RECURRENCE RATE IN STAGE IV BREAST CANCER PATIENTS: A RETROSPECTIVE COHORT STUDY

Leanda Grobler

A research report in the publication submissible format submitted to the Faculty of Health Science, University of Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science in Medicine (Pharmaceutical Affairs).

Johannesburg, 2023.

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DECLARATION

I Leanda Grobler, student number 1439966, declare that this research report is my own work and that I contributed adequately towards research findings published in the article stated below which are included in my research report. It is being submitted for the Degree of Master of Science in Medicine (Pharmaceutical Affairs) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

Signature of Student:  **Date:** 07/03/2023

Name of Primary Supervisor: Mrs. Razeeya Khan

Signature of Primary Supervisor:  **Date:** 07/03/2023

Agreement by Co-authors: By signing this declaration, the co-authors listed below agree to the use of the article by the student as part of her research report.

Article 1: Title: Recurrence rate in stage IV breast cancer patients: A retrospective cohort study.

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ABBREVIATIONS

(ABC)	Advanced Breast Cancer
(AI)	Aromatase Inhibitor
(ALT)	Alanine Transaminase
(AST)	Aspartate Aminotransferase
(CDK)	Cyclin-dependent Kinase
(CTCAE)	Common Terminology Criteria for Adverse Events
(CYP450)	Cytochrome P450
(ECG)	Electrocardiogram
(ECOG)	Eastern Cooperative Oncology Group
(EMA)	Emergency Medicines Agency
(ESMO)	European Society of Medical Oncology
(ET)	Endocrine Therapy
(HER2)	Human Epidermal Growth Factor Receptor 2
(HREC)	Human Research Ethics Committee
(HR)	Hormone Receptor
(mBC)	Metastatic Breast Cancer
(OS)	Overall Survival
(PFS)	Progression-free Survival
(QTc)	QT Corrected for Heart Rate Interval
(ULN)	Upper Limit of Normal

ACKNOWLEDGEMENTS

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ABSTRACT

Metastatic breast cancer (mBC) remains incurable, with a median overall survival (OS) of approximately three years and a five-year survival rate of approximately 25%, irrespective of the economic classification of the country where treatment is received. Cyclin-dependent kinase (CDK) inhibitors increase overall survival in both first and second-line settings in the treatment of human epidermal growth factor receptor 2 (HER2)-negative, hormone receptor (HR)-positive mBC. This retrospective cohort study investigated the progression-free survival in women with mBC receiving combination therapy with abemaciclib (CDK4/CDK6 inhibitor) and letrozole or fulvestrant as opposed to abemaciclib only. The study included all eligible women with stage IV breast cancer treated with abemaciclib at a private oncology facility in Johannesburg over the study period. Data was collected from medical records for the period 01 April 2019 to 31 March 2021. In women with stage IV mBC, analyses were performed to evaluate the overall survival rate, the likelihood of progression-free survival, and the safety of abemaciclib. The progression-free survival probability was 60% after a period of 17 months irrespective of treatment options. After 17 months, the OS of women on a combination of abemaciclib and letrozole was 80%, a combination of abemaciclib and fulvestrant was 80%, and abemaciclib monotherapy was 70%. The most noted adverse effects were diarrhoea (92.0%), fatigue (48.0%), hepatotoxicity (16.0%) and neutropenia (92.0%). Abemaciclib with endocrine therapy or an aromatase inhibitor (AI) provided an improvement in the OS compared to abemaciclib monotherapy. These findings are representative of the use of abemaciclib in a local population and are similar to those of larger studies carried out internationally.

Key words: abemaciclib, breast cancer, progression-free survival

PUBLICATION

At the time of submission, the article had been submitted to the European Journal of Oncology Pharmacy on 19 November 2022, and is presented in its submissible format.

RECURRENCE RATE IN STAGE IV BREAST CANCER PATIENTS: A RETROSPECTIVE COHORT STUDY

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1. INTRODUCTION

Cancer remains one of the leading causes of death and a barrier to increasing life expectancy world-wide (JAMA Oncology, 2022). The burden of cancer incidence and mortality reflects population growth and changes in socioeconomic development (Roth and Abate, 2018). The burden of non-infectious diseases, including cancer is increasing throughout Africa (Sharma, *et al*., 2022). Epidemiological studies from a regional public sector hospital in South Africa indicated that irrespective of the geographical status, the majority of patients with breast cancer consulted late in both rural and peri-urban areas of developing countries (Kakudji, *et al*., 2020). Numerous therapeutic strategies have been researched since the 1980s in an effort to increase the chance in survival of patients with advanced breast cancer (ABC) (Mutebi, *et al.*, 2020).

International clinical guidelines advocate endocrine therapy (ET) as the first line of treatment for advanced breast cancer with human epidermal growth factor receptor 2 (HER2) negative and hormone receptor (HR) positive characteristics. However, over 50% of HR-positive individuals experience lifetime ET resistance, which ultimately results in disease recurrence and a minimal therapeutic benefit from this treatment (Roberto, *et al*., 2021). Preclinical models suggest that HR-positive breast cancer cells have biological characteristics that lend themselves to targeted therapy with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors (Mayer, 2015). There are currently two CDK4/6 inhibitors registered for use in South Africa: ribociclib and abemaciclib.

Emerging therapies require the skills of a multidisciplinary team (MDT) to ensure optimum patient care (Denton, *et al*., 2016). As the treatment landscape changes in the South African environment, it is important to reflect on the use of these medicines in local cohorts of patients to understand and enhance the contribution of professionals in the MDT. For pharmacists, this includes management of medicine safety and patient education (Avery, *et al*., 2020).

This study reports on the progression-free survival in South African women with mBC receiving monotherapy with abemaciclib, combination therapy with abemaciclib and

letrozole and combination therapy with abemaciclib and fulvestrant. Analyses were carried out to assess the overall survival rate, progression-free survival probability and safety of abemaciclib in a local cohort of patients and to compare the findings with those in other studies.

2. METHOD

2.1 Design and participants

Ethical approval for this study (Ethical Committee clearance certificate number; M220113) was provided by the Human Research Ethics (HREC) Committee of the University of the Witwatersrand, Johannesburg, South Africa on 22 April 2022. A retrospective cohort study was carried out in a private oncology facility in Johannesburg. Data was collected on thirty-two South African women with stage IV breast cancer enrolled in a compassionate use programme with abemaciclib during the period 01 April 2019 to 31 March 2021. All patients had HER2-negative and HR-positive stage IV breast cancer and had had at least four lines of chemotherapy and/or alternative endocrine treatment in an early and metastatic context. Patient records with an appropriate Eastern Cooperative Oncology Group (ECOG) performance status 1, adequate renal, hepatic, and myeloid reserve, and normal corrected for heart rate (QTc) interval on electrocardiogram (ECG) were included.

Pre/peri-menopausal and postmenopausal women were considered for enrolment. Women in pre/peri-menopause received 10.8mg of goserelin for at least one month prior to initiation of abemaciclib and continued to take goserelin every three months. Within this group of patients, those on monotherapy each received 200mg of abemaciclib twice daily and those on combination therapy each received 150mg of abemaciclib twice daily.

Each patient attended a follow-up consultation after one month of treatment and continued follow-up consultations on a three-month basis. Abemaciclib use was discontinued in patients who presented with disease progression in line with treatment protocol. Clinical retrospective data were retrieved from medical records including clinical features and radiological imaging. Informed consent for this retrospective analysis was obtained from

surviving participants.

2.2 Statistical analysis

All participant median progression-free survival (PFS) and overall survival (OS) results were determined using the Kaplan-Meier method (Goel, *et al.,* 2010). Categorical data are described as percentages. All statistical analyses were carried out using the STATISTICA™ Version 13.1 programme (University of Witwatersrand, Johannesburg, 2022).

3. RESULTS

3.1 Baseline characteristics

The first patient was enrolled five months after initiation of the compassionate use programme. The data is representative of all patients enrolled over the remaining 17 month period. Of the 32 patients selected (Figure 1), five patients did not take abemaciclib due to disease progression and two patients absconded. Patients are categorised into three subgroups, (1) those on abemaciclib alone, (2) those on abemaciclib in combination with letrozole (2.5mg) daily, and (3) those on abemaciclib in combination with fulvestrant (250mg) once per month.

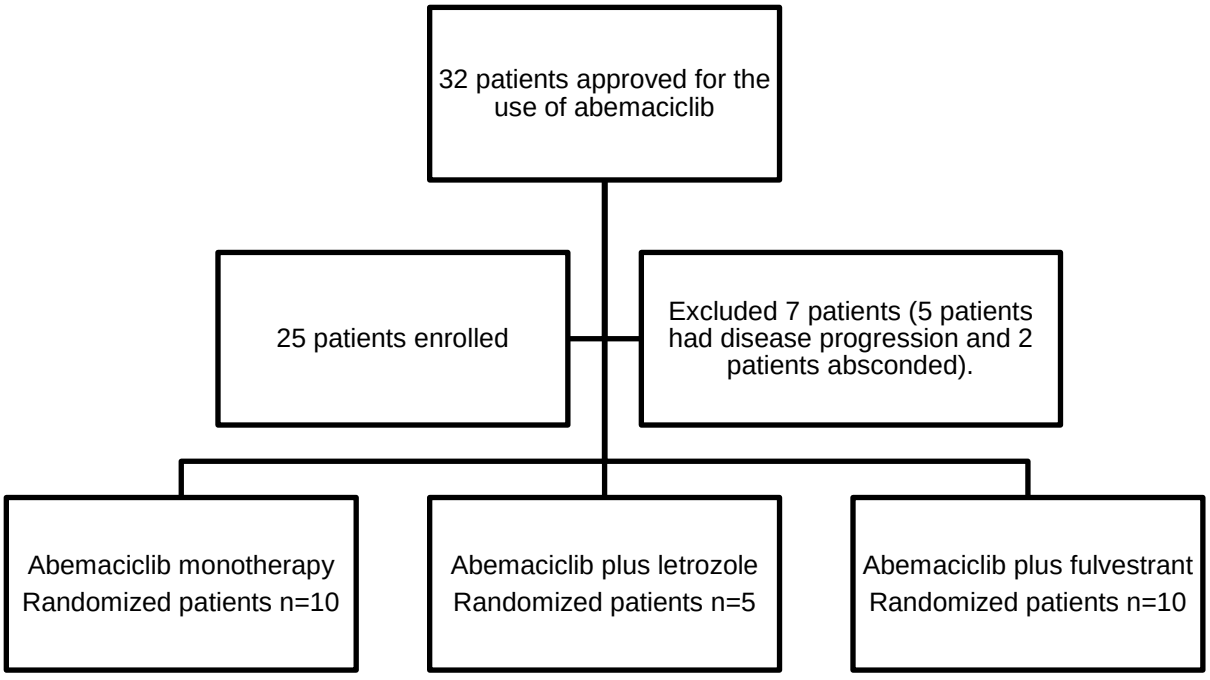

Figure 1. Subgroups of patients enrolled in the compassionate programme

3.2 Demographic and clinical features

The median age of all patients was 52.0 (46.0-60.5) years (Table 1). Of the 25 patients on abemaciclib, 10 patients were selected at random for the use of monotherapy and 70% of these patients were post-menopausal. Five patients were selected at random for the use of abemaciclib and letrozole as combination therapy and 60% of these patients were post-menopausal. Ten patients were selected at random for the use of abemaciclib and fulvestrant as combination therapy and 70% of these patients were post-menopausal.

Eight of the patients were pre/peri-menopausal and had been treated with goserelin prior to initiation of abemaciclib and continued to take goserelin throughout the study. Among these women, 32.0% had lung and liver metastases, 32.0% had bone metastases, 16.0% had lung and bone metastases, 16.0% had bone and liver metastases, 8.0% had lung, liver, and bone metastases and 4.0% had bone and mediastinal involvement.

The Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 grading system was used to report adverse medication responses. Patients taking abemaciclib experienced severe (Grade 3) diarrhoea, hepatotoxicity, and neutropenia (Table 2). One patient discontinued treatment due to severe diarrhoea and four patients succumbed to the disease during the study. Patients with diarrhoea were managed with loperamide as needed and discontinuation of abemaciclib for a period of three days followed by re-initiation of abemaciclib. Patients who presented with a neutrophil count of <2.00 x10g/L were managed with discontinuation of abemaciclib and daily administration of pegfilgrastim daily followed by re-initiation of abemaciclib after seven days.

Table 1. Demographic and clinical features of stage IV breast cancer patients on abemaciclib

Characteristic	**Patients (N=25)**
Age n (%)	

Median age (interquartile range), years	52.0 (46.0-60.5)
Ethnic groups n (%)	
White ethnicity	10 (40.0)
Black ethnicity	7 (28.0)
Coloured ethnicity	4 (16.0)
Indian ethnicity	4 (16.0)
Number of patients on goserelin	
Pre/peri-menopausal	8
Postmenopausal n (%)	
Monotherapy	7 (70.0)
Letrozole	3 (60.0)
Fulvestrant	7 (70.0)
Site of metastases n (%)	
Lung and liver	8 (32.0)
Bone metastases	8 (32.0)
Lung and bone metastases	4 (16.0)
Bone and liver metastases	4 (16.0)
Lung, liver and bone metastases	2 (8.0)
Bone and mediastinal involvement	1 (4.0)

Table 2. Severe adverse effects in patients undergoing treatment with abemaciclib (N=25)

Adverse Effect	All Grades (%)	< Grade 3 (%)	≥ Grade 3 (%)
Gastrointestinal Disorders (%)			
Diarrhoea	92.0	60.0	32.0
Vomiting	4.0	4.0	0
Abdominal Pain	4.0	4.0	0
Hepatotoxicity	16.0	0	16.0
Upper Respiratory Disorders (%)			
Sinusitis	4.0	4.0	0
General Disorders (%)			
Fatigue	48.0	48.0	0
Disorders of the Circulatory and Lymphatic System (%)			
Neutropenia	92.0	80.0	12.0

3.3 Clinical outcomes

A survival analysis is presented in Figure 2. The findings from the remaining sample of 25 patients yielded a progression-free survival (PFS) of all patients at 60% after 17 months. The median probability of recurrence of all patients on abemaciclib during the 17 months was 24%. The median overall survival (OS) of patients on abemaciclib was 70% after 17 months. The median OS of patients on a combination of abemaciclib and letrozole was 80% after 17 months and that of patients on a combination of abemaciclib and fulvestrant was 80% after 17 months.

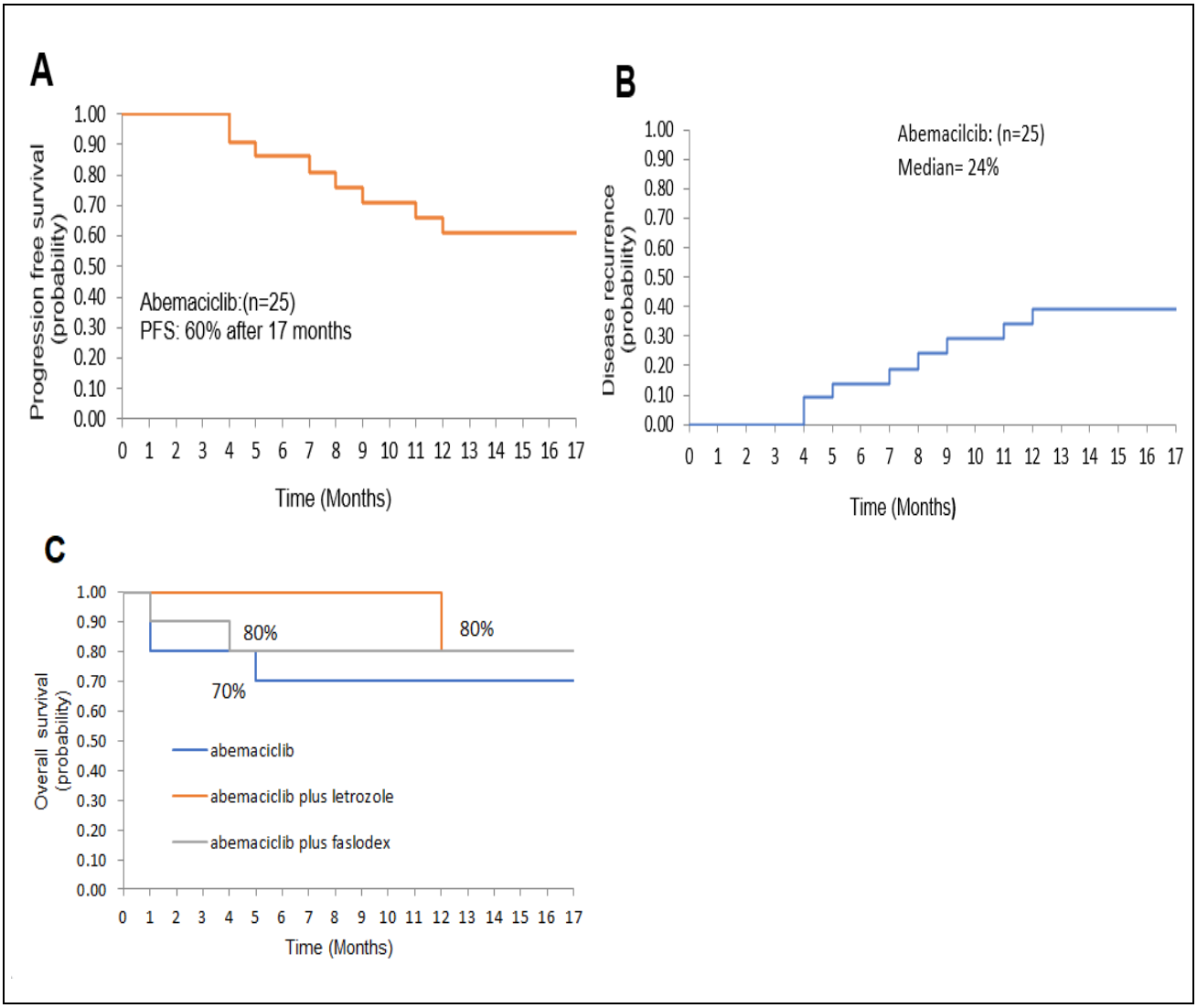

Figure 2. Survival analysis captured as Kaplan-Meier curves. (A) Kaplan-Meier plot of PFS for all patients on abemaciclib. (B) Kaplan-Meier plot of median probability of disease recurrence for all patients on abemaciclib. (C) Kaplan-Meier plot of OS for patients on abemaciclib versus abemaciclib plus letrozole versus abemaciclib plus fulvestrant.

4. LIMITATIONS

Abemaciclib in combination with letrozole/fulvestrant provided an improvement in the OS when compared to abemaciclib monotherapy (Figure 2). The sample size of women enrolled in the compassionate use programme is small; however, the findings in this South African cohort coincide with those of international studies (Martin *et al.*, 2020). Similar findings of subgroups of women who were studied with poor prognostic indicators

(including visceral disease and high proliferative index) in the MONARCH 2 and 3 studies, have shown to benefit the most from the addition of abemaciclib to endocrine therapy (Martin *et al*., 2020).

Caution should be taken when comparing the median PFS with international studies as a multivariate analysis could not be performed. However, the risk of disease recurrence remains below the 50th percentile after a period of 17 months (Figure 2). In terms of toxicity profile, diarrhoea and neutropenia were managed with minimal hospitalisations (Table 2). Although four patient deaths were documented in patients with existing liver metastases, the cause of death could not be confirmed as liver failure due to abemaciclib use in this study. It would be beneficial to investigate the number of patients with liver metastases requiring dose reductions of abemaciclib. No documented incidents of clinically obvious liver impairment related to abemaciclib treatment have been reported in major multinational trials (Krens, *et al*., 2019). Since abemaciclib is a CYP3A4 substrate, it is sensitive to drug-drug interactions with treatments that inhibit or stimulate this particular hepatic microsomal activity (Roncato, *et al*., 2020). Critical review of medical records would be required to identify whether any of the four patients had any pre-existing comorbidities for which they were taking treatment.

To our knowledge there are no published articles that discuss abemaciclib toxicity within the South Africa context. The European Medicines Agency (EMA) provides the most credible guidance, recommending that patients with (Child Pugh C) hepatic impairment reduce abemaciclib dose frequency to once daily (European Medicines Agency, 2018). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be checked before beginning abemaciclib treatment, every two weeks for the first two months and monthly for the next two months (European Medicines Agency, 2018). The European Medicines Agency also advises that abemaciclib be discontinued if the increase in AST and/or ALT is higher than 3 times the upper limit of normal (ULN), with a total bilirubin larger than 2 times the ULN, in the absence of cholestasis, or in the case of Grade 4 (greater than 20.0 times the ULN) hepatotoxicity. According to the European Society for Medical Oncology (ESMO) guidelines, it is important for the physician to recognise the difference between visceral disease and a visceral crisis. In the presence of a visceral

crisis, the presence of metastases is not as important as the consideration of organ compromise which should guide clinical management and decision making (Cardoso, *et al.*, 2020).

Human Epidermal Growth Factor 2 (HER2)-negative, HR-positive breast cancer incidences among South African ethnic groups are widely underreported. In this study, the majority of the patients were of white ethnicity (Table 1) however, it needs to be considered that this study was conducted in a private oncology facility in an urban area. In order to assess a true reflection of ethnicity on CDK4/6 inhibitor therapeutic potential, a meta-analysis conducted on a larger population of South African women would be beneficial. Cost of treatment is a major barrier to the inclusion of abemaciclib as a treatment option within the breast cancer policy framework in the public sector of South Africa, (Meyer, *et al.* 2021). The scarcity of affordability data is one of the major barriers in the development of effective pricing policy in low-middle income countries, (Matilla, *et al.* 2021).

5. CONCLUSION

In conclusion, this analysis indicates that patients who were eligible for the compassionate-use programme received beneficial treatment with minimal risk while on monotherapy or combination therapy with abemaciclib for mBC. The findings of this study provide focus for the management of patients receiving abemaciclib by the MDT. Education and early screening within rural areas of South Africa remains the most effective method in prevention of late/end stage disease. Continued research and the testing of novel abemaciclib-based combinations could create opportunities for reduction in cost and accessibility of treatment for South African women with mBC.

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Appendix A

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18 November 2021
Person No: 1439966
PAG

Miss L Grobler
Po. Box 40826
Moreleta Park
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South Africa

Dear Miss Leanda Grobler

Master of Science in Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *Recurrence rate in stage IV breast cancer patients on abemaciclib: a retrospective cohort study* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix B

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

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CC:	Supervisor: Ms R Khan and Dr A Orchard <Razeeya.Khan@wits.ac.za> and <HREC-Medical Research Office@wits.ac.za>
FROM:	Mr Iain Burns Human Research Ethics Committee (Medical) Tel: 011 717 1252 E-mail: Iain.Burns@wits.ac.za
DATE:	2022/04/22
REF:	R14/49
PROTOCOL NO:	**M220113** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)
PROJECT TITLE:	*Recurrence rate in stage IV breast cancer patients on abemaciclib: a retrospective cohort study*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Ms L Grobler

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220113

NAME: (Principal Investigator)	Ms L Grobler
DEPARTMENT:	School of Therapeutic Sciences Department of Pharmacy and Pharmacology Medical School University
PROJECT TITLE:	*Recurrence rate in stage IV breast cancer patients on abemaciclib: a retrospective cohort study*
DATE CONSIDERED:	2022/01/28
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Ms R Khan and Dr A Orchard
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/04/22

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **January** and therefore reports and re-certification will be due in the month of **January** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

24/04/2022
Date

Appendix C

WITS UNIVERSITY

FACULTY OF HEALTH SCIENCES

This is to certify that

Ms Leanda Grobler

CA0009490

HPCSA NUMBER

has been awarded a total of 8 CPD points for attending the Biennial Research Day and Postgraduate Expo organised by the Faculty of Health Sciences on the 15th of September 2022

ACCREDITATION NUMBER

MDB08/009/07/2022

Dr Joshua Davimes

Chair: Research Day and Postgraduate Expo

Appendix D

European Journal of Oncology Pharmacy

RECURRENCE RATE IN STAGE IV BREAST CANCER PATIENTS: A RETROSPECTIVE COHORT STUDY

--Manuscript Draft--

Manuscript Number:	
Full Title:	RECURRENCE RATE IN STAGE IV BREAST CANCER PATIENTS: A RETROSPECTIVE COHORT STUDY
Article Type:	Original Research
Keywords:	breast cancer, abemaciclib, progression-free survival
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Order of Authors Secondary Information:	
Manuscript Region of Origin:	SOUTH AFRICA
Abstract:	Introduction Metastatic breast cancer (mBC) remains incurable, with a median overall survival (OS) of approximately three years and a five-year survival rate of approximately 25%, irrespective of the economic classification of the country where treatment is received. Cyclin-dependent kinase (CDK) inhibitors increase overall survival in both first and second-line settings in the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative mBC. This retrospective cohort study investigated the progression-free survival in women with mBC receiving combination therapy with abemaciclib (CDK4/CDK6 inhibitor) and letrozole or fulvestrant as opposed to abemaciclib only. Methods The study included all eligible women with stage IV breast cancer treated with abemaciclib at a private oncology facility in Johannesburg over the study period. Data was collected from medical records for the period 01 April 2019 to 31 March 2021. Analyses were carried out to assess the overall survival rate, progression-free survival probability and safety of abemaciclib in women with stage IV breast cancer. Results The progression-free survival probability was 60% after a period of 17 months

	irrespective of treatment options. After 17 months, the OS of women on a combination of abemaciclib and letrozole was 80%, a combination of abemaciclib and fulvestrant was 80%, and abemaciclib monotherapy was 70%. The most noted adverse effects were diarrhoea (92%), neutropenia (92%), fatigue (48%) and hepatotoxicity (16%). Discussion Abemaciclib with endocrine therapy or an aromatase inhibitor (AI) provided an improvement in the OS compared to abemaciclib monotherapy. These findings are representative of the use of abemaciclib in a local population and are similar to those of larger studies carried out internationally.
Suggested Reviewers:	Razeeya Khan, MSc Lecturer, University of the Witwatersrand Johannesburg razeeya.khan@wits.ac.za Extensive knowledge and expertise in the field of oncology pharmacy.

Appendix E

COVERING LETTER
PROTOCOL REF NO: M211025
PROTOCOL TITLE: RECURRENCE RATE IN STAGE IV BREAST CANCER PATIENTS: A RETROSPECTIVE COHORT STUDY
PRINCIPAL INVESTIGATOR: LEANDA GROBLER
STUDENT NUMBER: 1439966
DEPARTMENT OF PHARMACY AND PHARMACOLOGY

This serves to confirm that the following changes have been made to the research protocol in response to the Human Research Ethics Committee (Medical) for approval for year 2022. Approval is required for completion of the degree of MSc. Medicine (Pharmaceutical Affairs).

Response to application 1:

Conditions:

Ethics Application Form:

- The study period and number of patients within the protocol has been corrected back to 32 due to amended exclusion criteria- some patients did not make use of the product despite being approved for use.

Permission:

- Written permission has been obtained from the WDGMC CEO.

Other:

- Participant consent sheet used to obtain patient data and participant information sheet has been added- initial consent form was denied as it seemed more like a billing sheet used by the practice.
- Proof of postgraduate committee approval (GM form) and list of corrections has been attached.

Response to application 2:

Conditions:

Application Form:

- Generic patient consent form (permission to use personal data for research purposes) has been added. All patients sign this form on an electronic platform used by WDGMC called 'Logbox'. An additional letter of agreement between the physician and drug company has been added for review however the drug company does not wish to be affiliated with this research report. In response to HREC Chair feedback- participant sheet and participant information sheet has been added.
- Section 6.4 start and end dates of data collection on the online application form were estimated dates and no data has been collected for secondary analysis. The aim is to complete the research report by 31 Dec 2022.
- The HREC application form section 8.9 has been re-signed by only the necessary parties required.

Data Collection Sheet:

- Identifiers (initiation and progression) have been removed from the data collection sheet.
- Supervisors need to meet with the chair to discuss the research amendments.

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

CANDIDATE'S SURNAME: Grobler	FIRST NAME/S: Leanda	STUDENT NUMBER: 1439966	

CURRENT QUALIFICATIONS: B. Soc. Sci (Hons. in Psychology) (UFS) BCMP(UP)

TEL:011 356 6900/01	CELL:067 651 2611	E-MAIL: Leandag@witsoncology.co.za	FAX:011 356 6526

DEGREE FOR WHICH PROTOCOL IS BEING SUBMITTED: MSc. in Medicine (Pharmaceutical Affairs)

PART-TIME OR FULL-TIME: Part-time (Research Report)	Sex:	F	X	M	

FIRST REGISTERED FOR THIS DEGREE:	TERM: 2 Years	YEAR: 2020

DEPARTMENT: Pharmacy and Pharmacology

TITLE OF PROPOSED RESEARCH: Recurrence rate in stage IV breast cancer patients on abemaciclib: a retrospective cohort study

CANDIDATE'S SIGNATURE: 	DATE: 25/03/2021
SUPERVISOR 1 (NAME & SURNAME): Mrs. Razeeya Khan	60% Supervision

SUPERVISOR'S QUALIFICATIONS: B. Pharm; MSc.

SUPERVISOR'S DEPARTMENT: Pharmacy and Pharmacology

SUPERVISOR'S ADDRESS / TEL / E-MAIL: Razeeya.khan@wits.ac.za

SUPERVISOR 2 (NAME & SURNAME): Dr. Ané Orchard	40% Supervision

SUPERVISOR'S QUALIFICATIONS: B. Pharm; PhD; PgDipHSE

SUPERVISOR'S ADDRESS / TEL / E-MAIL: ane.orchard@wits.co.za

SYNOPSIS OF RESEARCH:

Introduction and Justification of the study:

Approximately 0.5 million people worldwide die from metastatic breast cancer (mBC) every year. The 5th European Society for Medical Oncology (ESMO) international consensus guidelines report that advanced stage breast cancer or mBC remains incurable, with a median overall survival (OS) of about 3 years and a 5-year survival rate of around 25%, irrespective of the economic classification of the country where treatment is received. Metastatic breast cancer, or stage IV breast cancer, is associated with lymph node involvement and is highly dependent on molecular profiling, stage of

diagnosis and biological subtyping. Over the last two years, cyclin-dependent kinase (CDK) inhibitors such as CDK4 inhibitors and CDK6 inhibitors have been trialled both in first line and second-line settings in the treatment of hormone receptor (HR) -positive, human epidermal growth factor receptor 2 (HER2)-negative mBC. In the United States, both CDK4 and CDK6 inhibitors have become the standard of care for use in women with HR-positive and HER2-negative breast cancer as a last line of therapy, consistent with evidence of survival rates of more than 5 years. Abemaciclib, a selective CDK inhibitor, was recently available via Section 21A application for compassionate use in eligible patients with HR-positive, HER2-negative mBC. This study is a retrospective cohort study focussed on the clinical outcomes in patients treated with abemaciclib, provided via a compassionate use programme to eligible women with stage IV breast cancer at a private oncology facility in Johannesburg.

Aim of the study:

The purpose of the proposed study is to retrospectively review the use of abemaciclib in patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative mBC to determine the disease-free survival rate in these patients.

Method:

Raw data collected on a small cohort of thirty-two patients South African women with stage IV breast cancer treated with abemaciclib during the period of 31st March 2019 and 31st March 2021 will be analysed. Patients would have received either monotherapy following prior chemotherapy in metastatic setting or combination therapy or combination therapy following endocrine therapy. Each patient on monotherapy received 200 mg of abemaciclib twice daily and attended a follow-up consultation after 1 month of treatment. Each patient on combination received 150 mg of abemaciclib twice daily and attended a follow-up consultation after 1 month of treatment. All patients had continued follow-up consultations with the physician on a 3-month basis. The data set will include the following variables: 1. allocated patient number; 2. age; 3. gender; 4. site of metastases, 5. monotherapy; 6. combination therapy; 7. adverse effects; 8. date of initiation of abemaciclib; 9. date of disease progression- determined by clinical response, imaging, or an increase in tumour markers on blood results; 10. deceased; 11. living; 12. recurrence (days). Patients who have passed away during this period will be included in the study. Patients who have qualified for the compassionate programme but did not start treatment will be excluded from the study.

Expected Outcomes:

The researcher aims to add to the existing body of evidence on the overall survival, tumour recurrence rate and safety of abemaciclib in women with stage IV mBC treated at a private oncology facility in Johannesburg.

WITS ETHICS NOT REQUIRED:	Yes	No
WITS ETHICS PENDING:	Yes	No
WITS ETHICS APPROVED:	(Yes)	No
(Circle appropriate symbol) *		
***Please note the final human ethics clearance certificate or animal ethics certificate must be available prior to starting research**		

IF YES SUPPLY ETHICS CLEARANCE CERTIFICATE AS ATTACHMENT AND INCLUDE ETHICS NUMBER HERE: APPENDIX A

As supervisor/s, I/we confirm that I have read the protocol which has been submitted for assessment.		
SIGNATURE OF SUPERVISOR/S:		
PROTOCOL ACCEPTED BY HEAD OF DEPARTMENT/RESEARCH COORDINATOR	 SIGNATURE	14 October 2021 DATE

1. Introduction

1.1 Background Information

According to Johnsen *et. al.*, (2021), molecular profiling has remodelled the definition of breast cancer. Currently, radiological imaging allows for the identification of four molecular breast cancer subtypes: (1) luminal A, (2) luminal B, (3) HER2-enriched, and (4) basal-like type breast cancer. Each subtype has a variation of differences which can influence the incidence; how well it responds to treatment. Johnsen *et. Al.*, (2021) further maintains that there are two main types of HER2-negative breast cancer: HR-positive breast cancers and triple-negative breast cancer. Treatments for these cancers differ. HR-positive breast cancers have a better prognosis than triple-negative breast cancers.

Research from the Cancer Genome Atlas (TCGA) indicates that there is at least a 14% gain in HER 2-negative tumour response when using CDK4 inhibitors (Cancer Genome Atlas Network, 2021). Preclinical models suggest that HR-positive breast cancer cells display biological features conducive to the use of targeted therapy with CDK4 inhibitors (Mayer, 2015). Furthermore, the additional incorporation of biomarker data into classic tumour anatomy, such as nodal involvement and the site of metastases (TNM) can largely influence and guide clinicians in the management of extensive disease (Mayer, 2015).

1.2 Literature Review

Presently, there are three Food and Drug Administration (FDA) approved CDK4/6 inhibitors for the treatment of HER2-negative and HR-positive metastatic breast cancer. These include palbociclib (Ibrance; Pfizer Inc.), ribociclib (Kisqali; Novartis) and abemaciclib (Verzenio; Eli Lilly). In 2015, palbociclib was the first FDA approved CDK4/6 inhibitor for the use of first-line treatment in postmenopausal woman with HR-positive, HER2-negative advanced breast cancer in combination with endocrine therapy (Letrozole) (Beaver, *et al.*, 2015). Results from the Palbociclib and Letrozole of post-menopausal women in advanced breast cancer (PALOMA-2) study, a phase 3 double-blind randomized controlled study, evaluated the period of no recurrence or worsening of disease in terms of Progression Free Survival (PFS). The study provided evidence of this combination therapy with the mean, PFS of 24.8 months as opposed to woman who received monotherapy or a placebo with the mean PFS of 14.5 months (Hazard Ratio (HR) = 0.58; $p < 0.000001$) (Cristofanilli, *et al.*, 2016). Patients on combination therapy survived almost twice as long as on monotherapy.

In the PALOMA-3, study which alternatively evaluated fulvestrant in combination with palbociclib as opposed to palbociclib and a placebo in pre- and postmenopausal patients with HR-positive, HER2-negative advanced breast cancer, it was found that the median PFS favoured the positive arm (median PFS 9.5 vs. 4.6 months; HR = 0. 46; P < 0.001) (Loibl, *et al.*, 2016). In terms of toxicity, the most common adverse effects observed in both trials were non-febrile neutropenia and fatigue (Beaver, *et al.*, 2015).

Similarly, ribociclib (LEE0011) (Kisqali; Novartis) has been investigated as treatment in postmenopausal woman with HR-positive, HER2-negative advanced breast cancer in combination with endocrine therapy across a variety of Mammary Oncology Assessment of LEE0011 Safety and Efficacy (MONALEESA) clinical trial programmes (Shah, *et al.*, 2018). After receiving FDA approval in July 2017 for showing significance in median PFS as opposed to a placebo (25.3 and 16 months, HR=0.568; p= 9.63 x 10−8) (MONALEESA-2) and (20.5 and 12,8 months, HR= 0.593; one-sided p < 0.001) respectively, the focus shifted towards combination therapy (Yardley, 2019). In the MONALEEESA-7 trial, a subgroup of patients who received Tamoxifen showed an increase in PFS to 22.1 months, versus 11.0 months in the placebo group (HR=0.59; 95% CI: 0.39-0.88) (Yardley, 2019). Alternatively, combined use of ribociclib and a non-steroidal aromatase inhibitor showed a further increase in PFS of up to 27.5 months in comparison to the placebo group of 13.8 months (HR=0.57; 95% CI: 0.44-0.74) (Yardley, 2019).

Two months after ribociclib approval, abemaciclib received FDA approval; to be used as monotherapy in patients who have had disease progression after being on both endocrine therapy and chemotherapy or as combination therapy with fulvestrant (faslodex) (Dickler, *et al.*, 2017). The MONARCH 1 trial, a single-arm, open-label clinical trial evaluating 132 patients who received taxane in any setting and 1 or 2 previous chemotherapy regimens in the metastatic setting, indicated an Overall Recurrence Rate (ORR) of 19.7% and median duration response of 8.6 months (Dickler, *et al.*, 2017). In contrast, the MONARCH 2 trial, a randomized, placebo-controlled multicentre clinical trial involving 669 participants, indicated a median PFS of 7.1 months longer with the use of combination therapy (abemaciclib plus fulvestrant), versus fulvestrant and a placebo (Sledge, *et al.*, 2017).

In the MONARCH 3 trial, a double-blinded study of 493 participants who had not previously received systemic therapy in the advanced disease setting, received abemaciclib as monotherapy or a placebo plus a non-steroidal aromatase inhibitor.

The abemaciclib arm was unobtainable versus 14.7 months in the placebo arm (Goetz, *et al*., 2017). The most common adverse reactions reported were diarrhoea, neutropenia, nausea, abdominal pain, fatigue, vomiting and thrombocytopenia (Dickler, *et al*., 2017). Evidence regarding efficacy in terms of PFS and ORR in both monotherapy and combination therapy is still being studied. The use of abemaciclib in the local population is in its early stages and has only recently been approved for use in South Africa. Therefore, it is worthwhile investigating treatment response in patients receiving monotherapy or combination therapy in South African women.

1.3 Problem Statement

Cancer survival rate refers to the percentage of people who are alive after a certain amount of time following initial diagnosis. The survival rate for breast cancer patients depends on many factors, including the grade and stage of the cancer. The prognosis for stage IV breast cancer is considered poor, however, the preliminary research indicates that targeted therapy may prolong life expectancy (Beaver, *et. al*., 2015). Abemaciclib, a targeted therapy used extensively overseas, is only recently available in South Africa. Prior to its registration, it was available via a compassionate use programme. Data on the progression free survival rate and the overall survival of patients in the South African population of women is still lacking.

1.4 Significance of the study

Abemaciclib in combination with hormonal therapy is found to be the most effective in the treatment of aggressive disease in the United States (US) population (Cristofanilli, *et al*., 2016). As abemaciclib has only recently been approved for use in South Africa, research on the response to treatment with abemaciclib within the South African context is necessary.

1.5 Research question

What is the disease-free survival rate in South African women with Stage IV breast cancer receiving abemaciclib at a private oncology facility in Johannesburg?

1.6 Aim of the research

This study aims to retrospectively review the disease-free survival rate in a small cohort of South African women with stage IV mBC treated with abemaciclib.

2. Objectives of the study

1. To determine the overall survival rate (OS) in women with HER2-negative, HR-positive stage IV breast cancer treated with abemaciclib.
2. To determine the tumour recurrence rate (days) in women with HER2-negative, HR-positive stage IV breast cancer treated with abemaciclib as either monotherapy or combination therapy.
3. To document the adverse events experienced by patients treated with abemaciclib in terms of the toxicity profile.

3. Methodology

The study will be quantitative in nature and the researcher will be making use of a non-experimental research design as well as convenience sampling. It will involve a retrospective analysis by evaluating data collected on thirty-two South African women with stage IV breast cancer who received abemaciclib monotherapy following endocrine therapy or prior chemotherapy in a metastatic setting or as combination therapy following endocrine therapy, through a compassionate use programme.

3.1 Participants and Sampling

The study population will include thirty-two South African women who enrolled in a compassionate use programme at a private oncology facility in Johannesburg. Data will be collected for women with HER2-negative, HR-positive stage IV breast cancer on both monotherapy (abemaciclib only) and combination therapy (abemaciclib in combination with fulvestrant/aromatase inhibitor) in line with recommendations of the compassionate use programme. The sample size includes all female patients who have qualified for the compassionate programme. Data collected over a period of two years (31st of March 2019 to the 31st of March 2021) will be reviewed.

3.2 Inclusion Criteria

The sample population will include women with HER2-negative and HR-positive stage IV breast cancer at a private oncology practice. Each woman must have had at least ≥ 4 lines of chemotherapy and/or alternative endocrine therapy in an early and metastatic setting. Only records of patients with adequate performance status (ECOG1), adequate renal, hepatic, and myeloid reserve as well as normal QTc interval on ECG will be used.

3.4 Exclusion Criteria

Men with breast cancer have been excluded from this study. Patients who have not had prior chemotherapy and/or endocrine therapy will be excluded from this study. Patients who have qualified

for the compassionate programme but did not make use of abemaciclib will be excluded from this study.

4. Data Collection and Analysis

Data will be collected on a specially designed data collection sheet. Data will be analysed using descriptive statistics and median overall survival will be estimated with the use of the Kaplan-Meier statistical analysis. All statistical analyses will be conducted with the use of the STATISTICA version 13.1 programme. Tables and charts will be used to describe demographics and indicate the clinical and pathological characteristics of each participant. The data set will include the following variables: 1. allocated patient number; 2. age; 3. gender; 4. site of metastases, 5. monotherapy; 6. combination therapy; 7. adverse effects; 8. date of initiation of abemaciclib; 9. date of disease progression-determined by clinical response, imaging, or an increase in tumour markers on blood results; 10. deceased; 11. living; 12. recurrence (days). Patient outcomes will be presented using charts and tables.

5. Ethical considerations

All information generated by the study will be treated in line with the beneficence, non-maleficence, autonomy, and justice principles. The data is only made available to the treating physician, the clinical associate, and the responsible pharmacist. The data will be analysed retrospectively. No patient identifiers will be used. Unique study numbers will be allocated to each study participant and data will be stored in a password-protected document accessible to the principal investigator and supervisors alone. Data will be stored digitally under password protection for two years after a publication, or six years if there is no publication. Permission to make use of the patient data has been approved by the treating physician. A participant information sheet and participant consent sheet has been attached in response to feedback from the HREC chair. An application has been made to the Human Research Ethics Committee; the certificate of approval is pending.

6. Time Frame

Table 1

Year: 2021	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Literature review and writing of protocol												
Submit protocol												
Assessor's meeting and ethics application												
Submit protocol post assessor's meeting												
Submit protocol post HREC feedback												
Received approval from Wits												

Table 2

Year: 2022	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Received feedback from HREC												
Meet with supervisors to discuss feedback												
Re-submit protocol post HREC feedback												
Literature search and data collection post HREC approval												
Data analysis and write up												
Final editing and hand in report for evaluation												

7. Research Proposal Budget

Table 3

Expense	**Cost**
Printing costs	R100.00
Access to patient files after hours facility fees	R500.00 per month
STATISTICA programme	R350.00
Statistician	R2000.00
Airtime/data	R500.00
Total projected expenses	**R3450.00**

7. Funding

This is an independent retrospective study on data that has already been collected. The study will be self-funded.

8. Ethics Approval

Approval has been obtained from the treating physician (see Appendix F) to conduct an independent study. Ethics approval from the University of the Witwatersrand Human Ethics Research Committee is pending.

9. Conflict of Interest

I am an employee of the Wits Health Consortium and have access to readily available raw data. This is a research project independently conducted from any pharmaceutical sponsor.

Reference List

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Appendix A

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

18 November 2021

Miss L Grobler Person No: 1439966

Po. Box 40826
Moreleta Park
Pretoria East
0044
South Africa

Dear Miss Leanda Grobler

Master of Science in Medicine: Approval of Title

PAG

We have pleasure in advising that your proposal entitled Recurrence rate in stage IV breast cancer patients on abemaciclib: a retrospective cohort study has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Faculty of Health Sciences, Postgraduate Office
Phillip V Tobias Building, 2nd Floor
Cnr York & Princess of Wales Terrace, Parktown 2193
Tel: (011) 717 2745 | Fax: (011) 717 2119
Email: Mathoto.senamela@wits.ac.za

Appendix B

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS SENATE PLAGIARISM POLICY: APPENDIX ONE

I Leanda Grobler (Student number: 1439966) am a student registered for the degree of MSc. Medicine (Pharmaceutical Affairs) in the academic year 2020/2021.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature:  Date: 26/03/2021

Appendix C

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

RECOMMENDATION FOR APPOINTMENT OF SUPERVISOR(S) OF RESEARCH REPORT, DISSERTATION OR THESIS

Motivation / Reason for Appointment: I was originally allocated to conduct a lab- based project with Prof. Kondiah After contracting covid-19 in July 2020 it was recommended that I conduct my own independent study with the appropriate supervisors in the field of oncology.

Recommendation of Division / Department / School:
Recommendations were made to conduct an independent study within my field of knowledge.

Student Surname and full name(s)	Ms. Leanda Grobler
Student number	1439966
Degree	MSc. Medicine (Pharmaceutical Affairs)
Dept	Pharmacy and Pharmacology
Title	Recurrence rate in stage IV breast cancer patients on abemaciclib: a retrospective cohort study

Supervisor 1: Razeeya Khan

Supervision %: 60

Supervisor Qualifications: B. Pharm (Wits) M. Sc (Rhodes)

Supervisor Department: Pharmacy and Pharmacology

Supervisor Telephone: 011 717 2552 E-mail: razeeya.khan@wits.ac.za

Supervisor 2: Ané Orchard

Supervision %: 40

Supervisor Qualifications: BPharm (Wits) PhD (Wits) PGdip HSE (Wits)

Supervisor Department: Pharmacy and Pharmacology

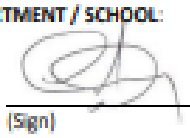
Supervisor Telephone: 0117172317 E-mail: ane.orchard@wits.ac.za

Student Signature:

Supervisor 1 Signature:

Supervisor 2 Signature: 

RECOMMENDATION BY HEAD OF DIVISION / DEPARTMENT / SCHOOL:

Prof Yahya E Choonara		14 October
(Full name(s) and Surname)	(Sign)	(Date)

Appendix D

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

FACULTY OF HEALTH SCIENCES

University of the Witwatersrand Student Ethics Declaration Form
(To be completed during the protocol assessor meeting)

Background

All Research conducted by a University of the Witwatersrand student, with human subjects or animals, requires approval by the Wits Human Research Ethics Committee or Animal Research Ethics Committee, respectively. If research has been undertaken without the necessary ethics approvals, this is considered an ethics violation. This will be reported to the relevant structures, the data will have to be discarded, and in the case of students, they cannot use the data towards their degree. To prevent any ethics violations, the ethics requirements for the proposed project will be discussed with you at the protocol assessment.

Declaration
Based on the current protocol assessment (and any proposed changes suggested by the assessor committee), we, the undersigned, understand that the proposed research requires:

1. Human Research Ethics clearance certificate	Yes	No
a. Covered under existing supervisor ethics	Yes	No
b. Requires a new HREC application	X	No
2. Animal Research Ethics clearance certificate	Yes	No
3. No Human or Animal Ethics Clearance	Yes	No

4. Unclear, will seek appropriate guidance from the HREC/AREC committees (whichever relevant)

Signatures:

Supervisor 1:
Supervisor 2:
Student:

Appendix E

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

DECLARATION:

Adherence to HREC (Medical) Ethics Application Terms and Conditions

I, the undersigned, hereby declare that I have not collected data/ done secondary data analysis or any other form of research, prior to obtaining clearance certificate from the HREC (Medical) for study no: M211025.

I have read and understood the terms and conditions on section 9 of HREC (Medical) application form, confirm that it is my responsibility to ensure that I have received final HREC (Medical) Clearance before commencing any research.

Leonida Gadaleta

Name, Surname and Signature

Student/Staff no if applicable: 1439966

Date: 09/11/21

Name, Surname and Signature

Supervisor (if applicable)

Date:

Appendix F

8.9. Signatures:

I understand that no data may be collected until I have received the full ethics clearance certificate.

Title of the Research Project:
Recurrence rate in stage IV breast cancer patients: a retrospective cohort study

Applicant's Signature:

Date: 2 March 2022 **WHO WILL SUPERVISE THE PROJECT? (Where applicable)**

Name: Mrs. Razeeya Khan **Department:** Pharmacy and pharmacology

Telephone No: 011 717 2317 **Email:** razeeya.khan@wits.ac.za

Signature: **Date:** 4 March 2022

WHO WILL SUPERVISE THE PROJECT? (Where applicable)

Name: Dr. Ané Orchard **Department:** Pharmacy and pharmacology

Telephone No: 011 717 2317 **Email:** ane.orchard@wits.ac.za

Signature: **Date:** 4 March 2022

HEAD / RESEARCH COORDINATOR OF DEPARTMENT / ENTITY IN WHICH STUDY WILL BE CONDUCTED (Where applicable) (Wits Students Academic HOD must sign)

Name: Prof Yahya E Choonara **Department/Entity:** Pharmacy and Pharmacology

Tel No: 011 717 2052 **Email:** yahya.choonara@wits.ac.za

Signature: **Date:** 4 March 2022

Appendix H

Statement of principles for postgraduate supervision

In a context of academic freedom and within a framework of individual autonomy and the pursuit of knowledge, this statement is written in the belief that there is a reciprocal relationship and mutual accountability between supervisor and student

THE SUPERVISOR AND THE STUDENT:

1. Will establish agreed roles and clear processes to be maintained by both parties. In the case of joint supervision, the roles and responsibilities of each supervisor and the student need to be clarified.
2. Will meet regularly and as frequently as is reasonable to ensure steady progress towards the completion of the proposal, research report, dissertation, or thesis. This time varies bu the normal minimum requirement for face-to-face contact spread across each year of registration is: 10 contact hours for an Honours project, 15 contact hours for a master's by coursework and research report and 24 contact hours for a master's by dissertation and a PhD.
3. Will keep appointments, be punctual and respond timeously to messages.
4. Will keep one another informed of any planned vacations or absences as well as changes in his or her personal circumstances that might impact on the work schedule. Unplanned absences or delays should be discussed as soon as possible and arrangements should be made, to catch up lost time.
5. Will ensure that research on animal or human subjects is conducted with prior approval and according to the procedures and the requirements of the relevant Ethics committee.
6. Will both complete Progress Reports on the research project as required/requested by the relevant Faculty Graduate Studies Committee.

THE SUPERVISOR:

1. Undertakes to provide guidance for the student's research project in relation to the design and scope of the project, the relevant literature and information sources, research methods and techniques and methods of data analysis.
2. Will provide guidance at the commensurate NQF level requirements for autonomy and accountability that the student is expected to demonstrate.
3. Has a responsibility to be reasonably accessible to the students.
4. Will be prepared for meetings with the student. This includes being up to date on the latest work in his/her area of expertise.
5. Will expect written work as jointly agreed and will return that work with constructive criticism within a timeframe (a suggestion of 2-4 weeks) jointly agreed at the outset of the research.
6. Will provide advice that can help the student to improve his/her writing. This may include referrals for language training and academic writing. The supervisor will provide guidance on technical aspects of writing such as referencing as well as on discipline specific requirements. Detailed correction of drafts and instruction in aspects of language and style are **not** the responsibility of the supervisor.
7. Will guide the student in the production of a research report, dissertation, or thesis. Provision should be allowed for adequate, mutually respectful, discussion around recommendations made.
8. Will assist with the construction of a written time schedule, which outlines the expected completion dates of successive stages of the work.
9. Will encourage the student to present work at postgraduate/ staff seminars/national/international conferences as appropriate.
10. Will assist with the publication of research articles as appropriate.
11. Will discuss the ownership of research conducted by the student in accordance with the University rules on intellectual property, copyright, **guidelines on authorship/co-authorship**, and **policy on research integrity.**
12. Will ensure that the student is aware of the University's Plagiarism Policy, knows what plagiarism is, and what the consequences are for academic dishonesty and violation of research integrity and intellectual property.
13. Will ensure that the student is made aware in writing of the inadequacy of progress and/or of any work where the standard is below par. Acceptability will be according to criteria previously supplied to the student.
14. Has a duty to refuse to allow the submission of sub-standard work for examination, regardless of the circumstances. If the student chooses to submit without the consent of the supervisor, then this should be clearly recorded and the appropriate procedures followed.

THE STUDENT:

1. Takes full responsibility for the research and its successful completion, including managing the process under the guidance of supervisor (s).
2. Will attend such courses and lectures that are compulsory for the degree, and undertakes to catch up fully on any work, lectures and/or assignments, that are missed.
3. Undertakes to work independently under the guidance of the supervisor(s). This includes reading widely and critically to ensure that the seminal **and** current literature pertinent to his/her chosen topic has been identified, consulted, and critiqued.
4. Undertakes to work in accordance with the academic standards expected by the University for the commensurate NQF level of qualification.
5. Is obliged to make appointments to consult the supervisor(s) and arrange meeting times convenient to both parties well in advance.
6. Should submit written work for discussion with the supervisor(s) well in advance of a scheduled meeting. The kind and frequency of written work should be agreed with the supervisor(s) at the outset of the research.
7. Written work that is submitted to the supervisor, including final submissions to examiners, should be relatively free from basic spelling mistakes, incorrect punctuation and grammatical errors. Responsibility for the accuracy of language, the overall structure and coherence of the final research report, dissertation or thesis rests with the student.
8. Cannot expect the supervisor to be proof-reader and editor of his/her work or to approve work with any of the weaknesses spelt out in 7 above.
9. Undertakes to heed the advice given by the supervisor(s) and to engage in discussion around suggestions made. Ultimately the student must take

We confirm that we have read and understood this statement and agree to be guided by its principles for as long as we continue to work together.

Name of student: Leanda Grobler

Student Number: 1439966

Student's signature: 

Name of Supervisor: Riaaleya Khan

Supervisor's signature: 

Name of Co-Supervisor: Ané Orchard

Co-Supervisor's signature: 

The broad area of study is: Oncology

Provisional submission date is: 27/03/2021

Degree: MSc. in Medicine (Pharmaceutical Affairs)
School: Medicine
Faculty: Health Sciences

Date: 25/03/2021

Specific agreements pertaining to: ownership, joint publication, funding, confidentiality and disclosures pertinent to the Certificate of Clearance and ETD Form which the student and/or supervisor are required to sign, must be attached to this agreement as and when appropriate and kept in the Faculty Office. In the event of disagreements between the supervisor(s) and student, the parties should act in accordance with the University Grievance Policy.

***Note: Consent by supervisor(s)** to submit work for examination does NOT guarantee that the work will pass. The appointed examiners assess and determine whether the work is of a passable standard.

(2015/09/30)

	responsibility for the quality, integrity, and presentation of the work. 10. Should strive to maintain a focus on his/her research area and to work diligently within the agreed time schedule. 11. Agrees to honour agreements about ownership of the research and in accordance with the University's guidelines and rules in relation to co-authorship, copyright and intellectual property. 12. Will ensure that the work contains no instances of plagiarism, violation of intellectual property and research integrity standards, that all citations are properly referenced, and that the list of references is accurate, complete, and consistent. 13. Agrees to work in accordance with the criteria of acceptability as supplied by the supervisor(s). 14. Undertakes not to place the supervisor(s) under undue pressure to submit work for examination until the supervisor is satisfied that it has reached an acceptable, **examinable*** level of quality.	

Appendix I

Dr S D Moodley

MBBCh (Wits) FCP (SA)

Specialist Physician / Medical Oncologist

Practice number 2306141

University of Witwatersrand
Donald Gordon Medical Centre,
17 Eton Road,
Parktown 2193,
South Africa.

P O Box 2366,
Houghton,
2041,
South Africa.

+2711-356-6800(s)(f)(f) | smadevenn@gmail.com | +2711-321-1418 | +2711-726-7436.

25/05/2021

Re: Ms. Leanda Grobler
Attention: Research Ethics Committee

To whom it may concern,

This serves to confirm that Ms. Grobler works under my supervision at the above-mentioned facility. She is actively involved in the application processes and management of patients during the current ongoing clinical drug trials. She has met with me and a representative from Eli Lilly and Company regarding an independent research study. The drug company/ sponsor does not wish to be involved in the study and therefore, no reference may be made to Eli Lilly and Company. I have granted her permission to conduct an independent research study on the data obtained on the drug **Abemaciclib (Verzenio®)** supplied to my practice (site 153) for compassionate use in HER2-negative, PR-positive breast cancer patients. Should the study cause any disruption with the current ongoing clinical trials, it may be suspended. Should Ms. Grobler apply for publication of the results, it will first need to be reviewed by myself and the University of the Witwatersrand to ensure that findings supplied are correct and reliable.

Please feel free to contact me for any additional information.

Sincerely Yours,

Dr S D Moodley
MBBCh (Wits) FCP (SA)
Specialist Physician/Medical Oncologist

Appendix J

Eligibility Criteria Form Template

Country: South Africa

1. **Each patient must meet the following criteria to be enrolled in this Program:**

- **Confirmed hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer: YES / NO**

- **Treatment with Abemaciclib will be: (CHECK ONE)**

  - **As monotherapy,**
  - **In combination with fulvestrant,**
  - **In combination with an aromatase inhibitor**

2. **Previous medical treatments _____**

3. **Performance status _____**

4. **Most recent laboratory assessment of bone marrow, renal, and hepatic function _____**

Item	Value	Lower limit of normal	Upper limit of normal	Unit
WBC				
ANC				
Platelet				

Haemoglobin				
Total Bilirubin				
ALT				
AST				
Creatinine				

5. Is any alternate standard of care or clinical trial available for this patient?
    a. YES
    b. NO

6. Brief justification in English of non-existence of any alternative therapies in South Africa, including clinical trials or medical treatments _____

7. Please specify if there is information available regarding any markers suggesting potential sensitivity to CDK inhibitors such as CDKN2A abnormalities _____

Name of Doctor _____

Signature and Date _____

Appendix K

HUMAN RESEARCH ETHICS
COMMITTEE (MEDICAL)

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Office of the Deputy Vice-Chancellor Research & Post Graduate Affairs

MEMORANDUM
(This memo is not a clearance certificate)

TO: Miss Leanda Grobler
Pharmacy
E-mail: 1439966@students.wits.ac.za

FROM: Miss Mapula Ramaila
Administrative Officer: Human Research Ethics Committee (Medical)
Tel: 011 717-1234/2656/2700
E-mail: Mapula.Ramaila@wits.ac.za or HREC-Medical.ResearchOffice@wits.ac.za

DATE: 03 November 2021

REF: *R14/49*

PROTOCOL NO: M211025 *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

The protocol below was considered at the Human Research Ethics Committee (Medical) Meeting **on Friday, 29 October 2021**. The Committee requires the following amendments/corrections/information from you before your application can be approved.

Project Title: Recurrence rate in stage IV breast cancer patients: a retrospective cohort study

Conditions: Not approved in the present form: Full online resubmission

(This memo is not a clearance certificate; no research should commence prior to obtaining a clearance certificate)

- Ethics Application Form:
  - Correcting and resubmitting HREC form with consistent study period and numbers of patients to be included and the correct protocol once approved by postgraduate committee.
- Permission:

- Providing written permission from WDGMC CEO.

- Other:
  - Providing the form which is used to obtain patient consent for use of their data.
  - Providing proof of postgraduate committee approval.

NB:

1. Read this memo entirely and then address the issues raised under condition/s and comment/s sections.
2. This memo is not a clearance certificate; no research should commence prior to obtaining a clearance certificate.
3. Please resubmit via the online ethics system and submit **two hard copies** of the following to the Research Office:
   - **Covering letter** (submit X 2 hard copies): list all the conditions above and write your response below each condition and **attach relevant documentation,** highlight/track any changes made and the other must be a clean copy without track changes/highlight.
   - **Signed declaration** (submit X 2 hard copies) confirming that data has not been collected for the study. It must be signed by the applicant and supervisor (for degree studies). For non-degree studies only the applicant must sign.
   - **Amendments** must be sent within **6 months** after receipt of the outcome of the application.
   - **Delivery Address for amendments:** Research Office, Faculty of Health Sciences, Phillip Tobias Building, Third Floor, Corner York Road and 29 Princess of Wales Terrace.
4. **Office hours:** 08h30-16h30.

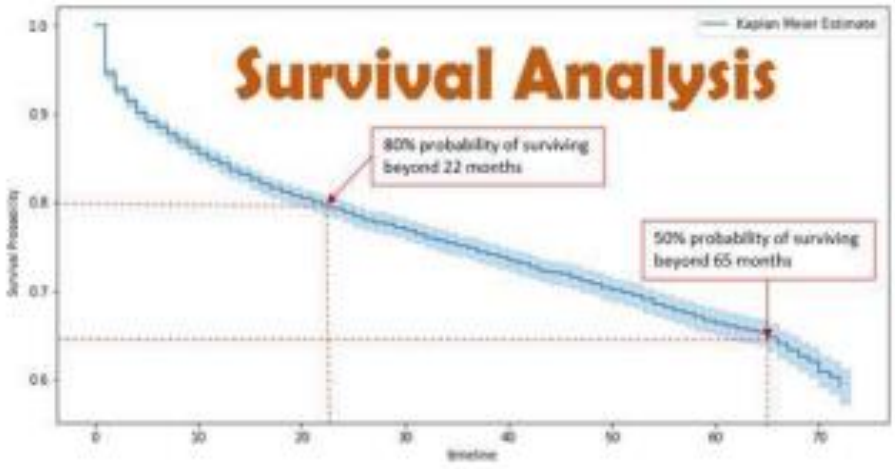
Appendix L

Example of raw data – list of identifiers

Patient no.	Age	Gender	Site of metastases	Therapy type	Adverse effects	Deceased	Living	Recurrence (days)
X	45	F	Liver	Mono	Diarrhoea	0	1	Y

Example of charts which will be used in data analysis

Kaplan-Meier Method



Appendix O

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PROTOCOL ASSESSORS MEETING

Candidate Full Name: . Leanda Grobler. . . . . .

Student Number: . 1439996. . . . . Date: . . 14/07/2021. . . . . .

School / Department / Division: School of Therapeutic Sciences / Department of Pharmacy and Pharmacology. . . . . .

1. **Type of study** *(tick all that apply)*:

✓ Quantitative
○ Qualitative
○ Mixed Methods
○ Laboratory
○ Clinical
○ Other, please specify. . . . . .

2. **Is title of the study appropriate** *(preferably fewer than 20 words)*? Yes ✓ No

Comments: Refer to the comments sheet attached herewith.

3. **Are the study objectives clear and linked to the research aim and title?** Yes ✓ No

Comments: Refer to the comments sheet attached herewith.

4. **Is the design of the study appropriate to meet the study objectives?** Yes ✓ No

Comments: Refer to the comments sheet attached herewith.

11 March 2019/MP

1

5. **Are the proposed methods and tools appropriate to meet the research objectives?** Yes ☑ No

Comments: Refer to the comments sheet attached herewith.

6. **Is the study feasible within the resources of:**

a) The applicant? Yes ☑ No

b) The department? Yes ☑ No

c) The time frame? Yes ☑ No

7. **If this is a PhD protocol assessment:**

a) Is the content original? Yes No

b) Does the content show the scope and depth of a PhD? Yes No

Comments:

Do you recommend:

i. Additional revision/amendment of the protocol? Please be specific on the recommendations being made:

Refer to the comments sheet attached herewith.

ii. The appointment of the proposed Supervisor? Yes ☑ No

Nominee/s:

11 March 2019/MP

5. **Are the proposed methods and tools appropriate to meet the research objectives?** Yes ☑ No

Comments: Refer to the comments sheet attached herewith.

6. **Is the study feasible within the resources of:**

a) The applicant? Yes ☑ No

b) The department? Yes ☑ No

c) The time frame? Yes ☑ No

7. **If this is a PhD protocol assessment:**

a) Is the content original? Yes No

b) Does the content show the scope and depth of a PhD? Yes No

Comments:

Do you recommend:

i. Additional revision/amendment of the protocol? Please be specific on the recommendations being made:

Refer to the comments sheet attached herewith.

ii. The appointment of the proposed Supervisor? Yes ☑ No

Nominee/s:

11 March 2019/MP

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Appendix P

Wits University
Donald Gordon
Medical Centre

MEDICLINIC

Date: 11th November 2021

Attention:

The Chairperson

Human Research Ethics Committee (Medical), FHS, University of the Witwatersrand

Re: Protocol Ref No: M211025

Protocol Title: Recurrence rate in stage IV breast cancer patients on abemaciclib: a retrospective cohort study.

Principal Investigator: Leanda Grobler

In fulfillment of the degree: MSc. in Medicine (Pharmaceutical Affairs)

I hereby grant permission to Ms Leanda Grobler, in fulfillment of the requirements for her MSc degree for her to conduct her clinical research at WDGMC.

Please be aware that no data collection will commence until an amended Clearance Certificate that approves WDGMC as a study site has been obtained from the Wits Human Research Ethics Committee (Medical).

Please submit the final HREC approval to Dr June Fabian (june.fabian@mweb.co.za) from WDGMC Research.

Yours faithfully,

Dr Sue Tager
CEO
Wits Donald Gordon Medical Centre
Tel: (+27) 011 356 6302; Mobile: 082 457 7134
Email: sue.tager@mediclinic.co.za

Wits University Donald Gordon Medical Centre (Proprietary) Limited
Upper level, St Joseph Wing, 21 Eton Road, Parktown, Johannesburg, 2193, South Africa
P O Box 2072, Houghton, 2041, South Africa. Tel +27 11 356 6303 Fax +27 11 356 6333
www.dgmc.co.za

Appendix R

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG | HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Office of the Deputy Vice-Chancellor Research & Post Graduate Affairs

MEMORANDUM
(This memo is not a clearance certificate)

TO: **Miss Leanda Grobler**
Department of Pharmacy
E-mail: Leandag@witsoncology.co.za

FROM: **Mr Rhulani Mkansi**
Administrative Officer: Human Research Ethics Committee (Medical)
Tel: 011 717-1234/2656/2700
E-mail: Rhulani.Mkansi@wits.ac.za or HREC-Medical.ResearchOffice@wits.ac.za

DATE: 01 February 2022

REF: *R14/49*

PROTOCOL NO: M220113 *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

The protocol below was considered at a virtual meeting of the Human Research Ethics Committee (Medical) **on Friday 28 January 2022.** The Committee requires the following amendments/corrections/information from you before your application can be approved.

Project Title: Recurrence rate in stage IV breast cancer patients on abemaciclib: a retrospective cohort study

Conditions: **Decision Deferred:**
(This memo is not a clearance certificate, no research should commence prior to obtaining a clearance certificate)

- Provide post graduate assessor group approval.
- *Application Form:*
  - Patients have not provided permission as stated in HREC (Medical) application form to use their data for research – only for medical and billing purposes – and those who have not died must still be patients at the practice. The PGA group also requested clarification about consent form.
    - Confirm if patients have signed a TARA type consent form (generic) at Wits Donald Gordon Medical Centre. Please provide template.
  - Section 6.4 states that the start date for the research is 16 December 2021 and completion date 26 January 2022 so the applicant may have already done the study and must advise HREC (Medical).
  - The oncologist has signed the HREC application form Section 8.9.
- *Data Collection Sheet:*
  - Dates on initiation and progression are identifiers, and in the notes to address the PGA comments and the protocol, these dates are listed as variables.
    - Remove identifiers on data collection sheet.
- **Supervisors** (their contact details not provided on HREC form section 2) should meet Chair of HREC (Medical) to discuss the research and amendments before proceeding. Please email the Chair and arrange a meeting: Clement.Penny@wits.ac.za

NB:

Appendix U

PARTICIPANT CONSENT SHEET

Recurrence rate in stage IV breast cancer patients on abemaciclib: a retrospective cohort study

By signing this document, I confirm that;

1. I have been given a Participant Information Sheet which explains the nature and processes involved in this study, which is attached hereto;
2. I was given time to read it in the language I best understand;
3. I was given time to ask any questions I wanted to and found any answers given to me to be reasonable and satisfactory;
4. I believe I fully understand why the study is being conducted and what the intended outcomes will be;
5. I understand that there will be no immediate benefit to me, should I agree to participate, nor will I receive any payment; conversely, participation will not cost me anything but my time;
6. I understand that, even if I initially consent to take part in the study, I may subsequently withdraw at any time and would not be required to give any reasons; if that happened, any data collected about me for the purposes of the study would immediately be destroyed, unless I give consent for it to be retained
7. I have been given a range of contact details, listed below. If I require further information or become concerned about any aspect of this study, I am free to speak to any of these contacts.

Contact details:

- Ms. Leanda Grobler, Principal Investigator, telephone no. 067 651 2811, or by e-mail on 1439966@students.wits.ac.za
- Dr. S.D. Moodley, Supervising Physician, telephone no. 011 356 6900, or by e-mail on smsdevanm@gmail.com
- Mrs. Razeeya Khan, Supervisor, on telephone no. 011 717 2552, or by e-mail on razeeya.khan@wits.ac.za
- Dr. Ané Orchard, Supervisor, on telephone no. 011 717 2317, or by e-mail on ané.orchard@wits.ac.za

- Professor CB Penny, Chairperson of the Human Research Ethics Committee (Medical) at the University of Witwatersrand, on telephone no. 011 717 2301, or by e-mail at Clement.Penny@wits.ac.za.
- Ms. Z Ndlovu or Mr Rhulani Mkansi, Committee Secretariat, telephone nos.: 011 717 2700 or 1234, or by e-mail at: Zanele.Ndlovu@wits.ac.za or Rhulani.Mkansi@wits.ac.za

Name of Participant: _____
Date: _____
Place: _____
Signature or mark _____

Witnessed by:
Name of Witness: _____
Signature: _____
Date: _____

L. Grobler April 2022

Appendix V

STUDY INFORMATION DOCUMENT

Study Title: Recurrence rate in stage IV breast cancer patients on abemaciclib: a retrospective cohort study

Greetings

I am conducting research on the survival rate of South African women with stage IV breast cancer who have participated in the compassionate use programme between the 31st of March 2019 and 31st of March 2021. The focus would be on a specific medication named 'abemaciclib.'

Research is a process in which we aim to seek new knowledge. The purpose of this study would be to understand how well this treatment works in treating breast cancer in women before the disease spreads to other organs.

You have been invited to participate in this much needed research study. In doing so, I require your permission to make use of your personal medical records by signing a letter of consent.

How will the study be conducted?

The following clinical data from your patient file will need to be obtained;

- Age
- Gender
- The organs in which your cancer is currently in or has spread to (Site of metastases)
- If you have been prescribed abemaciclib with additional medication or by itself
- The side effects which you may be experiencing from the medication

In order to determine how well the treatment is working, I would need to make use of the following information from your patient file;

- CT Scan/ MRI/ PET/CT Scan/ Mammogram/ Breast ultrasound reports
- Routine blood results including the tumour marker
- Clinical notes from the physician

Risks involved in the study are minimal as you need not complete a questionnaire and are not required to actively participate. Participation is granted at own free will. You will not be compensated for participation and may at any time during the study choose to withdraw your permission for the use of your personal information should you feel uncomfortable. In agreeing to participate in this study, your information will only be made available to your physician and the responsible pharmacist at Wits Donald Gordon Medical Centre.

You will be allocated a unique study number in order to keep your identity hidden. All participant data will be stored digitally in a password-protected document only accessible to myself and your treating physician. If this study is published as a peer-reviewed article, your data will remain stored in a password-protected document for a period of two years or for a period of six years if not published. Thereafter it will be destroyed accordingly. The outcome of this article will be made available to you should you wish to obtain the results.

This research study is also being overseen by professional supervisors from the University of the Witwatersrand. An application for permission to access patient data has been approved by the ethics committee and CEO at Wits Donald Gordon Medical Centre.

This patient information sheet forms part of an application made to the Human Research Ethics Committee which will ensure that no harm will be done to you as a participant and that the results generated from this information will be treated in line with the beneficence, non-maleficence, autonomy, and justice principles.

By participating in this study, you will be adding vital information to an existing body of research on abemaciclib. Additionally, it will provide physicians with data on how well the

medication works on patients within the South African population. By identifying single versus combination use, it will provide information on the most effective method of treating stage IV breast cancer. A series of side effects of this medication may also be identified and may provide physicians with a better understanding of how to treat them.

If you wish to gain further information about the study, you may contact the Principal Investigator Ms. Leanda Grobler on telephone no. 067 651 2611, or by e-mail on 1439966@students.wits.ac.za. Alternatively, you may contact the Supervisors, Mrs. Razeeya Khan on telephone no. 011 717 2552, or by e-mail on razeeya.khan@wits.ac.za or Dr. Ané Orchard on telephone no. 011 717 2317, or by e-mail on ané.orchard@wits.ac.za respectively.

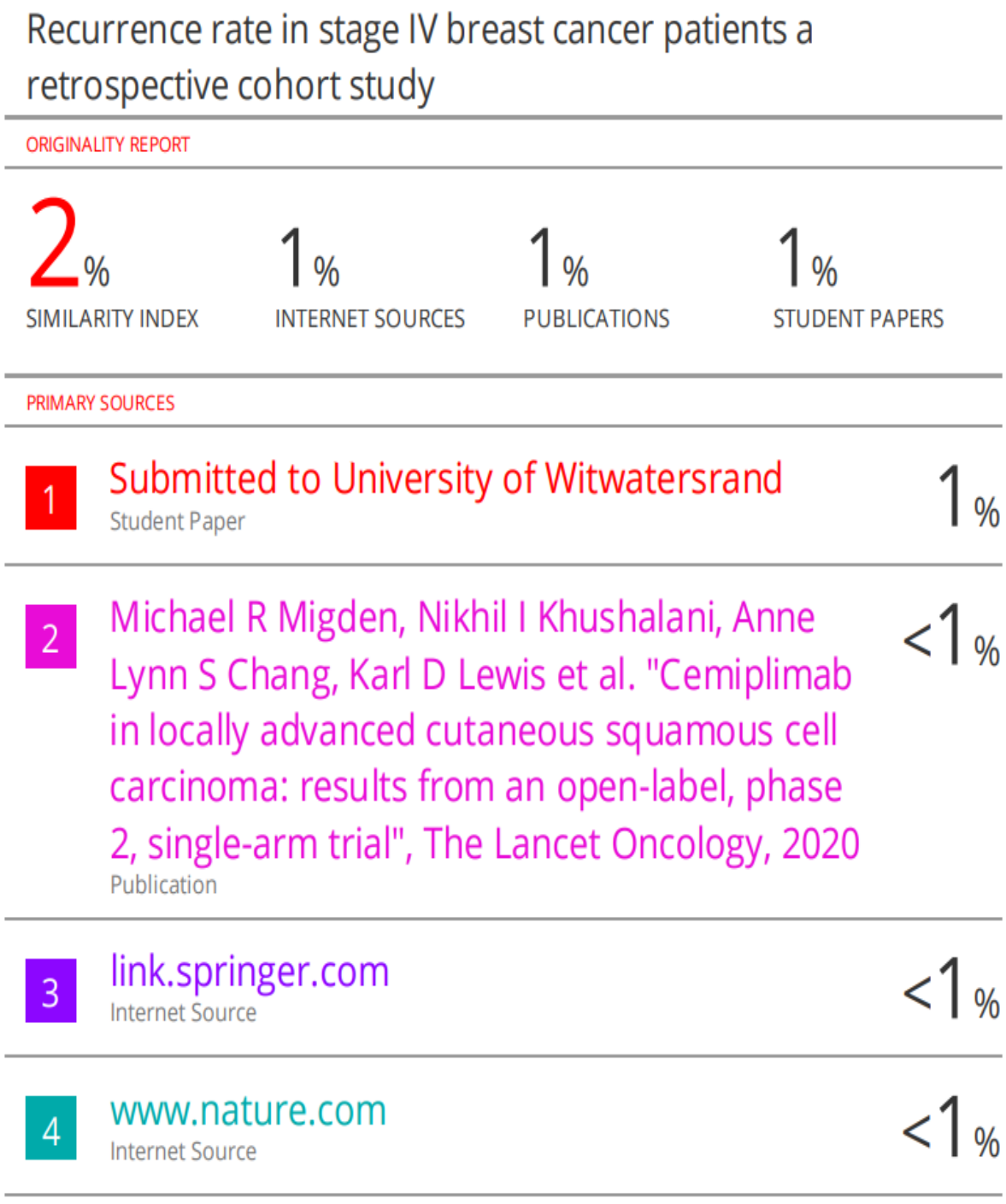
If you have any concerns over the way in which the study is being conducted, please contact the Chairperson of the Human Research Ethics Committee, Professor Clement Penny on telephone no. 011 717 2301, or by e-mail on Clement.Penny@wits.ac.za. The telephone numbers for the Committee secretariat are 011 717 2700/1234 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za

Thank you for reading this Study Information Sheet.

Leanda Grobler
B.SocSc. Hons (Psychology) (UFS) BCMP (UP)
MSc. Med (Pharmaceutical Affairs) (Wits) Candidate
Clinical Associate to Dr. S.D. Moodley
HPCSA 0009490
PN 2300141

April 2022

Appendix F



Recurrence rate in stage IV breast cancer patients a retrospective cohort study

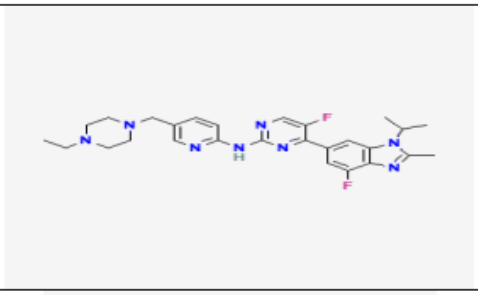
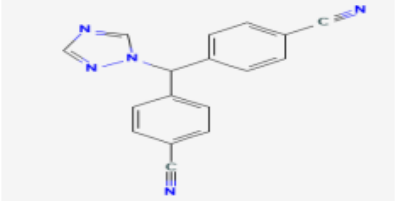
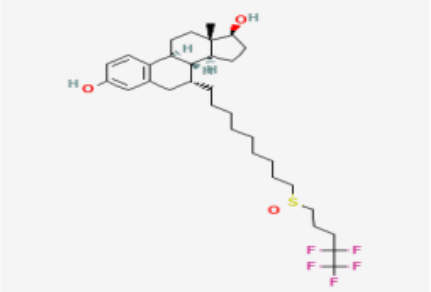
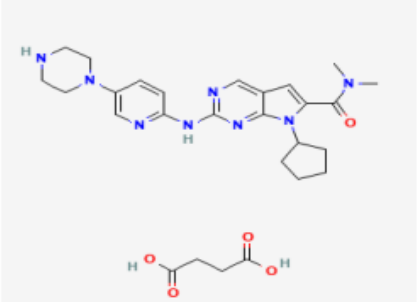
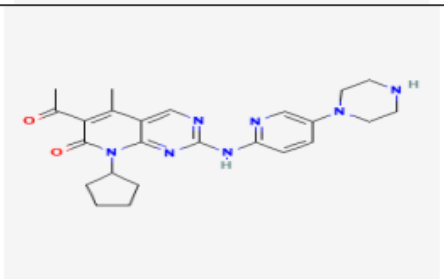
ORIGINALITY REPORT

2%	1%	1%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Submitted to University of Witwatersrand Student Paper	1%
2	Michael R Migden, Nikhil I Khushalani, Anne Lynn S Chang, Karl D Lewis et al. "Cemiplimab in locally advanced cutaneous squamous cell carcinoma: results from an open-label, phase 2, single-arm trial", The Lancet Oncology, 2020 Publication	<1%
3	link.springer.com Internet Source	<1%
4	www.nature.com Internet Source	<1%

Appendix G

Drug name	Chemical structure
Abemaciclib	
Letrozole	
Fulvestrant	
Ribociclib	
Palbociclib	

Appendix H

RECURRENCE RATE IN STAGE IV BREAST CANCER PATIENTS: A RETROSPECTIVE COHORT STUDY

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Abstract

Introduction: Metastatic breast cancer (mBC) remains incurable, with a median overall survival (OS) of approximately three years and a five-year survival rate of approximately 25%, irrespective of the economic classification of the country where treatment is received. Cyclin-dependent kinase (CDK) inhibitors increase overall survival in both first and second-line settings in the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative mBC. This retrospective cohort study investigated the progression-free survival in women with mBC receiving combination therapy with abemaciclib (CDK4/CDK6 inhibitor) and letrozole or fulvestrant as opposed to abemaciclib only.

Methods: The study included all eligible women with stage IV breast cancer treated with abemaciclib at a private oncology facility in Johannesburg over the study period. Data was collected from medical records for the period 01 April 2019 to 31 March 2021. Analyses were carried out to assess the overall survival rate, progression-free survival probability and safety of abemaciclib in women with stage IV breast cancer.

Results: The progression-free survival probability was 60% after a period of 17 months irrespective of treatment options. After 17 months, the OS of women on a combination of abemaciclib and letrozole was 80%, a combination of abemaciclib and fulvestrant was 80%, and abemaciclib monotherapy was 70%. The most noted adverse effects were diarrhoea (92.0%), neutropenia (92.0%), fatigue (48.0%) and hepatotoxicity (16.0%).

Discussion: Abemaciclib with endocrine therapy or an aromatase inhibitor (AI) provided an improvement in the OS compared to abemaciclib monotherapy. These findings are representative of the use of abemaciclib in a local population and are similar to those of larger studies carried out internationally.

1 Introduction

Cancer remains one of the leading causes of death and a barrier to increasing life expectancy world-wide.[1] The burden of cancer incidence and mortality reflects population growth and changes in socioeconomic development.[2] The disease landscape in Africa is also undergoing significant changes, with rising morbidity and mortality due to non-infectious diseases such as cancer.[3] Epidemiological studies from a regional public sector hospital in South Africa indicated that irrespective of the geographical status, the majority of patients with breast cancer consulted late in both rural and peri-urban areas of developing countries.[4] Since the 1980s various treatment options have been explored in an attempt to improve survival in patients with advanced breast cancer (ABC).[5]

International clinical guidelines recommend endocrine therapy (ET) as the first line of therapy for HER2−negative, HR-positive, advanced breast cancer. However, approximately 50% of HR-positive patients develop resistance to ET within their lifetime; ultimately leading to disease recurrence and limited clinical benefit of this therapy.[6] Preclinical models suggest that HR-positive breast cancer cells display biological features that are conducive to the use of targeted therapy with CDK4/6 inhibitors.[7] There are currently two CDK4/6 inhibitors registered for use in South Africa: ribociclib and abemaciclib.

Emerging therapies require the skills of a multidisciplinary team (MDT) to ensure optimum patient care.[8] As the treatment landscape changes in the South African environment, it is important to reflect on the use of these medicines in local cohorts of patients to understand and enhance the contribution of professionals in the MDT. For pharmacists, this includes management of medicine safety and patient education.[9]

This study reports on the progression-free survival in South African women with mBC receiving monotherapy with abemaciclib, combination therapy with abemaciclib and letrozole and combination therapy with abemaciclib and fulvestrant. Analyses were carried out to assess the overall survival rate, progression-free survival probability and safety of abemaciclib in a local cohort of patients, and to compare the findings with those in other studies.

2 Method

2.1 Design and participants

Ethical approval for this study (Ethical Committee clearance certificate number; M220113) was provided by the Human Research Ethics (HREC) Committee of the University of the Witwatersrand, Johannesburg, South Africa on 22 April 2022. A retrospective cohort study was carried out in a private oncology facility in Johannesburg. Data was collected on thirty-two South African women with stage IV breast cancer who were enrolled in a compassionate use programme with abemaciclib during the period 01 April 2019 to 31 March 2021. All patients had HER2-negative and HR-positive stage IV breast cancer with at least 4 or more lines of chemotherapy and endocrine therapy in an early and metastatic setting. Records of patients with adequate Eastern Cooperative Oncology performance status (ECOG) 1, adequate renal, hepatic, and myeloid reserve as well as normal QT corrected for heart rate (QTc) interval on electrocardiogram (ECG) were included.

Both pre/peri-menopausal and postmenopausal women were considered for participation. Women in pre/peri-menopause received 10.8mg of goserelin for at least one month prior to initiation of abemaciclib and continued to take goserelin every three months. Within this group of patients, those on monotherapy each received 200mg of abemaciclib twice daily and those on combination therapy each received 150mg of abemaciclib twice daily.

Each patient attended a follow-up consultation after one month of treatment and continued follow-up consultations on a three-month basis. Abemaciclib use was discontinued in patients who presented with disease progression in line with treatment protocol. Clinical retrospective data were retrieved from medical records including clinical features and radiological imaging. Informed consent for this retrospective analysis was obtained from surviving participants.

2.2 Statistical analysis

The Kaplan-Meier method was used to estimate the median progression-free survival (PFS) and median overall survival (OS) of all participants. Categorical data are prescribed as percentages. All statistical analyses were carried out using the STATISTICA™ Version 13.1 programme (University of Witwatersrand, Johannesburg, 2022).

3 Results

3.1 Baseline characteristics

The first patient was enrolled five months after initiation of the compassionate use programme. The data is representative of all patients enrolled over the remaining 17-month period. Of the 32 patients selected (Figure 1), five patients did not take abemaciclib due to disease progression and two patients absconded. Patients are categorised in three subgroups, (1) those on abemaciclib alone, (2) those on abemaciclib in combination with letrozole (2.5mg) daily, and (3) those on abemaciclib in combination with fulvestrant (250mg) once per month.

3.2 Demographic and clinical features

The median age of all patients was 52.0 (46.0-60.5) years (Table 1). Of the 25 patients on abemaciclib, 10 patients were selected at random for the use of monotherapy and 70% of these patients were post-menopausal. Five patients were selected at random for the use of abemaciclib and letrozole as combination therapy and 60% of these patients were post-menopausal. Ten patients were selected at random for the use of abemaciclib and fulvestrant as combination therapy and 70% of these patients were post-menopausal.

Eight of the patients were pre/peri-menopausal and had been treated with goserelin prior to initiation of abemaciclib and continued to take goserelin throughout the study. Among these women, 32.0% had lung and liver metastases, 32.0% had bone metastases, 16.0% had lung and bone metastases, 16.0% had bone and liver metastases, 8.0% had lung, liver, and bone metastases and 4.0% had bone and mediastinal involvement.

Adverse drug reactions were reported according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 grading scale. Severe (≥ Grade 3) diarrhoea, hepatotoxicity and neutropenia were observed in patients receiving abemaciclib (Table 2). One patient discontinued treatment due to severe diarrhoea and four patients succumbed to the disease during the study.

Patients with diarrhoea were managed with loperamide as needed and discontinuation of abemaciclib for a period of three days followed by re-initiation of abemaciclib. Patients who

presented with a neutrophil count of <2.00 x10g/L were managed with discontinuation of abemaciclib and daily administration of pegfilgrastim daily followed by re-initiation of abemaciclib after seven days.

3.3 Clinical outcomes

A survival analysis is captured in Figure 2. Findings from the remaining sample of 25 patients yielded a progression-free survival (PFS) of all patients at 60% after 17 months. The median probability of recurrence of all patients on abemaciclib during the 17 months was 24%. The median overall survival (OS) of patients on abemaciclib was 70% after 17 months. The median OS of patients on a combination of abemaciclib and letrozole was 80% after 17 months and that of patients on a combination of abemaciclib and fulvestrant was 80% after 17 months.

4 Discussion

In this study patients on abemaciclib alone had a 10% lower chance of survival after 17 months than patients who had received abemaciclib in combination with endocrine therapy agents specifically; letrozole and fulvestrant. Unfortunately the study did not investigate the OS of participants on letrozole or fulvestrant alone, which may have allowed for a more apt comparison. The sample size of women enrolled in the compassionate use programme is small; however, the findings in this South African cohort coincide with those of international studies. The risk of disease recurrence remains below the 50th percentile after a period of 17 months. Caution should be taken when comparing the median PFS with international studies as a multivariate analysis could not be performed.

In terms of toxicity profile, diarrhoea and neutropenia were managed with minimal hospitalisations. Although four patient deaths were documented in patients with existing liver metastases, the cause of death could not be confirmed as liver failure due to abemaciclib use. It would be beneficial to investigate the number of patients with liver metastases requiring dose reductions of abemaciclib. In larger international studies no known cases of clinically apparent liver injury attributed to abemaciclib have been reported.[10] As abemaciclib is a substrate for Cytochrome P450 3A4 (CYP 3A4), it is susceptible to drug-drug interactions with agents that inhibit or induce this specific hepatic microsomal activity.[10]

Critical review of medical records would be required to identify whether any of the four patients had any pre-existing comorbidities for which they were taking treatment. There are minimal published articles that discuss abemaciclib toxicity within the South Africa context. The most reliable guideline available is that of the European Medicines Agency (EMA) which recommends that patients with (Child Pugh C) hepatic impairment should decrease dosing frequency of abemaciclib to once daily.[11] Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) should be monitored prior to the start of abemaciclib therapy, at every two weeks for the first two months and monthly for the next two months.[11] The use of abemaciclib should be discontinued if the elevation in AST and/or ALT is > 3 x Upper Limit of Normal (ULN) with a total bilirubin of > 2 x ULN, in the absence of cholestasis or in the case of Grade 4 (> 20.0 x ULN) hepatotoxicity.[11] According to the European Society of Medical Oncology (ESMO) guidelines, it is important for the physician to recognise the difference between visceral disease and a visceral crisis. In the presence of a visceral crisis, the presence of metastases is not as important as the consideration of organ compromise which should guide clinical management and decision making.[12]

Human Epidermal Growth Factor 2 (HER2)-negative, HR-positive breast cancer incidences among South African ethnic groups are widely underreported. In this study, the majority of the patients were of white ethnicity (table 1); however, it needs to be considered that this study was conducted in a private oncology facility in an urban area. In order to assess a true reflection of ethnicity on CDK4/6 inhibitor therapeutic potential, a meta-analysis conducted on a larger population of South African women would be beneficial. Cost of treatment is a major barrier to the inclusion of abemaciclib as a treatment option within the breast cancer policy framework in the public sector in South Africa.[13] The scarcity of affordability data is one of the major barriers in the development of effective pricing policy in low-middle income countries.[14]

In conclusion, this analysis indicates that patients who were eligible for the compassionate-use programme received beneficial treatment with minimal risk while on monotherapy or combination therapy with abemaciclib for mBC. The findings of this study provide focus for the management of patients receiving abemaciclib by the MDT. Education and early screening

within rural areas of South Africa remains the most effective method in prevention of late/end stage disease. Continued research and the testing of novel abemaciclib-based combinations could create opportunities for reduction in cost and accessibility for South African women with mBC. Furthermore, there is scope for further research into the use of abemaciclib in addition to endocrine therapy as opposed to endocrine therapy alone for both first and second-line settings.

Acknowledgments

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Conflicts of interest: None

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List of Figures

Table 1. Demographic and clinical features of stage IV breast cancer patients on abemaciclib	
Characteristic	**Patients (N=25)**
Median age (interquartile range), years	52.0 (46.0-60.5)
Ethnic groups (%)	
White ethnicity	10 (40.0)
Black ethnicity	7 (28.0)
Coloured ethnicity	4 (16.0)
Indian ethnicity	4 (16.0)
Number of patients on goserelin	
Pre/peri-menopausal	8
Postmenopausal (%)	
Monotherapy	7 (70.0)
Letrozole	3 (60.0)
Fulvestrant	7 (70.0)
Site of metastases (%)	
Lung and liver	8 (32.0)
Bone metastases	8 (32.0)
Lung and bone metastases	4 (16.0)

Bone and liver metastases	4 (16.0)
Lung, liver and bone metastases	2 (8.0)
Bone and mediastinal involvement	1 (4.0)

Table 2. Severe adverse effects in patients undergoing treatment with abemaciclib (N=25)			
Adverse Effect	**All Grades (%)**	**< Grade 3 (%)**	**≥ Grade 3 (%)**
Gastrointestinal Disorders			
Diarrhoea	92.0	60.0	32.0
Vomiting	4.0	4.0	0
Abdominal Pain	4.0	4.0	0
Hepatotoxicity	16.0	0	16.0
Upper Respiratory Disorders			
Sinusitis	4.0	4.0	0
General Disorders			
Fatigue	48.0	48.0	0
Blood and Lymphatic Disorders			
Neutropenia	92.0	80.0	12.0

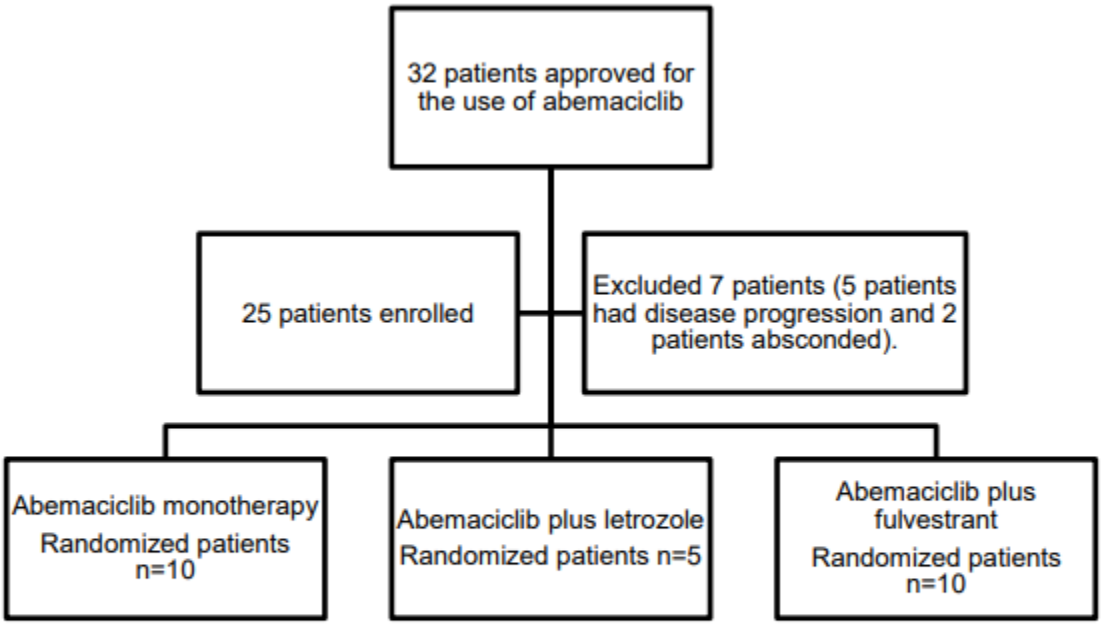

Figure 1. Subgroups of patients enrolled in the compassionate programme

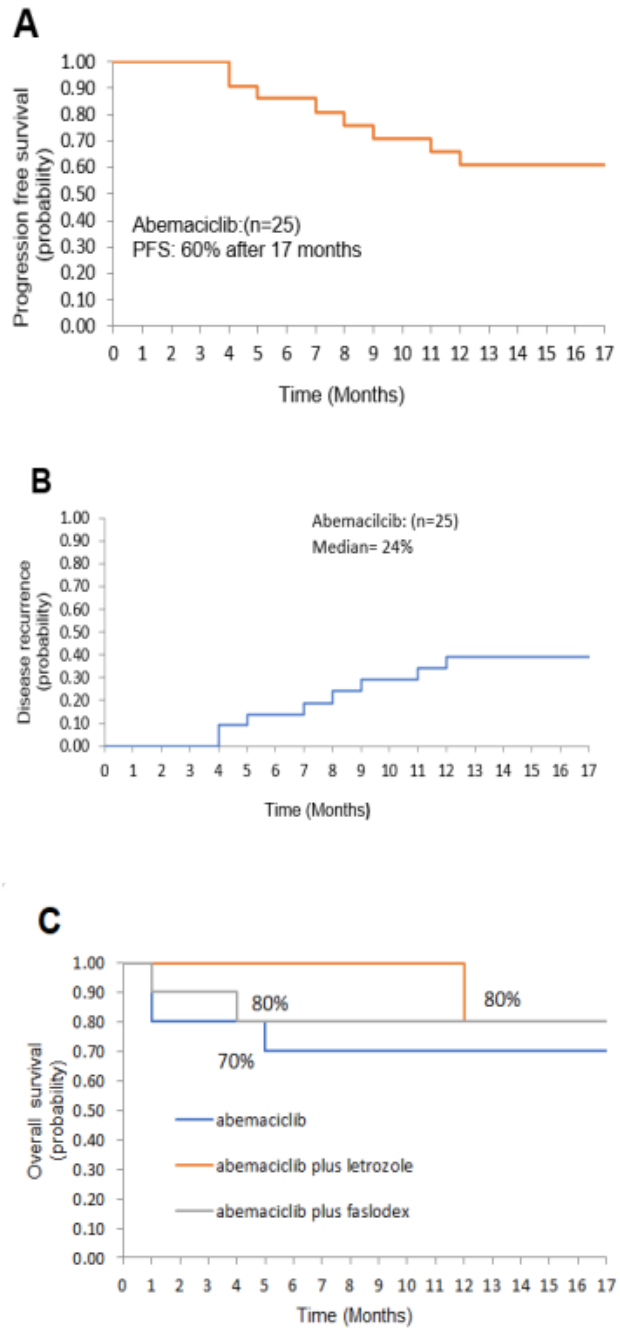

Figure 2. Survival analysis captured as Kaplan-Meier curves. (A) Kaplan-Meier plot of PFS for all patients on abemaciclib. (B) Kaplan-Meier plot of median probability of disease recurrence for all patients on abemaciclib. (C) Kaplan-Meier plot of OS for patients on abemaciclib versus abemaciclib plus letrozole versus abemaciclib plus fulvestrant.