Background

- Local and distant recurrences are frequent problems following resection of pancreatic adenocarcinoma with invasive intent.
- As a result, adjuvant and neoadjuvant protocols using radiotherapy, chemotherapy, or multimodality treatment have been investigated with adjuvant gemcitabine-based chemotherapy standard of care [1, 2, 3].
- Unfortunately, up to 50% of patients will not be fit for post-operative therapy after pancreatic resection.
- Up to 25% patients will have progressive disease during neoadjuvant therapy [1, 2, 4]. Thus, neoadjuvant therapy is able to identify patients with aggressive tumour biology who may be spared the morbidity of resection.
- The administration of pre-operative chemotherapy or chemoradiation has been postulated as a factor that may affect the prognostic significance and rate of R0 margin status [6].
- Recently, nab-paclitaxel and gemcitabine chemotherapy has been shown to improve survival in advanced pancreatic ductal adenocarcinoma (PDAC) compared with gemcitabine alone with acceptable toxicity [10].

Study Design and Schema

A multi-centre, single-arm, non-randomised phase 2 trial with parallel arms based on intention-to-treat principle.

- Patients with resectable pancreatic cancer; FNA+/ Core biopsy (n=42).
- Randomisation: Computer generated allocations (1:1) by computer generated randomisation (overall balance).
- Baseline CT or MRI and PST scan, Ca 19.9, CA 19.5.
- Treatment:
  - Gemcitabine 1000 mg/m² and nab-paclitaxel 125 mg/m² D1, D8, D15 every 28 days (n=41).
  - Day 15 FOG PST scan plus Ca 19.9, CA 19.5.
- Regressing with CT or MRI at completion of therapy prior to surgery.

Surgery:

- Patients with regressing disease or status N0 (R0).
- No evidence of metastatic disease.
- Patient is eligible on central review.

Primary endpoint: (>2+) R0 resection rate.

Baseline characteristics (n=42)

- Characteristics
  - Patients, n (including 1 non-eligible): 42
  - Age (years, median, range): 65 (37-78)
  - Gender (male): 17 (41%)
  - Ca 19.9 (U/mL), median, range: 81 (3-710)
  - Tumour size on final pathological assessment (median, range): 26 (11-50).

Outcomes (n=42)

- Underwent surgery: 36 (86%)
- Pancreatic resection: 30 (73%)
- Radical resection: 24 (57%)
- Two patients with cancer on central review excluded from tumour related outcomes but included in safety and surgical outcomes.

Study Aim

- To evaluate R0 surgical resection rates in patients with resectable cancer following peri-operative nab-paclitaxel and gemcitabine for resectable PDAC.

Methods

- Histologically or cytologically confirmed resectable adenocarcinoma of the pancreas with radiological criteria of:
  - 1. Evidence of extra-pancreatic disease.
  - 2. No evidence of portal vein involvement at the portal confluence.
  - 3. No evidence of portal vein involvement of more than 180° of the circumference or occlusion of the superior mesenteric vein (SMV) or portal vein (PV) confluence.
  - Sample size: We aimed to recruit 50 patients to produce an R0 rate of 85% using a 1 mm margin assessing all margins [11].
  - Primary endpoint: R0 resection defined as all margins microscopically clear (minimum distance from tumour resection margin ≥ 1 mm).

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Compliance with Planned Treatment

- 19/41 (95%) of pts completed the planned induction chemotherapy (although dose modifications and omissions were required by 21/41 of the patients during the cycles).
- 14/30 (47%) of pts completed 4 cycles of the planned post-op chemotherapy.
- 12/90 (40%) of pts that had successful resection did not complete 4 cycles of the planned post-op chemotherapy.
- 14/18 (78%) of pts who commenced post-op chemotherapy completed all 4 cycles of the planned post-op chemotherapy.
- 9/14 (64%) of pts who received chemo radiotherapy. 2/4 pts completed post-op chemotherapy and 2/4 withdrew prior to post-op chemotherapy due to disease progression.

Surgeon (n=42)

- Baseline characteristics (n=42)

- Outcomes (n=42)

- Surgical complications (n=36)

Pathological Tumour Characteristics (n=29)

- Most common symptomatic events:
  - Neutrophil count decreased: 21 (59%)
  - Alkaline aminotransferase (ALT) increased: 7 (17%)
  - Bilirubin: 5 (12%)
  - Fatigue: 4 (10%)
  - Aspartate aminotransferase (AST) increased: 3 (7%)

Resection rates and Primary Outcome (RO)

- Number of patients, 1 mm margin
  - Number of patients, 0 mm margin

Summary and Conclusion

- For pre-treatment with gemcitabine and nab-paclitaxel chemotherapy, was delivered safely and associated with an R0 resection rate of 52% which is comparable or higher than the mean of surgical series using a minimum 1 mm margin-definition.
- After review by independent data and safety monitoring committees, although there were no safety concerns, it was apparent that the primary endpoint of the trial was 112% of 85% or greater could not be met and recruitment was stopped at 42 patients. However an R0 0.9 mm margin greater than 83% was met.
- The pancreatic resectability rate of 79% is comparable to recent neoadjuvant trial in resectable pancreas cancer.
- Pre op gemcitabine and nab-paclitaxel chemotherapy was offered to 95% of patients but in contrast post op chemotherapy was less acceptable with only 47% treated patients proceeding.
- Adjunct chemotherapy was tolerable however with 14/24 completing the protocol planned chemotherapy.
- In conclusion, preoperative gemcitabine and nab-paclitaxel chemotherapy is safe and feasible, and appears to achieve better compliance than post-operative treatment. Post-operatively there were no deaths.

Further follow up is required to evaluate the impact of peri-operative treatment on outcome measures such as recurrence rates and survival, and will be reported in future analysis.