AN EDUCATIONAL SUPPLEMENT IN ASSOCIATION WITH

BJN
British Journal of Nursing

Roche Products Ltd is entirely responsible for the production and funding of this promotional educational supplement. Roche Products Ltd has identified, briefed and remunerated the authors of this supplement

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.

RXUKMBCO00033 | July 2017

CONTENTS

Declaration of interest

Roche Products Ltd planned and funded the publication of this supplement. The authors are all independent clinicians who were selected by Roche and they received a fee for their contributions.

How to cite this document

Ryan C, Burcombe R, Coleby T (2017) HER2-targeted therapies in breast cancer. *Br J Nurs* **26**(16 Suppl): S1–32

MA HEALTHCARE
A MARK ALLEN GROUP COMPANY

Although the editor, MA Healthcare and Roche Products Ltd have taken great care to ensure accuracy, neither MA Healthcare nor Roche Products Ltd will be liable for any errors of omission or inaccuracies in this publication.

Published on behalf of Roche Products Ltd by MA Healthcare.

Printed by Pensord Press, Blackwood, NP12 2YA

Publisher: Andrew Iafrati
Associate publisher, medical education and editor: Tracy Cowan
Editorial project manager and coordinator: Camila Fronzo
Designer: Maddy Porter
Published by MA Healthcare Ltd, St Jude's Church, Dulwich Road, London SE24 0PB, UK

Tel: +44 (0)20 7501 6732. Email: andrew.iafrati@markallengroup.com
www.markallengroup.com

RXUKMBCO00033 | July 2017

RXUKMBCO00033 | July 2017

FOREWORD

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.

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 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 innovating 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'.

Claire Ryan, Macmillan Nurse Clinician Metastatic Breast Cancer, Kent Oncology Centre, Maidstone & Tunbridge Wells NHS Trust

Russell Burcombe, Consultant Clinical Oncologist, Kent Oncology Centre, Maidstone & Tunbridge Wells NHS Trust

Tracey Coleby, Macmillan Breast Palliative Care Lead, The Christie NHS Foundation Trust

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 care 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 breast tumour metastasise from the breast to other parts of the body via the blood or lymphatic systems. 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 are 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). Nevertheless, it is estimated that more than 9500 women die of breast cancer every year in England (Cancer Research UK, 2014).

The median survival from diagnosis of MBC is 2–3 years, although in indolent disease it may be as long as 10–15 years (Johnston and Swanton, 2006).

Claire Ryan Mamillan Nurse Clinician Metastatic Breast Cancer Kent Oncology Centre, Maidstone & Tunbridge Wells NHS Trust.
clairery4@nhs.net

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.

> "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. The complex psychosocial needs of these patients can pose a major challenge for health professionals, primary and secondary health services, and social care services"

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

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 not 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 of control and uncertainty (Warren, 2010; Schmid-Büchi 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 overriding theme 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, incorporating psychosocial care and, ultimately, preparing for end of life.

Patients with MBC will inevitably confront disease progression, and thus face changing physical, psychosocial and emotional demands. Understanding these changes will enable expert health professionals to deliver interventions that are tailored to meet 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 shared 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"

This shift towards support for self-management might encourage patients with MBC to increase their understanding of what the cancer journey might look like (Fenlon 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 multiple 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. It provides evidence of the benefits to patient care, highlighting the advantages of working within a cancer community to share practices.

In recent years, oncology treatment for MBC in the UK has moved to the ambulatory setting, resulting in less face-to-face time for patients within the hospital setting. In response, there has been a shift to support self-care in parallel with shared care delivered by health professionals and health organisations within primary care (King's Fund, 2012). However, there are risks that care can become fragmented and patients exposed to multiple health providers. This validates the need for a specialist nurse or key worker to 'thread together' care. The literature reports feelings of abandonment and isolation, and raises concerns about less

RXUKMBCO00033 | July 2017
RXUKMBCO00033 | July 2017

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, a sound relationship between the patient, oncologist and, if accessible, specialist nurse is needed to facilitate shared decision-making (Filleron et al, 2015). Patients need to understand their choices 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 crucial, it is not the sole aspect of how patients manage living with their cancer. The patient experience is also influenced by health policy, society and community factors.

Nurses play a key role in the health community, and can help shape policy for cancer services at a national level and through clinical leadership. Nurses can, and should, learn from each other by sharing promising practices, exchanging information and insights, and promoting knowledge-sharing. Future projections of increased prevalence of MBC (NICE, 2009; 2014) highlight the value of bringing the nursing community together to best meet the needs of people living with MBC.

Breast Cancer Care (2016) *Secondary. Not second rate.* http://tinyurl.com/ycaxopow (accessed 11 July 2017)

Cancer Research UK (2014) Breast cancer incidence (invasive) statistics. http://tinyurl.com/oap7tmc (accessed 11 July 2017)

Cardoso F, Costa A, Norton L et al (2014) ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2)†. *Ann Oncol* **25**(10): 1871–88. doi: 10.1093/annonc/mdu385

Coulter A, Collins A (2011) *Making Shared Decision-making a Reality. No Decision About me, Without me.* King's Fund, London. http://tinyurl.com/ln8tunc (accessed 7 August 2017)

Department of Health, Macmillan Cancer Support, NHS Improvement (2010) *National Cancer Survivorship Initiative Vision*. http://tinyurl.com/y8he5kp6 (accessed 7 August 2017)

Fenlon D, Reed E (2008) What do women with advanced breast cancer want from their treatment? *Advances in Breast Cancer: Psychosocial Issues* **December**

Filleron T, Bonnetain F, Mancini J et al (2015) Prospective construction and validation of a prognostic score to identify patients who benefit from third-line chemotherapy for metastatic breast cancer in terms of overall survival: the METAL3 study. *Contemp Clin Trials* **40**: 1–8. doi: 10.1016/j.cct.2014.11.005

Findlay M, von Minckwitz G, Wardley A (2008) Effective oral chemotherapy for breast cancer. *Ann Oncol* **19**(2): 212–22

Johnston SR (2010) Living with secondary breast cancer: coping with an uncertain future with unmet needs. *Eur J Cancer Care (Engl)* **19**(5): 561–63. doi: 10.1111/j.1365-2354.2010.01216.x

Johnston S, Swanton C (2006) *Handbook of Metastatic Breast Cancer*. Informa UK

King's Fund (2012) *Leadership and Engagement for Improvement in the NHS: Together we can*. http://tinyurl.com/y7ahdnoy (accessed 11 July 2017)

Mayer M, Grober SE (2006) *Silent Voices: Women with Advanced (Metastatic) Breast Cancer Share their Needs and Preferences for Information, Support and Practical Services*. https://tinyurl.com/y9udxffd (accessed 11 July 2017)

National Cancer Action Team (2010) *Excellence in Cancer Care: The Contribution of the Clinical Nurse Specialist*. https://tinyurl.com/y9ft7g3g (accessed 11 July 2017)

National Institute for Health and Care Excellence (2009; 2014) *Advanced Breast Cancer: Diagnosis and Treatment*. https://tinyurl.com/z3twxhw (accessed 11 July 2017)

National Institute for Health and Care Excellence (2012) *Patient Experience in Adult NHS Services: Improving the Experience of Care for People using Adult NHS Services*. https://tinyurl.com/j7w2njl (accessed on 7 August 2017)

Nelson JP (1996) Struggling to gain meaning: living with the uncertainty of breast cancer. *ANS Adv Nurs Sci* **18**(3): 59–76

Pfizer Oncology, European School of Oncology, ABC3 (2016) *Global Status of Advanced/Metastatic Breast Cancer: 2005–2015 Decade Report*. https://tinyurl.com/ybxg57uq (accessed 11 July 2017)

Quality Health (2014) National cancer patient experience survey. https://tinyurl.com/y8jyq7u4 (accessed 11 July 2017)

Reed E, Scanlon K, Fenlon D (2010) A survey of provision of breast care nursing for patients with metastatic breast cancer: implications for the role. *Eur J Cancer Care (Engl)* **19**(5): 575–80. doi: 10.1111/j.1365-2354.2010.01213.x

Reed E, Simmonds P, Haviland J, Corner J (2012) Quality of life and experience of care in women with metastatic breast cancer: a cross-sectional survey. *J Pain Symptom Manage* **43**(4): 747–58. doi: 10.1016/j.jpainsymman.2011.05.005

Schmid-Büchi S, van den Borne B, Dassen T, Halfens RJ (2011) Factors associated with psychosocial needs of close relatives of women under treatment for breast cancer. *J Clin Nurs* **20**(7–8): 1115–24. doi: 10.1111/j.1365-2702.2010.03376.x

Swain SM, Baselga J, Kim SB et al (2015) Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med* **372**(8): 724–34. doi: 10.1056/NEJMoa1413513

Verma S, Miles D, Gianni L et al (2012) Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* **367**(19): 1783–91. doi: 10.1056/NEJMoa1209124

Warren M (2010) Uncertainty, lack of control and emotional functioning in women with metastatic breast cancer: a review and secondary analysis of the literature using the critical appraisal technique. *Eur J Cancer Care (Engl)* **19**(5): 564–74. doi: 10.1111/j.1365-2354.2010.01215.x.

Warren M, Mackie D (2014) Co-ordination of supportive care needs in metastatic breast cancer. *Cancer Nursing Practice* **13**(1): 23–27

Wise PH (2016) Cancer drugs, survival and ethics. *BMJ* **355**: i5792

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

CURRENT TREATMENT OF HER2+ METASTATIC BREAST CANCER

HISTORICALLY, HER2-POSITIVE BREAST CANCER HAD A POOR PROGNOSIS. THE DEVELOPMENT OF MOLECULAR THERAPIES THAT TARGET THE HER2 RECEPTOR HAS TRANSFORMED OUTCOMES. HERE, THE EVIDENCE ON ANTI-HER2 THERAPIES IS SUMMARISED

Approximately 20–30% of breast cancers overexpress human epidermal growth factor receptor 2 (HER2) (Slamon et al, 1987; 1989). 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; Seshadri et al, 1993; Press et al, 1993; Ravdin and Chamness, 1995).

Two decades ago, the prognosis for patients with HER2+ metastatic breast cancer (MBC) was very poor (King et al, 1985; Slamon et al, 1987; 1989; Gusterson et al, 1992; Hynes and Stern, 1994; Chia et al, 2007). However, the development of molecular 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 include patients with hormone receptor (HR) and HER2 positive and/or negative cancers.

HOW ARE HER2+ BREAST CANCERS IDENTIFIED?

HER2+ tumours can be identified using immunohistochemistry (IHC) or 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) (Junttila et al, 2009). It is indicated for the treatment of adult patients with HER2+ MBC (Herceptin summary of 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

Russell Burcombe Consultant Clinical Oncologist, Kent Oncology Centre, Maidstone & Tunbridge Wells NHS Trust.
russell.burcombe@nhs.net

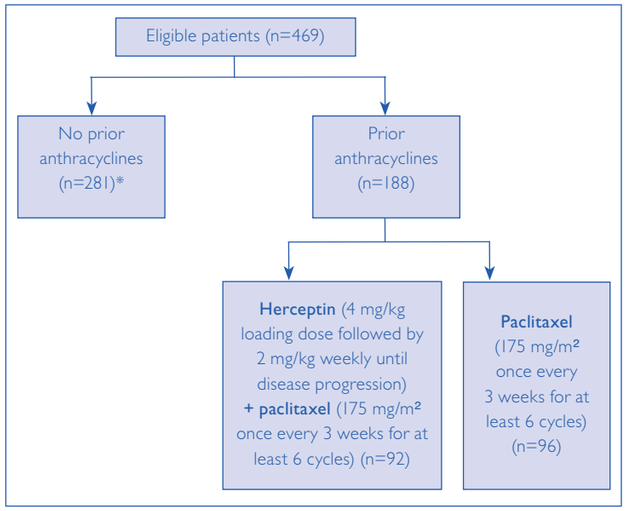


Figure 1: Slamon et al (2001) study design.
*The comparator arm included an anthracycline combination, which is off label and so cannot be shown here

- In combination with paclitaxel for those who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable
- In combination with docetaxel for those who have not received chemotherapy for their metastatic disease
- In combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone receptor-positive MBC not previously treated with trastuzumab.

In 2001, a pivotal landmark study demonstrated the efficacy of Herceptin plus chemotherapy as a first-line HER2-targeted therapy for patients with HER2+ MBC (Slamon et al, 2001). Patients were randomly assigned to receive chemotherapy (either anthracycline or paclitaxel, depending on prior exposure to either in the adjuvant setting) with or without Herceptin (*Figure 1*) (Slamon et al, 2001).

TABLE 1. SUMMARY OF HERCEPTIN PLUS PACLITAXEL VS. PACLITAXEL ALONE; RESULTS FROM SLAMON'S (2001) TRIAL OF HERCEPTIN PLUS CHEMOTHERAPY VS CHEMOTHERAPY ALONE

	HERCEPTIN + CHEMOTHERAPY	PACLITAXEL
Median duration of response	10.5 months	4.5 months
Time to progression (TTP)*	6.9 months	3.0 months*
Overall survival (OS)	22.1 months	18.4 months†
Objective response rate (ORR)	41.0%	17.0%

*$p<0.001$; †$p=0.17$

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 anthracycline and cyclophosphamide alone; 13% for paclitaxel and Herceptin; and 1% for paclitaxel alone). This was potentially severe and, 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, 2005). In this small randomised controlled trial (RCT) (n=186) 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=24), which compared resource use and socioeconomic impact, but not treatment outcomes, showed that substituting intravenous (IV) infusion with subcutaneous 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).

RXUKMBCO00033 | July 2017

Lapatinib

Lapatinib is an orally active small molecule dual tyrosine kinase inhibitor (TKI) of HER2 and epidermal growth factor receptor (EGFR) (Burris, 2004; Geyer et al, 2006; Higa and Abraham, 2007).

In a pivotal phase III study, patients with HER2+ MBC who had progressed after first-line treatment with regimens including an anthracycline, a taxane and Herceptin were randomly assigned in a 1:1 ratio to receive capecitabine with or without lapatinib (*Figure 2*) (Geyer et al, 2006). Response rates to single-agent capecitabine were low, but in combination with lapatinib, TTP almost doubled compared with capecitabine alone (8.4 vs 4.4 months, $p<0.001$), although no OS benefit was observed (Geyer et al, 2006).

The results demonstrated that the addition of lapatinib improves outcomes compared with capecitabine chemotherapy alone in HER2+ mBC (Geyer et al, 2006). The most common adverse events associated with the combination arm versus monotherapy were diarrhoea (60% vs 39%, any grade), nausea (44% vs 42%) and vomiting (26% vs 24%), but the majority of cases were mild to moderate. Addition of lapatinib to capecitabine was not associated with an increase in serious toxic effects or discontinuation rates.

Perjeta® ▼ (pertuzumab)

Perjeta is a humanised monoclonal antibody that binds to a different epitope (a different section of the HER2 receptor) to Herceptin, thereby preventing HER2 from joining with other HER receptors, most notably HER3; this inhibits a process known to activate cell-survival (Franklin et al, 2004; Landgraf, 2007; Baselga et al, 2012). The combination of Perjeta and Herceptin therefore induces a more complete 'dual blockade' of the HER signalling pathways than either agent alone (*Figure 3*) (Franklin et al, 2004; Baselga et al, 2012; Swain et al, 2015).

Perjeta is indicated for use in combination with Herceptin and docetaxel in adult patients with HER2+ metastatic or locally recurrent unresectable breast cancer who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease (Perjeta smPC).

The pivotal randomised phase III CLEOPATRA trial explored the role of dual HER2 blockade with Perjeta and Herceptin in combination with a first-line treatment for HER2+ MBC (Swain et al, 2015). In this study, 808 patients who had not received previous chemotherapy for metastatic disease were randomly assigned to receive Herceptin and docetaxel, plus either Perjeta or placebo (Baselga et al, 2012; Swain et al, 2015) (*Figure 4*).

RXUKMBCO00033 | July 2017

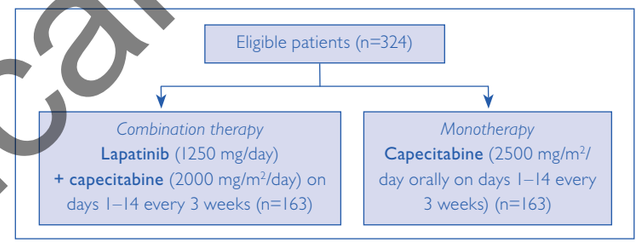
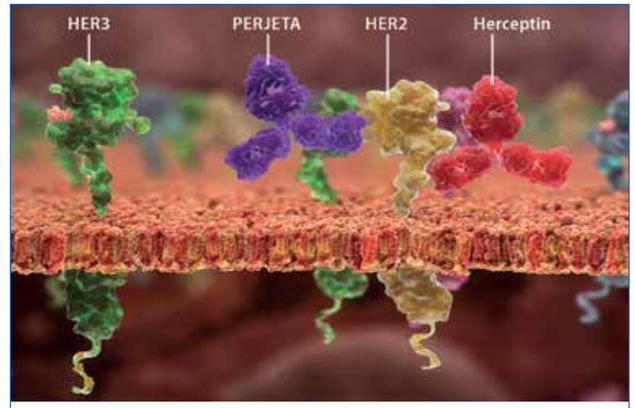


Figure 2: Geyer et al (2006) study design



Perjeta and Herceptin have complementary mechanisms of action (Swain et al, 2015). Perjeta specifically blocks HER2 dimerisation with other HER2 proteins, thereby inhibiting the signalling pathways that are essential for tumour growth (Franklin et al, 2004).

Perjeta binds to subdomain II, preventing dimerization and inducing antibody-dependent cell-mediated cytotoxicity (ADCC) (Cho et al, 2003). Herceptin binds to subdomain IV, preventing formulation of p95 and inducing ADCC (Franklin et al, 2004)

Figure 3: Perjeta and Herceptin mechanisms of action (Roche Products Ltd)

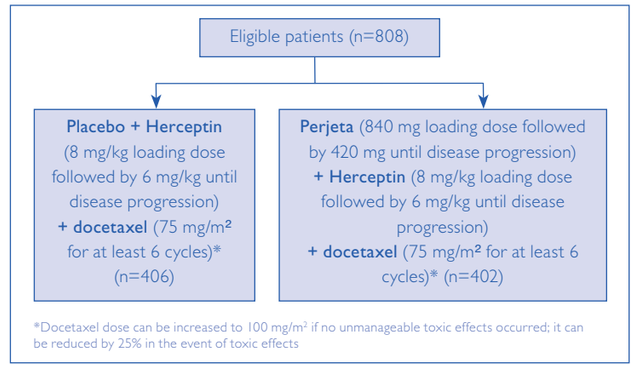


Figure 4: CLEOPATRA dosing schedule (Baselga et al, 2012; Swain et al, 2015)

Response rates following treatment with dual HER2 blockade using Perjeta plus Herceptin and docetaxel were impressive: the ORR was 80.2% in the Perjeta arm vs 69.3% in the placebo arm (Baselga et al, 2012). The second interim analysis reported that Perjeta extended median progression-free survival (PFS) by 6.3 months and median OS by 15.7 months in patients with

TABLE 2. SUMMARY OF RESULTS FROM THE CLEOPATRA TRIAL (SWAIN ET AL, 2013; SWAIN ET AL, 2015; BASELGA ET AL, 2012)

	PERJETA + HERCEPTIN + DOCETAXEL	PLACEBO + HERCEPTIN + DOCETAXEL
Median duration of response	20.2 months	12.5 months
Progression-free survival (PFS)	18.7 months	12.4 months*
Overall survival (OS)	56.5 months	40.8 months†
Objective response rate (ORR)	80.2%	69.3%

*$p<0.001$; †$p<0.001$

TABLE 3. THE FIVE MOST COMMON ADVERSE EVENTS REPORTED IN CLEOPATRA TRIAL (SWAIN ET AL, 2013)

ADVERSE EVENT	PERJETA + PERCEPTIN + DOCETAXEL (N=408)	PLACEBO + HERCEPTIN + DOCETAXEL (N=396)
Diarrhoea	278 (68.1%)	191 (48.2%)
Alopecia	248 (60.8%)	240 (60.6%)
Neutropenia	216 (52.9%)	197 (49.7%)
Nausea	179 (43.9%)	168 (42.4%)
Fatigue	155 (38.0%)	148 (37.4%)

HER2+ MBC compared with placebo (*Table 2*). Nearly half the patients who received dual blockade were alive 5 years after entering the study.

Following the release of the interim study results, 11.8% of the placebo arm patients crossed over to Perjeta. When these patients were excluded from the intention-to-treat (ITT) analysis, the OS advantage approached 2 years (56.5 vs 34.7 months, $p<0.001$) (Swain et al, 2015).

By way of comparison, previous studies of Herceptin plus chemotherapy in patients with HER2+ MBC reported a median OS ranging from 25.1 to 38.1 months (Slamon et al, 2001; Marty et al, 2005; Andersson et al, 2011; Valero et al, 2011; Baselga et al, 2014).

Dual blockade with the 'triple therapy' regimen containing Perjeta, Herceptin and docetaxel has therefore defined a new standard of care for the first-line treatment of HER2+ MBC (Santa-Maria and Gradishar, 2015), allowing nearly half of HER2+ MBC patients to live 5 years or more with breast cancer with manageable side effects (Swain et al, 2015).

The most common adverse events reported were diarrhoea, alopecia, neutropenia, nausea and fatigue (*Table 3*). The incidence was similar between the two arms, except for diarrhoea, which was more frequently observed with Perjeta. The majority of adverse events occurred during the docetaxel-containing phase of treatment. Following the discontinuation of chemotherapy, maintenance dual antibody blockade was extremely well tolerated, with diarrhoea and rash being the most commonly reported adverse events in the Perjeta arm.

Treatment with Perjeta/Herceptin/docetaxel did not increase the rate of left ventricular systolic dysfunction (LVSD) compared with treatment with placebo/Herceptin/docetaxel. Furthermore, a reduction of 4.6% in left ventricular ejection fraction (LVEF) was found in the Perjeta arm compared with 7.4% in the placebo arm. These observations confirmed that cardiac safety was maintained with long-term treatment; indeed, the addition of Perjeta to Herceptin and docetaxel did not increase cardiac toxicity (Swain et al, 2013).

There are two distinct phases to the type of 'triple therapy' approach used in the CLEOPATRA trial (*Figure 4*): the chemotherapy-containing phase and the maintenance phase, in which treatment with Perjeta and Herceptin is continued without docetaxel chemotherapy (Baselga et al, 2012; Swain et al, 2015). The majority of adverse events occurred during the chemotherapy-containing phase (Swain et al, 2015). Adverse events known to impact on daily life (diarrhoea, nausea, fatigue and decreased appetite) were reduced after docetaxel was discontinued (Swain et al, 2015). Docetaxel can be dose-reduced or discontinued if side effects are unmanageable. The risk of neutropenia can be reduced with the prophylactic administration of granulocyte-colony stimulating factor (G-CSF), and anti-diarrhoeal treatment is effective in managing symptoms of severe diarrhoea.

Kadcyla® ▼ (trastuzumab emtansine)

Kadcyla is a novel anti-HER2 therapy: an antibody-drug conjugate of emtansine, a potent microtubule-inhibitor chemotherapy drug, linked to Herceptin (Kadcyla SmPC, 2017). The antibody provides targeted delivery of emtansine to HER2+ tumour cells where it is internalised into the cell, ensuring maximal cytotoxic delivery while limiting systemic toxicity (Lewis et al, 2008; Kadcyla SmPC; Verma et al, 2012).

Kadcyla, as a single agent, is indicated for the treatment of adults with HER2+, unresectable locally advanced or MBC, who previously received Herceptin and a taxane, separately or in combination (Kadcyla SmPC, 2017). To be eligible for treatment, patients should have either:

- Received prior therapy for locally advanced or metastatic disease *or*
- Developed disease recurrence during or within 6 months of completing adjuvant therapy.

RXUKMBCO00033 | July 2017

RXUKMBCO00033 | July 2017

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 3.6 mg/kg intravenously every 21 days until disease progression or the development of unmanageable toxic 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 extended by 5.8 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 thrombocytopenia (12.9%) 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, nausea, diarrhoea and neuropathy, were observed. Cardiac toxicity was extremely low compared with that in the CLEOPATRA study: only 1.7% 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).

The EMILIA study confirmed that the intracellular delivery of a cytotoxic agent specifically to HER2+ tumour cells reduces systemic toxicity compared with lapatinib plus capecitabine, and significantly prolongs PFS and OS with a manageable safety profile. The superior efficacy compared with previous standard second-line treatment for locally advanced or MBC (lapatinib plus capecitabine) made Kadcyla the preferred agent for patients with HER2+ MBC after progression on Herceptin plus docetaxel (National Comprehensive Cancer Network, 2017).

TREATMENT OPTIONS FOR CO-POSITIVE BREAST CANCER

Approximately 50% of all HER2+ breast cancers co-express oestrogen receptors (ER) and/or progesterone receptors (PgR); these tumours are classed as co-positive (Kaufman et al, 2009). Crosstalk between HR and HER2 pathways is believed to contribute to resistance to hormonal (endocrine) therapy (Jones, 2003; Schiff et al, 2003; Shou et al, 2004; Johnston, 2005; Osborne et al, 2005). Therefore, simultaneous blockade of both pathways using combination therapy with targeted anti-HER2 agents and aromatase inhibitors for MBC has been evaluated.

TABLE 4. SUMMARY OF RESULTS FROM EMILIA STUDY (VERMA ET AL, 2012)

	KADCYLA	LAPATINIB + CAPECITABINE
Progression-free survival (PFS)	9.6 months	6.4 months*
Overall survival (OS)*	30.9 months	25.1 months†
Objective response rate (ORR)	43.6%	30.8%‡

*OS at the second interim analysis. *$p<0.001$; †$p<0.001$; ‡$p<0.001$

Herceptin plus anastrozole

The TAnDEM study was the first phase III RCT to examine the efficacy of endocrine therapy with Herceptin. In this study, postmenopausal estrogen-receptor-positive (ER+) patients with HER2+ MBC were randomised to receive anastrozole plus HER2-targeted therapy Herceptin (without chemotherapy) or anastrozole alone (*Figure 5*) (Kaufman et al, 2009). Crossover was allowed on progression.

Patients in the ITT population who were randomised to receive Herceptin plus anastrozole had a superior PFS (4.8 vs 2.4 months) and partial response rate (20.3% vs 6.8%) compared with those who received anastrozole alone. However, no statistically significant difference in median OS was observed: 28.5 months in the Herceptin plus anastrozole arm vs 23.9 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 23%

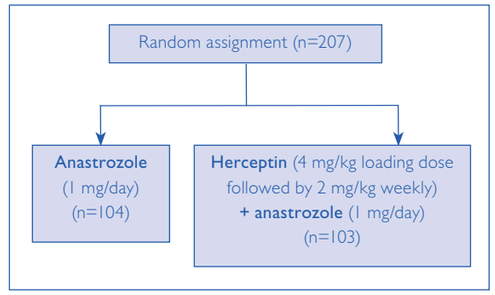


Figure 5: Kaufman et al (2009) dosing schedule

and 5% of patients in the Herceptin plus anastrozole arm and 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 anastrozole improved outcomes for the 15% of patients with co-positive (HER2+/HR+) MBC compared with anastrozole alone and suggested that HER2-targeted therapy combined with an aromatase inhibitor can substantially delay the need for chemotherapy in some patients. However, this was associated with an increase in adverse and serious adverse events, compared 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 3.3 months), response rates (27% vs 13%) and clinical benefit (65% vs 39%) (Huober et al, 2012).

Lapatinib plus letrozole

Johnston et al conducted a randomised phase III trial of letrozole plus 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 (8.2 vs 3.0 months) but no OS difference was apparent between the two arms (Johnston et al, 2009).

In summary, for patients with co-positive HER2+/HR+ MBC for whom chemotherapy is not an option, or patients with bone-only disease and indolent disease progression, the combination of anti-HER2 therapy plus endocrine therapy can be considered as a treatment option to delay chemotherapy. However, PFS gains were modest and no survival benefit, compared with endocrine therapy alone, was demonstrated (Johnston et al, 2009).

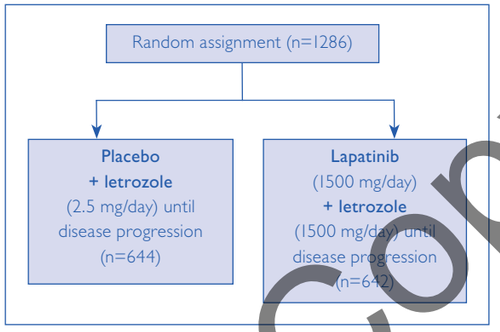


Figure 6: Johnston et al (2009) dosing schedule

THIRD-LINE TREATMENT

Several of the second-line trials mentioned above, including EMILIA, enrolled previously-treated patients, some of whom had received Herceptin in both the adjuvant and metastatic settings (Blackwell et al, 2012; Verma 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 6.9 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 indicate it is reasonable to continue 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 capecitabine, or Herceptin (Giordano et al, 2014).

SUMMARY OF NICE GUIDANCE AND CANCER DRUGS FUND AVAILABILITY

The National Institute for Health and Care Excellence (NICE) produces 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 interim funding 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 first-line Perjeta (awaiting NICE appraisal), Herceptin and docetaxel, and with Kadcyla in the second-line setting (Santa-Maria 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.

TABLE 5. SUMMARY OF RESULTS FROM THE TH3RESA STUDY (KROP ET AL, 2014; WILDIERS ET AL, 2015)

	KADCYLA	TREATMENT OF PHYSICIAN'S CHOICE
Progression-free survival (PFS)	6.2 months	3.3 months
Overall survival (OS)	22.7 months	15.8 months
Objective response rate (ORR)	31.3%	8.8%†

*$p<0.0001$; †$p<0.0001$

Herceptin monotherapy 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 antibody therapy with Perjeta and Herceptin is now considered first-line standard of care for HER2+ MBC (Santa-Maria and Gradishar, 2015). This combination provides significant 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 capecitabine, has defined the place of Kadcyla as a second-line option for patients with HER2+ MBC (Verma et al, 2012).

RXUKMBCO00033 | July 2017
RXUKMBCO00033 | July 2017

Andersson M, Lidbrink E, Bjerre K et al (2011) Phase III randomized study comparing docetaxel plus trastuzumab with vinorelbine plus trastuzumab as first-line therapy of metastatic or locally advanced human epidermal growth factor receptor 2-positive breast cancer: the HERNATA study. *J Clin Oncol* **29**(3): 264–71. doi: 10.1200/JCO.2010.30.8213

Baselga J, Cortés J, Kim SB et al (2012) Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* **366**(2):109–19. doi: 10.1056/NEJMoa1113216

Baselga J, Manikhas A, Cortés J et al (2014) Phase III trial of nonpegylated liposomal doxorubicin in combination with trastuzumab and paclitaxel in HER2-positive metastatic breast cancer. *Ann Oncol* **25**(3): 592–8. doi: 10.1093/annonc/mdt543

Blackwell KL, Burstein HJ, Storniolo AM et al (2012) Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. *J Clin Oncol* **30**(21): 2585–92. doi: 10.1200/JCO.2011.35.6725

Burcombe R, Chan S, Simcock R, Samanta K, Percival F, Barrett-Lee P (2013) Subcutaneous trastuzumab (Herceptin®): a UK time and motion study in comparison with intravenous formulation for the treatment of patients with HER2-positive early breast cancer. *Adv Breast Cancer Res* **2**(4), 133–40. http://tinyurl.com/ycynxq6r (accessed on 19 July)

Burris HA 3rd (2004) Dual kinase inhibition in the treatment of breast cancer: initial experience with the EGFR/ErbB-2 inhibitor lapatinib. *Oncologist* **9**(Suppl 3): 10–5

Cho HS, Mason K, Ramyar KX et al (2003) Structure of the extracellular region of HER2 alone and in complex with the Herceptin Fab. *Nature* **421**(6924): 756–60

Chia SK, Speers CH, D'yachkova Y et al (2007) The impact of new chemotherapeutic and hormone agents on survival in a population-based cohort of women with metastatic breast cancer. *Cancer* **110**(5): 973–9

Franklin MC, Carey KD, Vajdos FF, Leahy DJ, de Vos AM, Sliwkowski MX (2004) Insights into ErbB signaling from the structure of the ErbB2-pertuzumab complex. *Cancer Cell* **5**(4): 317–28

Geyer CE, Forster J, Lindquist D et al (2006) Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* **355**(26): 2733–43

Giordano SH, Temin S, Kirshner JJ et al (2014) Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* **32**(19): 2078–99. doi: 10.1200/JCO.2013.54.0948

Gusterson BA, Gelber RD, Goldhirsch A et al (1992) Prognostic importance of c-erbβ-2 expression in breast cancer. *J Clin Oncol* **10**:1049–56. http://tinyurl.com/ybezub38 (accessed 19 July 2017)

Higa GM, Abraham J (2007) Lapatinib in the treatment of breast cancer. *Expert Rev Anticancer Ther* **7**(9): 1183–92

Huober J, Fasching P, Barsoum M et al (2012) Higher efficacy of letrozole in combination with trastuzumab compared to letrozole monotherapy as first-line treatment in patients with HER2-positive, hormone-receptor-positive metastatic breast cancer: results of the eLEcTRA trial. *Breast* **2**(1): 27–33. doi: 10.1016/j.breast.2011.07.006

Hynes NE, Stern DF (1994) The biology of erbB-2/neu/HER-2 and its role in cancer. *Biochim Biophys Acta* **1198**(2–3): 165–84

Johnston SR (2005) Combinations of endocrine and biological agents: present status of therapeutic and presurgical investigations. *Clin Cancer Res* **11**(2 Pt 2): 889s–99s

Johnston S, Pippen J Jr, Pivot X et al (2009) Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor–positive metastatic breast cancer. *J Clin Oncol* **27**: 5538–46. doi: 10.1200/JCO.2009.23.3734

Jones A (2003) Combining trastuzumab (Herceptin) with hormonal therapy in breast cancer: what can be expected

and why? *Ann Oncol* **14**(12): 1697–704
Junttila TT, Akita RW, Parsons K et al (2009) Ligand-independent HER2/HER3/PI3K complex is disrupted by trastuzumab and is effectively inhibited by the PI3K inhibitor GDC-0941. *Cancer Cell* **15**(5): 429–40. doi: 10.1016/j.ccr.2009.03.020
Kadcyla Summary of Product Characteristic (2017) www.medicines.org.uk/emc/medicine/28568 (accessed 13 July 2017)
Kaufman B, Mackey J, Clemens MR et al (2009) Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. *J Clin Oncol* **27**(33): 5529–37. doi: 10.1200/JCO.2008.20.6847
King CR, Kraus MH, Aaronsen SA (1985) Amplification of a novel v-erbB-related gene in a human mammary carcinoma. *Science* **229**(4717): 974–6
Krop IE, Kim SB, González-Martín A et al (2014) Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. *Lancet Oncol* **15**(7): 689–99. doi: 10.1016/S1470-2045(14)70178-0
Landgraf R (2007) HER2 therapy. HER2 (ERBB2): functional diversity from structurally conserved building blocks. *Breast Cancer Res* **9**(1): 202
Lewis Phillips GD, Li G, Dugger DL et al (2008) Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. *Cancer Res* **68**(22): 9280–90. doi: 10.1158/0008-5472.CAN-08-1776.
Marty M, Cognetti F, Maraninchi D et al (2005) Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol* **23**(19): 4265–74
National Comprehensive Cancer Network. Breast Cancer (2017) (version 1.2014). http://tinyurl.com/y8wrxran (accessed 4 August 2017)
National Institute for Health and Care Excellence (NICE) (2012) *Lapatinib or Trastuzumab in Combination with an Aromatase Inhibitor for the First-Line Treatment of Metastatic Hormone-Receptor-Positive Breast Cancer that Overexpresses HER2*. Technology Appraisal Guidance [TA257]. http://tinyurl.com/y88z7ro3 (accessed 13 July 2017)
National Institute for Health and Care Excellence (NICE) (2009; 2014) *Advanced Breast Cancer: Diagnosis And Treatment Clinical Guideline* [CG81]. https://tinyurl.com/z3twxhw (accessed 13 July 2017)
Osborne CK, Shou J, Massarweh S, Schiff R (2005) Crosstalk between estrogen receptor and growth factor receptor pathways as a cause for endocrine therapy resistance in breast cancer. *Clin Cancer Res* **11**(2 Pt 2): 865s–870s
Perjeta Summary of Product Characteristics (2015) www.medicines.org.uk/emc/medicine/27473 (accessed 13 July 2017)
Press MF, Pike MC, Chazin VR et al (1993) Her-2/neu expression in node-negative breast cancer: direct tissue quantitation by computerized image analysis and association of overexpression with increased risk of recurrent disease. *Cancer Res* **53**(20): 4960–70
Rakha EA, Pinder SE, Bartlett JM et al (2015) Updated UK recommendations for HER2 assessment in breast cancer. *J Clin Pathol* **68**(2): 93–9. doi: 10.1136/jclinpath-2014-202571
Ravdin PM, Chamness GC (1995) The c-erbB-2 proto-oncogene as a prognostic and predictive marker in breast cancer: a paradigm for the development of other macromolecular markers: a review. *Gene* **159**(1): 19–27
Santa-Maria CA, Gradishar WJ (2015) Changing treatment paradigms in metastatic breast cancer: lessons learned. *JAMA Oncol* **1**(4): 528–34. doi: 10.1001/jamaoncol.2015.1198
Schiff R, Massarweh S, Shou J, Osborne CK (2003) Breast cancer endocrine resistance: how growth factor signaling and estrogen receptor coregulators modulate response. *Clin Cancer Res* **9**(1 Pt 2): S447–S54
Seshadri R, Firgaira FA, Horsfall DJ et al (1993) Clinical significance of HER-2/neu oncogene amplification in primary breast cancer: the South Australian Breast Cancer Study Group. *J Clin Oncol* **11**(10): 1936–42
Shou J, Massarweh S, Osborne CK Wakeling AE, Ali S, Weiss H, Schiff R (2004) Mechanisms of tamoxifen resistance: increased estrogen receptor-HER2/neu cross-talk in ER/HER2-positive breast cancer. *J Natl Cancer Inst* **96**(12): 926–35
Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL (1987) Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* **235**(4785): 177–82
Slamon DJ, Godolphin W, Jones LA et al (1989) Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science* **244**(4905): 707–12
Slamon DJ, Leyland-Jones B, Shak S et al (2001) Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* **344**(11): 783–92
Swain SM, Baselga J, Kim SB et al (2015) Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med* **372**(8): 724–34. doi: 10.1056/NEJMoa1413513.
Swain SM, Kim SB, Cortés J et al (2013) Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol* **14**(6): 461–71. doi: 10.1016/S1470-2045(13)70130-X
Valero V, Forbes J, Pegram MD et al (2011) Multicenter phase III randomized trial comparing docetaxel and trastuzumab with docetaxel, carboplatin, and trastuzumab as first-line chemotherapy for patients with HER2-gene-amplified metastatic breast cancer (BCIRG 007 study): two highly active therapeutic regimens. *J Clin Oncol* **29**(2): 149–56. doi: 10.1200/JCO.2010.28.6450
Verma S, Miles D, Gianni L et al (2012) Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* **367**(19): 1783–91. doi: 10.1056/NEJMoa1209124
Wildiers H, Kim SB, González-Martín A (2015) Trastuzumab emtansine (T-DM1) improves overall survival versus treatment of physician's choice in patients with previously treated HER2-positive metatstatic breast cancer: final overall survival results from the phase 3 TH3RESA study. Presentation: SABCS 2015 S5–05. http://tinyurl.com/y8yan3rn (accessed 13 July 2017)

DEFINING WHAT MATTERS MOST TO PATIENTS

ADVANCED COMMUNICATION SKILLS ARE NEEDED TO IDENTIFY PATIENTS' NEEDS AND PROVIDE THE PSYCHOLOGICAL AND SOCIAL SUPPORT THEY REQUIRE. MEANWHILE, EARLY ACCESS TO PALLIATIVE CARE WILL IMPROVE SYMPTOM CONTROL

Metastatic breast cancer (MBC) is complex and unpredictable due to it being a heterogeneous disease with varied biological influences and responses to treatment (Tacca et al, 2009). Patients can have differing levels of disease, from minimal sites of slow-growing disease to diffuse organ involvement with rapid progression (Filleron et al, 2015). In recent years, developments in treatment have significantly improved survival times and disease management. However, this has increased the complexity of the disease trajectory in terms of end-of-life planning and when to introduce palliative care (Reed and Corner, 2013).

Patients can now live many years with MBC and, during this time, can be very well, often continuing active treatment until nearing the end of life. Reed and Corner (2013) even suggested that MBC may be becoming a chronic illness, with which patients learn to live while their lives are dominated by active treatment, pain and symptom management. Some patients experience repeated cycles of decline and reprieve, which adds to the complexity of identifying those who are entering the terminal phase of their illness (Reed and Corner, 2013). The author's personal experience of caring for patients with MBC suggests that the disease tends to progress slowly, with patients remaining relatively well until a sudden deterioration towards the end of life. In some cases, this can require crisis intervention, necessitating emergency admission for end-of-life care.

There is a need for an integrated oncology and palliative care approach to support both women and oncologists in making decisions about treatment and end-of-life care (Reed and Corner, 2013).

This chapter examines patients' information needs and what they should expect from treatment, as well as the provision of psychological support and palliative care. It includes examples of key questions patients might wish to ask their doctors during the management of their disease.

CHALLENGES OF LIVING WITH METASTATIC BREAST CANCER

Prognostication in MBC is very challenging. Several factors are predictive of survival, including age at initial diagnosis, stage of disease, hormone receptor status of the primary tumour and the number of organs with metastases (Murthy et al, 2016; Largillier et al, 2008). Furthermore, a patient's response to one line of treatment can predict how well they are likely to respond to subsequent lines (Roché and Vahdat, 2011; Bonotto et al, 2015; García-Sáenz et al, 2005). Patients who progress through the first two lines of chemotherapy without any disease stability are unlikely to benefit from treatment in the third line and beyond; these patients are likely to be in their last 12 months of life (Banerji et al, 2007; Dufresne et al, 2008; Vauléon et al, 2010).

HER2-positive metastatic breast cancer

Approximately 20% of MBC is HER2-positive (HER2+). HER2+ MBC is a more aggressive form

Tracey Coleby Macmillan Breast Palliative Care Lead, The Christie NHS Foundation Trust.
tracey.coleby@christie.nhs.uk

RXUKMBCO00033 | July 2017
RXUKMBCO00033 | July 2017

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

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 can 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'.

For this patient, her concerns centred on her children, her ability to care for them and her fear of them seeing her confused and forgetting things, including who they are. As a result, there was an open discussion on how her children could be protected and how she could maintain her role as a mother for as long as possible.

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 on 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

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 (Dawood et al, 2010). For women starting first-line treatment for HER2+ MBC, the median survival is approximately 3 years for single-agent HER2-targeted therapy and 4.5 years for dual HER2-targeted therapy, with some patients living longer than 10 years (Vasista et al, 2017; Swain et al, 2015).

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 assisting an increasing number of patients with MBC. Despite this, 57% of breast care nurses have acknowledged that the care they provide for patients with MBC is inadequate, as are their skills for supporting patients with advancing disease (Reed et al, 2010). It is vital, therefore, 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; this will help determine what additional information they require to make an informed decision about their future care or needs.

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 can then ensure that 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 burden.

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).

RXUKMBCO00033 | July 2017

RXUKMBCO00033 | July 2017

Honest prognostic information

As a patient's disease advances, it 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). Denying patients honest prognostic information can prevent them from preparing for death, reflecting on life and saying goodbye to their loved ones (Bakhurst, 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 (Davies and Spue, 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 (*Box 1*) (Fallowfield et al, 1990; Heaven and Maguire, 1996; Butow et al, 1995; Schofield et al, 2003).

Question prompt list

When supporting patients with MBC, nurse specialists need to help patients think about what types of questions they want 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. Walczak et al (2013) therefore developed a question prompt list (QPL), which comprises questions that patients may want answered in their 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 clinic (Walczak et al, 2013). More recently, Rodenbach et al (2017) identified that, when combined with the provision of support and guidance to patients and carers, the QPL promoted more open discussions on advancing disease, regardless of the health professional's training.

How long have I got?

From personal experience, patients with MBC want to know their prognosis and often ask their specialist nurse, rather than their doctors, about this. Health professionals sometimes ignore these cues as a defence mechanism, but patients will often notice this and will stop giving these cues if this occurs repeatedly. This is often referred to as blocking cues (Heaven and Maguire, 1996). Furthermore, some patients will only disclose certain cues to health professionals

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

Section 1: my cancer and what to expect in the future
- What is currently happening with my cancer?
- What can I expect in the future?
- Will this cancer shorten my life?
- Is it possible to give me a time frame? How long can I expect to live?
- What is the best-case scenario? What is the worst-case scenario?

Section 2: treating my cancer
- What options are available to treat my cancer?
- What are the pros and cons of further treatment for my cancer?
- Is it still possible to cure my cancer?
- How likely is it that these treatments will control my cancer?
- If the treatment works, will I live longer?
- Will these treatments make me feel better or worse?

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, holidays)

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 for me?
- 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 my carer or me to contact? (e.g. support organisations, respite care, disability parking)
- What financial assistance is available for my carer or me?
- Who can I talk to 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 help me to do this?
- 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 disagree about my decisions?

Section 8: making sure my best 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 their concerns (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 if time is short. 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 unwarranted precision, 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 as 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, 2013).

When patients are well, they might attend support groups or seek support from the media via television, the press, social sites and web-based support groups (Davies and Spue, 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 centres 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 good 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 are nearing the end of their life (Reed and Corner, 2013). This may be due to the negative connotations associated with palliative care, which suggest it is only used in terminal and end-of-life settings. However, palliative/supportive care can be integrated into care from diagnosis onwards, helping to manage the patient's disease, symptoms and treatment side effects, and promoting the best possible quality of life (Multinational Association of Supportive Care in Cancer (MASCC), 2015).

A large part of the palliative/supportive care role concerns having open and honest conversations with patients and their loved ones on advance care planning. This not only involves ascertaining their wishes regarding end-of-life care, but also on what is important to them during the disease trajectory, which often helps with decision-making about future treatments. For example, as the disease progresses, this can involve focusing on what is important to the patient when discussing the next treatment options; if this is a special event or milestone, the management plan might need to be adjusted to accommodate this.

As well as improving quality of life, early integration of palliative/supportive care has been shown to prolong survival in some patients and promote less aggressive disease management towards the end of life (Temel et al, 2010; Bakitas et al, 2015; Greer et al, 2012). For instance, earlier initiation of symptom control will improve quality of life and might prolong the duration of active treatment, potentially improving overall survival. Palliative/supportive care should therefore be an integral part of oncology management (Fitzsimons et al, 2007; Illman, 2002), and be given alongside active treatment. It will also aid the transition from active treatment to optimum supportive care (Greer et al, 2012).

DEVELOPING BEST PRACTICE: CHRISTIE NHS FOUNDATION TRUST, MANCHESTER

Palliative/supportive care health professionals are highly skilled in managing patients with progressive disease and can help to support patients in decision-making before and during end-of-life care. For the past 9 years, at The Christie NHS Foundation Trust, a clinical nurse specialist in palliative care has worked closely with breast oncology consultants. This has been key to improving their knowledge of (Farrell and Coleby, 2016):

- Palliative/supportive care
- The specific needs patients might have as their disease progresses
- The importance of open and honest conversations throughout the disease trajectory
- The value of collaborative working.

This has let to a wider multidisciplinary (MDT) approach to managing patients with advancing disease and ensuring the right care is given at the right time by the right person.

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 Manchester Cancer Improvement Partnership (MCIP) to develop best practice for patients with MBC. The breast care nursing team has become a solely metastatic service. It has introduced nurse-led clinics for all new patients and piloted 'living with MBC' study days in which palliative/supportive care plays an integral part.

To ensure the delivery of best practice, The Christie and the MCIP 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 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 changed to facilitate this"

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

RXUKMBCO00033 | July 2017
RXUKMBCO00033 | July 2017

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).

Aranda S, Schofield P, Weih L, Milne D, Yates P, Faulkner R (2006) Meeting the support and information needs of women with advanced breast cancer: a randomized controlled trial. *Br J Cancer* **95**(6): 667–73

Bakhurst D (1992) On lying and deceiving. *J Med Ethics* **18**(2): 63–6

Bakitas MA, Tosteson TD, Li Z et al (2015) Early versus delayed initiation of concurrent palliative oncology care: patient outcomes in the ENABLE III randomized controlled trial. *J Clin Oncol* **33**(13): 1438–48. doi: 10.1200/JCO.2014.58.6362

Banerji U, Kuciejewska A, Ashley S et al (2007) Factors determining outcome after third line chemotherapy for metastatic breast cancer. *Breast* **16**(4): 359–66

Bonotto M, Gerratana L, Iacono D, Minisini AM, Rihawi K, Fasola G, Puglisi F (2015) Treatment of metastatic breast cancer in a real-world scenario: is progression-free survival with first line predictive of benefit from second and later lines? *Oncologist* **20**(7): 719–24. doi: 10.1634/theoncologist.2015-0002

Butow PN, Dunn SM, Tattersall MH, Jones QJ (1995) Computer-based interaction analysis of cancer consultation. *Br J Cancer* **71**(5): 1115–21

Davies M, Sque M (2002) Living on the outside looking in: a theory of living with advanced breast cancer. *Int J Palliat Nurs* **8**(12): 583–90

Dawood S, Broglio K, Buzdar AU, Hortobagyi GN, Giordano SH (2010) Prognosis of women with metastatic breast cancer by HER2 status and trastuzumab treatment: an institutional-based review. *J Clin Oncol* **28**(1): 92–8. doi: 10.1200/JCO.2008.19.9844

Dufresne A, Pivot X, Tournigand C et al (2008) Impact of chemotherapy beyond the first line in patients with metastatic breast cancer. *Breast Cancer Res Treat* **107**(2): 275–9

Fallowfield LJ, Hall A, Maguire GP, Baum M (1990) Psychological outcomes of different treatment policies in women with early breast cancer outside a clinical trial. *BMJ* **301**(6752): 575–80

Farrell C, Coleby T (2016) An integrated model for breast cancer and palliative care. *Cancer Nurs Pract* **15**(7): 28–31

Fitzsimons D, Mullan D, Wilson JS et al (2007) The challenge of patients' unmet palliative care needs in the final stages of chronic illness. *Palliat Med* **21**(4): 313–22

Filleron T, Bonnetain F, Mancini J, Martinez A, Roché H, Dalenc F (2015) Prospective construction and validation of a prognostic score to identify patients who benefit from third-line chemotherapy for metastatic breast cancer in terms of overall survival: the METAL3 study. *Contemp Clin Trials* **40**: 1–8. doi: 10.1016/j.cct.2014.11.005

García-Sáenz JA, Martín M, Puente J et al (2005) Trastuzumab associated with successive cytotoxic therapies beyond disease progression in metastatic breast cancer. *Clin Breast Cancer* **6**(4): 325–9

Greer JA, Pirl WF, Jackson VA et al (2012) Effect of early palliative care on chemotherapy use and end-of-life care in patients with metastatic non-small-cell lung cancer. *J Clin Oncol* **30**(4): 394–400. doi: 10.1200/JCO.2011.35.7996

Heaven CM, Maguire P (1996) Training hospice nurses to elicit patient concerns. *J Adv Nurs* **23**(2): 280–6

Illman J (2002) UK initiative aims to broaden definition of palliative care. *J Natl Cancer Inst* **94**(19): 1431

Kiely BE, McCaughan G, Christodoulou S et al (2013) Using scenarios to explain life expectancy in advanced cancer: attitudes of people with a cancer experience. *Support Care Cancer* **21**(2): 369–76

Lam WW, Soong I, Yau TK et al (2013) The evolution of psychological distress trajectories in women diagnosed with advanced breast cancer: a longitudinal study. *Psychooncology* **22**(12): 2831–9. doi: 10.1002/pon.3361

Largillier R, Ferrero JM, Doyen J et al (2008) Prognostic factors in 1038 women with metastatic breast cancer. *Ann Oncol* **19**(12): 2012–9

Multinational Association of Supportive Care in Cancer (MASCC) (2017) www.mascc.org (accessed on 8 August 2017)

Murthy P, Kidwell KM, Schott AF et al (2016) Clinical predictors of long-term survival in HER2-positive metastatic breast cancer. *Breast Cancer Res Treat* **155**(3): 589–95. doi: 10.1007/s10549-016-3705-3

Reed E, Scanlon K, Fenlon D (2010) A survey of provision of breast care nursing for patients with metastatic breast cancer: implications for the role. *Eur J Cancer Care* **19**(5): 575–80. doi: 10.1111/j.1365-2354.2010.01213.x

Reed E, Corner J (2013) Defining the illness trajectory of metastatic breast cancer. *BMJ Support Palliat Care* **0**: 1–8. doi:10.1136/bmjspcare-2012-000415

Roché H, Vahdat LT (2011) Treatment of metastatic breast cancer: second line and beyond. *Ann Oncol* **22**(5): 1000–10. doi: 10.1093/annonc/mdq429

Rodenbach RA, Brandes K, Fiscella K et al (2017) Promoting end-of-life discussions in advanced cancer: effects of patients coaching and question prompt lists. *J Clin Oncol* **(35)**8: 842–51. doi: 10.1200/JCO.2016.68.5651

Schofield PE, Butow PN, Thompson JF, Tattersall MH, Beeney LJ, Dunn S (2003) Psychological responses of patients receiving a diagnosis of cancer. *Ann Oncol* **14**(11): 48–56.

Swain SM, Baselga J, Kim S-B et al (2015) Pertuzumab, trastuzumab and docetaxel in HER2-positive metastatic breast cancer. *New Engl J Med* **372**(8): 724–34. doi: 10.1056/NEJMoa1413513

Tacca O, LeHeurteur M, Durando X et al (2009) Metastatic breast cancer: overall survival related to successive chemotherapies. What do we gain after the third line? *Cancer Invest* **27**(1): 81–5. doi: 10.1080/07357900802291

Taylor C, Shewbridge A, Harris J, Green JS (2013) Benefits of multidisciplinary teamwork in the management of breast cancer. *Breast Cancer: Targets and Therapy* **5**: 79–85. doi: 10.2147/BCTT.S35581

Temel JS, Greer JA, Muzikansky A et al (2010) Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* **363**(8): 733–42. doi: 10.1056/NEJMoa1000678

Vasista A, Stockler MR, West T, Wilcken N, Kiely BE (2017) More than just the median: calculating survival times for patients with HER2 positive, metastatic breast cancer using data from recent randomised trials. *Breast* **31**: 99–104. doi: 10.1016/j.breast.2016.10.007

Vauléon E, Mesbah H, Laguerre B et al (2010) Usefulness of chemotherapy beyond the second line for metastatic breast cancer: a therapeutic challenge. *Cancer Chemother Pharmacol* **66**(1): 113–20. doi: 10.1007/s00280-009-1141-3

Walczak A, Mazer B, Butow PN et al (2013) A question prompt list for patients with advanced cancer in the final year of life: development and cross-cultural evaluation. *Palliat Med* **27**(8):779–88. doi: 10.1177/0269216313483659

Wilkinson S, Bailey K, Aldridge J, Roberts A (1999) A longitudinal evaluation of a communication skills programme. *Palliat Med* **13**(4): 341–8

Zimmermann C, Del Piccolo L, Finset A (2007) Cues and concerns by patients in medical consultations: a literature review. *Psychol Bull* **133**(3): 438–63

Zimmermann C, Swami N, Krzyzanowska M et al (2014) Early palliative care for patients with advanced cancer: a cluster–randomised controlled trial. *Lancet* **383**(9930): 1721–30. doi: 10.1016/S0140-6736(13)62416-2

RXUKMBCO00033 | July 2017

IMPROVING PATIENT CARE: EXPERT NURSING AND SERVICE DEVELOPMENT

EARLY ACCESS TO A CLINICAL NURSE SPECIALIST WILL ENSURE THAT PATIENTS RECEIVE THE INTERVENTIONS AND SUPPORT THEY NEED. OPTIMUM OUTCOMES WILL BE ACHIEVED IF SPECIALISTS WORK IN COLLABORATION WITH A WIDER TEAM

An advanced level of practice is required to deliver high-quality nursing care to patients with metastatic breast cancer (MBC) throughout their disease trajectory and treatment pathway. As many patients are now living longer with MBC (Johnston and Swanton, 2013), greater demands are being placed on those delivering complex multidisciplinary care: health and social care professionals need to meet patients' information needs, help patients access symptom control to maximise their quality of life, prevent hospital admissions and support patients during shared clinical decision-making (National Cancer Action Team and Macmillan Cancer Support, 2010).

This article describes the provision of high-quality services and care for patients with MBC. It shows how this was achieved following a collaboration between the Kent Oncology Centre, patients, a large multidisciplinary team and charities. It illustrates how such collaboration can drive the improvements in care required to fulfil the Independent Cancer Taskforce's ambitious strategy for achieving world-class cancer outcomes (Cancer Research UK, 2015). The Taskforce's recommendations that have a direct impact on MBC care include:

- Data collection on all secondary cancers must be improved (recommendation 90)
- All patients with a cancer diagnosis must have access to a clinical nurse specialist (CNS) or other key worker (recommendation 61)
- Multidisciplinary processes should be streamlined so that specialist time focuses on cancer cases that do not follow well-established clinical care pathways (recommendation 38).

ACCESS TO A CLINICAL NURSE SPECIALIST

The national charity Breast Cancer Care 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 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 and coordination 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

Claire Ryan Macmillan Nurse Clinician Metastatic Breast Cancer, Kent Oncology Centre, Maidstone & Tunbridge Wells NHS Trust. claireryan4@nhs.net

RXUKMBCO00033 | July 2017

TABLE 1. THE PURPOSE AND FUNCTION OF THE MBC MULTIDISCIPINARY TEAM

BENEFITS FOR THE PATIENT	BENEFITS FOR THE MULTIDISCIPLINARY TEAM
Peer discussion reassures patients (Secondary Breast Cancer Pledge Improvement Goal)	Peer discussion, which highlights options in treatment eligibility to trials and enables conversations about individual patients through patient advocates
Timely review and reporting	Radiological assessment and review of images to assess response to cancer treatments. Radiological assessment and review of images to assess disease and accessibility for repeat biopsy. Radiological assessment for localised radiotherapy options, which was valuable for the medical oncologists to discuss with clinical oncologists. Radiological assessment and review for measurement of target lesions for clinical trial eligibility and screening
Preparation for patient consultation	Peer discussion and preparation for patient consultation
Screening for clinical trials	Review of potential clinical trial options from the local and national portfolio of clinical trials
Formal check for palliative care engagement and access to support for symptom management	Formal check for palliative care engagement and access to community support

widely shared experience of feeling forgotten or invisible; women commented that their care was inferior to that given for 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 over 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 hospital admission—can reduce costs for both patients and healthcare organisations (Reed et al, 2012).

When patients established a good relationship with the healthcare team involved in their care, they felt respected and treated as an individual (Breast Cancer Care, 2017). Similarly, a good relationship with patients will 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 cancer 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, 2016) 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 commissioners 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, therefore, to identify and address variations in practice and link models of care and collaborative enterprise for transformation of services.

ACCESS TO A NURSING COMMUNITY

Clearly, the complex needs of patients with MBC are often not met locally, nationally and globally (Reed et al, 2010; Warren, 2010; Pfizer Oncology et al, 2016). Education on supportive care and clinical practice guidelines for MBC and palliative care should focus on training multidisciplinary professionals and improving coordination between health and social care (Royal College of Nursing, 2007; Breast Cancer Care, 2012). Nurses have reported a lack of skills training and access to the tools needed to provide adequate supportive and palliative care, which has in turn resulted in a loss of confidence (Reed et al, 2010; Cleary et al, 2013). An established or developing workforce must be supported in terms of learning, innovation and sharing best practice.

Such support could be provided by practices outside the boundaries of local services and the nursing community. For example, the MBC Nursing Forum, provided by Breast Cancer Care, is an invaluable resource: its purpose is to bring together nurses who work with women with MBC, enabling them to share expertise and improve patient care by learning about and sharing best practice.

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 increase their social isolation (Aranda et al, 2005; NHS England, 2014; Breast Cancer Care, 2016).

Some women find it helpful to read about or listen to others' experiences (Mayer, 2010). Peer support groups can alleviate anxiety, help participants gain better medical 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 survey of 1273 people 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 messaging and negative perceptions associated with a life-limiting diagnosis.

In 2015, in recognition of the benefits of peer support, a collaborative enterprise was progressed with Breast Cancer Care and the Kent Oncology Centre to implement the living with secondary breast cancer (LWSBC) service in West Kent. This service provides an opportunity for those diagnosed with MBC to talk about it with others in a similar situation and in a supportive environment. In recognition that many women living with MBC do not have access to a CNS, the LWSBC is aimed at those with a diagnosis of MBC who want access to support, advice and expert information to help them adjust to difficult changes in their lives. Another factor that led to the development of the service was the results of a local Secondary Breast Cancer Pledge patient survey that, due to lack of resource, the local nurse clinician for MBC was unable to meet all patients' complex needs (Maidstone and Tunbridge Wells NHS Trust, 2016).

> "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"

LWSBC 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 in managing psychological symptoms 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.

RXUKMBCO00033 | July 2017
RXUKMBCO00033 | July 2017

IMPROVING MULTIDISCIPLINARY CARE

Multidisciplinary care describes an integrated health-team approach in which health professionals consider relevant treatment options and collaboratively develop individual treatment care plans (Chirgwin et al, 2010). However, these teams do not routinely 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 treatment and 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 (Chirgwan 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"

In the Kent Oncology Centre in Maidstone, Kent, quality care service innovation led to the launch of a local multidisciplinary team for MBC in 2015. This was seen as a way to deliver better treatment and improve care pathways. Previous problems included:

- Slow reporting of radiological assessments, which had resulted in increased anxiety for patients and their families, and lack of shared decision-making if a treatment was no longer able to stabilise the disease
- Lack of peer review and discussion among the healthcare team about complex care, which may have affected options when planning treatment and care with a patient
- Poor screening for clinical trial eligibility
- A clinical trial portfolio that did not fully meet 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 primary 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 members such as 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 internal 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.

RXUKMBCO00033 | July 2017

RXUKMBCO00033 | July 2017

Advanced Breast Cancer Community (2013) Count us, Know us, Join us Survey. http://tinyurl.com/y79rtqef (accessed 14 July 2017)

Aranda S, Schofield P, Weih L et al (2005) Mapping the quality of life and unmet needs of urban women with metastatic breast cancer. *Eur J Cancer Care (Engl)* **14**(3): 211–22

Breast Cancer Care (2012) *Ensuring Nursing Provision for People with Metastatic Breast Cancer: A Toolkit for Healthcare rofessionals*. http://tinyurl.com/pgcwnkp (accessed 14 July 2017)

Breast Cancer Care (2016) *Secondary. Not Second Rate. Part 3*. http://tinyurl.com/y9sq76zy (accessed 14 July 2017)

Breast Cancer Care (2017) *Secondary. Not Second Rate. Part 4: Nursing Care*. http://tinyurl.com/mnsctrz (accessed 24 July 2017

Breast Cancer Now (2015) *Maidstone and Tunbridge Wells NHS Trust Secondary Breast Cancer Pledge. The Standards of Care and Support You can Expect and How to Have Your Say*. http://tinyurl.com/yatvze5m (accessed 14 July 2017)

Cancer Research UK (2015) *Achieving World-Class Cancer Outcomes: A Strategy for England 2015–2020*. http://tinyurl.com/zzlrynh (accessed 14 July 2017)

Cardoso F, Di LA, Lohrisch C et al (2002) Second and subsequent line of chemotherapy for metastatic breast cancer: what did we learn in the last two decades? *Ann Oncol* **13**(2): 197–207

Cardoso F, Harbeck N, Mertz S, Fenech D (2016) Evolving psychosocial, emotional, functional and support needs of women with advanced breast cancer: results from the Count US, Know Us, Join Us and Here & Now surveys. *Breast* **28**: 5–12. doi: 10.1016/j.breast.2016.04.004

Chirgwin J, Craike M, Gray C et al (2010) Does multidisciplinary care enhance the management of advanced breast cancer? Evaluation of advanced breast cancer multidisciplinary team meetings. *J Oncol Pract* **6**(6): 294–300

Cleary J, Ddungu H, Distelhorst SR et al (2013) Supportive and palliative care for metastatic breast cancer: resource allocations in low- and middle-income countries. A Breast Health Global Initiative 2013 consensus statement. *Breast* **22**(5): 616–27

Harding V, Afshar A, Krell J et al (2013) 'Being there' for women with metastatic breast cancer: a pan-European patient survey. *Br J Cancer* **109**(6): 1543–8. doi: 10.1038/bjc.2013.492

Johnston S, Swanton C (2013) *Handbook of Metastatic Breast Cancer*. http://tinyurl.com/ya9mepvg (accessed 14 July 2017)

Macmillan Cancer Support (2014) *Specialist Adult Cancer Nurses in England. A census of the Specialist Adult Cancer Nursing Workforce in the UK*, 2014. http://tinyurl.com/ybpuu6ut

Maidstone and Tunbridge Wells NHS Trust (2016) Trust makes secondary breast cancer pledge. http://tinyurl.com/y94l7ns3 (accessed 14 July 2017)

Mayer M (2010) Lessons learned from the metastatic breast cancer community. *Semin Oncol Nurs* **26**(3): 195–202

Metastatic Breast Cancer Alliance (2014) Changing the landscape for people living with metastatic breast cancer. Metastatic breast cancer landscape analysis: research report October 2014. http://tinyurl.com/ydh86akl (accessed 14 July 2017)

NHS England (2014) *Cancer Patient Experience Survey*. http://tinyurl.com/yawyf3w2 (accessed 21 January 2017)

National Cancer Action Team, NHS and Macmillan Cancer Support (2010) *Quality in Nursing. Excellence in Cancer Care: the Contribution of the Clinical Nurse Specialist*. http://tinyurl.com/yca4s9dj (accessed 14 July 2017)

National Institute for Health, Care Excellence (NICE) (2009; 2014) *Advanced Breast Cancer: Diagnosis and Treatment. Clinical Guideline [CG81]*. https://www.nice.org.uk/guidance/cg81 (accessed 14 July 2017)

Pfizer Oncology, European School of Oncology, ABC3 (2016) *Global Status of Advanced/Metastatic Breast Cancer: 2005–2015 Decade Report*. https://tinyurl.com/ybxg57uq (accessed 11 July 2017)

Reed E, Scanlon K, Fenlon D (2010) A survey of provision of breast care nursing for patients with metastatic breast cancer: implications for the role. *Eur J Cancer Care* **19**(5): 575–80

Reed E, Simmonds P, Haviland J, Corner J (2012) Quality of life and experience of care in women with metastatic breast cancer: a cross-sectional Survey. *J Pain Symptm Manage* **43**(4): 747–58

Royal College of Nursing (2007) *Clinical Standards for Working in a Breast Specialty: RCN Guidance for Nursing Staff*. http://tinyurl.com/ybbzar8a (accessed 14 July 2017)

Vilhauer RP (2011) 'Them' and 'us': the experiences of women with metastatic disease in mixed-stage versus stage-specific breast cancer support groups. *Psychol Health* **26**(6): 781–97

Warren M (2010) Uncertainty, lack of control and emotional functioning in women with metastatic breast cancer: a review and secondary analysis of the literature using the critical appraisal technique. *Eur J Cancer Care (Engl)* **19**(5): 564–74

PRESCRIBING INFORMATION

HERCEPTIN® (trastuzumab) 600 mg solution for injection in vial

Indication: Treatment of HER2-positive early breast cancer (EBC): (i) following surgery, chemotherapy (CT) (neo/adjuvant) and radiotherapy (RT) (if applicable). (ii) following adjuvant CT with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel. (iii) in combination with adjuvant CT consisting of docetaxel and carboplatin. (iv) for locally advanced (including inflammatory) disease or tumours >2 cm in diameter, in combination with neoadjuvant CT followed by adjuvant Herceptin. Treatment of HER2-positive metastatic breast cancer (MBC): (i) as monotherapy following at least two CT regimens for MBC. Prior CT to have included at least an anthracycline and a taxane, unless unsuitable. Hormone-receptor-positive patients must have failed hormonal therapy, unless unsuitable. (ii) in combination with paclitaxel for patients who have not received CT for MBC and where anthracyclines are not suitable. (iii) in combination with docetaxel for patients who have not received CT for MBC. (iv) in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor-positive MBC, not previously treated with Herceptin.

Dosage and Administration: Please refer to Herceptin Subcutaneous 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 product labels to ensure correct Herceptin formulation is being administered. HER2 testing is mandatory prior to Herceptin. Tumours should have HER2 overexpression and should be validated by recognised laboratory tests. Only physicians experienced with cytotoxic CT should initiate treatment with Herceptin. Limited information is available regarding switching patient from Herceptin intravenous formulation to Herceptin SC fixed-dose formulation. The recommended fixed dose for Herceptin SC formulation is 600 mg irrespective of the patient's body weight. No loading dose is required. This dose should be administered subcutaneously over 2–5 minutes every three weeks. Patients with EBC should be treated with Herceptin SC fixed-dose formulation for 1 year or until disease recurrence, whichever occurs first. Patients with MBC should be treated with Herceptin SC fixed-dose formulation until progression of disease. Observe for administration-related reactions (ARRs) for at least 6 hours after the first injection and for 2 hours after subsequent injections. If the patient misses a dose of Herceptin SC fixed-dose formulation, it is recommended to administer the next 600 mg dose (i.e. the missed dose) as soon as possible. The interval between subsequent Herceptin SC fixed-dose formulation doses should not be less than 3 weeks. Switching treatment between Herceptin intravenous and Herceptin subcutaneous formulation and vice versa using the three-weekly (qw3) dosing regimen has been investigated in study MO22982.

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 SmPC for further information. To improve traceability of medicinal products, the trade name of the administered product should be clearly recorded in the patient file. Congestive heart failure (CHF) observed in patients receiving monotherapy or in combination with paclitaxel or docetaxel; particularly following anthracycline-containing regimen may be moderate to severe and has been fatal. Avoid concomitant use of anthracyclines in the adjuvant and metastatic settings and only use neoadjuvantly in CT-naïve patients in conjunction with low-dose anthracycline regimens. Clinical experience in the neoadjuvant setting is limited in patients >65 years. Avoid anthracycline-based therapy for up to 7 months after stopping Herceptin. Caution should be exercised in patients with the following: symptomatic CHF, history of hypertension, coronary artery disease, those patients with an LVEF of <55%, older age. Monitor cardiac function at baseline every 3 months during treatment and every 6 months following discontinuation of treatment for up to 24 months. Further monitoring recommended for patients who receive anthracycline containing CT; yearly up to 5 years from last administration, or longer if a continuous decrease of LVEF is observed. Most who developed CHF in clinical trials improved with appropriate treatment and continued Herceptin therapy without additional clinical cardiac events. ARRs are known to occur with Herceptin subcutaneous formulation. Pre-medication may be used to reduce risk of occurrence of ARRs. Although serious ARRs were not reported in the clinical trial with the Herceptin SC fixed-dose formulation, caution should be exercised as the following have been associated with the Herceptin IV formulation: dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress. Serious reactions to Herceptin IV have been successfully treated with oxygen, beta-agonists and corticosteroids. Fatal outcomes were rare. Severe pulmonary events have been reported and occasionally been fatal; may occur as part of ARR or with delayed onset; patients with dyspnoea at rest may be at increased risk of fatal ARR and/or pulmonary events; these patients should not be treated with Herceptin. Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes.

Drug Interactions: No formal drug interaction studies have been performed. Clinically significant interactions with the concomitant medication used in clinical trials have not been observed based on the results of a population PK analysis.

Pregnancy and Lactation: Avoid during pregnancy unless potential benefit outweighs risk. Oligohydramnios reported in post-marketing, some associated with fatal pulmonary hypoplasia of the foetus. Women of childbearing potential should be advised to use effective contraception during Herceptin and for at least 7 months after last dose. Women should not breast-feed during Herceptin therapy and for 7 months after last dose. Close monitoring of pregnant women receiving Herceptin or within 7 months following the last dose of Herceptin is recommended.

Side-effects and Adverse Reactions: Cardiac dysfunction, ARRs, haematotoxicity (neutropenia), infections and pulmonary adverse events are amongst the most serious and/or common adverse reactions reported with Herceptin usage (IV and SC). The safety profile of Herceptin SC from the pivotal trial in EBC was overall similar to the known safety profile of the IV formulation. 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. For full information and listings, please refer to the Herceptin SmPC.

+Reported in association with a fatal outcome.

1 Reported largely in association with ARRs. Specific percentages for these are not available.

*Observed in combination therapy following anthracyclines and combined with taxanes.

Very common reactions: Infection, nasopharyngitis, febrile neutropenia, anaemia, neutropenia, leukopenia, thrombocytopenia, weight loss, anorexia, insomnia, tremor[1], dizziness, headache, paraesthesia, dysgeusia, conjunctivitis, increased lacrimation, change in blood pressure[1], irregular heart beat[1], palpitation[1], cardiac flutter[1], ejection fraction decreased*, hot flush, wheezing+[1], dyspnoea+, cough, epistaxis, rhinorrhoea, diarrhoea, vomiting, nausea, lip swelling[1], abdominal pain, dyspepsia, constipation, stomatitis, erythema, rash, swelling face[1], alopecia, nail disorder, hand-foot syndrome, arthralgia, muscle tightness[1], myalgia, asthenia, chest pain, chills, fatigue, influenza-like symptoms, infusion-related reactions, pain, pyrexia, mucosal inflammation, peripheral oedema.

Common reactions: Neutropenic sepsis, cystitis, herpes zoster, influenza, sinusitis, skin infection, rhinitis, URTI, UTI, erysipelas, cellulitis, pharyngitis, hypersensitivity, anxiety, depression, abnormal thinking, peripheral neuropathy, hypertonia, somnolence, ataxia, dry eye, congestive cardiac failure+, supraventricular tachyarrhythmia+[1], cardiomyopathy, hypotension+[1], vasodilatation, pneumonia+, asthma, lung disorder, pleural effusion+, pancreatitis, haemorrhoids, dry mouth, hepatocellular injury, hepatitis, liver tenderness, acne, dry skin, ecchymosis, hyperhydrosis, maculopapular rash, pruritus, onychoclasis, dermatitis, arthritis, back pain, bone pain, muscle spasms, neck pain, pain in the extremity, renal disorder, breast inflammation, malaise, oedema, contusion.

Other serious adverse reactions associated with a fatal outcome (reaction frequency cannot be estimated) anaphylactic reaction/shock, pulmonary fibrosis, respiratory distress/failure, lung infiltration, acute pulmonary oedema, acute respiratory distress syndrome, bronchospasm, hypoxia, oxygen saturation decreased.

Other serious adverse reactions (frequency not known) interstitial lung disease, renal hypoplasia, pulmonary hypoplasia.

Legal Category: POM

Presentation and Basic NHS Cost: Pack of one 6mL vial containing 5mL of solution (600mg of trastuzumab) —£1222.20 per vial excluding VAT

Marketing Authorisation Number: EU/1/00/145/002

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

Herceptin is a registered trade mark

RXUKMEDI00204

Date of Preparation: April 2015

RXUKMBCO00033 | July 2017

RXUKMBCO00033 | July 2017

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 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 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

If a pregnancy occurs while using 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 a 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 Providers 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 the safe use of Herceptin during pregnancy and lactation has not 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 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 secreted 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.

PRESCRIBING INFORMATION

HERCEPTIN® (trastuzumab) 150 mg powder for concentrate for solution for infusion

Indication: Treatment of HER2-positive early breast cancer (EBC): (i) following surgery, chemotherapy (CT) (neo/adjuvant) and radiotherapy (RT) (if applicable). (ii) following adjuvant CT with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel. (iii) in combination with adjuvant CT consisting of docetaxel and carboplatin. (iv) for locally advanced (including inflammatory) disease or tumours >2 cm in diameter, in combination with neoadjuvant CT followed by adjuvant Herceptin. Treatment of HER2-positive metastatic breast cancer (MBC): (i) as monotherapy following at least two CT regimens for MBC. Prior CT to include at least an anthracycline and a taxane, unless unsuitable. Hormone-receptor-positive patients must have failed hormonal therapy, unless unsuitable. (ii) in combination with paclitaxel for patients who have not received CT for MBC and where anthracyclines are not suitable. (iii) in combination with docetaxel for patients who have not received CT for MBC. (iv) in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone receptor positive MBC, not previously treated with Herceptin.

Dosage and Administration: Please refer to 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) is being administered, as prescribed. HER2 testing mandatory prior to Herceptin. Tumours should have HER2 overexpression at 3+ level by immunohistochemistry (IHC) or HER2 gene amplification by fluorescence or chromogenic in situ hybridisation (FISH or CISH). Physicians experienced with cytotoxic CT should initiate treatment with Herceptin. Dose (EBC): (i) loading dose 8 mg/kg body weight; subsequent doses 6 mg/kg repeated at 3-weekly intervals; alternatively (ii) loading dose 4 mg/kg body weight; subsequent doses weekly 2 mg/kg concomitantly with paclitaxel following chemotherapy with doxorubicin and cyclophosphamide. Dose (MBC): (i) loading dose 8 mg/kg body weight; subsequent doses 6 mg/kg repeated at 3-weekly intervals; alternatively (ii) loading dose 4 mg/kg body weight; subsequent doses weekly 2 mg/kg. Patients with EBC should be treated for 1 year or until disease recurrence, whichever occurs first. In MBC, administer until disease progression. Initial loading dose should be administered as 90 minute IV infusion; if loading dose well tolerated, subsequent doses can be administered as 30 minute IV infusion. Do not administer as an IV push or bolus. Observe for infusion-related symptoms for at least 6 hours following start of first infusion and for 2 hours for subsequent infusions. Interruption of infusion may help control symptoms; consider resuming when symptoms abate. Resuscitation equipment must be available. Switching treatment between Herceptin intravenous and Herceptin subcutaneous formulation and vice versa using the 3-weekly (qw3) dosing regimen has been investigated in study MO22982.

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 SmPC for further information. To improve traceability of medicinal products, the tradename of the administered product should be clearly recorded in the patient file. HER2 testing must be performed in a specialised laboratory to ensure adequate validation of test. Congestive heart failure (CHF) observed in patients receiving monotherapy or in combination with paclitaxel or docetaxel; particularly following anthracycline-containing regimen may be moderate to severe and has been fatal. Avoid concomitant use of anthracyclines in the adjuvant and metastatic settings and only use neoadjuvantly in CT-naïve patients in conjunction with low-dose anthracycline regimens. There is limited experience of neoadjuvant use, with concurrent anthracyclines in patients >65 years. Avoid anthracycline based therapy for up to 7 months after stopping Herceptin. Patients receiving Herceptin are at increased risk of developing CHF and caution should be exercised in treating patients with increased cardiac risk e.g. symptomatic CHF, history of hypertension or coronary artery disease and in EBC or in those patients with an LVEF of <55%. Monitor cardiac function at baseline every 3 months during treatment and every 6 months for up to 24 months following discontinuation of treatment. Further monitoring recommended for patients who receive anthracycline containing CT; yearly up to 5 years from last administration, or longer if a continuous decrease of LVEF observed. Consider discontinuing treatment in patients with asymptomatic LVEF decreases, symptomatic CHF or patients who develop clinically significant heart failure unless benefits outweigh risks. Most who developed CHF in clinical trials improved with appropriate treatment and continued Herceptin therapy without additional clinical cardiac events. Serious infusion-related reactions (IRR) reported infrequently (see side effects and adverse reactions), majority within 2.5 hours of start of first infusion. Should IRR occur, discontinue or slow the rate of infusion and monitor patient until resolution. Majority of patients experienced resolution and subsequently received further infusions. Serious IRRs have been successfully treated with oxygen, beta-agonists and corticosteroids. Fatal outcomes are rare and have occurred within hours and up to one week following the infusion. Severe pulmonary events reported rarely; occasionally fatal; may occur as part of IRR or with delayed onset; patients with dyspnoea at rest may be at increased risk of fatal IRR and/or pulmonary events; these patients should not be treated with Herceptin. Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes.

Drug Interactions: No formal drug interaction studies have been performed. Clinically significant interactions with the concomitant medication used in clinical trials have not been observed based on the results of a population PK analysis.

Pregnancy and Lactation: Avoid during pregnancy unless potential benefit outweighs risk. Oligohydramnios reported in post-marketing, some associated with fatal pulmonary hypoplasia of the foetus. Women of childbearing potential should be advised to use effective contraception during Herceptin and for at least 7 months after last dose. Women should not breast-feed during Herceptin therapy and for 7 months after last dose. Close monitoring of pregnant women receiving Herceptin or within 7 months following the last dose of Herceptin is recommended.

RXUKMBCO00033 | July 2017

RXUKMBCO00033 | July 2017

Side-effects and Adverse Reactions: Cardiac dysfunction, IRRs, haematotoxicity (neutropenia), infections and pulmonary adverse events are amongst the most serious and/or common adverse reactions reported in association with the use of Herceptin alone or in combination with CT in pivotal clinical trials and in the post-marketing setting. For full listings please refer to the Herceptin SmPC.

+Reported in association with a fatal outcome.

1Reported largely in association with IRRs. Specific percentages for these are not available.

*Observed in combination therapy following anthracyclines and combined with taxanes. *Very common reactions*: Infection, nasopharyngitis, febrile neutropenia, anaemia, neutropenia, leukopenia, thrombocytopenia, weight loss, anorexia, insomnia, tremor[1], dizziness, headache, paraesthesia, dysgeusia, conjunctivitis, increased lacrimation, change in blood pressure[1], irregular heart beat[1], palpitation[1], cardiac flutter[1], ejection fraction decreased*, hot flush, wheezing+[1], dyspnoea+ , cough, epistaxis, rhinorrhoea, diarrhoea, vomiting, nausea, lip swelling[1], abdominal pain, dyspepsia, constipation, stomatitis, erythema, rash, swelling face[1], alopecia, nail disorder, hand-foot syndrome, arthralgia, muscle tightness[1], myalgia, asthenia, chest pain, chills, fatigue, influenza-like symptoms, infusion-related reactions (majority of infusion-related reactions are mild to moderate in intensity and tend to occur earlier in treatment; reactions include, but are not limited to, chills, fever, rash, nausea and vomiting, dyspnoea and headache), pain, pyrexia, mucosal inflammation, peripheral oedema. *Common reactions:* Neutropenic sepsis, cystitis, herpes zoster, influenza, sinusitis, skin infection, rhinitis, URTI, UTI, erysipelas, cellulitis, pharyngitis, hypersensitivity, anxiety, depression, abnormal thinking, peripheral neuropathy, hypertonia, somnolence, ataxia, dry eye, congestive cardiac failure+, supraventricular tachyarrhythmia+[1], cardiomyopathy, hypotension+[1], vasodilatation, pneumonia+, asthma, lung disorder, pleural effusion+, pancreatitis, haemorrhoids, dry mouth, hepatocellular injury, hepatitis, liver tenderness, acne, dry skin, ecchymosis, hyperhydrosis, maculopapular rash, pruritus, onychoclasis, dermatitis, arthritis, back pain, bone pain, muscle spasms, neck pain, pain in extremity, renal disorder, breast inflammation, malaise, oedema, contusion.

Other serious adverse reactions associated with a fatal outcome (reaction frequency cannot be estimated) anaphylactic reaction/shock, pulmonary fibrosis, respiratory distress/failure, lung infiltration, acute pulmonary oedema, acute respiratory distress syndrome, bronchospasm, hypoxia, oxygen saturation decreased. Other serious adverse reactions (frequency not known) interstitial lung disease, renal hypoplasia, pulmonary hypoplasia.

Legal Category: POM

Presentation and Basic NHS Cost: Pack of one 150 mg single dose vial (reconstituted solution contains 21 mg/ml trastuzumab): £407.40 excluding VAT

Marketing Authorisation Number: EU/1/00/145/001

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

Herceptin is a registered trade mark

RXUKMEDI00202

Date of Preparation: April 2015

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 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 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

If a pregnancy occurs while using 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 a 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 Providers 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 the safe use of Herceptin during pregnancy and lactation has not 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 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 secreted 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.

PRESCRIBING INFORMATION

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 combination with trastuzumab and chemotherapy for adult patients with HER2-positive, locally advanced, inflammatory, 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, (IHC 3+ and/or ISH ≥2.0 using a validated test). Loading dose: 840 mg as 60 minute intravenous (IV) infusion; maintenance dose: 420 mg 3-weekly, administered over 30-60 minutes. Trastuzumab loading dose: 8 mg/kg IV; maintenance dose 6 mg/kg IV 3-weekly. Recommended docetaxel dose is 75mg/m2 administered 3-weekly. Docetaxel may subsequently be escalated to 100mg/m^2 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 full 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 neoadjuvant 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. *Left ventricular ejection fraction (LVEF)*: decreases reported with anti-HER2 therapies, including Perjeta. Left ventricular systolic dysfunction (LVD) seen in neoadjuvant setting. Not studied in patients with: a pre-treatment LVEF value of <50%; prior history of congestive heart failure; LVEF declines to ≤50% during adjuvant trastuzumab therapy; or conditions that may impair left ventricular function. Previous anthracyclines or radiotherapy to the chest area may increase risk. Assess LVEF prior to initiation and every three cycles (mBC) and two cycles (neoadjuvant) and suspend or discontinue as per SmPC guidance. Refer to SmPC for cardiac risks of Perjeta with anthracyclines. Infusion reactions: closely observe patient for 60 minutes after the first infusion, and during and 30–60 minutes following subsequent infusions. For significant infusion reaction, slow or interrupt infusion and administer appropriate medical therapies. Evaluate and monitor patient until resolution of signs and symptoms; consider permanent discontinuation for severe infusion reactions. *Hypersensitivity reactions/anaphylaxis*: discontinue permanently in Grade 4 hypersensitivity (anaphylaxis), bronchospasm or acute respiratory distress syndrome. Ensure medicines and emergency equipment is immediately available. *Febrile neutropenia*: increased risk with Perjeta, trastuzumab and docetaxel combination vs trastuzumab and docetaxel alone, especially during the first three cycles. In the mBC trial CLEOPATRA, no events of febrile neutropenia were reported after docetaxel cessation. *Diarrhoea*: institute anti-diarrhoeals if severe. Interrupt treatment if not improved. Re-instate Perjeta when controlled.

Pregnancy and Lactation: Women of childbearing potential should use effective contraception during Perjeta therapy and for 6 months following the last dose. Not recommended during pregnancy if not using contraception. Discontinue breast-feeding or treatment taking into account the benefit of nursing for the child and Perjeta therapy for the woman.

Side-effects: Refer to SmPC for further information. Assignment of a causal relationship between adverse event and a particular product is difficult due to the combinations of Perjeta, trastuzumab and chemotherapy used. Incidence and frequency of Adverse Drug Reactions (ADRs) varies according to whether Perjeta was administered as monotherapy or with other agents. *Serious ADRs*: Anaphylaxis, febrile neutropenia, neutropenia, diarrhoea and uncommonly interstitial lung disease. Fatal outcomes seen with febrile neutropenia and/or infection. ADRs reported less frequently after docetaxel discontinuation in mBC. Incidence and frequency of specific reactions varied for each regimen. Refer to SmPC. Safety of neoadjuvant Perjeta for more than 6 cycles not established. *Very common and common reactions (metastatic and neoadjuvant setting)*: Upper respiratory tract infection, nasopharyngitis, paronychia, febrile neutropenia, neutropenia, leucopenia, anaemia, hypersensitivity/anaphylactic reaction, infusion reaction/cytokine release syndrome, decreased appetite, insomnia, peripheral neuropathy, peripheral sensory neuropathy, headache, dysgeusia, dizziness, lacrimation increased, left ventricular dysfunction (including congestive heart failure), cough, pleural effusion, dyspnoea, diarrhoea, vomiting, stomatitis, nausea, constipation, dyspepsia, alopecia, rash, nail disorder, pruritus, dry skin, myalgia, arthralgia, mucositis/mucosal inflammation, pain, oedema, pyrexia, fatigue, asthenia, chills.

Legal Category: POM

Presentation and Basic NHS Cost: Pack of one 14 ml (30 mg/ml) glass vial – £2395 per vial excluding VAT

Marketing Authorisation Number: EU/1/13/813/001

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

PERJETA is a registered trade mark

RXUKMEDI00218

Date of Preparation: July 2015

RXUKMBCO00033 | July 2017

RXUKMBCO00033 | July 2017

▼ 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.

Enhanced Safety Reporting for Potential Herceptin-Exposed Pregnancies

- Perjeta should be avoided during pregnancy. There is a limited amount of data from the use of Perjeta in pregnant women and the safe use of Perjeta during pregnancy and lactation has not 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 closely for oligohydramnios.
- If Perjeta is used during pregnancy or if a patient becomes pregnant while being treated with Perjeta or within 6 months following the last dose of Perjeta, immediately report exposure to the Roche Drug Safety Centre by emailing welwyn.uk_dsc@roche.com or by calling +44(0)1707 367554.
- Additional information will be requested during a Perjeta-exposed pregnancy 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.

PRESCRIBING INFORMATION

Kadcyla ® ▼ (trastuzumab emtansine) Please refer to Summary of Product Characteristics (SmPC) prior to use of Kadcyla. 100 mg powder for concentrate for solution for infusion, 160 mg powder for concentrate for solution for infusion.

Indications: Treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have received prior therapy for locally advanced or metastatic disease, or developed disease recurrence during or within six months of completing adjuvant therapy.

Dosage and Administration: Patients should have HER2-positive tumour status, scored as 3+ by immunohistochemistry or a ratio of ≥2.0 by in situ hybridization. Kadcyla should be administered by a healthcare professional at a dose of 3.6 mg/kg bodyweight as an intravenous (IV) infusion every 3 weeks (21 day cycle). Kadcyla should not be mixed with glucose. Use of in-line filter is required for the infusion when the concentrate for infusion is diluted with sodium chloride 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-week cycle. To prevent medication errors check vial labels to ensure the medicinal product being prepared and administered is Kadcyla (trastuzumab emtansine) and not Herceptin (trastuzumab).

Contraindications: Hypersensitivity to trastuzumab emtansine or any excipients.

Precautions: Management of symptomatic adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation; monitor patients closely for these adverse reactions. Symptomatic adverse reactions may include IRR, increased transaminases, hyperbilirubinemia, decreased left ventricular ejection fraction (LVEF), peripheral neuropathy, interstitial lung disease (ILD), including pneumonitis, nodular regenerative hyperplasia, or hypersensitivity reactions. Refer to SmPC for management of adverse reactions. Monitor patients with thrombocytopenia and patients on anti-coagulant treatment closely, and monitor platelet counts in all patients prior to each dose. Cases of bleeding events with a fatal outcome have been observed. Perform standard cardiac function testing prior to initiation and at regular intervals. Monitor liver function prior to initiation of treatment and each dose. Patients with baseline elevation of ALT may be predisposed to liver injury with a higher risk of a Grade 3–5 hepatic event or liver function test increase. Patients with dyspnoea at rest due to complications of advanced malignancy and co morbidities may be at increased risk of pulmonary events.

Drug Interactions: No formal interaction studies have been performed. *In vitro* studies suggest that concomitant use of strong CYP3A4 and CYP3A5 inhibitors should be avoided. If not possible, consider a delay in administration of Kadcyla until the CYP3A4 inhibitor has cleared. If Kadcyla treatment cannot be delayed, monitor patients closely.

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

RXUKMEDI00223(1)

Date of Preparation: February 2016

▼ 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.

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 breast-feeding 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.

RXUKMBCO00033 | July 2017