In the Ovarian Cancer Study Comparing Efficacy and Safety of Chemotherapy and Anti-Angiogenic Therapy in Platinum-Sensitive Recurrent Disease [OCEANS; NCT00434642] trial, patients with platinum-sensitive recurrent ovarian cancer who had not previously received chemotherapy were randomized to either bevacizumab with gemcitabine plus carboplatin, or gemcitabine and carboplatin alone [Aghajanian C et al. *J Clin Oncol* 2012]. Dr. Eisenhauer said that bevacizumab resulted in "a striking PFS increase in this trial."

The AURELIA [NCT00976911] trial, included patients with platinum-resistant ovarian cancer who had received 2 or less prior cancer therapies [Poveda A et al. ESMO 2012. Abstract LBA26]. All patients received 1 of 3 chemotherapy options chosen by the investigator and were randomized to receive either bevacizumab plus chemotherapy or chemotherapy alone. To date, data from this trial have indicated a PFS advantage for bevacizumab regardless of which chemotherapy regimen was chosen.

For all four Phase 3 bevacizumab trials, toxicity was greater in the bevacizumab arms and the cost of bevacizumab is considerable compared with chemotherapy. In addition, although these trials showed an impact of treatment on PFS, no trial has shown significant overall survival data in the analyses performed to date; however, with this observation it must be noted that the overall survival data are not yet mature for any of these trials. The investigators also need to analyze available data to clarify whether delay in progression is associated with freedom from symptoms for patients with ovarian cancer.

Dr. Eisenhauer said that "great progress in completion of Phase 3 trials of angiogenesis inhibitors has been made in ovarian cancer over the past 2 to 3 years," and these trials have shown clear evidence of a biological effect for bevacizumab through improvement in PFS; nonetheless, it will be the final overall survival data that will determine whether bevacizumab is truly paradigm changing for ovarian cancer management. She argued that validated selection biomarkers are urgently needed to identify patient subsets that are truly benefiting from angiogenesis inhibition—this knowledge may reveal those who do experience survival gains and reduce unnecessary treatment of those who do not, improving both therapeutic index and cost-effectiveness. Many of the studies discussed in the presentation included tissue, blood, and other sample collections that may serve as valuable resources for addressing these questions.

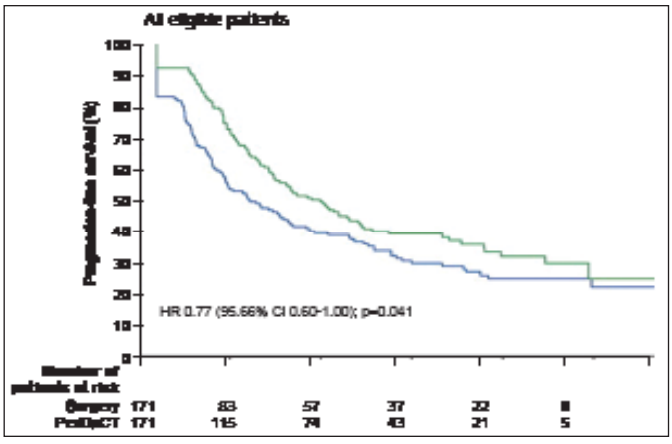
Pursuing the No Evidence of Disease Condition in Advanced Colorectal Cancer

Written by ***Toni Rizzo***

The clinical value of achieving no evidence of disease (NED) in patients with advanced colorectal cancer (CRC) depends on the balance between the duration of the NED state and the toxicity of the treatments to achieve it, particularly with multimodal interventions. Alberto Sobrero, MD, Hospital San Martino, Genova, Italy, discussed the rationale for pursuing the NED state and factors to consider in the decision to pursue this goal.

The chance of achieving NED is marginal with systemic therapy alone but substantial with local approaches. However, local approaches can be toxic and the addition of adjuvant chemotherapy after local treatment is not as effective as it should be. Results of a pooled analysis from two trials of 278 patients with advanced CRC showed that patients treated with surgery and adjuvant 5-fluorouracil (5-FU) chemotherapy had a 7% higher progression-free survival (PFS) rate than those treated with surgery alone (p=0.058) [Mitry E et al. *J Clin Oncol* 2008]. Nordlinger et al. [*Lancet* 2008] reported an 8.1% improvement in PFS at 3 years in patients with advanced CRC treated with surgery and perioperative chemotherapy versus surgery alone (HR, 0.77; 95% CI, 0.60 to 1.00; p=0.041; Figure 1). Another study found no significant difference in disease-free survival between patients treated with 5-FU/folinic acid (LV5FU) alone versus LV5FU plus irinotecan (HR, 0.89; 95% CI, 0.66 to 1.19) [Ychou M et al. ASCO 2008. Abstract LBA4013].

Figure 1. PFS at 3 Years: All Eligible Patients.

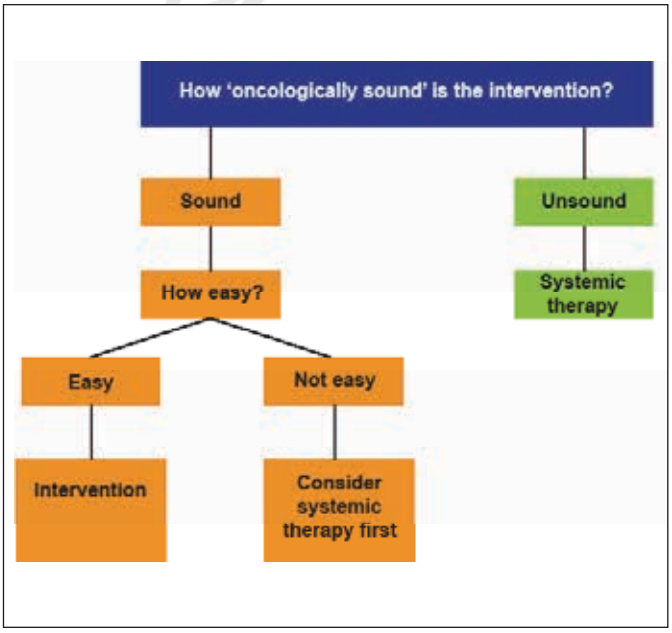


Reprinted from Nordlinger B et al. Perioperative Chemotherapy with FOLFOX4 and Surgery Versus Surgery Alone for Resectable Liver Metastases from Colorectal Cancer (EORTC Intergroup Trial 40983): A Randomised Controlled Trial. *The Lancet*;371(9617):1007-16. Copyright 2008, with permission from Elsevier.

Achieving NED for at least 12 months gives patients hope for a cure, and is considered beneficial and relevant, whereas the value of achieving NED for 6 months is questionable and for <6 months, can be harmful. In a highly selected population of patients treated with surgery for liver metastases, 5- and 10-year survival rates were 40% and 20% for overall survival (OS), and 20% and 10% for relapse-free survival (RFS). Among unselected patients, the actual cure rate ranged from 1% to 4%.

Prof. Sobrero cautioned against using overly aggressive local treatment approaches because of the high rate of failure to achieve a NED state, the typically very short RFS, possible acceleration of the clinical course, treatment complications, and high mortality. Verwaal et al. [*Ann Surg Oncol* 2005] concluded that the key issue in selecting patients for cytoreduction and adjuvant therapy is selecting patients in whom it is feasible to reach complete cytoreduction. Laparotomy to diagnose peritoneal carcinomatosis provides the best information for selecting such candidates. According to Prof. Sobrero, this is an example of a simplified approach that can be generalized and used to determine the chance of achieving relevant NED, by evaluating the "soundness" of an intervention and the ease of performing the intervention (Figure 2).

Figure 2. A Simplified Approach to Determine Chance of Achieving Relevant No Evidence of Disease.



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High originality and relevance coupled with low intrinsic and external validity of the results are the classic features and limits of most trials in this patient population. The main hurdles facing clinical trials in this field are poor feasibility and methodology. Trials must be designed to minimize bias (systematic error) and variability (random error). Bias can be minimized by randomization, treatment masking, eligibility criteria, and intention-to-treat analysis. Variability can be minimized by randomization, the number of patients, target delta, and patient stratification. However, these methods of minimizing bias and variability can be difficult to implement in this field.

Prof. Sobrero concluded that achieving the NED condition in patients with advanced CRC is very relevant. Physicians should not deceive themselves and patients but should, instead, aim for plausible results. The goal includes identifying appropriate patients for this approach, recognizing but not being paralyzed by the limitations of clinical trials in this field, and taking into consideration the toxicities associated with local therapy.

Eliminating Cervical Cancer: Novel Options in Vaccination and Screening

Written by ***Toni Rizzo***

The recognition that cervical cancer is caused by human papillomavirus (HPV) has opened new opportunities for preventing this devastating cancer. Jack Cuzick, PhD, Saint Bartholomew's Medical School, London, United Kingdom, presented evidence for the feasibility of eliminating cervical cancer through combined screening and HPV vaccination.

HPV and Cytology Screening for Cervical Cancer

To detect cervical cancer, European and North American screening studies have suggested primary HPV screening as a better method than traditional cytological methods. In a large pooled analysis which included 60,000 women included, HPV screening was more sensitive than cytology (96.1% vs 53%) in detecting cervical intraepithelial neoplasia grade 2 or greater (CIN2+) but less specific (90.7% vs 96.3%) [Cuzick J et al. *Int J Cancer* 2006]. In a multinational cohort, the cumulative incidence of cervical intraepithelial neoplasia grade 3 or cancer (CIN3+) after 6 years was considerably lower among women negative for HPV at baseline than among women with negative cytology at baseline [Dillner J et al. *BMJ* 2008]. The data support the use of HPV testing as the primary screening test for cervical cancer.

Figure 1 shows a proposed new screening algorithm beginning with HPV testing, followed by cytology screening for those with positive HPV results and