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Nab-Paclitaxel (Abraxane®) as first-line therapy for metastatic adenocarcinoma of the pancreas

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1 Drug description

Generic/Brand name/ATC code:

Paclitaxel/Abraxane®/L01CD01

Developer/Company:

Celgene Corporation

Description:

Paclitaxel, a natural mitotic inhibitor, belongs to the family of taxanes and is obtained via a semi-synthetic process from Taxus baccata, a conifer. It is used as cancer chemotherapy by targeting tubulin. It stabilises the microtubule polymer and protects it from disassembly. Thereby the chromosomes are unable to achieve a metaphase spindle configuration that blocks the progression of mitosis. This blockade triggers apoptosis or the reversion to the G-phase of the cell cycle without cell division [1, 2]. Abraxane® is the albumin-bound formulation of paclitaxel (nab-paclitaxel) which was designed to overcome the insolubility problems associated with conventional paclitaxel formulations [3].

paclitaxel is a natural mitotic inhibitor

triggers apoptosis or revision of the cell cycle

The drug is administered intravenously as an infusion over 30-40 minutes. For the treatment of pancreatic cancer an Abraxane® dose of 125 mg/m^2 of body surface is suggested. Patients use the drug on days 1, 8 and 15 of each 28-day cycle. Gemcitabine is administered immediately after Abraxane® on the same days. The therapy should be continued until the disease progresses or toxicity gets intolerable [4].

for pancreatic cancer: 125 mg/m² intravenously

nab-paclitaxel to overcome insolubility problems

2 Indication

Patients with metastatic adenocarcinoma of the pancreas who have not received prior therapy for their metastatic disease.

patients with metastatic pancreas carcinoma

3 Current regulatory status

In the European Union and the USA, paclitaxel monotherapy is licensed for second-line therapy for metastatic breast cancer [5-8]. In the USA, the drug is also approved in combination with carboplatin for the first-line treatment of non-small cell lung cancer [9].

EMA and FDA: in combination with gemcitabine for the first-line treatment of patients with metastatic pancreatic cancer

In September 2013, the U.S. Food and Drug Administration (FDA) authorised nab-paclitaxel in combination with gemcitabine for the first-line treatment of patients with metastatic pancreatic cancer [10]. This new indication for Abraxane® was assessed under the agency's priority review programme. In addition, orphan product designation was granted for pancreatic cancer [11, 12].

FDA: orphan drug status

In November 2013, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended nab-paclitaxel in combination with gemcitabine for the use in patients with metastatic pan-

creatic cancer [13]. Accordingly, the European Commission has amended the marketing authorisation in December 2013 [14, 15]. In 2010, the European Commission granted an orphan designation for nanoparticle albumin-bound paclitaxel for the treatment of pancreatic cancer which was withdrawn from the Community Register of designated Orphan Medicinal Products at the sponsor's request in February 2013 [16].

4 Burden of disease

fourth most frequent cause of cancer-related death in North America and Western Europe

In 2008, about 340,000 people were diagnosed with pancreatic cancer worldwide with over 330,000 patients dying from this disease. Highest incidence rates are found in North America and Western Europe [17]. In these parts of the world pancreatic cancer is the fourth most frequent cause of cancer-related death [18, 19]. This holds also true for Austria, where 1,424 men and women died of pancreatic cancer in 2009 although it only accounts for 4% of all cancers diagnosed [20]. This is attributable to the high lethality and the poor prognosis of the disease. Men are more frequently affected than women. Per 100,000 people in Austria, 10.3 men and 7.6 women were diagnosed with pancreatic cancer in 2009 [20]. 8 out of 10 pancreatic cancers occur in patients 60 years or older [21].

2009: 1,424 persons died of pancreatic cancer in Austria

various risk factors for development, e.g. smoking, chronic pancreatitis and obesity

Risk factors for the development of pancreatic cancer include cigarette smoking, chronic pancreatitis, family history, obesity, type 1 and type 2 diabetes mellitus and processed meat [21, 22]. In the UK, smoking causes over 25% of pancreatic cancers and smokeless tobacco increases the risk further. In people with diabetes mellitus type I or II the risk of pancreatic cancer approximately doubles. Inflammatory diseases of the pancreas increase the risk as well as a family history of pancreatic cancer. Overweight and obesity cause about 1,000 pancreatic cancer cases in the UK every year and processed meat may also raise the pancreatic cancer risk [21].

four stages according to the TMN system

The seventh edition of the tumour node metastasis (TNM) system classifies pancreatic cancer into the stages Ia, Ib, IIa, IIb, III and IV. The division is based on the size of the primary tumour (T), the affection of lymph nodes (N) and the presence of distant metastases (M). Stages Ia and Ib describe tumours limited to the pancreas with ≤ 2 and > 2 cm in the greatest dimension, respectively. Local lymph node metastases or distant metastases are absent. Stage IIa tumours extend beyond the pancreas without affecting the celiac axis or the superior mesenteric artery. Lymph nodes and other body parts are still not involved. Stage IIb describes tumours of different sizes with regional lymph node metastases. Stage III tumours are no longer resectable and stage IV tumours finally include distant metastases [22].

stage IV: metastatic disease

often diagnosed in advanced stages and highly lethal

Since pancreatic cancer generally does not cause early symptoms, cancers are usually diagnosed at advanced stages and are thus highly lethal [20]. Prognosis depends on whether tumours are located and fully resectable or have already spread to other body parts. The former stage has the best prognosis and is present in less than 20% of patients. The median survival time of patients with metastatic pancreatic cancer is about 6 months [18]. Patients with completely resectable small tumours and no lymph node metastases have a 5-year survival rate of 18% to 24% [22]. Among patients with metastatic disease, the 5-year survival rate is only 2% [18]. A further prog-

5-year survival rate for metastatic disease: 2%

nostic factor is age, where younger patients are more likely to survive than older ones [21].

5 Current treatment

surgery and post-operative chemotherapy for stage I and II

Therapies for stage I and stage II pancreatic cancer include surgery and post-operative chemotherapy. The more advanced stages of pancreatic cancer, i.e. stage III or higher, are incurable. The primary treatment modality for patients with locally advanced cancer is chemotherapy with gemcitabine at conventional dosing (1000 mg/m^2 over 30 min) [22, 23].

metastatic disease: treatment focuses on palliative therapy

The preferred treatment of metastatic (stage IV) pancreatic cancer in eligible patients is chemotherapy. In addition, all patients are eligible for palliative treatment.

- Palliative therapy: Palliative therapy focuses on pain-relieving techniques like celiac or intrapleural blocks and supportive care. Surgical procedures include biliary bypass surgery, percutaneous radiologic biliary stent placement or endoscopically placed biliary stents.

chemotherapy shows low response rates

- Chemotherapy: Gemcitabine alone or in combination with other agents or a chemotherapy regimen consisting of folinic acid, 5-FU, irinotecan and oxaliplatin (FOLFIRINOX) are used in chemotherapy. In general, existing therapies with gemcitabine alone or in combination with erlotinib show low response rates and do not sufficiently improve survival in patients with metastatic pancreatic cancer.

first-line treatment: gemcitabine monotherapy

  - Nevertheless, based on the results of phase II and phase III clinical trials, single-agent therapy with gemcitabine was standard first-line chemotherapy until recently [23], especially for patients with poor performance status (ECOG ≥ 2) [24, 25].

combination therapy: gemcitabine plus erlotinib

  - Patients may also be treated with a combination of gemcitabine and erlotinib, but the actual benefit might be rather small and is limited to patients who develop skin rash within the first 8 weeks of treatment [23,25].

for patients with ECOG performance status 0 or 1: FOLFIRINOX or gemcitabine plus nab-paclitaxel

  - For patients with good performance status, (i.e. ECOG 0 or 1 or a corresponding Karnofsky performance-status score of 70 or more [26]), the following combination chemotherapies are recommended as first-line therapy [25]:
    FOLFIRINOX showed a significantly prolonged survival in comparison to gemcitabine. Median overall survival was 11.1 months versus 6.8 months and the response rate was 31.6% versus 9.4%, but at the cost of more adverse events in the FOLFIRINOX group [24]. The same study investigated only patients aged 75 years and younger, with an adequate liver function (i.e. bilirubin ≤ 1.5 times the upper

limit of the normal range). Therefore this therapy regimen is only suitable for this limited patient group.

- As an alternative to FOLFIRINOX, a combination of gemcitabine plus nab-paclitaxel is recommended for patients with a bilirubin level within the normal range. [24].

- Combinations of gemcitabine and other cytotoxic agents, such as 5-FU or capecitabine, irinotecan, cis- or oxaliplatin, did not show any significant advantage in survival even in large randomised controlled trials (RCTs) and therefore are not recommended as first-line treatment of metastatic pancreatic cancer [23].

no widely accepted standard for second-line therapy

There is no widely accepted standard of care for patients who have failed gemcitabine-containing chemotherapy [24]. The only data indicating a survival benefit for second-line therapy come from a study comparing 5-FU, leucovorin and oxaliplatin (OFF regimen) versus best supportive care. The median survival was 4.82 months versus 2.30 months in favour of the OFF treatment. Since this study had a very small number of participants and closed early, the evidence for this effect appears to be rather weak [22].

6 Evidence

A systematic literature search was conducted on the 16th of January 2014 in the medical databases Ovid Medline, EMBASE, the Cochrane Library and the databases of the Centre for Review and Dissemination (CRD), resulting in 343 records. Of those, 12 records reporting results of 1 phase III trial [27-33] and 3 phase I/II trials [34-38] were included.

In addition, a hand search was performed including reference lists of topic-related reviews or articles, a free web search as well as the EMA and the FDA websites. This resulted in 3 additional relevant conference abstracts [39-41]. No further relevant articles or conference abstracts were found among the material that the manufacturer had sent on request.

1 phase III trial and 3 phase I/II trials

In summary, 3 full-text publications and 12 conference abstracts reporting on one phase III trial [27-33, 39-41] and 3 phase I/II trials [34-38] were included.

6.1 Efficacy and safety – phase III studies

Table 1: Summary of efficacy

Study title A randomised phase III study of weekly ABI-007 plus gemcitabine versus gemcitabine alone in patients with metastatic adenocarcinoma of the pancreas (MPACT) [27, 40]			
Study identifier	NCT00844649, EudraCT 2009-011305-17		
Design	Randomised controlled, open-label, international, multicentre trial; N = 861 (431 vs 430); allocation randomly (1:1 ratio) to nab-paclitaxel plus gemcitabine or gemcitabine alone; stratified by geographic region, Karnofsky performance status and by the presence of liver metastases		
	Duration	*Enrolment:* NR *Median follow-up:* NR (Maximum time in follow-up was 37 months) *Cut-off date for analysis:* 17 September 2012	
Hypothesis	Superiority		
Funding	Celgene Corporation		
Treatment groups	Intervention (n=431)	Nab-paclitaxel 125 mg/m², 30 to 40 minutes IV; Gemcitabine 1000 mg/m² IV; Cycle 1: on days 1, 8, 15, 29, 36 and 43, subsequent cycles: on days 1, 8 and 15 every 4 weeks.	
	Control (n=430)	Gemcitabine 1000 mg/m² IV; Cycle 1: weekly for 7 of 8 weeks, subsequent cycles: on days 1, 8 and 15 every 4 weeks.	
Endpoints and definitions	Overall survival (primary efficacy outcome)	OS	Time from randomisation to death due to any cause.
	Progression-free survival (secondary outcome)	PFS	Time from the date of randomisation to the date of disease progression or death (any cause) on or prior to the clinical cut-off date, whichever occurred earlier. Assessed by independent radiological review (IRR)
	Overall response rate (secondary outcome)	ORR	Percentage of participants who achieved a confirmed complete (CR) or partial response (PR) based on an independent blinded radiologic review (IRR) assessment of response using Response Evaluation Criteria in Solid Tumors (RECIST) guidelines
	Treatment-related adverse event	TRAE	Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (CTC version 3.0)
	Disease control rate	DCR	Percentage of participants with stable disease for ≥16 weeks
	Complete response	CR	Disappearance of all known disease sites and no new sites or disease-related symptoms confirmed at least 4 weeks after initial documentation
	Partial response	PR	At least a 30% decrease in the sum of the longest diameters of target lesions and no progression in non-target lesions
	Stable disease	SD	NR

<table>
<tr><td colspan="5">Results and analysis</td></tr>
<tr><td>Analysis description</td><td colspan="4">ITT-analysis;
Primary endpoint: OS analysed with the use of Kaplan-Meier method and a stratified log-rank test; Sample size: 842 patients were needed to observe 608 OS events with a statistical power of 90% to detect a hazard ratio for death with nab-paclitaxel plus gemcitabine versus gemcitabine monotherapy of 0.769 at a two-sided αlevel of 0.049.</td></tr>
<tr><td rowspan="3">Analysis population</td><td>Inclusion</td><td colspan="3">❁ adults at least 18 years of age
❁ histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas, measurable according to RECIST 1.0 criteria
❁ initial diagnosis of metastatic disease must have occurred within 6 weeks before randomisation
❁ no previous chemotherapy for metastatic disease
❁ Karnofsky performance-status score ≥70 (on a scale from 0 to 100, with higher scores indicating better performance status)</td></tr>
<tr><td>Exclusion</td><td colspan="3">❁ Cytotoxic doses of gemcitabine or any other chemotherapy in the adjuvant setting
❁ Islet-cell neoplasms
❁ Locally advanced disease
❁ Haemoglobin level <9 g per dl
❁ Absolute neutrophil count <1.5x10^9 per litre
❁ Bilirubin level above upper limit of normal range</td></tr>
<tr><td>Characteristics</td><td colspan="3">Median age (years): 62 (27–86) vs 63 (32–88)
Female (%): 43 vs 40
Ethnicity_White/Black/Asian/Hispanic/Others (%): 88/4/2/6/1 vs 87/4/2/6/1
Karnofsky performance status score_100/90/80/70/60 (%): 16/42/35/7/<1 vs 16/46/30/8/0
Pancreatic tumour location_head/body/tail/unknown (%): 44/31/24/1 vs 42/32/26/1
Site of metastatic disease_liver/lung/peritoneum (%): 85/35/4 vs 84/43/2
No. of metastatic sites_1/2/3/>3 (%): 8/47/32/14 vs 5/48/33/15</td></tr>
<tr><td rowspan="8">Results (main analysis 17 September 2012)</td><td colspan="2">Treatment group</td><td>Gemcitabine</td><td>Nab-Paclitaxel + Gemcitabine</td></tr>
<tr><td colspan="2">Number of subjects</td><td>N=430</td><td>N=431</td></tr>
<tr><td colspan="2">OS (months)
median
95% CI</td><td>6.7
6.0–7.2</td><td>8.5
7.9–9.5</td></tr>
<tr><td colspan="2">12 months survival rate (%)
95% CI</td><td>22
18–27</td><td>35
30–39</td></tr>
<tr><td colspan="2">24 months survival rate (%)
95% CI</td><td>4
2–7</td><td>9
6–13</td></tr>
<tr><td colspan="2">PFS (months)
median
95% CI</td><td>3.7
3.6–4.0</td><td>5.5
4.5–5.9</td></tr>
<tr><td colspan="2">ORR (%)
95% CI</td><td>7
5.0–10.1</td><td>23
19.1–27.2</td></tr>
<tr><td colspan="2">DCR (%)
95% CI</td><td>33
28–37</td><td>48
43–53</td></tr>
</table>

	CR No of patients (%)	0	1 (<1)
	PR No of patients (%)	31 (7)	98 (23)
	SD No of patients (%)	122 (28)	118 (27)
Results (post-hoc update analysis 1 April 2013)	OS (months) median 95% CI	6.6 NR	8.7 NR
	24 months survival rate (%) 95% CI	5 NR	10 NR
	36 months survival rate (%) 95% CI	0 NR	4 NR
Effect estimate per comparison (main analysis 17 September 2012)	*Comparison groups*		*Nab-Paclitaxel + Gemcitabine vs Gemcitabine*
	OS	HR	0.72
		95% CI	0.62–0.83
		P value	<0.001
	12 months survival rate	Effect estimate	NR
		95% CI	NR
		P value	<0.001
	24 months survival rate	Effect estimate	NR
		95% CI	NR
		P value	0.02
	PFS	HR	0.69
		95% CI	0.58–0.82
		P value	<0.001
	ORR (independent review)	HR	3.19
		95% CI	2.18 4.66
		P value	<0.001
	RDC	HR	1.46
		95% CI	1.23–1.72
		P value	<0.001
Effect estimate per comparison (post-hoc update analysis 1 April 2013)	OS	HR	0.72
		95% CI	0.62–0.83
		P value	<0.001

Abbreviations: AE = adverse event, CR = complete response, CI = confidence interval, DD = participants with dose delays/doses not given, DI = participants with dose interruptions, DR = participants with dose reductions, HR = hazard ratio, IRR = independent radiological review, ITT = intent to treat, IV…intravenous, NR = not reported, ORR = overall response rate, OS = overall survival, PFS = progression-free survival, PR = partial response, RDC = rate of disease control, RECIST = Response Evaluation Criteria in Solid Tumors, SD = stable disease, TRAE = treatment-related adverse event

Table 2: Common adverse events

MPACT (NCT00844649)			
Grade (according to CTC version 3.0)	**Outcome** [n (%)]	**Nab-Paclitaxel + Gemcitabine** (n=421)	**Gemcitabine** (n=402)
Adverse event leading to death		18 (4)	18 (4)
All grades	Fatigue	248 (59)	183 (46)
	Peripheral oedema	194 (46)	122 (30)
	Pyrexia	171 (41)	114 (28)
	Asthenia	79 (19)	54 (13)
	Mucositis	42 (10)	16 (4)
	Nausea	228 (54)	192 (48)
	Diarrhoea	184 (44)	95 (24)
	Vomiting	151 (36)	113 (28)
	Alopecia	212 (50)	21 (5)
	Rash	128 (30)	45 (11)
	Peripheral neuropathy	227 (54)	51 (13)
	Dysgeusia	68 (16)	33 (8)
	Headache	60 (14)	38 (9)
	Decreased appetite	152 (36)	104 (26)
	Dehydration	87 (21)	45 (11)
	Hypokalaemia	52 (12)	28 (7)
	Cough	72 (17)	30 (7)
	Epistaxis	64 (15)	14 (3)
	Urinary tract infections	47 (11)	20 (5)
	Pain in extremity	48 (11)	24 (6)
	Arthralgia	47 (11)	13 (3)
	Myalgia	44 (10)	15 (4)
	Depression	51 (12)	24 (6)
Grade 1–4	Neutropenia	NR (73)	NR (58)
	Thrombocytopenia	NR (74)	NR (70)
Grade ≥3	Fatigue	77 (18)	37 (9)
	Peripheral oedema	13 (3)	12 (3)
	Pyrexia	12 (3)	4 (1)
	Asthenia	29 (7)	17 (4)
	Mucositis	6 (1)	1 (<1)
	Nausea	27 (6)	14 (3)
	Diarrhoea	26 (6)	6 (1)
	Vomiting	25 (6)	15 (4)
	Alopecia	6 (1)	0
	Rash	8 (2)	2 (<1)
	Peripheral neuropathy	70 (17)	3 (1)
	Dysgeusia	0	0
	Headache	1 (<1)	1 (<1)

	Decreased appetite	23 (5)	8 (2)
	Dehydration	31 (7)	10 (2)
	Hypokalaemia	18 (4)	6 (1)
	Cough	0	0
	Epistaxis	1 (<1)	1 (<1)
	Urinary tract infections	10 (2)	1 (<1)
	Pain in extremity	3 (1)	3 (1)
	Arthralgia	3 (1)	1 (<1)
	Myalgia	4 (1)	0
	Depression	1 (<1)	0
	Neutropenia [n/N]	153/405 (38)	103/388 (27)
	Leukopenia [n/N]	124/405 (31)	63/388 (16)
	Thrombocytopenia [n/N]	52/405 (13)	36/388 (9)
	Anaemia [n/N]	53/405 (13)	48/388 (12)

Abbreviations: CTC = Common Terminology Criteria

international, multicentre, open-label RCT

The MPACT trial, an international, multicentre, open-label phase III randomised controlled trial (RCT), conducted in the European Union, North America and Australia, investigated the efficacy and safety of nab-paclitaxel plus gemcitabine in comparison to gemcitabine alone as first-line treatment of metastatic adenocarcinoma of the pancreas [27]. The primary efficacy end point was overall survival (OS). Additional end points were progression-free survival (PFS), overall response rate (ORR) – both assessed by independent radiographic review – and treatment-related adverse events (TRAE).

nab-paclitaxel plus gemcitabine vs gemcitabine alone

861 patients randomised

To be included, patients had to have a histologically or cytologically confirmed metastatic disease according to RECIST version 1.0, a Karnofsky performance-status score of 70 or more and had to not have previously received chemotherapy for their metastatic disease. 861 patients were randomly assigned in a 1:1 ratio to the intervention group or the control arm. Randomisation was stratified by geographic region, Karnofsky performance status and by the presence of liver metastases. Patients in the intervention group received a 30–40-minute intravenous (IV) infusion of nab-paclitaxel 125 mg/m^2 followed by gemcitabine 1000 mg/m^2 IV on days 1, 8 and 15 of each 28-day cycle. Patients in the control group received gemcitabine alone 1000 mg/m^2 IV weekly for 7 of 8 weeks in cycle 1, and 1000 mg/m^2 on days 1, 8 and 15 of each subsequent 28-day cycle. In both groups treatment was continued until disease progression or unacceptable toxicity. Crossover was not allowed at any time after randomisation.

The mean age in the study population was 63 years. The majority of patients were Caucasian (87%), 58% were men and 60% had a Karnofsky performance status score of 90 or 100. Regarding disease characteristics, 93% of the patients had two or more metastatic sites and 84% had liver metastases.

at final analysis about 80% had died

significantly longer OS (8.5 vs 6.7 months)

2-year survival rate: 9% vs 4%

In the final analysis at the data-cutoff date (17 September 2012), 333 (77%) of patients treated with nab-paclitaxel plus gemcitabine and 359 (83%) patients treated with gemcitabine alone had died. In the ITT population the median OS was 8.5 months in the intervention group and 6.7 months in the control group, showing a statistically significant improvement in favour of the intervention group (HR for death 0.72 (95% CI 0.62–0.83; $p<0.001$)). There were also statistically significant higher 1-year and 2-year survival rates for the nab-paclitaxel plus gemcitabine group with 35% vs 22% ($p<0.001$) and 9% vs 4% ($p=0.02$) respectively. An updated post-hoc OS analysis on 1 April 2013 reported that at this date, 380 (88%) patients of the nab-paclitaxel plus gemcitabine group and 394 (92%) patients of the gemcitabine-alone group had died and the statistically significant difference in OS remained unchanged in this analysis [40]. Due to the longer follow-up an estimate of the 3-year survival rates was possible, which was 4% in the intervention group and 0% in the control group.

PFS and ORR significantly better

For the secondary efficacy endpoint, the main analysis at data-cutoff date showed a statistically significant longer median PFS in the intervention group as determined per independent radiographic review (nab-paclitaxel plus gemcitabine 5.5 months vs gemcitabine alone 3.7 months, HR 0.69 (95% CI 0.58–0.82, $p<0.001$)). In addition, ORR was significantly better in the nab-paclitaxel plus gemcitabine group (23% vs 7%, HR 3.19 (95% CI 2.18–4.66, $p<0.001$), with all but one person in the intervention group being partial responses (PR).

Subgroup analyses for OS and PFS showed a significant benefit of nab-paclitaxel plus gemcitabine for most of the predefined subgroups, but it is not reported if there were differences in the magnitude of the effect between these subgroups.

most frequent grade ≥3 AEs: neutropenia, leukopenia, fatigue and peripheral neuropathy

In general, the majority of the adverse events (AEs) in both groups were of lower grade and all of them occurred more often in the intervention group (see table 2). The most frequent AEs of grade 3 or higher were neutropenia (nab-paclitaxel plus gemcitabine 38% vs gemcitabine alone 27%), leukopenia (nab-paclitaxel plus gemcitabine 31% vs gemcitabine alone 16%), fatigue (nab-paclitaxel plus gemcitabine 17% vs gemcitabine alone 7%) and peripheral neuropathy (nab-paclitaxel plus gemcitabine 17% vs gemcitabine alone 1%). The median time to first occurrence of peripheral neuropathy grade 3 or higher was 140 days in the intervention group and the median time to improvement from grade 3 to grade ≤ 1 was 29 days [4, 27].

number of SAEs and AEs leading to death comparable, but more patients discontinued treatment in intervention group

There was no significant difference in serious AEs (50% vs 43%) and AEs leading to death between the two treatment groups (4% vs 4%) [27], but 20% in the nab-paclitaxel plus gemcitabine group discontinued treatment due to unacceptable toxicities compared to only 7% in the gemcitabine-alone group [42].

6.2 Efficacy and safety – further studies

An open-label phase I/II dose-finding study in 4 centres in the USA investigated the maximum-tolerated dose (MTD) of first-line treatment with gemcitabine plus nab-paclitaxel in metastatic pancreatic adenocarcinoma and also provided efficacy and safety data [34-36]. 67 patients were treated with 100, 125 or 150 mg/m^2 nab-paclitaxel followed by gemcitabine 1,000 mg/m^2 on days 1, 8 and 15 every 28 days. The MTD was 1,000 mg/m^2 of gemcitabine plus 125 mg/m^2 of nab-paclitaxel once a week for 3 weeks, every 28 days. For all 67 patients, the median PFS was 7.1 months (95% CI 5.7–8.0 months) and median OS was 10.3 months (95% CI 8.4–13.6). The ORR was 46%, with 3 patients (4%) having complete responses. Analysis including only patients treated at the MTD (n=44) resulted in a median PFS of 7.9 months (95% CI 5.8–11.0 months) and a median OS of 12.2 months (95% CI 8.9–17.9 months). One patient in the 150 mg/m^2 nab-paclitaxel group died due to sepsis. The most common treatment-related AEs of grade ≥ 3 were neutropenia (67%), leukopenia (44%), thrombocytopenia (23%), fatigue (21%) and sensory neuropathy (15%).

phase I/II dose-finding study

MTD: 125 mg/m²

OS: 10.3 months
PFS: 7.1 months

AEs: neutropenia, leukopenia, fatigue and sensory neuropathy

There was another open-label phase I/II dose-finding study, conducted in China, which investigated the MTD and the dose limiting toxicities (DLT) of induction treatment with nab-paclitaxel plus gemcitabine in patients with metastatic pancreas carcinoma [37]. 21 patients received nab-paclitaxel at the dose levels of 80 mg/m^2, 100 mg/m^2 and 120 mg/m^2, followed by gemcitabine (1,000 mg/m^2) on days 1 and 8, and repeated every 21 days. MTD was not met in this study. Median PFS was 4.4 months (95% CI 4.0–4.8 months) and median OS was 12.2 months (95% CI 9.5–14.8 months), with a 1-year survival rate of 65%. The ORR rate in this study was 28.6%, with all of them being partial responses. Most frequent treatment-related grade ≥ 3 AEs were the neutropenia (9.5%), febrile neutropenia (4.8%), thrombocytopenia (4.8%) and sensory neuropathy (4.8%).

phase I/II dose-finding study in China

OS: 12.2 months

AEs: neutropenia, thrombocytopenia and sensory neuropathy

One conference abstract publication reported an interim analysis of a single-arm phase II study of first-line therapy with gemcitabine and nab-paclitaxel followed by consolidation with FOLFIRINOX [38], but no fully published results are available.

single-arm phase II trial for nab-paclitaxel + gemcitabine fol-lowed by FOLFIRINOX

interim results not sufficient

7 Estimated costs

In Austria, the price for a 100 mg vial of Abraxane® is € 369.75 [43]. Administered as first-line therapy for metastatic pancreas carcinoma, the recommended treatment regimen is 125 mg/m^2 on days 1, 8 and 15 of a 28-day cycle. With an average body surface area of 1.73 m^2, this results in costs of € 2,398 per treatment cycle. As nab-paclitaxel is given in combination with gemcitabine 1000 mg/m^2, these costs accrue in addition to € 1,278 for the gemcitabine treatment for 3 days assuming that 2 vials are needed on each of the 3 days (€ 213.05 for 1000 mg vial).
In the MPACT trial, the mean duration of treatment in the intervention group was 3.9 months, resulting in a median cumulative dose of 1,425 mg/m^2 for Abraxane® and of 11,400 mg/m^2 for gemcitabine [31]. Therefore the costs for a whole treatment period would be € 9,115 for Abraxane® and € 4,202 for gemcitabine respectively.

€ 2,398 for Abraxane® and € 1,106 for gemcitabine per treatment cycle

8 Ongoing research

only one observational follow-up phase III study for metastatic disease

A search in the databases ClinicalTrials.gov and cinicaltrialsregister.eu yielded only one ongoing phase III trial investigating paclitaxel as first-line therapy for patients with metastatic pancreas carcinoma, which is an observational follow-up study of the MPACT trial (NCT00844649, EudraCT: 2009-011305-17), of which results are presented in this report:

- NCT02021500: MPACT extension study: Multicentre, survival data collection in subjects previously enrolled in protocol CA046. The completion of the study is planned for March 2015.

3 phase III trials for locally advanced or resected pancreas carcinoma

In addition to this study, there are 3 ongoing phase III trials investigating paclitaxel in combination with chemotherapy or radiation therapy for patients with locally advanced or resected pancreas carcinoma.

- NCT01836432: Immunotherapy study in borderline resectable or locally advanced unresectable pancreatic cancer. The completion of the study is planned for June 2017.
- NCT02024009: Systemic therapy and chemoradiation in advanced localised pancreatic cancer – 2. The completion of the study is planned for September 2019.
- NCT01964430: Study to compare disease-free survival of subjects with surgically resected pancreatic cancer in the adjuvant setting who are taking nab-paclitaxel in combination with gemcitabine vs gemcitabine alone. The completion of the study is planned for October 2020.

12 phase II trials for metastatic pancreas carcinoma

In addition, 12 ongoing phase II trials for combination therapies including paclitaxel in patients with metastatic pancreas carcinoma and more than 100 ongoing phase III/IV studies evaluating paclitaxel in a broad variety of indications such as breast cancer, non-small cell lung cancer, gastric cancer or ovarian cancer were found.

9 Commentary

pancreatic cancer is often diagnosed in advanced stages and is highly lethal

Pancreatic cancer is the 4th leading cause of cancer-related death in North America and Western Europe [18, 19]. Since it does not cause early symptoms, cancers are often diagnosed in advanced stages and are highly lethal with a 5-year survival rate of only 2% for metastatic disease [18]. Beside palliative care, chemotherapy with gemcitabine is the standard first-line treatment for metastatic pancreas carcinoma, but it shows low response rates and does not sufficiently improve survival [22]. Therefore the clinical need for new treatment options is high, which is also indicated by assessing Abraxane® under the FDA's priority review programme [11, 12].

nab-paclitaxel approved for metastatic pancreas carcinoma by FDA and EMA

Based on the results of one phase III RCT, the FDA and the European Commission have now approved nab-paclitaxel (Abraxane®) in combination with gemcitabine as first-line treatment for patients with metastatic pancreas carcinoma [10,14,15].

In this study (MPACT) [27], nab-paclitaxel plus gemcitabine was compared to gemcitabine alone in 861 patients previously not treated for their metastatic disease. At the data-cutoff date on 17 September 2012, a statistically significant improvement in OS (8.5 vs 6.7 months), PFS (5.5 vs 3.7 months) and ORR (23 vs 7%) was reported. An updated survival analysis on 1 April 2013 showed a 2-year survival rate of 9% vs 4% and a 3-year survival rate of 4% vs 0% [40].

one RCT comparing nab-paclitaxel + gemcitabine vs gemcitabine alone

significant benefit in OS, PFS and ORR

The majority of AEs were lower-grade, with higher rates in patients receiving nab-paclitaxel plus gemcitabine. In terms of SAEs and AEs leading to death, there was no statistically significant difference between the groups reported. Most frequent AEs of grade 3 or higher were neutropenia, leukopenia and fatigue. Beside these, it has to be pointed out that more than 50% of the patients in the intervention group developed a peripheral neuropathy, with 17% of them being of grade ≥ 3. In the control group, this grade ≥ 3 AE was present in only 1% of the patients. Although this adverse reaction seems to be reversible after suspension of nab-paclitaxel, the median time to improvement from grade 3 peripheral neuropathy to grade ≤ 1 was 29 days in the study, which is about half of the period of OS improvement.

17% of patients develop grade ≥ 3 peripheral neuropathy

Despite the results of the MPACT trial, some limitations occur for the treatment with nab-paclitaxel in patients with metastatic pancreas carcinoma. In the study population a proportion of 92% had good performance status with a Karnofsky status score of 80 and higher [26]. In addition, this study included only patients with a bilirubin level within the normal rage. Data for patients with an increased bilirubin level causing jaundice, which is present in 56% of all patients with pancreatic cancer [44], are not available. So the effect of a combination of nab-paclitaxel and gemcitabine cannot be directly translated to the general population of patients with metastatic pancreas carcinoma, for whom it is approved.

study included only patients with good performance status and bilirubin level within normal range

Improving quality of life (QoL) is an important aim for any cancer therapy and is urgently needed, especially when it comes to therapeutic decision-making in the palliative setting. While for instance a recent study comparing FOLFIRINOX to gemcitabine provided data on QoL showing a significant delay in its deterioration, the current study did neither include a measurement of patients' quality of life nor of the change in cancer symptoms.

no results for QoL

In addition, the MPACT trial only addresses the question of safety and efficacy of nab-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic pancreas carcinoma, which was standard chemotherapy at the start of the trial in 2009. Looking at recent guidelines for pancreatic carcinoma, gemcitabine monotherapy is a treatment option for patients with metastatic disease and poor performance status but also for patients not eligible for more intensive therapy due to other factors (e.g. age or abnormal bilirubin level). For patients with ECOG performance status 0 or 1 and a bilirubin level within or slightly above the normal range, a combination chemotherapy is preferred [23, 25]. Therefore, from the present point of view, treatment with gemcitabine alone may not be an appropriate comparator for the examined patient group. To date, there is no study investigating the benefits and harms of nab-paclitaxel plus gemcitabine in comparison to

comparison to FOLFIRINOX is missing

other standard-of-care options for patients with good performance status, such as FOLFIRINOX. Such studies might be relevant for a treatment decision, especially since an indirect comparison between data from the MPACT trial for nab-paclitaxel plus gemcitabine and data from a FOLFIRINOX study showed slightly better results for FOLFIRINOX [45].

costs are 2 times higher, but probably no major budgetary impact

Compared to standard chemotherapy with gemcitabine alone, the costs per treatment cycle for nab-paclitaxel plus gemcitabine are about 2 times higher, but this might be different when compared to the costs of recently recommended combination chemotherapies. Since nab-paclitaxel in combination with gemcitabine is only recommended for metastatic pancreas carcinoma and good performance status affecting only a small group of patients, there will probably be no major budget impact at the moment. However, the impact will increase if the treatment indication is extended to earlier tumour stages or different treatment settings (e.g. adjuvant therapy) which are under investigation in several studies.

nab-paclitaxel plus gemcitabine is treatment option with longer OS but higher rate of AEs

suitable only for patients without hyperbilirubinemia

Therapeutic options for metastatic pancreatic carcinoma are limited. The regulatory approval by the FDA and the European Commission for nab-paclitaxel in combination with gemcitabine means that a new therapy is now available which has demonstrated an increase in PFS and OS in patients with a good performance status and a bilirubin level within the normal range. This combination may be a treatment option, especially for patients who may not be eligible for FOLFIRINOX, e.g. people older than 75 years of age. Nevertheless, this treatment is also associated with higher rates of adverse events, especially a strongly increased rate of peripheral neuropathy.

Besides data on survival and costs, differences in toxicity profiles and ease of administration as well as the patients' preferences are aspects that should be considered in deciding on the recommended combination therapies. As data on QoL for nab-paclitaxel plus gemcitabine are missing and as there are no studies comparing this treatment regimen to the other recommended combination chemotherapy (i.e. FOLFIRINOX), many unresolved questions still remain.

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