Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2018-B-209 Olaparib

Stand: Juni 2020

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Olaparib
[zur Erhaltungstherapie des metastasierten Adenokarzinoms des Pankreas]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	*Nicht angezeigt*
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	keine
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Olaparib Lynparza® L01XX46	„Lynparza wird als Monotherapie für die Erhaltungstherapie von erwachsenen Patienten mit BRCA1/2-Mutationen in der Keimbahn angewendet, die ein metastasiertes Adenokarzinom des Pankreas haben und deren Erkrankung nach einer mindestens 16-wöchigen Platin-basierten Erstlinien-Chemotherapie nicht fortgeschritten ist.“
Gemcitabin L01BC05 Gemcitabin-GRY®	Gemcitabin ist zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem Adenokarzinom des Pankreas angezeigt.
5-Fluorouracil L01BC02 Benda-5 FU	− Fortgeschrittenes Pankreaskarzinom
Folinsäure V03AF03 Leucovorin	Calciumfolinat ist indiziert: − in Kombination mit 5-Fluorouracil in der zytotoxischen Therapie.
Erlotinib L01XE03 Tarceva®	<u>Pankreaskarzinom</u> Tarceva in Kombination mit Gemcitabin ist zur Behandlung von Patienten mit metastasiertem Pankreaskarzinom angezeigt. Beim Verschreiben von Tarceva sollten Faktoren, die im Zusammenhang mit einer verlängerten Überlebenszeit stehen, berücksichtigt werden *[…]*.
Mitomycin L01DC03 Mitomycin medac	Mitomycin wird in der palliativen Tumortherapie eingesetzt. Die intravenöse Anwendung von Mitomycin ist in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei Erwachsenen mit folgenden Erkrankungen angezeigt: − fortgeschrittenes Pankreaskarzinom
Nab-Paclitaxel L01CD01 Abraxane®	Abraxane ist in Kombination mit Gemcitabin indiziert für die Erstlinienbehandlung von erwachsenen Patienten mit metastasiertem Adenokarzinom des Pankreas.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Liposomales Irinotecan L01XX19 ONIVYDE	Zur Behandlung des metastasierten Adenokarzinoms des Pankreas in Kombination mit 5-Fluorouracil (5-FU) und Leucovorin (LV) bei erwachsenen Patienten, deren Erkrankung unter einer Gemcitabin-basierten Therapie fortgeschritten ist.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2018-B-209 (Olaparib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	16. Oktober 2018

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization
Gem	gemcitabine
GemCis	Gemcitabine plus cisplatin
OS	Overall Survival
ORR	overall response rate
TTP/PFS	time to progression/progression-free survival
CBR	clinical benefit rate
HR	Hazard Ratio
NMA	Network meta analysis
FOLFIRINOX	oxaliplatin + irinotecan + fluorouracil + leucovorin
S-1	tegafur
PC	pancreatic cancer
CR	Complete response
PR	Partial response

SD	Stable disease
PD	Progressive disease
LA/MPC	Locally advanced/metastatic pancreatic cancer
DCR	disease control rate
OXA	Oxaplatin
FA	Folic acid
IRI	Irinotecan
G-CSF	Granulozyten-koloniestimulierenden Faktoren
GURU	Guideline Resource Unit
IHC	Immunhistochemie
NGS	Next Generation Sequencing
PCR	Polymerase-Kettenreaktion
ECOG	Eastern Cooperative Oncology Group
5-FU	5-Fluorouracil

1 Indikation

Geplantes Anwendungsgebiet laut Beratungsanforderung: (…) für die Erhaltungstherapie von Patienten mit metastasiertem duktalem Adenokarzinom des Pankreas, deren Erkrankung auf einer Platin-basierten Erstlinien-Chemotherapie nicht fortgeschritten ist.

Indikation der Synopse: zur Behandlung von Patienten mit metastasiertem duktalem Adenokarzinom des Pankreas, deren Erkrankung auf einer Platin-basierten Erstlinien-Chemotherapie nicht fortgeschritten ist.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Pankreaskarzinom durchgeführt. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, IQWiG, NICE, SIGN, TRIP, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien.

Die Erstrecherche wurde am 05.01.2018 beendet, die Folgerecherche am 08.10.2018. Die Recherchestrategie der Erstrecherche wurde für die Folgerecherche übernommen und der Suchzeitraum jeweils auf die letzten 5 Jahre eingeschränkt. Die letzte Suchstrategie ist am Ende der Synopse detailliert dargestellt.

Die Recherchen ergaben insgesamt 829 Quellen, die in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Es wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen und nur die Quellen der letzten 5 Jahre berücksichtigt. 19 Quellen wurden in die synoptische Evidenz-Übersicht aufgenommen.

3 Ergebnisse

3.1 G-BA-Beschlüsse/IQWiG-Berichte

Es wurden keine relevanten G-BA-Beschlüsse/IQWiG-Berichte identifiziert.

3.2 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.3 Systematische Reviews

Ottaiano A et al., 2017 [13].

Siehe auch: Chen L et al., 2014 [2].

Gemcitabine mono-therapy versus gemcitabine plus targeted therapy in advanced pancreatic cancer: a meta-analysis of randomized phase III trials

Fragestellung

to quantify the effect size on survival of adding targeted therapy to single agent gemcitabine.

Methodik

Population:

- locally advanced and/or metastatic disease,

Intervention:

first-line therapy

- gemcitabine

Komparator:

- gemcitabine plus target-therapy

Endpunkte:

- OS

Recherche/Suchzeitraum:

- from 2007 to September 2016

Qualitätsbewertung der Studien:

- The Method for Evaluating Research and Guideline Evidence (MERGE) criteria were applied to assess quality of studies. All studies had an overall quality score of A (low risk of bias) or B1 (low to moderate risk of bias)

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 studies met the meta-analysis inclusion criteria including 4564 patients

Weitere Charakteristika:

- The target therapies were: erlotinib, cetuximab, rigosertib, elpamotide, bevacizumab, aflibercept, axitinib, masitinib and ganitumab.

Qualität der Studien:

- high quality scores according to MERGE criteria

Studienergebnisse:

- There was no statistically significant heterogeneity among the nine trials. The hazard ratio (HR) of the pooled analysis was 0.998 (CI 95%: 0.932–1.068).
- Subgroup meta-analysis was also performed in anti-EGFR and anti-angiogenesis trials: the pooled HR were 0.94 (CI 95%: 0.705–1.175) and 1.055 (CI 95%: 0.913–1.197), respectively

Anmerkung/Fazit der Autoren

The present meta-analysis does not show significant improvements in survival for targeted drugs in advanced pancreatic cancer. The possible reason of these results could be linked to the biology of pancreatic cancer as well as to the absence of predictive factors.

Kommentare zum Review

- Keine Angabe zum metastasiertem Stadium oder Status allgemein (z.B. ob stabil oder progredient)

Ouyang G et al., 2016 [14].

Siehe auch: Jin SF et al., 2017 [6].

Gemcitabine plus cisplatin versus gemcitabine alone in the treatment of pancreatic cancer: a meta-analysis

Fragestellung

to compare the efficacy and safety of GemCis versus gemcitabine (Gem) alone in the treatment of pancreatic cancer.

Methodik

Population:

- Patients with cytologically or histologically confirmed advanced stage and/or metastatic pancreatic cancer

Intervention:

- Gemcitabine plus cisplatin

Komparator:

- Gemcitabine alone

Endpunkte:

- The primary end point was overall survival (OS) and secondary end points included 6-month survival, 1 year survival, overall response rate (ORR), clinical benefit rate (CBR), time to progression/progression-free survival (TTP/PFS), and toxicities

Recherche/Suchzeitraum:

- The databases of MEDLINE (PubMed), EMBASE, and Cochrane Library were systematically searched for retrieving the relevant publications prior to 31 September 2014.

Qualitätsbewertung der Studien:

- Jade Score

Ergebnisse

Anzahl eingeschlossener Studien:

- A total of nine randomized controlled trials involving 1354 patients

Qualität der Studien:

- Jade Score ranged between 0-4

Studienergebnisse:

- Overall, as compared with Gem alone, GemCis significantly improved the 6-month survival rate (relative risk (RR) = 1.303, 95 % confidence interval (CI) 1.090–1.558, P = 0.004), ORR (RR = 1.482, 95 % CI 1.148–1.913, P = 0.003), PFS/TTP (hazard ratio (HR) = 0.87; 95 % CI 0.78–0.93, P = 0.022), and the overall toxicities (RR = 2.164, 95 % CI 1.837–2.549, P = 0.000).
- However, no significance difference existed in overall survival, 1-year survival rate and CBR
- As for grade III/IV toxicity, seven kinds of toxicities were higher in the GemCis group. However, no significant inter-group statistical differences existed in the incidence of leukopenia, thrombocytopenia, or diarrhea.

Anmerkung/Fazit der Autoren

The present study meta-analysis revealed a significant improvement in the 6-month survival rate, PFS/TTP, and ORR of pancreatic cancer. However, no significant difference existed in OS, 1-year survival, and CBR. The incidence of grade III/IV toxicity was higher for GemCis than for Gem alone. Yet, the incidence of adverse events for GemCis remained generally tolerable. In conclusion, a combined use of Gem and cisplatin is superior to Gem alone as an alternative chemotherapy for pancreatic cancer. However, owing to the above limitations, more convincing studies are warranted.

Kommentare zum Review

- Keine Angaben zur Therapielinie, Status (stabil oder progredient) und Stadium (advanced/metastatic)

Zhang SH et al., 2018 [19].

Efficacy of different chemotherapy regimens in treatment of advanced or metastatic pancreatic cancer: A network meta-analysis

Fragestellung

network meta-analysis (NMA) to compare the short- and long-term efficacy of Gemcitabine, Gemcitabine + S-1 (tegafur), Gemcitabine + nab-paclitaxel, Gemcitabine + Capecitabine, Gemcitabine + Cisplatin, FOLFIRINOX (oxaliplatin + irinotecan + fluorouracil + leucovorin), Gemcitabine + oxaliplatin, Gemcitabine + irinotecan, Gemcitabine + Exatecan, Gemcitabine + pemetrexed, Gemcitabine + 5-FU, and S-1 in treating advanced or metastatic pancreatic cancer (PC).

Methodik

Population:

- Patients with advanced or metastatic pancreatic cancer

Intervention/Komparator:

- Gemcitabine, Gemcitabine + S-1 (tegafur), Gemcitabine + nab-paclitaxel, Gemcitabine + Capecitabine, Gemcitabine + Cisplatin, FOLFIRINOX, Gemcitabine + oxaliplatin, Gemcitabine + irinotecan, Gemcitabine + Exatecan, Gemcitabine + pemetrexed, Gemcitabine + 5-FU and S-1

Endpunkte:

- CR, PR, ORR, SD, PD, DCR, 6-month OS rate, 12-month OS rate, OS, and PFS

Recherche/Suchzeitraum:

- Cochrane Library, Embase, and PubMed from inception up until June 2017

Qualitätsbewertung der Studien:

- Quality of evidence for each study was based on six domains: random allocation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective outcome reporting, and other sources of bias.

Ergebnisse

Anzahl eingeschlossener Studien:

- 20 studies (6,264 patients)

Charakteristika der Population:

- most of the patients were treated with Gemcitabine

Qualität der Studien:

- the quality of the included studies was good and the potential risks of literature bias were low.

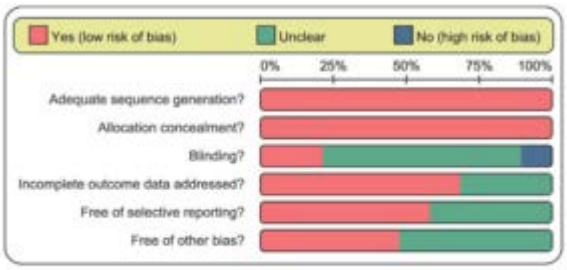


FIGURE A2 Cochrane collaboration risk of bias in included studies

Studienergebnisse:

- Pairwise meta-analysis
  - o the short-term efficacies of Gemcitabine + S-1, Gemcitabine + Cisplatin and FOLFIRINOX were all better, while the long-term efficacies of Gemcitabine + S-1 and FOLFIRINOX were also better among the 12 chemotherapy regimens.
- Relevant results of NMA
  - o SUCRA values: for PR, ORR, DCR, 6-month-OS rate, 12-month-OS rate, OS (months), and PFS (months), the SUCRA of FOLFIRINOX was recorded to be the highest (PR: 92.89%; ORR: 92.80%; DCR: 84.00%; 6-month-OS rate: 90.20%; 12-month-OS rate: 97.42%; OS: 92.90%; PFS: 98.50%), respectively. With regards to CR, the SUCRA of Gemcitabine + Capecitabine was the highest (84.00%). The SUCRA of Gemcitabine + Cisplatin was the highest (81.00%) with regard to SD while the SUCRA of Gemcitabine + S-1 was the highest (88.50%) for PD. To summarize, the short-term and long-term efficacies of FOLFIRINOX, Gemcitabine + Capecitabine, Gemcitabine + Cisplatin, and Gemcitabine + S-1 were better for treating patients who are suffering from existing advanced or metastatic PC.

Anmerkung/Fazit der Autoren

To conclude, our network meta-analysis suggested that the short- and long-term efficacies of FOLFIRINOX involved in the treatment of advanced or metastatic PC were relatively better, while the short- and long-term efficacies of Gemcitabine were relatively poorer for patients with advanced or metastatic PC. Besides FOLFIRINOX, we Gemcitabine + S-1 presented with a good efficacy in the treatment of advanced or metastatic PC, and the side effects of the Gemcitabine + S-1 drug regimen may be lesser, serving as a new ulterior option for patients. Due to unavoidable limitations in this study, our research will focus on the emergence of new studies, particularly larger sample studies in the future in order to strengthen our results. Altogether, our study is still useful for guideline development, and for the setting of clinical trials for the treatment of advanced or metastatic PC. What is more, further research is needed which could focus on the side effects, adverse reactions and complications of different chemotherapies in treating PC.

Kommentare zum Review

- Keine Informationen wie viele Patienten metastasiert bzw. Zum Status (stable disease vs. progredient)

Li Q et al., 2014 [8].

Efficacy and Safety of Gemcitabine-Fluorouracil Combination Therapy in the Management of Advanced Pancreatic Cancer: A Meta-Analysis of Randomized Controlled Trials

Fragestellung

Because fluorouracil drugs have shown promising activity in LA/MPC patients, many RCTs have been designed to evaluate whether GEM combined with fluorouracil drugs is superior to GEM alone, but the conclusions are not consistent. Therefore, we undertook a systematic assessment of relevant RCTs in this study.

Methodik

Population:

- LA/MPC patients

Intervention:

- GEM monotherapy

Komparator:

- GEM combined with 5-FU/CAP/S-1 therapy

Endpunkte:

- primary end point was OS, secondary end points were one year survival rate, objective response rate (ORR) and toxicity rates (TRs)

Recherche/Suchzeitraum:

- PubMed, EMBASE and the Central Registry of Controlled Trials of the Cochrane Library were searched for original articles written in English and published before January 31, 2014.

Qualitätsbewertung der Studien:

- Cochrane Handbook for Systematic Reviews of Interventions

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs (2,126 patients)

Charakteristika der Population:

- 1,059 patients received GEM+5-FU/CAP/S-1 therapy and 1,067 patients received GEM alone therapy. In subgroup analysis, 416 patients received GEM+5-FU versus GEM alone therapy, 935 patients received GEM+CAP versus GEM alone therapy, and 775 patients received GEM+S-1 versus GEM alone therapy.

Table 1. Characteristics of the eligible trials included in the systematic assessment.

Trial	Phase	Arms	Case (n)	Male (%)	Median age (y)	LA (%)/MPC (%)	Regimens
Berlin JD	III	GEM+5-FU	160	51.8	65.8	11/89	GEM 1000 mg/m^2, then 5-FU 600 mg/m^2 d1,8,15, q4w, IV.
2002 [21]	Multicenter	GEM alone	162	53.7	64.3	10/90	GEM 1000 mg/m^2 d1,8,15, q4w, IV.
Scheithauer W	II	GEM+CAP	41	66.0	64.0	0/100	GEM 2200 mg/m^2 d1, q2w, IV; CAP 2500 mg/m^2 d1-7, q2w, PO.
2003 [22]	Multicenter	GEM alone	42	55.0	66.0	0/100	GEM 2200 mg/m^2 d1, q2w, IV.
Di Costanzo F	II	GEM+5-FU	45	63.0	62.0	33/67	GEM 1000 mg/m^2/w, 5-FU 200 mg/m^2/d×6weeks followed by 1-week rest; then d1,8,15, q4w, IV.
2005 [23]	Multicenter	GEM alone	49	48.0	64.0	27/73	GEM 1000 mg/m^2/w×7 weeks followed by 2-weeks rest, then d1,8,15, q4w, IV.
Herrmann R	III	GEM+CAP	160	54.0	Unknown	20/80	GEM 1000 mg/m^2 d1,8, q3w, IV; CAP 650 mg/m^2 twice daily d1-14, q3w, PO.
2007 [24]	Multicenter	GEM alone	159	53.0	Unknown	21/79	GEM 1000 mg/m^2/w×7 weeks followed by 1-week rest, then d1,8,15, q4w, IV.
Cunningham D	III	GEM+CAP	267	60.0	62.0	30/70	GEM 1000 mg/m^2 d1,8,15, q4w, IV; CAP 830 mg/m^2 twice daily d1-21, q4w, PO.
2009 [25]	Multicenter	GEM alone	266	58.0	62.0	29/71	GEM 1000 mg/m^2/w×7 weeks followed by 1-week rest, then d1,8,15, q4w, IV.
Nakai Y	II	GEM+S-1	53	79.2	63.0	28/72	GEM 1000 mg/m^2 d1,15, q4w, IV; S-1 40 mg/m^2 twice daily d1-14, q4w, PO.
2012 [26]	Multicenter	GEM alone	53	62.3	67.0	24/76	GEM 1000 mg/m^2 d1,8,15, q4w, IV.
Ozaka M	II	GEM+S-1	58	60.3	Unknown	25/75	GEM 1000 mg/m^2 d1,8, q3w, IV; S-1 40 mg/m^2 twice daily d1-14, q3w, PO.
2012 [27]	Multicenter	GEM alone	59	59.3	Unknown	31/69	GEM 1000 mg/m^2 d1,8,15, q4w, IV.
Ueno H	III	GEM+S-1	275	57.5	Unknown	25/75	GEM 1000 mg/m^2 d1,8, IV; S-1 60/80/100 mg/m^2 d1-14, q3w, PO.
2013 [28]	Multicenter	GEM alone	277	61.4	Unknown	24/76	GEM 1000 mg/m^2 d1,8,15, q4w, IV.

GEM, gemcitabine; 5-FU, 5-fluorouracil; CAP, capecitabine; LA/MPC, locally advanced/metastatic pancreatic adenocarcinoma; OS, overall survival.

Qualität der Studien:

- Four RCTs were assessed to have an unclear risk of selection bias due to insufficient detail on random sequence generation or allocation concealment. Three RCTs were assessed to have a high risk of performance and detection bias due to open label in trial design. Six RCTs were assessed to have an unclear risk of other bias due to insufficient details, such as lacking an adequate description of patients' the uptake of the therapeutic drug monitoring recommendations by physicians.

Studienergebnisse:

- OS was significantly improved (HR 0.83, P=0.01; HR 0.87, P = 0.03; HR 0.80, P = 0.01; respectively) and ORR was significantly increased (OR 0.51, P,0.01; OR 0.66, P = 0.03; OR 0.35, P,0.01; respectively) in the GEM+5-FU/CAP/S-1, GEM+CAP and GEM+S-1 groups compared to the GEM alone group.
- In addition, the one-year survival rate was significantly increased (OR 0.78 P = 0.01; OR 0.47, P = 0.04; respectively) in the GEM+5-FU/CAP/S-1 and GEM+S-1 groups compared to the GEM alone group.
- The frequency of grade 3/4 TRs were higher in GEM+5-FU/CAP/S-1 group, the significant increase of grade 3/4 neutropenia, thrombocytopenia and diarrhea were observed.

Anmerkung/Fazit der Autoren

GEM combined with fluorouracil drugs significantly improved OS and increased one-year survival rate and ORR compared to GEM alone in LA/MPC patients. GEM combined with fluorouracil drugs may be considered as an acceptable alternative treatment for LA/MPC patients.

Kommentare zum Review

- Linie (vermutlich 1. Linie) bzw. Status (stable disease/progedient) der Patienten unklar

Liu GF et al., 2018 [9].

Efficacy and Toxicity of Different Chemotherapy Regimens in the Treatment of Advanced or Metastatic Pancreatic Cancer: A Network Meta-Analysis

Fragestellung

to compare the efficacy and toxicity of different chemotherapy regimens in treating advanced or metastatic pancreatic cancer (PC)

Methodik

Population:

- patients with advanced or metastatic PC

Intervention/Komparator

- performing traditional pairwise meta-analyse & NMA (siehe Ergebnisteil)

Endpunkte:

- overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS) or incidence of toxicity (Anemia, Neutropenia, Thrombocytopenia, Diarrhea, Fatigue, Nausea

Recherche/Suchzeitraum:

- PubMed, Cochrane Library and EMBASE databases from inception to June 2016 were searched.

Qualitätsbewertung der Studien:

- The PEDro scale was used to assess the quality of the included studies

Ergebnisse

Anzahl eingeschlossener Studien:

- Twenty randomized controlled trials were enrolled. Twelve chemotherapy regimens included Gemcitabine, S-1 (Tegafur), Gemcitabine+Cisplatin, Gemcitabine+Capecitabine, GemcitabineþS-1, Gemcitabine+5-FU (5-fluorouracil), Gemcitabine+Exatecan, Gemcitabine+Irinotecan, GemcitabineþNab-paclitaxel, FOLFIRINOX (OxaliplatinþIrinotecan+Fluorouracilþ Leucovorin), Gemcitabine+Oxaliplatin, and Gemcitabine+Pemetrexed.

Qualität der Studien:

- *Anmerkung FBMed: Die hierzu verfügbare zusätzliche Datei kann nicht geöffnet werden.*

Studienergebnisse:

- Higher overall response rate (ORR) was observed in patients treated with the gemcitabine+S-1 and FOLFIRINOX regimens.

TABLE II. OR (Odds Ratio)/Weighted Mean Difference (WMD) and 95%CI of Pairwise Meta-Analysis in Terms of Efficacy Outcomes

		Pairwise meta-analysis	
Included studies	Comparisons	OR/WMD	95%CI
ORR			
1 study	Gem vs. S-1	0.63	0.39 ~ 1.02
5 studies	Gem vs. Gem + Cisplatin	0.63	0.45 ~ 0.87
3 studies	Gem vs. Gem + Capecitabine	0.70	0.48 ~ 1.02
4 studies	Gem vs. Gem + S-1	0.41	0.28 ~ 0.59
1 study	Gem vs. Gem + 5-FU	0.72	0.18 ~ 2.84
1 study	Gem vs. Gem + Exatecan	0.75	0.31 ~ 1.84
2 studies	Gem vs. Gem + Irinotecan	0.37	0.20 ~ 0.70
1 study	Gem vs. FOLFIRINOX	0.30	0.16 ~ 0.54
1 study	Gem vs. Gem + Oxaliplatin	0.65	0.38 ~ 1.10
1 study	S-1 vs. Gem + S-1	0.71	0.48 ~ 1.07
DCR			
1 study	Gem vs. S-1	0.99	0.74 ~ 1.32
4 studies	Gem vs. Gem + Cisplatin	0.74	0.58 ~ 0.94
2 studies	Gem vs. Gem + Capecitabine	0.84	0.64 ~ 1.12
4 studies	Gem vs. Gem + S-1	0.82	0.65 ~ 1.02
1 study	Gem vs. Gem + 5-FU	0.95	0.43 ~ 2.07
1 study	Gem vs. Gem + Irinotecan	0.69	0.35 ~ 1.36
1 study	Gem vs. FOLFIRINOX	0.73	0.51 ~ 1.03
1 study	Gem vs. Gem + S-1	0.89	0.67 ~ 1.17
PFS (months)			
1 study	Gem vs. S-1	0.30	0.27 ~ 0.33
1 study	Gem vs. Gem + Cisplatin	1.00	0.39 ~ 1.61
2 studies	Gem vs. Gem + Capecitabine	−1.50	−1.56 ~ −1.43
2 studies	Gem vs. Gem + S-1	−1.60	−1.67 ~ −1.54
1 study	Gem vs. Gem + 5-FU	−1.00	−1.76 ~ −0.24
1 study	Gem vs. Gem + Exatecan	0.10	0.02 ~ 0.18
1 study	Gem vs. Gem + Irinotecan	0.10	−0.53 ~ 0.73
1 study	Gem vs. FOLFIRINOX	−3.10	−3.17 ~ −3.03
1 study	Gem vs. Gem + Pemetrexed.	−0.60	−0.65 ~ −0.55
1 study	Gem vs. Gem + S-1	−1.90	−1.97 ~ −1.83
OS (months)			
1 study	Gem vs. S-1	−0.90	−0.99 ~ −0.81
1 study	Gem vs. Gem + Cisplatin	−0.20	−1.55 ~ 1.15
3 studies	Gem vs. Gem + Capecitabine	−0.96	−1.03 ~ −0.90
2 studies	Gem vs. Gem + S-1	−1.43	−1.52 ~ −1.34
1 study	Gem vs. Gem + 5-FU	0.30	−0.87 ~ 1.47
1 study	Gem vs. Gem + Exatecan	−0.50	−0.63 ~ −0.37
2 studies	Gem vs. Gem + Irinotecan	0.30	0.17 ~ 0.42
1 study	Gem vs. FOLFIRINOX	−4.30	−4.46 ~ −4.14
1 study	Gem vs. Gem + Pemetrexed.	0.10	0.04 ~ 0.16
1 study	S-1 vs. Gem + S-1	−0.40	−0.50 ~ −0.30

ORR and DCR are stated with ORs while PFS and OS are stated with WMD.
Bolded numbers represent the differences are of significance.
OR, odds ratio; WMD, weighted mean difference; 95%CI, 95%confidence intervals; ORR, overall response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; Gem, Gemcitabine; S-1, Tegafur; 5-FU, 5-Fluorouracil; FOLFIRINOX, Oxaliplatin + Irinotecan + Fluorouracil + Leucovorin.

- Thrombocytopenia reduced in patients treated with the S-1 regimen.
- The Gemcitabine+S-1 and FOLFIRINO regimens had better short- and long-term efficacies than the other regimens; S-1 regimen had the lowest hematologic toxicity, while Gemcitabine+Nab-paclitaxel, FOLFIRINOX, and Gemcitabine+Pemetrexed regimens had higher incidence of non-hematologic toxicity among twelve chemotherapy regimens.
- The efficacy of Gemcitabine+S-1 and FOLFIRINOX regimens may be better in treating patients with advanced or metastatic pancreatic cancer, while FOLFIRINOX and Gemcitabine+Pemetrexed regimens may have relatively higher incidence of toxicity than other regimens.

→ *siehe detaillierte Ergebnistabellen der NMA im Anhang!*

Anmerkung/Fazit der Autoren

To conclude, our preliminary results indicated that Gemcitabine+S-1 and FOLFIRINOX regimens might serve as the preferred options for patients while treating advanced or metastatic PC. The incidence of toxicity of FOLFIRINOX and Gemcitabine+Pemetrexed regimens might be relatively higher than other regimens. This might be of important clinical significance in the treatment of PC. However, PC still remains as one of the most difficult cancers to be cured in the world, although even after several multiple clinical trials and continuous efforts, some limitations might have affected the results of our study due to the existence of various interventions between the paired comparisons of the different inclusive studies. We hope in the future there are more studies, which would investigate the interventions between the paired comparisons of different chemotherapy regimens, and further studies and analyses are required to explore the better means to improve the efficacy of the treatment in the humans with advanced PC.

Kommentare zum Review

Linie/Status unklar: Lediglich Information bei den Ausschlusskriterien → *Excluded: (iii) patients who previously underwent radiation therapy or adjuvant chemotherapy (…)*

Dorjee P et al., 2018 [4].

A mixed treatment comparison of toxicity of gemcitabine combined with different targeted drugs in the treatment of advanced or metastatic pancreatic cancer

Fragestellung

A mixed treatment comparison study was performed in order to compare the toxicities of Gemcitabine and different targeted drug combinations in the treatment of advanced/metastatic pancreatic cancer (PC).

Methodik

Population:

- patients with advanced or metastatic PC aging from 26 to 93

Intervention/Komparator:

- Gemcitabine C Placebo, Gemcitabine C Axitinib, Gemcitabine C Trametinib, Gemcitabine C Sorafenib, Gemcitabine C Bevacizumab, Gemcitabine C Erlotinib and Gemcitabine C Tipifarnib

Endpunkte:

- Anemia, Neutropenia, Thrombocytopenia, Rash, Diarrhea and Stomatitis

Recherche/Suchzeitraum:

- from the inception of PubMed and Cochrane Library databases to February 2017

Qualitätsbewertung der Studien:

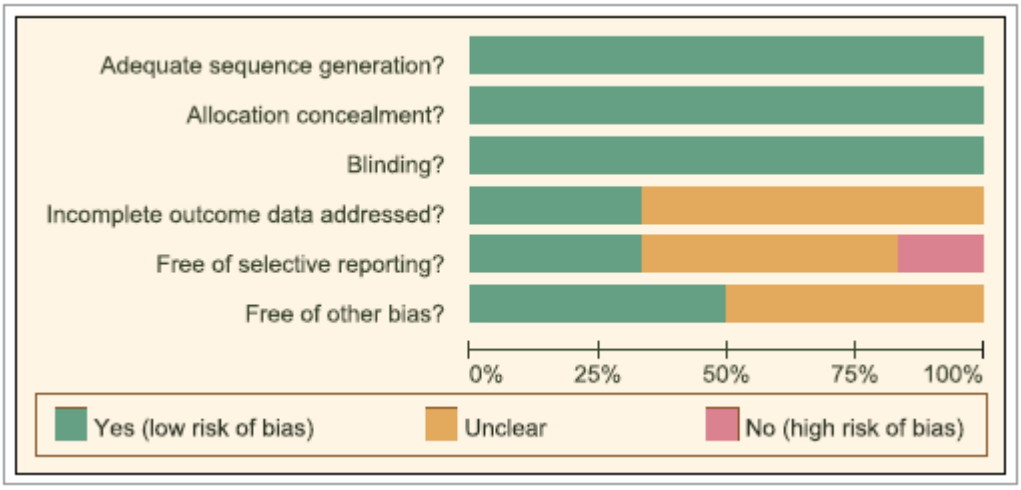
- Cochranes Collaboration’s tool for assessing the risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 RCTs were incorporated in the network meta-analysis. The study included 2,753 advanced or metastatic PC patients and a majority of the patients took Gemcitabine C placebo.

Qualität der Studien:



Studienergebnisse:

- Paired Meta-analyses of six Gemcitabine combinations with different target drugs in the treatment of advanced/ metastatic PC
  - The paired comparisons of the targeted drugs combined with chemotherapy for the treatment of PC found that Gemcitabine C Placebo combination showed lower incidence rates of toxicity.
- main results of network meta-analysis
  - The network meta-analysis showed the following results for non-hematologic toxicities: compared: The Gemcitabine C Axitinib patients showed lower incidence of rash rates compared to the patients receiving the Gemcitabine C Trametinib and Gemcitabine C Erlotinib combinations (all grades) (95%CI = 0.01-0.79, OR = 0.11, 95%CI = 0.01-0.98; OR = 0.10, 95%, respectively).
  - Whereas patients receiving Gemcitabine C Axitinib combinations showed lower incidence rates of diarrhea compared to the patients receiving Gemcitabine C Trametinib combinations (grades ≥3).
  - None of the Gemcitabine and varied drug combination patient groups showed any significant difference in terms of anemia, neutropenia and thrombocytopenia in hematologic toxicities.

Table 3. OR and 95%CI of six treatment modalities of six hematologic endpoint outcomes.

OR (95%CI) Hematologic (all grades)					
Anemia					
A	0.14 (0.00, 8.15)	1.17 (0.02, 81.35)	0.02 (0.00, 2.03)	1.09 (0.02, 69.54)	
7.16 (0.12, 572.91)	B	8.60 (0.02, 3494.09)	0.18 (0.00, 82.00)	7.97 (0.02, 3123.86)	
0.85 (0.01, 65.16)	0.12 (0.00, 44.41)	C	0.02 (0.00, 8.45)	0.92 (0.00, 342.54)	
43.12 (0.49, 4169.92)	5.68 (0.01, 2891.05)	47.49 (0.12, 27841.94)	D	45.57 (0.11, 22388.71)	
0.92 (0.01, 59.19)	0.13 (0.00, 44.59)	1.08 (0.00, 462.62)	0.02 (0.00, 9.31)	G	
Neutropenia					
A	0.38 (0.04, 3.49)	1.10 (0.11, 11.19)	0.13 (0.01, 1.50)	1.27 (0.13, 12.42)	
2.63 (0.29, 24.32)	B	2.90 (0.12, 73.62)	0.34 (0.01, 8.66)	3.33 (0.13, 89.14)	
0.91 (0.09, 8.88)	0.34 (0.01, 8.51)	C	0.12 (0.00, 3.19)	1.16 (0.05, 29.09)	
7.66 (0.67, 99.25)	2.94 (0.12, 94.27)	8.52 (0.31, 278.91)	D	10.05 (0.38, 306.85)	
0.79 (0.08, 8.00)	0.30 (0.01, 7.45)	0.86 (0.03, 22.05)	0.10 (0.00, 2.65)	G	
Thrombocytopenia					
A	0.40 (0.12, 1.40)	1.88 (0.55, 6.38)	1.49 (0.37, 6.22)	1.28 (0.41, 4.07)	
2.50 (0.71, 8.53)	B	4.71 (0.81, 26.25)	3.76 (0.60, 24.32)	3.20 (0.59, 17.18)	
0.53 (0.16, 1.82)	0.21 (0.04, 1.23)	C	0.81 (0.13, 5.22)	0.68 (0.13, 3.92)	
0.67 (0.16, 2.69)	0.27 (0.04, 1.66)	1.24 (0.19, 7.99)	D	0.87 (0.14, 4.96)	
0.78 (0.25, 2.45)	0.31 (0.06, 1.68)	1.46 (0.25, 7.73)	1.15 (0.20, 7.12)	G	
Hematologic (grade≥3)					
Anemia					
A	0.08 (0.00, 1.87)	2.32 (0.15, 37.97)	0.08 (0.00, 1.71)	0.58 (0.03, 9.64)	1.22 (0.09, 18.18)
12.62 (0.53, 581.06)	B	30.19 (0.48, 3188.84)	1.07 (0.01, 136.24)	7.51 (0.12, 829.90)	16.98 (0.27, 1652.03)
0.43 (0.03, 6.49)	0.03 (0.00, 2.10)	C	0.03 (0.00, 2.06)	0.25 (0.00, 12.43)	0.56 (0.01, 24.31)
12.03 (0.59, 268.43)	0.93 (0.01, 81.93)	29.80 (0.49, 1710.19)	D	7.10 (0.11, 365.84)	14.92 (0.28, 901.17)
1.72 (0.10, 28.67)	0.13 (0.00, 8.29)	4.08 (0.08, 213.72)	0.14 (0.00, 8.80)	E	2.26 (0.04, 106.91)
0.82 (0.06, 11.62)	0.06 (0.00, 3.73)	1.79 (0.04, 101.93)	0.07 (0.00, 3.60)	0.44 (0.01, 23.35)	G
Neutropenia					
A	0.46 (0.17, 1.39)	1.16 (0.39, 3.38)	0.90 (0.27, 2.67)	1.11 (0.39, 2.98)	1.45 (0.51, 3.89)
2.17 (0.72, 6.05)	B	2.44 (0.52, 11.47)	1.92 (0.37, 8.51)	2.36 (0.53, 9.90)	3.13 (0.67, 12.77)
0.86 (0.30, 2.56)	0.41 (0.09, 1.91)	C	0.75 (0.15, 3.62)	0.92 (0.23, 4.26)	1.29 (0.28, 5.46)
1.11 (0.37, 3.66)	0.52 (0.12, 2.67)	1.34 (0.28, 6.48)	D	1.20 (0.28, 5.93)	1.69 (0.37, 7.62)
0.90 (0.34, 2.55)	0.42 (0.10, 1.90)	1.09 (0.23, 4.44)	0.84 (0.17, 3.53)	E	1.37 (0.30, 5.33)
0.69 (0.26, 1.97)	0.32 (0.08, 1.50)	0.78 (0.18, 3.52)	0.59 (0.13, 2.67)	0.73 (0.19, 3.30)	G
Thrombocytopenia					
A	0.53 (0.12, 2.03)	0.89 (0.26, 3.13)	0.43 (0.11, 1.72)	0.95 (0.28, 3.04)	1.29 (0.39, 4.23)
1.89 (0.49, 8.66)	B	1.69 (0.29, 12.58)	0.82 (0.13, 6.31)	1.82 (0.29, 12.47)	2.53 (0.42, 16.83)
1.12 (0.32, 3.80)	0.59 (0.08, 3.46)	C	0.48 (0.07, 3.01)	1.05 (0.19, 5.84)	1.45 (0.26, 7.95)
2.35 (0.58, 9.38)	1.22 (0.16, 7.98)	2.09 (0.33, 14.01)	D	2.23 (0.35, 13.74)	3.02 (0.49, 18.93)
1.05 (0.33, 3.52)	0.55 (0.08, 3.46)	0.96 (0.17, 5.33)	0.45 (0.07, 2.86)	E	1.37 (0.26, 7.53)
0.77 (0.24, 2.55)	0.40 (0.06, 2.36)	0.69 (0.13, 3.90)	0.33 (0.05, 2.04)	0.73 (0.13, 3.87)	G

Notes: OR and 95%CI below the treatments should be read from row to column while above the treatments should be read from column to row. OR = odds ratio; 95%CI = 95% confidence intervals; A = Gemcitabine+Placebo; B = Gemcitabine+Axitinib; C = Gemcitabine+Trametinib; D = Gemcitabine+Sorafenib; E = Gemcitabine+Bevacizumab; G = Gemcitabine+Tipifarnib.

Table 4. OR and 95%CI of six treatment modalities of six non-hematologic endpoint outcomes.

OR (95%CI) Non-hematologic (all grades)					
Rash					
A	0.29 (0.06, 1.36)	2.71 (0.57, 13.27)	2.99 (0.67, 14.14)	1.23 (0.24, 6.52)	
3.50 (0.74, 17.16)	B	9.36 (1.02, 92.76)	10.33 (1.26, 90.71)	4.21 (0.45, 41.90)	
0.37 (0.08, 1.76)	0.11 (0.01, 0.98)	C	1.08 (0.12, 10.36)	0.44 (0.05, 4.68)	
0.33 (0.07, 1.50)	0.10 (0.01, 0.79)	0.93 (0.10, 8.41)	F	0.41 (0.04, 3.77)	
0.81 (0.15, 4.14)	0.24 (0.02, 2.21)	2.25 (0.21, 21.84)	2.47 (0.27, 24.25)	G	
Diarrhea					
A	0.42 (0.01, 26.80)	3.15 (0.05, 208.59)	64.04 (0.61, 7704.44)	1.41 (0.02, 82.20)	1.58 (0.03, 88.60)
2.39 (0.04, 131.89)	B	7.39 (0.02, 2343.83)	148.77 (0.31, 79234.08)	3.32 (0.01, 948.13)	3.80 (0.01, 1189.69)
0.32 (0.00, 19.63)	0.14 (0.00, 41.70)	C	20.62 (0.04, 10762.48)	0.47 (0.00, 140.96)	0.50 (0.00, 173.64)
0.02 (0.00, 1.63)	0.01 (0.00, 3.27)	0.05 (0.00, 26.26)	D	0.02 (0.00, 12.55)	0.02 (0.00, 10.07)
0.71 (0.01, 45.20)	0.30 (0.00, 114.65)	2.15 (0.01, 795.46)	46.81 (0.08, 25274.19)	F	1.12 (0.00, 345.72)
0.63 (0.01, 37.35)	0.26 (0.00, 91.23)	1.99 (0.01, 692.07)	41.16 (0.10, 18905.66)	0.89 (0.00, 294.60)	G
Stomatitis					
A	1.48 (0.05, 54.85)	6.13 (0.18, 221.89)	19.76 (0.46, 798.39)	1.64 (0.05, 57.51)	
0.68 (0.02, 22.11)	B	4.17 (0.03, 610.35)	13.37 (0.07, 2238.47)	1.11 (0.01, 156.96)	
0.16 (0.00, 5.56)	0.24 (0.00, 34.47)	C	3.21 (0.02, 611.15)	0.27 (0.00, 39.83)	
0.05 (0.00, 2.16)	0.07 (0.00, 13.80)	0.31 (0.00, 50.19)	D	0.08 (0.00, 11.77)	
0.61 (0.02, 21.86)	0.90 (0.01, 146.27)	3.73 (0.03, 577.73)	12.03 (0.08, 2208.64)	F	
Non-hematologic (grade≥3)					
Rash					
A	0.99 (0.08, 11.05)	6.81 (0.46, 292.28)	9.07 (0.62, 370.88)	2.30 (0.12, 97.36)	
1.01 (0.09, 12.15)	B	7.28 (0.16, 533.29)	9.84 (0.23, 733.82)	2.37 (0.06, 192.09)	
0.15 (0.00, 2.18)	0.14 (0.00, 6.15)	C	1.38 (0.01, 110.68)	0.35 (0.00, 35.15)	
0.11 (0.00, 1.61)	0.10 (0.00, 4.26)	0.73 (0.01, 70.12)	F	0.24 (0.00, 24.51)	
0.44 (0.01, 8.54)	0.42 (0.01, 17.58)	2.86 (0.03, 305.85)	4.19 (0.04, 419.48)	G	
Diarrhea					
A	0.11 (0.00, 1.60)	8.64 (0.62, 370.49)	0.63 (0.06, 5.82)	3.51 (0.32, 55.29)	1.32 (0.13, 15.29)
9.10 (0.63, 526.96)	B	91.68 (1.78, 13496.48)	5.80 (0.18, 652.52)	33.71 (0.86, 3857.15)	12.35 (0.32, 1109.38)
0.12 (0.00, 1.61)	0.01 (0.00, 0.56)	C	0.07 (0.00, 2.38)	0.39 (0.01, 17.62)	0.15 (0.00, 5.27)
1.60 (0.17, 15.69)	0.17 (0.00, 5.66)	15.23 (0.42, 1064.71)	D	5.86 (0.20, 192.49)	2.18 (0.08, 61.23)
0.28 (0.02, 3.16)	0.03 (0.00, 1.16)	2.58 (0.06, 187.55)	0.17 (0.01, 4.95)	F	0.37 (0.01, 12.76)
0.76 (0.07, 7.77)	0.08 (0.00, 3.11)	6.86 (0.19, 513.41)	0.46 (0.02, 12.78)	2.72 (0.08, 92.84)	G
Stomatitis					
A	0.92 (0.02, 33.25)	2.44 (0.13, 96.04)	5.59 (0.42, 224.30)	0.85 (0.02, 28.95)	
1.09 (0.03, 46.55)	B	2.79 (0.02, 455.98)	7.23 (0.06, 925.05)	0.90 (0.00, 178.08)	
0.41 (0.01, 7.73)	0.36 (0.00, 41.16)	C	2.26 (0.03, 238.49)	0.30 (0.00, 37.95)	
0.18 (0.00, 2.35)	0.14 (0.00, 17.48)	0.44 (0.00, 33.19)	D	0.14 (0.00, 12.52)	
1.18 (0.03, 51.95)	1.11 (0.01, 220.96)	3.36 (0.03, 728.13)	7.36 (0.08, 1096.69)	F	

Notes: OR and 95%CI below the treatments should be read from row to column while above the treatments should be read from column to row. OR = odds ratio; 95%CI = 95% confidence intervals; A = Gemcitabine+Placebo; B = Gemcitabine+Axitinib; C = Gemcitabine+Trametinib; D = Gemcitabine+Sorafenib; F = Gemcitabine+Erlotinib; G = Gemcitabine+Tipifarnib.

- SUCRA values of six targeted drugs combined with gemcitabine in the treatment of advanced/metastatic PC:
  - The SUCRA value of cumulative probability sorting of seven regimens showed that Gemcitabine C Sorafenib combination showed the highest incidence rates of anemia (all grades), neutropenia (all grades), anemia (grade ≥3) and thrombocytopenia (grade ≥3) [anemia (all grades): 92.4%; neutropenia (all grades): 91.8%, anemia (grade ≥3): 86.8%, thrombocytopenia (grade ≥3): 83.3%].
  - Gemcitabine C Axitinib combination showed the highest incidence rates of thrombocytopenia (all grades) and neutropenia (grade ≥3) [thrombocytopenia (all grades): 95.2%, neutropenia (grade ≥3): 91.5%].
  - Gemcitabine C Trametinib combination showed the lowest incidence rates of for anemia (all grades), thrombocytopenia (all grades) and anemia (grades ≥3) [anemia (all grades): 43.2%, thrombocytopenia (all grades): 36.8%, anemia (grade ≥3): 30.2%]. Gemcitabine C Tipifarnib combination showed the lowest incidence rates of neutropenia (all grades), neutropenia (grade ≥3) and thrombocytopenia (grade ≥3) [neutropenia (all grades): 40.4%, neutropenia (grade ≥3): 35.5%, thrombocytopenia (grade ≥3): 37.8%].

Table 5. SUCRA values of seven treatment modalities under twelve endpoint outcomes.

	Treatments						
SUCRA values (%)	A	B	C	D	E	F	G
			Hematologic (all grades)				
Anemia	44.6	75.2	43.2	92.4	NR	NR	45.0
Neutropenia	47.0	74.2	45.6	91.8	NR	NR	40.4
Thrombocytopenia	68.0	95.2	36.8	47.2	NR	NR	53.0
			Hematologic (grade≥3)				
Anemia	47.2	86.7	30.2	86.8	58.0	NR	41.8
Neutropenia	57.3	91.5	49.5	65.2	51.7	NR	35.5
Thrombocytopenia	47.3	76.3	53.8	83.3	52.2	NR	37.8
			Non-hematologic (all grades)				
Rash	70.6	96.8	36.8	NR	NR	34.4	61.8
Diarrhea	72.3	84.5	48.5	22.7	NR	62.0	60.2
Stomatitis	83.0	71.0	45.8	30.2	NR	69.0	NR
			Non-hematologic (grade≥3)				
Rash	81.6	78.6	41.8	NR	NR	36.8	60.8
Diarrhea	63.67	94.2	26.5	72.0	NR	37.3	55.8
Stomatitis	72.0	69.2	51.4	36.4	NR	71.0	NR

Notes: SUCRA = surface under the cumulative ranking curves; NR = not report; A = Gemcitabine+Placebo; B = Gemcitabine+Axitinib; C = Gemcitabine+Trametinib; D = Gemcitabine+Sorafenib; E = Gemcitabine+Bevacizumab; F = Gemcitabine+Erlotinib; G = Gemcitabine+Tipifamib.

- The SUCRA value results for non-hematologic toxicities were also recorded.
  - o Gemcitabine C Axitinib combination showed the highest incidence rate of rash (all grades), diarrhea (all grades) and diarrhea (grade ≥3)[rash (all grades): 96.8%, diarrhea (all grades): 84.5%, diarrhea (grade ≥3): 94.2%].
  - o Gemcitabine C Trametinib combination showed the lowest incidence rates of diarrhea (grade ≥3), (26.5%). Gemcitabine C Sorafenib combination showed the lowest incidence rates of diarrhea (all grades), stomatitis (all grades) and stomatitis (grade ≥3) lowest [diarrhea (all grades): 22.7%, stomatitis (all grades): 30.2%, stomatitis (grade ≥3): 36.4%]. Gemcitabine C
  - o Erlotinib combination showed the lowest incidence rates of rash (all grades) and rash (grade ≥3) [rash (all grade): 34.4%, rash (grade ≥3): 36.8%].
- Cluster analyses were used in order to group the treatments according to their similarities regarding both outcomes → The cluster analyses results revealed that Gemcitabine C Axitinib combinations and Gemcitabine C Sorafenib combinations showed lower incidence rates of hematotoxicity, while Gemcitabine C Axitinib combinations showed lower incidence rates of non-hematotoxicity.

Anmerkung/Fazit der Autoren

In conclusion, the results indicate that Gemcitabine combinations with different target drugs regimens may show more frequent toxicities in the treatment of advanced or metastatic PC, which provides us with significant insight for their clinical use and treatment of advanced or metastatic PC.

Kommentare zum Review

- Gemischte Population (advanced/metastatic)
- Status/Linie unklar. Lediglich Information bei den Ausschlusskriterien → *Exlusion criteria (…) PC patients who previously undergone chemotherapy, gemcitabine, targeted drugs and radiotherapy in the last two weeks*

3.4 Leitlinien

Deutsche Krebsgesellschaft (DKG), 2013 [7].

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften)

S3-Leitlinie zum exokrinen Pankreaskarzinom; Langfassung, Version 1.0

Leitlinienorganisation/Fragestellung

Zielsetzung dieser Leitlinie ist die Sicherstellung einer evidenzbasierten, flächendeckenden optimalen Versorgung von Patienten mit exokrinem Pankreaskarzinom.

Methodik

Grundlage der Leitlinie

- Expertengruppe/Formulierung PICO Fragen
- Literaturrecherche und Bewertung der Literatur
- Interessenskonflikte dargelegt

LoE/GoR

- Schema der Evidenzgraduierung nach Oxford sowie bei Empfehlungen zusätzlich die Stärke der Empfehlung (Empfehlungsgrad) ausgewiesen.

Tabelle 7: Schema der Evidenzgraduierung bei der Erstellung der Leitlinie 2006

Level of Evidence (LoE)	Definition
1	Systematischer Review (SR) mit Homogenität (keine Heterogenität bzgl. der Ergebnisse der einzelnen Studien) von randomisierten kontrollierten Studien (RCT)
2a	Systematischer Review mit Homogenität von Kohortenstudien
2b	Individuelle Kohortenstudien plus RCTs geringer Qualität (z. B. Follow Up < 80 %):
3	Systematische Übersichten mit Homogenität von Fall-Kontroll-Studien sowie Individuelle Fall-Kontroll-Studien.
4	Fallserien und Kohortenstudien sowie Fall-Kontroll-Studien niedriger Qualität (d.h. Kohorte: Keine klar definierte Vergleichsgruppe, keine Outcome/ Expositionsmessung in experimenteller und Kontrollgruppe, kein ausreichender Follow-Up; Fall-Kontroll-S.: Keine klar definierte Vergleichsgruppe)
5	Expertenmeinung oder inkonsistente bzw. nicht schlüssige Studien jedes Evidenzgrades

Tabelle 8: Schema der Empfehlungsgraduierung für die Empfehlungen aus 2006

Empfehlungsgrad	Bedeutung
A	Konsistent Studien mit Evidenzgrad 1 vorhanden
B	Konsistent Studien mit Evidenzgrad 2 oder 3 bzw. Extrapolationen von Studien mit Evidenzgrad 1
C	Studien mit Evidenzgrad 4 oder Extrapolationen von Studien mit Evidenzgrad 2 oder 3
D	Expertenmeinung oder inkonsistente bzw. nicht schlüssige Studien jedes Evidenzgrades

Tabelle 9: Schema der Empfehlungsgraduierung für die aktualisierten Empfehlungen aus 2013

Empfehlungsgrad	Beschreibung	Syntax
A	Starke Empfehlung	soll
B	Empfehlung	sollte
0	Empfehlung offen	kann

Tabelle 10: Konsensusstärke

Konsensstärke	Prozentuale Zustimmung
Starker Konsens	> 95 % der Stimmberechtigten
Konsens	> 75 – 95 % der Stimmberechtigten
Mehrheitliche Zustimmung	> 50 – 75 % der Stimmberechtigten
Dissens	< 50 % der Stimmberechtigten

Sonstige methodische Hinweise

- Bei diesem Dokument handelt es sich um die aktualisierte Fassung der 2006 erstmals erstellten S3-Leitlinie zum exokrinen Pankreaskarzinom. → 1. Aktualisierung der Leitlinie 2013. **Die Gültigkeit der Leitlinie wurde nach inhaltlicher Überprüfung durch das Leitliniensekretariat bis zum 30.10.2018 verlängert!** *→ Anmerkung FBMed: Die LL war bei Fertigstellung der Synopse noch gültig, ist jedoch zum Zeitpunkt der Beratung abgelaufen.*

Palliative Therapie des Pankreaskarzinoms

Indikation zur Chemotherapie

8.1.	Evidenzbasierte Empfehlung	modifiziert 2013
Empfehlungsgrad **A**	Beim metastasierten bzw. lokal fortgeschrittenen Pankreaskarzinom soll bei einem ECOG Performance Status von 0 bis 2 eine palliative Chemotherapie durchgeführt werden.	
Level of Evidence **1a**	Literatur: [305, 370-372, 374-382]	
	Starker Konsens	

8.2.	Evidenzbasierte Empfehlung	2013
Empfehlungsgrad **B**	Gemcitabin sollte als Erstlinientherapie des lokal fortgeschrittenen und/oder metastasierten Pankreaskarzinoms eingesetzt werden.	
Level of Evidence **1a**	Literatur: [374, 375, 383-388]	
	Starker Konsens	

Erläuterung: Das Gemcitabin wird trotz überzeugender Nutzenbelege nur mit einer schwachen Empfehlung (Empfehlungsgrad B) empfohlen, weil mit FOLFIRINOX (siehe Empfehlung 8.8.) bzw. Gemcitabin plus Erlotinib bei rash (siehe Empfehlung 8.5.) zwei wirksamere Therapien bei bestimmten Patientengruppen in Frage kommen. Gemcitabin mono kann daher nicht grundsätzlich für alle Patienten mit lokal fortgeschrittenem und/oder metastasiertem Pankreaskarzinom empfohlen werden.

8.4.	Evidenzbasierte Empfehlung	2013
Empfehlungsgrad **A**	5-FU mit oder ohne Folinsäure soll nicht als alleinige Erstlinientherapie eingesetzt werden.	
Level of Evidence **1b**	Literatur: [374]	
	Starker Konsens	

Kombinationen mit „Targeted agents“

8.5.	Evidenzbasierte Empfehlung	modifiziert 2013
Empfehlungsgrad 0	Alternativ zur Gemcitabin Monotherapie kann eine Kombinationstherapie aus Gemcitabin und dem EGF-Rezeptortyrosinkinaseinhibitor Erlotinib beim metastasierten Pankreaskarzinom eingesetzt werden.	
Level of Evidence 1b	Literatur: [385]	
	Konsens	

8.7.	Evidenzbasierte Empfehlung	modifiziert 2013
Empfehlungsgrad A	Weitere Kombinationen von Gemcitabin mit sogenannten “Targeted Therapies” wie Cetuximab, Bevacizumab oder Axitinib besitzen keinen Stellenwert in der Therapie des Pankreaskarzinoms und sollen außerhalb von prospektiven, kontrollierten Studien nicht eingesetzt werden. Diese Kombinationen werden nicht empfohlen.	
Level of Evidence 1b	Literatur: [311, 386, 389, 390]	
	Starker Konsens	

Chemotherapiekombinationen: FOLFIRINOX

8.8.	Evidenzbasierte Empfehlung	Neu 2013
Empfehlungsgrad 0	Die Kombination von 5-FU/Folinsäure, Irinotecan und Oxaliplatin nach dem sogenannten FOLFIRINOX-Protokoll kann bei Patienten mit metastasiertem Pankreaskarzinom und einem günstigen Risikoprofil (ECOG 0-1, Bilirubinwert unter dem 1,5-fachen des oberen Normwertes, Alter bis 75 Jahre) eingesetzt werden.	
Level of Evidence 1b	Literatur: [376]	
	Starker Konsens	

Erläuterung: In einer großen randomisierten Studie wurde ein deutlicher Vorteil des FOLFIRINOX Regimes im Vergleich zu Gemcitabin gezeigt. Bei Patienten mit metastasiertem Pankreaskarzinom und günstigen Risikofaktoren wurde das mediane Überleben von 6,8 auf 11,1 Monate verlängert ($p<0,0001$; HR 0,57). Ebenso konnte das progressionsfreie Überleben von 3,3 auf 6,4 Monate und die Ansprechrate von 9,4 % auf 31,6 % durch Gabe des FOLFIRINOX-Protokolls im Vergleich zu Gemcitabin verbessert werden. Dem klinisch relevanten Nutzen steht eine deutlich höhere Toxizität des FOLFIRINOX-Regimes gegenüber, die sich im Vergleich zu Gemcitabin in einer Steigerung der Rate an Grad III/IV Neutropenie (45,7 % vs. 18,7 %), an febriler Neutropenie (5,4 vs. 0,6 %) und Grad III/IV Diarrhoe (12,7 % vs. 1,2 %) niederschlägt. In der Studie wurde die Therapie bereits ab einer Grad II Neutropenie oder Thrombopenie passager pausiert und eine Dosisanpassung gemäß den Studienkriterien vorgenommen. G-CSF wurde im Laufe der Therapie mit FOLFIRINOX

bei insgesamt 42,5 % der Patienten gegeben. Aufgrund der relativ niedrigen Rate an febrilen Neutropenien (5,4 %) wurde keine generelle primäre G-CSF Prophylaxe empfohlen. Wegen der strengen Selektionskriterien wurden in diese Studie nur 36 % Patienten mit Pankreaskopftumoren und nur 14 % mit biliären Stents eingeschlossen. Ob eine prophylaktische Antibiotikatherapie bei Stentträgern indiziert ist, kann anhand der Studiendaten nicht beurteilt werden.

8.9.	Evidenzbasierte Empfehlung	modifiziert 2013
Empfehlungsgrad **B**	Die Kombination von Gemcitabin mit Oxaliplatin, Cisplatin oder Capecitabin sollte nicht als Standard in der Erstlinientherapie des metastasierten oder lokal fortgeschrittenen, inoperablen Pankreaskarzinoms eingesetzt werden.	
Level of Evidence **1a**	Literatur: [375, 383, 384, 387, 388, 391, 392]	
	Starker Konsens	

Folgetherapien bei Progress unter einer Erstlinientherapie

8.11.	Evidenzbasierte Empfehlung	modifiziert 2013
Empfehlungsgrad **B**	Bei Progress unter einer Therapie mit Gemcitabin sollte bei einem ECOG ≤ 2 eine Zweitlinientherapie mit 5-FU und Oxaliplatin durchgeführt werden.	
Level of Evidence **1b-**	Literatur: [395]	
	Starker Konsens	

Alberta Provincial Gastrointestinal Tumour Team, 2017 [1].

Alberta Health Services

Adenocarcinoma of the pancreas

Leitlinienorganisation/Fragestellung

- What are the recommendations for the diagnostic workup of adult patients with adenocarcinoma of the pancreas?
- What are the treatment recommendations for adult patients with potentially curable adenocarcinoma of the pancreas?
- What are the management recommendations for adult patients with unresectable cancer of the pancreas?

Methodik

Grundlage der Leitlinie

This guideline was reviewed and endorsed by the Alberta Provincial Gastrointestinal Tumour Team. Members of the Alberta Provincial Gastrointestinal Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, hepatologists, gastroenterologists,

interventional radiologists, nurses, nurse practitioners, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Gastrointestinal Tumour Team and a Knowledge Management Specialist from the Guideline Resource Unit.

Recherche/Suchzeitraum:

- This guideline was developed to promote evidence-based practice in Alberta. It was compiled from the results of randomized controlled trials and systematic reviews, derived from an English language and relevant term search of PubMed and MEDLINE from 1990 forward. It takes into consideration related information presented at local, national, and international meetings as well as the Alberta Provincial Gastrointestinal Tumour Team's interpretation of the data. For the 2017 update of this guideline, recommendations were modified based on a consensus discussion at the 2017 Annual Gastrointestinal Tumour Team Meeting. However, no formal update of the literature was performed.

LoE/GoR

- Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations. Guideline Resource Unit (GURU) does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines thatwere taken into consideration when formulating the recommendations including: Description of all known benefits and possible harms; Evidence summary, quality/quantity/consistency of discussion; Discussion of the role of clinical experience, theory, values and opinions in developing the recommendation

Sonstige methodische Hinweise

- This guideline was originally developed in January 2008. This guideline was revised in March 2009, August 2009, March 2010, June 2011, October 2013, March 2014, June 2015 and November 2017.

Empfehlungen

Management Recommendations for Unresectable Adenocarcinoma of the Pancreas

Stage	Recommendations

Locally Advanced
Stage III $T_4N_{any}M_0$
 	
Metastatic Disease
Stage IV $T_{any}N_{any}M_1$
	First line treatment
	A discussion addressing patient preferences concerning the balance of toxicity and efficacy should guide the decision for first line therapy for patients with good performance status.
	
	FOLFIRINOX
	• For carefully selected patients with metastatic disease, performance status (ECOG 0 or 1), age ≤ 75 years, and a normal or nearly normal bilirubin, FOLFIRINOX prolongs overall survival (11.1 months *versus* 6.8 months, HR 0.57, 95% CI 0.45-0.73, p = 0.0001) and delays the deterioration in quality of life when compared to Gemcitabine alone.[11,12] The rate of grade 3/4 toxicities emphasizes the need for education, monitoring, and active management (see Table 4 and 5 below). It should only be administered in the Tertiary or Regional Cancer Centres.
	• The Provincial Gastrointestinal Tumour Team agree that FOLFIRINOX may also be considered for patients with locally advanced disease given that a high response rate may result in the conversion of some patients to resectable disease. At present, no randomized studies have explored the use of FOLFIRINOX in locally advanced pancreatic cancer patients (see Appendix A for a list of current clinical trials using this regimen). Several retrospective reviews have demonstrated the efficacy and tolerability of FOLFIRINOX in this patient group, despite the use of dose modifications and adverse events.[13-15]
	
	nab-Paclitaxel plus Gemcitabine
	• Patients may also be considered for treatment with nab-Paclitaxel plus Gemcitabine. An international, phase III trial of 861 metastatic pancreatic cancer patients compared the efficacy and safety of nab-Paclitaxel plus Gemcitabine versus Gemcitabine alone.[16] Median overall survival was 8.5 months in the intervention arm compared to 6.7 months in the control arm (HR 0.72, 95% CI 0.62–0.83, p<0.001). Median progression-free survival was 5.5 months versus 3.7 months in the nab-Paclitaxel plus Gemcitabine versus Gemcitabine alone group, respectively (HR 0.69, 95% CI 0.58–0.82, p<0.001). According to independent review, the response rate was 23% versus 7% in the nab-Paclitaxel plus Gemcitabine group versus the control group, respectively (p<0.001). The Provincial Gastrointestinal Tumour Team adapts the eligibility criteria based on the above mentioned phase III study.[16] The Provincial Gastrointestinal Tumour Team agree that nab-Paclitaxel plus Gemcitabine may also be considered for patients with locally advanced disease.
	• Patients eligible for nab-Paclitaxel plus Gemcitabine should meet the following criteria:
	  • ≥18 years of age
	  • Karnofsky performance status score ≥70
	  • Have not previously received chemotherapy for metastatic disease (patient could have received treatment with Fluorouracil or Gemcitabine as a radiation sensitizer in the adjuvant setting if the treatment had been received at least 6 months ago)
	  • Have histologically or cytologically confirmed metastatic or locally advanced adenocarcinoma of the pancreas
	  • Have adequate hematologic, hepatic, and renal function, including:
	  ○ Absolute neutrophil count of ≥1.5x10^9 per litre
	  ○ Hemoglobin level of ≥9 g per deciliter
	  ○ Bilirubin level at or below the upper limit of the normal range
	
	Gemcitabine
	• For patients with a performance status of ECOG ≤2, Gemcitabine (1,000 mg/m^2 IV over thirty minutes once weekly for seven of eight weeks and subsequently weekly for three of four weeks) has been shown to offer a "clinical benefit response" (improvement in pain, performance status, and weight) in 23.8%.[17,18] In addition, it may prolong median survival (to 5.65 months) and improve twelve-month survival (to 18%). Treatment should be continued until progression or until significant clinical deterioration secondary to tumour-related symptoms.

Stage	Recommendations
	Second line treatment • After progression on Gemcitabine, treatment with Leucovorin (200 mg/m² IV over thirty minutes) followed by a continuous intravenous infusion of 5-Fluorouracil (2,000 mg/m² over twenty-four hours) on days 1, 8, 15, and 22 with Oxaliplatin (85 mg/m² IV over two hours) on days 8 and 22 of every six week cycle ("OFF" regimen) has been shown to increase median overall survival compared to Leucovorin and 5-Fluorouracil alone; from 3.3 months to 5.9 months (p =0.010) in patients with a good performance status.[19] Note that FOLFOX is not interchangeable with "OFF" as it has been shown to be inferior to Leucovorin and 5-Fluorouracil in terms of OS in the second line[20]. • Nanoliposomal irinotecan (80 mg/m², equivalent to 70 mg/m² of irinotecan base)with 5-Fluorouracil and Leucovorin is an acceptable second line treatment option and may be considered for use after Health Canada approval is obtained as the addition of nanoliposomal irinotecan increased median overall survival to 6.1m (95%CI 4.8-8.9) compared to 4.2m (95%CI 3.3-5.3m) in the fluorouracil and folinic acid alone group (HR 0.67, 95% CI 0.49-0.92; p=0.012).[12]

Ducreux M et al., 2015 [5].

European Society for Medical Oncology (ESMO)

Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

Leitlinienorganisation/Fragestellung

Evidence-based recommendations for the diagnosis, treatment and follow-up of pancreatic cancer

Methodik

Grundlage der Leitlinie

These clinical practice guidelines were developed in accordance with the ESMO standard operating procedures for clinical practice guidelines development. The relevant literature has been selected by the expert authors.

This manuscript has been subjected to an anonymous peer review process.

LoE/GoR

Table 5. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, …), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [58].

Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

Treatment of advanced/metastatic disease

recommendation for palliative and supportive care in advanced/metastatic disease

- Duodenal obstruction is preferably managed by endoscopic placement of an expandable metal stent when possible, and is favoured over surgery [IV, B]
- Oncologic treatment: there are threeoptions to treat patients with a metastatic pancreatic cancer according to their general status:
  - For patients with performance status of 3/4, with significant morbidities and a very short life expectancy: only symptomatic treatment can be considered. Even chemotherapy with gemcitabine cannot be considered for such patients.
  - In very selected patients with ECOG performance status 2 due to heavy tumour load, gemcitabine and nab-paclitaxel can be considered for best chance of response [II, B].
  - For patients with performance status of 2 and/or bilirubin level higher than 1.5× ULN: monotherapy with gemcitabine could be considered [I, A]
  - If the performance status of the patient is 0 or 1 and the bilirubin level is below 1.5× ULN two types of combination chemotherapy—the FOLFIRINOX regimen or the combination of gemcitabine and nab-paclitaxel—should be considered [I, A]

The efficacy of the treatment has to be evaluated every two months with a comparative CT scan. The treatment has to be stopped if a RECIST progression is observed and second-line treatment has to be discussed.

second-line treatment

- A first randomised trial (168 patients) has shown, in patients with advanced gemcitabine-refractory pancreatic cancer, that second-line 5-FU, folinic acid and oxaliplatin, significantly extend the duration of OS when compared with 5-FU, folinic acid alone. These results have not been confirmed by a more recent Canadian trial. Very recently, combination of MM-398, a nanoliposomal encapsulation of irinotecan, and 5-FU, folinic acid has shown an improvement of OS (6.1 versus 4.2 months), PFS and ORR in the intent-to-treat population over 5-FU/LV alone. Second-line therapy of pancreatic cancer has to be considered in terms of risk benefit for the patient. If the general status remains correct, considering the conflicting results on the use of oxaliplatin, MM-398 when available in all countries may be the best option for second-line treatment of these patients [II, B].

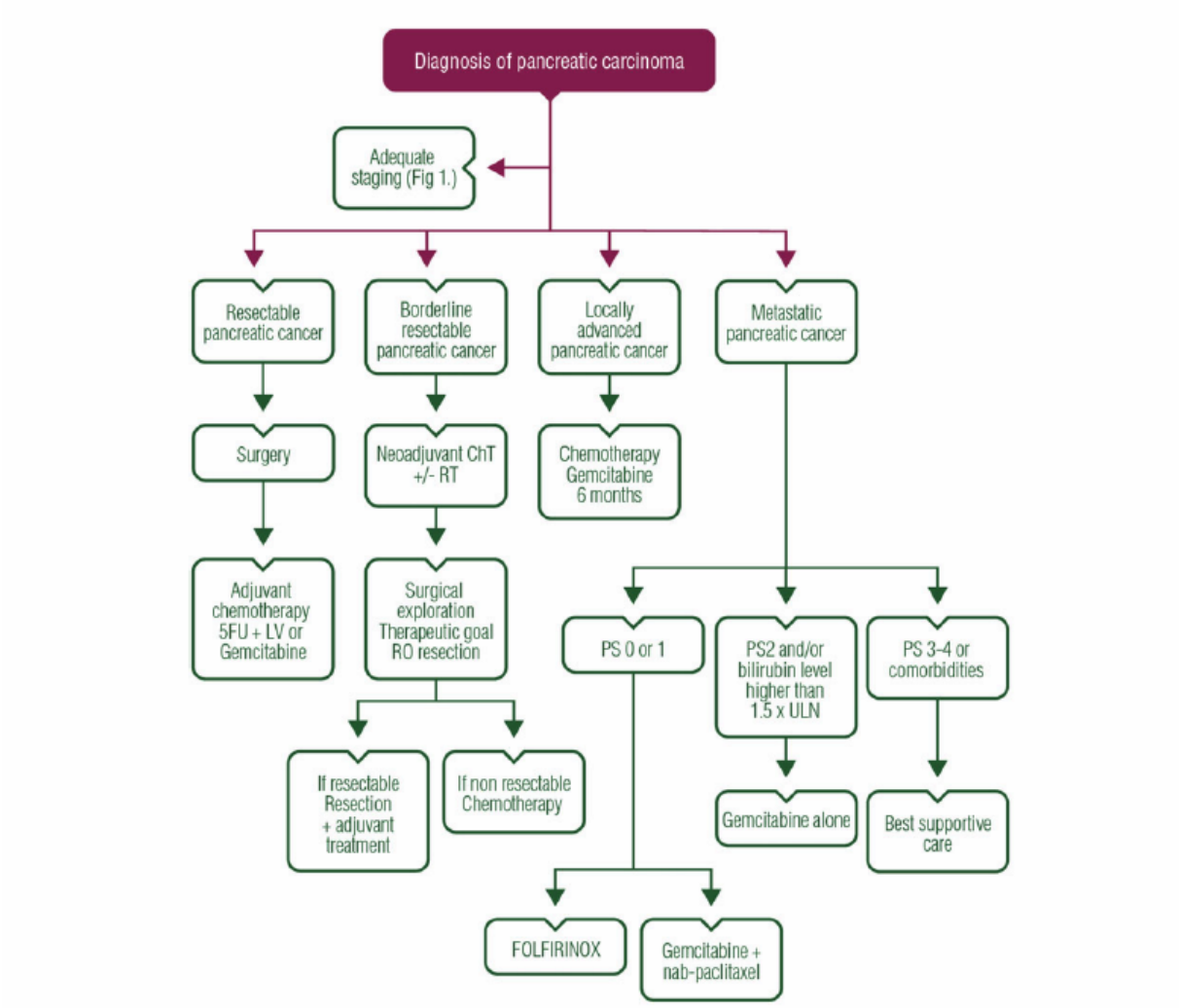


Figure 2. Treatment strategy. ChT, chemotherapy; RT, radiotherapy; 5-FU, 5-fluorouracil; LV, leucovorin; PS, performance status; ULN, upper limit of normal.

Recommendations for follow-up:

Considering the poor prognosis of the disease upon diagnosis of a recurrence, there is no evidence that regular follow-up after initial therapy with curative intent has any impact on the outcome. Follow-up visits should concentrate on symptoms, nutrition, and psycho-social support. recommendations for follow-up

- There is no evidence that regular follow-up after initial therapy with curative intent is useful [IV, D].

Sohal DP et al., 2016 [15] & Sohal DP et al., 2018 [16]

American Society of Clinical Oncology (ASCO)

Metastatic Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline & Metastatic Pancreatic Cancer: ASCO Clinical Practice Guideline Update

Leitlinienorganisation/Fragestellung

What is the treatment of patients with metastatic pancreatic cancer?

Methodik

Grundlage der Leitlinie

- An Expert Panel developed clinical practice guideline recommendations that are based on a systematic review of the medical literature (from April 2004 to June 2015)
- Update for second-line: ASCO convened an Expert Panel to conduct a systematic review of the literature on second-line therapy published between June 2015 and January 2018. → Two new studies were found that met the inclusion criteria.

LoE/GoR

- Study quality was formally assessed for the studies identified. Design aspects related to the individual study quality were assessed by one reviewer and included factors such as blinding, allocation concealment, placebo control, intention to treat, funding sources, etc. The risk of bias is assessed as low, intermediate or high for most of the identified evidence.

Type of Recommendation	Definition
Evidence based	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.
Formal consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the Expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Expert Panel may choose to provide a rating for the strength of the recommendation (ie, "strong," "moderate," or "weak"). The results of the formal consensus process are summarized in the guideline and reported in the Data Supplement.
Informal consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the Expert Panel. The Expert Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Expert Panel may choose to provide a rating for the strength of the recommendation (ie, "strong," "moderate," or "weak").
No recommendation	There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Expert Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of Expert Panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on (1) good evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of Expert Panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on (1) limited evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of Expert Panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

Rating for Strength of Evidence	Definition
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits *v* harms) and that further research is very unlikely to change either the magnitude or direction of this net effect.
Intermediate	Moderate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect.
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction this net effect.
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic.

Treatment

Clinical Question 2: What Is the Appropriate First-Line Treatment of Patients With Metastatic Pancreatic Cancer?

- Recommendation 2.1. Leucovorin, fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) is recommended for patients who meet all of the following criteria: ECOG PS 0 to 1, favorable comorbidity profile, patient preference and support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).
- Recommendation 2.2. Gemcitabine plus nanoparticle albuminbound (NAB)-paclitaxel is recommended for patients who meet all of the following criteria: ECOG PS 0 to 1, relatively favorable comorbidity profile, and patient preference and support system for relatively aggressive medical therapy (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).
- Recommendation 2.3. Gemcitabine alone is recommended for patients who have either an ECOG PS 2 or a comorbidity profile that precludes more-aggressive regimens and who wish to pursue cancer-directed therapy. The addition of either capecitabine or erlotinib to gemcitabine may be offered in this setting (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).
- Recommendation 2.4. Patients with an ECOG PS ≥3 or with poorly controlled comorbid conditions despite ongoing active medical care should be offered cancer-directed therapy on only a case-by-case basis. The major emphasis should be on optimizing supportive care measures (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Clinical Question 3:What Is the Appropriate Therapy for Patients With Metastatic Pancreatic Cancer Who Experience Either Disease Progression or Intolerable Toxicity With Prior Regimens for Metastatic Pancreatic Cancer?

- From Update: Recommendation 3.1. Routine testing for dMMR or MSI-H is recommended, using IHC, PCR, or NGS for patients who are considered to be candidates for checkpoint inhibitor therapy (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).
- From Update: Recommendation 3.2. PD-1 immune checkpoint inhibitor pembrolizumab is recommended as second-line therapy for patients who have tested positive for dMMR or MSI-H (Type: evidence-based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).
- Recommendation 3.3. Gemcitabine plus NAB-paclitaxel can be offered as second-line therapy for patients who meet all of the following criteria: first-line treatment with FOLFIRINOX, ECOG PS 0 to 1, relatively favorable comorbidity profile, and patient preference and a support system for aggressive medical therapy (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).
- From Update: Recommendation 3.4. Fluorouracil plus nanoliposomal irinotecan, or fluorouracil plus irinotecan where the former combination is unavailable, is preferred as second-line therapy for patients who meet all of the following criteria: first-line treatment

with gemcitabine plus NAB-paclitaxel, an ECOG PS of 0 to 1, a relatively favorable comorbidity profile, patient preference and a support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

- From Update: Recommendation 3.5. Fluorouracil plus oxaliplatin may be considered as second-line therapy for patients who meet all of the following criteria: first-line treatment with gemcitabine plus NAB-paclitaxel, an ECOG PS of 0 to 1, a relatively favorable comorbidity profile, patient preference and a support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

  From Update: Qualifying statement for recommendations 3.4 and 3.5. A recent phase III trial comparing mFOLFOX with FU + LV demonstrated a higher rate of grade 3 or 4 adverse events and significantly reduced OS within the mFOLFOX6 arm of the trial. However, previous phase III data have demonstrated a benefit with the OFF regimen compared with FU + LV. Considering the inconsistency of these results, although fluorouracil plus nanoliposomal irinotecan is preferred, the Expert Panel continues to support the use of fluorouracil plus oxaliplatin as an option where the availability of fluorouracil plus nanoliposomal irinotecan is limited or where residual toxicity from first-line therapy or comorbidities preclude the use of fluorouracil plus nanoliposomal irinotecan.
- Recommendation 3.6. Gemcitabine or fluorouracil can be considered as second-line therapy for patients who have either an ECOG PS of 2 or a comorbidity profile that precludes moreaggressive regimens and who wish to pursue cancer-directed therapy(Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).
- Recommendation 3.7. No data are available to recommend third line (or greater) therapy with a cytotoxic agent. Clinical trial participation is encouraged (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

<u>Clinical Question 6: What Is the Recommended Frequency of Follow-Up Care/Surveillance for Patients With Metastatic Pancreatic Cancer?</u>

- Recommendation 6.1. For patients on active cancer-directed therapy outside a clinical trial, imaging to assess first response should be offered at 2 to 3 months from the initiation of therapy. CT scans with contrast are the preferred modality. Thereafter, clinical assessment conducted frequently during visits for cancer-directed therapy should supplant imaging assessment. The routine use of positron emission tomography scans for the management of patients with pancreatic cancer is not recommended. CA19-9 is not considered an optimal substitute for imaging for assessing treatment response (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong).
- Recommendation 6.2. No data exist on the duration of cancer-directed therapy. An ongoing discussion of goals of care and assessment of treatment response and tolerability should guide decisions to continue or hold/terminate cancer-directed therapy (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong).

  Literature review and analysis: At present, no evidence-based data exist to guide the frequency of imaging for patients with metastatic cancer. The two approved chemotherapy combinations of

FOLFIRINOX (once every 2 weeks) and gemcitabine plus NAB-paclitaxel (days 1, 8, 15 every 4 weeks) lend themselves naturally to follow-up imaging after 8 or 12 weeks of chemotherapy. The clinical practice for physicians in this panel would be to reimage after 8 to 12 weeks of chemotherapy.

NICE, 2018 [11].

National Institute for Health and Care Excellence

Pancreatic cancer in adults: diagnosis and management

Leitlinienorganisation/Fragestellung

Provide recommendations for the treatment and care of people with pancreatic cancer

Methodik

Grundlage der Leitlinie

- A multidisciplinary committee comprising healthcare professionals and researchers as well 2 as lay members developed this guideline
- Development of review questions and outcomes/ full literature searches (June 2016 and October 2016), critical appraisals and evidence reviews were completed for all review questions.

LoE/GoR

- GRADE methodology/ Cochrane Risk of Bias tool, for observational studies, quality was assessed using the Newcastle-Ottawa Scale

Table 6: Description of quality elements in GRADE for intervention studies

Quality element	Description
Risk of bias (study limitations)	Limitations in the study design and implementation may bias the estimates of the treatment effect. High risk of bias for the majority of the evidence decreases confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results or findings.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made, such that the effect estimate is changed. This is also related to applicability or generalisability of findings.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect. Imprecision results if the confidence interval includes the clinically important threshold. For qualitative research this can relate to the sufficiency of data within each theme.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table 11: Summary of Cochrane risk of bias tool

Risk of bias	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (this is a major problem in 'pseudo' or 'quasi' randomised trials with allocation by, for example, day of week, birth date, chart number).
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes or data analysts are aware of the arm to which patients are allocated.
Incomplete accounting of patients and outcome events	Missing data not accounted for and failure of the investigators to adhere to the intention to treat principle when indicated.
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results.
Other risks of bias	For example: • stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • use of unvalidated patient-reported outcomes • recruitment bias in cluster randomised trials.

Table 12: Summary of Newcastle and Ottawa scale

Risk of bias category	Quality assessment item
Selection	Representativeness of the cohort
	Selection of the non-exposed cohort
	Ascertainment of exposure
	Demonstration that the outcome of interest was not present at the start of the study
Comparability	Comparability of cohorts on the basis of the design or analysis
Outcome	Assessment of outcome
	Was follow-up long enough for outcomes to occur
	Adequacy of follow-up of cohorts

Management of unresectable pancreatic 1 cancer

Management of metastatic pancreatic cancer

- First-line treatment
  - Offer FOLFIRINOX to people with metastatic pancreatic cancer and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1.
  - Consider gemcitabine combination therapy[5] for people who are not well enough to 22 tolerate FOLFIRINOX. For guidance on combination therapy with gemcitabine and 23 nab–paclitaxel, see the NICE technology appraisal guidance on paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer.
  - Offer gemcitabine to people who are not well enough to tolerate combination chemotherapy.
- Second-line treatment
  - Consider oxaliplatin-based chemotherapy as second-line treatment for people who have not had first-line oxaliplatin.

- Consider gemcitabine-based chemotherapy as second-line treatment for people whose cancer has progressed after first-line FOLFIRINOX.

Quality of evidence

- *The quality of the outcomes for the comparisons identified by this review were as follows:*
  - *Chemotherapy versus immunochemotherapy for second line treatment - very low.*
  - *5-FU combination chemotherapy versus other chemotherapy regimens – ranged from very low to low*
  - *Second-line chemotherapy versus other chemotherapy regimens for metastatic disease –ranged from very low to low*
  - *Gemcitabine versus novel agents – ranged from very low to moderate*
  - *5-FU alone versus 5-FU combination chemotherapy (both metastatic and locally advanced disease) – ranged from very low to moderate*
  - *Second-line chemotherapy versus other chemotherapy regimens for mixed metastatic and locally advanced disease – ranged from low to moderate*
  - *Chemotherapy versus immunochemotherapy for first line treatment - ranged from low to moderate quality.*
  - *Chemotherapy (second-line) versus best supportive care – ranged from low to moderate*
  - *Standard-dose versus low-dose gemcitabine – ranged from low to moderate*
  - *Intra-arterial chemotherapy versus systemic chemotherapy – ranged from low to moderate*
  - *Chemotherapy versus prophylactic anticoagulation + chemotherapy – ranged from low to moderate*

A substantial number of studies in the evidence base included mixed locally advanced and metastatic cancer populations, but did not report the subgroups separately. Given that there is a continuum between locally advanced and metastatic disease, the committee agreed it was appropriate to use evidence with mixed populations to base their recommendations on. However, during their discussions the committee applied more weight to those studies that had exclusively metastatic populations or had reported metastatic populations separately.
The committee noted that no RCT evidence was identified which evaluated surgical resection of metastases in people with pancreatic cancer. The committee therefore agreed to recommend further research in this area, as the role of surgery in managing metastatic pancreatic cancer is a common question asked by patients.

Neuzillet C et al., 2018 [12].

Pancreatic cancer: French clinical practice guidelines for diagnosis, treatment and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, ACHBT, AFC)

Leitlinienorganisation/Fragestellung

The primary aim was to develop recommendations using only methodologically established evidence-based guidelines or primary evidence, and to achieve an interdisciplinary consensus.

Methodik

Grundlage der Leitlinie

This guideline is a collaborative work under the auspices of all French medical and surgical societies involved in the management of pancreatic cancer.

A writing multidisciplinary committee (from nine medical societies) gathering experts from different specialties involved in the management of pancreatic cancer (pathologist, surgeons, radiation oncologists, medical oncologists, and gastroenterologists)was designated to review recent literature (PubMed search until December 2017 and international congress abstracts of randomized trials) and to write a first document after interactive discussions.

This initial document was reviewed and modified after further evaluation by a review committee and the last version was finally validated by the steering committee of the participating National Societies.

LoE/GoR

- Recommendations based on this level of evidence were scored in 3 categories (grade A–C) according to the GRADE system with only expert opinion (agreement or not, grade D) when no scientific evidence was validated. All the statements in the present article completely match the original full guidelines, with no additional data or comments.

Treatments

Metastatic PDAC

- First line

  Recommendations

  - Supportive care from diagnosis (recommendation: grade A) (same as locally advanced PDAC).
  - ECOG PS 3–4: best supportive care (expert agreement)
  - Age <75 years, ECOG PS 0–1 and bilirubin <1.5 ULN: FOLFIRINOX or gemcitabine plus nab-paclitaxel (recommendation: grade A).
  - ECOG PS 2 and bilirubin <1.5 ULN: gemcitabine plus nab-paclitaxel (recommendation: grade B) or gemcitabine (recommendation: grade A).
  - ECOG PS 0–2 and bilirubin ≥1.5 ULN or comorbidities: gemcitabine (recommendation: grade A).

  Options

  - ECOG PS 0–1: gemcitabine plus platinum or gemcitabine plus 5-FU (or capecitabine) (recommendation: grade B)
  - ECOG PS 2 and/or bilirubin ≥1.5 ULN: FOLFOX (expert opinion).

Clinical trials

- *PRODIGE 63 (TEDOPaM) trial*
- *APACaP trial*
- *URGENCE Pancreas Study (NCT02979483): prospective cohort evaluating an early supportive care program for symptomatic (ECOG PS 2) advanced PDAC*
- *PRODIGE GEMFOX trial: first-line FOLFOX versus gemcitabine in patients with metastatic PDAC who are not eligible for FOLFIRI-NOX (phase III study)*

- Second line

  Recommendations

  - Chemotherapy if ECOG PS 0–1 (recommendation: grade A).
  - FOLFOX (recommendation: grade B) after failure of gemcitabine.
  - 5-FU/FA plus nal-IRI (recommendation: grade B) after failure of gemcitabine.

  Options

  - FOLFIRI after failure of gemcitabine (recommendation: grade C).
  - Gemcitabine after failure of FOLFIRINOX (expert agreement).
  - Gemcitabine plus nab-paclitaxel after failure of FOLFIRINOX if ECOG PS 0–1 (expert opinion).
  - Gemcitabine or 5-FU single agent if ECOG PS 2 (expert opinion).
  - Paclitaxel alone or with gemcitabine (expert opinion).

Clinical trials

- *PRODIGE GEMPAX trial: gemcitabine plus paclitaxel versus gemcitabine alone after failure of FOLFIRINOX (phase III study).*
- Treatment of tumor relapse: Metastatic relapse

  Recommendations: No reference.

  Options:

- Chemotherapy (recommendation: grade B): Type depends on: (i)patient's general condition, (ii) extension of the disease and associated symptoms, (iii) residual toxicity of previous treatments,(iv) initial efficacy, (v) and treatment-free time interval.
- In very selected cases of long time interval between tumor resection and recurrence, oligometastatic pulmonary involvement, prolonged disease control with chemotherapy, and possibility of R0 resection: surgery or local destruction can be discussed (expert opinion). In patients who underwent PD and biliodigestive anastomosis, surgery recommended rather than local destruction (risk of liver abscess on ischemic cholangitis secondary to the reduction of the biliary arterial blood supply).

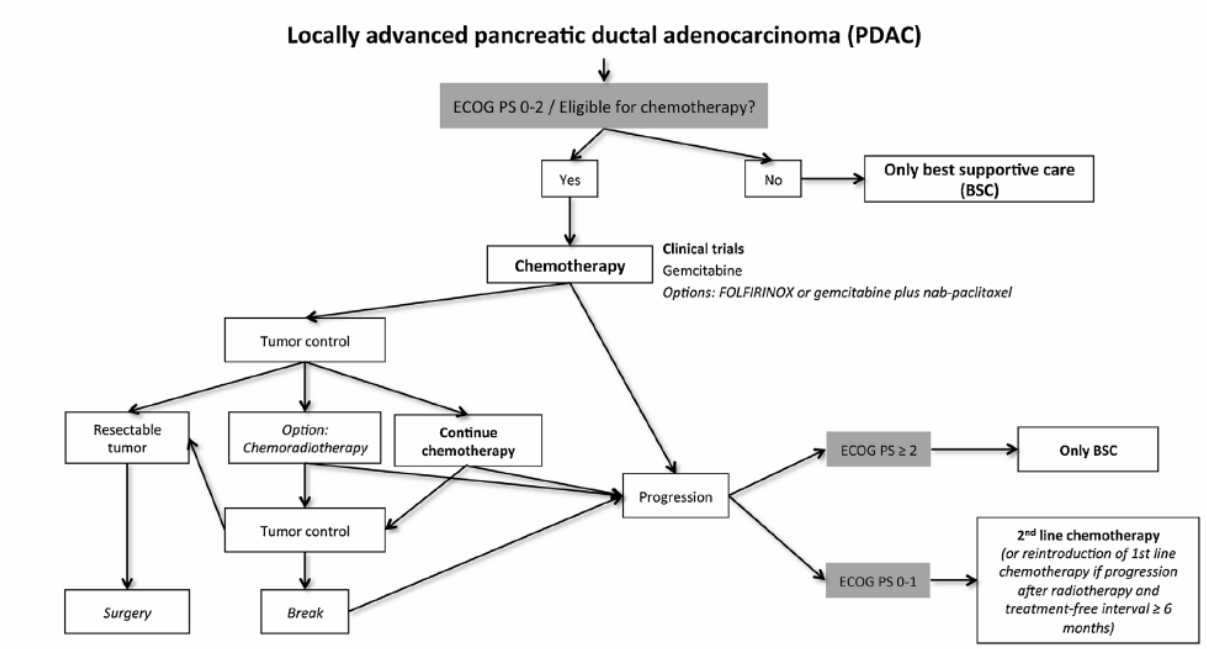


Fig. 2. Algorithm for treatment of locally advanced tumor pancreatic ductal adenocarcinoma (PDAC).
ECOG PS: Eastern Cooperative Oncology Group performance status.

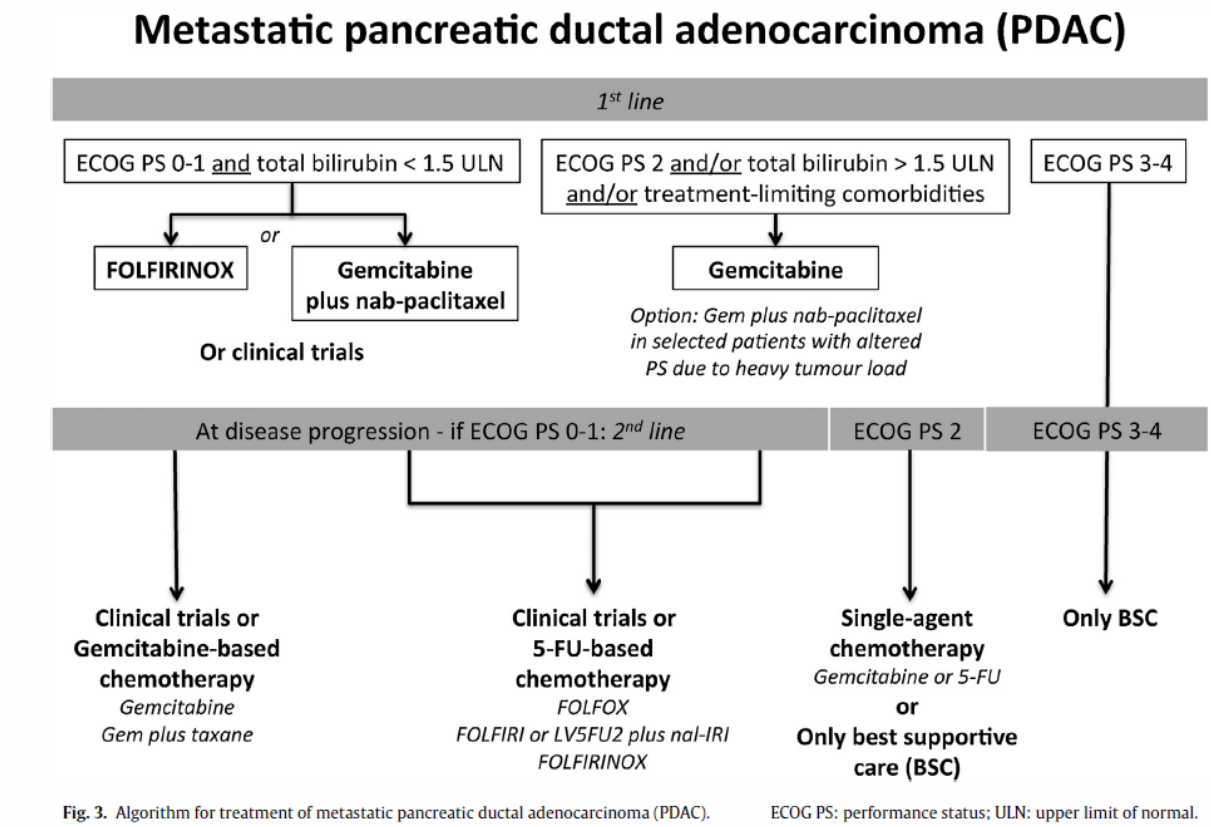


Fig. 3. Algorithm for treatment of metastatic pancreatic ductal adenocarcinoma (PDAC). ECOG PS: performance status; ULN: upper limit of normal.

Evaluation and surveillance

- After treatment
  - No reference.

- Options: May be useful after curative surgical resection to detect recurrence at an early stage.
- Proposal: (i) clinical examination, (ii) serum CA19-9 measurement when elevated at diagnosis, (iii) thoraco-abdomino-pelvic MDCT, every 3 months during 2–3 years, then every 6–12 months up to 5 years (expert opinion).

- During treatment
  - No reference.
  - Options: No data in the literature to define optimal surveillance modalities.
  - Proposal: same modalities as “after treatment” (expert agreement): Neoadjuvant or induction setting: every 2 months; Adjuvant setting: every 3 months; Advanced setting: every 2–3 months.

Veereman G et al., 2017 [17,18].

Belgian Health Care Knowledge Centre (KCE)

Management of pancreatic cancer – Part 1: Introduction and methodology & Management of pancreatic cancer – Part 4: Recurrent and metastatic cancer

Leitlinienorganisation/Fragestellung

This guideline provides recommendations based on current scientific evidence for three specific RQs about pancreatic cancer.

Methodik

Grundlage der Leitlinie

The KCE guideline is produced according to highly codified principles, based on scientific information regularly updated from the international literature. This guideline was developed using a standard methodology based on a systematic review of the evidence.

questions were selected and the inclusion and exclusion criteria were defined in collaboration with a scoping group, consisting of members of the GDG and stakeholders. The composition of the different groups is documented in the Colophon. In a second step, a systematic literature review was conducted. The third step involves formulation of recommendations based on the literature review and grading according to the GRADE approach.

What is the optimal treatment strategy in patients with recurrent/metastatic pancreatic cancer?

- In patients with unresectable or advanced PC a difference in OS or QoL between various types of anti-cancer therapy and BSC could neither be demonstrated nor refuted (low to very low level of evidence).
- There is evidence of moderate quality that compared to 5-FU, gemcitabine leads to better OS in patients with symptomatic advanced PC (moderate level of evidence). QoL was not assessed.
- There is evidence of high quality that compared to gemcitabine, FOLFIRINOX leads to better OS in patients with MPC (high level of evidence).
- There is evidence of moderate quality that compared to gemcitabine, FOLFIRINOX leads to better QoL in patients with MPC (moderate level of evidence).

- In patients with LAPC or MPC a difference in OS between various types of chemotherapy (CO-101 or ZD9331) and gemcitabine could neither be demonstrated nor refuted (low level of evidence). QoL was not assessed.
- There is evidence that compared to gemcitabine alone gemcitabine in combination with fluoropyrimidine (low level of evidence), oxaliplatin/capecitabine (GEMOXEL) or cisplatin/epirubicin/5-FU (low level of evidence) leads to better survival in patients with advanced PC.
- For patients with MPC gemcitabine in combination with taxane leads to better survival than gemcitabine alone (high level of evidence).
- In patients with advanced PC a difference in OS between gemcitabine in combination with platinum agent (low level of evidence), topoisomerase inhibitor (low level of evidence) or various types of other additional interventions (very low level of evidence) and gemcitabine alone could neither be demonstrated nor refuted.
- In patients with advanced PC a difference in QoL between gemcitabine combinations versus gemcitabine alone could neither be demonstrated nor refuted (very low level of evidence).
- In patients with unresectable PC, LAPC or MPC a difference in OS between fluoropyrimidine combinations versus fluoropyrimidine alone could neither be demonstrated nor refuted (very low level of evidence).In patients with LAPC or MPC a difference in QoL between fluoropyrimidine combinations versus fluoropyrimidine alone could neither be demonstrated nor refuted (very low level of evidence).
- No RCT or comparative observational study could be identified that adressed the effect CRT in patients with recurrent or MPC.
- No RCT or comparative observational study could be identified that adressed the effect of re-resection in patients with recurrent or MPC.

NCCN, 2018 [10].

National Comprehensive Cancer Network (NCCN)

Pancreatic adenocarcinoma: Version 2.2018

Leitlinienorganisation/Fragestellung

Recommendations for the treatment of Panceatic adenocarcinoma

Methodik

Grundlage der Leitlinie

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Pancreatic Adenocarcinoma, an electronic search of the PubMed database was performed to obtain key literature in the field of pancreatic cancer using the following search terms: (pancreatic cancer) OR (pancreatic adenocarcinoma) OR (pancreas adenocarcinoma) OR (pancreas cancer). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[10]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Practice Guideline; Guidelines; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The potential relevance of the PubMed search citations over the past year was examined. The data from key PubMed articles and articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website (www.NCCN.org).

LoE/GoR

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

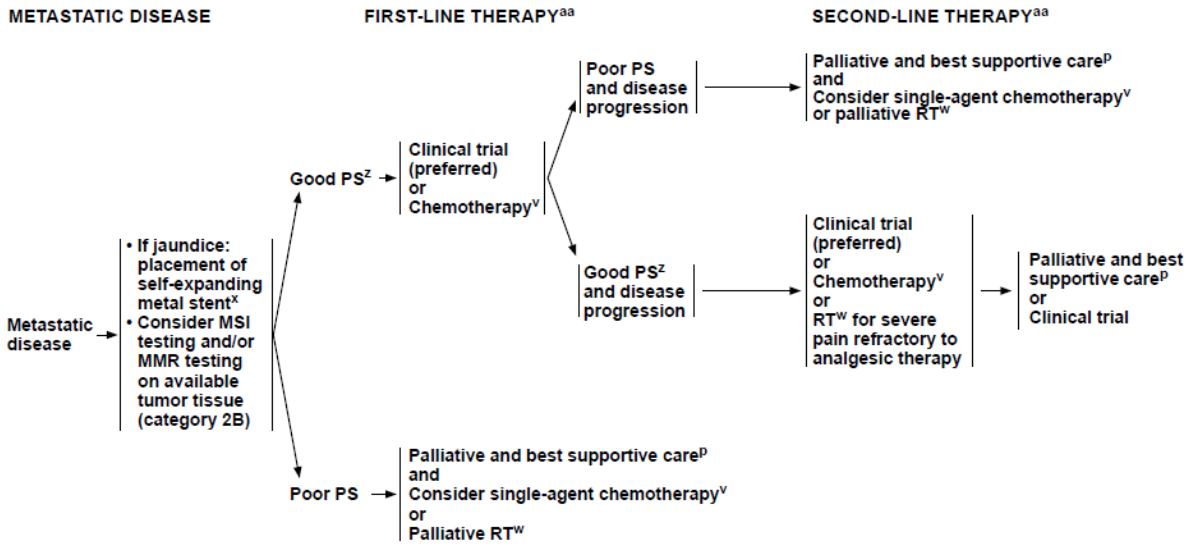
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

Sonstige methodische Hinweise

- Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund fehlender höherwertiger Evidenz zur Fragestellung der Erhaltungstherapie, wird die LL jedoch ergänzend dargestellt.

Recommendations



[p]See Principles of Palliation and Supportive Care (PANC-E).
[v]See Principles of Chemotherapy (PANC-G).
[w]See Principles of Radiation Therapy (PANC-F).
[x]Unless biliary bypass performed at time of laparoscopy or laparotomy.
[z]Defined as ECOG 0-1, with good biliary drainage and adequate nutritional intake, and ECOG 0-2 if considering gemcitabine + albumin-bound paclitaxel.
[aa]Serial imaging as indicated to assess disease response. See Principles of Diagnosis, Imaging, and Staging #10 (PANC-A).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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PANC-7

PRINCIPLES OF CHEMOTHERAPY

Metastatic Disease (First-Line Therapy)

- Patients who progress with metastatic disease are not candidates for radiation unless required for palliative purposes.
- Good performance status:
  - Preferred Options
    - ◊ FOLFIRINOX[b,f,6] (category 1)
    - ◊ Gemcitabine + albumin-bound paclitaxel[f,7] (category 1)
  - Other Options
    - ◊ Gemcitabine + erlotinib[c,8] (category 1)
    - ◊ Gemcitabine (category 1)
    - ◊ Gemcitabine + capecitabine[9]
    - ◊ Gemcitabine + cisplatin[10] (only for known *BRCA1/2* mutations)
    - ◊ Fixed-dose-rate gemcitabine, docetaxel, capecitabine (GTX regimen)[11] (category 2B)
    - ◊ Fluoropyrimidine + oxaliplatin (category 2B) (eg, 5-FU/leucovorin/oxaliplatin [OFF][12] or CapeOx[13])
- Poor performance status:
  - Gemcitabine
    - ◊ 1000 mg/m^2 over 30 minutes, weekly for 3 weeks every 28 days (category 1)
    - ◊ Fixed-dose-rate gemcitabine (10 mg/m^2/min) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B)
  - Capecitabine (category 2B)
  - CI 5-FU (category 2B)

See Second-Line Therapy on PANC-G (5 of 6)

[b]Due to the high toxicity of this regimen, bolus 5-FU is often omitted.
[c]Although this combination significantly improved survival, the actual benefit was small, suggesting that only a small subset of patients benefit.
[f]FOLFIRINOX should be limited to those with ECOG 0-1. Gemcitabine + albumin-bound paclitaxel is reasonable for patients with ECOG 0-2. 5-FU + leucovorin + liposomal irinotecan is a reasonable second-line option for patients with ECOG 0-2.

References

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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PRINCIPLES OF CHEMOTHERAPY

Second-line Therapy for Locally Advanced/Metastatic Disease

Good Performance Status

- If previously treated with gemcitabine-based therapy:
  - 5-FU + leucovorin + liposomal irinotecan[f,17] (category 1 for metastatic disease)
  - 5-FU + leucovorin + irinotecan (FOLFIRI)[18-20]
  - FOLFIRINOX[f]
  - Oxaliplatin/5-FU/leucovorin (OFF)
  - FOLFOX
  - Capecitabine/oxaliplatin
  - Capecitabine
  - CI 5-FU
  - Pembrolizumab (only for MSI-H or dMMR tumors)
  - Chemoradiation* (only for locally advanced disease; if not previously given, and if primary site is the sole site of progression)
- If previously treated with fluoropyrimidine-based therapy:
  - Gemcitabine + albumin-bound paclitaxel[f]
  - Gemcitabine
  - Gemcitabine + cisplatin (only for known *BRCA1/2* mutations)
  - Gemcitabine + erlotinib
  - 5-FU + leucovorin + liposomal irinotecan[f] (if no prior irinotecan)
  - Pembrolizumab (only for MSI-H or dMMR tumors)
  - Chemoradiation* (only for locally advanced disease; if not previously given, and if primary site is the sole site of progression)

Poor performance status

- Gemcitabine
  - 1000 mg/m^2 over 30 minutes, weekly for 3 weeks every 28 days (category 1)
  - Fixed-dose-rate gemcitabine (10 mg/m^2/min) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B)
- Capecitabine (category 2B)
- CI 5-FU (category 2B)

Recurrent Disease

- Following resection, if a patient with good performance status relapses after receiving adjuvant therapy, fluoropyrimidine-based regimens and gemcitabine-based regimens are options depending on the length of time since completion of adjuvant therapy.
  - If recurrence occurs ≥ 6 months following primary therapy, options include repeating the systemic therapy previously used, or switching to any other regimen.
  - If recurrence occurs < 6 months from completion of primary therapy, options include:
    - ◊ Switching to a gemcitabine-based regimen if a fluoropyrimidine-based regimen was previously used; or
    - ◊ Switching to a fluoropyrimidine-based regimen if a gemcitabine-based regimen was previously used.

*Chemoradiation:
- Fluoropyrimidine (capecitabine, CI 5-FU) + concurrent RT (preferred)
- Gemcitabine + concurrent RT[5]

[f]FOLFIRINOX should be limited to those with ECOG 0-1. Gemcitabine + albumin-bound paclitaxel is reasonable for patients with ECOG 0-2. 5-FU + leucovorin + liposomal irinotecan is a reasonable second-line option for patients with ECOG 0-2.

References

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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Possible Role of Maintenance Therapy in Advanced Disease

With the success of more effective regimens in patients with advanced disease, questions have been raised about how best to manage the treatment-free interval prior to disease progression. Options include stopping treatment, dropping the most toxic agents, and using different agents for maintenance therapy.

A randomized phase II trial (PACT-12) had intriguing results that suggest maintenance therapy with sunitinib after a full course of first-line treatment may have a benefit in some patients with metastatic disease.[283] Patients without evidence of progression after 6 months of initial therapy (n = 55; mostly gemcitabine combinations) were randomized to sunitinib or observation. Median OS was 9.2 months in the observation group versus 10.6 months in the sunitinib group (HR, 0.71; 95% CI, 0.40–1.26; *P* = .11). The small sample size precludes strong conclusions; however, the 1- and 2-year survival rates were 36% and 7% in the observation arm compared with 41% and 23% in the sunitinib arm, suggesting that a subset of patients derive significant benefit. Anti-angiogenic agents have not been successful in the treatment of pancreatic cancer to date. However, results of the PACT-12 trial suggest that there may in fact be a role for these compounds in this disease. Angiogenesis inhibitors may be more useful after more effective first-line treatments. Clearly, additional trials are needed in this important area.

3.5 Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Citterio C et al., 2018 [3].

Second-line chemotherapy for the treatment of metastatic pancreatic cancer after first-line gemcitabine-based chemotherapy: a network meta-analysis

Fragestellung

to compare, through a Bayesian network meta-analysis of published randomized clinical trials, the currently available therapies to treat metastatic pancreatic cancer in the second line, after a first line treatment based on GEM/GEM combination.

Methodik

Population:

- Patients with metastatic pancreatic cancer

Intervention/Komparator:

- currently available therapies to treat metastatic pancreatic cancer in the second line, after a first line treatment based on GEM/GEM combination (siehe Ergebnisteil)

Endpunkte:

- OS, PFS

Recherche/Suchzeitraum:

- between 2009 and 2017

Qualitätsbewertung der Studien:

- keine Angaben

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 studies (1,587 patients), phase 2-3 studies. Four studies were conducted in Japan, 1 in China, 1 in Canada, 1 in Germany and 1 involved multiple countries.

Charakteristika der Population:

- Only for 3 studies (52.74% of the 1,587 patients) information was available about the exact first line therapy used: 498 patients were treated with gemcitabine monotherapy and 339 with gemcitabine combinations. The patients performance status was reported in 6 studies (84% of the 1,587 patients): patients have a performance status between 0 (502 patients), 1 (741 patients) and 2 (55 patients). The second line chemotherapy drugs studied in various combinations were IRI, FP, folinic acid (FA) and OXA. A total of 7 treatments were compared: IRI + FP + FA (1), FP + FA (2), IRI (3), OXA + FP + FA (4), FP (5), IRI + FP (6), FP + OXA (7).

Qualität der Studien:

- Keine Angaben

Studienergebnisse:

- Network meta-analysis:
  - The combination IRI-FP-FA had better performance than all the other treatments, especially in respect of FP and OXA-FP, both in terms of OS and PFS.
  - Differences among treatments were more evident when focusing on PFS. Results for IR-FP changed according to the outcome: when comparing IRI-FP with OXA-FP-FA, IRI-FP was better in terms of OS while OXA-FP-FA was better in terms of PFS; when comparing IRI-FP with IRI, IRI-FP was better in term of OS while IRI was better in terms of PFS. The median of the I_2 distribution was around 85% for OS (90% CrI: 34,2%–97,9%) and close to 55% for PFS (90% CrI: 0.99%–97.7%).
  - The combination IRI-FP-FA resulted as having the largest probability of being the best and the lower posterior average rank, in particular when the focus was on PFS.
  - FP was the worst treatment in terms of best and average rank in both analyses. These results are confirmed by the analysis of the cumulative probabilities of the treatment rank.
  - When considering OS the most effective therapeutic combinations (SUCRA = 75%) were treatment schemes containing Irinotecan: IRI-FP-FA, followed by IRI-FP (58%), and IRI
  - The SUCRA for the remaining treatments was similar, with values varying between 47% and 50%. As far as PFS is concerned, the best treatment was IRI-FP-FA (90%), followed by OXA-FP-FA plus IRI, both having similar performance in terms of SUCRA (70% and, 69%, respectively). Also in this setting, the worst results were observed for the combinations OXA-FP and FP (11% and 20% respectively).

Anmerkung/Fazit der Autoren

The results suggested that the use of IRI-FP-Folinic Acid scheme in the second-line treatment of metastatic pancreatic cancer may offer a benefit in terms of OS and PFS for patients not previously treated with these drugs.

Kommentare zum Review

- Dieser Review erfüllt nicht ausreichend die methodischen Anforderungen (z.B. keine Angabe zu Qualitätsbewertung der Studien). Aufgrund limitierter höherwertiger Evidenz zur relevanten Fragestellung, wird die Quelle jedoch ergänzend dargestellt.
- Status Patienten (stable disease vs. progredient) unklar

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 10 of 12, Oktober 2018) am 04.10.2018

#	Suchfrage
#1	MeSH descriptor: [Pancreatic Neoplasms] explode all trees
#2	MeSH descriptor: [Pancreas] explode all trees
#3	(pancreas or pancreatic or islet* or nesidioblas* or "islands of langerhans" or (island next cell*) or (duodenal next papilla*) or gastroenteropancrea*):ti,ab,kw
#4	duct*:ti,ab,kw and (santorini* or wirsung*):ti,ab,kw
#5	#2 or #3 or #4
#6	(tumor or tumors or tumour* or carcinoma* or adenocarcinoma* or neoplasm* or sarcoma* or cancer*):ti,ab,kw
#7	MeSH descriptor: [Carcinoma] explode all trees
#8	#6 or #7
#9	#5 and #8
#10	#1 or #9
#11	#10 with Cochrane Library publication date from Sep 2013 to Sep 2018

Systematic Reviews in Medline (PubMed) am 04.10.2018

#	Suchfrage
1	Pancreatic Neoplasms[MeSH Terms]
2	pancreas[MeSH Terms] OR (Pancreas[Title/Abstract] OR pancreatic[Title/Abstract] OR islet*[Title/Abstract] OR Nesidioblast*[Title/Abstract] OR “islands of Langerhans”[Title/Abstract] OR island cell*[Title/Abstract] OR duodenal papilla*[Title/Abstract] OR gastroenteropancrea*[Title/Abstract])
3	(duct*[Title/Abstract]) AND (Santorini*[Title/Abstract] OR wirsung*[Title/Abstract])
4	(#2 OR #3)
5	(((((((tumor[Title/Abstract]) OR tumors[Title/Abstract]) OR tumour*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR adenocarcinoma*[Title/Abstract]) OR neoplasm*[Title/Abstract]) OR sarcoma*[Title/Abstract]) OR cancer*[Title/Abstract] OR carcinoma[MeSH Terms]
6	(#4 AND #5)
7	(#1 OR #6)
8	(#7) AND ((((advanced[Title/Abstract]) OR metastat*[Title/Abstract]) OR metastas*[Title/Abstract]) OR recurren*[Title/Abstract] OR "neoplasm metastasis"[MeSH Terms])
9	(#8) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
10	(#8) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR

	(systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
11	(#9 OR #10)
12	(#11) AND ("2013/10/01"[PDAT] : "3000"[PDAT])
13	(#12) NOT "The Cochrane database of systematic reviews"[Journal]
14	(#13) NOT retracted publication[ptyp]

Leitlinien in Medline (PubMed) am 04.10.2018

#	**Suchfrage**
1	Pancreatic Neoplasms[MeSH Major Topic]
2	pancreas[MeSH Major Topic] OR (Pancreas[Title] OR pancreatic[Title] OR islet*[Title] OR Nesidioblast*[Title] OR “islands of Langerhans”[Title] OR island cell*[Title] OR duodenal papilla*[Title] OR gastroenteropancrea*[Title])
3	(duct*[Title]) AND (Santorini*[Title] OR wirsung*[Title])
4	(#2 OR #3)
5	(((((((tumor[Title/Abstract]) OR tumors[Title/Abstract]) OR tumour*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR adenocarcinoma*[Title/Abstract]) OR neoplasm*[Title/Abstract]) OR sarcoma*[Title/Abstract]) OR cancer*[Title/Abstract] OR carcinoma[MeSH Terms]
6	(#4 AND #5)
7	(#1 OR #6)
8	(#7) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title])
9	(#8) AND ("2013/10/01"[PDAT] : "3000"[PDAT])

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Anhang

Tabelle 1: Liu et al. 2018

TABLE III. Odds Ratios/Weighted Mean Difference and 95% Confidence Intervals of Eleven Treatment Modalities of Efficacy Outcomes

OR/WMD (95% CI)									
ORR & DCR									
Gem	**1.84 (1.17,2.89)**	**1.80 (1.29,2.50)**	**1.52 (1.04,2.24)**	**2.97 (2.02,4.37)**	1.45 (0.36,5.78)	1.35 (0.55,3.29)	**2.89 (1.52,5.51)**	**4.47 (2.44,8.21)**	**1.74 (1.01,3.01)**
0.90 (0.63,1.27)	**S-1**	0.98 (0.56,1.71)	0.83 (0.46,1.50)	**1.62 (1.08,2.42)**	0.79 (0.18,3.38)	0.73 (0.27,2.00)	1.57 (0.72,3.46)	**2.43 (1.14,5.19)**	0.95 (0.47,1.93)
0.46 (0.34,0.63)	**0.52 (0.32,0.82)**	**Gem + Cisplatin**	0.85 (0.51,1.41)	1.65 (0.99,2.75)	0.80 (0.19,3.34)	0.75 (0.29,1.94)	1.61 (0.78,3.32)	**2.49 (1.25,4.96)**	0.97 (0.51,1.84)
0.71 (0.52,0.99)	0.80 (0.50,1.28)	1.54 (0.99,2.44)	**Gem + Capecitabine**	**1.95 (1.13,3.36)**	0.95 (0.23,4.00)	0.89 (0.34,2.34)	1.90 (0.90,4.02)	**2.93 (1.43,6.02)**	1.14 (0.59,2.23)
0.56 (0.42,0.76)	**0.63 (0.44,0.90)**	1.22 (0.79,1.85)	0.79 (0.51,1.22)	**Gem + S-1**	0.49 (0.12,2.05)	0.45 (0.17,1.20)	0.97 (0.46,2.06)	1.51 (0.73,3.09)	0.59 (0.30,1.15)
0.92 (0.39,2.13)	1.02 (0.41,2.56)	2.00 (0.81,5.00)	1.28 (0.52,3.13)	1.64 (0.67,4.00)	**Gem + 5-FU**	0.93 (0.18,4.84)	2.00 (0.43,9.20)	3.09 (0.68,14.01)	1.21 (0.27,5.34)
NR	NR	NR	NR	NR	NR	**Gem + Exatecan**	2.14 (0.71,6.43)	**3.31 (1.13,9.74)**	1.29 (0.45,3.67)
0.56 (0.27,1.16)	0.63 (0.28,1.41)	1.20 (0.55,2.70)	0.78 (0.35,1.72)	0.99 (0.45,2.17)	0.61 (0.20,1.85)	NR	**Gem + Irinotecan**	1.55 (0.64,3.75)	0.60 (0.26,1.40)
0.44 (0.28,0.68)	**0.49 (0.28,0.86)**	0.95 (0.55,1.64)	0.61 (0.36,1.06)	0.78 (0.46,1.33)	0.48 (0.18,1.25)	NR	0.79 (0.33,1.85)	**FOLFIRINOX**	**0.39 (0.17,0.88)**
NR	NR	NR	NR	NR	NR	NR	NR	NR	Gem + Oxaliplatin
PFS (month) & OS (month)									
Gem	−0.29 (−0.62,0.04)	−1.00 (−2.12,0.12)	**1.47 (1.12,1.81)**	**1.62 (1.30,1.94)**	1.00 (−0.22,2.22)	−0.10 (−0.51,0.31)	−0.10 (−1.21,1.01)	**3.10 (2.74,3.46)**	**0.60 (0.28,0.92)**
−1.71 (−3.92,0.50)	**S-1**	−0.71 (−1.88,0.45)	**1.76 (1.28,2.23)**	**1.91 (1.65,2.16)**	**1.29 (0.02,2.55)**	0.19 (−0.34,0.71)	0.19 (−0.97,1.34)	**3.39 (2.90,3.87)**	**0.89 (0.43,1.34)**
−0.20 (−3.01,2.61)	1.51 (−2.06,5.08)	**Gem + Cisplatin**	**2.47 (1.30,3.64)**	**2.62 (1.45,3.78)**	**2.00 (0.34,3.66)**	0.90 (−0.29,2.09)	0.90 (−0.67,2.47)	**4.10 (2.93,5.27)**	**1.60 (0.44,2.76)**
−1.11 (−2.55,0.32)	0.60 (−2.03,3.23)	−0.91 (−4.07,2.24)	**Gem + Capecitabine**	0.15 (−0.32,0.62)	−0.47 (−1.74,0.80)	**−1.57 (−2.10,−1.03)**	**−1.57 (−2.73,−0.41)**	**1.63 (1.13,2.13)**	**−0.87 (−1.34,−0.40)**
−2.90 (−4.62,−1.18)	−1.19 (−3.39,1.01)	−2.70 (−5.99,0.59)	−1.78 (−4.02,0.45)	**Gem + S-1**	−0.62 (−1.88,0.65)	**−1.72 (−2.24,−1.20)**	**−1.72 (−2.87,−0.56)**	**1.48 (1.00,1.96)**	**−1.02 (−1.47,−0.57)**
0.30 (−2.46,3.06)	2.01 (−1.53,5.55)	0.50 (−3.44,4.44)	1.41 (−1.70,4.53)	3.20 (−0.06,6.45)	**Gem + 5-FU**	−1.10 (−2.39,0.19)	−1.10 (−2.75,0.55)	**2.10 (0.83,3.37)**	−0.40 (−1.66,0.86)
−0.50 (−2.87,1.87)	1.21 (−2.03,3.23)	−0.30 (−3.97,3.37)	0.61 (−2.15,3.38)	2.40 (−0.53,5.32)	−0.80 (−4.44,2.84)	**Gem + Exatecan**	0.00 (−1.18,1.18)	**3.20 (2.66,3.74)**	**0.70 (0.18,1.22)**
0.21 (−1.55,1.97)	−1.92 (−0.90,4.74)	0.41 (−2.90,3.72)	1.33 (−0.94,3.59)	**3.11 (0.65,5.57)**	−0.09 (−3.37,3.19)	0.71 (−2.24,3.66)	**Gem + Irinotecan**	**3.20 (2.04,4.36)**	0.70 (−0.45,1.85)
−4.30 (−6.68,−1.92)	−2.59 (−5.84,0.66)	**−4.10 (−7.78,−0.42)**	**−3.19 (−5.96,−0.41)**	−1.40 (−4.34,1.53)	**−4.60 (−8.25,−0.95)**	**−3.80 (−7.16,−0.44)**	**−4.51 (−7.47,−1.55)**	**FOLFIRINOX**	**−2.50 (−2.98,−2.02)**
0.10 (−2.24,2.44)	1.81 (−1.40,5.02)	0.30 (−3.35,3.95)	1.21 (−1.53,3.95)	**3.00 (0.10,5.90)**	−0.20 (−3.82,3.42)	0.60 (−2.73,3.93)	−0.11 (−3.04,2.81)	**4.40 (1.06,7.74)**	**Gem + Pemetrexed**

ORs and 95% CI of ORR is above the treatments while DCR's is below the treatments, WMDs and 95% CI of PFS is above the treatments while OS's is below the treatments. Comparisons between treatments of ORR, DCR, PFS and OS should be read from column to row.
Bolded numbers represent the differences are of significance.
OR, odds ratio; WMD, weighted mean difference; 95%CI, 95% confidence intervals; ORR, overall response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; Gem, Gemcitabine; S-1, Tegafur; 5-FU, 5-Fluorouracil; FOLFIRINOX, Oxaliplatin + Irinotecan + Fluorouracil + Leucovorin.

Tabelle 2: Liu et al. 2018

TABLE IV. Odds Ratios and 95% Confidence Intervals of Twelve Treatment Modalities of Toxicity Outcomes

OR (95% confidence intervals)

Anemia & Neutropenia											
Gem	NR	1.93 (1.19,3.14)	0.91 (0.50,1.66)	1.24 (0.55,2.81)	0.76 (0.32,1.82)	1.18 (0.23,6.05)	1.11 (0.74,1.68)	1.34 (0.57,3.15)	0.60 (0.26,1.36)	5.36 (2.45,11.71)	
8.33 (4.35,14.29)	S-1	NR	NR	NR	NR	NR	NR	NR	NR	NR	
0.41 (0.26,0.65)	0.05	Gem + Cisplatin	0.47 (0.22,1.02)	0.64 (0.25,1.66)	0.40 (0.15,1.07)	0.61 (0.11,3.36)	0.57 (0.30,1.09)	0.70 (0.26,1.86)	0.31 (0.12,0.80)	2.77 (1.10,6.96)	
0.64 (0.42,0.98)	0.08	1.54 (0.83,2.86)	Gem + Capecitabine	1.35 (0.49,3.74)	0.84 (0.29,2.40)	1.28 (0.22,7.35)	1.21 (0.59,2.51)	1.47 (0.52,4.16)	0.65 (0.24,1.80)	5.85 (2.19,15.68)	
0.46 (0.32,0.68)	0.06	1.12 (0.62,2.00)	0.72 (0.40,1.30)	Gem + S-1	0.62 (0.19,2.04)	0.95 (0.15,5.93)	0.90 (0.36,2.24)	1.08 (0.33,3.54)	0.48 (0.15,1.54)	4.32 (1.39,13.43)	
0.39 (0.20,0.78)	0.05	0.95 (0.42,2.13)	0.62 (0.28,1.39)	0.85 (0.39,1.85)	Gem + Exatecan	1.54 (0.24,9.82)	1.45 (0.55,3.80)	1.76 (0.52,5.94)	0.78 (0.24,2.58)	7.00 (2.18,22.55)	
0.51 (0.20,1.33)	0.06	1.23 (0.43,3.57)	0.81 (0.28,2.27)	1.11 (0.40,3.13)	1.30 (0.40,4.17)	Gem + Irinotecan	0.94 (0.17,5.12)	1.14 (0.18,7.25)	0.51 (0.08,3.17)	4.56 (0.74,28.01)	
0.60 (0.36,1.00)	0.07	1.45 (0.75,2.86)	0.94 (0.49,2.27)	1.30 (0.69,2.44)	1.54 (0.66,3.57)	1.18 (0.40,3.45)	Gem + Nab-paclitaxel	1.21 (0.47,3.12)	0.54 (0.21,1.35)	4.83 (1.99,11.68)	
0.31 (0.17,0.59)	0.04	0.76 (0.35,1.64)	0.49 (0.23,1.05)	0.68 (0.33,1.43)	0.80 (0.32,2.00)	0.61 (0.20,1.92)	0.52 (0.23,1.16)	FOLFIRINOX	0.44 (0.14,1.45)	3.99 (1.25,12.70)	
1.49 (0.77,2.86)	0.18	3.57 (1.61,7.69)	2.23 (1.06,5.00)	3.23 (1.49,6.67)	3.85 (1.47,10.00)	2.94 (0.91,9.09)	2.44 (1.08,5.56)	4.76 (1.89,11.11)	Gem + Oxaliplatin	9.00 (2.89,28.02)	
0.18 (0.10,0.32)	0.02	0.43 (0.21,0.91)	0.28 (0.14,0.58)	0.39 (0.19,0.78)	0.45 (0.19,1.12)	0.35 (0.11,1.06)	0.30 (0.14,0.65)	0.57 (0.24,1.35)	0.12 (0.05,0.29)	Gem + Pemetrexed	
Thrombocytopenia & Diarrhea											
Gem	0.15	1.99 (0.86,4.63)	1.02 (0.35,2.95)	2.45 (0.99,6.08)	3.67 (0.11,119.74)	3.92 (0.81,18.98)	8.58 (0.33,223.92)	1.40 (0.35,5.62)	2.70 (0.53,13.89)	4.92 (0.94,25.71)	3.29 (0.78,13.90)
0.26 (0.06,1.06)	S-1	13.62 (2.23,83.00)	6.98 (1.02,47.64)	16.75 (3.41,82.35)	25.04	26.80	58.61	9.54 (1.15,79.39)	18.44	33.61	22.50 (2.62,193.24)
0.75 (0.29,1.89)	2.86	Gem + Cisplatin	0.51 (0.13,1.97)	1.23 (0.36,4.26)	1.84 (0.05,66.40)	1.97 (0.33,11.76)	4.30 (0.15,125.01)	0.70 (0.14,3.57)	1.35 (0.21,8.54)	2.47 (0.39,15.79)	1.65 (0.31,8.76)
0.59 (0.21,1.61)	2.27	0.79 (0.19,3.33)	Gem + Capecitabine	2.40 (0.59,9.79)	3.59 (0.09,137.08)	3.84 (0.57,25.64)	8.40 (0.27,259.01)	1.37 (0.24,7.85)	2.64 (0.38,18.57)	4.81 (0.68,34.29)	3.22 (0.54,19.25)
0.37 (0.11,1.22)	1.43	0.50 (0.11,2.22)	0.63 (0.13,3.13)	Gem + S-1	1.49 (0.04,54.83)	1.60 (0.26,9.86)	3.50 (0.12,103.34)	0.57 (0.11,3.00)	1.10 (0.17,7.16)	2.01 (0.30,13.23)	1.34 (0.24,7.37)
0.83 (0.04,16.67)	3.23	1.12 (0.05,25.00)	1.41 (0.06,33.33)	2.22 (0.09,50.00)	Gem + 5-FU	1.07 (0.02,49.09)	2.34 (0.02,277.09)	0.38 (0.01,16.26)	0.74 (0.02,34.66)	1.34 (0.03,63.59)	0.90 (0.02,39.03)
0.53 (0.04,7.14)	2.04	0.71 (0.04,11.11)	0.91 (0.06,14.29)	1.43 (0.08,25.00)	0.64 (0.01,33.33)	Gem + Exatecan	2.19 (0.06,81.88)	0.36 (0.04,2.92)	0.69 (0.07,6.68)	1.25 (0.13,12.32)	0.84 (0.10,7.10)
0.85 (0.09,7.69)	3.33	1.15 (0.10,12.50)	1.45 (0.13,16.67)	2.33 (0.18,33.33)	1.02 (0.02,50.00)	1.61 (0.05,50.00)	Gem + Irinotecan	0.16 (0.00,5.65)	0.31 (0.01,12.10)	0.57 (0.01,22.21)	0.38 (0.01,13.57)
0.12 (0.03,0.57)	0.46	0.16 (0.03,0.98)	0.20 (0.03,1.30)	0.32 (0.04,2.27)	0.14 (0.00,4.17)	0.22 (0.11,4.76)	0.14 (0.01,2.13)	Gem + Nab-paclitaxel	1.93 (0.23,16.57)	3.52 (0.41,30.56)	2.36 (0.32,17.45)
0.12 (0.03,0.60)	0.48	0.17 (0.03,1.04)	0.21 (0.03,1.37)	0.33 (0.05,2.44)	0.15 (0.01,4.35)	0.23 (0.01,5.00)	0.15 (0.01,2.22)	1.04 (0.11,10.00)	FOLFIRINOX	1.82 (0.18,18.68)	1.22 (0.14,10.80)
0.21 (0.03,1.33)	0.83	0.29 (0.04,2.27)	0.36 (0.04,2.94)	0.57 (0.06,5.26)	0.26 (0.01,8.33)	0.40 (0.02,10.00)	0.25 (0.01,4.55)	1.79 (0.16,20.00)	1.72 (0.15,20.00)	Gem + Oxaliplatin	0.67 (0.07,5.99)
0.24 (0.04,1.54)	0.94	0.33 (0.04,2.56)	0.42 (0.05,3.45)	0.66 (0.07,5.88)	0.29 (0.01,10.00)	0.46 (0.02,11.11)	0.29 (0.02,5.26)	2.04 (0.18,25.00)	1.96 (0.17,25.00)	1.15 (0.08,16.67)	Gemcitabine + Pemetrexed
Fatigue & Nausea											
Gem	1.56	1.73 (0.60,4.98)	0.97 (0.06,16.28)	0.98 (0.32,2.96)	1.95 (0.75,5.09)	NR	2.91 (1.74,4.87)	1.43 (0.81,2.55)	NR	2.50 (1.35,4.66)	
0.99 (0.30,3.33)	S-1	1.11 (0.28,4.35)	0.62 (0.03,11.88)	0.63 (0.26,1.49)	1.25 (0.34,4.54)	NR	1.87 (0.68,5.10)	0.92 (0.33,2.60)	NR	1.60 (0.55,4.65)	
0.44	(0.24,0.81)	0.45	Gem + Cisplatin	0.56	0.57	1.12	NR	1.68	0.83	NR	1.44 (0.42,4.92)

TABLE IV. (*Continued*)

OR (95% confidence intervals)

(0.24,0.81)		(0.12,1.69)		(0.03,11.38)	(0.12,2.61)	(0.27,4.68)		(0.52,5.44)	(0.25,2.75)	
0.79 (0.44,1.41)	0.79	1.79 (0.78,4.17)	Gem + Capecitabine	1.01 (0.05,20.71)	2.00 (0.10,39.16)	NR	2.99 (0.17,52.33)	1.47 (0.08,26.07)	NR	2.57 (0.14,45.94)
0.40 (0.16,1.00)	0.40	0.89 (0.30,2.70)	0.50 (0.17,1.49)	Gem + S-1	1.99 (0.46,8.60)	NR	2.97 (0.88,10.06)	1.46 (0.42,5.09)	NR	2.56 (0.72,9.09)
0.70 (0.20,2.56)	0.71	1.59 (0.39,6.67)	0.89 (0.22,3.70)	1.79 (0.37,9.09)	Gem + Exatecan	NR	1.50 (0.50,4.44)	0.74 (0.24,2.25)	NR	1.29 (0.41,4.03)
1.72 (0.15,20.00)	1.75	3.85 (0.32,50.00)	2.22 (0.18,25.00)	4.35 (0.33,50.00)	2.44 (0.16,33.33)	Gem + Irinotecan	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	Gem + Nab-paclitaxel	0.49 (0.23,1.06)	NR	0.86 (0.38,1.92)
NR	NR	NR	NR	NR	NR	NR	NR	FOLFIRINOX	NR	1.75 (0.75,4.07)
0.54 (0.23,1.27)	0.54	1.22 (0.43,3.45)	0.68 (0.25,1.92)	1.37 (0.39,4.76)	0.76 (0.16,3.57)	0.31 (0.02,4.00)	NR	NR	Gem + Oxaliplatin	NR
0.88 (0.34,2.33)	0.89	2.00 (0.64,6.25)	1.12 (0.36,3.45)	2.22 (0.58,8.33)	1.25 (0.25,6.25)	0.51 (0.04,7.14)	NR	NR	1.64 (0.45,5.88)	Gem + Pemetrexed

ORs and 95% CI of Anemia, Thrombocytopenia and Fatigue are above the treatments while Neutropenia's, Diarrhea's and Nausea's are below the treatments. Comparisons between treatments of all the outcomes should be read from column to row.
Bolded numbers represent the differences are of significance.
NR, not report; Gem, Gemcitabine; S-1, Tegafur; 5-FU, 5-Fluorouracil; FOLFIRINOX, Oxaliplatin + Irinotecan + Fluorouracil + Leucovorin.