SAS Journal of Medicine
Abbreviated Key Title: SAS J Med
ISSN 2454-5112
Journal homepage: https://saspublishers.com

OPEN ACCESS

Medical Oncology

Double Anti-Her2 Blockade in Metastatic Breast Cancer: Experience of the Oncology Department of the Moulay Ismail Military Hospital in Meknes

M. Toreis[1*], Az Bazine[1], Y. Touimri[1], M. Fetohi[1]

[1]Docteur Mehdi Toreis, Department of Medical Oncology, Military Hospital of Meknes- Morocoo

DOI: https://doi.org/10.36347/sasjm.2024.v10i10.046 | **Received:** 07.09.2024 | **Accepted:** 15.10.2024 | **Published:** 21.10.2024

***Corresponding author:** M. Toreis
Docteur Mehdi Toreis, Department of Medical Oncology, Military Hospital of Meknes- Morocoo

Abstract **Original Research Article**

Metastatic breast cancer is recognized as an incurable disease andwhose management is palliative, but in recent years there has been an increase in the overall survival of patients with metastatic Her2 + breast cancer, this is thanks to the development new, particularly targeted therapies. Our study aims to assess the value of the double combination pertuzumab to the reference dual therapy (trastuzumab + chemotherapy) in patients with metastatic breast cancer and its impact on overall survival. This is a retrospective study spread over a period of 2 years (2018- 2019) carried out in the medical oncology department of the Moulay Ismail military hospital in Meknes.

Keywords: Metastatic breast cancer, Her2 + breast cancer, Pertuzumab, Trastuzumab, Overall survival.

I- INTRODUCTION

Breast cancer is currently the most common malignant tumour in women, both in Morocco and worldwide. It is also the leading cause of death from cancer in women. Its incidence is rising steadily, making it a major public health problem throughout the world.

According to the latest Globocan 2018 statistics, breast cancer accounts for 24.2% of all new female cancers worldwide, with around 2.1 million new cases for a mortality of 626,679 deaths [1].

In Morocco, breast cancer is the most common cancer in women (36.9%), with an estimated 1,016 new cases and 3,518 deaths in 2018, compared with statistics for 2008 (5,396 new cases and 2,804 deaths from breast cancer) [2, 3].

Approximately one third of women with breast cancer will develop metastatic disease [4], although most would have initially responded to endocrine therapy or chemotherapy. As a result, the average survival of patients is estimated to be between 2 and 4 years at the time of diagnosis of metastatic disease [5, 6].

Metastatic breast cancer is recognised as an incurable disease, and its management is palliative. The aim of the treatments administered is to control tumour growth in order to reduce symptoms and induce as few toxicities as possible, with the aim of increasing survival while preserving a good quality of life [7].

Approximately 15-20% of breast cancers show overexpression of the HER2 protein and/or amplification of the HER2 gene [8, 9], which is overexpressed in 22% of non-advanced cancers, 35% of locally advanced and metastatic cancers and 40% of inflammatory cancers [10].

In breast cancer, HER-2 status is a biological marker that is both prognostic and predictive [11]. Positive HER-2 status is associated with a poor prognosis in terms of recurrence-free survival and overall survival.

The advent of targeted therapy has completely altered this notion, and the survival curve for HER2-positive patients treated with Trastuzumab is similar to that for HER2-negative patients. This humanised monoclonal antibody (mAb) has completely revolutionised breast cancer prognosis, whether in metastatic, adjuvant or neoadjuvant settings. However, resistance to treatment often occurs, and there are many potential mechanisms for this. New anti-HER2 therapies have been developed, such as lapatinib, a dual

EGFR/HER2 tyrosine kinase inhibitor; more recently, pertuzumab and T-DM1 [12].

Pertuzumab is indicated in combination with docetaxel and trastuzumab in the treatment of patients with HER2-positive metastatic or locally recurrent unresectable breast cancer who have not received prior anti-HER2 treatment or chemotherapy for their metastatic disease. [13, 14].

The main objective of this retrospective study is to evaluate the benefit of the dual combination of pertuzumab and the reference dual therapy (trastuzumab + chemotherapy) in patients with metastatic breast cancer.

HER2-positive metastatic breast cancer and its impact on overall survival, in the medical oncology department of the Moulay Ismail Hospital in Meknes.

II- MATERIALS AND METHODS

1. Type of Study

This is a retrospective observational study, carried out over a period of 2 years from January 2018 to December 2019, and involving 17 women with HER2+ metastatic breast cancer who received anti-HER2 treatment by double blockade in the medical oncology department of the Moulay Ismail military hospital in Meknes.

2. Inclusion and Exclusion Criteria:

2.1. Inclusion Criteria:

- Patients with histologically proven breast cancer.
- Patients with metastatic breast cancer.
- Patients with HER2 status determined by IHC and/or FISH.
- Patients treated with double block (Pertuzumab +Trastuzumab + chemotherapy).

2.2 Exclusion Criteria:

- Male gender.
- Patients with non-metastatic breast cancer.
- Patients with HER2-negative breast cancer or HER2 status undetermined.
- Patients who have not received double block therapy.
- Patients whose medical records are incomplete (regarding tumour characteristics) or cannot be found.

3. Parameters Studied:

We selected the records of women with HER2+ metastatic breast cancer from the archives of the medical oncology department of the Moulay Ismail military hospital in Meknes. The data were obtained from the clinical records, then collated on previously drawn up data sheets containing the various information to be collected for each patient.

III- RESULTS

1. EPIDEMIOLOGICAL DATA

1.1 Frequency of HER2+ breast cancer

During the study period, 104 cases of breast cancer were treated in the medical oncology department of HMMI, including 21 with HER2 overexpression, i.e. 21%.

After selection of the patients and application of the exclusion criteria, the data from 17 patients were used, this population representing 16.29% of all breast cancers recorded during the same period.

1.2 Age

The average age of our patients was 56.3 years, with extremes ranging from 35 to 74 years. The highest frequency was in the 40 to 69 age group (82%).

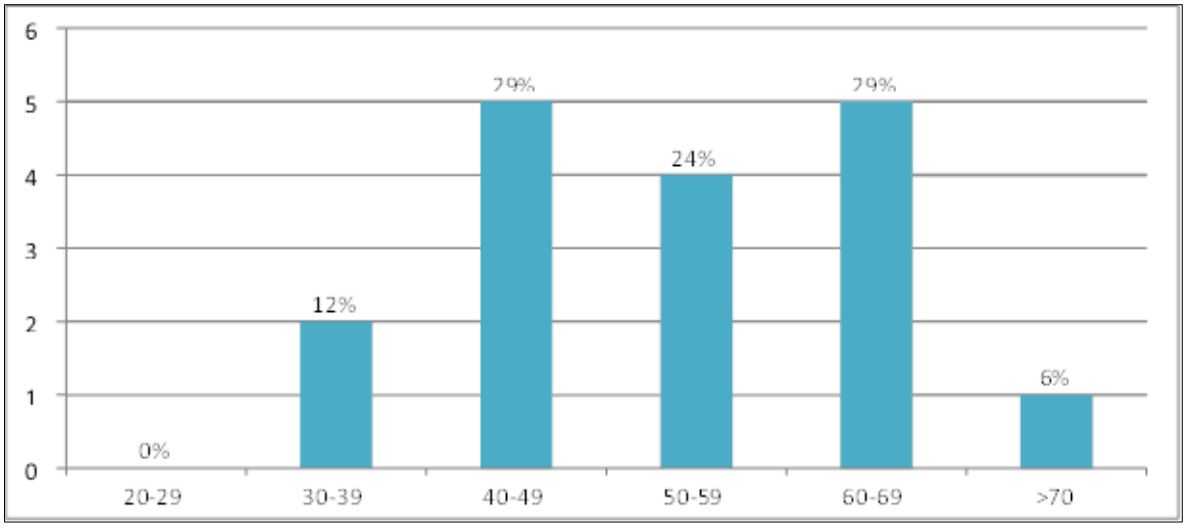

Figure 1: Breakdown of patients by age group

1.3 Patient Origin

In our series, the patients came from different towns and regions, with a rural predominance estimated at 59%

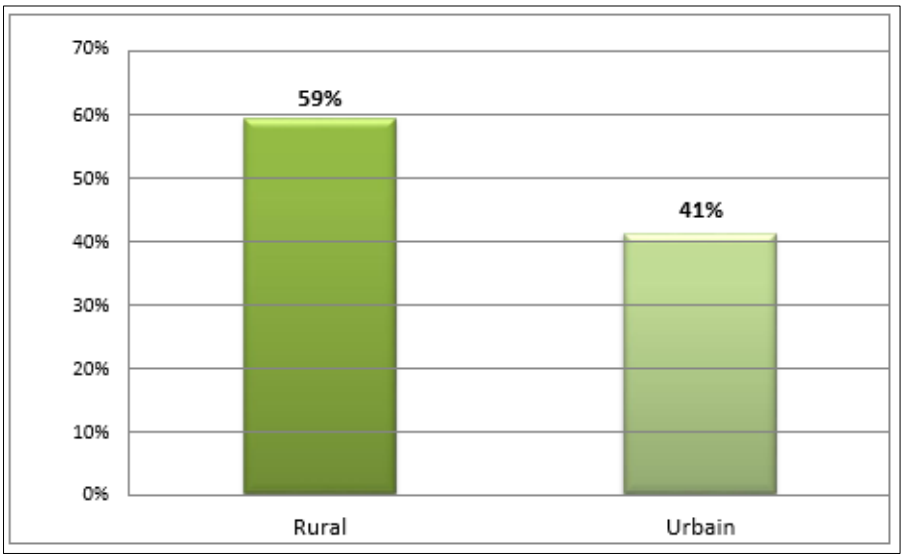

Figure 2: Breakdown of patients by geographical origin

1.4 Comorbidities

In our series, 7 of our patients, i.e. 41.17% of cases, had comorbidities: Diabetes, arterial hypertension and asthma.

1.5 Gynaeco-Obstetrical History

a. Age at Menarche

The age of menarche was specified for all patients, 5 of whom (29.4%) had menarche at <12 years of age, while 12 patients (70.6%) had menarche at >12 years of age.

Table 1: Distribution of patients by age at menarche

Age	Frequency	Percentage (%)
≤ 12ans	5	29,4%
>12ans	12	70,6%
Total	17	100%

b. Parity

In our series, 14 patients (82.35%) were multiparous, 2 patients (11.76%) were pauciparous and one patient was nulliparous.

Table 2: Distribution of patients according to parity

Parity	Frequency	Percentage (%)
Nullipare	1	5,88%
Paucipares	2	11,76
Multipares	14	82,35
Total	17	100%

C. Hormonal Status

In our series, patients who were still genitally active at the time of diagnosis accounted for 41.17% of cases (7 patients), whereas postmenopausal patients accounted for 58.82% of cases (10 patients).

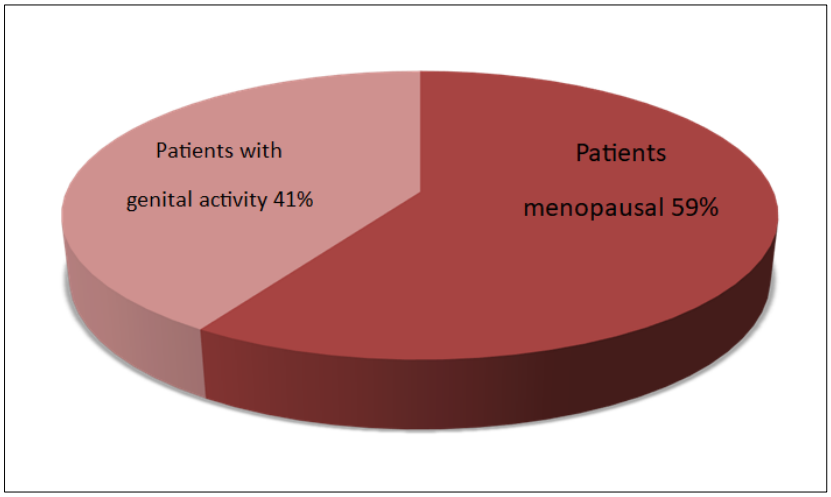

Figure 3: Breakdown by hormonal status

D. Oral Contraception

Contraceptive pill use was reported in 6 patients in our series, a rate of 35%.

The duration of hormonal contraception was not reported.

Table 3: Distribution according to contraceptive pill use

	Case name	Percentage (%)
Prise de CO	6	35%
Pas de prise de CO	11	65%
Total	17	100%

E. Hormonal Treatment of the Menopause

In our series, no postmenopausal patients were on hormone replacement therapy.

F. History of Mastopathy or Gynaecological Cancer

In our series, no personal history of gynaecological cancer or benign mastopathy was reported.

1.6 Family History

In our series, 2 patients (11.7%) had a family history of breast cancer, all of them first-degree relatives.

Table 4 I: Breakdown of patients by family history

	Family History	No family history
Number of patients	2	15
Percentage (%)	11,7%	88,3%

2 CLINICAL DATA

2.1 Revealing Clinical Signs

The most frequent functional signs in our series were bone pain, respiratory signs, asthenia and hepatic colic.

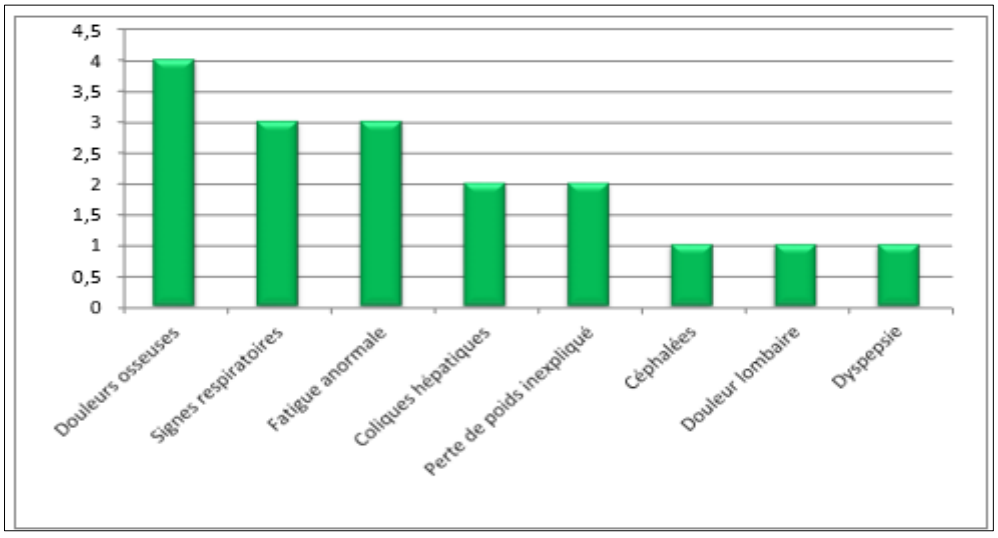

Figure 4: Breakdown by clinical warning signs

2.1 Types of Metastases

Almost all of our patients (88%) were diagnosed at an advanced stage with the presence of metastases from the outset (de novo), while 12% of patients had metastatic relapses after adjuvant treatment with different relapse intervals.

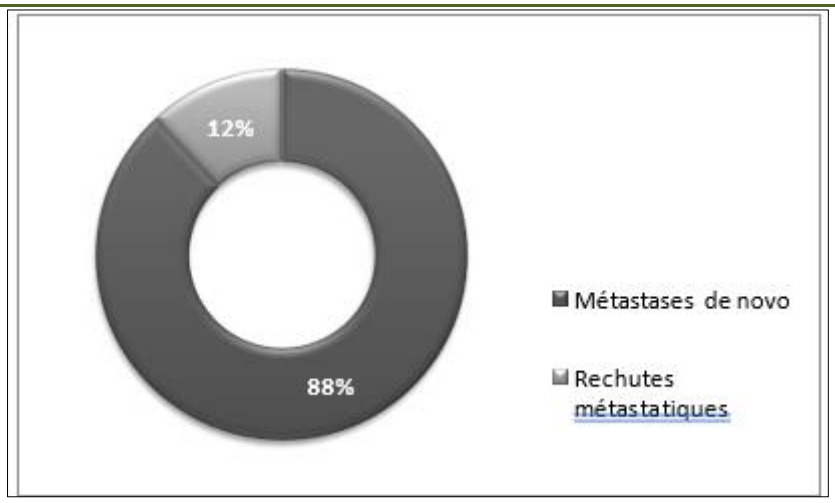

Figure 5: Distribution of patients by type of metastasis

In our series, one patient (6%) presented with a metastatic relapse between 6 and 12 months after treatment and another patient presented with a relapse after one year of adjuvant treatment.

Table 5 I: Breakdown by relapse interval

Relapse interval	Number of patients	Percentage (%)
< 6mois	0	0%
6-12mois	1	6%
> 12mois	1	6%
Total	2	12%

2.2 WHO Performance Index

In our series, all patients were in good general condition with a PS<1

2.1 Extension Work-Up

An extension work-up, including bone scintigraphy and Thoracoabdomino-pelvic CT scan for metastases, was performed in all our patients. A PET scan was performed in 3 patients (18%), and a CT scan with brain MRI in a single patient (6%).

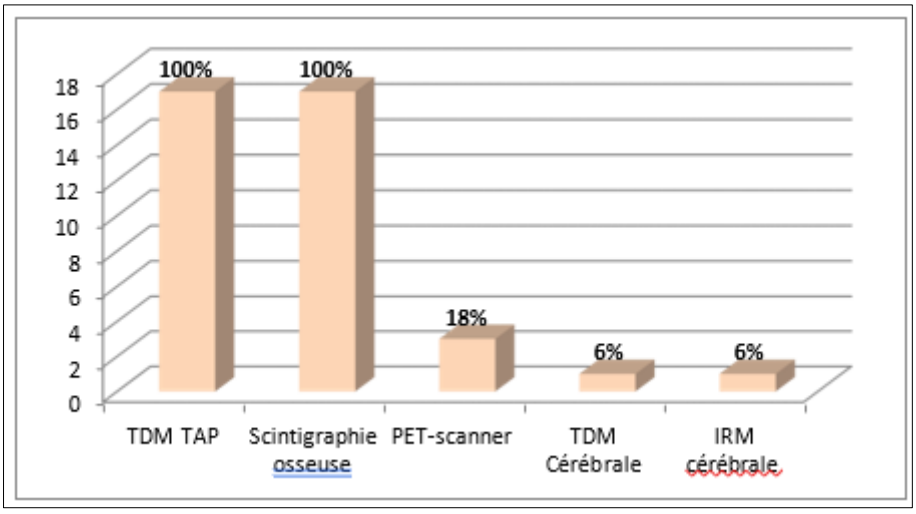

Figure 6: Extension assessment performed in our series

3 PARACLINICAL DATA

3.1 Metastatic Sites

Lung metastases ranked first with a percentage of 53% (9 cases), followed by bone and liver metastases with a rate of 41% (7 cases) and 35% (6 cases) respectively, while the rate of brain metastases in our study did not exceed 6% of all metastases (1 case).

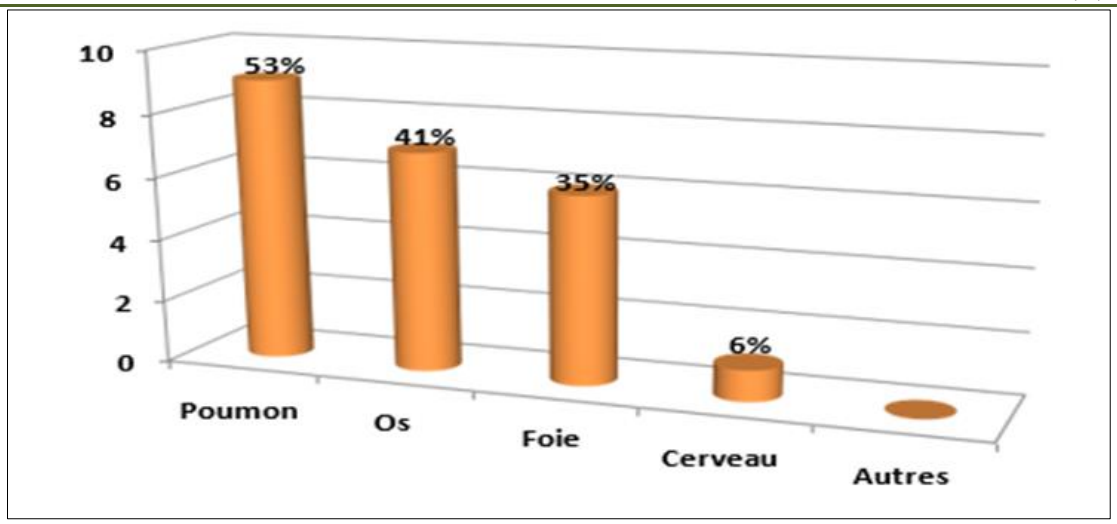

Figure 7: Distribution of metastases according to site

In our series, the majority of patients had a single metastatic site (12%).

Table 6 I: Breakdown by number of metastatic sites

Number of metastatic sites	Effective	Percentage (%)
1site	12	70,6%
2sites	4	23,5%
3sites	1	5,9%

4 ANATOMOPATHOLOGICAL DATA

4.1 Histological Study

A. Histological Type

Invasive ductal carcinoma (IDC) was the histological type found in the entire study population (17 patients), whereas invasive lobular carcinoma (ILC) was not found in any patient.

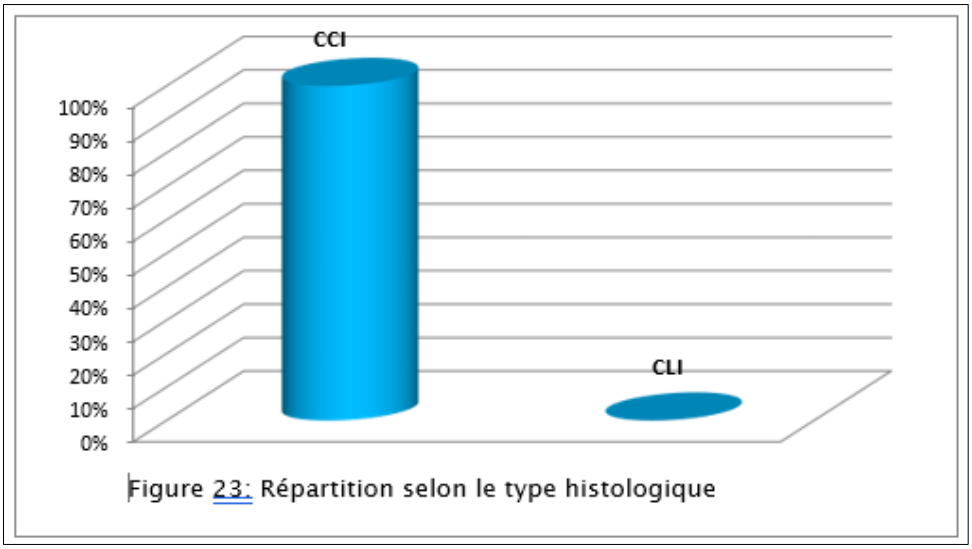

Figure 8: Distribution by histological type

b. SBR Grade

The Scarff-Bloom and Richardson (SBR) histopronostic grade was specified for all patients. In our series, 58.82% of patients were classified as SBRIII, while 41.17% were classified as SBRII.

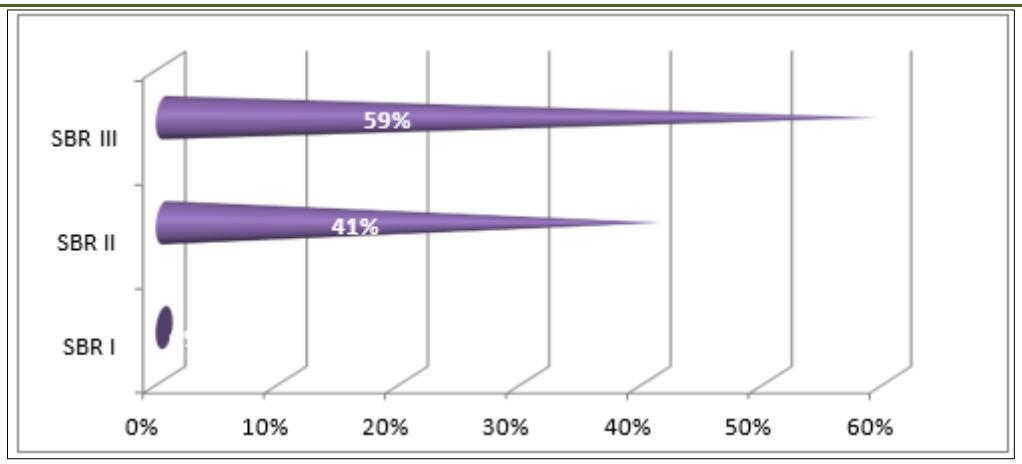

Figure 9: Distribution of patients by SBR grade

A. Immunohistochemical Study

C.1 Hormone Receptors

In all our patients, hormone receptors (HR) were found in 59% of patients compared with 41% with negative hormone receptors.

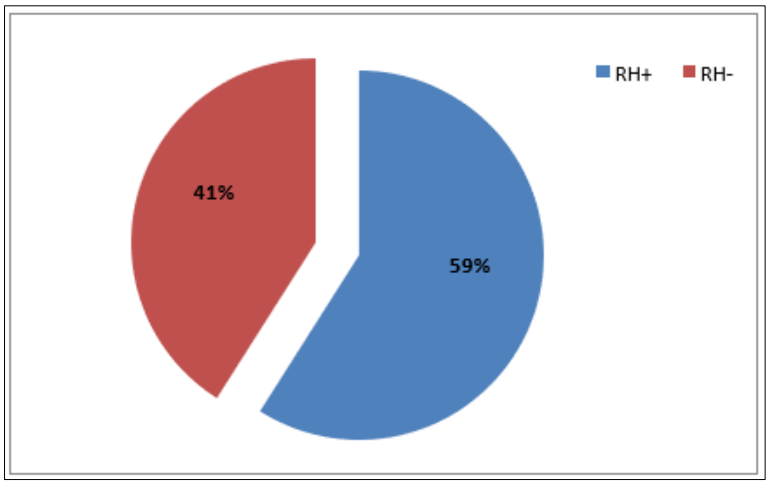

Figure10: Results of hormone receptor testing in our patients

Expression of oestrogen receptors (ER) was found in 59%, while expression of progesterone receptors (PR) was found in progesterone receptor (PR) expression was found in 47%.

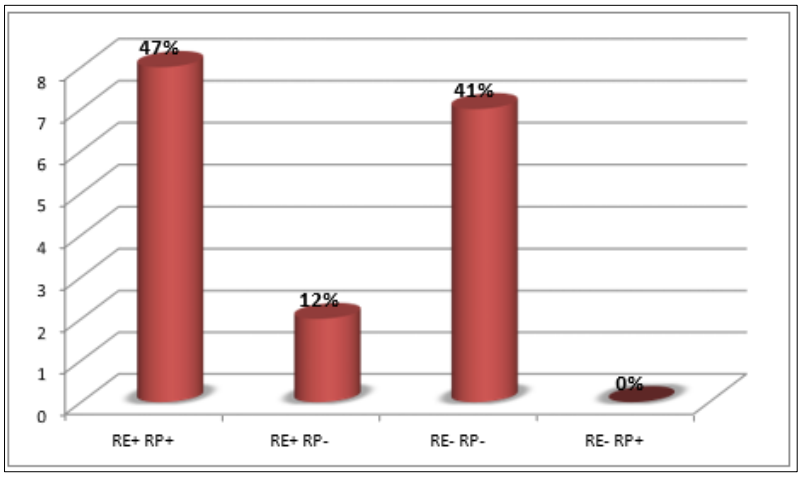

Figure 11: Distribution of patients by hormone receptor (HR)

C.2 HER2 Oncogene Status

HER2 status was investigated in 100% of cases. The tumour was characterised as HER2 positive by immunohistochemistry (IHC) in 15 patients, i.e. 88.23% of the population studied. An additional test using fluorescence in situ hybridization (FISH) was required in 2 other patients in whom IHC showed 2+ expression.

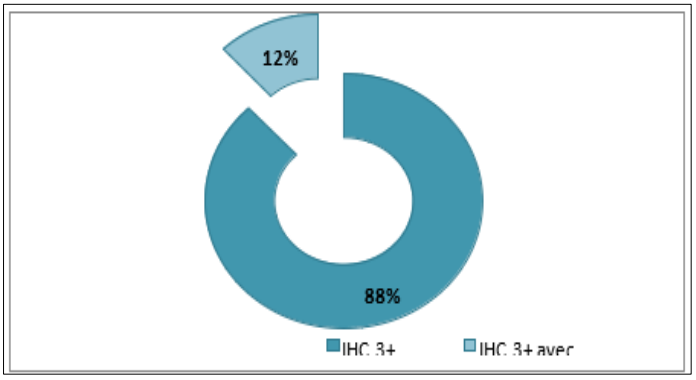

Figure 12: Distribution according to HER2 overexpression

5. THERAPEUTIC APPROACH

A. Treatment Administered

In our series, all patients received treatment with double anti-HER2 blockade combined with chemotherapy.

I. Protocol

Of the patients included, 15 (88%) received Pertuzumab + Trastuzumab + Docetaxel, and 2 (12%) received Pertuzumab + Trastuzumab + Paclitaxel.

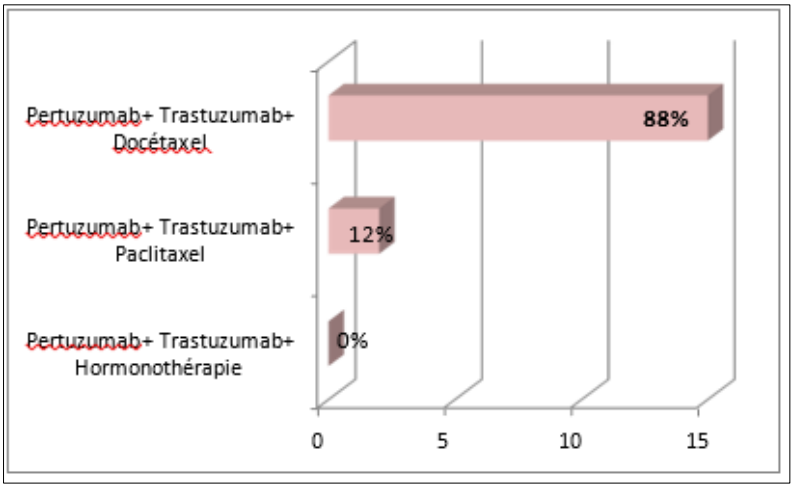

Figure13: Distribution of patients according to treatment protocol administered

Table 7: Therapeutic protocols used in our series

Protocol	Composition	Number of patients	Percentage (%)
PHT	6 courses of : Docetaxel (Taxotere®): 75-100 mg /m² + Trastuzumab (Herceptin®): 8mg/kg loading dose, followed by 6mg/kg + (Herceptin®): 8mg/kg loading dose, followed by 6mg/kg + (Herceptin®) Pertuzumab (Perjeta®): 840mg then 420mg = (1 course every 3 weeks) Followed by courses of : Pertuzumab + Trastuzumab Combined with hormone therapy in the case of HR+.	15	88%
PHP	Paclitaxel (Taxol®) (80 mg / m 2) =weekly + Trastuzumab (Herceptin®) loading dose 8 mg /kg → 6 mg /kg) = every 3 weeks + Pertuzumab (Perjeta®) loading dose 840 mg → then 420 mg = every 3 weeks	2	12%

I. Number of Treatments

The number of treatments administered in our series varied according to each patient, ranging from 11 to 30 treatments.

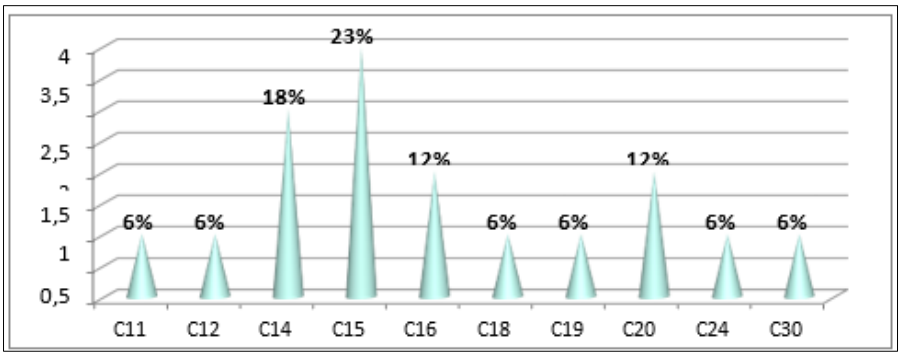

Figure 14: Breakdown by number of treatments administered

B. Hormonal Maintenance Treatment

In our series, hormone maintenance treatment was prescribed after chemotherapy in 70% of RH+ patients (7 cases).

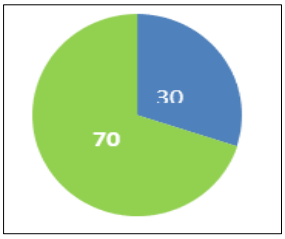

Figure 15: Percentage of RH+ patients receiving maintenance hormone therapy

Patients not treated with hormonotherapy

Of the HR+ patients who received hormonal maintenance treatment (57%), either 4 patients were treated with letrozole (43%) or 3 patients were treated with anastrozole.

Table 8: Breakdown by hormone treatment administered to RH+ patients

Hormone treatment	Number of patients	Percentage (%)
Létrozole	4	57%
Anastrozole	3	43%
Total	7	100%

6. EVALUATION

6.1 Progression-Free Survival

The mean progression-free survival (PFS) in our series is estimated at 16 months.

6.2 Toxicity

The most frequent adverse events in our series were neutropenia in 5 patients (29.4%) and diarrhoea in 4 patients (23.5%). However, none of our patients experienced cardiotoxicity.

Table 9: Distribution of patients according to therapeutic toxicity

Toxicity	Number of patients	Percentage (%)
Neutropénie	5	29,4%
Neutropénie fébrile	1	5,9%
Diarrhée	4	23,5%
Prurit	2	11,7%
Lésions cutanées	1	5,9%
Cardiotoxicité (FEVG<50%)	0	0%

DISCUSSION

I. EPIDEMIOLOGY OF BREAST CANCER

a. INCIDENCE

The HER2 gene is amplified or overexpressed in 20-30% of breast cancers [14, 15], 22% of non-advanced cancers, 35% of locally advanced and metastatic cancers and 40% of inflammatory cancers [15].

In our series, HER2 was overexpressed in 21% of cases. This rate remains within the recommended limits of positivity.

This rate is also respected in several studies: the Dickens C *et al*., study in South Africa (24%) [16], the Tunisian study by Fourati A *et al*., [17], the Egyptian study by Salhia B *et al*., (25%) [18], and the Moroccan study by El Idrissi E *et al*., (29%) [19]. Other authors, Clarks Ca *et al*., [20], and Melissa R *et al*., [21], found lower expression rates.

Table 10: Comparison of HER2 overexpression according to different series in the literature

Series	Number of patients	Percentage
C. Dickens *et al*., Afrique du sud [16]	8857	24%
A. Fourati *et al*., Tunis [17]	966	27%
B. Salhia *et al*., Egypte [18]	359	25%
E. El Idrissi *et al*., Maroc [19]	2260	29%
C.A. Clarke *et al*., USA [20]	91 908	16%
R. Melissa *et al*., Angleterre [21]	103 568	10%
Notre série	104	21%

B. Age

Age is the most important risk factor for breast cancer [22]. From the age of 50 onwards, one woman in 10 will develop breast cancer in the 30 years remaining to her life: around 64% of women are over 55 when their cancer is diagnosed [21]. However, some breast cancers occur at a young age, and around 15-20% of breast cancers are diagnosed before the age of 50. It is among these cancers that a BRCA1 or BRCA2 gene mutation is most common [22].

According to the Casablanca cancer register, the average age at onset of breast cancer is 49.5 years [23]. According to the Rabat cancer register, the average age is 50.7 [24].

In our series, the average age of onset of breast cancer was 56.3 years, which is not consistent with the data in the literature, where the average age of onset is 61 years [25], and which is slightly higher than that reported by the cancer registries in our country.

In all cases, we agree with the results obtained from the various series carried out in Morocco and other Maghreb countries such as Tunisia.

In Morocco

- Tajeddine series [26]. (Marrakech oncology centre) where the mean age was 53.3 years.
- Series by F.Koali [27]. (General surgery department HMA 2015- 2016) where the mean age of onset was 53 years.

Tunisia

- Series by Laamouri [28]. (Salah Azaiez Institute) where the mean age was 55.5 years, higher than that reported in the registries of southern and northern Tunisia (mean age 52.9 years) [25].

In Algeria

- Sakhri series [29]. (Tizi Ouzou oncology centre) the average age of onset of breast cancer is lower than ours and estimated at 49 years, which corresponds to the age of diagnosis in the various Algerian registers [30]. The average age of our patients was also close to that reported in developed countries, particularly France and the United States, where the average age at diagnosis is 60 [31, 32].

Table 11 I: Mean age in our series compared with the literature.

Series	Average age
Notre série	56,3 ans
Registre national du Grand Casablanca [23]	49,5 ans
Registre national de Rabat [24]	50,7 ans
Série de Tajeddine [26], Maroc	53,3 ans
Série de F.Koali [27], Maroc	53 ans
Série de Laamouri [28], Tunisie	55,5 ans
Série de Sakhri [29], Algérie	49 ans
France [31]	60 ans
Etats-Unis [32]	60 ans

C. METASTASES

C.1 EARLY RESUSCTIONS

Approximately 25-30% of women are diagnosed with metastases during surveillance after adjuvant treatment for localised or locally advanced breast disease [33]. Epidemiological studies have shown that the risk of relapse is increased above all in the presence of a positive lymph node status at initial diagnosis, a large tumour size and a high Ki67 proliferation index. As well as overexpression of the HER-2 oncogene.

The age of patients at diagnosis is also one of the prognostic factors predicting relapse. Older women have a higher rate of relapse, which can be explained both by a lower response rate to chemotherapy in postmenopausal women and by an increase in side effects, leading to a reduction in chemotherapy doses and therefore a decrease in efficacy [34]. Overall, adjuvant chemotherapy reduces the risk of relapse by ≥ 40%. The interval between initial treatment and the appearance of the first metastasis is one of the factors to be taken into account. The longer the interval between the initial tumour and the onset of metastatic disease, the better the prognosis [35].

The median time to relapse varied between studies:

- Lakhrissi.M series [36]. Of the 55 non-metastatic patients, 25 developed distant metastases, i.e. 41.7%. The mean time to onset of metastases was 30 months (6 to 70 months). In all patients with distant metastases, a single metastatic site was found in all 23 patients. The most frequent site of metastasis was bone in 60% of cases.
- Corina J. G. van den Hurk *et al*., study [37]. Of 33,771 M0 patients followed for more than 5 years, (24%) developed metastatic relapse, (67%) within 5 years of initial diagnosis. The risk of developing metastases was highest within 2.5 years of diagnosis.
- Bensouda *et al*., [38]. Retrospective study including 240 patients followed for breast cancer during an imprecise period. The median time to metastatic relapse was 73 months.
- In our series, metastatic relapse was observed in only 12% (2 cases) of all our patients who had received adjuvant chemotherapy. The mean time to relapse for these 2 patients was 29 months (10-48 months).

Table 12: Median time to metastatic relapse in our series compared with other series

Etude	Frequency of metastatic relapses	Relapse time
Lakhrissi.M [36]	41,7%	30mois
Corina J. G. van den Hurk *et al*., [37]	24%	<30mois
Bensouda *et al*., [38]		73 mois
Notre étude	12%	29mois

2 DE NOVO METASTASES

De novo metastatic breast cancer accounts for 5 to 6% of all breast cancers in Western countries, i.e. around 2,500 new cases per year in France [39].

In our series, the rate of de novo metastases was 88% of all cases studied, which is not consistent with the results of the Albain KS et al study [40], which found a rate of de novo metastases estimated at 80%. This far exceeds the data in the literature, which reports a frequency of up to 30%, and that reported in the Beslija S. *et al*., study (6 to 10%) [41].

And according to study C, Darcourt J *et al*., [42]. The extension work-up revealed distant metastases at the time of diagnosis in 12 patients, i.e. 5.7% of cases. The distribution of metastatic sites was as follows: hepatic in 58.3%, pulmonary in 16.6%, and bone in 16.6%.

In the Ben Ahmed S. *et al*., series, distant metastases were diagnostic in 7% of cases. Metastatic sites were bone (56%), lung (32%), liver (30%), metastases were single in 60% of cases [43]. In contrast, the most frequent metastatic sites in our series were pulmonary (53%) followed by bone metastases (41%).

Table 13: The rate of de novo metastases in our series compared with different series in the literature

Series	De novo metastases (%)
Notre série	88%
Albain KS *et al*., [40]	80%
Beslija S *et al*., [41]	6 à 10%
C, Darcourt J *et al*., [42]	5,7%
Ben Ahmed S *et al*., [43]	7%

3 ASSESSMENT OF TREATMENT EFFICACY

1. Progression-Free Survival

In the context of metastatic breast cancer, PFS is one of the intermediate measures widely used in phase III clinical trials in advanced cancers to assess the efficacy of new anti-cancer treatments, and is defined as the time between randomisation and tumour progression or death from any cause [44]. To date, there is no

standard criterion for defining cancer progression. Numerous criteria can be used, in particular the Response Evaluation Criteria in Solid Tumors (RECIST) [45], and the World Health Organization Response Criteria [46], and they must be clearly specified in a clinical trial protocol.

In general, progression of a cancer is defined by a certain percentage increase in the size of a tumour or metastatic lesion (increase ≥ 20% of the sum of the largest diameters of the target lesions, RECIST criteria), the appearance of new lesions, abnormal blood test results or radiological examinations or the appearance/ worsening of symptoms of the disease [47].

Several authors have reported a better progression-free survival rate for patients with HER2+ metastatic breast cancer receiving double HER2 blockade combining chemotherapy (docetaxel or paclitaxel) with trastuzumab and pertuzumab:

- The CLEOPATRA trial [48], randomised 808 patients to trastuzumab plus pertuzumab plus docetaxel or trastuzumab plus docetaxel plus placebo. The addition of pertuzumab to the combination of trastuzumab and docetaxel prolonged progression-free survival by a median of 6.1 months (18.5 versus 12.4 months).
- PERUSE trial [49]. A phase II trial of pertuzumab in combination with trastuzumab and paclitaxel was subsequently published, with 6-month PFS as the primary endpoint. Patients received paclitaxel weekly, and trastuzumab and pertuzumab every 3 weeks. The result reported in this study was that double blockade combined with paclitaxel resulted in progression-free survival at 6 months in (75%) of cases.

A mean progression-free survival estimated at 16 months (7-26 months) was observed in all our patients, of whom 15 patients received the PTH protocol (88%), and 2 patients were treated with the PTP protocol (12%).

Table 14: Mean PFS in our study compared with other studies

Etude	Average SSP (months)
CLEOPATRA [48]	18 mois
PERUSE [49]	6 mois
Notre étude	16 mois

2. TOXICITY

Chemotherapy may cause complications, many of which disappear in the short term: nausea, vomiting, alopecia, bone marrow aplasia, neuropathy, etc.

In non-menopausal women, chemotherapy can induce an early menopause, with major side-effects that are a source of poor quality of life: hot flushes, reduced libido, vaginal dryness and atrophy, and osteoporosis.

However, certain side-effects such as fatigue, cognitive impairment, fertility problems, rare cases of cardiotoxicity [50], and secondary leukaemia remain a cause for concern in the long term.

- Trastuzumab [51]. Its toxicity can be cardiac, which is why the concomitant combination of Trastuzumab and Anthracyclines should not be recommended.
- Pertuzumab [51]. The trial (TRYPHAENA) evaluated the cardiac tolerance of several treatment regimens with or without anthracyclines, it did not highlight any major cardiotoxicity when pertuzumab was combined with anthracyclines. In all our patients, the most frequently observed adverse events were: Neutropenia (29.4%) and diarrhoea (23.5%) followed by pruritus (11.7%) and febrile neutropenia in a single patient (6%). However, cardiotoxicity (LVEF< 50%) was not present in our series
  - The CLEOPATRA study [48]. The side effects observed in this phase III study, with a higher frequency in the pertuzumab, trastuzumab and docetaxel arms, were diarrhoea, skin rash or xerosis, mucositis and febrile neutropenia. In terms of severe side effects (grade 3 or more), only febrile neutropenia (13%) and diarrhoea (7.9%) were reported.

The important point in terms of safety is that the addition of pertuzumab to the reference treatment of trastuzumab-docetaxel does not increase the incidence of cardiac side effects. Severe left ventricular toxicities (decline in LVEF of more than 10%) occurred in 3.8% of cases in the pertuzumab arm. - According to the PERUSE trial (Bachelot *et al.*, [49]. Toxicities associated with double blockade combined with weekly paclitaxel included alopecia (100%), fatigue (94%), ALAT/ASAT elevation (88%), neuropathy (88%), diarrhoea (75%), skin rash (56%), nail changes (50%), nausea (44%), mucositis (44%) and dry skin (38%). Grade 3/4 toxicities included sepsis (6%), cholecystitis (6%), fatigue (6%), skin ulceration (6%) and cystic macular degeneration (6%). The median LVEF was 58%, with no cardiac events at 6 months.

Table 15: Percentage of frequent adverse reactions in our study compared to other studies

Study	Neutropenia feverish	Diarrhoea	Neutropenia	Cardiotoxicity (LVEF<50%)
CLEOPATRA	13 %	7,5%	-	3,8%
PERUSE	-	75%	88%	0%
Our study	6%	23,5%	29,4%	0%

3. MAINTENANCE HORMONE THERAPY FOR PATIENTS (RH+)

Hormone therapy in metastatic disease is of particular interest to tumours presumed to be hormone-sensitive RE+ and/or RP+, with slow kinetics, a long interval between initial tumour and metastatic development, and bone or skin rather than visceral metastases. In the event of therapeutic urgency, treatment should be started with chemotherapy until stabilisation, after which hormone therapy should be prescribed [52]. In metastatic breast cancer, blocking oestrogen signalling was the first therapeutic strategy used in this type of cancer and remains the reference treatment (Tamoxifen, IA, Fulvestrant). In multifactorial analyses, three retrospective studies observed a benefit of maintenance HT for relapse-free survival and for overall survival in two of them. Although the level of evidence in these studies is insufficient, the magnitude of the benefit observed (approximately one year for time to progression, and 20% for survival), the consistency of the results, and the low toxicity of such a maintenance treatment mean that maintenance HT should be proposed after a first line of CT for an RH+ tumour. As a result, randomised trials evaluating a new CT should authorise the possibility of giving maintenance HT after a response has been obtained [53]. The updated ESMO guidelines of 2020 recommend the use of hormonal treatment combined with targeted therapy as maintenance treatment after chemotherapy has been stopped for patients with ER-positive / HER2-positive metastatic breast cancer for whom treatment with double blockade: chemotherapy + an anti-HER2 targeted therapy has been chosen as first-line treatment and has provided benefit [54].

V- CONCLUSION

Breast cancer is a multifactorial disease. A number of risk factors for breast cancer are known, although there is still uncertainty as to the involvement and weight of several of these factors. There are internal risk factors within individuals (genetic predisposition, obesity, genital life, etc.) and external risk factors linked to the environment and to lifestyles and living conditions. However, no factor has been directly implicated in the aetiopathogenesis of this cancer, with the exception of the hereditary transmission of certain predisposition genes, in particular the BRCA1 and 2 genes, which are involved in 5-10% of cases of breast cancer. Many treatments are part of the therapeutic armoury for metastatic breast cancer, and the choice of the best treatment depends on a number of factors such as hormone receptor status, HER2 status, the location of metastases and the patient's overall state of health. The therapeutic standard for first-line metastatic HER2-amplified patients is therefore currently based on the combination of Pertuzumab - Trastuzumab - Docetaxel chemotherapy, which has significantly prolonged survival and improved quality of life in patients with HER2+ metastatic breast cancer, without major overtoxicity. However, patient management should be multidisciplinary, encompassing all aspects of treatment, particularly palliative. However, primary prevention of breast c a n c e r seems difficult given its multifactorial aetiology. Breast cancer needs to be included in national health policies. This can be achieved by implementing a screening policy, promoting information and training programmes for women (breast selfexamination), and training health workers and medical practitioners.

REFERANCES

1. Ferlay. (2018). Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int. J. Cancer, 00, 1–13, 2018 UICC.
2. World Health Organization. International Agency for Research on Cancer. MOROCCO GLOBOCAN 2018 (IARC) Section of Cancer Information.
3. World Health Organization. International Agency for Research on Cancer. MOROCCO GLOBOCAN 2008 (IARC) Section of Cancer Information.
4. O'Shaughnessy, J. (2005). Extending survival with chemotherapy in metastatic breast cancer. *The oncologist*, *10*(S3), 20-29.
5. Mariani, G. (2005). New developments in the treatment of metastatic breast cancer: from chemotherapy to biological therapy. *Annals of oncology: official journal of the European Society for Medical Oncology*, *16*, ii191-ii194.
6. Marty, M., Cognetti, F., Maraninchi, D., Snyder, R., Mauriac, L., & Tubiana-Hulin, M. (2006). Superior long-term survival benefits of trastuzumab plus docetaxel compared to docetaxel alone in patients with HER2-positive metastatic breast cancer: patients surviving more than 4 years in the M77001 study. *Breast Cancer Res Treat*, *100*, S103.
7. Thomas, B. (2011). Olivier Tredan. Chapitre 15.

Cancers du sein métastatiques. Maladies du sein (2ème édition). 129-136.
8. Slamon, D. J., Clark, G. M., Wong, S. G., Levin, W. J., Ullrich, A., & McGuire, W. L. (1987). Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *science*, *235*(4785), 177-182.
9. Yaziji, H., Goldstein, L. C., Barry, T. S., Werling, R., Hwang, H., Ellis, G. K., ... & Gown, A. M. (2004). HER-2 testing in breast cancer using parallel tissue-based methods. *Jama*, *291*(16), 1972-1977.
10. Gianni, L., Eiermann, W., Semiglazov, V., Manikhas, A., Lluch, A., Tjulandin, S., ... & Baselga, J. (2010). Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. *The Lancet*, *375*(9712), 377-384.
11. Ferretti, G., Felici, A., Papaldo, P., Fabi, A., & Cognetti, F. (2007). HER2/neu role in breast cancer: from a prognostic foe to a predictive friend. *Current Opinion in Obstetrics and Gynecology*, *19*(1), 56-62.
12. Guiu, S., & Fumoleau, P. (2015). Pertuzumab and T-DM1: New perspectives in the treatment of HER2-positive breast cancer. *Oncologie*, *17*, 263-270.
13. Sabatier, R., & Goncalves, A. (2014). Pertuzumab (Perjeta®) approval in HER2-positive metastatic breast cancers. *Bulletin Du Cancer*, *101*(7-8), 765-771.
14. Dr. Ananya Mandal, MDReviewed by April Cashin-Garbutt, MA (Editor) Histoire du cancer du sein https://www.news-medical.net/health/History- of-Breast-Cancer-(French).aspx
15. Gianni, L., Eiermann, W., Semiglazov, V., Manikhas, A., Lluch, A., Tjulandin, S., ... & Baselga, J. (2010). Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. *The Lancet*, *375*(9712), 377-384.
16. Dickens, C., Pfeiffer, R. M., Anderson, W. F., Duarte, R., Kellett, P., Schüz, J., ... & McCormack, V. A. (2016). Investigation of breast cancer sub-populations in black and white women in South Africa. *Breast cancer research and treatment*, *160*, 531-537.
17. Fourati, A., Boussen, H., El May, M. V., Goucha, A., Dabbabi, B., Gamoudi, A., ... & Ben Abdallah, M. (2014). Descriptive analysis of molecular subtypes in T unisian breast cancer. *Asia-Pacific Journal of Clinical Oncology*, *10*(2), e69-e74.
18. Salhia, B., Tapia, C., Ishak, E. A., Gaber, S., Berghuis, B., Hussain, K. H., ... & Carpten, J. (2011). Molecular subtype analysis determines the association of advanced breast cancer in Egypt with favorable biology. *BMC women's health*, *11*, 1-9.
19. Elidrissi Errahhali, M., Elidrissi Errahhali, M., Ouarzane, M., El Harroudi, T., Afqir, S., & Bellaoui, M. (2017). First report on molecular breast cancer subtypes and their clinico-pathological characteristics in Eastern Morocco: series of 2260 cases. *BMC women's health*, *17*, 1-11.
20. Clarke, C. A., Keegan, T. H., Yang, J., Press, D. J., Kurian, A. W., Patel, A. H., & Lacey Jr, J. V. (2012). Age-specific incidence of breast cancer subtypes: understanding the black–white crossover. *Journal of the National Cancer Institute*, *104*(14), 1094-1101.
21. Gannon, M. R., Dodwell, D., Jauhari, Y., Horgan, K., Clements, K., Medina, J., & Cromwell, D. A. (2020). Initiation of adjuvant chemotherapy and trastuzumab for human epidermal growth receptor 2-positive early invasive breast cancer in a population-based cohort study of older women in England. *Journal of geriatric oncology*, *11*(5), 836-842.
22. Espie, M. A. R. C., Tournant, B., Cuvier, C., & Cottu, P. H. (2001). Épidémiologie des lésions malignes du sein. *EMC–Gynécologie*, *15*, 840-850.
23. REGISTRE DES CANCERS de la Région du Grand Casablanca pour la période 2008 - 2012 registre des cancers - Fondation Lalla Salma Édition 2016
24. RECRAB : Registre des cancers de Rabat, Incidence des cancers à Rabat 2006-2008. Ministère de la santé Juin 2012.
25. Ries.LAG, Eisener .MP,Kosary.CL,Hankey. BF, Miller.Cleeg.L Seer. CANCER STATISTICS REVIEW ,1975-2002, National cancer institute. Bethesda, MD
26. Tajeddine, F., & HASSANI, A. T. J. (2009). *Place de la chimiothérapie néoadjuvante dans les cancers du sein localement avancés* (Doctoral dissertation, Thèse de médecine 17. Marrakech).
27. Kouali, F. (2017). Traitement conservateur du cancer du sein revue des indications, étude rétrospective (à propos de 20 cas).
28. Laamouri, B. (2011). *Les cancers du sein localement avancés (T4b): Caractéristiques épidémiologiques, cliniques et pronostiques* (Doctoral dissertation, Thèse en médecine. Université de Tunis El Manar).
29. Sakhri, S. (2015). *Chimiotherapie neoadjuvante associee a l'acide zoledronique dans le cancer du sein localement avancee: etude prospective 2012-2014* (Doctoral dissertation, Tizi Ouzou).
30. SELLAMI, A., BOUDAWARA, T. S., HSAIRI, M., JLIDI, R., & ACHOUR, N. Incidence des Cancers dans le Gouvernorat de Sfax.
31. Binder-Foucard, F., & Aurélien, B. (2013). Estimation nationale de l'incidence et de la mortalité par cancer en France entre 1980 et 2012 ; Etude à partir des registres des cancers du réseau Francim.Partie 1 – Tumeurs solides.
32. https://WWW.e-cancer.fr/Patients Etproches/Lescancers/Cancerdusein/Quelques-

chiffres Edition 2016
33. Lopez-Trabada, D., Ataz. (2015). Le nab-paclitaxel Reçu le 20 mars 2015 Accepté le 23 mars 2015 Disponible sur internet le.
34. Largillier, R., Ferrero, J. M., Doyen, J., Barriere, J., Namer, M., Mari, V., Courdi, A., HannounLevi, J. M., Ettore, F., & Birtwisle-Peyrottes, I. (2008). Prognostic factors in 1038 women with metastatic breast cancer. *Ann Oncol*, *19*, 2012–2019.
35. Chang, J., Clark, G. M., Allred, D. C., Mohsin, S., Chamness, G., & Elledge, R. M. (2003). Survival of patients with metastatic breast carcinoma: importance of prognostic markers of the primary tumor. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, *97*(3), 545-553.
36. Lakhrissi M Cancer Du Sein Localement Avancé Service de Gynécologie Obstétrique de l'hôpital Militaire Moulay Ismail - Meknés (à propos de 60 cas) THESE POUR L'OBTENTION DU DOCTORAT EN MEDECINE
37. van den Hurk, C. J., Eckel, R., van de Poll-Franse, L. V., Coebergh, J. W. W., Nortier, J. W., Hölzel, D., ... & Engel, J. (2011). Unfavourable pattern of metastases in M0 breast cancer patients during 1978-2008: a population-based analysis of the Munich Cancer Registry. *Breast cancer research and treatment*, *128*, 795-805.
38. Bensouda, Y., Andre, F., Boulet, T., Al-Ghuzlan, A., Conforti, R., Troalen, F., ... & Delaloge, S. (2009). Prevalence de l'elevation du CA 15-3 lors de la rechute metastatique des cancers du sein: correlation avec l'expression des recepteurs hormonaux et de Her2. *Bulletin du cancer*, *96*(10), 923-928.
39. Ghannam, Y., Bourgier, C., Legouté, F., Gonzalez-Moya, A., Lizée, T., Trémolières, P., & Hennequin, C. (2020). Irradiation de la tumeur primitive en cas de cancer du sein métastatique synchrone. *Cancer/Radiothérapie*, *24*(6-7), 567-575.
40. Albain, K. S., Allred, D. C., & Clark, G. M. (1994). Breast cancer outcome and predictors of outcome: are there age differentials?. *Journal of the National Cancer Institute. Monographs*, (16), 35-42.
41. Beslija, S., Bonneterre, J., Burstein, H. J., Cocquyt, V., Gnant, M., Heinemann, V., ... & Central European Cooperative Oncology Group (CECOG. (2009). Third consensus on medical treatment of metastatic breast cancer. *Annals of oncology*, *20*(11), 1771-1785.
42. Balu-Maestro, C., Chapellier, C., Carrier, P., Darcourt, J., Ettore, F., & Raoust, I. (2005). Imagerie dans le bilan d'extension ganglionnaire et métastatique du cancer du sein. *Journal de radiologie*, *86*(11), 1649-1657.
43. S. Ben, A. Pronostic du cancer du sein chez les femmes tunisiennes : analyse d'une série hospitalière de 729 patientes Dans Santé Publique 2002/3 (Vol. 14), pages 231 à 241)
44. Center for Drug Evaluation and Research (CDER). (2007).nCenter for Biologics Evalation and Research (CBER). Guidance for Industry; Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. Food and Drug Administration (FDA).
45. Therasse, P., Arbuck, S. G., Eisenhauer, E. A., Wanders, J., Kaplan, R. S., Rubinstein, L., ... & Gwyther, S. G. (2000). New guidelines to evaluate the response to treatment in solid tumors. *Journal of the national cancer institute*, *92*(3), 205-216.
46. World Health Organization. WHO Handbook for Reporting Results of Cancer Treatment. Geneva: WHO offset publication no. 48, 1979?
47. Dancey, J. E., Dodd, L. E., Ford, R., Kaplan, R., Mooney, M., Rubinstein, L., ... & Therasse, P. (2009). Recommendations for the assessment of progression in randomised cancer treatment trials. *European journal of cancer*, *45*(2), 281-289.
48. Sabatier, R., & Goncalves, A. (2014). Pertuzumab (Perjeta®) approval in HER2-positive metastatic breast cancers. *Bulletin Du Cancer*, *101*(7-8), 765-771.
49. Mikhail, F. D. Étude de phase II sur le pertuzumab, le trastuzumab et le paclitaxel hebdomadaire chez des patientes atteintes d'un cancer du sein métastatique (MBC) surexprimant HER2.
50. Jeyakumar, A., DiPenta, J., Snow, S., Rayson, D., Thompson, K., Theriault, C., & Younis, T. (2012). Routine cardiac evaluation in patients with early-stage breast cancer before adjuvant chemotherapy. *Clinical Breast Cancer*, *12*(1), 4-9.
51. Coussy, F., Teixeira, L., Giacchetti, S., Cuvier, C., Hocini, H., & Espié, M. (2014). Nouveautés sur les thérapies ciblées dans le cancer du sein. *Gynécologie Obstétrique & Fertilité*, *42*(11), 787-794.
52. Guastalla, J. P., Catimel. G., Blay, J. Y., Helfre, S., Rebattu, P., Desseigne, F., Bremond, A., Tigaud, J. D., Merrouche, Y. E. T., & Barbet, N. (1997). Traitement du cancer du sein métastatique et des formes cliniques particulières. Encycl. Méd. Chir. (Elsevier, Paris), *Gynécologie*, 871-A-10, 14.
53. Traitements médicaux des cancers du sein RH+ Her2− Medical treatments of endocrine-sensitive Her-2 negative breast cancers: a review
54. E Penault-Llorca Prise en charge du cancer du sein: place du pathologiste cancer du sein 2007.