



Submitted by:
Albert Kodersha, Pharm.D.
Celgene Corporation
86 Morris Avenue
Summit, NJ 07901
Ph: 908-673-1653
Email: akodersha@celgene.com
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NCCN Guidelines Panel: Breast Cancer

Dear NCCN Breast Cancer Guidelines Panel:

On behalf of Celgene Corporation, we respectfully request the NCCN Breast Cancer Guidelines Panel review the following recently presented data regarding the use of Abraxane® (albumin-bound paclitaxel) in combination with carboplatin for the first-line treatment of triple-negative metastatic breast cancer (TNMBC).

Specific Changes:

Recommend the use of albumin-bound paclitaxel in combination with carboplatin for recurrent or metastatic breast cancer, with a Category 2A recommendation, based on results from the Phase II, randomized tnAcity trial in patients with TNMBC

FDA Clearance:

Abraxane is not approved in combination with carboplatin for the first-line treatment of metastatic breast cancer. Please refer to the enclosed prescribing information for the FDA-approved indications and safety information.

Rationale for Suggested Change:

The tnAcity trial was a multicenter, randomized, Phase II study (N=191) that compared three doublet combination regimens in patients with TNMBC as first-line therapy (Yardley et al., 2016):

- albumin-bound paclitaxel 125 mg/m² + carboplatin AUC2 on days 1 and 8 of a 21-day cycle
- albumin-bound paclitaxel 125 mg/m² + gemcitabine 1000 mg/m² on days 1 and 8 of a 21-day cycle
- gemcitabine 1000 mg/m² + carboplatin AUC2 on days 1 and 8 of a 21-day cycle

The primary endpoint was investigator-assessed progression free survival (PFS). Secondary endpoints included investigator-assessed overall response rate (ORR), overall survival (OS), the percentage of patients who initiated cycle 6 receiving doublet combination therapy, and safety. The median age was 53 to 59 years, and the percentage of patients who had received prior neoadjuvant/adjuvant taxane therapy \geq 12 months prior to study start ranged from 56-67%. Median PFS was significantly longer with albumin-bound paclitaxel + carboplatin (7.4 months) vs. albumin-bound paclitaxel + gemcitabine (5.4 months; $P=0.02$) or gemcitabine + carboplatin (6.0 months; $P=0.03$). The median treatment durations were 25, 18.1, and 20.1 weeks, respectively. While not powered for OS as a secondary endpoint, median OS was numerically, but not significantly, improved with albumin-bound paclitaxel + carboplatin vs. the comparator doublet regimens (16.4 months vs. 12.1 and 12.6 months, respectively). ORR for the albumin-bound paclitaxel + carboplatin arm vs comparator doublet regimens was 72% vs. 39% vs. 44%, respectively.

Fewer Grade \geq 3 AEs of neutropenia (42% vs. 52%), anemia (13% vs. 27%), and thrombocytopenia (9% vs. 28%) were reported in the albumin-bound paclitaxel + carboplatin arm as compared with gemcitabine + carboplatin, although no statistical testing was performed. The rate of discontinuation due to a treatment-emergent AE was 45%, 25%, and 25% for albumin-bound paclitaxel + carboplatin, albumin-bound paclitaxel + gemcitabine, and gemcitabine + carboplatin, respectively.

Please refer to the enclosed poster regarding the tnAcity trial by Yardley et al. 2016 for full study design and results. Additional references containing clinical evidence of albumin-bound paclitaxel in various combinations for the first-

line treatment of TNMBC (Rugo et al., 2015) (Hamilton et al., 2013) (Lobo et al., 2010) (Roy et al., 2009) have also been enclosed for your reference. Your consideration of this submission is greatly appreciated.

Sincerely,



Albert Kodersha, Pharm.D.
Senior Manager, Medical Information Oncology



Francois LaFleur, MPH
Executive Director, US Medical Affairs Oncology

Reference List

1. Hamilton E, Kimmick G, Hopkins J, et al. Nab-paclitaxel/bevacizumab/carboplatin chemotherapy in first-line triple negative metastatic breast cancer. *Clin Breast Cancer*. 2013;13(6):416-20. <http://www.ncbi.nlm.nih.gov/pubmed/24099649>.
2. Lobo C, Lopes G, Baez O, et al. Final results of a phase II study of nab-paclitaxel, bevacizumab, and gemcitabine as first-line therapy for patients with HER2-negative metastatic breast cancer. *Breast Cancer Res Treat*. 2010;123(2):427-35. <http://www.ncbi.nlm.nih.gov/pubmed/20585851>.
3. Roy V, LaPlant BR, Gross GG, Bane CL, Palmieri FM. Phase II trial of weekly nab (nanoparticle albumin-bound)-paclitaxel (nab-paclitaxel) (Abraxane) in combination with gemcitabine in patients with metastatic breast cancer (N0531). *Ann Oncol*. 2009;20(3):449-53. <http://www.ncbi.nlm.nih.gov/pubmed/19087987>.
4. Rugo HS, Barry WT, Moreno-Aspitia A, et al. Randomized Phase III Trial of Paclitaxel Once Per Week Compared With Nanoparticle Albumin-Bound Nab-Paclitaxel Once Per Week or Ixabepilone With Bevacizumab As First-Line Chemotherapy for Locally Recurrent or Metastatic Breast Cancer: CALGB 40502/NCCTG N063H (Alliance). *J Clin Oncol*. 2015;33(21):2361-9. <http://www.ncbi.nlm.nih.gov/pubmed/26056183>.
5. Yardley D, Coleman R, Conte P, et al. nab-Paclitaxel + Carboplatin or Gemcitabine vs Gemcitabine + Carboplatin as First-Line Treatment for Patients With Triple-Negative Metastatic Breast Cancer: Results From the Randomized Phase II Portion of the tnAcity Trial [Poster]. Poster presented at: 39th Annual CTRC-AACR San Antonio Breast Cancer Symposium (SABCS); December 6-10, 2016; San Antonio, TX, USA.