CELEGENE PROVIDES UPDATE ON ABRAXANE® COMBINATION THERAPY IN THE TREATMENT OF METASTATIC TRIPLE-NEGATIVE BREAST CANCER AND PANCREATIC CANCER

TECENTRIQ® in Combination with ABRAXANE® receives accelerated approval for people with PD-L1-Positive, Metastatic Triple-Negative Breast Cancer

Top-line results announced from the international Phase 3 study evaluating adjuvant therapy with ABRAXANE in combination with gemcitabine vs. gemcitabine alone for patients with surgically resected pancreatic cancer


Genentech, a member of the Roche Group, recently announced the accelerated approval of TECENTRIQ® (atezolizumab) in combination with ABRAXANE® for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 as determined by an FDA-approved test. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). This combination is the first cancer immunotherapy regimen approved for breast cancer and is based on results from the Phase 3 IMpassion130 study, which demonstrated that the combination of TECENTRIQ plus ABRAXANE compared to ABRAXANE monotherapy, as an initial (first-line) treatment, significantly reduced the risk of disease worsening or death (progression-free survival) in patients with metastatic or unresectable locally advanced triple negative breast cancer (TNBC) in the PD-L1 positive populations who had not received chemotherapy for metastatic disease.

“This is the second approval from the U.S. Food and Drug Administration of a PD-1/PD-L1 antibody in combination with ABRAXANE,” said Alise Reicin, M.D., President, Global Clinical Development for Celgene. “ABRAXANE continues to be studied with immunotherapy agents as a combination partner across a range of solid tumors.”

In addition, the Celgene-sponsored, pivotal, Phase 3 apact® study evaluating the investigational use of ABRAXANE in combination with gemcitabine following surgical resection (adjuvant treatment) in patients with pancreatic cancer did not achieve the primary endpoint of improvement in disease-free survival, as confirmed by independent radiological review, compared to gemcitabine alone. Overall survival, a secondary endpoint of the study, was improved, reaching nominal statistical significance, with ABRAXANE in combination with gemcitabine compared to gemcitabine alone. The safety profile observed in the apact study was consistent with previously reported studies of ABRAXANE. Data from apact will be submitted to a future medical meeting.

Currently, there are more than 130 studies evaluating the use of ABRAXANE in patients with pancreatic cancer in combination with more than 50 novel agents.

About apact
apact is an international, multicenter, randomized, open-label, controlled Phase 3 study (ClinicalTrials.gov, NCT01964430) to assess the efficacy of ABRAXANE in combination with gemcitabine versus gemcitabine alone as adjuvant therapy for patients with surgically resected pancreatic adenocarcinoma. The primary endpoint of the study was the independent assessment of disease-free survival (DFS); secondary endpoints included overall survival (OS) and safety. The study enrolled 866 patients randomized 1:1 to receive either ABRAXANE 125 mg/m² followed by gemcitabine 1000 mg/m², or gemcitabine 1000 mg/m² monotherapy. Treatment was administered intravenously, weekly on Days 1, 8, and 15 of a 28-day cycle for a total of 6 cycles.

About Pancreatic Cancer
Each year, more than 350,000 people worldwide are diagnosed with pancreatic cancer – one of the deadliest cancers – with the majority of cases diagnosed in late stage. Despite advances in therapy over the past two decades that have led to doubled 5-year survival rates, pancreatic cancer 5-year survival is still only in the single digits – 8% – due to the complex nature of the disease and lack of symptoms until the disease has progressed.

Even among patients with localized pancreatic cancer, for whom surgery is potentially curative, survival remains poor and the rate of relapse is high. However, adjuvant chemotherapy has been proven to significantly improve survival compared with surgery alone. Despite the noted improvements with chemotherapy following surgery, recurrence rates of pancreatic cancer are still high with 69 to 75% of patients having a relapse within 2 years. There remains a high unmet medical need for more effective adjuvant therapies.

About Triple Negative Breast Cancer
Breast cancer is the second most common cancer among women in the United States. According to the American Cancer Society, it is estimated that about 266,000 American women will be diagnosed with invasive breast cancer in 2018, and nearly 41,000 will die from the disease. Approximately 10-20 percent of breast cancers are triple negative breast cancer (TNBC). TNBC is an aggressive form of the disease with a high unmet need. It can be more difficult to treat because it is not sensitive to hormone therapy or medicines that target HER2.

TECENTRIQ® is a registered trademark of Genentech, a member of the Roche Group.

About ABRAXANE in Pancreatic Cancer
In September 2013, the U.S. Food and Drug Administration (FDA) approved ABRAXANE in combination with gemcitabine as first-line treatment of patients with metastatic pancreatic cancer. The current indication remains unchanged and clinical trials continue building on the foundation of ABRAXANE in combination with gemcitabine for a new wave of potential treatments, such as an ongoing Phase 2 cooperative group trial with SWOG S1505 (ClinicalTrials.gov, NCT02562716) investigating the safety and effectiveness of ABRAXANE in combination with gemcitabine as neoadjuvant treatment for localized pancreatic head adenocarcinoma.

ABRAXANE is not approved for the adjuvant treatment of pancreatic cancer.
About ABRAXANE

Indications

ABRAXANE is indicated for the treatment of 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 clinically contraindicated.

ABRAXANE is indicated for the first-line treatment of locally advanced or metastatic non–small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.

ABRAXANE is indicated for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

Important Safety Information

WARNING - NEUTROPENIA

- Do not administer ABRAXANE therapy to patients who have baseline neutrophil counts of less than 1500 cells/mm³. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ABRAXANE.

- Note: An albumin form of paclitaxel may substantially affect a drug’s functional properties relative to those of drug in solution. DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS.

CONTRAINDICATIONS

Neutrophil Counts

- ABRAXANE should not be used in patients who have baseline neutrophil counts of <1500 cells/mm³.

Hypersensitivity
- Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be rechallenged with the drug

**WARNINGS AND PRECAUTIONS**

**Hematologic Effects**
- Bone marrow suppression (primarily neutropenia) is dose-dependent and a dose-limiting toxicity of ABRAXANE. In clinical studies, Grade 3-4 neutropenia occurred in 34% of patients with metastatic breast cancer (MBC), 47% of patients with non–small cell lung cancer (NSCLC), and 38% of patients with pancreatic cancer
- Monitor for myelotoxicity by performing complete blood cell counts frequently, including prior to dosing on Day 1 (for MBC) and Days 1, 8, and 15 (for NSCLC and for pancreatic cancer)
- Do not administer ABRAXANE to patients with baseline absolute neutrophil counts (ANC) of less than 1500 cells/mm³
- In the case of severe neutropenia (<500 cells/mm³ for 7 days or more) during a course of ABRAXANE therapy, reduce the dose of ABRAXANE in subsequent courses in patients with either MBC or NSCLC
- In patients with MBC, resume treatment with every-3-week cycles of ABRAXANE after ANC recovers to a level >1500 cells/mm³ and platelets recover to a level >100,000 cells/mm³
- In patients with NSCLC, resume treatment if recommended at permanently reduced doses for both weekly ABRAXANE and every-3-week carboplatin after ANC recovers to at least 1500 cells/mm³ and platelet count of at least 100,000 cells/mm³ on Day 1 or to an ANC of at least 500 cells/mm³ and platelet count of at least 50,000 cells/mm³ on Days 8 or 15 of the cycle
- In patients with adenocarcinoma of the pancreas, withhold ABRAXANE and gemcitabine if the ANC is less than 500 cells/mm³ or platelets are less than 50,000 cells/mm³ and delay initiation of the next cycle if the ANC is less than 1500 cells/mm³ or platelet count is less than 100,000 cells/mm³ on Day 1 of the cycle. Resume treatment with appropriate dose reduction if recommended

**Nervous System**
- Sensory neuropathy is dose- and schedule-dependent
- The occurrence of Grade 1 or 2 sensory neuropathy does not generally require dose modification
- If ≥ Grade 3 sensory neuropathy develops, withhold ABRAXANE treatment until resolution to Grade 1 or 2 for MBC or until resolution to ≤ Grade 1 for NSCLC and pancreatic cancer followed by a dose reduction for all subsequent courses of ABRAXANE

**Sepsis**
- Sepsis occurred in 5% of patients with or without neutropenia who received ABRAXANE in combination with gemcitabine
- Biliary obstruction or presence of biliary stent were risk factors for severe or fatal sepsis
- If a patient becomes febrile (regardless of ANC), initiate treatment with broad-spectrum antibiotics
- For febrile neutropenia, interrupt ABRAXANE and gemcitabine until fever resolves and ANC ≥1500 cells/mm³, then resume treatment at reduced dose levels

**Pneumonitis**
- Pneumonitis, including some cases that were fatal, occurred in 4% of patients receiving ABRAXANE in combination with gemcitabine
Monitor patients for signs and symptoms and interrupt ABRAXANE and gemcitabine during evaluation of suspected pneumonitis
- Permanently discontinue treatment with ABRAXANE and gemcitabine upon making a diagnosis of pneumonitis

**Hypersensitivity**
- Severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, have been reported
- Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be rechallenged with this drug
- Cross-hypersensitivity between ABRAXANE and other taxane products has been reported and may include severe reactions such as anaphylaxis. Patients with a previous history of hypersensitivity to other taxanes should be closely monitored during initiation of ABRAXANE therapy

**Hepatic Impairment**
- Because the exposure and toxicity of paclitaxel can be increased with hepatic impairment, administration of ABRAXANE in patients with hepatic impairment should be performed with caution
- Patients with hepatic impairment may be at an increased risk of toxicity, particularly from myelosuppression, and should be monitored for development of profound myelosuppression
- For MBC and NSCLC, the starting dose should be reduced for patients with moderate or severe hepatic impairment
- For pancreatic adenocarcinoma, ABRAXANE is not recommended for patients with moderate to severe hepatic impairment (total bilirubin >1.5 x ULN and AST ≤10 x ULN)

**Albumin (Human)**
- ABRAXANE contains albumin (human), a derivative of human blood

**Embryo Fetal Toxicity**
- Based on mechanism of action and findings in animals, ABRAXANE can cause fetal harm when administered to a pregnant woman
- Advise females of reproductive potential of the potential risk to a fetus.
- Advise females of reproductive potential to use effective contraception and avoid becoming pregnant during treatment with ABRAXANE and for at least six months after the last dose of ABRAXANE
- Advise male patients with female partners of reproductive potential to use effective contraception and avoid fathering a child during treatment with ABRAXANE and for at least three months after the last dose of ABRAXANE

**ADVERSE REACTIONS**

**Randomized Metastatic Breast Cancer (MBC) Study**
- The most common adverse reactions (≥20%) with single-agent use of ABRAXANE vs paclitaxel injection in the MBC study are alopecia (90%, 94%), neutropenia (all cases 80%, 82%; severe 9%, 22%), sensory neuropathy (any symptoms 71%, 56%; severe 10%, 2%), abnormal ECG (all patients 60%, 52%; patients with normal baseline 35%, 30%), fatigue/asthenia (any 47%, 39%; severe 8%, 3%), myalgia/arthritis (any 44%, 49%; severe 8%, 4%), AST elevation (any 39%, 32%), alkaline phosphatase elevation (any 36%, 31%), anemia (any 33%, 25%; severe 1%, <1%), nausea (any 30%,
22%; severe 3%, <1%), diarrhea (any 27%, 15%; severe <1%, 1%) and infections (24%, 20%), respectively

- Sensory neuropathy was the cause of ABRAXANE discontinuation in 7/229 (3%) patients
- Other adverse reactions of note with the use of ABRAXANE vs paclitaxel injection included vomiting (any 18%, 10%; severe 4%, 1%), fluid retention (any 10%, 8%; severe 0%, <1%), mucositis (any 7%, 6%; severe <1%, 0%), hepatic dysfunction (elevations in bilirubin 7%, 7%), hypersensitivity reactions (any 4%, 12%; severe 0%, 2%), thrombocytopenia (any 2%, 3%; severe <1%, <1%), neutropenic sepsis (<1%, <1%), and injection site reactions (<1%, 1%), respectively.
- Dehydration and pyrexia were also reported
- Renal dysfunction (any 11%, severe 1%) was reported in patients treated with ABRAXANE (n=229)
- In all ABRAXANE-treated patients (n=366), ocular/visual disturbances were reported (any 13%; severe 1%)
- Severe cardiovascular events possibly related to single-agent ABRAXANE occurred in approximately 3% of patients and included cardiac ischemia/infarction, chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension
- Cases of cerebrovascular attacks (strokes) and transient ischemic attacks have been reported

Non–Small Cell Lung Cancer (NSCLC) Study

- The most common adverse reactions (≥20%) of ABRAXANE in combination with carboplatin are anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue
- The most common serious adverse reactions of ABRAXANE in combination with carboplatin for NSCLC are anemia (4%) and pneumonia (3%)
- The most common adverse reactions resulting in permanent discontinuation of ABRAXANE are neutropenia (3%), thrombocytopenia (3%), and peripheral neuropathy (1%)
- The most common adverse reactions resulting in dose reduction of ABRAXANE are neutropenia (24%), thrombocytopenia (13%), and anemia (6%)
- The most common adverse reactions leading to withholding or delay in ABRAXANE dosing are neutropenia (41%), thrombocytopenia (30%), and anemia (16%)
- The following common (≥10% incidence) adverse reactions were observed at a similar incidence in ABRAXANE plus carboplatin–treated and paclitaxel injection plus carboplatin–treated patients: alopecia (56%), nausea (27%), fatigue (25%), decreased appetite (17%), asthenia (16%), constipation (16%), diarrhea (15%), vomiting (12%), dyspnea (12%), and rash (10%); incidence rates are for the ABRAXANE plus carboplatin treatment group
- Adverse reactions with a difference of ≥2%, Grade 3 or higher, with combination use of ABRAXANE and carboplatin vs combination use of paclitaxel injection and carboplatin in NSCLC are anemia (28%, 7%), neutropenia (47%, 58%), thrombocytopenia (18%, 9%), and peripheral neuropathy (3%, 12%), respectively
- Adverse reactions with a difference of ≥5%, Grades 1-4, with combination use of ABRAXANE and carboplatin vs combination use of paclitaxel injection and carboplatin in NSCLC are anemia (98%, 91%), thrombocytopenia (68%, 55%), peripheral neuropathy (48%, 64%), edema peripheral (10%, 4%), epistaxis (7%, 2%), arthralgia (13%, 25%), and myalgia (10%, 19%), respectively
- Neutropenia (all grades) was reported in 85% of patients who received ABRAXANE and carboplatin vs 83% of patients who received paclitaxel injection and carboplatin

Pancreatic Adenocarcinoma Study
Among the most common (≥20%) adverse reactions in the phase III study, those with a ≥5% higher incidence in the ABRAXANE/gemcitabine group compared with the gemcitabine group are neutropenia (73%, 58%), fatigue (59%, 46%), peripheral neuropathy (54%, 13%), nausea (54%, 48%), alopecia (50%, 5%), peripheral edema (46%, 30%), diarrhea (44%, 24%), pyrexia (41%, 28%), vomiting (36%, 28%), decreased appetite (36%, 26%), rash (30%, 11%), and dehydration (21%, 11%).

Of these most common adverse reactions, those with a ≥2% higher incidence of Grade 3-4 toxicity in the ABRAXANE/gemcitabine group compared with the gemcitabine group, respectively, are neutropenia (38%, 27%), fatigue (18%, 9%), peripheral neuropathy (17%, 1%), nausea (6%, 3%), diarrhea (6%, 1%), pyrexia (3%, 1%), vomiting (6%, 4%), decreased appetite (5%, 2%), and dehydration (7%, 2%).

Thrombocytopenia (all grades) was reported in 74% of patients in the ABRAXANE/gemcitabine group vs 70% of patients in the gemcitabine group.

The most common serious adverse reactions of ABRAXANE (with a ≥1% higher incidence) are pyrexia (6%), dehydration (5%), pneumonia (4%), and vomiting (4%).

The most common adverse reactions resulting in permanent discontinuation of ABRAXANE were peripheral neuropathy (8%), fatigue (4%), and thrombocytopenia (2%).

The most common adverse reactions resulting in dose reduction of ABRAXANE are neutropenia (10%) and peripheral neuropathy (6%).

The most common adverse reactions leading to withholding or delay in ABRAXANE dosing are neutropenia (16%), thrombocytopenia (12%), fatigue (8%), peripheral neuropathy (15%), anemia (5%), and diarrhea (5%).

Other selected adverse reactions with a ≥5% higher incidence for all-grade toxicity in the ABRAXANE/gemcitabine group compared to the gemcitabine group, respectively, are asthenia (19%, 13%), mucositis (10%, 4%), dysgeusia (16%, 8%), headache (14%, 9%), hypokalemia (12%, 7%), cough (17%, 7%), epistaxis (15%, 3%), urinary tract infection (11%, 5%), pain in extremity (11%, 6%), arthralgia (11%, 3%), myalgia (10%, 4%), and depression (12%, 6%).

Other selected adverse reactions with a ≥2% higher incidence for Grade 3-4 toxicity in the ABRAXANE/gemcitabine group compared to the gemcitabine group are thrombocytopenia (13%, 9%), asthenia (7%, 4%), and hypokalemia (4%, 1%).

Postmarketing Experience With ABRAXANE and Other Paclitaxel Formulations

Severe and sometimes fatal hypersensitivity reactions have been reported with ABRAXANE. The use of ABRAXANE in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied. In postmarketing experience, cross-hypersensitivity between ABRAXANE and other taxanes has been reported.

There have been reports of congestive heart failure, left ventricular dysfunction, and atrioventricular block with ABRAXANE, primarily among individuals with underlying cardiac history or prior exposure to cardiotoxic drugs.

There have been reports of extravasation of ABRAXANE. Given the possibility of extravasation, it is advisable to monitor closely the ABRAXANE infusion site for possible infiltration during drug administration.

DRUG INTERACTIONS

Caution should be exercised when administering ABRAXANE concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4.
USE IN SPECIFIC POPULATIONS

Pregnancy

- Based on the mechanism of action and findings in animals, ABRAXANE can cause fetal harm when administered to a pregnant woman. Advise females of the potential risk to a fetus and to avoid becoming pregnant while receiving ABRAXANE.

Lactation

- Paclitaxel and/or its metabolites were excreted into the milk of lactating rats. Nursing must be discontinued when receiving treatment with ABRAXANE and for two weeks after the last dose.

Females and Males of Reproductive Potential

- Females of reproductive potential should have a pregnancy test prior to starting treatment with ABRAXANE.
- Advise females of reproductive potential to use effective contraception and avoid becoming pregnant during treatment with and for at least six months after the last dose of ABRAXANE [see Warnings and Precautions].
- Advise males with female partners of reproductive potential to use effective contraception and avoid fathering a child during treatment with ABRAXANE and for at least three months after the last dose of ABRAXANE [see Warnings and Precautions].
- Based on findings in animals, ABRAXANE may impair fertility in females and males of reproductive potential.

Pediatric

- The safety and effectiveness of ABRAXANE in pediatric patients have not been evaluated.

Geriatric

- A higher incidence of epistaxis, diarrhea, dehydration, fatigue, and peripheral edema was found in patients 65 years or older who received ABRAXANE for MBC in a pooled analysis of clinical studies.
- Myelosuppression, peripheral neuropathy, and arthralgia were more frequent in patients ≥65 years of age treated with ABRAXANE and carboplatin in NSCLC.
- Diarrhea, decreased appetite, dehydration, and epistaxis were more frequent in patients 65 years or older compared with patients younger than 65 years old who received ABRAXANE and gemcitabine in adenocarcinoma of the pancreas.

Renal Impairment

- There are insufficient data to permit dosage recommendations in patients with severe renal impairment or end stage renal disease (estimated creatinine clearance <30 mL/min).

DOSAGE AND ADMINISTRATION

- Do not administer ABRAXANE to any patient with total bilirubin greater than 5 x ULN or AST greater than 10 x ULN.
For MBC and NSCLC, reduce starting dose in patients with moderate to severe hepatic impairment
For adenocarcinoma of the pancreas, do not administer ABRAXANE to patients who have moderate to severe hepatic impairment
Dose reductions or discontinuation may be needed based on severe hematologic, neurologic, cutaneous, or gastrointestinal toxicity
Monitor patients closely

Please see full Prescribing Information, including Boxed WARNING.

About Celgene
Celgene Corporation, headquartered in Summit, New Jersey, is an integrated global biopharmaceutical company engaged primarily in the discovery, development and commercialization of innovative therapies for the treatment of cancer and inflammatory diseases through next-generation solutions in protein homeostasis, immuno-oncology, epigenetics, immunology and neuro-inflammation. For more information, please visit www.celgene.com.

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FORWARD-LOOKING STATEMENTS
This press release contains forward-looking statements, which are generally statements that are not historical facts. Forward-looking statements can be identified by the words "expects," "anticipates," "believes," "intends," "estimates," "plans," "will," "outlook" and similar expressions. Forward-looking statements are based on management's current plans, estimates, assumptions and projections, and speak only as of the date they are made. We undertake no obligation to update any forward-looking statement in light of new information or future events, except as otherwise required by law. Forward-looking statements involve inherent risks and uncertainties, most of which are difficult to predict and are generally beyond our control. Actual results or outcomes may differ materially from those implied by the forward-looking statements as a result of the impact of a number of factors, many of which are discussed in more detail in our Annual Report on Form 10-K including factors related to the proposed transaction between Bristol-Myers Squibb and Celgene, such as, but not limited to, the risks that: management's time and attention is diverted on transaction related issues; disruption from the transaction makes it more difficult to maintain business, contractual and operational relationships; pending legal proceedings or any future litigation instituted against Bristol-Myers Squibb, Celgene or the combined company could delay or prevent the proposed transaction; and Bristol-Myers Squibb, Celgene or the combined company is unable to retain key personnel.

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