Luminal Metastatic Breast Cancer

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Question 1: What Is Your Preferred Therapy in ER- and/or PgR-Positive Luminal Metastatic Breast Cancer in the First- or Second-Line Setting?

Bartsch: Results from several phase III trials have consistently demonstrated that the combination of endocrine therapy with CDK4/6 inhibitors prolonged progression-free survival (PFS) over endocrine therapy alone to a clinically relevant extent. This effect was not counter-balanced by excessive additional toxicity. While no significant overall survival improvement has been observed to date, a prolongation of time to chemotherapy was repeatedly reported. Currently, a large subset of patients with luminal metastatic breast cancer receives only one line of endocrine therapy before being switched to chemotherapy, emphasizing the importance of prolonging first-line PFS. Therefore, for the average patient, an upfront combination approach is my preferred way to treat; naturally, patient-specific factors such as frailty, comorbidities or compliance issues may prevent the use of a more intense treatment. Some debate also exists regarding the role of upfront CDK4/6 inhibitors in women with nonvisceral disease and low metastatic burden (e.g., bone only). While these patients may remain stable on endocrine therapy alone for up to 2 years, combination treatment still results in a clinically relevant PFS benefit [1].

Marmé: My preferred therapy in this setting is endocrine therapy plus CDK4/6 inhibition for the majority of patients, with the usual exceptions based on patient fac-

tors, etc. My choice of the endocrine backbone depends mostly on prior endocrine therapies and approval status.

Pagani: Endocrine therapy +/- CDK4/6 inhibitors according to their clinical history. I prefer the combination (even though this is not the population treated in clinical trials with CDK4/6 inhibitors) in patients with a short relapse-free interval and with visceral disease, endocrine therapy alone in patients with a long disease-free interval and with bone only disease or limited visceral involvement.

Thomssen: We would routinely treat with endocrine-based therapy depending on the type of previous treatments. Most frequently, treatment with nonsteroidal aromatase inhibitor plus a CDK4/6 inhibitor is recommended. In case of recent aromatase inhibitor therapy, we also use fulvestrant plus CDK4/6 inhibitor. We consider the proven and substantial prolongation of PFS time by the use of CDK4/6 inhibitors as a relevant benefit for patients with metastatic breast cancer.

Question 2: Which Patient with Luminal Metastatic Breast Cancer Would You Treat with Chemotherapy as First-Line Therapy?

Bartsch: First-line combination of endocrine therapy with CDK4/6 inhibitors resulted in response rates resembling single-agent chemotherapy. In addition, time to response seems to be shorter with CDK4/6 inhibitor-

based combination treatment compared to endocrine therapy alone. These facts suggest that the role of single-agent induction chemotherapy today is limited as in patients with highly symptomatic immediately life-threatening disease, combination chemotherapy should be considered.

Marmé: This is a rare exception. I would limit this treatment option to those patients for whom I would assume that if this line of therapy doesn't work, I would not have the chance to try another. Obviously, this judgment is based on many factors which are not well defined. It would, however, also take into account the type of therapies used in the adjuvant setting, the response to these (if available), the treatment-free interval, and the duration of adjuvant endocrine therapy prior to relapse. If the disease has shown resistance to chemotherapy and endocrine therapies in a similar way, it is difficult to choose.

Pagani: Patients with life-threatening visceral disease requiring fast response as per ABC guidelines.

Thomssen: Actually, even in patients with advanced liver metastases we try to treat with endocrine-based therapy. However, in case of visceral crisis we would use chemotherapy (e.g., paclitaxel weekly or epirubicin weekly).

Question 3: What Is Your Preferred Treatment after Progression on CDK4/6 Inhibitors?

Bartsch: The optimal treatment strategy after progression on a CDK4/6 inhibitor-based combination therapy is currently one of the most challenging issues in breast oncology. To date, no information from randomized sequencing trials is available but some data suggest limited activity of endocrine therapy alone in patients pretreated with a combination of endocrine therapy and targeted drugs [2, 3]. Therefore, I would suggest that a combination of endocrine therapy and everolimus may be reasonable with PIK3CA inhibitors being a potential future option.

Marmé: If disease is slowly progressing my first choice would be to try an alternative endocrine-based therapy, e.g., exemestane plus everolimus or the participation in a trial looking into this (e.g., selective PIK3CA inhibitors). Alternatively, an endocrine monotherapy might be an option to avoid chemotherapy if disease is only slowly progressing and asymptomatic, e.g., if the use of mTOR inhibitors is problematic (uncontrolled diabetes, chronic infections like hepatitis or prior therapy with everolimus, etc.). However, my expectations as to the efficacy of endocrine monotherapies after CDK4/6 inhibitors are low.

If disease progresses more rapidly or has not been controlled by endocrine therapy + CDK4/6 at all and there is substantial disease burden, I would preferentially choose chemotherapy.

Pagani: Depends on the individual clinical situation; if the progression is limited I try another line of endocrine therapy, if the progression is clinically relevant I start single-agent chemotherapy.

Thomssen: Since there is no data and no standard in this situation, we discuss all options, including chemotherapy, fulvestrant as single agent, endocrine therapy plus alternative targeted drug (e.g., exemestane plus everolimus), as well as maintenance of CDK4/6 inhibitor and switch of the endocrine therapy. However, after combination therapy with aromatase inhibitor and a CDK4/6 inhibitor, most patients will receive fulvestrant as single agent; after fulvestrant plus CDK4/6 inhibition, most patients will receive first-line chemotherapy. Actually, we only have little experience with exemestane-everolimus after CDK4/6 inhibitor therapy.

Question 4: Should All Patients with Luminal Metastatic Breast Cancer Be Tested for Their BRCA Status?

Bartsch: In triple-negative breast cancer patients, a higher rate of *BRCA* mutation carriers was observed as *BRCA1* mutated breast cancer commonly has a triple-negative phenotype. In contrast, the rate of *BRCA* mutation carriers is considerably lower among luminal breast cancer patients. The majority of breast cancer cases belong to the luminal subtypes; however, the absolute number of luminal breast cancer patients harboring *BRCA* mutation is relatively high. In the light of PARP inhibitors becoming available for routine clinical use, all patients with metastatic luminal breast cancer should eventually be tested for *BRCA* mutations as PARP inhibitors offer the chance for a chemotherapy-free targeted therapy approach even after the exhaustion of endocrine treatment options.

Marmé: Ideally yes, if questions on how this will be reimbursed and how the capacities for the testing can be guaranteed are solved. There is still a lack of knowledge on the prevalence of *BRCA* mutations in sporadic luminal breast cancers and we need to fill this gap and also find out about potential subgroups that may not warrant testing. However, as *BRCA* status will serve as an important predictive biomarker, it is hard to argue to whom this testing could be denied. If, for example, we would apply the arbitrary 10% cut-off used for *BRCA* testing for the

information of risk of disease to other predictive factors, we would not perform HER2 testing in early breast cancer as our rate of HER2 positivity is just below this 10%. Whether PARP inhibitors will live up to HER2-targeted agents is still unclear, and we also have to define how PARP inhibitors fit in with the treatment landscape of metastatic luminal breast cancer and how they would directly compare to platinum-based therapies or if they would still be effective after resistance to platinum.

Pagani: Currently not, but testing should be considered along their clinical course.

Thomssen: In first-line treatment, we have a good option with CDK4/6 inhibition. However, in further lines it can be reasonable to consider a treatment with a PARP inhibitor, although data are not consistent, whilst the EMBRACA trial with talazoparib demonstrated an equal and significant efficacy in both triple-negative metastatic breast cancer patients and hormone receptor (HR)-positive metastatic breast cancer patients (hazard ratio for PFS in HR-positive 0.47, 95% CI 0.32–0.71), the parallel OlympiAD trial showed a significant benefit of olaparib in triple-negative breast cancer only (hazard ratio for PFS in HR-positive 0.82, 95% C.I. 0.55–1.26) [4, 5]. Summarizing the results of both trials, the trend seems to be more in favor of using PARP inhibitors also in HR-positive metastatic breast cancer if a germline *BRCA* mutation has been found. Since FDA recently ap-

proved the use of olaparib and talazoparib and approval by EMA for olaparib is expected soon, now ER-positive patients with metastatic breast cancer, at least for later lines of therapy, should also be tested for *BRCA* mutations.

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References

- 1 Rugo HS, et al. Abstract P5-21-03: Palbociclib (PAL) + letrozole (LET) as first-line therapy in estrogen receptor-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC): Efficacy and safety updates with longer follow-up across patient subgroups. *Cancer Res.* 2018 Feb;78(4 Suppl).
- 2 Di Leo A, Johnston S, Lee KS, Ciruelos E, Lønning PE, Janni W, et al. Buparlisib plus fulvestrant in postmenopausal women with hormone-receptor-positive, HER2-negative, advanced breast cancer progressing on or after mTOR inhibition (BELLE-3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2018 Jan;19(1):87–100.
- 3 Juric D, et al. Abstract GS3-08: Alpelisib + fulvestrant for advanced breast cancer: Subgroup analyses from the phase III SOLAR-1 trial. *Cancer Res.* 2019 Feb;79(4 Suppl).
- 4 Litton JK, Rugo HS, Ettl J, Hurvitz SA, Gonçalves A, Lee KH, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline *BRCA* Mutation. *N Engl J Med.* 2018 Aug; 379(8):753–63.
- 5 Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline *BRCA* Mutation. *N Engl J Med.* 2017 Aug; 377(6):523–33.