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Title: Long-term follow-up of CALGB 40502/NCCTG N063H (Alliance): A randomized phase III trial of weekly paclitaxel (P) compared to weekly nanoparticle albumin bound nab-Paclitaxel (NP) or ixabepilone (Ix) +/- bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer (MBC)

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Body: Background: CALGB 40502/NCCTG N063H (Alliance) compared weekly NP or Ix to P; most patients received bevacizumab. Ix was inferior to P, and NP was not superior with a trend toward inferiority. Toxicity was increased in the experimental arms compared to P (Rugo et al, JCO 2015). We report long-term follow-up (FU) of this trial with an unplanned subset analysis in hormone receptor positive (HR+) and triple negative (TNBC) breast cancer.
Methods: Patients were randomized 1:1:1 to receive P (90 mg/m^2), Ix (16 mg/m^2) or NP (150 mg/m^2) on a 3 week (wk) on, 1 wk off schedule, stratified by prior adjuvant taxane use and hormone receptor status. B was initially given to all patients, but became optional in 3/2011 and was added to stratification. The primary endpoint was progression-free survival (PFS); secondary endpoints included safety and overall survival (OS). With a target N=900 patients, the study was powered to detect a hazard ratio of 1.36 (median PFS 10 vs 13.6 months). Eligibility included no prior chemotherapy for MBC, ≥12 mo from adjuvant P and measurable disease.
Results: 799 patients were randomized between 11/08 and11/11 (283 to P, 271 to NP, 245 to Ix); 98% received bevacizumab. 68% (546) had HR+ disease, 25% (201) had TNBC. Median FU is 5 years. Median PFS is unchanged at 10.8, 9.2 and 7.4 mo for P, NP and Ix with hazard ratios (95% CIs) of 1.13 (0.94-1.34) and 1.44 (1.2-1.72) for NP and Ix to P, respectively. Median OS was 27.1, 24.2 and 23.6 months for P, NP and Ix with hazard ratios of 1.10 (0.91-1.34) and 1.3 (1.07-1.57) for NP and Ix to P, respectively. The effects of NP vs P on PFS and OS were significantly modified by subtype (interaction p=0.0018 and 0.0073), whereas Ix vs P was unchanged (interaction p's > 0.9, Table). More patients discontinued treatment due to adverse events in the experimental arms (14 vs 27 vs 23% for P, NP and Ix).

Table

	P (mo)	NP (mo)	NP to P; HR (95% CI)	Ix (mo)	Ix to P, HR (95% CI)
TNBC, PFS	6.4	7.4	0.79 (0.55-1.12)[1]	5.6	1.39 (0.99-1.96)[3]
HR+, PFS	**12.2**	9.6	1.29 (1.04-1.59)[1]	8	1.5 (1.21-1.86)[3]
TNBC, OS	15.3	**21**	**0.74 (0.51-1.07)[2]**	15.1	1.28(0.9-1.82)[4]
HR+, OS	33.2	26.6	1.25 (0.99-1.58)[2]	25.4	1.35(1.07-1.71[4]

Interaction tests: 1. p=0.0018; 2. p=0.0073; 3. p=0.96; 4. p=0.92 mo: months; HR: hazard ratio··

Conclusion: In patients with chemotherapy-naive MBC, Ix was inferior to P for PFS, and P was better tolerated than either NP or Ix. In this retrospective subset analysis, Ix and NP were inferior to P in HR+ disease, with a suggestion of improved PFS and OS with NP in patients with TNBC. Further investigation is required to explain and validate the subtype specificity seen in this exploratory analysis.
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