Horizon Scanning in Oncology

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1 Drug description

Generic/Brand name:

Lapatinib ditosylate (Tyverb® - Europe/Tykerb® – U.S.)

Developer/Company:

Glaxo Group Limited

Description:

lapatinib inhibits intracellular tyrosine kinase domain of EGFR and HER2

The active substance of Tyverb®/Tykerb® is lapatinib ditosylate monohydrate which belongs to the group of protein kinase inhibitors. The mechanism of action is the inhibition of the intracellular tyrosine kinase domain of Epidermal Growth Factor Receptor (EGFR [ErbB1]) and of Human Epidermal Growth Factor Receptor 2 (HER2 [ErbB2]) receptors [1, 2] which demonstrated (in vitro, animal models) an inhibition of ErbB-driven tumour growth [1].

orally administered

for treatment of breast cancer in combination with capecitabine or…

Tyverb®/Tykerb® is available in 250mg tablets. The recommended dosing regimen for the treatment of HER2+, advanced/metastatic progressive breast cancer is 1,250mg daily, corresponding to 5 tablets orally, continuously. Lapatinib should be taken in combination with capecitabine 2,000mg/m²/day administered in 2 doses and a 12 hour interval on days 1 and 14 in a 21 days cycle [2].

…letrozole

For HER2+, hormone receptor (HR) positive, metastatic breast cancer (MBC), 1,500mg Tyverb®/Tykerb® daily are recommended in addition to 2.5mg letrozole [1].

As observed side-effects include a decrease in left ventricular ejection fraction, pulmonary toxicity and hepatotoxicity, control of this parameters prior to, and monitoring during, treatment with lapatinib is indicated [2].

2 Indication

as first-line therapy for advanced/metastatic BC

Lapatinib ditosylate (Tyverb®/Tykerb®) is indicated for the treatment of patients with advanced/metastatic breast cancer (BC) who have not received prior chemotherapy for the treatment of their advanced disease.

3 Current regulatory status

EM(E)A:

The EM(E)A granted market authorization for Tyverb®,

for advanced/metastatic HER2+ BC after prior therapy

- in combination with capecitabine for the treatment of patients with HER2 over-expressing advanced or metastatic BC whose disease should have progressed following prior therapy (including anthracyclines and taxanes and therapy with trastuzumab) in the metastatic setting in June 2008 [2]. EM(E)As market authorization is based on a "conditional approval" scheme where further evidence is awaited and newly generated data are reviewed annually.

for HER2+, HR+ metastatic BC in combination with aromatase inhibitor

- "for patients with HER2 over-expressing tumours in combination with an aromatase inhibitor for postmenopausal women with HR+ metastatic disease, not currently intended for chemotherapy in May 2010. The patients in the registration study were not previously treated with trastuzumab or an aromatase inhibitor [3]."

FDA:

In the U.S., the FDA licensed Tykerb® for

for advanced/metastatic HER2+ BC after prior therapy and for postmenopausal women with HER2+/HR+ metastatic BC in addition to letrozole

- the treatment of patients with HER2 over-expressing advanced or metastatic BC in combination with capecitabine after prior therapy including anthracyclines, taxanes or trastuzumab in March 2007.
- for postmenopausal women with HR+, HER2 over-expressing MBC in combination with letrozole when hormonal therapy is indicated in January 2010 [1].

4 Burden of disease

BC is most common type of cancer in females

risk factors

In 2007, about 4,600 women were diagnosed with and 1,550 died of BC in Austria [4] making breast cancer the most common type of cancer in females with more than 80% of all cases of cancer occurring in women aged over 50 years [5]. Risk factors associated with the development of BC are age, family history, nulliparity, early menarche or genetic factors (e.g genetic mutations such as of the BRCA1, BRCA2) [6, 7].

prognostic factors

Prognostic factors are age, menopausal status, tumour stage, histology, hormone receptor status, clinical response and lymph node status after induction therapy, out of which clinical response to initial treatment and lymph node status are the most important ones [6].

TNM staging informs management decisions determines prognosis

The Tumor Node Metastasis (TNM) staging classification is used to determine the disease stage. This staging system reflects the extent of disease which is used to inform management decisions and to determine prognosis [6]. Besides the primary tumour, the extent of which the regional lymph nodes are involved and the absence or presence of distant metastases are taken into account, leading to four main stage groupings (stage I to IV) [6]. Advanced BC belongs to stage III, whereas metastatic disease corresponds to stage IV. Metastases are most common in the bones, liver or the lungs.

Metastatic disease at diagnosis is present in less than 10% of women. [6], but the majority of patients, that is about 50%, initially presenting with earlier forms of breast cancer, will develop MBC eventually [8]. Evidence suggests that 20% to 25% of all women diagnosed with BC have tumours over-expressing HER2 [9-11], but due to various methods for determining HER2 status it might be the case that these numbers are slightly overestimated [12]. However, applying these estimates to an Austrian context would result in about 100 women with HER2+ advanced MBC. Cure of MBC and complete remissions after chemotherapy are rare, resulting in a median survival of about 18 to 24 months [7] and in only 5 -10% of women who survive five or more years [6].

metastatic disease in about 10% of women

HER2 over-expression in about 20% of 25% of all women diagnosed with BC

Besides the TNM staging, more important factors to determine the best management strategy are estrogen-receptor (ER) and progesterone-receptor (PR) levels in the tumour tissue, HER2 status, menopausal status, and the general health of the patient [7]. Predictive factors for response to hormone therapy are a long relapse-free interval, isolated bone and soft tissue involvement, and prior response to endocrine therapy. ER+/PR+ tumours are most likely to respond to hormone therapy, but even of them, up to 25% are refractory to hormone therapy in the first instance and nearly all tumours become refractory at one point [6].

ER/PR, HER and menopausal status important factors for choosing management strategy

BC with amplification and over-expression of HER2 are usually more aggressive [6, 11] corresponding to a reduced overall survival (OS) and a shortened time to relapse [10]. However, HER2 status is used to predict response to drugs such as trastuzumab or lapatinib [6], but even then, many patients over-expressing HER2 do not respond to HER2-targeted therapies [10, 13]. Additionally, primary resistance to endocrine therapy might be associated with HER2 over-expression due to a cross-talk between ErbB1/ErbB2 and ER pathways. Moreover, a link between responsiveness to chemotherapy and HER2 over-expression might exist [6].

tumours over-expressing HER2 more aggressive, reduced OS, shortened time to relapse

HER2 status for predicting response to trastuzumab or lapatinib therapy

5 Current treatment

Choice of therapy for BC is based on numerous factors like tumour histology, axillary node status, hormone and HER2 receptor status, presence of metastases as well as patients characteristics including menopausal status, age and co-morbidities [9].

choice of therapy influenced by hormone status and HER2 status, metastases, histology

For advanced BC a combined modality approach is regarded as standard of care. After determination of histology, ER/PR levels, and HER2 over-expression by biopsy, options are

- neoadjuvant chemotherapy: initial treatments are either anthracycline–containing regimens (e.g. 5-fluorouracil, and cyclophosphamide ± doxorubicin/epirubicin) and/or taxane-containing therapies (e.g. docetaxel, paclitaxel) [6, 7].
- locoregional therapy: depends on the tumour response to neoadjuvant therapy and comprises

for advanced BC: chemotherapy,

surgery,

- surgery either in form of breast-conserving therapy if a good partial or a complete response after neoadjuvant chemotherapy was achieved (in about 50%-90% of women) [6] or total mastectomy with axillary lymph node dissection.
- postoperative radiation therapy: after surgery, to the chest wall and regional lymphatics.

radiation therapy,

trastuzumab,

capecitabine

- Adjuvant therapy: if the initial response was a less than complete or a good partial response, chemotherapy with non cross-resistant drug(s), that is if neoadjuvant therapy included a taxane an anthracycline is indicated and vice-versa. Hormone therapy with tamoxifen or an aromatase inhibitor should be administered to patients whose tumours are ER-positive or unknown.
- trastuzumab: is indicated either in the adjuvant or in the neoadjuvant setting if tumours over-express HER2 [6, 9].
- capecitabine: is recommended by some guidelines [9] either preoperatively or to sensitize for radiation therapy.

for metastatic BC

Therapy of MBC usually aims at symptom palliation, improvement of quality of life (QoL) and extension of life [7]. Under careful consideration of toxicities arising from therapy and the likelihood of achieving palliation, available treatment options are:

surgery,

- surgery

radiation therapy,

- radiation therapy

chemotherapy

- chemotherapy: either single agents (e.g. anthracyclines, taxanes), or chemotherapy combinations (e.g. cyclophosphamide/ doxorubicin/fluorouracil) or chemotherapeutic agents in combination with molecular targeted therapies (e.g. bevacizumab/paclitaxel, trastuzumab/paclitaxel ± carboplatin [9].

hormone therapy

- hormone therapy: for example tamoxifen, letrozole or fulvestrant either neoadjuvant or adjuvant for postmenopausal women when the tumour is ER, PR positive or the ER/PR status is unknown [7]. Other factors predicting response to endocrine therapy are a long relapse-free interval and response to previous endocrine therapies. Then, hormone therapy is preferred over chemotherapy as the toxicity profile is in favour for the former one [6].
- molecular targeted therapies:

molecular targeted therapies

  - trastuzumab for HER2 overexpressing tumours +/- chemotherapy (but not with anthracyclines) for tumours refractory to standard endocrine therapy, trastuzumab + endocrine therapy for HR+/HER2+ tumours,
  - bevacizumab [6, 7].

6 Evidence

two phase III trials

Two phase III trials with different inclusion criteria and different treatment regimens were identified [14, 15]. In these trials, lapatinib was administered either in addition to paclitaxel or letrozole, and both demonstrated improvements for patients with HER+ BC. Adverse events occurred more often in those groups where lapatinib was given in addition to other drugs, but were mostly of grade 1 or grade 2. Results on QoL demonstrated no differences in the overall population, but a subgroup analyses indicated improved QoL scores for a group (n= 86 pts) of HER2+ patients [14].

one study assessing two different dosing regimens

Another trial [16] assessed two different dosing regimens of lapatinib. Here, adverse events occurred in up to 70% of all patients out of which 24% were classified as serious ones.

one meta-analysis

With 64%, a high frequency of adverse events was also shown in a meta-analysis which incorporated results of three individual studies [17]. Improvements in progression-free survival (PFS) as well as in OS were found for HER2+ patients, but these results have to be interpreted with caution as the sample sizes within the included studies were small.

6.1 Efficacy and safety - Phase III studies

Reference	EGF30001, published [15][1]	EGF30008, published [14, 18][2]
Sponsor	GlaxoSmithKline	GlaxoSmithKline
Country	multicenter: Italy, Brazil, US, Peru, Pakistan, Latvia	multicenter: UK, US, France, Peru, Russia, Ireland
Design	randomized, double-blind, placebo-controlled, phase III	randomized, double-blind, controlled, parallel group, phase III, intention-to-treat (ITT) population consisted of hormone receptor (HR)+ patients out of these, 218 pts were confirmed being HER2+

[1] TTP= time to progression, ORR = objective response rate (= complete or partial response confirmed ≥ 4 weeks from first response), CBR = clinical benefit rate (= complete response, partial response, stable disease ≥ 24 weeks), EFS = event free survival, OS= overall survival, OR = odds ratio, NA = not available, ECOG = Eastern Cooperative Oncology Group, p.o. = per os, QoL= quality of life, FACT-B= Functional Assessment of Cancer Therapy-Breast, TOI = trial outcome index, BCS = breast cancer subscale, Q-TWiST = quality-adjusted time without symptoms or toxicity

[2] PFS = progression-free survival, ORR = overall response rate, CBR = clinical benefit rate (= complete response (CR) , partial response (PR), stable disease ≥6 months (SD)), OS = overall survival, ECOG = Eastern Cooperative Oncology Group, p.o. = per os

Participants characteristics	579 pts I(ntervention) 291, mean age 51 (range 23-87) years, ER+ and or PR+: 44%, ER/PR status unknown 21% C(ontrol): 288, mean age 52 (range 25-78) years, ER+ and/or PR+: 50%, ER/PR status unknown: 16%	1,286 pts I(ntervention): ITT: 642 pts, median age: 62 (range 31-97) years, HER2+: 111 pts, median age: 60 (range 44-85) years C(ontrol):: ITT: 644 pts, median age 62 (range 35-95) years, HER2+: 108 pts, median age 59 (range 45-87) years
Treatments	I(ntervention): 1,500 mg lapatinib p.o daily + 175mg/m² paclitaxel iv. over 3 hours on day 1, every 3 weeks for up to 6 cycles C(ontrol): placebo + 175mg/m² paclitaxel iv. over 3 hours on day 1, every 3 weeks for up to 6 cycles	I(ntervention): 1,500 mg lapatinib p.o + 2.5 mg letrozole p.o. daily until disease progression C(ontrol): placebo pill + 2.5 mg letrozole p.o. daily until disease progression
In-/exclusion criteria	Inclusion: histologically confirmed stage III or IV HER2 negative or untested BC and untreated in the metastatic setting, previous therapy with antracyclines, taxanes was allowed + a disease free interval of > 6 months was required between completion of taxane-based therapy and disease relapse/study enrolment, ECOG ≤ 1	Inclusion: postmenopausal, histologically confirmed IIIB/IIIC or IV ER+ ± PR+ invasive BC, antiestrogen, aromatase inhibitor and/or trastuzumab therapy completed > 1 year prior to study entry was allowed, ECOG ≤ 1 , normal LVEF Exclusion: prior therapy for advanced/metastatic BC, extensive symptomatic visceral disease,
Follow-up	96 weeks	Median: 1.8 years
Outcomes	Primary: TTP Secondary: ORR, CBR, duration of response, EFS, OS	Primary: (investigator assessed) PFS in the HER2+ population Secondary: ORR, CBR, OS, safety for the HER2+ population, PFS for the ITT HR+ population
Key results	Primary: Median TTP: I 29 weeks vs C 22.9 weeks, HR= 0.87, 95% CI 0.72 to 1.05, p= 0.14 Secondary: - ORR: OR = 1.7, 95% CI 1.1 to 2.4, p= 0.008 - CBR: OR = 1.5, 95% CI 1.0 to 2.1, p = 0.025 - EFS + OS (OS after 46% of events occurred) not significant Pre-planned subset analysis in HER2+ subgroup (I 49 pts C 37 pts): - TTP: I 36.4 weeks vs C 25.1 weeks, HR= 0.53, 95% CI 0.31 to 0.89, p = 0.005 - CBR: I 69.4% vs C 40.5%, p=0.011 - EFS: I 35.1 vs C 21.9 weeks HR = 0.52, 95% CI 0.31 to 0.86, p =0.004 - ORR: 63.3% vs 37.8%, p=0.023 - OS not statistically significant	1) HER2+ population Primary: - median PFS: I 8.2 months vs C 3.0 months, HR= 0.71, 95% CI 0.53 to 0.96, p= 0.019 Secondary: - ORR: I 28% vs C 15%, OR= 0.4, 5% CI 0.2 to 0.9, p= 0.021 - CBR: I 48% vs C 29%, OR= 0.4, 95% CI 0.2 to 0.8, p =0.003 - OS: I 33.3 months vs C 32.3 months, HR= 0.74, 95% CI 0.5 to 1.1, p= 0.113 (less than 50% of OS events recorded) 2) ITT analysis in HR+ population: - Median PFS: I 11.9 months vs C 10.8 months, HR= 0.86, 95% CI 0.76 to 0.98, p=0.026 - CBR + ORR : no statistically significant difference
QoL [19, 20] (according to publications in addition to efficacy studies)	QoL [19]: - ITT: QoL scores stable over time in both groups with no statistically significant difference - post-hoc analyses of HER2+ subgroup: FACT-B, TOI, BCS scores significantly more favourable results for I Q-TWiST difference range: 2 to 15 weeks, favouring I	QoL in HER2+ population [20]: Mean changes in subscale and total QoL stable over time in both groups quality-adjusted survival difference 8 – 9.5 weeks favouring I, but not statistically significant
Adverse effects	- treatment discontinuation: I 16% vs C 7% - LVEF decrease: I 2% vs C 2% - at least one SAE reported (e.g. neutropenia, diarrhea): I 35% vs C 22% - SAE- related deaths: I 2.7% due to septic shock ± diarrhea, cardiac arrest, heart failure vs C 0.6%	- most common: diarrhea, rash, nausea, arthralgia of grade 1 or 2 - LVEF decline: I 0.8% vs C 0.3% - hepatotoxicity: I 8 pts vs C 1 pt - any serious adverse event (drug related) I 8% vs C 4% - deaths: related to serious adverse events: I 8 pts vs C 8 pts, related to study drug: I 1 vs C 2
Commentary	primary activity of lapatinib in BC patients is mediated through HER2 inhibition	combination of letrozole and lapatinib significantly enhances PFS and CBR rates in MBC patients co-expressing HR and HER2

One phase III trial [15], comprising 579 patients with HER2- or HER2 uncharacterized MBC compared paclitaxel and lapatinib with paclitaxel plus placebo. Overall, improved outcomes for the combination arm were seen for ORR and CBR. However, favourable results were found for a pre-planned subgroup of retrospectively identified HER2+ patients where increases in TTP (11.3 weeks difference), ORR and EFS were observed. Nonetheless, this subgroup was with, overall, 86 patients (I 49, C 37) considerably small and even the authors themselves state that these results "should be considered as hypothesis generating". For HER- patients, on the other hand, no improvements in any of the outcome measures occurred. With regards to adverse events, rash, diarrhae, mucositis and vomiting were overall significantly more frequent in the combination arm, as well was the occurrence of at least one serious adverse event (I 35% vs C 22%). 16% in the intervention arm and 7% in the control group discontinued treatment. Another study [19], which had calculated the QoL scores, found no improvements for the whole study population but favourable results for the HER2+ group.

lapatinib + paclitaxel in comparison to paclitaxel only in HER2- or uncharacterized patients

subgroup analysis: increases in TTP and quality of life in HER2+ patients

but small subgroup

Johnston et al. assessed lapatinib in combination with letrozole in comparison to letrozole and placebo [14]. 1,286 HR+, postmenopausal women with ECOG status 0 or 1 suffering from MBC and with no prior therapy for the metastatic disease were enrolled and formed the intention to treat population. Out of these, 219 patients were confirmed as HER2+. Primary outcome was PFS in the HER2+ population which showed, after a median follow-up of 1.8 years, a difference of 5.2 months in favour of the intervention group. Improvements were also found for CBR and ORR, both achieving statistical significance. After less than 50% of OS events recorded, OS differed by 1 month. Improvements in PFS were also found for the intention to treat population (HR+ patients), but not for the HER2- group. Some preliminary data (full text not yet published) on QoL were presented at the Breast Cancer Symposium 2009 but showed no significant differences in between the treatment arms [20].

another trial: lapatinib + letrozole in comparison to letrozole only

primary outcome: PFS in HER2+/HR+ women

improved by 5.2 months in lapatinib group

quality of life: no significant differences

6.2 Efficacy and safety - further studies

Gomez et al. evaluated two different dosing regimens of lapatinib, either 1,500mg once daily or 500mg twice daily in 138 women with HER2 amplified advanced or metastatic BC [16]. 69 patients were allocated to each group, and showed, overall, an ORR of 24% and a median time to response of 7.9 weeks. PFS rates at 4 months and 6 months were 63% and 43% respectively. Most common adverse events were grade 1 or grade 2 diarrhea and rash. In total, 71% were affected by treatment related side-effects. Serious AEs occurred in 24% with 7% being treatment related which led 7 patients to discontinue lapatinib therapy. Out of six deaths, one was considered to be due to therapy.

another study assessed two different dosing regimens

adverse events occurred in 71% of patients, but mostly grade 1 or grade 2

A meta-analysis incorporated in addition to the aforementioned phase III trials another study where patients had previously received other forms of therapy [17]. For PFS improved outcomes for HER2+ patients were found (HR = 0.61, 95%CI 0.5 to 0.74). The same held true for OS (HR = 0.76, 95% CI 0.6 to 0.96) even though the results of the individual studies were not statistically significant. These findings were not repeated in HER- patients. Patients treated with lapatinib, however, were 64% more likely to develop any side effect and 2.3 times more likely to discontinue treatment. The authors

meta-analysis found improved OS and PFS in HER2+ patients but results are based on small sample sizes

acknowledge, although, that the statistical power of subgroup analysis was diminished due to considerably small sample sizes for these groups.

7 Estimated costs

monthly cost of lapatinib about € 3,200

One package Tyverb® containing 70 250mg tablets costs € 1,235.- [21]. If administered as first-line therapy in the advanced/metastatic disease setting and in addition to letrozole, the recommended dose is 1,500 mg daily continuously. This results in daily costs of € 106 and, accordingly, in monthly costs of about € 3,200. As mentioned above, these expenses occur in addition to letrozole, any subsequent therapies as well as costs for HER2 testing.

8 Ongoing research

plenty phase III studies ongoing

Limiting the search terms on clinicaltrials.gov to "metastatic breast cancer", "first-line" and "lapatinib" yielded one study currently recruiting patients:

evaluation of lapatinib in broad variety of indications and combinations

NCT00667251: assesses taxane based chemotherapy with lapatinib or trastuzumab for women with HER2+ metastatic breast cancer. Final data collection for the primary outcome measure PFS is expected to be in July 2011.

In addition, 20 ongoing phase III were found, evaluating lapatinib in a broad variety of indications such as for earlier stages of BC, in combination with bevacizumab and everolimus in the neoadjuvant setting or as adjuvant treatment in comparison to trastuzumab.

9 Commentary

two phase III studies indicating benefits for HER2+ patients

Two phase III trials assessing lapatinib as first-line therapy in the advanced/metastatic BC disease setting were identified [14, 15]. Di Leo et al., evaluated this tyrosine kinase inhibitor in HER2- or HER2 uncharacterized patients [15]. Improvements for the whole study population were observed for overall response rates and clinical benefit rates, but showed no improvements for any other outcomes. In a retrospectively identified subgroup of HER+ women, an increase of time-to-progression by about 11 weeks and for event-free survival by about 13 weeks was shown. Nonetheless, this subgroup consisted of only 86 patients and was hence considerably small. Accordingly, improved QoL outcomes for this subgroup should also be interpreted with caution [19].

Another phase III trial, which formed the basis for FDA's decision on granting market authorization for lapatinib for the treatment of postmenopausal women with HR+, HER2 over-expressing metastatic breast cancer in combination with letrozole, assessed the TKI in 1,286 postmenopausal women with HR+ MBC. Letrozole was administered either in combination with lapatinib or alone. The primary outcome was PFS in HER2+ patients (n=219) and showed a difference of about 5 months in favour of the lapatinib group. OS data were not mature but no differences between the two groups have been demonstrated so far. Preliminary data on QoL were presented for this trial at the Breast Cancer Symposium 2009 and showed no differences, neither for the overall population nor for the HER2+ subgroup [20].

PFS increase by about 5 months in HER2+/HR+ postmenopausal women in combination with letrozole

no differences in QoL

In terms of adverse events, both studies showed somehow similar results. Most common adverse events of patients receiving lapatinib were of grade 1 or 2 and included symptoms such as rash, diarrhea or nausea. The only AEs of higher grades which occurred in more than 1% of patients were grade 3 diarrhea (9% of pts), fatigue and back pain (each in 2% of patients). Cardiotoxicity, an adverse event related to lapatinib, was observed in 2% and 0.8% of patients, showing no differences to the control groups. These findings are in concordance with data on cardiac toxicity of 18 studies encompassing more than 1,600 BC patients where an incidence of 1.8% for a symptomatic or asymptomatic decline in left ventricular ejection fraction was reported [13].

adverse events similar in both studies, most common rash, diarrhea, nausea of grade 1 or grade 2

cardiac adverse events in about 2%

Despite an increase of PFS by 5 months it has to be kept in mind that an increase in PFS must not necessarily translate into gains of OS, as happened with bevacizumab where similar gains of PFS did not lead to improvements of OS [22, 23]. Moreover, even though PFS in HER2+ patients was primary outcome at least in one of the studies, the group of HER2+ individuals was with 219 and 86 patients quite small. Additionally, as interaction of signalling pathways of receptors might change receptor status of tumours [6] and resistance to lapatinib can either exist in the first place or can develop during therapy [13, 24], implications for the suitability of subsequent lines of treatment might arise. Hence, predictors of tumour response have to be explored further to identify patients most likely to benefit from individual drugs and to establish the most beneficial sequence of therapies. Also of interest is the direct comparison of trastuzumab to lapatinib in a prospectively defined HER2+ population.

increase in PFS must not necessarily translate into gains of OS

groups of HER2+ patients in both trials small

possible implications for subsequent lines of therapies

comparison to trastuzumab of interest

Treatment of metastatic BC aims at palliating symptoms, prolonging survival and maintaining good quality of life. So far, study results indicate that lapatinib can extended PFS without improving or compromising QoL when added to other active treatments for metastatic BC. As long as data for OS are missing, it seems that the primary benefit of orally administered lapatinib is the potential of delaying more aggressive therapies with considerable toxicities in a well-defined (preferably by fluorescent in situ hybridization [11]) HR+/HER2+ population.

no data on OS, no changes in QoL

benefit: delay of more aggressive therapies in well defined HR+/HER2+ patients

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