health
Department:
Health
REPUBLIC OF SOUTH AFRICA

Essential Medicines List
Medication Review Summary

MEDICINE MOTIVATION:

1. Executive Summary

Date: March 2018
Medicine(s) (INN): Capecitabine plus gemcitabine (adjuvant therapy)
Medicine (ATC): L01BC06 plus L01BC05
Indication(s) (ICD10 code(s)): C77.2 Adjuvant chemotherapy of fully resected potentially curable pancreatic adenocarcinoma (only fully resected patients)
Patient population: Estimated at approximately 81 patients per year
Incidence/prevalence of condition: Although the most recent data from the pathology-based National Cancer Registry (2013) www.ncr.ac.za[1] reported newly diagnosed pancreatic cancer in 328 patients (176 males, ASR per 100,000 = 1.04, Lifetime Risk (under age of 74 years) = 1 in 726; and 152 females, ASR per 100,000 = 0.63, Lifetime Risk = 1 in 1314), it probably represents under-reporting due to lack of tissue diagnoses in many patients.
Level of Care: Tertiary
Prescriber Level: Specialist
Current standard(s) of Care: Gemcitabine
Efficacy estimates: (preferably NNT): 8[2] (5 year survival)
Odds Ratio: 1.77
Absolute benefit: 12.5%
(Estimated 5 year survival was 16·3% (10·2–23·7) for patients randomised to gemcitabine, and 28·8% (22·9–35·2) for patients randomised to gemcitabine plus capecitabine.)
Motivator/reviewer name(s): Prof Paul Ruff
PTC affiliation: Gauteng

2. Name of author(s)/motivator(s): Prof Paul Ruff

3. Author affiliation and conflict of interest details:

Various Pharma Companies involved in Oncology Research.	Clinical Trials and Honorarium - all funds to University of Witwatersrand Health Consortium.

4. Disease process

Advanced/metastatic pancreatic adenocarcinoma has a very poor outlook with intravenous gemcitabine being the international standard of care since late 1990s following a 1:1 randomized study in 126 patients receiving gemcitabine 1g/m2 weekly x 7 weeks with 1 weeks rest followed by weekly x 3 every 4 weeks compared to 5FU 600mg/m2 weekly. Median overall survival (OS) was 5.65 months versus 4.41 months (p=0.0025) with a 12 month survival rate of 18% versus 2% (Burris et al, *J Clin Oncol* 1997).[3] As a result of limited survival benefit, gemcitabine has not been put approved for EML in advanced/metastatic pancreas cancer.

Recent advances in advanced/metastatic pancreatic cancer:

1. A recent French study randomized FOLFIRINOX (oxaliplatin 85mg/m2 + irinotecan 180mg/m2 + leucovorin 400mg/m2 + 5-fluorouracil 400mg/m2 bolus followed by 2400 mg/m2 as a 46-hour continuous infusion, every 2 weeks) or gemcitabine 1g/m2 weekly for 7 of 8 weeks, and then weekly for 3 of 4 weeks. Six months of chemotherapy were recommended in both groups in patients who had a response. Median overall survival was 11.1 months in the FOLFIRINOX group compared with 6.8 months in the gemcitabine group (HR 0.57; 95% CI, 0.45-0.73; p<0.001). Median progression-free survival was 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group (HR 0.47; 95% CI, 0.37-0.59; p<0.001). The objective response rate was 31.6% in the FOLFIRINOX group vs. 9.4% in the gemcitabine group (p<0.001) (Conroy et al, *N Engl J Med* 2011).[4]

2. A recent multinational study randomly assigned 861 patients to nab-paclitaxel 125mg/m2 x 3 weeks every 4 weeks plus gemcitabine 1g/m2 weekly x 3 every 4 weeks or gemcitabine alone . The median overall survival was 8.5 months in the nab-paclitaxel-gemcitabine group as compared with 6.7 months in the gemcitabine group (HR 0.72; 95% CI, 0.62-0.83; p<0.001). The 12 month and 24 month survival rates were 35% in the nab-paclitaxel-gemcitabine group versus 22% in the gemcitabine group at 1 year and 9% versus 4% at 2 years, respectively. The median progression-free survival was 5.5 months in the nab-paclitaxel-gemcitabine group compared with 3.7 months in the gemcitabine group (HR 0.69; 95% CI, 0.58-0.82; p<0.001) and the objective response rate by independent review was 23% versus 7% (p<0.001) (von Hoff et al, *N Engl J Med* 2013).[5]

Resected pancreatic cancer: The only potential for long-term survival however is complete surgical resection although the long term outlook remains poor, with 5-year survival rates of less than 10%, making the need for effective adjuvant therapy essential.

Indications: Adjuvant chemotherapy of fully resected potentially curable pancreatic adenocarcinoma.

5. Medicine(s)

- **Gemcitabine** (2', 2'-difluoro 2'deoxycytidine) is an intravenous cytidine nucleoside analogue, which prevents DNA chain elongation by being incorporated into DNA as a false nucleotide. It has been used to treat a number of cancers including breast, ovarian, pancreatic, bladder and non-small cell lung cancer, and is on EML for advanced non-small cell lung in combination with cisplatin or carboplatin.

- **Capecitabine** is an oral fluoropyrimidine prodrug of 5-fluorouracil (5FU) which is converted by tumour specific thymidine phosphatase to 5FdUMP (5-fluorodeoxyuridine monophosphate) which competitively inhibits thymidylate synthase (TS) and thereby DNA synthesis during the S-phase of the cell cycle. It is used to treat a number of cancers including breast, pancreatic, gastric and colorectal cancer and is on EML for advanced gastric and colorectal cancer in combination with oxaliplatin.

6. Purpose/Objective i.e. PICO question:

-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

Evidence Synthesis:

Author, date	*Type of study*	n	Primary end-point	Effect sizes
ESPAC-1 *Neoptolemos et.al.* ***2001***[6]	*Simple pragmatic trial, 2 by 2 factorial design*	**541** • 285 in the two-by-two factorial design (70 chemo-radiotherapy, 74 chemotherapy, 72 both, 69 observation); • 68 patients were randomly assigned chemo-radiotherapy or no chemo-radiotherapy and • 188 chemotherapy or no chemotherapy.	OS	Overall results showed no benefit for adjuvant chemo-radiotherapy (median OS 15.5 months in 175 patients with chemo-radiotherapy *vs* 16.1 months in 178 patients without; HR 1.18 [95% CI 0.90–1.55], p=0·24). There was evidence of a survival benefit for adjuvant chemotherapy (median OS 19.7 months in 238 patients with chemotherapy *vs* 14.0 months in 235 patients without; HR 0.66 [0.52–0.83], p=0.0005).
ESPAC-3 *Neoptolemos et.al.* ***2010***[7]	*Phase3 Open-label Multicentre Randomised Clinical Trial*	**1088** • Gemcitabine – 537 • Fluorouracil plus folinic acid - 551	OS and 5 year survival rates	Median OS: 5-Fluorouracil plus folinic acid was 23.0 months (95% CI 21.1 - 25) compared with 23.6 months (21.4 – 26.4) with gemcitabine (HR 0·94 [95% CI 0·81–1.08]. 5 year survival was 17·5% (14·0–21·2) for patients with gemcitabine and 15·9% (12·7–19·4) for patients with 5-fluorouracil plus folinic acid.
ESPAC-4 *Neoptolemos et.al.* ***2017***[2]	*Phase3 Open-label Multicentre Randomised Clinical Trial*	**730** • Gemcitabine alone – 366 • Gemcitabine plus capecitabine - 364	OS and 5 year survival rates	Median OS: Gemcitabine plus capecitabine 28·0 months (95% CI 23·5–31·5) compared to 25·5 months (22·7–27·9) with gemcitabine (HR 0·82 [95% CI 0·68–0·98], p=0·032). 5 year survival rate was 28.8% (95% CI 22·9–35·2) versus 16.3% (95% CI 10·2–23·7) (OR 1.77).

Evidence for adjuvant chemotherapy in fully resected pancreatic cancer (details):

1. The **European Study for Pancreatic Adenocarcinoma (ESPAC)-1** randomly assigned patients post resection to adjuvant chemo-radiotherapy (20 Gy in 10 daily fractions over 2 weeks with 5FU 500 mg/m2 intravenously on days 1-3, repeated after 2 weeks) or chemotherapy (intravenous 5FU 425 mg/m2 and folinic acid 20 mg/m2 daily for 5 days, monthly for 6 months). 541 patients were randomised into a two-by-two factorial design (observation, chemo-radiotherapy alone, chemotherapy alone, or both) or into one of the main treatment comparisons (chemo-radiotherapy versus no chemo-radiotherapy (68) or chemotherapy versus no chemotherapy (188)). The primary endpoint was OS. Results showed no benefit for adjuvant chemo-radiotherapy (median OS 15.5 months in 175 patients with chemo-radiotherapy vs 16.1 months in 178 patients without; HR 1.18 [95% CI 0.90-1.55], p=0.24). There was however an OS benefit for adjuvant chemotherapy (median survival 19.7 months in 238 patients with chemotherapy vs 14.0 months in 235 patients without; HR 0.66 [0.52-0.83], p=0.0005). (Neoptolemos et al, *Lancet* 2001).

2. The **European Study for Pancreatic Adenocarcinoma (ESPAC)-3** randomized 1088 patients 1:1. Patients received either 5FU 425mg/m2 plus folinic acid 20mg/m2 for 1-5 days every 28 days or gemcitabine 1g/m2 once a week for 3 of every 4 weeks) for 6 months. Primary objective was overall survival with secondary end-points toxicity, progression-free survival, and quality of life. Final analysis was carried out on an ITT basis after a median of 34.2 (interquartile range, 27.1-43.4) months' follow-up after 753 deaths (69%). Median OS was 23.0 months (95% CI, 21.1-25.0) for 5FU plus folinic acid and 23.6 months (95% CI, 21.4-26.4) for gemcitabine (HR 0.94 [95% CI, 0.81-1.08]). 77 patients (14%) receiving 5FU plus folinic acid had SAEs compared to 40 patients (7.5%) with gemcitabine. 5 year survival was 17·5% (14·0–21·2) for patients on gemcitabine and 15·9% (12·7–19·4) for patients on 5-fluorouracil plus folinic acid. (Neoptolemos et al. *JAMA* 2010).

   The ESPAC-3 trial therefore showed that adjuvant gemcitabine to be the standard of care based on similar survival to and less toxicity than adjuvant 5-fluorouracil/folinic acid in patients with resected pancreatic cancer.

3. In the **European Study for Pancreatic Adenocarcinoma (ESPAC)-4**, 366 patients were randomly assigned to receive gemcitabine and 364 to gemcitabine plus capecitabine, within 12 weeks of an R0 or R1 resection. The median OS for gemcitabine plus capecitabine was 28·0 months (95% CI 23·5-31·5) compared with 25·5 months (22·7-27·9) for gemcitabine alone (HR 0·82 [95% CI 0·68-0·98], p=0·032).

   The estimated 5 year survival was 16·3% for patients randomised to gemcitabine, and 28·8% for patients randomised to gemcitabine plus capecitabine (OR 1.77) representing a 12.5% absolute 5 year survival improvement with a NNT of 8.

   608 grade 3-4 adverse events were reported by 226 of 359 patients in the gemcitabine plus capecitabine group compared with 481 grade 3-4 adverse events in 196 of 366 patients in the gemcitabine group (Neoptolemos et al, Proc ASCO 2017 and *Lancet* 2017.

Clinical efficacy:
Adjuvant gemcitabine plus capecitabine in fully resected adenocarcinoma of the pancreas increases the median OS to 28 months from 25·5 months with gemcitabine alone (HR 0·82 [95% CI 0·68-0·98], p=0·032) with an absolute 5 year survival rate improvement of 12.5% (from 16.3% to 28.8%) and a **NNT of 8**.

Safety concerns:
Gemcitabine: Myelosuppression, mild emesis.
Capecitabine: HFS, mucositis, diarrhoea

Quality of evidence:

Trial	Method of randomisation	Method of concealment of allocation	Blinding of intervention/ outcome assessors	Were treatment and control groups balanced	Intention to treat (ITT) analysis
ESPAC-4 *Neoptolemos et.al.* ***2017***[2]	1:1 (Stratification by European country)	Computer generated	Open-label	Yes	Yes

*Funded by Cancer Research UK that had no role in study design, data collection/analysis/interpretation, or writing of report.

Cost:

Cost of a 4 week course of therapy with capecitabine plus gemcitabine	
Capecitabine	R16,366.16
Gemcitabine	R6,617.61
TOTAL	**R22,983.77**

**Prices used: RT290-2018, valid from 1 July 2018*

Budget impact

The number of patients who undergo R0 or R1 pancreas adenocarcinoma resection per year in South Africa was assessed. It was estimated, based on actual resection data provided by each major center that about 80 patients would be eligible for this therapy each year. The budget impact would thus be about R2 million.

	Resected pancreas cancer patients per year	Budget impact with gemcitabine plus capecitabine
KZN	17	R390,724.08
Gauteng	30	R689,513.08
WC	32	R735,480.61
FS	2	R45,967.54
TOTAL	81	**R1,861,685.31**

The estimated cost per Whipple Procedure in the public sector is estimated at a mean of R86 220.65. (See annexure – Pancreatectomy analysis and modelling). In the public sector, approximately 136 Whipple procedures at a cost are performed per year, of which 85 would be eligible for chemotherapy. The total modelled costs for 136 cases is R11, 3 million [R5.9 million – R20million] while true costs for 85 cases are estimated to be R7, 1million [R3, 6 million – R12, 6 million].

With the above investment in surgical intervention, the addition of adjuvant capecitabine plus gemcitabine to optimize this intervention outcomes should be considered.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [X] Not confident [ ] Uncertain [ ]	
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	

THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [ ] No [X] List the members of the group. List specific exclusion from the group:	Rationale for therapeutic alternatives included: References: Rationale for exclusion from the group: References:
VALUES & PREFERENCES / ACCEPTABILITY	**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 [ ]	
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [ ] Uncertain [ ]	
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [ ] Uncertain [ ]	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes [ ] No [ ] Uncertain [ ]	

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	[ ]	[ ]	[ ]	[ ]	[X]

Level of Evidence: II Low quality systematic review, small RCTs

Recommendation:

Combination gemcitabine (once weekly for 3 of 4 weeks) plus capecitabine x 21 days, (both for 6 cycles) is recommended for inclusion of the Essential Medicines List for the adjuvant treatment of fully resected adenocarcinoma of the pancreas based on a 12.5% absolute 5 year survival rate representing a NNT of 8.

Review indicators:

- New adjuvant chemotherapy data in patients with R0 or R1 resected adenocarcinoma of the pancreas.

References:

[1] National Cancer Registry, 2013. www.ncr.ac.za

[2] Neoptolemus JP, Palmer DH, Ghaneh P et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomized phase 3 trial. Lancet 2017; 389(10073): 1011-1024. doi: 10.1016/S0140-6736(16)32409-6.

[3] Burris HA, Moore MJ, Andersen J 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 Oncol 1997; 15(6): 2403-2413.

[4] Conroy T, Desseigne F, Ychou M et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011; 364(19): 1817-25. doi: 10.1056/NEJMoa1011923

[5] Von Hoff, D, Ervin T, Arena F et al. Increased survival in pancreatic cancer with nab-Paclitaxel plus gemcitabine. N Engl J Med 2013; 369: 1691-703. doi: 10.1056/NEJMoa1304369

6 Neoptolemos JP, Dunn JA, Stocken DD et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer. A randomized controlled trial. Lancet 2001; 358(6293): 1576-1585.

[7] Neoptolemos JP, Stocken DD, Bassi C et al. Adjuvant chemotherapy with fluorouracil plus folinic acid following pancreas cancer resection: a randomized controlled trial. *JAMA* 2010; 304(10): 1073-1081. doi: 101001/jama.2010.1276