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三阳性乳腺癌的治疗进展

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摘要 三阳性乳腺癌是指雌激素受体（estrogen receptor，ER）、孕激素受体（PR）和人类表皮生长因子受体2（human epidermal growth factor receptor 2，HER2）均为阳性，约占HER2阳性乳腺癌病人总数的50%～60%。三阳性乳腺癌中存在的ER信号通路和HER2信号通路之间的交互作用可能会削弱其抗HER2治疗和内分泌治疗的疗效，这一特点引起了广泛的关注。越来越多的证据显示，同时阻断HER2信号通路和ER信号通路，如采用抗HER2双靶向+内分泌治疗±CDK4/6抑制剂，可有效规避治疗之间的相互耐药，提高治疗效果且安全性良好。同时，生物标志物也在积极探索中，包括Ki67、内生亚型及多基因检测等，有助于选择真正获益的人群，指导精准治疗。

关键词 三阳性乳腺癌；交互作用；治疗策略；生物标志物

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人类表皮生长因子受体2（human epidermal growth factor receptor 2，HER2）作为驱动基因[1]，可形成同源二聚体，或与HER家族其它成员形成异源二聚体，将下游酪氨酸激酶信号级联激活，通过激活MAPK和PI3K/AKT等信号通路，促进肿瘤生长、侵袭和转移[11]。同时，HER2还是独立的预后因子[2]，HER2的高表达与无病生存（disease free survival，DFS）和总体生存（overall survival，OS）有着明显的负相关。但是，HER2阳性乳腺癌具有明显的异质性，存在不同的生物学特点，内生亚型及相关基因的表达、治疗反应和临床预后特点。其中，激素受体（hormone receptor，HR）是重要的异质性因素，根据HR的表达状态，HER2阳性乳腺癌可分为HR+HER2+和HR-HER2+两个亚型的乳腺癌，约有半数以上是HR+HER2+亚型，即为三阳性乳腺癌（triple positive breast cancer，TPBC）[3-4]。既往HER2阳性乳腺癌的临床研究结果显示，三阳性乳腺癌对HER2靶向治疗的反应不如HR-HER2+亚型。临床前数据表明，三阳性乳腺癌中存在的雌激素受体（estrogen receptor，ER）信号通路和HER2信号通路之间的交互作用可能削弱其抗HER2治疗和内分泌治疗的疗效。因此，深入研究三阳性乳腺癌独特的生物学特点，使其能够进一步指导临床治疗，成为了乳腺癌领域研究的热点。

1 激素受体状态是HER2阳性乳腺癌的重要异质性因素

HER2阳性乳腺癌具有明显的异质性，其中，激素受体状态是异质性的重要因素之一。三阳性乳腺癌的病人即HR+HER2+，其预后较HR+HER2-乳腺癌病人差。但与HR-HER2+的乳腺癌病人相比，三阳性乳腺癌病人预后更好，出现向脑、肝和肺等器官远转移的几率较低[5-6]。在表达水平，三阳性乳腺癌中HER2蛋白的表达水平与ER蛋白的表达水平呈明显的负相关性，同时，出现

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*ERBB2*基因拷贝数扩增的概率较低[7]；在内生亚型方面，通过由50个基因的mRNA表达定义的内在分子亚型PAM50的内生亚型分析发现，三阳性乳腺癌中管腔型内生亚型占比高，而HR-HER2+乳腺癌中HER2富集型占比最高[8]；从分子机制方面，三阳性乳腺癌存在不同的细胞激活通路，如在三阳性乳腺癌中，GATA3、BCL2和ESR1等管腔型相关的基因高表达，而在HR-HER2+乳腺癌中，HER2相关的基因及酪氨酸激酶受体都出现高表达[8-9]；从免疫微环境方面，与三阳性乳腺癌相比，HR-HER2+乳腺癌病人的肿瘤浸润性淋巴细胞（tumor infiltrating lymphocytes，TILs）比例更高，其PD-L1阳性比例更高[10-11]；在基因突变方面，三阳性乳腺癌的*PI3KCA*突变率较HR-HER2乳腺癌更高（23% *vs.* 18%）[12]；在治疗疗效方面，针对早期HER2阳性乳腺癌接受新辅助治疗的临床研究发现，三阳性乳腺癌病人的病理性完全缓解率（pathological complete response，pCR）更低，但由于术后长期的内分泌治疗，三阳性乳腺癌病人的远期生存并不比HR-HER2+乳腺癌病人差[13-14]。由此可见，三阳性乳腺癌有着独特的分子生物学行为、特有的疾病特征、不同的治疗反应和复发模式，成为了研究的热点。

2　三阳性乳腺癌中ER和HER2的交互作用及临床意义

对于三阳性乳腺癌，临床前研究发现ER信号通路和HER2信号通路之间存在交互作用，可导致内分泌治疗耐药和抗HER2治疗效果不佳。在HR阳性乳腺癌病人中，ER的表达水平与HER2表达水平呈现负相关，即HER2阳性的乳腺癌的ER表达水平显著低于HER2阴性的乳腺癌病人，差异具有统计学意义[15]。同时，ER水平与内分泌治疗的反应呈明显的正相关性，因此，三阳性乳腺癌病人因ER水平略低，内分泌治疗的疗效也有所下降。另外，研究还证实了HER2信号通路可直接或间接导致内分泌治疗（他莫昔芬）耐药[16]。其机制可能有：HER2介导的PI3K/Akt/mTOR和p42/44 MAPK信号通路的激活，使得ER表达水平下调；在细胞水平，他莫昔芬治疗期间，可通过乳腺癌扩增基因1（amplified in breast cancer 1，AIB1）上调*ERBB2*基因转录，使得HER2蛋白水平升高，导致他莫昔芬的耐药[17-18]，因而，他莫昔芬可能并不是三阳性乳腺癌病人在接受抗HER2治疗期间的内分泌治疗的最佳选择。在临床前研究发现，接受了曲妥珠单抗、帕妥珠单抗和吉非替尼靶向治疗的内分泌耐药动物模型，可恢复对他莫昔芬的治疗敏感性[19]。细胞膜上的ER可能通过EGFR、HER2、IGFR1及其转导途径促进肿瘤细胞的生长、增殖等作用。EGFR、IGF1和HER2等酪氨酸激酶受体可通过磷酸化作用激活雌激素受体，这个过程无需依赖于雌激素，因而，形成了ER信号通路与酪氨酸激酶受体信号通路间的交互作用[20]。

ER信号通路和HER2信号通路的交互作用，也会导致抗HER2治疗疗效不佳。在接受了拉帕替尼新辅助治疗的临床乳腺癌组织标本中，发现ER和Bcl2的表达水平上调，可能是抗HER2治疗耐药的潜在机制[21]。在接受曲妥珠单抗治疗的晚期HER2阳性乳腺癌中，抗HER2治疗反应性下降后随即会出现ER表达水平上调[22]。拉帕替尼单独或联合曲妥珠单抗对三阳性乳腺癌细胞增殖持续的抑制作用可被ER信号通路的激活所阻断，而采用氟维司群下调雌激素信号通路后，三阳性乳腺癌癌细胞可恢复对拉帕替尼和曲妥珠单抗的敏感性[23]。在异种移植肿瘤模型中，靶向抗HER2（曲妥珠单抗、帕妥珠单抗、拉帕替尼）联合内分泌治疗，可呈现出明显的抗肿瘤效果[24]，显著延迟肿瘤的进展。以上这些临床前数据均表明，ER信号通路和HER2信号通路之间的交互作用，可能同时削弱了抗HER2靶向治疗和内分泌治疗的有效性，而同时靶向阻断ER信号通路和HER2信号通路可有效规避治疗之间的相互耐药，从而提高联合治疗的效果，改善病人的预后。

3　三阳性乳腺癌的治疗进展

早期HER2阳性乳腺癌的新辅助治疗数据分析显示，激素受体状态是HER2阳性乳腺癌新辅助治疗重要的异质性因素。汇总了12项全球新辅助治疗的临床研究CTneoBC及一项Meta分析的结果都一致地显示：对于三阳性乳腺癌的病人，新辅助治疗后的pCR率和生存获益明显不如

HR-HER2+乳腺癌病人，且pCR与生存预后并无明显的相关性[13]。在大量的临床研究中，采用不同的抗HER2靶向治疗，如曲妥珠单抗联合帕妥珠单抗，或曲妥珠单抗联合小分子酪氨酸激酶抑制剂（tyrosine kinase inhibitors，TKIs），均发现三阳性乳腺癌病人pCR率不如HR-HER2+乳腺癌病人[25-32]（表1）。因此，对于三阳性乳腺癌，pCR并不能预测病人的长期生存，对于新辅助治疗后未达到pCR的早期三阳性乳腺癌病人，或许是由于后续的长期辅助内分泌治疗可进一步改善病人的预后，所以远期预后不一定较差[13]。因此，对于早期三阳性乳腺癌病人，在靶向抗HER2治疗的同时，优化对ER信号通路的阻断，可为病人带来生存的获益。TBCRC023和TBCRC006研究，在新辅助治疗阶段给予曲妥珠单抗联合拉帕替尼联合来曲唑治疗，pCR率可达30%[33-34]。另外，ADAPT伞形研究下针对HR+HER2+乳腺癌的新辅助治疗组（WSG-ADAPT-TP），采用T-DM1靶向治疗联合他莫昔芬或芳香化酶抑制剂内分泌治疗，与曲妥珠单抗联合他莫昔芬或芳香化酶抑制剂内分泌治疗的对照组相比（pCR：6.7%），T-DM1单独或联合内分泌治疗组的pCR率更高，可分别达40.5%和45.8%[35-36]。另一项II期PerELISA研究旨在探索经过2周的芳香化酶抑制剂来曲唑治疗，Ki67显著下降的病人，给予免化疗的曲妥珠单抗联合帕妥珠单抗及来曲唑联合治疗的疗效及安全性[37]。对于早期乳腺癌，NA-PHER2这一项开放标签多臂非对照的II期研究中，HR+HER2+早期乳腺癌病人在接受了帕博西利、曲妥珠单抗、帕妥珠单抗联合氟维司特的联合新辅助治疗2周后及术前Ki67水平都显著下降，16周临床完全缓解率达50%，病理性完全缓解率达27%，同时，新辅助治疗后Ki67水平得到快速而显著的下降[38-39]。但由于样本量小和缺乏对照组等局限性，有待进一步的研究来探索免化疗的曲帕双靶联合CDK4/6抑制剂在HR+HER2+早期乳腺癌的价值。由于老年乳腺癌病人在进行抗HER2靶向治疗时存在心脏毒性等风险，TOUCH研究（NCT03644186）则针对65岁以上的早期三阳性乳腺癌病人，在新辅助治疗阶段给予曲妥珠单抗和帕妥珠单抗联合帕博西利及来曲唑或紫杉醇治疗，旨在探索对于老年三阳性乳腺癌病人如何进行化疗降阶[40]。

表1　早期HER2阳性乳腺癌的新辅助治疗研究的汇总

临床研究	抗HER2靶向治疗	pCR	
		HR+HER2+	HR-HER2+
NeoSphere[25]	曲妥珠单抗+帕妥珠单抗	26%	63%
NeoALTTO[26-27]	曲妥珠单抗+拉帕替尼	42%	61%
CALGB 40601[28]	曲妥珠单抗+拉帕替尼	42%	77%
CHERLOB[29]	曲妥珠单抗+拉帕替尼	36%	59%
TRYPHAENA[30]	曲妥珠单抗+帕妥珠单抗	46%～50%	65%～84%
NSABP B-41[31]	曲妥珠单抗+拉帕替尼	55%	70%
TRAIN-2[32]	曲妥珠单抗+帕妥珠单抗	51%～55%	84%～89%

目前，三阳性乳腺癌的辅助治疗方案主要以化疗联合抗HER2靶向治疗，随后给予内分泌治疗维持。而对于高危的HER2阳性早期乳腺癌病人，ExteNET研究发现，在接受含曲妥珠单抗治疗1年后，给予奈拉替尼辅助强化治疗可显著提高病人的生存。相比起HR-HER2+乳腺癌，三阳性乳腺癌从中获益更为明显，分析其原因可能与ER信号通路及HER2信号通路间的交互作用相关[41]。另一项针对HER2阳性新辅助治疗后未达到pCR的高危乳腺癌病人的KATHERINE研究发现，T-DM1辅助治疗效果显著优于曲妥珠单抗，可降低50%的疾病复发及死亡的风险，奠定了T-DM1成为高危non-pCR病人辅助治疗的标准，研究中约有72%是三阳性乳腺癌，与HR-HER2+相比，T-DM1可带来相似的iDFS获益[42]。

针对复发、转移性三阳性乳腺癌，需综合考

虑病情、既往治疗用药情况等来选择个体化的治疗方案。随着新型药物的不断涌现，CLEOPATRA研究、EMILIA研究、Destiny Breast-03研究及HER2CLIMB研究等一次又一次确立了新的晚期HER2阳性乳腺癌治疗标准，目前对于晚期HER2阳性乳腺癌，不论激素受体状态如何，抗HER2治疗联合化疗，或是ADC类药物进行治疗都可为病人带来一致的生存获益[43-48]。但是，也有些临床研究的探索性分析值得关注：NALA研究中，Neratinib在HR-人群中获益，而在HR+人群中没有优于拉帕替尼[49]。SOPHIA研究中，Margetuximab在三阳性乳腺癌亚组中也未显示优于曲妥珠单抗[50]。KATE-2研究中，T-DM1联合Atezolizumab的研究中在PD-L1+人群中带来无进展生存期（progression-free survival，PFS）获益，而获益见于HR-HER2+亚组，但三阳性乳腺癌即使PD-L1阳性，可能也无法从免疫治疗中获益[51]。值得注意的是，CLEOPATRA等临床研究纳入的三阳性乳腺癌不允许在试验阶段给予内分泌治疗，但是真实世界数据的分析发现，对于晚期三阳性乳腺癌，在抗HER2靶向治疗（曲妥珠单抗+帕妥珠单抗）联合紫杉化疗后，采用曲妥珠单抗+帕妥珠单抗联合内分泌治疗进行维持治疗，与不加内分泌治疗相比，可让病人有更好的生存获益。

因此，如何优化三阳性晚期乳腺癌的治疗，让病人获益更大，成为了研究热点。一系列研究探索了抗HER2靶向治疗（曲妥珠单抗/拉帕替尼）联合内分泌治疗（芳香化酶抑制剂）在三阳性晚期一线乳腺癌病人的治疗疗效，如TAnDEM研究、EGF3008研究及eLEcTRA研究都证实了在芳香化酶抑制剂内分泌治疗的基础上，联合抗HER2靶向治疗可为病人带来PFS的显著获益[52-54]。PERTAIN研究证实了在曲妥珠单抗联合芳香化酶抑制剂的基础上，加用帕妥珠单抗，可为病人带来显著的PFS获益[55]。ALTERNATIVE研究显示，对于晚期三阳性乳腺癌病人，在曲妥珠单抗联合芳香化酶抑制剂的基础上加用拉帕替尼也可为病人带来更长的PFS[56]。一项回顾性小样本的研究显示，三阳性晚期后线难治的乳腺癌病人接受氟维司群联合曲妥珠单抗治疗，中位PFS达6.4个月，中位总生存OS为35.3个月[57]。目前三阳性晚期一线乳腺癌的标准治疗为，曲妥珠单抗、帕妥珠单抗联合紫杉类，化疗结束后采用曲帕双靶联合内分泌治疗。真实世界研究显示，对于三阳性乳腺癌，这种标准一线治疗模式可为病人带来显著的PFS获益[58]。因此，针对晚期三阳性乳腺癌的一线治疗，可否安全地豁免化疗成为了研究热点。SYSUCC-002研究[59]证实了针对晚期一线的三阳性乳腺癌病人，曲妥珠单抗联合内分泌治疗非劣效于曲妥珠单抗联合化疗组，中位PFS：19.2个月 *vs.* 14.8个月。这是第一个头对头比较了抗HER2靶向治疗联合化疗与联合内分泌治疗在晚期一线三阳性乳腺癌病人中的疗效和安全性，同时，亚组分析发现既往治疗的无疾病间期（disease free interval，DFI）在24个月以内的病人更能从化疗中获益。虽然由于研究设计的时效性，其结果并未能改变现有的标准一线治疗模式，也未能评价CDK4/6抑制剂等在晚期三阳性乳腺癌中的价值，但也有着重要指导意义。内分泌治疗联合抗HER2靶向治疗也被国内外指南所认可，可被用于不能耐受化疗，或是疾病进展缓慢的病人。

CDK4/6抑制剂作用于CyclinD-CDK4/6复合物，阻止细胞从G1期进入S期[60]。CDK4/6抑制剂联合内分泌治疗，为HR+HER2-晚期乳腺癌病人带来PFS及OS的获益，已被批准用于HR+/HER2-转移性乳腺癌病人的一线标准治疗，也是二线或辅助强化治疗时内分泌治疗的最佳选择。考虑到CDK4/6是HER2信号通路的下游靶点，并且参与了HER2靶向治疗耐药性的产生，那么靶向CDK4/6是HER2阳性乳腺癌治疗的重要新策略。对于三阳性乳腺癌，抗HER2靶向治疗联合CDK4/6抑制剂这种双重阻断的有效性和安全性在前期临床研究中有所证实。在MonarcHER研究[61]中，237例治疗后线的晚期三阳性乳腺癌病人，被随机分配接受阿贝西利+曲妥珠单抗+氟维司群（A组）；阿贝西利+曲妥珠单抗（B组）；或标准化疗+曲妥珠单抗（C组）。与C组相比，A组的PFS有显著改善［分别为8.3个月和5.7个月；HR 0.67（95%CI 0.45-1.00），*P*=0.051］，但B组和C组之间无差异［HR 0.94（95%CI 0.64-1.38），*P*=0.77］。虽然MonarcHER研究的结果证实了对于晚期三阳

性乳腺癌，曲妥珠单抗联合CDK4/6抑制剂与曲妥珠单抗联合化疗的疗效相当，但该研究也有些不容忽视的局限性，如未设置曲妥珠单抗联合氟维司群治疗组，因此不能明确氟维司群带来的获益；同时，入组人群中仅50%的病人之前接受过帕妥珠单抗治疗，但目前对于HER2阳性晚期一线标准治疗是曲妥珠单抗联合帕妥珠单抗及紫杉类，因此，MonarcHER研究的结果未能改变临床实践。同样，PATRICIA研究[62]证实了帕博西利联合曲妥珠单抗治疗晚期HER2阳性乳腺癌的疗效及安全性。对于晚期三阳性乳腺癌病人，在接受帕博西利+曲妥珠单抗联合治疗（B1组）或联合治疗后续贯来曲唑治疗（B2组），6个月时的PFS可达42.8%（12/28）和46.4%（13/28）。一项Ib期的临床试验LORDSHIPS显示，“免除静脉用药、全口服”的治疗方案（达尔西利+来曲唑+吡咯替尼）展现出积极的抗肿瘤效果，客观缓解率（objective response rate，ORR）达到66.7%，PFS为11.3个月，同时，还展现出良好的安全性[63]。小样本的NA-PHER2研究[39]探索了在新辅助治疗阶段给予曲妥珠单抗、帕妥珠单抗、帕博西利和氟维司群，直至手术时，Ki67从基线的31.9%下降至12.1%，pCR达到27%。一项Ib/II期研究（NCT03054363），纳入了20例HR+HER2+转移性乳腺癌（45%病人有脑转移），接受图卡替尼、帕博西利和来曲唑联合治疗。初步数据分析显示治疗的安全性是可接受的，同时，展现出良好的抗肿瘤效果，目前正在进行相关的II期临床研究以期探索其疗效和安全性[64]。因此，HER2靶向治疗和CDK4/6抑制剂的联合治疗是三阳性乳腺癌具有前景的治疗策略，在早期乳腺癌和晚期乳腺癌的临床研究中，均在积极地探索其疗效及安全性，包括DETECT V/CHEVENDO研究[65]、PATINA研究[66]、TOUCH研究[40]等。

另外，由于磷脂酰肌醇3-激酶（PI3K）通路也是HER2靶向治疗耐药的分子机制[67]。同时，CDK4/6抑制剂及PI3K抑制剂具有免疫调节作用，可明显增加肿瘤的免疫原性，最终促进细胞毒性T细胞介导清除肿瘤细胞。因而，将HER2靶向治疗，分子靶向治疗（CDK4/6抑制剂、PI3K抑制剂）与免疫治疗相结合的新型治疗策略，也可能成为未来的研究方向。

4 三阳性乳腺癌的生物标志物

对于早期三阳性乳腺癌病人，pCR缺乏预后的价值，因而寻找更有效的预后预测生物标志物成为了研究的热点。

增殖指数Ki67是一种潜在的有效生物标志物，可作为新辅助内分泌治疗病人生存获益的替代指标。在接受新辅助化疗的乳腺癌病人中，基线Ki67水平可预测治疗反应和预后，基线Ki67越高，pCR率和无复发生存期（relapse free survival，RFS）越高；除了基线水平，新辅化疗后的残留病灶的Ki67水平更具预后价值，可预测病人的预后[38]。Ki67在三阳性乳腺癌治疗早期的变化可预测肿瘤的治疗反应，在NeoPhoebe[68]、PerELISA[37]研究中进行了探索，同时，也期待能从中找到那些可能并不能从化疗中真正获益的病人。NeoPhoebe研究中，接受PI3K抑制剂联合曲妥珠单抗的三阳性早期乳腺癌病人，治疗早期15 d时，Ki67下降20%的发生率明显高于与曲妥珠单药组（66.7% *vs.* 26.1%，P=0.013）。PerELISA研究中，两周来曲唑治疗窗后再次评估Ki67的表达水平，与基线相比，Ki67下降超20%的病人对内分泌治疗敏感，而后续给予来曲唑联合曲妥珠单抗和帕妥珠单抗新辅助治疗即可，无需再接受化疗。但在WSG-ADAPT-TP研究[36]中，T-DM1新辅助治疗4周期的pCR达41%，而在T-DM1的基础上，内分泌治疗并未提升pCR。同时，根据治疗早期的Ki67的变化分为反应组和无反应组，两组间未显示出显著的生存获益差异，究其原因，可能与入组人群中有半数为TNM分期I期有关。

此外，系列临床研究已经开始尝试在术前使用分子图谱来指导乳腺癌新辅助治疗的决策。PerELISA[37]、PAMELA[69]等研究发现，将三阳性早期乳腺癌进行PAM50分析，内生亚型为HER2富集的pCR率较其它内生亚型的pCR率高（41%～54% *vs.* 13.8%～28%）。另外，I-SPY研究采用综合数据集（转录组、蛋白组以及临床反应等数据）[70]，以10种不同的治疗药物/策略的治疗疗效为切入点，以最佳疗效对乳腺癌进行再分型，构建了反应预测亚型（response predictive subtypes，

RPS-5）模式，结果显示三阳性乳腺癌病人接受RPS-5再分型后pCR率可从51%提高至67%，提示RPS-5对预测治疗药物的疗效有着重要的意义，具有应用前景。

另外，也有些研究在分析pCR和多基因检测之间的相关性，以发现肿瘤的生物学特点、预测pCR率和生存预后。其中，研究最多的是HER2DX，指27个基因结合临床病理特征（肿瘤大小、淋巴结状态等）进行综合评估的分值，其具有预后和预测pCR的价值[71]。也有结果提示在HER2阳性乳腺癌中，免疫特征和pCR之间有较强的相关性，成为了有前景的研究方向[72]。

5　总结

曲妥珠单抗显著提高了早期和晚期HER2阳性乳腺癌的生存获益。然而，曲妥珠单抗带来的获益在ER阴性的肿瘤中最高，并随着肿瘤中ER表达的增加而逐渐降低。这也促使人们优化三阳性乳腺癌病人的治疗策略，聚焦于如何延长生存且减少不良反应。同时，CDK4/6抑制剂等新型分子靶向治疗药物与抗HER2药物联合治疗，在临床研究中展现出具有前景的抗肿瘤活性，这两类药物的协同作用使其成为研究热点和探索的方向。最后，预测治疗疗效的生物标志物的探索也在进行中，Ki67、内生亚型及多基因检测等，将有助于选择真正获益的人群。

参考文献

[1] Spector NL, Blackwell KL. Understanding the mechanisms behind trastuzumab therapy for human epidermal growth factor receptor 2-positive breast cancer [J]. J Clin Oncol, 2009, 27: 5838-5847.

[2] Ménard S, Fortis S, Castiglioni F, et al. HER2 as a prognostic factor in breast cancer [J]. Oncology, 2001, 61 (Suppl.2): 67-72.

[3] Balduzzi S, Mantarro S, Guarneri V, et al. Trastuzumab-containing regimens for metastatic breast cancer [J]. Cochrane Database Syst Rev, 2014, 2014(6): CD006242.

[4] Howlader N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status [J]. J Natl Cancer Inst, 2014, 106(5): dju055.

[5] Lee HJ, Park IA, Park SY, et al. Two histopathologically different diseases: hormone receptor-positive and hormone receptor-negative tumors in HER2-positive breast cancer [J]. Breast Cancer Res Treat, 2014, 145 (3): 615-623.

[6] Arciero CA, Guo Y, Jiang R, et al. ER(+)/HER2(+) breast cancer has different metastatic patterns and better survival than ER(-)/HER2(+) breast cancer [J]. Clin Breast Cancer, 2019, 19(4): 236-245.

[7] Loi S, Dafni U, Karlis D, et al. Effects of estrogen receptor and human epidermal growth factor receptor-2 levels on the efficacy of trastuzumab: A secondary analysis of the HERA trial [J]. JAMA Oncol, 2016, 2: 1040-1047.

[8] Cejalvo JM, Martinez de Duenas E, Galvan P, et al. Intrinsic subtypes and gene expression profiles in primary and metastatic breast cancer [J]. Cancer Res, 2017, 77(9): 2213-2221.

[9] Cancer Genome Atlas N. Comprehensive molecular portraits of human breast tumours [J]. Nature, 2012, 490(7418): 61-70.

[10] Dieci MV, Conte P, Bisagni G, et al. Association of tumor-infiltrating lymphocytes with distant disease-free survival in the ShortHER randomized adjuvant trial for patients with early HER2+ breast cancer [J]. Ann Oncol, 2019, 30(3): 418-423.

[11] Barroso-Sousa R, Barry WT, Guo H, et al. The immune profile of small HER2-positive breast cancers: a secondary analysis from the APT trial [J]. Ann Oncol, 2019, 30(4): 575-581.

[12] Guarneri V, Dieci MV, Bisagni G, et al. PIK3CA mutation in the ShortHER Randomized Adjuvant Trial for Patients with Early HER2(+) Breast Cancer: Association with Prognosis and integration with PAM50 subtype [J]. Clin Cancer Res, 2020, 26(22): 5843-5851.

[13] Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis [J]. Lancet, 2014, 384: 164-172.

[14] Cortes J, Saura C, Bellet M, et al. HER2 and hormone receptor-positive breast cancer--blocking the right target [J]. Nat Rev Clin Onco, 2011, 8(5): 307-311.

[15] Konecny G, Pauletti G, Pegram M, et al. Quantitative association between HER-2/neu and steroid hormone

receptors in hormone receptor-positive primary breast cancer [J]. J Natl Cancer Inst, 2003, 95(2): 142-153.

[16] Montemurro F, Di Cosimo S, Arpino G. Human epidermal growth factor receptor (HER2)-positive and hormone receptor-positive breast cancer: new insights into molecular interactions and clinical implications [J]. Ann Oncol, 2013, 24(11): 2715-2724.

[17] Shou J, Massarweh S, Osborne CK, et al. Mechanisms of tamoxifen resistance: increased estrogen receptor-HER2/neu cross-talk in ER/HER2-positive breast cancer [J]. J Natl Cancer Inst, 2004, 96(12): 926-935.

[18] Ropero S, Menéndez JA, Vázquez-Martín A, et al. Trastuzumab plus tamoxifen: anti-proliferative and molecular interactions in breast carcinoma [J]. Breast Cancer Res Treat, 2004, 86(2): 125-137.

[19] Arpino G, Gutierrez C, Weiss H, et al. Treatment of human epidermal growth factor receptor 2-overexpressing breast cancer xenografts with multiagent HER-targeted therapy [J]. J Natl Cancer Inst, 2007, 99: 694-705.

[20] Osborne CK, Schiff R. Mechanisms of endocrine resistance in breast cancer [J]. Annu Rev Med, 2011, 62: 233-247.

[21] Giuliano M, Hu H, Wang YC, et al. Upregulation of ER signaling as an adaptive mechanism of cell survival in HER2-Positive breast tumors treated with anti-her2 therapy [J]. Clin Cancer Res, 2015, 21: 3995-4003.

[22] Nahta R, O'Regan RM. Therapeutic implications of estrogen receptor signaling in HER2-positive breast cancers [J]. Breast Cancer Res Treat, 2012, 135(1): 39-48.

[23] Liu L, Greger J, Shi H, et al. Novel mechanism of lapatinib resistance in HER2-positive breast tumor cells: activation of AXL [J]. Cancer Res, 2009, 69(17): 6871-6878.

[24] Rimawi MF, Wiechmann LS, Wang YC, et al. Reduced dose and intermittent treatment with lapatinib and trastuzumab for potent blockade of the HER pathway in HER-2/neu overexpressing breast tumor xenografts [J]. Clin Cancer Res, 2011, 17(6): 1351-1361.

[25] Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial [J]. Lancet Oncol, 2012, 13(1): 25-32.

[26] Baselga J, Bradbury I, Eidtmann H, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial [J]. Lancet, 2012, 379(9816): 633-640.

[27] de Azambuja E, Holmes AP, Piccart-Gebhart M, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response [J]. Lancet Oncol, 2014, 15(10): 1137-1146.

[28] Carey LA, Berry DA, Cirrincione CT, et al. Molecular heterogeneity and response to neoadjuvant human epidermal growth factor receptor 2 targeting in CALGB 40601, a randomized phase III trial of paclitaxel plus trastuzumab with or without lapatinib [J]. J Clin Oncol, 2016, 34(6): 542-549.

[29] Guarneri V, Dieci MV, Frassoldati A, et al. Prospective biomarker analysis of the randomized CHER-LOB Study Evaluating the Dual Anti-HER2 treatment with trastuzumab and lapatinib plus chemotherapy as neoadjuvant therapy for HER2-positive breast cancer [J]. Oncologist, 2015, 20(9): 1001-1110.

[30] Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA) [J]. Ann Oncol, 2013, 24(9): 2278-2284.

[31] Robidoux A, Tang G, Rastogi P, et al. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomised phase 3 trial [J]. Lancet Oncol, 2013, 14(12): 1183-1192.

[32] Mette S van Ramshorst, Anna van der Voort, Erik D van Werkhoven, et al. Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial [J]. Lancet Oncol, 2018, 19(12): 1630-1640.

[33] Rimawi MF, Niravath P, Wang T, et al. TBCRC023: A

randomized phase ii neoadjuvant trial of lapatinib plus trastuzumab without chemotherapy for 12 versus 24 weeks in patients with HER2-positive breast cancer [J]. Clin Cancer Res, 2020, 26(4): 821-827.

[34] Veeraraghavan J, De Angelis C, Mao R, et al. A combinatorial biomarker predicts pathologic complete response to neoadjuvant lapatinib and trastuzumab without chemotherapy in patients with HER2+ breast cancer [J]. Ann Oncol, 2019, 30(6): 927-933.

[35] Nitz UA, Gluz O, Christgen M, et al. De-escalation strategies in HER2-positive early breast cancer (EBC): final analysis of the WSG-ADAPT HER2+/HR- phase II trial: efficacy, safety, and predictive markers for 12 weeks of neoadjuvant dual blockade with trastuzumab and pertuzumab +/- weekly paclitaxel [J]. Ann Oncol, 2017, 28(11): 2768-2772.

[36] Harbeck N, Nitz UA, Christgen M, et al. De-escalated neoadjuvant trastuzumab-emtansine with or without endocrine therapy versus trastuzumab with endocrine therapy in HR+/HER2+ early breast cancer: 5-year survival in the wsg-adapt-tp trial [J]. J Clin Oncol, 2023, JCO2201816. doi: 10.1200/JCO.22.01816

[37] Guarneri V, Dieci MV, Bisagni G, et al. De-escalated therapy for HR+/HER2+ breast cancer patients with Ki67 response after 2-week letrozole: results of the PerELISA neoadjuvant study [J]. Ann Oncol, 2019, 30 (6): 921-926.

[38] Gianni L, Colleoni M, Bisagni G, et al. Effects of neoadjuvant trastuzumab, pertuzumab and palbociclib on Ki67 in HER2 and ER-positive breast cancer [J]. NPJ Breast Cancer, 2022, 8(1): 1.

[39] Gianni L, Bisagni G, Colleoni M, et al. Neoadjuvant treatment with trastuzumab and pertuzumab plus palbociclib and fulvestrant in HER2-positive, ER-positive breast cancer (NA-PHER2): an exploratory, open-label, phase 2 study [J]. Lancet Oncol, 2018, 19(2): 249-256.

[40] https://clinicaltrials. gov / ct2 / show / NCT03644186?term=TOUCH&cond=Breast+Cancer&draw=2&rank=1

[41] Chan A, Moy B, Mansi J, et al. Final efficacy results of neratinib in HER2-positive hormone Receptor-positive early-stage breast cancer from the Phase III ExteNET trial [J]. Clin Breast Cancer, 2021, 21(1): 80-91 e87.

[42] von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer [J]. N Engl J Med, 2019, 380: 617-628.

[43] Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer [J]. N Engl J Med, 2012, 366(2): 109-119.

[44] Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer [J]. N Engl J Med, 2015, 372(8): 724-734.

[45] Swain SM, Miles D, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study [J]. Lancet Oncol, 2020, 21(4): 519-530.

[46] Véronique Diéras, David Miles, Sunil Verma, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial [J]. Lancet Oncol, 2017, 18(6): 732-742.

[47] Cortés J, Kim SB, Chung WP, et al. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer [J]. N Engl J Med, 2022, 386(12): 1143-1154.

[48] Curigliano G, Mueller V, Borges V, et al. Tucatinib versus placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB): final overall survival analysis [J]. Ann Oncol, 2022, 33(3): 321-329.

[49] Saura C, Oliveira M, Feng YH, et al. Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-Positive metastatic breast cancer previously treated with >/= 2 HER2-directed regimens: Phase III NALA trial [J]. J Clin Oncol, 2020, 38(27): 3138-3149.

[50] Rugo HS, Im SA, Cardoso F, et al. Efficacy of margetuximab vs trastuzumab in patients with pretreated ERBB2-positive advanced breast cancer: A Phase 3 randomized clinical trial [J]. JAMA Oncol, 2021, 7(4): 573-584.

[51] Emens LA, Esteva FJ, Beresford M, et al. Trastuzumab emtansine plus atezolizumab versus trastuzumab emtansine plus placebo in previously treated, HER2-positive advanced breast cancer (KATE2): a phase 2, multi-

centre, randomised, double-blind trial [J]. Lancet Oncol, 2020, 21(10): 1283-1295.

[52] Kaufman B, Mackey JR, Clemens MR, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study [J]. J Clin Oncol, 2009, 27(33): 5529-5537.

[53] Johnston S, Pippen J, Jr Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer [J]. J Clin Oncol, 2009, 27(33): 5538-5546.

[54] Huober J, Fasching PA, Barsoum M, et al. Higher efficacy of letrozole in combination with trastuzumab compared to letrozole monotherapy as first-line treatment in patients with HER2-positive, hormone-receptor-positive metastatic breast cancer - results of the eLEcTRA trial [J]. Breast, 2012, 21(1): 27-33.

[55] Rimawi M, Ferrero JM, de la Haba-Rodriguez J, et al. First-line trastuzumab plus an aromatase inhibitor, with or without pertuzumab, in human epidermal growth factor receptor 2-positive and hormone receptor-positive metastatic or locally advanced breast cancer (PERTAIN): A randomized, open-label phase II trial [J]. J Clin Oncol, 2018, 36(28): 2826-2835.

[56] Johnston SRD, Hegg R, Im SA, et al. Phase III, randomized study of dual human epidermal growth factor receptor 2 (HER2) blockade with lapatinib plus trastuzumab in combination with an aromatase inhibitor in postmenopausal women with her2-positive, hormone receptor-positive metastatic breast cancer: Updated results of ALTERNATIVE [J]. J Clin Oncol, 2021, 39(1): 79-89.

[57] Ozaki Y, Aoyama Y, Masuda J, et al. Trastuzumab and fulvestrant combination therapy for women with advanced breast cancer positive for hormone receptor and human epidermal growth factor receptor 2: a retrospective single-center study [J]. BMC Cancer, 2022, 22(1): 36.

[58] Loft M, Lok SW, Boer RD, et al. Addition of endocrine therapy to dual anti-HER2 targeted therapy in initial treatment of HER2 + /HR + metastatic breast cancer [J]. Breast Cancer Res Treat, 2023, 198(1): 67-74.

[59] Hua X, Bi XW, Zhao JL, et al. Trastuzumab plus endocrine therapy or chemotherapy as first-line treatment for patients with hormone receptor-positive and HER2-Positive metastatic breast cancer (SYSUCC-002) [J]. Clin Cancer Res, 2022, 28(4): 637-645.

[60] Spring LM, Wander SA, Andre F, et al. Cyclin-dependent kinase 4 and 6 inhibitors for hormone receptor-positive breast cancer: past, present, and future [J]. Lancet, 2020, 395(10226): 817-827.

[61] Tolaney SM, Wardley AM, Zambelli S, et al. Abemaciclib plus trastuzumab with or without fulvestrant versus trastuzumab plus standard-of-care chemotherapy in women with hormone receptor-positive, HER2-positive advanced breast cancer (monarcHER): a randomised, open-label, phase 2 trial [J]. Lancet Oncol, 2020, 21(6): 763-775.

[62] Ciruelos E, Villagrasa P, Pascual T, et al. Palbociclib and trastuzumab in HER2-positive advanced breast cancer: Results from the phase II SOLTI-1303 PATRICIA trial [J]. Clin Cancer Res, 2020, 26(22): 5820-5829.

[63] Zhang J, Meng Y, Wang B, et al. Dalpiciclib combined with pyrotinib and letrozole in women with HER2-positive, hormone receptor-positive metastatic breast cancer (LORDSHIPS): A phase Ib study [J]. Front Oncol, 2022, 12: 775081.

[64] Shagisultanova E GW, Brown-Glaberman U, et al. Abstract PS10-03: Interim safety and efficacy analysis of Phase IB/II clinical trial of tucatinib, palbociclib and letrozole in patients with hormone receptor and HER2-positive metastatic breast cancer [J]. Cancer Res, 2021, 81(84 Supplement): PS10-03-PS10-03.

[65] Schramm A, Friedl TW, Schochter F, et al. Therapeutic intervention based on circulating tumor cell phenotype in metastatic breast cancer: Concept of the DETECT study program [J]. Arch Gynecol Obstet, 2016, 293(2): 271-281.

[66] Metzger O, Mandrekar S, Loibl S, et al. Abstract OT3-02-07: PATINA: A randomized, open label, phase III trial to evaluate the efficacy and safety of palbociclib + anti-HER2 therapy + endocrine therapy (ET) vs. anti-HER2 therapy + ET after induction treatment for hormone receptor positive (HR +)/HER2-positive metastatic breast cancer (MBC) [J]. Cancer Res, 2019, 79 (4_Supplement): OT3-02-07-OT03-02-07.

[67] Andre F, Hurvitz S, Fasolo A, et al. Molecular alterations and everolimus efficacy in human epidermal growth factor receptor 2-overexpressing metastatic breast cancers: combined exploratory biomarker analysis from BOLERO-1 and BOLERO-3 [J]. J Clin Oncol, 2016, 34(18): 2115-2124.
[68] Loibl S, de la Pena L, Nekljudova V, et al. Neoadjuvant buparlisib plus trastuzumab and paclitaxel for women with HER2 + primary breast cancer: A randomised, double-blind, placebo-controlled phase II trial (NeoPHOEBE) [J]. Eur J Cancer, 2017, 85: 133-145.
[69] Llombart-Cussac A, Cortes J, Pare L, et al. HER2-enriched subtype as a predictor of pathological complete response following trastuzumab and lapatinib without chemotherapy in early-stage HER2-positive breast cancer (PAMELA): An open-label, single-group, multicentre, phase 2 trial [J]. Lancet Oncol, 2017, 18 (4): 545-554.
[70] Wolf DM, Yau C, Wulfkuhle J, et al. Redefining breast cancer subtypes to guide treatment prioritization and maximize response: Predictive biomarkers across 10 cancer therapies [J]. Cancer Cell, 2022, 40(6): 609-623 e606.
[71] Prat A, Guarneri V, Pascual T, et al. Development and validation of the new HER2DX assay for predicting pathological response and survival outcome in early-stage HER2-positive breast cancer [J]. EBioMedicine, 2022, 75: 103801.
[72] Fernandez-Martinez A, Pascual T, Singh B, et al. Prognostic and predictive value of immune-related gene expression signatures vs tumor-infiltrating lymphocytes in early-stage ERBB2/HER2-Positive breast cancer: A correlative analysis of the CALGB 40601 and PAMELA trials [J]. JAMA Oncol, 2023, 9(4): 490-499.

Treatment progress of triple positive breast cancer

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ABSTRACT Triple positive breast cancer overexpress ER (estrogen receptor), PR and HER2 (human epidermal growth factor receptor 2, HER2), accounting for about 50%-60% of the HER2 positive breast cancer patients. Based on the data from clinical trials, the crosstalk between the ER signaling pathway and the HER2 signaling pathway in triple-positive breast cancer may weaken the efficacy of anti-HER2 therapy and endocrine therapy, and this feature has attracted widespread attention. Emerging evidence shows that while blocking HER2 signaling pathway, together with enhancing blocking of ER signaling pathway, such as anti-HER2 dual-targeting + endocrine therapy ± CDK4 / 6 inhibitors, could effectively overcome drug resistance, and improve the efficacy. Predictive biomarkers including Ki67, intrinsic subtypes, and multi-gene assay, which have the potential benefit for personalized treatment.

KEYWORDS triple positive breast cancer; crosstalk; treatment strategy; biomarkers