TURKISH REPUBLIC OF NORTH CYPRUS
NEAR EAST UNIVERSITY
HEALTH SCIENCES INSTITUTE

# EFFICACY AND SAFETY OF CAPECITABINE ALONE OR IN COMBINATION IN ADVANCE METASTATIC BREAST CANCER PATIENTS PREVIOUSLY TREATED WITH ANTHRACYCLINE AND TAXANE; A SYSTEMATIC REVIEW AND META-ANALYSIS

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Prof. Dr. Bilgen Basgut

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# *Efficacy and Safety of Capecitabine Alone or in Combination in Advance Metastatic Breast Cancer Patients Previously Treated with Anthracycline and Taxane; a Systematic Review and Meta-Analysis*

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2020

## DEDICATION

I dedicate my dissertation work to my family and many friends. A special feeling of gratitude to my loving parents, **Mayada** and **Mohammad** whose words of encouragement and push for tenacity ring in my ears.

My sisters **Dr.Sajeda, Eng.Dana, Deema** and **Tala** and my brothers **Acc.Qusai** and **Eng.Wael** have never left my side and are very special.

I also dedicate this dissertation to my many friends and church family who have supported me throughout the process. I will always appreciate all they have done, especially **Dr.Wael Abdullah** for helping me develop my technology skills.

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Louai Alsaloumi

# STATEMENT (DECLARATION)

Hereby I declare that this thesis study is my own study, I had no unethical behavior in all stages from planning of the thesis until writing thereof, I obtained all the information in this thesis in academic and ethical rules, I provided reference to all of the information and comments which could not be obtained by this thesis study and took these references into the reference list and had no behavior of breeching patent rights and copyright infringement during the study and writing of this thesis.

Louai Alsaloumi

APPROVAL

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## ABBREVIATIONS

MBC: Metastatic breast cancer.
CMA: Comprehensive meta analysis.
VEGF :Vascular endothelial growth factor.
ABC: advanced breast cancer.
CMF: cyclophosphamide/methotrexate/fluorouracil.
FAC: Fluorouracil/anthracycline/cyclophosamide.
AC: Doxorubicin and cyclophosphamide
OS: overall survival.
PFS: progression free survival
RR: Risk ratio/Relative risk/response rate
TNBC: triple-negative breast cancer (TNBC)
CAP: Capecitabine.
CES:carboxyleterase.
CDD: cytidine deaminase
TP: thymidine phosphorylase
UP: uridine phosphorylase
DFCR:deoxyfluorocytidine.
DFUR:deoxyfluorouridine
FU: fluorouridine.
CD: Capeeciatbinedocitaxel
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PICOS: Population Intervention Comparison Outcome Study
GWAS: Genome wide association study.
HFS: Hand and foot syndrome
HR: Hazard ratio
PPE: Palmar-Plantar Erythrodysesthesia
SNP: single nucleotide polymorphism

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**Name of the student:** Louai Alsaloumi
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## ABSTRACT

**Background:** Capecitabine is frequently used alone or combined with other chemotherapies for the treatment of metastatic breast cancer in relapsed patients.

**Objective:** The objective of this meta-analysisis to evaluate the effectiveness and safety of capecitabine monotherapy versus combination in the treatment of metastatic breast cancer patients pretreated with anthracycline and taxane.

**Methods:** Eligible randomized controlled trial examining the efficacy and safety of capecitabine alone compared to capecitabine combination was systematically searched. Progression-free survival, overall survival, overall response rate, and grades 3–4 drug-related adverse events were the outcomes.

**Results:** A total of 6714 patients of nine trials were involved in the pooled analysis. Our findings demonstrated that capecitabine combination is significantly superior to capecitabine monotherapy in improving progression free survival (HR 1.32, 95% CI 1.13 to 1.54, $P < 0.0001$) and overall response rate (RR 0.67, 95% CI 0.54 to 0.83, $p< 0.001$) but it was insignificant in overall survival (HR 1.09, 95% CI 0.98 to 1.22, p =0.12). On the other hand, the incidence of non-hematological adverse events such as hand and foot syndrome and diarrhea was lower in capecitabine combination compared to capecitabine monotherapy.

**Conclusion:** Capecitabine-based combination chemotherapy showed superiority over capecitabine monotherapy in terms of PFS and ORR, with no significant difference in overall survival. Non-hematological adverse effects suchas hand and foot syndrome were less with a combination regimen. However, hematological adverse events were less with capecitabine monotherapy regimen.

**Keywords:** Capecitabine, Capecitabine combination, Metastatic breast cancer, meta-analysis, anthracycline, taxan.

# ÖZET

**Öğrenci İsmi:** Louai Alsaloumi
**Danışman Öğretmen:** Prof .Dr. Bilgen Basgut
**Bölüm:**KlinikEczacılık

**Özet:**

**Geçmiş:** Kapesitabin sıklıkla metastatik göğüs kanseri tedavisinde tek başına veya diğer kemoterapi ilaçları ile birleştirilerek hastalığı nükseden hastalar üzerinde kullanılan bir ilaçtır.

**Amaç:**Bu metaanalizin amacı, antrasiklin ve taksan ile önceden tedavi edilmiş metastatik meme kanseri hastalarının tedavisinde kombinasyona karşı kapesitabin monoterapisinin etkinliğini ve güvenilirliğini değerlendirmektir.

**Yöntemler: Kapesitabin kombinasyonuna kıyasla tek başına kapesitabinin etkinliğini ve güvenilirliğini inceleyen uygun randomize kontrollü çalışma sistematik olarak araştırılmıştır.**Sonuçlar, progresyonsuz sağkalım, genel sağkalım, genel yanıt oranı ve 3-4 derece ilaçla ilişkili yan etkiler olarak bulunmuştur.

**Bulgular: Havuz sistemine dayalı analize dokuz denemeden toplam 6714 hasta katılmıştır. Bulgularımız, kapesitabin kombinasyonunun, progresyonsuz sağkalımı (HR 1.32,% 95 CI 1.13 ila 1.54, P <0.0001) ve genel yanıt oranını (RR 0.67,% 95 CI 0.54 ila 0.83, p <0.001) iyileştirmede kapesitabin monoterapisine göre anlamlı derecede üstün olduğunu göstermiş olsa da, genel sağkalıma bakıldığında bu oranın yetersiz olduğu görülmüştür (HR 1.09,% 95 CI 0.98 ila 1.22, p = 0.12).**
Havuzlanmış analize dokuz denemeden toplam 6714 hasta katılmıştır. Bulgularımız, kapesitabin kombinasyonunun, progresyonsuz sağkalımı (HR 1.32,% 95 CI 1.13 ila 1.54, P <0.0001) ve genel yanıt oranını (RR 0.67,% 95 CI 0.54 ila 0.83, p <0.001) iyileştirmede kapesitabin monoterapisine göre anlamlı derecede üstün olduğunu göstermiştir. ) ancak genel sağkalımda önemsizdi (HR 1.09,% 95 CI 0.98 ila 1.22, p = 0.12). Öte yandan, el ve ayak sendromu ve ishal gibi hematolojik olmayan yan etkilerin oluşumu kapesitabin kombinasyonunda monoterapiye göre daha düşüktü.

**Sonuç: Kapesitabin bazlı kombinasyon kemoterapisi, PFS ve ORR açısından kapesitabin monoterapisine göre üstünlük göstermiştir, genel sağkalımda gözle görülür bir fark izlenmemiştir.**El ve ayak sendromu gibi hematolojik olmayan yan etkiler bir kombinasyon rejiminde daha az görülmüştür.Bununla birlikte, hematolojik yan etkiler kapesitabin monoterapi rejiminde daha azdır.

**AnahtarKelimeler:** Kapesitabin, Kapesitabinkombinasyonu, MetastatikGöğüsKanseri, meta-analiz, antrasiklin, taksan.

## 1. INTRODUCTION

Being diagnosed with breast cancer is a life-changing experience. Sometimes is difficult to handle the news at the beginning, and sometimes may get even harder of how to proceed.

Nowadays, breast cancer has ranked the first malignancy cancer in women. The incidence is sharpening toward the top in western countries, which accounted to be 30%(Jemal, Siegel, Xu, & Ward, 2010).

In spite developments in diagnostic techniques of early stages breast cancer, 30 % gets recurrent or develop metastases (Jiang et al., 2018). Although significant improvements in survival outcomes over the past two decades, breast cancer remains the most common malignancy among women and the second leading cause of cancer deaths in the United States (Lundqvist, Andersson, Ahlberg, Nilbert, & Gerdtham, 2016; Seidman et al., 2010).

One in every three women diagnosed with breast cancer develops locally advanced or metastatic disease (O'Shaughnessy, 2005). The median survival for patients with Advanced breast cancer remains 2–3 years despite late advances in treatment (O'Shaughnessy, 2005).

### 1.1. Aims and Scope

The aim of this project is to evaluate the efficacy of capecitabine monotherapy compared to capecitabine combination regimens in advanced metastatic breast cancer patients previously treated with anthracycline and taxane.

The second aim of this project is to evaluate the safety of capecitabine monotherapy compared to capecitabine combination chemotherapy treatments.

### 1.2. Overview and Incidence of Breast Cancer

Breast cancer cells usually shape a tumor that can occasionally be seen on an x-ray or felt as a lump. Cancer cells could pop up anywhere in breast but ductal (in ducts) and Lobular (in glands) are the most common (Runowicz et al., 2016)( American Cancer Association).

Beside, cancer cells spread through blood and lymph system which are the reasons for metastasis. Once metastasize, the main regions are lung, liver, brain and bones and could be any organ affected (Xu et al., 2019).

Angiogenesis plays an essential role in breast cancer development, invasion, and metastasis (McLeskey et al., 1998). Vascular endothelial growth factor (VEGF), maintain angiogenesis, inhibit apoptosis, besides, produce proteinases to remodel extracellular matrix, induce permeability,vasodilatation and inhibit Ag-presenting dendritic cells (McLeskey et al., 1998; K. D. Miller et al., 2005).

### 1.3.Breast Cancer Staging

Staging is important in a way to notice how extensive breast cancer is which is related to tumor size, spread to lymph nodes and different parts of the human body and which biomarkers are connected to it.

Before or after patient's surgery, the staging could be done. Physicians utilize the tests to figure out the cancer stage. Thus, tests are required to determine the correct of stage of breast cancer. In staging, physician have a better idea in determine the better way for patient's treatment, prognosis, and cancer recovery(Cabioglu, Yavuz, & Aydiner, 2019).

### 1.4. TNM Staging System

Physicians assess the stage of the tumor through Staging system of combining the T, N, and M classifications, the tumor grade, and the results of ER/PR and HER2 testing. It is essential in identifying the prognosis(Cabioglu et al., 2019).

The most common tool that doctors use to describe the stage is the TNM system. Doctors use the results from diagnostic tests and scans to answer these questions, in which the results are combined to determine the stage of cancer for each person:

- Tumor (T): confine the size of the primary tumor? What are its biomarkers?
- Node (N): does the tumor has spread to Lymph nodes? If so, where, what size, and how many?
- Metastasis (M): Has the cancer spread to other parts of the body?

Staging can be clinical or pathological. Pathological staging is based on what is found during surgery to remove breast tissue and lymph nodes. Clinical staging is based on the results of tests done before surgery, which may include physical examinations, mammogram, ultrasound, and MRI scans. In general, pathological staging provides the most information to determine a patient's prognosis(Piñeros et al., 2019).

**Tumor (T)**

T with a letter or number (0 to 4) is utilized to determine the the location and size of the tumor that the size measured in centimeters (cm).

Stage may also be divided into smaller groups that help describe the tumor in even more detail. Specific tumor stage information in listed below.

**TX:** The primary tumor cannot be evaluated.

**T0 (T plus zero):** There is no evidence of cancer in the breast.

**Tis:** Refers to carcinoma in situ. The cancer is confined within the ducts of the breast tissue and has not spread into the surrounding tissue of the breast. There are 2 types of breast carcinoma in situ: Tis (DCIS) which is not invasive and has to be removed to prevent it from becoming invasive (Cancer cells in ducts but did not spread yet). However, Tis( Pagets ) which is only in skin cells of the nipple (early non invasive). But it could be associated with the invasive breast cancer(Plichta et al., 2020).

**T1:** The cancer size in breast area is 20 millimeters (mm) or smaller; the substages depending on tumor size are:

- T1mi is a tumor that is 1 mm or smaller.
- T1a is a tumor that is larger than 1 mm but 5 mm or smaller.
- T1b is a tumor that is larger than 5 mm but 10 mm or smaller.
- T1c is a tumor that is larger than 10 mm but 20 mm or smaller.

**T2:** The tumor size is (>=20 mm and <50 mm).

**T3:** The tumor is > 50 mm.

**T4:** The tumor falls into 1 of the following groups:

- T4a: the tumor moved to chest wall.
- T4b is when the tumor has grown into the skin.
- T4c is cancer that has grown into the chest wall and the skin.
- T4d is considered to be inflammatory one.

**Node (N)**

As know, the lymph nodes responsible to fight infection. The staging of lymph nodes in breast cancer which is as follow:

NX: The lymph nodes were not evaluated.

N0: Either of the following:

- No cancer was found in the lymph nodes.

- Less than 0.2 mm of cancer cells are found in the lymph nodes.

N1: tumor cells spread to 1 to 3 lymph nodes of axillary or internal of mammary lymph nodes.
N2: The cancer has spread to 4 to 9 axillary lymph nodes. Or, it has spread to the internal mammary lymph nodes, but not the axillary lymph nodes.

N3: ≥ 10 of axillary lymph nodes have been affected by cancer cells.

**Metastasis (M)**

MX: could not evaluate the distant metastasis.

M0: No evidence of distant metastases.

M0 (i+): There is microscopic evidence of tumor cells in the blood, bone marrow, or other lymph nodes that are <= 0.2 mm. However, no clinical or radiographic evidence of distant metastases.

M1: An proof of metastasis in another parts or organs(Kim et al., 2020).

**Staging system**

Treatment of breast cancer is based on its stage. Stage 0 is called carcinoma in situ since the cancer has not formed yet. In stage 1; the cancer is formed which could be didvided into stage A (has not spread outside the breast and tumor is ≤2 in size, however in stage B, there is small clusters of cancer cells in lymph node. In stage IIA, Stage IIA is known as tumor (2-5cm) and no spread into lymph node, or no tumor is present in the breast, or the tumor is< 2cm, but there are cancer cells in 1 to 3 axillary lymph nodes or in the lymph nodes near the breastbone.

In stage IIB, the tumor is either: between 2 and 5 centimeters in size, and small clusters of breast cancer cells are found in the 1 to 3 axillary or near breast bones lymph nodes, or the tumor is > 5 cm and, cancer has not spread to the lymph nodes. Stage 3 breast cancer, stage IIIA, the tumor is either: > 5 cm, and small clusters of breast cells are found in the lymph nodes; and has diffuse to 1 - 3 axillary lymph nodes or to the lymph nodes nearby the breastbone; or, no tumor is present

in the breast, or the tumor may be any size, and themalignant cells are established in 4 - 9 axillary lymph nodes or in the lymph nodes close to the breastbone.

In stage IIIB, tumor could be any size and malignant cells have diffused to the skin of the breast and/or to the chest wall and caused ulcer or swelling (considered inflammatory), and, cancer may have spread to up to 9 axillary lymph nodes or the lymph nodes near the breastbone. In stage IIIC, the tumor could be any size. Malignant cells may have diffused to the skin of the breast and caused swelling or an ulcer and/or has spread to the chest wall. Beside, cancer has spread to 10 or more axillary lymph nodes, lymph nodes above or below the collarbone, or axillary lymph nodes and lymph nodes near the breastbone. In stage 4 breast cancer, any spread of breast cancer outside of the breast and draining lymph node regions (ACS).

### 1.5.Breast Cancer Treatment

The second international guidelines for metastatic breast cancer signalize that the main goals of metastatic breast cancer treatment are to enhance both length and quality of life. However, regarding the use of chemotherapeutic agents, the main recommendation relates to the sequential use of single agents, with combination chemotherapy are maintained for situations of visceral metastases, rapidly progressive or highly symptomatic disease(Cardoso et al., 2014a).

Systemic drug therapies, are the main treatments for advanced breast cancer (stage IV). These may include: hormone (estrogen/progesterone), immunotherapy (induction patient immune cells), targeted drug as trastuzumab (Herceptin) and pertuzumab (Perjeta), and chemotherapy(Saslow et al., 2007).

Chemotherapeutic agent is considered the main choice for advanced breast cancer for whom hormonal treatments were inappropriate or failed to respond to these therapies. A number of cytotoxic agents, as single agent, approved to have anti-tumor activity. furthermore, the combination of active single agents was found to be more effective, and still well tolerated(Giordano, Hortobagyi, Kau, Theriault, & Bondy, 2005).

The drugs move toward the bloodstream to reach cancer cells in most parts of the body. Intermittently, the drug might be given directly into the spinal fluid. Chemotherapeutic agents can be given after surgery (adjuvant chemo) to try to kill any cancer cells that might have been left behind or have spread but can't be seen.

Furthermore, it can be given before surgery (neoadjuvant chemo), to shrink tumor size for locally advanced breast cancer. Nevertheless, for advanced breast cancer (ABC), chemotherapeutic agents are considered the cornerstone. The main medications for ABC are Taxanes, Anthracyclines, Platinum agents, Vinorelbine, Capecitabine, Gemcitabine, Ixabepilone, Eribulin(American cancer society).

Anthracyclines appeared to be considered as higher single agent activity in metastatic breast cancer. Thus, anthracyclines became a standard in first-line chemotherapy for metastatic breast cancer and for adjuvant chemotherapy in suitable patients(Jasra & Anampa, 2018).

Moreover, taxanshave antitumor activity (40%) as single agent after failure of anthracycline treatment. However, recently increased the problem of being resistance to taxan/anthracycline therapy or relapse shortly(Gradishar, 2012).

Recently comprehensive treatments are available, but vary from patient to another(Runowicz et al., 2016)(American Cancer Association).The main target treatment focused on combinational therapy of anthracycline/cyclophosphamide, followed by taxan/Epirubicin/cyclophosamide, followed bypaclitaxel/doxorubicin/cyclophoamide as first line therapy(Xu et al., 2019).

Other combinations could be, cyclophosphamide/methotrexate/fluorouracil (CMF), and Fluorouracil/anthracycline/cyclophosamide(FAC)(American Cancer Society).Anthracyclinesare the frontline treatment of metastatic breast cancer, but limits its use because of cardiotoxicity and resistance (Andreopoulou & Sparano, 2013; Martin et al., 2018; Piccart-Gebhart et al., 2008; Seidman et al., 2010).

Furthermore, docetaxel monotherapy, in advanced breast cancer, improved response rate to 48%, and median survival times up to 16 months (Reichardt et al., 2003).
However, decisions to choose the treatment of metastases breast cancer are rising perplexing, and no single standard pathaccessible after failure of anthracycline/taxan therapy (Moreno-Aspitia & Perez, 2009).

Capecitabine, gemcitabine, and vinorelbine, as a sequential single-agent therapy, are favored to combination regimens for advanced breast cancer after anthracyclines and taxanes. However,capecitabinebeing the only approved monotherapy(Conlin & Seidman, 2007; Dean-Colomb & Esteva, 2008).

In addition, capecitabine is commonly used in the first-, second-, and third-line settings for advanced breast cancer (Geyer et al., 2006; Hortobagyi et al., 2010; K. D. Miller et al., 2005; Thomas et al., 2008).
Jiang et al observed that Capecitabine monotherapy in pretreated anthracycline/taxan patients in metastatic breast cancer might have a promising discovery. It appeared that it improved PFS (Progression Free Survival), ORR (Overall Response Rate), and QoL (Quality of Life) in estrogen receptor positivity (Jiang et al., 2018).Future studies are needed with a focus point on biomarkers for a better selection(Barchiesi et al., 2019).

### 1.6. Neoadjuvant and Adjuvant Management in Breast Cancer

One of the most global and popular health issues in developing and developed countries is breast cancer. The lifetime probability of developing breast cancer is one in six overall (one in eight for invasive disease). It is a heterogeneous, phenotypically diverse disease contained of multiple biologic subtypes that have variable behaviors and with distinct responses to therapy(Feng et al., 2018).

It is widely recommended to intake adjuvant systemic therapy for the best much of the reduction in cause-specific mortality from breast cancer which is noticed in most of worldwide world (Lips et al., 2012). After breast surgery, adjuvant chemotherapeutic agents are given to these patients to eradicate any microscopic foci of tumor cells which is if left untreated or removed could grow and metastasizes to other regions and make the condition worse.

Regardless as to whether cancer is estrogen (ER) or progesterone (PR) receptor positive or negative, occasionally, similar chemotherapy protocols are utilized. It is important to take into account the expression of estrogen receptor (ER), histology of cancer, progesterone receptor(PR), cancer stage and grade, patient age and lymph node invasions(Lips et al., 2012).

Neoadjuvant therapy defined to be as breast cancer systemic therapy before surgical procedure. Usually, the use of these therapies has been widely increased and expanding in certain patients. Neoadjuvant therapy goals to reduce cancer metastasis and recurrence and observe if any response which will allow down staging the tumor of less extensive surgery provided, in addition, to avoid any further risks associated with breast reconstruction in patients able to undergo breast-conserving surgery in place of mastectomy, improving cosmetic outcomes, and minimizing postoperative complications such as lymphedema (Shannon & Smith, 2003). Neoadjuvant therapy also allows assessment of efficacy of systemic chemotherapy as a guide for adjuvant therapy.

The presence and extent or absence of residual invasive cancer after neoadjuvant therapy is a strong prognostic factor for risk of recurrence, especially in triple-negative breast cancer (TNBC) and human epidermal growth factor receptor 2-positive breast cancer(Mamtani et al., 2016).

Moreover, it helps researcher and clinicians the best procedures to get the imaging studies, cancer specimens, blood samples prior to, during, and, in patients with sufficient residual disease at surgery, after the preoperative treatment, that it helps in determining cancer-patient's certain biomarkers of resistance or response to treatment.

Neoadjuvant therapy is thought to improve the overall survival (OS) since it gives an early start up with systemic therapy especially for high-risks patients(Spring et al., 2016).

Selection of patients to start a neoadjuvants therapy is based on mastectomy might not be an option, locally advanced breast cancer, early breast cancer, and with temporary contraindication to therapy. In phase II pilot study, patients with invasive, HER2-negative, non-metastatic breast cancer, showed improvement of adding neoadjuvant therapy of bevacizumab , capecitabine and docetaxel combination. Yet, it increased the 22% pCR rate in these patients, however further evaluations are needed(Greil et al., 2009).

Before initiation any treatment, it is important to evaluate the pathological and histological pictures of the tumor through biopsies, imaging, and node evaluation. Adjuvant therapy is given based on neoadjuvant ones, cancer stage, receptor expression, and patient age.

Overall, adjuvant chemotherapy reduces risk of recurrence and improves survival, but in low risk patients, and the benefits might be small and must take this into consideration. Thus, it depends on disease risk factors, patient age and chronic diseases. The administration of anthracycline and taxane therapy in the adjuvant setting come from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). The use of an anthracycline-containing regimen compared with no treatment, resulted in the following outcomes (Clarke et al., 2005; Peto et al., 2012; Symmans et al., 2006):

- Recurrence reduced from 47 to 39 percent (relative risk [RR] 0.73, 95% CI 0.68-0.79)
- Reduced mortality of breast cancer 36 to 29 percent (RR 0.79, 95% CI 0.72-0.85)
- Reduced overall mortality from 40 to 35 percent (RR 0.84, 95% CI 0.78-0.91)

Moreover, the use of cyclophosphamide, methotrexate, and fluorouracil (CMF)compared to no treatment, was also related with better effectiveness in these results at 10 years (Clarke et al., 2005).

The associated risks of chemotherapy include nausea, vomiting, hair loss, myelosuppression, early cognitive impairment, and amenorrhea. Immunosuppression associated with chemotherapy may also lead to severe infections in some patients. Taxanes are associated with neuropathy, which usuallyrecovers weeks to months after treatment, but may be incomplete in severe cases. Other side effects include the risks of cardiotoxicity associated with anthracyclines and the rare risk of chemotherapy-related leukemia (Shannon & Smith, 2003).

To choose which regimen to start is depend in patients and the tumor characteristics. The general protocol varies widely by clinician, institution, and geographic region. For most patients is advised to start on.

Doxorubicin and cyclophosphamide (AC) followed by paclitaxel (T), which known as AC-T, administered on a dose-dense schedule(Mamtani et al., 2016). Non-anthracycline-based regimens may be a considered a better protocol for certain groups of patients:

- Patients with lower-risk disease
- Patients with a history of cardiac disease.
- Advanced age and chest wall radiation are additional risk factors for anthracycline-related cardiotoxicity.
- Patients unwilling to accept the risks of anthracycline-based therapy.

Docetaxel and cyclophosphamide are given in patients for whom anthracyclines are not an appropriate choice. We generally offer taxane-based treatment to patients receiving adjuvant therapy. However, taxane therapy generally needs supportive care with some form of steroid treatment to prevent hinder allergic reactions and other side effects of therapy.

For patients in whom steroid treatment or risk of peripheral neuropathy is a particular concern, and where there are concerns about anthracycline exposure, we occasionallyrecommend cyclophosphamide, methotrexate, and fluorouracil (CMF) rather than an anthracycline- or taxane-containing regimen(Ntellas et al., 2019).

The regimen of doxorubicin and cyclophosphamide followed by paclitaxel (AC-T) delivered on a dose-dense schedule is the preferred regimen for most patients. For patients with lower-risk disease or a history of cardiac disease, non-anthracycline regimens may be preferable. Because this regimen is very equivalent to anthracycline, and once adding taxan to anthracycline improves the results(Peto et al., 2012).

In over 5000 women, when anthracycline was given at standard doses in regard to CMF, it showed that the similarity in recurrence risk (41 versus 42 percent), overall mortality (33 versus 35 percent), and breast cancer mortality (32 versus 33 percent) at 10 years. Patients receiving higher cumulative doses of anthracyclines had marginal improvements in these measures compared with CMF.

However, improvement in recurrence risk (35 to 30 percent) (relative risk [RR] 0.84, 95% CI 0.78-0.91), mortality of breast cancer (reduction in the risk of breast cancer mortality from 24 to 21 percent (RR 0.86, 95% CI 0.79-0.93), and overall mortality (27 to 24 percent )(RR 0.90, 95% CI 0.79-0.93) compared to others when adding taxanes to anthracycline-containing chemotherapy (Peto et al., 2012).

The benefits of taxane incorporation seen were independent of age, nodal status, tumor size, tumor grade, and estrogen receptor (ER) status. It is shown that AC-T is superior but the preference is anthracycline/taxan regimens for high-risk patients who are candidates for an anthracycline.

However, the non-anthracycline-based regimens of docetaxel and cyclophosphamide (TC) given every three weeks for four cycles (TC) may be an appropriate alternative for patients who have indications for chemotherapy but have lower-risk disease.

In these settings, TC may be preferable to AC-T, because are given in shorter period of time (12 versus 16 weeks) and prevention of cardiotoxicities and secondary leukemia's associated with anthracyclines. Patients with a history of cardiac disease and those unwilling to accept the risks of anthracycline-based therapy are also candidates for TC(Ntellas et al., 2019).

Without subsequent treatment with taxanes, previous data showed that TC is more effective than AC alone. Patients with stage I to III HER2-negative breast cancer in a United States Oncology

Trial 9735, over 1016 women were randomly analyzed to AC or TC. TC showed in a notably larger DFS (81 versus 75 percent) and overall survival (OS; 87 versus 82 percent) when compared with AC.

In addition, in regard to the 2012 EBCTCG meta-analysis, AC is equivalent to an alternative non-anthracycline-based regimen, CMF(Peto et al., 2012). Therefore, the evidence approve that TC is superior to CMF as the preferred non-anthracycline-based protocol.

In case of ordering the treatment might affect the efficacy and response. IN spite that anthracyclines are more commonly administered first, depending on patient and provider preferences. Administration of taxans ahead of anthracycline, did not improve OS, DFS or response rate (Gianni et al., 2005). But it is recommended to follow the schedule of chemotherapy which support using of dose-dense (frequent administration) over standard dosing. Yet, it led to better DFS results and similar tolerability compared to standard dosing(Gianni et al., 2005).

### 1.7. Special Populations

- **Neoadjuvant therapy patients**

Most patients who got the neoadjuvant therapy, it is advised not to take further adjuvant chemotherapy in this setting. However, use of capecitabine will improve survival benefits particularly in those with triple-negative breast cancer (TNBC), which suggests that these patients a good candidate for capecitabine. in addition, who did not finish the neoadjuvant course, it is recommended to take adjuvant chemotherapy in these settings with observed toxicities(Masuda et al., 2017).

It is recommended for patients neoadjuvant therapy course for example doxorubicin and cyclophosphamide followedby paclitaxel [AC/T] or docetaxel and cyclophosphamide [TC], or variants) prior to surgery will achieve complete response. However, patients with TNBC, will have residual disease, thus capecitabine is recommended(Masuda et al., 2017).

- **Older women**

Prior to making a decision regarding chemotherapy, older women should be evaluated using a comprehensive geriatric assessment. Adjuvant chemotherapy is usually advised for older women (≥65 years) with a good performance status. Previous study showed that older women can tolerate cyclophosphamide, methotrexate, and 5-fluorouacil (CMF) and doxorubicin plus cyclophosphamide (AC) chemotherapy reasonably well. Moreover, they can tolerate taxane-based chemotherapy (Muss et al., 2009).

- **Male breast cancer**

Breast cancer in male is a rare but treatment might not differ and the prognosis is similar(Ravandi-Kashani & Hayes, 1998).

- **Pregnancy**

Most chemotherapy agents are considered teratogenic in human. However, chemotherapy could be given after first trimester(Leslie, Koil, & Rayburn, 2005).

- **Obesity**

Obese patients are associated with poor survival and worse prognosis compared to normal BMI, since of comorbidities. However, chemotherapy is given based on standard, weight-based drug regardless of body mass index(Carroll et al., 2014).

- **Covid-19**

The complexity of breast cancer has been increased and made the things complicated with widen the complexity. It is paramount to balance issues from risk from therapy delay in contrast to the harm to get the COVID-19 since of this pandemic, in addition to the ways to reduce negative effects of social distancing during care delivery, and appropriately and fairly allocating limited health care resources.

## 2. LITERATURE REVIEW

### 2.1 Capecitabine and Advanced Breast Cancer

Capecitabine (Xeloda) is orally administered prodrug,cell cycle specific (S phase), known as antimetabolic fluoropyrimidine deoxynucleoside carbamate novel drug (Figure 1). In vivo, Xeloda with aid of thymidine phosphorylase (dThdPase), will be converted into 5-fluorouracil (5-FU) concentrate mainly in tumor tissues(Xu et al., 2019).

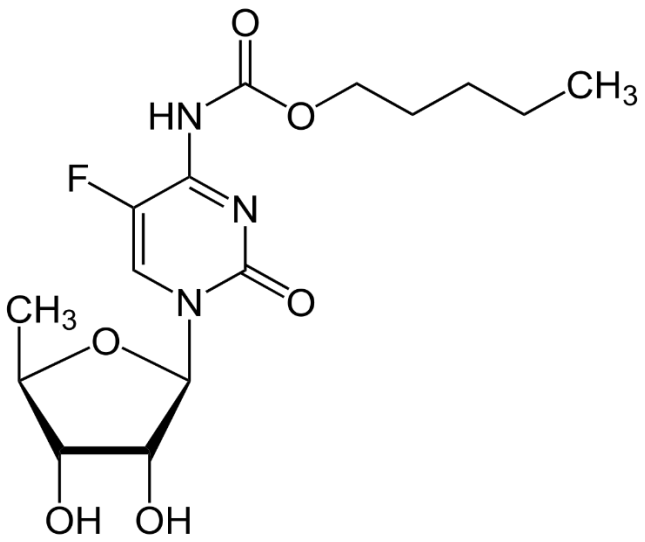



Figure 1: Capecitabine chemical structure

Capecitabine is considered with high oral bioavailability (almost 80%).Capecitabine is inactive it needs three subsequent activating step induced by enzyme catalysis. The two preceding steps involve first step deesterification followed by second step deamination.

However, the third step is the conversion of 5'-deoxy-5-fluorouridine (5'-dFdU) to 5-fluorouracil (5-FU), a step catalyzed by thymidine phosphorylase (TP). occurs in tumor tissue therefore allowing selective 5-FU activation in the target tissue. Moreover, TP is higher in tumor tissues (Figure 2)(Matloff, 2013).

5-Fluorouracil, on the other hand, is metabolized to two active metabolites, 5-fluorouridine triphosphate (FUTP), and 5-fluoro-2-deoxyuridine monophosphate (FdUMP) within normal and tumor cells. FUTP inhibits protein and RNA synthesis by competing with uridine triphosphate. Moreover, FdUMP inhibits DNA synthesis by reducing normal thymidine production.However, Dihydropyrimidine dehydrogenase(DPD) catalyzes the conversion of fluorouracil to the non-cytotoxic dihydrofluorouracil (DHFU) (Figure 3) (Gerbrecht, 2003).

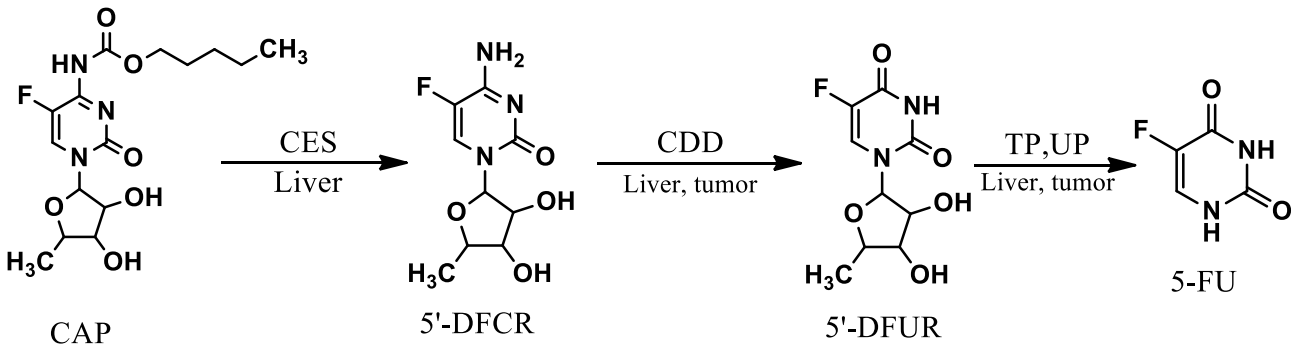



Figure 2. Capecitabine metabolic pathway. CAP: Capecitabine, CES:carboxyleterase; CDD: cytidine deaminase, TP: thymidine phosphorylase, UP: uridine phosphorylase, 5'-DFCR: 5'deoxyfluorocytidine, 5'-DFUR: 5'deoxyfluorouridine, 5-FU: 5-fluorouridine.

Xeloda has been approved for treatment of several cancers including:metastatic breast cancer unresponsive to a regimen containing paclitaxel and an anthracycline, metastatic breast cancer when used in combination with docetaxel in those patients who have previously received an anthracycline-containing regimen, and for metastatic colorectal cancer (Aras, Tecen-Yucel, Bayraktar-Ekincioglu, & Güllü, 2019).

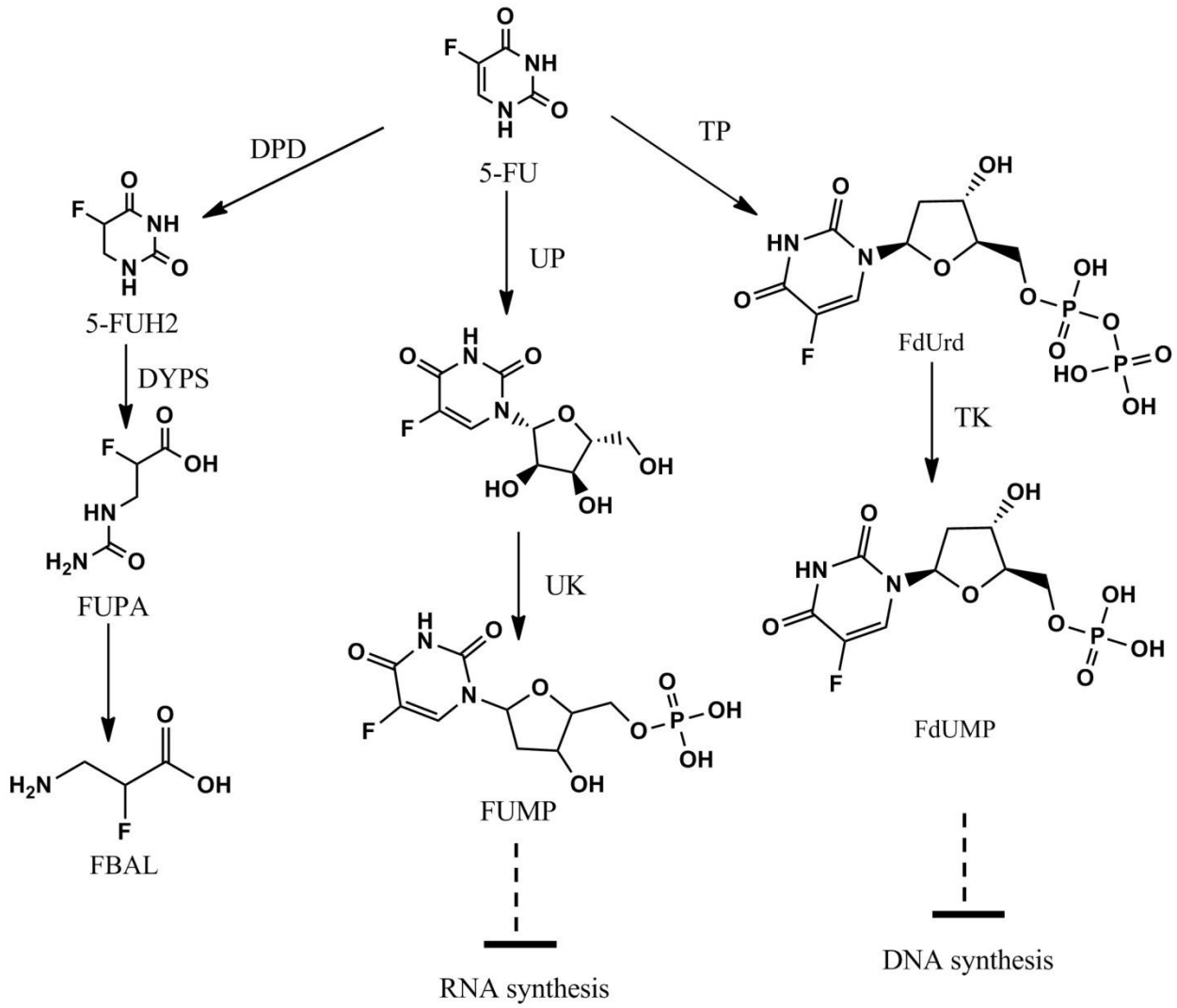



Figure 3. 5-Flourouracil metabolism pathway. 5'FU:5-Flourouracil, FUH2:dihydrofluorouracil,FUPA: a-fluoro-b-ureidopropionate, FUrd:fluorouridine, FUMP:fluorouridine monophosphate, FdUMP:fluorodeoxyuridine monophosphate, FBAL:a-fluoro-b-alanine,FdUrd:fluorodeoxyuridine, DPD:dihydropyrimidinedeshydrogenase, DPYS: dihydropyrimidine,UPB 1:β-ureidopropionase TP: thymidine phosphorylase,TK: thymidine kinase, UP: uridine phosphorylase, UK: uridine kinase.

The main toxicities of capecitabine are diarrhea along with Hand-foot syndrome (HFS). However, myelosuppression, stomatitis, alopecia, vomiting, and nausea are observed following capecitabine administration occur less frequently than following intravenous 5-FU administration (Chu & Sartorelli, 2007; Katzung & Trevor, 2015).

Capecitabine, like any regular drug, might have drug interactions. These interactions must be taken into account, as anticoagulant, phenytoin, CYP2C9 substrates, and leucovorin. As for the latter one, the concentration of 5-FU will be increased, yet toxicities will be increased as dehydration, diarrhea and entercolitis.

### 2.2.Capecitabine and Other Conventional Therapy; Efficacy and Safety

Capecitabine is an approved treatment for metastatic breast cancer (MBC), both as combination with docetaxel after failure of prior anthracycline-containing therapy and as monotherapy in patients' resistant to paclitaxel and an anthracycline-containing regimen. Combinational therapy with Capecitabine can be more challenging. A remarkable survival advantage over single-agent Docetaxel was clarified with the combination of Capecitabine plus Docetaxel in patients with anthracycline-pretreated locally advanced BC in open-label, randomized phase III trial(O'Shaughnessy et al., 2002).

Capecitabine could have synergistic activity with docetaxel (Sawada et al., 1998). Yet, docetaxel could upregulates the thymidine phosphorylase activity and in turn improve Capecitabine response (Eda et al., 1993).

As a result, it improved the response rate (RR), time to progression(TTP) and overall survival (OR)(Miles et al., 2004). Certain terms are needed to understand to measure capecitabine efficacy. Such terms are, overall survival; the time from subject randomization to the time of death from any cause which is considered the most clinically relevant and convincing endpoint in clinical trial design as long as it is accompanied by preservation in quality of life(Villaruz & Socinski, 2013).

OS accompanied with certain advantages as clinically meaningful, precisely measured and, assessed on continual basis (Villaruz & Socinski, 2013).

However, OS disadvantages are affected by crossover, subsequent therapies, longer duration and larger studies and also from noncancer deaths (Villaruz & Socinski, 2013). On the other hand, Progression Free survival (PFS) defined as the time from randomization until objective tumor progression or death (Food & Administration, 2007).

Moreover, PFS advantages are measurement of stable diseases, shorter follow up, smaller sample size and not affected by crossover. However, PFS disadvantages are definitions vary among studies, subject to internal censoring, and not precisely measured (Villaruz & Socinski, 2013).

In another study, showed addition of Capecitabine to docetaxel, improved OS, progression free, and response rate. Median survival was 14.5 months vs. 11.5 months who received docetaxel alone. In addition, among patients randomized to single-agent docetaxel, only those given post study single-agent capecitabine had significantly prolonged survival compared with those given any other post study chemotherapy (median survival, 21.0 months vs. 12.3 months, respectively).

Beside, median survival was 18.3 months in patients who stopped docetaxel and continued to receive capecitabine versus 15.8 months in patients who discontinued capecitabine and continued to receive docetaxel, which conclude that Capecitabine improve the survival response(Miles et al., 2004).

Blum observed that Capecitabine is active in metastatic breast cancer. When was given in anthracycline resistant patients, response rate was 36%, as opposed to paclitaxel 26% (Blum, 1999).However, Chan et al showed that treatment of metastases breast cancer with monotherapy regimen as Capecitabine was less effective (S. Chan et al., 2009).

Moreover, flared toxicities, since of combinational regimens, could be managed with dose flexibility(Seidman et al., 2010). Once combined with docetaxel in anthracyclin-resistent advanced breast cancer, showed an effective, well tolerable and no overlapping regimen(Blum et al., 1999; O'Shaughnessy et al., 2002; Reichardt et al., 2003).

For further clarification, Kaufman et al conducted a study compared Eribulin versus Capecitabine, no superiority was found against OS (overall survival), PFS, QoL, in randomized phase III trial. Moreover, both drugs were consistent with own adverse effects (Kaufman et al., 2015).

Be that it may seem, Gluck et al concluded in a randomized phase III trial that Estrogen Receptor (ER) plays a role in efficacy (Glück et al., 2013). Gluck et al showed that patients with ER-positive advanced breast cancer who treated with Capecitabine/Docetaxel (CD) therapy produced significantly longer OS and TTP than those treated with Docetaxel alone. Moreover, Patients

with ER-negative advanced breast cancer, who were treated with CD therapy achieved significantly longer TTP than those receiving D alone, but no statistically significant OS benefit from adding of Capecitabine to Docetaxel was observed in these patients(Glück et al., 2013).

In anthracycline-pretreated patients with advanced breast cancer, a number of chemotheraputic agents, as capecitabine, gemcitabine, and docetaxel, have proven efficacy as monotherapy (Blackstein et al., 2002; Reichardt et al., 2003; Sjöström et al., 1999).

Moreover, taxane-based combination regimens have proven improvements in efficacy compared with single agents alone. For instance, the combinations of gemcitabine plus paclitaxel (GP) and capecitabine plus docetaxel (CD) both showed improved time to disease progression (TtP), ORR, and OS compared with single-agent taxanes as first-line treatment of advanced breast cancer after prior anthracycline therapy(Albain et al., 2008; O'Shaughnessy et al., 2002).

In another studies, it was revealed no statistically significant in PFS, ORR, OS in both arms which suggest equivalent efficacy (S. Chan et al., 2009; Seidman et al., 2010). Notwithstanding, time to treatment failure (TTF) was longer in GD, in addition, nonhematologic toxicity profile (mucusitis, diarrhea, HFS) was better compared to CD arm (S. Chan et al., 2009; Seidman et al., 2010).

Despite these differences, nonhematologic toxicity-related discontinuations in the CD arm (28.4%) were significantly higher (P = 0.009) than in the GD arm (18.0%)(Seidman et al., 2010). The results were consistent with toxicity-related discontinuations noticed in the Chan experiment (CD = 29.3%, GD = 13.8%)(S. Chan et al., 2009).

As for chemotherapeutic drug, Capecitabine would cause side effects. Masci et al showed that low dose of Capecitabine in advanced breast cancer has lower toxicity profile and similar overall response rate and survival data in comparison to approved dose (Masci et al., 2017).

In three randomized controlled trials, low doses of Capecitabine did not affect the efficacy (1000, 950, 825 mg/m2) (Bachelot et al., 2008; Bertelsen et al., 2015; Mavroudis et al., 2009; Soto et al., 2006).Yet, low dose of Capecitabine (825mg/m2) was effective and well tolerated (Hennessy, Gauthier, Michaud, Hortobagyi, & Valero, 2005; H.-q. Wang et al., 2010).

Despite the proven tolerability and efficacy profile of capecitabine, selection of an optimal starting dosage remains a challenge, and clinical practices for treatment initiation differ worldwide(Haller et al., 2008). Be that as it may, there are no conclusive data showing that reducing the starting dose of single agent capecitabine does not affect efficacy(Martín et al., 2015).

Miller et al noticed that when integrate Bevacizumab (monoclonal antibody/VEGF) to Capecitabine in previously treated patients with anthracyclin/ taxan, it improved response rate (RR) but not OS, PFS (K. D. Miller et al., 2005). However, HFS increased by 25% (K. D. Miller et al., 2005).

In Seidman et al study, two arms were compared (GD, CD) (Gemcitabine/Docetaxel and Capecitabine/Docetaxel) in pretreated anthracyclin/taxans patients. Seidman et al revealed the lower capecitabine dose was tolerated with the lower incidence of neutropenia (30.5% versus 78.6%), febrile neutropenia (6.2% versus 14.7%), and mucositis (4.4% versus 15.3%) noticed when compared with the Chan trial (S. Chan et al., 2009; Seidman et al., 2010).

Campone et al showed that with non-overlapping toxicities, vinflunine was evaluated in combination with capecitabine (VC) in advanced breast cancer, showing a 44% increase overall response rate (ORR)(Campone et al., 2012). Moreover, VC was superior IRC-assessed PFS compared with Capecitabine alone in phase III trial (Martin et al., 2018).

Add up, VC combination offers improved PFS and DCR compared with capecitabine alone in taxane-resistant anthracycline pretreated/resistant advanced breast cancer(Martin et al., 2018). In regarding to safety profile, HFS was lower in VC (25%, versus 47% with capecitabine alone) since low dose of Capecitabine alone) (Martin, Campone et al. 2018).

Zhang et al study phase III trial comparing utidelone (an epothilone analogue) plus capecitabine (1000 mg/m2 b.i.d., days 1–14) versus capecitabine monotherapy (1250 mg/m2 b.i.d., days 1–14) in advanced breast cancer patients with pretreated (refractory to anthracyclines and taxanes)(P. Zhang et al., 2017).

The study showed that IRC-assessed PFS was significantly higher in the combination treatment(PFSmedian 8.4 versus 4.3 months with capecitabine alone). The combination arm was prone with a high incidence of grade 3 peripheral neuropathy (22% versus <1% in the capecitabine alone arm). Interestingly, grade 3 hand-foot syndrome occurred at a similar incidence in the two treatment arms (7% with utidelone/capecitabine versus 8% with capecitabine alone)(P. Zhang et al., 2017). Yet, comparison of incidence of toxicities among population is complicated because of differences in the tolerability of fluoropyrimidines in Asian versus non-Asian populations(Martin et al., 2018). Additionally, tolerance to Capecitabine could differ from one population to another (Haller et al., 2008).

Most phase III trials in pretreated advanced breast cancer have failed to show improved outcomes with novel agents combined or compared with capecitabine (Barrios et al., 2010; Baselga et al., 2017; Crown et al., 2013; K. D. Miller et al., 2005).

However, combination of ixabepilone and capecitabine was superior to capecitabine alone in this setting (Sparano et al., 2010).In two phase III trials, addition of ixabepilone (microtubule stabilizing agents known as epothilones) to capecitabine improved PFS, OS, and ORR over capecitabine alone in each of the two studies(Roché et al., 2011).

The combination increased median OS by 2.8 months with a 25% reduction in the risk of death (P = 0.0015), recommending a clinically sequential OS benefit. However, the treatment effects might vary depending on Karnofsky's index performance status (KPS). New advanced treatment is warranted, especially who with reduced performance status. Patients with of performance status (KPS) 70 are unable to do regular activity, and patients with KPS 80 are able to do normal activity and have some symptoms. On the other hand, patients with KPS 90 are able to carry on normal activity and experience minor signs/ symptoms while patients with KPS 100 have no signs or symptoms of disease(Roché et al., 2011).

Combination of Ixabepilone plus capecitabine appeared to show better efficacy compared to capecitabine monotherapy in advanced breast cancer patients previously treated with

anthracyclines and taxanes, regardless of performance status, with a possible OS benefit favoring KPS 70–80 patients (Roché et al., 2011).

As it may seem, the safety profile showed increased toxicity as Grade 3/4 neuropathy since of combination more frequently in patients with KPS 70-80 (Roché et al., 2011). However, Vahdat et al revealed that the combination of ixabepilone plus capecitabine maintains its efficacy in elderly patients with anthracycline and taxane pretreated advanced breast cancer (Vahdat et al., 2013). The safety profile of ixabepilone plus capecitabine was also similar between patients aged <65 and ≥65 years (Vahdat et al., 2013).

The improved ORR, PFS were maintained and was independent on age (Thomas et al., 2008). Nevertheless, OS, was insignificant in both groups. Thus, combination of ixabepilone with capecitabine appeared consistent efficacy and toxicity profile in both aged group patients (65 years and <65 years) (Vahdat et al., 2013). As a result, further examinations are warrented to overcome any further toxicities and expenses.

In another study, subsequent Phase III trial did not show any superiority of vinorelbine/gemcitabine combined over single-agent capecitabine in terms of PFS, OS and ORR (Pallis et al., 2011).

Furthermore, Sunitinib (tyrosin kinase receptor inhibitor), showed less efficacy than Capecitabine and even lowered the PFS in pretreated taxan/anthracyclin(Barrios et al., 2010). Further research has been made on combining sunitinib plus Capecitabine was compared to capecitabine monotherapy in phase III trial, however, the outcome was not promising (Crown et al., 2013).

The most common adverse effects of combinational therapy were Grade ¾ hematologic toxicities due to effect on suppression of bone marrow. However, there were no significant differences in nonhematologic adverse effects. Moreover, Grade 3–4 hypertension in bevacizumab/sunitinib group were more frequent than capecitabine monotherapy(Jiang et al., 2018).

Oostendorp et al observed an overall response rate (ORR) of 18%, a median PFS of 4.2 months and a median OS of 13.5 months in patients treated with capecitabine monotherapy, who had pretreated with taxan/anthracyclin(Oostendorp, Stalmeier, Donders, van der Graaf, & Ottevanger, 2011). Barchiesi et al analyzed the phosphoproteomic and genomic profiles of patients with breast cancer, who had remarkable response to capecitabine, it might be related to alteration in DNA repair, chromatin remodeling genes or may be other variations. Some preclinical data suggest that sensitivity to 5-fluorouracil may be improved by deficiencies in chromatin remodeling and homologous recombination genes(Barchiesi et al., 2019).

### 2.3. Hand and Foot Syndrome –Induced ByCapecitabine

#### 2.3.1.Overview and Incidence of HFS

Hand and foot syndrome (HFS) is a skin reaction (also known palmar-plantar erythrodysesthesia (PPE), which allude to a condition where the palms of the hands and soles of the feet turn dry, crimped, red, numb, and tingling, and swelling(Aras et al., 2019).

Hand and foot syndrome (HFS) is the main prominent side effect of Capecitabine, despite Capecitabine is well tolerated (Hennessy et al., 2005). It was first described by Zuehlke in 1974(Miller, Gorcey et al. 2014).Other chemotherapeutic drugs have shown to cause HFS as fluorouracil (5-FU), liposomal doxorubicin (Doxil®), doxorubicin (Adriamycin®), cytarabine (Ara-c®), sunitinib (Sutent®) and sorafenib (Nexavar®)(K. K. Miller, Gorcey, & McLellan, 2014; Palaniappan, Srinivasamurthy, Dubashi, & Chandrasekaran, 2014; Webster-Gandy, How, & Harrold, 2007).

In study of Palaniappan et al of overall 112 cases, rate of developed HFS due to 5-FU was (0.9%), Capecitabine (33.9%), docetaxel (8.8%), gemcitabine (1.9%), and due to imatinib (1%) (Palaniappan et al., 2014).Therefore, capecitabine is commonly implicated drug followed by docetaxel(Palaniappan et al., 2014).

Incidence of HFS is around 50-60%(Aras et al., 2019).The reaction may overlap with daily activities,particularly when skin becomes blistered, desquamated, accompanied with severe pain

and ulceration(Gressett, Stanford, & Hardwicke, 2006; Mrozek-Orlowski, Frye, & Sanborn, 1999).

Capecitabine is considered a more selective substitutional to 5-FU. Capecitabine, in tumor cells, will be converted into the active form (5-FU). Therefore, side effects as neutropenia and stomatitis, associated with 5-FU, will be reduced(Xu et al., 2019). However, HFS occurs in a large percentage (almost 50%) of capecitabine –treated patients, with 17% of grade 3 HFS(Palaniappan et al., 2014).

**2.3.2. Clinical Manifestations**

It occasionally occurs during the early cycles, however, might appear in later cycles of Capecitabine. There are different grading system for the HFS severity, the WHO system classifies the severity into four different grades, grade I- IV, the grade IV is the most sever, while the U.S. National Cancer Institute (NCI) grading system for HFS consists of three (Aras et al., 2019).

In grade I, Skin changes (as numbness, dysesthesia, paresthesia, tingling, erythema) with discomfort but not disrupting normal activities. Dosage adjustments of capecitabine are needed based on severity of HFS. In case of grade II, skin changes (e.g., erythema, swelling) with pain intervening diurnal efficiency, accompanied with changes in doses events of Capecitabine.

As for grade III, there is Severe skin changes (as ulceration, moist desquamation, blistering) with pain, causing severe annoyance and difficulty to perform daily activities, and accounted to be 10-70% of all cases (Aras et al., 2019; Palaniappan et al., 2014). Thus, HFS of grade $\geq 2$, capecitabine therapy should be stopped instantly and restart at a reduced dose when the toxicity settled down to grade 1.

Table 1. Summary of the HFS WHO grading system table

| Grades | Clinical domain | Functional domain |
|---|---|---|
| 1 | Dysesthesia/paresthesia, tingling in hands and feet | Inconvenience without disturbing daily activities |
| 2 | Difficult in walking and holding objects, painless swelling and erythema. | Difficulty in doing daily activities. |
| 3 | Swelling in palms and soles with Painful erythema, periungual erythema and swelling. | Severe discomfort, unable to work or perform activities of living life. |
| 4 | Desquamation, ulceration, blistering, severe pain | Severe discomfort, unable to work or perform activities of living live |

Although HFS symptomsusually subside within 1 to 2 weeks of stoppingtreatment, perpetualcomplicationmight occur(Lou et al., 2016; Webster-Gandy et al., 2007).

In previous report showed that with use of capecitabine, epidermaldestruction could occur which lead to Loss of fingerprints(Kamil et al., 2010). In addition, repeated episodes ofHFS can result in thickening of palmoplantar area as a cornified layer resembling a keratoderma(Lou et al., 2016).

### 2.3.3. Pathogenesis of Capecitabine-Induced HFS

Up to now, the mechanism of action of HFS still unknown, and there are limited data available on prevention and its management(Gressett et al., 2006; Lou et al., 2016).The HFS development could be considered as drug/dose-dependent, however, the pathogenies are still poorly understood. The total cumulative dose, peak plasma drug concentrations, and administration protocol impacting the onset and severity(Scheithauer & Blum, 2004).

Once treatment is initiated, the HFS symptoms may develop as early as 24 hours and as late as 10 months after continued therapy(Scheithauer & Blum, 2004). HFS evolves when tiny quantity of chemotherapeutic agents seep out of the capillaries into the hands and feet (Oncology, 2009). However, there are different hypotheses of capecitabine-induced HFS pathogenesis (Lou et al., 2016).

It is believed that capecitabine cause keratinocytes vascular degeneration, apoptosis, perivascular lymphocytic filtration, and edema. Firstly, capecitabine excretion by eccrine sweat glands which

are abundant in palmsand plantar leads to accumulation of its metaboliteswhich may explain the reason for affecting these areas more than the others.

Moreover,the elevated thymidylate phosphorylase (TP),UP (uridine phosphorylase) and lower level ofDPD expression in the keratocytes, could contribute to the increased capecitabine metabolite level(Lou et al., 2016).

As a result, capecitabine-induced HFS may be somehow because of overexpression of TP in the skin mainly in hands and feet. Moreover, rapid cell proliferation in these areas and the increased of TP activity are due to active epidermal regeneration(Palaniappan et al., 2014).

For further clarification, basal keratinocytes proliferation rate of the palm was notably higher than that of cells in the back, significantly increasing cell sensitivity to cytotoxic drugs. Furthermore, TP expression was 3 to 10fold higher in cancerous cells than in neighboring normal cells, which allows a better selectivity of drug-tumor specific activation of 5-FU and reduce systemic toxicity(Farr & Safwat, 2011; Lee et al., 2007).

Moreover, orotate phosphoribosyl transferase (OPRT), in different pathway, could metabolize 5-FU. Therefore, TP and UP Inhibition did not hinder the 5-FU synthesis. Moreover, TP is considered an angiogenic marker; which is related to the increased blood flow in the palm, thus HFS might be connected to increased blood flow in the area. However, as it may seem, further studies are required, if TP, or DPD have a key main role in the pathogenesis of capecitabine induced – HFS for full clarification (Lou et al., 2016).

It is also believed that increased vascularization, temperature, and pressure in the hands and feet may lead to HFS(Lou et al., 2016). For further clarification,metabolite accumulation in those areas, yet oxidative stress will be generated, mediated by chemokines as (interleukin ( IL-8, IL-1b, IL-1a, IL-6), GRO, fractalkine (K. K. Miller et al., 2014; Yokomichi et al., 2013).

Thermoreceptor TRPM2, which is expressed on the keratinocyte surface,willbe sensed to Reactive Oxygen Species (ROS) in the environment, this will lead to chemokine productions.

Consequently, TRPM2 receptors will create a hole on skin surface through $Ca^{+2}$ influx. Chemokines will induce death factors productions as Tumor Necrotic Factor (TNF)and Fas ligand which cause apoptosis (Yokomichi et al., 2013).

These observations highlight the connection between the concentration of anticancer medications in eccrine sweat and subsequently clinical and histological changes in the skin (Horn, 1997; Kamil et al., 2010).

Secondly, another suggested hypothesis states that cyclooxygenase (COX-2) overexpression, in palm and feet, by capecitabine and its metabolites. COX-2 enzyme plays a key role in inflammation and pain. Thus, celecoxib is selective (COX-2) inhibitor, , may play a key role in the HFS treatment plan(Aras et al., 2019; Lou et al., 2016; R.-X. Zhang et al., 2011).

Thirdly, carrier system as ATP-binding cassette (ABC) is one of the membrane transport systems containing proteins that transfer miscellaneous drugs and endogenous compounds as capecitabine metabolites from the membrane.

In addition, it removes chemotherapeutic agents from cancerous cells and prohibits drug accumulation in the tumor cells, therefore results in drug failure. Thus, these ATP-binding cassettes might have a key role in fluoropyrimide-based response by defining the drug concentration within the cell which drives to skin reactions on hands and feet (Aras et al., 2019; Lou et al., 2016). For example, three ABCB1 SNPs showed a significant association with moderate-sever HFS(Lou et al., 2016).

### 2.3.4. Management and Prophylaxis of HFS

As for the best, up to now, HFS management is through treatment interruption, or dose modification which may also affect the treatment efficacy (Aras et al., 2019; Lou et al., 2016; K. K. Miller et al., 2014).On the other hand, in randomized controlled trial suggested effective prevention of HFS associated with pegylated liposomal doxorubicin (PLD), docetaxel, 5-FU, and capecitabine(Corrie et al., 2012; Jain & Dubashi, 2012).Furthermore, the prevention of HFS-exacerbation is warranted. As it may seem, avoid prolonged heat exposure, hand tools and knives, keep the pressure off, and take a break from exercise(Lou et al., 2016).

Besides, few tips are required to reduce the pain as patting the skin rather than rubbing, keep the skin moist, trying to wear slippers or ventilated shoes and avoid the unbreathable ones, staying away from harsh chemicals, and elevating the hand and feet when sitting or lying down (Lou et al., 2016).

Preventativemeasures against HFS are considered the cornerstone. They are targeted toward symptomscontrol which usually shows improvement after 1 or 2 weeks andinvolve pain control, frequent emollient use, wound care, high-potency topical corticosteroids, and topical keratolytics (Lou et al., 2016). The discontinuation of chemotherapeutic drugs or dose reduction of the involved medicine is usually the mainstay of HFS management (Palaniappan et al., 2014). Usually the main approach is treatment interruption once grade 2, 3 HFS appear, until incidence resolves or subsides to grade 1.

If frequent flares of grade 2, 3 HFS, then dose reductions and treatment interruptions. However, drug discontinuation at 50% of the recommended dose of the drug when severe case of HFS occurrence (Kwakman, Elshot, Punt, & Koopman, 2020).

In previous study of 86 patients with colon cancer treated with capecitabine, 22 patients (26%) were under dose reduction, and 15 patients (17%) were discontinued capecitabine because incidence of HFS(Leicher, de Graaf, Coers, Tascilar, & de Groot, 2017).

In addition, in another study, 10% of 81 patients, who received capecitabine, discontinued the treatment because of HFS(Kwakman et al., 2017).

Switching to more tolerable drug with similar mechanism of action, lower incidence of HFS, and equivalent efficacy is the best strategy. In previous study observed that switching to S-1 in 52 patients, 94% showed a lower incidence of grade 2, 3 HFS, with complete remission in 56% of the patients. (Kwakman et al., 2020). Subsequently, moderate to severe HFS which associated with capecitabine, can be switched to intravenous 5-fluorouracil, which is also associated with a lower incidence of HFS(Cassidy et al., 2002). On the other hand, further clinical studies on this approach are needed. (Figure 1).

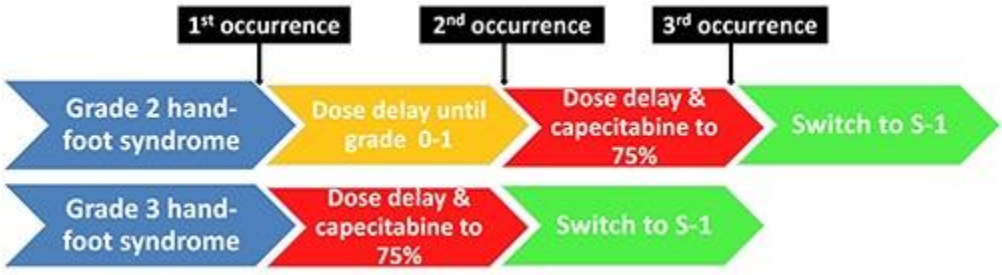



Figure 4. Flowchart for treatment management of capecitabine-induced hand-foot syndrome (Kwakman et al., 2020)

In penultimate, pharmacologic interventions such as dexamethasone(Drake et al., 2004), celecoxib(Lin, Morris, & Ayers, 2002), and vitamin E(Kara, Sahin, & Erkisi, 2006), which exhibited an eminent reduction in symptoms of HFS, are extremely important (K. K. Miller et al., 2014).Other studies showed that using vitamin E was effective in minimizing the incidence of capecitabine-induced HFS without the need to reduce the dose or to influence its efficacy (Nikolaou, Syrigos, & Saif, 2016; Yamamoto, Yamamoto, & Tanaka, 2008).

There are contradictory results regarding the use of pyridoxine in capecitabine-induced HFS prevention. Zhou et al noticed that pyridoxine was not able to reduce capecitabine-induced HFS (Zhou, Peng, Li, & Chen, 2013).

There is different trials showed to be effective in prevention of episodes of HFS as shown in hydroxy-β-methylbutyrate (HMB), L-arginine and L-glutamine supplementation (Naganuma et al., 2019), topical aluminum chlorohydrate(Templeton et al., 2014), topical ointment(Lademann et al., 2014), and application of antioxidant ointment (Jung et al., 2017).

Thus, Further research and prospective randomizedstudies, are required to further recognize the pathogenesis and management options.

### 2.4. Capecitabine and Pharmacogenomics

“If it were not for the great variability among individuals, medicine might as well be a science and not an art "Osler, 1892. As a human being, we are 99.9 percent genetically identical and only 0.1 percent make us unique and thus variation will come up which could be harmless or harmful such as cancer, diabetes, and Alzheimer. To get to the point of genetic variations, pharmacogenetics science will shine up(Huddart et al., 2019).

Pharmacogenetics is the study of gene influences on therapeutic choices and adverse effects of the drug, the term was coined by Vogel 1959. Pharamacogenetics focuses on patients variability by using one single drug in different patients to predict drug toxicity . The most common types of variations are single nucleotide polymorphism(SNP) and INSERTION/DELETION (INDEL)(Palmirotta et al., 2018).

On the other hand; pharmacogenomics studies multigenic effects on drug response and focus on drug variability through working on many drugs for single genome to anticipate drug efficacy which is very beneficial in drug discoveries and developments. There are currently over 190 drugs such as Carbamazepine, Warfarin, Clopidogril, and Azathioprine have been labeled in pharmacogenetics discoveries and FDA documented a guideline to use pharmacogenetics discoveries in drug developments(Huddart et al., 2019).

Personalized medicine: is individual targeted therapy to include right patient, time, drug, indication and right dose to improve safety and efficacy for each patient when prescribing the best suitable drug based on genetic profile which enhance outcome prediction, and therefore, pharmacogenetics is the heart of precision medicine and thus is considered an evolution not a revolution(Seredina, et al., 2012).

Pharmacogenetics can affect drug responses through , firstly , drug disposition (pharmacokinetic)which includes absorption , distribution , metabolism and elimination , for example; a variation in drug metabolizing pathway may lead to a change of drug metabolism and therefore substrate may increase or decrease in concentration which in turn lead to toxicity or lack of efficacy respectively, as in case of capecitabine and CYP450 2C9 polymorphism which in turn results in loss activity of enzyme and increase capecitabine toxicity(Seredina et al., 2012).

Secondly; drug-target pharmacodynamics where there is a variation in receptor gene or enzyme itself will alter drug response, polymorphism in the gene will change chemotherapy response and lead to toxicity. Studies in pharmacogenetics can be classified into candidate gene studies or Genome wide association study (GWAS).

In candidate gene study focus on studying the frequency of allele or sets of allele regarding drug response, as the study gene polymorphism and chemotherapy, is considered less costly and need less number of samples but need previous knowledge on gene. GWAS which genotype a large

number of SNPs sets to determine sets of the allele are more common in patients with certain diseases or drug responses which in turn discover gene function and determine biomarker for it(Palmirotta et al., 2018; Seredina et al., 2012).

Interindividual and inter-regional heterogeneity subsists with regard to toxicity and efficacy profiles, and may be partially elucidated by genetic variation (Syn, Lee, Goh, & Yong, 2016). Gene polymorphisms can describe a vicinity of patient pharmacodynamic variability of anticancer drugs, especially fluoropyrimidines. Genes polymorphisms may notablyaffect pharmacodynamics of fluoropyrimidines, including capecitabine, are thymidylate synthase (TS), methylenetetrahydrofolate reductase (MTHFR), and dihydropyrimidine dehydrogenase (DPD). DPD deficiency in breast cancer patients receiving capecitabine, has a role in efficacy and toxicity, which require further investigations (Largillier et al., 2006). The *DPYD* gene encodes DPD, which catalyzes the rate-limiting step in the breakdown of fluoropyrimidines.

The nonfunctional *DPYD* variants which have been associated with low DPD activity and an increased risk of toxicity with fluoropyrimidines (Dean, 2016). One of the toxicities is HFS, was strongly associated with higher levels of DPD due to elevation of Capecitabine catabolites (Milano et al., 2008).

The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published dosing recommendations for fluoropyrimidines (capecitabine, fluorouracil) based on *DPYD* genotype. CPIC recommends using an alternative drug for patients who are “poor metabolizers”. These individuals bear two copies of non-functional *DPYD* variants and typically have complete DPD deficiency.

Moreover, they have the increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs. CPIC also suggests a 50% reduction in initial dose for “intermediate metabolizers”. These individuals carry a combination of a normal-function and a non-functional variant and typically have reduced DPD activity (Caudle et al., 2013).

Overall, the prevalence of individuals who are heterozygous for nonfunctional variant *DPYD* alleles (partially DPD deficient) that place them at risk of severe drug reactions is

estimated to be as high as 3-5%, but this varies in different populations. For example, in the Dutch population, the *DPYD*2A* had an allele frequency of 0.91% in Caucasians (Dean, 2016).

Moreover, DPD polymorphisms rs12132152 and rs76387818 were strongly associated with HFS (Lou et al., 2016). Thus, Both the Clinical Pharmacogenetics Implementation Consortium and Royal Dutch Association for the Advancement of Pharmacy–Pharmacogenetics Working Group have recommended fluoropyrimidine dosing guidelines based on *DPYD* genotypes (Caudle et al., 2013).

Besides, thymidylate synthase (TS), encoded by TYMS gene, it's inhibition by the active metabolite fluorodeoxyuridine monophosphate prevents the formation of thymidylate (dTMP), which is a precursor for DNA synthesis, leading to cell-cycle arrest and apoptosis. TYMS is an enzyme which catalyzes the conversion of dUMP to dTMP, and is the main intracellular target of the active 5-FU metabolite, 5-FdUMP, which composes a ternary complex with TYMS and 5-10 MTHF. However, mechanism of resistance to 5-FU is due to mainly raised TYMS expression(Syn et al., 2016).

Ooyama et al observed that the copy number of *TYMS* (18p11.32) exhibited a strong association with drug resistance, which may lead to the use of *TYMS* copy number as a predictive marker for fluoropymidines drug sensitivity (Ooyama et al., 2007).Moreover, TYMS polymorphisms rs2612091 and rs2741171 were strongly associated with HFS (Lou et al., 2016). Thus, as it may seem, the clinical relevance of pharmacogenetics in capecitabine-containing regimens, should be investigated (Syn et al., 2016).

The science of pharmacogenetics is the core principle for understanding genetic makeup of the individual and look at mutations would occur which could happen environmentally, chemically or interaction of multiple genes(Frigon et al., 2019).

Fatal adverse reactions to drugs are known the fifth leading cause of death, therefore; Understanding the pharmacogenetics science is imperative to identify new drug targets, optimize

doses and most importantly, improve patient outcomes and prevent fatal reactions(Frigon et al., 2019).

Following such a research comes from education, communication and willing to initiate it. No science without obstacles and some limitation are ; researcher use it if it is free, and needs clinical validation, sometimes is costly mostly for multiple genes, could create anxiety between healthcare providers and public when gathering genetic information without permission which leads to problems and genetic discrimination(Palmirotta et al., 2018).

Pharmacogenetics science serves as a foundation of molecular/ biologicalscience and results in technological and pharmacological advancements indiagnosis of patients with spectrum of clinical disease s, will come up byunderstanding gene expression, signaling, and regulation. To sum up,having an education about pharmacogenetics is important which lead tostart practicing on Manipulating the genomic research, the physician willbe willing to translate these approaches to patient's care(Huddart et al., 2019).

At the end, patient health outcomes are our concern, looking at geneticprofile of patients is a good step to prescribe medications, in addition,avoiding side effects.

### 2.5. Pharmacist Role and Capecitabine

Pharmacist in oncology care plays an important worthy role in improving safety, efficacy, and quality of delivery care for cancer patients. Pharmacist represents a high level of expertise, practice, skills and responsibilities. They have a rigid responsibility in patient care with cancer during all phases and stages of treatment. From point of assessment and diagnosis to treatment plan, symptoms management with supportive care(Holle & Boehnke Michaud, 2014).

Pharmacist are responsible to ensure safety in administration, dispensing and compounding of chemotherapeutic agents, and maintain adequate supply of medications. Moreover, provide direct patient care as integral part work collaboratively with other healthcare provider in creating institutional guidelines. Pharmacist experts are considered cornerstone in patient education with decision making involvement(Hoppe-Tichy, 2010).

As it may seem, pharmacists are important in minimizing drug waste, unnecessary exposure and managing the costs. Furthermore, they are responsible in management of patient complications as pain, diarrhea, dehydration, depression, nausea and vomiting. Therefore, pharmacist should contribute in clinical research studiesand supporting investigational drug service programs(Holle & Boehnke Michaud, 2014).

Pharmacist in oncology care is paramount in patient and provider education. They are accountable in developing medication therapy management, developing a role in cancer prevention and treatment, and developingan independent prescribing protocol. Furthermore, they are in charge in training and practices settings (Holle & Boehnke Michaud, 2014).

Capecitabine is one of Oral chemotherapeuticagents. Oral regimen is considered convenience, however, it could be complex and with challenge adherence. Therefore, pharmacist should focus on patient education about oral capecitabine, monitoring toxicities with better prescribing practice protocols. In addition, the importance of counseling, through specific model, to facilitate standardization of pharmacist training and assessment of competency in patient counseling.

By this, it will improve patient education, compliance, adherence and toxicities (Allen & Williamson, 2014). Pharmacist should realize any drug/food interaction when patient taking oral capecitabine, add up, should know any previous allergies and ability to manage the toxicities and reducing it to lowest possible limit.

There is a notable interaction between capecitabine and warfarin, pharmacist should be aware of this interaction. Since venous thromboembolism is common complication of malignant disorders. Capecitabine or its metabolite will down regulate CYP2C9, as a result, area under the curve (AUC) will increase, and elimination half-life will decrease ($t_{1/2}$).
Therefore, prothrombin time (PT), and international normalized ratio (INR) will be elevated after introducing capecitabine and might be last 2 months after stopping it (Giunta, 2010).

Warfarin is a vitamin K antagonist that blocks vitamin K–dependent clotting factors II, VII, IX, and X and proteins C and S synthesis.Warfarincontain 2 enantiomers, (*S*) and (*R*), with (*S*)-enantiomer is being 2 - 5 times more potent than (*R*)-enantiomer. Furthermore, (*S*)-enantiomer is mostly metabolized by cytochrome CYP2C9, while (*R*)-enantiomer is metabolized by CYP1A2 and 3A4(Kaminsky & Zhang, 1997).

Thus, it is important to investigate which enantiomer is involved in this interaction and, dose adjustment to avoid risk of bleeding (Giunta, 2010).

Another risk factor pharmacist should be focused on is coronary vasospasm/cardiotoxicity.Cardiotoxicity might lead to form of arrhythmia and ventricular dysfunction(Nguyen, Nguyen, & Tsu, 2015).

Patient taking capecitabine might have increased risk to ischemic heart disease (Papadopoulos & Wilson, 2008). The main clinical manifestation of symptomatic cardiotoxicity from capecitabine is chest pain, and then other subjective symptoms with ECG changes (almost 50%).

Cardiotoxicity –induced capecitabine accounted to be 5% (Polk et al., 2016). The cardiotoxic effects of capecitabine is noticed mostly in patients with a history of cardiac disease and is considered reversible upon discontinuation of the agent. However, the exact mechanism still unknown(Steingart, Yadav, Manrique, Carver, & Liu, 2013). It might be related to smooth muscles spasms and direct vasoconstriction. Nevertheless, nitrates and calcium channel blockers were not seen as effective preventative agents for the cardiotoxic events. Moreover, 5-FU might be catabolized to fluoroacetate, which is a known cardiotoxic agent. Furthermore, oxidative stress on cardiomyocyte play a role(Nguyen et al., 2015).

As a result, premature halt of capecitabine treatment could be related to cardiotoxic event, thus it might hinder breast cancer treatment besides worsening in the heart. Therefore, pharmacist have crucial responsibility in recognizing high risk patient as hypercholesterolemia and smoking, dosing and frequency adjustment, and utilizing cardio protective drugs when applicable (Nguyen et al., 2015; Polk et al., 2016; Sentürk, Kanat, Evrensel, & Aydinlar, 2009).

Other complication the cancer patient might suffer is diarrhea. Diarrheacould cause fatigue, weight loss, skin blister and malnutrition since of dehydration(Richards & Ross, 2020). In addition to the therapy of chemotherapy as capecitabine , diarrhea could result of surgery (celiac plexus block, cholecystectomy, esophagogastrectomy, gastrectomy, whipple procedure, intestinal resection, vagotomy), bone-marrow transplantation-related, cancer itself, (carcinoid syndrome, colon cancer, lymphoma, medullary carcinoma of the thyroid, pancreatic cancer or pheochromocytoma), or Radiation-therapy related. Knowing the exact cause is important for the pharmacist as according to the National Cancer Institute's Common Terminology Criteria for diarrhea(Richards & Ross, 2020; Wadler et al., 1998). Severity grade of diarrhea as follow;

- Grade 1: the frequency of stool in day of less than 4.
- Grade 2: the frequency of stool in a day 4 to 6.
- Grade 3: the frequency of stool increase of greater than 7 in a day which require hospitalization.
- Grade 4: for life threatening consequences (urgent intervention indicated).
- Grade 5: might lead to death.

It is important that pharmacist ascertains the grade status of the patient's diarrhea before counseling patients. The need to know and to confirm which grade of diarrhea because it could be early sign (< 24 hr after administration of therapy) or late (> 24 hrs after administration of therapy) and after persistent (present for > 4 weeks) or not persistent (of less than 4 weeks)(Bines et al., 2020; Wadler et al., 1998).

Dietary modifications by counselling patients to begin on a protocol of the BRAT diet (bananas, rice, apple, toast) in addition increase water intake (~ 3 liters per day), eat small frequent meals that do not stimulate the intestines (lactose-containing food, spicy food, alcohol, caffeine containing beverages, high fat or fiber containing food and carbonated drinks) to manage uncomplicated diarrhea (grade 1 and 2). Pharmacist should recommend also to take probiotic supplements which enhance beneficial microflora in the intestine to stop diarrhea(Bowen et al., 2019).

The main goals of medication therapies are to inhibit intestinal motility to promote absorption. Loperamide, Octreotide, and opium are used to treat uncomplicated diarrhea. Moreover, pharmacists recommend for patients to take bismuth subsalicylate (anti-secretory agents)whichdecrease intestinal secretion and should with cautions with other salicylates like aspirin or has bloody stools. In this case, loperamide is the safer alternative that can be suggested by the pharmacist(Bowen et al., 2019).

The pharmacist should be aware that a grade 1 or 2 with added risk factor of severe cramping, nausea, fever, bleeding or dehydration should be treated as complicated diarrhea (>=3). Thus, immediate management are needed to abstain diarrhea(Aziz, Fatima, Douglass, Abughanimeh, & Raza, 2019).

Nausea and vomiting are very common among cancer patients with incidence of 30 to 90%. Which have a huge impact on patient quality of life. Nausea and vomiting could be classified into acute (within 24 hr), or delayed (after 24 hrs)(Jookanti et al., 2019).

Pharmacists can use the rating system developed by The American Society of Clinical Oncology for chemotherapeutic drugs and their risk for acute and delayed emesis to prepare the patient before chemotherapy round. On the day of the treatment, the pharmacist can enhance the patient to introducedeep breathing and meditation, acupuncture to relax. In addition, advice patients Pharmacist can ask the patients to keep a diary so that they can learn the best time to eat or not to eat before treatment depending on their previous experience(Jookanti et al., 2019).
Also, when it comes to food and drinks, the pharmacists should counsel the patient to ingest nutrition that is easy on the stomach(Henson et al., 2020).

Pharmacological agents that are occasionally given to cancer patients as 5-hydroxytryptamine receptor antagonist and dexamethasone with or without lorazepam. Pharmacists should promote the patients to take antinausea medication as prescribed even on days the patient is feeling well. In addition, it is advised to do counseling for patients to be a way from food which stimulate

nausea as greasy, fried, salty, or spicy food and even the smell or hot food could have a impacts on patients and it is recommended to let food cool down before eating. The pharmacist should counsel the patient to take small sips of water throughout the day and breakdown the meals into 5 to 6 portion during the whole day instead of drinking and eating a lot of food in one siting(Navari, 2020).

## 3. MATERIAL and METHOD

This segment portrays the procedures and strategies applied to systematically review in breast cancer patients to see the effect of capecitabine alone and its combination notwithstanding the wellbeing (safety) profile of the medication. Cochrane guidelines has been used for systemic review to write the protocols on the effects of healthcare interventions (2011). The review guideline is recorded with PROSPERO (ID:CRD42020168540)

### 3.1. Eligible Criteria

The standards for excluding and considering the related studies for this systematic review were led as per the Population Intervention Comparison Outcome Study (PICOS) structure system (Santos et al., 2007). In order to determine medical literature for systematic reviewing, the PICOS protocol assorted these search terms into thematic ones. Standard search strategies of the chemotherapeutic agents, with additional equations, were utilized to determine the applicable terms.

### 3.2. Population

The target groups included all patients who aged >=18 years old and have advanced or metastatic breast cancer. All population received previously anthracycline and taxanes treatment and receiving capecitabine alone or capecitabine in combination were included in the review.

Patients with another cancer rather than breast cancer, patients who didn't receive before anthracycline and taxan, patients who are not on capecitabine or capecitabine combination orany missing information in relation to patient's characteristics or related to the clinical settings in the studies, were excluded from this systematic review.

### 3.3. Intervention and Comparator

Adults who received capecitabine alone or in combination with other agents will be included in this review. No active or what we call it "placebo" has been considered too. Furthermore, it is important to state drug doses in both arms (intervention, comparator), or at least in the intervention one. The drugs in both arms (intervention and comparator) must be given in oral

route and should be continued to be received as outpatient patients.Any additional agents from different classes have been permited to be received as a stepped therapy. Theseadditional agents should be stated and followed the same strategy in both arms. According to a stringent trial protocol, trial patients and the treatment provider are maintained, with any certain issues (as adherence or compliance), should be reported.

### 3.4. Outcome

Certain terms asProgression free survival (PFS), Overall survival (OS) and Objective response rate (ORR) (complete or partial), should be stated in the review in sake of cancer outcomes.
The first two outcomes were assessed by the hazard ratio and 95% confidence interval, the third outcome was assessed by the risk ratio which reported as the patients who achieve partial or complete response out of the total patient.

Adverse events/toxicity (diarrhea, abdominalpain, nausea, vomiting, stomatitis, hand–foot syndrome (also known as hand–foot skin reaction or palmar–plantar erythrodysesthaesia (PPE), fatigue, anemia, dermatitis and any other adverse effects judged to be appropriate)

Progression-free survival (PFS) is the length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. To measure theprogression-free survivalin a clinical trial, is one way to see how well a new treatment works.

Overall survival (OS) defined as the length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive. In a clinical trial, identifying the overall survival is considered another way to see how well a new treatment works.

Objective response rate (ORR) is a patient probability of having a reduced tumor burden of pre-specified quantity after initiating the regimen.

Table 2. Outcomes have advantages and disadvantages

| **Outcome** | **Advantages** | **Disadvantages** |
|---|---|---|
| Overall survival | • Internationallyagreed estimate of direct benefit.<br>• Readily and accurately estimated. | • Might need a considerable trial population with prolonged follow-up to appear statistical variations between groups.<br>• Might be impacted by crossover or subsequent therapies.<br>• Contains deaths unallied to cancer. |
| Progression-free survival | • Needs small sample size with shortened follow-up time against to OS.<br>• Contains assessments of stable disease (SD).<br>• It not impacted by crossover or following treatments.<br>• Normally related to quantitative and objective measurements. | • Validation as a replacement for survival could be hard in some therapy settings.<br>• Not accurately estimated (ie, assessment might be affected by bias).<br>• Definition may alter among trials.<br>• Needs repeated radiologic or other measurements.<br>• Needs stabilized measurement timing among therapy arms. |
| Objective response rate | • Can be measured in single-arm trials.<br>• Needs a smaller population and can be measured earlier, parallel with survival trials.<br>• Effect is affected proportionately to medication not the disease. | • Not extensive estimate of medication activity. |

### 3.5. Search Strategy

The subsequent search databases were investigated for pertinent published literature.

- Medline.
- Embase.
- Cochrane
- clinicaltrial.gov
- webofscience.com
- European society for medical oncology (ESMO).
- BIOSIS

### 3.6. Inclusion and Exclusion Criteria

The independent screening of the searched abstracts and titles of the determined studies from the predefined sources and searches were made by two authors. A reviewer should get a copy of paper in related to the judged study and should be relevant. Moreover, it will be then determined for inclusion by one reviewer and then scanned for the accuracy by another (second) reviser through the identified criteria. In turn, any study if did not fall within the inclusion picture were removed from the review.

### 3.7. Study Design

Our study design included only the randomized-controlled trials (RCTs) in this review which contented the subsequentstandards: [1] equivalent designing withinequivalentdistribution to the treatment armscontrasting the medications as mentioned in the search protocol in men, [2] should include at least 100 patients to be randomized in the treatment arm, and [3] and should keep with the patients and follow their therapy for at least 52 week or one year.

This systematic review removed studies in case of randomization protocol was not at participant level (cluster-randomized), when the similar participant works as control (cross-over studies), quasi-experimental protocol in which the patients or individuals were not fall in randomization picture according to the treatment arm, and all kinds of observational studies (cohorts, case

control, cross-sectional, case-reports, editorials, commentaries, opinions). It is removed any studies if these clinical trials that made a randomization of less than 100 individuals per treatment arm and/ or kept individuals for less than 52 weeks or one year of active therapy. In addition, it is removed any study which use samples in a fixed area outside humanbody (in vitro). Any study protocol containing animals were excluded.

### 3.8 Data Extraction Strategy

The extraction of data from the studies which allied with inclusion protocols was done by one reviewer who utilized a predetermined data extraction copy form into an access database. The papers wereinvestigated for the precision by the second investigator and if were any judgments, it were solved through the discussion.

### 3.9. Methods of Analysis/Synthesis

The study quality investigations of clinical efficacious and data extraction outcomes were outlined in the modified tables and structured tables and as a recitative outline. The probable impacts of the study efficacy on the outcomes of review were stated within the paragraph.

### 3.10. Fixed-Effect (FE) Model Meta-Analysis

The FE modelsuppositions in which there is only one right effect size which are measured in the analysis by all studies and those dissimilarities in the effect assessments noticed are because of the sampling errors(Michael Borenstein, Hedges, Higgins, & Rothstein, 2010). The FE meta-analysis produce an effect assessmentwhich is true effect size. In case of effect, the null hypothesis for the difference is zero, and for ratio is one(Michael Borenstein et al., 2010). The points distribution which are showed in the analysis states that the within-study error and sampling error is deduced by determine weights to every study in the meta analysis.

### 3.11. Random-Effects (RE) Model Meta-Analysis

It is supposed the dissimilar studies are considering a study-specified true effect under RE model assumed that different studies in the meta-analysis are estimating study-specific true effect (Borenstein et al., 2010).

Thus, the outlined effect produced from the RE model assess all true effect mean. The summary null hypothesis shows a mean for a difference is 0.0 and for the ratio is 1.0(Michael Borenstein et al., 2010). The RE model calculates the and therefore it needs two origins of variance to be considered: 1) within the study error, and 2) true effect deviations throughout the studies. The origins of variances are reduced through determine the weight to every study.

For RE models, Both models are utilized (DerSimonian and Laird random-effects models0. CMA and meta package in Rstudio both utilized this model as assessor. Which is considered the most popular RE model utilized in most of metaanalysis. CMA and R studio permit analysis display graphically like the analysis flow diagram, forest plots, funnel plots, and risk of bias graph and summary.

### 3.12. Heterogeneity Assessment:

Heterogeneity is known to be any type of deviation or variability among the contained studies in systematic review(Higgins et al., 2011). These deviations could be because of clinicaldifference (variability in individuals, exposure, interventions,or results), and/ or methodological differences (variability in study protocol and bias risk). Thus, when this a difference in risk factor effect or true treatment could results in statistical heterogeneity as a result of variabilities in methodological or clinical or both (Higgins et al., 2011; Higgins & Thompson, 2002).

Heterogeneity could be determined and assessed through statistical tests. Cochran's chi-square test or also known as the *Q*-statistic for heterogeneity is considered one of the main methods to estimate the heterogeneity (Higgins & Thompson, 2002). Q is defined as

$$\mathrm{Q} = \sum_{i=1}^{k} \mathrm{Wi}(\mathrm{Yi} - \mathrm{M})^2$$

Where

- Wi is the study weight
- Yi is the study effect size
- M is the study effect
- K is the number of studies.

Q is a standardizedestimate pointing that it is not influenced by the metric of the effect size index, but usually is the degrees of freedom (*df*)

$$df = k - 1,$$

Where *k* is the number of studies.

Thus, the more differences will lead to variations in the true effects among the studies is calculated as $Q\text{-}df$.

It measures the null hypothesis which all the contained studies own the similar impact on the population . This review shows a p-value of <0.05 as statistically significant for the existence of heterogeneity. It is important to know that the *Q*-statistic owns a weak strength specifically in the presence of sparse information and unreasonable power of identifying clinically insignificant heterogeneity in case of excess studies(Hardy & Thompson, 1998). To control this obsatacle, I squared ($I^2$) statistics have been utilized to measure conflicts among the studies.

According to Higgins (2011), I2 statistics defined as the variability percentage in the effect measurement which is because of heterogeneity rather than chance. It is calculated as

$$I^2 = \left(\frac{\mathrm{Q} - \mathrm{df}}{\mathrm{Q}}\right) \times 100\%$$

That is the ratio of excess dispersion to total dispersion.

The $I^2$ value ranges between 0% (represent no showed heterogeneity) and a maximum of 100% (larger values represents huge heterogeneity). Tentatively, $I^2$ can be represented as follows (Higgins et al., 2011):

- 0% to 40%: maybe not be valuable;
- 30% to 60%: might show a moderate heterogeneity;
- 50% to 90%: may indicate substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

If there are very insignificants variations among the studies, the $I^2$ will be low and the FE model is more valuable. The FE model presume that there is one true effect size which undergoes all the studies in the metaanalysis and which all the variations in the spotted effects are because of the sampling error (Michael Borenstein et al., 2010). Therefore, the main variation, between the studies, is the power to identify the result of interest.

Significant heterogeneity is usually considerably showed if $I^2$ is 50% or more. It is important to take into account that $I^2$ is not aestimate of absolute heterogeneity and it does not give data on the true effect dispersion (Cooper, Hedges, & Valentine, 2019).

It could not significantly states to us of which of two meta-analyses present more heterogeneity in true effects. Thus, $I^2$ should be utilized along with the noticed effects to present to the reviewers a meaning of the true effects.

When there is an existence of statistically significant heterogeneity, one analytical protocol is to combine it into a RE model. The RE model does not maintain the heterogeneity, however, it permits for variations in the treatment effect from study to study(Riley, Higgins, & Deeks, 2011)since it presume that there is a true effect sizes allocation. The RE model utilized the tau-squared ($T^2$) statistics to measure among studies variance from the noticed effects.

**3.13. Publication bias assessment:**

Publication bias is the inability to contain whole applicable trials due to unpublished studies and therefore, they are not attainable. Publication bias could be estimated through contrasting unpublished and published studies which assigning the same question. Funnel plots, in this meta analysis, could measure the publication bias visually . Funnel plots are mainly utilized as a visual

tool in the publication investigation and different kind of bias in the meta-analysis(Sterne, Gavaghan, & Egger, 2000).

To estimate the internal validity of the contained studies, we utilize the Cochrane tool for measurement the risk of bias. This tool is considered significant to preferable to compound scoring systems of low, moderate, and high. Five domains are contained in the tool: randomization, allocation concealment, participants and study personnel blinding, outcome assessors blinding, overall bias, and selective outcome reporting as shown in Figure 5. Publication bias was estimated by Begg's test and Egger funnel plot. No publication bias was shown for PFS, OS or ORR ($P$ = 0.32, $P$ = 0.91 and $P$ = 0.216, respectively).

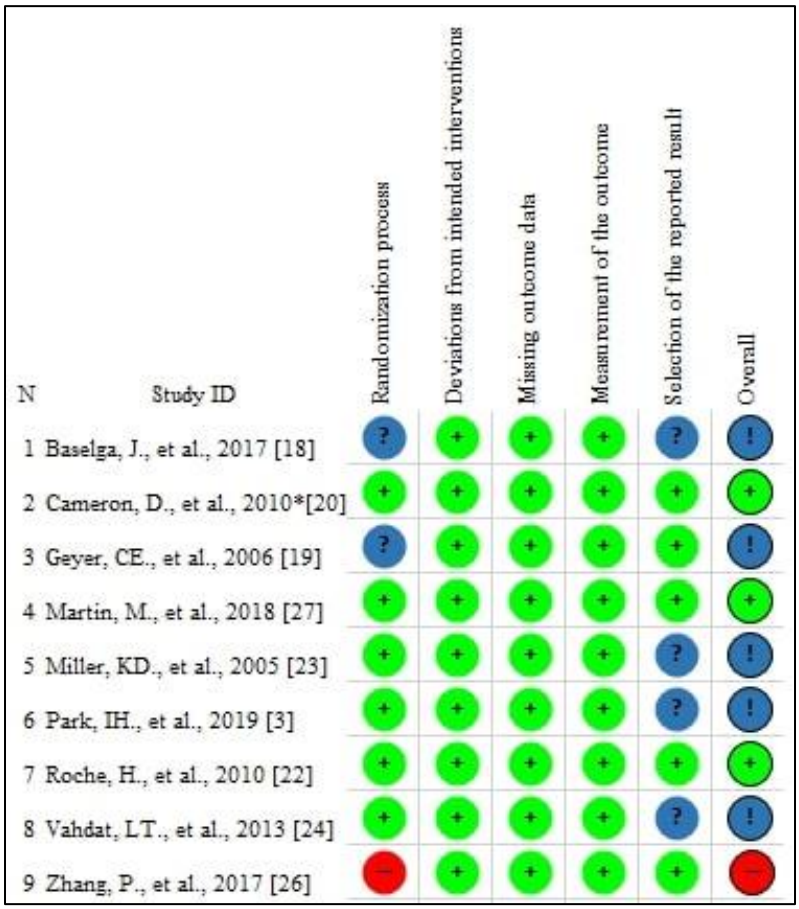



Figure 5. Risk of bias assessment tool. * The study not included in PFS and ORR analysis. Green: low risk, blue: some concerns, red: high risk.

A funnel plot is a simple scatter plot of the intervention effect assessment from participant studies in contrast to study size estimate(Higgins et al., 2011; Sterne et al., 2000; Sterne et al., 2011).

The effect assessment of studies was plotted on the horizontal axis while the estimate of a studies size was plotted on the vertical axis. Therefore, the outcomes from small studies will be scattered at the bottom of the graph, with the diffusiongetting close among larger studies. If at least ten studies in the meat analysis, the Funnel plots will be utilized, otherwise, the power of the tests is too low to discriminate chance and real asymmetry(Higgins et al., 2011). The plot nearlyidentified a symmetrical reversed funnel in the lack of bias.

### 3.14. Statistical Analysis

The analysis was evaluated through a comprehensive meta-analysis (CMA) 3.0 software and R studio meta package. The ORR and grade 3 and 4 drug-related adverse events were evaluated by risk ratio (RR). The PFS and OS were assessed by hazard ratio (HR). The level of significance was defined as $\alpha = 0.05$. The HRs and their 95% CIs were acquired from the articles directly. The $\chi^2$ test or $I^2$ statistics evaluated the heterogeneity of meta analysis outcomes. When the P-value was $< 0.05$ or$I^2$ was $> 50\%$, the heterogeneity was considered statistically significant. The data were analyzed using a random-effects model if significant heterogeneity existed; otherwise, a fixed-effects model was used.

Data were expressed as odds ratio (OR) with 95% confidence intervals (CI). The number of the patients who experienced HFS and the total number of the patients in each arm were obtained directly from the selected articles, also the number needed to treat was calculated. The analysis was performed in R-Studio using the meta package (R-Studio version 1.1.456. Development for R. RStudio, Inc., Boston, MA, USA; meta package version 4.13-0)(Schwarzer, 2007; Team, 2014). The level of significance was defined as $\alpha = 0.05$. The Q statistics or $I^2$ statistics evaluated the heterogeneity of meta analysis outcomes. When the P-value was $< 0.05$ or $I^2$ was $> 50\%$, the heterogeneity was considered statistically significant. The data were analyzed using a random-effects model if significant heterogeneity existed; otherwise, a fixed-effects model was used.

### 3.15. Limitations of Meta-Analysis

Limitations are found in meta-analysis. The limitations presented because forth are displayed as garbage in garbage out, contrasting oranges to apples, the file drawer problem and publication bias. Most methodologies have access to these limitations but they are most commonly assigned to meta-analysis(M Borenstein, Cooper, Hedges, & Valentine, 2009).

#### 3.15.1. Comparing apples to oranges.

From the 1970's to the present, critics have shown that metaanalysis is considered as wrong methodology since it contrasts "apples to oranges". Glass has committed protected the meta-analysis by saying, "Of course it mixes apples and oranges; in the study of fruit nothing else is sensible; comparing apples and oranges is the only endeavor worthy of true scientists; comparing apples to apples is trivia"(Glass, 2000).

Sets of data from different studies are evaluated and compounded for effect size in meta analysis. Critics judges that usually data sets are very different to be contained in meta analysis, leading in skewed outcomes and supporting the belief of garbage in garbage out (see below). On the other hand, the target of meta-analysis is to be capable to assess all the research and therefore, result in strictness of the meta-analysis. Exclusion and inclusion criteria will aid in controlling the combining data that is very variable(Littell, Corcoran, & Pillai, 2008).

#### 3.15.2. Garbage in, garbage out.

One more critique of meta-analysis is the belief of "garbage in garbage out". In which indicates to know the volubility of the studies utilized in meta-analysis research. Since the target of meta-analysis is to have all research, the quality of certain research contained might have absence elegance. So in that situation, the meta analysis integrity lead to question. Lipsey and Wilson (2001) propose only containing the research which is perfect in design (Lipsey & Wilson, 2001). On the other hand, there are no agreements to what represents quality research. Strict coding strategies could aid in identifying which studies are to be contained or removed.

### 3.15.3. File drawer problem.

The file drawer problem represents to fugitive or gray literature which is hard to obtain because of unpublished and might be laid in the 'file drawer' of a researcher because of invaluable results. Unpublished research is sometimes as valuable as published research but might not published since of the outcomes are being invaluable. It noteworthy to have fugitive data to identify the effect sizes for research but to also measure and control for publication bias in meta analysis(M Borenstein et al., 2009).

### 3.15.4. Publication bias.

An upwards bias into the effect sizes could be the outcome when gathering *p*-values acquired in the published studies (Lipsey & Wilson, 2001). It is essential when assessing any studies, mainly meta-analyses, to minimize this effect as much as possible. Thus, to have gray or fugitive literature is considered different way to reduce the publication bias. Since most published studies disagree a null hypothesis of no effect at 0.05, unpublished research and presentations will be contained in this study to aid in reducing the selection bias(Kulinskaya, Morgenthaler, & Staudte, 2008).

Besides to problems of bias from the included trials, systematic reviews may be affected to other shapes of bias. Publication bias refers to the favorablepublication ofpositive trials by journals or favorable reporting of positive results within a study ($p<0.05$).

These outcomes in bias in effect assessment in regard of the treatment under review. One cohort study of 218 studies(Egger, Smith, Schneider, & Minder, 1997)stated that trials with positive results, known as a $p<0.05$, were had the chance to be published (hazard ratio (HR) 2.32; 95% CI 1.47 to 3.66)and published quicker (median time to publication 4.8 versus 8 years) than studies with negative results.

Different study has shown an equivalent outcomes(Easterbrook, Gopalan, Berlin, & Matthews, 1991), with positive studies more probable to be published (adjusted OR 2.32; 95% CI 1.25 to 4.28) than those with negative outcomes. In a recent systematic review(Dwan et al., 2008) and Cochrane review (Hopewell, Loudon, Clarke, Oxman, & Dickersin, 2009) were in consensus

with the outcomes above and even determined the proof of selective outcomes reporting bias, the belief that statistically significant outcomes within studies are more probable to be stated in manuscripts when contrasted to insignificant outcomes.

Publication bias is known to have an impact on published meta analyses around 25%-40% (Egger et al., 1997; Sterne et al., 2000).

Scott Ramsey in 2008 observed that among cancer clinical trials finished as of September 2007, 17.6% were reported as published in PubMed or by the registry. Terminated trials had a very low publication rate (3.4%) contrasted to completed trials (19.5%)(Ramsey & Scoggins, 2008).

Stratified by treatment type, protocols had the highest probability of publications to trials accounted. Phase III trials were more probable to be published (26.3%) in contrast to other study kinds, including Phase IV studies (14.0%). Studieswere the most probable to be published (59.0%) which are funded by Networks. However, the industry funded trials were the least probable to be published (5.9%).

University/Research Organization have the main and primary factor for funding and sponsored the researches, which is considered the largest proportion. Randomized trials (19.6%) were more probable to be published than non-randomized trials (4.4%). Trials which are have been registered before September 1, 2004, the month the ICMJE started the need trial registration, were more probable to be published (21.0%) than those published after this date (11.9%).

Publication bias can be corrected and determined through methods. So potential publication bias or imprecise study effects can be estimated through funnel plot (that is graphical plot of effect) plotted against their standard error and regression methods. Using these methods, publication bias could be determined as being in charge of contradiction in conclusions from meta-analyses that were later disagreed by large RCTs(Egger et al., 1997).

Different methods as rank correlation tests could be appropriate. However, the regression method owns a better power to identify the differences when being contrasted to rank correlation tests,

inspite that regression tests , in different cases, have various obstacles of false positives as in case of; trials of similar sample sizes, treatments with large effects, or trials with a low numbers of events(Sterne et al., 2000).

Egger's regression test is an experiment for asymmetry of funnel plot and measures in which the Y intercept from a regression line equals zero. It reverts the standard normal skewness (effect size divided by standard error) with the accuracy (reciprocal of standard error) as the predictor variable (Illustration 1.1). The intercept will be equal zero in case of symmetry of funnel plot, (the regression line should intercept the Y axis at 0).

It can be noticed from the below plot that this is not the case, showing funnel plot asymmetry. It is due to of smaller studies (with less accuracy) prone for maximum outcomes against to the effect assessment and thus the prevalence of positive studies (with publication bias) will 'shift' the intercept away from 0 (as seen in figure 6).

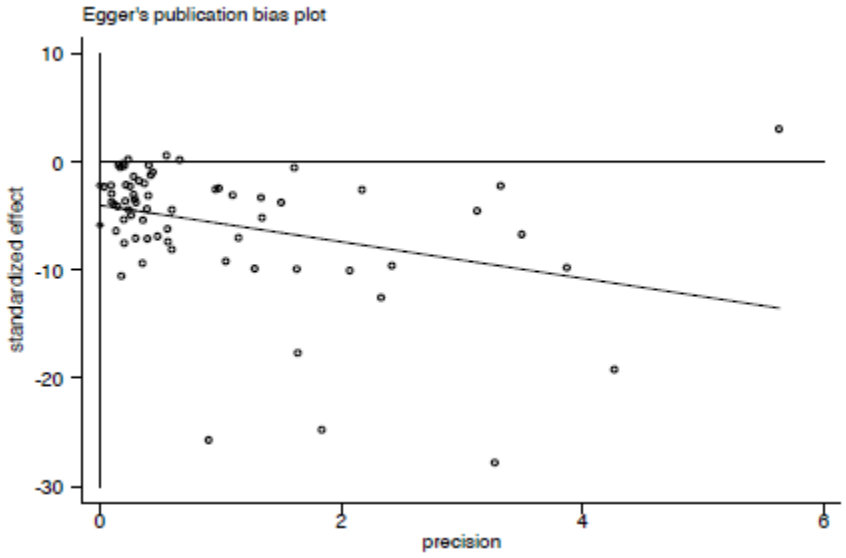



Figure 6. Egger's linear regression test. Y-axis is standard normal deviate (effect size divided by the standard error) and the X-axis is the study precision (1 / standard error). The intercept is significantly different from zero ($p<0.05$).Attempts have been made to devise statistical tests to correct for publication bias.

Trim and fill analysis is one such method(Duval & Tweedie, 2000).it is trimming the extreme cases from funnel plot, and then reassess the effect estimate and then generate a modified effect estimate in the existence of a symmetrical plot. (figure 4).

On the other hand, the true effect could be minified in the existence of large between-study heterogeneity where no publication bias is found. Moreover, this method depends on the hypothesis that an asymmetric funnel plot is mainly because of publication bias(Peters, Sutton, Jones, Abrams, & Rushton, 2007). There are other reasons of the asymmetric funnel plot foundlike internal validity concerns in smaller trials and probable deception.

Orwin's failsafe N is another analysis which is utilized to identify the possibility effect of publication bias(Orwin, 1983). This test computes the number of supplementary negative studies required to alter the effect assessment to a pre-identified, clinically inconsiderable level. Despite neither computation is advised for Cochrane reviews, such analysis can act as sensitivity analyses to estimate the degree of publication bias in any given review.

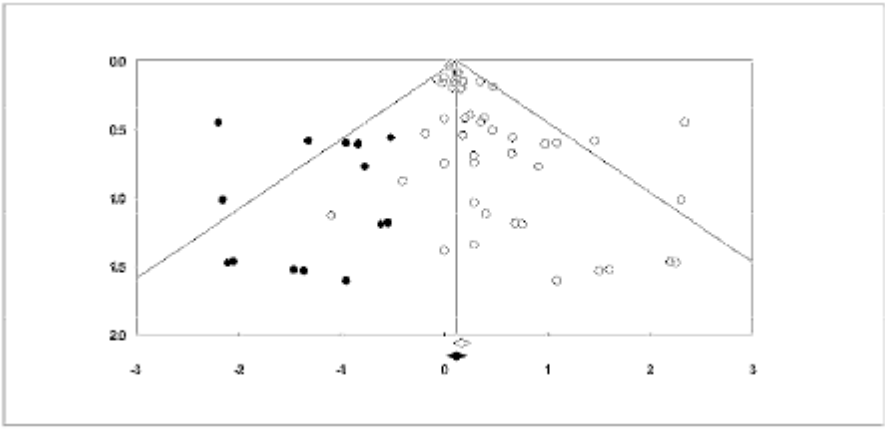



Figure 7. Funnel plot with log risk ratio on the X-axis and the standard error (on a reverse scale) on Y-axis. Original studies (white circles) and effect estimate (white diamond) show the original studies in the meta-analysis, which show clear asymmetry. The new effect estimate (black diamond) and plotted studies (black circles) show the new symmetrical plot following trim and fill analysis.

As indicated previously, that the publication bias is not the only reason for funnel asymmetry. Other reasons could be related to trivial methodological protocol, deception and variations in the

techniques of the intervention was transferred in smaller studies(Sterne et al., 2011). Thus, additionstoconventional funnel plots have been produced such as the utilizeling of contour enhanced funnel plots (Figure 8). On each individual study, these plots can put on areas of statistical significance. Thus, studies which fall in these areas are considered statistically significant at the level selected (in our example $p<0.05$ and $p<0.01$).

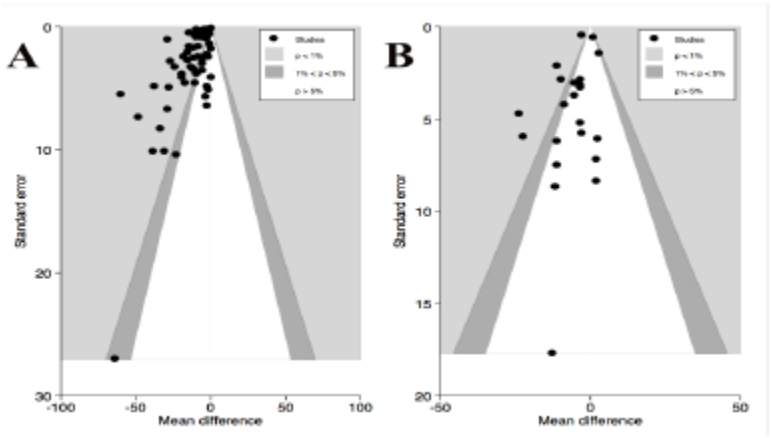



Figure 8. Contour enhanced funnel plots. Plot A shows the majority of studies in regions of statistical significance (grey $p<0.01$ and dark grey $p<0.05$) suggesting publication bias as a cause. Plot B shows more studies in the region of statistical non-significance ($p>0.05$) suggested another cause for asymmetry.

We can notice from the illustration overleaf that in plot A, studies are situated in shaded areas of statistical significance, as the studies in the analysis are statistically significant (the mechanism behind publication bias) making publication bias more probably. However, plot B display studies in areas of non-statistical significance, recommended other reasons for funnel plot asymmetry should be outlined(Sterne et al., 2011).

Previously, authors have showed to be weak visually in determine the funnel plot asymmetry (Terrin, Schmid, & Lau, 2005)so putting on a contour lines for statistical significance might help interpretation(Sterne *et al.* 2011). Thus in turn to try to minimize the publication bias, an comprehensive search for unpublished studies is needed and recommended via clinical trial databases, conference proceedings and grey literature databases(Thornton & Lee, 2000).

None of the previously published meta-analyses have sought unpublished studies.

## 4. RESULTS:

### 4.1. Characteristics of The Selected Studies

As exhibited in the PRISMA statement flow chart **(Figure 9)**, 1846 potentially relevant published articles in the five databases were produced initially for this systematic review and 16 additional abstracts were identified from other sources. A review of the titles and abstracts of these articles produced 494 promising articles. The remaining 476 articles were chosen for analysis and assessed in a major characteristic by evaluating the full articles. Of these, 467 articles were eliminated for several reasons **(Figure 9)**. Eventually, 9 phase III RCTs were included in the analysis.

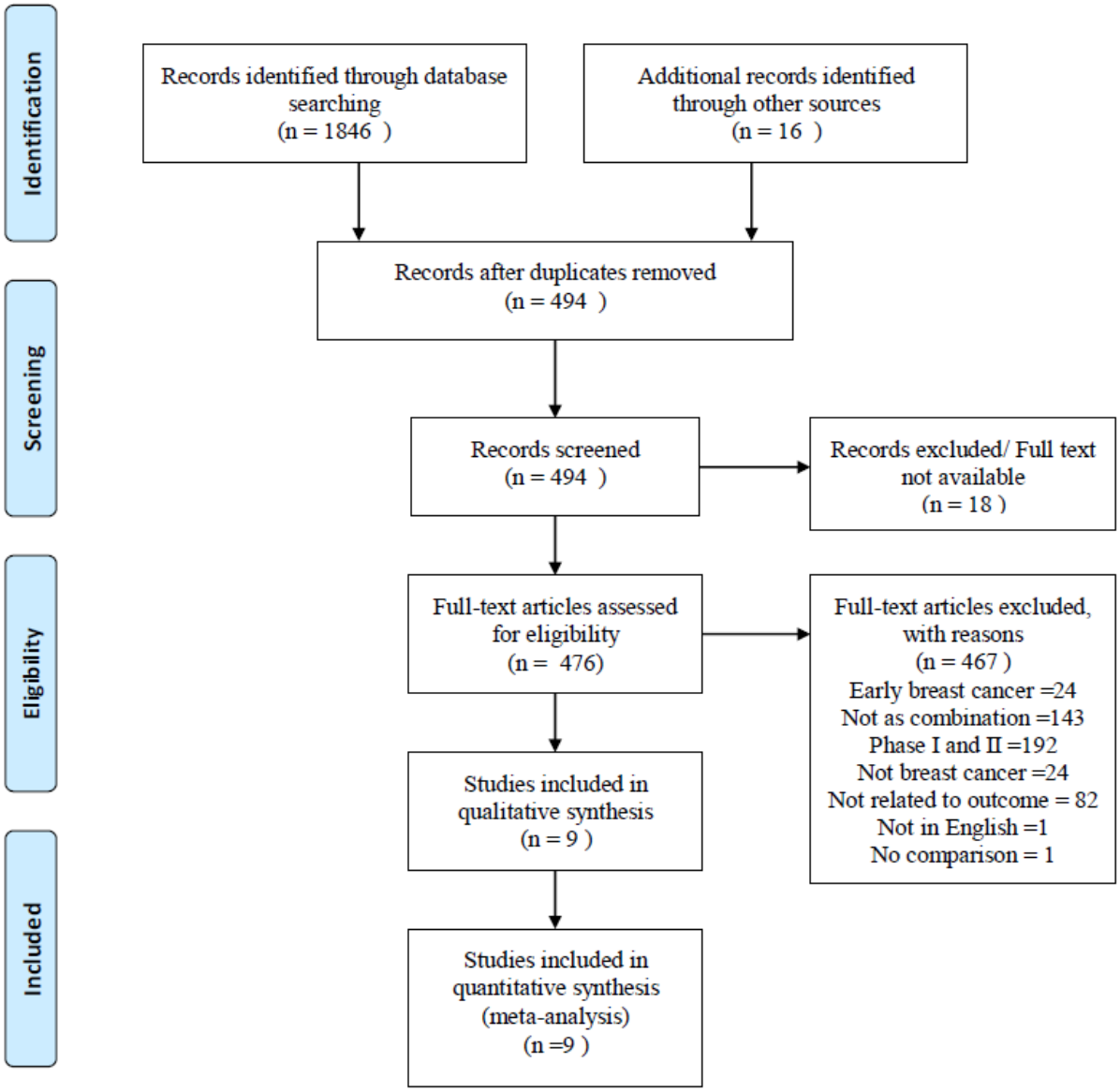



Figure 9. PRISMA statement flow diagram: summary of systematic search and review process.

Data from nine RCTs were included in the meta-analysis.From a total of 6714 participants 3257 patients used capecitabine as monotherapy and 3439 in combination with other chemotherapies. The median age of the participants was 52 years in the capecitabine group and 54 years in the combination group. The dose of capecitabine differed from RCT to another, the lowest dose was 1000 mg twice a day to 2500 mg once daily. The combination with capecitabine also differed from one study to another; two studies compared capecitabine monotherapy to capecitabine combination with lapatinib, two RCTs combined capecitabine with ixabepilone, and sorafenib, utidelone, vinflunine, irinotecan, and bevacizumab was combined with capecitabine in the five remaining RCTs **(Table 3)**.

Table 3. Characteristics of the included trials on the analysis

| Author/year of publication | Patient number | country | Median age CAP | Median age combination | CAP arm regimen | Combination arm regimen | Cycles in CAP | Cycles num in combination |
|---|---|---|---|---|---|---|---|---|
| Baselga J., et al., 2017 | 537 | USA | 55 | 53 | Capecitabine 1000 mg/m$^2$ orally twice a day. | Capecitabine 1000 mg/m$^2$ twice a day plus sorafenib 600 mg/d. | 10 | 9 |
| Cameron D., et al., 2010 | 399 | Scotland | 51 | 54 | Capecitabine 2,500 mg/m$^2$ in two divided doses | Capecitabine 2,000 mg/m$^2$ in two divided doses plus Lapatinib 1,250 mg daily | NR | |
| Geyer CE, et al.,2006 | 324 | UK | 51 | 54 | Capecitabine 2500 mg/m$^2$/day. | Capecitabine, 2000 mg/m$^2$/day plus lapatinib, 1250 mg /day continuously. | NR | |
| Martin M., et al., 2018 | 770 | Spain | 54 | 54 | Capecitabine 1250 mg/m$^2$ twice daily. | Capecitabine 825 mg/m$^2$ twice daily plus vinflunine 280 mg/m$^2$. | 5 | 6 |
| Miller KD, et al., 2005 | 462 | USA | 52* | 51* | Capecitabine 2,500 mg/m$^2$ daily. | Capecitabine 2,500 mg/m$^2$ twice daily on plus bevacizumab 15 mg/kg. | 35 | 35 |
| Park IH, et al., 2019 | 221 | Korea | 49 | 50 | Capecitabine alone 1,250 mg/m$^2$ twice a day. | Capecitabine 1,000 mg/m$^2$ twice a day, plus Irinotecan 80 mg/m$^2$. | 11 | 11 |
| Roché H., et al., 2010 | 1973 | international | 54 | 54 | Capecitabine 1,250 mg/m$^2$ twice daily. | Capecitabine 1,000 mg/m$^2$ twice plus ixabepilone 40 mg/m$^2$. | 4 | 5 |
| Vahdat LT. et al., 2013 | 1973 | USA | 59 | 59 | Capecitabine alone 1250 mg/m$^2$ twice a day. | Capecitabine 1000 mg/m$^2$ twice a day plus ixabepilone 40 mg/m$^2$. | 4 | 5 |
| Zhang P, et al., 2017 | 417 | China | 50 | 50 | Capecitabine 1250 mg/m$^2$ twice a day. | Capecitabine 1000 mg/m$^2$ twice a day plus utidelone 30 mg/m$^2$. | 6 | 6 |

*Presented in the article as mean. CAP: capecitabine, NR: not reported.

### 4.2. Progression Free Survival

PFS information was collected from eight clinical trials. The PFS pooled HR showed that capecitabine -based combination regimen was significantly superior (longer PFS) to capecitabine monotherapy for the patients with advanced or metastatic breast cancer (HR 1.32, 95% CI 1.13 to 1.54, $P < 0.0001$) **(Figure 10)**. Because the heterogeneity was significant between the trials, a random-effects model was used ($I^2 = 79.5\%$, $P = 0.025$).

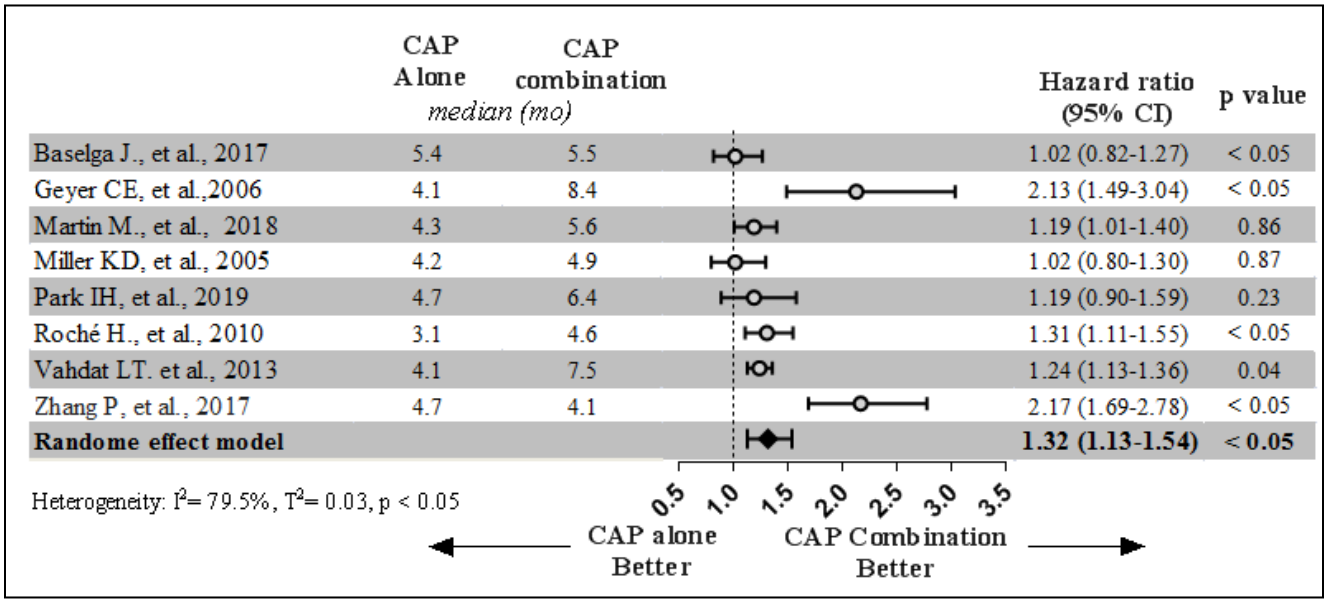



Figure 10. Progression free survival (PFS) of capecitabine alone compared to combination. CAP: capecitabine, mo: months, CI: confidence interval.

### 4.3.Overall Survival

In nine trials, 1943 patients were involved in the extraction of overall survival data. Capecitabine therapy overall median was with a range of 13.1 (8-24) months and 15.1 (10-20.4) for combination treatment. Based on results assessed from individual studies, the pooled HR for death from any cause of 1.09 (95% CI = 0.98 to 1.22, *P* =0.12) indicates insignificant better overall survival in the combination treatment group compared with the capecitabine-alone group. Because the heterogeneity was significant between the trials, a random-effects model was used (I2 = 64.8%, *P*< 0.05) **(Figure 11)**.

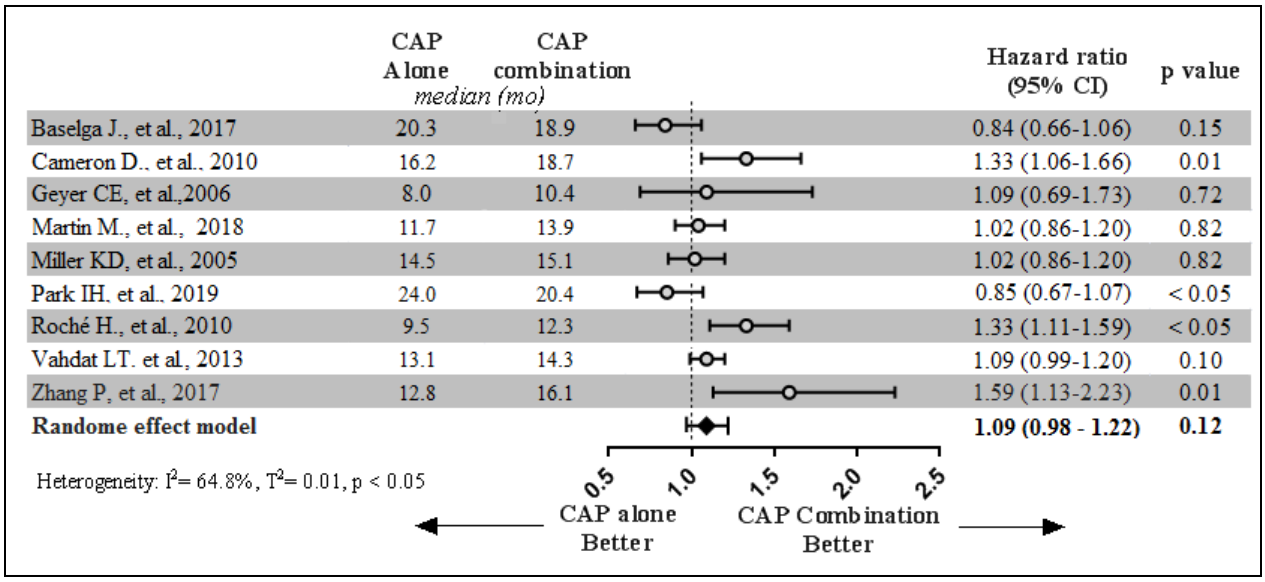



Figure 11. Overall survival (OS) of capecitabine alone compared to combination. CAP: capecitabine, mo; months, CI: confidence interval.

### 4.4. Objective Response Rate

The relative risk (RR) was obtained directly from eight trials and included in the analysis, 5305 patients were involved and ORR outcomes were informed. In advanced or metastatic breast cancer treatment, it showed a significant improvement with capecitabine combination chemotherapy over the capecitabine monotherapy regimen from the pooled analysis of ORR (RR 0.67, 95% CI 0.54 to 0.83, *P*< 0.001) **(Figure 12)**.

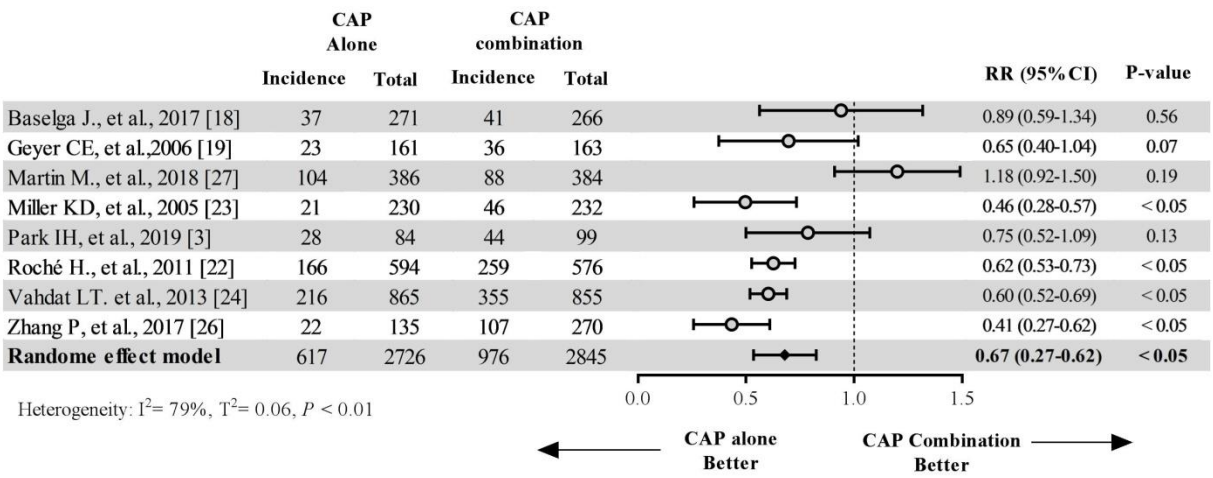



Figure 12. Overall response rate (ORR) of capecitabine alone compared to combination, CAP: capecitabine, RR: risk ratio, CI: confidence interval.

### 4.5. Safety:

The majority of the adverse effects in the nine RCTs were mild and moderate. In our analysis, we focused only on grade 3 and 4 adverse events, which weregistered in **(Table 4)**. The RCTs reported the number of patients with the events and the total number of the patients in each arm. The incidence of non-hematological adverse events such as hand and foot syndrome was higher in capecitabine alone chemotherapy compared to capecitabine combination chemotherapy (RR=1.66 95% CI 1.02 to 2.69, *P*=0.04). There was no significant difference between the two treatment groups in diarrhea with a higher incidence of grade 3 and 4 events in capecitabine alone treatment compared to capecitabine combination (RR=1.13 95% CI 0.91 to 1.38, *P* = 0.29).

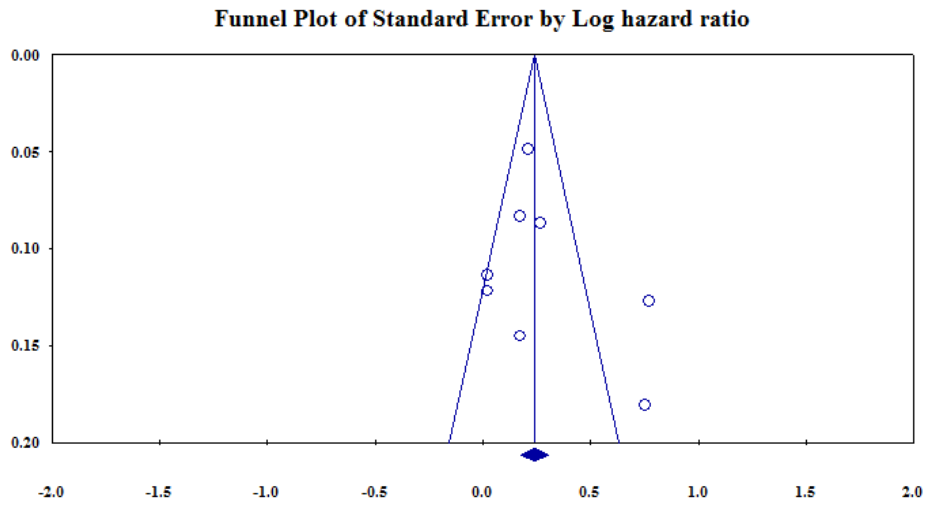
Vomiting was reported in 7 RCTs out of 9, the incidence of grade 3 and 4 events was significantly lower in capecitabine alone chemotherapy compared to combination (RR= 0.61 95% CI 0.43 to 0.88, *P* =0.005. The anemia and neutropenia showed a lower incidence in capecitabine chemotherapy alone compared to combination with other chemotherapy agents (RR = 0.64 95% CI 0.41to 0.99, *P* =0.04, RR= 0.22 95% CI 0.11 to 0.44, *P*< 0.0001), respectively.

Table 4. Grade 3 and grade4 adverse events of capecitabine alone compared to capecitabine combination regimens

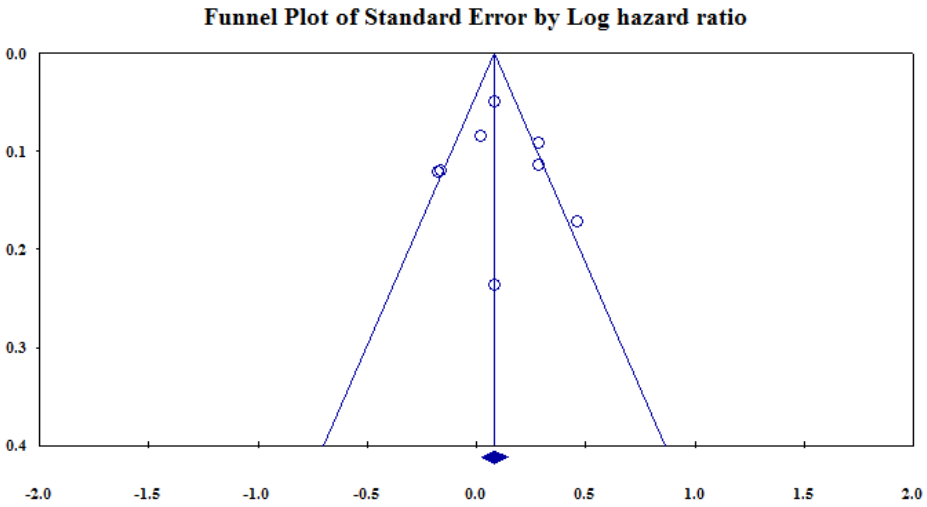
| **Adverse events** | **No. of trials** | **RR and 95% CI** | ***P-value*** | **Heterogeneity** | |
|---|---|---|---|---|---|
| | | | | **$I^2$** | ***P-value*** |
| Anemia | 5 | 0.64 (0.41-0.99) | 0.04 | 34 | 0.19 |
| Neutropenia | 5 | 0.22 (0.11-0.44) | < 0.0001 | 87 | < 0.0001 |
| Thrombocytopenia | 4 | 0.45 (0.45-0.84) | 0.01 | 0.0 | 0.58 |
| Nausea | 7 | 0.75 (0.53-1.05) | 0.09 | 42 | 0.11 |
| Vomiting | 7 | 0.61 (0.43-0.88) | 0.005 | 48 | 0.07 |
| Diarrhea | 9 | 1.13 (0.91-1.38) | 0.29 | 22 | 0.21 |
| Fatigue | 4 | 0.48 (0.25-0.92) | 0.02 | 69 | 0.02 |
| Cardiotoxicity | 4 | 0.49 (0.20-1.2) | 0.12 | 0.0 | 0.59 |
| Hand and Foot syndrome | 8 | 1.66 (1.02-2.69) | 0.04 | 88 | < 0.0001 |
| Mucositis/ stomatitis | 6 | 0.59 (0.35-0.97) | 0.04 | 0.0 | 0.81 |

## 4.6. Publication Bias:

**A**




**B**




**C**

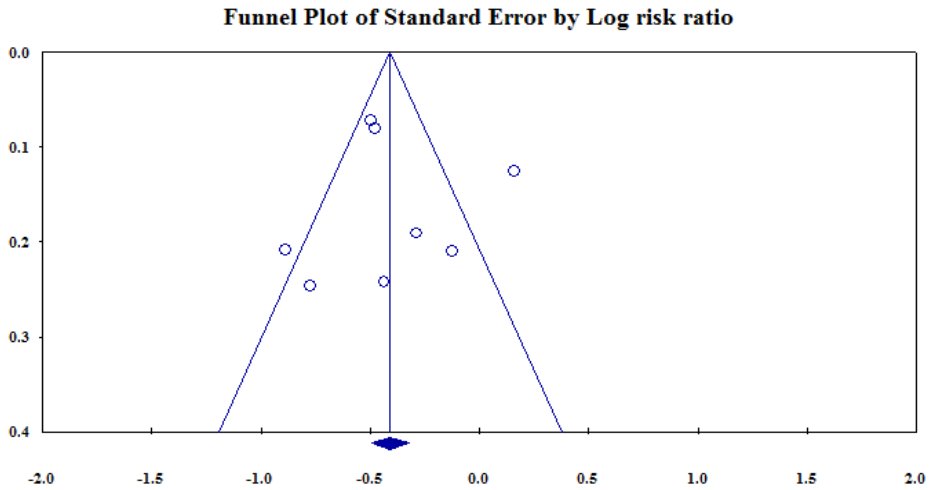



Figure 13. A) Funnel plot analysis to detect publication bias for PFS. B) Funnel plot analysis to detect publication bias for OS. C) Funnel plot analysis to detect publication bias for ORR.

### 4.7. HFS Prevention Strategy

#### 4.7.1. Pyridoxine

Pyridoxine information was collected from seven clinical trials compared the use of the drug to placebo in prevention of HFS. 294 patients out of 487 patients used pyridoxine to prevent HFS had an incidence of HFS. The pooled OR showed that Pyridoxine was insignificantly superior to placebo in preventing HFS (OR 0.90, 95% CI 0.67 to 1.20, $P$ = 0.48) (**Figure 14**). Because the heterogeneity was insignificant between the trials, a fixed-effects model was used ($I^2$ =0.0%, $P$ = 0.73).

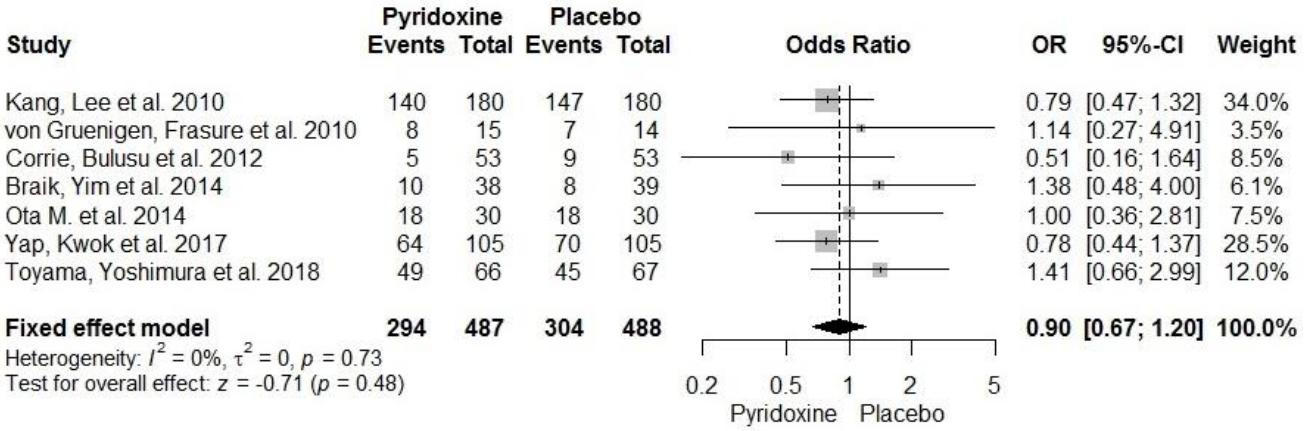



Figure 14. Pyridoxine effect in preventing hand and foot syndrome compared to placebo. OR: odds ratio. CI: confidence interval.

#### 4.7.2 Celecoxib

Four studies were included in the analsysis of the effect of celecoxib in preventing the HFS in cancer patients. In the analysis 200 patients were included in each group to assess the effect of celecoxib compared to placebo. The pooled OR showed that celecoxib was significantly superior to placebo in preventing HFS (OR 0.30, 95% CI 0.14 to 0.87, $P$ = 0.02) (**Figure 15**). Random-effect model was used because of the significant heterogeneity between the studies ($I^2$ = 73%, $P$ = 0.01).

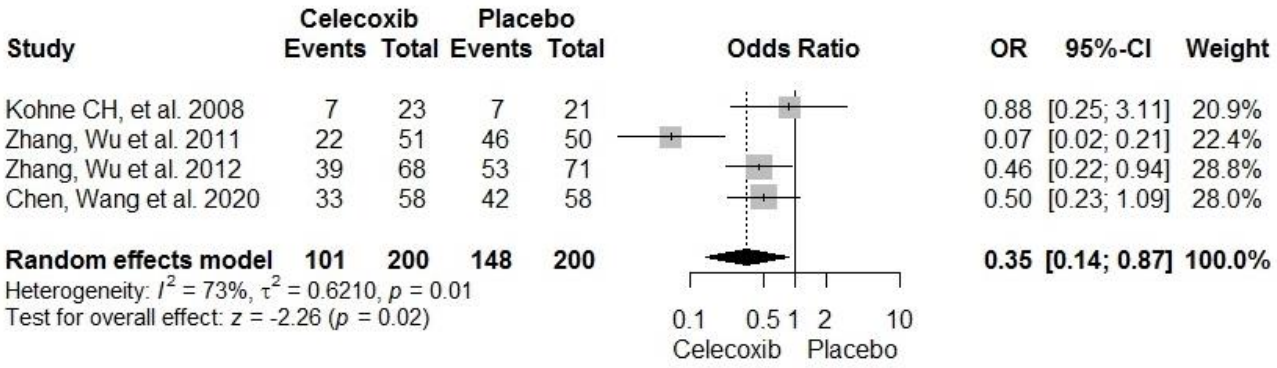



Figure 15. Celecoxib effect in preventing hand and foot syndrome compared to placebo. OR: odds ratio. CI: confidence interval.

### 4.7.3 Urea:

Three studies were included in the analsysis of the effect of urea in preventing the HFS in cancer patients. In the analysis 1150 patients were analyzed to assess the effect of urea compared to placebo. The pooled OR showed that urea was insignificantly superior to placebo in preventing HFS (OR 0.62, 95% CI 0.35 to 1.12, *P* = 0.11) (**Figure 16**). Random-effect model was used because of the significant heterogeneity between the studies ($I^2$ = 68%, *P* = 0.04).

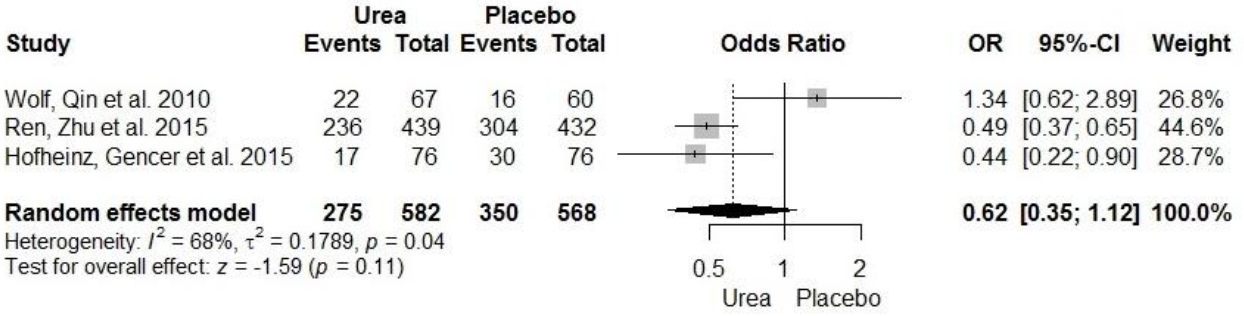



Figure 16. Urea effect in preventing hand and foot syndrome compared to placebo. OR: odds ratio. CI: confidence interval

### 4.7.4. Antiperspirant:

Two studies were included in the analysis of the effect of antiperspirant in preventing the HFS in cancer patients. In the analysis () were analyzed to assess the effect of antiperspirant compared to placebo. The pooled OR showed that antiperspirant was insignificantly superior to placebo in preventing HFS (OR 0.73, 95% CI 0.42 TO 1.27, *P*= 0.27) (**Figure 17**). Random-effect model was used because of the significant heterogeneity between the studies ($I^2$ = 0%, *P* = 0.78).

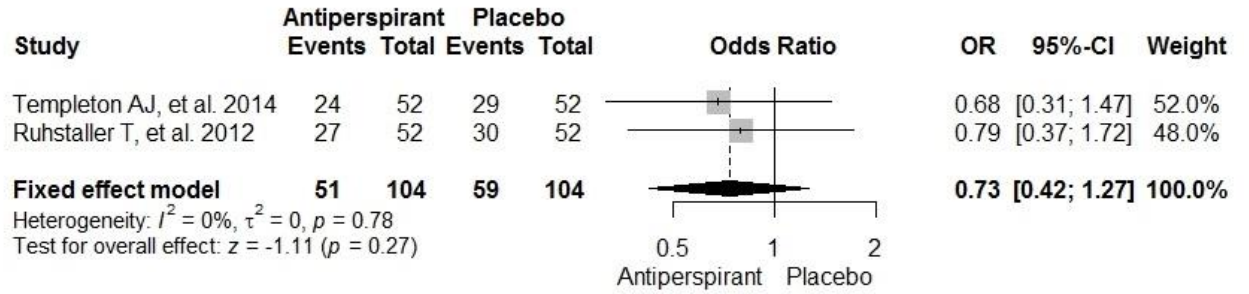



**Figure 17. Antiperspirant effect in preventing hand and foot syndrome compared to placebo. OR: odd ratio. CI: confidence interval**

## 5. DISCUSSION

The current meta analysis has identified and assessed nine RCTs, with 3257 patients using capecitabine as monotherapy in monotherapy arm and another 3439 patients using a combination with other chemotherapiesin the second arm.

Monotherapy was found to be inferior to capecitabine based combination therapy in terms of effect (progression free survival (HR 1.32, 95% CI 1.13 to 1.54, $P < 0.0001$) and overall response rate (RR 0.67, 95% CI 0.54 to 0.83, $P< 0.001$) with no difference in overall survival in terms of safety and incidence of adverse effects.

In advanced breast cancer, capecitabine based-combination therapy exhibited improved PFS with elevated response rate parallel to capecitabine alone. Although, such favorable consequences did not result in improved OS (Belfiglio et al., 2012; O'Shaughnessy et al., 2002; Sparano et al., 2010). Taxane and anthracycline-based regimens are considered the standard mainstay essential chemotherapy for advanced or metastatic breast cancer as stated by contemporary guidelines (Kurosumi et al., 2000; Tryfonidis, Senkus, Cardoso, & Cardoso, 2015).

Nevertheless, older people are sensitive to certain complications, therefore, strong regimens may be inconvenient for them. In general, as treatment strategy plan pre-treated patients with taxanes or anthracycline, capecitabine-based chemotherapy can be used with these patients (Baselga et al., 2017).

Capecitabine was suggested as a choice for advanced or metastatic breast cancer first-line treatment according to the European School of Oncology and the European Society for Medical Oncology (ESO-ESMO) 2014 guidelines (Cardoso et al., 2014b).

In our analysis, we compared the efficacy and safety of capecitabine monotherapy to capecitabine combination in patients pretreated with anthracycline and taxan. We found out that PFS (HR 1.32, 95% CI 1.13 to 1.54, $P < 0.0001$) and ORR (RR 0.67, 95% CI 0.54 to 0.83, $P< 0.001$) in combination-based regimen wassignificantly higher than withcapecitabine alone.

However, OS (95% CI = 0.98 to 1.22, *P* =0.12) was maintained in both groups 13.1 vs 15.1 months in combination groups. Previous studies showed that the addition of lapatinib, which is a dual tyrosine kinase inhibitor, hinders the HER2/ neu and epidermal growth factor receptor (EGFR) pathways to capecitabine, and improves the efficacy and overall survival (Cameron et al., 2010; Geyer et al., 2006).

Studies also proved that lapatinib modulate TS expression makes it a promising way when combined with capecitabine in breast cancer treatment (Chefrour et al., 2012). As consistent with Roche et al. study, when Ixabepiloneis combined with capecitabine, asuperior improvement efficacy compared to capecitabine alone (Roché et al., 2011). Roche et al. showed that median OS 16.7 vs 16.2 months, median PFS 6 vs 4.4 months, and ORR of 45% vs 28% in capecitabine alone (Roché et al., 2011).

Moreover, the addition of bevacizumab to capecitabine resulted in a notable increase in objective response rates (ORR), however, it did not significantly improve PFS or OS (K. D. Miller et al., 2005). Another study, as it may seem, argued for amodest improvement in PFS while maintaining its efficacy when ixabepilone (Li, Ren, & Sun, 2017; Sparano et al., 2010; Vahdat et al., 2013), utidelone(P. Zhang et al., 2017),Vinflunine (Martin et al., 2018), are combined with capecitabine.

To our knowledge, this is the first analysis of efficacy and safety data available for capecitabine in MBC patients. Capecitabine isfrequently used alone or combined with other cytotoxics for the treatment of MBC. Weijiao Yin et al. analysis has shown that such regimens are not inferior to other MBC therapies and reported a significant improvement in ORR and PFS with no detected difference in impact on OS (Yin et al., 2015).

Also, a comprehensive analysis of other first-line chemotherapeutic agents; (i.e. the taxanes in MBC), has involved 20 RCTs that randomized 6,577 patients to different taxane-based regimens. The analysis also found that paclitaxel-based combinations were more effective than paclitaxel alone for efficacy in ORRwhich is similar to the case of Capecitabine in our

analysis.Furtherimprovement in OS was associated with the taxane combination regimens, an evidence which motivated us to embark on the current analysis(Dong et al., 2019).
Despite the reported efficacy in Weijiao Yin et al. analysis, the main concern with capecitabine regimens was more incidences of side effects compared to capecitabine-free chemotherapy regimens.

Also, current cancer guidelines (Network, 2012) would slightly prefer the use of single-agent due to mainly decreased rates of adverse events and toxicities compared to combination.This was not absolute in the case for capecitabine because in our findings, combination therapy resulted in less non-hematological adverse events such as hand and foot syndrome compared to capecitabine alone chemotherapy, and the insignificant difference in diarrhea at a time whenincidences of vomiting, anemia, and neutropenia wereseen in combination regimens. Hand-foot syndrome (HFS) is a potentially dose-limiting cutaneous toxicity seen in almost 50% of patients treated with Capecitabine (Milano et al., 2008).

Although HFS isn't a life-threatening toxicity, the syndrome has a significant impact on treatment schedules and quality of life which areboth important in palliative care (Milano et al., 2008). The management of HFS is challenging as no standard therapies have demonstrated 100% efficacy (A. Chan et al., 2015).

The USA Food and Drug Administration recommends 1250 mg/m2 twice daily of capecitabine dose in monotherapy regimens (Kaklamani & Gradishar, 2003). In fact, lower doses such as 850 and 1000 mg/m2 were used in combination regimens in several trials included in the analysis, while in capecitabine monotherapy regimens, the dose ranged between 1250 and 2500 mg/m2.This may justify the higher incidence of HFS in the monotherapy arm.

However, anemia and neutropenia in combination arm weresignificantly higherincapecitabine monotherapy arm due to synergistic cytotoxic side effects on bone marrow suppression (RR = 0.64 95%CI = 0.41-0.99, $P$ =0.045,RR = 0.22 95%CI = 0.11-0.44, $P$<0.0001), respectively (Y. Wang, Probin, & Zhou, 2006). In addition, vomiting was significantly noticeablein combination-based chemotherapy (RR = 0.61 95%CI = 0.43-0.88m $P$ =0.005).

There were several potential limitations to this study. Its findings and interpretations were limited by the quality and quantity of information available. The lack of ability to perform subgroup analysis due to the lack of data and head to head analysis might have undermine the credibility and authenticity of our analysis.

The capecitabine-based combination regimens differed vastly in the involved trials and this may have affected the results. The variety in the dose of capecitabine in both arms and between the trials may haveaffected the findingsaswell.

On the other hand, the cost-effectiveness of interventions was not carried out due to the difficulty of such an assessment in our setting. Considering these potential limitations, further trials and head to head comparisons are required to confirm the superiority of capecitabine combination regimens and adopt this as mainstream practice in the management of advanced MBC patients.

The unexpected constellation of side effects has emerged –mainly cutaneous toxicities- since of long term use of chemotherapeutic agents. One of the most notable toxicities is HFS. Although HFS does not consider life-threatening toxicity, however, it has a considerable effect on the patient's quality of life and treatment protocol. Thus, it is needed to manage the HFS which geared toward symptoms treatment in an effective tolerable way and preventing it from progressing toward debilitation. In our meta-analysis, pyridoxine, celecoxib, and urea were compared to placebo in terms of HFS prevention.

Pyridoxine is also known as B6, 294 patients out of 487 who used pyridoxine, experienced the HFS syndrome. It is observed in our meta-analysis that pyridoxine has insignificantly prevented the incidence of HFS compared to placebo (OR 0.9, 95% CI 0.67 to 1.2, P=0.48). In consistent with other studies, which demonstrated pyridoxine was ineffective in the prevention of HFS incidence(Braik et al., 2014; Corrie et al., 2012; Kang et al., 2010; Ota et al., 2014; Toyama et al., 2018; von Gruenigen et al., 2010). In another randomized trial, 210 patients who received capecitabine monotherapy did not show any significant reduction in HFS incidence when treated with pyridoxine (31.4%) compared to placebo (37.1%; P=0.38)(Yap et al., 2017). A previous meta-analysis study of 890 patients received PLD, vincristine,

capecitabine, cyclophosphamide, or 5-FU, observed that the efficacy of pyridoxine supplements compared to no treatment or placebo for the prevention of HFS did not show a significant decrement in the incidence of HFS (relative risk [RR]: 0.95, 95% confidence interval [CI] 0.87-1.05). Therefore, further trials are needed to prevent episodes of HFS (Jo, Shin, Jo, Kwon, & Myung, 2015).

On the other hand, our meta-analysis highlighted that celecoxib was superior to placebo in the prevention of HFS (OR 0.30, 95% CI 0.14 to 0.87, P = 0.02). In compatible with other studies that observed significant results in the prevention of HFS events (J.-C. Chen et al., 2020; Köhne et al., 2008; R.-X. Zhang et al., 2011; R. Zhang et al., 2012).

Since HFS is an inflammatory reaction, celecoxib showed to be effective in its management (R. Zhang et al., 2012). In a systematic review, it is noticed that administration of celecoxib in patients treated with capecitabine could reduce the incidence of HFS by 50% (Macedo, Lima, dos Santos, &Sasse, 2014). On the other hand, larger studies are needed to confirm its efficacy, not to forget its cardiovascular/ gastrointestinal–associated adverse effects (Y. Chen et al., 2008).

Equivalently, urea-based cream studies were entailed in our meta-analysis. 1150 patients were evaluated to estimate the effect of urea-based creams compared to placebo in HFS prevention. It is showed insignificant effects in HFS protection (OR 0.62, 95% CI 0.35 to 1.12, P = 0.11). In consistent with Wolf et al. study which showed that in patients treated with capecitabine in the first three weeks, were randomized into urea/lactic acid cream versus placebo. He observed that the incidence of grade 2, 3 HFS was not significantly reduced between two groups (13.6% *versus* 10.2%, respectively; P=0.77)(Wolf et al., 2010).

Hofheinz *et al.* observed reduction in HFS incidence when using Mapisal cream, is an antioxidant cream, in patients treated with capecitabine, compared to urea based creams group (39.5% versus 22.4%; P=0.02) (Hofheinz et al., 2015). However, in study of 871 patients with hepatocellular carcinoma treated with sorafenib observed a reduction of HFS incidence of any grade when received Urea-based cream compared to best supportive care ( 74% versus 56% ; P<0.0010029)(Ren et al., 2015). Urea-based creams may also be effective in increasing the

median time for the first episode, and reducing the severity of the HFS (Ren et al., 2012). Therefore, further appraisals are required for better perceptiveness.

In case of antiperspirant, two studies were assessed in this analysis. Antiperspirant was insignificantly differing from placebo in prevention the event of HFS (OR 0.73, 95% CI 0.42 TO 1.27, *P*= 0.27). In contrast to the previous studies, antiperspirant was effective in reduction the incidence of Palmar-Plantar Erythrodysesthesia(Ruhstaller et al., 2012; Templeton et al., 2014). Therefore, further trials are paramount to assess antiperspirant effectiveness.

## 6. CONCLUSION

Based on the findings of the current analysis, monotherapy was found to be inferior to capecitabine based combination therapy in terms of progression free survival and overall response rate, with no difference in overall survival. Less incidence of non-hematological adverse reaction mainly hand-foot syndrome was associated with combination regimens, while hematological adverse effects were less apparentincapecitabine monotherapy.

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## 8. APPENDIX

### Appendix 1 Search strategy

The core search strategy used for this reviewwas as follows:

((((("capecitabine") OR "xeloda") AND stage 4 breast cancer[MeSH Terms]) OR "capecitabine") OR "xeloda") AND advanced breast cancer[MeSH Terms]) OR "capecitabine") OR "xeloda") AND metastatic breast cancer[MeSH Terms]

This strategy was designed for searching theMEDLINE electronic database,and was adapted as appropriate for all otherdatabases searched, taking into account differencesin indexing terms and search syntax for eachdatabase. Search strategies were not designed torestrict the retrieved results by study type.

## Appendix 2

## Hand and foot syndrome grading scale

| | NIC grading system | WHO grading system | | |
|---|---|---|---|---|
| **Grade** | **Definition** | **Definition** | **clinical lesion** | **histological findings** |
| 1 | Minimal skin changes or dermatitis (e.g., erythema, peeling) with altered sensations (e.g., numbness, tingling, burning) but do not interfere with activities of daily living. | Dysesthesia/paraesthesia, tingling of hands and feet | Erythema | Dilated blood vessels of the superficial dermal plexus |
| 2 | Skin changes present with accompanying pain interfering little with activities of daily living; skin surfaceremains intact. | Discomfort in holding objects and upon walking,<br>painless swelling or erythema | 1+ edema | |
| 3 | Ulcerative dermatitis or skin changes with severe pain interfering with activities of daily living; tissue breakdown is evident (e.g., peeling, blisters, bleeding, edema) | Painful erythema and swelling of pains and soles,<br>periungual erythema, and swelling | 2+ fissuration | Isolated necrotic keratinocytes in higher layer of the epidermis |
| 4 | NA | Desquamation, ulcartion, blistering, severe pain | 3+ blister | Complete epidermal necrosis |

**Appendix 3**

## Data extraction details

### Efficacy studies data

Clinical effectiveness data were extracted from the selected articles and entered into an Excelsheet under the following headings:

[ ] indicates a list of options included in a pulldown box

( ) indicates a click on/off button, where on represents 'yes' and off 'no'

{ } indicates free text entered in a box.

### Study details

- Name of trial {trial name, I.D. or 'not stated'}
- Endnote reference {endnote reference number}
- Primary source [database, hand searching, company submission]
- First author {i.e. Jones et al}
- Date {i.e. year of publication}
- Type of report [abstract, full manuscript, interim report]
- Type of study phase [phase II, phase III …, not stated)
- Comparison group included [capecitabine, other drugs,…]
- Intervention 1 {i.e. drug(s) name(s)}
- Dose or doses of first intervention 1 {dose of capecitabine (i.e. 1000 mg daily)}
- Cycles of first intervention {number}
- Cycle of first intervention {length}
- Second intervention or the comparison group {i.e. drug(s) name(s)}
- Dose of second intervention {dose}
- Cycles of second intervention {number}
- Cycles of second intervention {length}
- Any other comments related to second intervention {summary of comments or 'none'}

### Participants

- Inclusion/exclusion criteria {summary of trial inclusion/exclusion criteria}

- Other drugs used previously such as anthracycline and taxan
- Refractory disease present after first treatment [yes, no, unclear, not stated, not applicable]
- Metastatic site {state whether visceral or non-visceral, summary of numbers and specific site such as lung, liver etc …}
- Mean age and SD or median age with range of participants {age(s)}
- Other participant characteristics such as family history or other risk factors

**Numbers in conditions**

- Number recruited or accrued {summary or 'not stated'}
- Length of follow-up after treatment finishes {summary or 'not stated'}
- Number and times of follow-up measurements {summary or 'not stated'}
- Attrition intervention 1 {summary of number involved and reasons for loss}
- Attrition intervention 2 {summary of number involved and reasons for loss}
- Per protocol analysis performed [yes, no, not stated, unclear]
- Comments {summary of comments or state 'none'}

**Results (data for all outcomes specified in the protocol were entered in the following format)**

- Progression free survival {summary of PFS}
- Baseline data of first intervention {data for PFS}
- Baseline data of second intervention {data for PFS}
- Follow up data for first intervention {data for PFS}
- Follow up data for second intervention {data for PFS}
- Comments about PFS

The same process was applied for the second and third outcomes (i.e. overall survival and objective response rate)

**For safety "Only focused on grade 3 or grade 4adverse drug reactions" in addition to the same data we obtained from efficacy studies.**

- Total number of the patient in the first intervention {number}
- Number of the patient in the first intervention who developed the adverse reaction such as HFS.

- Total number of the patient in the second intervention {number}
- Number of the patient in the second intervention who developed the adverse reaction such as HFS.

## Appendix 4

### Functional Relationship of Survival Parameters

The parameter conversions in this tool assume an exponential survival distribution. Using the hazard rateequations below, any of the four survival parameters can be solved for from any of the other parameters.

Exponential Distribution

The density function of the exponential is defined as

$$\int(\boldsymbol{t}) = \mathbf{he^{-ht}}$$

The probability of surviving the first t years is

$$\boldsymbol{S(t)} = \mathbf{e^{-ht}}$$

The mortality (probability of dying during the first t years) is

$$\boldsymbol{M\ (t)} = \mathbf{1 - e^{-ht}}$$

For an exponential distribution, the mean survival is 1/h and the median is ln(2)/h.

Notice that it is easy to translate between the hazard rate, the proportion surviving, the mortality, and the mediansurvival time. The choice of which parameterization is used is arbitrary and is selected according to theconvenience of the user.

**Hazard Rate from Median Survival Time**

Here, the median survival time is specified. These are transformed to hazard rates using the relationship:

$$h = \frac{\ln(2)}{MST}$$

**Note: NCSS demo version was used to transfer the median to hazard ratio in one study.**

Median for group 1 =4.17
Median for group 2 =4.86
Probability of surviving in group 1 = 0.84
Probability of surviving in group 2 = 0.86
Hazard rate for group 1 =0.16 ($h_1$)
Hazard rate for group 2 =0.14 ($h_2$)

$$\textbf{Hazard ratio } = \frac{\boldsymbol{h1}}{\boldsymbol{h2}} = \mathbf{1.16}$$

**CURRICULUM VITAE**

| | | | |
|---|---|---|---|
| **Name** | **Louai** | **Surname** | **Alsaloumi** |
| **Place of birth** | **Kuwait** | **Date of birth** | **29-04-1990** |
| **Nationality** | **Syria** | **Telephone** | **00905338765143** |
| **Email** | **louaisaloumi@hotmail.com** | | |

**Education level**

| | **Name of the Institution where he/she was graduated** | **Graduation year** |
|---|---|---|
| **Postgraduate/Specialization** | **NEU** | **2020** |
| **Masters** | **NEU** | **2017** |
| **Undergraduate** | **Jordan University of Science and Technology** | **2014** |
| **High school** | **Alasousi high school** | **2008** |

**Job experience**

| **Duty** | **Institution** | **Duration (Year – Year)** |
|---|---|---|
| **Lecturer** | **NEU** | **2015-2020** |
| **Pharmacist** | **NEUH** | **2017-2020** |

| **Foreign Languages** | **Reading comprehension** | **Speaking*** | **Writing*** |
|---|---|---|---|
| **English** | **Very good** | **Very good** | **Very good** |
| **Turkish** | **Good** | **Good** | **Good** |

**Computer knowledge**

| **Program** | **Use proficiency** |
|---|---|
| **SPSS** | **Professional** |

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Arsoy G, Varış A, **Saloumi L**, Abdi A, Başgut B. Insights on allergic rhinitis management from a Northern Cyprus perspective and evaluation of the impact of pharmacist-led educational intervention on patients' outcomes. Medicina. 2018;5(54):83.

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