Since the importance of the HER2 signaling pathway has been highlighted in breast cancers, the treatment strategies have consisted, on one hand, in optimizing the blockage of this pathway, and on the other hand by improving the associated chemotherapy strategies, considering that there has been a significant synergy between these two components (1). After exposure to trastuzumab and progression of the disease, the first explored treatment strategy modified both antiHER2 treatment and chemotherapy. Thus, the combination of lapatinib with capecitabine became the first therapeutic option when progression occurred following trastuzumab and taxanes (2). However, in this same clinical situation of progression, the efficacy of maintaining a trastuzumab blockade and just switching the associated chemotherapy was effective (3). In addition, the comparison of the two HER2 blocking strategies with the same chemotherapy did not demonstrate the superiority of lapatinib over trastuzumab (4). Since then, from a pharmacological and strategic point of view, “trastuzumab beyond progression” based strategies were considered. Of interest the chemical conformation of trastuzumab allows to link a cytotoxic agent on the antibody without any interference with its ability to bind on HER2. Then, the internalization of the receptor triggered by the binding from the antibody conjugated with the cytotoxic agent provides an innovative approach to fight cancer cell. The antibody-drug conjugate concept was born, allowing such a “Trojan horse” to deliver a cytotoxic agent preferentially, even almost exclusively, within the HER2-positive cancer cells. After demonstrating the clinical activity of trastuzumab-emtansine (T-DM1) (5), the first antiHER2 antibody-drug conjugates, EMILIA trial was designed, to assess the efficacy and the safety of T-DM1, compared with the validated regimen combining lapatinib plus capecitabine, in patients with HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. Lancet Oncol 2017;18:732-42.

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sub-seven percent of the patients (n=136) crossed over from control to T-DM1 after the second interim OS analysis. Of patients originally randomly assigned to T-DM1, 51% (n=254) received capecitabine and 49% (n=241) received lapatinib (separately or in combination) after study drug discontinuation. In this long terms OS analysis, less death were reported in the T-DM1 arm than in the control arm over the time (HR =0.75; 95% CI: 0.64–0.88). The median OS was longer with T-DM1 (29.9 months) than with lapatinib-capecitabine (25.9 months). Moreover, consistent with previous reports, T-DM1 was associated with a favorable safety profile. Definitively, these results support T-DM1 as a standard of care in second line following previous exposure to taxane—trastuzumab containing regimen.

The name Emilia comes from the Latin aemulus, “rival”, or from the Greek baimulos, “cunning”. A therapeutic trial has never been so well named. For the oncological community, Emilia is associated with the first clinical trial demonstrating that a strategy using an antibody-drug conjugate which is not only active, but also superior and less toxic than a HER2 targeted treatment with chemotherapy regimen. From a strategic point of view, Emilia is the trial demonstrating that “cancer cells” specifically targeted by chemotherapy might be sufficient for disease control compared to our old nonspecific chemotherapy strategies in this situation. Together with the survival benefit observed in the TH3RESA study (8), EMILIA study data support two important conclusions and perspectives. The first one is of course the importance of T-DM1 in HER2-positive breast cancer treatment strategies (9). But, moreover, the antibody engineering had permitted a paradigm evolution regarding the role of the antibodies treatments. Among them, antibody-drug conjugates approach is particularly of interest in cancer models were a specific overexpressed targetable receptor is a gateway for highly effective and low-toxicity treatment (10).

Regarding the first point, the particular properties of T-DM1 led to the development of clinical trials to substitute the combination of trastuzumab with taxanes by this drug. This substitution yields comparable efficacy at first line metastatic setting (11) and this approach is actually evaluated in low risk HER2-positive early breast cancers in adjuvant setting (12). Nevertheless, pertuzumab-trastuzumab combination is highly synergistic and the results from CLEOPATRA trial in first line have been impressive regarding the OS outcome and they have changed the standard of first line for metastatic disease (13). Then, there was a need to explore T-DM1-pertuzumab combinations in clinical trials. Unfortunately, and without clear biological and/or pharmacological explanations, this combination failed to demonstrate a synergistic activity in clinics (14). How T-DM1 could become the backbone of the anti-HER2 treatment strategies is still a matter of debate.

The antibody engineering approach has been emerging as a future important class of new drugs for cancer treatments. Several antibody-drug conjugates have been approved for the treatment of hematological malignancies. Gemtuzumab-ozogamicin targeting CD33 was the first one to be approved by the FDA in 2000 as a monotherapy in patients over the age of 60 with acute myelogenous leukemia who were not candidates for cytotoxic chemotherapy (15). Brentuximab vedotin which selectively targets tumor cells expressing the CD30 antigen, have reached a registration in Hodgkin’s lymphoma and anaplastic large cell lymphomas (16).

Two antibody-radionuclide conjugates were also approved 10 years ago for cancer treatment (ibritumomab tiuxetan and tositumomab-iodine). They both target CD20 and are used in refractory CD20 positive non-Hodgkin lymphoma’s (17).

The research and development regarding antibody-drug conjugates is very active with actually more than 100 ongoing clinical trials. The majority of them are focusing on hematological malignancies, but some of them are also targeting HER2-positive disease (18). First results, of the phase I dose-escalation trial evaluating trastuzumab deruxtecan antibody-drug conjugate, were recently published with promising results. Forty-three percent of the 23 evaluable patients, including six patients with low HER2-expressing tumors, achieved an objective response (19). T-DM1 was the first in class which open a new chapter for the treatments of breast cancers.

The best understanding of the biology of cancers, the importance of signaling pathways and the potential targeting of key proteins in these pathways have been the first fundamental step in the progresses made in oncology. The second step included the development of therapeutic approaches using specific targeting agents like monoclonal antibodies. The exponential evolution of biotechnological possibilities has allowed to carry these discoveries and to develop today new therapeutic approaches with the synthesis of new therapeutic antibodies. Among them, the antibody-drug conjugates represent a new fundamental therapeutic class. The results of EMILIA are the reflects of this clinical translation allowing major developments for
patients with better results including survival improvements and less toxicity.

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Footnote

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