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# *Viscum album* [L.] extract therapy in patients with locally advanced or metastatic pancreatic cancer: A randomised clinical trial on overall survival ☆

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**Abstract** ***Background:*** The unfavourable side-effects of late-stage pancreatic cancer treatments call for non-toxic and effective therapeutic approaches. We compared the overall survival (OS) of patients receiving an extract of *Viscum album* [L.] (VaL) or no antineoplastic therapy.

***Methods:*** This is a prospective, parallel, open label, monocentre, group-sequential, randomised phase III study. Patients with locally advanced or metastatic cancer of the pancreas were stratified according to a binary prognosis index, composed of tumour stage, age and performance status; and were evenly randomised to subcutaneous injections of VaL extracts or no antineoplastic therapy (control). VaL was applied in a dose-escalating manner from 0.01 mg up to 10 mg three times per week. Patients in both groups received best supportive care. The primary end-point was 12-month OS, assessed in a group-sequential analysis.

***Findings:*** We present the first interim analysis, including data from 220 patients. Baseline characteristics were well balanced between the study arms. Median OS was 4.8 for VaL and



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2.7 months for control patients (prognosis-adjusted hazard ratio, HR = 0.49; $p < 0.0001$). Within the 'good' prognosis subgroup, median OS was 6.6 versus 3.2 months (HR = 0.43; $p < 0.0001$), within the 'poor' prognosis subgroup, it was 3.4 versus 2.0 months respectively (HR = 0.55; $p = 0.0031$). No VaL-related adverse events were observed.

***Conclusion:*** VaL therapy showed a significant and clinically relevant prolongation of OS. The study findings suggest VaL to be a non-toxic and effective second-line therapy that offers a prolongation of OS as well as less disease-related symptoms for patients with locally advanced or metastatic pancreatic cancer.



## 1. Introduction

Patients suffering from pancreatic cancer in a locally advanced or metastatic stage do not have many treatment options if their general condition is bad or if standard therapies have failed.[1–4] Recent studies on second-line therapies for pancreatic cancer showed benefit[5,6]; however, Gemcitabine, 5-FU, capecitabine and combinations of Gemcitabine with capecitabine, erlotinib, oxaliplatin and cisplatin have serious side-effects leading to poor compliance of patients and physicians. Best Supportive Care (BSC) is often the only option,[7] and looking for other therapeutic approaches is desirable.

Medicinal plants have a long tradition in the treatment of cancer and play a major role in the development of new drugs today. Over 60% of currently used anticancer agents originally derive from natural products.[8] In central Europe, extracts of *Viscum album* [L.] (VaL) are registered for parenteral use and are widely used in adjuvant and palliative cancer therapy, alone or in addition to conventional therapies.[9]

VaL contains a variety of biologically active constituents such as lectins, viscotoxins and other low-molecular-weight proteins; furthermore, a chitin-binding agglutinin, oligo- and polysaccharides, flavonoids, vesicles, triterpene acids and others.[10] The manufacturing of VaL adheres to 'good Medical Practise' – requirements for injectable medications; the typical proteins of VaL (mistletoe lectins and viscotoxins) are analysed to ensure consistent quantity and quality. Whole VaL extracts as well as several of the compounds are cytotoxic, and the lectins in particular have strong apoptosis-inducing effects via expression of mitochondrial Apo2.7 molecules.[11] VaL and its compounds stimulate the activation of monocytes/macrophages, granulocytes, natural killer cells, T-cells and dendritic cells; they induce granulocyte–macrophage colony-stimulating factor, tumour necrosis factor α, interferon γ and a variety of cytokines, and they enhance endorphins *in vivo*.[9,10,12] Accordingly, low-dose but not high-dose VaL-lectin-I reduces melanoma growth in a mouse model, probably by immunosignalling.[13] Intratumoral injections of VaL result in partial and complete remissions in an animal model using human pancreatic cancer xenografts[14] and also in patients with inoperable pancreatic carcinoma.[15]

A phase I interaction study of VaL and gemcitabine in patients with advanced solid tumours demonstrated VaL to be safe and well tolerated, allowing a 30% higher gemcitabine dose to be applied. Gemcitabine pharmacokinetics was not affected.[16] A recent review of safety data concerning higher VaL dosages confirmed the favourable safety profile[17] which is particularly desirable for late-stage cancer patients.

Here we present a phase III, open-label, randomised, group-sequential study (ISRCTN70760582). It investigated whether VaL treatment has an effect on overall survival (OS) in patients with locally advanced or metastatic cancer of the pancreas. Because in countries with widespread use of VaL there is a low patient compliance constraining the conduct of randomised VaL trials,[18] we conducted this study in Serbia where VaL therapy is practically unknown. We report the results of the first interim analysis.

## 2. Methods

This is a prospective randomised open-label study on overall survival. Blinding is not essential in cancer studies with overall survival as primary end-point according to the Food and Drug Administration (FDA) guidelines.[19] The study was conducted at the Hepato-Biliary Surgical Unit of the First Surgical Clinic of the Clinical Centre of Serbia (CCS), Belgrade, Serbia. Patients were referred to the study site from seven different centres in Serbia. The study was conducted according to the Declaration of Helsinki and was approved by the ethics committee of the Clinical Centre of Serbia in Belgrade (No. 60/6 from 04.03.2008) and by the Serbian Drug Agency (No. 587/2008/4000 from 10.11.2008). All patients provided written informed consent before study entry. The study was subject of GCP-conform on-site monitoring. Two independent audits reported no critical or major findings relating to the conduct of the study. Results of the interim analysis were reviewed by an Independent Data Monitoring Committee (IDMC).

### 2.1. Patients

Inclusion criteria for patients were: adults aged ⩾18; with locally advanced or metastatic cancer of the pancreas (Union for International Cancer Control [UICC]

stage III/IV); with any history of previous therapies but not eligible for antineoplastic therapies anymore; leucocytes $\geqslant$ 3000 /mm$^3$; platelets $\geqslant$ 100,000 /mm$^3$; serum creatinine $\leqslant$ 2 mg%; serum glutamic oxaloacetic transaminase (SGOT) $\leqslant$ 2.5-fold upper institutional limit; serum glutamic pyruvic transaminase (SGPT) $\leqslant$ 2.5-fold upper institutional limit; negative pregnancy test and contraception (where appropriate); and no other antineoplastic therapies planned during the study except 5-fluorouracil (FU)/leucovorin for symptom alleviation. After the first 47 patients, the inclusion criteria SGOT, SGPT and creatinine were omitted by protocol amendment, since many of the screened patients had very advanced disease and failed to meet these criteria.

Specific exclusion criteria were: life expectancy less than 4 weeks; weight loss $\geqslant$ 20% in the preceding 6 weeks; brain metastasis.

### 2.2. Patient assignment

The Clinical Centre of Serbia (CCS), Belgrade, has about 3700 hospital beds and about 880,000 ambulatory patients. Study centre is the First Surgical Clinic of CCS, the main referral centre for surgical treatment of patients with hepatobiliary and pancreatic malignancies in Serbia. Decisions on treatments of cancer patients are made in a weekly multidisciplinary oncology consultation based on local regulations: inoperable patients with advanced or metastatic pancreatic cancer, not willing to receive chemotherapy or with at least one of the following conditions were candidates for this study: Eastern Cooperative Oncology Group (ECOG) > 2, Bilirubine > 50 μmol/l, transaminases > 100 U/l, leukocytes > 10.0*10$^9$ /l, missing histological confirmation of the disease and therefore not eligible for chemotherapy. After eligibility assessment, signed and witnessed informed consent, and after passing all in- and exclusion criteria, patients were enrolled into the study (Fig. 1).

Patients were stratified into two groups regarding their expected prognosis: 'Poor prognosis' was defined as presenting with at least two out of the three following criteria: UICC class = IV; age > 65; and ECOG $\geqslant$ 2. All other patients were classified as having 'good prognosis'. Within each stratum, patients were randomised 1:1 to either the VaL or control group.

### 2.3. Study medication

The *Viscum album* (L.) extract (VaL) applied in this study is an approved drug and has a marketing authorisation under the name 'Iscador® Qu spezial' in Germany, Switzerland and Austria. It is extracted from the mistletoe of oak trees (Qu = Quercus).The fresh plant is fermented with special starter cultures (lactobacilli). The drug substance Iscador® is then diluted with isotonic saline solution, sterile-filtered and subsequently filled into ampoules as an aseptic injection preparation. The manufacturing adheres to GMP requirements for injectable medications; typical proteins of VaL (mistletoe lectins and viscotoxins) are analysed to ensure consistent quantity and quality.

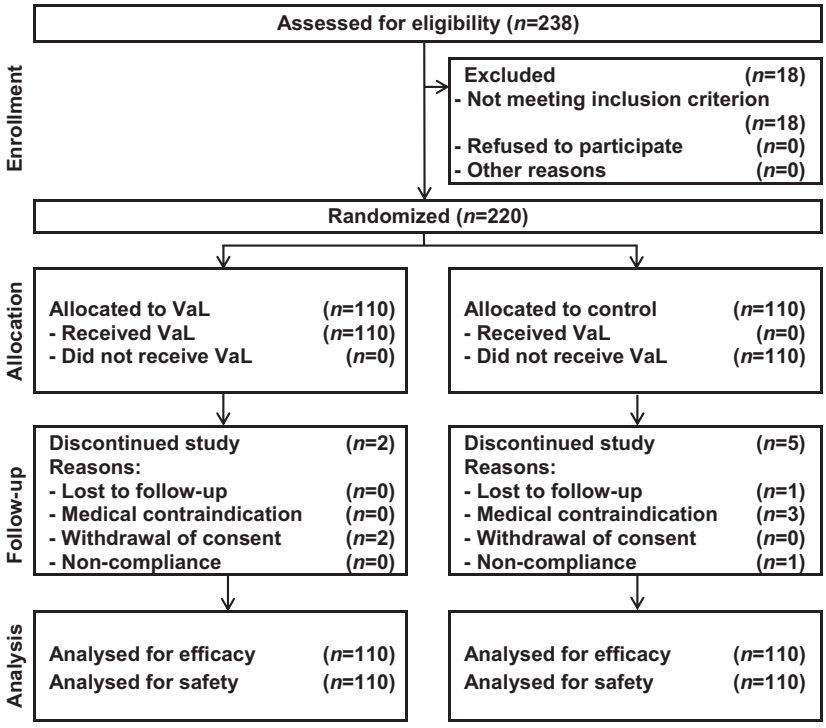


Fig. 1. Flow chart according to Consolidated Standards of Reporting Trials (CONSORT). *Abbreviation:* VaL, *Viscum album* [L.].

### 2.4. Treatment

During the course of the study, all patients received best supportive care which was individually tailored to patient needs at the scheduled follow-up visits (at month 1, 2, 3, 6, 9 and 12), at additional intermediate consultation visits of patients in the study centre and by additional telephone consultations.

Patients in the VaL group received 1 ml subcutaneous injections of VaL three times per week. Patients were taught how to self-administer the subcutaneous injections of VaL. For the time intervals between the follow-up visits at the study centre, patients were provided with sufficient ampoules of VaL and syringes for administration at home or at local health centres. Injections were either self-administered or given by relatives or nurses. VaL dosage was escalating: two injections of 0.01 mg, two of 0.1 mg, five of 1 mg, five of 2 mg and eight of 5 mg, followed by constant doses of 10 mg thrice weekly, maintained throughout the study. In case of local inflammatory skin reactions >5 cm or body temperature >38 °C, Val was to be reduced to the last well tolerated dosage.

### 2.5. End-points

Our primary hypothesis was: Advanced pancreatic cancer patients receiving VaL will show an improvement of 12-month OS. Reference point for OS was the date of inclusion into the study. Primary end-point was the date of death from any reason, obtained from family members and cross-checked by the Serbian residents' registration office. This first interim analysis included 220 patients enrolled in the study, using the intention-to-treat approach.

The secondary end-points of this study were: quality of life parameters, vital signs, performance status, weight and concomitant medication. The respective results will be published elsewhere.

### 2.6. Safety

All 220 enrolled patients were included in the safety evaluation.

At each visit, patients were asked for adverse events which were documented according to the Common Toxicity Criteria for Adverse Events (CTCAE).

After the inclusion of the first 47 patients, a more consistent record of all adverse events was considered desirable, and a standardised documentation of disease-related symptoms was additionally provided in the case report form. These disease-related symptoms consisted of weight loss, pain, loss of energy, nausea/emesis, diarrhoea, anxiety, vertigo, jaundice and abnormal values of bilirubin, SGOT and SGPT. Their severity was rated according to CTCAE as: none, mild, moderate, severe and life-threatening or disabling. All patients received diaries to document episodes of fever. VaL patients were additionally asked to document the applied dose and the occurrence of local skin reactions at the injection site which are considered a desirable immune response and not classified as an adverse event in this study if less than 5 cm in diameter.

### 2.7. Determination of the sample size

Previous VaL studies in patients with advanced pancreatic cancer showed a prolongation in median OS from 5 to 7 months, from which a hazard ratio of 0.714 could be deduced.[20,21] For a two-sided group-sequential hypothesis test with two pre-planned interim analyses including 50% and 75% of the foreseen total sample size, respectively, assuming a power of 85% and 5% level of significance as well as an accrual period of 53 months with an additional follow-up time of 12 months and an even allocation scheme, it was estimated that 173 evaluable patients per group would be needed to confirm a statistically significant treatment effect according to Freedman's formula.[22] To account for dropouts the study was designed for a maximum of 428 patients.

### 2.8. Randomisation

A special department of the data management created for each of the two prognosis strata a separate, evenly balanced randomisation list with variable permutation block sizes of 4, 6 and 8 using SAS® version 9.1 (SAS® Institute, Cary, NC, USA). Following these two randomisation lists, one for each prognosis stratum, two series of opaque and sealed consecutively numbered allocation letters were produced and stored at the study centre. When a patient had been included and attributed to one of the prognosis strata, the investigator opened the next consecutive allocation letter of that stratum and assigned the patient, as determined in this letter, either to the Val or the control group. The monitor checked the sealed as well as the opened random letters at each monitoring visit.

### 2.9. Statistical methods

The study design is based on a group-sequential test procedure with pre-planned analyses after 220, 320 and 428 patients meeting one of the off-study criteria. An alpha-spending approach as suggested by Lan and DeMets[23] with an O'Brien/Fleming-like alpha spending function was used to define the test boundaries of the group-sequential procedure. The primary analysis regarding OS uses a Cox Proportional Hazard Model with treatment and prognosis groups as predictor variables to calculate the Z score needed for the group-sequential procedure. Stagewise ordering was used to

compute the unbiased median estimate and confidence limits for the prognosis-group-adjusted hazard rates.[24] The non-parametric Kaplan–Meier product-limit estimator of the survival function was used to visualise differences between treatment groups and to calculate median survival times.

The Wilcoxon rank sum test and Fisher's exact test were used to check the balance of demographic and clinical baseline characteristics. Prognosis-group-adjusted odds ratios for the occurrence of at least one adverse event during the course of the study were calculated by logistic regression. The worst reported post-baseline CTCAE grade of a patient for each item of the disease-related symptom section was analysed by a Cochran–Mantel–Haenszel test stratified for its baseline value. All tests were two-sided, and a $p$-value of 0.05 was considered statistically significant. The statistical analysis was performed with SAS® version 9.2.

## 3. Results

### 3.1. Patients' characteristics

This first interim analysis referred to 238 screened patients, of whom 220 had been enrolled into the study between January 2009 and December 2010 (Fig. 1). Eighteen patients were not enrolled because their condition was too bad (major weight loss, life expectancy <4 weeks). All enrolled patients had locally advanced or metastatic pancreatic cancer: 195 patients were diagnosed during surgery and 25 were diagnosed by imaging methods only. Baseline patient characteristics were well balanced between VaL and control groups (Table 1). Seven patients dropped out: two in the VaL group and five in the control group (Fig. 1). None of the dropouts were related to treatment with VaL. The recruitment into this study was stopped due to proven efficacy after obtaining the decision of the IDMC in May 2012.

Table 1
Demographic and clinical baseline-characteristics of 220 patients with locally advanced or metastatic pancreatic cancer, treated with VaL extracts or no antineoplastic therapy (control).

| Patient characteristic | Group | | |
|---|---|---|---|
| | Control ($n = 110$) | VaL ($n = 110$) | Test (2-sided) |
| Gender | | | |
| Male | 63 (57.3%) | 65 (59.1%) | $p = 0.891$ FET |
| Female | 47 (42.7%) | 45 (40.9%) | |
| Age (years) | | | |
| Median | 65 | 61 | $p = 0.097$ Wilcoxon |
| Range | 27–90 | 24–87 | |
| Race | | | |
| Caucasian | 110 (100%) | 110 (100%) | – |
| ECOG | | | |
| 0–1 | 56 (50.9%) | 56 (50.9%) | $p = 1.000$ FET |
| 2–4 | 54 (49.1%) | 54 (49.1%) | |
| UICC | | | |
| III | 64 (58.2%) | 57 (51.8%) | $p = 0.416$ FET |
| IV | 46 (41.8%) | 53 (48.2%) | |
| Prognosis group | | | |
| Poor | 56 (50.9%) | 55 (50.0%) | $p = 1.000$ FET |
| Good | 54 (49.1%) | 55 (50.0%) | |
| Tumor-related surgery | | | |
| No | 9 (8.2%) | 6 (5.5%) | $p = 0.594$ FET |
| Yes | 101 (91.8%) | 104 (94.5%) | |
| Affected part of pancreas | | | |
| Head | 56 (50.9%) | 58 (52.7%) | $p = 0.564$ FET |
| Body | 12 (10.9%) | 12 (10.9%) | |
| Tail | 3 (2.7%) | 7 (6.4%) | |
| Head and body | 18 (16.4%) | 18 (16.4%) | |
| Body and tail | 21 (19.1%) | 14 (12.7%) | |
| Head, body and tail | - (-%) | 1 (0.9%) | |
| TNM (T) | | | |
| 3 | 1 (0.9%) | 2 (1.8%) | $p = 0.622$ FET |
| 4 | 109 (99.1%) | 107 (97.3%) | |
| X | - (-%) | 1 (0.9%) | |
| TNM (N) | | | |
| 0 | 1 (0.9%) | - (-%) | $p = 1.000$ FET |
| 1 | 13 (0.9%) | 14 (12.7%) | |
| X | 96 (87.3%) | 96 (87.3%) | |
| TNM (M) | | | |
| 0 | 64 (58.2%) | 57 (51.8%) | p = 0.416 FET |
| 1 | 46 (41.8%) | 53 (48.2%) | |

*Abbreviations:* Wilcoxon, Wilcoxon rank sum test; FET, Fisher's Exact test; ECOG, Eastern Cooperative Oncology Group (performance scale); UICC, Union for International Cancer Control (for grading); TNM, TNM classification according to UICC; VaL, *Viscum album* [L.].

### 3.2. Treatment administration

During the study, patients in the VaL group received three 1 ml subcutaneous injections of VaL per week. In total, 8136 subcutaneous injections were recorded for 110 patients (per patient median = 61.5; minimum = 3; maximum = 156). For all patients in the VaL group, dose escalation followed the planned scheme without any need for dose reduction. No patients in the control group received VaL. All patients in both groups were provided with best supportive care and none of them received 5-FU/Leucovorin or any other antineoplastic therapies.

### 3.3. Overall survival

Median OS for patients was 4.8 months in the VaL group and 2.7 months in the control group (Fig. 2). A prognosis-group adjusted hazard ratio (HR) of 0.49 (95% confidence interval (CI) = 0.36–0.65, $p < 0.0001$) was estimated by the group-sequential procedure.

Subgroup analysis for patients with 'good prognosis' showed a median OS of 6.6 months in the VaL group compared to 3.2 months in the control group ($Chi^2 = 15.5$, HR = 0.43; 95% CI = 0.28–0.65, $p < 0.0001$) (Fig. 3). For patients with 'poor prognosis' the median OS was 3.4 months and 2.0 months, respec-

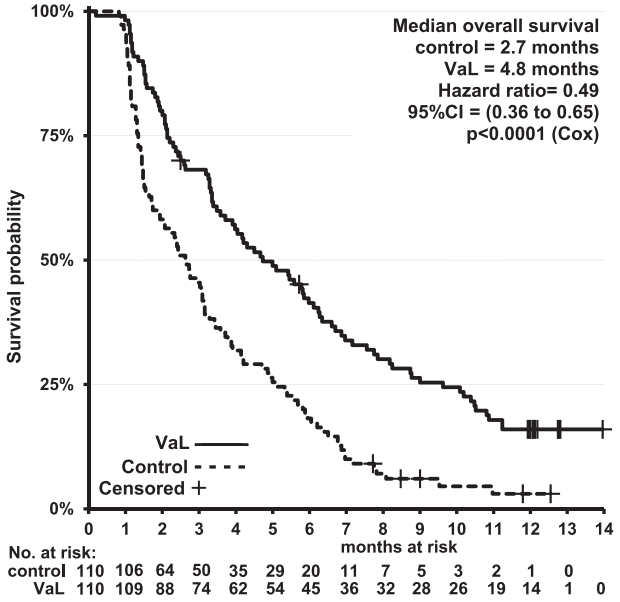


Fig. 2. Kaplan–Meier estimates of 12-month overall survival of 220 patients with advanced or metastatic pancreatic cancer assigned to a therapy with extract of VaL or to no antineoplastic therapy (Control). *Abbreviations:* Cox, Cox regression adjusted for prognosis state; VaL, *Viscum album* [L.]. *Note:* All patients surviving for more than 12 months are censored and therefore not at risk any more.

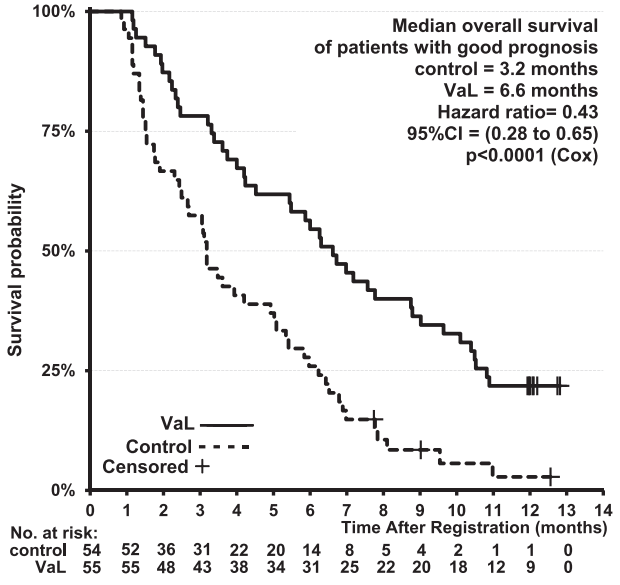


Fig. 3. Kaplan–Meier estimates of 12-month overall survival of 109 patients with advanced or metastatic pancreatic cancer assigned to a therapy with extract of VaL or to no antineoplastic therapy (Control) and good prognosis. *Abbreviations:* Cox, Cox regression; VaL, *Viscum album* [L.].

tively ($Chi^2 = 8.8$, HR = 0.55; 95% CI = 0.37–0.82, $p = 0.0031$) (Fig. 4). Seventeen patients in the VaL group and no patient in the control group ended the study with a regular exit visit after 12 months. Two patients in the control group dropped out without an exit visit, but survived study day 360. Subgroup analyses

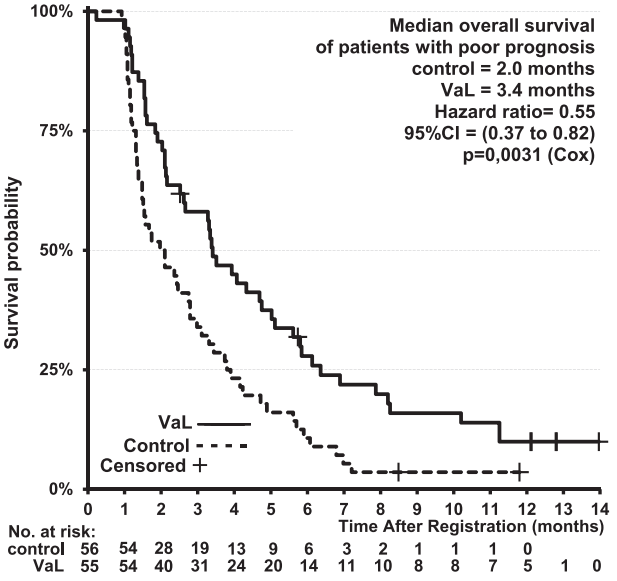


Fig. 4. Kaplan–Meier estimates of 12-month overall survival of 111 patients with advanced or metastatic pancreatic cancer assigned to a therapy with extract of VaL or to no antineoplastic therapy (Control) and poor prognosis. *Abbreviations:* Cox, Cox regression; VaL, *Viscum album* [L.].

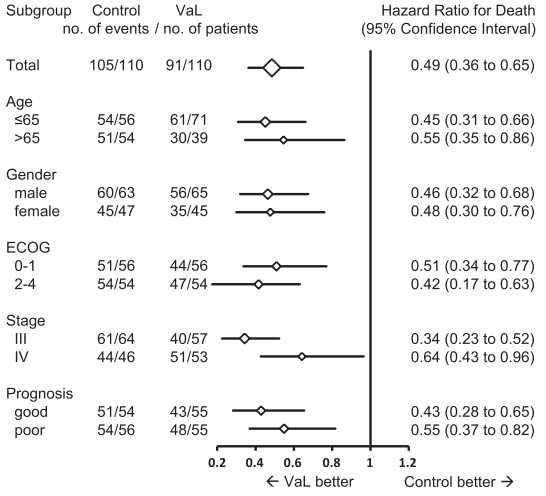


Fig. 5. Forest plot (multivariate cox regression including interactions) of the treatment effect on 12-month overall survival of 220 patients with advanced or metastatic pancreatic cancer assigned to a therapy with extract of VaL or to no antineoplastic therapy (Control). *Abbreviations:* ECOG, Eastern Cooperative Oncology Group (performance scale); VaL, *Viscum album* [L.]. The squares represent the hazard ratio and their sizes are proportional to the sizes of the subgroups. The horizontal lines show the confidence intervals.

showed superiority for the VaL group in all analysed subsets (Fig. 5).

### 3.4. Safety

In the VaL group, 16 adverse events and one serious adverse event (cerebral infarction) occurred in 11 patients; in the control group, 53 adverse events

Table 2
Summary of adverse event analysis: number of AEs by MedDRA preferred term and CTCAE grade with total frequency ⩾2 in patients with locally advanced or metastatic pancreatic cancer assigned to a therapy with extract of VaL or to no antineoplastic therapy (Control).

| Adverse event | Grade | Control $n = 53$ (100%) | VaL $n = 17$ (100%) |
|---|---|---|---|
| Back pain | CTC 2 | 8 (15%) | 4 (24%) |
| | CTC 3 | 12 (23%) | 0 |
| Dyspepsia | CTC 2 | 11 (21%) | 2 (12%) |
| Dehydration | CTC 2 | 6 (11%) | 1 (6%) |
| Headache | CTC 1 | 1 (2%) | 0 |
| | CTC 3 | 1 (2%) | 0 |
| Metastases to liver | CTC 1 | 2 (4%) | 0 |
| Urinary tract infection | CTC 1 | 0 | 2 (12%) |
| Abdominal pain/upper abdominal pain | CTC 1 | 1 (2%) | 1 (6%) |
| | CTC 2 | 1 (2%) | 1 (6%) |

*Note:* None of the adverse events was related to the therapy with VaL.
*Abbreviation:* VaL, *Viscum album* [L.].
The Medical Dictionary for Regulatory Activities (MedDRA).

occurred in 34 patients. The odds ratio of 0.25 (95% CI = 0.12–0.52) calculated by logistic regression adjusted for the prognosis group was in favour of the VaL group. The most frequent adverse event (AE) was back pain (four in the VaL group and 20 in the control group; Table 2). None of the adverse events was causally related to VaL.

Local side-effects of VaL injections such as erythema or swellings were reported in the diaries of 67 VaL patients but were always below the AE-defining size of 5 cm in diameter. The validity of the diary data, however, seemed questionable, since substantial number of diary entries could not undoubtedly be attributed to patients but may have been done by relatives or nurses.

Prevalence of pre-specified post-baseline disease-related symptoms in patients was: pain (96.9%); loss of energy (70.9%); abnormal SGPT (55.4%); abnormal SGOT (50.6%); weight loss (42.5%); abnormal bilirubin (38.1%); jaundice (26.0%); nausea/emesis (18.9%); diarrhoea and anxiety (both 2.4%). No cases of vertigo were reported. In the VaL group, the frequency and severity of post-baseline disease-related symptoms was significantly lower for: pain, weight loss, loss of energy, nausea/emesis ($p < 0.0001$ for all parameters), diarrhoea ($p = 0.0033$) and anxiety ($p = 0.046$) (Table 3).

## 4. Discussion

In this randomised phase III study on patients with locally advanced or metastatic cancer of the pancreas, patients in the VaL group had a significant longer OS. No VaL-related side-effects were observed, and fewer disease-related symptoms were reported for patients in the VaL group.

Based on the findings of this interim analysis, the IDMC recommended the termination of the study, and to give all study patients unrestricted access to VaL therapy. However, due to the lack of a marketing authorisation in Serbia, legal restrictions prohibit the provision of any patient with VaL outside of the clinical trial. Therefore, the local ethics committee allowed to stop the recruitment after 376 patients and to treat patients with VaL within the study.

The non-blinding of study treatment always is a concern in confirmatory clinical trials. However, according to a FDA-guideline blinding is not essential in cancer studies with overall survival as primary end-point. And apart from that a recent Cochrane review[25] on controlled trials comparing placebo groups with untreated groups found no significant effects on continuous or binary outcomes. Regarding our study, it may be of concern that different qualities of BSC may influence the patients' OS. To prevent such bias, we centralised the medical care (BSC) during the study, guaranteeing a high and equal standard of BSC for both patient groups and prompting the patients to come to the follow-up visits at the study centre. The very low drop-out rate in both groups may be a sign of the effectiveness of this measure. Up to the point of time of this interim analysis no differences in BSC in the two groups were found.

Previous VaL studies on OS of cancer patients had either an epidemiologic design[20,26]; had a small number of participants or were not properly randomised[27,28]; or, as criticised,[27,28] may have had unbalanced baseline characteristics and a large number of dropouts and verum patients not receiving VaL,[29] or too low doses.[30] Strengths of the present study are its prospective randomised study design, a sufficient number of participants, OS as primary end-point, baseline characteristics balanced between groups, a small number of dropouts, all patients in the verum group receiving VaL treatment and sufficient VaL dosage.

The absence of a histopathological confirmation of the diagnosis for tumour identification is justified by the high risk of pancreatic fistula for the patients when direct tumour biopsy is taken and represents the institutional policy: a histopathological examination is considered unnecessary in local non-resectable stage of the disease (infiltration of both superior mesenteric artery and vein, infiltration of mesentery root and infiltration of retroperitoneal space and major blood vessels) and in patients not consenting in chemotherapy. Imaging of the tumour in the pancreatic body and/or tail, and metastasis in the liver and/or spread in the peritoneum is also considered to be a sufficient diagnosis.

Table 3
Summary of maximum post-baseline CTCAE grade of disease related symptoms of patients* with locally advanced metastatic pancreatic cancer assigned to a therapy with extract of VaL or to no antineoplastic therapy (Control).

| Symptom | Grade | Group | | |
|---|---|---|---|---|
| | | Control $n = 51$ (100%) | VaL $n = 76$ (100%) | Mantel–Haenszel** $Chi^2/p$ (2-sided) |
| Weight loss | CTC 0 | 18 (35.3%) | 74 (97.4%) | $52.23/p < 0.0001$ |
| | CTC 1 | 25 (49.0%) | 2 (2.6%) | |
| | CTC 2 | 8 (15.7%) | 0 | |
| Pain | CTC 0 | 0 | 4 (5.3%) | $26.90/p < 0.0001$ |
| | CTC 1 | 12 (23.5%) | 46 (60.5%) | |
| | CTC 2 | 38 (74.5%) | 26 (34.2%) | |
| | CTC 3 | 1 (2.0%) | 0 | |
| Loss of energy | CTC 0 | 0 | 37 (48.7%) | $40.39/p < 0.0001$ |
| | CTC 1 | 44 (86.3%) | 39 (51.3%) | |
| | CTC 2 | 7 (13.7%) | 0 | |
| Nausea/emesis | CTC 0 | 29 (56.9%) | 74 (97.4%) | $32.06/p < 0.0001$ |
| | CTC 1 | 22 (43.1%) | 2 (2.6%) | |
| Diarrhea | CTC 0 | 48 (94.1%) | 76 (100%) | $4.54/p = 0.0331$ |
| | CTC 1 | 3 (5.9%) | 0 | |
| Anxiety | CTC 0 | 48 (94.6%) | 76 (100%) | $4.00/p = 0.0455$ |
| | CTC 1 | 3 (5.9%) | 0 | |
| Vertigo | CTC 0 | 51 (100%) | 76 (100%) | –/– |
| Jaundice | CTC 0 | 36 (70.6%) | 58 (76.3%) | $0.34/p = 0.5578$ |
| | CTC 1 | 12 (23.5%) | 12 (15.8%) | |
| | CTC 2 | 3 (5.9%) | 6 (7.9%) | |
| Bilirubin | CTC 0 | 43 (59.7%) | 61 (63.5%) | $1.03/p = 0.3097$ |
| | CTC 1 | 9 (12.5%) | 14 (14.6%) | |
| | CTC 2 | 9 (12.5%) | 12 (12.5%) | |
| | CTC 3 | 7 (9.7%) | 8 (8.3%) | |
| | CTC 4 | 4 (5.6%) | 1 (1.0%) | |
| SGOT | CTC 0 | 32 (44.4%) | 51 (53.1%) | $1.86/p = 0.1730$ |
| | CTC 1 | 24 (33.3%) | 31 (32.3%) | |
| | CTC 2 | 12 (16.7%) | 11 (11.5%) | |
| | CTC 3 | 4 (5.6%) | 3 (3.1%) | |
| SGPT | CTC 0 | 31 (43.1%) | 44 (45.8%) | $0.92/p = 0.3382$ |
| | CTC 1 | 29 (40.3%) | 43 (44.8%) | |
| | CTC 2 | 9 (12.5%) | 8 (8.3%) | |
| | CTC 3 | 3 (4.2%) | 1 (1.0%) | |

*Abbreviations:* CTCAE, common terminology for adverse events; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; VaL, *Viscum album* [L.].
* Patients with symptom documentation that survived at least until visit 2 (=100%).
** Cochran–Mantel–Haenszel test, stratified for baseline value.

To assess the external validity, we compared the outcome of our control group with that of untreated patients as reported in the literature. The literature search outcome of a previous review[31] was updated in January 2013 yielding 20 publications with OS times in a total of 754 untreated patients with advanced or metastatic pancreatic cancer.[31–50] The range of median survival times from 2.1 to 7.0 months (median = 3.9; weighted mean = 3.7; SD = 1.5 months) reported there also encloses the median OS of 2.4 months observed in the control patients of this study.

At present, the exact pharmacological working principle of VaL is unclear as VaL contains a wide variety of biologically active constituents (lectins, viscotoxins, other low-molecular-weight proteins, a chitin-binding agglutinin, oligo- and polysaccharides, flavonoids, vesicles and triterpene acids) exerting cytotoxic, apoptosis-inducing and immunostimulatory effects. For the subcutaneous injections used in this study, some immunosignalling can be assumed, induced by perhaps a variety of substances.

The study findings suggest VaL may be a non-toxic and effective second-line therapy that offers a prolongation of OS as well as fewer disease-related symptoms for patients with locally advanced or metastatic pancreatic cancer. Further research on non-toxic and effective cancer therapies is warranted.

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## Independent Data Monitoring Committee (IDMC)

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The members of the IDMC confirmed in writing their independence from the sponsor with regard to any financial or commercial interest.

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## Conflict of interest statement

None declared.

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