The Role of CDK 4/6 Inhibitors in Breast Cancer Treatment

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Question1: Considering Treatment Options Currently Available, such as Tamoxifen, Aromatase Inhibitors, Fulvestrant and Exemestane plus Everolimus: Is There an Optimal Strategy of Sequencing Endocrine Therapy in Metastatic Breast Cancer Patients? What Is Your Preferred Treatment Algorithm?

Fitzal: When we talk about postmenopausal patients, currently outside clinical trials we have several good options for first-line endocrine treatment. Clearly it is important to start with those drugs that have the lowest side effects and the best outcome, which are in fact aromatase inhibitors or fulvestrant (FIRST trial). However, recent phase III trials exploring the efficacy of combination therapy such as BOLERO2 or PALOMA3 demonstrated a 64% (BOLERO2) and 54% (PALOMA3) improvement in progression-free survival combining an inhibitor with endocrine treatment. The side effects from everolimus (mTOR inhibitor BOLERO2) are different from those of CDK4/6 inhibitors (PALOMA3). We have more experience with the mTOR inhibitor everolimus and are very satisfied with handling the side effects. Stomatitis is a common early finding which can be easily treated by patient information, mouth wash solutions and starting with a lower dosage and increasing later if necessary. Pneumonitis is rare and hyperglycemia is also easy to handle. Neutropenia caused by palbociclib (CDK4/6 inhibitor) is very common, however, not as difficult to handle as chemotherapy-induced neutropenia. Thus our options for postmenopausal patients are as follows:

First line: Our current clinical practice after an adjuvant aromatase inhibitor is *first line exemestane with everolimus*. Depending on comorbidities and compliance *fulvestrant* is a good second

option. However, if patients had no aromatase inhibitor treatment so far, we start with either *fulvestrant* or *letrozole* depending on comorbidities, patients' drug list and compliance.

Second line (if no chemotherapy indicated): exemestane and everolimus will be followed by *fulvestrant with palbociclib*; fulvestrant or letrozole will be followed by *exemestane and everolimus*.

Third line (if no chemotherapy indicated): fulvestrant with palbociclib will be followed by *tamoxifen*; exemestane and everolimus will be followed by *fulvestrant with palbociclib*.

Hubalek: Results from the phase III registration study PALOMA3 show that adding the CDK 4/6 inhibitor palbociclib (Ibrance) to the standard hormonal therapy fulvestrant (Faslodex) more than doubled the duration of disease control, delaying disease progression by roughly 5 months in women with previously treated, hormone receptor-positive, HER2-negative (HER2-) advanced breast cancer. Patients in this trial had received 1 prior endocrine treatment for metastatic breast cancer. The randomized phase II trial evaluating letrozole with or without palbociclib in postmenopausal hormone receptor-positive (HR+), treatment-naïve patients, metastatic breast cancer demonstrated a marked improvement in progression-free survival (26.1 vs. 7.5 months) associated with palbociclib. These data indicate that the combination of palbociclib in combination with letrozole or fulvestrant is more efficacious than one of the two agents alone. Previously, an aromatase inhibitor (AI) or fulvestrant were considered a standard first-line treatment for metastatic breast cancer. This view has been changed in the light of the new data on the CDK4/6 inhibitor palbociclib. In my opinion, the combination of letrozole with palbociclib will move into the first-line treatment. The treatment has al-

ready been approved by the FDA. Exemestane plus everolimus seems a viable option as second-line therapy. However, there is no data on the efficacy of everolimus after a CDK4/6 inhibitor. I would only consider a single agent endocrine agent (AI or fulvestrant) as an alternative in patients with oligometastatic and slow progressing tumors in the first and second line.

Knauer: Having this variety of endocrine options for individual patients is a necessary enrichment for our daily practice, since oncology is more than just strictly obeying guidelines. In St. Gallen we do not adhere to a strict sequence, however, the 'optimal' treatment depends on patient's needs and our treatment goal. Expected side effects play a major role as well as the need for response in certain patients. Fulvestrant has made a step forward in the algorithm after presentation of the survival data from the FIRST study, for example.

Untch: In our national guideline commission of the AGO, the optimal strategy of sequencing endocrine therapy for patients with metastatic breast cancer is the following:

Try to have a biopsy from the leading metastatic site and to prove that the HR status is still positive (including HER2 status of the metastases); in patients who have been on adjuvant tamoxifen, first line treatment is with an AI; in patients who have been on adjuvant AI, the first step is either the combination of exemestane and everolimus or fulvestrant. In patients who have been on both, sequence of tamoxifen and AI, the first-line treatment is exemestane with everolimus or fulvestrant 500 mg. After treatment with a non-steroidal AI, there is also the possibility to treat with a steroidal AI, or vice versa.

Question 2: Based On Available Clinical Data – Do You Believe that CDK 4/6 Inhibitors Are a Valuable Addition to the Therapeutic Armamentarium?

Fitzal: As soon as a breast center has more experience with CDK4/6 inhibitors, they should move into first-line treatment before mTOR inhibitors, as their side effects seem to be less critical.

Hubalek: The PALOMA3 results are very important for women with HR+ advanced or metastatic breast cancer and represent a new standard of care option for women with previously treated HR+, HER2– metastatic breast cancer. The follow-up data on overall survival and quality of life are awaited and will further improve our knowledge on these new agents.

Knauer: From a clinical point of view the PALOMA1 and recently reported PALOMA3 studies are really encouraging. A doubling of progression-free survival in the phase II study and the early stopping of the phase III study due to high efficacy turned the attraction of the oncology community to this new class of agents, which definitely will be incorporated into our daily practice in the near future.

Untch: According to the data of the PALOMA3 study, which have been presented at the ASCO Meeting 2015, and published at the same time in the New England Journal of Medicine by Nicholas Turner and colleagues, the combination of palbociclib 125 mg 3 weeks on, 1 week off, plus 500 mg i.m. fulvestrant every 4 weeks is significantly better than fulvestrant 500 mg i.m. every 4 weeks in patients with HR+, metastatic breast cancer who have been on prior endocrine therapy and have progressed.

Question 3: How Do Toxicity Data of CDK 4/6 Inhibitors Compare to Side Effects of mTOR Inhibitors and PI3K Inhibitors? Are There Differences in the Toxicity Profiles of Different CDK 4/6 Inhibitors such as Palbociclib, Ribociclib, or Abemaciclib?

Fitzal: Clearly there are more possible side effects such as pneumonitis, hyperglycemia, and stomatitis from mTOR inhibitors and very strong side effects from PI3K inhibitors such as diarrhea, rash, pneumonitis, and hyperglycemia. In one case we also noticed epidermolysis of the fingertips. Although all side effects diminish after dose reduction or a complete medication stop, about 10–15% are grade 3–4 and patients need hospitalization.

In contrast palbociclib as CDK4/6 inhibitor induces neutropenia and leukopenia grade 3–4 in more than 50%, however all other grade 3–4 side effects are below 1%. These types of neutropenia and leukopenia are, according to experienced centers, easy to handle and should not be regarded as contraindication. In our center, we have no experience with different CDK4/6 inhibitors.

Hubalek: Side effect profiles of CDK4/6 inhibitors and mTOR inhibitors differ significantly. Even though toxicities such as fatigue, anemia, nausea, stomatitis, diarrhea, thrombocytopenia, decreased appetite, vomiting, asthenia etc. may occur under both agents the intensity of stomatitis under mTOR inhibitors is frequently a reason for dose reductions or even termination of this treatment. In contrast to the toxicity profile of everolimus, the palbociclib combination is generally well tolerated, with only 2.6% of patients having to stop treatment due to side effects, the most common being blood count abnormalities. Despite frequent occurrences of low white blood cell counts, the rates of a serious complication known as febrile neutropenia were very low (0.6%).

The toxicity profile of CDK 4/6 inhibitors is variable depending on the agent studied, with neutropenia being common among all drugs in this class. Grade 3 neutropenia has been noted in up to 50% of patients but is generally uncomplicated, without subsequent febrile neutropenia. In addition, dose delays and reductions result in prompt recovery. Interestingly, anemia and thrombocytopenia are less common. This effect is thought to be due to growth phase arrest of bone marrow cells. Additional reported toxicities include primarily grade 1 and 2 nausea, vomiting, and diarrhea, and, with ribociclib (LEE011), uncomplicated QTc prolongation. For abemaciclib, the most commonly reported all-grade toxicity is

diarrhea, although the most common grade 3 toxicity is still neutropenia. These side effects are less severe than those commonly seen with chemotherapy, but are important complications requiring careful monitoring for patients who are undergoing treatment with this class of drugs.

Knauer: Although in the PALOMA3 study 92% relative dose intensity could be administered, dose interruptions occurred in 54% of all patients on palbociclib with neutropenia being the most common reason leading to dose reductions and interruptions. This clearly tells us that management of these frequent, mostly hematologic side effects is crucial. However the incidence of febrile neutropenia was only 0.6%. There seemed to be less skin and liver toxicity, for example with palbociclib, as compared to the mTOR inhibitors or PI3K-inhibitors, which are also challenging in routine practice. Except from palbociclib we have no institutional experience with other CDK 4/6 inhibitors at our breast center yet.

Untch: In this study with more than 500 patients, the progression free survival was 9.2 months in the palbociclib - fulvestrant arm vs. 3.8 months in the fulvestrant arm. In the central blinded review audit performed in 211 patients, the median progression free survival was not even reached in the 147 patients with palbociclib and fulvestrant. The global quality of life with palbociclib was generally maintained, major side effects have been febrile neutropenia in less than 1%, and somewhat more infections of any grade, but no death due to adverse effects or toxicity. This compares very favorable to PI3K inhibitors and mTOR inhibitors where we see more side effects and toxicities, such as pneumonitis, skin reactions, fatigue, and hyperglycemia.

Question 4: In Your Opinion, What Will Be the Place of CDK 4/6 Inhibitors in the Treatment Sequence of Metastatic Breast Cancer? What Would Be Your Preferred Endocrine Combination Partner for CDK 4/6 Inhibitors? Is There a Potential Role in HER2-Positive Disease?

Fitzal: In the future, CDK4/6 inhibitors will be used as first-line treatment with fulvestrant. Regarding their role in HER2-positive (HER2+) disease: we have some idea that this might work, but as long as we have no long-term data from randomized phase III trials we will not know.

Hubalek: As the results of the clinical phase II and phase III studies indicate, the place of CDK 4/6 inhibitors is in the early lines of treatment of estrogen receptor-positive (ER+) breast cancer. Palbociclib in combination with letrozole has been recently approved by the FDA for the first-line treatment of metastatic breast cancer. The combination of this CDK4/6 inhibitor with fulvestrant appears to be very effective in the combat of metastatic breast cancer that was previously treated with a single endocrine agent. Palbociclib is synergistic with tamoxifen and trastuzumab in ER+ and

HER2+ cell lines, respectively. These preclinical data clearly indicate that the role of CDK 4/6 inhibitors in HER2+ breast cancer has to be investigated in clinical trials in various settings. The subgroup of triple-positive cancers may especially benefit from these new agents.

Knauer: The ideal sequence again might depend on patient's needs and tumor burden for example. Given the subgroup analysis in PALOMA3 at the moment we cannot define specific subgroups that will not benefit from palbociclib. Especially premenopausal women could be an important treatment population. Having said that, patients with increased tumor load and a need for response might be candidates for earlier treatment rather than elderly and frail patients with limited tumor burden who progress on an aromatase inhibitor only after 2–3 years and who are asymptomatic. A head-to-head comparison with an mTOR inhibitor might give us important insights into the question of optimizing treatment algorithms. Regarding the combination partner we theoretically have 2 options at the moment: fulvestrant has recently shown to improve survival in the phase II study FIRST as a single agent and was also used in PALOMA3 as combination partner, which resulted in a hazard ratio of 0.42 for improvement of PFS. The accelerated FDA approval of palbociclib, however, is so far restricted to the combination with letrozol, which is also an oral agent and therefore comfortable for our patients. At the moment I do not see a role for CDK 4/6 inhibitors in clinical routine in HER2+ disease due to lack of clinical study results.

Untch: Until now CDK 4/6 inhibitors have shown additive or synergistic effects with tamoxifen, steroidal and non-steroidal AI (PALOMA1 and PALOMA2), and with fulvestrant (PALOMA3). Therefore, any of the ongoing treatment algorithms for patients with metastatic, HR+ breast cancer is a candidate for the combination with CDK 4/6 inhibitors.

Question 5: Do You Believe that there Is a Potential Role for CDK 4/6 Inhibitors in the Adjuvant and/or Neoadjuvant Setting?

Fitzal: I am quite sure that CDK4/6 inhibition as well as mTOR inhibitors will be good options for neoadjuvant treatment, however, I cannot imagine an adjuvant role so far due to their side effects.

Hubalek: Numerous trials with CDK4/6 in these settings are ongoing. The ABCSG co-lead PALLAS study, is a prospective, two-arm, international, multicenter, randomized, open-label phase III study which evaluates the addition of 2 years of palbociclib to standard adjuvant endocrine therapy for patients with HR+ / HER2– early breast cancer. The purpose of the PALLAS study is to determine whether the addition of palbociclib to adjuvant endocrine therapy will improve outcomes over endocrine therapy alone for HR+ / HER2– early breast cancer. In the post-neoadjuvant setting the PENELOPE-B study explores the efficacy of anCDK4/6

inhibitor in ER+ breast cancer in patients with residual disease after neoadjuvant chemotherapy. CDK4/6 inhibitors will definitely play an important role in the adjuvant and neoadjuvant setting.

Knauer: We are all awaiting the start of the adjuvant PALLAS/ABCSG 42 trial, where we soon will get the opportunity to use palbociclib as adjuvant treatment and find out whether the toxicity in the adjuvant setting is manageable for this large group of patients. A very interesting indication of course is the neoadjuvant setting where we do have a tumor to look closely at and get answers within a few months of treatment rather than after several years of expensive observation. Nevertheless we have learned that results of neoadjuvant studies like pCR-rates cannot easily and always be translated into the adjuvant setting and the implications on long-term survival rates. Many people who thought that no large adjuvant study would ever be possible again or even necessary, had to appreciate that things are not as easy as they seemed to be – a recognition we frequently have to face.

Untch: Obviously, we wait for data from ongoing neoadjuvant, adjuvant and postneoadjuvant studies to prove the role of CDK 4/6 inhibitors in much earlier steps of treatment in breast cancer. In patients with HER2+, HR+ disease a combination of endocrine treatment with the anti HER2-treatment and CDK 4/6 inhibitors has to be awaited. Preclinical data are quite encouraging for this patient population as well.

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