Therapy Standards in HER2-Positive Breast Cancer

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Question 1. Dual Blockade for HER2-Positive Breast Cancer – How to Select Patients for Neoadjuvant Chemotherapy in Combination with Trastuzumab / Pertuzumab?

Liedtke: Dual blockade including a combination regimen with trastuzumab and pertuzumab has been shown to increase pathological complete remission (pCR) rates in comparison to chemotherapy and trastuzumab alone. However, despite its favorable toxicity profile, the addition of pertuzumab in all patients with HER2-positive breast cancer in the neoadjuvant setting carries the risk of both overtreatment and increased treatment costs. Therefore, there is an urgent need to identify subgroups of patients who carry an overall prognosis that is favorable enough to allow exclusion of pertuzumab from their treatment regimen. Predictive factors relevant to this aspect still need to be defined. In the NeoSphere trial, for instance, negative hormone receptor status was significantly and positively associated with an increased chance of pCR. Unless there will be valid parameters in the future, strategies to decide for or against the addition of pertuzumab may rely on baseline prognostic factors (such as tumor size or nodal status) and predictive markers (such as hormone receptor status).

Marmé: Several strategies can be used to select patients for dual blockade strategies. Today, in routine clinical practice stage of the disease to assess the patient's risk is probably the most commonly used method to select patients for dual blockade, additional factors, such as age, hormone receptor status and concomitant diseases, also play a role. Patients who fulfill the inclusion criteria of the APT trial [1] are likely to fare well with trastuzumab plus chemotherapy alone and dual blockade is likely to be overtreatment as long as survival

data of the APHINITY trial are still pending. In the near future, efforts should be taken to validate promising biomarkers, such as tumor infiltrating lymphocytes, estrogen receptor-positive (ER+) status and PI3K mutations. In addition, early response evaluation should also be assessed as a possible stratification factor.

Thill: Adding pertuzumab to trastuzumab in the neoadjuvant setting (NEOSPHERE [2] and TRYPHAENA [3] study) led to a significantly higher pCR rates. Again, the benefit for HER2-positive patients was improved. The survival data of the NEOSPHERE study that were presented at ASCO 2015 showed an increased disease free survival (DFS) for patients who achieved a pCR and consequently another evidence for a translation of an increased pCR into a higher DFS [4]. In my institution patients with a tumor size of ≥ 2 cm – along with the inclusion criteria of the NEOSPHERE study – are treated with the combination of trastuzumab and pertuzumab in addition to chemotherapy. In case of tumors < 2 cm with unfavorable characteristics (i.e. Ki67 of $> 35\%$ or pL1 or pV1) the dual blockade in addition to chemotherapy is also preferred.

Question 2. Less Is More – Which De-Escalation Strategies Are Promising for Which Patients with HER2-Positive Breast Cancer?

Liedtke: In my opinion, the most promising aspect is the reduction in chemotherapy intensity through the use of dual blockade strategies. It is imaginable that the addition of pertuzumab may allow for either developing an anthracycline-free chemotherapy backbone or even a chemotherapy-free treatment schedule. Studies, such as the ADAPT HR-/HER2+ trial [5], explore these strategies.

Patients are randomized to a 12-week therapy with either trastuzumab/pertuzumab alone or trastuzumab/pertuzumab in combination with paclitaxel. Yet, patients are recommended to complete standard taxane (and anthracycline) chemotherapy as postneoadjuvant therapy – however, it seems possible, that in case of a) demonstration of solid treatment efficacy and b) identification of response predictors, this recommendation might be alleviated in the future.

Marmé: The thought of a chemotherapy-free treatment for a subset of HER2-positive breast cancer patients is provoking and promising. However, we need strategies to identify suitable patients (e.g. lymphocyte predominant breast cancers) or reliable methods for early response evaluation. These may include PET imaging (like in the AVATAXHER trial) and could help to implement such a ‘dual blockade without chemotherapy’ strategy or other strategies that spare our patients chemotherapy and toxicity (e.g., dual blockade plus less toxic chemotherapies, such as vinorelbine, eribuline, or T-DM1). Patients with a poor response to these regimens could then go on to receive salvage chemotherapy plus targeted therapy. Optimal duration of these de-escalated regimens will also have to be evaluated.

Thill: The study by Tolaney et al. [1] examined trastuzumab plus single weekly paclitaxel in early HER2 positive breast cancer and showed excellent data with a 3-year-survival free from invasive disease of 98.7% and a 3-year-recurrence free survival of 99.2%. The survival was better than expected. 62.2% of the patients had tumors of ≤ 1 cm and 10.1% an age of >70 years. Therefore, these results offer an option to treat smaller or more favorable HER2-positive tumors or maybe older patients with a single chemotherapy instead of a combination chemotherapy.

In metastatic disease, the recent published study by Dang et al. [6] showed excellent survival data for the first-line treatment with trastuzumab + pertuzumab and paclitaxel instead of the combination with docetaxel. This might be a combination with a more favorable toxicity.

Question 3. What Is the Optimal ‘Place’ for T-DM1 in the ‘HER2 Space’?

Liedtke: The most important aspects with regard to T-DM1 are its solid efficacy and, most importantly, good tolerability. In the ADAPT HR+/HER2+ trial we have seen pCR rates of close to 50% in association with an excellent toxicity profile. Similar to concepts relevant to dual blockade as mentioned above, inclusion of T-DM1 into the neoadjuvant setting may allow for reduced treatment toxicity without the cost of reduced treatment efficacy.

Marmé: Currently, T-DM1 is the standard second-line regimen for HER2-positive breast cancer and standard first-line treatment in patients relapsing early after adjuvant chemotherapy + trastuzumab (and pertuzumab). However, T-DM1, due to its very favorable toxicity profile, is an interesting agent in the neoadjuvant setting and has demonstrated convincing activity in the triple-positive arm of the ADAPT trial. Individualizing therapy, e.g. by giving 4–6 cycles T-DM1 as neoadjuvant therapy, and offering additional adjuvant therapy, e.g. including trastuzumab plus pertuzumab and chemotherapy, to those not achieving pCR with a high Neo-Bioscore could be attractive strategies.

Thill: To date, T-DM1 is the compound of choice in second-line treatment of HER2-positive metastatic breast cancer and, based on the retrospective analysis of the EMILIA study, in the treatment of brain metastases of HER2 positive breast cancer. It is conceivable that due to better tolerability and lower toxicity T-DM1 will replace trastuzumab and chemotherapy in metastatic breast cancer as shown in the MARIANNE trial [7]. It will not replace the dual blockade in combination with docetaxel in first-line treatment [8], unless that is not feasible due to patient’s comorbidities. However, further studies could show the advantage of T-DM1 as a more tolerable HER2-directed approach in early breast cancer.

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