

## **ASCO 2024: personal insights and a look into the future from an international expert group [Letter]**

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# ASCO 2024: Personal Insights and a Look into the Future from an International Expert Group

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## **In your own opinion, which study/presentation at ASCO 2024 was the most important one that changes the daily treatment recommendations for your patients and that you would apply tomorrow?**

*Tarantino:* The presentation of the results of the DESTINY-Breast06 (DB06) phase 3 trial certainly was a highlight of ASCO 2024, leading to an immediate change in practice for the treatment of metastatic breast cancer (MBC).

*Ditsch:* In my opinion, the Destiny Breast 06 study – presented by Prof. Guiseppe Curigliano – was the most important one at ASCO 2024 that will have an impact on the everyday treatment of our patients with breast cancer. Following the outstanding data from DB 04 (ASCO 2022), which showed a significant improvement in PFS and OS with T-DXd in HR-positive Her2-low MBC from line 2 onward, data on Her2-low expression using TDxd in the chemo-naive setting were now shown, which were also associated with a significant benefit over the therapy chosen by the physician. The study thus shows for the first time an excellent efficacy of TDxd, which also persisted when the group of Her2-ultralow tumors ( $\leq 10\%$  membrane staining) was added. In special cases and in consideration of the side effects, this has great significance for future use in everyday clinical practice.

*Wolfrum:* There is no doubt that DB-06 is the most impactful study for HR+ Her2-negative patients in the metastatic setting. The good news is that 85% of patients in this subgroup express Her2 and could benefit from TDxd. So we can treat a broader spectrum of patients with an anti-Her 2-directed therapy in the future. But there are still questions about testing methods and Her2 thresholds. So for me and my patients, the most interesting abstract in terms of what would I apply tomorrow is abstract 513: the impact of adjuvant endocrine omission in ER-low (1–10%) early-stage breast cancer presented by Grace M. Choong from Mayo clinic.

A national cancer database analysis between 2018 and 2020 was performed and identified 10,396 patients as ER-low. A median 3-year follow-up showed a 25% higher risk of death for those patients who omitted adjuvant endocrine therapy compared to those who received endocrine therapy. Clear data to encourage patients in ER-low early-stage breast cancer to stick to endocrine therapy in the adjuvant setting.

*Marmé:* To pick one single study, DESTINY-Breast06 will impact our clinical practice most in the near future. This study will ultimately extend the population of patients with HR+ MBC that will be able to benefit from trastuzumab deruxtecan and include more 1st-line patients as well as patients with HER2-ultralow status (IHC0 with faint and incomplete membrane staining

in  $\leq 10\%$  of cells). While we await the formal extension of the label, these data will help to apply for reimbursement for individual patients at least in some countries.

**DB06 showed an improvement in survival for HER2-low and -ultralow MBC patients. What was the most important aspect of this trial for you? How do you interpret the present study in terms of choosing one ADC over another? Does it influence your daily practice? Do we actually still need to test for HER2?**

*Tarantino:* The importance of DB-6 is twofold: on one side, the demonstration of the relevant activity of T-DXd in patients with HER2-ultralow (i.e., IHC 0 with up to 10% of cells having weak staining) MBC will significantly expand the use of this drug in clinical practice. Approximately 20–25% of patients with HR+ MBC have HER2-ultralow disease, and DB06 found an ORR  $>60\%$  and an mPFS of 13 months with T-DXd in this population, which was impressive. Based on this finding, T-DXd will now become a treatment option for 90% of patients with HR+ MBC. Of note, HER2 IHC seemed to matter in DB06: the largest PFS benefit (HR: 0.43) was seen in IHC 2+, followed by IHC 1+ (HR: 0.74) and IHC 0 ultralow (HR: 0.78). Given this observation, I think it remains relevant to test for HER2 within the HER2-negative space, although I hope we will have available fit-for-purpose quantitative assays soon.

On the other side, the major aim of the trial was to evaluate the role of T-DXd in chemo-naïve patients. In this population, T-DXd significantly improved PFS (13.2 vs. 8.1 months, HR: 0.62,  $p < 0.0001$ ) compared with chemotherapy, becoming the preferred ADC for chemo-naïve patients and a new first-line chemotherapy option. Given that the trial mostly included patients with visceral metastases, this represents the population where I would consider an early use of T-DXd (i.e., before chemotherapy), whereas for patients with non-visceral and/or indolent disease, I will still consider capecitabine a valid alternative, given the oral route of administration, lack of alopecia, and low cost.

*Ditsch:* For me, the most important aspect is the significant effect on PFS of TDxd has now been shown for the earlier use in chemo-naïve (after endocrine therapy) situation (HR+ and Her2-low) as well as in an extended patient group (Her2-ultralow). This also results in a temporal sequence in favor of TDxd when using ADCs. Whether Her2 still needs to be tested cannot currently be conclusively assessed with this study. However, as Prof. Curigliano mentioned in his presentation, there is already an effect from a single positive cell. For me, this is at least an indication of a possible positive effect for Her2-negative tumors as well.

*Wolfsum:* The most impressive aspect of DB06 is the comparatively long mPFS of around 13 months in the Her2-low and -ultralow situation. Therefore, according to the results of DB-04 and now new from ASCO 2024 of

DB-06, the preferred ADC to start with would be TDxd in the endocrine-resistant setting while we are waiting on more robust phase III data from Dato-DXd. In the triple-negative metastatic setting, sacituzumab deruxtecan would be the preferred initial ADC since DB-04 included only a small number of triple-negative patients.

It is obvious that IHC is not the best methodology to test Her2 and that we need new quantitative Her2 testing assays or alternative biomarker scoring strategies. Several assays are in development and are actually incorporated into trials. For some ADCs, levels of biomarkers do not matter, e.g., Nectin-4 and Trop-1. But for trastuzumab deruxtecan, preclinical data suggest that there is a lower limit of Her2 expression below which TDxd shows no efficacy. So we need those assays. Until then, we have to talk to our pathologists and tell them that any staining matters. DESTINY-Breast15, an ongoing phase 3 study, will answer the question if patients with IHC 0 will profit from TDxd as well.

*Marmé:* DB-06 has clearly demonstrated compelling activity in terms of ORR and PFS in patients HR+ HER2-low and -ultralow MBC. A response rate approaching 60% is unprecedented in this patient population; thus, this is a very effective treatment option.

One of the most important questions to me is, if every eligible patient should receive T-DXd in the first-line setting. In other words, what is the ideal treatment sequence in individual patients? For some patients, the tolerability of alternative mono-chemotherapies might be preferable, so different options could be discussed in the first-line setting. It is also important to note that patients included in DB-06 have been selected based on endocrine resistance (either  $\geq 2$  lines of ET  $\pm$  targeted therapy for MBC or 1 prior line for MBC and either progression within 6 months of first-line CDK4/6i or within the first 2 years of adjuvant endocrine). We are now able to base our treatment decisions on 2 large randomized trials, DB-04 and DB-06. DB-04 was largely run in the second-line setting with few first-line patients with rapid progression after chemotherapy. DB-04 demonstrated significant and clinically meaningful improvements in ORR, PFS, and also OS. The absolute difference in median PFS was very similar in DB-04 and DB-06 (4.7 and 5.1 months) with a slightly better HR in DB-04 (0.51 vs. 0.62). The first OS interim analysis did not yield significant results yet. In DB-04, OS was significantly improved at the first analysis with a very similar maturity. This might be partly due to 20% of patients receiving post-study T-DXd in DB-06, which was not possible in DB-04, but also due to a worse performance of the control arm in second-line, while T-DXd retained most of its activity. This can be demonstrated by looking at the ORR in the control arm and the delta between arms in both trials. The ORR in the control arms was 32% in DB-06 but only 16% in DB-04, whereas response rates were more similar for T-DXd in both studies (57% vs. 53%). To make a point, similar

benefit from T-DXd could be obtained in both settings. So this will leave room for individual discussion with select patients. Patients with a high tumor burden, rapid disease progression, etc., should definitely receive the most efficacious treatment option in the first-line (chemo) setting, which undoubtedly is T-DXd. There will remain some select patients with comparably indolent disease which might opt for capecitabine in first-line and go on to T-DXd subsequently. The problem of attrition from one line of therapy to the next should also be discussed. The data for the ultralow population are in line with what we have seen in the DAISY-study and looks convincing, even if a smaller cohort, so this will become a new option for these patients altogether. To conclude: for me, T-DXd in the first-line will become the standard of care for most patients with HR+ HER2-low and -ultralow MBC, with maybe few exceptions. Do we still need to test for HER2? This is what we have evidence for. However, we have now provided evidence that T-DXd is better than standard monochemotherapy for 90% of patients, so one could ultimately postulate that you need to prove that the remaining 10% are truly not benefitting. This evidence is lacking. We have also learned that there is temporal and spatial heterogeneity in terms of HER2-low status; this will likely also hold true for HER2-ultralow, so getting retesting and re-biopsies in truly HER-zero patients makes sense. Above all, we will have to stick to the label.

**We continue to see data on ADCs and discuss that those will probably substitute chemotherapy in MBC. With the DB06 data, efficacy data from another study was added to the journey of ADCs in breast cancer. The data on sequencing ADCs so far were retrospective with little success for the second ADC. Were there any new data presented at ASCO that would help us in sequencing ADCs? And were there any new studies on the ADCs' safety?**

*Tarantino:* At ASCO24, we presented an analysis of T-DXd by prior SG in the Flatiron database ( $n = 119$ ): we found shorter rwPFS (3.4 vs. 5.7 months,  $p = 0.005$ ) among patients that received T-DXd after SG. This is consistent with most studies and suggests some degree of cross-resistance between Topo1 ADCs. We're now about to open at DFCI the first randomized trial in the field, TRADE-DXd (PI: Garrido-Castro), which will randomize patients to the sequence of T-DXd -> Dato-DXd or the opposite, hoping to produce prospective clinical data and translational insights in this important field.

In terms of safety, I believe we're doing a great job as a community at raising awareness on the side effects of ADCs, but DB06 reminded us about the importance to keep working hard at this: similar to prior studies with T-DXd, there were still approximately 11% of the patients

experiencing ILD, including three deaths. Cardiotoxicity also needs to be kept in mind: 8% of the patients had decreases in LVEF, although these were mostly low grade. All patients receiving T-DXd should be followed with periodic CT scans of the chest (every 6–12 weeks) and echo (every 3–6 months).

An interesting study presented at ASCO24 was PRIMED: among 50 patients receiving SG with prophylactic G-CSF and loperamide, none experienced febrile neutropenia, and the rates of neutropenia and diarrhea were low. I believe that the most compelling component pertains the neutropenia, supporting the use of G-CSF prophylaxis to ensure a safe administration of the drug.

*Ditsch:* Looking at the data, presented at ASCO 2024, sequencing of ADCs in an earlier line is favored for TDxd compared to SG. First results of a study which used SG prior to TDxd showed worse rwPFS.

Regarding safety, ILD (11%) remains one of the most important side effects. Within the TDxd arm, 3 deaths occurred. Cardiotoxicity is also important: 8% of the patients had decreases of the LVEF.

*Wolftrum:* New data from studies including TDxd, SG, and datotomab deruxtecan show consistent safety profiles even in new combinations, e.g., with immunotherapy. Interestingly, ADCs that target similar antigen can have different toxicities. Datotomab deruxtecan causes stomatitis and dry eyes which is different from SG and TDxd. With SG, we see more neutropenia, and interstitial lung disease occurs with TDxd. In DB06, there were 3 deaths caused by interstitial lung disease. This emphasizes again the importance of being aware of the symptoms of interstitial lung disease among therapists and patients.

Data on sequencing ADCs are still not very encouraging. At this year's ASCO, there was a poster presentation from the Memorial Sloan Kettering Cancer Center showing real-world outcomes of sequential ADC therapy in heavily pretreated MBC patients. Patients were treated with sacituzumab govitecan and then trastuzumab deruxtecan and vice versa. The clinical activity of the following ADC was only modest with PFS of around 3 months for each ADC. Soon, the TBCRC064 trial will start recruiting, addressing the question if switching the target can overcome resistance (TDxd followed by Dato-Dxd and vice versa).

*Marmé:* Our current problem in sequencing ADCs is based on the fact that the 3rd-generation ADCs approved for breast cancer rely on payloads with similar mode of action, namely, topoisomerase I inhibitors. So for now, we can only change the targets when sequencing ADCs. This shows in the limited data that has been presented through the last year at ASCO, SABCS, which is in line with what has been demonstrated at ASCO 2024. Most prominently, these were real-world data from the flatiron database. Tarantino et al. demonstrated a shorter rwPFS with T-DXd in patients with prior sacituzumab govitecan (3.4

vs. 5.7 months). Another study looking at the sequential use of T-DXd and SG presented at ASCO (Huppert et al., Abstr. 1083) confirms these data. In this study, thus, rwPFS was distinctly shorter for the second ADCs, regardless of the order of sequence and HR-status. The mechanisms of resistance to ADCs are manifold; some relating to the target; some to the payload; but others also on ADCs internalization, trafficking, and the cleavage of the payload. So it remains to be seen if changing the target as well as the payload mode of action will lead to ADCs sequencing with similar efficacy for the second ADC.

The toxicity profiles for the currently approved ADCs are well described, and we have seen safety data from DB-06 which reminds us that identifying ILD early remains an issue and is key for retaining patients on therapy. Rechallenge is only an option after resolution of grade 1 (asymptomatic) ILD; thus, CT scans remain the gold standard, and they should be done frequently. In most studies, this was done 6-weekly. Each institution will have to find a way how to screen in clinical routine, but in addition, education of the patients as well as the entire interprofessional team is key. Echocardiograms should also be done regularly. For sactizumab govitecan, a small prospective study has demonstrated that with prophylactic measures, including GCSF and loperamide rates of dose reduction and discontinuations can be decreased and patients' safety increased. We have used this liberally already from our clinical experience, but now, there is prospective data to support this approach. We have also seen data on novel ADCs, like ARX788, with distinct safety profiles. If and how all these new ADCs will enter the clinic is yet unclear, but being able to manage ocular toxicities or stomatitis will be of importance in future. Management of ocular toxicities has been established for ADCs used outside the breast cancer world (mirvetuximab soravtansin and tisutumab vedotin), and we'll be able to learn from these experiences. Prophylactic measures for stomatitis will also be in the focus if Dato-DXd enters the clinic.

**We have seen more data from NATALEE and MonarchE at ASCO. The studies have overlapping patient population. If both CDKi are suitable for your patient, which would you choose and do the presented new data influence your decision?**

*Tarantino:* The positive data from both trials raise hope that we can prevent recurrences and improve outcomes with adjuvant CDK4/6 inhibitors. At present, only abemaciclib is approved for the adjuvant use; this is also the agent with longest follow-up available and has shown relevant reduction in the risk of recurrence at 5 years. Therefore, for patients that would have met both

the monarchE and NATALEE enrollment criteria, I tend to prioritize abemaciclib.

However, for patients with lower risk disease (e.g., node-negative), who would have only met the NATALEE criteria, offering ribociclib is reasonable. In this sense, the updated analysis presented at ASCO24, showing nearly 4% reduction in the absolute risk of distant recurrence at 3 years among patients with node-negative disease receiving ribociclib, was quite promising.

*Ditsch:* MonarchE (abemaciclib) as well as NATALEE (ribociclib) reached their primary endpoint and therefore are positive studies. Both studies primarily show an effect in the high-risk situation of early breast cancer.

Currently, only abemaciclib is approved. MonarchE has a longer follow-up.

Ribociclib is expected to be approved toward the end of the year. There is also an advantage for the node-negative subgroup, but this must be weighed up in relation to the side effects.

*Wolfrum:* Data from NATALEE at ASCO 2024 show that there is a signal that node-negative patients at higher risk benefit from treatment with ribociclib as well. Here, we carefully should keep in mind the suggested adjuvant duration of treatment of 3 years. It is so far unclear whether these patients actually need 3 years of therapy or not. Considering this long duration of treatment, we need new biomarkers that indicate possible benefit from adjuvant CDK4/i therapy. In our clinic, if both CDKi were suitable for the patient, we would prefer abemaciclib over ribociclib because of longer follow-up data. With ribociclib, we have to be aware of more interactions with additional medication, e.g., antidepressants. And last but not least, still olaparib is an alternative option in the adjuvant setting for those patients that are BRCA-mutated.

*Marmé:* In patients with HR+/HER2- EBC and high risk of recurrence, defined by stage and biology, the risk of recurrence remains substantial even after (neo)adjuvant chemotherapy and optimal endocrine therapy. Adjuvant CDK4/6 inhibitors offer a clinically meaningful improvement in DDFS. Neither of the two studies has demonstrated an improvement in overall survival yet, but follow-up with respect to this endpoint remains short. In patients for which both options would apply, I currently prefer abemaciclib, mainly because of the maturity of the data with longer follow-up and the convincing demonstration of a carry-over effect. In addition, the shorter duration of therapy of only 2 years might be preferred by many patients as well as from an economic stand point. We have to bear in mind that there have been negative studies with adjuvant CDK4/6 inhibition (PALLAS, PENELOPE B), so sufficient follow-up is key to interpret data of these trials. It could be projected that data of NATALEE will evolve in a similar fashion to what we have seen in monarchE with longer follow-up, but

especially for the intermediate risk population (which is unique in NATALEE), namely, the node-negative population, follow-up currently is too short to have a definitive answer as to the absolute benefit for these patients. However, ribociclib offers an additional option that can be discussed weighing risks and benefits for patients otherwise not covered by adjuvant abemaciclib. Approval of adjuvant ribociclib in Europe is still pending. Currently, apart from differences in follow-up and robustness of data, different patient populations covered by the labels, different toxicity profiles, and treatment duration, there are no further useful selection criteria for one CDK4/6 inhibitor over the other in the adjuvant setting. The additional data of the baseline characteristics in NATALEE with a 5-month longer follow-up confirm the data but do substantially add to it. Dynamics of ctDNA in monarchE was also presented and confirms the prognostic role of ctDNA, especially with respect to early relapses. It will be important to see the potential influence of treatment on the conversion of patients positive for ctDNA at baseline to negative during the course of therapy.

### **A look into the future: How do you think do we treat early breast cancer in 5 and 10 years in regards to systemic therapy as well as surgery?**

*Tarantino:* My prediction (and hope) is that we will progressively move away from one-size-fits-all paradigms for all breast cancer subtypes, with the help of novel biomarkers and innovative drugs.

ctDNA, gene signatures, TILs, and dynamic imaging will help us understanding the intensity of treatment required for each patient, with some patients cured by de-escalated regimens and who may even be spared surgery, if their tumor is found to be exquisitely sensitive to systemic treatment. For those patients with higher risk tumors, however, novel drugs will play an increasing role. Immunotherapy is established in TNBC and may soon expand to the high-risk HR+ disease. ADCs are clearly more effective than chemo and in some instances will substitute this in the (neo)adjuvant setting. CDK4/6 inhibitors and PARP inhibitors will remain key for many patients, as will some form of chemotherapy. The tolerability of our treatments will likely be further improved by innovative technologies, possibly by wearable devices and/or AI-assisted techniques to predict side effects.

One aspect will remain key even in 10 years: listening to the patient. Some patients may wish to maximize the chances of cure, while some others may favor avoiding the risk of unnecessary side effects. This may be the single most important opportunity offered by novel biomarkers and drugs: personalizing care according to

patients' preferences and making sure that our treatments align with the values of each patient we meet in the clinic.

*Ditsch:* Currently, system-therapeutic approaches, which, e.g., require evidence of several positive axillary lymph nodes before a certain medication can be used, are in contrast to the surgical development with more and more de-escalation. Future therapies will be based more on jointly coordinated approaches (surgical and systemic). In my opinion, it will be possible to further minimize surgical procedures and combine them with systemic therapeutic approaches in a meaningful way.

In addition, more precise methods of determining biomarkers will allow significantly more individualized treatment methods than was previously possible. What should not be neglected, especially in the age of artificial intelligence, is taking time for communication with patients and their caregivers.

*Wolfrum:* Clearly the surgical goal is to deescalate whenever it is oncologically safe. I am sure that in early breast cancer, the sentinel procedure will be replaced by imaging in early breast cancer. The results of the Sound trial are promising, and several other study results will follow until 2027 including data from the INSEMA trial with a sample size of over 5,000 patients at the end of 2024. Hopefully, data from the Taxis trial will show that we can omit axillary dissection in cN+ patients as well.

New techniques will help to engineer substances that modify and target the tumor immune microenvironment to overcome resistance to immunotherapy and other therapies. So the chance to prolong OS will improve. But there is still room for improvement in identifying patients that are in higher risk of relapse and who need more treatment; so, hopefully, will get more tools to better select them. But on the other hand, we need to avoid a spiral to escalation and more toxicity, especially in the adjuvant setting.

*Marmé:* In very general terms, ADCs will be part of earlier settings including neoadjuvant and post-neoadjuvant setting. Immune checkpoint inhibitors could also become a standard in selected high-risk HR+/HER2- EBC as neoadjuvant and adjuvant therapy, further improving prognosis of EBC.

We will have to address the question, what the best treatment option are post adjuvant CDK4/6i, post ADC, and post immunotherapy. In the post-CDK4/6i setting, AKT and PIK3CA inhibitors will play a role in biomarker defined populations. Hopefully, the ADC toolbox will have grown to include options that make sequencing ADCs more promising, i.e., new targets and payloads, bispecific ADCs, and dual payload ADCs. With a variety of options against divers targets, AI shows promise to help pathology to define biomarkers, to select the best ADC (or any drug) for the individual patient.

Hopefully, in 10 years, we'll have leveraged the potential clinical utility of ctDNA in terms of defining risk to spare or escalate treatment, early response evaluation, and early detection of recurrences with corresponding therapeutic strategies. My hope is that we will turn MBC into a potentially curable disease. With all technological advances, oncology will remain an art which must be patient-centered and reflect the patients' wishes and requirements.

### Conflict of Interest Statement

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