SUMMITS


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II – Her 2 positive Advanced Breast Cancer (Participants, pre Congress questions, Answers, Conclusions, Bibliography)
General Objectives

The therapeutical decision in the management of advanced cancer is based on the identification of predictive and prognostic factors which include the evaluation of involved organs, the full extent of the illness, its biological characteristics, the performance status, previous treatments and their results. This variability requires the doctor to conduct an ongoing assessment among the clinical evidence available, the particular situation of each patient and the technical resources available at each location where the doctor offers his-her services.

To have predetermined recommendation guides as a platform for the treatment of this pathology will be helpful in the decision making process.

Specific Objectives

1. Analyze variables which affect the treatment selection in advanced breast cancer.

2. Discuss the staging procedures which influence the proposed therapeutical treatment.

3. Analyze the biological variables of advanced breast cancer that impact the clinical treatment of the patient.

4. Discuss palliative aspects in the treatment of advanced breast cancer.

5. Analyze procedures and methodologies required in the biological classification.

6. Discuss the response criteria and opportunity of modification of established therapies in the patient.
7. Analyze the possible therapies in specific situations such as brain metastasis, meningitis, medullar involvement, plural effusion and pericarditis.

**Methodology**

The consensus panel will have three stages:

1. **Discussion by electronic mail of the theoretical and practical aspects of advanced breast cancer (May, June, July).**

   During this stage the team coordinators will create sets of questions to be sent by electronic mail to all the panelists along with the appropriate bibliography to respond them. This will allow building the theoretical frame work of each team using the most relevant bibliography.

   Finally the coordinators will pose, via electronic mail, practical, concrete or controversial situations to the participants so they can share their experiences and criteria in the handling of such situations based on the best available evidence and adapted to their surroundings or work place.

2. **Team work during the congress**

   The program will provide two slots of one hour each in two consecutive days to the participants so they can get together to discuss the issues related to their topic in order to draw conclusions and come up with categorized recommendations.

   The coordinators and the secretaries will have to report the discussion’s conclusions. The recommendations must adapt the bibliographical evidence to the practice in the field with the goal of elaborating a platform with minimum necessary for the treatment of advanced breast cancer.

3. **Reading and publishing.**

   The conclusions presented in the categorized recommendations will be read at a conference and published under the guidance of Glaxo, the “Asociación Argentina de Mastología” and the “Sociedad de Patología Mamaria.”
The presence of an external observer will allow the recommendations reached by the consensus to respond to a minimum platform validated by the evidence.

**Workshop Discussion: Breast Cancer Stage Iv Experts’ Meeting**

**TOPIC: ADVANCED BREAST CANCER HER2 POSITIVE**

**PARTICIPANTS:**

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QUESTIONS

(Questions elaborated in the meeting of Dr. Luis Martinez and Dr. Jose Zarba)

1- Which method/methods are used to evaluate HER2 in order to set up a therapeutical approach?

2- Is it appropriate to conduct a biopsy in a metastasis in order to re-evaluate the molecular profile of the illness’s progression? Discuss special situations.

3- Which do you consider the most optimal line of treatment for a new patient who presents a metastasis HER2 positive breast cancer?

4- In regards to the optimal treatment duration, in the case of limiting toxicity and persistence to response which is your decision if the cause is:
   a. Chemotherapy Agent
   b. Trastuzumab

5- Which chemotherapy would you associate to an anti-HER2 therapy for patients who received as additional treatment:
   a. Anthracyclines
   b. Anthracyclines and Taxanes

6- Which line of treatment would you choose for patients with advanced HER2 positive cancer, positive Hormone Receptor, hormone dependent clinical pattern having received TAM in adjuvant?

7- What treatment would you choose in an advanced HER2 positive cancer patient having received Trastuzumab in adjuvant?
   a- Was there any progress before the year end of the treatment with Trastuzumab?
   b- Was there any relapsed after the year end treatment with Trastuzumab?
8- What anti HER therapy do you use in second line advanced illnesses in progression with Trastuzumab?

9- Which is the treatment of brain metastasis in HER2 positive patients?

10 Strategy to follow in the presence of single metastatic resectable hepatic or pulmonary disease.

11 What line of neo-adjuvant treatment would you use in a localized advanced (EIII) illness with HER2 positive?

12 Do you consider appropriate to combine directed target agents anti-HER in an advanced illness?

13 Is there any molecular marker that can help you decide in a line of treatment for HER2 positive patients?

**ANSWERS**

1-

Dr. Cáceres: IHC. In the case of error or doubt FISH

Dr. Ciocca: Agrees with Dr. Cáceres

Dr. Frahm: In doubtful cases, FISH, CISH can be performed.

Dr. Lewi: Agrees with Dr. Cáceres.

Dr. Lacava: Immunohistochemistry in all cases, FISH to confirm doubtful cases (++), for central confirmation and in cases with few viable cells.

Dr. Lerzo: First, reconfirm positivity with Immunohistochemistry and my referred pathologist; If is 2 positive request FISH/CISH.

2-
Dr. Cáceres: To discuss special situations. It is ideal to do a re-biopsy whenever possible.

Dr. Ciocca: I also believe that based on elapsed time and the location of the biopsy; it is possible to do conduct an evaluation in a new biopsy.

Dr. Lewi: Different scenarios 1) if the primary tumor is HER2 positive and was duly diagnosed, 10% of the times, the metastasis loses HER2 which could be the result of emergent resilient-resistant clones. In these cases if it is possible I do a biopsy as well as plan to modify the treatment. The following factors must also be taken in consideration: a) Rh negative, in this case a biopsy should be done since there is 10-15% Rh gain and a change in treatment, b) Time to the metastasis less than 2 years vs. more than 2 years, c) location of the metastasis, non-visceral or brain patterns have a higher probability of being HER2 negative, so they should be biopsied.

In conclusion: for patients with HER2 negative, What I propose is to do a biopsy on the metastasis of HER2 positive, Rh negative patients tend to have less metastasis, late relapses and the metastasis’ sites are no visceral/cerebral. In case of any doubts the original sample should be re-biopsied. A special situation is a HER2 positive patient who responds fast to the treatment with Trastuzumab. This patient should be re-biopsied using FISH in order to rule out p95 which would make TKI treatment possible. Therefore, discuss all special situations and when needed re-biopsy the patients.

Dr. Lacava: Discussing special situations. Different scenarios: 1) If the primary tumor is HER2 negative and it was appropriately detected, it is highly unlikely that the metastasis gains HER2, thus no biopsy is required, 2) if the primary tumor is HER2 positive and was properly diagnosed, 10 to 20% of the times the metastasis loses HER2 which could be the result of a phylogenetic evolution or the rising of resistant clones in a tumor heterogeneity context. In these cases, I conduct a biopsy if possible and plan to replace the treatment. Four additional factors with little evidence should also be taken in consideration: a) Rh negative in this context a biopsy should be conducted since there is 10-15% probability of an Rh increase and change the treatment; b) Time of the metastasis: less than 2 years vs. more than 2 years; c) metastasis load, oligometastatic patients
must be biopsied, probability of resistant clone, multimetastatic patients, false probability due to tumor heterogeneity; d) metastasis site, non-visceral or cerebral patterns present higher probability of being HER2 negative and should be biopsied.

In conclusion, since there are no differential approved treatments for HER2 negative patients, I propose to biopsy the metastasis of HER2 positive patients who are Rh negative, have few metastasis, show a late relapse and have non-visceral/cerebral metastatic sites. The goal of this re-biopsy is to evaluate the suspension of antiHER2 treatment in order to reassess the findings and reorganize resources.

In case of any doubts on the original test results, perform a second biopsy. Patients with HER2 positive, appropriately diagnosed, which evolves rapidly to the treatment with Trastuzumab could be re-biopsied with FISH in order to discard p95 which in turn would allow TKI treatment.

Dr. Lerzo: Discussing special situations. Although there is no level of evidence 1 when the biopsy is accessible (above all in triple negative)

3-

Dr. Cáceres: If the patient is able to tolerate chemotherapy treatment with Taxanes in combination with Trastuzumab. If the patient has no adverse indications to systemic chemotherapy or presents a low risk illness, the choice would be an aromatase inhibitor with Lapatinib or Trastuzumab.

Dr. Lewi: Trastuzumab along with Taxane chemotherapy in all cases. Patients with luminal enriched with HER2 (double positive), and hormone sensitive patterns, I consider Lapatinib with Letrozole. Pertuzumab could be used in the future. Therefore if the patient is able to withstand chemotherapy, use a combination of Taxanes and Trastuzumab. If the patient has any adverse reactions to systemic chemotherapy or presents a low risk illness, the choice should be aromatase inhibitor with Lapatinib or Trastuzumab.

Dr. Lacava: Trastuzumab along with Taxane chemotherapy in all cases. Patients with luminal enriched with HER2 (double positive), and hormone sensitive patterns and without visceral load or crisis, I consider using
Lapatinib with Letrozole. In the future a combination of Pertuzumab or TDM1 could be weighted in. I would also consider using Anthracycline but further studies are required. I would not advise it for the moment.

Dr. Lerzo: Without previous Taxanes: Taxanes and antiHER2 (Trastuzumab). In cases of adjuvant progression latent to Trastuzumab and Taxanes, lapatinib and Capecitabine should be considered. Remember that Pertuzumab has been approved by the FDA on first line with Trastuzumab and Taxanes. If during adjuvant treatment the patient received Taxanes, Vinorelbine and Trastuzumab should be considered.

4-a

Dr. Cáceres: Chemotherapeutic Agent: suspension and continue with Trastuzumab. In the case of a positive hormonal receptor, continue with HT associated to Trastuzumab.

Dr. Lewi: Chemotherapeutic Agent: suspension and continue with Trastuzumab. In the case of a positive hormonal receptor, continue with Trastuzumab plus chemotherapy.

Dr. Lacava: Chemotherapeutic agent: continue with Trastuzumab with or without second line QMT depending on tumor load or crisis. In summary only in selected patients with low load, asymptomatic, non-visceral patterns should be considered for molecular monotherapy. In all other instances I propose Trastuzumab with second-line QMT without adverse reactions.

Dr. Lerzo: Chemotherapeutic agent: use Trastuzumab alone (studies of Trastuzumab as a single drug in treatment show response in CMM)

4-b

Dr. Cáceres: Trastuzumab: It is highly infrequent the need to suspend Trastuzumab, literary reports indicates that the only instance for suspension is heart failure which in many of the cases is reversible and asymptomatic. However, in my private practice experience, I had never had to suspend Trastuzumab because of limited toxicity.

Dr. Lewi: Trastuzumab: Remember that there is usefulness in First-line treatment with Paclitaxel plus Lapatinib (104535).
Dr. Lacava: Trastuzumab, I would switch to another anti-HER therapy due to the oncogenic addiction of HER2 tumors. I would consider Lapatinib and weight in other options when available.

Dr. Lerzo: Trastuzumab: If the toxicities derived from the falling of FCY, suspend treatment until FCY regains a normal value and then continue (Waiting until the patient’s disease becomes more severe could be a possibility if the patient is in remission)

5- a

Dr. Cáceres: (Anthracyclines) Taxanes

Dr. Lewi: Anthracyclines: Taxanes if it is a negative hormone receptor consider TCH.

Dr. Lacava: Anthracyclines. Taxanes in cases of voluminous, crisis or Rh negative TCH illness.

Dr. Lerzo: Anthracyclines: Taxanes (plus carboplatin?)

5-b

Dr. Cáceres: (Anthracyclines and Taxanes) If more than a year has gone by, I would reinduce with Taxanes, generally the one I had not use in adjuvant. Otherwise capecitabine

Dr. Lewi: Anthracyclines and Taxanes: For first-line treatment it is possible to use Capecitabine and Lapatinib while still using Vinorelbine, gemcitabine and Ixabepile

Dr. Lacava: Anthracyclines and Taxanes. Capecitabine and alternative single-therapies such as Vinorelbine and gemcitabine. Pending results of other antimicrotubuunicos (Ixa, Nab, Eribuline)

Dr. Lerzo: Anthracyclines and Taxanes: Use a Taxane not used before such as capecitabine or Vinorelbine.

6-

Dr. Cáceres: Although the illness is presented as hormone-responsive, the patients HER2 positive show certain hormone refractoriness thus the studies of ANTIHER2 agent plus aromatase inhibitor show a PFS shorter than Taxane with Trastuzumab. I would use the later treatment unless the patient was not a Taxane candidate or that the illness had a minimal load.
Dr. Lewi: Do not forget the clinical study 30008 (Lapatinib and Letrozole) and its superiority in regards to Tandem (Trastuzumab and Anastrazol)

Dr. Lacava: First-line treatment Letozol/Lapatinib.

Dr. Lerzo: Trastuzumab and Anastrazol, Lapatinib and letrozole. Consider chemotherapy in high risk, visceral involvement, etc.

7-

Dr. Cáceres: If the patient relapses use intra-Trastuzumab or before the year is complete I would use Trastuzumab and Taxanes. If the patient relapses before the year is over or in intra-treatment, I would use Lapatinib and Capecitabine.

Dr. Lewi:

a) It progressed before the year end in adjuvant with Trastuzumab (Lapatinib and Capecitabine)

b) It relapsed before the year end in adjuvant with Trastuzumab

Dr. Lacava:

a) It progressed before the end of the year of adjuvant with Trastuzumab. I would not re-induce using Trastuzumab alone. Lapatinib is the first selection.

b) It relapsed after the end of the year of adjuvant with Trastuzumab, Lapatinib or re-inducing Trastuzumab. Evaluation of the combination of both as well as other emerging antiHER2 should be observed in the future.

Dr Lerzo: Depends on the elapsed time of progression: Consider that the FDA approved Pertuzumab. Although TDM1 is better than Cape and laptinib, it has not been approved yet.

8-

Dr. Cáceres: Depends on the progression free-survival (PFS). If this is prolonged, I would try second-line with trastuzumab rotating the chemotherapy. In any case the re-challenge with trastuzumab o the change to lapatinib and Capecitabine are valid options in this situation.

Dr. Lewi: Lapatinib – Capecitabine
Dr. Lacava: Mainly Lapatinib, especially with fast progressions. In patients with a long response to Trastuzumab, I usually change QMT and continue (under close follow up) with Trastuzumab. I do not advise combinations at the present time.

Dr. Lerzo: If the patient did not receive Capecitabine earlier: capecitabine and lapatinib. Consider participation in clinical studies and take into consideration Bolero 3’s results soon to be published.

Dr. Cáceres: If it is the only progression site, radiotherapy/radiosurgery and lapatinib-capecitabine.

If the patient is in treatment due to other lesions with Trastuzumab and there is no progression with similar therapies, I would do brain radiotherapy/radiosurgery.

Dr. Lewi: There is better data with Lapatinib independently of the surgical use and other forms of radiotherapy.

Dr. Lacava: Aggressive surgery, radiotherapy or radiosurgery if the extracerebral illness is under control or could be. Continue with Lapatinib if the patient had been receiving Trastuzumab. If the extracerebral illness is significative and not controlled, continue with Lapatinib and radiotherapy.

The cause of death in patients with HER2 positive and the cerebral-brain relapse is mainly due to the impact on CNS.

Dr. Lerzo: Outside the local management (RT, surgery) I do not believe it should be any different to any other breast cancer treatment.

Dr. Cáceres: Each case should be discussed-reviewed individually since there are no studies in HER2 positive illness. It should also be taken in consideration the patient’s DFS and whether or not she/he received Trastuzumab in adjuvant.

Dr. Lewi: Each case should be discussed-reviewed individually since there are no studies in HER2 positive illness. It should also be taken in consideration the patient’s DFS and whether or not she/he received Trastuzumab in adjuvant.
Dr. Lacava: mandatory biopsy, adjuvant with antiHER2 and QMT. Local treatment, if possible for R0. If there is an uncertain evolution of the illness do not create false expectations for the patient. There is a need for clinical studies and

Dr. Lerzo: There should be a systemic therapy and later on surgical intervention could be considered as part of the treatment.

Dr. Cáceres: In patients who have progressed to both agents separately, based on the evidence known, I would use a double blocking without chemotherapy.

Dr. Lewi: Adriamycin and cyclophosphamide for four cycles and then 12 weeks of Taxane and trastuzumab.

Dr. Lacava: AC followed by taxanes both combined with Trastuzumab.

Dr. Lerzo: The FDA approved Peruzumab and Trastuzumab. Trastuzumab and Lapatinib in multi-treatments which is in the NCCN guidelines.

Dr. Lewi: Yes. It should be considered in patients who have progressed to both agents separately, based on the evidence known, I would use a double blocking without chemotherapy,

Dr. Lacava: Yes. The affectedness to the oncogenic hub by dual paths or unexpected alterations is fitted way for its inactivation (Wainstein)

Dr. Lewi: Data from study 104535 showed PTEN lost and pi3k mutation with equal efficiency to the difference happening with trastuzumab (resistance mechanism to Trastuzumab)

Dr. Lacava: Actually no. It could be useful Topo II, Beta 3 tubuline, p95.

POST-WORKSHOP CONCLUSIONS
1. Which method/methods do you use for the assessment of HER2 and decide on a therapy course?

To determine the protein overexposure IHC must be conducted. It is recommended to participate in a multidisciplinary team with a trained pathologist. In the case of erroneous/doubtful results (score 2), fluorescent in situ hybridization test (FISH/CISH) will be used. In those cases with little cellular sample it is recommended to start with FISH/CISH. For a positive sample it must be the result of IHQ+++ with a complete intensity of positivity higher than 10%.

2. Do you consider appropriate to biopsy the metastasis to get a new assessment of the molecular progression profile of the illness?

Taking into consideration the tumor variability and heterogeneity, whenever possible it is recommended to re-biopsy. It is recommended to compare and assess the primary tumor’s biopsy results with the new one.

3. Which do you consider is the optimal first-line treatment for a patient who starts with a HER2 positive metastasis?

If the patient is candidate to XQT: Trastuzumub plus Taxane. In patients that can be treated with hormone therapy: anti-her2 plus aromatase inhibitors. Recommended strategy: Lapatinib/letrozole or Trastuzumab/Astraazol.

4. Regarding the most appropriate length of treatment in limiting toxicity and response persistence what is your decision if the cause is:

When toxicity is due to XQT: consider continuing with Trastuzumub single drug until progression or toxicity. B- if the cases requires to change cytotoxic and Trastuzumab.

In the case of hormone sensitive cases: ht and trastuzumab. In the case of toxicity to trastuzumub (fay decrease) suspend anti-her2 until fey levels are recovered. Reinitiate according to recommendations.

5. What chemotherapy would you associate to anti-HER2 patients who received therapy in adjuvant?

If the patient received Anthracyclines: Taxane.
If the patient received anthracyclines/taxanes: capacitabine, vinorelbine, and taxane may be used if the relapse takes places 12 months after the end of adjuvant therapy.

6. What treatment would you choose for patients with advanced HER2 positive, Rh negative and low risk hormone dependency clinical pattern who have received Tamoxifen in adjuvant?

Premenopausal: XQT and anti-HER2.

Postmenopausal: consider IA and anti-HER2.

7. What treatment would you choose for a patient with advanced HER2 positive, who has received Trastuzumab in adjuvant?

Consider lapatinib and capecitabine if there is progression before the adjuvant with Trastuzumab year end. In case of relapse after the end of the year in adjuvant, Trastuzumab and XQT could be indicated again.

8. What anti-HER2 therapy do you use on second-line of an advanced illness progressing with Trastuzumab?

It is recommended to continue with anti-her therapy if the patient has not received capecitabine previously, consider capecitabine and lapatinib.

If the progression free survival was prolonged on the first-line attempt on a second-line with Trastuzumab rotating QMT.

9. What is the treatment of brain metastasis in advanced HER2 positive patients?

It is imperative to prioritize local treatment. Lapatinib-capecitabine is the recommended therapy when there is local post TTO cerebral illness or systemic progression of the illness. if the patient is under treatment with extra-cerebral lesions with Tratuzumab and there is no progression, an option is to continue with a likewise therapy.

10. Treatment plan to follow in the presence of a single resectable liver or lung metastasis.

There is no scientific support that attests systemic treatment with surgery of a metastasis lesion. In selected cases consider local therapy and must continue or start anti-HER treatment.
11. Do you consider appropriate to combine target agents directed to anti-HER in an advanced illness?

Although there are published studies that show favorable data on first-line treatment with Trastuzumab and Pertuzumab or Lapatinib and Trastuzumab on patients progressed to both therapies, Argentina still has not considered a standardized treatment for this type of illness.

12. Is there a molecular marker that can help you decide the type of treatment to be used in HER2 positive patients?

Although there are useful potential resolutions, prospective results are awaited for. Until now, there is no marker that can guide us in the treatment selection.

**Workshop’s Discussion: Breast Cancer Stage IV Experts’ Meeting**

**TOPIC:** TRIPPLE NEGATIVE ADVANCED BREAST CANCER

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Definition

These are tumors that neither present RT, RP nor HER2. They make up a heterogeneous population with a more aggressive biological constitution. They are more frequent in young women and are dominant in patients with BRCA1 germinal mutation. They have a global occurrence of about 15% (10 to 20%) in our environment. This information is similar to what has been reported in many studies which indicates that the epidemiology data included an important percentage of Hispanic population.

Dr. Arroyo’s Comments:

All publications show that TNBC (Triple Negative Breast Cancer) is the sum or mixture of many factors that probably present a different biology. Therefore they need different therapeutical targets and have different responses to treatments.

Dr. Kowalyszyn’s Comments:

We do not know the impact in our environment. We should be around 10 to 20%.

Is it a different disease?

It will be addressed during the workshops.

Are they all basal-Like?
The molecular make up of TN is superimpose with a Basal-Like (BL) (70-90% concordance rate) But not all TN are BL since there is a small percentage that show hormone receptors and HER2. The definition of TN depends on the pathological anatomy while the term Basal-Like derives from genetic expression studies.

**IHC Panel. Can we identify subgroups? Future implications**

The cutoff point for RH expression: <1% should be considered negative (The ASCO’s guidelines and College of American Pathologists recommend that the tests which determine RT and RP should be considered positive when the sample shows at least 1% of tumor cells expressed by the receptor.) The expression of certain markers for IHC could identify the true BL: triple negativity (ER negative, RP negative and HER2 negative) basal CKs (CK5/6, CK14 and CK17), EGFR and C-kit (CD117). Some have created the term “core basal phenotype” to define those tumors which not only show triple negativity but also present CK5 and EGFR; it has been proposed that these tumors would have a worse prognosis than tumors which are negative for all five markers. Genetic expression studies among TN have identified sub-groups that apparently would have differences in prognosis: Claudin-low, high gene expression to immune response, gene expression of DNA repairing, etc. But this is premature and not applicable to today’s medical practice. In 2011, Saint Gallen concluded that there was no consensus to use cytokeratin 5/6 or EGFR tests in order to take decisions in the field (not reproducible enough, absence of well-defined cutoffs, heterogeneity in the staining patterns.)

Keep in mind all the medullar subtypes and cystic adenoma which have a favorable prognosis despite of the fact that they have TN phenotype.

For now the only sub-groups well differentiated (with implications in the filed/medical practice) would be medullar carcinomas, cystic adenoma and mutated BRCA1.

Dr. Kowalsyn´s Comments:

RT-RP-HER2-CK5/6/14/17-EGFR-CD117

Relation with BRCA mutations: There are many studies which have assessed the BRCA1 mutations sample in TN. The BRCA mutations
incidence in TN varies between 10% and 20%. The somatic and germinal mutations frequency in a selected population ranges from 11% to 39%. Other mechanisms which result in down-regulation of BRCA1 and 2 (apigenin alterations and overexposure of BRCA 1 inhibitors) are also associated to TN and probably contribute to the genomic instability and aneuploidy which are characteristics of this sub-group. The 2012 NCCN guidelines recommend testing for BRCA1 mutation to patients with TN 60 years old or younger. In contrast with BRCA1, there is no BRCA2 mutation association with TN.

Dr. Arroyo’s comments:

There appears to be a special sub-group non-functioning NTBC BRCA (epigenetically mutated or annulated – that last one is not mutated but with alterations such as methylation. For example: they stop the normal expression of proteins). On the other hand 16% to 42% of the NTBC have BRCA mutations with another (smaller) percentage which does not have such mutation but show failure in BRCA protein expression. Should we study the alterations of the BRCA protein in all the patients with NTBC? Based on the BRCA test cost, we should take in consideration only the cost of one chemotherapy cycle with the agents we usually use in NTBC. From my point of view, this is widely justified.

Dr. Lina Nunez’s comments:

I am attaching two recent studies which have assessed the mutations prevalence in the series of genes of triple negative breast cancer, not selected because of family history.

These findings are the base for the inclusion of triple negative breast cancer as a sample to test for the 2012 NCCN recommendations (also attached.) The patients’ cutoff age in which triple negative breast cancer should be studied has not been defined yet. I believe that in our situation the difficulties that we still have in accessing to the studies of the at-risk population are a lot more evident and it is an important point to consider. Nevertheless, it cannot be ignored the clear evidence of carrying a gene mutation for any triple negative breast cancer in patients younger than 50 years old, reason for which I think that we should exchange and discuss ideas about the best way of handling this topic in our reality.

Dr. Kowalysin’s comments:
Yes but the mutated BRCA are NTBC not vice versa. BRCA ness definition....

**Treatment**

Triple Negative (TN) metastatic breast cancer is an aggressive disease which is associated to a high rate of spreading, visceral and CNS metastasis with poor results despite treatment. The media for survival rate (SV) is 12 months (a lot less that the survival rate of other CM sub-types)

Chemotherapy continues to be the core treatment. Nevertheless, the results and impact in the long term prognosis vary. Many studies conducted in neo-adjuvant suggest that there is a sub-group of women whose TN tumors are extremely sensitive to chemotherapy. However there are many other patients to which chemotherapy has an unknown or uncertain result. This reflects the heterogeneity of this sub-type of breast cancer. Currently there is no chemotherapy standard regimen and the treatment should be selected according to the parameters used in other sub-types.

Dr. Arroyo’s comments:

The great promise and boom of PARP inhibitors failed (Phase IIIO Shaughnessy) but not in the BRCA positive sub-group. I think that PARP inhibitors are not in the market yet but I believe (correct me if I am wrong) that the answer to the agents available today is not the same for BRCA positive as to the rest of NTBC.

**Anthracyclines and Taxanes**

They continue to be the most important drugs with the most evidence in adjuvant and metastasis but there is no evidence that this is different in TN. Although it is known that the lasting response in metastatic TN is short (compered to non-TN), due to their relation with BRCA genes, it has been hypothesized that TN could be particular sensitive to agents that cause damage to the DNA such as platinum salts and PARP inhibitors.

**Platinum Salts**

Platinum has gained a protagonist role due to the promising results in neo-adjuvant (in NT and mutated BRCA1) with full response rates of 20% and 30%. Also, it has worked in advanced breast cancer (not
by sub-groups) pre-treated with anthracyclines and taxanes. There is higher evidence in the benefits in mutated BRCA.

The results with single therapy platinum have been modest. Treatment with double or triple platinum appears to be more active. One of the proposed and most used treatments is cisplatin/gemcitabine or carboplatin/gemcitabine (data studies phase II.) Randomized studies phases II and III have compared treatments based on platinum associated to target therapies. From these, one phase II study showed ORR improvement with the addition of carboplatinum to cetuximab without impact in survival.

A phase II study in MTS setting (N=126), showed improvement in SLP with a 6 month media, adding cisplatin to a metronomic therapy with cyclophosphamide and methotrexate (on second-line) and SG of 4 months with manageable toxicity.

Although results are promising, they are limited to simple institutions.

In conclusion, the true roll of platinum in TN is still being studied. It would be premature to signal it as a therapy of choice, except for mutated BRCA or on third-line, after failure with anthracyclines and taxanes.

Dr. Kowalysin´s comments:

Anthracyclines are useful in adjuvant and neo-adjuvant.

Taxanes are useful without being able to remove them from the other sub-types of breast cancer.

Platinum is very useful specially with mutated BRCA, BRCAness or associated to PARP inhibitors.

Capecitabine (no answer yet)

Epothilones Ixabepilone

Two major studies phases III have shown the benefits in the use of Ixabepilone combined with capacitabine (vs. capecitabine alone) in MTS breast cancer patiens who have relapsed or present a resistance to anthracyclines and taxanes. Both studies had a sample of around 20% of NT breast cancer patients. The benefits are seen on SLP and ORR with an acceptable toxicity profile.

A/T resistants: n=752. SLP 5.8 v 4.2 months; HR _ 0.75; P _ .0003
A/T pre-treated: n= 1221. SLP. 6.24 months vs 4.4 months HR_0.79; P_.0005; ORR: 43 vs 29%. For the sub-group NT, SLP: HR_0.64.

These results support the use of this combination in anthracyclines and taxanes resistant TN or pre-treated patients. Also there is evidence that Ixabepilone indices pCR in neo-adjuvant with greater ORR in TN sub-group.

Single therapy Ixabepilona is also approved for capecitabine resistance MTS patients.

PARP Inhibitors

The benefits in the initial studies of SLP and SG with PARP inhibitors were promising; however phase III results have been disappointing.

Olaparib is active CM (breast cancer) with BRCA mutations (all sub-types, including NT) studies on phases I and II but not in TN without BRCA mutation.

Iniparib showed activity in MTS NT phase II when chemotherapy base on platinum was added (Carbo+Gem, O´Shaugnessy´s study): 41% reduction of progression risk (PFS; median, 3.6 versus 5.9 months; P = 0.01) and 43% reduction of death risk (OS; median, 7.7 versus 12.3 months; P = 0.01) with a minimum toxicity increase. This could not be proved on phase III (PFS, 4.1 versus 5.1 months; hazard ratio (HR) = 0.79), P = 0.027; and OS 11.1 vs 11.8 months; HR = 0.88 (95% CI 0.69–1.12), P = 0.28; questionable uniformity of subjects) and the results are confusing when it comes to the usefulness of Iniparib.

Dr. Kowalysin´s comments:

Without a doubt PARP inhibitor in BRCA, Iniparib was beneficial but only for OS, it did not seem the same for other PARP inhibitors.

Other targeted therapies

The possible ways to be blocked during TN treatment are:

Angiogenesis mediated by VEGFR
Differentiation mediated by EGFR
Proliferation mediated by mTOR

Anti-angiogenic
VEGFR expression is significantly greater in TN

Three studies have researched the use of Bevacizumab in a metastatic setting: E2011: the weakly addition of avastin to paclitaxel in first-line reduces the progression risk in 51% and doubles SLP (5.3 versus 10.6 months)

AVADO1: Similar to the information stated above

Ribbon 1: No difference

A meta-analysis on first-line of TN sub-group in the referred studies showed a 2.7% net benefit in SLP (35% risk progression reduction) (P < 0.0001). Similar results have been obtain in second-line (Ribbon 2: cape o tax o vin o gem +/- bev; 51% progression risk reduction y SLP de 2.7 vs 6 months (S) y SG 17 vs 12 months (NS). In BEY patients ICC risk would increase 4 times.

Dr. Kowalsin’s comments:

Bevacizumab: benefited in PFS

ITK

Sunitinib: Little activity as single agent, much toxicity when combined with chemotherapy.

Sorafenib: Three studies phase II show SLP improvement of approximately 2 months and a tendency to improve in SG. More toxicity G3-4 (fatigue and stomatitis, SMP)

Anti-EGFR

Cetuximab: BALI 1 study: SLP improved (3.7 vs 1.5 months) but neither ORR nor SG (12.9 vs. 9.4) and the SLP difference was not standard maybe due to the inferior control branch (cisplatine.)

mTor Inhibitor

Only studies in neo-adjuvant with overolimus but does not improve RC. Other studies are still ongoing.

Single therapy or combinations?
Still answered

What would be the recommended treatment sequence?
Still unanswered

**Does maintained therapy have a role? Involved agents.**
Still not answered.

**Post- Workshop Conclusions**

**Current definition. Impact in our environment**

Breast cancer (BC) triple negative (TN) includes a group of tumors which does not express estrogenic receptors (ER), progesterone receptors (PR) or HER2. They make up a heterogenous population with a more aggressive biology. \(^1, 2, 3, 4, 5, 18\) It is more frequent in younger women and is the predominant sub-type in patients with BRCA1 germinal mutation. It has a global incidence of around 15% (10% to 29%) reported in the general bibliography \(^1, 2, 3, 18\); In our country, Argentina, the data from Plan Nacional reveal a 15% incidence, including invasive carcinomas (4,500) in 8 years. (At Roffo Institute: 10%, Spain enrollment of 6 hospitals: 13.6%, Chile 12% and Brazil: 15%)

**Is it a different disease?**

The panel agreed that it is a different disease (from non-TN) but it appeared to be more than one disease.

**Are all Basal-like?**

The TN molecular make up is superimposed with Basal-like (BL) (70% - 90% concordance rate) \(^1, 2, 3, 5, 6, 7\). But not all TN are BL since a small percentage of TN express hormone receptors and HER2 \(^1, 2, 18\). The definition of TN depends on the pathological anatomy while the term Basal-Like derives from genetic expression studies.
Histopathological characterization. What immunohistochemical (IHC) panel must be used? Can we identify sub-groups? Prognosis implications.

A cutoff point of less than 1% of positivity was established for the hormone receptors (HR) of tumor cells in order to be considered negative, following the recommendations and guidelines of ASCO and the College of American Pathologists.

The panelists acknowledged that there was certain evidence of the existence of subgroups such as true BL (Basal-Like) which present CK5/6, EGFR and other markers like CK14 and c-KIT with worst prognosis.

Some have chosen the term “core basal phenotype” to define those tumors that aside from being triple negative they express CK5 and EGFR; it has been proposed that these tumors will have worst prognosis than those which are negative for 5 markers.

The techniques for CK5/6 determination are being worked on. Nevertheless the panel does not recommend using them in any of the markers because they are not reproducible enough, there is heterogeneity in the staining patterns and there is absence of well-defined cut points (margins).

The medullar and cystic adenoid subtypes which have a favorable prognosis despite having a TN phenotype should be mentioned and the panel agreed that these subtypes should be left out of the TN debate.

The identification of patients with BRCA1 mutations would have implications in the selected therapy, Thus they are subtype to be considered.
The panel recommends determining the Ki 67 of all patients even though up to now the prognosis or treatment implications are unknown for this subgroup.

In conclusion, currently for the panel the only subgroups clearly defined (with implications in the practice) are medullar carcinomas, cystic adenoids and mutated BRCA1.

The immunohistochemical panel to be used would be: RE, RP, HER2 and Ki 67.

BRCA\textsuperscript{10, 11, 12, 13} mutations relations

The incidence of BRCA1 mutations in TN varies between 10% and 20% (in non-selected samples is around 20% and in germinal selected samples ranges between 11% and 39%)

Two recent studies have evaluated the prevalence of BRCA genes mutations in a series of non-selected triple negative breast cancers due to family background \textsuperscript{11, 12}. These findings are the base for the inclusion of triple negative BC patients as a sample to test in the 2012 NCCN\textsuperscript{13} recommendations.

The cutoff age for studying triple negative BC has not been defined yet and in our environment we still have difficulties accessing to the genetic studies of the at-risk population. Nevertheless, the clear risk evidence of carrying the gene mutation for any triple negative BC in patients under 50 years old cannot be ignored. Therefore, the panel concluded that the appearance of a TN breast cancer should be taken as a warning sign to consider a BRCA1 mutation and a genetic assessment should be suggested based on other risk factors (family history and age, especially if is less than 50 years old) and eventually conduct a BRCA1 mutation study.
On the contrary to BRCA1, no relations have been reported between BRCA2 and TN breast cancer.

**Staging/monitoring response: PET?**

There is no evidence that there was a role for PET for completing the staging or the monitoring response to TN treatment. Therefore, the panel does not recommend the use of PET in these patients. The monitoring response has to be the same for TN and non-TN patients.

**Is it necessary re-biopsy when there is a relapse?**

The panel recommends to re-biopsy as long as is accessible and the health of the patient allows it.

**Should the local-regional treatment vary?**

While speaking of an advanced disease, there is evidence that surgery in the primary tumor would improve the results in patients with BC\(^{15}\). Although this evidence would not be enough to answer the question, the panel concluded that there is a subgroup, TN group, which would not beneficiate from the local-regional treatment. Thus no definite recommendations can be given.

If local-regional treatment was chosen as a therapy, it should only be done after systemic treatment.

**Treatment**

The panel recommends trying to include the patients in the clinical studies whenever possible.

**Anthracyclines and taxanes**

They continue to be the drugs of choice in first-line treatment.

**Capecitabine and Epothilones**
There are at least two randomized studies that included a considerable percentage of TN patients that show benefits with the use of Capecitabine-ixabepilone\textsuperscript{23, 24}.

**Platinum**

The usefulness of platinum (cisplatinum, carboplatinum) in TN patients is encouraged but the favorable results obtained in neo-adjuvant studies (primarily phase II with high rate of full response) and in patients with BRCA1 mutations \textsuperscript{18, 19, 20, 21, 22}. Nevertheless, in the advanced setting its role has not been defined and it is even controversial.

The panel agreed that they would be active drugs and could be used in second or third line; but not in patients with BRCA1 mutations where the evidence stills supports their use in first-line treatment.

**Mono-therapy or combinations?**

The panel recommends start treatment with combinations. Accepted combinations are: anthracycline-taxane, capecitabine-docetaxel, capcitabine-ixabepilone. Other drug combinations actives on second or third line are: carboplatinum-gemcitabine, ciplatinum-gemcitabine, especially in BRCA1 mutation carriers.

**Which would be the recommended treatment sequence?**

There is no specific sequence recommended; nor about the use of mono or polychemotherapy in second and third line. There was a consensus as to start (first-line) with Anthracyline-Taxane.

**Target therapies**

PARP inhibitors are attractive because of their mechanism related to the alteration in the DNA reparation (mechanism deregulated in BCTN.) Nevertheless the results of a study phase III with Iniparib could not demonstrate the benefits it promised at phase II\textsuperscript{28, 29}. 
The same happens with EGFT inhibitor Cetuximab, since around 50% of the patients overexpress EGFR. Nonetheless, the usefulness of this agent is still being investigated.

There is some evidence about the benefits of Bevacizumab, along with paclitaxel; data from a meta-analysis with TN subgroups showed benefits in the progression-free survival rate.

In conclusion, the panelists do not recommend the use of molecular therapies unless it is for a clinical study.

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**Workshop Discussion: Breast Cancer Stage IV Experts’ Meeting**

**TOPIC: HORMONE DEPENDANT ADVANCED BREAST CANCER**

**PARTICIPANTS:**

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<td>Dra. Adriana Borello – Cordoba, Argentina – Oncologist</td>
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<td>Dr. Enrique Diaz Canton – Buenos Aires, Argentina – Oncologist</td>
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<td>Dr. Anibal Roberto Nuñez del Pierro – Buenos Aires, Argentina – Mastologist</td>
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QUESTIONS

(This is a summary of the questions submitted by doctors: Anibal Núñez del Pierro, Enrique Diaz Canton, Jorge Nadal, Hugo Japaze and Adriana Borello)

1. Do you think that ETP is the default resource in MBC without compromising and risking life?

2. How do you define “compromising high risk (of mortality)“?

3. At your clinical practice; how do you define hormone-sensitive as a whole?

   At your clinical practice; how do you define hormone-sensitive at stage IV?
4. What factors do you consider when modifying the ETP indication?

5. What ETP do you prescribe to relapsed or progressed patients after receiving

   a) Tamoxiphen? Differentiate between pre and postmenopausal patients

   b) Non-steroidal IA

   c) Non-steroidal TAM-IA in switch for 5 years

   d) Steroidal IA

   e) Non-steroidal TAM-IA in extended adjuvant.

6. In what line do you usually prescribe Fulvestrant?

7. If you prescribe Fulvestrant, do you use it as a single drug or do you associate it to another ETP?

8. Do you have experience or a set criterion about the association of ETP and Everolimus?

9. Do you associate biphosphonates to ETP?

10. In which cases?

11. What pharmaco do you use?

12. Do you have experience or a set criterion about Denosumab?

13. In which category do you place post-mastectomy local relapse?

14. How do you manage post conservative treatment relapse? (out of the customary theme but interesting)

15. How do you interpret the disease ER – PR positive?

16. In an advanced illness, do you prefer global survival or progression-free survival when prescribing a drug? If the patient does not show improvement in SG, would you prescribe it?

17. What do you use in ER positive/HER2 positive MBC?

18. In post-menopause, do you always start with aromatase I? And in what cases do you use other options?
19. What doses and how do you use Fulvestrant?

20. Do you use HT neo-adjuvant? In what cases do you use it? How do you use it? And how do you evaluate the response?

21. What opinion do you have about using HT and CMT (chemotherapy)?

22. Do you biopsy a relapse? What if it has short disease-free intervals (e.g. < 6 months)?

23. In patients with metastasis and the primary tumor still in its place, what do you do with the primary tumor aside from the systemic treatment? If you use a conservative treatment, do you add radiotherapy?

24. If the patient has bone metastasis, soft tissue, asymptomatic and is RE negative, do you have a period of hormone treatment?

25. In ER positive and HER2 positive patients, do you use chemotherapy or hormone therapy?

26. If you use HT (ER positive / HER2 positive), do you utilize IA + lapatinib or IA + Trastuzumab?

27. In your opinion, do biphosphonates have a proven antitumor effect in advanced illness?

28. How long do you prescribe biphosphonates in patients with bone metastasis?

29. When do you do surgery in metastasis?

30. In minimum metastatic disease, what strategy do you suggest?

31. Do you use hormone therapy post-chemotherapy (as maintenance)?

32. What strategy do you use in patients who run out of hormonal options?

33. Removal of primary tumor, is there a chance?

34. What type of post-therapeutic results assessment do you indicate to your patients?
35. If the response is oriented towards accepting an anatomopathological evaluation, then I would ask: Which are the anatomopathological parameters that you would request your pathologist in order to evaluate the results?

36. Complementing the question above: Based on the anatomopathological results and indicators obtained, what is the treatment to follow?

ANSWERS

1-

Dr Diaz Canton:

I believe that it is the most attractive option. Other factors should be also considered such as HER2 stage since in this cases it is appropriate to ad latatinib or trastuzumab.

Until we have tried many different hormone therapy types, in a patient who is clinically stable, I do not believe that we should move out of HT.

Currently there have been included other options in HT treatment such as IA + Averolimus (Baselga et al NEJM 2012) and Tamoxiphen + Averolimus (Baselga et al NEJM 2012) which will significantly delay the use of chemotherapy in these patients.

Dr. Borello:

I try to exhaust all the available hormone therapy options in a stage IV, hormone-dependent patient before starting chemotherapy and taking into consideration tumor biology/comorbidities.

This answer possibly is related to question four.

Dr Nadal:

Yes. It is the proper treatment in hormone-dependent patients without visceral involvement or extensive symptomatic bone involvement. One should offer it as first approach and dismiss when no treatment with HT is possible.
Dr Diaz Canton:

Visceral disease and symptoms

Visceral disease and fast evolution

I do not consider visceral disease without the two factors mentioned above as a CVP because there are patients with visceral metastasis that could have a slow evolution and/or be asymptomatic which do not necessarily require chemotherapy at the beginning.

Dr Borello:

In the dictionary synonymous for perentorio are: co-adjuvant, decisive, determining, urgent and pressing. I guess that it refers to a metastatic disease with involvement of a vital organ and life-threatening. It surprised me that I could not find this expression in the English literature. It might be LIFE-THREATENING DISEASE

Dr Nadal:

It is a fast evolving disease with multiple visceral compromise. It is a symptomatic visceral disease with a disease-free interval of less than one year. It also presents multiple symptomatic bone compromise not controllable with radiotherapy and no response or resistance to previous hormone treatment.

Dr. Diaz Canton:

E Hormone sensitive >1% of ER and PR., in stage IV asymptomatic and with slow evolution. Some authors suggest hormone therapy trial even in ER – PR. I am not sure when ER negative and low PR positive

Dr. Borello:

>1% RE/RP, following international ASCO/CAP recommendations. I have the same doubt as Enrique in RE negative and low RP. NCCN recommends a trial hormonal treatment in patients with RH negative and stage IV.

Dr. Nadal:
Always use hormone therapy in a metastatic RE>1% RP>1% and when the clinical criteria matches with hormone dependency.

In adjuvant, it is considered as a negative RE o RP <10% for the indication of chemotherapy but for the use of hormone therapy it is considered >1%.

4-

Dr. Diaz Canton:

Factors to initiate Hormone therapy: Positive receptors, asymptomatic - oligosymptomatic, slow evolving, non-visceral (with the exceptions described earlier) disease with a life risk that prevents chemotherapy even if it was the most appropriate treatment.

Dr. Borello:

RH positive

Hormone sensitive disease shown in previous lines; I do not believe that we can use everolimus on a massive scale in hormone resistant patients or at least in my currently situation.

Asymptomatic or oligosymptomatic, interval-free disease with low tumor load and exclusive bone compromise; I do not believe that visceral compromise is excluding. Slow growing visceral lesions, asymptomatic or with minor symptoms, single lesion or small size. Some bibliography indicates that patients with more than one organ compromised have been included in trials. Life risk that prevents chemotherapy even if it is the most appropriate treatment.

Patient preference: I discuss with the patients based on biological function of the disease, toxicity, different options hormone chemotherapy.

Particular situation: CNS disease controlled.

Dr. Nadal:

Hormone status, previous exposure to hormone therapeutic agents, life risk. History of thrombosis occurrences, osteoporosis, allergies, retinopathy, antidepressant, oral ingestion capacity and compliance.
5-

Dr. Diaz Canton:

Relapses – progressed to TMX

Premenopause: Similar lhrh alone or with aromatase inhibitors
Postmenopause: aromatase inhibitors or fulverstrant.
In both there is the option of adding everolimus to tamoxiphen (very expensive)

Dr. Borello:

a) Tamoxiphen – Premenopause:
   - Surgical Oforectomy or radiation. O...
   - LHRH agonist and IA
     If tamoxiphen has been suspended for > 12 months, Tamoxiphen and
     - LHRH analogs or surgical ablation (IB evidence)

b) Non-steroid IA: Exemestane or fulvenstrant

c) Non-steroid TAM-IA in switch for 5 years: Exemestane or Fulvenstrant

d) Steroid IA: Tamoxiphen, Fulvenstrant or non-steroid IA

e) TAM-IA non-steroids in extended adjuvant: Fulvenstrant.

According to NCCN/ESMO/ESO guidelines, pre and post-menopausal RH positive benefit with progression sequential hormone therapy. Progestagen and anabolic steroids are mentioned.

Dr. Nadal:

If exposed to a tamoxiphen

a) premenopause: ovary ablation (goserelin or bilateral oorectomy)
   and non-steroid inhibitors.

b) postmenopause: non-steroid inhibitors.
Exposed to non-steroid inhibitors (postmenopause): Tamoxiphen.

Exposed to non-steroid inhibitors and TMX in switch: Exemestane/everolimus o Fulvestrant.o Capecitabine

Exposed to TMX and non-steroid inhibitors in extended adjuvant: Fulvestrant, Exemestane + Everolimus o Capecitabine

Exposed to steroid inhibitors: TMX, (± everolimus?) Fulvestrant, Capecitabine.

6-

Dr Diaz Canton:

Fulvestrant: Second or third line.

Dr. Borello:

Second or third line

Dr Nadal:

Fulvestrant in second or third line, after exposure to Tamoxiphen and non-steroid inhibitors. The indication of monotherapy exemestane in this instance will decrease since there is the possibility to associate it with Everolimus (and for possibly better results with Fulvestrant 500 mg; because Exemestance is equivalent to the results of Fulvestrant at 250 mg.) Never associated to other hormonal agents.

7-

Dr Diaz Canton:

Although there are two studies analyzing this, the results are beneficial for the combination in one and neutral for the other. I use it only in 500 mg.

Dr. Borello:

Fulvestrant alone or associated?

I use it as monotherapy in doses of 250 mg. I would like to discuss at the workshop the 500 mg doses because the benefit in the CONFIRM study was in PFS of one month. If we analyze this statistically speaking HR 0.80, CI 0.68 to 0.94 is significant, which
corresponds to a 20% risk progression reduction. According to ESMO guidelines, there is no rationality for the use of combined hormone therapy.

Enrique showed the results of two studies which must be taken into consideration: FACT-An and SWOG S0226. According to NCCN guidelines the reason for this divergence is unknown.

Dr Nadal:

Although SWOG S0226 showed a slight increment in PFS in first line, this was not corroborated in any other study. Multiple research works show the inefficiency of the associations with hormone agents.

8-

Dr Diaz Canton:

ETP/everolimus: Experience: Yes; PS3 move to one in two weeks with relapse of CA15-3 of 1600 to 400.

Criteria: is notably beneficial in PFS and BRC improves but very low improvement in RR. This is the situation with IA and Tamoxiphen use.

It will delay a lot the starting of chemotherapy. I believe that in the long range it will extend survival rates.

Dr. Borello:

ETP/everolimus

Experience: I have prescribed it only in two patients, one of them with fast improvement of PS for controlling pain but it is too soon to re-evaluate them.

Opinion: It seems like an attractive option since is a way to modulate hormone resistance and delay the use of chemotherapy. It was shown in two advanced breast cancer studies, one including Exemestane and the other Tomoxiphen, that PFS was prolonged with Exemestane and survival rates as well as PFS were also prolonged with Tomoxiphen. This hypothesis was also tested in neo-adjuvant with positive results.
Dr Nadal:

I have two patients treated with Exemestane/Everolimus with a short follow up. In one I had to reduce the doses due to toxicity (mucositis and diarrhea)

9-

Dr Diaz Canton:

Biphosphonates: I do use it. They are quite unpleasant in a patient treated orally for obvious reasons.

Dr. Borello:

Biphosphonates:

Yes we associate them with hormone therapy.

Dr Nadal:

I use bisphophonates associated to bone metastasis exclusively. The usage of Pamifronate or Xolendronate is preferred even though the IV is an obstacle for patients with oral treatment. In the practice, it is for selected cases and always when they have parentenal treatment indicated.

10-

Dr Diaz Canton:

I use it with bone metastasis, above all if they are symptomatic, lytic or are in places prone to fracture. I believe it should be started in adjuvant (?)

Dr. Borello:

We use it practically as routine treatment in all patients with bone lesions, especially lytic lesions with normal renal function (category 1)

11-

Dr Diaz Canton:

1. Zolendronic Acid
2. Pamidronate
Dr. Borello:

1. Pamidronate
2. Zolendronic Acid

Dr. Diaz Canton:

Denosumab?

It is very interesting, powerful and possible the best of all, easy to use (SBC) even though severe toxicity such as osteonecrosis of the jaw and hypocalcaemia do exist. If it was available (it is available for osteoporosis), it would be my first selection.

Dr. Borello:

It has recently been approved in our area. Its action mechanism is attractive; a priori it would be more effective than its predecessors to retrace skeletal events. Since it is administer by s/c it makes things easier for the patient however its cost can be a limiting factor. I believe that studies have not shown high ONJ (osteonecrosis of the jaw) frequency (category 1.)

Dr. Nadal:

I have experience with Denosumab because I took part of clinical studies. It appears to be superior to bisphosphonates since it decreases bone events and it is easier to administer to patients. It has not been approved for bone metastasis yet.

Dr Diaz Canton:

Local relapse post-mastectomy

It represents a high risk of systemic failure (50%). When they are hormone sensitive, I treat them and if they are not, I follow them closely.

Dr. Borello:

Local relapse post-mastectomy
Try surgical removal of the local relapse if it is possible. It is difficult to get negative margins. XRT value to the wall and supraclavicular areas if the patient was not radiated previously or if there still is doses margin.

We have a similar approach to Enrique’s systemic treatment. If there is a margin for hormonal treatment, we will do it. We do not support the idea of chemotherapy “pseudo-adjuvant” (evidence 2b.)

Dr. Nadal:

The clinical suspicion of relapse post-mastectomy is considered a systemic event even if there are possibilities of long survival and in some patients is a onetime event. In general, it is therapeutically seen as metastatic disease treating it with local treatment whenever possible.

14-

Dr. Diaz Canton:

Local removal post conservative treatment.

The standard procedure would be a mastectomy. But I believe there are other options besides the standard treatment.

Conservative cx and follow up (low risk)

Conservative cx and partial RT

Conservative cx and IORT

Systemic treatment and local treatment less aggressive; of course the systemic treatment should be according to indication.

Dr. Borello:

We discuss it as a multidisciplinary team among Cx mastologists, plastic surgeons, and radiotherapists according to each case.

Options:

Mastectomy and axillary dissection level I/II or sentinel lymph node...NCCN expert’s panel recommendation.

Conservative Cx

The guidelines suggest that in inoperable patients, systemic therapy at the beginning is used to decrease the size of the tumor and
attempt a surgical rescue afterwards. Re-radiation, selecting carefully the patient and technique even though its value has not been approved. Discuss again sentinel lymph node.

About the systemic treatment, if it is RH positive, hormone therapy (ESMO/experts ‘opinion)

Assess other biological factors, especially Cerb2. Trastuzumab. “Pseudo-adjuvant” If it was conducted previously to dx. (ESMO/experts ‘opinion)

There is an ongoing study about the role of chemotherapy after treatment of relapse loco-regional isolated without metastasis at a distance (IBSCG)( NSABP)(BIG)

Hyperthermia (category 3) is not available in my environment.

Dr. Nadal:

In relation to relapse post conservative treatment, the attitude is even more variable and the bibliography does not give us convincing elements, only limited retrospective experiences. Personally unless that unequivocally it is a true local relapse, it should be treated systematically as a 2º primary. About the local treatment, a mastectomy is orthodox but in selected cases a re-quadrantectomy with wide margins is acceptable. Re-radiation is impracticable.

15-

Dr. Borello:

There are authors who consider it a technical skill and suggest repeating it.

I have discussed it with my pathologist and she says that CAP has not been sent out. In the practice, I prescribe hormone therapy, luckily is infrequent. I will get more literature for the day of the discussion.

16-

Dr. Borello:

I would like that pharmacos showed the benefits in survival but at the stage of the clinical investigation it is difficult to have the results due to various reasons such as early results publication
without enough follow up, branches ‘crossover, new investigation lines, compassionate use, etc.

I have even attended at ASCO to conferences that deal with this topic. It is difficult to interpret some trials; I like HR as the work of Everolimus/Examestane.

17-

Dr. Borello:

Initially we used chemotherapy + Trastuzumab and then when suspending cytostatic, it was replaced with IA+ Tratuzumab. I believe that this clinical situation deserves a change in thought.

18-

Dr. Borello:

According to COCHRANE, IA in advanced breast cancer in postmenopausal patients generate a survival benefit of 10% HR 0.90, CI 0.84 to 0.96 (37 studies/11,403 women) vs. other hormonal therapy. Personally I do not always start IA, the selection depends on many factors such as absence of previous therapy with Tomoxiphen, comorbidities, type of health insurance (coverage.) This last factor, I am not sure if it is correct but the province’s health insurance does not contemplate it.

19-

Dr. Borello:

250 mg...see above

20-

Dr. Borello:

In few occasions, possible older ones, it is hard to believe that it is not a good option but unfamiliarity with the indication.

21-

Dr. Borello:

According to the ESMO guidelines, chemotherapy/ hormone concomitante is not advisable.
22-

Dr. Borello:

We have included it as routine in our institution but I do not believe is necessary in short intervals.

In its guidelines, ESMO, defines a short interval between initial diagnosis and metastasis such as <1-2 years.

23-

Dr. Borello:

It is difficult to decide about it. If we operate, we prefer cx conservative but we do not add XRT.

There is retrospective data about the importance of the cx of a primary tumor; there is even an ongoing prospective study. The benefits could be due to the selection of patients; we could discuss it a posteriori. It is a recommended practice by ESO-MBC TASK FORCE.

24-

Dr. Borello:

No, I do not believe that this must be done within a clinical study.

25-

Dr. Borello:

It is difficult to give an opinion on this point; when deciding, one is tempted to be inclined to choose chemotherapy. I believe it would be useful to discuss this with Cristian Villanueva on the scheduled day for discussions since he took part in the Lapatinib+Letrozole study as a researcher along Dr. Pivot at Besancon.
NCCN recommends to this group of patients to start chemotherapy if there is visceral crisis.

ESMO suggests hormone therapy + antiHER2, if the patient does not need chemotherapy or cannot tolerate it.

26-

Dr. Borello:

I have had the opportunity of using IA + Trastuzumab but the other option I also find it useful.

27-

Dr. Borello:

No.

28-

Dr. Borello:

The timing and optimal duration of biphosphonates is unknown, and the benefits passed the two years has not been shown in clinical trials ESMO.

We use them for two years.

29-

Dr. Diaz Canton:

Metastasis surgery when:

Single metastasis or oligometastases in the same organ and technically attainable.

Interval-free disease over one year.

Good functioning state

Low co-morbidity

Adverse indications (absolute or relative of treatment systems)

Nevertheless, if it is not like that, the systemic treatment is given for previous cytoreduction and live evaluation of response.
30-

Dr. Diaz Canton:

With a minimum metastatic disease what approach do you suggest?

In general terms, is very similar to what has been said earlier in regards to surgery.

I would try to achieve a complete remission depending on the biological subtype.

This would prolong survival and in odd cases, it could become healed.

If chemotherapy is indicated: chemo with or without Bevecizumab or Trastuzumab and Pertuzumab. Hormone therapy is also indicated.

If chemotherapy is not indicated: hormone therapy with or without Trastuzumab or Lapatinib.

Ablative radiotherapy also can have a role as radiosurgery (Cns and body gamma knife) or percutaneous techniques such as radiofrequency in specific metastasis (e.g.:liver)

31-

Dr. Diaz Canton:

Maintenance hormone therapy

I use it. Little or no documentation of its usefulness (at least from level 1 evidence)

Less toxic and potentially effective

Intellectually attractive

32-

Dr. Diaz Canton:

Strategy in patients who exhaust hormonal treatments.

a) Chemotherapy

b) Ad Everolimus
The study bolero2 included patients with more than three lines of hormonal treatment and although FDA and ANMAT approve its use in failure to hormone therapy, ANMAT does not specify which one.

33-

Dr. Diaz Canton:

Removal of primary tumor, can it be done?

Various studies show that it prolongs survival (all retrospective) in some cases with visceral metastasis, and in other cases with lymph and soft tissue metastases; almost always oligometastases.

I frequently do it, although I am not clear in what to do with a clinically negative axilla and with radiotherapy post-surgery if it were necessary.

34-

Dr. Diaz Canton:

Depends on the affected organ. This can include:

CT
PET/CT
CEA/CA 15-3
Bone Centellogram
Physical examination
Patient interview

35-

Dr. Diaz Canton:

Understanding that the question refers to locally advanced tumors:

Symmans criterion (MDACC) for pathological remission
RE, RP, HER2

36-

Dr. Diaz Canton:

There is pRC observation
If there is residual disease continue treatment according to the biological subtype, for example: more chemotherapy, hormone therapy, anti-HER2

**Conclusions for Advanced Breast Cancer**

Hormone Dependent

1) Hormonal treatment is the preferred option in hormone dependent metastatic breast cancer, unless there is a visceral, symptomatic and/or fast evolving, extensive systemic bone compromise disease that needs a fast response with cytostatic agents.

2) The factors to consider to initiate hormonal treatment would be:
   a) Hormonal receptors expression
   b) Asymptomatic or oligosyntamic disease
   c) Slow evolving disease
   d) Number and place of visceral compromise
   e) Co-morbidity or PS deteriorated that prevent the start of chemotherapy even if it is indicated
   f) Disease-free interval
   g) Oral ingest capacity and compliance.

3) The hormonal agent to select depends on various factors:
   a) Pre or post-menopausal stage.
   b) Endocrine therapy used previously in adjuvant
   c) Relapse time: early or late

4) In pre-menopausal women ovary suppression/ablation combined with additional hormonal therapy is the first selection.

5) In pre-menopausal women the agent to use in first-line should be Tamoxiphen, unless there is proven resistance to it.
6) In pre-menopausal women, the use of Aromatase inhibitors is an option but it is mandatory the use of ovary ablation/suppression.

7) For the majority of the panelists, in post-menopausal women first-line hormonal therapy should be an Aromatase inhibitor, nonetheless, Tomoxiphen continues to be the viable option in selected patients. The type and duration of adjuvant endocrine therapy should be taken into consideration.

8) The election of a hormonal agent after progression to Aromatase inhibitors is uncertain. The options proposed were Tamoxiphen, another aromatase inhibitor with different action mechanism, Fulvestrant and megestrol acetate.

9) Fulvestrant it is used by the majority in second or third hormonal line after exposure to Tamaxiphen and non-steroid inhibitors in a 500 mg doses.

10) The majority of the panelists do not use association of hormonal agents.

11) The use chemotherapy and hormonal therapy at the same time, it is not recommended.

12) The use of maintenance hormonal therapy post chemotherapy sounds like a reasonable option eventhough it has not been proven in randomized studies.

13) The association of Everolimus to a non-steroid aromatase inhibitor has shown favorable results in hormone refractory patients, overcoming the resistance and prolonging progression-free survival. This would be an option to use, before prescribing chemotherapy.

14) The panelists associate biphosphonates to hormonal therapy in breast cancer with bone metastasis.

Los panelistas asocian bifosfonatos a terapia hormonal en cancer de mama con metástasis óseas.

15) In hormone dependent and with expression of HER-2 metastatic breast cancer patients, the panelists consider as a useful
approach the association of hormonal agents and anti-HER-2 (Trastuzumab or Lapatinib) because the combination has shown benefit to progression-free survival compared to hormone therapy alone.

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Randomized Study of Lapatinib Alone or in Combination With Trastuzumab in Women With ErbB2-Positive, Trastuzumab-Refractory Metastatic Breast Cancer Kimberly L. Blackwell, Harold J. Burstein, Anna Maria Storniolo, Hope Rugo, George Sledge, Maria Koehler, Catherine Ellis, Michelle Casey, Svetislava Vukelja, Joachim Bischoff, Jose Baselga, and Joyce O’Shaughnessy


Compare first-line lapatinib plus letrozole (LþLet) versus letrozole monotherapy (Let) in hormone-receptorpositive HER2þmetastatic breast cancer, employing Q-TWiST (quality-adjusted time without symptoms and toxicity) analysis to account for differences in progression times, with offsets for the impact of adverse events during the treatment period.

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Workshop Discussion: Breast Cancer Stage IV Experts’ Meeting

**TOPIC: SPECIAL SITUATIONS IN ADVANCED BREAST CANCER**

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QUESTIONS

(Questions created by Dr. Nora Mohr de Krause and Dr. Luis Fein)

1. In metastatic breast cancer (MBC) in the era of target therapies, Should surgery to the primary tumor be considered as a useful therapeutic strategy?

2. Does the singling out of marker Ca15-3 show clinical usefulness in the follow up of breast cancer patients?

   a. implications in the different levels of Ca 15-3 and the diverse subtypes at initial diagnosis and relapse.
      
      o In which subtype of breast cancer it should be considered useful in the field practice?

   b. Could it be considered as providing prognostic value?


4. Duration of chemotherapy in metastatic breast cancer. What is the appropriate length of time?

5. Maintenance chemotherapy in metastatic breast cancer. Yes – No

   o If yes, which patients should be considered for this strategy?
   o Risk and benefits

6. Does chemotherapy followed by maintenance hormone therapy improve the survival rate in metastatic breast cancer patients?

   o In which patients should be indicated?

7. In MBC triple negative, progressed to chemotherapy treatment with anthracycliens and taxanes; which would be the follow up treatment? Should the subtypes be taken in consideration in this group of patients?
8. Does metronomic treatment increase the efficiency in terms of clinical benefits for MBC? Yes – No
   - If yes, is the clinical benefit for the four molecular subgroups?
   - Assess risk, benefits and its impact on quality of life (QOL)

9. What standard procedure do you recommend for CNS metastasis?
   - Set up the role of conventional RDT and other modalities in the radiation treatment.
   - Set up the role of surgery in single or multiple lesions.
   - State the role of chemotherapy

10. Is the treatment different in the case of carcinomatous meningitis?
    - How do you do the differential diagnosis?
    - How do you certify the localized meningeal diagnosis?
    - What treatments do you recommend?
    - Do you have any experience in intrathecal or intraventricular treatment?

11. What is the standard procedure you take with hepatic metastasis?
    - What is the role of surgery in single lesions?
    - Does it have any role in multiple lesions?
    - Do you believe that RDT has any indication in single lesions?
    - Do you have any experience in radiofrequency ablation?
    - Do you believe that hormone therapy has a role in single hepatic MTTs?
    - Hepatic MTTs condition the treatment selection; would you treat any different a patient with hepatic metastasis? What if it was a single lesion? And multiple lesions?

12. Do you believe that by reviewing the literature triple positive patients have a good prognosis?
    - What criteria do you use to treat a triple positive advanced cancer patient?
    - From your point of view, when is hormonetherapy an option?
    - Do you believe that Trastuzumab must be always administered at the starting of the treatment?
    - In which patients you would not use Trastuzumab?
Which is your first-line chemotherapy? And how do you choose it?

13. Extensive local disease; what are the solutions?
15. Management of pleural effusion
17. How do you define futility, limitation, abstention and therapeutic withdrawal in breast cancer?
18. Treatment of older and comorbid patients with or low performance status.
19. Oncological management of patients with hepatic or renal failure.

**ANSWERS**

(by Dr. Diego Kaen)

1. The true value of the surgery on a primary breast cancer stage IV tumor is controversial. Nevertheless there are retrospective studies which suggest that controlling the primary disease could improve the patients’ survival rate (surgery or radiotherapy.)

Personal opinion: studying each case on an individual basis, I recommend the treatment of the primary tumor in metastatic breast cancer.

2. Although the tumor markers CA15-3 in metastatic breast cancer are controversial, it would be useful to conduct a follow up of MBC.

In practice, we use it in the metastatic field, independently form the molecular subtype.

The CA15.3 is not useful as filtering test since that only 21% of the patients in early stages of the illness (stage I, II and III) will present high levels.
Only pre-surgical increased CA15-3 levels are bad prognosis since they are correlated with advance stages, large tumors, lymphatic nodes metastasis and lymphatic spreading.

Changes in the CA 15-3 value overtime are more efficient than absolute values.

Personal Opinion: we use CA 15-3 to monitor metastatic breast cancer as well as early breast cancer (we believe it is useful to assess relapses.)

3. It should be clear that polychemotherapy has not demonstrated improvement in the survival of patients; therefore we recommend monchemotherapy for metastatic breast cancer. Polychemotherapy should be set aside for patients with fast clinical progression, life threatening visceral metastasis (E.G.: Carcinomatous lymphangitis) and the need to control symptoms fast. Since polychemotherapy has a higher rate of response, it benefits these cases.

4. The span of chemotherapy should be evaluated in an individual case and discussed with the patients.

We recommend continuing until the progression or toxicity is unacceptable. Since there is meta-analysis (Gennari A, JCO 2011) concluding that the duration of first-line chemotherapy is associated to PFS and SG improvements.

5. I believe this question has been answered in the previous response.

6. Endocrine therapy followed by chemotherapy (maintenance therapy) is a reasonable option, but this has not been assessed in randomized studies.

Personal Opinion: In the practice we do this.

7. This is a peculiar case; first we should know what the patient’s SLE is and if he/she progressed after a year of taxanes. This would give us the possibility to re-use taxane.
Personally, I believe that in triple negative breast cancer antiangiogenic and ixabelipone therapies have shown good effectiveness. In clinical practice, the subtypes have not modified the treatments.

8. The truth is that this is a controversial topic. While in clinical practice we do not use metronimic treatment, there are many phase II studies that show its clinical efficiency with low toxicity profile and some of them with improvement in the quality of life in almost all molecular subtypes.

AFTER WORKSHOP CONCLUSIONS

1. In metastatic breast cancer in the era of target therapies, Should surgery to the primary tumor be considered as a useful therapeutic strategy?

The true value of the surgery on a primary breast cancer stage IV tumor is controversial. Nevertheless, there are retrospective studies which suggest that controlling the primary disease could improve the patients’ survival rate.

It is undisputed that this is an advice or suggestion in emergencies or toilette cases (hemorrhage, ulcerations, etc.) Each case should be evaluated in an individual basis. In the cases where patients present a primary tumor with metastasis, we propose that the asymptomatic and stable patients with a slow evolution should undergo surgery of the primary tumor with free surgical margins as long as the main objective is to provide a better quality of life and not as a treatment for the underlying disease.

2. Does the singling out of marker Ca15-3 show clinical usefulness in the follow up of breast cancer patients?

Although tumor markers CA 15-3 in metastatic breast cancer (MBC) have been controversial, they would be useful in the following of patients that are under systemic treatment (chemotherapy or hormone therapy) to assess the change in therapeutic behavior.

It is a useful marker for evaluating relapses.
3. Monochemotherapy or polychemotherapy in the metastatic breast cancer treatment? Duration or span. What is the appropriate length of time? Maintenance chemotherapy?

Polychemotherapy should be set aside for patients with fast clinical progression, life threatening visceral metastasis (e.g.: carcinomatous lymphagitis) and the need to control fast symptoms, due to a higher rate of beneficial response in these cases. We recommend evaluate according to the tumor biology of each case.

Based on the meta-analysis (Gennari A, JCO 2011) which concludes that the span of first-line chemotherapy is associated with the improvement on the disease-free time and global survival rates, treatment should be done until progression of the disease or unacceptable toxicity.

In patients that reach a maximum response (full response or long lasting stable disease) assess the stopping of treatment followed according the maintenance therapy.

Although there are not randomized studies that back us up, endocrine therapy followed by chemotherapy in patients with positive hormone receptors (maintenance therapy) is a reasonable option and in clinical practice we do use it.

4. Behavior for dealing CNS metastasis

Take into consideration that HER2 triple positive and triple negative are highly frequent in brain metastasis and the results of these patients are different according to the molecular subtypes.

In patients with triple negative breast cancer, brain metastasis take place early in the course of the illness and are associated to poor results due to the great systemic compromise of the patient. On the other hand, in HER2 triple positive, brain metastasis appear later on and have a better response to anti-HER2 therapy with a better control of the illness, extra cranial and good survival after diagnosis.

As far as the treatment it will depend of the number and location. Patients with singles lesion should be treated with surgery or radiosurgery, depending on the size, location and multidisciplinary team experience. In patients with irresacable lesions radiosurgery is a good option.
In the case of multiple lesions or systemic uncontrolled illness the best option continues to be cranial radiotherapy.

In these cases the role of chemotherapy should be personalized.

5. In the case of carcinomatous meningitis, how do you conduct the differential diagnosis? How do you certify a meningeal localization diagnosis?

The leptomeninges carcinomatosis diagnosis is based on LCR test and MRI. Only 3% of the patients with leptomeninges carcinomatosis have a normal LCR. The presence on the increase of LCR pressure (50% of the cases), pleocitosis, mild or strong hypoglycorrachia (75%), protein increase (75%) is unspecific. The definite demonstration of leptomeninges carcinomatosis is based on the verification of neoplastic cells in LCR. The first spinal tap shows a positive neoplastic cytology in 50% of the cases.

MRI with contrast and without it is very sensitive to metastasis and contrast captation by leptomeninges, could also show parenchymal metastasis.

6. What is the standard procedure you take with hepatic metastasis? What is the role in single lesions? Do you have any experience in radiofrequency ablation? Do you believe that hormone therapy has a role in single hepatic MTTs?

Hepatic metastases have a bad prognosis. Although is true that each case should be evaluated on an individual basis, taking into consideration if the disease presents a single lesion with prolonged disease-free time or stability could make that patient a good candidate for surgical resection.

Radiofrequency is always an option in single, small lesions. Hepatic lesions should be treated with chemotherapy depending on the molecular subtype. However there are cases where hormone treatment is used.

7. Bone metastasis management.

It must be advised the routine use of bone modifying agents (biphosphonates o denosumab) in combination with systemic treatment of MBC.
The treatment with these agents should start from the image (MRI) detection of the lesion. It is not clear the time span for using these agents. In our practice, we discuss it with the patient and if the patient is asymptomatic we finish after 24 months (without evidence level.)

The radiological evaluation is required in patients with localized or persistent pain in order to dismiss pathological fracture. If there is a long bone fracture, an orthopedic evaluation should be conducted since the preferred treatment is surgical stabilization, followed by radiotherapy.

In refractory bone pain due to metastasis, radiotherapy is the selected option as it is in a disease with high bone risk (e.g. fracture). In these cases, it is also suggested an orthopedic evaluation.

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Duration of Chemotherapy for Metastatic Breast Cancer: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Stage IV breast cancer in the era of targeted therapy: does surgery of the primary tumor matter?

Neuman HB, Morrogh M, Gonen M, Van Zee KJ, Morrow M, King TA.

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Maintenance Hormonal Treatment Improves Progression Free Survival After A First Line Chemotherapy In Patients With Metastatic Breast Cancer

Armelle Dufresne1, Xavier Pivot2, Christophe Tournigand3, Thomas Facchini4, Thierry Alweeg5, Loic Chaigneau2, Aimery De Gramont3 © 2011 by American Society of Clinical Oncology

10- 2011 by American Society of Clinical Oncology Taxane Doublets for Metastatic Breast Cancer: Do We Need Another Cytotoxic Pair or Another Approach?


12 -Favorable response to doxorubicin combination chemotherapy does not yield good clinical outcome in patients with metastatic breast cancer with triple-negative phenotype

Seong Y Yi1, Jin S Ahn1*, Ji E Uhm1, Do H Lim1, Sang H Ji1, Hyun J Jun1, Kyoung H Kim1, Myung H Chang1, Min J Park1, Eun Y Cho2, Yoon La Choi2, Yeon H Park1 and Young-Hyuck Im1 .BMC Cancer 2010, 10:527 doi:10.1186/1471-2407-10-527

Increased gene copy number of KIT and VEGFR2 at 4q12 in primary breast cancer is related to an aggressive phenotype and impaired prognosis.


European Institute of Oncology, Medical Oncology, Milan, Italy
European Institute of Oncology, Division of Biostatistics and Epidemiology, Milan, Italy.
