health
Department:
Health
REPUBLIC OF SOUTH AFRICA

2030 NDP

Essential Medicines List
Cost-Effectiveness Analysis

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Purpose/Objective (PICO):
-P (patient/population): Adult fully resected pancreatic cancer patients (R0 and R1 surgical resection)
-I (intervention): Gemcitabine plus Capecitabine
-C (comparator): Gemcitabine alone (previous standard of care based on ESPAC-3 data)
-O (outcome): Improved median overall survival (OS) and 5 year survival rates

INTRODUCTION

Pancreatic cancer is an aggressive disease that is almost always fatal and one of the leading causes of cancer mortality worldwide (1). Several chemotherapy regimens have been shown to increase survival in patients with advanced pancreatic cancer (2, 3). Gemcitabine has been the standard treatment since 1997, following a trial which showed that compared to 5-fluorouracil, gemcitabine produced significant improvements in disease-related symptoms and prolonged median survival from 4.4 to 5.7 months (4). Several combination therapies have shown improvements in one-year survival (3, 5). The ESPAC-4 trial compared the adjuvant gemcitabine and capecitabine to gemcitabine monotherapy and concluded that the combination therapy (Gem plus Cap) should be the standard of care for resected pancreatic cancer, as it showed marked improvement in survival (6).

This economic evaluation compares the cost-effectiveness of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in adult patients with fully resected pancreatic cancer.

METHODOLOGY

A cost-effectiveness analysis was conducted to investigate the value for money of amending the EML recommendation of Gemcitabine alone to Gemcitabine plus Capecitabine for the treatment of adult, fully resected, pancreatic cancer patients (R0 and R1 surgical resection).

Perspective

The setting for this study is the South African public health sector and the evaluation takes the perspective of the payer (government). Only direct costs to the government are considered and indirect costs such as loss of productivity and worker absenteeism are not included.

The economic model

A decision tree model was created in Microsoft Excel, to compare adjuvant gemcitabine and capecitabine with gemcitabine monotherapy (Figure 1). In the model, patients could get the combination therapy or

monotherapy, following which they could suffer adverse events and survive or die. The decision tree does not account for metastatic disease progression due to time and resource constraints. This would have required constructing a Markov model and the collection of necessary data such as percentages of patients moving between different Markov states, and resource use for each state. The model was run over a five-year time horizon following treatment.

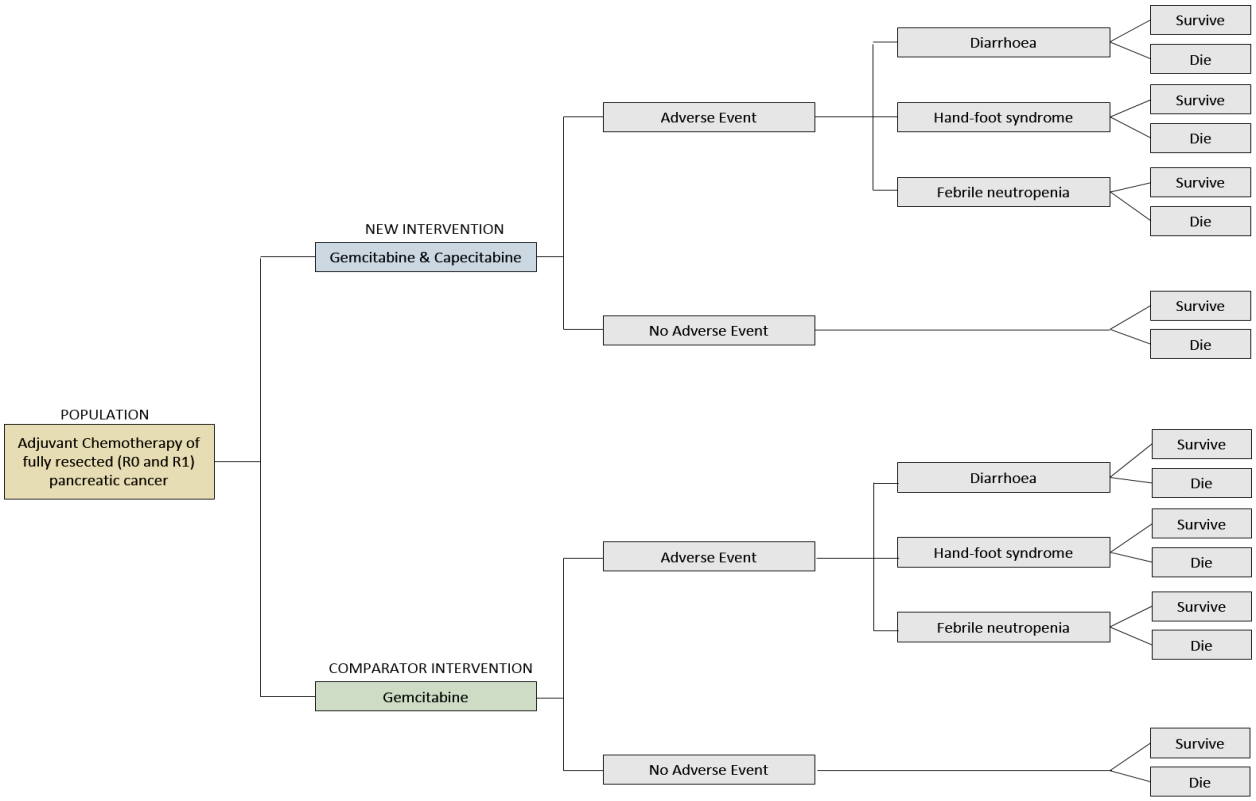

Figure 1. Decision tree model comparing adjuvant gemcitabine and capecitabine with gemcitabine monotherapy

Costs

The costs of treatment were obtained from the National Department of Health Master Procurement Catalogue of February 2018 (Table 1). Only the prices of medications were included since resource use for administering of capecitabine is assumed to be minimal as the drug is in tablet form. Thus, other resource costs such as health worker and facility costs were not included as the number of cycles for chemotherapy administration are the same for both interventions. The full breakdown of cost variables is included in Appendix 1.

Table 1. Treatment costs

Description	Value	Reference
Cost of Treating one patient with the Gemcitabine only regimen	R 7 620,98	1

[1] Drug costs as per National Department of Health Master Procurement Catalogue (NDoH MPC) February 2018, resource use based on expert clinical opinion

Cost of Treating one patient with the Gemcitabine and Capecitabine regimen	R 16 441,27	**Error! Bookmark not defined.**
Cost of treating Diarrhoea	R 2 108,00	2
Cost of treating Hand-foot Syndrome	R 2 108,00	**Error! Bookmark not defined.**
Cost of treating Neutropenia	R 4 528,90	**Error! Bookmark not defined.**
Cost of treating a patient who does not experience an adverse event	R 0,00	NA

Other model parameters

Data to populate the model were obtained from the literature and mainly informed by the ESPAC-4 trial (Table 2). Only data on three adverse events were captured due to availability of data and to keep the decision tree simple. Nausea and vomiting was not included as an adverse event, as antiemetic IV treatment is provided during drug administering of gemcitabine for both interventions. Specific utility data for quality of life for patients who survive was assumed to be 0.8 for both interventions. In the probabilistic sensitivity analysis, an estimate of +/- 15% was used for parameters where confidence intervals and/or standard deviation values could not be found in literature.

Table 2. Model parameters

Description	Value	Reference
Percentages		
Percentage of patients who develop Diarrhoea with the Gemcitabine Only regimen	0,020	3
Percentage of patients who develop Diarrhoea with the Gemcitabine and Capecitabine regimen	0,050	3
Percentage of patients who develop Hand-foot Syndrome with the Gemcitabine Only regimen	0,000	3
Percentage of patients who develop Hand-foot Syndrome with the Gemcitabine and Capecitabine regimen	0,070	3
Percentage of patients who develop Neutropenia with the Gemcitabine Only regimen	0,240	3
Percentage of patients who develop Neutropenia with the Gemcitabine and Capecitabine regimen	0,380	3
Percentage of patients who do not develop an adverse event with Gemcitabine Only regimen	0,740	NA
Percentage of patients who do not develop an adverse event with Gemcitabine and Capecitabine regimen	0,500	NA
Percentage of patients survive after 5 years with the Gemcitabine Only regimen	0,167	4

[2] Assumptions on adverse events – drugs and resource use calculated from NDoH MPC and Uniform Patient Fee Schedule 2018

[3] Percentage of Grade 3/4 Events - Neoptolemas et al. (2017). Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet. 11; 389 (10073): 1011-1024

[4] Five Year Survival and Median Overall Survival - Neoptolemas et al. (2017). Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet. 11; 389 (10073): 1011-1024

Percentage of patients survive after 5 years with the Gemcitabine and Capecitabine regimen	0,228	4
Percentage of patients die after 5 years with the Gemcitabine Only regimen	0,833	NA
Percentage of patients die after 5 years with the Gemcitabine and Capecitabine regimen	0,772	NA
Median Overall Survival Rate of patients with the Gemcitabine Only regimen in months	2,125	4
Median Overall Survival Rate of patients with the Gemcitabine and Capecitabine regimen in months	2,333	4
Utilities		
Quality of Life of a patient with Diarrhoea	0,510	5
Quality of Life of a patient with Hand-Foot Syndrome	0,410	5
Quality of Life of a patient with Neutropenia	0,590	5
Quality of Life of a patient with No Adverse Event	0,800	6
Quality of Life of a patient who survives after the Gemcitabine Only regimen	0,800	6
Quality of Life of a patient who survives after the Gemcitabine and Capecitabine regimen	0,800	6
Quality of life of death	0,000	NA

Other assumptions

Only data on three adverse events were captured due to availability of data and to prevent unnecessary complication of the decision tree. Only Grade ¾ events were captured. Nausea and vomiting was not included as an adverse event as antiemetic IV treatment is provided during drug administering of gemcitabine for both interventions. Hospitalisation was assumed to be 1 day for Grade ¾ diarrhoea and Hand-Foot Syndrome and 5 days for Neutropenia.

RESULTS

Table 3 shows the base case cost-effectiveness analysis. The total cost of Gemcitabine was estimated to be R8,295, and the cost of Gemcitabine plus Capecitabine was R18,415.21. The associated QALYs were 0.524 for Gemcitabine and 0.674 for the combination therapy. The incremental cost-effectiveness ratio (ICER) was estimated at R64,547.19.

Table 3. Base case cost-effectiveness analysis

	TOTAL COST	TOTAL QALYS	Incremental Costs	Incremental QALYs	ICER (Cost per QALY)
Gemcitabine	R 8 750,08	0,524	0	0	0
Gemcitabine + Capecitabine	R 18 415,21	0,674	R 9 665,13	0,150	R 64 547,19

Figure 2 presents the comparison of the ICERs for gemcitabine and gemcitabine plus capecitabine on the cost-effectiveness plane. The combination therapy is shown to be positive and dominates the monotherapy and is thus potentially cost-effective.

[5] Tufts CEA Registry - Grade3/4 Diarrhoea (Tam, V C, Chan, K K W, Cheung, M C, Hassan, S, Ko, Y J, Kumar, K, Mittmann, N, Cost-effectiveness of systemic therapies for metastatic pancreatic cancer., Curr Oncol,; 20(2):e90-e106)

[6] Assumed to be the same as stable pancreatic cancer : Tufts CEA Registry - Stable Pancreatic Cancer (Zhou, Jing, Chen, Hongdou, Li, Qiu, Tang, Ruilei, Wen, Feng, Wu, Yifan, Zhang, Jian, Zhang, Pengfei, Zhao, Rongce, Cost-effectiveness analysis of treatments for metastatic pancreatic cancer based on PRODIGE and MPACT trials., Tumori,2016 Jun 02; 2016(3):0)

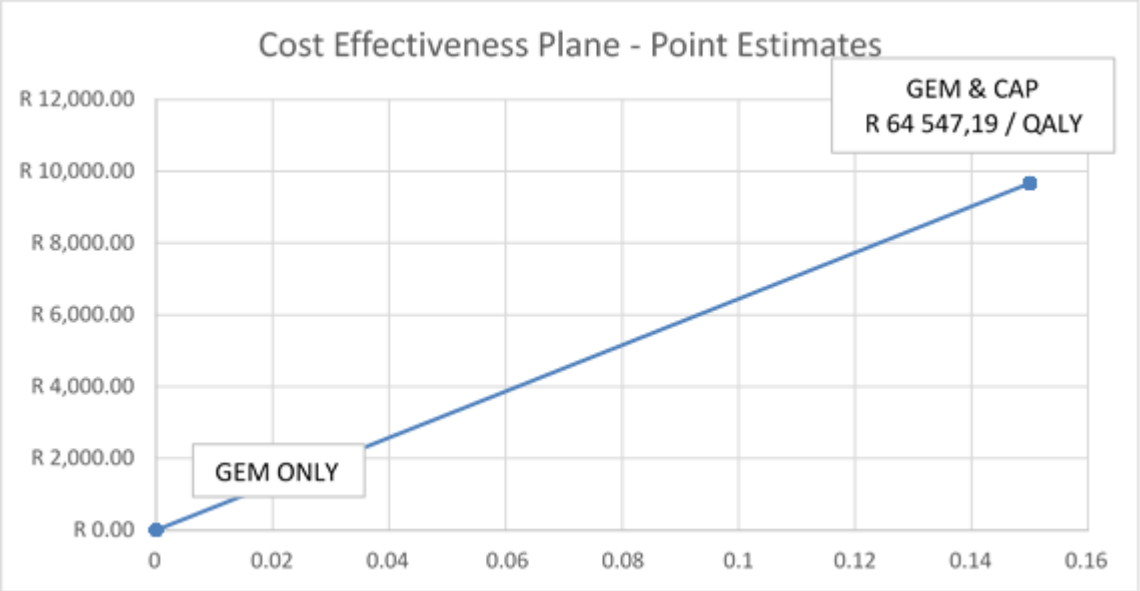

Figure 2. Comparison of incremental cost-effectiveness ratios for gemcitabine and gemcitabine plus capecitabine

Sensitivity analysis

One-way sensitivity analyses were conducted on uncertain parameters to test the impact of changing assumptions on the ICER (Figure 3). The most variation was observed when the annual life expectancy and medication costs were varied (+/-15%) for the combination therapy.

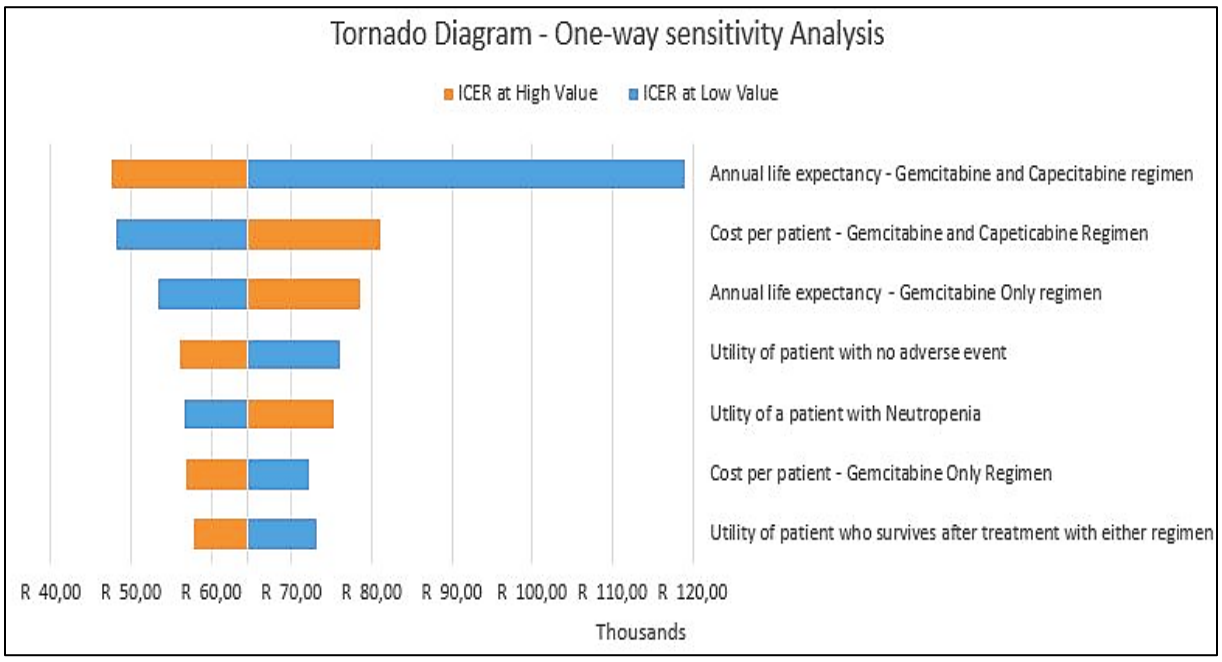

Figure 3. Tornado diagram for one-way sensitivity analysis

Results of the multi-way sensitivity analyses are given in Appendix 2 shows the results of the one-way and two-way sensitivity analyses.

A probabilistic sensitivity analysis was conducted to account for parameter uncertainty, where all model parameters were varied at the same time, using statistical distributions. Distributions were based on confidence intervals in the ESPAC-4 trial. A microsimulation was undertaken with 10,000 runs. The results presented in Figure 4 show that the new intervention (combination therapy) is likely to be the cost-effective option at least 90% of the time.

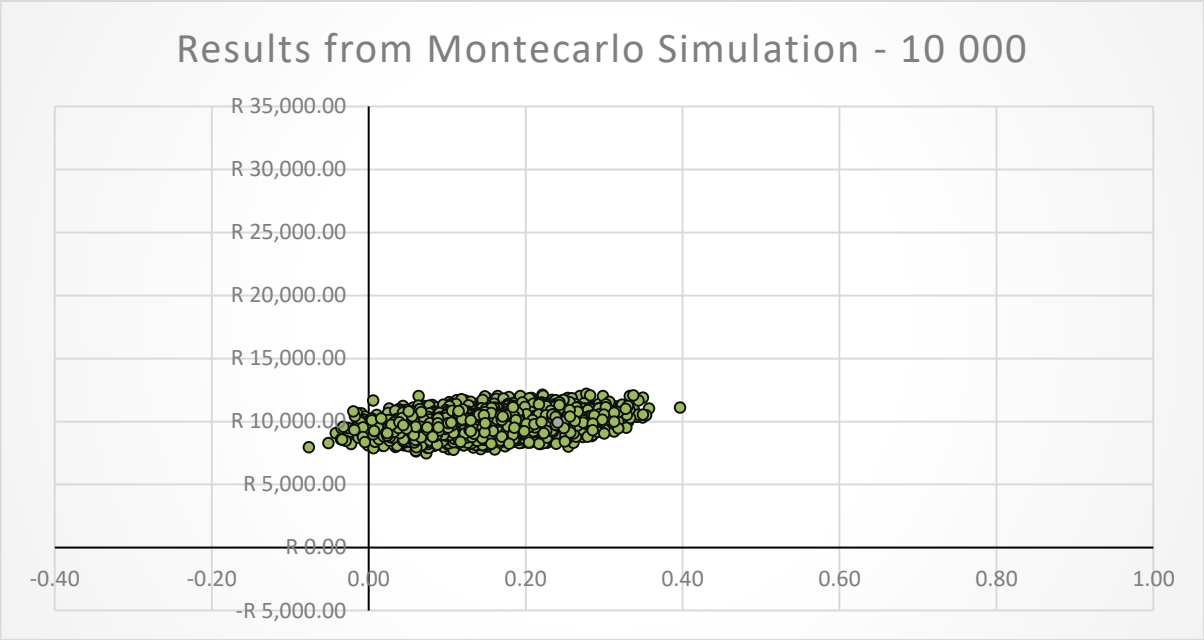

Figure 4. Scatter plot showing results of the Monte Carlo Simulation

Aiding decisions using a cost-effectiveness threshold

The results show that the new intervention, Gemcitabine plus Capecitabine is more beneficial however more costly than the comparator intervention, Gemcitabine Only at an ICER of R64 547,19 per QALY gained. Thus, the decision to fund the intervention rests with the willingness to pay or ability to pay of the payer. As there is no standard cost-effectiveness threshold value for South Africa, a cost-effective acceptability analysis was conducted using three different threshold values. The first threshold used was the World Health Organization threshold of 1 x GDP[7], a demand-side threshold, which converted to R95 538,00 per QALY[Error! Bookmark not defined.,Error! Bookmark not defined.]. The second was a supply-side threshold sourced from a paper by Woods *et al.* 2016, with a lower value of R16 265,00 and upper value of R65 252,00[8]. Calculations with the point estimate resulted in an ICER of R64 547,19 per QALY. If the above thresholds are considered, the new intervention would be not cost-effective at the lower Woods et al., value, borderline cost-effective at the upper value and deemed highly cost-effective at the WHO threshold.

[7] Many studies have revealed that the 3 x GDP WHO threshold is unsuitable for LMICS, thus the lowest threshold 1 x GDP is explored here instead.

[8] Woods B, Revill P, Sculpher M, Claxton K. Country-Level Cost-Effectiveness Thresholds: Initial Estimates and the Need for Further Research. Value Health. 2016 Dec; 19(8): 929–935. doi: 10.1016/j.jval.2016.02.017

Another threshold value that could be applied is that used in the private sector in South Africa of R200,000 per QALY gained.[9] At this value, the new intervention could be considered to be highly cost-effective.

Figure 5 shows the cost-effectiveness acceptability curve. This illustrates the probability of an intervention being cost-effective at a given threshold value. The new intervention will be the cost-effective option at any threshold value above R66,000 per QALY gained. Below this value, gemcitabine only would be the intervention of choice.

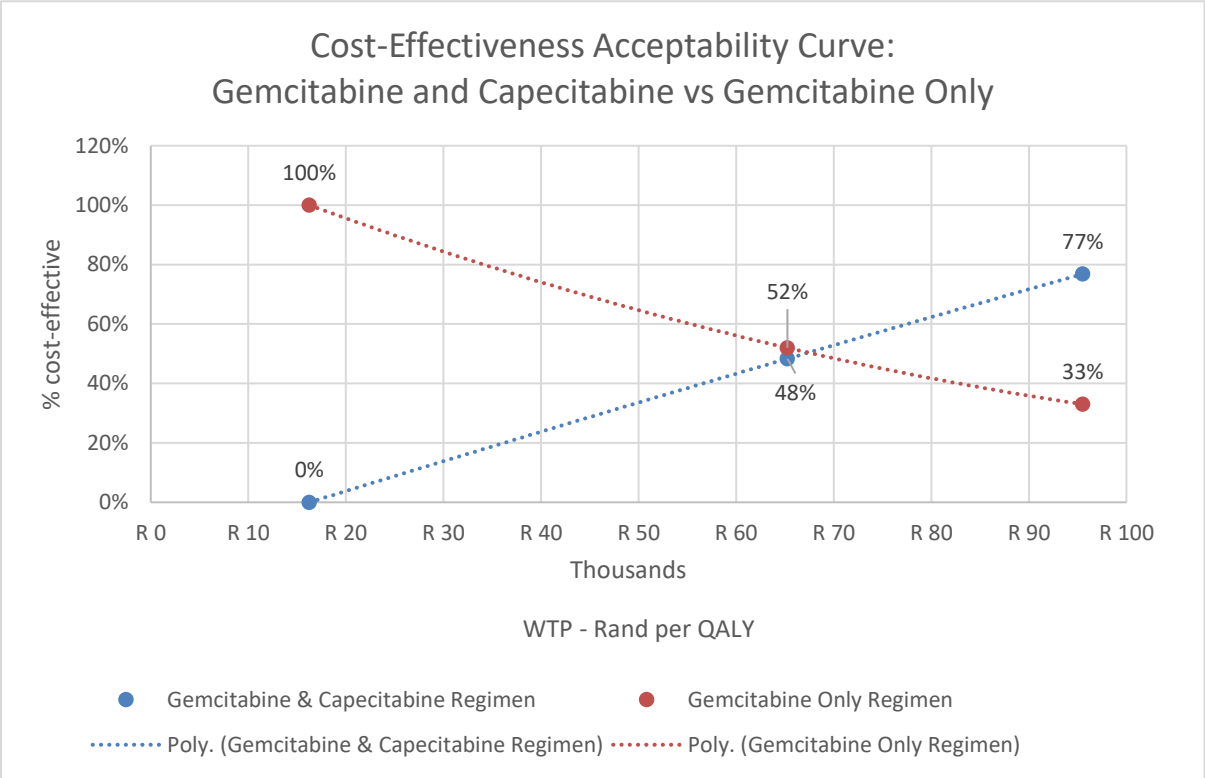

Figure 5. Cost-Effectiveness Acceptability Curve

In Table 4, we show how the information in figure 6 applies to the various cost-effectiveness thresholds used. When applying the Woods et al. threshold at its lowest value (R16 265,00 per QALY) the new intervention (Gemcitabine plus Capecitabine) was found to be not cost-effectiveness in any of the 10 000 runs. However, at the higher Woods et al., value (R65 252,00) the new intervention was cost-effective for 48% of the 10 000 runs. The new intervention was cost-effective 77% of the 10 000 runs when applying the WHO threshold.

Table 4. Cost-effectiveness of new and comparator interventions at different cost-effectiveness thresholds

[9] Discovery Health. Personal Communication

	WTP - Rand per QALY	Gemcitabine & Capecitabine Regimen	Gemcitabine Only Regimen
Woods et al Lower	R 16 265,00	0%	100%
Woods et al Upper	R 65 252,00	48%	52%
1 x GDP	R 95 538,00	77%	33%

CONCLUSION

The new intervention (Gemcitabine and Capecitabine) is likely to be cost-effective. We have attempted to provide guidance using cost-effectiveness thresholds, which aid in decision making when adopting cost-effective options. This is done for illustrative purposes, to show how decisions can be made once a threshold value is adopted.

References

1. Lucas AL, Malvezzi M, Carioli G, Negri E, La Vecchia C, Boffetta P, et al. Global Trends in Pancreatic Cancer Mortality From 1980 Through 2013 and Predictions for 2017. Clin Gastroenterol Hepatol Oct;14(10):1452-62 e4.
2. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med May 12;364(19):1817-25.
3. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med Oct 31;369(18):1691-703.
4. Burris HA, 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol1997 Jun;15(6):2403-13.
5. Cunningham D, Chau I, Stocken DD, Valle JW, Smith D, Steward W, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol2009 Nov 20;27(33):5513-8.
6. Neoptolemos JP, Palmer DH, Ghaneh P, Psarelli EE, Valle JW, Halloran CM, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet Mar 11;389(10073):1011-24.

Appendices

Appendix 1. Breakdown of Cost Variables

Drug Administration Costs

Intervention	Drug Costs	Consumables	Total
Gemcitabine	7 137.36	483.62	R7 620.98
Gemcitabine + Capecitabine	15 957.64	483.62	R16 441.26

Breakdown of drug Costs[10]

Intervention	Drug	Cost per treatment	No. of treatments per cycle	Cost per cycle	No. of Cycles	Cost per regimen
Gemcitabine	Gemcitabine (IV)	389.52	3	1 168.56	6	7 011.36
	Ondansetron (IV)	7.00	3	21.00	6	126.00
	TOTAL					7 137.36
Gemcitabine + Capecitabine	Gemcitabine (IV)	389.52	3	1 168.56	6	7 011.36
	Ondansetron (IV)	7.00	3	21.00	6	126.00
	Capecitabine (Oral)	70.00	21	1470.05	6	8820.28
	TOTAL					15 957.64

Consumable Costs[11]

Intervention	Category	Cost per treatment	No. of treatments per cycle	Cost per cycle	No. of Cycles	Cost per regimen
Gemcitabine	Pharmacy Prep	4.23	3	12.70	6	76.19
	Treatment Room	18.40	3	55.21	6	331.23
	TOTAL					483.62
Gemcitabine + Capecitabine	Pharmacy Prep	4.23	3	12.70	6	76.19
	Treatment Room	18.40	3	55.21	6	331.23
	TOTAL					483.62

[10] Costs based on National Department of Health Master Procurement Catalogue February 2018, resource use based on expert clinical opinion

[11] Tufts CEA Registry - Grade3/4 Diarrhoea (Tam, V C, Chan, K K W, Cheung, M C, Hassan, S, Ko, Y J, Kumar, K, Mittmann, N, Cost-effectiveness of systemic therapies for metastatic pancreatic cancer., Curr Oncol,; 20(2):e90-e106)

Breakdown of Adverse Event [12]

COSTS for Adverse Events	Once-off, cyclic or annual treatment	Treatment	Cost per treatment	Cost for Healthcare Worker	Cost for facility	Days of treatment	Number of cycles	Cost per treatment	Total Cost	Reference
Diarrhoea Grade 3/4	Once off	Hospitalisation	Included	R 276,00	R 1 832,00	1	Na	R 6 324,00	**R 6 324,00**	13
Hand-Foot Syndrome Grade 3/4	Once off	Hospitalisation	Included	R 276,00	R 1 832,00	1	Na	R 2 108,00	**R 2 108,00**	13
Neutropenia Grade 3/4	Once-off	Filgrastrim	Included	R 241,00	R 103,00	5	NA	R 1 720,00	R 1 720,00	14
	Cyclic	Filgrastrim	R 468,15	NA	NA	1	6	R 468,15	R 2 808,90	13
									R 4 528,90	

[12] Assumptions on adverse events – drugs and resource use
[13] Uniform Patient Fee Schedule (UPFS) 2018 - inpatient general ward, specialist
[14] 6 cycles (treatment and then prophylaxis) - MPC 2018 NDOH website + UPFS 2018 medical specialist consult

Appendix 2. One-way and Two-way Sensitivity Analyses

A multiple univariate sensitivity analysis was conducted in excel. Lower and upper values for parameters were based on confidence intervals in the ESPAC-4 trial article by Neoptolemos et al., 2017. Where no confidence intervals were available +/- 15% was applied.

Results of multiple univariate analysis

Parameter	*Lower Value*	LV ICER	Difference	*Point Estimate*	ICER	*Upper Value*	UV ICER	Difference
cGEM_Treatment	R 6 477,83	R 72 181,54	-R 7 634,35	R 7 620,98	R 64 547,19	R 8 764,13	R 56 912,85	R 7 634,34
cGEMCAP_Treatment	R 13 975,08	R 48 077,09	R 16 470,10	R 16 441,27	R 64 547,19	R 18 907,46	R 81 017,29	-R 16 470,10
cDiarrhoea	R 1 791,80	R 64 483,84	R 63,35	R 2 108,00	R 64 547,19	R 2 424,20	R 64 610,54	-R 63,35
cHandFootSyndrome	R 1 791,80	R 64 399,37	R 147,82	R 2 108,00	R 64 547,19	R 2 424,20	R 64 695,01	-R 147,82
cNeutropenia	R 3 849,57	R 63 912,04	R 635,15	R 4 528,90	R 64 547,19	R 5 208,24	R 65 182,35	-R 635,16
pGEM_Diarrhoea	0,023	R 64 663,93	-R 116,74	0,020	R 64 547,19	0,023	R 64 430,73	R 116,46
pGEMCAP_Diarrhoea	0,058	R 64 014,72	R 532,47	0,050	R 64 547,19	0,0575	R 65 164,64	-R 617,45
pGEM_HandFootSyndrome	0,060	R 64 547,19	R 0,00	0,000	R 64 547,19	0,06	R 61 071,74	R 3 475,45
pGEMCAP_HandFootSyndrome	0,081	R 63 578,44	R 968,75	0,070	R 64 547,19	0,0805	R 65 642,38	-R 1 095,19
pGEM_Neutropenia	0,276	R 65 913,41	-R 1 366,22	0,240	R 64 547,19	0,276	R 63 192,42	R 1 354,77
pGEMCAP_Neutropenia	0,437	R 60 408,66	R 4 138,53	0,380	R 64 547,19	0,437	R 69 030,33	-R 4 483,14
pGEM_LE_Annual	2,325	R 53 454,53	R 11 092,66	2,125	R 64 547,19	2,325	R 78 536,52	-R 13 989,33
pGEMCAP_LE_Annual	2,625	R 118 916,49	-R 54 369,30	2,333	R 64 547,19	2,625	R 47 626,16	R 16 921,03
uDiarrhoea	0,434	R 65 045,66	-R 498,47	0,510	R 64 547,19	0,5865	R 64 053,12	R 494,07
uHandFootSyndrome	0,349	R 65 488,60	-R 941,41	0,410	R 64 547,19	0,4715	R 63 625,14	R 922,05
uNeutropenia	0,502	R 56 577,86	R 7 969,33	0,590	R 64 547,19	0,6785	R 75 199,31	-R 10 652,12
uNoAdverseEvent	0,680	R 76 020,24	-R 11 473,05	0,800	R 64 547,19	0,92	R 56 083,08	R 8 464,11
uGEM_Survive & UGEMCAP_Survive	0,680	R 73 174,16	-R 8 626,97	0,800	R 64 547,19	0,92	R 57 739,87	R 6 807,32

The parameters for treatment costs and life expectancy were the most sensitive to adjustment. A two-way sensitivity analysis was then carried out on the parameters for treatment cost and life expectancy for the new intervention (Gemcitabine and Capecitabine)