ViP: A prospective, phase II, double blind multicenter randomised controlled trial comparing Gemcitabine plus Vandetanib with Gemcitabine plus Placebo in locally advanced or metastatic pancreatic carcinoma

A brief title, author name(s), preferred degree (one only), affiliation(s), and full address(es) of the authors must be included. The name and address of the corresponding author should be separately and clearly indicated along with email and telephone details.

Authors

Summary (300 words)

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# Manuscript (4500 words max)

## Introduction

## Methods

**Study Design:** The ViP trial was a~~n~~ phase II placebo controlled blinded randomised controlled trial to compare ~~the~~ Gemcitabine plus Vandetanib against Gemcitabine alone in patient with advanced or metastatic pancreatic ductal adenocarcinoma. Patients were recruited from 18 UK hospitals which were centrally coordinated by the Cancer Research United Kingdom Liverpool Cancer Trials Unit (LCTU). The trial was reviewed ~~for ethics~~ by the West London REC 2 Research Ethics Committee (MREC REF: 11/LO/0097).

**Participants:** Patients were eligible if they were diagnosed with locally advanced of metastatic carcinoma of the pancreas. Patients had to have an Eastern Cooperative Oncology Group (ECOG) score of zero, one or two and a documented life expectancy greater than 3 months. Patients undergoing curative of definitive locally directed therapies were excluded as were any patients who had undergone major surgery or radiotherapy within 4 weeks previous to randomisation. Patients were further excluded if they had received previous chemotherapy for locally advanced or metastatic disease. All patients entering the study gave their written informed consent following a full explanation of the study and after reading the patient information sheet.

**Randomisation and masking:** Fisher Clinical Services were contracted to manage the drug, randomisation, dispensing, discontinuation and unblinding of all patients. Patients were randomised to each treatment group on a 1:1 basis according to computer generated variable size blocked randomisation. Patients were stratified at randomisation by their disease stage (locally advanced vs metastatic) and their ECOG performance status (0 vs 1 vs 2). Prior to randomisation, patient details and eligibility criteria were verified by staff at the Liverpool Cancer Trials Unit (LCTU) before being forwarded to Fisher to complete the randomisation process. Masking was achieved by using tablets with identical appearance in numbered bottles. Fisher allocated patients to each treatment group and directly informed the Pharmacy at each site ~~of~~ which bottle numbers to distribute to which patients. Only Fisher were ~~unmasked~~ unblinded to treatment allocation prior to the end of the study. Patients were ~~unblinded~~ unmasked only in the event of a possible Suspected Unexpected Serious Adverse Reaction (SUSAR). Unblinding was carried out by an independent clinical coordinator via direct communication with Fisher.

**Procedures:** Gemcitabine was administered at 100mg/m2weekly as a 30 minute infusion for 7 continuous weeks followed by a one week break. Following this, Gemcitabine was prescribed on a cycle of 3 continuous weeks followed by a one week break. Vandetanib was prescribed orally once a day at 300mg/day. Placebo was prescribed to replicate the Vandetanib prescription. Patients were followed up continually until either death or end of study.

**Outcomes** The primary outcome was overall survival. Secondary outcomes were progression free survival (PFS), objective response rate, disease control rate, toxicity and patient pain assessments. Toxicity assessments were assessed following the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 definitions. Patient response to therapy was measured using the Response Evaluation Criteria in Solid Tumors (RECIST). Best patient response was defined as Complete Response (CR), Partial Response (PR), Stable Disease (SD) or Progressive Disease (PD). Objective response rate~~s~~ was defined by all patients obtaining CR or PR. Disease control rate~~s~~ was defined by all patients with SD or better. Patient pain assessments were made using a 100 point Visual Analogue Scale (VAS). The trial was subject to 100% source data verification of all outcome data.

**Statistical analysis** Study design and sample size calculations were performed with reference to similar trials performed in the same type of patient group1-3. From these, it was estimated that a survival rate of 51% at 6 months would be observed for the control group in the upcoming trial. It was estimated that the inclusion of Vandetanib would results in an increase in 6 month survival rate to 67%, an absolute improvement of 16% corresponding to a hazard ratio of 0.6. Using a one-sided **α** level of 0.1, a total of 100 deaths were required to obtain 90% Power resulting in a total sample size of 120 patients (60 in each treatment group). The study design incorporated a single interim analysis to assess the study for futility after 50 deaths had been observed. The inclusion of this analysis reduced the overall type I error rate from 0.1 to 0.096 for assessment of the primary endpoint at the point of final analysis. During the course of the study, the decision to extend recruitment to recruit 140 patients was made to account for patient drop-out and ensure sufficient quality translational materials were collected. The impact was to extend the target number of deaths to 109 and to increase the trial Power to 91.8%.

Overall survival was measured as the time from randomisation until death by any cause. Patients still alive at the point of final analysis were censored at the date last seen alive. Progression-free survival was measured as the time from randomisation until disease progression or death by any cause. Patients alive and without progression at the point of final analysis were censored at the date last seen alive. Survival estimates were obtained using the Kaplan-Meier4 method and compared across treatment groups using a stratified log-rank test5. The effect of treatment allocation is expressed as a hazard ratio (Gemcitabine plus Vandetanib vs Gemcitabine plus placebo) with an associated 95% confidence interval. Secondary analyses included adjusting the treatment effect using multivariable regression techniques based on Cox proportional hazards models6. Stratification factors and treatment effects are included in all models. Factors with a log rank significance of P<0.25 are considered for inclusion. A forward step-wise regression approach is used with terms included based on Akaikes Informaion Criteria (AIC)7.

Analyses of translational material as potential ~~prognostic~~ predictive factors for treatment effect were also performed, including Cancer Antigen 19.9 (CA19.9), C-Reactive Protein and Single-Nucleotide Polymorphisms (SNPs). SNPs targeted were, RET rs1799939, IL-8 rs4073, VEGFA rs699947 and VEGF (FLT1) rs9582036.

Treatment administration was reported as the median (range) of cycles of each drug received. Toxicity was reported as the number of high grade toxic events (grade 3 or 4) and compares the risk of experiencing a high grade event during the treatment period using the TAME8 guidelines.

All statistical analyses were carried out using the statistical package R (version 3.2). All analyses were carried out on an intention to treat principle, retaining patients in their randomised groups irrespective of any protocol violations. A ~~a~~ one sided P-value of 0.096 (with 80.8% CI) was considered significant for the analysis of the primary endpoint and assessment of the treatment effect. For all secondary analyses a nominal two sided P < 0.05 was used.

The trial was assessed at regular intervals by an Independent Data and Safety Monitoring Committee (IDSMC) who were responsible for assessing the trial in terms of safety and efficacy. The IDSMC were unblinded to treatment allocation throughout the full course of the trial. The trial was registered with the UK CRN (2007-004299-38)

**Role of the funding source:** The funder of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

A total of 142 patients were randomised between the 24th October 2011 and 7th October 2013. Two further patients were recruited beyond the recruitment target as they had already returned written informed consent at the point at which randomisation was complete. One patient was lost-to-follow up in the study and one patient withdrew consent. Figure 1 shows the trial flow diagram. The final database was locked for analysis on 15th July 2015.

Seventy patients were randomised to the Gemcitabine plus Placebo arm and 72 were randomised to Gemcitabine plus Vandetanib. The baseline characteristics of all randomised patients is shown in Table 1. Forty-one patients (29%) were locally advanced and 101 (71%) were metastatic.

One-hundred and thirty one patients had died at the time of analysis, 61 (87%) in the Placebo arm and 70 (97%) in the Vandetanib group. Univariate analysis of survival factors by baseline characteristics is given in Table 2. Survival estimates are given in Figure 2. Median survival estimates are 8.95 (6.55-11.7) months and 8.83 (7.11-11.6) months for the Placebo and Vandetanib arms respectively. A stratified log-rank test gives HR =1.31 (80.8% CI 0.951-1.53; P=0.3).

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## Discussion

## Panel: Research in context

## References (30 max) (Vancouver)

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## Figures and Tables (INC. consort Diagram)

Figure 1: Consort Diagram



Figure 2: Kaplan Meier Plot



Table 1: Baseline characteristics of the intention to treat population

|  |  |  |  |
| --- | --- | --- | --- |
| ***Clinical Characteristic*** | **Gemcitabine plus Placebo (n=70)** | **Gemcitabine plus Vandetanib (n=72)** | **TOTAL** |
| **Gender,** n (%) |  |  |  |
| Male | 30 (43%) | 29 (40%) | 59 (42%) |
| Female | 40 (57%) | 43 (60%) | 83 (58%) |
| **Age,** median (IQR) | 67.5 (61, 73) | 66.5 (61, 73) | 67 (61, 73) |
| **Disease Stage** |  |   |  |
| Locally advanced | 20 (29%) | 21 (21%) | 41 (21%) |
| Metastatic | 50 (71%) | 51 (79%) | 101 (79%) |
| **ECOG Performance Status** |  |   |  |
| 0 | 19 (27%) | 21 (29%) | 40 (28%) |
| 1 | 43 (61%) | 43 (60%) | 86 (61%) |
| 2 | 8 (11%) | 8 (11%) | 16 (11%) |
| **ECG,** median (IQR) | 426 (408.25, 436.75) | 418.5 (399, 435.75) | 423 (403, 436.75) |
| **Tumour Histology,** n (%) |  |   |  |
| Panc. ductal adenocarcinoma | 62 (89%) | 66 (92%) | 128 (90%) |
| Undiff. carcinoma of the panc. | 8 (11%) | 6 (8%) | 14 (10%) |
| **Tumour Site,** n (%) |  |   |  |
| Body | 13 (19%) | 24 (33%) | 37 (26%) |
| Head | 47 (67%) | 31 (43%) | 78 (55%) |
| Tail | 5 (7%) | 13 (18%) | 18 (13%) |
| Uncinate | 5 (7%) | 4 (6%) | 9 (6%) |
| **Tumour Differentiation,** n (%) |  |   |  |
| Well | 7 (10%) | 6 (8%) | 13 (9%) |
| Moderate | 12 (17%) | 16 (22%) | 28 (20%) |
| Poor | 15 (21%) | 16 (12%) | 30 (22%) |
| Unknown | 29 (41%) | 30 (42%) | 59 (42%) |
| Cannot be assessed | 7 (10%) | 4 (6%) | 11 (8%) |
| **Smoking Status,** n (%) |  |   |  |
| Current Smoker | 10 (15%) | 19 (28%) | 29 (21%) |
| Ex Smoker | 23 (34%) | 30 (43%) | 53 (39%) |
| Never Smoked | 34 (51%) | 20 (29%) | 54 (40%) |
| **CA19-9 KU/I\*,** median (IQR) | 1259.5 (264.75,6080.25) | 1018 (199, 6104) | 1100 (223, 6104) |
| **CRP\*,** median (IQR) | 9 (0, 15) | 6.5 (0, 32) | 8 (0, 23) |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ***Prognositc Variable*** | **No Pts. (Deaths)** | **Median OS** | HR | P |
|
| **Arm,** n (%) |  |  |  |  |
| Gemcitabine plus Placebo | 70 (61) | 8.95 (6.55, 11.7) |  |  |
| Gemcitabine plus Vandetanib | 72 (70) | 8.83 (7.11, 11.6) | 1.17 (0.83, 1.65) | 0.376 |
| **Gender,** n (%) |  |  |  |  |
| Female | 59 (55) | 8.32 (5.82, 11.4) |  |  |
| Male | 83 (76) | 9.38 (6.68, 11.9) | 0.94 (0.67, 1.34) | 0.744 |
| **Age** |  |  |  |  |
| <65 | 60 (53) | 10.08 (4.87, 12.70) |  |  |
| >65 | 82 (78) | 8.75 (6.68, 11.0) | 1.01 (0.99, 1.03) | 0.546 |
| **Disease Stage** |  |  |  |  |
| Locally advanced | 41 (37) | 11.53 (9.97, 15.16) |  |  |
| Metastatic | 101 (94) | 7.11 (4.74, 9.97) | 1.42 (0.97, 2.08) | 0.071 |
| **ECOG Performance Status** |  |  |  |  |
| 0 | 40 (36) | 11.58 (8.16, 15.2) |  |  |
| 1 | 86 (79) | 8.91 (7.40, 11.3) | 1.32 (0.88, 1.97) |  |
| 2 | 16 (16) | 4.59 (3.91, 10.2) | 2.46 (1.34, 4.51) | 0.012 |
| **Tumour Histology,** n (%) |  |  |  |  |
| Panc. ductal adenocarcinoma | 128 (117) | 8.95 (7.70, 11.5) |  |  |
| Undiff. carcinoma of the panc. | 14 (14) | 6.23 (3.39, 11.6) | 2.06 (1.17, 3.64) |  0.013 |
| **Tumour Site,** n (%) |  |  |  |  |
| Body | 37 (36) | 8.22 (5.82, 12.3) |  |  |
| Head | 78 (70) | 9.97 (7.73, 11.6) | 0.84 (0.56, 1.26) |  |
| Tail | 18 (16) | 9.67 (3.59,NA) | 0.81 (0.45, 1.46) |  |
| Uncinate | 9 (9) | 5.00 (2.4, NA) | 1.33 (0.64, 2.77) | 0.52 |
| **Tumour Differentiation,** n (%) |  |  |  |  |
| Well | 13 (11) | 13.59 (12.43, NA) |  |  |
| Moderate | 28 (24) | 10.69 (8.22, 19.14) | 1.47 (0.70, 307) |  |
| Poor | 31 (29) | 6.25 (4.38, 11.58) | 2.47 (1.20, 5.08) |  |
| Unknown | 59 (57) | 7.11 (4.54, 9.97) | 2.490 (1.22, 4.72) |  |
| Cannot be assessed | 11 (10) | 10.86 (8.03, NA) | 1.37 (0.57, 3.31) | 0.018 |
| **Smoking Status,** n (%) |  |  |  |  |
| Current Smoker | 54 (47) | 8.32 (5.07, 11.2) |  |  |
| Ex Smoker | 29 (27) | 11.02 (7.83, 13.6) | 1.02 (0.63, 1.64) |  |
| Never Smoked | 53 (51) | 9.61 (7.11, 13.4) | 0.98 (0.65, 1.46) | 0.98 |

***Table 2: Univariate Analysis***

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ***Prognositc Variable*** | **No Pts. (Deaths)** | **Median OS** | **HR** | **P** | **Placebo** | **Vandetanib** | **HR** | **P** |
| **No Pts. (Deaths)** | **Median OS** | **No Pts. (Deaths)** | **Median OS** |
| **CA19-9 KU/I\*** |  |  |  |   |  |  |  |  |  |  |
| <1000 | 65 (57) | 12.1 (10.23, 16.05) |  |   | 32 (24) | 11.74 (8.03, 20.46) | 34 (33) | 12.09 (11.02, 15.16) | 1.33 (0.77, 2.28) |  |
| >1000 | 72 (69) | 6.89 (4.84, 8.91) | 1.19 (1.09, 1.29) | <0.001 | 37 (35) | 7.50 (5.07, 9.97) | 35 (34) | 5.79 (4.21, 8.91) | 1.17 (0.74, 1.85) | 0.4 |
| **CRP** |   |   |   |   |   |   |   |   |   |   |
| < 8 | 33 (32) | 12.11 (10.86, 16.05) |  |   | 14 (14) | 10.86 (8.95, 20.5) | 19 (18) | 12.43 (11.15, 19.10) | 0.67 (0.33, 1.39) |  |
| > 8  | 30 (30) | 4.39 (3.78, 9.24) | 1.78 (1.27, 2.50) | <0.001 | 15 (15) | 6.68 (4.34, 13.0) | 15 (15) | 3.78 (3.09, 12.10) | 1.96 (0.93, 4.16) | 0.543 |
| **RET rs1799939** |   |   |   |   |   |   |   |   |   |   |
| Homo. Common | 76 (6) | 9.10 (7.11, 11.0) |  |   |  | 9.31 (4.87, 13.00) |  | 8.83 (4.84, 12.4) | 1.18 (0.73, 1.89) |  |
| Homo. Rare | 3 (0) | 9.64 (6.68, NA) | 1.25 (0.39, 3.98) |   |  |  |  |  |  |  |
| Hetero. | 42 (40) | 9.56 (7.40, 12.8) | 1.03 (0.70, 1.53) | 0.932 |   | 7.73 (6.35, 18.3) |   | 10.89 (7.40, 16.20) | 1.10 (0.58, 2.06) | 0.88 |
| **IL-8 rs4073** |   |   |   |   |   |   |   |   |   |   |
| Homo. Common | 28 (25) | 8.37 (4.21, 15.60) |  |   | 10 (8) | 5.13 (2.80, NA) | 18 (17) | 9.36 (4.44, 16.10) | 0.93 (0.40, 2.18) |  |
| Homo. Rare | 34 (30) | 8.49 (5.07, 12.3) | 1.10 (0.64, 1.88) |   | 17 (14) | 9.24 (5.07, NA) | 17 (16) | 7.70 (4.54, 12.40) | 1.57 (0.73, 3.35) |  |
| Hetero. | 66 (64) | 10.10 (8.16, 12.7) | 1.06 (0.66, 1.69) | 0.947 | 33 (31) | 9.64 (7.50, 13.0) | 33 (33) | 11.15 (7.83, 13.00) | 1.08 (0.66, 1.78) | 0.74 |
| **VEGFA rs699947** |   |   |   |   |   |   |   |   |   |   |
| Homo. Common | 32 (31) | 8.85 (7.50, 12.10) |  |   | 11 (10) | 8.95 (6.35, NA) | 21 (21) | 8.75 (5.79, 12.70) | 1.05 (0.49, 2.27) |  |
| Homo. Rare | 40 (37) | 7.98 (4.38, 10.90) | 0.88 (0.54, 1.42) |   | 21 (19) | 9.24 (4.38, 13.0) | 19 (18) | 7.40 (4.11, 19.10) | 1.04 (0.55, 1.99) |  |
| Hetero. | 56 (51) | 11.58 (8.03, 15.60) | 0.70 (0.435, 1.11) | 0.289 | 28 (24) | 9.38 (5.07, 18.7) | 28 (27) | 11.92 (7.70, 15.70) | 1.28 (0.73, 2.25) | 0.98 |
| **VEGF (FLT1) rs9582036** |   |   |   |   |   |   |   |   |   |   |
| Homo. Common | 69 (66) | 8.32 (6.68, 11.0) |  |   | 30 (37) | 8.55 (6.35, 13.0) | 39 (39) | 8.22 (4.87, 12.10) | 1.20 (0.73, 1.97) |  |
| Homo. Rare | 6 (6) | 5.26 (2.73, NA) | 1.36 (0.59, 3.16) |   | 5(5) |  |  |  |  |  |
| Hetero. | 53 (47) | 11.15 (9.64, 12.8) | 0.82 (0.56, 1.20) | 0.38 | 25 (21) | 10.86 (5.00, 17.0) | 28 (26) | 11.50 (8.22, 15.20) | 1.10 (0.62, 1.97) | 0.66 |

Table 3: Overall survival by prognostic translational factors

|  |  |  |  |
| --- | --- | --- | --- |
| Factor | beta (se) | HR (95% CI | P-value |
| **ECOG Performance Status** |  |  |  |
| 0 |  |  |  |
| 1 | 0.25 (0.21) | 1.29 (0.86, 1.95) | 0.219 |
| 2 | 1.02 (0.34) | 2.78 (1.42, 5.43) | 0.003 |
| **Tumour Histology,** n (%) |  |  |  |
| Panc. ductal adenocarcinoma |  |  |  |
| Undiff. carcinoma of the panc. | 0.59 (0.30) | 1.81 (1.00, 3.27) | 0.049 |
| **CA19.9** | 0.14 (0.04) | 1.15 (1.06, 1.25) | 0.001 |
| **Arm,** n (%) |  |  |  |
| Gemcitabine plus Placebo |  |  |  |
| Gemcitabine plus Vandetanib | 0.28 (0.18) | 1.33 (0.93, 1.90) | 0.12 |

Table 4: Multivariate analysis