The bevacizumab plus chemotherapy arm was associated with a higher incidence of grade ≥2 peripheral sensory neuropathy and grade ≥3 neutropenia in the paclitaxel cohort, and grade ≥2 hand-foot syndrome and grade ≥3 hypertension in the PLD cohort. Incidence rates of grade ≥3 neutropenia and leucopenia were higher in the chemotherapy-alone arm.

The effects of bevacizumab on PFS within the individual chemotherapy cohorts were consistent with the results in the overall population. Increased chemotherapy exposure associated with prolonged PFS accounted for some increase in cumulative chemotherapy toxicity. However, overall, there was no indication that bevacizumab exacerbates chemotherapy-related adverse events. The authors concluded that bevacizumab plus chemotherapy should be considered a new standard option in platinum-resistant ovarian cancer.

Results and Subgroup Analyses of the PETACC-8 Trial

Written by ***Toni Rizzo***

FOLFOX4 (leucovorin, 5-fluorouracil, and oxaliplatin) has been the standard adjuvant therapy for resected stage III colon cancer since 2004, producing 3-year disease-free survival (DFS) rates of ~70%. The aim of the Combination Chemotherapy with or Without Cetuximab in Treating Patients with Stage III Colon Cancer That Was Completely Removed by Surgery [PETACC-8; NCT00265811] trial presented by Julien Taïeb, MD, PhD, Hôpital Européen Georges Pompidou, Paris, France, was to assess the potential benefit of adding cetuximab to standard treatment for colon cancer.

Patients with fully resected stage III colon cancer were randomized to FOLFOX4 every 2 weeks, with or without cetuximab (initial dose, 400 mg/m^2; 250 mg/m^2 weekly; Days 1 and 8), for 12 cycles. The primary endpoint was DFS in patients with KRAS wild-type (WT) tumors. The secondary endpoints were overall survival (OS), and treatment compliance and toxicity. A preplanned subgroup analysis focused on demographic, oncologic, and molecular data. An interim analysis was planned after 65% of planned events occurred.

At interim analysis, 2559 patients were enrolled, 62.5% of whom had KRAS WT tumors. A total of 1602 patients of these patients were randomized. The median follow-up for DFS was 3.33 years in the FOLFOX4 plus cetuximab arm and 3.30 years in the FOLFOX4 alone arm. Baseline characteristics were similar in both arms.

The 3-year DFS rate was 75.1% with FOLFOX4 plus cetuximab versus 78.0% with FOLFOX4 alone (HR, 1.047; 95% CI, 0.853 to 1.286; p=0.6562). The OS rate was 88.3% with FOLFOX4 plus cetuximab versus 90.5% with FOLFOX4 alone (HR, 1.092; 95% CI, 0.813 to 1.466; p=0.5583). Grade 3/4 adverse events occurred in 80.9% of patients treated with FOLFOX4 plus cetuximab versus 66.2% of those treated with FOLFOX4 alone. Patients with KRAS/BRAF WT tumors treated with FOLFOX4 plus cetuximab (n=492) versus FOLFOX4 alone (n=492) had no significant differences in DFS (115 vs 108 events; HR, 0.985; 95% CI, 0.755 to 1.284; p=0.9117) or OS (55 vs 52 events; HR, 0.981; 95% CI, 0.669 to 1.438; p=0.9236).

Worse DFS outcomes in patients treated with FOLFOX4 plus cetuximab versus FOLFOX4 alone were observed in females (adjusted HR, 1.45; 95% CI, 1.03 to 2.03; p=0.031), patients aged >70 years (adjusted HR, 1.97; 95% CI, 0.99 to 3.93; p=0.051), and patients with right-sided tumors (adjusted HR, 1.40; 95% CI, 1.01 to 1.94; p=0.043). Patients with pT4N2 tumors treated with FOLFOX4 plus cetuximab (n=79) versus FOLFOX4 alone (n=67) had significantly better DFS (32 vs 41 events; HR, 0.555; 95% CI, 0.348 to 0.885; p=0.0122).

Adding cetuximab to FOLFOX4 offered no DFS or OS benefit to patients with resected stage III KRAS WT or KRAS/BRAF WT colon cancer. Subgroup analyses suggested that patients with pT4N2 tumors may benefit from treatment with cetuximab, while females, patients aged >70 years, and patients with right-sided colon cancer may have worse outcomes with cetuximab—results that, according to Prof. Taïeb, suggest stage III and IV colon cancers have a different biology. Microsatellite instability status is being determined to explore interaction with poor outcomes in the 3 latter subgroups.

Single-Agent Doxorubicin Versus Doxorubicin plus Ifosfamide in Advanced Soft Tissue Sarcoma

Written by ***Toni Rizzo***

Patients with locally advanced unresectable or metastatic soft tissue sarcoma have poor outcomes. Palliative chemotherapy is standard treatment for these patients, but it generally results in considerable toxicity. Previous studies have compared single-agent doxorubicin with doxorubicin plus ifosfamide, but the optimal doses remain unclear. The European Organisation for Research and Treatment of Cancer (EORTC) 62012 Phase 3 study [NCT00061984] presented by Winette van der Graaf, MD, PhD, Radboud

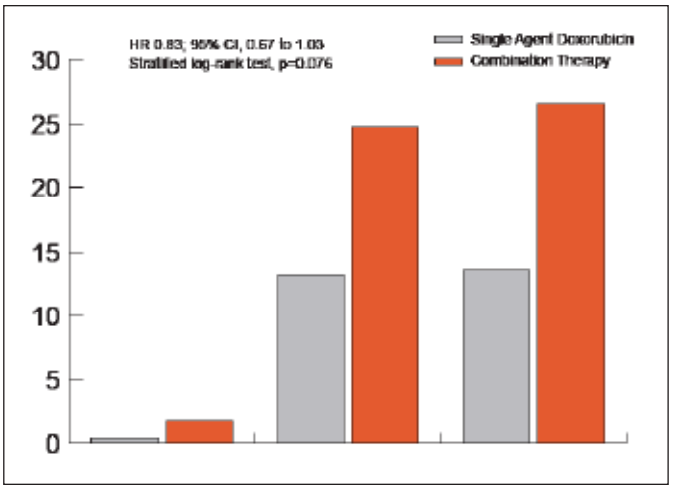
University Nijmegen Medical Center, Nijmegen, Netherlands, compared single-agent doxorubicin (75 mg/m^2) with doxorubicin (75 mg/m^2) plus ifosfamide (7.5 g/m^2) in patients with advanced soft tissue sarcoma (ASTS).

A total of 455 patients with high-grade ASTS were randomized to doxorubicin (n=228) versus doxorubicin plus ifosfamide plus pegfilgrastim (n=227). Patients were stratified according to age, performance status, liver metastases, and histologic grade. The most common histologic diagnoses were liposarcoma, leiomyosarcoma, and synovial sarcoma. The primary endpoint was overall survival (OS). The secondary endpoints were response, toxicity, and treatment-related mortality. The median follow-up was 56 months. An improvement in survival was defined as clinically significant if 1-year survival was at least 10% higher in the combination arm, corresponding with an HR <0.737. Allocated treatment was started by 217 patients in the doxorubicin arm and 215 patients in the combination arm.

There was no significant difference in OS with doxorubicin versus combination treatment (HR, 0.83; 95.5% CI, 0.67 to 1.03; p=0.076; Figure 1). At 1year, OS was 51% in the doxorubicin arm versus 60% in the combination arm. The median OS was 12.8 months with single-agent doxorubicin versus 14.3 months with combination treatment. Progression-free survival (PFS) was significantly better in the combination arm compared with the doxorubicin arm (HR, 0.74; 95% CI, 0.60 to 0.90; p=0.003). The median PFS was 4.6 months with single-agent doxorubicin versus 7.4 months with doxorubicin plus ifosfamide. Patients treated with single-agent doxorubicin versus the combination had a complete response rate of 0.4% versus 1.8%, partial response rate of 13.2% versus 24.7%, and overall response rate of 13.6% versus 26.5%, respectively (Figure 1).

Patients treated with doxorubicin plus ifosfamide versus single-agent doxorubicin had considerably higher rates of grade 3 or higher adverse events, including neutropenia (41.5% vs 37.2%), leukopenia (43.3% vs 17.9%), febrile neutropenia (45.9% vs 13.5%), anemia (34.9% vs 4.6%), and thrombocytopenia (33.5% vs 0.4%), respectively. A total of 121 patients in the doxorubicin arm versus 109 patients in the combination arm discontinued treatment because of progression of disease (PD) or death from PD (41.7% vs 20.7%); toxicity, including toxic death (2.6% vs 17.6%); patient refusal (1.8% vs 4.4%); death not related to malignant disease or toxicity (1.8% vs 0.4%); and other reasons (5.3% vs 4.8%), respectively.

Figure 1. Response Rates with Single Agent Versus Combination Therapy.



Doxo=single-agent doxorubicin; Dxlf=doxorubicin plus ifosfamide.

The combination of doxorubicin and ifosfamide doubled the response rate and significantly improved PFS but did not significantly improve OS in patients with high-grade ASTS. Doxorubicin combined with ifosfamide was considerably more toxic than single-agent doxorubicin. The investigators concluded that single-agent doxorubicin should remain the standard treatment for this population.

The Efficacy and Safety of Docetaxel plus Prednisone with or Without Lenalidomide in Patients with Castrate-Resistant Prostate Cancer: The MAINSAIL Trial

Written by ***Phil Vinall***

Lenalidomide, has been used to treat myeloma and myelodysplastic syndrome. When used in combination with docetaxel and prednisone, or as a single agent, it has been shown to demonstrate activity and tolerability in patients with castrate-resistant prostate cancer (CRPC) [Petrylak DP et al. *J Clin Oncol* 2009]. Daniel P. Petrylak, MD, Yale Cancer Center, New Haven, Connecticut, USA, reported results from the Study to Evaluate Safety and Effectiveness of Lenalidomide in Combination with Docetaxel and Prednisone for Patients with Castrate-Resistant Prostate Cancer [MAINSAIL; NCT00988208] trial, which showed that the addition of lenalidomide to docetaxel and prednisone did not improve overall survival (OS) in CRPC patients and its use was associated with greater toxicity.