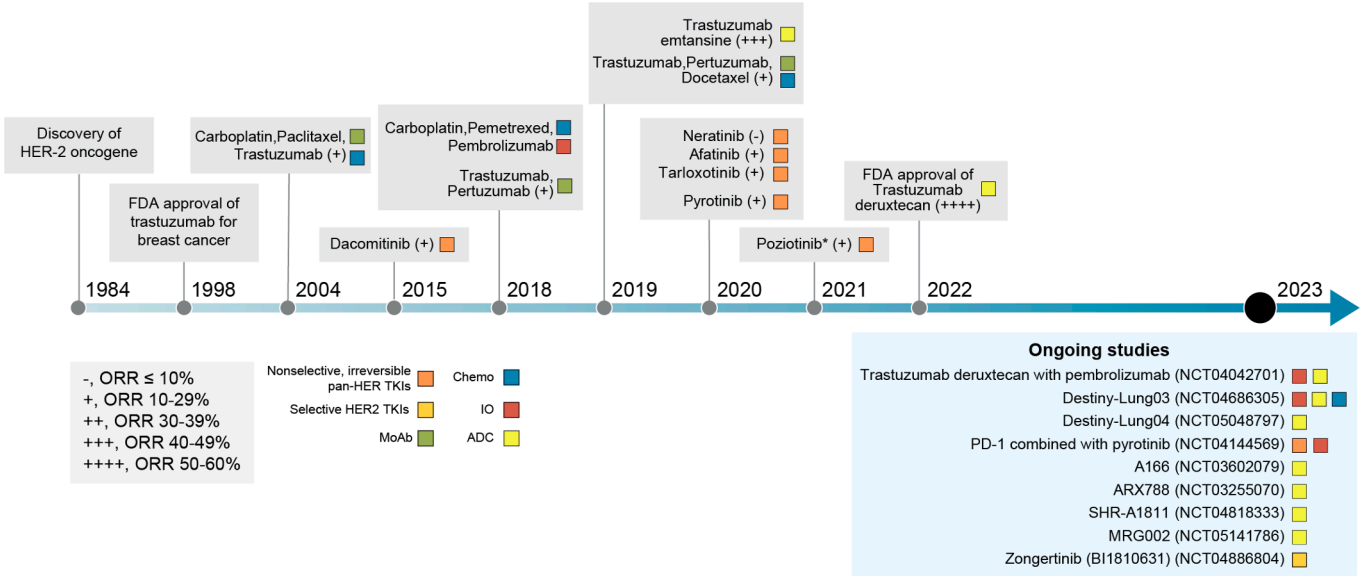


Fig. 1. Timeline of development of HER2 targeted therapies in *HER2*-mutant NSCLC.

HER2 amplification increases NSCLC cell invasiveness in vitro and constitutively activates both HER2 and EGFR independent of ligands [24]. It is strongly associated with pleural invasion [1], never smoking and female sex [25,26] but its prognostic significance is unclear [42].

The definition of *HER2* amplification is derived from breast cancer diagnostics and is typically defined as the average ratio of the *HER2* gene copy number to centromeres (*HER2*/CEP ratio $\geq$ 2) and/or gene copy number > 6. It must be noted that other cut off values have also been used, resulting in variations among different studies [18]. Furthermore, it is posed to modify the current used breast cancer classification as it may not be adequate for NSCLC [27]. As stated earlier, polysomy can be found and while it is believed not to drive oncogenesis, its predictive or prognostic value is unclear [14].

FISH is used as the gold standard for detection [28,29] and evaluation of *HER2* amplification is advised in clinical studies or in case of EGFR TKI resistance [30]. Another method to assess *HER2* amplification in clinical practice is NGS, which also lacks universal standard for defining amplification across NGS platforms but may offer advantages because it can simultaneously test alterations in several hundred genes [31].

2.5. *HER2* mutations

HER2 mutations comprise heterogenous alterations in the extracellular (ECD), transmembrane (TMD), and tyrosine kinase domains (TKD). They are found in 2–4 % of NSCLC [1,5,32], have low genetic diversity and are associated with female gender, never smokers, adenocarcinoma histology and brain metastases [33]. *HER2*-mutant NSCLC patients have a worse prognosis than patients with *EGFR* mutations or *ALK* rearrangements due to a lack of effective selective targeted agents.

HER2 mutations occur mostly in the intracellular tyrosine kinase domain (TKD) and induce conformational changes in the ATP-binding pocket, which increases kinase activity and downstream induction of PI3K/AKt and MEK oncogenic pathways [34]. The most frequent mutations occur as in-frame insertions within exon 20. The 12 base-pair duplicated insertion at codon 775 - A775_G776insYVMA, which affects the αC-B4 loop of the kinase domain, is the most common followed by G776delinsVC and G778_P780insGSP [5,35,36]. The exon 20 YVMA mutation, in particular, is associated with a high incidence of brain metastasis and inferior outcome of chemotherapy [37]. *HER2* exon 20 insertions share structural homology with *EGFR* exon 20 insertions and effect the same structural regions: the αC-helix, at residues 770–774, and the loop region comprising residues 775–783. Similar to EGFR, HER2 activity is regulated by the αC-helix, which switches between an inactive, outward conformation and an active, inward conformation. *HER2* exon 20 insertions exhibit greater activation of signal transduction, EGFR phosphorylation, cell proliferation, and invasiveness compared to wild-type HER2 signaling. Different insertions have unique behavior and drug resistance profiles depend on their conformational configuration (Figs. 3 and 4) [36].

More TKD-affecting point mutations exist with lower prevalence and more recent a few less common mutations affecting the transmembrane and the juxtamembrane domains (G660D, R678Q, E693K and Q709L) have been described and can be targeted [38,39].

Although earlier studies have proposed *HER2* mutations to be mutually exclusive to other oncogenic drivers, the widespread use of NGS has revealed accompanying mutations in *EGFR* mutations, *ALK* translocations and *ROS* translocations [40]. While most studies do not detail the use of previous targeted treatments, a small percentage of *HER2* mutations have been described as a possible mechanism of primary or acquired resistance during EGFR TKI treatment [18,41,42].

As stated earlier, HER2 overexpression detected by FISH or IHC staining is not a reliable substitute marker for *HER2* mutation [14] and although targeted assays like RT-PCR are highly specific, they are limited in their ability to detect only known and well characterized gene alterations, potentially missing less common alterations Therefore, sequencing methods remain the gold standard when testing for *HER2* mutations [30].

2.6. *Genomic profile and tumor microenvironment of HER2-mutant NSCLC*

Whole exome sequencing of NSCLC harbouring *HER2* exon 20 insertion have revealed low tumor mutational burden (TMB) and few co-driver mutations, findings similar to *EGFR*-mutated NSCLC [43]. Other non-exon 20 insertion *HER2* mutations show features similar to *EGFR*-

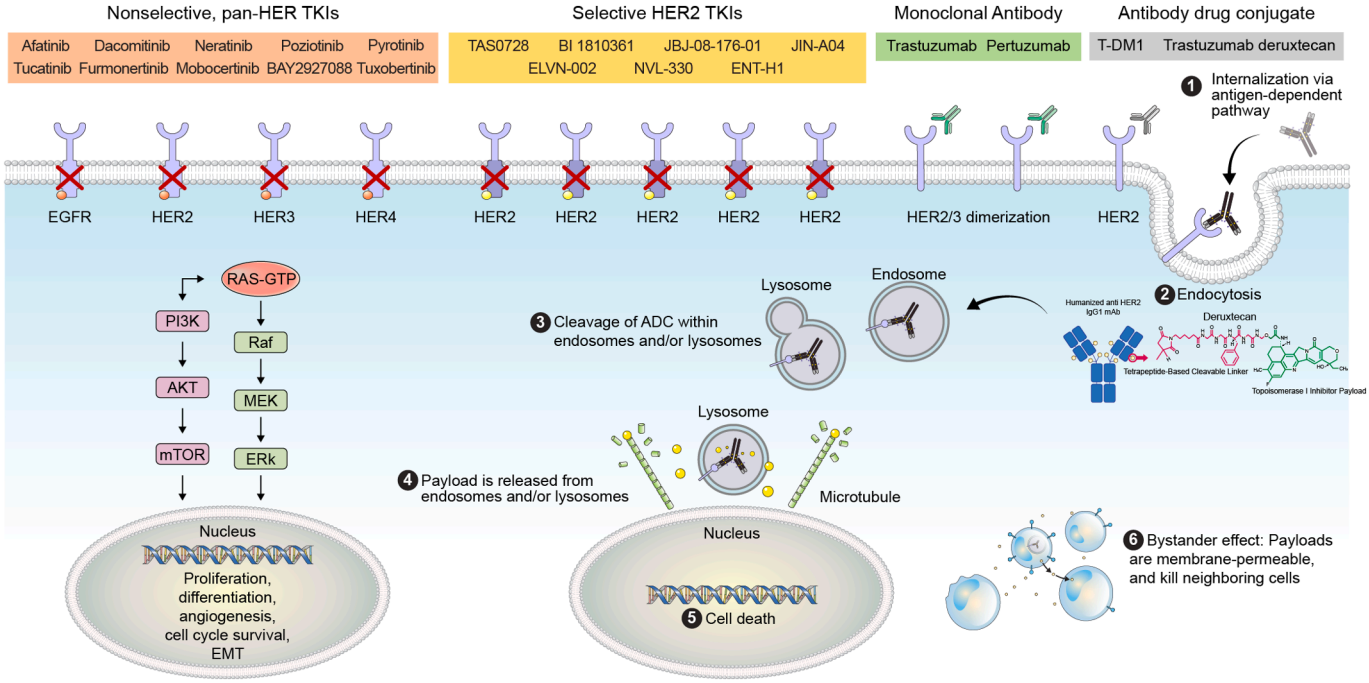


Fig. 2. Mechanism of action for HER2 targeted therapies in *HER2*-mutant NSCLC.

HER2 variant	Afatinib [35]	Dacomitinib [35]	Neratinib [35]	Poziotinib [35]	Pyrotinib [35]	Osimertinib [35]	Tucatinib [84]	Furmonertinib [72]	Mobocertinib [114]	BAY2927088 [114]	TAS0728 [82]	JBJ-08-176-01 [82]	JIN-A04 [83]	ELVN-002 [84]
WT EGFR	20.2	19.26	38.75	6.49	639.95	142.27	>10,000	162.6	15.9	221	399.15	368.14	NA	>10,000
HER2 S310F	NA	NA	NA	NA	NA	NA	11	NA	0.8	2.8	238.2	41.49	NA	3
HER2 S310Y	NA	NA	NA	NA	NA	NA	12	NA	NA	NA	NA	NA	NA	3
HER2 S335C	NA	NA	NA	NA	NA	NA	NA	NA	2.5	5.9	NA	NA	NA	NA
HER2 V659E	NA	NA	NA	NA	NA	NA	NA	NA	10.1	13.4	NA	NA	NA	NA
HER2 R678Q	NA	NA	NA	NA	NA	NA	29	NA	NA	NA	NA	NA	NA	5
HER2 L755P	20.54	25.16	19.71	3.65	55.18	69.58	1284	NA	5.7	11.6	NA	NA	NA	21
HER2 L755S	4.37	12.49	3.28	0.53	41.6	12.41	418	NA	5.9	1.9	3757	139.92	NA	8
HER2 D769N	0.81	2.65	0.51	0.12	4.53	8.1	7	NA	NA	NA	NA	NA	NA	2
HER2 D769Y	1.48	3.67	1.02	0.36	0.78	7.38	NA	NA	NA	NA	NA	NA	NA	NA
HER2 D769H	2.71	7.04	2.5	0.35	5.36	13.8	NA	NA	NA	NA	NA	NA	NA	NA
HER2 Y772dupYVMA	42.05	143.43	31.08	1.87	118.8	577.77	NA	NA	NA	NA	NA	NA	NA	NA
HER2 V773M	3.27	15.19	2.99	1.07	0.57	29.44	64	NA	NA	NA	NA	NA	NA	4
HER2 M774delinsWLV	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	894.16	21.03	NA	NA
HER2 L775A	NA	NA	NA	NA	NA	NA	NA	NA	4.7	7	NA	NA	NA	NA
HER2 V777L	1.17	3.42	1.62	0.13	0.74	6.96	11	NA	NA	NA	19.24	2.71	NA	3
HER2 A775_G776insYVMA	NA	NA	NA	NA	NA	NA	225	118	NA	NA	256.45	13.58	11.1	11
HER2 775_757LREdelinsRP	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	7.24	NA	NA
HER2 A775-G776-ins-C	NA	NA	NA	NA	NA	NA	24	NA	NA	NA	NA	NA	NA	2
HER2 A775-776-ins-YVMS	NA	NA	NA	NA	NA	NA	510	NA	NA	NA	NA	NA	NA	15
HER2 A775-G776-ins-SVMA	NA	NA	NA	NA	NA	NA	157	NA	NA	NA	NA	NA	NA	6
HER2 A775-G776-ins-VVMA	NA	NA	NA	NA	NA	NA	294	NA	NA	NA	NA	NA	NA	12
HER2 A775-G776-ins-MMAY	NA	NA	NA	NA	NA	NA	287	NA	NA	NA	NA	NA	NA	7
HER2 A775-G776-ins-YVMA-R678Q	NA	NA	NA	NA	NA	NA	642	NA	NA	NA	NA	NA	NA	14
HER2 G776delinsVC	29.34	84.87	33.59	4.85	89.82	412.6	NA	NA	NA	NA	625.55	6.01	0.3	NA
HER2 G776delinsLC	7.01	25.11	6.55	1.13	11.42	46.96	88	NA	NA	NA	NA	NA	NA	13
HER2 G776delinsVV	14.9	45.37	20.85	2.99	1665.65	188.06	1239	NA	NA	NA	NA	NA	NA	34
HER2 A776VC	NA	NA	NA	NA	NA	NA	499	NA	NA	NA	NA	NA	NA	17
HER2 P776delinsIC	NA	NA	NA	NA	NA	NA	1104	NA	NA	NA	NA	NA	NA	41
HER2 P776-V777delinsCVC	NA	NA	NA	NA	NA	NA	209	NA	NA	NA	NA	NA	NA	13
HER2 G776-delinsAVGC	NA	NA	NA	NA	NA	NA	438	NA	NA	NA	NA	NA	NA	14
HER2 L777L	NA	NA	NA	NA	NA	NA	NA	NA	1	1.1	NA	NA	NA	NA
HER2 V777_G778insGC	NA	NA	NA	NA	NA	NA	20	25	NA	NA	NA	NA	NA	5
HER2 G778insLPS	1.67	3.39	1.99	0.18	0.98	16.9	NA	NA	NA	NA	NA	NA	NA	NA
HER2 P780insGSP	27.59	95.57	32.27	4.12	23.1	440.31	NA	NA	NA	NA	80.08	7.38	1.4	NA
HER2 P780-Y781insGSP	NA	NA	NA	NA	NA	NA	29	NA	NA	NA	NA	NA	NA	3
HER2 L786V	5.02	9.78	1.41	1.22	2.26	8.3	NA	NA	NA	NA	NA	NA	NA	NA
HER2 T789M	NA	NA	NA	NA	NA	NA	3412	NA	NA	NA	NA	NA	NA	194
HER2 V842I	4.05	6.48	1.51	0.45	0.65	24.31	21	NA	NA	NA	NA	NA	NA	4
HER 2 V862I	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1316.4	284.03	NA	NA
HER 2 L869R	1.44	3.07	0.96	0.81	4.96	27.61	148	NA	NA	NA	NA	NA	NA	2
HER2 L869R/T798I	NA	NA	NA	NA	NA	NA	2524	NA	NA	NA	NA	NA	NA	43

Fig. 3. Heat map representation of IC_{50} for proliferation (nmol/L) of indicated TKIs for Ba/F3 cells harboring each HER2 mutation subtypes, including non-selective pan-HER TKIs (afatinib [35], dacomitinib [35], neratinib [35], poziotinib [35], pyrotinib [35], osimertinib [35], tucatinib [84], furmonertinib [72], mobocertinib [114], BAY2927088 [114]) and selective HER2 TKIs (TAS0728 [82], JBJ-08–176-01 [82], JIN-A04 [83], ELVN-002 [84]). For NVL-330 and ENT-H1 there was no detailed IC50 data available at the time of publication. The colors mark the sensitivity to different agents: sensitive (green, <10), intermediate (yellow, 10–99) and resistant (red, ≥100). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

wild type NSCLC with relatively higher TMB, co-altering mutations, and smoking mutational signature. Concurrent mutations such as *TP53* and *PIK3CA* alterations are identified with *HER2* mutations [44].

HER2-altered NSCLC has an uninflamed TME, is associated with lower rates of high PD-L1 expression and a lower median tumor mutational burden (TMB) [74,76,90]. *HER2* exon 20 mutated NSCLC express low levels of mature NK cells, and upregulate *TNFSF4 (OX-40)* and *CXCR4*. Preclinical studies show that HER2-altered NSCLC inhibit cCAS-STING pathway regulating innate immune mechanism, to prevent TBK1-STING signaling [45]. Taken together, these characteristics result in immune-cold environment in HER2-altered NSCLC.

3. HER2 targeted therapy

3.1. Chemotherapy

In patients with *HER2*-mutant NSCLC treated with first line pemetrexed based chemotherapy, the overall response rate (ORR) was 36 % and the PFS of 5.1 months, similar to the *KRAS*-mutant and *EGFR*-mutant group with a PFS of 5.0 and 6.5 months, respectively but was significantly shorter than the *ALK/ROS1*-rearranged group with a PFS of 9.2 months ($p = 0.004$). Among the *HER2* mutation variants, there was also a trend towards inferior PFS in A775_G776insYVMA group compared with other variants (4.2 vs 7.2 months, $p = 0.085$) [46].

Several phase II studies have reported the efficacy of chemotherapy in combination with HER2 targeting agents (Table 1). Treatment was well tolerated and results were consistent with those from chemotherapy alone [47]. Similarly, a randomized phase 2 study assessed the addition of trastuzumab to cisplatin and gemcitabine in HER2 positive NSCLC with no clear clinical benefit [48]. In the subset of NSCLC with HER2 overexpression of + 3, the ORR was 25 % [49] but these results should be viewed with caution given the small sample size.

3.2. Immunotherapy

While ICI therapy has become a key component of the treatment for non-oncogene driver NSCLC, its role in oncogene-driven NSCLC such as those with HER2 alterations is less certain. Responses to ICI as a monotherapy appear to be modest at best, with ORR ranging from 0 to 27.3 % and PFS ranging from 1.88 to 2.5 months [44,50–53]. The

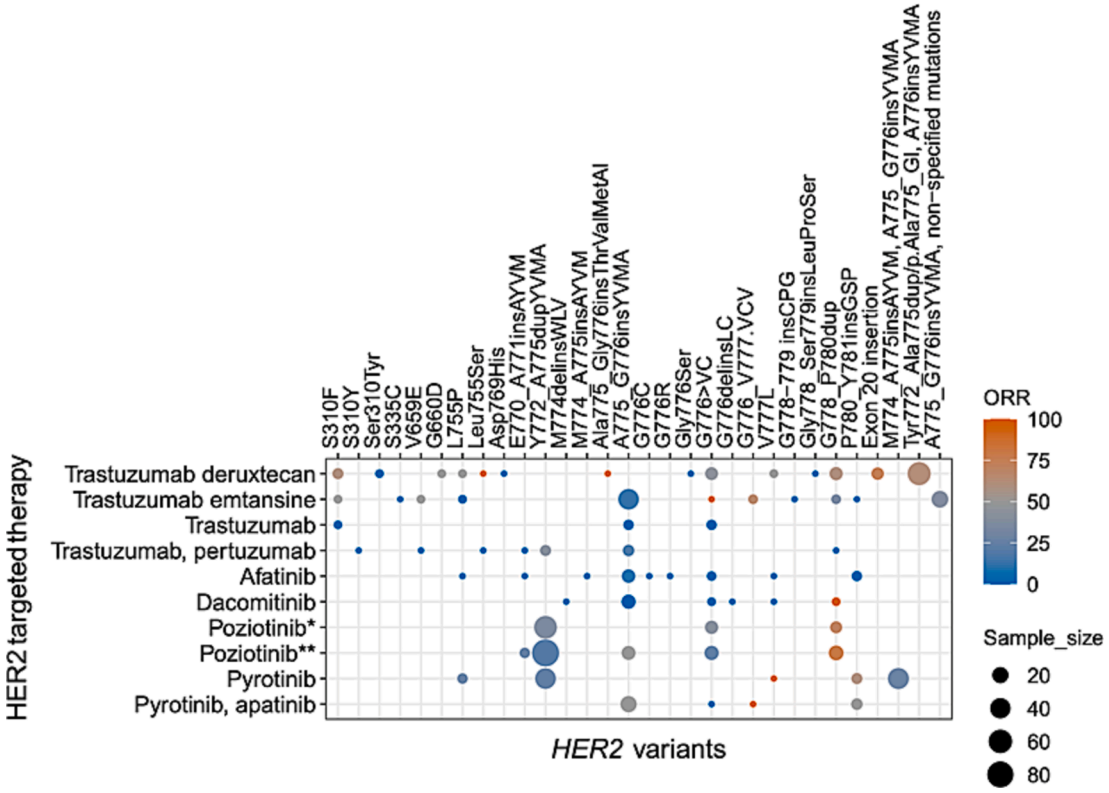


Fig. 4. ORR of HER2 agents versus HER2 mutation subtypes. Trastuzumab deruxtecan [99,101], trastuzumab emtansine [92,94–96], trastuzumab [88], trastuzumab and pertuzumab [90], afatinib [58,115], dacomitinib [61], poziotinib for treatment naive* [35,116–118], poziotinib for treatment refractory** [66], pyrotinib [68], and pyrotinib and apatinib [69].

IMMUNOTARGET registry reported an ORR of 7.4 % and PFS of 2.5 months [52], whereas The French Lung Cancer Group reported an ORR of 27.3 % and a median PFS of 2.2 months [53].

A retrospective study of first-line ICI plus chemotherapy reported an ORR of 52 % and a median PFS of 6 months [54], results comparable to that of an unselected NSCLC cohort in KEYNOTE-189 [55]. Another retrospective study reported an ORR of 28.9 % and median PFS of 5.2 months. While the ORR was higher, there was no statistically significant improvement in median PFS compared to chemotherapy alone (5.2 vs 4.03 months, $p = 0.20$) [56].

Overall, the current evidence does not support the use of ICIs as a single agent in the treatment of HER2-altered NSCLC. Immunochemotherapy combinations, albeit with limited supporting evidence, remain a viable first-line treatment option.

3.3. *HER2 targeted tyrosine kinase inhibitors (TKIs)*

3.3.1. *Non-selective HER2 inhibitors*

Non-selective HER2 inhibitors include the pan-HER TKIs: afatinib, dacomitinib, neratinib, poziotinib, pyrotinib, tucatinib, furmonertinib, mobocertinib, BAY2927088, tarloxotinib and tuxobertinib (Figs. 2, 3).

Afatinib

Afatinib, an irreversible pan-HER TKI, has modest clinical activity with a partial response (PR) rate of 13–19 % [57]. In a single arm phase 2 study of afatinib in pre-treated patients with *HER2* exon 20 mutations (ETOP NICHE), the ORR was 0 %, and the study was halted as it did not meet prespecified efficacy threshold [58].

Responses to afatinib may vary according to the *HER2 mutation* variant (Fig. 4). The most frequent variant, p.A775_G776insYVMA, found in up to 42 % of *HER2* mutations has been reported to be resistant to afatinib [59]. Afatinib may be active in non-YVMA variants such as p. G776delinsVC, p.Y772_A775dup and p.G778_P780dup with a higher ORR (50 % vs 0 %, $p = 0.077$) and longer PFS (9.53 vs 1.8 months, $p = 0.057$) than other *HER2* mutation subtypes [60]. TP53 co-mutations and PI3K/AKT/mTOR pathway activations may also confer additional resistance to afatinib [59].

Dacomitinib

In a phase 2 trial of dacomitinib, an irreversible pan-HER TKI, the PR rate was 12 % in patients harbouring *HER2* mutations and 0 % with *HER2* amplification. No responses were seen in the common YVMA subtype [61]. The IC_{50} of dacomitinib was higher in Ba/F3 cells harbouring YVMA insertion whereas the IC_{50} was lower with *HER2* variants with GSP insertion, WLV insertion, and CPG insertion (Fig. 3).

Neratinib

Neratinib, an irreversible pan-HER TKI, was evaluated in the SUMMIT phase II basket trial across multiple cancer types with *HER2* or *HER3* mutations. Of the 26 patients with NSCLC, only one patient with a kinase domain missense mutation (L755S) had a PR [3].

A randomized phase II study of neratinib with or without temsirolimus in patients with advanced *HER2*-mutant NSCLC reported an ORR of 19 % with combination therapy and no responses were seen in patient who received neratinib alone [62].

The activity of non-selective HER2-TKIs has yielded disappointing results although some responses have been reported in certain *HER2* mutant variants which may be explained by differences in drug binding affinity. For instance, 3D modelling of the YVMA insertion demonstrated the presence of two bulky side chains leading to steric hindrance, thus affecting afatinib binding to the binding pocket [59]. Dacomitinib sensitive *HER2* mutation variants contained a glycine in a position two residue beyond the end of the C helix instead of Asp770 found in wild-

Table 1
Pivotal trials of HER2 targeted therapies in *HER2*-mutant NSCLC.

Study	Patient population	N	Agents	ORR (%)	PFS	G3 + TRAE	Dose reduction, %	Dose discontinuation, %	Reference
Chemotherapy									
ECOG 2598	Untreated HER2 1–3+	56	Carboplatin, paclitaxel, trastuzumab	24.50 %	3.25 months	35.8 % G4	NR	NR	[49]
MSKCC	untreated HER2 0–3+	64	Trastuzumab with docetaxel or paclitaxel	28 %	2.4 months for Docetaxel + T, 3.9 months for Paclitaxel + T	G3 diarrhea (10 %, docetaxel)	NR	NR	[47]
U Gatzemeier et al	Untreated HER2 1–3+	101	Cisplatin, gemcitabine +/- transtuzumab	36 % (vs 41 % in control)	6.3 months (vs 7.2 in control)	NR	NR	NR	[48]
Immunotherapy									
Negrao et al, MDACC, Retrospective	*HER2* mutation (codons 775 and 770–785)	15	ICI monotherapy (pembrolizumab, atezolizumab, nivolumab, or durvalumab)	8 %	1.88 months	NR	NR	NR	[44]
Chen et al, Retrospective	*HER2* mutation (Exon20 insertion)	6	ICI monotherapy (drug not specified)	0 %	NA	NR	NR	NR	[51]
Lai et al, Retrospective	*HER2* mutation	26	ICI monotherapy (drug not specified)	12 %	1.9 months	NR	NR	NR	[52]
Mazieres et al, Retrospective	*HER2* mutation (Exon20 insertion)	29	ICI monotherapy (pembrolizumab, atezolizumab, nivolumab, or durvalumab)	7.4 %	2.5 months	NR	NA	NA	[52]
Guisier et al, Retrospective	*HER2* mutation (Exon20 insertion)	23	ICI monotherapy (nivolumab, pembrolizumab, or other)	27.3 %	2.2 months	NR	NA	NA	[53]
Saalfeld et al, Retrospective	*HER2* mutation (Exons 8, 19, 20)	22	Immuno-chemotherapy combination	52 %	6 months	NR	NA	NA	[54]
Chu et al, Retrospective	*HER2* mutation	16	Immuno-chemotherapy combination	37.5 %	8.4 months	11.5 %	NR	NR	[119]
Yang 2022, Retrospective	HER2-altered (mutant or amplification) advanced NSCLC	46	Immuno-chemotherapy combination	28.9 %	5.2 months	NR	NR	NR	[56]
Non-selective HER2 TKIs									
Niche et al	*HER2* mutation (Exon20 insertion)	13	Afatinib	53.80 %	15.9 weeks	<10 %	NR	NR	[58]
Victoria Lai et al	*HER2* mutation (Exon20 insertion)	27	Afatinib	13 % (3/23 evaluable patients)	NR	NR	NR	NR	[57]
MG Kris et al	*HER* mutations/ amplification	30	Dacomitinib	12 % (3/26 with *HER2* mutations), 0 % (HER2 amplification)	3 months	NR	17 %	13 %	[61]
B. Besse et al	*HER* mutations	27	Neratinib +/- temsirolimus	0 % (neratinib alone), 21 % (3/14 in combination group)	2.9 months in neratinib alone, 4 months in combination	G3 diarrhea (8 % in neratinib alone, 14 % in combination)	NR	NR	[120]
PUMA-NER-4201	*HER* mutations	62	Neratinib +/- temsirolimus	0 % (neratinib alone), 19 % (8/43 in	3 months in neratinib alone, 4.1	G3 diarrhea (12 % in neratinib alone, 14 % in combination)	NR	NR	[67]

(*continued on next page*)

Table 1 (*continued*)

Study	Patient population	N	Agents	ORR (%)	PFS	G3 + TRAE	Dose reduction, %	Dose discontinuation, %	Reference
				combination group)	months in combination				
Summit	*HER2/3* mutations	26 (lung cohort)	Neratinib	4 % (1/26)	5.5 months	G3 diarrhea (22 %)	NR	2.8 % DD due to diarrhea	[50]
ZENITH-20 (cohort 2)	Previously treated *HER2* mutation (Exon20 insertion)	90	Poziotinib	27.8 %	5.5 months	G3 rash (48.9 %), G3 diarrhea (25.6 %), G3 stomatitis (24.4 %)	76.7 %	13.3 %	[116]
ZENITH-20 (cohort 4)	Treatment naïve *HER2* mutation (Exon20 insertion)	80	Poziotinib	39 %	5.6 months	G3 rash (QD, 45 %; BID, 39 %), stomatitis (QD, 21 %; BID, 15 %), diarrhea (QD, 15 %; BID, 21 %)	75 % (QD, 79 %, BID, 70 %)	88 % (QD, 89 %; BID, 85 %)	[66]
Wang et al	*HER2* mutation	15	Pyrotinib	53.3 % (8/15)	6.4 months	NR	NR	NR	[121]
Zhou et al	*HER2* mutation	60	Pyrotinib	30 %	6.9 months	G3 or G4 (28.3 %), G3 diarrhea (20 %)	5 % due to diarrhea	1.7 %	[67]
Song et al	*HER2* mutation	78	Pyrotinib	19.2 % (exon 20, 17.7 %; non-exon 20 25 %)	5.6 months	G3 (20.5 %), G3 diarrhea (16.7 %)	2.5 % (2/78)	5.1 % (4/78)	[68]
PATHER2	*HER* mutations/ amplification	33	Pyrotinib with apatinib	51.5 %	6.9 months	G3 diarrhea (3 %), G3 hypertension (9.1 %)	30.3 % (pyrotinib)	3 % (both), 15 % (apatinib)	[69]
Zhao et al	*HER2* mutation	48	Pyrotinib with inetetamab	0 % (pyrotinib 240 mg), 36.6 % (pyrotinib 320 mg)	5.5 months	14.5 % (7/48; 1 in pyrotinib 240 mg; 6 in pyrotinib 320 mg)	NR	NR	[70]
Selective HER2 TKIs									
Beamion Lung 1	*HER* mutations/ amplification		BI 1,810,631	46 %	NR	G3 (9.3 %), alanine aminotransferase increased (7 %)	4.7 %	4.7 %	[81]
Monoclonal antibody									
HOT1303-B Trial	HER2 IHC 3 + or IHC 2+/ DISH +, and/ or presence of mutation	10	Trastuzumab	0 %	5.2 months	10 % (n = 1, pneumonitis)	NR	NR	[88]
California Cancer Consortium Screening and Phase II Trial	HER2 IHC 3 + or IHC 2+	13	Trastuzumab, Docetaxel	31 % (single agent followed by combination therapy)	4.3 months	NR	NR	NR	[87]
Zinner et al	HER2 IHC 1, 2, 3 + or > 15 ng/mL of serum shed antigen ELISA	21	Trastuzumab, Gemcitabine, Cisplatin	38 %	8.5 months	NR	NR	NR	[89]
ECOG Study 2598	HER2 IHC ≥ 1+	56	Trastuzumab, Paclitaxel, Carboplatin	24.5 %	3.3 months	35.8 %*G4	NR	NR	[49]
Gatzemeier et al	HER2 IHC ≥ 2+, HER2/ CEP17 ratio ≥ 2, or serum HER2 ECD 15 ng/mL by ELISA	103	Trastuzumab, Gemcitabine, Cisplatin	36 %	6.1 months (8.5 months in IHC 3 +)	G3/G4 neutropenia 57 %, thrombocytopenia 35 %, leukopenia 33 %	NR	NR	[48]
Herbst et al	NSCLC with previous treatment with chemotherapy	43	Pertuzumab	0 %	6.1 weeks	9.3 %	NR	NR	[122]
IFCT 1703-R2D2	HER2 alteration (exon 20 mutation or insertion)	47	Pertuzumab, Trastuzumab, Docetaxel	29 %	6.8 months	64 %	47 % (Docetaxel)	None	[123]

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Table 1 (*continued*)

Study	Patient population	N	Agents	ORR (%)	PFS	G3 + TRAE	Dose reduction, %	Dose discontinuation, %	Reference
Targeted Agent and Profiling Utilization Registry Study	*HER* mutations/ amplification	28	Pertuzumab, Trastuzumab	11 %	16 weeks	18 %	NR	NR	[90]
Antibody drug conjugate									
Phase II basket trial (MSKCC)	*HER2* mutation	18	Ado Trastuzumab-Emtansine	44 %	5 months	6 %	None	None	[92]
Iwama et al	*HER2* mutation (Exon20 insertion)	22	Ado Trastuzumab-Emtansine	38.1 %	2.8 months	22.7 %	None	14 %	[94]
Hotta et al	HER2 IHC ≥ 2+, HER2/ CEP17 ratio > 2, or HER2 exon 20 mutation	15	Ado Trastuzumab-Emtansine	6.7 %	2 months	G3/G4 thrombocytopenia 40 %	NR	NR	[95]
Peters et al	HER2 IHC ≥ 2+	49	Ado Trastuzumab-Emtansine	0 % (IHC 2 +), 20 % (IHC 3 +)	2.6 months (IHC 2 +), 2.7 months (IHC 3 +)	22 %	NR	4 %	[96]
Tsurutani et al, Phase I	HER2 IHC ≥ 1 + or HER2 mutation	18	Trastuzumab deruxtecan	55.6 %	11.3 months	11.1 %*serious TRAE	23.7 % (all tumors)	8.5 % (all tumors)	[99]
DESTINY-Lung01	HER2 IHC 2, 3+	49	Trastuzumab deruxtecan	24.5 %	5.4 months	73.5 %	34.7 %	22.4 %	[100]
DESTINY-Lung01	*HER2* mutation	91	Trastuzumab deruxtecan	55 %	8.2 months	46 %	34 %	25 %	[101]
DESTINY-Lung02	*HER2* mutation	80	Trastuzumab deruxtecan at 5.4 mg/kg and 6.4 mg/kg	53.8 % (5.4 mg/kg), 42.9 % (6.4 mg/ kg)	NR	31.7 % (5.4 mg/ kg),			
58 % (6.4 mg/kg)	9.9 % (5.4 mg/ kg), 26 % (6.4 mg/kg)	7.9 % (5.4 mg/ kg), 16 % (6.4 mg/ kg)	[104]						

Abbreviations: BID, twice daily; DD, dose delay; DISH, dual color in situ hybridization; ELISA, enzyme-linked immunosorbent assay; G3 + TRAE, >3 grade 3, treatment-related adverse events; HER2 ECD, HER2 extracellular domain; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; N, number; NR, not reported; NSCLC, non-small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; QD, once daily; T, Trastuzumab.

type EGFR. The presence of glycine reduces steric hindrance which would have occurred in patients with wild-type Asp 770 and acquired *HER2* exon 20 insertions, facilitates C-helix conformational changes, allowing binding of drug [63]. In view of these challenges, other novel pan-HER2 TKIs have been developed.

Poziotinib

Poziotinib is an irreversible pan-HER TKI. The phase II ZENITH-20 study reported an ORR of 27.8 % and median PFS of 5.5 months in patients with previously treated NSCLC with *HER2* exon 20 insertion mutations [64]. Grade 3 or higher treatment-related adverse events (TRAEs) included rash (48.9 %), diarrhea (25.6 %), and stomatitis (24.4 %) and dose reduction in 77 % of patients. FDA approval was not granted based as the benefits of poziotinib did not outweigh its toxicities and the development of poziotinib was subsequently de-prioritized [65].

The activity of pozitotinib 16 mg QD and 8 mg BID in treatment naïve *HER2*-mutant patients have been reported recently [66]. A BID dosing was studied as it could lower Cmax and maintain Ctrough and overall drug exposure, potentially reducing toxicity. The ORR was 39 % (QD 45 % vs BID 30 %), DCR was 73 % (QD 75 % vs BID 70 %), and the median PFS was 5.6 months (QD 5.6 vs BID 5.6). The G778_P780dupGSP subtype was particularly sensitive to poziotinib with an ORR of 71 %. The most frequent grade 3 TRAE was rash (43 %) with 45 % in the QD group and 39 % in the BID group. Other grade 3 TRAEs included stomatitis (overall 19 %; QD: 21 %; BID: 15 %), diarrhea (overall 18 %; QD: 15 %; BID: 21 %), and grade 5 pneumonitis (one patient in QD group), leading to treatment discontinuation in 5 % (4/80) of the treated patients.

Pyrotinib

Pyrotinib is an irreversible pan HER TKI. In a phase II study of pyrotinib in patients with previously treated *HER2*-mutant NSCLC, the ORR was 30 % (95 % CI, 18.8–43.2 %) [67]. The ORR for A775_G776insYVMA and M774_A775insAYVM combined was 27 % (Fig. 4). The mPFS was 6.9 months (95 % CI, 5.5–8.3), and mOS was 14.4 months (95 % CI, 12.3–21.3) in the overall population. The most common TRAE was grade 3diarrhea (20 %). In treatment naïve patients, the ORR and PFS was 19.2 % and 5.6 months, respectively [68]. The ORR was 50 % and 100 % for A755_G776insYVMA and G776_V777.VCV variants, respectively. A phase III trial, Pyramid-1 evaluating pyrotinib vs docetaxel in patients after failure with platinum based chemotherapy in NSCLC harboring *HER2* exon 20 mutation is underway

(NCT04447118).

Pyrotinib has been combined with apatinib and inetetamab [69,70]. PATHER2, a phase 2 study of pyrotinib in combination with apatinib, a TKI vascular endothelial growth factor receptor-2 (VEGFR2) TKI reported an ORR of 51.5 % (95 % CI, 33.5–69.2 %), and mPFS (6.9 months) and mOS (14.8 months) [69]. Inetetamab, a recombinant humanized anti-HER2 mAb, was evaluated in *HER2*-mutant NSCLC in a phase IB study [70]. There were no DLT and adverse events were mainly grade 1–2 diarrhea, rash, and vomiting. Preliminary efficacy reported an ORR and median PFS of 5.5 months.

Tucatinib

Tucatinib is a reversible pan-HER TKI that was recently granted FDA approval in combination with trastuzumab for the treatment of HER2 positive metastatic colorectal cancer [71]. In NSCLC, the combination's efficacy is currently being evaluated in a phase II basket trial (NCT04579380).

Furmonertinib

Furmonertinib (AST5902) is an irreversible, highly brain-penetrant pan-EGFR inhibitor with demonstrated activity against *HER2* exon 20 insertion mutations [72]. The efficacy and safety of furmonertinib is currently being evaluated in a phase I clinical trial (NCT05364073).

Mobocertinib

Mobocertinib (TAK-788), an irreversible TKI targeting *EGFR* and *HER2* exon 20 insertion mutations, was granted FDA approval in 2021 for the second line treatment of *EGFR* exon 20 insertion mutant NSCLC [73]. Preclinical data in *HER2*- mutant NSCLC showed promising results in vitro and in mouse models, with varying activity against specific variants [74]. Currently, there are no published clinical studies investigating the effects of mobocertinib on NSCLC harboring *HER2* exon 20 insertion [75].

BAY2927088

BAY2927088 is a reversible, highly potent TKI targeting *EGFR* and *HER2* driver mutations [76]. Preclinically, it showed significant dose-dependent inhibition of in vivo tumor growth in NSCLC *EGFR* ex20ins and *C797S* mutations. Phase 1 testing, which includes *HER2*-mutant lung cancer patients, is implemented (NCT05099172).

Tarloxotinib

Tarloxotinib is a hypoxia-activated prodrug of a pan-HER kinase inhibitor. First analysis of the phase II RAIN-701 study showed an ORR of 22 % in the HER2 activating mutation group [77]. However, its development was terminated mid-2022 and it is no longer under clinical investigation.

Tuxobertinib (BDTX-189)

Tuxobertinib (BDTX-189) is an irreversible selective inhibitor of allosteric EGFR and HER2 oncogenic mutations, including *EGFR/HER2* exon 20 insertion mutation [78]. The MasterKey-01 study showed promising anti-cancer activity in a heavily pre-treated patient population, including patients who had received prior EGFR/HER2 TKI's with the added benefit of novel new generation TKIs being designed to inhibit HER mutations while sparing HER wildtypes with aims to reduce off target toxicities [79].

3.3.2. Selective HER2 inhibitors

Novel HER2 TKIs that are highly HER2 selective with EGFR sparing activity currently being developed include TAS0728, BI 1810631, JBJ-08–176-01, JIN-A04, ELVN-002, NVL-330 and ENT-H1 **(**Fig. 2**,3)**.

TAS0728

TAS0728 is a HER2-selective inhibitor that specifically targets HER2. It has demonstrated potent inhibitory activity against overexpressed/amplified HER2 and mutated *HER2* in cancer cells [80]. Assessment of TAS0728 in ongoing clinical trials is awaited (NCT03410927).

BI 1810361

BI 1,810,361 (zongertinib) is an orally active, potent, covalent, and highly selective HER2 inhibitor [111,112]. Encouraging anti-tumor activity was observed in pantumor harboring HER2 aberrations in the ongoing Phase I Beamion Lung 1 (NCT04886804) [81]. In *HER2*-mutant NSCLC refractory to platinum-based chemotherapy, the ORR was 46 %. Dose taken into dose optimization for BI 1810631 are 240 mg and 120 mg. Diarrhea was the most common adverse event (32.6 %) that were grade 1 or 2.

JBJ-08-176-01

JBJ-08–176-01 is a HER2 selective, covalent TKI, that targets multiple *HER2* activating mutations including exon 20 insertion as well as amplification. JBJ-08–178-01 displayed strong selectivity toward HER2 mutations while sparing wild type EGFR, compared to other EGFR/HER2 TKIs [82]. JBJ-08–178–01 covalently binds to the HER2 kinase domain, suggesting that the selectivity for HER2 stems from a hydrogen bond between the triazolopyridine ring of JBJ-08–178–01 and Ser783. The efficacy of JBJ-08–178-01 was seen in various HER2 mutant cell lines including patient-derived cells, and in vivo.

JIN-A04

JIN-A04 is a TKI selectively targeting *HER2* exon 20 insertion mutations, including HER2 VVMA and HER2 P780_780_Y781insGSP mutations [83]. JIN-A04 significantly inhibited Ba/F3 cell lines harboring these mutations with an IC_{50} of 11.1 and 1.4 nM for *HER2* YVMA and GSP, respectively.

ELVN-002

ELVN-002 is a CNS-penetrant, irreversible potent HER2 inhibitor against key *HER2* mutations, including exon 20 insertion mutations in NSCLC whilst sparing EGFR [84]**.** A phase I study evaluating ELVN-002 in patients with solid cancers harboring an abnormal *HER2* gene is ongoing (NCT05650879).

NVL-330

NVL-330 is a highly selective, CNS-penetrant, covalent HER2 inhibitor with promising in vivo activity targeting crucial HER2 mutations, particularly exon 20 insertions in NSCLC. Evaluation in clinical setting is awaited [85].

ENT-H1

ENT-H1 is an irreversible HER2 inhibitor that targets both wild-type and mutated HER2, including exon 20 insertion mutation. In vitro analysis show potency in various cell lines, including A775G776insYVMA and G776VC [86].

3.4. HER2-targeted monoclonal antibodies

Early attempts to target NSCLC with *HER2* amplification have been

unsuccessful with modest responses (Table 1). Previously, HER2 overexpression (IHC 2 + or 3 +) identified in ~ 30 % of cases of NSCLC was associated with worse prognosis [87]. Initially, trastuzumab, a humanized monoclonal antibody (mAb) directly targeting *HER2*, was administered as monotherapy in the HOT1303-B Trial [88]. The ORR was 0 % and median PFS was 5.2 months. Subsequently, various phase II studies included HER2-overexpressed NSCLC, and chemotherapy combination such as gemcitabine and cisplatin [48,89], paclitaxel and carboplatin [49], or docetaxel [87] to overcome limitations to trastuzumab monotherapy. Although a more favorable ORR (24.5–38 %) was noted with the addition of chemotherapy, the PFS benefit was modest with a median of 3.3–8.5 months.

Pertuzumab, a HER2 humanized mAb, combined with trastuzumab in *HER2* mutation and amplification resulted in a modest ORR of 11 % in heavily pretreated patients [90]. Responses were reported in *HER2* exon 20 mutation variants Y772_A775dup, A775_G776insYVMA and in *HER2* amplification.

In a phase II study (IFCT-1703) of patients with HER2-mutated, advanced NSCLC after ≥ 1 platinum-based treatment treated with pertuzumab, trastuzumab and docetaxel, the ORR and PFS was 29 % and 6.8 months, respectively [21].

3.5. HER2-targeted antibody-drug conjugates (ADCs)

An exciting emerging therapeutic class of agents are ADCs which is composed of a monoclonal antibody, payload and chemical linker designed to selectively target cancer cells [91]. By increasing efficacy via cleaving, internalizing, and releasing payload to HER2-positive cancer cells to induce cancer cell death, ADCs are able to maximize clinical efficacy and minimize unwanted toxicities, thereby overcoming the disadvantages of conventional chemotherapeutic agents.

3.5.1. T-DM1

T-DM1 (ado-trastuzumab emtasine), is a HER2-targeted ADCs linking trastuzumab with emtasine, an antimicrotubule agent with a drug-to-antibody ratio (DAR) of 3 to 4 [92,93]. In a phase II basket trial of T-DM1 in heavily pre-treated patients with *HER2*-mutant cancers, the ORR and PFS in patients with NSCLC was 44 % and 5 months, respectively. TRAEs were mainly grade 1 or grade 2 infusion reactions, thrombocytopenia and elevated AST and ALT. Biomarker analysis showed that responders were those with *HER2* mutations with differences in ORR according to mutation subtypes: 55 % in *HER2* exon-20 insertion mutation, 29 % in other subtypes, and no responses in exon-19 mutation. Although concurrent *HER2* amplification was seen in 11 % of *HER2*-mutant NSCLC, no association was seen between HER2 IHC and clinical response. This landmark study highlighted the importance of molecular selection by *HER2* mutation and the clinical utility of NGS.

A subsequent phase II trial of T-DM1 included patients with NSCLC harbouring *HER2* exon20 insertion mutations with A775_G776insYVMA the most frequently identified mutation (86.4 %) [94]. The ORR and PFS was 38.1 %, and 2.8 months, respectively. In contrast to the efficacy observed in HER2-overexpressed breast or gastric cancer, studies of T-DM1 in metastatic NSCLC with HER2 overexpression have showed modest efficacy with an ORR of 7–20 % (Table 1) [95,96].

3.5.2. Trastuzumab deruxtecan

Trastuzumab deruxtecan (T-DXd; DS-8201a) is an ADC consisting of humanized anti-HER2 antibody, peptide-based cleavable linker and topoisomerase I inhibitor payload with a DAR of approximately 8 [97]. The membrane-permeable cytotoxic payload enables efficient delivery of payload to HER2-expressing tumor cells as well as cytotoxic bystander effect on nearby tumor cells [98].

In a dose-expansion, phase 1 study of trastuzumab deruxtecan in advanced HER2-altered NSCLC, the ORR and median PFS was 55.8 % and 11.3 months, respectively [99]. The ORR in the *HER2*-mutant subset was 72.7 % and the median PFS was 11.3 months. Four patients experienced interstitial lung disease (ILD) and pneumonitis, and 3 cases were adjudicated as related to trastuzumab deruxtecan.

In the phase II study of trastuzumab deruxtecan (DESTINY-Lung01) in patients with metastatic NSCLC with HER2 overexpression or *HER2*-activating mutation, the ORR was 24.5 % and 20.0 % for IHC 2 + and 3 + cohorts, respectively [100]. In patients with *HER2*-mutant NSCLC, the ORR was 55 %. With *HER2* mutation variants A776insYVMA and Tyr772_Ala775dup/p.Ala775_Gl associated with an ORR 61 % (Fig. 4). The median PFS and median OS were 8.2 months and 17.8 months, respectively [101]. Preclinical studies have shown activating *HER2* mutations enhance receptor internalization and intracellular uptake of trastuzumab deruxtecan [102], and the DESTINY-Lung01 study affirms this finding with trastuzumab deruxtecan more active in *HER2*-mutant NSCLC than HER2-overexpressing NSCLC. TEAE of grade 3 or more related to trastuzumab deruxtecan were reported in 55.1 % of patients, including neutropenia (20.4 %) and adjudicated ILD (6.6 %). Dose interruption, reduction and treatment discontinuation were reported in 53.1 %, 34.7 %, and 22.4 % of patients, respectively. Increasing awareness on trastuzumab deruxtecan related ILD/pneumonitis is crucial for better patient outcomes. [103].

Subsequently, a non-comparative, randomized phase II trial (DESTINY-Lung02) of trastuzumab deruxtecan 5.4 or 6.4 mg/kg every 3 weeks was conducted to assess the benefit-risk profile for *HER2*-mutant NSCLC [104]. Interim analysis reported an ORR of 53.8 % and 42.9 % for 5.4 mg and 6.4 mg/kg, respectively. However, safety profile was more tolerable in the 5.4 mg/kg cohort with adjudicated ILD rates of 5.9 %, versus 14 % with the 6.4 mg/kg. Trastuzumab deruxtecan is the first FDA approved HER2 ADC for treatment refractory *HER2*-mutant NSCLC [105]. Companion diagnostic test include Guardant360 CDx (Guardant Health, Redwood, CA) and Oncomine Dx Target Test (Life Technologies Corporation, MD) for plasma-based and tissue-based assay, respectively.

4. Mechanisms of resistance

Similar to other molecular targeted therapies, acquired resistance to HER2-targeted therapy is inevitable. While there are resistance mechanisms to HER2-targeted therapy in gastroesophageal adenocarcinoma [106] and breast cancer [107], there is currently insufficient data to describe the landscape of acquired resistance to HER2-targeted therapy in lung cancer. Theoretically, acquired resistance may evolve both HER2-dependent and HER2-independent pathways [108]. More specifically, *HER2* secondary mutations may occur, or bypass activation such as RAS/MAPK signaling pathway or PI3K/AKT pathways may evolve. Evidence on the acquired resistance to ADCs in *HER2*-mutant NSCLC patients is scarce and further investigations are needed.

5. Future perspectives and conclusion

The optimal sequencing strategy and exploration of the best combination treatment still awaits to be clarified for HER2-altered NSCLC patients. Currently, only NSCLC patients with *HER2* mutations are indicated for the use of HER2 directed targets as overexpression and amplifications of HER2 do not have the same benefits [30].

Identifying *HER2* mutations is pivotal for NSCLC patients to benefit from these targeted therapies. Platinum based chemotherapy currently remains the preferred first line treatment for patients with *HER2*-mutant lung cancer. Trastuzumab deruxtecan remains the next line treatment option for patients with previously treated, advanced NSCLC with *HER2* mutation on the basis of DESTINY-Lung01 and -Lung02 studies [101,104]. Upfront use of trastuzumab deruxtecan will be evaluated in the currently ongoing DESTINY-Lung 04 study in the first-line treatment of advanced NSCLC with *HER2* Exon 19 or 20 mutations (NCT05048797) [30]. The intracranial efficacy for the HER2 ADCs is also not fully established. In DESTINY-Lung04, CNS PFS is being explored as one of the secondary outcome measures [30].

Combinations of HER2 directed antibody-drug conjugates and ICIs

are a promising approach, and a few phase I trials are currently underway to investigate their safety and efficacy in previously treated *HER2*-mutant advanced NSCLC patients. DESTINY-Lung03 is an ongoing phase Ib study evaluating the combination of trastuzumab deruxtecan and durvalumab with chemotherapy as a 1st line treatment in NSCLC patients with HER2 overexpression (NCT04686305) [109]. Trastuzumab deruxtecan plus durvalumab are given as a second-line treatment (HUDSON study phase II basket trial), and trastuzumab deruxtecan in combination with pembrolizumab for HER2-expressing and *HER2*-mutant lung cancer (NCT04042701) are awaiting results [110].

The addition of immunotherapy to HER2 TKIs is also being explored with *HER2*-mutated NSCLC after failure of 1st line chemotherapy in a phase II trial using pyrotinib and PD-1 inhibitors (NCT04144569). The main concern for the combination strategies would be potential overlapping toxicities such as ILD.

Other novel targets such as bi-specific antibodies have now been explored to provide opportunities to enable dual targeting of different epitopes or antigens. Zenocutuzumab (MCLA-128) is a humanized IgG1bsAb that targets the extracellular domains of HER2 and HER3 [111]. It also has enhanced antibody-dependent cellular cytotoxicity (ADCC) activity.

Newer concepts in development include dual-payload ADCs which utilize two separate payloads, with different mechanisms of action with aims of synergetic payloads delivery for a more potent cytotoxic response [112]. Several other HER2 ADCs such as A166, ARX788, SHR-A1811, and MRG002 are being evaluated in NSCLC with HER2 alteration in Phase I/II clinical trials (NCT03602079, NCT03255070, NCT04818333, NCT05141786) [113].

Many exciting opportunities have emerged in the arena of *HER2*-mutant NSCLC since the initial FDA approval of the first HER2 ADC. Ongoing clinical trials may provide further streamlining of the sequencing, viable combinations and understanding of resistance mechanisms of these novel agents.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

MID (Medical Illustration & Design), a part of the Medical Research Support Services of Yonsei University College of Medicine, for providing excellent support with medical illustrations, and Sujin Choi, who supported us with figure illustration.

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