Editorial Commentary

Can ADCs broaden the treatment landscape of metastatic ER+/HER2– breast cancer resistant to CDK4/6 inhibition?

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For decades, first line single agent endocrine treatment has been the most important pillar when treating patients with metastatic oestrogen receptor positive (ER+)/human epidermal growth factor receptor 2 negative (HER2–) breast cancer. This single agent approach has recently changed in most patients, with the exception of asymptomatic patients with a very long disease-free interval and a very low tumour burden (1). The addition of any of the three registered CDK4/6 inhibitors (CDK4/6i) to an endocrine drug in the first line of treatment like in MONALEESA 2, 3 and 7 (ribociclib) (2-4), PALOMA-2 (palbociclib) (5) and MONARCH-3 (abemaciclib) (6) showed a significant increase in the median progression-free survival (PFS). Clinical meaningful overall survival (OS) benefit, on the other hand, was only seen so far for ribociclib in the final OS analysis and abemaciclib in the interim analysis (4,7). The optimal position of CDK4/6i in either first or second line in patients with metastatic breast cancer is currently still being investigated in the SONIA trial with first results being expected in the beginning of 2023 (8). For premenopausal patients with rapid progressive or highly symptomatic (including visceral crisis) metastatic ER+/HER2– disease, the RIGHT CHOICE trial has demonstrated that the use of ribociclib with endocrine treatment was similar in comparison to combination chemotherapy regarding time to onset of response and superior considering median PFS (9).

When patients do acquire resistance to combined endocrine treatments using CDK4/6i, they often get switched to classic chemotherapy regimens because efficacy of follow-up therapy with single agent fulvestrant is disappointing (10). Recent developments suggest that the treatment landscape post CDK4/6i can be broadened by use of antibody-drugs conjugates (ADCs) and oral selective ER degraders (SERDs) (11,12). In a recent paper by Rugo *et al.* published in the *Journal of Clinical Oncology* the use of one such ADC, sacituzumab-govitecan (SG) in ER+/HER2– disease is explored (11).

At present, SG is only FDA approved for use in patients with metastatic triple negative breast cancer (13). SG makes use of an antibody directed at binding TROP-2, an epithelial antigen expressed in multiple solid cancers (14,15). The TROP-2 antibody is linked to a topoisomerase-1 inhibitor payload with a high drug to antibody ratio (DAR; 7:1). The linker is cleavable and thus can hydrolysis of the linker lead to payload release in the microenvironment of the tumour leading to a bystander effect. Therefore, the

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effect of SG is not only dependent on the internalization of SG and payload release in the tumour cell. In the phase 3 ASCENT trial, SG was compared to treatment of physician's choice (TPC) in patients with metastatic triple negative breast cancer who had received at least 2 lines of prior chemotherapy (16). Patients treated with SG had a clear improvement of OS in comparison to patients who received TPC (median OS 12.1 *vs.* 6.7 months respectively, hazard ratio (HR) 0.48, P value <0.001).

Since TROP-2 is expressed in all types of breast cancer, a phase 3 study TROPiCS-02 was set up to evaluate the therapeutic impact of SG in patients with metastatic or locally recurrent ER+/HER2– disease (11). Patients should have at least been treated with endocrine treatment, CDK4/6 inhibition and a taxane and should have received at least 2 but not more than 4 lines of chemotherapy in the metastatic setting. Similarly, to the ASCENT trial, SG was compared to TPC (11,16). Median PFS improved by 1.5 month in comparison to TPC (5.5 *vs.* 4.0 months, HR 0.66, P value <0.001) and median OS by 3.2 months (14.4 *vs.* 11.2 months, HR 0.79, P value 0.020) (11). Furthermore, in TROPiCS-02, survival analyses by level of TROP-2 expression made clear that an improvement in PFS and OS were seen irrespective of TROP-2 expression. It is hypothesized that this finding is at least partly explained by the release of payload in the tumour microenvironment and bystander effect (11). The level of intra-patient heterogeneity of TROP-2 expression is currently unknown in patients with breast cancer.

The importance of the bystander effect as well as the DAR was also clearly demonstrated in a direct comparison of trastuzumab-emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd) (17), both drugs that have been FDA approved for use in HER2+ breast cancer. Both directed to the HER2-receptor, T-DM1 makes use of the anti-microtubule emtansine, while the payload of T-DXd is a topoisomerase-1-inhibitor, similar to SG. T-DXd has a higher DAR (8:1 *vs.* 3:1) in comparison to T-DM1 and has a cleavable linker. In DESTINY-BREAST-03 a comparison of T-DXd with T-DM1 was performed in patients with metastatic HER2+ breast cancer. Patients treated with T-DXd had a clear improvement of PFS (28.8 *vs.* 6.8 months) and recent presented OS data also seems to be in favour of treatment with T-DXd (18).

The cleavable linker and bystander effect make the ADC less dependent on overexpression of the target on the surface of the cancer cells. A minimal amount of expression might suffice. This led to the hypothesis that T-DXd might also have a therapeutic effect in tumours with lower expression of HER2: the lesions that were considered 1+ or 2+ [with negative in situ hybridization (ISH)] by immunohistochemistry (IHC), the so called HER2-low breast cancers (19). DESTINY-BREAST-04 aimed at investigating the effect of T-DXd in HER2-low metastatic breast cancer. Both patients with ER+ and ER– breast cancer where included. In case of ER+ disease, the tumour had to be resistant to endocrine treatment and patients could have received 1–2 lines of prior chemotherapy. T-DXd was then compared to TPC. The primary endpoint was the PFS in the cohort of patients with ER+ disease. Secondary endpoints consisted of PFS in the entire cohort and OS in both the ER+ and overall cohort. In the ER+ subgroup, median PFS increased with 4.7 months in the group treated with T-DXd (10.1 *vs.* 5.4 months, HR 0.51, P value <0.001). Similar results were found in the overall cohort with an increase in PFS of 4.8 months (9.9 *vs.* 5.1 months, HR 0.50, P value <0.001). OS improved by 6.4 months (23.9 *vs.* 17.5 months, HR 0.64, P value 0.003) and 6.6 months (23.4 *vs.* 16.8 months, HR 0.64, P value 0.001) in the ER+ and overall cohort respectively. This demonstrates the potential of T-DXd when HER2-low expression was found.

The phase 2 DAISY trial demonstrated activity in patients with a tumour that was classified as being HER2 0 by latest ASCO/CAP guidelines, leading to the introduction of HER2-ultra-low where IHC shows incomplete staining for HER2 in <10% of the cells (20). The benefit of T-DXd in HER2-low and HER2-ultra-low is currently being investigated for patients with ER+ disease in the DESTINY-BREAST-06 trial (21). T-DXd is compared with single agent TPC in patients that priorly either received at least 2 lines of endocrine treatment or who progressed on treatment with CDK4/6i. The primary endpoint that is being evaluated is PFS.

Questions have arisen if HER2-low and HER2-ultra-low should even be considered as a separate entity. One major point of discussion is the reliability of a single biopsy to define the HER2 expression (22). Results of the rapid autopsy program UPTIDER (NCT04531696) were recently presented at SABCS and demonstrated a clear heterogeneity in HER2 expression within one patient and even within the same organ (23). Therefore, treatment decisions based on the expression of HER2 in either the primary tumour or a single biopsy of a metastatic lesion might lead to wrongfully denying a patient a potentially beneficial treatment since HER2 absent lesions might even

benefit from the bystander effect. Nevertheless T-DXd certainly has a lot of potential in the treatment of metastatic endocrine and CDK4/6i resistant ER+/HER2– breast cancer (19). FDA approval was recently given for the use of T-DXd in case of proven HER2 IHC 1+ or 2+ with positive ISH (24).

The targeted release of cytotoxic agents is expected to be less associated with side effects than the use of standard chemotherapy regimens. However, in the ASCENT trial, the use of SG was associated with more neutropenia (63 *vs.* 43%), anaemia (34 *vs.* 24%), diarrhea (59 *vs.* 12%), nausea (57 *vs.* 26%) and fatigue (45 *vs.* 30%) than classic regimens with chemotherapy (15). Most side effects were of low grade and did not lead to treatment discontinuation. Treatment related interstitial lung disease (ILD) occurred only in one of the patients treated with SG and was reversible. In the recent safety analyses of the TROPiCS-02, similar increase in haematological and gastro-intestinal side effects were observed along with an increase in fatigue and alopecia (11). No patients treated in the SG arm experienced any grade of ILD. For patients treated with T-DXd the most common side effects are anaemia, neutropenia, nausea, constipation or diarrhea, alopecia and fatigue (17,19). The most common side effects that were related to discontinuation of the therapy in DESTINY-BREAST-03 were pneumonitis, ILD, and pneumonia (17).

Besides the abovementioned ADCs, other drugs are currently being investigated for their potential use once endocrine and CDK4/6i resistance has occurred. In preclinical setting, multiple drugs that could directly overcome CDK4/6i resistance mechanisms are investigated in combination with endocrine treatment and CDK4/6i (24,25) as well as the use of drugs targeting other CDKs (26). Furthermore, novel ADCs are being develop and tested to be used in al subtypes of breast cancer (27). In clinical setting, the use of elacestrant, an oral selective ER degrader (SERD), presented with improvement of median PFS in the EMERALD trial where prior use of CDK4/6i was required (12). Similarly, the use of camizestrant in SERENA-2 was associated with improved outcomes, although prior use of CDK4/6i was permitted but not required (28). For amcenestrant (AMEERA-3) (29) and giredestrant (acelERA) (30), no increase in median PFS was observed. EMBER-3, which investigates the use of imlunestrant, is still ongoing (31). Additionally, a new proteolytic targeting chimeras (PROTAC) ER degrader called ARV-471 is currently being investigated in a phase 2 trial (32). In preclinical setting these PROTAC ER degraders seem more powerful than SERDs. The CAPItello-291 trial compared the combination of the AKT inhibitor, capivasertib and fulvestrant with the use of fulvestrant alone (33). Patients were allowed to have prior use of CDK4/6i. Overall, the addition of capivasertib increased the median PFS by 3.6 months. A subgroup analysis confirmed beneficial impact of capivasertib in patients with prior CDK4/6i treatment. In BRCA mutated patients, PARP inhibition can be used as another treatment option (34).

The first line(s) of treatment of metastatic ER+/HER2– breast cancer will remain the use of endocrine treatment mostly in combination with CDK4/6i (35). The difficulties lie in the post CDK4/6i treatments. First and foremost, insights into the mechanisms behind the resistance might help to guide the decision for the next line of therapy. One needs to be able to differentiate the ER-driven from the non-ER-driven disease by quantitative assessment and molecular testing of liquid or metastatic biopsies (36). Both can determine the presence or absence of *ESR1* mutations. When the combination of endocrine therapy and CDK4/6i leads to prolonged disease control, the cancer progression often remains ER-driven. In that case, one might first consider the adaption of either the endocrine drug or CDK4/6i which might extend the duration of endocrine treatment for these patients overall as was seen in the PACE (37) and MAINTAIN (38) trial respectively. ESMO guidelines for metastatic breast cancer also support the rechallenge of CDK4/6i (35). Oral SERDs can be used to overcome the resistance mechanisms initiated by *ESR1* mutations (12,39). Mutational analyses can also detect other targetable pathways like AKT/PIK3Ca for the use of alpelisib and everolimus respectively (40,41). While the benefit of everolimus is independent of *PIK3CA* mutational status, the presence of *PIK3CA* mutations is required for the use of alpelisib (42).

Once resistance mechanisms for endocrine and CDK4/6i can no longer be overcome, ADCs form the next reasonable step. T-DXd has been approved for use as second line treatment in metastatic ER+/HER2– breast cancer in case of HER2-low (24). SG has not been approved yet in this setting, but also has great potential and might be used in 3th line after progression on T-DXd although the benefit of SG after T-DXd has not yet been investigated. Use of standard chemotherapy lines are therefore further postponed.

Future trials could additionally offer more insights in the use of these drugs in specific patient populations with

different clinical characteristics like ethnicity or BMI. Considering BMI, abemaciclib seem to work better in patients with underweight or normal weight in comparison to patients with overweight or obesity, although a PFS benefit was seen in all patients regardless of BMI (43). For T-DM1, a higher toxicity was seen in obese patients compared to non-obese patients leading to more treatment modifications (44). Furthermore, the benefit of these therapies needs to be analysed by histological subtype of breast cancer. The differences of underlying pathological and biological features between non-special type breast cancer and invasive lobular breast cancer for instance, lead to differences in treatment response and resistance mechanisms that require further exploration (45). So far, to the best of our knowledge, nothing is known regarding the use of more recent ADCs in these specific clinical or histological groups.

Conclusions

The appliance of treatment regimens with ADCs in patients with metastatic ER+/HER2– breast cancer has great potential to postpone standard chemotherapy lines and increase OS significantly in these patients. T-DXd is approved to be used as second line treatment in metastatic ER+/HER2– breast cancer with low expression of HER2. Further research is needed to look into the impact of the heterogeneity of HER2 on these treatments. The use of SG has demonstrated to be beneficial irrespective of TROP-2 expression and FDA approval for SG in metastatic ER+/HER2– breast cancer is awaited.

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Footnote

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