South African National Department of Health
Brief Report – Evaluation of previous negative recommendation
Component: Tertiary

TITLE: Gemcitabine for patient with metastatic pancreatic cancer with the following status:

- Select patients with an ECOG performance status 0 - 2 and a bilirubin level lower than 1.5 × ULN.

Date: September 2023

Date of previous review: 29 October 2012
Sub-group review as adjuvant chemotherapy with gemcitabine and capecitabine in patients who have undergone pancreatic surgery (full resection) potentially curable pancreatic adenocarcinoma: approved 6 December 2018

Review Indicator: Price

TERTIARY AND QUATERNARY EXPERT REVIEW COMMITTEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

The Tertiary and Quaternary Expert Review Committee recommends that gemcitabine monotherapy may be used as a palliative care option for patients with locally advanced unresectable or metastatic pancreatic cancer, and have an ECOG performance status of 0-2 and a bilirubin level lower than 1.5 x ULN.

Rationale: The cost of gemcitabine has decreased since this agent was first reviewed; and since cost was a review indicator, a limited review was conducted in light of more favourable pricing. A rapid search of literature did not result in any more evidence for monotherapy with gemcitabine, and it is acknowledged that the evidence is of very low quality. However it is unlikely that further trials will be conducted in this setting as general standard of care is now FOLFIRINOX (Tertiary review to still be conducted), but gemcitabine is a good alternative in patients who are unable to tolerate more than monotherapy. While the evidence for gemcitabine in this setting is of very low quality, this maybe a beneficial palliative care intervention.

Level of Evidence: *III (very low quality, single, unblinded trial)*
Review Indicator: *New evidence of efficacy and safety in this patient population group.*

(Refer to appendix 1 for the evidence to decision framework)

BACKGROUND

Historically, patients with locally advanced or metastatic pancreatic adenocarcinoma were treated with 5-flourouracil (5-FU) or symptomatically only. Gemcitabine demonstrated activity in this cancer type in early Phase I and II studies[i,ii] prompting the initiation of a Phase III trial. This compared treatment outcomes of 5FU and Gemcitabine monotherapy in the first-line setting for patients with locally advanced pancreatic adenocarcinoma and was published in 1996.[iii] Results showed a modest median survival benefit as well as an appreciable improvement in cancer-related symptoms (termed 'clinical benefit') both of which were statistically significant. Based on the findings of this trial, gemcitabine became the standard of care in this oncological setting.

Two subsequent Phase II trials confirmed that Gemcitabine was well-tolerated in the setting of locally advanced/metastatic pancreatic adenocarcinoma and resulted in improved disease-related symptoms

and modest antitumoural activity. [iv,v] The data supporting the use of Gemcitabine monotherapy as first-line stand-of-care treatment for locally advanced/metastatic pancreatic adenocarcinoma is not robust. Nonetheless, it received FDA-approval in this setting in 1996, followed by approval for use in Europe in 1998.[vi]

In 2012 gemcitabine was reviewed for advanced pancreatic cancer by the Tertiary Expert Review Committee. The agent was not approved for inclusion onto the Essential Medicines List due to the small survival benefit in context with the cost of the agent. A review indicator of price was set (see appendix 3). Subsequently in December 2018 gemcitabine in combination with capecitabine were reviewed and approved for adjuvant chemotherapy in patients with fully resected potentially curable pancreatic adenocarcinoma.

Extract from Tertiary and Quaternary Essential Medicines List

MEDICINE	INDICATION	NEMLC RECOMMENDATION	REVIEW INDICATORS	DATE RATIFIED
Gemcitabine	Pancreatic cancer	**Not Approved**	Reduction in cost of gemcitabine	29 October 2012
Capecitabine plus Gemcitabine	Adjuvant chemotherapy in patients with fully resected potentially curable pancreatic adenocarcinoma.	**Approved** • Only for fully resected patients.	New adjuvant chemotherapy data in patients with R0 or R1 resected adenocarcinoma of the pancreas	6 December 2018

Over the last 10 years the cost of gemcitabine has decreased, prompting re-evaluation of gemcitabine in pancreatic carcinoma outside of fully resected patients (unresectable or metastatic), particularly those with an ECOG performance status 0-2 and a bilirubin level lower than 1.5 x ULN.

The South African National Cancer Registry reported 502 cases of pancreatic cancer diagnosed on histology in 2020. However not all pancreatic cancers are amenable to biopsy, so this figure understates the true incidence of this malignancy. Depending on performance status, patients may or may not be eligible for to receive chemotherapy. FOLFIRINOX (not yet reviewed) has now become standard of care in patients' with a good performance status and able to tolerate chemotherapy, however gemcitabine monotherapy presents as an option for patients not able to tolerate more than monotherapy.

METHODS

The evaluation comprised two parts; a rapid search update of evidence published since the last review (October 2012), and an updated costing. The search was conducted in PubMed and the Cochrane Library in May 2023. The search strategy is outlined in Appendix 2. The following PICO was utilised when assessing eligible studies.

Population	Patients with biopsy/cytology-confirmed pancreatic ductal adenocarcinoma, which is locally advanced and unresectable or metastatic, who are fit enough to receive chemotherapy (ECOG performance status 0, 1 or carefully selected 2).
Intervention	Gemcitabine 1000mg/m2 day 1, 8, 15, 4-weekly X 6 cycles (continue only if tolerated or until disease progression).
Comparators	Best supportive care
Outcomes	Improved overall survival and quality of life.
Studies	Systematic reviews, RCTs

The costing document submitted with the NEMLC report in 2012 was updated with current prices.

RESULTS

For the previous 2012 review, a single investigator unblinded study (Burris et al)[iii] comparing gemcitabine to 5-flourouracil was identified and appeared to be the basis for a change in practice to regard gemcitabine use as standard of care at that time. The trial showed an unexpectedly low survival (2% at one year compared with expected 10 to 12%) in the control group. The study yielded a difference in median survival of 1.2 months in favour of gemcitabine (5.65 vs 4.41 months p 0.0025, survival rate at 1 year 18% versus 2% ARR 16%, NNT 6.3, 95% CI for NNT 3.8 to 16.9.) An investigator-developed composite endpoint called the "clinical benefit response" also yielded a significant difference (24% vs. 5% p = 0.0022.)

The cost of the intervention was taken into account when valuing the 1.2 month difference in median survival contributed by gemcitabine, it at the time it was deemed not cost-effective, and not recommended for inclusion.

Twenty-six systematic reviews and meta-analyses were selected for appraisal. The following key factors emerged:

1. Gemcitabine has never been compared with best supportive care for locally advanced/metastatic pancreatic cancer.
2. The benefit of Gemcitabine is modest in terms of median survival and durable response and significantly improves cancer-associated morbidity (reported as clinical benefit, not QALYs).
3. All trials conducted subsequent to the Burris trial used Gemcitabine monotherapy as the comparator arm i.e., it was considered standard of care.
4. FOLFIRINOX has subsequently emerged as standard of care for the indication under consideration, but only in fit patients.

No new relevant data identified

Costing

Table 1: Costing update of gemcitabine for metastatic pancreatic cancer

Contract (average over contract)	Regimen	Strength/ vial	Price	Dose (1.73m2)	Vials per dose	Cost per dose	Cost per cycle	Cost per 6 cycles
HP04-2012	Gemcitabine 1000mg/m^2 day 1, 8, 15, 4-weekly X 6 cycles	1000mg	R382.52	1730	2	R765.04	R2,295.12	R13,770.72
HP04-2014			R289.71	1730	2	R579.42	R1,738.26	R10,429.56
HP04 -2016			R176.70	1730	2	R353.40	R1,060.20	R6,361.20
RT290- 2018			R155.25	1730	2	R310.50	R931.50	R5,589.00
HP04-2020-01			R235.75	1730	2	R471.50	R1,414.50	R8,487.00
HP04 -2022			R236.90	1730	2	R473.80	R1,421.40	R8,528.40

Table 2: Price adjustments for inflation

Date	Product	Price	Price difference Nominal	Price difference relative	% difference nominal	% difference relative
2023	Gemcitabine 1000 mg injection	R249.02	-R 133.50	-R 362.84	-35%	-94.86%
2012 price adjusted for inflation		R611.86				
2012		R382.52				
2023	Gemcitabine 200 mg	R110.42	R 30.42	-R 28.43	38%	-35.54%
2012 price adjusted for inflation		R138.85				
2012		R80.00				

**inflation: average 4.5% percentage rate each year*[vii] *https://inflationcalc.co.za/*

Table 3: Regimen cost

	Regimen	Price (1000mg)	Dose (1.73m2)	Vials/ dose	Cost per dose	Cost per cycle	Cost per 6 cycles	Difference in price per cycle (nominal)	Difference in price per cycle (relative)
HP04-2012 (average over CONTRACT)	Gemcitabine 1000mg/m2 day 1, 8, 15, 4-weekly X 6 cycles	R382.52	1730	2	R765.04	R2,295.12	R13,770.72	-R4,806.00	-R13,062.24
HP04-2014 (average over CONTRACT)		R289.71	1730	2	R579.42	R1,738.26	R10,429.56		
HP04 -2016 (average over CONTRACT)		R176.70	1730	2	R353.40	R1,060.20	R6,361.20		
RT290- 2018 (average over CONTRACT)		R155.25	1730	2	R310.50	R931.50	R5,589.00		
HP04-2020-01 (average over CONTRACT)		R235.75	1730	2	R471.50	R1,414.50	R8,487.00		
HP04 -2022 (average over CONTRACT)		R249.02	1730	2	R498.04	R1,494.12	R8,964.72		
2012 price converted to 2023 price adjusted for inflation		R611.86	1730	2	R1,223.72	R3,671.16	R22,026.96		

- Gemcitabine single agent is considered to have a low-emetic-risk. Anti-emetic drugs which may be used in this setting include dexamethasone (4 to 8 mg, oral or IV) as a single agent or

a 5-HT3 receptor antagonist. Ondansetron or granisetron are the currently available 5HT3 receptor antagonists available in public sector health.

CONCLUSION

Since the Burris et al trial, no new data was found evaluating gemcitabine monotherapy in patients with biopsy/cytology-confirmed locally advanced and unresectable or metastatic pancreatic ductal adenocarcinoma, and who are fit enough to receive chemotherapy (ECOG performance status 0, 1 or carefully selected 2). Thus, the effect size, as documented in the 2012 review, remains the same. However, since this 2012 review, the price of gemcitabine (particularly the 1000 mg vials) has decreased.

Consequently, the Tertiary/Quaternary ERC recommends that gemcitabine monotherapy be considered as a palliative care option for selected patients with metastatic pancreatic cancer, with an ECOG performance status 0-2 and a bilirubin level lower than 1.5 × ULN.

Appendix 1: Evidence to decision framework

	JUDGEMENT	**EVIDENCE & ADDITIONAL CONSIDERATIONS**
QUALITY OF EVIDENCE	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ Very low ☐	*Single investigator unblinded study (Burris et al)*[viii]
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☒ None ☐	*Burris et al showed a low survival (2% at one year compared with expected 10 to 12%) in the control group. The study yielded a difference in median survival of 1.2 months in favour of gemcitabine (5.65 vs 4.41 months p 0.0025, survival rate at 1 year 18% versus 2% ARR 16%, NNT 6.3, 95% CI for NNT 3.8 to 16.9.)*
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ Very low ☐	
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge ☐ Moderate ☐ Small ☒ None ☐	

<table>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable harms?
Favours intervention: [X] Favours control: [ ] Intervention = Control or Uncertain: [ ]</td><td></td></tr>
<tr><td>FEASABILITY</td><td>Is implementation of this recommendation feasible?
Yes: [ ] No: [ ] Uncertain: [X]</td><td></td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive: [ ] Less intensive: [ ] Uncertain: [X]</td><td><table><tr><td>Cost per cycle</td><td>Cost per 6 cycles</td></tr><tr><td>R1,494.12</td><td>R8,964.72</td></tr></table></td></tr>
<tr><td>VALUES, PREFERENCES, ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor: [X] Major: [ ] Uncertain: [ ]
Is the option acceptable to key stakeholders?
Yes: [X] No: [ ] Uncertain: [ ]</td><td></td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes: [ ] No: [X] Uncertain: [ ]</td><td>None anticipated</td></tr>
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Appendix 2: Search Strategy

Previous (2012 Review) search strategy

("gemcitabine"[Supplementary Concept] OR gemcitabine[Acknowledgments] OR gemcitabine[Figure/Table Caption] OR gemcitabine[Section Title] OR gemcitabine[Body - All Words] OR gemcitabine[Supplementary Concept] OR gemcitabine[Title] OR gemcitabine[Abstract]) AND (("pancreatic neoplasms"[MeSH Terms] OR pancreatic cancer[Acknowledgments] OR pancreatic cancer[Figure/Table Caption] OR pancreatic cancer[Section Title] OR pancreatic cancer[Body - All Words] OR pancreatic cancer[Title] OR pancreatic cancer[Abstract]) OR ("pancreas"[MeSH Terms] OR pancreas[Acknowledgments] OR pancreas[Figure/Table Caption] OR pancreas[Section Title] OR pancreas[Body - All Words] OR pancreas[Title] OR pancreas[Abstract] OR pancreas[Journal])) AND (controlled[All Fields] AND ("clinical trials as topic"[MeSH Terms] OR trial[Acknowledgments] OR trial[Figure/Table Caption] OR trial[Section Title] OR trial[Body - All Words] OR trial[Title] OR trial[Abstract] OR trial[Author]))

PubMed

Search	Query	Search Details	Results
#4	#3 plus date range	(("gemcitabine"[Supplementary Concept] OR ("gemcitabine"[MeSH Terms] OR "gemcitabine"[All Fields] OR "gemcitabin"[All Fields] OR "gemcitabine s"[All Fields]) OR ("gemcitabine"[MeSH Terms] OR "gemcitabine"[All Fields] OR "gemcitabin"[All Fields] OR "gemcitabine s"[All Fields]) OR ("gemcitabine"[MeSH Terms] OR "gemcitabine"[All Fields] OR "gemcitabin"[All Fields] OR "gemcitabine s"[All Fields]) OR ("gemcitabine"[MeSH Terms] OR "gemcitabine"[All Fields] OR "gemcitabin"[All Fields] OR "gemcitabine s"[All Fields]) OR "gemcitabine"[Supplementary Concept] OR "gemcitabine"[Title] OR ("gemcitabine"[MeSH Terms] OR "gemcitabine"[All Fields] OR "gemcitabin"[All Fields] OR "gemcitabine s"[All Fields])) AND ("pancreatic neoplasms"[MeSH Terms] OR ("pancreatic neoplasms"[MeSH Terms] OR ("pancreatic"[All Fields] AND "neoplasms"[All Fields]) OR "pancreatic neoplasms"[All Fields] OR ("pancreatic"[All Fields] AND "cancer"[All Fields]) OR "pancreatic cancer"[All Fields]) OR ("pancreatic neoplasms"[MeSH Terms] OR ("pancreatic"[All Fields] AND "neoplasms"[All Fields]) OR "pancreatic neoplasms"[All Fields] OR ("pancreatic"[All Fields] AND "cancer"[All Fields]) OR "pancreatic cancer"[All Fields]) OR ("pancreatic neoplasms"[MeSH Terms] OR ("pancreatic"[All Fields] AND "neoplasms"[All Fields]) OR "pancreatic neoplasms"[All Fields] OR ("pancreatic"[All Fields] AND "cancer"[All Fields]) OR "pancreatic cancer"[All Fields]) OR ("pancreatic neoplasms"[MeSH Terms] OR ("pancreatic"[All Fields] AND "neoplasms"[All Fields]) OR "pancreatic neoplasms"[All Fields] OR ("pancreatic"[All Fields] AND "cancer"[All Fields]) OR "pancreatic cancer"[All Fields]) OR "pancreatic cancer"[Title] OR ("pancreatic neoplasms"[MeSH Terms] OR ("pancreatic"[All Fields] AND "neoplasms"[All Fields]) OR "pancreatic neoplasms"[All Fields] OR ("pancreatic"[All Fields] AND "cancer"[All Fields]) OR "pancreatic cancer"[All Fields]) OR ("pancreas"[MeSH Terms] OR ("pancrea"[All Fields] OR "pancreas"[MeSH Terms] OR "pancreas"[All Fields]) OR ("pancrea"[All Fields] OR "pancreas"[MeSH Terms] OR "pancreas"[All Fields]) OR ("pancrea"[All Fields] OR "pancreas"[MeSH Terms] OR "pancreas"[All Fields]) OR ("pancrea"[All Fields] OR "pancreas"[MeSH Terms] OR "pancreas"[All Fields]) OR "pancreas"[Title] OR ("pancrea"[All Fields] OR "pancreas"[MeSH Terms] OR "pancreas"[All Fields]) OR ("pancreas"[Journal] OR "pancreas fairfax"[Journal])))) AND ((fha[Filter]) AND (meta-analysis[Filter] OR systematicreview[Filter]) AND (2012/1/1:2023/8/31[pdat]))	114
#3	#1 plus systematic review and meta-analysis	(("gemcitabine"[Supplementary Concept] OR ("gemcitabine"[MeSH Terms] OR "gemcitabine"[All Fields] OR "gemcitabin"[All Fields] OR "gemcitabine s"[All Fields]) OR ("gemcitabine"[MeSH Terms] OR "gemcitabine"[All Fields] OR "gemcitabin"[All Fields] OR "gemcitabine s"[All Fields]) OR ("gemcitabine"[MeSH Terms] OR "gemcitabine"[All Fields] OR "gemcitabin"[All Fields] OR "gemcitabine s"[All Fields]) OR ("gemcitabine"[MeSH Terms] OR "gemcitabine"[All Fields] OR "gemcitabin"[All Fields] OR "gemcitabine s"[All Fields]) OR "gemcitabine"[Supplementary Concept] OR "gemcitabine"[Title] OR ("gemcitabine"[MeSH Terms] OR "gemcitabine"[All Fields] OR "gemcitabin"[All Fields] OR "gemcitabine s"[All Fields])) AND ("pancreatic neoplasms"[MeSH Terms] OR ("pancreatic neoplasms"[MeSH Terms] OR ("pancreatic"[All Fields] AND "neoplasms"[All Fields]) OR "pancreatic neoplasms"[All Fields] OR ("pancreatic"[All Fields] AND "cancer"[All Fields]) OR "pancreatic cancer"[All Fields]) OR ("pancreatic neoplasms"[MeSH Terms] OR ("pancreatic"[All Fields] AND "neoplasms"[All Fields]) OR "pancreatic neoplasms"[All Fields] OR ("pancreatic"[All Fields] AND "cancer"[All Fields]) OR "pancreatic cancer"[All Fields]) OR ("pancreatic neoplasms"[MeSH Terms] OR ("pancreatic"[All Fields] AND "neoplasms"[All Fields]) OR "pancreatic neoplasms"[All Fields] OR ("pancreatic"[All Fields] AND "cancer"[All Fields]) OR "pancreatic cancer"[All Fields]) OR ("pancreatic neoplasms"[MeSH Terms] OR ("pancreatic"[All Fields] AND "neoplasms"[All Fields]) OR "pancreatic neoplasms"[All Fields] OR	

		("pancreatic"[All Fields] AND "cancer"[All Fields]) OR "pancreatic cancer"[All Fields]) OR "pancreatic cancer"[Title] OR ("pancreatic neoplasms"[MeSH Terms] OR ("pancreatic"[All Fields] AND "neoplasms"[All Fields]) OR "pancreatic neoplasms"[All Fields] OR ("pancreatic"[All Fields] AND "cancer"[All Fields]) OR "pancreatic cancer"[All Fields]) OR ("pancreas"[MeSH Terms] OR ("pancrea"[All Fields] OR "pancreas"[MeSH Terms] OR "pancreas"[All Fields]) OR ("pancrea"[All Fields] OR "pancreas"[MeSH Terms] OR "pancreas"[All Fields]) OR ("pancrea"[All Fields] OR "pancreas"[MeSH Terms] OR "pancreas"[All Fields]) OR ("pancrea"[All Fields] OR "pancreas"[MeSH Terms] OR "pancreas"[All Fields]) OR "pancreas"[Title] OR ("pancrea"[All Fields] OR "pancreas"[MeSH Terms] OR "pancreas"[All Fields]) OR ("pancreas"[Journal] OR "pancreas fairfax"[Journal]))))) AND (meta-analysis[Filter] OR systematicreview[Filter])	
#2	#1 plus controlled trial	("gemcitabine"[Supplementary Concept] OR gemcitabine[Acknowledgments] OR gemcitabine[Figure/Table Caption] OR gemcitabine[Section Title] OR gemcitabine[Body - All Words] OR gemcitabine[Supplementary Concept] OR gemcitabine[Title] OR gemcitabine[Abstract]) AND (("pancreatic neoplasms"[MeSH Terms] OR pancreatic cancer[Acknowledgments] OR pancreatic cancer[Figure/Table Caption] OR pancreatic cancer[Section Title] OR pancreatic cancer[Body - All Words] OR pancreatic cancer[Title] OR pancreatic cancer[Abstract]) OR ("pancreas"[MeSH Terms] OR pancreas[Acknowledgments] OR pancreas[Figure/Table Caption] OR pancreas[Section Title] OR pancreas[Body - All Words] OR pancreas[Title] OR pancreas[Abstract] OR pancreas[Journal])) AND (controlled[All Fields] AND ("clinical trials as topic"[MeSH Terms] OR trial[Acknowledgments] OR trial[Figure/Table Caption] OR trial[Section Title] OR trial[Body - All Words] OR trial[Title] OR trial[Abstract] OR trial[Author]))	739
#1	Gemcitabine and pancreatic cancer	("gemcitabine"[Supplementary Concept] OR gemcitabine[Acknowledgments] OR gemcitabine[Figure/Table Caption] OR gemcitabine[Section Title] OR gemcitabine[Body - All Words] OR gemcitabine[Supplementary Concept] OR gemcitabine[Title] OR gemcitabine[Abstract]) AND (("pancreatic neoplasms"[MeSH Terms] OR pancreatic cancer[Acknowledgments] OR pancreatic cancer[Figure/Table Caption] OR pancreatic cancer[Section Title] OR pancreatic cancer[Body - All Words] OR pancreatic cancer[Title] OR pancreatic cancer[Abstract]) OR ("pancreas"[MeSH Terms] OR pancreas[Acknowledgments] OR pancreas[Figure/Table Caption] OR pancreas[Section Title] OR pancreas[Body - All Words] OR pancreas[Title] OR pancreas[Abstract] OR pancreas[Journal]))	8231

Cochrane Library

search	Query	Results
#1	MeSH descriptor: [Gemcitabine] explode all trees	2316
#2	MeSH descriptor: [Pancreatic Neoplasms] explode all trees	2471
#3	MeSH descriptor: [Drug Therapy] explode all trees	
#3	#1 AND #2	678
#4	#1 OR #3 AND #2	2639
#5	#4 PLUS Filter date range 2012 - 2023	2639

- 2637 trials
- 2 Cochrane reviews

Appendix 3: Appendix 4: Previous review (2012)


Gemcitabine_PanCa_Review_4N_29Octo


Gemcitabine_Summary_DN_29October2

References

[i] Casper ES, Green MR, Kelsen DP, Heelan RT, Brown TD, Flombaum CD, Trochanowski B, Tarassoff PG. Phase II trial of gemcitabine (2,2'-difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. Invest New Drugs. 1994;12(1):29-34. doi: 10.1007/BF00873232. PMID: 7960602.

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