HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
15 October 2014

ABRAXANE 5 mg/ml, powder for suspension for infusion

B/1 100 ml vial (CIP: 34009 384 418 7 1)

Applicant: CELGENE

INN	Paclitaxel (formulated as albumin bound nanoparticles)
ATC code (2014)	L01CD01 (taxanes)
Reason for the review	**Extension of indication**
List concerned	**Hospital use (French Public Health Code L.5123-2)**
Indication concerned	**"ABRAXANE in combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas."**

Actual Benefit	**Important in the extension of indication “first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas”.**
Improvement in Actual Benefit	**The Committee considers that ABRAXANE in combination with gemcitabine provides a minor improvement in actual benefit (level IV) compared with gemcitabine monotherapy in the treatment of metastatic adenocarcinoma of the pancreas, in adult patients, as first-line treatment.**
Therapeutic use	**The ABRAXANE/gemcitabine combination is a therapeutic alternative in the first-line treatment of pancreatic adenocarcinoma at the metastatic stage. This combination should ideally be reserved, after a decision taken at a multidisciplinary consensus meeting, for patients in good general condition (Karnofsky score ≥ 80%). An oncogeriatric assessment of patients aged over 75 years is necessary prior to starting this therapeutic combination.**
Target population	**The target population of ABRAXANE in adenocarcinoma of the pancreas can be estimated at 5400 patients.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	11/01/2008 (centralised procedure); Date on which the extension of indication was granted: 20/12/2013
Prescribing and dispensing condition/special status	List I Medicinal product requiring special supervision throughout treatment Medicinal product subject to prescription in a hospital Medicinal product reserved for prescription by cancerology, haematology and medical oncology specialists and services

ATC Classification	2014	
	L	Antineoplastic and immunomodulating agents
	L01	Antineoplastic agents
	L01C	Plant alkaloids and other natural products
	L01CD	Taxanes
	L01CD01	paclitaxel

02 BACKGROUND

This is an examination of the request for inclusion in a new indication (as first-line treatment of metastatic adenocarcinoma of the pancreas in adult patients, in combination with gemcitabine), of the proprietary medicinal product ABRAXANE 5 mg/ml, powder for suspension for infusion, on the list of medicines approved for hospital use.

ABRAXANE is made up of human serum albumin-paclitaxel nanoparticles (*nab*-paclitaxel). It differs from the standard formulation paclitaxel already available for hospital use in the albumin nanoparticles that transport paclitaxel into the cells. Albumin is known to facilitate endothelial transcytosis of plasma components and in vitro studies have shown that its presence favours the transport of paclitaxel across endothelial cells.

As a reminder, the Committee first assessed the proprietary medicinal product ABRAXANE on 27/01/2010 in another indication "treatment, as monotherapy, of metastatic breast cancer in patients who have failed first-line treatment, and for whom standard, anthracycline containing therapy is not indicated". In this indication, it considered that the AB of ABRAXANE was substantial and that it contributed a minor IAB compared with TAXOL.

03 THERAPEUTIC INDICATIONS

"ABRAXANE monotherapy is indicated in the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated (see section 4.4).

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

04 DOSAGE

In the indication metastatic adenocarcinoma of the pancreas

"The recommended dose of ABRAXANE in combination with gemcitabine is 125 mg/m^2 administered intravenously over 30 minutes on Days 1, 8 and 15 of each 28-day cycle. The concurrent recommended dose of gemcitabine is 1000 mg/m^2 administered intravenously over 30 minutes immediately after the completion of ABRAXANE administration on Days 1, 8 and 15 of each 28-day cycle.

Dose adjustments during treatment of pancreatic adenocarcinoma
(see SPC)

Special populations:
Patients with hepatic impairment
For patients with moderate to severe hepatic impairment, there are currently insufficient data to recommend a dose adjustment that would enable an acceptable level of toxicity while maintaining the efficacy of ABRAXANE. Patients with severe hepatic impairment should not be treated with paclitaxel (see "Special Warnings and Precautions for Use", "Pharmacokinetics").

Patients with renal impairment
No studies have been done in patients with renal impairment and there are currently insufficient data to recommend dose modifications of ABRAXANE in patients with renal impairment (see "Pharmacokinetics").

Older people
No additional dosage reductions, other than those for all patients, are recommended for patients 65 years and older. Of the 229 patients in the randomised study who received ABRAXANE monotherapy for breast cancer, 13% were at least 65 years of age and < 2% were 75 years or older. No toxicities occurred notably more frequently among patients at least 65 years of age who received ABRAXANE.
Of the 421 patients with pancreatic adenocarcinoma in the randomised study who received ABRAXANE in combination with gemcitabine, 41% were 65 years and older and 10% were 75 years and older. In patients aged 75 years and older who received ABRAXANE and gemcitabine, there was a higher incidence of serious adverse reactions and adverse reactions that led to treatment discontinuation (see "Special Warnings and Precautions for Use"). Patients with pancreatic adenocarcinoma aged 75 years and older should be carefully assessed before treatment is considered (see "Special Warnings and Precautions for Use").

Paediatric population
The safety and efficacy of ABRAXANE in children and adolescents aged 0-17 years have not been established. There is no relevant use of ABRAXANE in the paediatric population in the indication of metastatic breast cancer or pancreatic adenocarcinoma."

05 THERAPEUTIC NEED

Pancreatic adenocarcinoma accounts for 90% of pancreatic tumours. It is a tumour affecting the exocrine part of the pancreas. The diagnosis is most commonly made at an advanced stage due to the late clinical expression of the disease (80-85% of newly diagnosed patients). It is a cancer with a poor prognosis; for all stages combined, 5-year survival is currently 5%[1] and 5-year survival in patients with metastatic-stage pancreatic adenocarcinoma is 2%.[2]

According to the ESMO guidelines,[3] until recently, the standard first-line treatment for pancreatic adenocarcinoma at the metastatic stage was gemcitabine monotherapy (with a median survival of 6.2 months and a 1-year survival rate of 20%).
In patients in good general condition, the FOLFIRINOX protocol (a combination of 5-FU, irinotecan and oxaliplatin), having demonstrated in a phase II/III[4] study an improvement in overall survival (median of 11.1 months, 1-year survival rate = 48.4%) compared with standard treatment with gemcitabine, represents a new treatment option in patients aged less than 75 years, with an ECOG (performance status) score of 0-1 and a bilirubin level ≤ 1.5 N. This gain in efficacy was obtained at the cost of a higher level of toxicity than with gemcitabine alone, with in particular 46% of grade 3-4 neutropenia with the FOLFIRINOX protocol.

In case of disease progression:
- The 5-FU/oxaliplatin combination is recommended as second-line treatment in patients previously treated with first-line gemcitabine monotherapy.
- Gemcitabine monotherapy is recommended as second-line treatment in patients previously treated with a first-line FOLFIRINOX protocol.

As a reminder, the Committee, in its opinion of 19 March 2008, considered that the actual benefit provided by TARCEVA was insufficient bearing in mind the available clinical data: results of an exploratory subgroup analysis defined a posteriori, which showed a 26-day gain in median

[1] Guide ALD [chronic conditions] 30 - Pancreatic cancer – HAS; INCa – November 2010
[2] Cancer facts and figures 2013. Atlanta: American Cancer Society, 2013.
[3] Seufferlein T, Bachet JB, Van Cutsem E, Rougier P; ESMO Guidelines Working Group. Pancreatic adenocarcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012; 23: vii33-40.
[4] Conroy T, Desseigne F, Ychou M et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011; 364: 1817-25.

overall survival in favour of the TARCEVA/gemcitabine combination versus gemcitabine alone, with no improvement in patients' quality of life; an increased frequency of diarrhoea and skin involvement on TARCEVA/gemcitabine.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

Name (INN) Company	TC*	Indication	Date of opinion	AB	IAB	Cover Yes/no
GEMZAR** (gemcitabine) LILLY	Antimetabolites - Pyrimidine antagonists	Gemcitabine is indicated for the treatment of patients with locally advanced or metastatic adenocarcinoma of the pancreas.	07/04/1999	Substantial	IAB III	YES
TARCEVA (erlotinib) ROCHE	Tyrosine kinase inhibitor	TARCEVA in combination with gemcitabine is indicated for the treatment of patients with metastatic pancreatic cancer.	19/03/2008	Insufficient	-	No cover in this indication
FOLFIRINOX protocol (combination of 5-FU, irinotecan and oxaliplatin)		The FOLFIRINOX protocol is recommended by the ESMO[3] in metastatic pancreatic cancer in patients aged less than 75 years, who have an ECOG (performance status) score of 0-1 and a bilirubin level ≤ 1.5 N	Not assessed by HAS	-	-	

* therapeutic category
** and its generics

Conclusion

The clinically relevant comparators are gemcitabine monotherapy in the general population and the FOLFIRINOX protocol in patients aged less than 75 years, who have an ECOG (performance status) score of 0-1 and a bilirubin level ≤ 1.5 N.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

	COVER	
	YES/NO If no, why	Population(s) That of the MA or restricted
Austria	YES	
Denmark	YES	"Patients ≥ 18 years, with a KPS ≥ 70%"
United Kingdom	YES (Assessment carried out by the Cancer Drugs Fund; no assessment by NICE)	"Patients with stage IV pancreatic adenocarcinoma confirmed by histology or cytology (patients with locally advanced disease not eligible), no previous chemotherapy treatment except for patients who have received radiotherapy at least 6 months earlier, performance status 0-1."
Germany	YES (no AMNOG assessment)	
Greece	YES	

08 ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

In support of its request for inclusion in the extension of indication, the company has provided a phase III, randomised, open-label study to compare the combination of *nab*-paclitaxel with gemcitabine versus gemcitabine alone: MPACT (Metastatic Pancreatic Adenocarcinoma Clinical Trial).[5]

MPACT Study (CA046)

This is a phase III, randomised, open-label study to compare the efficacy and safety as first-line treatment of the *nab*-paclitaxel plus gemcitabine combination versus gemcitabine alone in 861 patients with metastatic pancreatic adenocarcinoma.

Treatment schedule

Randomisation was stratified according to: the Karnofsky performance index (70-80 versus 90-100), the presence or absence of liver metastases and geographical region (Australia versus Eastern Europe, Western Europe versus North America).

The patients in the *nab*-paclitaxel plus gemcitabine group were treated with *nab*-paclitaxel at the dose of 125 mg/m^2 followed by gemcitabine at the dose of 1000 mg/m^2 by intravenous infusion on D1, D8 and D15 during each 28-day cycle. This corresponds to the administration of the *nab*-paclitaxel plus gemcitabine combination each week for 3 weeks followed by one week's rest.

The patients in the gemcitabine alone group were treated with gemcitabine 1000 mg/m^2 by intravenous infusion on D1, D8, D15, D22, D29, D36 and D43 during cycle 1 (in other words

[5] Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013; 369: 1691-703.

weekly for 7 weeks) then on D1, D8 and D15 during a 28-day cycle for subsequent cycles. A rest period of 1 week was observed between each cycle.

Inclusion and non-inclusion criteria

The inclusion criteria consisted, in particular, of:

- patients aged over 18 years with metastatic pancreatic adenocarcinoma confirmed by histology or cytology (diagnosis ≤ 6 weeks before randomisation);
- (one or more) metastatic lesions measurable by CT scan or magnetic resonance imaging;
- absence of previous surgery, radiotherapy, chemotherapy or experimental treatment for metastatic disease. Previous treatment with 5-FU or gemcitabine adjuvant to radiotherapy > 6 months before randomisation was accepted;
- KPS (Karnofsky Performance Status) ≥ 70;
- adequate haematological, hepatic and renal function (defined by absolute neutrophil count ≥ 1.5 x 10^9/l, Hb ≥ 9 g/dl, bilirubin ≤ ULN).l

The non-inclusion criteria consisted, in particular, of:

- brain metastases, if not treated and controlled at least 3 months earlier;
- locally advanced disease only;
- ≥ 10% reduction in KPS between the inclusion visit and 72 hours prior to randomisation;
- history of cancer in the last 5 years, except cancer in situ or basal cell carcinoma or squamous cell carcinoma. Patients with other malignant tumours (except chronic leukaemias) were eligible if they had been cured by surgery alone or surgery plus radiotherapy, and had been disease free for at least 5 years;
- uncontrolled infections requiring systemic treatment, HIV, hepatitis B or C;
- major surgery < 4 weeks before the start of the study;
- high cardiovascular risk;
- history of interstitial lung disease, slowly progressive dyspnoea and dry cough,
- sarcoidosis, silicosis, idiopathic pulmonary fibrosis, hypersensitivity pneumonitis or several allergies;
- history of chronic leukaemia;
- patients treated with warfarin.

Primary efficacy endpoint

The primary efficacy endpoint was overall survival, defined as the duration between randomisation and death of the patient.

Secondary endpoints

- Progression-free survival defined as the duration between randomisation and the first occurrence of one of the following events: disease progression or death, from any cause.
- Percentage of objective response (complete response + partial response) evaluated every 8 weeks by independent radiological review of CT (or magnetic resonance imaging) scans based on RECIST version 1.0 criteria. Quality of life data were not collected.

Statistical analysis

- ITT population: All randomised patients
- Modified ITT population: All randomised patients who received at least one dose of treatment.

A total of 421 patients in each treatment group was planned to observe a statistically significant difference in terms of overall survival between the two groups, with the occurrence of at least 608 events, with a two-sided alpha level of 0.049 and a power of 90%.

Survival curves were estimated according to the Kaplan-Meier method and compared using a stratified log-rank test. In addition, for overall survival and progression-free survival, multivariate analyses using a Cox proportional risk model were performed to evaluate the influence of potential prognostic factors.

Results:
Between May 2009 and April 2012, a total of 861 patients were randomised (ITT population) in a ratio of 1:1, i.e. 431 patients in the *nab*-paclitaxel plus gemcitabine treatment group and 430 in the gemcitabine alone group.

Patient characteristics were similar in the different treatment groups. The mean patient age was 62.2 years (58% men). The percentage of patients aged over 75 years was 10% (90/861 patients). More than 60% of patients were included in North American centers and only 9% of patients in Western European centers.
The majority of patients included were in good general condition: 60% had a Karnofsky performance index of 90-100 and 39% had an index of 70-80.

Primary efficacy endpoint
On the date of attainment of the expected events, 80% of patients randomised had died: 333 deaths (77%) in the *nab*-paclitaxel plus gemcitabine group and 359 in the gemcitabine alone group (83%).

Median overall survival was longer in the *nab*-paclitaxel plus gemcitabine group (8.5 months) than in the gemcitabine alone group (6.7 months), i.e. an absolute gain of 1.8 months: HR = 0.72; 95% CI = [0.617; 0.835]; p<0.0001.

Estimated percentage survival at 12 months was 35%, 95% CI = [29.7; 39.5] (108 patients) in the *nab*-paclitaxel plus gemcitabine group versus 22%, 95% CI = [18.1; 26.7] (69 patients) in the gemcitabine group.
Estimated percentage survival at 24 months was 9%, 95% CI = [6.2; 13.1] (16 patients) in the *nab*-paclitaxel plus gemcitabine group versus 4%, 95% CI = [2.3; 7.2] (7 patients) in the gemcitabine group.

By way of information: in exploratory analyses performed in pre-defined subgroups, efficacy in terms of overall survival was in favour of the *nab*-paclitaxel plus gemcitabine group in the majority of the subgroups[6] except 2: the subgroup with normal CA 19-9 level at inclusion (RR = 1.07, 95% CI = [0.692-1.661] (CA 19-9: a low-sensitivity and low-specificity marker for pancreatic cancer) and the subgroup of patients aged 75 years and older (n=41/431 in the *nab*-paclitaxel plus gemcitabine group and n=49/430 in the gemcitabine alone group) with a RR = 1.08 95% CI [0.653-1.797]).

Moreover, the proportion of patients receiving second-line cancer treatment was similar between the two treatment groups, with 162 patients (38%) in the *nab*-paclitaxel plus gemcitabine group and 179 patients (42%) in the gemcitabine alone group.
Of those patients: 112 (26%) in the *nab*-paclitaxel plus gemcitabine group and 130 (30%) in the gemcitabine alone group received other 5-FU-based or capecitabine-based chemotherapies, 19 patients (4%) versus 25 patients (6%) were treated with the FOLFIRINOX protocol, modified or not, and finally, 27 patients (6%) in the gemcitabine alone group received the *nab*-paclitaxel plus gemcitabine combination. The patients were censored on the date of initiation of this new treatment.

Secondary endpoints
Median progression-free survival was greater in the *nab*-paclitaxel plus gemcitabine group (5.5 months, 95% CI = [4.47; 5.95]) than in the gemcitabine alone group (3.7 months, 95% CI = [3.61; 4.04]); HR = 0.69, 95% CI = [0.581; 0.821]; p<0.0001.

[6] Sex, Age, KPS, geographical region, primary site of the pancreatic cancer, stage at time of diagnosis, presence of liver metastases, presence of peritoneal carcinosis, history of cephalic pancreaticoduodenectomy (Whipple procedure), presence of a biliary stent at inclusion, presence of lung metastases and number of metastatic sites, CA 19-9 level.

Percentage of objective response (complete response + partial response) was greater in the *nab*-paclitaxel plus gemcitabine group (23%, 95% CI = [19.1; 27.2]) than in the gemcitabine alone group (7%, 95% CI = [5.0; 10.1]): response rate ratio R = 3.19; 95% CI = [2.178; 4.662]; p<0.0001.

08.2 Adverse effects

8.2.1 MPACT study (CA046)

The safety data were analysed in the modified ITT population (all randomised patients who received at least one dose of treatment), and the cohort sizes were as follows:
- *nab*-paclitaxel plus gemcitabine group: n=421/431
- gemcitabine group: n=402/430

The percentage of adverse events was 99% (417/421 patients) in the *nab*-paclitaxel plus gemcitabine group and 98% (395/402 patients) in the gemcitabine alone group.
Treatment discontinuation due to an adverse event was more common in the *nab*-paclitaxel plus gemcitabine group (35%, 149/421) than in the gemcitabine alone group (24%, 95/402).

The most common adverse events were (*nab*-paclitaxel plus gemcitabine versus gemcitabine alone):
- gastrointestinal disorders (84% versus 78%):
  - nausea (54% versus 48%),
  - vomiting (36% versus 28%),
  - diarrhoea (44% versus 24%),
- myelosuppression (67% versus 59%):
  - neutropenia (42% versus 30%) of which febrile neutropenia (3% versus 1%),
  - anaemia (42% versus 33%),
  - thrombocytopenia (30% versus 29%), haemorrhages (23% versus 13%), epistaxis (15% versus 3%),
  - leukopenia (14% versus 10%) of which sepsis (5% versus 2%),
- fatigue (59% versus 46%),
- peripheral neuropathy (54% versus 13%),
- alopecia (50% versus 5%),
- peripheral oedema (46% versus 31%),
- skin rashes (28% versus 10%).

The percentage of ≥ grade 3 adverse events was higher in the *nab*-paclitaxel plus gemcitabine group (89%) than in the gemcitabine group (75%), consisting mainly of: neutropenia (33% versus 21%), thrombocytopenia (13% versus 8%), anaemia (12% versus 8%), fatigue (18% versus 9%) and peripheral neuropathy (17% versus 1%).

Adverse effects resulting in death within 30 days of the last dose of treatment were reported for 4% of patients in each treatment group.

Median duration of treatment was 3.9 months in the *nab*-paclitaxel plus gemcitabine group and 2.8 months in the gemcitabine alone group (mean duration: 4.8 versus 3.7 months).
The mean number of cycles administered was 4.4 cycles versus 3.3.
- The percentage with dose reduction due to adverse eventwas 50% (209/421) in the *nab*-paclitaxel plus gemcitabine group versus 31% (125/402) in the gemcitabine alone group.
- The percentage of patients with dose interruption due to adverse event was 3% (11/421) in the *nab*-paclitaxel plus gemcitabine group versus 2% (10/402) in the gemcitabine alone group.
- The percentage of patients with a dose delay due to adverse eventwas 66% (276/421) in the *nab*-paclitaxel plus gemcitabine group versus 48% (192/402) in the gemcitabine alone group.

The percentage of patients who received a concomitant administration of erythropoietin was 16% versus 11%, and of blood transfusions 12% versus 7%.

In a limited subgroup of patients aged 75 years and older (n=41/431 in the *nab*-paclitaxel plus gemcitabine group and n=49/430 in the gemcitabine alone group), the incidence of serious adverse events and events resulting in treatment discontinuation were higher in the *nab*-paclitaxel plus gemcitabine group than in the gemcitabine alone group.

8.2.2 SPC and Risk Management Plan

The company has provided the latest pharmacovigilance report (PSUR 9) covering the period from 07/01/2012 to 06/01/2013.

New safety signals, warnings and precautions for use were issued during that period and included in the summary of product characteristics (SPC), in particular:

- Sepsis, which was reported with an incidence of 5% in patients with or without neutropenia who were receiving the *nab*-paclitaxel plus gemcitabine combination.
- Pneumonitis, reported in 4% of patients treated with *nab*-paclitaxel plus gemcitabine.
- Patients aged 75 years and older in whom no benefit was demonstrated with the *nab*-paclitaxel plus gemcitabine combination over gemcitabine alone with a higher frequency of serious adverse effects and adverse effects resulting in treatment discontinuation, including haematological toxicities, peripheral neuropathy, decreased appetite and dehydration.
- Although the available data are limited, no benefit in terms of prolonged overall survival was demonstrated for patients with pancreatic adenocarcinoma who had a normal CA 19-9 level prior to starting treatment with ABRAXANE plus gemcitabine.
- The warning on hypersensitivity reactions.
- The addition of cystoid macular oedema as a rare event.
- The addition of sepsis and neutropenic sepsis as rare events.

08.3 Summary & discussion

In a phase III, randomised, open-label study (MPACT CA046 study, n=861) conducted in 861 adult patients with metastatic pancreatic adenocarcinoma in good general condition (Karnofsky index ≥ 70), median overall survival (primary efficacy endpoint) with the combination of *nab*-paclitaxel (125 mg/m^2 by IV infusion) and gemcitabine (1000 mg/m^2 by IV infusion) (8.5 months) was superior to treatment with gemcitabine alone (1000 mg/m^2 by IV infusion) (6.7 months); HR = 0.72; 95% CI = [0.617; 0.835]; p<0.0001.

In terms of safety, the rate of treatment discontinuation due to an adverse event was higher in the *nab*-paclitaxel plus gemcitabine group (35%, 149/421) than in the gemcitabine alone group (24%, 95/402), as well as adverse events ≥ grade 3 (89% versus 75%).
The toxicity of the combination was primarily haematological, with grade 3-4 neutropenia in a third of cases (33% versus 21%), neurological, with grade 3-4 peripheral neuropathy (17% versus 1%) and gastrointestinal.

Finally, the most common adverse events were: nausea (54% versus 48%), diarrhoea (44% versus 24%), alopecia (50% versus 5%), fatigue (59% versus 46%), peripheral oedema (46% versus 31%), peripheral neuropathy (54% versus 13%), neutropenia (42% versus 30%), anaemia (42% versus 33%), thrombocytopenia (30% versus 29%) and haemorrhages (23% versus 13%).

In conclusion, the *nab*-paclitaxel plus gemcitabine combination showed a gain in terms of overall survival (primary efficacy endpoint) of 1.8 months (8.5 versus 6.7 months) over gemcitabine alone at the expense of increased toxicity. The quality of life data are not available.

09 THERAPEUTIC USE

The current management of pancreatic adenocarcinoma at the metastatic stage is as follows:
- Until recently, the conventional treatment for metastatic pancreatic adenocarcinoma was gemcitabine monotherapy.
- The use of the FOLFIRINOX chemotherapy protocol (a combination of 5-FU, irinotecan and oxaliplatin) is a new therapeutic option, validated in the ESMO 2012,[3] TNCD[7] and NCCN 2014 guidelines, for patients in good general condition, given the toxicity profile, in other words those aged under 75 years and with an ECOG (performance status) score between 0 and 1 and a bilirubin level ≤ 1.5 N.

The ABRAXANE-gemcitabine combination is a first-line therapeutic alternative for the treatment of pancreatic adenocarcinoma at the metastatic stage. This combination should ideally be reserved, after a decision taken at a Multidisciplinary Consensus Meeting, for patients in good general condition (Karnofsky score ≥ 80%). An oncogeriatric assessment of patients aged over 75 years is necessary before starting this therapeutic combination.

Overall, considering the absence of an alternative validated by a MA, the Committee highlights the value of having this treatment option available at this stage of the disease.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above data and information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

Pancreatic adenocarcinoma is a cancer with high metastatic potential, is usually diagnosed at an advanced stage and is life-threatening in the short term.

ABRAXANE in combination with gemcitabine is a specific treatment for metastatic pancreatic adenocarcinoma.

The efficacy/adverse effects ratio of ABRAXANE in combination with gemcitabine is high.

There are treatment alternatives such as gemcitabine monotherapy or the FOLFIRINOX protocol (only for patients aged less than 75 years, with an ECOG score between 0 and 1 and a bilirubin level ≤ 1.5 N).

It is a first-line therapy for patients in good general condition, given the toxicity profile (patients aged under 75 years, with a Karnofsky performance score ≥ 80%).

◗ Public health benefit: In France, the incidence of pancreatic cancer was estimated to be about 11,662 new cases per year in 2012.[8] A sharp rise in the incidence of this cancer has

[7] Thésaurus National de Cancérologie Digestive. Available online: [URL]: http://www.tncd.org.
[8] Binder-Foucard F, Belot A, Delafosse P, Remontet L, Woronoff A-S, Bossard N. Estimation nationale de l'incidence et de la mortalité par cancer en France entre 1980 et 2012. Partie 1 - Tumeurs solides. Saint-Maurice (Fra) : Institut de veille sanitaire ; 2013. http://www.inversus.sante.fr/Dossiers-

been evident since 1980; the average annual percent change has been around 5% per year since 2005. Pancreatic cancer now ranks 6th in terms of incidence, among all cancers. The prognosis of pancreatic cancer is among the worst of all cancers. The relative 5-year survival rate for all stages combined is 6%.[9] The public health burden of this cancer is, therefore, large (405,194 DALYs - WHO Euro Zone A). Although the diagnosis is usually made at an advanced stage due to the late clinical expression of the disease, 20% of patients are diagnosed at a stage when the tumour is resectable.[10]
The burden of this cancer for the subpopulation of patients with metastatic pancreatic adenocarcinoma who are likely to benefit from a treatment combining ABRAXANE and gemcitabine remains substantial.
The improvement in the management of cancer patients and their quality of life is a public health need that falls within the established priorities (Law of 9 August 2004 on public health policy, Cancer Plan 2014-2018, Plan for the improvement of the quality of life of patients with chronic diseases).

In view of the available results of the only phase III study MPACT demonstrating a clear benefit in terms of overall survival of 1.8 months compared with gemcitabine alone (relative reduction HR = 0.72 [95% CI = 0.62-0.84]) and 1.8 months in progression-free survival (HR = 0.69 [95% CI = 0.58-0.82], there is expected to be a low additional impact in terms of morbidity and mortality of the ABRAXANE + gemcitabine combination.
Patients' quality of life was not evaluated in the pivotal study and an increase in myelosuppression (48% versus 32% grade 3 events) and neurotoxicity (17% of grade 3 peripheral neuropathies versus 1%), likely to result in premature treatment discontinuation, was observed in particular in this same study.

The results of the pivotal study can only be translated to clinical practice in the population in good general condition (Karnofsky score ≥ 80%).

No impact on the healthcare system is expected.
The proprietary medicinal product ABRAXANE provides an additional solution to the identified public health need.
Consequently, the impact of ABRAXANE on public health, when used in combination with gemcitabine in this indication, is expected to be low.

Taking account of these points, the Committee considers that the actual benefit of ABRAXANE in combination with gemcitabine is <u>substantial</u> in the extension of indication "first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas".

010.2 Improvement in actual benefit (IAB)

The Committee considers that ABRAXANE in combination with gemcitabine provides a <u>minor (level IV) improvement in actual benefit</u> in comparison with gemcitabine monotherapy in the treatment of metastatic adenocarcinoma of the pancreas, in adult patients, as a first-line treatment.

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thematiques/Maladies-chroniques-et-traumatismes/Cancers/Surveillance-epidemiologique-des-cancers/Estimations-de-l-incidence-et-de-la- mortalite/Estimation-de-l-incidence-et-de-la-mortalite-par-cancer-en-France-entre-1980-et-2012-Tumeurs-solides [Access 17/7/2014].

[9] Grosclaude P ; Remontet L ; Belot A ; Danzon A ; Rasamimanana Cerf N ; Bossard N Survie des personnes atteintes de cancer en France, 1989-2007. Etude à partir des registres des cancers du réseau Francim. Saint-Maurice : Institut de veille sanitaire, 02/2013. http://opac.inversus.sante.fr/doc_num.php?explnum_id=8758 [Access 17/7/2014].

[10] Guide – Affection de longue durée ALD 30 - Tumeur maligne, affection maligne du tissu lymphatique ou hématopoïétique. Cancer du pancréas. HAS, Inca. Novembre 2010 *[Guide – Chronic condition CC 30 – Malignant tumour, malignant disorder of lymphatic or haematopoietic tissue. Pancreatic cancer. HAS, Inca. November 2010*].

010.3 Target population

The target population of ABRAXANE in combination with gemcitabine is adult patients with metastatic pancreatic adenocarcinoma.
In 2012, the incidence of pancreatic cancer in France was estimated to be 11,662 new cases per year.[8] Exocrine pancreatic cancer or ductal pancreatic adenocarcinoma accounts for 90% of all forms of this cancer, or nearly 10,500 patients per year.
The percentage of patients diagnosed at a metastatic stage was not found in the literature.
The programme for clinical information systems (PMSI) 2012 database identifies 5386 patients with metastatic pancreatic adenocarcinoma and treated with chemotherapy.
Pancreatic adenocarcinoma is characterised by an incidence equivalent to annual mortality.

Therefore, the target population of ABRAXANE in pancreatic adenocarcinoma can be estimated to be 5400 patients.
This target population is probably an overestimate inasmuch as the ABRAXANE/gemcitabine combination should ideally be reserved for patients in good general condition (Karnofsky score ≥ 80%), the number of whom cannot be identified.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends inclusion on the list of medicines approved for hospital use in the extension of indication "first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas" and at the dosages in the Marketing Authorisation.