Dear NCCN Breast Cancer Guidelines Panel:

On behalf of Celgene Corporation, we request the NCCN Breast Cancer Guidelines Panel review the following recently presented and published data regarding the use of Abraxane® (albumin-bound paclitaxel) for the treatment of breast cancer in the neoadjuvant setting.

Specific Changes:
We respectfully request the Panel’s consideration for an update to the current Guidelines surrounding Preoperative/Adjuvant Therapy for breast cancer to include albumin-bound paclitaxel as a neoadjuvant induction regimen prior to consolidation at a dose of 125 mg/m² dosed weekly for 12 consecutive weeks to reflect recently published results from two Phase III studies in early breast cancer: the GeparSepto trial and the ETNA trial.

FDA Clearance:
Abraxane is not approved for neoadjuvant treatment of early breast cancer. Please refer to the enclosed prescribing information for the FDA-approved indications and safety information (Celgene Corporation, 2015).

Rationale for Suggested Change:
The GeparSepto trial was a German multicenter, randomized Phase III study that compared weekly dosing of albumin-bound paclitaxel to solvent-based paclitaxel 80 mg/m² for 12 consecutive weeks, both followed by 12 consecutive weeks of q3w EC (with trastuzumab and pertuzumab administered only to HER2+ patients) as neoadjuvant treatment in patients with breast cancer (N=1206). An interim safety analysis of 60 patients revealed that more dose reductions and discontinuations were observed in the albumin-bound paclitaxel arm, requiring a protocol amendment to reduce the albumin-bound paclitaxel dose from 150 mg/m² to 125 mg/m². At baseline, 29% were cT1, 56% were cT2, and 16% were cT3 or cT4 in the albumin-bound paclitaxel arm.

The rate of pCR (ypT0 ypN0) was significantly improved in the albumin-bound paclitaxel arm (both doses) compared with solvent-based paclitaxel (38.4% vs. 29.0%, respectively; \( P=0.0065 \)) (Untch et al., 2016) and still significantly improved with the reduced 125 mg/m² dose (41.4% vs. 32.4%, respectively; \( P=0.013 \)) (Von Minckwitz et al., 2015). There were also significant improvements in pCR in the subgroups of patients with TNBC (48.2% vs. 26.3%, respectively; \( P=0.0027 \)) and HER2-negative disease (27.0% vs. 16.9%, respectively; \( P=0.007 \)) (Untch, 2016). The rates of Grade \( \geq 3 \) peripheral neuropathy for albumin-bound paclitaxel 150 mg/m², albumin-bound paclitaxel 125 mg/m², and solvent-based paclitaxel 80 mg/m² were 14.5%, 8.1%, and 2.7%, respectively.

The second study, orally presented at the 2016 ASCO Annual Meeting, was the ETNA trial, which also compared albumin-bound paclitaxel (125 mg/m²) to solvent-based paclitaxel (90 mg/m²), but both arms were administered as intermittent weekly dosing (3 weeks on, 1 week off), followed by AC, EC, or FEC in the neoadjuvant setting (Gianni et al., 2016). The primary endpoint of this randomized, phase III (N=695) study, which only enrolled patients with HER2-negative breast cancer and required a clinical tumor stage of at least cT2, was to determine at least a 10% pCR rate difference between both arms. The trial had a planned dose intensity that was lower than that of the GeparSepto study (92.5 mg/m² per week for albumin-bound paclitaxel and 72.5 mg/m² for solvent-based...
paclitaxel for ETNA vs. 125 mg/m² per week and 80 mg/m² for GeparSepto, respectively). Although the primary endpoint of the ETNA trial was not met for pCR (ypT0/is ypN0), it was improved with albumin-bound paclitaxel compared with solvent-based paclitaxel (22.5% vs. 18.6%; \( P = .1858 \)). The rate of Grade \( \geq 3 \) peripheral neuropathy was 4.5% for albumin-bound paclitaxel and 1.8% for solvent-based paclitaxel.

Together, these phase III studies evaluated three different dosing intensities for albumin-bound paclitaxel (150 mg/m² weekly, 125 mg/m² weekly, and 125 mg/m² weekly for 3 out of 4 weeks) in a diverse range of early breast cancer subgroups of patients. Given these data, we request the Panel to include albumin-bound paclitaxel as a neoadjuvant induction regimen prior to consolidation at a dose of 125 mg/m² dosed weekly for 12 consecutive weeks.

The GeparSepto (Untch et al., 2016) (Von Minckwitz et al., 2015) and ETNA (Gianni et al., 2016) studies are enclosed for your review (see Enclosure A). Several additional studies previously conducted to assess the efficacy and/or safety of albumin-bound paclitaxel in the neoadjuvant and adjuvant breast cancer settings have also been enclosed for completeness of the Panel’s review (see Enclosure B). Your consideration of this submission is greatly appreciated.

Sincerely,

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List of Abbreviations:
AC: doxorubicin and cyclophosphamide, cT: Clinical Tumor Stage, EC: epirubicin and cyclophosphamide, FEC: 5-fluorouracil, epirubicin, and cyclophosphamide, pCR: pathologic complete response

Cited References:
5. Von Minckwitz G, Untch M, Jakisch C, et al. nab-Paclitaxel at a dose of 125 mg/m² weekly is equally efficacious but less toxic than at 150 mg/m² - Results from the neoadjuvant randomized GeparSepto study (GBG 69) [Poster]. Poster presented at: 38th Annual CTRC-AACR San Antonio Breast Cancer Symposium (SABCS); December 8-12, 2015; San Antonio, TX, USA.