

POLICY: Oncology - Abraxane® (paclitaxel albumin-bound for injectable suspension – Celgene Corporation)

APPROVAL DATE: 11/06/2019

OVERVIEW

Abraxane is indicated for the following uses:¹

- 1) Breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline (unless contraindicated); AND
- 2) Non-small cell lung cancer (NSCLC) in combination with carboplatin injection for the first-line treatment of locally advanced or metastatic disease in patients who are not candidates for curative surgery or radiation therapy; AND
- 3) Adenocarcinoma of the pancreas in combination with gemcitabine injection for the first-line treatment of patients with metastatic disease.

Premedication to prevent hypersensitivity reactions is generally not needed before giving Abraxane.

Abraxane, a microtubule inhibitor, is an albumin-bound form of paclitaxel.¹ This formulation of paclitaxel uses nanotechnology to combine human albumin with paclitaxel allowing for the delivery of insoluble paclitaxel in the form of nanoparticles.

Abraxane is available as a lyophilized powder in single-use vials containing 100 mg of paclitaxel bound to approximately 900 mg of human albumin.¹ Abraxane must be reconstituted with 20 mL of 0.9% sodium chloride injection before use. The final solution will contain 5 mg of paclitaxel per mL. The appropriate amount of reconstituted Abraxane is injected into an empty, sterile intravenous bag and administered as a 30-minute intravenous infusion.

GUIDELINES

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines on breast cancer (version 3.2019 – September 6, 2019) recommend Abraxane in combination with Tecentriq (atezolizumab for injection) as one of the preferred regimens for HER2-negative recurrent or metastatic disease (category 2A). It is specifically listed as an option for patients with PD-L1 positive triple-negative breast cancer. Abraxane, as a single agent, is also listed under “other recommended regimens”. It is noted that Abraxane may be substituted for paclitaxel or docetaxel due to medical necessity (i.e., hypersensitivity reaction). Paclitaxel or docetaxel are recommended in many preoperative/adjuvant therapy regimens for HER2-negative or -positive disease and in chemotherapy regimens for recurrent or metastatic breast cancer.

The NCCN clinical practice guidelines on NSCLC (version 1.2020 – November 6, 2019) recommend Abraxane for treatment of recurrence or metastasis of adenocarcinoma (with mixed subtypes), squamous cell carcinoma, or large cell carcinoma as a single-agent or in combination with carboplatin for the following uses:^{3,7}

- first-line therapy for *EGFR*, *ALK*, *ROS1*, and PD-L1 negative or unknown;
- first-line or subsequent therapy for *BRAF V600E*-mutation positive or neurotrophic tyrosine receptor kinase (NTRK) gene fusion-positive tumors;
- subsequent therapy for sensitizing *EGFR* mutation-positive tumors after targeted therapy;
- subsequent therapy for *ROS1* rearrangement-positive tumors and prior Xalkori therapy;
- subsequent therapy for PD-L1 expression-positive ($\geq 50\%$) and *EGFR*, *ALK*, *ROS1* and *BRAF* negative or unknown and prior Keytruda therapy.

The NCCN clinical practice guidelines on pancreatic adenocarcinoma (version 3.2019 – July 2, 2019) recommend therapy with Abraxane for the following uses:⁹

- Neoadjuvant therapy in combination with gemcitabine with or without subsequent chemoradiation [category 2A];
- In combination with gemcitabine as first-line chemotherapy, or as induction therapy followed by chemoradiation in selected patients without systemic metastases, for patients with locally advanced unresectable disease and good performance status (category 2A);
- Preferred first-line therapy for metastatic disease in patients with good performance status (Karnofsky Performance Scale [KPS] ≥ 70) in combination with gemcitabine (category 1);
- Second-line therapy in combination with gemcitabine for locally advanced unresectable or metastatic disease as gemcitabine-based therapy (category 2A);
- Second-line therapy for recurrence after resection in combination with gemcitabine for local recurrence in the pancreatic bed OR for metastatic disease with or without local recurrence (category 2A).

The NCCN clinical practice guidelines on melanoma (version 3.2019 – October 22, 2019) recommend Abraxane for metastatic or unresectable disease as second-line or subsequent therapy for disease progression or after maximum benefit from *BRAF*-targeted therapy for patients with PS 0 to 2.¹¹

The NCCN clinical practice guidelines on ovarian cancer (version 2.2019 – September 17, 2019) recommend Abraxane as therapy for persistent disease or recurrence as preferred therapy, 1) if platinum sensitive, in combination with carboplatin, for patients with confirmed taxane hypersensitivity or 2) as a single agent (category 2A).¹⁷ For platinum-sensitive disease, carboplatin plus Doxil® (doxorubicin liposome injection for intravenous use) and carboplatin plus paclitaxel are preferred agents (category 1 recommendations). The NCCN panel, in general, recommends combination platinum-based regimens for platinum-sensitive recurrent disease, especially in first relapses. Single-agent therapy with Abraxane is included as a potentially active agent.

The NCCN guidelines for uveal melanoma (version 1.2019) recommends Abraxane as a single agent option for metastatic or unresectable disease.²² The NCCN guidelines for uterine neoplasms (endometrial carcinoma) [version 4.2019] recommends Abraxane as a single agent option for metastatic, recurrent, or high-risk disease.²³ The NCCN clinical practice guidelines on bladder cancer (version 5.2018) recommend Abraxane as a single agent for urothelial carcinoma of the bladder in various clinical stages or for recurrence post cystectomy or for metastatic disease subsequent systemic therapy as an alternate regimen for select patients.²⁰ The NCCN guidelines for small bowel adenocarcinoma (version 1.2020) recommends use of Abraxane as initial or subsequent therapy. For subsequent therapy it can be used in metastatic disease that is microsatellite stable or proficient mismatch repair (MSS or pMMR) OR in disease with deficient MMR/microsatellite instability-high (MSI-H). The NCCN guidelines for hepatobiliary cancers (version 3.2019) also recommend Abraxane for intra- or extrahepatic cholangiocarcinoma (category 2A) in combination with gemcitabine.

POLICY STATEMENT

This policy involves the use of Abraxane. Prior authorization is recommended for medical benefit coverage of Abraxane. Approval is recommended for those who meet the conditions of coverage for **Criteria and Dosing**. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration listed below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Abraxane as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Abraxane to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Abraxane is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Breast Cancer.** Approve for 1 year if the patient must meet the following criteria (A AND B):
 - A) Abraxane is prescribed by or in consultation with an oncologist; AND
 - B) The patient meets ONE of the following criteria (i or ii):
 - i. The patient has recurrent or metastatic breast cancer and ONE of the following applies (a, b, or c);²
 - a) The patient has human epidermal growth factor receptor 2 (HER2)-negative disease; OR
 - b) The patient has programmed death ligand-1 (PD-L1)-positive, triple-negative breast cancer and medication will be used in combination with Tecentriq (atezolizumab for injection); OR
 - c) The patient has human epidermal growth factor receptor 2 (HER2)-positive disease and Abraxane will be used in combination with trastuzumab; OR
 - ii. The patient meets both of the following criteria (a and b):²
 - a) The patient has had a hypersensitivity reaction to paclitaxel or docetaxel; AND
 - b) Abraxane will be used for human epidermal growth factor receptor 2 (HER2)-negative disease OR for HER2-positive disease in combination with trastuzumab.

Dosing. Approve ONE of the following (A OR B):

- A) 260 mg per m² administered as an intravenous infusion not more frequently than once every 3 weeks.^{1,2,4}
- B) 100 mg per m², 125 mg per m², or 150 mg per m² administered as an intravenous infusion on Days 1, 8 and 15, every 28 days.^{5,6,15}

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2. **Non-Small Cell Lung Cancer (NSCLC).** Approve for 1 year if the patient meets the following criteria (A, B, AND C):^{1,7}
 - A) Abraxane is prescribed by or in consultation with an oncologist; AND
 - B) The patient has recurrent or metastatic non-small cell lung cancer (NSCLC); AND
 - C) The patient has one of the following histologic subtypes of NSCLC (i or ii):
 - i. Non-squamous cell carcinoma (that is, adenocarcinoma, large cell, or NSCLC not otherwise specified) AND the following conditions are met (a, b, or c):
 - a) If the NSCLC tumor is positive for any of the targetable mutations (e.g., epidermal growth factor receptor [*EGFR*] mutation, anaplastic lymphoma kinase [*ALK*] fusions, ROS proto-oncogene 1 [*ROS1*]), at least one of the specific targeted therapy options have been tried and Abraxane is used as subsequent therapy; OR

- b) If the NSCLC tumor is *BRAF V600E* mutation-positive or neurotrophic tyrosine receptor kinase (*NTRK*) gene-fusion positive, Abraxane is used as either first-line or subsequent therapy; OR
- c) The NSCLC tumor is negative or unknown for targetable mutations (e.g., *EGFR*, *ALK*, *ROS1*, *BRAF*) and Abraxane is used as initial therapy either as a single agent or in combination with platinum chemotherapy (cisplatin or carboplatin) with or without an immune checkpoint inhibitor (e.g., Keytruda [pembrolizumab intravenous injection], Tecentriq [atezolizumab intravenous injection]); OR
- ii. Squamous cell carcinoma and Abraxane is used as a single agent or in combination with platinum chemotherapy (cisplatin or carboplatin) with or without an immune checkpoint inhibitor (e.g., Keytruda [pembrolizumab intravenous injection], Tecentriq [atezolizumab intravenous injection]).

Dosing. Approve 100 mg per m² administered as an intravenous infusion on Days 1, 8, and 15 every 21-days.^{1,8}

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- 3. Pancreatic Adenocarcinoma.** Approve for 1 year if the patient meets the following criteria (A and B):^{3,9}
- A) Abraxane is prescribed by or in consultation with an oncologist; AND
 - B) Abraxane will be used in combination with gemcitabine.

Dosing. Approve 125 mg per m² as an intravenous infusion on Days 1, 8, and 15 every 28-days.¹⁰

Other Uses with Supportive Evidence

- 4. Melanoma.** Approve for 1 year if the patient meets the following criteria (A, B, AND C):
- A) Abraxane is prescribed by or in consultation with an oncologist; AND
 - B) The patient has unresectable, advanced or metastatic melanoma; AND
 - C) At least one other systemic therapy for melanoma has been tried.
- Note: Examples of systemic therapy are Keytruda [pembrolizumab for intravenous use], Opdivo® [nivolumab injection for intravenous use], Yervoy® [ipilimumab intravenous injection], high dose Proleukin® [aldesleukin for intravenous infusion]; cytotoxic agents [e.g., dacarbazine, temozolomide, paclitaxel, carboplatin]; Gleevec® [imatinib tablets]; Zelboraf® [vemurafenib tablets]; Tafinlar® [dabrafenib capsules]; Mekinist® [trametinib tablets].

Dosing. Approve up to 150 mg per m² administered as an intravenous infusion on Days 1, 8, and 15, every 28 days.^{12,13,16}

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- 5. Ovarian, Fallopian Tube, or Primary Peritoneal Cancer.** Approve for 1 year if the patient meets the following criteria (A, B, AND C):
- A) Abraxane is prescribed by or in consultation with an oncologist; AND
 - B) The patient has persistent or recurrent disease; AND
 - C) At least one other systemic chemotherapy regimen has been tried.
- Note: Examples of chemotherapy are docetaxel or paclitaxel plus carboplatin.

Dosing. Approve one of the following (A OR B):

- A) 260 mg per m² given as an intravenous infusion not more frequently than once every 3 weeks;¹⁸
OR
- B) 100 mg per m² administered as an intravenous infusion on Days 1, 8, and 15 every 28 days.¹⁹

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- 6. Urothelial Carcinoma.** Approve for 1 year if the patient meets the following criteria (A, B, AND C):
- A) Abraxane is prescribed by or in consultation with an oncologist; AND
 - B) The patient has recurrent, locally advanced or metastatic urothelial carcinoma; AND
 - C) Abraxane is used as subsequent therapy after disease progression on at least one prior therapy.

Note: Examples of prior therapy are cisplatin- or carboplatin-containing regimen, immunotherapy [Keytruda® {pembrolizumab injection}, Tecentriq® {atezolizumab injection}, Imfinzi™ {durvalumab injection}, Bavencio® {avelumab injection}], gemcitabine plus carboplatin, gemcitabine alone, gemcitabine plus paclitaxel, ifosfamide with doxorubicin plus gemcitabine.

Dosing. Approve 260 mg per m² administered as an intravenous infusion not more frequently than once every 21 days.²⁰

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- 7. Uveal Melanoma.** Approve for 1 year if the patient meets the following criteria (A and B):
- A) Abraxane is prescribed by or in consultation with an oncologist; AND
 - B) The patient has metastatic or unresectable disease; AND

Dosing Approve doses between 100 mg/m² and 260 mg/m² administered as an intravenous infusion not more frequently than once every 21 days.¹

Limited dosing is available regarding use of Abraxane for uveal melanoma; however, doses between 100 mg/m² and 260 mg/m² administered as an intravenous infusion once every 21 days or 28 days are recommended in the product labeling for approved uses.¹

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- 8. Endometrial Carcinoma.** Approve for 1 year if the patient meets the following criteria (A and B):
- A) Abraxane is prescribed by or in consultation with an oncologist; AND
 - B) The patient has metastatic, recurrent, or high-risk disease.

Dosing. Approve doses between 100 mg/m² and 260 mg/m² administered as an intravenous infusion not more frequently than once every 21 days.¹

Limited dosing is available regarding use of Abraxane for endometrial carcinoma; however, doses between 100 mg/m² and 260 mg/m² administered as an intravenous infusion once every 21 days or 28 days are recommended in the product labeling for approved uses.¹

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- 9. Cholangiocarcinoma (Intra- or Extrahepatic).** Approve for 1 year if the patient meets the following criteria (A, B, and C):
- A) The patient has unresectable or metastatic disease; AND
 - B) The medication is used in combination with gemcitabine; AND
 - C) The medication is prescribed by or in consultation with an oncologist.

Dosing: Approve doses between 100 mg/m² and 260 mg/m² administered as an intravenous infusion not more frequently than once every 21 days.

Limited dosing is available regarding use of Abraxane for endometrial carcinoma; however, doses between 100 mg/m² and 260 mg/m² administered as an intravenous infusion once every 21 days or 28 days are recommended in the product labeling for approved uses.¹

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- 10. Small Bowel Adenocarcinoma.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
- A) The patient has advanced or metastatic disease; AND

- B) If the disease has deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H), the patient has progressed on Keytruda (pembrolizumab for injection) or Opdivo (nivolumab for injection); AND
- C) The medication is prescribed by or in consultation with an oncologist.

Dosing: Approve one of the following doses (A or B)²⁴:

- A) 260 mg per m² given as an intravenous infusion not more frequently than once every 3 weeks; OR
- B) 125 mg per m² administered as an intravenous infusion on Days 1, 8, and 15 every 28 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Abraxane has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Abraxane® for injectable suspension [prescribing information]. Summit, NJ: Celgene Corporation; August 2018.
2. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 3.2019 – September 6, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on October 27, 2019.
3. The NCCN Drugs & Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on October 27, 2019. Search terms: paclitaxel, albumin bound.
4. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol*. 2005;23:7794-7803.
5. 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;33:2361-2369.
6. Gradishar WJ, Krasnojon D, Cheporov S, et al. Significantly longer progression-free survival with nab-paclitaxel compared with docetaxel as first-line therapy for metastatic breast cancer. *J Clin Oncol*. 2009;27:3611-3619.
7. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 7.2019 – August 30, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on November 4, 2019.
8. Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. *J Clin Oncol*. 2012;30:2055-2062.
9. The NCCN Pancreatic Adenocarcinoma Clinical Practice Guidelines in Oncology (Version 3.2019 – July 2, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on October 27, 2019.
10. Von Hoff DD, Ervin TJ, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013;369:1691-703.
11. The NCCN Melanoma Clinical Practice Guidelines in Oncology (Version 3.2018 – July 12, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on November 1, 2018.
12. Kottschade LA, Suman VJ, Amatruda T 3rd, et al. A phase II trial of nab-paclitaxel (ABI-007) and carboplatin in patients with unresectable stage IV melanoma: a North Central Cancer Treatment Group Study, N057E. *Cancer*. 2011;117:1704-1710.
13. Hersh EM, O'Day SJ, Ribas A, et al. A phase 2 clinical trial of nab-paclitaxel in previously treated and chemotherapy-naïve patients with metastatic melanoma. *Cancer*. 2010;116:155-163.
14. Belani CP, Ramalingam S, Perry MC, et al. Randomized, phase III study of weekly paclitaxel in combination with carboplatin versus standard every-3-weeks administration of carboplatin and paclitaxel for patients with previously untreated advanced non-small-cell lung cancer. *J Clin Oncol*. 2008;26:468-473.
15. Arpino G, Marmé F, Cortés J, et al. Tailoring the dosing schedule of nab-paclitaxel in metastatic breast cancer according to patient and disease characteristics: Recommendations from a panel of experts. *Crit Rev Oncol Hematol*. 2016;99:81-90.
16. Hersh EM, Del Vecchio M, Brown MP, et al. A randomized, controlled phase III trial of nab-Paclitaxel versus dacarbazine in chemotherapy-naïve patients with metastatic melanoma. *Ann Oncol*. 2015;26:2267-2274.

17. The NCCN Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer Clinical Practice Guidelines in Oncology (Version 2.2018 – March 9, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on November 1, 2018.
18. Teneriello MG, Tseng PC, Crozier M, et al. Phase II evaluation of nanoparticle albumin-bound paclitaxel in platinum-sensitive patients with recurrent ovarian, peritoneal, or fallopian tube cancer. *J Clin Oncol*. 2009;27:1426-1431.
19. Coleman RL, Brady WE, McMeekin DS, et al. A phase II evaluation of nanoparticle, albumin-bound (nab) paclitaxel in the treatment of recurrent or persistent platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2011;122:111-115.
20. The NCCN Bladder Cancer Clinical Practice Guidelines in Oncology (Version 5.2018 – July 3, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on November 1, 2018.
21. Ko YJ, Canil CM, Mukherjee SD, et al. Nanoparticle albumin-bound paclitaxel for second-line treatment of metastatic urothelial carcinoma: a single group, multicentre, phase 2 study. *Lancet Oncol*. 2013;14:769-776.
22. The NCCN Uveal Melanoma Clinical Practice Guidelines in Oncology (Version 1.2019 – June 14, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on October 27, 2019.
23. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (Version 1.2019 – October 17, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on November 1, 2018.
24. The NCCN Small Bowel Adenocarcinoma Clinical Practice Guidelines in Oncology (Version 1.2020 – July 30, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on November 4, 2019.
25. The NCCN Hepatobiliary Cancers Clinical Practice Guidelines in Oncology (Version 3.2019 – August 1, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on November 4, 2019.

APPENDIX A

Metastatic Breast Cancer Clinical Trials

In one Phase III open-label, non-inferiority trial, patients (n = 460) with metastatic breast cancer were randomized to therapy every 3 weeks with Abraxane 260 mg/m² as a 30-minute intravenous infusion without corticosteroid or antihistamine premedication (n = 229) or paclitaxel 175 mg/m² as a 3-hour intravenous infusion with premedication (n = 225).^{1,4} The intent-to-treat population was 454 patients (Abraxane, n = 229; paclitaxel, n = 225).⁴ At study entry 64% of patients had impaired PS (ECOG 1 or 2). Fifty-nine percent of patients received the study drug as second or greater than second-line therapy; 77% of patients had previously received an anthracycline. **Results:** ORR based on the investigator reported response rates and on all cycles of therapy for all patients was 33% of patients on Abraxane (95% CI: 27.09, 39.29) vs. 19% of patients on paclitaxel (95% CI: 13.58, 23.76) [P = 0.001]. In all of the randomized patients, the Abraxane group had a statistically significantly higher reconciled target lesion response rate (TLRR) of 21.5% (95% CI: 16.2%, 26.7%) vs. 11.1% (95% CI: 6.9%, 15.1%) of patients receiving paclitaxel (P = 0.003).¹ In patients who had failed combination chemotherapy or relapsed within 6 months of adjuvant chemotherapy, the reconciled TLRR (which was based on the first 6 cycles of therapy) was 15.5% (n = 20/129) with Abraxane (95% CI: 9.26, 21.75) and 8.4% (n = 12/143) with paclitaxel (95% CI: 3.85, 12.94).¹ Median time to progression (TTP) was 23.0 weeks with Abraxane and 16.9 weeks with paclitaxel (HR 0.75; P = 0.006).⁴ Median survival for Abraxane and paclitaxel was 65.0 weeks and 55.7 weeks, respectively (P = 0.374) for all patients. There was no statistically significant difference in OS between the two therapies.¹ There was no difference between the two groups in survival in patients receiving first-line therapy.⁴ In patients who received second-line or greater therapy, survival was 56.4 weeks and 46.7 weeks for Abraxane and paclitaxel, respectively (HR 0.73; P = 0.024). There was no difference in quality of life between the two groups. The incidence of hypersensitivity reactions of any grade was < 1% with Abraxane vs. 2% with paclitaxel. Grade 3 hypersensitivity reactions occurred in five patients receiving paclitaxel. No Grade 3 or 4 hypersensitivity reactions occurred with Abraxane, but premedication was given for emesis, myalgia/arthritis, or anorexia in 18 patients (8%) in the Abraxane group in 2% of the treatment cycles. Grade 4 neutropenia (< 500 cell/mm³) was reported in 9% of patients on Abraxane and in 22% of patients on paclitaxel (P < 0.001);^{1,4} neutropenia (< 2,000 cells/mm³) was reported in 80% vs. 82% with Abraxane and paclitaxel, respectively.¹ Grade 3 sensory neuropathy occurred in 10% vs. 2% of patients on Abraxane and paclitaxel, respectively (P < 0.001) and were managed with dose reduction and treatment interruption.⁴

In one Phase III trial, the efficacy of weekly paclitaxel was compared to weekly Abraxane or Ixempra® (ixabepilone intravenous injection) with or without Avastin as *first-line therapy* in patients with chemotherapy naïve locally recurrent or metastatic breast cancer.⁵ Patients were randomized to paclitaxel 90 mg/m², Ixempra 16 mg/m², or Abraxane 150 mg/m² given once weekly for 3 weeks with 1 week off. Initially all patients received Avastin but this became optional after the study was started. The primary endpoint was PFS. **Results:** In all, 799 patients were enrolled (n = 283, paclitaxel; n = 271 Abraxane; n = 245, Ixempra) and 783 patients received treatment (97% of patients received Avastin). At the first interim analysis (165 events) accrual to Ixempra was closed for futility. At the second interim analysis (236 events) the study was closed for futility. Median PFS was 11 months, 9.3 months, and 7.4 months for paclitaxel, Abraxane, and Ixempra, respectively. Ixempra was inferior to paclitaxel (HR 1.59; 95% CI: 1.31, 1.93; P < 0.001). Abraxane was not superior to paclitaxel (HR 1.20; 95% CI: 1.00, 1.45; P = 0.054). Grade ≥ 2 sensory neuropathy occurred in 54% of patients on Abraxane, and 46% of patients on paclitaxel. The percentage of patients with Grade ≥ 3 hematologic toxicity was 55% with Abraxane, 12% for Ixempra, and 22% for paclitaxel. Grade ≥ 3 non-hematologic toxicity was reported in 49% of patients on paclitaxel, 65% of patients on Abraxane, and 58% of patients on Ixempra. When compared with paclitaxel, Abraxane was reported to have worse hematologic and non-hematologic toxicity (P < 0.001 for both), including peripheral neuropathy, with more frequent and earlier dose reductions with Abraxane than with paclitaxel. In the 783 patients who began treatment, the ORR was 38% for paclitaxel, 34% for Abraxane, and 27% for Ixempra with no difference in response between paclitaxel and Abraxane (odds ratio 0.84; P = 0.33). Time to treatment failure was a median of 5.2 months vs. 6.6 months (P < 0.001) for Abraxane and paclitaxel, respectively. Regarding OS, a post hoc test of inferiority did not reach significance for Abraxane compared with paclitaxel (median OS was 23.5 months with Abraxane vs. 26.5 months with paclitaxel [HR 1.17; 95% CI: 0.92, 1.47; P = 0.20]).

Unresectable NSCLC Clinical Trial

In one multicenter Phase III open-label trial, 1052 chemotherapy naïve patients with unresectable Stage IIIb or IV NSCLC were randomized to Abraxane 100 mg/m² given over 30 minutes on Days 1, 8, and 15 of each 21-day cycle or to paclitaxel 200 mg/m² given over 3 hours every 21 days.¹⁸ Patients receiving paclitaxel were premedicated. In both treatment arms carboplatin AUC 6 mg•minute/mL was given on Day 1 of every 21-day cycle after completing the Abraxane or paclitaxel infusion. Patients had an ECOG PS of 0 to 1. Treatment was given until disease progression or unacceptable toxicity. The primary outcome was the ORR as determined by a central independent committee. For all randomized patients the median age was 60 years; 75% of patients were men; 49% of patients had adenocarcinoma and 43% had squamous cell carcinoma. The median number of cycles was six in both study arms. **Results:** The ORR in patients receiving Abraxane/carboplatin was 33% (95% CI: 28.6%, 36.7%) vs. 23% of patients receiving paclitaxel/carboplatin (95% CI: 21.2%, 28.5%) [P = 0.005].⁸ For Abraxane/carboplatin and paclitaxel/carboplatin, the respective ORRs in patients with squamous cell histology were 41% (95% CI: 34.7%, 47.4%) vs. 24% (95% CI: 18.8%, 30.1%) [P < 0.001]. For patients with non-squamous cell histology, the ORR were 26% vs. 25%, respectively (P = 0.808). There was no statistically significant difference in median OS between the two groups (12.1 months with Abraxane vs. 11.2 months with paclitaxel) [HR 0.922; 95% CI: 0.797, 1.066; P = 0.271]. Median PFS was 6.3 months with Abraxane/carboplatin vs. 5.8 months with paclitaxel/carboplatin (HR 0.902; 95% CI: 0.767, 1.060; P = 0.214). Median duration of response was 6.9 months (95% CI: 5.6, 8.0) in patients on Abraxane/carboplatin and 6.0 months (95% CI: 5.6, 7.1) in patients on paclitaxel/carboplatin.

Paclitaxel has been given weekly in combination with carboplatin in patients with advanced NSCLC.¹⁴

Melanoma Clinical Trials

In one Phase II trial, adults (n = 73) with unresectable Stage IV melanoma who were either previously treated with chemotherapy (no prior taxane therapy) [n = 34; Cohort 1] or who were chemotherapy naïve (n = 39; Cohort 2) received therapy with Abraxane 100 mg/m² and carboplatin given weekly on Days 1, 8, and 15 of a 28-day cycle for a maximum of 8 cycles.¹² Median number of cycles was 4 (range 1 to 10 cycles). **Results.** In Cohort 1, no complete responses (CR) were reported and 3 patients had a partial response (PR); median PFS was 4.2 months and median OS was 10.9 months. In Cohort 2, 10 patients had a tumor response (one CR and nine PR); median PFS was 4.3 months and median OS was 11.1 months. In one Phase II trial, adults (n = 74) with malignant melanoma with inoperable loco regional recurrence or distant metastasis received Abraxane once weekly for 3 weeks followed by 1 week of rest (28-day cycle).¹³ The Abraxane doses were 100 mg/m² in patients previously treated with cytotoxic chemotherapy and 150 mg/m² in patients who were chemotherapy naïve. Patients with prior therapy with bio- or immunotherapy as adjuvant treatment were included. The dose could be increased in Cycle 2 and onward in the patients previously treated if dose-limiting toxicities were absent. Median number of cycles was 4 (range 1 to 21 cycles). **Results.** In the previously treated cohort, 2.7% of patients (n = 1/37) had a PR. In the chemotherapy naïve patients 21.6% (n = 8/37) had a PR. The duration of response in previously treated patients was 12.9 months vs. 24.9 months in chemotherapy naïve patients. Median PFS was 3.5 months in previously treated patients (95% CI: 1.7, 5.6) and 4.5 months in chemotherapy naïve patients (95% CI: 3.4, 6.7). Respective OS rates were 12.1 months (95% CI: 6.5, 17.5) and 9.6 months (95% CI: 6.7, 23.7). In another open-label, multicenter Phase II trial, patients (n = 50) with unresectable melanoma were treated in 28-day cycles with Abraxane 150 mg/m² every week for 3 weeks plus Avastin 10 mg/kg every 2 weeks.¹⁶ Patients were chemotherapy naïve; 96% of patients (n = 48/50) had Stage IV disease. Patients were offered ongoing therapy for up to 2 years until disease progression or unacceptable toxicity. If either drug was discontinued because of toxicities, the other drug was continued. A median of 7.6 cycles were given. **Results.** The PFS rate at 4 months was 75% (95% CI: 63, 87%). Median PFS was 7.63 months (95% CI: 5.56, 9.93). In one open-label Phase III trial, chemotherapy naïve patients with metastatic melanoma were randomized to receive Abraxane 150 mg/m² on Days 1, 8, and 15 of a 28-day cycle (n = 264) or intravenous dacarbazine 1,000 mg/m² every 3 weeks (n = 265).²² **Results.** The ORR was 15% and 11% with Abraxane and dacarbazine, respectively. Median PFS (the primary endpoint) was 4.8 months with Abraxane and 2.5 months with dacarbazine (HR: 0.792 [95.1% CI: 0.631, 0.992]; P = 0.044). Median OS was 12.6 months with Abraxane and 10.5 months with dacarbazine (HR 0.897; 95.1% CI: 0.738, 1.089; P = 0.271). The median treatment duration with Abraxane was 11.1 weeks and 6.4 weeks with dacarbazine. The median number of cycles was three for each of the therapies.

HISTORY

Type of Revision	Summary of Changes	Approval Date
Annual	--	07/01/2015
Annual	<p>Criteria for breast cancer were revised to include Herceptin-exposed disease. For NSCLC removed criteria requiring that the patient is not a candidate for curative surgery or radiation therapy and that Abraxane will be used in combination with carboplatin or cisplatin. Also for non-squamous cell NSCLC added that testing for <i>EGFR</i> mutations, <i>ALK</i> fusions, and <i>ROS1</i> rearrangements is required.</p> <p>Criteria were added for ovarian, fallopian tube, or primary peritoneal cancer and for urothelial carcinoma.</p>	07/27/2016
Annual	<p>Criteria for Breast cancer were revised to add preoperative or adjuvant therapy. For non-squamous cell NSCLC the list of targeted therapies used for each aberration was removed; <i>EGFR</i>, <i>ALK</i>, and <i>ROS1</i> are negative was added as an option after testing. For non-squamous cell and squamous cell histologies, criterion requiring testing for PD-L1 was added and requirement to try Keytruda therapy for patients with PD-L1 expression $\geq 50\%$ was added.</p> <p>Urothelial carcinoma criteria were revised to add that in addition to having tried chemotherapy, immunotherapy with Keytruda or Tecentriq would be an option. The exception for a platinum-containing chemotherapy regimen or other chemotherapy is contraindicated was removed. Keytruda or Tecentriq could be used in this circumstance.</p>	08/23/2017
Annual revision	<ul style="list-style-type: none"> • For all approval conditions, the approval duration was changed to 1 year. Labs/Diagnostics was deleted, if not required as noted in criteria. • Criteria stating “Patient has been started on Abraxane” has been deleted. • Breast Cancer: Deleted “Preferred Drug” criterion. • Non-Small Cell Lung Cancer: Deleted all criteria requiring testing for targetable mutations and for programmed death ligand 1 expression. <ul style="list-style-type: none"> • Added criteria for metastatic disease that if NSCLC tumor is positive for targetable mutation, the patient has tried at least one targeted therapy and Abraxane will be used as subsequent therapy. • Added new criteria for BRAF V600E mutation that Abraxane can be used either as first-line or subsequent therapy. Under Labs/Diagnostics, added Note that BRAF V600E mutation may be checked as part of above new criteria. Also, added criteria that if NSCLC tumor is negative or unknown for targetable mutation, that Abraxane is used as initial therapy in combination with platinum chemo with or without immune checkpoint inhibitors. • For squamous cell carcinoma deleted testing for Keytruda. Added criteria stating Abraxane can be used as single agent or in combination with platinum chemotherapy with or without immune checkpoint inhibitors. • Urothelial Carcinoma: Re-worded previous criteria (C) to state that “Abraxane is used as subsequent therapy after disease progression on at least one prior therapy” and provided examples of prior therapies in parentheses. • Uveal Melanoma: Added new approval condition based on NCCN guidelines and compendium. • Endometrial Carcinoma: Added new approval condition based on NCCN guidelines and compendium. 	10/17/2018

HISTORY (continued)

Type of Revision	Summary of Changes	Approval Date
Annual revision	<ul style="list-style-type: none"> • For all approval conditions deleted duration of therapy section. For all Dosing, added wording to state “Approve” dosing and for dosing frequency, added wording to state “not more frequently than” every 21 days or 28 days. • Breast Cancer: Added criteria for use in triple-negative breast cancer, if PD-L1-positive, in combination with Tecentriq. For HER2-positive disease, deleted criteria that patient has previously received trastuzumab. • Non-Small Cell Lung Cancer: Added Abraxane can be used as initial or subsequent therapy for neurotrophic tyrosine receptor kinase (NTRK) gene fusion-positive tumors. • Pancreatic Adenocarcinoma: Deleted criteria that medication is used for advanced/metastatic disease or neoadjuvant therapy, since it can be used in any setting. • Cholangiocarcinoma (Intra-or Extrahepatic): Added new approval condition and criteria • Small Bowel Adenocarcinoma: Added new approval condition and criteria • Other Cancer-Related Indications: Deleted, in-line with other policies 	11/06/2019