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Review

A Comprehensive Review on the Role of Human Epidermal Growth Factor Receptor 2 (HER2) as a Biomarker in Extra-Mammary and Extra-Gastric Cancers

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Simple Summary: Human epidermal growth factor receptors (HERs) are present in our body and are responsible for regulating cell growth. When there is an overexpression of HER2/neu receptors, it can lead to the development of certain cancers. Studies have shown that this overproduction of HER2/neu is found in 25–30% of breast cancers and 10–30% of stomach and food pipe cancers. HER2/neu has been identified as a useful marker for predicting and treating breast and stomach cancers. However, research suggests that HER2 also plays a role as a marker in other cancers. This article reviews the latest research on HER2 and its link to other cancers besides breast and gastric cancers.

Abstract: The human epidermal growth factor receptors (HERs) are expressed abundantly in the human body. The tumorigenic potential of HER2/neu is linked to its overexpression, amplification or somatic mutation. The HER2 gene amplification leading to protein overexpression has been reported in 25–30% of breast cancers and 10–30% of gastric/gastroesophageal cancers. While HER2 is a well-documented predictive, prognostic, and therapeutic marker in breast and gastric/gastroesophageal cancers, its relevance has also been demonstrated in multiple other malignancies. In this article, we will conduct an extensive review of current data pertaining to HER2 amplification, overexpression, or mutation in cancers other than breast and gastric cancers.

Keywords: human epidermal growth factor receptors; biomarker; extra-mammary HER2; extra-gastric HER2; HER2 gene amplification; HER2 overexpression

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1. Introduction

1.1. Nomenclature, Structure and Function

HERs belong to a family of epidermal growth factor receptor (EGFR) and have four subtypes: HER1 (EGFR, erbB1), HER2 (erbB2, HER2/neu), HER3 (erbB3), and HER4 (erbB4). As far as nomenclature is concerned, erbB2 is used to represent the gene in both humans and rodents, whereas neu is used to refer to rodent gene and product in rodent species and HER2 in human species. HER2, also known as CD340 (cluster of differentiation) is a 185 kD transmembrane glycoprotein encoded by ERBB2 (erythroblastic oncogene 2) proto-oncogene present on the long arm of chromosome 17 (17q12) [1]. The neu oncogene was discovered by Shih et al. in 1981 in ethyl nitrosourea-induced rodent neuroblastoma [2].

It was described as a transforming oncogene with similarities to ErbB (avian erythroblastosis oncogene B) oncogene and the epidermal growth factor receptor (EGFR) gene [3,4]. King et al. found an EGFR-related gene amplification in human mammary cells in 1984 and named it as the human epidermal growth factor receptor 2 (HER2) [5].

The HER family is usually present as monomers on the surface of the cell. Their structure comprises three domains: transmembrane lipophilic, an intracellular tyrosine kinase, and an extracellular ligand-binding domain [6] (Figure 1). The extracellular domain (ECD) has 630 amino acids with four domains arranged in repetitive pairs of domain I-III (190 amino acids) followed by domain II-IV (120 amino acids). The extracellular domain pivots between active-inactive conformation and accelerate dimer formation only on the binding of the ligand. In HER1 and 3, domain II has finger-like projections which overlay on domain IV to occlude the dimerization surface [7]. When a ligand binds, there is domain rearrangement decreasing the proximity between domains I and III, making domain II projection free for dimer formation. HER2 differs from HER1 and 3 in that domains II and IV have no contact and HER2 has no known activating ligand, and its extracellular domain is constitutively in active configuration due to lack of internal autoinhibitory structure. Additionally, HER2 can form heterodimerization with other members, such as HER1 or HER3 or insulin-like growth factor receptor 1. On the contrary, other HERs have several known activating ligands [8].

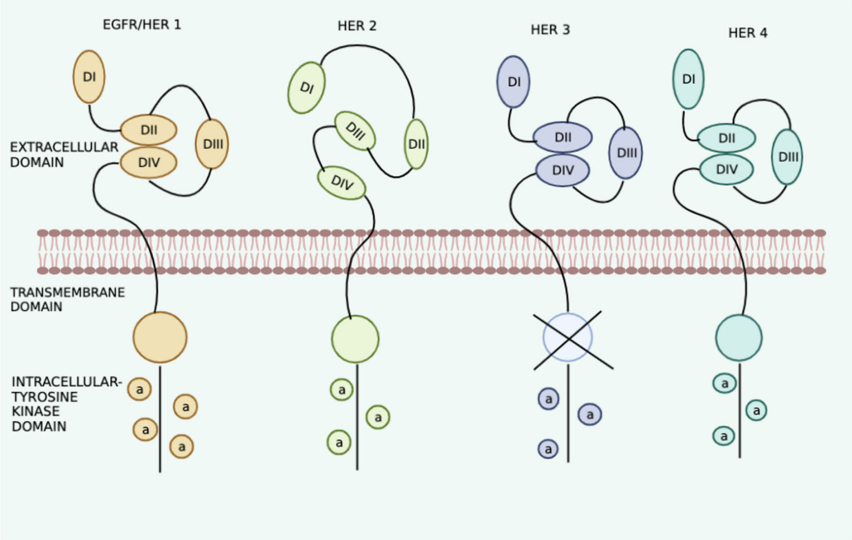

Figure 1. Schematic diagram representing the structure of HERs. Extracellular domains include I and III and II and IV, and transmembrane domain and intracellular domain include juxtmembranous part, tyrosine kinase catalytic part and C-terminal tail (dotted line) which contains the tyrosine residues.

The HERs are expressed normally in neuronal tissues, epithelial cells, and mammary glands, playing an important role in cellular proliferation, survival, differentiation, and angiogenesis. Heterodimerization of HERs lead to autophosphorylation of cytoplasmic domain of tyrosine kinase initiating various downstream signaling pathways, important ones being mitogen-activated protein kinase (MAPK), signal transducer and activator of transcription (STAT), phospholipase C gamma, protein kinase C(PKC) and phosphoinositide 3-kinase (PI3K) (Figure 2). These signaling pathways which regulate the proliferation and survival of cells, angiogenesis and invasion are recognized as the targets of HER2/neu upon activation in different malignancies. HER3 lacks ATP (adenosine triphosphate) binding within its catalytic domain, making it dependent on its heterodimers for its kinase activity [9]. Studies have shown that HER2-HER3 are obligate partners, and this heterodimer is the most potent activating stimulus for PI3L/Akt pathway [10]. Aberrant HER2 signaling can lead to tumorigenesis through the above-mentioned pathways and other reported mechanisms including Src kinase activation; loss of cell polarity and adhesion; invasive

phenotype promotion; and cell cycle dysregulation, particularly G1/S checkpoint control via two important downstream targets, cyclin D1 and p27 [11,12].

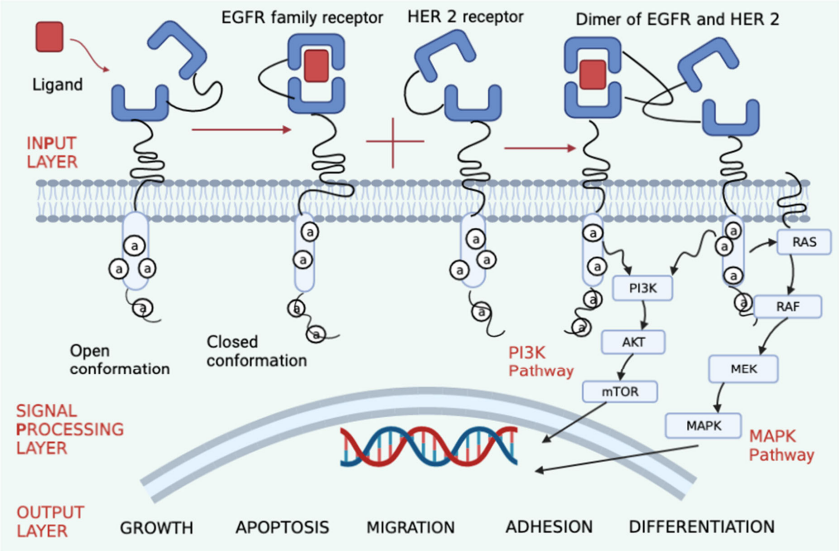

Figure 2. Schematic diagram of the function of HER2 with downstream signaling pathways: mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K), activated on homo or heterodimerization.

1.2. Testing for HER2 Neu

Immunohistochemistry (IHC) is a technique that utilizes monoclonal as well as polyclonal antibodies to identify tissue distribution of antigen of interest. Scoring criteria is summarized in (Table 1). IHC is a faster technique utilizing conventional bright-field microscopes and there is no degradation of stained tissue over time [13]. Moreover, it allows for parallel viewing of morphological features of tumor cells under the microscope [13]. Despite conferring these advantages, test results can vary based on primary antibodies and the scoring criteria used. Furthermore, it is a semi-quantitative method based on subjective determination of color intensity with a host of pre-analytic, analytic, and post-analytic parameters affecting the results.

Table 1. Summarizing the scoring criteria for IHC results in breast cancer.

IHC Score	Result	Staining Pattern	Percentage Of Stained Cells
0	Negative	Absent staining	0
1+	Negative	Faint or weak incomplete staining	<10%
2+	Equivocal	Thin circumferential membrane staining or heterogeneity in staining distribution	>10% but < 30%
3+	Positive	Diffuse intense circumferential membrane "chicken-wire"	>30%

Fluorescence in situ hybridization (FISH) is a technique utilizing single-stranded deoxyribonucleotide (DNA) or ribonucleotide (RNA) sequence (probe) to detect a specific DNA sequence on the chromosome by forming complementary base pairs with DNA or RNA of the tissue sample. Apart from being more precise, sensitive, and reproducible [14], results are more quantitative and less dependent on processing techniques. However, given the time-consuming nature and the requirement of fluorescent microscopy for integration, it is usually reserved for IHC equivocal samples (IHC score 2+) to confirm HER2 status. IHC scores 0 and 1+ are considered as HER2-negative and score 3+ is considered HER2-positive. If the IHC score is 2+, then it is reflex tested via FISH. If the HER2 gene is

amplified in the FISH testing, it is considered as HER2-positive. Newer techniques using peroxidase enzyme-labeled probes, such as CISH (chromogenic in situ hybridization) and SISH (silver in situ hybridization), have emerged in recent years. Instead of using a fluorescent microscope, they employ a normal bright-field microscope for interpretation, thus conferring an advantage over FISH analysis [13].

Other techniques include serum detection of HER2 ECD using enzyme-linked immunosorbent assay or HER2 in circulating tumor cells [15,16]. RT-PCR is a technique utilizing reverse transcription of RNA (ribonucleic acid) into DNA (deoxyribonucleic acid) followed by polymerase chain reaction mediated amplification of DNA targets to measure the amount of specific RNA in the sample. It has no interobserver variability, can be used in small samples, and is automated [17]. However, there is a chance of false-negative results as during RNA extraction, non-tumor and tumor cells are mixed, thus diluting the influence of tumor cells [18].

2. Strategies for Review

We carried out an electronic systematic search in PubMed database using keywords "Receptor, ErbB-2 [MeSH]" OR "Genes, erbB-2 [MeSH]" OR "HER-2 protein [Supplementary concept]" OR "ERBB2 protein, human [Supplementary concept] and "Neoplasms [MeSH]". All cancers, except for breast and gastro-esophageal malignancies with which association was reported, were noted.

Original articles with HER2/neu overexpression or amplification or mutation status reported in a malignancy were included. Articles other than original research (i.e., review articles, case reports, letter to editor, editorial or commentaries), duplicate publications or non-English publications were excluded. Titles and abstracts were independently screened by two authors (FA, and PM). Full texts of the included articles with extraction of data were independently conducted by three authors (FA, PS, and NG). Any discrepancy was resolved by a consensus of the authors. Additional articles were included by cross-referencing the reference list of the included articles. Descriptive analysis in the form of percentages has been used to describe HER2 amplification, expression, and mutation status with cumulative range to express the overall results.

We have also incorporated clinical trials utilizing HER2 agents in some malignancies (ovarian, endometrial, colorectal, salivary gland, pancreatic, bladder and prostate cancer) in the last two decades, between 1 January 2000 and 21 February 2022 (Figure 3).

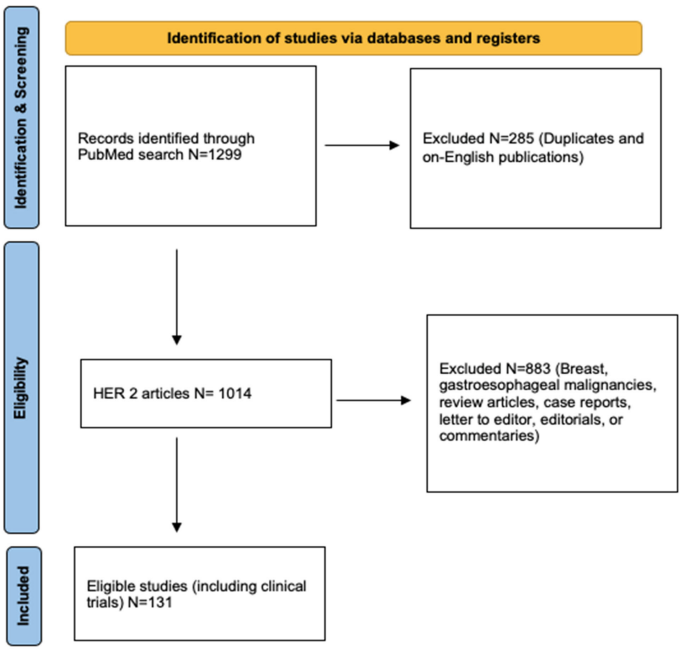

Figure 3. PRISMA flow diagram of the literature search process.

3. Results

3.1. Ovarian Cancer

Ovarian cancer is the second leading cause of gynecologic cancer in the USA. Approximately 95% of ovarian cancers are epithelial and the other 5% include sex cord stromal and germ cell tumors. HER2/neu overexpression and amplification has been reported in 5–50% and 2–25% of ovarian cancer cases, respectively, especially in the mucinous histologic subtype (Tables 2 and 3).

Table 2. Summarizing studies on HER2 overexpression or amplification in epithelial ovarian carcinoma.

Name of the Study	Number of Patients	Protein Overexpression (%)	Amplification (%)
Rubin SC et al., 1994 [19]	40	20	-
Seki A et al., 2000 [20]	48	-	25
Gao D et al., 2002 [21]	54	25.9	-
Hogdall et al., 2003 [22]	181	13.3	-
Bookman MA et al., 2003 [23]	837	11.4	-
Camilleri-Broet et al., 2004 [24]	95	15.8	-
Mano MS et al., 2004 [25]	64	-	12.5
Lee CH et al., 2005 [26]	102	4.9	2
Tuefferd M et al., 2007 [27]	320	12.8	6.6
Sasaki N et al., 2007 [28]	141	12.8	-
Sueblinvong et al., 2007 [29]	74	10.2	-
Stefensen KD et al., 2008 [30]	99	14.1	-
Vermeij et al., 2008 [31]	52	35	10
Farley J et al., 2009 [32]	133	-	6.8
Chekerov R et al., 2009 [33]	50	52	-
Slyvia MT et al., 2012 [34]	60	21	-
Jafri A et al., 2017 [35]	56	37.5	-
Pankaj S et al., 2019 [36]	98	22.45	-

Table 3. Summarizing clinical trials (only in the last 20 years) using anti-HER2 agents in epithelial ovarian cancer.

Clinical Trial	Study Description	Indication	PEP and Treatment Arms	Outcomes
1. Bookman MA et al., 2003 [23]	Single arm, Phase II, N = 95	HER2 2+ or 3+ overexpressing refractory epithelial ovarian or primary peritoneal cancer	ORR and Trastuzumab	- Limited clinical value due to the low frequency of HER2 overexpression - Low rate of objective response among patients with HER2 overexpression
2. Makhija S et al., 2010 [37]	Phase II, Randomized, N = 130	Advanced, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who had received a maximum of one prior treatment for recurrent cancer	Safety/PFS and Pertuzumab + Gemcitabine vs. Gemcitabine	- Clinical response observed - Low HER3 mRNA expression predict clinical benefit

N—number of patients; PEP—Primary end point; PFS—Progression free survival; ORR—Objective response rate.

Some studies have reported somatic HER2 mutations—insertional mutation in exon 20 and missense mutations (R970W and E971G) [38,39]. Berchuck et al., reported that patients with high HER2 overexpression were significantly less likely to have complete response to primary therapy or negative second-look laparotomy when serum CA 125 levels were normal pre-operatively [40]. Danish 2003 MALOVA ovarian cancer study concluded HER2 overexpression to be a negative prognostic marker [22]. As mentioned in (Table 3), two phase II clinical trials showed variable response to anti-HER2 agents; one study reported lack of clinical response after using trastuzumab whereas another study using pertuzumab showed clinical benefit, especially in the presence of low HER3 mRNA expression.

3.2. Endometrial Cancer

Endometrial cancer is the leading cause of gynecologic malignancy in the USA. The most common histologic subtype is endometroid carcinoma and it has the most favorable prognosis as compared to the other subtypes. HER2 gene amplification and protein expression is postulated in 3–47% and 14–80% of endometrial cancers, respectively, most commonly in serous histologic subtype (Table 4). Rolitsky et al., reported that whereas amplification was detected in both clear cell and serous subtypes, overexpression was only associated with clear cell type [41]. For all histologic subtypes, including endometrioid type, both expression and amplification corroborate a high stage and grade, implying poor overall survival [41,42]. Satin et al., reported that African American women harbor a significantly higher proportion of amplified HER2/neu gene in serous papillary uterine carcinoma and have overall poorer prognosis [43]. As mentioned in (Table 5), two phase II clinical trials have been conducted, one using trastuzumab alone and another in combination with carboplatin/paclitaxel with no overall benefit, however, they had manageable toxicity profile although full accrual of HER2 expressing tumors was not achieved in one of them.

Table 4. Summarizing studies on HER2 overexpression or amplification in uterine serous carcinoma.

Name of the Study	Number of Patients	Protein Overexpression (%)	Amplification (%)
Santin AD et al., 2002 [44]	10	80	-
Solomovitz BM et al., 2004 [45]	68	18	2.9
Santin AD et al., 2005 [46]	30	-	47
Santin AS et al., 2005 [43]	26	62	42
Diaz-Montes TP et al., 2006 [47]	25	48	-
Villella JA et al., 2006 [48]	19	26	-
Odicino FE et al., 2008 [49]	12	16.6	16.6
Ren Y et al., 2011 [50]	36	36.1	11.1
Togami S et al., 2012 [51]	71	14	-
Banet et al., 2021 [52]	68	9	-

Table 5. Summarizing clinical trials (only in the last 20 years) using anti-HER2 agents in uterine serous carcinoma.

Clinical Trial	Study Description	Indication	PEP and Treatment Arms	Outcomes
1. Fleming GF et al., 2009, [53]	Single arm, Phase II, N = 34	Stage III, IV or recurrent endometrial carcinoma with either 2+/3+ HER2 overexpression or gene amplification	ORR and Trastuzumab	- No demonstrated activity, although full planned accrual of women with HER2 amplified tumors was not achieved due to slow recruitment - Serous and clear cell endometrial carcinomas appear to be more likely to demonstrate HER2 amplification
2.Tymon-Rosario J et al., 2021 [54]	Multi-center, Phase II, N = 60	Recurrent/Advanced (Stage III–IV) HER2/neu overexpressing uterine serous carcinoma	PFS and Carboplatin/Paclitaxel +Trastuzumab vs. Carboplatin/Paclitaxel alone	- Safe and has a manageable toxicity profile

N—number of patients; PEP—Primary end point; PFS—Progression free survival; ORR—Objective response rate.

3.3. Lung Cancer

Lung cancer is the most prevalent cause of cancer-related death in both males and females worldwide. Majority of the lung cancers (85%) are non-small cell lung cancer (NSCLC). HER2 overexpression and amplification has been reported in 10–30% and 10–20% of the analyzed surgical specimens of non-small cell lung cancers, respectively, in retrospective studies. Somatic mutations have been frequently reported in 1–4% cases, most commonly in exon 20 and C-helix region of the kinase domain (Table 6). Two large studies by Sasaki et al., (in Japanese population) and Arcila et al., (in Caucasian population) have reported insertion mutations (YVMA) in exon 20 at codon 775 [55,56]. In different meta-analysis, Nakamura H et al. (2579 patients) and Liu L et al., (6135 patients) found that there is a significant negative prognostic effect of HER2 overexpression [57,58]. In lung adenocarcinomas, HER2 mutations have been reported, especially in Asian patient population, female sex and light/non-smokers [59,60]. As mentioned in (Table 7), initial phase II clinical trials conducted in the early 2000s with trastuzumab alone or in combination with either cisplatin-gemcitabine, paclitaxel and carboplatin or docetaxel did not improve the overall survival in HER2-positive NSCLC although it was suggested that HER2 3+/FISH-positive patient might benefit from these therapies [61–63]. IHC is not the most optimal test for detecting HER2 status and it was used in these trials. Later, studies using antibody drug conjugates, such as Ado-trastuzumab emastine or trastuzumab deruxtecan, in HER2 mutated NSCLC patients demonstrated a durable response irrespective of the absence or presence of HER2 protein expression or amplification [64–66]. Gefitinib or afatinib when used in EGFR TKI naïve HER2 mutated advanced NSLC showed no benefit but dacomitinib showed clinical activity [67–69]. More recently, trials using other TKIs in HER2-mutated NSCLC, such as Pyrotinib (PRIDE TRIAL), are ongoing [55].

Table 6. Summarizing studies reporting HER2 somatic mutations in lung cancer.

Name of the Study	Number of Patients	Mutations (%)
Shingematsu, H.I. et al., 2005 [59]	671	2.6
Buttitta, F.L. et al., 2006 [70]	403	2.2
Sasaki, Y. et al., 2006 [71]	122	0.8
Sun, Y. et al., 2010 [72]	52	3.8
Tomizawa, K. et al., 2011 [73]	504	2.6
Li, C. et al., 2012 [74]	224	3.6
Arcila, M. et al., 2012 [75]	1478	1.7
Mazieres, J.I. et al., 2013 [76]	3800	1.7

Table 7. Summarizing clinical trials (only in the last 20 years) using anti-HER2 agents in lung cancer.

Clinical Trial, Study Description	Study Description	Indication	PEP and Treatment Arms	Outcomes
1. Cappuzzo, F. et al., 2003 [77]	Phase II, N = 63	Advanced NSCLC	TP and Gefitinib	- No difference
2. Langer, C.J. et al., 2004 [78]	Phase II, N = 56	HER2 overexpressing advanced NSCLC	OS and Trastuzumab + Paclitaxel + Carboplatin	- Tolerable toxicity - Overall survival is similar to historical data using carboplatin and paclitaxel alone. - However, patients with 3+ HER2/neu expression did well, in contrast to historical data suggesting potential benefit for trastuzumab in this rare subset of NSCLC.
3. Gatzemeier, U. et al., 2004 [61]	Phase II Randomized, N= 103	Untreated stage IIIB/IV HER2-positive NSCLC	ORR and Trastuzumab + Cisplatin + gemcitabine vs. Cisplatin + gemcitabine alone	- Combination is well tolerated but has no clinical benefit - Although HER2 3+/FISH-positive patients may benefit from trastuzumab, the subgroup is too small to provide definitive information.
4. Zinner, R.G. et al., 2004 [62]	Phase II, N = 21	HER2-overexpressing (IHC >1+ or HER2 neu antigen in serum) stages IIIB or IV NSCLC	ORR and Trastuzumab + cisplatin +Gemcitabine	8 (38%) patients had a partial response - Combination was well tolerated but conclusions regarding superiority over chemotherapy alone cannot be made
5. Lara, P.N., Jr. et al., 2004 [63]	Phase II, N = 13	Advanced NSCLC in which primary platinum-based therapy had failed	Screening for HER2, ORR and Single agent Trastuzumab or docetaxel followed by combination Trastuzumab + Docetaxel	- HER2-positive disease in 19% - Limited clinical activity
6. Clamon, G. et al., 2005 [79]	Phase II, N = 29	Stage IIIB or Stage IV NSCLC with 2+/3+ HER2 expression with at least 1 prior chemotherapy regimen.	Screening for HER2, ORR Single agent Trastuzumab	- HER2-positive disease in 11% - Limited clinical activity
7. Krug, L.M. et al., 2005 [80]	Phase II, Randomized, N = 169	Previously untreated advanced NSCLC	ORR and Trastuzumab + Docetaxel or Trastuzumab + Paclitaxel	- No difference in response or toxicities in both arms, though survival in both arms was better than expected. - HER2 expression status did not appear to affect outcomes

Table 7. *Cont.*

Clinical Trial, Study Description	Study Description	Indication	PEP and Treatment Arms	Outcomes
8. Kris, M.G. et al., 2015 [67]	Phase II, N = 30	Stage IIIB/IV lung cancers with HER2 mutations in exon 20 or amplification.	PRS, OS, toxicity and Dacomitinib	- Clinical response in patient with exon 20 mutations but not HER2 amplifications
9. Li, B.T. et al., 2018 [64]	Phase II, N = 18	HER2 mutant lung adenocarcinomas	ORR and Ado-Trastuzumab emastine	- Responses were seen in patients with *HER2* exon 20 insertions and point mutations in the kinase, transmembrane, and extracellular domains. - HER2 protein expression or amplification does not predict response
10. De Langen, A.J. et al., 2018 [81]	Phase II, N = 24	NSCLC with a sensitizing EGFR mutation who show HER2 expression after progression on EGFR TKI treatment	ORR and Trastuzumab + Paclitaxel	- Combination induces tumor responses in 46% patients - There is relation between tumor response and HER2 expression level/copy number
11. Peters, S. et al., 2019 [65]	Phase II, N = 49	HER2-overexpressing advanced NSCLC who have received previous platinum-based chemotherapy and targeted therapy in the case of *EGFR* mutation or *ALK* gene rearrangement	ORR and Ado-Trastuzumab emastine	- Clinical response in 3+ HER2 expressing cancers
12. ETOP TRIAL, Dziadziuszko et al., 2019 [68]	Phase II, N = 13	Pretreated advanced NSCLC harboring HER2 exon 20 mutations	ORR and Afatinib	- No clinical response
13. Fan, Y. et al., 2020 [69]	Phase II, N = 18	HER2 mutation positive Stage IIIB/IV non-small cell lung cancer had failed one or two prior lines of chemotherapy and were EGFR/HER2-inhibitor naïve.	ORR and Afatinib followed by Afatinib + Paclitaxel	- No clinical response
14. DESTINYLUNG01 TRIAL (NCT03505710) 2022 [66]	Phase II, N = 91	HER2 mutant metastatic NSCLC refractory to standard treatment	ORR and Trastuzumab Deruxtecan	- Clinical response in patients with HER2 mutations with or without HER2 expression or amplification

N—number of patients; PEP—Primary end point; OS—Overall survival; ORR—Objective response rate.

3.4. Colorectal Cancer (CRC)

HER2/neu overexpression and amplification has been noted in 2.5–80% and 1.5–60% of the CRC's, respectively (Table 8). While a significant amount of research has been undertaken to elucidate the role of membranous HER2/neu in CRC, the clinical significance of cytoplasmic expression remains yet to be deciphered. Somatic HER2 mutations have been reported on the kinase domain in 3 out of 104 patients in a study by Lee et al. [82]. HER2/neu positivity is linked with high UICC (Union for International Cancer Control) stage and nodal positive metastases, as well as T-category and nodal status in sigmoidal and rectal subgroups [83,84]. Conradi et al. found that in advanced rectal carcinomas, HER2-positive tumors have better 5-year cancer-specific survival than HER2/neu-negative tumors post neoadjuvant radio chemotherapy [85]. As mentioned in (Table 9), initial trials using trastuzumab with irinotecan or cetuximab and pertuzumab showed some activity but studies were limited due to low overexpression rate or drug toxicity [86,87]. More recently, dual anti-HER2 therapies, such as trastuzumab with pertuzumab and trastuzumab with lapatinib, have been tried with significant clinical responses [87–89]. Furthermore, trastuzumab deruxtecan alone has shown a promising activity against metastatic HER2 expressing CRC refractory to standard treatment, thereby offering newer insights into treatment of this subset of tumor [90].

Table 8. Summarizing studies on HER2 overexpression or amplification in colorectal carcinoma.

Name of the Study	Number of Patients	Protein Overexpression (%)	Amplification (%)
Rossi, H. et al., 2002 [91]	156	24	-
Knosel, T. et al., 2002 [92]	74	51	-
Nathanson, D.R. et al., 2003 [93]	139–169	3.6 (5/139)	2.4 (4/169)
Park, D.I. et al., 2004 [56]	88	12.5	-
Schuell, B. et al., 2006 [94]	77	3.8	-
Kountourakis, P. et al., 2006 [95]	106	5.6	-
Park, D.I. et al., 2007 [96]	137	47.4	1.4
Ismail, H.M. et al., 2007 [97]	104	9.6	-
Kavanagh, D.O., 2009 [98]	132	11	3
Marx, A.H. et al., 2010 [99]	1439	2.5	2.7
Li, Q. et al., 2011 [100]	317	15.5	-
Herreros Villanaueva, M. et al., 2011 [101]	186	-	26.3
Pappas, A. et al., 2013 [102]	51	3.9	-
Shabbir, A. et al., 2016 [83]	95	78.9	-
Kwak, Y. et al., 2017 [103]	334	-	6
Ross, J.S. et al., 2018 [104]	8887	-	58.5
Hasan, R. et al., 2018 [105]	83	40.96	-
Richman et al., 2019 [106]	3256	1.6	1.4

Table 9. Summarizing clinical trials (only in the last 20 years) using anti-HER2 agents in colorectal carcinoma.

Clinical Trial	Study Description	Indication	PEP and Treatment Arms	Outcomes
1. Ramanathan, R.K. et al., 2014 [107]	Phase II, N = 9	HER2 overexpressing advanced CRC	HER2 expression rate, MTD and Trastuzumab + Irinotecan	- The low overexpression rate of HER2/neu (8.0%) in advanced CRC limits the potential for further investigation - Evidence suggestive of activity (partial responses were seen in 5 of 7 evaluated patients)
2. Rubinson, D.A. et al., 2014 [86]	Open label, Multi-center Phase I/II, N = 13	Metastatic colorectal cancer with cetuximab resistance	Dose-limiting toxicity and Pertuzumab + cetuximab	- Combination was associated with potential antitumor activity - However, the combination was not tolerable due to overlapping toxicities.
3. HERCALESA TRIAL, 2016 [87]	Multi-center, Open label, Phase II, N = 27	*KRAS* exon 2 (codons 12 and 13) wild-type and HER2-positive metastatic colorectal cancer refractory to standard of care (including cetuximab or panitumumab)	ORR and Trastuzumab + lapatinib	- Overall 8 of 27 patients achieved an objective response (30%) with good tolerability
4. MY PATHWAY TRIAL (NCT02091141) 2019 [88]	Phase IIA, Multiple Basket, N = 57	Refractory, histologically confirmed HER2-amplified metastatic colorectal cancer	ORR and Trastuzumab +Pertuzumab	- Overall 18 of 57 patients achieved an objective response (32%) with good tolerability
5. HERACLESB TRIAL (NCT03225937) 2020 [89]	Single arm, Phase II, N = 31	Histologically confirmed *RAS/BRAF* wild-type and HER2+ metastatic CRC refractory to standard treatments	ORR and Trastuzumab emtansine +Pertuzumab	- No clinical response - However, high disease control and PFS similar to other anti-HER2 regimens, and lower toxicity, this should be a therapeutic option
6. DESTINYCRC01 TRIAL (NCT03384940) 2021 [90]	Open label, Multi-center, Phase II, N = 78	HER-positive metastatic colorectal cancer that had progressed on two or more previous regimens (HER2-targeted therapies other than trastuzumab deruxtecan permitted)	ORR and Trastuzumab deruxtecan vs. standard treatment	- Promising and durable activity

N—number of patients; PEP—Primary end point; PFS—Progression free survival; ORR—Objective response rate.

3.5. Salivary Gland Cancer

Salivary gland cancer is a subset of head and neck cancers constituting various histologic subtypes, such as mucoepidermoid carcinoma, salivary ductal carcinoma (SDC), adenoid cystic carcinoma mammary analogue secretory carcinoma and carcinoma ex pleomorphica (CEPA). Adenocarcinoma, not otherwise specified, is the most common malignant subtype followed by salivary ductal carcinoma. HER2 gene amplification and protein expression has been reported in 20–100% and 2–100% of the samples, respectively, most commonly being reported in salivary ductal carcinoma (Table 10). HER2 overexpression has been reported as the marker of pleomorphic adenoma to CEPA malignant transformation [108]. In both CEPA and salivary ductal carcinoma, HER2 gene expression and amplification are suggested to have poor prognosis. As mentioned in (Table 11), initial phase II clinical trials on HER2 positive salivary gland cancer using trastuzumab or lapatinib have shown limited clinical response [109,110]. These trials did not have patients with salivary ductal carcinoma and there have been many retrospective studies and case reports demonstrating the effect of trastuzumab on salivary ductal carcinoma [111,112]. A most recent single center trial in Japan on HER2 expression in SDC patients showed a 70.2% response to the trastuzumab + docetaxel combination therapy [113].

Table 10. Summarizing studies on HER2 overexpression or amplification in salivary gland cancers with histologic subtype.

Name of the Study	Histology	Number of Patients	Protein Overexpression (%)	Amplification (%)
Press, M.F. et al., 1994 [114]	Mucoepidermoid carcinoma	58	38	21
Skalova et al., 2001 [115]	SDC	15	93.3	-
Skalova, A. et al., 2003 [116]	SDC	11	100	36.4
Erges, A. et al., 2003 [117]	SDC	5	80	-
Jaehne et al., 2005 [118]	SDC	50	20.6	-
Cornolti, G. et al., 2007 [119]	SDC	13	10/13	8/10
Johnson, C.J. et al., 2008 [120]	SDC	12	33.3	33.3
Santana, T. et al., 2019 [121]	SDC	25	42	
William, M.D. et al., 2010 [122]	SDC	66	10/66	6/10
Clauditz, T.S. et al., 2011 [123]	SDC	14	3/14	3/3
Nardi, V. et al., 2013 [124]	SDC	27	-	29.6
Xia, L. et al., 2017 [125]	Invasive carcinoma ex pleomorphic adenoma	140	25	

3.6. Pancreatic Cancer

Despite recent advances, treatment for pancreatic cancer remains an enigma, portraying a dismal prognosis with surgical resection being the only potential curative option. The prevalence of HER2 overexpression and amplification is approximately 10–70% and 2–20%, respectively (Table 12). HER2/neu protein expression has been significantly associated with grade and not stage [126]. As mentioned in (Table 13), studies have been conflicting, as trial comparing combined trastuzumab with capecitabine or gemcitabine did not show any improvement in overall survival but recently published GATE 1 trial using it with gemcitabine and erlotinib as first line agent showed clinical activity [127–129].

Table 11. Summarizing clinical trials (only in the last 20 years) using anti-HER2 agents in salivary gland cancers.

Clinical Trial	Study Description	Indication	PEP	Treatment Arms	Outcomes
1. Haddad, R. et al., 2003, [109]	Single arm, Phase II, N = 14	HER2 overexpressing (2+/3+) advanced incurable salivary gland tumors	TP	Trastuzumab	- The study was closed early as majority of tumors screened did not overexpress HER2/neu. - One patient with metastatic mucoepidermoid carcinoma has received 40 cycles of herceptin to date with a documented partial response. - Herceptin given as a single agent has low activity in salivary gland tumors overexpressing HER2/neu
2. Agulnik, M. et al., 2007 [110]	Single arm, Phase II, N = 40	Progressive, recurrent, or metastatic adenoid cystic carcinoma (ACC) immunohistochemically expressing at least 1+ EGFR and/or 2+ erbB2	ORR	Lapatinib	- No clinical response - Well tolerated, with prolonged tumor stabilization of > or = 6 months in 36% (95% CI, 21% to 54%) of assessable patients.
3. Takahashi, H. et al., 2019 [113]	Single center, Single arm, Open label, Phase II, N = 57	Locally advanced and/or recurrent or metastatic HER-positive SDC	ORR	Trastuzumab + Docetaxel	- Overall response rate was 70.2% with manageable toxicity

N—number of patients; PEP—Primary end point; ORR—Objective response rate; TP—Time to progression.

Table 12. Summarizing studies on HER2/neu overexpression or amplification in pancreatic carcinoma.

Name of the Study	Number of Patients	Protein Overexpression (%)	Amplification (%)
Lei, S. et al. 1995 [130]	27	44.4	-
Day, J.D. et al. 1996 [131]	19	69	-
Dugan, M.C. et al. 1997 [132]	79	58	-
Safran, H. et al., 2001 [133]	154	21	7.1
Novotny, J. et al., 2001 [134]	57	19.2	-
Potti et al., 2003 [135]	39	None	-
Hermanova, M. et al., 2004 [136]	49	18.75	4
Tamiolakis, D. et al., 2004 [137]	100	21	-
Sroecklein, N.H. et al., 2004 [138]	50	10	24
Tsiambas E et al., 2006 [126]	50	59, 22, 12, 8 (0, 1+, 2+ and 3+ expression)	16
Sharif, S. et al., 2008 [139]	63	-	25
Komoro, M. et al., 2009 [140]	129	61.2	-
Harder, J. et al., 2012 [141]	207	26	3.9
Chou, A. et al., 2013 [127]	469	7.2	2.1

Table 13. Summarizing clinical trials (only in the last 20 years) using anti-HER2 agents in pancreatic carcinoma.

Clinical Trial	Study Description	Indication	PEP and Treatment Arms	Outcomes
1. Safran, H. et al., 2004 [128]	Phase II, N = 34	HER2 overexpressing metastatic pancreatic cancer	OS and Trastuzumab + Gemcitabine vs. Gemcitabine alone	- Response rate was similar in both arms - 7-month median survival suggests that there may be a modest benefit for some patients. - Infrequent HER2/neu overexpression limits the role of targeting the HER2/neu gene and prevents definitive conclusions
2.Harder, J. et al., 2012 [141]	Multi-center, Phase II, N = 17	HER2 overexpressing metastatic Pancreatic adenocarcinoma	PFS and Trastuzumab + capecitabine	- +3 HER2 expression or gene amplification in 11% of patients. - Although the therapy was well tolerated, PFS and OS did not perform favorably compared with standard chemotherapy.

Table 13. *Cont.*

Clinical Trial	Study Description	Indication	PEP and Treatment Arms	Outcomes
3. THERAPY TRIAL (NCT00923299) 2015 [129]	Multi-center, Phase I/II, Single arm, Non-randomized	Advanced pancreatic cancer patients after first-line gemcitabine-based chemotherapy failure	ORR, OS, PFS and Trastuzumab + Cetuximab	- Cutaneous toxicity led to arrested treatment
4. GATE I TRIAL (NCT01204372) 2021 [142]	Multi-center, Phase II, N = 63	Metastatic pancreatic adenocarcinoma	DCR and Gemcitabine, Trastuzumab, Erlotinib vs. standard therapy	- Combination is effective in terms of disease control, PFS and OS, and acceptable for safety. - In multivariate analyses, progression-free and overall survival were correlated to EGFR and HER2, while HER2 expression was linked to tumor response.

N—number of patients; PEP—Primary end point; OS—Overall survival; PFS—Progression free survival; ORR—Objective response rate; DCR—Disease control rate.

3.7. Bladder Cancer

Bladder cancer is the most common malignancy of urinary system with urothelial (transitional cell) carcinoma being the most prevalent histologic subtype in the USA. The exact numbers are uncertain, but HER2 overexpression and gene amplifications have been reported in 10–70% and 5–10%, respectively. A metanalysis in 2021 showed that HER2 expression was associated with CIS, large tumor size, high tumor grade and stage, multifocal tumor, lymph node metastasis, progression, recurrence papillary tumor and poor prognosis [143]. As mentioned in (Table 14), trials using trastuzumab in combination with gemcitabine, carboplatin and paclitaxel have observed higher cardiotoxicity rates, although most were grade 2 or lower with 70% clinical response rates but promising response has been obtained with use of HER2 targeting the antibody-drug conjugate RC48-ADC.

Table 14. Summarizing studies clinical trials (only in the last 20 years) using anti-HER2 agents in bladder cancer.

Clinical Trial	Study Description	Indication	PEP	Treatment Arms	Outcomes
1. Hussain, M.H.A. et al., 2007 [144]	Multi-center, Phase II, Non-randomized prospective trial, N = 57	HER2 overexpressing advanced urothelial carcinoma with no prior chemotherapy for metastasis	Cardiac toxicity	Trastuzumab+ Paclitaxel +Carboplatin +Gemcitabine (TPCG)	- 22.7% experienced grade 1 to 3 cardiac toxicity - 31 (70%) of 44 patients responded (5 complete and 26 partial), and 25 (57%) of 44 were confirmed responses. - TPCG is feasible
2. Powles, T. et al., 2016 [145]	Phase III, Double blinded, Randomized, N = 232	HER1/HER2 expressing metastatic urothelial bladder cancer after first-line chemotherapy for maintenance	PFS	Lapatinib	- No additional benefit of adding lapatinib to standard therapy even in subgroup analysis
3. Sheng, X. et al., 2021 [146]	Multi-center, Phase II, Single arm, N = 43	HER2 expressing (2+/3+) locally advanced or metastatic urothelial carcinoma who previously failed at least one line of systemic chemotherapy.	ORR	RC48-ADC	- 51.2% objective response rate - Promising efficacy with manageable safety profile

N—number of patients; PEP—Primary end point; ORR—Objective response rate; PFS—Progression free survival.

3.8. Prostate Cancer

Prostate cancer is the second leading cause of cancer-related mortality in men in the USA after lung cancer. Initially being hormone-dependent, androgen receptor overexpression and mutations are the most implicated pathophysiological reasons that lead to the eventual progression to androgen-independent prostate cancer. HER2/neu overexpression has been demonstrated in androgen-independent prostate cancer and is associated with advanced disease, high recurrence and poor prognosis [147–149]. As mentioned in (Table 15), multiple phase II trials using trastuzumab or pertuzumab as single agent or in combination with docetaxel or single agent TKIs, such as lapatinib or gefitinib, in hormone refractory prostate cancer have shown no clinical response.

Table 15. Summarizing studies clinical trials (only in the last 20 years) using anti-HER2 agents in prostate cancer.

Clinical Trial	Study Description	Indication	PEP	Treatment Arms	Outcomes
1. Ziada, A. et al., 2004 [150]	Single arm, Phase II, N = 18	HER2 overexpressing advanced hormone refractory prostate cancer	ORR	Trastuzumab	- Little efficacy - Two patients demonstrated stable disease based on a decrease in PSA level to less than 50% of baseline - No patient demonstrated a regression of radiographic bony or soft tissue metastatic disease.
2. Lara, P.N., Jr. et al., 2004 [151]	Open label, Phase II, N = 4	HER2 overexpressing advanced hormone refractory prostate cancer	OS	Trastuzumab or Docetaxel alone followed by Trastuzumab + Docetaxel	- HER2 overexpression was < 20%, trial was closed due to no feasibility.
3. Curigliano, G. et al., 2007 [152]	Phase II, N = 23	Hormone-refractory prostate cancer.	PSA measurement	Gefitinib + antiandrogen + Luteinizing releasing hormone analogue	- No clinical response
4. De Bono, J.S. et al., 2007 [153]	Open label, Phase II, N = 23	Castrate patient with hormone refractory prostate cancer	Prostate-specific antigen (PSA) 50% decline rate within 24 weeks	Pertuzumab at 420 mg vs. 1050 mg	- No clinical response
5. Agus, D.B. et al., 2007 [154]	Phase II, N = 42	Castration-resistant prostate cancer (CRPC) patients who had experienced progression after at least one taxane-based regimen.	Safety, ORR	Single agent Pertuzumab	- No objective responses - Retrospective analysis suggested prolonged median survival time with pertuzumab compared with historical controls. - Thus, inhibition of HER dimerization may have clinical utility in CRPC patients
6. Vuky, J. et al., 2009 [155]	Phase II, N = 31	Neoadjuvant therapy in high-risk localized prostate cancer before radical prostatectomy	PCR	Gefitinib + Docetaxel	- No clinical response
7. Whang, Y.E. et al., 2013 [156]	Multi-center, Phase II, Open label, N = 29	Rising PSA levels on androgen deprivation therapy and chemotherapy naïve prostate cancer	>50% confirmed PSA decline from baseline	Lapatinib	- Activity in small sunset of unselected patients

N—number of patients; PEP—Primary end point; OS—Overall survival; ORR—Objective response rate; PCR—Pathologic complete response.

3.9. Biliary Tract Cancer (BTC)

Gall bladder cancer is a rare and an aggressive cancer with heterogenous genetic makeup, with so far published data showing 0–25% HER2/neu protein expression with

most studies being from India, Japan or South America [157–159]. HER2 gene amplification have been reported in 5–8% cases [160]. Sampling 186 patients with gall bladder cancer, of which 74 had high grade biliary intra-epithelial neoplasia, Albrecht et al. found that 5.9% of patients had a 2+ IHC score and 5.4% of the patients had an IHC score of 3+ with clear-cut gene amplification. [161]. A single-center study on HER2 expressing BTC showed that none of the cholangiocarcinoma patients (five) but eight out of nine patients with gall bladder cancer (three disease stability, four partial response and one complete response) responded to HER2/neu-directed therapy [162]. There have been demonstrated antiproliferative activity of lapatinib in in vitro models of BTCs [163]

3.10. Other Malignancies

3.10.1. Osteosarcoma (OS)

OS is the most prevalent and aggressive primary pediatric bone cancer, with HER2/neu overexpression been postulated to be a poor prognostic marker [164,165]. Akastsuka et al. found that HER2 overexpression decreases in osteosarcoma as they metastasized to the lungs [166]. However, a retrospective study conducted in Michigan in 2002 and in Netherlands in 2004 [167,168] demonstrated the absence of HER2 mRNA or protein overexpression in OS. Two clinical trials to study the use of trastuzumab in recurrent osteosarcoma (Clinicaltrials.gov Identifier: NCT00005033) and metastatic osteosarcoma (Clinicaltrials.gov Identifier: NCT00023998) have been undertaken but the results have not yet been published.

3.10.2. Thyroid Cancer

Thyroid cancers can originate from either epithelial-derived follicular cells or from parafollicular C-cells, called medullary thyroid cancer, or appear as primary thyroid lymphoma. Epithelial-derived cancers can be subgrouped into differentiated thyroid cancers (follicular 12% and papillary cancer 85%) or undifferentiated cancers (anaplastic < 3%). HER2/neu overexpression was associated to a predictive factor in differentiated thyroids carcinomas (both papillary and follicular) with a tendency towards distant metastasis [169–171]. Another study showed decreased HER2 expression in anaplastic and poorly differentiated thyroid cancer correlating with aggressive behavior [172]. High HER2/neu oncoprotein levels have been associated with extrathyroidal growth in medullary thyroid cancer and C-cell hyperplasia [173].

3.10.3. Glioblastoma Multiforme (GBM)

Glioblastoma multiforme is the most common primary malignant tumor of the central nervous system (CNS), and is regarded as one of the most chemo-resistant malignancies. Although HER2 is not expressed in adult CNS but its expression increases with increase in glioma cell anaplasia. HER2/neu overexpression has been reported in 20–90% patients with GBM and is a poor prognostic marker [174,175]. Mineo et al. demonstrated that use of trastuzumab in GBM cell lines (A172 and U251MG) expressing HER2/neu leads to apoptosis and cellular-dependent cytotoxicity of the cell lines [176].

3.10.4. Acute Lymphoblastic Leukemia (ALL)

In B-ALL or T-ALL, HER2/neu is known to be expressed in 30% of patients, with no expression in blasts [177,178]. Some studies have suggested HER2/neu overexpression to be related with chemoresistance and worse clinical outcomes in ALL patients [178,179]. Haen et al. reported no prognostic significance of HER2/neu in ALL patients on long-term follow-up of 15 years in accordance with the overall survival, disease-free survival or response to chemotherapy [180]. Using trastuzumab alone or in combination with other monoclonal antibodies, such as rituximab, for relapsed or refractory HER2/neu-positive ALL is a promising strategy [180,181].

3.10.5. Soft Tissue Sarcoma

Synovial sarcoma (SS) is a high-grade tumor which has t(X;18) (p11:q11) translocation and contributes to 10% of the sarcomas. Nuciforo et al. studied 13 patients with SS and found that increased HER2/neu expression correlated with statistically significant favorable clinical outcome [182] Another study conducted in Germany on patients with soft tissue sarcoma found no significant effect of HER2/neu expression on prognosis [183].

3.10.6. Wilms Tumor

Wilms tumor is an embryonal tumor arising from the remnants of renal tissue and is the most common solid malignancy in children. A study conducted by Babashahi et al. in 2013 found that epithelial differentiation (68.5% in 38 patients), especially in the early stages of tumor (81.5%), had higher HER2 expression [184]. Another study from Egypt on 28 patients suggested HER2/neu expression as a favorable indicator of overall survival and longer recurrence-free survival [185].

3.10.7. Melanoma

Melanoma is a primary skin cancer and the fifth leading cause of cancer-related death in men and women in the USA. In a large cohort of 600 patients, HER2/neu overexpression was found in 5.2% cases, many of them being primary cutaneous lesions with Breslow depth < 2 mm rather than metastatic or recurrence cancer [186].

4. Discussion

HER2/neu plays a significant role in the pathogenesis of various cancers and has garnered attention in the field of oncology due to its therapeutic potential. The overexpression, mutations, and gene amplification of HER2/neu in different malignancies have been the subject of extensive research over the years [17]. Given that HER2/neu is a targetable entity, it is evaluated in clinical settings, particularly for advanced malignancies. In clinical practice, HER2/neu testing may be performed for extra-mammary and extra-gastric tumors based on the clinician's judgment and the availability of anti-HER2 agents for that specific malignancy of interest and based on the availability of clinical trials enrolling patients with HER2/neu biomarker positivity. In several malignancies, HER2/neu testing is performed in the metastatic setting for further lines of treatment. In non-small cell lung cancer, anti-HER2 agents are approved for use in previously treated patients with HER2/neu mutations [66]. Similarly, anti-HER2 agents are approved for use in HER2-positive advanced/metastatic CRC and endometrial carcinoma [54,88,90]. However, most of the anti-HER2 agents are currently utilized in clinical trial settings for specific extra-mammary and extra-gastric malignancies as they are not FDA-approved for use in all HER2/neu-positive cancers.

The prognostic and therapeutic significance of HER2 differs between breast, gastric/gastroesophageal, and other malignancies. Several anti-HER2 agents have been approved for use in breast, gastric, and gastroesophageal malignancies, and have been utilized for therapeutic purposes for several years [187–189]. Anti-HER2 agents are also approved for use in certain other malignancies, such as colorectal cancer, lung cancer, and uterine cancer [54,88,90,190]. However, the utilization of anti-HER2 agents is limited in extra-mammary and extra-gastric/gastroesophageal tumors, as studies have shown conflicting results. Additionally, several trials are still ongoing, as mentioned in our article.

Considering the prevalence of HER2/neu protein overexpression, gene amplification, and somatic mutation in several malignancies beyond breast, gastric, and gastroesophageal tumors, it is advisable to test for the HER2/neu biomarker, especially in metastatic cases where patients often require multiple lines of treatment. Testing for HER2/neu is beneficial in malignancies, such as lung cancer, endometrial cancer, and colorectal cancer, as anti-HER2 agents have been approved for use in the metastatic setting for these malignancies. HER2/neu testing can also be considered in other malignancies, particularly for patients who are candidates for clinical trials. However, there are challenges associated

with HER2/neu testing in extra-mammary and extra-gastric/gastroesophageal settings. These challenges include the lack of testing algorithms, the absence of standardized laboratory testing, and the difficulties in obtaining insurance approval. It should be noted that HER2/neu testing is not approved in some of these malignancies, as mentioned in our article.

There are several knowledge gaps in our understanding regarding the prevalence of HER2/neu protein overexpression, gene amplification, and somatic mutation in extra-mammary and extra-gastric malignancies. The expansion of the HER2 spectrum to include HER2-low disease status (IHC 1+, 2+ and FISH negative) has sparked novel research in the field of HER2/neu disease. By gaining a better understanding of HER2-low disease status and its therapeutic potential, HER2-low can be utilized as a therapeutic target in extra-mammary and extra-gastric malignancies.

5. Conclusions

HER2/neu is one of the most well-characterized molecular markers in breast and gastric/gastroesophageal junction cancers, with several HER2-targeted agents currently being used alone or in combination with other agents for their treatment. As underscored in this review, HER2 protein overexpression, gene amplification, and somatic mutations have been reported and studied in many other different types of malignancies. With wide variation in HER2 protein expression and response rates to HER2 targeted therapy, there is a pressing need to establish a defined HER2 testing algorithm and reporting system for other solid and hematologic malignancies, as they currently exist only for breast and gastric cancers. This will allow to refine the HER2-targeted therapies for these malignancies.

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