"SMALL MOLECULES IN TREATMENT OF BREAST CANCER"

A PROJECT SUBMITTED TO

NIRMA UNIVERSITY

In partial fulfillment of the requirements for the degree of

Bachelor of Pharmacy

BY

PATEL DHAIRYA V. (16BPH015)

Semester VIII

UNDER THE GUIDANCE OF

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MAY 2020

CERTIFICATE

This is to certify that ***"SMALL MOLECULES IN TREATMENT OF BREAST CANCER"*** *is the bonafide work carried out by* ***PATEL DHAIRYA*** *(16BPH015), B.Pharm semester VIII under our guidance and supervision in the Institute of Pharmacy, Nirma University, Ahmedabad during the academic year 2016-2020. This work is up to my satisfaction.*

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CERTIFICATE OF SIMILARITY OF WORK

This is to undertake that the B.Pharm. Project work entitled ***"SMALL MOLECULES IN TREATMENT OF BREAST CANCER"*** *Submitted by* ***PATEL DHAIRYA*** *(16BPH015), B.Pharm. Semester VIII is a bonafide review/research work carried out by me at the Institute of Pharmacy, Nirma University under the guidance of Dr. Mayur M. Patel & Ms. Palak K. Parikh. I am aware about the rules and regulations of Plagiarism policy of Nirma University, Ahmedabad. According to that, the review work carried out by me is not reported anywhere as per best of my Knowledge.*

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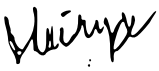
DECLARATION

*I, **PATEL DHAIRYA (16BPH015)),** student of VIIIth Semester of B.Pharm at Institute of Pharmacy, Nirma University, hereby declare that my project entitled **"SMALL MOLECULES IN TREATMENT OF BREAST CANCER"** is a result of culmination of my sincere efforts. I declare that the submitted project is done solely by me and to the best of my knowledge, no such work is done by any other person for the award of degree or diploma or for any other means. I also declare that all the information was collected from various primary sources (journals, patents, etc.) has been duly acknowledged in this project report.*



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ACKNOWLEDGEMENTS

The success of the project depends on the contribution and support of many people whom I would like to appreciate for their support during the entire working of this project.

I owe my deepest gratitude to my guide, **Dr. Mayur M. Patel** (Associate Professor, Department of Pharmaceutics, Institute of Pharmacy, Nirma University) & co-guide, **Ms. Palak K. Parikh** (Assistant Professor, Department of Pharmaceutical Chemistry, Nirma University) for their continuous support & support and guidance as well as providing valuable inputs for this thesis.

I owe my deepest gratitude to our Director, **Dr. Manjunath D. Ghate** and all faculty members of Institute of Pharmacy, Nirma University for providing world class facilities for education and research.

Regards,

Dhairya V. Patel
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Abstract

Breast cancer is the second highest prevalent disease and is considered to be among the highly prominent world's leading causes of death. While it has been prevalent since centuries, its treatment has been tedious and unreliable until the later years. Its forms of diagnosis include surgeries, radiation therapy and chemotherapy. Chemotherapy includes treatment by various small molecules along with various immunological products such as antibodies. These agents can target the tumor region specifically to provide effective treatment of cancer. Recently, there has been a rise in the development of various small molecules in treatment of BC. The USFDA has approved a number of such small molecules for its treatment. This includes various kinase inhibitors, antimetabolites, endocrine therapy, hormonal therapy etc. Plenty clinical trials are being conducted to determine the efficacy of such small molecules as well as their combination therapies in various breast cancer subtypes. The following review discusses all the approved small molecules for treatment of BC, the clinical trial findings of them and their resistance.

1. Introduction

Cancer consists of a group of diseases in which normal cells tend to divide incessantly and develop into tumors which may or may not spread into the surrounding tissues and systems [1]. The WHO has stated that cancer has been found to be the 2nd leading reason of deaths around the globe which numbered 9.6 million in 2018. It has also stated that about one in six deaths occurs due to cancer or complications which arise due to it [2]. Of all the types of cancers, breast cancer constitutes the second highest number of new cases. In 2018 about 2,088,849 cases of BC were diagnosed which is 11.6% of total diagnosed cancers. Breast cancer has also led to 626,679 deaths worldwide, which accounts for 6.6% of deaths caused by cancer & is the 2nd highest reason for demise in women [3]. It has been estimated that about 4,571,210 women will be diagnosed with BC in the US in 2026 [4].

While breast cancer has been prevalent since 3500 BC, only in the recent few decades, owing to the advancements made in science and technology, there has been an upsurge

in research and studies related to breast cancer leading to the availability of detailed information, insight and knowledge about it. Numerous risk factors which may lead to breast cancer have been identified. In addition, effective prognostic tools and methods have also been devised which can detect breast cancer in its earliest stages, enabling efficient and early treatment and management which can improve survival chances. A significant rise has also been observed in the development of potential treatment options and therapies of various breast cancer subtypes [5].

It is classified either based on size of tumor, effect on nodes and metastasis or based on prognosis [6]. Tumor biopsies have also revealed the presence of various biomarkers such as ER (Estrogen receptors), PR (Progesterone receptors) & HER2 (Human epidermal growth factor receptor 2) which are responsible for tumor progression & metastasis [7]. The choice of optimal route of treatment as well as the chemotherapeutic agent is based on the type of disease that patient has. Its treatment is done mainly by surgery, radiation therapy or chemotherapy. For nonmetastatic tumors, surgery is generally employed follow by radiation therapy following the removal of tumor. Chemotherapy is employed for metastatic tumors along with adjuvant or neoadjuvant therapy with surgery or irradiating certain parts of the breast. All these treatments are prone to recurrence of cancer [8], [9].

While the advances in treatment options and managing breast cancer have increased by leaps and bounds, so too has the cancer itself. It has been frequently observed to metastasize into surrounding tissues, including but not limited to the bone, liver, brain, blood etc. which severely decreases the survival rate of the patient and makes treatment more difficult [10]. Additionally, these metastasized tumors have been observed to evade conventional therapies which have proved efficacious in its treatment by following alternative pathways hence leading to resistance to the currently used agents [5], [11]. TNBC (Triple negative BC) has been detected in various patients. It consists of decreased expression of all 3 aforementioned receptors and is thus, more difficult to treat than those breast cancers which show a positive expression of those aforementioned biomarkers [7].

All these complications associated with breast cancer highlight the need to develop targeted therapeutic agents and formulations targeting specific type of condition for its

management & treatment. Currently, US FDA has approved 70 different formulations which are used for treating various types of breast cancers. Out of these 70 formulations, 11 formulations consist of monoclonal antibodies while the rest are small molecules and chemotherapeutic agents [12]. The two most widely used chemotherapies include HER2 therapy and endocrine therapy. The former treatment includes mainly the usage monoclonal antibodies, namely trastuzumab and pertuzumab while the latter utilizes anti-estrogenic molecules [13]. Recent findings have discovered other molecular pathways, the inhibition of which can help in treating of breast cancer. It consists of, among others, the mammalian target of rapamycin (mTOR), cyclin dependent kinase 4 and 6 (CDK4 and CDK6), Poly ADP-Ribose polymerase (PARP) to name a few [13], [14].

With a wide number of small molecules available for treating breast cancer and its complications, the following thesis aims to discuss all those chemotherapeutic agents which have been granted an approval by USFDA in treatment and management of the disease as well as provide a general outline on the mechanisms of those molecules, their development, various clinical trials that have been conducted, combination therapies and comparing different formulations for their efficacy in treating the disease with hopes that it will assist in developing novel treatment options including novel molecules for treating the disease [15].

2. Cyclin dependent kinase 4/6 (CDK 4/6) inhibitors

CDK 4 & CDK 6 are responsible for progressing the cell cycle which ultimately leads to cell division. They form a complex with cyclin D which further goes downstream, onward and causes the phosphorylation of retinoblastoma protein which is responsible for suppressing various tumor suppressor proteins in the cell. The ability of CDK 4 and CDK 6 to contribute to cell division as well as suppress the tumor suppressant genes makes them a primary driving force behind the development of cancer [16]. In cancer cells, these CDK 4/6 kinases become hyperactive which leads to uncontrollable cell growth and tumor formation. This has made their inhibition a prime target in order to suppress tumor growth. Currently, the FDA has approved 3 CDK 4/6 inhibitors in treatment of BC, as discussed below [17].

Palbociclib, chemically consisting of pyridopyrimidine structure, is developed by Pfizer, acts as a CDK 4/6 inhibitor. It has shown to have a synergistic effect with anti-estrogenic agents used in treating breast cancer. It was the 1st such inhibitor which was granted approval for treatment of BC by the FDA in 2015 wherein it was granted a special kind of early approval followed by a regular approval based on phase III studies later on. In order to assess its effectiveness with letrozole and to equate it with the letrozole monotherapy regimen, a Phase II study, called PALOMAI, was performed on those whom had not yet diagnosed of ER and HER2, has done so. Half the patients were given palbociclib + letrozole while the rest patients administered with only letrozole. PFS of upto 20.2 months was observed in group which received both palbociclib and letrozole while a PFR of only 10.2 months was seen in the other group which received letrozole alone (Hazard ratio = 0.488) [18]. For another clinical experiment, which combined with the previous Phase II clinical test, the findings derived from the PALOMA I test were further improved. In the PALOMA II trial, 666 patients were divided into a 2/1 ratio. The former group administered with palbociclib + letrozole and latter with placebo + letrozole. All patients were postmenopausal women and had ER+ and HER2- BC and had not undergone any previous chemotherapeutic treatment. The results obtained were tremendous wherein the group which received palbociclib along with letrozole was found to have mPFS of 2 years on comparison with those who received a placebo + letrozole who had mPFS of 1 year and 2.5 months (HR = 0.58) [19]. A study, termed as PALOMA3, was done in about which 500 people who had previously been on endocrine therapy with HR+ and HER2- BC were divided in two arms in a 2/1 ratio, one of which was given palbociclib plus fulvestrant, while the other group received a placebo and fulvestrant. It was observed that those receiving both therapies demonstrated a longer mPFS of up to 6 months more than those receiving a placebo and fulvestrant alone. However, it was observed that palbociclib led to high occurrence of neutropenia (62%) & leukopenia (25.2%) in some patients [20]. The ability of palbociclib in treating and managing BC and increasing the PFS up on administration with other endocrine therapies led to its approval by the US FDA. As of now, palbociclib has been approved as a 1st line therapy for of metastatic BC including HR+ and HER2+ BCs. It has been used in conjunction with both fulvestrant and letrozole [21].

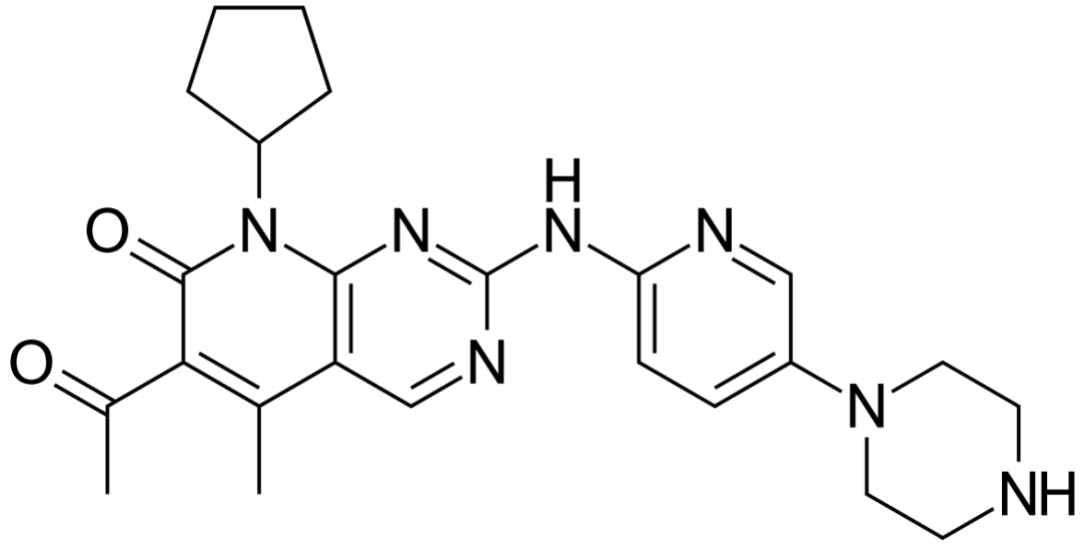

Figure 1 Palbociclib

The second CDK 4/6 inhibitor to be approved for use in treating various BCs is ribociclib, an orally bioavailable CDK 4/6 inhibitor, which is developed by Novartis. Dose of ribociclib and letrozole in postmenopausal women was correlated with that of letrozole alone in randomised phase III clinical trials for ER+ and HER2- BC. Patients were historically not treated for metastatic disease. The findings were indicative that both ribociclib and letrozole showed a higher PFS than letrozole by itself. In this study, 668 postmenopausal women meeting the above-mentioned criteria were assigned randomly to either ribociclib and letrozole as opposed to placebo + letrozole is to be offered. It was found that the PFR was 63% in the group receiving combination therapy while it PFR in the group receiving letrozole was found to be 42.2% (Hazard ratio = 0.56) [22]. Another phase III study called MONALEESA-3 was conducted to test the combination of ribociclib plus fulvestrant in treating HR+ and HER2- BC. In a random ratio of 2:1 were allocated a total of 726 patients. 484 people got fulvestrant + ribociclib while the others got fulvestrant + placebo. In the earlier study, the mean PFS was 20.5 months while in the later, with a HR of 0.577, it was 12.8 months. Response rate of patients to the therapy was also higher in the group receiving ribociclib plus fulvestrant of 40.9% while it was 28.7% for patients who received a placebo and fulvestrant. However, the major adverse reaction observed the same as that observed with palbociclib, however, it caused neutropenia in 46.6% people [23]. It has currently USFDA approval in treating HR+ and HER2- BC in conjunction with an aromatase inhibitor [21].

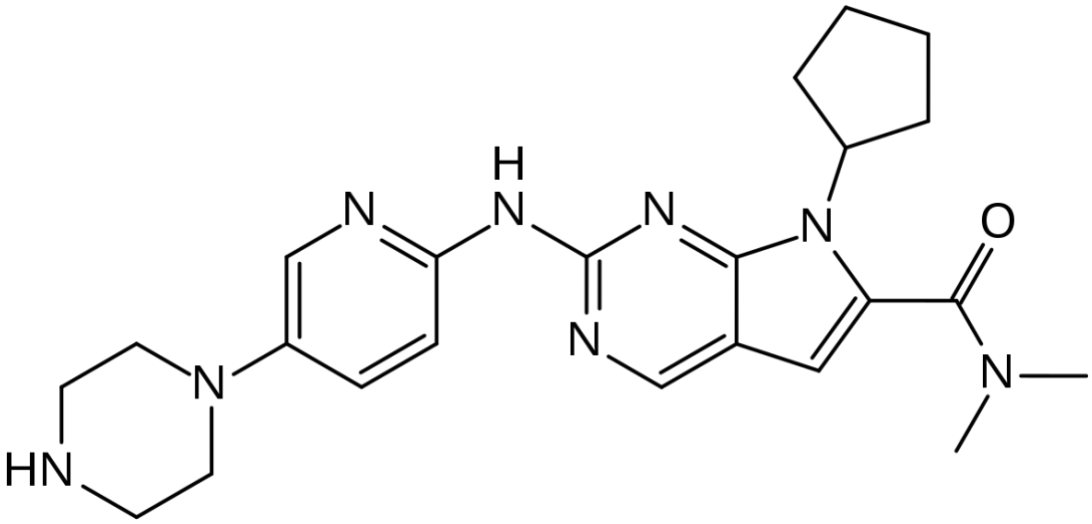

Figure 2 Ribociclib

The third and final CDK 4/6 inhibitor is abemaciclib. It is orally active and is developed by Eli Lilly and is currently the only CDK 4/6 inhibitor with an approval for use in MBC as a monotherapy. Three studies termed MONARCH have been performed to assess efficacy of abemaciclib as a singular agent and simultaneously with other agents. A phase II study termed MONARCH I tested the safety and the objective response rate of abemaciclib as singular drug in treating HR+ and HER2- BC. 132 individuals were offered abemaciclib as a monotherapy in a total of 132 patients that had HR+ and HER2- MBC with previously endocrine-based care. The results found that abemaciclib garnered a response of 19.7% and a median PFS of half a year and its safety profile was found to be in line with previously conducted studies [24]. In order to assess the efficacy of abemaciclib + fulvestrant for HR+ and HER2- metastatic BC, phase III study called MONARCH 2 had been performed. 669 patients underwent prior at most one endocrine therapeutic agent and had observed progression of disease were divided in a ratio of 2:1 with the former group being given abemaciclib plus fulvestrant with better results of a mPFS of 1.3 years as opposed to the latter group of patients who were given a placebo plus letrozole and showed a mPFS of 0.775 years (HR = 0.554) [25]. Subsequent phase III study, MONARCH III was performed in order to assess performance of abemaciclib along with a NSAI. This study was conducted on 493 people without prior therapy for ABC. 328 patients were given abemaciclib along with either anastrozole or letrozole and 165 patients were given a placebo along with anastrozole or letrozole. The results indicated that the median PFS increased significantly those receiving abemaciclib as opposed to the other group of patients. The mPFS was not arrived at in patients of

former arm while the patients of the latter group showed a mPFS of 1.225 years (HR = 0.54). However, as with other CDK 4/6 inhibitors, abemaciclib led to side effects such as neutropenia, diarrhea and leukopenia [26]. Currently, abemaciclib has been approved for treating BC either as a monotherapy or in conjunction with other aromatase inhibitors [15].

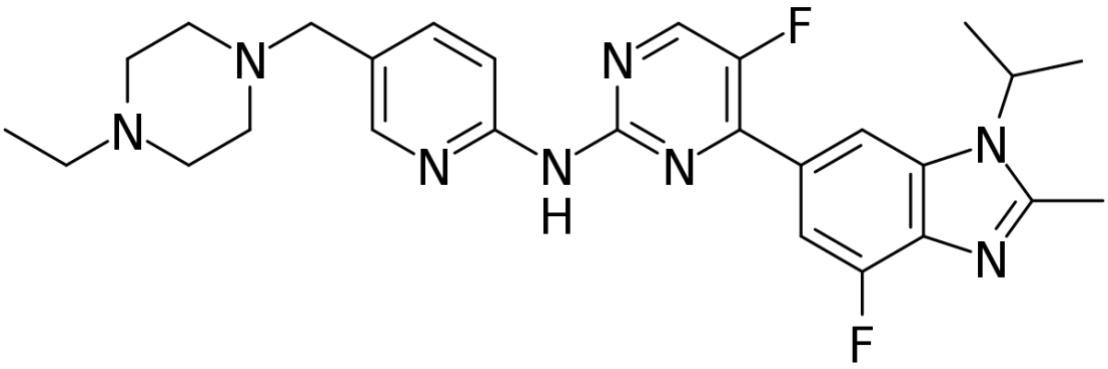

Figure 3 Abemaciclib

3. Inhibitors of the PI3k/Akt/mTOR pathway

Extensive research has reported that this pathway plays a major role in the pathogenesis of tumor formation & proliferation. Activation of PI3k leads to phosphorylation of Akt, hence causing its activation. Activation of Akt can also occur by several other kinases. After Akt is phosphorylated, it is capable of activating mTOR either directly or indirectly by its other downstream kinases. Tumors occurring in breast cancer are known to be associated with several different aberrations in this pathway. The most common of those aberrations are mutations in PIK3 and Akt. Uncontrolled activation of this pathway leads to uncontrolled cell division, hence tumor formation and proliferation. Currently, the FDA has approved two inhibitors which act on this pathway. They are everolimus which is an inhibitor of mTOR and alpelisib which inhibits PI3k [27].

Everolimus, developed by Abbott, is currently the only mTOR inhibitor which has been granted an approval by the USFDA in treatment of HR+ BC. In combination with Exemestane, the influence of everolimus is evaluated in phase III study called as BOLERO 2. 724 patients having HR+ BC and who had undergone prior therapy with anastrozole or letrozole were selected and were divided into a 2:1 ratio. 485 patients

were given everolimus + exemestane while the rest were given a placebo plus exemestane. This study found that the mPFS was 0.883 years in the patients who were given both drugs while PFS of those who received a placebo and exemestane was found to be 4.1 months. It proved that combination of exemestane with aromatase inhibitors significantly improved the PFS of patients having HR positive BC. this resulted in the approval of everolimus plus exemestane in treating HR+ BC [28].

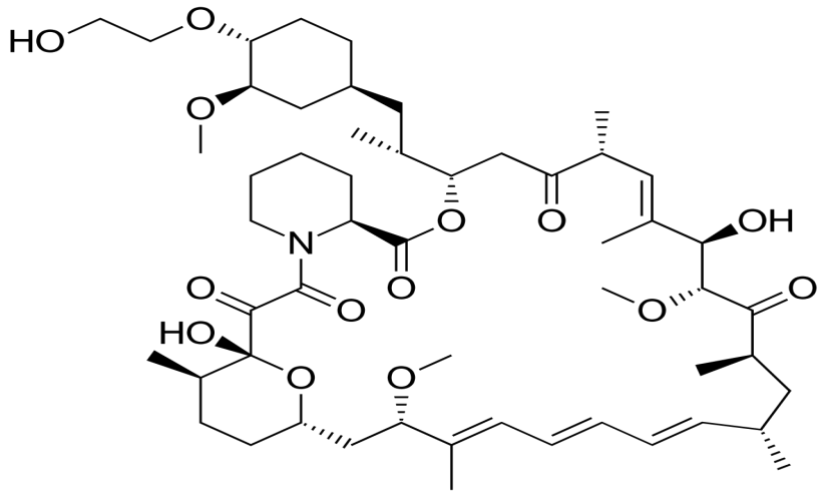

Figure 4 Everolimus

The only PI3 K inhibitor that has been licensed for BC treatment is Alpelisib, developed by Novartis. The authorisation was granted in accordance with fulvestrant based on findings of phase III clinical study named SOLAR 1, which measured alpelisib safety and effectiveness. In this analysis, 572 patients were randomly allocated either alpelisib or fulvestrant and placebo. This was presented on HR+ and HER2- BC patients. In the alpelisib arm, the median PFS was observed at 11 months while in the other, it was observed at 5.7 months. However, several side effects were also observed due to alpelisib which included hyperglycemia, diarrhea and rash [29].

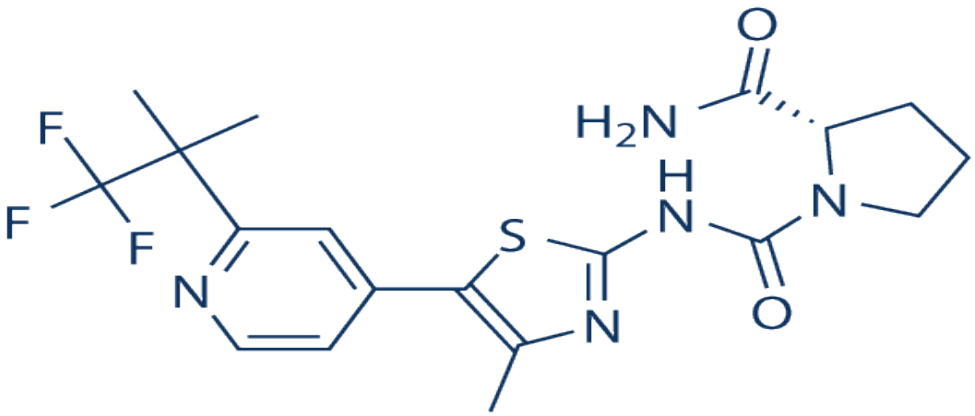

Figure 5 Alpelisib

4. Poly(ADP-ribose) polymerase (PARP) inhibitors:

PARP (Poly ADP ribose polymerase) is an enzyme present in cells which is responsible for repairing of broken DNA strands. Mainly, it is known to repair single strand breaks (SSBs). These broken DNA strands when undergo replication lead to formation of double strand breaks (DSBs). The proteins responsible for fixing double strand breaks in the cell are BRCA1 and BRCA2. Cells which are deficient in these proteins or those cells in which DNA replication and protein synthesis is hindered due to excess amount of double strand breakages, ultimately undergo apoptosis. PARP inhibitors act to inhibit the action of PARP which leads to an increase in single strand breaks, combining PARP irreversibly to DNA strand, ultimately causing cell apoptosis, preferably of cancer cells which undergo rapid proliferation as compared to normal cells. Since BRCA1 and BRCA2 are often mutated in cases of breast cancer, they are unable to fix the resultant double strand breakages which have been induced by a PARP inhibitor. This eventually leads to death of the cells, causing a decrease in tumor growth [30]. Presently, the US FDA has approved two PARP inhibitors for treating and managing of breast cancer, namely olaparib and talazoparib [1].

Olaparib was developed by AstraZeneca and is the 1st PARP inhibitor which has been accepted for treating advanced BC. Its acceptance was granted due to findings of OlympiAD clinical study. In this phase III trial, patients having HR+ and HER2-

metastatic BC were selected. 205 patients were given olaparib as a monotherapy while 97 were given either capecitabine, eribulin mesylate or vinorelbine. It was found that PFS in the patients who received olaparib was 7 months as compared to those who received other chemotherapeutic agents in whom PFS was found to be 4.2 months (HR = 0.58). The occurrence of adverse effects was also comparatively lower in the group which received olaparib [31].

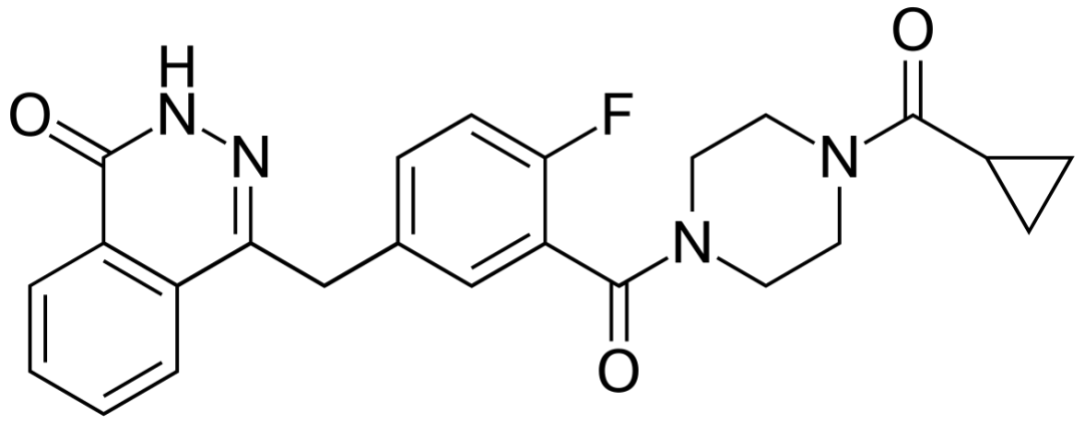

Figure 6 Olaparib

Talazoparib is the second PARP inhibitor to be granted an approval for use in BC by FDA. It was developed by Pfizer. A phase II trial, ABRAZO was performed to analyze and determine its the activity in patients having advanced BC and had BRCA1 or BRCA2 mutation and was conducted on two different groups. The first group of patients included those who were sensitive to platinum treatment while the second cohort consisted of patients who had received at least 3 chemotherapeutic non-platinum agents. All patients were given talazoparib and the observed response rate was assessed. The ORR was found to be 21% in the first cohort and 37% in the second cohort. Common adverse effects observed included anemia, fatigue and nausea [32]. The findings of the above trial wherein talazoparib demonstrated sufficient antitumor activity paved way for a phase III study named EMBRACA, which was conducted wherein talazoparib's efficacy was compared with several other chemotherapeutic agents. Patients having a local or metastatic disease and who had BRCA1 or BRCA2 and had received not more than three drug regimens beforehand were selected. 287 patients were given talazoparib while 144 patients received other agents. Median PFS of the patients receiving talazoparib and other agents was found to be 8.6 months and

5.6 months respectively with patients showing a significantly higher response rate of 62.6% to talazoparib as compared to that of other therapies wherein ORR was found to be 27.2% [33]. Based on the results of EMBRACA study, talazoparib was granted approval in treating patients having advanced BC with BRCA1/2 aberrations [1].

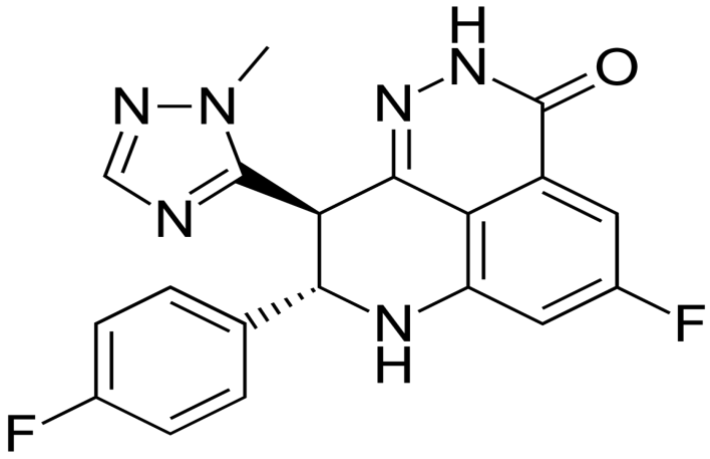

Figure 7 Talazoparib

A number of other PARP inhibitors are still being investigated in a number of clinical trials for treating of various types of BCs. One such chemotherapeutic agent is veliparib which has been approved for use in treating BRCA positive ovarian cancers. Its efficacy in treating TNBC is being determined by numerous studies. ISPY2 study aimed to determine effectiveness of veliparib alongwith carboplatin in patient population having TNBC. The findings of this study indicated that this combination of drugs showed a higher rate of response, almost double than that observed in the control group (51% vs 26%) [34]. Another study aimed to compare this drug alongwith temozolomide or carboplatin-paclitaxel therapies in BRCA+ population. Median PFS of 1.183 vs 1 year was observed in the arm which was given veliparib and a placebo alongwith carboplatin-paclitaxel respectively while that of the arm receiving temozolomide + veliparib as found to be merely 7.2 months. A phase 3 BrighTNess study was performed to assess activities of veliparib and carboplatin versus that of the latter's monotherapy wherein all patients received paclitaxel alongwith the randomly assigned drug regimen in patients with TNBC. However, the findings reported that the arm who received carboplatin + paclitaxel showed similar improvements as the arm that receivined both those drugs plus veliparib, although, that group reported more adverse effects owing to carboplatin such as neutropenia and anemia [35]. Another such inhibitor is rucaparib which has also been approved for treating BRCA+ ovarian cancers. Its safety &

effectiveness was assessed in a phase 2 trial wherein patients with advanced breast & ovarian cancer were selected, wherein it was found to stabilise the disease for as long as 52 weeks [36]. In another study aimed to determine its dosing when administered alongwith carboplatin, the findings suggested that rucaparib can be safely combined with carboplatin however neutropenia and thrombocytopenia were observed in some patients [37]. Another study compared effectiveness of rucaparib with cisplatin wherein it was found that the DFS of 2 years was slightly greater in the rucaparib + cisplatin arm as compared to the cisplatin arm (63.1% vs. 58.3% respectively) [38]. Another drug, niraparib, was found to have good tolerability and activity in treating TNBC patients as reported by the findings of TOPACIO study [39]. A phase 2 trial conducted on advanced or TNBC patients reported that neraparib when given with pembrolizumab for metastatic TNBC was highly efficacious and demonstrated good ORR in 21% of study population alongwith good disease control rate (DCR = 49%). Some other agents, namely 2X-121 and CEP-9722 are currently undergoing various clinical trials with different interventions in addition to those agents mentioned above [40]. These newer PARP inhibitors have the potential to be a lucrative treatment option for TNBC owing to their efficaciousness and lesser occurrence of side effects as compared to other agents used for treating the same [38].

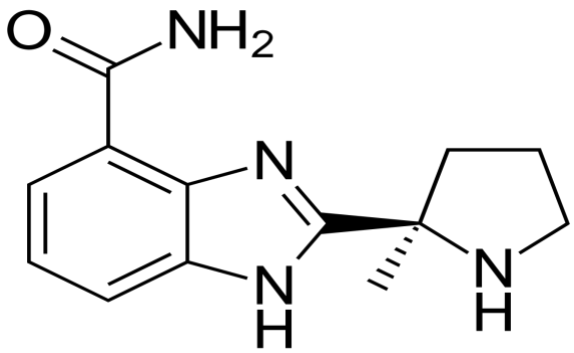

Figure 8 Veliparib

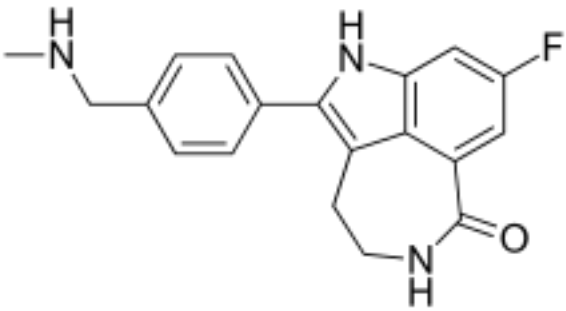

Figure 9 Rucaparib

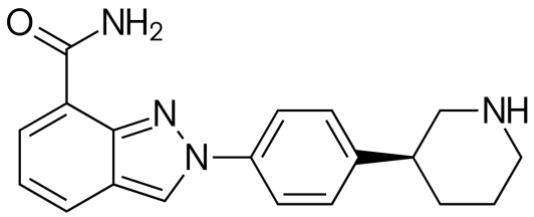

Figure 10 Niraparib

5. EGFR (Human epidermal growth factor receptor) inhibitors

The human EGFR group consists of 4 receptor tyrosine kinases namely HER1-4. Their activation leads to formation of various downstream molecules which are then accountable for cell growth and development and providing resistance to cell apoptosis. About 30% of overexpression of HER1 and HER2 is observed in breast cancer cells making them a target of prime importance in battling HER positive breast cancers. Treatment of such type of cancer is done mainly by using various antibodies such as trastuzumab. However, the FDA has also approved two small molecules namely lapatinib and neratinib for treatment of HER+ BCs [41].

Lapatinib is one such compound developed by Novartis. It acts on HER1 and HER2 domains of the EGFR kinase by reversibly binding to it hence preventing its phosphorylation which prevents its activation, hence blocking cell proliferation, leading to suppression of tumor growth [42]. Numerous clinical studies have been performed on lapatinib in conjunction to different anti-BC agents. LANDSCAPE, a stage II clinical trial evaluated the safety of lapatinib with capecitabine. It found that the most observed side effect was diarrhea in 20% of the population while the 49% of people had grade 3 or 4 toxic effects. It bolstered the safety profile of lapatinib [43]. Another phase III study conducted on 291 patients demonstrated that a treatment consisting of both lapatinib with trastuzumab as compared to monotherapy by lapatinib alone. A major 4.5-month PFS was observed in the patients who had MBC. who had been previously treated heavily by other drug regimens [44]. NeoALTTO, a phase III study was done to assess effectiveness of lapatinib and trastuzumab versus trastuzumab and lapatinib monotherapies. It concluded that the patients who received a combination of both the above mentioned formulations that the combination therapy improve

progression free survival by up to 78% as compared to the other two therapies [45]. A separate phase III study contrasted lapatinib with paclitaxel vs a placebo and latter drug in patients with MBC. It demonstrated that patients with HER2+ BC showed significant benefits from the combination regimen while those with HER2- did not [46]. Another study evaluated potency of letrozole and lapatinib in treating hormone receptor positive MBC patients. A mPFS of 0.683 years was seen in patients who were given both lapatinib and letrozole which was significantly greater than that seen in those who were given letrozole alone, which was of 3 months [47]. Another phase II study also reported that lapatinib is useful in treating patients who have HER2+ BC and in those whom the tumors have metastasized to the brain and that combining capecitabine along with letrozole showed better responses in treating said tumors [48]. However, numerous studies have shown that for treating patients with HER+ BCs, using trastuzumab instead of lapatinib has proven to be more efficacious when combined with other chemotherapeutic agents [49], [50].

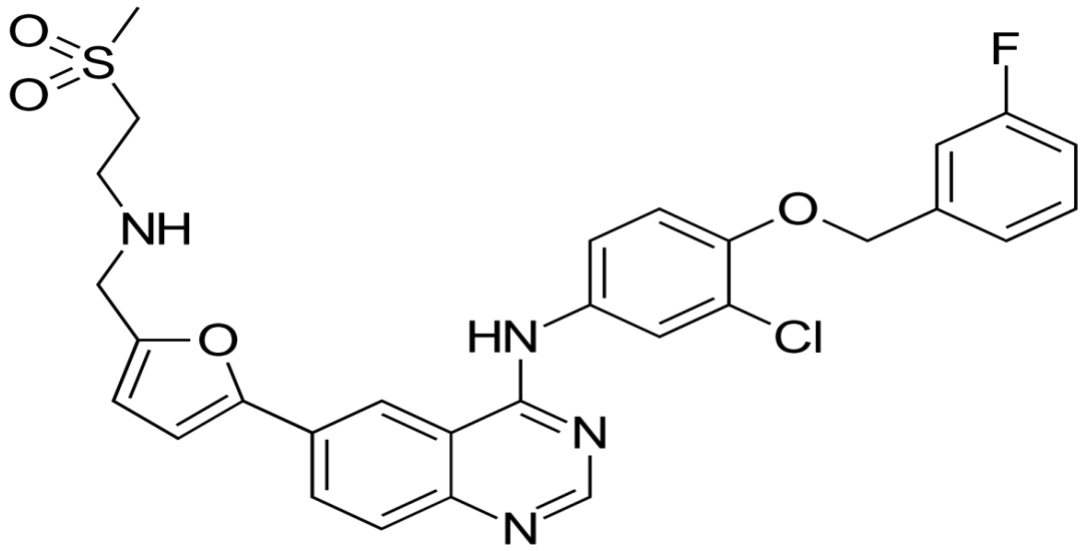

Figure 11 Lapatinib

Neratinib is the second TRK (tyrosine receptor kinase) inhibitor which has been granted an approval for use in BC by the FDA. A phase II trial evaluated its safety along with vinorelbine in HER2+ BC. It found that the most common side effect was diarrhea (96%) followed by neutropenia (57%) while also showing prominent antitumor activity [51]. Another phase II study was done to know its toxicity and effectiveness along with trastuzumab in people having HER2+ advanced stage BC who had received prior therapy with the latter agent. It showed that combination of both drugs significantly

improved PFS [52]. In another randomized, phase III study done on those having HER2+ BC in any stage and who had undergone prior treatment by trastuzumab. Half of them received neratinib as a monotherapy while the other half received a placebo. The DFS was 93.9% in those who received neratinib while it was 91.6% in the other group. The most common adverse effects found were similar to those observed with lapatinib, i.e. diarrhea and neutropenia [52].

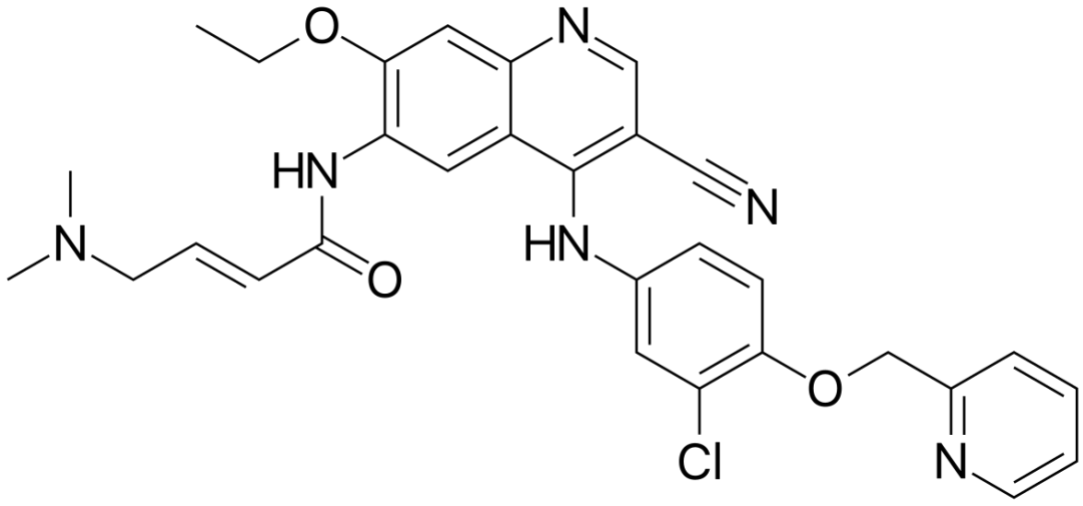

Figure 12 Neratinib

6. Aromatase inhibitors

These are used in treating HR+ BC. These tumors need estrogen to proliferate. Its activity has been linked to bring about transcription of numerous genes as well as proliferation and angiogenesis in BC These agents block the formation of estrogens by blocking action of aromatase enzyme which is necessary for converting androgens to estrogens. This creates a deficit in estrogen levels in the blood causing tan inhibition in tumor growth which has been shown to be estrogen receptor positive. As of now, the 3rd gen. of these compounds has been approved for use in treating of HR+ BCs. These are anastrozole, letrozole and exemestane. Anastrozole and letrozole are non-steroidal triazole derivatives while exemestane is a steroid scaffold containing molecule [15].

A randomized control trial termed IBIS-II studied the effect of anastrozole for long term breast cancer prevention. 1920 women were given anastrozole for 5 years while 1944 women were given a placebo for the same time period. A 49% reduction in BC

with a HR of 0.51 was observed in the patients who received anastrozole. However, it did not have a significant effect on the deaths that occurred due to breast cancer [53]. A study conducted on patients having invasive BC was done in order to determine and compare the efficacies of anastrozole and exemestane wherein it was found that the PFS was better in those who received anastrozole versus those who were given exemestane [54]. A randomized phase III TanDEM study concluded that anastrozole when given with trastuzumab led to an improvement in PFS by up to 100% when compared with treatment by anastrozole alone in patients who were diagnosed with HR+ BC [55].

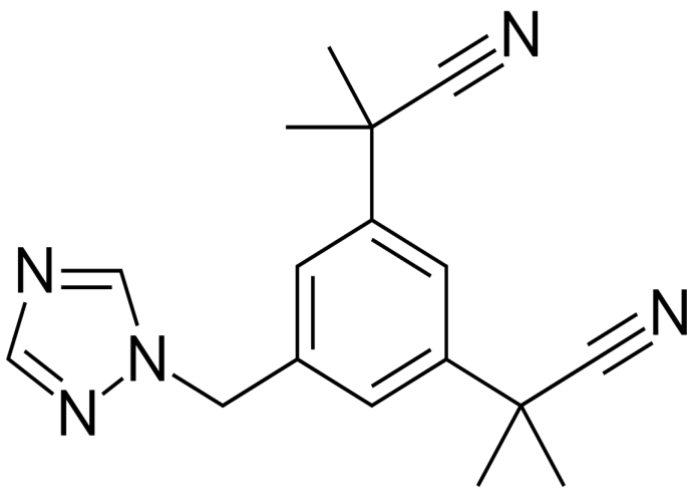

Figure 13 Anastrozole

Letrozole is the second non steroidal triazole containing aromatase inhibitor used in treating hormone positive breast cancers. Letrozole has been proven to have a tremendously better DFS as well as a better overall survival in those with breast cancer after being treated with tamoxifen as compared to a placebo based on findings of a clinical study [56]. In a phase III, double blind trial which was performed on those with HR+ BC showed that a better reduction of recurrence of cancer and mortality was observed when they were given letrozole as compared to tamoxifen and as compared to combination of both letrozole and tamoxifen, thus signifying treatment of hormone receptor positive cancers based on monotherapy of letrozole [57].

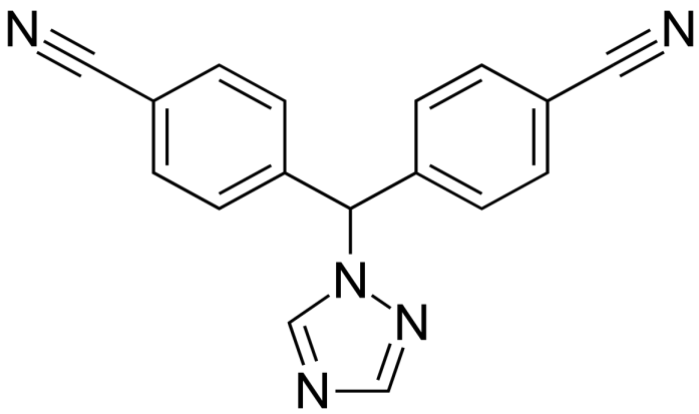

Figure 14 Letrozole

Exemestane is the only steroidal aromatase inhibitor employed in treatment of BC with FDA approval. A study conducted on disease free patients after 3 years following tamoxifen therapy are selected. 423 patients were given exemestane while 507 patients were given tamoxifen. Mortality was lesser in exemestane arm than that of the other (352 vs. 450 deaths). Hence, it concluded that exemestane is more beneficial than tamoxifen in preventing disease relapse [58]. Exemestane was also tested in a related trial to avoid BC in postmenopausal people. 4560 people got either exemestane or placebo on the random basis. It was found that the annual incidence of BC was significantly lower in those patients who were given exemestane in contrast to who were not (0.35% vs. 0.77%). It was found to decrease the occurrence of BC in women at moderate risk with no significant adverse effects on health in postmenopausal women [59]. However, a separate study reported that exemestane is responsible for loss of bone density in postmenopausal women inspite of Ca and Vit. D supplementation [60]. Resistance to this therapy has been observed in some patients. Its resistance is attributed to its weak estrogen like activity which can lead to cell proliferation. Intermittent treatment with exemestane in breast cancer patients has showed that it may help decrease resistance [61].

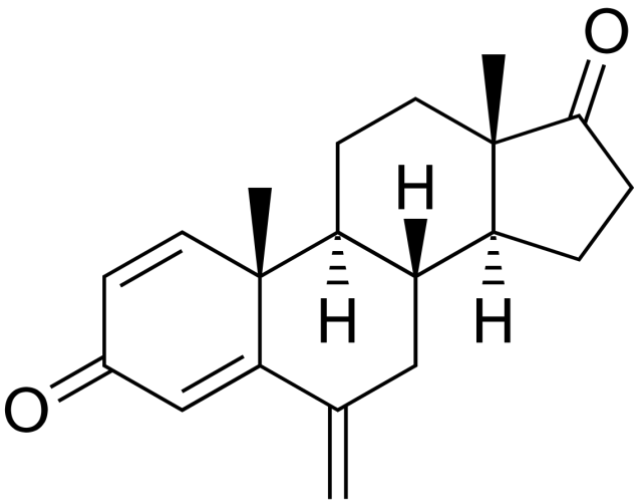

Figure 15 Exemestane

7. Estrogen Receptor Antagonist

Tamoxifen is a SERM (selective estrogen receptor modulator) that binds to estrogenic receptors in cancer cells. This is extremely useful in patients having HR+ BC as it can have effects such as inhibiting tumor growth by blocking cell proliferation and blocking gene formation by the same pathway as discussed previously. Tamoxifen has been approved as a 1st line for HR+ BC and MBC. However, resistance to tamoxifen has been observed, its exact cause and mechanism are not yet clearly understood. However, it is believed that it occurs mainly due to loss of estrogen receptor activity in patients or conformational alterations in the receptor which prevent binding of tamoxifen to the receptor. It may also be brought up by an increase in the beta isoform of the receptor than the alpha form which reduces tamoxifen levels in the cell [15]. ATLAS was a randomized trial conducted on women having ER+ BC in which 12894 women who have had previous half a decade of tamoxifen dosage regimen were divided equally in two groups, one of which was continued with tamoxifen for subsequent period of 5 years while the other group was not. It was observed that the women who were allocated to take tamoxifen showed a lesser recurrence of the disease as compared to those who did not. However, it had no effect on patients who had ER- BC [62]. A separate study conducted to evaluate the same results demonstrated that taking tamoxifen for half a decade reduced potential of BC reoccurrence for up to 15 years as well as reduced risk for cardiovascular disease and death [63]. Tamoxifen continues being used extensively

in treatment of BC owing to its minimal side effects and high efficacy to target estrogen receptor positive breast cancers [15].

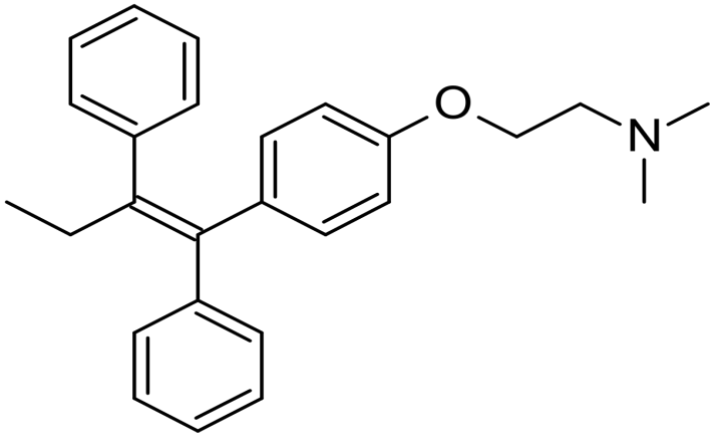

Figure 16 Tamoxifen

Another selective estrogen receptor downregulator is fulvestrant which is an analog of 7α-alkyl sulfinyl 17β-estradiol. It causes complete blockage of ER without any estrogenic properties, as compared to tamoxifen which shows some estrogen effects. Additionally, it has a higher affinity for the estrogen receptor as compared to tamoxifen. The binding of fulvestrant to the estrogen receptor causes a conformational transition, leading to a degradation of the receptor and ultimately its disintegration into individual units of proteins forming an inactive substance that prevents encoding of estrogen receptor genes downstream. This becomes damaged and contributes to the irreversible loss of the estrogen receptor gene, which eliminates estrogen based signaling completely. A clinical trial termed FALCON evaluated the strength of fulvestrant vs. anastrozole in HR+ BC patients or those patients having metastatic disease. Patients were randomized and were allocated to obtain either of the drugs as a monotherapy. It was observed that PFS was vastly superior in the fulvestrant arm as opposed by the anastrozole arm (1.383 years vs. 1.15 years). However, arthralgia was manifested in 37% of the patients who were given fulvestrant. Despite it, the higher efficacy of fulvestrant to treat HR+ BC or MBC far outweighed the occurrence of any adverse effects [64]. Fulvestrant + alpelisib also demonstrated considerable lengthening of PFS in SOLAR-1 trials [29]. MONARCH II trials also demonstrated the efficacy of fulvestrant when used with abemaciclib in treating HR+ and HER2- BC [25]. The MONALEESAIII trials showed an increased PFS in population having HR+ & HER2- BC when treated with a combination of fulvestrant and ribociclib [23]. It has approval

for treating HR+ in conjunction with CDK 4/6 inhibitor viz. abemaciclib and palbociclib. Fulvestrant therapy is also shown to be beneficial when used in combination with a PDK3 inhibiting agent in HR positive disease. Adverse effects observed with fulvestrant are similar to those with tamoxifen, however, fulvestrant shows lesser negative effects on the GIT as well as less prone to cause endometrial cancer [15].

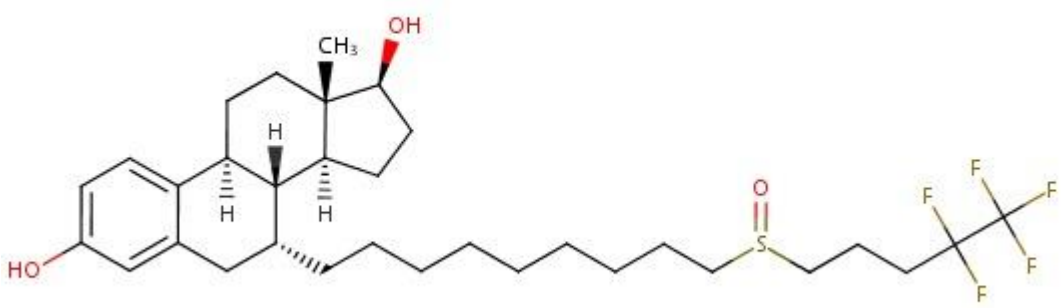

Figure 17 Fulvestrant

8. Dehydrogenase inhibitor

Methotrexate is a small molecule which is every now and again utilized as an antimetabolite and it has been found to have an improved effect when used in conjunction with 5-fluorouracil. It has been utilized to treat a wide assortment of tumors. It is a folate inhibitor since it hinders protein synthesis brought about by DHFR (dihydrofolate reductase), the compound which goes about as an impetus for the transformation of DHF (dihydrofolate) to THF (tetrahydrofolate). This outcomes in a collection of folates that are significant during purine base synthesis which can't proceed to shape a DNA which at in the end, prompts cell apoptosis. A study to determine efficaciousness of methotrexate when used along cyclophosphamide was carried out on patients who had been pretreated severely with other chemotherapeutic agents for MBC with 48 patients tested & mPFS was 0.416 years with an overall survival of 9 months. Some patients developed neutropenia and leukemia however, in such patients, a higher progression free survival was observed, hence making this combination treatment beneficial [65]. Simultaneous radiation and intrathecal

methotrexate for the treatment of leptomeningeal metastasis of strong tumors including breast cancer were carried out in a single-arm test of 59 people. The results indicate that a better quality of life was seen in people receiving intrathecal treatment with methotrexate in combination with radiotherapy and it also showed a vast increase in PFS [66]. Another study revealed a case report in which mitomycin C joined with methotrexate had been fruitful for metastatic breast cancer which, following a dosing of anthracycline, taxane, capecitabine and a few hormonal medications, were safe to eribulin, vinorelbine and bevacizumab chemotherapy with paclitaxel. This case shows that mitomycin C in addition to methotrexate treatment can be successful against metastatic breast cancer in patients, after an extensive and rigorous previous medication regimen [67]. Methotrexate's resistance mechanisms include diminished cell folate take-up or DHFR yield amplification. Common adverse effects of methotrexate include ulceration of the mucous layers, renal inadequacy, neurotoxicity, hypersensitive pneumonitis, meningitis and hepatotoxicity [15].

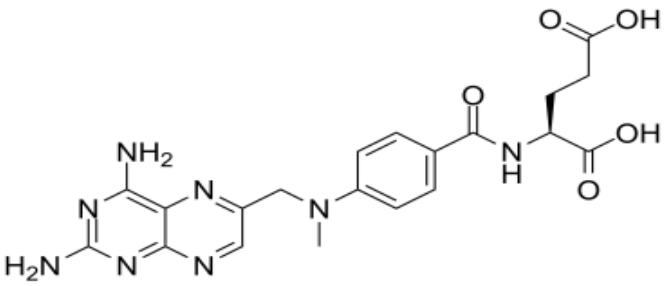

Figure 18 Methotrexate

9. Nucleoside inhibitors

Nucleoside inhibitors are chemotherapeutic agents that interfere with DNA and RNA synthesis by inhibiting their replication and transcription. These agents get converted into 5-fluorouracil up on administration which is a structural analog of uracil, which is required for RNA synthesis. Additionally, 5-fluorouracil also is responsible for inhibiting thymidylate synthase which inhibits formation of folic acid downstream

without which DNA synthesis cannot occur. Currently, two nucleoside inhibitors, namely capecitabine and gemcitabine are approved by USFDA for treatment of BC [15].

Capecitabine is a nucleoside inhibitor and has shown its efficacy in MBC patients and is often used in patients that have diseases that are immune to anthracycline, taxane, or both as second line monotherapy. The activity and tolerability of capecitabine is higher than that of 5-fluorouracil and it also has a lower toxicity profile in comparison. In the CREATE-X clinical trial, capecitabine's efficacy was tested in treating invasive BC on those who have had prior surgery, previously given an anthracycline, taxol or both. Subjects were allocated to be administered capecitabine or a placebo. It was found that PFS improved in those who received capecitabine versus those who did not. Patients with TNBC also favored capecitabine treatment [68]m. In another trial, the performance of capecitabine was compared with docetaxel. HER2- patients and who had been beforehand on anthracycline regimen were selected. The median PFS of 10.5 months was found to be in those who received both docetaxel and capecitabine as compared to those who received only docetaxel who showed that of 9.8 months [69]. VICTOR-2 study was done to demonstrate the effectiveness of both, this agent + vinorelbine. Out of the 80 patients screened, 65% had hormone receptor positive tumors. The combination showed to be highly efficacious in improving the PFS as well as demonstrating a higher response rate in patients [70]. Commonly noted effect with this compound is hand-foot syndrome which was observed in all three of the above clinical trials [15].

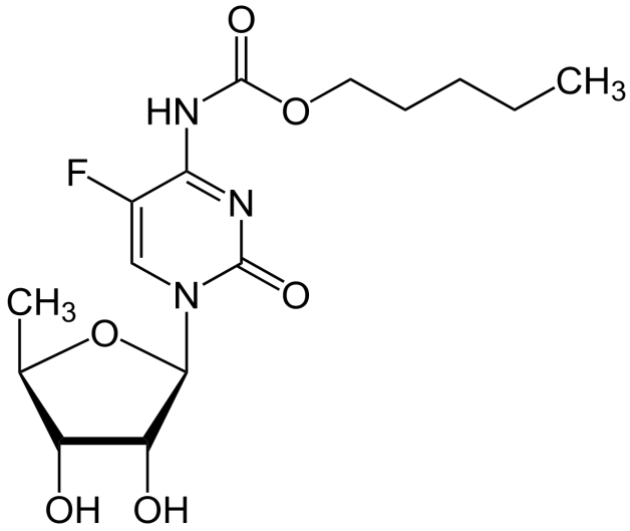

Figure 19 Capecitabine

5-fluorouracil is a fluorinated analog of uracil analog and acts as a thymidylate synthetase inhibitor, which acts as a similar mechanism to capecitabine. A clinical study has shown that the 5-fluorouracil and Na-folate concurrently infused in advanced BC patients is a viable alternative to capecitabine. 5-fluorouracil has a high-dose therapy manually confirmed a desirable profile of toxicity. Increased thymidylate synthetase expression may lead to resistance of both drugs. Cardiotoxicity is also associated with the administration of both medications [13].

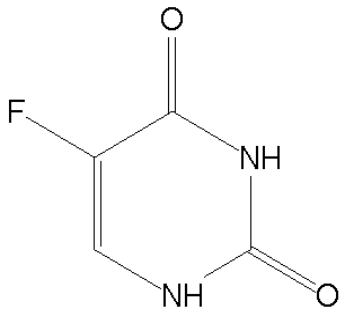

Figure 20 5-fluorouracil

Gemcitabine is a nucleoside deoxycytidine defluorinated analog. This is used for treating a number of cancers, including TNBC in conjunction with other medicines. Gemcitabine is carried into cells by transmembrane proteins of human nucleoside. It has a number of phosphorylation response within the cell before targeting DNA, preventing the chain elongation, deoxynucleotide metabolism from being inhibited and apoptosis from being inducted by the caspase signaling method. Metastatic breast cancer efficacy evaluation of gemcitabine has been evaluated by recent studies. The multicenter phase II trial, one-arm trial, treated patients intravenously with gemcitabine + vinorelbine in population with chronic HER2- BC which had been previously treated by a taxane. In those patients in whom neutropenia manifested as a side effect, this therapy was found to be well tolerated, and the most common toxicity was moderate, transient fatigue [71]. In another clinical trial for treating TNBC patients following a failed treatment with anthracycline and plant derived mitotic agents, evaluated the effectiveness of vinorelbine + cisplatin in contrast to gemcitabine + cisplatin. Most important toxicities include suppression of bone marrow & GIT reactions. In those who were given vinorelbin, lesser occurrence of thrombocytopenia was observed and a high ocurrence was observed relative to gemcitabine arm. In a further review, the potency

of both above drugs was compared with vinorelbine + cisplatin were evaluated in HER2- MBC patients pretreated with anthracyclin and taxane. Researchers concluded that the dosage regimen of vinorelbine + gemcitabine is better than vinorelbine plus cisplatin in first line treatment regimens [72].

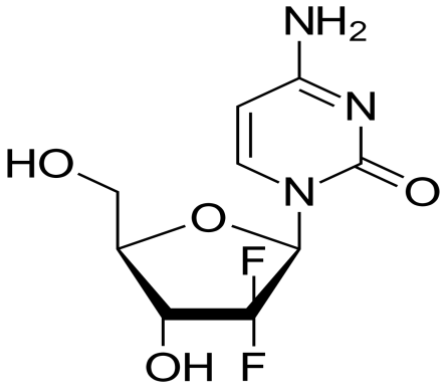

Figure 21 Gemcitabine

10. Topoisomerase II inhibitors

Topoisomerase II is an enzyme responsible for uncoiling and recoiling the DNA chain for replication. As DNA synthesis and replication is a major step in formation of newer cells, its inhibitors can be useful in treating various cancerous tumors in which cell proliferation and hence DNA synthesis occurs frequently. Doxorubicin is one such agent which irreversibly blocks topoisomerase II and thus prevents DNA from recoiling which ultimately leads to cell apoptosis [15].

Doxorubicin is an anthracycline antibiotic that is obtained from the bacteria *Streptomyces peucetius*. This, an inhibitor of topoisomerase II, disrupts DNA synthesis which would be induced by it, as well as produces toxic byproducts destroying cell components and organelles. It is used in numerous cancers, its use is discouraged by cardiotoxic effects. The rise in ceramide glycosylation, which decreases cell-medium-adulterated death via the doxorubicin-ceramide pathway, is a resistance mode of it. Doxorubicin comp-bonded alongwith cyclophosphamide is efficacious fortreatment of MBC, although the above-mentioned cardiovascular toxicity restricts its administration in metastatic breast cancer [15]. Doxorubicin liposomes were prepared for reducing its toxicity. In a phaseII open-label analysis in population having MBC, this formulation was tested with metronomic oral cyclophosphamide. 75% of the subjects showed it to

be beneficiary, including six partial respondents and 15 stable disease patients. In the undesired effects no infections or feverish neutropenia were found in any patient, while uncomplicated myelosuppression was observed in several patients [73].

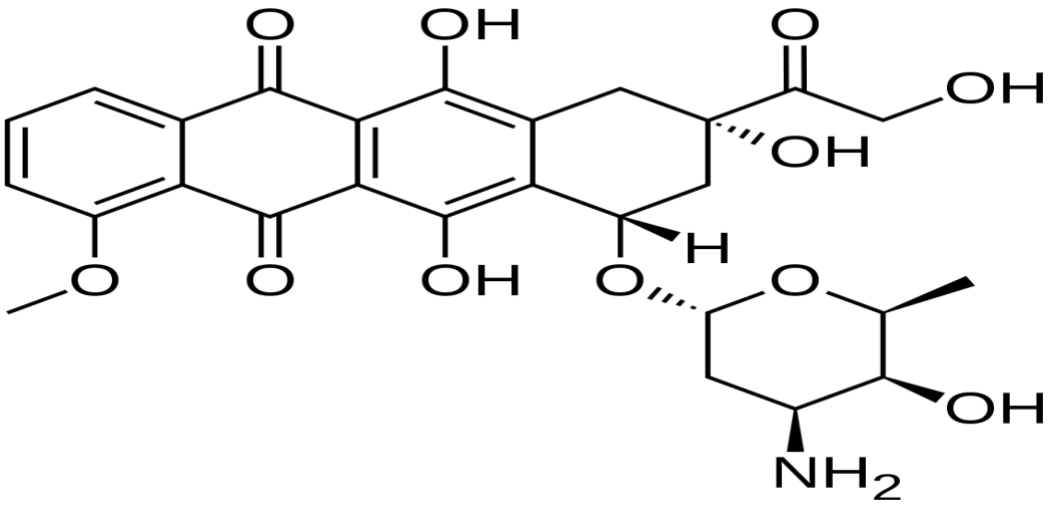

Figure 22 Doxorubicin

11. Anti gonadotropin releasing hormone

GRH controls the formation and release of FSH and LH. These hormones are responsible for promoting secretion of estrogen and progesterone from the ovary, excess levels of which are harmful for patients with HR+ BC. Goserelin is an anti GnRH agent which blocks production of LH and FSH thereby inhibiting production of estrogens and progesterones from the ovary. This makes it a suitable choice of agent for treating HR+ BC patients. However, side effects of goserelin include decrease in bone density. A study conducted on premenopausal women with HR+ BC aimed to evaluate the safety of goserelin + tamoxifen. Their results showed that goserelin induced FSH level decreaseaimed to study drug regimen of goserelin + exemestane in treating patients with MBC. DFS of up to 32 months was observed with a median PFS of 13 months. They concluded that endocrine therapy combining goserelin and exemestane is highly efficacious for treating premenopausal women with HR+ BC or MBC. The most common side effects observed due to goserelin were arthralgia and myalgia [74].

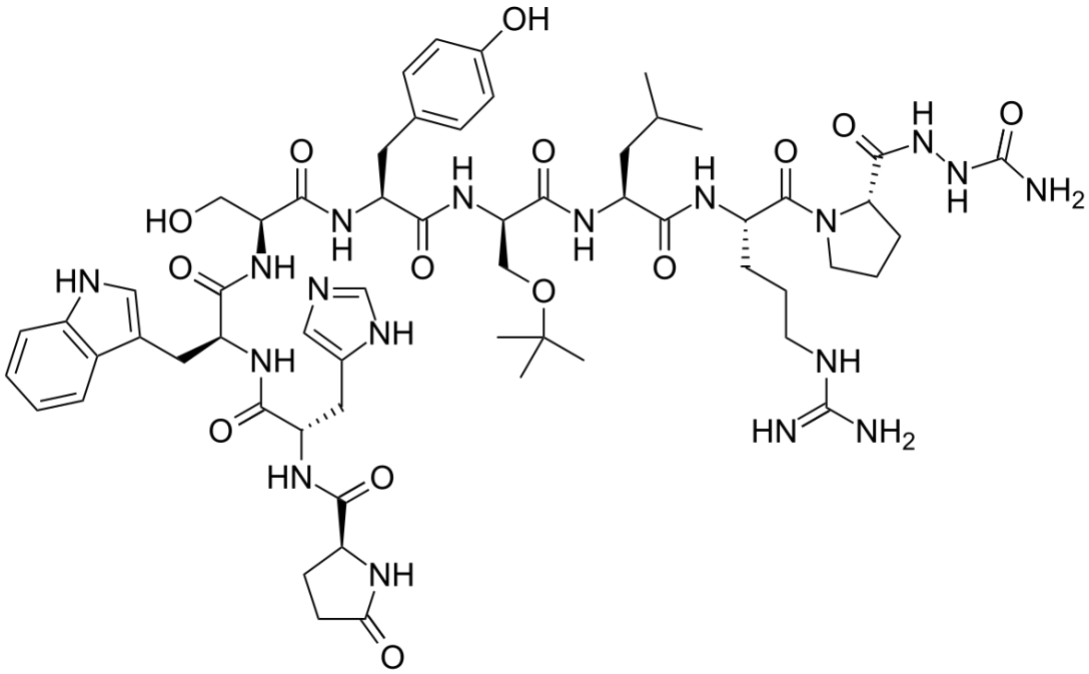

Figure 23 Goserelin

12. Antiprogestine

The third-line synthetic progestin analog is Megestrol acetate which is commonly used for treating of MBC in patients having HR+ BC and endometrial cancer. It has so-called progesterone physiology; it suppresses the synthesis of estrogen and reduces adrenal and ovarian steroids. Nausea, sweating and constipation are widely observed negative adverse effects. A two stage phase II trial was done to determine its antitumor activity in population having HR+ advanced BC. All patients selected had MBC and had prior treatment with a NSAI. The median PFS of 3.9 months was observed. Widely occurring side effects included dyspnea & thrombosis [75].

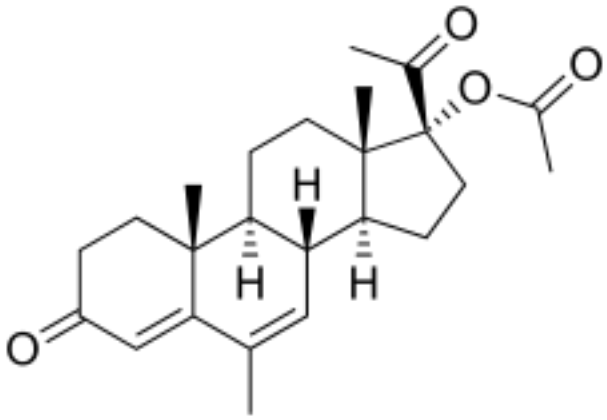

Figure 24 Megestrol acetate

13. DNA alkylating agents

These agents intercalate in the DNA, alkylating it and blocking the cell cycle hence inhibiting further proliferation of cells. Nitrogen mustards are one of the earliest known chemotherapeutic agents. The most effective and widely used chemotherapy medication is cyclophosphamide which is a nitrogen mustard prodrug. This is selectively split into the cancer cells and thus expresses huge amounts of nitrogen mustard phosphamidases. These compounds go through numerous cyclical stages in physiological settings, which generate an etheyleneimine cation, which in reacts with DNA. Its detoxification is by dehydrogenase enzyme intracellularly. Latest research in combination with other breast cancer medication investigate the role of cyclophosphamide as an antitumor agent. It is well tolerated in those with MBC in conjunction with doxorubicin. [15].

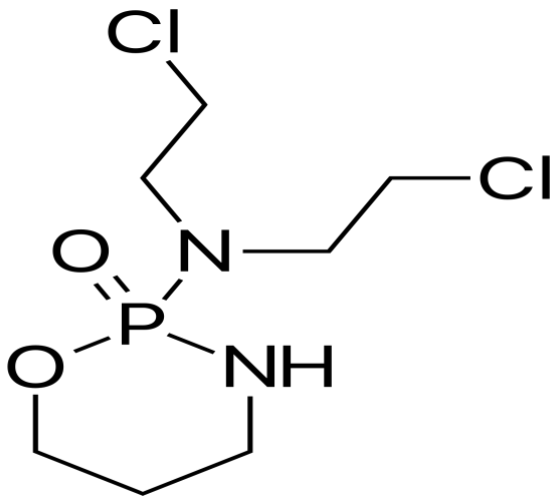

Figure 25 Cyclophosphamide

Thiotepa, an organophosphorus compound and sulfur analog of N',N'-triethylenethiophosphoramide. Thiotepa is a drug that interacts with DNA and thus opens the DNA chain and breaks the DNA. A clinical trial consisting of thiotepes, cyclophosphamides and carboplatins, accompanied by metronomic cyclophosphamides regimen demonstrated successful safety and efficacy in the care of younger metastatic patients with TNBC (n = 23). Neutropenia (100.0%) and anemia (69.7%) were the most common serum toxicities; mortality associated with treatment was not found [76].

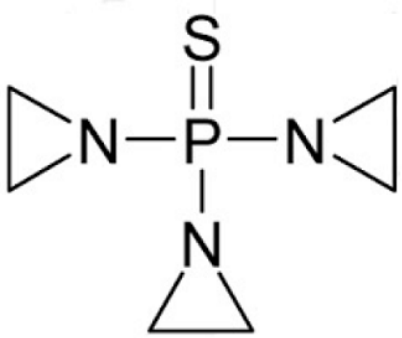

Figure 26 Thiotepa

14. Antimitotic agents

The targeting of cancer cells is being done by antimitotic chemotherapeutic regimes. Such medications alter the role of the microtubulum, a significant element in the segregation of the chromosome in mitosis. Therefore, a microtubular deficiency leads

to an apoptosis or cell-cycle arrest. Microtubules are composed of a free-living global protein, tubulins, occurring in isoforms α and β, assembled during division according to cellular need. Antimitotic chemotherapeutic agents combine with tubulin and thereby prevent the division of cells and initiation of programmed cell death. This leads to an inevitable shift in function. Inhibiting agents of the microtubules are listed according synthesized or naturally occurring sea products or derived from plants [15].

Ixabepilone is a semi-synthetic analog derived from Sorangiumcellulosum myxobacteria and is a derivative of epothilone B. Its efficiency to inhibit tumor cell lines is higher than taxanes. It is a stabilizer that combines with microtubule. It leads to polymer formation of the tubulins which then leads to the G2/M stage of mitotic arrest. Its resistance is owed to presence of various efflux mechanisms in cancer cells which are composed of proteins and pump the molecule out of the cell. Peripheral neuropathy, accompanied by neutropenia are widely observed adverse side effects attributed to ixabepilone. In a two-armed, randomized phase Ib clinical trial, which aimed to build up on the promising preclinical results for the combined regimen of vorinostat and ixabepilone in treatment of MBC. The findings were positive and fair clinical activity was observed with neutropenia as one of the observed adverse effects in patients. Numerous phase II/III trials of ixabepilone conducted alongwith other anti BC agents have been reported. A median PFS of up to 10.4 months has been observed in those having MBC resistant to taxanes. Additionally, when ixabepilone was used in combination with docetaxel, a mPFS of 0.5416 years wherein in those who had undergone previous treatment for metastatic disease by anthracyclines [15], [77]

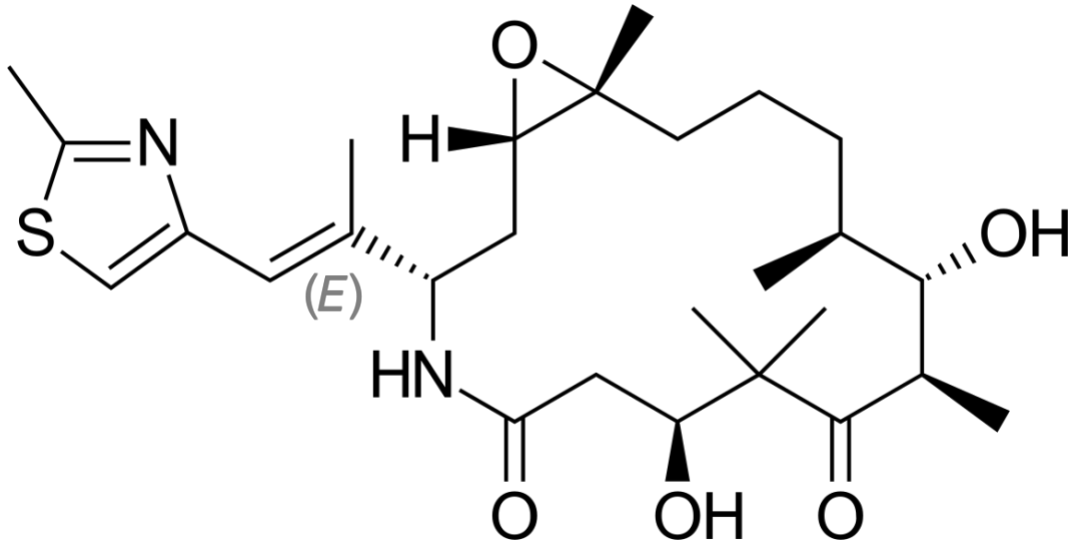

Figure 27 Ixabepilone

The antimitotic agent, an analog of Halichondrin B (polyether macrolide derived from sponges found in aqueous environments) is eribulin mesylate. It has a high tolerance and decreased frequency of neuropathological ocurrences in contrast to plant and epithilone derivatives of antimitotic agents. It prevents the growth of microtubules, which contribute to irregular mitotic spindles being leased to anaphase or metaphase for arrest. Phase II study conducted up on population having HER2- MBC to evaluate tolerance of eribulin, results showed a 17% of observed response rate and PFS of 0.4083 years [78]. A separate trial was done to determine effectiveness of eribulin + gemcitabine when used in combination with paclitaxel. The results indicated that both the therapies were equivalent in treating HER2- MBC, however, there were fewer side effects in those who were given eribulin as opposed to those given gemcitabine [79]. Another study determined effectiveness of eribulin + trastuzumab or pertuzumab. People having MBC were selected and ORR was 34.8 with a median PFS 42.6 weeks while grade III neutropenia was observed as an adverse effect [80]. EMBRACE, a phase III study, conducted to study eribulin as single agent against other drug regimens. Median overall survival in those who received eribulin was significantly greater, of 13.1 months as compared to those who received other medications. However, those who received eribulin showed peripheral neuropathy (30%) [81].

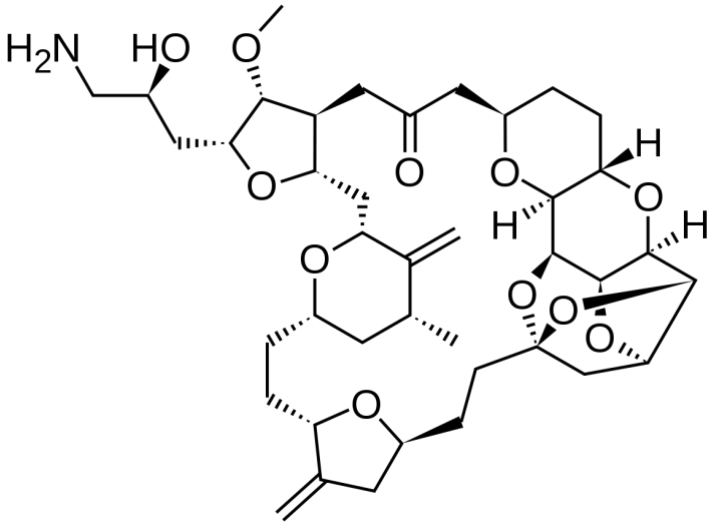

Figure 28 Eribulin

Taxanes are dervied from plant sources. They work by binding beta tubulins to prevent formation and elongation of microtubules, causing a stoppage of cell cycle and cell death. Neurological & hematopoietic side effects, however, typically hamper their use. Taxane resistance exists because of the overexpression of the medication efflux proteins and the isoforms of βIII-tubulin. Furthermore, anti-allergy medicines must be given before administration, because they can cause allergic reactions. Paclitaxel is a drug derived from terpene and the first chemotherapeutic taxane to be used. Mechanism of action of paclitaxel is that it binds to microtubules, polymerizes and stabilizes them. A large number of free and bundled microtubules are found in paclitaxel treated cells that lead to their functional disorder leading eventually to apoptosis. Their side effects involve destruction of the bone marrow, alopecia, myalgia, arthragias and reactions to hypersensitivity. The albuminous paclitaxel nanoparticles (nab-paclitaxel), a dosage form of devoid of any solvent, inside which paclitaxel is administered to avoid premedication or special infusion sets by suspension of nanoparticles in the albumin and show less toxic effect alongwith improved drug delivery to the tumor site. A recent large-scale, randomized trial involving this formulation + carboplatin superior to it + gemcitabine in TNBC has a high degree of efficacy and superior tolerability [82]. In randomized Phase II (SNAP trial) investigated various nab-paclitaxel maintenance schedules. In contrast to previous research of first line docetaxel, it was mainly aimed at evaluating the effectiveness of increasing maintenance plan for progression-free survival. This research demonstrated the use and operation of alternative nab-paclitaxel

maintenance schedules for the first line MBC therapy, following a short induction at traditional doses. Grade 2 and 3 sensory neuropathy was observed in most patients [83].

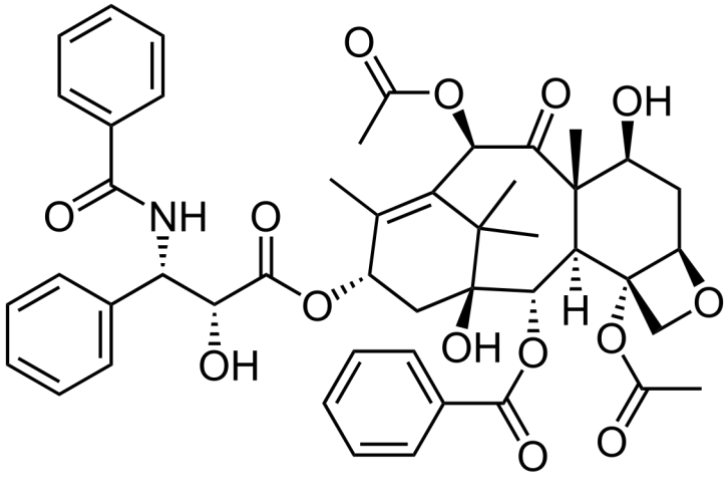

Figure 29 Paclitaxel

Docetaxel is a synthetic analog of paclitaxel. Bone-marrow depletion, particularly neutropenia, is the dose-dependent toxicity of docetaxel. Occasionally, hypersensitivity reactions occur. In CLEOPATRA, randomized controlled trial, the impact of docetaxel was examined on clinical outcomes and was a recommended 1st line therapy for HER2 + MBCs. Investigators summarized that more than six docetaxel therapy cycles were not linked to major clinical outcome changes relative to 6 cycles after accounting for the benefits of pertuzumab [84].

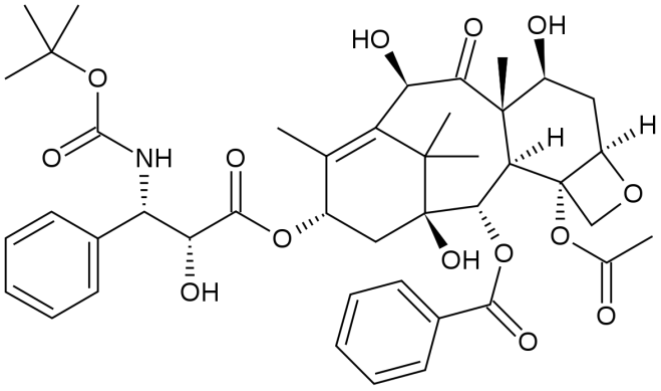

Figure 30 Docetaxel

15. Conclusion

Even though a number of chemotherapeutic agents are currently available and are useful in treating of various stages of breast cancer, there is a significant need for

discovering and developing of novel agents with a higher efficacy in treating and managing breast cancers. Numerous trials are underway to determine and evaluate novel and currently known molecules for treatment of BC, however, it is a process that often spans a decade before such an agent is completely identified and made available as a general treatment for the disease. Currently, a number of agents are shown to be getting less and less efficacious in treating this disease owing to the development of various resistance mechanisms. Focus should also be given to identifying novel targets and biological or signaling pathways which may help devise a new or different strategic approach to the development of novel chemotherapeutic agents which would be better suited to treat the rapidly developing resistance to current dosing therapies and regimens. Additionally, the number of options available for TNBC & MBC are fairly limited. Subsequent efforts for early detection, prognosis, diagnosis and prevention of BC are also needed to improve therapeutic outcomes and to start treatment as early as possible with an aim to develop precision breast cancer therapies and improving or prolonging the survival of breast cancer patients [5].

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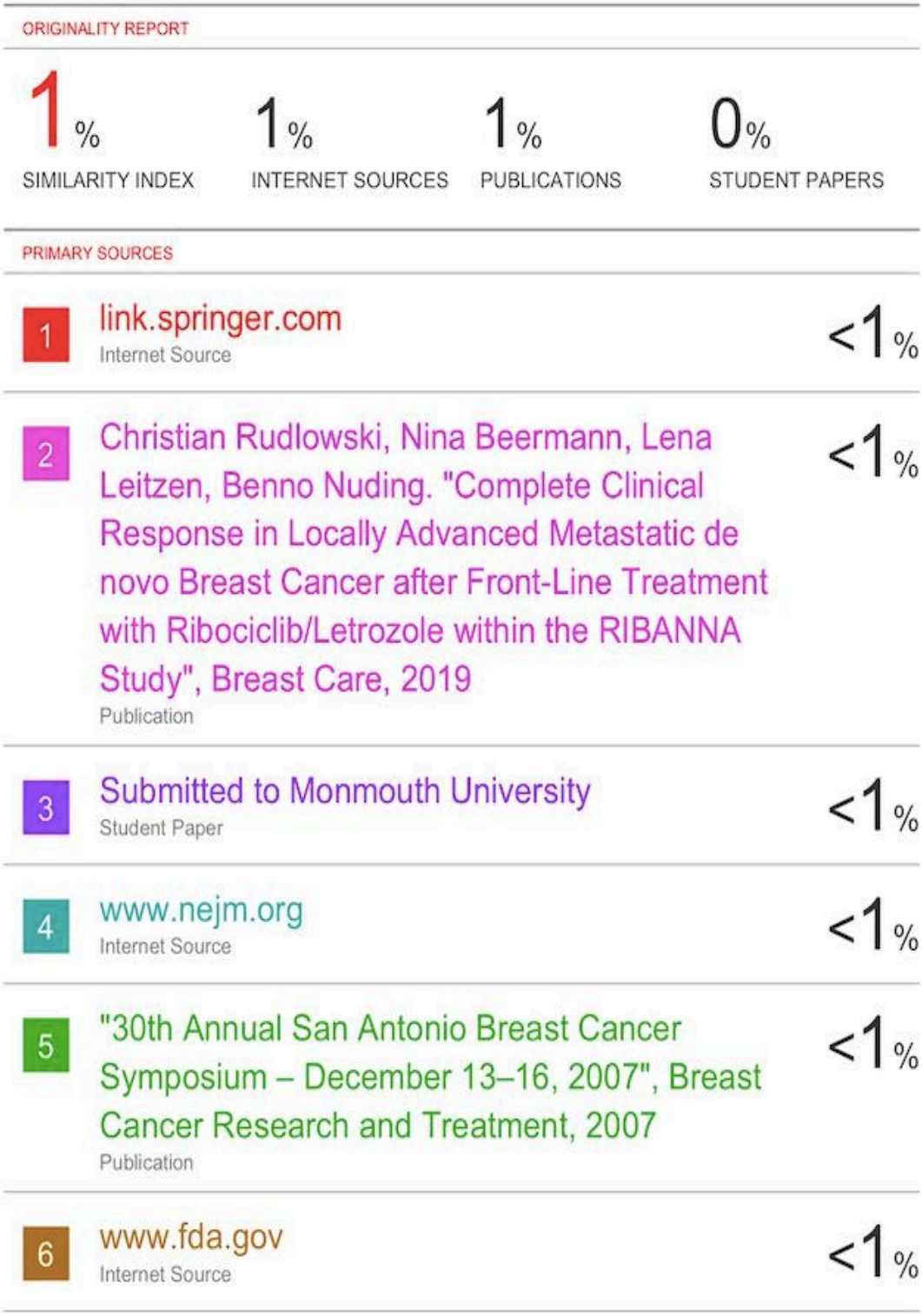

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