Management of HER2-Positive Early Breast Cancer

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Question 1: Is neoadjuvant systemic therapy your standard of care for all patients with operable HER2-positive disease who are fit for therapy or do you recommend specific selection criteria leading to some patients being operated first and receiving postoperative, adjuvant treatment only?

Lüftner: Most HER2-positive, primary breast cancers are larger in size than T1b at diagnosis and qualify for neoadjuvant chemotherapy. I would consider this as the standard of care. Rarely, individual patients prefer up-front surgery as they do not want to bear the psychological burden of leaving the tumor in loco for nearly half a year. Then, primary surgery is the preferred option while losing prognostic information like time to response, clinical residual disease, or even progression under chemotherapy plus anti-HER2-targeted agents.

Stöger: Women with locally advanced (stage IIB (T3N0) or stage III) HER2-positive breast cancer should receive neoadjuvant rather than adjuvant therapy anyhow. Given the fact that adjuvant chemotherapy and HER2-directed therapy are to be offered to all women with HER2-positive, node-positive or node-negative tumors > 5 mm in size, I prefer the neoadjuvant setting to provide the linked advantages for this cohort, too. This includes less extensive surgery with improved outcome, better acceptance of therapy in women perceiving response to treatment, and the assessment of pathological response as a surrogate outcome measure for disease prognostication and the possibility to extend therapy in non-responders.

Thürlimann: We believe that the St. Gallen Consensus recommendations are reasonable, and we follow these. We operate first in patients, stage 1, with favorable tumor breast size ratio and favorable location in the breast. The breast surgeons help us with the indication.

Untch: In our breast cancer center, all patients with operable HER2-overexpressing breast cancer receive neoadjuvant chemotherapy with the addition of anti-HER2 treatment without any exceptions. If the patient is not fit for medical treatment, we obviously perform primary surgery.

Question 2: The addition of pertuzumab to the standard of care, i.e. adjuvant trastuzumab for 12 months, has been demonstrated to result in a statistically significant prolongation of progression-free survival (PFS) at 3 years. The difference was rather modest (94.1 vs. 93.2%, hazard ratio 0.81) but it appears that some patient subgroups might potentially benefit more than others. Which criteria do you use to recommend or not recommend pertuzumab in the adjuvant setting, and are there differences in patients having already received pertuzumab in the neoadjuvant treatment phase and those patients naïve to the drug?

Lüftner: This therapeutic setting is quite complex as we do not have study results for all clinically relevant situations. The majority of HER2-positive patients will have had neoadjuvant chemotherapy plus the dual blockade with trastuzumab and pertuzumab. It is unclear whether patients reaching a pathological complete response (pCR) still need the longer dual blockade of pertuzumab in combination with trastuzumab for 1 year or not. Very probably, the co-expression of the estrogen and/or progesterone system distinguishes two biologically different diseases in HER2 positivity: triple-positive breast cancer patients form a different subentity where pCR does not correlate that clearly with survival endpoints like in hormone receptor-negative disease. I inform my patients about this complex situation and try to balance the potential effect

versus toxicity of the dual blockade. Missing clear data, in my view, this is a question of informed consent. In nodal-positive patients and/or estrogen receptor(ER)-/progesterone receptor-negative patients, I try to complete the dual blockade for 1 year anyway. This is in line with the approval status of pertuzumab.

Stöger: The treatment effect of additional pertuzumab was most detectable among women who were at higher risk for relapse because of lymph node involvement or hormone receptor negativity without relevant cardiac toxicity. I therefore recommend additional adjuvant pertuzumab for these patients, keeping in mind the small benefit and very high expense. As patients having received pertuzumab in the neoadjuvant setting were excluded in the pivotal trial, there are no data to guide the use of adjuvant pertuzumab in this cohort. However, for such patients, presenting with a high risk of relapse, my approval is to continue pertuzumab for the duration of 12 months in the adjuvant setting.

Thürlimann: We recommend pertuzumab in patients at higher risk and with a higher likelihood of reasonable risk reduction.

This includes patients with node-positive and/or hormone-insensitive disease. The 'pièce de résistance' is the access of the patients to pertuzumab in this indication.

Untch: The addition of pertuzumab to trastuzumab in patients with HER2-overexpressing tumors is recommended if lymph nodes are histologically involved (by biopsy or fine needle aspiration) or if the primary tumor has negative hormone receptors. If the patients have residual disease in the breast and/or in the lymph nodes, postoperative double antibody combination is given. According to the press release of the KATHERINE study, these patients will be candidates for switching to anti-HER2 treatment with TDM1 in the near future.

Question 3: According to the results of a recently published large phase III trial, 6 months of adjuvant trastuzumab are statistically non-inferior to the current standard of care of 12 months of treatment in terms of PFS at 4 years, and congruent results were found for overall survival (OS) as well as for survival landmark analyses after 6 months of trastuzumab treatment. Do you consider these data as immediately practice-changing for all patients, for some patients, or not practice-changing at all?

Lüftner: An upcoming meta-analysis of all trials with a shorter duration of trastuzumab therapy <1 year will help us to make final recommendations for our medical system. So far, we have just signals from individual trials while the dataset on 1-year treatment is abundant. I would be cautious to reduce the duration based on just one significant trial. However, these data still help in the case of patients with special insurance situations or even privately paying patients. In this context, a shorter duration of trastuzumab will

help the patient economically if she can afford only shorter trastuzumab exposure. This is especially true when biosimilar trastuzumab is being used. Short exposure of trastuzumab is better in any case than no trastuzumab at all.

Stöger: Non-inferiority in the PERSEPHONE trial was defined as a PFS 'no worse than 3% below the 12 months arm', reflecting a reasonable confinement of clinical efficacy. Furthermore, the subgroup analysis of patients with concomitant chemotherapy and trastuzumab, complying with contemporary practice, revealed a benefit of 12 months over 6 months. Therefore, I continue to suggest 1 year of trastuzumab in the adjuvant setting. For patients who, for whatever reasons, cannot tolerate 12 months of therapy, such as those with cardiac comorbidity or experienced cardiac toxicity, results from PERSEPHONE are reassuring that the greatest amount of benefit is achieved within the first 6 months.

Thürlimann: It is practice-changing for some patients. However, there is an ongoing debate in our breast center concerning the interpretation of the data and transfer into daily routine, and we decide case by case.

Furthermore, it is reassuring to have this data in cases with toxicity/tolerability problems of trastuzumab or those at higher risk to experience such problems. Furthermore, this is an important information for patients living and physicians practicing in less economically favorable conditions than we do.

Untch: The recently published data with a shorter duration of 6 months of adjuvant trastuzumab is very challenging. It is not immediately practice-changing. This shorter duration of trastuzumab exposure can be done in a more intelligent setting: We should treat our patients with 6 months of neoadjuvant chemotherapy with the addition of anti-HER2 treatment (trastuzumab ± pertuzumab. If there is no more residual disease in the breast and/or in the lymph nodes, we can stop further anti-HER2 treatment. Obviously, this is just a hypothesis (but with a good scientific and clinical background).

Question 4: Extended adjuvant treatment with neratinib after 1 year of trastuzumab-based adjuvant standard therapy has demonstrated a further statistically significant benefit in PFS and has already been licensed by the US Food and Drug Administration for all patients with HER2-positive breast cancer. It is expected that neratinib will soon be available also in Europe with a restricted label for patients with endocrine-responsive disease. Based on the trial results and given the added toxicity of neratinib, will you use or recommend this drug for extended adjuvant treatment, and if yes, are there also other selection criteria beyond the ER status?

Lüftner: The data on neratinib is important as, again, it distinguishes the group of HER2-positive patients into two biologically

different subsets. In the case of a patient with hormone receptor-positive disease who did not receive any pertuzumab in the (neo-) adjuvant setting (for whatever reason), I would suggest to start neratinib under thorough follow-up during the beginning of treatment when the incidence and grades of diarrhea are most pronounced. We must always keep in mind that the disease-free survival (DFS) benefit for the EMA (European Medicines Agency)-approved subset of patients from the EXTENET trial is roughly 5%, which is certainly clinically relevant. Prophylactic loperamide is certainly unavoidable in these patients, ideally combined with budesonide.

Stöger: Neratinib provides a modest benefit in the invasive DFS, and no data on OS are available. Furthermore, the expected monetary cost is exorbitant, and the tolerability of 1 year of neratinib using prophylactic loperamide is not clearly established in a large, defined population. The enthusiasm in prescribing these newer classes of drugs must be balanced with financial pragmatism, anticipated treatment-related toxicities, and a realistic estimation of the degree of benefit in the individual patient.

Neratinib might be provided for HER2-positive, ER-positive tumors with a very high risk of relapse, e.g. locally advanced breast cancer with many positive lymph nodes and residual disease after neoadjuvant therapy including pertuzumab. Given these conditions, I would discuss extended adjuvant neratinib therapy with the patient.

Thürlimann: The implementation and prescription of niraparib in this indication will obviously depend on the registration and reimbursement conditions as it is expected that the drug cannot easily be paid 'out of pocket' by most patients.

We will consider the prescription of niraparib in the given label (and reimbursement solved) for patients at higher risk, evaluating the treatment burden, toxicity, and utility in a given patient and considering that niraparib is a new drug so that all of us still have to learn how to use it best. In the meantime, I am looking forward

to Saturday morning at the St. Gallen Consensus Meeting in Vienna on March 23, 2019 and wonder how the panelists will deal with this issue.

Untch: Extended adjuvant treatment with neratinib after trastuzumab-based adjuvant standard therapy has been approved by the EMA and is also included in some of the international guidelines. Especially in those patients with a prolonged risk despite optimal adjuvant anti-HER2 treatment and with hormone receptor-positive tumors, the treatment option with neratinib is a very good option to be discussed with the patients. Obviously, the side effects have to be weighed against the potential benefits, and prophylactic treatment with loperamide is mandatory.

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