MOS News

MEDITERRANEAN ONCOLOGY SOCIETY

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Dear Board Members,

In order to increase the collaboration in cancer research among our countries and to strenghten the ties of MOS members, we should find ways for our young researchers to visit the oncology institutes and research labs of our members. EMBO (www.embo.org) –Short Term Fellowships may serve such a purpose. They find research visits of up 3 months to labs in Europe and elsewhere in the world to fascilitate collaboration with research group applying techniques unavailable in their own labs.

Those centers, who have research labs, may introduce and advertise their facilities and ongoing research projects in MOS news. For example, we have a "Cancer Genetic Research Lab" where some MS and PhD students are working and several projects, including one sponsored by 'Turkish Technical and Scientific Research Institution' and titled as 'Mesenchymal Stem Cell Targeted Cancer Gene Therapy', are going on.

I will be waiting for your response and your suggestions related to this, and any other project of scientific collaboration among us.

Best regards,

Prof. Dr. Fikri Icli MOS President, Director
A.U. Cancer Research and Treatment Center

Preliminary Program of the X MOS Conference in Tunis

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News from EBCC-8 Vienna

The magnificent and imperial Vienna hosted from 21 to 24 march the EBCC-8 European Breast Cancer Conference. As part of a biennial series of pioneering meetings, the eighth European Breast Cancer Conference (EBCC-8) was devoted to presenting, educating on, and debating the most up-to-date developments, topics and ideas within the field of breast cancer.

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Expert Opinion

Colorectal Cancer: treatment duration

Enrique Aranda - Medical Oncology Cordoba Uni - Spain

In metastatic colorectal cancer (MCRC) treatment is generally continued until unacceptable toxicity, disease progresión or death. During the last fifteen years a series of clinical trials has considered whether it is possible to stop treatment and introduce chemotherapy-free periods without impact on survival. Continuing chemotherapy during prolonged periods frequently increases toxicity, especially fatigue, hand-foot syndrome and oxaliplatin related neuropathy, all of which can be detrimental to quality of life.

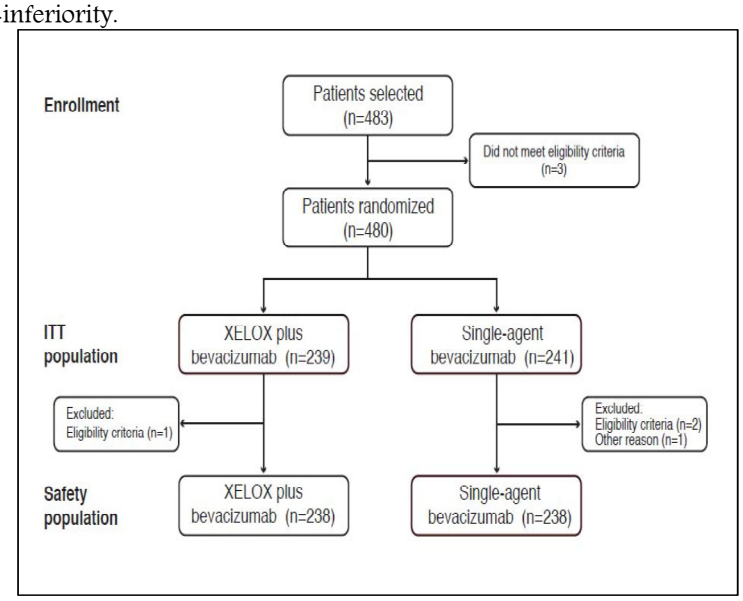
Stop and go.

In the MRC CRO6 trial 354 patients from 42 centres in the United Kingdom were randomized, with stable disease or after 3 months chemotherapy with single agent fluoropyrimidine (De Gramont, Lockich or raltitrexed) to continue with the same treatment or introduce a break, restarting chemotherapy at progression. There was no clear difference respect to overall survival (OS) between the two treatment groups (HR = 0,87 in favour of intermittent treatment; 95% CI, 0,69-1,09; p = 0,23). The patients who received intermittent chemotherapy suffered fewer secondary effects and serious adverse events than those who continued with chemotherapy. Several clinical trials have assessed strategies of intermittent chemotherapy with combination regimens. In the study OPTIMOX 1, patients were assigned to 5-FU plus oxaliplatin (FOLFOX 4: oxaliplatin dose of 85 mg/m2) until progression or intolerance, or FOLFOX 7 with a higher dose of oxaliplatin (130 mg/m2) during six cycles, after which patients with disease response continued with 5FU maintenance and oxaliplatin was reintroduced at disease progression . Differences between the two treatment arms respect to OS were not observed, which indicates that the oxaliplatin-free intervals did not reduce OS. There was a tendency to reduce the rate of serious neuropathy in the intermittent oxaliplatin group (17,9 versus 13,3%; p = 0,12), although a greater difference could have been

[... Page 2 ...]

obtained using FOLFOX 4 regimen in both treatment arms.
Later the OPTIMOX 2 and MRC COIN trials assessed the intermittent treatment without 5FU maintenance. In OPTIMOX 2, all the patients received modified FOLFOX 7 (oxaliplatin dose of 100 mg/m2) and were randomized to maintenance with 5-FU/LV or a treatment-free interval .
The trial was prematurely closed with only 216 patients included. A difference in OS was observed (23,8 versus 19,5 months in favour of continuous treatment), although this was not statistically significant (HR = 0,88; p = 0,42), which indicated that the treatment-free intervals could harm patient prognosis. The MRC COIN offers evidence that suggests that any difference in survival will probably be small and could be compensated by differences in toxicity 63.
In the COIN trial 1.630 patients were randomized to receive chemotherapy with oxaliplatin plus fluoropirimidine (5-FU or capecitabine) until progression or intolerance or intermittent chemotherapy suspending oxaliplatin/fluoropirimidine after twelve weeks of treatment. The principle aim was a predefined non-inferiority boundary of 1.162 (a lower value would indicate inferiority). Median OS was 15,6 months for continuous treatment versus 14,3 months for the intermittent treatment strategy (HR = 1,09). For this reason it was not possible to confirm non-inferiority.

Patients with intermittent chemotherapy received 10 weeks less chemotherapy and developed significantly lower grade 3 or 4 toxicity (hand-foot syndrome 2 versus 4%; p = 0,044) and lower peripheral neuropathy (5 versus 19%; p < 0,001).

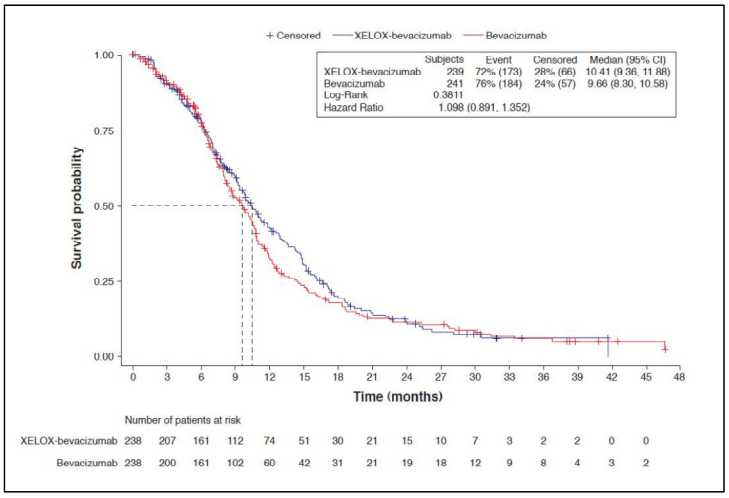


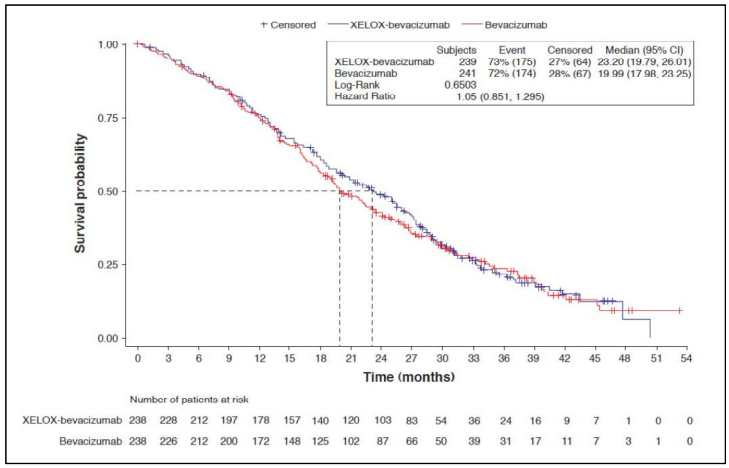
Intermittent (on-off)

Intermittent treatment is another strategy that has been tested in clinical trials.
In a clinical trial with 337 patients, the GISCAD group compared the efficacy of the administration of continuous FOLFIRI with intermittent, both regimens administered until progression. The primary aim was OS, the secondary aims were progression-free interval and toxicity. With a median follow-up of 41 months, no difference in OS was observed (18 versus 17 months), HR of 0,88; similarly, the progression-free interval was comparable in both groups (6 months) with an HR of 1,03. A second line of treatment was administered in both arms in similar percentage (66%). The average break from chemotherapy in the intermittent group was 3,5 months, with no decrease in efficacy in this treatment group and with cost reduction.

Maintenance

Maintenance is a further strategy. One single agent is maintained following the response to treatment after a limited number of cycles (after 3-6 months of treatment). The CONcept65 trial compares the intermittent administration of oxaliplatin versus continuous oxaliplatin with FOLFOX and bevacizumab. Time to progression was 5,6 versus 4,2 months, with a HR of 0,58 (p= 0,025) and a progression free interval of 12 versus 6,6 months, with p = 0,044 in favour of intermittent treatment.
Lastly, in the multicentre trial of the Spanish group TTD MACRO 480 patients were randomized to receive 6 cycles of bevacizumab-XELOX and later maintain the same scheme or bevacizumab alone. The intent-to-treat population comprised 480 patients (XELOXbevacizumab, n=239; bevacizumab, n=241); there were no significant differences in baseline characteristics. Median follow-up was 29.0 months (range 0–53.2). Therewere no statistically significant differences in median PFS (10.4 months with XELOX-bevacizumab vs. 9.7 months with bevacizumab; HR 1.10; 95% CI 0.89-1.35; p=0.38), median OS (23.2 vs. 20.0





months; HR 1.05; 95% CI 0.85–1.30) and RR (47% vs. 49%; OR 0.95; 95% CI 0.66–1.36) between the 2 arms. Most common grade 3/4 toxicities in the XELOX–bevacizumab vs. bevacizumab arms were diarrhea (11% vs. 13%), hand–foot syndrome (13% vs. 7%), and neuropathy (26% vs. 8%).
In Conclusion**,** While non–inferiority of bevacizumab vs. XELOX–bevacizumab cannot be confirmed, we can reliably exclude a median PFS detriment of longer than 3 weeks. This study suggests that maintenance therapy with single–agent bevacizumab may be an appropriate option following induction XELOX bevacizumab in patients with MCRC.

[News from EBCC-8 Vienna] **New combination therapy improves bone health in older patients with breast cancer**
Older women with breast cancer tend to suffer more from bone metastases and osteoporosis as a result of resistances that they develop to hormone therapy.
In the international BOLERO-2 study, which involved experts from the Comprehensive Cancer Centre at the MedUni Vienna and in particular Michael Gnant from the University Department of Surgery, the effectiveness of a therapy has now been proven that counteracts these resistances: the combination of two cancer medications – everolimus and exemestane – significantly improves bone strength and reduces the risk of bony metastases.
“These results are able to set a new standard of treatment for women with advanced breast cancer resistant to hormone therapies,” said Dr M.Gnant
Until now, it was impossible to counteract the resistances that can develop through conventional hormone therapy with aromatase inhibitors such as exemestane. This does occur, however, if conventional hormone therapy is combined with aromatase inhibitors such as exemestane with everolimus.
The study included 724 postmenopausal patients worldwide with an average age of 62. Three bone markers were analysed in one purely exemestane group and in one everolimus plus exemestane group. It became apparent that, in the women who had also been given everolimus, the values of all three bone markers had fallen significantly after six to twelve months.
Everolimus appears to make it harder for metastases to form and grow in the bones, thereby breaking through the resistance, stated Dr. Gnant, The plan in future is therefore to offer all women with hormone-resistant, advanced cancer a new option of also taking everolimus (an mTOR inhibitor with numerous functions involved in regulating cell growth).

Translating study results into practical knowledge enables women to make lifestyle choices to protect their own health.
Breast cancer is the most common cancer in women worldwide. Research has identified multiple risk factors that women are exposed to. These may be divided into those that cannot be modified and those that individuals have the power to change. Diet is a modifiable risk factor, as is life style. There is also an accumulating body of evidence showing that physical activity at any age will have beneficial effects on decreasing the risk for breast cancer and also on increasing survival. A role for diet and life style in cancer etiology can therefore be identified.
The EUROPA DONNA (ED) Teaching Lecture on *Lifestyle Factors and Breast Cancer – Recent Study Results and What they Mean* focused on the latest findings in relation to lifestyle and breast cancer prevention, and provide practical recommendations.
A key issue that concerns many health professionals is how to translate scientific findings for the public. Many oncology professionals and healthcare advocates believe that it is important for women to know that their lifestyle choices strongly influence their breast health. This knowledge empowers women and young girls to identify preventative actions they could take to protect their own health. Over time, this could lead to a reduction in occurrences of breast cancer.
Efforts to spread the news about study results are wide-ranging and include social networking campaigns on Facebook and Twitter as well as establishing a new BHD website in 2010 to reach a wider audience. The 2011 campaign entitled “Make Healthy Choices” reached 11, 470 people on Facebook and 177,990 on twitter; 4,934 visited the BHD website. 75 percent of BHD Facebook fans are under 44 years of age.

Ongoing phase II trial evaluating neoadjuvant anthracycline based regimens followed by a combination of nanoparticle albumin-bound paclitaxel and trastuzumab in patients with operable T1c-3, N0-1, HER2-positive breast cancer.
Anthracycline and taxane have been widely used and studied in neoadjuvant setting for treatment of locally advanced breast cancer. Various regimens have explored the addition of newer agents to determine safety and efficacy. Pathological complete response (pCR) has been demonstrated to be associated with favourable overall survival in primary breast cancer. Notably, three year median follow-up data of the TECHNO Trial revealed that the neoadjuvant combination of trastuzumab and chemotherapy resulted in a high percentage of pCR, and the NOAH trial showed that neoadjuvant trastuzmab should be offered to patients with HER2-positive locally advanced breast cancer alongside neoadjuvant chemotherapy.
In the running phase II trial that is presented by Mitsuhiko Iwamoto from Osaka Medical College (Japan), patients are treated with four cycles of one of the following three regimens: neoadjuvant EC (epirubicin 90 mg/m2, cyclophosphamide 600 mg/m2) or AC (doxorubicin 90 mg/m2, cyclophosphamide 600 mg/m2) or FEC (fluorouracil 500mg/m2, epirubicin 100 mg/m2, cyclophosphamide 500 mg/m2) every 21 days, followed by a combination of nanoparticle albumin-bound paclitaxel (260 mg/m2) and trastuzumab. Patients undergo surgery four to six weeks after completion of chemotherapy. Primary endpoint is pCR, defined as no evidence of invasive tumours in the final surgical sample both in the breast and axillary lymph nodes. Secondary

endpoints include objective clinical response rate, disease-free interval, overall survival, rate of breast-conserving surgery, and safety of the treatment. Five patients have been included since the start of the study. A total of 45 patients will be recruited by the last quarter of 2013.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG) updated results

The EBCTCG was established in 1983-85 as a worldwide collaborative platform that tries to bring together all institutions that run clinical trials in any aspect of the treatment of early breast cancer where the trial endpoints include recurrence and death. "The basic idea was, and still is, to generate reliable data on recurrence and long-term survival by accumulating information from as many clinical trials as possible for as many years as possible. In other words: we try to get the trial evidence straight," says Sir Richard Peto, Professor of Medical Statistics & Epidemiology and co-director of the Clinical Trial Service Unit (CTSU) at the University of Oxford, UK. The EBCTCG reported on in 2011, we were given data on more than 99 percent of all patients ever randomised. For 2012-2015, the EBCTCG hopes to have access to data from one million women who have joined a randomised trial over the past half-century, one-third in treatment trials and two-thirds in screening trials. What researchers get in exchange for sharing their data is the opportunity to discuss the interim analyses and help shape the final reports from the collaborative process. A recent meta-analysis on the long-term effects of various types of adjuvant chemotherapy was published in the Lancet on 4 February 2012 (379:432-444). The Lancet publication included results from 123 randomized trials of various different adjuvant polychemotherapy regimens. It reported moderate effects on 10-year survival from older regimens such as standard CMF or 4AC, and moderately greater effects from more modern anthracycline-based regimens such as CAF or CEF or from taxane-plus anthracycline-based regimens, suggesting that modern regimens can reduce the 10-year risk of death from breast cancer by about one-third. What was controversial was that this one-third reduction in risk seemed to apply to everybody.

Herceptin given by subcutaneous injection offers greater convenience to patients and reduces overall healthcare costs compared to standard IV infusion

Results from the Phase III HannaH study in women with HER2-positive early breast cancer (eBC) showed for the first time that a new way of giving Herceptin (trastuzumab) by subcutaneous (SC) injection leads to comparable efficacy (based on pathological complete response (pCR); complete eradication of the tumour cells in the breast) to the current way of giving the medicine by intravenous (IV) route. Herceptin SC may provide greater convenience to patients versus the traditional IV method due to its lessinvasive administration route and quicker administration time (5 minutes versus 30 - 90 minutes). The HannaH study also demonstrated Herceptin SC had comparable mean concentrations of Herceptin in the blood (pharmacokinetics; PK) versus the IV formulation. The overall safety profile in both arms of the HannaH study was consistent with that expected from treatment with Herceptin and standard chemotherapy in this setting.

Predicting chemotherapy side effects through understanding of individual genetic variation

Dr. Christof Vulsteke, from the Catholic University of Leuven, Belgium illustrated the largest study ever on the effect of genetic variability on the toxicity of chemotherapy in breast cancer showing that it is possible to predict which patients are most likely to suffer serious side effects,).

The researchers examined germline DNA from blood samples of 1089 breast cancer patients who were treated between 2000 and 2010 with three commonly used chemotherapy drugs (fluorouracil, epirubicin and cyclophosphamide). For each patient, the variability in the genes that are important for metabolising these three chemotherapeutic drugs was compared with the side effects experienced. "We found that genetic variation in one gene was highly correlated with chemotherapy side effects," said Dr. Vulsteke. Investigating this gene before starting chemotherapy would allow us to support the patient with either growth factors to increase the patient's immunity, or dose modifications, or a different chemotherapy regimen better adapted to the patient, or a combination of these.

The most important side effects of chemotherapy are mainly caused by immune system depression which can result in potentially life threatening infections. Even though patients may take every precaution to avoid contamination, the vast majority of these infections are caused by naturally occurring microorganisms in the patient's own gastrointestinal tract. Other serious side effects noted in patients receiving chemotherapy are bleeding, severe infection of the mouth mucosa, severe bowel inflammation, nausea, and vomiting with dehydration.

The researchers now intend to look for data from other European countries in order to further validate their results. They will also continue to follow up on their own patients; currently the patients are followed up, on average, for five years.

Francesco Giotta, MD,
Medical Oncology Department
National Cancer Institute – BARI (ITALY)

All members, who want to send their scientific & informative news to be published in this journal, are kindly requested to send their contributions to:

colucci@goim.it

info@organizzazioneagora.it

10th Mediterranean Conference on Oncology

Hotel Ramada Plaza, Cotes de Carthage, Tunis, Tunisia

Improving Clinical Practice in Oncology

President: Hamouda Boussen

Thursday november 8th, 2012

Workshop Joint MOS-AROME-MTCC-STOM
Morning : Epidemiology workshop with MOS epidemiology group and MTCC/AROME

Afternoon : Workshop on medical writing for Mediterranean young oncologists
MOS-AROME-STOM-University of Tunis
Reading and criticizing a medical paper
How to write and publish a paper
Construction of a clinical trial

Friday November 9th, 2012
Morning : Breast cancer
Session 1
Epidemiologic transition
Young women
Inflammatory
Hereditary breast cancer
Coffee-break

Session 2
MRI of breast cancer
Pet-scan in breast cancer
Targeting therapy in breast cancer Ginestier
Lunch

Afternoon
Session 3
Targeted therapy in BC : Molecular basis and perspectives
Radiotherapy modalities after neoadjuvant medical therapy
Breast conservation : Indications and tools
Coffee break
Session 4
Chemotherapy
Hormonotherapy
Personnalized therapy

Saturday November 10th, 2012
Session 5 : Digestive cancers
Targeted therapies in digestive cancers
Surgery innovations in rectal cancer (Robotic, ceolioscopy)
Neoadjuvant therapy in colo-rectal cancer
Coffee-break
Young oncologists oral communications
Lunch
Afternoon
Session 6 : Neurooncology
Histopathology of brain tumors
Glioblastoma
Pediatric brain tumors
Functional surgery in brain tumors
Closing remarks

We program also Posters presentations and some selected oral communications for young oncologists

XI MOS – Conference in Taranto 2013

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Lung Cancer

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adda_doc2000@yahoo.fr
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saverio.cinieri@ieo.it
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chahine_georges@hotmail.com
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fernandodevita@yahoo.it
Di Costanzo Francesco, *Italy*
dicostanzofrancesco@tiscali.it
Dosen Daniel, *Croatia*
danijel.dosen@kbcsm.hr
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h_errihani@yahoo.fr
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Ibrahim Amal Samy, *Egypt*
amalsamyibrahim@yahoo.com
Maiello Evaristo, *Italy*
e.maiello@libero.it
Pizza Carmine, *Italy*
carmine.pizza@virgilio.it
Siala Ismail, *Libya*
isiala@yahoo.com