

agents for HER2-positive disease; docetaxel or paclitaxel in combination with Herceptin are listed as “other” agents for HER2-positive disease. For Herceptin-exposed HER2-positive disease, Herceptin can be combined with non-anthracycline agents listed as preferred or other singles agents. This would include paclitaxel, docetaxel, and Abraxane.

Abraxane may be substituted for paclitaxel or docetaxel in patients with a hypersensitivity reaction.²⁻³ 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. If substituted for weekly paclitaxel or docetaxel, the weekly dose of Abraxane should not be greater than 125 mg/m². Abraxane is not included in preoperative/adjuvant regimens for HER2-positive or HER2-negative disease. However, in patients with a hypersensitivity reaction to paclitaxel or docetaxel, Abraxane could be used.

A summary of the clinical trials comparing Abraxane with paclitaxel in metastatic breast cancer is included in Appendix A.

Dosing in Recurrent or Metastatic Breast Cancer in Adults. Dosing must meet ONE of the following (A OR B):

- A) 260 mg per m² given as an intravenous infusion every 3 weeks.^{1-2,4}
- B) 100 mg per m², 125 mg per m², or 150 mg per m² given as an intravenous infusion on Days 1, 8 and 15, cycled every 28 days.^{5-6, 17}

The approved dosing of Abraxane after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy, is 260 mg/ m² administered intravenously over 30 minutes every 3 weeks.¹ An alternative regimen recommended in the NCCN guidelines is 100 mg/ m² or 125 mg per m² given as an intravenous infusion on Days 1, 8, and 15 and cycled every 28 days.^{2,5-6}

Note: Dose modifications are recommended for the management of toxicities and are determined by the prescribing physician. Dosing modifications are recommended in the prescribing information and are dependent on diagnosis, baseline hepatic function, concomitant therapy, patient variability, and toxicity.¹ Alternate dosing will be assessed individually on a case-by-case basis.

Initial Approval/Extended Approval.

- A) Initial Approval: Initial approval is for 6 months of therapy.
- B) Extended Approval: Approve at additional 6-month intervals if the patient is responding, as determined by the prescribing physician.

Duration of Therapy in Recurrent or Metastatic Breast Cancer. Indefinite if the patient is responding as determined by the prescribing physician.

Labs/Diagnostics. Detection of HER2 protein overexpression or gene amplification is necessary for selection of patients appropriate for Herceptin therapy. See criteria above. Treatment guidelines indicate that HER2-tumor status should be determined for all newly diagnosed invasive breast cancers and for first recurrences of breast cancer whenever possible if previously unknown or negative.^{2,18}

Non-Small Cell Lung Cancer (NSCLC).

Criteria. *The patient must meet the following criteria (A, B, AND C):*^{1,7}

D) Abraxane is prescribed by or in consultation with an oncologist; AND The patient has recurrent or metastatic non-small cell lung cancer (NSCLC); AND

E) If the patient has non-squamous cell NSCLC AND

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 and b):

a) Testing has been completed for epidermal growth factor receptor (*EGFR*) mutations, anaplastic lymphoma kinase (*ALK*) fusions, or *ROS1* rearrangements, AND the patient meets the ONE of the following (1 or 2):

(1) The patient's tumor is sensitizing *EGFR* mutation positive, *ALK* positive, or *ROS1* positive and the patient has received targeted drug therapy for the specific mutation; OR

(2) *EGFR*, *ALK*, and *ROS1* tests are negative;

AND

b) Testing has been completed for programmed death-ligand 1 (PD-L1) expression for Keytruda® (pembrolizumab intravenous injection) as determined by a FDA-approved test and ONE of the following applies (1 or 2):

(1) The patient's tumor proportion score (TPS) is $\geq 50\%$ AND therapy with Keytruda (pembrolizumab) has been tried; OR

(2) The patient's tumor proportion score (TPS) is $< 50\%$ or unknown.

OR

ii. Squamous cell carcinoma AND the following condition is met (a):

a) Testing has been completed for programmed death-ligand 1 (PD-L1) expression for Keytruda (pembrolizumab intravenous injection) as determined by a FDA-approved test and ONE of the following applies (i or ii):

(1) The patient's tumor proportion score (TPS) is $\geq 50\%$ AND therapy with Keytruda (pembrolizumab) has been tried; OR

(2) The patient's tumor proportion score (TPS) is $< 50\%$ or unknown.

Preferred Drug. The patient is required to try paclitaxel. Patients are not required to try paclitaxel if they have tried docetaxel (Docefrez™, Taxotere®, generics) OR if the patient cannot receive standard hypersensitivity premedication with dexamethasone or another corticosteroid according to the prescribing physician.

The NCCN clinical practice guidelines on NSCLC (version 8.2017) recommend Abraxane for treatment of recurrence or metastasis of adenocarcinoma (with mixed subtypes), squamous cell carcinoma, or large cell carcinoma as a single-agent in patients with performance status (PS) 2 or in combination with carboplatin for patients with PS 0 to 2 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 tumors;

- subsequent therapy for sensitizing *EGFR* mutation-positive tumors and prior Tarceva® (erlotinib tablets), Gilotrif® (afatinib tablets), Iressa® (gefitinib tablets), or Tagrisso® (osimertinib tablets) therapy;
- subsequent therapy for *ALK* rearrangement-positive tumors and prior therapy with Xalkori® (crizotinib capsules), Zykadia™ (ceritinib capsules), Alecensa® (alectinib capsules), or Alunbrig™ (brigatinib tablets) 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.

Abraxane plus carboplatin for patients with PS 0 to 1 is a category 1 recommendation and for patients with PS 2 is category 2A. Single agent therapy has a category 2A recommendation.

These guidelines also state that Abraxane may be substituted for either paclitaxel or docetaxel in patients who have hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or if patients have contraindications to standard hypersensitivity pre-medications (category 2A).

In patients with non-squamous cell NSCLC or NSCLC not otherwise specified, the NCCN guidelines recommend testing for *EGFR* mutations and *ALK* gene rearrangements (category 1) so that patients with genetic abnormalities can receive therapy with targeted agents.⁷ Testing for *ROS1* rearrangements is also recommended (category 2A). Testing for *EGFR* mutations, *ALK* rearrangements, and *ROS1* rearrangements can be considered in patients with squamous cell histology if they are never smokers, small biopsy specimens were used for testing, or mixed histology was reported. *EGFR*, *ALK*, and *ROS1* genetic alterations do not usually overlap. *BRAF* mutations typically do not overlap with *EGFR* mutations or *ALK* rearrangements. *BRAF* mutations testing is also recommended. For patients with metastatic NSCLC, the NCCN panel recommends testing for *EGFR* mutations, *BRAF* mutations, *ALK* rearrangements, *ROS1* rearrangements, and PD-L1 expression levels. PD-L1 testing is recommended before first-line treatment in patients with metastatic NSCLC with negative or unknown test results for *EGFR* mutations, *ALK* rearrangements, and *ROS1* rearrangements. The NCCN panel strongly advises broader molecular profiling to identify rare driver mutations to ensure that patients receive appropriate therapy.

The NCCN guidelines state that PD-L1 expression levels of $\geq 50\%$ are a positive test result for first-line Keytruda therapy.⁷ Patients with PD-L1 expression levels just below and just above 50% will probably have similar responses. Testing for PD-L1 expression is recommended before first-line treatment in patients with metastatic NSCLC with negative or unknown test results for *EGFR* mutations, *ALK* rearrangements, and *ROS1* rearrangements.

The American Society of Clinical Oncology (ASCO) Clinical Practice Guideline on systemic therapy for Stage IV NSCLC recommends that targeted therapy be used first-line in patients with sensitizing *EGFR* mutations, *ALK* rearrangements, or *ROS1* rearrangements.¹⁹ In patients with non-squamous cell or squamous cell carcinoma without positive markers, but with high PD-L1 expression (TPS $\geq 50\%$) and no contraindications, Keytruda should be used alone. In patients with low PD-L1 expression (TPS $< 50\%$), standard chemotherapy should be used. In 2014, the ASCO endorsed a

guideline on molecular testing for the selection of patients with lung cancer for EGFR and ALK tyrosine kinase inhibitors.²⁰ Testing for *EGFR* mutations and *ALK* rearrangements should be used to guide patient selection for therapy with EGFR or ALK inhibitors in all patients with advanced stage lung adenocarcinoma or tumors with an adenocarcinoma component, irrespective of clinical characteristics (e.g., smoking history, sex, race, or other clinical factors). Small tumor samples of other histologies for which an adenocarcinoma component cannot be excluded because of sampling can be considered especially if clinical criteria are suggestive (e.g., younger age, lack of smoking history). Testing should be completed at the time of diagnosis of advanced disease or recurrence. In patients with earlier stage (i.e., Stage I to III) disease who undergo surgical resection, expert consensus encourages testing at the time of diagnosis so that molecular information is available to an oncologist at the time of recurrence.

Abraxane is not included in NCCN chemotherapy regimens for neoadjuvant and adjuvant therapy or as a chemotherapy regimen that is used with radiation therapy in NSCLC.⁷ However, paclitaxel and docetaxel are taxanes that may be used for neoadjuvant/adjuvant therapy and paclitaxel may be used sequentially or concurrently with radiation therapy. The NCCN guidelines also do not include Abraxane in the recommendations for continuation maintenance (i.e., continuing at least one of the agents given first line beyond 4 to 6 cycles, in the absence of disease progression).

A summary of the clinical trial comparing Abraxane to paclitaxel in patients with unresectable Stage IIIb or IV NSCLC is included in Appendix A.

Dosing in NSCLC in Adults. Dosing must meet the following: 100 mg per m² as an intravenous infusion on Days 1, 8, and 15 of each 21-day cycle.^{1,8}

The approved dosing of Abraxane in NSCLC is 100 mg per m² given as an intravenous infusion over 30 minutes on Days 1, 8, and 15 of each 21-day cycle.¹

Note: Dose modifications are recommended for the management of toxicities and are determined by the prescribing physician. Dosing modifications are recommended in the prescribing information and are dependent on diagnosis, baseline hepatic function, concomitant therapy, patient variability, and toxicity.¹ Alternate dosing will be assessed individually on a case-by-case basis.

Initial Approval/Extended Approval.

- A) Initial Approval:** Initial approval is for 6 cycles of Abraxane.
- B) Extended Approval:** Not recommended.

NCCN guidelines state that for first-line therapy of advanced disease, patients with responsive or stable disease after the first cycle of chemotherapy can continue to receive a total of 4 to 6 cycles of systemic therapy or until the disease progresses.⁷ The NCCN guidelines do not include Abraxane for continuation maintenance or switch maintenance therapy.

Duration of Therapy in NSCLC. Duration of treatment is usually 4 to 6 cycles.⁷

Labs/Diagnostics. Detection of *EGFR* mutations, *ALK* fusions, ROS1, and PD-L1 expression for Keytruda (pembrolizumab) rearrangements is necessary for selection of patients appropriate for targeted therapies prior to using Abraxane therapy. For first-line treatment with Keytruda as a single agent, the TPS must be $\geq 50\%$ tumor cells as determined by the PD-L1 IHC 22C3 pharmDx kit. See criteria above. This applies to patients initiating therapy with Abraxane for recurrent or metastatic disease.

2. Pancreatic Adenocarcinoma.

Criteria. *The patient must meet the following criteria (A, B, AND C).*^{3,9}

- A) Abraxane is prescribed by or in consultation with an oncologist; AND
- B) The patient has locally advanced unresectable or metastatic disease OR Abraxane is being used for neoadjuvant therapy; AND
- C) Abraxane will be used in combination with gemcitabine.

The NCCN clinical practice guidelines on pancreatic adenocarcinoma (version 2.2017) recommend therapy with Abraxane for the following uses:⁹

- Neoadjuvant therapy in combination with gemcitabine with or without subsequent chemoradiation for biopsy positive borderline resectable disease OR for resectable disease with high-risk features (i.e., very highly elevated CA 19-9, large primary tumors, large regional lymph nodes, excessive weight loss, extreme pain) [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 for patients with good performance status, KPS ≥ 70 , and disease progression who were previously treated with fluoropyrimidine-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 ASCO Clinical Practice Guideline on metastatic pancreatic cancer recommends gemcitabine plus Abraxane in patients with Eastern Cooperative Oncology Group (ECOG) PS 0 to 1, relatively favorable comorbidity profile, and patient preference and support system for relatively aggressive medical therapy.²⁸ Gemcitabine plus Abraxane can be offered as second-line therapy for patients who have had first-line treatment with FOLFIRINOX (leucovorin, 5-FU, irinotecan, and oxaliplatin), ECOG PS 0 to 1, relatively favorable comorbidity profile, and patient preference and support system for aggressive medical therapy.

In one Phase III, open-label multicenter, multinational trial (IMPACT) in adults with metastatic adenocarcinoma of the pancreas and no prior chemotherapy, Abraxane in combination with



gemcitabine (n = 431) was compared to gemcitabine monotherapy (n = 430).^{1,10} Patients were randomized to Abraxane 125 mg/m², followed by gemcitabine 1,000 mg/m² on days 1, 8, and 15 of every 4-week cycle OR to gemcitabine 1,000 mg/m² weekly for 7 weeks followed by 1 week off and then on Days 1, 8, and 15 of each subsequent 28-day cycle. Treatment continued until disease progression or unacceptable toxicity. **Results:** In all, 841 patients received therapy. Median overall survival (OS), the primary endpoint, was 8.5 months with Abraxane plus gemcitabine and 6.7 months with gemcitabine (hazard ratio [HR] for death 0.72; 95% confidence interval [CI]: 0.62, 0.83; P < 0.0001). One-year survival was 35% of patients on the combination and 22% of patients on gemcitabine alone (95% CI: 0.617, 0.835; P = 0.0002).¹⁰ Median progression-free survival (PFS) was 5.5 months vs. 3.7 months with Abraxane plus gemcitabine and gemcitabine alone, respectively (HR 0.69 [95% CI: 0.58, 0.82]; P < 0.0001).^{1,10} The overall response rate (ORR) was 23% of patients on the combination vs. 7% of patients on gemcitabine alone. The median duration of treatment was 3.9 months (range, 0.1 to 21.9 months) with Abraxane plus gemcitabine vs. 2.8 months (range, 0.1 to 21.5) with gemcitabine.¹⁰ In an update on longer-term survival in the IMPACT trial with median follow-up of 13.9 months, median OS was 8.7 months and 6.6 months in patients on Abraxane plus gemcitabine and in patients on gemcitabine alone, respectively (HR 0.72; 95% CI: 0.62, 0.83; P < 0.001).¹⁵ With extended follow-up, 4% of patients on gemcitabine plus Abraxane survived at least 36 months. No patients on gemcitabine alone survived for 36 months.

In one prospective study conducted in 12 centers in France, patients (n = 57) with metastatic pancreatic adenocarcinoma, who had failed on FOLFIRINOX therapy, received Abraxane 125 mg/m² plus gemcitabine 1,000 mg on Days 1, 8, and 15 of a 28-days cycle.²¹ The median number of cycles was four (range, 1 to 12). The ORR was 17.5% (n = 10/57). Median OS was 8.8 months (95% CI: 6.2, 9.7) and median PFS was 5.1 months (95% CI: 3.2, 6.2). Since the start of first-line chemotherapy, median OS was 18 months (95% CI: 16, 21).

Dosing in Pancreatic Adenocarcinoma in Adults. Dosing must meet the following: 125 mg per m² as an intravenous infusion on Days 1, 8, and 15 of each 28-day cycle for 4 cycles.¹⁰

The approved dose of Abraxane in adenocarcinoma of the pancreas is 125 mg per m² as an intravenous infusion over 30 to 40 minutes on Days 1, 8, and 15 of each 28-day cycle.¹ Note: Dose modifications are recommended for the management of toxicities and are determined by the prescribing physician. Dosing modifications are recommended in the prescribing information and are dependent on diagnosis, baseline hepatic function, concomitant therapy, patient variability, and toxicity.¹ Alternate dosing will be assessed individually on a case-by-case basis.

Initial Approval/Extended Approval.

- A) Initial Approval:** Initial approval is for four months which is doses given on Days 1, 8, and 15 of each 28-day cycle.¹⁰
- B) Extended Approval:** Approve at additional 4-month intervals if the patient is responding as determined by the prescribing physician.

Duration of Therapy in Pancreatic Adenocarcinoma. Indefinite if the patient is responding as determined by the prescribing physician. Abraxane has been given for 4 cycles (doses given on Days 1, 8, and 15 of each 28-day cycle).¹⁰

Labs/Diagnostics. None required.

Other Uses with Supportive Evidence

3. Melanoma.

Criteria. *The patient must meet 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 (e.g., 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]).

The NCCN clinical practice guidelines on melanoma (version 1.2017) recommend Abraxane as a single-agent 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 Other cytotoxic regimens for systemic therapy of metastatic disease include dacarbazine, temozolomide, and paclitaxel with or without carboplatin. In general, options for front-line therapy for metastatic melanoma include immunotherapy (e.g., Keytruda, Opdivo) or targeted therapy.

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.

Dosing in Melanoma in Adults. Dosing must meet the following: 100 mg per m² or 150 mg per m² given as an intravenous infusion on Days 1, 8, and 15, cycled every 28 days.^{12-13,22}

Note: Dose modifications are recommended for the management of toxicities and are determined by the prescribing physician. Dosing modifications are recommended in the prescribing information for the approved indications and are dependent on diagnosis, baseline hepatic function, concomitant therapy, patient variability, and toxicity.¹ Alternate dosing will be assessed individually on a case-by-case basis.

Initial Approval/Extended Approval.

- A) **Initial Approval:** Initial approval is for four months which is doses given on Days 1, 8, and 15 of each 28-day cycle.
- B) **Extended Approval:** Approve at additional 4-month intervals if the patient is responding as determined by the prescribing physician.

Duration of Therapy in Melanoma. Indefinite if the patient is responding as determined by the prescribing physician. The median number of cycles was four in two Phase II studies.¹²⁻¹³

Labs/Diagnostics. None required.

4. Ovarian, Fallopian Tube, or Primary Peritoneal Cancer.

Criteria. The patient must meet 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 (e.g., docetaxel or paclitaxel plus carboplatin).

The NCCN clinical practice guidelines on ovarian cancer (version 2.2017) recommend Abraxane as therapy for persistent disease or recurrence (including epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer) 1) as preferred therapy, if platinum sensitive, in combination with carboplatin, for patients with confirmed taxane hypersensitivity or 2) as a single agent (category 2A).²³ 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.

In one Phase II trial, patients (n = 44) with platinum-sensitive recurrent ovarian, peritoneal or fallopian tube cancer received Abraxane 260 mg/m² on Day 1 of a 21-day cycle for six cycles or until disease progression.²⁴ Patients in complete response could receive an additional two cycles for a maximum of eight cycles. **Results.** The ORR was 64% (95% CI: 49.4%, 77.9%) with 15 CRs and 13 PRs. Estimated median PFS was 8.5 months. Median OS had not been reached. In one Phase II trial, patients (n = 47 evaluable) with recurrent or persistent platinum- and taxane-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer received Abraxane 100 mg/m² on Days 1, 8, and 15 of a 28-day cycle.²⁵ Abraxane was continued until withdrawal of consent, disease progression, side effects precluding further administration, or inability to tolerate the lowest doses. The response rate was evaluated in a two-stage design. **Results.** There was one CR and 10 PRs with an ORR of 23% (95% CI: 12%, 38%); 36% of patients (n = 17/47) had stable disease. Median PFS and OS were 4.5 months and 17.4 months, respectively. The median number of cycles administered was four.

Dosing in Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Adults. *Dosing must meet one of the following (A OR B):*

- A) 260 mg per m² given as an intravenous infusion every 3 weeks;²⁴ OR
- B) 100 mg/m² on Days 1, 8, and 15 of a 28-day cycle.²⁵

Note: Dose modifications are recommended for the management of toxicities and are determined by the prescribing physician. Dosing modifications are recommended in the prescribing information for the approved indications and are dependent on diagnosis, baseline hepatic function, concomitant therapy, patient variability, and toxicity.¹ Alternate dosing will be assessed individually on a case-by-case basis.

Initial Approval/Extended Approval.

- A) *Initial Approval.* Initial approval is for 6 months of therapy.
- B) *Extended Approval.* Approve at additional 6-month intervals if the patient is responding, as determined by the prescribing physician.

Duration of Therapy in Ovarian, Fallopian Tube, or Primary Peritoneal Cancer. Limited information is available. Therapy may be extended based on the opinion of the prescribing physician.

Lab/Diagnostics. None required.

6. Urothelial Carcinoma.

Criteria. *The patient must meet 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) The patient meets ONE of the following conditions (i, ii, or iii):
 - i. The patient has disease progression after trying platinum- (cisplatin, carboplatin) containing chemotherapy; OR
 - ii. The patient has tried chemotherapy (e.g., gemcitabine [Gemzar®, generics] plus carboplatin, gemcitabine alone, gemcitabine plus paclitaxel, ifosfamide [Ifex®, generics] with doxorubicin plus gemcitabine) or immunotherapy (that is Keytruda or Tecentriq® [atezolizumab intravenous injection]).

The NCCN clinical practice guidelines on bladder cancer (version 5.2017) recommend Abraxane as a single agent for urothelial carcinoma of the bladder for clinical Stage T4b or T2-T4a, N1-3 disease, or for recurrence post cystectomy or for metastatic disease subsequent systemic therapy as an alternate regimen for select patients.²⁶ Abraxane is also recommended as a single agent for the following: for recurrent or metastatic disease as subsequent systemic therapy as an alternate regimen for select patients for urothelial carcinoma of the urethra; as subsequent systemic therapy for metastatic upper genitourinary tract tumors as an alternate regimen for select patients; or for subsequent systemic therapy for metastatic urothelial carcinoma of the prostate as an alternate regimen for select patients.

All of the standard neoadjuvant or adjuvant regimens recommended for systemic therapy include cisplatin (i.e., DDMVAC [dose-dense methotrexate {MTX}, vinblastine, doxorubicin, and cisplatin] with growth factor support, gemcitabine plus cisplatin, CMV [cisplatin, MTX, and vinblastine]). For patients who are not candidates for cisplatin, there are no data supporting a recommendation for neoadjuvant or adjuvant therapy. *First-line systemic chemotherapy* for locally advanced or metastatic disease *in patients who are eligible for cisplatin*, include gemcitabine plus cisplatin (category 1) or DDMVAC with growth factor support (category 1). In patients who are ineligible for cisplatin the standard regimens are gemcitabine and carboplatin, Tecentriq, or Keytruda. Alternative regimens are gemcitabine alone or in combination with paclitaxel or the combination of ifosfamide, doxorubicin, and gemcitabine (for patients with good kidney function and good performance status). A substantial number of patients cannot receive cisplatin-based chemotherapy due to renal impairment or other comorbidities, and participation in clinical trials of new or more tolerable therapy is recommended. For *subsequent systemic therapy* of locally advanced or metastatic disease participation in clinical trials of new agents is recommended. Standard regimens include Keytruda (category 1), Tecentriq, Opdivo, Imfinzi™ (durvalumab intravenous injection), Bavencio® (avelumab intravenous injection), paclitaxel, docetaxel, gemcitabine, or Alimta® (pemetrexed intravenous injection). Alternate regimens for select patients include Abraxane, ifosfamide, MTX, the combination of ifosfamide, doxorubicin, and gemcitabine, gemcitabine with paclitaxel or cisplatin, and DDMVAC.

In one Phase II trial, patients (n = 47) with locally advanced or metastatic platinum-refractory urothelial cancer of the bladder, ureter or renal pelvis received Abraxane 260 mg/m² every 3 weeks.²⁷ Abraxane was continued until disease progression or unacceptable toxicity. Patients received a median of six cycles. The ORR was 27.7% (95% CI: 17.3%, 44.4%) with one patient having a CR and 12 patients having a PR. Ten patients had stable disease for at least 4 months as their best response. Median PFS was 6.0 months and median OS was 10.8 months.

Dosing in Urothelial Carcinoma in Adults. Dosing must meet the following: 260 mg per m² as an intravenous infusion every 3 weeks.²⁷

Note: Dose modifications are recommended for the management of toxicities and are determined by the prescribing physician. Dosing modifications are recommended in the prescribing information for the approved indications and are dependent on diagnosis, baseline hepatic function, concomitant therapy, patient variability, and toxicity.¹ Alternate dosing will be assessed individually on a case-by-case basis.

Initial Approval/Extended Approval.

- A) Initial Approval. Initial approval is for 6 cycles (doses) of Abraxane given every 21 days.
- B) Extended Approval. Approve additional 6 cycles (doses) if the patient has a response, as determined by the prescribing physician.

Duration of Therapy in Urothelial Carcinoma. Limited information is available. Therapy may be extended based on the opinion of the prescribing physician.

In one Phase II trial, the median number of cycles administered was six (range, 1 to 15 cycles).²⁷

Lab/Diagnostics. None required.

- 7. **Patient has been started on Abraxane.** Approve if the patient meets the conditions for **Dosing, Extended Approval, Duration of Therapy, and Labs/Diagnostics** for an approved use in this *Abraxane Utilization Review* policy.
- 8. **Other Cancer Indications.** Forward to the Medical Director for review on a case-by-case basis. An example of another indications supported in the *NCCN Compendium* with a category 2B recommendations includes cervical cancer.³

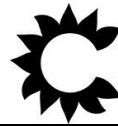
Waste Management for All Indications.

Dosing is based on body surface area (m²). The dose should be calculated and the number of vials needed assessed.

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. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of

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CFR		
WAC	284-43-2050	
RCW		
Contract Citation	<input type="checkbox"/> WAH	
	<input type="checkbox"/> IMC	
	<input type="checkbox"/> MA	
Other Requirements		
NCQA Elements		

Revision History

Revision Date	Revision Description	Revision Made By
12/02/2015	New	Kelly Force; Yusuf Rashid, RPh
12/24/2015	Approval	MMLT
01/11/2017	No revisions	Fran McGaugh
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06/18/2017	Updated indications and references	Sonya Ou, Pharm.D.
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07/25/2017	Approved	MMLT
04/16/2018	Transferred to new template	Cindy Bush
04/23/18	Updated indications and references	Jennifer Farley, PharmD
05/10/2018	Approval	UM Committee

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. Seventy-seven percent 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 overall survival 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/arthralgia, 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 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 overall survival, a post hoc test of inferiority did not reach significance for Abraxane compared with paclitaxel (median overall survival 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.^{1,8} 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 overall survival 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