



**FACULTAD DE MEDICINA
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MEDICINE DEGREE AT UNIVERSITY OF CANTABRIA

**TRATAMIENTO DEL CÁNCER DE MAMA METASTÁSICO
HER2 + CON VINOELBINA ORAL Y BLOQUEO DUAL CON
PERTUZUMAB Y TRASTUZUMAB**

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**METASTASIC HER2 + BREAST CANCER TREATMENT WITH
PERTUZUMAB, TRASTUZUMAB AND ORAL VINOELBINE IN
COMBINATION**

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ABSTRACT

Approximately 20% of breast carcinomas are 'HER2 positive': they behave aggressive by overexpression of HER2 membrane protein, in turn by amplification of c-erbB2 encoding gene. Current 1st line therapy includes 2 targeted anti-HER2 antibodies (trastuzumab and pertuzumab) in combination with a cytotoxic. CLEOPATRA phase 3 trial supports docetaxel, although vinorelbine is less toxic and can be acceptable, according VELVET phase 2 experience. Because vinorelbine has an advantageous oral formulation, we started an intramural protocol with PO vinorelbine plus pertuzumab/trastuzumab as a 1st line for metastatic HER2+ tumors. We did a retrospective evaluation of the first 24 women (Nov 2019/Jun 2020). As expected, alopecia and febrile neutropenia, among other toxicities, were much less common than with docetaxel. However, median time to treatment failure (8 months) compares unfavorably with reported 14 months with IV vinorelbine. Of note, we had an unusual 70% of estradiol receptor expression, a factor of resistance to HER2 blockade. On the other hand, concerns on pertuzumab and oral vinorelbine dosages have emerged, so we advise protocol amendments, especially an escalation of oral vinorelbine from 60 mg/m² to 80 mg/m², if previous toxicity was not limiting.

Resumen

El 20% de los carcinomas de mama son 'HER2+', forma agresiva de sobreexpresión de la proteína de membrana HER2 por amplificación de su gen codificante c-erbB2. Hoy, la 1ª línea terapéutica combina 2 anticuerpos anti-HER2 (trastuzumab y pertuzumab) con un citotóxico. El ensayo CLEOPATRA aconseja docetaxel, aunque la vinorelbina es menos tóxica y puede ser aceptable, según el estudio fase 2 VELVET. Dada la ventajosa presentación de la vinorelbina en cápsulas, se inició un protocolo intramural con vinorelbina PO más pertuzumab / trastuzumab como 1ª línea frente a tumores metastásicos HER2+. Se presenta una evaluación retrospectiva de las primeras 24 mujeres así tratadas (Nov 2019 / Jun 2020). Como se esperaba, la alopecia y la neutropenia febril, entre otras toxicidades, fueron mucho menos comunes que con docetaxel. Sin embargo, el tiempo hasta el fallo terapéutico (mediana de 8 meses) se compara desfavorablemente con los 14 logrados con vinorelbina IV. Encontramos un inusual 70% de co-expresión de receptor estrogénico, un factor de resistencia al bloqueo HER2. Consideramos que las dosis de pertuzumab y vinorelbina PO deben ser enmendadas, especialmente en el sentido de incorporar el escalamiento de vinorelbina PO de 60 mg/m² a 80 mg/m², si la toxicidad no resulta limitante.

Key Words

Oral vinorelbine, efficacy, toxicity, HER2 breast cancer

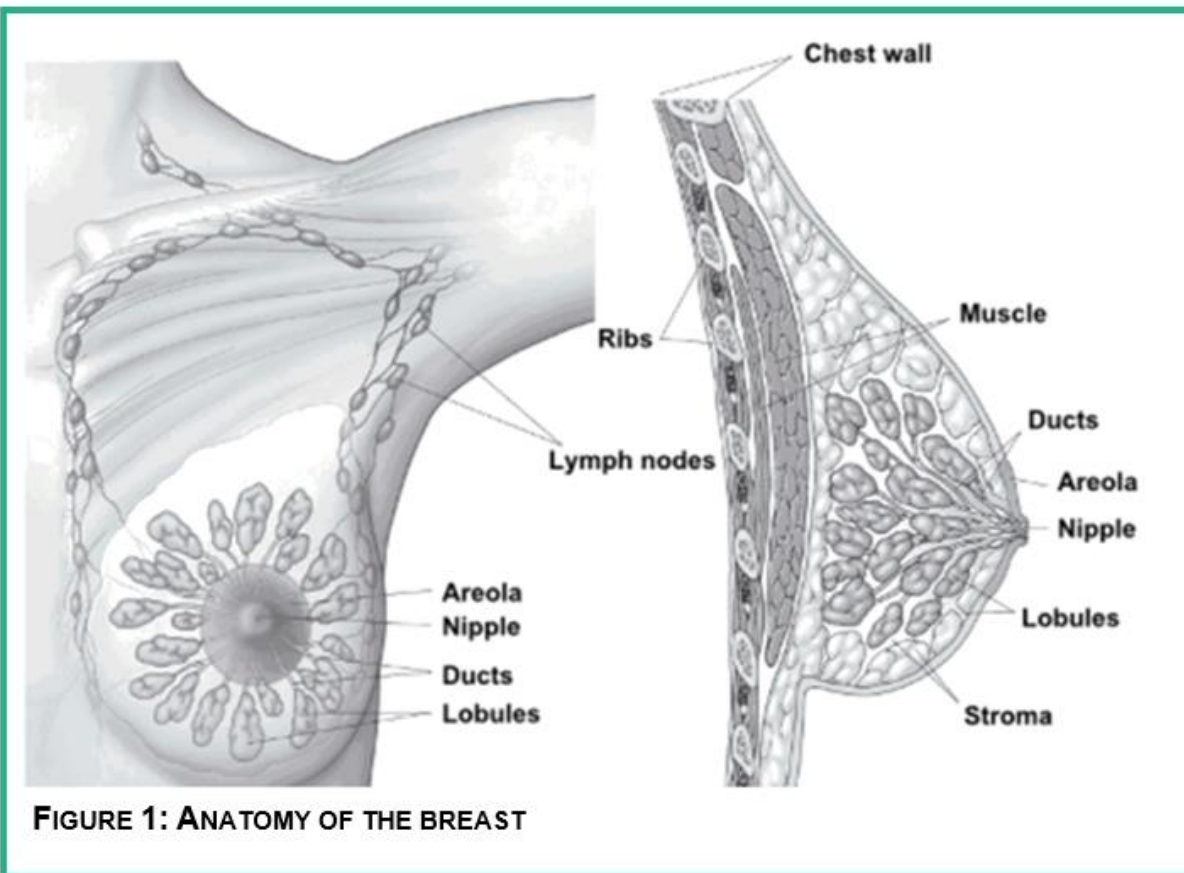
INTRODUCTION

1. Breast Anatomy

Adult breast lies between second and sixth ribs with a medium diameter of 10 cm and a 5 to 7 cm of rankness.

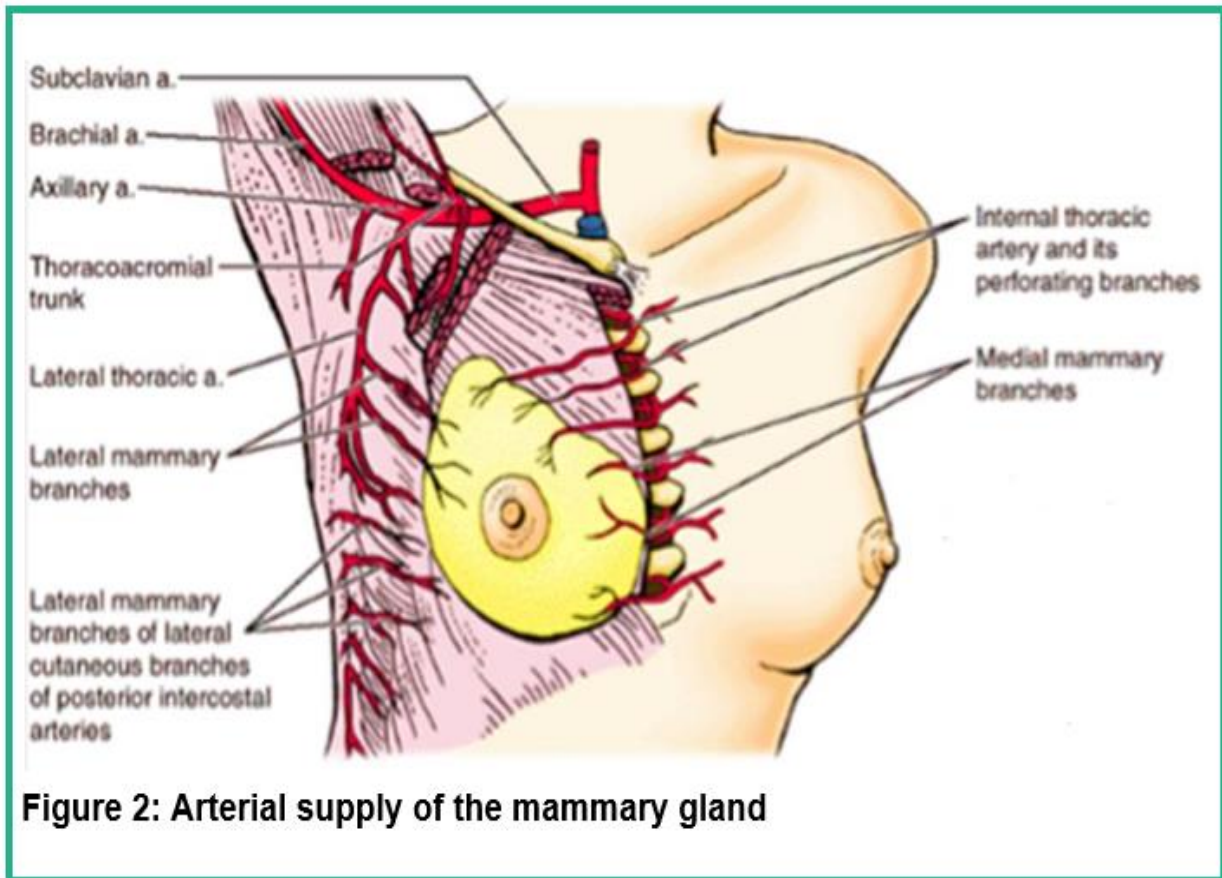
Three main frames fence the breast: breast tissue (that contains stroma and parenchyma), subcutaneous tissue, and skin.

The mammary gland is composed of 10-20 sections so called lobes (Figure 1). Lobes contain essentially adipose tissue and the exocrine parenchyma, which is divided into lobules -where secretory cells do lie-, and ducts that lead the milk to the nipple¹.



About vascularity, the internal mammary artery supplies the central part of the gland while the lateral thoracic artery irrigates the upper and outer quadrants (Figure 2).

The perforating branches of internal thoracic vein (axillary vein) and dorsal branches of posterior intercostal vein are responsible for the venous drainage of the mammary gland².



The lymphatic drainage of the breast consists of a subepithelial plexus of lymph vessels and a number of regional nodes. Lymph vessels of the breast get confluent with the over-surface lymphatic system of the body. A subareolar plexus does receive drainage from the nipple and the areola. Lymph flows only from superficial to deeper areas, 97% of the breast's lymph goes to axillary nodes and the other 3% flows to the internal mammary chain.

2. Carcinogenesis

Stem cells have the ability of divide into daughter cells that are able to renew themselves and they that can specialize and differentiate into distinct cell lines (pluripotential capacity).

In mammary gland these lines can create three specific kind of cells: ductal epithelial cells, alveolar epithelial cells (milk-producing cells), and myoepithelial ones.

Cancer arise from the transformation of a stem cell, through successive mutations causing uncontrolled growth and dissemination³. (Figure 3)

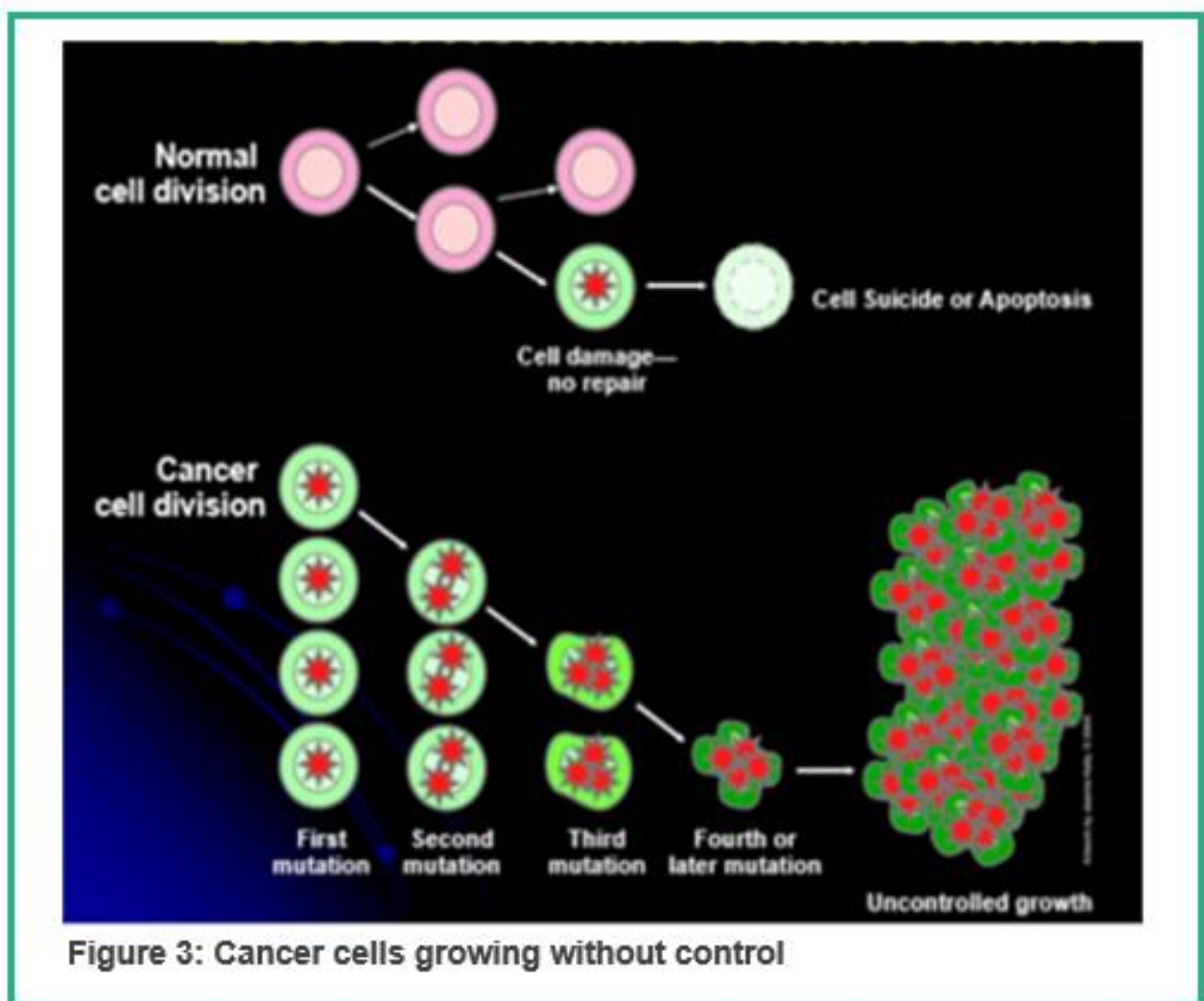


Figure 3: Cancer cells growing without control

As usual, breast cancer does arise from epithelial cells, either from ductal or lobular structures, so it is commonly a carcinoma.

Other histologic patterns, such as angiosarcoma or lymphoma, are less common and remain beyond our scope.

Breast carcinoma tends to spread through lymphatic drainage (Figure 1). Near 30% of cases are diagnosed with axillary nodal involvement.

Among cancer surgeons, it is common to distinguish spreading to different anatomic levels, as follows:

- **Level I:** Nodes that lie lateral to the lateral pectoral minus' border.
- **Level II:** Those that lie behind the pectoralis minus muscle.
- **Level III:** Nodes located medial to the medial pectoral minus' limit.

Moreover, in a minority of cases, spreading to intercostal nodes (internal mammary chain) or mediastinal nodes does occur. Infrequently also, tumor can progress through the rectus abdominis to subdiaphragmatic plexuses, rising perihepatic and retroperitoneal nodes.

3. Epidemiology

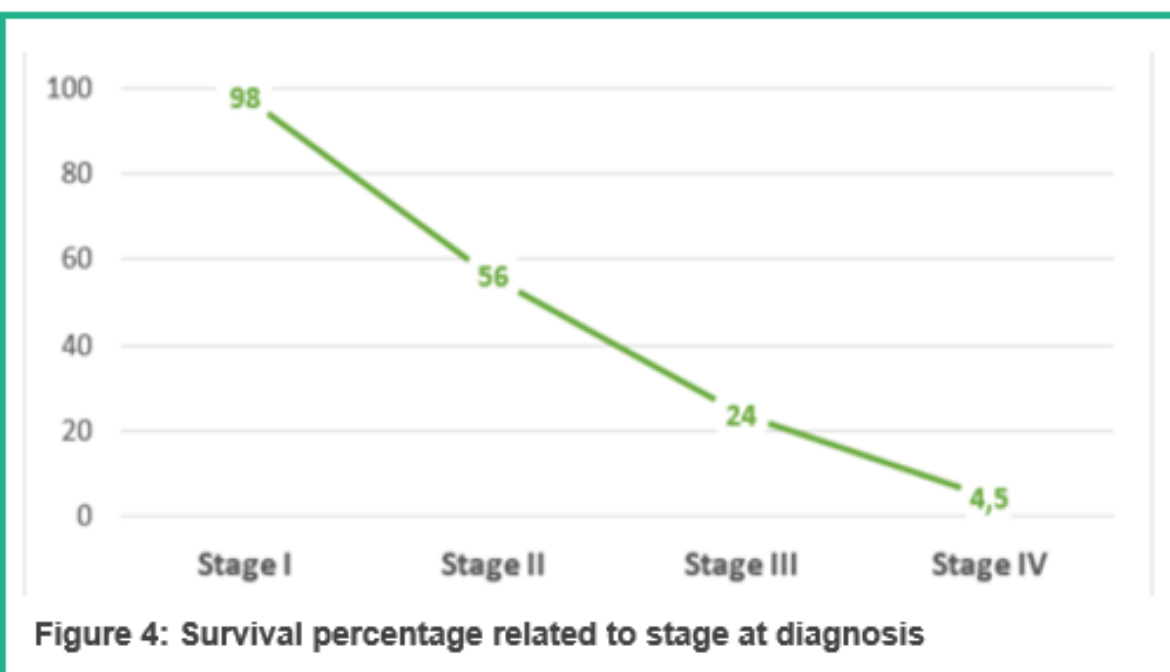
Breast cancer is the most common invasive neoplasm in women and the second leading cause of cancer death in women after lung cancer.

In Spain, 30 978 new cases were diagnosed in 2012 and the estimation for 2020 is near 33 000 new cases (1 out of 8 women) ⁴.

Table I shows the current distribution of incident cases in Spain, through different groups of age.

Table I. Distribution of breast cancer new cases (Spain, 2019)	
Group of age (years)	Frequency inside groups (%)
All	0.12
15-64	0.10
> 65	0.24

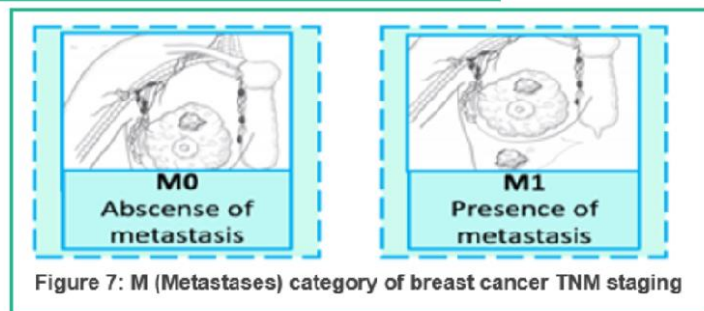
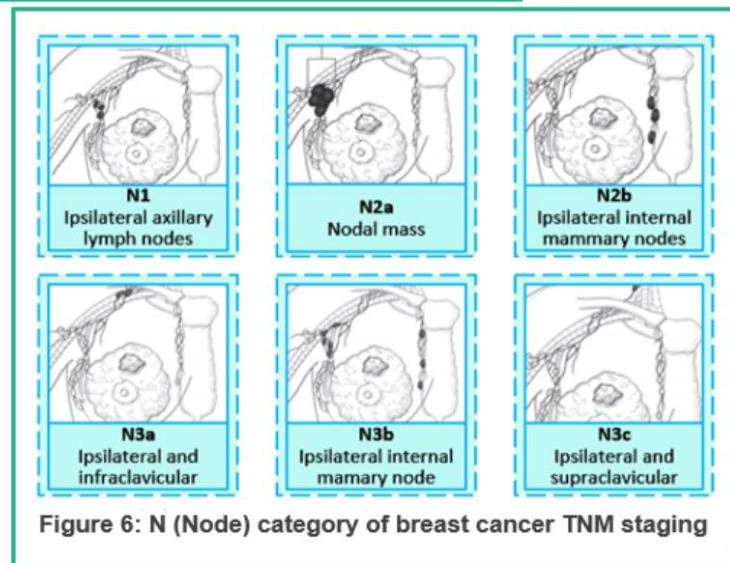
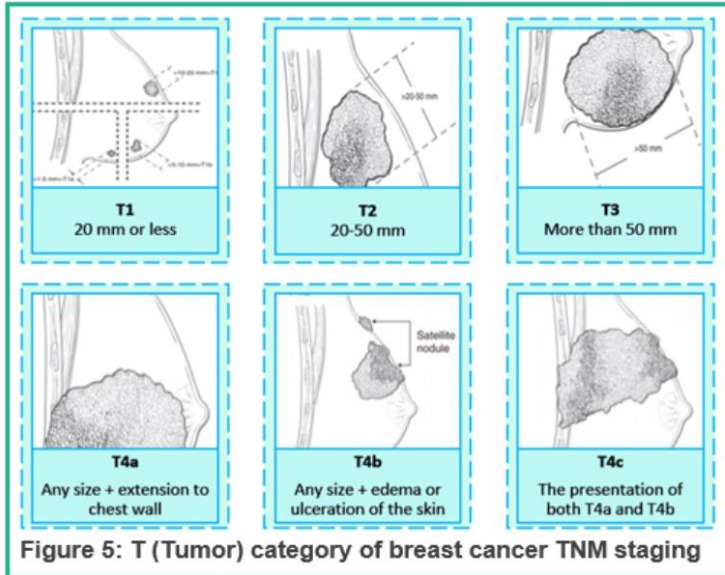
Advances in screening and treatment have improved survival rates dramatically during the last 30 years. Currently, the 89.2 % of breast cancer patients in Spain do survive more than 5 years after the diagnosis. However, it depends on the stage at diagnosis (Figure 4), a solid support for efficient screening programs.



4. Staging

Classical prognostic evaluation was based on TNM system, including clinical and image techniques^{5,6}.

Figures 5-7 illustrate factors T (tumor), N (nodes), and M (metastases).

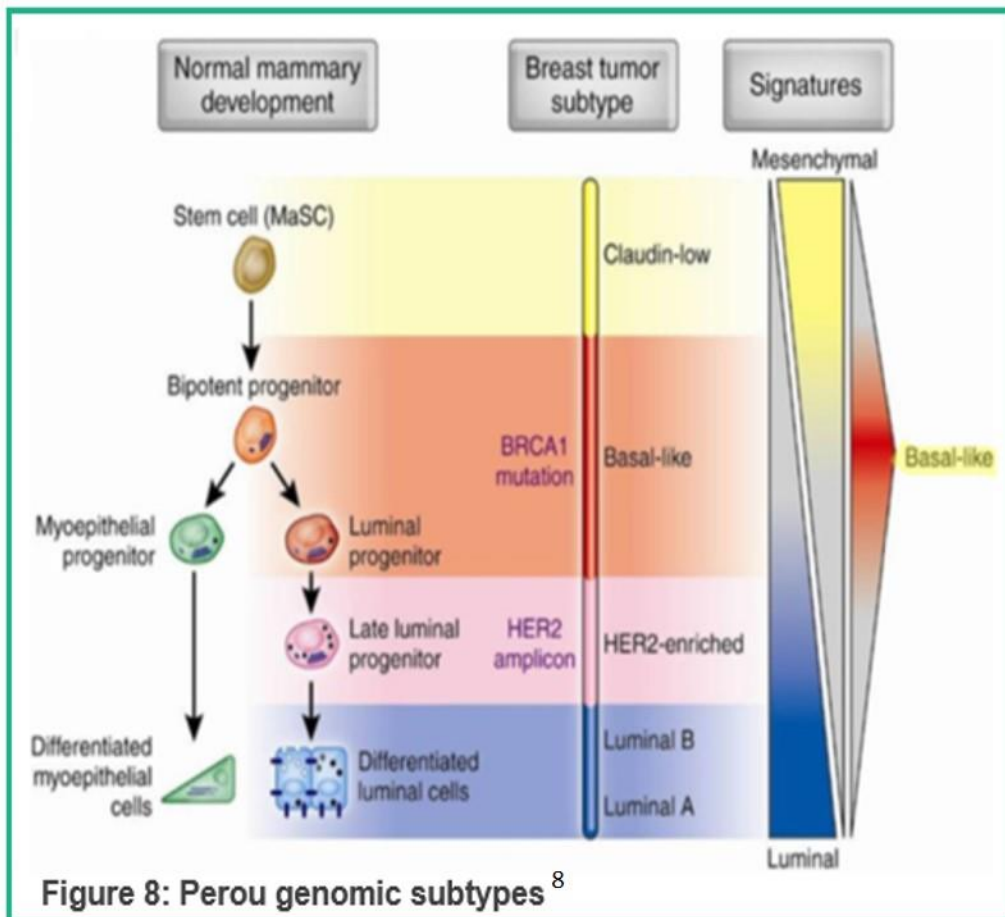


5. Molecular classification

In recent years, some molecular profiles are giving us additive prognostic information. Here we describe some commercial genomic platforms⁷:

- **Oncotype®**: It looks at 21 genes set and is able to give a RS ('Recurrence Score'). Values < 25 mean a 'low risk' and adjuvant chemotherapy can be avoided. Values > 25 are considered 'high risk' and chemotherapy should be given.
- **Mammaprint®**: Similarly, according the expression of a 70 genes panel, it gives a so-called *MMP index* that divides tumors into *low* or *high risk* of developing distant metastases.
- **Prosigna®**: It reviews 55 genes; together with some pathological traits, they are able to distinguish a ROR ('Risk of Recurrence') low, medium, or high.

Before giving a ROR, Prosigna® was designed to identify Perou's classes or signatures, which can be conceived as malignant counterparts of normal mammary gland development⁸ (Figure 8).



Thus, according its gene expression profile, current classification panel consists of 4 fundamental subtypes: luminal cancers (A and B), HER2 enriched tumors, and basal-like carcinomas. Prognosis is poorer in parallel with them, but it is interesting to be aware a conversion between primary tumor and metastatic foci is possible. Basal-like and HER2 enriched tend to maintain stable, but luminal cancers tend to progress from a to B, and from B to HER2 enriched⁹.

Theoretically, a genomic platform should be repeated, particularly if a change would determine a therapeutic new approach, but multigene expression tools are expensive. As a consequence, for pragmatic purposes, genomic profiles tend to be expressed as immunohistochemistry patterns, as shown in Table II.

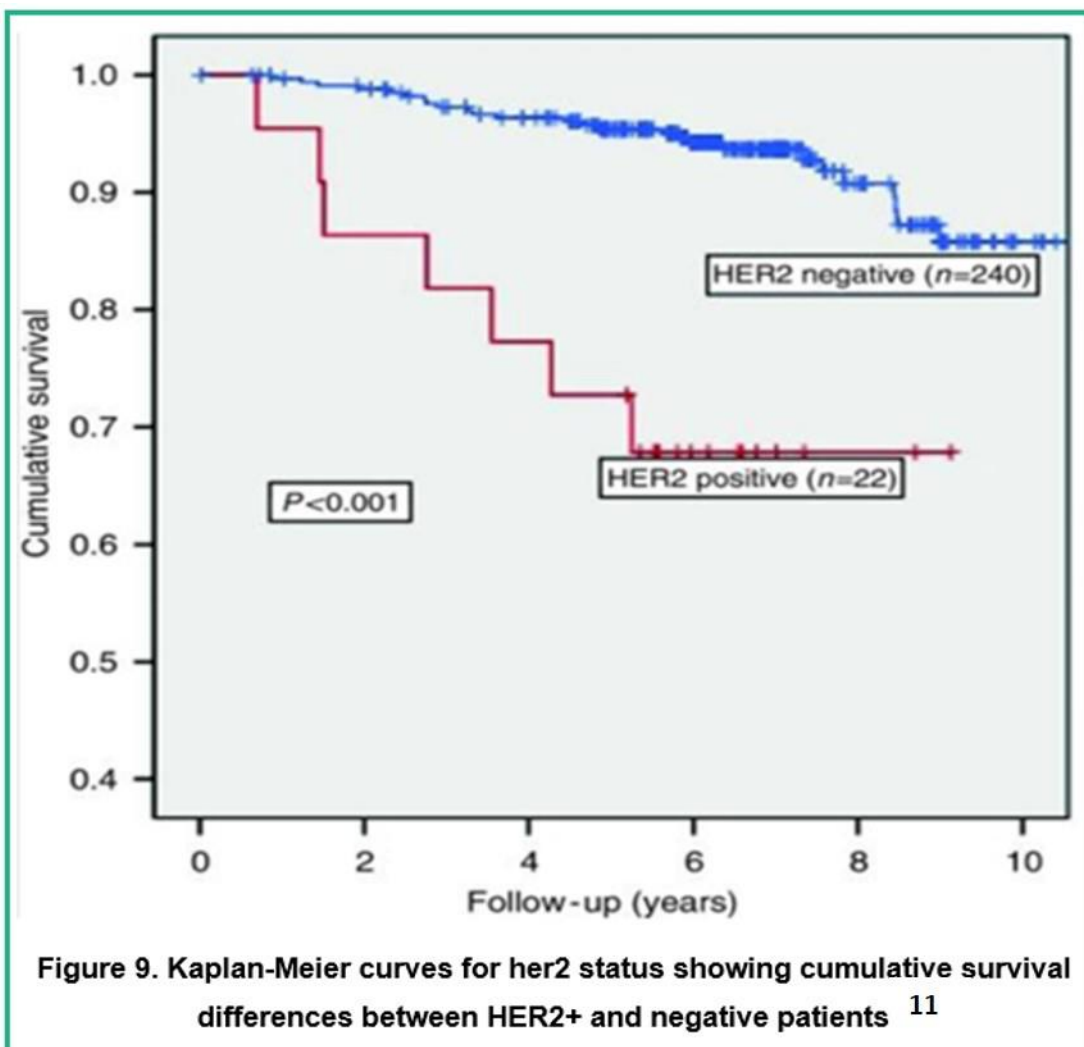
Table II. Immunohistochemistry correlation with Perou's genomic classes				
PEROU'S CLASS	ER	PR	HER2 PROTEIN	Ki67
LUMINAL A	+	+	-	< 14 %
LUMINAL B	+	-	- (+)	> 14 %
HER2 ENRICHED	-	-	+	n.d.
BASAL-LIKE	-	-	-	n.d.
ER: estradiol receptor PR: progesterone receptor n.d. Not defined				

6. HER2 enriched subtype

HER2 (Human Epidermal Growth Factor Receptor 2) is a transmembrane tyrosine kinase receptor encoded by ERBB2, a proto-oncogene located at the long arm of chromosome 17 (17q12).

Normally, this protein helps breast cells grow, divide, and repair themselves, but an abnormal amplification of gene copies does occur in 18-20% of breast cancers, leading to greater amounts of protein and uncontrolled growth¹⁰.

These tumors, so called 'HER2 positive' or 'enriched', are associated with a poor prognosis, an increased rate of metastasis, and a decreased overall survival (Figure 9).

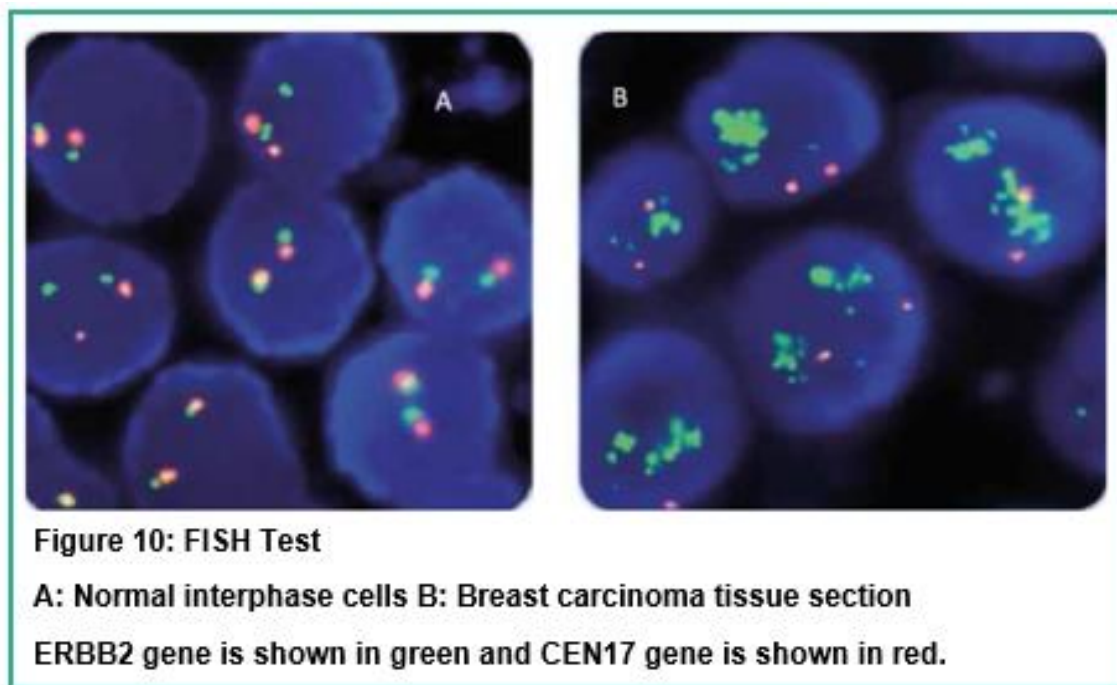


Standard testing of HER2 status is mandatory and it consist of an immunohistochemistry (IHC) test, by using antibodies that identify the HER2 protein in a conventional histologic sample of breast cancer tissue¹¹.

Findings are expressed in a semiquantitative score, as follows:

- **0 or 1+:** The tumor is considered HER2 **negative**.
- **2+ staining:** It is **equivocal**, until a deeper investigation by FISH or similar technique is done.
- **3+ staining:** It means a HER2 **positive** cancer.

FISH and relatives consist of marking simultaneously erbB2 gene and the centromeric region of the chromosome 17. Normal cells do show 2 alleles with 2 centromeric signals (ratio 1:1). A ratio ≥ 2.0 means abnormal amplification of oncogene copies (Figure 10).



Once identified a HER2 enriched tumor (either by IHC 3+ or FISH positive), it is predictable a response to cytotoxic chemotherapy (particularly anthracyclines and/or taxanes), but it is crucial to keep on mind it shall be specifically sensitive to trastuzumab and other anti-HER2 targeted therapies¹².

JUSTIFICATION

1. Standard therapy

A first major step was the combination of trastuzumab, a monoclonal antibody targeted to HER2 protein, with the cytotoxic agents known as taxanes.

Combined protocols with trastuzumab/paclitaxel in second line (patients previously treated with anthracyclines)¹³ or with trastuzumab/docetaxel in chemo-naïve patients¹⁴ have reduced the mortality associated with only taxane-based chemotherapy¹⁵.

Afterwards, the CLEOPATRA phase III trial, facing the combination trastuzumab/docetaxel to a triple combination adding pertuzumab, another monoclonal antiHER2 antibody, did improve the progression free survival by 6.1 months and the overall survival by 15.7 months, on average¹⁶.

Nevertheless, alopecia and neutropenic fever remain disturbing adverse events of docetaxel, so alternative schedules have been proposed with vinorelbine instead.

The HERNATA phase III trial showed that doublet trastuzumab/vinorelbine does offer the same efficacy than trastuzumab/docetaxel, with milder toxicity, particularly less febrile neutropenia episodes¹⁷.

As represented in Figure 11, a later development consisted of a phase II experience with the combination of dual HER2 blockade (trastuzumab plus pertuzumab) with vinorelbine. Although efficacy seems to be slightly inferior, alopecia and other typical docetaxel toxicities are lesser, so it could be a reasonable option when docetaxel is considered to be inconvenient¹⁸.

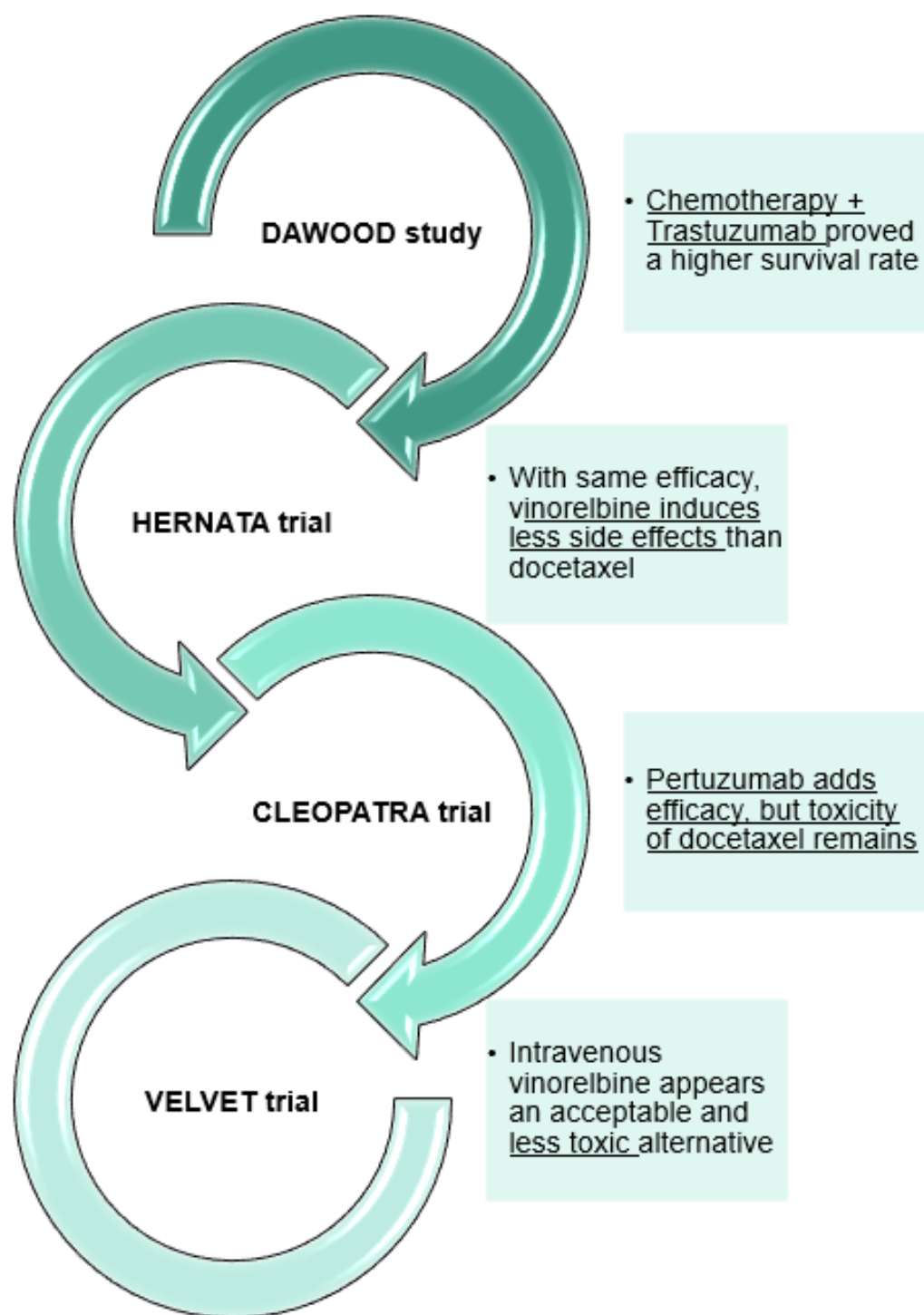


Figure 11. Timeline of HER2+ breast cancer treatments

2. Vinorelbine: Role of intravenous and oral formulations

Vinorelbine is a semisynthetic vinca alkaloid that binds to tubulin and prevents formation of the mitotic spindle, stopping the tumor cells growing in metaphase. It can be used in lung cancer and in breast cancer, either as monotherapy or in combination¹⁹.

The more relevant findings from its pharmacokinetic profile are as follows²⁰:

- A large volume of distribution (70–75.61 l/kg)
- The ability of bind reversible to blood platelets (> 70%), and sparsely to proteins (13%).
- The metabolism pathway of vinorelbine primarily involves liver CYP3A4 enzymes to form a majority of inactive metabolites, but 4'-O-deacetylvinorelbine, which retains activity.
- Elderly patients or those with liver disease do not need changes in vinorelbine doses.
- Bile is the main elimination route; less than 10% of vinorelbine is eliminated via urine.
- Pharmacokinetics of vinorelbine has been mainly studied in European patients. However, a recent Pharmacokinetics of vinorelbine has been mainly studied in European patients. However, a recent study showed that intravenous vinorelbine clearance was similar in Asian patients.

Distinctly from most cytotoxic agents, vinorelbine is available both in IV and oral formulations. Oral absorption of vinorelbine is fast, with a bioavailability around 40% of IV usage, with the same intra-personal variability. Drug exposure is not significantly influenced by meals.

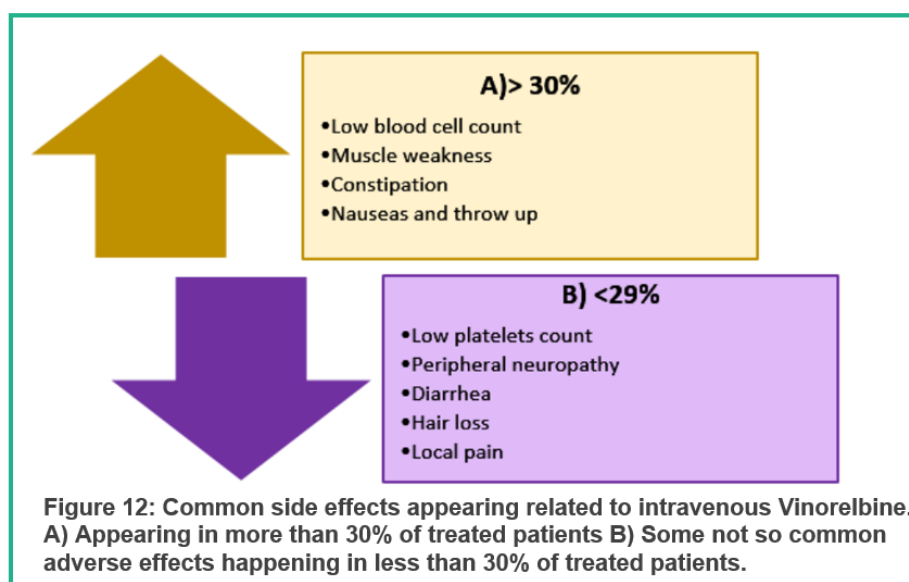
Table III reflects that vinorelbine clearance and bioavailability are nor influenced by ethnicity, regardless vinorelbine is delivered PO or IV.

Table III. Estimates from the population pharmacokinetic models for oral and intravenous vinorelbine¹⁹

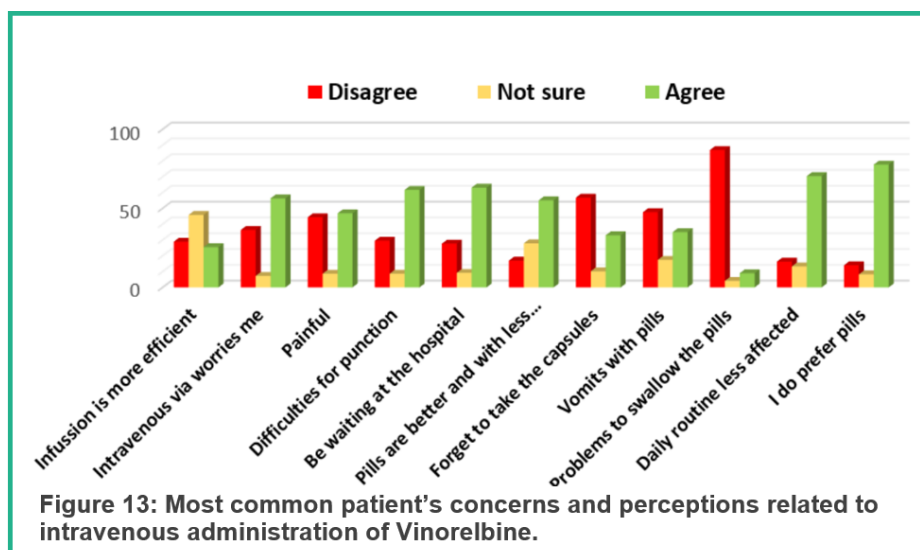
	Oral vinorelbine (n = 222)		Intravenous vinorelbine (n = 111)	
	Control model	Test model	Control model	Test model
Objective function value (OFV)	17,819.5	17,818.2	5,217.4	5,216.7
Change in OFV*	-	- 1.3 (n.s.)	-	- 0.7 (n.s.)
Inter-individual variability in Cl_{tot} (CV%)	33.9	33.7	28.1	28.0
Inter-individual variability in Bioavailability (CV%)	20.5	20.6	-	-
Estimated magnitude of ethnic effect (%) [95% CI]	-	5.3 [-19 to 29.6]	-	- 5.1 [-17.5 to 7]

* n.s. unless decrease is higher than 3.8 and 7, at significance levels of 5% and 0.5%, respectively

However, most clinical information comes from with IV Vinorelbine. In fact, its combination in HER2 positive breast cancer with trastuzumab and pertuzumab was studied with IV delivery¹⁸. Figure 12 shows common adverse events related to vinorelbine-based protocols. Moreover, vinorelbine acts as a vesicant when extravasated, potentially causing a severe tissue damage. Oral vinorelbine overcomes this problem, besides it is an easier, less invasive, more respectful with social life of patients, but equally effective alternative to IV vinorelbine.



In a preference study by Jensen et al, the majority of complaints were related to the IV administration, as shown in Figure 13²¹.



HYPOTHESIS and OBJECTIVES

1. Hypothesis

In HER2 metastatic breast cancer, oral vinorelbine should be an useful and safe partner for dual HER2 blockade with trastuzumab and pertuzumab, as a palliative first line chemotherapy.

In comparison to IV delivery, we expect oral vinorelbine shall offer similar activity, and better convenience to patients and health caregivers.

2. Objectives

1. To describe demographic and clinical data of a series of breast cancer patients treated with a dual HER2 blockade (trastuzumab and pertuzumab) in combination with oral vinorelbine.
2. To estimate the efficacy of the therapeutic program, in terms of time to treatment failure.
3. To tabulate its main toxic events.
4. To ascertain if PO vinorelbine in combination with antiHER2 antibodies does retain clinical usefulness previously reported with the conventional IV formulation.

PATIENTS and METHODS

1. Study Design

We carried out a retrospective survey on clinical records from women diagnosed of HER2 positive metastatic breast cancer and treated at Medical Oncology Department of 'Marques de Valdecilla' University Hospital (MVUH), between November 2019 and June 2020.

HER2 status was defined at Pathology Department of MVUH either by immunohistochemistry (IHC, 3+ score) or SISH gene amplification (ratio HER2/CEP17 > 2), at any time of tumor progression.

Registries were drawn from Pharmacy Department, from therapeutic flowcharts containing trastuzumab, pertuzumab, and oral vinorelbine, all of them applied simultaneously as first-line palliative chemotherapy.

Excluding criteria were as follows:

- Males.
- HER status neither fully checked, nor negative.
- Treatment in second or further palliative chemotherapy lines.

2. Therapy

First line systemic therapy consisted of:

- Trastuzumab, 600 mg SC on day 1.
- Pertuzumab, 420 mg IV on day 1.
- Vinorelbine, 60 mg/m² PO on days 1 and 8.

Vinorelbine capsules were administered once per day, swallowed with a glass of water, approximately 30 minutes after a light breakfast.

Antiemetic prophylaxis was not systematically applied, unless nausea or vomiting were noted in previous cycles. In such cases, premedication with 4 mg PO ondansetron was prescribed.

Cycles were repeated every 3 weeks, until progression or unacceptable toxicity.

Dose or intervals modifications were decided by the oncologist on charge, according to pragmatic clinical judgment. Radiographic evaluation methods (CT scans and others), and follow-up intervals as well, were in agreement with standard current policies.

3. Data Collection

Clinical records were managed on anonymized Hospital Registry Number. From each record, the following data were tabulated:

- Diagnosis date.
- Age at diagnosis.
- Personal and familial background.
- Pathologic report: location, cancer type and HER2 status.
- Primary treatment, including surgery, radiotherapy, and adjuvant systemic therapy, both chemo or endocrine therapy.
- Previous toxicity and persistent side effects as well as relevant comorbidities.
- Date of relapse
- Metastatic sites.
- Number of cycles.
- Toxicity.
- Reason to stop therapy.

4. Statistics

Data analysis was done through IBM® SPSS® Statistics Pack, version 26. Quantitative variables were expressed by medians and ranges. Qualitative ones were expressed by numbers and percentages appropriated for Chi² or Fisher tests.

Time to failure (TTF) was defined from the day 1 -when first monoclonal antibody infusion took place- until definitive interruption of therapy was decided, due to progressive disease or unacceptable toxicity, by clinical judgment. TTF was plotted according Kaplan-Meier method. Differences were studied by log Rank test.

RESULTS

Cohort

We retrieved 26 patients, two out of whom were excluded (one male, one medical record hidden by special confidentiality concerns).

Thus, our series is composed of 24 women, all Caucasian. Median age was 56 years (range 35-77). Performance status according ECOG scores, were distributed as follows: score 0, 11; score 1, 11; and score ≥ 2 , two patients else.

Biomarkers

HER2 overexpression was assessed by IHC in all cases: 22 were 3+ (91.7 %), and 2 were 2+ (8.3 %), then confirmed by a SISH technique.

Concurrent expression of ER and PR expression was noted in 17 patients (70.8 %); the remaining 7 (29.1 %) did not show endocrine receptors expression.

Tumor burden

At diagnosis, sixteen patients (75 %) were in stages I-III, while 8 (25 %) did start with metastases already.

At start of medication under study, all patients had metastatic spread. Visceral disease was present in 19 (79.2 %), and 5 patients (21.8 %) were treated with soft tissues involvement alone.

Previous therapies

Seventeen women (70.8 %) had not been treated previously with systemic antineoplastic therapy.

A previous adjuvant therapy with chemotherapy (anthracyclines and/or taxanes) was registered in 7 patients; 3 out of them did receive endocrine adjuvant therapy also.

In addition, 4 patients did receive adjuvant trastuzumab. The median interval free from trastuzumab was 61 months.

Efficacy

A total number of 340 cycles was administered, 15 per patient on average.

Time to failure treatment (TTF) is plotted in Figure 14. Median TTF was 8 months.

Main reason to interrupt therapy was disease progression (n = 23). In one patient, therapy was changed due to cardiotoxicity after 14 months.

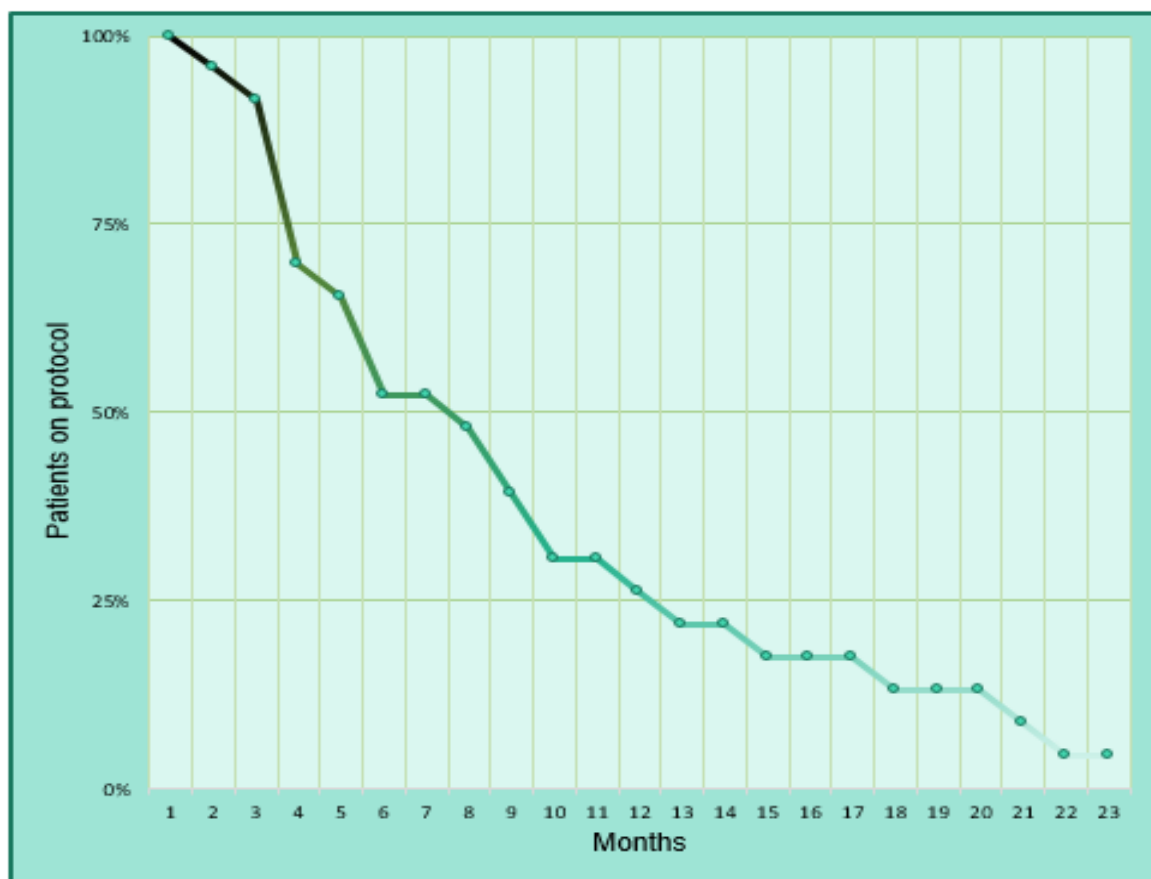


Figure 14. Patients on therapeutic protocol along the time (Kaplan Meier estimate)

Toxicity

Significant hematological toxicity (febrile neutropenia) was seen in 1 patient (4,16%).

Non-hematological toxicity does appear in Table IV:

TABLE IV. Observed non-hematological toxicity (grades 1-2)		
Adverse event	N	%
Alopecia	6	25
Stomatitis	5	20.8
Asthenia	4	16.6
Emesis	4	16.6
Diarrhea	2	8.3
Peripheral neuropathy	2	8.3
Onycholysis	2	8.3
Hand-foot syndrome	1	4.1
Rash	1	4.1
Epistaxis	1	4.1
Abdominal pain	1	4.1
Conjunctivitis	1	4.1

DISCUSSION

Efficacy

We have obtained a TTF of only 8 months, while progression free survival (PFS) in VELVET trial reached 14,3 months¹⁸. In fact, TTF and PFS are not strictly equivalent, the latter more linked to changes in imaging techniques, the former more influenced by toxicity, because of the investigational dimension of clinical trial, and the palliative nature of our approach.

However, there are some clinical-biological differences between VELVET-included patients and the ours. Age, ethnicity, and stage disease at diagnosis were similar. By contrast (Table V), there was only a factor in favor of us (the scarcity of previous therapies), whereas visceral involvement and ECOG suboptimal status were in the

Table V. Patients under IV or PO vinorelbine, plus trastuzumab/pertuzumab		
N (%)	VELVET trial¹⁸	Our series
Prior systemic therapy	N = 106	N = 24
Taxane	40 (37.7)	2 (8.3)
Anthracycline	41 (38.7)	5 (20.8)
Trastuzumab	44 (41.5)	4 (16.6)
Performance status		
0	74 (69.8)	11 (45.8)
1	32 (30.2)	11 (45.8)
2 or worse	-	2 (8.3)
Organ involvement		
Visceral	78 (73.6)	19 (79.1)
Non-visceral	28 (26.4)	5 (20.8)
Hormone receptor status		
ER and/or PR positive	70 (66)	17 (70.8)
ER and/or PR negative	36 (34)	7 (29.6)

opposite way. Moreover, we had more endocrine-dependent tumors, whose lower responsiveness to HER2 blockade is well known²².

Other difference was route of trastuzumab administration, intravenous in VELVET, subcutaneous in our cohort. Nevertheless, it is improbable that determines a reduced efficacy, because the equivalence of both formulations has been well established²³. Regarding pertuzumab, our protocol is composed by a fixed dose of 420 mg, which is in agreement with former studies showing a dose ≥ 5 mg/kg every 3 weeks is enough²⁴, although most current programs contain a loading dose of 840 mg in first cycle, and we cannot rule out a deleterious effect from not doing that.

Concerning vinorelbine itself, individuals reluctant to oral chemotherapy do think that IV infusions are always under caregiver supervision, whereas intake of pills belongs to patient's responsibility. A reduced individual compliance remains speculative, albeit such compliance has been estimated 'optimal' in 76% of other cohorts under oral chemotherapy²⁵.

Interestingly, we choose a 60 mg/m² unitary dose of oral vinorelbine according pharmacokinetic data showing its equivalence with 25 mg/m² intravenously²⁰, and we maintained the same dose all along the study, albeit some oncologists do escalate the IV dose to 30 mg/m², even to 35 mg/m², if toxicity does not appear²⁵. As a consequence, we think a dose amendment is warranted, in order to escalate oral vinorelbine to 80 mg/m² when appropriate.

Toxicity

According previous evidence, vinorelbine yields worse PFS figures than docetaxel (in part due to differences in populations under study), but causing less febrile neutropenia and alopecia. Likewise, our 8 months TTF seem far from 20 months PFS in CLEOPATRA trial¹⁶. To be remarked, 68%, 31% and 1% of patients in that trial were classified respectively as ECOG 0, 1 or 2. By contrast, corresponding figures in our study were 45%, 45% and 8%. Also moving to caution in comparing efficacy, in CLEOPATRA docetaxel was prescribed to 47% of tumors expressing endocrine receptors, while we treated a 70% of hormone-dependent tumors.

Anyway, Table VI shows main adverse events observed in CLEOPATRA trial and our series:

Table VI. Adverse events of pertuzumab and trastuzumab with different cytotoxic partners

Effect	CLEOPATRA¹⁶ (docetaxel, % of 404 patients)	Our survey (PO vinorelbine, % of 24 patients)
Diarrhea	68	8.3
Alopecia	60	25
Neutropenia	53	4.1
Febrile neutropenia	14	4.1
Mucositis	27	16.6
Emesis	25	16.6

They used docetaxel at 100 mg/m², which is near maximum tolerated dose (MTD), to treat patients of a better intrinsic prognosis. On the contrary, in a cohort in worse basal condition, we used oral vinorelbine at an IV equivalent dose of 25 mg/m², far below of its MTD.

Using more than 6 cycles of docetaxel looks unfeasible and inconvenient²⁷, but oral vinorelbine does permit longer deliveries. Subgroup analyses in CLEOPATRA suggested adding pertuzumab is less brilliant in older patients with non-visceral metastases¹⁶, and perhaps that populations were more prone to be treated with oral vinorelbine, at more flexible number of cycles and/or doses.

Limitations and prospects

Sample size (n=24) is the main weakness of our study. Previous experiences with IV vinorelbine reported more than 200 patients, thus a selection bias is unavoidable. By chance, a simultaneous expression of HER2 and ER was much frequent than generally reported²⁸.

In order to improve TTF, a concern with dose of oral vinorelbine has emerged. A protocol amendment shall be made, in order to maintain 60 mg/m² in cycle 1, but increasing to 80 mg/m² in subsequent ones, if no toxicity was recorded.

It lacks to check a translation of TTF into overall survival, because further lines can be relevant in the long run²⁹. Trastuzumab-emtansine has emerged as a reference 2nd line therapy³⁰, and it would be interesting to check its impact on our patients after progression, because data from trastuzumab-emtansine after pertuzumab are scant, yet³¹. Work shall be in progress, both with dose adjustments and survival analyses.

CONCLUSIONS

1. We have reviewed a cohort of 24 HER2 positive breast cancer patients. Co-expression of hormone receptors, a known factor of resistance, reached an unusual 70% frequency.
2. Median time to treatment failure was 8 months, in fact lower than previously reported with IV cytotoxics. These remain standard for severely ill patients.
3. Febrile neutropenia and non-hematological toxicity were much more convenient than currently observed with docetaxel.
4. Our protocol can be recommended for some patients with milder clinical pictures and for those rejecting venous access. However, 2 amendments are warranted: a loading dose of pertuzumab at first cycle, and above all an escalation of PO vinorelbine in second and further cycles.

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