·综　述·

HER2低表达乳腺癌的靶向治疗研究进展

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［**摘要**］乳腺癌是全球女性的第一大恶性肿瘤，发病率在逐年增加。人表皮生长因子受体2（human epidermal growth factor receptor 2，HER2）在乳腺癌的生物学行为及发病机制中起着重要作用。乳腺癌HER2低表达是指HER2免疫组织化学染色1+或2+且原位杂交（*in situ* hybridization，ISH）阴性，占全部类型的45%～55%。尽管在目前的临床实践中，HER2低表达大多数仍被报告为HER2阴性或三阴性乳腺癌，但HER2低表达与HER2未检出乳腺癌不仅在HER2蛋白表达水平上不同，在雌激素受体（estrogen receptor，ER）状态、原发肿瘤体积、淋巴结受累情况、新辅助治疗后的病理学完全缓解率（pathologic complete response，pCR）以及无病生存期（disease-free survival，DFS）等方面也存在差异。在针对早期HER2低表达乳腺癌靶向治疗的临床试验中，NSABP B-31及N9831试验表现出乳腺癌患者受益于曲妥珠单抗辅助治疗的可能性，然而，在Ⅲ期前瞻性随机对照研究NSABP B-47中，曲妥珠单抗并未改变HER2低表达乳腺癌患者的无浸润性肿瘤复发生存期（invasive disease-free survival，iDFS）、5年无远处复发间期及总生存期（overall survival，OS）。近年来针对晚期HER2低表达乳腺癌靶向治疗开展的临床试验层出不穷，主要围绕曲妥珠单抗、拉帕替尼、恩美曲妥珠单抗（trastuzumab emtansine，T-DM1）、DS-8201（又名trastuzumab deruxtecan, T-DXd, Enhertu）及SYD985等新型抗体-药物偶联物（antibody-drug conjugate，ADC）类药物。Ⅲ期临床试验CALGB9840表明曲妥珠单抗对HER2非过度表达的乳腺癌缺乏治疗效果，改变鲁妥珠单抗剂量后仍无法克服治疗窗口窄的问题。两项随机Ⅲ期试验（EGF30001和EGF100151）均发现接受拉帕替尼并未改善HER2低表达乳腺癌患者的无进展生存期（progression-free survival，PFS）。单臂Ⅱ期研究4258g及4374g初步发现HER2低表达乳腺癌患者对T-DM1的敏感性，但由于患者数量较少，结论尚不明确。Ⅲ期临床研究DESTINY-Breast04证实了DS-8201（5.4 mg/kg）与医师选择方案（2∶1随机分配）在HER2低表达转移性乳腺癌中的安全性和有效性。针对SYD985的Ⅰ期临床试验显示了其治疗HER2低表达乳腺癌的效果和安全性（1.2 mg/kg）。除此之外，以新型ADC药物（RC48-ADC、ARX788、A166等）、双特异性抗体（KN026、ZW25、ertumaxomab等）及乳腺癌疫苗（nelipepimut-S、GP2、AE37等）为代表的一系列新型抗HER2治疗手段的临床研究也正在进行中。本文将对近年HER2低表达乳腺癌靶向治疗药物的主要临床试验进行综述。

［**关键词**］乳腺癌；HER2低表达；靶向治疗

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Advances in targeted therapy for HER2-low breast cancer

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［**Abstract**］Breast cancer is the most common cancer in women worldwide with rising prevalence. The human epidermal growth factor receptor 2 (HER2) is crucial to the biological behavior and pathogenic mechanism of breast cancer. Approximately 45%-55% of all subtypes of breast cancer have low expression of HER2, which are classified as HER2 immunohistochemistry staining 1+ or 2+ and *in situ* hybridization (ISH) negative. Although in most cases, HER2 low expression (HER2-low) breast cancer is still classified as HER2 negative or triple negative in clinical practice, HER2-low differs from HER2 not detected (HER2-0) breast cancer not only in HER2 expression levels, there are also differences in terms of estrogen receptor (ER) status, primary tumor volume, lymph node involvement, and pathologic complete response (pCR) following neoadjuvant therapy and disease-free survival (DFS).

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In clinical trials targeting early-stage HER2-low breast cancer, the NSABP B-31 and N9831 trials demonstrated the possibilities for breast cancer patients to benefit from adjuvant trastuzumab therapy; however, in phase Ⅲ prospective randomized controlled study NSABP B-47, trastuzumab did not alter invasive disease-free survival (iDFS), 5-year interval without distant recurrence, or overall survival (OS) in patients with HER2-low breast cancer. Recent years have seen the emergence of clinical trials for targeted treatments for advanced HER2-low breast cancer, focusing mostly on trastuzumab, lapatinib, and antibody-drug conjugate (ADC), such as trastuzumab emtansine (T-DM1), DS-8201 (also known as trastuzumab deruxtecan, T-DXd, Enhertu), and SYD985. Phase Ⅲ trial CALGB9840 demonstrated a lack of therapeutic effect of trastuzumab and a narrow therapeutic window that could not be overcome by changing the dose of lumretuzumab in HER2 non-over-expressed breast cancer, respectively. Two randomized phase Ⅲ trials (EGF30001 and EGF100151) both found that receiving lapatinib did not improve progression-free survival (PFS) in patients with HER2-low breast cancer. T-DM1 sensitivity was initially observed in patients with HER2-low breast cancer in the single-arm phase Ⅱ studies 4258g and 4374g, but results were still uncertain because of the small number of patients. The phase Ⅲ clinical study DESTINY-Breast04 proved the safety and efficacy of DS-8201 (5.4 mg/kg) in HER2-low metastatic breast cancer. The phase Ⅰ clinical trial proved the efficacy and safety of 1.2 mg/kg SYD985 intravenously in HER2-low breast cancer. Additionally, there are currently ongoing clinical trials for several novel anti-HER2 therapeutics, including novel ADC drugs (RC48-ADC, ARX788, A166, etc.), bispecific antibodies (KN026, ZW25, ertumaxomab, etc.), and breast cancer vaccines (nelipepimut-S, GP2, AE37, etc.). In this paper, we will review the major clinical trials of targeted therapies for HER2-low breast cancer.

［**Key word**］Breast cancer; HER2-low expression; Targeted therapies

2014—2018年女性乳腺癌的发病率持续增加（每年增加0.5%），至2020年，全球女性乳腺癌新发病例约226万例、死亡病例约68万例，均居全球女性癌症新发、死亡病例数的首位[1]。根据基因表达模式的差异，乳腺癌可以被划分为在临床工作中具有预后和预测意义的4种主要临床亚型：管腔A型、管腔B型、人表皮生长因子受体2（human epidermal growth factor receptor 2，HER2）过表达型和基底样型[2]。*HER*2原癌基因是ErbB类肿瘤基因家族的成员，该基因在乳腺癌的生物学行为及发病机制中起到重要作用[3]。Cox多变量分析显示，无论是淋巴结阴性或阳性患者，*HER*2拷贝数≥3或≥5与较短的无病生存期（disease-free survival，DFS）相关[4]。一项来自19个中国代表性临床中心的数据显示，HER2阳性在所有乳腺癌中占24.7%（13.7%~35.7%）[5]。抗HER2类药物的发展极大地改善了HER2阳性乳腺癌治疗效果，包括曲妥珠单抗、拉帕替尼、帕妥珠单抗和恩美曲妥珠单抗（trastuzumab emtansine，T-DM1）等药物[6]。目前，HER2状态的判定方法主要为免疫组织化学法（immunohistochemistry，IHC）和原位杂交法（*in situ* hybridization，ISH）[7]，实时荧光定量聚合酶链反应（real-time fluorescent quantitative polymerase chain reaction，RTFQ-PCR）也是一种快速、灵敏、高通量的*HER*2基因扩增检测技术[8]。

美国临床肿瘤学会（American Society of Clinical Oncology, ASCO）/美国病理学家协会（College of American Pathologists, CAP）于2018年提出将IHC 0/1+或IHC 2+且ISH阴性诊断为HER2阴性；IHC 3+或IHC 2+且ISH阳性诊断为HER2阳性[7]。然而，IHC 0和IHC 1+乳腺癌不仅在HER2蛋白表达上存在不同，有研究发现IHC 0乳腺癌的雌激素受体（estrogen receptor，ER）与IHC 1+H-cores［平均值±95%置信区间（confidence interval，CI）］分别为90±19和134±19（$P=0.001\ 3$），差异有统计学意义[9]。并且相较于IHC 0，IHC 1+乳腺癌显现出更大的原发肿瘤体积（$P=0.007$）和更多的淋巴结受累（$P=0.010$）[10]。激素受体状态是决定HER2低表达乳腺癌基本生物学特性的关键因素。与HER2未检出肿瘤相比，HER2低表达乳腺癌在新辅助治疗前、后的病理学完全缓解率（pathologic complete response，pCR）差异有统计学意义（15.9% *vs* 37.5%，$P=0.042$），各随访时间点的复发/进展患者比例（$P=0.031$）明显较低，但有相当的DFS（$P=0.271$）[11]。二元分析发现，在激素受体阳性乳腺癌中，HER2低表达相比于HER2未检出往往呈现出的Ⅲ级肿瘤

较少、Ki-67增殖指数较低和*TP*53突变较少等特征，这可能解释了HER2低表达乳腺癌对新辅助治疗的pCR的降低[3]。

有学者为IHC 1+或2+且ISH阴性的乳腺癌提出了一个新术语，即HER2低表达乳腺癌，这类患者占全部类型的45%～55%，在目前的临床实践中，大多数仍被报告为HER2阴性或三阴性乳腺癌[12]。

本文回顾了近年HER2低表达乳腺癌靶向治疗药物如曲妥珠单抗、拉帕替尼、T-DM1、DS-8201（又名trastuzumab deruxtecan, T-DXd, Enhertu）、SYD985等的主要临床试验相关研究。

1 早期HER2低表达乳腺癌

曲妥珠单抗是一种针对HER2的重组单克隆抗体，其针对HER2过表达的转移性乳腺癌（metastatic breast cancer，MBC）的一线化疗的临床获益已被证实[13]。乳腺癌细胞系研究中发现HER2抑制剂对*HER2*基因单拷贝、低水平（但激活）的肿瘤具有一定疗效[14]。动物实验发现曲妥珠单抗对已建立的管腔乳腺癌小鼠异种移植的生长没有影响，但在肿瘤接种后给药可阻止随后的肿瘤生长，辅助性曲妥珠单抗的临床疗效可能与该药在不需要*HER2*基因扩增的情况下针对肿瘤干细胞的能力有关[15]。

国家外科辅助乳腺和肠道项目（NSABP）试验B-31比较了标准化疗（4个周期的多柔比星和环磷酰胺加4个周期紫杉醇（ACT方案）和ACT加曲妥珠单抗（ACTH方案）在辅助治疗中的作用。荧光原位杂交（flurescence *in situ* hybridization，FISH）实验阴性且IHC＜3+的肿瘤被定义为“HER2阴性”。在有随访数据的1 787例患者中，174例患者的乳腺癌被发现为中央HER2阴性（9.7%），这些患者似乎可从曲妥珠单抗中获益，但未观察到*HER2*基因扩增水平与曲妥珠单抗反应之间存在线性剂量效应[16]。N9831试验是一项研究多柔比星和环磷酰胺后每周紫杉醇联合或不联合曲妥珠单抗作为乳腺癌辅助治疗的Ⅲ期试验，其中纳入了103例FISH＜2.0，IHC结果为0、1和2的患者，主要研究终点为DFS。结果显示，该部分患者似乎可以从曲妥珠单抗中获益，但差异无统计学意义（HR=0.51，P=0.14）[17]。

然而，在NSABP B-47研究中，曲妥珠单抗不能使非IHC 3+或FISH阳性的乳腺癌患者受益。NSABP B-47是一项Ⅲ期前瞻性随机对照研究，目的是确定在辅助化疗中加入曲妥珠单抗是否可以改善HER2阴性乳腺癌患者的无浸润性肿瘤复发生存期（invasive disease-free survival，iDFS）。3 270例高危原发性浸润性乳腺癌且IHC 1+或2+、FISH＜2.0的患者被随机分配到接受或不接受曲妥珠单抗1年的辅助化疗组中，中位随访时间为46个月。结果显示，辅助化疗联合曲妥珠单抗并未改善iDFS（5年iDFS：辅助化疗联合曲妥珠单抗组为89.8%，辅助化疗组为89.2%；HR＝0.98，95% CI：0.76～1.25，P=0.85），且在HER2 IHC表达水平，淋巴结受累或激素受体状态方面差异无统计学意义。两组的5年无远处复发间期及总生存期（overall survival，OS）差异亦无统计学意义（HR=1.10，95% CI：0.81～1.50，P=0.550；HR=1.33，95% CI：0.90～1.95，P=0.150），但辅助化疗中添加曲妥珠单抗的毒性明显[8]。一项研究汇总了4项前瞻性新辅助临床试验（GeparSepto，NCT01583426；GeparOcto，NCT02125344；GeparX，NCT02682693；Gain-2新辅助治疗，NCT01690702）中接受新辅助化疗的1 098例HER2低表达和1 212例HER2阴性原发性乳腺癌患者的DFS和OS数据，中位随访时间为46.6个月，四分位距（interquartile range，IQR）为（35.0～52.3）。结果显示，HER2低表达肿瘤的pCR显著低于HER2阴性肿瘤（29.2% *vs* 39.0%，P=0.000 2），但OS明显长于HER2阴性患者（3年DFS：83.4% *vs* 76.1%，P=0.008 4；3年OS：91.6% *vs* 85.8%，P=0.001 6）[3]。

2 晚期HER2低表达乳腺癌

2.1 曲妥珠单抗及鲁妥珠单抗

CALGB9840是一项比较每周与每3周1次紫杉醇，以及联合或不联合曲妥珠单抗在HER2非过度表达患者的疗效及安全性的Ⅲ期临床研

究，228例HER2表达正常（即未检测出IHC3+或FISH+）的MBC患者被1∶1随机分配为接受或不接受曲妥珠单抗。主要终点是缓解率（response rate，RR）；次要终点是疾病进展时间（time to progress，TTP）、OS和毒性。结果显示，曲妥珠单抗并没有显著提高HER2非过度表达乳腺癌的RR（38% *vs* 32%；P=0.28）。在紫杉醇中加入曲妥珠单抗与显著延长的TTP无关（7个月 *vs* 6个月，P=0.28）。HER2非过度表达患者中接受曲妥珠单抗治疗对OS也没有显著影响。因此，这项研究表明曲妥珠单抗对HER2非过度表达的乳腺癌缺乏治疗效果[18]。一项Ⅰb期、开放标签、剂量递增研究（ClinicalTrials.gov注册号：NCT01918254）研究评估了鲁妥珠单抗（lumretuzumab）与帕妥珠单抗（pertuzumab）和紫杉醇联合治疗HER3阳性、HER2低表达的MBC患者（大于或等于一线）的安全性和耐受性以及临床活性。35例受试者被分至3个队列（队列1为2例，队列2为20例，队列3为13例）。队列1患者接受鲁妥珠单抗（1 000 mg，q3w）、帕妥珠单抗［840 mg负荷剂量（loading dose，LD），后续420 mg，q3w）和紫杉醇（80 mg/m^2，qw）；队列2患者接受鲁妥珠单抗（500 mg，q3w）、帕妥珠单抗（840 mg LD，后续420 mg，q3w）和紫杉醇（80 mg/m^2，qw）；队列3患者接受鲁妥珠单抗（500 mg，q3w）、帕妥珠单抗（420 mg，q3w）、紫杉醇（80 mg/m^2，qw）。结果显示，鲁妥珠单抗、帕妥珠单抗和紫杉醇的联合治疗与腹泻的高发生率有关，鲁妥珠单抗的最大耐受剂量为每3周500 mg。在一线MBC患者中，队列2和3的客观缓解率（objective response rate，ORR）分别为55.0%和38.5%。剂量改变后仍无法克服治疗窗口窄的问题，不值得进一步临床应用[19]。

2.2 拉帕替尼

拉帕替尼是一种口服活性小分子，可抑制酪氨酸激酶如HER2和表皮生长因子受体（epidermal growth factor receptor，EGFR）1型[20-21]。ErbB-2的过量表达导致EGFR系统的信号转导增强，从而抑制了其本身和EGFR的下调[22]。研究者对两项随机Ⅲ期试验（EGF30001和EGF100151）的生物标志物进行了分析，以优化拉帕替尼治疗的患者选择。EGF30001（Clinicaltrials.gov注册号：NCT00075270）是一项随机、多中心、双盲、安慰剂对照、双臂、Ⅲ期临床试验，比较了579例患有局部HER2阴性（IHC 0或1+或2+/FISH阴性）或未接受过转移性疾病治疗的妇女的临床结果，其中有408例患者检测为HER2阴性。患者接受拉帕替尼与紫杉醇或紫杉醇加安慰剂治疗。EGF100151（Clinicaltrials.gov注册号：NCT00078572）是一项随机、多中心、双臂、Ⅲ期临床试验，比较了399例既往接受过蒽环类药物和曲妥珠单抗治疗的HER2阳性（IHC 3+或2+/FISH阳性）女性乳腺癌患者对卡培他滨-拉帕替尼治疗的临床结果，HER2阴性患者55例。HER2阴性状态定义为FISH＜2或IHC 2+、1+或0（如果FISH未知）。对乳腺癌FISH阴性、IHC阳性（IHC＞0）女性患者的无进展生存期（progression-free survival，PFS）进行分析结果显示：在患有HER2 FISH检测结果阴性、IHC阳性的女性乳腺癌患者中，接受拉帕替尼化疗的71例患者（HR=0.97，P=0.88）和单独接受化疗的72例患者的PFS差异无统计学意义。对FISH阴性、IHC阴性（IHC 0）的患者，化疗联合拉帕替尼治疗（n=123例）与单独接受化疗（n=114）相比，其PFS差异无统计学意义（HR=1.13，P=0.426 1）[23]。

2.3 T−DM1

T-DM1是曲妥珠单抗与抗微管剂maytansine衍生物的结合物，二者通过硫醚连接剂［N-马来酰亚胺甲基］环己烷-1-甲酸酯连接[24]，同时具有HER2的靶向特性和DM1的细胞内递送能力[25]，T-DM1保留了未结合曲妥珠单抗的作用机制，包括抑制PI3K/AKT信号转导通路，抑制HER2的脱落和Fcγ受体介导的免疫细胞参与，这可能导致抗体依赖的细胞毒性（antibody-dependent cell-mediated cytotoxicity，ADCC）[26]。T-DM1与HER2结合，并通过HER2介导的内吞作用进入细胞，诱导细胞毒性[27]。

TDM4258g研究为一项单臂Ⅱ期临床试验，评估静脉注射T-DM1（3.6 mg/kg，每3周1次，持续1年）对HER2阳性MBC患者的疗效和安全性，这些患者在之前接受HER2靶向治疗后肿瘤出现进展，并且接受过化疗。HER2阳性被定义为IHC 3+（10%的肿瘤细胞有强而完整的膜染色）和（或）FISH的HER2/CEP17比率为2.0。在112例接受治疗的患者中，21例患者为HER2正常的肿瘤，随访时间≥12个月。主要终点是ORR。在确认为HER2正常肿瘤的患者中，ORR为4.8%（95% CI：1.0%～21.8%），中位PFS为2.6个月（95% CI：1.4～3.9个月）[28]。4374g是一项单臂Ⅱ期研究，给予既往接受过曲妥珠单抗、拉帕替尼、蒽环类药物和卡培他滨治疗的MBC患者T-DM1 3.6 mg/kg（静脉注射），HER2阳性标准为IHC 3+或FISH 阳性。共纳入110例患者，其中15例（15.8%）HER2正常（HER2 FISH比率＜2.0及IHC≤2+），随访中位时间为17.4个月，主要研究终点是ORR。结果显示，HER2正常患者的ORR为20%（95% CI：5.7%～44.9%），中位PFS 2.8个月（95% CI：1.3个月～N/E）。这一观察结果表明，HER2表达低于目前使用的临床阈值可能足以赋予对T-DM1的敏感性，也有可能是肿瘤的HER2状态随时间变化（即治疗时的肿瘤HER2状态与存档的肿瘤样本不同）。但由于患者数量较少，不能得出明确的结论，需要对该问题进行进一步研究[29]。

2.4 DS−8201

DS-8201是一种新型HER2靶向ADC，由人源化抗HER2抗体、可酶切的肽连接体和一种新型拓扑异构酶Ⅰ（topoisomeraseⅠ，TOPOⅠ）抑制剂组成，其抗HER2抗体是参照与曲妥珠单抗相同的氨基酸序列而生产的人单克隆IgG1[30]。TOPOⅠ抑制剂通过被捕获的TOPOⅠ裂解复合物，干扰DNA复制和转录，从而发挥细胞毒性活性[31]。由于DS-8201具有高度膜渗透性的有效载荷，其旁观者杀伤作用可在邻近HER2阳性细胞的细胞中观察到，全身毒性很低[32]。

DS8201-A-J101是一项开放标签的剂量递增Ⅰ期试验，在日本的两个研究地点进行。符合条件者为患有乳腺癌、胃癌或胃食管癌，标准疗法难治，无论HER2状态。参与者接受DS-8201的初始静脉注射剂量为0.8～8.0 mg/kg。结果显示，在23例可评估的患者中，包括13例以前接受过T-DM1治疗的患者和6例HER2低表达的肿瘤患者（定义为IHC1+/FISH阴性、IHC1+/FISH未检测或IHC2+/FISH阴性），10例（95% CI：23.2～65.5）获得了ORR（10例部分反应者，包括3例未确认的总体缓解）。在这个小规模、重度预处理的研究人群中，DS-8201显示了抗肿瘤活性，甚至在低HER2表达的肿瘤中[33]。NCT02564900是一项首次进行的Ⅰ期非随机、开放标签、多剂量研究，在美国的8个地点和日本的6个地点进行。这项研究报道了DS-8201在HER2低表达（IHC1+或2+/ISH−）乳腺癌患者中以推荐剂量进行扩增（recommended doses for expansion，RDE）的结果。HER2低表达被定义为IHC 2+/ISH2，IHC 1+/ISH2，或IHC 1+/ISH未检测。有54例晚期HER2低表达乳腺癌患者入选并接受5.4（21例）或6.4 mg/kg（33例）的DS-8201≥1个剂量的治疗。54例受试者既往中位治疗线数为7.5线，83.3%既往经历≥5线治疗，5例（9.3%）患者的HER2表达为IHC 0，30例（55.6%）为IHC 1+，14例（25.9%）为IHC 2+。经独立中心审查确认，ORR为37.0%（95% CI：24.3%～51.3%），中位反应时间为10.4个月（95% CI：8.8个月～无法评估）。DS-8201在HER2低表达乳腺癌患者中表现出初步抗肿瘤活性。大多数毒性是消化道或血液不良反应。间质性肺疾病是一个重要的识别风险，应密切监测并积极管理[34]。DAISY是一项多中心、开放标签的Ⅱ期临床试验，评估了5.4 mg/kg剂量的单药DS-8201在HER2过表达（IHC3+或IHC 2+/ISH+，$n=72$）、HER2低表达（IHC2+/ISH-或IHC1+，$n=74$）和HER2未检出（IHC0+，$n=40$）且接受过≥1次化疗方案的MBC患者的疗效，并进行生物标志物分析。主要终点是研究者评估的最佳疗效（best of response，BOR），次要终点为中心评估的BOR、临床获益率（clinical benefit rate，CBR）、疗效持续时间（duration

of response，DoR）、PFS及OS。中位随访15.6个月后，HER2低表达队列研究者评估的BOR为37.5%（27/72），中位DoR为7.6个月（95% CI：4.2个月~9.2个月），中位PFS为6.7个月（95% CI：4.4个月~8.3个月）；HER2未检出队列的BOR为29.7%（11/37），中位DoR为6.8个月（95% CI：2.8个月~无法评估），中位PFS为4.2个月（95% CI：2.0个月~5.7个月）。安全性方面，共有173例患者（96.6%）发生了至少1次治疗相关的不良事件（treatment-related adverse event，TRAE）。13例患者因治疗相关的不良事件而中止治疗（5例患者为间质性肺病）[35]。

DESTINY-Breast04（ClinicalTrials.gov注册号：NCT03734029）是首个聚焦于HER2低表达乳腺癌患者并获得阳性结果的Ⅲ期临床研究，这是一项随机、双臂、开放标签、多中心研究，旨在比较DS-8201（5.4 mg/kg）与医师选择方案（2∶1随机分配）在HER2低表达、不可切除和（或）MBC中的安全性和有效性，包括HER2表达呈IHC 2+/ISH-或IHC 1+（ISH-或未检测）的肿瘤。来自亚洲、欧洲和北美洲的557例受试者既往接受过1~2次化疗等辅助治疗，其中494例（88.7%）为激素受体阳性，63例（11.3%）为激素受体阴性。主要研究终点为基于盲法独立中心审查（Blind Independent Center Review，BICR）的HR阳性患者的PFS；次要研究终点包括基于BICR评估的PFS、OS、ORR、基于BICR和调查员评估的DoR。在激素受体阳性队列中，DS-8201组的中位PFS为10.1个月，医师选择组为5.4个月（HR=0.51，P<0.001）；OS分别为23.9个月和17.5个月（HR=0.64，P=0.003）。在所有患者中，DS-8201组的中位PFS为9.9个月，医师选择组为5.1个月（HR=0.50，P<0.001）；OS分别为23.4个月和16.8个月（HR=0.64，P=0.001）。≥3级不良事件的发生率在接受DS-8201和医师选择方案的患者中分别为52.6%和67.4%。使用DS-8201的患者有12.1%发生了药物相关的间质性肺病或肺炎；其中0.8%发生了5级事件[36]。2022年4月27日，DS-8201获得美国食品药品管理局突破性疗法认定（breakthrough therapy designation，BTD），用于治疗不可切除或转移性HER2低表达乳腺癌成年患者。这是DS-8201在乳腺癌中的第3个BTD，其曾在2021年和2017年分别获得针对二线及后线HER2阳性MBC的BTD[37]。

DESTINY-Breast06是一项全球、随机、多中心、开放标签的Ⅲ期临床试验，比较DS-8201与研究者选择的化疗对接受过≥2线内分泌治疗的HER2低表达和极低表达MBC的疗效和安全性。纳入的850例（HR+、HER2 IHC1+或IHC2+/ISH-者700例；IHC>0，<1+者150例）受试者以1∶1的比例随机分配，每3周接受DS-8201 5.4 mg/kg或研究者选择的化疗方案（紫杉醇、白蛋白结合型紫杉醇或卡培他滨）。主要研究终点为基于BICR的HER2低表达人群的PFS，次要终点为HER2低表达人群的OS及意向治疗（intention-to-treat，ITT）人群的OS、PFS。这项研究将为DS-8201在无化疗环境中的作用提供参考[38]。

2.5 SYD985

抗体-药物偶联物SYD985对HER2低表达乳腺癌患者显示出良好疗效（无论是否有激素受体表达）。一项Ⅰ期临床试验（ClinicalTrials.gov注册号：NCT02277717）评估了SYD985对HER2低表达MBC患者的安全性和疗效。HER2低表达定义为IHC1+/2+/ISH-。该研究共纳入HER2低表达乳腺癌受试者49例，包括激素受体阳性型乳腺癌（32例）和三阴性乳腺癌（17例）。患者每3周接受1.2 mg/kg SYD985静脉注射治疗。结果显示，ORR分别为27%和40%，安全可控。最常见的药物不良反应是疲劳、眼睛干燥、结膜炎。≥3级药物不良反应中最常见中性粒细胞减少（6%）和结膜炎（4%）[39]。

3 其他治疗手段及临床试验

除了前述靶向HER2的单克隆抗体、小分子抑制剂以及初步取得可喜结果的DS-8201等ADC药物，全世界的研究者们也将目光投向其他新型ADC药物（RC48-ADC、ARX788、A166[40]等）、双特异性抗体（KN026、ZW25、ertumaxomab[41]等）和乳腺癌疫苗（nelipepimut-S[42]、GP2[43]、AE37[44]等），

并在此基础上开展了相关的临床试验，以期为早期或晚期HER2低表达乳腺癌患者提供新希望。部分正在开展或已取得结果的抗HER2药物及临床试验的信息见表1。

表1 抗HER2药物及HER2低表达乳腺癌相关临床试验概览

Tab. 1 Summary of anti-HER2 agents and the related clinical trials of HER2-low breast cancer

Drug	Clinical trials	Phase	Inclusion criteria	Primary outcome	Results
ADC					
RC48-ADC	NCT04400695	Ⅲ	Participants with HER2-low, unresectable, locally advanced, or metastatic breast cancer who had previously been treated with an anthracycline and received 1 or 2 systemic chemotherapy regimens after relapse or metastasis	PFS	Ongoing
ARX788	NCT05018676	Ⅱ	Unresectable and/or metastatic HER2-low breast cancer. Patients with recurrent or metastatic disease should receive≥2 lines of systemic chemotherapy regimens; Hormone receptor-positive objects need to have received ≥2-line endocrine therapy ± targeted therapy (including neoadjuvant/adjuvant therapy)	ORR	Ongoing
A166	CTR20181301	Ⅰ	Patients with HER2-expressing locally advanced or metastatic solid tumors (51 HER2-positive (3+ or 2+/ISH+), 6 HER2-low (1+ or 2+/ISH-)	ORR	The efficacy of 36 HER2-positive breast cancer patients with measurable disease was evaluated; the best ORR was 59.1% (13/22) and 71.4% (10/14) in the 4.8 and 6.0 mg/kg cohorts, respectively. Corneal epitheliopathy (73.7%), blurred vision (59.6%), peripheral sensory neuropathy (26.3%), dry eye (21.1%), anemia (19.3%), and hyponatremia (19.3%) were the most common TRAEs. Corneal epitheliopathy (17.5%), hypophosphatemia (5.3%), and dry eye (5.3%) were the most common grade 3 TRAEs
Bispecific antibody					
KN026	NCT04165993	Ⅱ	Patients with HER2-low and hormone receptor positive MBC failed standard chemotherapy and hormone therapy; patients with HER2-low and hormone receptor negative/weak positive MBC failed standard chemotherapy	ORR; DOR	Ongoing
ZW25	NCT02892123	Ⅰ	Patients with HER2-expressing cancer that was locally advanced (unresectable) or metastatic	DLTs	Ongoing
Ertumaxomab	NCT00522457	Ⅱ	Enrolled patients had advanced breast cancer that was ER and/or PgR positive with low HER2 expression (IHC 1+ or 2+ and FISH negative). Patients were required to have PD after hormonal therapy that included at least one aromatase inhibitor, but no prior chemotherapy for advanced disease	ORR	The evaluable population's median TTP was 65.5 days (95% CI: 43-98). Pyrexia (74.1%), headache (40.7%), chill (33.3%), and vomitting (29.6%) were the most frequently observed AEs. The majority (73.8%) of AEs were mild or moderate in severity and resolved within one day

续表1 抗HER2药物及HER2低表达乳腺癌相关临床试验概览

Drug	Clinical trials	Phase	Inclusion criteria	Primary outcome	Results
Vaccine					
Nelipepimut-S	NCT01479244	Ⅲ	Patients with HER2/neu-positive, node-positive, or high-risk node-negative breast cancer	Disease recurrence	At the interim analysis with the median follow-up (16.8 months), there was no discernible between-arms difference in DFS events. Imaging identified 54.1% of recurrence episodes in NP-S participants as opposed to 29.2% in the placebo group (P=0.069). Injection-related erythema (84.3%), induration (55.8%), and pruritus (54.9%) were the most prevalent
GP2	NCT00524277	Ⅱ	Breast cancer patients with tumors expressing HER2 (IHC 1-3+) who were clinically disease-free, node-positive, and high-risk node-negative were enrolled	Disease recurrence	The 5-year DFS rate in the ITT analysis was 88% (95% CI: 78%-94%) in the vaccine-eligible patients versus 81% (95% CI: 69%-89%) (P=0.43), in the control group
AE37	NCT00524277	Ⅱ	Patients with tumors expressing any level of HER2 (IHC 1-3+) who were node-positive and high-risk node-negative for breast cancer and were clinically disease-free	Disease recurrence	Relative risk decreased 12%, HR=0.885, 95% CI: 0.472-1.659, P=0.70; recurrence rate in the immunized group was 12.4% against 13.8% in the control group. Vaccinated patients had a 5-year DFS rate of 80.8%, compared to 79.5% for control patients. The 5-year DFS was 77.2% in patients who received the vaccine (n=76) compared to 65.7% in those who received a placebo (n=78) in planned subset analyses of patients with IHC 1+/2+ HER2-expressing tumors (P=0.21). DFS was 77.7% in the vaccinated patients (n=25) against 49.0% in the control patients (n=25) in patients with TNBC (HER2 IHC 1+/2+ and hormone receptor negative) (P=0.12)

ADC: Antibody-drug conjugates; AEs: Adverse events; DFS: Disease-free survival; DLTs: Dose-limiting toxicities; ER: Estrogen receptor; iDFS: Invasive disease-free survival; ITT: Intention-to-treat; HER2: Human epidermal growth factor receptor 2; IHC: Immunohistochemistry; mBC: Metastatic breast cancer; ORR: Objective response rate; PD: Progression disease; PFS: Progression-free survival; PgR: Progesterone receptor; TNBC: Triple-negative breast cancer; TRAEs: Treatment-related adverse events.

4 总 结

HER2低表达乳腺癌在全部类型中约占半数，其重要性逐渐凸显。这类乳腺癌的分子特征、临床预后、治疗方式不同于HER2未检出或HER2阳性乳腺癌。自20世纪起，研究者们利用多种靶向治疗药物，在临床试验中以HER2低表达为亚组或全部受试者，寻找有效的攻克方法。HER2阳性乳腺癌的经典靶向药物如曲妥珠单抗、拉帕替尼、T-DM1等，在HER2低表达中效果欠佳，无论是辅助治疗或晚期解救治疗。直至新型抗体-药物偶联物DS-8201的临床试验结果表现出初步、具有希望的疗效与安全性。同时，其他治疗手段如双特异性抗体、乳腺癌疫苗等的临床试验也在进行中，期待后续的结果。

利益冲突声明：所有作者均声明不存在利益冲突。

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