HER2-TARGETED THERAPIES IN BREAST CANCER

HOW TO ACHIEVE SYMPTOM CONTROL, PROLONG ACTIVE TREATMENT AND OPTIMISE END-OF-LIFE CARE

Prescribing Information can be found on pages S26–S32.
FOREWORD

Claire Ryan

DEFINING WHAT MATTERS MOST TO PATIENTS
Tracey Coleby

IMPROVING PATIENT CARE: EXPERT NURSING SERVICE DEVELOPMENT
Claire Ryan

ABOUT THE AUTHORS
Claire Ryan gained her general nurse training from University College London Hospitals in 1991 and completed her cancer nursing training in London at The Royal Marsden. She was appointed to the Macmillan nurse clinician for MBC partnership post in October 2014. Before that, she was the lead oncology research nurse for Maidstone & Tunbridge Wells NHS Trust. Her clinical focus and research interests lie within the portfolio of clinical trials for MBC. In this newly created partnership role with Macmillan, Ryan has been developing new services for women with MBC in West Kent. As an advanced nurse practitioner, she has driven forward innovative nurse-led services that have bridged primary and secondary care, resulting in a patient-centred approach for improving the health and wellbeing of those living with MBC.

Russell Burcombe qualified at The London Hospital and trained in oncology to integrate palliative care and collaboratively with patients with advancing disease. In 2013, this work won a national award for ‘best multidisciplinary team project.’

Delivering multifaceted, quality care to women living with metastatic breast cancer (MBC) demands professional competence and an advanced level of practice. The breast cancer nursing community is evolving to meet this need as more nurses are appointed specifically for the advanced disease setting, while nurses who previously worked only in early stage disease are now delivering care across the disease trajectory, fulfilling a ‘diagnosis to death’ nursing model.

The MBC nursing community, linked by UK charity Breast Cancer Care and the Roche Nursing Matters programme, offers forums for learning, and provides ongoing support to this group of nurses. This supplement has been commissioned by Roche Products Ltd to continue supporting nurses who treat patients with MBC by sharing learning and best practice, with a view to encouraging innovation in service delivery.

The London Hospital and trained in oncology at Mount Vernon Cancer Centre and the Middlesex and St Bartholomew’s Hospitals before becoming a fellow of The Royal College of Radiologists in 1998. He completed an MD research fellowship in prediction of response to neoadjuvant chemotherapy for breast cancer at Mount Vernon’s Gray Laboratory in 2001. Thereafter, he sought more experience as a consultant radiation oncologist in Christchurch, New Zealand, before being appointed consultant clinical oncologist at the Kent Oncology Centre in 2004.

As well as running a clinical practice and treating breast and lung cancers, Burcombe takes a special interest in providing patient-friendly information. The innovative breast radiotherapy information film he created was awarded first prize for best patient support initiative at the 2012 UK Excellence in Oncology Awards. This was followed, in 2014, by a film on chemotherapy, which is now used widely to educate patients in Kent and is endorsed by the UK Chemotherapy Partnership.

He continues to run a programme of clinical audit and research, with publications in peer-reviewed journals and presentations at national breast and lung cancer meetings.

Tracey Coleby has worked within the supportive care team at The Christie in Manchester for more than 11 years. During this time, she held a variety of positions alongside her clinical nurse specialist role including end-of-life project lead and a clinical nurse specialist role within the private sector. She has worked closely with NHS Improvement and the National Gold Standards Framework team in innovation change. She has a keen interest in breast oncology, communication skills training and end-of-life care.

For the past 8 years, Coleby has been working closely with consultants in medical breast oncology to integrate palliative care and collaboratively with patients with advancing disease. In 2013, this work won a national award for ‘best multidisciplinary team project.’

She is the Macmillan breast palliative care lead for a 22-month project that is building on this work across the whole breast disease group. She is also undertaking a master’s in medical ethics and palliative care on advanced cancer planning for patients who are still undergoing active treatment.
INTRODUCTION

Metastatic breast cancer (MBC), also known as secondary breast cancer (SBC), occurs when cells from the primary tumour metastasise to other parts of the body via the blood or lymphatic system. The disease may range from limited bone metastases to widespread and life-threatening metastases in visceral organs such as the liver, lung and brain (National Institute for Health and Care Excellence (NICE), 2009, 2014). MBC is incurable, and the primary goal of treatment is to extend life and palliate symptoms, while preserving quality of life (NICE, 2009, 2014).

Sequential life-prolonging treatments and access to novel agents as a result of participating in clinical trials with endpoints that address the burden of MBC have resulted in many patients living with a diagnosis of MBC and its complications. It is estimated that, in England, almost 500,000 people are living with a diagnosis of breast cancer, but it is not known how many have a recurrence or MBC (Cancer Research UK, 2014). It is difficult to gain a true understanding of the scale of the matter, as data on the number of women diagnosed with MBC is not routinely collected. The continuum of the disease is highly variable, with some women living for prolonged periods with a good quality of life, and others experiencing rapid disease progression. Data on the diagnosis of MBC have not been collected, meaning that the duration of survival and exposure to treatments is unknown (Reed et al, 2010; Breast Cancer Care, 2016). The complex psychosocial needs of these patients can pose a major challenge for health professionals, primary and secondary health services, and social care services.

Due to sequential life-prolonging treatments and the use of novel drug therapies, many women are living with a diagnosis of metastatic breast cancer and its complications for longer. Sites of spread, disease biology, performance status and patient choice guide oncology management. A significant change in one area of oncology management is our understanding of human epidermal growth factor receptor 2 (HER2)-positive breast cancer, which has changed from being considered an aggressive disease with a poor prognosis, to a disease that can be treated with anti-HER2 therapy to prolong survival (Verma et al, 2012; Swain et al, 2015). An improved understanding of HER2 biology and treatment, and the administration of HER2-targeted drug therapies, can optimise the medical management of HER2-positive MBC. Despite the presence of international consensus guidelines for the management of advanced breast cancer, which of course should be adhered to (Cardoso et al, 2014), oncology treatment in the advanced disease setting remains complex, with few proven standards of care in MBC overall.

Chapter 1 of this supplement explores oncology treatment approaches and goal setting, as exposure to sequential treatments can extend survival for some patients.

The complex psychosocial needs of women living with MBC continue to pose a major challenge to health professionals, primary and secondary health services, and social care services. These issues, which have been identified across the care continuum and reflect political, economic and scientific landscapes, are unique to the UK. Global international surveys, such as that by Mayer and Grober (2006) and more recently the Global Status of Advanced/MBC Decade Report (Pfizer Oncology et al, 2016), show that MBC receives inadequate attention. The Global Status of Advanced/MBC Decade Report analysed key factors that will contribute to health policy and service developments for the care and wellbeing of those diagnosed and living with MBC.

A diagnosis of MBC can be traumatic for patients, as reflected in increased feelings of vulnerability, loss and uncertainty (Warren, 2010; Schmid-Bächli et al, 2011). Living with MBC is a multifaceted and personal experience that is influenced by a range of factors, many of which are under-researched compared with those for early breast cancer (Johnston, 2010; Warren, 2010). Living with uncertainty is an experience borne in much of the literature, which describes experiences of loss of control and coping with existential distress (Nelson, 1996; Warren, 2010). Despite this, globally, there is a lack of data on support needs at particular stages of the disease continuum, as well as inconsistency in the reporting of supportive care for MBC (Pfizer Oncology et al, 2016). Confusingly, the terms supportive and palliative care are sometimes used interchangeably. Improved training is required for the multidisciplinary health team to define what ‘recognition that each patient’s individual treatment path is unique means in practice (NICE, 2012). Palliative care tends to focus on end-of-life care after active cancer therapies have been withdrawn, however, palliative care has an equally important role to play during the period of living with MBC, as it can focus on effective management of often distressing symptoms, improving patients’ quality of life, and, ultimately, preparing for end of life.

Patients with MBC will inevitably confront disease progression, and thus face changing physical, psychological and social demands. Understanding these changes will enable expert health professionals to deliver interventions that are tailored to patients’ holistic needs, thereby resulting in person-centred quality care (Coulter and Collins, 2011; King’s Fund, 2012). At some point in the disease continuum, the aim of treatment will shift from active treatment to palliative care for symptom management only, with preparation for end of life. Chapter 2 examines these changes and attempts to define what matters most to patients at different stages of the disease continuum, offering insight into how health professionals can be supported in delivering specialist care.

The vision that everyone affected by MBC has an equally important role to play at this stage of the disease continuum as it can be used to manage often distressing symptoms, provide psychosocial care and, ultimately, prepare patients for the end of life.”

This shift towards support for self-management might encourage patients with MBC to increase their understanding of what the cancer journey might look like (Penton and Reed, 2008). However, the cancer journey is complex and uncertain, punctuated by challenges to physical and emotional wellbeing, and inevitable relapses (Reed et al, 2012). People living with cancer who have access to a clinical nurse specialist (CNS) are significantly more likely to be more positive about the multitude of aspects of their care and treatment, such as the provision of information and support (Department of Health (DH) et al, 2010; Quality Health, 2014; Warren and Mackie, 2014). However, access to support is variable across the UK, and people with MBC have less access to support from a CNS at a time when they need it most (Breast Cancer Care, 2016; Johnston, 2010).

Chapter 3 explores the value of the nursing role within this context, and demonstrates how it can drive service development to meet evolving demands. Understanding these changes will enable expert health professionals to deliver interventions that are tailored to patients’ holistic needs, thereby resulting in person-centred quality care (Coulter and Collins, 2011; King’s Fund, 2012). At some point in the disease continuum, the aim of treatment will shift from active treatment to palliative care for symptom management only, with preparation for end of life. Chapter 2 examines these changes and attempts to define what matters most to patients at different stages of the disease continuum, offering insight into how health professionals can be supported in delivering specialist care.

The vision that everyone affected by MBC should receive the highest quality care, treatment, information and support highlights the need for a shift from a one-size-fits-all medical model approach towards assessment, information, education and person-centred care plans based on individual risks, needs and preferences. Patients with MBC face increasingly complex decisions about their care, as some will live longer and have more treatment choices. A diagnosis of metastatic breast cancer can bring increased feelings of vulnerability, loss of control and uncertainty. Palliative care can have an important role to play at this stage of the disease continuum as it can be used to manage often distressing symptoms, provide psychosocial care and, ultimately, prepare patients for the end of life.”
**Introduction**

Health professional involvement when treatment is received on an outpatient basis (Findlay et al, 2008; National Cancer Action Team, 2010). Ensuring good liaison and communication between patients and health providers across primary and secondary care remains challenging. Given the increasing complexities involved in balancing the goals of care and treatment planning, a sound relationship between the patient, oncologist and, if accessible, specialist nurse is needed to facilitate shared decision-making (Filleter et al, 2015). Patients need to understand and have a choice in care decisions before, during illness and at the end of life (Wise, 2016).

MBC is a complex and far-reaching disease. While direct clinical and psychosocial care is paramount, the work of nurses can also extend to the community, and can help shape policy for society and community factors. While direct clinical and psychosocial care is needed, the nurse is needed to facilitate shared decision-making. Patients also need to be involved in this process. To achieve this, they need to understand and have a choice in care decisions before, during illness and at the end of life. Nurses can play a vital role in facilitating this process.

**Current treatment of HER2+ metastatic breast cancer**

Approximately 20–30% of breast cancers overexpress human epidermal growth factor receptor 2 (HER2) (Slamon et al, 1989, 1998). These HER2-positive (HER2+) breast cancers display aggressive tumour biology and, historically, were associated with a poorer prognosis, with an increased risk of disease recurrence, secondary spread and shorter overall survival (OS) compared with tumours that do not overexpress HER2 (Slamon et al, 1987, 1989; Sessaali et al, 1993, Press et al, 1993, Ravdin and Chammness, 1995).

Two decades ago, the prognosis for patients with HER2-positive metastatic breast cancer (MBC) was very poor (Keng et al, 1985; Slamon et al, 1987, 1989; Gusterson et al, 1992; Hynes and Stern, 1994; Chia et al, 2007). However, the development of HER2-targeted therapies that target the HER2 receptor has altered the natural history of the disease and dramatically transformed outcomes for this patient group: a recent study of dual HER2-targeted treatment in patients with HER2+ MBC reported a median OS of 56.5 months compared with monotherapy (p<0.001) (Swain et al, 2015).

This chapter summarises key developments and clinical trial data on HER2+ MBC, and details the benefits of maximising dual HER2 blockade for these patients. It should be noted that the inclusion criteria for the studies presented here differ: some of the data presented included patients who do not overexpress the HER2 receptor (HR) and HER2 positive and/or negative cancers.

**How are HER2+ breast cancers identified?**

HER2+ cancers can be identified using immunohistochemistry (IHC) on fluorescent in situ hybridisation (FISH). IHC testing measures the number of receptors on the cell surface, which are graded from 0 to 3+.

- Tumours scored between 0 and 1+ which is the normal level of HER2, are classed as HER2-negative.
- Tumours scored 3+ are defined as HER2-positive.

In tumours scored 2+, a further FISH test measures the number of copies of the HER2 gene in each cell. Tumours that are overexpressing the gene are confirmed as HER2+ (Rakha et al, 2015).

**Treatment options for HER2+ breast cancer**

Herceptin® (trastuzumab) with chemotherapy

Herceptin® is a humanised, anti-HER2 monoclonal antibody, which is a potent mediator of antibody-dependent cell-mediated cytotoxicity (ADCC) (Juntilla et al, 2009). It is indicated for the treatment of adult patients with HER2+ MBC (Herceptin summary product characteristics (SmPC)).

- As monotherapy for those who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane, unless the patients are unsuitable for these treatments. Hormone receptor-positive patients must also have failed hormonal therapy where indicated.

**Historical, HER2-positive breast cancer patient for prognosis. The development of molecular therapies that target the HER2 receptor has transformed outcomes. Here, the evidence on anti-HER2 therapies is summarised.**

**A sound relationship between the patient, oncologist and, if accessible, the clinical nurse specialist is needed to facilitate shared decision-making. Patients also need to be involved in this process. To achieve this, they need to understand and have a choice in care decisions before, during illness and at the end of life. Nurses can play a vital role in facilitating this process.**

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The addition of Herceptin to chemotherapy was associated with a significant increase in time to disease progression (TTP), objective response rate (ORR) the proportion of patients whose tumour had reduced in size by a predefined amount over a minimum time period) and median duration of response, as well as a lower death rate at one year, longer median OS and a 20% reduction in the risk of death (Slamon et al, 2001) (Table 1).

The most important adverse event was cardiac dysfunction (27% for those on an anthracycline, cyclophosphamide and trastuzumab; 8% for an anthracycline and cyclophosphamide alone, 13% for paclitaxel and Herceptin, and 1% for paclitaxel alone). This was potentially fatal, in some cases, life threatening but, with proper medical management, cardiac side effects were manageable and generally improved with time (Slamon et al, 2001).

The cardiac toxicity data demonstrated in this study led to a recognition that Herceptin and anthracyclines should not be given concurrently for MBC (Herceptin SmPC). Patients with MBC who have previously received anthracyclines are also at increased risk of cardiac dysfunction with Herceptin (Herceptin SmPC). Subsequently, Herceptin, in combination with paclitaxel or docetaxel chemotherapy, became the standard of care for patients with HER2+ MBC who had not been previously treated with chemotherapy for metastatic disease (Giordano et al, 2014).

Due to the high rate of cardiac dysfunction seen with the anthracycline and Herceptin combination (Slamon et al, 2001), a subsequent study evaluating the efficacy and safety of Herceptin as a first-line treatment for HER2+ MBC used docetaxel chemotherapy instead of anthracycline (Marty et al, 2004). In this small randomised controlled trial (186 patients) involving HER2+ MBC patients, the addition of Herceptin to docetaxel almost doubled TTP (from 6.1 to 11.7 months) and substantially improved median OS from 22.7 to 31.2 months (Marty et al, 2005).

Herceptin subcutaneous (SC)

In 2013, a subcutaneous formulation of Herceptin was approved for use in England. A small time and motion study (n=28), which compared resource use and socioeconomic impact, but not treatment outcomes, showed that substituting intravenous (IV) infusion with subcutaneous (SC) administration of Herceptin can lead to a substantial reduction in health professionals’ time, patient chair and unit time, consumable use and overall costs (Burcombe et al, 2013).

Lapatinib

Lapatinib is an orally active small molecule dual tyrosine kinase inhibitor (TKI) of HER2 and epidermal growth factor receptor (EGFR) and can be used as a first-line treatment in combination with either capecitabine or trastuzumab. Despite these signalling pathways that are essential for cancerous growth (Franklin et al, 2004).

Lapatinib plus capecitabine demonstrated a statistically significant OS benefit (2000 mg/day) compared with placebo (1000 mg/day) in patients with HER2+ MBC who had not received previous chemotherapy for metastatic disease (Baselga et al, 2012). The second interim analysis reported that Perjeta extended median progression-free survival (PFS) by 6.3 months and a 20% reduction in the risk of death (Slamon et al, 2001) (Table 1).

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The most common adverse events reported in the Perjeta arm were diarrhoea, alopecia, neutropenia, nausea, and fatigue (Table 3). The incidence was similar for treatment, patients should have either:

- HER2+ breast cancer at metastatic disease
- received prior therapy for locally advanced or metastatic disease
- developed disease recurrence during or within 18 months from completion of chemotherapy
- previous treatment with Herceptin, capecitabine, and anthracycline

In the key phase III EMILIA study, Verma et al (2012) compared the efficacy and safety of Kadcyla as a second-line therapy with that of lapatinib plus capecitabine. The trial involved 991 patients with HER2+ MBC who had previously received Herceptin and a taxane for unresectable, locally advanced or metastatic disease. Patients randomly assigned to Kadcyla received 5.6 mg/kg intravenously every 21 days until disease progression or the development of manageable toxicity effects. Kadcyla significantly improved the two trial primary endpoints, PFS and OS, compared with lapatinib plus capecitabine: median PFS was prolonged by 3.2 months and median OS at the second interim analysis was 12.4 months (Table 4). Among the ITT population, 85% of the Kadcyla patients were alive at one year (Verma et al, 2012). Overall, compared with lapatinib plus capecitabine, Kadcyla was better tolerated, associated with fewer grade 3 and 4 adverse events (40.8% vs 57.0%) and significantly improved quality of life (Verma et al, 2012). The most commonly reported grade 3 or 4 adverse events in the Kadcyla group were diarrhoea (11.2%) and elevated liver function enzymes (aspartate transaminase 4.3%, alanine aminotransferase 2.9%). Some lower-grade toxicities that can potentially affect quality of life, including fatigue, diarrhoea and neuropathy, were observed. Cardiac toxicity was extremely low compared with that in the CLEOPATRA study: only 1% of patients experienced a significantly reduced LVEF with Kadcyla compared with 1.6% with lapatinib plus capecitabine (Verma et al, 2012, Swain et al, 2015). OS for patients in the Kadcyla group was 30.9 months compared with 25.1 months for patients receiving lapatinib plus capecitabine (p<0.001). Although 70% of patients in the placebo arm were alive at the second interim analysis, *p<0.001 compared with the lapatinib group.

Figure 5: Kaufman et al (2009) dosing schedule

Table 4: Summary of results from EMILIA study (Verma et al, 2012)

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>OS at the second interim analysis (months)</th>
<th>p-value</th>
<th>PFS at the second interim analysis (months)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kadcyla</td>
<td>30.9</td>
<td>&lt;0.001</td>
<td>12.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lapatinib + C</td>
<td>25.1</td>
<td></td>
<td>9.6</td>
<td></td>
</tr>
</tbody>
</table>

Adverse events and serious adverse events were more commonly reported in the group that received Herceptin after progression (Kaufman et al, 2009). Grade 5 and 4 adverse events were seen in 25% of patients who were randomised to receive Herceptin plus anastrozole had a superior PFS (4.8 vs 2.4 months) and parallel response (20.3% vs 6.8%) compared with those who received anastrozole alone. However, no statistically significant difference in median OS was observed: 285 months in the Herceptin plus anastrozole arm vs 259 months in the anastrozole alone arm (p=0.325), although 70% of patients in the anastrozole alone arm crossed over to receive Herceptin after progression (Kaufman et al, 2009). Adverse events and serious adverse events were more commonly reported in the group that received the combination (Kaufman et al, 2009). Grade 3 and 4 adverse events were seen in 25% of patients who were randomised to receive Herceptin plus anastrozole had a superior PFS (4.8 vs 2.4 months) and parallel response (20.3% vs 6.8%) compared with those who received anastrozole alone. However, no statistically significant difference in median OS was observed: 285 months in the Herceptin plus anastrozole arm vs 259 months in the anastrozole alone arm (p=0.325), although 70% of patients in the anastrozole alone arm crossed over to receive Herceptin after progression (Kaufman et al, 2009). Adverse events and serious adverse events were more commonly reported in the group that received the combination (Kaufman et al, 2009). Grade 3 and 4 adverse events were seen in 25% of patients who were randomised to receive Herceptin plus anastrozole had a superior PFS (4.8 vs 2.4 months) and parallel response (20.3% vs 6.8%) compared with those who received anastrozole alone. However, no statistically significant difference in median OS was observed: 285 months in the Herceptin plus anastrozole arm vs 259 months in the anastrozole alone arm (p=0.325), although 70% of patients in the anastrozole alone arm crossed over to receive Herceptin after progression (Kaufman et al, 2009). Adverse events and serious adverse events were more commonly reported in the group that received the combination (Kaufman et al, 2009). Grade 3 and 4 adverse events were seen in 25%
Figure 6: Johnston et al (2009) dosing schedule was associated with a significant improvement over anastrozole alone, in a study of 57 postmenopausal patients. Recruitment closed early due to poor accrual, so the findings must be interpreted with caution. However, the addition of Herceptin to letrozole was associated with a significant improvement in TTP (14.1 vs 3.5 months), response rates (27% vs 15%) and clinical benefit (65% vs 39%) (Huober et al, 2012). However, the only phase III trial to specifically address the efficacy of anti-HER2 therapy in the third-line setting with patients pre-treated with Herceptin and lapatinib is the randomised, open-label TH3RESA study (Krop et al, 2014).

Eligible patients were randomised to receive either Kadcyla or treatment of the physician’s choice (TPC), thereby reflecting clinical practice. Kadcyla was found to significantly improve median PFS by 2.9 months, OS by 60 months and ORR by 22.7 percentage points (Table 5) and was associated with fewer grade 3 and 4 adverse events (Krop et al, 2014; Wildiers et al, 2015). A total of 44 patients crossed over to the Kadcyla arm.

After progression on CLEOPATRA triple therapy (Perjeta, Herceptin and docetaxel) and second-line Kadcyla, there is no standard third-line treatment. American Society of Clinical Oncology guidelines recommend continuing the anti-HER2 therapy in patients fit enough for additional systemic therapy (Giordano et al, 2014). Following progression after Herceptin, Perjeta and Kadcyla, treatment options include: lapatinib and cetuximab, or Herceptin (Giordano et al, 2014).

SUMMARY OF NICE GUIDANCE AND CANCER DRUGS FUND AVAILABILITY

The National Institute for Health and Care Excellence (NICE) provides evidence-based recommendations for health and care in England. The Cancer Drugs Fund (CDF) is a source of funding for cancer drugs in England, which offers patients faster access to new cancer treatments through independent arrangements. These drugs can be obtained either via a NICE draft recommendation for routine commissioning, or directly from the CDF. Different funding arrangements exist in Scotland and Wales.

NICE last published guidance for the management of MBC in 2009 (updated July 2014), however, the medical consensus is to treat HER2+ MBC with second-line Perjeta (awaiting NICE appraisal), Herceptin and docetaxel, and with Kadcyla in the second-line setting (Santa-Marta and Gradishar, 2015). Perjeta is available via the CDF in England but not in Wales. Kadcyla is approved for use in England, Scotland and Wales. CDE is recommended by NICE as an option for patients with HER2+ tumours who have received two or more chemotherapy regimens, which must have included an anthracycline and a taxane, where appropriate, and hormonal therapy in suitable ER+ patients.

Patients receiving Herceptin for MBC are required to discontinue treatment at the time of disease progression.

Lapatinib or Herceptin in combination with an aromatase inhibitor are not recommended as a first-line treatment in postmenopausal women with HER2+ MBC, and lapatinib is not currently approved for use in the UK (NICE, 2012).

CONCLUSION

The identification of HER2 and development of targeted anti-HER2 therapies has transformed the outlook for patients with HER2+ MBC, many of whom can now live for more than 5 years with manageable side effects (Swain et al, 2015). Triple therapy using the CLEOPATRA regimen (Perjeta plus Herceptin and docetaxel) followed by maintenance dual blockade anti-HER2 therapy with Perjeta and Herceptin is now considered first-line standard of care for HER2+ MBC (Santa-Marta and Gradishar, 2015). This combination provided median PFS improvements and unprecedented OS benefits (Baselga et al, 2012; Swain et al, 2015).

The novel antibody-drug conjugate Kadcyla provides targeted delivery of a chemotherapy agent directly into HER2+ tumour cells, thereby maximising HER2 targeting and limiting systemic toxicity. Its manageable safety profile, combined with superior efficacy to lapatinib plus cetuximab, has defined the place of Kadcyla as a first-line treatment in postmenopausal women with HER2+ MBC, and lapatinib is not currently approved for use in the UK (NICE, 2012).

and 5% of patients in the Herceptin plus letrozole arm achieved a partial response, 15% and 1% in the anastrozole alone arm, respectively, although the majority of events were grades 1 and 2.

The authors concluded that Herceptin plus letrozole improved outcomes for the 15% of patients with co-positive (HER2+/HR+) MBC compared with anastrozole alone and suggested that Herceptin targeted 15% and combined with aromatase inhibitor can substantially delay the need for chemotherapy in some patients. However, this was associated with an increase in adverse events, events not associated with anastrozole alone (Kaufman, 2009).

Herceptin plus letrozole

The combination of letrozole plus Herceptin was compared with letrozole alone in a small study of 57 postmenopausal patients. Recruitment closed early due to poor accrual, so the findings must be interpreted with caution. However, the addition of Herceptin to letrozole was associated with a significant improvement in TTP (14.1 vs 3.5 months), response rates (27% vs 15%) and clinical benefit (65% vs 39%) (Huober et al, 2012).

Lapatinib plus letrozole

Johnston et al conducted a randomised phase III trial comparing either lapatinib or placebo (Figure 6) administered orally in postmenopausal women with co-positive MBC (Johnston et al, 2009). Median PFS was superior for the combination treatment (9.2 vs 5.0 months) but no OS difference was apparent between the two arms (Johnston et al, 2009).

Eligible patients were randomised to receive either Kadcyla or treatment of the physician’s choice (TPC), thereby reflecting clinical practice. Kadcyla was found to significantly improve median PFS by 2.9 months, OS by 60 months and ORR by 22.7 percentage points (Table 5) and was associated with fewer grade 3 and 4 adverse events (Krop et al, 2014; Wildiers et al, 2015). A total of 44 patients crossed over to the Kadcyla arm.

After progression on CLEOPATRA triple therapy (Perjeta, Herceptin and docetaxel) and second-line Kadcyla, there is no standard third-line treatment. American Society of Clinical Oncology guidelines recommend continuing the anti-HER2 therapy in patients fit enough for additional systemic therapy (Giordano et al, 2014). Following progression after Herceptin, Perjeta and Kadcyla, treatment options include: lapatinib and cetuximab, or Herceptin (Giordano et al, 2014).

SUMMARY OF NICE GUIDANCE AND CANCER DRUGS FUND AVAILABILITY

The National Institute for Health and Care Excellence (NICE) provides evidence-based recommendations for health and care in England. The Cancer Drugs Fund (CDF) is a source of funding for cancer drugs in England, which offers patients faster access to new cancer treatments through independent arrangements. These drugs can be obtained either via a NICE draft recommendation for routine commissioning, or directly from the CDF. Different funding arrangements exist in Scotland and Wales.

NICE last published guidance for the management of MBC in 2009 (updated July 2014), however, the medical consensus is to treat HER2+ MBC with second-line Perjeta (awaiting NICE appraisal), Herceptin and docetaxel, and with Kadcyla in the second-line setting (Santa-Marta and Gradishar, 2015). Perjeta is available via the CDF in England but not in Wales. Kadcyla is approved for use in England, Scotland and Wales. CDE is recommended by NICE as an option for patients with HER2+ tumours who have received two or more chemotherapy regimens, which must have included an anthracycline and a taxane, where appropriate, and hormonal therapy in suitable ER+ patients.

Patients receiving Herceptin for MBC are required to discontinue treatment at the time of disease progression.

Lapatinib or Herceptin in combination with an aromatase inhibitor are not recommended as a first-line treatment in postmenopausal women with HER2+ MBC, and lapatinib is not currently approved for use in the UK (NICE, 2012).

CONCLUSION

The identification of HER2 and development of targeted anti-HER2 therapies has transformed the outlook for patients with HER2+ MBC, many of whom can now live for more than 5 years with manageable side effects (Swain et al, 2015). Triple therapy using the CLEOPATRA regimen (Perjeta plus Herceptin and docetaxel) followed by maintenance dual blockade anti-HER2 therapy with Perjeta and Herceptin is now considered first-line standard of care for HER2+ MBC (Santa-Marta and Gradishar, 2015). This combination provided median PFS improvements and unprecedented OS benefits (Baselga et al, 2012; Swain et al, 2015).
of MBC, however, with the development of new and effective HER2-targeted therapies, survival outcomes have improved significantly. Many patients with HER2+ MBC are surviving much longer than those with HER2-negative MBC (Farrell and Coleby, 2016). Evidence has confirmed that these patients also receive specialist support from palliative/supportive care nurses, who are skilled in managing patients with advancing disease (Farrell and Coleby, 2016).

### INFORMATION NEEDS

Patients’ information needs can vary immensely depending on the stage of their disease and the specific information they might require. The level of information provided to patients is often inadequate, and can be limited or excessive depending on the individual’s preferences for information (Fallowfield et al, 1990; Butow et al, 1995; Schofield et al, 2003).

Health professionals should therefore tailor any information to the patient’s needs. To achieve this, it is important to gain an understanding of the patient’s perception and understanding of their disease, which will help determine what additional information they require to make an informed decision about their future care or needs.

### CASE STUDY

A patient recently gave a cue about still ‘being her’ as she deteriorated. A young mother of two small children, this patient has MBC with extensive brain metastases, which have just progressed. At the last meeting, she said: ‘It’s important that I’m still me’. This was acknowledged and followed with the question, ‘I hear that “being you” is important, what is it about the future that worries you?’. To which she responded, ‘It’s bad enough that I’m going to die, without my children having to see me losing my mind too’.

### BOX 1. EXAMPLES OF EFFECTIVE COMMUNICATION SKILLS

**Suggested open questions:**
- What do you understand about your current condition?
- Have you any thoughts about your future care?
- What is important to you at the moment?

**Picking up cues:**
- A cue is a clear expression or hint of a negative emotion—for example, being frightened

**Examples of showing empathy:**
- It must be really hard to think about the future
- I can see how distressing this is for you

**Cues**

A cue-based approach is recommended, whereby the health professional acknowledges and explores the patient’s cues (Zimmermann et al, 2007). Cues are a clear verbal/non-verbal expression or hint of a negative emotion, which may need clarifying in order to detect the underlying concern (Table 1).

This approach will identify the patient’s underlying concern(s) and give further insight into her awareness and perception of her disease. The health professional will have an understanding of the patient is fully aware of the situation and work with her to identify priorities.

Advanced communication skills are vital in achieving such a cue-based approach. The identification and acknowledgement of all cues is key, and the health professional needs to demonstrate empathy, where possible, when addressing them. If the health professional is unable to address the concerns, the patient should be referred to someone who can. For example, the concerns may be due to a mental health illness, which will require specialist input from a psychiatrist or counsellor.

A cue-based approach can help promote greater patient satisfaction and information recall, as well as increase hope and reduce psychological morbidity (Fallowfield et al, 1990). Failure to identify and acknowledge cues can cause patients to stop disclosure, which can lead to further distress or psychological morbidity (Fallowfield et al, 1990).

### Honest prognostic information

As a palliative care approach, this becomes increasingly important for health professionals to be open and honest with them and their families about the prognosis, allowing them to make informed decisions about their end of life care and preventing them undergoing futile treatment (Fallowfield et al, 1990). Deming nurses proficiently handling information can prevent them from preparing for death, reflecting on life and saying goodbye to their loved ones (Balhurt, 1992).

In their last year of life, patients have a higher level of need and require care from skilled health professionals who understand how to support them during this final stage of their disease (O’Connell, 2002; Aranda et al, 2006; Temel et al, 2010; Reed and Corner, 2013; Zimmermann et al, 2014; Farrell and Coleby, 2016). Advanced communication skills will help develop rapport and build a meaningful relationship with patients. Such skills include use of open questions, picking up on cues, listening and showing empathy (Fallowfield et al, 1990; Heaven and Maguire, 1996; Butow et al, 1995; Schofield et al, 2003).

### Question prompts list

When supporting patients with MBC, nurse specialists need to help patients think about what types of questions they want to ask. They need to ask their oncologist in order to gain some sense of their disease and learn how best to live with it.

Both health professionals and patients can find end-of-life discussions challenging. Walszak et al (2013) therefore developed a question prompt list (QPL), which comprises questions that patients may have about their disease and last year of life (Table 2). Endorsed by patients and health professionals, this can be an effective tool for overcoming barriers to end-of-life discussions in the clinical setting.

### Guidance on Treatment

**MBC is an incurable disease, for which patients often continue receiving active treatment until nearing the end of life. It is vital that they are supported and guided during this phase of their illness. Treatments can have a gruelling effect on their psychological wellbeing, physical health and quality of life.**

Supporting and guiding patients is a large part of the breast care nurse’s role. This role was developed primarily to support patients with primary breast cancer, but these nurses are now also supporting the family of patients with MBC. Despite this, 57% of breast care nurses feel inadequately, and can be limited or excessive depending on the individual’s preferences for information (Fallowfield et al, 1990; Butow et al, 1995; Schofield et al, 2003).

**TABLE 1. CASE EXAMPLE OF USING A CUE-BASED APPROACH TO EXPLORE AN UNDERLYING PATIENT CONCERN**

<table>
<thead>
<tr>
<th>CUES</th>
<th>SUGGESTED RESPONSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>If it’s bad enough that I’m going to die, without my children having to see me losing my mind too.</td>
<td>“It’s going to be hard for you and your children, isn’t it?”</td>
</tr>
<tr>
<td>I can see how distressing this is for you.</td>
<td>“I can imagine how tough this must be for you.”</td>
</tr>
<tr>
<td>It must be really hard to think about the future.</td>
<td>“It must be really hard to think about the future.”</td>
</tr>
<tr>
<td>I can see how distressing this is for you.</td>
<td>“I can see how distressing this is for you.”</td>
</tr>
</tbody>
</table>

**TABLE 2. QUESTION PROMPT LIST FOR PATIENTS WITH METASTATIC CANCER (WALCZAK ET AL, 2013)**

<table>
<thead>
<tr>
<th>Section 1: my cancer and what to expect in the future</th>
</tr>
</thead>
<tbody>
<tr>
<td>• What is currently happening with my cancer?</td>
</tr>
<tr>
<td>• What can I expect in the future?</td>
</tr>
<tr>
<td>• Will this affect my children?</td>
</tr>
<tr>
<td>• Is it possible to give me a time frame? How long can I expect to live?</td>
</tr>
<tr>
<td>• What is the best-case scenario? What is the worst-case scenario?</td>
</tr>
</tbody>
</table>

**Section 2: treating my cancer**

<table>
<thead>
<tr>
<th>What options are available to treat my cancer?</th>
</tr>
</thead>
<tbody>
<tr>
<td>What are the pros and cons of further treatment for my cancer?</td>
</tr>
<tr>
<td>Is it possible to cure my cancer?</td>
</tr>
<tr>
<td>How likely is it that these treatments will control my cancer?</td>
</tr>
<tr>
<td>If the treatment works, will I live longer?</td>
</tr>
<tr>
<td>Will these treatments make me feel better or worse?</td>
</tr>
</tbody>
</table>

**Section 3: palliative care**

| What options are available to control things like pain, anxiety or nausea? |
| What is palliative care and do you think it might help me? |
| When would it be helpful for me to see someone from the palliative care team? |

**Section 4: making a decision**

| Should I consider stopping anti-cancer treatments now and focus more on treatments to make me feel better? |
| Is there anyone else I should talk to before making these decisions? (e.g. other doctors, organisations, websites) |
| Will you tell my GP and the other doctors looking after me about my decisions? |

**Section 5: my lifestyle**

| Are there any lifestyle changes that may help me make the most of my life, living with this cancer? (e.g. diet, exercise) |
| What can I expect to be able to do in the future? (e.g. working, driving, holidaying) |

**Section 6: support for me**

| If I decide not to have anti-cancer treatment, who will look after me? |
| If I decide not to have anti-cancer treatment, can I still see you? |
| What other support is available? |
| What information is available about my future care and what is happening to me? (e.g. books, videos, pamphlets) |
| Are there any organisations or services that would be useful for me (e.g. support organisations, respite care, disability parking) |
| What financial assistance is available for my carer or me? |
| Who can talk about my spiritual, religious and emotional needs? |

**Section 7: support for my family**

| How can I help my family and children understand what is happening? Can someone from the palliative care team help me? |
| What support is available now and in the future for my carer, my children and my family? |
| What should I do if members of my family discuss my decisions? |

**Section 8: making sure my wishes are honoured**

| Is there a way to plan and document my wishes for care at the end of life? |
| If my wishes change, how do I make sure people know and respect that? |
| Should I appoint someone to make medical decisions on my behalf in case of emergency situations or if I am too unwell to speak for myself? |
| Is there anything I need to do to make these arrangements official? |
| How can I make sure that others involved in my care know my wishes? |

**Section 9: other questions your family, friends or carer may like to ask**

| What skills will I need to support the person I am caring for? |
| What can I do to look after myself while caring for my partner/relative/friend? |
| Who can I talk to if I am concerned about the care my partner/relative/friend is receiving? |
| What help can I get if I can’t cope with caring for my partner/relative/friend? |
who are stronger and more able to explore and support in more detail (Heaven and Maguire, 1996). Health professionals who have undertaken advanced communication skills training have been found to be more confident and more likely to explore patients’ cues (Wilkinson et al, 1999).

Before exploring a patient’s cues and questions in more detail, it is important to ascertain what the patient already understands about their prognosis and the reasons behind their questions. Patients will often ask because an important future life event is pending, knowing this is important, the specialist nurse might need to consider advising that the event be brought forward or postponed. For example, the specialist nurse might say: ‘Before I give you my thoughts, can I just check what’s going through your mind about likely timescales and why it’s important to know these likely timescales?’

“A large part of the palliative/supportive care role involves open and honest conversations with patients on advance care planning. This includes identifying what is important to them throughout the disease trajectory.”

When estimating survival time, the type of information the patient would prefer should be determined. For example, some patients want numerical estimates, while others want a general idea such as days to weeks, or months to years. For patients who want numerical information, it is best to present ranges illustrating the best-case, worst-case, and most likely scenarios for expected survival, rather than providing a single number estimate of average survival, such as 12 months, as this implies unvaried progression, leaving little room for hope (Kiely et al, 2013).

Additionally, if the expected survival time is measured in weeks to a few months, it is important to explain that things may change sooner than expected due to the unpredictable nature of cancer.

It is very difficult to accurately predict a time frame; more importantly, this can be extremely difficult for patients and their loved ones as they might then focus on this time point, counting down, which can act as a constant reminder of the terminal nature of their disease.

Giving a general time frame can act as a guide rather than a definite point in time. However, personal experience shows that even a rough guide can be very difficult to predict, especially earlier on in the disease trajectory or with ‘well’ patients. Over time, the time frame often becomes more apparent, particularly when it is clear the patient is approaching the end of life. It is very important, therefore, that the uncertainty of survival estimates is explained to patients.

**SOCIAL/PSYCHOLOGICAL SUPPORT**

Patients with MBC can be inclined to social isolation, often a result of living with an incurable disease, the ongoing nature of treatment and inevitability of disease progression (Davies and Sque, 2002; Lam et al, 2015).

When patients are well, they will engage with support groups or seek support from the media via television, the press, social sites and web-based support groups (Davies and Sque, 2002). However, they do not often receive much dedicated, professional, face-to-face support when they do, this might be from a breast care nurse who does not specialise in MBC. The breast cancer nurse’s expertise centre on supporting patients undergoing treatment (from surgery through to chemotherapy), which includes providing physical and psychological support, and signposting and referring them to other services as needed.

Lack of face-to-face support for patients with MBC can preclude in-depth conversations and thus the opportunity to pick up on cues, develop a rapport and gain a fuller understanding of the patient’s perceptions, all of which are vital to preparing her for end-of-life care and preventing the need for crisis intervention.

**PALLIATIVE/SUPPORTIVE CARE**

Very few patients access palliative/supportive care until they have reached the end of their life (Reed and Corner, 2013). This may be due to the negative connotations associated with palliative care, which suggests it is only used in terminal and end-of-life settings (Keeley et al, 2013).

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The work within The Christie is still evolving, but early findings from as yet unpublished audits within the Macmillan Breast Palliative Care Project have shown significant improvements in patient care.

**CONCLUSION**

Patients with MBC have a complex disease and high levels of need, which requires an MDT approach to ensure care and support is provided throughout the disease trajectory. Integrating palliative/supportive care into breast oncology treatment and inevitability of disease progression, all patients should care should therefore be an integral part of oncology management (Fitzsimons et al, 2007; Illman and Williams, 2006). This will also aid the transition from active treatment to optimum supportive care (Greer et al, 2012).

To ensure the delivery of best practice, The Christie and the Macmillan Breast Palliative Care Project have developed the following recommendations:

• All patients with newly diagnosed MBC who are starting their first-line treatment should have access to a breast care nurse, be offered a holistic needs assessment and considered for inclusion in clinical trials, if appropriate

• At disease progression, all patients should receive care from both a MDT and the breast care nurse; they should continue to be considered for inclusion in clinical trials, if appropriate

• If symptomatic, all patients should be referred to palliative/supportive care along with those considered to be in their last 12 months of life. All patients with extensive disease burden at diagnosis should be referred to and supported by palliative/supportive care, as well as their breast care nurse.

A MDT approach is vital to ensure effective decision-making (Taylor et al, 2013). Personal experience of working in breast cancer care suggests that very few MDTs discuss metastatic patients. At The Christie, practice has changed to ensure that all women with MBC are discussed by a MDT (there are two MDTs, one with a dedicated time slot to discuss MBC patients with disease progression and another that focuses solely on patients with MBC with no disease progression). In this way, a treatment plan is developed before the patient attends the clinic. Such a proactive approach means she can be offered more support in the clinic. As a result, more patients with MBC are receiving palliative care earlier than was the case previously.

“A multidisciplinary team approach is vital to ensure effective decision-making. Personal experience indicates that very few multidisciplinary teams discuss metastatic patients. At The Christie, practice has changed to facilitate this”.

Recently, The Christie received funding from Macmillan to further develop the integration of palliative care into breast oncology. For the past few years, the Macmillan breast palliative care lead, breast clinicians, breast care nurses and patients at The Christie have been working closely with the Christie Cancer Improvement Partnership (MCIP) to develop best practice for patients with MBC. The breast care nursing team has become a solely metastatic service, which has worked closely with multidisciplinary teams for all new patients and piloted ‘living with MBC’ study days in which palliative/supportive care plays an integral part.

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care has promoted a proactive, holistic approach to patient management, with better identification of advancing disease, which ensures increased support in the last 12 months of life. Improved care and support given within the hospital and community settings should help to improve patient satisfaction and quality of life, and prevent the need for crisis intervention (Farrell and Coleby, 2016).


Butow PN, Olmsted M, Tattersall MH, et al (2015) Early versus delayed access to a clinical nurse specialist will ensure optimum outcomes will be achieved if specialists work in collaboration with a wider team.


More than just the median: calculating survival times for breast cancer.


Vasista A, Stockler MR, West T, Wilcken N, Kiely BE (2017) The national charity Breast Care Cancer profiled a standard of care required to meet the needs of a person diagnosed with MBC (Breast Cancer Care, 2012). It states that, from the moment of diagnosis, a woman with MBC should have access to a CNS who is knowledgeable about the disease, its treatment, and the support required. Breast Cancer Care (2012) emphasised that the CNS not only should coordinate care, but also act as the patient’s advocate and ensure that she has access to relevant information.

Patients with MBC need a multidisciplinary, holistic and individualised approach to care throughout the metastatic disease trajectory. The Breast Cancer Patient Experience Survey (NHS England, 2014) highlighted that support from a CNS is the most important contributing factor to a person’s experience of care. The CNS plays a crucial role in providing information, enabling communication and ensuring continuity of care (Breast Cancer Care, 2012). Nevertheless, many women living with MBC do not have access to a CNS (National Cancer Action Team and Macmillan Cancer Support, 2010). Breast Cancer Care (2016). In its report, Secondary. Not Second Rate, Breast Cancer Care noted that many patients with MBC stated that their care was inadequate, with gaps in the provision of care and information adding to a
TABLE I. THE PURPOSE AND FUNCTION OF THE MBC MULTIDISCIPLINARY TEAM

<table>
<thead>
<tr>
<th>Benefits for the Patient</th>
<th>Benefits for the Multidisciplinary Team</th>
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<tbody>
<tr>
<td>Peer discussion ensures patients (Secondary Breast Cancer Pledge Improve Goal)</td>
<td>Peer discussion, which highlights options in treatment eligibility to trials and enables conversations about individual patients through patient advocates</td>
</tr>
<tr>
<td>Radiological assessment and review of imaging to assess response to cancer treatments</td>
<td>Radiological assessment and review of imaging to assess disease and accessibility for repeat biopsy</td>
</tr>
<tr>
<td>Radiological assessment for localised radiotherapy options, which was valuable for the medical oncologists to discuss with clinical oncologists</td>
<td>Radiological assessment and review for assessment of target lesions for clinical trial eligibility and screening</td>
</tr>
<tr>
<td>Formal check for palliative care engagement and access to support for symptom management</td>
<td>Review of potential clinical trial options from the local and national portfolio of clinical trials</td>
</tr>
<tr>
<td>Formal check for palliative care engagement and access to support for symptom management</td>
<td>Formal check for palliative care engagement and access to community support</td>
</tr>
</tbody>
</table>

widely shared experience of feeling forgotten or invisible; women commented that their care was inferior to that of patients with early breast cancer (Reed et al, 2010, Breast Cancer Care, 2017). Progress in improving nursing services for MBC patients has been slow. In 2010, Reed et al found that only half of the breast care nurses they surveyed (n=276) felt the provision of care for these patients was inadequate, with many feeling ill-equipped to care for them (Reed et al, 2010). However, in 2016, a campaign by Breast Cancer Care to geographically map access to a specialist nurse or key worker provided encouraging evidence of a slowly growing nursing workforce, in designated roles, that is providing care for patients with MBC (Breast Cancer Care, 2016).

Early access to a CNS or key worker, as recommended by the Independent Cancer Taskforce (Cancer Research UK, 2015), means that patients will receive support when making decisions about their treatment and care and have better access to symptom control, thereby improving their quality of life. In addition, interventions from such specialists—which, for example, might prevent notification—can reduce costs for both patients and healthcare organisations (Reed et al, 2012).

When patients established a good relationship with the care team involved in their care, they felt respected and treated as an individual (Breast Cancer Care, 2017). Similarly, a good relationship with the care team is known to improve nurses’ understanding of their preferences and goals, which is vital for shared decision-making about treatment and care (Metastatic Breast Cancer Alliance, 2014; Macmillan Cancer Support (2014) proposed that, as more people live longer with treatable but incurable disease, the specialist adult nurse workforce will need to be optimised and expanded to ensure a good patient experience for them.

However, lack of information on how many people have been diagnosed and are living with MBC (Breast Cancer Care, 2016) means there is no thorough understanding of the scale of the problem and its significance as a public health issue. Indeed, the Secondary Not Second Rate report (Breast Cancer Care, 2010) demonstrated through its Who’s counting campaign that two-thirds of hospital trusts do not know how many patients with MBC they are treating. The report highlighted that our understanding of the number of people living with MBC and the support they receive is woefully inadequate. This makes it difficult to match resource with demand and thus meet present and future challenges.

As a starting point, the routine collection by hospitals of these data and their public dissemination by cancer networks and local health services could identify local patient population needs and enable services to be planned more effectively. However, meeting the needs of people living with MBC poses multifaceted challenges to the health service at a time of demanding political agendas and economic constraints. There is a need for a workforce with optimal targeted skills that can address these challenges and transform patient care. It is crucial that nurses, through their expertise and experience of diagnosis, treatment and care (Metastatic Breast Cancer Alliance, 2014), are recognized that partners, friends and relatives are unable to completely understand what they are going through (Vilhauer, 2011). Results of a global study with MBC in 12 countries demonstrated that, regardless of the country’s wealth, women with MBC felt that others do not empathise with their experience (Advanced Breast Cancer Community, 2013; Cardoso et al, 2016). This sense of isolation and lack of support from the larger breast cancer community can be attributed to inadequate access to resources that might meet their needs, lack of access to appropriate medicines and negative perceptions associated with a life-limiting diagnosis.

In 2012, the national charities Breast Cancer Care and Breast Cancer Now developed the Secondary Breast Cancer Pledge partnership to address issues faced by patients with MBC and health professionals. It aims to improve patients’ experience of diagnosis, treatment and care within a given trust. Qualitative and quantitative data are gathered through surveys, telephone interviews and patient focus groups. The Pledge also recruits and trains patient representatives, who act as the patient voice in the development of a hospital’s improvement goals (Breast Cancer Now, 2015).

Living with Secondary Breast Cancer Service

Following a diagnosis of MBC, psychological anxiety and distress prevents some women from doing what they want and living their usual lifestyle, which can lead to their social isolation (Aranda et al, 2005, NHS England, 2014; Breast Cancer Care, 2016). For many, then, it is difficult to read about or listen to others’ experiences (Mayer, 2010). Peer support groups can alleviate anxiety, help patients manage psychological care and, by sharing experiences, reduce the need for social support and increase openness to others (Pfizer Oncology et al, 2016). Participation can also reduce the sense of isolation often caused by the recognition that partners, friends and relatives are unable to completely understand what they are going through (Vilhauer, 2011). Results of a global study with MBC in 12 countries demonstrated that, regardless of the country’s wealth, women with MBC felt that others do not empathise with their experience (Advanced Breast Cancer Community, 2013; Cardoso et al, 2016). This sense of isolation and lack of support from the larger breast cancer community can be attributed to inadequate access to resources that might meet their needs, lack of access to appropriate medicines and negative perceptions associated with a life-limiting diagnosis.

In 2012, the national charities Breast Cancer Care and Breast Cancer Now developed the Secondary Breast Cancer Pledge partnership, which aims to improve patients’ experience of diagnosis, treatment and care.“Nurses have reported a lack of skills training and access to the tools needed to provide adequate supportive and palliative care. To address this, the charities Breast Cancer Care and Breast Cancer Now have developed the Secondary Breast Cancer Pledge partnership, which aims to improve patients’ experience of diagnosis, treatment and care”

LWMBM services are run throughout the UK by Breast Cancer Care and, in part, offer a solution on how to meet the information and support needs of patients with MBC outside of secondary care. An experienced therapist who is expert at managing grief and anxiety facilitates the monthly face-to-face group meetings. On alternate months, an expert speaker attends, providing information and answering questions about a topic related to living with MBC. The service aims to reduce isolation, giving patients a chance to talk openly about their feelings and discuss their concerns, while helping them to feel more in control by accessing expert information that may enable them to make informed decisions about their care.
MULTIDISCIPLINARY CARE

Multidisciplinary care describes an integrated health-care approach in which health professionals from different relevant treatment options and collaboratively develop individual treatment care plans (Chirgwin et al, 2010). However, these teams do not necessarily or specifically discuss secondary cancers or people with MBC (Breast Cancer Care, 2016).

A high-quality service is best achieved if there are clear standards on what constitutes good care (Harding et al, 2013). Multidisciplinary teamwork is the gold standard for planning care (Table 1). As such, these meetings have clear objectives, structures, processes and content. The focus of care and treatment for women with MBC is very different to that for early disease, with the primary goal being to extend life and palliate symptoms while preserving quality of life (National Institute for Health and Care Excellence (NICE), 2009; 2014). The value of multidisciplinary teams for those with MBC has not been sufficiently researched, although it seems logical that a multidisciplinary team approach would benefit patients with complex needs requiring a wide range of healthcare interventions (Chirgwin et al, 2010).

In the Kent Oncology Centre, a local multidisciplinary team was developed specifically for patients with metastatic breast cancer. It has improved workflow patterns and communication between professionals, and gives patients access to the right professional for their stage in the disease continuum. Such developments can have a positive impact on patient care.*

- Meeting the needs of the local patient group
- Poor and sometimes late referrals to community palliative care services
- Additional hospital appointments for assessment of local treatment, such as radiotherapy

Clearly, the breast cancer multidisciplinary team was apportioning little time to MBC, mainly because the large number of new cases were taking precedence. To address this, weekly meetings were arranged with participants, including a consultant radiologist, consultant oncologists, research nurses, the multidisciplinary team coordinator and the nurse clinician for MBC, with frequent visiting meetings between some staff from the acute oncology services and hospital-based palliative care services.

Purposeful planning ensures that patient reports, results and other relevant information are read by the designated MBC team the day before the patient consultation. This approach has helped to improve the patient experience by improving workflow patterns and communication, and providing patients with access to the right health professional, given that the evolution of their treatment and care and possible variations in the value systems of the patient and health team, can result in complex consultations.

Objective evidence of the improvement in clinical outcomes as a result of multidisciplinary team meetings is difficult to obtain. However, an audit showed a 50% improvement in clinical trial recruitment, both inhouse and through cross-trust referral. This also helped to identify disparities in the clinical trial portfolio. Other areas that have performed well are the appropriateness and checks for palliative care referrals beyond second-line treatments, as there is a general consensus that the benefit of second and subsequent lines of chemotherapy is uniformly poor (Cardoso et al, 2002).

CONCLUSION

Those living with MBC and those supporting them face numerous challenges. It is important to explore the provision of care provided for this patient group, as this might identify potential clinical improvements and innovations. Effective service development can be demonstrated in a variety of ways, but has to be supported by the clinical leadership of motivated individuals and teams. Even the smallest change can have a positive impact on patient care; as illustrated by collaborative enterprises described in this article.


PRESCRIBING INFORMATION HERCEPȚIN® (trastuzumab) 600 mg solution for injection in vials

Indication: Treatment of HER2-positive early breast cancer (EBC): (i) following surgery, chemotherapy (CT) (neo/adjuvant) or RT (if applicable) (ii) following adjuvant CT with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel. Eligible patients should have HER2 overexpression and should be administered Herceptin (trastuzumab) and not Kadcyla (pertuzumab).

Dosage and Administration: Please refer to Herceptin SmPC.

Herceptin.

Herceptin.

Cardiac: A thorough cardiac evaluation should be performed prior to Herceptin therapy and for 7 months after last dose. Close monitoring should be exercised as the following have been associated with the Herceptin IV formulation: dyspnoea, hypotension, tachyarrhythmia+1, cardiomyopathy, hypotension+1, chest pain, palpitations, angina, and arrhythmia. Cardiac adverse reactions reported with the Herceptin SC fixed-dose formulation: atrial fibrillation, ventricular tachycardia, atrial premature complexes, and ventricular premature complexes. It is recommended that full ECG be performed at baseline, before each cycle, and if symptoms occur.

Some adverse events were reported with a higher frequency for the SC formulation: Serious AEs (14.1% IV vs 21.5% SC) mainly due to infections with/without neutropenia. Important for serious AEs are important.

Previously mentioned, the safety profile of Herceptin SC vs Herceptin IV has been successfully treated with oxygen, or intravenous fluids and in some instances with anechoic. Hypotension, tachycardia, reduced oxygen saturation, hypoxia, and respiratory distress/failure, lung infiltration, acute respiratory distress syndrome, ARDS, pulmonary oedema, contusion.

Drug Interactions: No formal drug interaction studies have been performed. Clinically significant interactions with Herceptin have not been observed. Herceptin is administered as an off-label treatment with concomitant anti-neoplastic therapy. Therefore, it is recommended that patients be closely monitored for adverse events. Serious adverse reactions (frequency not known) interstitial lung disease, acute hypoplasia, pulmonary fibrosis.

Legal Category: POM

Presentation and Basic NHS Cost: Pack of one 6mL vials of Herceptin 600 mg (6mL of trastuzumab) —£1222.20 per vial excluding VAT —£222.20 per vial excluding VAT.

Marketing Authorisation Number: EU/1/00154/002

Marketing Authorisation Holder: Roche Registration Limited, Welwyn Garden City, AL7 1TW, United Kingdom.

Herceptin is a registered trade mark

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Adverse events should also be reported. Reporting forms and information can be found at: www.mhra.gov.uk/yellowcard.

Enhanced Safety Reporting for Potential HER2-Exposed Pregnancies

Women should be advised if treated with Herceptin or within 7 months following the last dose of Herceptin, please immediately report the pregnancy to the Roche Drug Safety Centre by emailing welwyn_uk_dsc@roche.com or calling: +44(0)1707 367554.

Additional information will be requested during the Herceptin-exposed pregnancy and the first year of the infant’s life. This will enable Roche to better understand the safety of Herceptin and to provide appropriate information to Health Authorities, Healthcare professionals and the patient.

Warnings for pregnant and potentially pregnant women

Herceptin should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus. There is a limited amount of data from the use of Herceptin in pregnant women, and the safe use of Herceptin during pregnancy and lactation has not been established. There are fertility data available.

In the post-marketing setting, cases of foetal renal growth and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving Herceptin. Verify pregnancy status prior to the initiation of Herceptin.

Women of childbearing potential should use effective contraception while receiving Herceptin and for 7 months following the last dose of Herceptin.

Monitor patients who become pregnant during Herceptin therapy or within 7 months following the last dose of Herceptin closely for oligohydramnios. It is not known whether Herceptin is excreted in human milk. As human IgG1 is secreted into human milk, and the potential for harm to the infant is unknown, women should not breastfeed during Herceptin therapy or for 7 months after the last dose.
HER2-targeted therapies due to complications of advanced malignancy or requiring murine proteins or any excipients. Severe dyspnoea at rest.

Contraindications:

Hypersensitivity to trastuzumab, anaphylactic reaction/shock, pulmonary fibrosis, respiratory failure, acute respiratory distress syndrome, bronchospasm, anaphylactic reaction, angioedema, angio-oedema, anaphylactoid, anaphylactoid reaction.

Hypersensitivity to human IgG1: rash, hives, angio-oedema, anaphylactoid reaction, hepatitis, interstitial pneumonitis, pneumonitis, pneumonitis and pleuritis, pulmonary oedema, pleural effusion, rapidly progressive renal failure, acute tubular necrosis and renal failure.

Useful effects of trastuzumab may be delayed. Women should not breast-feed during Herceptin therapy or for 7 months following the last dose of Herceptin. Human milk is not known whether Herceptin is secreted in human milk. As human IgG1 is secreted into breast milk, breastfeeding should be advised during Herceptin therapy or within 7 months following the last dose of Herceptin.

Pregnancy and Lactation:

Avoid during pregnancy. Women should not breast-feed during Herceptin therapy or for 7 months after the last dose of Herceptin. Herbal and Homeopathic Medicines: It is not known whether Herceptin is secreted in human milk. As human IgG1 is secreted into breast milk, breastfeeding should be advised during Herceptin therapy or within 7 months following the last dose of Herceptin.}

Reporting suspected adverse reactions after authorisation of the medicinal product. Adverse events should be reported. Reporting forms and information can be found on: www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Roche Products Ltd. Please contact Roche Drug Safety Centre by emailing welwyn.vsk@roche.com or calling: +44(0)1707 367554.

As Herceptin is a biological medicine, healthcare professionals should report adverse reactions by brand name and batch number.

Enhanced Safety Reporting for Potential Herceptin-Exposed Pregnancies

Democratic Republic of Herceptin or within 7 months following the last dose of Herceptin, please immediately report the pregnancy to the Roche Drug Safety Centre by emailing welwyn.vsk@roche.com or calling: +44(0)1707 367554. Additional information will be requested during a maternal-exposed pregnancy and the first year of the infant’s life. This will enable Roche to better understand the safety of Herceptin and to provide appropriate information to Health Authorities, Healthcare Professionals and patients. Warnings for pregnant and potentially pregnant women

Herceptin should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus. There is a limited amount of data from the use of Herceptin in pregnant women, and no adequate studies during pregnancy and lactation have been established. There are no fertility data available. In the post-marketing setting, cases of foetal renal growth and/or function impairment in association with olodaterol bromide, some associated with fatal pulmonary hypoaesthesia of the foetus, have been reported in pregnant women receiving Herceptin. Verify pregnancy status prior to the initiation of Herceptin. Women who become pregnant during Herceptin therapy or within 7 months following the last dose of Herceptin should use effective contraception while receiving Herceptin and for 7 months following the last dose of Herceptin. Monitor patients who become pregnant during Herceptin therapy or within 7 months following the last dose of Herceptin closely for olodaterol bromide. It is not known whether Herceptin is excreted in human milk. As human IgG1 is secreted into human milk, and the potential for harm to the infant is unknown, women should not breastfeed during Herceptin therapy or for 7 months after the last dose.

Contraindications:

Hypersensitivity to trastuzumab, murine proteins or any excipients. Severe dyspnoea at rest due to complications of advanced malignancy or requiring oxygen therapy.

Precautions:

Please refer to the Herceptin Summary of Product Characteristics (SmPC) for full guidance. To prevent medication error, check vial labels to ensure the drug being prepared and administered is Herceptin (trastuzumab) and not Kadcyla (trastuzumab emtansine). Check the product labels to ensure the correct Herceptin formulation (intravenous or subcutaneous fixed dose containing 10 mg/ml or 8 mg/kg body weight). Herceptin is being administered, as prescribed. HER2 testing is mandatory prior to Herceptin. Tumours should have HER2 overexpression at 3+ level by immunohistochemistry (IHC) or HER2 gene amplification by fluorescence in situ hybridisation (FISH or CISH), confirms the diagnosis of breast cancer.

SUMMARY OF PRODUCT CHARACTERISTICS

In combination with neoadjuvant CT followed by docetaxel and carboplatin. (iv) for locally advanced HER2+ breast cancer, with the concomitant medication used in clinical trials before giving access to any potential benefit. Most who developed CHF in clinical trials improved with appropriate treatment and continued Herceptin therapy, unless benefits outweigh risks. Most who developed CHF in clinical trials improved with appropriate treatment and continued Herceptin therapy, unless potential benefit outweighs risk. Oligohydramnios should be reported. Reporting forms and information can be found on: www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Roche Products Ltd. Please contact Roche Drug Safety Centre by emailing welwyn.vsk@roche.com or calling: +44(0)1707 367554.

Additional information will be requested during a maternal-exposed pregnancy and the first year of the infant’s life. This will enable Roche to better understand the safety of Herceptin and to provide appropriate information to Health Authorities, Healthcare Professionals and patients. Warnings for pregnant and potentially pregnant women

Herceptin should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus. There is a limited amount of data from the use of Herceptin in pregnant women, and no adequate studies during pregnancy and lactation have been established. There are no fertility data available. In the post-marketing setting, cases of foetal renal growth and/or function impairment in association with olodaterol bromide, some associated with fatal pulmonary hypoaesthesia of the foetus, have been reported in pregnant women receiving Herceptin. Verify pregnancy status prior to the initiation of Herceptin. Women who become pregnant during Herceptin therapy or within 7 months following the last dose of Herceptin should use effective contraception while receiving Herceptin and for 7 months following the last dose of Herceptin. Monitor patients who become pregnant during Herceptin therapy or within 7 months following the last dose of Herceptin closely for olodaterol bromide. It is not known whether Herceptin is excreted in human milk. As human IgG1 is secreted into human milk, and the potential for harm to the infant is unknown, women should not breastfeed during Herceptin therapy or for 7 months after the last dose.
PERJETA® (pertuzumab) 420 mg concentrate for solution for infusion

**Indication:** Metastatic breast cancer (mBC); in combination with trastuzumab and docetaxel for adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. Neoadjuvant treatment of BC in patients with HER2-positive, unresectable and chemotherapy-naive locally advanced or early breast cancer (eBC) at high risk of recurrence.

**Dosage and Administration:** Refer to Perjeta Summary of Product Characteristics (SmPC) for full guidance. Patients treated with Perjeta must have HER2-positive breast cancer and have not received prior therapy for locally advanced or metastatic disease. Perjeta may be administered 3-weekly. Docetaxel may subsequently be administered 3-weekly. Docetaxel may subsequently be escalated to 100mg/m² if well tolerated but not escalated when used with carboplatin, trastuzumab and Perjeta. Administer products sequentially. Do not mix in same infusion bag. Perjeta and trastuzumab can be given in any order. Docetaxel should be administered after Perjeta and trastuzumab. Perjeta should be administered by a healthcare professional prepared to manage anaphylaxis with the necessary resuscitation facilities immediately available. Treat mBC patients with Perjeta and trastuzumab until disease progression or unmanageable toxicity. For early BC, treat for three to six cycles of pertuzumab with or without docetaxel. Following BC, treat for three to six cycles of pertuzumab with or without docetaxel. Following mBC, treat for three to six cycles of Perjeta and trastuzumab and chemotherapy. Following surgery, treat with adjuvant trastuzumab to complete one year of treatment. 

**Contraindications:** Hypersensitivity to Perjeta or to any of the excipients.

**Precautions:** Refer to SmPC for further information. To improve traceability, clearly record tradename and batch number of administered product in patient file. Labelling: Use in-line filter is required for the infusion when the concentration for infusion is diluted with sodium chloride 0.9 mg/ml (0.9%) solution for infusion (refer to SmPC). Initial dose should be administered as 90-minute IV infusion, followed by 90 minutes of observation for infusion-related reactions (IRR). If well tolerated, subsequent doses may be administered as 30-minute infusions, followed by 30 minutes of observation. If a dose is missed, it should be administered as soon as possible; the dosing schedule adjusted to maintain a 3-weekly dosing interval. All patients should be additionally informed that use of strong CYP3A4 and CYP3A5 inhibitors should be avoided. If a patient is pregnant, breastfeeding or planning to breastfeed, all patients should be advised that breastfeeding should be avoided. If not possible, consider a delay in administration of Perjeta until the CYP3A4 inhibitor has cleared. If Perjeta treatment cannot be delayed, monitor patients closely.

**Adverse drug reactions**

- **Diarrhoea:** Incidence and frequency of adverse drug reactions may include: diarrhea, nausea, vomiting, anorexia, dyspepsia, abdominal pain, and/or infection. ADRs reported less frequently after Perjeta. Women of child bearing potential should use effective contraception during and 30–60 minutes following the last dose of Perjeta. Monitor patients who become pregnant during Perjeta therapy or within 6 months following the last dose of Perjeta.

**Legal Category:** POM

**Marketing Authorisation Number:** EU/1/13/103/001

**Marketing Authorisation Holder:** Roche Registration Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, United Kingdom.

**PERJETA is a registered trade mark**

**Date of Preparation:** July 2015

**This medicinal product is subject to additional monitoring. This will allow quick identification of any new safety information. Healthcare professionals are asked to report any suspected adverse drug reactions.**

**Adverse drug reactions should be reported. Reporting forms and information can be found at: www.mhra.gov.uk/yellowcard.**

**Enhanced Safety Reporting for Potential Herceptin-Exposed Pregnancies**

- This summary is derived from Perjeta SmPC as at date of approval.
- Please refer to SmPC for full guidance.
- May apply when used with Herceptin, trastuzumab and Perjeta.
- Women of child bearing potential should use effective contraception during Perjeta therapy for the woman.
- Perjeta should be avoided during pregnancy. There is a limited amount of data from the use of Perjeta in pregnant women and the safety of Perjeta during pregnancy and lactation has not yet been established.
- Verify pregnancy status prior to the initiation of Perjeta. Women of child-bearing potential should use effective contraception while receiving Perjeta and for 6 months following the last dose of Perjeta.
- Monitor patients who become pregnant during Perjeta therapy or within 6 months following the last dose of Perjeta, immediately report exposure to the Roche Drug Safety Centre by emailing welwyn.uks_dsc@roche.com or by calling +44(0)707 367554.
- Additional information will be requested during a Perjeta-pregnancy registry and the first year of the infant’s life. This will enable Roche to better understand the safety of Perjeta and to provide appropriate information to Health Authorities, Healthcare Providers and patients.
**Pregnancy and Lactation:** See box titled “Enhanced Safety Reporting for Potential Kadcyla-Exposed Pregnancies”.

**Adverse reactions:** The most common serious reactions seen in clinical trials were haemorrhage, pyrexia, dyspnoea, musculoskeletal pain, thrombocytopenia, abdominal pain and vomiting. *Very common and common reactions:* urinary tract infection, thrombocytopenia, anaemia, neutropenia, leucopenia, drug hypersensitivity, hypokalaemia, insomnia, peripheral neuropathy, headache, dizziness, dysgeusia, memory impairment, dry eye, conjunctivitis, blurred vision, lacrimation increased, left ventricular dysfunction, haemorrhage, hypertension, epistaxis, cough, dyspnea, stomatitis, diarrhoea, vomiting, nausea, constipation, dry mouth, abdominal pain, dyspepsia, gingival bleeding, rash, pruritus, alopecia, nail disorder, palmar-plantar erythrodysaesthesia syndrome, urticaria, musculoskeletal pain, arthralgia, myalgia, fatigue, pyrexia, asthenia, chills, peripheral oedema, transaminases increased blood alkaline phosphatase increased, infusion related reactions. *Other serious reactions:* Pneumonitis (ILD), hepatic failure. *Laboratory abnormalities:* Both hepatic and haematological abnormalities were observed.

**Legal Category:** POM

**Presentation, Basic NHS Cost and Marketing Authorisation Number:** Kadcyla (trastuzumab emtansine) one 100 mg glass vial — £1641.01. EU/1/13/885/001.
Kadcyla (trastuzumab emtansine) one 160 mg glass vial —£2625.62. EU/1/13/885/002.

**Marketing Authorisation Holder:** Roche Registration Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, United Kingdom

Kadcyla® is a registered trade mark

RXUKMED100223(1)

**Date of Preparation:** February 2016

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This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Roche Products Ltd. Please contact Roche Drug Safety Centre by emailing welwyn.uk_dsc@roche.com or calling +44(0) 1707 367554.

As Perjeta is a biological medicine, healthcare professionals should report adverse reactions by brand name and batch number.

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**Enhanced Safety Reporting for Potential Herceptin-Exposed Pregnancies**

If a pregnancy occurs while using Kadcyla or within 7 months following the last dose of Kadcyla, please immediately report the pregnancy to the Roche Drug Safety centre by emailing welwyn.uk_dsc@roche.com or calling +44(0) 1707 367554.

Additional information will be requested during a Kadcyla-exposed pregnancy and the first year of the infant’s life. This will enable Roche to better understand the safety of Kadcyla and to provide appropriate information to Health Authorities, Healthcare Providers and patients.

**Contraception in males and females**

Women of childbearing potential should use effective contraception while receiving Kadcyla and for 7 months following the last dose of Kadcyla. Male patients or their female partners should also use effective contraception.

**Pregnancy**

There are no data from the use of Kadcyla in pregnant women. Trastuzumab, a component of Kadcyla, can cause foetal harm or death when administered to a pregnant woman. In the post-marketing setting, cases of oligohydramnios, some associated with fatal pulmonary hypoplasia, have been reported in pregnant women receiving trastuzumab. Animal studies of maytansine, a closely related chemical entity of the same maytansinoid class as DM1, suggest that DM1, the microtubule-inhibiting cytotoxic component of Kadcyla, is expected to be teratogenic and potentially embryotoxic.

Administration of Kadcyla to pregnant women is not recommended and women should be informed of the possibility of harm to the foetus before they become pregnant. Women who become pregnant must immediately contact their doctor. If a pregnant woman is treated with Kadcyla, close monitoring by a multidisciplinary team is recommended.

**Breast-feeding**

It is not known whether Kadcyla is excreted in human milk. Since many medicinal products are excreted in human milk and because of the potential for serious adverse reactions in breastfeeding infants, women should discontinue breast-feeding prior to initiating treatment with Kadcyla. Women may begin breast-feeding 7 months after concluding treatment.

**Fertility**

No reproductive and developmental toxicology studies have been conducted with Kadcyla.