European Journal of Cancer 117 (2019) 1–4

Available online at www.sciencedirect.com

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Editorial Comment

Treatment in real-life patients with HER2-positive metastatic breast cancer: What we learn from the KAMILLA trial?

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Received 18 April 2019; accepted 26 April 2019
Available online 21 June 2019

KEYWORDS
T-DM1

The advent of anti-HER2 agents dramatically changed the natural history of HER2-positive breast cancer. Strong research efforts have brought, starting with trastuzumab, a class of anti-HER2–targeted therapies, which includes, at present, four approved agents in the metastatic setting: trastuzumab, lapatinib, pertuzumab and trastuzumab emtansine (T-DM1). These agents have led to doubling median overall survival (OS), which is currently longer than 55 months, and more than tripling the 5-year survival rate [1].

Notably, trastuzumab, pertuzumab and lapatinib have very modest activity as monotherapy, and concomitant chemotherapy administration is needed for optimal activity. With T-DM1, the chemotherapy backbone has been directly linked to the antibody allowing a targeted tumour delivery of an otherwise extremely toxic compound, DM1. T-DM1 is approved for treatment of patients with HER2-positive metastatic breast cancer who previously received trastuzumab and a taxane or relapsed shortly after surgery based on results from two randomised trials. A study of trastuzumab emtansine versus capecitabine + lapatinib in participants with HER2-positive locally advanced or metastatic breast cancer (EMILIA) demonstrated a significantly longer progression-free survival (PFS; 9.6 versus 6.4 months; $p < 0.001$) and OS (30.9 versus 25.1 months; $p < 0.001$) and fewer grade ≥ 3 adverse events (AEs; 41% versus 57%) compared with capecitabine plus lapatinib [2]. A study of trastuzumab emtansine in comparison with treatment of physician's choice in

DOI of original article: https://doi.org/10.1016/j.ejca.2018.12.022.
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https://doi.org/10.1016/j.ejca.2019.04.028

participants with HER2-positive breast cancer who have received at least two prior regimens of HER2-directed therapy (TH3RESA) demonstrated improved PFS (6.2 versus 3.3 months; $p < 0.0001$) and OS (22.7 versus 15.8 months; $p = 0.0007$) over treatment of physicians' choice in patients with prior progression on ≥2 anti-HER2 therapies [3,4]. Also in this study, the incidence of grade ≥3 AEs was lower with T-DM1 (32% vs 43%). As many patients with metastatic HER2-positive breast cancer are candidates for T-DM1 treatment, it is paramount to carefully understand T-DM1 safety and tolerability.

In the current issue of the *European Journal of Cancer*, Montemurro *et al.* [5] reported the results of the KAMILLA trial. This is a single-arm, open-label, phase IIIb safety study of T-DM1 (3.6 mg/kg every 3 weeks) in patients with HER2-positive advanced breast cancer with progression after prior treatment with chemotherapy and a HER2-targeted agent for metastatic breast cancer or within six months of completing adjuvant therapy. The primary objective was to assess T-DM1 safety and tolerability. KAMILLA, with 2002 patients, is the largest cohort of T-DM1–treated patients studied so far. Notably, the inclusion criteria were less strict as compared with registration studies, thus better mirroring the population observed in clinical practice. Indeed, the KAMILLA population has a higher proportion of patients aged ≥65 years and more patients with symptomatic disease (e.g. Eastern Cooperative Oncology Group = 2), visceral disease, baseline CNS metastases and hormone receptor–positive breast cancer, and patients received a greater range of prior lines of treatment [2,3,6].

Consistently with previous studies [2,3,6], the KAMILLA trial reassures that the favourable safety profile is maintained even in a population closer to real life, without unexpected or new side effects. AEs and serious AEs occurred in 1862 (93.0%) and 427 (21.3%) patients, respectively. The most common grade ≥III AEs were anaemia, thrombocytopaenia, fatigue, gamma-glutamyltransferase elevation and asthenia; each of which occurred in ≤3% of patients. In the KAMILLA trial, 11.8% of patients discontinued drug because of adverse event of any grade. This proportion was 5.9% and 9.8% in the EMILIA and TH3RESA trials, respectively [2,3].

Concerning efficacy, median PFS was 6.9 months (95% confidence interval [CI], 6.0–7.6) and OS was 27.2 months (95% CI, 25.5–28.7). Although indirect comparisons should be carried out with caution, considering the different population enrolled in this trial, the results are in line with those reported by the EMILIA and TH3RESA study [2,3]. As expected, in the KAMILLA trial, median PFS decreased from 8.3 to 5.6 months and median OS from 31.3 to 22.5 months with increasing number of prior treatment lines (0–1 versus 4+).

The KAMILLA trial does not add information on the efficacy of T-DM1 in a population pretreated with pertuzumab, which has become the standard of care for first-line HER2-positive metastatic breast cancer and, for this reason, represents the majority of the patients treated now with T-DM1 in the real-life setting. However, other real-life data and an exploratory analysis from the study to evaluate pertuzumab + trastuzumab + docetaxel vs. placebo + trastuzumab + docetaxel in previously untreated HER2-positive metastatic breast cancer (CLEOPATRA) and study of a combination of trastuzumab and capecitabine with or without pertuzumab in patients with HER2-positive metastatic breast cancer (PHEREXA) trials with the small number of patients treated with T-DM1 at any time after pertuzumab suggest that T-DM1 is active in this population. Recently, T-DM1 in the KATHERINE trial has demonstrated to lower the rate of recurrence by 50% among patients with HER2-positive early breast cancer who had residual invasive disease after completion of neoadjuvant therapy as compared with trastuzumab [7]. In perspective, on one hand, safety results from KAMILLA trial reassure on the use of T-DM1; on the other hand, T-DM1 will likely become the standard of care in this early setting population, dictating future research to clarify the role of T-DM1 in the metastatic setting after previous T-DM1 exposure. The clinical heterogeneity of benefit from T-DM1 clearly appears also in the KAMILLA trial, with more than 25% of patients progressing at the first assessment and almost 20% of them progression-free at 2 years. Unfortunately, this trial does not help identifying who are those patients who will benefit the most from T-DM1 administration and who are those who should be considered for different therapeutic options. Considering the mechanism of action of T-DM1, capturing the heterogeneity of HER2 membrane expression represents one of the most promising biomarkers. As an example, the HER2 imaging study to identify HER2 positive metastatic breast cancer patient unlikely to benefit from T-DM1 (ZEPHIR) used zirconium-89 (89Zr)-trastuzumab (HER2–positron-emission tomography) to capture this heterogeneity in patients with HER2-positive metastatic breast cancer suitable to T-DM1 therapy. Patients with a weak or very heterogeneous HER2 signal benefit the less from treatment [8]. This and similar approaches deserve further investigation to improve treatment tailoring.

Overall, the KAMILLA trial confirmed the efficacy and the favourable safety profile of T-DM1, reinforcing its role in the therapeutic algorithm of advanced HER2-positive breast cancer. However, despite the remarkable outcome improvement, resistance to anti-HER2 therapies invariably emerge and metastatic HER2-positive breast cancer is still an incurable disease. Thus, new therapeutic options are needed.

Considering the success of T-DM1, the intense development of new antibody-drug conjugates (ADCs) should not surprise [9]. The two ADCs at the most advanced stage of development are DS-8201a, a molecule combining an anti-HER2 antibody and an exatecan derivate, and SYD-0985, an agent composed by trastuzumab conjugated with duocarmycin.

Considering that trastuzumab works at least partly through antibody-dependent cellular toxicity [10,11], another new therapeutic approach is the generation of anti-HER2 antibodies in which the Fc portion has been engineered to increase the antibody-dependent cellular cytotoxicity (ADCC) engagement, and margetuximab is one of the most promising examples [12].

HER2-enriched tumours are considered immunogenic [13–16], and preclinical models suggest a synergistic effect combining immune checkpoint inhibitors and HER2-targeted antibodies [17,18]. Considering also the success of immunotherapy in most of solid tumours, many clinical trials combining anti-PD-(L)1 agents with HER2-targeted agents have been started. The phase Ib/II pembrolizumab plus trastuzumab in trastuzumab-resistant, advanced, HER2-positive breast cancer (PANACEA) trial evaluated the addition of pembrolizumab to trastuzumab in patients who previously progressed on trastuzumab [19]. In the PD-L1–positive cohort, a promising 15% response rate was observed, whereas no responses were seen in the PD-L1–negative tumours [19]. Recently, results from study to evaluate the efficacy and safety of trastuzumab emtansine in combination with atezolizumab or atezolizumab-placebo in participants with human epidermal growth factor-2 (HER2) positive locally advanced or metastatic breast cancer (BC) who received prior trastuzumab and taxane based therapy (KATE2), a randomised phase II study of atezolizumab + T-DM1 vs placebo + T-DM1 in pretreated HER2-positive breast cancer, have been presented. The addition of atezolizumab to T-DM1 did not demonstrate a meaningful PFS benefit in the intent to treat (ITT) population, but consistently with the PANACEA trial, there was some PFS benefit for the combination in PD-L1+ patients. However, it is difficult to estimate the magnitude of the benefit, given the small population and the corresponding wide confidence interval of the hazard ratio.

A growing list of bispecific antibodies (BsAbs) are currently being investigated as additional therapeutic options for HER2-positive metastatic breast cancer. BsAbs are monoclonal antibodies targeting two different epitopes together, either in the same receptor or in different receptors, thus allowing deeper pathway suppression, multiple pathway suppression or compulsory link between cancer cells and immune cells [20,21].

Several new tyrosine kinase inhibitors (TKIs) are in development. One of the most promising is tucatinib, a selective HER2 inhibitor, which may reduce toxicity, thus ultimately improving dose intensity and efficacy. Initial data suggest a significant activity, remarkably also in patients with brain metastasis due to its ability to cross the blood–brain barrier [22]. Currently, tucatinib is being tested in patients after second line, who previously received both trastuzumab and T-DM1, with or without brain metastasis. So far, in the metastatic setting, neratinib has shown disappointing efficacy with remarkable toxicity [23]. Currently, the study of neratinib plus capecitabine versus lapatinib plus capecitabine in patients with HER2+ metastatic breast cancer who have received two or more prior HER2 directed regimens in the metastatic setting (NALA) (NCT01808573) trial is testing neratinib + capecitabine vs lapatinib + capecitabine in third line or more. For this drug, it is necessary to find also an adequate regimen of diarrhoea control.

Further efforts are needed to improve patient selection and treatment response with the ultimate goal of avoiding unnecessary toxicity and improving cost-effectiveness. Many drugs, both as single agents and in combinations, are about to be studied in phase III clinical trials and hopefully will become the new standard of care. Additional translational research efforts are needed to develop validated biomarkers beyond HER2 itself.

Conflict of interest statement

Dr Curigliano received fees for advisory board from Roche, Novartis, Lilly and SEAGEN. Dr Criscitiello has no conflict of interest to declare.

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