HER2 positive metastatic breast cancer: what happens after first line failure?

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Abstract
For women with metastatic HER2 positive breast cancer, the introduction of trastuzumab into routine practice was transformative. More recently, the addition of pertuzumab has further improved the outlook. However in almost all cases, the disease unfortunately progresses. Much research has gone into what to do next. Fortunately we now have evidence to support a number of strategies, with the underlying understanding that HER2 blockade should be continued for as long as possible. Historically, lapatinib was the first anti-HER2 agent to show activity after relapse on trastuzumab. Subsequently the effectiveness of T-DM1 (Kadcyla) has been demonstrated, as has the use of alternating chemotherapy agents with trastuzumab. Research is now focussed on understanding and combatting the mechanisms of resistance to anti-HER2 agents that inevitably develop. Promising data suggest that mTOR inhibitors, PI3 kinase inhibitors and immune-activating therapies may be helpful.

It is universally accepted that the ideal first line treatment of HER2 positive metastatic breast cancer is a taxane combined with both trastuzumab and pertuzumab. This combination is approved and funded in Australia. What is less clear is the best sequence of treatment choices to make after first line failure.

Preclinical and clinical evidence suggests that in patients with HER2 positive metastatic breast cancer who have progressed beyond first-line anti-HER2 treatment, it remains important to provide ongoing HER2 suppression if tumour control is to be achieved. To date, the published studies have largely included patients who had received trastuzumab and chemotherapy in the first-line setting.

In this setting, the first trial to demonstrate an improvement in time to progression was the EGF100151 trial, which randomised HER2 positive metastatic breast cancer patients to lapatinib and capecitabine versus capecitabine alone. The primary endpoint was achieved with a hazard ratio of 0.57 (95%CI 0.43-0.77, p<0.001), demonstrating that maintaining HER2 blockade halved the risk of cancer progression.

A particular subset of patients with HER2 positive disease who appeared to benefit from lapatinib were those with progressive cerebral metastases. The EGF105084 trial evaluated lapatinib as monotherapy and in combination with capecitabine, and was able to demonstrate a reduction in volume of cerebral disease by MRI assessment. Monotherapy led to a ≥ 20% central nervous system (CNS) volumetric reduction in 21.4% of patients, whilst lapatinib and capecitabine led to ≥ 20% CNS volumetric reduction in 40% of patients. In both treatment groups, there was a significant improvement in progression-free survival (PFS) in those patients who showed reduction in CNS disease. However, to date these gains in PFS have not translated into an overall survival (OS) benefit.

The development of T-DM1 and its evaluation in the pivotal trial, EMILIA, establishes this agent as the most effective anti-HER2 agent after patients have progressed on trastuzumab-based treatment, anthracycline and taxanes. The development of this monoclonal antibody- emtansine conjugate was evaluated in this phase III trial, where 991 patients were randomised to T-DM1 monotherapy versus lapatinib and capecitabine in the second-line setting. The dual primary endpoints of PFS and overall survival were significantly in favour of T-DM1 with a hazard ratio of 0.65 (95% CI 0.55-0.77; p<0.001) and 0.68 (95%CI 0.55-0.85; P<0.001), respectively.
An exploratory assessment for CNS progression in the two treatment arms showed a similar PFS in those patients with baseline CNS disease or who developed CNS disease on treatment, while overall survival continued to favour the patients receiving T-DM1. Of particular interest was that the PFS and OS findings occurred in the setting of higher rates of CNS progression on treatment in the T-DM1 compared to lapatinib and capecitabine arm (22.2% vs. 16%, respectively); and new CNS disease (2% vs. 0.7%, respectively).  

Other therapies that have shown efficacy in the second-line setting after trastuzumab and taxane chemotherapy in the first-line setting include the combination of lapatinib and trastuzumab (EGF104900), where PFS and OS favoured the dual anti-HER2 therapy as compared to lapatinib alone; hazard ratio 0.74 for both endpoints.  

In addition, in the era prior to T-DM1, a number of retrospective studies showed efficacy for continuation of trastuzumab with a change in chemotherapy partner. GBG26 was the first prospective study to demonstrate an improvement in PFS with continuation of trastuzumab in combination with capecitabine versus capecitabine alone. Despite early cessation of the study due to a slowing of recruitment, the 5.5 months improvement in PFS was significant with a p value of 0.02. Following a median follow-up of 20.7 months, patients who continued or resumed trastuzumab or lapatinib after second progression had superior post-progression survival of 18.8 months versus 13.3 mths (p=0.02). Further, a pooled analysis of 29 studies that compared continuation of trastuzumab and chemotherapy against the chemotherapy agent alone, favoured the combination regimen with an overall time to progression of seven months and OS of 23 months.  

In the era of pertuzumab and T-DM1, a new challenge for management of patients with HER2-positive metastatic breast cancer in the second-line setting arises. There are no published studies which evaluated the efficacy of T-DM1 in patients previously treated with dual HER2 blockade with trastuzumab and pertuzumab. Given the oncogenic addiction to the HER2 pathway as supported by preclinical and clinical studies, it is likely that the efficacy of the antibody-cytotoxic drug conjugate will persist. However it remains to be determined how effective T-DM1 will be in patients who have already received trastuzumab and pertuzumab. As T-DM1 is considered an effective option in the first-line setting in patients who have a short disease-free interval following adjuvant trastuzumab chemotherapy treatment, the second-line setting treatment for these patients may be another circumstance where other therapeutic approaches are needed.  

A number of studies have demonstrated that the PI3K/Akt/mTOR pathway is a predominant pathway by which trastuzumab resistance may develop. Bolero 3 randomised 569 patients with HER2 positive metastatic breast cancer who had received trastuzumab, a taxane and up to three lines of chemotherapy to trastuzumab and vinorelbine versus trastuzumab, vinorelbine and everolimus. The primary endpoint of PFS was significantly better in the triplet combination arm with a hazard ratio 0.78 (95%CI 0.65-0.96, p=0.0067), although overall survival results are still awaited. A number of pan-PI3K inhibitors and alpha-specific PI3K inhibitors are in clinical trial evaluation in HER2-negative, hormone receptor positive breast cancer, paving the way for a smaller number of trials now accruing in which agents such as buparlisib, BEZ235, coPANlisib are being given with trastuzumab in HER2-positive metastatic breast cancer.  

Other investigators are evaluating the efficacy of CDK4/6 inhibitors (palbociclib, abemaciclib) with trastuzumab with or without endocrine treatment. Preclinical and clinical data support the importance of the immune environment – both innate and adaptive – in the mechanism of tumour cell evasion of immune-surveillance. The two breast cancer subtypes in which the immune environment appears to have the greatest role, are HER2 positive and triple negative disease. Immune mechanisms that have been postulated to be in play include: heightened antibody-dependent cell-mediated or complement-dependent cytotoxicity, triggering of Fc receptor positive cells, activated CD8-positive lymphocytes and NK cells. As such the development of checkpoint inhibitors which has shown efficacy in other solid tumours such as melanoma, are now under active clinical trial evaluation. This matter is further discussed in the final article in this Forum.
References


