**434** Invited

**Meta-analysis of taxanes alone or in combination with anthracyclines versus non taxane-based regimens as first-line therapy of patients with metastatic breast cancer (MBC): a lesson from the past and a message for the future**

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**Introduction:** After a decade of randomized clinical trials, clear guidelines for the optimal use of taxanes in MBC are still lacking, in part because of inconsistency in the results generated and the lack of an overall survival benefit in most trials.

We thought that a meta-analysis of *individual* patient data from all relevant trials investigating advantages of taxanes (sequenced or combined with anthracyclines) in *first-line* treatment of patients with MBC might disclose a survival benefit overall or in the subset of patients with visceral metastases. We also investigated whether tumor response and PFS were surrogate endpoints of OS in this setting.

**Material and Methods:** We succeeded in collecting key individual patient data for all 3953 patients randomized in 11 trials. Odds ratio of non response and hazard ratios for progression-free survival (PFS) and overall survival (OS) were estimated in each trial.

**Results:** In the entire patient population (n = 3953), the median follow-up is 41 months, the median PFS 7 months and the median OS 19 months. Information on sites of disease (eg visceral vs non visceral) could be obtained in 2519 women. A total of 3034 women contributed to the comparison of taxane-anthracycline combinations versus anthracycline regimens, while 919 were enrolled in trials comparing single agent taxanes to single agent anthracyclines.

The table summarizes the results in terms of "non-response" odds ratios, PFS hazard ratios and OS hazard ratios in the entire group (taxane versus no taxane).

| | Non-response | PFS | OS |
|---|---|---|---|
| Odds/Hazard ratio[a] | 0.73 | 0.98 | 0.97 |
| p-value for test of treatment effect | 0.006 | 0.52 | 0.34 |
| p-value for test of heterogeneity | <0.001 | <0.001 | 0.09 |
| p-value for test of interaction (combination vs. single-agent regimen) | <0.001 | 0.001 | 0.49 |

[a]Odds ratio for Non-response, hazard ratio for PFS and OS.

The analysis of treatment effects in the subgroups with or without visceral disease did not reveal a "subgroup" benefit for either PFS or survival. Tumor response was found to be predictive of longer PFS and longer OS while PFS was poorly correlated with OS. Treatment effects on response did correlate with treatment effects on PFS but not on OS. Finally, treatment effects on PFS were poorly correlated with treatment effects on OS.

**Conclusion:** This metaanalysis of empirical trials conducted in the past century failed to disclose a survival gain associated with the introduction of taxanes in first line chemotherapy regimens for MBC but firmly establishes their contribution to higher chances of response.

Clinical judgment remains the best guide for chemotherapy selection in the advanced disease setting. Tailored trials asking relevant biological questions are the way forward. The results of the current analysis indicate that tumor response could be an acceptable surrogate for PFS but no endpoint would be a good surrogate for OS in these trials.

**435** Invited

**Adjuvant chemotherapy treatment tailoring**

Abstract not received.

**436** Invited

**Herceptin adjuvant trials – 2006 update**

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HER2 overexpressing breast cancers display an aggressive clinical course. Trastuzumab (Herceptin)a recombinant monoclonal antibody against HER2, improves the survival in women with advanced HER2 overexpressing breast cancer. In order to test the hypothesis of whether its use in the adjuvant setting may prolong survival, four large multicenter trials were designed to test the role of trastuzumab as adjuvant therapy after surgical treatment of primary breast cancer. These trials have enrolled over 11,000 patients and their initial results have been recently reported (the HERA trial, the combined analysis of the B-31 and N9831 studies, and the BCIRG006 study) [1–3]. Importantly, these trials had different designs that looked at the trastuzumab question from different angles: The HERA trial was a pure sequential study with trastuzumab given for 1 or 2 years after the chemotherapy of choice; the B-31 and N9831 trials were anthracycline and taxane-based and included one arm with concomitant administration of a taxane and trastuzumab. Finally, the BCIRG study had a non-anthracycline containing arm. With a very brief follow-up (one to two and a half years), all four trials show highly significant reductions in the risk of recurrence. The HERA trial at a one year of follow up shows a 46 percent reduction in risk and an absolute benefit in terms of disease-free survival at 2 years of 8.4%. The trials B-31 and N9831 result in a risk reduction of a breast cancer event at 3 years by 52% and with a longer follow than the HERA trial shows a survival advantage. Finally, the BCIRG at a median follow up of 23 months shows an improvement in disease free survival of 51% in the trastuzumab-anthracycline containing arm and of 39% in the trastuzumab non-anthracycline arm (no statistically significant difference between the 2 trastuzumab containing arms)Unresolved questions remain. What is the optimal schedule for therapy with trastuzumab: should it be given simultaneously with or sequentially after chemotherapy? What is the nature and reversibility of cardiac dysfunction? The data so far provides reassuring information about recovery and symptomatic control of heart failure in the majority of patients, although longer follow up is required. It will also be important to have a longer follow up in the non-anthracycline containing arm in the BCIRG trial. Finally, the adequate duration of trastuzumab administration is still unknown.

In the meantime, the results of the these 4 are sufficiently compelling to consider adjuvant trastuzumab as a standard option at completion of locoregional therapy and (neo) adjuvant chemotherapy for women who fulfil the study eligibility criteria for these trials.

**References**

[1] Piccart-Gebhart, M. J. et al. N Engl J Med 353, 1659–1672 (2005).
[2] Romond, E. H. et al. N Engl J Med 353, 1673–1684 (2005).
[3] Slamon, D. et al. 28th Annual San Antonio Breast Cancer Symposium (2005).

## Friday, 24 March 2006 11:00–12:45

**KEYNOTE SESSION**

# Metastatic breast cancer – are guidelines possible?

**438** Invited

**Consensus on medical treatment of metastatic breast cancer: a Central European initiative**

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Breast cancer is the most common malignancy among women in the Western hemisphere. Whereas a series of consensus statements have established neoadjuvant and adjuvant treatment as state-of-the-art management in early breast cancer, there have been virtually no internationally accepted recommendations on therapy of MBC. Treatment of MBC aims primarily at improving the quality of life by prevention and palliation of symptoms, and at prolongation of survival. Medical treatment of MBC may include endocrine agents, cytotoxic chemotherapy, "targeted therapies", bisphosphonates, and supportive measures. Treatment choices for MBC are guided by several factors, in particular by hormone receptor

and HER-2/neu status, duration of disease-free interval, location of metastases and previous therapy.

The CECOG expert panel included specialists in clinical oncology and translational research from Europe, USA and Australia. Systematic review of the literature on management of MBC was performed and articles or conference abstracts reporting randomized controlled trials with appropriate control groups or meta-analyses were selected for inclusion. Data from phase II clinical trials or retrospective analyses were considered only if there was no evidence from phase III trials. Overall survival was the primary endpoint of interest. Disease-free survival, response rate and treatment toxicity were also considered as secondary outcomes. Evidence-based recommendations for state-of-the-art treatment of MBC were defined depending on clinical and biologic variables. The first consensus on medical treatment of MBC was reached and published in 2003. An updated version of this document, developed in 2005, will be presented at the conference.

### References

[1] Beslija S, et al: Consensus on medical treatment of metastatic breast cancer (statement for Central European Cooperative Oncology Group). Breast Cancer Res Treat 2003, 81(Suppl. 1), S1-S7.

**439** Invited

**Therapeutic management of metastatic breast cancer. Are guidelines (GL) possible?: the French approach**

M. Namer. *Nice-Mougins, France*

Metastatic breast cancer management is a dificult and a complex task.

**Oncologists have to take the following things into account:**

- The component of the adjuvant treatment received and the Disease Free Interval.
- The biological profile of the tumor,
- The location and the number of the metastases
- Symptoms and the threaten on life due to the disease
- The age and the co morbidity of the patients
- The knowledge that these treatments are palliative and not curative.

**Some points are known:**

- The review done by the Cochrane group has shown that polychemotherapy (PCT) is more efficient than monochemotherapy (MCT) in terms of objective remissions, time to progression and overall survival. These results have been found in both situations: drug A versus the same drug plus others and drug A versus a chemotherapy combination excluding the drug A.
- For PCT regimens, concomitant addition of the drugs is not more efficient than the same combination in a sequential way

**However, there are several points which have not been tackled:**

- *The influence of the proliferation rate on the therapeutic choice*. It is widely accepted that a high proliferation rate is associated with a good chemosensitivity of the tumor. We would have liked the Cochrane meta analysis comparison in high and slow proliferative tumor separately. We are tempted to think that for high proliferative tumors concomitant PCT could be more efficient than either MCT or PCT sequentially prescribed.
- *The definition of the chemoresistance*. It is obvious that a recurrence occurring early after the adjuvant chemotherapy could be resistant for the products used during this treatment. However, there are still questions:
- What is the time interval linked with this resistance: 6, 12 or 24 months?
- Does the resistance vary according to the anthracyclin used?
- Does the resistance vary according to the number of cycles done before:

**Are guidelines possible in this setting?** There are two ways of setting up a GL:

- The dogmatic one: several meetings of an expert group has been done last year, ending, with the help of medical literature, to an "evidence based medicine" report. Unfortunately several problems have not been solved yet. Furthermore, there are several parameters, like the patient's preference which are difficult to analyze objectively.
- The pragmatic one: we performed this form of guideline. After designing an algorithm, we have highlighted 8 different situations according to disease free interval, hormone receptor setting and HER2 expression. We have gathered 25 experts and we have set up a vote in order to know their decision for each situation

**Conclusion:** the management of metastatic breast cancer patients is difficult. There are many parameters to consider: some of them are known and others not; some of them are objective and others are subjective. New targeted treatments and new predictive parameters could soon modify our old principles.

We hope that GLs will help us in a near future.

**440** Invited

**Should there be guidelines for the treatment of metastatic breast cancer: the U.S. perspective**

E.P. Winer. *Dana-Farber Cancer Institute and Harvard Medical School, Boston, Massachusetts, USA*

Metastatic breast cancer is a highly heterogeneous clinical entity. A variety of pathologic and clinical factors can explain the variability in patient outcomes. Some of the most important factors include ER, PgR, and HER2 status, disease free interval, site(s) of disease, response to prior therapy, performance status, and presence of co-morbidity. The median overall survival of patients with metastatic breast cancer is in the range of 2–3 years, but it is highly variable and ranges from a matter of weeks to 10 or more years.

As a consequence of the variability in presentation and natural history, it is impossible to identify a single preferred treatment program for all patients with metastatic disease. For that matter, it would be difficult even if one were to consider separately the three major subtypes of breast cancer (HER2 positive, triple negative, and hormone receptor positive). Many treatment decisions for women with metastatic disease will depend on the specific site of disease, the prior treatment and response to prior treatment, and the tempo of the disease.

In general, guidelines for patients with metastatic breast cancer should be based on general principles. For example, guidelines should strongly encourage the use of endocrine therapy in patients with hormone receptor positive disease and the use of trastuzmab in those with HER2 positive disease. Furthermore, guidelines can encourage biopsies to confirm the receptor status of the metastases and suggest imaging studies to evaluate the outcome of treatment. An effective guideline generally should not prescribe specific treatment regimens, since individualization is often necessary both for medical reasons and to optimize quality of life. As the number of biologic therapies increase and the cost of these therapies place a growing strain on the health care system, guidelines surrounding the use of specific agents, such as bevacizumab, may be extremely helpful.

## Friday, 24 March 2006 9:00–10:30

**EUROPA DONNA WORKSHOP**

# Should advocates be involved in the design of clinical trials?

**441** Proffered Paper Oral

**A breast cancer terminology for lay people**

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Many studies show that patients want to get more information about their illness, and to participate in the decision relative to their treatment. Some studies indicate that from 79% to 96% cancer patients prefer to know as much as possible about their illness. Another study showed that only 19% of 232 patients were satisfied with the information they received from their physicians.

The Internet is becoming an important resource for patients seeking health information. Despite the increasing availability of medical information, lay people often encounter barriers in health information seeking. Studies have identified some of these obstacles. The main obstacle being the differences in language use between patients and health professionals.

In order to improve information retrieval for breast cancer patients the TIMC laboratory and CHU of Grenoble collaborated with the French League against Cancer to build a patient oriented terminology. The latter relates every day expressions about breast cancer to technical terms or jargon used by health professionals. It will be used like an interpretative layer to help lay people understand the information retrieved and write accurate queries with the proper concepts and terms.

We used a corpus of texts to extract terms and expressions used by lay people to speak about breast cancer. This corpus was collected from online health information web sites targeted to patients and web-based discussion forums on breast cancer. N-Grams have then been automatically extracted from the corpus (a n-gram is a sequence of n consecutive words). We then analyzed the terms extracted to decide which should be kept in the terminology. Since the terminological properties of patient discourse on medical topics are not well characterized, this work