Title: Systemic Anti-Cancer Therapy (SACT) Guidelines for Pancreatic Adenocarcinoma

Author(s): Dr Colin Purcell, Consultant Medical Oncologist & on behalf of the GI Oncologists Group, Cancer Centre Belfast City Hospital

Ownership: NICaN

Approval by: NICaN Drugs & Therapeutics committee

Approval date: 12/05/16

Operational Date: June 2016

Next Review: June 2018

Version No. 2.0 Supercedes 1.0

Links to other policies: NICaN Pancreatic Adenocarcinoma SACT protocols

Version control for drafts:

<table>
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<th>Date</th>
<th>Version</th>
<th>Author</th>
<th>Comments</th>
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<tr>
<td>December 2013</td>
<td>1.0</td>
<td>Dr C Purcell</td>
<td>Final version issued.</td>
</tr>
<tr>
<td>February 2016</td>
<td>2.0</td>
<td>Dr C Purcell</td>
<td>Gemcitabine/abraxane®(nab-paclitaxel) for the treatment of metastatic pancreatic cancer added.</td>
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Authorisation of Systemic Anti-Cancer Therapy (SACT) Guidelines for Pancreatic Cancer

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<td>Dr Colin Purcell, Consultant Medical Oncologist</td>
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<td>26/09/2016</td>
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<td>Dr Martin Eatock, Consultant Medical Oncologist, Chair of the NICaN Drugs &amp; Therapeutics committee</td>
<td>28/09/16</td>
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<tr>
<td>Review Date</td>
<td>June 2018</td>
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These SACT guidelines are being submitted by the author on behalf of the GI oncologists group.
1.0 INTRODUCTION / PURPOSE OF POLICY

1.1 Background
Systemic anti-cancer therapy (SACT) is an important modality in the management of patients with a diagnosis of pancreatic adenocarcinoma. This guideline describes the agreed management for these patients.

1.2 Purpose
To ensure consistent use of SACT for patients with pancreatic adenocarcinoma.

2.0 SCOPE OF THE POLICY
This document is aimed at all clinical staff involved in the management of patients receiving SACT for pancreatic adenocarcinoma.

3.0 ROLES/RESPONSIBILITIES
It is the responsibility of all clinical staff involved in the management of patients receiving SACT for pancreatic adenocarcinoma to familiarise themselves with these guidelines.

4.0 KEY POLICY PRINCIPLES

4.1.1 Adjuvant therapy following resection of pancreatic adenocarcinoma

Background

Approximately 20% of patients present with pancreatic cancer amenable to local surgical resection. Complete resection can yield 5-year survival rates of 18% to 24%, but ultimate control remains poor because of the high incidence of both local and distant tumour recurrence (1,2).

Postoperative adjuvant chemotherapy can reduce the risk of disease relapse following surgical resection. The evidence for this comes from two randomised clinical trials.

The ESPAC-3 trial randomly assigned 1,088 patients who had undergone complete macroscopic resection to either 6 months of fluorouracil and folinic acid or 6 months of gemcitabine. Median OS was 23.0 months (95% CI, 21.1–25.0) for patients treated with fluorouracil plus folinic acid and 23.6 months (95% CI, 21.4–26.4) for those treated with gemcitabine (HR = 0.94; 95% CI, 0.81–1.08; P = .39) (3).

The CONKO-001 trial, a multicentre phase III trial, randomised 368 patients with resected pancreatic cancer to receive six cycles of adjuvant gemcitabine or observation. Median DFS was 13.4 months in the gemcitabine arm (95% CI, 11.6–15.3) and 6.7 months in the observation arm (95% CI, 6.0–7.5; P < .001) (4).
With a median follow-up of 136 months, long-term follow-up of the CONKO-001 study demonstrated a significant improvement in OS favouring gemcitabine (median survival 22.8 months vs. 20.2 months; HR, 0.76; 95% CI, 0.61–0.95, P = .01). Gemcitabine compared with observation alone yielded improved survival rates at 5 years of 20.7% for the gemcitabine arm versus 10.4% for the observation-alone arm.

**Patient selection**
Consider adjuvant therapy for post-operative patients with
- Macroscopic (R0 or R1) resection
- ECOG performance status of 0-2
- Adequate hepatic and bone marrow function

**Treatment Regimens**
The oral fluoropyrimidine, capecitabine, is preferred to the fluorouracil regimen used in the ESPAC-3 study.

- Capecitabine 1250mg/m\(^2\) PO BD D1-14 q21D x 8 cycles

For patients where fluoropyrimidine is contraindicated gemcitabine can be considered.

- Gemcitabine 1000mg/m\(^2\) IV D1, 8, 15 q28D x 6 cycles

**Follow up**
Repeat CT scanning should be considered on completion of adjuvant treatment to ensure absence of residual / metastatic disease and provide a baseline for comparative purposes if future imaging is required. Subsequent follow up will be clinically based with further imaging reserved for situations where there is clinical concern.

### 4.2 Advanced (Unresectable or Metastatic) Disease

**Background**
Patients presenting with locally advanced unresectable or metastatic pancreatic adenocarcinoma, including those who have previously undergone resection of their primary tumour and develop recurrent disease, can be considered for SACT. Treatment in this setting is given with palliative intent. In this setting, SACT can be associated with symptomatic benefit and an improvement in survival when compared to best supportive care.
4.2.1 First Line Therapy in Advanced Disease

**Patient selection**

Patients with locally advanced unresectable or metastatic disease should be considered for systemic therapy providing they demonstrate:

- ECOG performance status of 0-2
- Adequate liver and bone marrow function

**Treatment Regimens**

Palliative chemotherapy using single agent gemcitabine was the mainstay of treatment for several years on the basis of clinical trial evidence which demonstrated superior symptomatic benefit and survival with gemcitabine when compared to fluorouracil (5). For patients who are gemcitabine intolerant, treatment with single agent fluoropyrimidine such as oral capecitabine may be considered as an alternative.

In recent years, clinical trials have demonstrated that combination chemotherapy regimens including gemcitabine/capecitabine (GemCap), irinotecan/oxaliplatin/fluorouracil (FOLFIRINOX) and gemcitabine/nab-paclitaxel (Gem/Abraxane) can achieve superior outcomes to gemcitabine treatment alone.

GemCap significantly improved objective response rate (19.1% v 12.4%; P = .034) and progression-free survival (hazard ratio [HR], 0.78; 95% CI, 0.66 to 0.93; P = .004) and was associated with a trend toward improved OS (HR, 0.86; 95% CI, 0.72 to 1.02; P = .08) compared with GEM alone (6).

For the FOLFIRINOX vs gemcitabine comparison, median overall survival was 11.1 months in the FOLFIRINOX group as compared with 6.8 months in the gemcitabine group (hazard ratio for death, 0.57; 95% confidence interval [CI], 0.45 to 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 (hazard ratio for disease progression, 0.47; 95% CI, 0.37 to 0.59; P<0.001). The objective response rate was 31.6% in the FOLFIRINOX group versus 9.4% in the gemcitabine group (P<0.001). P<0.001) (7).

Gem/Abraxane achieved a median overall survival of 8.5 months in patients with metastatic pancreatic adenocarcinoma compared with 6.7 months in the gemcitabine control arm (hazard ratio for death, 0.72; 95% confidence interval [CI], 0.62 to 0.83; P<0.001). The median progression-free survival was 5.5 months in the Gem/Abraxane group, as compared with 3.7 months in the gemcitabine group (hazard ratio for disease progression or death, 0.69; 95% CI, 0.58 to 0.82; P<0.001). Response rate was 23% versus 7% in the two groups (P<0.001) (8). Gem/Abraxane is currently not routinely funded in an NHS setting but may be an option for self-funding patients or on an IFR basis.

Combination treatment regimens can be associated with additional toxicities and should only be considered in those patients with good performance status.
- Gemcitabine 1000mg/m² IV D1, 8, 15 q28d
  CT scan at baseline and every three months subsequently
  Treatment continued until disease progression or unacceptable toxicity

- Capecitabine 1250mg/m² PO BD D1-14 q21D (Gemcitabine intolerant patients)
  CT scan at baseline and every three months subsequently
  Treatment continued until disease progression or unacceptable toxicity

- Gemcitabine Capecitabine (Gem/Cap)
  PS 0 or 1
  Gemcitabine 1000mg/m² IV D1, 8, 15
  Capecitabine 830mg/m² PO BD D1-21
  28 day cycle
  CT scan at baseline and every three months subsequently
  Treatment continued until disease progression or unacceptable toxicity

- FOLFIRINOX
  PS 0
  Oxaliplatin 85mg/m² IV D1
  Irinotecan 180mg/m² IV D1
  Folinic acid 350mg IV D1
  5FU 400mg/m² IV D1
  5FU 2400mg/m² IVI over 48hr D1
  14 day cycle for up to 12 cycles
  CT scan at baseline, three months and 6 months

- Gemcitabine/nab-paclitaxel (not routinely funded)
  PS 0 or 1
  Nab-paclitaxel 125mg/m² IV D1,8,15
  Gemcitabine 1000mg/m² IV D1,8,15
  28 day cycle
  CT scan at baseline and every three months subsequently
  Treatment continued until disease progression or unacceptable toxicity

### 4.2.2 Chemoradiotherapy

Chemoradiotherapy has not been shown to offer an advantage to patients with locally advanced pancreatic cancer compared to SACT alone (9). While not a routine treatment option, chemoradiotherapy may be considered on an individual case basis in patients who have localised disease that has not progressed following a period (typically 6 months) of SACT.
4.2.3 Second Line Therapy

There is no standard of care for the second line treatment of advanced pancreatic cancer. This is due, in part, to the paucity of trials in this patient population. In addition, only a proportion of patients who fail first-line treatment will be fit enough to consider second line therapy. Treatment options will be influenced by treatment received in the first line setting. For patients who progress following first line treatment with FOLFIRINOX, gemcitabine based regimens are often considered as second line treatment. This approach is not proven in clinical trials but is based on the known activity of gemcitabine in first line treatment (5,6). For patients who have progressed following first line gemcitabine treatment, there is limited evidence for benefit from fluoropyrimidine based treatment or fluoropyrimidine in combination with oxaliplatin (10).

Patient selection

Patients with locally advanced unresectable or metastatic disease that has progressed following first line treatment could be considered for second line systemic therapy providing they demonstrate

- ECOG performance status of 0-2
- Adequate liver and bone marrow function

Treatment Regimens

- Gemcitabine 1000mg/m² IV D1, 8, 15 q28d
  CT scan at baseline and every three months subsequently
  Treatment continued until disease progression or unacceptable toxicity

- Capecitabine 1250mg/m² PO BD D1-14 q21D
  CT scan at baseline and every three months subsequently
  Treatment continued until disease progression or unacceptable toxicity

- OMDG
  Oxaliplatin 85mg/m² IV D1
  Folinic acid 200mg/m² (maximum dose 350mg) IV D1
  Fluorouracil 400mg/m² IV D1
  Fluorouracil 2400mg/m² IVI over 48hr D1
  14 day cycle for up to 12 cycles
  CT scan at baseline, three months and 6 months
5.0 IMPLEMENTATION OF POLICY

5.1 Dissemination
This policy will be agreed by all consultant oncologists treating patients with SACT for upper GI malignancies. The guideline will form the basis for development of the SACT regimen specific protocols. It will be available on the intranet for use by all doctors, nurses and pharmacists involved in all stages of SACT assessment and delivery in patients with pancreatic cancer.

6.0 MONITORING
Use of these guidelines will be monitored using audit.

7.0 EVIDENCE BASE / REFERENCES

3) Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA. 2010 Sep 8;304(10):1073-81
9) Pascal Hammel, Florence Huguet, Jean-Luc Van Laethem, et al. Comparison of chemoradiotherapy (CRT) and chemotherapy (CT) in patients with a locally advanced pancreatic cancer (LAPC) controlled after 4 months of gemcitabine with or without erlotinib: Final results of the
international phase III LAP 07 study. J Clin Oncol 31, 2013 (suppl; abstr LBA4003)


8.0 **CONSULTATION PROCESS**
GI oncologists group.

10.0 **EQUALITY STATEMENT**
In line with duties under the equality legislation (Section 75 of the Northern Ireland Act 1998), Targeting Social Need Initiative, Disability discrimination and the Human Rights Act 1998, an initial screening exercise to ascertain if this policy should be subject to a full impact assessment has been carried out. The outcome of the Equality screening for this policy is:

- Major impact [ ]
- Minor impact [ ]
- No impact. ☒