improves maintenance PFS, PFS from registration, OS from maintenance, and OS from registration compared with the same induction therapy followed by BEV monotherapy. This effect is independent of the KRAS mutational status; a significant difference in response rate is observed during the chemotherapy-free maintenance therapy in KRAS mutated tumors.

The safety of BEV + ERL is acceptable despite increased incidence of severe skin rash and diarrhea. The survival benefit for BEV + ERL is independent of the subsequent therapy. Anti-EGFR mAb remains active in patients who received prior erlotinib. BEV and a short period of ERL therapy may provide a new treatment option in first-line therapy following induction chemotherapy with BEV for patients with unresectable mCRC.

No Benefit to Adding BEV to Adjuvant CAP in CRC

Written by Lynne Lederman

Although bevacizumab (BEV) has a role in the treatment of colorectal cancer (CRC), it has not been shown to increase the efficacy of doublet chemotherapy in the adjuvant setting. The final results from the Multicentre International Study of Capecitabine ± Bevacizumab as Adjuvant Treatment of Colorectal Cancer [QUASAR 2; ISRCTN45133151], a randomized phase 3 trial that tested capecitabine (CAP) with and without BEV in the adjuvant setting of stage II/III CRC, were presented by Rachel Midgley Kerr, PhD, University of Oxford, Oxford, United Kingdom.

Eligibility criteria included stage III and high-risk stage II CRC after complete resection. The primary end point was 3-year disease-free survival (DFS). Secondary end points included DFS in stage III disease, overall survival (OS), toxicity, and translational analyses. Of 1941 patients recruited, 968 were assigned to CAP and 973 were assigned to CAP + BEV. The demographics appeared balanced across treatment arms, although overall there were more patients with stage II disease (40%) and fewer patients with rectal cancers (12%) than expected.

Toxicities that were significantly higher in the CAP + BEV arm included all grades of hypertension, proteinuria, and epistaxis ($P < .001$ for all), all grades of poor wound healing ($P = .05$), and grade 3/4 hand-foot syndrome ($P = .002$). An excess of possibly treatment-related deaths occurred in the CAP + BEV arm (RR, 2.3; 95% CI, 1.0 to 5.2; $P = .05$), although Prof Kerr suggested that this could be related to the definition of "treatment-related" used in the trial.

There was no difference in 3-year DFS between CAP and CAP + BEV (78.4% vs 75.4%; HR, 1.06; $P = .5$). This was not due to a difference in CAP dose intensity, which was the same in both arms. No DFS advantage for either arm was detected in the analysis of subgroups, including age, disease site, stage, country, and sex. There was no difference in 3-year OS for CAP (89.4%) vs CAP + BEV (87.5%; HR, 1.11; $P = .3$).

A high tumor stroma ratio (TSR) in CRC is predictive of poorer prognosis [Huijbers A et al. *Ann Oncol.* 2013]. The mechanism is not known, but it could be related to upregulated proangiogenic pathways; if so, patients with a high TSR might benefit from therapy with BEV. Tumor DNA was extracted from 1028 formalin-fixed, paraffin-embedded tissue blocks and tested for biomarkers, including chromosomal instability positivity, and KRAS, BRAF, and POLE mutations. None of these were prognostic or predictive. TSR by immunohistochemistry was high at 33%, as previously reported.

Microsatellite instability (MSI) positivity was 14% (n = 135). MSI status had no effect on DFS for treatment arms combined. For patients with microsatellite stability (MSS; n = 840), CAP was associated with significantly longer DFS vs CAP + BEV (HR, 1.43; 95% CI, 1.12 to 1.84; $P = .005$). For patients with MSI, there was no difference in DFS between treatment arms.

Patients with low TSR had a significantly longer 3-year DFS (HR, 1.58; 95% CI, 1.22 to 2.05; $P = .001$ for treatment groups combined). However, there were no differences in DFS between treatment arms when analyzed by TSR.

The results of this study indicated that there is no role for BEV in combination with CAP in the adjuvant treatment of CRC in the general patient population or in any identifiable patient subgroup. In fact, the addition of BEV to CAP monotherapy worsens prognosis for patients with MSS. Although the study confirmed that TSR has prognostic value, it is not related to response to BEV.

Neoadjuvant B and N Safe and Effective With D and H in HER2-Positive Breast Cancer

Written by Nicola Parry

Günther Steger, MD, Medical University of Vienna, Vienna, Austria, presented data from a study demonstrating that neoadjuvant docetaxel (D) plus trastuzumab (H), DH plus bevacizumab (B; DHB), DH plus nonpegylated liposomal doxorubicin (N; DHN), and DHNB treatment regimens are feasible and can be safely administered to patients with early HER2-positive breast cancer.

According to Prof Steger, neoadjuvant treatment regimens resulting in high pathologic complete response (pCR) rates are needed for patients with HER2-positive breast cancer because they are correlated with favorable prognoses. Although N in combination with H is highly effective in HER2-positive breast cancer, this regimen is unsuitable because of high cardiotoxicity. HER2-positive breast cancer cells have, however, been shown to produce high levels of vascular endothelial growth factor, he added.

Consequently, the Phase 2 Study of Neoadjuvant Trastuzumab + Docetaxel + Non-pegylated Liposome-Encapsulated Doxorubicin (NPLD) ± Bevacizumab in HER2-Positive Early Breast Cancer [ABCSG-32; NCT01367028] was conducted to evaluate the cardiotoxicity and efficacy of N and B in combination with DH in the neoadjuvant treatment of early HER2-positive breast cancer.

Inclusion criteria included patients ≥ 18 years with (1) pathologically confirmed invasive primary breast adenocarcinoma, with or without palpable lymph nodes, who were scheduled for taxane-containing neoadjuvant systemic therapy and (2) HER2 protein overexpression as determined by immunohistochemistry 3 + or by *HER2* (c-erbB2) gene amplification according to fluorescent in situ hybridization or chromogenic in situ hybridization of the primary tumor. Exclusion criteria included patients with metastatic disease, HER2-negative disease, or a history of prior local or systemic antitumor therapy.

This open-label phase 2 trial enrolled 100 patients with biopsy-proven, invasive, early HER2-positive breast cancer who were randomized to 6 cycles (every 21 days) of the following:

DH: D (100 mg/m^2) + H (8/6 mg/kg; n = 25)
DHB: DH + B (15 mg/kg; n = 25)
DHN: D (75 mg/m^2) + H + N (50 mg/m^2; n = 26)
DHNB: D (75 mg/m^2) + H + N + B (15 mg/m^2; n = 24)

All patients received pegfilgrastim (6 mg, subcutaneously) on day 2.

Cardiotoxicity was low in all 4 regimens, with only 3 cardiac toxicity events documented (DH, n = 0; DHB, DHN, and DHNB, all n = 1). A cardiac toxicity event was defined as the occurrence of symptomatic left ventricular dysfunction, NYHA class 2 to 4; an asymptomatic drop of ejection fraction > 15% from baseline or < 50%; or the appearance of significant arrhythmias requiring treatment.

Although noncardiac toxicity was also acceptable, it was more pronounced in patients receiving the 3- and 4-drug combinations (Table 1).

All 4 regimens were highly effective. The overall pCR rate was 52%, with 63% and 62% of patients experiencing pCR in the DHN and DHNB regimens, respectively. The total pCR rate was also highest after DHN (58%) and DHNB (57%).

Table 1. Noncardiac Toxicity of the 4 Neoadjuvant Regimens, No.

	All	DH	DHB	DHN	DHNB
Patients	100	25	25	26	24
Events					
Serious adverse	50	8	12	14	16
Significant safety	114	23	31	29	31

B, bevacizumab; D, docetaxel; H, trastuzumab; N, nonpegylated liposomal doxorubicin.
Reproduced with permission from G Steger, MD.

Prof Steger concluded that neoadjuvant DH, DHB, DHN, and DHNB can be safely administered to patients with HER2-positive early breast cancer. He emphasized, however, that although noncardiac toxicity is acceptable, its increase with the 3- and 4-drug combinations may lead to early treatment termination in some patients.

Interim Safety Analysis of nP in High-Risk Early Breast Cancer

Written by Nicola Parry

Stefanie Noeding, MD, Gynecologic-Oncology Practice, Hannover, Germany, presented data from the first interim safety analysis of the Study of Nab-Paclitaxel in High-Risk Early Breast Cancer [GAIN2; NCT01690702], demonstrating acceptable initial toxicity profiles.

According to Dr Noeding, owing to acute and cumulative toxicities, combination chemotherapy requires compromises in drug dosage and treatment intervals. The sequential use of monotherapies, however, allows for the use of high doses of single agents and dose-dense treatment intervals, and such regimens have been very effective in cases of early breast cancer with high risk of recurrence [Moebus V et al. *J Clin Oncol.* 2010].

Compared with the solvent-based taxanes, paclitaxel and docetaxel, nab-paclitaxel (nP) provides a more favorable toxicity profile and a higher efficacy and might therefore be preferable in an intense dose-dense regimen [Ibrahim NK et al. *J Clin Oncol.* 2005].

Consequently, the GAIN2 study was an adjuvant phase 3 trial in patients with high-risk early breast cancer that was designed to compare a predefined intense dose-dense adjuvant treatment (epirubicin followed by nP followed by cyclophosphamide [ddEnPC]) with a dose-dense tailored therapy. In the study, single doses