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TOPIC HIGHLIGHT

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Therapeutic options for HER-2 positive breast cancer: Perspectives and future directions

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Abstract

During the last 15 years we have witnessed an unprecedented expansion in the drugs developed to target human epidermal growth factor receptor-2 (HER-2) positive breast cancer. Trastuzumab, pertuzumab, adotrastuzumab emtansine and lapatinib are currently food and drug administration (FDA)-approved for the treatment of breast cancer patients with HER-2 overexpressed. However, given the amount of information gathered from years of uninterrupted clinical research, it is essential to have periodic updates that succinctly recapitulate what we have learnt over these last years and help us to apply that information in our daily practice. This review will pursue that objective. We will summarize the most relevant and updated information related to the state of the art management of HER-2 positive breast cancer in all the clinical scenarios including the adjuvant, neoadjuvant and metastatic settings. But we will also critically appraise that literature in order to highlight some key clinical concepts that should not be overlooked. Lastly, this review will also point out some of the most promising strategies that are currently being tested and may soon become available.

Key words: Breast cancer; Human epidermal growth factor receptor-2; Trastuzumab; Pertuzumab; Adotrastuzumab; Lapatinib

Core tip: This is a review manuscript with the most updated information regarding the state of the art management of human epidermal growth factor receptor-2 positive breast cancer. It summarizes the most relevant and updated information derived from more than 40 phase Ⅱ and Ⅲ clinical trials that constitute the theoretical framework to support our daily practice. It also highlights some key clinical concepts that should not be overlooked by critically appraising the current literature. Finally, it gives the reader with a compilation of potential new agents that are currently being tested and may soon become the next step in the battle against this disease.

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INTRODUCTION

Breast cancer is the most prevalent cancer in women, representing approximately 25% of all new cancers worldwide and accounting for one sixth of the total cancer-related deaths[1]. Human epidermal growth factor receptor-2 (HER-2) positive breast cancer represents a special subtype that has clear epidemiological, clinical, molecular and prognostic differences that make it a separate entity with recognized worse prognosis and poor response to conventional chemotherapy agents alone.

The epidermal growth factor receptor (EGFR) family is composed by four different receptors: EGFR (ErbB1/HER-1), ErbB2 (HER-2/Neu), ErbB3 (HER-3) and ERbB4 (HER-4)[2]. These membrane receptors have an intracellular domain with tyrosine kinase activity. Following the union of its ligands, ErbB receptors are activated by dimerization which can happen between identical or different type of receptors, a process named homo- and hetero-dimerization, respectively[3]. Following dimerization, multiple tyrosine residues located in the membrane receptors become phosphorylated, ultimately leading to activation of downstream signaling pathways. EGFR activation has been linked to the regulation of key processes involved in tumor growth, proliferation, differentiation, adhesion, motility and migration. Multiple intracellular substrates participate in essential pathways such as Ras, Raf, mitogen-activated protein kinase (MAPK) and PI3K/AKT[4-6]. To understand the role of HER-2 in breast cancer, it is important to highlight that this is a ligand-free receptor. HER-2 is always present in an active configuration and prepared to dimerize with any other family member. In breast cancer cells, HER-2 and EGFR are frequently over-expressed, conferring an aggressive tumor behavior and consequently, increased mortality in this population[7]. HER-2 can be amplified in 20%-25% of breast cancers and is associated with adverse prognostic outcomes in early and advanced disease. The study of HER-2 and its intracellular and extracellular domains has led us into a deeper understating of the tumor biology and helped to develop pharmacological agents able to block this pathway.

Trastuzumab (Herceptin®, Genentech, United States/Hoffman-Roche, Switzerland) was the first monoclonal antibody approved for breast cancer treatment directed against HER-2. It binds to HER-2 in its extracellular domain. Pertuzumab (Perjeta®, Genentech, United States/Hoffman-Roche, Switzerland) is a humanized recombinant monoclonal antibody that binds HER-2 at a different extracellular domain than trastuzumab. Trastuzumab blocks homo-dimerization but cannot inhibit hetero-dimerization. Pertuzumab prevents also hetero-dimerization, resulting in more potent growth inhibition[8]. Ado-trastuzumab emtansine (Kadcyla®, Genentech, United States/Hoffman-Roche, Switzerland) is a conjugation of trastuzumab with a potent microtubule inhibitor agent, derivative of maytansine (DM-1)[9]. This molecule has 3 properties, anti-HER-2 inhibition by trastuzumab, cytotoxic effect by DM-1 and certain level of tissue specificity by directing the cytotoxic agent only to those cells that express HER-2. It has recently being approved for refractory metastatic disease. Lapatinib (Tykerb TM, GlaxoSmithKline, Research Triangle, NC, United States) is the only intracellular blocker approved. It is a dual reversible tyrosine kinase inhibitor of HER-2 and EGFR. It acts on both receptors simultaneously, achieving greater inhibitory effects[10].

Given the enormous amount of information accumulated from almost 20 years of continuous basic and clinical research, it is important to have periodic updates in this topic that can succinctly recapitulate what we have learnt over the last years and help us to apply that information in our daily practice. This review will pursue that objective and also will allow the reader to envision some of the promising agents that may soon become part of our armament against this disease.

STATE OF THE ART ANTI-HER-2 THERAPY

In this section we will summarize all those relevant clinical trials that constitute the theoretical framework to support our daily practice. For practical reasons we will subdivide this section according to the clinical setting: adjuvant, neoadjuvant and metastatic disease. Also, given the breadth of this topic we will mainly focus only on phase Ⅲ and some phase Ⅱ clinical trials. Tables 1-3 recap the most important published clinical trials.

Adjuvant treatment

In the adjuvant scenario, treatment with trastuzumab is the standard of care for patients with HER-2 over-expressing breast cancer. Trastuzumab can be administered in combination with paclitaxel or docetaxel following an anthracycline-based chemotherapy (*i.e.*, doxorubicin and cyclophosphamide) or be given concurrently with carboplatin and docetaxel. Several phase Ⅲ trials have consistently validated trastuzumab as the cornerstone of adjuvant chemotherapy. The question of the optimal therapy duration has been addressed and even though the answer is still pending, the actual evidence suggests that treatment for one year is probably the most appropriate. Cardiac toxicity is a major concern since anti-HER-2 therapy can result in decreased left ventricular ejection fraction (LVEF) and symptomatic heart failure. However, this is usually reversible after treatment discontinuation.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 and the North Central Cancer Treatment Group (NCCTG) N9831 were two pivotal studies[11]. The NSABP B-31 compared four cycles of doxorubicin and cyclophosphamide (AC) followed by four cycles of paclitaxel every three weeks to the same regimen plus trastuzumab given for 52 wk starting concurrently with paclitaxel. The NCCTG N9831 randomized patients to receive four cycles of AC followed by weekly paclitaxel for 12 cycles with or without trastuzumab, administered concurrently or sequentially

Table 1 Selected clinical trials in the adjuvant setting for human epidermal growth factor receptor-2 positive breast cancer

Drug or study name	Population included	No. of patients	Comparison	Median follow-up	DFS	OS	CHF/ Drop LVEF	Ref.
Trastuzumab (H)								
NCCTG N9831	LN (+) or	1087	AC → T *vs*		71.8% (5-yr)	88.4% (5-yr)	0%/0%	Perez *et al*[14]
	high risk LN (-)	949	AC → T → H (52 wk) *vs* AC	72 mo	80.1% (5-yr)	89.7% (5-yr)	2.2%/7%	
		954	→ TH (H then 40 wk)		84.4% (5-yr)	91.9% (5-yr)	1.5%/3.6%	
HERA	LN (+) or	1552	Std QT → H (52 wk) *vs*	96 mo	75.9% (5-yr)	86.9% (5-yr)	1%/7.2%	Goldhirsch *et al*[16]
	high risk LN (-)	1553	Std QT → H (104 wk) *vs*		76.5% (5-yr)	88.7% (5-yr)	0.8%/4.1%	
		1697	Std QT → Observation		70.0% (5-yr)	84.5% (5-yr)	0.1%/0.9%	
FINHER	LN (+) or	58	Docetaxel → FEC *vs*	62 mo	74.1% (5-yr)	82.0% (5-yr)	1.7%/10.5%	Joensuu *et al*[18]
	high risk LN (-)	58	Vinorelbine → FEC *vs*		72.0% (5-yr)	82.8% (5-yr)	(QT only)	
		54	Docetaxel + H → FEC *vs*		92.5% (5-yr)	94.4% (5-yr)	0.9%/6.8%	
		61	Vinorelbine + H → FEC		75.2% (5-yr)	88.4% (5-yr)	(QT + H)	
BCIRG 006	LN (+) or	1073	AC → Docetaxel *vs*	65 mo	75% (5-yr)	87% (5-yr)	0.7%/11.2%	Slamon *et al*[19]
	high risk LN (-)	1074	AC → Docetaxel + H *vs*		84% (5-yr)	92% (5-yr)	2.0%/18.6%	
		1075	TCH		81% (5-yr)	91% (5-yr)	0.4%/9.4%	
PACS 04	LN (+)	260	FE100C or ED75 → Obser *vs*	62 mo	77.9% (3-yr)	96% (3-yr)	0.3%/14.2%	Spielmann *et al*[20]
		268	FE100C or ED75 → H		80.9% (3-yr)	95% (3-yr)	1.5%/35.4%	
PHARE	HER-2 (+) early breast cancer	1690	Std QT → H (26 wk) *vs*	42.5 mo	91.1% (2-yr)	96.1% (2-yr)	5.7% (both)	Pivot *et al*[21]
		1690	Std QT → H (52 wk)		93.8% (2-yr)	94.5% (2-yr)	1.9% (both)	
Lapatinib (L)								
TEACH	Stage Ⅰ-Ⅲc - H naïve	1230 (HER-2 +)	Std QT → L (52 wk) *vs*	47.4 mo	87% (4-yr)	94% (4-yr)	3.0% (both)	Goss *et al*[22]
		1260 (HER-2 +)	Std QT → Observation	48.3 mo	83% (4-yr)	94% (4-yr	3.0% (both)	

LN: Lymph nodes; AC → T: Adriamycin cyclophosphamide paclitaxel; FEC: 5-FU epirubicin cyclophosphamide; ED: Epirubicin docetaxel; Std QT: Standard chemotherapy; OS: Overall survival; DFS: Disease free survival; CHF: Cardiac heart failure; LVEF: Left ventricular ejection fraction.

Table 2 Selected clinical trials in the neo-adjuvant setting for human epidermal growth factor receptor-2 positive breast cancer

Study	Neo-adjuvant chemotherapy	No. of patients	Pathological complete response (%)	Comments	Ref.
Trastuzumab (H)					
MD Anderson Group	T → FEC *vs* T → FEC + H	19 *vs* 23	26% (95%CI: 9%-51%) *vs* 65% (95%CI: 43%-84%)	Probably the first study to emphasize better pCR with H	Buzdar *et al*[24]
The NOAH Trial	A + T → T → CMF *vs* A + T → T → CMF + H	117 HER-2 (+) *vs* 118 HER-2 (+)	22% (95%CI: not reported) *vs* 43% (95%CI: not reported)	Not originally designed to test the effects of neoadjuvance	Gianni *et al*[26]
The TECHNO Trial	EC → TH	217	38.7% (95%CI: 32%-45%)	Suggest pCR correlate with DFS	Untch *et al*[27]
The Z1041 Trial	FEC → TH *vs* T + H → FEC + H	138 *vs* 142	56.5% (95%CI: 48%-65%) *vs* 54.2% (95%CI: 46%-62%)	Concurrent use of H with anthracyclines is not better	Buzdar *et al*[28]
The HannaH Trial	Doc + H (SQ) → FEC + H *vs* Doc + H (IV) → FEC + H	260 *vs* 263	45.4% (95%CI: 39%-52%) *vs* 40.7% (95%CI: 35%-47%)	H can be administered subcutaneously	Ismael *et al*[30]
Lapatinib(L) +/- (H)					
The GeparQuinto Trial	ECH → TH *vs* ECL → TL	309 *vs* 311	30.3% (95%CI: 25%-36%) *vs* 22.7% (95%CI: 18%-28%)	Lapatinib is less effective that H	Untch *et al*[31]
The NeoALLTO Trial	TH *vs* TL *vs* THL	149 *vs* 154 *vs* 152	29.5% (22%–37%) *vs* 24.7% (22% -37%) *vs* 51.3% (43%-59%)	Suggested that combination H + L could be quite effective	Baselga *et al*[32]
The NSABP B-41 Trial	AC → TH or TL or THL	181 *vs* 174 *vs* 174	52.5% (50%-59.5%) *vs* 53.2% (45%-60%) *vs* 62.0% (54%-69%)	H + L no better. All patients received anthracyclines	Robidoux *et al*[33]
Pertuzumab (P)					
The NeoSphere Trial	Do + H *vs* Do + P + H *vs* Do + P *vs* P + H	107 *vs* 107 *vs* 107 *vs* 96	29.0% (21%-38.5%) *vs* 45.8% (36%-56%) *vs* 24.0% (16%-34%) *vs* 16.8% (10%-25%).	Combination P + H result in better pCR.	Gianni *et al*[34]
The Tryphaena Trial (Abstract Only)	FEC + HP → Do + HP *vs* FEC → Do + HP *vs* TCHP	223 patients in total	62% *vs* 57% *vs* 66%	TCH + P is an active combination	N/A

T: Paclitaxel; F: 5-FU; E: Epirubicin; C: Cyclophosphamide; A: Adriamycin; M; Methotrexate; Do: Docetaxel; TC: Docetaxel carboplatin.

Table 3 Selected clinical trials in metastatic human epidermal growth factor receptor-2 positive breast cancer

Drug or study name	Population included	No. of patients	Comparison	Median OS (mo)	Median TTP (mo)	ORR	1-yr Survival	Ref.
Single agents								
Trastuzumab (H)	Phase Ⅱ, first line, MBC	114	None-2 doses of H used	24.4	3.8	26% (18%-34%)	N/A (approximately 65%)	Vogel *et al*[45]
Ado-trastuzumab	Phase Ⅱ, refractory MBC	110	None	N/A	6.9 (4.2–8.4)	34% (26%-44%)	N/A	Krop *et al*[48]
Anti-HER-2 + QT								
H + Paclitaxel (T)	Phase Ⅲ, first line, MBC	469	QT (AC or T) + H *vs* QT	25.1 *vs* 20.3	7.4 *vs* 4.6	50% *vs* 32%	78% *vs* 67%	Slamon *et al*[44]
Cont. Anti-HER-2 after failing 1st line								
Lapatinib (L)	Phase Ⅲ, failed to H	324	Cape + L *vs* Cape alone	N/A	8.4 *vs* 4.4	22% *vs* 14%	N/A (approximately 60%)	Geyer *et al*[54]
EMILIA Trial (Ado-trastuzumab)	Phase Ⅲ, MBC who failed TH	991	Ado-T *vs* Cape + L	30.9 *vs* 25.1	9.6 *vs* 6.4	43.6% *vs* 30.8%	85% *vs* 78%	Verma *et al*[55]
Dual Anti-HER-2								
CLEOPATRA	Phase Ⅲ, first line, MBC	808	Do + H + P *vs* Do + H	Not reached	18.5 *vs* 12.4	80% *vs* 69%	N/A (approximately 90%-95%)	Baselga *et al*[57]
Lap + Trastuzumab	Phase Ⅲ, failed to H	296	L + H *vs* L alone	11.8 *vs* 8.9	2.75 *vs* 1.85	10% *vs* 7%	70% *vs* 36%	Blackwell *et al*[59]
H + Pertuzumab (P)	Phase Ⅱ, failed to H	66	None-H + P single arm	N/A	5.5	24.20%	N/A	Baselga *et al*[61]
Anti-HER-2 + AI								
Anastrozole + H	Phase Ⅲ, HR and HER-2 positive, 1st line in MBC	207	Anastrozole + H *vs* Anastrozole alone	28.5 *vs* 23.9	4.8 *vs* 2.4	20% *vs* 6.8%	N/A (approximately 78%)	Kaufman *et al*[63]
Letrozole + L	Same	219	Letrozole + L *vs* Letrozole alone	33.3 *vs* 32.3	8.2 *vs* 3.0	28% *vs* 15%	N/A	Johnston *et al*[64]

QT: Chemotherapy; AI: Aromatase Inhibitor; MBC: Metastatic breast cancer; HR: Hormones receptor; Do: Docetaxel; AC: Adriamycin cyclophosphamide; T: Paclitaxel; OS: Overall survival; TTP: Time to progression; N/A: Not available or not reported.

to paclitaxel, for 52 wk. A joint analysis of these clinical trials was first presented in 2005. Initially both trials were designed to include patients with node positive breast cancer. But later on, the NCCTG trial included patients with high-risk node negative disease defined as tumors ⩾ 2 cm and positive for hormone receptors or tumors larger than 1 cm with negative hormone receptors. The primary endpoint of these trials was disease-free survival (DFS) and overall survival (OS) was part of the secondary endpoints. On the initial report with a median follow-up of two years the hazard ratio (HR) for DFS was 0.48 (95%CI: 0.39 to 0.59; $P < 0.001$). At four years, 85.3% of patients treated with trastuzumab were alive and free of disease compared to only 67.1% in the control group. Mortality was reduced by 33%. Updated results were consistent with previous observations[12]. The final analysis of these studies was presented at the 2012 San Antonio Breast Cancer Symposium (SABCS) and reported a 10-year DFS of 73.7% *vs* 62.2% ($P < 0.001$) and a OS of 84% *vs* 75.2% ($P < 0.001$) all favoring trastuzumab[13]. Overall, treatment with trastuzumab resulted in a 40% risk reduction benefit in terms of 10-year DFS and 37% in OS. The NCCTG trial compared, as well, the efficacy of concurrent *vs* sequential administration of trastuzumab, showing a trend toward improvement in DFS in the concurrent arm[14]. However, sequential was still better than placebo ($P < 0.001$).

Published simultaneously, the Herceptin Adjuvant Trial (HERA), a randomized phase Ⅲ trial designed to compare adjuvant treatment with trastuzumab for one or two years *vs* observation reported similar results. At the first interim analysis DFS was superior in the trastuzumab treated population[15]. An absolute 8% difference between arms in DFS events was achieved ($P < 0.001$). Unlike other studies, patients included in this trial had already undergone adjuvant (90%) or neoadjuvant treatment and could have nodal involvement. Following the interim analysis, 52% of patients in the observation arm crossed over to trastuzumab before an event had occurred[16]. At a median follow-up of 8 years, the HRs for DFS and OS in the trastuzumab arm compared to observation were 0.76 for both oucomes. Importantly, given the persistent benefits in terms of DFS and OS found even after a mean time from randomization to crossover of 22.7 mo, in clinical practice trastuzumab must be used even in delayed scenarios. This study also proved that 2-year adds no benefit to 1-year of treatment, but adds a slight increment in cardiologic adverse events.

The Finland Herceptin (FinHer) trial aimed to determine the role of vinorelbine compared to docetaxel in the adjuvant setting in patients with node positive and high risk node negative breast cancer[17]. A total of 1010

patients were randomized to treatment with vinorelbine or docetaxel for 3 cycles followed by three cycles of 5-FU, epirubicin and cyclophosphamide. A group of 232 patients with HER-2 amplified tumors were again randomized to receive nine weekly cycles of trastuzumab concurrently with docetaxel or vinorelbine. The primary end point was distant DFS and with a median follow-up of 5 years, it favored treatment with docetaxel over vinorelbine (P = 0.010)[18]. OS also tended to be better in patients treated with docetaxel compared to vinorelbine (39 *vs* 55 death, respectively; P = 0.086). In HER-2 positive patients, trastuzumab arms had favorable recurrence free survival irrespectively of the chemotherapy used (80% *vs* 73%; P = 0.12). This benefit was maintained when adjusted for nodal involvement and in patients treated with docetaxel over vinorelbine. The main limitation of this trial is the small number of patients with HER-2 positive tumors included, undermining the study power to detect a statistically significant benefit with trastuzumab. Also, even though the results suggested a benefit in patients treated with trastuzumab in combination with chemotherapy, the short course of treatment might have underestimated the real efficacy of the drug in this population.

Cardiotoxicity is the most important adverse effect derived from treatment with trastuzumab, which is worse when combined with anthracyclines. Therefore, there has been a special interest in studying anthracycline-free regimens in order to avoid synergistic deleterious cardiac toxicities. The BCIRG 006 study was designed to provide information on this matter[19]. This phase Ⅲ clinical trial randomized 3222 patients with HER-2 positive and node positive or high-risk node negative tumors to treatment with doxorubicin, cyclophosphamide and docetaxel (AC→T), the same regimen plus trastuzumab (AC→TH) or docetaxel, carboplatin and trastuzumab (TCH). The primary end-point was DFS and secondary end-points were OS, safety and cardiac toxicity. With a median follow-up of 65 mo, 5-year DFS was 84% (P < 0.001) in the ACTH arm, 81% (P = 0.04) in the TCH arm and 75% in the ACT arm (control). OS was also improved with trastuzumab (92% with ACTH, 91% with TCH and 87% in the ACT; P < 0.001 and 0.04, respectively). ACTH was slightly better than TCH, though this study was not designed to compare efficacy between these two regimens. The incidence of cardiac toxicity was five times more with ACTH (2%) compared with TCH (0.4%). Reductions in LVEF, over 10% from basal measurements, were more frequently associated with ACTH than with TCH (18.6 *vs* 9.4%; P < 0.001). As well, the rate of symptomatic congestive heart failure favored treatment with TCH (P < 0.001). According to these results, anthracycline-free chemotherapy is efficient and is a valid treatment option in patients at high risk of cardiac toxicity. Although the combination of doxorubicin and trastuzumab resulted in better DFS and OS, the difference seemed to be insignificant. To confirm that one regimen is better than the other, further evidence is required.

The French PACS 04 was the only negative study reported[20]. A total of 3010 patients with early stage breast cancer were randomly assigned to adjuvant treatment with anthracycline-based chemotherapy with or without docetaxel. Patients with HER-2 over-amplified tumors (n = 528) were subsequently randomized to receive trastuzumab sequentially every 3 wk. The primary endpoint was DFS. Treatment with trastuzumab resulted in a non-significant 14% reduction in the risk of relapse (P = 0.41) and there was no difference in OS. However, 10% of the patients assigned to trastuzumab were never treated and 25% of patients discontinued before the 16th cycle. Also, sequential use seems to be inferior to concurrent.

Duration of adjuvant treatment in HER-2 positive breast cancer is a matter of current discussion. Based on the previously analyzed HERA trial, two years of treatment with trastuzumab is not superior to one year. There is a special interest in investigating whether treatment duration could be shortened. The PHARE trial is a non-inferiority study designed to answer this question. This study evaluated adjuvant treatment length with trastuzumab for 6 mo compared to one year[21]. A total of 1691 patients were treated with trastuzumab for 12 mo and 1693 for 6 mo after receiving at least 4 cycles of adjuvant chemotherapy. Patients were stratified according to sequential or concurrent treatment and ER status. The primary endpoint was DFS and with a median follow-up of 42.5 mo, 2-year DFS was 93.8% for the 12-mo group and 91.1% for the 6-mo group (HR = 1.28; 95%CI, 1.05-1.56), concluding that 6 mo of treatment did not reach the non-inferiority criteria. However, cardiac events were more common in the 12 mo treatment arm (5.7% *vs* 1.9%; P < 0.001). Two other ongoing phase Ⅲ trials, SHORT-HER (NCT00629278) and PERSEPHONE (NCT00712140), will contribute to clarify this issue. Nonetheless, on the basis of the current available evidence, 12 mo of adjuvant treatment with trastuzumab remains the standard of care.

Lapatinib is currently approved for metastatic disease but its use in the adjuvant setting could be interesting due to its oral bioavailability. The TEACH trial studied the efficacy of lapatinib in trastuzumab-naïve patients as adjuvant treatment[22]. A total of 3147 patients were randomized to 12 mo of treatment, or until progression, with lapatinib or placebo. DFS was non-significantly prolonged in patients treated with lapatinib (87% *vs* 83%; P = 0.09). In patients with centrally confirmed HER-2 status the HR was 0.92 (P = 0.94). In conclusion, single agent lapatinib seems to be quite ineffective in the adjuvant treatment. The ongoing ALTTO trial is evaluating the efficacy of lapatinib in combination with trastuzumab and lapatinib sequential to trastuzumab *vs* trastuzumab alone. A treatment arm with single agent lapatinib was prematurely closed by an independent data and safety committee (NCT00490139).

Neo-adjuvant treatment

The original rationale behind the use of neo-adjuvant chemotherapy was to attempt tumor volume reduction

whenever the tumor size precluded an optimal surgical resection. However, clinical researchers rapidly understood that pre-surgical chemotherapy could represent an excellent way to assess the real *in vivo* response of the tumor, a fact obviously impossible to achieve in the adjuvant setting. Moreover, it is at least theoretically feasible that the response obtained in the primary tumor could be a good surrogate to what happens with the invisible micrometastases. In that sense, if some cells remain viable in the primary site, then the chances of having resistant micrometastases are higher. On the contrary, complete pathological response (pCR) should correlate with fewer future relapses. This concept has been more strongly established in triple negative breast tumors and though quite appealing intellectually, there are some caveats in this assumption that requires further discussion (see later)[23].

Probably the first evidence addressing the role of anti-HER-2 therapies in the neo-adjuvant scenario came from a small randomized trial published by the MD Anderson group[24]. With only 42 patients randomized, the addition of trastuzumab to sequential paclitaxel followed by FEC (P x 4 → FEC x 4) resulted in an impressive 2.5 times higher rate of pCR than chemotherapy alone (66.7 *vs* 25%; $P = 0.02$). Given the small sample, the confidence intervals were wide and also no clinical endpoints were reported. An updated version of the study confirmed the findings[25]. The results of the NOAH trial, a randomized phase Ⅲ study, helped to give further enthusiasm to this approach[26]. The study was originally designed to compare neoadjuvant chemotherapy plus trastuzumab followed by 1-year trastuzumab to neoadjuvant chemotherapy alone in patients with locally advanced or inflammatory HER-2 positive tumors. But with the approval of trastuzumab all patients were allowed to receive this drug as adjuvant therapy. From 238 patients originally randomized to neoadjuvant treatment with or without trastuzumab, the addition of anti-HER-2 therapy improved the pCR from 22% to 43% ($P < 0.001$). Trastuzumab also resulted in a 40% risk reduction of recurrence, progression or death when compared to chemotherapy alone, but this was already known due to the adjuvant studies. Moreover, in 2011 German investigators published the results of an open label, phase Ⅱ study - TECHNO trial - where 217 patients with HER-2 positive and ⩾ 2 cm tumors received four cycles of epirubicin and cyclophosphamide, followed by four cycles of paclitaxel and trastuzumab before surgery[27]. Complete pathological response was achieved in 38.7% of the cases. However, the most relevant observation from this study was that pCR correlated with better 3-year DFS (88% *vs* 71%; $P = 0.003$) and 3-year OS (96% *vs* 85%; $P = 0.007$). Obviously, the small number of patients and the fact that this was a phase Ⅱ study limited the generalization of these findings but sparked the idea the pCR could correlate with harder clinical endpoints. Also, the American Z1041 trial randomized 282 women with similar inclusion criteria as the TECHNO study to receive trastuzumab and paclitaxel concurrently with FEC-75 or after this regimen[28]. Both arms showed a high proportion of pCR (54% and 56%) but the concurrent use of anthracyclines and trastuzumab resulted in a greater drop in the cardiac ejection fraction (2.9 % *vs* 0.8% at 12 wk, respectively). Lastly, similar rates of pCR were described in patients treated with chemotherapy and trastuzumab in the GeparQuattro study (32%) as well as in the HannaH trial (41% and 45% for intravenous *vs* subcutaneous trastuzumab, respectively)[29,30].

In an attempt to improve the efficacy of anti-HER-2 therapies, some researchers started exploring the use of lapatinib or its addition to trastuzumab. Recently, at least three randomized phase Ⅲ clinical trials were published testing that hypothesis. In the German GeparQuinto study, 620 patients received four cycles of epirubicin and cyclophosphamide (EC) followed by docetaxel and were randomized to have trastuzumab or lapatinib[31]. All patients received standard of care trastuzumab for 1-year after surgical resection. Primary outcome was pCR and trastuzumab showed approximately 7% more complete responses than lapatinib (30.3% *vs* 22.7%; $P = 0.04$). Given these results and the significant number of adverse events described in this study, it is unlikely that lapatinib could replace trastuzumab in the neoadjuvant setting; however, dual HER-2 inhibition seems to be a better option. The NeoALLTO international, randomized, phase Ⅲ study compared the use of single agent lapatinib, trastuzumab or the combination of both in addition to paclitaxel for neo-adjuvant treatment[32]. Interestingly, the combination arm showed a remarkable improvement in pCR almost duplicating the two other single agent anti-HER-2 arms (51% *vs* 29.5% trastuzumab *vs* 24.7% lapatinib; $P < 0.001$). As expected the addition of lapatinib resulted in worse side effects, mainly related to diarrhea and rash. However, in contraposition to the NeoALLTO, the freshly published NSABP B-41 study showed no statistical difference with the combination of trastuzumab and lapatinib when compared to either drugs used as single agent[33]. Two issues though deserves further discussion. First, even though the population included in both trials was similar, the chemotherapy regimens were not. In the NSABP study all patient received four cycles of AC and then they were randomized to paclitaxel plus trastuzumab, lapatinib or both. Second, the rates of pCR in all three arms were unusually high (62% for the combination, 53% for trastuzumab and 52.5% for lapatinib).

Up to this date, lapatinib has not received FDA approval to use in the neoadjuvant setting. Nonetheless, the FDA has recently granted accelerated approval to pertuzumab for its use before surgery when combined with trastuzumab and chemotherapy. This controversial decision was based on the results of two phase Ⅱ clinical trials. The already published NeoSphere trial was a multicenter, open-label, randomized phase Ⅱ study where 417 patients were randomized to one of four possible arms: pertuzumab (P) + trastuzumab (T) + docetaxel (Do); T + Do; P + Do or P + T alone[34]. All eligible patients then underwent surgical resection followed by adjuvant FEC and 1-year of trastuzumab. The primary

endpoint was pCR and no information regarding harder clinical outcomes (*i.e.*, DFS, OS, *etc.*) was reported. The three drug arm (P + T + Do) showed the maximal rate of pCR (46%) and was statistically different from T + Do (29%; $P = 0.014$). Pertuzumab + docetaxel resulted in a 24% pCR and the chemotherapy-free arm had a 17% pCR. Importantly, the addition of pertuzumab did not produce any significant drop in the cardiac function (4-5% EF drop across all groups). The second study - TRYPHAENA trial - is only available as an abstract but its importance relies on the fact that it incorporates the trastuzumab + pertuzumab combination to an anthracycline-free regimen[35,36]. One of its three arms use the very popular TCH regimen (carboplatin, docetaxel and trastuzumab) with pertuzumab for six cycles before surgery followed by one year of trastuzumab. Even though more information will be available when the study become fully published, preliminary data suggest that all three arms achieved > 55% pCR.

The preceding paragraph served to describe the current available evidence supporting the use of anti-HER-2 drugs as a neoadjuvant treatment. But, how should we apply all this information? In our own opinion, there are a couple of important points to emphasize. First, dual blockage of the HER-2 receptor, even without chemotherapy, results in an at least 15% pCR (NeoSphere Trial), meaning that 1 in 6 patients may not need chemotherapy. This certainly represents an attractive option for patients who cannot tolerate more than targeted agents. Second, the addition of chemotherapy leads to a more robust effect with values between 40%-50% when trastuzumab alone is used or even more than 50% when dual blockage is applied. Moreover, anthracyclines seem to play a significant role in HER-2 positive tumors; however, results from NeoALLTO and TRYPHAENA trials suggest that when dual blockage is used, anthracyclines toxicity might be spared. In this regard clinicians have now two options; to follow the NeoSphere protocol that requires the use of FEC post-surgically or to use TCH + pertuzumab (TRYPHAENA). Until further information is available, the anthracycline-free option might better serve the lower risk tumor (*i.e.*, small tumors with negative lymph nodes) or in patients with serious cardiovascular comorbidities and leave the anthracyclines for more advanced disease and younger women. Third, in all of the clinical trials available pCR is markedly diminished in tumors expressing hormone receptors in addition to HER-2.

Nonetheless, probably the most important question to ask ourselves is how reliable is pCR as a valid surrogate for real clinical outcomes. It is important to consider that these drugs are utilized in potentially curable disease and there are still some doubts about whether pCR always correlates with DFS and OS. It has been established by many authors, including the FDA, that pCR is a surrogate of survival in patients with localized breast cancer previously treated with chemotherapy[37]. This may well be the case for anti-HER-2 therapy when used in this fashion. A Cochrane meta-analysis evaluating preoperative with postoperative chemotherapy evidenced that the risk of dying among patients who had a pCR was approximately 50% less than that in patients with residual disease[38]. The FDA has presented in SABCS 2012 and is in process to publish a meta-analysis with 12900 patients enrolled in randomized neoadjuvant trials, with the objective to identify those patients in whom a pCR was most likely to predict survival[39]. There was a marked correlation between pCR and relapse free survival in all the subgroups analyzed. However, a recent German study showed that pCR was correlated with OS in triple negative breast cancer (TNBC) as well as HER-2 positive and non-luminal tumors but was not the case in the cohort of HER-2 positive and luminal patients[40]. In this last group pCR may not be a good surrogate for survival; but, from a hypothetical view, it is also true that ER positive disease tends to progress more slowly. It is possible that more events would be needed to have mature results. Perhaps, with longer follow-up curves might separate, becoming more consistent with the meta-analysis presented in SABCS 2012 by Cortazar and colleagues. Up for today, neoadjuvant with anti-HER-2 agents is a valid and approved option especially in those patients with locally advanced, unresectable tumors. Its use in small resectable cancer is probably appropriate but has to be balanced with the practical consideration as well as the patient's own preferences.

Lastly, some studies have also reported on different biomarkers which could predict pCR after neoadjuvant chemotherapy. They include estrogen receptor status, the PI4K pathway and p95HER-2 among others. However, no one is currently validated and available to use. An interesting niche where the use of biomarkers could be tremendously useful would be on patients with residual cancer cells at surgery after optimal neoadjuvant therapy. Since these patients have a poor prognosis, the analysis of the residual tumor cells for predictive biomarkers could unfold potential targets[41].

Metastatic disease

It has now been close to 15 years since the first publications reporting the use of trastuzumab for metastatic breast cancer[42-44]. Since those seminal studies, we have made major progress in our understanding of the anti-HER-2 therapies and some concepts should be highligthed.

Anti-HER-2 therapies are active even as single agents: Single agent anti-HER-2 molecules seem to have a modest but consistent activity even when used alone. This has been well proven for the case of trastuzumab (ORR = 15%-25%)[45], but also for pertuzumab (ORR = 5%)[46], lapatinib (ORR = 5%-7%)[47] and ado-trastuzumab emtansine (ORR = 35%)[48]. For the newer drugs, this holds true even after failing first line trastuzumab containing regimens. The vast majorities are only partial response, but some patients experience sustained stable disease which also adds to the clinical benefit.

The addition of conventional chemotherapeutics maximizes the efficacy of anti-HER-2 drugs: The addition of chemotherapy to anti-HER-2 agents increases the ORR up to 60%-70%. Paclitaxel is probably the most frequently used drug, but the benefit is seen regardless of the type of chemotherapy administered and there is solid evidence to support the combination of trastuzumab with vinorelbine or docetaxel[49] and even carboplatin[50]. Lapatinib is also frequently combined with capecitabine[51].

The HER-2 target should remain blocked even after progression: Patients seem to achieve considerable clinical benefit if the HER-2 axis remained blocked even after experiencing progression from regimes containing anti-HER-2 therapies. This was categorically proven by the German Breast Group in the BIG 305 trial where 146 patients were randomized to capecitabine or capecitabine plus trastuzumab after having progressed to a trastuzumab containing regimen[52]. The median progression-free survival (PFS) was 3 mo longer (8.2 *vs* 5.6; $P = 0.033$) and there was better ORR (48% *vs* 27%; $P = 0.015$) in the trastuzumab continuation arm. However, updated results showed no significant difference in OS[53]. These results are somehow comparable with the earlier tested combination of capecitabine and lapatinib. In the study reported by Geyer and colleagues in 2006, patients with locally advanced or metastatic disease who had failed trastuzumab regimens (> 95% of the population enrolled) were randomly assigned to either capecitabine alone or combined with lapatinib[54]. Time to progression (TTP) was similar in both trials, BIG 305 and the lapatinib study, in terms of the control arm (single agent capecitabine 4.5 and 5.5 mo, respectively) as well as the experimental arm (8.2 mo in trastuzumab + capecitabine and 8.5 mo in lapatinib + capecitabine). Irrespectively of the obvious difference in side effects of each drug and some intrinsic disparities in these two studies, the proof of concept brought by these investigations was the fact that the HER-2 target must continue to be attacked probably indefinitely. In accordance to this principle, a new molecule has recently gained FDA approval for trastuzumab refractory cases. Ado-trastuzumab emtansine, an interesting conjugation between the trastuzumab antibody and the chemotherapy agent DM-1, proved to be better than lapatinib and capecitabine combination. The EMILIA trial randomized 991 patients with metastatic (84%) or locally advanced (16%) disease, who have been previously treated with trastuzumab and a taxane, to T-DM1 or lapatinib plus capecitabine[55]. PFS, the primary endpoint of the study, was significantly improved with T-DM1 (9.6 *vs* 6.4 mo; $P < 0.001$) as it was OS (31 *vs* 25 mo; $P < 0.001$) and ORR (44 *vs* 31%; $P < 0.001$). Currently, ado-trastuzumab emtansine is considered the best option for patient progressing after first line trastuzumab. Nonetheless, early data from phase Ⅱ studies showed promising results with ado-trastuzumab as a front line option[56]. What happened after progression with T-DM1? Options will include either switching to trastuzumab + lapatinib (see below) or to consider lapatinib and capecitabine. But irrespectively of the option selected, the HER-2 targeted therapy should continue.

Two different anti-HER-2 therapies could be combined to exploit the benefit: Apparently, the conjunction of two different anti-HER-2 agents could result in better outcomes. Three combinations are particularly important: (1) Pertuzumab + trastuzumab + docetaxel; (2) Trastuzumab + lapatinib; and (3) Pertuzumab + trastuzumab alone. The CLEOPATRA study randomly assigned 808 patients with metastatic and chemotherapy naïve HER-2 positive breast cancer to either what was up to that moment the standard of care (trastuzumab + docetaxel) or the same combination plus pertuzumab[57]. The study was strongly positive with almost 50% prolongation in PFS favoring the experimental arm (18.5 *vs* 12.4 mo; $P < 0.001$). Updated results also confirmed a significant improvement in OS[58]. Currently, pertuzumab, trastuzumab and docetaxel are considered the standard of care for first line treatment in metastatic disease. Notably, this regimen takes advantage of two of the previously mentioned concepts: dual HER-2 blockage and addition of a chemotherapy agent. However, even without adding a chemotherapeutic, dual blockage is still an active alternative especially on those heavily pretreated patients who may not tolerate chemotherapy. The EGF104900 was an open-label, phase Ⅲ study where women vastly treated with trastuzumab-containing schemas (median 3 prior regimens) were randomly assigned to single agent lapatinib or lapatinib and trastuzumab[59]. The dual blockage arm showed longer PFS (12 *vs* 8 wk; $P = 0.008$) as well as OS (14 *vs* 9.5 mo; $P = 0.026$)[60]. Another appealing strategy tested in phase Ⅱ setting is the combination of pertuzumab and trastuzumab with no chemotherapy agents. Baselga and colleagues reported a 24% ORR and a median PFS of 5.5 mo in 66 patient with previous trastuzumab-based therapy failure, using this combination alone[61].

Triple positive patients (ER/PR positive and HER-2 positive) benefit from dual blockage: This is a very relevant issue because close to 50% of the tumors that overexpressed HER-2 also have some expression of ER and there is significant cross-talk between them[62]. Moreover, chemotherapy-free alternatives are always appealing. Two phase Ⅲ trials have been reported testing the hypothesis that dual blockage is better than anti-hormonal therapy alone. In the TAnDEM study, 207 patients with no brain metastases and no prior chemotherapy received either anastrozole alone or combined with trastuzumab[63]. The primary efficacy point was PFS which was extended by 2.4 mo with the use of trastuzumab (4.8 *vs* 2.4 mo; $P = 0.0016$). OS was not statistically different but crossover was allowed. Importantly, up to 15% of the patients in the combination arm did not experience relapse for up

to 2 years, suggesting that for at least a small proportion of patients this regimen was quite useful. The second study (EGF 30008 trial) compared letrozole alone or with lapatinib[64]. No prior therapy for metastatic disease was allowed and 219 of the total 1286 patients randomized were HER-2 positive. In the HER-2 positive subgroup the experimental arm showed a significant extension in PFS (8.2 *vs* 30 mo; $P = 0.019$) but once again no benefit was seen in terms of OS and there were more serious adverse events (8% *vs* 4%) compared with letrozole alone ($P < 0.05$). Lastly, the small eLEcTRA trial was discontinued due to slow enrollment with only 57 patients analyzed[65]. The cohort was similar to the TAnDEM trial but letrozole was used instead of anastrozole. The authors reported a trend towards improvement in TTP (14.1 *vs* 3.3 mo; $P = 0.23$). Lack of significance, though, could be due to a type 2 error (false negative) based on less than expected accrual. These studies support the use of HER-2 targeted treatments combined with non-steroidal aromatase inhibitors, in post-menopausal patients, as a valid chemotherapy-free option for triple positive patients[66].

Central nervous system metastases are probably different than the rest: A recent meta-analysis showed a higher risk of brain metastases as initial-only site of recurrence in patients relapsing after receiving adjuvant treatment with trastuzumab *vs* chemotherapy alone[67]. As expected given its molecular structure, most of the currently available anti-HER-2 drugs - trastuzumab, pertuzumab and ado-trastuzumab - have probably limited access into the central nervous system (CNS). Small molecules have in theory better chances to obtain therapeutic concentrations within the brain sanctuary. The combination of lapatinib and capecitabine has been correlated with a lower rate of CNS relapse compared with capecitabine as a single agent[68]. Nonetheless, the recent CEREBEL study showed no difference in the rate of CNS relapse as a first-site of disease progression (3.0% *vs* 5.0%; $P = 0.360$) between trastuzumab + capecitabine and lapatinib + capecitabine treatment[69]. However, the low incidence of CNS metastases might have undermined the ability of the study to show a significant difference. Also, a recently published French phase Ⅱ trial showed that in patients with previously untreated HER-2 positive diffuse CNS metastases the combination of capecitabine and lapatinib lead to an impressive high response rate (ORR = 66%) when given as initial approach. The regimen was effective in treating both, CNS and extra-CNS disease, and delayed whole brain radiotherapy by a median of 8 mo[70]. The conclusions from a planned randomized study evaluating capecitabine plus lapatinib plus whole brain radiotherapy are expected soon[66].

NEW TARGETS

Since this field is quite dynamic and the frontiers are in continuously expansion, it will be appropriate to discuss some of the new strategies that are currently being investigated for HER-2 positive breast cancer.

Afatinib

Afatinib is an oral small molecule that irreversibly inhibits HER-1, 2 and 4[71]. A phase Ⅱ study in trastuzumab-resistant metastatic patients showed 4 out of 35 partial responses[72]. Adverse events included diarrhea and rash. LUX-Breast 1 is a phase Ⅲ study of vinorelbine plus trastuzumab or afatinib for metastatic patients who progressed to one chemotherapy regimen containing trastuzumab (NCT01125566)[73]. A phase Ⅱ trial is also evaluating afatinib with or without vinorelbine in patients with inflammatory or metastatic breast cancer (NCT01325428).

Neratinib

Neratinib is also an oral, irreversible inhibitor of HER-1, -2 and -4[74]. A phase Ⅱ trial evaluated neratinib in 136 HER-2-positive patients[75]. In pretreated as well as trastuzumab-naïve patients, median PFS were 22.3 and 39.6 wk and ORR were 24% and 56%, respectively. Diarrhea was the most common grade 3/4 adverse effect. Another phase Ⅰ-Ⅱ trial combined neratinib plus trastuzumab in 45 metastatic and trastuzumab-resistant patients showing an encouraging 27% ORR[76]. Finally, a phase Ⅰ-Ⅱ trial evaluated neratinib plus vinorelbine in trastuzumab or lapatinib pretreated patients ($n = 77$)[77]. ORR was 42% in lapatinib-treated and 51% in lapatinib-naive patients. Open label phase Ⅱ trials are currently testing neratinib monotherapy in patients with HER-2 positive metastatic brain tumors (NCT01494662). Also a phase Ⅲ trial (ExteNET) in the adjuvant setting is ongoing (NCT00878709).

MM-111

MM-11 is a bi-specific monoclonal antibody that reversibly targets the HER-2 and -3 heterodimer[78]. A phase Ⅰ-Ⅱ study is currently evaluating its efficacy as single agent in HER-2 positive advanced breast cancer patients who have received prior trastuzumab or lapatinib therapy (NCT00911898)[79]. Another phase Ⅰ trial is studying MM-111 plus trastuzumab in HER2-positive, heregulin-positive, advanced and refractory breast cancer (NCT01097460).

HER2-targeted vaccines

Cancer vaccines designed to induce specific anti-HER-2 immunity are being investigated. Different strategies include protein-based vaccines, plasmid DNA-based vaccines, and vaccines that deliver HER-2 in a viral vector. HER-2 peptide-based vaccines have been tested in patients with metastatic HER-2 positive breast cancer[80,81]. Patients immunized developed delayed-type hypersensitivity reactions and strong $CD8^+$ cell responses specific for HER-2[82]. A dendritic cell based vaccine was also tested in a small group of patients with stage Ⅳ breast cancer[83]. One patient showed a partial response and three had stable disease for ⩾ 12 mo. Using a different

strategy, cell-based GM-CSF secreting vaccines were tested in combination with trastuzumab[84,85].

Pi3k/Akt/mTOR blocking drugs

PI3K/Akt/mTOR is an intracellular signal pathway that is frequently deregulated in breast cancer and mediates primary or secondary resistance to anti-HER-2 agents[86]. A phase I study tested the combination of everolimus plus weekly paclitaxel and trastuzumab in 33 patients with heavily pretreated metastatic disease[87]. Encouraging activity was reported, with an overall disease control rate at 6 mo of 74%. There are currently two ongoing phase Ⅲ trials of everolimus in this setting: BOLERO-1 which assesses the combination of everolimus, trastuzumab, and paclitaxel as first-line therapy and BOLERO-3 which explores the addition of vinorelbine to everolimus plus trastuzumab in patients previously treated. With 569 patients completing the BOLERO-3 study, median PFS was 7.0 *vs* 5.78 mo in the placebo arm ($P = 0.0067$)[88].

Histone deacetylase inhibitors

Histones acetylation status regulates the access of transcription factors to DNA and influences gene expression. Histone deacetylase (HDAC) activity reduces acetylation of histones. HDAC inhibitors induce growth arrest and apoptosis of tumor cells. Vorinostat is approved for cutaneous T-cell lymphoma. A phase Ⅱ trial of vorinostat together with tamoxifen in patients with hormone therapy-resistant breast cancer showed that the combination is reasonably tolerated and exhibits activity in reversing hormone resistance[89]. Clinical trials combining vorinostat with chemotherapy, EGFR inhibitors and bevacizumab are ongoing.

Heat shock protein 90 pathway

Heat shock protein 90 (Hsp-90) is a molecular chaperone that provides stability and supports the functionality of several proteins. Many of these proteins (*i.e.*, Brc-Abl, c-Kit and PDGF-α) are pro-oncogenic. Sustained inhibition of Hsp-90 chaperone induces proteosomal degradation of the free proteins. HER-1 and HER-2 require chaperoning by Hsp-90 for their stability[90]. Clinical data from a phase I trial with the Hsp-90 inhibitor tanespimycin used in combination with trastuzumab as second-line therapy showed evidence of antitumor activity in 63% of patients[91]. A phase Ⅱ trial enrolled 31 patients with HER-2 positive metastatic breast cancer whose disease has progressed on trastuzumab. Patients were administered weekly treatment with tanespimycin and trastuzumab. The ORR was 22% and the clinical benefit reached 59%[92].

Other exploratory anti-HER-2 blocking strategies

Ongoing trials combining anti-HER-2 agents with drugs blocking other signaling pathways hold the promise of further improvement. An auspicious approach seems to be the combination of anti-HER-2 therapy with insulin growth factor receptor (IGFR-1) blocking agents. IGFR-1 inhibition has been shown to restore sensitivity to trastuzumab in animal models[93]. Another potential combination is the dual blockade of HER-2 and SRC which was recently shown to work as a central node downstream of multiple trastuzumab-resistance mechanisms[94]. Finally, HER-3 is another strong activator of PI3K/Akt signaling pathway that has been demonstrated to be up-regulated after HER-2 blockade[95]. Although still in early phases of development, Rb disruption strategies and the use of CDK-4/6 inhibitors may be clinically useful[96].

CONCLUSION

We have recently witnessed an unprecedented expansion in the drugs developed to target HER-2 positive breast cancer. Transcendental advances were made and substantial improvements in all relevant outcomes and in all the clinical scenarios for either early or advanced disease were accomplished. However, patients still progress and cure for metastatic disease is still a utopia. We can only envision the arrival of newer and more sophisticated weapons to keep on fighting this lethal disease and we can already start asking ourselves some questions. Would neratinib, for example, soon become available? Could adotrastuzumab be ever used as a first line treatment? Can we make an anti-HER-2 drug with no cardiac effects? We will soon have some answers to these and many other questions, but up to that moment comes the state of the art management of HER-2 positive breast cancer relies on the more than 40 phase Ⅲ and Ⅱ clinical trials that were concisely described in the preceding pages.

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