

**REGIONAL DRUG AND THERAPEUTICS CENTRE
(NEWCASTLE)**

**THE USE OF LAPATINIB IN THE
MANAGEMENT OF METASTATIC BREAST
CANCER**

**Wolfson Unit
Claremont Place
Newcastle upon Tyne
NE2 4HH**

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CONTENTS

SUMMARY	4
BACKGROUND	5
LAPATINIB	6
EFFICACY	6
Lapatinib in refractory metastatic breast cancer	6
<i>Table 1: Efficacy endpoints for lapatinib + capecitabine vs capecitabine alone</i>	8
<i>Table 2: Updated results to April 2006</i>	8
ADVERSE EFFECTS	9
<i>Table 3: Adverse events in the combination and capecitabine groups</i>	9
DOSAGE, ADMINISTRATION AND COST	10
PLACE IN TREATMENT	11
ARRANGEMENTS FOR PRESCRIBING	11
FUTURE DEVELOPMENTS.....	11
ACKNOWLEDGEMENTS.....	12
REFERENCES	13
Appendix I – EGF 100151	15

SUMMARY

- In England breast cancer is the most common malignancy in females and accounts for about 32% of all cancer cases in women. In 2005 there were 38,212 new cases of female breast cancer registered in England, representing a crude incidence rate of 149 per 100,000 of the female population.
- Approximately 10% of patients present with advanced disease with distant metastases at first diagnosis and around 50% of women diagnosed with early or localised breast cancer will eventually relapse and develop metastatic or advanced disease.
- Lapatinib (Tyverb[®]) is an orally active, dual tyrosine kinase inhibitor that targets epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor-2 (HER2). Over-expression of EGFR occurs in 27-30% of breast tumours and HER2 is over-expressed in about 15 - 25% of new breast cancers.
- Lapatinib, in combination with capecitabine, is licensed for the treatment of patients with advanced or metastatic breast cancer whose tumours over-express HER2 and who have received prior therapy including an anthracycline, a taxane and trastuzumab.
- One randomised study has published interim results evaluating the efficacy and safety of lapatinib combined with capecitabine, compared to capecitabine monotherapy in patients with refractory metastatic breast cancer. The lapatinib combination was significantly more beneficial than monotherapy for the primary endpoint of time to progression; 8.4 and 4.4 months, respectively. There was no significant difference in overall survival between the two groups.
- Adverse effects were similar in the two arms: the most common being diarrhoea, hand-foot syndrome, nausea, rash, vomiting and fatigue.
- Due to concerns about cardiotoxicity, the left ventricular ejection fraction (LVEF) was monitored throughout the study. Four patients in the lapatinib group experienced grade 2 and 3, asymptomatic and reversible decreases in the ejection fraction. Patients with pre-existing heart disease were excluded from the trial, so the trial population may not be representative of the wider UK population.
- The cost of lapatinib for 21 days is £1,206. The total combined costs for lapatinib and capecitabine for a 21 day cycle are £1,447, and when extrapolated to one year is £25,150 per patient.
- Lapatinib treatment will be an additional cost following prior treatment with anthracyclines, taxanes and trastuzumab. Oral administration will limit service impact but there will be ongoing LVEF monitoring to consider.
- There is an urgent need for further good quality trials to assess the longer term safety and efficacy of lapatinib in patients with breast cancer. A number of trials are ongoing and they may provide better evidence as to the exact place in the treatment of breast cancer of lapatinib.

BACKGROUND

In England, breast cancer is the most common malignancy in females and accounts for about 32% of all cancer cases in women.¹ In 2005, there were 38,212 new cases of female breast cancer registered in England, representing a crude incidence rate of 149 per 100,000 of the female population.¹ Mortality from breast cancer in the UK has fallen dramatically since the introduction of the national breast screening programme for women aged between 50 and 70.^{2,3} In the period 1989 to 2006, age-standardised death rates for female breast cancer fell by 34%. Around 10,243 women died from breast cancer in England in 2006, a rate of 39.9 deaths per 100,000 women.² Earlier detection and improved treatment have meant that survival rates have risen. The five-year survival rate among the 170,700 women diagnosed with breast cancer during 1999-2003 was 81%.⁴

Approximately 10% of patients present with advanced disease with distant metastases at first diagnosis (~3,820 women per year).⁵ In addition, around 50% of women diagnosed with early or localized breast cancer will eventually relapse and develop metastatic disease (~19,100 women).⁵ The risk of developing metastatic disease relates to known prognostic factors, including oestrogen-receptor negative status, primary tumour > 3cm and axillary node involvement.⁵

Advanced and metastatic breast cancer (MBC) are defined by clinical staging based on the tumour, node and metastasis system.⁶ Locally advanced breast cancer (stage III) includes tumours > 5 cm or those with direct invasion of the skin of the breast or chest wall, and any tumour that has spread to the lymph nodes. MBC stage IV is characterised by the presence of disease at distant sites such as the bone, liver, chest wall or lung.

Although systemic treatment of MBC can result in modest improvements in survival time, the disease at this stage is considered incurable. Treatment is largely palliative, with the primary aim of improving quality of life through control of disease progression.⁷ The average period of survival after diagnosis with MBC is around 18-24 months.⁸

There is currently no single standard of care for patients with MBC, as treatment plans require an individualised approach. Endocrine therapy, chemotherapy or biological therapies are treatment options for many patients with MBC. However, the choice of a specific drug or regimen will depend on a number of factors, including patient characteristics (age, menopausal status, performance status and co-morbidities) and tumour factors (hormone-receptor status and human epidermal growth factor [HER2] status). The history of prior adjuvant therapy and response to treatment, the extent and site of metastatic disease, and patient preference will also affect treatment choice.^{5,9}

First-line systemic treatment of MBC will usually involve hormone therapy for women with oestrogen-receptor-positive disease (usually tamoxifen or an aromatase inhibitor), and chemotherapy for oestrogen-receptor-negative patients (usually an anthracycline-based regimen, or occasionally cyclophosphamide, methotrexate and 5-fluorouracil (CMF)).⁸ Targeted biological therapies offer an entirely new treatment option for patients with MBC. For patients with over-expression of HER2 on tumour cells, the monoclonal antibody trastuzumab is an option.

Trastuzumab is recommended to be used in combination with paclitaxel for patients who have not received chemotherapy and in whom anthracycline treatment is inappropriate, or as monotherapy as an option for patients who have received at least two chemotherapy regimens.⁸

LAPATINIB

Lapatinib (Tyverb, GlaxoSmithKline UK[®]▼) is an orally active dual tyrosine kinase inhibitor that targets epidermal growth factor receptor (EGFR) and HER2.¹⁰ These two receptors are members of the EGFR family of receptors: EGFR/ErbB1, HER2/ErbB2, HER3/ErbB3 & HER4/ErbB4,¹¹ which following autophosphorylation, activate various downstream signalling pathways that regulate cell proliferation, growth, differentiation and survival.¹² In cancer, the over-expression or mutation of these receptors often results in activation of these growth and proliferation pathways.¹² The over-expression of EGFR occurs in about 27% - 30% of breast tumours¹³ and HER2 is over-expressed in 15% - 25% of new breast cancers diagnosed annually worldwide.^{8, 13} Lapatinib reversibly binds to the intracellular tyrosine kinase domain of EGFR and HER2 receptors blocking receptor phosphorylation and activation, thereby inhibiting the downstream signalling events that result in tumour growth.^{12,13}

Lapatinib, in combination with capecitabine, is licensed for the treatment of patients with advanced or metastatic breast cancer whose tumours over-express HER2. Patients should have progressive disease following prior therapy which must have included an anthracycline, a taxane and trastuzumab in the metastatic setting.¹⁰ Licensing was delayed in early 2008 due to a standard pharmacovigilance review by the manufacturers, disclosing liver toxicity in four out of a 1,000 patients taking lapatinib.¹⁴ The advisors were required to re-assess the risks and on the 24th April 2008, the Committee for Medicinal Products adopted a positive opinion, recommending to grant a conditional marketing authorisation.¹⁵ Lapatinib was launched in the United Kingdom in June 2008.¹⁶ The purpose of this report is to review the efficacy and place in treatment of lapatinib in patients with advanced or metastatic breast cancer.

EFFICACY

The evidence base for the licensed indication consists of one pivotal trial, upon which the marketing authorisation was based on.

LAPATINIB IN REFRACTORY METASTATIC BREAST CANCER

A multicentre, randomised, open-label study (EGF100151)¹⁷ was designed to evaluate the efficacy and safety of combining lapatinib with capecitabine in patients with HER2 positive, locally advanced or metastatic breast cancer.^{17,18,19} A total of 324 patients were randomised to receive either capecitabine alone (n = 161) or a combination of lapatinib and capecitabine (n = 163).¹⁷ Patients randomised to capecitabine monotherapy received a dose of 2,500 mg/m²/day on days 1 - 14 of a 21 - day cycle. Those randomised to the lapatinib combination group received 1,250 mg lapatinib once daily and capecitabine 2,000 mg/m²/day on days 1 - 14 of a 21 day cycle. All patients received treatment until disease progression or unacceptable toxicity developed.

Eligible patients had HER2 positive, locally advanced or metastatic breast cancer that had progressed following treatment with anthracyclines, taxanes and trastuzumab. Further inclusion criteria included patients with measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria, an Eastern Cooperative Oncology Group (ECOG) status of 0 or 1, a left ventricular ejection fraction (LVEF) within the normal range, life expectancy of at least 12 weeks and adequate renal, hepatic and haematological function. Women with central nervous system (CNS) metastases were eligible if they were clinically stable for at least three months after discontinuation of corticosteroid and anticonvulsant treatment. Exclusion criteria included women previously treated with capecitabine, and those with pre-existing heart disease or conditions that could affect gastrointestinal absorption.¹⁷

The primary endpoint was the time to progression (TTP) defined as the time from randomisation to disease progression or death due to breast cancer. Secondary endpoints included progression-free survival, overall survival, overall response rate, and rate of clinical benefit, defined as complete response, partial response or stable disease for at least six months, and safety. The study was designed to have a 90% power, with a two-sided, 5% type one error, to detect a 50% increase in the median TTP, requiring 266 TTP events. A planned interim analysis of disease progression was to be conducted after approximately 133 independently assessed events. To adjust for any differences in assessments, the date for the interim analysis data lock was set to allow investigator reported events to be 10% higher than the specified 133 (i.e. interim analysis to be conducted after 146 events had been reported) and the final analysis would occur after 266 independently assessed disease progression events had occurred.

Enrolment began in March 2004, with the interim analysis data lock set in November 2005 when 146 disease progression events were reported in 324 randomised patients. Status and disease assessments were available for independent evaluation in 274 patients, documenting 114 disease progression events. After a review in March 2006, the data and safety monitoring committee recommended reporting the study results and offering lapatinib with capecitabine to the monotherapy group.¹⁷ This interim analysis showed 45 and 69 disease progression events occurred in the combination and monotherapy groups respectively, hazard ratio (HR) 0.51 [95% confidence interval (CI), 0.35 - 0.74, $p < 0.001$]

The monitoring committee's review did not include seven patients whose deaths from breast cancer were unreported before the data lock, so these deaths were subsequently added to the 114 disease progression events, giving 121 independently assessed events by the time of the data lock.

Of these 121 events, progressive disease accounted for 101 events and there were 20 breast cancer-related deaths.

Table 1 shows the results for the primary and secondary endpoints in the intention to treat population:

Table 1: Efficacy endpoints for lapatinib + capecitabine vs capecitabine alone

Endpoint	Lapatinib + Capecitabine (n = 163)	Capecitabine (n = 161)
Primary		
Median TTP	8.4 months	4.4 months
	HR 0.49, 95%CI 0.34 - 0.71, p < 0.001	
Secondary		
Median progression-free survival	8.4 months	4.1 months
	HR 0.47; 95%CI 0.33 - 0.67; p < 0.001	
Overall Response	22% (95%CI, 16 - 29)	14% (95%CI, 9 - 21)
	p = 0.09	
Clinical Benefit	n = 44 (27%)	n = 29 (18%)
Disease progression or death events	n = 49	n = 76
	HR 0.47; 95%CI 0.33 - 0.67; p < 0.001	
Death	n = 36 (22%)	n = 35 (22%)
	HR 0.92; 95%CI 0.58 - 1.46; p = 0.72	

The results demonstrated an improvement in the primary endpoint indicating that lapatinib plus capecitabine was superior to capecitabine alone, with median time to progression of 8.4 months and 4.4 months respectively. There was, however, no significant difference in overall survival, with 36 (22%) and 35 (22%) deaths occurring in the combination and capecitabine-only groups, respectively.

Updated efficacy data has been published covering up until the time of the cross over, April 2006.¹⁹ Results are shown in table 2:

Table 2: Updated results to April 2006

Endpoint	Lapatinib + Capecitabine (n = 198)	Capecitabine (n = 201)
Primary		
Median TTP	6.2 months (27.1 weeks)	4.3 months (18.6 weeks)
	HR 0.57; 95%CI 0.43 - 0.77; p < 0.001	
Secondary		
Median progression free survival	6.2 months (27.1 weeks) ¹⁸	4.0 months (17.6 weeks) ¹⁸
	HR 0.55; 95%CI 0.41 - 0.74 p < 0.001	
Overall Response	23.7% (95%CI, 18.0 - 30.3)	13.9% (95%CI, 9.5 - 19.5)
Death	n = 55 (28%)	n = 64 (32%)
	HR 0.78; 95%CI, 0.55 - 1.12; p = 0.177	

The results demonstrate a statistically significant benefit observed with the lapatinib combination compared to capecitabine alone for the primary endpoint.

The difference between the two groups has narrowed as has progression free survival, however, no difference between the two regimens in terms of overall survival has yet been demonstrated. It is important however, to remember that overall survival was a secondary endpoint, and due to the crossover that occurred in the trial, the control arm then received the active drug which will affect the accuracy of this data.

In summary, only one published trial provides evidence for the use of lapatinib in combination with capecitabine in advanced or metastatic breast cancer following prior chemotherapy regimens. The published results of this study contain data from an interim analysis which demonstrated that lapatinib plus capecitabine significantly improved the time to progression compared to capecitabine alone. This combination did not demonstrate any improvement in the overall survival rates. This was confirmed five months later with further published data.

ADVERSE EFFECTS

In the initial published study,¹⁷ the rates of adverse events (AE) were similar between the lapatinib combination arm and the capecitabine arm. The most common adverse events of any grade are shown in Table 3

Table 3: Adverse events in the combination and capecitabine groups

Adverse event	Lapatinib + Capecitabine (n = 164)	Capecitabine (n = 152)	p-value
Diarrhoea	n = 98 (60%)	n = 60 (39%)	p < 0.001
Hand-Foot Syndrome	n = 80 (49%)	n = 74 (49%)	p = 1.00
Nausea	n = 72 (44%)	n = 64 (42%)	p = 0.83
Rash	n = 45 (27%)	n = 23 (15%)	p = 0.011
Vomiting	n = 43 (26%)	n = 37 (24%)	p = 0.80
Fatigue	n = 29 (18%)	n = 41 (27%)	p = 0.06

Updated AE data to April 2006 showed similar levels of AE in both groups to the original published trial. Four and seven patients in the combination and capecitabine groups respectively, had a fatal AE. None of the fatal events were considered by the investigator to be related to lapatinib.¹⁹

Due to the potential cardiotoxicity of HER2 inhibitors, the LVEF was monitored throughout the original study. Three patients in the lapatinib arm experienced grade two and one patient a grade three LVEF AE.²⁰ All four reactions were asymptomatic. There was one asymptomatic cardiac event in the capecitabine alone arm. There were no differences in mean LVEF values of the two groups at the scheduled assessments.¹⁷ Five patients (3%) in the combination group and two (1%) in the capecitabine group experienced a decrease in LVEF, although no further details are provided.¹⁸ LVEF returned to normal on follow up.¹⁹ One patient in the combination group developed Prinzmetal's angina and had an asymptomatic decline in LVEF.¹⁸ There were no differences quoted in mean LVEF values between the two arms.

It is important to remember that all women with pre-existing heart disease were classed as ineligible for this trial, which would have a bearing on the numbers of cardiac adverse events expected.

A meta-analysis studying cardiac function of 3,127 patients treated with lapatinib from 18 phase I - III trials, was presented as an abstract at the 2006 American Society of Clinical Oncology (ASCO) annual meeting. This analysis revealed a decreased LVEF in 1.3% of patients with 0.1% becoming symptomatic. Sixty six percent of patients who had deterioration in LVEF developed this within nine weeks of starting treatment.²¹

Lapatinib should be discontinued in patients with symptoms associated with a decreased LVEF (grade 3 or greater by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events), and in patients with an LVEF which drops below the institution's lower limit of normal. LVEF should be evaluated in all patients before initiation of treatment to ensure the baseline LVEF is within the institution's normal limits and LVEF should continue to be evaluated throughout treatment.¹⁰ Women were assessed in the trial every six weeks for the first 24 weeks and then every 12 weeks while they received study treatment.¹⁷

Hepatotoxicity has occurred in patients treated with lapatinib. Liver function tests should be monitored before initiation and monthly thereafter. The SPC states that as diarrhoea, and severe diarrhoea has been reported with lapatinib treatment, proactive management of diarrhoea with anti-diarrhoeal agents is important.¹⁰

DOSAGE, ADMINISTRATION AND COST

The recommended dose of lapatinib is 1,250 mg (five tablets) taken orally once daily on days 1 - 21 continuously in combination with capecitabine 2,000 mg/m²/day, (administered orally in two doses approximately 12 hours apart) on days 1-14 of a repeating 21-day cycle. Treatment should be continued until disease progression or unacceptable toxicity occurs.¹⁰

The basic price for lapatinib is £804 for 70 x 250mg tablets which equates to a 21 day cost of £1,206.²² Assuming a mean adult female body surface area of 1.75m², capecitabine costs £241 for 14 days treatment in a 21 day cycle.²³ The total combined costs for a 21 day cycle are therefore £1,447, and extrapolated to one year are £25,150.

GlaxoSmithkline (GSK) offered a risk sharing proposal to NICE whereby they would cover the cost of lapatinib for all eligible patients up to the first 12 weeks of treatment. The NHS would then continue to fund only in patients demonstrating clinical benefits.²⁴ In its most recent draft guidance, NICE rejected this proposal due to it not being cost effective.²⁵

As lapatinib is indicated for the treatment of patients who have already received prior therapy including an anthracycline, a taxane and trastuzumab, costs will be additional to existing treatment costs. Oral administration will limit the service impact but ongoing LVEF monitoring will need to be taken into consideration. Patients will have already been HER2 tested (for the prior regimen of trastuzumab) so there should not be additional HER2 testing costs to be considered.

PLACE IN TREATMENT

In a single published study, lapatinib in combination with capecitabine demonstrated an increase in the time to disease progression by four months compared to capecitabine alone. This was later updated to a difference of two months in the time to disease progression. The limited data have failed to show that this increase translates into an increase in overall survival. The published data show efficacy and safety up to 25 months, but longer-term data are needed to provide evidence on disease progression and whether there are any survival benefits. Until this further evidence is available, the exact place in treatment and benefits of lapatinib remain to be established.

The National Institute for Health and Clinical Excellence (NICE) has issued a consultation document on lapatinib in advanced or metastatic breast cancer. Its preliminary recommendations are that lapatinib, within its licensed indication, is not recommended for the routine treatment of women with advanced or metastatic breast cancer whose tumours over-express HER2 except in the context of clinical trials.²⁵ Health economic analyses, as discussed in this consultation document, may complicate the decision making with regards to place in therapy, and costs to the health economy as a whole need to be carefully considered alongside other competing health priorities. This may lead many commissioners to not approve funding for lapatinib, except within the context of further clinical studies. As this guidance is still out for consultation, this information may change.

Following the conditional marketing authorisation, GSK need to perform and submit an updated analysis of survival data for study EGF100151 and conduct a phase III randomised controlled study to evaluate the incidence of brain metastases as the site of relapse with a lapatinib containing therapy compared to an appropriate trastuzumab containing arm.²⁵

ARRANGEMENTS FOR PRESCRIBING

Lapatinib should only be prescribed in a specialised setting, by experienced oncologists for the treatment of breast cancer, where patients can be closely monitored.

FUTURE DEVELOPMENTS

In view of the limited evidence available, there is a need for good quality randomised controlled trials to investigate the long-term efficacy and safety of lapatinib when used in combination with other chemotherapy agents. A phase III trial, comparing lapatinib in combination with trastuzumab with lapatinib alone in 270 patients with metastatic breast cancer with progressive disease despite prior trastuzumab therapy has completed.²⁶ Another study also completed, compares lapatinib in combination with paclitaxel, with paclitaxel alone in first-line advanced or metastatic breast cancer.²⁷

Lapatinib is also being evaluated in the adjuvant setting in 3,000 women with early-stage HER2 over-expressing breast cancer. This trial is ongoing but is not recruiting any further.²⁸ Two further ongoing studies are evaluating adjuvant lapatinib and trastuzumab both alone and in sequenced combination in 8,000 patients with HER2 over-expressing breast cancer²⁹ and chemotherapy and lapatinib or trastuzumab in treating 600 women with metastatic HER2 breast cancer.³⁰

A future development in this area may be the use of lapatinib compared to the unlicensed use of trastuzumab. Patients who have not responded to initial trastuzumab/chemotherapy combinations, are reported to be either continuing the trastuzumab and changing the chemotherapy, or changing to lapatinib/chemotherapy. For the NICE lapatinib consultation for advanced or metastatic breast cancer, the manufacturer additionally presented data on this unlicensed comparison. NICE said there was not enough evidence to show lapatinib was more cost-effective than this unlicensed trastuzumab use, and found that GSK's analysis for this was 'unsupportable'.²⁵

The NICE technology appraisal on the use of lapatinib in advanced or metastatic breast cancer is expected to be published in March 2009.³¹ Clinical Guidance on the diagnosis and treatment of advanced breast cancer is expected to be published in February 2009.³²

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APPENDIX I – EGF 100151

Key: AE - adverse events; BC – breast cancer; CI – confidence interval; CNS – central nervous system; ECOG - Eastern Cooperative Oncology Group; HR – hazard ratio; HER2 - human epidermal growth factor receptor 2; LVEF - left ventricular ejection fraction; MC – multicentre; OL – open label; OS – overall survival; ORR – overall response rate; PFS – progression-free survival; RECIST - Response Evaluation Criteria in Solid Tumours; RCT - randomised controlled trial; TTP – time to progression.

Reference	Design	Intervention	Patient numbers	Inclusion Criteria	Exclusion Criteria	Primary outcome	Results	Adverse events
Geyer C E et al ¹⁷ (EGF100151)	Phase III, RCT, OL, MC	Lapatinib 1,250 mg daily + capecitabine 2,000 mg/m ² in two divided doses, on days 1-14 of a 21-day cycle compared to capecitabine 2,500 mg/m ² , in two divided doses, on days 1-14 of a 21-day cycle	324 patients were randomised to capecitabine alone (n=161) or lapatinib + capecitabine (n=163).	HER2 positive, locally advanced or metastatic BC that had progressed following treatment with anthracyclines, taxanes and trastuzumab; measurable disease according to RECIST criteria, an ECOG status of 0 or 1, a LVEF within normal range, life expectancy of at least 12 weeks and adequate renal, hepatic and haematologic function. Women with CNS metastases were eligible if they were clinically stable for at least 3 months after discontinuation of corticosteroid and anticonvulsant treatment.	Women previously treated with capecitabine, and those with pre-existing heart disease or conditions that could affect gastrointestinal absorption.	Primary endpoint was TTP. Secondary endpoints included PFS, OS, ORR, rate of clinical benefit and safety.	For the primary endpoint, lapatinib + capecitabine showed a median TTP of 8.4 months compared to 4.4 months with capecitabine alone (HR 0.49, 95%CI 0.34-0.71, p<0.001). For the secondary endpoints, results included: median PFS was 8.4 months vs 4.1 months, respectively (HR 0.47; 95%CI 0.33-0.67; p<0.001). Death (n=36, 22%) and (n=35, 22%) respectively (HR 0.92; 95%CI 0.58-1.46; p=0.72).	AE rates were similar in both arms. The most common AE in the combination and monotherapy groups respectively were: diarrhoea [60% (n=98) and 39% (n=60)], Hand-foot syndrome [49% (n=80) and 49% (n=74)], nausea [44% (n=72) and 42% (n=64)] and rash [27% (n=45) and 15% (n=23)]. Four patients in the combination group experienced grade 2 and 3 decreases in LVEF, all were asymptomatic. One patient in the monotherapy group experienced an asymptomatic cardiac event.